DRUGS ACTING ON SOMATIC NERVOUS SYSTEM

(Skeletal muscle relaxants, Local anaesthetics)

Skeletal muscle relaxants

- Skeletal muscle relaxants are drugs that **act either peripherally at the neuromuscular junction/ skeletal muscle fibre** or **centrally in the cerebrospinal axis to reduce skeletal muscle tone and/or cause paralysis.**

- These agents are **clinically useful during surgery to produce complete muscle relaxation** (e.g., neuromuscular blockers) or in the **treatment of neurological spastic disorders and muscle spasms.**

Classification

On the basis of site of action, skeletal muscle relaxants have been divided into 2 major groups

1. **Peripherally acting muscle relaxants**

Neuromuscular blocking drugs → Nondepolarising
Neuromuscular blocking drugs → Depolarising

Directly acting drugs

2. **Centrally acting muscle relaxants**

Peripherally acting muscle relaxants

1. **Neuromuscular blocking drugs**

a) **Non-depolarising/Competitive neuro-muscular blocking drugs**

Long acting drugs; --d-tubocurarine,
pancuronium,
gallamine
doxacurium

Intermediate acting drugs--vecuronium,
atracurium
rocuronium

Short acting drugs:-- mivacurium

b) **Depolarising/ Non-competitive neuromuscular blocking drugs-**
suxamethonium and
decamethonium.

2. **Directly acting drugs--**e.g., dantrolene and quinine.

Centrally acting muscle relaxants

- Carbamate derivatives
  - methocarbamol, carisoprodol and meprobamate.
- Glyceryl ethers
  - guaiphenesin, mephenesin, chlorzoxazone and chlormezanone.
- Benzodiazepines
  - diazepam and chlordiazepoxide.
- Gamma-aminobutyric acid derivatives
  - baclofen.

Centrally acting muscle relaxants

- These are also called skeletal muscle spasmolytiçs, act through by interfering with internuntial pathways in spinal cord and reticular activating system.
- These are given either orally or parenterally.

Mefenesin and Guaiafenesin:

- Act as glycine agonists and **thus antagonize strychnine or tetanus** but not those of picrotoxin or pentylenetetrazol (GABA antagonism).
- Guaifenesin has wide and used 5% in 5% dextrose as IV infusion in horses for casting.

Dose of Guaifenesin: Dog: 45-90 mg/kg IV;

Large animals: 60-120 mg/kg IV.

Diazepam:

- Causes paralysis of muscles through GABA facilitation, and thus **antagonizes convulsions of picrotoxin or nikethamide.**
- Dog: 0.5-1 mg/kg IV or 1M.
- Cat: 2.5-5 mg/kg orally, thrice a day.

Baclofen:

- $GABA_B$ agonist.
- Causes paralysis of muscles by inhibition of motor neurons in spinal cord.

Methocarbamol:

- Mechanism of action unknown. Used in **tetanus and strychnine poisoning**.
- Dog & Cat 45 mg/kg IV
- Horse: 5-20 mg/kg IV.

	Centrally acting muscle relaxants	Peripherally acting muscle relaxant
1.	Selectively inhibit polysynaptic reflexes in CNS	Block neuromuscular transmission
2.	Decrease muscle tone without reducing voluntary power	Cause muscle paralysis, voluntary movement lost
3.	Cause some CNS depression.	No effect on CNS
4.	Given orally sometime parenterally	Practically always given iv
5.	Used in chronic spastic condition	Used for short-term purposes

Peripherally Acting Muscle Relaxants

Non-Depolarising/Competitive Neuro-muscular Blocking Drugs:

- Non-depolarising drugs are **competitive antagonists of acetylcholine** at nicotinic receptors on the motor end plates.
- They do not cause depolarisation, but **protect receptors from depolarisation by acetylcholine**, so they cause **flaccid paralysis**.
- The non-depolarising or competitive neuromuscular blockers generally have thick bulky and rigid molecule and are termed **Pachycurare**.
- Most of the non-depolarising neuromuscular blocking agents have **two or more quaternary atoms**, which provide necessary attraction to the negatively charged anionic sites of the nicotinic receptors.

Mechanism of action:

- Non-depolarising neuromuscular blocking agents combine with nicotinic receptors in the neuromuscular junction and **prevent the binding of acetylcholine.**
- **Normally,** binding of the cationic head of ACh with the negatively charged sites of nicotinic receptors **causes opening of Na^+ channels** allowing depolarisation of muscle cell membrane and **contraction of skeletal muscle cell.**
- **Occupation** of these sites by the molecularly rigid competitive neuromuscular blockers **do not allow conformational changes in the nicotinic receptors needed for opening of the channel** and subsequent depolarisation of cell membranes and muscular contraction.

- As the antagonism is of competitive type, the actions of non-depolarising blockers can be **overcome by increasing concentration of acetylcholine at the neuromuscular junction**, for example, by administration of anticholinesterase agents like neostigmine or edrophonium.

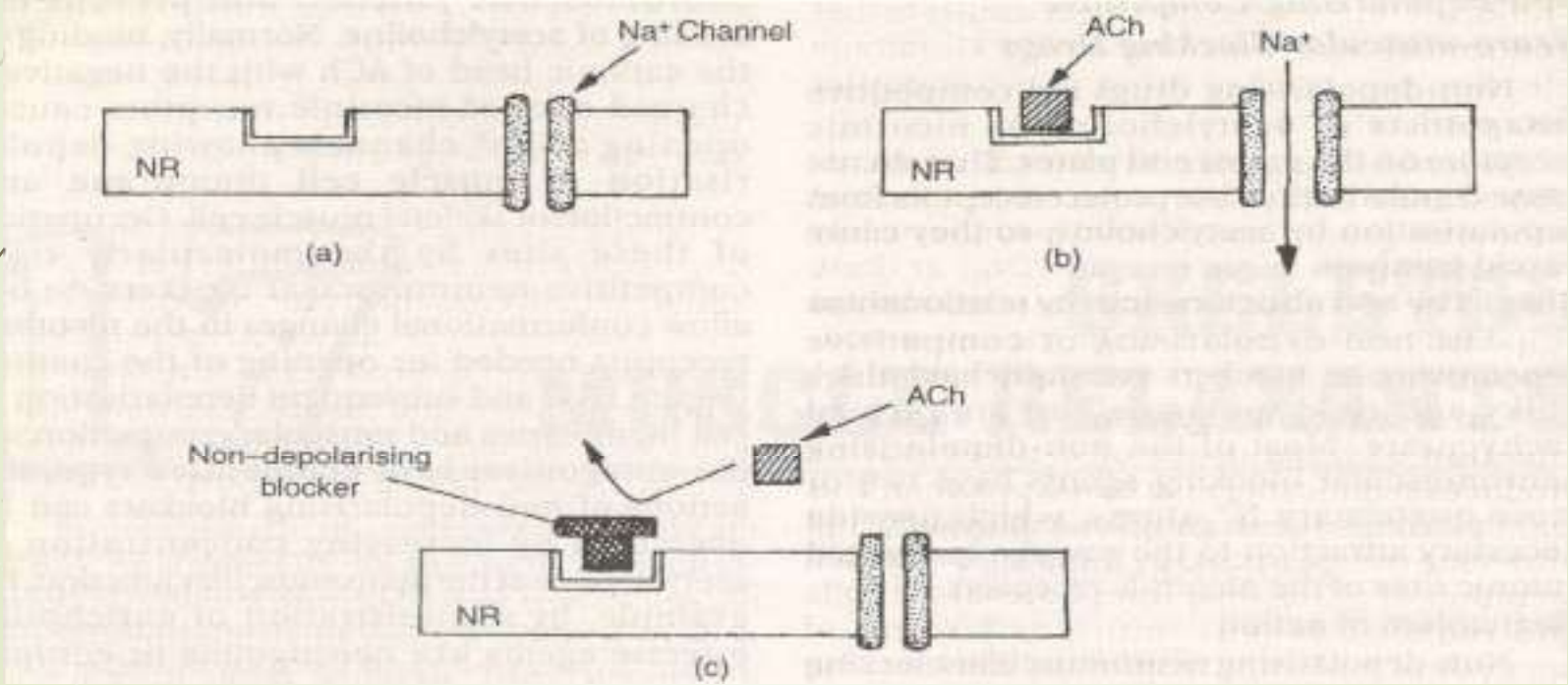
- **At very high concentration**, non-depolarising agents **directly block Na^+ channels** to produce non-competitive neuromuscular blockade.
- This reduces ability of acetylcholinesterase inhibitors to reverse the actions of non-depolarising muscle relaxants.

Mechanism of action of non-depolarising neuromuscular blocker.

a.Nicotinic receptor without ligand: Na+ channel closed.

b.Acetylcholine occupying nicotinic receptor: Na+ channel opened.

c. Non-depolarising drug displaces acetylcholine and occupies nicotinic receptor:Na+ channel closed.



Depolarising/ Non-competitive neuromuscular blocking drugs:

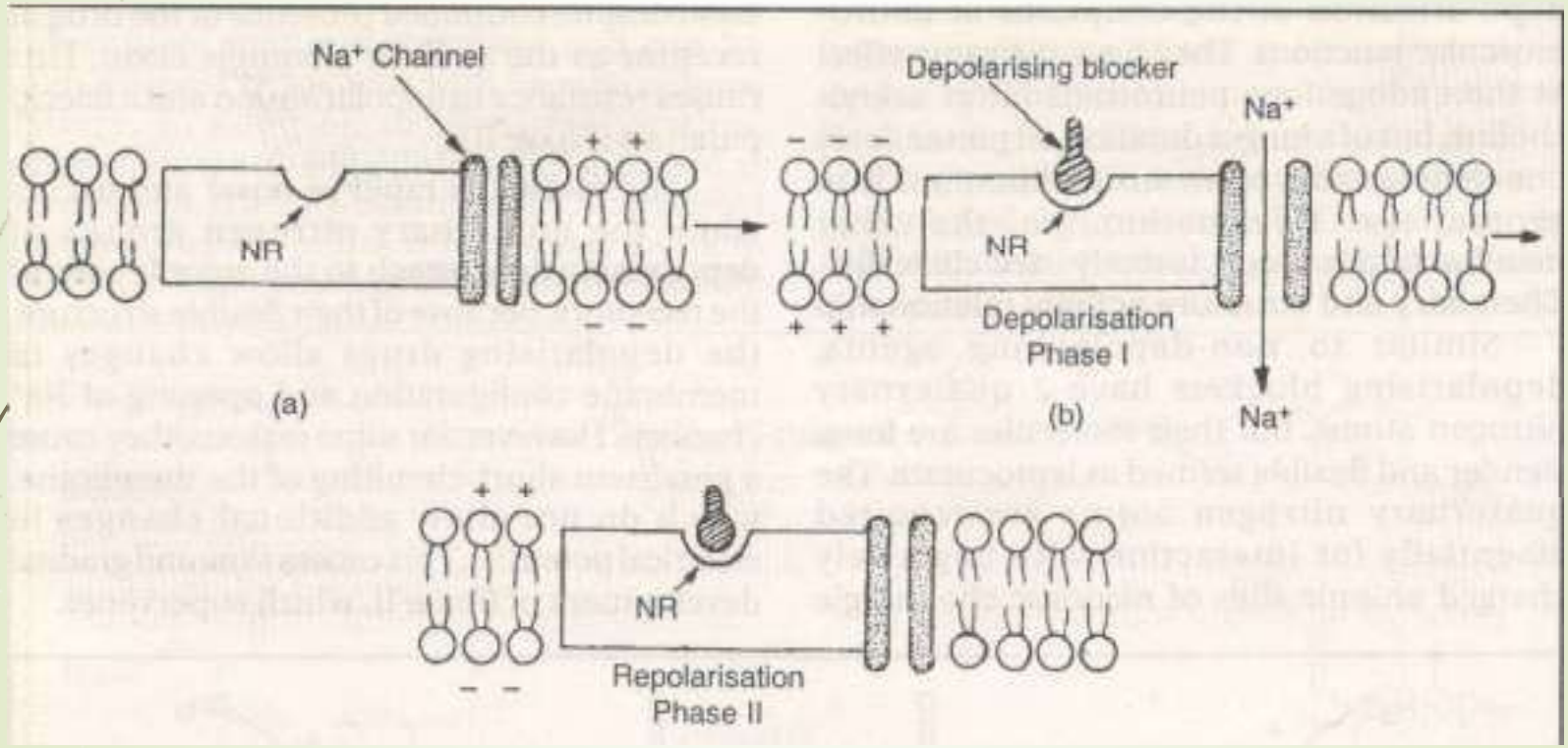


Fig. Schematic representation of mechanism of action of depolarising neuromuscular blocking drugs.

(a) Nicotinic receptor with closed sodium channel.

(b) Depolarising neuromuscular blocker occupying nicotinic receptor. Sodium channel opens to produce depolarisation (Phase-I)

(c) Depolarising neuromuscular blocker still occupying nicotinic receptor. Sodium channel closes as persistent depolarisation changes to repolarisation (Phase II).

NR = nicotinic receptor

Differences between Competitive and Non-competitive NMBs:

Featurs	Competitive NMBs	Non-competitive NMBs
1. Action at motor end plate	No depolarization	Persistent depolarization
Initial effect on muscles	No effect	Transient fasciculation's
Type of muscle paralysis	Flaccid	Tonic
Effect of Anti-ChE agents	Antagonism	Synergistic effect
Species sensitivity	Rat > Rabbit > Cat	Cat > Rabbit > Rat

LOCAL ANAESTHETICS

Local anaesthetics

- ***Local anaesthetics*** are drugs which cause reversible loss of sensation of a particular area or region of the body.
- The effect is not accompanied by loss of consciousness.
- The local anaesthetic solutions are **injected near or in vicinity of the nerves** and applied topically for localized desensitization.

Mechanism of action:

- The local anaesthetics ***prevent depolarization of the neurons*** by interfering with Na^+ ion permeability resulting in blockade of impulse conduction.
- This effect is due to ***reversible binding to the Na^+ ion channels*** in the neuronal membrane.

Differential features of :local and general anaesthetics

Parameters	Local anaesthetics	General anaesthetics
1. Site of action	PNS: Peripheral nerves	CNS: Brain
2. Mode of action	Blocks axonal conduction	Alters synaptic transmission
3. Consciousness	Unaffected	Lost
4. Analgesia	Localized	Generalized
5. Administration	Local deposition away from systemic circulation	Systemic – Inhalation or parenteral
6. Systemic availability	Undesirable, responsible for toxicity	Requisite for action
7. Toxic potential & toxicity	Low, CNS stimulation (convulsive seizures)	High, CNS depression

Classification of local anaesthetics

Categories	Duration of action	Examples
1. Ultra-short acting	Less than or equal to 15 min.	Proparacaine, Benoxinate
2. Short acting	Approx. 1 hour	Procaine, Chlorprocaine, Cocaine
3. Intermediate acting	1 – 4 hour	Lidocaine (Xylocaine), Mepivacaine, Prilocaine
4. Long acting	4 – 10 hours or longer	Bupivacaine, Ropivacaine, Tetracaine, Etidocaine, Hexylcaine, Cinchocaine

Clinical applications of local anaesthetic agents:

- ***Topical anaesthesia*** (Surface anaesthesia): Eyes-4% ***Xylocaine jelly***, 0.5-1% ***Tetracaine solution***.
- These are used for catheterization in ***urethra and endotracheal incubation*** in the trachea.
- ***Infiltration and field block:*** Local anaesthetics used are ***Procaine*** (1% in small animals and 2% in large animals), ***Lignocaine*** (2%).
- ***Conduction/ Nerve block:*** Local anaesthetics used are ***Procaine*** (2%), ***Lignocaine*** (2%)***and Mepivacaine*** (2%). (Mepivacaine is best suited in case of horse).

Potentiation of Local Anaesthetics

By decreasing absorption of injected local anesthetic:

- Adrenaline is added to local anaesthetic solutions at concentrations ranging from 1:1,00,000 to 1:50,000, which causes constriction of blood vesselsand reduces the absorption of local anesthetic .

By increasing the spread of local anaesthetic :

- Addition of Hyaluronidase to local anaesthetic solutions increases the diffusion or spread of the local anaesthetic and enhances the area of anaesthetization.

Cocaine:

- It is the "**mother of all local anaesthetics".**
- It was the first local anaesthetic alkaloid isolated from the leaves of *Erythroxylon coca* by Albert Nieman in the year 1860.
- Due to its marked CNS stimulant (toxicity) limits its use.

Procaine:

- It is used for infiltration , 1% in small animals and 2% in large animals.
- For conduction block (2.5 ml of a 2% solution in small animals and 5-10 ml of 4% solution in large animals).
- It is also used in epidural anaesthesia as 2%.
- Horse- highly sensitive- convulsive effect.
- **Parakeets- highly sensitive- lethal effect**.
- It is ineffective topically due to its poor lipid solubility.
- Procaine (Procainamide)is used as an effective **antiarrhythmic agent**.
- It is **not recommended in patient** along with **sulphonamide therapy**.

  (it favour growth of pathogens by providing their growth factor PABA.)

Lidocaine (Lignocaine or Xylocaine):

- LAP is about 2 times that of procain.
- It is a multipurpose local anesthetic.
- It is reported to be immunosressant compound (both humoral as well as cell mediated).
- It is also used as antiarrhythmic agent.
- It is used as 1-2% solution for epidural and nerve block anaesthesia in large and small animals.
- It is also used i.v. @ 2 mg/kg b.wt. (every 15-30 minutes) to control cardiac arrhythmia in dog.

Tetracaine:

- It is long acting and one of the most potent ester type local anaesthetic.
- It is one of the choice topical opthalmic anaesthesia (0.5 % in small animals and 1% in large animals), and for spinal anaesthesia.

Benzocaine:

- **It is comparatively non irritant and recommonded for use on skin,** dentistry, gums & buccal mucosa.
- **It is also used as fast- acting fish immobilizing agent.**
- **It absorb UV light and has been used in sunscreen creams and lotions.**

Bupivacaine:

- It has been recommonded as **post-operative topical analgesic**, superior to phenylbutazone.
- Four times more potent than Lidocaine and has duration of action - 3 to 8 hours.
- It has been recommonded also for during labour or during **post –operative** period as it tends to produce **more sensory then motor nerve blocked**.

THANK YOU

PHARMACOKINETICS

Quantitative study of drug movement in, through and out of body

Pharmacokinetics (PK) & pharmacodynamics (PD)

- PK - What the body does to the drug?
  - Absorption; distribution, metabolism, excretion (ADME)
- PD - What the drug does to the body?
  - Drug concentration at the site of action or in the plasma is related to a magnitude of effect

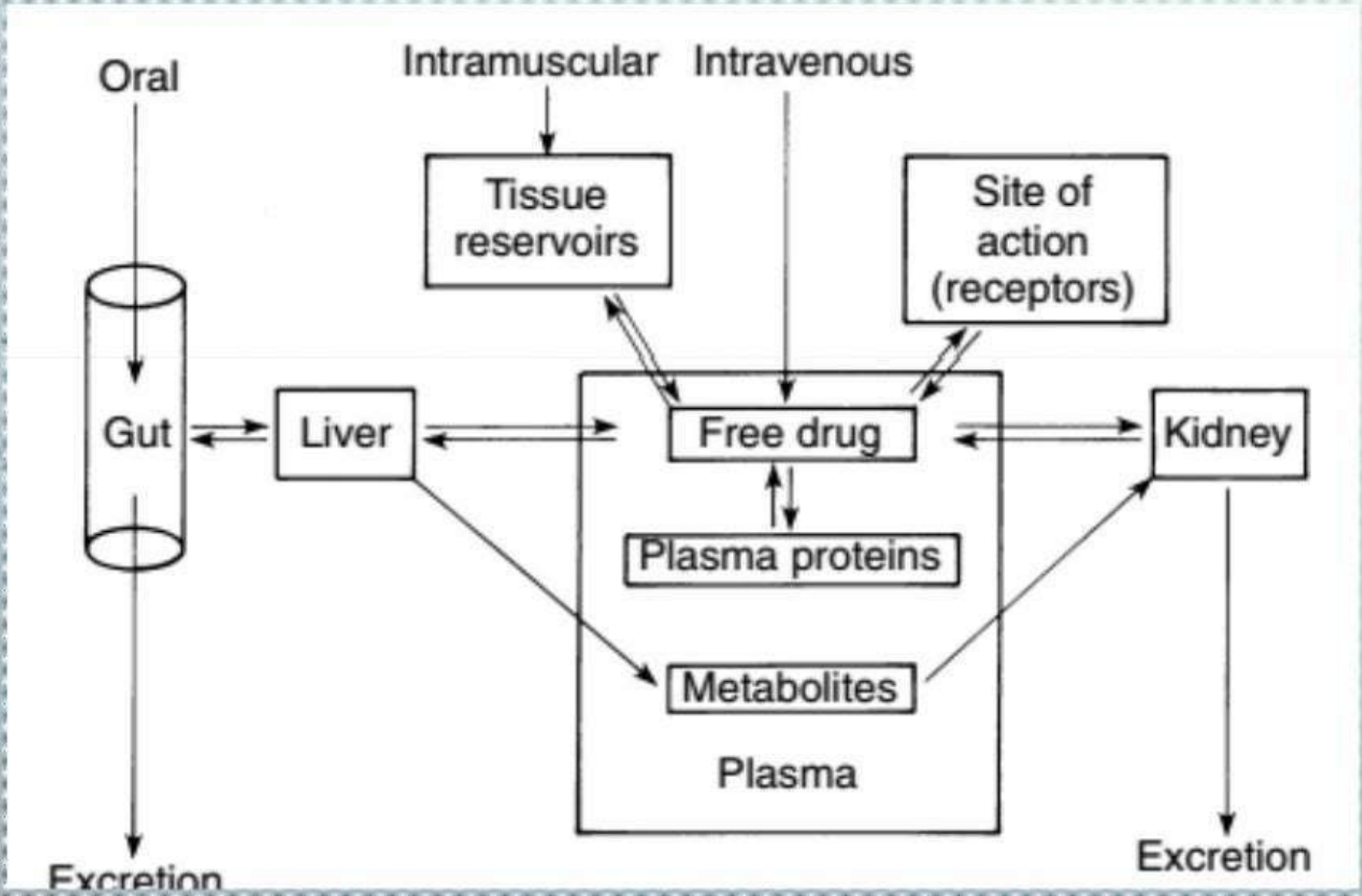
What is clinical pharmacokinetics ?

- Study of the time course of a drug's movement through the body.
- Understanding of what the body does to (or with) the drug.
- Application of Therapeutic Drug Monitoring (TDM) and individualisation of drug therapy.

Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Elimination

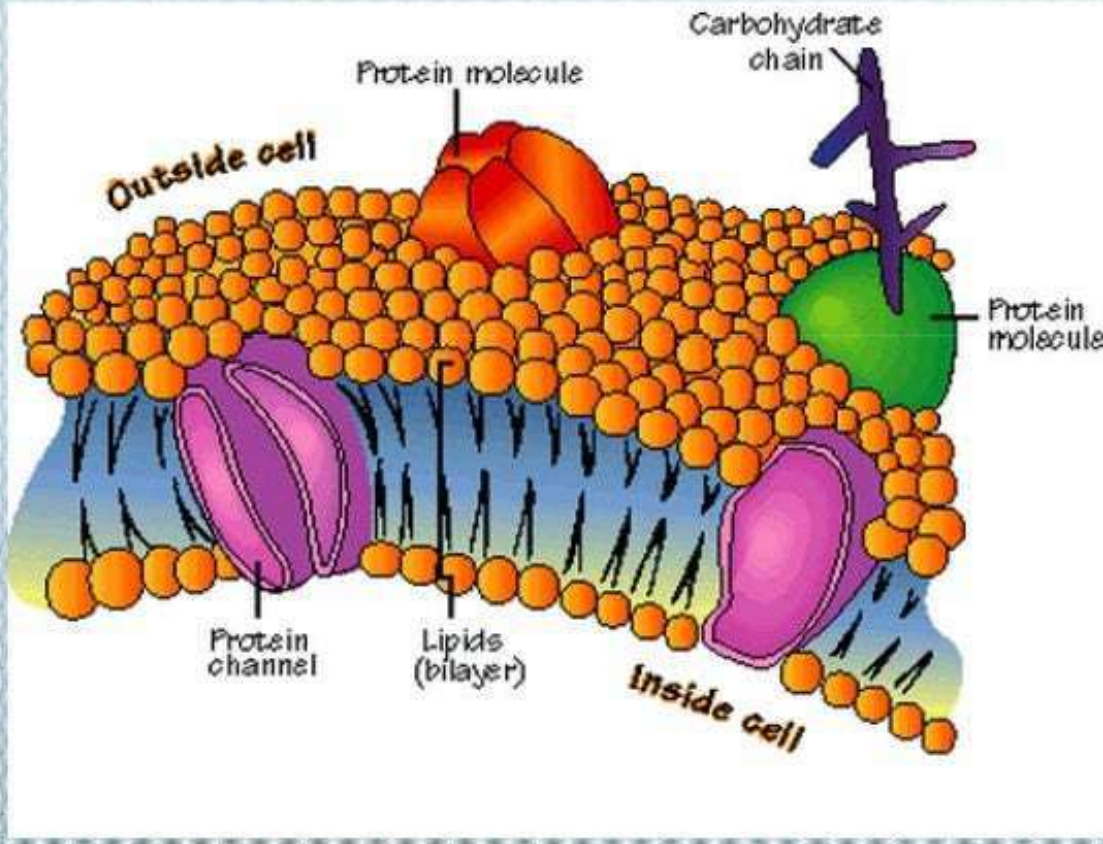
Study of [drug] over time



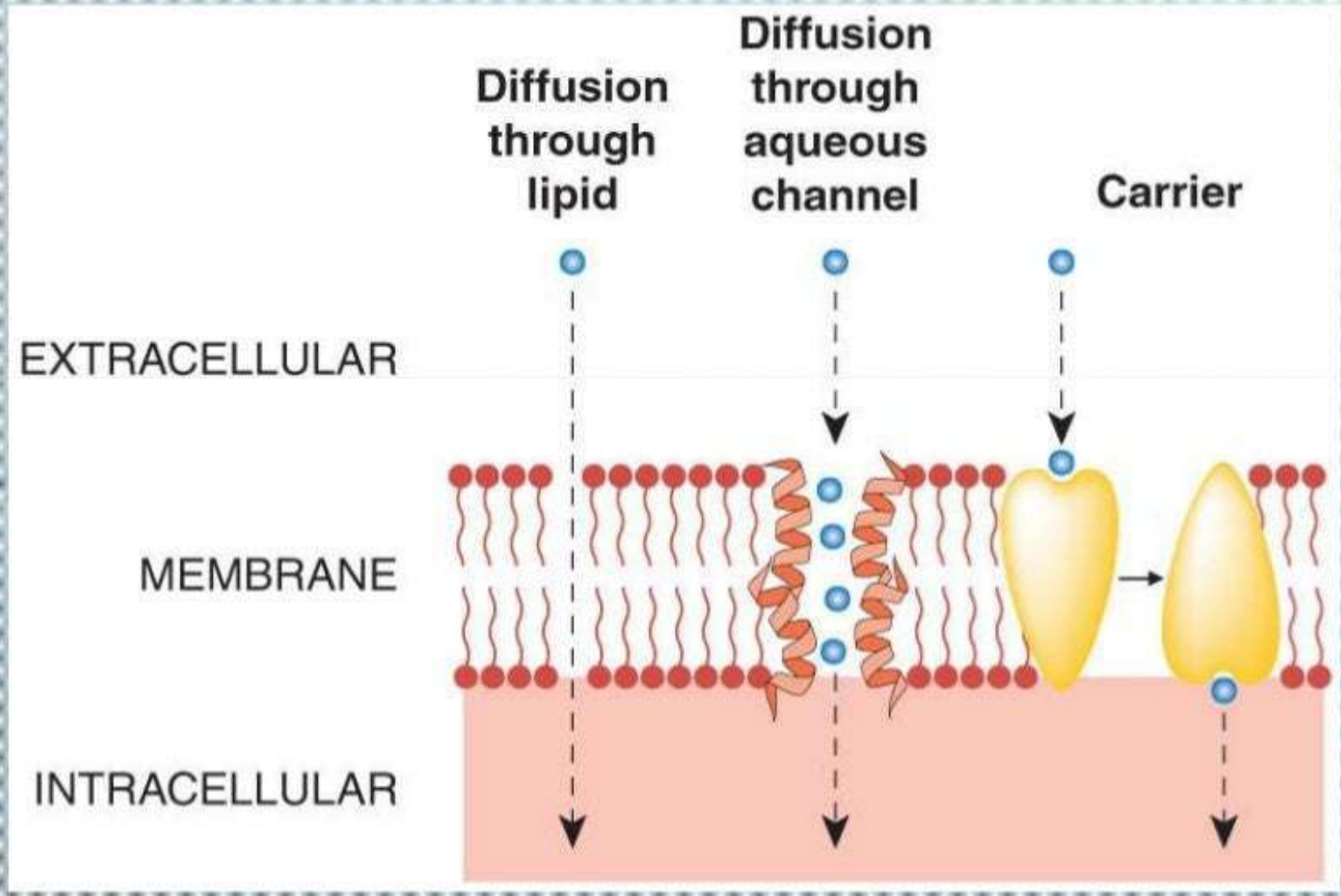
Transportation

Biological Membrane

- Bilayer of phospholipid and cholestrol molecule – 100 Å thick
- Extrinsic and intrinsic protein are embedded in the membrane
- Glycoprotein – on the surface
- This proteins varies from cell to cell.
- Paracellular spaces and channels are also present



Transportation

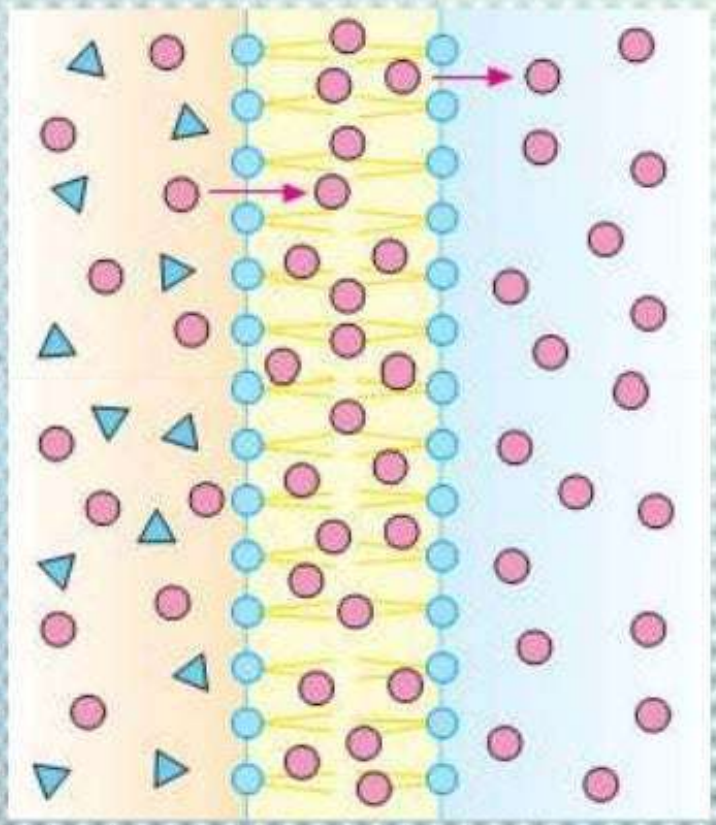


Transportation

- Drugs are transported through
  - Passive diffusion
  - Filteration
  - Specialized transport

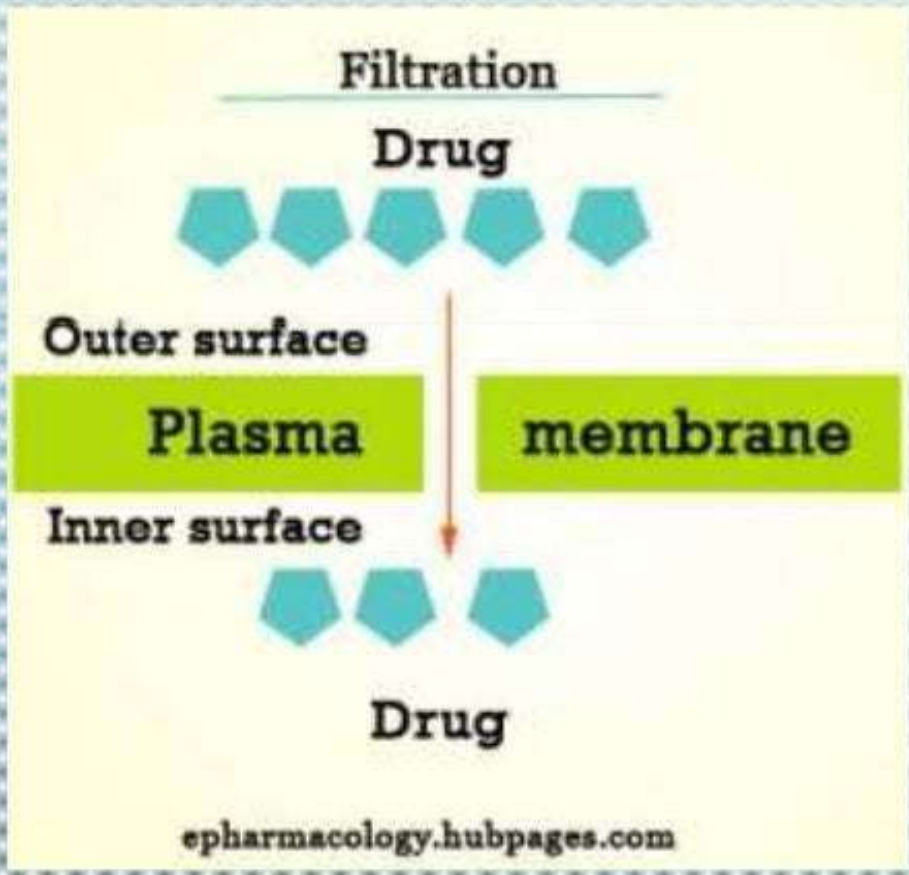
Transportation : Passive diffusion

- Drug diffuses from higher concentration to lower concentration across the membrane.
- Lipid soluble drugs – dissolving lipoidal matrix of membrane.
- Diffusion will depend on
  - Lipid solubility of drug
  - Difference in concentration
  - pH of tissue

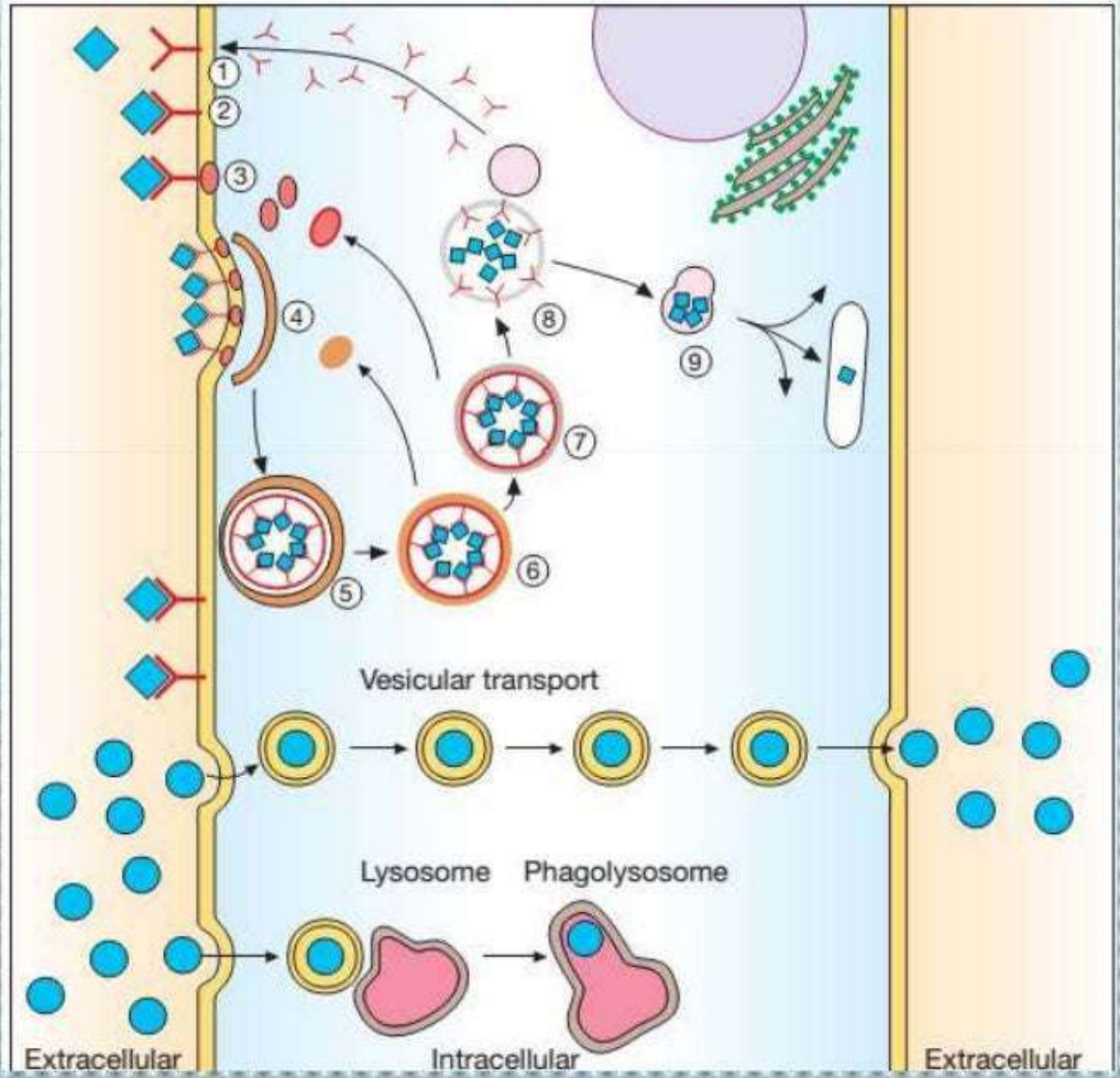


Transportation : Filtration

- Passage of drug across the aqueous pores in the membrane or through the para-cellular spaces.
- Lipid insoluble drugs crosses membrane
  - Size of pores and drug molecule

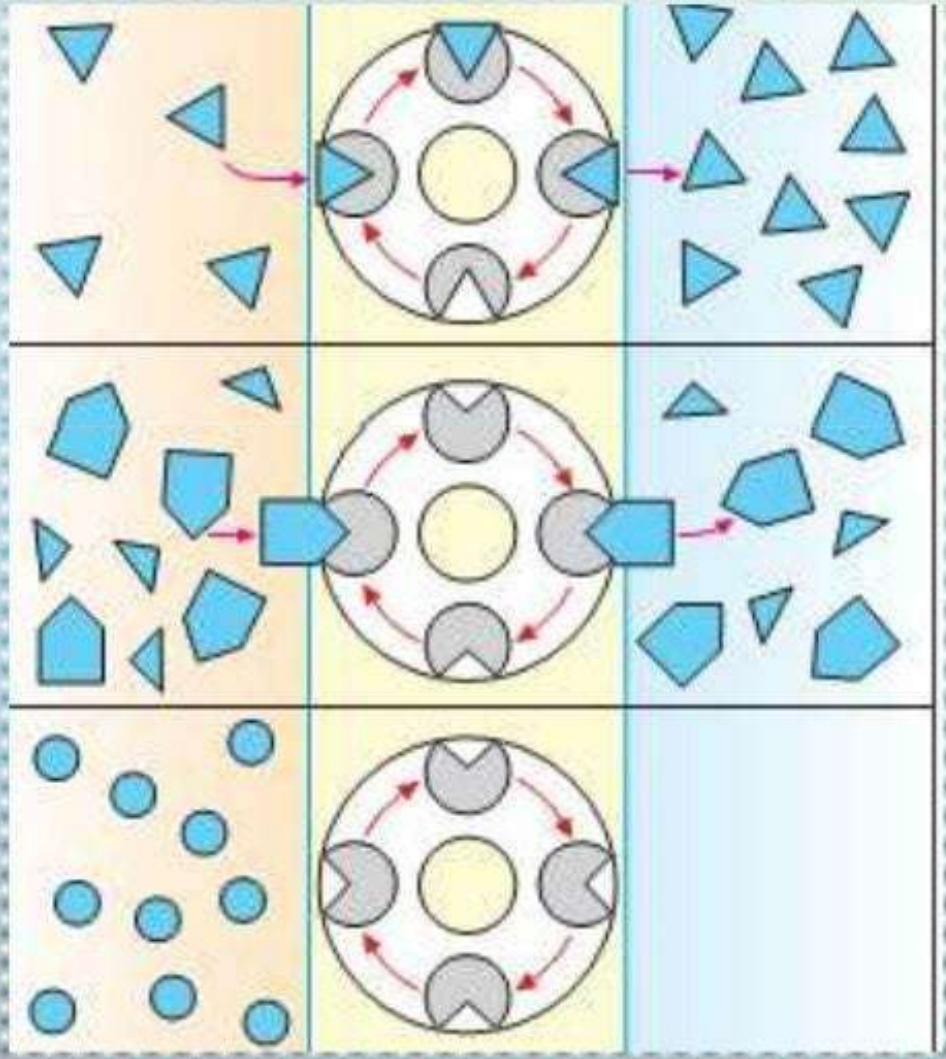


Specialized Transport



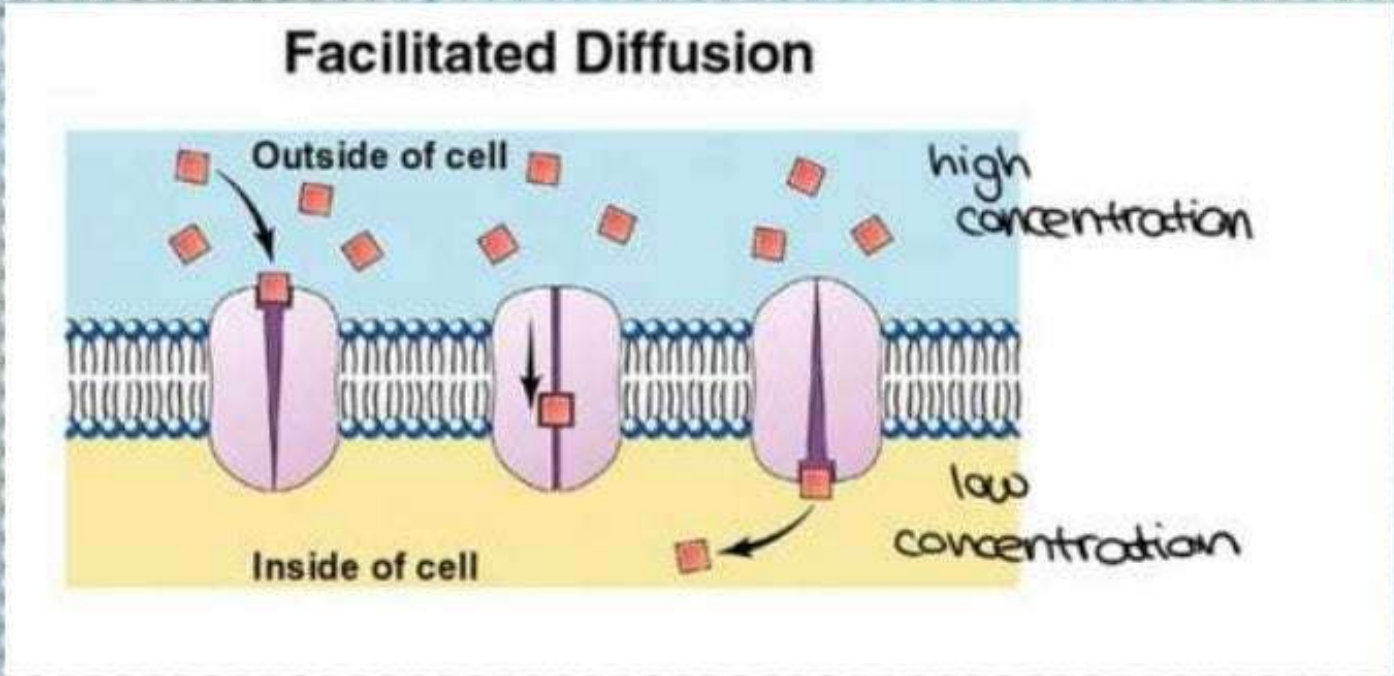
Specialized : Carrier Transport

- **Transmembrane protein** – carriers and transporters for physiologically important ions, nutrients, metabolites, transmitters
- Beside this they also translocate xenobiotics including drugs metabolites
- Specific for the substrate



Specialized : Carrier Transport

1. Transmembrane protein binds with their substrate transiently.
2. Conformational changes – carrying the substrate to the other side of membrane.
3. Dissociates
4. Return back to its original position

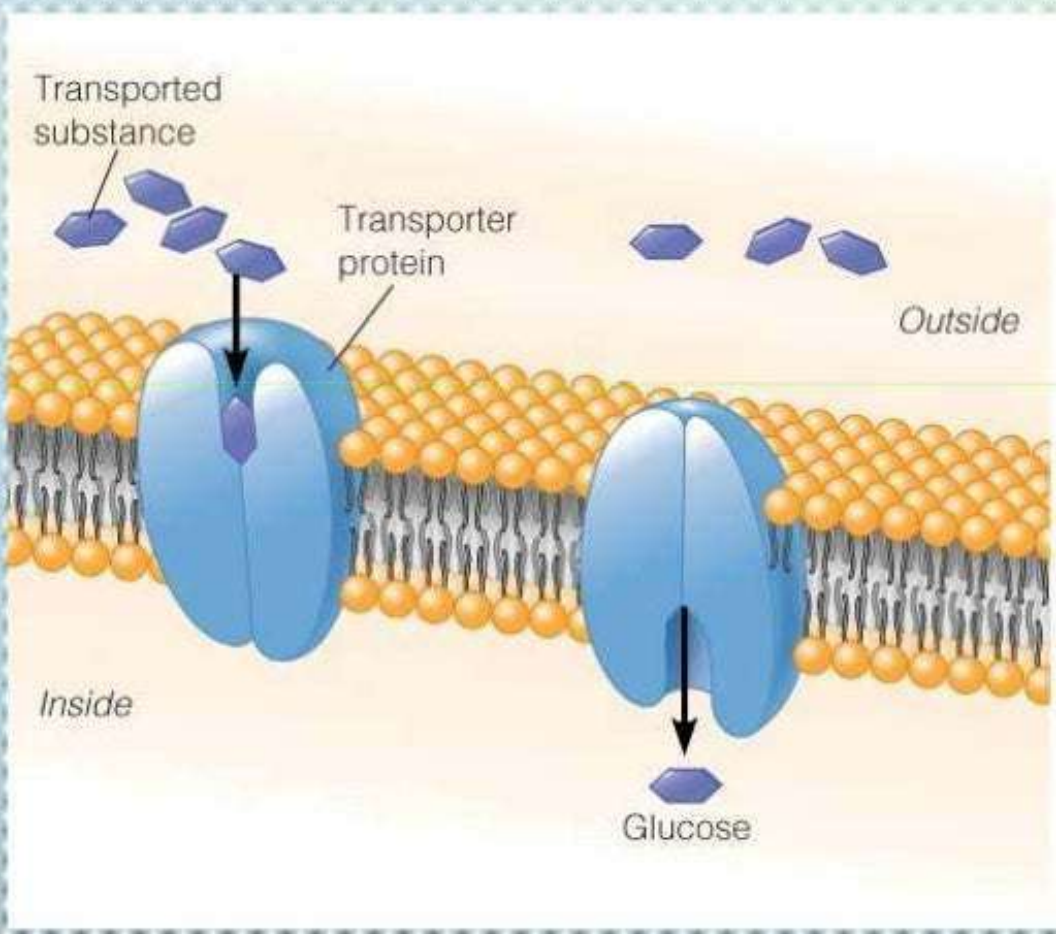


Specialized : Carrier Transport

- Depending on the requirements of energy
  - Facillated diffusion
  - Active transport
    - Primary active transport
    - Secondary active transport

Carrier Transport : Facilitated diffusion

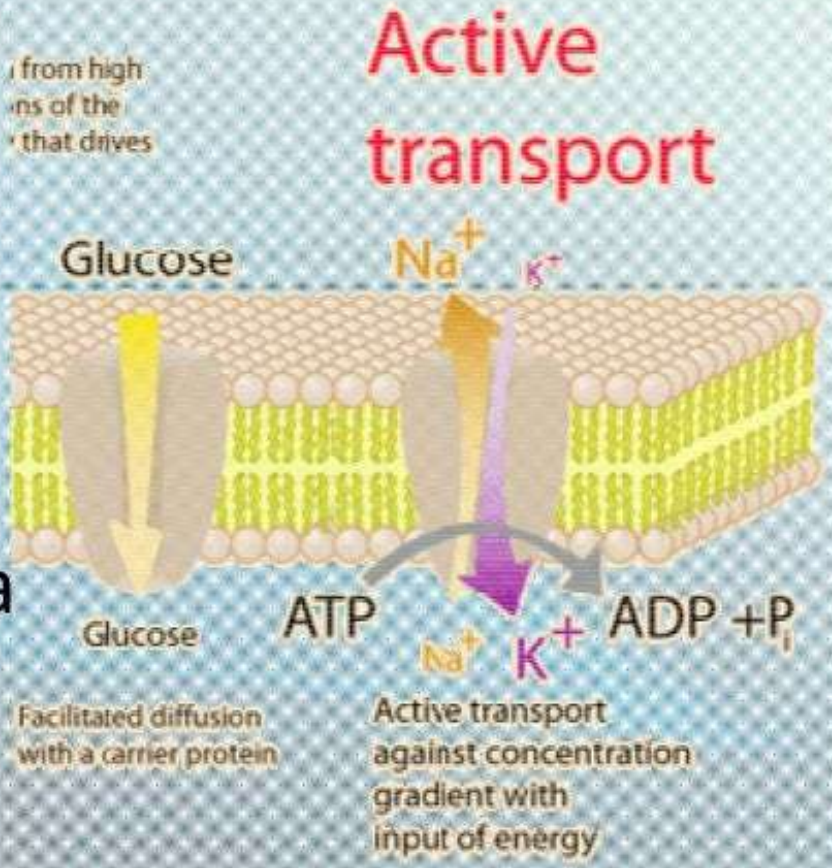
- Belongs to super family of solute carrier (SLC) transporter
- Operates without need of energy – transport in the direction electrochemical gradeint
- Higher to lower concentration
- Ex: glucose in muscle and fat cells by GLUT 4



Carrier Transport : Active transport

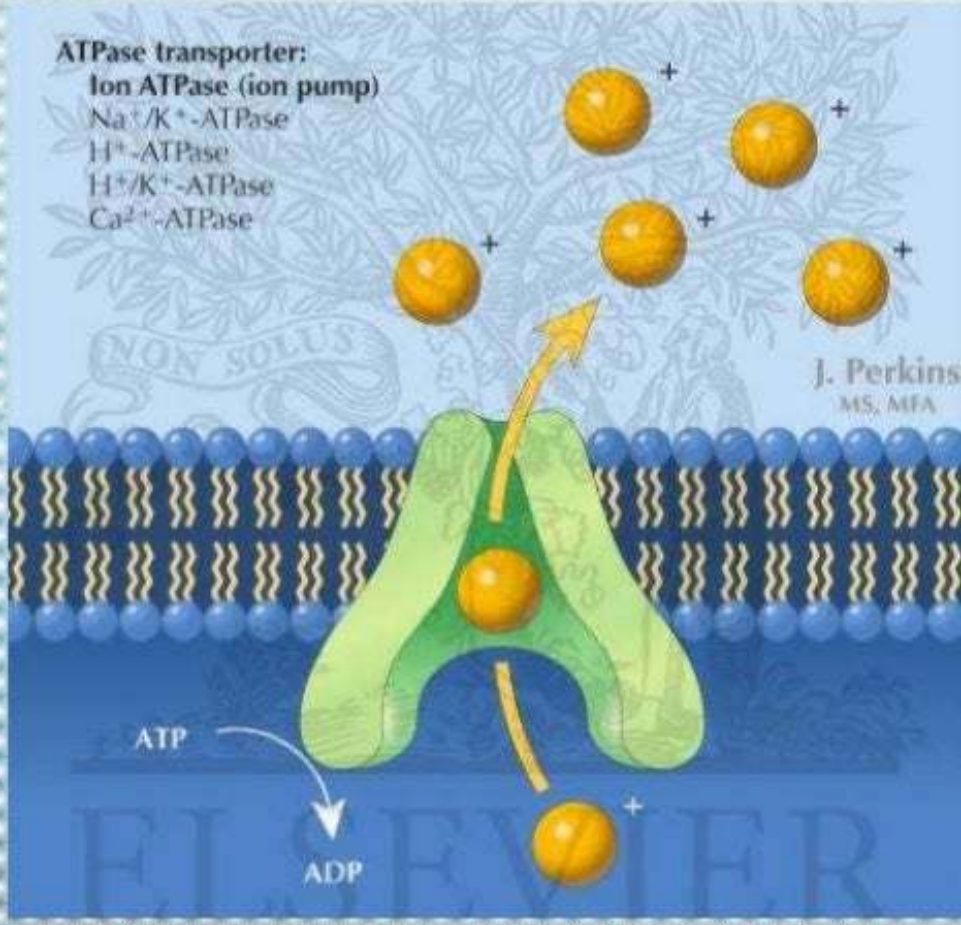
- It requires energy and acts against the electrochemical gradient
- Selective accumulation of solutes on 1 side
- Inhibited by metabolic poison

Ex: levodopa and methyl dopa absorbed from the gut - aromatic amino acid transport



Active transport : Primary

- Directly by the hydrolysis of ATP
- Transporter belongs to superfamily of ATP bindinig cassette (ABC)
- Only efflux of solute from cytoplasm i.e. to extracellular fluid or intracellular organelli
- Also known as uniport

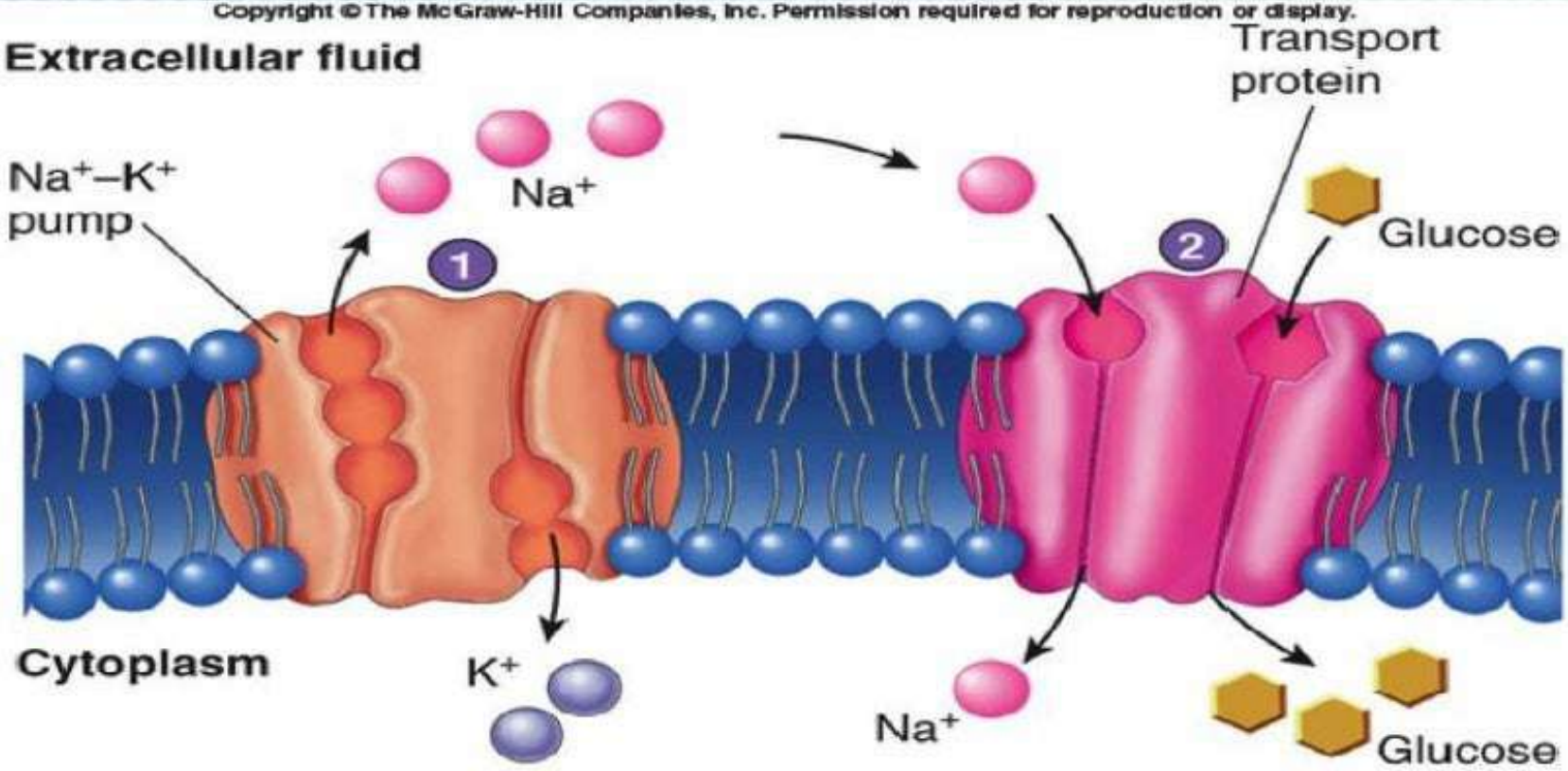


Active transport : Secondary

- Another type of SLC
- Energy to pump one solute is derived from downhill movement of another solute (mostly Na +)
- **Symport/cotransport** : concentration gradeint is such that both solute move in same direction
- **Antiport/exchange** transport : move in opposite direction
- Mediates uptake and efflux of drug and metabolite

Ex: Na + Cl – dependendent neurotransmittor

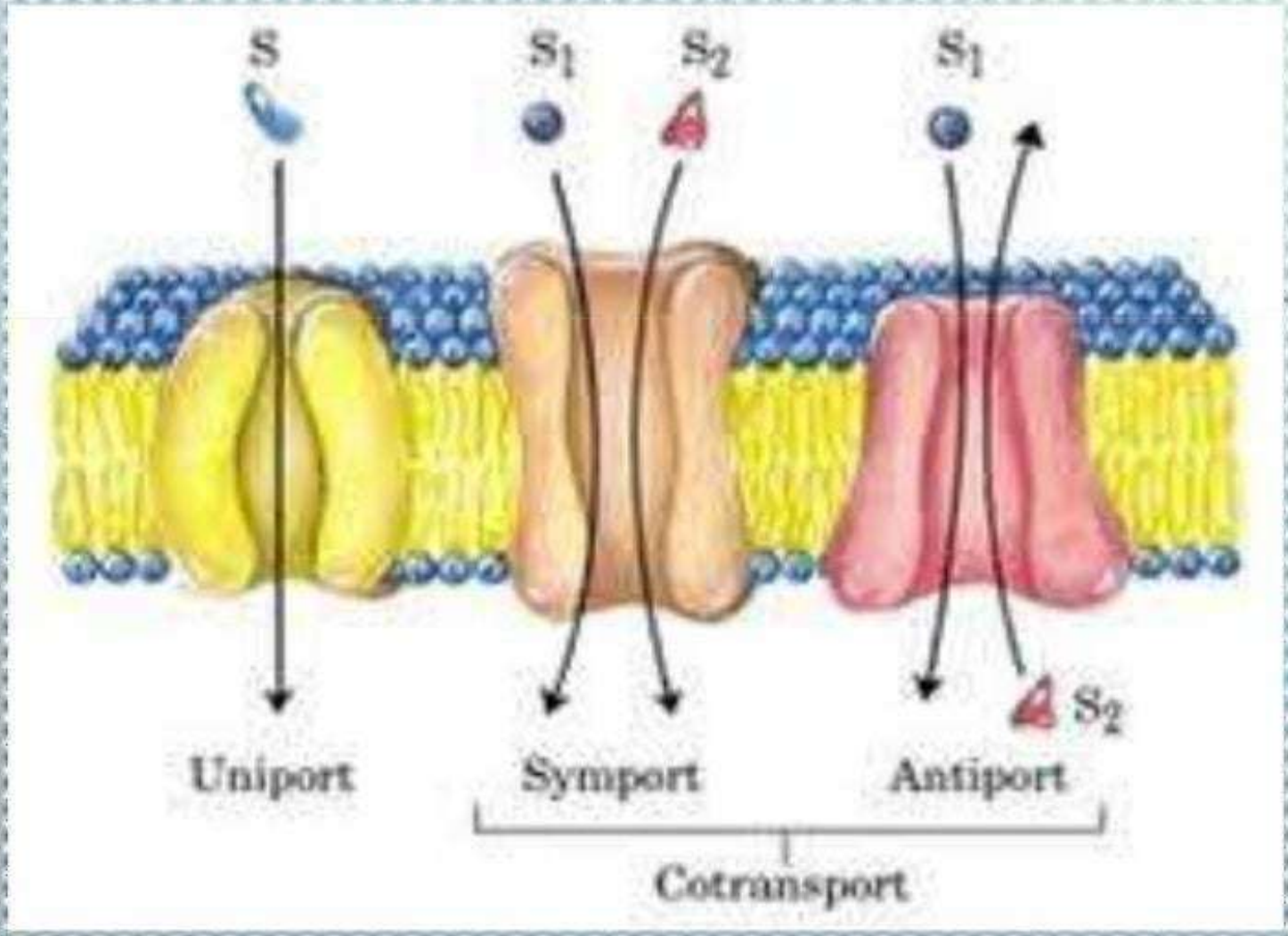
Active transport : Secondary



1. A Na^+–K^+ pump maintains a concentration of Na^+ that is higher outside the cell than inside.

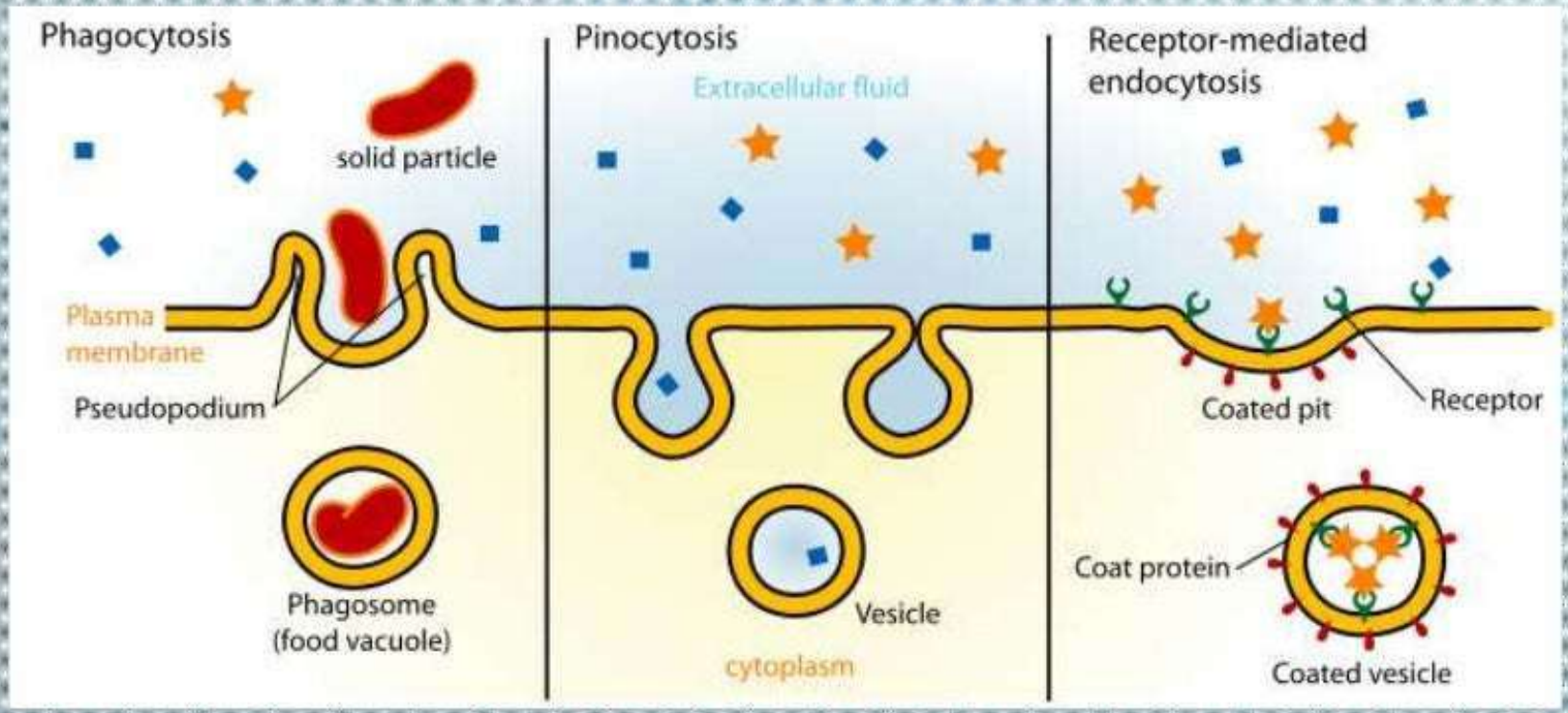
2. Sodium ions move back into the cell through a transport protein that also moves glucose. The concentration gradient for Na^+ provides energy required to move glucose against its concentration gradient.

Active transport



Specialized transport : Endocytosis

- Very little importance to the drug translocation
- Large protein molecules and other metabolic waste



Absorption

- Movement of drug from its site of administration into circulation
- Not only amount of absorption but also rate of absorption is important
- Except when given i.v., the drug has to cross biological membrane which is governed by following factor
  - Aqueous solublity
  - Concentration
  - Area of absorbing surface
  - Vascularity of absorbing surface
  - Route of administration

Bioavailability

- A concept for oral administration
- Useful to compare two different drugs or different dosage forms of same drug
- Rate and extent of absorption of a drug
- Fraction of administered drug that reaches systemic circulation in unchanged form
- Bioavailablity by i.v. is 100 % but by other routes it decreases to some extent
  - Incompletely absorbed
  - First pass metabolism
  - Sc/im – local binding

Bioavailability

- Bioavailability is not a characteristic solely of the drug preparation: variations in
  - enzyme activity of gut wall or liver,
  - in gastric pH or
  - intestinal motility all affect it.

Distribution

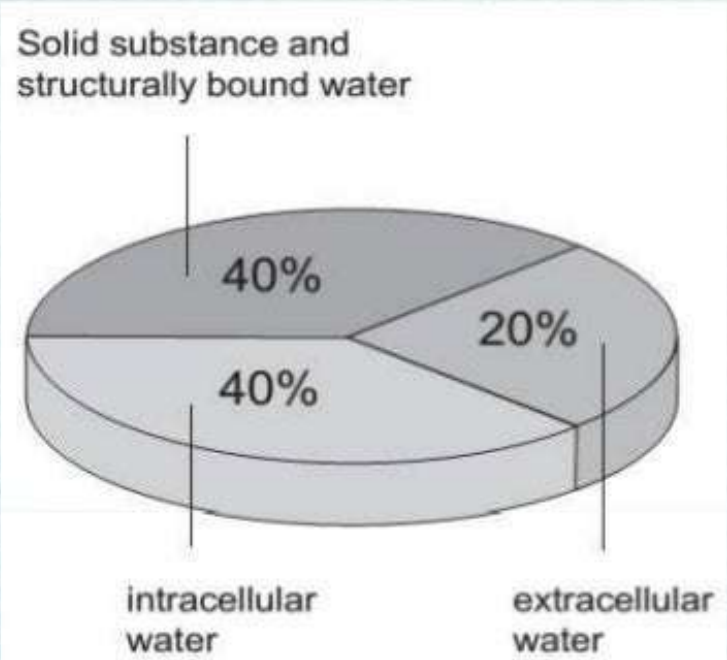
Distribution

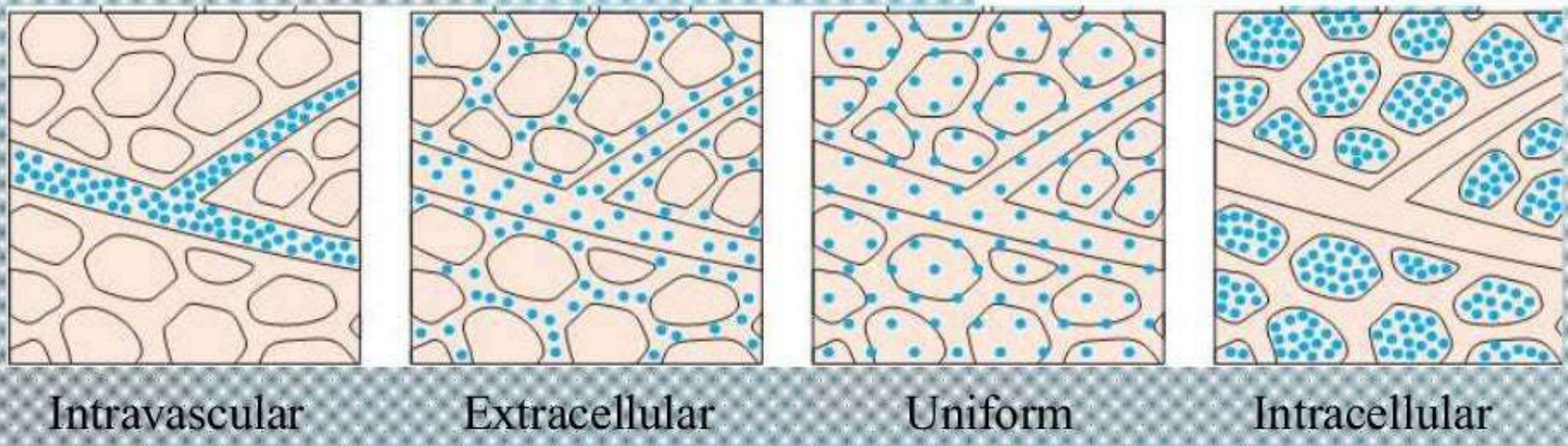
- Once the drug has gained access to blood it gets distributed to other tissues
- the extent of distribution of a drug depends on:
  - Lipid solublity
  - Ionization at physiological pH
  - Extent of binding to plasma
  - Tissue protein : Fat
  - Difference in regional blood flow
  - Disease like CHF, Uremia, cirrhosis

Apparent volume of Distribution

- Volume that accommodate all the drugs in body, if the concentration throughout was same as in plasma

  V = dose administered/plasma drug concentration

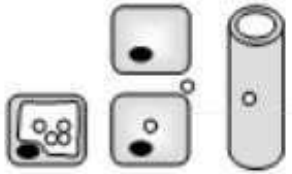




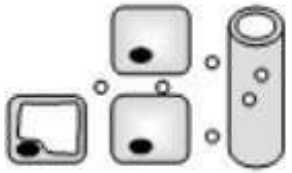
Apparent volume of Distribution

- Lipophilic drugs – sequestration.
  - Digoxin (6L/Kg), propranolol (4 L/Kg), Morphine (3.5 L/Kg)
  - Not easily removed by haemodialysis in case of toxicity
- Lipophobic drugs – extracellular
  - Streptomycin, gentamycin (0.25 L/Kg)
- Plasma protein bounded – intravascular
  - Diclofenac & warfarin (0.15 L/Kg

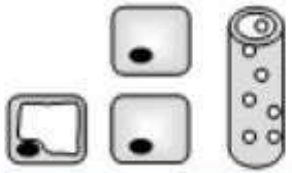
$$V_d = \frac{\text{Amount of drug in the body}}{\text{Drug plasma concentration}}$$



Lipophilic drugs: V_d > total available volume



Extracellularly confined drugs: V_d < total available volume



Intravascularly confined drugs: V_d << total available volume

Apparent volume of Distribution

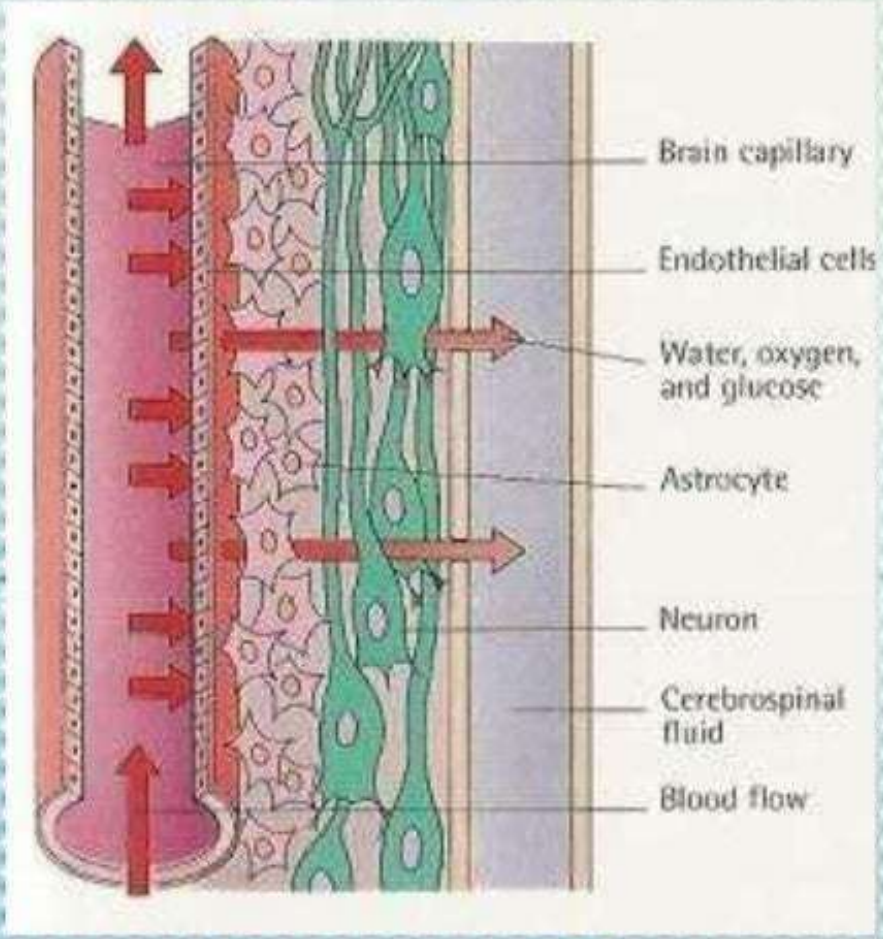
- Pathological states alters the V
  - Congestive heart failure
  - Uremia
  - Cirrhosis
- Multiple compartment models of drugs have been worked out but single compartment model is highly accepted ????

Redistribution

- Highly lipid soluble drugs gets distributed to
  - High perfusion low capacity , i.e. heart, brain, kidney
  - Low perfusion high capacity – muscle fat
- When plasma concentration of drug falls, drug is withdrawn from this site prolonging the action of drug
- Greater the lipid solubility faster is its redistribution. Ex : thiopentene sodium
- Short acting drugs can be prolonged by administering slowing and continuously – low perfusion high capacity tissues

Blood Brain barrier

- Capillary endothelial cells in brain have tight junction and lack large intercellular pores and above that there is layer of neural tissue – *Blood brain barrier.*
- In Choroid plexus, capillaries are lined by choroidal epithelium with tight junction – *blood-CSF barrier*



Blood Brain barrier

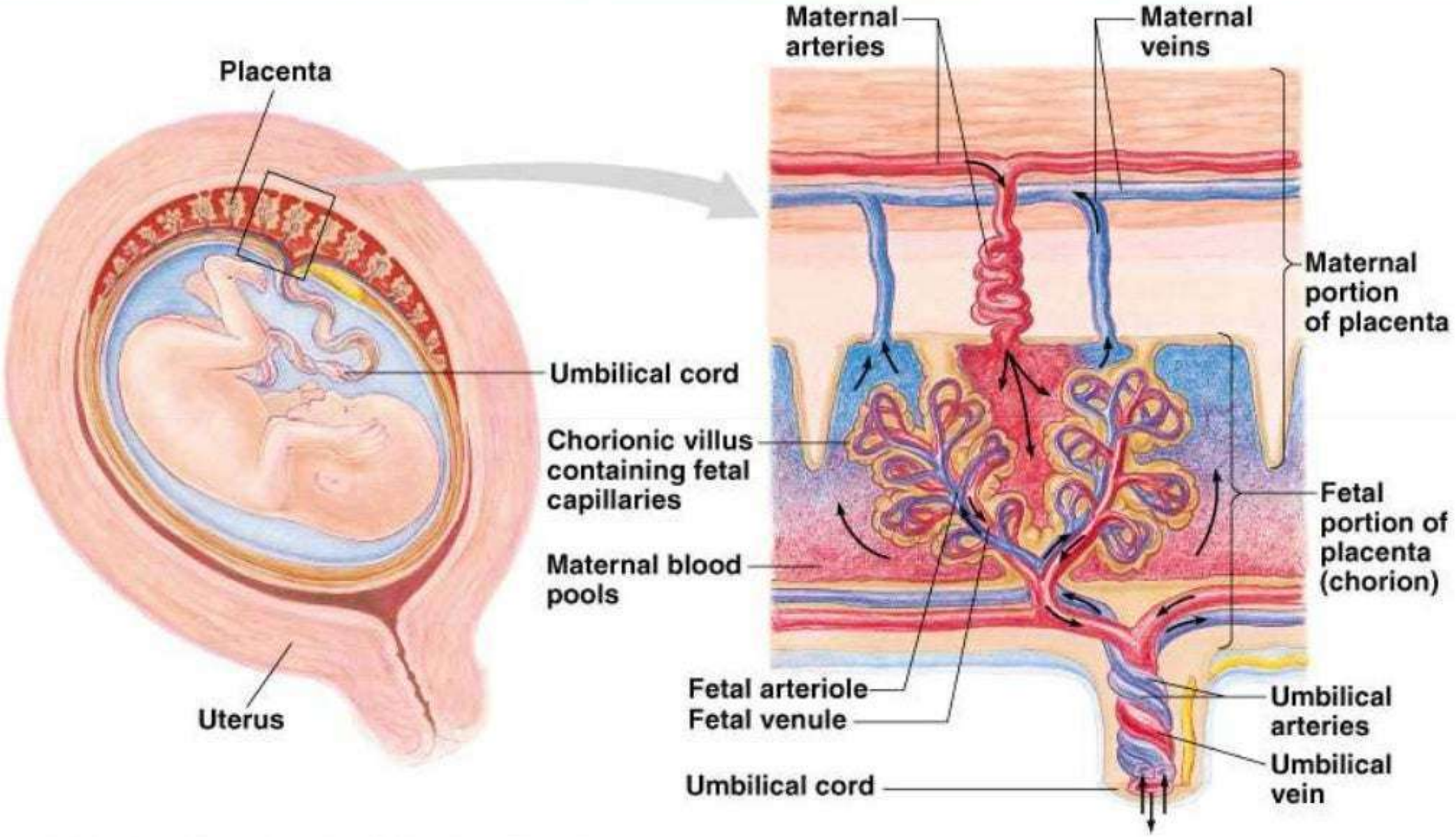
- Both this membrane allows lipoidal drug and limit the entry of non-lipoidal drug. Ex: streptomycin, neostigmine.
- Beside this,
  - P-gp and anion transporter (OATP) extrude drugs from brain.
  - Enzymatic BBB : monoamine oxidase (MAO), cholinesterase and some other enzymes – inhibit catecholamines, 5-HT, acetylcholine
- Ex: Dopamine doesn't enter but its percursor levodopa does.

Blood Brain barrier

- BBB is deficient
  - Chemoreceptor Trigger Zone (CTZ) in medulla oblongota – action of emetic drugs
  - Peri-ventricular site – anterior hypothalmus.
- Exit of drug from brain is not dependent on lipid solubility
  - Bulk flow of CSF – arachnoid villi
  - Non specific organic anion and cation transport

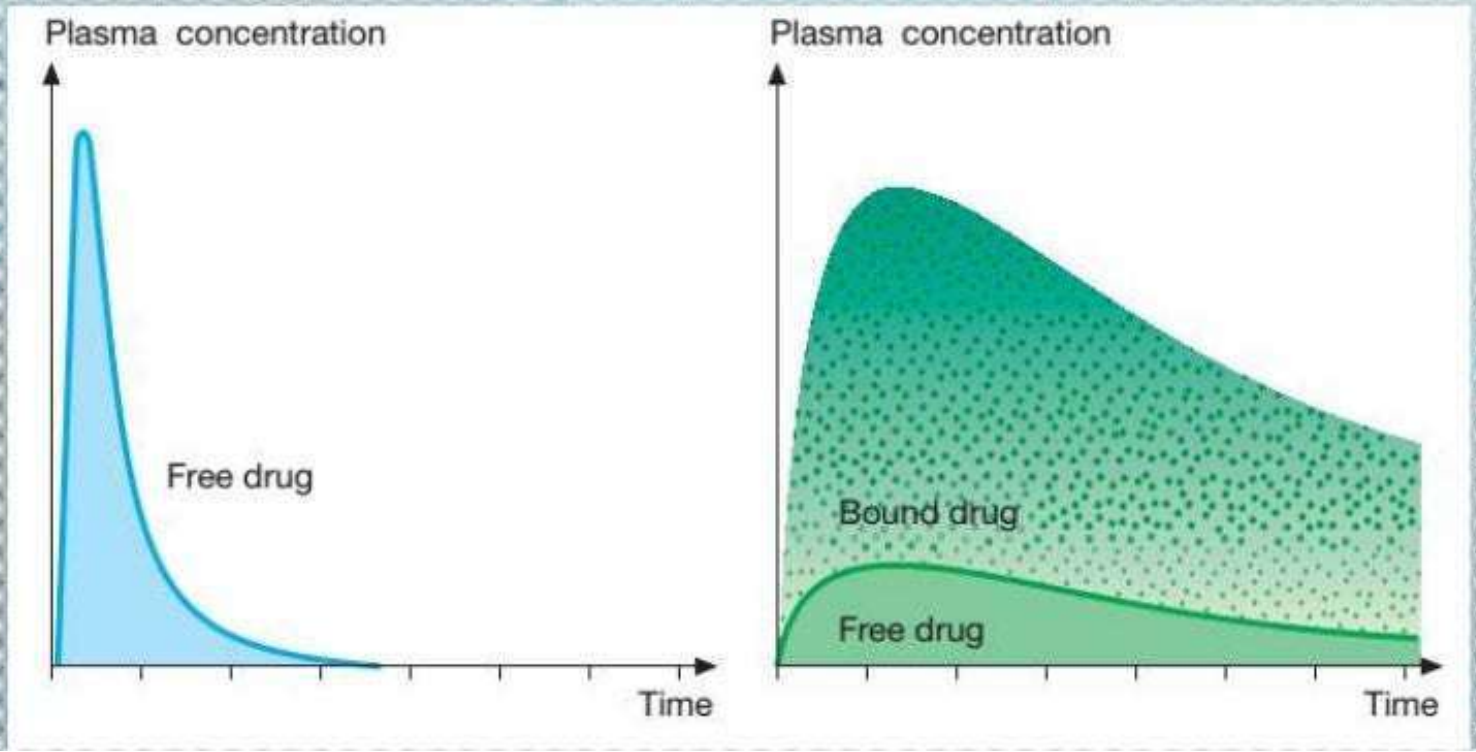
Placental Barrier

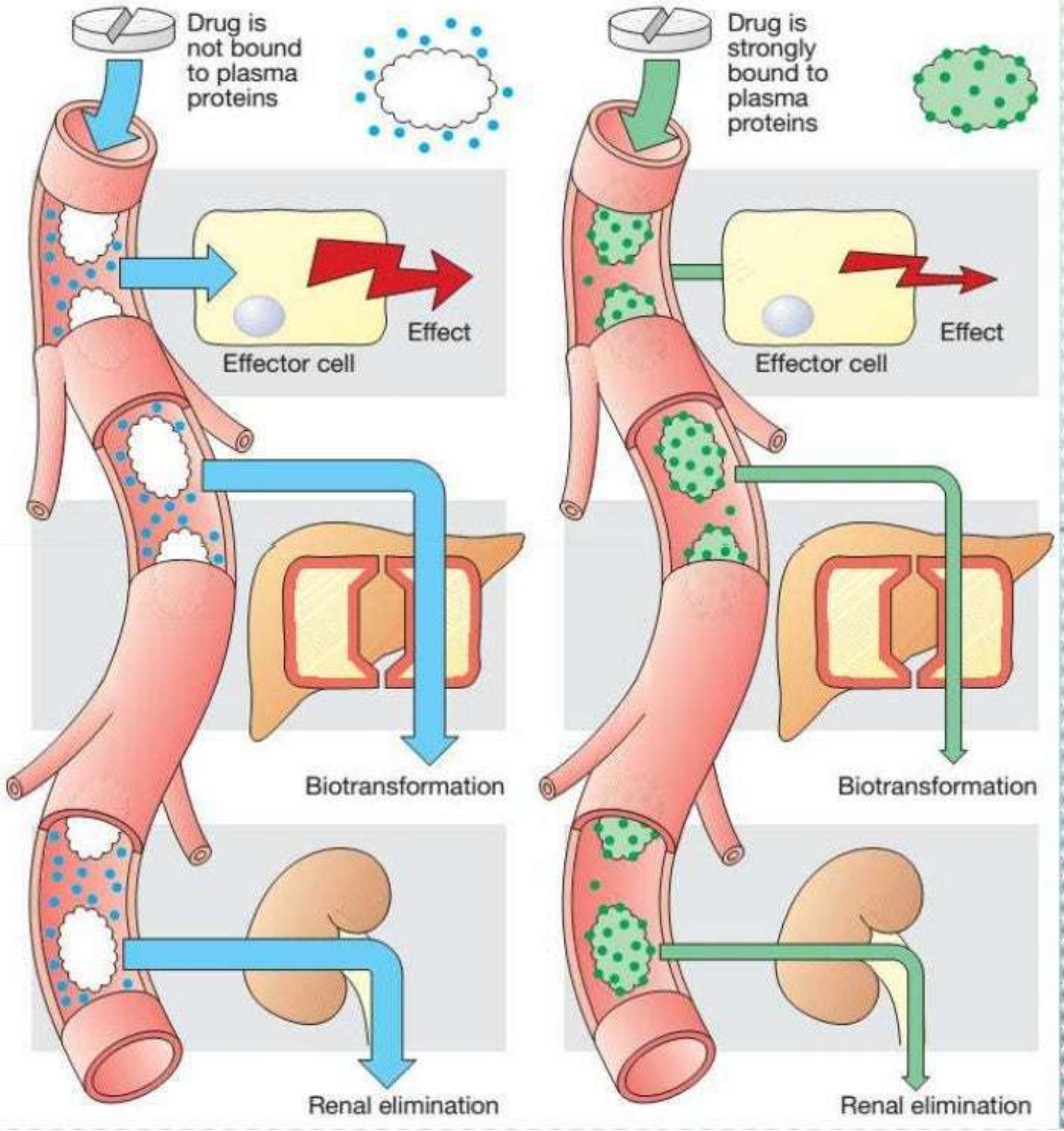
- Placental membrane is lipoidal and allows free passage of lipophillic drugs, while restricting lypophobic drugs.
- But higher concentration of lypophobic drugs in maternal circulation – gain access to foetus.
- Beside this
  - Placental efflux – P-gp
  - Influx transporter

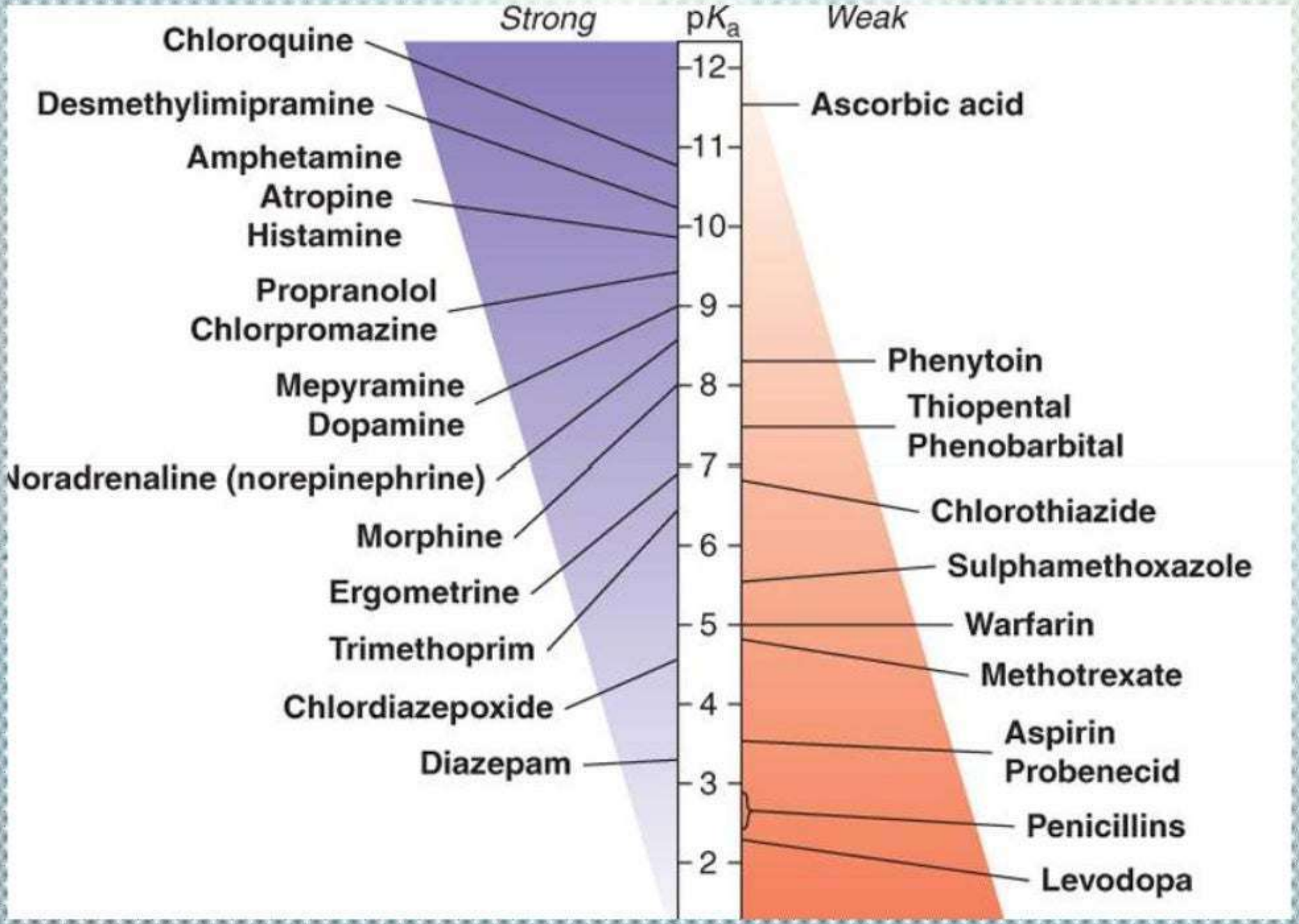


Plasma Protein Binding

- Physiochemical affinity for plasma proteins
  - Acidic drugs – albumin
  - Basic drugs – α1 acid glycoprotein
- Extent of binding depends on individual compound – no generalization for pharmacological class can be made.




Drug is not bound to plasma proteins
Effector cell
Effect
Biotransformation
Renal elimination
Drug is strongly bound to plasma proteins
Effector cell
Effect
Biotransformation
Renal elimination


Strong
pKa
Weak
Chloroquine
Desmethylimipramine
Amphetamine
Atropine
Histamine
Propranolol
Chlorpromazine
Mepyramine
Dopamine
Noradrenaline (norepinephrine)
Morphine
Ergometrine
Trimethoprim
Chlordiazepoxide
Diazepam
12
11
10
9
8
7
6
5
4
3
2
Ascorbic acid
Phenytoin
Thiopental
Phenobarbital
Chlorothiazide
Sulphamethoxazole
Warfarin
Methotrexate
Aspirin
Probenecid
Penicillins
Levodopa

Clinical Significance of PPB

- Highly PPB drugs – intravascular compartment except large paracellular spaces (capillaries) smaller volume of distribution
- Temporary storage of drug – bound protein is not available for action
- High degree of PPB – long acting – bound fraction is not available for metabolism, unless it is exclusively extracted by liver or kidney,

Clinical Significance of PPB

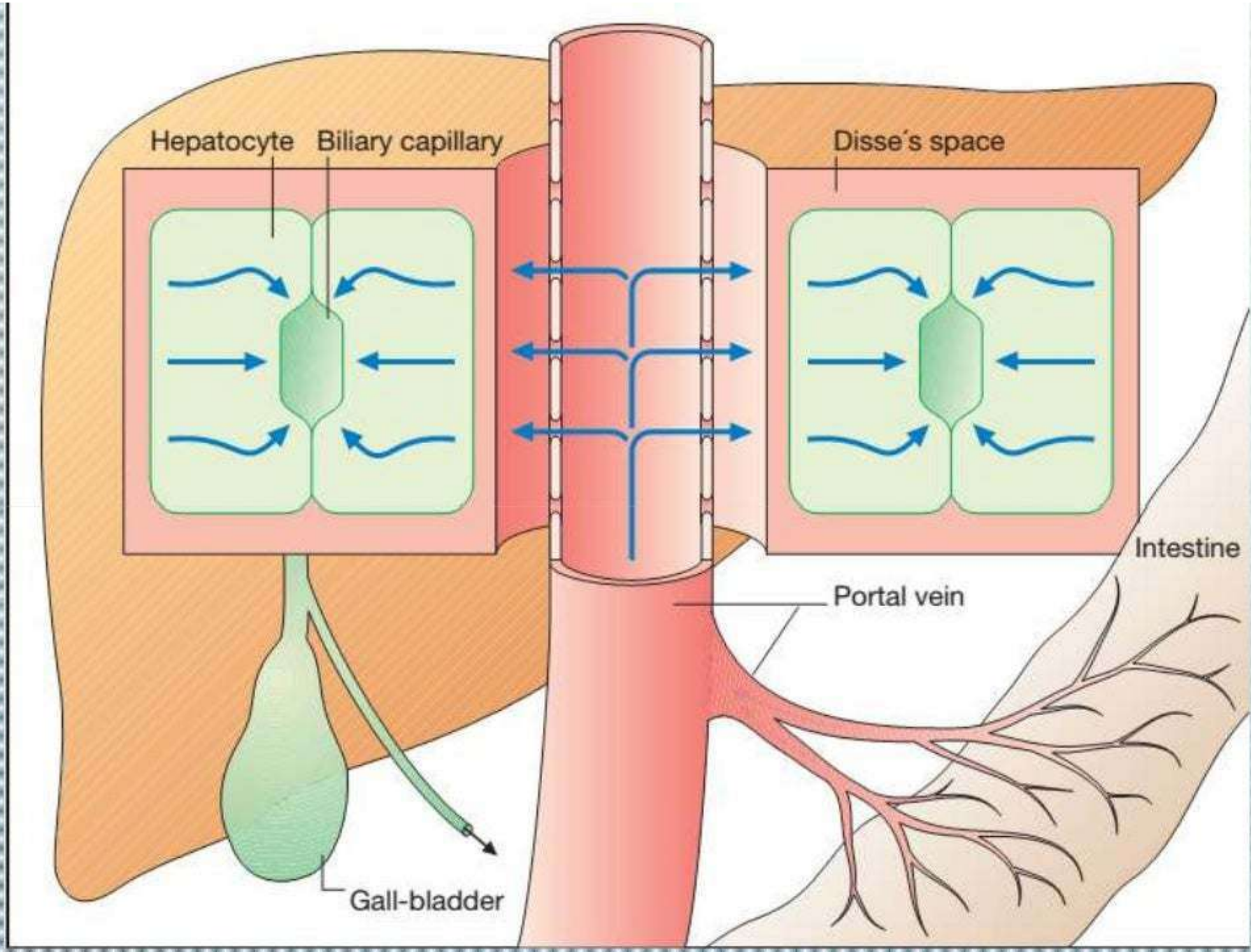
- One drug can bind to many sites of the protein or two or more drug can bind at same site
  - Displacement interaction
    - Salicylate – sulfonylureas
    - Indomethacin, phenytoin – warfarin
    - Sulfonamides, vit K – bilirubin (kernicterus in neonates)
    - Salicylates displaces methotrexate
- Hypoalbuminemia – binding is reduced, thus high concentration of free drug may be attained

Metabolism

Metabolism

Also known as biotransformation

- Chemical alteration in the body
- Causes loss of biological activity and thereby excretion via renal route – increases hydrophilicity
- Primary site of drug metabolism – liver
  - Kidney, intestine, lungs and plasma.


Hepatocyte
Biliary capillary
Disse´s space
Intestine
Portal vein
Gall-bladder

Biotransformation

- **Activation –** few drugs are administered in inactive form (PRODRUG) and needs to be activated to form active metabolite
  - Stablity
  - Good bioavailability
  - Less side effect or toxicity
  - Desirable pharmacokinetic properties

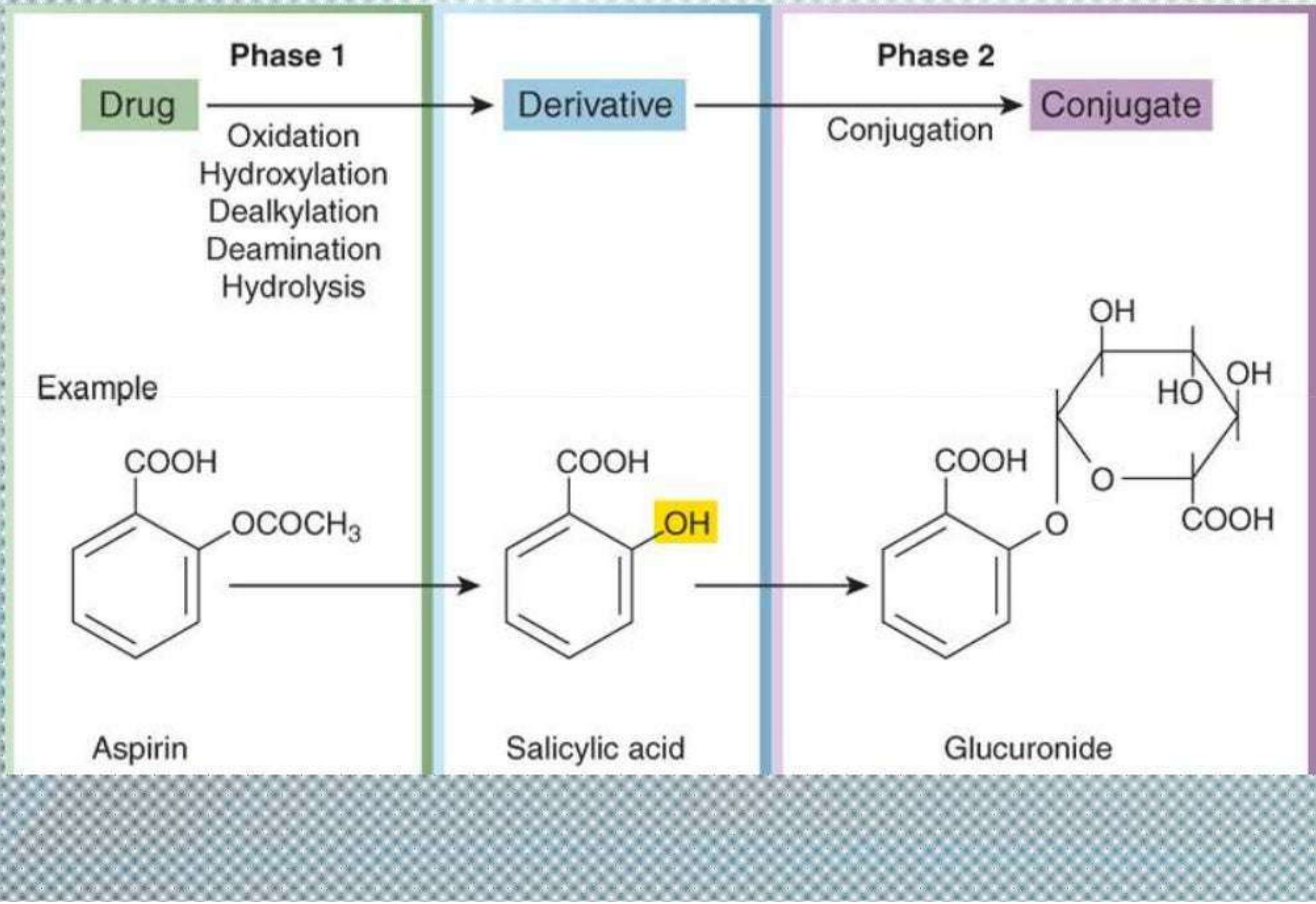
  Ex: Morphine, cefotaxime, codeine, amitriptyline, digitoxin, diazepam, losartan
- **Inactivation –** active metabolite and most drugs are inactivated. Ex: Ibuprofen, paracetamol, lidocaine, chloramphenicol, propranolol.

Biotransformation

- Phase I (Non-synthetic/functionalization/ catabolic)
  - Functional group is generated - more chemically reactive
  - oxidation, reduction or hydrolysis
- Phase II (Synthetic/Conjugation/Anabolic)
  - results in inactive products (Exception : active sulfate metabolite of **minoxidil**)

Both phases decrease lipid solubility, thus increasing renal elimination.

Mostly occurs in liver, although some drugs are metabolised in plasma (e.g. hydrolysis of **suxamethonium** by plasma cholinesterase), lung (e.g. various prostanoids) or gut (e.g. **tyramine**, **salbutamol)**


Phase 1
Drug
Oxidation
Hydroxylation
Dealkylation
Deamination
Hydrolysis
Derivative
Phase 2
Conjugation
Conjugate
Example
COOH
OCOCH3
COOH
OH
OH
HO
OH
O
COOH
O
COOH
Aspirin
Salicylic acid
Glucuronide

Phase I : Oxidation

- Addition of oxygen/negatively charged radical or removal of hydrogen/positively charged radical.
- Insertion of O - short lived highly reactive quinone/epoxide/superoxide
- Most important metabolizing drug reaction and various oxidation reactions are
  - Hydroxylation,
  - oxygenation at C, N or S atoms
  - N/O dealkylation
  - Oxidative deamination

Phase I

- Cylcization
  - Formation of ring from straight carbon chain
  - Ex: Proguanil
- Decylization
  - Opening of the ring of the cyclic molecule
  - Ex: Barbiturates & Phenytoin

Phase I : Oxidation

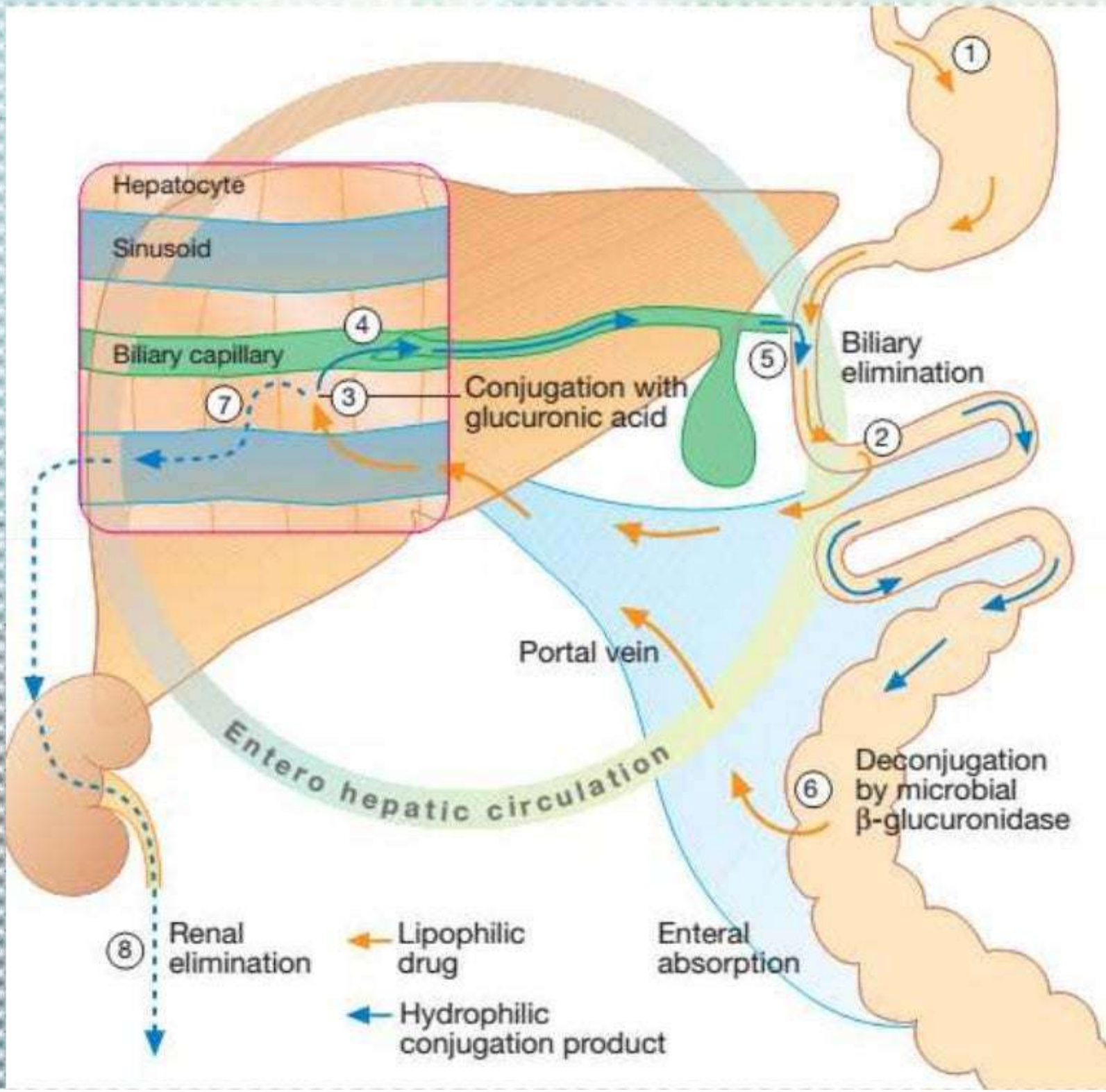
Oxidizing Centre	Enzyme	Site	Example of Drug
Carbon atom	Monoxygenase - CYP-450 haemoprotein, NADPH, CYP-450 reductase, molecular O_2	Liver	Barbiturates, phenothiazine, imipramine. Ibrufen, paracetamol, steroids, phenytoin, benzodiazepines, theophlline and many other drugs
N, P or S atom	Monoxygenase – flavinoids FMN	Liver	Cimetidine, Ranitidine, Clozapine
Carbon	Mitochondrial/cytoplasmic enzyme		Adrenaline, alcohol, mercatopuriine

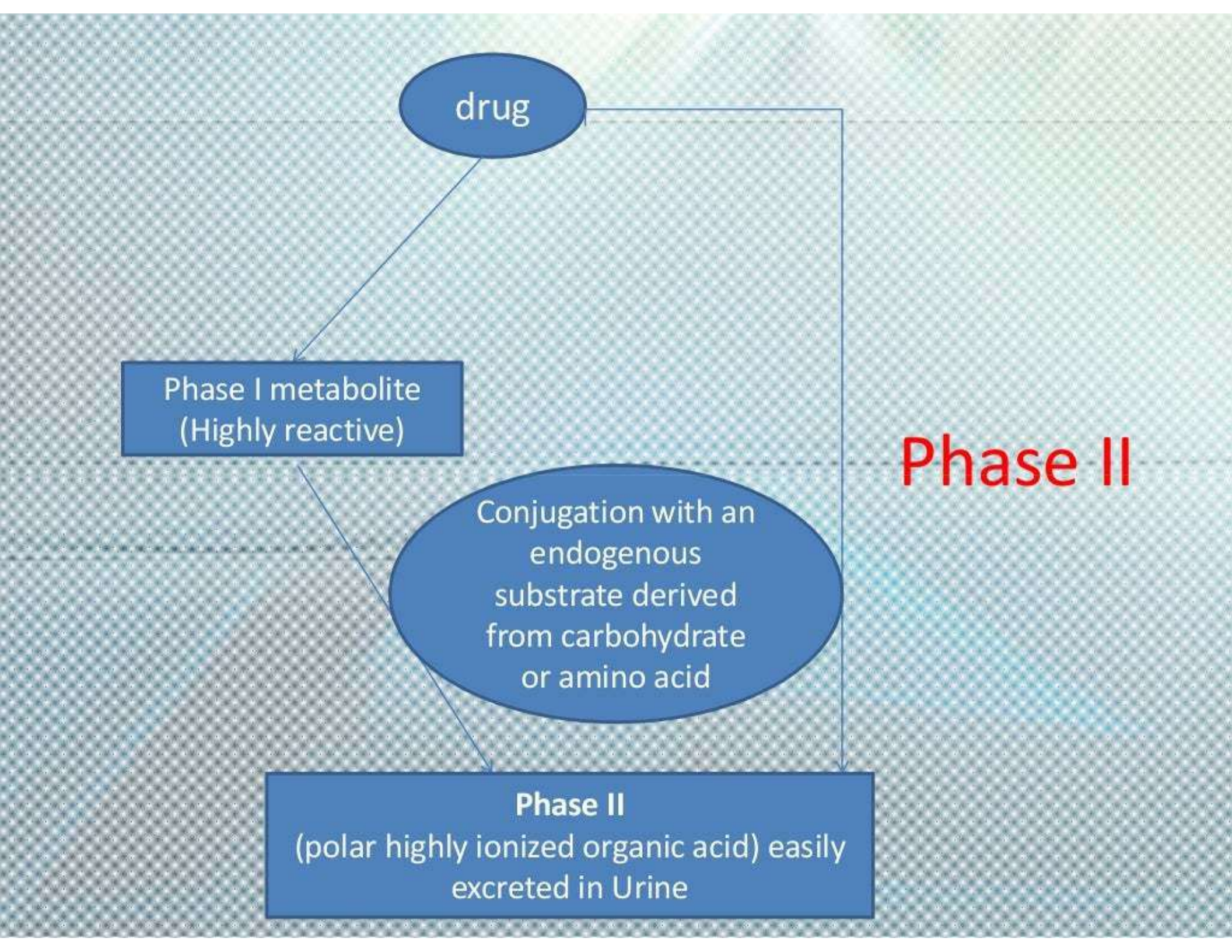
Phase I

- Reduction
  - Opposite of oxidation but involves CYP-450 in opposite direction
  - Ex: Chloralhydrate, chloramphenicol, halothane and warfarin
- Hydrolysis
  - Cleavage of drug molecule by uptake of water with help of enzyme like esterase, amidases, peptidases
  - Ex: Choline esters, procaine, lidocaine, procainamide, aspirin, carbamazepine-epoxide, pethidine, oxytocin

ENTEROHEPATIC CYCLE

Drug glucouronides – hydrolyzed by bacteria and again absorbed goes through same fate prolonging the action Ex: Phenolphthalein, oral contraceptives




drug
Phase I metabolite
(Highly reactive)
Conjugation with an
endogenous
substrate derived
from carbohydrate
or amino acid
Phase II
Phase II
(polar highly ionized organic acid) easily
excreted in Urine

Phase II : Glucouronide Conjugation

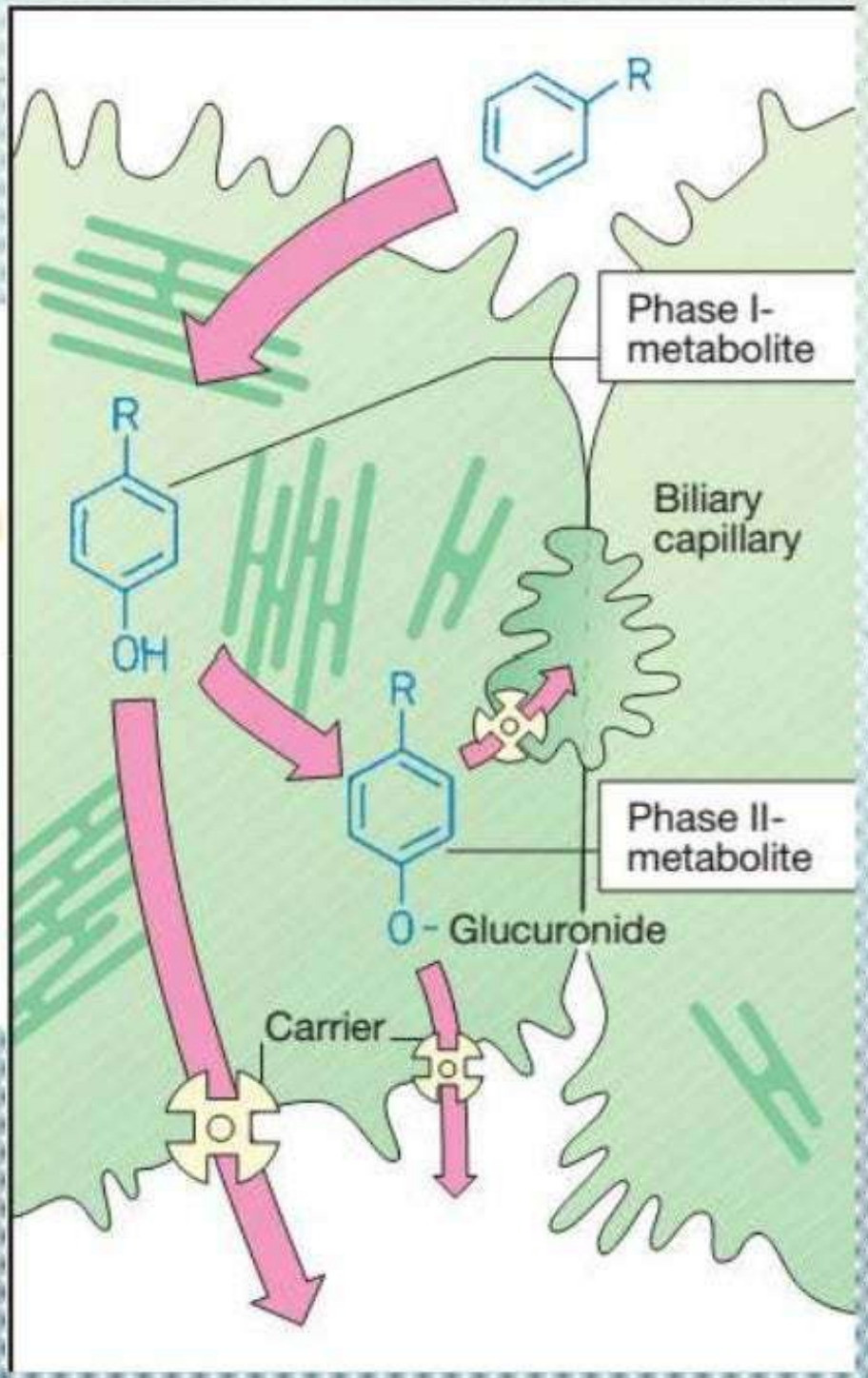
- Drug containing hydroxyl or carboxylic acid group gets conjugated with glucouronic acid (Derivative of glucose) by enzyme UDP-glucouronosyl transferase
- Ex: Chloramphenicol, aspirin, paracetamol, lorazopam, morphine, metrondiazole
- Other than drugs: bilirubin, steroidal hormone and thyroxine
- Increases the weight – favors bile excretion

UDP-α-glucuronide

Glucuronyl transfer — UDP-glucuronyl transferase

Drug — Glucuronide

Drug-β-glucuronide conjugate



Phase II

- Acetylation
  - Compounds having amino or hydrazine residues conjugates – acetyl CoA
  - Ex: Sulphonamides, isoniazides, PAS, hydralazine, clonazapam, procainamide
- Methylation
  - Amine and phenols gets methylated – methionine and cysteine
  - Ex – Adrenaline, histamine, nicotinic acid, methyldopa, captopril, mecarptopurine

Phase II

- Sulphate conjugation
  - Phenolic and steroid compounds – sulfated by sulfotransferase (SULTs)
  - Ex: Chloramphenicol, methyldopa, adrenal and sex steroids
- Glycine conjugation
  - Salicylates and other drugs having carboxylic acid – conjugated with glycine
  - Not a major pathway

Phase II

- Glutathione Conjugation
  - Inactivates highly reactive quinones or epoxides intermediates – paracetamol
  - When glutothione falls short (toxicity)– toxic adducts formed causing tissue damage
  - Minor pathway
- Ribonucleoside/nucleotide synthesis
  - Activation of purine and pyrimidine antimetabolites – cancer chemotheraphy

Metabolic Enzymes

- Most of drug gets metabolized by non specific enzyme – directed to types of molecules rather than specific drugs
- Few drugs metabolized by specific enzyme (Intermediarry metabolism)
  - Alcohol – dehydrogenase
  - Allopurinol – Xanthine oxidase
  - Succinylcholine and procaine – plasma cholinisterase
  - Adrenaline – monoamine oxidase MOA

Metabolic Enzymes

- Drug Metabolizing enzyme is divided in two types
  - Microsomal Enzyme
  - Non-microsomal enzyme
- Both of this is deficit in new born – susceptible to many drugs (chloramphenicol, opioids)
  - Develops in 1st month partially and completely in 3 month.
- Amount and kind – genetically controlled, altered by environmental factors
  - Drug response variation

Microsomal Enzyme

- Located in smooth ER primarily in liver, also in kidney, intestinal mucosa and lungs
- Catalyze most of oxidations, reductions, hydrolysis and glucouronide conjugation.
- Inducible by drugs, diet and other agencies
- Ex: Monooxygenases, cytochrome P 450, glucouronyl transferase

Non-microsomal Enzyme

- Present in cytoplasm and mitochondria of hepatic cells as well as other tissue including plasma
- Some oxidation and reduction, many hydrolytic reactions and all conjugating except glucouronidation
- Ex: Flavoprotein oxidases, esterases, amidases

Hoffman Elmination

- Inactivation of drug in body fluids by spontaneous molecular rearrangement without use of any enzyme

Inhibition of Drug Metabolism

- One drug can competitively inhibit the metabolism of another if it utilizes the same enzyme or co factors
- But its very rare as there 100 isoenzyme of CYP-450 alone.
- Quinidine is metabolized by CYP3A4 but inhibits CYP2D6
- Ex: Allopurinon, Erythromycin, Verapamil, Metronidazole, Diltiazem

Microsomal Enzyme Induction

- Many drugs, insecticides and carcinogens interacts with DNA and increases the synthesis of microsomal enzyme protein especially CYP-450 and glucouronyl transferase
- As a result metabolism of inducing drugs or other drugs increases.
  - Anticonvulsant (Phenobarbitone, rifampin, glucocorticoid) – CYP3A
  - Isoniazid and chronic alcohol consumption – CYP2E1

Consequence of Microsomal Enzyme Induction

- **Decreased intensity** and duration of drug – inactivated by metabolism (Oral Contraceptive)
- **Increase intensity** – activated by metabolism (Paracetamol toxicity)
- **Tolerance** – autoinduction (carbamazipine, rifampin)

Use of Enzyme Induction

- **Congenital non-haemolytic jaundice** (deficient glucouronidation of bilirubin) – phenobarbitone hastens clearance of jaundice
- **Cushing Syndrome** – phenytoin enhances degradation of adrenal steroids
- **Chronic Poisoning** – faster metabolism of poison
- Liver Disease

Excretion

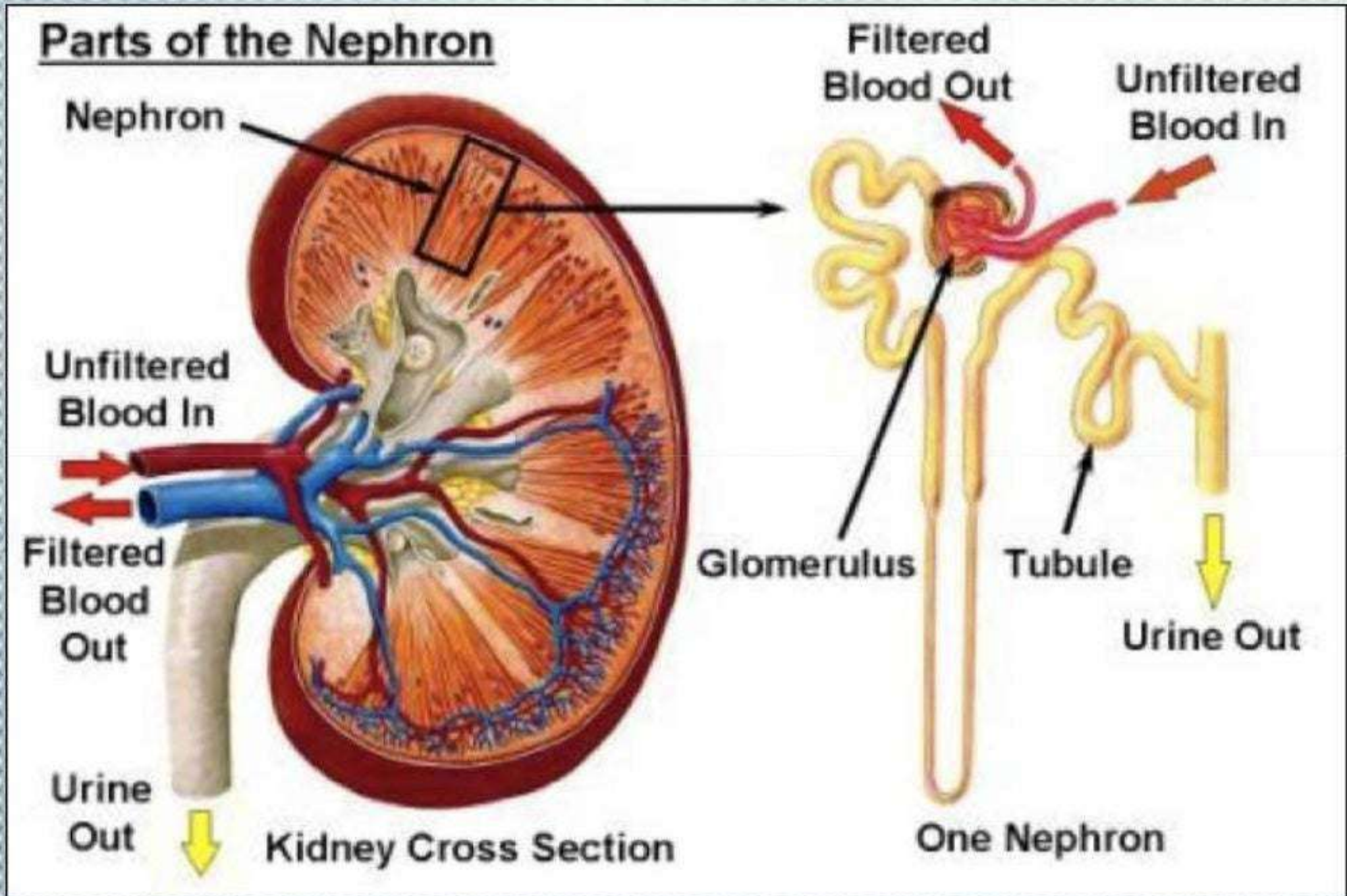
Excretion

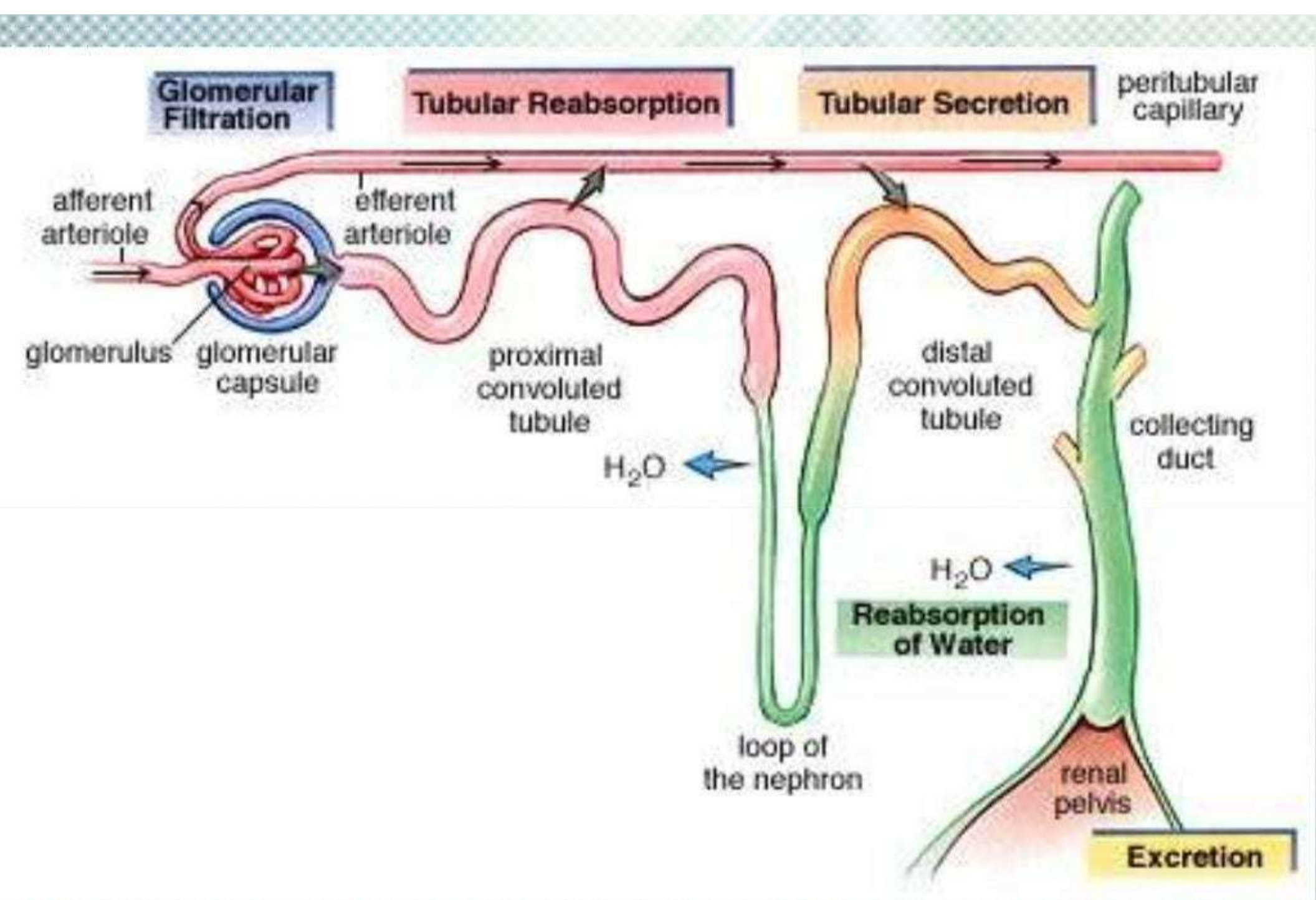
- Passage out of systemically absorbed drug,
- Its excreted in
  1. Urine
  2. Faeces
  3. Exhaled Air
  4. Saliva & sweat
  5. Milk

Excretion : Urine

- Most important channel for excretion of drugs.
- It eliminates water soluble substances.
- Amount of drug or its metabolites depends on
  - Glomerular filteration (GFR)
  - Tubular Resorption (TR)
  - Tubular Secretion (TS)

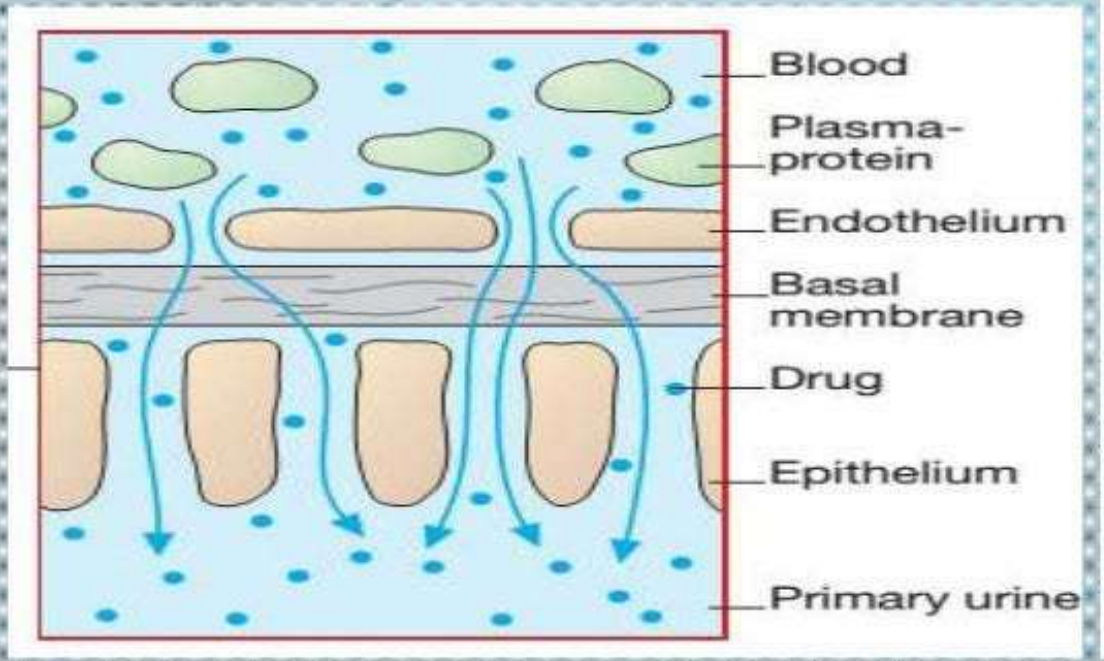
Net Renal Excretion = (GFR+TS) - TR

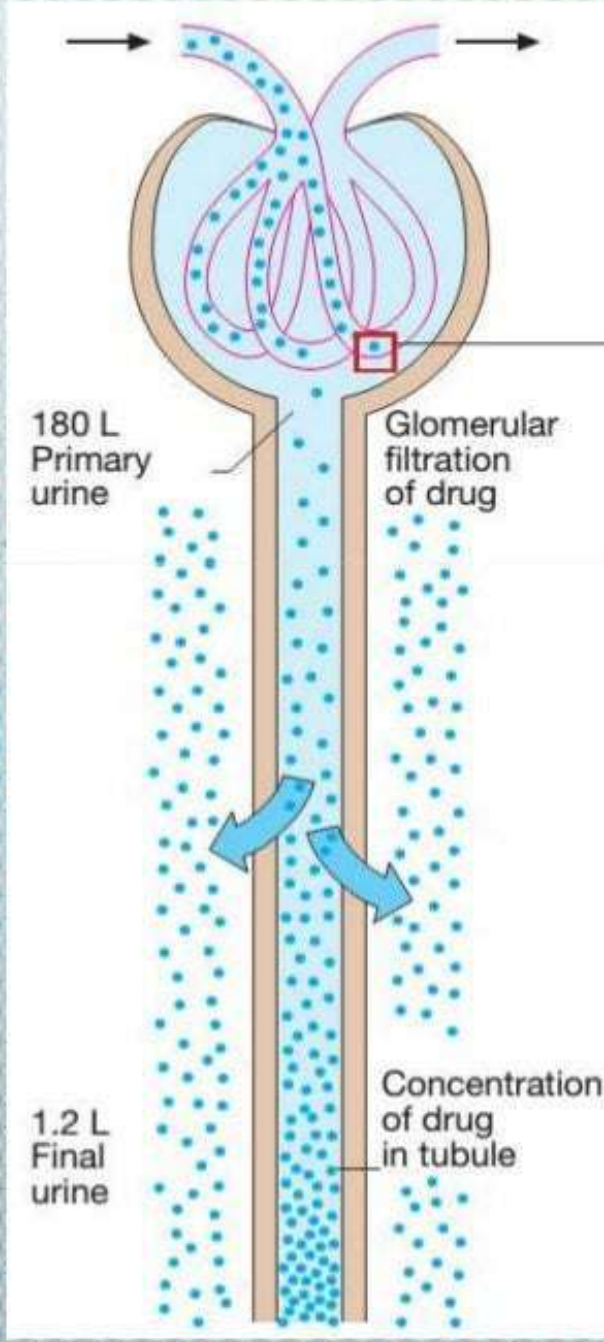

Parts of the Nephron
Nephron
Unfiltered Blood In
Filtered Blood Out
Urine Out
Kidney Cross Section
Filtered Blood Out
Unfiltered Blood In
Glomerulus
Tubule
Urine Out
One Nephron


Glomerular Filtration
Tubular Reabsorption
Tubular Secretion
peritubular capillary
afferent arteriole
efferent arteriole
glomerulus
glomerular capsule
proximal convoluted tubule
distal convoluted tubule
collecting duct
H_2O
H_2O
Reabsorption of Water
loop of the nephron
renal pelvis
Excretion

Glomerular Filtration

- Glomerular capillaries – larger pore than usual
- All non-protein bound drugs (lipophillic/lipophobic) gets filtered in glomerulus.



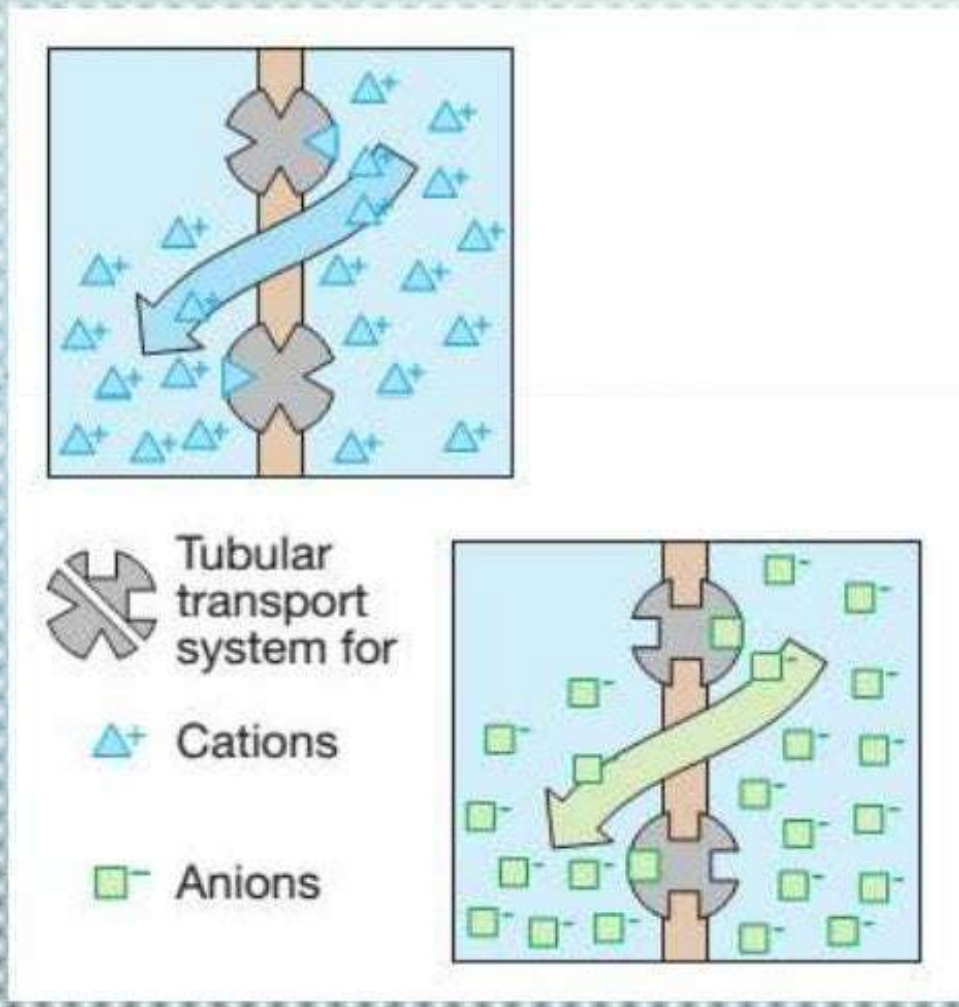


Glomerular Filtration

- It depends on renal blood flow and PPB.
- GFR = 120 ml/min normally
- Declines with age

Tubular Secretion

- Certain cations and anions
- Epithelium of the proximal tubules into the tubular fluid via special, energy consuming transport systems – non specific (OAT & OCT)
- limited capacity
- Competition inhibition can occur



Tubular Secretion

- If renal clearance is greater than 120 ml/min – TS is assumed to occur
- It reduces the amount of free form of drug
- PPB drugs gets dissociated to get eliminated via this route
- Organic Acid Transporter (OAT) : penicillin, probencid, uric acid, salicylates, indomethacin, methotrexate, glucouronides etc
- Organic base transporter (OCT) : thiazides, amiloride, triamterene, furosemide, quinine, choline, cimetidine

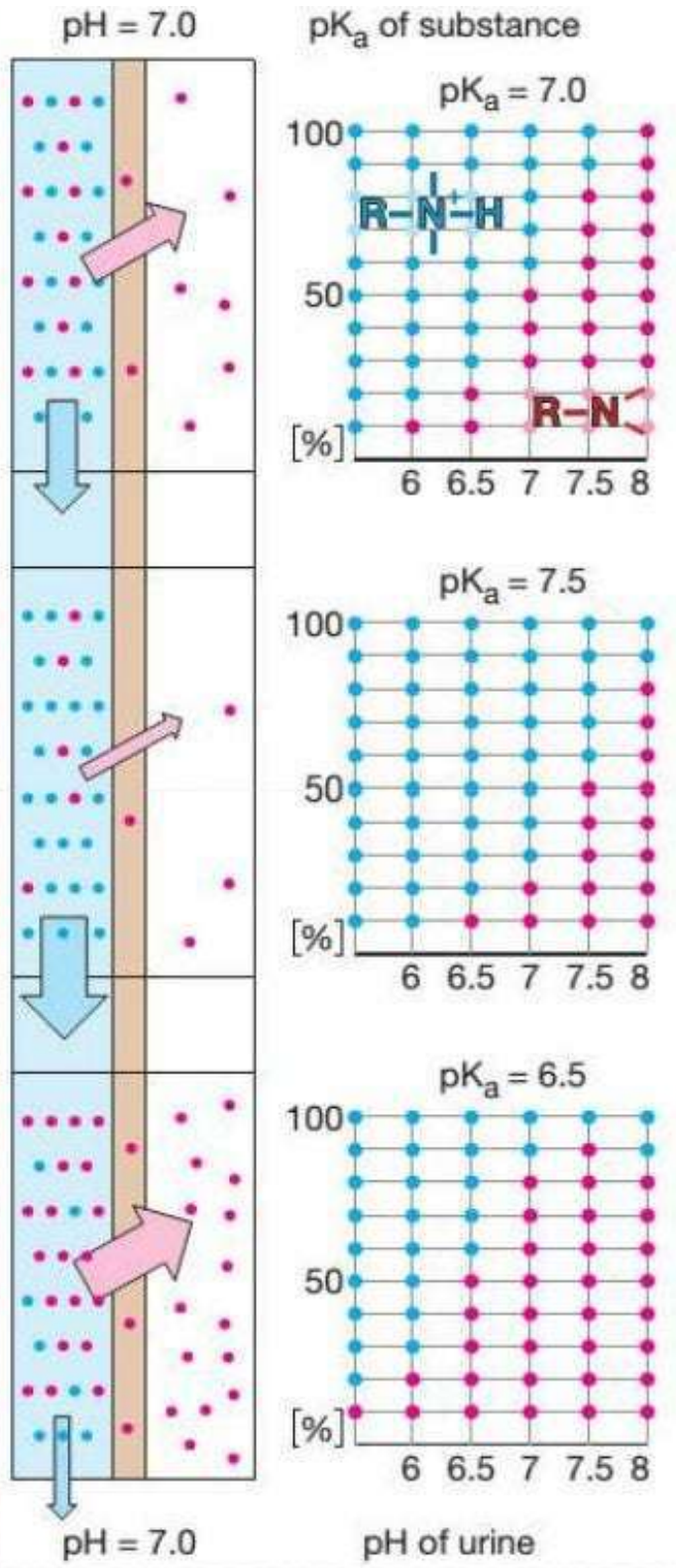
Tubular Secretion

- Both transporter are bi-directional
- Its not well developed at birth – prolongs the action of drugs (penicillin, cephalosporin)
- Gets matured in infancy
- Progressively declines after the age of 50 yrs and almost lowers for most drugs after 75 yrs

Tubular Resorption

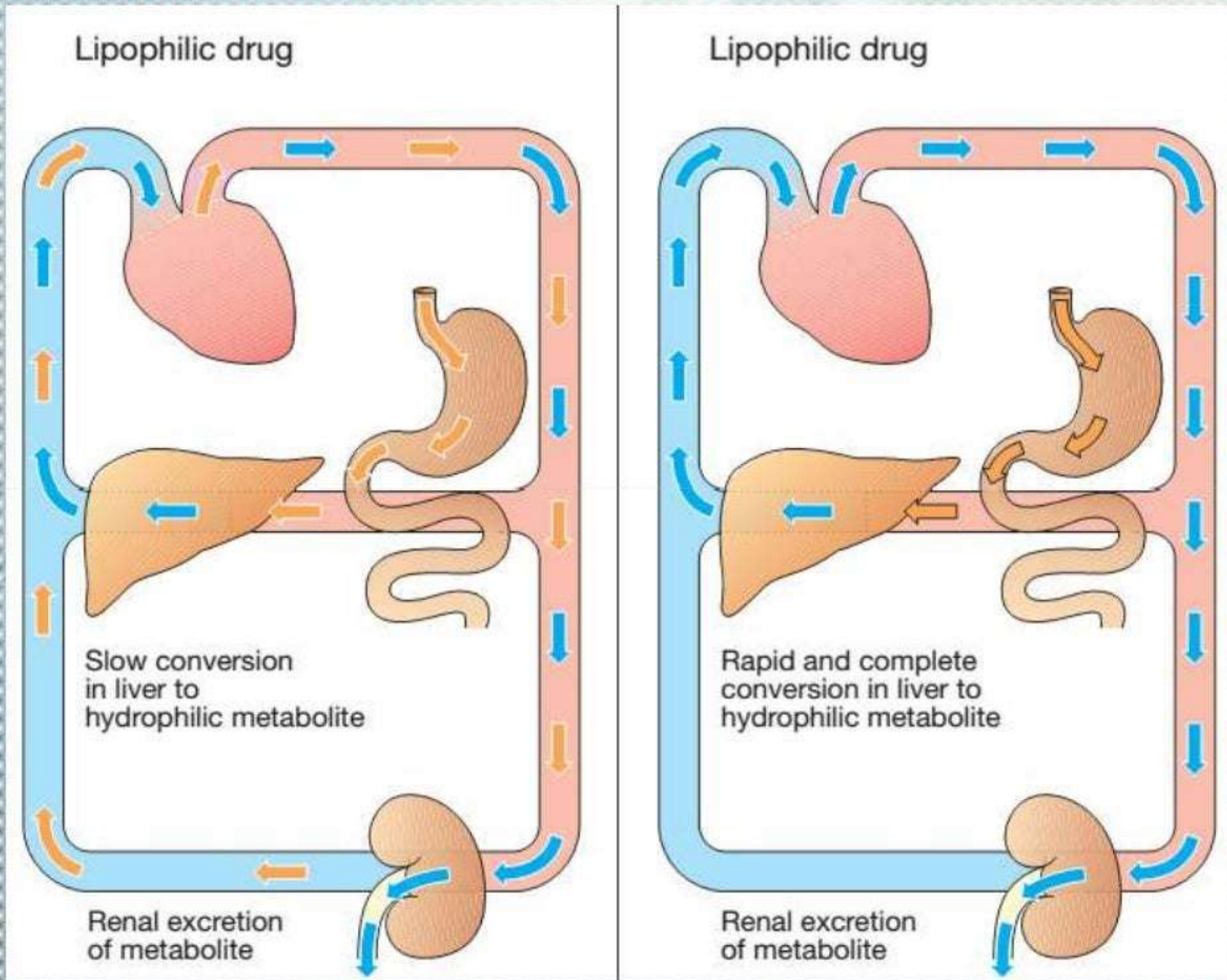
- Passive diffusion and depends on
  - Lipid solubility
    - 99 % of lipid soluble GF gets resorbed
    - Non-lipid soluble are unable to do so
  - Ionization of drug at existing pH – highly ionized drugs not resorbed

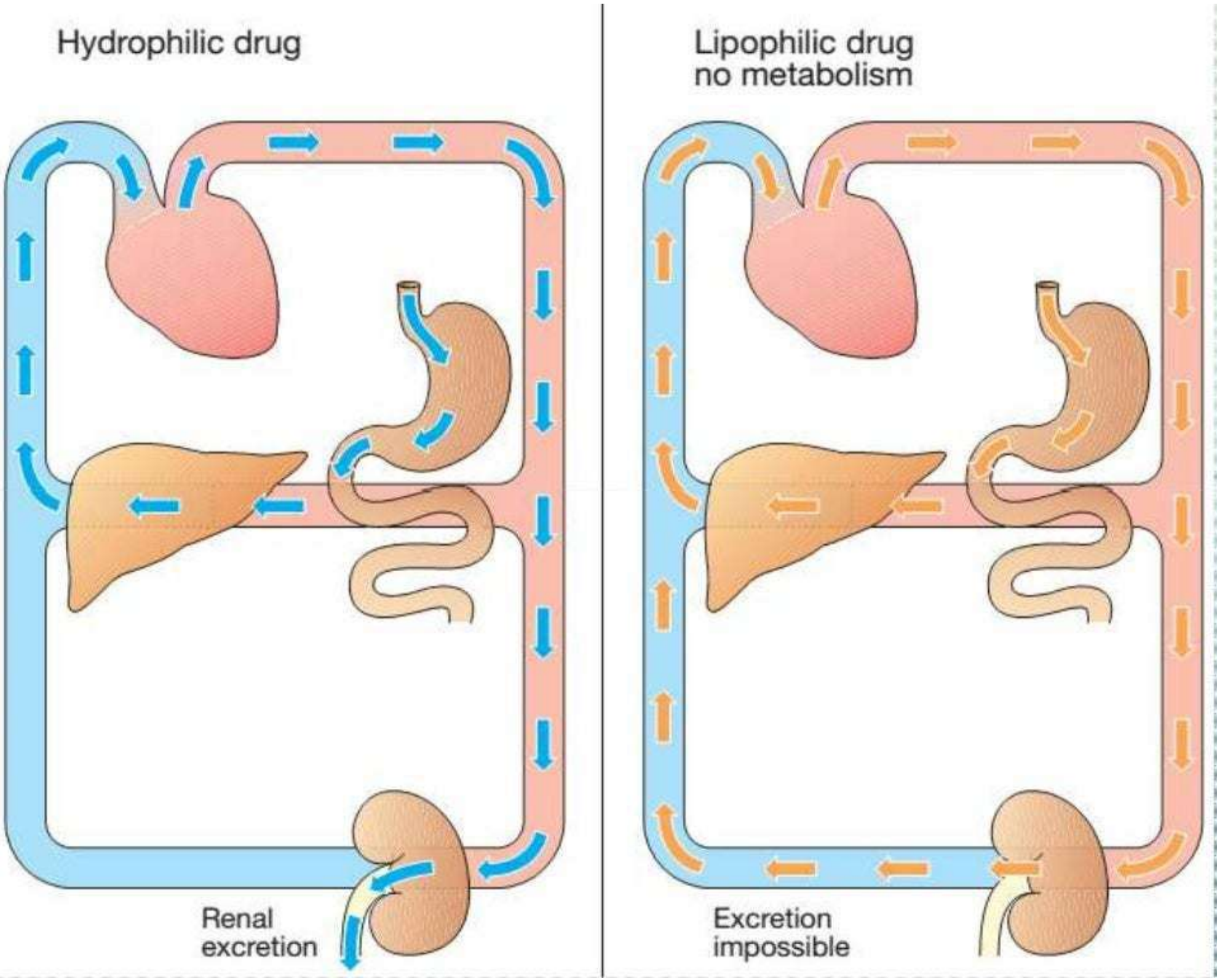
More Ionization	
Nature of Drugs	pH of urine
Weakly basic	Acidic
Weakly acidic	Alkaline



Excretion : Faeces

- Most of it derived from bile
- Large molecular drug is transported by this route
- Deconjugation by glucouronide drug
- Ex: Erythromycin, ampicillin, rifamipin, tetracycline, oral contraceptives, phenolphthalein
- Drugs gets directly eliminated – anthracene purgatives, heavy metals


Lipophilic drug
Slow conversion
in liver to
hydrophilic metabolite
Renal excretion
of metabolite
Lipophilic drug
Rapid and complete
conversion in liver to
hydrophilic metabolite
Renal excretion
of metabolite


Hydrophilic drug
Renal excretion
Lipophilic drug no metabolism
Excretion impossible

Excretion

Exhaled air

- Gases and volatile drugs or paticulate matter – irrespective of lipid solubility
- Alveolar transfer of gas – partial pressure in blood
- Ex: G.A., paraldehyde, alcohol

Saliva & Sweat

- Minor importance for drug excretion
- Ex: Lithium, pot. Iodide, rifampin and heavy metal

Excretion : Milk

- Important for infant sucking milk of mother on drug
- Most of drug enter – breast milk by passive diffusion
- Lipid soluble and PPB drugs do it better
- % of drug reaching infant is very less – majority of drugs can be given to lactating mothers without ill effect
- But lactating mother should be prescribed with drugs with caution
- Contraindicated drugs : Amidarone, Anthraquinone, Chloramphenicol, Ciprofloxacin, cyclosporine, indomethacin, methotrexate, tetracyclin
- Special precaution : Ampicillin, aspirin, losarton, metaclopromide, sulfonamide

Kinetics of Elmination

Kinetics of Elmination

- understand how dosage recommendations has been arrived in the product information
- use the drug optimally and understand its limitations
- Severly ill patient
  - individualise the dose regimen depending on how rapidly a therapeutic plasma concentration is required,
  - whether the clearance of the drug is impaired because of renal or liver disease.

Pharmacokinetics Parameters

- **Bioavailability (F)** : Fraction of administered drug that reaches systemic circulation in unchanged form

  $$F = \frac{\text{amt. Of drug that enters systemic circulation (AUC)}}{\text{Dose administered}}$$

- **Volume of Distribution (V)**: Volume that accommodate all the drugs in body, if the concentration throughout was same as in plasma

  $V = \text{dose administered/plasma drug concentration}$

- **Clearance (CL)** : the volume of plasma containing the total amount of drug that is removed from the body in unit time

  $CL = \text{Rate of elimination}/C$

Rate of elimination

- 1st order Kinetics : most of the drug
  - Rate of Elimination of drug is directly proportional to drug concentration
  - CL remains constant
- Zero order kinetics : few drugs
  - Rate of elimination remains constant irrespective of concentration
  - CL decreases with increase of concentration
  - Constant amount of drug is eliminated in unit time

Plasma Half Life

- Half-life = time required for serum plasma concentrations to decrease by one-half (50%)
- Mathematically

$$t_{½} = 0.693/k$$

k = elimination rate constant i.e fraction of total amount of drug removed per unit time

k = CL/V

- Complete drug elimination can occur in 4-5 half life

Steady Plasma concentration

- Steady Plasma concentration (Cpss) – repeated drug administration at relatively short interval of time
- Input of drug balance = clearance

$$Cpss = \text{dose rate}/CL$$

From this equation, it is clear that dose rate can be calculated if CL and target Cpss of drug is known.

Steady Plasma concentration

- Earlier equation is valid for drug route administration where the bioavailability (F) is 100 %, but where it falls short the equation turns to be

$$\text{dose rate} = (\text{target Cpss} \times \text{CL}) / \text{F}$$

Both this equation stands valid for the drugs following 1st order kinetics

Michelis Menten Kinetics

- Elimination changes from first order to 0 order over the therapeutic range.
- This signifies that till the saturation level of drug, Cpss is related to dose rate.
- But it turns out of proportion beyond it

Rate of drug elmination = $(V_{max})\ (C) / K_m + C$

Km = plasma conc. at which elimination rate is half maximal

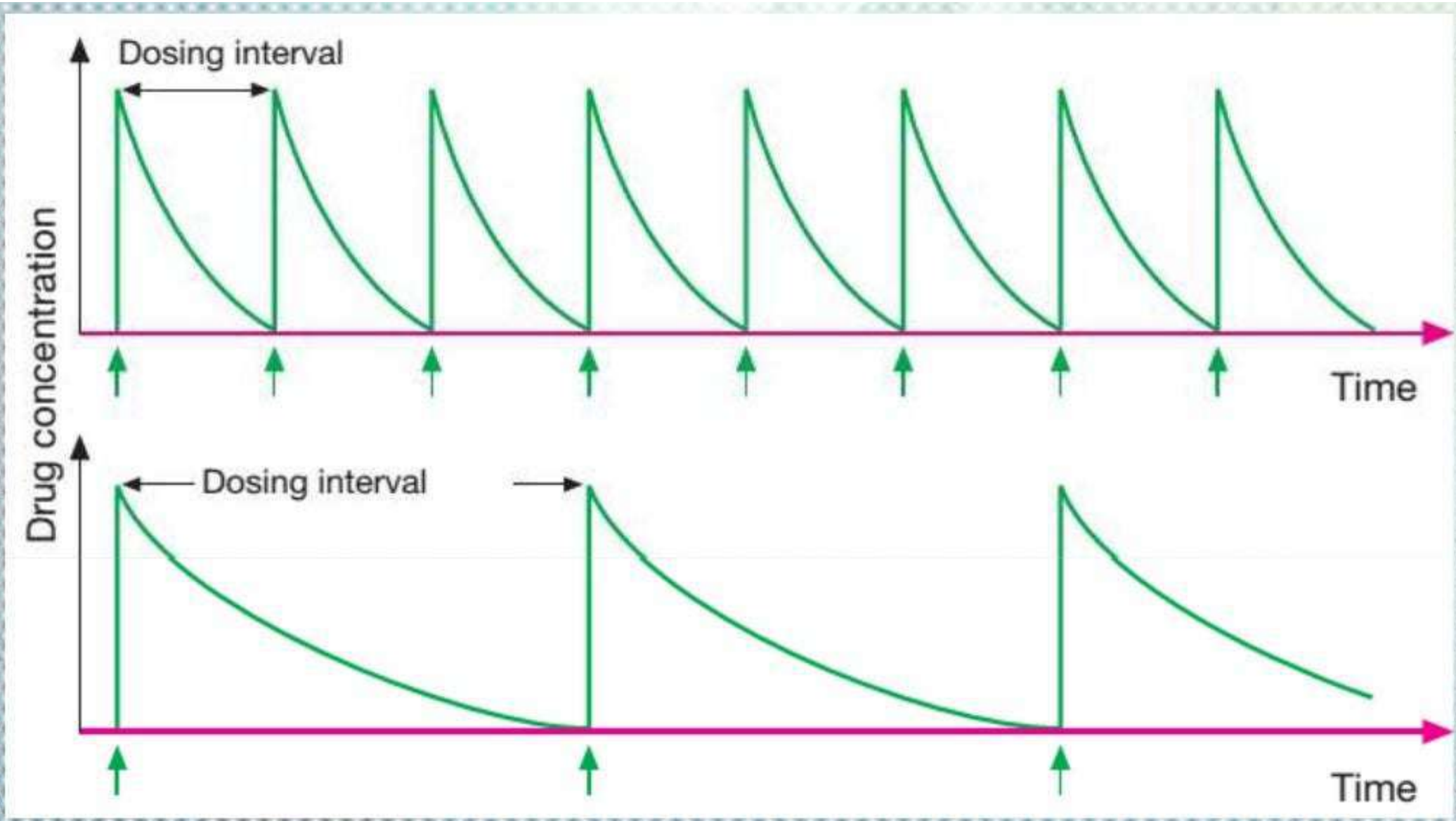
C = plasma concentration of drug

Vmax = maximum rate of drug elimination

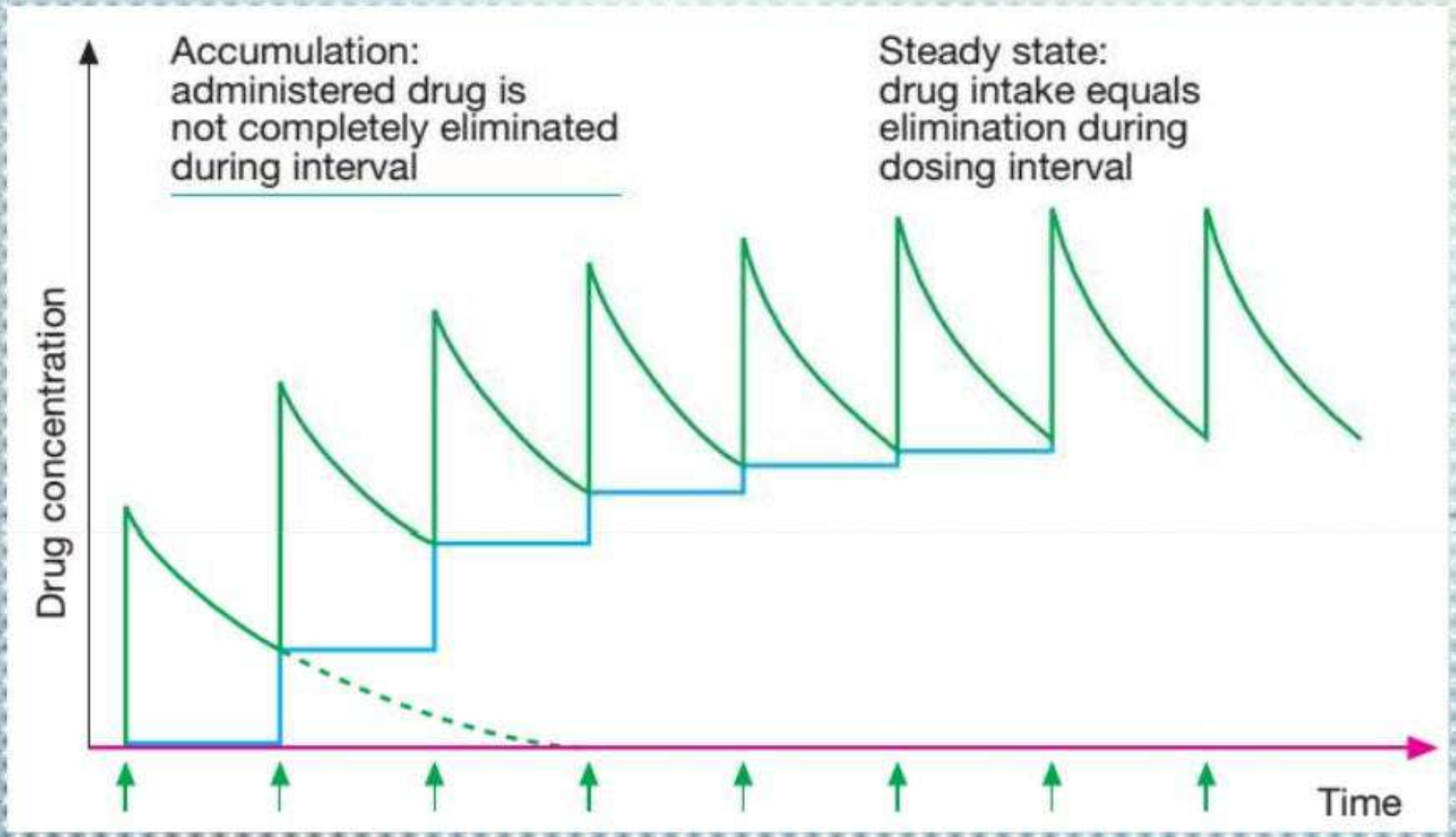
Ex: Phenytoin

Plateau Principle of drug accumulation

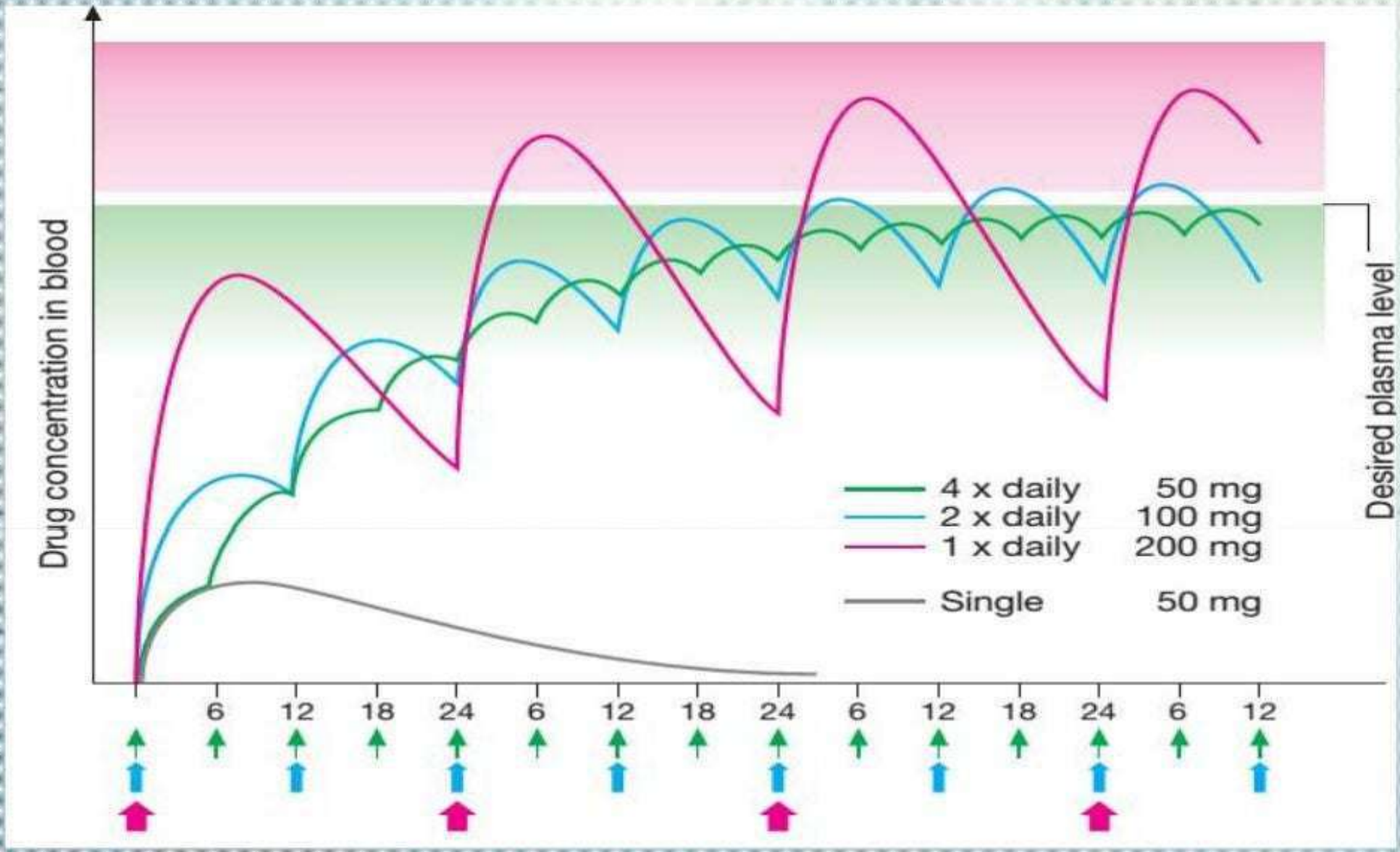
- When constant dose of a drug is repeated before the expiry of 4 $t_{½}$, it would achieve higher peak concentration, because some remnant drug will be present in the body.
- Subsequently plasma concentration becomes constant and forms a plateau and fluctuates around desired therapeutic level of drug.
- Desired therapeutic level reaches 4-5 half lives



After every 4-5 half life the drug concentration falls to almost 3-4 %



So if the dose is repeated before the expiry of 4-5 half life, the concentration of drug keeps on increasing after every subsequent dose.



So its better to administer the drug in small dose over small regular interval rather than large dose in large interval of time

Target Level Strategy

Target Level	Strategy	Example
Narrow safety margin with unquantified pharmacokinetic data	Range of therapeutic concentration	Anticonvulsant, antidepressant, lithium, antirythmics, theophyline and some antimicrobials
Short half life	Conventional interval (6-12 hrs) – fluctuating plasma concentration	Penicilllin, amipicillin, chloramphenical, erythromycin, propranolol
Long half life	Daily/weekly/Single dose	MAO inhibitors, reserpine, omeprazole
Steady drug concentration	Loading Dose and maintenance dose	Steroids

Loading Dose

- Single or few quickly repeated dose to attain target concentration rapidly

  Loading dose = (target Cp x V)/ F

  So loading dose is governed by V not CL or half life of drug

Maintenance dose

- The amount of drug given to maintain the steady state plasma concentration (Cpss) of drug at regular interval so as to balance the elimination.

  dose rate = (target Cpss X CL)/ F

  So its dependent on CL or half life of drug

Therapeutic drug monitoring (TDM)

- Cpss of a drug depends on its F, V and CL – each of this parameters varies from patient to patient
- Measurement of plasma concentration of drug after initial drug administration (based on average patient) can give all this parameter of a individual
- This helps for the subsequent quantification of drug dose regimen

Use of TDM

- Low safety margin – digoxin, anticonvulsants, antiarrythmics, theophylline, aminoglycerides, lithium, TCA
- If individual variation are large – antidepressant, lithium
- Potentially toxic drug used in renal failure – aminoglycoside antibiotics, vancomycin
- In case of poisoning
- Failure of response without any reason
- Check patient compliane

Prolongation of drug action

- Frequency of drug administration
- Improved patient compliance
- Large fluctuation of plasma concentration should be avoided
- Drug effect could be maintained overnight without disturbing sleep

All drugs cant be made long acting, Ex: Sedatives, headache remedy) or longer acting drugs

Method to achieve this objective

- Prolonging the absorption from site of administration
  - Entral : Sustained relase tablets, spansules
  - Parentral: Insoluble form (oily), pellet implantation, sialistic and biodegradable implant, inclusion of vasoconstriction
  - Transdermal patches
- Increasing plasma protein binding
- Retarding metabolism
- Retarding elmination

Refrences

- Essential of medical Pharmacology 4th edition – KD Tripathi
- Rang_and_Dales_Pharmacology__6th_Ed_2007
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- Color Atlas Of Pharmacology, 2Nd Ed (Lüllmann, Thieme 2000)
- Bertram G. Katzung-Basic & Clinical Pharmacology(9th Edition)
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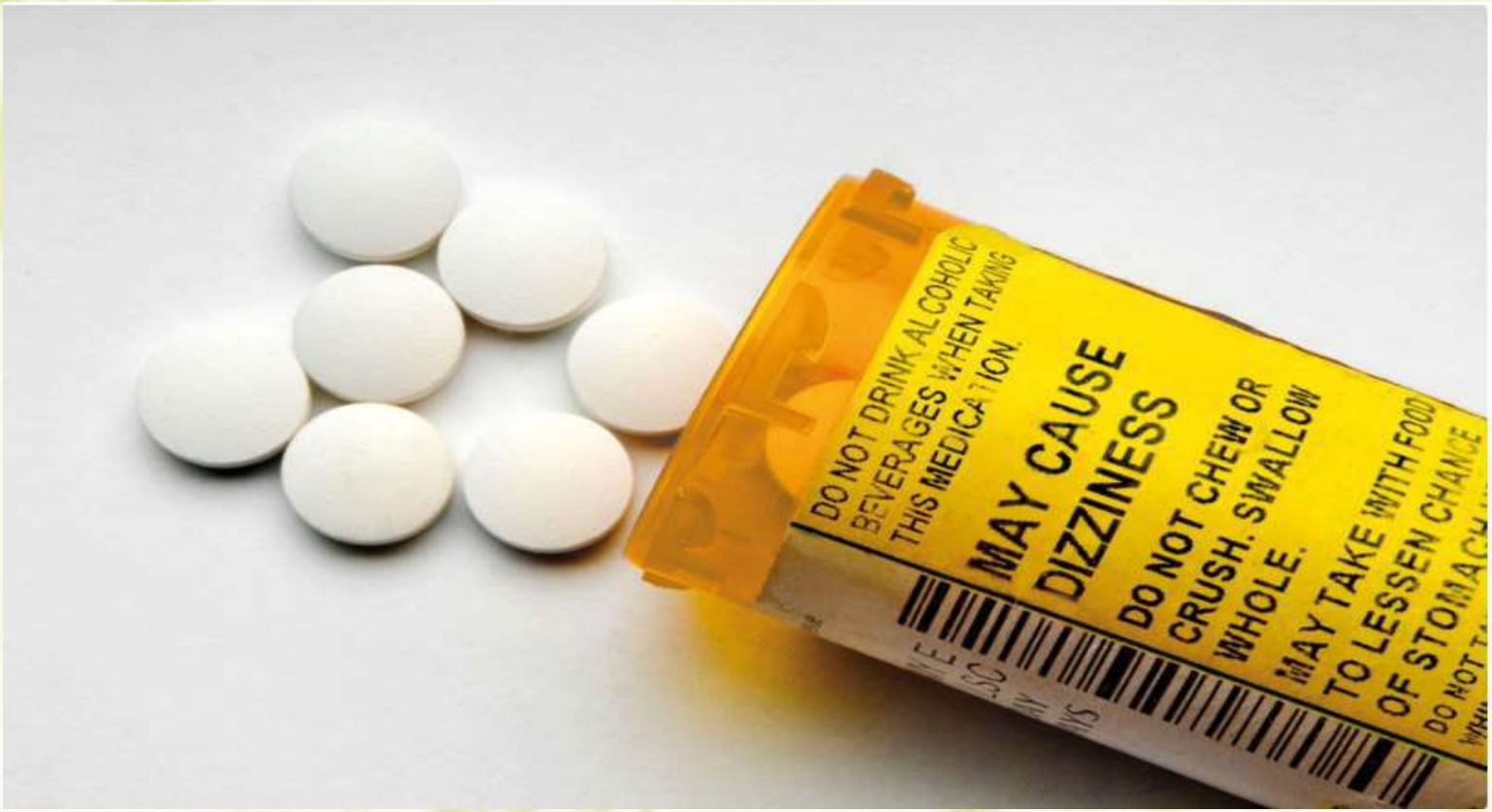
ADVERSE DRUG REACTIONS



Lesson plan

- **Definition of terms associated with Adverse Drug Reactions (ADRs)**
- **Classification of ADRs**
- **Discussion on each type of ADR with examples**

What is ADRs?

Cur'd yesterday of my disease
I died last night of my physician.

WHO Definition

Any response to a drug which is noxious & unintended & which occurs at doses in man for prophylaxis, diagnosis or treatmant.

History about ADRs

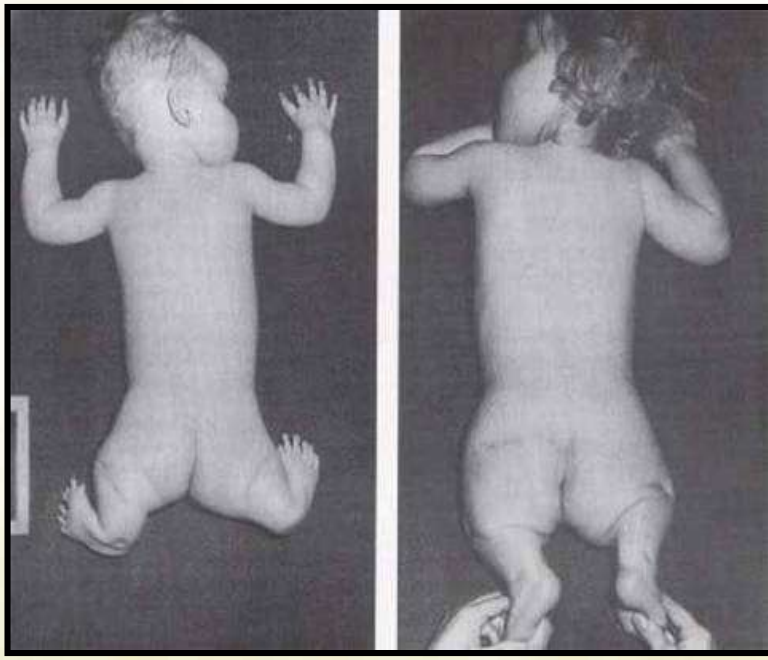
1922 : JAUNDICE associated with the use of SALVARSAN, an organic arsenical used in the treatment of Syphillis.

In 1937: In USA, 107 people died from taking an ELIXIR OF SULFANILAMIDE that contained the SOLVENT DIETHYLENE GLYCOL

Establishment of the FOOD AND DRUG ADMINISTRATION (FDA), which was given the task of enquiring into the safety of new drugs before allowing them to be marketed.

.

- 1958: Thalidomide markated in West Germany as a non barbiturate hypnotic & for morning sickness during pregnancy based on animal toxicity report.



1959-61 thalidomide disaster

(4000-100000 case)

- In 1959 - 1961, it was reported in that there was an outbreak of **PHOCOMELIA** (**hypoplastic and aplastic limb deformities**) in the new born babies.

- The **THALIDOMIDE INCIDENT** led to a public outcry, to the institution all round the world of **DRUG REGULATORY AUTHORITIES**, to the development of a much more sophisticated approach to the preclinical testing and clinical evaluation of drugs before marketing, and to a greatly increased **awareness of adverse effect of drugs** and **methods of detecting them…**

Classification of ADRs

- Depending on….
- **Onset of event:** Acute (<60 minutes), Sub-acute (1-24 hrs) and Latent (>2 days)
- **Type of reaction:** (**Wills and brown)**

  Type A (Augmented), B (Bizarre), C (Chronic),

  D (Delayed), E (End of treatment)

- **Severity:** Minor, Moderate, Severe, Lethal ADRs

- **Others:** Side effects, Secondary effects, Toxic effects, Intolerance, Idiosyncrasy, Drug allergy, Mutagenicity, Photosensitivity, Drug Dependence, Drug Withdrawal Reactions, Teratogenicity, Carcinogenicity, Drug induced disease (Iatrogenic).

Type A (Augmented) reactions

- Reactions which can be predicted from the known pharmacology of the drug
- Dose dependent
- Can be alleviated by a dose reduction
- common
- Skilled management reduces their incidence.

E.g.

- Anticoagulants → Bleeding
- Beta blockers → Bradycardia
- Nitrates → Headache
- Prazosin → Postural hypotension

Type B (Bizarre) reactions

- Predictable where the mechanism is known, otherwise unpredictable for the individual, although the incidence may be known.
- Dose independent, rare
- Host dependent factors important in predisposition
- unwanted effects due to inherited abnormalities (idiosyncrasy) and immunological processes(drug allergy).
- These account for most drug fatalities.

E.g. Penicillin → Anaphylaxis,

Anticonvulsant → Hypersensitivity

Type C (Chronic)

- Reactions due to long time exposure.
- e.g. Analgesic neuropathy

  Dyskinesia with levodopa

Type D (Delayed) reactions

- Occur due to prolonged exposure.
- Can be due to accumulation.

E.g.

Carcinogenesis, or short term exposure at a critical time e.g.teratogenesis.

Type E (End of use) reactions

- Occur on withdrawal especially when drug is stopped abruptly

E.g.

- Phenytoin withdrawal → Seizures
- Steroid withdrawal → Adrenocortical insufficiency.
- opioid causing the withdrawal syndrome.

Types of ADRs……..

Type	Type of effect	characteristics	example
A	Augmented	Dose dependent predicted from the known pharmacology of the drug	Hypoglycaemia-insulin
B	Bizarre	Unpredictable Dose independent Rare,fatal	Anaphylaxis to penicillin
C	Chronic	Prolong treatment	Analgesic neuropathy
D	Delayed	After years of treatment	Antipsycotic –turdive dyskinesia
E	End of use	Withdrawal effect	GC withdrawal→ adrenocortical

Classification of ADRs :Depending on Severity

- **Minor ADRs:** No therapy, antidote or prolongation of hospitalization is required.
- **Moderate ADRs:** Requires change in drug therapy, specific treatment or prolongs hospital stay by atleast 1 day.
- **Severe ADRs:** Potentially life threatening, causes permanent damage or requires intensive medical treatment.
- **Lethal:** Directly or indirectly contributes to death of the patient.

Side effects

- Unwanted but often unavoidable, occur at therapeutic doses
- Predicted from the pharmacological profile of a drug
- Known to occur in a given percentage of drug recipients
- **E.g.**

  Atropine →dryness of mouth

  Promethazine (anti-allergic)→ sedation

  Codeine(anti-tussive)→constipation →Used in Traveller's diarrhoea

Side effects….(Drug discovery)

- Occasionally, "adverse" effects may be exploited to develop an entirely new indication for a drug.
- **E.g:**
- Unwanted hair growth during Minoxidil treatment of severely hypertensive patients → development of the drug for hair growth.

- Sulfonamides used as antibacterials were found to produce hypoglycemia and acidosis as side effects → development of Hypoglycemic Sulfonylureas…

- **Untoward effect –**

- Slight more serious effect than side effect produced with therapeutic dose.
- Seriously unpleasant.
- Harmful.
- e.g. Superinfection produced by broad spectrum antibiotic, vomiting by morphine in postoperative patients, hypokalamia by thiazide diuretics.

» Toxic effects

- Predictable
  - Dose dependent
  - Rebound response
- Excess pharmacological effect in high dose.
- These are known. Detected by pharmacologist

Unpredictable

- Allergy
- Idiosyncrasy

Not found in clinical trial.

Pharmacologist may not be able to detect this during study of drug development

Predictable toxic effects

- Dose dependent adverse effect may be –

- **Direct damaging effect to tissue** e.g. Paracetamol overdose leads to hepatotoxicity, Aminoglycoside (Gentamicin) causes nephrotoxicity.

- **Rebound response** – (due to R-upregulation) abrupt withdrawl after chronic use. e.g.propranolol stoppage leads to precipitation of MI, Glucocorticoid withdrawal leads to acute adrenal insufficiency.morphine – due to R supersensitivity.

Pharmacologically Predictable ADRs

Type	Example	Toxicity	Mechanism
Pharmaceutical	Phenytoin	Phenytoin toxicity (ataxia, nystagmus, etc)	Increase in bioavailability as a result of a change in formulation
Pharmacokinetic (can involve absorption, distribution, metabolism and excretion)	Digoxin	Digoxin toxicity (nausea, arrhythmias, etc)	Decreased elimination if renal function is impaired
Pharmacodynamic	Indomethacin	Left ventricular failure	Water and sodium retention
Genetic	Nortriptyline	Confusion	Reduced hepatic elimination as a result of a deficiency of CYP2D6
Drug-drug interactions (can involve any of the above processes)	Lithium-nonsteroidal anti-inflammatory drugs	Lithium toxicity	Inhibition of excretion of lithium

- **Excess pharmacological effect:** Result of excessive pharmacological action of the drug due to over dosage or prolonged use.
- e.g. Excess insulin-hypoglycemia even death from hypoglycemic shock

  Antihypertensive - hypotension

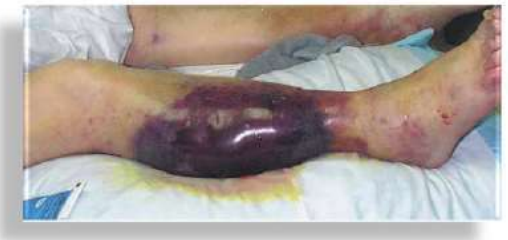
  Anticoagulant-

  severe bleeding.

Warfarin

- Number of users UK:
  600,000
- Dose (mg) range per day:
  0.5-20
- Fold variability in dose:
  40
- Major bleeding rate per 100-person years:
  2.6
- Ranking in ADR list:
  3

Approved for human use in 1954



Unpredictable toxic effects

- **Dose independent**
- Less than therapeutic dose may lead to toxic effect

Idiosyncrasy -

- unusual response to a drug due to genetic abnormality.
- Drug interacts with some unique feature of the individual, not found in majority subjects, and produces the uncharacteristic reaction.
- **E.g.**
- **Isoniazid:** *N*-Acetylation affects the metabolism of isoniazid
- **Slow *N*-Acetylation**: Isoniazid is more likely to cause peripheral neuritis.
- **Fast *N*-Acetylation**:cause hepatotoxicity in this group.

- **Succinylcholine** can produce **apnea** in people with abnormal serum cholinesterase. Their cholinesterase is incapable of degrading the succinylcholine, thus it builds up and depolarization blockade results.

- **Primaquine, Sulfonamides** induce acute hemolytic anemia in patients with **Glucose-6-Phosphate Dehydrogenase deficiency**.

--They have an inability to regenerate NADPH in RBC.G-6-p deficiency is most prevalent in blacks & Semitics. It is rare in Caucasians & Asians.

Drug allergy

- Acquired, altered reaction of the body to drug.
- Immunologically mediated reaction.
- occur even with much smaller doses
- Also called Drug hypersensitivity
- Not genetic,not occurred in all
- Occurs on reexposure
- E.g. penicillin→1st time →stimulate antibody →Ag-Ab reaction →allergy
- Chief organ: Skin, respiratory tract,GIT,Blood & blood vessels

Type of reaction	Time before clinical sign	Characteristics	Example
Anaphylactic (Immediate IgE-mediated anaphylaxis)	< 30 min	IgE binds to must cell or basophil,causes degranulation of must cell & basophil& release of reactive subs. histamine	**Penicillin anaphylaxis**
Cytotoxic (Antibody-Dependent Cellular Cytotoxicity	5 – 12 hr	Antigen cause formation of IgG or IgM antibodies to bind that . Drug forms an antigenic complex with the surface of the cell and combination with antibody activate complement system causing cell destruction.	**Hemolytic anemia**: Penicillin or Methyldopa **Thrombocytopenia** : Quinidine **SLE**:Hydralazine or Procainamide.
Immune complex mediated	8-10	antigen antibody form complexes that causes inflammation	**Steven-Johnson Syn Serum Sicknessdrome**
Cell mediated allergy(delayed type)	24 to 48 hrs	Antigen specific receptors develop on T-lymphocytes. Subsequent administration leads to local or tissue allergy.	Contact dermatitis Rejection of transplanted tissue

Certain tissues which are vulnerable

- **Hemopoietic system & bone marrow –**

- Quinine, Rifampicin, Sulfonamide, Thiazide – drug allergy (type II reaction) – Throimbocytopenia.
- Carbamazepine, Sulfonamide, carbimazole, clozapine (fatalneutropenia) - drug allergy (type II reaction) – Granulocytopenia.
- Chloramphenicol (idiosyncracy) -Aplastic anemia.
- Anti cancer, cytotoxic drugs -direct bone marrow depression
- primaquine, quinine, chloroquine, dapsone, sulfonamide(due to idiosyncracy) Methyldopa used in pregnancy – Hemolytic anemia.

- **Liver damage/ Hepatic injury** –

- Chloroform, Halothane, Enflurane – when given in repeated dose – hepatotoxicity – jaundice (so, before anesthesia H/O jaundice taken).
- Chlorpromazine, Flucloxacillin, OCP –(type II) cholestatic jaundice(causes edematous bile canaliculi-stasis of bile)
- INH, Rifampicin, Methyldopa – hepatocellular necrosis – jaundice (cause is unknown).
- Methotrexate, Alcohol – cirrhosis of liver.
- Paracetamol overdose (8 – 10 gm of paracetamol in 10 – 24 hours if taken) – toxic metabolite (Epoxide) – Hepatocellular necrosis.
- Minocycline (newer tetracycline) – Chronic Active Hepatitis.

- **Renal damage** –

- Phenylbutazone, Sulfonamide, Hydralazine – damage to glomerular membrane – Glomerulonephritis.

- Aminoglycoside (Gentamicin), Amphotericin (antifungal), High dose paracetamol, Cefalothin –Acute tubular necrosis.

- NSAID, Lithium, Penicillamine – long term use in rheumatoid arthritis – Acute interstitial nephritis.
- ACEI – Renal vascular damage.

Intolerance

- Appearance of characteristic toxic effects of a drug in an individual at therapeutic doses
- Converse of tolerance
- Indicates a low threshold of the individual
- **E.g.**
- Trifluprομazine (single dose) → Muscular dystonias in some individuals
- Carbamazepine (few doses) →Ataxia in some individuals
- Chloroquine (single tablet) → Vomiting and abdominal pain in some individuals

Tolerance –

- ↓ pharmacological effect on repeated administration of the drug.
- **Pharmacokinetic Tolerance**: ↑ the enzymes responsible for metabolizing the drug.

  e.g.Phenobarbitone induces metabolism of its own by increasing its own metabolic enzyme**.**
- **Pharmacodynamic Tolerance**: Cellular tolerance, due to down-regulation of receptors.
- **Depletion of stores** e.g.Amphetamine

Tachyphylaxis:

- When responsiveness diminishes rapidly after administration of a drug, the response is said to be subject to tachyphylaxis.

- Tyramine can cause depletion of all NE stores if you use it long enough, resulting in tachyphylaxis.

Photosensitivity

- Cutaneous reaction resulting from drug induced sensitization of the skin to UV radiation. The reactions are of two types

- **Phototoxic:** Drug or its metabolite accumulates in the skin, absorbs light and undergoes a photochemical reaction resulting in local tissue damage (sunburn-like, i.e., erythema, edema, blistering, hyper pigmentation)

  E.g. Tetracyclines (esp. Demeclocycline), and Tar products, Nalidixic acid, Fluoroquinolones, Sulfones etc

- **Photoallergic:** Drug or its metabolite induces a cell mediated immune response which on exposure to light (longer wave length) produces a papular or eczematous contact dermatitis like picture.

  E.g. Sulfonamides, Sulfonylureas, Griseofulvin, Chloroquine, Chlorpromazine

Drug dependence

- Drugs capable of altering mood and feelings are liable to repetitive use to derive euphoria, withdrawal from reality, social adjustment, etc.
- **Psychological dependence:** Individual believes that optimal state of well being is achieved only through the actions of the drug.
- **E.g.** Opioids, Cocaine.
- **Physical dependence:** Altered physiological state produced by repeated administration of a drug which necessitates the continued presence of the drug to maintain physiological equilibrium. Discontinuation of the drug results in a characteristic withdrawal (abstinence) syndrome.
- **E.g.** Opioids, Barbiturates, Alcohol, Benzodiazepines

Drug dependence….

- **Drug abuse:** Use of a drug by self medication in a manner and amount, that deviates from the approved medical and social patterns in a given culture at a given time.

  Drug abuse refers to any use of an illicit drug.

- **Drug addiction:** Compulsive drug use characterized by overwhelming involvement with the use of a drug.

- **Drug habituation:** Less intensive involvement with the drug, withdrawal produces only mild discomfort.
- Habituation and addiction imply different degrees of psychological dependence.

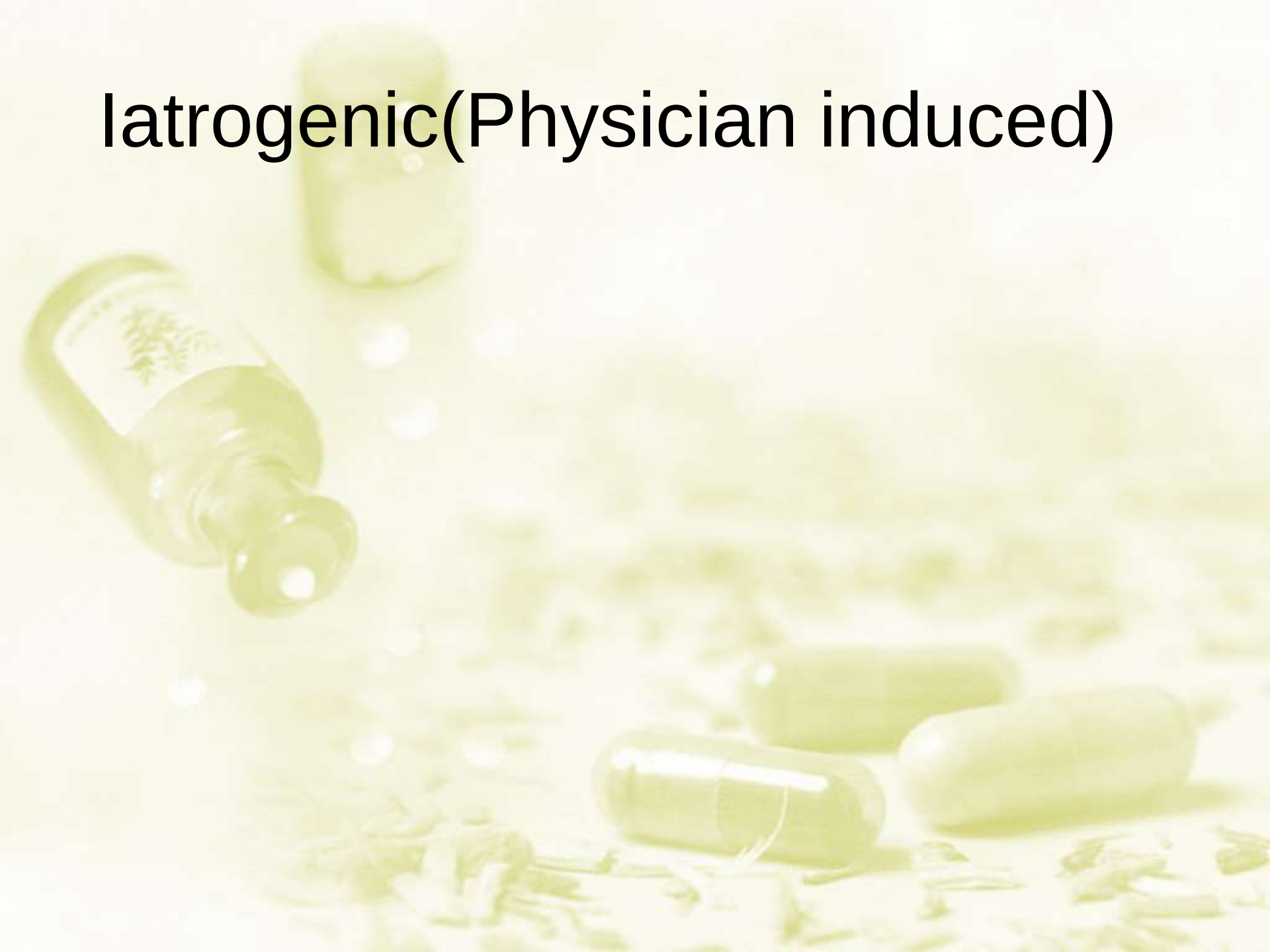
Mutagenecity and Carcinogenicity

- Capacity of a drug to cause genetic defects and cancer respectively.
- Chemical carcinogenesis generally takes several (10-40) years to develop.
- Unpredictable

e.g.

- Estrogen- Endometrial carcinoma.
- OCP- Ca cervix, breast Ca
- Iron S/C or I/M – blackening of area – increase incidence of sarcoma (cause is unknown).
- Anticancer drug.

Iatrogenic(Physician induced)



Teratogenicity

- Capacity of a drug to cause foetal abnormalities when administered to the pregnant mother.
- Drugs can affect the foetus at 3 stages:
    1. Fertilization and implantation (Conception to 17 days): failure of pregnancy which often goes unnoticed.
    2. Organogenesis(18 days to 55 days): most vulnerable period, deformities are produced.
    3. Growth and development (> 56 days): developmental and functional abnormalities can occur. **E.g:**
- Thalidomide →Phocomelia, multiple defects
- Anticancer drugs → Cleft palate, hydrocephalus, multiple defects

FDA Pharmaceutical Pregnancy Categories	
Category A	Adequate and well-controlled human studies demonstrate no risk.
Category B	Animal studies demonstrate no risk, but no human studies have been performed. OR Animal studies demonstrate a risk, but human studies have demonstrated no risk.
Category C	Animal studies demonstrate a risk, but no human studies have been performed. Potential benefits may outweigh the risks.
Category D	Human studies demonstrate a risk. Potential benefits may outweigh the risks.
Category X	Animal or human studies demonstrate a risk. The risks outweigh the potential benefits.

Drugs known to be teratogenic

- Anticancer drugs – Methotrexate – multiple deformity.
- Steroid – cleft palate and other.
- Oral anticoagulants – bony abnormality (Hypoplastic nasal structures), optic atrophy, mental retardation.
- Oral hypoglycemic agents - multiple deformity.
- Androgenic hormone – virilization, hermaphrodite, lid retraction.
- Tetracycline – inhibit bony growth.

Cont'd

- Trimethoprim – cleft palate.
- Phenytoin, carbamazepine, valproate - Malformation of fingers,cleft palate,neural tube defect(spina bifida)
- Diethylstilbestrol - Oral contraceptive is no longer used because it causes reproductive cancers in daughters born to mothers taking the drug.
- Androgen- virulization of female fetus
- Aminoglycosides, Chloroquine – Deafness.

Teratogens in first trimester

- Phenytoin, carbamazepine, valproate - neura tube defects (spina bifida)
- lithium – cardiac malformations
- Warfarin - bone deformation, chondrodysplasy, CNS defects
- Heparin (demineralization of bone in mother – switch to LMW)
- Retinoids-def. CNS, heart, limbs, liver
- oncologic drugs (fluorouracil, metotrexate, cyclofosfamid, busulfan)

Drugs cannot be given in last trimester

- Antithyroid drugs: Hypothyroidism in neonates
- Streptomycin - Ototoxicity
- Morphine: Respiratory depression
- Chloroquine: Retinopathy of fetus
- Aspirin: delay labour pain.

Individual variation in response to drug

- Variation due to age, sex, body weight, surface area, nutrition, alcoholic, cigarette smoking, pregnancy, genetic factor, environment, and pathological condition.

- 4 general mechanism:

- A) **Alteration in concentration of drug that reaches the receptors** –
- rate of absorption of a drug
- distributing it through body compartments
- clearing the drug from the blood.

- B) **Variation in concentration of an endogenous receptor ligand** –
- variability in responses to pharmacological antagonist.
- propranolol will markedly slow the HR of a patient whose endogenous catecholamine are elevated (as in pheochromocytoma), but will not affect the resting HR of a well trained marathon runner.
- C) **Alteration in number or function of receptor** – ↑ or ↓ in number or alteration in efficiency of coupling of receptor to distal effector mechanism – change in responsiveness.

e.g.Thyroid hormone increase number of **β** receptor in heart and increase sensitivity of cardiac muscle to catecholamine – tachycardia of thyrotoxicosis.

- **D) Changes in components of response distal to the receptor** – Response depend on the functional integrity of biochemical process in the responding cell and physiological regulation by interacting organ system.

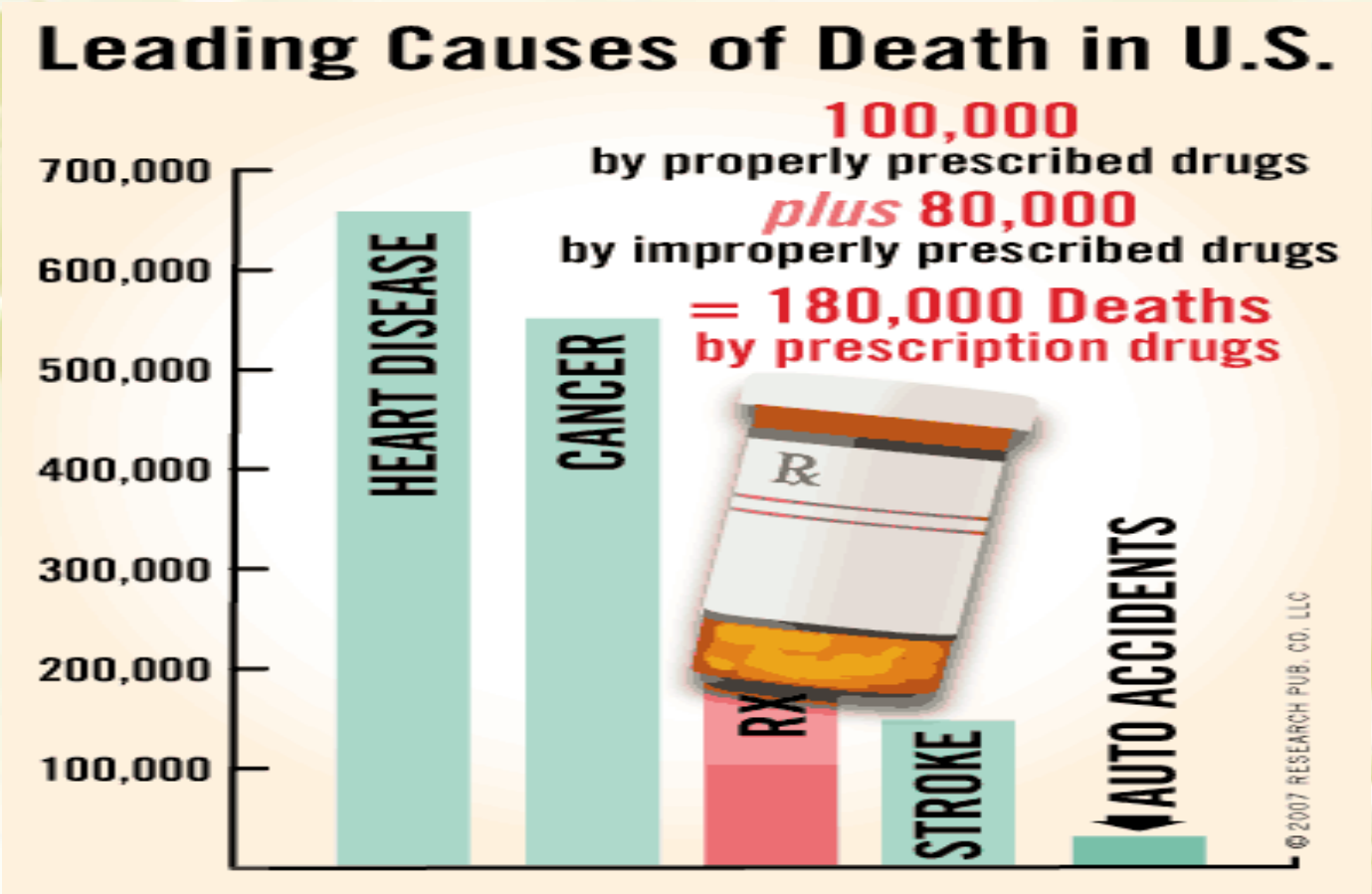
Cont'd…

- Medicines are supposed to save lives

  Dying from a disease is sometimes unavoidable; dying from a medicine is unacceptable. Lepakhin V. Geneva 2005

Cont'd…

- Among the Leading cause of death-



Cont'd…

- **ADRs are expensive !!**

Cost of ADRs in the US:

Cost of drug related morbidity and mortality exceeded $177.4 billion in 2000 (*Ernst FR & Grizzle AJ, 2001: J American Pharm. Assoc)*

ADR related cost to the country exceeds the cost of the medications themselves.

Cont'd…

- Ethics:

To know of something that is harmful to another person who does not know, and not telling, is unethical.

- No medicine is risk free, Vigilant assessment of the risks and benefits of medicine promote safety.

Aims of knowing ADRs

- To improve patient care and safety
- To improve public health and safety
- To contribute to the assessment of benefit, harm, effectiveness and risk of medicine.

Adverse drug reactions[ADRs] monitoring

- Monitoring centre:

  - WHO collaborating centre for international drug monitoring , Uppsala Monitoring Centre, Sweden.

  - Established in1968.

- In Bangladesh:

  - Directorate General of Drug Administration.

  105-106, Motijheel Commercial Area, Dhaka-1000, Bangladesh.

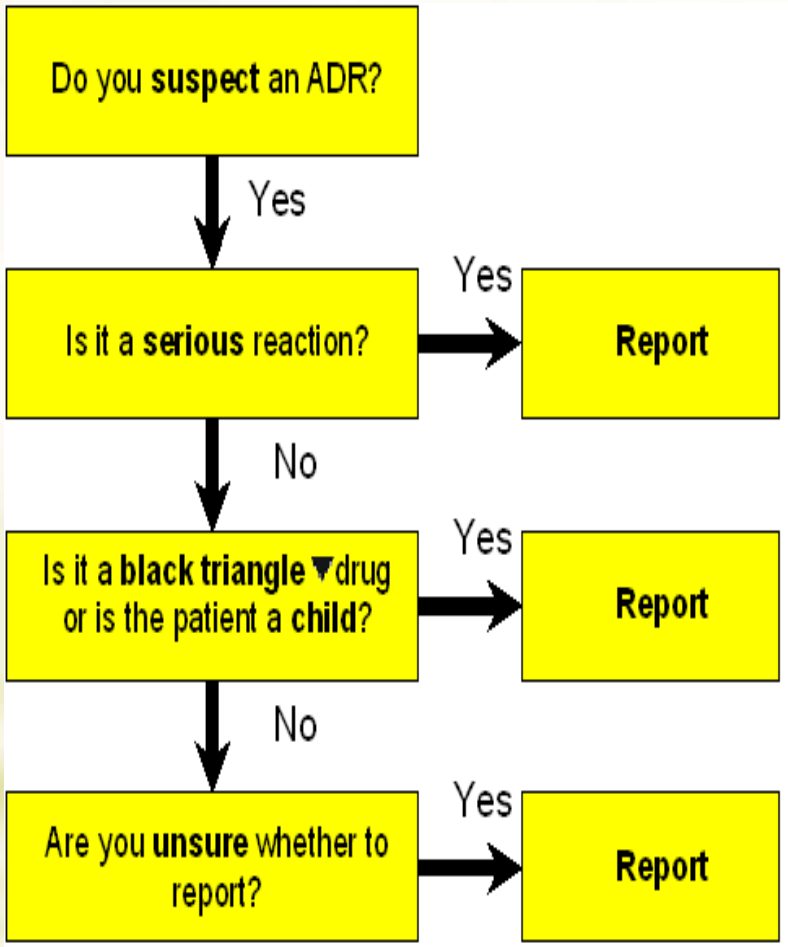
Cont'd…

- Monitoring of ADRs:
  - Clinical trial monitoring
  - Prescription event monitoring
  - Yellow card system

ADRs reporting:

- Who to report:

- All health care professionals.



- What to report:

-Apparent ADRs previously unknown to the reporters

-Serious ADRs

-**All suspected ADRs** to new drugs

Cases of suspected dependence

Cont'd…

- How to report:

  - ADRs form

  - Assessment tool: Naranjo scale

- Where to report:

  - National body (Directorate General of Drug Administration. 105-106, Motijheel Commercial Area Dhaka-1000, Bangladesh

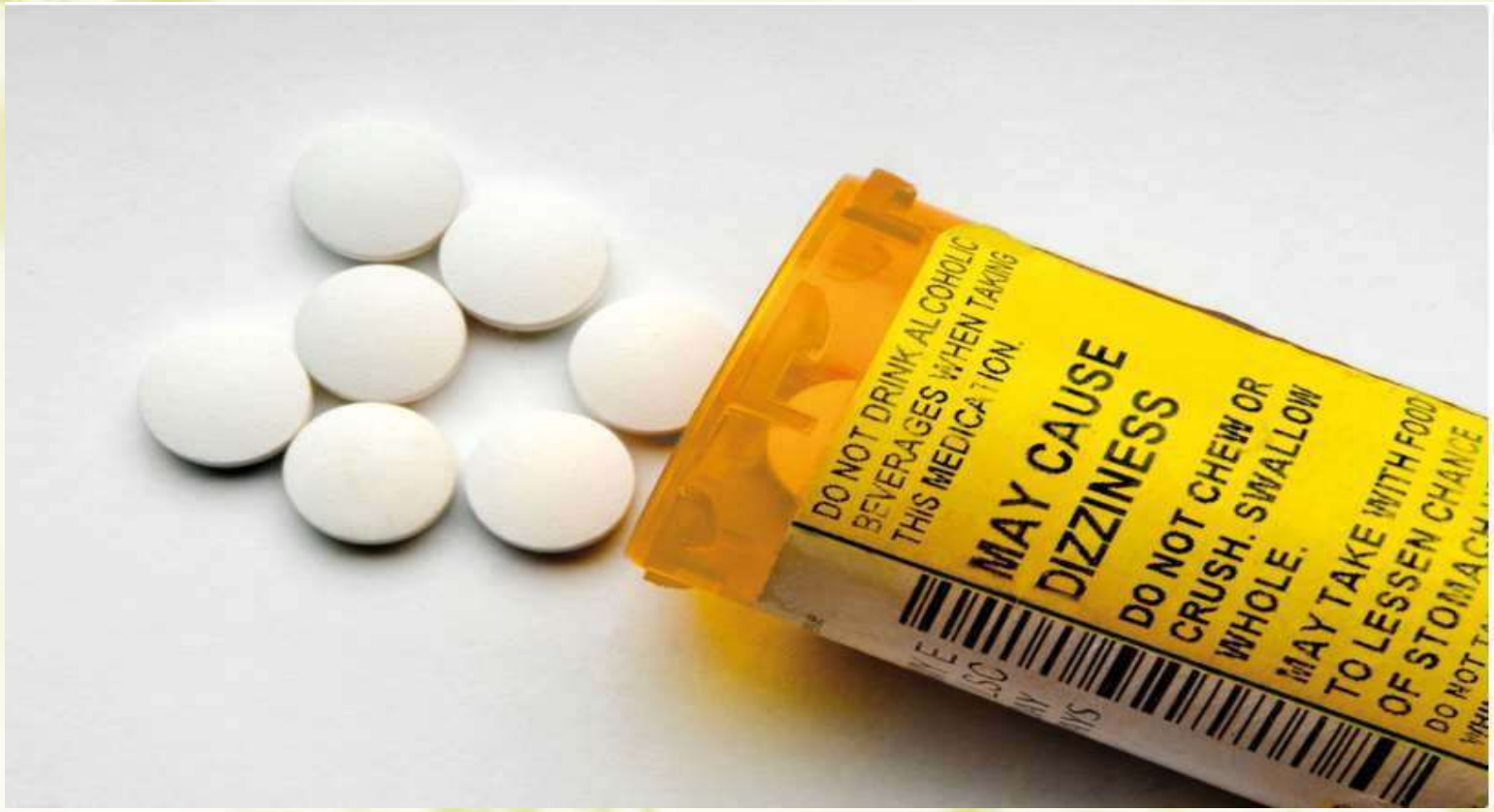
Safety comes first

La seguridad es lo primero

La sécurité d'abord

Thank you……..

ADVERSE DRUG REACTIONS



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I died last night of my physician.

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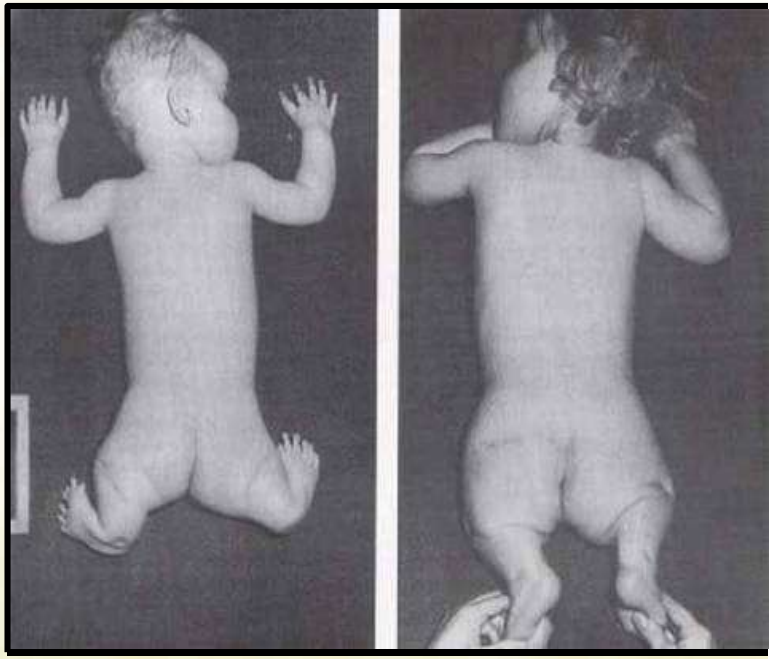
Establishment of the FOOD AND DRUG ADMINISTRATION (FDA), which was given the task of enquiring into the safety of new drugs before allowing them to be marketed.

.

- 1958: Thalidomide markated in West Germany as a non barbiturate hypnotic & for morning sickness during pregnancy based on animal toxicity report.



1959-61 thalidomide disaster

(4000-100000 case)

- In 1959 - 1961, it was reported in that there was an outbreak of **PHOCOMELIA** (**hypoplastic and aplastic limb deformities**) in the new born babies.

- The **THALIDOMIDE INCIDENT** led to a public outcry, to the institution all round the world of **DRUG REGULATORY AUTHORITIES**, to the development of a much more sophisticated approach to the preclinical testing and clinical evaluation of drugs before marketing, and to a greatly increased **awareness of adverse effect of drugs** and **methods of detecting them…**

Classification of ADRs

- Depending on….
- **Onset of event:** Acute (<60 minutes), Sub-acute (1-24 hrs) and Latent (>2 days)
- **Type of reaction:** (**Wills and brown)**
  Type A (Augmented), B (Bizarre), C (Chronic),
  D (Delayed), E (End of treatment)

- **Severity:** Minor, Moderate, Severe, Lethal ADRs

- **Others:** Side effects, Secondary effects, Toxic effects, Intolerance, Idiosyncrasy, Drug allergy, Mutagenicity, Photosensitivity, Drug Dependence, Drug Withdrawal Reactions, Teratogenicity, Carcinogenicity, Drug induced disease (Iatrogenic).

Type A (Augmented) reactions

- Reactions which can be predicted from the known pharmacology of the drug
- Dose dependent
- Can be alleviated by a dose reduction
- common
- Skilled management reduces their incidence.

E.g.

- Anticoagulants → Bleeding
- Beta blockers → Bradycardia
- Nitrates → Headache
- Prazosin → Postural hypotension

Type B (Bizarre) reactions

- Predictable where the mechanism is known, otherwise unpredictable for the individual, although the incidence may be known.
- Dose independent, rare
- Host dependent factors important in predisposition
- unwanted effects due to inherited abnormalities (idiosyncrasy) and immunological processes(drug allergy).
- These account for most drug fatalities.

E.g. Penicillin → Anaphylaxis,

Anticonvulsant → Hypersensitivity

Type C (Chronic)

- Reactions due to long time exposure.
- e.g. Analgesic neuropathy

  Dyskinesia with levodopa

Type D (Delayed) reactions

- Occur due to prolonged exposure.
- Can be due to accumulation.

E.g.

Carcinogenesis, or short term exposure at a critical time e.g.teratogenesis.

Type E (End of use) reactions

- Occur on withdrawal especially when drug is stopped abruptly

E.g.

- Phenytoin withdrawal → Seizures
- Steroid withdrawal → Adrenocortical insufficiency.
- opioid causing the withdrawal syndrome.

Types of ADRs……..

Type	Type of effect	characteristics	example
A	Augmented	Dose dependent predicted from the known pharmacology of the drug	Hypoglycaemia-insulin
B	Bizarre	Unpredictable Dose independent Rare,fatal	Anaphylaxis to penicillin
C	Chronic	Prolong treatment	Analgesic neuropathy
D	Delayed	After years of treatment	Antipsycotic –turdive dyskinesia
E	End of use	Withdrawal effect	GC withdrawal→ adrenocortical

Classification of ADRs :Depending on Severity

- **Minor ADRs:** No therapy, antidote or prolongation of hospitalization is required.
- **Moderate ADRs:** Requires change in drug therapy, specific treatment or prolongs hospital stay by atleast 1 day.
- **Severe ADRs:** Potentially life threatening, causes permanent damage or requires intensive medical treatment.
- **Lethal:** Directly or indirectly contributes to death of the patient.

Side effects

- Unwanted but often unavoidable, occur at therapeutic doses
- Predicted from the pharmacological profile of a drug
- Known to occur in a given percentage of drug recipients
- **E.g.**

  Atropine →dryness of mouth

  Promethazine (anti-allergic)→ sedation

  Codeine(anti-tussive)→constipation →Used in Traveller's diarrhoea

Side effects….(Drug discovery)

- Occasionally, "adverse" effects may be exploited to develop an entirely new indication for a drug.
- **E.g:**
- Unwanted hair growth during Minoxidil treatment of severely hypertensive patients → development of the drug for hair growth.

- Sulfonamides used as antibacterials were found to produce hypoglycemia and acidosis as side effects → development of Hypoglycemic Sulfonylureas…

- **Untoward effect –**

- Slight more serious effect than side effect produced with therapeutic dose.
- Seriously unpleasant.
- Harmful.
- e.g. Superinfection produced by broad spectrum antibiotic, vomiting by morphine in postoperative patients, hypokalamia by thiazide diuretics.

»Toxic effects

- Predictable
  - Dose dependent
  - Rebound response
- Excess pharmacological effect in high dose.
- These are known. Detected by pharmacologist

Unpredictable

- Allergy
- Idiosyncrasy

Not found in clinical trial.

Pharmacologist may not be able to detect this during study of drug development

Predictable toxic effects

- Dose dependent adverse effect may be –

- **Direct damaging effect to tissue** e.g. Paracetamol overdose leads to hepatotoxicity, Aminoglycoside (Gentamicin) causes nephrotoxicity.

- **Rebound response** – (due to R-upregulation) abrupt withdrawl after chronic use. e.g.propranolol stoppage leads to precipitation of MI, Glucocorticoid withdrawal leads to acute adrenal insufficiency.morphine – due to R supersensitivity.

Pharmacologically Predictable ADRs

Type	Example	Toxicity	Mechanism
Pharmaceutical	Phenytoin	Phenytoin toxicity (ataxia, nystagmus, etc)	Increase in bioavailability as a result of a change in formulation
Pharmacokinetic (can involve absorption, distribution, metabolism and excretion)	Digoxin	Digoxin toxicity (nausea, arrhythmias, etc)	Decreased elimination if renal function is impaired
Pharmacodynamic	Indomethacin	Left ventricular failure	Water and sodium retention
Genetic	Nortriptyline	Confusion	Reduced hepatic elimination as a result of a deficiency of CYP2D6
Drug-drug interactions (can involve any of the above processes)	Lithium-nonsteroidal anti-inflammatory drugs	Lithium toxicity	Inhibition of excretion of lithium

- **Excess pharmacological effect:** Result of excessive pharmacological action of the drug due to over dosage or prolonged use.
- e.g. Excess insulin-hypoglycemia even death from hypoglycemic shock

  Antihypertensive - hypotension

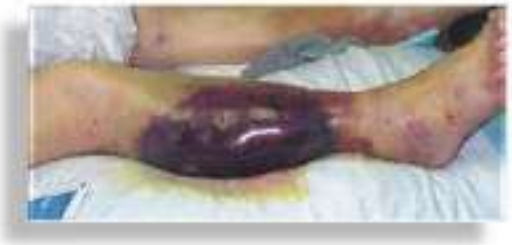
  Anticoagulant-

  severe bleeding.

Warfarin

- Number of users UK:
  600,000
- Dose (mg) range per day:
  0.5-20
- Fold variability in dose:
  40
- Major bleeding rate per 100-person years:
  2.6
- Ranking in ADR list:
  3

Approved for human use in 1954



Unpredictable toxic effects

- **Dose independent**
- Less than therapeutic dose may lead to toxic effect

Idiosyncrasy -

- unusual response to a drug due to genetic abnormality.
- Drug interacts with some unique feature of the individual, not found in majority subjects, and produces the uncharacteristic reaction.
- **E.g.**
- **Isoniazid:** N-Acetylation affects the metabolism of isoniazid
- **Slow *N*-Acetylation**: Isoniazid is more likely to cause peripheral neuritis.
- **Fast *N*-Acetylation**:cause hepatotoxicity in this group.

- **Succinylcholine** can produce **apnea** in people with abnormal serum cholinesterase. Their cholinesterase is incapable of degrading the succinylcholine, thus it builds up and depolarization blockade results.

- **Primaquine, Sulfonamides** induce acute hemolytic anemia in patients with **Glucose-6-Phosphate Dehydrogenase deficiency**.

--They have an inability to regenerate NADPH in RBC.G-6-p deficiency is most prevalent in blacks & Semitics. It is rare in Caucasians & Asians.

Drug allergy

- Acquired, altered reaction of the body to drug.
- Immunologically mediated reaction.
- occur even with much smaller doses
- Also called Drug hypersensitivity
- Not genetic,not occurred in all
- Occurs on reexposure
- E.g. penicillin→1st time →stimulate antibody →Ag-Ab reaction →allergy
- Chief organ: Skin, respiratory tract,GIT,Blood & blood vessels

Type of reaction	Time before clinical sign	Characteristics	Example
Anaphylactic (Immediate IgE-mediated anaphylaxis)	< 30 min	IgE binds to must cell or basophil,causes degranulation of must cell & basophil& release of reactive subs. histamine	**Penicillin anaphylaxis**
Cytotoxic (Antibody-Dependent Cellular Cytotoxicity	5 – 12 hr	Antigen cause formation of IgG or IgM antibodies to bind that . Drug forms an antigenic complex with the surface of the cell and combination with antibody activate complement system causing cell destruction.	**Hemolytic anemia**: Penicillin or Methyldopa **Thrombocytopenia** : Quinidine **SLE**:Hydralazine or Procainamide.
Immune complex mediated	8-10	antigen antibody form complexes that causes inflammation	**Steven-Johnson Syn Serum Sicknessdrome**
Cell mediated allergy(delayed type)	24 to 48 hrs	Antigen specific receptors develop on T-lymphocytes. Subsequent administration leads to local or tissue allergy.	Contact dermatitis Rejection of transplanted tissue

Certain tissues which are vulnerable

- **Hemopoietic system & bone marrow –**

- Quinine, Rifampicin, Sulfonamide, Thiazide – drug allergy (type II reaction) – Throimbocytopenia.
- Carbamazepine, Sulfonamide, carbimazole, clozapine (fatalneutropenia) - drug allergy (type II reaction) – Granulocytopenia.
- Chloramphenicol (idiosyncracy) -Aplastic anemia.
- Anti cancer, cytotoxic drugs -direct bone marrow depression
- primaquine, quinine, chloroquine, dapsone, sulfonamide(due to idiosyncracy) Methyldopa used in pregnancy – Hemolytic anemia.

➢ Liver damage/ Hepatic injury –

- Chloroform, Halothane, Enflurane – when given in repeated dose – hepatotoxicity – jaundice (so, before anesthesia H/O jaundice taken).
- Chlorpromazine, Flucloxacillin, OCP –(type II) cholestatic jaundice(causes edematous bile canaliculi-stasis of bile)
- INH, Rifampicin, Methyldopa – hepatocellular necrosis – jaundice (cause is unknown).
- Methotrexate, Alcohol – cirrhosis of liver.
- Paracetamol overdose (8 – 10 gm of paracetamol in 10 – 24 hours if taken) – toxic metabolite (Epoxide) – Hepatocellular necrosis.
- Minocycline (newer tetracycline) – Chronic Active Hepatitis.

- **Renal damage** –

- Phenylbutazone, Sulfonamide, Hydralazine – damage to glomerular membrane – Glomerulonephritis.

- Aminoglycoside (Gentamicin), Amphotericin (antifungal), High dose paracetamol, Cefalothin –Acute tubular necrosis.

- NSAID, Lithium, Penicillamine – long term use in rheumatoid arthritis – Acute interstitial nephritis.
- ACEI – Renal vascular damage.

Intolerance

- Appearance of characteristic toxic effects of a drug in an individual at therapeutic doses
- Converse of tolerance
- Indicates a low threshold of the individual
- **E.g.**
- Trifluprομazine (single dose) → Muscular dystonias in some individuals
- Carbamazepine (few doses) →Ataxia in some individuals
- Chloroquine (single tablet) → Vomiting and abdominal pain in some individuals

Tolerance –

- ↓ pharmacological effect on repeated administration of the drug.
- **Pharmacokinetic Tolerance**: ↑ the enzymes responsible for metabolizing the drug.

  e.g.Phenobarbitone induces metabolism of its own by increasing its own metabolic enzyme.
- **Pharmacodynamic Tolerance**: Cellular tolerance, due to down-regulation of receptors.
- **Depletion of stores** e.g.Amphetamine

Tachyphylaxis:

- When responsiveness diminishes rapidly after administration of a drug, the response is said to be subject to tachyphylaxis.

- Tyramine can cause depletion of all NE stores if you use it long enough, resulting in tachyphylaxis.

Photosensitivity

- Cutaneous reaction resulting from drug induced sensitization of the skin to UV radiation. The reactions are of two types

- **Phototoxic:** Drug or its metabolite accumulates in the skin, absorbs light and undergoes a photochemical reaction resulting in local tissue damage (sunburn-like, i.e., erythema, edema, blistering, hyper pigmentation)

  E.g. Tetracyclines (esp. Demeclocycline), and Tar products, Nalidixic acid, Fluoroquinolones, Sulfones etc

- **Photoallergic:** Drug or its metabolite induces a cell mediated immune response which on exposure to light (longer wave length) produces a papular or eczematous contact dermatitis like picture.

  E.g. Sulfonamides, Sulfonylureas, Griseofulvin, Chloroquine, Chlorpromazine

Drug dependence

- Drugs capable of altering mood and feelings are liable to repetitive use to derive euphoria, withdrawal from reality, social adjustment, etc.
- **Psychological dependence:** Individual believes that optimal state of well being is achieved only through the actions of the drug.
- **E.g.** Opioids, Cocaine.
- **Physical dependence:** Altered physiological state produced by repeated administration of a drug which necessitates the continued presence of the drug to maintain physiological equilibrium. Discontinuation of the drug results in a characteristic withdrawal (abstinence) syndrome.
- **E.g.** Opioids, Barbiturates, Alcohol, Benzodiazepines

Drug dependence….

- **Drug abuse:** Use of a drug by self medication in a manner and amount, that deviates from the approved medical and social patterns in a given culture at a given time.

  Drug abuse refers to any use of an illicit drug.

- **Drug addiction:** Compulsive drug use characterized by overwhelming involvement with the use of a drug.

- **Drug habituation:** Less intensive involvement with the drug, withdrawal produces only mild discomfort.
- Habituation and addiction imply different degrees of psychological dependence.

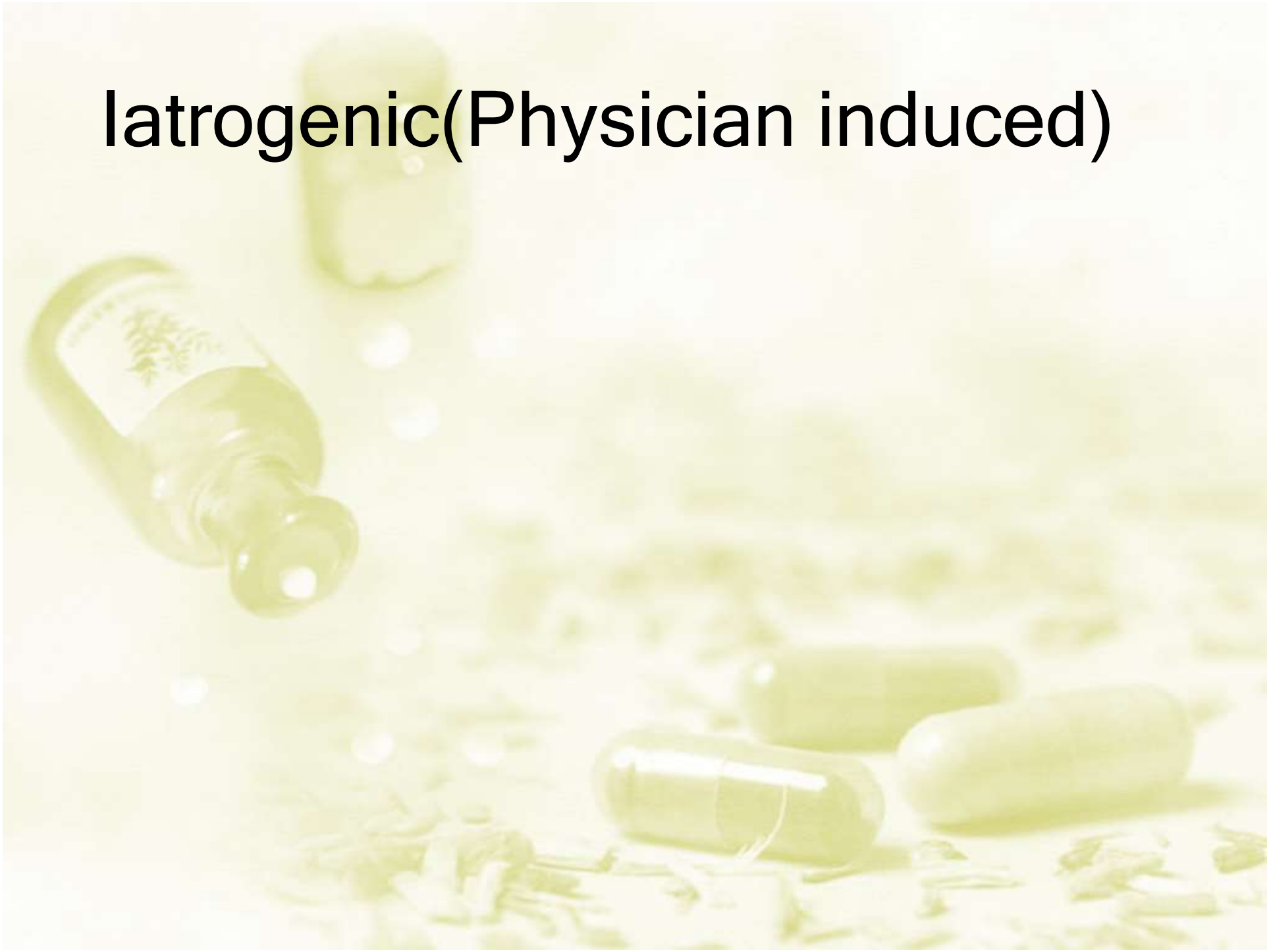
Mutagenecity and Carcinogenicity

- Capacity of a drug to cause genetic defects and cancer respectively.
- Chemical carcinogenesis generally takes several (10-40) years to develop.
- Unpredictable

e.g.

- Estrogen- Endometrial carcinoma.
- OCP- Ca cervix, breast Ca
- Iron S/C or I/M – blackening of area – increase incidence of sarcoma (cause is unknown).
- Anticancer drug.

Iatrogenic(Physician induced)



Teratogenicity

- Capacity of a drug to cause foetal abnormalities when administered to the pregnant mother.
- Drugs can affect the foetus at 3 stages:
    1. Fertilization and implantation (Conception to 17 days): failure of pregnancy which often goes unnoticed.
    2. Organogenesis(18 days to 55 days): most vulnerable period, deformities are produced.
    3. Growth and development (> 56 days): developmental and functional abnormalities can occur. **E.g:**
- Thalidomide →Phocomelia, multiple defects
- Anticancer drugs → Cleft palate, hydrocephalus, multiple defects

FDA Pharmaceutical Pregnancy Categories	
Category A	Adequate and well-controlled human studies demonstrate no risk.
Category B	Animal studies demonstrate no risk, but no human studies have been performed. OR Animal studies demonstrate a risk, but human studies have demonstrated no risk.
Category C	Animal studies demonstrate a risk, but no human studies have been performed. Potential benefits may outweigh the risks.
Category D	Human studies demonstrate a risk. Potential benefits may outweigh the risks.
Category X	Animal or human studies demonstrate a risk. The risks outweigh the potential benefits.

Drugs known to be teratogenic

- Anticancer drugs – Methotrexate – multiple deformity.
- Steroid – cleft palate and other.
- Oral anticoagulants – bony abnormality (Hypoplastic nasal structures), optic atrophy, mental retardation.
- Oral hypoglycemic agents - multiple deformity.
- Androgenic hormone – virilization, hermaphrodite, lid retraction.
- Tetracycline – inhibit bony growth.

Cont'd

- Trimethoprim – cleft palate.
- Phenytoin, carbamazepine, valproate - Malformation of fingers,cleft palate,neural tube defect(spina bifida)
- Diethylstilbestrol - Oral contraceptive is no longer used because it causes reproductive cancers in daughters born to mothers taking the drug.
- Androgen- virulization of female fetus
- Aminoglycosides, Chloroquine – Deafness.

Teratogens in first trimester

- Phenytoin, carbamazepine, valproate - neura tube defects (spina bifida)
- lithium – cardiac malformations
- Warfarin - bone deformation, chondrodysplasy, CNS defects
- Heparin (demineralization of bone in mother – switch to LMW)
- Retinoids-def. CNS, heart, limbs, liver
- oncologic drugs (fluorouracil, metotrexate, cyclofosfamid, busulfan)

Drugs cannot be given in last trimester

- Antithyroid drugs: Hypothyroidism in neonates
- Streptomycin - Ototoxicity
- Morphine: Respiratory depression
- Chloroquine: Retinopathy of fetus
- Aspirin: delay labour pain.

Individual variation in response to drug

- Variation due to age, sex, body weight, surface area, nutrition, alcoholic, cigarette smoking, pregnancy, genetic factor, environment, and pathological condition.

- 4 general mechanism:

- A) **Alteration in concentration of drug that reaches the receptors** –
- rate of absorption of a drug
- distributing it through body compartments
- clearing the drug from the blood.

- B) **Variation in concentration of an endogenous receptor ligand** –
- variability in responses to pharmacological antagonist.
- propranolol will markedly slow the HR of a patient whose endogenous catecholamine are elevated (as in pheochromocytoma), but will not affect the resting HR of a well trained marathon runner.
- C) **Alteration in number or function of receptor** – ↑ or ↓ in number or alteration in efficiency of coupling of receptor to distal effector mechanism – change in responsiveness.

e.g.Thyroid hormone increase number of **β** receptor in heart and increase sensitivity of cardiac muscle to catecholamine – tachycardia of thyrotoxicosis.

- **D) Changes in components of response distal to the receptor** – Response depend on the functional integrity of biochemical process in the responding cell and physiological regulation by interacting organ system.

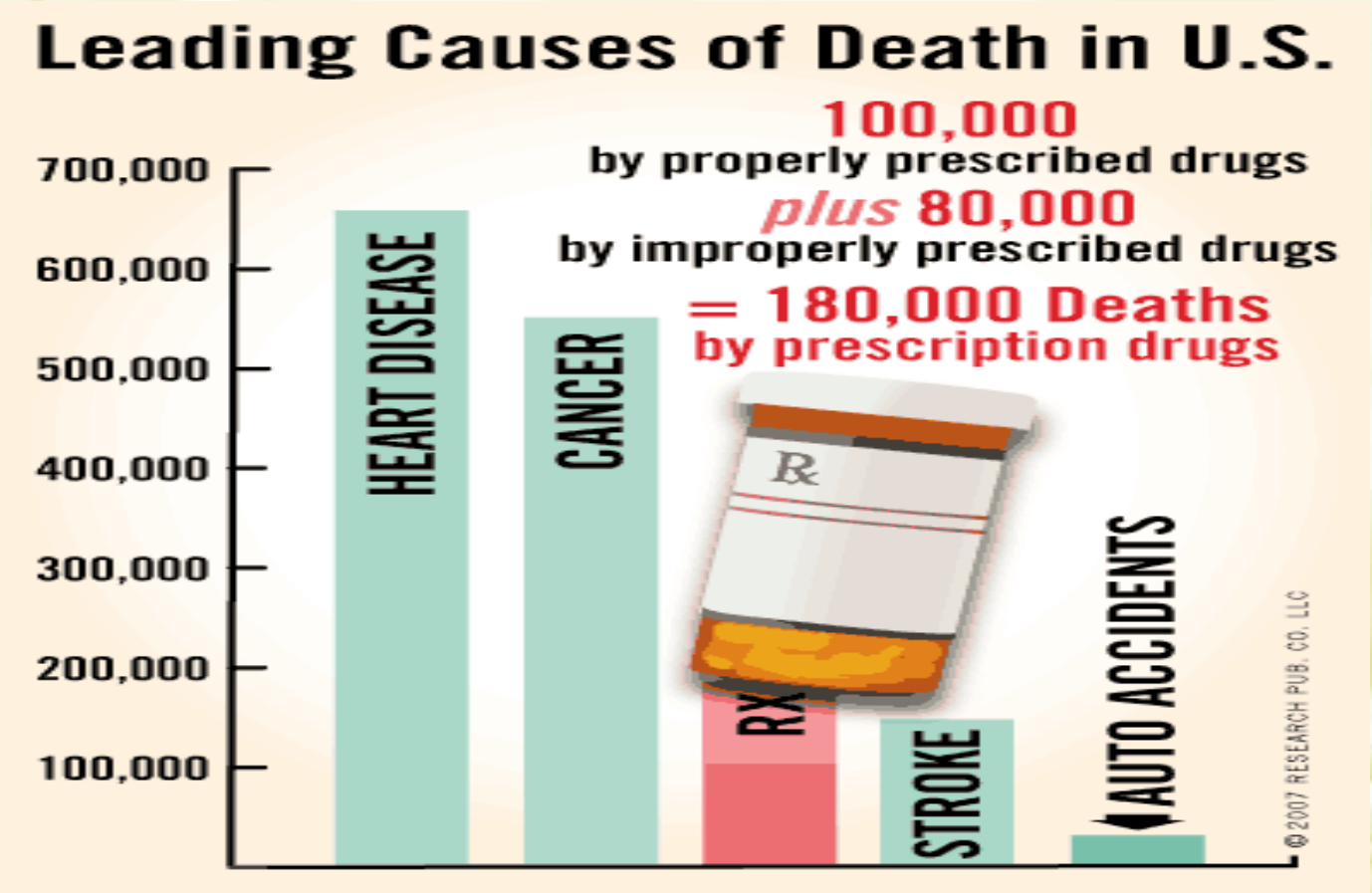
Cont'd…

- Medicines are supposed to save lives

  Dying from a disease is sometimes unavoidable; dying from a medicine is unacceptable. Lepakhin V. Geneva 2005

Cont'd…

- Among the Leading cause of death-



Cont'd…

- **ADRs are expensive !!**

Cost of ADRs in the US:

Cost of drug related morbidity and mortality exceeded $177.4 billion in 2000 (*Ernst FR & Grizzle AJ, 2001: J American Pharm. Assoc)*

ADR related cost to the country exceeds the cost of the medications themselves.

Cont'd…

- Ethics:

To know of something that is harmful to another person who does not know, and not telling, is unethical.

- No medicine is risk free, Vigilant assessment of the risks and benefits of medicine promote safety.

Aims of knowing ADRs

- To improve patient care and safety
- To improve public health and safety
- To contribute to the assessment of benefit, harm, effectiveness and risk of medicine.

Adverse drug reactions[ADRs] monitoring

- Monitoring centre:

  -WHO collaborating centre for international drug monitoring , Uppsala Monitoring Centre, Sweden.

  - Established in1968.

- In Bangladesh:

  - Directorate General of Drug Administration.

  105-106, Motijheel Commercial Area, Dhaka-1000, Bangladesh.

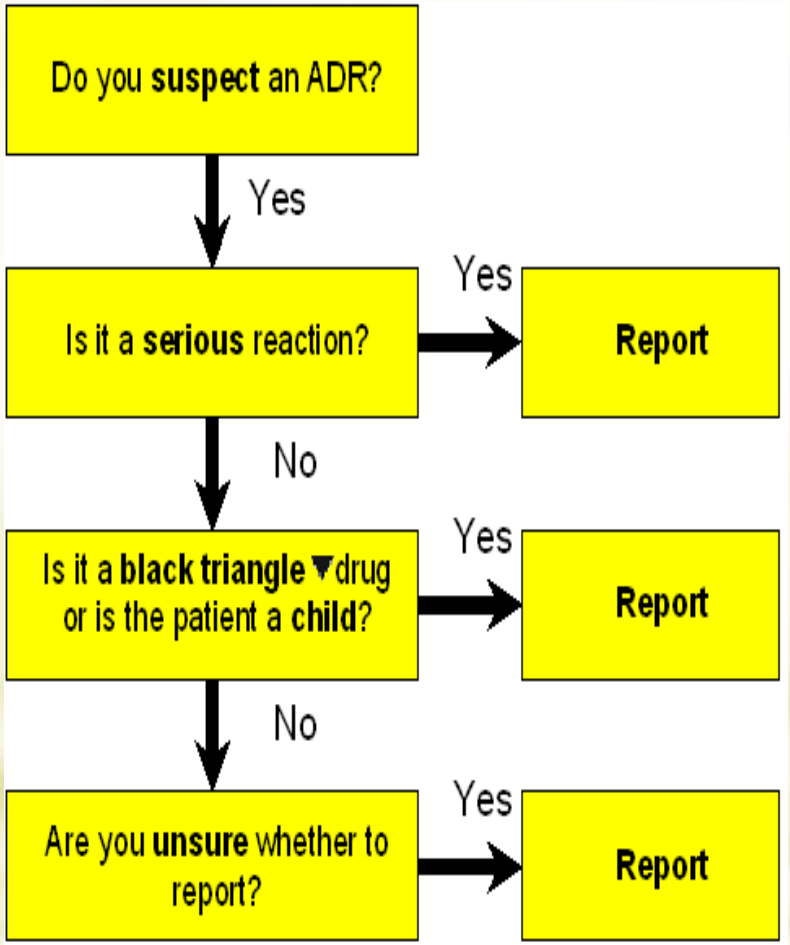
Cont'd…

- Monitoring of ADRs:
  - Clinical trial monitoring
  - Prescription event monitoring
  - Yellow card system

ADRs reporting:

- Who to report:

- All health care professionals.



- What to report:

-Apparent ADRs previously unknown to the reporters

-Serious ADRs

-**All suspected ADRs** to new drugs

Cases of suspected dependence

Cont'd…

- How to report:

  - ADRs form

  - Assessment tool: Naranjo scale

- Where to report:

  - National body (Directorate General of Drug Administration.
    105-106, Motijheel Commercial Area Dhaka-1000, Bangladesh

Safety comes first

La seguridad es lo primero

La sécurité d'abord

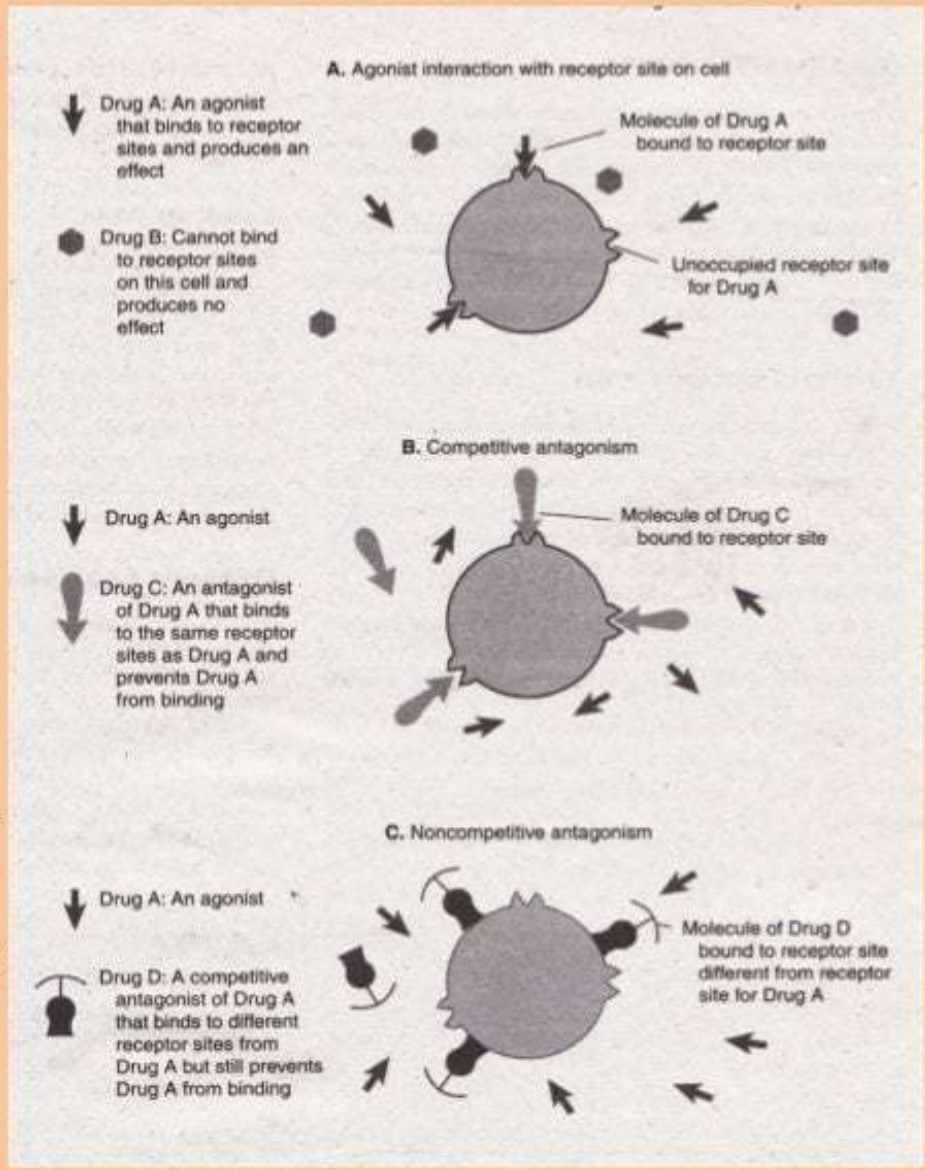

Thank you……..

Drug –
WHO scientific group definition

Any substance or product that is used/ intended to be used to modify or explore physiological systems or pathological systems or pathological states for the benefit of the recipient

Drug Attachment

- Medication chemically binds to specific sites called "receptor sites"
  - **Agonist**-chemical fits at receptor site well
  - **Antagonist**- a chemical blocks another chemical from getting to a receptor
  - **Partial agonist** - attach to the receptor but only produce a small effect



Basics of Drug Action

- ***Desired action*** – the expected response of a medication

- ***Side effects*** –known and frequently experienced, expected reaction to drug.

- ***Adverse reaction*** –unexpected, unpredictable reactions that are not related too usual effects of a normal dose of the drug.

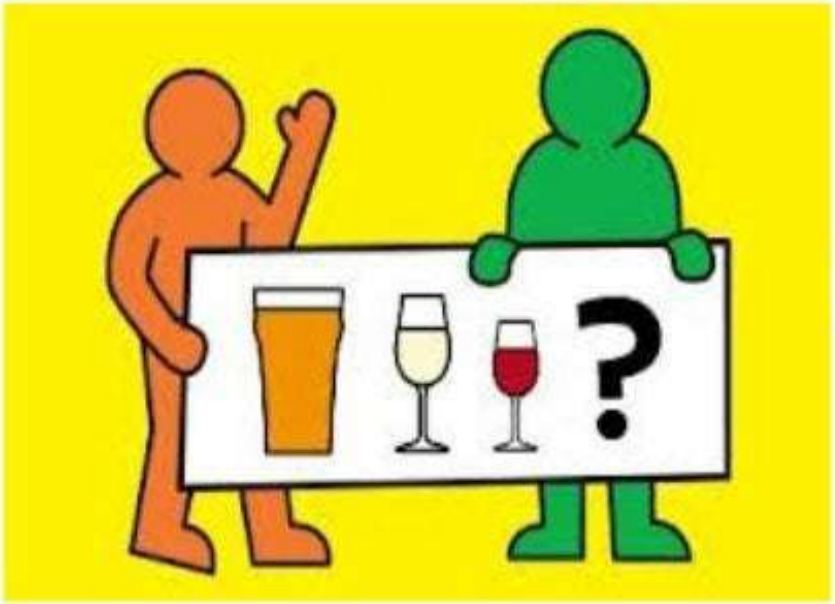
Drug Interaction

- Takes place when one drug alters the action of another drug.
- Some are helpful but often produce adverse effects.

Common Drug Interactions

- **Additive effect-** takes place when 2 drugs are given together & double the effect is produced.

Alcohol + aspirin= Pain relief



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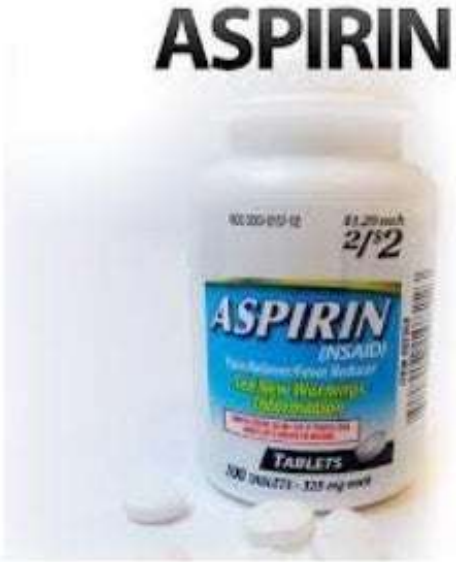


Common Drug Interactions

- **Antagonist**- a chemical blocks another chemical from getting to a receptor
- **Antagonistic effect- takes place when 1 drug interferes with the action of another drug.**
- **Eg. Protamine sulpha to counteract heparin toxicity**

Common Drug Interactions

- **Displacement effect -** takes place when 1 drug replaces another at the drug receptor site, increasing the effect of the 1st drug.

Common Drug Interactions

- **Incompatibility** –occurs when 2 drugs mixed together in a syringe produce a chemical reaction so they cannot be given.

  e.g. Protamine sulfate & vitamin K

Common Drug Interactions

- **Interference**- occurs when 1 drug promotes the rapid excretion of another, thus reducing the activity of the 1st.

- **Synergistic effect** takes place when the effect of 2 drugs taken at the same time is greater than the sum of each drug given alone.

E.g. combining diuretics & adrenergic blockers to lower the BP

Pharmaco-dynamics: Actions, therapeutic Adverse, toxic.

Pharmacotherapeutics: Types of Therapies

- Acute therapy
- Maintenance therapy
- Supplemental therapy
- Palliative therapy
- Supportive therapy
- Prophylactic therapy

Pharmacotherapeutics: Monitoring

- The effectiveness of the drug therapy must be evaluated.
- One must be familiar with the drug's
- intended therapeutic action (beneficial)
- and the drug's unintended but potential side effects (predictable, adverse drug reactions).

Pharmacotherapeutics: Monitoring

- Therapeutic index
- Drug concentration
- Patient's condition
- Tolerance and dependence
- Interactions
- Side effects/adverse drug effects

Pharmacotherapeutics: Monitoring

Therapeutic Index

- The ratio between a drug's therapeutic benefits and its toxic effects

Pharmacotherapeutics: Monitoring

Tolerance

- A decreasing response to repetitive drug doses

Dependence

- A physiologic or psychological need for a drug

Pharmacotherapeutics: Monitoring

Interactions may occur with other drugs or food

- Drug interactions: the alteration of action of a drug by:
  - Other prescribed drugs
  - Over-the-counter medications
  - Herbal therapies

Pharmacotherapeutics: Monitoring

Interactions

- Additive effect
- Synergistic effect
- Antagonistic effect
- Incompatibility

Pharmacotherapeutics: Monitoring

Medication Misadventures

Adverse drug events

- ALL are preventable
- Medication errors that result in patient harm

Adverse drug reactions

- Inherent, not preventable event occurring in the normal therapeutic use of a drug
- Any reaction that is unexpected, undesirable, and occurs at doses normally used

Pharmacotherapeutics: Monitoring

Some adverse drug reactions are classified as side effects.

- Expected, well-known reactions that result in little or no change in patient management
- Predictable frequency
- The effect's intensity and occurrence is related to the size of the dose

Pharmacotherapeutics: Monitoring

Adverse Drug Reaction

An undesirable response to drug therapy

- Idiosyncratic
- Hypersensitivity reactions
- Drug interactions

Pharmacotherapeutics: Monitoring

Iatrogenic Responses

Unintentional adverse effects that are treatment-induced

- Dermatologic
- Renal damage
- Blood dyscrasias
- Hepatic toxicity

Pharmacotherapeutics: Monitoring

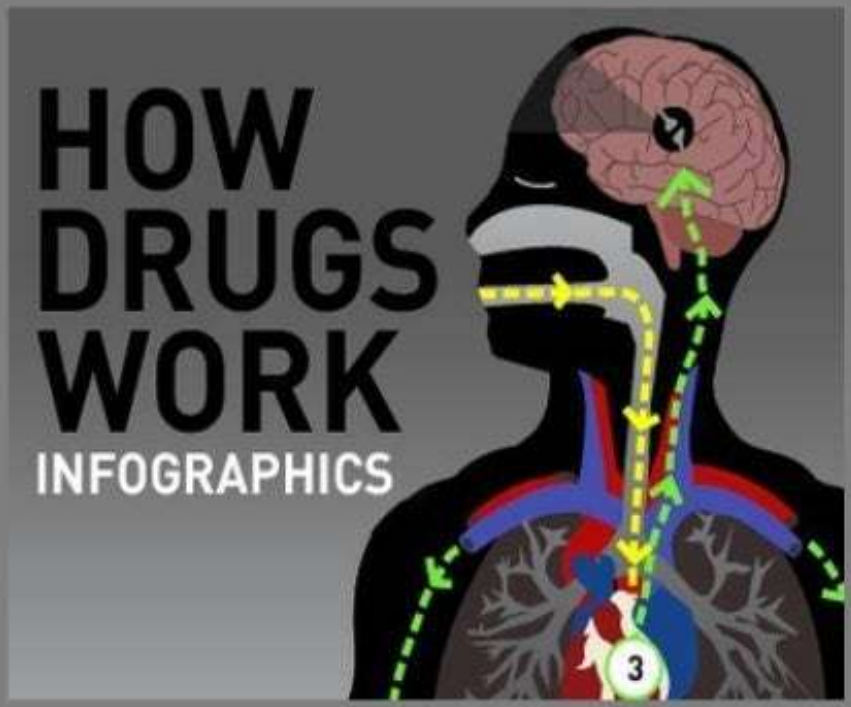
Other Drug-Related Effects

- Teratogenic
- Mutagenic
- Carcinogenic

Pharmacokinetics: Absorption, distribution, metabolism, interaction, excretion.

Pharmacokinetics

Absorption
Distribution
Metabolism
Excretion
Bioavailability



Factors influencing the efficacy of a drug are:

- The route of Administration
- The rate of Absorption
- The distribution of the drug to the required site
- The rate of biotransformation or metabolism
- The presence of active metabolites
- The rate of excretion

Absorption

To be effective a drug must be absorbed - except for topical and IV

This means drugs have to cross cell membranes

The ability of the drug to cross the cell membrane is influenced by its solubility in water or fat, its size and shape

Drug Absorption of Various

Oral Preparations

Liquids, elixirs, syrups	Fastest
Suspension solutions	↓
Powders	↓
Capsules	↓
Tablets	↓
Coated tablets	↓
Enteric-coated tablets	Slowest

Absorption

- Drugs cross membranes by:
  - Filtration - only small water-soluble molecules which flow through the hydrophilic pores
  - Passive Transport - Diffusion i.e. from high concentrations to low concentrations
  - Active Transport - Energy and carriers are required to move non-fat soluble substances across the cell membrane e.g against concentration gradient

Absorption

 # IV injection

 # delivered straight to bloodstream
 # rapid action

 # *All other routes*

 # need to be *absorbed* from site of administration
 # speed of action depends on *absorption rate (ka)*

Absorption

Factors affecting the absorption rate (*ka*)

#Route of administration

Blood supply to the site of absorption

Formulation of the drug

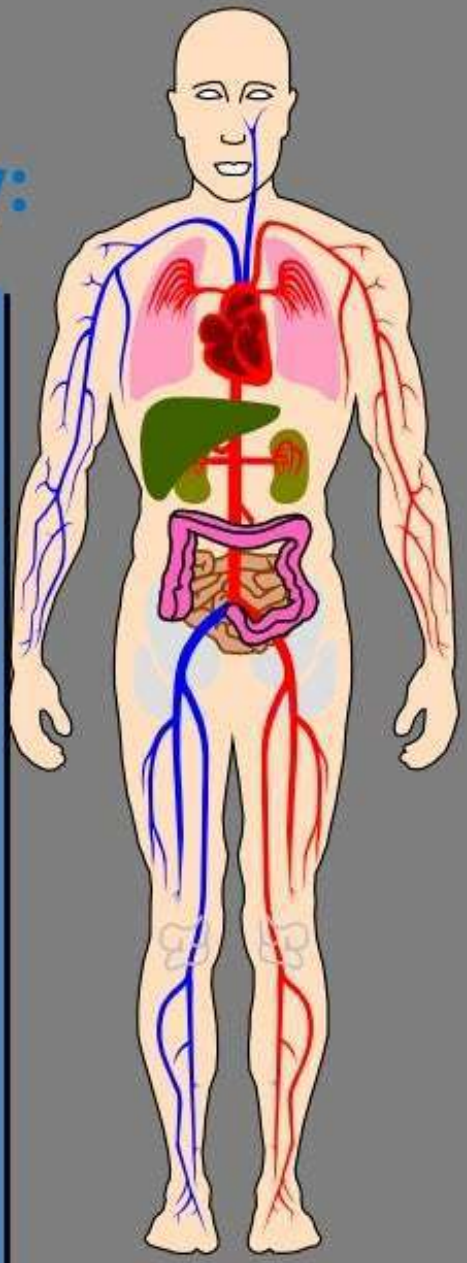
Gut transit time

pH in the gut

Solubility of the product

Distribution

Drug in bloodstream is *distributed* to body:



Central compartment

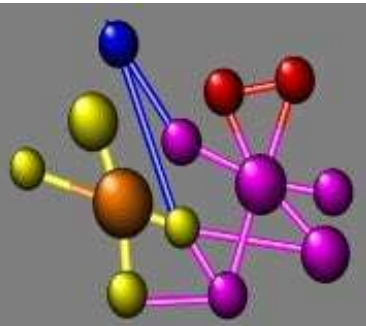
-(major organs & blood vessels)

- **– low lipid solubility (hydrophilic)**
- **– low volume of distribution (low Vd)**

Peripheral compartment

- ***(skin & fat stores)***
  - **– high lipid solubility (lipophilic)**
  - **– high volume of distribution (high Vd)**

Distribution



Plasma protein binding:

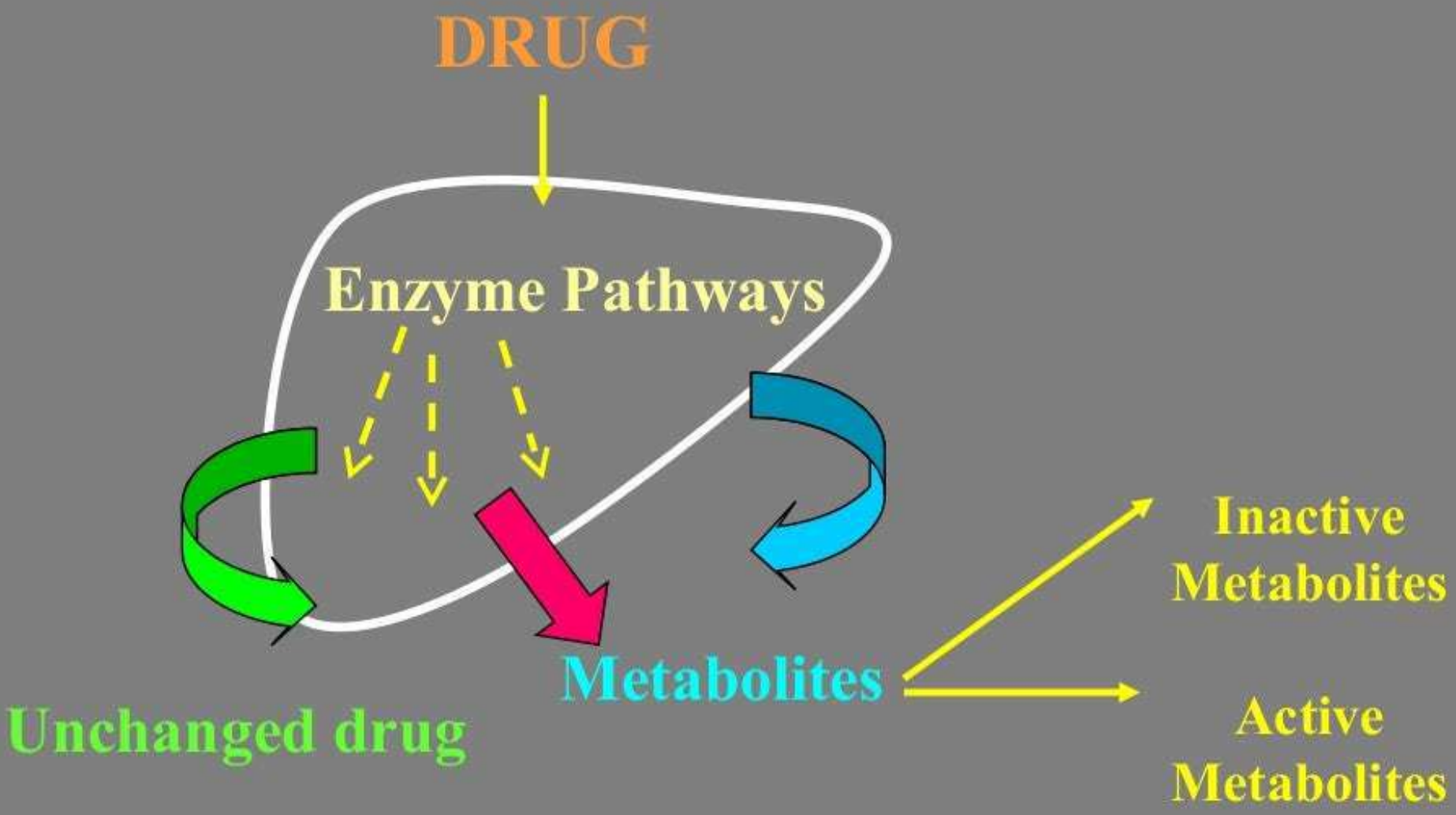
#Only 'free fraction' can move to target site (e.g. 80% bound / 20% free)

#Dynamic process i.e. as free drug moves into tissues, protein-bound drug is released into plasma to maintain ratio *(ratio of 'free fraction' : 'plasma protein bound' remains constant)*

#Drugs vary in the degree to which they are plasma protein bound (< 99.9%)

Metabolism

Major organ of metabolism - LIVER



Metabolism

Major organ of metabolism - LIVER

- **Active metabolites :**
  Clinical or side effects
- **Inactive metabolites**

N.B. Patients with hepatic impairment may require:

- higher doses (where metabolism ➡ active metabolites)

- lower doses (where metabolism ➡ inactive metabolites)

Metabolism

Factors affecting metabolism
(i.e. compete for enzyme pathways in the liver)

Genetic factors

Other drugs *e.g. Cimetidine / Ciproxen*

Smoking

#Enzyme induction/inhibition(CYP450/others)

Some foods

#Liver disease

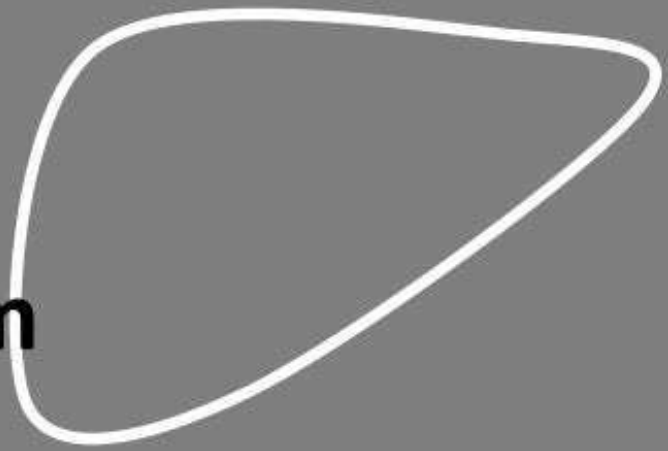
#Age

First-Pass Effect

The metabolism of a drug and its passage from the liver into the circulation.

- A drug given via the oral route may be extensively metabolized by the liver before reaching the systemic circulation (high first-pass effect).
- The same drug—given IV—bypasses the liver, preventing the first-pass effect from taking place, and more drug reaches the circulation.

Metabolism



First pass metabolism

Gut → **Liver** → **Body**

(Portal vein) *(General circulation)*

 # the breakdown of a drug in the liver before it reaches the site of action

#oral dose may need to be higher than parenteral dose

 # Prodrug

First Pass (Presystemic) Metabolism

Metabolism of orally administered drugs in a single passage thru the gut wall and (principally) the liver.

Drugs for which presystemic elimination is significant – Isosorbide dinitrate, Propranolol etc.

First pass elimination is reduced in severe hepatic cirrhosis

Clinical Pharmacology, Laurence,, 1997, p92

First-Pass Effect

- Routes that bypass the liver:
  - Sublingual
  - Buccal
  - Rectal
  - Intravenous
  - Intranasal
  - Transdermal
  - Vaginal
  - Intramuscular
  - Subcutaneous
  - Inhalation

  *Rectal route undergoes a higher degree of first-pass effects than the other routes listed.

Elimination

Elimination

=

Metabolism

+

Excretion

Excretion

#The process by which drug is removed from the body.

Primary

via the kidneys (in urine) also

via the gut (faeces), the skin (sweat), the lungs (breath), saliva

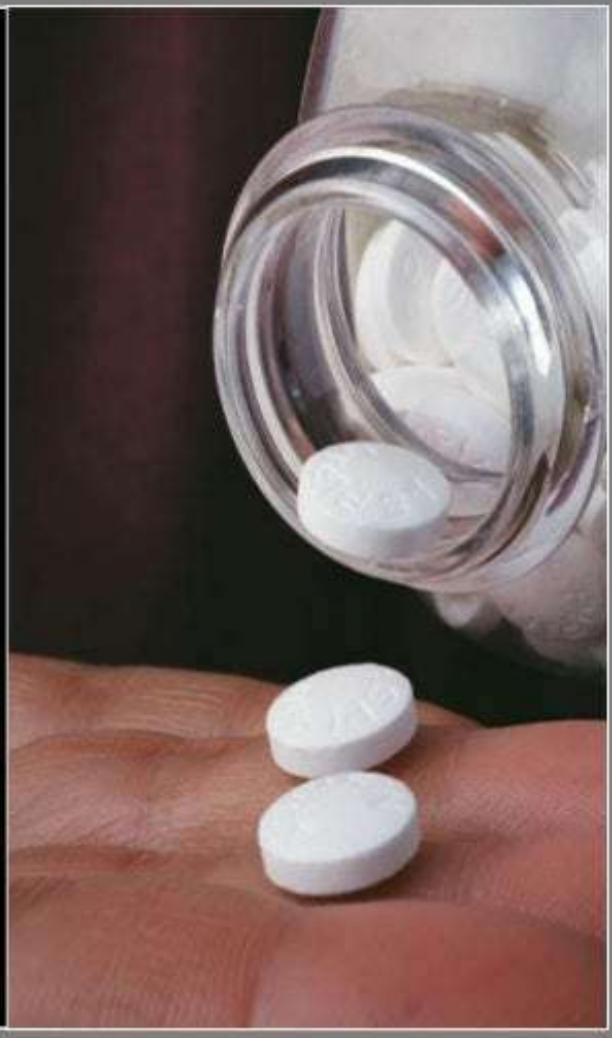
 # N.B. Patients with renal disease or dysfunction (elderly/heart disease) may require lower doses as the drug will be retained for longer than in 'normal' patients

Bioavailability

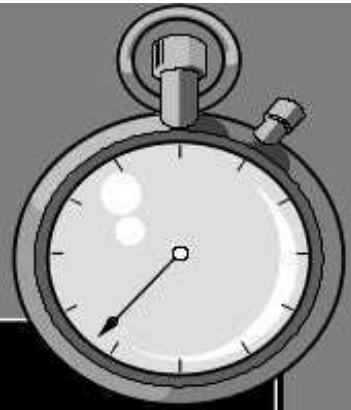
- It is defined as the extent to which active ingredients *are absorbed and transported* to sites of action.
- ***Factors***
  1. Drug solubility
  2. Pharmaceutical formulation
  3. pH
  4. Food

Dose regimes

- *Factors determining Dosage :*
  - Half Life
  - Age
  - Sex
  - Body Weight and Surface area
  - Tolerance
  - Specific disease



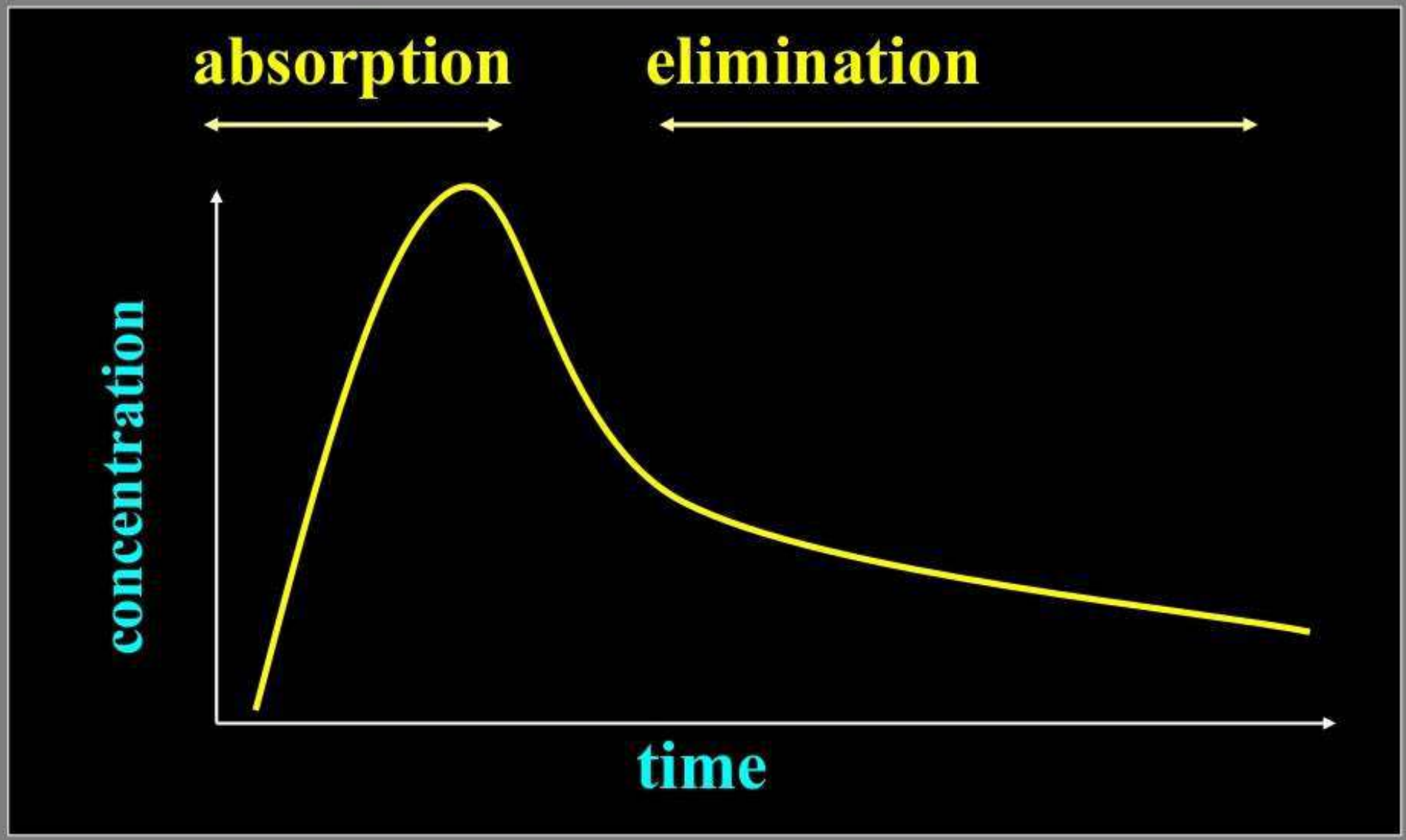
Dose regimes



- OD *(mane / nocte)*
- BD *(12 hourly)*
- TDS *(8 hourly)*
- QDS *(6 hourly)*
- PRN *(as required)*
- Depot *(weekly / monthly / quarterly)*
- Stat *(immediately)*

Plasma profiles

- Single dose plasma profile

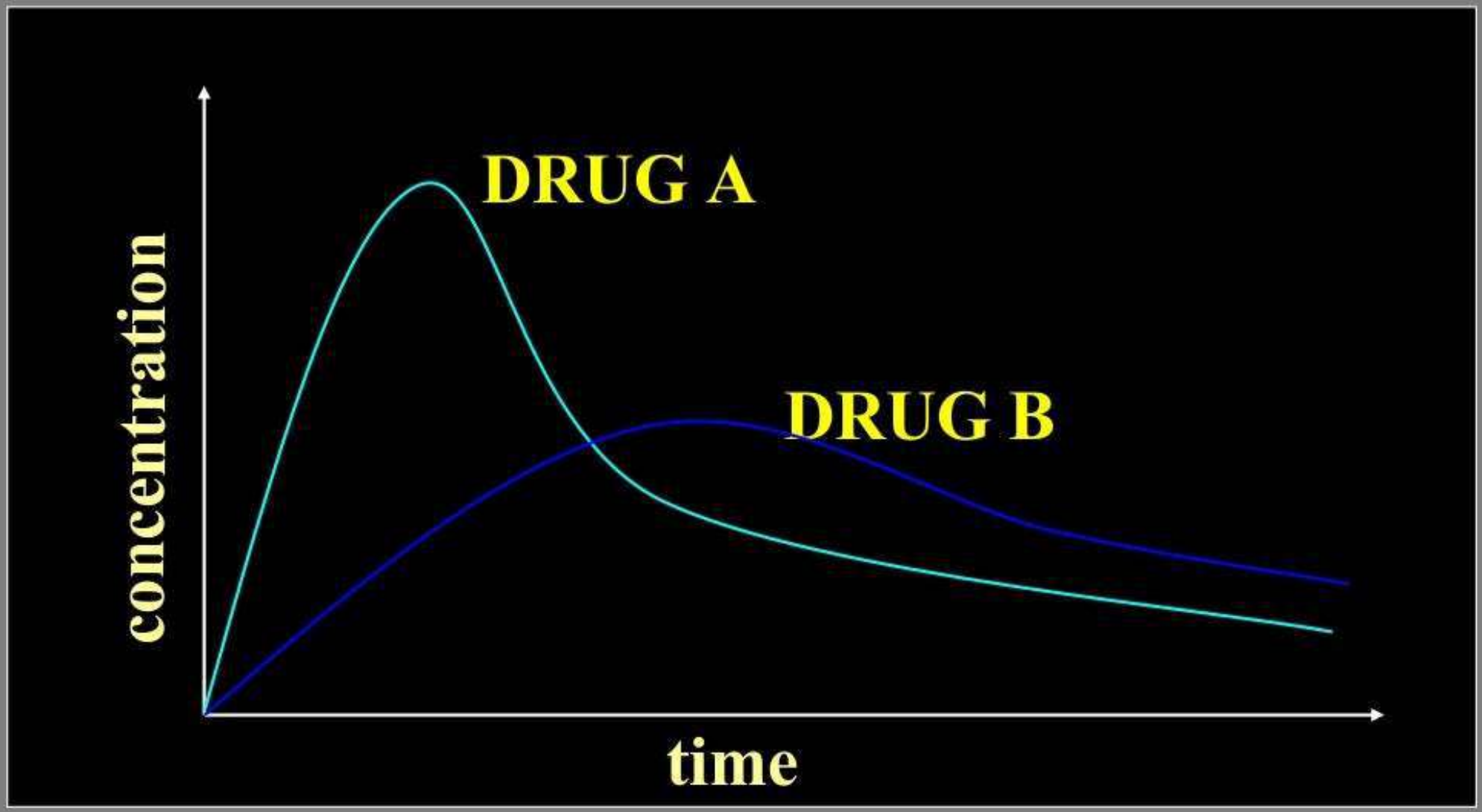


Plasma levels

- Constant plasma levels only with constant I.V. infusion.
- Peaks & troughs in plasma levels with all other routes of administration (due to absorption & elimination)
- Dose regimes are calculated to maintain therapeutic plasma levels

Plasma profiles

Dose plasma profile



Half-life

- Refers to the time required for the body to eliminate 50% of the drug.
  - It is important in planning the *frequency* of dosing.
- Short half-life (2-4 hours) : needs to be given frequently
- Long half life: (21-24 hours): requires less frequent dosing

Note: It takes 5 to 6 half lives to eliminate approximately 98% of a drug from the body

Half-life

- Liver and kidney disease patients may have problems of excreting a drug.
- Difficulty in excreting a drug increases the half-life and increases the risk of toxicity.
- Implication: may require frequent diagnostic tests and measuring renal and hepatic function.

Half Life = ½

Time in which a measure (concentration effects) declines by one half

Measured in 3 ways : -

1) Plasma half life
2) Biological effect half life
3) Biological half life

Plasma – Half Life

- Time in which the plasma concentration falls by one half
- Influenced by various factor – tissue diffusion, protein binding , renal excretion

Biological effect half life

- Time in which a the pharmacological effect of the drug, and of any of the active metabolites, has declined by one half
- Eg. For antibiotics, varies with each infection

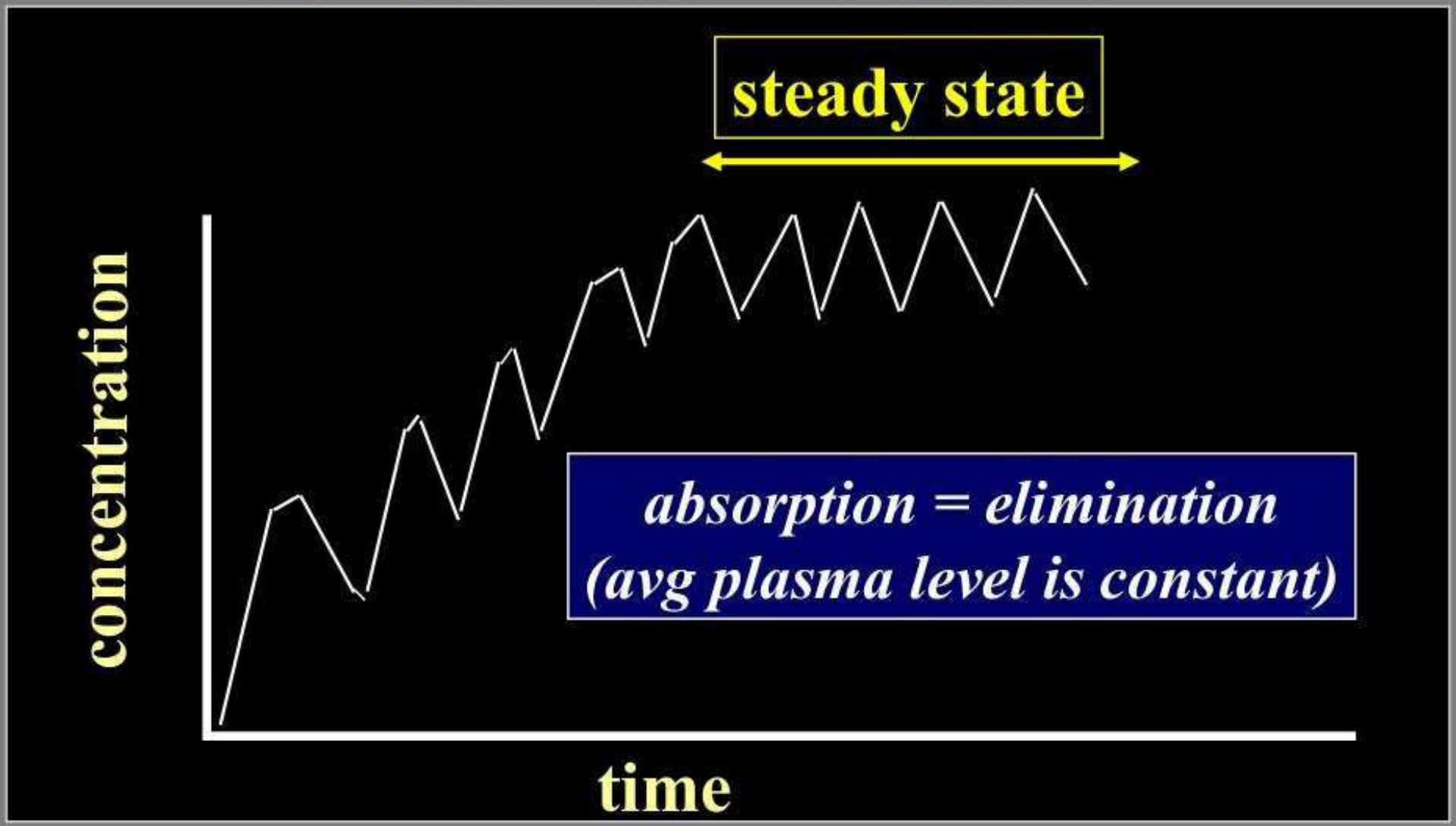
Biological half life

Time in which a the total amount of drug in the body after equilibrium of plasma with other compartments (fat, muscle) is halved

Measured using radioisotopes, rates of excretion

Plasma profiles

Multiple dose plasma profile



Steady state concentration

- Plateau concentration
- Rate of input of drug to the body is matched by rate of elimination
- Has to be in therapeutic range to maintain effect
- Affected by half life of drug

Therapeutic Index/Ratio

- Devised by Ehrlich
- Maximum tolerated dose / minimum curative dose
- Gives indication of safety
- Especially applicable to antibiotics
- Defines safety in relation to efficacy

Review: Routes and principles of administration of drugs

Routes of Administration

To be effective a drug must :

- Be present in an active form
- At the correct site
- At the right concentration
- For the right duration of time

The formulation of the product for each delivery route is vital to ensure optimal activity and consistent delivery

Thus choose the right Route of Administration and Formulation

Route of Administration & Formulation (Dosage forms)

Oral	**Tablets / Capsules / Elixirs / Syrups / Suspensions /Granules / Powders / Caplets / Drops**
Parenteral	**Intra-dermal / Subcutaneous / Intra-muscular / Intra-venous / Intra-thecal / Epidural / Spinal / Depot**
Sub-lingual / buccal	**Tablets / Sprays**
Inhaled	**Aerosol inhalers / Dry powder inhalers / Nebuliser solutions / Spacers**

Route of Administration & Formulation (Dosage forms)

Rectal (PR)	→	Suppositories / Enemas
Vaginal (PV)	→	Pessaries / Creams / Vaginal tablets
Transdermal	→	Creams / Gels / Patches
Topical	→	Creams / Lotions / Gels / Nasal sprays / Shampoos / Suppositories / Peccaries

Oral Route

- Absorption hampered by food
- Drug may be destroyed (insulin)
- Drug may not be absorbed (Streptomycin)
- First pass metabolism

Sublingual route

- Abundant blood supply
- Quick effect
- No degradation by digestive juices
- No first pass metabolism
- Irritation of mucous membranes

Rectal Route

Rich blood supply
No irritation of GIT
Useful in patients who cannot swallow/vomiting / uncooperative patient

Effects of Protein Binding on Drugs

Assists oral absorption of a drug

Delays metabolic degradation

Delays excretion

Diminishes penetration into the CNS

Significance – acts as reservoir and thereby prolongs action of drug

Pharmaclogy & Pharmacotherapeutics, Satokar, 1997, p14

Enteric Coating

Pills or tablets are coated with substances which resist the acid juice of the stomach but permit disintegration in intestinal juices.

- # To prevent gastric irritation & alteration of drug in stomach
- # To get desired concentration of the drug in small intestine
- # To retard the absorption of the drug.

Pharmaclogy & Pharmacotherapeutics, Satokar, 1997, p5

SR Preparations
SR = TR = XL

Sustained release or time release preparations for oral use

- **Release the active drug over an extended period of time.**
- **Particles of drug covered with coatings which dissolve at different time intervals.**

Pharmacology & Pharmacotherapeutics, Satokar, 1997, p5

Basic pharmacology - Agenda

#Classification of Drugs
#Routes of administration & drug formulations
#A.D.M.E.
#Dose regimes & plasma levels
#Package insert information
#Scheduling of drugs
#Pharmacodynamics
#Drug uses & ADR
#Clinical pharmacology

Indian pharmacopoeia: Legal issues, Storage of various drugs

Indian Pharmacopeia

- The central drug authority is based in Nirman bhavan, New Delhi.
- It is the body which is controlled by the govt. for manufacturing, sale, import and export of drugs.
- The drug authority of state is mostly based on their capitals.
- The central drug authority formulate the policies and authority of state follows and implement the policies.

Implementation is under the control of drug controller.

1. **Advisory Agency:** It include Drug technical advisory board (DTAB) and drug consultative committee (DCC). They frames and modify rules regarding drugs.
2. **Analytical Agency:** It includes central drug laboratory (situated at Kolkata) and drug laboratories in respective state, these laboratories test, analyse the sample of drugs and cosmetics.

3. **Executive Agency:** Authorities which grants license to various organizations for manufacturing, storing, recapping, selling, importing and exporting drugs.

Scheduling of medicines

- Scheduling based on potential effects on the body :the molecule, and it's concentration Expressed with an 'S' and a number 7 schedule classes.
- Unscheduled - can be sold through any outlet.
- S2 upwards only in pharmacies
- S1 and S2 - do not require a prescription
- S3 upwards must be sold with a prescription by a pharmacist or doctor
- S5 upwards is highly controlled
- Schedule 6 &7 are kept under lock and key, the prescription cannot be repeated
- Schedules 8 and 9 - banned substances

Scheduling of drugs

- S1
  - Miscellaneous
- S2
  - Analgesics, Flu preparations, Antihistamines, Anticholinergics
- S3
  - Non-steroidal anti-inflammatories, Anti-hypertensives, Topical steroid preparations, Anti-diabetic medicine, The Pill
- S4
  - Antibiotics, Hormones, Steroid anti-inflammatory medicines, statins

Scheduling of drugs

- S5
  - Psychotropic drugs, e.g anti-depressants, sleeping tablets, tranquilisers
- S6
  - Anorexigenics, Short-acting barbiturates, Opoid drugs
- S7
  - Opoid drugs
- S8,S9
  - Prohibited except for research e.g. heroin, LSD, cannabis (dagga)

Storage and Maintenance of Drugs

Introduction

- The Drugs which are supplied to ward are stored in drug cupboards to provide a uniform supply of drugs to the patients.
- The drugs are stocked in containers, such as boxes and on flexible racks and shelves etc.
- It must be ensure that drugs which are stored remain preserved during their storage.
- There should not be any damage due to high temperature or exposure to sunlight.
- The drugs are to be stored as per the prescribed conditions of their storage.

Introduction - contd

- The drugs stored in a drug store be arranged in such a way that they are easily traceable as and when required.

1. According to pharmacological action
2. Alphabetically

Drug Storage

1. Proper drug storage
2. Storage Environment
3. Arrangement of drugs on shelves
4. The storeroom
5. The dispensary

1. Proper drug storage

Drugs are stored in a specially designed secure area or space of a building in order to:

- Avoid contamination or deterioration,
- Avoid disfiguration of labels,
- Maintain integrity of packaging and so guarantee quality and potency of drugs during shelf life,
- Prevent or reduce pilferage, theft or losses,
- Prevent infestation of pests and vermin.

- The storage should not hinder the cleaning and should have sufficient space for movement of stocks and handling.

- Products are to be stored in a manner that prevents damage due to excessive vertical stacking heights and not to exceed eight stacks.

- Store the products as per product storage condition (As per label) to prevent deterioration of finished product on storage.

- Monitor and record the temperature of storage area on daily basis.

2. Storage Environment

The storage environment should possess the following:

- Adequate temperature,
- Sufficient lighting,
- Clean conditions,
- Humidity control,
- Cold storage facilities,
- Adequate shelving to ensure integrity of the stored drugs.

Storage and Maintenance

- Drugs to be stored under condition that prevent contamination & as far as possible, deterioration.
- **"Well closed container"** precautions to be taken in relation to the effects of the atmosphere, moisture, heat &light.
- **"Protected from moisture"** means that the product is to be "stored in air tight container"

Protected from light

- **"Protected from light"** the product is to be stored either in a container made of material that absorbs actinic light sufficiently to protect the contents from change induced by such light.

Temperature

- In a deep freeze (-15°C)
- In a refrigerator 2°C -8°C
- Cold or cool 8°C-15°C
- Room temperature 15°C-25°C

Storage Premises

- The Storage area must be free from unsanitary conditions(Ex Rodents, insects, Birds, litter etc).
- The floor of the warehouse should be made of hard floor (Concrete /Kota/Epoxy) and must be in a good state of repair and appearance at all times.
- The floors are kept clean and free of trash, dirt, sippage water, drain water etc.
- The area must be kept clean and free of refuse.

Storage Premises

- The area used for storage of IV fluids should have adequate space and to prevent exposure to direct sunlight.
- Secured area availability for damaged, rejected and expired goods.
- Ensure adequate pest control program in place and shall be carried out at a minimum frequency of a year.
- The Pest control shall cover treatment for Termite and Rodents.

3. Arrangement of drugs on shelves

- Shelves should be made of steel or treated wood.
- Shelves should be strong.
- Drugs are arranged in alphabetical order of generic names.
- Each dosage form of drug is arranged in separate and distinct areas.
- Sufficient empty space should demarcate one drug or dosage form from another.

- Most recently received drugs are placed behind old stock on the shelf except where new drugs have shorter expiration dates.

- Always put lids properly on tins always and at the close of the day.

- Put drugs in a dry place protected from light and heat.
- Store liquids on a pallet on the floor or on the lowest shelf.
- The store must be cleaned daily and mopped at least once a week.

4. The store-room

- A well-arranged store enables easy identification of drugs and saves time when picking a drug from the shelves.

- This helps remove drugs quickly and makes for easy inventory control.

- The rule of **FIRST IN FIRST OUT (FIFO)** should be applied always.

- So, drugs that were received first should be used first, except where the new stock has shorter expiration dates than the old stock.

- In this regard, the principle of **FIRST TO EXPIRE FIRST OUT (FEFO)** should apply.

- To have access to drugs with shorter expiration dates first, put these in front of the shelves.

- Those with longer expiration dates should be placed behind those with shorter dates.

5. The dispensary

- Clean after each use tablet counters and place within easy reach on the table.
- Avoid dispensing wrong drugs by arranging drugs on the table in alphabetical order so that the drug being dispensed is not confused with another.
- Always close drug containers from which drugs are not being dispensed to prevent spillage or dispensing the wrong drug.

Drug expiry

- **Shelf life-** the time where a given product stored under reasonable condition, is expected to remain stable (>90%potency)

- **Essential drugs-** drugs that satisfy the health care needs of the majority of the population.

- Essential drugs should there fore available at all times in adequate amounts & in appropriate dosage forms.

Expiry dates

- Medications must not be administered, and products and equipment must not be used beyond their expiry dates.
- All medical equipment, dressings and solutions used during invasive procedures must be sterile.
- Single-use devices are meant for single use only and must not be re-used.

Storage, Maintenance & Security

- All drugs, including samples, should be maintained separate from non-medications in a locked cabinet which is sufficiently secure to deny access to unauthorized persons.

- Key should be available only to authorized personnel who are assigned medication-related responsibilities.

- Store medications that are “for external use only” separate from medications intended for internal use.

Storage, Maintenance & Security

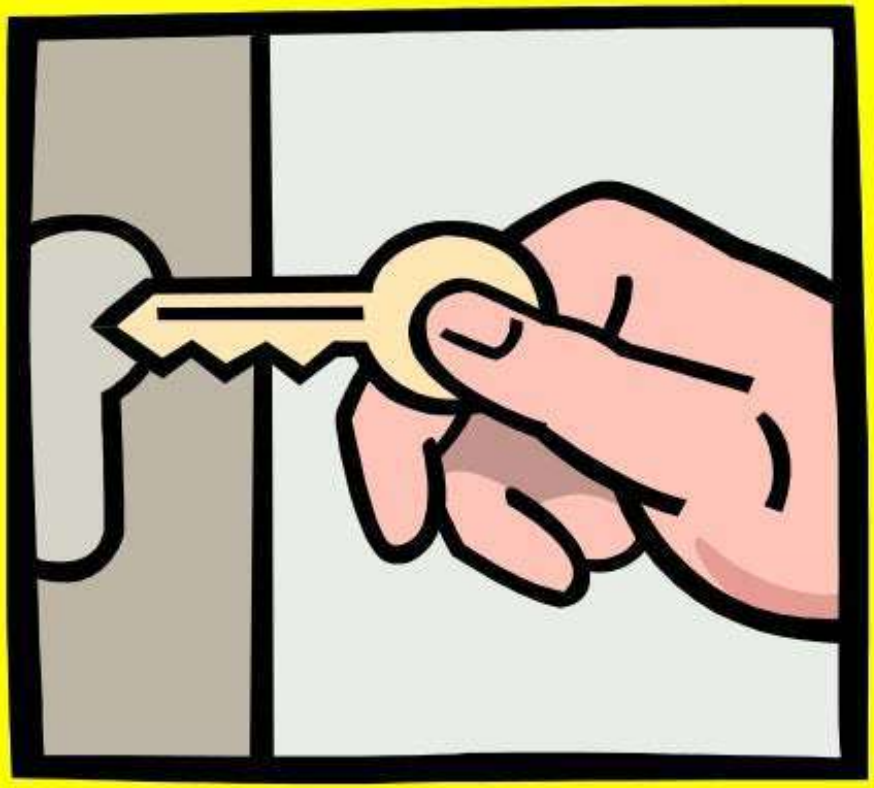
- Store look-alike and sound-alike drugs separately.
- Maintain temperature between 59 degree and 86 degrees Fahrenheit for non-refrigerated medications.
- Where refrigeration is necessary use a “Medications Only” refrigerator and maintain temperature between 36 degrees and 46 degrees Fahrenheit.

Storage, Maintenance & Security

- On daily basis check, verify and document the proper temperature.
- All multiple-dose injectable medications should be initialed and have the date of first entry recorded on the label.
- Rotate medication stock monthly employing a "FIFO" (first in/first out) process.

Controlled Drug Regulations

- Double Locked Container



Controlled Drug Regulations

- 2 licensed personnel count (or verify any discrepancies) every shift (8 hours)
- Witness to all discards
- Record on Control Substance Sheet all administrations and wastes.

Controlled Drugs

All details must be completed in the Doctors own handwriting, like:

- Name of drug
- Dose of drug
- Number of doses or length of course
- Signature of prescribing doctor and date

Storage of Controlled Drugs

- They must be kept in a locked cabinet or cupboard
- The keys to the cabinet must be in the possession of an authorised person
- Authorised person, refers to Ward Manager or deputy who must be a Trained Nurse or Midwife
- Students should not be responsible for the controlled drug cupboard keys

Recording of Controlled Drug Use

- Records in the form of **CONTROLLED DRUG REGISTERS** must be kept
- Each drug must have its own specified page which is Headed with the Drugs name and Strength
- The Number of Ampoules of a drug must be entered and updated with every use.

Recording of Controlled Drug Use

- Must record:
  - Date
  - Time
  - Dose of every administration
  - Name of receiving patient/client
  - Number of ampoules at start and finish of administration

  Entry must be signed by 2 people **one of who must be registered**

  No alterations must be made to the entry

  All entries must be in **Black Ink**

Rational use of drugs & Calculation of drug dosage

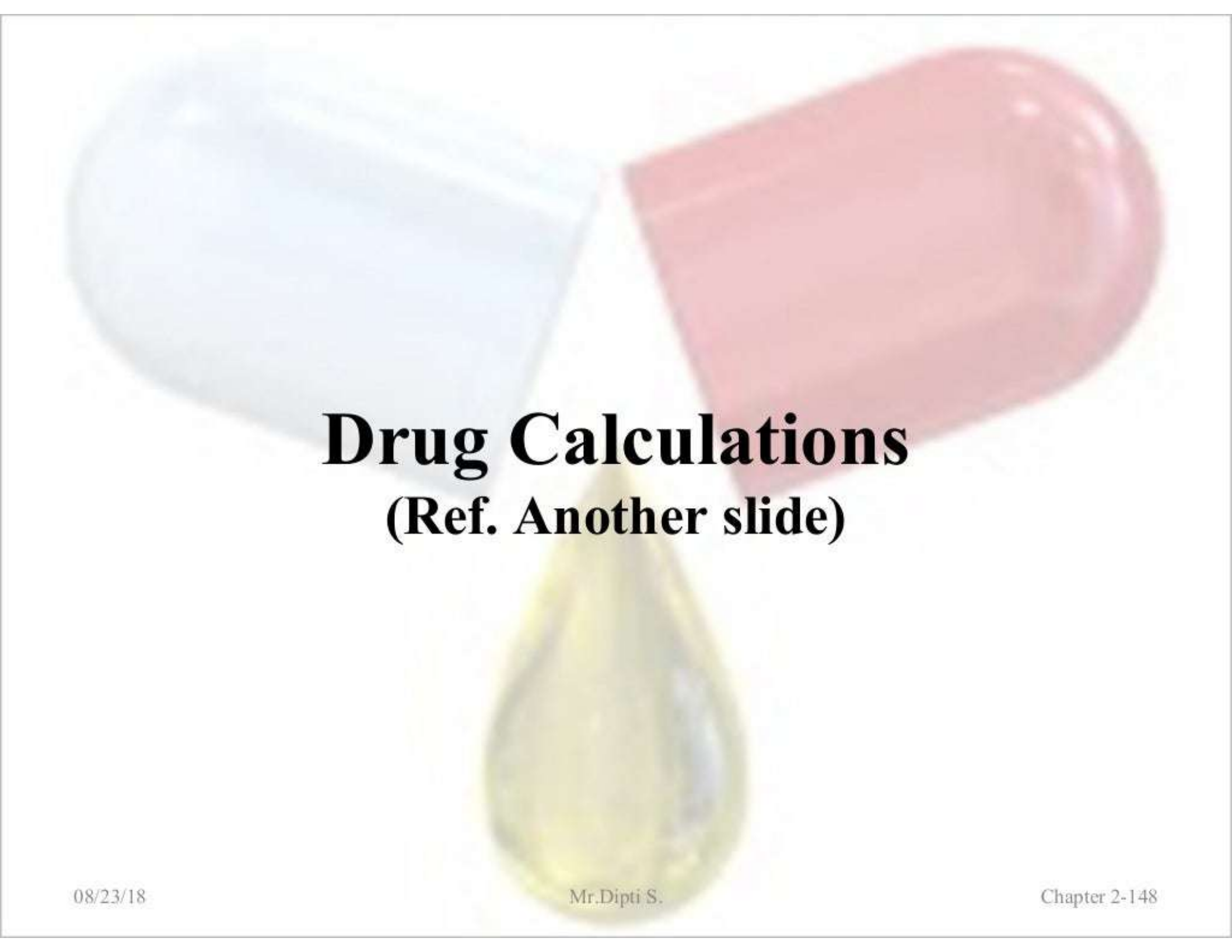
Rational use of drugs

- Any drug is made with help of combination or mixture of the chemicals which some times harm to the other parts of body.
- Rational use: Eg. Patient is having hypertension then the goal is to reduce blood pressure to the normal level in order to prevent prolonged hypertension, thus creating complication.
- Once identifying the person suffering from specific disease, the physician or nurse should find out other factors contribution the ill effect of the prescribed drug.

- Any drug required good renal or hepatic system to pass drug and to be drain out or metabolize in the body.
- The choice of drug has to be make wisely by the physician or nurse to avoid side effects, drug interaction, contraindication.
- Nurse should follow the 6 Rights of drug administration to avoid wrong administration of drug.
- Use of combination drug can be one option in treatment, eg. Ibufen (Brufen+Paracetamol)

Conclusion

Rational use of drugs requires that the patients receiving medications appropriate to their clinical needs, in does that meet their own requirement of an adequate period for time and at lowest cost to them and their community.



Drug Calculations
(Ref. Another slide)

Pharmacotherapeutics: Principles of therapeutics

Drug – WHO scientific group definition

Any substance or product that is used/ intended to be used to modify or explore physiological systems or pathological systems or pathological states for the benefit of the recipient

Pharmacology

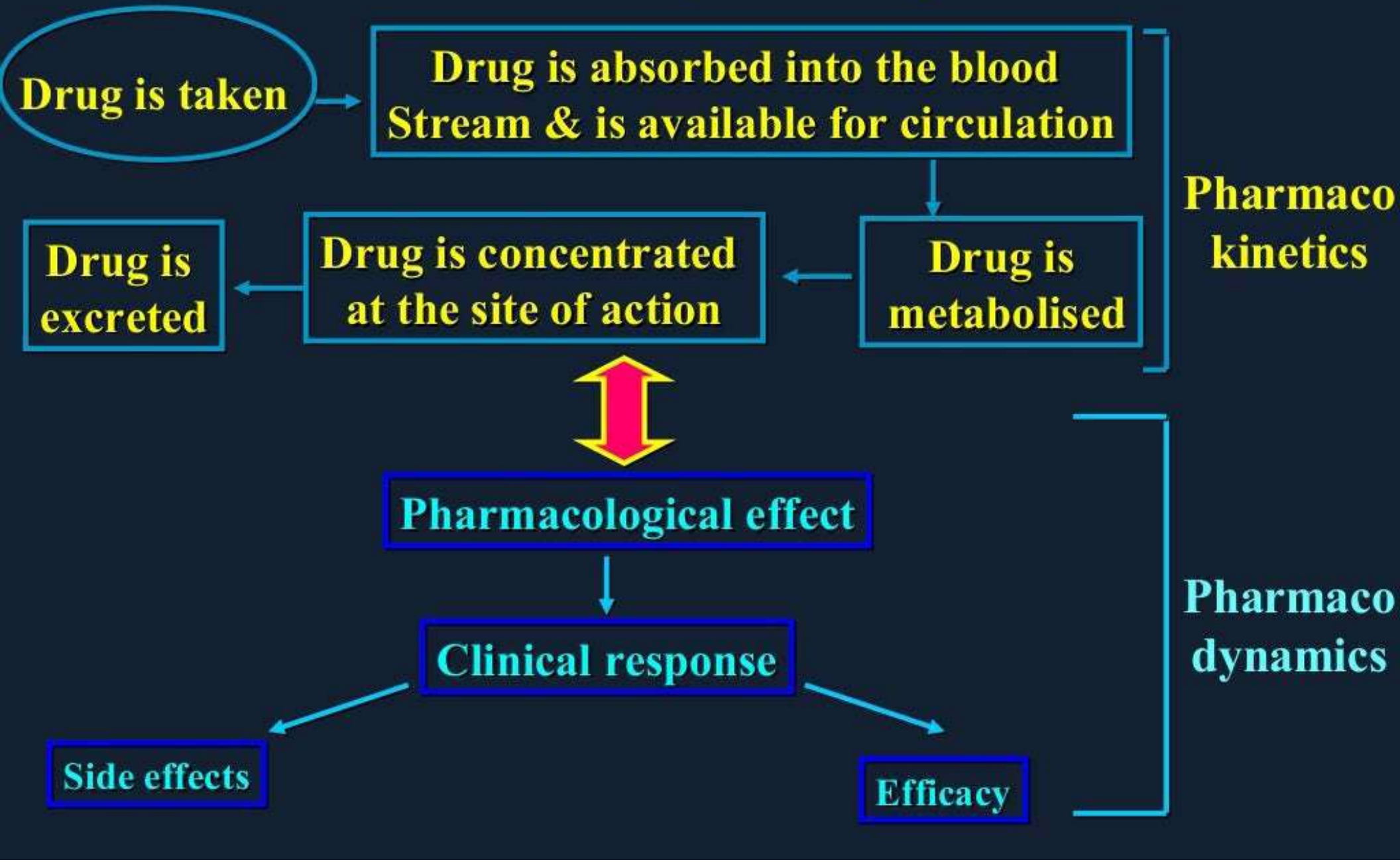
Pharmacodynamics

- Biological and therapeutic effects of drugs

pharmacokinetics

- Absorption, Distribution, Metabolism & Excretion of drugs

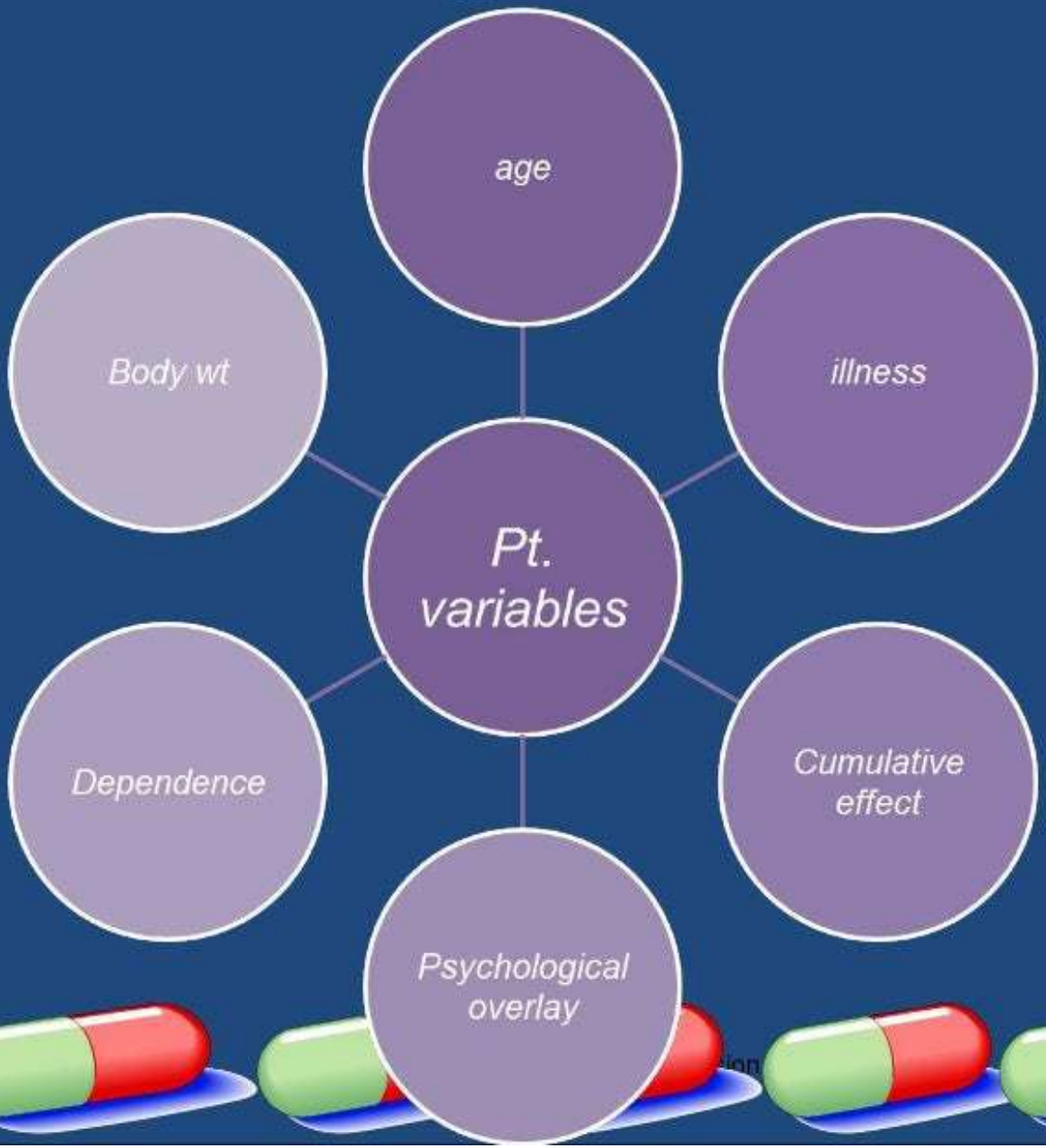
The Relationship between Pharmacokinetic and Pharmacodynamic processes



Drug – and – patient related factors.

- Drug and patient related factors determined the selection of routes for drug administration. These are:
- Characteristics of the drug.
- Emergency/ Routine use.
- Condition of the patient (Unconscious, Vomiting and Diarrhoea)
- Age of patient.
- Associated disease.
- Patients/ Doctors choice (Sometimes)

Patient Variables that may affect Drug Action



Pharmacokinetics

Absorption

Distribution

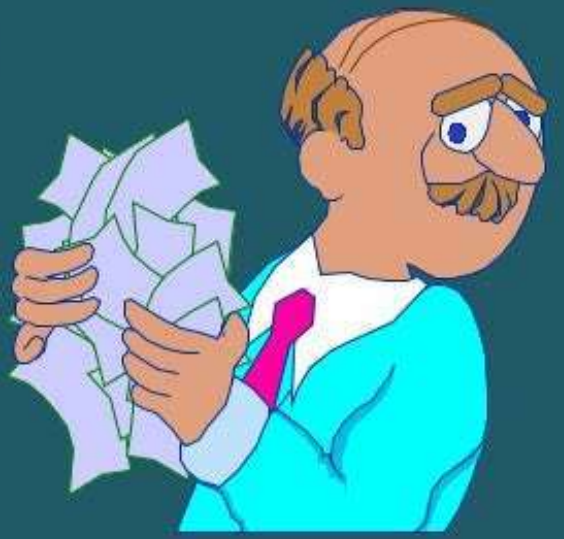
Metabolism

Excretion

Basic pharmacology - Agenda

- Definitions
- Classification of Drugs
- Routes of administration & drug formulations
- Dose regimes & plasma levels
- Package insert information
- Scheduling of drugs
- Pharmacodynamics

Package insert information (Literature)



- Composition (drug/dose per tablet)
- Schedule
- Pharmacological classification
- Pharmacological action
- Indications
- Contra-indications
- Dosage & directions for use
- Side effects & special precautions
- Known symptoms of overdose & particulars of its treatment
- Identification (physical description of tablet)
- Presentation (package details)
- Storage instructions
- Registration number
- Name of applicant

Pharmacodynamics: Mechanisms of Action

The ways by which drugs can produce therapeutic effects:

- Once the drug is at the site of action, it can modify the rate (increase or decrease) at which the cells or tissues function.
- A drug cannot make a cell or tissue perform a function it was not designed to perform.

Pharmacodynamics

- The effect the drug has on the body
- Based on either:
  - Non-specific action
  - Binding with a receptor
  - Enzyme interaction

Pharmacodynamics

Non-specific action depends on the drug's accumulation in cell membranes

Specific actions result from the drug becoming affixed to the receptor i.e. binding to receptors

Drugs can only increase or decrease cell function - they cannot totally alter the action of the specific cell

Mechanism of Action

Mechanism of action

- **Cell membrance**
- **Metabolic processes Within the cells**
- **Outside the cell**

Clinical Pharmacology,Laurence;1997: pg 7812

Cell Membrance

Specific receptors-agonists and antagonists on adrenoceptors

Interference with selective passage of ions across membracnes eg: Calcium channel blockers

Outside the cell

Direct chemical interaction eg: chelating agents, antacids

Osmosis with diuretics like mannitol

Receptor

Protein macromolecules

Agonist to receptor → proteins alter → induces changes within cell → response to drug

Agonists : activate receptors

Antagonists : blockers of receptors

Clinical Oharmacology, Laurence; 1997, pg:78

Additive Effect

1 + 1 = 2

When the total pharmacological action of Two or more drugs administered together Is equivalent to the summation of their Indicidual pharmacological actions

Eg: ephedrine + aminophylline in treatment of bronchial asthma

Pharmacology & Pharmacotherapeutics, Satoskar;1997: pg 45

Synergistic effect

1 + 1=X (>2)

When the total pharmacological action of Two or more drugs administered together Is more than the summation of their individual pharmacological actions

Eg: cotrimoxazole(sulphamthoxazole +pyrimethamine) Septran

Pharmacology & Pharmacotherapeutics, Satoskar;1997: pg 45

Terminology

 # Bioavailability

- *the extent of the drug which is delivered to the circulation (expressed as %)*

 # Bioequivalence

- *the rate and extent of absorption of two products is equivalent - 'no significant difference'*

Drug uses

- # Curative, as primary therapy (bacterial / parasitic infections), or auxilary therapy (anaesthetics, ergometrine and oxytocin in obstetrics)
- # Suppressive of disease/symptoms, used continuely or intermittently to maintain health with out attaining cure as in hypertension, diabetes, epilepsy, asthama/ to control symptoms such as pain and cough, while awaiting recovery from cause
- # Preventive (prophylactic), as when a non-immune person enters a malarial area or contraception

Using more than one drug simultaneously

Possible responses:

- The drugs have no effect on each other
- Antagonism - the combination results in a lower response than when either is given on its own
- Potentiation - the response rate of the two drugs when combined is more than the sum of their independent response rates
- Synergy - the combination offers greater effect than the sum of the two products given individually I.e. 1+1=3 or more
- Globally there is a move away from polypharmacy

Adverse Drug Reaction (ADR)

An adverse reaction is a harmful or seriously unpleasant effect caused by a drug at doses intended for therapeutic effect/prophylaxis/ diagnosis which warrants reduction of dose/ withdrawal of the drug and/or foretells hazard from future administration

Degrees of certainty of (ADR)

Definite : time from taking drug is reasonable event corresponds to what is known of drug event ceases on stopping drug even returns on restarting drug

Probable: time sequence reasonable corresponds to what is known of drug ceases on stopping drug not reasonably explanined by patient's disease

Degrees of certainty of (ADR)

Possible : time sequence reasonable corresponds to what is known of drug could be due to disease / other therapy

Conditional : time sequence reasonable corresponds not to what is known of drug cannot be explained by patients disease

Doubtful : event not meeting above criteria

Anaphylaxis

Systemic reaction in a sensitized human subject following repeat injection of a drug like penicillin characterized by laryngeal edema, severe bronchospasm leading to asphyxia, or circulatory collapse.

Eg: Penicillin

Pharmacology & Pharmacotherapeutics, Satoskar;1997: pg 35

Clinical Pharmacology

Scientific study of drug in man

Provides facts for –

- Improving treatment of patients
- Understanding drugs
- Understanding effects of drugs in different age groups

Clinical Pharmacology

#Phase I(pharmacokinetic, dose, safety)

#Phase II(safety & efficacy in Small population)

#Phase III (safety & efficacy in large population)

#Phase IV (Post-marketing Study, safety in special population & new indication)

Clinical Pharmacology

Clinical Trial

Randomized
Non randomized
Controlled
Open
Cross over

Placebo

Latin – "I will please"

Placebo are used for two purposes :

- As a control in scientific evaluation of drugs
- To benefit or please a patient not by any pharmacological actions, but by psychological means

Therapeutic evaluations

Whether a drug is of value and how it may Best be used :

a) formal therapeutic trials

b) surveillance studies for both efficacy and adverse effects

Patient Compliance

Patient takes prescribed drug

Failure due to :

1) Non comprehension of instructions
    a) Inadequacy of doctor
    b) Inadequacy of patient
2) Comprehension, but failure to carry out instructions

Factors for Noncompliance

Disease –

Regimen –

Source of Medicine –

Doctor / Patient Relation –

Patient -

- **# Psychiatric diagnosis**
- **# Complexity**
- **# Long duration**
- **# Time wasting**
- **# Inconvenient clinics**
- **# Inadequate supervision**
- **# Patient dissatisfaction**
- **# Inappropriate health beliefs**

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4. Marilyn Herbert – Ashton, Nancy Clarkson, Pharmacology, Jones & Barlet pub 2010 India, Pg no 1-2.
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Thanks

Drugs

" Poisons in small doses are the best medicines; and useful medicines but in too large doses they are poisonous"

Willam Withering (1741 – 1799) MD, FRS

AGONISTS VS ANTAGONISTS

Deepankar Ratha
Assistant Professor
CUTM, Rayagada

AGONISTS

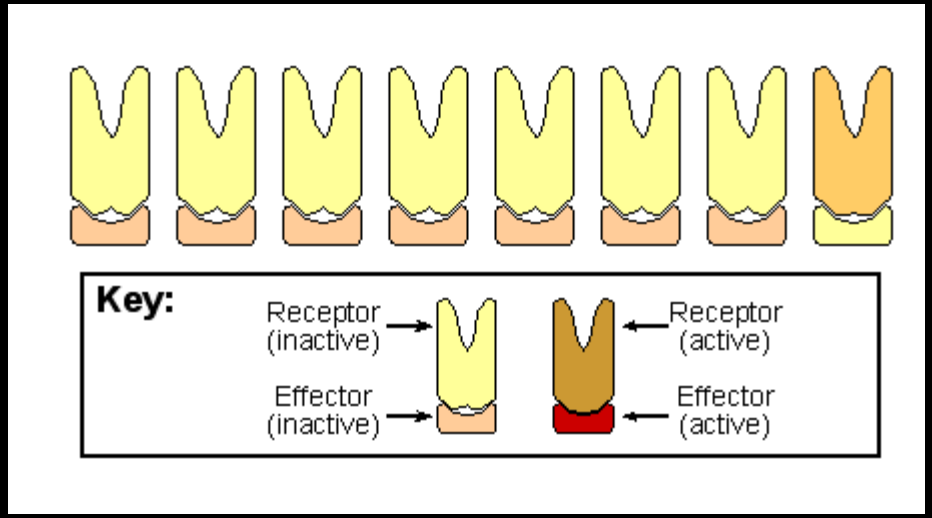
- MOLECULES WHICH BIND TO RECEPTORS ON CELLS
- THINK OF LOCK AND KEY; ONLY CERTAIN KEYS WILL WORK IN CERTAIN LOCKS
- HORMONES, NEUROTRANSMITTERS, AND ENDOGENOUS REGULATORS OF THE BODY
  - HORMONE: ESTROGEN
  - NEUROTRANSMITTER: HISTAMINE
  - ENDOGENOUS REGULATOR: SERATONIN
- DRUGS WHICH ACT LIKE REGULATORY MOLECULES OF THE BODY

AGONIST FACTS

- REACTIONS MAY NOT PROCEED FASTER DUE TO AN AGONIST BINDING
- JUST BECAUSE THE KEY IS IN THE LOCK DOES NOT MEAN THE DOOR WILL OPEN ANY FASTER
- SOME AGONIST ACTION MAY ACTUALLY RESULT IN A SLOWER BODY FUNCTION
- A KEY MAY UNLOCK THE DOOR AND YOU WILL MOVE IN SLOW MOTION

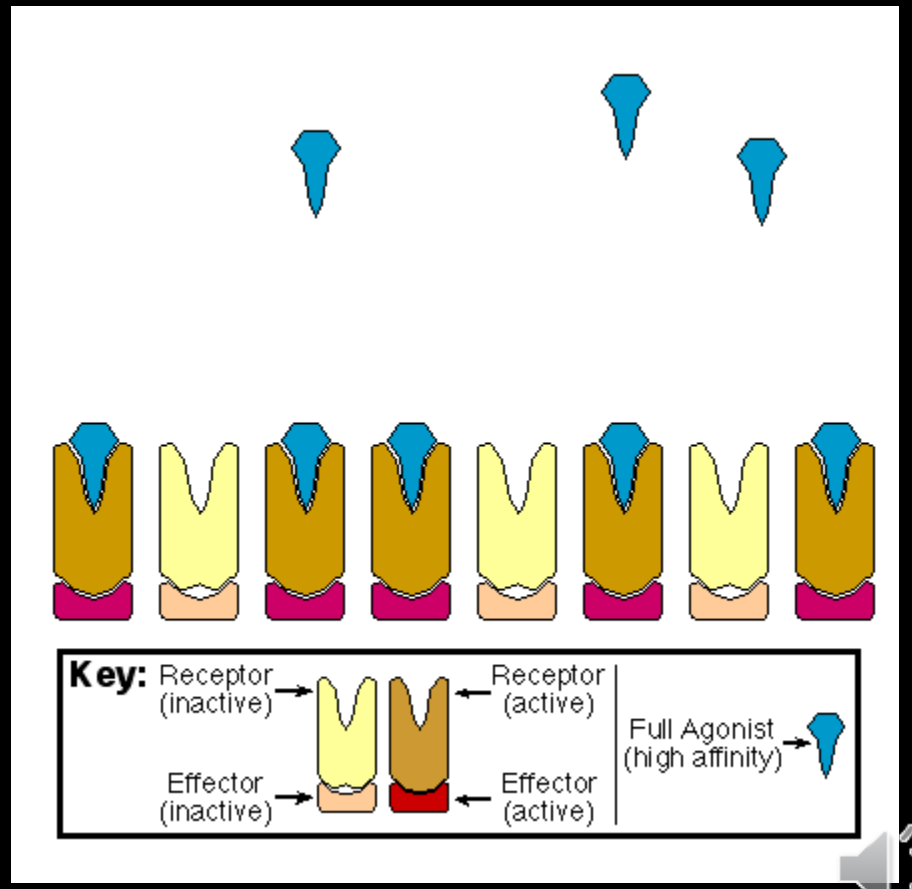
BASELINE

- LOW BASELINE ACTIVITY MAY BE POSSIBLE IN ANY SYSTEM WITHOUT AN AGONIST TO REPRESENT THE RECEPTOR/EFFECTOR; BRIEF ACTIVATION IS POSSIBLE
- THERE IS NOT ALWAYS A NEED FOR A KEY TO UNLOCK SOME DOORS; THEY CAN OPEN WITHOUT A KEY
- THESE DOORS DON'T STAY OPEN VERY LONG, BUT THEY ARE SUFFICIENT ENOUGH TO ALLOW OTHERS TO ENTER AND EXIT



HIGH EFFICACY AGONISTS

- LOW CONCENTRATIONS OF A FULL AGONIST MEANS THAT ONLY SOME AVAILABLE RECEPTORS WILL ACTUALLY BE OCCUPIED AT ANY GIVEN TIME
- WHEN THERE ARE A LOT OF DOORS AND NOT ENOUGH KEYS AVAILABLE, NOT ALL DOORS WILL BE OPENED
- THE EFFECTOR SYSTEM IS ACTIVATED BY EACH EVENT OF BINDING COMPLETED BY THE AGONIST – "HIGH EFFICACY"
- KEYS REALLY LIKE DOOR LOCKS; THEY WILL ENTER A LOCK AS OFTEN AS POSSIBLE; A KEY UNLOCKING A DOOR SIMPLY MEANS THAT THIS DOOR CAN BE OPENED



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- ALMOST ALL RECEPTORS MAY BE OCCUPIED WHEN A FULL AGONIST IS PRESENT AT A HIGH CONCENTRATION
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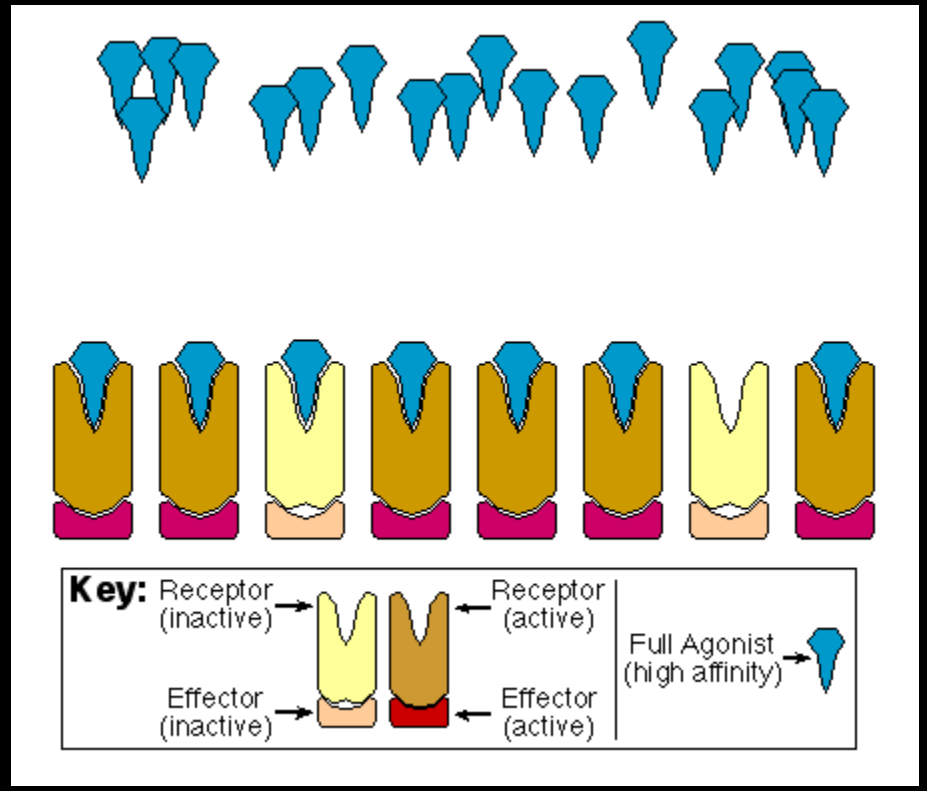
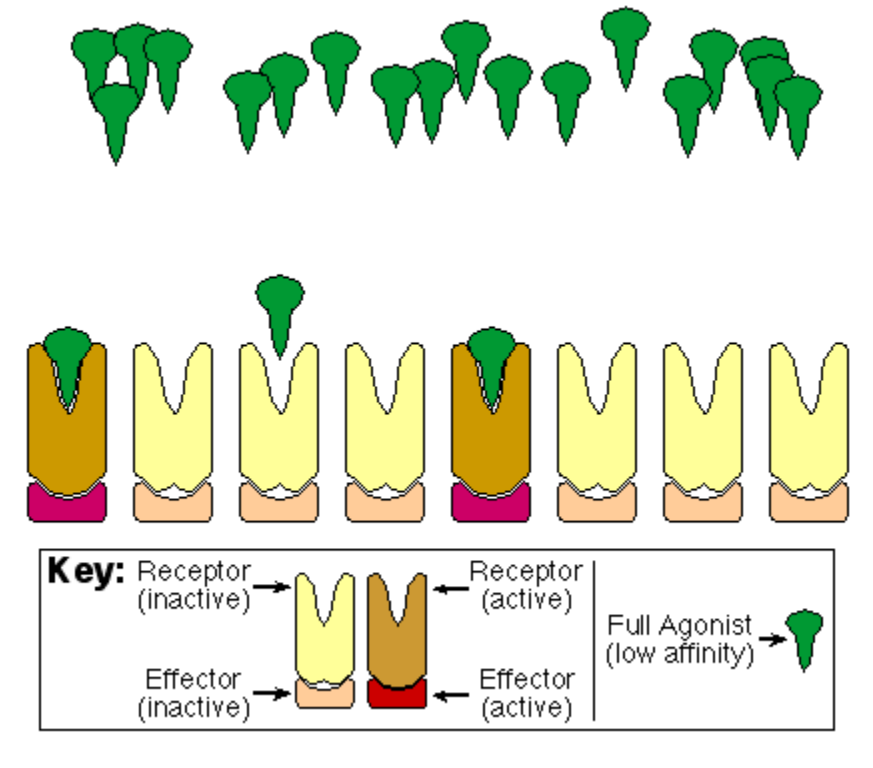


LOW AFFINITY AGONISTS



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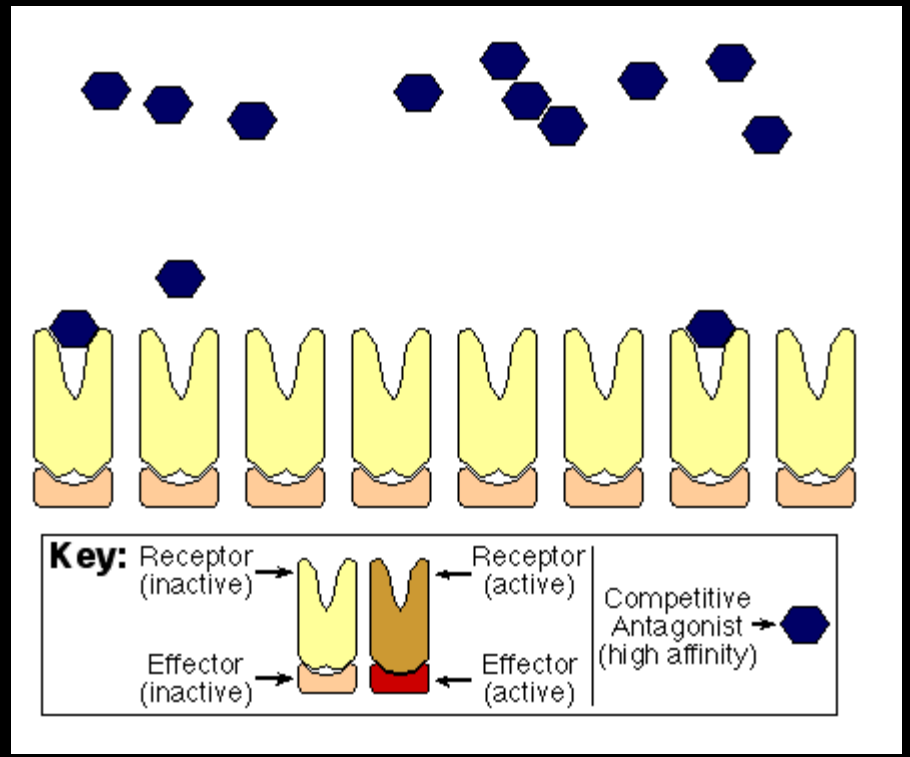

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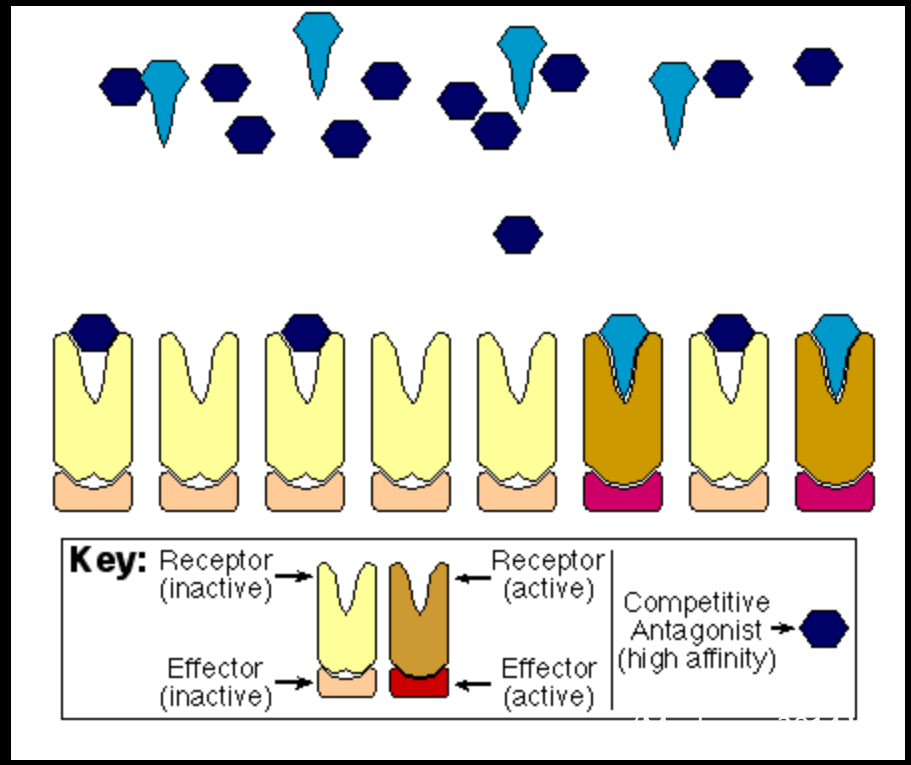

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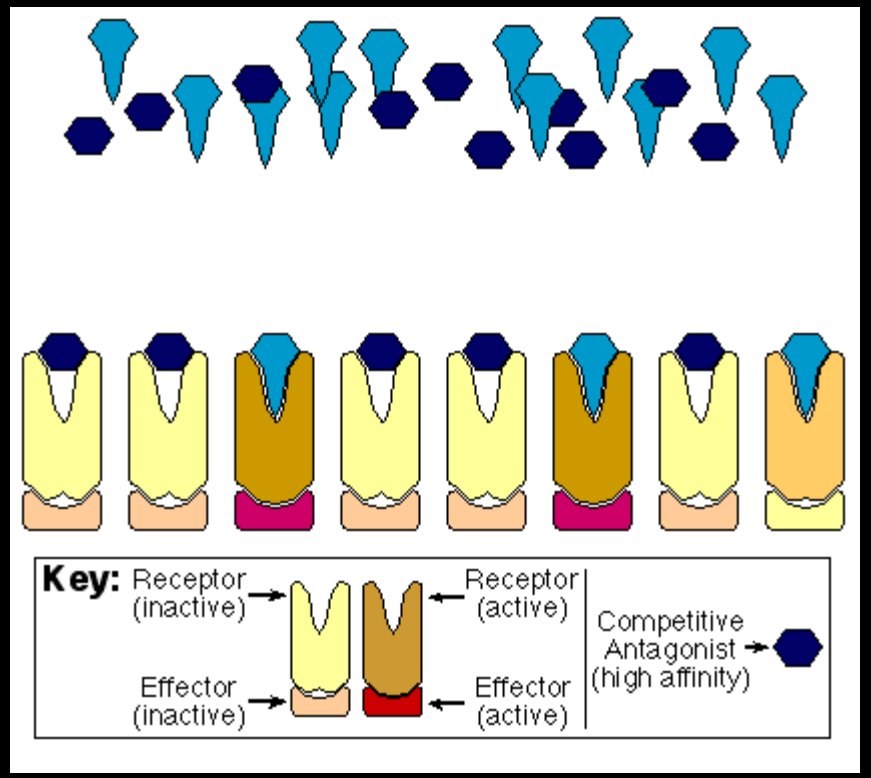

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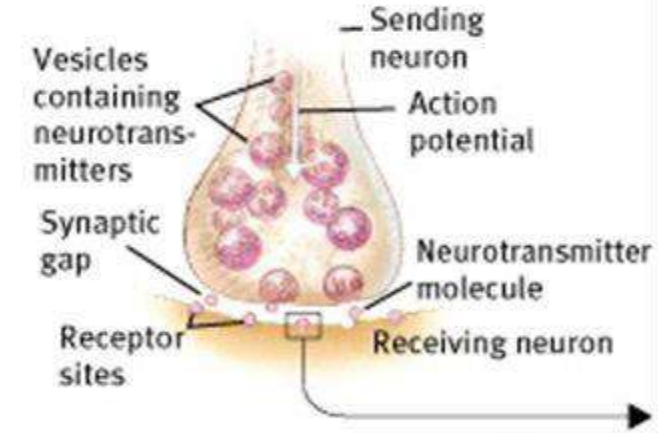

Neurotransmitters carry a message from a sending neuron across a synapse to receptor sites on a receiving neuron.

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This agonist molecule excites. It is similar enough in structure to the neurotransmitter molecule that it mimics its effects on the receiving neuron. Morphine, for instance, mimics the action of endorphins by stimulating receptors in brain areas involved in mood and pain sensations.

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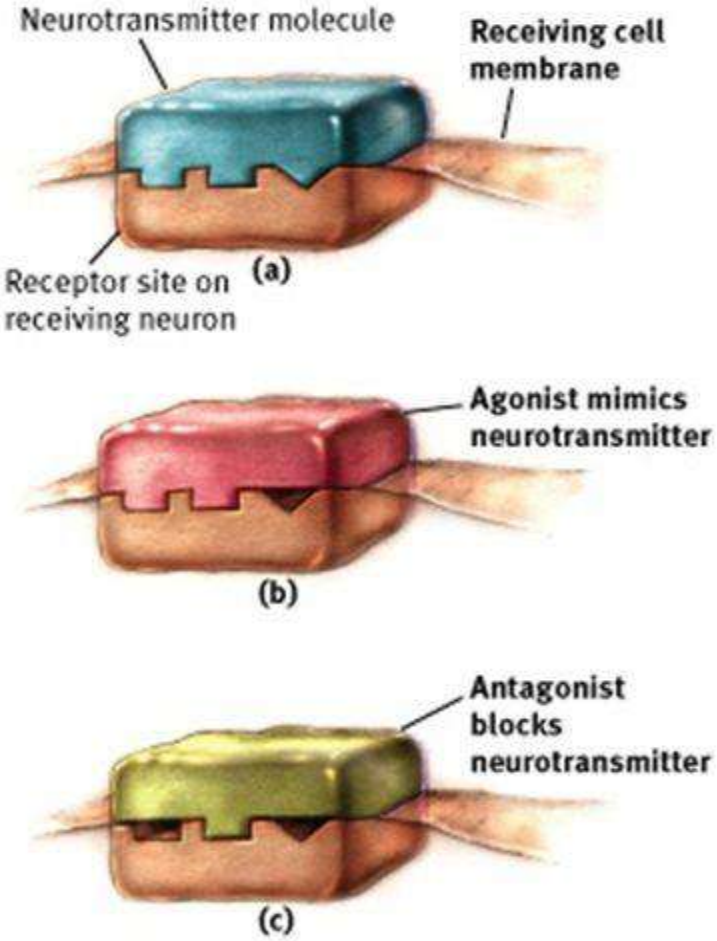

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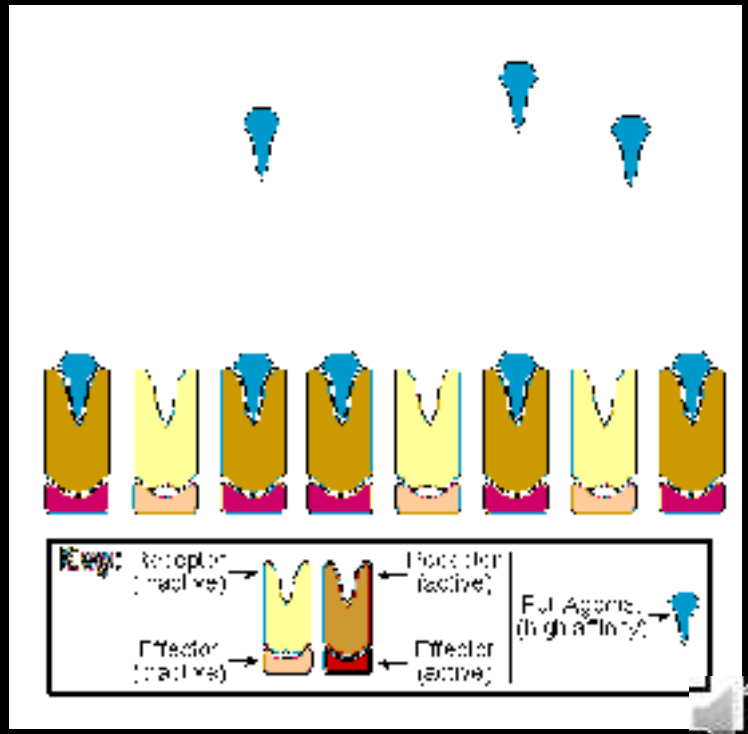

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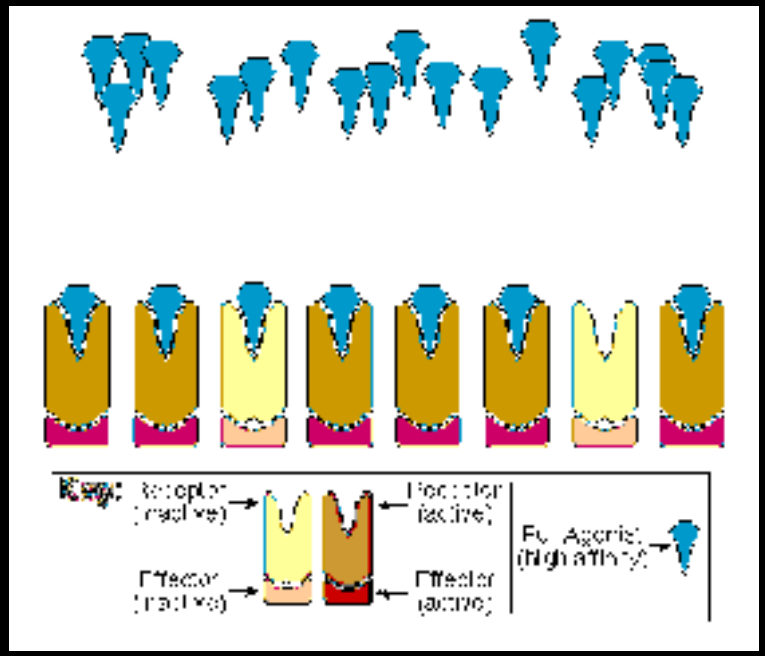

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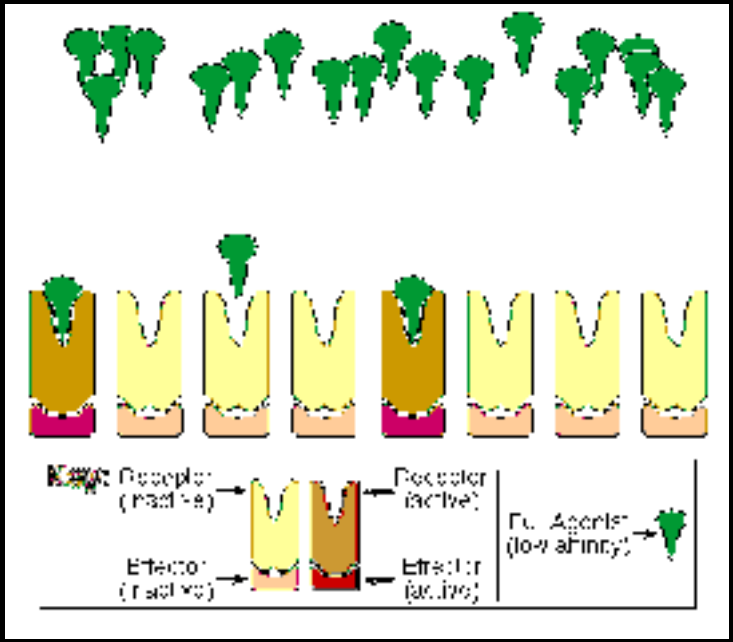

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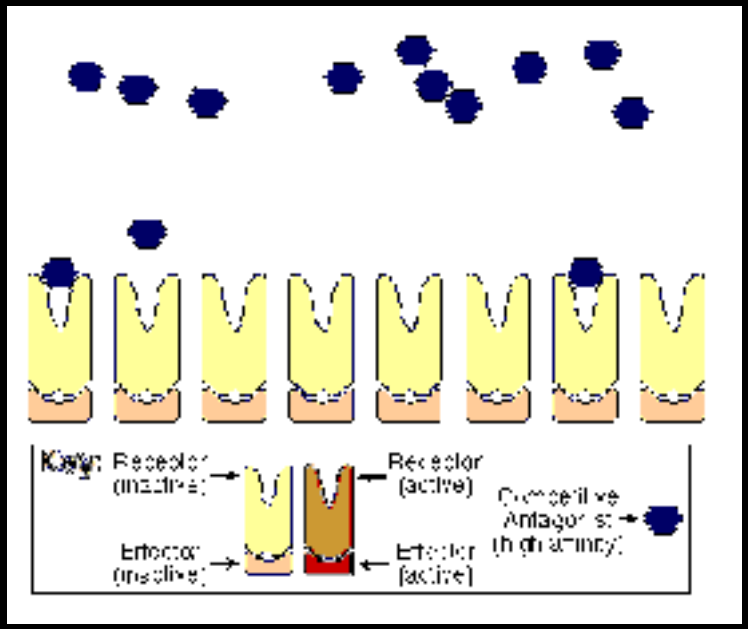

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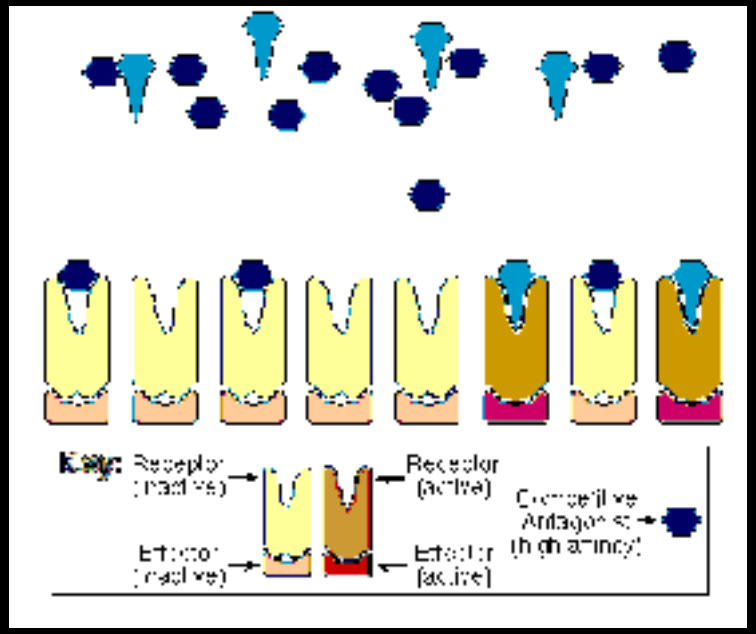

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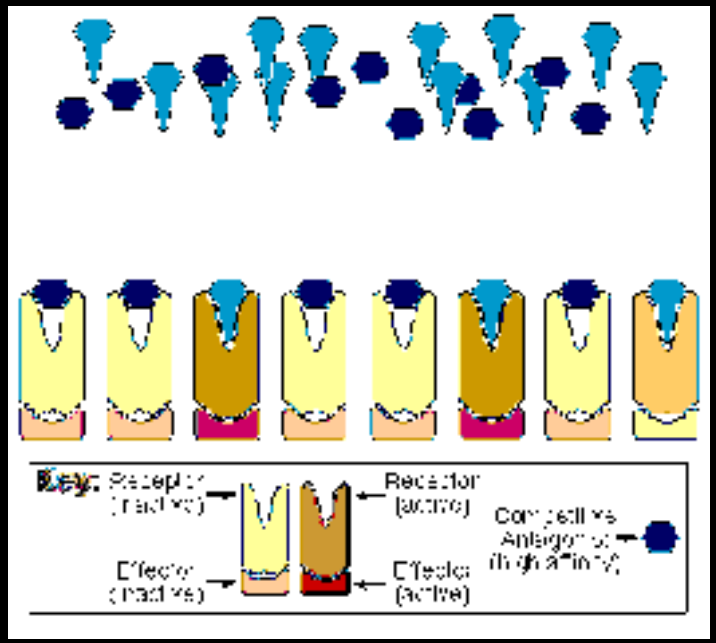

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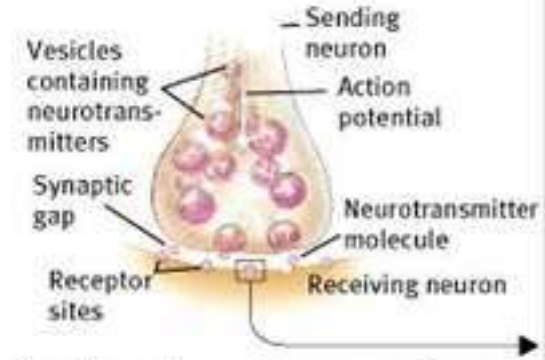

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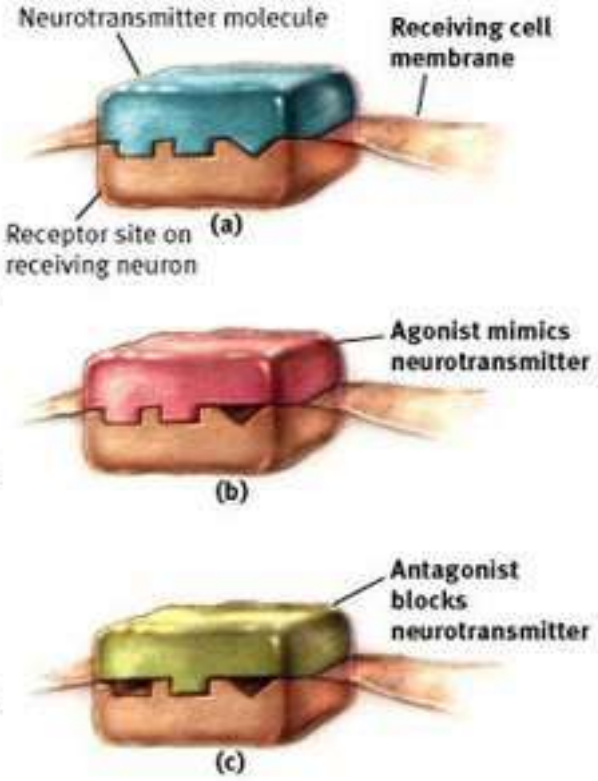
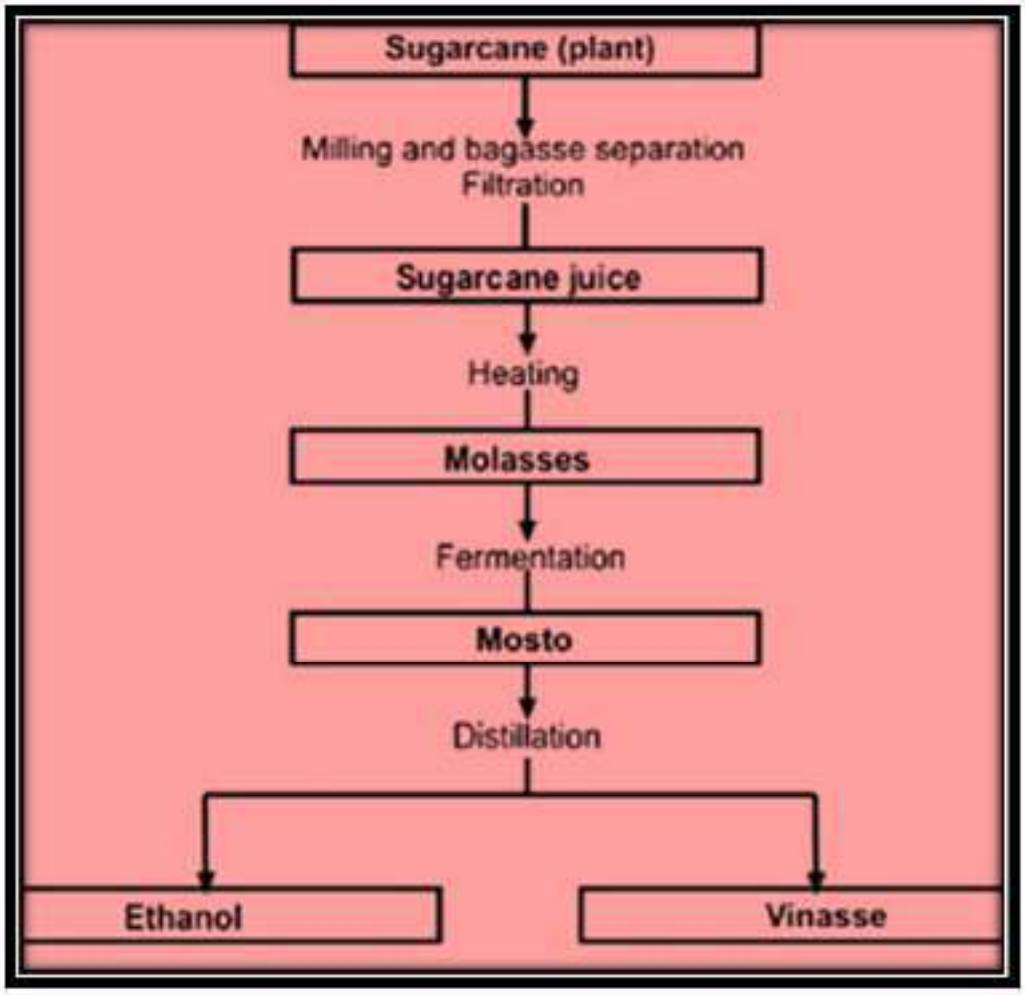


ALCOHOL

INTORODUTION

- Ethanol is traditionally referred to as alcohol occupies a place in medicine and pharmacology mainly because of the consequences of its misuse or absuse.
- About 10% of alcohol users are unable to limit their alcohol consumption and become alcohol absures.
- A section of population who continue to drink alcohol despite the Adverse medical consequences suffer from alcoholism, a dis order difficult to treat.

PREPARATION OF ALCOHOL



TYPES OF ALCOHOL

Anhydrous alcohol(99.99%)w/w

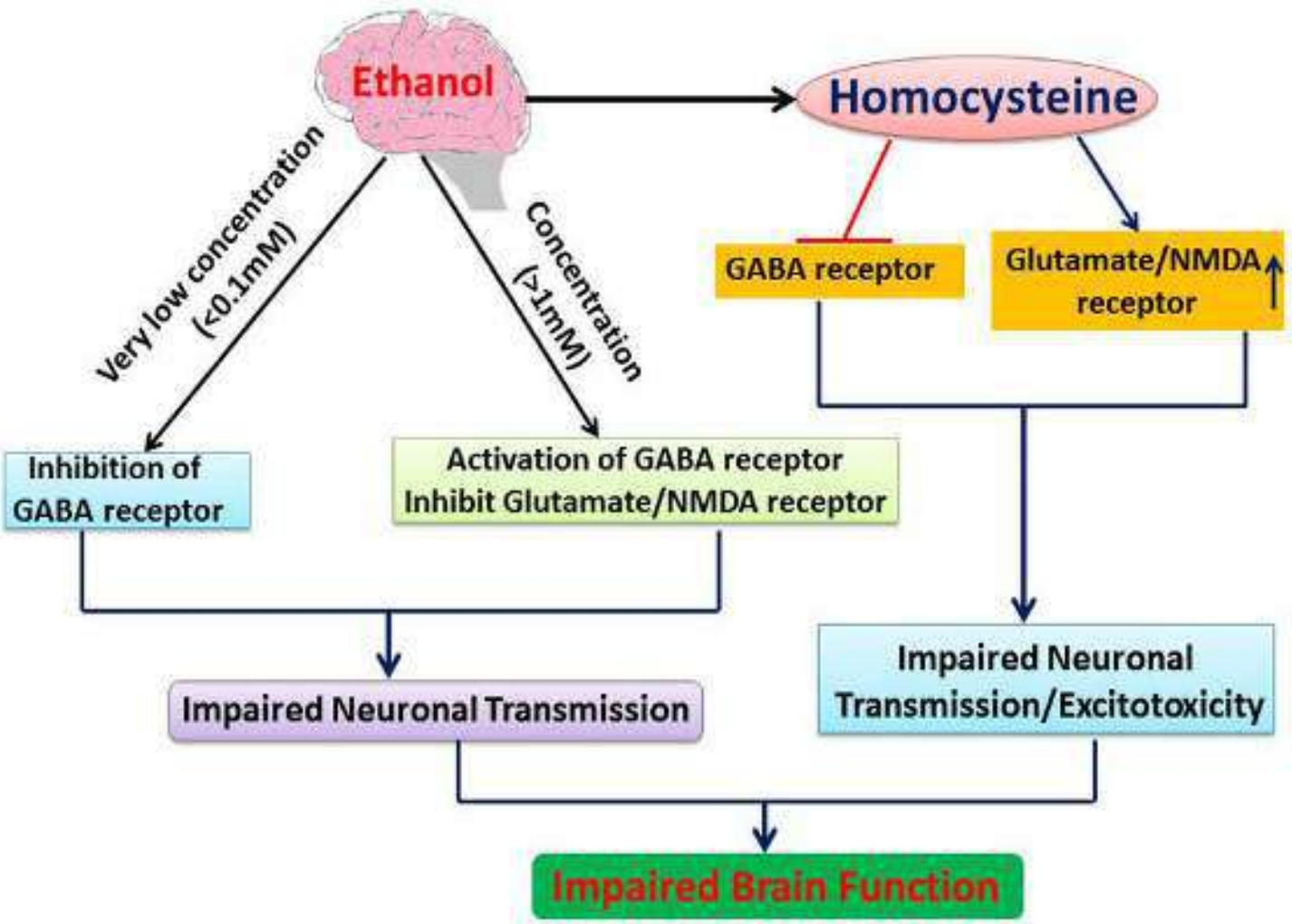
Absolute alcohol(99%)w/w/

Rectified spirit(90%)w/w/

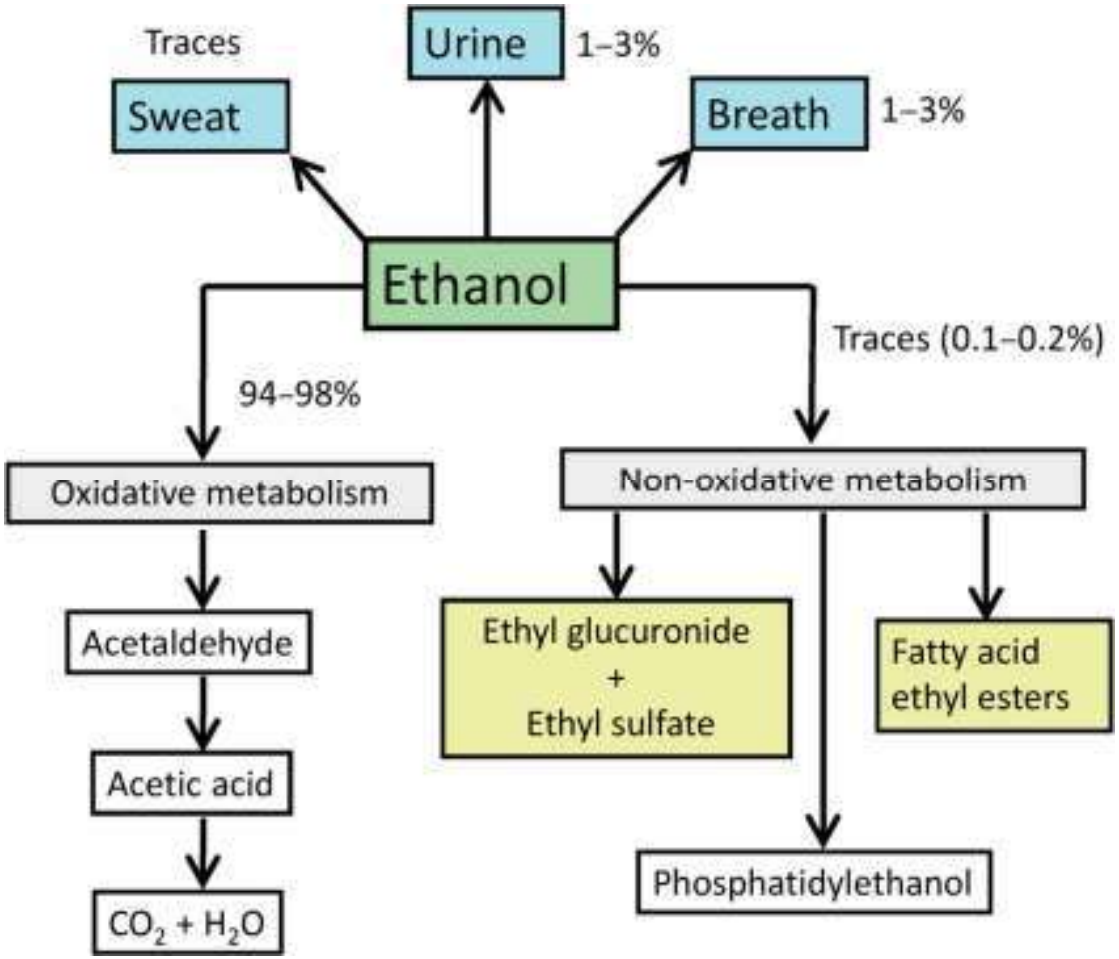
Denatured alcohol(eg: methanol,camphor,terpinol,aniline dyes or diethylphthalate)

Alcoholic bevarages, Light beers(5-6%),strong beers(10%),Rum,Jin,Whiskey,Vodka,and brandy SPIRITS

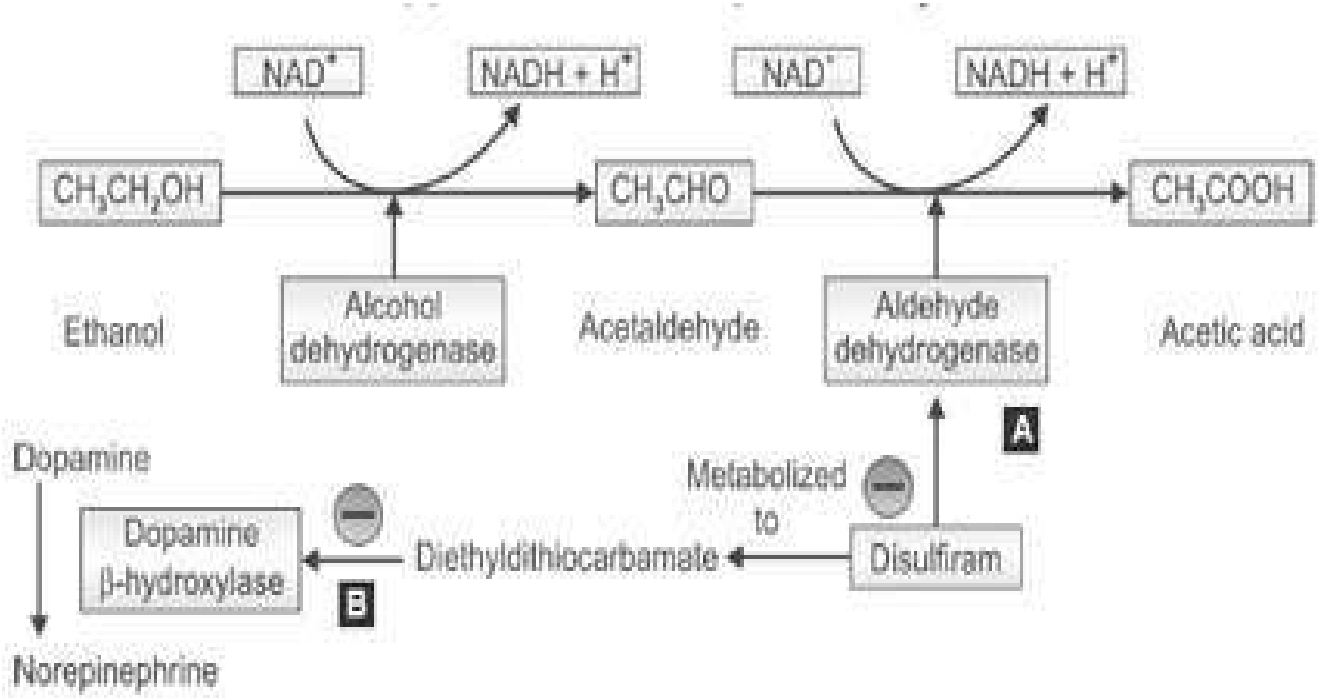
MECHANISM OF ACTION



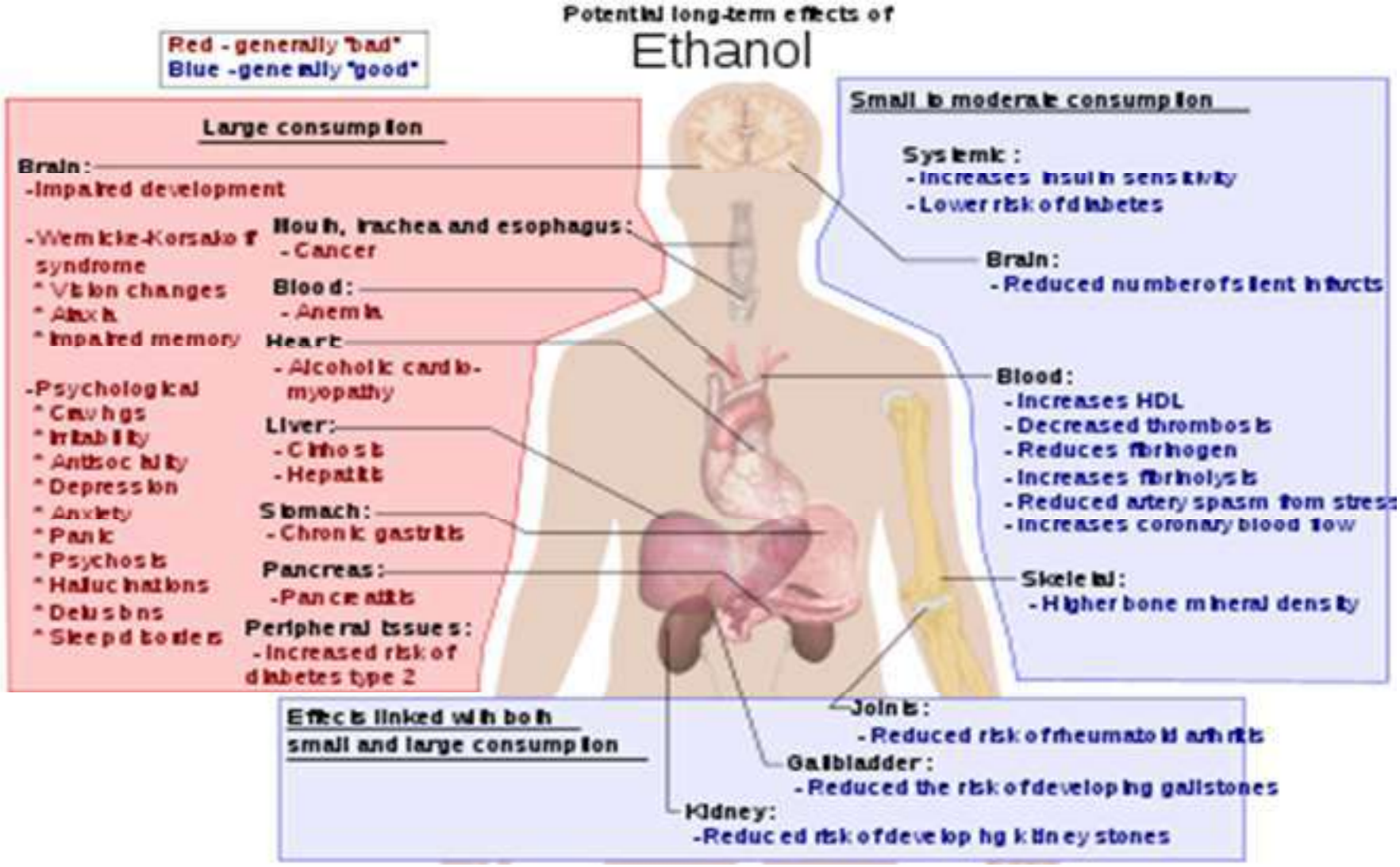
PHARMACOKINETICS



METABOLISM OF ALCOHOL



PHARMACOLOGICAL EFFECTS OF ALCOHOL



Effects on acute ethanol consumption

Central Nervous System:

- Alcohol can reach the brain in short amount of time and the brains ability to contorl the body is greatly affected. Fine motor skills, speech, and visison may be affected.
- The most deadly short term effect of alcohol is driving under the influence of alcohol (DUI).
- Alcohol can effect a persons ability to control decisions, behavior,and emotions.

Heart:

- Ethanol significnatly decreases myocardial contarctility.
- Large doses depress vasomotor center also leading to a fall in BP

Smooth muscle and other effects:

1. Ethanol causes cutaneous vasodilation which leads to feeling warmth,but actually increases heat loss.
2. Diuresisi is ofeten associated with after alcohol intake
3. Aggressive sexual behaviour is due to loss of inhibitions.
4. Alcohol causes catecholamine release and also reduces glucose uptake by the tissues; this results in hyperglycaemia.
5. Acute intake causes NAD+depletion and inhibits gluconeosgenesis leading to hypoglycaemia

EFFECTS OF CHRONIC ALCOHOL CONSUMPTION

- NERVOUS SYSTEM:

➢ TOLERANCE AND PHYSICAL DEPENDANCE:

- On chronic consumption of alchoho tolerance develops and behavioural effects of alcohol. Chronic alcoholics may function almost normally at much high blood llevels (above 180mg/dl)than occasional drinkers.
- Tolerance develops both cellular as well as pharmacokinetic type of tolerance.
- The reduced rate of absorption due to induration of gastric mucosa and faster metabolism due to induction of mixed function oxidases are responsible for the development of pharmacokinetic tolerance.
- The withdrawal effects comprise hyperexcitability, toxic psychosis, delirium tremens and seizures.
- Delirium tremens characterised by confusion, agitation, aggressiveness and hallucinations.

Neurotoxicity :

- Neurological deficits occur in chronic heavy drinkers causing ataxia, dementia and pheripheral neuropathies.
- Wernicke-Korsakoff syndrome, through rare, is important as it is rarely seen in absence of alcoholism. It is associated with thiamine deficiency occurring due to consumption of large amount of alcohol over extended periods
- This syndrome is characterized by ataxia, confusion, and paralysis of the extraocular muscles. Prompt treatment with I.V. or I.M. thiamine is essential to prevent permanent brain damage.
- Alcohol also impairs visual acuity with painless blurring of the vision on chronic consumption

➢ Liver and GIT:

- A long term excessive ethanol consumption causes fatty liver which progress to hepatitis(inflammation of liver) and eventually to irreversible hepatic necrosis, fibrosis, and failure.
- Cellular toxicity of ethanol also promotes inflammatory changes in liver. Women appear to be more susceptible to alcohol hepatotoxicity than men.
- Chronic alcohol consumption is by far the most common cause of chronic pancreatitis.
- Irritation, inflammation, bleeding, scarring or induration of the gut mucosa occur after chronic heavy use of ethanol.

➢ CVS:

1. Dilated cardiomyopathy with ventriculay hypertrophy and fibrosis
2. Ventricular arrhythmias.
3. Hypertension

➢ Blood lipoproteins and platlet functions:

- Moderate intake of alcohol(10-20 mmol/L) increases HDL and decrease LDL, which may account for the protective effect against ischemic heart diseases.
- Ethanol also protects against ischemic heart disease by inhibiting platlet aggregation.
- Megaloblastic anaemia has been observed in chronic alcoholism due to alcohol related folic acid deficiency.
- Iron deficiency anaemia also may result from garstrointestinal bleeding.

➢ Endocrine effects and electrolyte balance:

- Chronic aloholism can produce testicular atrophy, gynaecomastia and impotence.
- A Pseudo-cushing syndrome is observed in chronic alcoholics which is partly due to an increase in plasma hydrocortisone levels because ethanol inhibits hydrocortisone metabolism in the cirrhotic liver.
- Chronic alcoholism can cause hypokalalemia which contributes to muscle weakness.

➢ Effects on Foetal Development:

- Alcoholic women suffer from amenorrhoea secondary to liver damage.
- Consumption of alcohol above 6-10 units per day during pregnancy causes *foetal alcohol syndrome.*
- This syndrome is charecterised by microcephaly, mental retardation, flattened face, retarded growth and other major (cardiac) or minor(malformations of eyes and ears) congenital abnormalities.
- A lesser degree of impairment called ‘’alcohol related neurodevelopmental disorder’’ characterised by behavioural aswellas cognitive and motor deficits.
- Alcohol is easily secreted through mothers milk which may delay motor development in the child.

TREATMENT OF ACUTE AND CHRONIC ALCOHOLISM

A.MANAGEMENT OF ACUTE ALCHOL TOXICITY:

- ✓ Intoxication due to intake of ethanol is managed by vital signs and prevention of aspiration of vomitus.

B.MANAGEMENT OF WITHDRAWAL SYNDROME:

- ✓ The withdrawal syndrome is usually managed by administaration of long acting sedative-hypnotics(eg: chlordiazepoxide or diazepam)
- ✓ The intensity of withdrawal syndrome may be reduced by clonidine and propranolol.

C.MANAGEMENT OF ALCOHOL DEPENDANCE:

- ✓ The first pharmacotherapy is by avesrsion therapy by giving disulfiram at adose od 1gm on 1^{st} day, reduce by 250gm daily; keep 250mg as maintainance once daily.
- ✓ Another approach is to use such a drug which reduces the craving for alcohol.one such drug is Naltrexon an opioid receptor anatagonist in a dose, of 50mg once a day is used to treat alcohol dependance.
- ✓ Anti –convulsant drug Topiramate is also effective in reducing craving in chronic alcoholics.
- ✓ The selective seratonin reuptake inhibitors such as Fluoxetine and Ondansetron a 5-HT3 antagonist has also been succefully used.

DRUG-INTERACTIONS:

- Chronic consumption of alcohol increases the risk of hepatoxicity due to paracetamol.
- All cerebral depressants can synergise with ethanol.
- Chronic alcohics are relatively tolerant of general anesthetic like halothane.
- Alcohols enhances the hypoglycaemic effects of insulin and sulfonylureas

CLINICAL USES OF ETHANOL:

- As skin antiseptic is most effective.
- Alcohol has astringent action and is used to harden the skin to prevent bed sores
- To treat methanol poisoning.

Antianxiety, Mood Disorder and Antipsychotic Medications

Antianxiety and Sedative-Hypnotic Drugs

- Anti-anxiety and sedative-hypnotics are CNS depressants with similar effects
- Hypnotics promote sleep
- Anti-anxiety and sedative-hypnotics promote relaxation
- The difference between the effects depends on dosages
- Will have overlap of S/S with anxiety and insomnia

Anxiety

- Pathophysiology unclear
- Imbalances in neurotransmitter substances
- ? Excess of neurotransmitter substances such as norepinephrine or deficiency of inhibitory substances such as gamma aminobutyric acid (GABA)

Anxiety

- Serotonin also plays a role in anxiety, mechanism unclear
- SSRI and serotonin receptor agonists are used to treat anxiety disorders

Sleep and Insomnia

- Four Stages of NREM sleep—progressively deeper sleep, depressed body functions, nondreaming. Has restorative effects.
- NREM sleep: decreased body temp, metabolic rate, glucose consumption and production of catabolic hormones

Sleep and Insomnia

- Following Stage 4 NREM sleep, will have 5-20 minutes of REM sleep with dreaming and increased physiologic activity
- REM sleep is felt to be mentally and emotionally restorative
- REM deprivation can lead to psychological problems and psychosis

Insomnia

- Prolonged difficulty going to sleep or staying asleep long enough to feel rested
- Can result from pain, anxiety, illness, changes in environment and from certain medications

Benzodiazepines

- Used for anxiety and insomnia
- Schedule IV
- Prototype is diazepam
- Can result in physiologic dependency, thus, abuse
- Withdrawal symptoms can result if abruptly stoppped
- Should be gradually tapered and discontinued

Benzodiazepines

- Can cause excessive sedation, impairment of physical and mental activities, and respiratory depression
- Not for long-term use
- Do not suppress REM sleep
- Vary in plasma half-lives, metabolites and uses

Benzodiazepines

- Bind with benzodiazepine receptors in nerve cells of the brain; this receptor also has binding sites for GABA
- When GABA/Benzo binding occurs, then choloride ions enter the cells causing decreased response to excitatory neurotransmitters such as norepinephrine

Pharmacokinetics

- Well-absorbed orally
- Widely distributed in body tissues
- Highly bound to plasma proteins
- Lipid soluble so easily enter CNS
- Metabolized by liver by Cytochrome p450 enzymes and by CYP3A4 enzymes in intestines

Pharmacokinetics

- Most benzodiazepines are metabolized into active metabolites that require further metabolism before clearance
- Depending on half-life, can result in accumulation and subsequent adverse drug effects
- Example: diazepam to N-DMDZ to oxazepam (see discussion p. 135).

Pharmacokinetics-shorter-acting benzos

- Versed (midazolam) 30-60 minutes
- Halcion (triazolam) 4-6 hours
- Dalmane (flurazepam) 6-8 hours
- Xanax (alpraxolam) duration of action is only 4-6 hours
- Serax (oxazepam) 2-4 hours

Pharmacokinetics-Longer-acting benzos

- Klonopin (clonazepam) duration of action may last for weeks
- Librium (chlordiazepoxide) duration of action is several days
- Tranxene (chloraxepate) duration of action lasts for days
- (see text for specific half-lives, onset of action and duration of action)

Drug and its common uses

- Xanax (alprazolam) anxiety and panic disorder
- Librium (chlordiazepoxide) anxiety and alcohol withdrawal
- Klonopin (clonazepam) seizure disorders and panic disorder
- Valium (diazepam) anxiety, seizure disorders, alcohol withdrawal, muscle spasms and for preop medication

Drugs and uses cont.

- Dalmane (flurazepam) insomnia
- Ativan (lorazepam) anxiety and preop
- Versed (midazolam) preop sedation, anesthetic induction
- Restoril (temazepam) insomnia

Contraindications to use

- Respiratory disorders
- Severe liver or kidney disease
- History of alcohol or drug abuse
- Hypersensitivity reactions

Miscellaneous antianxiety and sedative-hypnotic agents

- Buspar (buspirone) affects serotonin and dopamine receptors. No anticonvulsant or muscle relaxant effects, no CNS depression or sedation. Used for anxiety.
- Noctec (chloral hydrate) oldest sleeping medication. Does not affect REM sleep. Tolerance after two weeks.

Miscellaneous

- Prozac (fluoxetine), Luvox (fluvoxamine), Paxil (paroxetine), Zoloft (sertraline) and Effexor (venlafaxine) are SSRIs used for depression and anxiety
- Sonata (zaleplon). Schedule IV, abuse potential, for short term tx of insomnia (7-10 days). Caution in pregnancy and with liver problems. Caution if on Tagamet.

Misc.

- Ambien (zolpidem) schedule IV hypnotic. Onset within 20-30 minutes. Caution if liver problems. Dosage reductions not required for clients with renal impairment. Withdrawal s/s can occur if stopped abruptly after one week of regular use.

Others

- Melatonin-hormone produced by pineal gland. Endogenous melatonin is derived from tryptophan which is converted to serotonin then to melatonin. Melatonin affects sleep-wake cycles, is released during sleep and levels are low during waking hours. Used for jet lag due to disruption of circadian rhythms. Caution w/patients with liver or renal problems.

Benzodiazepine Withdrawal

- Mild s/s occur in approximately half of clients taking doses for 6-12 weeks or longer
- Severe s/s if taking large doses for 4 months or longer and with abrupt discontinuation
- Affects are r/t decrease in GABA neurotransmission resulting in CNS stimulation

Benzodiazepine Withdrawal

- S/S include anxiety, psychomotor agitation, insomnia, irritability, HA, tremors and palpitations
- Others—confusion, depersonalization, psychosis and seizures
- Severe symptoms most pronounced in short-acting drugs such as Xanax, Ativan and Halcion. Reduce dose by 10-25% every 1 to 2 weeks over 4-16 weeks.

Benzodiazepine Toxicity

- Effects include: excessive sedation, respiratory depression and coma.
- Romazicon (flumazenil) is antidote. Has shorter duration than many benzos so repeated dosing may be necessary. For overdose, give 0.2mg over 30 seconds, wait 30 seconds, then 0.3mg over 30 seconds, then 0.5mg every 60 seconds up to max. of 3mg.

Drug Therapy for Anxiety

- Drugs not recommended for everyday stress
- Chronic pain, have not proven to be effective
- Ativan and Serax are drugs of choice for elderly and w/liver failure. These drugs do not depend on cytochrome p450.

Drug Therapy for Anxiety

- Buspar (buspirone) effective but may take 2-4 weeks to achieve therapeutic level. So, not useful for acute episodes of anxiety.

Drug Therapy for Insomnia

- Drugs of choice are benzodiazepines and BZ1 receptor specific drugs such as Sonata and Ambien. In those with major depression, tx of the depression will be more effective.
- Most benzodiazepine hypnotics lose their effectiveness in producing sleep after 4 weeks of daily use. It is not helpful to switch drugs as cross tolerance occurs.

Drug Therapy for Insomnia

- Restoril (temazepam) is the drug of choice for elderly, those with liver disease or in those who take drugs metabolized by hepatic metabolizing drugs.

Special Populations

- Dosing is different in children as their metabolism is faster. May need larger doses for their size and weight.
- Excretion is slower in elderly so effects of a given dose last longer.
- Benzodiazepines may produce paradoxical excitement and aggression in older adults.

Special Populations

- In critical care, Ativan is the benzodiazepine of first choice. Little accumulation and its elimination not significantly affected by hepatic or renal disease.
- Versed may be given IV infusion. Does accumulate and does have toxic metabolite.
- Diprivan (proprofol) rapid acting hypnotic. SE include hypotension, apnea, CNS depression. Recovery after drug stopped is within minutes.

Antipsychotics

- Psychosis—severe mental disorder charac. By disordered though processes, inappropriate emotional responses, bizarre behavior, agitation, aggressiveness, hostility, social withdrawal, deterioration in occupational and social functioning, hallucinations and paranoid delusions.

Psychosis

- Hallucinations—sensory perceptions of people or objects that are not present. Unable to distinguish between false perceptions and reality.
- In schizophrenia or bipolar disorder, usually auditory; in delirium, usually visual or tactile; in dementia usually are visual.

Psychosis

- Delusions are false beliefs that persist in absence of reason or evidence. May believe others control their thoughts, feelings or seek to harm them.
- Psychosis may be acute or chronic.
- When acute—may be confusion or *delirium*. Can be precipitated by illness, drug effects or superimposed on chronic dementias.

Schizophrenia

- Consists of a variety of related disorders
- Does have a genetic predisposition
- *Positive* symptoms include CNS stimulation, agitation, behavioral disturbances, delusions, hallucinations, insomnia, and paranoia.
- *Negative* symptoms include anhedonia, lack of motivation, blunted affect, poor hygiene, poor social skills and social withdrawal.

Etiology of Schizophrenia

- Evidence indicates abnormal neurotransmission systems in the dopaminergic, serotonergic, and glutaminergic systems. Also, seems to be interplay between the systems so one system may affect others.

Etiology of Schizophrenia cont.

- Imbalance in amount of neurotransmitters, most notably dopamine. Overactivity accounts for the positive symptoms of schizophrenia and underactivity in another part of the brain may account for the negative symptoms.

Etiology of schizophrenia

- Glutamatergic dysfunction may be genetically linked as well as causative in the cognitive impairments and negative s/s of this disorder.

Antipsychotic Drugs

- Categorized as “typical”, “first-generation” or “conventional”==phenothiazines
- “Atypical” or “second-generation”==newer nonphenothiazines

Mechanisms of Action

- Most bind to D2 dopamine receptors and block the action of dopamine but positive effects only occur over time
- Theory is that blockade of dopamine recptors leads to changes in receptors w/effects on cell metabolism and function
- With chronic drug administration, it is postulated that drugs re-regulate the abnormal neurotransmission systems

Indications

- Schizophrenia
- Psychotic symptoms associated with brain impairment (injuries)
- Useful in manic phase of bipolar affective disorder until Lithium (drug of choice) becomes effective

Phenothiazines--Uses

- Schizophrenia
- Nausea and vomiting—affect chemoreceptor trigger zone in medulla
- Intractable hiccups—mechanism of action is unclear

Contraindications of Phenothiazines

- Liver damage
- CAD
- Cerebrovascular disease
- Parkinsonism
- Bone marrow depression
- Severe hypotension and hypertension

Phenothiazines

- Use with caution in:
- BPH
- Seizure disorders
- glaucoma

Phenothiazines

- PO or IM
- Prototype Thorazine (chlorpromazine)
- Metabolized by the cytochrome p450 system
- No psychological dependency but physical dependency can occur. Withdrawal s/s may occur.

Phenothiazines

Side effects include:

- CNS depression
- Anticholinergic effects
- Antiemetic effects
- Lowering of body temperature
- Hypersensitivity reactions
- EPS
- Weight gain
- Orthostatic hypotension

Extrapyramidal Symptoms (EPS)

- Affects extrapyramidal system and basal ganglia. Is the system that includes descending fibers that reach the medulla other than by the corticospinal tracts. Is important in maintenance of equilibrium and muscle tone.
- Symptoms include: dystonia, akathisia, tardive dyskinesia and parkinsonism

EPS

- Dystonia—prolonged muscle contractions causing twisting and repetitive movements or abnormal posture. May have rhythmic jerks.
- Akathisia—restless. Unable to sit still. Most common symptom.
- Choreiform movements—involuntary muscular twitching.
- Tardive dyskinesia—hyperkinetic movements of the face (sucking and smacking lips, facial grimaces and tongue protrusion).

Treatment of EPS

- Treat with antiparkinson medications such as: Benadryl (diphendydramine), Symmetrel (amantadine) or Eldepryl (selegiline).

Phenothiazines

- Thorazine
- Prolixin (fluphenazine)
- Compazine (prochlorperazine)
- Stelazine (trifluoperazine)
- Mellaril (thioridazine) used less commonly due to cardiac side effects

Nonphenothiazines

- 1st generation
- Haldol (haloperidol)—potent, long-acting
- Causes high incidence of EPS
- Useful in mental retardation w/hyperkinesia, Tourette's and Huntington's disease
- Comes in oral form and even in once a month injection form

1st generation antipsychotics

- Loxitane (loxapine)
- Moban (molindone)
- Orap (pimozide) for Tourette's when Haldol not effective. Can cause tardive dyskinesia, motor seizures and even sudden death.

Second generation antipsychotics

- Now the drugs of choice
- Effective intreating the positive s/s of psychosis and have greater effectiveness in relieving the negative s/s
- Less likely to cause EPS

Second generation antipsychotics

- Clozaril (clozapine) Prototype of the atypicals.
- Effective but considered a second line drug because of its association with agranulocytosis. Weekly WBCs are indicated during the first 6 months of therapy.

Second generation antipsychotics

- Zyprexa (olanazapine)—can cause EPS but not agranulocytosis. Causes less sedation, less orthostasis, and anticholinergic effects.
- Seroquel (quietapine) blocks dopamine and serotonin. Relieves positive and negative symptoms. Many drug interactions as is metabolized by the cytochrome p450 system.

Second generation cont.

- Risperdal (risperidone)—blocks dopamine and serotonin. Affects both positive and negative symptoms. Often first choice treatment. Is also metabolized by cytochrome p450 system. Can cause parkinsonism.

2nd generation

- Abilify (aripiprazole)—newest atypical drug. Is called a partial dopamine agonist. Has ability to block overstimulated receptors and stimulate understimulate receptors. Can cause orthostatic hypotension, tardive dyskinesia, weight gain, hyperglycemia and neuroleptic malignant syndrome.

Drug Selection

- Atypicals are drugs of choice as they:
- May be more effective
- Produce milder adverse effects
- Patients display greater compliance in taking them
- Drawbacks include: glucose intolerance, weight gain
- Drawbacks also are costs

Drug Selection

- Duration of therapy is generally for many years as relapses can occur
- Drug withdrawal can occur if medications are stopped abruptly. Can result in cholinergic effects such as diarrhea, drooling and insomnia. Drugs should be tapered over several weeks.

Treatment of EPS

- More likely to occur with older antipsychotic drugs
- Treat with anticholinergic antiparkinson drugs
- Treatment is usually for three months then gradual discontinuation. S/S generally do not recur.

Special Populations

- Antipsychotics will have shorter half-lives and need for more frequent dosing
- Require caution in the elderly r/t cardiovascular effects, BPH, glaucoma, diabetes
- Metabolism may vary in different ethnic groups e.g. African Americans are slow metabolizers so dosages must be adjusted

Neuroleptic Malignant Syndrome

- Rare but potentially fatal reaction that may occur hours to months after initial antipsychotic drug use. Will present with fever, muscle rigidity, agitation, confusion, delirium, tachycardia, respiratory failure, acute renal failure.
- Tx—stop drug, supportive care, dantrolene and amandatine.

Antidepressants and Mood Stabilizers

- Mood disorders include: depression, dysthymia, bipolar disorder, and cyclothymia
- If have had one depressive episode, higher risk for having another

Monoamine Neurotransmitter Dysfunction

- Complex etiology affecting neurotransmitters and receptors
- Felt to be partially a result of deficiency in norepinephrine and/or serotonin
- Interplay between neurotransmitters: norepinephrine, serotonin, dopamine and acetylcholine

Neuroendocrine Factors

- Increased secretion of CRH by hypothalamus, ACTH by pituitary and cortisol by the adrenal cortex
- Increased cortisol may decrease the numbers or sensitivity of cortisol receptors and lead to depression

Other Factors

- Interplay with thyroid and growth hormones
- Genetics
- Immunity
- Environmental factors resulting in structural changes in brain such as child abuse

Types of Mood Disorders

- Depression
- Dysthymia—chronically depressed mood/2 other s/s and for at least 2 years
- Bipolar—depression alternating with mania
- Cyclothymia—mild type of bipolarity. S/S
- Must be present for 2 years.
- Details on p. 175

General Characteristics of Antidepressants

- Vary in adverse effects
- Must achieve serum level before improvement seen (2-4 weeks)
- Taken orally, undergo significant first pass metabolism
- Multiple drug interactions as are metabolized by cytochrome p450 enzymes

Mechanisms of Action

- Normalize neurotransmission systems by altering the transmitters and receptors
- Also modify interactions between neurotransmission systems and endocrine functions (ACTH and cortisol levels)
- Neurotransmitters that are not bound are inactivated by reuptake or are metabolized by monoamine oxidase

Contraindications to Use

- Use cautiously in schizophrenia, mixed mania and depression
- Suicidal tendencies
- In severe renal, hepatic or cardiovascular disease
- In narrow-angle glaucoma
- Seizure disorders

Tricyclics

- More serious adverse effects especially anticholinergic and cardiac effects, weight gain and sedation
- Tofranil (imipramine)
- Elavil (amitriptyline)
- Sinequan (doxepin)
- Norpramin (desipramine)

Selective Serotonin Reuptake Inhibitors

- Adverse effects include nausea, sexual dysfunction, headache, increased risk of GI bleed, **never** coadministration with MAOI
- Prozac (fluoxetine) long duration
- Zoloft (sertraline)
- Celexa (citalopam)
- Paxil (paroxetine) long duration

MAOIs

- Foods that contain tyramine, a monoamine precursor of norepinephrine, when taken with MAOIs can lead to severe hypertension, stroke or heart attack
- Rarely used because of food interactions
- Avoid: aged cheeses and meats, concentrated yeast extracts, sauerkraut and fava beans

MAOIs

- Marplan (isocarboxazid)
- Nardil (phenelzine)
- Parnate (tranylcypromine)

Mood Stabilizing Agent

- Lithium for bipolarity- mania phase
- Must be closely monitored
- Excreted by kidneys so must have adequate renal functioning
- Caution if hyponatremic as will cause lithium toxicity

ANTIEPILEPTIC DRUGS

Epilepsy

- It is a **Chronic** medical condition produced by sudden changes in the electrical function of the brain.

- It is a condition characterized by recurrent episodes of seizures.

- Seizure- a paroxysmal abnormal discharge at high frequency from neurons in cerebral cortex.

- Convulsions- involuntary, violent, spasmodic contractions of skeletal muscles.

Etiology

- Congenital defects, head injuries, trauma, hypoxia
- Infection e.g. meningitis, brain abscess, viral encephalitis
- Concussion, depressed skull, fractures
- Brain tumors (including tuberculoma), vascular occlusion
- Drug withdrawal, e.g. CNS depressants
- Fever in children (febrile convulsion)
- Hypoglycemia, hypocalcemia
- Photo epilepsy

Drugs and Other Substances that Can Cause Seizures

Drugs of abuse

- Amphetamine
- Cocaine
- Phencyclidine
- Methylphenidate

Anesthetics and analgesics

- Meperidine
- Tramadol
- Local anesthetics

Psychotropics

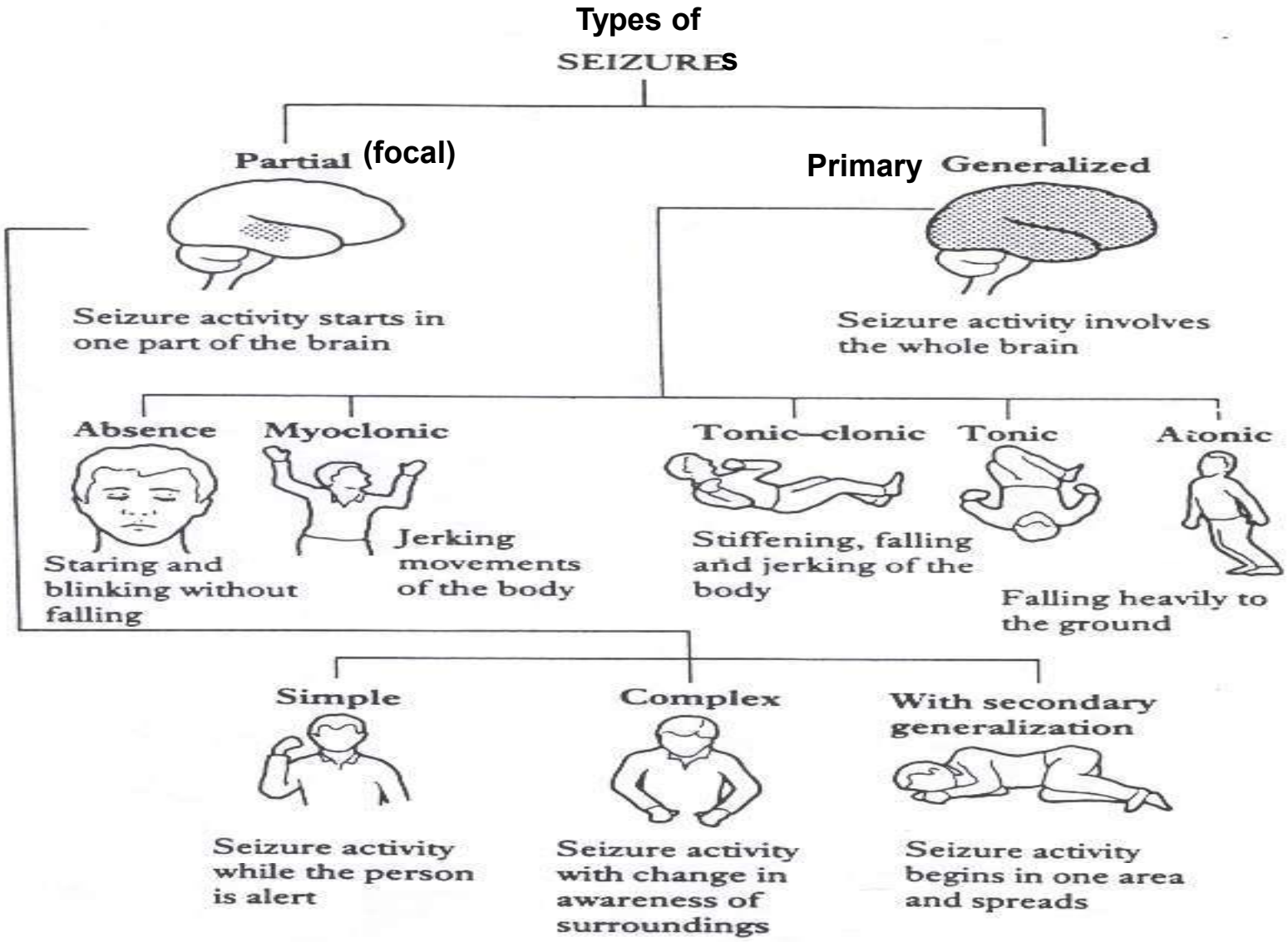
- Antidepressants
- Antipsychotics
- Li

Sedative-hypnotic drug withdrawal

- Alcohol
- Barbiturates
- Benzodiazepines

TRIGGERS:

Fatigue, stress, poor nutrition, alcohol and sleep deprivation.


Types of
SEIZURES
Partial (focal)
Primary Generalized
Seizure activity starts in one part of the brain
Seizure activity involves the whole brain
Absence
Myoclonic
Tonic–clonic
Tonic
Atonic
Staring and blinking without falling
Jerking movements of the body
Stiffening, falling and jerking of the body
Falling heavily to the ground
Simple
Complex
With secondary generalization
Seizure activity while the person is alert
Seizure activity with change in awareness of surroundings
Seizure activity begins in one area and spreads

A) Focal or partial

1) Simple partial(Jacksonian)- *The electrical discharge is cofined to the* ***motor area.***

2)Complex partial(psychomotor)- *The electrical discharge is confined in certain parts of the temporal lobe concerned with* ***mood*** *as well as* ***muscle.***

B) Primary generalized

1) ***Tonic- clonic****. Pt fall in convulsion & may bite his tongue & may lose control of his bladder or bowel.*

2) ***Tonic****. Some pts, after dropping unconscious experience only the tonic phase of seizure.*

3) ***Atonic (akinetic)****. Unconsciousness and relaxation of pt's muscles & he drops down.*

4) ***Myoclonic*** *. Sudden, brief shock like contraction which may involve the entire body or be confined to the face, trunk or extremities.*

5) ***Absence (petit mall)*** *.momentary loss of consciousness without involving motor area. Most common in children (4-12 yrs).*

EEG- symmetric 3 Hz spikes and wave pattern.

6) ***Status epilepticus (re-occuring seizure).*** *Continuous seizure (>30 min) without intervening return of consciousness.*

- **Lennox-Gastaut syndrome-** occurs in children and is defined by the following triad:
- (1) multiple seizure
- (2) EEG showing slow (<3 Hz) spike-and-wave discharges
- (3) impaired cognitive function,associated with CNS disease or dysfunction

Mesial temporal lobe epilepsy (MTLE)-

- characteristic hippocampal sclerosis
- refractory to treatment with anticonvulsants but responds extremely well to surgical intervention.

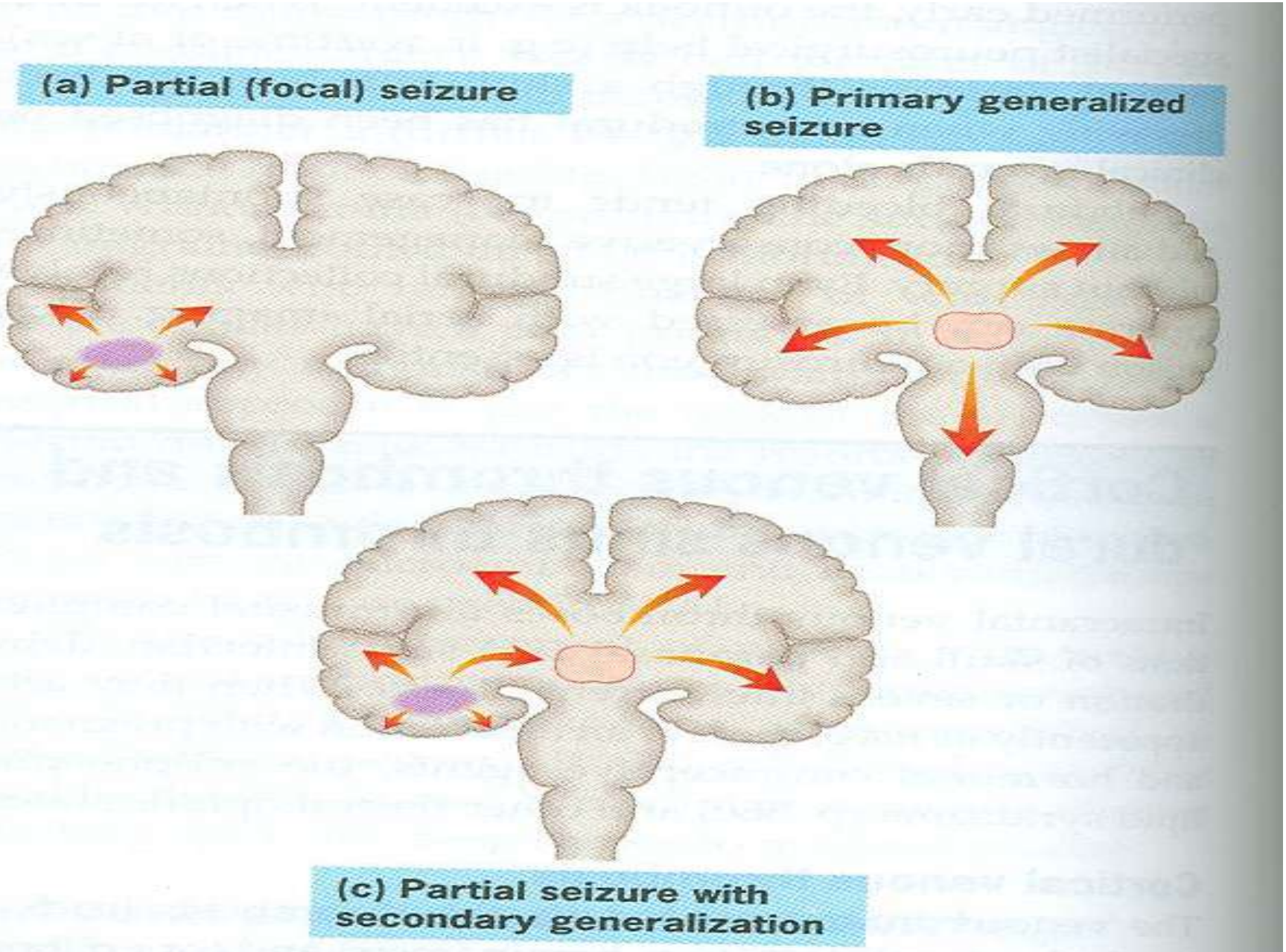


Fig. 20.23 **Seizure types.** **(a)** Partial (focal) seizure. **(b)** Primary generalized seizure. **(c)** Partial seizure with secondary generalization.

PROLONGATION OF N a+ CHANNEL INACTIVATION

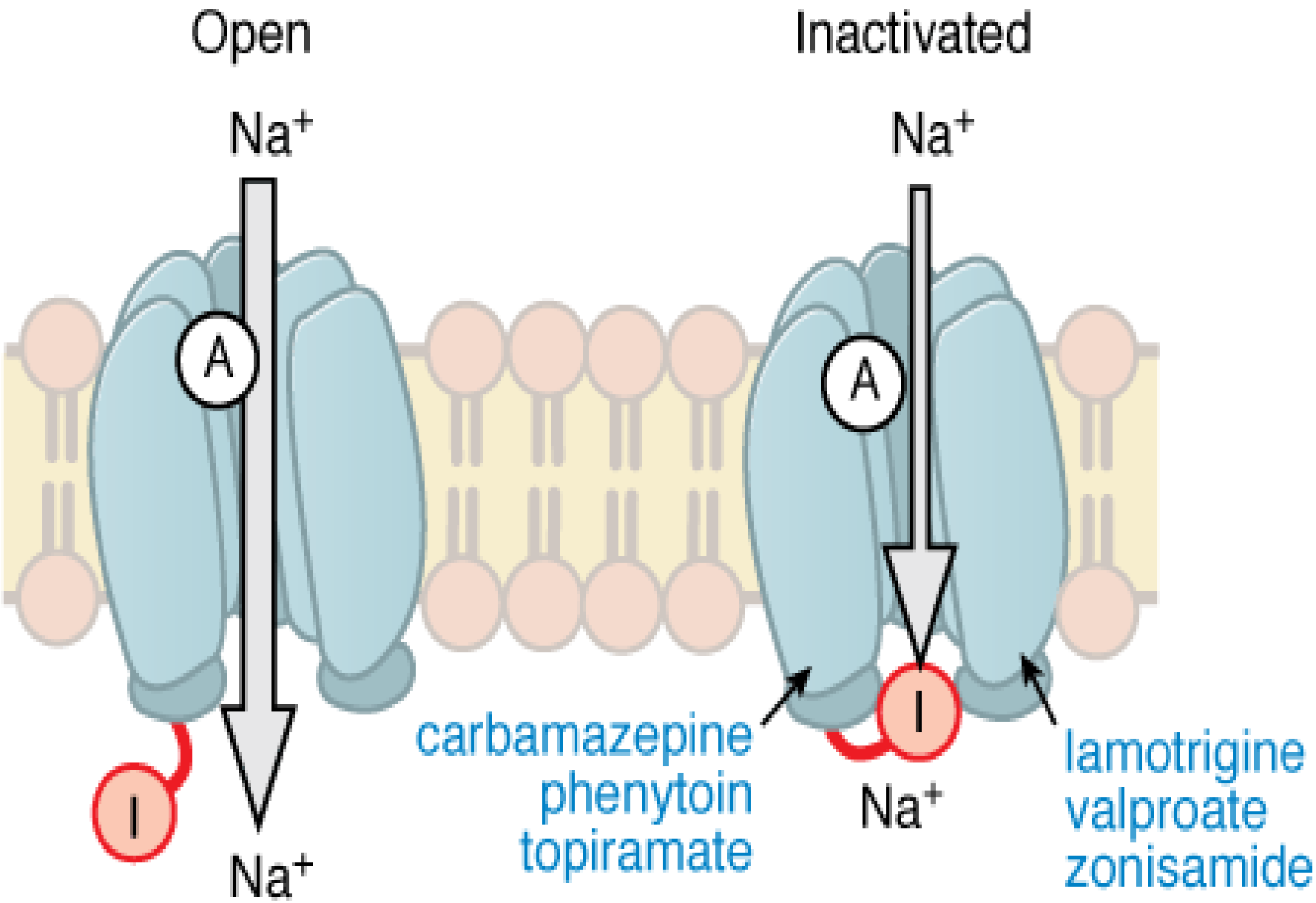
- Phenytoin
- Carbamazepine
- Valproate
- Lamotrigine
- Topiramate
- Zonisamide

INHIBITION OF 'T' TYPE Ca2+ CURRENT

- Ethosuximide
- Trimethadione
- Valproate

FACILITATION OF GABA MEDIATED Cl CHANNEL OPENING

- Barbiturate (Barb.)
- Benzodiazepine (Bzd.)
- Vigabatrin (Viga.)
- Valproate (Valpr.)
- Gabapentin (Gabp.)
- Tiagabine (Tiag.)


Open
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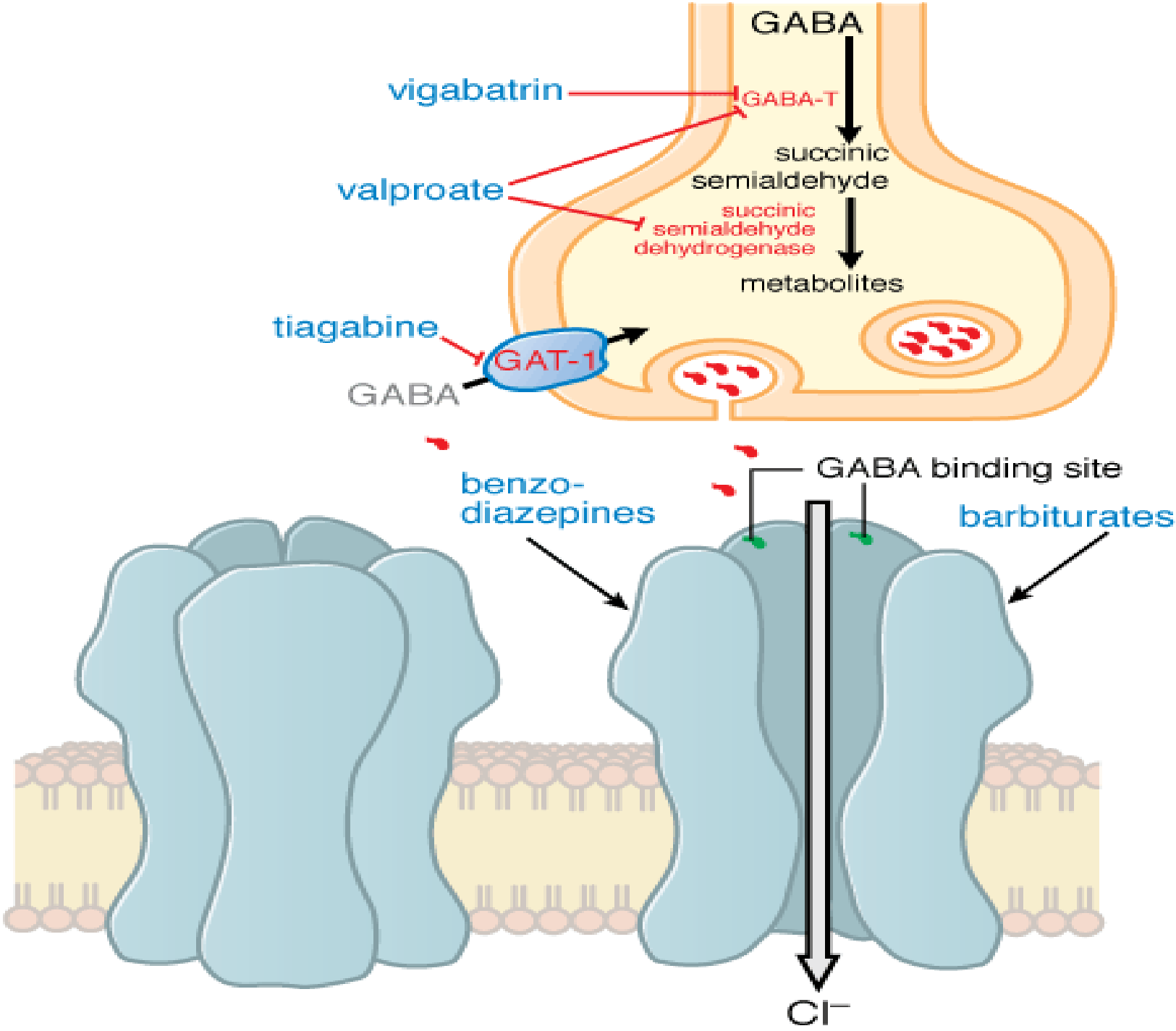
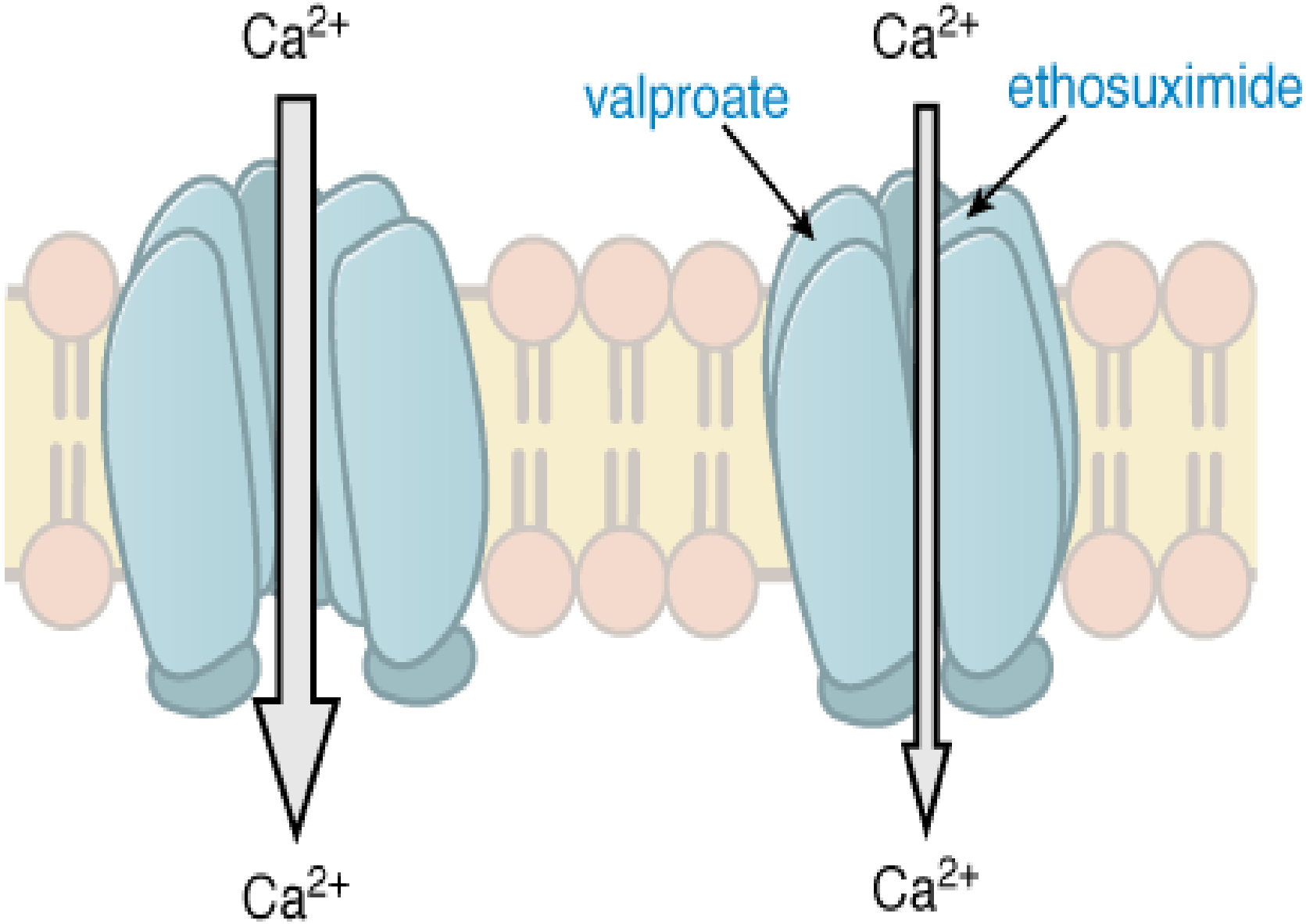
carbamazepine
phenytoin
topiramate
lamotrigine
valproate
zonisamide


GABA
vigabatrin
GABA-T
valproate
succinic
semialdehyde
succinic
semialdehyde
dehydrogenase
metabolites
tiagabine
GAT-1
GABA
benzo-
diazepines
GABA binding site
barbiturates
Cl⁻


Ca2+
Ca2+
valproate
ethosuximide
Ca2+
Ca2+

MOLECULAR TARGET AND ACTIVITY	DRUG	CONSEQUENCES OF ACTION
Na^+ channel modulators that:		
enhance fast inactivation	PHT, CBZ, LTG,	• block action potential propagation
	FBM, OxCBZ,	• stabilize neuronal membranes
	TPM, VPA	• ↓ neurotransmitter release, focal firing, and seizure spread
enhance slow inactivation	LCM	• ↑ spike frequency adaptation
		• ↓ AP bursts, focal firing, and seizure spread
		• stabilize neuronal membrane
Ca^{2+} channel blockers	ESM, VPA, LTG	• ↓ neurotransmitter release (N- & P-types)
		• ↓ slow-depolarization (T-type) and spike-wave discharges
$\alpha 2\delta$ ligands	GBP, PGB	• modulate neurotransmitter release
$GABA_A$ receptor allosteric modulators	BZDs, PB, FBM, TPM, CBZ, OxCBZ	• ↑ membrane hyperpolarization and seizure threshold • ↓ focal firing
		BZDs—attenuate spike-wave discharges
		PB, CBZ, OxCBZ—aggravate spike-wave discharges

GABA uptake inhibitors/ **GABA-transaminase inhibitors**	TGB, VGB	• ↑ extrasynaptic GABA levels and membrane hyperpolarization
		• ↓ focal firing
		• aggravate spike-wave discharges
NMDA receptor antagonists	FBM	• ↓ slow excitatory neurotransmission
		• ↓ excitatory amino acid neurotoxicity
		• delay epileptogenesis
AMPA/kainate receptor antagonists	PB, TPM	• ↓ fast excitatory neurotransmission and focal firing
Enhancers of HCN channel activity	LTG	• buffers large hyperpolarizing and depolarizing inputs • suppresses action potential initiation by dendritic inputs
SV2A protein ligand	LEV	• unknown; may decrease transmitter release
Inhibitors of brain carbonic anhydrase	ACZ, TPM, ZNS	• ↑ HCN-mediated currents • ↓ NMDA-mediated currents • ↑ GABA-mediated inhibition

TREATMENT OF SEIZURES

Seizure disorder	*Drugs*
Tonic-clonic(Grand mal) *Drug of Choice*	*Valproate* *Topiramte* *Lamotrigine*
Alternatives:	*Carbamazepine* *Phenobarbital* *Phenytoin*
Partial (simple or complex) *Drug of choice*	*Carbamazepine* *Phenytoin* *Valproate*
Alternatives:	*Phenobarbital* *Lamotringine (as adjunct or alone)* *Gabapentin (as adjunct)*

Treatament cont,d

Absence (petit mal) *Drug of choice*	*Valproate* *Ethosuximide*
Alternatives:	*Clonazepam, Lamotrigine*
Myoclonic, Atonic *Drug of choice*	*Valproate*
Alternatives:	*Clonazepam*
Status Epilepticus *Drug of choice*	*Lorazepam, Diazepam, i.v.* *or Phenytoin, i.v. or Vaproate*
Alternatives:	*Phenobarbital, i.v*
Febrile Seizures	*Diazepam, rectal** *Diazepam ,i.v* *Valproate*

Treatment:

- *Up to 80% of pts can expect partial or complete control of seizures with appropriate treatment.*
- *Antiepileptic drugs suppress but do not cure seizures*
- *Antiepileptics are indicated when there is two or more seizures occurred in short interval (6m -1 y)*
- *An initial therapeutic aim is to use only one drug (monotherapy)*

Treatment (Cont.)

- ***Advantage of monotherapy**:*
- *fewer side effects, decreased drug-drug interactions, better compliance, lower costs*
- *Addition of a second drug is likely to result in significant improvement in only approx. 10 % of patients.*

Treatment (Cont.)

- ***when a total daily dose is increased, sufficient time (about 5 t 1l2) should be allowed for the serum drug level to reach a new steady-state level.***

- ***The drugs are usually administered orally***

- ***The monitoring of plasma drug levels is very useful***

- ***Precipitating or aggravating factors can affect seizure control by drugs***

Treatment (Cont.)

- *The sudden withdrawal of drugs should be avoided*

  withdrawal may be considered after seizure- free period of 2-3 or more years

- *Relapse rate when antiepileptics are withdrawn is 20 - 40 %*

During pregnancy

Safer antiepileptics

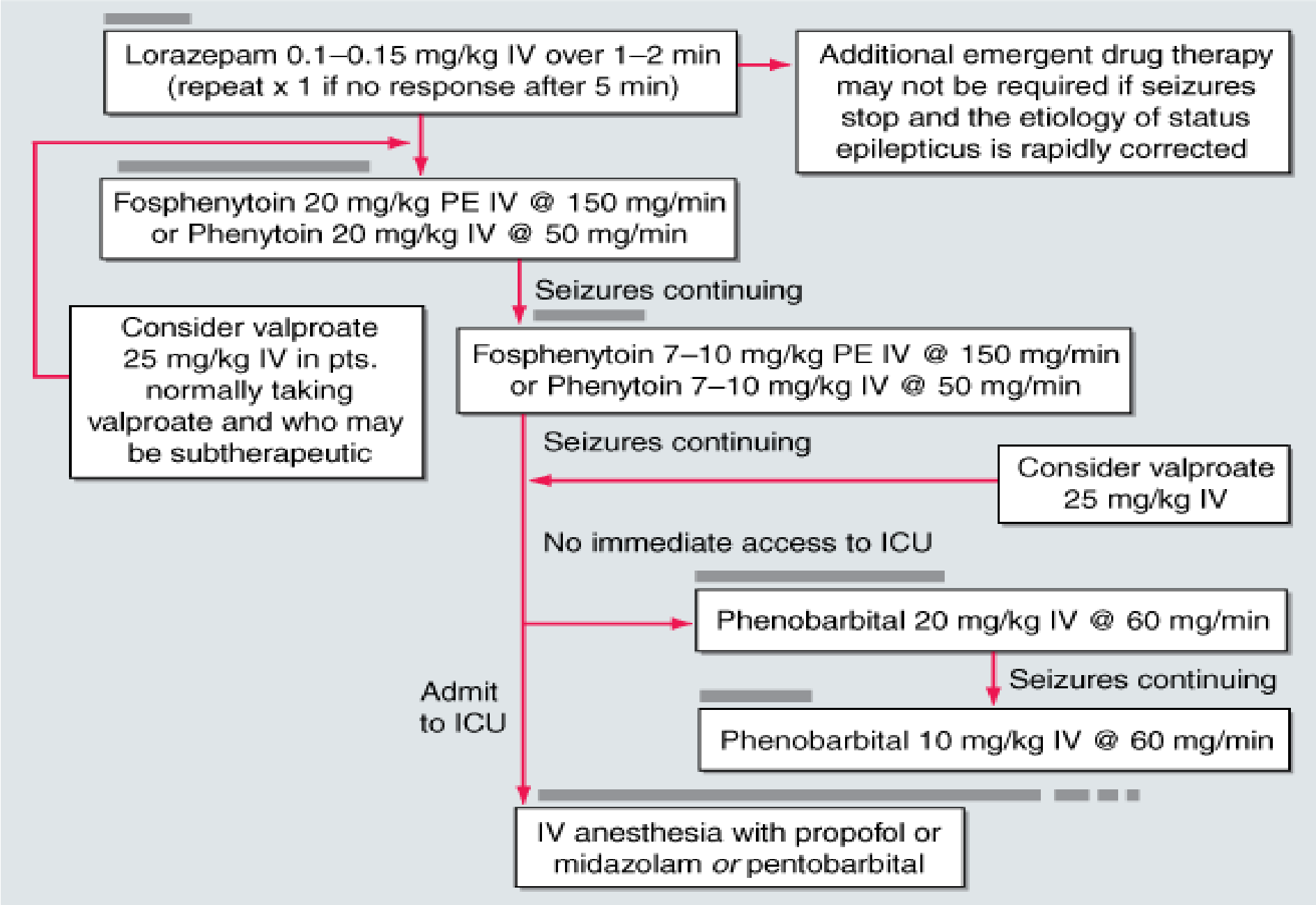
- Carbamazepine
- Oxcarbamazepine
- Lamotrigine
- Ethosuximide

Folic acid supplement

When to Withdraw Antiepileptic Drugs?

Normal neurological examination
Normal IQ
Normal EEG prior to withdrawal
Seizure- free for at least 3 yrs
NO juvenile myoclonic epilepsy

Status epilepticus management



Phenytoin

Pharmacokinetics

- ***Well absorbed when given orally, however, it is also available as iv. (for emergency)***
- ***80-90% protein bound***
- ***Induces liver enzymes (Very Important)***
- ***Metabolized by the liver to inactive metabolite***
- ***Metabolism shows saturation kinetics and hence t ½ increases as the dose increased***
- ***Excreted in urine as glucuronide conjugate***
- ***Plasma t ½ approx. 20 hours***
- ***Therapeutic plasma concentration 10-20 μg/ml (narrow)***
- ***Dose 200-400 mg/day***

Phenytoin (Cont.)

Mechanism of Action:

Membrane stabilization by blocking Na & Ca influx into the neuronal axon.

or inhibits the release of excitatory amino acids via inhibition of Ca influx

Clinical Uses:

Used for partial Seizures & generalized tonic-clonic seizures. But not effective for absence Seizures .

Also can be used for Rx of ventricular fibrillation.

Side effects:

Dose Related:

- ***G.I.T upset***
- ***Neurological like headache, vertigo, ataxia, diplopia, nystagmus***
- ***Sedation***
- ***Intimal damage & thrombosis of vein-***

  So rate of injection s/b < 50mg/min

Side effects of Phenytoin (Cont.)

Non-dose related:

- ***Hyperplasia of Gingival***
- ***Hirsutism***
- ***Hypersensitivity*** *reactions (mainly skin rashes and lesions, mouth ulcer)*
- ***Hepatitis*** *–rare*
- ***Hydantoin syndrome-*** *Fetal malformations- esp. cleft plate, hypoplastic phalanges, microcephaly)*
- *Bleeding disorders (infants)*
- ***Osteomalacia*** *due to abnormalities in vit D metabolism*
- ***Megaloblastic anaemia***

- **Side effects of phenytoin (Cont.)**

- ***Pharmacokinetic Interactions***

  – *Inhibitors of liver enzymes elevate its plasma levels e.g. Chloramphenicol, INH,etc.*

  – *Inducers of liver enzymes reduce its plasma levels e.g. Carbamazipine; Rifampicin.*

CARBAMAZEPINE

Its mechanism of action and clinical uses are similar to that of phenytoin. However, it is also commonly used for Rx of mania and trigeminal neuralgia.

Pharmacokinetics

available as an oral form only

Well absorbed

80 % protein bound

Strong inducing agent including its own (can lead to failure of other drugs e.g. oral contraceptives, warfarin, etc.

Metabolized by the liver

Pharmacokinetics of CBZ(Cont.)

- ***Excreted in urine as glucuronide conjugate***
- ***Plasma $t_{1/2}$ approx. 30 hours***
- ***Therapeutic plasma concentration 6-12 μg/ml (narrow).***
- ***Dose 200-800 mg/day (given BID as sustained release form)***

- **Side Effects of Carbamazepine:**
- *G.I upset*
- *Drowziness, ataxia and headache; diplopia*
- *Hepatotoxicity- rare*
- *Congenital malformation (craniofacial anomalies & neural tube defects).*
- *Hyponatraemia & water intoxication.*
- *Late hypersensitivity reaction (erythematous skin rashes, mouth ulceration and lymphadenopathy.*
- *Blood dyscrasias as fetal aplastic anemia (stop medication); mild leukopenia (decrease the dose)*

Pharmacokinetic interactions of CBZ

- Inducers of liver enzymes reduce its plasma level

  e.g. Phenytoin; Phenobarbital; Rifampicin

- inhibitors of liver enzymes elevate its plasma levels

  e.g. erythromycin,INH ,verapamil; Cimetidine

Phenobarbital

Mechanism of Action:

- Increases the inhibitory neurotransmitters (e.g: GABA) and decreasing the excitatory transmission.

Sodium Valproate or Valproic Acid

- **Pharmacokinetics :**
- Available as capsule, Syrup, I.V
- Metabolized by the liver (inactive)
- High oral bioavailability
- Inhibits metabolism of several drugs such as Carbamazepine; phenytoin, Topiramate and phenobarbital.
- Excreted in urine (glucuronide)
- Plasma t1/2 approx. 15 hrs

Sodium valproate (cont.)

Mode of action (by all possible methods)

- Increase in GABA content of the brain (inhibits GABA – transaminase and succinic semialdehyde dehydrogenase)

Sodium Valpraote (cont.)

- **Clinical Use:**
  - Very effective against absence, myoclonic seizures.
  - Also, effective in gen. tonic-clonic siezures (primarly Gen)
  - Less effective as compared to carbamazepine for partial seizures
  - Like Carbamazepine also can be used for Rx of mania

- **Side Effects of Sod. valproate:**
- Nausea, vomiting and GIT disturbances (Start with low doses)
- **Increased appetite & weight gain**
- Transient hair loss.
- **Hepatotoxicity**
- Thrombocytopenia
- **Neural Tube defect** (e.g. Spina bifida) in the offspring of women. (contraindicated in pregnancy)

Newer Antiepileptic Drugs
(Second- Generation)

1. Vigabatrin 1989
2. Gabapentin 1993**
3. Lamotrigine 1994**
4. Topiramate 1996**
5. Tiagabine 1997
6. levetiracetam 1999
7. Oxcarbazepine 2000 (safety profile similar to CBZ). Hyponatremia is also problem, however it is less likely to cause rash than CBZ.
8. Zonisamide 2000

- **NEWER AGENTS DIFFER FROM OLDER DRUGS BY**

  Relatively lack of drug-drug interaction (simple pharmacokinetic profile) Improved tolerability

  HOWEVER THEY ARE

  Costly with limited clinical experience

Lamotrigine

Pharmacological effects

Resembles phenytoin in its pharmacological effects

Well absorbed from GIT

Metabolised primarily by glucuronidation

Does not induce or inhibit C. P-450 isozymes (its metabolism is inhibitted by valproate)

Plasma t 1/2 approx. 24 hrs.

- **Mechanism of Action:**

  Inhibits excitatory amino acid release (glutamate & aspartate) by blockade of Na channels.

- **Uses**: As add-on therapy or as monotherapy

- **Side effects:**
- Skin rash, somnolence, blurred vision, diplopia, ataxia, headache, aggression, influenza – like syndrome

Gabapentin

- Structural analogue of GABA .May increase the activity of GABA or inhibits its re-uptake.

  Pharmacokinetics:

  Not bound to proteins

  Not metabolized and excreted unchanged in urine
- Does not induce or inhibit hepatic enzymes (similar to lamotrigine)
- Plasma $t_{½}$ 5-7 hours

Gabapentin (Cont.)

- **Side effects:**
- Somnolence, dizziness, ataxia, fatigue and nystagmus.

- **Uses**:
- As an adjunct with other antiepileptics
- Pain due to diabetic neuropathy, postherpetic neuralgia

Topiramate

- ***Pharmacological Effects:***
- *Well absorbed orally (80 %)*
- *Food has no effect on absorption*
- *Has no effect on microsomal enzymes*
- *9-17 % protein bound (minimal)*
- *Mostly excreted unchanged in urine*
- *Plasma t1l2 18-24 hrs*
- ***Mechanism of Action:***
- *Blocks sodium channels (membrane stabilization) and also potentiates the inhibitory effect of GABA.*

Topiramate (cont'd)

Side effects:

- ***Psychological or cognitive dysfunction***
- ***Weight loss***
- *Sedation*
- *Dizziness*
- *Fatigue*
- *Urolithiasis*
- *Paresthesias (abnormal sensation)*
- *Teratogenecity (in animal but not in human)*

Vigabatrin (restricted)

Pharmacological effects: Drug of choice for infantile spasms

- Not bound to proteins ,Not metabolized and excreted unchanged in urine
- Plasma t1/2 4-7 hrs

Mechanism of action :

Inhibits GABA metabolising enzyme & increase GABA content in the brain(similar to valproate).

Side effects:

Visual field defects, psychosis and depression (limits its use).

Zonisamide

Pharmacokinetics:

- Well absorbed from GIT (100 %)
- Protein binding 40%
- Extensively metabolized in the liver
- No effect on liver enzymes
- Plasma $t_{½}$ 50 -68 hrs

Mech of action: Prolongation of sodium channel inactivation

Clinical Uses:

Add-on therapy for partial seizures

Side Effects:

Drowsiness, ataxia , headache, loss of appetite, nausea & vomiting, Somnolence .

Tiagabine

- *Adjunctive therapy in partial and generalized tonic-clonic seizures*

• *Pharmacological effects*

- *Bioavailability > 90 %*
- *Highly protein bound (96%)*
- *Metabolized in the liver*
- *Plasma $t_{½}$ 4 -7 hrs*

• *Mode of action:*

- *inhibits GABA uptake and increases its level*

Tiagabine cont'd

- ***Side effects:***
- *Asthenia*
- *Sedation*
- *Dizziness*
- *Mild memory impairment*
- *Abdominal pain*

Clinical Advices for the Use of Drugs in the Treatment of Epilepsy.

- ***General features***:
- *It is essential to have an accurate and comprehensive diagnosis.*

- *Must treat underlying causes e.g. hypoglycemia , infection and tumor*

- *Diagnosis: Adequate description of symptoms both from patient and eye witness.*

- *EEG(supportive)*

Clinical Advices (Cont.)

- ***EEG should not be an indication for confirming epilepsy nor to stop treatment for seizure free patients.***
- ***20% of pts admitted after positive recording with EEG did not have the disorder (Betts,1983)***

Common Causes of Failure of Antiepileptics

1. Improper diagnosis of the type of seizures
2. Incorrrect choice of drug
3. Inadequate or excessive dosage
4. Poor compliance

Antiepeliptics and Pregnany:

- Seizure very harmful for pregnant women.
- Monotherapy usually better than drugs combination.
- Folic acid is recommended to be given for every pregnant women with epilepsy
- Phenytoin, sodium valproate are absolutely contraindicated and oxcarbamazepine is better than carbamazepine.
- Experience with new anticonvulsants still not reliable to say that are better than old ones.

MCQs

Q 1.Which one of the following antiepileptic drugs does NOT act by Na^+channel modulation?

A. Phenytoin
B. Carbamazepine
C. Lamotrigine
D. Phenobarbitone

- Ans D

Q2. Which one of the following antiepileptic drugs can cause permanent vision loss?

A. Lacosamide
B. Vigabatrin
C. Topiramate
D. Levetiracetam

- Ans - B

Q3. **Mechanism of action of vigabatrin is**

A. Increase in GABA concentration
B. Sodium channel blockade
C. NMDA receptor blockade
D. Calcium channel blockade

- **Ans- A**

Q4. Mechanism of action of ethosuximide is

A. Reduction of low threshold Ca^{2+} current (T-type current)
B. Sodium channel blockade
C. Increase in GABA
D. NMDA receptor blockade

- Ans- A

Q5. Ethosuximide is the drug of choice in:

A. Absence seizures
B. Febrile convulsions
C. Generalized tonic clonic seizures
D. Myoclonic seizures

Ans- A

Q6. **Which one of the following is broad-spectrum anti-seizure drug?**

A. Ethosuximide
B. Valproate
C. Phenytoin
D. Phenobarbital

- Ans-B

Thank you

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Drugs for Parkinson's disease

Pathogenesis of Parkinson's disease

- ***Parkinson's disease (PD) is a progressive disorder of movement that occurs mainly in the elderly. The chief symptoms are:***
- ***H ypokinesia***
- ***R igidity***
- ***T remors***

PARKINSON'S DISEASE

- Onset usually gradual, after age 50. (Slowly progressive)

- Mask-Like, Blank Expression
- Stooped Posture
- Pill Rolling Tremors

Bradykinesia
- Loss of normal arm swing while walking
- ↓ Blinking of the eyelids
- Loss of ability to swallow
- Blank expression
- Difficulty initiating movement

- Possible Mental Deterioration
- Depression

Tremor
- Commonly in hands and arm
- Pill rolling motion with the fingers
- Occurs most often at rest
- May involve diaphragm, tongue, lips and jaw
- Increases with stress

Muscle Rigidity
- ↑ Resistance to passive movement
- Cog wheel, jerky slow movement

- Rarely Occurs In Black Population

- Shuffling, Propulsive Gait

Parkinson's Disease

- A degenerative and progressive disorder
- Associated with neurological consequences of decreased dopamine levels produced by the basal ganglia (substantia nigra)
- Dopamine is a neurotransmitter found in the neural synapses in the brain
- Normally, neurones from the SN supply dopamine to the corpus striatum (controls unconscious muscle control)
- Initiates movement, speech and self-expression

- Balance, posture, muscle tone and involuntary movement depends on the roles of dopamine (inhibitory) and acetylcholine (Ach: excitatory)

- Basis to exploit by drugs:
  - Restore dopamine function
  - Inhibit Ach within corpus striatum

Consequences of dopamine reductions

- **Tremors** – hands and head develop involuntary movements when at rest; pin-rolling sign (finger and thumb)
- **Muscle rigidity** – arthritis-like stiffness, difficulty in bending or moving limbs; poker face
- **Bradykinesia** – problems chewing, swallowing or speaking; difficulty in initiating movements and controlling fine movements; walking becomes difficult (shuffle feet)
- **Postural instability** – humped over appearance, prone to falls

Clinical Presentation

- Altered body image (depression)
- Poor balance
- Bradykinesia (slow movement)
- Bradyphrenia (slowness of thought)
- Constipation
- Dribbling/drooling
- Dyskinesias (involuntary movements)
- Dysphagia (difficulty swallowing
- Dystonia (pain spasms)
- Excessive sweating (impaired thermoregulation)
- Festinating gait
- Hallucinations (visual)
- Postural hypotension
- Restless leg syndrome (leg aches, tingle, or burn)
- Rigidity
- Sleep disturbance
- Slurring/slowing of speech
- Tremor

Causes

- number of factors:
  - Environmental – toxins
  - Free Radicals – there is a increase in post-mortem brain sections
  - Aging – age related decline in dopamine production
  - Genetic – genes encode for

    -α-synuclein

    -Carboxy terminal hydroxylase of parkin & ubiquitin

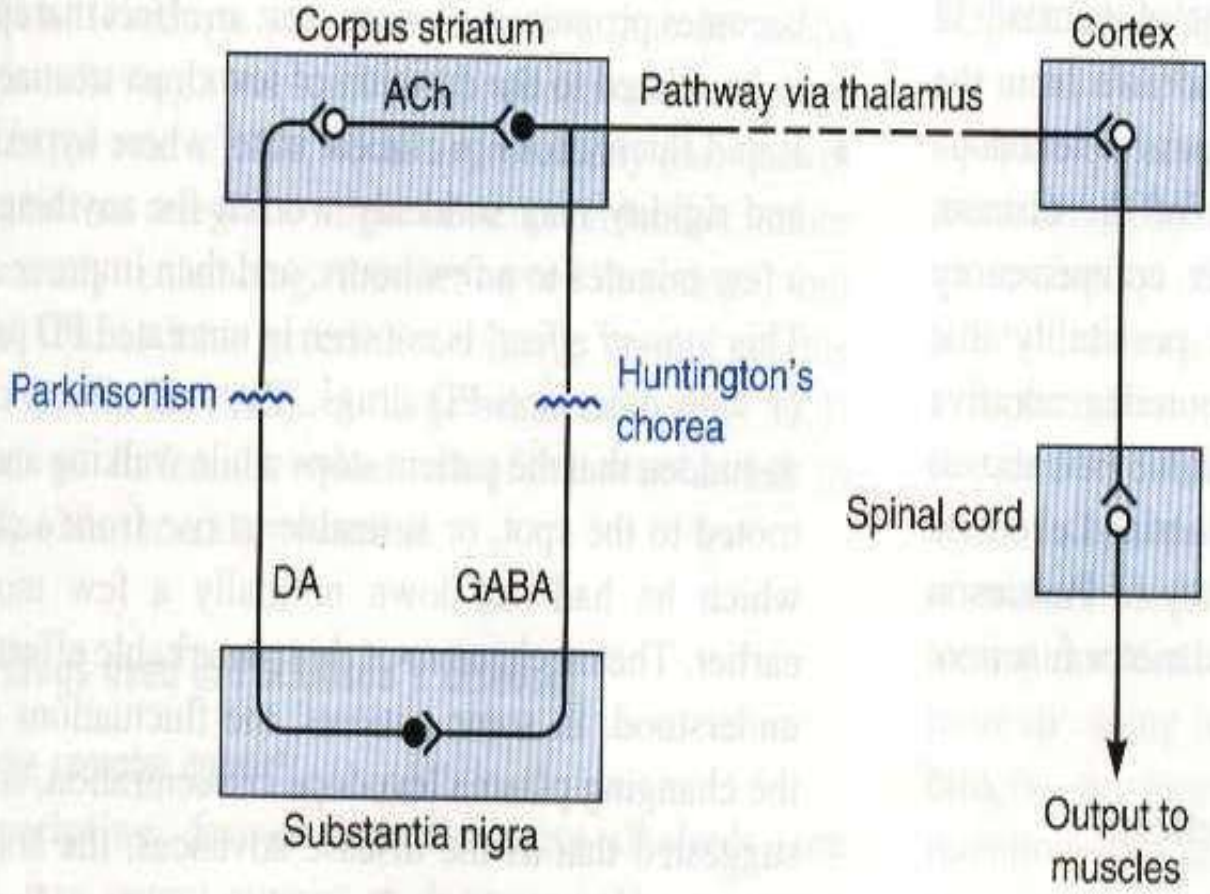
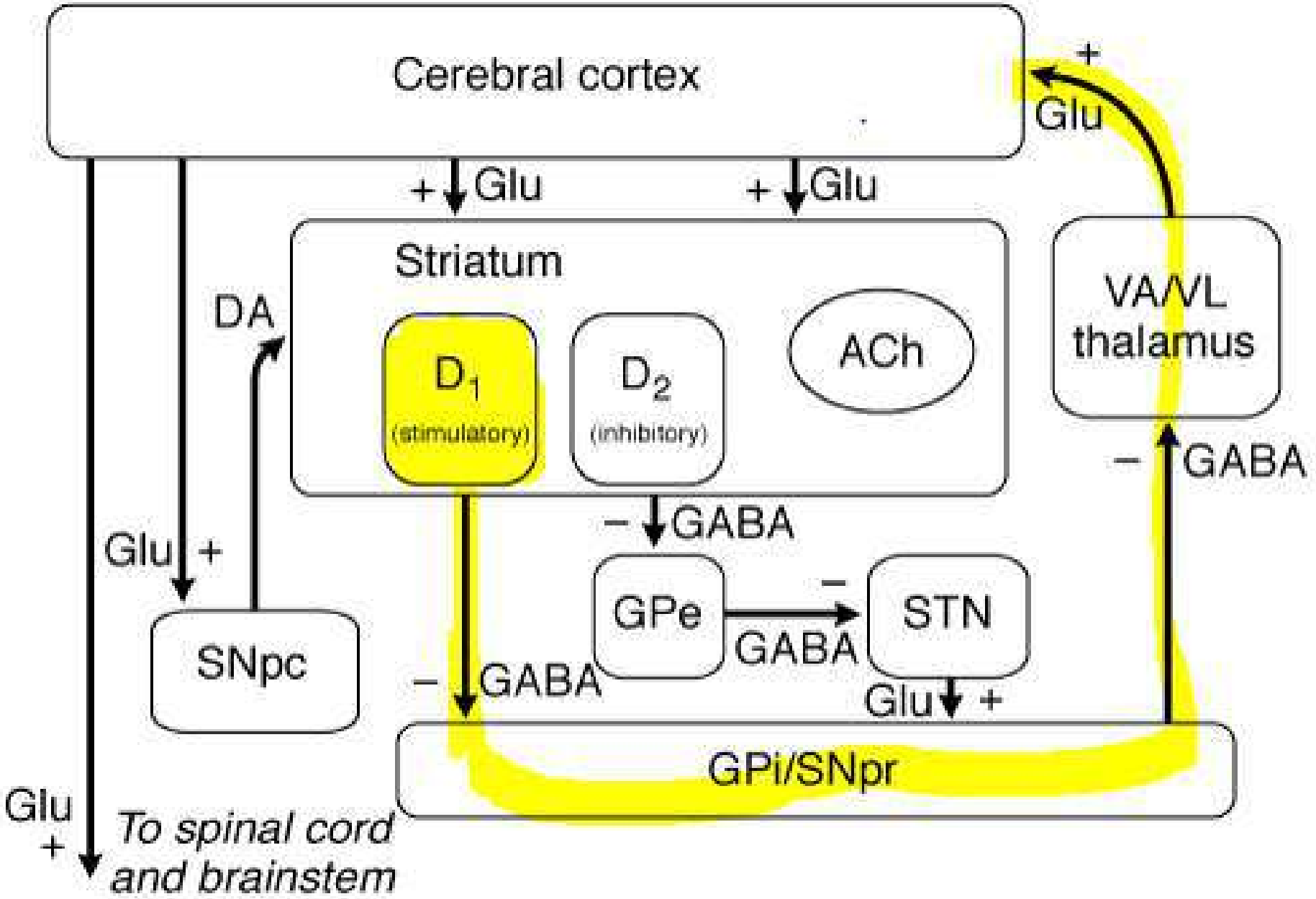
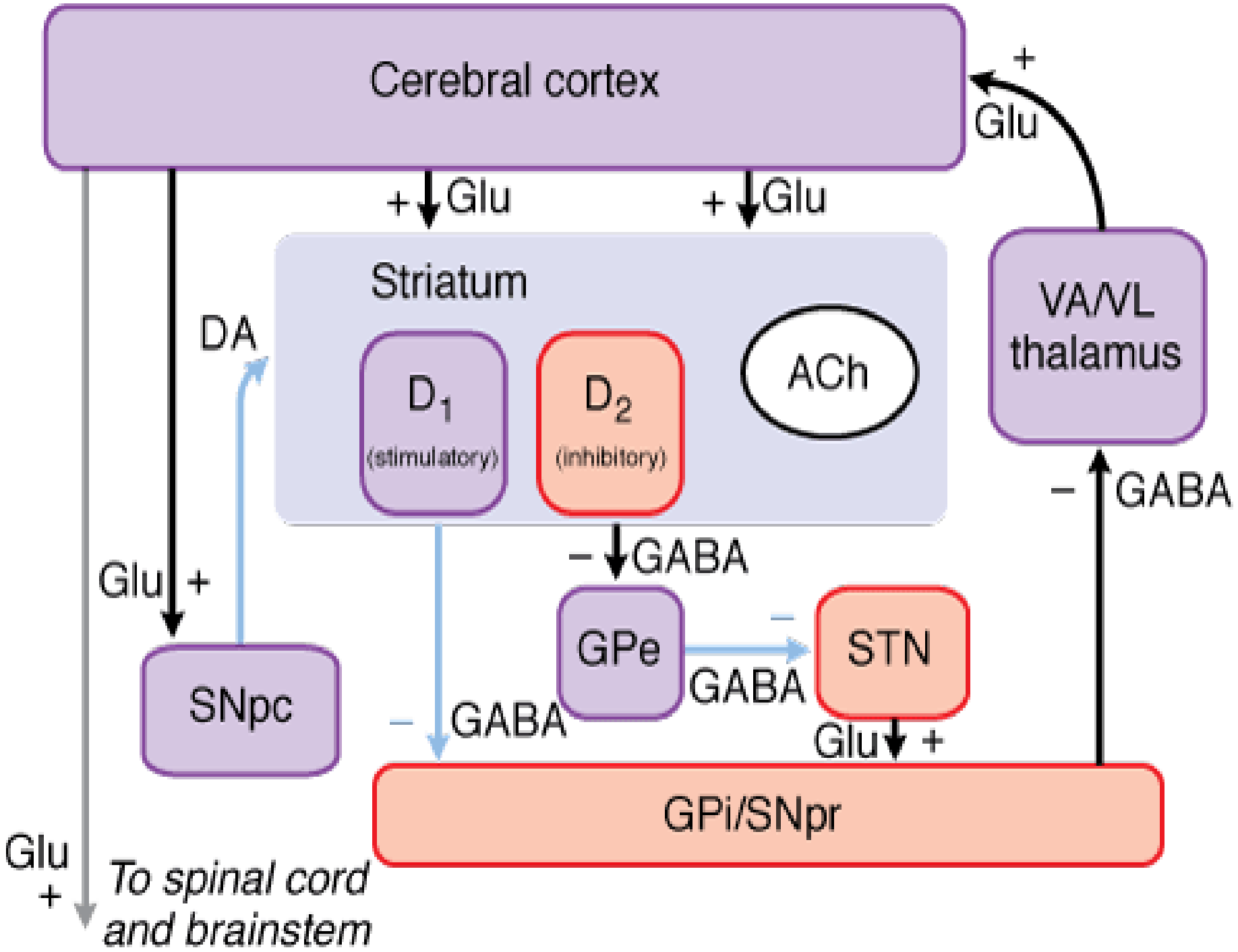


Fig. 31.3 Simplified diagram of the organisation of the extrapyramidal motor system, and the lesions that are believed to occur in Parkinson's disease and Huntington's disease.


Cerebral cortex
+
Glu
+ Glu
+ Glu
Striatum
DA
D1
(stimulatory)
D2
(inhibitory)
ACh
VA/VL
thalamus
– GABA
– GABA
Glu +
GPe
–
GABA
STN
SNpc
– GABA
Glu +
GPi/SNpr
Glu
+
To spinal cord
and brainstem


Cerebral cortex
+
Glu
+ Glu
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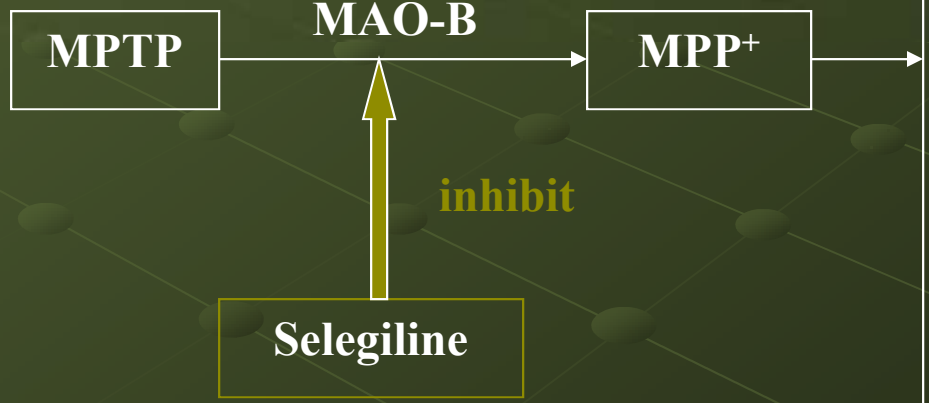
Striatum
DA
D1
(stimulatory)
D2
(inhibitory)
ACh
VA/VL
thalamus
– GABA
Glu +
– GABA
GPe
–
GABA
STN
SNpc
– GABA
Glu +
GPi/SNpr
Glu
+
To spinal cord
and brainstem

Action of MPTP

- 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) causes irreversible destruction of nigrostriatal dopaminergic neurons in various species, and produces a PD-like state in primates.



MPP^+ is taken up by the dopaminergic neurons, selective in destroying nigrostriatal neurons. It inhibits mitochondrial oxidation reactions, producing oxidative stress.

Medication Rational

- Replace depleted levels of dopamine
- Stimulate the nerve receptors enabling neurotransmission
- Increase the effect of dopamine on nerve receptors (agonist)
- Counteract the imbalance of Ach and Dopamine

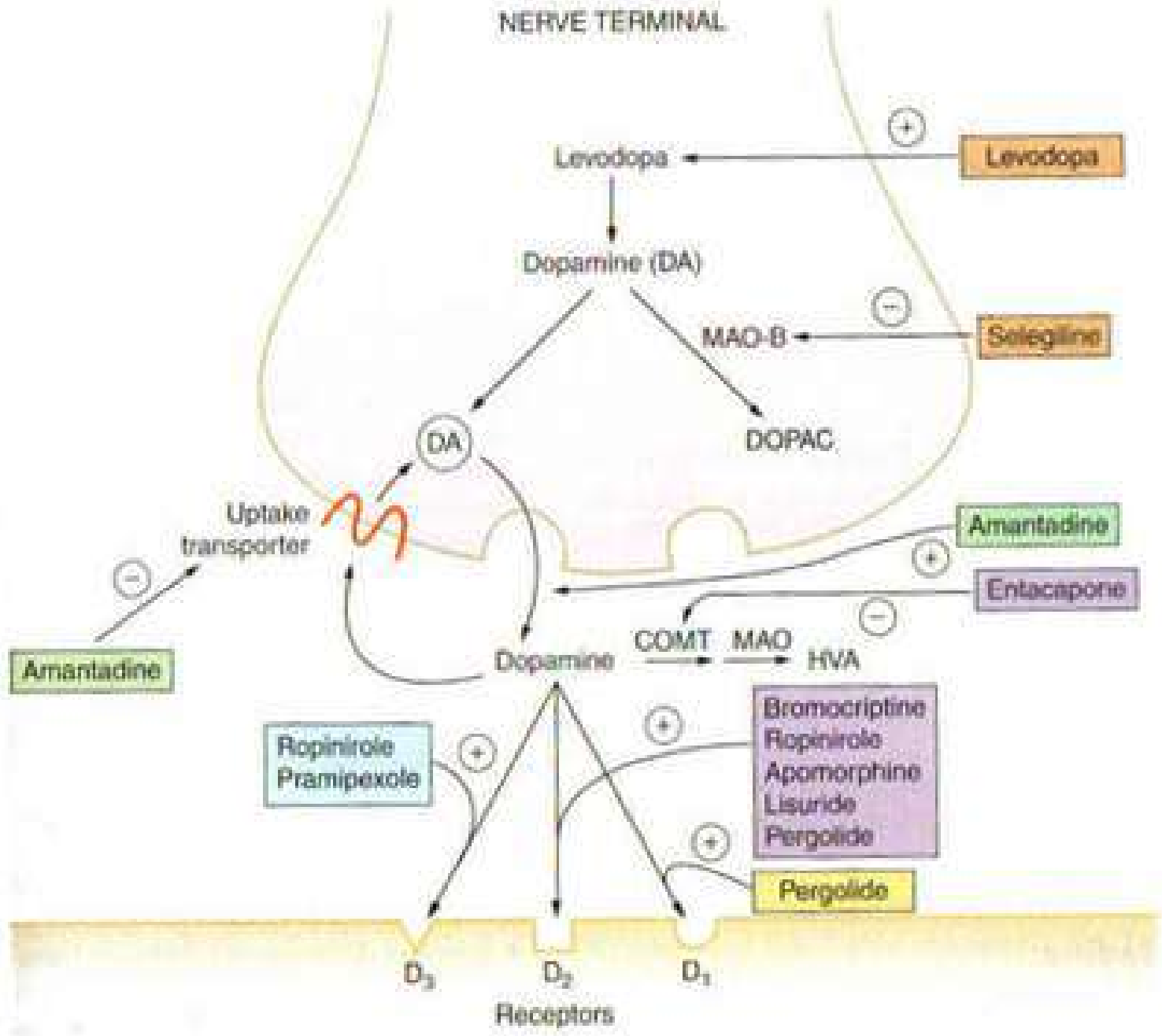
- The Drugs:
  - Dopaminergic drugs (improving dopamine functioning)
    - Levodopa
    - Dopamine receptor agonists
    - Amantadine
    - Selective monoamine oxidase B inhibitors
    - Catechol-O-methyltransferase inhibitors
  - Antimuscarinic drugs (Ach inhibitors)

Drugs Treatment of Parkinson's Disease

- Dopamine precursor –**levodopa**
- Peripherally dopa decarboxylase inhibitor (**carbidopa**)
- COMT inhibitors (entacapone, tolcapone)
- Drugs that mimic the action of dopamine (**bromocriptine**, **cabergoline, ropinirole, pramipexole**)

Drugs Treatment of Parkinson's Disease

- MAO-B inhibitors (e.g. **selegiline**)
- Drugs that release dopamine (e.g. **amantadine**)
- Centrally acting antimuscarinic drugs (e.g. trihexyphenidyl, procyclidine, orphenadrine, benztropine)


NERVE TERMINAL
Levodopa
Levodopa
Dopamine (DA)
MAO-B
Selegiline
DA
DOPAC
Uptake transporter
Amantadine
Entacapone
COMT
MAO
HVA
Amantadine
Dopamine
Ropinirole
Pramipexole
Bromocriptine
Ropinirole
Apomorphine
Lisuride
Pergolide
Pergolide
D_3
D_2
D_1
Receptors

Levodopa

- Mechanism:

(1) Because dopamine does not cross the blood-brain barrier levodopa, the precursor of dopamine, is given instead.

(2) Levodopa is formed from L-tyrosine and is an intermediate in the synthesis of catecholamines.

Levodopa

- Mechanism:

(3) **Levodopa itself has minimal pharmacologic activity, in contrast to its decarboxylated product, dopamine.**

(4) Levodopa is rapidly decarboxylated in the gastrointestinal tract. Prior to the advent of decarboxylase inhibitors (carbidopa), large oral doses of levodopa were required; thus, toxicity from dopamine was a limiting factor.

Levodopa

- **Pharmacokinetics**:

(1) Levodopa is well absorbed from the small bowel; however, 95% is rapidly decarboxylated in periphery.

(2) Peripheral dopamine is metabolized in the liver to dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), which are then excreted in urine.

Levodopa

- Pharmacologic effects:

  The effects on bradykinesia and rigidity are more rapid and complete than the effects on tremor. Other motor defects in PD improve. The psychological well-being of patient is also improved.

Levodopa

Pharmacologic effects:

- Tolerance to both beneficial and adverse effects occurs with time. Levodopa is most effective in the first 2-5 years of treatment.
- wearing off effect
- On-off phenomenon

Levodopa

- Adverse effect:

Principal adverse effects include:

(1) Anorexia, nausea, and vomiting upon initial administration, which often limit the initial dosage.

(2) Cardiovascular effects, including tachycardia, arrhythmias, and orthostatic hypotension.

Levodopa

- Adverse effect:

(3) Mental disturbances, including vivid dreams, delusions, and hallucination.

(4) Hyperkinesia

(5) On-off phenomena

Levodopa

- Adverse effect:

  Sudden discontinuation can result in fever, rigidity, and confusion. The drug should be withdrawn gradually over 4 days.

Levodopa

Drug interactions:

- Vit B6 reduces the beneficial effects of Levodopa by enhancing its extracerebral metabolism.

- Phenothiazines, reserpine, and butyrophenones antagonize the effects of levodopa because they lead to a junctional blockade of dopamine action.

Carbidopa

- Carbidopa is an inhibitor of dopa decarboxylase. Because it is unable to penetrate the blood-brain barrier, it acts to reduce the peripheral conversion of levodopa to dopamine. As a result, when carbidopa and levodopa are given concomitantly.

Carbidopa

Virtue:

a. It can decrease the dosage of levodopa.

b. It can reduce toxic side effects of levodopa.

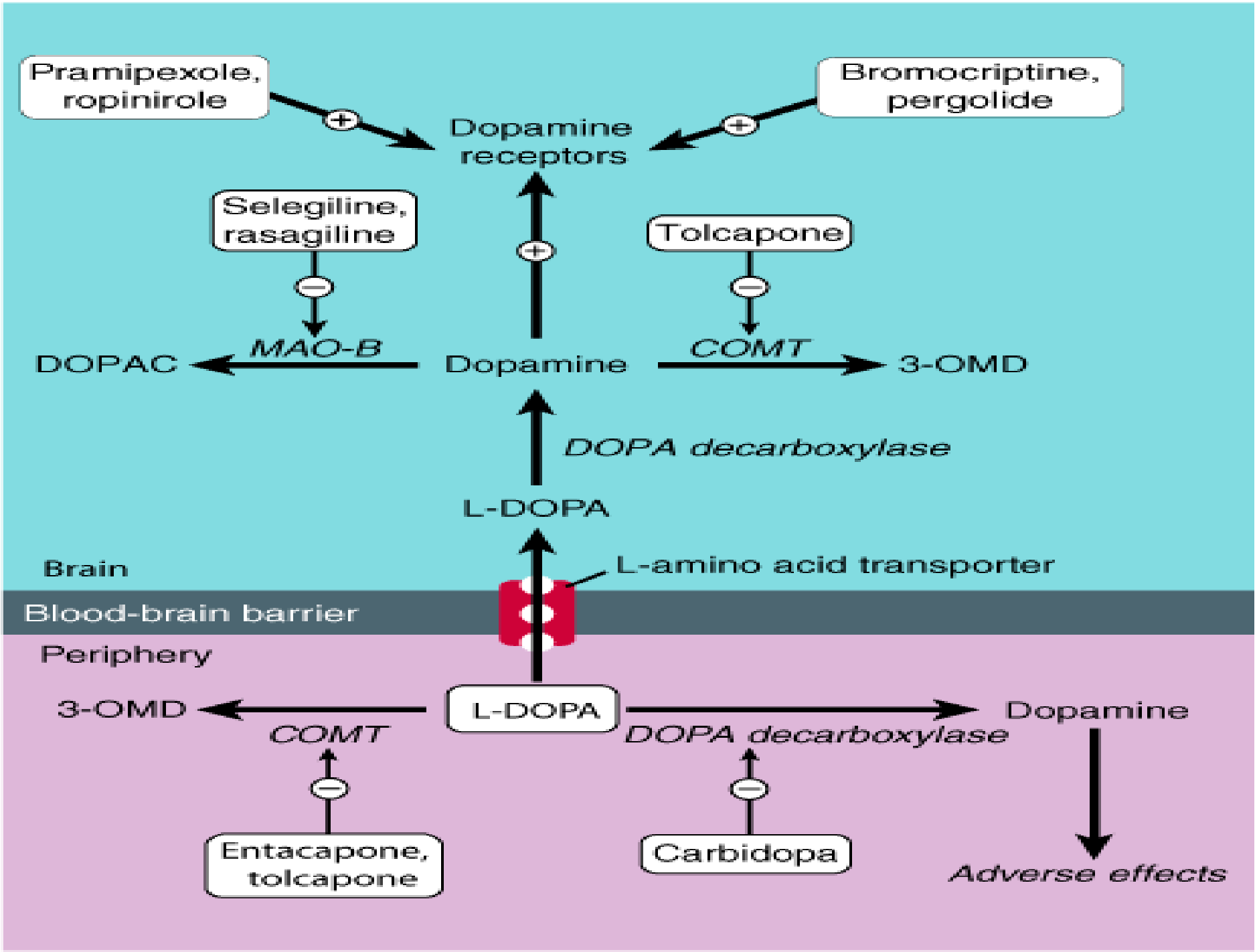
c. A shorter latency period precedes the occurrence of beneficial effects.

Selegiline

- A selective inhibitor of MAO-B, ***which predominates in DA-containing regions of the CNS and lacks unwanted peripheral effects of non-selective MAO inhibitors.***
- It enhances and prolongs the antiparkinsonism effect of levodopa.
- It may reduce mild on-off or wearing-off phenomena.

Selegiline

- Long-term trials showed that the combination of selegiline and levodopa was more effective than levodopa along in relieving symptoms and prolonging life.


Pramipexole, ropinirole
Bromocriptine, pergolide
Dopamine receptors
Selegiline, rasagiline
Tolcapone
MAO-B
COMT
DOPAC
Dopamine
3-OMD
DOPA decarboxylase
L-DOPA
Brain
L-amino acid transporter
Blood-brain barrier
Periphery
3-OMD
L-DOPA
Dopamine
COMT
DOPA decarboxylase
Entacapone, tolcapone
Carbidopa
Adverse effects

COMT- inhibitors (entacapone)

- MoA: inhibits the breakdown of levodopa
- Pharmacokinetics: variability of absorption, extensive first-pass metabolism, short half-life
- Adverse effects: dyskinesias, hallucinations

Amantadine

Therapeutic uses and mechanism of action

- Amantadine is an antiviral agent used in the prophylaxis of influenza A_2 .

- It improve parkinsonian symptoms by stimulating the release of DA from dopaminergic nerve terminals in the nigrostriatum and delaying DA reuptake.

Anticholinergic agents

Mechanism:

- **Since the deficiency of dopamine in the striatum augments the excitatory cholinergic system in the striatum, the blockade of this system by anticholinergic agents helps to alleviate the motor dysfunction.**

- **Improvement in the parkinsonian tremor is more pronounced than improvement in bradykinesia and rigidity.**

Therapeutic uses:

- Although not as effectives as levodopa, it may have an additive therapeutic effect at any stage of the disease when taken concurrently.

Adverse effects:

- Mental confusion and hallucinations.
- It can occur as can peripheral atropine-like toxicity (e.g. cycloplegia, urinary retention, constipation)

Huntington's Chorea

- Inherited autosomal dominant disorder
- Error in huntingtin gene
- Synthesis of huntingtin protein (repeats of polyglutamine cause excitotoxicity and apoptosis in cortex and striatum)
- Degeneration of GABAergic neurons in the striatum

Huntington's Chorea

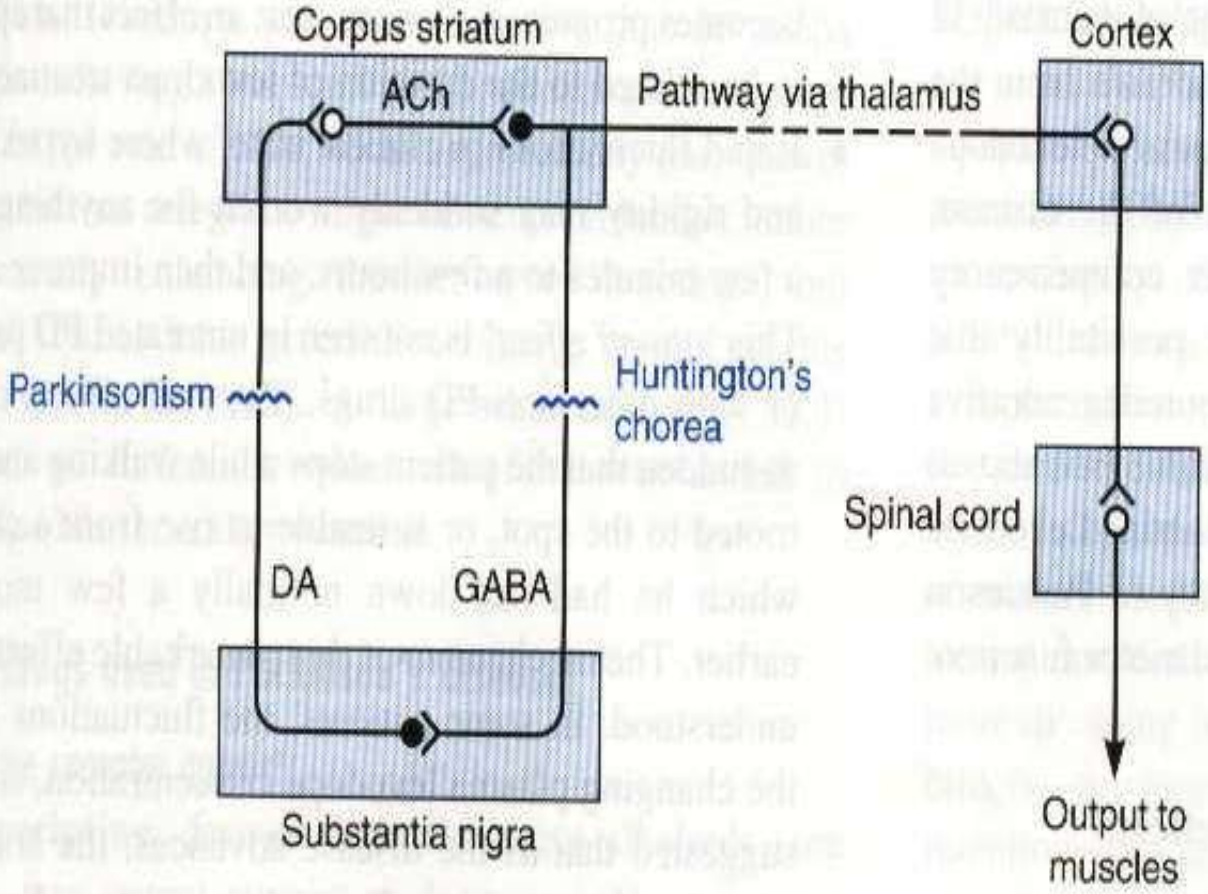


Fig. 31.3 Simplified diagram of the organisation of the extrapyramidal motor system, and the lesions that are believed to occur in Parkinson's disease and Huntington's disease.

Huntington's Chorea

- Dance like movements of limbs
- Rhythmic movements of tongue and face
- Dementia
- Progressive brain degeneration

Huntington's Chorea

Tx

- Chlorpromazine
- Haloperidol
- Olanzapine

Alzheimer's disease

- Progressive memory loss
- Disordered cognitive functions
- Reduced verbal fluency
- Bedridden as disease progresses
- Complications of immobility

Alzheimer's disease

- Amyloid plaque (extracellular deposits of β-amyloid protein)
- Intraneuronal neurofibrillary tangles (aggregates of highly phosphorylated neuronal protein)
- Loss of cholinergic neurons in brain (originates from nucleus basalis in forebrain and project to frontal cortex and hippocampus)

Alzheimer's disease Tx

- Anticholinesterases
  - Tacrine (hepatotoxic)
  - Donepezil
  - Rivastigmine
  - Galantamine
- NMDA antagonist
  - Memantine
- Nootropics
  - Piracetam
- Anti-oxidants
  - Vit. A, C,
  - Zinc, Selenium
- Miscellaneous
  - Statins
  - Ibuprofen

Multiple Sclerosis

- Demylenation in brain, spinal cord, optic nerves
- autoimmune
- Weakness, numbness, spastic paraparesis, diplopia, sphincter disturbances
- Tx
  - Interferon beta-1b
  - Natalizumab
  - Baclofen, Diazepam (for spasticity)

Amyotropic Lateral sclerosis

- Neurodegenerative dis. of motor neurons
- Muscle wasting and atrophy
- Defective superoxide dismutase (defective scavenging of superoxide free radicals)
- Defective glutamate uptake (excitotoxicity)
- Spontaneous twitching of motor units
- Difficulty in chewing & swallowing
- Respiratory failure & death within 5 yrs
- Tx – Riluzole (↓es glutamate release)

Psychostimulants

- Amphetamine & Methylphenidate
  (release NA & DA in brain) -ADHD

- Modafinil-
  inc alertness & keep awake

- Caffeine-
  Migraine, allay fatigue, apnoea in premature infants

Thank you

CHOLINERGIC TRANSMISSION

A:- Precursor - Choline

B :- Enzyme-

Synthesizing - Choline Acetylase

Degrading - Acetycholine Esterase **(TRUE)**

- Butyrylcholine Esterase**(PSEUDO)**

C :- 300,000 vesicles

Quantum - 0.1 to 0.3 mv

- 1mepp/sec

CHOLINERGIC TRANSMISSION (CONTD.)

RECEPTORS

N - Ligand gated ion channels N_n & N_m

M - Through G- protein signalling systems

M_1 – Stomach Glands - Release of hist.

- Secretion of acid

M_2 – (i) Myocardium

- ↓ generation of impulses –SA
- ↓ conduction of impulse – AV
- ↓ contractility –Atria & Ventricle

CHOLINERGIC TRANSMISSION (CONTD.)

(ii) Pre-synaptic

↓ Ach from cholinergic neurons

↓ NA Postgang. sym. Neurones

M_3 - Smooth muscle – Contraction

- Exocrine glands – ↑ secretion
- Vascular Endothelium – ↑ NO secretion

CLASSIFICATION

CHOLINE ESTERS
- Acetylcholine
- Methacholine
- Carbachol
- Bethanechol
- Cevimeline

NATURAL ALKALOID
- Muscarine
- Pilocarpine
- Arecoline
- Nicotine

ANTI- CHOLINESTERASES

A) Reversible

- Physostigmine
- Neostigmine
- Pyridostigmine
- Edrophonium
- Rivastigmine
- Donepezil

ANTI- CHOLINESTERASES(contd.)

B) Irreversible

- Parathion
- Malathion

(agricultural insecticides)

- Diazinon
- Propoxur

(Household)

- Tabun
- Sarin
- Soman

(Chemical warfare)

PHARMACOLOGICAL ACTIONS

1) **CVS (M_2)**

a) Heart :-

↓ G/C /C in Myocardium (PR ↑ – AV)

b) Blood Vessel(M_3)

Dilatation – ↓ BP → Reflex tachycardia

innervation is only on face to neck

2) **Exocrine glands (M_3)**

Sweating > Salivation > Lacrimation = TBT

secretion >> Gastric secretion

PHARMACOLOGICAL ACTIONS(contd.)

3) Smooth Muscle

a) G.I. – ↑ Tone & Peristalsis

b) Urinary System – ↑ Tone , Voiding

c) Bronchi – ↑ Tone (Bronchial Asthma)

4) Eye- Cont. of circular mus. of iris →Miosis.

- Cont. of ciliary mus.→ thickening of lens

PHARMACOLOGICAL ACTIONS(contd.)

5) Skeletal muscles (N_M)

Twitching & fasciculation

6) Autonomic ganglia(Nn)

Both Ad & Ch- unpredictable

7) CNS (M+N)

Rapid destruction + min. entry

→unpredictable response.

8) Stomach (M_1) – ↑ acid+ Pepsin

USES OF CHOLINE ESTERS

1) Cardiac – PSVT – Methacholine

2) Intestinal – Paralytic ileus ,Megacolon
(carbachol / bethanechol)

3) Urinary - Retention of urine
(carbachol /bethanechol)

4) Lacrimal Secretion & Sialogogue –
Cevimeline

CHOLINOMIMETIC ALKALOIDS

Pilocarpine :-

- As eye drops – Miosis
- Ch. simple glaucoma – Drops Vs. Ocusert
- To prevent and break adhesions between iris / lens and iris / cornea

Muscarine, Arecoline and Nicotine

CHOLINESTERASE INHIBITORS

Reversible

Physostigmine (Eserine) :-

-Natural ,lipid soluble compound

-Rapidly absorbed and crosses BBB – CNS effects

-Poisoning with Atropine , Phenothiazines & Tricyclic Antidepressants

CHOLINESTERASE INHIBITORS(contd.)

Neostigmine –

-Synthetic, much less lipid soluble

-Does not cross BBB – No central effects

- ACh action on NMJ – Myasthenia gravis

- If intolerable M effects – Atropine

-Steroids – ↓ production of N_m antibodies

-Thymectomy

- Also in paralytic ileus & bladder atony.

CHOLINESTERASE INHIBITORS (contd.)

Pyridostigmine - Less potent , Long duration

Edrophonium - Very short duration

- To identify between "Myasthenic" and "Cholinergic" crisis

Rivastigmine, **Donepezil** } Newer agents, AD, Long acting, Well tolerated

OTHER USES :- a) Cobra bite –venom

b) Decurarisation after G.A

c) Curare & other poisonings

d) Edrophonium (PSVT)

ChE INHIBITORS – IRREVERSIBLE

High efficacy ------ Toxicity (cross BBB)

High lipid soluble – Rapid absorption from all routes

Poisoning occurrence - Accidental , suicidal, homicidal

Muscarinic Effects

- Inhalation / ingestion/ vapours (Eye)
  Miosis , lacrimation
- ↑ secretion – Dehydration
- Fall in BP – Reflex Tachycardia
- ↑ dose –VMC at medulla (Bradycardia)
- ↑ contraction of smooth muscle
- Ataxia, convulsion , coma , death due to Respiratory Failure

TREATMENT

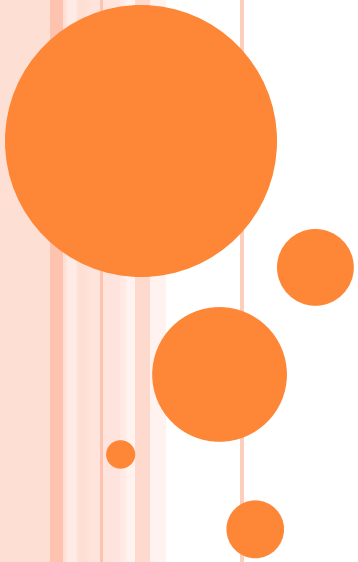
- Change clothes. Wash skin , eyes. Gastric lavage.
- Fresh air, Patent airway, PPR, Hydration
- Maintenance of BP- vasopressor agent
- CONVULSION – Diazepam i.v

  Atropine

  Enzyme Reactivator – Oximes

  DAM, Pralidoxime, Obidoxime

CNS INTRODUCTION



- Parkinson's disease:

  ↓ Dopamine (relatively ↑ Acetylcholine)

- Depression:

  ↓ Serotonin, ↓ NA

- Schizophrenia:

  ↑ Dopamine

INTRODUCTION

- Nearly all drugs with CNS effects act on specific receptors that modulate synaptic transmission.

- A very few agents such as general anesthetics and alcohol may have nonspecific actions on membranes, but even these non–receptor-mediated actions result in demonstrable alterations in synaptic transmission.

CNS

- Cerebrum
- Subcortical region
  - Thalamus
  - hypothalamus
- Mid brain
- Hind brain
  - Pons
  - Medulla
  - cerebellum
- Spinal cord

Cerebrum

- Frontal cortex
- Parietal lobe
- Temporal lobe
- Occipital lobe

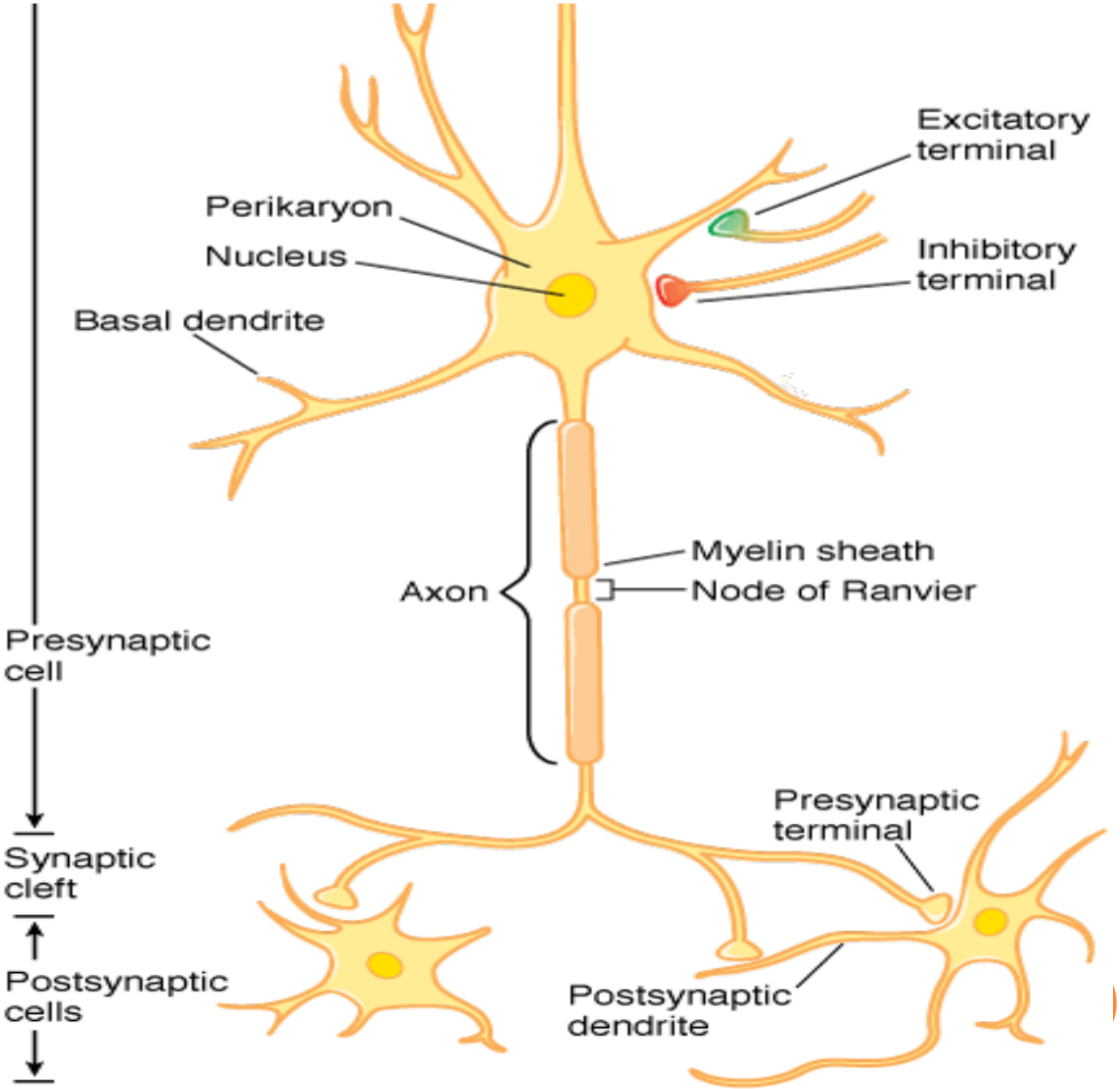
Subcortical Region

- Thalamus
  - act as relays between incoming sensory pathways and the cortex
- Hypothalamus
  - The *hypothalamus* is the principal integrating region for the autonomic nervous system and regulates body temperature, water balance, intermediary metabolism, blood pressure, sexual and circadian cycles, secretion from the adenohypophysis, sleep, and emotion.
- Limbic system

- Limbic system-The *limbic system* is an archaic term for an assembly of brain regions (hippocampal formation, amygdaloid complex, olfactory nuclei, basal ganglia, and selected nuclei of the diencephalon) grouped around the subcortical borders of the underlying brain core.

- Pons – motor & sensory control, consciousness & sleep
- Medulla- breathing, heart rate
- Cerebellum- maintaining the proper tone of antigravity musculature and providing continuous feedback during volitional movements of the trunk and extremities.
- Spinal cord- integrates sensory & motor reflexes, controls muscle tone.

Neurons


Excitatory terminal
Perikaryon
Nucleus
Inhibitory terminal
Basal dendrite
Myelin sheath
Axon
Node of Ranvier
Presynaptic cell
Presynaptic terminal
Synaptic cleft
Postsynaptic cells
Postsynaptic dendrite

SUPPORT CELLS OF NEURONS

- **Macroglia** – *astrocytes & oligodendroglia*
- **Microglia**

-***astrocytes*** (cells interposed between the vasculature and the neurons, often surrounding individual compartments of synaptic complexes). Astrocytes play a variety of metabolic support roles including furnishing energy intermediates and supplementary removal of neurotransmitters following release.

- ***oligodendroglia***, a second prominent category of macroglia, are myelin-producing cells. Myelin, made up of multiple layers of compacted membranes, insulate segments of axons bioelectrically and permit non-decremental propagation of action potentials.

- **Microglia-** related to the macrophage/monocyte lineage. Some microglia reside within the brain, while additional cells of this class may be recruited to the brain during periods of inflammation following either microbial infection or brain injury.

Blood-Brain Barrier (BBB)

- boundary between the periphery and the CNS that forms a permeability barrier to the passive diffusion of substances from the bloodstream into the CNS.
- An exception exists for lipophilic molecules, which diffuse fairly freely across the BBB and accumulate in the brain.

Organs not covered by BBB-

- median eminence
- area postrema (CTZ)
- pineal gland
- pituitary gland
- choroid plexus capillaries

Central Neurotransmitters

- Acetylcholine
- Amines
  - Dopamine, NE, E, Serotonin, Histamine
- Amino acids
  - Glutamate, Aspartate (excitatory)
  - GABA, Glycine (inhibitory)
- Peptides
  - Oxytocin, Tachykinins, VIP, Opioid peptides
- NO
- Miscellaneous
  - Anandamide, Adenosine, ATP

- **Acetylcholine**

  -cerebral cortex, cerebellum, spinal cord

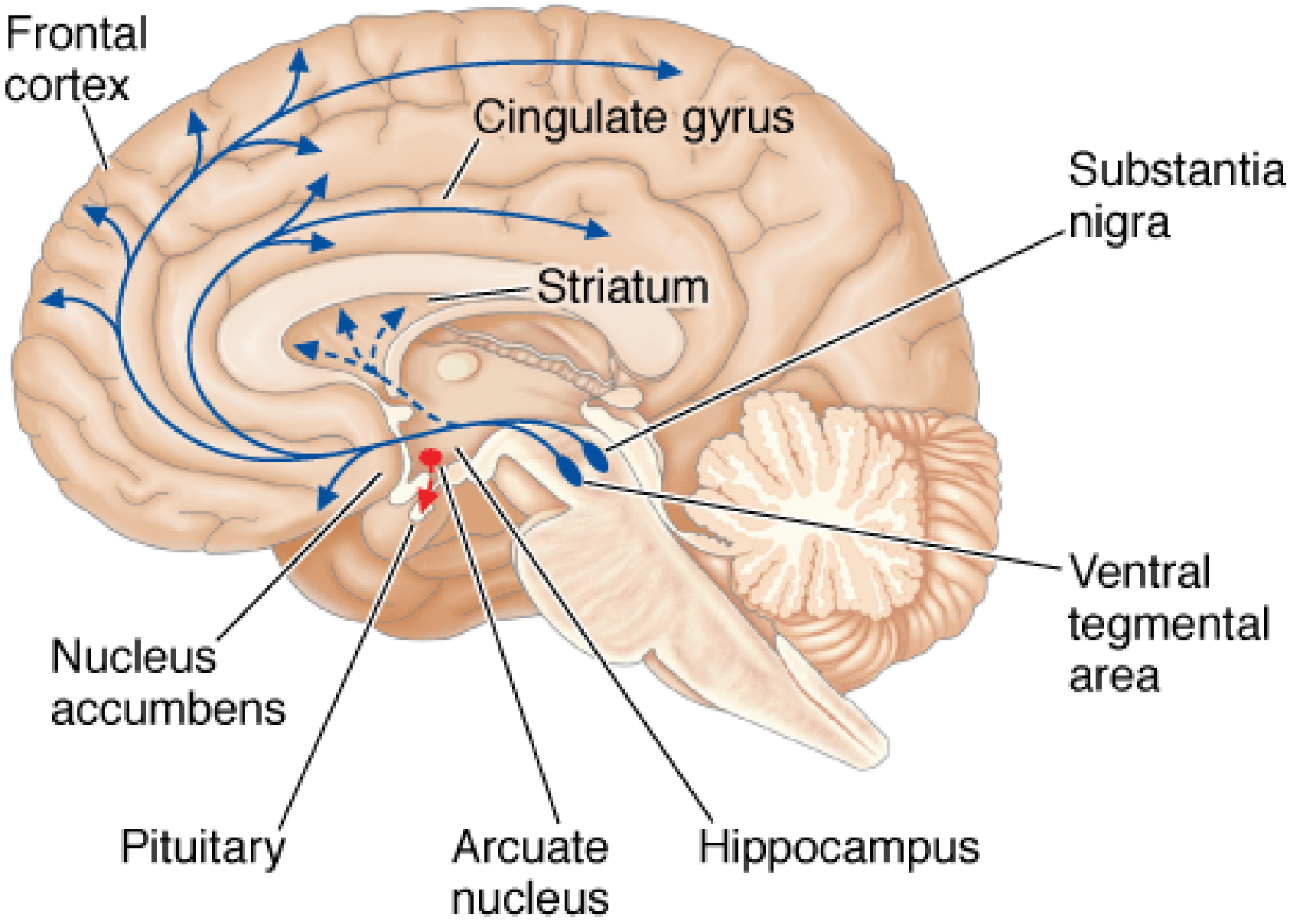
  -Receptors- muscarinic & Nicotinic

  -Functions- arousal, respiration, motor activity, vertigo, memory

- Amines (Dopamine, NE, E, Serotonin, Histamine)
  - **Dopamine**

    -hypothalamus, pituitary (intermediate lobe), substantia nigra, limbic structures, basal ganglia

    -Receptors- D_1, D_2, D_3, D_4, D_5
  - Parkinson's disease- ↓ DA in basal ganglia
  - Schizophrenia-↑ DA in mesolimbic-mesocortical-mesofrontal pathway


Frontal cortex
Cingulate gyrus
Substantia nigra
Striatum
Ventral tegmental area
Nucleus accumbens
Pituitary
Arcuate nucleus
Hippocampus

THE THREE MAJOR DOPAMINERGIC PROJECTIONS IN THE CNS

- 1. **Mesostriatal (or nigrostriatal) pathway**.

  Neurons in the substantia nigra pars compacta (SNc) project to the dorsal striatum (*upward dashed blue arrows*); this is the pathway that degenerates in Parkinson disease.
- 2. Neurons in the ventral tegmental area project to the ventral striatum (nucleus accumbens), olfactory bulb, amygdala, hippocampus, orbital and medial prefrontal cortex, and cinguate gyrus (*solid blue arrows*).
- 3. Neurons in the arcuate nucleus of the hypothalamus project by the **tuberoinfundibular pathway** in the hypothalamus, from which DA is delivered to the anterior pituitary (*red arrows*).

- **NE**

  -Locus ceruleus (pons & reticular formation), cortex, cerebellum

  -Modulate affective disorders, learning, memory, arousal

- **E**

  -Reticular formation

- **Serotonin**

  -Raphe nuclei of brain stem

  -Role in nociception, schizophrenia, depression, eating disorders, temp. regulation

- **Histamine**

  -Posterior hypothalamus, cortex, limbic system, brain stem

  -H_1

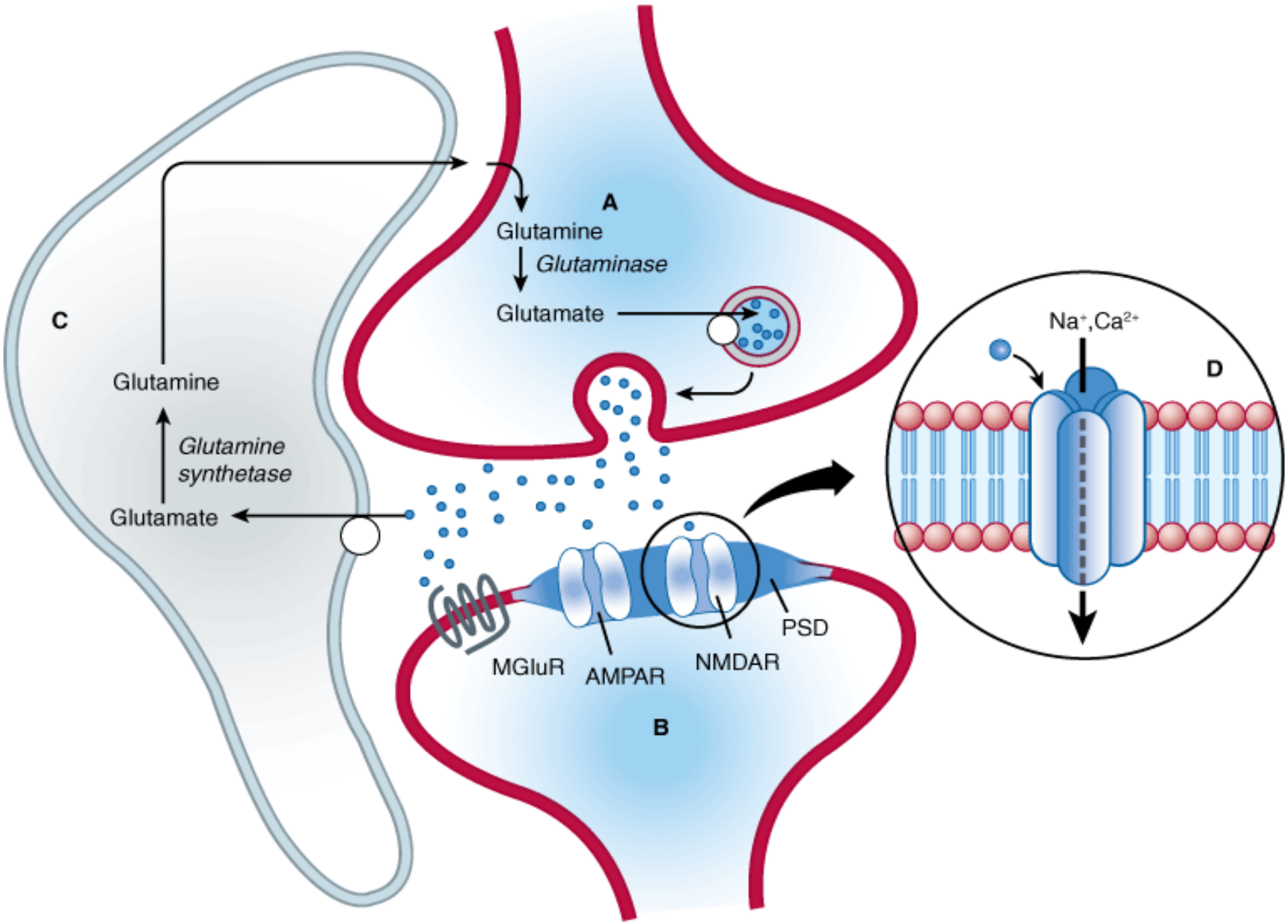
  -Role in arousal, regulation of food and water intake

- Amino acids
  - **Glutamate**, Aspartate (excitatory)

    -Cortex , basal ganglia

    -Receptors- NMDA, AMPA, Kainate, AP-4, ACPD

    -Synaptic plasticity, neurotoxicity


A
Glutamine
Glutaminase
Glutamate
C
Glutamine
Glutamine synthetase
Glutamate
B
MGluR
AMPAR
NMDAR
PSD
D
Na+,Ca2+

- **GABA**, Glycine (inhibitory)

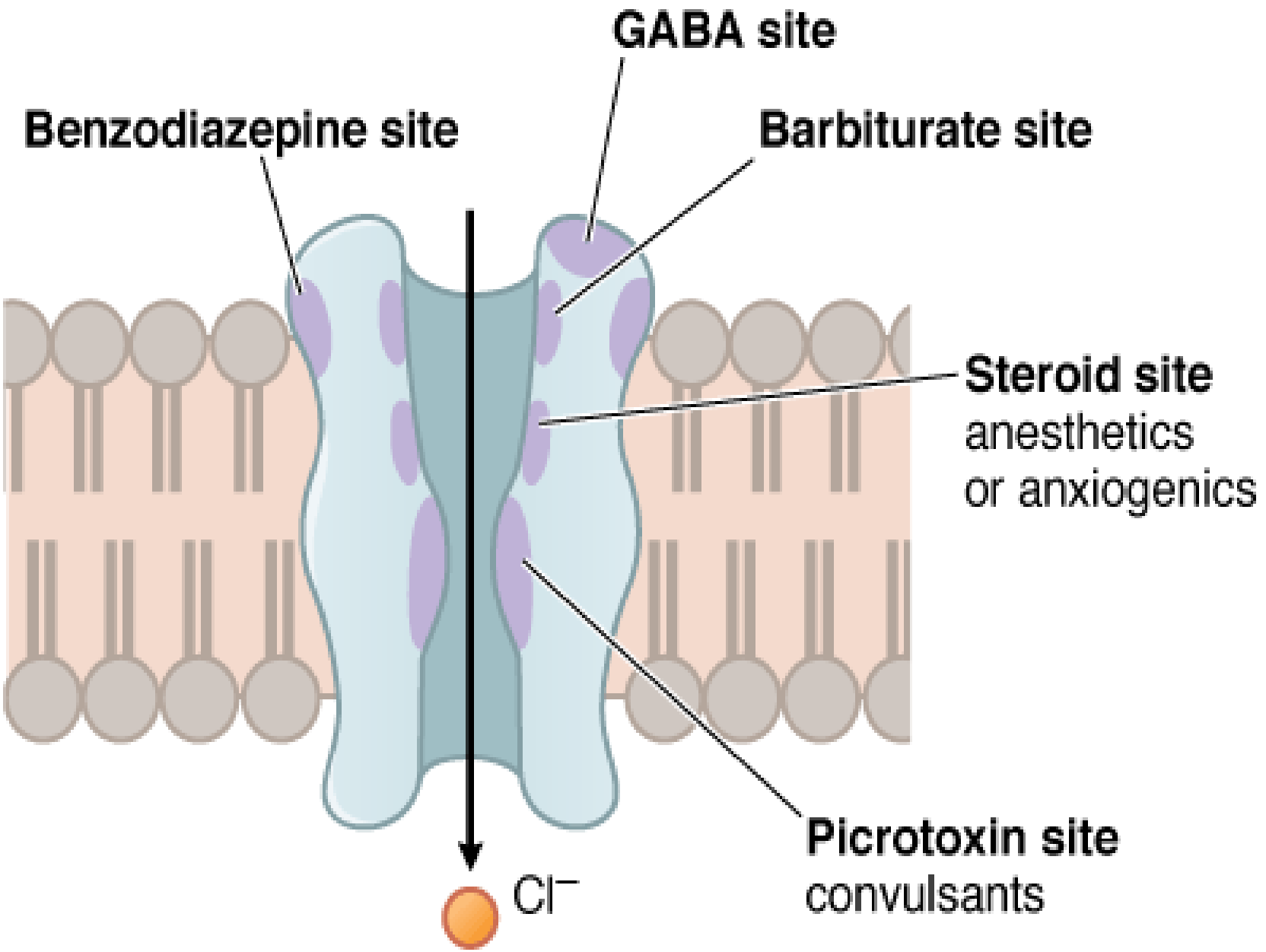
  -GABA present uniformly in brain

  -Receptors-

  $GABA_A$ (ligand-gated Cl^- ion channel, an ionotropic receptor)

  $GABA_B$ is a GPCR

  - ↑ GABAergic activity- sedation, amnesia, muscle relaxation, ataxia


GABA site
Benzodiazepine site
Barbiturate site
Steroid site
anesthetics
or anxiogenics
Picrotoxin site
convulsants
Cl⁻

- Peptides
  - Oxytocin, Tachykinins, VIP, Opioid peptides
- NO
- Miscellaneous
  - Anandamide, Adenosine, ATP

Neurochemical Transmission

- ***Transmitter synthesis***. Small molecules like ACh and NE are synthesized in nerve terminals; peptides are synthesized in cell bodies and transported to nerve terminals.

- ***Transmitter storage***. Synaptic vesicles store transmitters, often in association with various proteins and frequently with ATP.

- ***Transmitter release***. Release of transmitter occurs by exocytosis. Depolarization results in an influx of Ca^{2+}, which in turn appears to bind to proteins called **synaptotagmins**.

- ***Transmitter recognition***. Receptors exist on postsynaptic cells, which recognize the transmitter. Binding of a neurotransmitter to its receptor initiates a signal transduction event.

- ***Termination of action***.

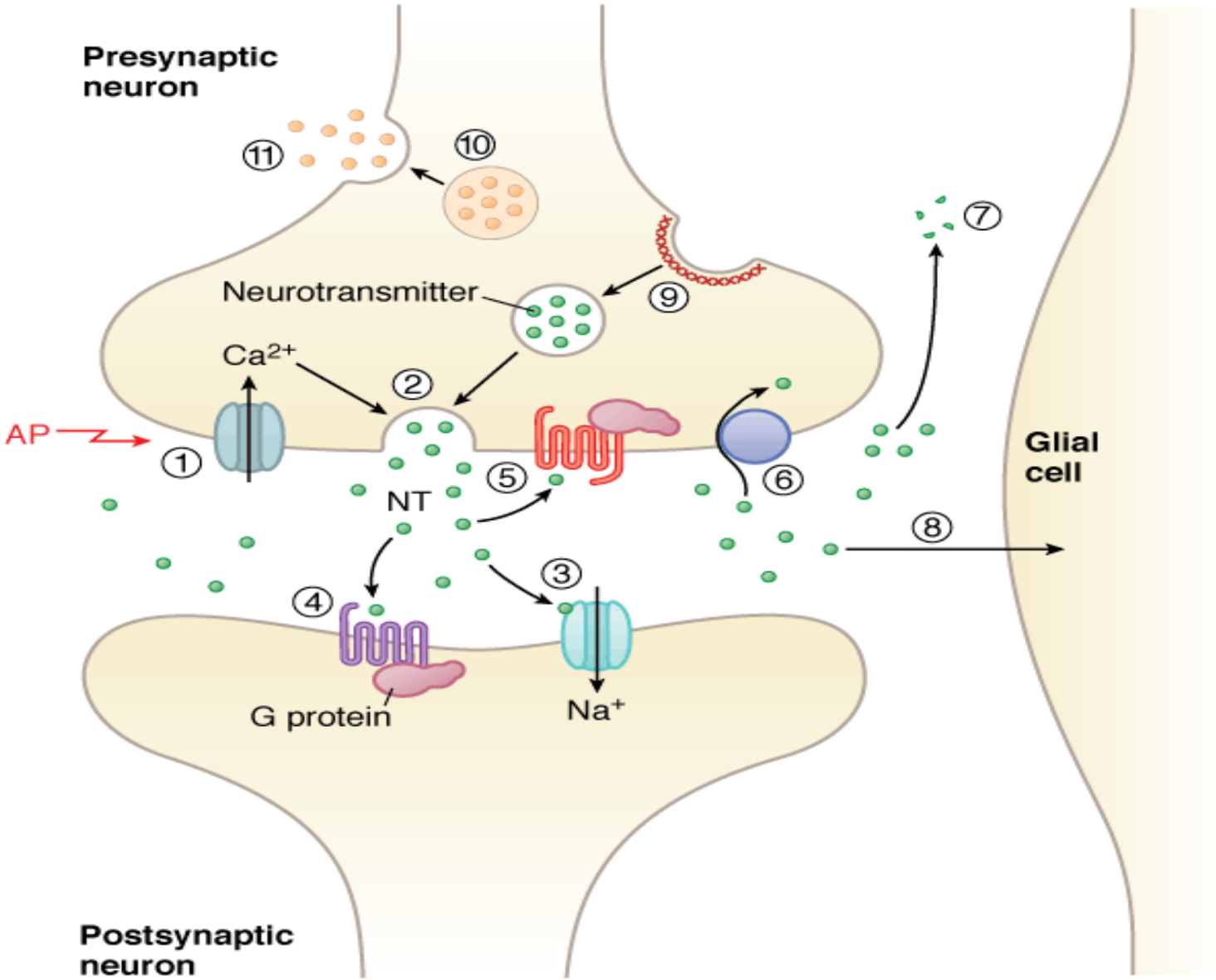
  -hydrolysis (for acetylcholine and peptides)

  -reuptake into neurons by specific transporters such as NET, SERT, and DAT (for NE, 5-HT, DA).

  -Inhibitors of NET, SERT, and DAT increase the dwell time and thus the effect of those transmitters in the synaptic cleft.

  -Inhibitors of the uptake of NE and/or 5-HT are used to treat depression and other behavioral disorders

NEUROTRANSMISSION

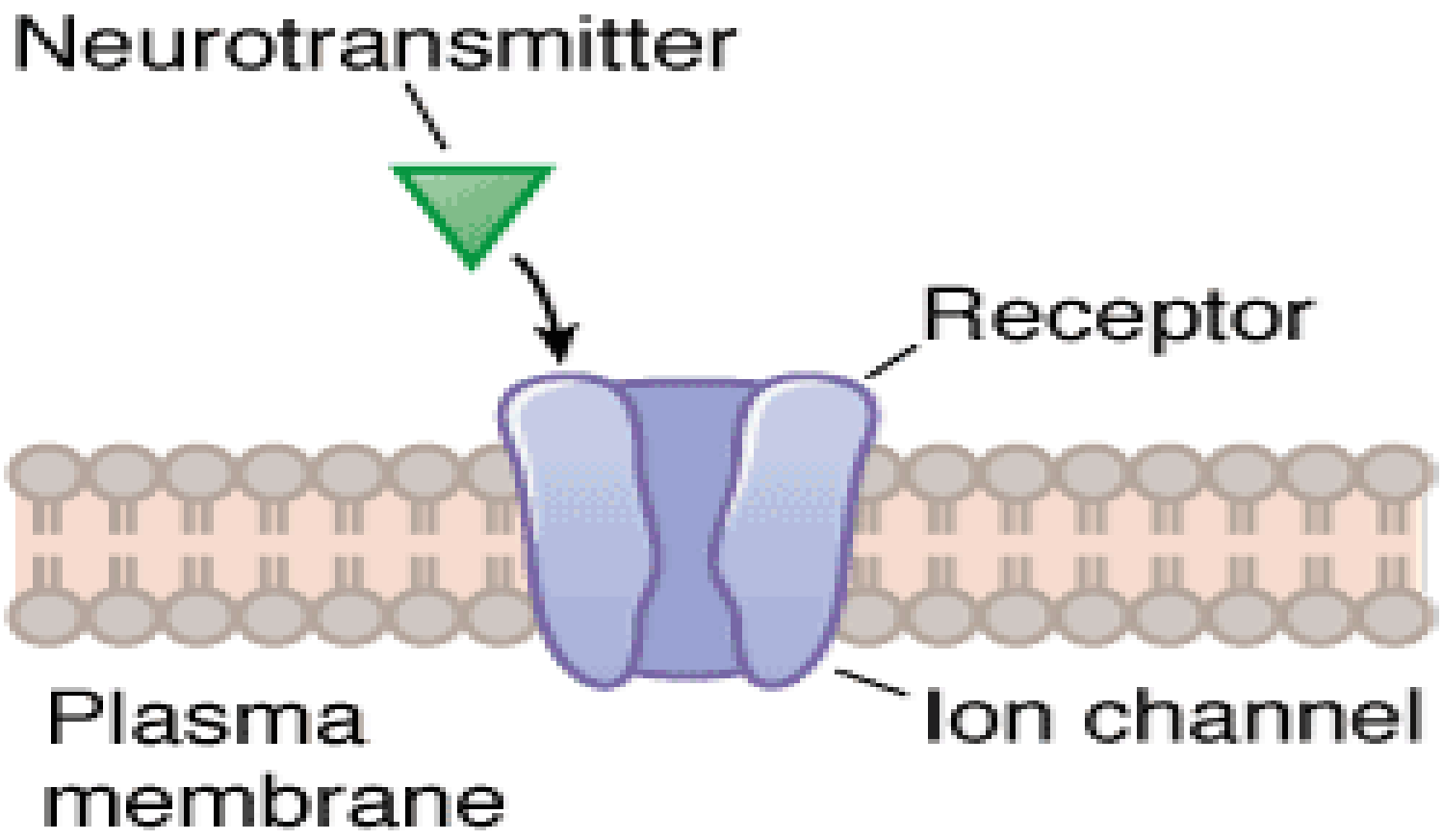


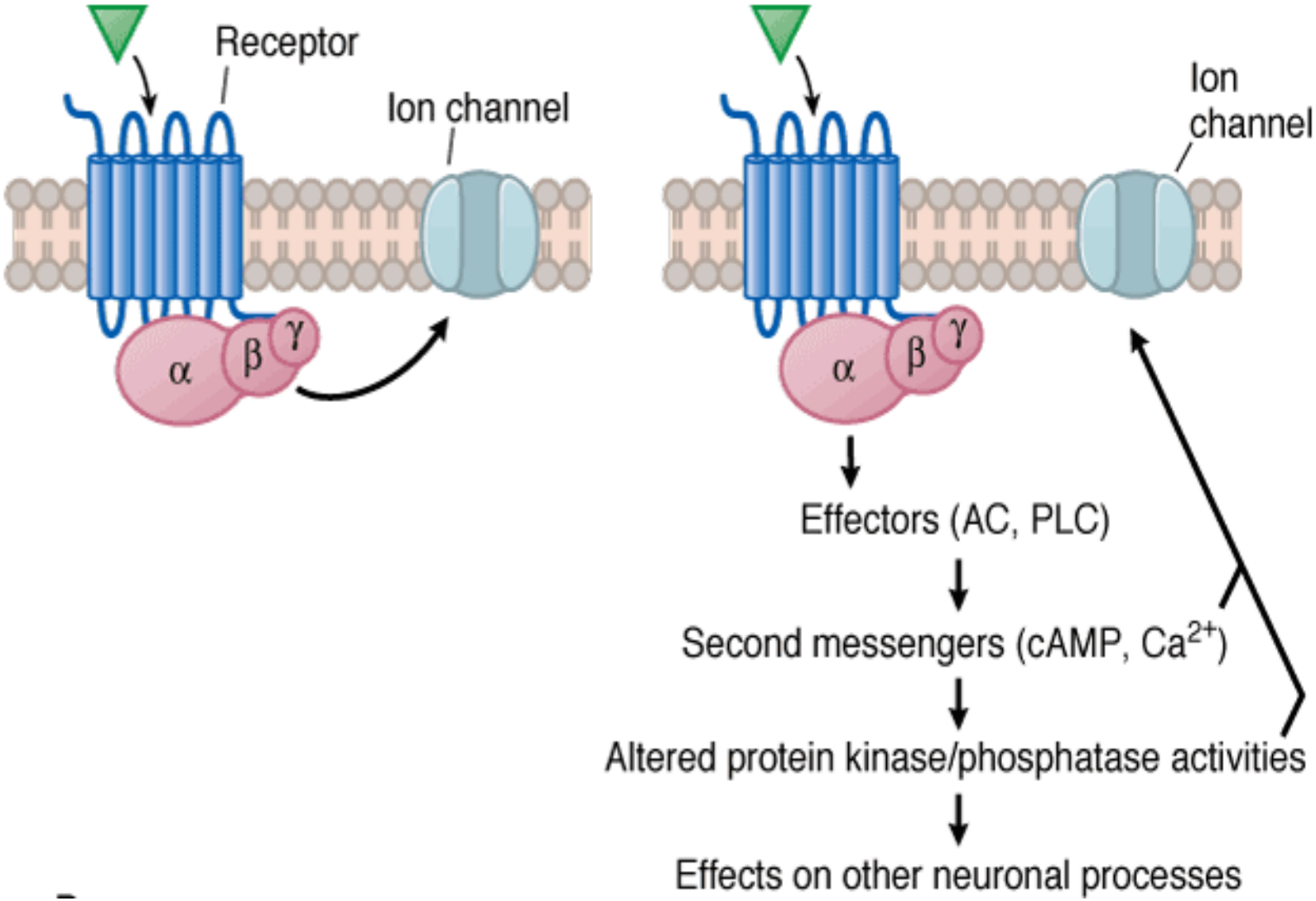
- Depolarization opens voltage-dependent Ca^{2+} channels in the presynaptic nerve terminal.
- the influx of Ca^{2+} during an action potential (AP) triggers the exocytosis of small synaptic vesicles that store neurotransmitter (NT) involved in fast neurotransmission.
- Released neurotransmitter interacts with receptors in the postsynaptic membranes that either couple directly with ion channels or act through second messengers, such as GPCRs.
- Neurotransmitter receptors in the presynaptic nerve terminal membrane can inhibit or enhance subsequent exocytosis.

- Released neurotransmitter is inactivated by reuptake into the nerve terminal by a transport protein coupled to the Na^+ gradient, for example, DA, NE, and GABA; by degradation (ACh, peptides); or by uptake and metabolism by glial cells (Glu).
- The synaptic vesicle membrane is recycled by clathrin-mediated endocytosis.
- Neuropeptides and proteins are stored in larger, dense core granules within the nerve terminal. These dense core granules are released from sites distinct from active zones after repetitive stimulation.

NEUROTRANSMITTERS

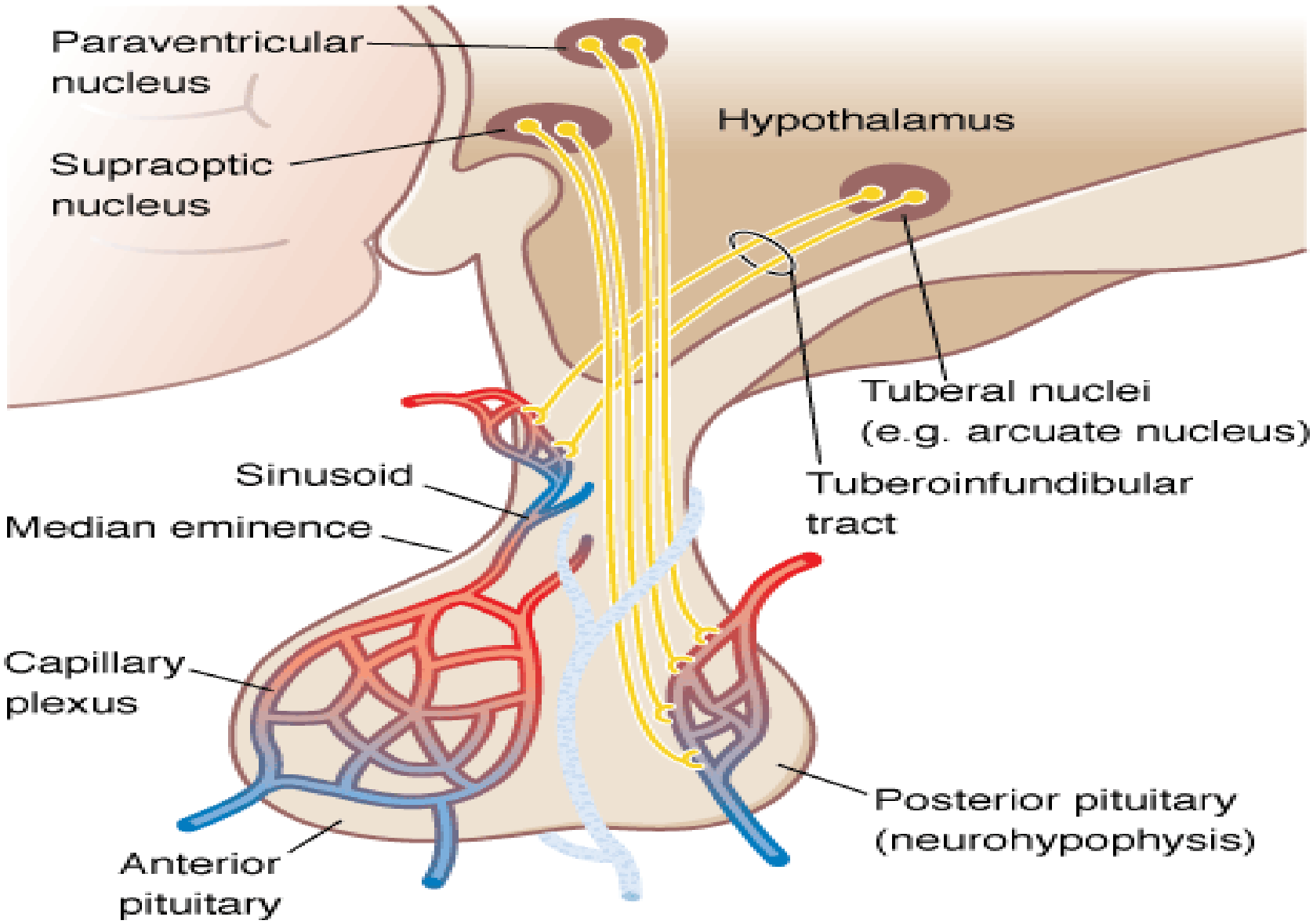
- *The transmitter must be present in the presynaptic terminals of the synapse.*
- *The transmitter must be released from the presynaptic nerve concomitantly with presynaptic nerve activity.*
- *When applied experimentally to target cells, the effects of the putative transmitter must be identical to the effects of stimulating the presynaptic pathway.*
- *Specific pharmacological agonists and antagonists should mimic and antagonize, respectively, the measured functions of the putative transmitter with appropriate affinities and order of potency.*


Neurotransmitter
Receptor
Plasma membrane
Ion channel


Receptor
Ion channel
α
β
γ
Ion channel
α
β
γ
Effectors (AC, PLC)
Second messengers (cAMP, Ca2+)
Altered protein kinase/phosphatase activities
Effects on other neuronal processes

NEUROHORMONES

- Hypothalamic neurons affecting the anterior pituitary release their hormones into the hypothalamic–adenohypophyseal portal blood system, which delivers them to the anterior pituitary, where they regulate the release of trophic hormones (i.e., ACTH, FSH, GH, LH, prolactin) into the blood.
- Other hypothalamic neurons project onto the posterior pituitary, where they release their peptide contents, oxytocin and arginine vasopression (anti-diuretic hormone, or ADH) into the systemic circulation.


Paraventricular nucleus
Supraoptic nucleus
Hypothalamus
Tuberal nuclei (e.g. arcuate nucleus)
Tuberoinfundibular tract
Sinusoid
Median eminence
Capillary plexus
Posterior pituitary (neurohypophysis)
Anterior pituitary

NEUROMODULATORS

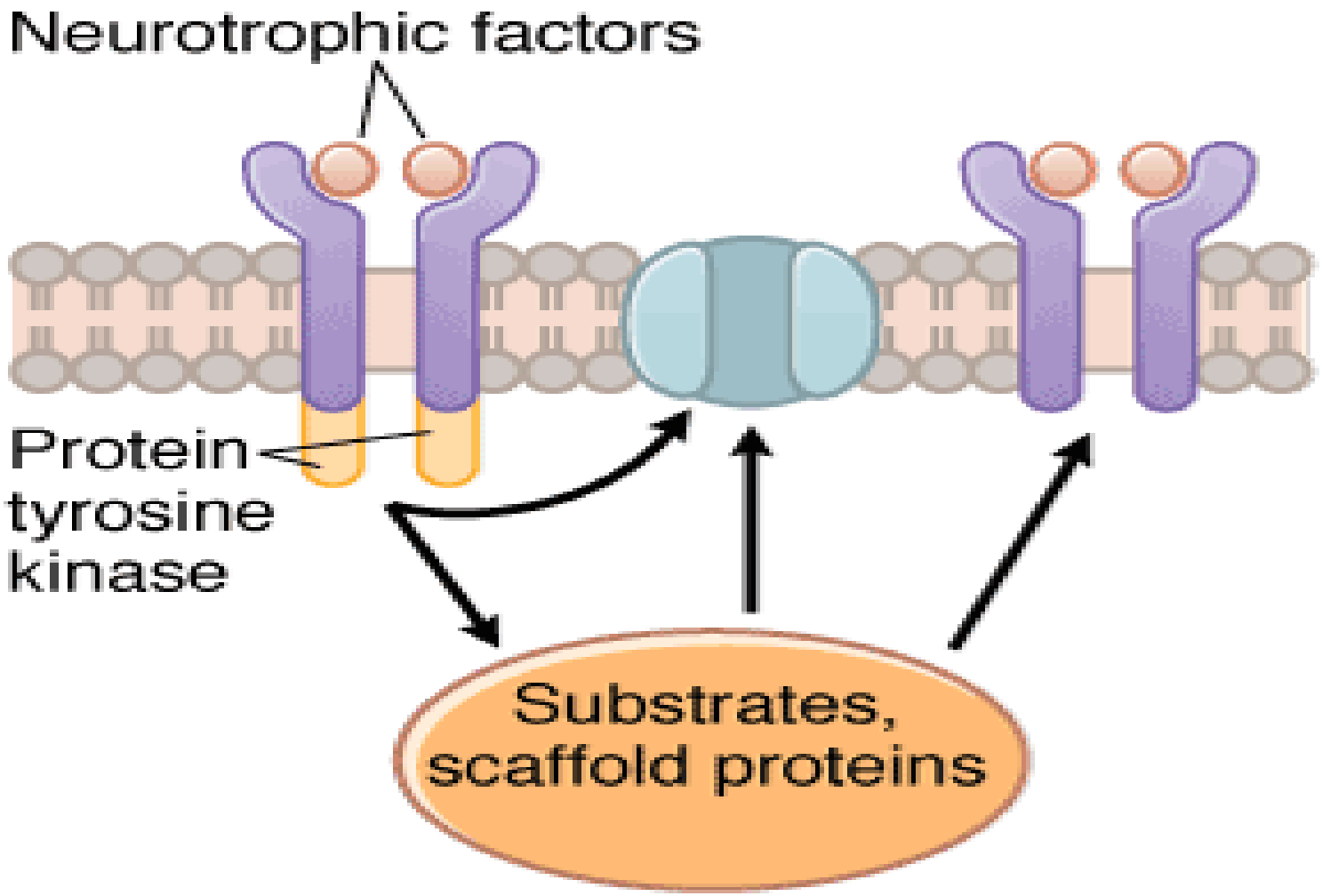
- The distinctive feature of a modulator is that it originates from non-synaptic sites, yet influences the excitability of nerve cells.

- Substances such as **CO, ammonia, neurosteroids**, locally released **adenosine**, **prostaglandins**, and **nitric oxide** (**NO**).

- Neuromodulation relates to synaptic plasticity.

Neurotrophic Factors

- Neurotrophic factors are substances produced within the CNS by neurons, astrocytes, microglia.
- These act over a longer time scale than neuromodulators to regulate the growth and morphology of neurons.
- The binding of neurotrophic factors to their receptors generally promotes receptor dimerization and protein tyrosine kinase activity in the intracellular domains of the receptors.


Neurotrophic factors
Protein tyrosine kinase
Substrates, scaffold proteins

Categories of neurotrophic peptides:

- classic neurotrophins
  -nerve growth factor
  -brain-derived neurotrophic factor (BDNF)

- growth factor peptides,
  -epidermal growth factor
  -activin A
  -fibroblast growth factors
  -insulin-like growth factors
  -platelet-derived growth factors

Central Neurotransmitters

- Acetylcholine
- Amines
  - Dopamine, NE, E, Serotonin, Histamine
- Amino acids
  - Glutamate, Aspartate (excitatory)
  - GABA, Glycine (inhibitory)
- Peptides
  - Oxytocin, Tachykinins, VIP, Opioid peptides
- NO
- Miscellaneous
  - Anandamide, Adenosine, ATP

MCQs

Q1. Drugs can NOT diffuse freely across the

A. the median eminence
B. area postrema
C. striatum
D.pineal gland

Ans-C

Q2. Which of the following is an inhibitory amino acid neurotransmitter?

A. glutamate

B. GABA

C. aspartate

D. PABA

Ans- B

Q3. The difference in concentration of a drug in blood from its concentration in brain after oral administration is due to:

A. preservatives used in drugs

B. blood brain barrier

C. liver metabolism

D. incomplete absorption of drug

Ans- B

Q4. Which of the following factor facilitates drugs diffusion fairly freely across the BBB (blood brain barrier)?

A. lipophobic

B. bioavailability

C. lipophilic

D. $t_{1/2}$ (half life)

- Ans- C

Q5. Which of the following is excitatory neurotransmitter?

A. Glutamate

B. GABA

C. Dopamine

D. Glycine

- Ans- A

Q6. $GABA_A$ receptor is a

A. ionotropic receptor
B. G-protein coupled receptor
C. voltage gated channel
D. kinase linked receptor

- Ans- A

Q7. $GABA_B$ receptor is a

A. ionotropic receptor
B. metabotropic receptor
C. voltage gated channel
D. kinase linked receptor

- Ans- B

Q8. In cell signaling and synaptic transmission, the chemical that originates from non-synaptic sites, yet influences the excitability of nerve cells is

A. neurotrophic factor

B. neurohormone

C. neuromodulator

D. neuromediators

Ans- C

Q9. Which of the following factors does NOT govern passage of drug across biological membranes?

A. charge

B. lipophilicity

C. the presence or absence of energy-dependent transport systems

D. t 1/2 (half life)

Ans- D

Q 10. Which of the following is NOT a criteria for Neurotransmitter:

- transmitter must be present in the presynaptic terminals of the synapse.
- The transmitter must be released from the presynaptic nerve concomitantly with presynaptic nerve activity.
- When applied experimentally, effects must be identical to the effects of stimulating the presynaptic pathway.
- Should be an excitatory transmitter.

- Ans- D

Thank you

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- Review of Pharmacology by Gobind Sparsh

I- CNS Stimulants Drugs

Nervous System

- The nervous system can be classified into
- **<u>The Central Nervous System (CNS)</u>** Brain and spinal cord
- **The Peripheral Nervous System (PNS)**The nervous system outside of the brain and spinal cord

Can be divided into-

1- Sensory division(affrent)

Conducts impulses from receptors to the CNS and Informs the CNS of the state of the body

2- **Motor division(effrent)**

Conducts impulses from CNS to effectors organs.

Peripheral Nervous System PNS

Motor Neurons

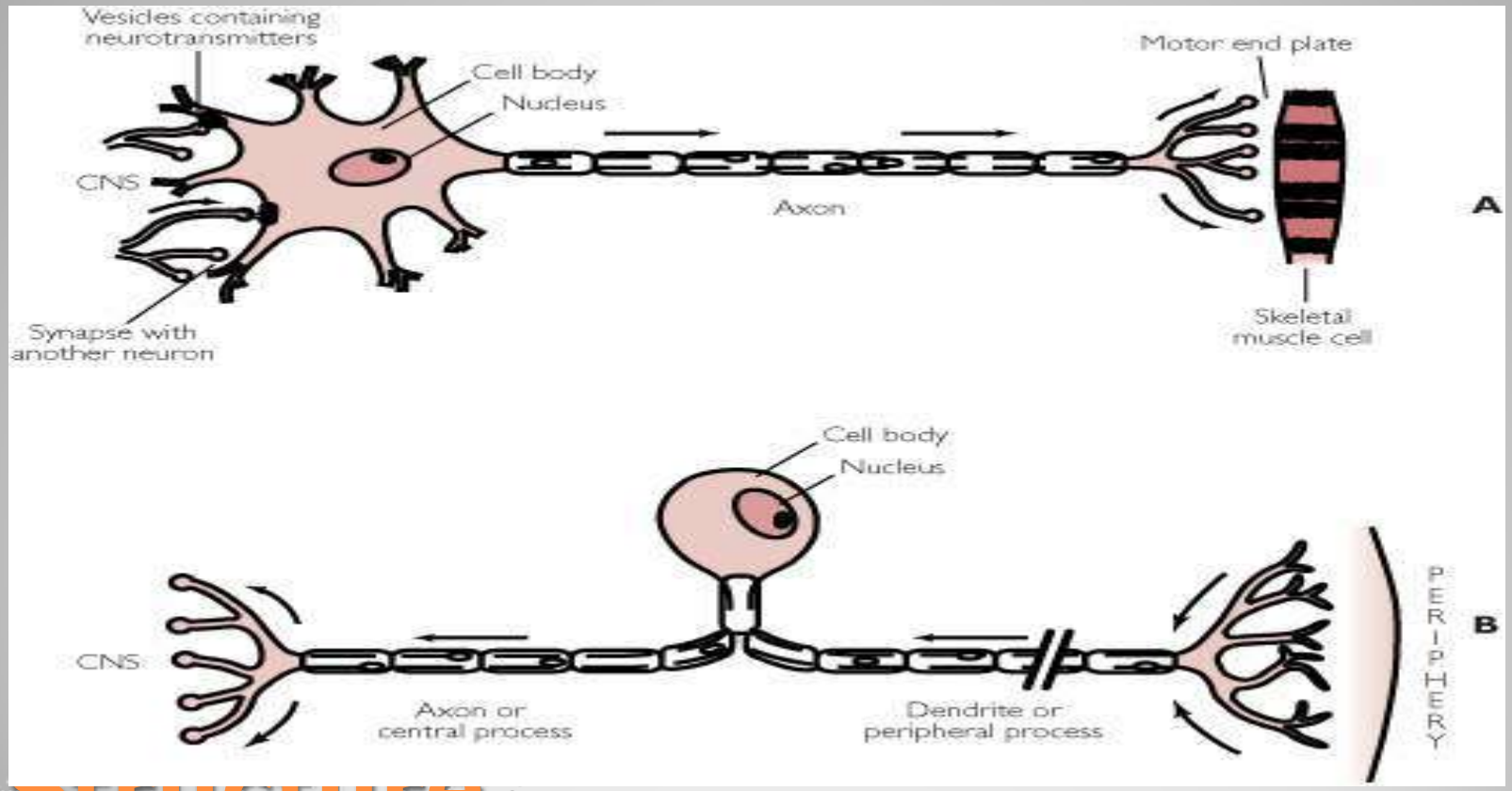
- The motor division is also divided into
- 1- **The somatic nervous system :**
- VOLUNTARY (generally) Somatic nerve fibers that conduct impulses from the CNS to skeletal muscles
- **2. The autonomic nervous system:**

INVOLUNTARY (generally) Conducts impulses from the CNS to smooth muscle, cardiac muscle, and glands

Neurons

- They are the basic functional unit of the nervous system.
- They contain three major parts:
- 1.cell body.
- 2. dendrites.
- 3. axon.

Structure


Vesicles containing neurotransmitters
Cell body
Nucleus
Motor end plate
CNS
Axon
A
Synapse with another neuron
Skeletal muscle cell
Cell body
Nucleus
CNS
Axon or central process
Dendrite or peripheral process
PERIPHERY
B

Neurotransmitters CNS

- They can be classified into :
- 1. Exitatory:
- - Ach, glutamate, aspartate , serotonin and NE.
- 2. Inhibitory:-
- - GABA , glycin .

- Defination

"Stimulants are a substance which tends to increase behavioral activity when administered"

CNS Stimulants

- Signs and symptoms:
- 1- Elevate Mood
- 2- Increase Motor Activity
- 3- Increase Alertness
- 4- Decrease need for Sleep
- In case of overdose lead to convulsion and death.

MOA of CNS Stimulants

- 1- Block neurotransmitters reuptake (Most reuptake inhibitors affect either NE or 5-HT(Serotonin) : Cocaine
- 2- Promote neurotransmitters release : Amphetamine
- 3- Block Metabolism - MAO inhibitors (monoamine oxidase):ex. Phenelzine
- 4. antagonize the effect of inhibitory neurotransmitter: Picrotoxin & Strychnine
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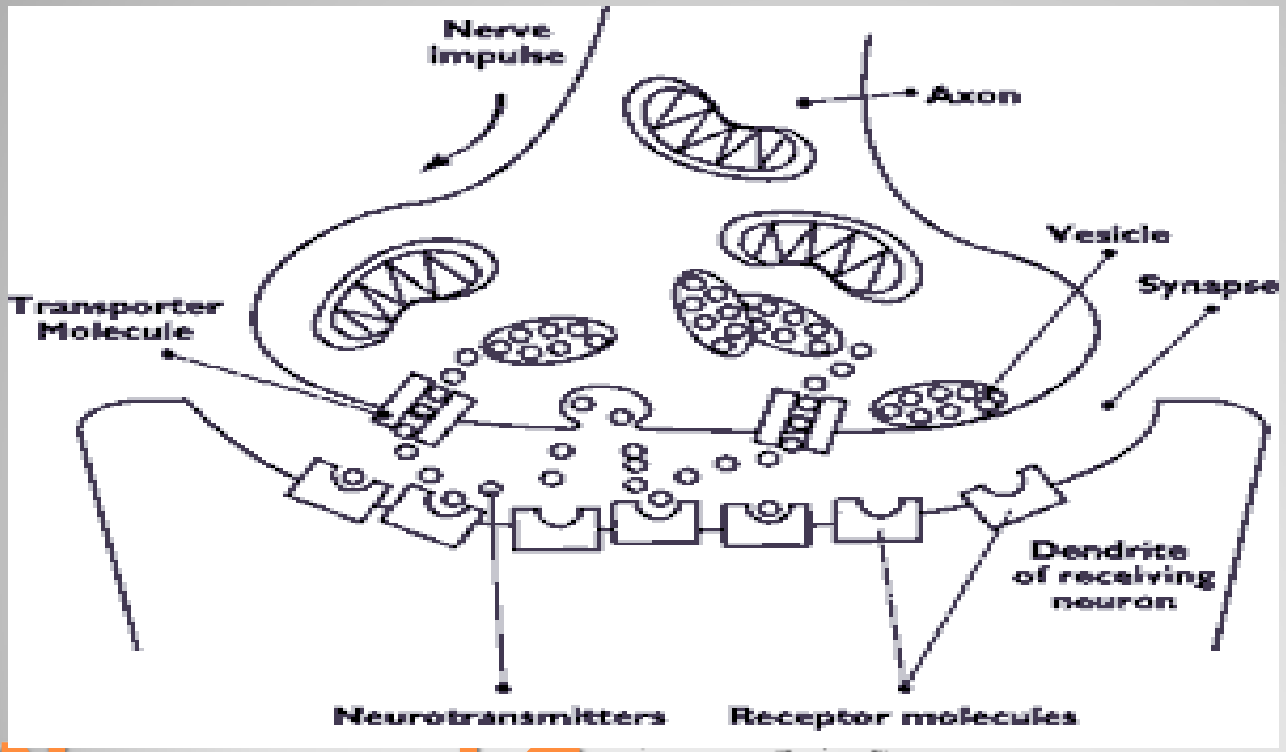
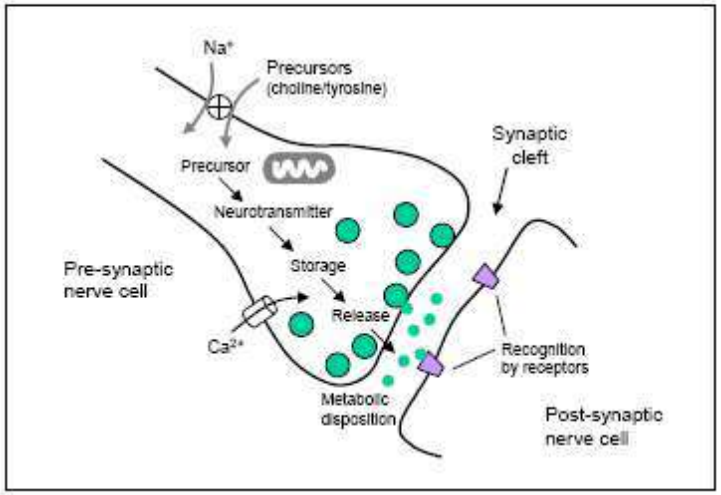


Neuronal Synapse

Definition of synapse:
A junctional connection between two neurons, across which a signal can pass



Pre-synaptic neuron: Where a neurotransmitter is synthesized, stored and released upon cell activation.

Post-synaptic neuron or effector cell: Where neurotransmitter is detected and its action translated into cellular activities.

CNS Stimulants

- - They can be divided based on their site of action:
- 1.Cerebral stimulants (amphetamines)
- 2.Medullary stimulants (picrotoxin)
- 3.Spinal stimulants (strychnine)

Lab Work

- **- <u>Objectives:</u>**
- 1- To demonstrate effects of some CNS stimulant on mice.
- 2- After the lab, you should able to handle and inject the mice correctly.
- 3- You should able to differentiate between amphetamine,picrotoxin and strychinine regarding the symptoms that induced by each of them.

- **MOAs :**
- Block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

  - Clinical use:
- 1. Narcolepsy.
- 2. Attention-deficit hyperactivity disorder

1- Amphetamine

Amphetamine

- Adverse effects:
- **- Cardiovascular:** Hypertension (7% to 22%, pediatric)
- **- Endocrine metabolic:** Weight loss (4% to 9%, pediatric; 11%, adults)
- **- Gastrointestinal:** Abdominal pain (11% to 14%, pediatrics), Loss of appetite (22% to 36%), Xerostomia (35%)
- **- Neurologic:** Headache (26%), Insomnia ارق (12% to 17%, pediatric; 27%, adults)
- **- Psychiatric:** Feeling nervous (6%)

- After injecting, the mice with amphetamine you well notice:
  - Hair erection
- - Licking, gnawing.
- - Stereotype
- - Sniffing

Amphetamine

Picrotoxin

- **MOA:**
- Non-competitive antagonist of GABA receptors.
- After injecting the mice with picrotoxin you well notice:
  - **Clonic convulsion** characterized by :
- 1. Asymmetric
- 2. Intermittent
- 3. Spontaneous
- 4. Coordinated

Strychinine

- **MOA:**
- Competitive antagonist of the glycin receptors.

- After injecting the mice with Strychinine you well
- notice:
  - **Tonic convulsion** characterized_by :
- 1. Symmetric
- 2. Reflex in origin
- 3. Continuous
- 4. Uncoordinated.

CNS STIMULANTS
&
COGNITIVE ENHANCERS

Dr. UMER SUFYAN M

MBBS, MD

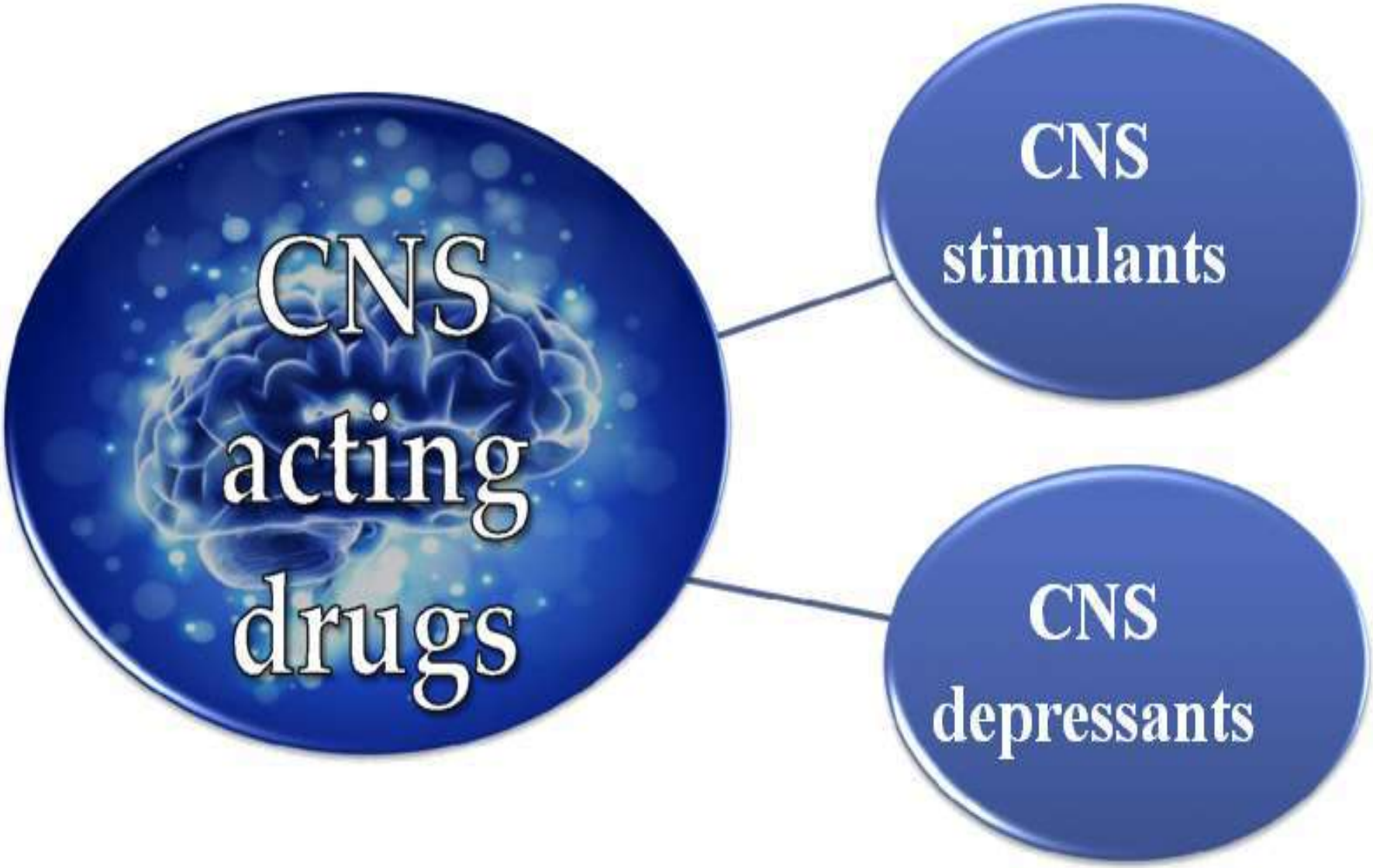
CNS STIMULANTS

The CNS stimulants mostly produce a generalized action which may, at high doses, result in convulsions.

They are drugs which increase the muscular (motor) and the mental (sensory) activities.

Their effects vary from the increase in the alertness and wakefulness (as with caffeine) to the production of convulsion (as with strychnine) and sometimes lead to death in over dose.

Classification of drugs acting on CNS



CLASSIFICATION

1. ***Convulsants:*** *Strychnine,Picrotoxin,*Bicuculline, Pentylenetetrazol (PTZ).
2. ***Analeptics:*** *Doxapram*
3. ***Psycho stimulants:*** *Amphetamines, Methylphenidate, Atomoxetine, Modafinil, Armodafinil, Pemoline, Cocaine, Caffeine.*

- Many other drugs are capable of causing CNS stimulation as side effect or at high doses.

CONVULSANTS

CONVULSANTS

1. **Strychnine:** It is an alkaloid from the seeds of *Strychnos nux-vomica, and a potent convulsant.*

Example	**Strychnine.**
Site of action	**Spinal cord.**
MOA	**Block the postsynaptic inhibitory response to glycine by blocking glycine receptors. Glycine is the main inhibitory transmitter acting on motor neurons.**
End point	**Tonic convulsion.**

Opisthotonus

Also seen in;

- Cerebral palsy
- Traumatic
- Brain injury tetanus

Picrotoxin :

Obtained from ‘fish berries’ of East Indies *Anamirta cocculus. It is a potent convulsant*— convulsions are clonic, spontaneous and asymmetrical. The convulsions are accompanied by vomiting, respiratory and vasomotor stimulation.

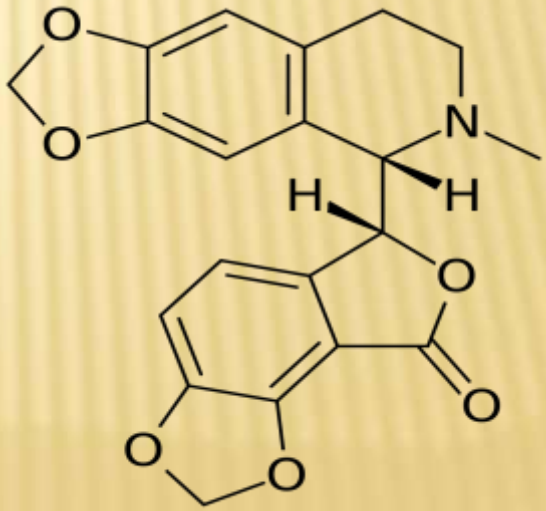
Examples	Picrotoxin
Site of action	Medulla oblongata.
MOA	1. It inhibits the presynaptic inhibition →decrease GABA. 2. Noncompetitive GABAA receptors blocker which is a chloride dependent →no hyperpolarization → excitation.
End point	Clonic convulsion.
Removed by	Decapitation.

Bicuculline :

This synthetic convulsant has picrotoxin like actions.

It is a competitive GABA-A receptor (intrinsic Cl^- channel receptor) antagonist.

It is only a research tool.



Pentylenetetrazol (PTZ)

It is a powerful CNS stimulant

Low doses cause excitation, larger doses produce

Convulsions

Antagonism of PTZ induced convulsions is an

established method of testing anticonvulsant drugs in laboratory animals

ANALEPTICS

ANALEPTICS (Respiratory stimulants)

These are drugs which stimulate respiration and can have resuscitative value in coma or fainting.

Mechanical support to respiration and other measures to improve circulation are more effective and safe.

Situations in which analeptics may be employed are:

(a) As an expedient measure in hypnotic drug poisoning untill mechanical ventilation is introduced.

(b) Suffocation on drowning, acute respiratory insufficiency.

(c) Apnoea in premature infant.

(d) Failure to ventilate spontaneously after general anaesthesia.

Doxapram:

It acts by promoting excitation of central neurones.

At low doses it is more selective for the respiratory centre.

Respiration is stimulated through carotid and aortic body chemoreceptors.

Continuous i.v. infusion of doxapram may abolish episodes of apnoea in premature infant not responding to theophylline.

Uses :

- Post-anaesthetic resp. depression
- COPD i.e. hypoxemic,hypercapnic res.fail
- Apnoea in premature infants

Dose- 2-5mg/min(max 4mg/kg) slow i.v infusion.

Contraindications:

- Resp.fail due to neurological & muscular diseases.
- Epilepsy

Side effect:

- Restlessness, Tachycardia
- High doses: convulsions & arrhythmias

PSYCHO STIMULANTS

PSYCHOMOTOR STIMULANTS

Amphetamine group:

- Amphetamine
- Dexamphetamine
- Methamphetamine
- Methylenedioxy Methampheta(MDMA)
- Methylphenedate
- Fenfluramine

Non-Amphetamine group

- Modafinil
- Atomoxetine
- Sibutramine
- Pemoline

Cocaine

Methylxanthines:

- Caffeine
- Theophylline
- Theobromine

PSYCHOMOTOR STIMULANTS

Amphetamine & Non- Amphetamine:

MOA:

- Drug enter N endings by active transport
- ↓
- Displace DA(also NE) from vesicles by altering pH
- ↓
- ↑DA conc. In synaptic cleft
- ↓
- Also inhibits MOA-B, ↓DA metabolism & ↑DA
- ↓
- Release to synaptic cleft

Pharmacological effects: (central)

- ↑ motor activity
- Euphoria & excitement
- Anorexia

PERIPHERAL EFFECTS

- ↑ BP, inhibition of GI motility
- Fatigue both physical & mental reduced.
- Amphetamine psychosis on repeated use- hallucinations.

PK:

- Well absorbed orally
- Freely penetrates BBB
- Unmetabolised drug excreted in urine

USES

ADHD with minimal brain dysfunction:

- Characterised by-
  - Hyperactivity
  - Inability to concentrate
  - Impulsive behavior

Dexamphetamine,

Methylphenedate,

Atomoxetine quite effective.

Narcolepsy: Characterised by-

- Sleep attacks during day time
- Night mares in awakening state

Methylphenedate is still used

Modafinil- devoid of abuse liability

APPETITE SUPPRESSION

- *Fenfluramine, dexfenfluramine* used earlier to treat obesity

  Discouraged due to:-

- Tolerance
- Insomnia, Pul.HTN, Abuse potential.

Sibutramine new drug used now

- Blocks neuronal uptake of mainly NE & 5HT (also dopamine) at hypothalamic site that regulates food intake.

Use:

- Severe obesity with risk factors like DM.

Adverse effects:

- Dry mouth
- Headache
- Insomnia
- Constipation
- ↑in HR & BP
- CI in CVS diseases, withdrawn from market

ADVERSE EFFECTS

- Tolerance
- Psychic dependence, rarely physical.

Amphetamine overdose:

- Euphoria, dizziness, tremors, HTN
  Irritability, anorexia, insomnia
- Higher doses- convulsions, psychotic manifestations, arrhythmias, coma
- Rx –diazepam(slow i.v), haloperidol
  Gastric lavage, acidification of urine
  HTN-nifedipine/labetolol, arry-esmolol

- Induces heat stroke like condition- rhabdomyolysis & renal failure

Methylenedioxy amphetamine (love drug)

75mg- psychotomimetic effects

150 mg-LSD like effects

300mg- amphetamine like

- SE: tachycardia, HTN, arrhythmias

METHYLXANTHINES

- Only caffeine if used as CNS stimulant

PK:

- Oral- rapid but irregular absorption
- PPB:<50%
- Distributed all over the body
- Metabolism: in liver by demethylation & oxid.
- Metabolites excreted in urine
- $T_{1/2}$: 3-6hrs

AE:

- Gastric irritation, Nause, Vomiting.
- Nervousness, insomnia, agitation
- Muscule twitch, rigidity
- ↑body temp, delirium, convulsions
- Tachy, extra systoles at high doses

Uses:

- In Analgesic mixture for headache
- Migraine
- Apnoea in premature infants

PSYCHOTOMIMETIC DRUGS

- Produce changes in sensory perceptions, thoughts, behaviour & mood.
- Actions mimic psychoses- psychedelics
- Lysergic acid diethylamide (LSD)
- Phencyclidine
- Cannabinoids

LYSERGIC ACID DIETHYLAMIDE

- Derived from cereal fungus ergot
- Hofmann synthesized & experimented on himself.
- Act as agonist at $5HT_2$ receptors.
- Excitation threshold of retina ↓- visual hallucinations, hyper arousal state
- Experiences may be bad or good trip.

CANNABINOIDS (Δ9THC)

- Extract of hemp plant-C.sativa, C.indica
- Bhang- paste of powdered dried leaves, used as drink
- Marijuana- dried leaves & flowering tops, smoked in pipes or rolled as cigarettes.
- Charas or hashish- resinous exudates leaves & flowering tops, potent smoked inpipe.
- THC content more in hashish

PHARMACOLOGICAL ACTIONS

- Initial CNS stimulation later sedation.
- Stimulatory phase- euphoria, ↑talkativeness, ↑appetite
- Felling of confidence, relaxation & well being
- Other- analgesia, antiemetic
- Peripheral effects- tachycardia, reddening of conjunctiva

MOA, USES

- Two types CB 1& 2 receptors
- CB1 in brain CB2 in periphery
- ***Anandamide***-endogenous ligand CB1.
- ***Dronabinol, Nabilone***- synt.analogues of THC
- Use: CB1 Agonists- ↑appetite in AIDS pts.
- ***Dronabinol***-antiemetic in cancer chemo.
- ***Rimonabant*** : CB1 antagonist, used for obesity, dose-20mg OD before Breakfast
- Smoking cessation

COGNITIVE ENHANCERS

COGNITION ENHANCERS

Cognition is "the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses.“

It encompasses processes such as knowledge, attention, memory and working memory, judgment and evaluation, reasoning and "computation", problem solving and decision making, comprehension and production of language,

COGNITION ENHANCERS

Indications:

- AD, multi infarct dementia
- Mild cognitive impairment
- learning defects, ADHD in children
- CVA, Stroke
- Organic psychosyndromes
- Sequale of head injury
- ECT, brain surgery

MECHANISMS

- ↑ global/regional blood flow
- Direct support of neuronal metabolism
- Enhancement of neurotransmission
- Improvement of discrete cerebral functions

ALZHEIMERS DISEASE

- Main pathological features:
- *Amyloid plaque*
- *Neurofibrillary tangles*
- Marked ↓ in choline acetyltransferase & loss of cholinergic neurons in brain.

CHOLINERGIC ACTIVATORS

- ACEs that cross BBB are preferred.

Tacrine:

- Longer acting, reversible ACE
- Palliative for mild to moderate AD
- Orally active
- Improves memory, cognition, well being
- Facilitates Ach release
- AE: hepatotoxicity

DONEPEZIL, RIVASTIGMINE & GALANTAMINE

- Newer reversible Anti cholinesterase
- Better penetration in to CNS
- Better tolerated & less toxic than tacrine
- Clinical results modest & temporary
- *Donepezil*: 5mg OD orally evening ↑ max 10mg after 4 wks
- *Rivastigmine*:1.5 mg orally BD ↑ to 3mg BD after 2 wks
- *Galantamine*:4mg BD orally ↑to 8mg BD after 2 wks

- Transdermal Rivastigmine patch –applied every 24hrs
- SE:diarrhoe, N, V, ↑urination

Acetyl-L-carnitine:

- Structural analogue of Ach
- ↓ signs & symptoms of dementia in AD
- ↑ cholinergic transmission
- Also have antioxidant properties, slows progression of AD

MEMANTINE

- Excitotoxicity due to enhanced Glutamate transmission via NMDA recp.
- Dose:5mg OD slowly ↑ to 10-20mg/day
- Non-comp. antagonist of NMDA recp.
- Better tolerated, less toxic.

Miscellaneous :

- Nootropics- ***piracetam, aniracetam***
- High doses of vit E(1000 IU B.D)
- Antioxidants-vit C, A, Zn, Se, bioflavonoids or spirulina ↓ progression even in middle stage AD.

THANK YOU

DIFFERENT TERMINOLOGIES

- **<u>Agonists</u>**

Binds to a receptor and activates the receptor to produce a biological response.

- Receptors can be activated by either **endogenous** agonists (like hormones or neurotransmitters) or **exogenous** agonists (like drugs).

- Agonists can be divided into following sub-categories:

- **Full agonists**
- They bind to and activate a receptor with the **maximum response** that an agonist can elicit at the receptor.
- **Co-agonists**
- A co-agonist works with other co-agonists to produce the desired effect **together**.

- **Selective agonists**
- A selective agonist is selective for a **specific** type of receptor only.

- **Partial agonists**
- Partial agonists like buprinorpine (Opioid dependence)also bind and activate a given receptor but have only **partial efficacy** at the receptor relative to a full agonist, even at maximal receptor occupancy.

- **Inverse agonists**
- An inverse agonist is an agent which binds to the same receptor binding-site as an agonist and inhibits the constitutive activity of the receptor. exert the **opposite** pharmacological effect to that of an agonist.

- **Super agonists**
- It is a term used to identify a compound which is capable of producing a **greater response than the endogenous agonists** for the target receptor.

- **Irreversible agonists**
- An irreversible agonist is a type of agonist which **binds permanently** to a receptor through formation of covalent bonds.

- **<u>Antagonists</u>**
- **Competitive Antagonists**
- Competitive antagonists bind to receptors at the same binding site (active site) as the endogenous ligand or agonist, but **without activating the receptor**.
- Agonists and antagonists compete for the **same binding site** on the receptor. Once bound, an antagonist will block binding of agonist. Sufficient concentration of an antagonist will displace the agonist from the binding sites, resulting in a lower frequency of receptor activation. The level of activity of the receptor will depend on relative affinity of each molecule for the site and their relative concentrations. Competitive antagonists are used to prevent the activity of drugs and to
- reverse the effects of drugs that have already been consumed.

- **non-competitive antagonist**

A non-competitive antagonist is a act in one of two ways:

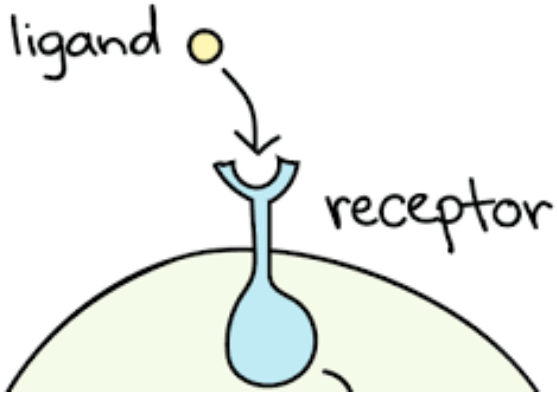
- By binding to the active site of receptor or by binding to an allosteric site of the receptor. If it binds to the allosteric site, it is called as **allosteric antagonist**.
- In both the cases, end-results are functionally similar. Unlike competitive antagonists, which affect the amount of agonists necessary to achieve a maximal response but do not affect the magnitude of that maximal response, non-competitive antagonists reduce the magnitude of the maximum response that can be attained by any amount of agonists.

Intrinsic activity

- Intrinsic activity is **a measure of the ability of a drug that is bound to the receptor to generate an activating stimulus and produce a change in cellular activity**. Both agonists and antagonists can bind to a receptor.

Receptors

- Receptors are **proteins, usually cell surface receptors, which bind to ligands and cause responses in the immune system**, including cytokine receptors, growth factor receptors. Receptors can be found in various immune cells like B cells, T cells, NK cells, monocytes and stem cells.



- **Spare Receptors**

Spare receptors are defined as **those receptors without combining with which maximal response can be obtained.**

- **Addiction**
- Addiction is a brain disorder characterised by compulsive engagement in rewarding stimuli despite adverse consequences. It is related to addictive behaviour which is bothrewarding and reinforcing. **Examples** include sedatives, such as diazepam (Valium), alprazolam
- **Tolerance**

Drug tolerance is defined as, "**the diminishing effect of drug resulting from repeated administration at a given dose**". Drug tolerance is a pharmacological concept describing subjects' reduced reaction to a drug following its repeated use.

- **Some medications and conditions with reports of tolerance include:**
- Anti-depressants. Depression symptoms can worsen in some people.
- Antibiotics. They can have weaker effects
- Anxiolytics

- **Pharmacodynamic tolerance** begins when the cellular response to a substance is reduced with repeated use.
- **Pharmacokinetic tolerance** occurs because of a decreased quantity of the substance reaching the site it affects, this may be caused by increase in induction of enzymes required for degradation of drug.
- **Behavioural tolerance** occurs with the use of some psycho-active drugs, where tolerance to a behavioural effect of a drug occurs with repeated use of the drug. Amphetamine causes behavioural tolerance.

- **Dependence**
- It is defined as, "an adaptive state associated with a withdrawal syndrome upon cessation of repeated exposure to a stimulus (e.g. drug intake)".
- Dependence include nicotine, morphine, heroin (also known as diamorphine), cocaine, amphetamine and alcohol

- **Tachyphylaxis**
- Describing an acute, sudden decrease in response to a drug after its administration; i.e. a rapid and short-term onset of drug tolerance. It can occur after an initial dose or after a series of small doses. Increasing the dose of the drug may be able to restore the original response.

- **Idiosyncrasy**
- Idiosyncratic drug reactions occur rarely and unpredictably amongst the population. They frequently occur with exposure to new drugs. They are listed as rare ADR. They do not appear to be concentration dependent.

- **Allergy**
- Allergic reaction to a drug will not occur on the first exposure to a substance. The first exposure allows the body to create antibodies and memory lymphocyte cells for the antigen. Subsequently antibodies or lymphocytes interact with the antigen causing what we understand as allergic reactions.

Deepankar Ratha
Assistant Professor
Department of Pharmacology,
CUTM Rayagada

WHAT IS ADDICTION?

- Addiction is not limited to drugs and alcohol. People can be addicted to many things, such as food, gambling, shopping, or most anything that gets in the way of a healthy lifestyle. When things get out of hand, and people behave compulsively, regardless of the consequences.

- When the person is no longer in charge of their life, regardless of the triggering mechanism, they are addicted. The addiction can take over a person’s entire life. Nothing else matters.

•Drug addiction is a chronic disease affecting the brain, and just about everyone is different.

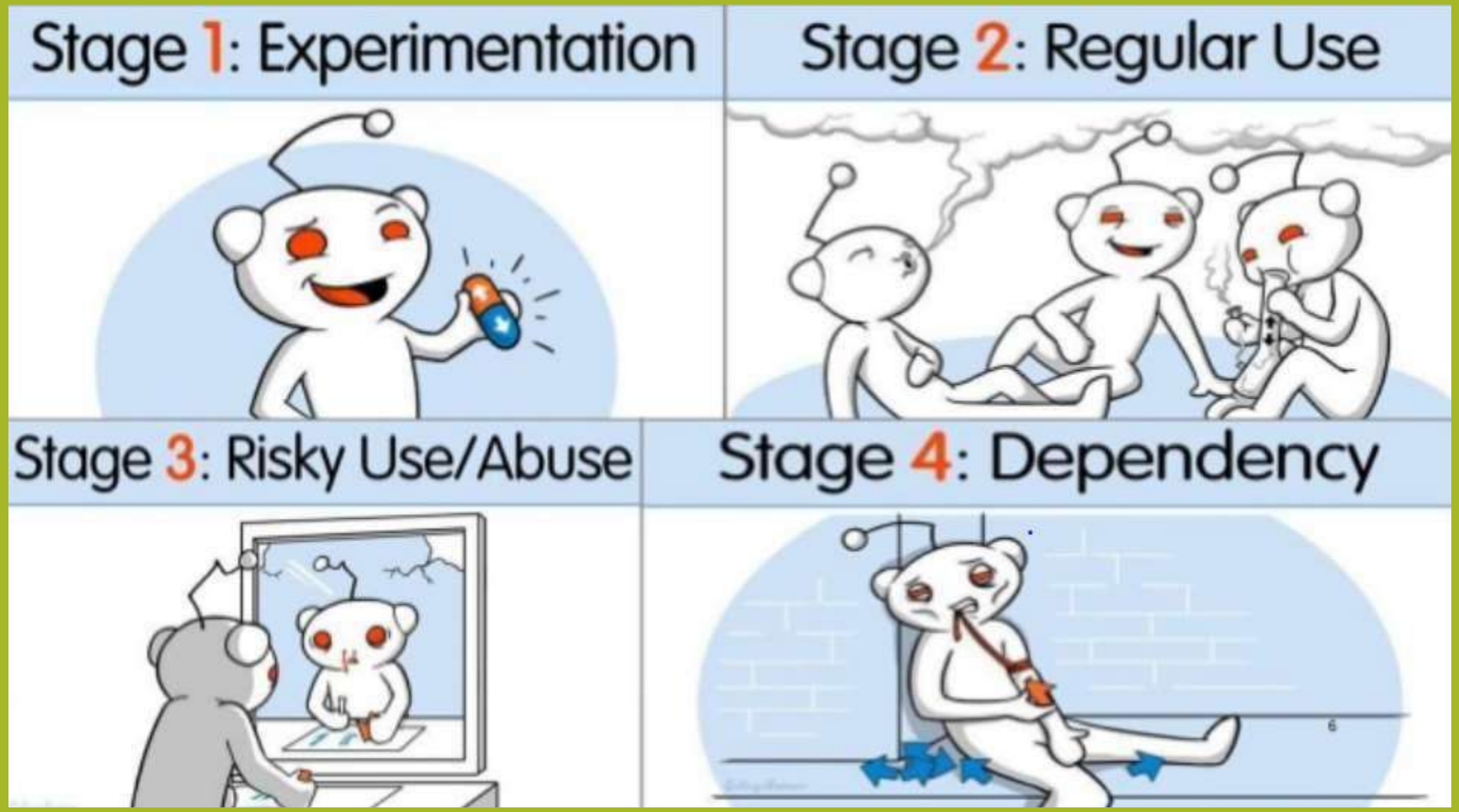
•Drugs affect different people in different ways. One person can take and abuse drugs, yet never become addicted, while another merely has one experience and is immediately hooked.

•There are several factors and causes to consider with addiction, first there is a genetic component, that is, what is passed on to you through your family.

•If your blood relatives had a predisposition to become addicted, chances are you have that same tendency.

• Personality contributes to drug addiction.

• Peer pressure is huge, both for teenagers and adults alike.


Stage 1: Experimentation
Stage 2: Regular Use
Stage 3: Risky Use/Abuse
Stage 4: Dependency

STAGE 1

- CURIOSITY IS THE MOTIVATOR
- LEARNING TO TRUST/MISTRUST THE DRUG USED
- “HIGH” IS STILL A NEWFEELING

STAGE 2

- USER IS THINKING MORE ABOUT DRUGS
- PREVIOUS RELATIONSHIP BECOMES DIFFICULT
- USER USES WHEN ALONE
- USER STILL THINKS THEY HAVE CONTROL

STAGE 3

- SEEKS OUT THE “HIGH”
- HAS CONFIDENCE IN USING THE DRUG
- USER THINK THE DRUG WON’T HURT THEM
- PEER GROUP USES

STAGE 4

- CAN NO LONGER GET HIGH
- USER USES THE DRUG TO AVOID BEING SICK
- DRUGS BECOME THE CENTER OF THEIR LIFE

- MARIJUANA
- HEROIN
- COCAINE
- ALCOHOL
- TOBACCO
- LSD (Lysergic acid diethylamide)
- SPEEDBALL
- MDMA
- KETAMINE
- CRYSTAL- METH

- LOSS OF APPETITE
- HEADACHES
- ANXIETY
- ELEVATED BLOOD PRESSURE
- CHEST PAIN
- IRREGULAR HEARTBEAT
- COLD/BLUISH FINGERS
- DIFFICULTY IN URINATING
- CHANGES IN BODY TEMPERATURE

Drugs are chemicals. Different drugs, because of their chemical structures, can affect the body in different ways. In fact, some drugs can even change a person's body and brain in ways that last long after the person has stopped taking drugs, maybe even permanently.

• Weaken the immune system, increasing susceptibility to infections.

•Cause cardiovascular conditions ranging from abnormal heart rate to heart attacks.

• Cause nausea, vomiting and abdominal pain.

•Cause the liver to have to work harder, possibly causing significant damage or liver failure.

• Cause seizures, stroke and widespread brain damage

•Produce global body changes such as breast development in men, dramatic fluctuations in appetite and increases in body temperature, which may impact a variety of health conditions.

BRAIN- All drugs of abuse - nicotine, cocaine, marijuana, and others - effect the brain's "reward" circuit, which is part of the limbic system.

• Drugs hijack this "reward" system, causing unusually large amounts of dopamine to flood the system.

• This flood of dopamine is what causes the "high" or euphoria associated with drug abuse.

BIRTH-

• These and other illicit drugs may pose various risks for pregnant women and their babies. Some of these drugs can cause a baby to be born too small or too soon, or to have withdrawal symptoms, birth defects or learning and behavioral problems.

• Pregnant women who use illicit drugs may engage in other unhealthy behaviors that place their pregnancy at risk, such as having extremely poor nutrition or developing sexually transmitted infections.

BEHAVIORAL PROBLEMS-

• PARANOIA

• AGGRESSIVENESS

• HALLUCINATIONS

• ADDICTION

• IMPAIRED JUDGMENT

• IMPULSIVENESS

• LOSS OF SELF-CONTROL

- It is the appearance of characteristic toxic effects of a drug in an individual at therapeutic doses.
- It is the converse of tolerance and **indicates a low threshold of the individual to the action of a drug**.

Examples are:

- A single dose of trifluprom azine (antipsychotic medication) induces muscular dystonias (movement disorder in which a person's muscles contract uncontrollably) in some individuals, specially children.
- Only few doses of carbamazepine (antipsychotic medication) may cause ataxia in some people.
- One tablet of chloroquine (anti malarial) may cause vomiting and abdominal pain in an occasional patient.

It is genetically determined abnormal reactivity to a chemical. The drug interacts with some unique feature of the individual, not found in majority of subjects, and produces the uncharacteristic reaction. As such, the type of reaction is restricted to individuals with a particular genotype. In addition, certain bizarre drug effects due to peculiarities of an individual (for which no definite genotype has been described) are included among idiosyncratic reactions, e.g.:

- **Barbiturates** cause excitement and mental confusion in some individuals.
- **Quinine/quinidine** cause cramps, diarrhoea, asthma and vascular collapse in some patients.
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Drugs capable of altering mood and feelings are liable to repetitive use to derive euphoria (experience (or affect) of pleasure), recreation, withdrawal from reality, social adjustment, etc. **Drug dependence is a state in which use of drugs for personal satisfaction is accorded a higher priority than other basic needs, often in the face of known risks to health.**

- **Psychological dependence** It is said to have developed when the individual believes that optimal state of wellbeing is achieved only through the actions of the drug. The subject feels emotionally distressed if the drug is not taken.

- **Physical dependence** It is an altered physiological state produced by repeated administration of a drug which necessitates the continued presence of the drug to maintain physiological equilibrium. Discontinuation of the drug results in a characteristic *withdrawal (abstinence) syndrome*. Since the essence of the process is adaptation of the nervous system to function normally in the presence of the drug, it has been called *'neuroadaptation'*.

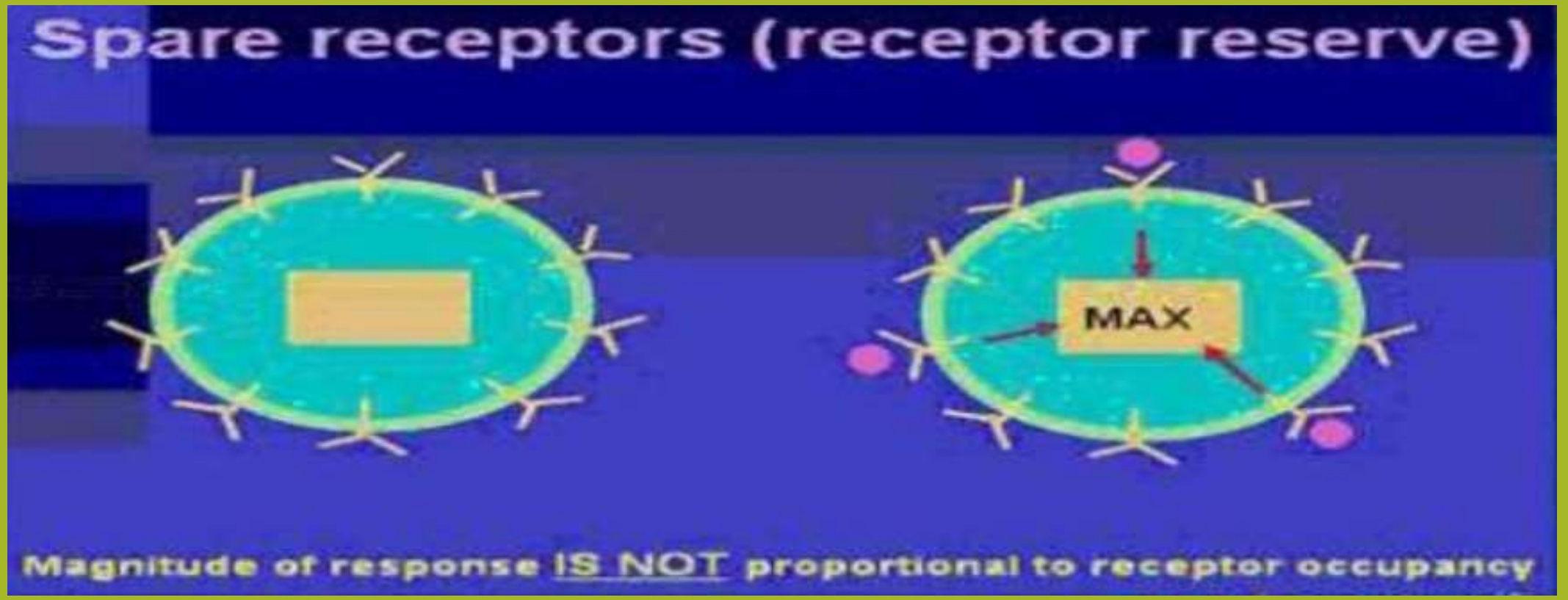
- *(Tachy*-fast, *phylaxis*-protection) It refers to rapid development of tolerance when doses of a drug repeated in quick succession result in marked reduction in response. This is usually seen with indirectly acting drugs, such as ephedrine, tyramine, nicotine. These drugs act by releasing catecholamines in the body, synthesis of which is unable to match the rate of release: stores get depleted. Other mechanisms like slow dissociation of the drug from its receptor, desensitization/ internalization or down regulation of receptor, etc. and/or compensatory homeostatic adaptation.

- Receptors may be considered spare when the maximal response is elicited by an agonist at a concentration that does not produce full occupancy of the available receptors.

History

- Nickerson (1957) - histamine on a guinea pig ileum preparation
- Furchgott (1964) - adrenaline induced contraction of the rabbit aortic strips
- Only small percentage of receptors had to be occupied by agonist to produce maximum contraction(response)
- ‘spare’ or ‘reserve’ receptor
- proposed by Stephenson

- Not all of the receptors in the tissue are required to achieve a maximal response.
- Spare receptors exist when maximum drug response is achieved prior to saturation of all receptors.



Deepankar Ratha
Assistant Professor
Department of Pharmacology,
CUTM Rayagada

WHAT IS ADDICTION?

- Addiction is not limited to drugs and alcohol. People can be addicted to many things, such as food, gambling, shopping, or most anything that gets in the way of a healthy lifestyle. When things get out of hand, and people behave compulsively, regardless of the consequences.

- When the person is no longer in charge of their life, regardless of the triggering mechanism, they are addicted. The addiction can take over a person's entire life. Nothing else matters.

•Drug addiction is a chronic disease affecting the brain, and just about everyone is different.

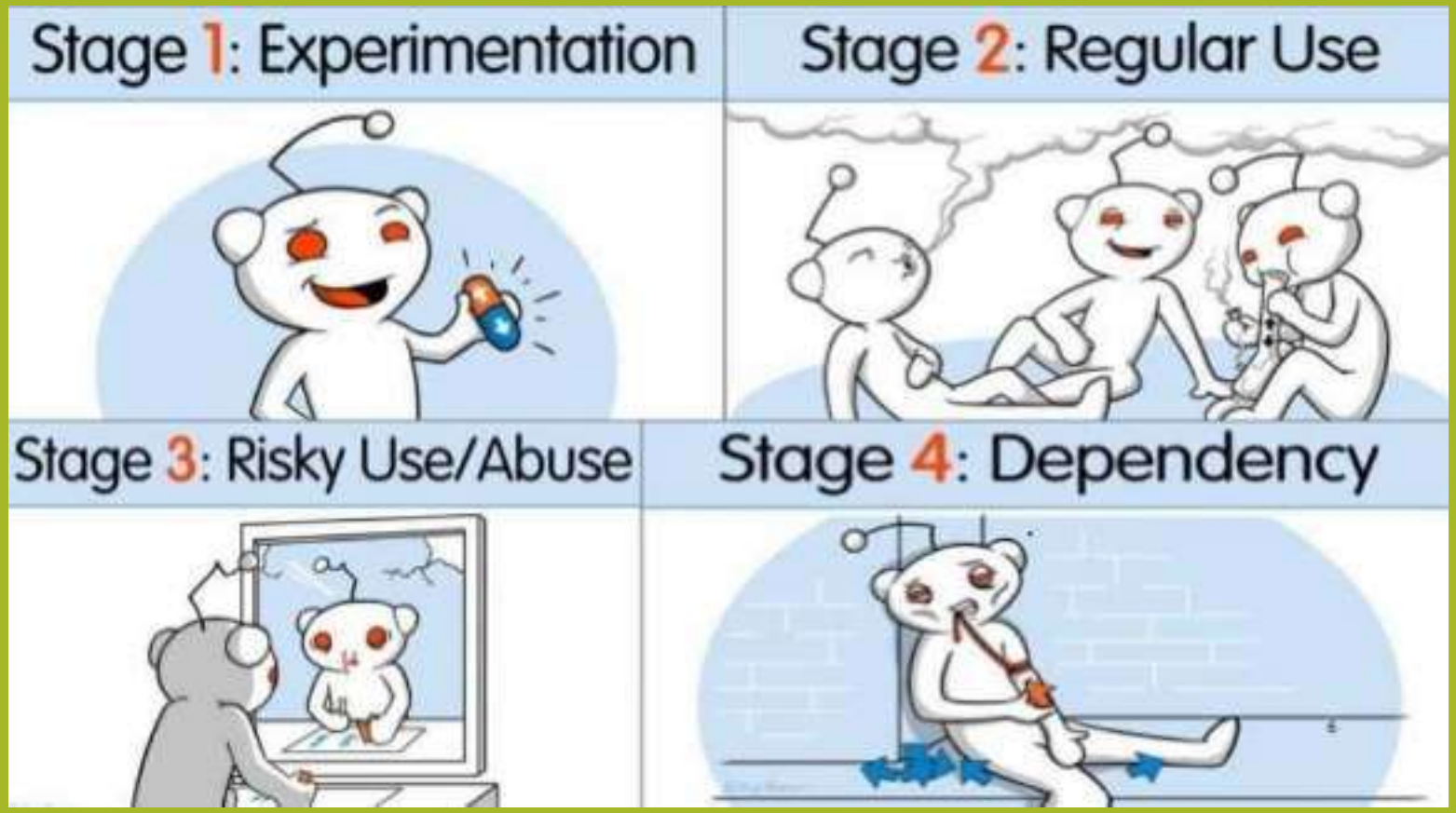
•Drugs affect different people in different ways. One person can take and abuse drugs, yet never become addicted, while another merely has one experience and is immediately hooked.

•There are several factors and causes to consider with addiction, first there is a genetic component, that is, what is passed on to you through your family.

•If your blood relatives had a predisposition to become addicted, chances are you have that same tendency.

• Personality contributes to drug addiction.

• Peer pressure is huge, both for teenagers and adults alike.


Stage 1: Experimentation
Stage 2: Regular Use
Stage 3: Risky Use/Abuse
Stage 4: Dependency

STAGE 1

- CURIOSITY IS THE MOTIVATOR
- LEARNING TO TRUST/MISTRUST THE DRUG USED
- "HIGH" IS STILL A NEW FEELING

STAGE 2

- USER IS THINKING MORE ABOUT DRUGS
- PREVIOUS RELATIONSHIP BECOMES DIFFICULT
- USER USES WHEN ALONE
- USER STILL THINKS THEY HAVE CONTROL

STAGE 3

- SEEKS OUT THE "HIGH"
- HAS CONFIDENCE IN USING THE DRUG
- USER THINK THE DRUG WON'T HURT THEM
- PEER GROUP USES

STAGE 4

- CAN NO LONGER GET HIGH
- USER USES THE DRUG TO AVOID BEING SICK
- DRUGS BECOME THE CENTER OF THEIR LIFE

- MARIJUANA
- HEROIN
- COCAINE
- ALCOHOL
- TOBACCO
- LSD (Lysergic acid diethylamide)
- SPEEDBALL
- MDMA
- KETAMINE
- CRYSTAL- METH

- LOSS OF APPETITE
- HEADACHES
- ANXIETY
- ELEVATED BLOOD PRESSURE
- CHEST PAIN
- IRREGULAR HEARTBEAT
- COLD/BLUISH FINGERS
- DIFFICULTY IN URINATING
- CHANGES IN BODY TEMPERATURE

Drugs are chemicals. Different drugs, because of their chemical structures, can affect the body in different ways. In fact, some drugs can even change a person's body and brain in ways that last long after the person has stopped taking drugs, maybe even permanently.

- Weaken the immune system, increasing susceptibility to infections.
- Cause cardiovascular conditions ranging from abnormal heart rate to heart attacks.
- Cause nausea, vomiting and abdominal pain.
- Cause the liver to have to work harder, possibly causing significant damage or liver failure.
- Cause seizures, stroke and widespread brain damage
- Produce global body changes such as breast development in men, dramatic fluctuations in appetite and increases in body temperature, which may impact a variety of health conditions.

BRAIN- All drugs of abuse - nicotine, cocaine, marijuana, and others - effect the brain's "reward" circuit, which is part of the limbic system.

• Drugs hijack this "reward" system, causing unusually large amounts of dopamine to flood the system.

• This flood of dopamine is what causes the "high" or euphoria associated with drug abuse.

BIRTH-

•These and other illicit drugs may pose various risks for pregnant women and their babies. Some of these drugs can cause a baby to be born too small or too soon, or to have withdrawal symptoms, birth defects or learning and behavioral problems.

•Pregnant women who use illicit drugs may engage in other unhealthy behaviors that place their pregnancy at risk, such as having extremely poor nutrition or developing sexually transmitted infections.

BEHAVIORAL PROBLEMS-

• PARANOIA

• AGGRESSIVENESS

• HALLUCINATIONS

• ADDICTION

• IMPAIRED JUDGMENT

• IMPULSIVENESS

• LOSS OF SELF-CONTROL

- It is the appearance of characteristic toxic effects of a drug in an individual at therapeutic doses.
- It is the converse of tolerance and **indicates a low threshold of the individual to the action of a drug**.

Examples are:

- A single dose of trifluprom azine (antipsychotic medication) induces muscular dystonias (movement disorder in which a person's muscles contract uncontrollably) in some individuals, specially children.
- Only few doses of carbamazepine (antipsychotic medication) may cause ataxia in some people.
- One tablet of chloroquine (anti malarial) may cause vomiting and abdominal pain in an occasional patient.

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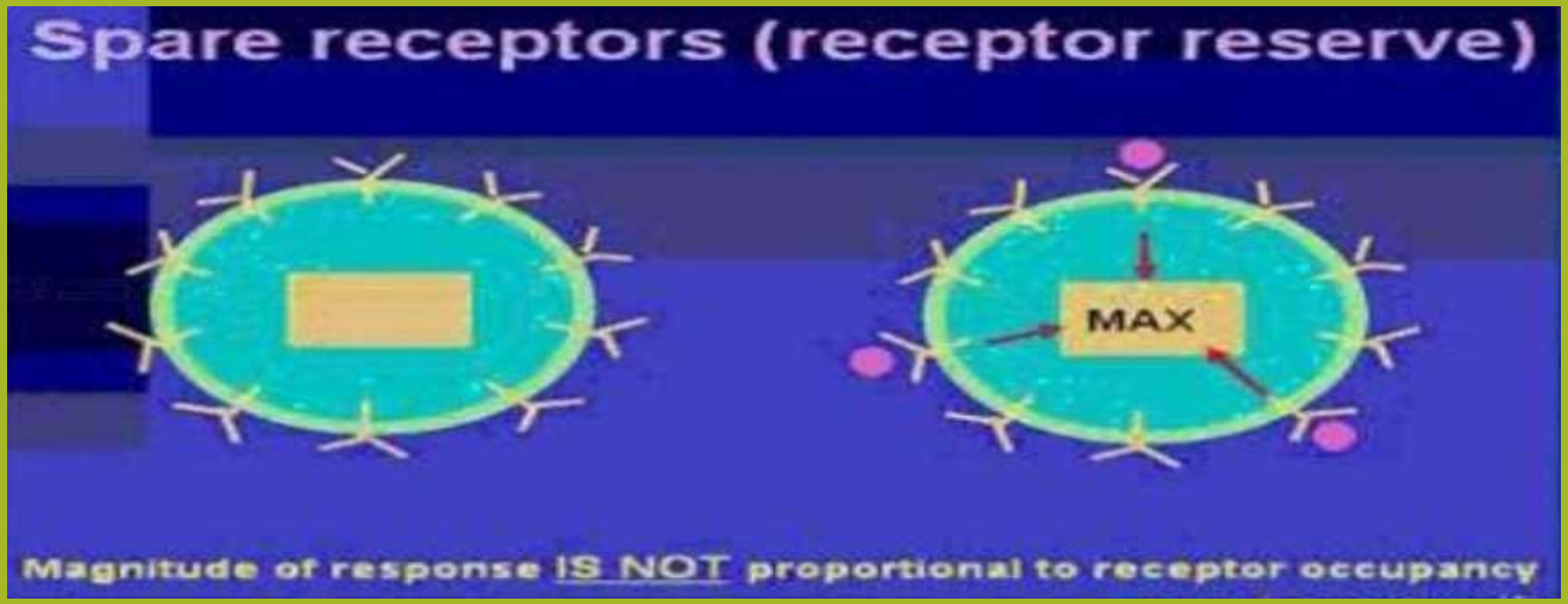
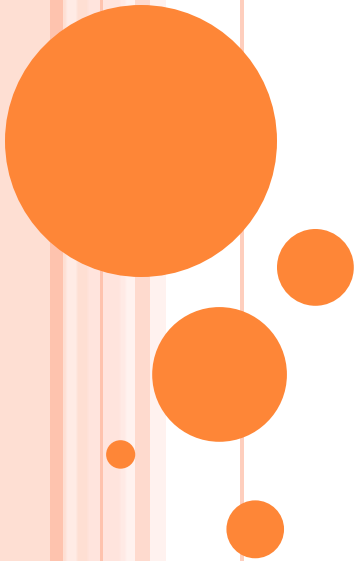


General Anesthetics



General anesthesia may be defined as a state which includes

1. A reversible loss of consciousness
2. Inhibition of sensory and autonomic reflexes (including nociceptive reflexes)
3. Skeletal muscle relaxation
4. Anterograde amnesia (upon recovery)

[the extent to which any individual anesthetic drug can exert these effects depend upon the drug, the dose, and the clinical circumstances}

MAIN CLASSES OF GENERAL ANESTHETICS

Inhaled anesthetics	**Intravenous anesthetics**
Halogenate agents halotane enflurane desflurane sevoflurane **Nitrous oxide**	**Barbiturates** (thiopental, methohexital) **Propofol** **Etomidate** **Ketamine** **Benzodiazepines** (midazolam, diazepam) **Opioids** (morphine, fentanyl)

SIGNS AND STAGES OF GENERAL ANESTHESIA

I. Stage of analgesia

- Analgesia
- Unaltered consciousness
- Normal pupils

II. Stage of excitement

- Disturbed consciousness (incoordinate movements, incoherent talk)
- Irregular respiration
- Retching and vomiting
- Incontinence (sometimes)
- Increased blood pressure
- Mydriasis

III. Stage of surgical anesthesia(surgical anesthesia)

Plane 1:roving movements of eye balls. Respiration and skeletal muscle tone are normal

Plane 2: Most of the surgical procedures are performed here. Loss of corneal, light and laryngeal reflexes. Respiration is slow but regular.

Plane 3: plane of marked muscle relaxation. Light, corneal and laryngeal reflexes are absent.

Plane 4 : Plane of complete muscle relaxation. Complete loss of all the reflexes. Respiration is only abdomianl.

IV. Stage of medullary depression

- Loss of consciousness
- No spontaneous respiration
- Cardiovascular collapse
- Mydriasis

PHARMACOKINETICS OF INHALED ANESTHETICS (1)

- ***ABSORPTION AND DISTRIBUTION***
  - The ***concentration*** of a gas in an environment is proportional to its ***partial pressure*** or ***tension*** (these terms are often used interchangeably)
  - Depth of anesthesia is determined by the concentration of the anesthetic in CNS.

In order to reach the CNS the anesthetic must be transferred from the alveolar air to blood and from blood to brain. *This transfer is influenced by*:

- Solubility in blood (blood/gas partition coefficient)
- Anesthetic concentration in the inspired air
- Pulmonary ventilation
- Pulmonary blood flow
- Uptake of the anesthetic by the tissues

PHARMACOKINETICS OF INHALED ANESTHETICS (2)

ELIMINATION

- Inhaled anesthetics are *mainly eliminated by respiratory route.*

-Respiratory elimination is affected by the same kinetic variables which affect absorption. The three most important are

1. Pulmonary ventilation

2. Blood flow

3.Solubility in blood and tissue

- Anesthetics that are relatively insoluble in blood and brain are eliminated faster than more soluble anesthetics.

- *Metabolism* may contribute to the elimination of some inhaled anesthetics. Some metabolites may be toxic for liver and other organs.

INHALED ANESTHETICS: MECHANISM OF ACTION

At the neurophysiological level

- Early depressive effect on substantia gelatinosa
- Blockade of small inhibitory neurons (e.g Golgi type II cells) in several brain areas.
- Progressive depression of the ascending pathways in the reticular activating system.

At the cellular level

- Depression of synaptic transmission (***the main cellular effect***). Neurons are hyperpolarized and their threshold for firing is increased.
- Depression of axonal conduction

INHALED ANESTHETICS: MECHANISM OF ACTION

At the molecular level

The two main physicochemical theories of general anesthesia are:

1) ***The lipid theory***

Anesthetics would bind to hydrophobic regions of membrane lipid bilayer so increasing membrane fluidity which in turn would cause a small membrane expansion that distorts ion channels.

2) **The protein theory**

Anesthetics would bind to hydrophobic regions of specific membrane protein channels so stabilizing the channel in its closed state.

- Both theories point out that the mechanism of action of inhaled anesthetics does not involve direct interaction with specific receptors

THE MINIMUM ALVEOLAR ANESTHETIC CONCENTRATION

- During general anesthesia the partial pressure of an anesthetic in the brain equal that in the lung when equilibrium is reached.
- ***The Minimum Alveolar Anesthetic Concentration (MAC) is defined as the concentration of the anesthetic that results in the immobility of 50% of patients when exposed to a noxious stimulus.***

THE MINIMUM ALVEOLAR ANESTHETIC CONCENTRATION

- A MAC > 100% indicates that even when all the molecules of the inspired gas are molecules of the anesthetic, the concentration is not able to cause immobility in 50% of patients.
- MAC decreases in ***elderly patients*** and in the presence of certain adjuvant drugs (***opioids, benzodiazepines, barbiturates,*** etc.)
- MACs of inhaled general anesthetic are additive

HALOTHANE PHARMACODYNAMICS

[most effects are concentration dependent, that is they increase as the partial pressure in the target tissue increases]

Nervous system effects

- Partial loss of nociceptive reflexes
- Good postoperative amnesia

Cardiac effects

- Direct depression of myocardial contractility
- Direct depression of cardiac rate
- Increase in cardiac automaticity
- 5-10% reduction of cardiac output
- Sensitization of myocardium to catecholamines

HALOTHANE

Vascular effects

- Decrease in brain vascular resistance (which leads to an increase in intracranial pressure)
- Little changes in total peripheral resistance
- Reduction of blood pressure due to:

a) reduced cardiac output

b) impairment of normal baroreceptor response

Respiratory effects

- Decrease in tidal volume
- Increase in respiratory rate
- Decrease in minute ventilation (the increased rate cannot compensate for the decreased tidal volume)
- Ventilatory response to CO2 is decreased
- Ventilatory response to hypoxia is decreased

[all these effects can be overcome by assisting the ventilation]

- Bronchodilation
- Depression of mucociliary clearance

HALOTHANE

Urogenital effects

- Decreased renal blood flow
- Decreased glomerular filtration rate
- Pronounced relaxation of the uterus

Skeletal muscle effects

- Modest relaxation of skeletal muscle
- Enhancement of the action of nondepolarizing skeletal muscle relaxants

Gastrointestinal effects

- Postoperative nausea and vomiting (» 15%)
- Decreased hepatic blood flow

HALOTHANE HEPATITIS

- **Occurrence:** seems very low (1:35000), but the risk seems to increase after repeated exposures.
- **Etiology:** halothane is partially (» 30%) metabolized to trifluoroacetic acid, bromide and chloride ions, which have been implicated as causative factors in halothane hepatitis.
- **Pathogenesis:** the mechanism of hepatotoxicity remains obscure. Two hypotheses are :
  - an immune response to certain fluoroacetylated liver enzymes *(allergic reaction).*
  - a genetically determined defect in hepatic cell membranes that make these cells more susceptible to halothane-induced injury *(idiosyncratic reaction).*
- **Pathology:** the syndrome is histologically indistinguishable from viral hepatitis.
- **Symptoms and signs:** anorexia, nausea and vomiting, fever.
- **Clinical course and prognosis**: the syndrome typically starts 3-5 days after anesthesia and may progress to hepatic failure. The prognosis is poor (death occurs in » 50% of these patients).

ISOFLURANE PHARMACODYNAMICS

[most effects are concentration dependent, that is they increase as the partial pressure in the target tissue increases]

Nervous system effects

- Partial loss of nociceptive reflexes
- Good postoperative amnesia

Cardiovascular effects

[direct effects are partially counteracted by a centrally mediated sympathetic activation; therefore the final effects are usually the following]

- Small depression of myocardial contractility
- Increased cardiac rate
- Cardiac automaticity is not affected
- Cardiac output is well maintained
- Decrease in brain vascular resistance (which leads to an increase in intracranial pressure)
- Decreased in total peripheral resistance
- Reduction of blood pressure

ISOFLURANE

Respiratory effects

- Decrease in tidal volume
- No change respiratory rate
- Minute ventilation is decreased
- Ventilatory response to CO2 is decreased
- Ventilatory response to hypoxia is decreased

[all these effects are lessened by surgical stimulation and can be overcome by assisting the ventilation]

- Bronchodilation
- Depression of mucociliary clearance

Urogenital effects

- Decreased renal blood flow
- Decreased glomerular filtration rate
- Pronounced relaxation of the uterus

Skeletal muscle effects

- Good relaxation of skeletal muscle
- Enhancement of the action of nondepolarizing skeletal muscle relaxants

Gastrointestinal effects

- Postoperative nausea and vomiting (» 15%)
- Decreased hepatic blood flow
- No evidence of direct hepatic toxicity

PHARMACOLOGY OF DESFLURANE AND SEVOFLURANE

- Desflurane and Sevoflurane resemble Isoflurane in most of their pharmacological properties. Main differences are:

Desflurane

- Rapid induction and recovery
- Coughing and sometimes laryngospasm (due to its irritant properties)
- No changes in renal blood flow

Sevoflurane

- Rapid induction and recovery
- No changes in heart rate
- Metabolism by the liver may release fluoride ions that could be nephrotoxic
- Chemically unstable when exposed to CO_2 absorbents

MALIGNANT HYPERTHERMIA

- **Occurrence:** is very low (1:20000)
- **Etiology:** general anesthesia with ***all halogenated anesthetics***, especially when supplemented with depolarizing muscle relaxants seems to be the causative factor.
- **Pathogenesis:** malignant hyperthermia is an autosomal dominant disorder which arises from a stimulus-elicited excessive release of Ca++ from the sarcoplasmic reticulum.
-
- **Symptoms and signs:**, hyperthermia, muscular rigidity, acidosis, tachycardia and shock. Hyperkalemia, hypercalcemia and myoglobinuria usually occur. Creatinine kinase levels are hugely elevated.
- **Clinical course and prognosis**: the syndrome can start during surgery or few days later, progresses rapidly and can be fatal (death occurs in 10-20% of these patients).
- **Therapy**: dantrolene is the drug of choice

NITROUS OXIDE PHARMACOLOGY

Chemistry and physicochemical properties

- A gas (N2O) without odor or taste.
- Blood/gas partition ratio = 0.47

Central nervous system effects

-The MAC is >100%, therefore surgical anesthesia can be reached only when is administered under hyperbaric conditions
- Analgesia is very good with 20% of N2O
- Induction and recovery are very rapid
- Postsurgical amnesia is incomplete

Cardiovascular system

- Slight direct depression of contractility which is completely counteracted by ***sympathetic stimulation***.
- No change or increase in heart rate.
- No effect on cardiac automaticity.
- Negligible effects on blood pressure

NITROUS OXIDE

Respiratory system
- Respiration is well maintained
- Ventilatory response to CO_2 is not affected
- Ventilatory response to hypoxia is reduced
- Respiratory depressant effects of other anesthetics are enhanced

Urogenital effects
- Little effects on renal blood flow
- No effect on uterine tone

Skeletal muscle effects
- No effect on skeletal muscle tone
- No enhancement of the action of nondepolarizing skeletal muscle relaxants

Gastrointestinal effects
- Postoperative nausea and vomiting (» 15%)

Blood effects
- Prolonged exposure to N_2O may cause megaloblastic anemia due to oxidation of the cobalt atom in Vit.B12

Clinical uses
- As a sole agent to provide analgesia for dental procedures and for parturition
- In combination with other drug for general anesthesia

COMPARATIVE PHARMACOLOGICAL PROPERTIES OF SOME INHALED ANESTHETICS

Effect on	Halothane	Isoflurane	N_2O
CNS-Analgesia	Incomplete	Incomplete	Very good
Heart			
-contractility	↓	0, ↓	0, ↑
-frequency	↓	↑	↑
-automaticity	ì	0	0
-cardiac output	↓	0	0
-sensitization to catecholamines	Yes	No	No
TPR	0	↓	0, ↑
Blood pressure	↓ ↓	↓	0
Baroreceptor reflex	↓		0
Respiration	↓	↓ ↓	0
Cerebral blood flow	↑ ↑	↑	0, ↑
Renal blood flow	↓	↓	0, ↓
Skeletal muscle tone	↓	↓ ↓	0
Uterine tone	↓	↓	0
Nausea and vomiting	↑	↑	↑

ì = increased ; □ = decreased ; 0 = negligible effect

INTRAVENOUS ANESTHETICS: BARBITURATES

Drugs

Thiopental sodium is the agents most commonly used.

Mechanism of action

- ***Neurophysiologica***l: Progressive depression of the ascending pathways in the reticular system.
- ***Molecular***: Enhancement of GABA-mediated inhibition (the opening of Cl- channels is prolonged by facilitating GABA action) or, at high doses, direct opening of Cl- channels.

Central nervous system effects

- Following a standard IV dose unconsciousness occurs in 10-20 seconds and returns in 15-20 minutes (due to the redistribution process)
- Inhibition of sensory and autonomic reflexes (including nociceptive reflexes) is ***negligible*** and so movements, vocalization and sympathetic responses can occur in response to surgery.

BARBITURATES

Respiratory effects

- Dose-dependent depression of the respiratory center which causes a decrease in:

a) minute ventilation; b)ventilatory response to CO2;

c) ventilatory response to hypoxia

- Coughing, bronchospasm and laryngospasm can occur (the basis of these reactions is unknown)

Cardiovascular effects

- Dose-dependent decrease in cardiac contractility
- Increased venous capacitance
- Negligible change in total peripheral resistance
- Decrease in cardiac output and blood pressure
- Brain blood flow is decreased and intracranial pressure is markedly reduced
- Baroreceptor reflex is not affected

Skeletal muscle effects

- Negligible effects on skeletal muscle tone.

Gastrointestinal effects

- Postanesthetic nausea and vomiting is » 15%
- Induction of P450 system in the liver

Use in anesthesia

- As a sole agent in case of short surgery
- For induction of anesthesia, in combination with inhaled anesthetics

INTRAVENOUS ANESTHETICS: PROPOFOL

Central nervous system effects

- Following a standard IV dose unconsciousness occurs in 20-40 seconds and returns in 4-8 minutes (due to the redistribution process)
- Analgesic effect is negligible

Respiratory effects

- Dose-dependent depression of the respiration with a marked decrease in minute ventilation, ventilatory response to CO2 and to hypoxia.

Cardiovascular effects

- Decrease in myocardial contractility
- Decrease in total peripheral resistance which leads to a marked dose-dependent decrease of blood pressure
- Brain blood flow is decreased and intracranial pressure is reduced
- Baroreceptor reflex is not affected

PROPOFOL

Skeletal muscle effects

- Negligible effects on skeletal muscle tone
- Tremors are sometimes seen on induction

Gastrointestinal effects

- The drug has an antiemetic activity which prevent

postanesthetic nausea and vomiting

Use in anesthesia

- Because of its rapid recovery and antiemetic properties propofol is mostly used in ambulatory anesthesia
- Sometimes used to obtain prolonged sedation in critically ill patients

INTRAVENOUS ANESTHETICS: ETOMIDATE

Central nervous system effects

- Following a standard IV dose unconsciousness occurs in 10-20 seconds and returns in 3-5 minutes (due to the redistribution process)
- Analgesic effect is negligible

Respiratory effects

- Respiration is well maintained and respiratory depression usually dos not occur

Cardiovascular effects

- Cardiac output is well maintained
- Blood pressure is normal or slightly reduced
- Brain blood flow is decreased and intracranial pressure is reduced
- Baroreceptor reflex is not affected

ETOMIDATE

Skeletal muscle effects

- Negligible effects on skeletal muscle tone
- Involuntary movements (myoclonus) occur in »40% of patients

Gastrointestinal effects

- Postoperative nausea and vomiting are frequent (> 30%)

Other effects

- Inhibition of steroidogenesis occurs and plasma levels of cortisol are reduced after a single dose

Use in anesthesia

- As an induction agent in patients with serious cardiovascular disease

INTRAVENOUS ANESTHETICS: KETAMINE

Mechanism of action

- ***Neurophysiological***: impairment of neuronal pathways in the cortex and limbic structures.
- ***Molecula***r: blockade NMDA-type glutamate receptors

(the mechanism is quite similar to that of the psychedelic drug phencyclidine)

Central nervous system effects

- The drug induces ***dissociative anesthesia*** which can be defined as ***a state of sedation, immobility, analgesia, anterograde amnesia and a strong feeling of dissociation from the environment without actual loss of consciousness***.
- Following a standard IV dose dissociation occurs in 10-15 seconds and last 10-15 minutes (due to the redistribution process), but complete recovery often required several hours
- Analgesic effect is very pronounced

Respiratory effects

- Respiration is well maintained
- Pharyngeal and laryngeal reflexes are retained
- Bronchodilation

KETAMINE

Cardiovascular effects

- Increase in heart rate, cardiac output and blood pressure (up to 25%)

(all these effects are due to central sympathetic stimulation)

- Brain blood flow and intracranial pressure are markedly increased

Skeletal muscle effects

- Muscle tone is increased (catatonia can occur)

Gastrointestinal effects

- Postoperative nausea and vomiting (» 15%)

Adverse effects

- Hallucination and delirium (» 30% of adult patients) that can recur weeks later (flash-backs)

Use in anesthesia

- In poor-risk patients or patients with shock
- In children

COMPARATIVE PHARMACOLOGICAL PROPERTIES OF SOME INTRAVENOUS ANESTHETICS

Effect on	Thi.	Pro.	Eto.	Ket.
CNS –Analgesia	0	0	0	very good
Heart				
-contractility	↓	↓	0	0 ↑
-frequency	0↑	0	0	↑
-automaticity	0 ↑	0	0	↑
-cardiac output	↓	↓	0	↑
-sensitization to catecholamines	No	No	No	No
TPR	0	↓ ↓	0	↑
Blood pressure	î	↓ ↓	0, ↓	↑
Baroreceptor reflex	0	0	0	0
Respiration	↓ ↓	↓ ↓	0	0
Cerebral blood flow	↓	↓	↓	↑ ↑
Renal blood flow	↓	↓	0	0
Skeletal muscle tone	0	0	0	↑
Uterine tone	0	0	0	0
Nausea and vomiting	↑	0, ↑	↑ ↑	↑

Thi= Thiopental Pro= Propofol
Eto= Etomidate Ket= Ketamine

ì = increased : 0 = negligible effect

BENZODIAZEPINES AS GENERAL ANESTHETIC DRUGS

Drugs

-Certain benzodiazepines (e.g. diazepam, lorazepam, midazolam) are used in anesthetic procedures

Mechanism of action

- ***Neurophysiologica***l: increased activity of small inhibitory GABAergic neurons in several brain areas
- ***Molecular***: Enhancement of GABA-mediated inhibition (the frequency of opening of Cl- channels is increased by facilitating GABA action)

Central nervous system effects

- Following a 70 mg IV dose of diazepam drowsiness occurs in 2-3 minutes, but a complete unconsciousness is not achieved
- Recovery from drowsiness is slow
- Anterograde amnesia occurs in > 50% of patients
- Analgesic effect is negligible

BENZODIAZEPINES

Effects on other organs

- Respiration and circulation are only moderately depressed, but cardiovascular and respiratory depression produced by of other drugs are enhanced
- Skeletal muscle tone is moderately reduced by a centrally mediated action. The effect of curare-like drugs is not modified.
- Renal and hepatic function are not affected.
-Postoperative nausea and vomiting are rare

Use in anesthesia

- As a sole agent in case of procedures that do not require analgesia (radiodiagnostic procedures, etc.)
- For induction of anesthesia, in combination with inhaled anesthetics (but thiopental is largely preferred)
- In the preanesthetic medication.

OPIOIDS AS GENERAL ANESTHETIC DRUGS

Drugs

- Morphine, fentanyl, sulfentanil, alfentanil

Central nervous system effects

In some situations very large dose of opioids may be infused to obtain anesthesia

- Large IV doses of morphine or fentanyl administered slowly induce unconsciousness and profound analgesia
- With fentanyl unconsciousness occurs in 10-20 seconds and returns in about 30 minutes (due to a redistribution process).
- Anterograde amnesia is negligible and ***postoperative recall of events may occur.***

Respiratory effects

- Respiration is severely depressed and ventilation must be mechanically controlled

OPIOIDS

Cardiovascular effects

- Cardiovascular system is moderately depressed with morphine (due to histamine release) and unaffected by fentanyl and congeners.

Skeletal muscle effects

- Rigidity of respiratory muscle may be prominent and administration of a muscle relaxant may be necessary to permit artificial respiration.

Gastrointestinal effects

- Postoperative nausea and vomiting are frequent

Use in anesthesia

- They are used (often together with nitrous oxide) in cardiac surgery or in case of surgery in patients with very serious cardiac disease.
- They are used widely to provide relief from pain during general anesthesia of all types.
- They are frequently used as preanesthetic medication in order to decrease pain-anticipatory anxiety.

NEUROLEPTANALGESIA AND NEUROLEPTANESTHESIA

NEUROLEPTANALGESIA

- When a potent opioid (***fentanyl***) is combined with a potent neuroleptic compound (***droperidol***) a state of neuroleptanalgesia is established
- This is a state of quiescence, with reduced motor activity reduced anxiety, indifference to the surrounding.
- Analgesia is profound, but consciousness is retained.
- Cardiovascular effects generally are not marked.
- Respiratory depression is severe but predictable.
- Neuroleptanalgesia can be used for minor surgical procedures like endoscopy, burn dressing etc.

NEUROLEPTANESTHESIA

- Neuroleptanalgesia can be converted to neuroleptanesthesia by the concurrent administration of 65-70% of nitrous oxide.

Adverse effects of the procedures

- Postoperative respiratory depression (which can be reversed by naloxone)
- Extrapyramidal muscle movements (which can be controlled by benztropine)

THE MODERN BALANCED GENERAL ANESTHESIA	
Phases	**Drug**
Preanesthetic care	-Diazepam, lorazepam -Chlorpromazine, haloperidol -Atropine -Morphine, meperidine
Induction of anesthesia	-Thiopental (propofol or etomidate or midazolam may be alternative drugs) *followed by* -one or two inhaled anesthetics ***(loading dose)***
Maintenance of anesthesia	-one or two inhaled anesthetics ***(maintenance dose)*** -adjuvant drugs (neuromuscular blocking agents, opioids)
Postanesthetic care	-Metoclopramide, ondansetron -Opioids, analgesic-antipyretics -Ranitidine

- Rudolf Buchheim (1820–1879) founded the first institute of pharmacology at the University of Dorpat (Tartu, Estonia) in 1847, ushering in pharmacology as an independent scientific discipline.
- In addition to a description of effects, he strove to explain the chemical properties of drugs.

- **Oswald Schmiedeberg (1838–1921), together** with his many disciples (12 of whom were appointed to chairs of pharmacology),helped establish the high reputation of pharmacology.

- Fundamental concepts such as structure–activity relationships, drug receptors, and selective toxicity emerged from the work of, respectively.

❖**Pharmacology** is the branch of biology concerned with the study of drug action, where a drug can be broadly defined as any man-made, natural, or endogenous (from within body) molecule which exerts a biochemical or physiological effect on the cell, tissue, organ, or organism (sometimes the word pharmacon is used as a term to encompass these endogenous and exogenous bioactive species).

- More specifically, it is the study of the interactions that occur between a living organism and chemicals that affect normal or abnormal biochemical function. If substances have medicinal properties, they are considered pharmaceuticals.

- The field encompasses drug composition and properties, synthesis and drug design, molecular and cellular mechanisms, organ/systems mechanisms, signal transduction/cellular communication, molecular diagnostics, interactions, toxicology, chemical biology, therapy, and medical applications and antipathogenic capabilities.
- The two main areas of pharmacology are pharmacodynamics and pharmacokinetics.
- Pharmacodynamics studies the effects of a drug on biological systems, and Pharmacokinetics studies the effects of biological systems on a drug.

- In broad terms, pharmacodynamics discusses the chemicals with biological receptors, and pharmacokinetics discusses the absorption, distribution, metabolism, and excretion (ADME) of chemicals from the biological systems.

- Pharmacology is not synonymous with pharmacy and the two terms are frequently confused.
- Pharmacology, a biomedical science, deals with the research, discovery, and characterization of chemicals which show biological effects and the elucidation of cellular and organismal function in relation to these chemicals.
- In contrast, pharmacy, a health services profession, is concerned with application of the principles learned from pharmacology in its clinical settings; whether it be in a dispensing or clinical care role.
- In either field, the primary contrast between the two are their distinctions between direct-patient care, for pharmacy practice, and the science-oriented research field, driven by pharmacology.

- Early pharmacologists focused on natural substances, mainly plant extracts.

- Pharmacology developed in the 19th century as a biomedical science that applied the principles of scientific experimentation to therapeutic contexts.

- Today pharmacologists use genetics, molecular biology, biochemistry, and other advanced tools to transform information about molecular mechanisms and targets into therapies directed against disease, defects or pathogens, and create methods for preventative care, diagnostics, and ultimately personalized medicine.

Divisions

- The discipline of pharmacology can be divided into many sub disciplines each with a specific focus.

Clinical pharmacology

Neuropharmacology

- **Toxicology**

- **Pharmacogenetics**
- **Posology**
- **Pharmacognosy**
- **Experimental pharmacology**
- **Dental pharmacology**

Pharmacoepidemiology

Safety pharmacology

Systems pharmacology

Psychopharmacology

Psychopharmacology

Clinical pharmacology

- Clinical pharmacology is the basic science of pharmacology with an added focus on the application of pharmacological principles and methods in the medical clinic and towards patient care and outcomes.

Neuropharmacology

- Neuropharmacology is the study of the effects of medication on central and peripheral nervous system functioning.

Psychopharmacology

- Psychopharmacology, also known as behavioral pharmacology, is the study of the effects of medication on the psyche (psychology), observing changed behaviors of the body and mind, and how molecular events are manifest in a measurable behavioral form.

- Psychopharmacology is an interdisciplinary field which studies behavioral effects of psychoactive drugs.

- It incorporates approaches and techniques from neuropharmacology, animal behavior and behavioral neuroscience, and is interested in the behavioral and neurobiological mechanisms of action of psychoactive drugs.

Psychopharmacology-1

- Another goal of behavioral pharmacology is to develop animal behavioral models to screen chemical compounds with therapeutic potentials.

- People in this field (called behavioral pharmacologists) typically use small animals (e.g. rodents) to study psychotherapeutic drugs such as antipsychotics, antidepressants and anxiolytics, and drugs of abuse such as nicotine, cocaine and methamphetamine.

- **Ethopharmacology** (not to be confused with ethnopharmacology) is a term which has been in use since the 1960s and derives from the Greek word ἦθος *ethos* meaning character and "pharmacology" the study of drug actions and mechanism.

Cardiovascular pharmacology

- Cardiovascular pharmacology is the study of the effects of drugs on the entire cardiovascular system, including the heart and blood vessels.

Pharmacogenetics

- Pharmacogenetics is clinical testing of genetic variation that gives rise to differing response to drugs.

Pharmacogenomics

- Pharmacogenomics is the application of genomic technologies to drug discovery and further characterization of older drugs.

Pharmacoepidemiology

- Pharmacoepidemiology is the study of the effects of drugs in large numbers of people.

Safety pharmacology

- Safety pharmacology specialises in detecting and investigating potential undesirable pharmacodynamic effects of new chemical entities (NCEs) on physiological functions in relation to exposure in the therapeutic range and above.

Systems pharmacology

- Systems pharmacology is the coding system principles in the field of pharmacology.

Toxicology

- Toxicology is the study of the adverse effects, molecular targets, and characterization of drugs or any chemical substance in excess (including those beneficial in lower doses).

Theoretical pharmacology

- Theoretical pharmacology is a relatively new and rapidly expanding field of research activity in which many of the techniques of computational chemistry, in particular computational quantum chemistry and the method of molecular mechanics, are proving to be of great value.
- Theoretical pharmacologists aim at rationalizing the relation between the activity of a particular drug, as observed experimentally, and its structural features as derived from computer experiments. They aim to find structure—activity relations.
- Furthermore, on the basis of the structure of a given organic molecule, the theoretical pharmacologist aims at predicting the biological activity of new drugs that are of the same general type as existing drugs.
- More ambitiously, it aims to predict entirely new classes of drugs, tailor-made for specific purposes.

Posology

- **Posology** is the study of how medicines are dosed. This depends upon various factors including age, climate, weight, sex, elimination rate of drug, genetic polymorphism and time of administration.

Pharmacognosy

- Pharmacognosy is a branch of pharmacology dealing especially with the composition, use, and development of medicinal substances of biological origin and especially medicinal substances obtained from plants.

SCOPE OF PHARMACOLOGY

- Scientific understanding of drugs enables us to predict the pharmacological effect of a new chemical that will produce a specified therapeutic effect.
- The scope of pharmacology has expanded greatly over the last decade to incorporate many new approaches such as computer-assisted drug design, genetic screens, protein engineering and use of novel drug delivery vehicles including viruses and artificial cells.
- Our society needs pharmacologists who understand the basis of modern therapeutics for careers within academic, pharmaceutical and governmental laboratories to study and develop tomorrow's drugs.

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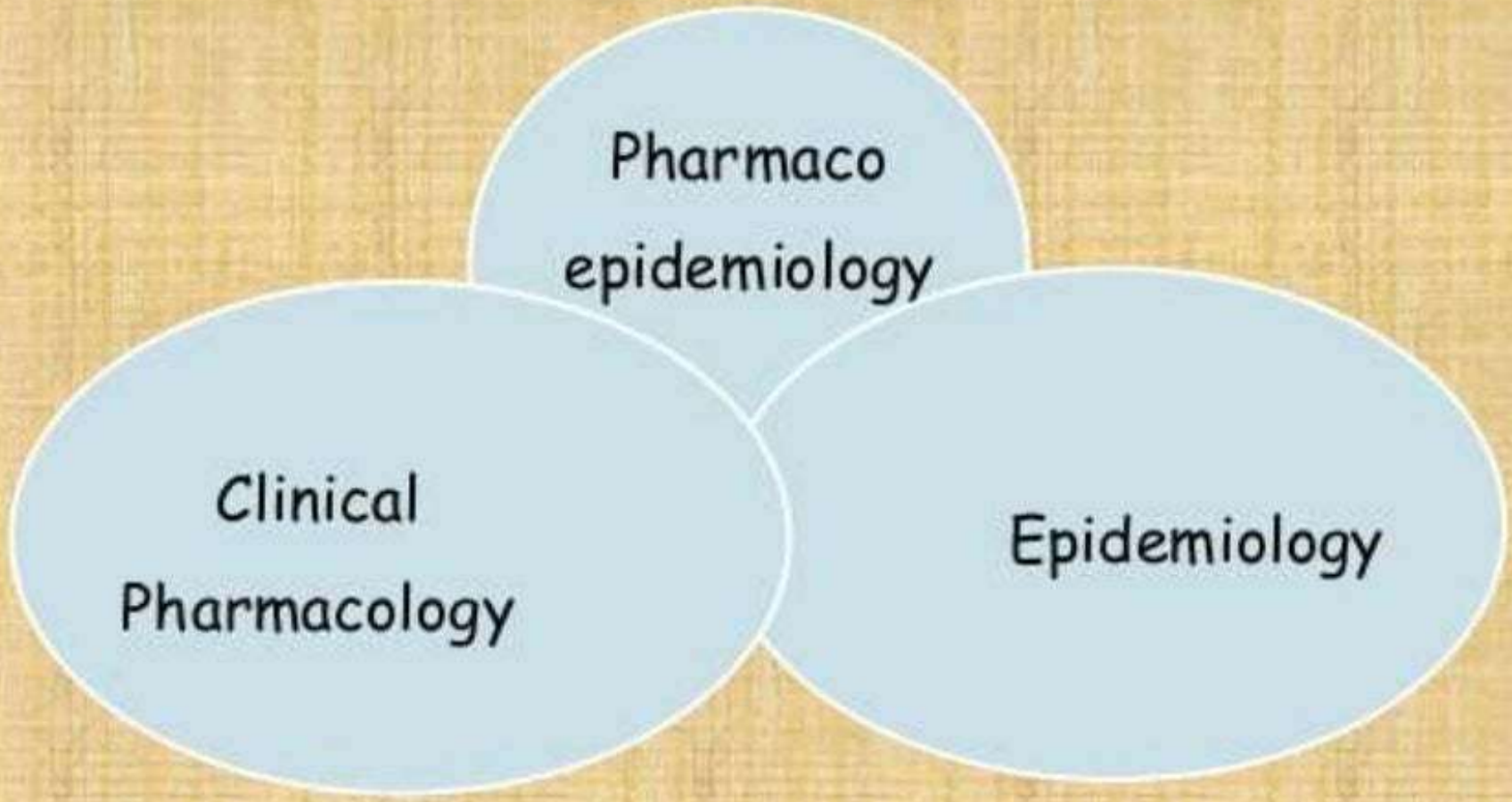
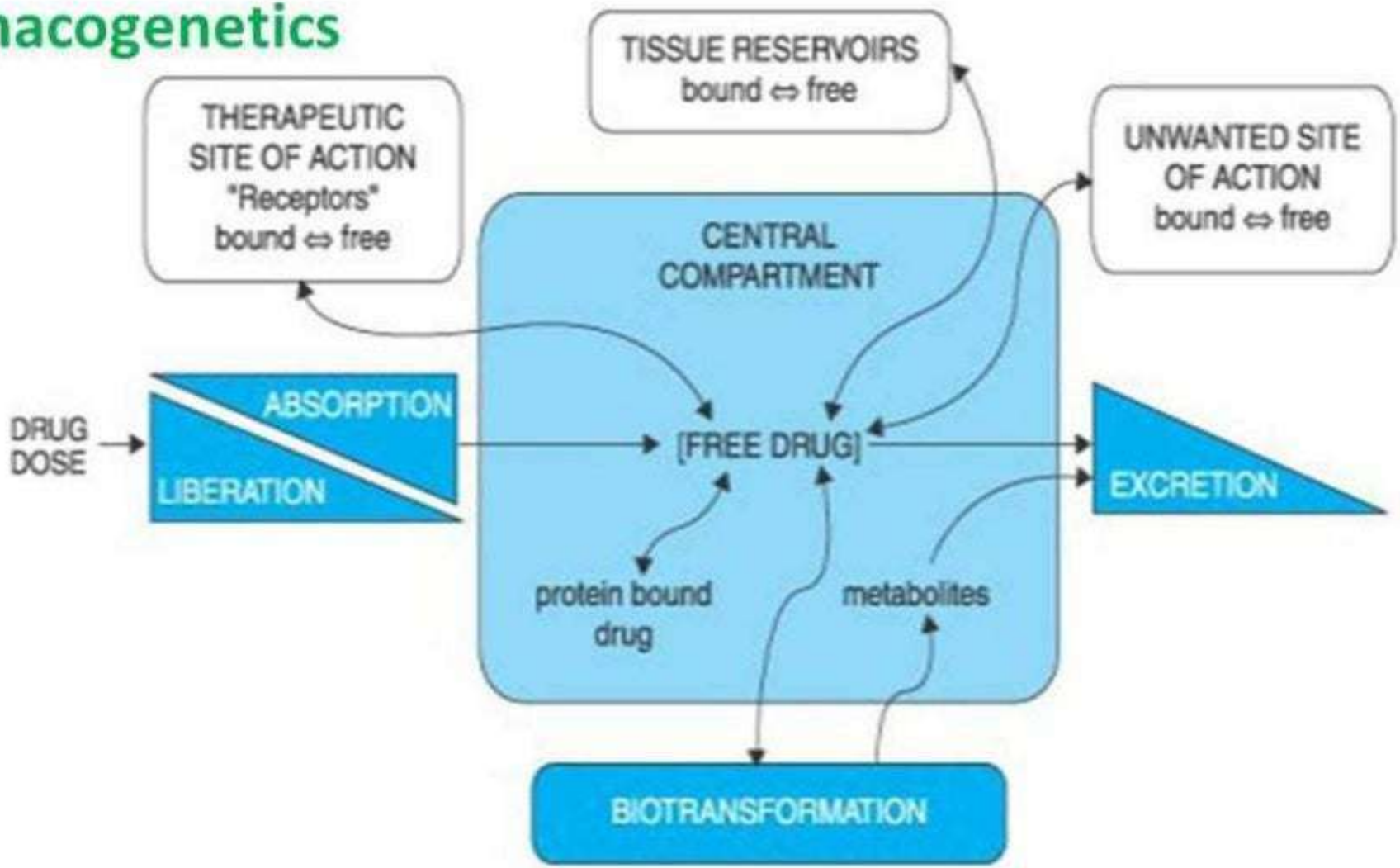
Pharmacoepidemiology is the application of epidemiologic reasoning ,methods , and Knowledge to the study of uses and effects of drugs in human population



Pharmacology: Its Scope

- ***Three important and interrelated areas:***
- **Pharmacokinetics**
- **Pharmacodynamics**
- **Pharmacogenetics**



Environmental pharmacology

- Environmental pharmacology is a new discipline. Focus is being given to understand gene–environment interaction, drug-environment interaction and toxin-environment interaction.

- There is a close collaboration between environmental science and medicine in addressing these issues, as healthcare itself can be a cause of environmental damage or remediation. Human health and ecology are intimately related.
- Demand for more pharmaceutical products may place the public at risk through the destruction of species.
- The entry of chemicals and drugs into the aquatic ecosystem is a more serious concern today.
- In addition, the production of some illegal drugs pollutes drinking water supply by releasing carcinogens.

- This field is intimately linked with Public Health fields.

Experimental pharmacology

- Experimental pharmacology involves the study of pharmacology through bioassay, to test the efficacy and potency of a drug.

Dental pharmacology

- Dental pharmacology relates to the study of drugs commonly used in the treatment of dental disease

Thank
you

Introduction to Pharmacology

Mr. Dipti Y. Sorte

Syllabus – (Unit I: Introduction to Pharmacology)

- Definitions: Terminology use.
- Pharmacognosy: Sources
- Types: Classification
- Pharmaco-dynamics: Actions, therapeutic Adverse, toxic effect.
- Pharmacokinetics: Absorption, distribution, metabolism, interaction, excretion

- **Review: Routes and principles of administration of drugs**
- **Indian pharmacopoeia: Legal issues, Storage of various drugs.**
- **Calculation of drug dosage.**
- **Rational use of drugs.**
- **Pharmacotherapeutics: Principles of therapeutics.**

Introduction to Pharmacology

History, Types of pharmacology, sources of Drug information etc.

INTRODUCTION TO PHARMACOLOGY

- Pharma=Drugs, Logos = Knowledge
  (Pharmacology = The study or science of drugs)
- **Pharmacology:** It is the science of drugs derived from two Greek words: *Pharmakon* (Greek word for drugs) and *logos* (the Greek word for science). It is the study of the actions of drugs on living system.
- It includes physical and chemical properties, biochemical and physiological effects, mechanism of action, therapeutic uses and adverse effects of drugs.

Drug

- Any chemical that affects the processes of a living organism

Pharma=Drugs, Logos = Knowledge

Pharmacology

- The study or science of drugs

History of Pharmacology

HISTORY OF PHARMACOLOGY

- Knowledge of drugs and their uses in diseases are as old as history of mankind.
- Primitive men gather the knowledge of healing and medicines by observing the nature, noticing the animals while ill and personal experience after consuming plants and herbs as remedies.
- Ancient civilizations discovered that extracts from plants, animals, and minerals had medicinal effects on body tissue. These discoveries became the foundation of pharmacology.

Pharmacology in the present form is relatively recent branch about hundred years old.

Historical developments in Pharmacology

- PEN PSAO (2700 BC) It was the great herbal materia medica written in china.
- Kahun Papyrus (2000 BC) is an oldest Egyptian document containing information about veterinary medicines and uterine diseases of women.
- Ebers papyrus (1550 BC) also an Egyptian document containing information about number of diseases and 829 prescription where castor oil, opium like drug are being used.

Historical developments in Pharmacology

- Hippocrates (460-375 BC) A greek physician consider **"father of Medicine"**. He was the first person who recognize disease as abnormal reaction of body. He introduce use of metallic salts for the treatment of disease.
- Theophrastus (380-287 BC) a great philosopher called father of Pharmacognosy. He classified medicinal plants on the base of medicinal characteristics.

Historical developments in Pharmacology

- Dioscorides (AD 57) a greek, produced one of the first materia medica of approximately 500 plants and remedies.
- Claudius Galen (AD 129–200) first attempted to consider the theoretical background of pharmacology.
- Paracelsus (1493–1541) a Swiss scholar and alchemist, often considered the "**grandfather of pharmacology**". He introduces the use of chemicals for treatment of disease.
- Valerius Cordus (1514-1544) He compiled the first pharmacopeia where he described techniques for the preparation of drugs.

MODERN PHARMACOLOGY

- Conversion of old medicines into the modern pharmacology start taking shape following the introduction of animal experimentation and isolation of active ingredients from plants.
- Francois Megendie (1783-1855) a first pharmacologist established the foundation of modern pharmacology. He developed experiment to elucidate the physiological processes and action of drugs on the body.
- Rudolph Buchheim (1820–1879) German pharmacologist a key figure in the development of pharmacology, a who at the University of Dorpat, created the first pharmacological institute.

MODERN PHARMACOLOGY

- Frederich Sertürner, German pharmacist's assistant, isolated morphine—the first pure drug—in 1805
- Claude Bernard (1813-1878) considered Father of experimental Medicine. He identifies the site of action of curare (arrow Poisoning).

MODERN PHARMACOLOGY

- Oswald Schmiedeberg (1838–1921) "**Father of Pharmacology**" established pharmacology as an independent discipline. He start teaching Pharmacology in University of Strasbourg (France).

- John Jacob Abel (1857-1938) founded first department of pharmacology in USA in the University of Michigan in 1893. In 1897 he established pharmacology department at Johns Hopkins University. Abel also co-founded the Journal of Pharmacology and Experimental Therapeutics in 1909.

MODERN PHARMACOLOGY

- L. mayer Jones (1912-2002) regarded as father of modern veterinary pharmacology. He authored first book of veterinary pharmacology therapeutics in 1954.

SCOPE OF PHARMACOLOGY

- It provides the rational basis for the therapeutic use of the drug. Before the establishment of this discipline, even though many remedies were used, but doctors were reluctant to apply scientific principles to therapeutics.
- In 1920s, many synthetic chemicals were first introduced and the modern pharmaceutical companies began to develop.

SCOPE OF PHARMACOLOGY

- Scientific understanding of drugs enables us to predict the pharmacological effect of a new chemical that will produce a specified therapeutic effect.
- The scope of pharmacology has expanded greatly over the last decade to incorporate many new approaches such as computer-assisted drug design, genetic screens, protein engineering and use of novel drug delivery vehicles including viruses and artificial cells.
- Our society needs pharmacologists who understand the basis of modern therapeutics for careers within academic, pharmaceutical and governmental laboratories to study and develop tomorrow's drugs.

Sources of Drug information

- The sources of drug information is received by pharmacopeia, that is a book which contains a list of established and officially approved drug with description of their physical and chemical characteristics and tests for their identification, purity, methods of storage etc. some of the pharmacopeia's are:
- Indian Pharmacopeia.(I.P.)
- British Pharmacopeia (B.P.)
- European Pharmacopeia.(E.P)
- United states Pharmacopeia.(U.S.P).

contd

- Other sources of drug information are
- National formulary (NF), Martindale – The extra Pharmacopeia,
- Physician desk Reference (PDR),
- American Medical Association drug Evaluation,
- Textbook & Journal of pharmacology and therapeutics, Drug bulletins, data bases like drug Micromedex, Medline, Cochrane library etc.
- Sources of drug information is also present in Formulary which provides information about available drugs – their use, dosage, adverse effect, contraindications, precautions, warnings and guidance on selecting right drugs for a range of conditions.

Definitions:
Terminology uses.

Definitions

Pharmacology	**Detailed study of drugs**
Pharmacognosy	**Science of identification of drug**
Pharmacy	**Science of identification,selection, preservation, standardization, compounding and dispensing of medical substances**

Pharmacology & Pharmacotherapeutics, Satoskar;1997: pg 2

Definitions (Contd)

Therapeutics	**Branch of medicine concerned With cure of disease or relief of Symptoms and includes drug Treatment**
Toxicology	**Science of poisons.** **# Measurement / detections of poisons** **# Treatment of poisoning**

Pharmacology & Pharmacotherapeutics, Satoskar;1997: pg 2

Definitions (Contd)

Chemotherapy	**Effect of drugs upon micro-organisms and parasites, living and multiplying in a living organism**
Pharmacopoeia	**An official code containing a selected list of the established drugs and medicinal preparations with description of their physical properties and tests for their identity, purity and potency**

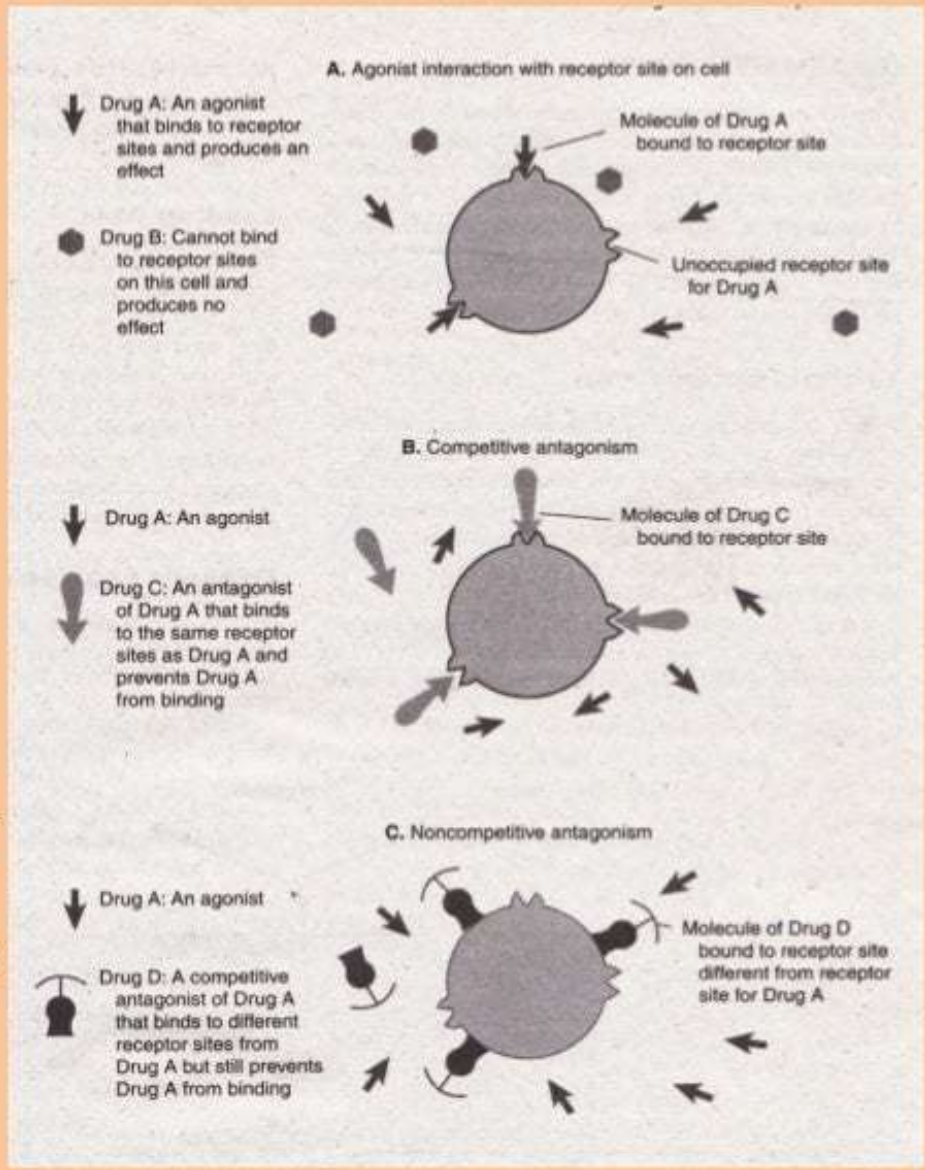
Pharmacology & Pharmacotherapeutics, Satoskar;1997: pg 2

Drug –
WHO scientific group definition

Any substance or product that is used/ intended to be used to modify or explore physiological systems or pathological systems or pathological states for the benefit of the recipient

Drug Attachment

- Medication chemically binds to specific sites called "receptor sites"
  - **Agonist**-chemical fits at receptor site well
  - **Antagonist**- a chemical blocks another chemical from getting to a receptor
  - **Partial agonist** - attach to the receptor but only produce a small effect



Basics of Drug Action

- ***Desired action*** – the expected response of a medication

- ***Side effects*** –known and frequently experienced, expected reaction to drug.

- ***Adverse reaction*** –unexpected, unpredictable reactions that are not related too usual effects of a normal dose of the drug.

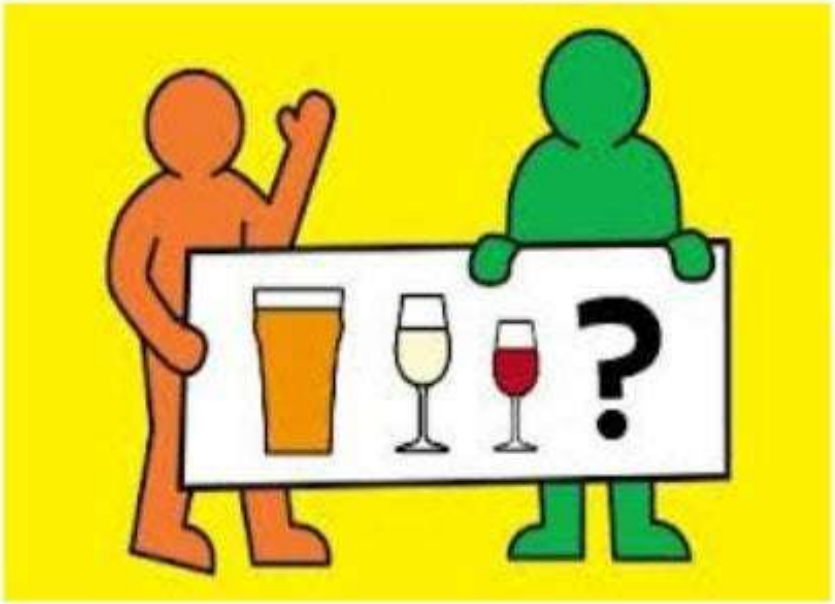
Drug Interaction

- Takes place when one drug alters the action of another drug.
- Some are helpful but often produce adverse effects.

Common Drug Interactions

- **Additive effect-** takes place when 2 drugs are given together & double the effect is produced.

Alcohol + aspirin= Pain relief



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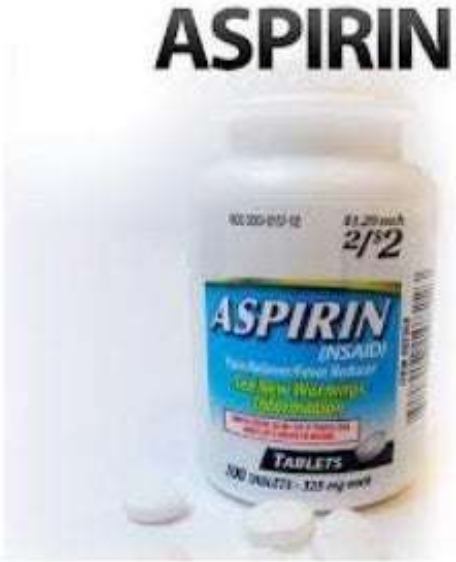


Common Drug Interactions

- **Antagonist**- a chemical blocks another chemical from getting to a receptor
- **Antagonistic effect- takes place when 1 drug interferes with the action of another drug.**
- **Eg. Protamine sulpha to counteract heparin toxicity**

Common Drug Interactions

- **Displacement effect -** takes place when 1 drug replaces another at the drug receptor site, increasing the effect of the 1st drug.

Common Drug Interactions

- **Incompatibility** –occurs when 2 drugs mixed together in a syringe produce a chemical reaction so they cannot be given.

  e.g. Protamine sulfate & vitamin K

Common Drug Interactions

- **Interference**- occurs when 1 drug promotes the rapid excretion of another, thus reducing the activity of the 1st.

- **Synergistic effect** takes place when the effect of 2 drugs taken at the same time is greater than the sum of each drug given alone.

E.g. combining diuretics & adrenergic blockers to lower the BP

Pharmacognosy: Sources of Drugs

Pharmacognosy

- The study of natural (plant and animal) drug sources

Sources of Drugs

- The different sources of drugs are:
- Plants:
- *Alkaloids*: eg. Morphine, Atropine, Quinine, reserpine, ephedrine.
- *Glycosides*: eg. Digoxin, Digitoxin.
- Animals: Insulin, Heparin.
- Minerals: ferrous sulphate, Magnesium sulphate.
- Microorganisms: Penicillins, Streptomycin, Grisiofulvin.
- Semisynthetic: Hydromorphone, Hydrocodone.
- Synthetic: Most of the drugs used today are synthetic. Eg. Aspirin, paracetamol.

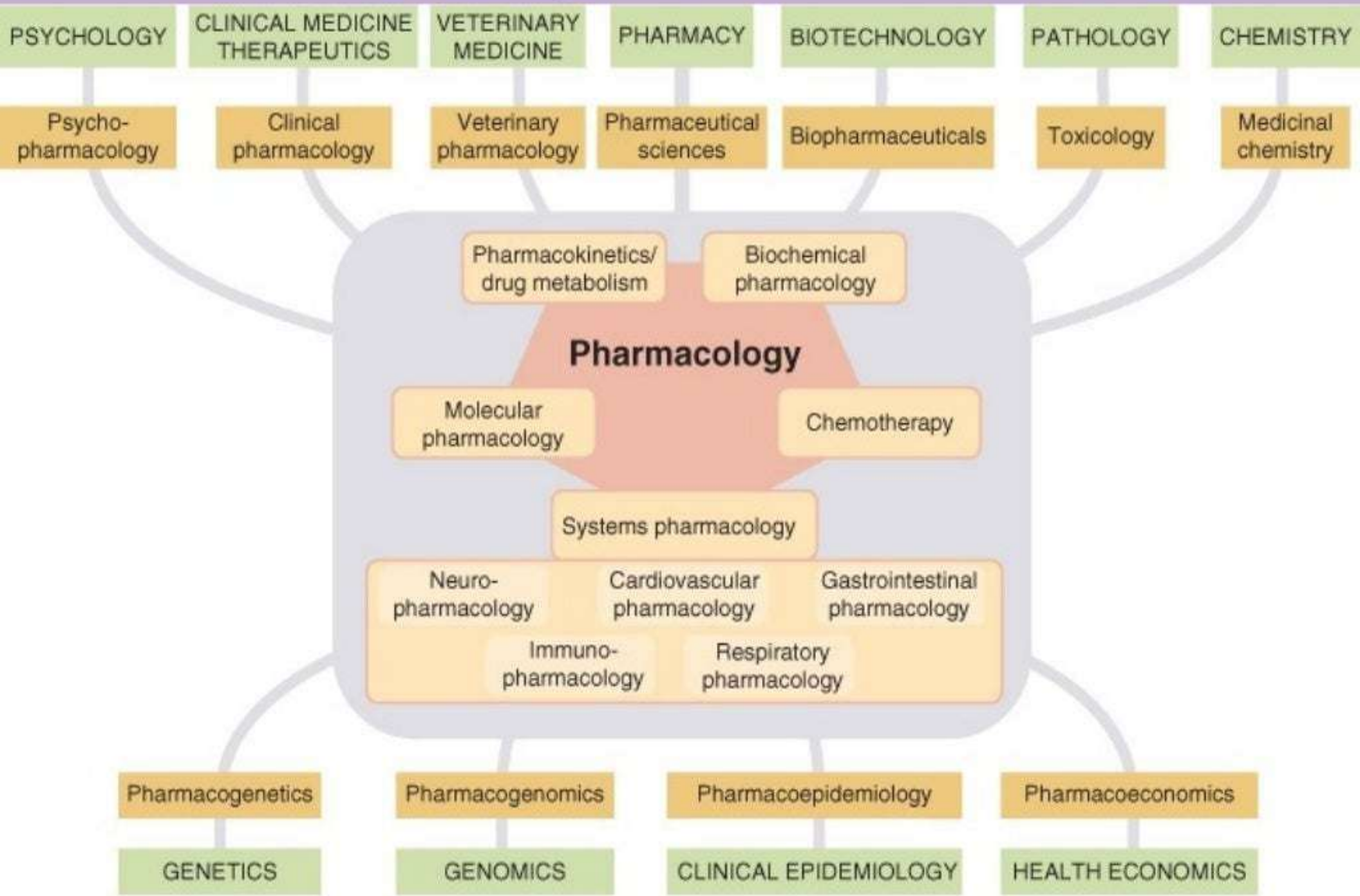
contd

- Drugs are also produced by genetic engineering (DNA recombinant technology) eg. Human insulin, Human growth hormone and Hepatitis B Vaccine.

Types: Classification of Pharmacology.

Classification - Pharmacology

PHARMACOLOGY, Link to other biomedical principles



Types of Pharmacology

1. **Experimental Pharmacology**: Done in the laboratory on experimental animals such as rodents and non rodents.
2. **Clinical Pharmacology**: On human subjects normal or deceased

CLASSIFICATION OF DRUGS

1. Chemical Nature
2. Source
3. Target organ/Site of Action
4. Mode of Action
5. Therapeutic Uses
6. Physiological system
7. Physical Effects

1. CLASSIFICATION BASED ON CHEMICAL NATURE

- Chemical Nature of drug is discussed by a Chemist and based on chemical nature we divide drugs into
- **INORGANIC DRUGS**

  Metals and their Salts (Ferrous Sulphate, Zinc Sulphate, Magnesium Sulphate.

  Non Metals Includes Sulphur.
- **ORGANIC DRUGS**
- **Alkaloids** (atropine, Morphine, Strychnine)
- **Glycosides** (Digitoxin, Digoxin).
- **Proteins**(Insuline, Oxytocin)
- **Esters, Amide, Alcohol, Glycerides.**

2. CLASSIFICATION BASED ON SOURCE

Sources of drugs are discussed by a Pharmacologist and Pharmacist

Natural Source

- **Plants** (Morphine, Atropine, Digitoxin)
- **Animals** (Insuline, eCG)
- **Micro organism** (Penicillin)
- **Mineral** (Sodium Chloride)

Synthetic Source

- (Sulphonamide, Procaine).

Semi-synthetic Source

- Amoxicillin, Ampicillin, Doxycycline

Bios-ynthetic Source

- Recombinant Human erythropiotin, Recombinant bovine somattotropine

3. CLASSIFICATION BASED ON TARGET ORGAN

Classification based on target organs are done by the Physicians.

- **Drugs acting on CNS** (Diazepam, Phenobarbitone).
- **Drugs acting on Respiratory System** (Bromhexaine).
- **Drugs acting on CVS** (Digitoxin, Digoxin).
- **Drugs acting on GIT** (Omeprazole, Kaoline, Sulphadimidine).
- **Drugs acting on Urinary System** (Magnesium Sulphate, Lasix
- **Drugs acting on reproductive system** (Oxytocin, Estrogen)

4. CLASSIFICATION BASED ON MODE OF ACTION

Classification based on mode of action is done by Physicians & Pharmacologists.

- **Inhibitor of bacterial cell wall synthesis** (penicillin)
- **Inhibitor of bacterial protein synthesis** (Tetracycline)
- **Calcium Channel blocker** (Verapamil, nifedipine)

5. CLASSIFICATION BASED ON THERAPEUTIC USE

Classification based on mode of action is done by Physicians & Pharmacologists.

- **Antimicrobials/Antibacterials** (Penicillin, Streptomycin, Quinolones, Macrolides).
- **Antihypertensive** (Clonidine, hydralazine, Enalpril).
- **Antidiarrheal** (Lopramide, Kaoline).
- **Antiemetics** (Domperidone, Meclizine and Metoclopramide).

6. CLASSIFICATION BASED ON PHYSIOLOGICAL SYSTEM

- **Sympathomimetics** (Adrenaline, Noradrenaline).
- **Parasympathomimetics** (Carbachol, Pilocarpine, Neostigmine).
- **Neuromuscular blockers** Suxamethonium, Gallamine).

7. CLASSIFICATION BASED ON PHYSICAL EFFECTS

- **Emollients** (Lanolin, Vaseline)
- **Caustics** (Silver nitrate)
- **Demulcents** (Zinc Oxide, Tannic Acid).

Site/Type of Action

This is another way of classifying drugs according to the system of the body on which it acts

- Vioxx would fall into the class called Musculo-Skeletal and Joint Diseases
- MIMS sets out these classes
- Use MIMS to find your drug's classification

Drug Nomenclature

Naming of drugs (Drug Nomenclature)

Three Names

 # The Chemical Name - technical description of the actual molecule e.g. Cozaar is 2-Butyl, 4 Chloro-tetrazol, 5 Phenylbenzylimidazole, 5 Methanol sodium

 # The Generic Name - The official medical name Cozaar's generic name is Losartan

 # The Brand or Propriety Name - The name under which the product is marketed i.e. Cozaar

Pharmaco-dynamics: Actions, therapeutic Adverse, toxic.

Pharmacotherapeutics: Types of Therapies

- Acute therapy
- Maintenance therapy
- Supplemental therapy
- Palliative therapy
- Supportive therapy
- Prophylactic therapy

Pharmacotherapeutics: Monitoring

- The effectiveness of the drug therapy must be evaluated.
- One must be familiar with the drug's
- intended therapeutic action (beneficial)
- and the drug's unintended but potential side effects (predictable, adverse drug reactions).

Pharmacotherapeutics: Monitoring

- Therapeutic index
- Drug concentration
- Patient's condition
- Tolerance and dependence
- Interactions
- Side effects/adverse drug effects

Pharmacotherapeutics: Monitoring

Therapeutic Index

- The ratio between a drug's therapeutic benefits and its toxic effects

Pharmacotherapeutics: Monitoring

Tolerance

- A decreasing response to repetitive drug doses

Dependence

- A physiologic or psychological need for a drug

Pharmacotherapeutics: Monitoring

Interactions may occur with other drugs or food

- Drug interactions: the alteration of action of a drug by:
  - Other prescribed drugs
  - Over-the-counter medications
  - Herbal therapies

Pharmacotherapeutics: Monitoring

Interactions

- Additive effect
- Synergistic effect
- Antagonistic effect
- Incompatibility

Pharmacotherapeutics: Monitoring

Medication Misadventures

Adverse drug events

- ALL are preventable
- Medication errors that result in patient harm

Adverse drug reactions

- Inherent, not preventable event occurring in the normal therapeutic use of a drug
- Any reaction that is unexpected, undesirable, and occurs at doses normally used

Pharmacotherapeutics: Monitoring

Some adverse drug reactions are classified as side effects.

- Expected, well-known reactions that result in little or no change in patient management
- Predictable frequency
- The effect's intensity and occurrence is related to the size of the dose

Pharmacotherapeutics: Monitoring

Adverse Drug Reaction

An undesirable response to drug therapy

- Idiosyncratic
- Hypersensitivity reactions
- Drug interactions

Pharmacotherapeutics: Monitoring

Iatrogenic Responses

Unintentional adverse effects that are treatment-induced

- Dermatologic
- Renal damage
- Blood dyscrasias
- Hepatic toxicity

Pharmacotherapeutics: Monitoring

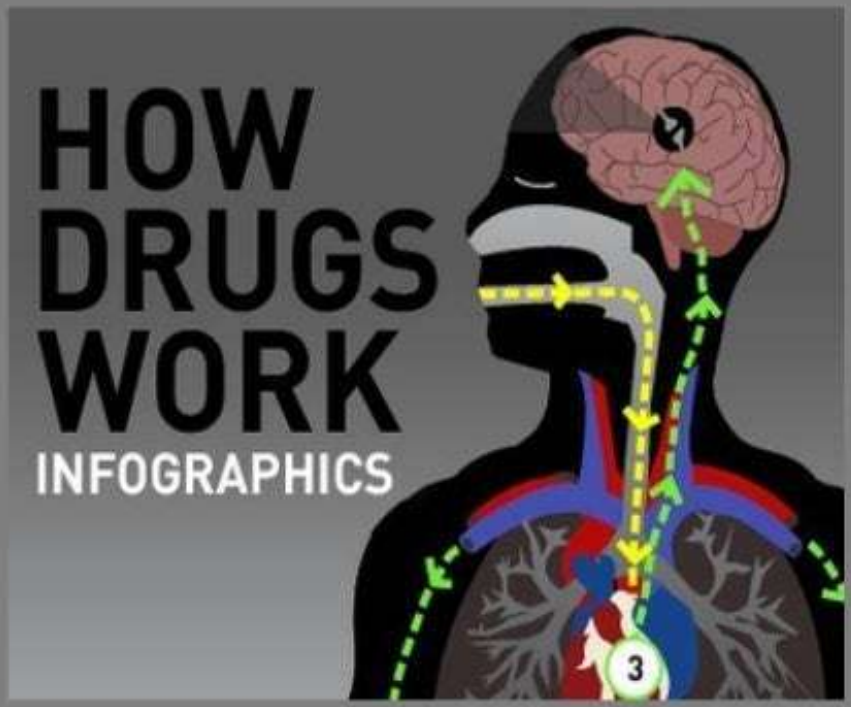
Other Drug-Related Effects

- Teratogenic
- Mutagenic
- Carcinogenic

Pharmacokinetics: Absorption, distribution, metabolism, interaction, excretion.

Pharmacokinetics

Absorption
Distribution
Metabolism
Excretion
Bioavailability



Factors influencing the efficacy of a drug are:

- The route of Administration
- The rate of Absorption
- The distribution of the drug to the required site
- The rate of biotransformation or metabolism
- The presence of active metabolites
- The rate of excretion

Absorption

To be effective a drug must be absorbed - except for topical and IV

This means drugs have to cross cell membranes

The ability of the drug to cross the cell membrane is influenced by its solubility in water or fat, its size and shape

Drug Absorption of Various

Oral Preparations

Liquids, elixirs, syrups	Fastest
Suspension solutions	↓
Powders	↓
Capsules	↓
Tablets	↓
Coated tablets	↓
Enteric-coated tablets	Slowest

Absorption

- Drugs cross membranes by:
  - Filtration - only small water-soluble molecules which flow through the hydrophilic pores
  - Passive Transport - Diffusion i.e. from high concentrations to low concentrations
  - Active Transport - Energy and carriers are required to move non-fat soluble substances across the cell membrane e.g against concentration gradient

Absorption

 # IV injection

 # delivered straight to bloodstream
 # rapid action

 # *All other routes*

 # need to be *absorbed* from site of administration
 # speed of action depends on *absorption rate (ka)*

Absorption

Factors affecting the absorption rate (*ka*)

#Route of administration

Blood supply to the site of absorption

Formulation of the drug

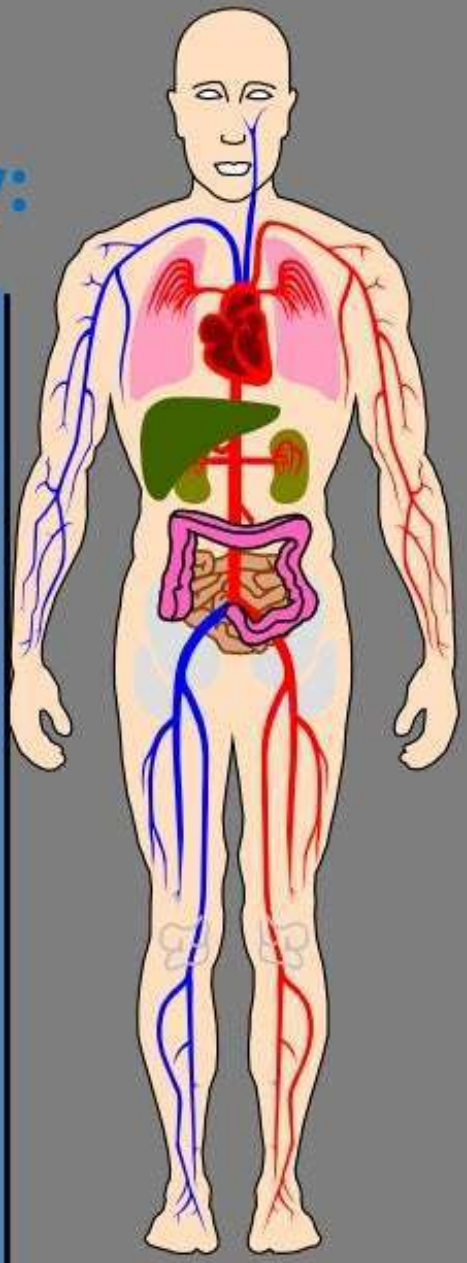
Gut transit time

pH in the gut

Solubility of the product

Distribution

Drug in bloodstream is *distributed* to body:



Central compartment

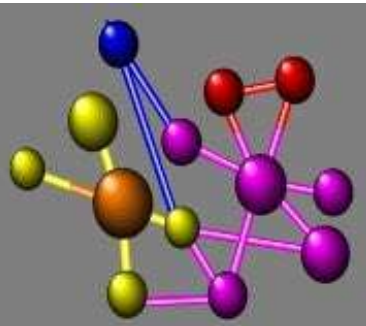
-(major organs & blood vessels)

- **– low lipid solubility (hydrophilic)**
- **– low volume of distribution (low Vd)**

Peripheral compartment

- ***(skin & fat stores)***
  - **– high lipid solubility (lipophilic)**
  - **– high volume of distribution (high Vd)**

Distribution



Plasma protein binding:

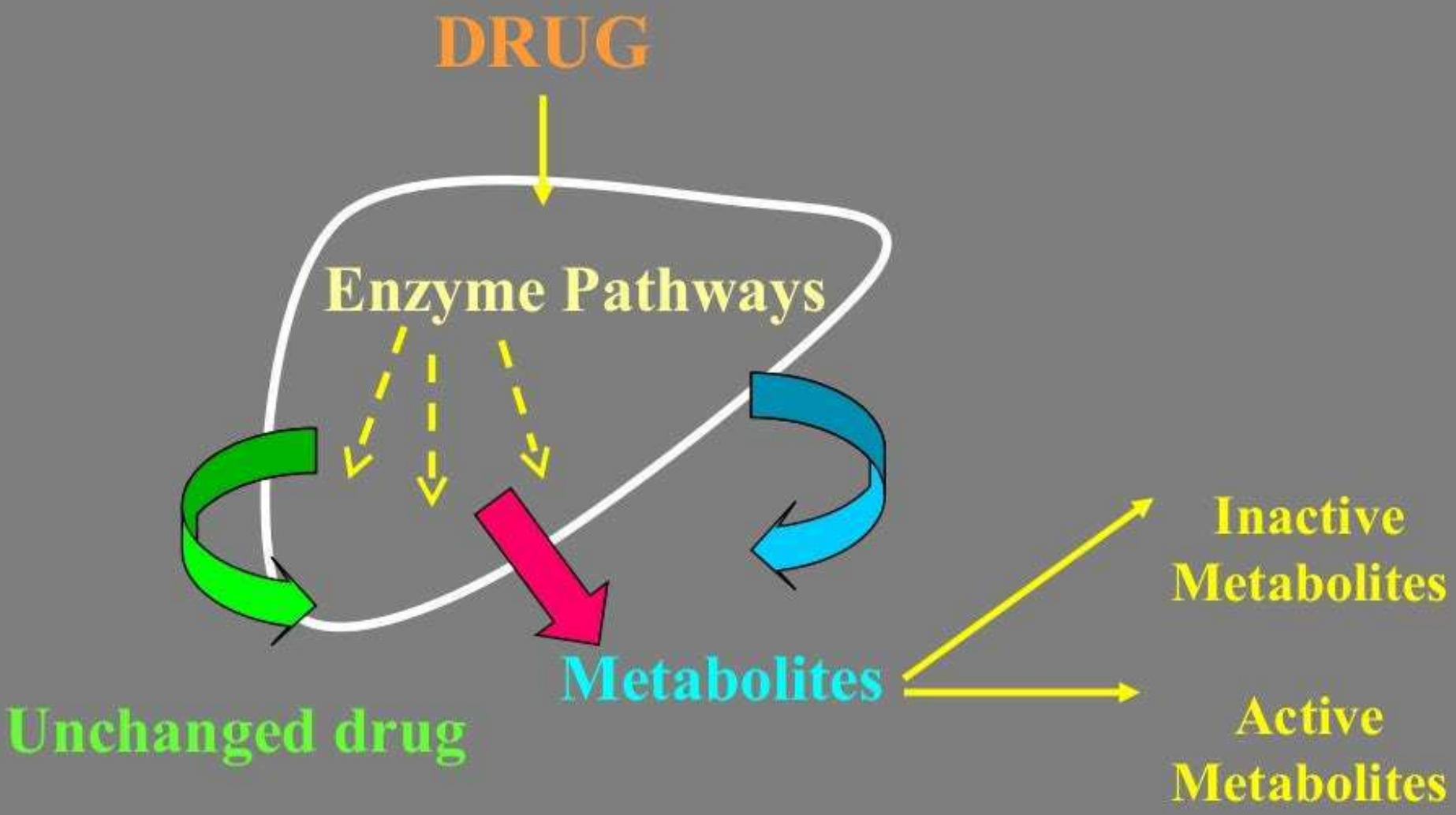
#Only 'free fraction' can move to target site (e.g. 80% bound / 20% free)

#Dynamic process i.e. as free drug moves into tissues, protein-bound drug is released into plasma to maintain ratio *(ratio of 'free fraction' : 'plasma protein bound' remains constant)*

#Drugs vary in the degree to which they are plasma protein bound (< 99.9%)

Metabolism

Major organ of metabolism - LIVER



Metabolism

Major organ of metabolism - LIVER

- **Active metabolites :**
  Clinical or side effects
- **Inactive metabolites**

N.B. Patients with hepatic impairment may require:

- higher doses (where metabolism ➡ active metabolites)

- lower doses (where metabolism ➡ inactive metabolites)

Metabolism

Factors affecting metabolism
(i.e. compete for enzyme pathways in the liver)

Genetic factors

Other drugs *e.g. Cimetidine / Ciproxen*

Smoking

#Enzyme induction/inhibition(CYP450/others)

Some foods

#Liver disease

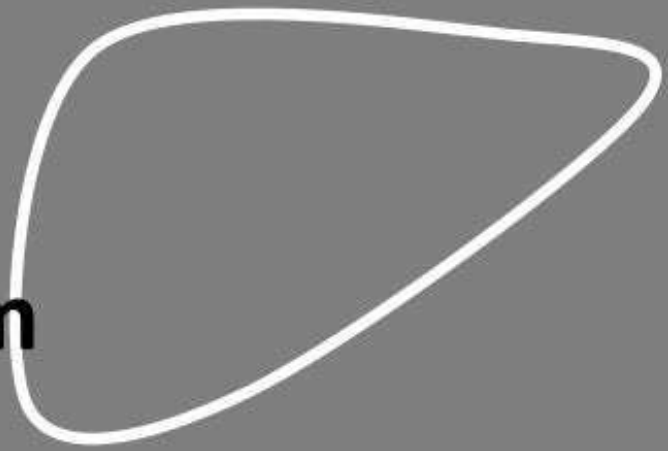
#Age

First-Pass Effect

The metabolism of a drug and its passage from the liver into the circulation.

- A drug given via the oral route may be extensively metabolized by the liver before reaching the systemic circulation (high first-pass effect).
- The same drug—given IV—bypasses the liver, preventing the first-pass effect from taking place, and more drug reaches the circulation.

Metabolism



First pass metabolism

Gut → **Liver** → **Body**

(Portal vein) *(General circulation)*

 # the breakdown of a drug in the liver before it reaches the site of action

#oral dose may need to be higher than parenteral dose

 # Prodrug

First Pass (Presystemic) Metabolism

Metabolism of orally administered drugs in a single passage thru the gut wall and (principally) the liver.

Drugs for which presystemic elimination is significant – Isosorbide dinitrate, Propranolol etc.

First pass elimination is reduced in severe hepatic cirrhosis

Clinical Pharmacology, Laurence,, 1997, p92

First-Pass Effect

- Routes that bypass the liver:
  - Sublingual
  - Buccal
  - Rectal
  - Intravenous
  - Intranasal
  - Transdermal
  - Vaginal
  - Intramuscular
  - Subcutaneous
  - Inhalation

  *Rectal route undergoes a higher degree of first-pass effects than the other routes listed.

Elimination

Elimination

=

Metabolism

+

Excretion

Excretion

#The process by which drug is removed from the body.

Primary

via the kidneys (in urine) also

via the gut (faeces), the skin (sweat), the lungs (breath), saliva

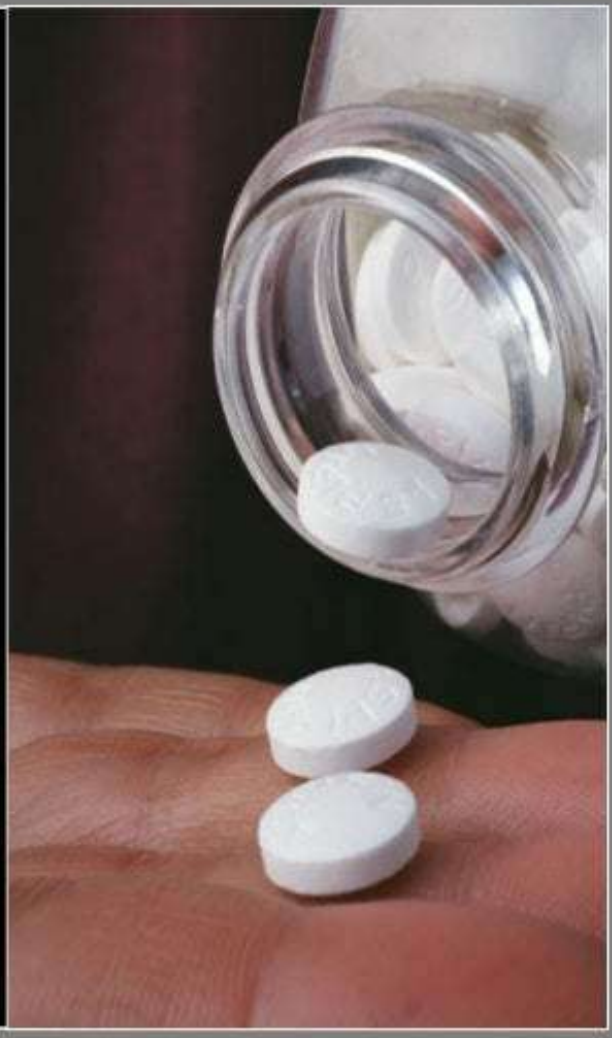
 # N.B. Patients with renal disease or dysfunction (elderly/heart disease) may require lower doses as the drug will be retained for longer than in 'normal' patients

Bioavailability

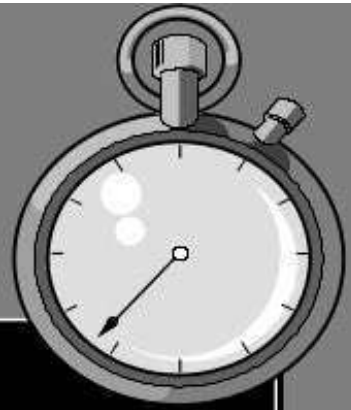
- It is defined as the extent to which active ingredients *are absorbed and transported* to sites of action.
- ***Factors***
  1. Drug solubility
  2. Pharmaceutical formulation
  3. pH
  4. Food

Dose regimes

- *Factors determining Dosage :*
  - Half Life
  - Age
  - Sex
  - Body Weight and Surface area
  - Tolerance
  - Specific disease



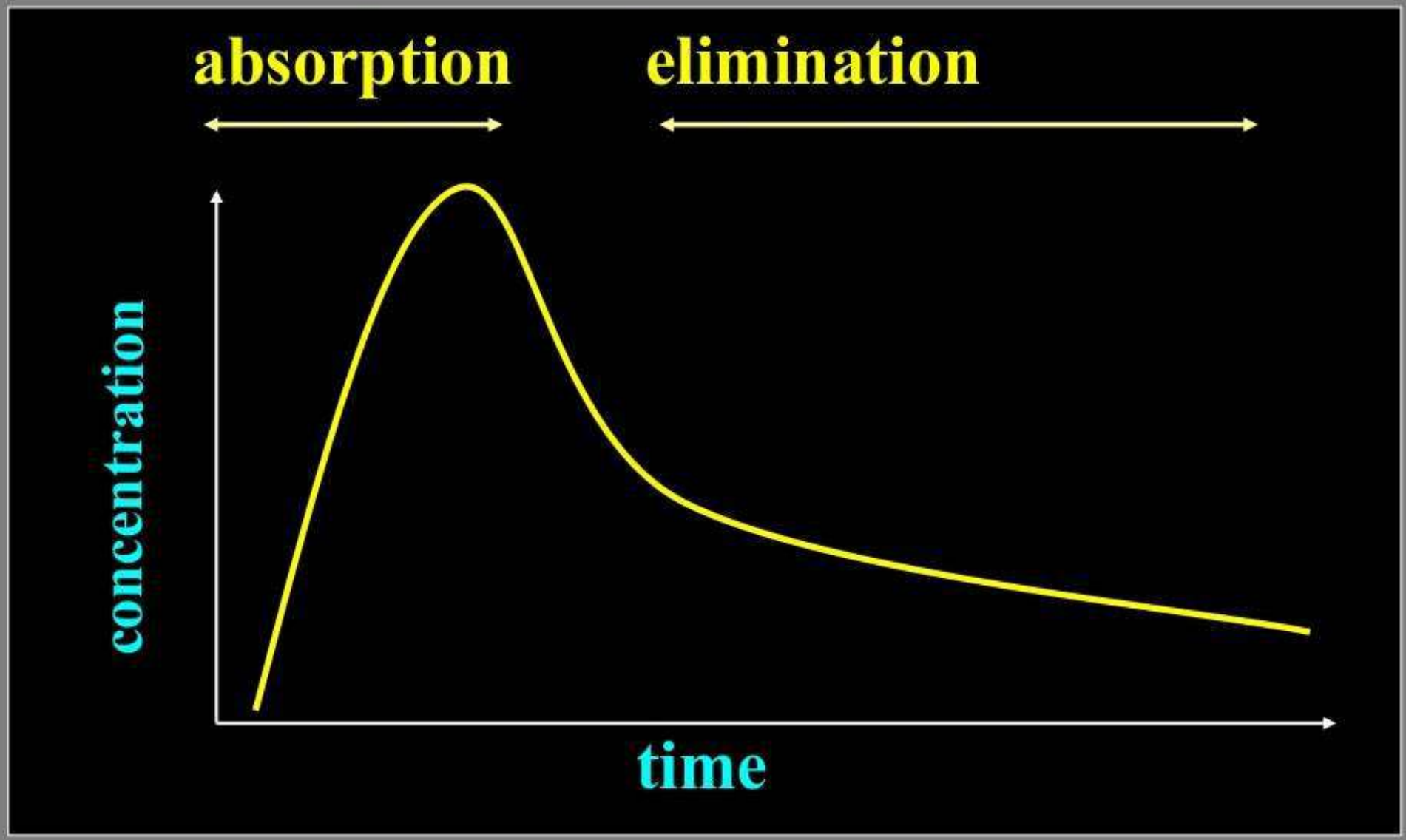
Dose regimes



- OD *(mane / nocte)*
- BD *(12 hourly)*
- TDS *(8 hourly)*
- QDS *(6 hourly)*
- PRN *(as required)*
- Depot *(weekly / monthly / quarterly)*
- Stat *(immediately)*

Plasma profiles

- Single dose plasma profile

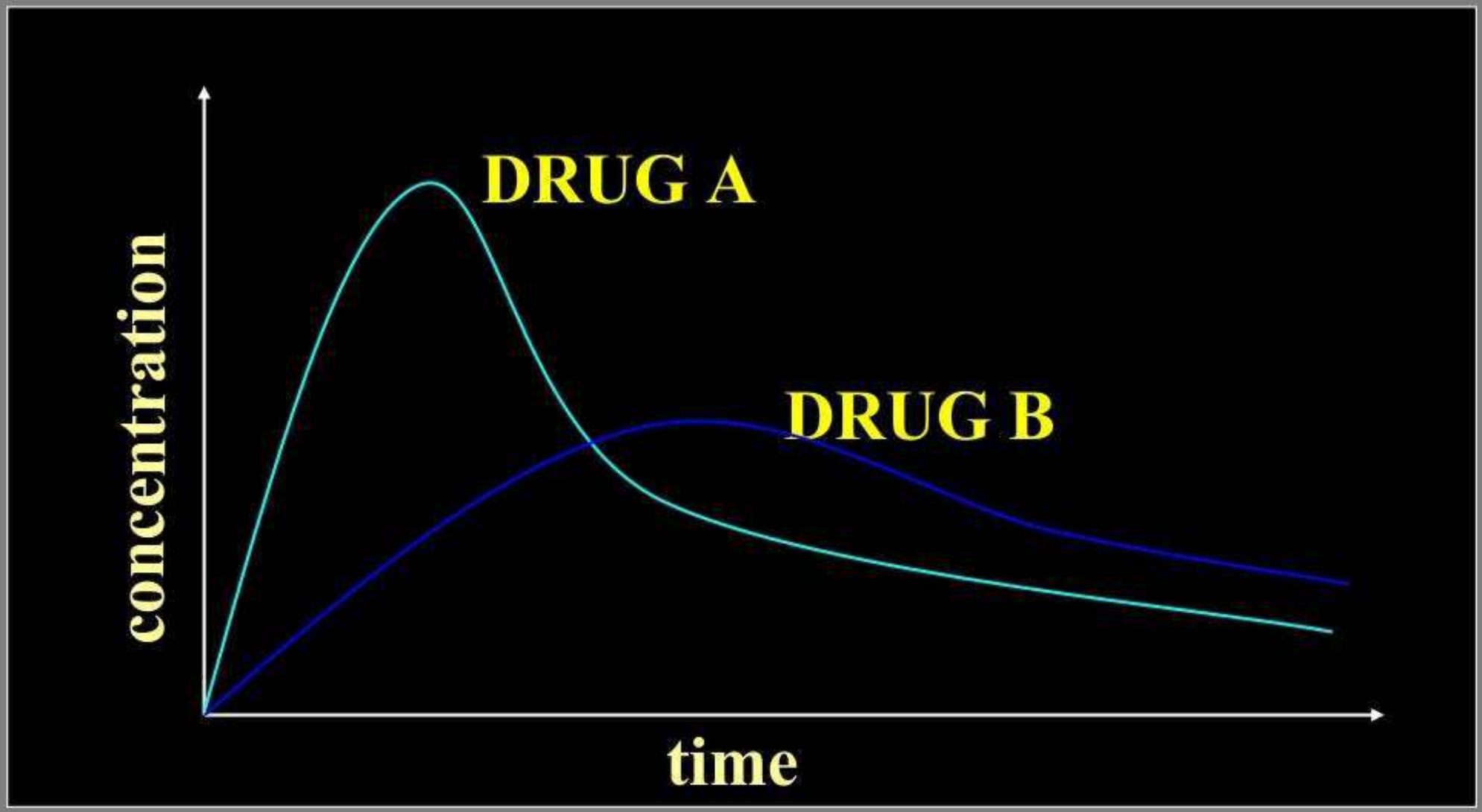


Plasma levels

- Constant plasma levels only with constant I.V. infusion.
- Peaks & troughs in plasma levels with all other routes of administration (due to absorption & elimination)
- Dose regimes are calculated to maintain therapeutic plasma levels

Plasma profiles

Dose plasma profile



Half-life

- Refers to the time required for the body to eliminate 50% of the drug.
  - It is important in planning the *frequency* of dosing.
- Short half-life (2-4 hours) : needs to be given frequently
- Long half life: (21-24 hours): requires less frequent dosing

Note: It takes 5 to 6 half lives to eliminate approximately 98% of a drug from the body

Half-life

- Liver and kidney disease patients may have problems of excreting a drug.
- Difficulty in excreting a drug increases the half-life and increases the risk of toxicity.
- Implication: may require frequent diagnostic tests and measuring renal and hepatic function.

Half Life = ½

Time in which a measure (concentration effects) declines by one half

Measured in 3 ways : -

1) Plasma half life
2) Biological effect half life
3) Biological half life

Plasma – Half Life

- Time in which the plasma concentration falls by one half
- Influenced by various factor – tissue diffusion, protein binding , renal excretion

Biological effect half life

- Time in which a the pharmacological effect of the drug, and of any of the active metabolites, has declined by one half
- Eg. For antibiotics, varies with each infection

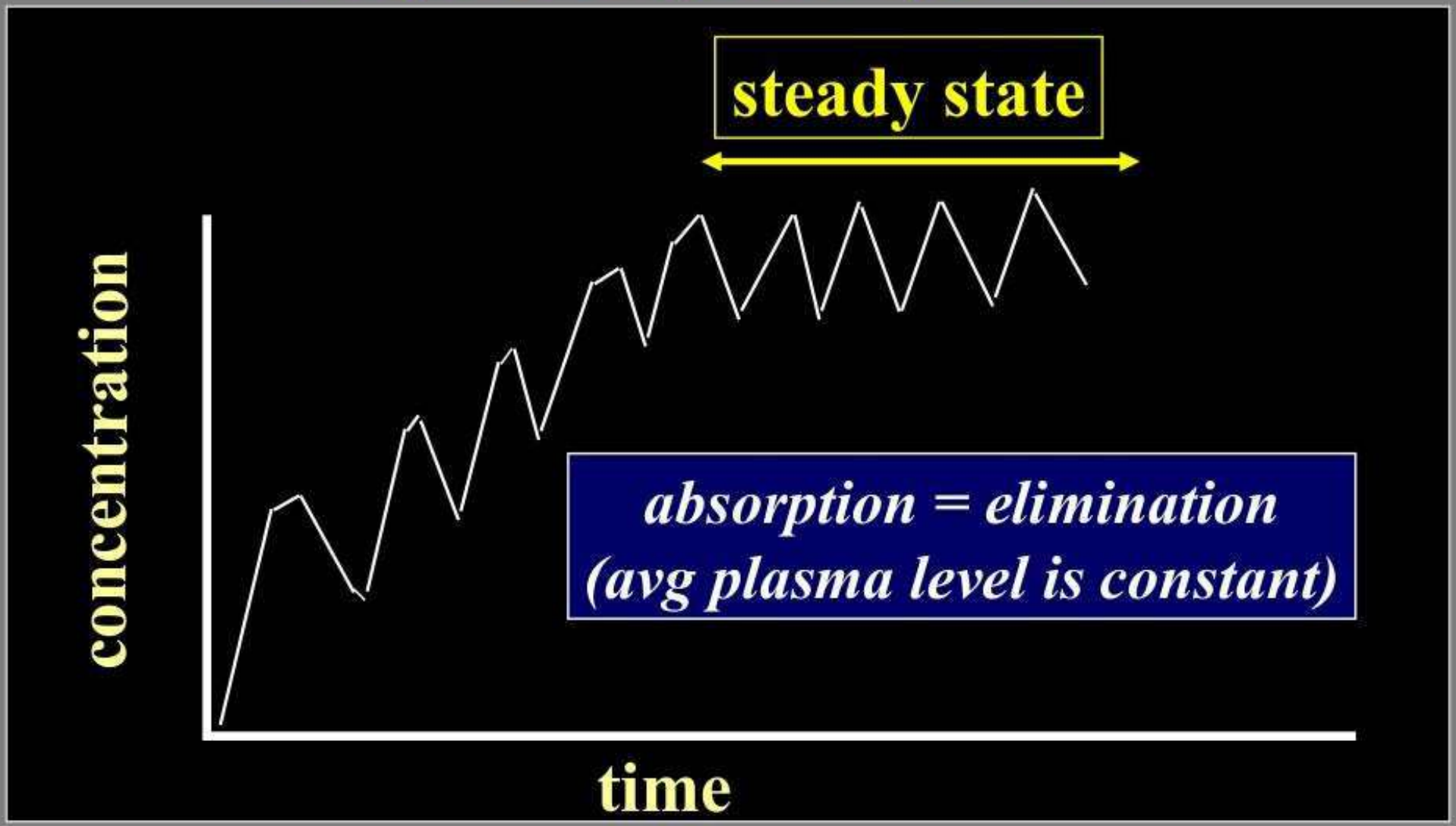
Biological half life

Time in which a the total amount of drug in the body after equilibrium of plasma with other compartments (fat, muscle) is halved

Measured using radioisotopes, rates of excretion

Plasma profiles

Multiple dose plasma profile



Steady state concentration

- Plateau concentration
- Rate of input of drug to the body is matched by rate of elimination
- Has to be in therapeutic range to maintain effect
- Affected by half life of drug

Therapeutic Index/Ratio

- Devised by Ehrlich
- Maximum tolerated dose / minimum curative dose
- Gives indication of safety
- Especially applicable to antibiotics
- Defines safety in relation to efficacy

Review: Routes and principles of administration of drugs

Routes of Administration

To be effective a drug must :

- Be present in an active form
- At the correct site
- At the right concentration
- For the right duration of time

The formulation of the product for each delivery route is vital to ensure optimal activity and consistent delivery

Thus choose the right Route of Administration and Formulation

Route of Administration & Formulation (Dosage forms)

Oral	**Tablets / Capsules / Elixirs / Syrups / Suspensions /Granules / Powders / Caplets / Drops**
Parenteral	**Intra-dermal / Subcutaneous / Intra-muscular / Intra-venous / Intra-thecal / Epidural / Spinal / Depot**
Sub-lingual / buccal	**Tablets / Sprays**
Inhaled	**Aerosol inhalers / Dry powder inhalers / Nebuliser solutions / Spacers**

Route of Administration & Formulation (Dosage forms)

Rectal (PR)	→	Suppositories / Enemas
Vaginal (PV)	→	Pessaries / Creams / Vaginal tablets
Transdermal	→	Creams / Gels / Patches
Topical	→	Creams / Lotions / Gels / Nasal sprays / Shampoos / Suppositories / Peccaries

Oral Route

- Absorption hampered by food
- Drug may be destroyed (insulin)
- Drug may not be absorbed (Streptomycin)
- First pass metabolism

Sublingual route

- Abundant blood supply
- Quick effect
- No degradation by digestive juices
- No first pass metabolism
- Irritation of mucous membranes

Rectal Route

Rich blood supply
No irritation of GIT
Useful in patients who cannot swallow/vomiting / uncooperative patient

Effects of Protein Binding on Drugs

Assists oral absorption of a drug

Delays metabolic degradation

Delays excretion

Diminishes penetration into the CNS

Significance – acts as reservoir and thereby prolongs action of drug

Pharmaclogy & Pharmacotherapeutics, Satokar, 1997, p14

Enteric Coating

Pills or tablets are coated with substances which resist the acid juice of the stomach but permit disintegration in intestinal juices.

- # To prevent gastric irritation & alteration of drug in stomach
- # To get desired concentration of the drug in small intestine
- # To retard the absorption of the drug.

Pharmaclogy & Pharmacotherapeutics, Satokar, 1997, p5

SR Preparations
SR = TR = XL

Sustained release or time release preparations for oral use

- **Release the active drug over an extended period of time.**
- **Particles of drug covered with coatings which dissolve at different time intervals.**

Pharmacology & Pharmacotherapeutics, Satokar, 1997, p5

Basic pharmacology - Agenda

#Classification of Drugs
#Routes of administration & drug formulations
#A.D.M.E.
#Dose regimes & plasma levels
#Package insert information
#Scheduling of drugs
#Pharmacodynamics
#Drug uses & ADR
#Clinical pharmacology

Indian pharmacopoeia: Legal issues, Storage of various drugs

Indian Pharmacopeia

- The central drug authority is based in Nirman bhavan, New Delhi.
- It is the body which is controlled by the govt. for manufacturing, sale, import and export of drugs.
- The drug authority of state is mostly based on their capitals.
- The central drug authority formulate the policies and authority of state follows and implement the policies.

Implementation is under the control of drug controller.

1. **Advisory Agency:** It include Drug technical advisory board (DTAB) and drug consultative committee (DCC). They frames and modify rules regarding drugs.
2. **Analytical Agency:** It includes central drug laboratory (situated at Kolkata) and drug laboratories in respective state, these laboratories test, analyse the sample of drugs and cosmetics.

3. **Executive Agency:** Authorities which grants license to various organizations for manufacturing, storing, recapping, selling, importing and exporting drugs.

Scheduling of medicines

- Scheduling based on potential effects on the body :the molecule, and it's concentration Expressed with an 'S' and a number 7 schedule classes.
- Unscheduled - can be sold through any outlet.
- S2 upwards only in pharmacies
- S1 and S2 - do not require a prescription
- S3 upwards must be sold with a prescription by a pharmacist or doctor
- S5 upwards is highly controlled
- Schedule 6 &7 are kept under lock and key, the prescription cannot be repeated
- Schedules 8 and 9 - banned substances

Scheduling of drugs

- S1
  - Miscellaneous
- S2
  - Analgesics, Flu preparations, Antihistamines, Anticholinergics
- S3
  - Non-steroidal anti-inflammatories, Anti-hypertensives, Topical steroid preparations, Anti-diabetic medicine, The Pill
- S4
  - Antibiotics, Hormones, Steroid anti-inflammatory medicines, statins

Scheduling of drugs

- S5
  - Psychotropic drugs, e.g anti-depressants, sleeping tablets, tranquilisers
- S6
  - Anorexigenics, Short-acting barbiturates, Opoid drugs
- S7
  - Opoid drugs
- S8,S9
  - Prohibited except for research e.g. heroin, LSD, cannabis (dagga)

Storage and Maintenance of Drugs

Introduction

- The Drugs which are supplied to ward are stored in drug cupboards to provide a uniform supply of drugs to the patients.
- The drugs are stocked in containers, such as boxes and on flexible racks and shelves etc.
- It must be ensure that drugs which are stored remain preserved during their storage.
- There should not be any damage due to high temperature or exposure to sunlight.
- The drugs are to be stored as per the prescribed conditions of their storage.

Introduction - contd

- The drugs stored in a drug store be arranged in such a way that they are easily traceable as and when required.

1. According to pharmacological action
2. Alphabetically

Drug Storage

1. Proper drug storage
2. Storage Environment
3. Arrangement of drugs on shelves
4. The storeroom
5. The dispensary

1. Proper drug storage

Drugs are stored in a specially designed secure area or space of a building in order to:

- Avoid contamination or deterioration,
- Avoid disfiguration of labels,
- Maintain integrity of packaging and so guarantee quality and potency of drugs during shelf life,
- Prevent or reduce pilferage, theft or losses,
- Prevent infestation of pests and vermin.

- The storage should not hinder the cleaning and should have sufficient space for movement of stocks and handling.

- Products are to be stored in a manner that prevents damage due to excessive vertical stacking heights and not to exceed eight stacks.

- Store the products as per product storage condition (As per label) to prevent deterioration of finished product on storage.

- Monitor and record the temperature of storage area on daily basis.

2. Storage Environment

The storage environment should possess the following:

- Adequate temperature,
- Sufficient lighting,
- Clean conditions,
- Humidity control,
- Cold storage facilities,
- Adequate shelving to ensure integrity of the stored drugs.

Storage and Maintenance

- Drugs to be stored under condition that prevent contamination & as far as possible, deterioration.
- **"Well closed container"** precautions to be taken in relation to the effects of the atmosphere, moisture, heat &light.
- **"Protected from moisture"** means that the product is to be "stored in air tight container"

Protected from light

- **"Protected from light"** the product is to be stored either in a container made of material that absorbs actinic light sufficiently to protect the contents from change induced by such light.

Temperature

- In a deep freeze (-15°C)
- In a refrigerator 2°C -8°C
- Cold or cool 8°C-15°C
- Room temperature 15°C-25°C

Storage Premises

- The Storage area must be free from unsanitary conditions(Ex Rodents, insects, Birds, litter etc).
- The floor of the warehouse should be made of hard floor (Concrete /Kota/Epoxy) and must be in a good state of repair and appearance at all times.
- The floors are kept clean and free of trash, dirt, sippage water, drain water etc.
- The area must be kept clean and free of refuse.

Storage Premises

- The area used for storage of IV fluids should have adequate space and to prevent exposure to direct sunlight.
- Secured area availability for damaged, rejected and expired goods.
- Ensure adequate pest control program in place and shall be carried out at a minimum frequency of a year.
- The Pest control shall cover treatment for Termite and Rodents.

3. Arrangement of drugs on shelves

- Shelves should be made of steel or treated wood.
- Shelves should be strong.
- Drugs are arranged in alphabetical order of generic names.
- Each dosage form of drug is arranged in separate and distinct areas.
- Sufficient empty space should demarcate one drug or dosage form from another.

- Most recently received drugs are placed behind old stock on the shelf except where new drugs have shorter expiration dates.

- Always put lids properly on tins always and at the close of the day.

- Put drugs in a dry place protected from light and heat.
- Store liquids on a pallet on the floor or on the lowest shelf.
- The store must be cleaned daily and mopped at least once a week.

4. The store-room

- A well-arranged store enables easy identification of drugs and saves time when picking a drug from the shelves.

- This helps remove drugs quickly and makes for easy inventory control.

- The rule of **FIRST IN FIRST OUT (FIFO)** should be applied always.

- So, drugs that were received first should be used first, except where the new stock has shorter expiration dates than the old stock.

- In this regard, the principle of **FIRST TO EXPIRE FIRST OUT (FEFO)** should apply.

- To have access to drugs with shorter expiration dates first, put these in front of the shelves.

- Those with longer expiration dates should be placed behind those with shorter dates.

5. The dispensary

- Clean after each use tablet counters and place within easy reach on the table.
- Avoid dispensing wrong drugs by arranging drugs on the table in alphabetical order so that the drug being dispensed is not confused with another.
- Always close drug containers from which drugs are not being dispensed to prevent spillage or dispensing the wrong drug.

Drug expiry

- **Shelf life-** the time where a given product stored under reasonable condition, is expected to remain stable (>90%potency)

- **Essential drugs-** drugs that satisfy the health care needs of the majority of the population.

- Essential drugs should there fore available at all times in adequate amounts & in appropriate dosage forms.

Expiry dates

- Medications must not be administered, and products and equipment must not be used beyond their expiry dates.
- All medical equipment, dressings and solutions used during invasive procedures must be sterile.
- Single-use devices are meant for single use only and must not be re-used.

Storage, Maintenance & Security

- All drugs, including samples, should be maintained separate from non-medications in a locked cabinet which is sufficiently secure to deny access to unauthorized persons.

- Key should be available only to authorized personnel who are assigned medication-related responsibilities.

- Store medications that are “for external use only” separate from medications intended for internal use.

Storage, Maintenance & Security

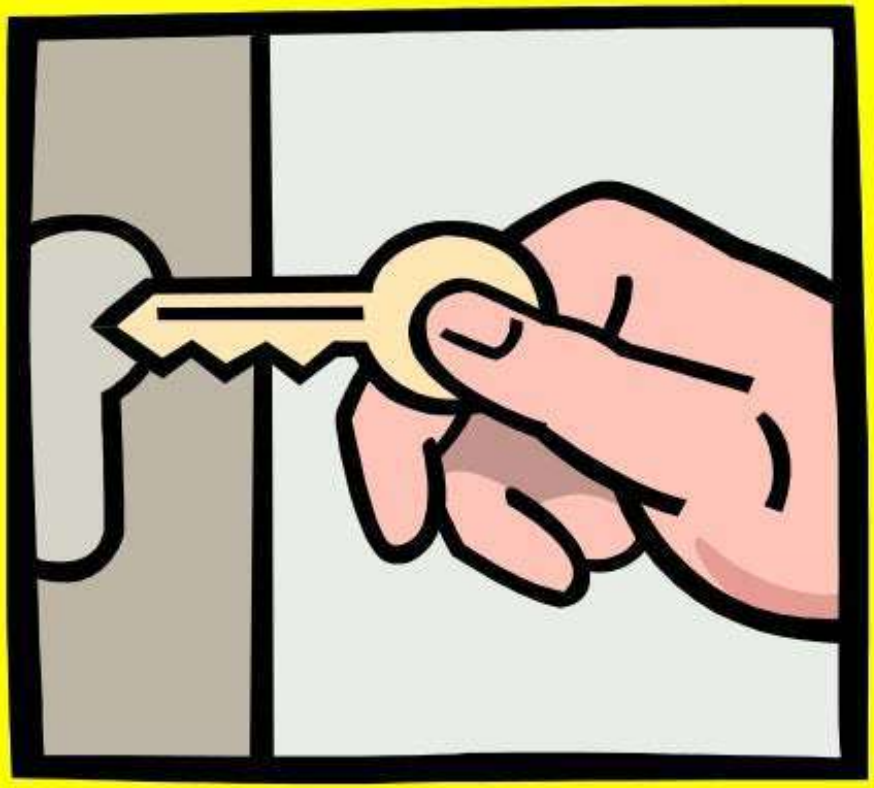
- Store look-alike and sound-alike drugs separately.
- Maintain temperature between 59 degree and 86 degrees Fahrenheit for non-refrigerated medications.
- Where refrigeration is necessary use a “Medications Only” refrigerator and maintain temperature between 36 degrees and 46 degrees Fahrenheit.

Storage, Maintenance & Security

- On daily basis check, verify and document the proper temperature.
- All multiple-dose injectable medications should be initialed and have the date of first entry recorded on the label.
- Rotate medication stock monthly employing a "FIFO" (first in/first out) process.

Controlled Drug Regulations

- Double Locked Container



Controlled Drug Regulations

- 2 licensed personnel count (or verify any discrepancies) every shift (8 hours)
- Witness to all discards
- Record on Control Substance Sheet all administrations and wastes.

Controlled Drugs

All details must be completed in the Doctors own handwriting, like:

- Name of drug
- Dose of drug
- Number of doses or length of course
- Signature of prescribing doctor and date

Storage of Controlled Drugs

- They must be kept in a locked cabinet or cupboard
- The keys to the cabinet must be in the possession of an authorised person
- Authorised person, refers to Ward Manager or deputy who must be a Trained Nurse or Midwife
- Students should not be responsible for the controlled drug cupboard keys

Recording of Controlled Drug Use

- Records in the form of **CONTROLLED DRUG REGISTERS** must be kept
- Each drug must have its own specified page which is Headed with the Drugs name and Strength
- The Number of Ampoules of a drug must be entered and updated with every use.

Recording of Controlled Drug Use

- Must record:
  - Date
  - Time
  - Dose of every administration
  - Name of receiving patient/client
  - Number of ampoules at start and finish of administration

  Entry must be signed by 2 people **one of who must be registered**

  No alterations must be made to the entry

  All entries must be in **Black Ink**

Rational use of drugs & Calculation of drug dosage

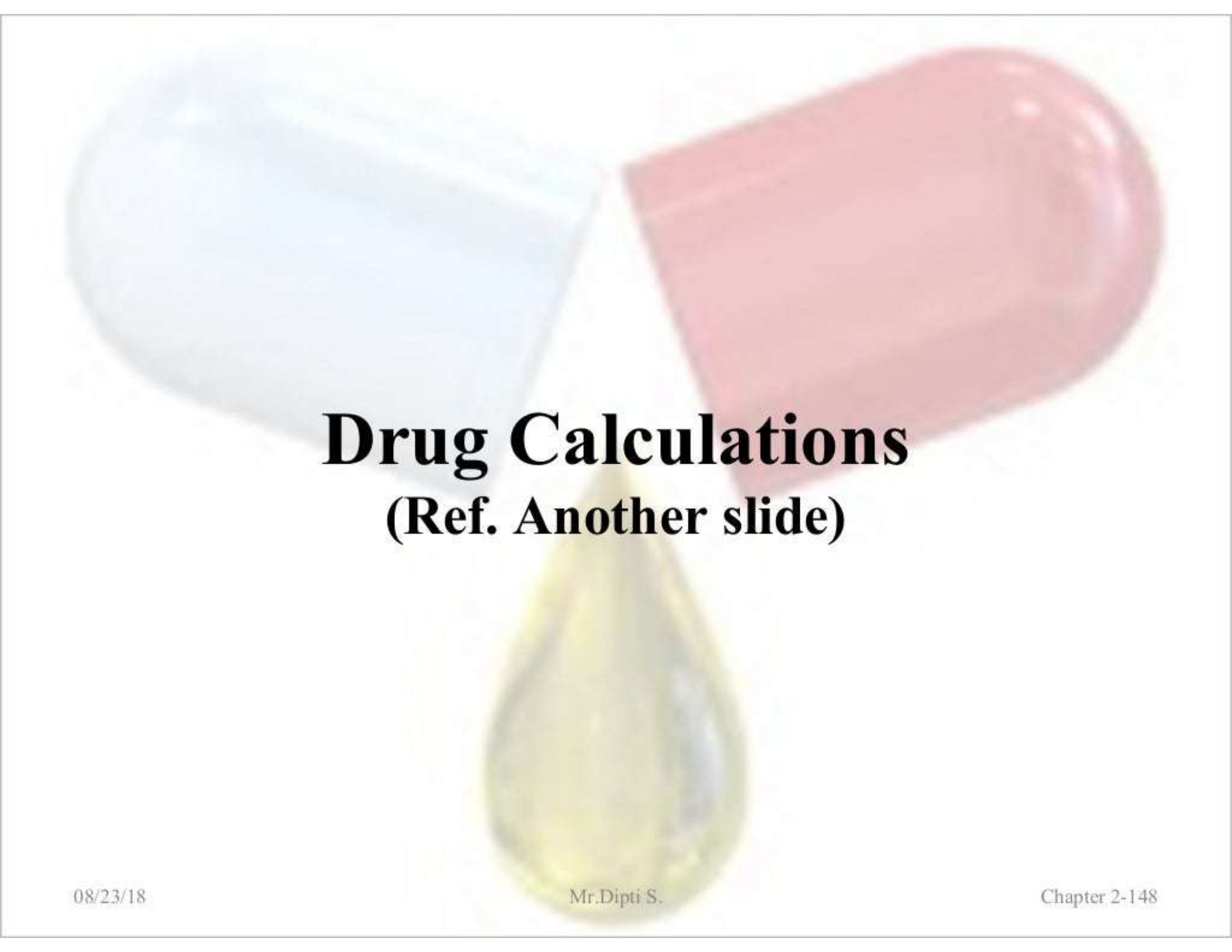
Rational use of drugs

- Any drug is made with help of combination or mixture of the chemicals which some times harm to the other parts of body.
- Rational use: Eg. Patient is having hypertension then the goal is to reduce blood pressure to the normal level in order to prevent prolonged hypertension, thus creating complication.
- Once identifying the person suffering from specific disease, the physician or nurse should find out other factors contribution the ill effect of the prescribed drug.

- Any drug required good renal or hepatic system to pass drug and to be drain out or metabolize in the body.
- The choice of drug has to be make wisely by the physician or nurse to avoid side effects, drug interaction, contraindication.
- Nurse should follow the 6 Rights of drug administration to avoid wrong administration of drug.
- Use of combination drug can be one option in treatment, eg. Ibufen (Brufen+Paracetamol)

Conclusion

Rational use of drugs requires that the patients receiving medications appropriate to their clinical needs, in does that meet their own requirement of an adequate period for time and at lowest cost to them and their community.



Drug Calculations
(Ref. Another slide)

Pharmacotherapeutics: Principles of therapeutics

Drug – WHO scientific group definition

Any substance or product that is used/ intended to be used to modify or explore physiological systems or pathological systems or pathological states for the benefit of the recipient

Pharmacology

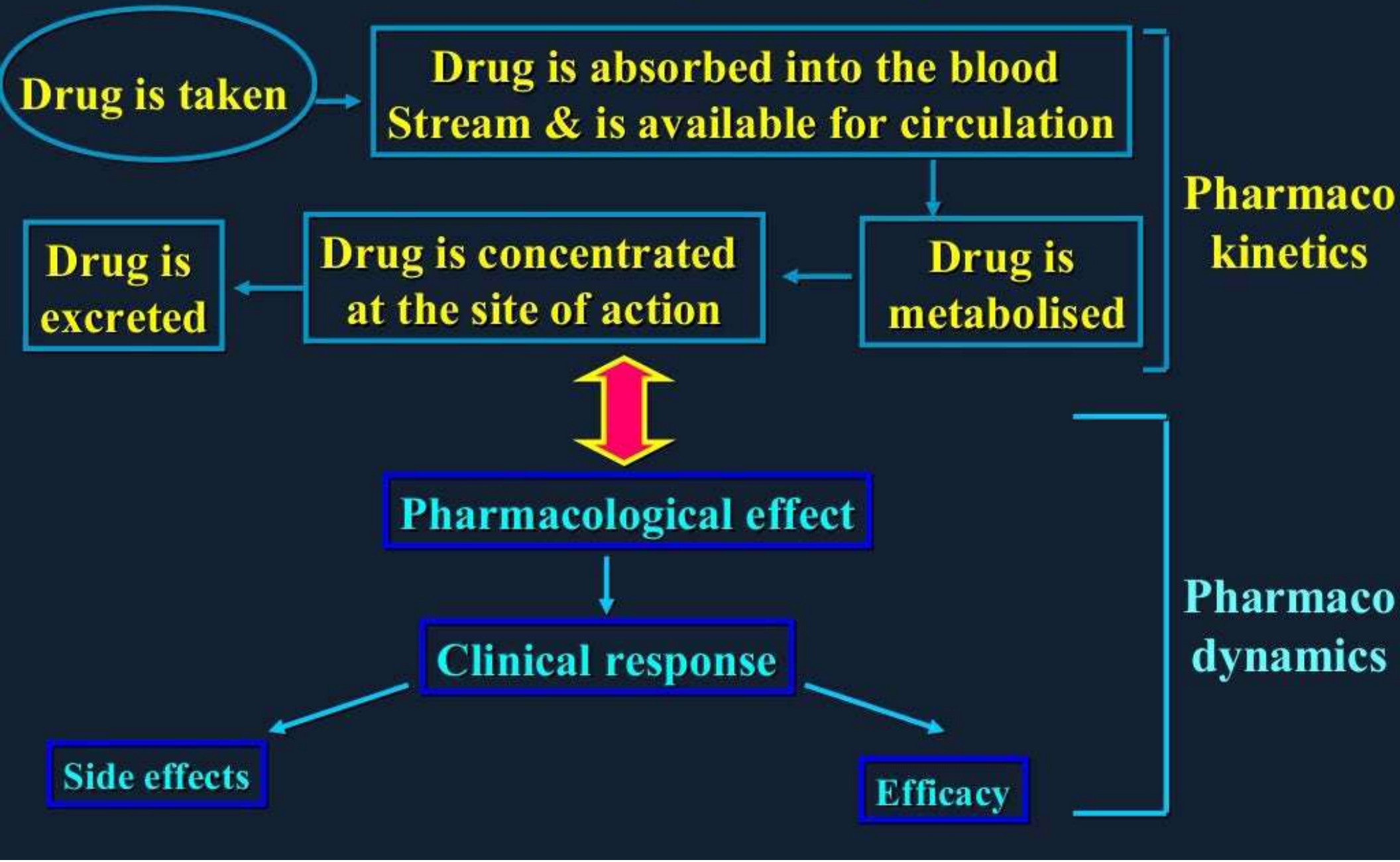
Pharmacodynamics

- Biological and therapeutic effects of drugs

pharmacokinetics

- Absorption, Distribution, Metabolism & Excretion of drugs

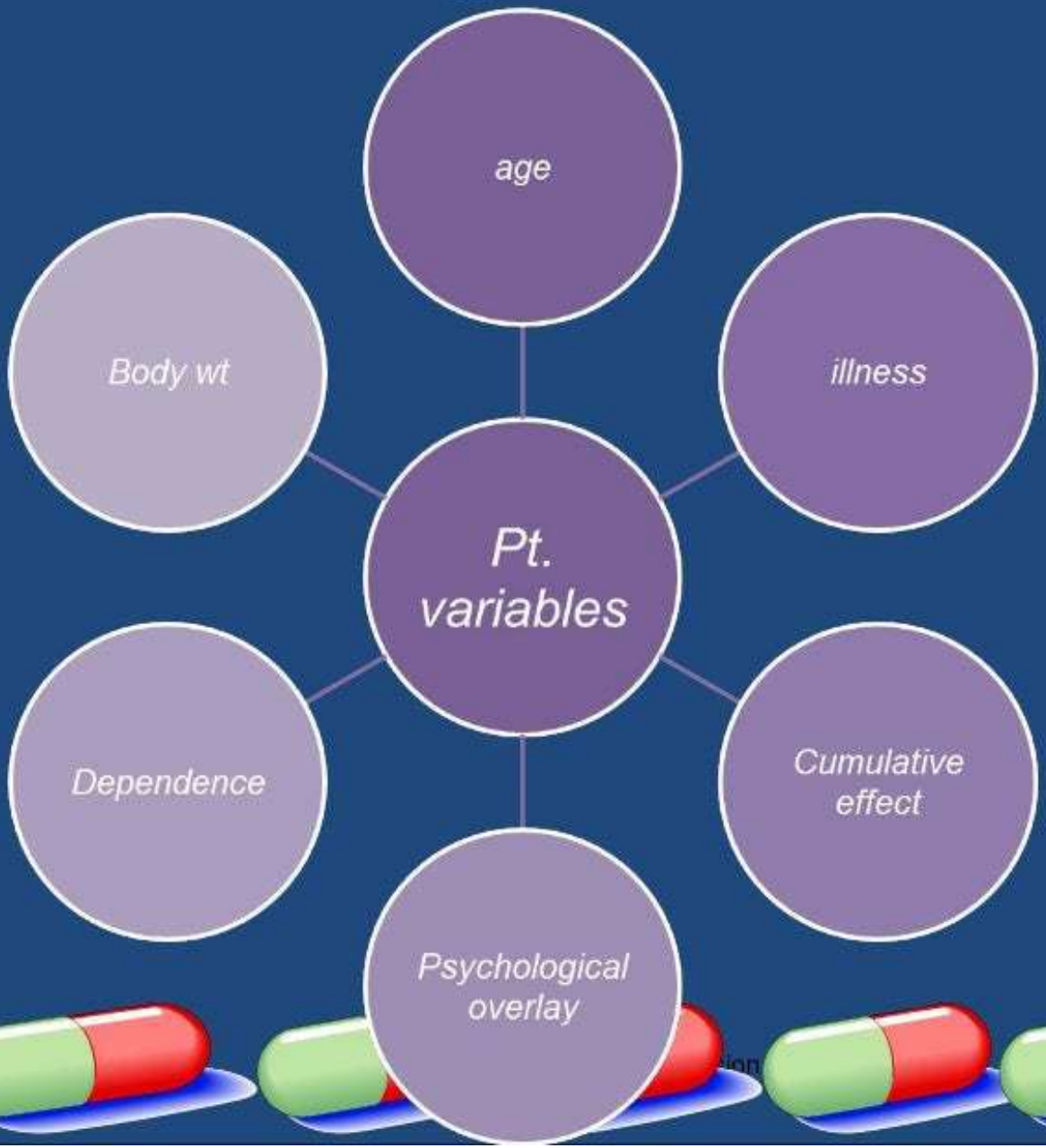
The Relationship between Pharmacokinetic and Pharmacodynamic processes



Drug – and – patient related factors.

- Drug and patient related factors determined the selection of routes for drug administration. These are:
- Characteristics of the drug.
- Emergency/ Routine use.
- Condition of the patient (Unconscious, Vomiting and Diarrhoea)
- Age of patient.
- Associated disease.
- Patients/ Doctors choice (Sometimes)

Patient Variables that may affect Drug Action



Pharmacokinetics

Absorption

Distribution

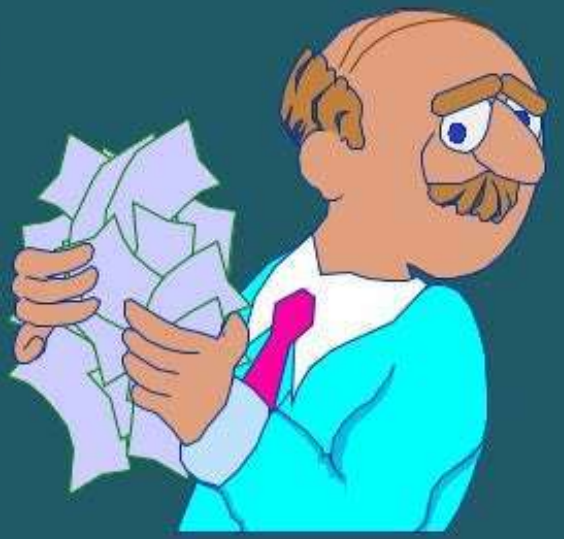
Metabolism

Excretion

Basic pharmacology - Agenda

- Definitions
- Classification of Drugs
- Routes of administration & drug formulations
- Dose regimes & plasma levels
- Package insert information
- Scheduling of drugs
- Pharmacodynamics

Package insert information (Literature)



- Composition (drug/dose per tablet)
- Schedule
- Pharmacological classification
- Pharmacological action
- Indications
- Contra-indications
- Dosage & directions for use
- Side effects & special precautions
- Known symptoms of overdose & particulars of its treatment
- Identification (physical description of tablet)
- Presentation (package details)
- Storage instructions
- Registration number
- Name of applicant

Pharmacodynamics: Mechanisms of Action

The ways by which drugs can produce therapeutic effects:

- Once the drug is at the site of action, it can modify the rate (increase or decrease) at which the cells or tissues function.
- A drug cannot make a cell or tissue perform a function it was not designed to perform.

Pharmacodynamics

- The effect the drug has on the body
- Based on either:
  - Non-specific action
  - Binding with a receptor
  - Enzyme interaction

Pharmacodynamics

Non-specific action depends on the drug's accumulation in cell membranes

Specific actions result from the drug becoming affixed to the receptor i.e. binding to receptors

Drugs can only increase or decrease cell function - they cannot totally alter the action of the specific cell

Mechanism of Action

Mechanism of action

- **Cell membrance**
- **Metabolic processes Within the cells**
- **Outside the cell**

Clinical Pharmacology,Laurence;1997: pg 7812

Cell Membrance

Specific receptors-agonists and antagonists on adrenoceptors

Interference with selective passage of ions across membracnes eg: Calcium channel blockers

Outside the cell

Direct chemical interaction eg: chelating agents, antacids

Osmosis with diuretics like mannitol

Receptor

Protein macromolecules

Agonist to receptor → proteins alter → induces changes within cell → response to drug

Agonists : activate receptors

Antagonists : blockers of receptors

Clinical Oharmacology, Laurence; 1997, pg:78

Additive Effect

1 + 1 = 2

When the total pharmacological action of Two or more drugs administered together Is equivalent to the summation of their Indicidual pharmacological actions

Eg: ephedrine + aminophylline in treatment of bronchial asthma

Pharmacology & Pharmacotherapeutics, Satoskar;1997: pg 45

Synergistic effect

1 + 1=X (>2)

When the total pharmacological action of Two or more drugs administered together Is more than the summation of their individual pharmacological actions

Eg: cotrimoxazole(sulphamthoxazole +pyrimethamine) Septran

Pharmacology & Pharmacotherapeutics, Satoskar;1997: pg 45

Terminology

 # Bioavailability

- *the extent of the drug which is delivered to the circulation (expressed as %)*

 # Bioequivalence

- *the rate and extent of absorption of two products is equivalent - 'no significant difference'*

Drug uses

- # Curative, as primary therapy (bacterial / parasitic infections), or auxilary therapy (anaesthetics, ergometrine and oxytocin in obstetrics)
- # Suppressive of disease/symptoms, used continuely or intermittently to maintain health with out attaining cure as in hypertension, diabetes, epilepsy, asthama/ to control symptoms such as pain and cough, while awaiting recovery from cause
- # Preventive (prophylactic), as when a non-immune person enters a malarial area or contraception

Using more than one drug simultaneously

Possible responses:

- The drugs have no effect on each other
- Antagonism - the combination results in a lower response than when either is given on its own
- Potentiation - the response rate of the two drugs when combined is more than the sum of their independent response rates
- Synergy - the combination offers greater effect than the sum of the two products given individually I.e. 1+1=3 or more
- Globally there is a move away from polypharmacy

Adverse Drug Reaction (ADR)

An adverse reaction is a harmful or seriously unpleasant effect caused by a drug at doses intended for therapeutic effect/prophylaxis/ diagnosis which warrants reduction of dose/ withdrawal of the drug and/or foretells hazard from future administration

Degrees of certainty of (ADR)

Definite : time from taking drug is reasonable event corresponds to what is known of drug event ceases on stopping drug even returns on restarting drug

Probable: time sequence reasonable corresponds to what is known of drug ceases on stopping drug not reasonably explanined by patient's disease

Degrees of certainty of (ADR)

Possible : time sequence reasonable corresponds to what is known of drug could be due to disease / other therapy

Conditional : time sequence reasonable corresponds not to what is known of drug cannot be explained by patients disease

Doubtful : event not meeting above criteria

Anaphylaxis

Systemic reaction in a sensitized human subject following repeat injection of a drug like penicillin characterized by laryngeal edema, severe bronchospasm leading to asphyxia, or circulatory collapse.

Eg: Penicillin

Pharmacology & Pharmacotherapeutics, Satoskar;1997: pg 35

Clinical Pharmacology

Scientific study of drug in man

Provides facts for –

- Improving treatment of patients
- Understanding drugs
- Understanding effects of drugs in different age groups

Clinical Pharmacology

#Phase I(pharmacokinetic, dose, safety)

#Phase II(safety & efficacy in Small population)

#Phase III (safety & efficacy in large population)

#Phase IV (Post-marketing Study, safety in special population & new indication)

Clinical Pharmacology

Clinical Trial

Randomized
Non randomized
Controlled
Open
Cross over

Placebo

Latin – "I will please"

Placebo are used for two purposes :

- As a control in scientific evaluation of drugs
- To benefit or please a patient not by any pharmacological actions, but by psychological means

Therapeutic evaluations

Whether a drug is of value and how it may Best be used :

a) formal therapeutic trials

b) surveillance studies for both efficacy and adverse effects

Patient Compliance

Patient takes prescribed drug

Failure due to :

1) Non comprehension of instructions
    a) Inadequacy of doctor
    b) Inadequacy of patient
2) Comprehension, but failure to carry out instructions

Factors for Noncompliance

Disease –

Regimen –

Source of Medicine –

Doctor / Patient Relation –

Patient -

- **# Psychiatric diagnosis**
- **# Complexity**
- **# Long duration**
- **# Time wasting**
- **# Inconvenient clinics**
- **# Inadequate supervision**
- **# Patient dissatisfaction**
- **# Inappropriate health beliefs**

References

1. Dr. P.K. Panwar, Essentials of pharmacology for nurses, AITBS pub. 2017, India, Pg no. 1 – 9.
2. Dr. Suresh k sharma, Textbook of pharmacology, pathology & genetics for nurses, Jaypee pub. 2016 India Pg no 5 – 22.
3. Tara v. Shanbhag, Smita shenoy, Pharmacology preparation manual for undergraduate, Elsevier pub. 2014. Pg no. 1 – 45.
4. Marilyn Herbert – Ashton, Nancy Clarkson, Pharmacology, Jones & Barlet pub 2010 India, Pg no 1-2.
5. Madhuri Inamdar, Pharmacology in nursing, Vora medical pub. 2006 India 1st edition, Pg no 1 – 13.

Thanks

Drugs

" Poisons in small doses are the best medicines; and useful medicines but in too large doses they are poisonous"

Willam Withering (1741 – 1799) MD, FRS

Local anesthetics

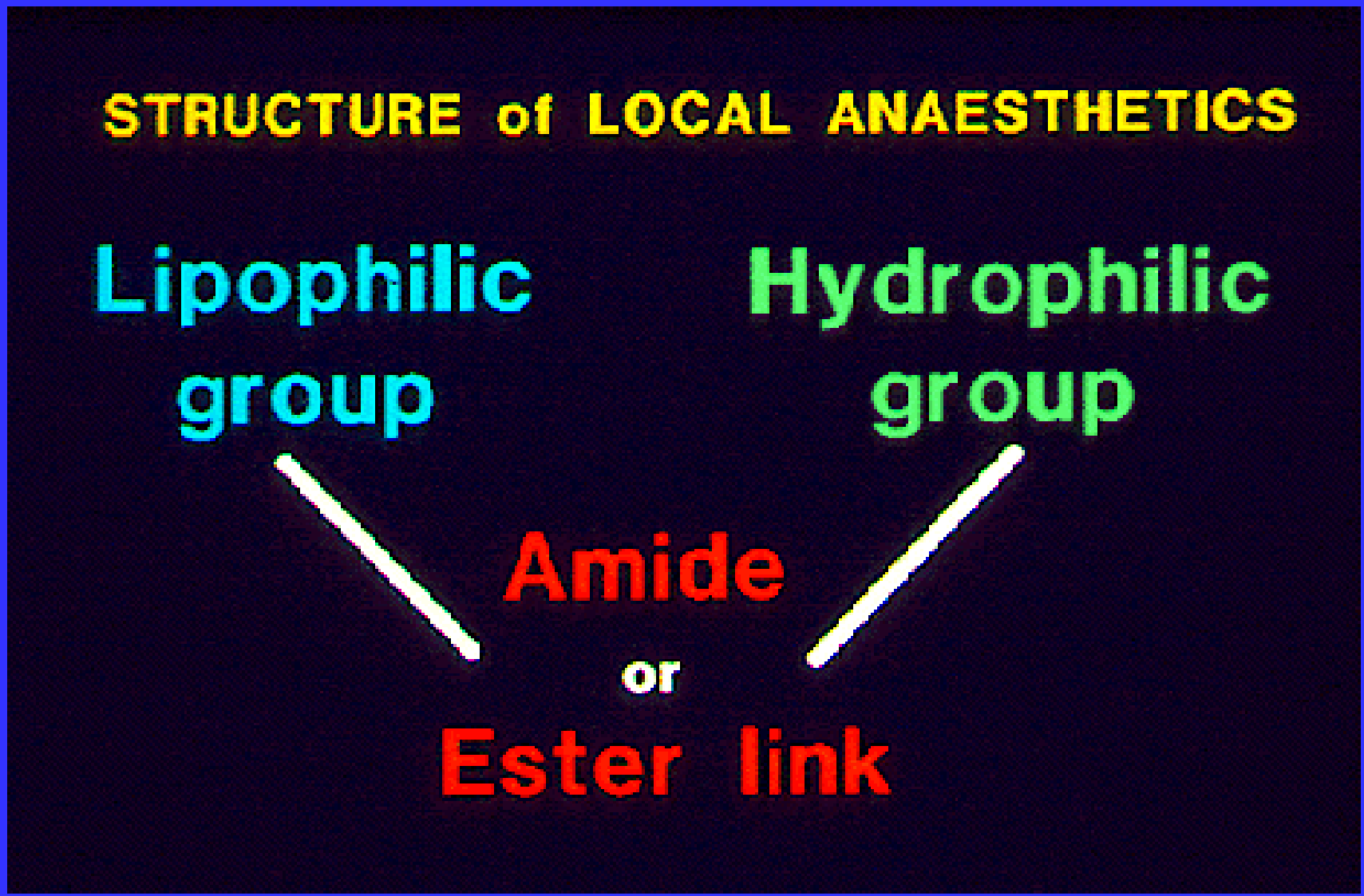
Objectives

- Recall how an action potential is generated and propagated
- Classify local anesthtics
- Describe the machanism of action, pharmacokinetics and toxic effects of local anesthetics
- Describe the different techniqes of use of LA
- Describe the risks and benefits of using vasoconstrictors with LA

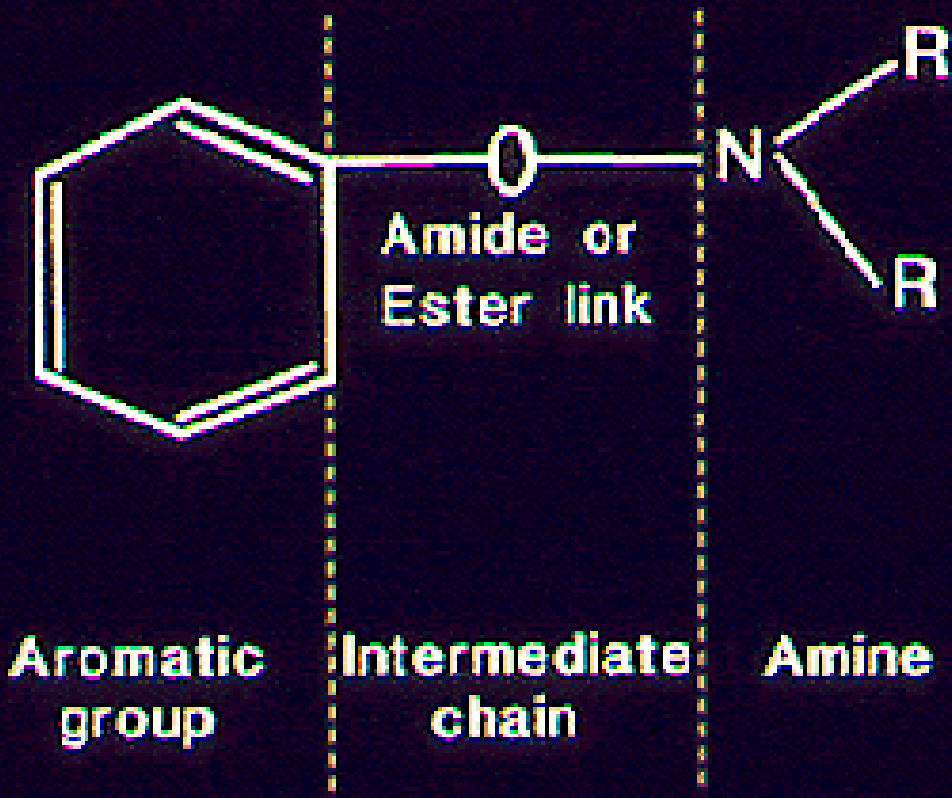
Overview

- Local anesthetics produce a transient and reversible loss of sensation (**analgesia**) in a circumscribed region of the body **without loss of consciousness.**

- Normally, the process is completely reversible.


STRUCTURE of LOCAL ANAESTHETICS
Lipophilic group
Hydrophilic group
Amide
or
Ester link

STRUCTURE OF LOCAL ANESTHETICS



- Local anesthetics - **esters** or **amides**
  - –a lipophilic aromatic group
  - –to a hydrophilic, ionizable amine.
- Most are weak bases

Classification of LA

Esters

Benzocaine

Procaine

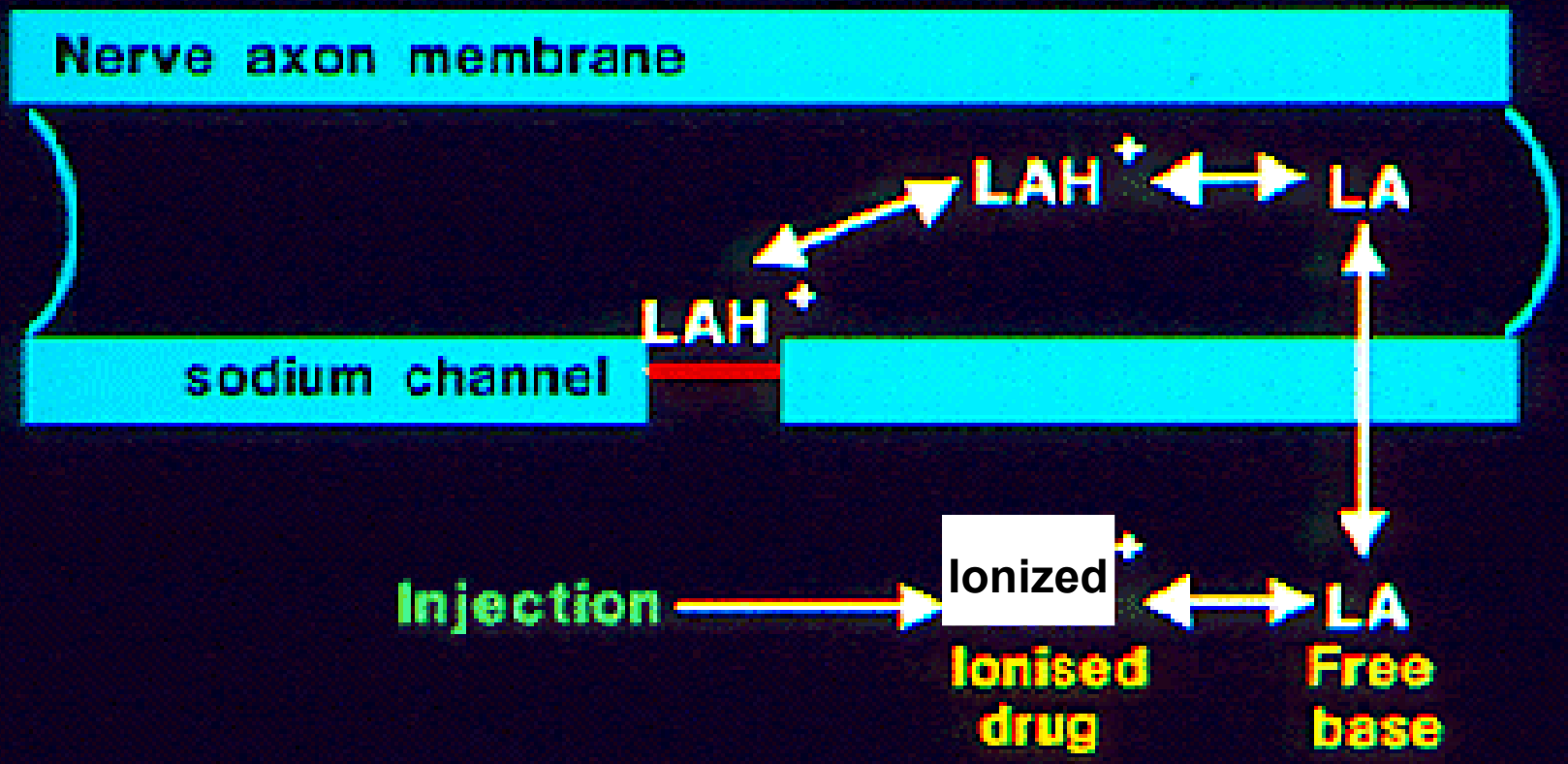
Proparacaine

Classification of LA

Amide

- Bupivacaine
- Levobupivacaine
- Lidocaine/Lignocaine
- Mepivacaine

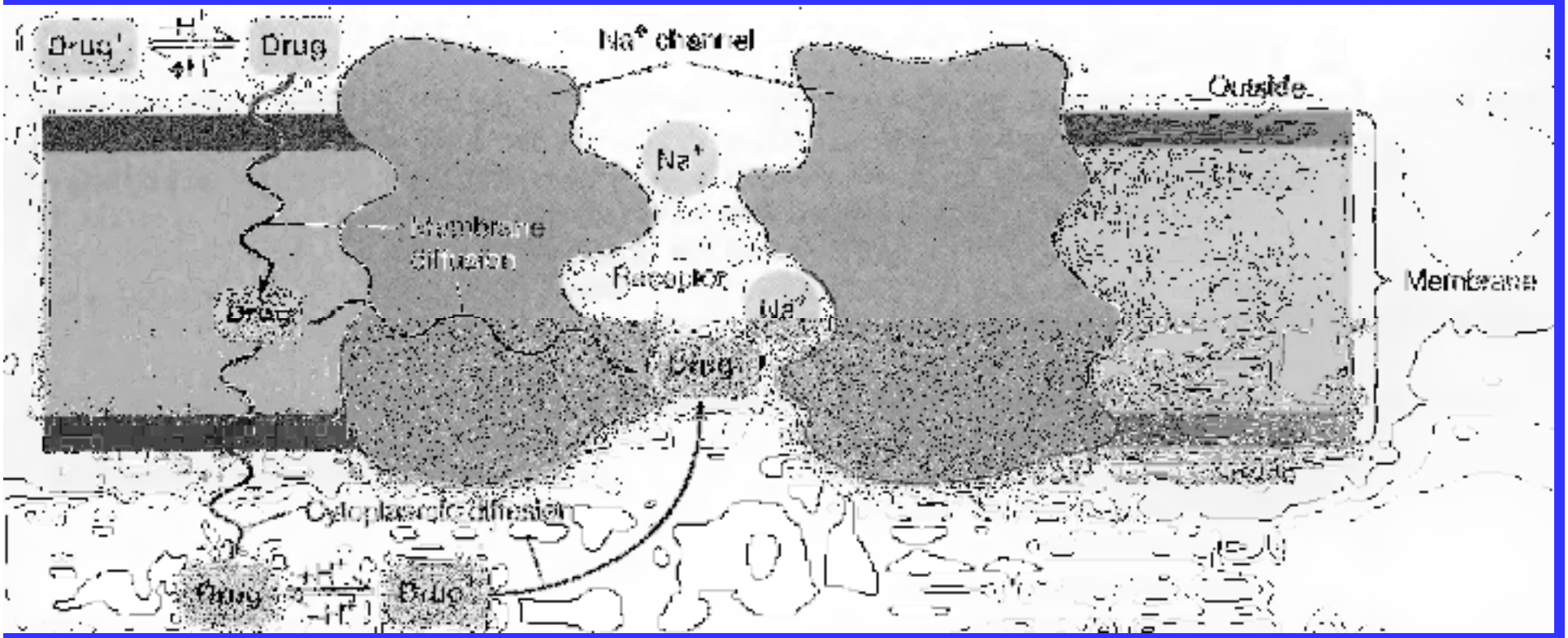
Mode of Action



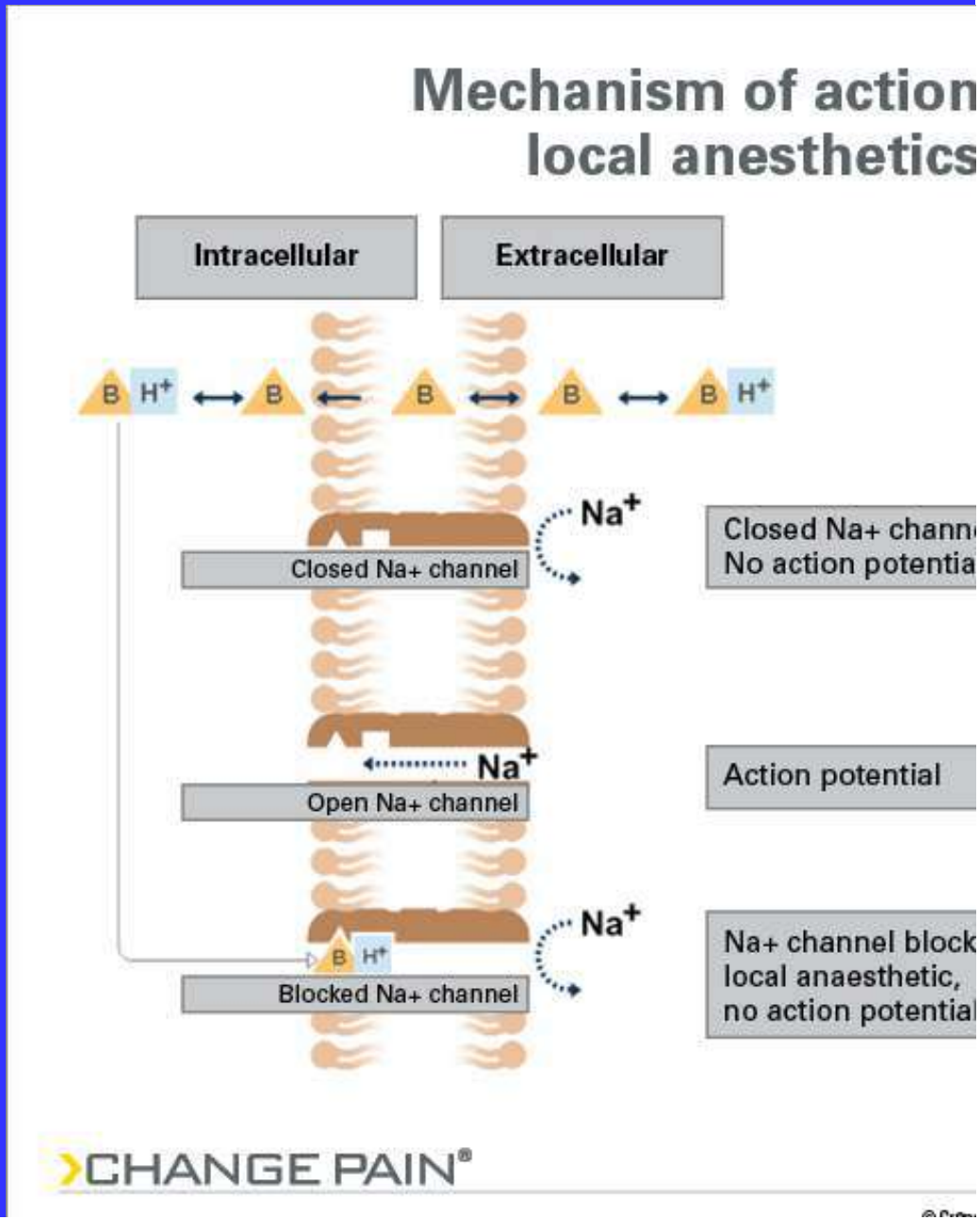
- Local anesthetics gain access to the inner axonal membrane by

  1. traversing sodium channels while they are more often in an open configuration

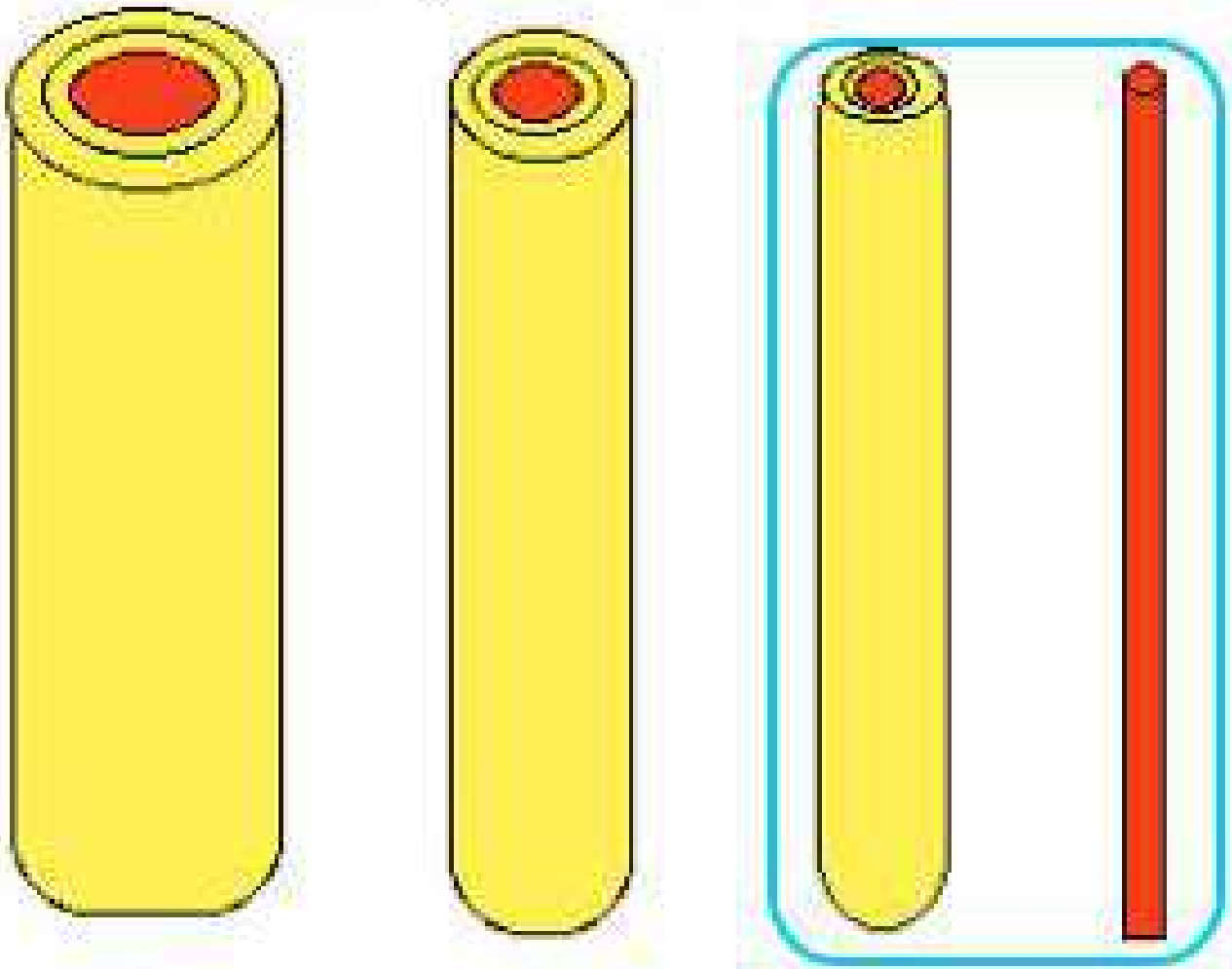
  2. passage directly through the plasma membrane


Drug+
Drug
Na+ channel
Outside
Na+
Membrane diffusion
Receptor
Membrane
Drug
Na+
Drug
Cytoplasmic diffusion
Drug
Drug

- Block inititation and propagation of action potential



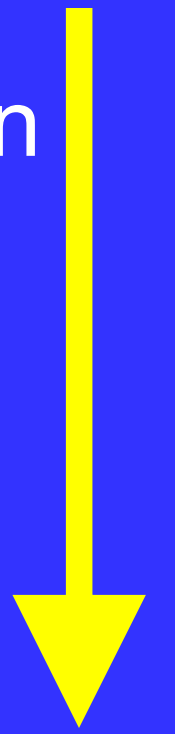
Primary Afferent Axons



Axon Type	Aα	Aβ	Aδ	C
Diameter (μm)	13-20	6-12	1-5	.2-1.5
Speed (m/s)	80-120	35-75	5-35	.5-2.0

Sequence of clinical anesthesia

- Sympathetic block (vasodilatation)
- Loss of pain and temperature sensation
- Loss of proprioception
- Loss of touch and pressure sensation
- Loss of motor function



Anesthetic Potency

- Potency = lipid solubility
- Higher solubility = can use a lower concentration and reduce potential for toxicity

DURATION OF ACTION

- Duration = protein binding
- Bupivacaine 95%
  Lidocaine 65%

Pharmacokinetics

- Effective within 5 min
- Duration of action – 1-1.5 h
- Activity is Ph dependent
- Increased action in acidic ph

CLEARANCE

- ESTERS
  hydrolysis via cholinesterase

- AMIDES
  metabolism via hepatic enzymes

LA

- Infiltration anesthesia
- Regional anesthesia
- Surface anesthesia

LA

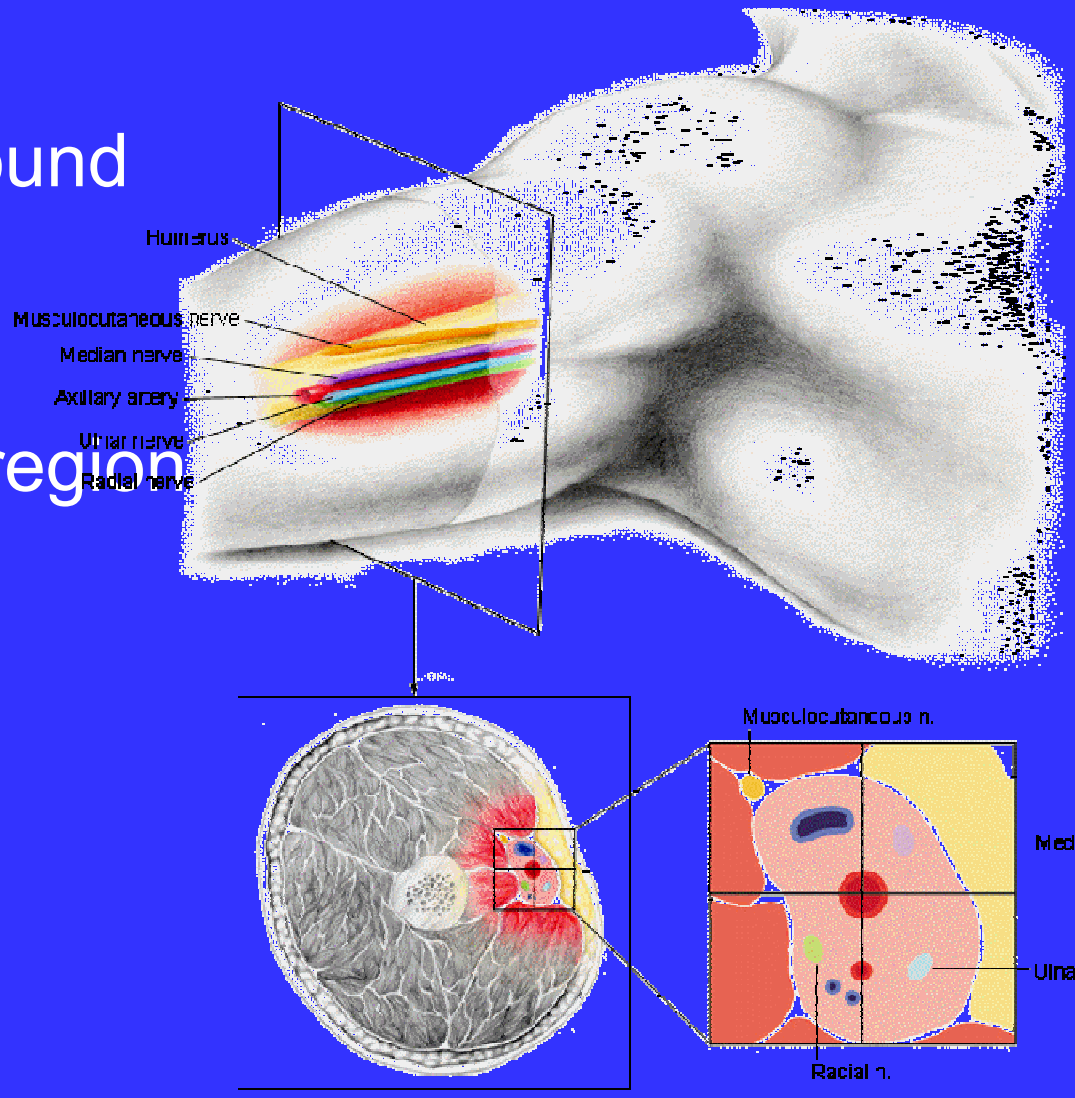
- Infiltration anesthesia
- Regional anesthesia
- Surface anesthesia

Gegional anaesthesia

- Nerve block
- Intravenous
- Extradural
- Intrathecal block/ spinal anaesthesia

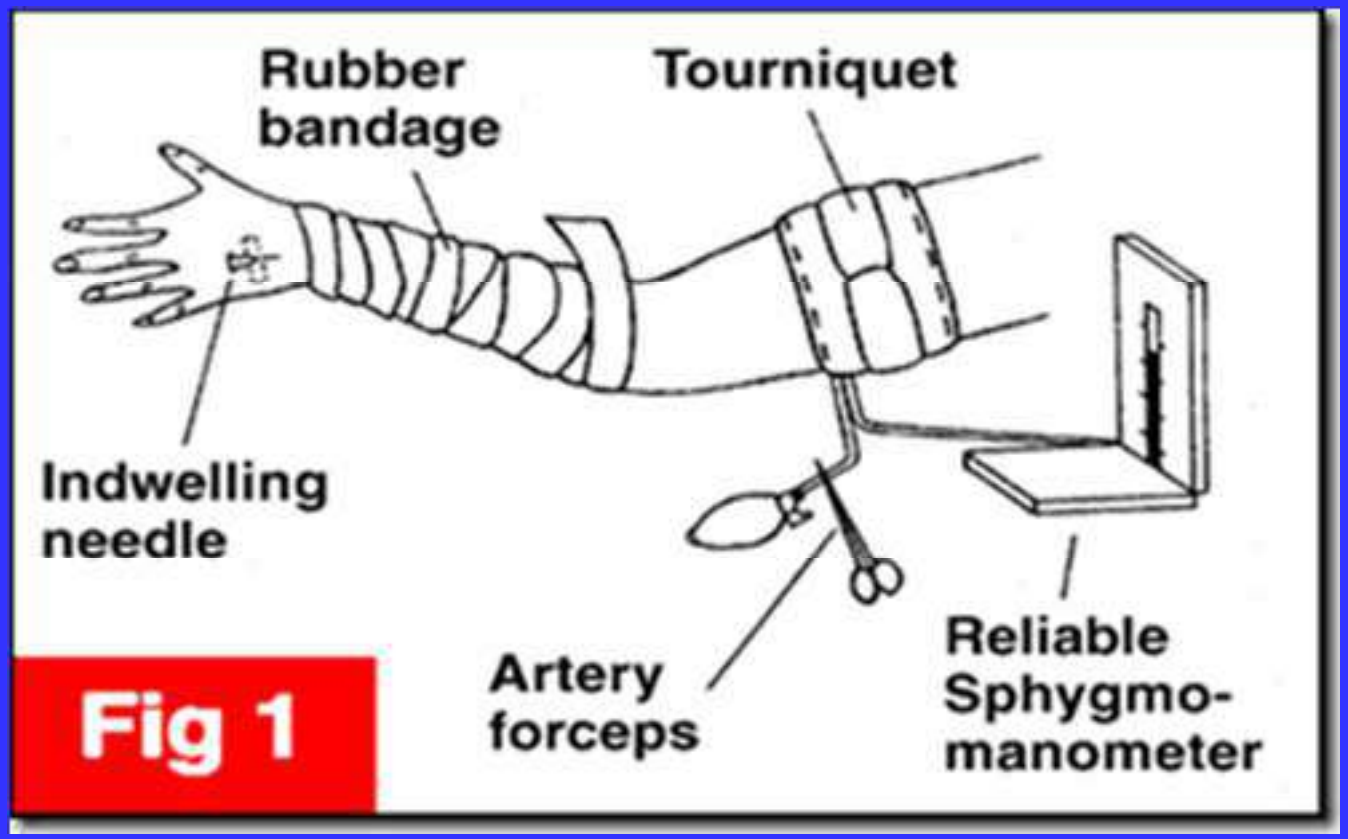
Nerve block

- Inject a drug around the nerve
- Anaesthetise a region



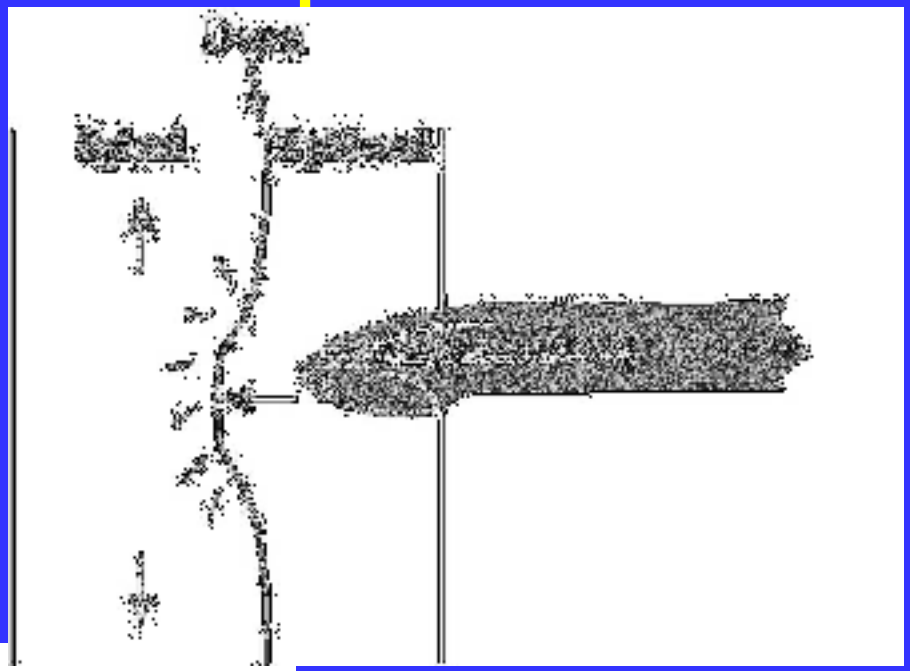
Intravenous

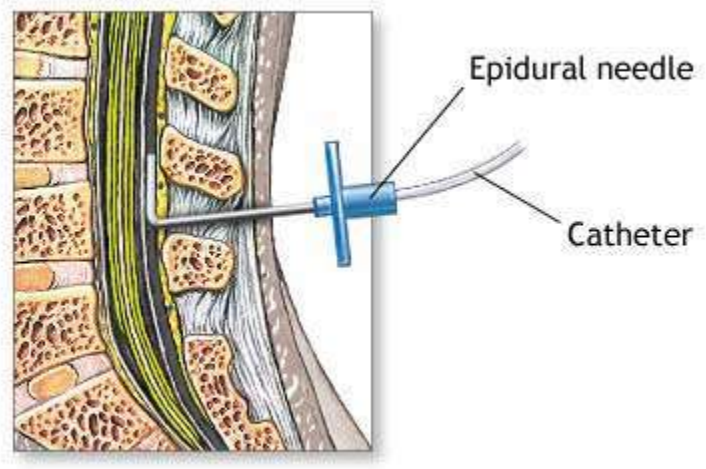
- 0.5-1% lidocaine without adrenaline

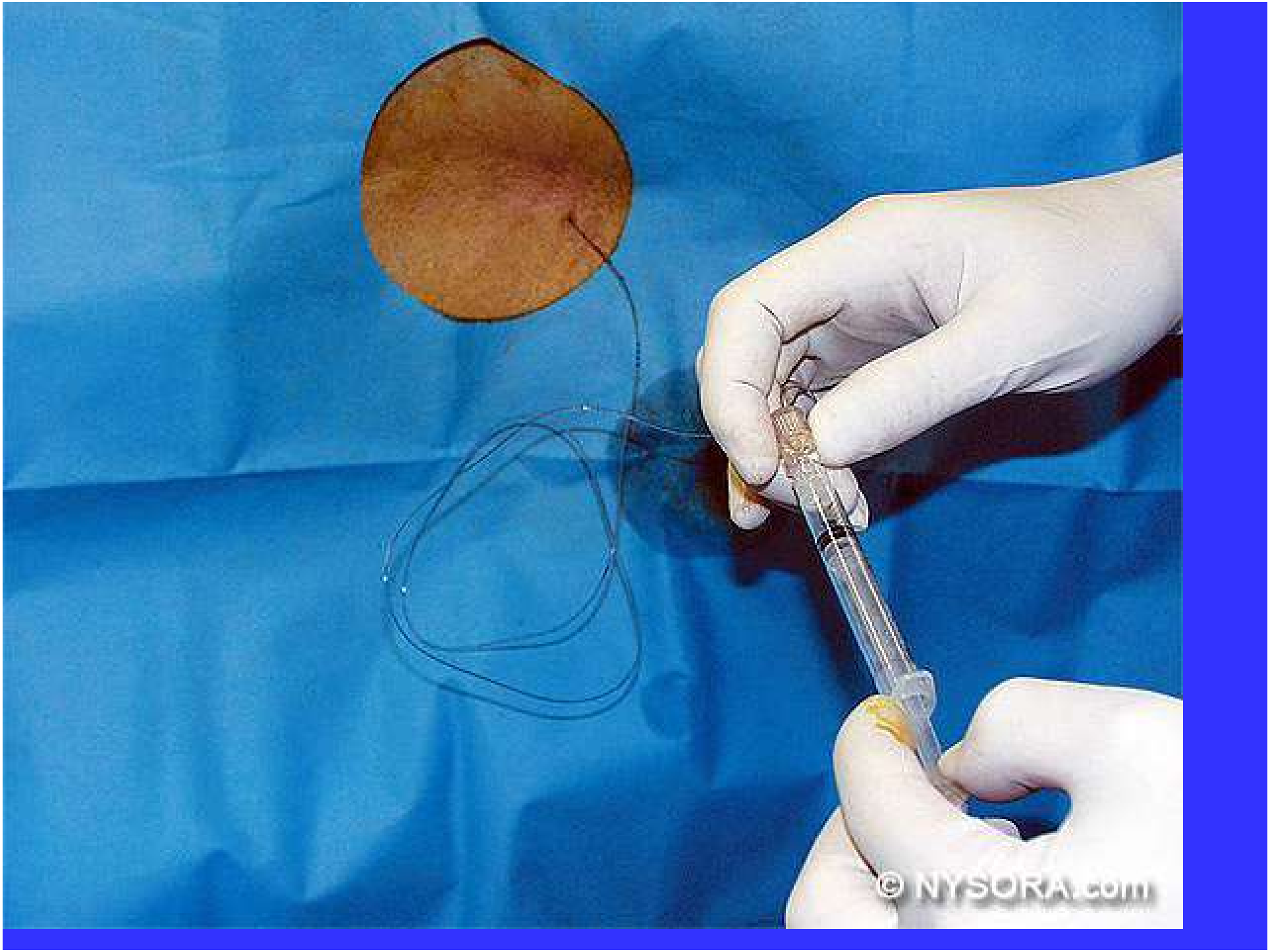


Extradural/epidural

- Thoracic, lumbar, sacral
- Act on nerve roots
- No hypotention



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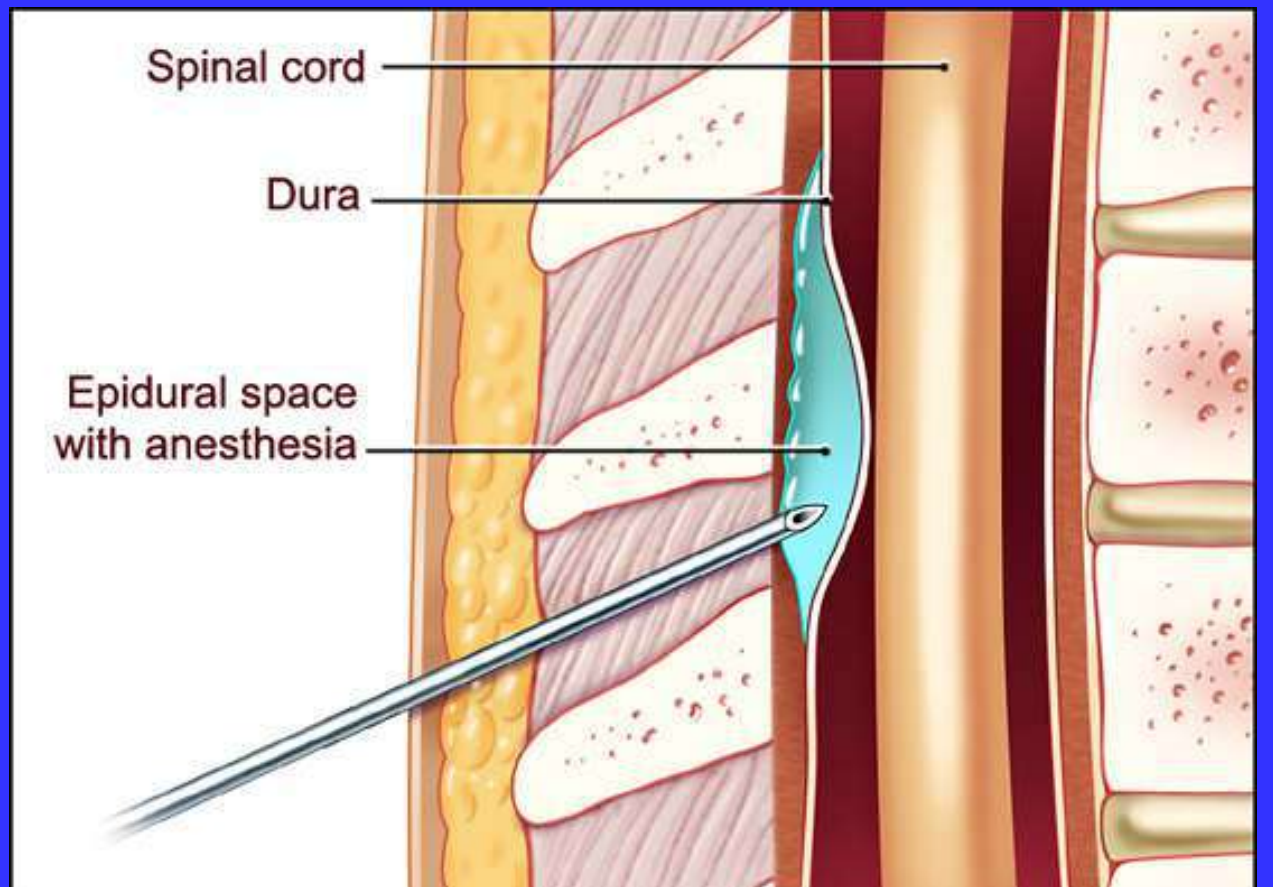
Spinal anesthesia

- Sympathetic nerve block
- hypotension



LA

- Infiltration anesthesia
- Regional anesthesia
- Surface anesthesia

- On intact skin – eutectic mixture of bases of prilocaine (EMLA)
- Slow absorption

Prolongation of action

- Add vasoconstrictor – adrenaline
- Can use a larger dose
- Not to – fingers, toes, nose, penis

Adverse effects

- LA's cause some vasodilatation at site
- LA toxicity related to rate of absorption via blood flow

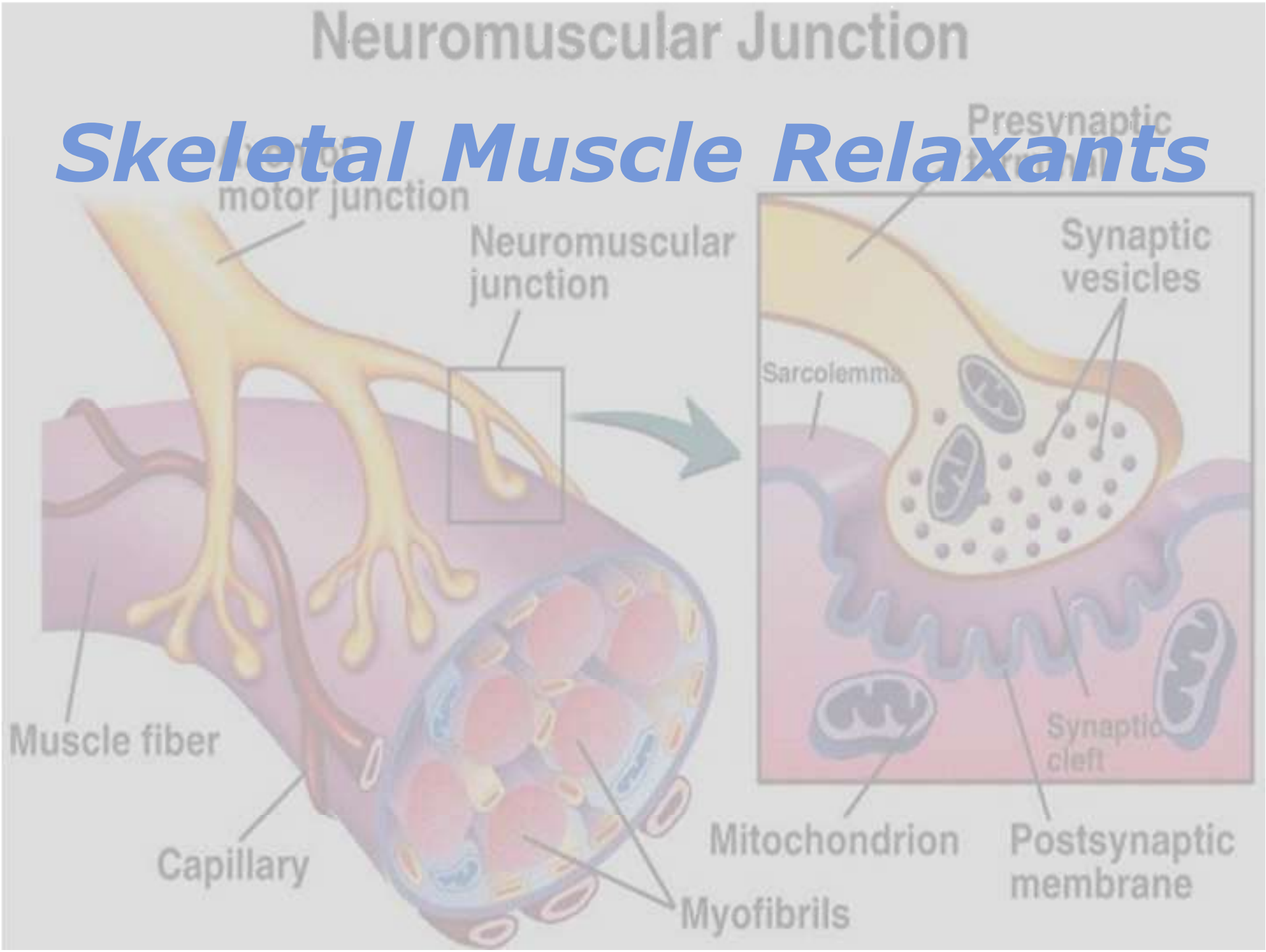
Systemic Toxicity

- Blockage of voltaged-gated Na channel affects action potential propagation throughout the body
- Potential is present for systemic toxicity

Effects of local anesthetics

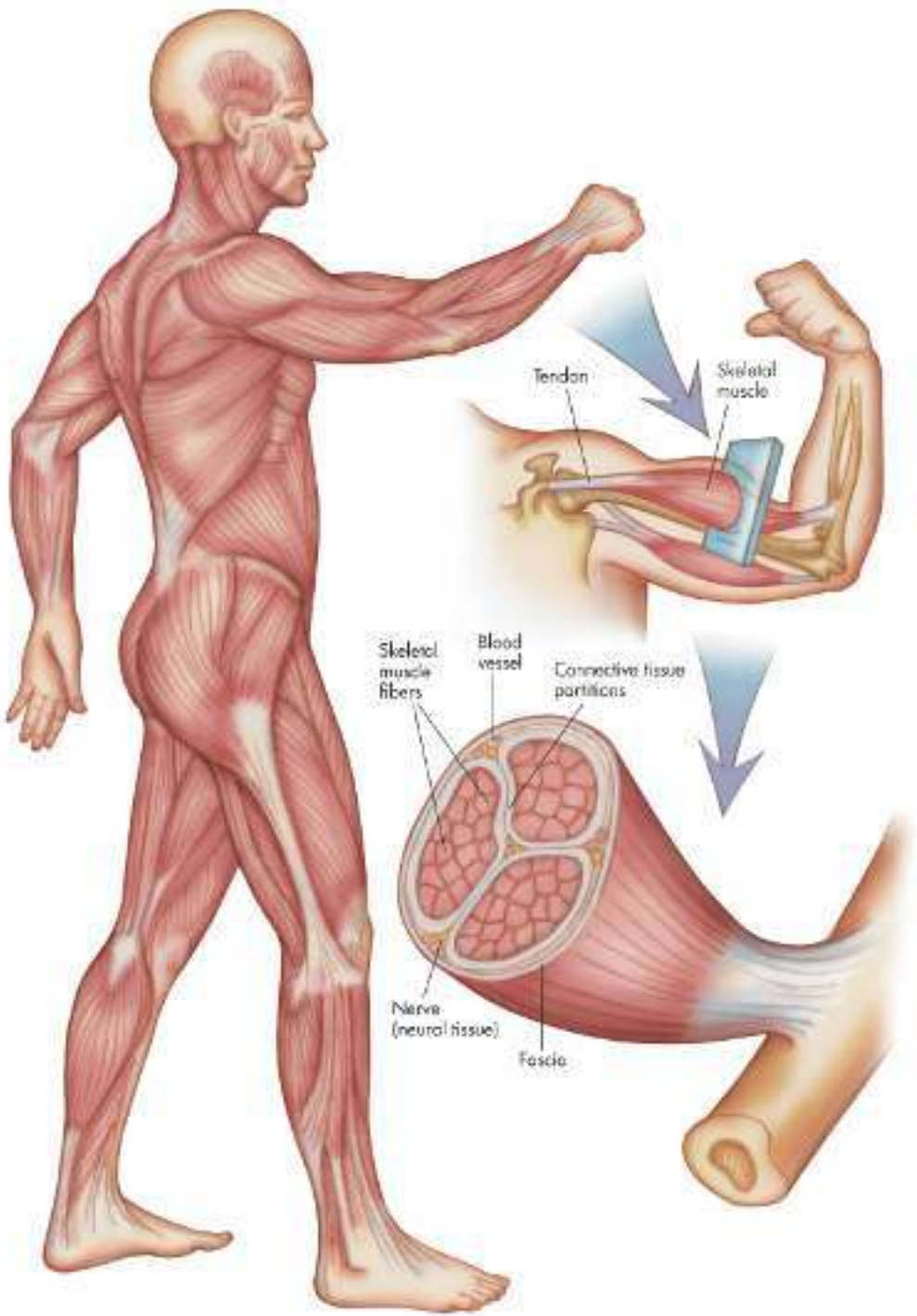
- Excitation – anxiety, agitation, restlessness
- Convulsions
- Reduced myocardial contractility
- Vasodilatation

Skeletal Muscle Relaxants



A skeletal muscle consists of a group of fibers held together by connective tissue.

It is enclosed in a fibrous sheath (fascia).



Types of Muscle Tissue

There are three basic types of muscle tissue classified according to their function and appearance:

- **Skeletal**
- **Smooth**
- **Cardiac**

The muscles have a cross-striped appearance; thus, striated muscle.

There are 600 skeletal muscles that are responsible for the movement of the body.

(continued)

Types of Muscle Tissue

There are three basic types of muscle tissue classified according to their function and appearance:

- **Skeletal**
- **Smooth**
- **Cardiac**

Muscles and nerves work together as a *motor unit*.

(continued)

Types of Muscle Tissue

There are three basic types of muscle tissue classified according to their function and appearance:

- **Skeletal**
- **Smooth**
- **Cardiac**

Also known as *voluntary muscle*.

They are controlled by the conscious part of the brain **(continued)**

MECHANISAM OF CONTRACTION

AP DEPENDS UPON Na^{+2} CHANNELS

⇓

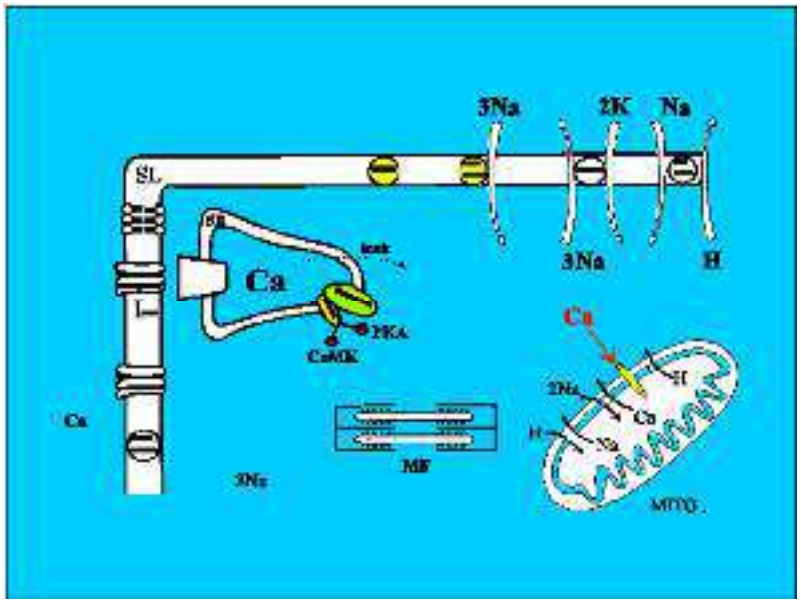
T TUBULE MEMB. CONTAIN DHPR

⇓

RESPOND TO MEMB. DEPOLAR^{N} CONDUCTED PASSIVELY ALONG THE T TUBULE WHEN PLASMA MEMB.INVADED BY AP

⇓

DHPR LINK TO RyR IN THE ADJUSTMENT SR



⇓

RELEASE Ca^{+2} FROM SR INTO SARCOPLASAM

⇓

BINDS TO TROPONIN WHICH BLOCKS THE INTERACTION B/W A & M

⇓

TROPONIN MOVES OUT OF THE WAY

⇓

ALLOWS CONTRACTILE MACHINERY TO OPERATE

-THE RELEASE OF Ca^{+2} IS RAPID & BRIEF

-MUSCLE RESPOND TO SHORT LASTING TWITCH RESPONSE

Skeletal muscle relaxant

"These are the drugs that act peripherally at neuromuscular junction/muscle fibre or centrally in the cerebrospinal axis to reduce muscle tone &/or cause paralysis"

History

16th century – Amazon basin – arrow poisoning (curare active material)

1805 – Von Humboldt – botanical sources
(strychnos sp, chondrodedron tomentosum)

1856 – Claude Bernard – paralytic action of curare.

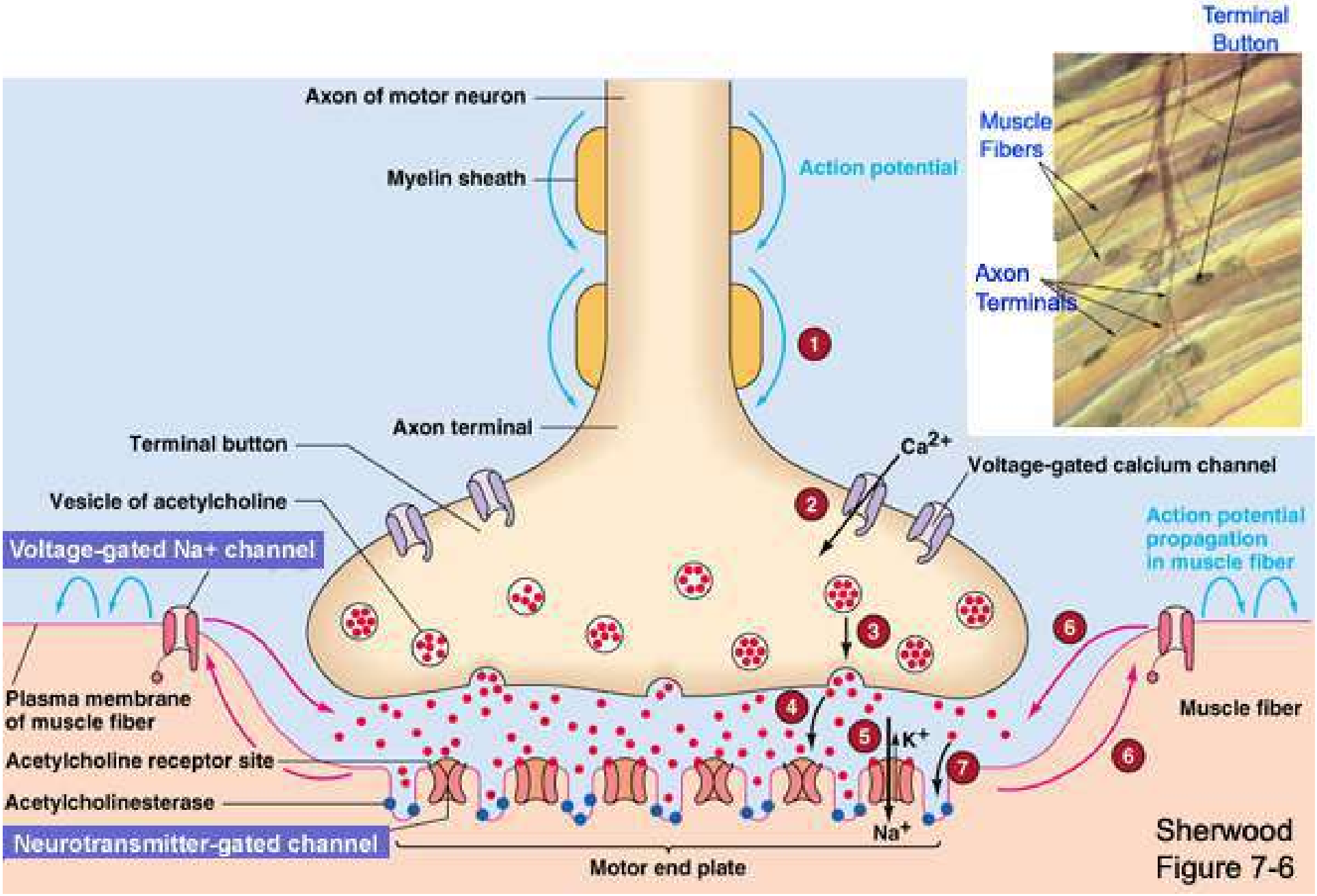
1932 – West – highly purified fraction of curare – tetanus & spastic disorders

1935 – King – structural formula of d-TC,its optical activity.

1942 – Griffith & Johnson – during surgery.Ist trial

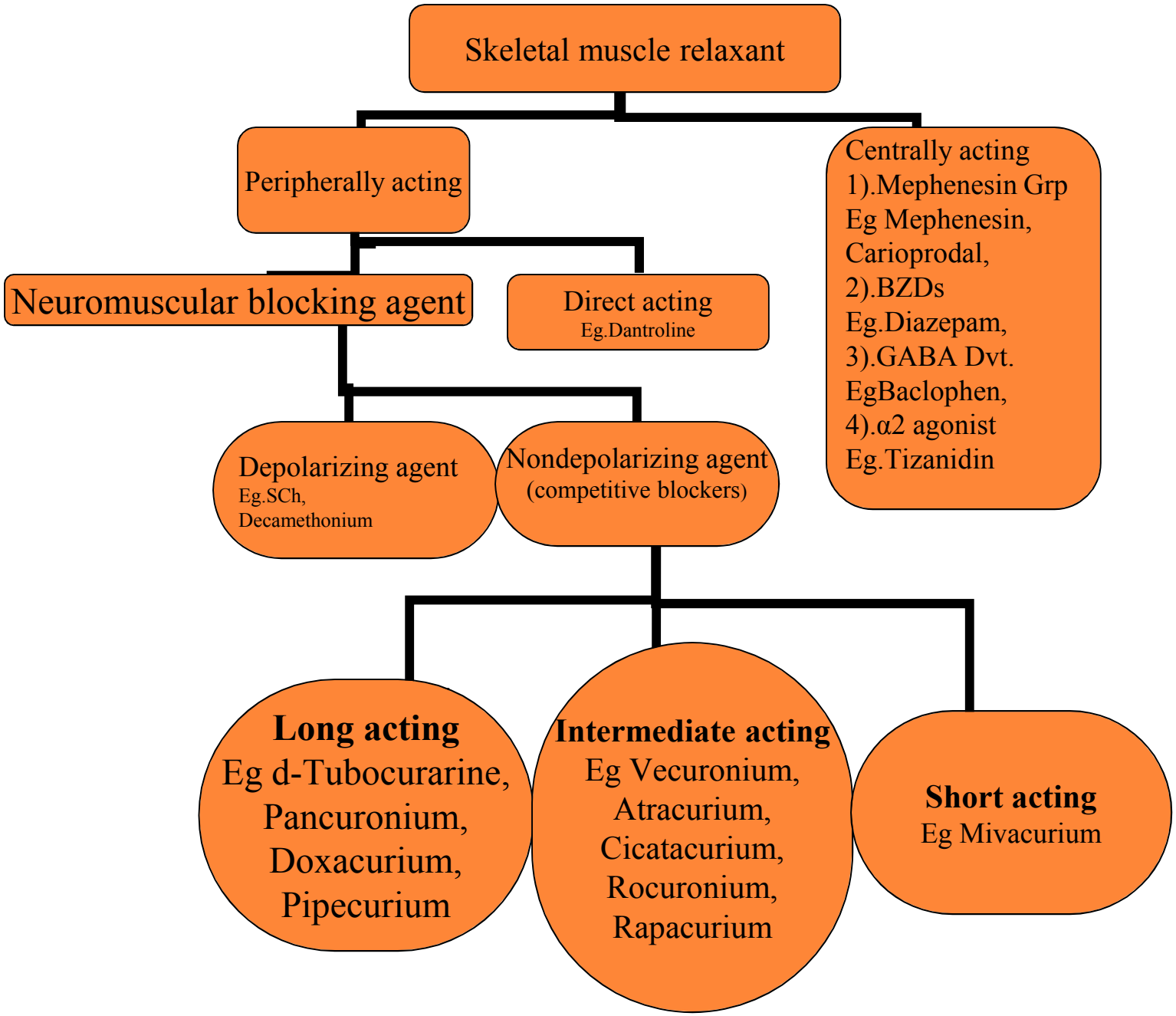
1949 – Bovet – Gallamine(semisyntetic)

The Neuromuscular Junction



CLASSIFICATION

1. SITE OF ACTION
2. DURATION OF ACTION
3. CHEMICAL NATURE.
4. ONSET OF ACTION


Skeletal muscle relaxant
Peripherally acting
Centrally acting
1).Mephenesin Grp
Eg Mephenesin,
Carioprodal,
2).BZDs
Eg.Diazepam,
3).GABA Dvt.
EgBaclophen,
4).α2 agonist
Eg.Tizanidin
Neuromuscular blocking agent
Direct acting
Eg.Dantroline
Depolarizing agent
Eg.SCh,
Decamethonium
Nondepolarizing agent
(competitive blockers)
Long acting
Eg d-Tubocurarine,
Pancuronium,
Doxacurium,
Pipecurium
Intermediate acting
Eg Vecuronium,
Atracurium,
Cicatacurium,
Rocuronium,
Rapacurium
Short acting
Eg Mivacurium

Agent	Pharmacological Properties	Onset time (min)	Duration (min)	Chemical Nature
Succinylcholine	Ultrashort acting; Depolarizing	**1-1.5**	**6-8**	Dicholine ester
D-tubocurarine	Long duration; Competitive	**4-6**	**80-120**	Natural alkaloids
Atracurium	Intermediate duration; Competitive	**2-4**	**30-40**	Benzyl isoquinolin
Mivacurium	Short duration; Competitive	**2-4**	**12-18**	Benzyl isoquinolin
Pancuronium	Long duration; Competitive	**4-6**	**4-6**	Ammonio Steroids
Rocuronium	Intermediate duration; competitive	**1-2**	**1-2**	Ammonio Steroids

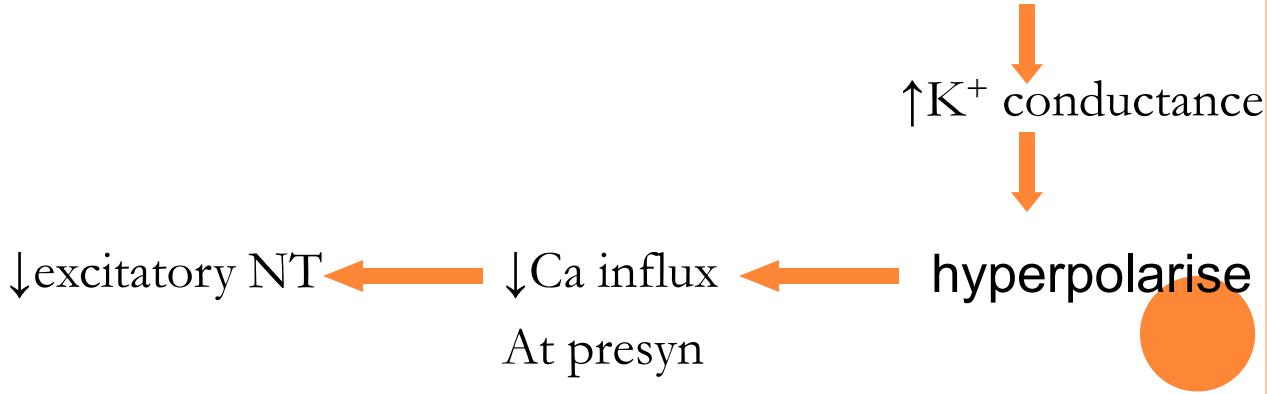
MOA - CENTRALLY ACTING

1).Benzodiazepines: diazepam

- Facilitating action of GABA in CNS.
- Acts at all $GABA_A$ synapses.

2).GABA Dvt.

Baclofen: orally active GABA mimetic- $GABA_B$



3).MEPHENESIN GRP

MEPHENESIN

4)A_2 AGONIST

TIZANIDINE

M/A

INHIBIT THE RELEASE OF EXCITATORY AA FACILITATE INHIBITORY TRANSMITTER GLYCINE

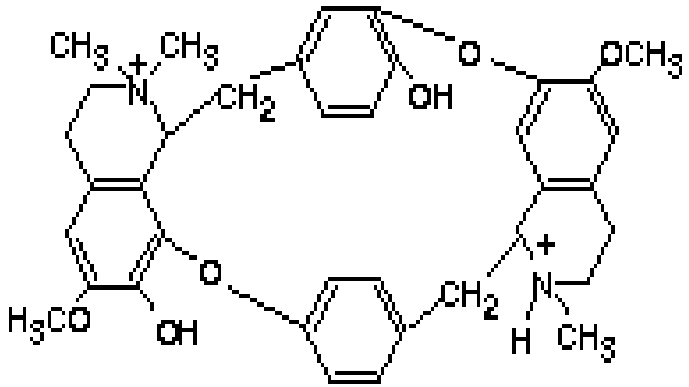
↓

INHIBITS POLYSYNAPTIC REFLEX

↓

DECREASE MUSCLE TONE & FREQUENCY OF SPASM

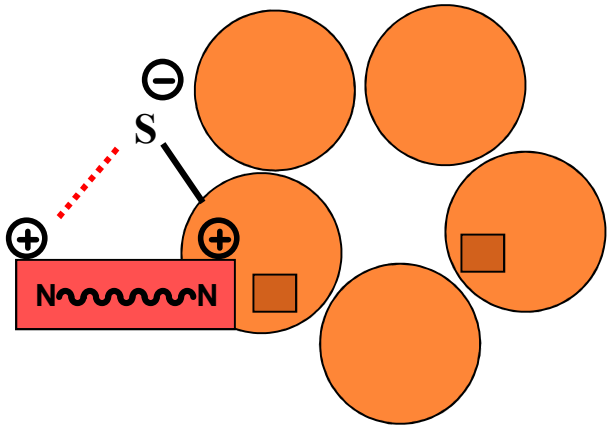
1. Nondepolarizing (competitive) blocking agents (antagonists):



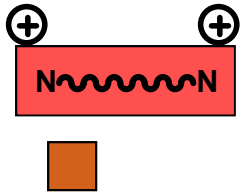
d-tubocurarine

MOA-nondepolarizing agents
Cholinergic Antagonists (Nicotinic receptor)

Binding



b) Interaction with tubocurarine

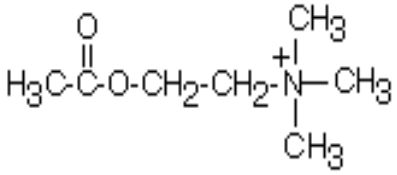


Tubocurarine

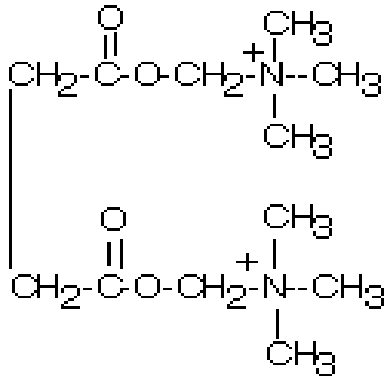
Acetylcholine binding site

BLOCKADE IS REVERSED BY ANTICHOLINESTERASE

2. Depolarizing blocking agents:



Acetylcholine



Succinylcholine

--compose of 2 ACh molecules linked together
-effects similar to ACh but longer effect
-nicotinic agonist (not antagonist) ----> flaccid paralysis

MOA OF DEPOLARIZING AGENTS

Phase I Block

Binding of Sch to nicotinic receptors

↓

Opening of Na+ channels & Na+ influx

↓

Depolar^{n} of muscle EP

↓

Contraction

↓

Unlike Ach not hydrolyzed by AchE

↓

Persist for longer duration at NMJ

↓

Depolarizing is long lasting

↓

Repetitive excitation

↓

Fasciculation & Twitching

Phase II Block

End plate depolarized from –80 to –50 mV during phase 1

↓

Ach bind with this memb.

↓

Resistant to further depolar^{n}

↓

Blockage of neurotransmission at receptor site

↓

Na+ channel block

↓

Gradual repolarization

↓

Flaccid Paralysis

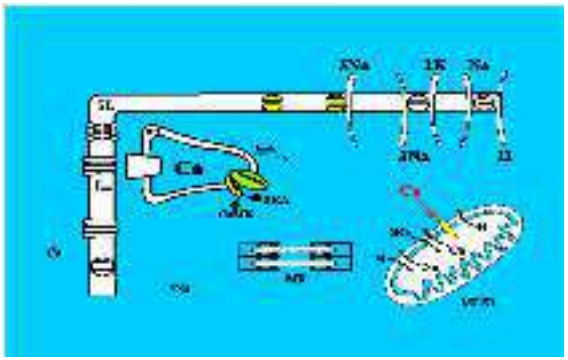
Reversal:

Cholinesterase inhibitors can't reverse effects of Sch or other depolarizing blockers in phase **II.**

MOA: DIRECTLY ACTING *DANTROLENE*

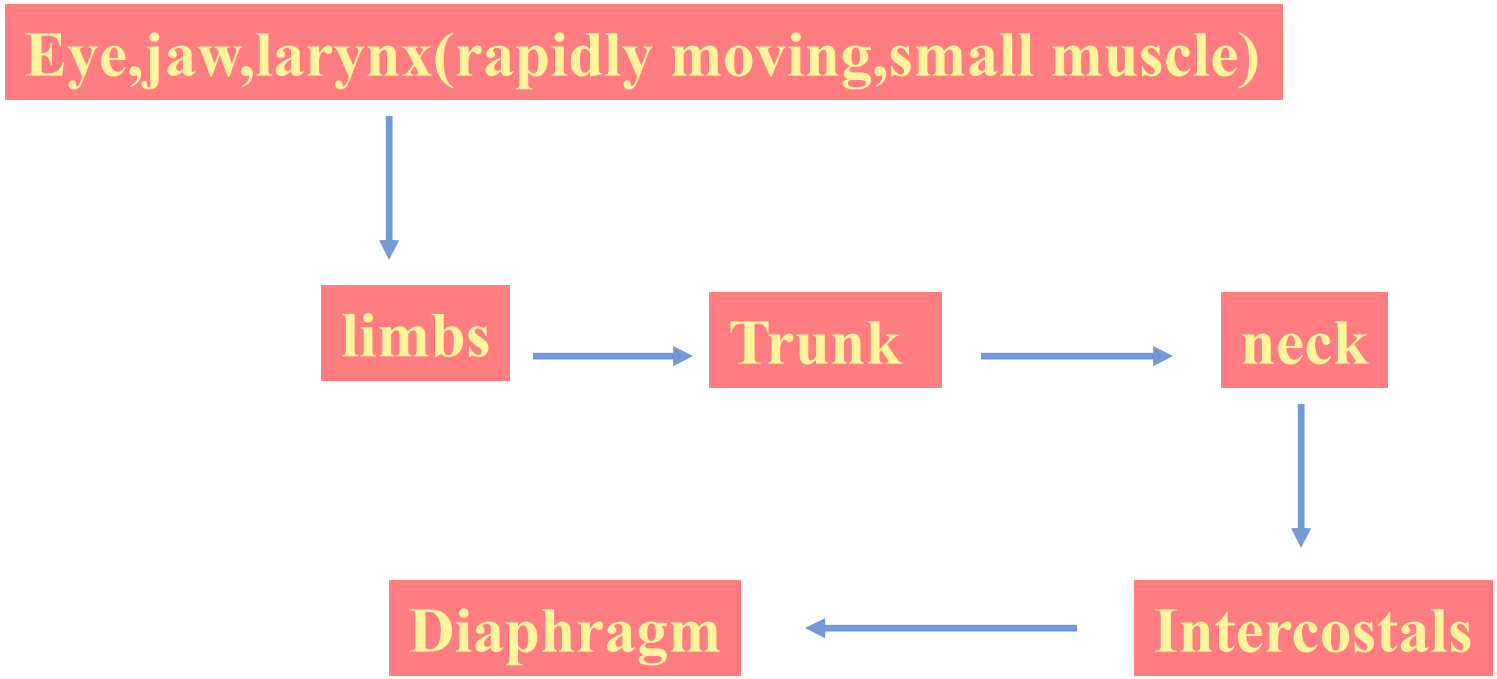
Ryanoid rec →
interferes with Ca
release from

sarcoplasmic reticulum



Rapid contracting Motor unit

Sequence of Paralysis (comp.)



Recovery in Reverse

PHARMACOLOGICAL ACTIONS

	Competitive	**Depolarising**
CNS:	-No action	-No action
Autonomic ganglia:	- partial blockade Aut G- ↓ BP Adr Med- ↑HR Pancuronium:vagal Bl,Gang+	Vagal +n → Bradycardia Aut Gang + → HTN, tachycardia

G I T

Competitive

- Enhance post operative paralytic ileus

Depolarising

Increases:

- Intragastric pressure
- Salivation
- Gastric secretion
- peristalsis

Respiratory system

Bronchosasm
atracurium

Histamine release

Competitive

d-tc→ mast cell

Mivacurium,doxacurium - +

Pancuronium, pipecuronium, Vancuronium } +/--

Cisatracurium rocuronium } –

Depolarizing

SCh → +

Cardiovasular system

Competitive

B.P. - ↓
Ganglion blockade
Histamine release
↓ venous return

HR - ↑
Vagal ganglionic blockade

Depolarizing

Bradycardia →tachycardia

↓ BP- vasodilatation-musc.
↑BP – aut gang +n

Prolonged administration-
cardiac arrhythmias→ arrest

ADVERSE EFFECTS:

- ✓ Tachycardia, arrhythmias – pancuronium
- ✓ Sever hypotention
- ✓ Sever bronchospasm
- ✓ Anaphylaxis
- ✓ Convusions – at high dose Atracurium (not d-tubocurarine)
- ✓ Hyperkalemia
- ✓ Muscle pain
- ✓ ↑ **IOP**
- ✓ **Malignant hyperthermia(RyR)** } SCh

Therapeutic Use

As an adjuvant in surgical anesthesia to obtain relaxation of SM,particularly of abdominal wall.

NMB of short duration use to facilitate intubations with endotrachial tube ,in laryngoscopy,bronchoscopy & esophagoscopy in combination with general anesthetic agent.

Pharmacokinetics:

Because of positively charged 4° ammonium nitrogen, neuromuscular blockers are highly polar

- don't cross membranes
- must be given IV
- small volume of distribution

Long acting muscle relaxants:

- -not metabolized
- -excreted by kidney
  eg. Tubocurarine

Intermediate acting muscle relaxants:

- -hepatic metabolism and biliary excretion
- -more commonly used but less potent
  eg. vecuronium and rocuronium

SUCCINYLCHOLINE

METABOLIZED BY PLASMA **PSEUDOCHOLINESTERASE**

-ACTIVITY OF PSEUDOCHOLINESTERASE MAY BE ABNORMAL DUE TO GENETIC ABNORMALITIES, TRAUMA, ALCOHOLISM, PREGNANCY

.: BLOCKADE MAY BE LENGTHENED OR SHORTENED

ATRACURIUM

UNUSUAL METABOLISM BY HYDROLYSIS OF ESTER MOIETY BY PLASMA CHOLINESTERASE & BY HOFFMAN DEGRADATION

BOTH THESE ROUTE REMAIN FUNCTIONAL IN RENAL FAILURE

Opioids

- Opioid
  - Compound with morphine-like activity
- Opiate
  - Substance extracted from opium
  - Exudate of unripe seed capsule of Papaver somniferum
  - Contain 2 types of alkaloids

Phenanthrene derivatives

- Morphine (10% in opium)
- Codeine (0.5% in opium)
- Thebaine (0.2% in opium), (Nonanalgesic)

Benzoisoquinoline derivatives

- Papaverine (1%)
- Noscapine (6%)

} Nonanalgeslic

Opioids

- Mordern definition of opioid
  - Molecule that interact with opioid receptor
- Opioid compound
  - Opioid receptor agoninsts, antagonists, agonists-antagonists
  - Natural products, synthetic and semisynthetic compounds
  - peptides synthesized by neurone and other cell

CLASSIFICATION OF OPIOIDS

Natural opium alkaloids:

- Morphine
- Codeine

Semisynthetic opiates:

- Diacetylmorphine (Heroin)
- Pholcodeine

Synthetic opioids:

- Pethidine (Meperidine)
- Fentanyl, Alfentanil, Sufentanil, Remifentanil
- Methadone
- Dextropropoxyphene
- Tramadol

COMPLEX ACTION OPIOIDS AND OPIOID ANTAGONISTS

Agonist-antagonists (κ analgesics)

- Nalorphine
- Pentazocine
- Butorphanol

Partial/weak μ agonist + κ antagonist

- Buprenorphine

Pure antagonists

- Naloxone
- Naltrexone
- Nalmefene

Pain Pathophysiology

- Pain is an ill-defined, unpleasant sensation, evoked by an external or internal noxious stimulus.
- Analgesic relieves pain without significantly altering consciousness.
- Pain perception has 2 components
  - Nociceptive component
  - Affective component

Tissue Injury

↓

Local release of active factors. (PG, BK, K)

↓

Persistent activation/ sensitization of Aδ/C.

↓

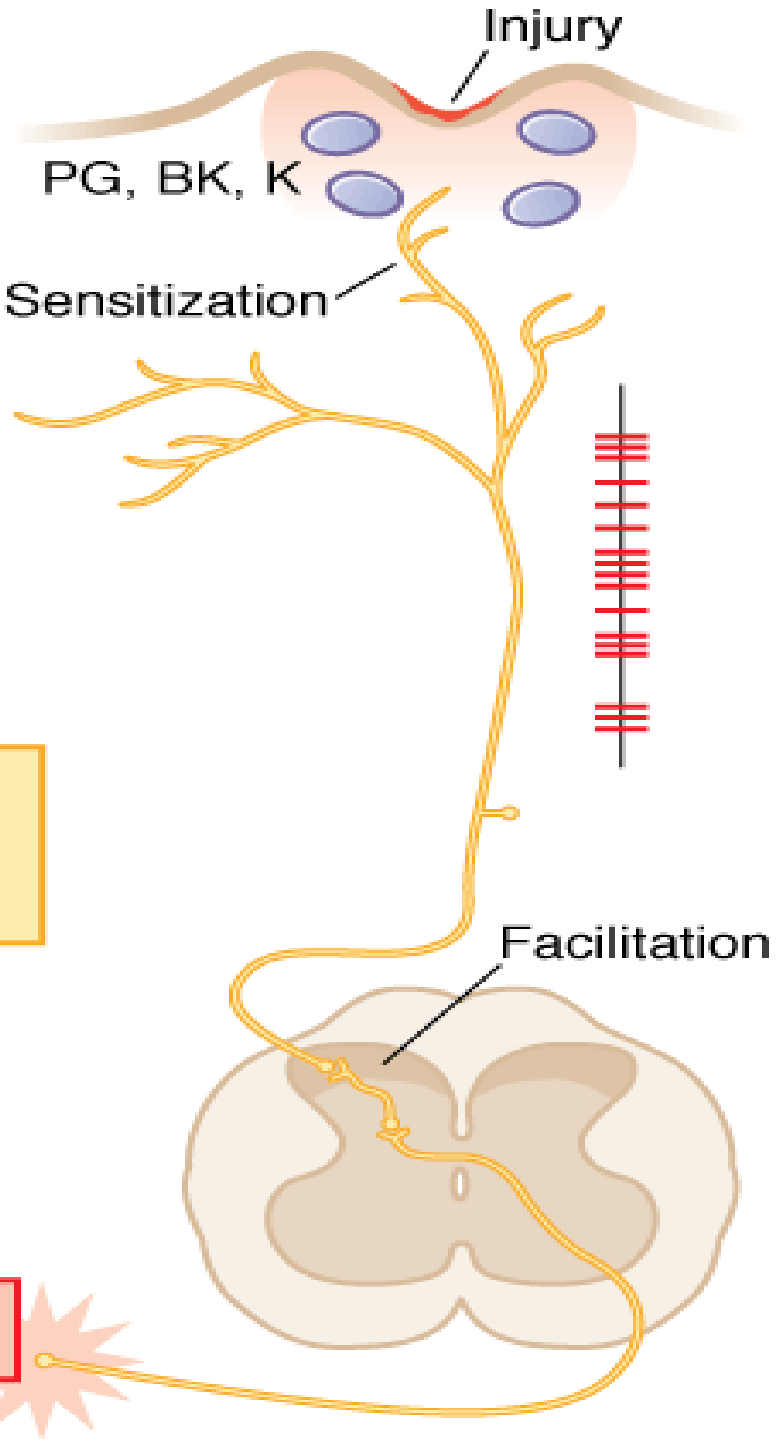
Activity in ascending pathways
+
spinal facilitation

↓

Exaggerated output for given stimulus input

↓

Ongoing pain + Hyperalgesia



Pain pathway & Sites of action of opioids

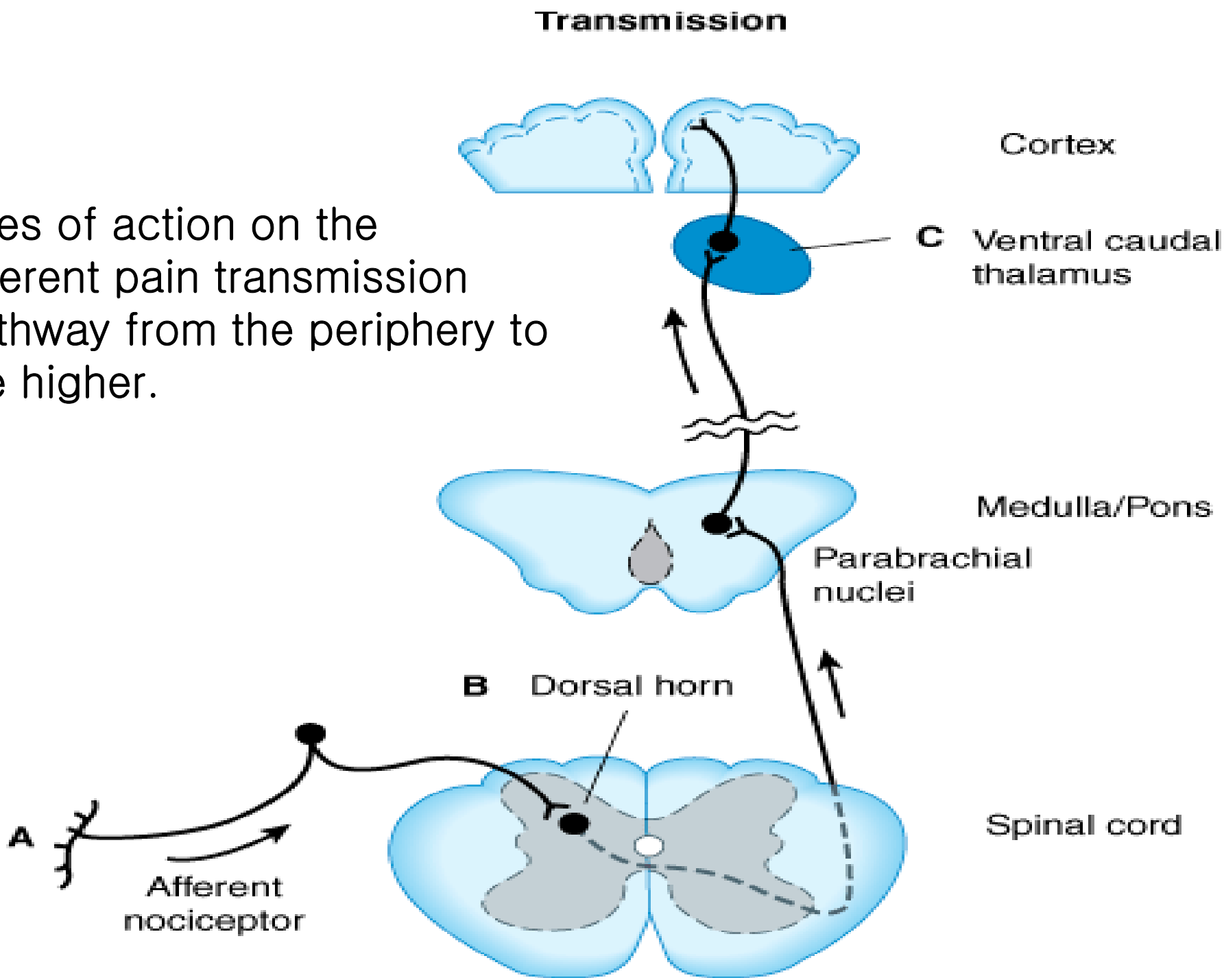
- Pain pathways (ascending & descending)

- Ascending pain pathway-

  Starts from terminals of primary afferent neurons fibres eg.

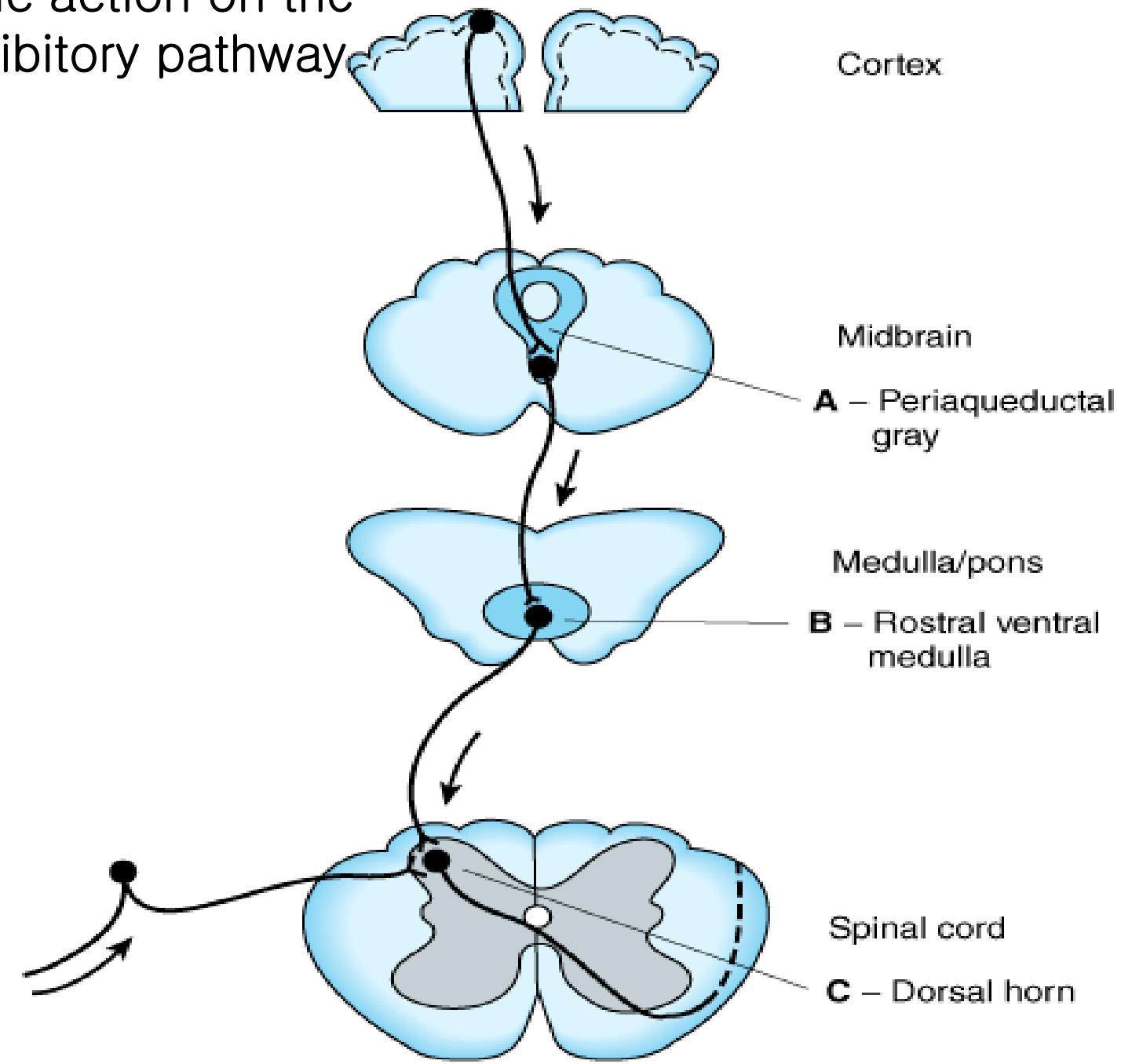
  - Aδ - fast conducting
  - C - slow conducting

Sites of action on the afferent pain transmission pathway from the periphery to the higher.

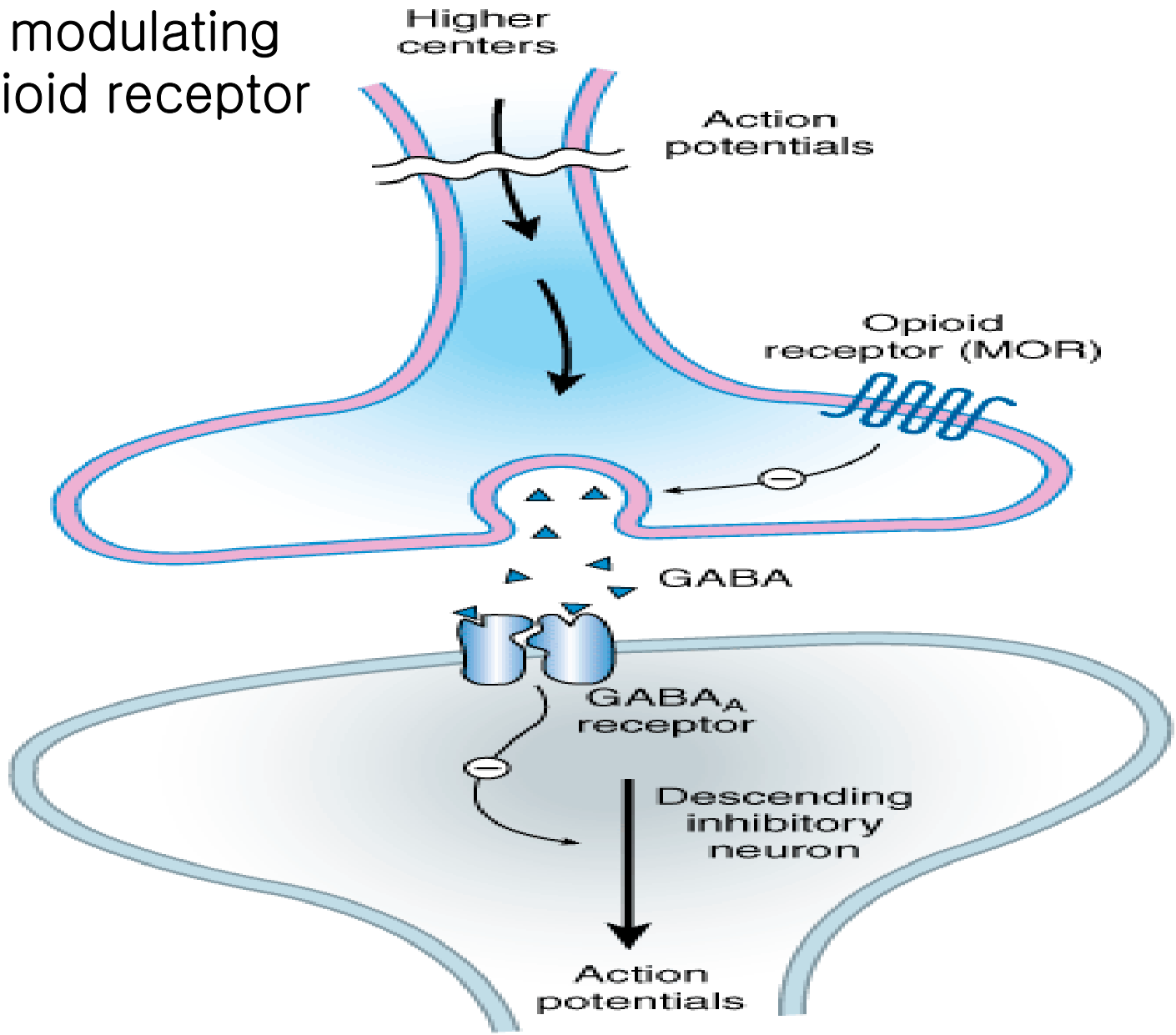


- Descending pathway exert inhibitory effect on pain transmission through Substantia Gelatinosa (SG)
- Sensory **Aβ fibres** (arising from peripheral tissues) stimulate release of **met-enkephlin** from interneurons of SG and block pain transmission
- So massaging, rubbing, acupunture, counter-irritants provide pain relief
- Morphine inhibit release of glutamate from primary afferent fibres in the spinal cord
- Gate control mechanism

Opioid analgesic action on the descending inhibitory pathway



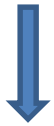
Brainstem local circuitry underlying the modulating effect of μ-opioid receptor (MOR)



- Brainstem local circuitry underlying the modulating effect of μ-opioid receptor (MOR)–mediated analgesia on descending pathways.
- The pain-inhibitory neuron is indirectly activated by opioids (exogenous or endogenous), which inhibit an inhibitory (GABAergic) interneuron.
- This results in *enhanced* inhibition of nociceptive processing in the dorsal horn of the spinal cord

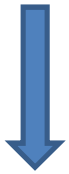
Opioid Receptor Transducer Mechanism

- Agonist binding

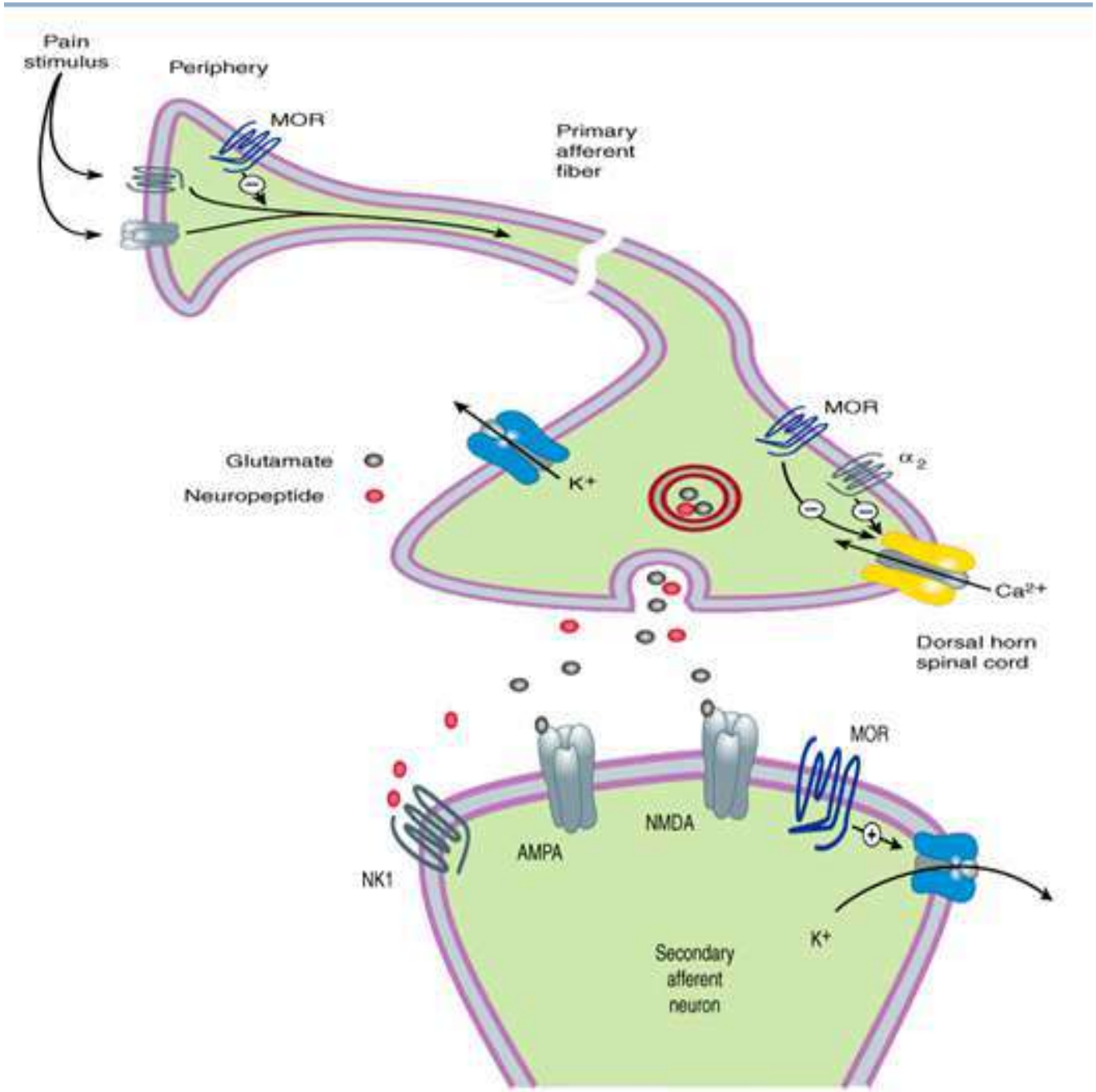


-conformational changes in the GPCR

-Inhibition of adenylyl cyclase activity (μ,δ)
-Stimulation of K^+ current (μ,δ)
-Inhibition of voltage-gated Ca^{2+} channels (κ)



-decreased release of neurotransmitter
(substance-P, neurokinin A, neurokinin B, glutamate)


Pain stimulus
Periphery
MOR
Primary afferent fiber
Glutamate
Neuropeptide
K+
MOR
α2
Ca2+
Dorsal horn spinal cord
MOR
NMDA
AMPA
NK1
K+
Secondary afferent neuron

- Most of available opioid analgesics
  - Act at μ-opioid receptor
- Activation of μ-opioid receptor

  → analgesia, euphoria, respiratory depress, nausea, vomiting, decreased gastrointestinal motility, tolerance, dependence
- δ-, κ-opioid receptor
  - analgesia
  - dysphoria, Psychotomimetic (κ)
  - Affective behaviour, proconvulsant (δ)
  - Not cause respiratory depression or to decease GI motility

    → Analgesia without μ-opioid side effect

- μ antagonist- β-funaltrexamine
- κ antagonist-Norbinaltorphimine
- δ antagonist- Naltrindole

- Morphine
  - μ, δ, κ receptor activation
- Fentanyl, sufentanyl
  - More selective μ-receptor agonist
  - High effective analgesia

Endogenous Opioid Peptides

- A number of endogenous opioid peptides having morphine like activity are found in brain, pituitary, spinal cord, GIT

- β-Endorphins - μ
- Enkephalins - μ & δ
- Dynorphins- κ
- Endomorphins- μ
- Nociceptin- NOP receptor (nociceptin opioid peptide receptor)

Effects of Morphine

Central Nervous System Effects

Analgesia

- Pain consists of both sensory and affective (emotional) components.
- Opioid analgesics reduce both aspects of the pain experience, especially the affective aspect.
- In contrast, nonsteroidal anti-inflammatory analgesic drugs have no significant effect on the emotional aspects of pain.

Euphoria

- intravenous drug users experience a pleasant floating sensation with lessened anxiety and distress (DA release in nucleus accumbance).
- However, dysphoria, an unpleasant state characterized by restlessness and malaise, may sometimes occur.

Sedation

- Drowsiness
- clouding of mentation
- little or no amnesia
- No motor incoordination
- Sleep is induced in the elderly (can be easily aroused from this sleep)

Respiratory Depression

- by inhibiting brainstem respiratory mechanisms.
- Alveolar PCO_2 may increase, but the most reliable indicator of this depression is a depressed response to a carbon dioxide challenge.
- In individuals with increased intracranial pressure, asthma, chronic obstructive pulmonary disease, or cor pulmonale, this decrease in respiratory function may not be tolerated.

Cough Suppression

- Codeine in particular
- However, cough suppression by opioids may allow accumulation of secretions and thus lead to airway obstruction and atelectasis.

Temperature regulating centre depression

- chances of hypothermia

Vasomotor centre depression

- Fall in BP

Morphine stimulates:

- CTZ (nausea, vomiting)

- Edinger Westphal nucleus of III nerve is stimulated (miosis)

- Vagal centre (bradycardia)

Miosis

- Constriction of the pupils
- By stimulating Edinger Westphal nucleus of III nerve
- Miosis is a pharmacologic action to which little or no tolerance develops
- valuable in the diagnosis of opioid overdose.

Truncal Rigidity-

- Truncal rigidity reduces thoracic compliance and thus interferes with ventilation.
- Truncal rigidity may be overcome by administration of an opioid antagonist, which of course will also antagonize the analgesic action of the opioid.
- Preventing truncal rigidity while preserving analgesia requires the concomitant use of neuromuscular blocking agents.

Peripheral Effects

Cardiovascular System

- Bradycardia
  Meperidine is an exception (can result in tachycardia)
- Hypotension - due to
  -peripheral arterial and venous dilation
  -depression of vasomotor centre
  -release of histamine.
- Increased PCO_2 leads to cerebral vasodilation associated with a decrease in cerebral vascular resistance, an increase in cerebral blood flow, and an increase in intracranial pressure.

Gastrointestinal Tract

Constipation

- no tolerance
- Opioid receptors exist in high density in the gastrointestinal tract
- constipating effects of the opioids are mediated through an action on the enteric nervous system as well as the CNS
- gastric secretion of hydrochloric acid is decreased
- propulsive peristaltic waves are diminished
- tone is increased
- this delays passage of the fecal mass and allows increased absorption of water, which leads to constipation
- so used in the management of diarrhea

Biliary Tract

- sphincter of Oddi may constrict
- contract biliary smooth muscle
- result in biliary colic

Renal

- Renal function is depressed by opioids
- decreased renal plasma flow
- enhanced renal tubular sodium reabsorption
- Ureteral and bladder tone are increased
- Increased sphincter tone may precipitate urinary retention
- ureteral colic caused by a renal calculus is made worse by opioid-induced increase in ureteral tone

Uterus-

- may prolong labor
- both peripheral and central actions of the opioids can reduce uterine tone

Neuroendocrine-

- stimulate the release of ADH, prolactin, and somatotropin
- inhibit the release of luteinizing hormone

Pruritus-

- CNS effects and peripheral histamine release may be responsible for these reactions
- pruritus and occasionally urticaria (when administered parenterally)

Miscellaneous

The opioids modulate the immune system by

- lymphocyte proliferation
- antibody production
- chemotaxis

Clinical Use of Opioid Analgesics

- **Analgesia**
- **Cough**
- **Diarrhea**
- **Acute Pulmonary Edema**
- **Balanced anaesthesia**
- **Preanaesthetic medication**
- **Relief of anxiety and apprehension**

Toxicity & Undesired Effects

Behavioral restlessness, tremulousness, hyperactivity (in dysphoric reactions)
Respiratory depression
Nausea and vomiting
Increased intracranial pressure
Postural hypotension accentuated by hypovolemia
Constipation
Urinary retention
Itching around nose, urticaria (more frequent with parenteral and spinal administration)

Acute morphine poisoning

- >50 mg of morphine
- Lethal dose is 250mg
- Stupor, coma, shallow breathing, cyanosis, pinpoint pupil, fall in BP, convulsions
- Death due to respiratory failure

Treatment

- Positive pressure respiration
- Iv fluids
- Gastric lavage with potassium permagnate
- Naloxone

Tolerance and Dependence

- With frequently repeated therapeutic doses of morphine, there is a gradual loss in effectiveness
- To reproduce the original response, a larger dose must be administered
- Along with tolerance, physical dependence develops
- Physical dependence is defined as a characteristic **withdrawal** or **abstinence syndrome** when a drug is stopped or an antagonist is administered

Tolerance and Dependence

- Maintenance of normal sensitivity of receptors requires **reactivation by endocytosis and recycling**.
- activation of receptors by endogenous ligands results in endocytosis followed by resensitization and recycling of the receptor to the plasma membrane.
- But morphine fails to induce endocytosis of the -opioid receptor - tolerance and dependence.
- In contrast, methadone, used for the *treatment* of opioid tolerance and dependence, does induce receptor endocytosis.

Tolerance and Dependence

- NMDA receptor ion channel complex play a critical role in tolerance development and maintenance

- NMDA-receptor antagonists such as ketamine can block tolerance development

Withdrawal

Withdrawal is manifested by significant somatomotor and autonomic outflow-

- agitation
- hyperalgesia
- hyperthermia
- hypertension
- diarrhea
- pupillary dilation

- release of all pituitary and adrenomedullary hormones

- affective symptoms

  -dysphoria

  -anxiety

  -depression

These phenomena are highly aversive and motivate the drug recipient to make robust efforts to avoid the withdrawal state

Contraindications and Cautions in Therapy

Use of Pure Agonists with Weak Partial Agonists

- morphine with pentazocine - risk of diminishing analgesia or even inducing a state of withdrawal

Use in Patients with Head Injuries

- Carbon dioxide retention caused by respiratory depression results in cerebral vasodilation.
- In patients with elevated intracranial pressure, this may lead to lethal alterations in brain function.
- Marked respi. depression
- Vomiting, miosis, altered mentation by morphine interferes with assessment of pt condition

Use during Pregnancy

- In pregnant women who are chronically using opioids, the **fetus may become physically dependent in utero** and manifest withdrawal symptoms in the early postpartum period.

- A daily dose as small as 6 mg of heroin (or equivalent) taken by the mother can result in a mild withdrawal syndrome in the infant, and twice that much may result in severe signs and symptoms, including irritability, shrill crying, diarrhea, or even seizures.

- When withdrawal symptoms are mild - diazepam
- with more severe withdrawal - methadone

Use in Patients with Impaired Pulmonary Function

- opioid analgesics may lead to acute respiratory failure.

Use in Patients with Impaired Hepatic or Renal Function

- morphine and its congeners are metabolized primarily in the liver
- Half-life is prolonged in patients with impaired renal function

Use in Patients with Endocrine Disease

-adrenal insufficiency (Addison's disease) and hypothyroidism (myxedema) –

-prolonged and exaggerated responses to opioids.

Related drugs

Pethidine

- $1/10^{th}$ in analgesic potency
- Spasmodic action on smooth muscles is less
- Tachycardia (**antimuscarinic** action)- it is related to atropine, even acts on opioid receptors
- Safer in asthmatics (less histamine release)
- Uses- analgesia, preanaesthetic medication
- Preferred opioid analgesic during labour (less neonatal respi depression)

Fentanyl

- 80-100 times more potent than morphine
- few cardiovascular effects
- little propensity to release histamine.
- Because of high lipid solubility, it enters brain rapidly and produces **peak analgesia in 5 min** after i. v. injection.
- The **duration of action is short**: starts wearing off after 30-40 min due to

  redistribution
- **Transdermal** fentanyl has become available for use in cancer

Methadone

- Slow & persistant action
- Sedative & subjective effects are less intense
- No kick
- Less abuse potential
- Use- as substitute therapy for opioid dependence
- 1mg methadone for 4 mg morphine.

Tramadol

- Analgesic action mechanism
  - Weak affinity for μ-opioid receptor
  - norepinephrine & 5-HT reuptake Inhibition

- Advantage
  - Less respiratory depression, nausea, vomiting, constipation
  - Less abuse potential
  - Rapid psychomotor recovery

- Labour pain, injury, surgery (other short lasting pain)
- Moderate pain treatment : as effective as morphine
- Severe pain treatment : less effective than morphine

Pentazocine (κ analgesic)

- It has agonistic actions and weak opioid antagonistic activity
- elicit dysphoric and psychotomimetic effects
- increase in blood pressure and heart rate

Uses-

- moderate to severe pain
- as a preoperative medication and
- as a supplement to anesthesia

Buprenorphine (weak μ agonist & κ antagonist)

- 25-50 times more potent than morphine
- Sublingual route
- Slower onset & longer duration of action
- Postural hypotension is marked
- Cannot be used during labour (respi dep not reversed by naloxone)

Uses-

- Long lasting pain- cancer
- Tt of morphine dependence

Naloxone (μ, κ, δ antagonist)

- Antagonizes all morphine actions
- Sedation is less completely reversed
- Blocks placebo, acupuncture, stress induced analgesia

Use

- Morphine poisoning
- Diagnostic test for opioid addiction
- Revert neonatal respi depression due to opioid use during labour

Peripherally Acting Opioid

- Opioid receptor – outside central nerve system
  - Peripherally acting opioid agonist
    → analgesia without CNS side effect
- Loperamide, Diphenoxylate
  - μ-opioid receptor agonist
  - Not cross blood-brain barrier
  - Treatment : inflammation-induced hyperalgesia
  - Relieve diarrhea
- Alvimopan
  - peri μ-opioid receptor antagonist
  - Relieves constipation in opium addicts
  - Without precipitating opioid withdrawl
  - Treat postoperative paralytic ileus

Opioid with Other Analgesics

- Goal of using analgesics in combination
  - Achieve superior analgesia
  - Reduce dose of each drug
  - Minimizing side effect
- NSAID
  - Synergistical action with systemic opioid to produce analgesia
- Local anesthetics and opioid
  - Synergistical pain relief when intrathecal or epidural administration

CHOLINOMIMETIC DRUGS

1.The cholinomimetic means the drugs which intimate or mimic the actions ofAch at muscarinic and or nicotinic receptors. This they amy do either by

(a) Binding directly to and by activating these recptors.

(b) By inhibiting the activity of true acetylcholinesterase enzyme.

BY INHIBITING THE TRUE ACETYLCHOLINESTERASENAPTIC CLEPT ENZYME THESE DRUGS PREVENT THE METABOLIC DEGRADATION OF ACH AND THUS INDIRECTLY INCREASES THE CONCENTRATION OF ACH IN THE SYNAPTIC CLEFT

DIRECTLY ACTING PARASYMPATHOMIMETIC

- Synthetic cholinesters: Methacholine, Carbochol and bethenechol(M&C are obsolete)

1.BETHENECHOL is totally resistant to hydrolysis by true AChE aswell as by pseudocholiesterase. It ha mainly muscarinic actions mainly at urinary bladder and GIT but devoid of nicotinic actions.

Its main uses are:

1. To reverse the posoperative atony of urinary bladder retention in neurogenic bladder. For acute retention 2.5mg of bethenechol daily with meals can be injected S.C.. In chronic cases 10-15 mg of the drug can be given orally daily.
2. To treat GIT atony to expel gases from intesitinee proor to radiological examinations.
3. To treat salivary gland malfunction xerostomia (dry mouth)

Precautions:

It should not be given by I.V route because the suddenrise in plasma concentrations of bethenechol may lead to cardivascular collapse.

Contraindications

1.Hyperthyroidism

2.Bronchial asthma

3.Peptic ulcer

4.Myocardial infraction

- Natural alkaloids: The three major alkaloids in this group are muscarine,arecoline and pilocarpine.

Muscarine: is obtained from poisonous muschroom *Amanita muscaria* and has mainly muscarine effects. It is not used therapeutically.

Treatment of its poisoning consists of parenteral administration of atropine(1-2 mg ., every 30min) with adequate supportive measures for respiration, circulation and pulmonary oedema.

Arecoline: is the chief alkaloid of areca or betel nuts. It has no therapeutic use

Pilocarpine: is the chief alkaloid obtained from the leaves of the shrub *Pilocarpus jaborandi .* It is teritary amine and hence crosses BBB. It ha dominant muscarinic and mild nicotinic receptors. Pilocaroine is too toxic for systemic use.

THERAPEUTIC USES

1.Opthalmic use:

a) For intial traetment of open angle glaucoma.

b) To counteract the mydrasis produced by atropine

c) To break the adhesions between the iris and the lens

2. As Sialagogue:

Pilocarpine (5-10mg orally) can also be used to stimulate sailavary galnd secretions in patients after largyngeal surgery and to treat xerostomia resulting after radiotherapy.

INDIRECTLY ACTING PARASYMPATHOMIMETICS(AChE INHIBITORS OR ANTICHOLINESTERASES)

- **Reversible(competative) inhibitors of AChE:**

Physostigmine, edrophonium, ambenonium, demecarium and rivastigmine.

Natural alkaloids:

PHYSOSTIGMINE is an alkaloid obtained from dried ripe seed of *Physostigmine venenosum.* It is highly lipid soluble and shoes better absorption in all body compartments including CNS.

It has marked muscarinic effects but nicotinic effects are negeligible.

Being highly toxic it has only limited use.

Therapeutic uses

A) Opthalmic use:

1. For reversal of mydriasis
2. To prevent adhesions between pupil and lens
3. For the tratment of open anlge glaucoma

Physostigmine though more potent than pilocarpine but highly lipid soluble very toxic and poorly tolerated and hence rarely used, rather it has become obsolete

B) Belladona (atropine) Poisoning:

Physostigmine is a specific antidote for atropine poisoning or for poisoining by any other anticholinergic drug and can antagonise central as well as peripheral toxocity of atropine.

Treatment of poisoning is then made by giving 2mg I.V. or I.M. of physostigmine intiially or additional doses thereafter if necessary.

- **Synthetic Quaternary compounds**:

These include edrophonium, neostigmine, pyridostigmine,distigmine, ambenonium and demecarium

Being quaternary compounds these drugs are least absorbed and do not cross BBB.

These drugs have important therapeutic effect on skeletal muscle neuromuscular junction. The

These drugs intensify the actions of physiologically released Ach at motor end plate results in strenthening of muscle weakened by curare like drugs or by the disease called myasthenia gravis.

Therapeutic uses

1. **Treatment of Myasthenia Gravis:** It is acquired autoimmune disorder causing skeletal muscle fatiguability and weakness
2. **Paralytic Ileus and Atony of Urinary Bladder:** This can be relieved by using 0.5-1mg S.C. dose of neostigmine.
3. **Glaucoma:** 0.25to 0.5% solution of demecarium is applied topically in the eye twice a week.
4. **Post operative Decurarization (treatment of curare poisoning and cobra bite):** Neostigmine (0.5-1mg,I.V.) or edrophonium (10mg, I.V.) along with atropine ,rapidly reverses muscle paralysis induced by d-TC given during anaesthesia or by poisoning due to snake venom neurotoxin.(cobra bite)
5. **Paroxysmal Atrial and supraventricular Tachycardia:** Edrophonium is preferred but it is not commonly used as ca2+ channel blockers are now preferred over edrophonium.

- **Irreversibleinhibitors of AChE:**

This group consists of organophosphorous compounds, e.g., diflos, ecothiophate,parathion,malathion,diazinon and carbamate derivatives, e.g., propoxurand carbaryl.

Pharmacological effects: These drugs are volatile non-polar substances of very high lipid solubility. As a result these are rapidly absorbed a through mucous membrane and even through unbroken skin.

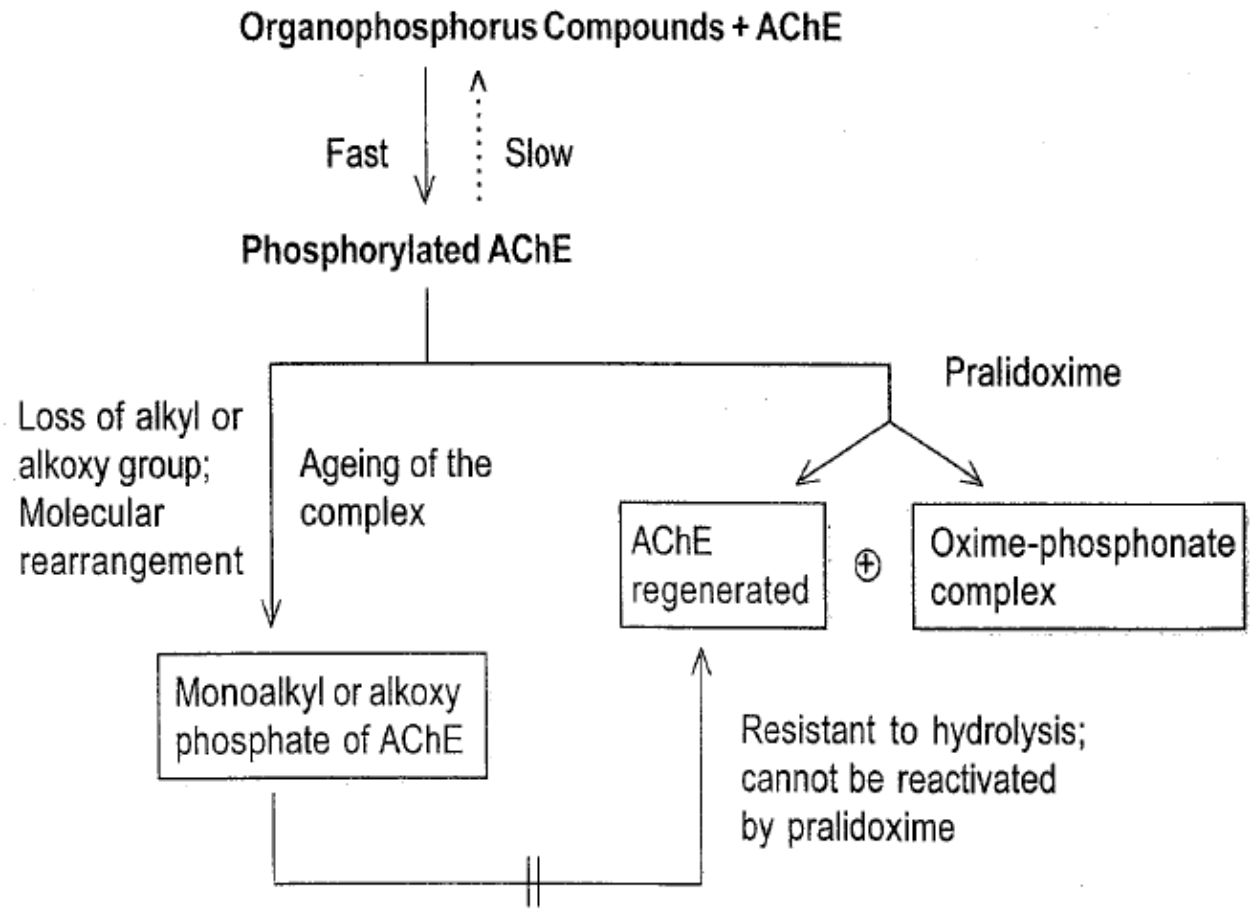
These are mainly used as insecticidesor pesticides and are better known for theit toxicity.

1.Muscarinic toxic manifestations: Diarrhoe,urination, miosis, bronchoconstiction, lacrimation, sailavation, sweating, bradycardia and hypotension.

2. Nicotinic toxic manifestations: Fasciculations of skeletal muscles leading to paralysis.

3. CNS toxic manisfestations: Restlessness, tremors, convulsions, ataxia and respiratory arrest.

Treatment for organophosporous compounds



ANTIMUSCARINIC DRUGS OR MUSCARINIC RECEPTOR ANTAGONIST

- The class of drugs referred to here are also called Parasympatholytics or anti-cholinergics.
- But the most precise term is anti-muscarinic or muscarinic recptor antagonist.
- The term ant-cholinergic means it should have both anti-nicotinic aswell as anti-muscarinic action.
- But some of the drugs like atropine lack anti-nicotinic effects.
- More over the drugs which block Nn are called **ganglionic blockers**, and the drugs which block Nm are **neuromuscular blockers**

Classification of Muscarinic Receptor Antagonist

NATURAL ALKALOIDS	SEMISYNTHETIC DERIVATIVES	SYNTHETIC DERIVATIVES
ATROPINE(dl-hyoscysamine)	HOMOTROPINE	EUCOTROPINE
SCOPALAMINE(l-hyoscine)	ATROPINE	CYCLOPENTOLATE
	HYOSCINE	TROPICAMIDE
	BENZTROPINE	DICYCLOMINE
	IPRATROPIUM	FLAVOXATE
	TIOTROPIUM	OXYBUTININ
		PIPRENZEPINE
		TELENZEPINE
		TRIHEXYPHENIDYL
		PROCYCLIDINE
		PROPHANTHELINE
		DROTAVERINE
		OXYPHENONIUM
		GLYCOPYROLATE
		CLIDINIUM
		PIPENZOLATE
		VALETHAMATE

PHARMACOKINETICS

- ABSORPTION:

1.Tertiary amine antimuscarinic drugs are well absorbed from the gut and across the conjunctival membrane. With suitable vehicle it can be absorbed by transdermal route eg., scopalamine transdermal patch.

2.Quaternary compound are poorly absorbed and do not cross BBB because of their poor lipid solubility.

- DISTRIBUTION:

1.Expect quaternary compounds rest of anti-muscarinic are well distributed to all the body compartments. Scopalamine when compared to othe drugs is well distributed to CNS and has greater effects when compared to other antimuscarinic drugs.

- METABOLISM:

1.About 50%of atropine and 80% of scopolamine is metabolised by liver as conjugates.

- EXCRETION:

1. About 50% of atropine is excreted unchanged through urine. Half life of atropine is about 3hrs

PHARMACODYNAMICS

Mechanism of action:

1. Atropine and scopalamine are non selective antagonists and hence block all (M1-M5) muscarinic receptors.
2. These drugs are competative antagonists of the action of Ach and other muscarinic agonists.
3. This antagonism is reversible and therefore the blockade by smaller doses of atropine can be overcome by large concentration Ach or muscarinic agonists.
4. It blocks all the actions of Ach or muscarinic agoinist
    i) release of IP3 from m1and m3 activation
    ii) inhibition of adenyl cyclase from M2 receptor

EFFECTS ON DIFFERENT ORGANS AND THERAPEUTIC APPLICATION

- Sweat, Brochial and sailavary glands>> Heart and Eye>> Bladder and GIT>> Gastric gland.
- The higher the parasympathetic tone, the more shall be the sensitivity of the organ toward the drug.

- **Central Nervous Sysytem:**

EFFECT:

Atropine

1. In normal therapeutic doses it stimulant effect on medullary centers
2. In higher doses it stimulates higher cerebral centers and in toxic doses leads central excitation leading to restlessness,irritability,disorientation,hallucinations and delirium.
3. With still larger doses leads to depression, circulatory collapse, paralysis, coma, respiratory failure leading to death.

Scopalamine

1. Scopalamine have greater permiability through BBB. *In contarst to atropine scopalamine at normal therapeutic doses causes CNS depression.* It produces drowsiness, amnesia, fatigue, dreamless sleep and depression of vomiting center.
2. *Toxic doses causes agitation, excitment and hallucinations.*
3. *Still larger doses causes coma and repiratory failure.*

Therapeutic uses

a) **Motion sickness**

b) **Parkinsons Disease:** combination of antimuscarinic drug with a dopamininergic drug provides more effective than the drug alone. Centrally anticholinergic drugs like *benztropine, benzhexol,procyclidine,biperiden.*

c) ***Diagnosis of Alzheimers Disease:***

- **EYE**

Effects:

1. Atropine blocks M3 receptors present in pupillary constrictor muscle and produces mydriasis.
2. Blockade of m3 receptor at ciliary muscles of the lens abolishes all responses of cholinergic stimulation.suspensory ligaments get tightened resulting in flatening of the lens. And the eyes get set for distant vision. This effect is termed as paralysis of accommodation or Cycloplegia.
3. Obstruction of aqueous humor because of crowding of iris.

- **Therapeutic doses**
- **1.As Mydriatic:**EUCOTROPINE CYCLOPENTOLATE TROPICAMIDE and HOMOTROPINE
- **2. To Prevent adhesions in inflammatory conditions of the eye: Iridocyclitis, iritis or uveitis.**

Cardiovascular system

EFFECT:

1. With usual clinical doses atropine I.M. or S.C. causes bradycardia intially.
2. No changes in blood pressure and CO.
3. Further doses of atropine causes progressive tachycardia by blocking vagal effects on m2 receptor on the SA node
4. The ventricles because of lesser degree of parasympathetic innervations are less effected by atropine like drugs in therapeutic doses.
5. Atropine may increase the ventricular rate in the patients with atrial flutter or fibrillation.

- **Therapeutic uses**: Limited use for CVS

1. To abolish reflex vagal cardiac slowing or asystole
2. Second degree heart block as with digitalis toxicity.

- **RESPIRATORY SYSTEM**

EFFECTS:

Smooth muscles and mucous glands parsymapthetic innervation and have predominant M3receptors.

⇩

Atropine tyrpe of drugs inhibit secretions of nose,mouth,pharynx and brochi and thus dry the mucous membrane of the respiratory tract.

⇩

Due to drying of mucous secretions leads to the formation of mucous plugs which can obstruct the airflow.

- **Therapeutic uses:**

1.Bronchial asthma and chronic obstrctive pulmonary disease(ipratropium+ beta2 adrenorecptor agonist: salbutamol, Tiotropium)

2.Preanaesthetic medication

PHARMACODYNAMICS

- **Pharmacodynamics** is the study of the biochemical and physiological effects of drugs and their mechanisms of action.

- Simply stated, pharmacodynamics refers to the effects of a drug on the body.

Two state receptor model

- A receptor may exist in two interchangeable states, active **(*Rα*)** & inactive **(*Ri*)** which are in equilibrium.

- Binding of drug shift this equilibrium in either direction.

- ***Ligand***- any molecule which attaches selectively to particular receptors.

- ***Affinity -***The strength of the reversible interaction between a drug and its receptor, as measured by the *dissociation constant*, is defined as the affinity of one for the other.

- ***Intrinsic activity*** – capacity to induce a functional change in the receptor.

- ***Specificity -*** A drug that interacts with a single type of receptor that is expressed on only a limited number of differentiated cells will exhibit high specificity.

Agonists

- Drugs that bind to physiological receptors and mimic the regulatory effects of the endogenous signaling compounds are termed *agonists*.

- If the drug binds to the same *recognition site* as the endogenous agonist (the primary or orthosteric site on the receptor) the drug is said to be a ***primary agonist***.

- ***Allosteric* agonists** bind to a different region on the receptor referred to as an allosteric site.

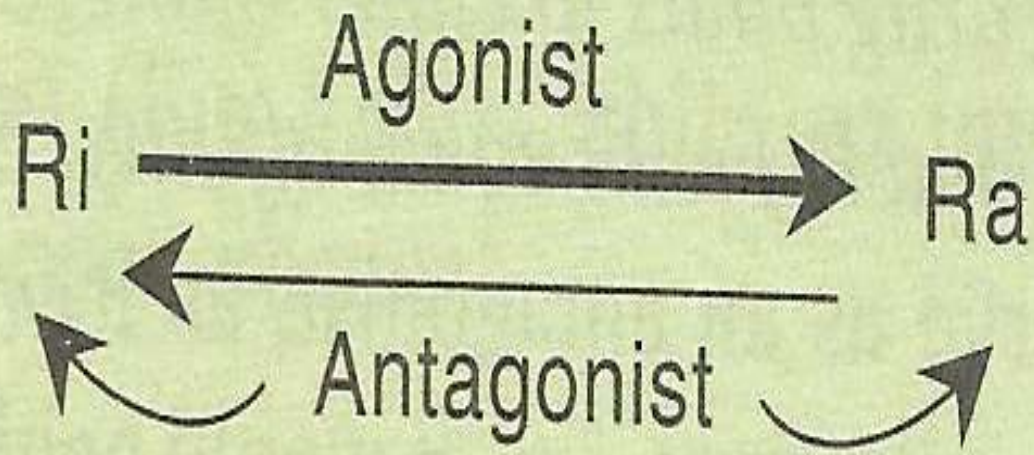


Fig 7.1 The Drug Action Viewed in Terms of Two-State Model of Receptor Activation.

Antagonist

- Drugs that block or reduce the action of an agonist are termed *antagonists*.
- Antagonism most commonly results from competition with an agonist for the same or overlapping site on the receptor (a *syntopic* interaction)

- **Physical antagonist** binds to the drug and prevents its absorption like charcoal binds to alkaloids and prevents their absorption.
- **Chemical antagonist** combines with a substance chemically like chelating agents binds with the metals.
- **Physiological antagonist** produces an action opposite to a substance but by binding to the different receptors e.g. adrenaline is a physiological antagonist of histamine because adrenaline causes bronchodilatation by binding to β2 receptors, which is opposite to bronchoconstriction caused by histamine through H1 receptors.
- **Pharmacological antagonists** produce no effect , shows no intrinsic activity.

- ***Partial agonists -***Agents that are only partly as effective as agonists regardless of the concentration employed.

- ***Inverse agonists -***Many receptors exhibit some constitutive activity in the absence of a regulatory ligand; drugs that stabilize such receptors in an inactive conformation are termed *inverse agonists* (produce effect opposite to that of agonist).

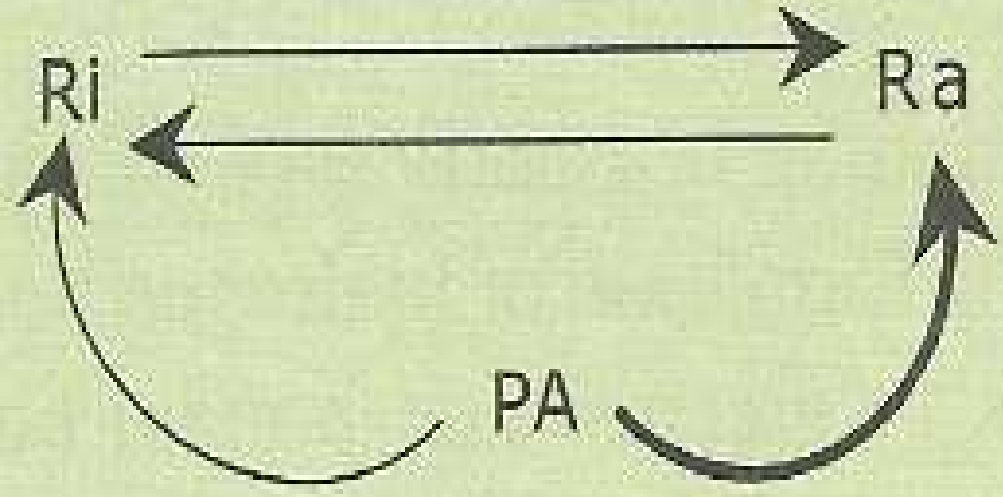


Fig 7.3 Partial Agonist (PA) has Slightly Higher Affinity for Ra (active state of the receptor), Although Lesser in Comparison to Agonist.

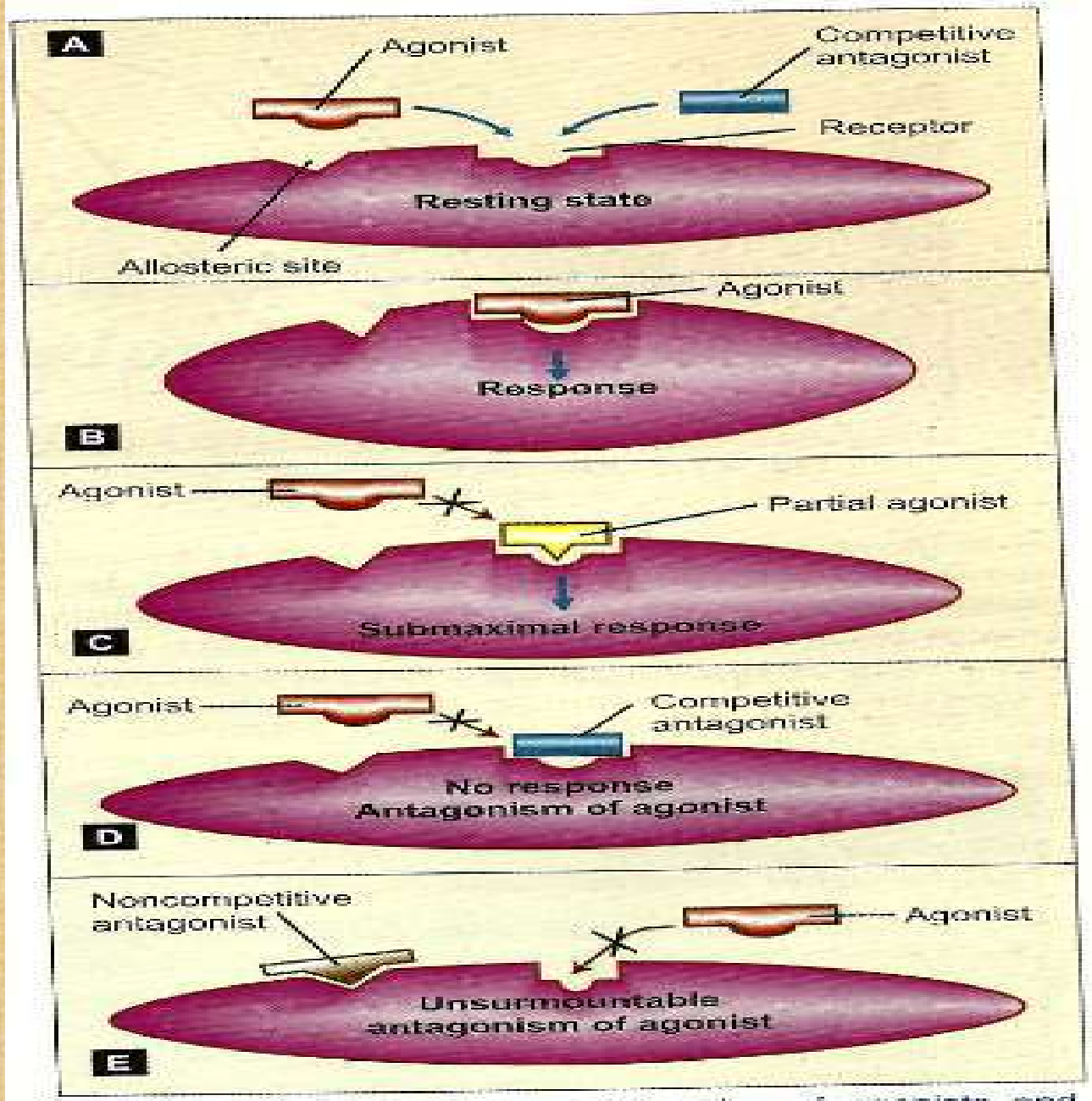


Fig. 4.16: Illustration of sites of action of agonists and antagonists (A), and the action of full agonist (B), partial agonist (C), competitive antagonist (D) and noncompetitive antagonist (E) on the receptor

Efficacy

- **A maximal effect (E_{max}) an agonist can produce.**
- **It can be measured with a graded dose-response curve only.**

POTENCY

- The amount of the drug needed to produce a given effect.
- potency is determined by the affinity of the receptor for the drug.
- The dose causing 50% from the maximal effect (EC50) can be obtained from graded dose-response curve.
- In quantal dose response curve, ED50, TD50 and LD50 are potency variables.

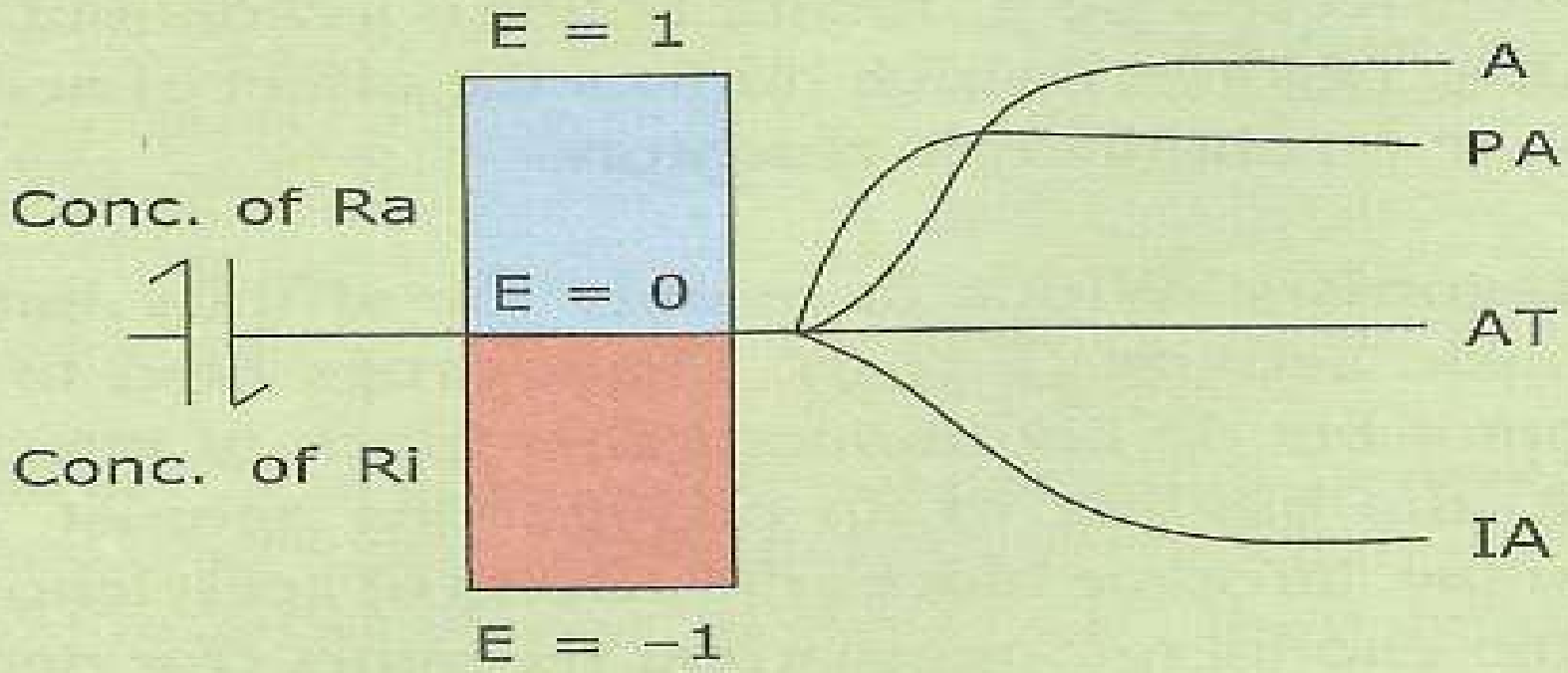
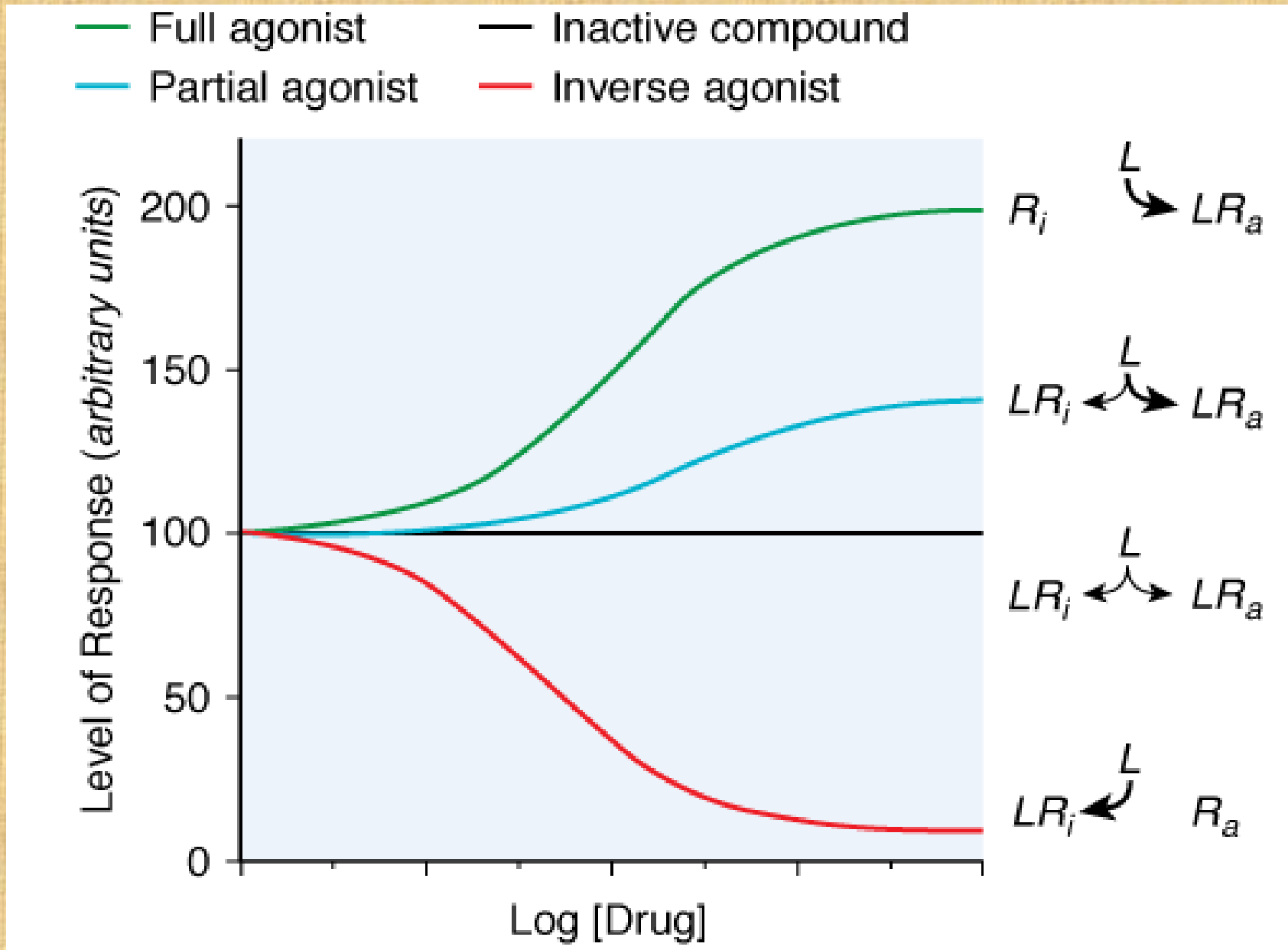
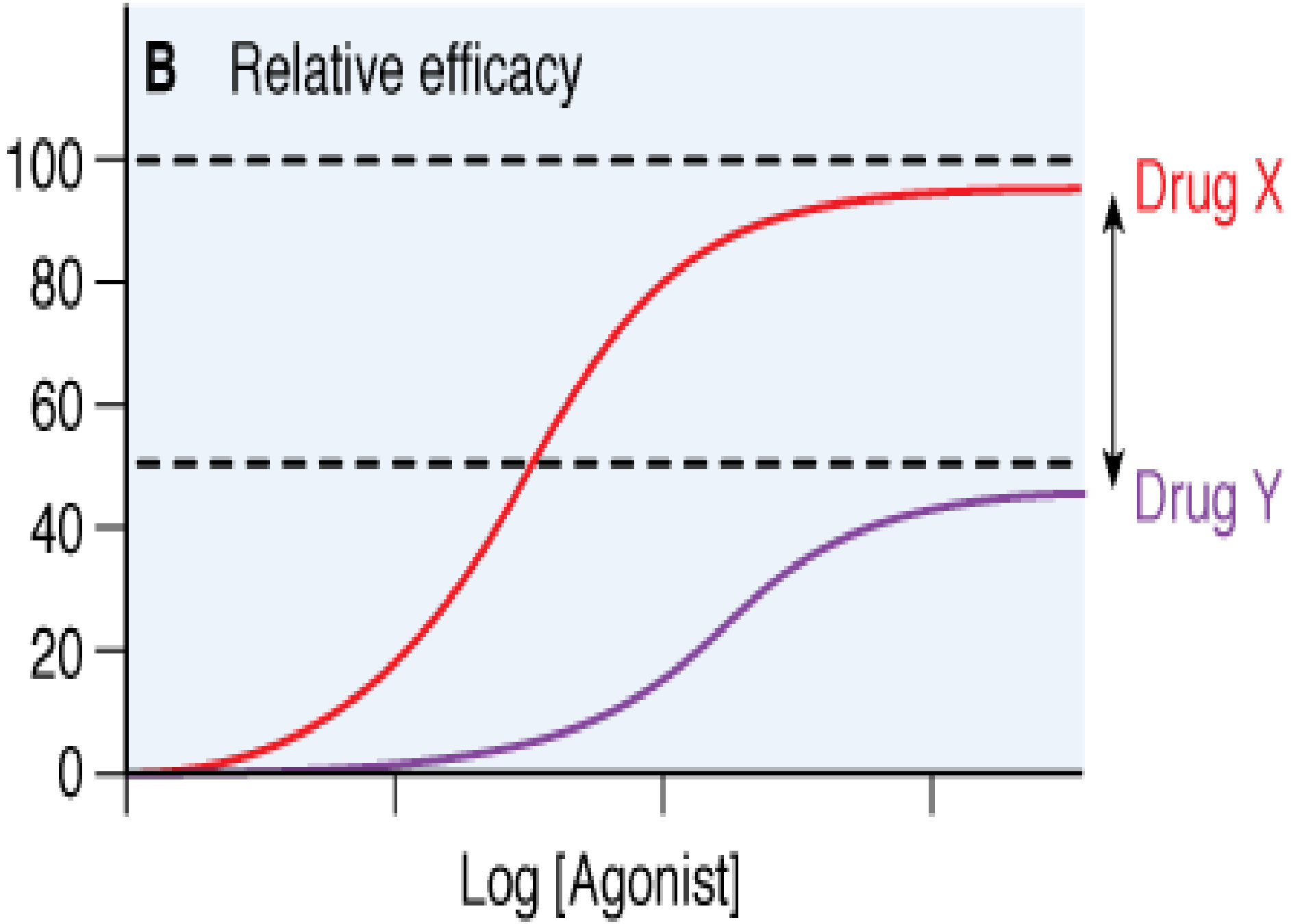
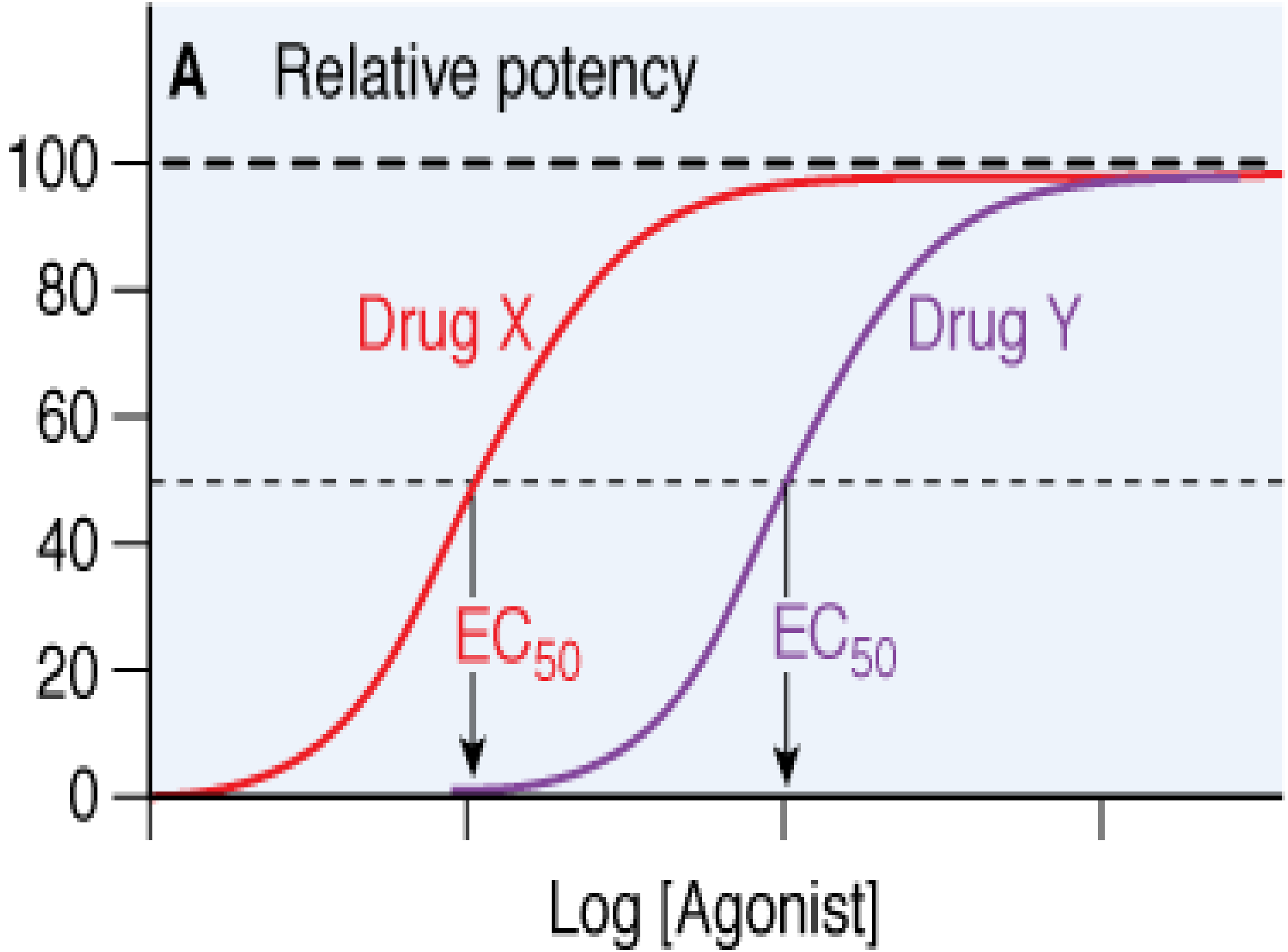


Fig 7.2

The Differential Influence of Agonist (A), Partial Agonist (PA), Antagonist (AT) and Inverse Agonist (IA) on Relative Distribution of Active (Ra) and Inactive (Ri) States of Receptors.


Full agonist
Partial agonist
Inactive compound
Inverse agonist
Level of Response (arbitrary units)
200
150
100
50
0
Log [Drug]
L
R_i
LR_a
L
LR_i
LR_a
L
LR_i
LR_a
L
LR_i
R_a


B Relative efficacy
100
80
60
40
20
0
Drug X
Drug Y
Log [Agonist]


A Relative potency
100
80
60
40
20
0
Drug X
Drug Y
EC50
EC50
Log [Agonist]

Repeated administration of a drug results in diminished effect "Tolerance".

- **Tachyphylaxis:** is a type of tolerance which occurs very rapidly.
- **Desensitization:** decreased response to the agonist after its repeated injection in small doses.

May be due to

1- Masking or internalization of the receptors.

2- Loss of receptors (down regulation)- decreased synthesis or increased destruction.

3- Exhaustion of mediators (depletion of catecholamine).

Competitive (equilibrium type)	Noncompetitive
1. Antagonist binds with the same receptor as the agonist	Binds to another site of receptor
2. Antagonist resembles chemically with the agonist	Does not resemble
3. Parallel rightward shift of agonist DRC	Flattening of agonist DRC
4. The same maximal response can be attained by increasing dose of agonist (surmountable antagonism)	Maximal response is suppressed (unsurmountable antagonism)
5. The antagonist appears to have inactivated a certain number of agonist molecules	The antagonist appears to have inactivated a certain number of receptors
6. Intensity of response depends on the concentration of both agonist and antagonist	Maximal response depends only on the concentration of antagonist
7. Examples: ACh—Atropine Morphine—Naloxone	Diazepam—Bicuculline

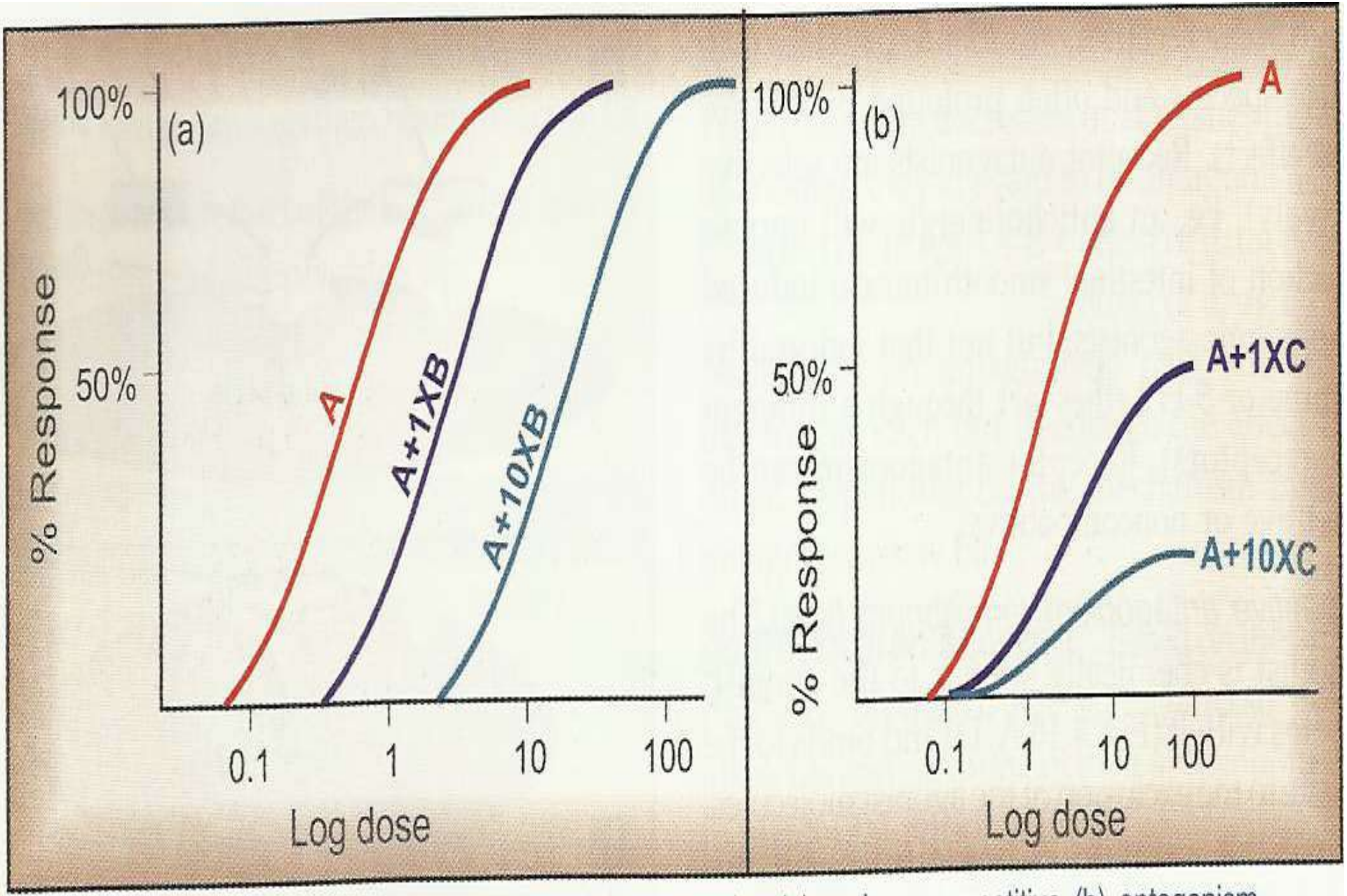


Fig. 4.17: Dose-response curves showing competitive (a) and noncompetitive (b) antagonism
A—agonist, B—competitive antagonist, C—noncompetitive antagonist

PHYSIOLOGICAL RECEPTORS

- GPCR
- Ion channels
- Transmembrane enzymes
- Transmembrane, non-enzymes
- Nuclear receptors
- Intracellular enzymes

Cellular Pathways Activated by Physiological Receptors

Signal Transduction Pathways

- Physiological receptors have at least two major functions, ligand binding and message propagation (i.e., signaling).
- Two functional domains within the receptor:

  -ligand-binding *domain* and

  -effector *domain*.
- The regulatory actions of a receptor may be exerted directly on its cellular target(s), on *effector protein(s),* or may be conveyed by intermediary cellular signaling molecules called ***transducers***.

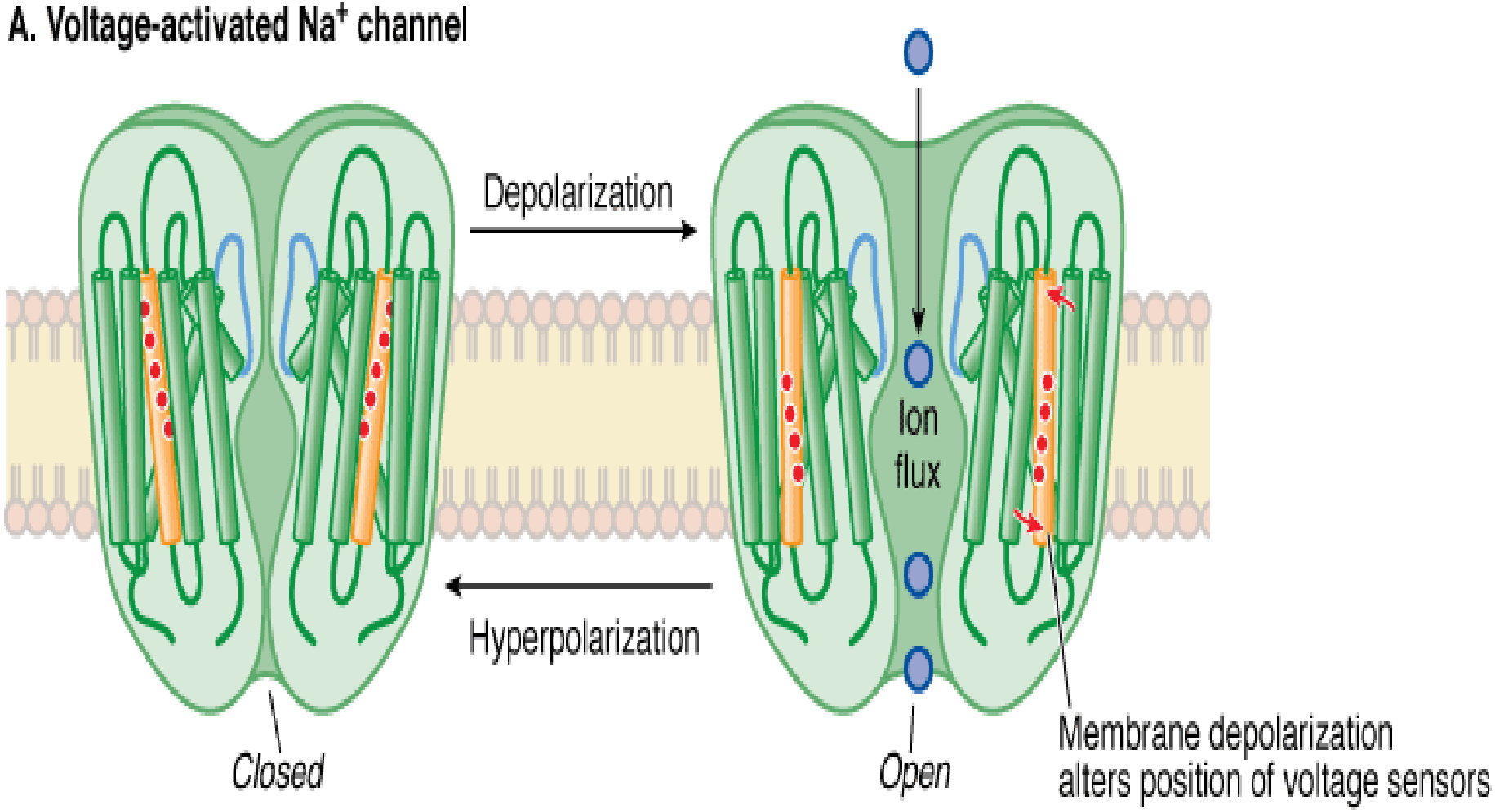
STRUCTURAL FAMILY	FUNCTIONAL FAMILY	PHYSIOLOGICAL LIGANDS	EFFECTORS AND TRANSDUCERS	EXAMPLE DRUGS
Ion channels	Ligand-gated	ACh (M_2), GABA, 5-HT	Na^+, Ca^{2+}, K^+, Cl^-	Nicotine, gabapentin
	Voltage-gated	None (activated by membrane depolarization)	Na^+, Ca^{2+}, K^+, other ions	Lidocaine, verapamil

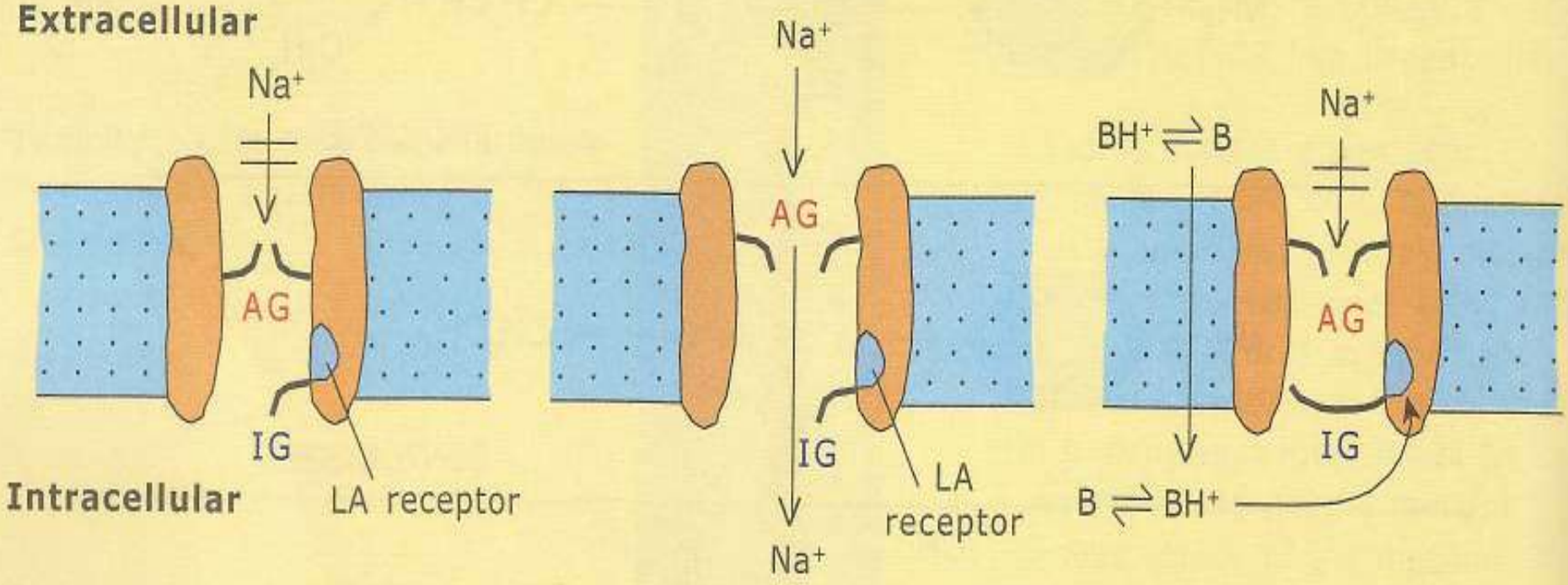
Receptors with intrinsic ion channel

- Ligand gated ion channels.
- No intervention of G-protein or second messenger.
- Response is fastest (in milliseconds).

e.g. $GABA_A$, $5HT_3$, NMDA

voltage-activated Na^+ channel with the pore in the open and closed state.





Resting or Closed State

The Activation Gate (AG) closed. The LA receptor is located in the trans-membrane pore of Na^+ channel.

Activated or Open State

Brief depolarisation opens AG and allows Na^+ permeation.

Inactivated or Blocked State

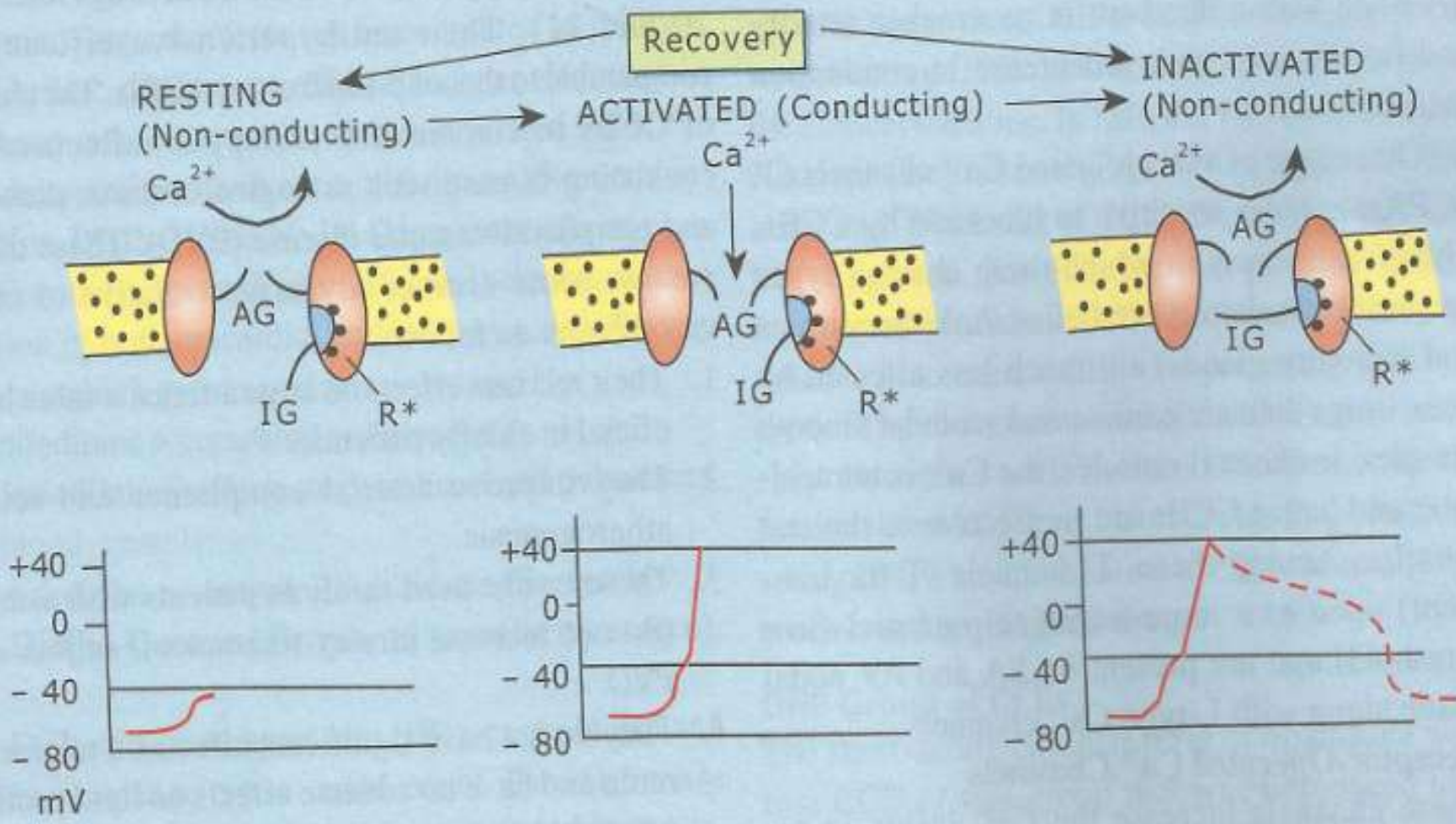
Ionised (BH^+) form of LA binds to LA receptor. IG closes, flow of Na^+ ceases.

Fig 15.2 A Model of Voltage-Gated Na^+ Channel Depicting the Site and Mechanism of Local Anaesthetic Action.

Table 19.1 Properties of Voltage-Sensitive Ca^{2+} Channels

Voltage-Sensitive Calcium Channels				
Properties	**L (long lasting)**	**T (transient)***	**N (neuronal)**	**P/Q** & R****
Activation threshold	High	Low	High	High
Inactivation rate	Slow	Fast	Medium	Slow
Location	Cardiac and smooth muscle, SA node and AV node	SA node Thalamic and other neurons	Neurons in CNS and Secretory glands	Cerebellar and Purkinje neurons
Function	Regulate excitation–contraction coupling; Regulate pacemaker activity; Regulate conduction velocity	Regulate pacemaker activity; Regulate T current and repetitive spikes in thalamic nuclei	Modulate transmitter release	Modulate transmitter release
Blockers	Verapamil Dihydropyridine group of CCBs, Cd^{2+}	Flunarizine Ethosuximide Ni^{2+}	Cd^{2+} Gabapentin	Toxin from funnel web spider

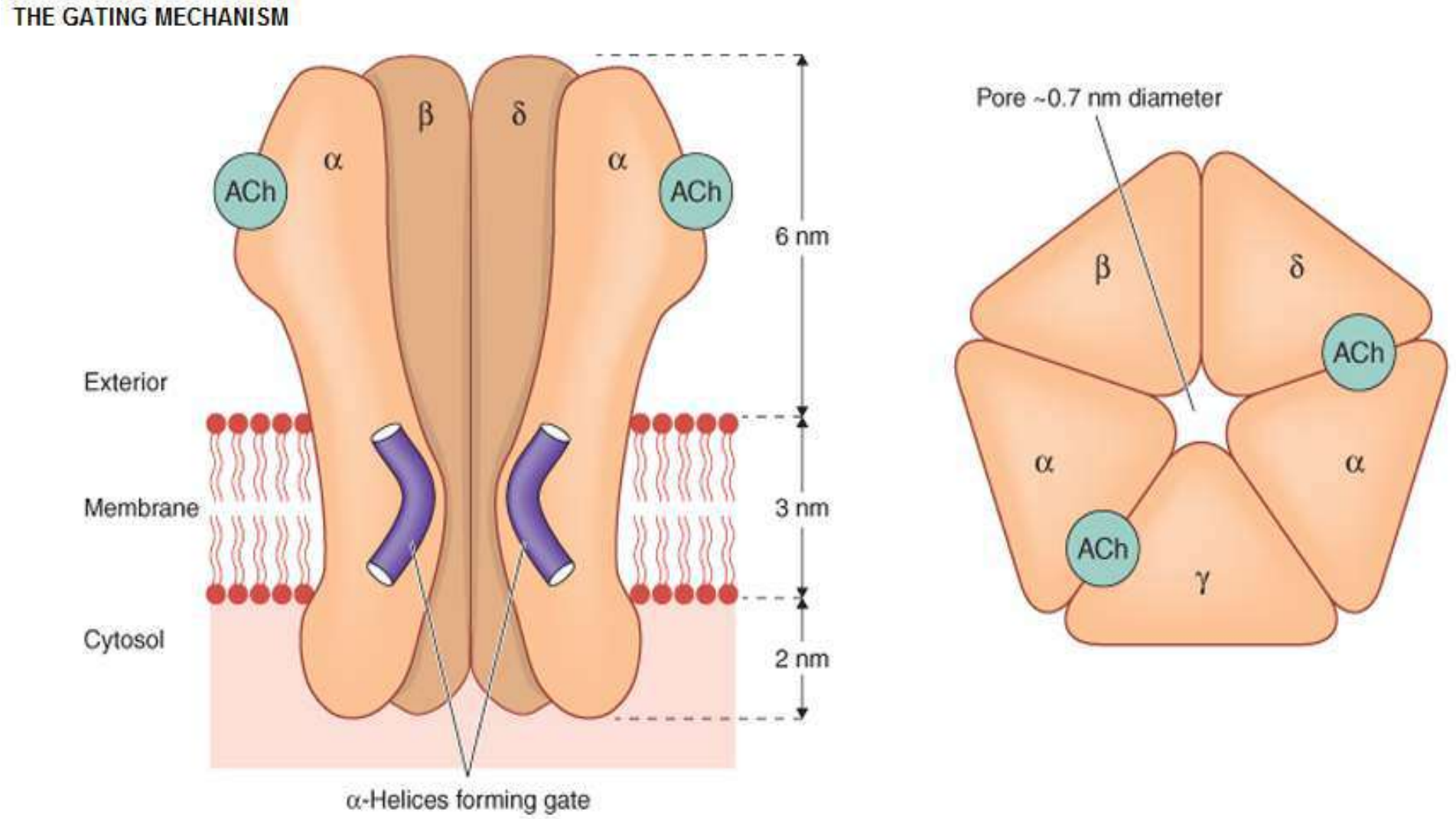
* T channels are resistant to be blocked by most of CCBs except for the drugs shown
** Q channels have properties similar to P channels. Not much is known about R channels. The neuronal pharmacology of CNS is modulated by N, P/Q and R channels. This underlines the normally observed weak effects of L channel blockers on CNS functions — The terminology of these channels sounds quite melodious. **L** stands for *long lasting*; **T** for *transient*; **N** for *neither* long lasting *nor* transient but *neuronal*; **O** somehow has been *omitted* but **P** and **Q** follow as simple English alphabets; Next is obviously **R**.



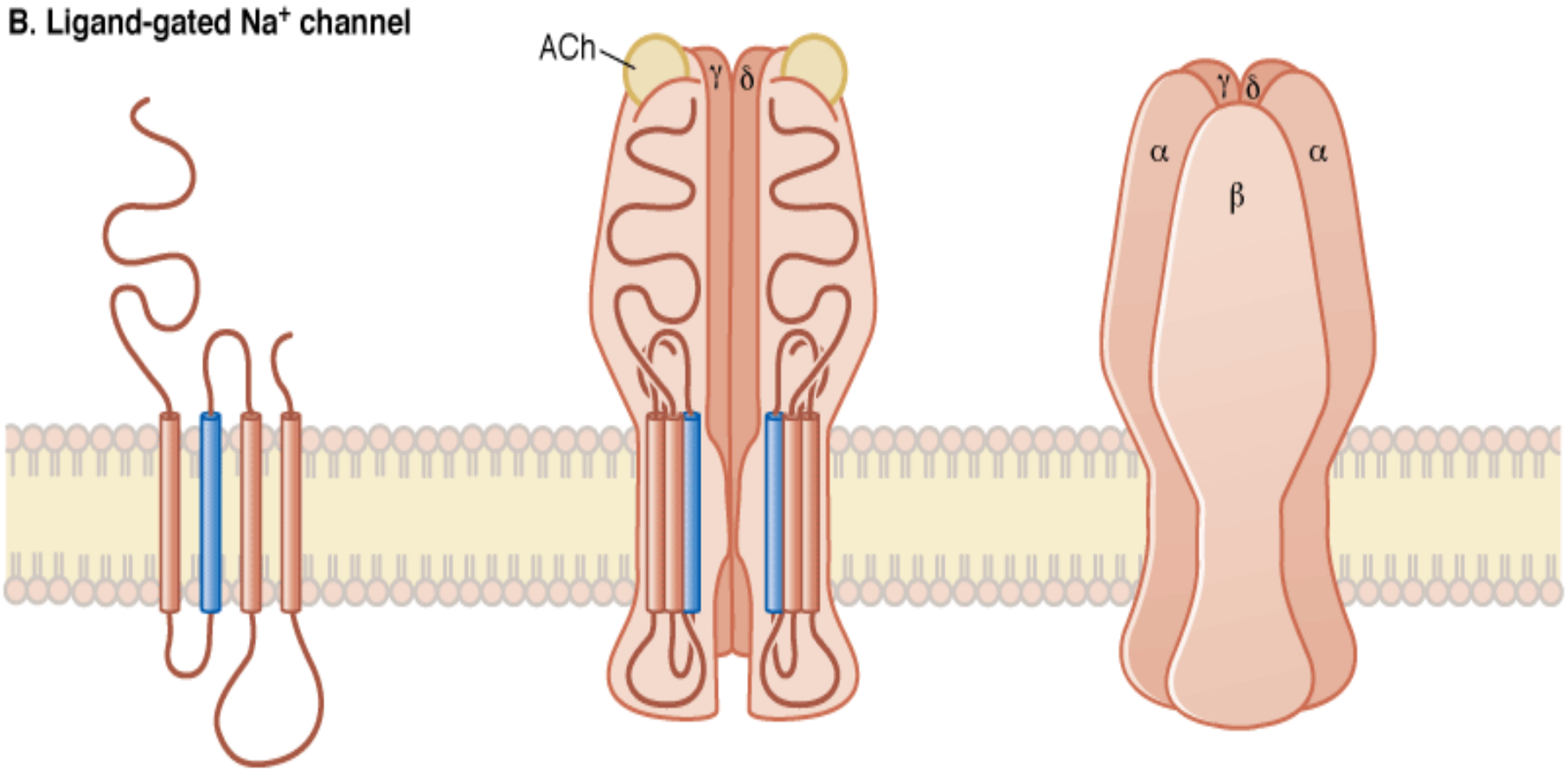
Key: AG—Activation gate; IG—Inactivation gate; R*—Receptor for CCBs with different binding sites. The part of AP during which most Ca^{2+} channels get completely or partly inactivated and not available for reactivation is shown by dashed line.

Fig 19.3 A Model of Voltage-Gated Ca^{2+} Channel Depicting the Site and Mechanism of CCBs Action

Structure of the nicotinic acetylcholine receptor (a typical ligand-gated ion channel. The five receptor subunits (α2, β, γ, δ) form a cluster surrounding a central transmembrane pore.



Ligand-gated nicotinic acetylcholine receptor expressed in the skeletal muscle neuromuscular junction. The pore is made up of five subunits, each with a large extracellular domain and four transmembrane helices. The helix that lines the pore is shown in blue.



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

PHYSIOLOGICAL RECEPTOR

STRUCTURAL FAMILY	FUNCTIONAL FAMILY	PHYSIOLOGICAL LIGANDS	EFFECTORS AND TRANSDUCERS	EXAMPLE DRUGS
GPCR	β Adrenergic receptors	NE, Epi, DA	G_s ; AC	Dobutamine
	Muscarinic cholinergic receptors	ACh	G_i and G_q; AC, ion channels, PLC	Atropine
	Eicosanoid receptors	Prostaglandins, leukotrienes, thromboxanes	G_s, G_i and G_q proteins	Misoprostol, montelukast

G Proteins

- **GPCRs** a family of heterotrimeric GTP-binding regulatory proteins termed **G proteins**.

- **G proteins** are signal transducers that convey the information that agonist is bound to the receptor from the receptor to one or more effector proteins.

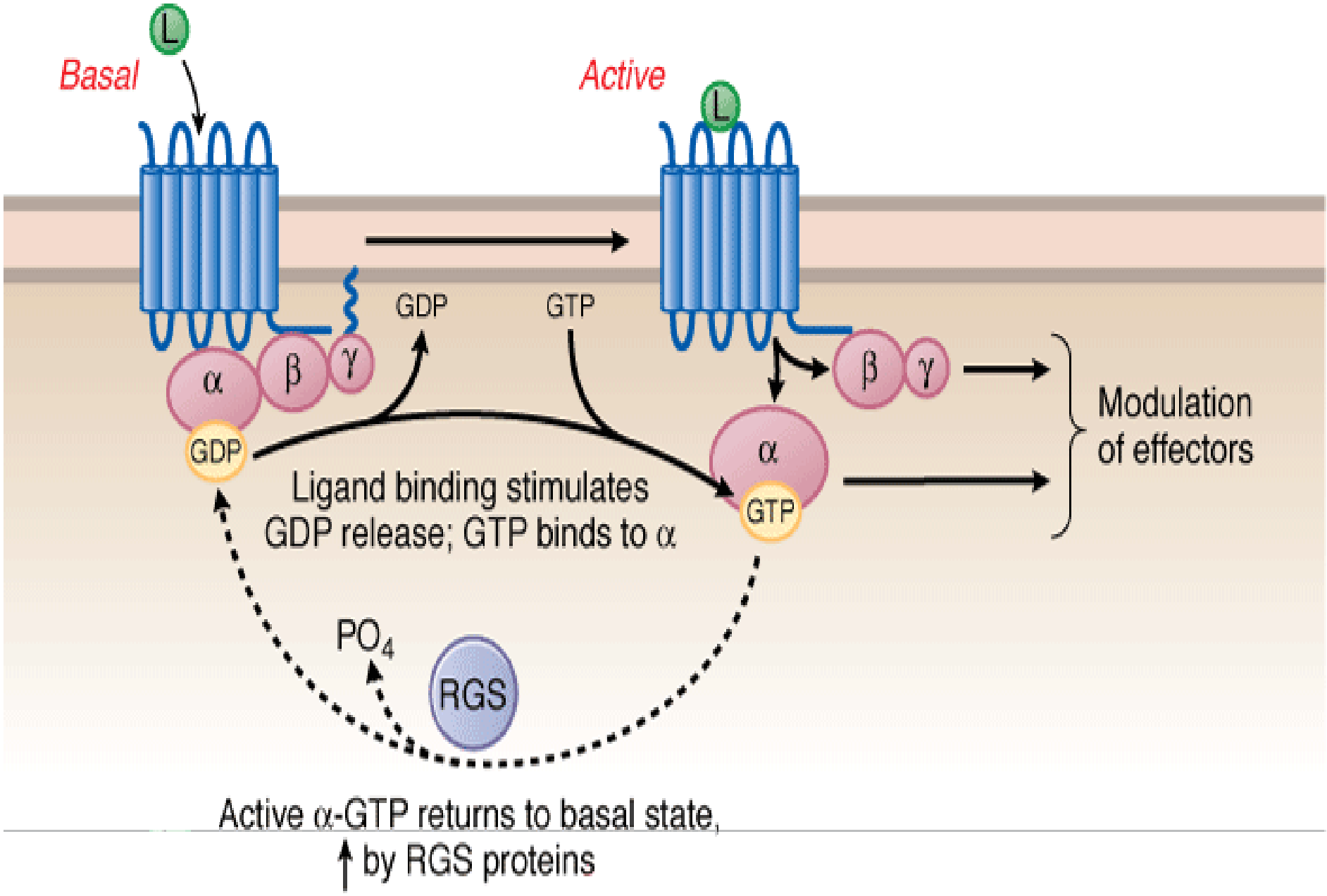
- The G protein heterotrimer is composed of a guanine nucleotide-binding **α subunit**, which confers specific recognition to both receptors and effectors, and an associated dimer of **β and ϒ subunits.**

- G–protein-regulated effectors include enzymes such as
  -**adenylyl cyclase,**
  -phospholipase C,
  -cyclic GMP phosphodiesterase (PDE6),
  -membrane ion channels selective for Ca^{2+} and K^{+}.

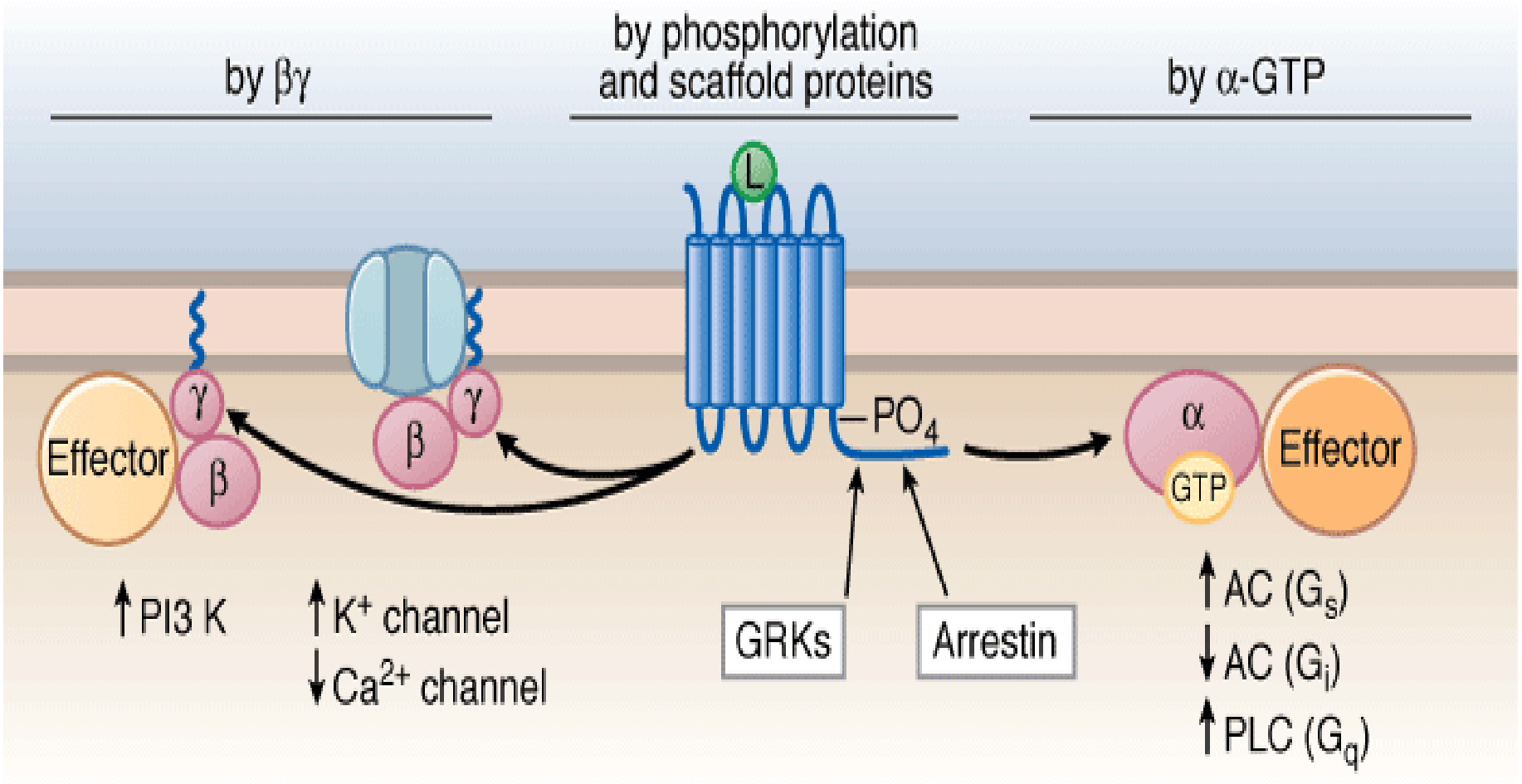
G Protein–Coupled Receptors (GCPRs)

- GPCRs span the plasma membrane as a bundle of seven alfa-helices.
- Extracellular binding site for ligand.
- Cytosolic binding site for transducer G-protein.

A. Activation by Ligand Binding of GPCR

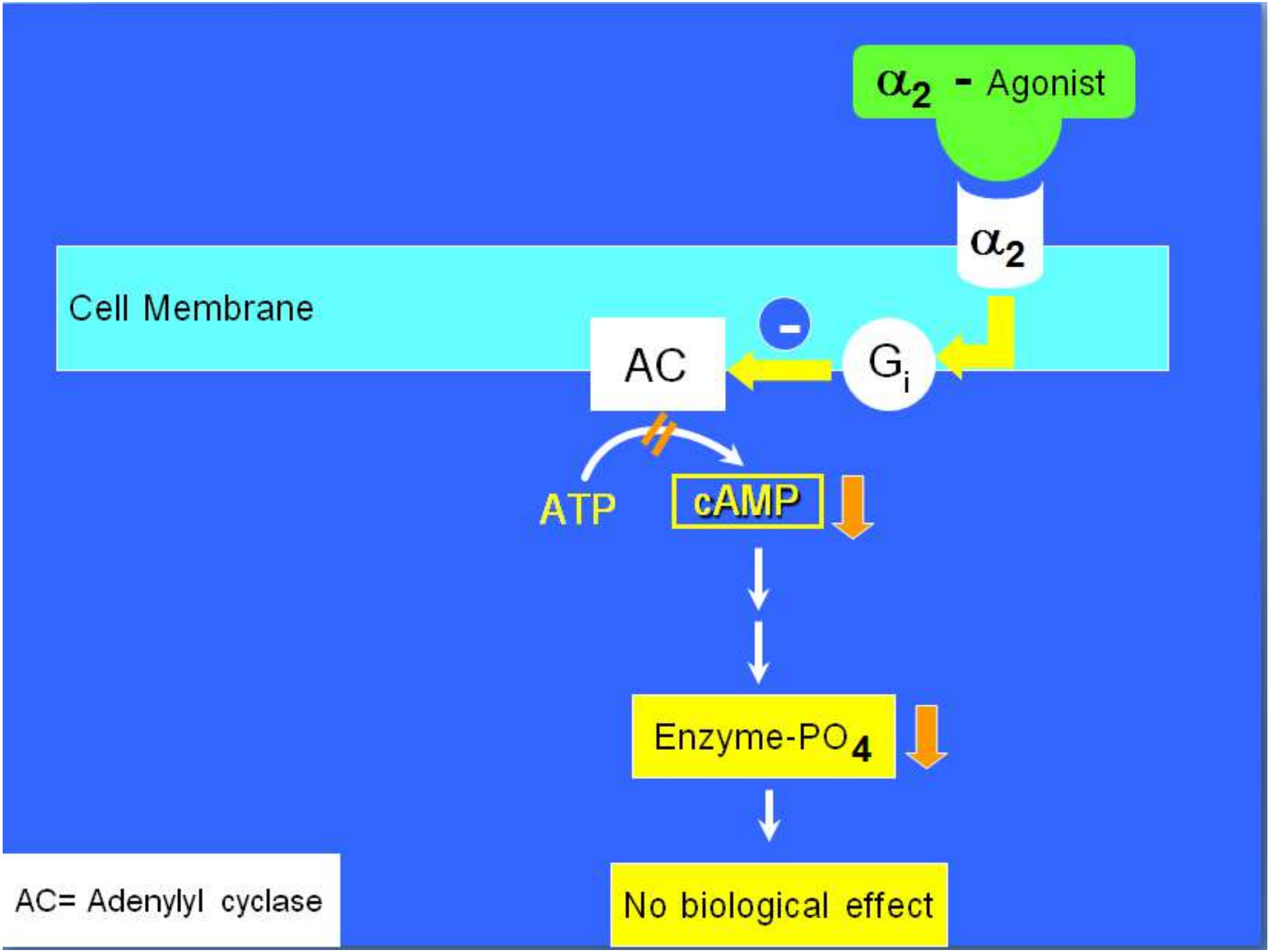


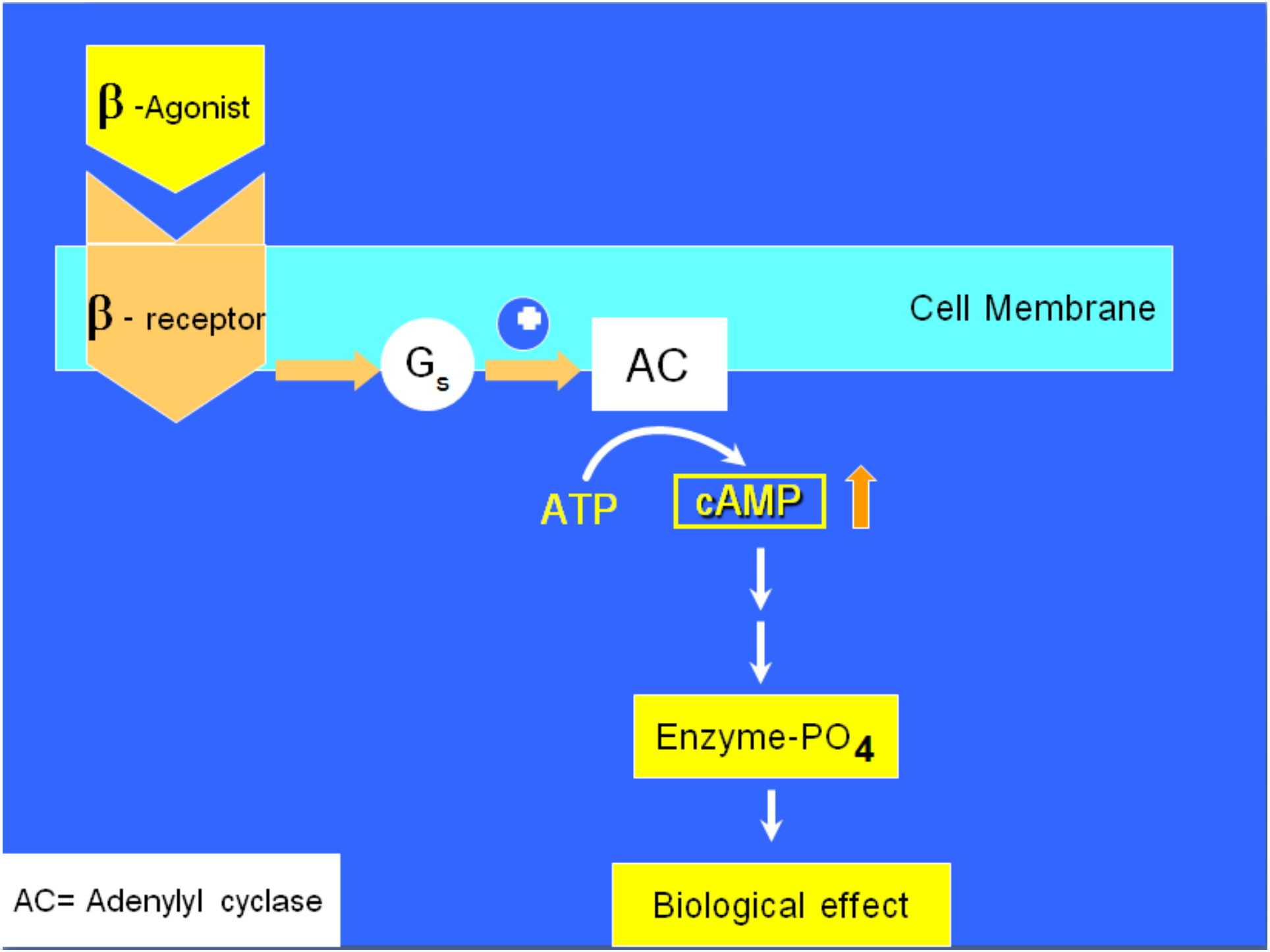
B. Modulation of Effectors

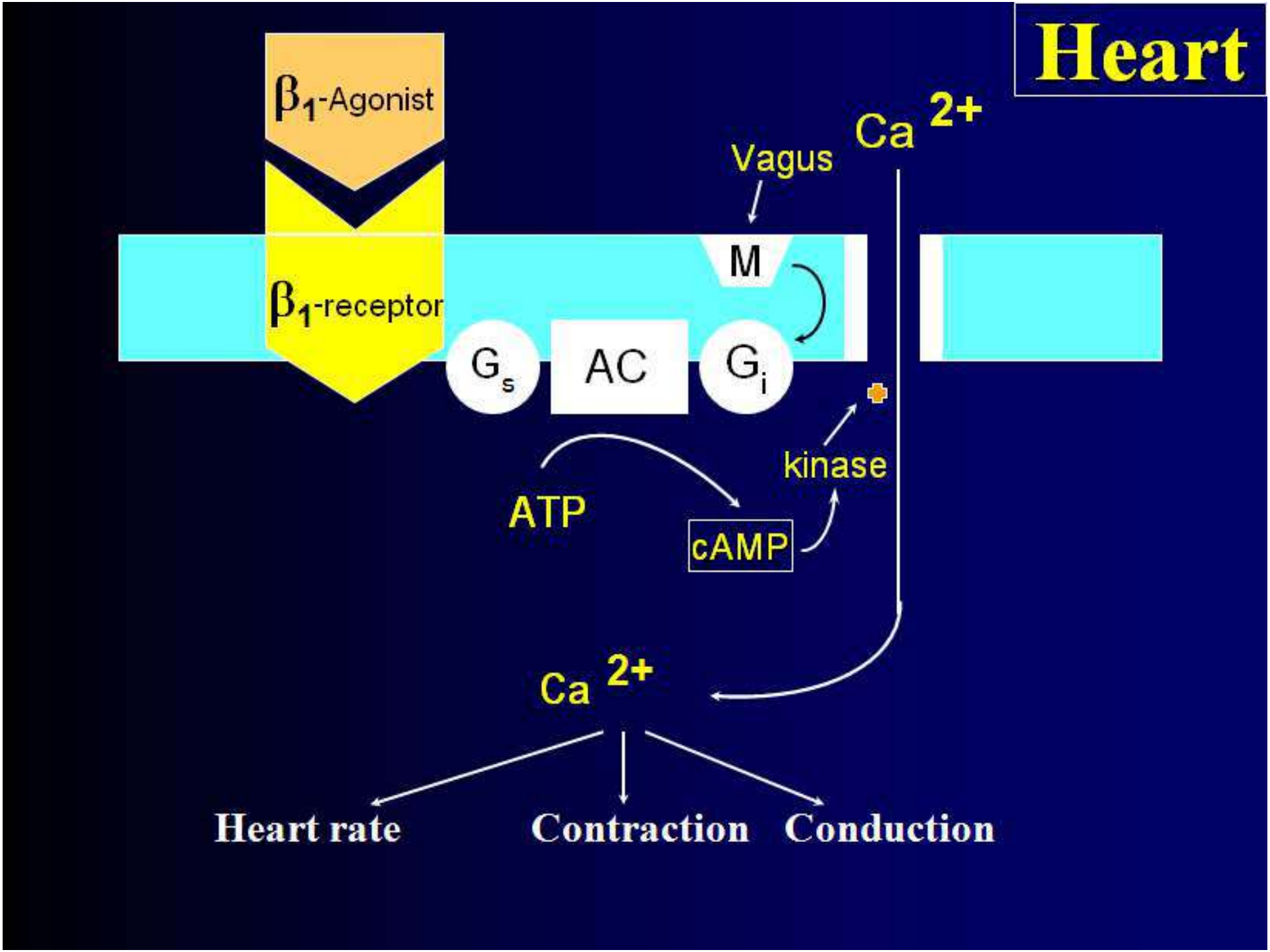


- The subunits fall into four families (G_s, G_i, G_q, and $G_{12/13}$).

- The **G_s** α-subunit uniformly activates adenylyl cyclase;
- the **G_i** α-subunit can inhibit certain isoforms of adenylyl cyclase;
- the **G_q** α-subunit activates all forms of phospholipase C;
- and the **$G_{12/13}$** α-subunits couple to guanine nucleotide exchange factors (GEFs), such as p115RhoGEF for the small GTP-binding proteins Rho and Rac.


α2 - Agonist
α2
Cell Membrane
AC
Gi
ATP
cAMP
Enzyme-PO4
No biological effect
AC= Adenylyl cyclase


β -Agonist
β - receptor
Cell Membrane
G_s
AC
ATP
cAMP
Enzyme-PO_4
Biological effect
AC= Adenylyl cyclase


Heart
β1-Agonist
β1-receptor
Vagus
Ca 2+
M
Gs
AC
Gi
ATP
cAMP
kinase
Ca 2+
Heart rate
Contraction
Conduction

Adenylyl cyclase-cAMP pathway

↑ cAMP (2nd messenger)

PK_A phosphorylation

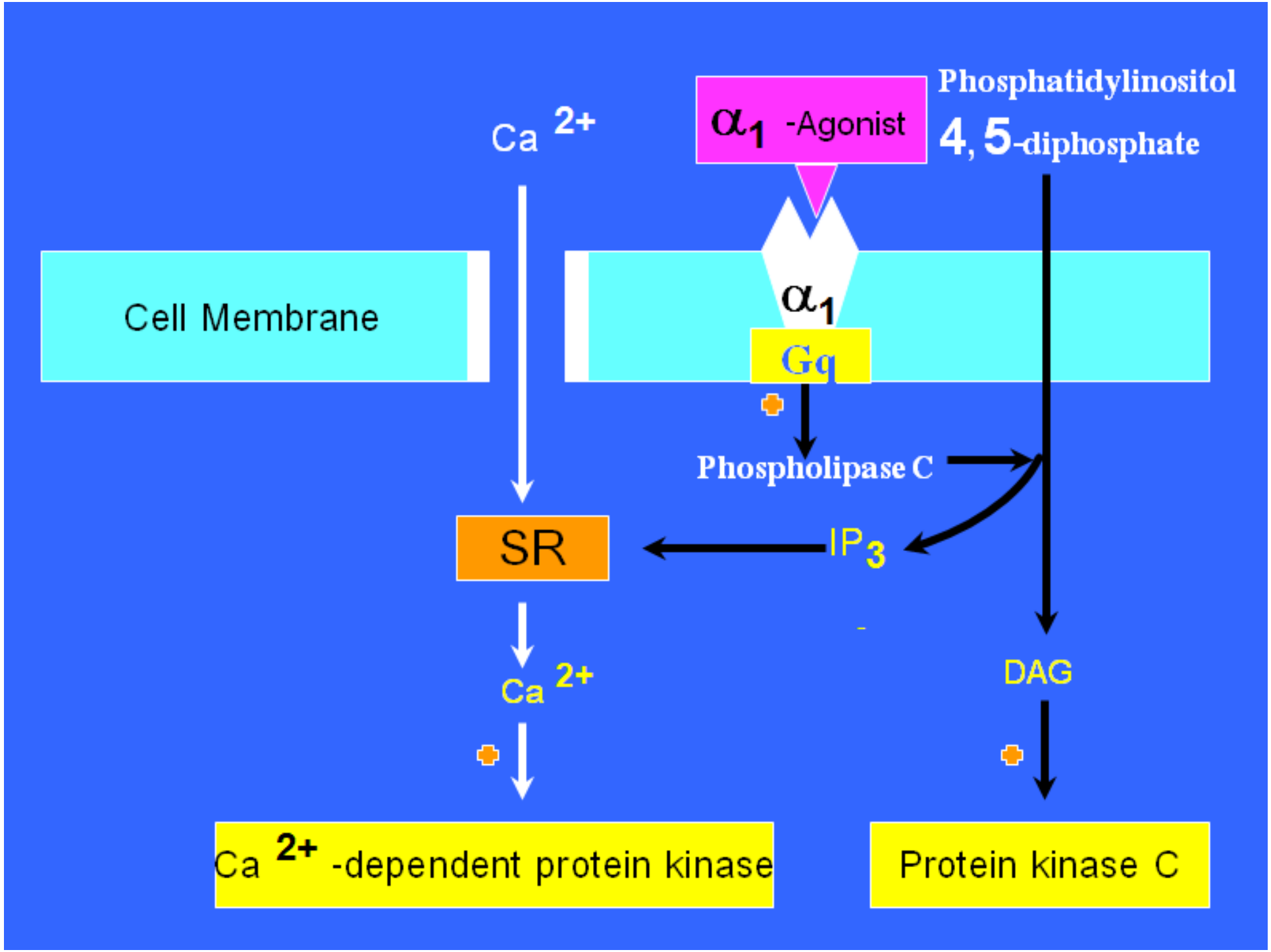
Various functions

-↑ heart contraction

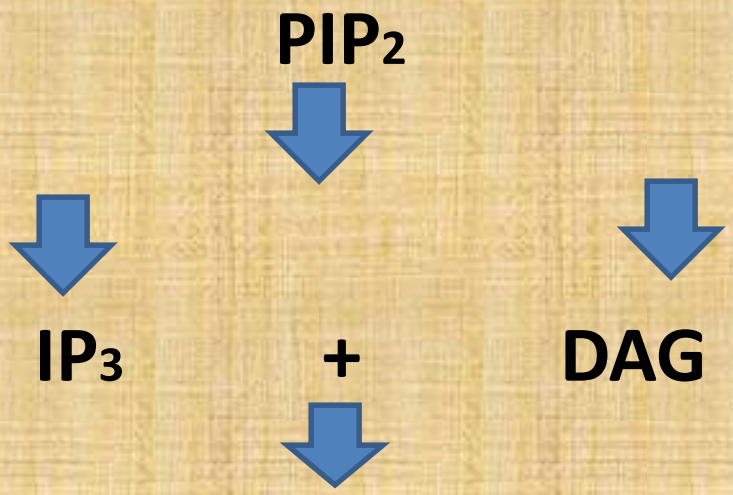
-Smooth mus relaxation

-Glycogenolysis

-lipolysis


Ca 2+
α1 -Agonist
Phosphatidylinositol
4, 5-diphosphate
Cell Membrane
α1
Gq
Phospholipase C
SR
IP3
Ca 2+
DAG
Ca 2+ -dependent protein kinase
Protein kinase C

Phospholipase C: IP_3-DAG pathway



Activation of **CCPK, MLCK, PKc**

-contraction

-neural excitation

-cell proliferation

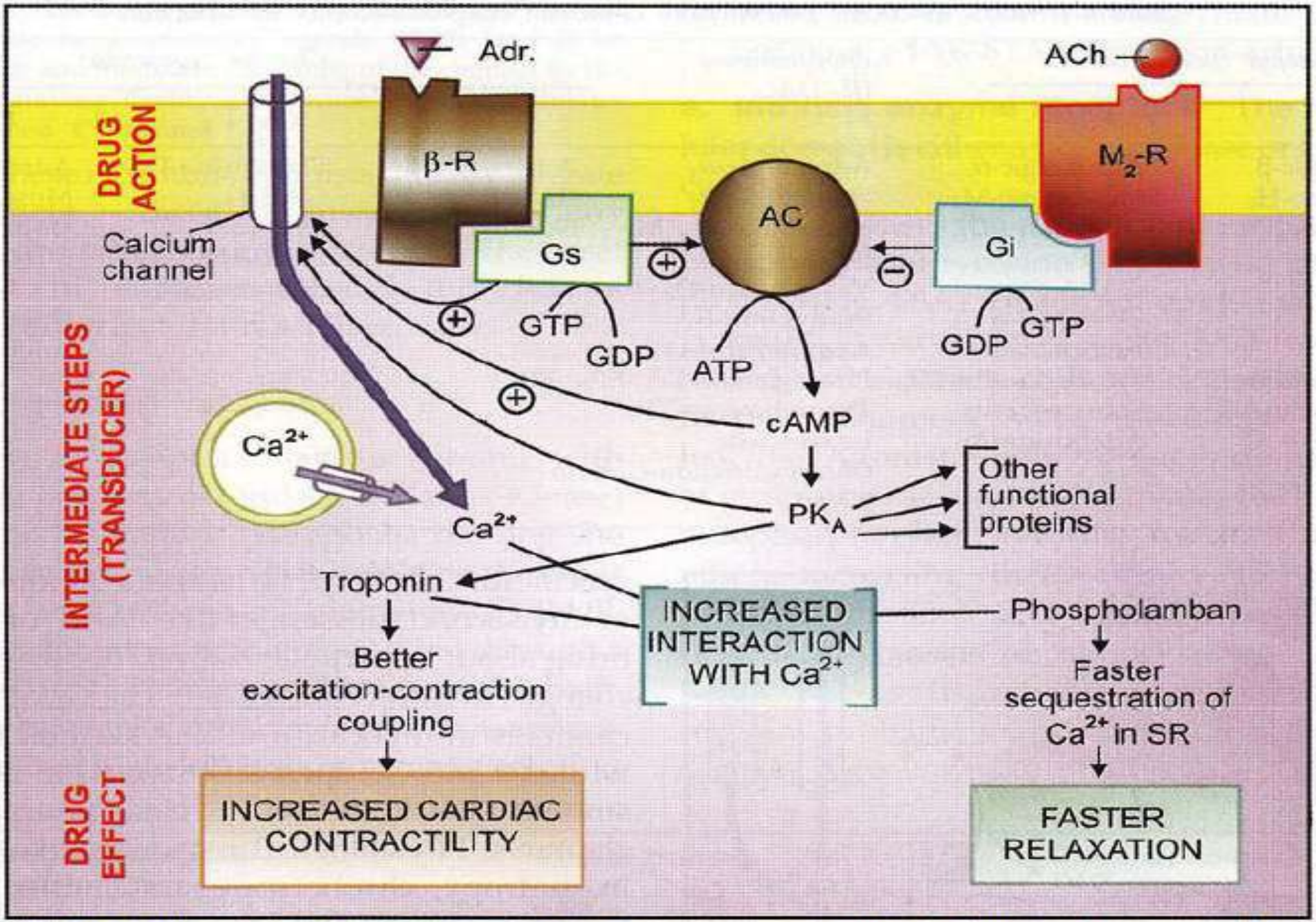


Fig. 4.6: The action-effect sequence of two G-protein coupled (β adrenergic and muscarinic M_2) receptor activation in myocardial cell

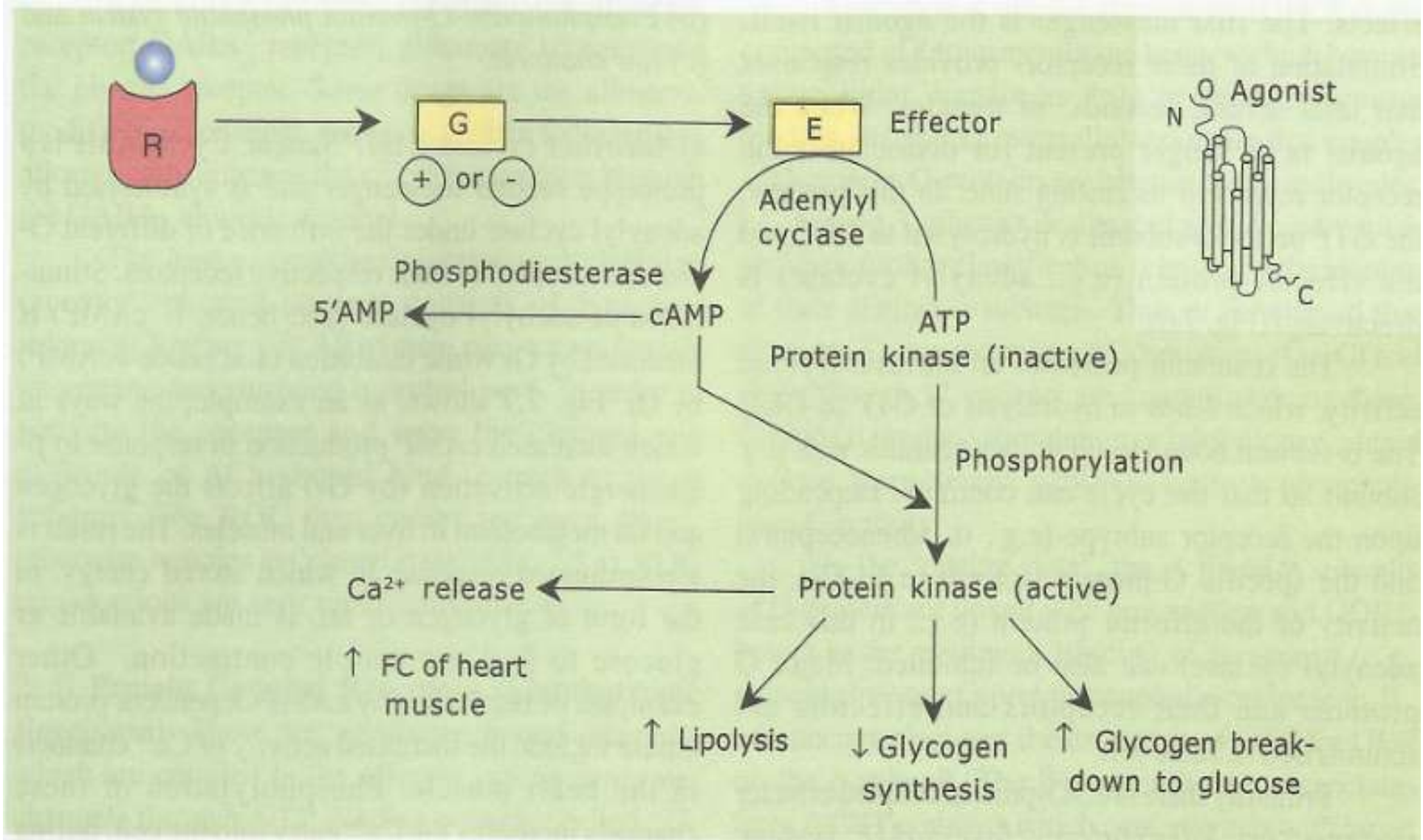


Fig 7.7 Regulation of Energy Metabolism and Contractility of the Heart by cAMP Dependent Protein Kinases. Inset: 7-transmembrane helical topology of G-protein coupled receptor (R). N terminal: Agonist binding domain; C terminal: G-protein coupling domain.

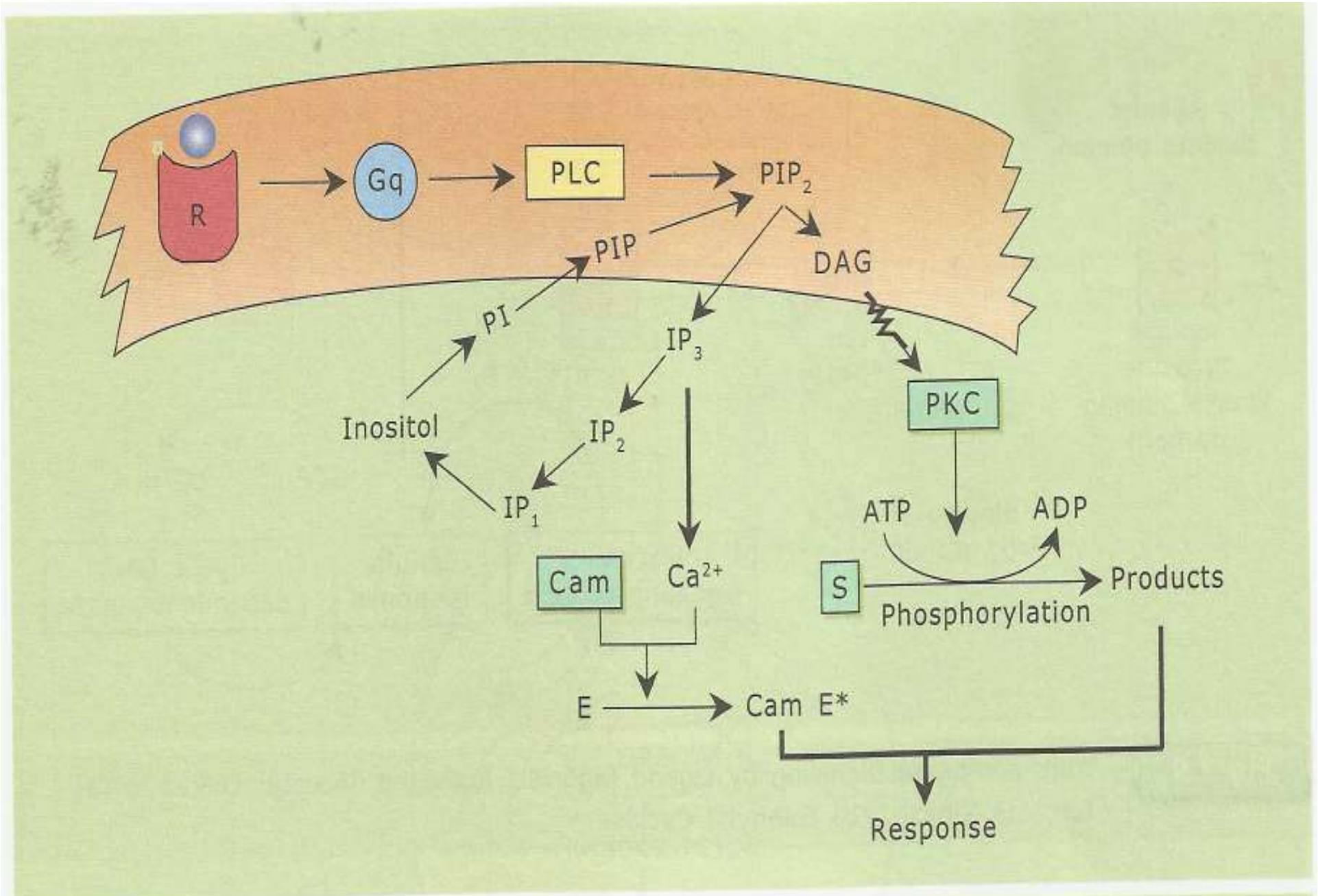


Fig 7.8 The Ca^{2+}-Phosphoinositide Signaling Pathway.

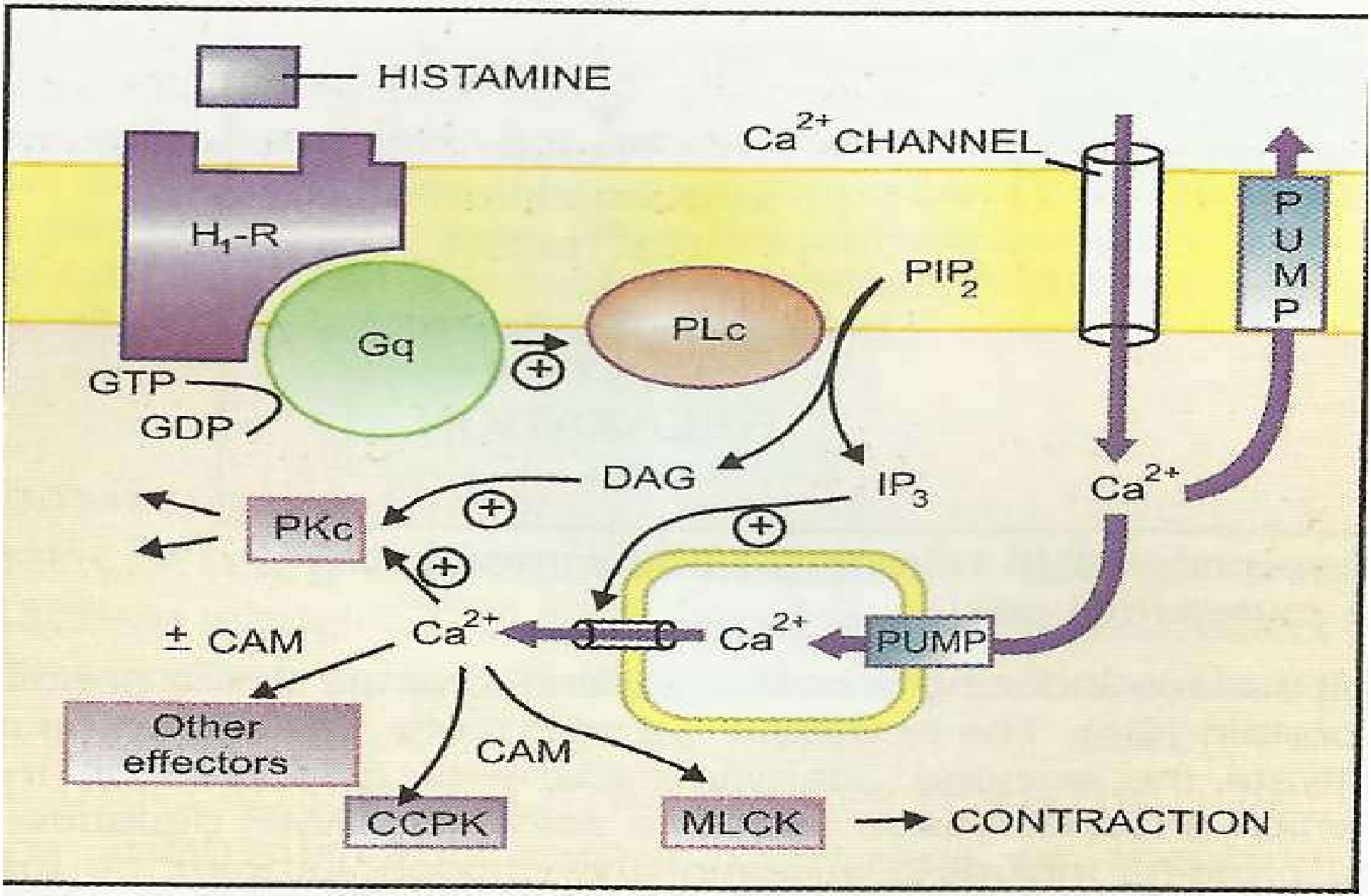


Fig. 4.7: The important steps of phospholipase C(PLc) pathway of response effectuation (in smooth muscle)

Table 4.1: Major functional pathways of G-protein coupled receptor transduction

Adenylyl cyclase: cAMP		*Phospholipase IP_3-DAG*	*Channel regulation*		
↑	↓		Ca^{2+}↑	Ca^{2+}↓	K^+↑
Adrenergic-β	Adrenergic-α_2	Adrenergic-α_1	Adrenergic-β_1	Dopamine-D2	Adrenergic-α_2
Histamine-H_2	Muscarinic-M_2	Histamine-H_1	(Heart,	$GABA_B$	Muscarinic-M_2
Dopamine-D1	Dopamine-D2	Muscarinic-M_1, M_3	Sk.muscle)	Opioid-κ	Dopamine-D2
Glucagon	5-HT_1	5-HT_2		Adenosine-A_1	5-HT_{1A}
FSH & LH	$GABA_B$	Vasopressin-Oxytocin		Somatostatin	$GABA_B$
ACTH	Opioid-μ, δ	Bradykinin-B_2			Opioid-μ, δ
TSH	Angiotensin-AT_1	Angiotensin-AT_1			Adenosine-A_1
Prostaglandin-EP_2	Prostaglandin-EP_3	Prostaglandin-FP, EP_1, EP_3			
Prostacyclin-IP	Somatostatin	Thromboxane-TP			
Adenosine-A_2	Adenosine-A_1	Leukotriene			
		Cholecystokinin-Gastrin			
		PAF			

RESENSITIZATION AND DOWN-REGULATION OF RECEPTOR

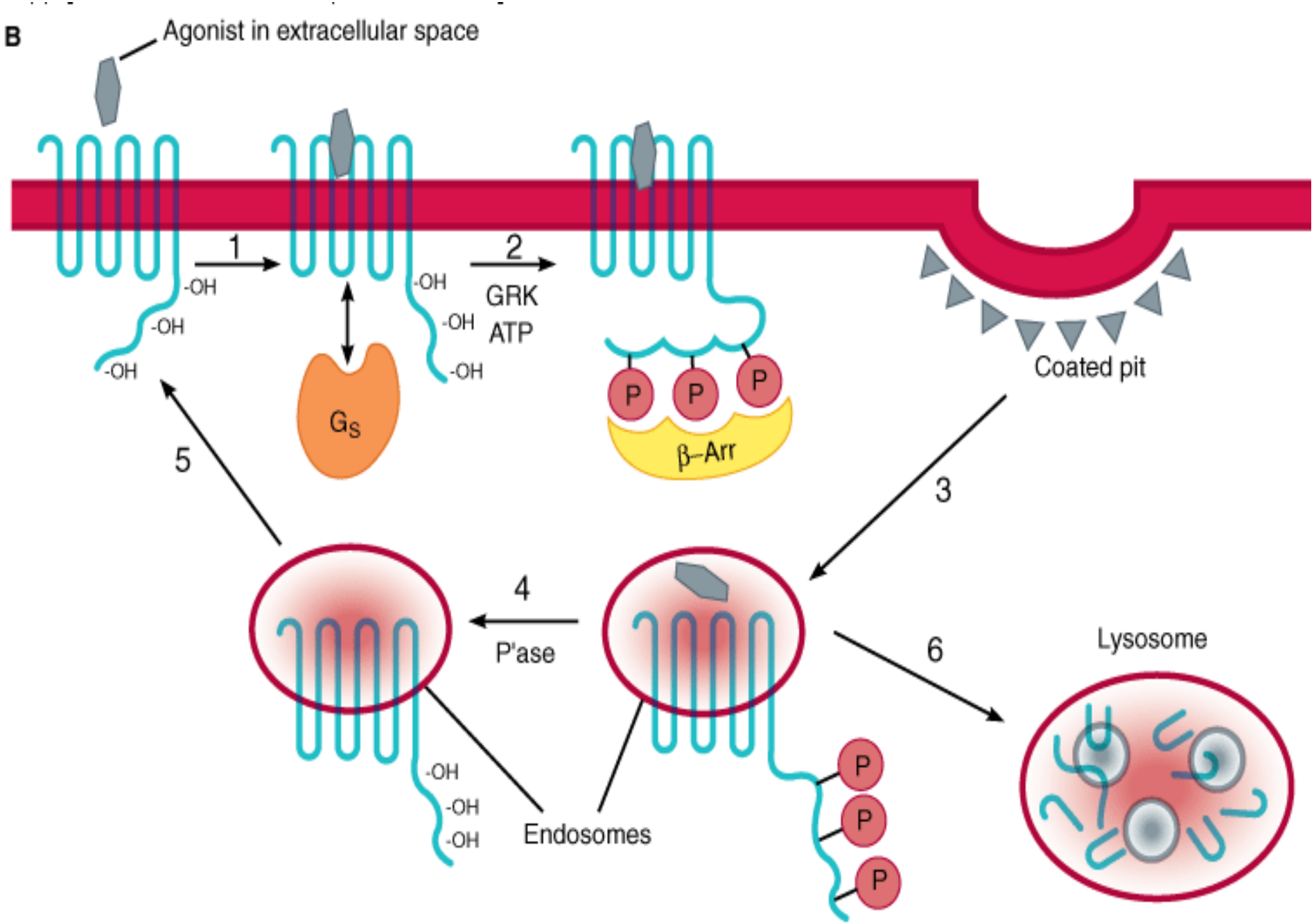
1. Agonist binding to receptors initiates signaling by promoting receptor interaction with G proteins (G_s) located in the cytoplasm.

2. Agonist-activated receptors are phosphorylated by a G protein-coupled receptor kinase (GRK), preventing receptor interaction with G_s and promoting binding of a different protein, - β arrestin (β-Arr), to the receptor.

3. The receptor- β arrestin complex binds to coated pits, promoting receptor internalization.

4. Dissociation of agonist from internalized receptors reduces - β Arr binding affinity, allowing dephosphorylation of receptors by a phosphatase.

5. Return of receptors to the plasma membrane result in the efficient resensitization of cellular responsiveness.
6. Repeated or prolonged exposure of cells to agonist favors the delivery of internalized receptors to lysosomes , promoting receptor down-regulation rather than resensitization.



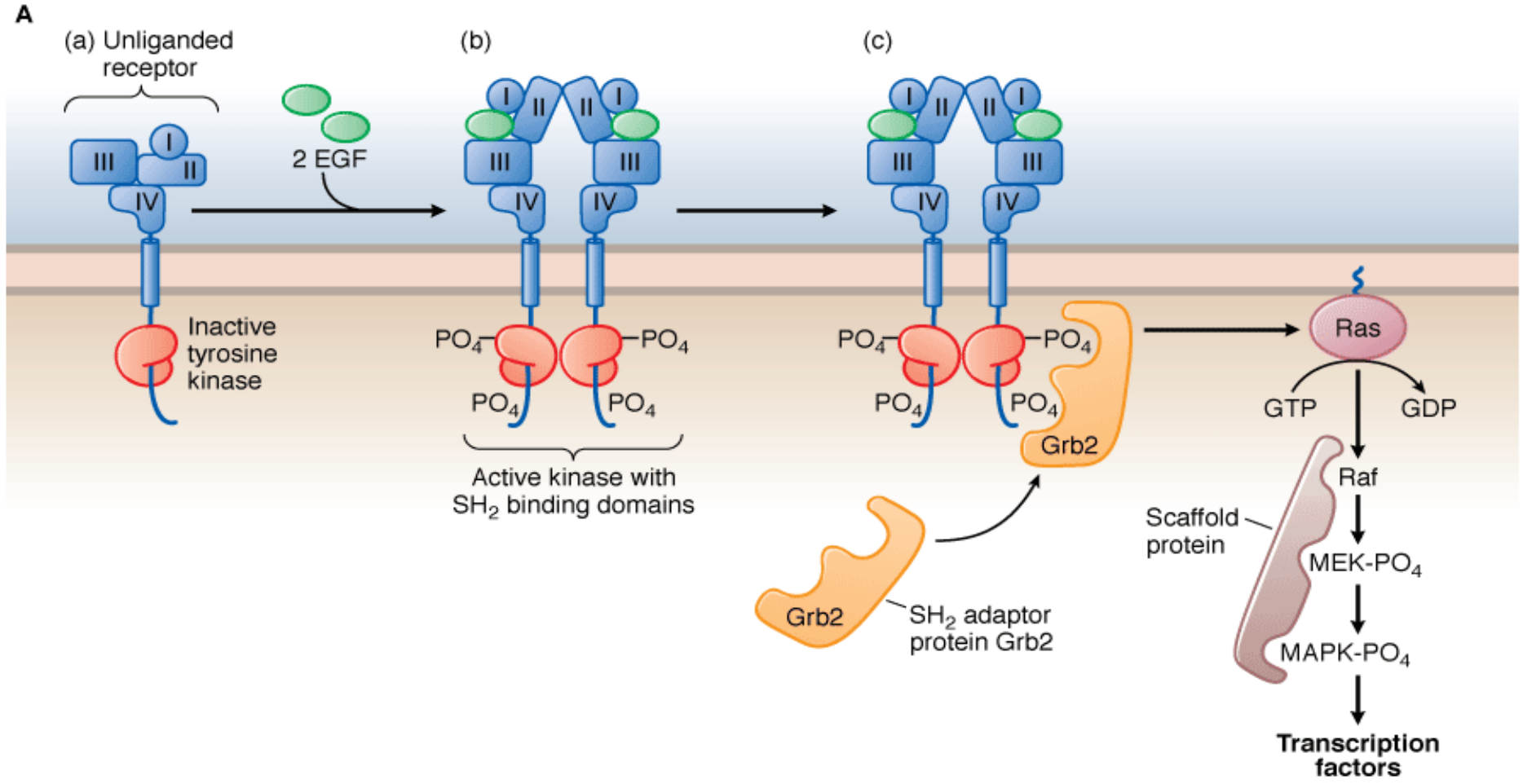
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

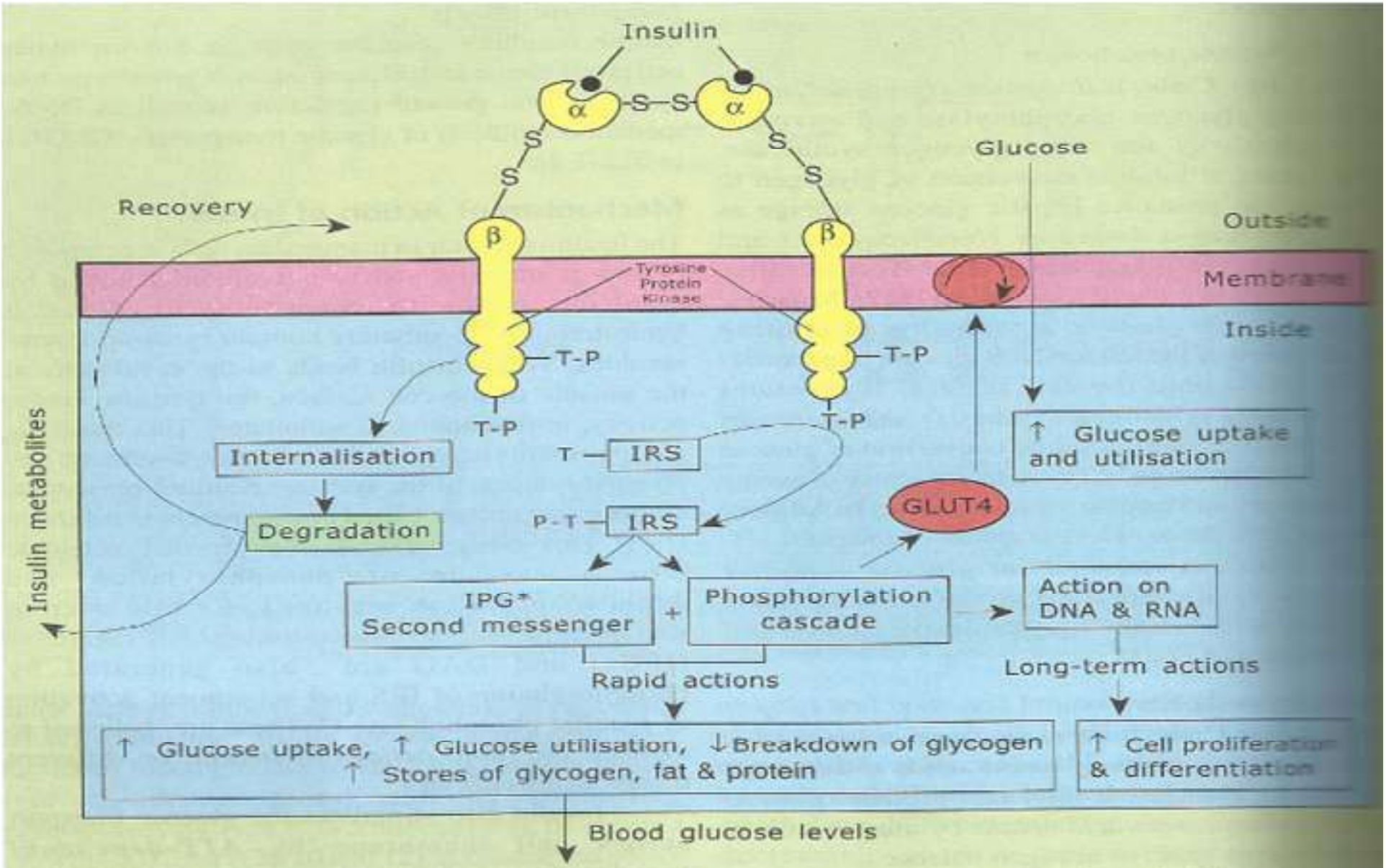
STRUCTURAL FAMILY	FUNCTIONAL FAMILY	PHYSIOLOGICAL LIGANDS	EFFECTORS AND TRANSDUCERS	EXAMPLE DRUGS
Transmembrane enzymes	Receptor tyrosine kinases	Insulin, PDGF, EGF, VEGF, growth factors	SH2 domain containing proteins	Herceptin, imatinib
	Membrane-bound GC Tyrosine phosphatases	Natriuretic peptides	Cyclic GMP	Neseritide

Enzyme linked receptors

- With intrinsic enzymatic activity.
- Without intrinsic enzymatic activity (but bind a JAK-STAT kinase on activation

receptor tyrosine kinase and a cytokine receptor. Activation of the EGF receptor. The extracellular structure of the unliganded receptor (a) contains four domains (I-IV), which rearrange significantly upon binding two EGF molecules. (b). The conformational changes lead to activation of the cytoplasmic tyrosine kinase domains and tyrosine phosphorylation of intracellular regions to form SH2 binding sites. (c). The adapter molecule Grb2 binds to the phosphoryated tyrosine residues and activates the Ras-MAP kinsase cascade





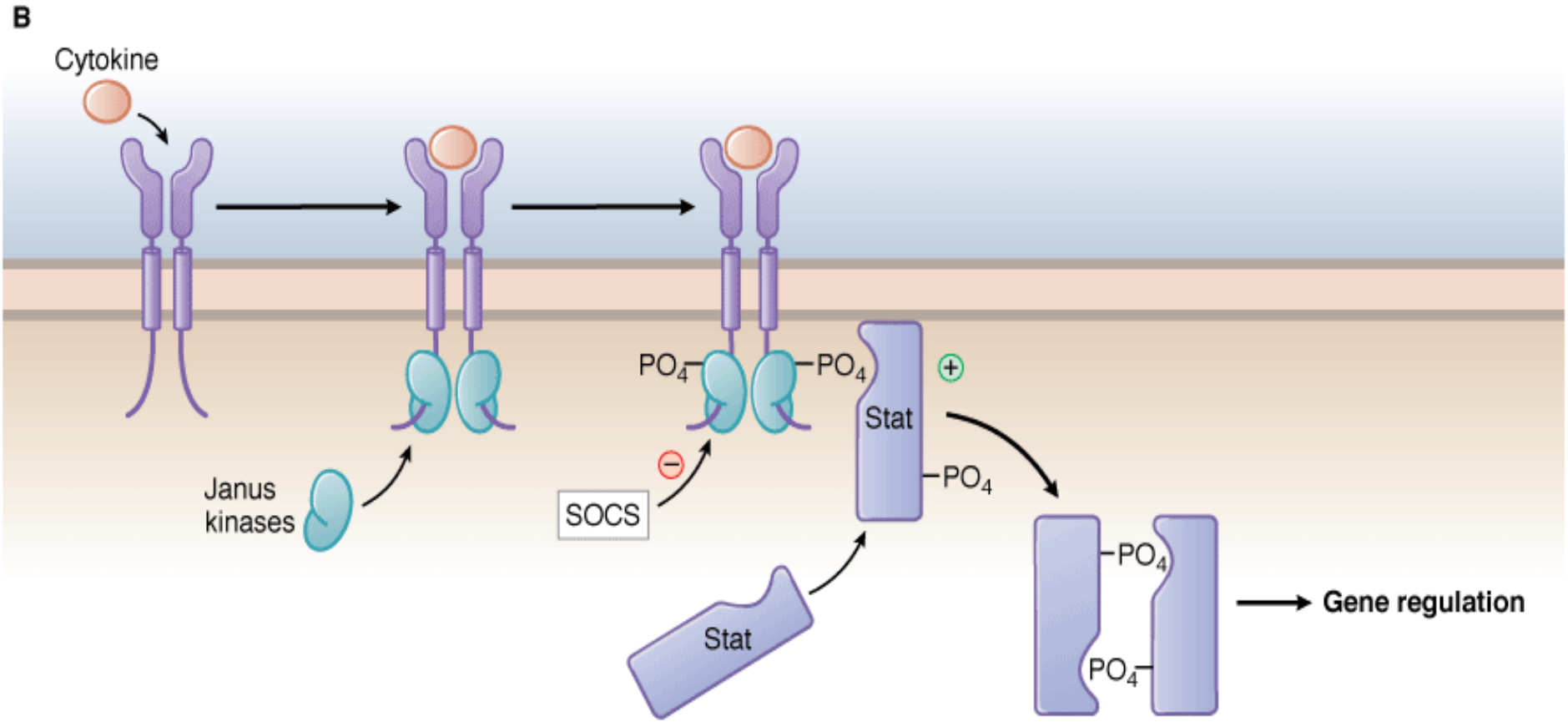
GLUT-4—Glucose transporter-4; IRS—Insulin receptor substrate; T—Tyrosine; P—Phosphate
*Inositolphosphoglycans (IPGs) are released outside of the cell but then transported back into the cell

Fig 47.3 Insulin Signaling Pathways

STRUCTURAL FAMILY	FUNCTIONAL FAMILY	PHYSIOLOGICAL LIGANDS	EFFECTORS AND TRANSDUCERS	EXAMPLE DRUGS
Transmembrane, non-enzymes	Cytokine receptors	Interleukins and other cytokines	Jak/STAT, soluble tyrosine kinases	

JAKs- STATS PATHWAY

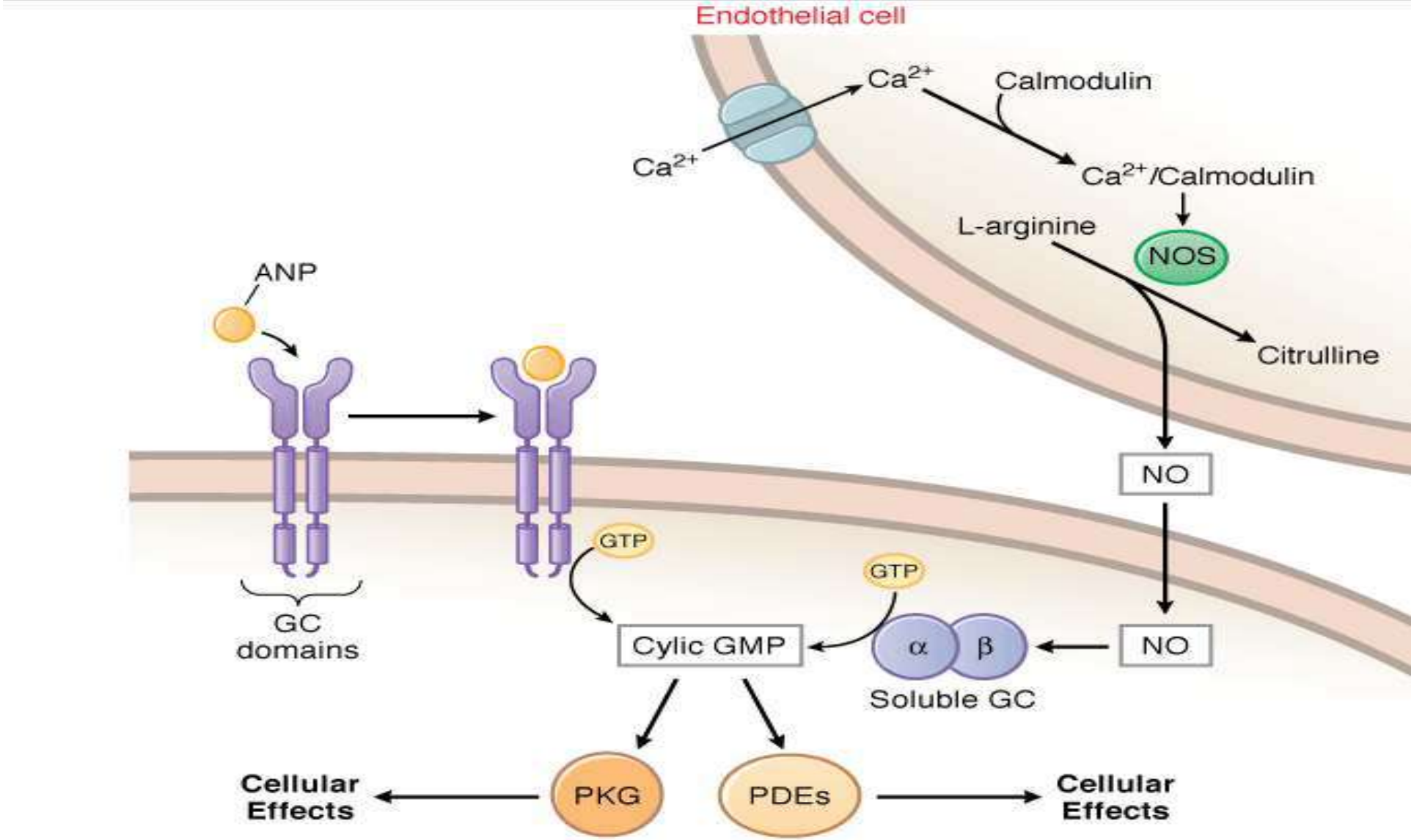
Binding of the cytokine causes dimerization of the receptor and recruits the Janus Kinases (JAKs) to the cytoplasmic tails of the receptor. JAKs trans-phosphorylate and lead to the phosphorylation of the signal transducers and activators of transcription (STATs). The phosphorylated STATS translocate to the nucleus and regulate transcription. There are proteins termed suppressors of cytokine signaling (SOCS) that inhibit the JAK-STAT pathway



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

STRUCTURAL FAMILY	FUNCTIONAL FAMILY	PHYSIOLOGICAL LIGANDS	EFFECTORS AND TRANSDUCERS	EXAMPLE DRUGS
Intracellular enzymes	Soluble GC	NO, Ca^{2+}	Cyclic GMP	Nitrovasodilators

NATRIURETIC PEPTIDE RECEPTORS



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

NO SYNTHASE AND SOLUBLE GUANYLATE CYCLASE

The cellular effects of cyclic GMP on the vascular system are mediated by a number of mechanisms, but especially by PKG. For example, in vascular smooth muscle, activation of PKG leads to vasodilation by:

- Inhibiting IP_3-mediated Ca^{2+} release from intracellular stores.
- Phosphorylating voltage-gated Ca^{2+} channels to inhibit Ca^{2+} influx.
- Phosphorylating phospholamban, a modulator of the sarcoplasmic Ca^{2+} pump, leading to a more rapid reuptake of Ca^{2+} into intracellular stores.
- Phosphorylating and opening the Ca^{2+}-activated K^+ channel leading to hyperpolarization of the cell membrane, which closes L-type Ca^{2+} channels and reduces the flux of Ca^{2+} into the cell.

STRUCTURAL FAMILY	FUNCTIONAL FAMILY	PHYSIOLOGICAL LIGANDS	EFFECTORS AND TRANSDUCERS	EXAMPLE DRUGS
Nuclear receptors	Steroid receptors	Estrogen, testosterone	Co-activators	Estrogens, androgens, cortisol
	Thyroid hormone receptors	Thyroid hormone		Thyroid hormone

Receptors regulating gene expression

- Several biologic ligands are sufficiently lipid-soluble to cross the plasma membrane and act on intracellular receptors.

  e.g.

  steroids (corticosteroids, mineralocorticoids, sex steroids, vitamin D), and thyroid hormone, whose receptors stimulate the transcription of genes by binding to specific DNA sequences near the gene whose expression is to be regulated.

- Target DNA sequences called **response elements.**

- In the absence of hormone, the receptor is bound to **hsp90**, a protein that appears to prevent normal folding of several structural domains of the receptor.

- Binding of hormone to the ligand-binding domain triggers release of hsp90.

- This allows the DNA-binding and transcription-activating domains of the receptor to fold into their functionally active conformations, so that the activated receptor can initiate transcription of target genes.

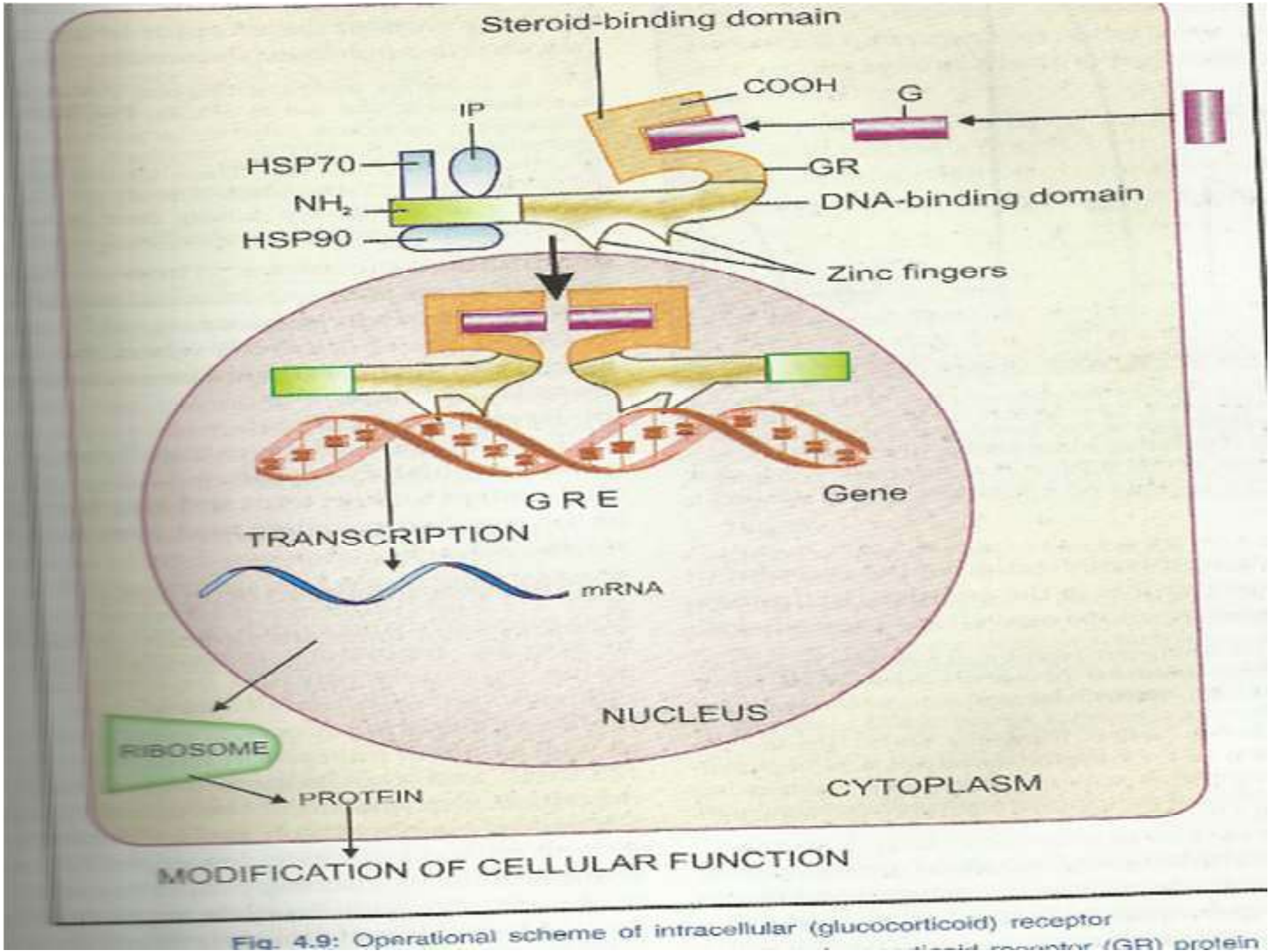
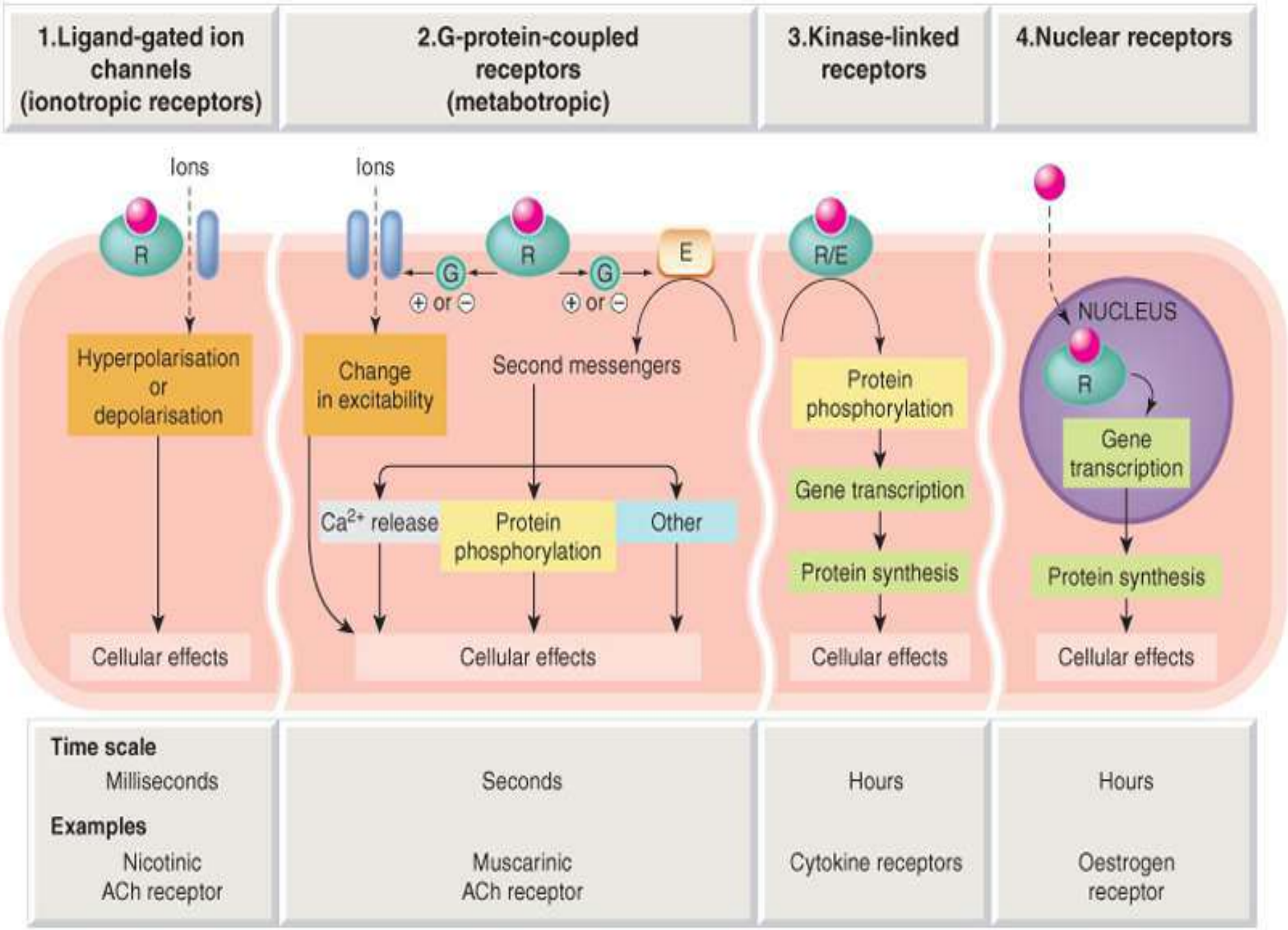
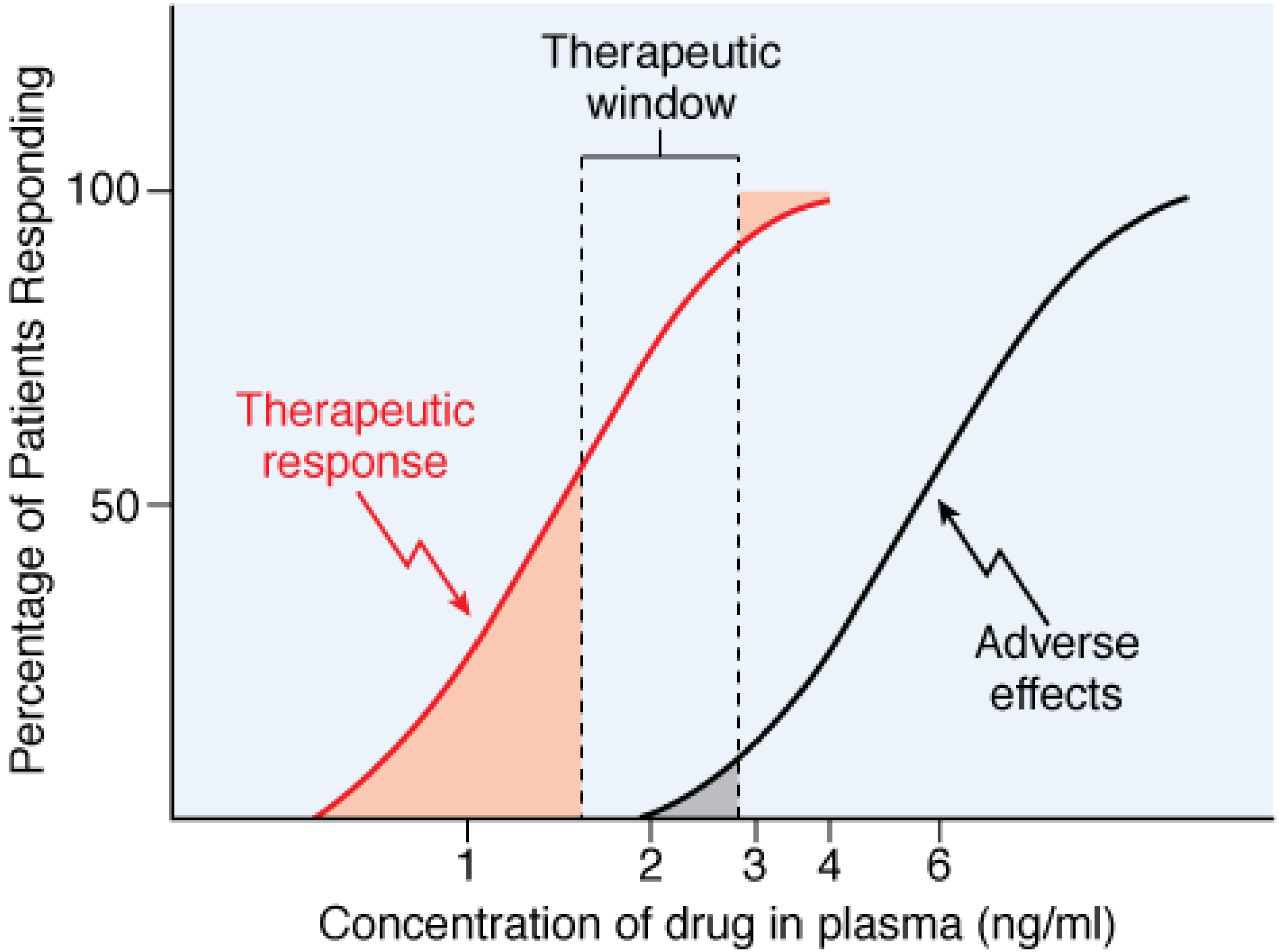


Fig. 4.9: Operational scheme of intracellular (glucocorticoid) receptor


1.Ligand-gated ion channels (ionotropic receptors)
2.G-protein-coupled receptors (metabotropic)
3.Kinase-linked receptors
4.Nuclear receptors
Ions
R
Hyperpolarisation or depolarisation
Cellular effects
Ions
R
G
⊕ or ⊖
R
G
⊕ or ⊖
E
Change in excitability
Second messengers
Ca^{2+} release
Protein phosphorylation
Other
Cellular effects
R/E
Protein phosphorylation
Gene transcription
Protein synthesis
Cellular effects
NUCLEUS
R
Gene transcription
Protein synthesis
Cellular effects
Time scale
Milliseconds
Seconds
Hours
Hours
Examples
Nicotinic ACh receptor
Muscarinic ACh receptor
Cytokine receptors
Oestrogen receptor

Therapeutic window

- Therapeutic effect is seen only with in a narrow range of plasma conc.
- Both above & below this range, beneficial effect is suboptimal.
- Drugs having low therapeutic window
  - Theophylline
  - Carbamazepine
  - Digoxin
  - Lithium
  - Phenytoin


Therapeutic window
Therapeutic response
Adverse effects
Percentage of Patients Responding
100
50
1
2
3
4
6
Concentration of drug in plasma (ng/ml)

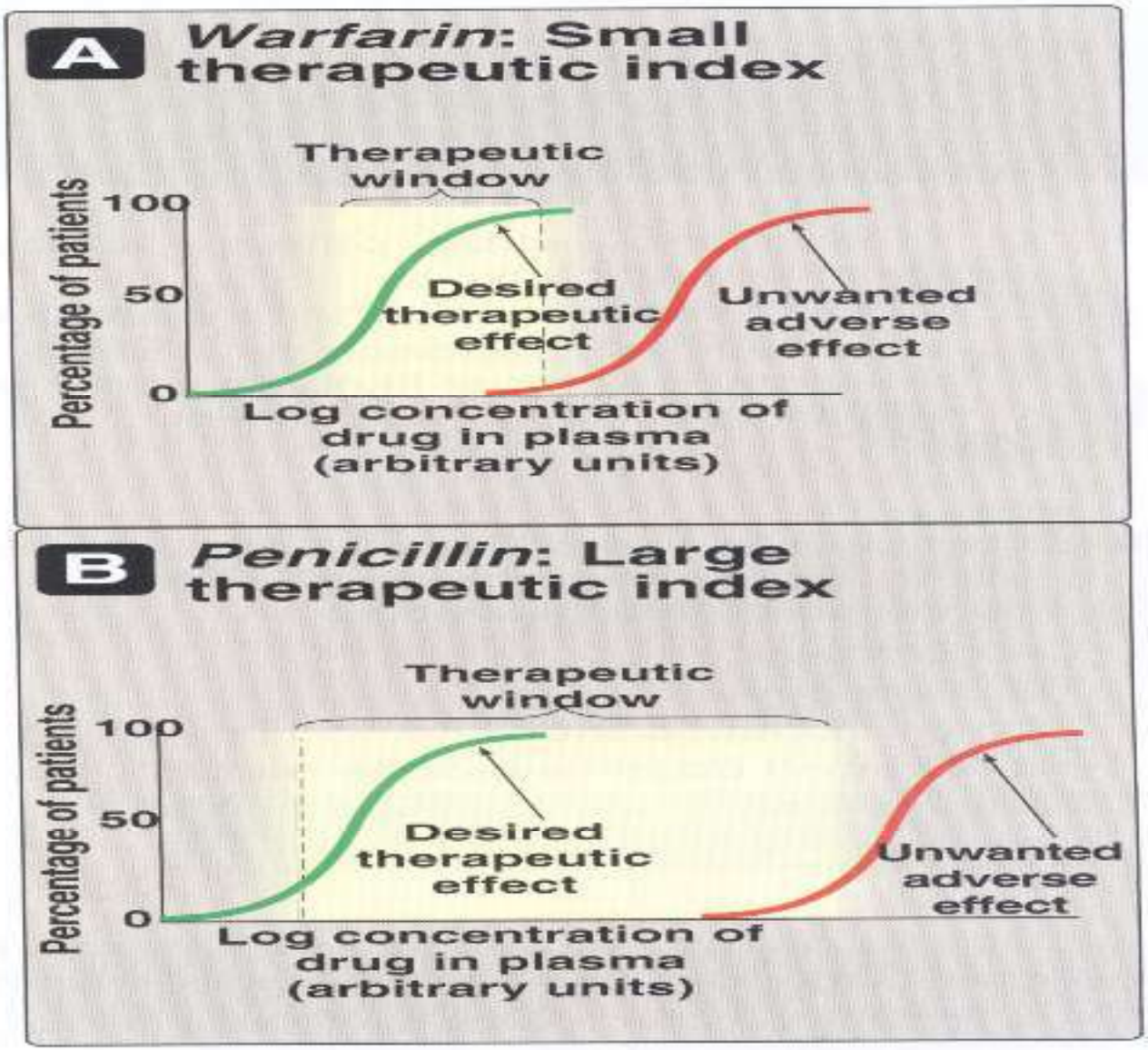


Figure 2.11
Cumulative percentage of patients responding to plasma levels of a drug.

Therapeutic Index

- **Is the ratio of the LD50 to ED50**
- **Represent an estimate of the safety of a drug.**

Importance of graded dose-response curves

1.Calculation of the ED50 (The dose that produces 50% of the maximum response in one animal

- Comparing ED50 of different drugs on the same animal gives an idea about the equieffective doses i.e the doses that produce the same effect.
- Comparing ED50 of the same drug in different patients gives an idea about the relative sensitivity of the patients to the same drug i.e the degree of biological variation inherent in a population.

2. Calculation of the maximum response

- Comparing the maximum response obtained by different drugs on the same organ gives an idea about the intrinsic activity.

3. Determination of the stepiness of the dose response

- Any small change in the drug concentration produces significant increase in the tissue response. This means that maximum response to the drug could be reached very fast and the toxicity could be reached very fast too.

SYNERGISM

(Greek: Syn-together; ergon-work)

- When the action of one drug is facilitated or increased by the other, they are said to be synergistic.

- In a synergistic pair, both the drugs can have action in the same direction or given alone one may be inactive but still enhance the action of the other when given together.

Additive

The effect of the two drugs is in the same direction and simply adds up:

effect of drugs A + B = effect of drug A + effect of drug B

Additive drug combinations	
Aspirin + paracetamol	as analgesic/ antipyretic
Nitrous oxide + halothane	as general anaesthetic
Amlodipine + atenolol	asantihypertensive
Glibenclamide + metformin	as hypoglycaemic
Ephedrine + theophylline	as bronchodilator

Supraadditive (potentiation)

The effect of combination is greater than the individual effects of the components:

effect of drug A+ B > effect of drug A+ effect of drug B

This is always the case when one component is inactive as such.

Supraadditive drug combinations

Drug pair	*Basis of potentiation*
Acetylcholine + physostigmine	Inhibition of break down
Levodopa + carbidopa/ benserazide	Inhibition of peri-pheral metabolism
Adrenaline + cocaine/ desipramine	Inhibition of neuronal uptake
Sulfamethoxazole + trimethoprim	Sequential blockade
Antihypertensives (enalapril+ hydrochlorothiazide)	Tackling two contributory factors
Tyramine + MAO inhibitors	Increasing release-able CA store

Antagonism

Competitive antagonist

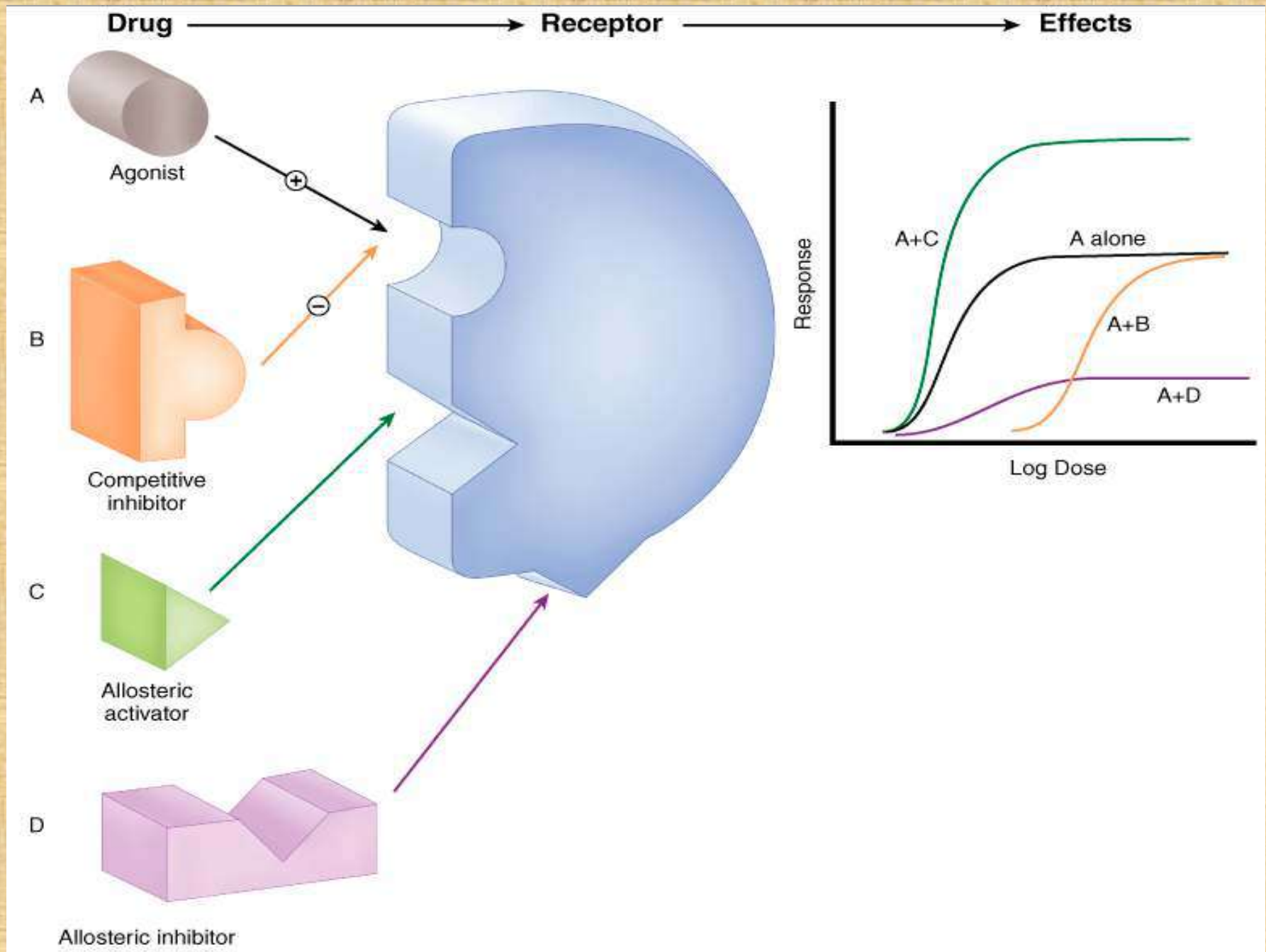
- Same binding site as of agonist
- resembles chemically with agonist
- Right shift of DRC
- Surmountable antagonism by increasing agonist dose
- Inactivation of certain agonist molecules
- Response depends on concentration of both

e.g Ach – Atropine, Morphine - Naloxone

Non-Competitive antagonist

- Different binding site as of agonist.
- Not resembles chemically with agonist.
- Flattening/downward shift of DRC.
- Unsurmountable antagonism (Maximum response is suppressed).
- Inactivation of certain receptors.
- Maximum response depends on concentration of antagonist

  e.g. Diazepam - Bicuculline


Drug
Receptor
Effects
A
Agonist
B
Competitive inhibitor
C
Allosteric activator
D
Allosteric inhibitor
Response
A+C
A alone
A+B
A+D
Log Dose

Body size

It influences the concentration of the drug attained at the site of action. The average adult dose refers to individuals of medium built. For exceptionally obese or lean individuals and for children dose may be calculated on body weight (BW) basis:

$$\text{Individual dose} = \frac{\text{BW (kg)}}{70} \times \text{average adult dose}$$

Age

The dose of a drug for children is often calculated from the adult dose

$$\text{Child dose} = \frac{\text{Age}}{\text{Age} + 12} \times \text{adult dose} \quad \text{... (Young's formula)}$$

$$\text{Child dose} = \frac{\text{Age}}{20} \times \text{adult dose} \quad \text{...(Dilling's formula)}$$

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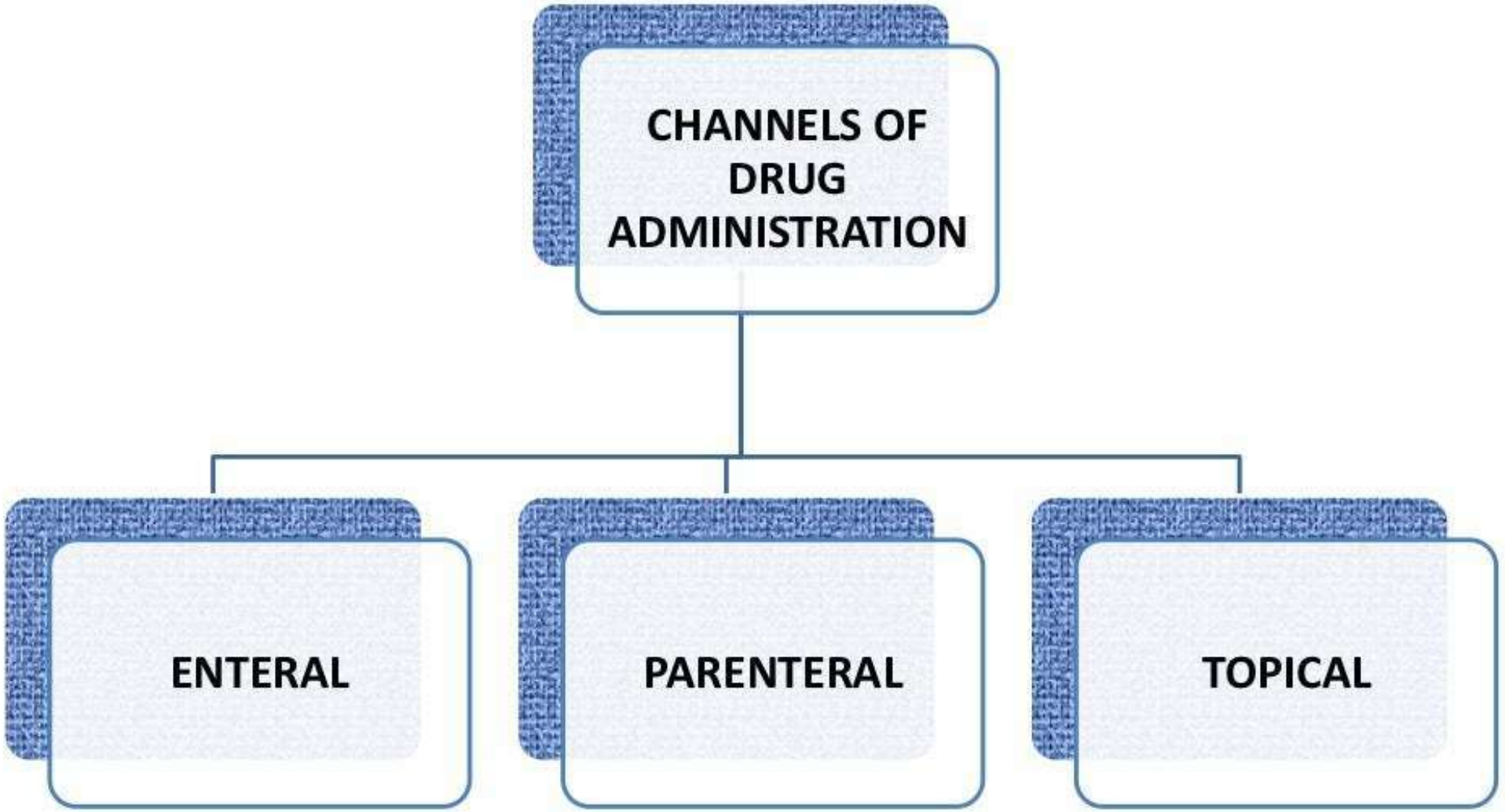
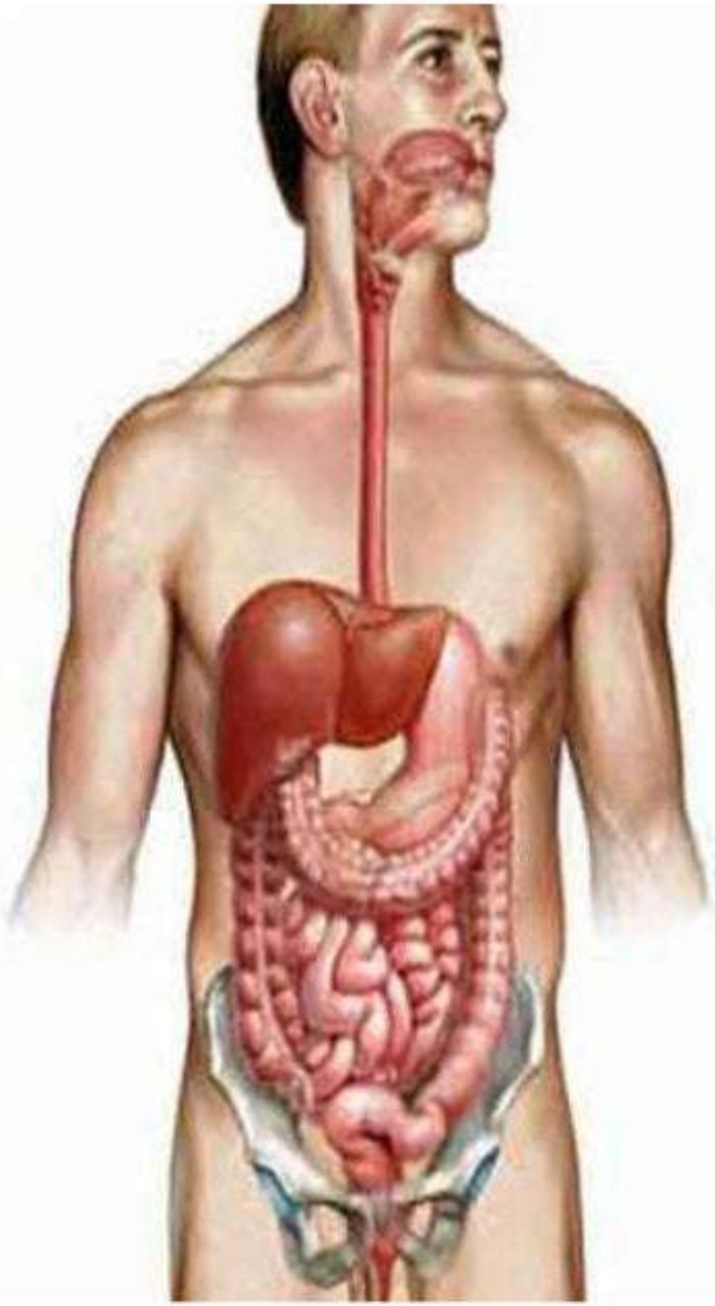
- Principles of Pharmacology 2nd edition by HL Sharma and KK Sharma
- Review of Pharmacology by Gobind Sparsh

ROUTES OF DRUG ADMINISTRATION


CHANNELS OF DRUG ADMINISTRATION
ENTERAL
PARENTERAL
TOPICAL



- ENTERAL
  - ORAL
  - SUBLINGUAL
  - BUCCAL
  - RECTAL

ORAL ROUTE

- Oral refers to

  two methods of administration:

  - applying topically to the mouth
  - swallowing for absorption along the gastrointestinal (GI) tract into systemic circulation

- *po* (from the Latin *per os*) is the abbreviation used to indicate oral route of medication administration

ORAL

- **Advantages**
  - **Convenient** - can be self- administered, pain free, easy to take
  - **Absorption** - takes place along the whole length of the GI tract
  - **Cheap** - compared to most other parenteral routes

ORAL

- **Disadvantages**
  - **Sometimes inefficient - only part of the drug may be absorbed**
  - **First-pass effect - drugs absorbed orally are initially transported to the liver via the portal vein**
  - **irritation to gastric mucosa - nausea and vomiting**

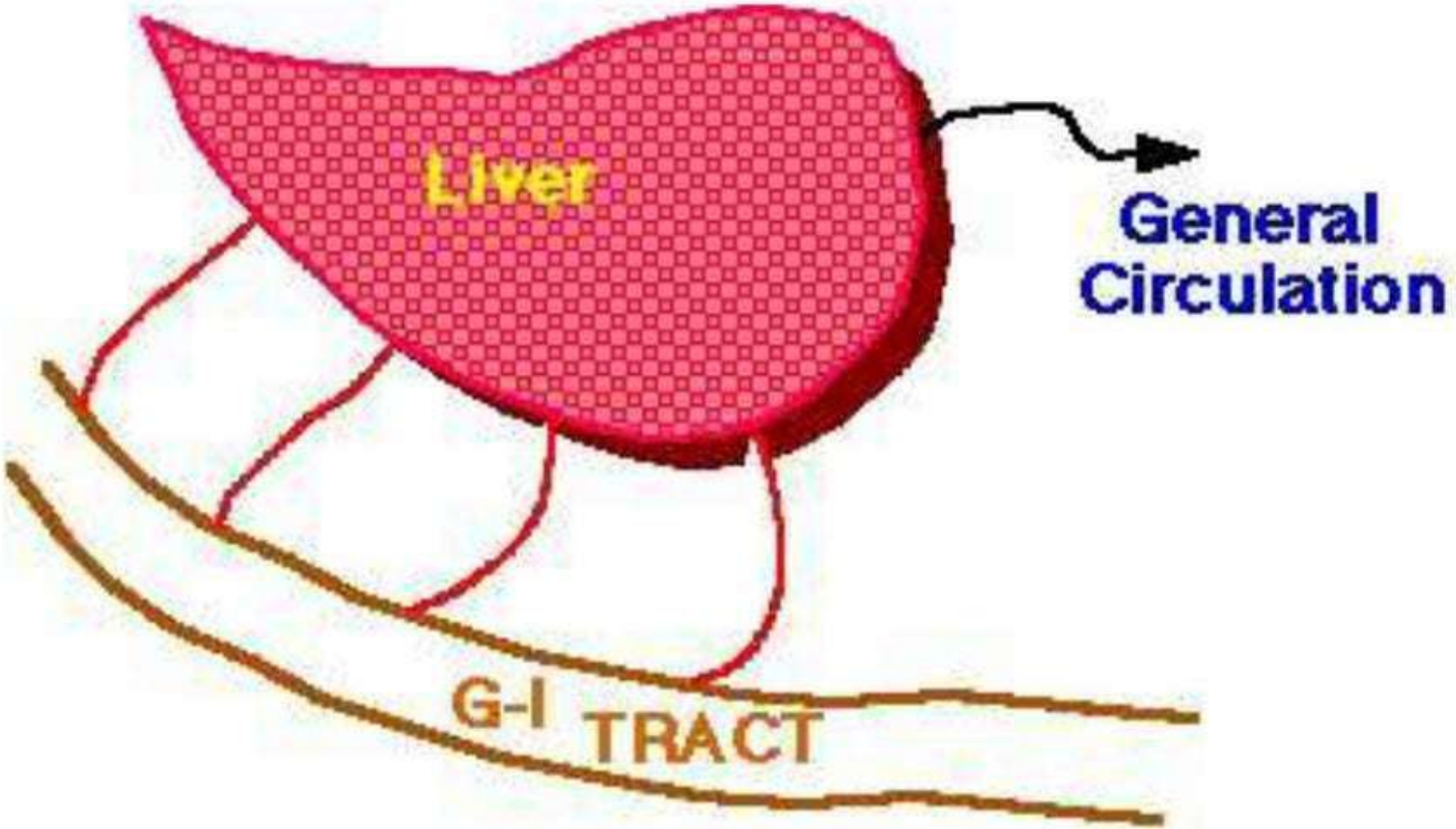
ORAL

- **Disadvantages cont.**
  - destruction of drugs by gastric acid and digestive juices
  - effect too slow for emergencies
  - unpleasant taste of some drugs
  - unable to use in unconscious patient

First-pass Effect

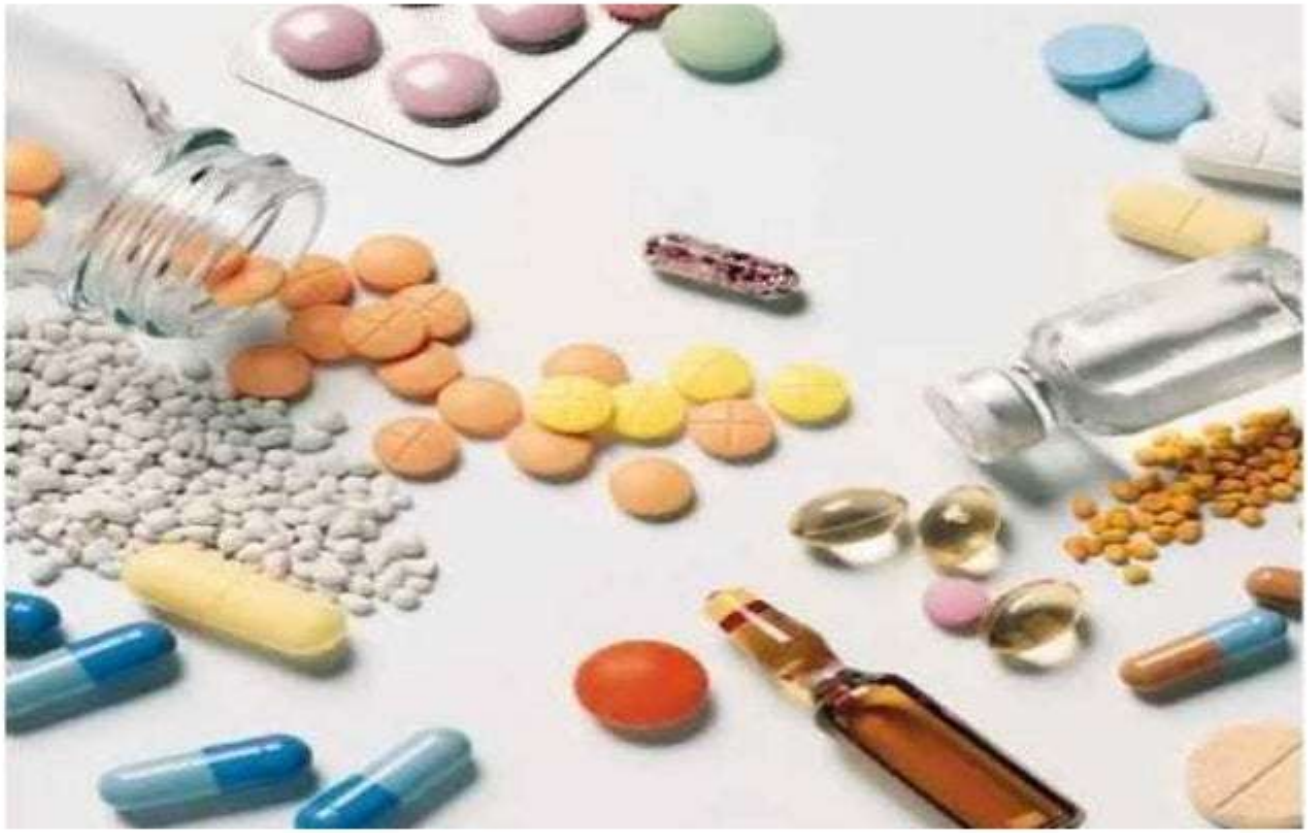
The first-pass effect is the term used for the hepatic metabolism of a pharmacological agent when it is absorbed from the gut and delivered to the liver via the portal circulation. The greater the first-pass effect, the less the agent will reach the systemic circulation when the agent is administered orally

First-pass Effect



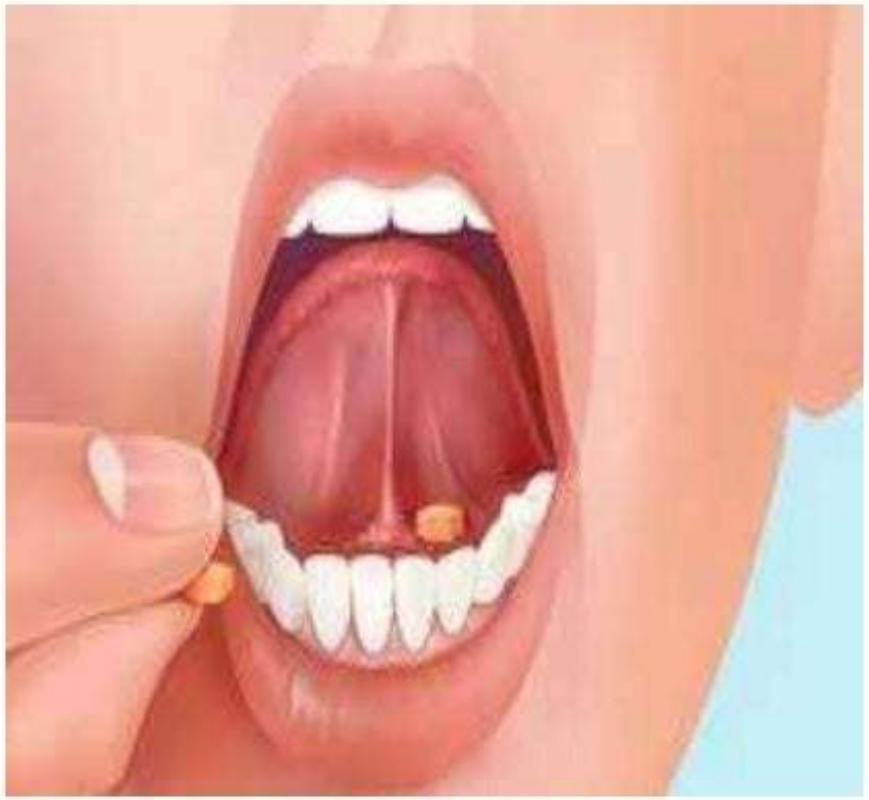
Oral Dosage Forms

- Common dose forms for ***oral administration***
  - tablets
  - capsules
  - liquids
  - solutions
  - suspensions
  - syrups
  - elixirs



SUBLINGUAL ROUTE

- ***Sublingual administration*** is where the dosage form is placed under the tongue
  - rapidly absorbed by sublingual mucosa



SUBLINGUAL ROUTE

ADVANTAGES

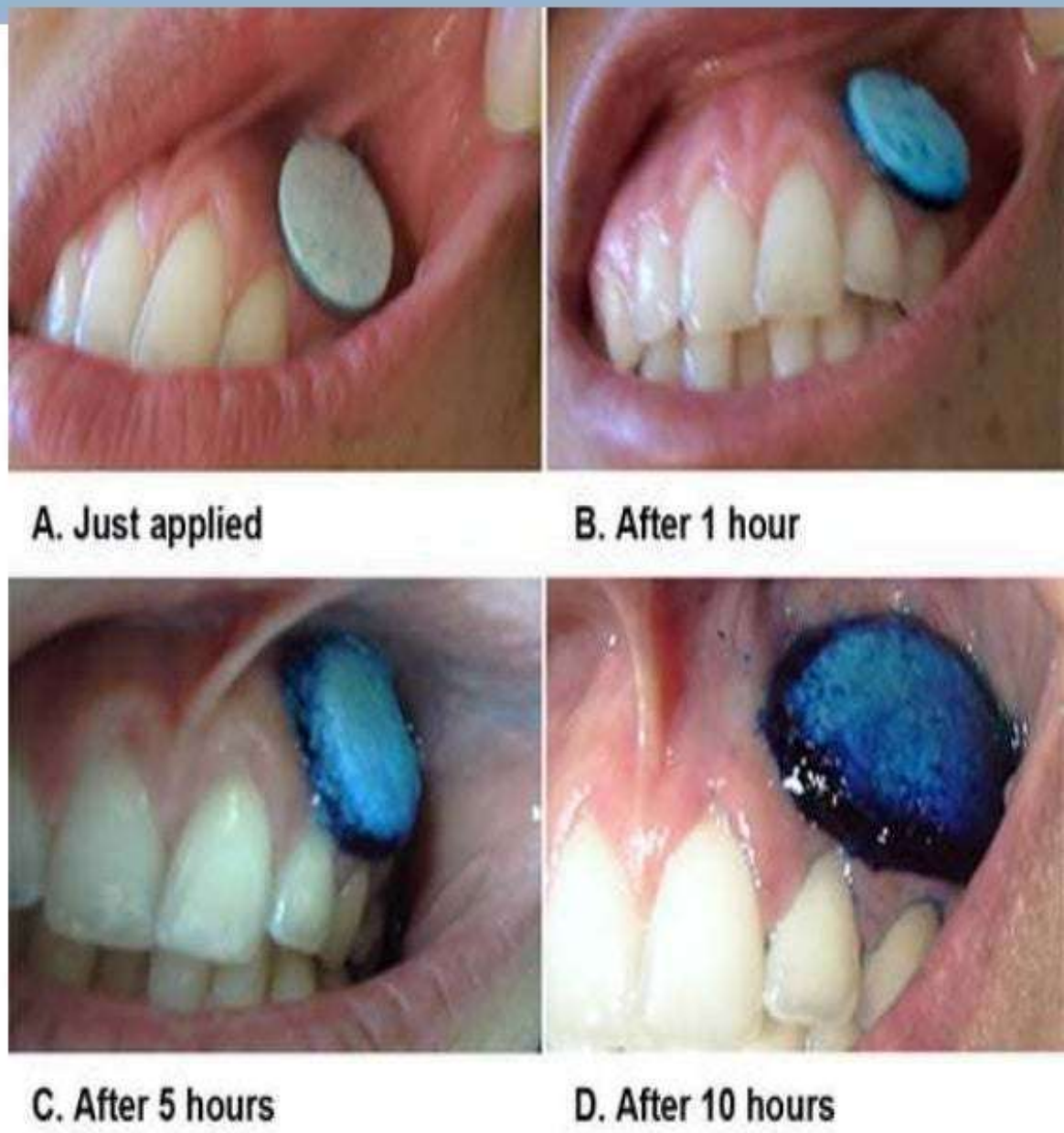
- ECONOMICAL
- QUICK TERMINATION
- FIRST-PASS AVOIDED
- DRUG ABSORPTION IS QUICK

DISADVANTAGES

- UNPALATABLE & BITTER DRUGS
- IRRITATION OF ORAL MUCOSA
- LARGE QUANTITIES NOT GIVEN
- FEW DRUGS ARE ABSORBED

BUCCAL ROUTE

- ***Buccal administration*** is where the dosage form is placed between gums and inner lining of the cheek (buccal pouch)
  - absorbed by buccal mucosa



BUCCAL ROUTE

ADVANTAGES

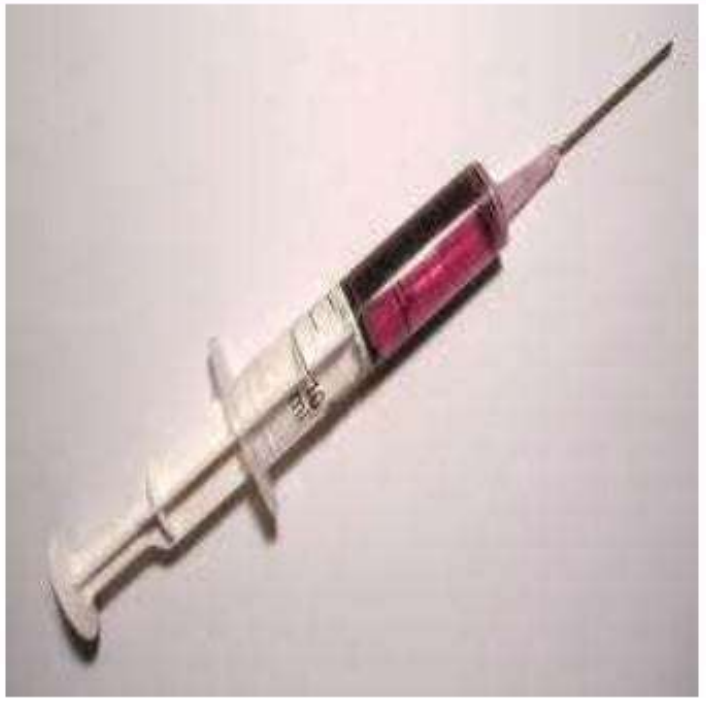
- Avoid first pass effect
- Rapid absorption
- Drug stability

DISADVANTAGES

- Inconvenience
  - advantages lost if swallowed
- Small dose limit

SYSTEMIC-PARENTERAL

- Parenteral administration is injection or infusion by means of a needle or catheter inserted into the body
- The term *parenteral* comes from Greek words
  - para, meaning outside
  - enteron, meaning the intestine
- This route of administration bypasses the alimentary canal



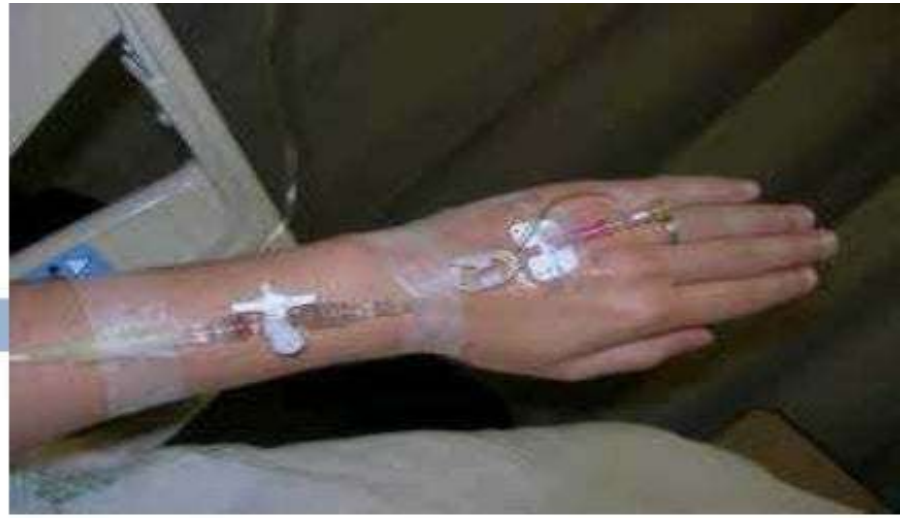
SYSTEMIC-PARENTERAL

- **INJECTABLES**

I. INTRAVENOUS
II. INTRAMUSCULAR
III. SUBCUTANEOUS
IV. INTRA-ARTERIAL
V. INTRA-ARTICULAR
VI. INTRATHECAL
VII. INTRADERMAL

- **INHALATION** - Absorption through the lungs

INTRAVENOUS



ADVANTAGES

- BIOAVAILABILITY 100%
- DESIRED BLOOD CONCENTRATIONS ACHIEVED
- LARGE QUANTITIES
- VOMITING & DIARRHEA
- EMERGENCY SITUATIONS
- FIRST PASS AVOIDED
- GASTRIC MANUPALATION AVOIDED

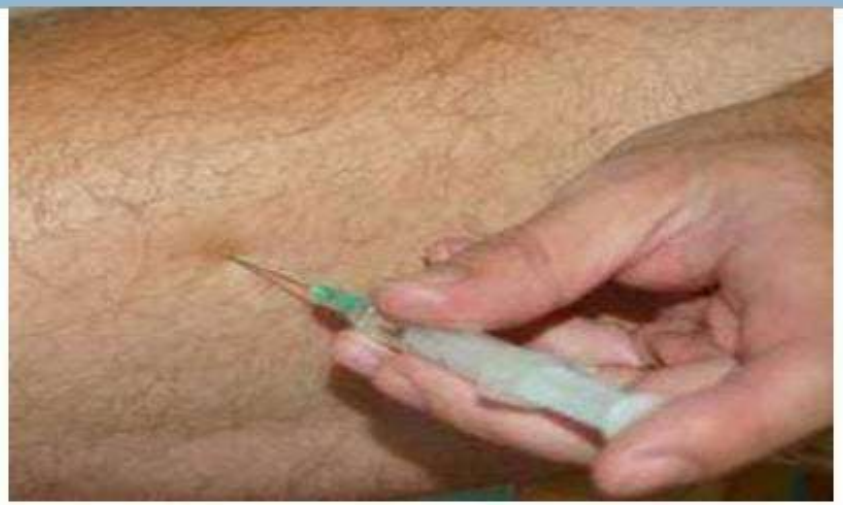
DISADVANTAGES

- IRRITATION & CELLULITIS
- THROMBOPHELEBITIS
- REPEATED INJECTIONS NOT ALWAYS FEASIBLE
- LESS SAFE
- TECHNICAL ASSISTANCE REQUIRED
- DANGER OF INFECTION
- EXPENSIVE
- LESS CONVENIENT AND PAINFUL

INTRAMUSULAR ROUTE

ADVANTAGES

- ABSORPTION REASONABLY UNIFORM
- RAPID ONSET OF ACTION
- MILD IRRITANTS CAN BE GIVEN
- FIRST PASS AVOIDED
- GASTRIC FACTORS CAN BE AVOIDED



DISADVANTAGES

- ONLY UPTO 10ML DRUG GIVEN
- LOCAL PAIN AND ABCESS
- EXPENSIVE
- INFECTION
- NERVE DAMAGE

SUBCUTANEOUS

- Injected under the skin.
- Absorption is slow, so action is prolonged.

IMPLANT :a tablet or porous capsule is inserted into the loose tissues by incision of the skin, which is then stiched up.

example : certain hormonal drugs

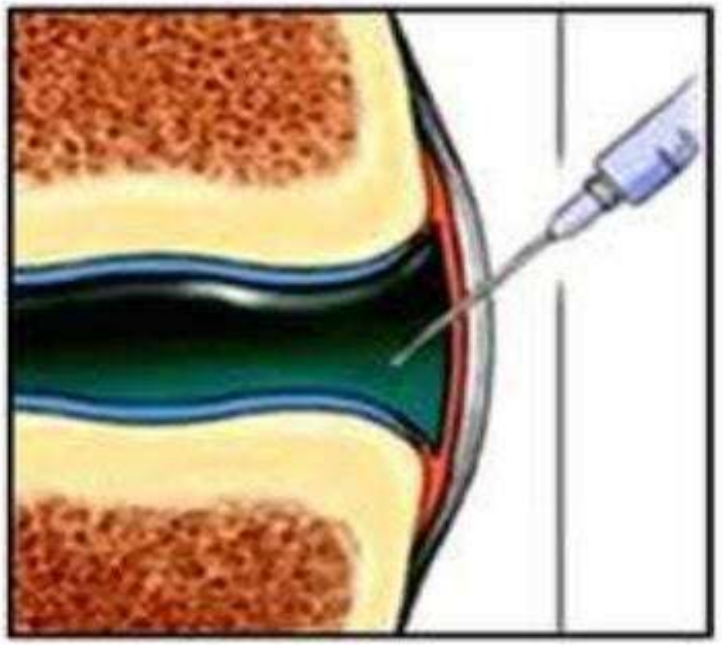
INTRA-ARTERIAL

- Rarely used
- Anticancer drugs are given for localized effects
- Drugs used for diagnosis of peripheral vascular diseases

INTRA-ARTICULAR

- injections of antibiotics and corticosteroids are administered in inflammed joined cavities by experts.

  example: hydrocortisone in rheumatoid arthritis

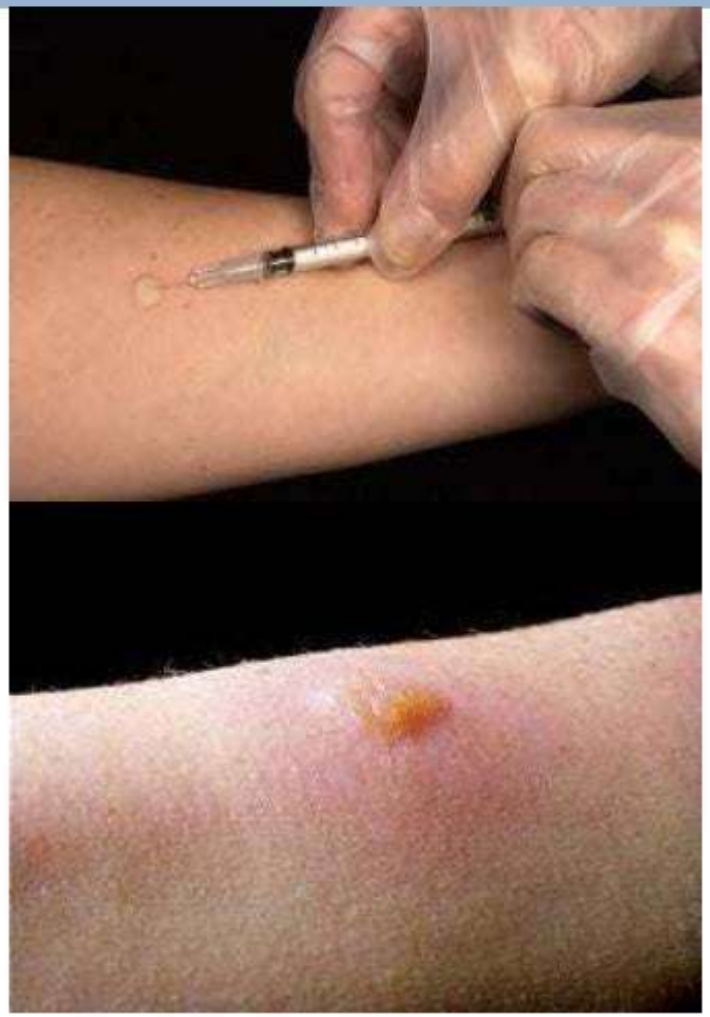


INTRADERMAL

- drug is given within skin layers (dermis)
- Painful
- Mainly used for testing sensitivity to drugs.

  e.g. penicillin, ATS (anti tetanus serum)

INOCULATION :administration of vaccine (like small pox vaccine)



Topical Routes of Administration

- ***Topical administration*** is the application of a drug directly to the surface of the skin
- Includes administration of drugs to any mucous membrane
  - eye
  - nose
  - ears
  - lungs
  - vagina
  - urethra
  - colon

Topical Dosage Forms

Dose forms for topical administration include:

- Skin:
  - creams
  - ointments
  - lotions
  - gels
  - transdermal patches
  - disks
- Eye or ear:
  - solutions
  - suspensions
  - ointments
- Nose and lungs:
  - sprays and powders

Advantages and Disadvantages of the Topical Route

- Local therapeutic effects
- Not well absorbed into the deeper layers of the skin or mucous membrane
  - lower risk of side effects
- Transdermal route offers steady level of drug in the system
  - sprays for inhalation through the nose may be for local or systemic effects

Transdermal

absorption of drug through skin (systemic action)

i. stable blood levels

ii. no first pass metabolism

iii. drug must be potent or patch becomes too large

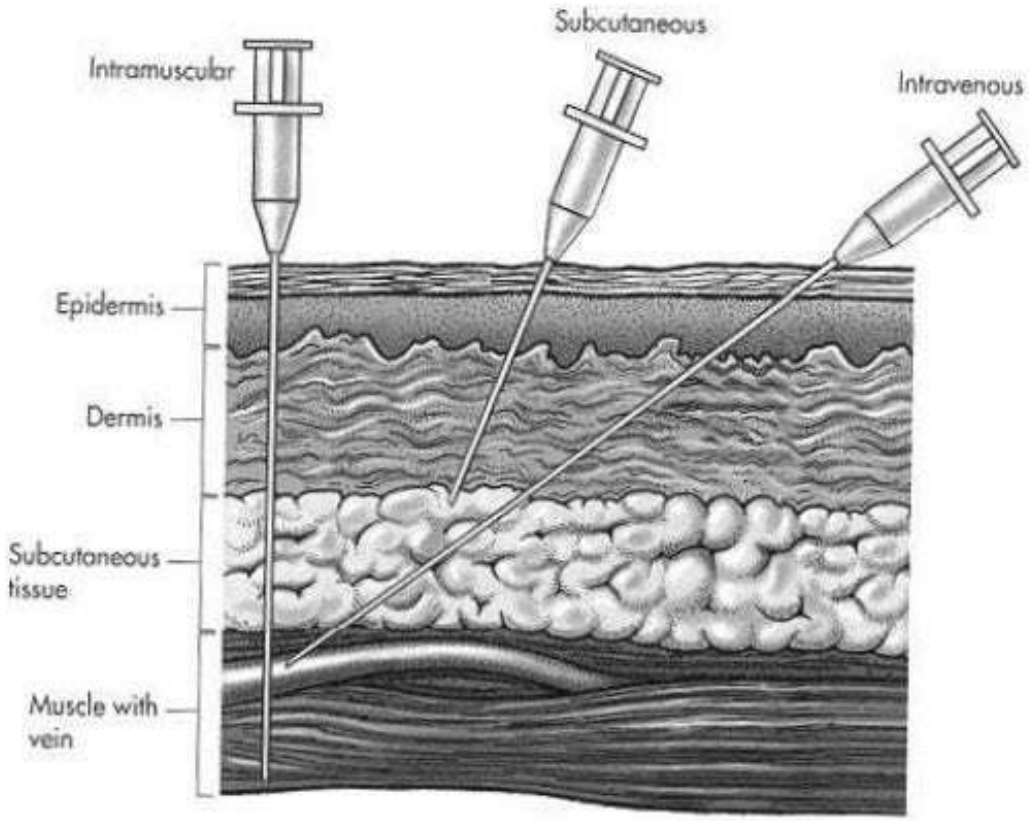
Route for administration
-Time until effect-

intravenous	30-60 seconds
intraosseous	30-60 seconds
endotracheal	2-3 minutes
inhalation	2-3 minutes
sublingual	3-5 minutes
intramuscular	10-20 minutes
subcutaneous	15-30 minutes
rectal	5-30 minutes
ingestion	30-90 minutes
transdermal (topical)	variable (minutes to hours)

SELECTION OF ROUT

The ROA is determined by :

- **the physical characteristics of the drug**
- **the speed which the drug is absorbed and/ or released**
- **the need to bypass hepatic metabolism**
- **to achieve high conc. at particular sites**
- **Accuracy of dosage**
- **Condition of the patient**


Intramuscular
Subcutaneous
Intravenous
Epidermis
Dermis
Subcutaneous tissue
Muscle with vein

Sublingual/Buccal

Some drugs are taken as smaller tablets which are held in the mouth or under the tongue.

- **Advantages**
  - rapid absorption
  - drug stability
  - avoid first-pass effect

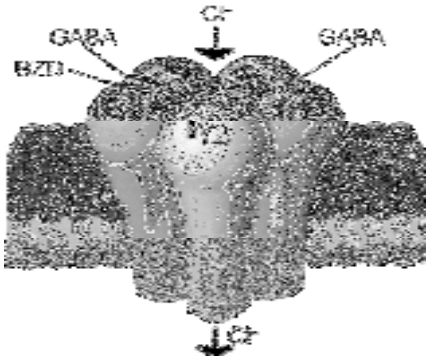
Sublingual/Buccal

- **Disadvantages**
  - **inconvenient**
  - **small doses**
  - **unpleasant taste of some drugs**

Rectal

1. unconscious patients and children
2. if patient is nauseous or vomiting
3. easy to terminate exposure
4. absorption may be variable
5. good for drugs affecting the bowel such as laxatives
6. irritating drugs contraindicated


Thanks!



SEDATIVE-HYPNOTICS

DEFINITIONS

- **Sedative:** A drug that subdues excitement and calms the subject without inducing sleep, though drowsiness may be produced – refers to decreased responsiveness to any level of stimulation; is associated with some decrease in motor activity and ideation - depression of awareness to the environment and reduction of responsiveness to external stimulation
  - Newer - An effective sedative agent should reduce anxiety and exert a calming effect with little or no effect on motor or mental functions

- **Hypnotic:** A drug that induces and/or maintains sleep, similar to normal sleep which is can be aroused. Should not be confused with "Trans like state" - hypnosis, meditation, magic, flow, and prayer etc. – subjects are passive and highly suggestible
- **Older drugs:** alcohol, opium, bromides, chloralhydrate, paraldehyde – obsolete now

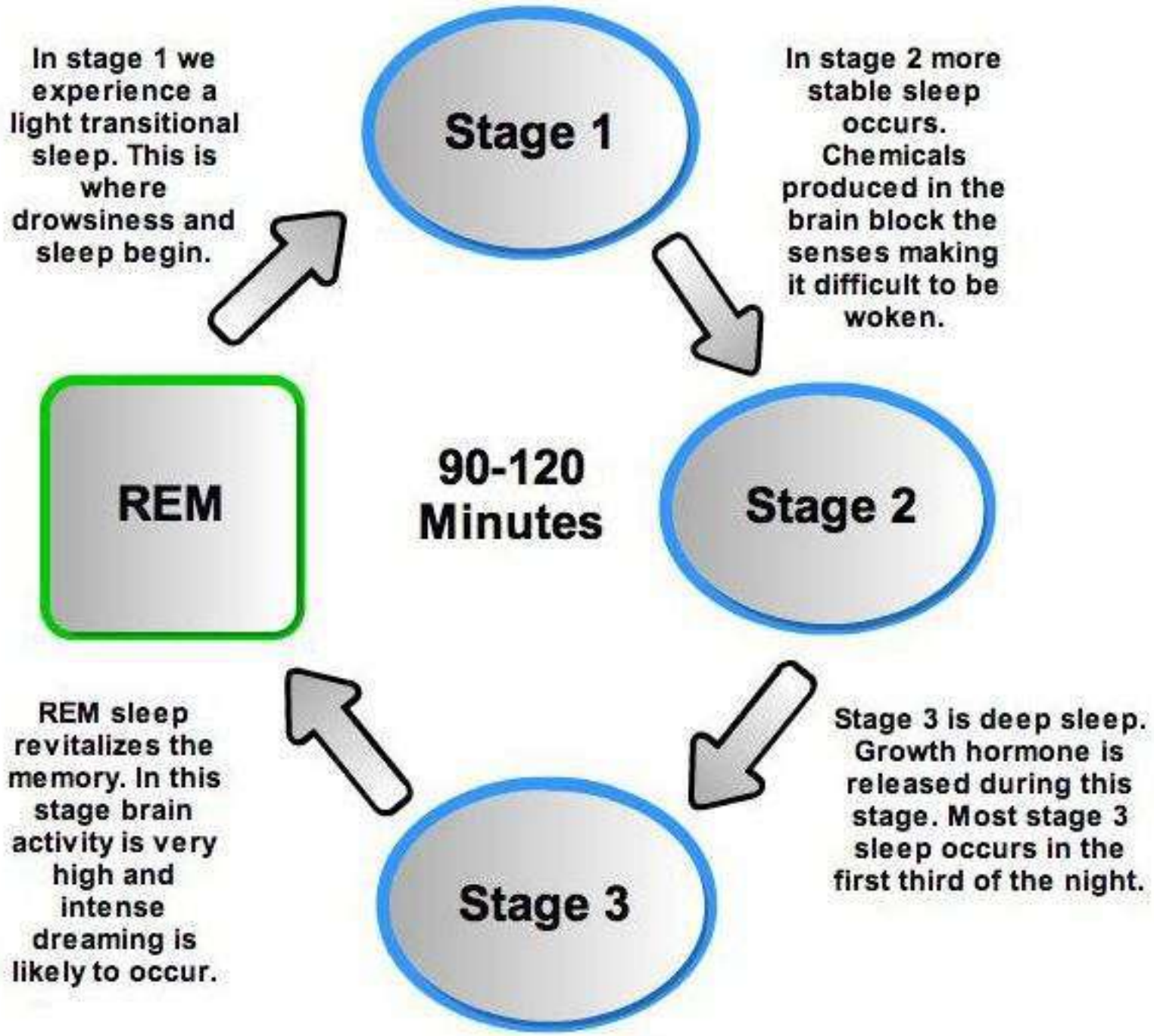
IN GENERAL …

- Sedative: Calm down, treat agitation

Sedative

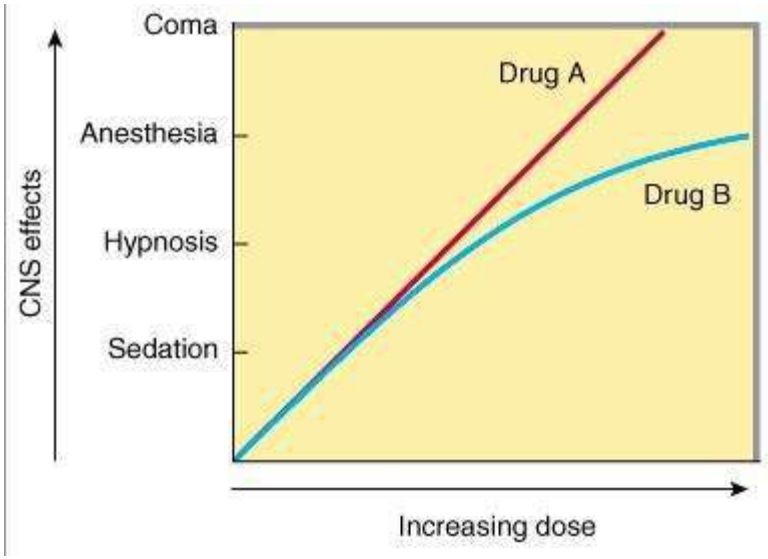
- Hypnotic: Induce sleep
  - go to sleep fast, feel refreshed tomorrow !
  - Treatment of Insomnia
- Anxiolytic: Reduce anxiety
  - physical, emotional, cognitive

Hypnotic


In stage 1 we experience a light transitional sleep. This is where drowsiness and sleep begin.
Stage 1
In stage 2 more stable sleep occurs. Chemicals produced in the brain block the senses making it difficult to be woken.
REM
90-120 Minutes
Stage 2
REM sleep revitalizes the memory. In this stage brain activity is very high and intense dreaming is likely to occur.
Stage 3
Stage 3 is deep sleep. Growth hormone is released during this stage. Most stage 3 sleep occurs in the first third of the night.

IN GENERAL …

- All are CNS depressants – different time-action and dose –action relationship
- Quick action. But short duration of action and steeper DRC – hypnotic
- Slowly acting and flatter DRC – sedative
- But, overlaps – hypnotic at lower doses may act as sedative
- Anxiolysis > Sedation > Hypnosis >General Anaesthesia (grades of CNS depression)



The linear slope for drug A is typical of many of the older sedative-hypnotics, including the barbiturates and alcohols - an increase in dose higher than that needed for hypnosis may lead to a state of general anesthesia. At still higher doses, these sedative-hypnotics may depress respiratory and vasomotor centers in the medulla, leading to coma and death.

Deviations from a linear dose-response relationship for drug B - proportionately greater dosage increments to achieve central nervous system depression more profound than hypnosis. This appears to be the case for benzodiazepines and for certain newer hypnotics that have a similar mechanism of action.

Dose-response curves for two hypothetical sedative-hypnotics.

AVAILABLE DRUGS

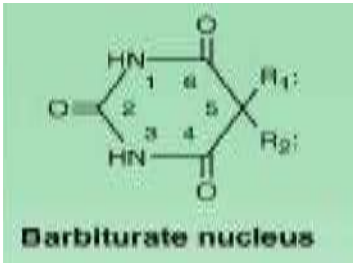
- Barbiturates:
  - Long acting: Phenobarbitone
  - Short acting (Intermediate): Pentobarbitone, Butobarbitone, Amylobarbitone
  - Ultra-short acting: Methohexitone, Thiopentone, Secobarbitone
- Benzodiazepines:

Hypnotic	Antianxiety	Anticonvulsant
Diazepam	Diazepam	Diazepam
Flurazepam	Chlordiazepoxide	Lorazepam
Nitrazepam	Oxazepam	Clonazepam
Alprazolam	Lorazepam	Clobazam
Temazepam and Triazolam	Alprazolam	

- Newer Non-benzodiazepines: Zopiclone, Zolpidem, Zaleplon etc.

(Chloral hydrate, paraldehyde, meprobamate – not used anymore)

BARBITURATES



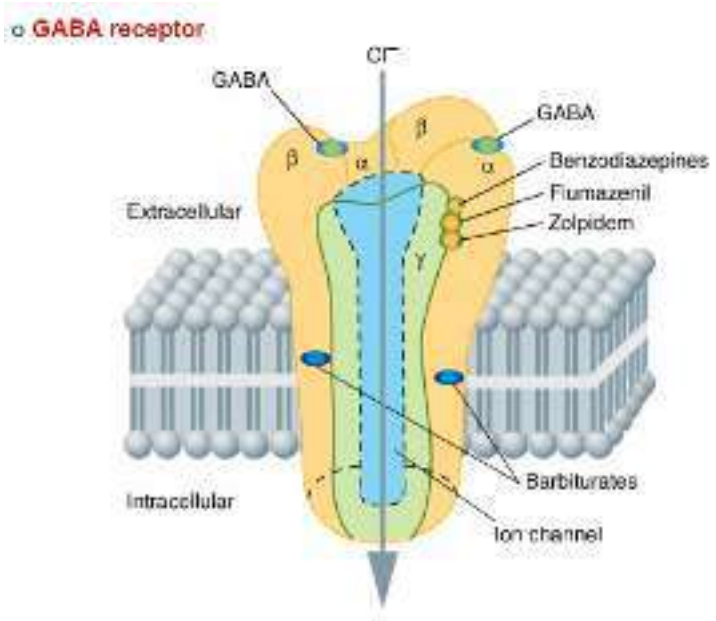
- Last century – upto 1960 – not used now – but prototype drug
- Chemically – condensation of malonic acid and urea – Barbituric acid
- Important drawbacks:
  - General depressants of all excitable cells (CNS)
  - Potentially Fatal Respiratory Depression
    - narrow therapeutic range
  - Potent liver inducers: interactions

BARBITURATE – CNS ACTION

- Dose dependant effect: sedation – sleep – anaesthesia – coma
- Short acting – hypnotic (100-200 mg)
  - Shortens time taken to fall asleep and increases sleep duration
  - Arousable – but confused and drowsy if aroused early
  - Night awakening – reduced
  - REM and stage 3 and 4 sleep reduced – disruption of sleep cycle
  - Progressively decreases effects on sleep – continuous use – rebound increase in REM sleep on discontinuation
  - Hang over in the morning – dizziness, distortions of mood, irritability and lethargy
  - Impair learning, short-term memory and judgment
  - No analgesic action – hyperalgesia instead
  - Phenobarbitone – higher anticonvulsant : sedative ratio

BARBITURATE - MOA

- Act primarily at GABA:BZD receptor-Cl^- channel
- Potentiates GABAergic inhibition by increasing the lifetime of Cl^- channel opening
- Bind to other site than GABA – located in α and βsubunit
- Also enhance BZD binding
- High doses – directly increases Cl^- conductance (GABA mimetic) and inhibit Ca^{++} dependent release of neurotransmitters
- Also depress Glutamate induced neuronal depolarization
- Very High doses – depress voltage sensitive Na^+ and K^+ channel



BARBITURATE – OTHER ACTIONS

- Respiration: Depressed – neurogenic, hypercapneic and hypoxic drives to respiratory centre depressed
- CVS: Slight decrease in BP and Heart Rate
  - Toxic doses: Marked fall in BP and HR – due to ganglion blockade, vasomotor centre depression and direct cardiac action – reflex tachycardia
- Skeletal Muscle: Little effect but anaesthetic doses reduce muscle contraction
- Smooth muscle: Tone and motility of bowel is decreased. Higher doses – more profound decrease
- Kidney: Reduce urine flow – due to decrease BP and ADH release

BARBITURATE - KINETICS

- Well absorbed orally – widely distributed
- Entry into CNS depends on lipid solubility – Phenobarbitone Vs Thiopentone
- Plasma protein binding – Phenobarbitone – 20%, Thiopentone – 75%
- Crosses placenta and secreted in milk
- Redistribution: highly lipid soluble barbiturates (ultra short acting) – IV injection – consciousness after 6-10 minutes, but actual elimination by metabolism – half life 9 hours - Short acting ones – TE 6 – 10 hours and elimination half life is 12-40 hours
- Metabolism: metabolized in liver by oxidation, dealkylation and conjugation
- Excretion: Long acting – excreted significantly unchanged - Alkalinization – ↑ excretion
- Microsomal enzyme inducer – induce own metabolism and Others

BARBITURATES – CONTD.

- Adverse Effects: Hang over, tolerance and dependence, metal confusion, impaired performance – accidents
  - Idiosyncrasy: Occasional excitement – In elderly
  - Hypersensitivity: Rashes, swelling of eyelids, lips etc.
  - Tolerance and dependence: Cellular and pharmacokinetic – on repeated use
    - Physical and psychological dependence – abuse liability
- Drug Interactions:
  1. Induce metabolism of many drugs – warfarin, steroids, OCP, chloramphenicol, tolbutamide
  2. Alcohol, antihistamines, opioids – CNS depression
  3. Sodium valproate – increases plasma conc. Of phenobarbitone
  4. Phenobarbitone – competitively induces phenytoin metabolism

ACUTE BARBITURATE POISONING

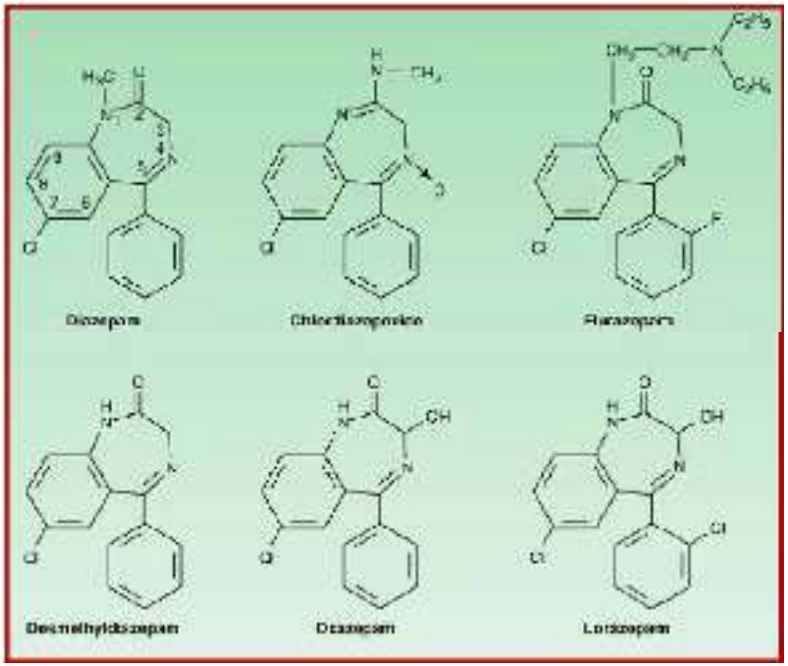
- Mostly suicidal – excessive CNS depression – flabby and comatose with shallow and failing respiration, CVS collapse, renal shut down, pulmonary complications
- Treatment:
  - Gastric lavage (activated charcoal)
  - Supportive – patent airway, assisted respiration, oxygen, IV fluid and vasopressors like Dopamine
  - Alkaline diuresis: Sodium bicarbonate 1 meq/kg IV with or without mannitol – for long acting ones
  - Haemodyalysis: highly effective in long as well as short acting ones
  - No specific antidote
- Contraindications: acute intermittent porphyria, Liver and kidney disease, severe pulmonary insufficiency

BENZODIAZEPINES (BZDS)

Chlordiazepoxide and Diazepam - Since 1960

BENZODIAZEPINES (BZDS)

- Chemically – all are 1,4-benzodiazepines, and most contain a carboxamide group in the 7-membered heterocyclic ring structure
- A substituent in the 7 position, such as a halogen or a nitro group, is required for sedative- hypnotic activity



BENZODIAZEPINES VS OLDER ONES

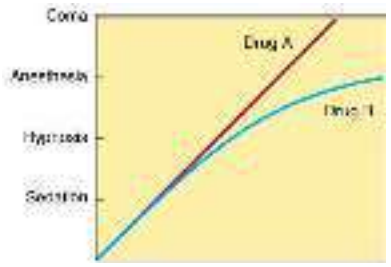
'Most widely used sedative-hypnotics now since 1960 and replaced Barbiturates

1. High therapeutic index – 20 hypnotic doses – no loss of consciousness or respiratory depression – patient can be aroused
2. Hypnotic doses – do not depress CVS or respiratory function. Higher doses may be
3. BZDs have no action on other body system – only IV injection BP may fall – Barbiturates?
4. BZDs cause less distortion of sleep architecture
5. No microsomal induction – less drug interaction
6. Low abuse liability, mild tolerance, psychological and physical dependence and less withdrawal symptoms
7. Specific antagonist - flumazenil

BZDS – CNS ACTIONS

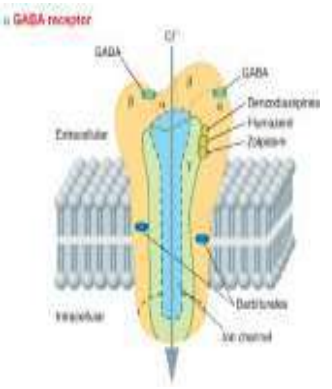
- All agents - Qualitatively similar, but different members are used for different purposes – selectivity and time course of action different
  - Midbrain (RAS), limbic system, medulla and cerebellum
- Not general CNS depressants – exert selective - anxiolytic, hypnotic, muscle relaxant and anticonvulsant effects
- Even anaesthetic doses of Diazepam – some degree of awareness maintained (although, events of recovery may not be remembered by patient anteretrograde amnesia)

BZDS –EFFECTS



- On sleep: Basic actions (Note the comparisons)
  - Hastens onset of sleep, reduce intermittent awakening and increased total sleep time – Like Barbiturates
  - Time spent in stage 2 (unequivocal sleep) is increased (Unlike Barbiturates) and stage 3 & 4 decreased (Like Barbiturates)
  - Regulates a Key on sleep - Shorten REM (Unlike Barbiturates), but more REM cycles (Unlike Barbiturates) – such that overall effects on REM less marked (Nitrazepam) – more sleep cycles
  - Night terror (at stage 4) and body movements are reduced
  - Stage shift to stage 1 and 0 are reduced (awake and dozing) and wake up fresh (no Hang over) – some degree of tolerance
- Centrally mediated muscle relaxant – Clonazepam and Diazepam
- Anticonvulsant: Clonazepam, diazepam and flurazepam
- Diazepam – on IV use - analgesia (no hyperalgesia) and decreases nocturnal gastric secretion – stress ulcer prevention

MOA – BZD



- Midbrain ascending reticular activating system (RAS) an system (thought and mental function); also medullary si cerebellum
- Acts via (inhibitory) ligand gated BZD: $GABA_A$ receptor- Cl^- channel complex
- α/γ subunits carries the BZD binding site - BZD receptors are integral to $GABA_A$ receptor
- BZDs modulate action on GABA receptor - increases frequency of channel opening (unlike Barbiturate - Potentiation)
- Also enhances binding of GABA to $GABA_A$ receptor
- Bicuculine ($GABA_A$ antagonist) antagonizes BZD action as non-competitive
- BZDs are GABA facilitator but not Mimetic (unlike Barbiturates)
- Constitutive action – fine tunes GABA action – bidirectional
- BZD agonists enhance GABA action (hyperpolarization) – but antagonists like dimethoxyethyl-carbomethoxy-β-carboline (DMCM) inhibits GABA

BZD - KINETICS

- Marked pharmacokinetic differences – differ in lipid solubility
- Oral absorption – some rapid, some slow; on IM injection – irregular absorption except lorazepam
- Plasma protein binding also varies (Flurazepam– 10%; Diazepam 99%)
- Usually short duration of action – with a single dose – REDISTRIBUTION – prediction of duration of action is difficult
- Metabolism: In Liver by dealkylation and hydroxylation to metabolites (some are active) – Biological half-life longer than plasma half life
- Enterohepatic circulation – Diazepam and excreted in urine as glucoronide conjugate
- BZDs are secreted in milk and crosses placenta

BZD - COMPARISON

Drugs	Half life (hour)
Diazepam	30 - 60
Nitrazepam	30
Flurazepam	50-100
Alprazolam	12
Chlordiazepoxide	15 - 40
Lorazepam	10 - 20
Temazepam	8 - 12

INDIVIDUAL DRUGS

- Slow elimination but rapid redistribution
  - Diazepam: Generates active metabolite (desmethyl-diazepam, oxazepam) – single dose no residual effects – regular use accumulation and prolonged anxiolytic effect – Difference with others
  - Nitrazepam: Accumulates - Residual effects – day time sedation (not on single dose) – for frequent nocturnal awakening patients (if day time sedation acceptable)
  - Flurazepam: Slow elimination of parent drug or metabolite - Produces active metabolite which have long half life – residual effects frequently (morning) – cumulation – day time sedation (if day time sedation acceptable)
- Rapid elimination and marked redistribution
  - Alprazolam: Basically used as anxiolytic – but also night time hypnotic – withdrawal phenimenon after regular use - sedation
  - Temazepam: No residual effect, no metabolite – used in sleep onset difficulty
- Ultrarapid elimination: Triazolam – potent, quick acting – for induction of sleep

BZDS – ADVERSE EFFECTS

- Older individuals are more susceptible – Be careful
- Hypnotic doses: Dizziness, vertigo, ataxia, disorientation, amnesia, prolongation of reaction time – impairment of psychomotor skill
  - Hang over with larger doses – long acting ones
  - Weakness, blurring of vision, dry mouth and urinary incontinence
  - Paradoxical stimulation, irritability and sweating– Flurazepam
  - Nightmares and behaviuoral alteration – Nitrazepam
  - Tolerance to sedative effect very slowly – little tendency to increase dose – cross tolerance to alcohol and other CNS depressants
  - Dependence liability and drug seeking behaviour – low (bland) - Midazolam
  - Low withdrawal syndrome – more with ultrarapid ones – anxiety, insomnia, restlessness, malaise, loss of appetite, bad dreams
  - Pregnancy – flaccidity and respiratory depression in neonate

NONBENZODIAZEPINES - ZOPICLONE

- Cyclopyrrolone derivative - active metabolite – N-desmethylzopiclone
- MOA: Binds to α subunit of BZD receptor (Unlike BZD)– hypnotic action
- Vs BZD: Sleep resembles but – does not alter REM and tends to prolong stage 3 and stage 4 (Unlike BZD)
- No sleep architecture distortion or withdrawal phenomena
- Uses: to wean off insomniacs on BZD and short term therapy for insomnia
- ADRs: Metallic taste, impairment of judgment and alertness, psychological disturbance – addictive property (rarely)
- Half life: 5 – 6 hours

ZOLPIDEM - IMIDAZOPYRIDINE

- MOA: Acts on α_1 subunit of BZD receptor (hypnotic)
- Actions: Sleep latency shortened, prolongs sleep time –but no anticonvulsant, antianxiety or muscle relaxant effects
  - Lack of effect on sleep stages (REM)
  - Minimal residual day time sedation or fading of effects on repeated use
  - Little rebound insomnia on discontinuation
  - Absence of tolerance, physical dependence and low abuse potential
- Kinetics: Completely metabolized in liver – half life – 2 hrs
- Uses: short term therapy of sleep onset insomnia – day time sedation less (short half life) – late night (!)
- Most popular – even large doses no respiratory depression

ZALEPLON

- Shortest acting - acts on α_1 subunit of BZD receptor (hypnotic)
- Rapidly absorbed (30% bioavailability – high first pass) – rapidly cleared by hepatic metabolism – Half life (1 hr) – no active metabolite
- Does not prolong total sleep time or reduce the number of awakenings
- Can be taken late night – no morning sedation, anxiety or insomnia
- No tolerance or dependence
- Uses: Sleep-onset insomnia (1-2 weeks therapy)

USES OF BZDS

- As Hypnotic: Not all are useful as hypnotic agents, although all have sedative or calming effects
- As anxiolytic and for day time sedation
- As anticonvulsant – status epilepticus, febrile convulsion, tetanus
- As Muscle relaxant (centrally acting)
- Preananesthetic medication, IV anaesthesia and conscious sedation
- Before procedures: ECT, electrical cardioversion of arrhythmias, cardiac catheterization, endoscopies and other minor procedures
- Alcohol and other sedative-hypnotic withdrawal
- Along with analgesics, NSAIDs, spasmolytics, antiulcer and many other drugs

AS HYPNOTIC

- A hypnotic should not be casually prescribed for every case of insomnia – BZDs and Non-BZDs are most frequently used
- The choice of a particular BZD to treat a sleep disturbance is generally based on Pharmacokinetic criteria:
  - Long-acting compounds (e.g. flurazepam) may ensure that a patient will sleep through the night, they also may cause cumulative effects resulting in daytime sluggishness or drug hangover
  - Short-acting compounds (e.g. triazolam) avoid the hangover problem, but their use may be associated with early awakening and an increase in daytime anxiety

BZD AS HYPNOTIC – GENERAL POINTS

- A hypnotic should be used – (1) shorten sleep latency, (2) to reduce nocturnal awakening and (3) to provide anxiolytic effect the next day
- Should consider onset of action and duration of action of the drug
- Should consider next day effects – prolonged sedation or rebound anxiety
- All become useless after regular use – except `z` drugs
- Should consider the subjects perception and assessment

INSOMNIA

- Chronic Insomnia (> 3 weeks) – Be cautious prescribing hypnotics
  - May be Personality disorder; chronic hypnotic user; alcoholic; somatic diseases – GERD, pain, COPD
  - Other measures - Exercise, yoga, counseling – advice avoiding anxiety, attempting sleep when maximum sleepiness, avoid napping day time, coffee/alcohol restriction treatment of concurrent diseases
  - Intermittent use of hypnotics
- Short term insomnia (3 – 21 days): Emotional problem – stress, bereavement and physical illness etc. – either induction difficulty or waking up early – Hypnotic free of residual effects (sometimes may be needed) - short acting drugs in elderly
- Transient insomnia (1 – 3 days): Alterations in the circumstances – new place, journey, work related, night shift, travel jetlag etc. – a short acting without residual effects

FLUMAZENIL

- BZD analogue, but specific BZD receptor antagonist – no IA – no effect on normal person
- Competes with BZD agonists and inverse agonists – reverses their action
- Absorbed orally (20% bioavailability), but used IV and intranasal - half life- 1 hr
- Uses:
  - To reverse BZD anesthesia – quick action within 1 minute – Resedation
  - BZD overdose

SUMMARY

- Name of different Barbiturates – Details of Phenobarbitone and Thiopentone
- Benzodiazepine Classification (long and short acting)
- Mechanism of action of BZD
- Uses of BZD
- Non-benzodiazepines
- Pharmacotherapy of Insomnia
- Remember Flumazenil

THANK YOU

ADRENERGIC DRUGS AND ITS ANTAGONIST AND CHOLINERGIC DRUGS

INTRODUTION

- Drugs that mimic the actions of adrenaline or nor-adrenaline that called as **sympathomimetic drugs or adrenomimetic drugs**
- The ultimate effects of sympathetic stimulation are mediated by release of adrenaline from nerve terminals that serve to activate the adrenoceptors on postsynaptic sites.
- Also, in response to a variety of stimuli, such as stress, the adrenal medulla releases adrenaline, which is transported in the blood to target tissues—in other words, adrenaline acts as a hormone.
- Adrenergic related to endogenous catecholamine

Adrenergic		
β_1	Heart and coronary blood vessels predominantly, but also kidneys, liver, and adipose tissue	Increases heart rate and strength; dilates coronary arterioles; stimulates renin release by kidneys
β_2	Lungs and most other sympathetic target organs; abundant on blood vessels serving the heart	Stimulates secretion of insulin by pancreas; other effects mostly inhibitory: dilation of blood vessels and bronchioles; relaxes smooth muscle walls of digestive and urinary visceral organs; relaxes pregnant uterus
β_3	Adipose tissue	Stimulates lipolysis by fat cells
α_1	Most importantly blood vessels serving the skin, mucosae, abdominal viscera, kidneys, and salivary glands; but virtually all sympathetic target organs except heart	Constricts blood vessels and visceral organ sphincters; dilates pupils of the eyes
α_2	Membrane of adrenergic axon terminals; blood platelets	Mediates inhibition of NE release from adrenergic terminals; promotes blood clotting

ADRENERGIC RECEPTOR

Adrenoceptors	Typical Locations	Result of Ligand Binding
$Alpha_1$	Postsynaptic effector cells, especially smooth muscle	Formation of IP_3 and DAG, increased intracellular calcium
$Alpha_2$	Presynaptic adrenergic nerve terminals, platelets, lipocytes, smooth muscle	Inhibition of adenylyl cyclase, decreased cAMP
$Beta_1$	Postsynaptic effector cells, especially heart, lipocytes, brain; presynaptic adrenergic and cholinergic nerve terminals	Stimulation of adenylyl cyclase, increased cAMP
$Beta_2$	Postsynaptic effector cells, especially smooth muscle and cardiac muscle	Stimulation of adenylyl cyclase and increased cAMP. Activates cardiac
		G_i under some conditions.
$Beta_3$	Postsynaptic effector cells, especially lipocytes	Stimulation of adenylyl cyclase and increased cAMP

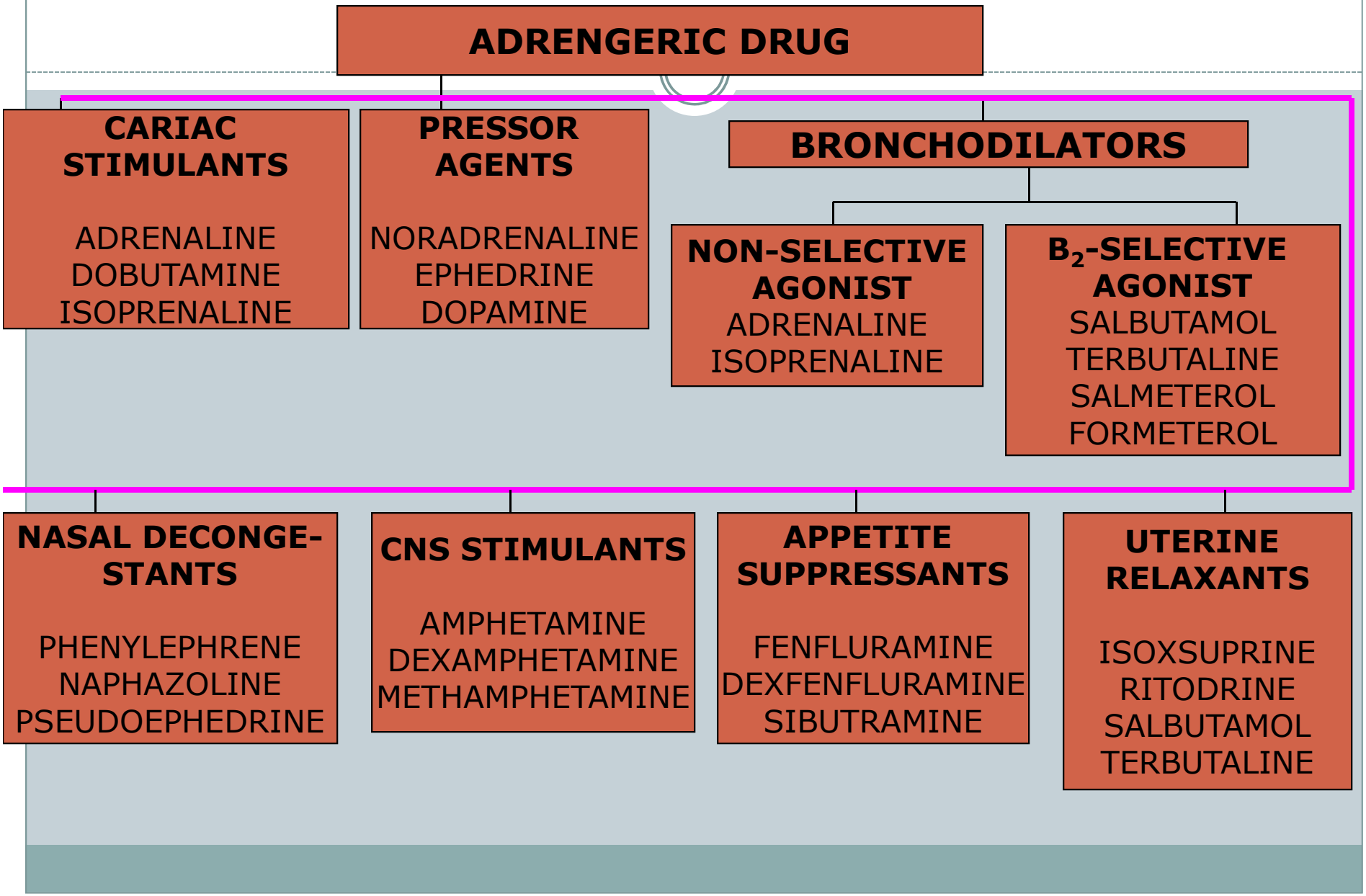
DIFFERENCE BETWEEN βRECEPTOR

perticulars	β1 receptor	β2 receptor	β3 receptor
Location	Heart, Kidney	Bronchi, eye Blood vessels Uterus, GI trunk	Adipose tissue
Selective Agonist	Dobutamine	Salbutamol Terbutaline	BRL 37344
Selective Antagonist	Metaprolol Atenolol	α methyl propranolol	ICI 118551

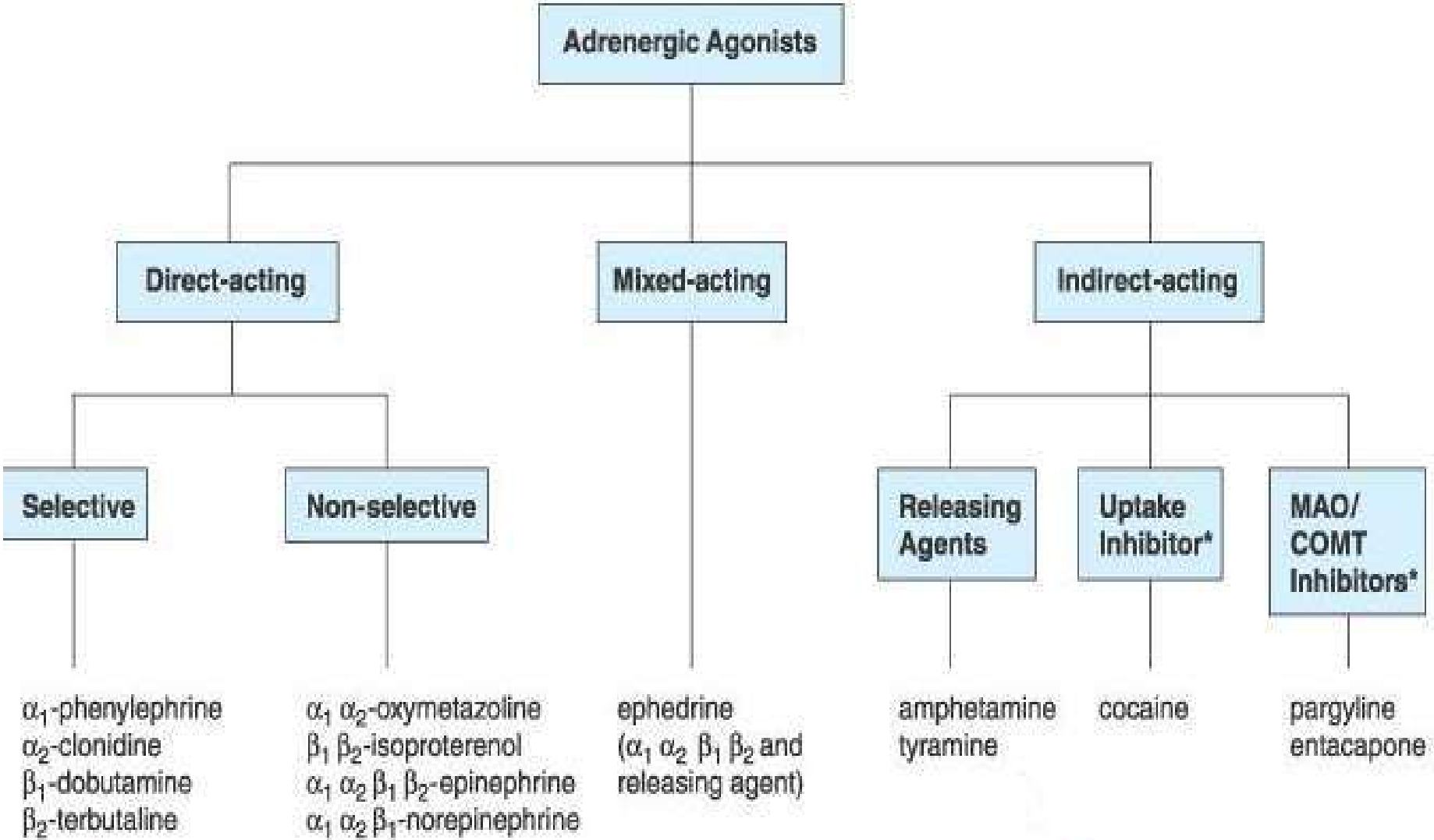
DIFFERENCE BETWEEN ALPHA-RECEPTOR

	α1-Receptor	α2-Receptor
LOCATION	Post junctional on effector organ	Pre junctional on nerve ending also pre junctional in Brain , Pancreatic β cell
Function	S. M. – Contraction, vasoconstriction Gland- Secretion Gut relaxation, Heart -Arrhythmia	Inhibition of transmitter release , vasoconstriction, Decrease sympathetic flow Decrease Insulin release Platelet aggregation
Agonist	Phenyl epinephrine Methoxamine,	Clonidine
Antagonist	Prazosin	Yohimbine
Effector Pathway	IP_3,/DAG Phospholipase A_2	C AMP K^+ channel Ca^+ channel IP_3,/DAG
Subtype	$\alpha 1_A$ $\alpha 1_B$ $\alpha 1_C$	$B2_A$ $\beta 2_B$ $\beta 2_C$

THERAPEUTIC CLASSIFICATION OF ADRENARGIC DRUG



CLASSIFICATION OF ADRENERGIC DRUGS BY ACTION



DIRECT ACTING ADRENERGIC AGONIST

- **Adrenaline, nor adrenaline isoprenaline** are directly acting drug.

- They are directly bind to adrenergic receptor and initiates its action by producing secondary messengers.

PHARMACOLOGICAL ACTION

- **CVS**

- Increases contractility of myocardium(B1)
- Increase rate of contraction(B1).
- Increase cardiac output
- It constrict arterioles in the skin,mucous membrane and viscera(a)

- **RESPIRATORY**
- Powerful bronchodilation by directly acting on bronchial smooth muscle(B2)
- This action relieves all known allergic or histamine induced bronchoconstriction
- In case of anaphylactic shock this can be lifesaving

- **HYPERGLYCEMIA**

- It increases glycogenolysis in the liver(B2)
- Increases release of glucagon(B2)
- Decreases release of insulin(A2)

- **LIPOLYSIS**

- It initiates lipolysis (B2)
- Which stimulates adenyl cyclase to increase cAMP levels
- And it stimulates hormone sensitive lipase which hydrolyzes triaceylglycerols to free fetty acids and glycerol

Therapeutic uses

- Bronhcospasm
- Glaucoma
- Anaphylactic shock
- In anesthetics-1:100000 parts of adrenaine is used,it increase the duration of action of local anesthesia
- It does this by producing vasoconstriction at the site of injection and allowing the local anesthetics to persists at the site.
- And also used topically to control oozing of capillary blood

ADVERSE EFFECT

- CNS disturbances
- Hemorrhage
- Cardiac arrhythmias(with digitalis)
- Pulmonary edema

INTERACTION

- **Hyperthyroidism** – Adr may increase cardiovasculer action in patients with Hyperthyroidism
- **Cocaine** –in presence of cocaine Adr produces exaggerated response due to the ability of cocaine to prevent re-uptake of Adr into the adrenergic neuron and thus Adr remains at the receptor site for longer time

INDIRECT ACTING ADRENERGIC AGONIST

- **Amphetamine**, **tyramine** and **cocaine** are act by this mechanism.
- Amphetamine and tyramine can enter the nerve terminal and displaced stored NA and Adr and then released catecholamines then acts on the adrenergic receptors.
- **Cocaine** inhibit the re uptake of Adr & NA to the presynaptic neuron.
- It increases release of Adr from presynaptic terminals but these drugs do not directly affect the postsynaptic receptor

AMPHETAMINES

- The pharmacological actions are same as Adr
- It stimulates respiratory centre, heart, hunger is suppressed as a result of inhibition of hypothalamic feeding centre, weak anticonvulsant action, analgesic and antiemetic action.
- The CNS action are more prominent
- The central actions are largely mediated by release of NA in the brain
- The central effects include alertness, increase attention and concentration, euphoria, talkativeness, increase work capacity
- Athletic performance is improved so this drug is included in 'dope test'.
- But this is short lived and may be accompanied by anxity, restlessness, tremor and dysporia

- Amphetamines are drug of abuse
- And abusers are generally teenagers seeking thrill or kick which is obtained on rapid i.v.injection
- Sometimes it causes toxicity so that time we should acidify the urine because amphetamines are more rapidly ionized and excretedfrom the body
- Chlorpromazine is administered which controls both central and peripheral alpha adrenergic effect

TYRAMINE

- It is not a clinically useful drug.
- It is found in fermented fruits.
- It is normal byproduct of tyrosine metabolism.
- Normally it is oxidised by MAO.
- But if the patient is taking MAO inhibitors then it can precipitate serious vasopressor episodes.

MIXED ACTION ADRENERGIC AGONIST

- Mixed action drugs induce the release of NA and Adr from presynaptic terminals and activate adrenergic receptor on the postsynaptic membrane also.
- **Ephedrine** is a brug which act by this mechanism

EPHEDRINE

- It ia a plant alkaloid, is now made synthetically
- It not only releases stored NA & Adr from nerve endings but also directly stimulates doth alpha & beta receptor
- Thus wide variety of adrenergic actions ensure that are sililar to those of Adr, altough less potent.
- Ephedrine is not a catechol and is poor substrate for COMT and MAO thus it has a long duration of action
- Ephedrine has axcellent absoption orally and penetrates into the CNS and eliminated unchanged in urine.

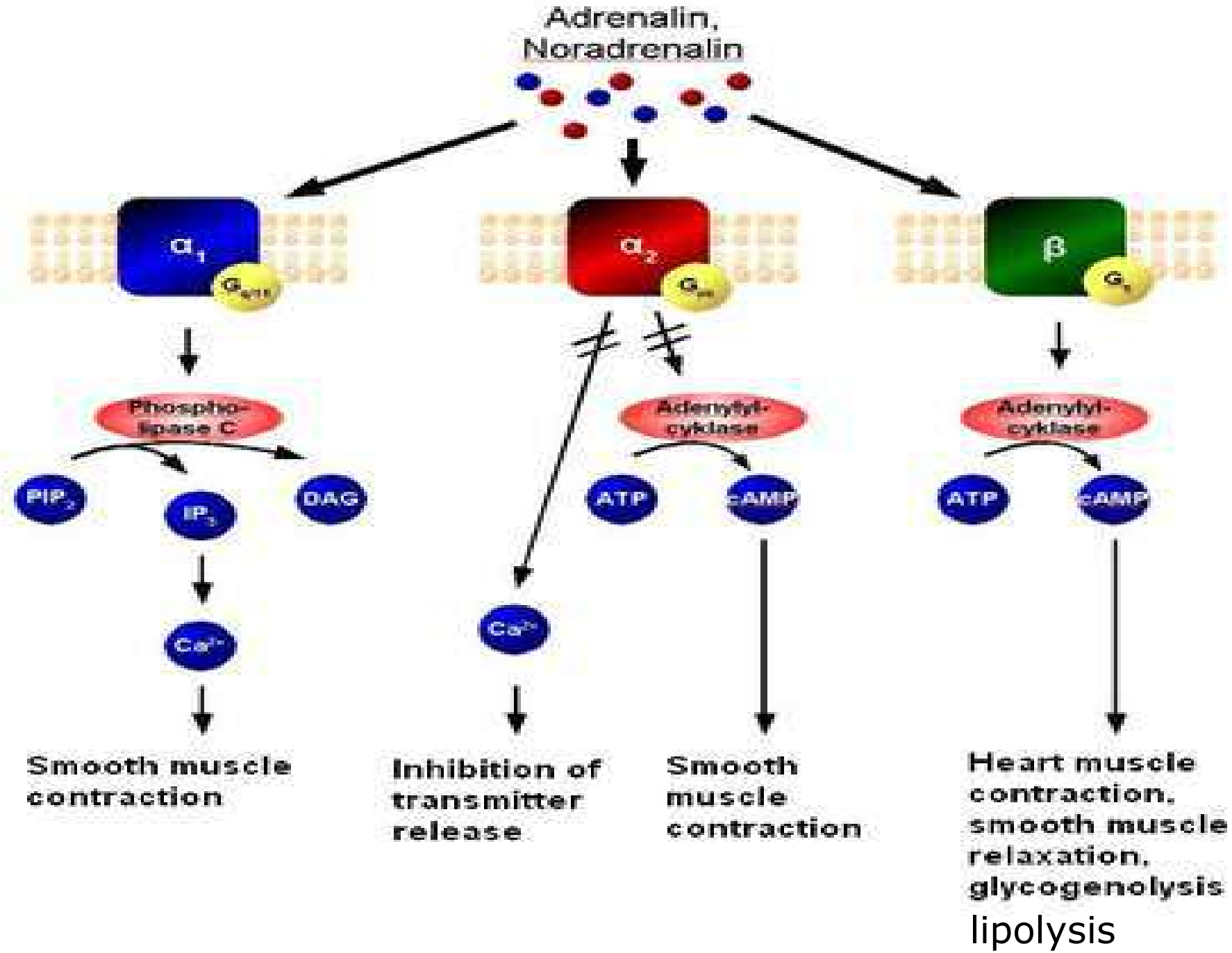
THERAPEUTIC USES OF ADRENERGIC DRUGS

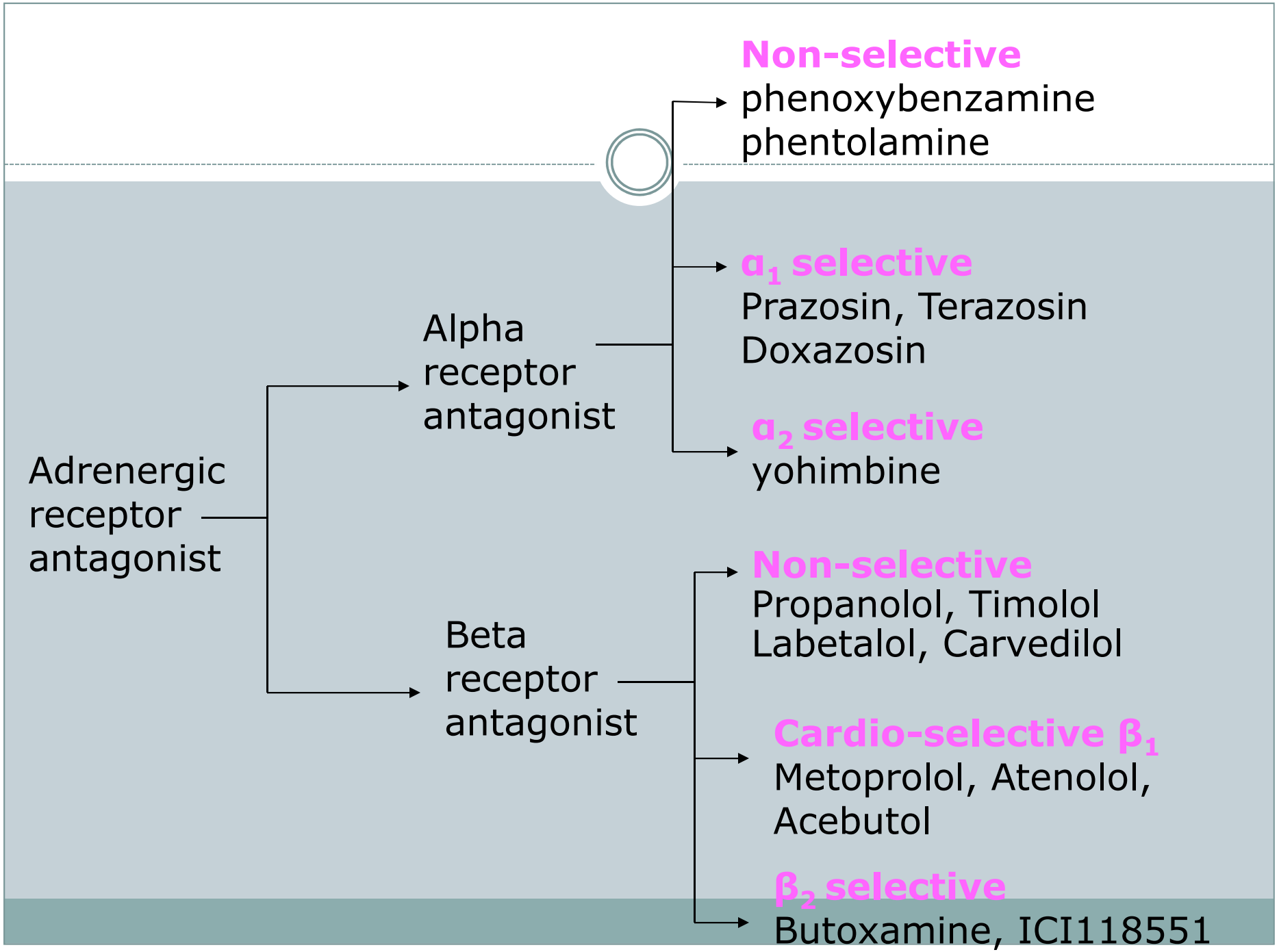
DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
ADRENALINE	α_1, α_2 β_1, β_2	ACUTE ASTHAMA, GLAUCOMA, ANAPHYLACTIC SHOCK, IN L.A.TO INCREASE DURATION OF ACTION
NOR ADRENALINE	$\alpha_1, \alpha_2, \beta_1$	TREATMENT OF SHOCK
ISOPROTERENOL	β_1, β_2	AS A CARDIAC STIMULANT
DOPAMINE	DOPAMINERGIC $\alpha_1, , \beta_1$	TREATMENT OF SHOCK, IN CONGESTIVE HEART FAILURE, TO RAISE BLOOD PRESSOR
PHENYLEPHRINE	α_1	AS A NASAL DECONGESTANT, RAISE BLOOD PRESSOR
DOBUTAMINE	β_1	TREATMENT OF CONGESTIVE HEART FAILURE,TREATMENT OF SUPRAVENTRICULAR TACHYCARDIA

METHOXAMINE	α_1	TREATMENT OF SUPRAVENTRICULAR TACHYCARDIA
CLONIDINE	α_2	TREATMENT OF HYPERTENSION
METAPROTERENOL	$\beta_{2.} > \beta_1$	TREATMENT OF BRONCHOSPASM AND ASTHMA
TERBUTALINE ALBUTEROL	β_2	TREATMENT OF BRONCHOSPASM
SALMETEROL FORMOTEROL	β_2	TREATMENT OF BRONCHOSPASM
AMPHETAMINE	α, β & CNS	AS A CNS STIMULANTIN TREATMENT OF CHILDREN WITH ATTENTION DEFICIT SYNDROME
EPHEDRINE	α, β & CNS	TREATMENT OF ASTHMA AS A NASAL DECONGESTANT RAISE BLOOD PRESSOR

ANTI ADRENERGIC DRUGS

- These are drugs which antagonize the receptor action of adrenaline and related drugs.


Adrenalin,
Noradrenalin
α1
α2
β
Phospho-
lipase C
Adenylyl-
cyklase
Adenylyl-
cyklase
PIP2
IP3
DAG
ATP
cAMP
ATP
cAMP
Ca2+
Ca2+
Smooth muscle
contraction
Inhibition of
transmitter
release
Smooth
muscle
contraction
Heart muscle
contraction,
smooth muscle
relaxation,
glycogenolysis
lipolysis


Adrenergic receptor antagonist
Alpha receptor antagonist
Non-selective
phenoxybenzamine
phentolamine
α1 selective
Prazosin, Terazosin
Doxazosin
α2 selective
yohimbine
Beta receptor antagonist
Non-selective
Propanolol, Timolol
Labetalol, Carvedilol
Cardio-selective β1
Metoprolol, Atenolol,
Acebutol
β2 selective
Butoxamine, ICI118551

α - ADRENERGIC BLOCKING AGENTS

- These drugs inhibit adrenergic responses mediated through the α-adrenergic receptors without affecting those mediated through β-receptors.

EFFECTS OF α BLOCKERS

1. Blockade of vasoconstrictor α_1 receptor reduces peripheral resistance fall in B.P. This causes postural hypotension.
2. Nasal stuffiness and miosis results from blockade of α receptors in nasal blood vessels and in radial muscles of iris respectively.
3. Reflex tachycardia occurs due to fall in mean arterial pressure and increased release of nor adrenaline due to blockade of pre-synaptic α_2 receptors.
4. Tone of smooth muscle in bladder, sphincter and prostate is reduced by blockade of α_1 receptor urine flow in patients with benign hypertrophy of prostate is improved.

5. Contraction of vas deferens and related organs which result in ejaculation are coordinated through α receptors. α blockers can inhibit ejaculation leads to sexual dysfunction.
6. Hypotension produced by α_1 blockers can reduce renal blood flow g.f.r. is reduced and more complete reabsorption of sodium and water occurs in tubules sodium retention and increase in blood volume.
7. Intestinal motility is increased due to partial inhibition of relaxant sympathetic influences diarrhea may occur.

PHENOXYBENZAMINE

- Phenoxybenzamine, is non selective, linking covalently to both α_1 post-synaptic and α_2 pre-synaptic receptors.
- The block is irreversible and non competitive.
- Dose: 20-60 mg/day oral.

  1 mg/kg by slow i.v infusion

  over 1 hr.

- **Cardiovascular effects:**
- By blocking α receptors, it prevents vasoconstriction of peripheral blood vessels.
- This decreased peripheral resistance provokes reflex tachycardia.
- The ability to block presynaptic α_2 receptors in heart increased cardiac output.
- Thus the drug is unsuccessful in hypertension and has been discontinued for this purpose.

PRAZOSIN, TERAZOSIN AND DOXAZOSIN

- These are selective blockers of α_1 receptors.
- In contrast to Phenoxybenzamine, these drugs are useful in treatment of hypertension.
- Dose:

  Prazosin 1-4 mg BD or TDS

  (generic, Minipress) 1, 2, 5 mg capsules

  Terazosin 2-10 mg OD

  (generic, Hytrin)1, 2, 5, 10 mg tablets, capsules

  Doxazosin 1 mg OD initially, ↑ upto 8 mg BD

  (generic, Cardura)1, 2, 4, 8 mg tablets

YOHIMBINE

- It is an alkaloid from West African tree yohimbehe.
- It is relatively selective α_2 blocker with shorter duration of action.
- Stimulation of presynaptic α_2 receptor inhibit the release of noradrenaline from the peripheral adrenergic nerve endings.
- Yohimbine by blocking these receptors, increases the sympathetic outflow and potentiates the release of NA.
- Given orally drug enjoys reputation as an aphrodisiac.

THERAPEUTIC USES

- Pheochromocytoma
- Hypertension
- Secondary shock
- Peripheral vascular diseases:

  e.g.Reynaud's disease
- CHF
- Benign hypertrophy of prostate

ADVERSE EFFECTS

- Postural hypotension
- Dryness of mouth
- Miosis
- Impotency
- Nasal stuffiness

B- ADRENERGIC BLOCKING AGENTS

- These drugs inhibits adrenergic responses mediated through β adrenergic receptors.

PHARMACOLOGICAL ACTIONS OF B BLOCKER

- **CVS**
- Heart:
- ↓heart rate, force of contraction and cardiac output (-ve ino and chronotropic effect).
- It directly depresses SA and AV activity.
- Cardiac output, work and oxygen consumption are decreased by blockade of β_1 receptors.
- These effects are useful in treatment of angina.

- Blood vessels

- Blockade of β receptors prevents β_2 mediated vasodilation.
- This blockade also inhibit the release of renin fall in B.P. hypotension.
- On balance, there is a gradual reduction of both systolic and diastolic B.P. in hypertensive patients.
- No postural hypotension occurs, because α_1 adrenergic receptors that control vascular resistance are unaffected.

- Respiratory tract
- Blockade of β_2 receptors in the lungs causes Broncho-constriction.
- This can precipitate a respiratory crisis in patients with COPD or asthma.
- β blockers are thus contraindicated in patients with asthma.

- Metabolic
- β blockade leads to decreased glycogenolysis and decreased glucagon secretion.
- Therefore if an insulin dependent diabetic is to be given β blocker, very careful monitoring of blood glucose is essential because pronounced hypoglycemia may occur.

- Skeletal muscles
- β blockers inhibit adrenergically provoked tremor.
- This is peripheral action exerted directly on the muscle fibres through β_2 receptors.
- It also tends to reduce exercise capacity by attenuating β_2 mediated increase in blood flow to exercising muscles as well as limiting glycogenolysis and lipolysis which provide fuel to working muscles.

- Eye
- β blockers reduces secretion of aqueous humor mediated through β_2 receptor.
- Hence i.o.t is reduced so they are useful in treatment of glaucoma.

PROPRANOLOL

- It is a nonselective β adrenergic antagonist which blocks both β_1 and β_2 receptors.
- Dose: oral 40-160 mg/day

  i.v. 2 to 5 mg injected over 10 mins

  Inderal, Ciplar 10, 40, 80 mg tab,

  1 mg/ml inj.

  Betabloc 10, 40 mg tab.

ATENOLOL, METAPROLOL, ACEBUTOLOL, BISPROLOL

- These are cardioselective β blockers, antagonize β_1 receptors at doses 50 to 100 fold less than those required to block β_2 receptors.
- This cardioselectivity is thus most pronounced at low doses and is lost at high doses.
- Dose: Atenolol oral 25-100 mg/day

  Betacard, Aten 25, 50, 100 mg tab

  Acebutolol oral 400mg/day, i.v 20-40 mg

  Sectral 200, 400 mg tab, 10 mg/ml amp

  Metoprolol oral100-400 mg/day, i.v. 10 mg

  Betaloc 50, 100 mg tab, 5 mg/ml inj

- Low propensity to cause bronchoconstriction, however should be avoided if possible in asthmatics.
- Less inhibition of glycogenolysis- safer in diabetics.
- Less chances of precipitating Reynaud's phenomenon.
- No/less deleterious effect on blood lipid profile.
- However they are ineffective in suppressing essential tremors (it occurs through β_2 action on muscle fibres).

LABETALOL AND CARVEDILOL

- They are reversible β blockers with concurrent α_1 blocking actions ($\alpha_1+\beta_1+\beta_2$) that produce peripheral vasodilation, thereby reducing B.P.
- They contrast with the other β blockers that produce peripheral vasoconstriction, and are therefore useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable.
- Dose: Labetalol 50-200 mg/day orally
  20-40 mg i.v.
  Normadate 50, 100, 200 mg tab.

THERAPEUTIC USES

- Hypertension
- Angina pectoris
- Hyperthyroidism (Cardiac arrhythmias)
- Migraine
- Tremor
- Glaucoma

ADVERSE EFFECTS

- Bronchoconstriction
- Arrhythmias
- Sexual impairment
- Disterbances in metabolism(cardioselective B blockers are preffered in treating insulin dependant asthmatics

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Review Article

The Stages of Drug Discovery and Development Process

Amol B. Deore*, Jayprabha R. Dhumane, Hrushikesh V Wagh, Rushikesh B. Sonawane

MVP's Institute of Pharmaceutical Sciences, Adgaon, Nashik-422003 (India)

A B S T R A C T

Drug discovery is a process which aims at identifying a compound therapeutically useful in curing and treating disease. This process involves the identification of candidates, synthesis, characterization, validation, optimization, screening and assays for therapeutic efficacy. Once a compound has shown its significance in these investigations, it will initiate the process of drug development earlier to clinical trials. New drug development process must continue through several stages in order to make a medicine that is safe, effective, and has approved all regulatory requirements. One overall theme of our article is that the process is sufficiently long, complex, and expensive so that many biological targets must be considered for every new medicine ultimately approved for clinical use and new research tools may be needed to investigate each new target. From initial discovery to a marketable medicine is a long, challenging task. It takes about 12 - 15 years from discovery to the approved medicine and requires an investment of about US $1 billion. On an average, a million molecules screened but only a single is explored in late stage clinical trials and is finally made obtainable for patients. This article provides a brief outline of the processes of new drug discovery and development.

Key words: Lead optimization, clinical trials, target validation, identification, new drug.

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***Address for Correspondence:**

Amol B. Deore, MVP's Institute of Pharmaceutical Sciences, Adgaon, Nashik-India

INTRODUCTION

Drug discovery is a multifaceted process, which involves identification of a drug chemical therapeutically useful in treating and management of a disease condition. Typically, researchers find out new drugs through new visions into a disease process that permit investigator to design a medicine to stopover or contrary the effects of the disease.[1] The process of drug discovery includes the identification of drug candidates, synthesis, characterization, screening, and assays for therapeutic efficacy. When a molecule avails its satisfactory results in these investigations, it will commence the process of drug development subsequent to clinical trials. Drug discovery and development is an expensive process due to the high budgets of R&D and clinical trials. It takes almost 12-15 years to develop a single new drug molecule from the time it is discovered when it is available in market for treating patients.[2] The average cost for research and development for each efficacious drug is likely to be $900 million to $2 billion. This figure includes the cost of the thousands of failures: For every 5,000-10,000 compounds that enter the investigation and development pipeline, ultimately only one attains approval. These statistics challenge imagination, but a brief understanding of the R&D process can explain why so many compounds don't make it and why it takes such a large, lengthy effort to get one medicine to patients.[3] The Success requires immense resources the best scientific and logical minds, highly sophisticated laboratory and technology; and multifaceted project management. It also takes persistence and good fortune.[4] Eventually, the process of drug discovery brings hope, faith and relief to billions of patients.[5]

Stages of drug discovery and development include:

- Target identification
- Target validation
- lead identification
- lead optimization
- Product characterization
- Formulation and development
- Preclinical research
- Investigational New Drug
- Clinical trials
- New Drug Application
- Approval

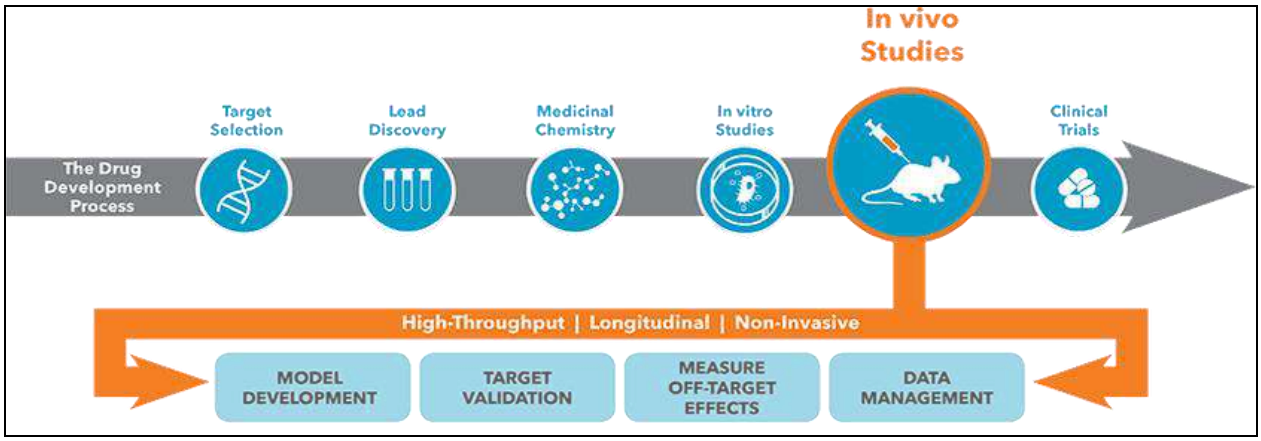

Figure 1: Stages of drug discovery and development process

Target Identification

The first step in the discovery of a drug is identification of the biological origin of a disease, and the potential targets for intervention. Target identification starts with isolating the function of a possible therapeutic target (gene/nucleic acid/protein) and its role in the disease. [6] Identification of the target is followed by characterization of the molecular mechanisms addressed by the target. An ideal target should be efficacious, safe, meet clinical and commercial requirements and be '**druggable**'. The techniques used for target identification may be based on principles of molecular biology, biochemistry, genetics, biophysics, or other disciplines.[7]

Approaches:

- Data mining using bioinformatics
  — identifying, selecting and prioritizing potential disease targets
- Genetic association
  — genetic polymorphism and connection with the disease
- Expression profile
  — changes in mRNA/protein levels
- Pathway and phenotypic analysis
  — *In vitro* cell-based mechanistic studies
- Functional screening
  — knockdown, knockout or using target specific tools[8]

Target Validation

Target validation is the process by which the expected molecular target – for example gene, protein or nucleic acid of a small molecule is certified. Target validation includes: determining the structure activity relationship (SAR) of analogs of the small molecule; generating a drug-resistant mutant of the presumed target; knockdown or over expression of the presumed target; and monitoring the known signaling systems downstream of the presumed target.[9]

Target validation is the process of demonstrating the functional role of the identified target in the disease phenotype. Whilst the validation of a drug's efficacy and toxicity in numerous disease-relevant cell models and animal models is extremely valuable – the ultimate test is whether the drug works in a clinical setting.[10]

Target validation can be broken down in to two key steps.

Reproducibility: Once a drug target is identified, whether it be via a specific technique or from review of literature, the first step is to repeat the experiment to confirm that it can be successfully reproduced. The target validation technique includes affinity chromatography, expression-cloning, protein microarray, reverse transfected cell microarray, biochemical suppression, siRNA, DNA microarray, system biology and study of existing drugs.[11,12]

Introduce variation to the ligand (drug)-target-environment

- Genetic manipulation of target genes (*in vitro*)
  knocking down the gene (shRNA, siRNA, miRNA), knocking out the gene (CRISPR), knocking in the genes (viral transfection of mutant genes)
- Antibodies
  interacting to the target with high affinity and blocking further interactions
- Chemical genomics
  chemical approaches against genome encoding protein[13]

Identification of Lead

A chemical lead is defined as a synthetically stable, feasible, and drug like molecule active in primary and secondary assays with acceptable specificity, affinity and selectivity for

the target receptor. This requires definition of the structure activity relationship as well as determination of synthetic feasibility and preliminary evidence of in vivo efficacy and target engagement. Characteristics of a chemical lead are:

- SAR defined
- Drug ability (preliminary toxicity, hERG)
- Synthetic feasibility
- Select mechanistic assays
- In vitro assessment of drug resistance and efflux potential
- Evidence of in vivo efficacy of chemical class
- PK/Toxicity of chemical class known based on preliminary toxicity or in silico studies

In order to decrease the number of compounds that fail in the drug development process, a drug ability assessment is often conducted. This assessment is important in transforming a compound from a lead molecule into a drug. For a compound to be considered druggable it should have the potential to bind to a specific target; however, also important is the compound's pharmacokinetic profile regarding absorption, distribution, metabolism, and excretion. Other assays will evaluate the potential toxicity of the compound in screens such as the Ames test and cytotoxicity assay. [14]

Lead Optimization

Lead optimization is the process by which a drug candidate is designed after an initial lead compound is identified. The process involves iterative series of synthesis and characterization of a potential drug to build up a representation of in what way chemical structure and activity are related in terms of interactions with its targets and its metabolism.

In initial drug discovery, the resulting leads from hit-to-lead high throughput screening tests undergo lead optimization, to identify promising compounds. Potential leads are evaluated for a range of properties, including selectivity and binding mechanisms during lead optimization, as the final step in early stage drug discovery. The purpose of lead optimization is to maintain favorable properties in lead compounds, while improving on deficiencies in lead structure. In order to produce a pre-clinical drug candidate, the chemical structures of lead compounds (small molecules or biologics) need to be altered to improve target specificity and selectivity. Pharmacodynamic and pharmacokinetic parameters and toxicological properties are also evaluated. Labs must acquire data on the toxicity, efficacy, stability and bioavailability of leads, in order to accurately characterize the compound and establish the route of optimization.[15]

Researchers in drug discovery need rapid methods to narrow down the selection of drug candidates for this downstream selectivity profiling and further investigation. High throughput DMPK (drug metabolism and pharmacokinetics) screens have become an essential part of lead optimization, facilitating the understanding and prediction of in vivo pharmacokinetics using in vitro tests. In order to make new drugs with higher potency and safety profiles, chemical modifications to the structure of candidate drugs are made through optimization.

Automated screening systems are becoming an important part of pharmaceutical and biopharmaceutical drug discovery labs. Mass spectrometry is used for the detection and quantitation of metabolites. MALDI imaging is a key technique for evaluating drug candidates and their metabolites in tissue structure rapidly and accurately. Additionally, NMR Fragment-based Screening (FBS) in the pharmaceutical industry has become a widely applied method for the discovery and optimization of lead molecules in targeted screening campaigns.[16]

Product Characterization

When any new drug molecule shows a promising therapeutic activity, then the molecule is characterized by its size, shape, strength, weakness, use, toxicity, and biological activity. Early stages of pharmacological studies are helpful to characterize the mechanism of action of the compound.

Formulation and Development

Pharmaceutical formulation is a stage of drug development during which the physicochemical properties of active pharmaceutical ingredients (APIs) are characterized to produce a bioavailable, stable and optimal dosage form for a specific administration route.

During preformulation studies the following parameters are evaluated:

- Solubility in different media and solvents
- Dissolution of the active pharmaceutical ingredient (API)
- Accelerated Stability Services under various conditions
- Solid state properties (polymorphs, particle size, particle shape etc.)
- Formulation services and capabilities
- Formulation development of new chemical entities (NCE)
- Optimization of existing formulations
- Process development for selected dosage forms
- Novel formulations for improved delivery of existing dosage forms
- Controlled release and sustained release formulations
- Self-emulsifying drug delivery systems
- Colloidal drug delivery systems
- Sub-micron and nano-emulsions

Preclinical Testing

Pre-clinical research in drug development process involves evaluation of drug's safety and efficacy in animal species that conclude to prospective human outcome. The pre-clinical trials also have to acquire approval by corresponding regulatory authorities. The regulatory authorities must ensure that trials are conducted in safe and ethical way and would give approval for only those drugs which are confirm to be safe and effective. ICH has established a basic guideline for technical necessities of acceptable preclinical drug development.[17]

The pre-clinical trials can be conducted in two ways: General pharmacology and Toxicology. Pharmacology deals with the pharmacokinetic and pharmacodynamic parameters of drug. It is essential to explore unwanted pharmacological effects in suitable animal models and monitoring them in toxicological studies. Pharmacokinetic studies are very important to make known the safety and efficacy parameters in terms of

absorption, distribution, metabolism and excretion. These studies give information on absorption rate for diverse routes of administration, which helps in selection of dosage form, distribution, rate of metabolism and elimination; which governs the half-life of the drug. Half-life of the drug clarifies the safety outline of the drug which is the obligatory for a drug to get approved by regulatory agencies. The drug distribution mechanism elucidates the therapeutic effectiveness of the drug as it depends on the drugs bioavailability and its affinity. Drug metabolism provides the probability of through phases of biotransformation process and formation of drug metabolites. It also helps in understanding the reactions as well as enzymes involved in biotransformation. [18]

Toxicological studies of the drug can be performed by in-vitro and in-vivo test which evaluate the toxicological effects of the drug. In-vitro studies can be performed to inspect the direct effects on cell proliferation and phenotype. In-vivo studies can be performed for qualitative and quantitative determination of toxicological effects. As many drugs are species specific, it is essential to select appropriate animal species for toxicity study. In-vivo studies to evaluate pharmacological and toxicological actions, including mode of action, are often used to support the basis of the proposed use of the product in clinical studies. [19]

The Investigational New Drug Process (IND)

Drug developers must file an Investigational New Drug application to FDA before commencement clinical research.[20] In the IND application, developers must include:

- Preclinical and toxicity study data
- Drug manufacturing information
- Clinical research protocols for studies to be conducted
- Previous clinical research data (if any)
- Information about the investigator/ developer[21]

Clinical Research

Clinical trials are conducted in people (volunteer)and intended to answer specific questions about the safety and efficacy of drugs, vaccines, other therapies, or new methods of using current treatments. Clinical trials follow a specific study protocol that is designed by the researcher or investigator or manufacturer. As the developers design the clinical study, they will consider what they want to complete for each of the different Clinical Research Phases and starts the Investigational New Drug Process (IND), a process they must go through before clinical research begins. Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives.[22] Then, they decide:

- Selection criteria for participants
- Number of people take part of the study
- Duration of study
- Dose and route of administration of dosage form
- Assessment of parameters
- Data collection and analysis

Phase 0 clinical trial

Phase 0 implicates investigative, first-in-human (FIH) trials that are conducted according to FDA guidelines. Phase 0 trials besides termed as human micro dose studies, they have single sub-therapeutic doses given to 10 to 15 volunteers and give pharmacokinetic data or help with imaging specific targets without exerting pharmacological actions. Pharmaceutical industries perform Phase 0 studies to pick which of their drug applicants has the preeminent pharmacokinetic parameters in humans.[24]

Phase 1: Safety and dosage

Phase I trials are the first tests of a drug with a lesser number of healthy human volunteers. In most cases, 20 to 80 healthy volunteers with the disease/condition participate in Phase 1. Patients are generally only used if the mechanism of action of a drug indicates that it will not be tolerated in healthy people. However, if a new drug is proposed for use in diabetes patients, researchers conduct Phase 1 trials in patients with that type of diabetes. Phase 1 studies are closely monitored and collect information about Pharmacodynemics in the human body. Researchers adjust dosage regimen based on animal study data to find out what dose of a drug can tolerate the body and what are its acute side effects. As a Phase 1 trial continues, researchers find out research mechanism of action, the side effects accompanying with increase in dosage, and information about effectiveness. This is imperative to the design of Phase 2 studies. Almost 70% of drugs travel to the next phase.

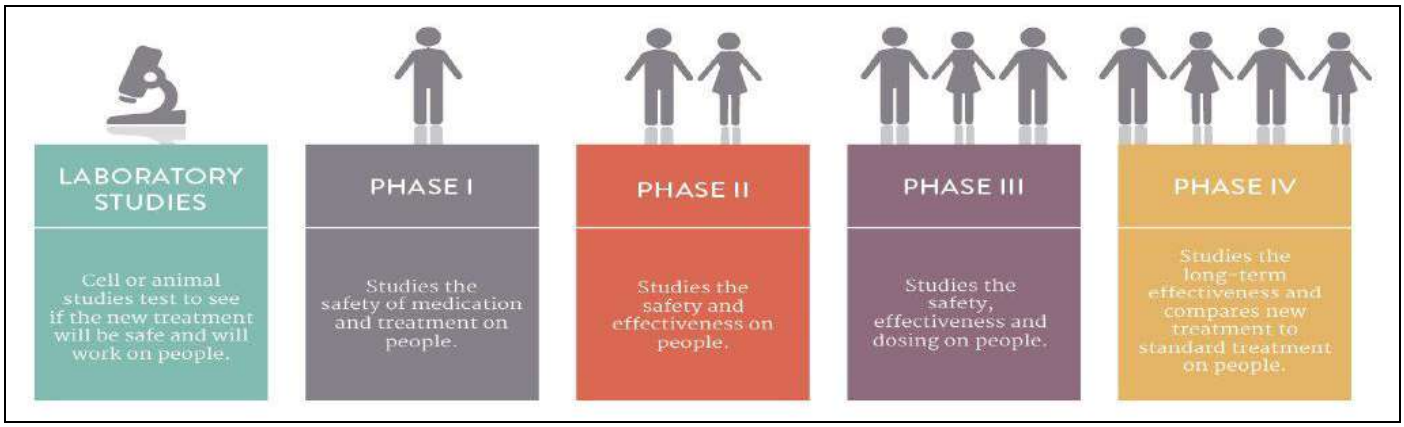

Figure 2: Phases of clinical trials

Phase 2: Efficacy and side effects

Phase II trials are conducted on larger groups of patients (few hundreds) and are aimed to evaluate the efficacy of the drug and to endure the Phase I safety assessments. These trials aren'tsufficient to confirm whether the drug will be therapeutic. Phase 2 studies provide with additional safety data to the researchers. Researchers use these data to refine research questions, develop research methods, and design new Phase 3 research protocols. Around 33% of drugs travel to the next phase.

Most prominently, Phase II clinical studies aid to found therapeutic doses for the large-scale Phase III studies.

Phase 3: Efficacy and adverse drug reactions monitoring

Researchers plan Phase 3 studies to prove whether a product deals anaction benefit to a specific peopleor not. Sometimes known as pivotal studies, these studies comprise 300 to 3,000 volunteers. Phase 3 studies deliver most of the safety data. Theprevious study might not able to detect less common side effects.Butphase 3 studies are conducted on large no. of volunteers and longer in duration, the results are more probable to detect long-term or uncommon side effects. Around 25-30% of drugs travel to the next phase of clinical research.

If a drug developer has data from its previous tests, preclinical and clinical trials that a drug is safe and effective for its intended use, then the industry can file an application to market the medicine. The FDA review team comprehensivelyinspects all submitted data on the drug and makes a conclusion to approve or not to approve it.[25]

New Drug Application

A New Drug Application (NDA) expresses the full story of a drug molecule. Its purpose is to verify that a drug is safe and effective for its proposed use in the people studied. A drug developer must include all about a drug starting from preclinical data to Phase 3 trial datain the NDA. Developers must include reports on all studies, data, and analysis.[26]Beside with clinical trial outcomes, developers must include:

- Proposed labeling
- Safety updates
- Drug abuse information
- Patent information
- Institutional review board compliance information
- Directions for use

FDA Review

Once FDA obtains a complete NDA then FDA team of review may require about 6 to 10 months to take a pronouncement on whether to approve the NDA. If Once FDA obtains a incomplete NDA then FDA team of review refuse the NDA.

If FDAgoverns that a drug has been revealed to be safe and effective for its proposed use, it is then essential to work with the developerforupgrade prescribing information. This is denoted as "labeling." Labeling preciselydefines the basis for approval and directionhow to use the drug. Although, remaining issues required to be fixed before the drug to be approved for marketing. In other cases, FDA have need of additional studies. At this situation, the developer can choose whether to continue further developmentor not. If a developer distresses with an FDA decision, there are tools for official appeal.[27]

Phase 4: Post-Market Drug Safety Monitoring

Phase 4 trials are conductedwhen the drug or devicehas been approved by FDA.These trials are also recognized as post-marketing surveillance involving pharmacovigilance and continuing technical support after approval. There are numerous observational strategies and assessmentpatterns used in Phase 4trials to evaluate the efficacy, cost-effectiveness, and safety of an involvement in real-world settings. Phase IV studies may be required by regulatory authorities (e.g. change in labelling, risk management/minimization action plan) or may be undertaken by the sponsoring company for competitive purposes or other reasons. Therefore, the true illustration of a drug's safety essentiallyrequires over the months and even years that mark up a drug'slifespan in the market. FDA reviews reports of complications with prescription and OTC drugs, and can decide to add precautions to the dosage or practice information, as well as other events for more serious adverse drug reactions. [28]

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