PHARMACOLOGY

BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024, Tamil Nadu,
India

Programme: M.Sc., Biomedical Science

Course Title : Pharmacology and Toxicology
Course Code : BM35C7

Unit-I
General Pharmacology Part-2

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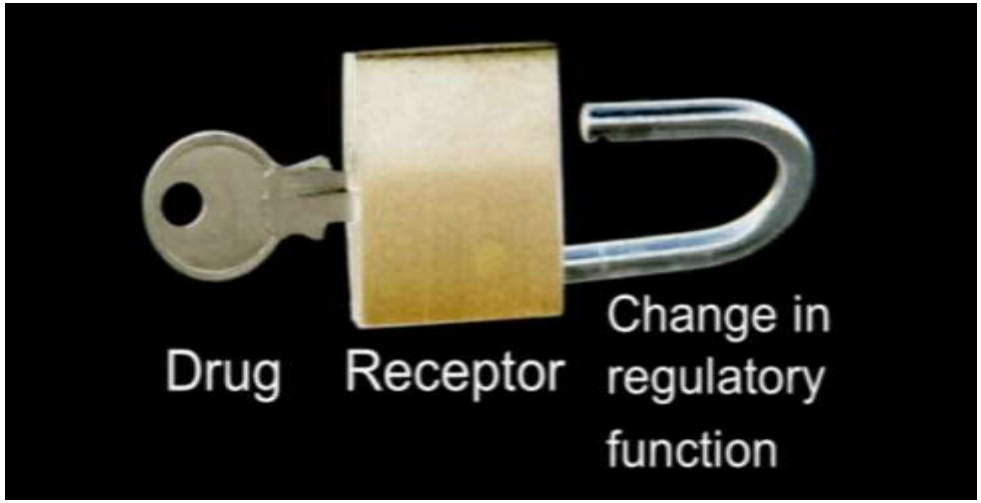
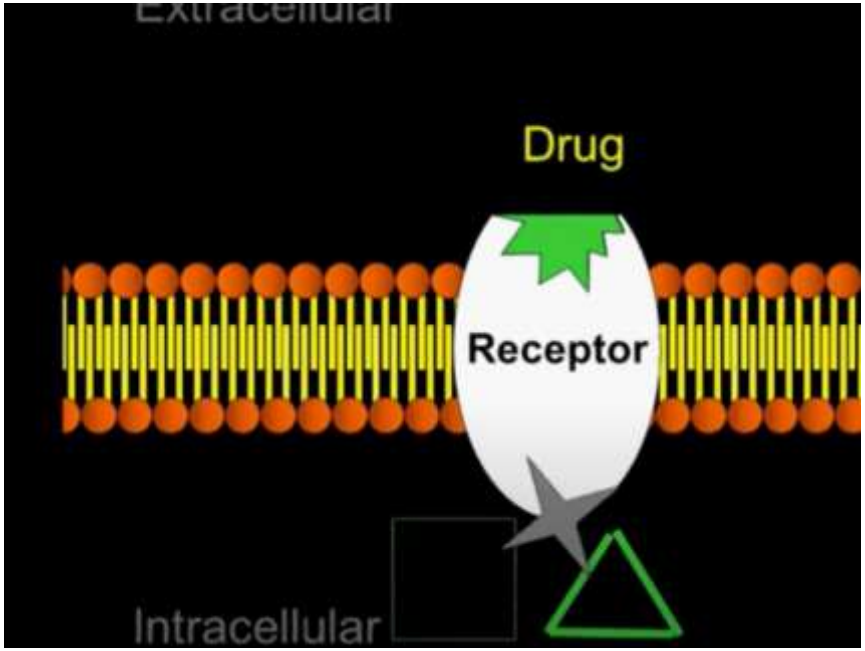
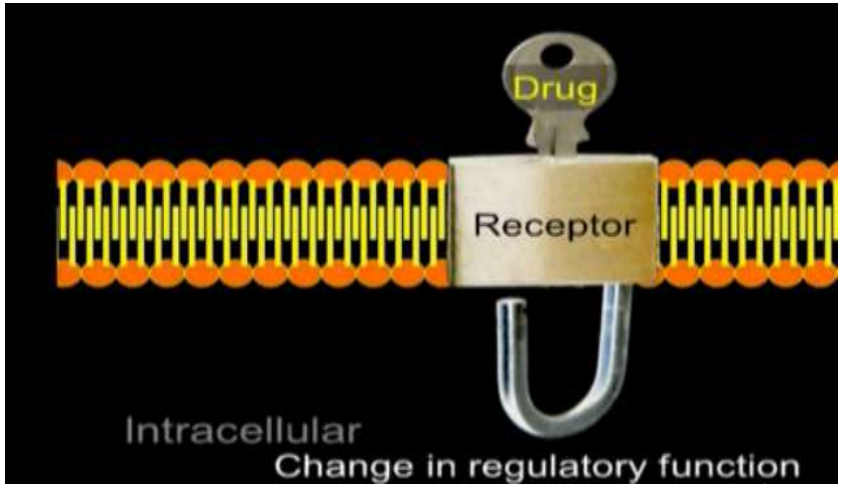

Drug
Receptor
Change in regulatory function


Drug
Receptor
Intracellular


Drug
Receptor
Intracellular
Change in regulatory function

Pharmacokinetics

(Greek: Kinesis-movement)

What the body does to the drug.

movement of the drug in and alteration of the drug by the body

- Absorption
- Distribution
- Binding/localization/ storage
- biotransformation
- Excretion of the drug

- Pharmacokinetics is the quantitative study of drug movement in, through and out of the body
- The intensity of response is related to concentration of the drug at the site of action
- Pharmacokinetic considerations, determine
  - Route(s) of administration
  - Dose
  - Latency of onset
  - Time of peak action
  - Duration of action
  - Frequency of administration of a drug.

Paracetamol

- Rapidly absorbed orally blood levels at 30-60 min.
- 25% bound to plasma proteins
- Uniformly distributed in the body
- (volume of distribution - lL/kg)
- Metabolized in the liver, primarily by glucuronide and sulfate conjugation into inactive metabolites
- Excreted in urine;
- Plasma half life (t1/2) of 2-3 hours and a clearance value of 5 ml/kg/min.

Pharmacokinetics

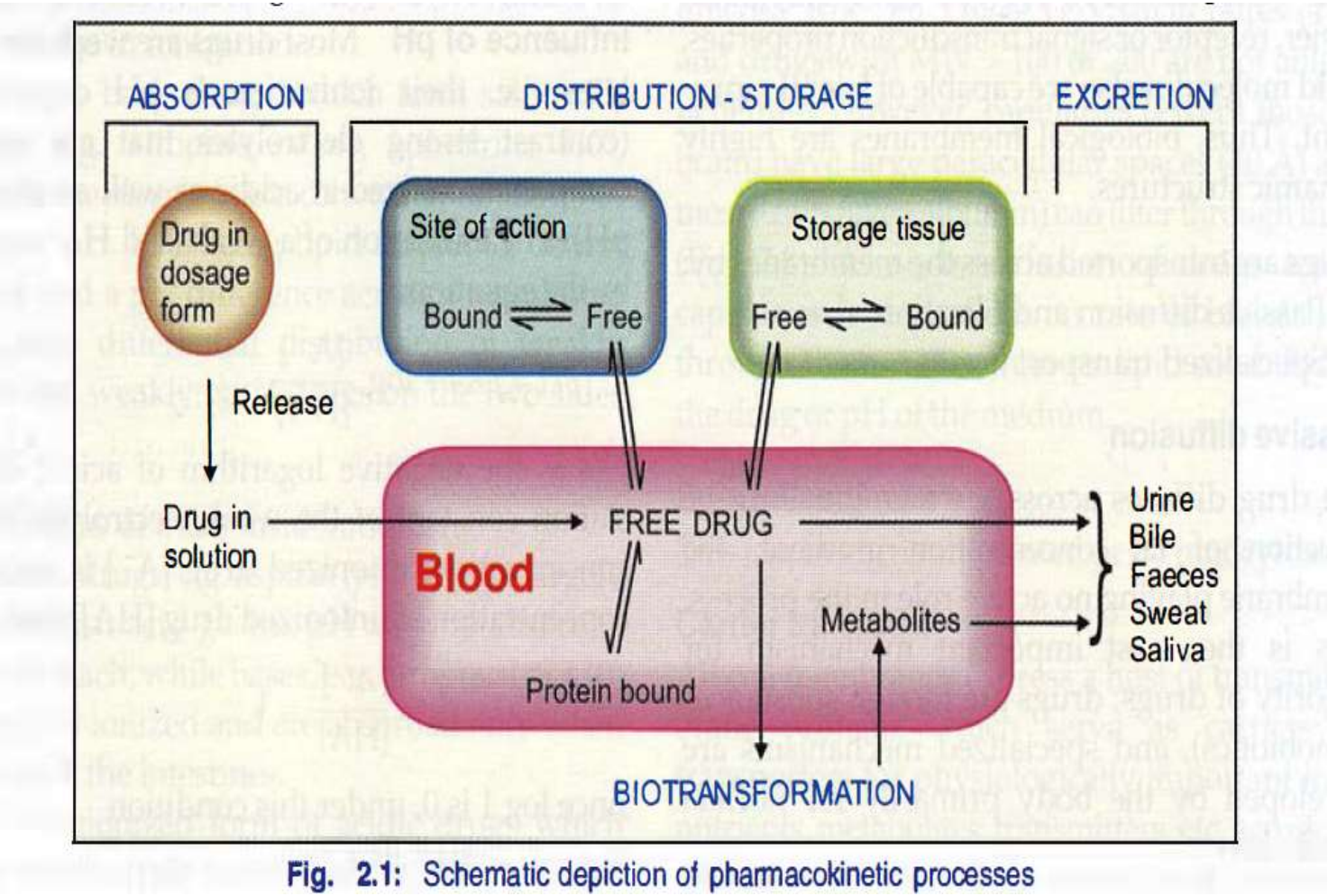


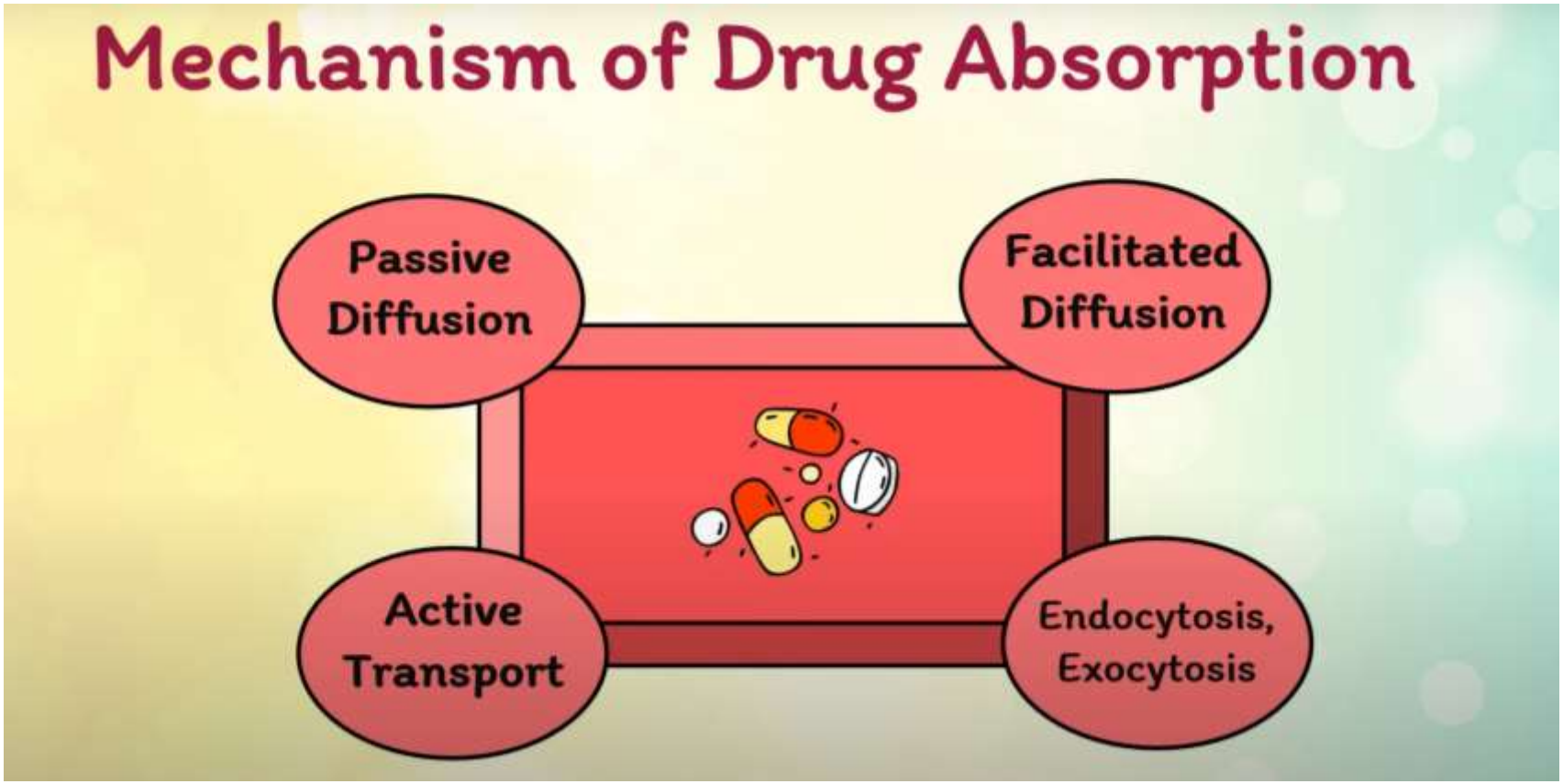
Fig. 2.1: Schematic depiction of pharmacokinetic processes

Is the quantitative study of drug movement in, through and out of the body.

ABSORPTION

- Drug movement from the site of drug administration to the systemic circulation
- It is quantified in terms of bioavailability.
- Bioavailability is the extent to which absorption occurs.
- Various factors impede or enhance absorption.
  - The lipid solubility
  - pH of the medium
  - Density of membrane transporters

Mechanism of Drug Absorption

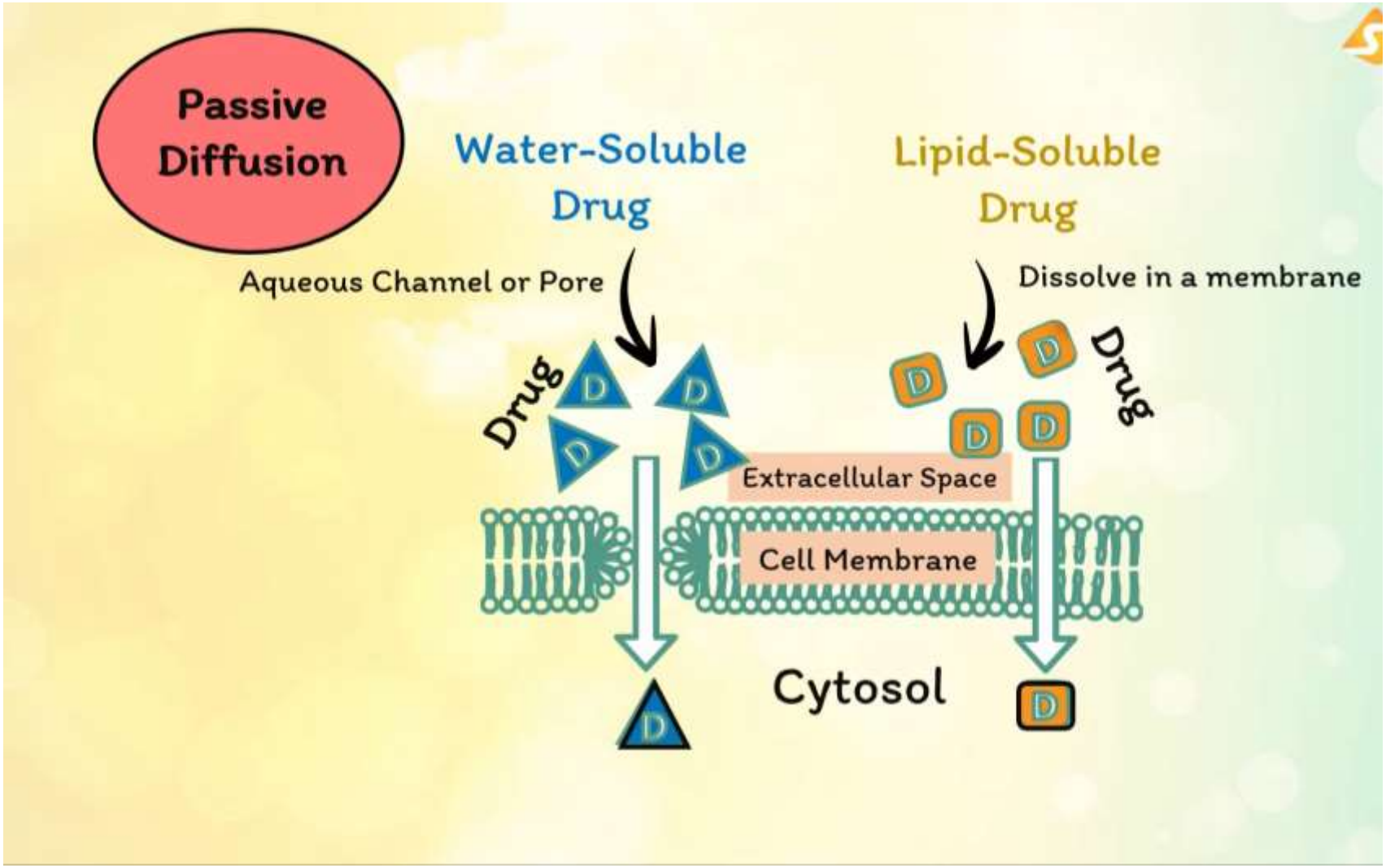


Biological membrane

- This is a bilayer of phospholipid and cholesterol molecules, the polar groups of these are oriented at the two surfaces and the nonpolar hydrocarbon chains are embedded in the matrix to form a continuous sheet.
- Extrinsic and intrinsic protein molecules are adsorbed on the lipid bilayer

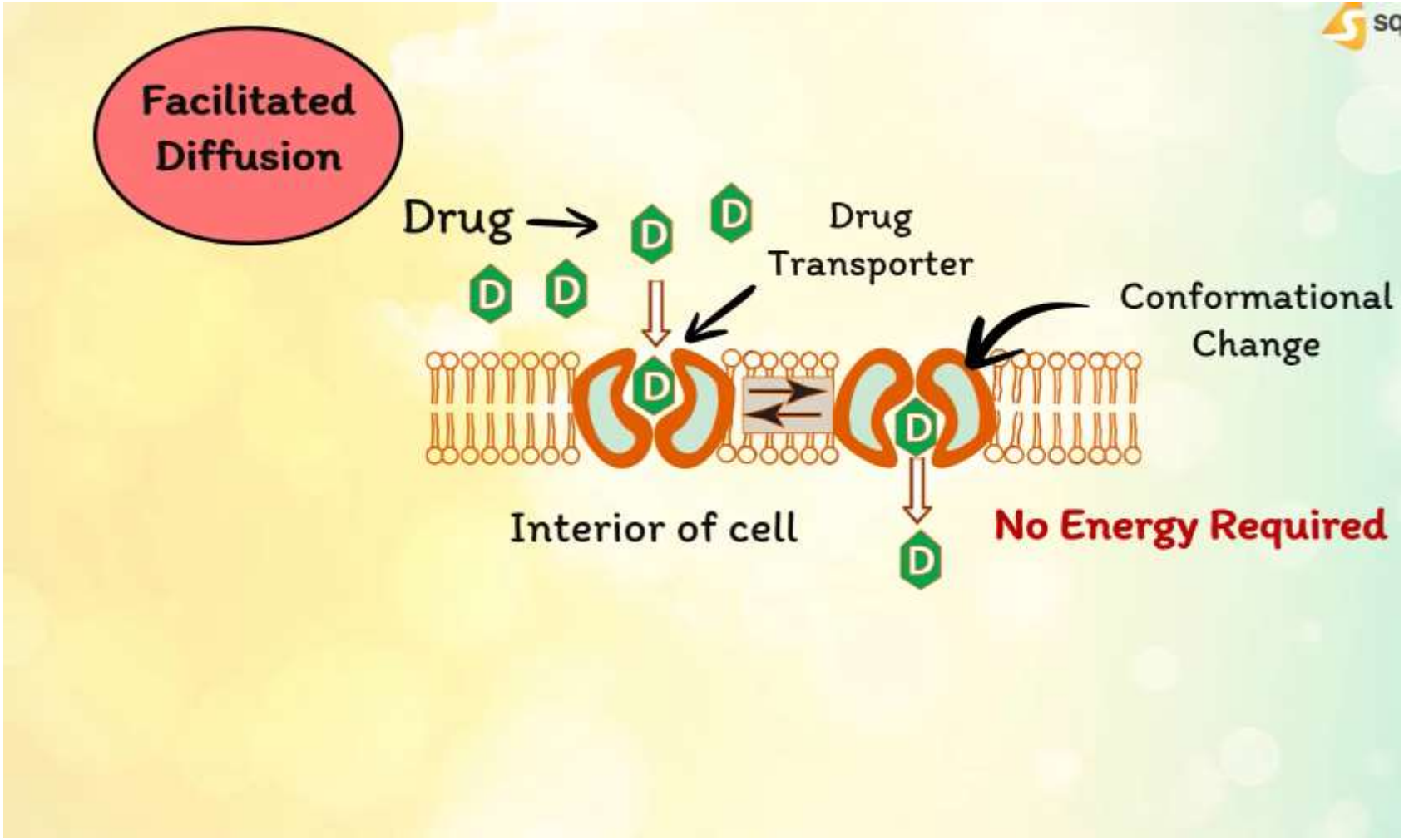
Passive Diffusion

- The movement of drug molecules is driven by a concentration gradient from a higher concentration to a lower concentration.
- Lipid-soluble drugs are able to diffuse easily through biological membranes.
- The rate of diffusion is directly proportional to the concentration gradient, the surface area available for diffusion, and the lipid-water partition coefficient of the drug.


Passive Diffusion
Water-Soluble Drug
Lipid-Soluble Drug
Aqueous Channel or Pore
Dissolve in a membrane
Drug
Drug
D
Extracellular Space
Cell Membrane
Cytosol

Facilitated Diffusion

- Carrier proteins are involved in facilitated drug transport.
- The movement of the drug molecules is driven by an electrochemical gradient from a higher to lower gradient.


Facilitated Diffusion
Drug
D
D
D
D
Drug Transporter
Conformational Change
D
D
D
Interior of cell
No Energy Required

- Facilitated diffusion: The carrier (SLC) binds and moves the poorly diffusible substrate along its concentration gradient (high to low) and does not require energy .
- Primary active transport: the carrier (ABC) derives energy directly by hydrolysing ATP and moves the substrate against its concentration gradient (low to high)
- Symport: the carrier moves the substrate 'A' against its concentration gradient by utilizing energy from downhill movement of another substrate 'B' in the same direction
- Antiport: the carrier moves the substrate 'A' against its concentration gradient and is energized by the downhill movement of another substrate 'B' in the opposite direction

Paracellular Transport

- The drug molecules move through intercellular gaps in the endothelium of capillaries and postcapillary venules.

- There is no specificity of the drug molecules transported; however, the drug must be of lower molecular weight. – This process is highly limited in organs with tight junctions

ABSORPTION

Absorption is movement of the drug from its site of administration into the circulation.

Factors affecting absorption are:

- Cross biological membranes
- Aqueous solubility Drugs
- Area of absorbing surface
- Vascularity of the absorbing surface
- Route of administration

Bioavailability

- **Is defined as the** fraction of a given drug dose that reaches the circulation in unchanged form and becomes available for systemic distribution.
- The larger the presystemic elimination, the smaller is the bioavailability of an orally administered drug.

Distribution

- The process of drug movement after absorption into various body compartments like the interstitial space and the intracellular space
- It is an important process which results in exposure of the target organ to the drug.
- The initial phase is highly influenced by the amount of blood flow to various organs and is responsible for the acute onset action of the drugs.
- The second phase is a slower phase where the drug equilibrates with the muscle, skin, and fat.

Factors governing volume of drug distribution

Lipid: water partition coefficient of the drug

- pKa,value of the drug
- Degree of plasma protein binding
- Affinity for different tissues
- Fat: lean body mass ratio, which can vary with age, sex, obesity, etc.
- Diseases like CHF, uremia, cirrhosis

Biotransformation

- Chemical alteration of the drug in the body
- Metabolize drugs (essentially foreign substances) have developed to protect the body from ingested toxins.
- Liver; kidney, intestine, lungs and plasma.

INACTIVATION

Most drugs and their active metabolites are rendered inactive or less active

ACTIVE METABOLITE FROM AN ACTIVE DRUG

Many drugs have been found to be partially converted to one or more active metabolite

ACTIVATION OF INACTIVE DRUG

Few drugs are inactive as such and need conversion in the body to one or more active metabolites.(Prodrug)

Metabolism

- Metabolism is the major pathway for the elimination of the majority of xenobiotics and endogenous molecules from the body.
- In the liver, the cytochrome P450 enzymes - role in the metabolism of drugs and have a significant role in "drug interaction" due to enzyme induction and inhibition during multiple drug administration.

Usually, the drug or any xenobiotic undergoes phase I metabolism wherein the toxic compound is structurally converted to non-toxic compound followed by phase II wherein modified metabolite is conjugated with endogenous molecules to make it water soluble for ease of excretion.

NONSYNTHETIC/ PHASE 1

(Oxidation, Reduction, Hydrolysis, Cyclization, Decyclization)

SYNTHETIC/ CONJUGATION/ PHASE II

(Glucuronide conjugation, Acetylation, Methylation, Sulfate conjugation, Glycine conjugation, Glutathione conjugation, Ribonucleoside/nucleotide synthesis)

Phase I - non-synthetic or functionalization reaction

- New functional groups (like –OH, –C=O, or –NH2) are created in the parent molecule so that the functional group can be attached with additional molecules in further steps.
- The metabolite generated may be inactive or active in this phase.
- Only a little effect will be seen in the water solubility of the molecule after phase I biotransformation, but a dramatic effect will be observed in its biological activity

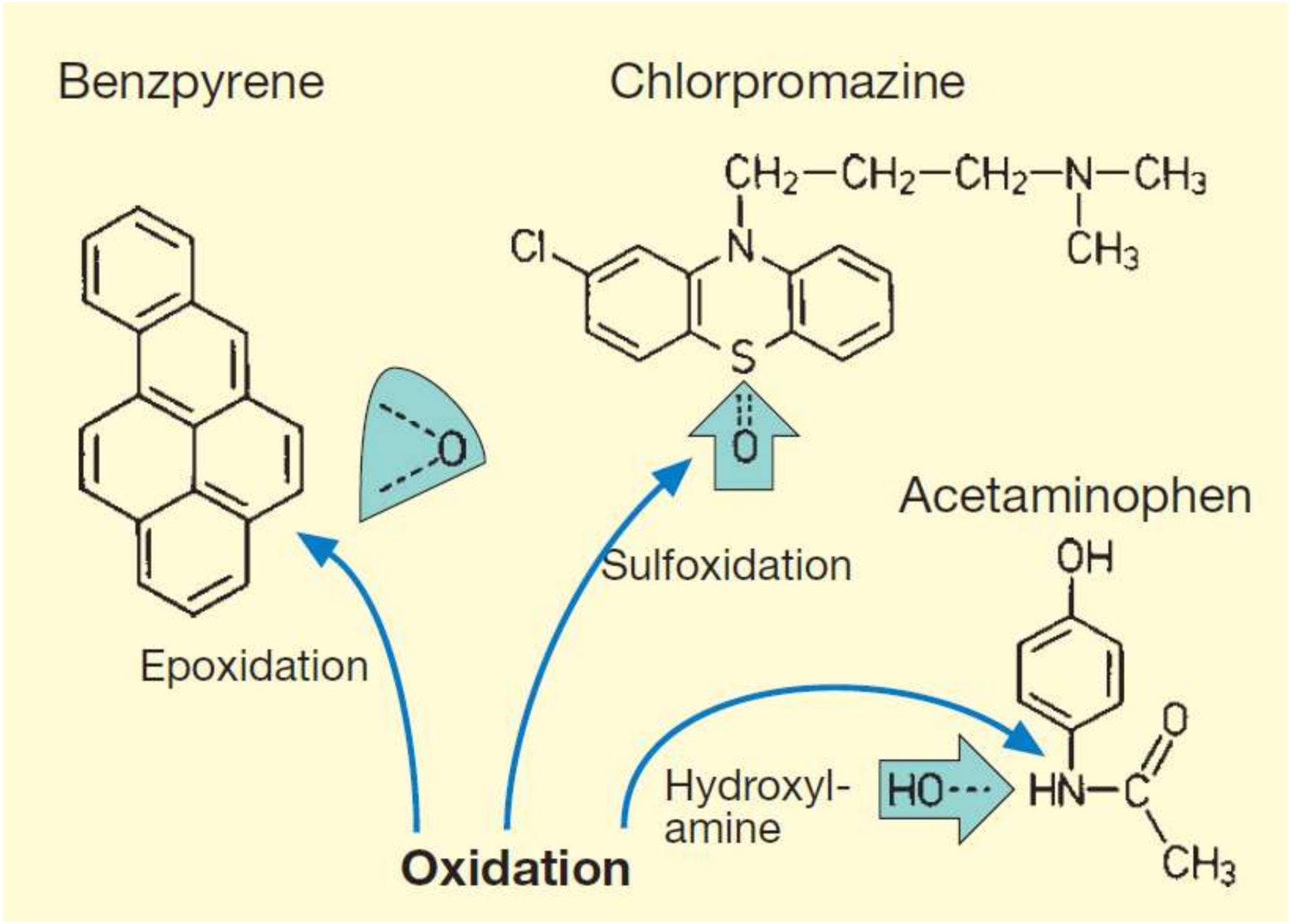
Phase II is also called as synthetic or conjugation reaction

- Molecular groups like alkyl, aryl, various amino acids, and glucuronyl are attached to the phase I metabolite in order to make it water soluble.
- Metabolite generated in this phase is mostly inactive.

Oxidative reactions

- They involve enzymes like CYP450 inside the microsomes and enzymes like MAO, xanthine oxidase (XO) outside the microsomes
- In oxidative reactions, one molecule of oxygen is inserted into the chemical structure with or without the removal of hydrogen molecule from the parent molecule.

- Hydroxylation (R–H to R–OH),
- Dehydrogenation (R–C–OH to R–C=O),
- Deamination (R–C–NH2 to R–C=O),
- Dealkylation (R–CH3 to R–H),
- Carboxylation (R– C=O to R-COOH),
- S-oxidation, and N-oxidation

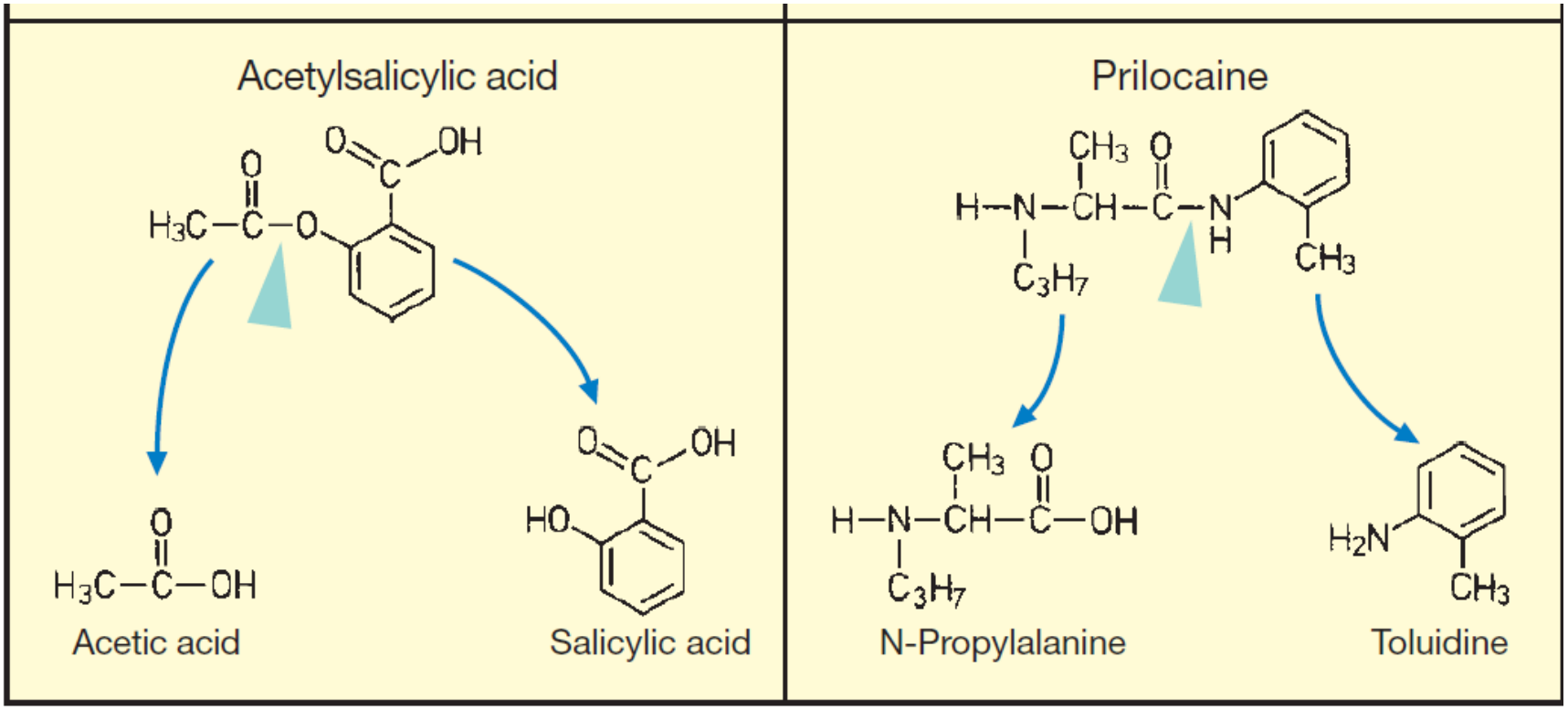

Benzpyrene
Chlorpromazine
Cl
N
S
O
Epoxidation
Sulfoxidation
Acetaminophen
OH
HO
HN
Hydroxyl-
amine
Oxidation

Reduction Reactions

- Dehydroxylation (R-OH to R-H),
- Hydrogenation (R-C=O to R-C-OH),
- Decarboxylation (R-COOH to R-C=O),
- Amination (R-NO2 to R-NH2),
- Methylation (R-C-H to R-CH3).
- P-nitro benzoic acid ➔nitro-reductase ➔p-aminobenzoic acid (amination)
- Chloramphenicol ➔nitro-reductase ➔ amine of chloramphenicol (amination)

Hydrolysis

- Drugs with esters and amides in their structure undergo cleavage metabolism
- Enzymes like pseudocholinesterase, arylcarboxylesterase, liver microsomal carboxylesterase, and paraoxonase
- Procaine, succinylcholine, procainamide, aspirin, and enalapril.



A. Examples of chemical reactions in drug biotransformation (hydrolysis)

Cyclization

- The drug with a straight-chain structure is converted to a ring structure.
- Proguanil ➔CYP2C19 ➔ cycloguanil

Phase II Reactions

- Phase II reactions utilize mainly “transferase” enzymes in order to transfer polar molecules to a functional group created in phase I reaction.
- Increasing the polarity of the drug metabolites in phase II results in poor cellular diffusion and low affinity for the receptor.
- Metabolites of phase II often are biologically inactive.

Glucuronidation

- The glucuronic acid is highly available in the liver, and many functional groups like alcohol, phenol, amine, and carboxylic acids undergo glucuronic acid conjugation.
- Glucuronidation is mediated by uridine diphosphate-glucuronosyl transferase (UGT), and in humans UGT1 and UGT2,
- UGT is present in the intestine, lung, nasal mucosa, brain, and kidneys

- Drugs conjugated with glucuronic acid are excreted in bile which then can undergo significant “enterohepatic circulation” after deconjugation by the gut microbes.
- Acetaminophen and morphine

  (O-glucuronidation)
- Ibuprofen (acyl glucuronidation)

Sulfation

- Enzyme sulfotransferase (SULT)
- Endogenous compounds like steroids, catecholamines, thyroxine, and bile acids
- Drugs with phenol moiety readily undergo sulfonation.
- SULT1 and SULT2

Acetaminophen ➔SULT1AI➔ acetaminophen sulfate

Acetylation

- Acetyl CoA can be transferred to the primary aliphatic amines, aromatic amines, and hydrazines in the structure of drug metabolites.
- N-acetyltransferase (NAT) is the enzyme responsible for acetylation reaction.
- Hydralazine ➔NAT ➔hydralazine acetone hydrazine

Glutathionylation

- Glutathione S-transferase (GST) mediates this reaction and utilizes glutathione as a substrate.

Glycine Conjugation

- Glycine N-acyl transferase (GLYAT)

Methylation

- O-Methyl metabolites formed by this reaction in some cases have higher lipophilicity and increased biological activity.
- Methyltransferase (MT) is the enzyme involved, and it requires S-adenosyl methionine as a cofactor.
- Norepinephrine ➔ COMT ➔epinephrine (active metabolite) Methylation

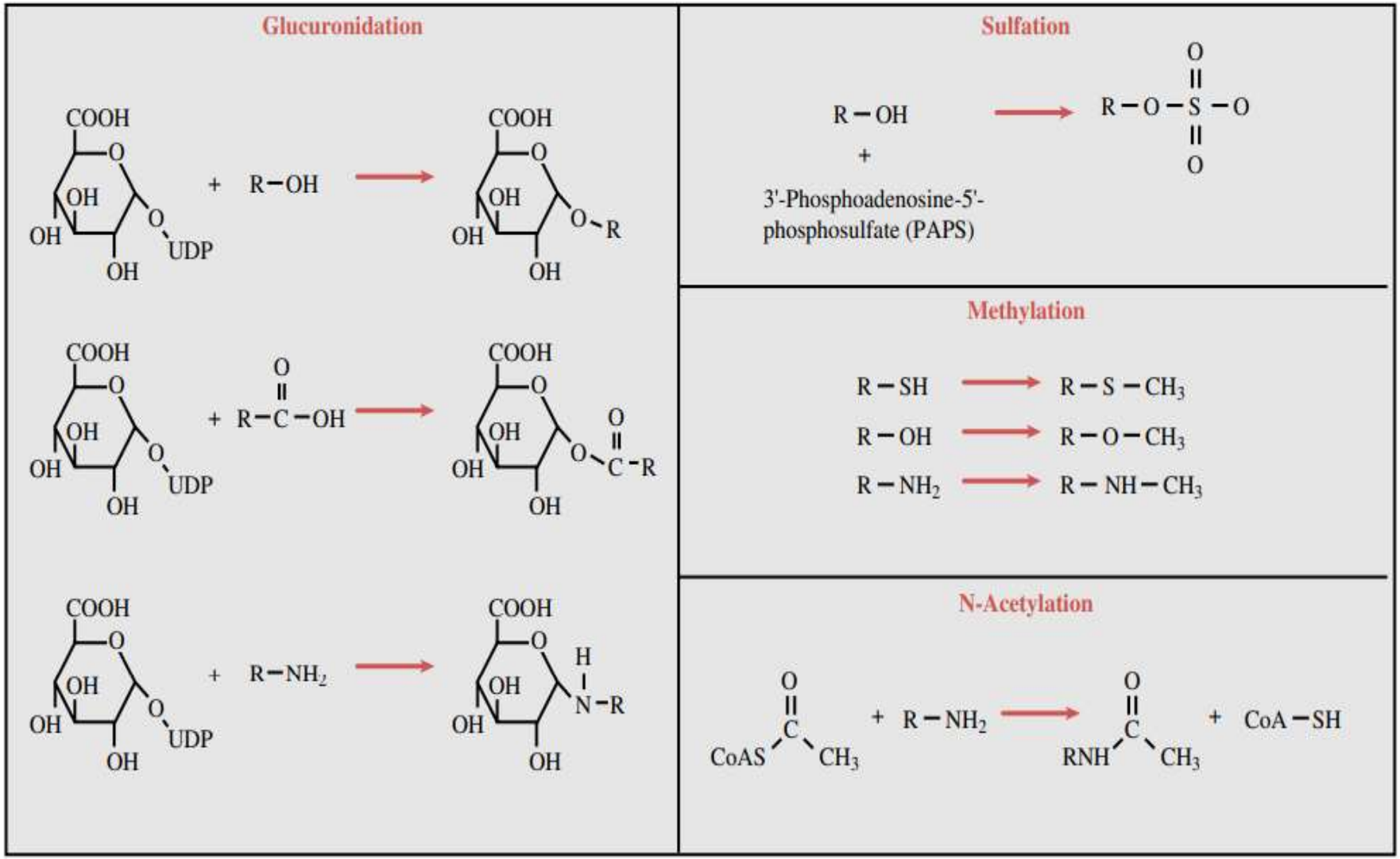


FIGURE 4.1

Examples of phase II conjugation reactions in drug metabolism.

Microsomal enzymes

- These are located on smooth endoplasmic reticulum primarily in liver, also in kidney, intestinal mucosa and lungs.
- The monooxygenases, cytochrome P450, UGTs, etc. are microsomal enzymes.
- They catalyse most of the oxidations, reductions, hydrolysis and glucuronide conjugation.
- Microsomal enzymes are inducible by drugs, certain dietary constituents, and other agencies.

Nonmicrosomal enzymes

- These are present in the cytoplasm and mitochondria of hepatic cells as well as in other tissues including plasma.
- The esterases, amidases, some flavoprotein oxidases and most conjugases
- Reactions catalysed are: Oxidations and reductions, hydrolytic reactions and all conjugations except glucuronidation

Microsomal Enzyme Induction

- Many drugs, insecticides and carcinogens interact with DNA and increase the synthesis of microsomal enzyme protein, especially cytochrome P-450 and UGTs.
- As a result the rate of metabolism of inducing drug itself (autoinduction) and/or some other co-administered drugs is accelerated

First-pass (Presystemic) Metabolism

- This refers to metabolism of a drug during its passage from the site of absorption into the systemic circulation.
- The hepatic extraction ratio ($_{ER}$liver) of a drug is the fraction of the absorbed drug prevented by the liver from reaching systemic circulation

Factors Influencing Drug Metabolism

- Age: Pediatric and geriatric populations are slow metabolizers when compared to adults due to immature and loss of enzyme activity in the respective populations.
- Sex: Males metabolize drugs faster than females. Drugs like ethanol, propranolol, and estrogens are metabolized faster in males than females.
- Liver size and liver function capacity: Metabolism of drugs is significantly affected in active liver diseases leading to toxic reactions and failure of therapy. Males and adults with bigger liver size metabolize the drugs faster than females and children.

- Body temperature: Hyperthermia increases blood flow to the organs including the liver and kidney, and one can expect drug clearance by metabolism at a faster rate.
- Metabolism of majority of drugs is reduced due to decreased function of CYP450, FMOs, and other enzymes. – Interleukins (IL 1, IL 4, and IL6), INF-y, and TNF-α secreted during fever decrease the activity of drug-metabolizing enzymes.
- Drugs like α-methyldopa, salicylamide, antipyrine, and sulfonamides are proven to undergo decreased metabolism during fever.

- Diet: CYP3A4, can be induced or inhibited by various dietary compounds, type of food intake
- Grapefruit juice inhibits CYP3A4, and hence midazolam, cyclosporine, and diazepam toxicity occur.
- Cruciferous vegetables (cabbage, cauliflower, and others) induce CYP1A1 and CYP1A2 leading to therapeutic failure of warfarin, carbamazepine, and theophylline therapy.
- Ethanol induces CYP2E1 and hence increases carcinogen generation by oxidative reaction in alcoholics.
- Polycyclic aromatic hydrocarbons in barbecued meat induce CYP1A2 and significantly affect the theophylline metabolism.

- Environmental factors: Insecticides and aromatic hydrocarbons are known to induce or inhibit CYP enzymes.
- Cigarette smoke and other plastic burnt smoke contain benzopyrene which induces CYP1A1 and CYP1A2.

- Co-administration of other drugs and comorbidity
- Hypothyroidism decreases the expression of various CYP450 enzymes.
- Presence of diabetic microvascular complication affects drug metabolism in the kidneys.
- Drugs taken for other comorbid conditions can cause significant drug-drug interactions.

Genetic polymorphisms:

Slow and fast acetylators:

Based on the polymorphism in the NAT2 gene, there are three sets of populations, namely, fast, intermediate, and slow acetylators.

NAT2*5/*7 and NAT2*6/*7 genotypes are slow metabolizers of isoniazid resulting in drug-induced hepatotoxicity.

CYP2C9 polymorphism:

CYP2C9 metabolizes S-warfarin, phenytoin, and various NSAIDs.

CYP2C9*2 and CYP2C9*3 alleles have reduced enzyme activity that can cause bleeding disorder when S-warfarin is administered.

EXCRETION

The process by which the drug and/or its metabolite(s) are transferred permanently from the internal to the external environment

Liver, lungs, skin, salivary glands, mammary glands, and semen

Urine- Majority of drugs

$$\text{Net renal excretion} = (\text{Glomerular filtration} + \text{tubular secretion}) - \text{tubular reabsorption}$$

Renal route of elimination

- Water soluble
- Non-volatile
- Small molecular size (<500 Da)

Process of Renal Drug Elimination

- Glomerular filtration
- Active tubular secretion
- Active or passive tubular reabsorption

Glomerular filtration

- Glomerular capillaries have pores larger
- All nonprotein bound drug (whether lipid-soluble or insoluble)
- Depends: Plasma protein binding and renal blood flow.
- GFR ~ 120 ml/min, declines progressively after the age of 50, and is low in renal failure.

Tubular reabsorption

- ✓ Passive diffusion
- ✓ Depends - Lipid solubility & Ionization of the drug at the existing urinary pH.
- ✓ Lipid-soluble drugs filtered at the glomerulus back diffuse in the tubules because 99% of glomerular filtrate is reabsorbed
- ✓ Nonlipid-soluble & highly ionized drugs are unable to do so.

- ✓ Changes in urinary pH affect tubular reabsorption of drugs that are partially ionized
- ✓ Weak bases ionize more and are less reabsorbed in acidic urine.
- ✓ Weak acids ionize more and are less reabsorbed in alkaline urine.
- This principle is utilized for facilitating elimination of the drug in poisoning. i.e. urine is alkalinized in barbiturate and salicylate poisoning.

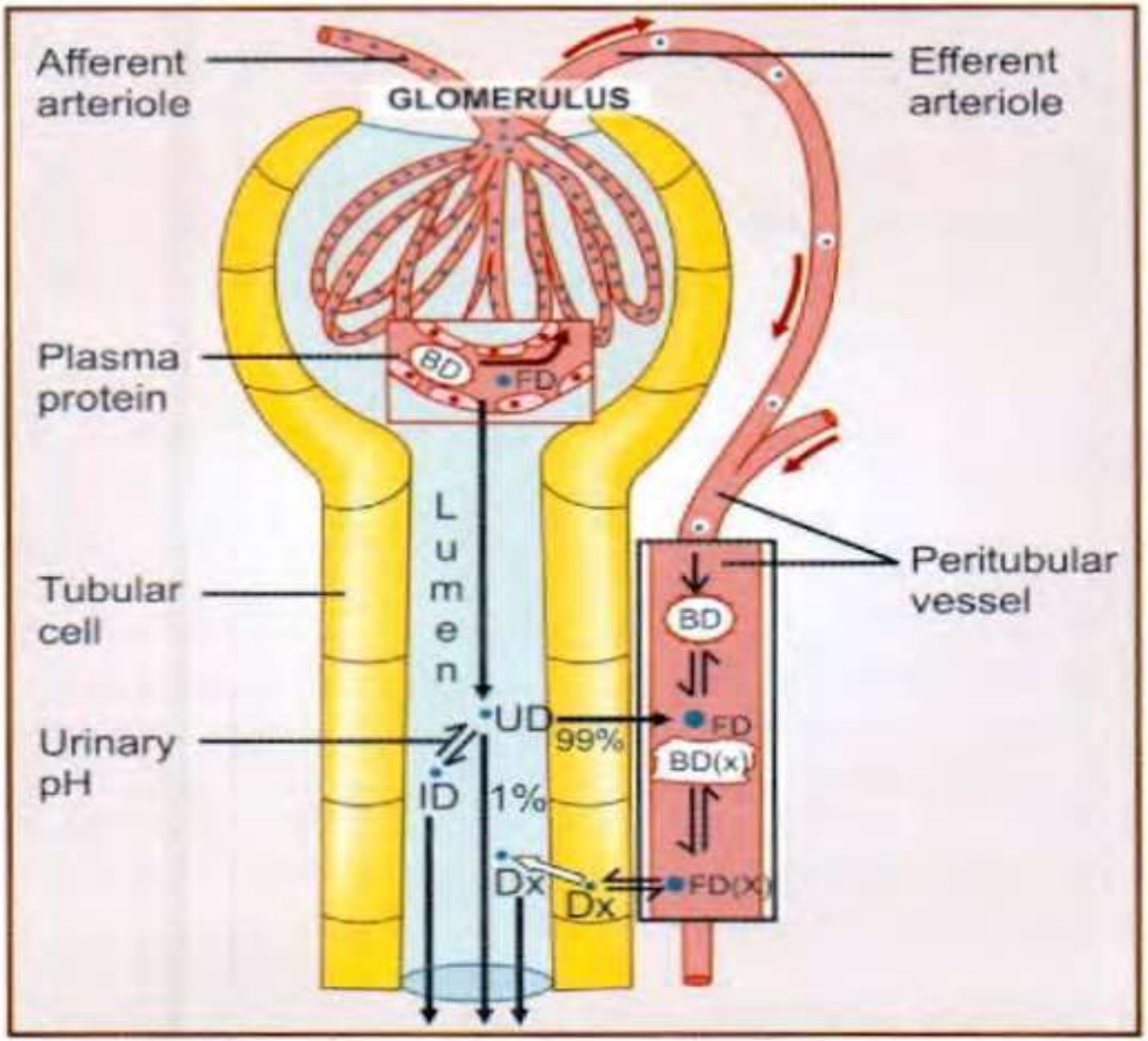


Fig. 3.3: Schematic depiction of glomerular filtration, tubular reabsorption and tubular secretion of drugs
FD—free drug; BD—bound drug; UD—unionized drug; ID—ionized drug; Dx—actively secreted organic acid (or base) drug

Tubular secretion

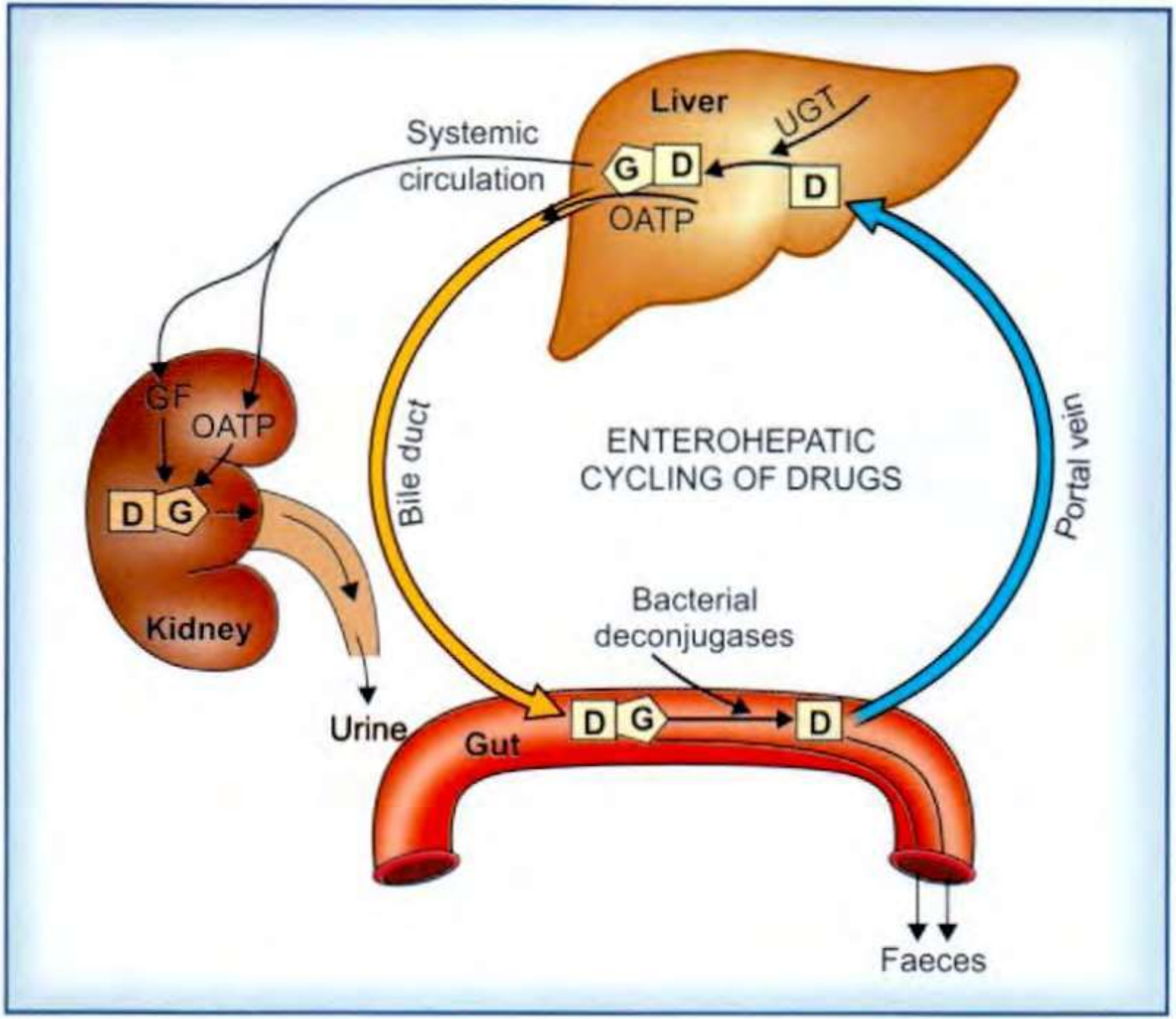
- Active secretion is a carrier-mediated process which requires energy for transportation against a concentration gradient.
- System for secretion of organic acids or anions (organic anion transport): Penicillin
- System for secretion of organic bases or cations (organic cation transport): Morphine

Faeces

- Apart from the unabsorbed fraction, is derived from bile.
- Liver actively transports into bile by nonspecific active transport Mechanism
- Relatively larger molecules (MW > 300) are preferentially eliminated in the bile.
- Enterohepatic cycling contributes to longer stay of the drug in the body.
- Drugs that attain high concentrations in bile include erythromycin, ampicillin,

Enlerohepatic cycling of drugs

- Drug (D), including steroids, are conjugated by the enzyme UDP-glucuronosyl transferases (UGTs) to form drug-glucuronide (DG).
- Part of the DG enters systemic circulation and is excreted into urine by the kidney through both glomerular filtration (GF) as well as active tubular secretion involving renal organic-anion transporting peptide (OATP).
- Another part of DG is actively secreted into bile by the hepatic OATP.
- On reaching the gut lumen via bile, a major part of DG is deconjugated by bacterial hydrolytic enzymes (deconjugases) while the remaining is excreted into faeces.


Liver
UGT
Systemic
circulation
G
D
D
OATP
GF
OATP
D
G
Kidney
Bile duct
ENTEROHEPATIC
CYCLING OF DRUGS
Portal vein
Bacterial
deconjugases
Urine
Gut
D
G
D
Faeces

Enterohepatic circulation

- Endogenous compounds like vitamin B12, vitamin D, folic acid, steroids, and bile salts.
- Drugs like carbenoxolone, oral contraceptives, have prolonged half-life due to the enterohepatic circulation.
- Any alteration in microbial flora by oral antibiotics will significantly affect the enterohepatic circulation process and thereby causes failure of therapy.

Exhaled air

Gases and volatile liquids

(General anaesthetics, alcohol) are eliminated by lungs, irrespective of their lipid solubility.

Alveolar transfer of the gas/vapour depends on its partial pressure in the blood.

Lungs also serve to trap and extrude any particulate matter that enters circulation.

Saliva and sweat

- These are of minor importance for drug excretion.
- Lithium, pot. iodide, rifampicn and heavy metals are present in these secretions in significant amounts.

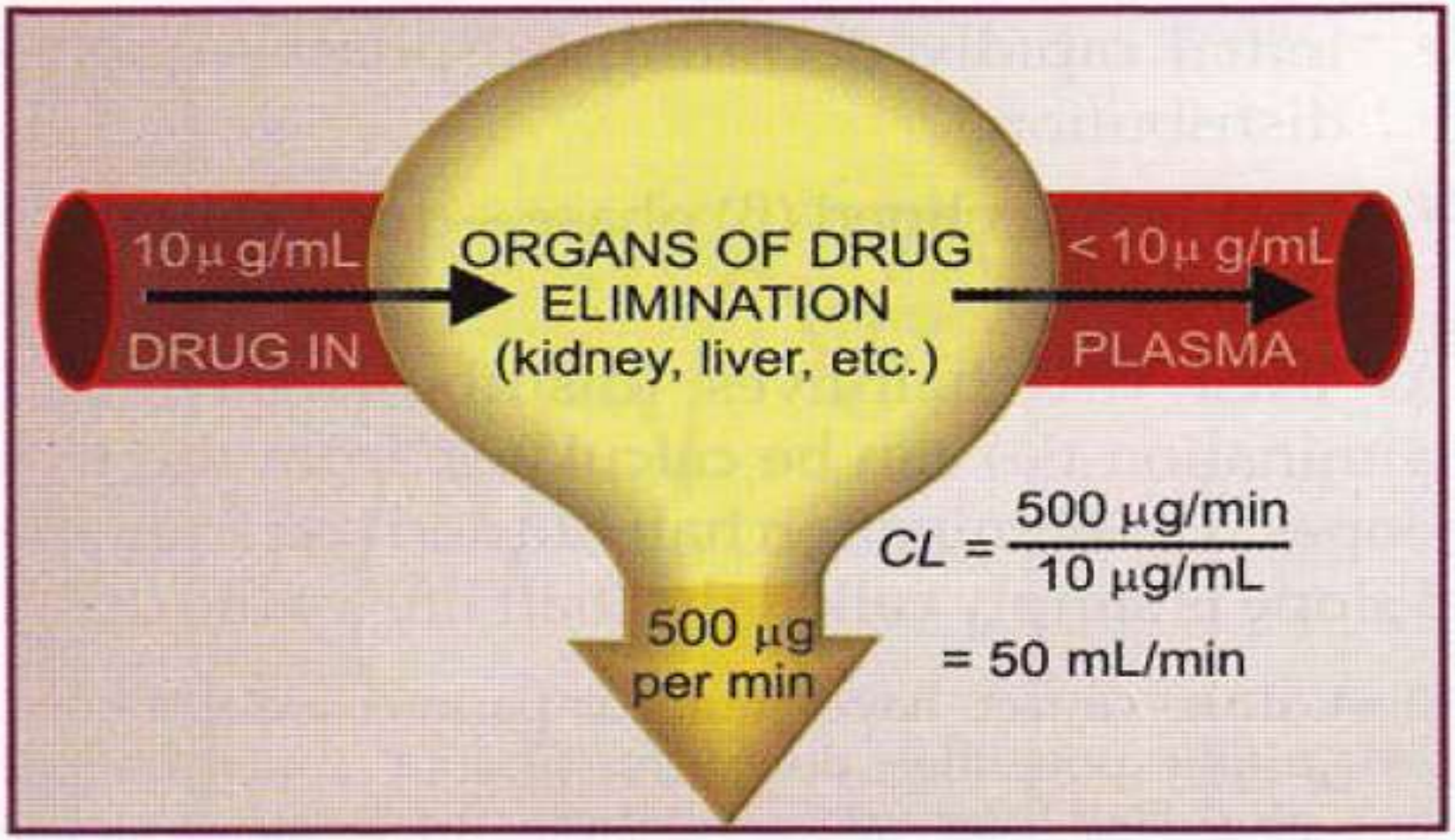
Milk

- Suckling infant inadvertently receives the drug.
- Most drugs enter breast milk by passive diffusion
- Lipid soluble & less protein bound drugs cross
- Milk has a lower pH (7.0) than plasma, basic drugs are concentrated in it.
- Administer any drug to a lactating woman only when essential.

Clearance (CL)

- The clearance of a drug is the theoretical volume of plasma from which the drug is completely removed in unit time
- CL =Rate of elimination/ C
- where C is the plasma concentration.

- Clearance is the single most parameter which determines the maintenance dose of any drug.
- Steady-state concentration, the dosing rate should be equal to the rate of elimination, i.e., Dosing rate = Rate of elimination = Clearance × Target plasma concentration


10 μ g/mL
DRUG IN
ORGANS OF DRUG ELIMINATION
(kidney, liver, etc.)
< 10 μ g/mL
PLASMA
500 μg per min
CL = 500 μg/min / 10 μg/mL
= 50 mL/min

FIRST ORDER KINETICS

The rate of elimination is directly proportional to the drug concentration, CL remains constant;

constant fraction of the drug present in the body is eliminated in unit time.

This applies to majority of drugs which do not saturate the elimination processes (transporters, enzymes. blood flow, etc.) over the therapeutic concentration range.

Zero order kinetics

- The rate of elimination remains constant irrespective of drug concentration
- Cl decreases with increase in concentration; or a constant amount of the drug is eliminated in unit time, e.g. ethyl alcohol.
- This is also called capacity limited elimination or Michaelis-Memen elimination.

Nonlinear kinetics

- Due to saturation in any of the components of ADME.
- Saturation of protein binding, saturation of metabolizing enzyme, and saturation of carriers or transport involved in the absorption or elimination lead to nonlinear kinetics.

half-life of the drug

- “metameter” which takes the account of drug clearance with its volume of distribution (Vd) after dosing.
- Predictor of drug fluctuation and accumulation in plasma concentration.

Loading dose

This is a single or few quickly repeated doses given in the beginning to attain target concentration rapidly.

Maintenance dose

This dose is one that is to be repeated at specified intervals after the attainment of target Cpss so as to maintain the same by balancing elimination.

Agonist: An agent which activates a receptor to produce an **effect similar to that of the physiological signal molecule**.

Inverse agonist : An agent which activates a receptor to produce an ***effect in the opposite direction to that of the agonist.***

Antagonist: An agent which **prevents the action of an agonist** on a receptor or the subsequent response, but does not have any effect of its own.

Partial agonist : An agent which **activates a receptor to produce submaximal effect** but antagonizes the action of a full agonist.

Ligand : Any molecule which attaches selectively to particular receptors or sites.

Ion Channels

- Proteins which act as ion selective channels participate in transmembrane signaling and regulate intracellular ionic composition.
- This makes them a common target of drug action

Ion channel linked receptors

- Cell membrane spanning proteins.
- Agents binding with them open a transmembrane channel and permit ions to cross the membrane phospholipid bilayer.
- Which ions flow and what voltage changes occur as a consequence depend upon the type of channel.
- Thus, opening of the nicotinic receptor channel permits sodium ions to cross the membrane into the cell and cause depolarisation of the membrane.
- Gamma-aminobutyric acid (GABA) receptor channel allows chloride ions to permeate into the cell, and hyperpolarises the cell membrane.
- Many drugs (phenytoin and benzodiazepines) act by modifying the function of receptor channels.

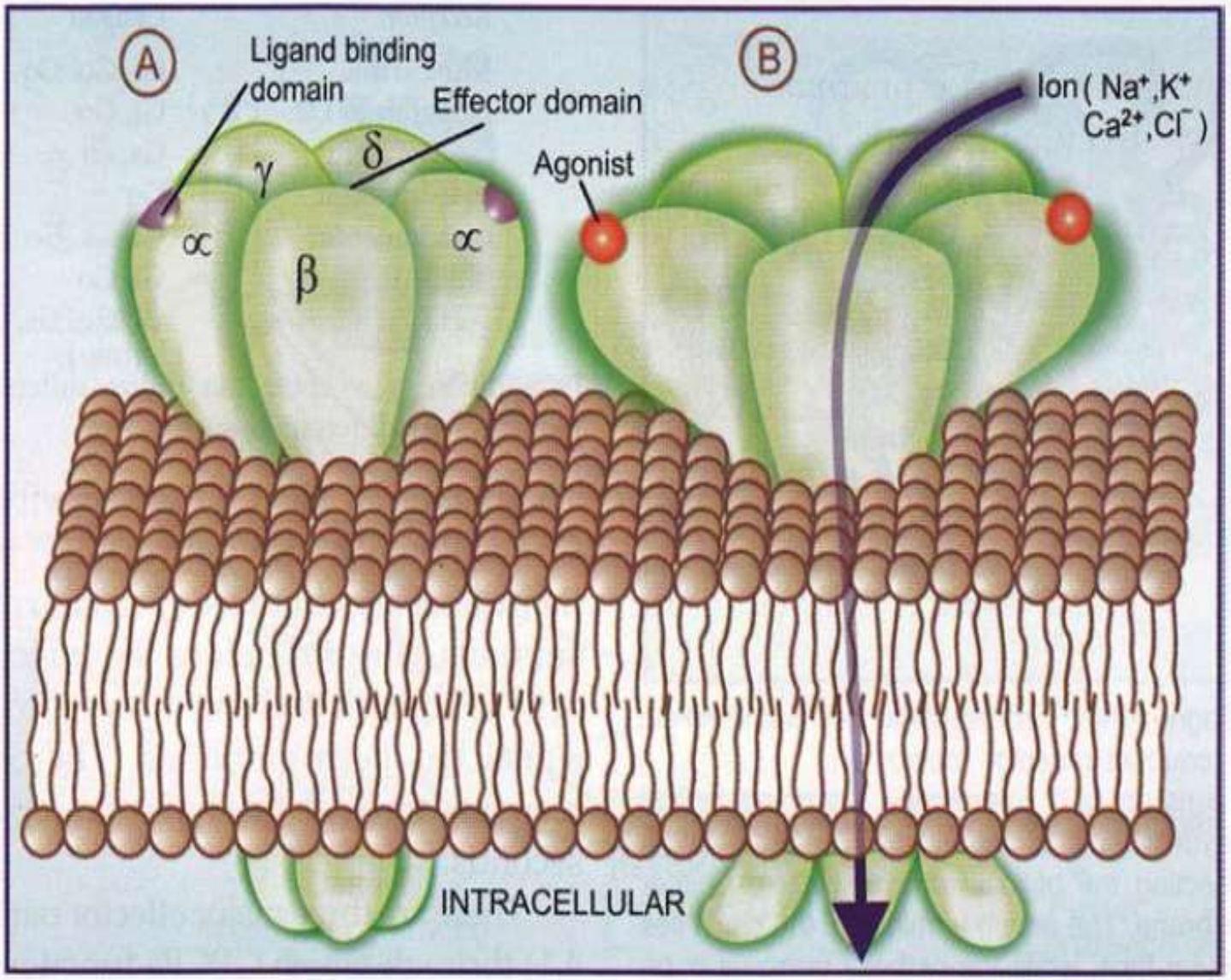


Fig. 4.4: Diagrammatic representation of receptor mediated operation of membrane ion channel.
In case of nicotinic cholinergic receptor, the molecule (8 nm in diameter) is composed of 5 subunits ($2\alpha + \beta + \gamma + \delta$) enclosing a cylindrical ion channel. Normally the channel is closed (A). When two molecules of acetylcholine bind to the two α subunits (B), all subunits move apart opening the central pore to 0.7 nm, enough to allow passage of partially hydrated Na^+

Transporters

- Substrates are translocated across membranes
- By binding to specific transporters (carriers)
- Either by facilitate diffusion in the direction of the concentration gradient
- or pump the metabolite/ion against the concentration gradient using metabolic energy
- solute carrier (SLC) class of transporter proteins to inhibit the ongoing physiological transport of the metabolite /ion
- Desipramine and cocaine block neuronal reuptake of noradrenaline by interacting with norepinephrine transporter(NET)

Receptors

- Specific protein macromolecules in the cell membrane, the cytosol or the nucleus.
- Numerous receptors for hormones, neurotransmitters and drugs have been identified, purified, cloned and their structure has been determined.
- Many drugs (ligands) bind to

  Receptors for the endogenous substances

  Enzymes

Receptor

- It is defined as a macromolecule or binding site located on the surface or inside the effector cell that serves to recognize the signal molecule / drug and initiate the response to it, but itself has no other function.

G-proteins or guanine nucleotide binding proteins

- Coupled to receptors & are involved in regulation of secondary messengers.
- GPCR are found on all cell types (brain and the gut).
- Stimulatory (Gs) or inhibitory (Gi) in action.
- Guanosine diphosphate or triphosphate.
- ACh and GABA can activate ion channels as well as GPCR.

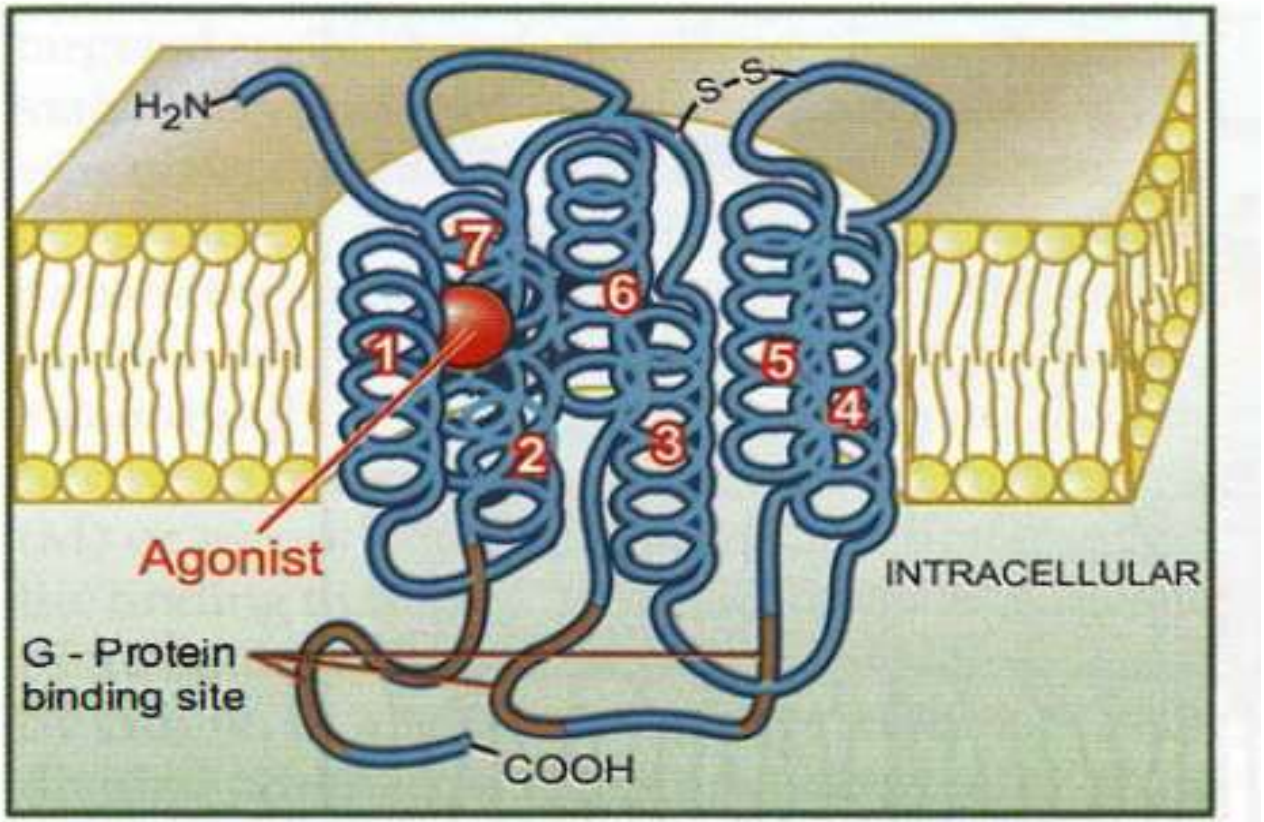


Fig. 4.5: Diagrammatic representation of G-protein coupled receptor molecule

The receptor consists of 7 membrane spanning helical segments of hydrophobic amino acids. The intervening segments connecting the helices form 3 loops on either side of the membrane. The amino terminus of the chain lies on the extracellular face, while the carboxy terminus is on the cytosolic side. The approximate location of the agonist and G-protein binding sites is indicated

- A ligand binding to GPCR promotes binding of GTP to G-proteins.
- The activated G-proteins in turn activate effector systems such as enzymes (adenylyl cyclase and phospholipase) and ion channels (Ca ++ & K+).
- The second messengers for such actions are:

❑intracytoplasmic calcium ion concentration

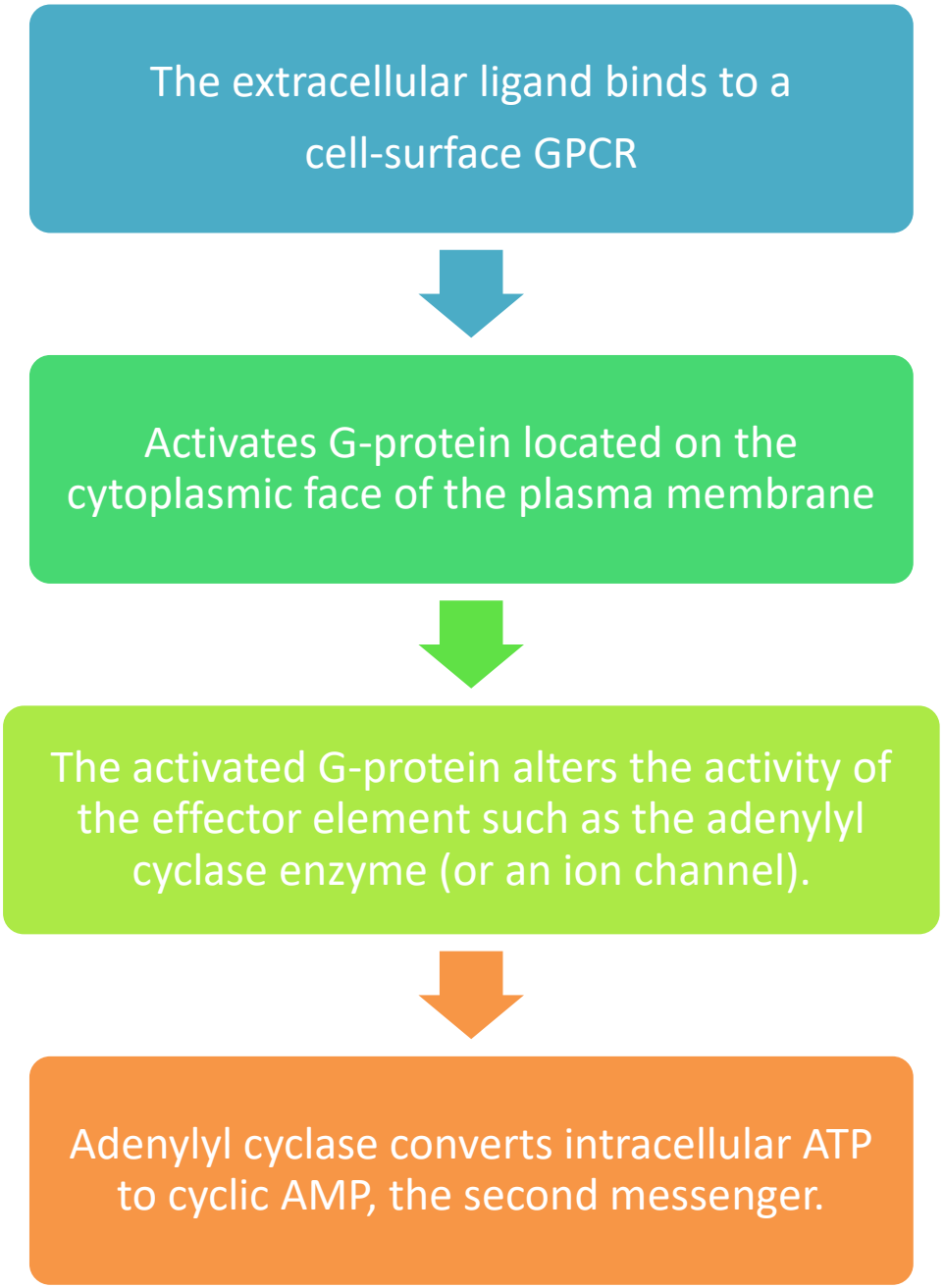
❑cyclic AMP

❑inositol 1, 3, 5-triphosphate (IP3)

❑diacylglycerol (DAG) released from the phospholipid in the cell membrane.

- GPCR - Adrenergic β1 and α2 and dopamine receptors.
- Opiates as agonists or as antagonists.
- Peptides (eg beta endorphins),
- Acetylcholine (muscarinic actions)
- Biogenic amines (5-HT)
- 65% of the drugs act via GPCRs.

https://www.youtube.com/watch?v=9Bq6qHJaSJs



Protein kinase linked receptors

- **Cell surface receptors, are enzymes like tyrosine kinases.**
- **They serve as receptors for insulin and epidermal growth factor.**
- **Tyrosine kinases activate themselves by autophosphorylation after the hormone binds to them.**
- **Autophosphorylated tyrosine kinase then phosphorylates intracellular proteins on the tyrosine residues**

Nuclear receptors

- Steroids are present in the cytoplasm
- Thyroid hormones are present in the nuclear chromatin.
- These receptors after activation by hormone binding, act on the genetic material in the nucleus to initiate or inhibit the process of transcription.

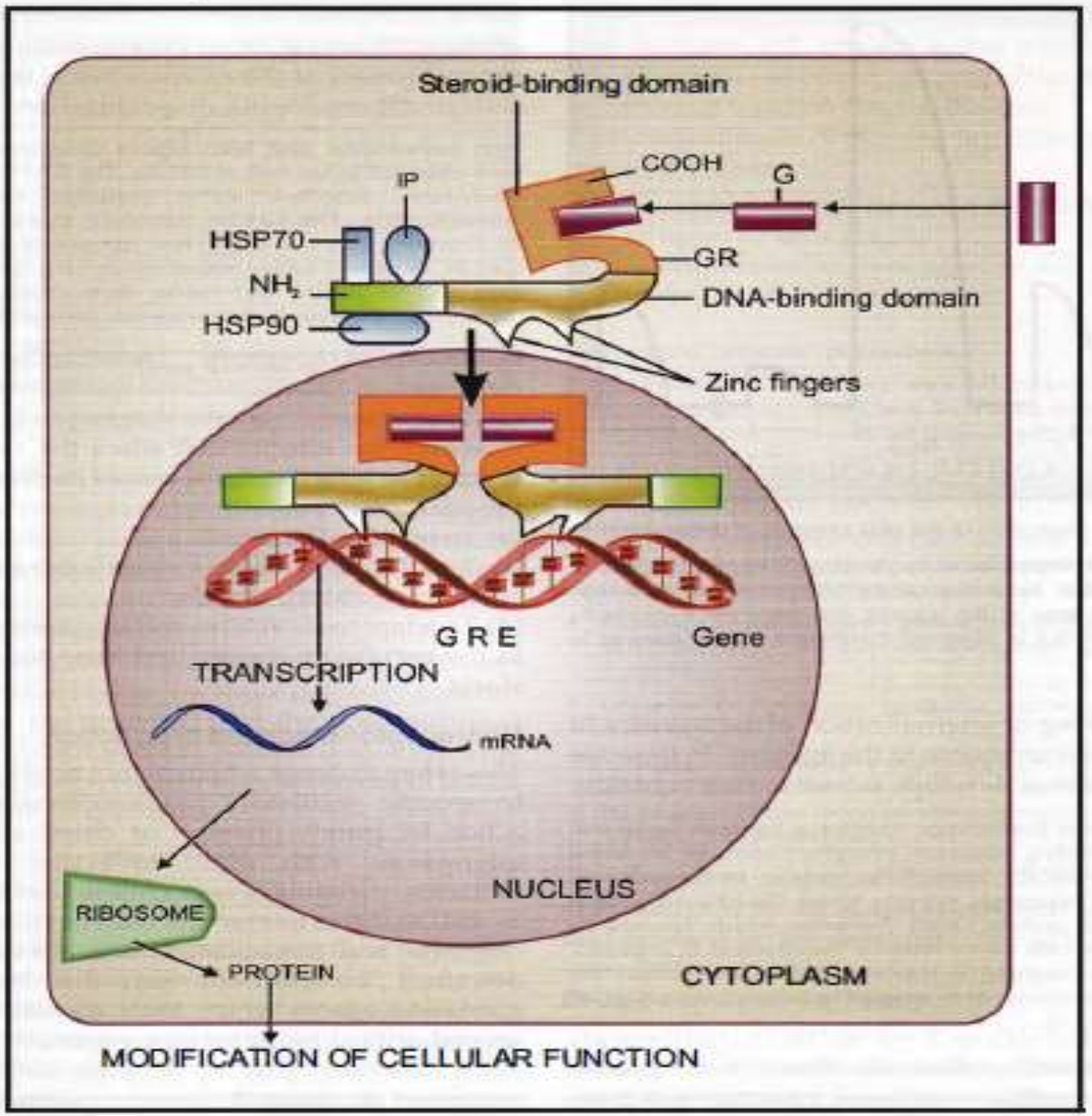


Fig. 4.9: Operational scheme of intracellular (glucocorticoid) receptor

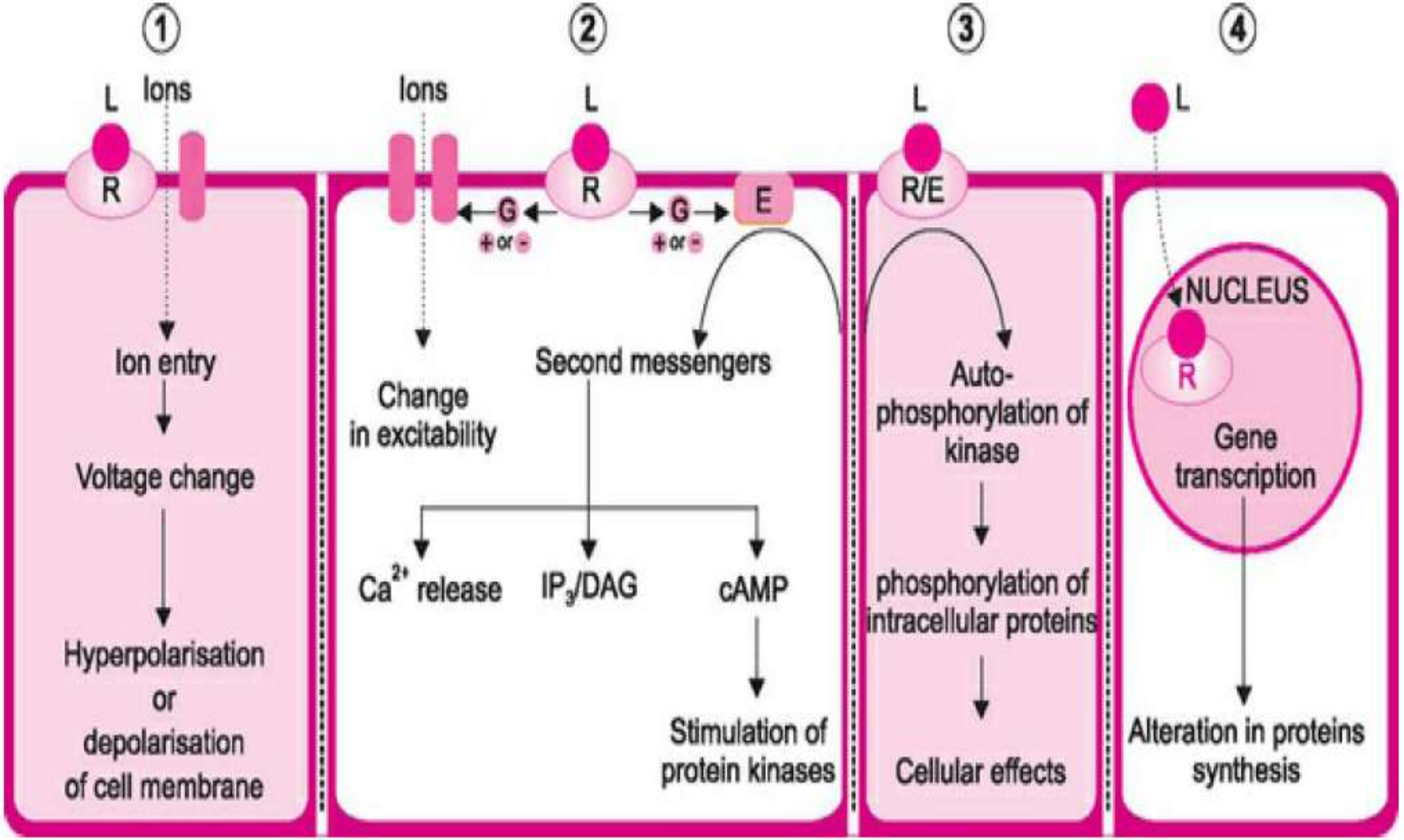


FIG. 2.2 Types of receptor-effector linkage. **1 = Ligand gated ion channel (ionotropic receptors); 2 = G-protein coupled receptor (Metabotropic); 3 = Kinase-linked receptors; 4 = Nuclear receptors;** R = receptor; G = G-proteins; E = Enzyme; L = Ligand (Modified from *Pharmacology* by Rang HP et al, 5th ed, Churchill Livingstone, 2003)

Acknowledgement

- The Presentation is being used for educational and non commercial Purposes
- Thanks are due to all the original contributors and entities whose pictures were used in the creation of this presentation.