Clinical Pharmacokinetics

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- ***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

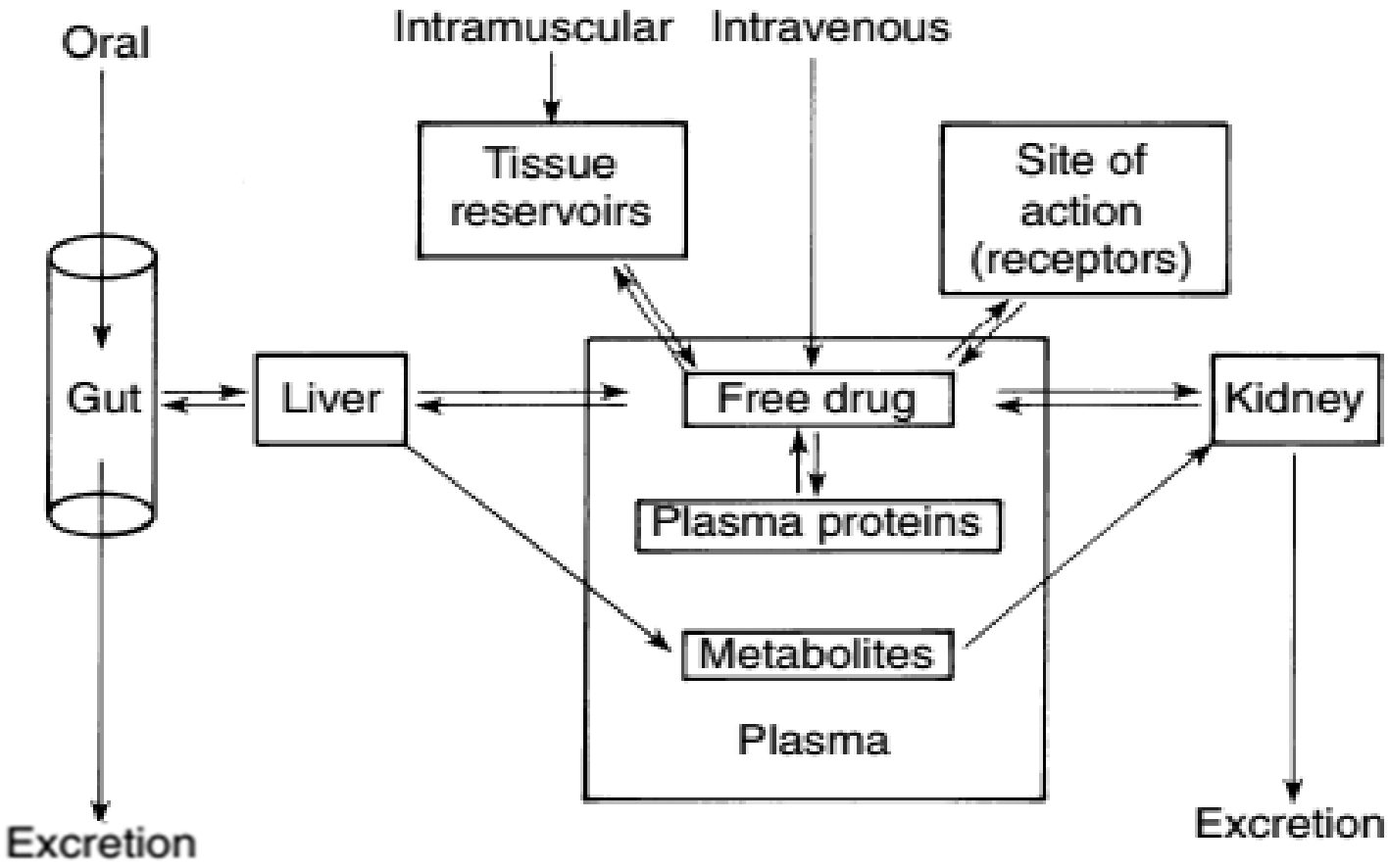
What is clinical pharmacokinetics ?

- • 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 individualization of drug therapy.

Pharmacokinetics

- • Absorption
- • Distribution
- • Metabolism
- • Elimination

Study of [drug] over time



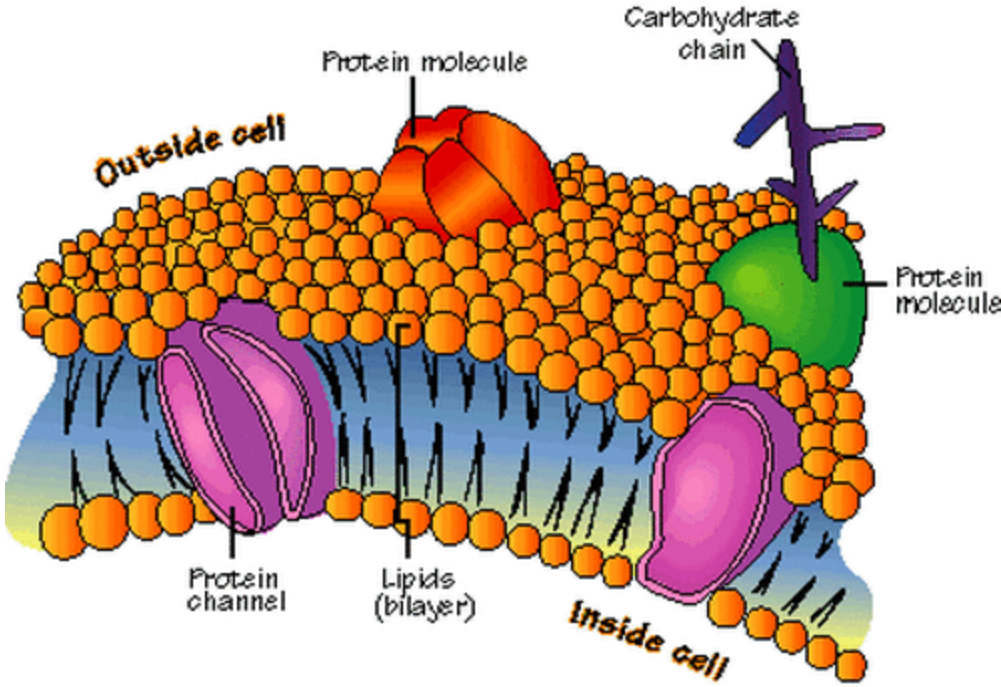
- **There are four main ways by which small molecules cross cell membrane**

- By diffusing directly through the lipid
- By combination with a solute career (SLC) or other membrane transporter
- By diffusing through aqueous pores formed by special proteins (aquaporins) that transverse the lipid
- By pinocytosis

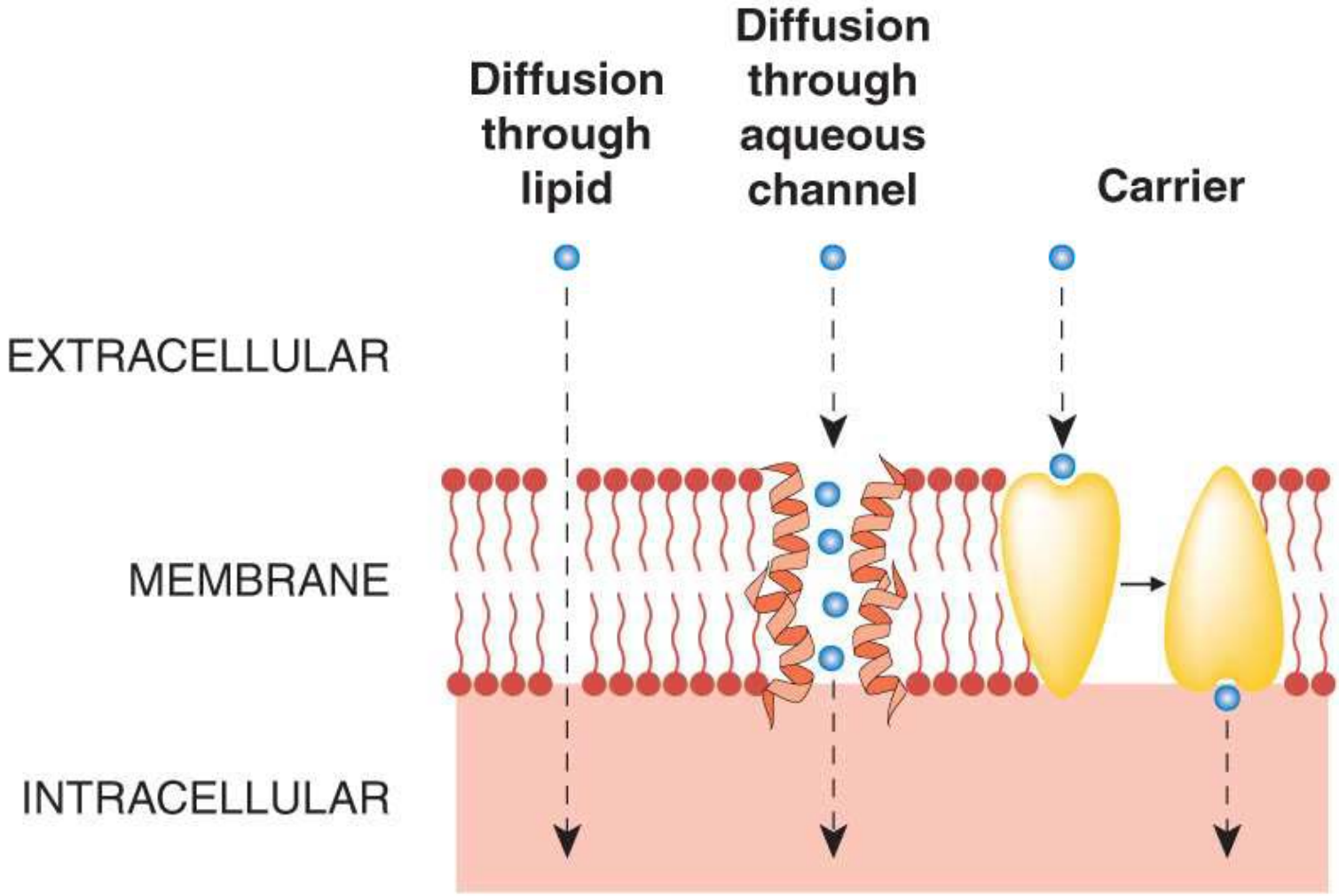
Transportation

Biological Membrane

- • Bilayer of phospholipid and cholesterol 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

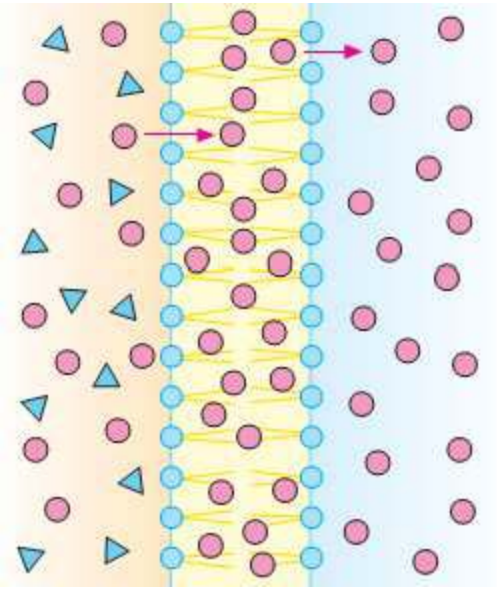


Transportation

- Drugs are transported through
- – Passive diffusion
- – Filtration
- – Specialized transport

Transportation : Passive diffusion

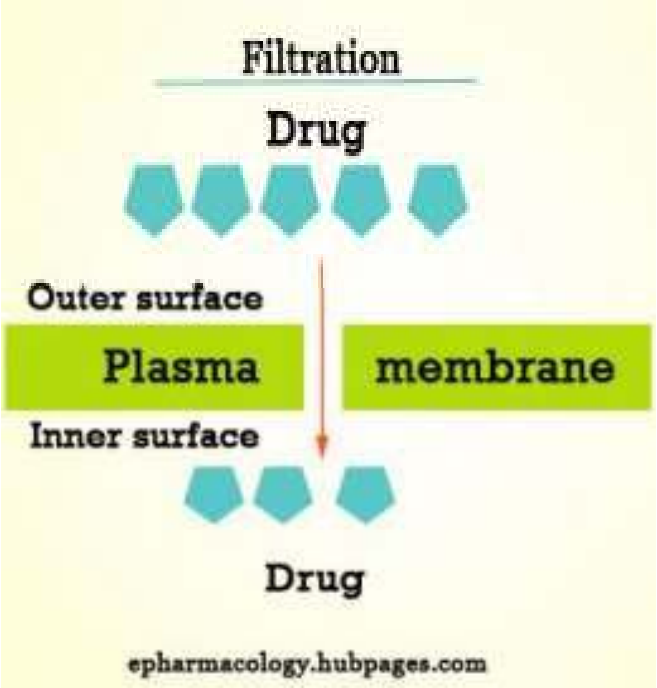
- Drug diffuses from higher concentration to lower concentration across the membrane.
- • Lipid soluble drugs – dissolving lipoidal matrix of membrane.
- • Diffusion will depend on
- – Lipid solubility of drug
- – Difference in concentration
- – pH of tissue



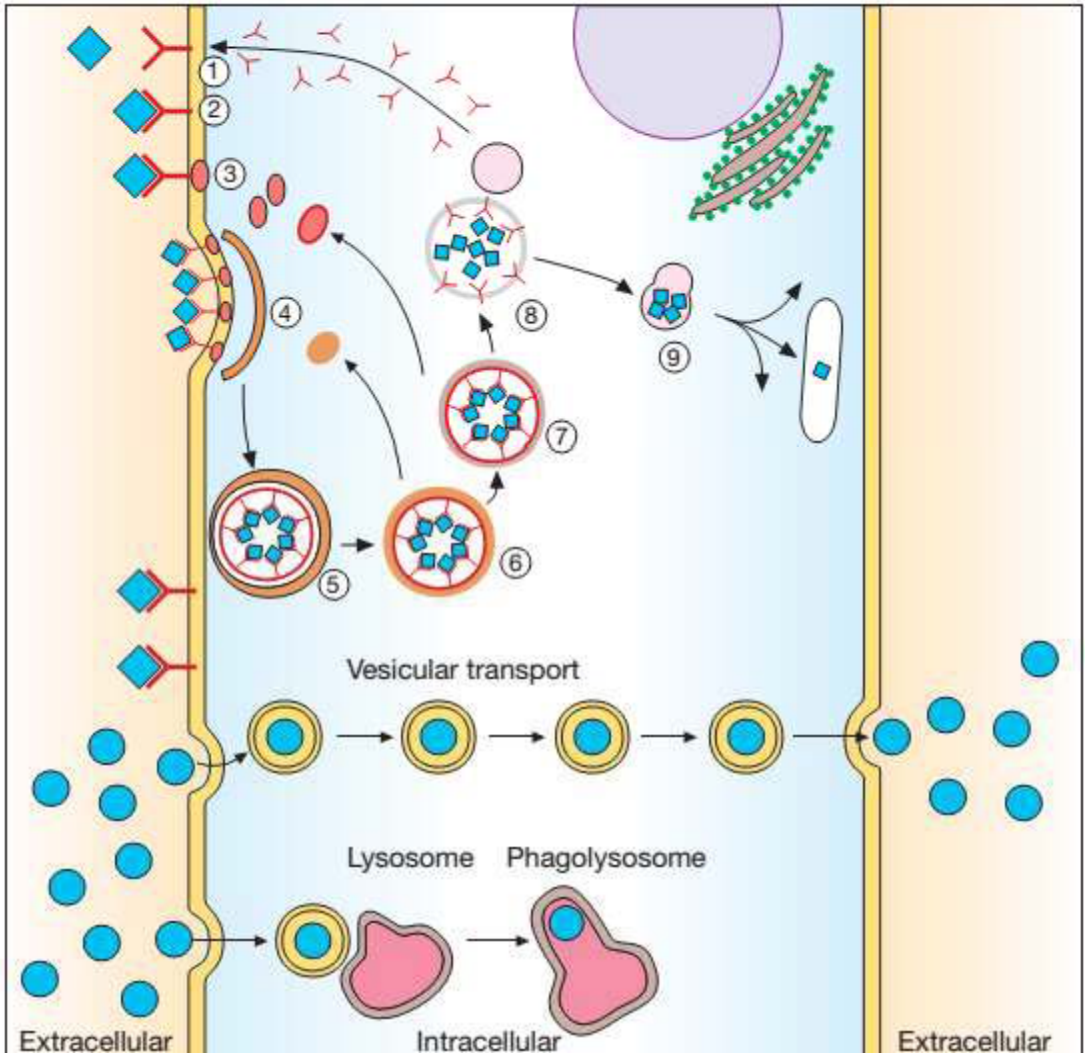
Transportation : Filtration

- • Passage of drug across the aqueous pores in the membrane or through the paracellular spaces.

- • Lipid insoluble drugs crosses membrane
- – Size of pores and drug molecule



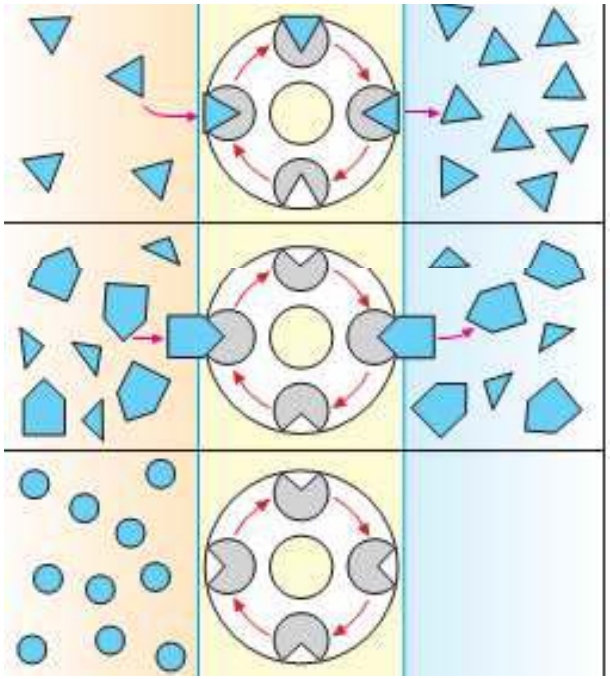
Specialized Transport



Specialized : Carrier Transport

- • **Trans membrane protein**

– carriers and transporters for physiologically important ions, nutrients, metabolites, transmitters

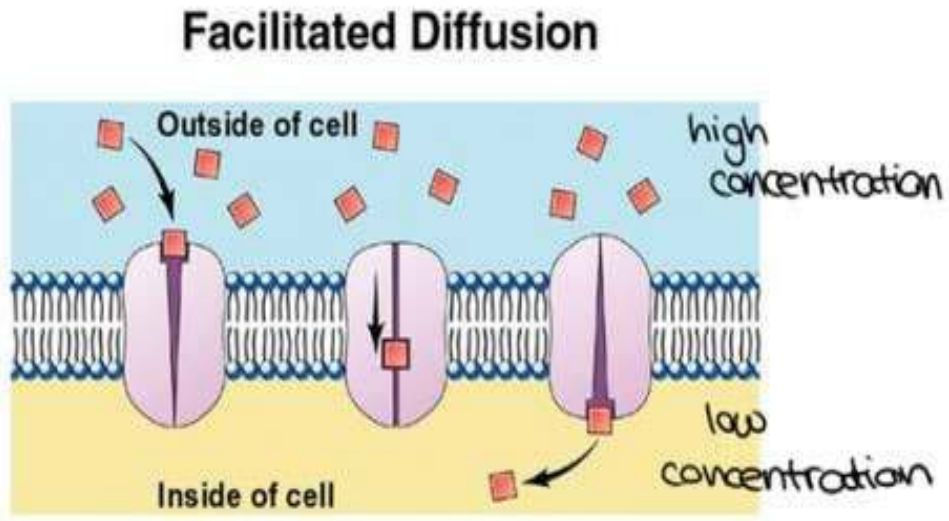


- • Beside this they also translocate xenobiotics including drugs metabolites

- • Specific for the substrate

Specialized : Carrier Transport

- 1. Trans membrane 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

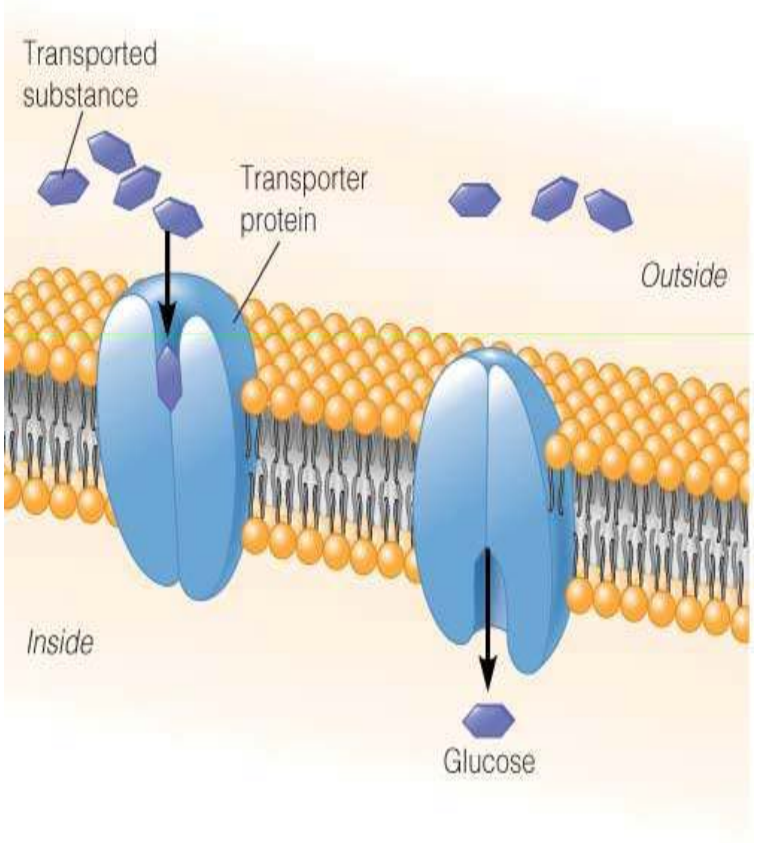


Specialized : Carrier Transport

- • Depending on the requirements of energy
  1. – **Facilitated diffusion**
  2. – **Active transport**
     - • Primary active transport
     - • Secondary active transport

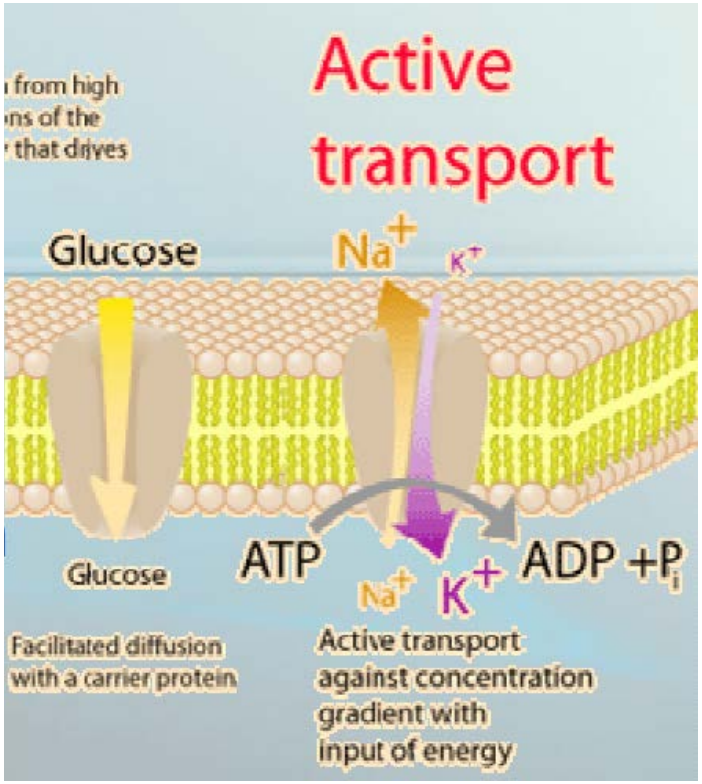
Carrier Transport : Facilitated diffusion

- • Belongs to super family of solute carrier (SLC) transporter
- • Operates without need of energy – transport in the direction electrochemical gradient
- • 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

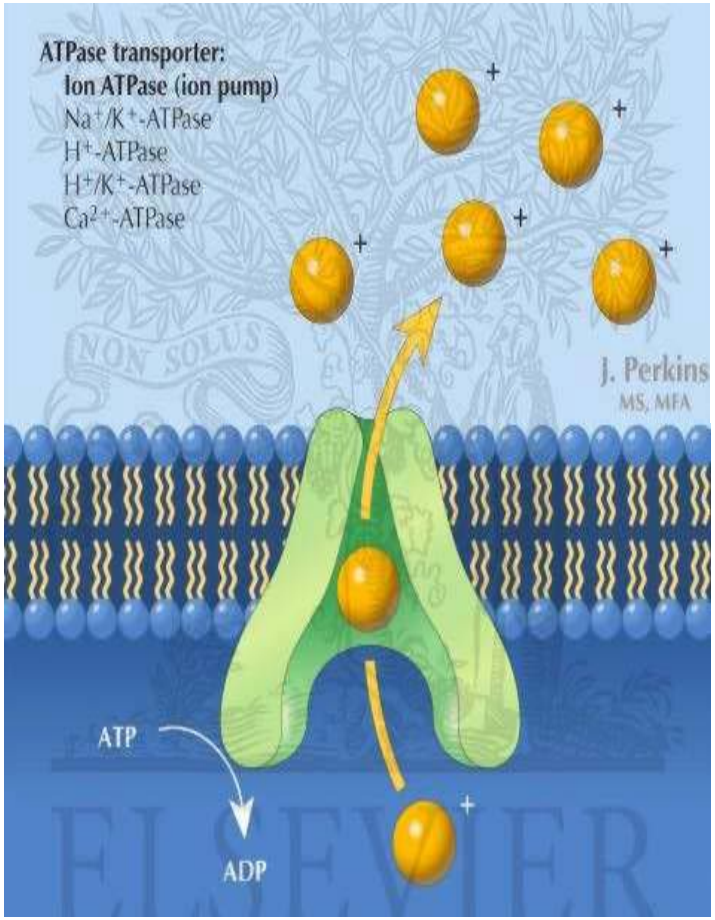


Active transport : Primary

- 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

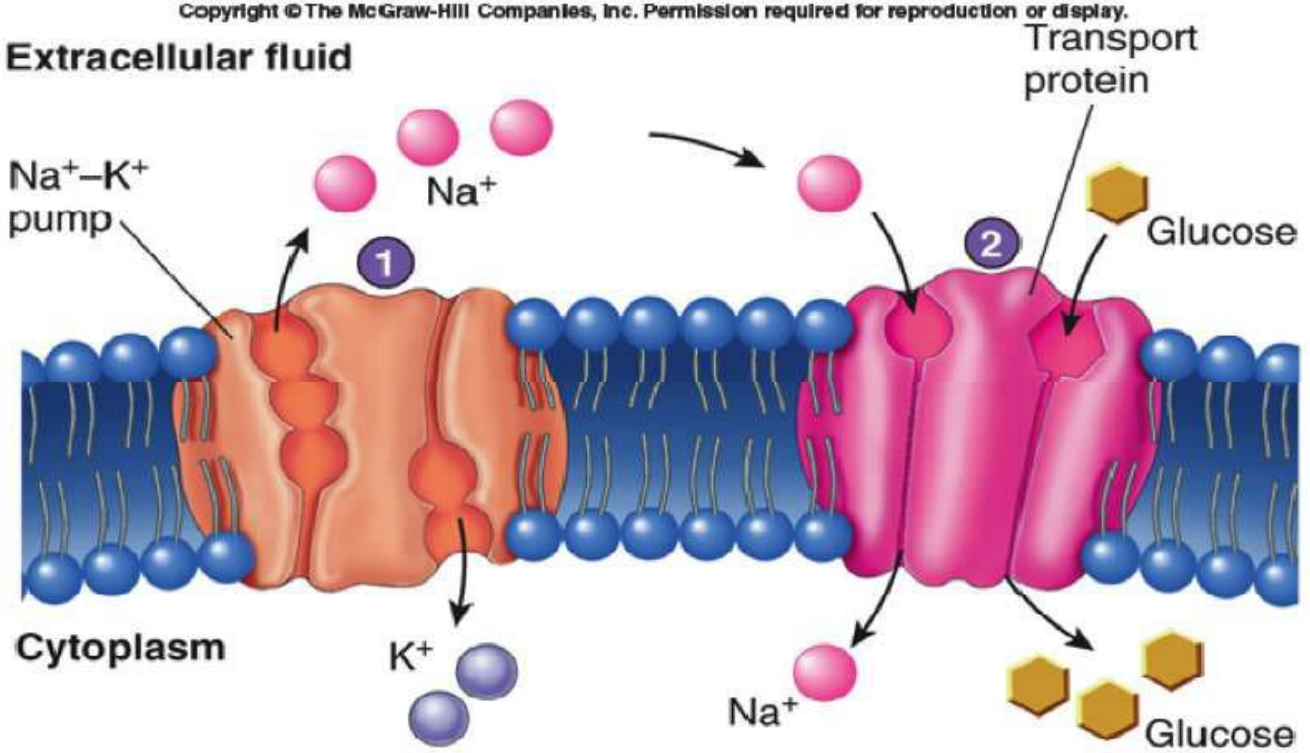
- • Also known as uniport



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 gradient 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

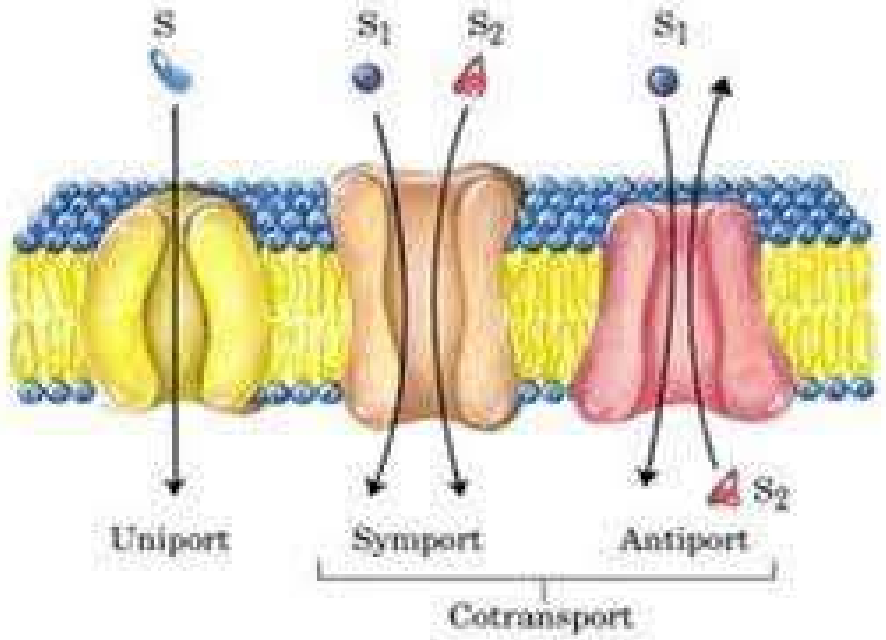
Active transport : Secondary



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

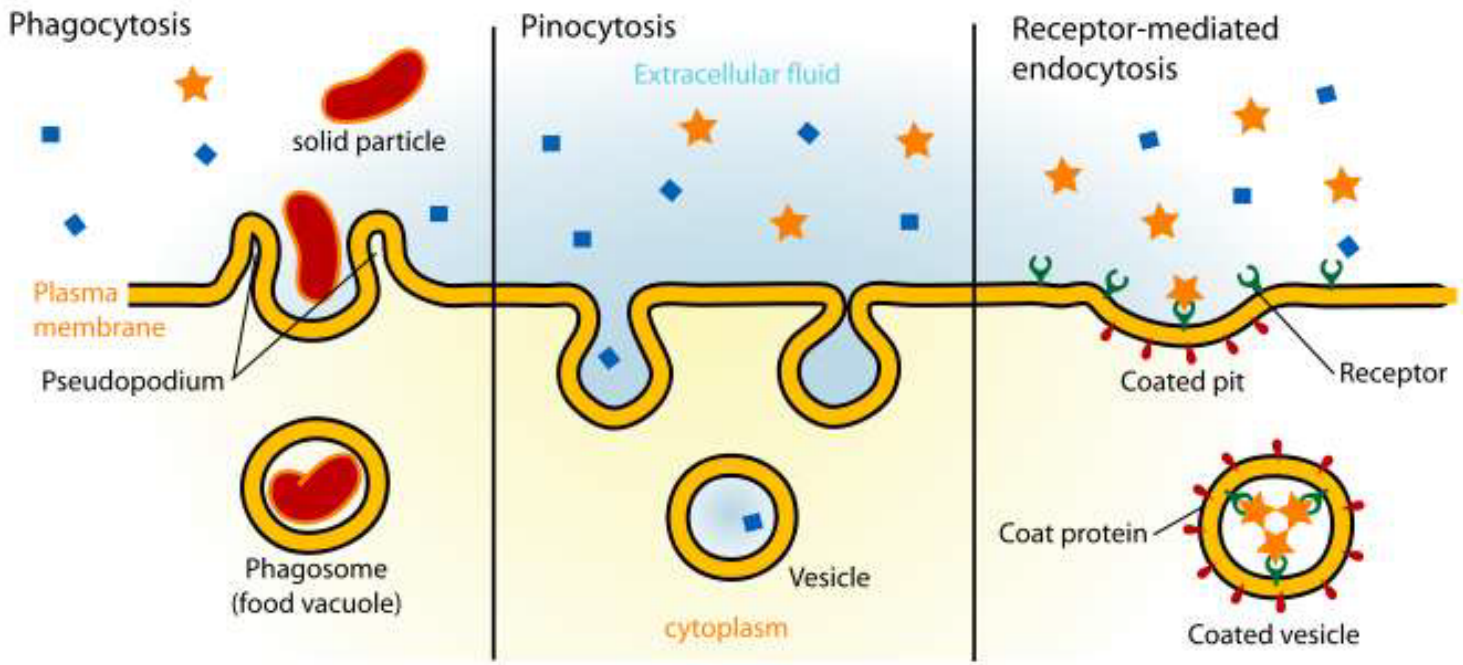
2. Sodium ions move back into the cell through a transport protein that also moves glucose. The concentration gradient for Na^+ provides energy required to move glucose against its concentration gradient.

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 factors

– Aqueous solubility
– 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
- • Bioavailability 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

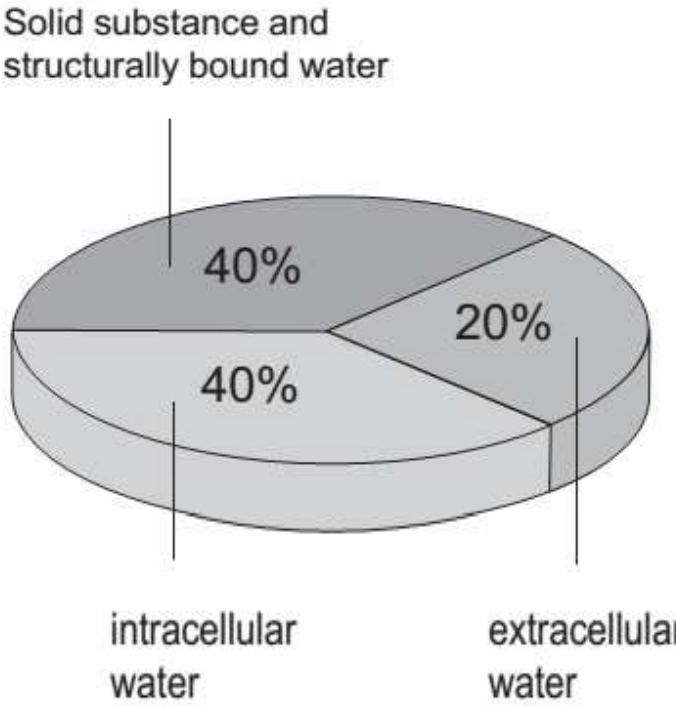
- • Once the drug has gained access to blood it gets distributed to other tissues

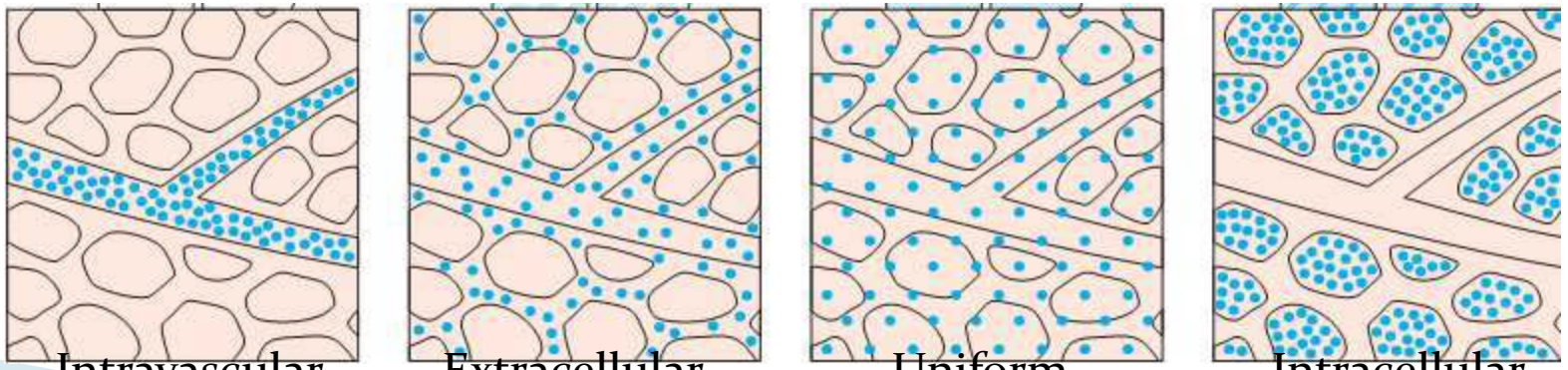
- • The extent of distribution of a drug depends on:

  – Lipid solubility
  – 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.

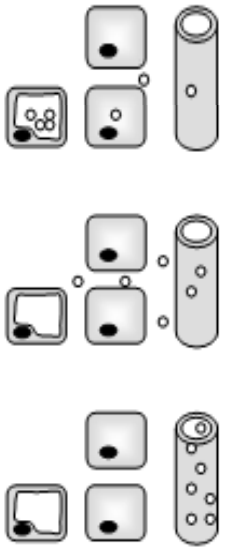
– Digoxin (6L/Kg), propranolol (4 L/Kg), Morphine (3.5 L/Kg)

- – 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

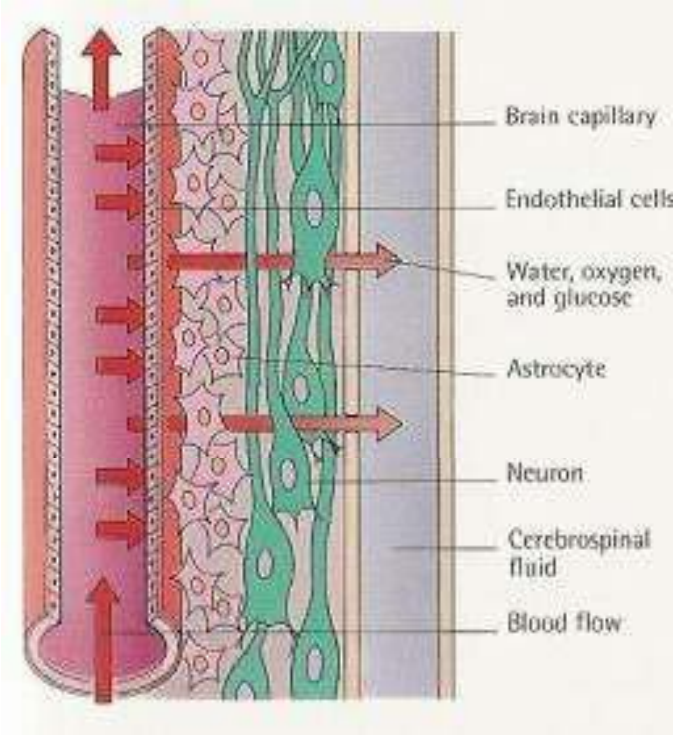
– Low perfusion high capacity – muscle fat

- • 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 precursor levodopa does.

Blood Brain barrier

- • BBB is deficient

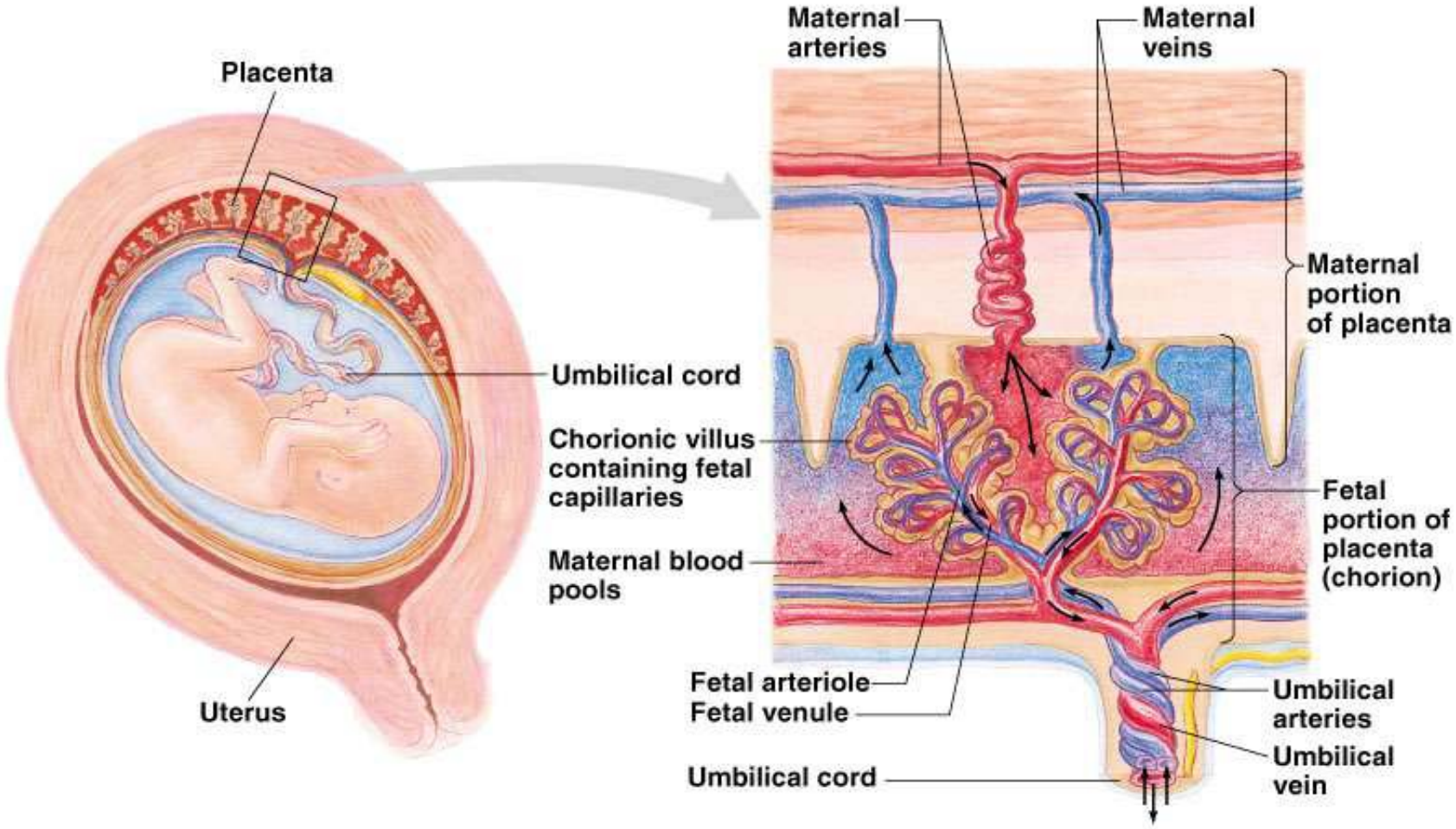
– Chemoreceptor Trigger Zone (CTZ) in medulla oblongota – action of emetic drugs, ex- Domperidone

– Periventricular 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

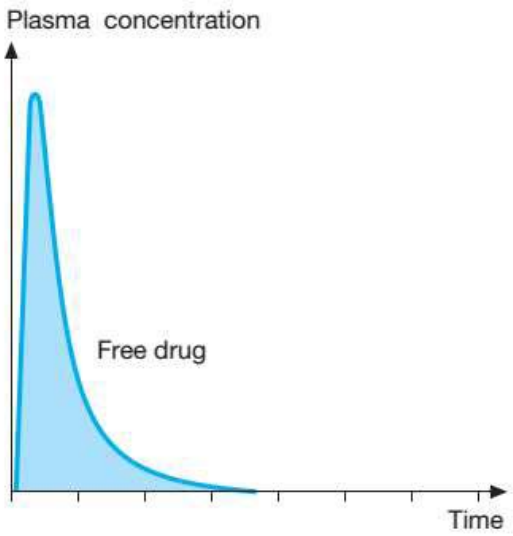
- • Placental membrane is lipoidal and allows free passage of lipophillic drugs, while restricting lypophobic drugs.
- • But higher concentration of lypophobic drugs in maternal circulation – gain access to foetus.
- • Beside this
  - – Placental efflux – P-gp
  - – Influx transporter

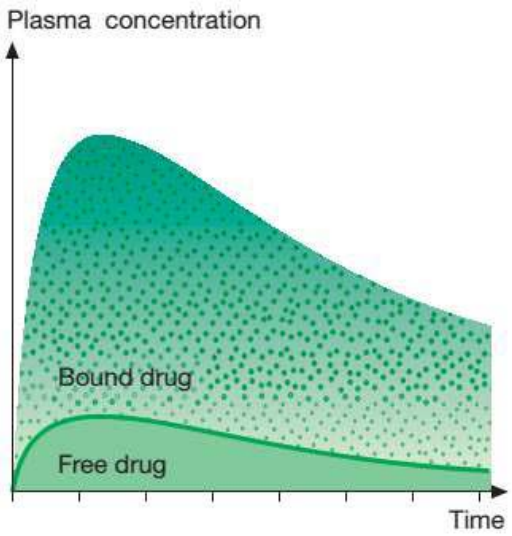


Plasma Protein Binding (PPB)

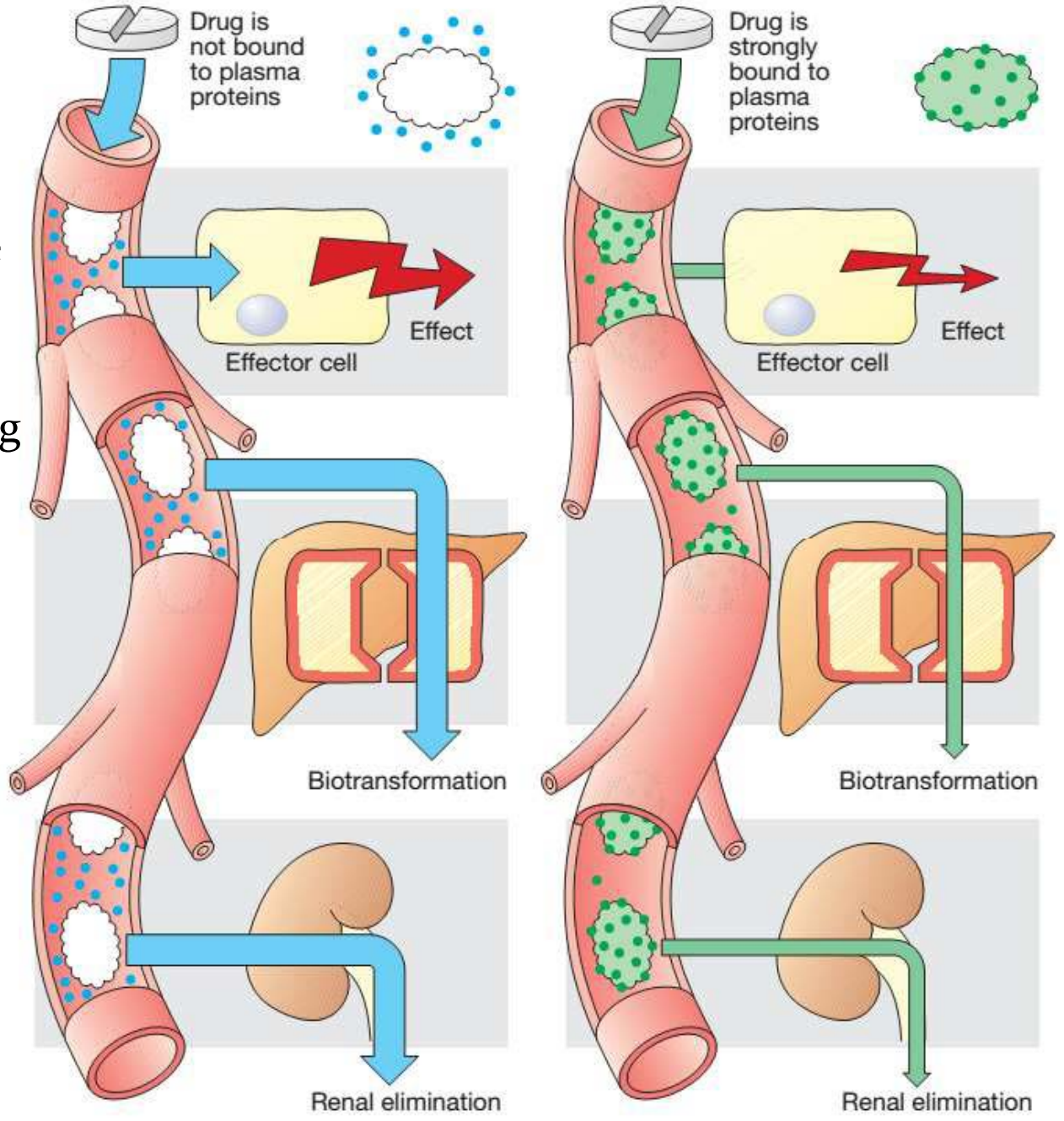
- • Physiochemical affinity for plasma proteins
  – Acidic drugs – albumin, Lipoproteins
  – Basic drugs – α1 acid glycoprotein

- • Extent of binding depends on individual compound – no generalization for pharmacological class can be made.

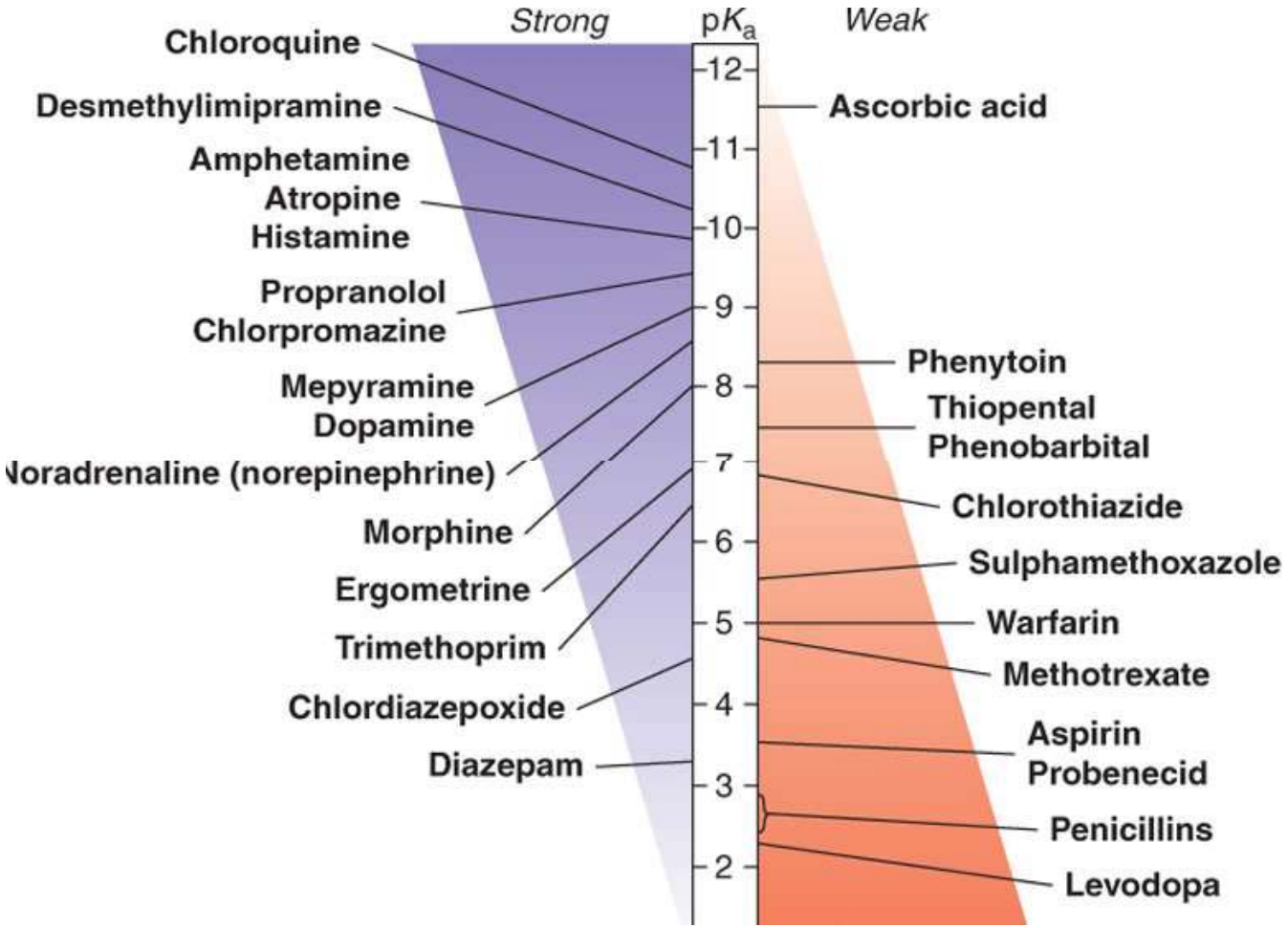




- • The amount of drug bound is depend on
- Concentration of free drug
- Affinity of the binding sites
- Concentration of proteins



pKa values for some acidic and basic drugs

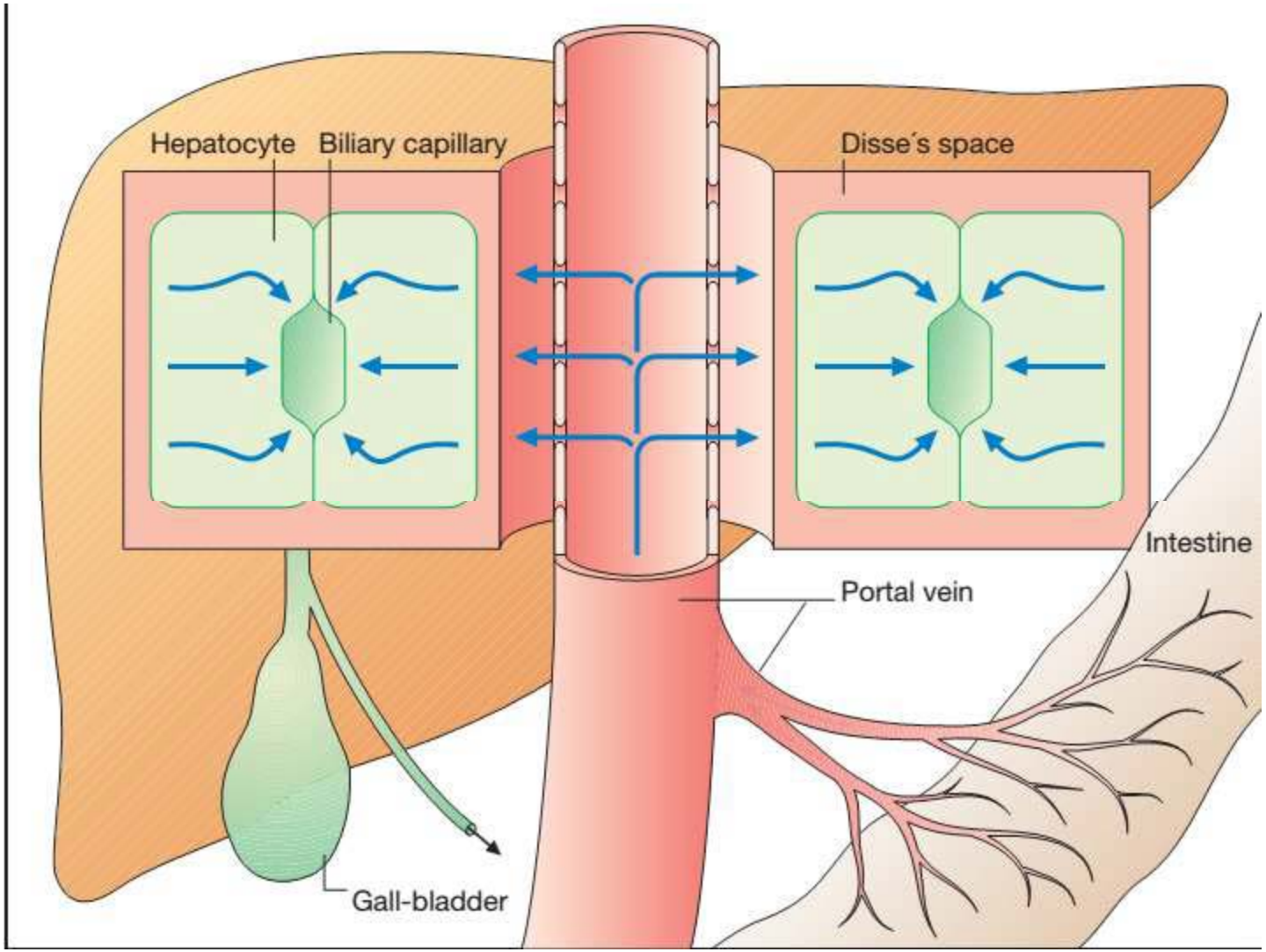


Clinical Significance of PPB

- • 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,

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

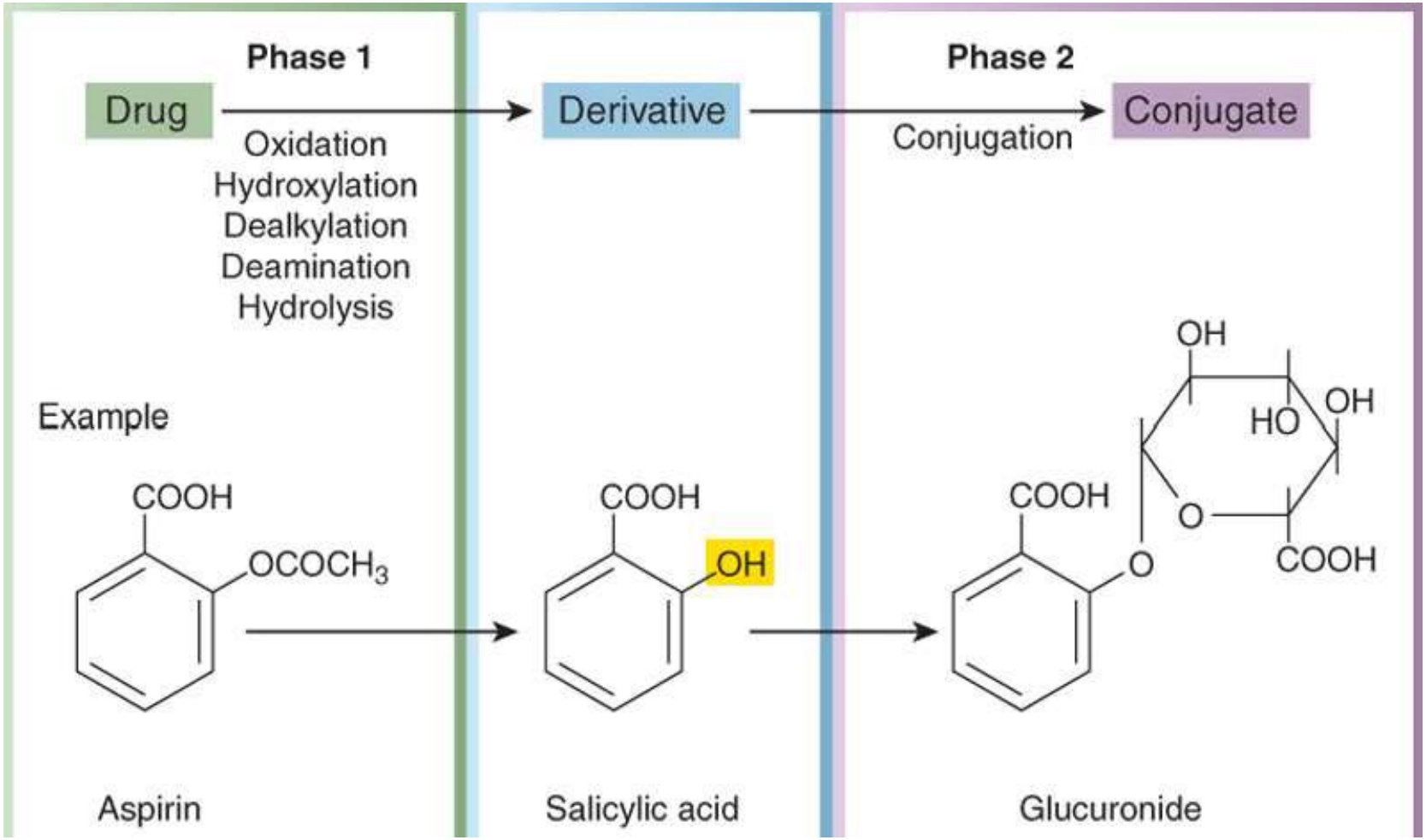
- **Activation** – few drugs are administered in inactive form (PRODRUG) and needs to be activated to form active metabolite
- • Stability
- • Good bioavailability
- • Less side effect or toxicity
- • Desirable pharmacokinetic properties

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**)

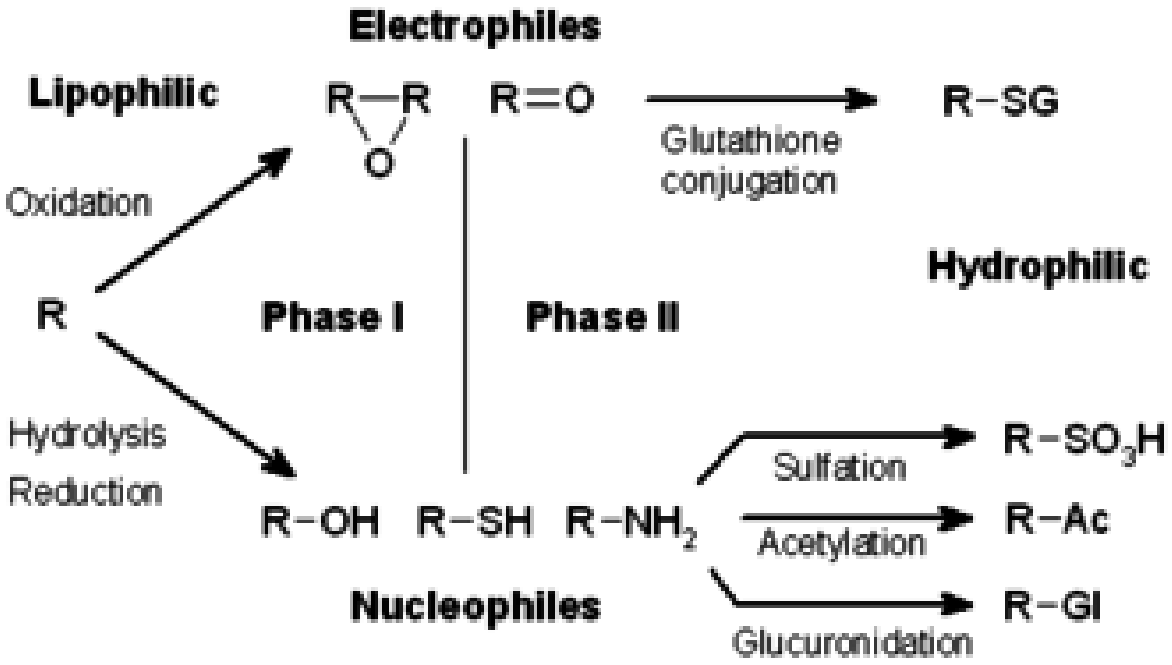

Phase 1
Drug
Oxidation
Hydroxylation
Dealkylation
Deamination
Hydrolysis
Derivative
Phase 2
Conjugation
Conjugate
Example
COOH
OCOCH3
COOH
OH
OH
HO
OH
O
COOH
O
COOH
Aspirin
Salicylic acid
Glucuronide

Phases of Metabolism

Modification

Conjugation

Excretion



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
  - - Cyclization

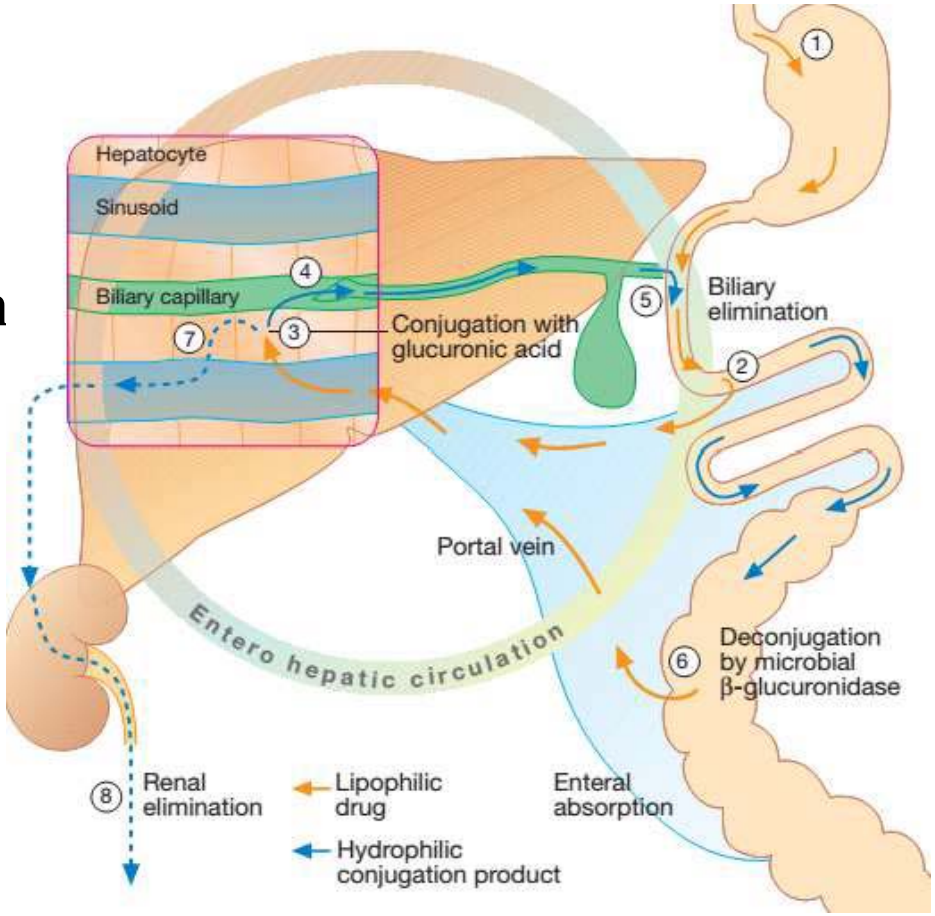
Phase I

- • Cyclization
  - – Formation of ring from straight carbon chain
  - – Ex: Proguanil
- • Decyclization
  - – Opening of the ring of the cyclic molecule
  - – Ex: Barbiturates & Phenytoin
- • 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

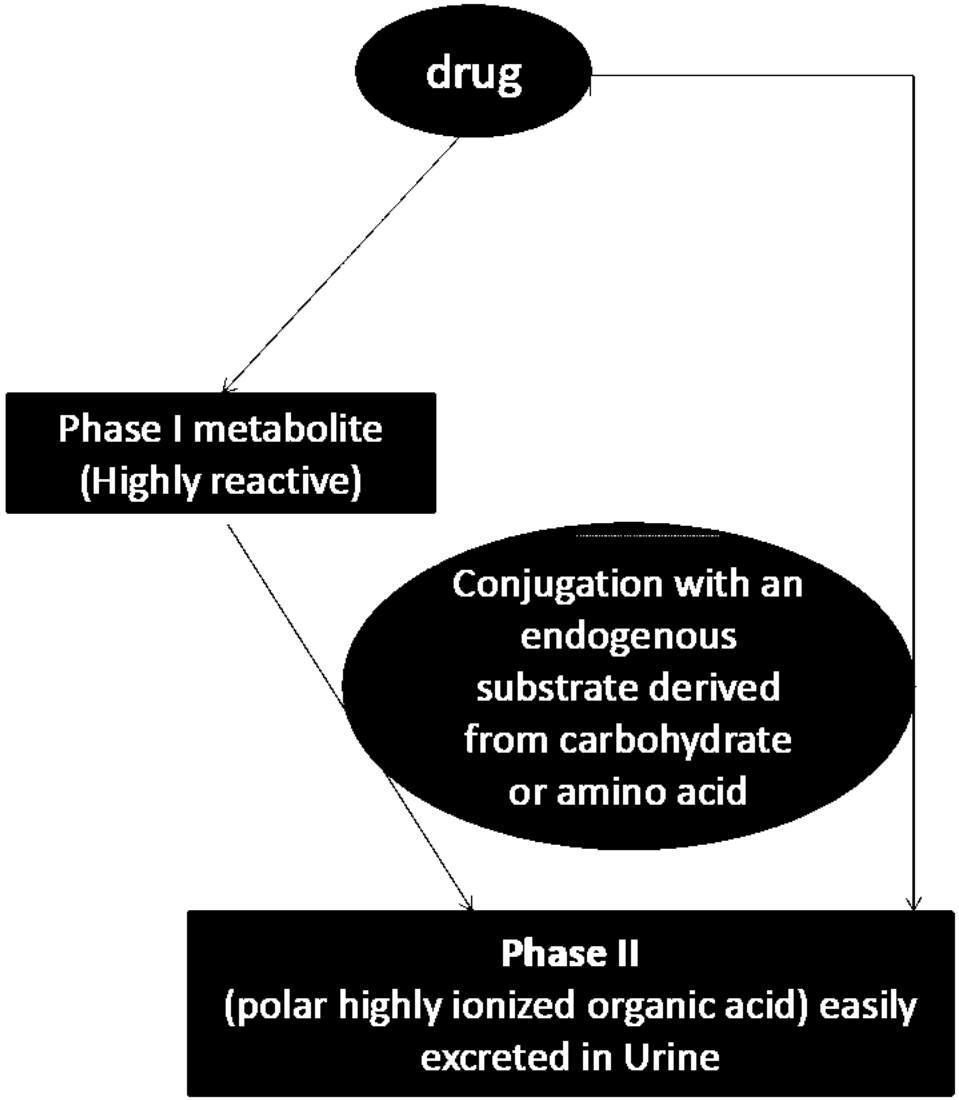
ENTEROHEPATIC CYCLE

Drug glucouronides
– hydrolyzed by bacteria and again absorbed goes through same fate prolonging the action

Ex: Phenolphthalein,
Oral contraceptives



Phase II

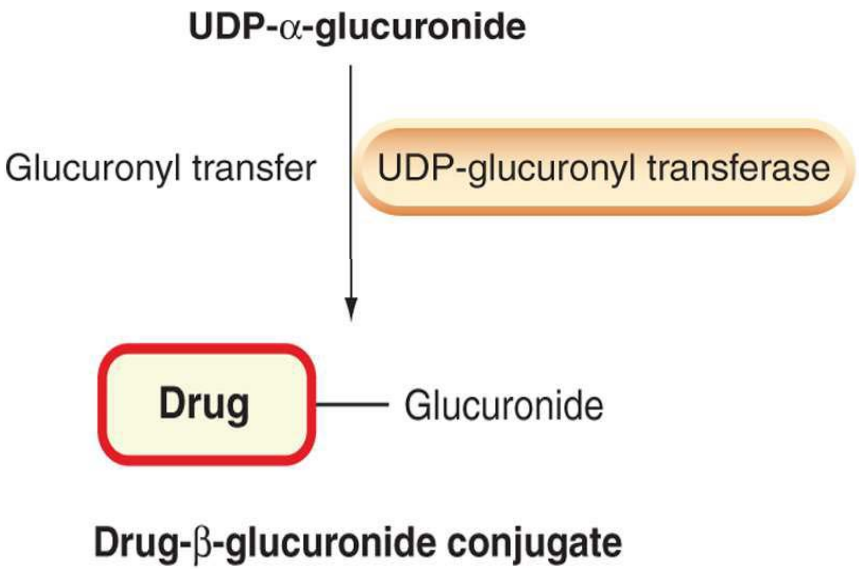


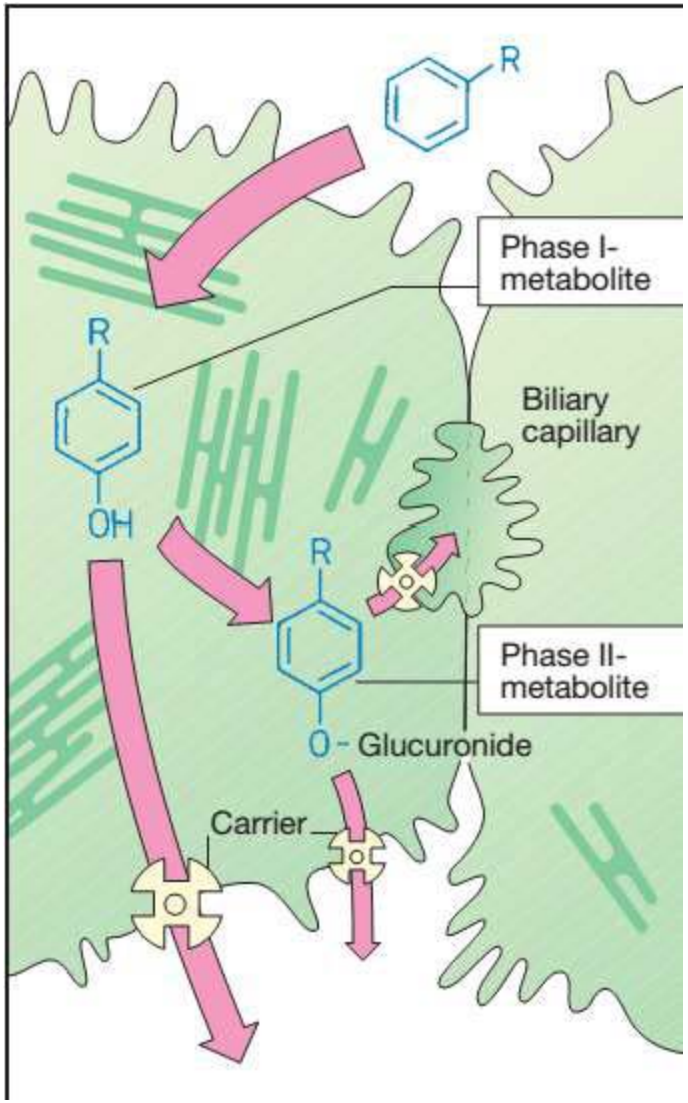
Phase II : Glucouronide Conjugation

- – 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


UDP-α-glucuronide
Glucuronyl transfer
UDP-glucuronyl transferase
Drug
Glucuronide
Drug-β-glucuronide conjugate


R
Phase I-
metabolite
R
OH
Biliary
capillary
R
Phase II-
metabolite
O - Glucuronide
Carrier

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

- • **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

- **• Glutathione Conjugation**
  - – Inactivates highly reactive quinones or epoxides intermediates – paracetamol
  - – When glutathione 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 (Intermediary 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 P450, 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

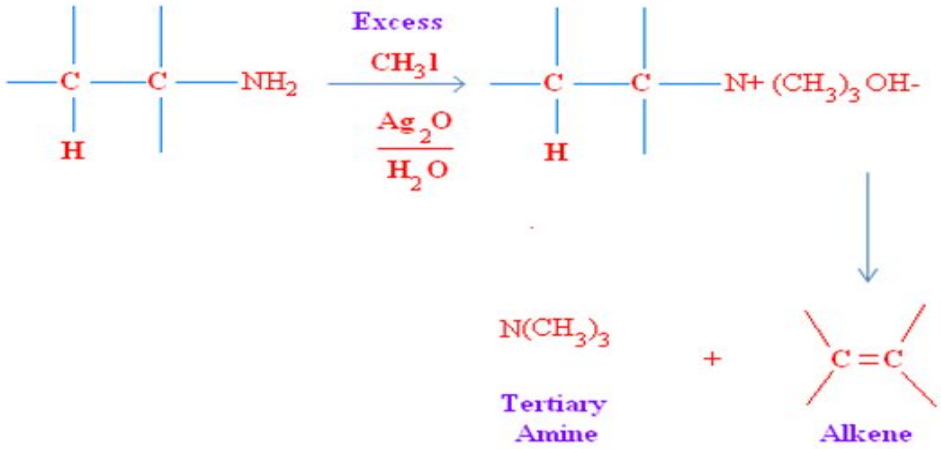
- Ex: **Flavoprotein oxidases, esterases, amidases**

Hoffman Elimination

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

Hofmann Elimination Mechanism

- The Hoffman elimination reaction mechanism has been proposed as the chemical pathway for the degradation of the quat. A strong base (the hydroxyl ion) is necessary to facilitate the elimination step.



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

Excretion

- • Passage out of systemically absorbed drug

• Excreted in

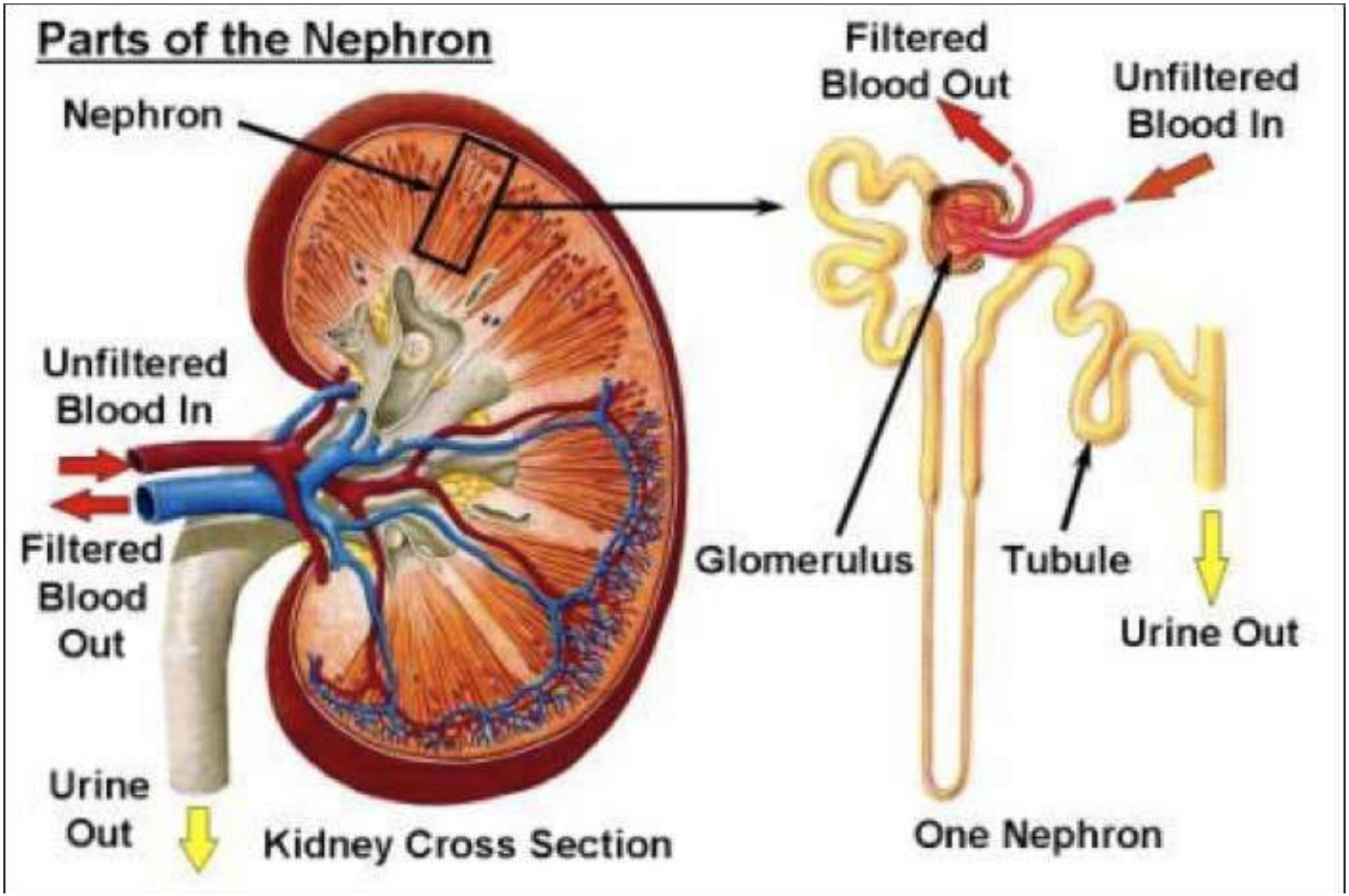
- 1. Urine
- 2. Faeces
- 3. Exhaled Air
- 4. Saliva & sweat
- 5. Milk

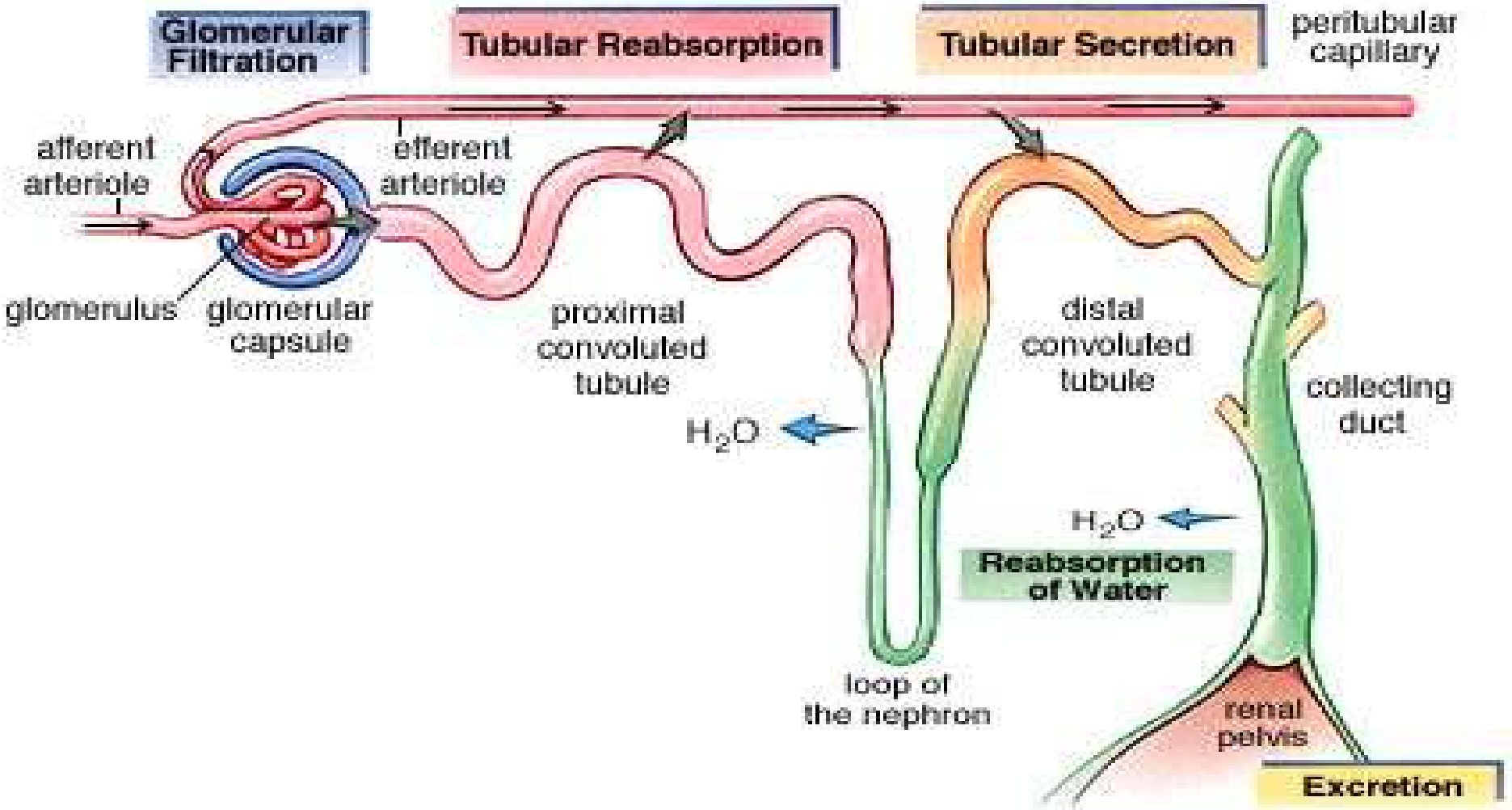
Excretion : Urine

- • Most important channel for excretion of drugs.
- • It eliminates water soluble substances.
- • Amount of drug or its metabolites depends on

  – Glomerular filtration (GFR)
  – Tubular Reabsorption (TR)
  – Tubular Secretion (TS)

- **Net Renal Excretion = (GFR+TS) - TR**

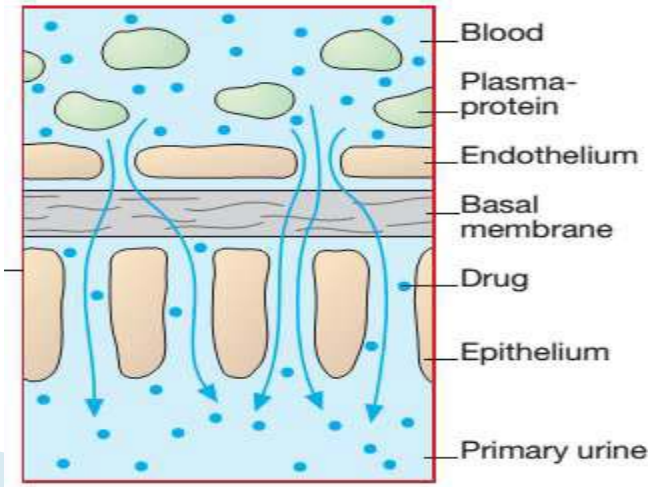

Parts of the Nephron
Nephron
Unfiltered Blood In
Filtered Blood Out
Urine Out
Kidney Cross Section
Filtered Blood Out
Unfiltered Blood In
Glomerulus
Tubule
Urine Out
One Nephron

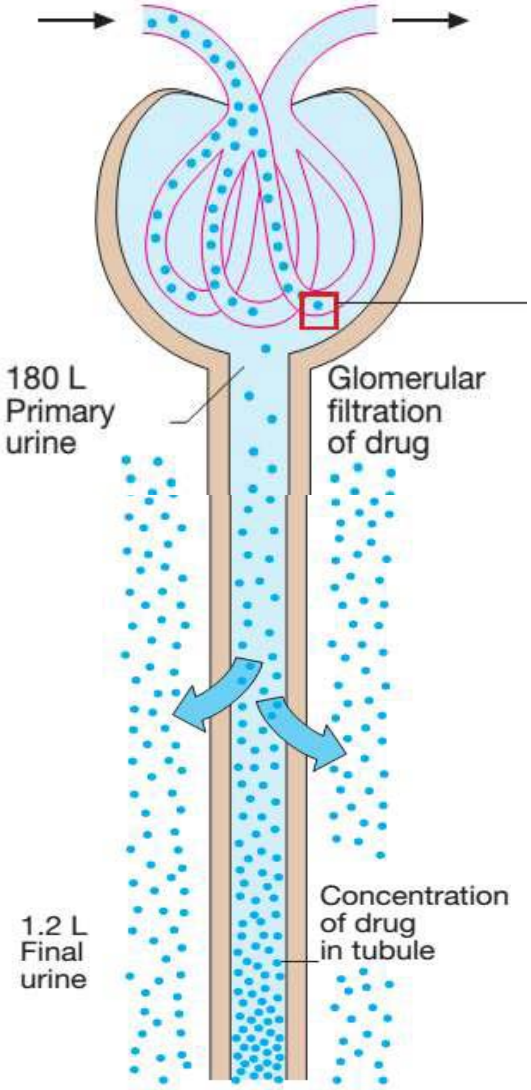

Glomerular Filtration
Tubular Reabsorption
Tubular Secretion
peritubular capillary
afferent arteriole
efferent arteriole
glomerulus
glomerular capsule
proximal convoluted tubule
distal convoluted tubule
collecting duct
H_2O
H_2O
Reabsorption of Water
loop of the nephron
renal pelvis
Excretion

Glomerular Filtration

- • Glomerular capillaries – larger pore than usual

- • All non-protein bound drugs (lipophillic/lipopho bic) gets filtered in glomerulus.



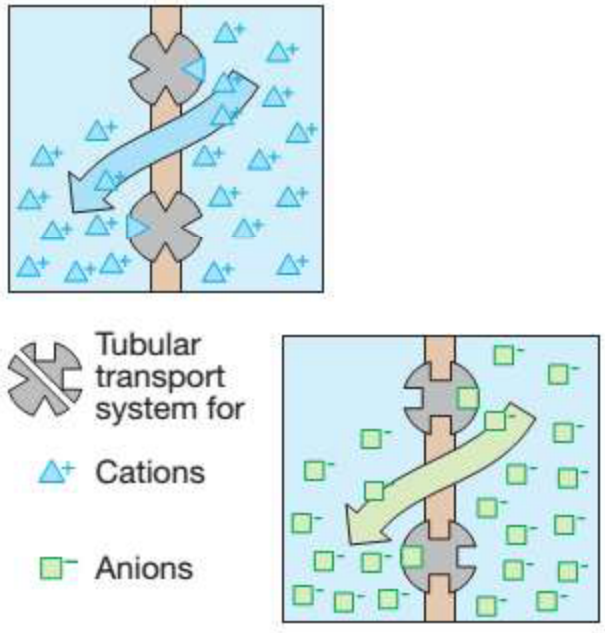


Glomerular Filtration

- • 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 (Organic Acid Transporter OAT & Organic base transporter OCT)
- limited capacity
- Competition inhibition can occur



Tubular Secretion

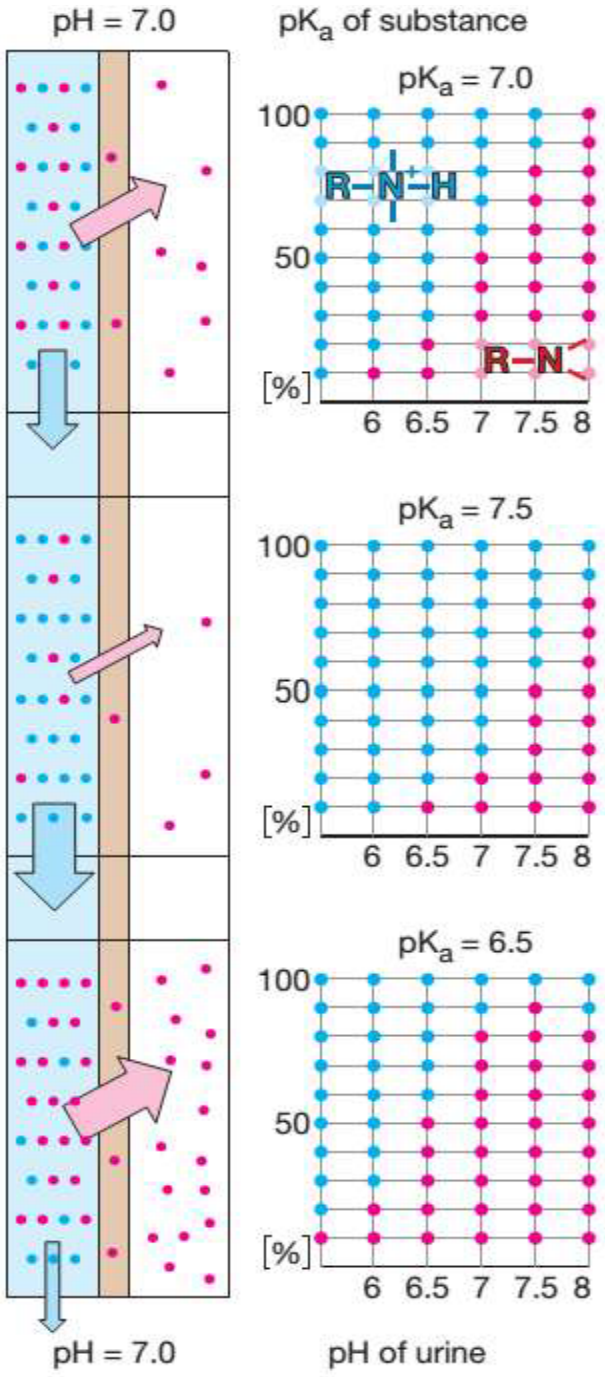
- • If renal clearance is greater than 120 ml/min – TS is assumed to occur
- • It reduces the amount of free form of drug
- • PPB drugs gets dissociated to get eliminated via this route
- • Organic Acid Transporter (OAT) : penicillin, probencid, uric acid, salicylates, indomethacin, methotrexate, glucouronides 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 Reabsorption

- • Passive diffusion 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



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 drugs with caution

- • **Contraindicated drugs** : Amidarone, Anthraquinone, Chloramphenicol, Ciprofloxacin, cyclosporine, indomethacin, methotrexate, tetracyclin

- • **Special precaution** : Ampicillin, aspirin, losarton, metaclopromide, sulfonamide

Why Kinetics of Elimination ?

- • Help us to understand how dosage recommendations has been arrived in the product information
- • Help to use the drug optimally and understand its limitations
- Ex • Severely ill patient

– individualization of 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 = amt. of drug that enters systemic circulation (AUC)

Dose administered

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

  V = 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 = Rate of elimination/C (plasma concentration)

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 = dose rate/CL (when bioavailability is 100%)
- 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

- dose rate = (target Cpss X CL)/ F

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

Michaelis Menten Kinetics

- • Elimination changes from first order to o 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 elimination = (Vmax) (C) / Km + C
- Km = plasma conc. at which elimination rate is half maximal
- C = plasma concentration of drug
- Vmax = maximum rate of drug elimination

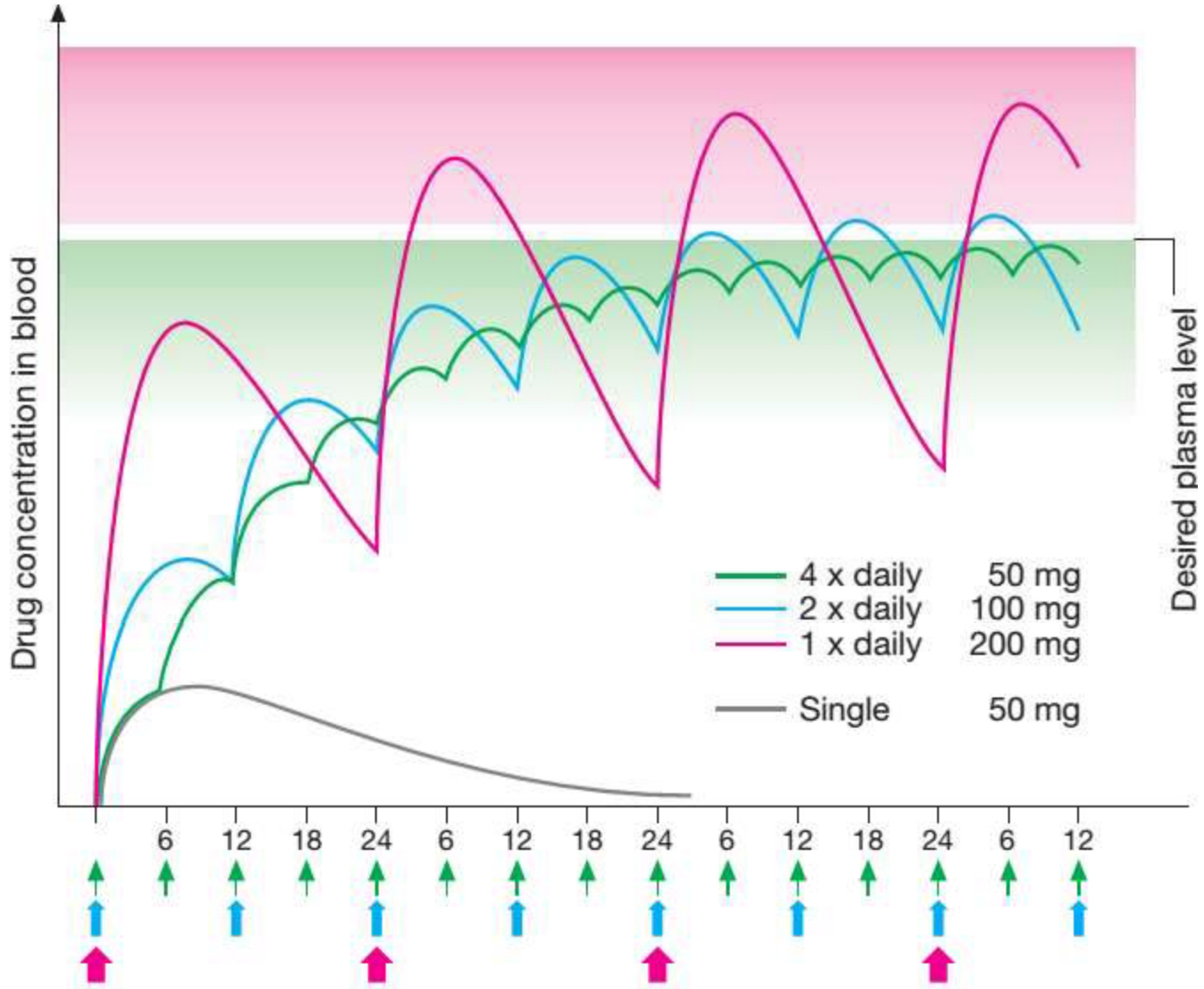
  Ex: Phenytoin

Plateau Principle of drug accumulation

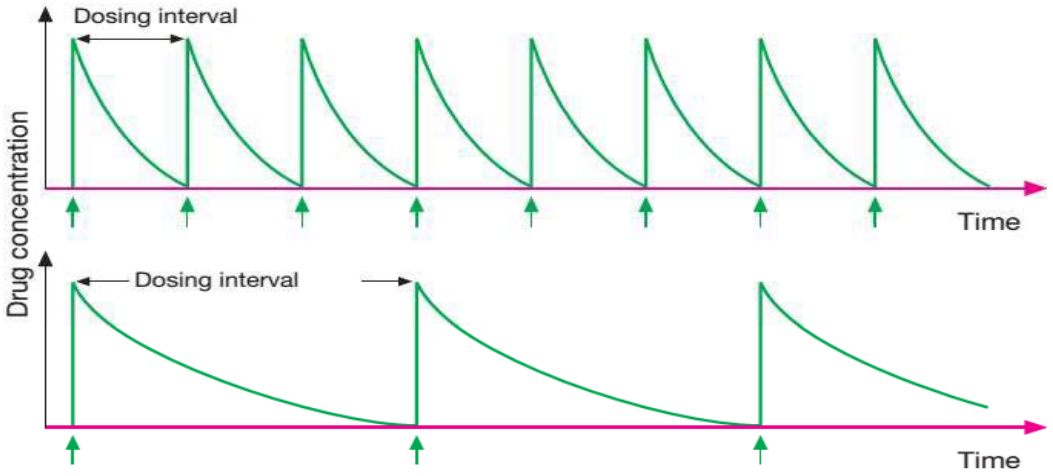
- • When constant dose of a drug is repeated before the expiry of 4 t ½ , it would achieve higher peak concentration, because some remnant drug will be present in the body.

- • Subsequently plasma concentration becomes constant and forms a plateau and fluctuates around desired therapeutic level of drug.

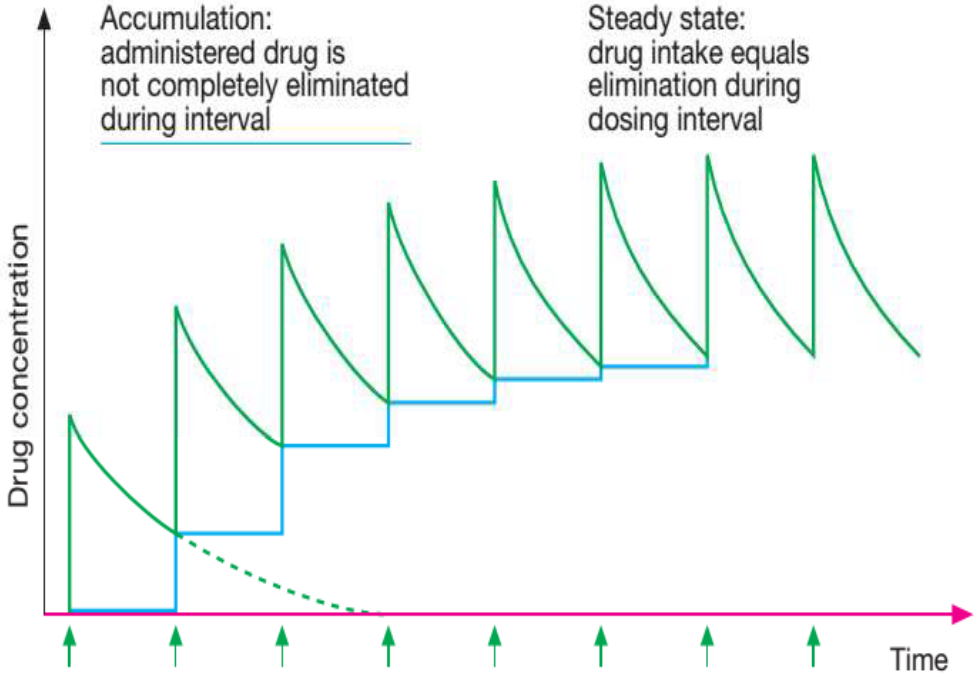
- • Desired therapeutic level reaches 4-5 half lives



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



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.

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 bioavailability (F), Volume of Distribution (V) and Rate of elimination (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 compliance

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
- – Enteral : Sustained release tablets, spansules
- – Parenteral: Insoluble form (oily), pellet implantation, silastic and biodegradable implant.

– Transdermal patches

- • Increasing plasma protein binding
- • Retarding metabolism
- • Retarding elimination

THANK YOU

HAPPY TO ANSWER IF U HAVE ANY QUESTION