Pharmacokinetics

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Learning Object

- **Know the processes involved in ADME of drugs**
- **Know how these processes may affect the action of xenobiotics**
- **Appreciate how these processes can affect the outcome of the treatment of patients with drugs**
- **Appreciate how differences in these processes between patients can affect therapy**
- **Know how these processes have been exploited to improve therapy**
- **Be able to exemplify the above**

- **Pharmacokinetics** is the quantitative study of drug movement **in and out** of the body.

- The **intensity of response** is related to concentration of the drug at the site of action,

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  dependent on its pharmacokinetic properties.

- Pharmacokinetic considerations therefore, determine:
  - The route (s) of administration,
  - Dose,
  - Latency of onset,
  - Time of peak action,
  - Duration of action,
  - And frequency of administration of a drug etc.

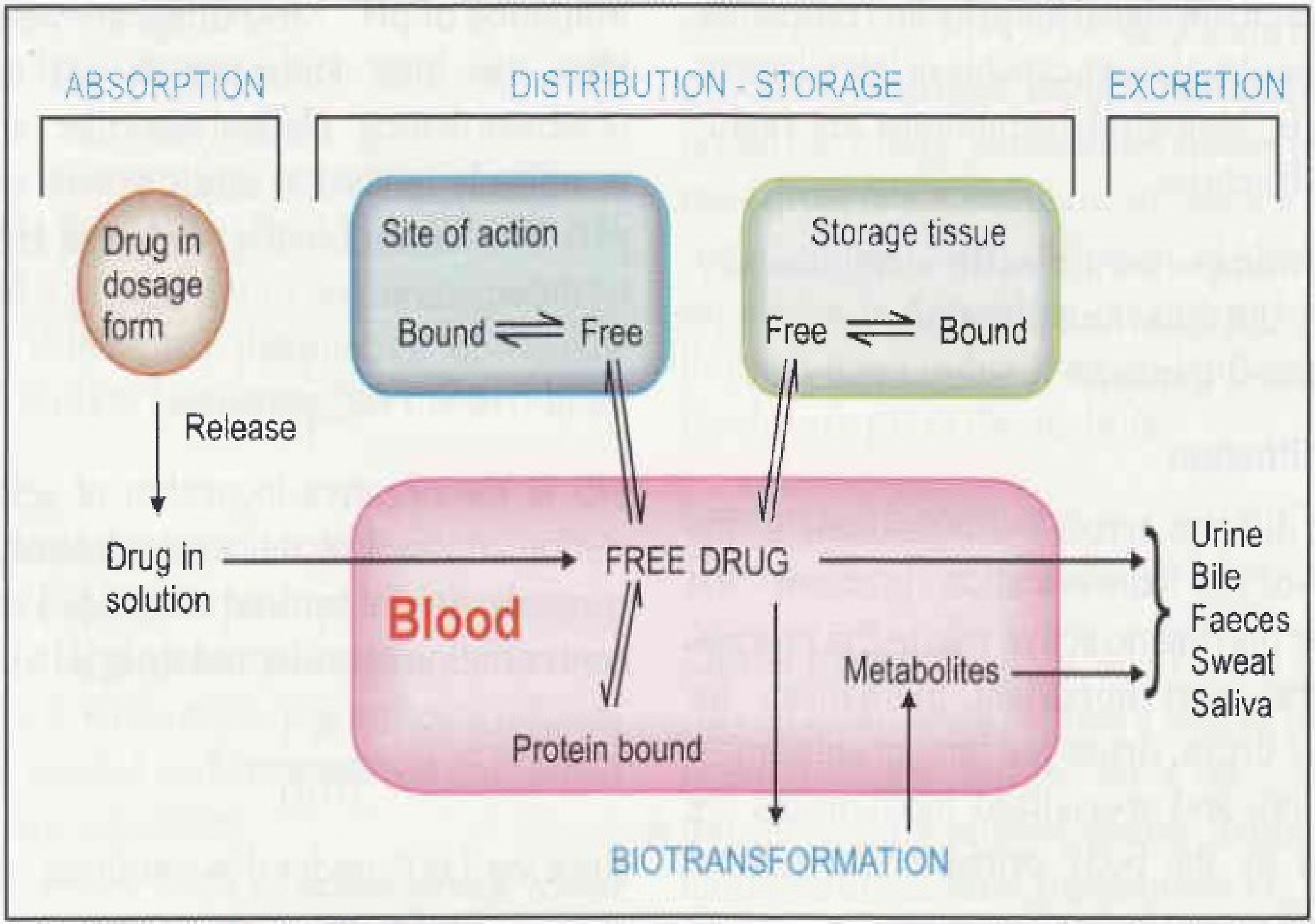

Fig. 2.1: Schematic depiction of pharmacokinetic processes

- All pharmacokinetic processes involve transport of the drug across biological membranes.

Biological membrane

- This is a bilayer (about 100 A thick) made up of phospholipid and cholesterol

- The **polar groups** 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

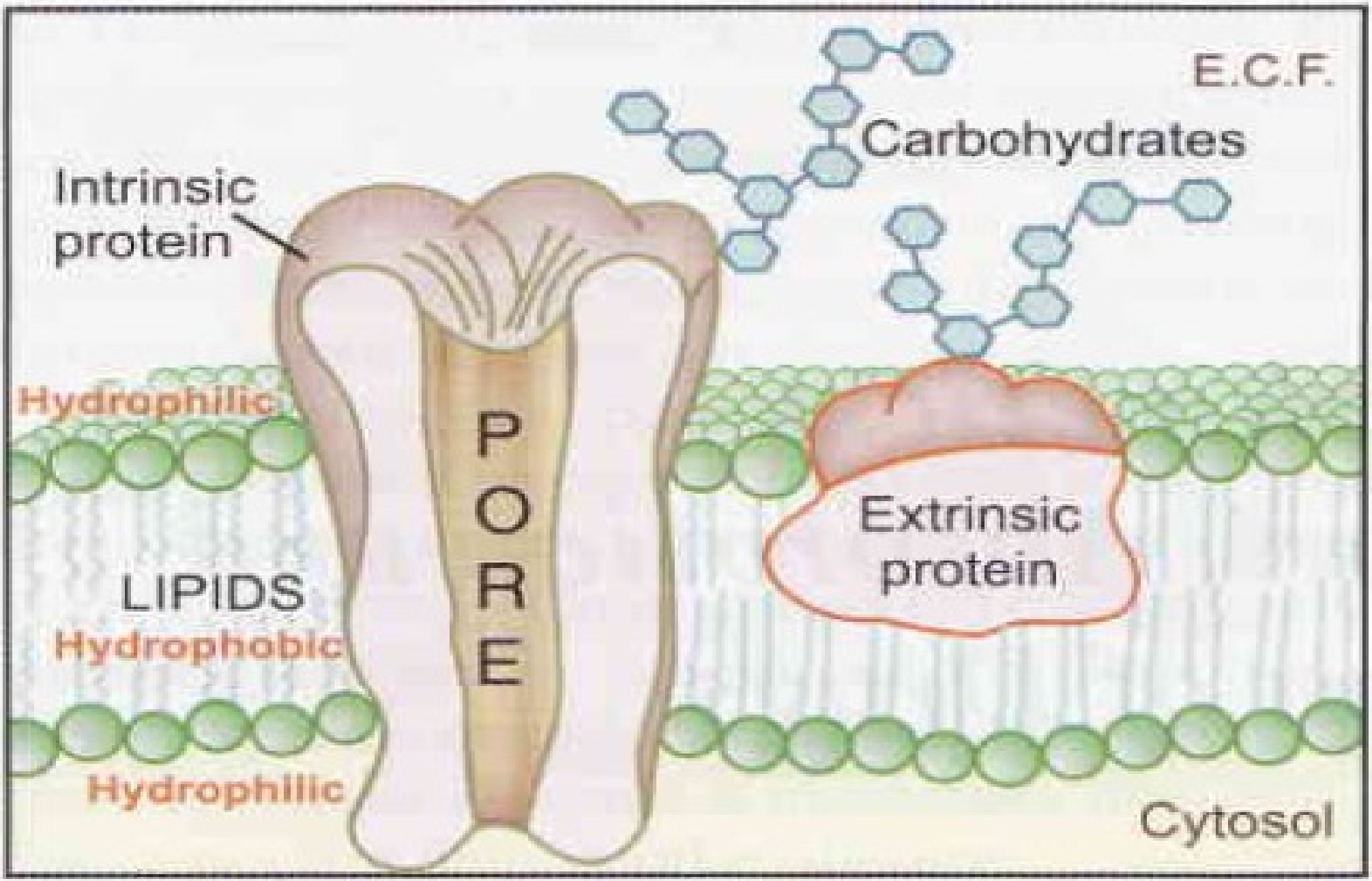

Fig. 2.2: Illustration of the organisation of biological membrane

- Other **adsorbed proteins** have enzymatic, carrier, receptor or signal transduction properties.

- The proteins are able to freely float through the membrane

- Some of the **intrinsic ones**, which extend through the full thickness of the membrane, **surround** fine aqueous pores.

- Paracellular spaces or channels also exist between certain **epithelial /endothelial cells**.

TRANSPORTATION OF DRUGS

- Drugs are transported across the membranes by:
  - (a) Passive diffusion and filtration
  - (b) Specialized transport

Passive diffusion

- The drug diffuses across the membrane in the direction of its concentration gradient

- the membrane playing no active role in the process.

Majority of drugs

- **<u>Lipid soluble drugs</u>** diffuse by dissolving in the lipoidal matrix of the membrane
- The rate of transport is proportional to the **lipid : water** partition coefficient of the drug.

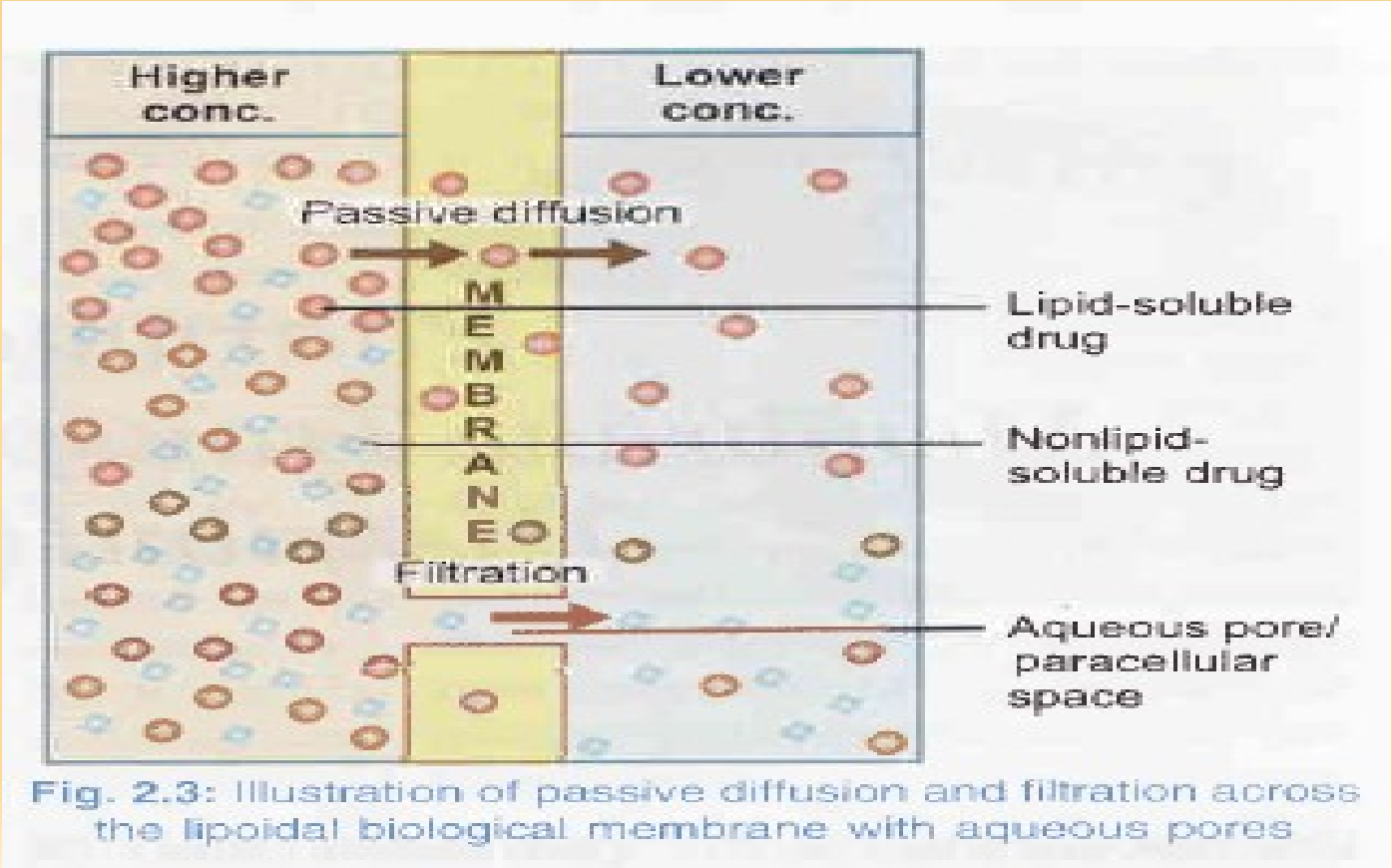

Fig. 2.3: Illustration of passive diffusion and filtration across the lipoidal biological membrane with aqueous pores

- A **more lipid-soluble drug** attains higher concentration in the membrane

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Diffuses quickly

- Also, **greater the difference** in the concentration of the drug on the two sides of the membrane

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faster is its diffusion.

- **Influence of PH:**
- Most drugs are weak electrolytes i.e. their ionization is pH dependent

- Strong electrolytes are **completely ionized** at acidic as well as alkaline pH- Not influenced by pH.

- The ionization of a **weak acid [HA]** is given by the equation:

$$pH = pKa + \log \frac{[A^-]}{[HA]}$$

- **pKa** is the negative logarithm of acidic dissociation constant of the weak electrolyte.

- If the concentration of ionized drug [A-] is equal to concentration of unionized drug [HA], then

$$\frac{[A^-]}{[HA]} = 1$$

- since log 1 is 0, under this condition

$$pH = pKa$$

- Thus, pKa is numerically equal to the pH at which the drug is **50% ionized**.

- Thus, weakly acidic drugs, which form salts with cations e.g. sod. phenobarbitone, sod. Sulfadiazine, pot. Penicllin-V

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Ionize more at alkaline pH.

- Weakly basic drugs, which form salts with anions, e.g. atropine sulfate, ephedrine HCl, chloroquine phosphate etc.

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Ionize more at acidic pH.

Implications of this Consideration are:

- (a) **Acidic drugs** e.g. aspirin **(pKa 3.5)** are largely unionized at acid gastric pH

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absorbed from stomach

- While bases e.g. atropine **(pKa 10)** are largely ionized

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absorbed only when they reach the intestines.

Ion trapping

- (b) The unionized form of acidic drugs which crosses the surface membrane of gastric mucosal cell

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reverts to the ionized form within the cell (pH 7.0)

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and then only slowly passes to the extracellular fluid.

↓

called as ion trapping.

↓

May contribute to **gastric mucosal cell damage** caused by aspirin.

Excretion and PH

- Acidic drugs are ionized more in alkaline urine- **and are excreted faster**.

- Accordingly, **basic drugs are excreted faster if urine is acidified**.

Lipid-soluble non electrolytes

- **Lipid-soluble non electrolytes** (e.g. Ethanol, diethyl-ether) readily cross biological membranes

transport is pH independent.

Lipid-insoluble drugs

- **Filtration** is passage of drugs through aqueous pores in the membrane or through paracellular spaces.

Lipid-insoluble drugs

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Cross biological membranes by filtration if their molecular size is smaller than the diameter of the pores.

- Majority of cells (intestinal mucosa, RBC etc.) have very small pores (4 A)

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drugs with **MW > 100 or 200** are not able to penetrate.

- However, capillaries (except those in brain) have large paracellular spaces (40 A) and most drugs (even albumin) can filter through these.

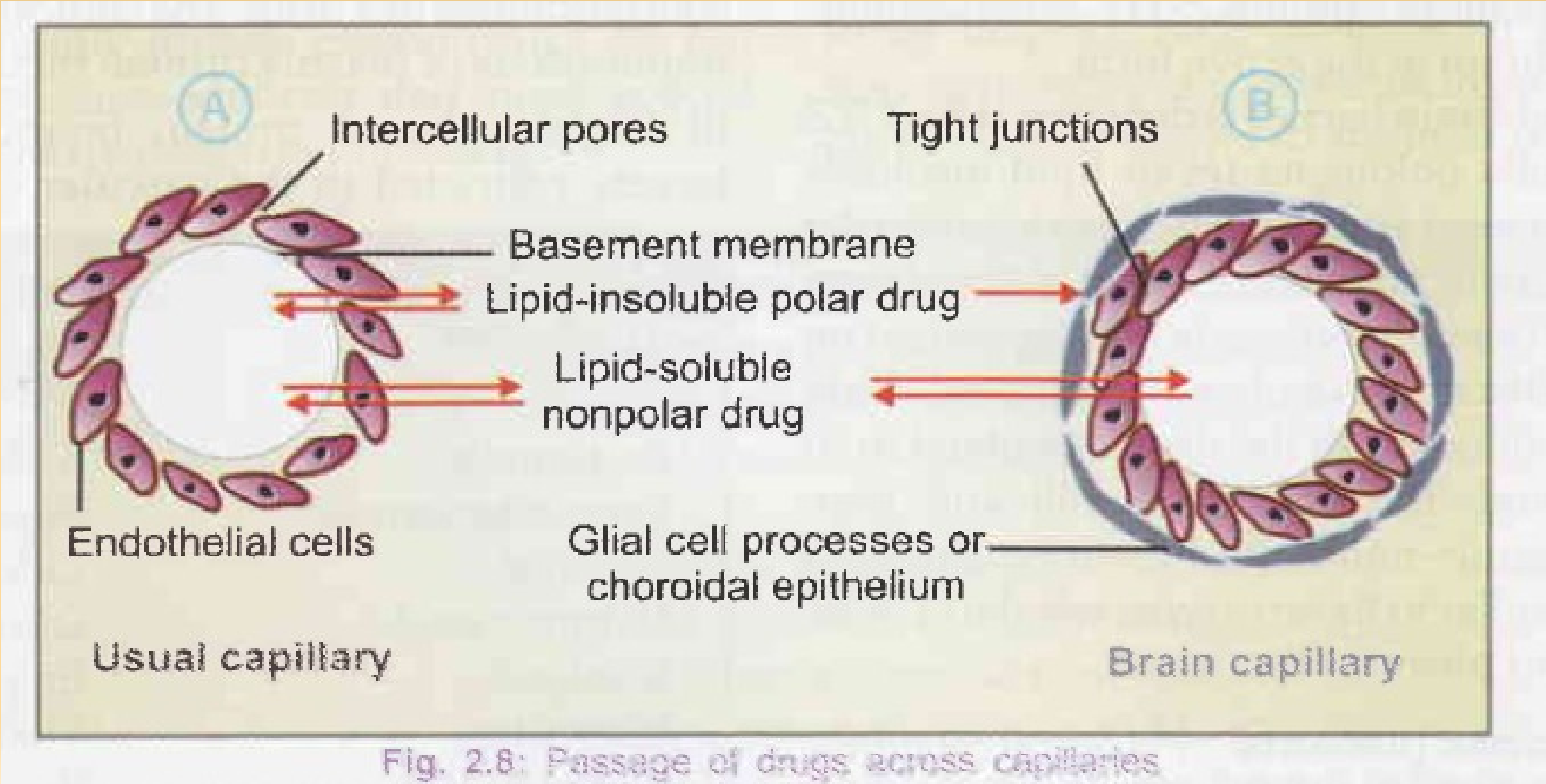

Fig. 2.8: Passage of drugs across capillaries

Specialized transport

- It is of 2 type
- i.e carrier mediated and pinocytosis.

Carrier mediated transport

- All cell membranes contain a **host of transmembrane proteins**

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serve as carriers or transporters

Carrier mediated transport

- **Transporters** combine transiently with their substrate (Drug).

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  And undergo a conformational change

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  carry the substrate to the other side of the membrane

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  substrate dissociates and releases

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  transporter returns back to its original state.

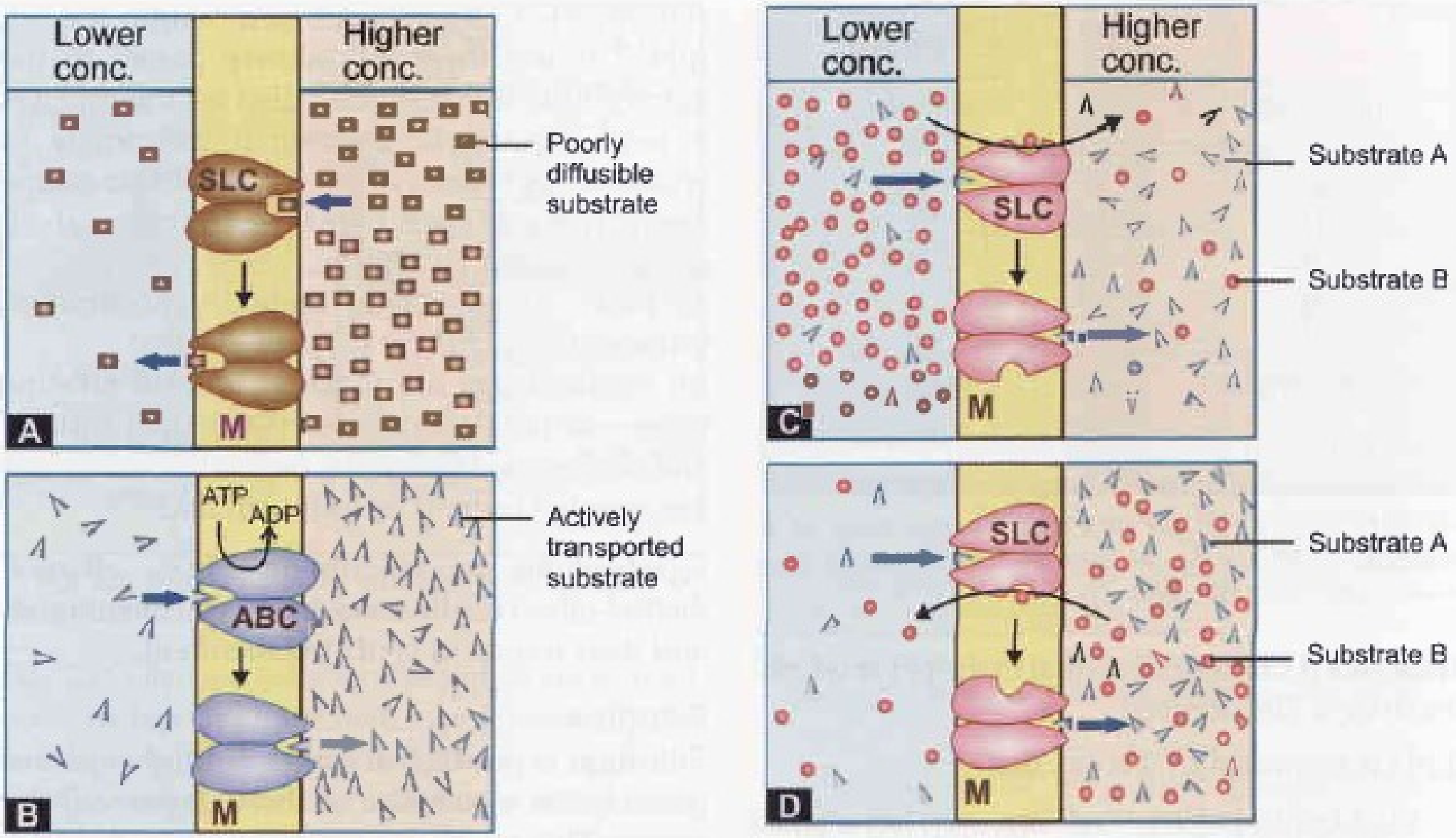

Fig. 2.5: Illustration of different types of carrier mediated transport across biological membrane

- Carrier trarsport is specific for the substrate e.g. An organic anion
- It is competitively inhibited by analogues which utilize the same transporter
- Much slower than flux through channels

Depending on requirement of energy, carrier transport is of 2 types:

a. Facilitated diffusion:

- Transporters: belonging to the super-family of **solute carrier (SLC) transporters**

- Operates passively and translocates the substrate in the direction of its electrochemical gradient i.e. from higher to lower concentration.

- Facilitates permeation of a poorly diffusible substrate e.g. the **entry of glucose into muscle and fat cells by GLUT 4**.

b. Active transport:

- It requires energy

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Transports the solute against its electrochemical gradient

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selective accumulation of the substance on one side of the membrane.

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Inhibited by metabolic poisons

- E.g. levodopa and methyl dopa are actively absorbed from gut by the **aromatic amino acid transporter**.

- In addition, the body has developed some relatively **nonselective transporters** like P-glycoprotein (P-gp) to deal with xenobiotics.

Types of active transport

- Active transport can be **primary or secondary** depending on the source of the driving force.

Type of active transport

I. Primary active transport

- Energy - obtained by the hydrolysis of ATP.

- The transporters belong to the superfamily of ATP binding cassette transporters whose intracellular loops have ATPase activity.

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  mediate only efflux of the solute from the cytoplasm, either to extracellular fluid or into an intracellular organelli

ii. Secondary active transport:

- In this type of active transport, the energy to pump one solute is derived from the down hill movement of another solute (mostly Na).

- When the concentration gradients are such that both the **solutes move in the same direction** (C), It is called symport or co-transport

- But when they move in opposite directions (D), it is termed **antiport or exchange transport.**

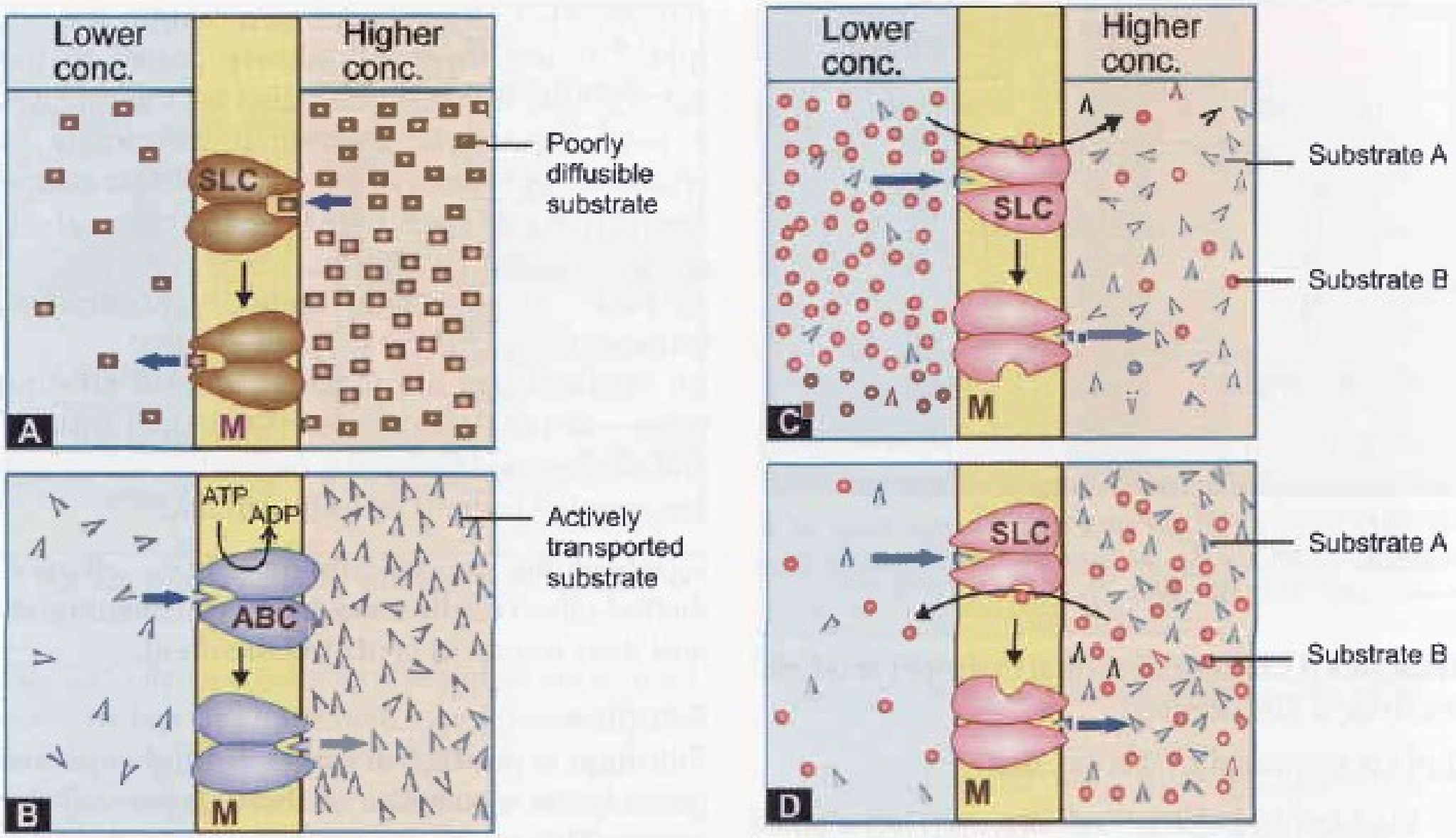

Fig. 2.5: Illustration of different types of carrier mediated transport across biological membrane

Limitation of Carrier mediated transport

- Carrier transport is saturable and **follows the Michaelis-Menten kinetics.**
- The maximal rate of transport is dependent on the
  - density of the transporter in a particular membrane,
  - and its rate constant (Km),

Genetic polymorphism and Tissue specific drug distribution

- Genetic polymorphism

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  Alter both the density and affinity of the transporter protein for different substrates

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  affect the pharmacokinetics of drugs.

- **Tissue specific drug distribution** can occur due to the presence of specific transporters in certain cells.

Specialized Transport
II. Pinocytosis

Pinocytosis

- It is the process of transport across the cell in particulate form by formation of vesicles.

- This is applicable to proteins and other big molecules

contributes little to transport of most drugs.

Factors affecting absorption

- **1. Aqueous solubility:** Drugs given in solid form must dissolve in the aqueous biophase before they are absorbed.
- **Poorly water soluble drugs** (aspirin, griseofulvin) rate of dissolution **governs rate of absorption**.
- A drug given as watery solution: is absorbed faster than when the same is given in solid form or as oily solution.

2. Concentration: Passive diffusion depends on concentration gradient

- Drug given as concentrated solution

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absorbed faster than from dilute solution.

- **3. Area of absorbing surface**:

  Larger is the area

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  faster is the absorption.

3. Route of administration:

affects drug absorption, because each route has its own peculiarities.

Oral

- The effective barrier to orally administered drugs is the epithelial lining of the git- which is lipoidal.

- **Nonionized lipid soluble drugs** e.g. ethanol are readily absorbed from stomach as well as intestine at rates proportional to their **lipid : water partition coefficient**.

- **Acidic drugs** e.g. salicylates, barbifurates, etc. are predominantly unionized in the acid gastric juice and are **absorbed from stomach**

- While **basic drugs** e.g. morphine, quinine etc. are largely ionized and are **absorbed only on reaching the duodenum.**

- However, even for acidic drugs absorption from stomach is slower- because
  - Mucosa is thick
  - Covered with mucus
  - And the surface area is small.

- Absorbing surface area is much larger in the small intestine due to villi.

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  Thus absorption of **basic drug** is faster as it is absorb in intestine.

- **Gastric emptying**- Faster gastric emptying accelerates drug absorption.

Particle size of drug and presense of food

- **Particle size** of the drug in solid dosage form **governs rate of dissolution** and in turn rate of absorption.

- Presence of food dilutes the drug

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Retards absorption.

- Further, certain drugs form **poorly absorbed complexes with food** constituents, e.g. tetracyclines with calcium present in milk

- Thus most drugs are absorbed better if taken in **empty stomach**.

- **Highly ionized drugs** e.g. Gentamicin, neostigmine

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poorly absorbed when given orally.

GIT degradation of drug

- Certain drugs are degraded in the GIT and are **ineffective orally** e.g.
  - penicillin G by acid,
  - insulin by peptidases

Pharmaceutical dosage forms to overcome GI degradation of drugs:

- **Enteric coated tablets** - having acid resistant coating
- **Sustained release preparations** coated with slowly dissolving materials

Influence of Efflux transporter P-gp

- The oral absorption of certain drug is low because a fraction of the absorbed drug is excreted back into the intestinal lumen by the **efflux transporter P-gp** located in the gut epithelium.

- Eg. The low oral bioavailability of digoxin and cyclosporine is partly accounted by this mechanism.

- **Inhibitors of P-gp** like quinidine/ verapamil erythromycin etc. enhance

- While **P-gp inducer** like rifampin and phenobarbitone reduce the bioavailability of these drugs.

Concurrent ingested drugs

- Absorption of a drug can be affected by **other concurrently ingested drugs**.

  May be a **luminal efect**

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  formation of insoluble complexes.

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  Eg tetracyclines with iron preparations, antacids, phenytoin with sucralfate.

- Such interaction can be minimized by administering the two drugs at 2-3 hr intervals.

Alteration of gut flora and gut wall effect

- Alteration of gut flora by antibiotics

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May disrupt the **enterohepatic cycling** of oral contraceptives and digoxin.

- Gut wall effects:

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altering motility (Eg. anticholinergics, tricyclic antidepressants, Metachlorpromide)

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causing mucosal damage (neomycin, methotrexate, vinblastine).

Subcutaneous and Intramuscular route

- By these routes the drug is **deposited directly** in the vicinity of the capillaries.

- **Lipid soluble drugs** pass readily across the whole surface of the capillary endothelium.

- **Large lipid insoluble molecules or ions**

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Capillaries (large paracellular spaces)

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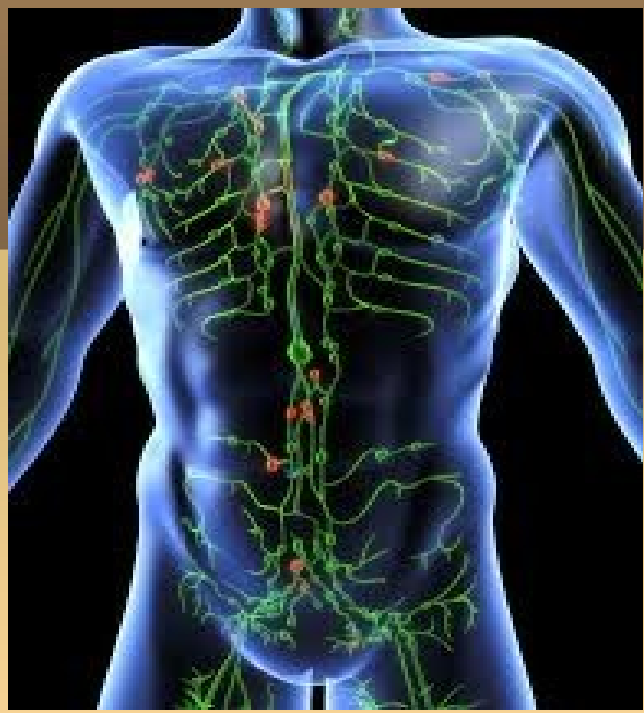
absorption



- **<u>Very large lipid insoluble molecules</u>**

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  absorbed through lymphatics

- Thus, many drugs not absorbed orally are **absorbed parenterally**.

<u>Speed of absorption:</u>

- s.c site is slower than that from i.m. site

- But both are generally faster and more consistent predictable than oral absorption.

Speed of absorption

- **Application of heat and muscular exercise**

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  Increases blood flow

  ↓

  Accelerate drug absorption

- **Vasoconstrictors e.g. adrenaline**

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  Retard absorption.

- Incorporation of hyaluronidase

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  catalyzes the hydrolysis of hyaluronan (a constituent of the extracellular matrix ECM)

  ↓

  increases tissue permeability

  ↓

  promote spread of drug

  ↓

  Facilitates drug absorption from s.c. injection

- Eg of drugs given by s.c and i.m routs are:

  - benzathine penicillin

  - protamine zinc insulin

  - depot progestins etc.

Topical appliaction and drug absorption

- **Topical sites** : skin, cornea, mucous membranes

- Systemic absorption after topical application

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  Depends primarily on lipid solubility of drugs.

- However, only few drugs significantly penetrate intact skin.

- Eg. Hyoscine, fentanyl, GTN, nicotine, testosterone, and estradiol ect.

- Corticosteroids applied over extensive areas

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produce systemic effects

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Pituitary-adrenal suppression.

- Absorption by topical application can be promoted by

  - by rubbing

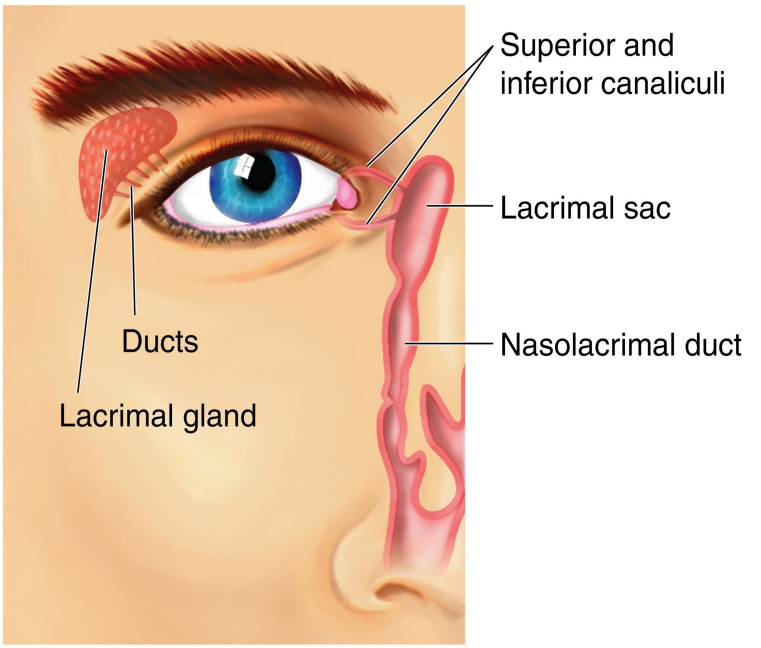
  - by incorporating drug in an olegenous base

  - or by use of occlusive dressing which increases hydration of the skin.

- **Organophosphate insecticides** coming in contact with skin can produce systemic toxicity.

- Abraded surfaces **readily absorb drugs**
  e.g. tannic acid applied over burn skin can produce hepatic necrosis

- Cornea is permeable to lipid soluble, **unionized physostigmine** but not to **highly ionized neostigmine.**



- **Drugs applied as eye drops**

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  absorbed through the nasolacrimal duct

- E.g. Timolol eye drops may produce bradycardia and precipitate asthma.

- Mucous membranes of mouth, rectum, vagina

  ↓

  absorb lipophilic drugs

- Eg. Estrogen cream applied vaginally has produced gynaecomastia in the male partner.

BIOAVAILABILITY

- The rate and extent of absorption of a drug from a dosage form is called as **bioavailability**.
- It is determined by
  - its **concentration- time curve** in blood
  - its excretion in urine.
- It is a measure of the fraction (F) of administered dose of a drug that reaches the systemic circulation in the unchanged form.

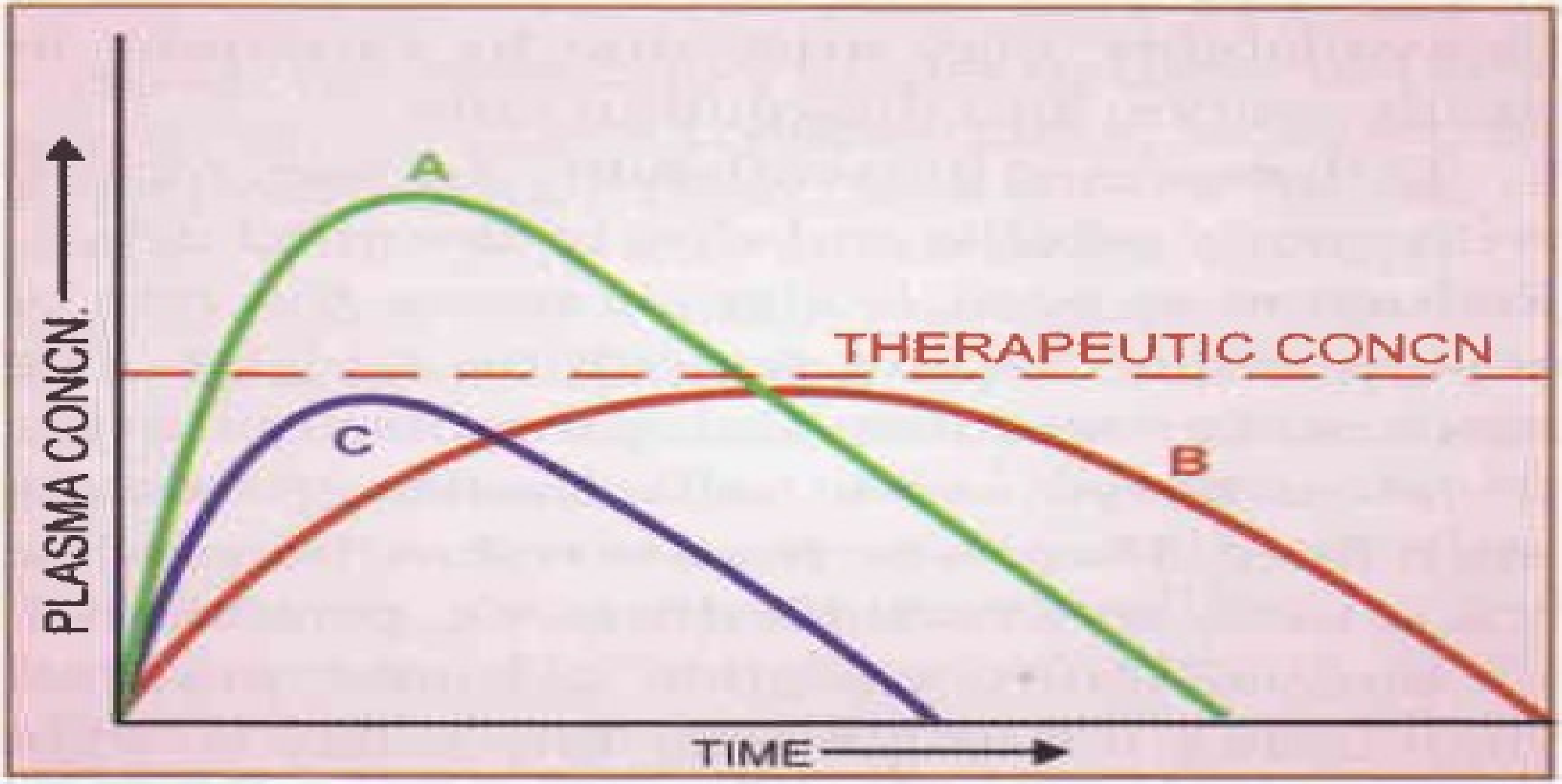

Fig. 2.6: Plasma concentration-time curves depicting bioavailability differences between three preparations of a drug containing the same amount

Note that formulation *B* is more slowly absorbed than *A*, and though ultimately both are absorbed to the same extent (area under the curve same), *B* may not produce therapeutic effect; *C* is absorbed to a lesser extent—lower bioavailability

- Bioavailability of drug injected i.v. is 100%,

- But is frequently lower after oral ingestion because:-

  (a) the drug may be incompletely absorbed.

  (b) the absorbed drug may undergo first pass metabolism in the intestinal wall/ liver or excreted in bile.

- Incomplete bioavailability after **s.c. or i.m. Injection** is less common

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  May occur due to local binding of the drug.

Biologically inequivalent

- Oral formulations of a drug from different manufacturers
- or different batches from the same manufacturer may have the same amount of the drug (**chemically equivalent**)
- but may not yield the same blood levels- **biologically inequivalent**.

Bioequivalent

- Two preparations of a drug are considered **bioequivalent** when the rate and extent of bioavailability of the drug from two formulations is not significantly different under suitable test conditions.

- **Bioavailability is depend on two important process:**

  1. Disintegration

  2. Dissolution

- Factor affecting disintegration are nature of
  - diluents
  - stabilizing agents
  - binders
  - lubricants
  - compression force used for tablets etc.

- The rate of dissolution is governed by the
  - inherent solubility
  - particle size
  - crystal form
  - And other physical properties of the drug.

- Differences in bioavailability may arise due to **variations** in disintegration and dissolution rates.

- And seen mostly with poorly soluble and slowly absorbed drugs.

Particle size

- Eg. Reduction in **particle size** increases the rate of absorption of aspirin (**microfine tablets**).

- The dose of griseofulvin and spironolactone in the tablet can be reduced to half if the drug particle is **microfined**.

- There is **no need** to reduce the particle size of freely water soluble drugs e.g. paracetamol.

Cases where bioavailability is important

- Bioavailability variation is important in case of

  1. Drugs with low safety margin (digoxin)

  2. Or where dosage needs precise control (oral hypoglycaemics, oral anticoagulants).

  3. Success or failure of an **antimicrobial regimen.**

DISTRIBUTION

Distribution

- The extent of distribution of a drug depends on its
  - Lipid solubility
  - Ionization at physiological pH
  - Extent of binding to plasma and tissue proteins
  - Presence of tissue-specific transporters
  - and differences in regional blood flow.

- Movement of drug proceeds

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  Until an equilibrium is established between unbound drug in plasma and tissue fluids.

Apparent volume of distribution (V)

- Assuming that the body behaves as a single homogeneous compartment with volume V

- It means it is **that volume** that would accommodate all the drug in the body.

Factor affecting volume of distribution (V)

- **Lipid-insoluble drugs** do not enter cells- Therefore **V** is approximatly equal to volume of extracellular fluid e.g. streptomycin, gentamicin 0.25 L / kg.

- **Drugs extensively bound to plasma proteins** are largely restricted to the vascular compartment and have low values e.g. diclofenac and warfarin (99 % bound), V =0.75L /kg.

- Drugs **sequestrated in other tissues** may have **V** much more than total body water or even body mass e.g. digoxin 6L/kg.

- Most of the drugs are present in other tissues

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  plasma concentration is low.

  ↓

  In case of poisoning, **drugs with large volumes of distribution** are not easily removed by haemodialysis.

- **Pathological states** e.g. congestive heart failure, uraemia, cirrhosis of liver etc. can alter the V of many drugs by altering

  - distribution of body water

  - permeability of membranes

  - binding proteins

  - accumulation of metabolites that displace the drug from binding sites.

Illustration of concept of V

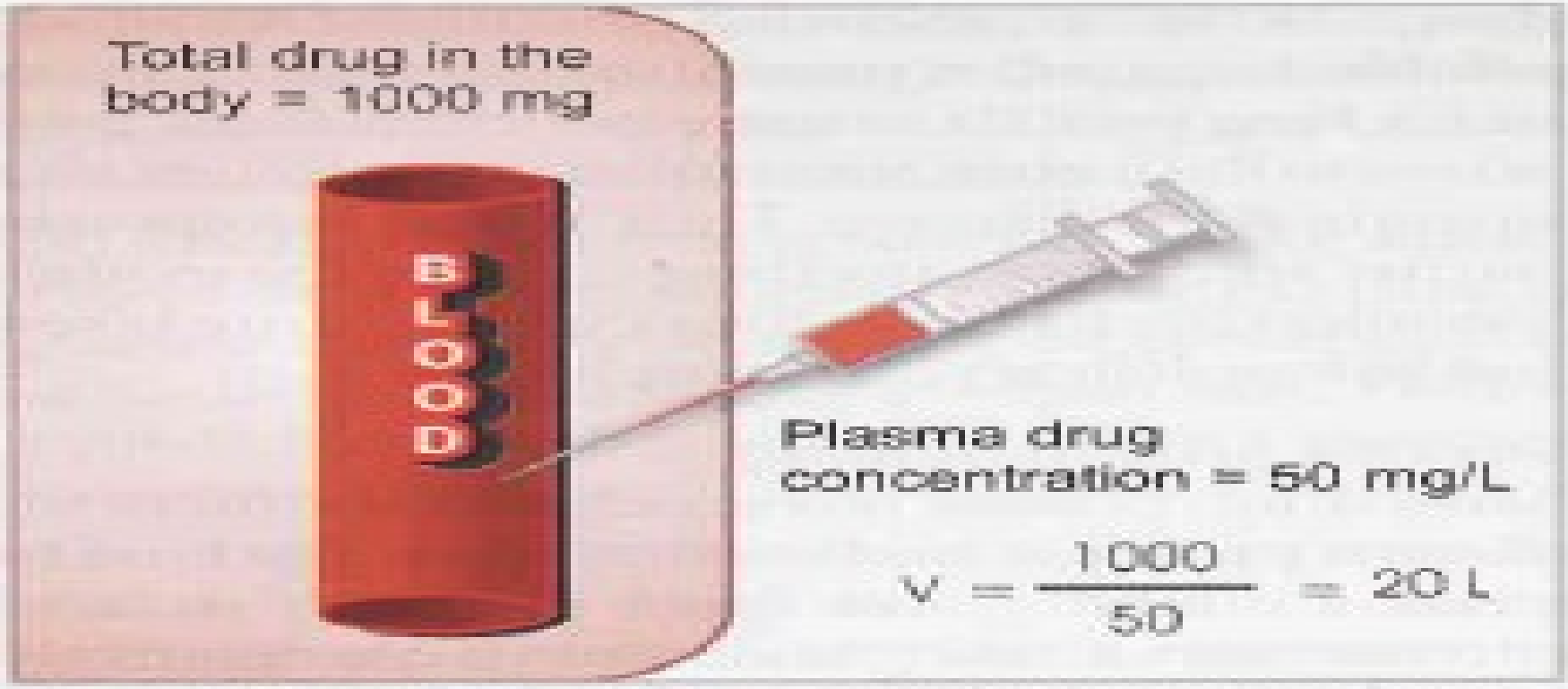

Fig. 2.7: Illustration of the concept of apparent volume of distribution (V).
In this example, 1000 mg of drug injected i.v. produces steady-state plasma concentration of 50 mg/L, apparent volume of distribution is 20 L

Redistribution

- **Redistribution:** Highly lipid-soluble drugs get initially distributed to organs with high blood flow i.e. **brain, heart, kidney, etc**.

- Later, it is **redistributed** into less vascular but more bulky tissues **(muscle, fat)** & it lead to fall in plasma concentration.

- If the site of action of the drug was in one of the **highly perfused organs**

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  Redistribution results in termination of drug action.

- **Greater the lipid solubility** of the drug

  ↓

  Faster is its redistribution.

- Eg. Anaesthetic action of thiopentone sod. injected i.v. is **terminated in few minutes** due to redistribution.

Solution:

- However, when the same drug is given repeatedly or continuously over long periods

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the sites get saturated

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And the drug becomes longer acting.

Penetration into brain and CSF:

- The capillary endothelial cells in brain have tight junctions and lack large intercellular pores.
- Further, neural tissue covers the capillaries.
- Together they constitute **blood-brain barrier**.

Usual capillaries & brain capillaries

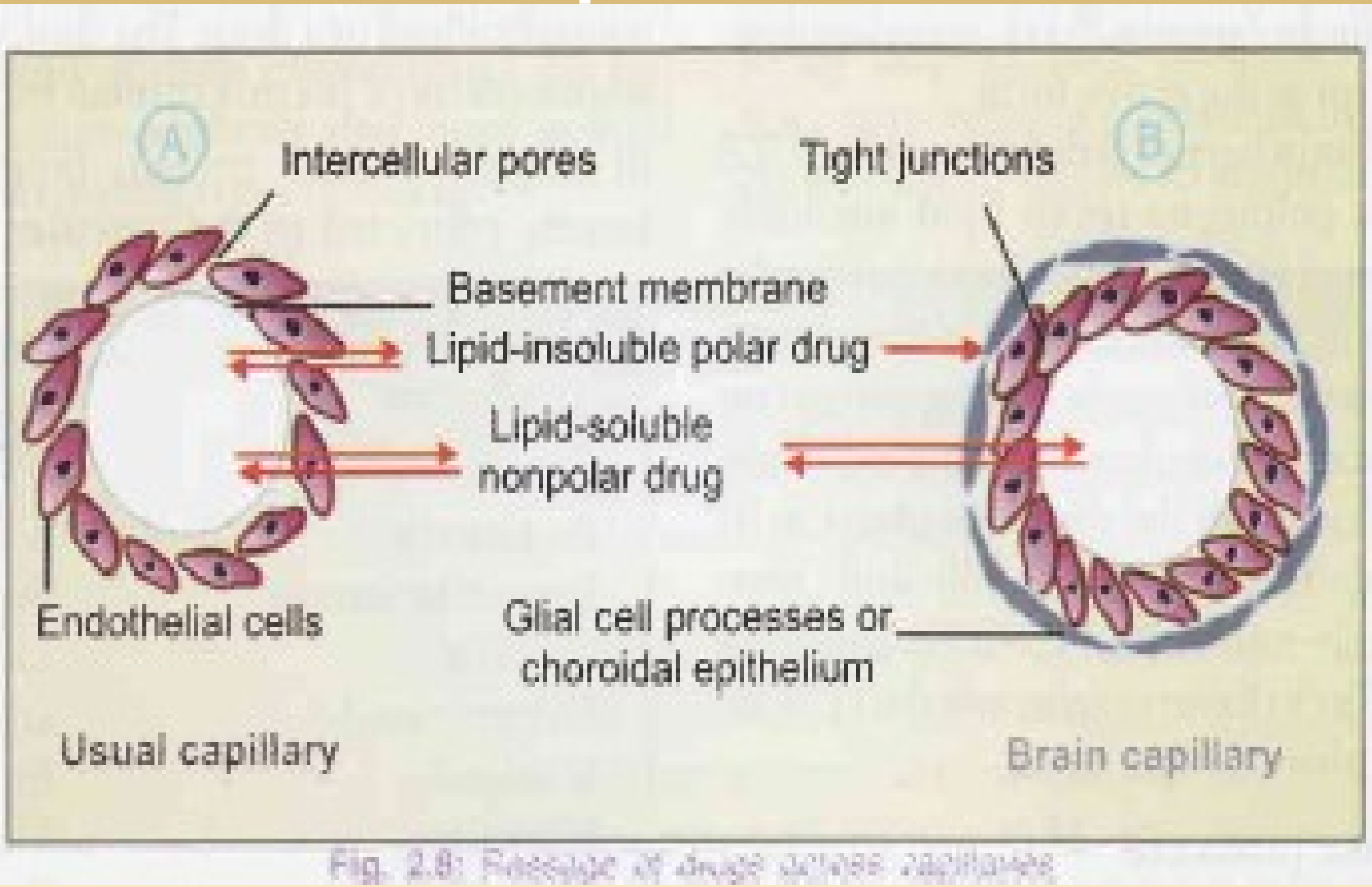

Fig. 2.8: Passage of drugs across capillaries

- A similar **blood-CSF barrier is located** in the choroid plexus: tight junctions.

- Both these barriers are lipoidal and limit the entry of nonlipid-soluble drugs e.g. Streptomycine, neostigmine etc.

- Therefore, Only lipid-soluble drugs are able to penetrate and have action on the central nervous system.
- Inflammation of meninges increases the permeability of these barriers.
- Some drugs accumulate in the brain by utilizing the transporters for endogenous substances.

Enzymatic blood-brain barrier:

- Some enzymes such as

  - Monoamine oxidase (MAO)

  - Cholinesterase

  - And some other enzymes are present in the capillary walls or in the cells lining the brain.

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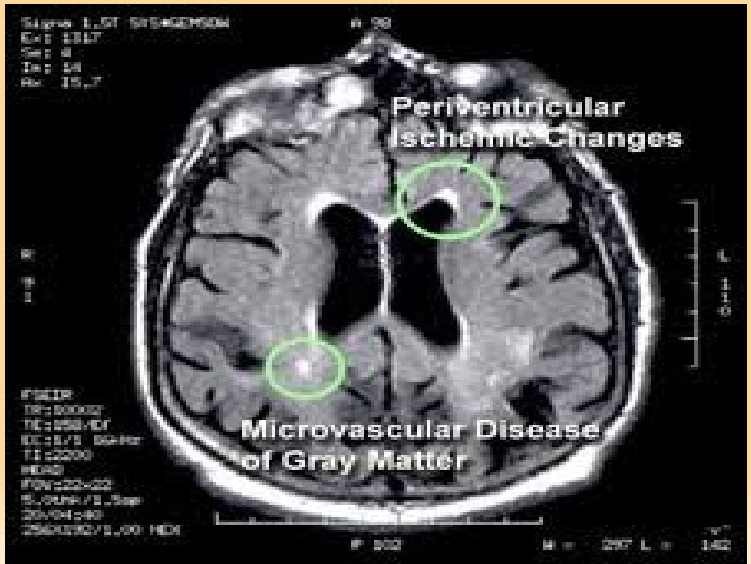
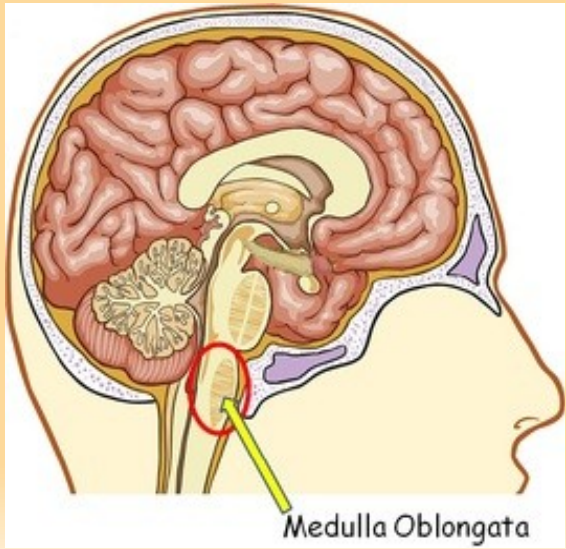
Do not allow catecholamines, 5-HT, acetylcholine etc. to enter brain in the active form.

Other sites for distribution of **lipid insoluble drugs in brain**:

- The blood-brain barrier is deficient at the
  - CTZ in the medulla oblongata
  - And at certain periventricular sites (anterior hypothalamus).

Even **lipid-insoluble drugs** are emetic





Exit of drugs from Brain

- Exit of drugs from the CSF and brain

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not dependent on lipid-solubility

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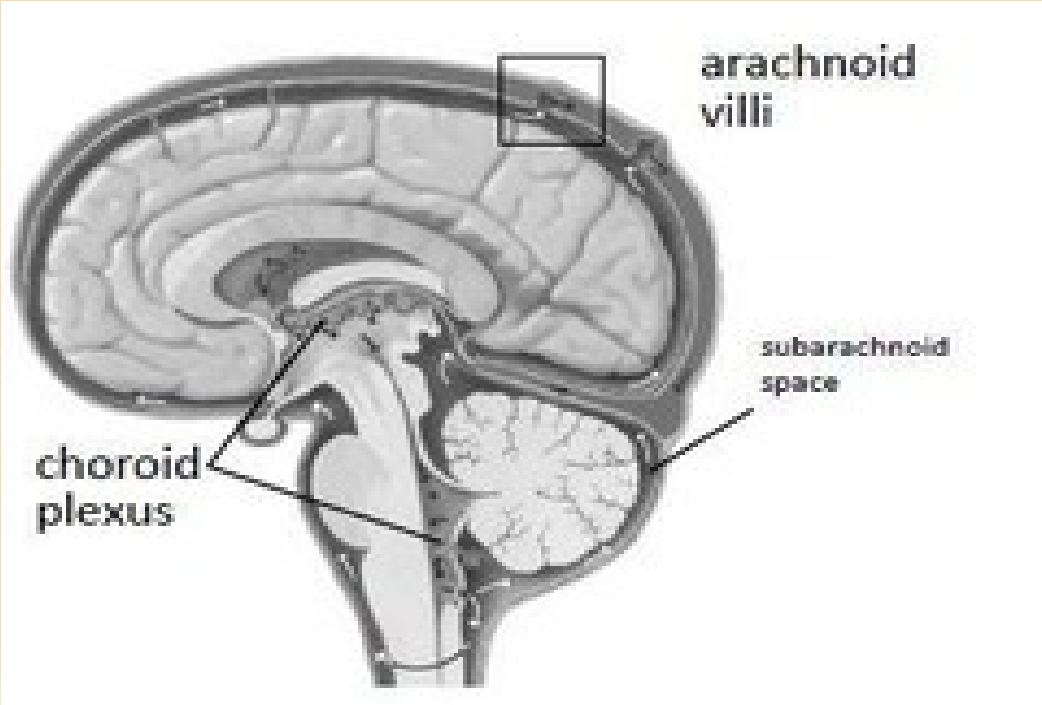
unrestricted

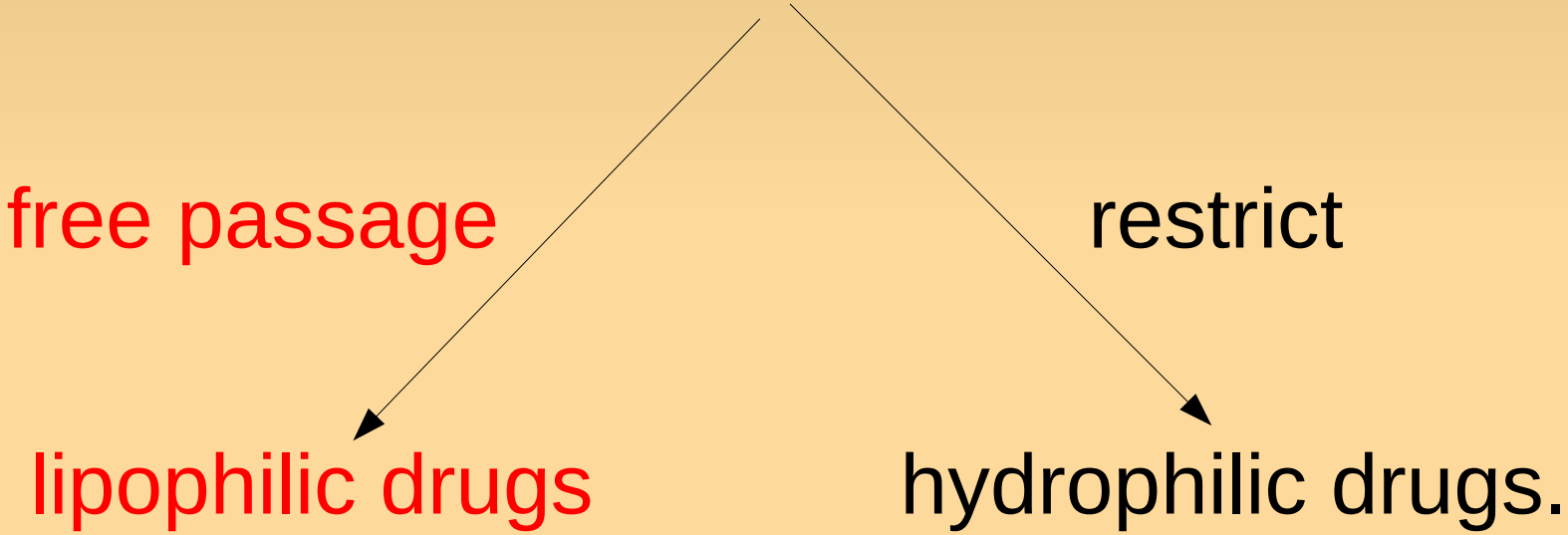
- **Bulk flow of CSF:** (along with the drug dissolved in it) occurs through
  - the arachnoid villi.
  - And **nonspecific organic anion** and **cation** transport processes.



Distribution across placenta

- **Passage across placenta**

Placental membranes (**lipoidal**)



- Placenta contain two type of transporter

  1. The placental efflux P-gp (efflux transporter)

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  limit foetal exposure to maternally administered drugs.

  2. Influx transporters-

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  Drug is transported into the placenta.

- **Nonlipidsoluble drugs**, when present in

  1. high concentration or

  2. for long periods in maternal circulation,

  ↓

  Enter into the foetus

- Placenta is an incomplete barrier and almost any drug taken by the mother can affect the foetus or the newborn.

Plama protein drug binding

- Drugs possess physicochemical affinity for plasma proteins.

bind to

Acidic drugs → plasma albumin

Basic drugs → alpha 1 acid glycoprotein.

- Albumin bindig is quantitatively more important.

- It is an Saturable process.

Binding may be lower

when large amounts of the drug are given.

Clinical implication of plasma protein binding

1. Highly plasma protein bound drugs

↓

restricted to the vascular compartment

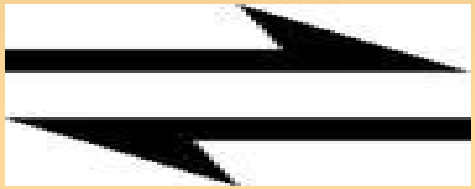
↓

Smaller volume of distribution

Drugs highly bound to plasma protein

To albumin	*To α_1-acid glycoprotein*
Barbiturates	β-blockers
Benzodiazepines	Bupivacaine
NSAIDs	Lidocaine
Valproic acid	Disopyramide
Phenytoin	Imipramine
Penicillins	Methadone
Sulfonamides	Prazosin
Tetracyclines	Quinidine
Tolbutamide	Verapamil
Warfarin	

- (ii) The bound fraction is not available for action, unless it is free.

Bound drug  Free drug

Therfore plasma protein binding provide temporary storage to the drugs in vascular compartment.

- (iii) High degree of protein binding generally makes the drug long acting, because

↓

bound fraction is not available for metabolism or excretion, unless it is actively extracted by liver or kidney tubules.

iv. **Plasma concentrations of the drug** =

Concentration of bound + Concentration of free drug.

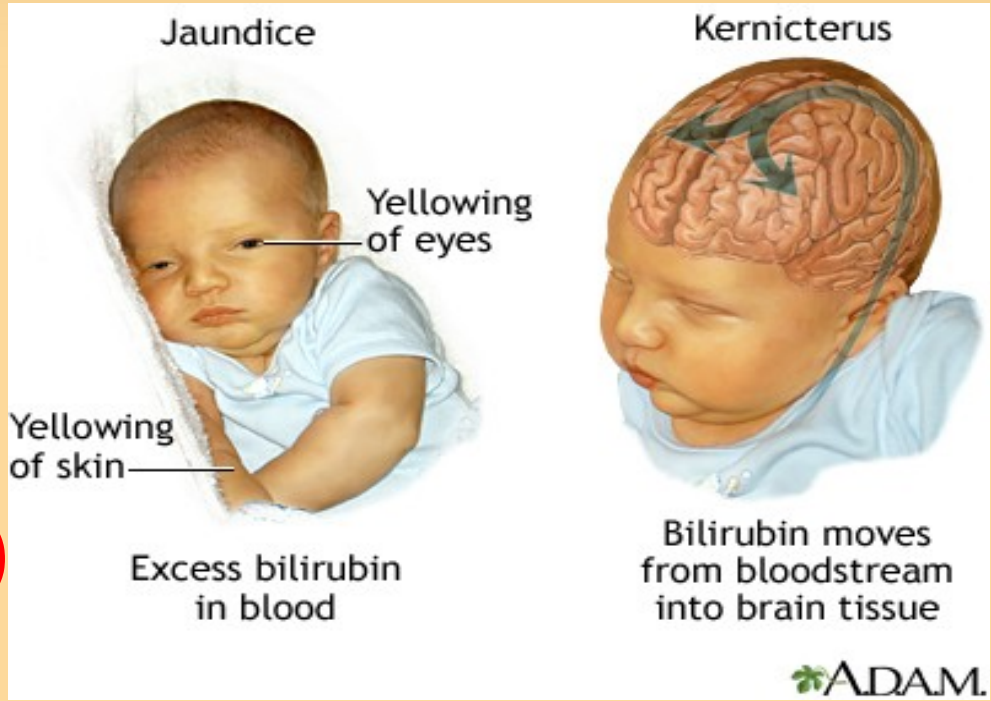
Displacement interactions

- V. One drug can bind to many sites on the albumin molecule.
- Conversely, more than one drug can bind to the same site.
- It lead to displacement interactions: drug bound with higher affinity will displace that bound with lower affinity.

- Two highly bound drugs do not necessarily displace each other.
- e.g. probenecid and indomethacin are highly bound to albumin but do not displace each other.
- Similarly, acidic drugs do not generally displace basic drugs and vice a versa

Clinically important displacement interactions

- Salicylates displace sulfonylureas.
- Indomethacin, phenytoin displace warfarin.
- Sulfonamides and vit K displace bilirubin (kernicterus in neonates)



- Salicylates displace methotrexate

(vi) In **hypoalbuminemia**,

↓

binding is reduced

↓

high concentrations of free drug

- e.g. phenytoin and furosemide.

- Some **diseases** may also alter drug binding

- Eg. propranolol binding is increased in
  - Pregnant women
  - And in patients with inflammatory disease.

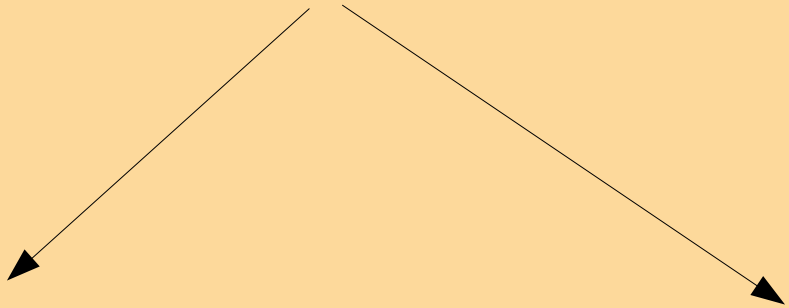
Plasma protein drug binding - Summary

- Acidic drug bind to albumine
- Basic drug bind to alpha1 acid glycoprotein
- It is Saturable process
- High plasma protein binding – small volume of distribution
- Bound fraction of drug is not available for action.
- High degree of protein binding generally makes the drug long acting
- Displacement interaction of drug from binding
- Disease: Hypoalbuminemia

Tissue storage

- Drugs may also accumulate in specific organs by active transport or get bound to specific tissue constituents.

Drugs sequestrated in various tissues



large volume of distribution

long duration of action.

Storage toxicity

- Some may exert local toxicity due to high concentration
- e.g. Tetracyclines on bone and teeth
  Chloroquine on retina.
- Drugs may also selectively bind to specific intracellular organelle
- e.g. Tetracycline to mitochondria
  Chloroquine to nuclei.

Drug concentrated in tissue

Skeletal muscle, heart	— digoxin, emetine (bound to muscle proteins).
Liver	— chloroquine, tetracyclines, emetine, digoxin.
Kidney	— digoxin, chloroquine, emetine.
Thyroid	— iodine.
Brain	— chlorpromazine, acetazolamide, isoniazid.
Retina	— chloroquine (bound to nucleoproteins).
Iris	— ephedrine, atropine (bound to melanin).
Bone and teeth	— tetracyclines, heavy metals (bound to mucopolysaccharides of connective tissue), bisphosphonates (bound to hydroxyapatite)
Adipose tissue	— thiopentone, ether, minocycline, phenoxybenzamine, DDT dissolve in neutral fat due to high lipid-solubility; remain stored due to poor blood supply of fat.