

ABSORPTION OF DRUGS

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ABSORPTION OF DRUGS

- The process by which a compound penetrates one or more biological membranes to gain entry into the body is called as absorption. Absorption is movement of the drug from its site of administration into the circulation. Not only the fraction of the administered dose that gets absorbed, but also the rate of absorption is important.
- Different route of administration like oral, transdermal, rectal, intramuscular, subcutaneous, nasal, inhalation etc. are used for administration of active ingredient inside the body. For a drug to be absorbed it needs to cross biological barriers to reach the general circulation and/or elicit a pharmacological response. Even drugs that are dosed intravenously may need to cross the vascular endothelium to reach the target tissue or distribute into blood cells.

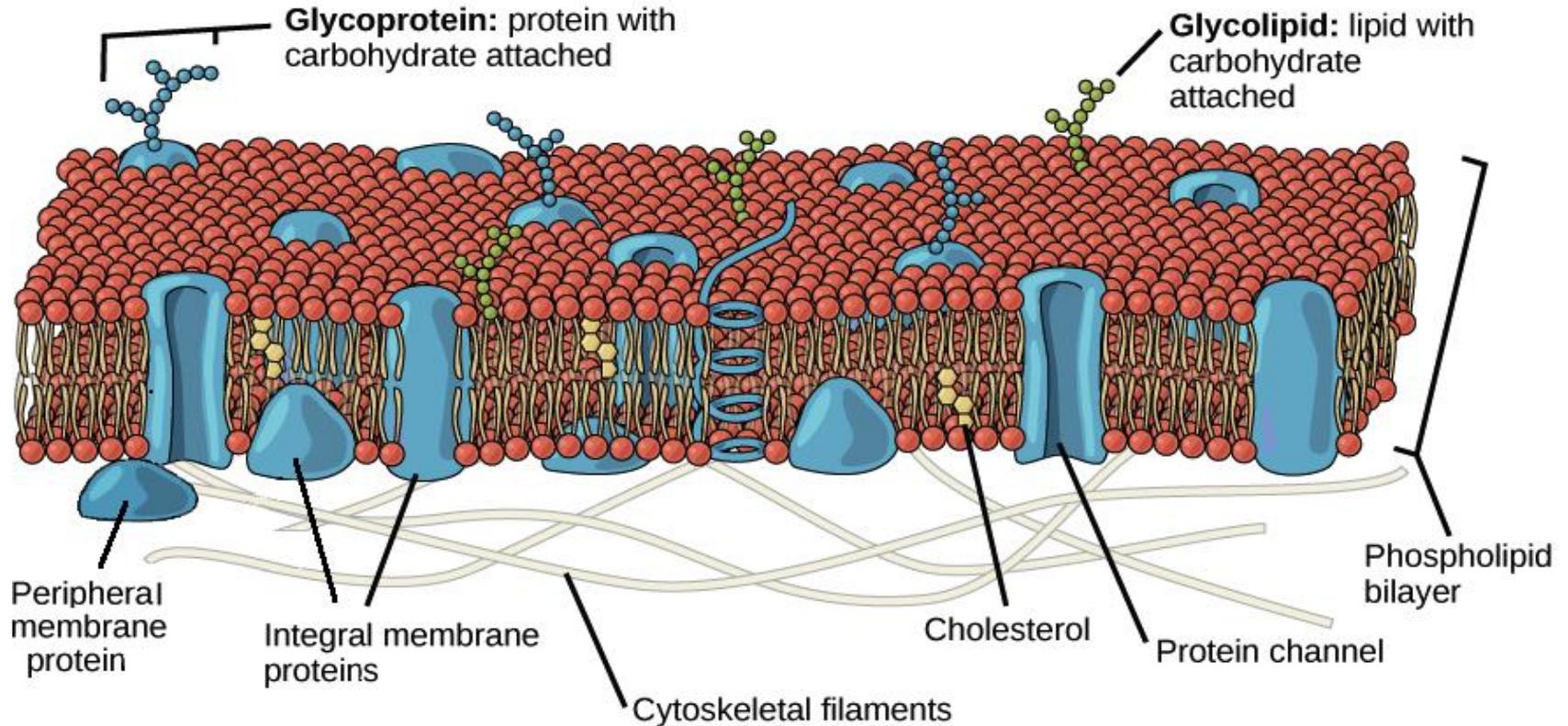
ABSORPTION OF DRUGS

- The onset of drug action depends on the rate of drug absorption. Like in case of i.v. injection, immediate and usually maximal pharmacological effect is seen whereas slow onset is seen when a drug is given by the oral route.

STRUCTURE OF CELL MEMBRANE

- Drugs administered by oral route must pass through a number of membranes in order to be absorbed into the systemic circulation. Therefore it is important to know about the cell membrane.
- The currently accepted model for the structure of the plasma membrane, called the **fluid mosaic model**, was first proposed in 1972.
- According to the fluid mosaic model, the plasma membrane is a mosaic of components—primarily, phospholipids, cholesterol, and proteins—that move freely and fluidly in the plane of the membrane.

STRUCTURE OF CELL MEMBRANE



STRUCTURE OF CELL MEMBRANE

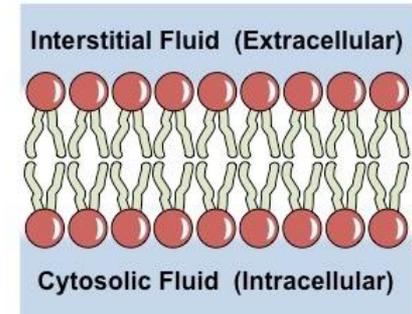
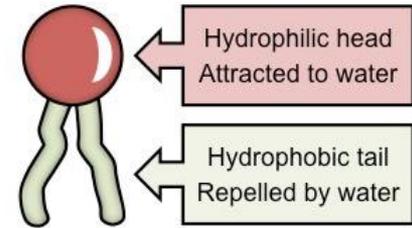
- The principal components of the plasma membrane are lipids (phospholipids and cholesterol), proteins, and carbohydrate groups that are attached to some of the lipids and proteins.
- A **phospholipid** is a lipid made of glycerol, two fatty acid tails, and a phosphate-linked head group. Biological membranes usually involve two layers of phospholipids with their tails pointing inward, an arrangement called a **phospholipid bilayer**.
- **Cholesterol**, another lipid composed of four fused carbon rings, is found alongside phospholipids in the core of the membrane.

STRUCTURE OF CELL MEMBRANE

- Membrane proteins may extend partway into the plasma membrane, cross the membrane entirely, or be loosely attached to its inside or outside face.
- Carbohydrate groups are present only on the outer surface of the plasma membrane and are attached to proteins, forming **glycoproteins**, or lipids, forming **glycolipids**.
- The proportions of proteins, lipids, and carbohydrates in the plasma membrane vary between different types of cells. For a typical human cell, however, proteins account for about 50 percent of the composition by mass, lipids (of all types) account for about 40 percent, and the remaining 10 percent comes from carbohydrates.

PHOSPHOLIPIDS

- Phospholipids, arranged in a bilayer, make up the basic fabric of the plasma membrane. They are well-suited for this role because they are **amphipathic**, meaning that they have both hydrophilic and hydrophobic regions.



PHOSPHOLIPIDS

- The **hydrophilic**, or “water-loving,” portion of a phospholipid is its head, which contains a negatively charged phosphate group as well as an additional small group, which may also be charged or polar. The hydrophilic heads of phospholipids in a membrane bilayer face outward, contacting the aqueous (watery) fluid both inside and outside the cell.
- The **hydrophobic**, or “water-fearing,” part of a phospholipid consists of its long, nonpolar fatty acid tails. The fatty acid tails can easily interact with other nonpolar molecules, but they interact poorly with water. Because of this, it’s more energetically favorable for the phospholipids to tuck their fatty acid tails away in the interior of the membrane, where they are shielded from the surrounding water.

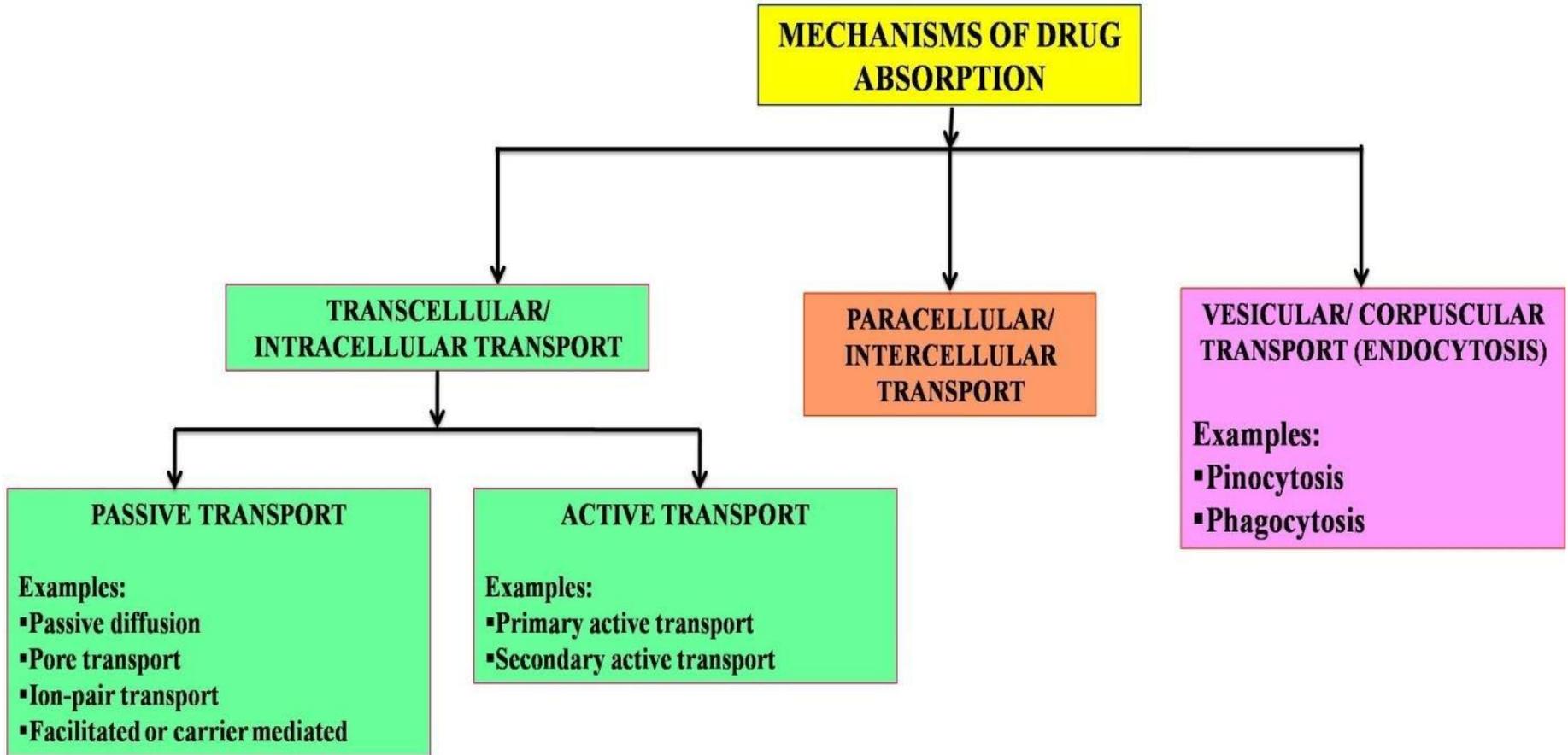
PROTEINS

- Proteins are the second major component of plasma membranes. There are two main categories of membrane proteins: integral and peripheral.
- Integral membrane proteins are integrated into the membrane. They have at least one hydrophobic region that anchors them to the hydrophobic core of the phospholipid bilayer. Proteins that extend all the way across the membrane are called transmembrane proteins.
- Peripheral membrane proteins are found on the outside and inside surfaces of membranes, attached either to integral proteins or to phospholipids. Unlike integral membrane proteins, peripheral membrane proteins do not stick into the hydrophobic core of the membrane, and they tend to be more loosely attached.

CARBOHYDRATES

- Carbohydrates are the third major component of plasma membranes. In general, they are found on the outside surface of cells and are bound either to proteins (forming **glycoproteins**) or to lipids (forming **glycolipids**). These carbohydrate chains may consist of 2-60 monosaccharide units and can be either straight or branched.
- Along with membrane proteins, these carbohydrates form distinctive cellular markers, sort of like molecular ID badges, that allow cells to recognize each other. These markers are very important in the immune system, allowing immune cells to differentiate between body cells, which they shouldn't attack, and foreign cells or tissues, which they should.

MECHANISM OF DRUG ABSORPTION



TRANSCELLULAR TRANSPORT

- This type of transport mechanism involves passage of drugs across the GI epithelium and is considered as the most common pathway for the drug transport.
- There are different transcellular transport processes through which the process of absorption takes place:
 - A. **Passive transport process** - This type of transport process does not require energy to traverse through the lipid bilayer. These are further classified as:
 - **Passive diffusion**
 - **Pore Transport**
 - **Ion pair transport**
 - **Facilitated Transport**

PASSIVE DIFFUSION

- Passive diffusion or non-ionic diffusion is considered as the major absorption process for more than 90% of drugs .
- It is the movement of the drug molecule from a region of higher concentration to a region of lower concentration. Concentration gradient or electrochemical gradient is considered as the driving force for this process.
- Movement of drugs across the membranes is a result of the kinetic energy of the molecule. Due to the fact that it does not require any energy, the process is known as passive diffusion.

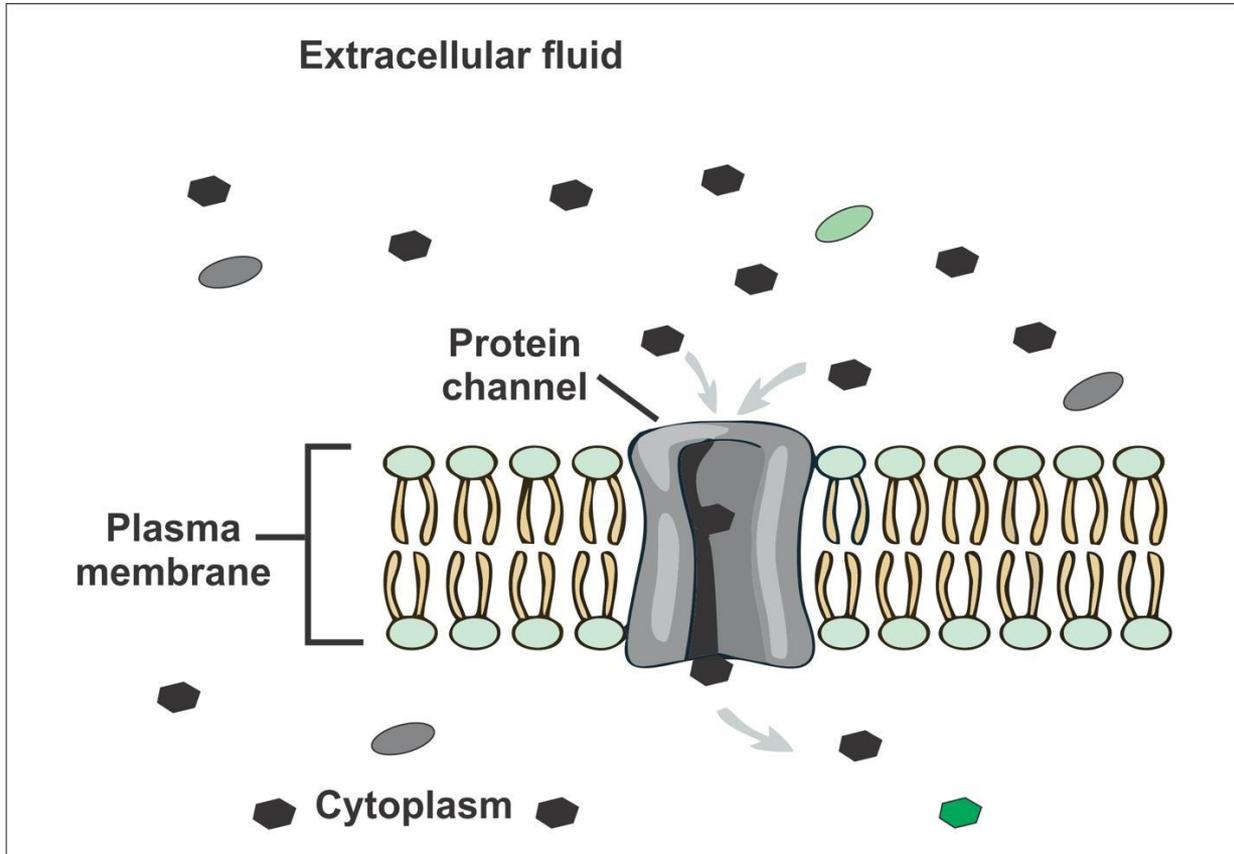
PASSIVE DIFFUSION

- Passive diffusion is expressed by Fick's law of diffusion which states that **“The drug molecules diffuse from a region of higher concentration to lower concentration until equilibrium is attained & rate of diffusion is directly proportional to the concentration gradient across the membrane”**.

PORE TRANSPORT

- Pore transport is also called as convective transport, bulk flow or filtration. This transport mechanism is responsible for the transportation of drug molecules via the protein channels into the cell.
- The hydrostatic pressure or the osmotic difference across the membrane constitutes the driving force such that the small solid molecules are transported along with the bulk flow of water through aqueous channels. This water flux is known as solvent drag.
- For absorption of molecules having low molecular weight (less than 100 daltons), low molecular size (i.e., smaller than pore diameter) and water soluble drugs, this process is of absorption is important.
- A certain type of protein called transport protein may form an open channel across the lipid membrane of the cell. Very small molecules, such as urea, water and sugars are able to rapidly cross the cell membrane through these pores.

PORE TRANSPORT



ION PAIR TRANSPORT

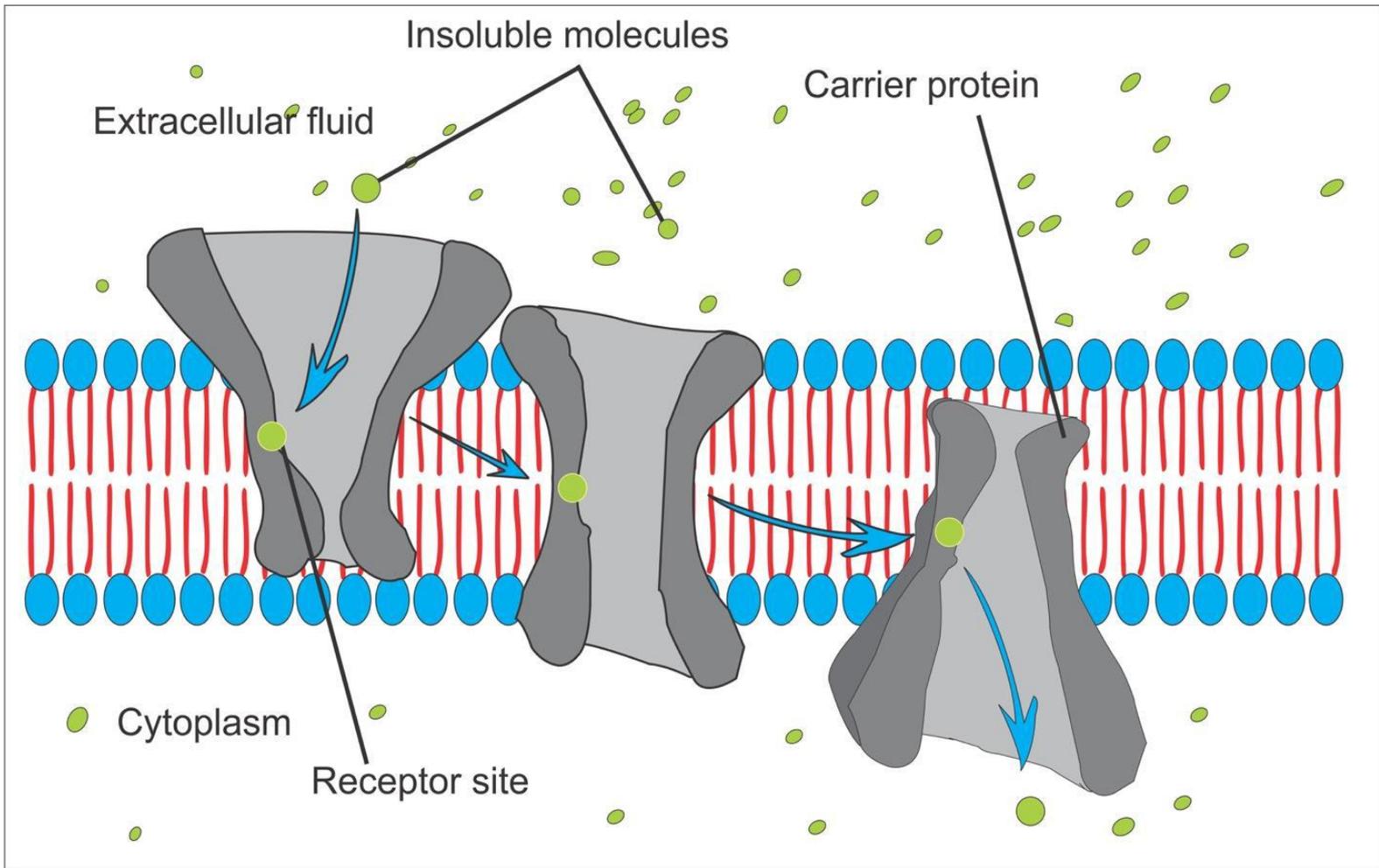
- This mechanism is particularly important for the absorption of drugs such as quaternary ammonium compounds and sulphonic acids, which readily ionise under all pH conditions.
- These compounds have low oil in water partition coefficient values, yet they are able to penetrate into the membrane by making reversible neutral complexes with endogenous ions of GIT like mucin. They form neutral complexes which have both suitable aqueous solubility as well as These compounds have low oil in water partition coefficient values, yet they are able to penetrate into the membrane by making reversible neutral complexes with endogenous ions of GIT like mucin. They form neutral complexes which have both suitable aqueous solubility as well as

FACILITATED OR CARRIER MEDIATED TRANSPORT

- The presence of some specialized transport mechanisms is suggested by the fact that some polar drugs traverse the cell membrane more easily than anticipated from their concentration gradient and partition coefficient values
- This mechanism involves a membrane component called as carrier which binds to the solute molecules reversibly or non-covalently. This complex crosses the membrane and then dissociates to release the solute molecule to the other side of the membrane. Carrier is then returned to the initial position across the membrane to start the cycle again.

FACILITATED OR CARRIER MEDIATED TRANSPORT

- Facilitated diffusion is a simple carrier mediated transport mechanism. The main features of this transport system is that transport occurs along the No energy expenditure is involved, because driving force is concentration gradient. This process is known as downhill transport process.
- Transport is saturable, and competition occurs between isomers. Facilitated diffusion has been used to explain cellular uptake of sugars and amino acids.
- A drug carrier is required but no energy is necessary. e.g. vitamin B12 transport. An intrinsic factor (IF), a glycoprotein produced by the gastric parietal cells, forms a complex with vitamin B12 which is then transported across the intestinal membrane by a carrier system.



FACILITATED OR CARRIER MEDIATED TRANSPORT

- Carrier proteins are composed of an uncharged (non-polar) outer surface which helps in the movement of the across the lipid membrane. The carrier proteins are not partial for any direction such that they work with the same efficiency on both the sides.
- This transport system works on a lock and key mechanism as the proteins are structure specific. As the process is structure specific, some false nutrients having the similar structure to that of the drug can also be transported.
- As there are limited sites on the carrier proteins so they are subjected to competition between the different agents having similar structure. This process is also capacity limited, since the number of carriers is limited. The system gets saturated at higher drug concentrations.

ACTIVE TRANSPORT

- Active transport process is a transport process in which materials are transported against the concentration gradient i.e. from a region of lower concentration to a higher concentration. It is also known as uphill transport.
- It uses energy from ATP to pull molecules from extracellular to intracellular side. It is a site specific transport i.e. it is not present throughout the GIT.
- The carrier molecule may be highly selective for the drug molecule, therefore, drugs of similar structure may compete for sites of adsorption on the carrier i.e. competitive inhibition is possible because only a certain amount of carrier is available. At times all the adsorption sites on the carrier may become saturated if the drug concentration gets very high.

PRIMARY ACTIVE TRANSPORT

- **Primary active transport:** This process involves direct requirement of the ATP molecules. The process is uniporter i.e. the process involves transfer of only one ion or molecule and is unidirectional. Carrier proteins which are involved in primary transport are further classified in two types:
 - 1. Ion transporters:** As the name suggests this process involves the transfer of ions across the cell membrane. Proton pump is a classic illustration of ATP-operated ion pump that is used when acidification of intracellular compartments take place. There are two types of ion transporters which play a vital role in the intestinal absorption-
 - a) **Organic anion transporter:** This helps in the absorption of active component like atorvastatin and pravastatin.
 - b) **Organic cation transporter:** This helps in the absorption of drugs like diphenhydramine.

ACTIVE TRANSPORT

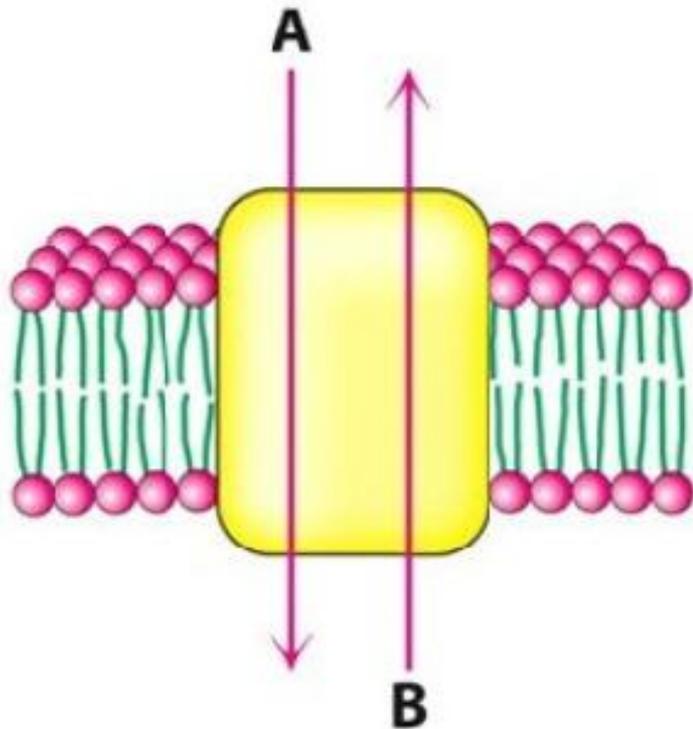
- 2. ABC (ATP- binding cassette) transporters:** Miniature foreign molecules (such as drugs and toxins) are primarily transported by this mechanism mainly out of the cells. They mediate only efflux of the solute from the cytoplasm, either to extracellular fluid or into an intracellular organelle (endoplasmic reticulum, mitochondria, etc.). P-glycoprotein (P-gp) is a classic illustration of such type of transport mechanism

SECONDARY ACTIVE TRANSPORT

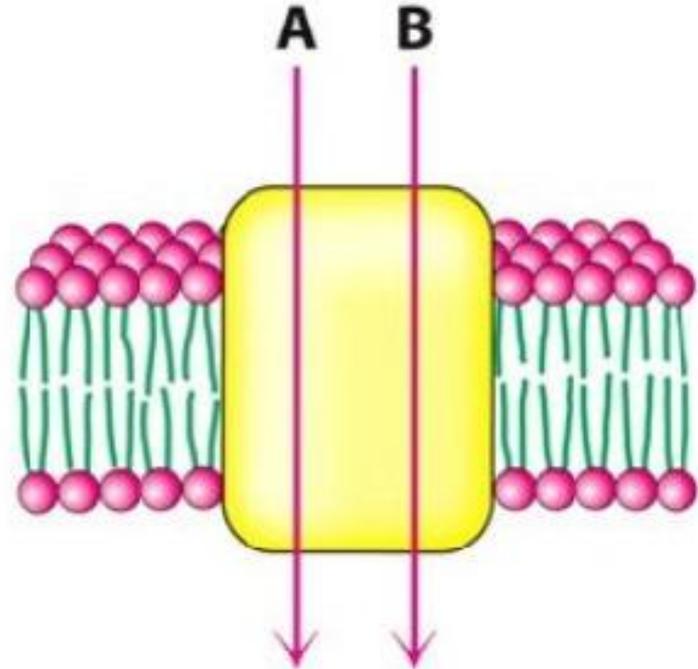
- **Secondary active transport:** In this transport there is no direct involvement of ATP because this process takes place due to previously existing concentration gradient. In this type of active transport effected by another set of SLC transporters, the energy to pump one solute is derived from the downhill movement of another solute (mostly Na^+).
- Transmembrane proteins involved in the secondary active transport are identified as cotransporters since they transport two types of molecules at the same time. On that account, secondary active transport is referred to the **ion-coupled transport**.

SECONDARY ACTIVE TRANSPORT

- Secondary active transport can further be classified into:
 1. **Symport (co-transport)**: In symport, both driving and driven molecules are transported in the same direction. The Na^+ /glucose cotransporter (SGLT1) is an example for symports in which both sodium and glucose are transported into the cell. It is found in kidney proximal tubules and the small intestine.
 2. **Antiport (counter-transport)**: In **antiport**, driving and driven ions are transported in the opposite directions. The Na^+ / Ca^{2+} exchanger (NCX) in muscle cells transports sodium ions into the cell while calcium ions are transported out of the cell.



Antiporter



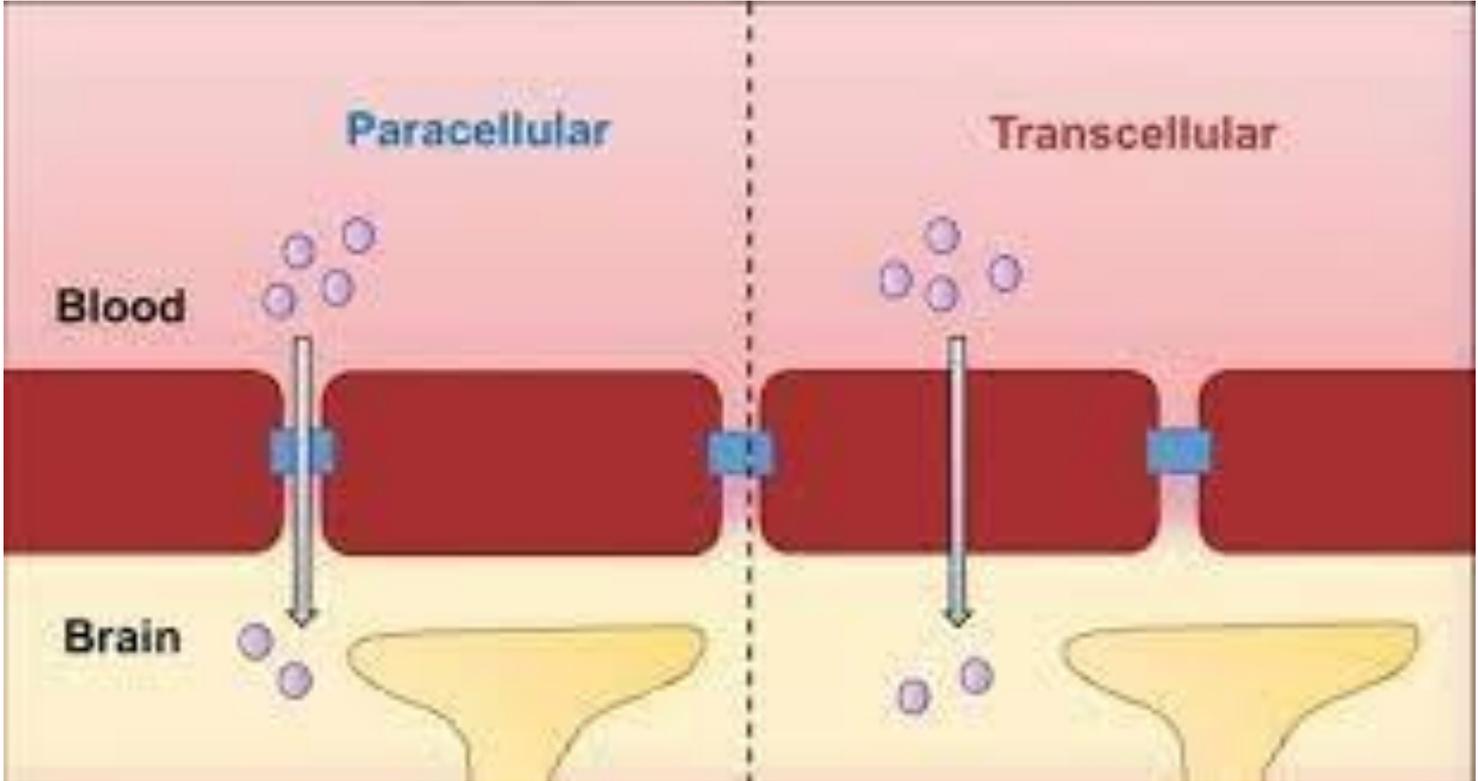
Symporter

PARACELLULAR/ INTERCELLULAR TRANSPORT

- This type of transport mechanism involves the transport of active components via the tight junctions between the GI epithelial cells.
- This pathway involves a small number of drugs so it is of less importance. The paracellular transport process has following two mechanisms:
 1. **Permeation via tight junctions of epithelial cells-** This process takes place through the tight junctions that are little wider than aqueous pores. Some examples of compounds which are taken up by this mechanism are insulin and cardiac glycosides.

PARACELLULAR/ INTRACELLULAR TRANSPORT

2. **Persorption** - This process involves the nonpermanent openings created by shedding of two adjacent epithelial cells into the lumen through which the drug is permeated.



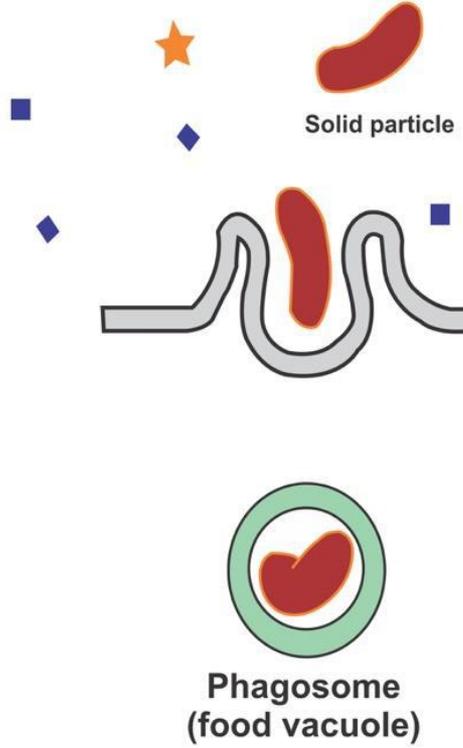
VESICULAR / CORPUSCULAR TRANSPORT

- Like active transport these process also involves the use of energy but differs in the case that it transports substances within the vesicles into the cell . The process can also be classified as transcellular, since the mechanism involves transport across the cell membrane.
- A mechanism for transcellular transport in which a cell encloses extracellular material in an invagination of the cell membrane to form a vesicle (endocytosis), then moves the vesicle across the cell to eject the material through the opposite cell membrane by the reverse process (exocytosis).
- Receptor-mediated endocytosis occurs when substrate binds to a specific membrane receptor. Substrates swallowed by cells in this way are stored in vesicles or they get degraded. Cellular uptake of immunoglobulin and low density lipoprotein occur when receptor-mediated endocytosis is involved.

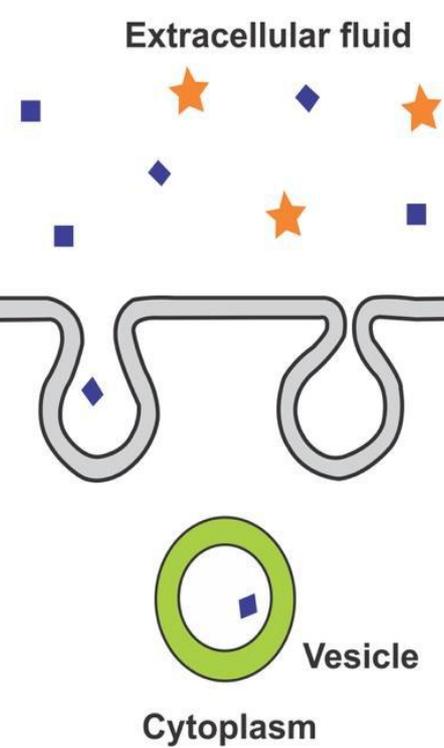
VESICULAR / CORPUSCULAR TRANSPORT

- Vesicular transport can be further distinguished into two categories such as:
 - 1. Pinocytosis (cell drinking):** Pinocytosis is a non-specific process whereby a substrate enters a cell by invagination to form an intracellular vesicle. Pinocytosis (“pino” means “to drink”) is a process by which the cell takes in the fluids along with dissolved small molecules. In this process, the cell membrane folds and creates small pockets and captures the cellular fluid and dissolved substances.
 - 2. Phagocytosis (cell eating):** In phagocytosis adsorptive uptake of solid substances takes place. **Phagocytosis** is the process by which a cell uses its plasma membrane to engulf a large particle ($\geq 0.5 \mu\text{m}$), giving rise to an internal compartment called the phagosome. It is one type of endocytosis. A cell that performs phagocytosis is called a phagocyte.

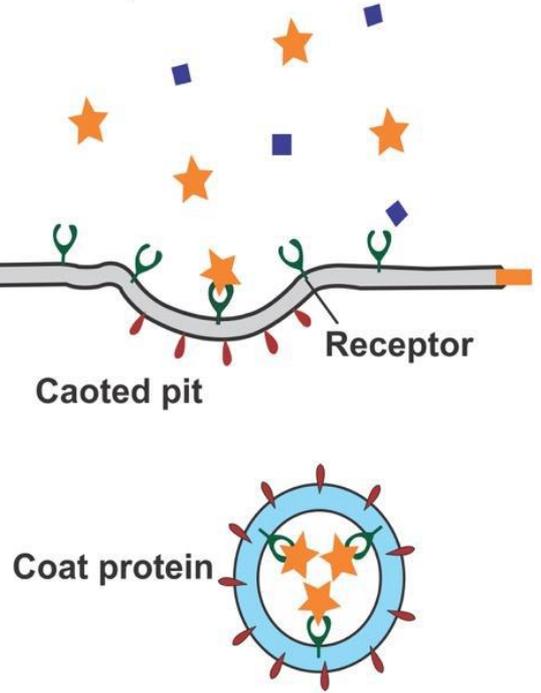
Phagocytosis



Pinocytosis



Receptor-mediated endocytosis



FACTORS AFFECTING ABSORPTION OF DRUGS

- Aqueous solubility- Drugs given in solid form must dissolve in the aqueous biophase before they are absorbed. For poorly water soluble drugs (aspirin, griseofulvin) rate of dissolution governs rate of absorption. Ketoconazole dissolves at low pH: gastric acid is needed for its absorption. Obviously, a drug given as watery solution is absorbed faster than when the same is given in solid form or as oily solution.
- Concentration- Passive diffusion depends on concentration gradient; drug given as concentrated solution is absorbed faster than from dilute solution.

FACTORS AFFECTING ABSORPTION OF DRUGS

- Area of absorbing surface- Larger is the surface area, faster is the absorption.
- Vascularity of the absorbing surface- Blood circulation removes the drug from the site of absorption and maintains the concentration gradient across the absorbing surface. Increased blood flow hastens drug absorption.
- Route of administration- This affects drug absorption, because each route has its own peculiarities.