Fluid balance & Transport across membranes

- Body is formed by solids and fluids.
- Fluid part is more than two third of the whole body.
- Water forms most of the fluid part of the body.
- In humans, the TBW varies from 45% to 75% of body weight.
- In females, water is less because of more amount of adipose tissue.
- In thin persons, water content is more than that in obese persons.
- In elderly, water content is decreased due to increase in adipose tissue.
- TBW in an average human weighing about 70 kg is about 42 L

COMPOSITION OF BODY FLUIDS

- Body fluids contain water and solids.
- Solids are organic and inorganic substances

Organic substances

- Organic substances are glucose, amino acids and other proteins, fatty acids and other lipids, hormones and enzymes

Inorganic substances

- Inorganic substances present in body fluids are sodium, potassium, calcium, magnesium, chloride, bicarbonate, phosphate and sulfate.

- ECF contains large quantity of Na^+, Cl^-, HCO_3^-, glucose, fatty acids and oxygen.
- ICF contains large quantities of K^+, Mg^{2+}, phosphates, sulfates and proteins.
- The pH of ECF is 7.4.
- The pH of ICF is 7.0.

- Maintenance of constant volume & stable composition important for homeostasis
- Abnormalities in control systems that maintain above causes many clinical symptoms
- There is continuous exchange of fluids & solutes with the external environment as well as different body compartments
- Fluid intake varies considerably & must be balanced by equal output from body to prevent body volumes to increase or decrease

Water intake

- Ingestion : about 1000ml/day
- End product of carbohydrate oxidation: 200ml/day
- Total intake about 1200ml/day but ingested water varies considerably

Water loss

- Evaporation through respiration & diffusion about 700ml/day (insensible water loss)
- Above independent of sweating
- Loss through sweat: variable but about 100ml/day
- Through faeces: about 100ml
- Loss through kidneys: most important and accounts for remaining loss
- Kidney most important regulator of water & electrolyte levels in body
- Loss varies from 0.5 l a day for a dehydrated person to 2 l daily.
- Electrolyte loss also varies considerably

body fluid compartments

- Two compartments

❖Extracellular fluid: mainly divided into plasma & interstitial fluid

❖Intracellular fluid

❖Also trans cellular fluid

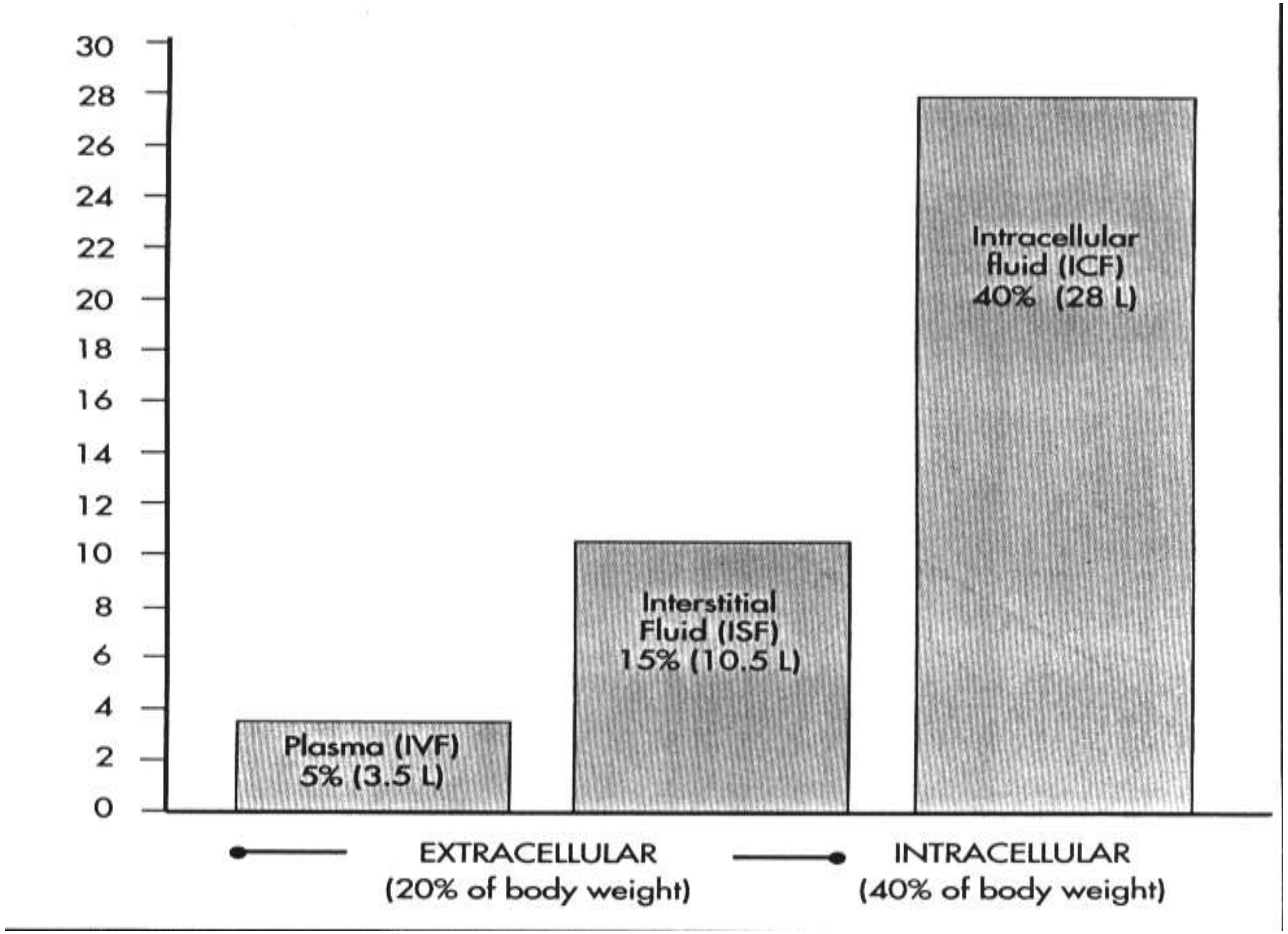
- An adult human being has about 42 liters fluids but varies with age

Intracellular fluid compartment

- Fluid inside cells
- About 28 liters
- Consists of different constituents but concetration’s are almost similar from cell to cell and in different animals

Major Compartments of Body Fluid

- 1. Intracellular fluid (ICF) - 40 % (2/3) TBW (in the adult)
- 2. Extracellular fluid (ECF) - 20 % (1/3) TBW
- a. interstitial fluid (ISF) - compartment between the cells (15 %)
- b. intravascular fluid (IVF)
- in addition to the ISF and IVF, special secretions (cerebrospinal fluid, intraocular fluid, and gastrointestinal secretions) form a small proportion (1 % to 2 % of body weight) of the extracellular fluid called transcellular fluid


30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
Plasma (IVF)
5% (3.5 L)
Interstitial
Fluid (ISF)
15% (10.5 L)
Intracellular
fluid (ICF)
40% (28 L)
EXTRACELLULAR
(20% of body weight)
INTRACELLULAR
(40% of body weight)

Extracellular fluid compartment

- All the fluid outside cells
- Is 20% body weight ---14 liters
- Interstitial fluid: is the fluid in the interstitial space between cells and is about 11 litres
- Plasma: the non cellular part of blood
- There is continuous exchange of substances between plasma & interstitial fluids through capillary pores
- The pores are permeable to most solutes except for proteins
- Due to above continuous mixing, composition is almost the same except for proteins

- MAJOR IONS

❖Extracellular fluid: sodium, calcium, chloride & bicarbonate

❖Intracellular fluid: potassium, magnesium, phosphates , proteins & other organic anions

❖Non electrolytes in plasma include cholesterol, phospholipids, neutral fats, glucose , urea, lactic acid , uric acid, creatinine, bilirubin & bile salts

Differences between extracellular fluid (ECF) and intracellular fluid (ICF)

	ECF	ICF
Sodium	142 mEq/L	14 mEq/L
Calcium	5 mEq/L	1 mEq/L
Potassium	4 mEq/L	140 mEq/L
Magnesium	3 mEq/L	28 mEq/L
Chloride	103 mEq/L	4 mEq/L
Bicarbonate	28 mEq/L	10 mEq/L
Proteins	2 g/dL	16 g/dL

Major electrolytes and their distribution

- Sodium (Na^+) - chief cation of the ECF
- Potassium (K^+) - the chief cation of the ICF
- Calcium (Ca^{++})
- Magnesium (Mg^{++})
- Chloride (Cl^-) - chief anion of the ECF
- Bicarbonate (HCO_3^-) - chief anion of the ECF
- Phosphate (HPO_4^{2--}) - chief anion of the ICF

Major electrolytes and their distribution - 2

- Sodium plays a major role in controlling total body fluid volume; potassium is important in controlling the volume of the cell
- The law of electrical neutrality states that the sum of negative charges must be equal to the sum of positive charges (measured in milliequivalents) in any particular compartment

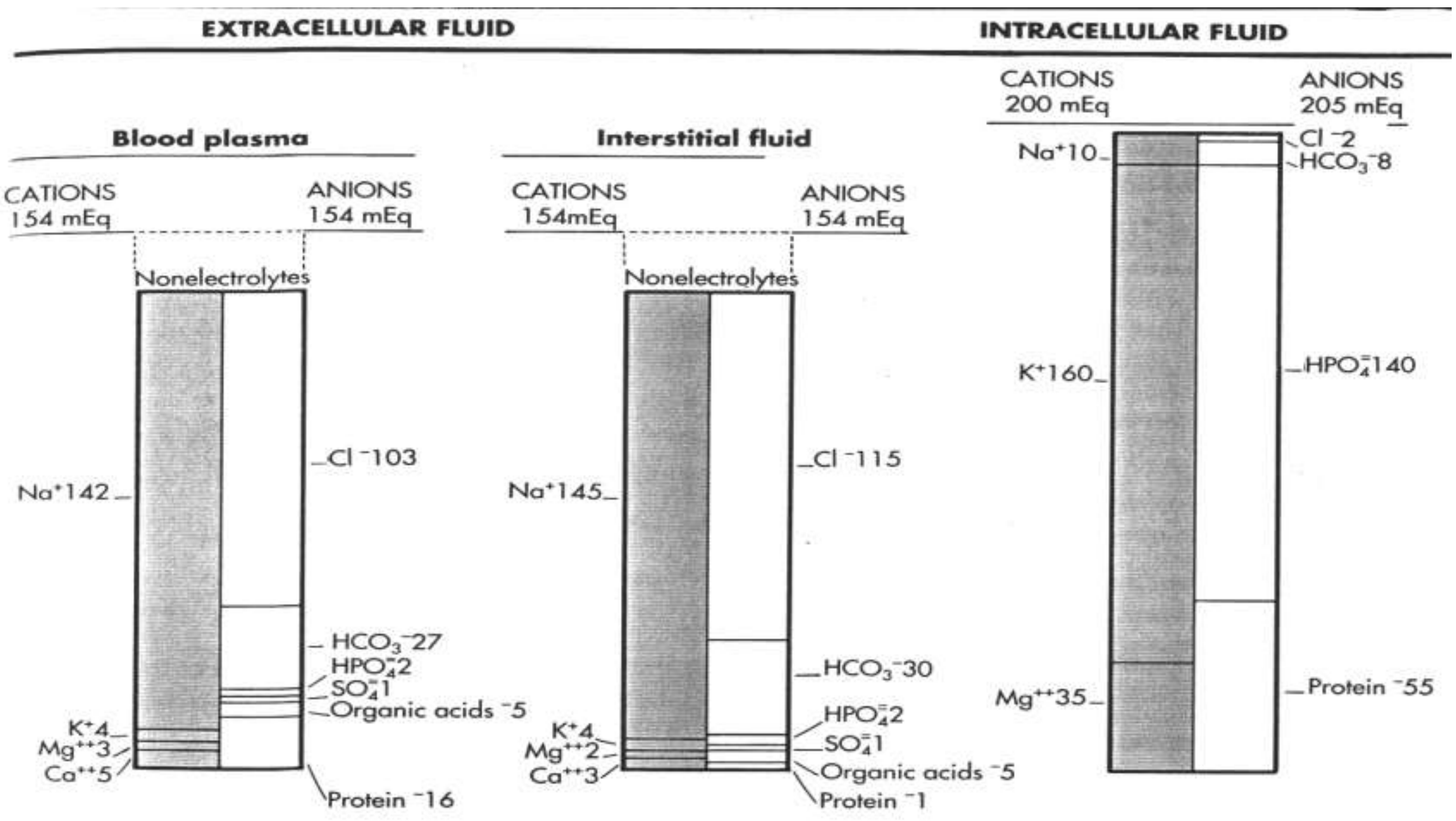
Major electrolytes and their distribution - 3

- Ionic composition of the ISF and IVF is very similar.
- Only difference being proteins since only a few proteins leak out of capillary membrane
- As such, ISF contains very little protein as compared with the IVF.
- The protein in plasma plays a significant role in maintaining the volume of the IVF.
- Conc’n of cations more in plasma than interstitial fluid(proteins have net –ve charge hence binding cations such as sodium & potassium
- Anions more in interstitial fluid due to the same above however, ionic conc’n considered equal in plasma & interstitial fluids

Composition of extracellular fluids and intracellular fluids

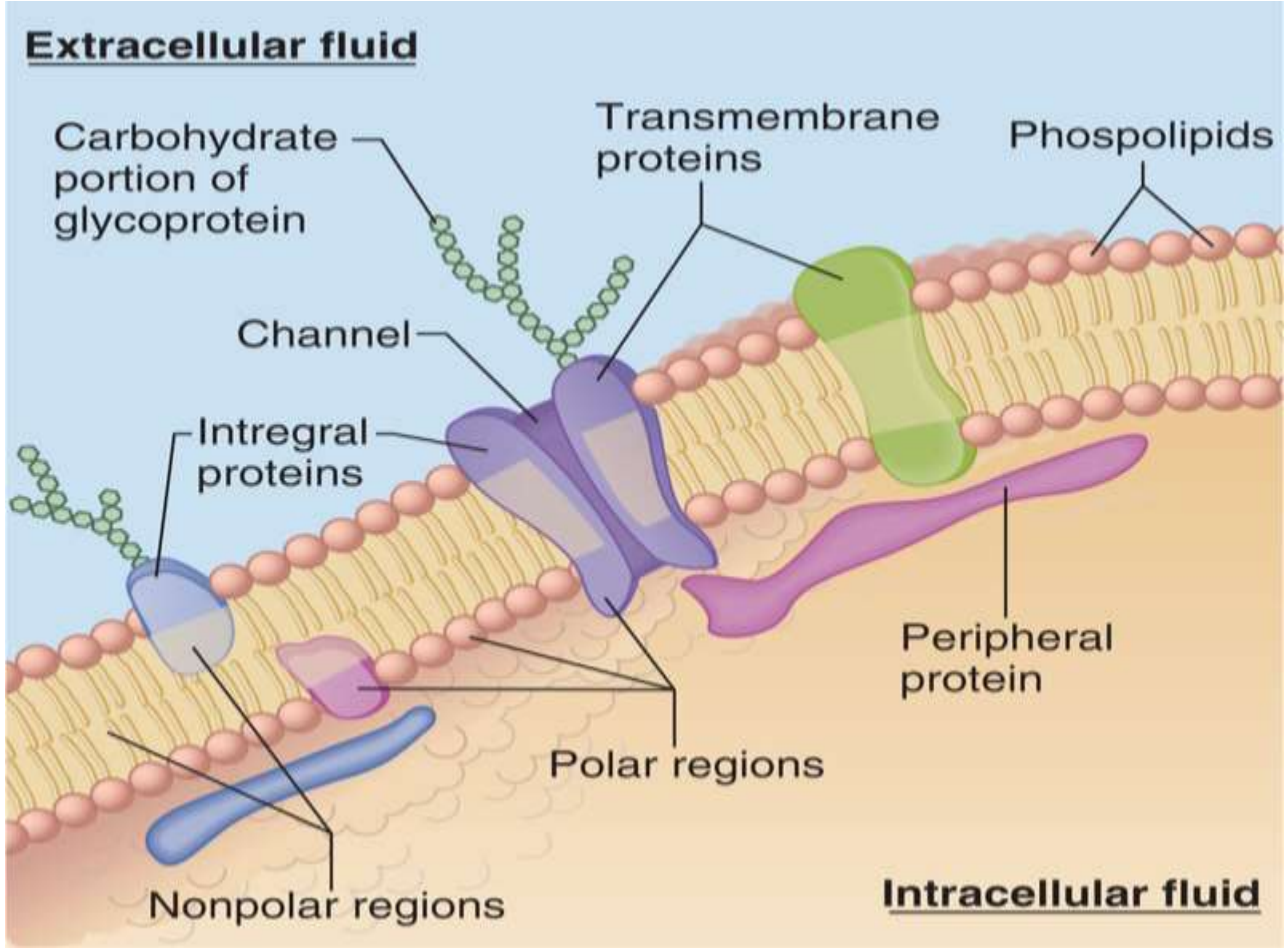
Ions	extracellular fluid (mOsm/l)	Interstitial fluid (mOsmol/l)
• Na+	142	139
• k+	4.2	4
• Ca++	1.3	1.2
• Mg++	0.8	0.7
• Cl-	108	108
• HCO3-	24	28.3
• HPO4-	2	2
• Glucose	5.6	5.6
• Protein	1.2	0.2
• Urea	4	4

Major electrolytes and their distribution



Transport across membranes

- All cells are surrounded by a plasma membrane.
- Cell membranes are composed of a lipid bilayer with globular proteins embedded in the bilayer.
- On the external surface, carbohydrate groups join with lipids to form glycolipids, and with proteins to form glycoproteins. These function as cell identity markers.



Transport across membranes

- Cell membrane consists a *lipid bilayer containing larg*e numbers of protein molecules in the lipid, many of which penetrate all the way through the membrane
- Lipid bilayer constitutes a barrier against movement of water and water-soluble substances between the ECF and ICF
- Lipid soluble substances can penetrate through this lipid bilayer by diffusion

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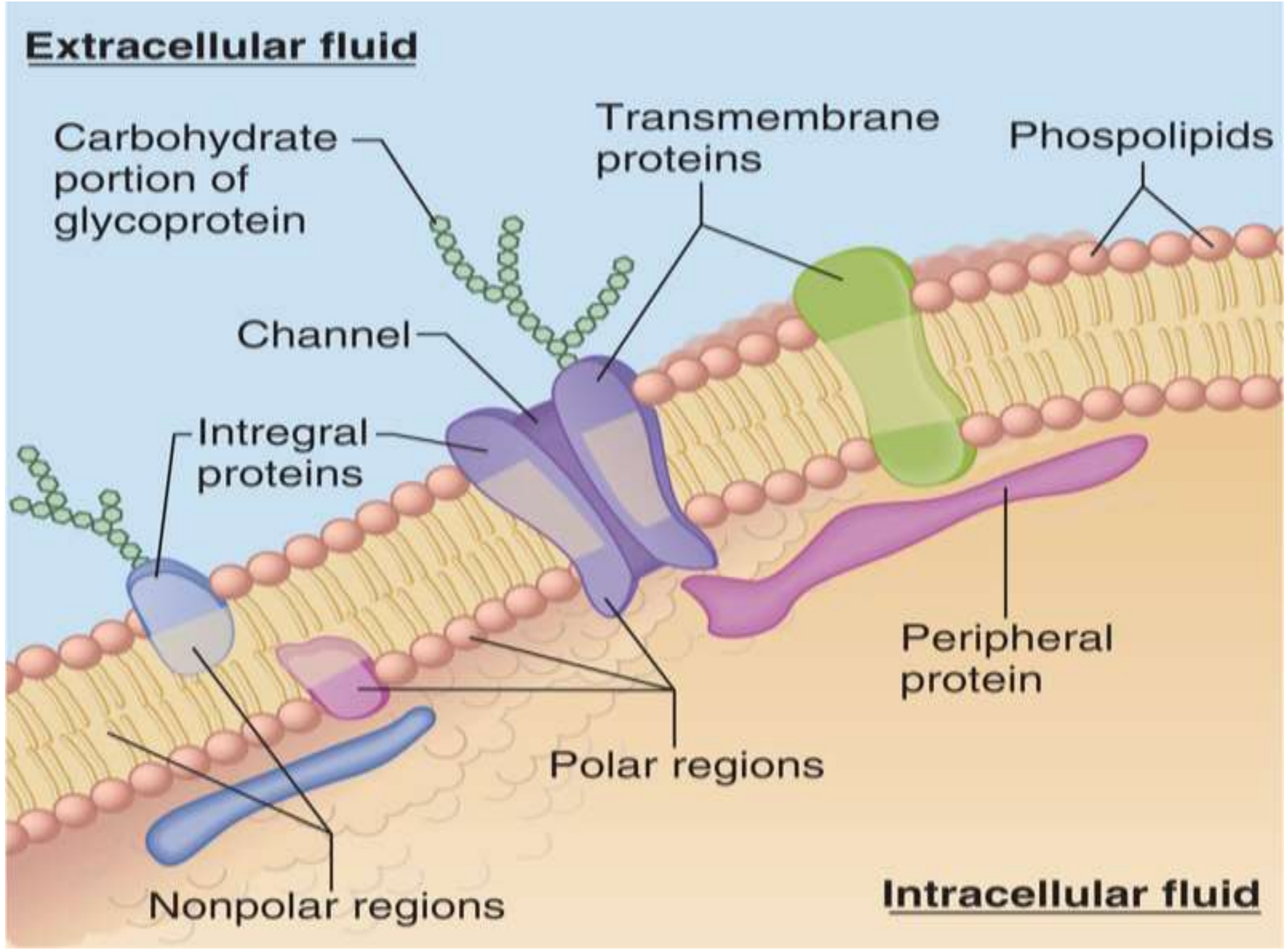
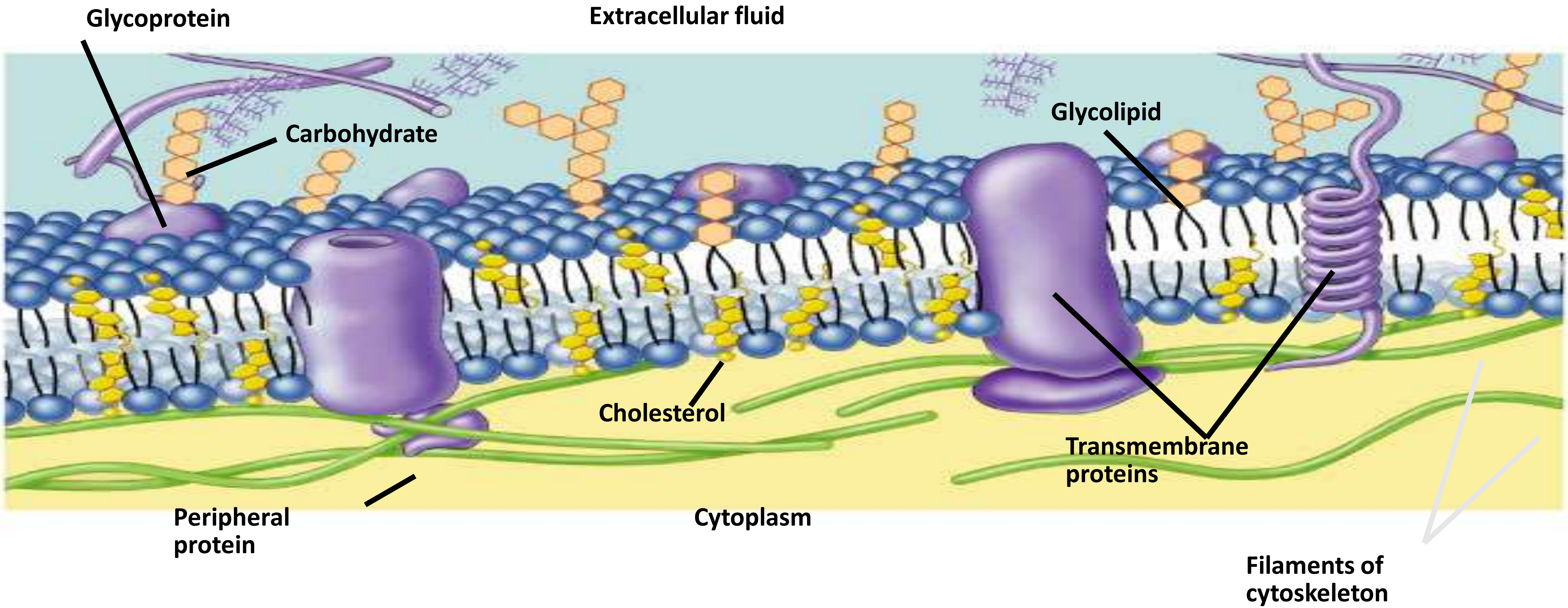


- protein molecules in the membrane have different properties for transporting substances.
- They interrupt the continuity of lipid bilayer, constituting an alternative pathway through the cell membrane.
- Most of these penetrating proteins function as *transport proteins.*
- Different proteins function differently.

- Some have watery spaces all the way through the molecule and allow free movement of water as well as selected ions or molecules and are called *channel proteins.*
- Others, called *carrier proteins,* bind with molecules or ions that are to be transported; conformational changes in the protein molecules then move the substances through the interstices of the protein to the other side of the membrane.

Fluid Mosaic Model



- Both the channel proteins and the carrier proteins are usually highly selective in the types of molecules or ions that are allowed to cross the membrane.

“Diffusion” Versus “Active Transport.

- Transport through the cell membrane, either through lipid bilayer or through proteins, occurs either by *diffusion* or *active transport.*
- Although there are many variations of these basic mechanisms, diffusion means random molecular movement of substances molecule by molecule, either through intermolecular spaces in the membrane or in combination with a carrier protein.
- Energy causing diffusion is the energy of the normal kinetic motion of matter.

- Active transport means movement of ions or other substances across the membrane in combination with a carrier protein in such a way that the carrier protein causes the substance to move against an energy gradient, such as from a low-concentration state to a high-concentration state.
- Movement requires an additional source of energy besides kinetic energy.

Diffusion

- All molecules and ions in the body fluids, including water molecules and dissolved substances, are in constant motion, each particle moving its own separate way.
- Motion of these particles is what physicists call “heat”—the greater the motion, the higher the temperature—
- The motion never ceases under any condition except at absolute zero temperature.

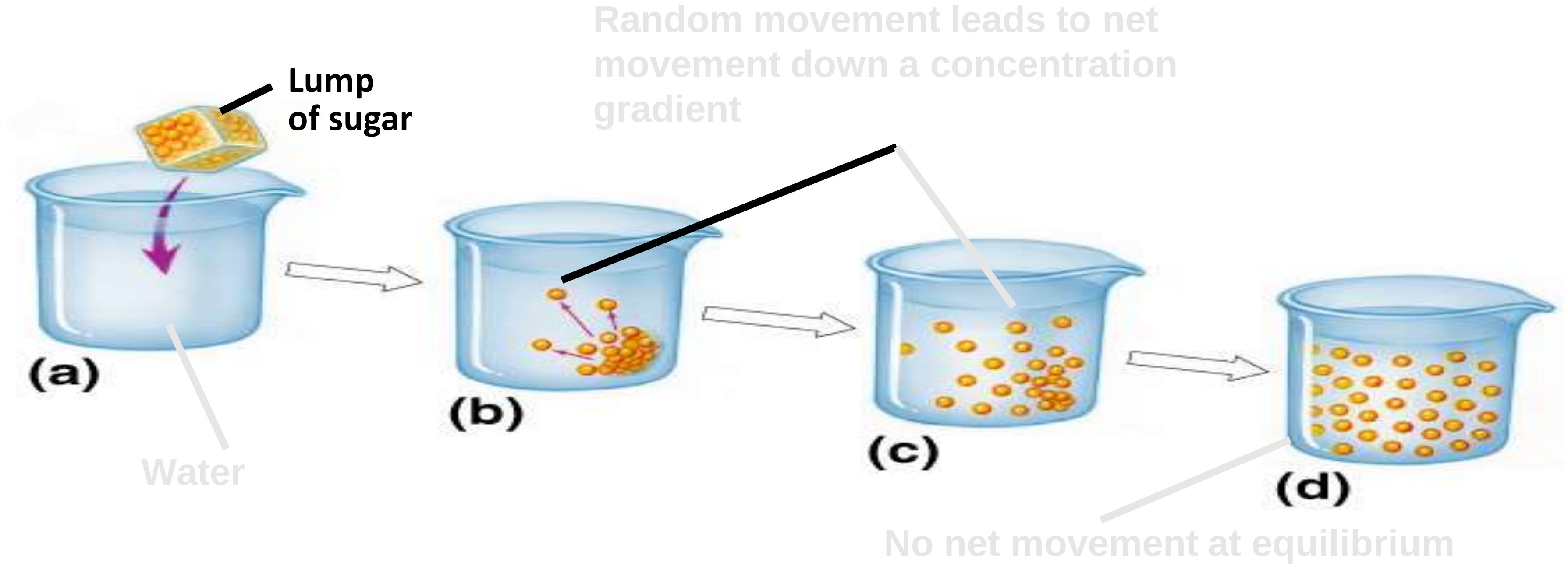
- When moving molecule, A, approaches a stationary molecule, B, the electrostatic and other nuclear forces of molecule A repel molecule B, transferring some of the energy of motion of molecule A to molecule B
- Consequently, molecule B gains kinetic energy of motion, while molecule A slows down, losing some of its kinetic energy.

- Thus, a single molecule in a solution bounces among the other molecules first in one direction, then another, then another, and so forth, randomly bouncing thousands of times each second.
- This continual movement of molecules among one another in liquids or in gases is called *diffusion.*

- Ions diffuse in the same manner as whole molecules, and even suspended colloid particles diffuse in a similar manner, except that the colloids diffuse far less rapidly than molecular substances because of their large size.

Diffusion

- The net movement of a substance from an area of higher concentration to an area of lower concentration - down a concentration gradient
- Caused by the constant random motion of all atoms and molecules
- Movement of individual atoms & molecules is random, but each substance moves down its own concentration gradient.



Diffusion Through the Cell Membrane

- divided into 2
- *simple diffusion* and *facilitated diffusion.*
- Simple diffusion means that kinetic movement of molecules or ions occurs through a membrane opening or through intermolecular spaces without any interaction with carrier proteins in the membrane.
- Diffusion rate determined by amount of substance available, the velocity of kinetic motion, and the number and sizes of openings in the membrane through which the molecules or ions can move.

- Facilitated diffusion requires interaction of a carrier protein.
- Carrier protein aids passage of the molecules or ions through the membrane by binding chemically with them and shuttling them through the membrane in this form.

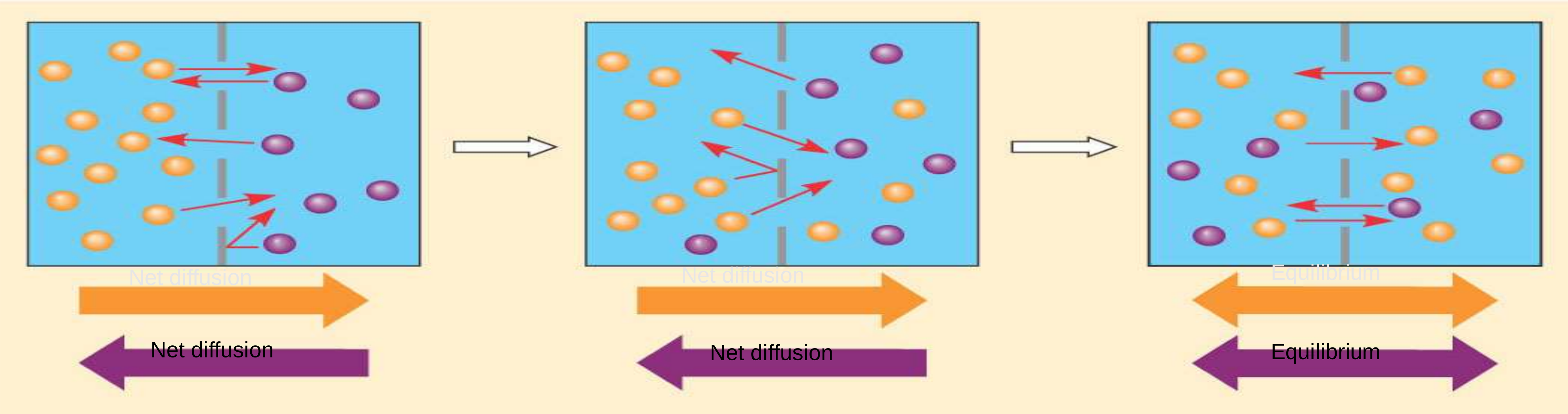
- Simple diffusion can occur through the cell membrane by two pathways:
- (1) through the interstices of the lipid bilayer if the diffusing substance is lipid soluble, and
- (2) through watery channels that penetrate all the way through some of the large transport proteins,

Diffusion Across a Membrane

- The membrane has pores large enough for the molecules to pass through.
- Random movement of the molecules will cause some to pass through the pores; this will happen more often on the side with more molecules. The dye diffuses from where it is more concentrated to where it is less concentrated
- This leads to a dynamic equilibrium: The solute molecules continue to cross the membrane, but at equal rates in both directions.

Diffusion Across a Membrane

- Two different solutes are separated by a membrane that is permeable to both
- Each solute diffuses down its own concentration gradient.
- There will be a net diffusion of the purple molecules toward the left, even though the total solute concentration was initially greater on the left side



FACTORS AFFECTING RATE OF DIFFUSION

- Rate of diffusion of substances through the cell membrane is affected by the following factors:
- 1. Permeability of the Cell Membrane
- Rate of diffusion is directly proportional to the permeability of cell membrane.
- Since the cell membrane is selectively permeable, only limited number of substances can diffuse through the membrane.
- 2. Temperature
- Rate of diffusion is directly proportional to the body temperature. Increase in temperature increases the rate of diffusion. This is because of the thermal motion of molecules during increased temperature

- 3. Concentration Gradient or Electrical Gradient of the Substance across the Cell Membrane
- Rate of diffusion is directly proportional to the concentration gradient or electrical gradient of the diffusing substances across the cell membrane.
- However, facilitated diffusion has some limitation beyond certain level of concentration gradient.
- 4. Solubility of the Substance
- Diffusion rate is directly proportional to the solubility of substances, particularly the lipid-soluble substances.
- Since oxygen is highly soluble in lipids, it diffuses very rapidly through the lipid layer

- 5. Thickness of the Cell Membrane
- Rate of diffusion is inversely proportional to the thickness of the cell membrane.
- If the cell membrane is thick, diffusion of the substances is very slow.
- 6. Size of the Molecules
- Rate of diffusion is inversely proportional to the size of the molecules.
- Thus, the substances with smaller molecules diffuse rapidly than the substances with larger molecules.

- 7. Size of the Ions
- Generally, rate of diffusion is inversely proportional to the size of the ions.
- Smaller ions can pass through the membrane more easily than larger ions with the same charge. However, it is not applicable always. For instance, Na^+ ions are smaller in size than K^+ ions. Still, Na^+ ions cannot pass through the membrane as K^+ ions because Na^+ ions have a tendency to gather water molecules around them thus making it difficult for Na^+ ions to diffuse through the membrane.

- 8. Charge of the Ions
- Rate of diffusion is inversely proportional to the charge of the ions.
- The greater the charge of the ions, lesser the rate of diffusion.

The Permeability of the Lipid Bilayer

- Permeability Factors
  - Lipid solubility
  - Size
  - Charge
  - Presence of channels and transporters
- Hydrophobic molecules are lipid soluble and can pass through the membrane rapidly
- Polar molecules do not cross the membrane rapidly
- Transport proteins allow passage of hydrophilic substances across the membrane

Diffusion of Lipid-Soluble Substances Through the Lipid Bilayer.

- most important factor determining how rapidly a substance diffuses through the lipid bilayer is the *lipid solubility* of the substance
- Oxygen, nitrogen, CO2 have high lipid solubility and dissolves rapidly through bilayer
- Diffusion rate through bilayer proportional to lipid solubility hence large amounts of O2 can be delivered to the interior of the cell almost as though the cell membrane did not exist

Diffusion of Water and Other Lipid-Insoluble Molecules Through Protein Channels

- water readily passes through channels in protein molecules that penetrate all the way through the membrane.
- It moves very rapidly through the cell membrane
- Eg, water that diffuses in each direction through the red cell membrane per second is about 100 times as great as the volume of the red cell itself.

- Other hydrophilic molecules can pass through the protein pore channels in same way as water if they are small enough.
- As they become larger, their penetration decreases
- off rapidly.
- Eg, Diameter of urea molecule only about 20% greater than that of water, yet penetration through the cell membrane pores is about 1000 times less
- Even so, given the astonishing rate of water penetration, this amount of urea penetration still allows rapid transport of urea through the membrane within minutes.

Diffusion Through Protein Channels, and “Gating” of These Channels

- These channels are tubular pathways all the way from the extracellular to the intracellular fluid
- Therefore, substances can move by simple diffusion directly along these channels from one side of the membrane to the other.
- The protein channels are distinguished by 2 characteristics:
- (1) Are often selectively permeable to certain substances,
- (2) many of the channels can be opened or closed by *gates.*

Selective Permeability of Protein Channels

- Many of protein channels very selective for transport of one or more specific ions or molecules.
- Results from the characteristics of the channel itself, such as diameter, shape, and nature of electrical charges and chemical bonds along its inside surfaces.
- Eg, The *sodium channel,* is 0.3 by 0.5 nanometer in diameter, with the inner surfaces being *strongly -vely*
- These –ve charges pull the Na ions into these channels
- Once in the channel, they diffuse in either direction according to the usual laws of diffusion.
- Thus, the Na channel is specifically selective for passage of Na ions

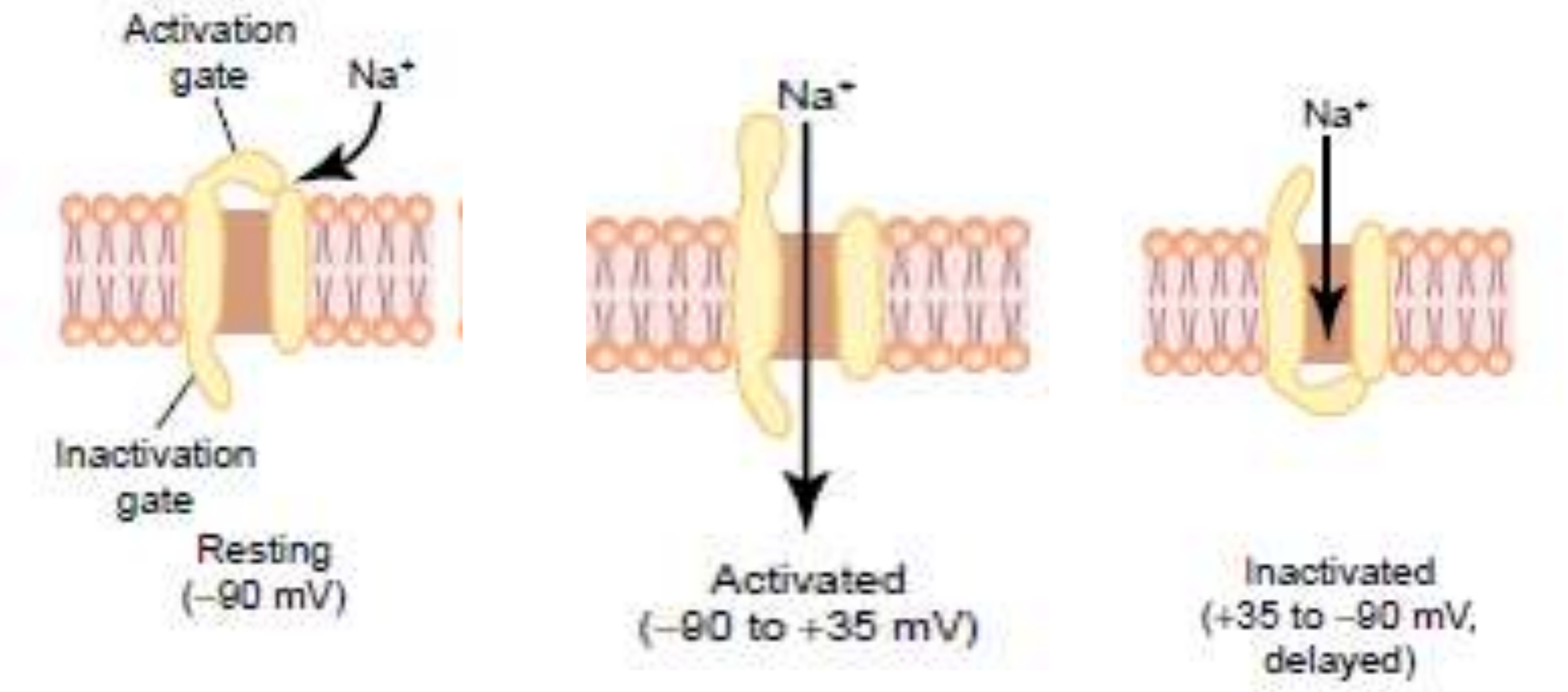
Gating of Protein Channels

- Gating of protein channels provides a means of controlling ion permeability of the channels.
- Some of the gates are actual gate like extensions of the transport protein molecule, which can close the opening of the channel or can be lifted away from the opening by a conformational change in the shape of the protein molecule itself.
- The opening and closing of gates are controlled in two principal ways

Voltage gating

- Here, molecular conformation of the gate or of its chemical bonds responds to the electrical potential across the cell membrane.
- For instance, in when there is an activation gate and an inactivation gate.
- At potential of -90mv, the activation gate is closed with inactivation gate open
- As voltage increases from -90 upwards, the activation gate opens allowing diffusion of Na ions
- As the voltage reaches 0 the inactivation gate closes stopping any further diffusion of Na

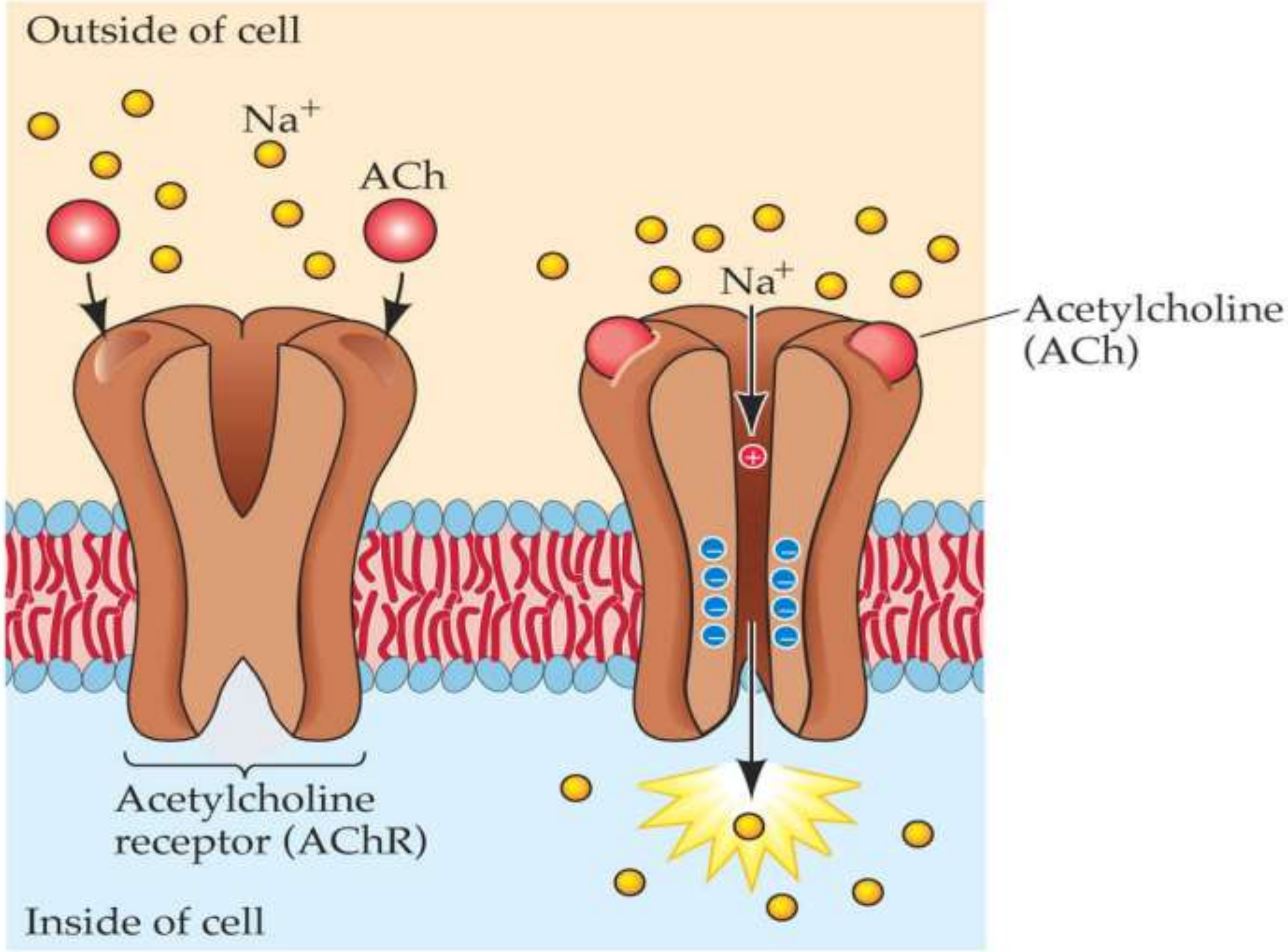
Voltage-Gated Sodium Channels



Chemical (ligand) gating

- Some protein channel gates are opened by the binding of a chemical substance (a ligand) with the protein; this causes a conformational or chemical bonding change in the protein molecule that opens or closes the gate.
- Called *chemical gating* or *ligand gating.*
- Most important is the effect of acetylcholine on the so-called *acetylcholine channel.*

Ion channel



LIFE: THE SCIENCE OF BIOLOGY, Seventh Edition, Figure 15.5 A Gated Ion Channel

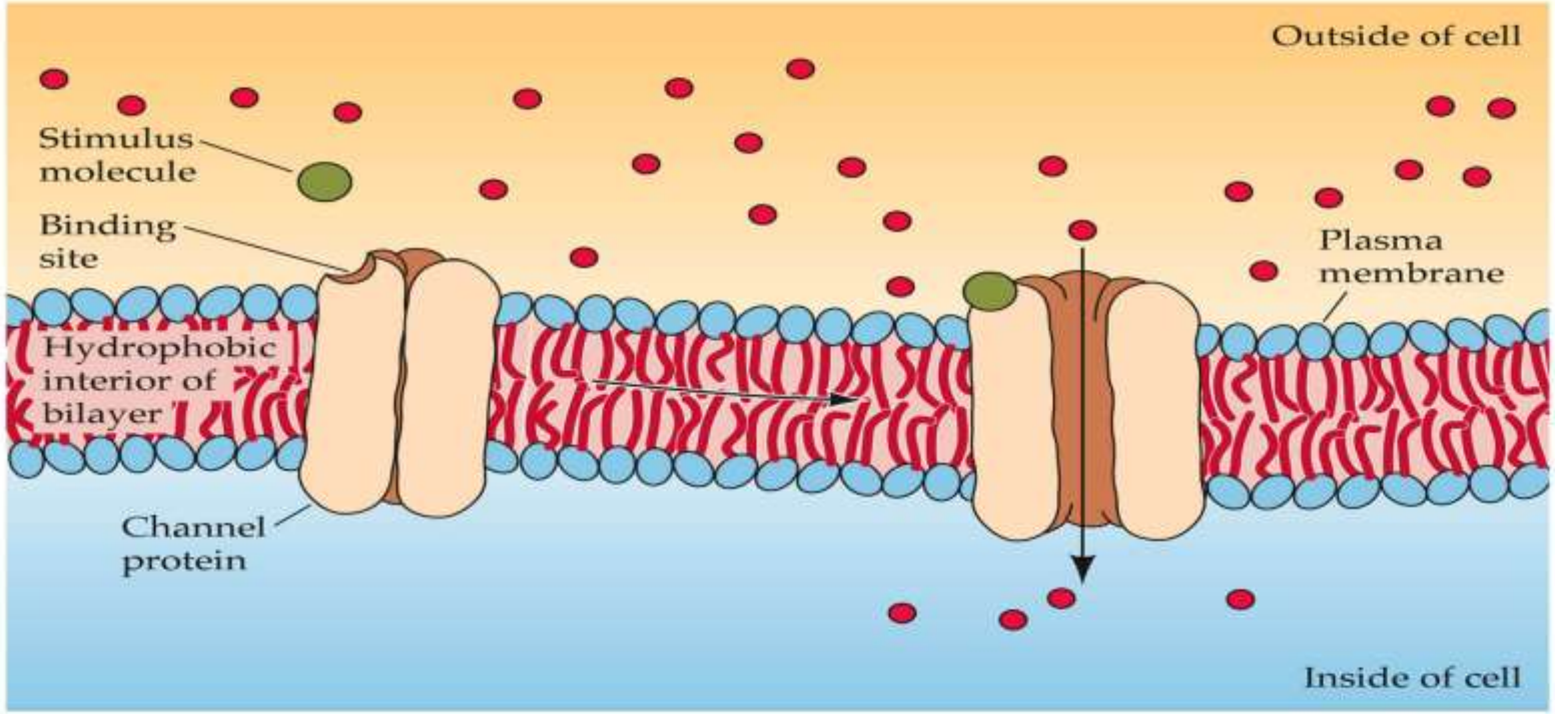
Facilitated Diffusion

- Acetylcholine opens the gate of this channel, providing a negatively charged pore allowing uncharged molecules or small positive ions to pass through.
- Gate very important for the transmission of nerve signals from one nerve cell to another and from nerve cells to muscle cells to cause muscle contraction
- substance diffuses through the membrane using a specific carrier protein to help.
- The carrier *facilitates* diffusion of the substance to the other side.
- In simple diffusion it is through an open channel and increases proportionately with the concentration of the diffusing substance

- In facilitated diffusion the rate of diffusion approaches a maximum, called Vmax, as the concentration of the diffusing substance increases.
- As the concentration of the diffusing substance increases, the rate of simple diffusion continues to increase proportionately,
- In case of facilitated diffusion, the rate of diffusion cannot rise greater than the Vmax level.

- The molecule to be transported enters the pore and becomes bound.
- Then, in a fraction of a second, a conformational or chemical change occurs in the carrier protein, so that the pore now opens to the opposite side of the membrane.
- Because the binding force of the receptor is weak, the thermal motion of the attached molecule causes it to break away and to be released on the opposite side of

Carrier proteins



LIFE: THE SCIENCE OF BIOLOGY, Seventh Edition, Figure 5.9 A Gated Channel Protein Opens in Response to a Stimulus

[Animation: How Facilitated Diffusion Works]

- Transport rate can never be greater than the rate at which the carrier protein molecule can undergo change back and forth between its two states.
- NB: Mechanism allows the transported molecule to move—that is, to “diffuse”—in either direction through the membrane

- Examples of facilitated diffusion are transport of *glucose* and most of the *amino acids.*
- For glucose, the carrier molecule is identified with a mwgt of 45,000
- Can also transport other monosaccharides with structures similar to that of glucose such as galactose.
- Also, insulin can increase the rate of facilitated diffusion of glucose as much as 10-fold to 20-fold.
- This is the principal mechanism by which insulin controls glucose use in body

Effect of Concentration Difference on Net Diffusion Through a Membrane

- Rate at which a substance diffuses *into a cell* is proportional to the conc’n of substance outside
- Rate at which substance diffuse *outward* is proportional to the conc’n *inside* the membrane.
- Thus, the rate of net diffusion into the cell is proportional to conc’n the outside *minus* the conc’n on the inside, or:
- Net diffusion µ (Co - Ci)
- in which Co is conc’n outside and Ci is conc’n inside

Osmosis & osmotic pressure

- Movement of water from region of high water(or low solute) conc’n to region of low water(or high solute) conc’n
- Wherever there is increase in solute conc’n either in extracellular fluid or in the cells, water will move rapidly from the opposite side through the cell membrane till a state of equilibrium is established
- Rate of this diffusion known as rate of osmosis

- Water conc’n depends on solute particles irrespective of composition
- Total number of solutes measured in osmoles
- 1 osmoles is equivalent to 6.02 x 10(23) particles
- For a pdt dissociating into two, it will have twice osmoles
- 80% osmolality of interstitial fluids is due to Na+ & cl- whereas for intracellular is due to K+ & other solutes
- Total osmolality for each compartment about 280mosm/l

- Osmotic pressure directly proportional to osmotically active particles
- True whether solute large(e.g. albumin: mwgt 70000) or small (e.g. glucose: mwgt 180)
- Sodium chloride has twice osmotic pressure of albumin.
- Osmotic pressure = CRT where C is solute conc'n, R the ideal gas constant & T the absolute temperature in degrees kelvin.
- Normally, osmolality of a 1mOsm/l is 19.3mmHg
- Osmolality of body fluids about 280mOsm/l
- Plasma osmolality slightly higher than in other compartments due to presence of plasma proteins

"Active Transport" of Substances Through Membranes

- When a cell membrane moves molecules or ions "uphill" against a concentration gradient (or "uphill" against an electrical or pressure gradient), the process is called *active transport.*
- Some of the substances actively transported through at least some cell membranes include Na^+, K^+, Ca^{++} ions, iron ions, H^+, several different sugars, and most of the amino acids.

Primary Active Transport and secondary Active Transport

- Active transport is divided into 2 types : 1° *active transport* & 2° *active transport.*
- In 1° *active transport* , energy derived from breakdown of ATP.
- In 2° active transport, energy derived secondarily from energy that has been stored in the form of ionic conc’n differences of 2° molecular or ionic substances between the 2 sides of a cell membrane, created originally by 1° active transport.
- In both cases , transport depends on *carrier proteins* that penetrate through the cell membrane, as is true for facilitated diffusion.

- However, in active transport, the carrier protein functions differently from the carrier in facilitated diffusion because it is capable of imparting energy to the transported substance to move it against the electrochemical gradient.
- Following are some examples of primary active transport and secondary active transport, with more detailed explanations of their principles of function.

"Active Transport" of Substances Through Membranes

- Primary Active Transport and Secondary Active Transport
- In primary active transport, the energy is derived directly from breakdown of ATP
- In secondary active transport, the energy is derived secondarily from energy that has been stored in the form of ionic concentration differences of secondary molecular or ionic substances between the two sides of a cell membrane, created originally by primary active transport

- both instances, transport depends on *carrier proteins* that penetrate through the cell membrane, as is true for facilitated diffusion
- in active transport, the carrier protein functions differently from the carrier in facilitated diffusion because it uses energy to transport substance against the electrochemical gradient

Primary Active Transport

- Sodium-Potassium Pump
- For transport of sodium, potassium, calcium, hydrogen, chloride, and a few other ions.
- complex of 2 globular proteins: an a subunit, with a mwght of about 100,000, and a b subunit, with a mwgt of about 55,000.
- A subunit has 3 specific features important important for the functioning of the pump:
- has 3 r*eceptor sites for binding Na ions on side* protruding to the inside of cell.
- 2 *receptor sites for K ions* on the outside.
- The inside portion of this protein near the Na binding sites has ATPase activity.

- When 2 K ions bind on the outside, of the carrier protein and 3 Na ions on the inside, the ATPase function of protein becomes activated.
- This then cleaves one ATP, to ADP and liberating a high-energy phosphate bond of energy.
- The energy causes conformational change in the protein carrier molecule, extruding the 3 Na ions to the outside and the 2 K ions to the inside.

Importance of the Na+-K+ Pump for Controlling Cell Volume.

- Most important functions of the pump is to control volume of each cell.
- Without the pump, most cells would swell until they burst.
- The mechanism for controlling the volume is as follows:
- Inside the cell are large numbers of proteins and other organic molecules that cannot escape from the cell.
- Most are –tively charged hence attract large numbers of Na, K and other positive ions as well.
- All these then cause osmosis of water to the interior of the cell. Unless this is checked, the

- Unless checked, cell would swell until it bursts.
- The Na^+-K^+ pump prevents this
- Pumps 3 Na^+ ions to the outside of the cell for every two K^+ ions pumped to the interior.
- Also, membrane is far less permeable to Na than to K hence once Na ions are on the outside, they have a strong tendency to stay there.
- This results in net loss of ions out of the cell, initiating osmosis of water out of cell
- If a cell begins to swell for any reason, this automatically activates the Na^+-K^+ pump, moving still more ions to the exterior and carrying water with them.
- Thus, the pump performs a continual surveillance role in maintaining normal cell volume.

Electrogenic Nature of the Na+-K+ Pump

- Pump moves more +ve ions out of cell leaving inside more electo-ve
- Thus electrogenic causing inside of cell to be more negative

Primary Active Transport of Calcium Ions

- Calcium pump
- On cell membrane and pumps Ca out of cell
- On cell organelles pumping Ca into organelles such as sarcoplasmic reticulum and endoplasmic reticulum
- Has ATPase activity hence utilizes energy

Primary Active Transport of Hydrogen Ions

- Occurs in 2 places in body: in the gastric glands of the stomach, and in late distal tubules and cortical collecting ducts of kidneys.
- Called proton pump in gastric glands and pumps H ions into stomach
- In kidneys involved in active secretion of H ions into renal tubules

Secondary Active Transport— Co-Transport and Counter-Transport

- When Na ions transported out of cells by 1ry active transport, a large concentration gradient of Na ions across cell membrane develops
- ↑conc’n outside the cell and very ↓ conc’n inside.
- Excess Na outside the cell membrane is always attempting to diffuse to the interior.
- Under appropriate conditions, this diffusion energy of sodium can pull other substances along with the sodium through the cell membrane.
- This phenomenon is called *co-transport;* it is oneform of *secondary active transport.*

- For Na to pull another substance along with it, a coupling mechanism is required.
- Achieved by means of another carrier protein in the cell membrane.
- The carrier serves as an attachment point for both the Na and the substance to be co-transported.
- Once both are attached, the energy gradient of the Na ion causes both the Na ion and the other substance to be transported together to the interior of the cell.

- In *counter-transport,* Na ions again attempt to diffuse into the cell because of their large concentration gradient.
- This time, the substance to be transported is on the inside of the cell and must be transported to the outside.
- The Na ion binds to the carrier protein to the outside of the membrane, while the substance to be counter-transported binds to the interior projection of the carrier protein.
- Once both have bound, a conformational change occurs, and energy released by the Na moving to the interior causes the other substance to move to the exterior.

Co-Transport of Glucose and Amino Acids Along with Sodium Ions

- Glucose and many amino acids are transported into most cells against large concentration gradients
- Mechanism of this co-transport
- The transport carrier protein has two binding sites on its exterior side, one for Na and one for glucose.
- The conc’n of Na is very high on the outside and very low inside
- This provides energy for the transport.

- A special property of the transport protein is that a conformational change to allow Na movement to the interior will not occur until a glucose molecule also attaches.
- When they both become attached, the conformational change takes place automatically, and the sodium and glucose are transported to the inside of the cell at the same time.
- Hence, this is a *sodium-glucose co-transport* mechanism.
- *Sodium co-transport of the amino acids* occurs in the same way except that it uses a different set of transport proteins.

Sodium Counter-Transport of Calcium and Hydrogen Ions

- In counter-transport mechanisms the transport is in a direction opposite to the primary ion
- are Na-Ca c*ounter-transport* and Na-H *counter-transport.*
- Na-Ca c*ounter-transport* occurs through almost all cell membranes, with Na ions moving to the interior and Ca ions to the exterior
- Both bound to the same transport protein in a countertransport mode.
- This is in addition to 1ry active transport of Ca occuring in some cell

- Sodium-hydrogen counter-transport occurs in several tissues.
- Especially important in the *proximal tubules* of the kidneys
- Na ions move from the lumen of the tubule to the interior of the tubular cell, while H Are counter transported into the tubule lumen.
- As a mechanism for concentrating hydrogen ions, it is not nearly as powerful as the primary active transport of H ions that occurs in the more distal renal tubules, but it can transport extremely *large numbers of hydrogen ions,* thus making it a key to hydrogen ion control in the body fluids

SPECIAL TYPES OF ACTIVE TRANSPORT

- In addition active transport systems, there are some special categories of active transport called vesicular transport. They are
- 1. Endocytosis
- 2. Exocytosis
- 3. Transcytosis.

ENDOCYTOSIS

- It is a mechanism by which the macromolecules enter the cell.
- Macromolecules (substances with larger molecules) cannot pass through the cell membrane either by active or by passive transport mechanism.
- Are transported into the cell by endocytosis
- 3 types
- 1. Pinocytosis
- 2. Phagocytosis
- 3. Receptor-mediated endocytosis

- 1. Pinocytosis
- Is a process by which macromolecules like bacteria and antigens are taken into the cells. Also known as cell drinking
- Stages
- i. Macromolecules (in the form of droplets of fluid) bind to the outer surface of the cell membrane
- ii. Now, the cell membrane evaginates around the droplets
- iii. Droplets are engulfed by the membrane
- iv. Engulfed droplets are converted into vesicles and vacuoles, which are called endosomes
- v. Endosome travels into the interior of the cell

- vi. Primary lysosome in the cytoplasm fuses with endosome and forms secondary lysosome
- vii. Hydrolytic enzymes present in the secondary lysosome are activated resulting in digestion and degradation of the endosomal contents.

Phagocytosis

- Is a process by which particles larger than the macromolecules are engulfed into the cells. Also called cell eating.
- Larger bacteria, larger antigens and other larger foreign bodies are taken inside the cell by means of phagocytosis.
- Mostly by white blood cells

Mechanism of phagocytosis

- i. When bacteria or foreign body enters the body, first the phagocytic cell sends cytoplasmic extension (pseudopodium) around bacteria or foreign body

- ii. The particles are engulfed and then converted into endosome like vacuole. – known as a phagosome
- iii. Phagosome travels into the interior of cell
- iv. Primary lysosome fuses with this phagosome and forms secondary lysosome
- v. Hydrolytic enzymes present in the secondary lysosome are activated resulting in digestion and degradation of the phagosomal contents

Receptor-mediated Endocytosis

- Is the transport of macromolecules with the help of a receptor protein.
- Surface of cell membrane has some pits which contain a receptor protein called clathrin- known as called receptor-coated pit.
- Mechanism of receptor-mediated endocytosis
- i. Receptor-mediated endocytosis is induced by substances like ligands
- Ligand molecules approach the cell and bind to receptors in the coated pits and form ligand-receptor complex
- iii. Ligand-receptor complex gets aggregated in the coated pits.
- Then, the pit is detached from cell membrane and becomes the coated vesicle. This coated vesicle forms the endosome

- Endosome travels into the interior of the cell.
- Primary lysosome in the cytoplasm fuses with endosome and forms secondary lysosome
- v. Hydrolytic enzymes in secondary lysosome are activated resulting in release of ligands into the cytoplasm
- vi. Receptor may move to a new pit of the cell membrane

EXOCYTOSIS

- Is a process by which the substances are expelled from the cell.
- The substances are extruded from cell without passing through the cell membrane.
- This is the reverse of endocytosis.

CHANNELOPATHIES OR ION CHANNEL DISEASES

- Are caused by mutations in genes that encode the ion channels.
- 1. Sodium Channel Diseases
- Dysfunction of sodium channels leads to muscle spasm and Liddle's syndrome (dysfunction of sodium channels in kidney resulting in increased osmotic pressure in the blood and hypertension).
- 2. Potassium Channel Diseases
- Potassium channel dysfunction causes disorders of heart, inherited deafness and epileptic seizures in newborn.

Major electrolytes and their distribution - 2

- Sodium plays a major role in controlling total body fluid volume; potassium is important in controlling the volume of the cell
- The law of electrical neutrality states that the sum of negative charges must be equal to the sum of positive charges (measured in milliequivalents) in any particular compartment

- 3. Chloride Channel Diseases
- Dysfunction of chloride channels results in formation of renal stones and cystic fibrosis.
- Cystic fibrosis is a generalized disorder affecting the functions of many organs such as lungs (due to excessive mucus), exocrine glands like pancreas, biliary system and immune system.