Chapter
1

General Physiology

Competencies

PY 1.1 Describe the structure and functions of a mammalian cell
PY 1.2 Describe and discuss the principles of homeostasis
PY 1.3 Describe intercellular communication
PY 1.4 Describe apoptosis—programmed cell death
PY 1.5 Describe and discuss transport mechanisms across cell membranes
PY 1.6 Describe the fluid compartments of the body, its ionic composition and measurements
PY 1.7 Describe the concept of pH and buffer systems in the body
PY 1.8 Describe and discuss the molecular basis of resting membrane potential and action potential in excitable tissue
PY 1.9 Demonstrate the ability to describe and discuss the methods used to demonstrate the functions of the cells and their products, their communications, and their applications in clinical care and research.

RAPID READING

BODY FLUID COMPARTMENTS

Total body water (TBW), which accounts for approximately 60% of body weight, is distributed across two major compartments separated by the cell membrane. The intracellular fluid (ICF) compartment is the larger containing approximately two-thirds of the total body water. The remaining one-third is contained in the extracellular fluid (ECF) compartment.

- Total body water (TBW) = 0.6 × (body weight)
- ICF = 0.4 × (body weight)
- ECF = 0.2 × (body weight)

The ICF and ECF compartments differ in their composition, specifically in their concentrations of electrolytes and proteins, as detailed in Table 1.1.

TABLE 1.1: Comparison of the compositions of ICF and ECF

Component	*Intracellular fluid (ICF)*	*Extracellular fluid (ECF)*
Total volume (L)	28	14
Na^+ (mEq/L)	15	150
K^+ (mEq/L)	150	4
Ca^{2+} (mEq/L)	0.001	5
Cl^- (mEq/L)	5	105
HCO_3^- (mEq/L)	10	24
Phosphates (mEq/L)	100	2
Proteins (mEq/L)	45	<0.1–14
pH	7.1	7.4

Note: As shown, Na^+ is the major cation in the ECF, and Cl^- and HCO_3^- are the major anions. Due to its abundance, Na^+ is the primary determinant of the osmolality of the ECF.

Additional Information

The total water content of individuals varies between 45% and 75% of body weight, depending on the amount of adipose tissue. Adipose tissue contains less than 10% water, while skeletal muscle contains 75% water, and skin is about 70% water. The total body water also varies with age: in newborns, it is 75% of body weight and decreases with age.

The approximation of ICF and ECF volumes excludes bone fluid (approximately 7.5% of total body water) and includes variable amounts of dense connective tissue fluid and transcellular fluid.

The ECF is further subdivided into:

- Interstitial fluid: Nearly 50% of the total ECF
- Intravascular compartment: Contains plasma (about 4.5% of body weight)
- Other smaller fluid compartments: Including bone fluid, dense connective tissue fluid, and transcellular fluid.

ECF composition: The two major compartments of ECF—plasma and interstitial fluid have similar compositions, with Na^+ as the predominant cation and Cl^- and HCO_3^- as the major anions. An important distinction is that plasma has a higher concentration of proteins compared to interstitial fluid. This difference occurs because the capillary endothelium is freely permeable to water and small solutes like inorganic ions, glucose, and urea (crystalloids), but is less permeable to larger solutes like proteins and lipids (colloids).

MEASUREMENTS OF THE VOLUME OF BODY FLUID COMPARTMENTS

The volumes of the various fluid compartments in the body cannot be directly measured. Instead, the principle of **volume dilution** is used. This method involves utilizing marker substances that are uniformly distributed within a specific fluid compartment.

A known quantity of a marker (M) is administered, and after it has evenly distributed throughout the compartment, a sample of the fluid from that compartment is obtained. The concentration of the marker (M) is then measured. The volume of the fluid compartment can be calculated using the following formula:

$$\text{The volume of the compartment} = \frac{\text{Mass of M administered}}{\text{Concentration of M in the compartment}}$$

If a marker is lost by excretion during the estimation, then

$$\text{The volume of the compartment} = \frac{\text{Mass of M administered} - \text{Mass of M lost}}{\text{Concentration of M in the compartment}}$$

Using this principle, the volumes of total body water (TBW), extracellular fluid (ECF), and plasma volume can be estimated.

Markers Used in Different Estimations

Total body water (TBW):
- Deuterium oxide (D_2O)
- Tritiated water (heavy water)
- Antipyrine (a drug)

Extracellular fluid (ECF) volume:
- Radioisotopes of ions
- Inulin
- Mannitol
- Sucrose

Plasma volume:
- Radioisotopes of albumin, (e.g. radio iodinated serum albumin, ^{131}I-albumin)
- Evans blue dye (T-1824)

Blood volume:
- Labeled red cells, (e.g. ^{51}Cr-erythrocytes)

Calculation of Total Blood Volume (TBV)

Total blood volume (TBV) can also be calculated indirectly from plasma volume (PV) and hematocrit (Hct) using the following formula:

$$\text{TBV} = \text{PV} \times \frac{1}{\text{1-Hct}}$$

where:
- **PV** is the plasma volume
- **Hct** is the hematocrit (the proportion of blood volume occupied by red blood cells)

TRANSPORT MECHANISMS ACROSS CELL MEMBRANE

Solutes and water molecules are transported across cell membranes by different transport mechanisms depending on the size of the substance, concentration difference, and the purpose of transport.

The different transport mechanisms include diffusion, active transport, and vesicular transport for solutes and osmosis for water molecules.

a. Simple Diffusion

Diffusion occurs because of the random motion of molecules and eventually results in a uniform distribution of these molecules. If two compartments, say A and B are separated by a removable partition and if side A contains a greater number of molecules of a compound than side B and then the partition is removed, all molecules show a random motion, both from A to B and B to A. Because there are many more molecules on side A than on side B, the total number of molecules moving from side A to side B will be greater than the number moving from side B to side A. Consequently, the number of molecules on side A will decrease whereas the number of molecules on side B will increase. This process of net diffusion of molecules will continue until the concentration on side A equals on side B. Thereafter the rate of diffusion of molecules from A to B will equal that from B to A, and no further net movement will occur, i.e. a dynamic equilibrium will exist.

Diffusion across the membrane

Diffusion across cellular membranes for solutes tends to equalize the concentration of solutes on the two sides of the membrane. The diffusion rate across a membrane

is proportional to the area of the membrane and the difference in the concentration of the solutes on the two sides of the membrane. It is inversely proportional to the thickness of the membrane (Fick's law of diffusion).

$$J = \frac{D \times A \times C}{X}$$

where,
J = Amount diffused per unit of time
D = Diffusion coefficient
A = Area of the membrane
C = Concentration in difference across the membrane
X = Thickness of the membrane

Salient features of simple diffusion

i. Diffusion occurs from an area of higher concentration of solutes to an area of lower concentration.
ii. Diffusion depends on the permeability of the cellular membranes to different solutes.
Permeability for lipid-soluble molecules is greater than for water-soluble substances. Ionic diffusion depends on the presence of the ion channels that span the membrane.
iii. The rate of transport is less (than that in facilitated diffusion)
iv. No energy is needed to transport the substance.

b. Facilitated Diffusion

Facilitated diffusion occurs via a transporter or carrier that does not require energy. Therefore, the transport occurs along the concentration or electrical gradient. These transporters are protein molecules in the membrane. Such protein-mediated transport processes can transport substances across membranes much more rapidly than simple diffusion. A transporter binds to the solutes to be transported on one side of the membrane and then undergoes a conformational change that allows these solutes to be released on the other side of the membrane.

Properties of facilitated diffusion

i. Rapid transport (*see* above)
ii. Saturation: As the concentration of the transported substances increases, the rate of transport at first increases, but eventually a concentration is reached above which, the transport rate does not increase further. At this point, the transport system is set to be saturated with the substance that is transported.
iii. Specificity: Only molecules with the requisite chemical structure are transported, e.g. one of the transport proteins may transport one amino acid or group of amino acids, while another transporter is one sugar or group of sugars.
iv. Competitive inhibition: Structurally related molecules may compete for transport.
v. Non-competitive inhibition: Transport may be inhibited by compounds that are not structurally related to the transport substances, e.g. the compound phlorizin does not resemble a sugar molecule, yet strongly inhibits the glucose transport across membranes.

Active Transport

Certain transporters are linked to metabolic energy, and they can use the energy to transport substances against their concentration gradient, i.e. from regions where they are less concentrated to where they are more concentrated. Such a type of carrier-mediated transport that needs energy is called 'active transport'. Active transport processes have most of the properties of facilitated transport. The energy required for active transport is derived from the hydrolysis of ATP. Active transport is of two types:

i. Primary active and
ii. Secondary active.

Primary Active Transport

It is an active transport process that is linked directly to cellular metabolism, e.g. Na^+ K^+ ATPase pump, calcium pump, and H^+ K^+ pump in gastric parietal cells.

Secondary Active Transport

When the concentration gradient for the substance (e.g. Na^+) created by an active transport system (Na^+, K^+ ATPase pump) is used to actively transport other solutes (amino acid, sugars), it is known as secondary active transport (Box 1.1).

BOX 1.1: Role of Na^+ powered secondary active transport in glucose absorption and oral dehydration therapy

In the small intestine, glucose and galactose are absorbed by Na^+-powered secondary active transport. The presence of Na^+ in the lumen enhances the absorption of glucose and *vice versa*. In severe diarrheal illness, oral dehydration therapy is based on this fact. Patients are given a solution containing both NaCl and glucose, along with K^+ and HCO_3^-. The absorption of Na^+ and glucose in small intestine helps to drive the osmotic absorption of water and thus facilitates the rehydration of the patient.

OSMOSIS AND OSMOTIC PRESSURE

Osmosis is defined as the flow of water across a semi-permeable membrane from a compartment in which the solutes concentration is lower, to a compartment in which the solute concentration is greater. A semipermeable membrane is a membrane that is permeable to water but impermeable to solutes.

Osmotic Pressure

Osmotic pressure is the pressure needed to prevent water molecules from entering from one compartment to the other by osmosis. The osmotic pressure of the solution depends on the number of particles in the solution. Thus, the degree of ionization of the solutes must be taken into account when osmotic pressure is calculated. If the total osmotic pressures of two solutions are equal, the solutions are set to be iso-osmotic solutions.

Osmotic Swelling and Shrinking of the Cells

The membranes of most of the cells in the body are relatively impermeable to many of the solutes of ECF but are highly permeable to water. Therefore, when the osmotic pressure of ECF is increased, water leaves the cells by osmosis and the cells shrink. When water leaves the cell, cellular solutes become more concentrated until the effective osmotic pressure of the cytoplasm is equal to that of ECF. Conversely, if the osmotic pressure of ECF is decreased, water enters the cells till the intracellular and extracellular osmotic pressures are equal. For example, in a sodium chloride concentration of 0.9%, the volume of red cells is the same as their volume in plasma. This concentration of NaCl is set to be isotonic to the red cell (Box 1.2).

BOX 1.2: Use of isotonic saline for intravenous rehydration and drug administration

Isotonic saline is used for intravenous rehydration or administration of drugs to the patients. Isotonic saline, also known as normal saline, is a solution of 0.9% sodium chloride in water, which matches the body's natural fluid concentration. It is commonly used for intravenous rehydration, helping to restore fluid balance in patients who are dehydrated due to conditions like vomiting, diarrhea, or excessive sweating. Additionally, isotonic saline is used to administer medications.

CONCEPT AND BASIS OF RESTING MEMBRANE POTENTIAL

Plasma membranes of all living cells exhibit a membrane potential, or are polarized electrically.

Membrane potential is due to the separation of opposite charges across the plasma membrane, i.e. there is a difference in the relative number of cations and anions in the ICF and ECF. Separated charges have the "potential" to do work, a separation of charges across the membrane is referred to as the membrane potential.

The attractive force between the separated charges causes them to accumulate in a thin layer along the outer and inner surfaces of the plasma membrane. These separated charges represent only a small fraction of the total number of charged particles (ions) present in the ICF and ECF; the vast majority of fluid inside and outside the cells being electrically neutral. The membrane potential is measured in units of millivolts (mV) and the magnitude of the potential depends on the degree of separation of the opposite charges. Membrane potential, especially in excitable cells, present when the cells are at rest, i.e. when they are not producing electrical signals, is known as 'resting membrane potential' (RMP).

BASIS OF RESTING MEMBRANE POTENTIAL

RMP is due to

i. Differences in the concentrations of ions in the ICF and the ECF
ii. Differential permeability of the membrane to certain key ions.
iii. Na^+, K^+ ATPase pump that is electrogenic

i. Unequal distributions of certain key ions between the ICF and the ECF: In the body, electrical charges are carried by ions. The key ions that contribute to the development of RMP are Na^+, K^+ and large negatively charged intracellular proteins. Table 1.2 compares the concentrations of these ions in the ICF and the ECF.

The distribution of Na^+ and K^+ in the ICF and ECF is maintained by the Na^+, K^+ ATPase pump present in all the cells of the body.

ii. Differential permeability of the cell membrane to ions: Cell membrane at rest is more permeable to K^+ than to Na^+ and virtually impermeable to protein anions. This is due to the larger size of the hydrated Na^+ ions.

Due to i and ii, K^+ diffuses out of the cell along the concentration gradient leaving behind the non-diffusible protein anions. This causes the inside of the membrane to become more negative compared to the outside.

iii. Na^+, K^+ ATPase pump: The Na^+, K^+ ATPase pump in the cell membrane pumps $3Na^+$ out of the cell for every $2K^+$ it transports into the cell. Both Na^+ and K^+ are positive ions, this unequal transport makes the inside of the membrane more negative (due to the net loss of one negative charge). Therefore, this pump is called 'electrogenic' and contributes to 20% of the magnitude of RMP.

Working of Ubiquitous Na^+, K^+ ATPase Pump

The plasma membrane of all cells contains a primary active transport system, the Na^+, K^+ ATPase pump, which involves the use of a protein carrier to transfer Na^+

TABLE 1.2: Comparison of ion concentrations in ICF and ECF

Ion	*ICF (mM)*	*ECF (mM)*
Na^+	15	150
K^+	150	5
Proteins	Nil	65

and K^+ in opposite directions, against their concentration gradients. To move these ions against the concentration gradient, energy in the form of ATP is required.

The Na^+, K^+ ATPase pump transports Na^+ out of the cell, concentrating it in the ECF, and picking up K^+ from the outside, concentrating it on the inside. As the name suggests, the carrier protein has an ATPase activity that hydrolyses ATP to yield ADP and free inorganic phosphate. The phosphate group is then attached to the carrier. This phosphorylation of the carrier on the intracellular side increases the carrier's affinity for Na^+ and induces a change in carrier shape, leading to the drop off of Na^+ on the exterior. The subsequent dephosphorylation of the carrier increases its affinity for K^+ on the extracellular side and restores the original carrier conformation, thereby transferring K^+ into the cytoplasm. The Na^+, K^+ ATPase pump moves three Na^+ out of the cell for every two K^+ it transports into the cell.

Utility of Na^+, K^+ ATPase Pump in Excitable Cells

1. Because both Na^+ and K^+ are positive ions, this unequal transport makes the inside of the membrane more negative (due to the net loss of one negative charge). Therefore,
2. This pump is called 'electrogenic' and contributes to the resting membrane potential.
3. It maintains sodium and potassium concentration gradients across the plasma membrane.
4. The energy of this pump is used indirectly to co-transport other substances (glucose, amino acids) along with sodium across intestinal and renal tubular cells (secondary active transport).

SIGNAL TRANSMISSION AT THE CELLULAR LEVEL AND INTERCELLULAR COMMUNICATION

Cells communicate with each other through signals mediated by chemicals. This communication system may take the form of any of the following:

- Neurocrine
- Endocrine
- Paracrine
- Autocrine
- Juxtacrine

Receptors for Ligands

The chemicals may be hormones, growth factors, cytokines, neurotransmitters, or neuromodulators. The name 'ligand' is sometimes used to denote the chemical. The ligands bind to specific receptors on the cell surface or inside the cells to bring about intracellular events and the desired cell response. Peptides bind to cell membrane receptors whereas small molecules like steroids which diffuse across the membrane, have receptors inside the cells. The intracellular receptors are called 'nuclear receptors' since their binding with a specific ligand brings about changes in gene transcription. The nuclear receptors may reside in the cytoplasm (e.g. glucocorticoid receptors) or may reside in the nucleus (e.g. thyroid hormone receptors).

The receptors for ligands have two important properties—'specificity' and 'affinity'.

Membrane Receptors

Ligands act by bindings to:

1. Receptors that behave as ion channels themselves, e.g. acetylcholine on muscarinic receptors on target cell opening K^+ channels in pacemaker cells.
2. G-protein coupled receptors (GPCR)—ligands that bind to GPCR are many of the peptides hormones (LH, PTH, TRH, SS, TSH, ACTH, glucagon, etc.), catecholamines, Ca^{2+}
3. Tyrosine kinase receptors—for insulin, IGF-1
4. Cytokine receptors—for GH, PRL (JAK-STAT), cytokines
5. Serine kinase receptors—for activins, MIS, etc.

GPCR

These receptors are membrane-spanning proteins with extracellular domains which bind ligands. The intracellular domain has sites that dock G-protein. G proteins are so-called because they bind guanosine nucleotides (GDP/GTP). GPCRs mediate different signaling pathways by their diverse interactions with chemicals.

G proteins have an α subunit and a βγ subunit, they have a GDR/GTP binding site and an intrinsic GTPase activity. βγ subunits are tightly associated and modulate the activity of the subunit.

Structural changes in G proteins when ligands bind GPCR

- No ligand—α subunit and a βγ subunits are associated; α subunit binds GDP.
- Ligand binding to GPCR—GTP replaces GDP in the α subunit; βγ subunits dissociate from the α subunit; Gα subunit gets activated; mediates signal transduction by the activation of different enzymes (adenylyl cyclase, phospholipase C and guanylyl cyclase)
- GTP hydrolysis into GDP by GTPase; reassociation of α subunit with βγ subunit and restoration of an inactive form
- The signal transduction occurs by the formation of second messengers such as cAMP, IP_3, DAG, and cGMP. Mutations in GPCRs alter their functions (loss or excess) and cause various disorders.

Nuclear receptors: Ligands that diffuse across the cell membrane bind to nuclear receptors (located in the cytoplasm or the nucleus). The ligand-activated receptor then binds to DNA and increases the transcription of RNA resulting in the formation of a new protein.

Second messengers: Hormones and ligands that bind to membrane receptors are considered as 'first messengers' and are located extracellularly. The intracellular mediators of the first messengers, which bring about cellular response are called second messengers.

Common second messengers:

- cAMP formed from ATP by the action of adenylyl cyclase via GPCR activation.
- IP_3, formed by the activation of phospholipase C via GPCR activation.
- DAG is formed by the activation of phospholipase C via GPCR activation.
- cGMP formed GTP by the action of guanylyl cyclase via GPCR activation.
- Ca^{2+} can enter the cell or can be released from the intracellular stores by another second messenger (IP_3). This is a good example of the release of a second messenger by the intracellular action of another second messenger.
- The second messengers have multiple roles in signaling pathways such as altering the enzyme activity (increase/decrease), triggering exocytosis, gene transcription, etc.

INTERPRETATIVE STUDY QUESTIONS

Questions 1 to 6 are based on the following pictorial representations (Fig. 1.1). Each of the images (A–E) depicts the osmolarity of body fluid compartments on the y-axis and the volume of compartments on the x-axis. ECF compartment is 1/3rd in length and represented by the rectangle on the right. ICF compartment is 2/3rd in length and represented by the rectangle on the left. The two compartments are seen separated by a narrow vertical bar representing the cell membrane. Changes brought about in either of the parameters (volume and/or osmolarity) by different interventions or clinical conditions are shown by dotted lines.

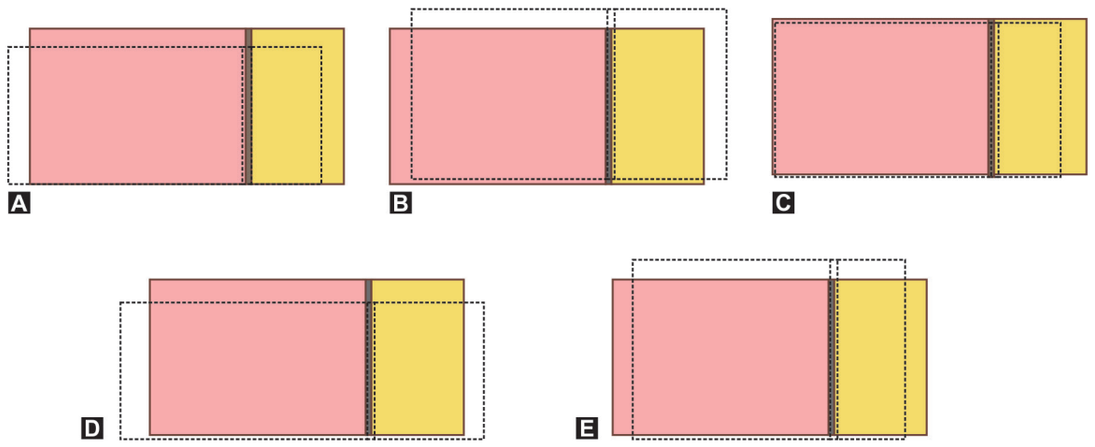

Fig. 1.1: Darrow-Yannet diagrams

1. Which of the diagrams depicts the changes caused by diarrhea, vomiting, or hemorrhage (loss of isotonic fluid) assuming that osmotic equilibrium has occurred? (You can ignore the loss of intracellular fluid by red cell loss in hemorrhage).

Answer: C

ECF volume decreases without a change in osmolarity. No change in ICF volume since ECF osmolarity has not changed.

2. Which of the diagrams depicts the changes caused by the loss of hypotonic fluid? (Example: Sweating, diabetes insipidus)

Answer: E

Loss of hypotonic fluid from ECF would decrease its volume but increase the osmolarity resulting in movement of water from ICF to ECF by osmotic force until osmolarity was equal (but higher) in both compartments. ICF volume decreases by fluid movement. ECF volume remains low since fluid

movement from ICF cannot completely compensate for the original insult.

3. Which of the diagrams represents the immediate changes induced by salt intake?

Answer: B

Salt ingestion would increase the ECF osmolarity (same as loss of hypotonic fluid) resulting in fluid movement from ICF to ECF. ECF volume increases but ICF volume decreases because of fluid shift into ECF. Osmotic equilibrium occurs at a higher osmolarity.

4. Which of the diagrams represents the changes induced by drinking tap water?

Answer: D

Hypotonic tap water increases ECF volume but decreases its osmolarity. Consequently, water shifts from ECF to ICF increasing its volume. Osmotic equilibrium occurs at a lower osmolarity.

5. Which of the diagrams represents the changes induced by infusion of isotonic saline?

Answer: None of the above diagrams depict this change. Create the diagram yourself.

This would increase ECF volume but osmolarity remains unaltered. ICF volume remains unaltered.

6. Which of the diagrams represents the changes induced by infusion of hypertonic saline?

Answer: B

This would increase both osmolarity and volume of ECF; Fluid shift occurs from ICF into ECF, and osmotic equilibrium occurs at a higher osmolarity. ICF volume decreases and ECF volume further increases.

Competency addressed: PY 1.6

7. The accompanying diagram (Fig. 1.2) shows two compartments M and N that are separated by a semipermeable membrane and contain water and solute (represented by stars that cannot pass through the semipermeable membrane). The letter I represents the initial volumes of the two compartments, which are identical.

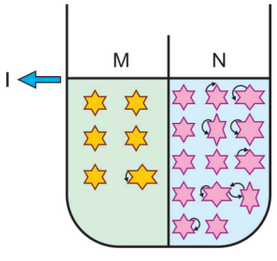

Fig. 1.2: Compartments M and N before equilibration

Which of the following diagrams (A–E) in Fig. 1.3 represents the volumes of M and N when the system reaches equilibrium? Justify your answer. Assume that in each of the compartments, the number of solutes remains the same.

Answer: B

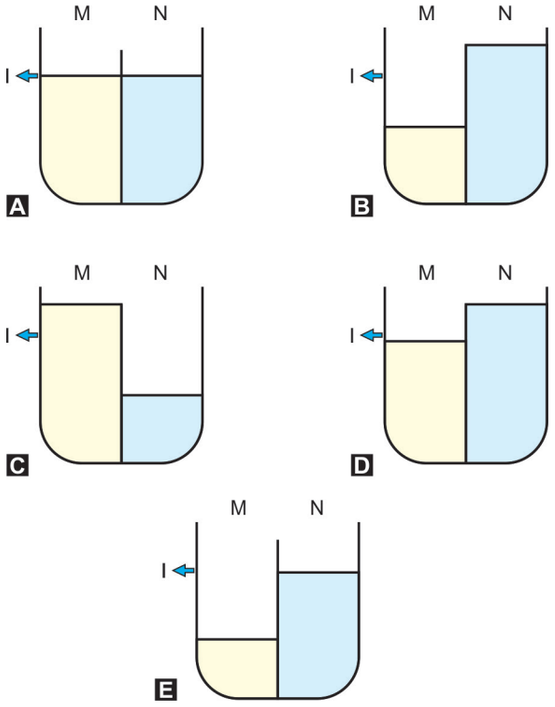

Fig. 1.3: Compartments M and N after equilibration

Water moves osmotically from compartment M into the compartment having higher solute concentration (N) through the semipermeable membrane and increases the volume of compartment Y till the osmotic equilibrium occurs between M and N. Volume of M decreases consequently.

Competency addressed: PY 1.5

8. A substance X is being transported across the membrane into an absorptive gut cell. The rate of transport is found to increase as the concentration of the substance is increased up to a point where a further increase in the concentration results in no further increase in the rate of transport. The transport is independent of ATP hydrolysis. Which of the following membrane transport mechanisms best describes the absorption of the substance X?

1. X is being transported by facilitated diffusion.
2. There is the involvement of a protein carrier, and it is the primary active transport.
3. Another substance is competing for the transport of X and is called secondary active transport.

4. This is an example of countertransport by simple diffusion.
5. The transporter gets saturated at a high concentration of X.
6. Competitive inhibition of X is a feature of this transport.

Select the best response

A. 1, 5 and 6
B. 1, 2 and 4
C. 3, and 4
D. 3 and 6
E. Only 2

Answer: A

The transport of the substance X is along the concentration gradient (downhill) since it is not energy-dependent and is called facilitated diffusion. Since the transport shows a maximum, it involves a protein carrier that gets saturated at high substance concentrations. Competitive inhibition is a feature of facilitated diffusion.

Competency addressed: PY 1.5

9. Each of the accompanying diagrams, A–D (Fig. 1.4) represents the volume (X-axis) and osmolality (Y-axis) of the intracellular fluid compartment (I) and extracellular fluid compartment (E). An intervention in the form of an infusion of 1 L of distilled water into the bloodstream shifts the fluid across the two compartments and affects the volume and/or osmolality of one or both compartment/s. If interrupted lines represent the original condition and the solid lines the final steady-state situation, which of the diagrams illustrates the change caused by the intervention?

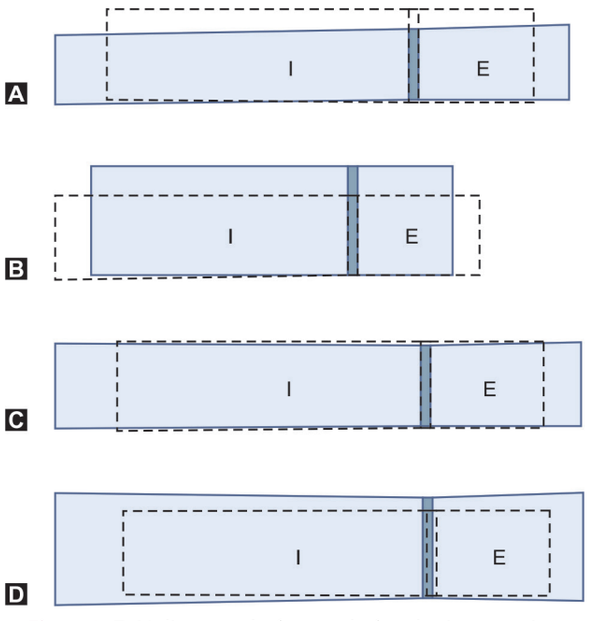

Fig. 1.4: D-Y diagrams before and after the intervention

Answer: B

See above for an explanation.

Competency addressed: PY 1.5 and 1.6

10. The following statements 1, 2 and 3 concern the intracellular fluid (ICF). They may be true or not true. Select the appropriate response from A to D.

1. Volume is more than 50% of total body fluid
2. Its osmotic pressure is greater than that of ECF
3. Its volume is about 40% of the body weight of a 70-kg-male

A. Statement 1 only is true
B. Statement 2 only is true
C. Statements 2 and 3 are true
D. Statements 1 and 3 are true

Answer: D

Review of 'Rapid Reading'

Competency addressed: PY 1.6

11. A 60-kg-male patient who has been admitted for treatment of anemia has a hematocrit of 0.4 and a plasma volume of 3 liters as measured using a dilution principle. Calculate the total blood volume.

Answer: TBV = PV × 1/1-Hct
= 3 × 1/0.6 = 5 L

Competency addressed: PY 1.6

12. 900 millimicrocuries of albumin labeled with radioactive iodine are injected intravenously into a lean 70 kg man. If there is uniform mixing in the plasma and no excretion of albumin, what approximate plasma concentration of the labeled albumin do you expect to find 10 minutes after injection (plasma volume assumed as 3 L)

A. 3 millimicrocuries/dl
B. 60 millimicrocuries/L
C. 30 millimicrocuries/dl
D. 500 millimicrocuries/L

Answer: C

Plasma volume = Quantity injected/concentration
3L = 900 millimicrocuries/C
C= 300 millimicrocuries/L = 30 millimicrocuries/dl

Competency addressed: PY 1.6

13. The process by which the number of receptors in the target cells for a hormone decreases when the hormone is present in excess is called:

A. Desensitization
B. Desynchronization

C. Diaschisis
D. Downregulation

Answer: D

When the hormones are present in excess, receptor downregulation occurs by a decrease in total receptor number in the cell by endocytosis and subsequent degradation of the receptors.

Competency addressed: PY 1.3

14. During cell signal transduction, the receptor-ligand interaction at a target cell is likely to bring about which of the following effects?

1. G-protein conformational change
2. Inhibition of membrane-bound enzyme
3. Direct activation of transcription
4. Opens or closes ion channels in the membrane
5. Phosphorylation of intracellular enzymes
6. Formation of second messengers
7. Triggering of exocytosis

A. 1, 3, and 6
B. 2, 4 and 6
C. 1 and 6 only
D. Only 6
E. All of the above

Answer: E

All of these are effects of receptor-ligand interaction at a target cell, it could be a hormone or a neurotransmitter.

Competency addressed: PY 1.3

15. A 34-year-old man presents with undue fatigue and splenomegaly. He has been diagnosed as having chronic myeloid leukemia following a hematological investigation. This hematopoietic stem cell disorder is characterized by marked white cell proliferation due to limited cell death caused by dysregulated membrane tyrosine kinase activity and defective cell signaling pathways. Which of the following ligands act by binding to the tyrosine kinase receptor of the cell membrane?

A. IGF-I; insulin growth factors
B. Glucagon, epinephrine and norepinephrine
C. T_3, T_4 and TSH
D. Cortisol, aldosterone, DHEA

Answer: A

Tyrosine kinase receptors are involved in the signal transduction for insulin, IGF-1, and a variety of growth factors (epidermal GF, NGF, platelet-derived GF, fibroblast GF, etc.). The cysteine-rich extracellular domain of the receptors binds these ligands. Upon binding these receptors undergo auto-phosphorylation that leads to signaling pathways.

Competency addressed: PY 1.3

16. Which of the following sequences correctly describes the events when G-protein-coupled receptors (GPCR) of target cells bind to a specific ligand?

A. Conversion of phosphatidylinositol diphosphate to IP_3 and diacylglycerol by GPCR > Subunits separate > Guanylyl cyclase activated by alpha subunit > Cell signaling triggered> Hydrolysis of GTP > Hormone action terminated
B. Formation of cAMP from ATP > GPCR activated and subunits reassociate > Adenylyl cyclase inhibited by alpha subunit > Cell signaling triggered > Intrinsic GTPase activity converts GTP to GDP> Hormone action terminated
C. GDP replaces GTP in the alpha subunit > Subunits reassociate > Phospholipase C activated by GPCR > Cell signaling triggered > Conversion of GDP to GTP> Hormone action terminated.
D. GTP replaces GDP in the alpha subunit > Subunits separate > Adenylyl cyclase activated by alpha subunit > Cell signaling triggered > Conversion of GTP to GDP > Hormone action terminated

Answer: D

Ligand when it binds to its receptor in the cell membrane, produces a conformational change in the α-subunit. GDP is released from the α subunit and is replaced by GTP. The α-GTP complex migrates within the cell membrane and binds to and activates enzymes triggering cell signaling. The hormone action is terminated when GTP is hydrolyzed to GDP.

Competency addressed: PY 1.3

17. A 28-year-old man is diagnosed with nephrogenic diabetes where vasopressin (V2) receptors fail to respond to the binding of vasopressin to cause changes in urine osmolality. V2 receptors are GPCRs that bring about activation of which of the following enzymes to increase cAMP in the tubular cells?

A. Phospholipase C
B. Phosphodiesterase
C. ATPase
D. Adenylyl cyclase

Answer: D

Vasopressin V2 receptors are G protein-coupled receptors that activate the adenylate cyclase pathway.

Competency addressed: PY 1.3

18. The cellular mechanism of action of two hormones (represented by red and blue stars) on a target cell is depicted in Fig. 1.5. The receptors for these hormones are least likely to be:

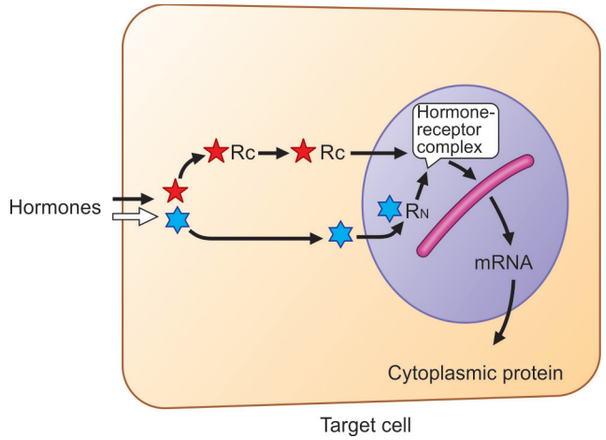

Fig. 1.5: Cellular mechanism of action of hormones

1. Cytoplasmic receptors
2. Nuclear receptors
3. G-protein coupled receptors
4. Cell membrane receptors

Select the best response

A. Only 2
B. 1 and 3
C. 2 and 4
D. 3 and 4

Answer: D

Refer to Chapter on 'Endocrinology'.

19. When compared to simple diffusion, facilitated diffusion:

A. Needs energy
B. Occurs against the concentration gradient
C. Requires transport protein
D. Does not show specificity
E. Is an uphill process

Answer: C

Facilitated diffusion involves the transport of larger solutes such as glucose and requires a carrier protein.

Competency addressed: PY 1.8

20. Which of the following is likely to occur when red cells are suspended in a hypotonic solution?

A. Solutes move into the red cells from the solution
B. Red cells shrink in size
C. Water moves from inside the cells to the solution
D. Red cells swell up
E. Solutes leave the red cells to come into the solution

Answer: D

Osmotic effect of hypotonic solution; water moves towards the area of greater osmolarity.

Competency addressed: PY 1.8

21. Insulin is necessary for the transport of glucose from plasma into muscle cells. In insulin deficiency (diabetes mellitus), plasma glucose level is increased. This is because of the absence of the following actions of insulin on the muscle membrane?

A. Inhibition of Na^+ K^+ ATPase pump
B. Decreased concentration gradient for glucose
C. Generation of ATP for glucose movement
D. Increased number of glucose transporters in the membrane
E. Opening of voltage-gated channels in the membrane

Answer: D

Insulin-induced glucose transport into the muscle cells requires transporters called GLUT4.

Competency addressed: PY 1.8

SUGGESTED READING

1. Ganong, W. F. (2021). Intercellular communication. In *Ganong's Review of Medical Physiology*, 26th edition. McGraw-Hill Education.