BCM 225 LECTURE

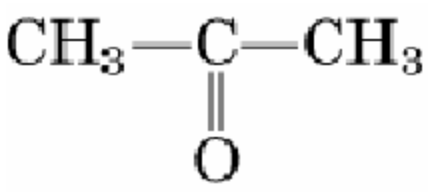
SALEMCITY, A.J

KETOSIS AND KETONE BODIES

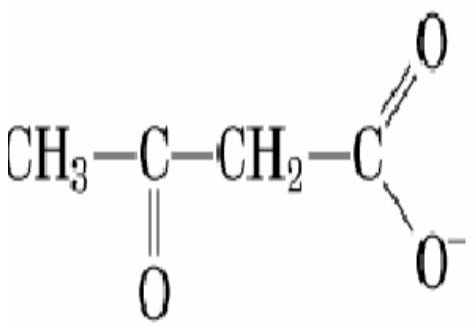
- What is ketosis?
- This is a condition in which the level of ketone bodies in the urine and the blood are elevated, conditions known as ketonuria and ketonemia respectively.
- This condition can result in ketoacidosis commonly experienced in diabetes mellitus.

Ketone Bodies

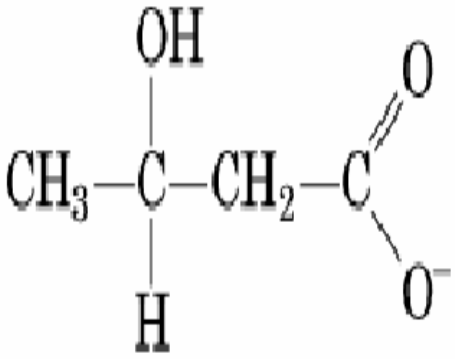
- These are the chemicals produced when fatty acids are broken down in excess.
- They include acetoacetic acid, β-hydroxy butyric acid and acetone.
- The ketone bodies are usually utilized in the heart and brain during starvation when glucose is not available.
- The synthesis of these compounds is referred to as ketogenesis.



Acetone

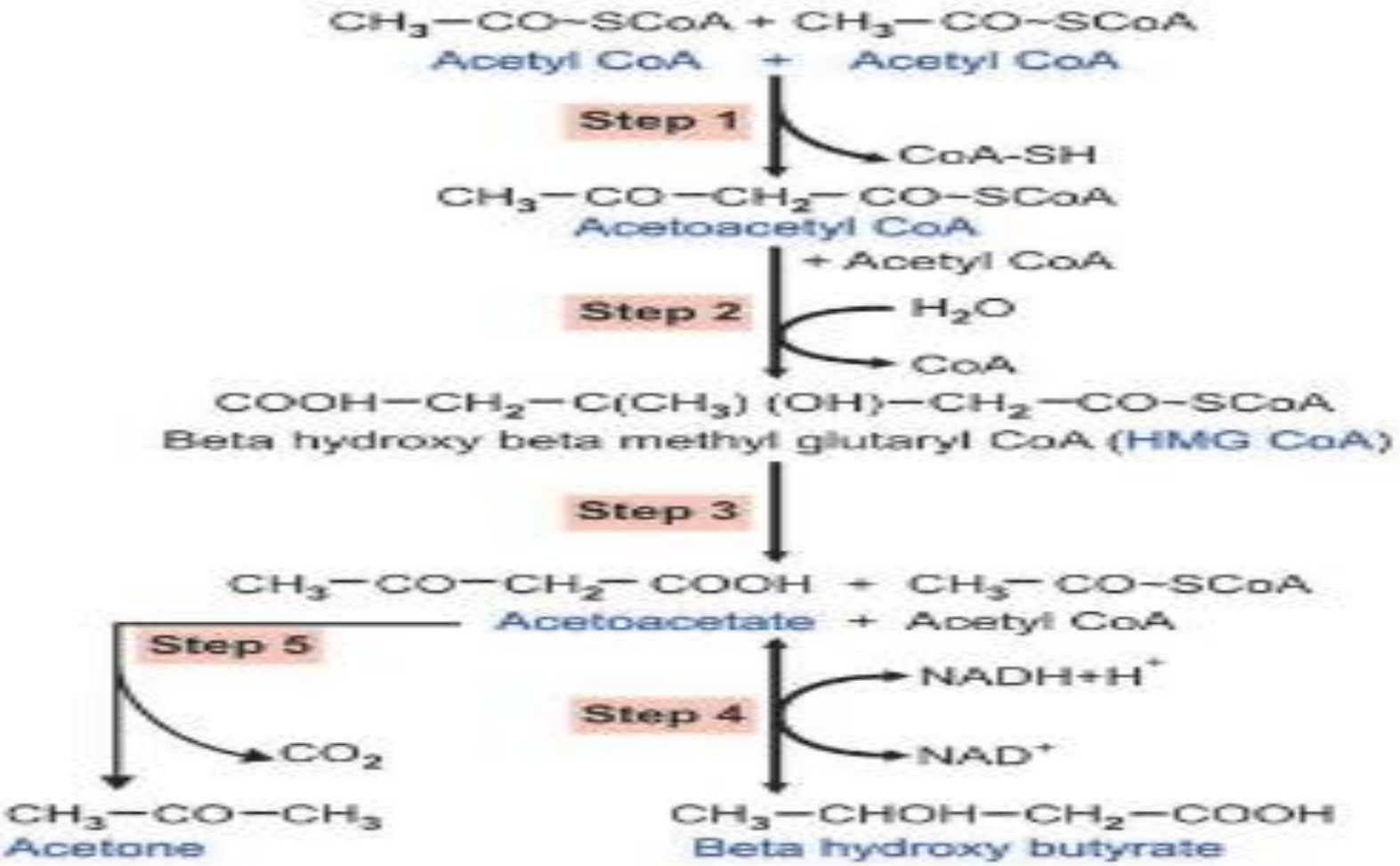


Acetoacetate

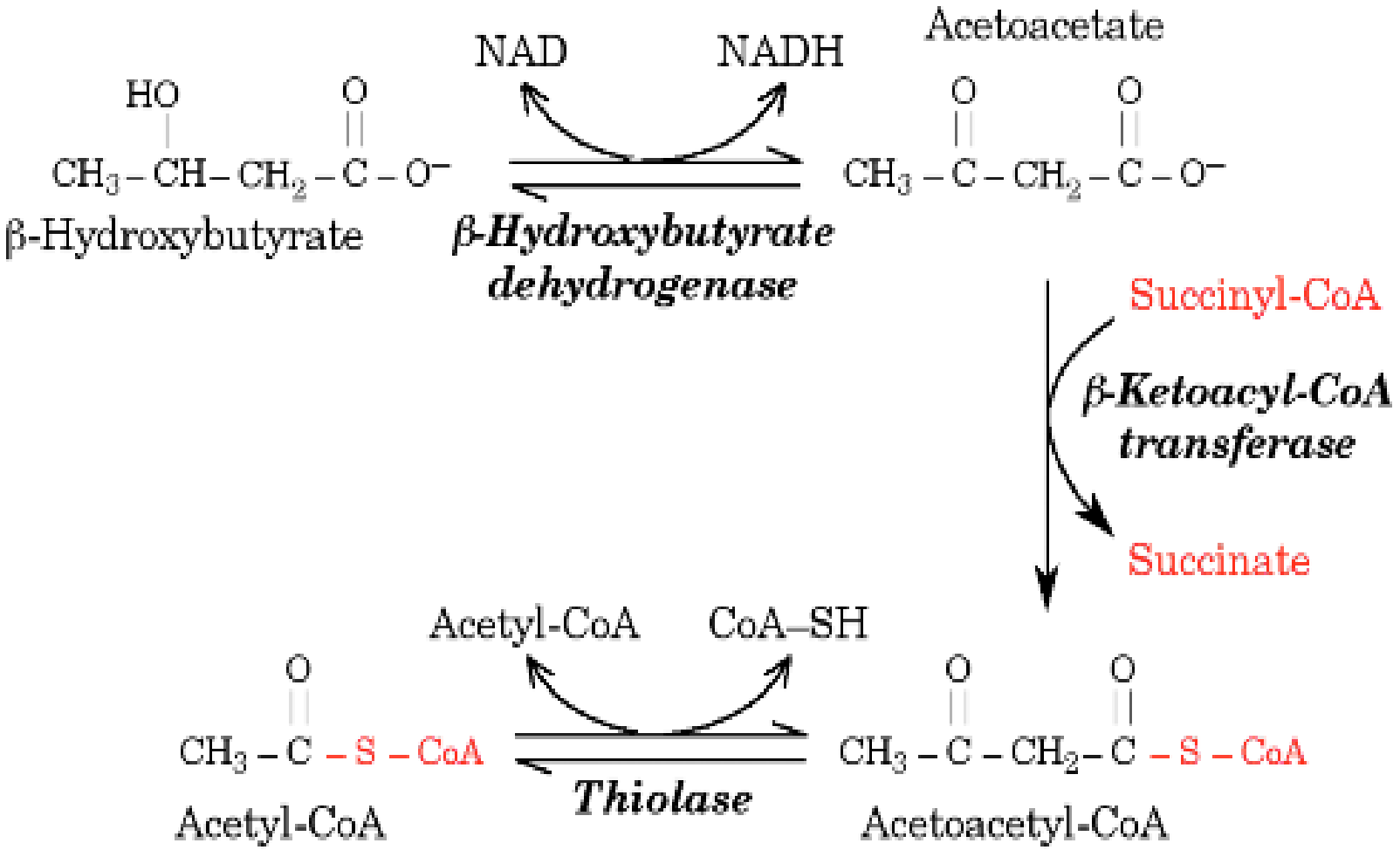


β - Hydroxybutyrate

KETOGENESIS



UTILIZATION OF KETONE BODIES



Fatty Liver and Obesity

- Fatty liver refers to the deposition of excess triglycerides in the liver cells.
- It associates with obesity and dyslipidemia accompanied by high triglycerides and low HDL.

Causes of Fat Deposition in Liver

- Mobilization of non-esterified fatty acids (NEFA) from adipose tissue.
- Deficiency in lipotropic factors may result in fatty liver. E.g vitamin E and selenium, choline, lecithin and methionine and omega 3 fatty acids.
- Excess calorie intake
- Liver insult
- Alcoholism

Obesity

- When fat droplets are overloaded, the nucleus of adipose tissue cell is degraded, cell is destroyed, and TAG becomes extracellular.

LIPIDOSES

- **Lipidoses** are genetic diseases due to disease-specific defects in the enzymatic catabolism of lipids, with accumulation of the respective lipid substrate in the nervous system and/or peripheral tissues.

Diseases	Deficient enzyme	Accumulating lipid	Salient features
Gaucher's disease	Beta glucosidase	Glucocerebroside	3 types—adult, infantile, juvenile. Hepatospleno megaly, erosion of bone, moderate anemia.
Niemann-Pick disease	Sphingo-myelinase	Sphingomyelin	Severe CNS damage, mental retardation, hepatosplenomegaly. Cherry red spot in macula Death occurs by 2 years of age.
Krabbe's leukodystrophy	Beta-galactosidase	Galactocerebroside	Severe mental retardation. Total absence of myelin in CNS. Globoid bodies in white matter.
Metachromatic leukodystrophy	Sulfatide sulfatase	Sulfogalacto-cerebroside	Accumulates in most tissues. Neurological deficit, difficulty in speech and optic atrophy. Demyelination is also seen.
Fabry's disease	alpha-galactosidase	Ceramide trihexoside	Kidney is the site of accumulation. Progressive renal failure. Death by 5 years of age. Purplish papules appear. 'X' linked inheritence.
Tay Sachs disease	Hexosaminidase A	Ganglioside (GM2)	Incidence 1 in 6000 births. Mental Retardation. Cherry red spot in the macula. Progressive deterioration. Death by 3-4 years.

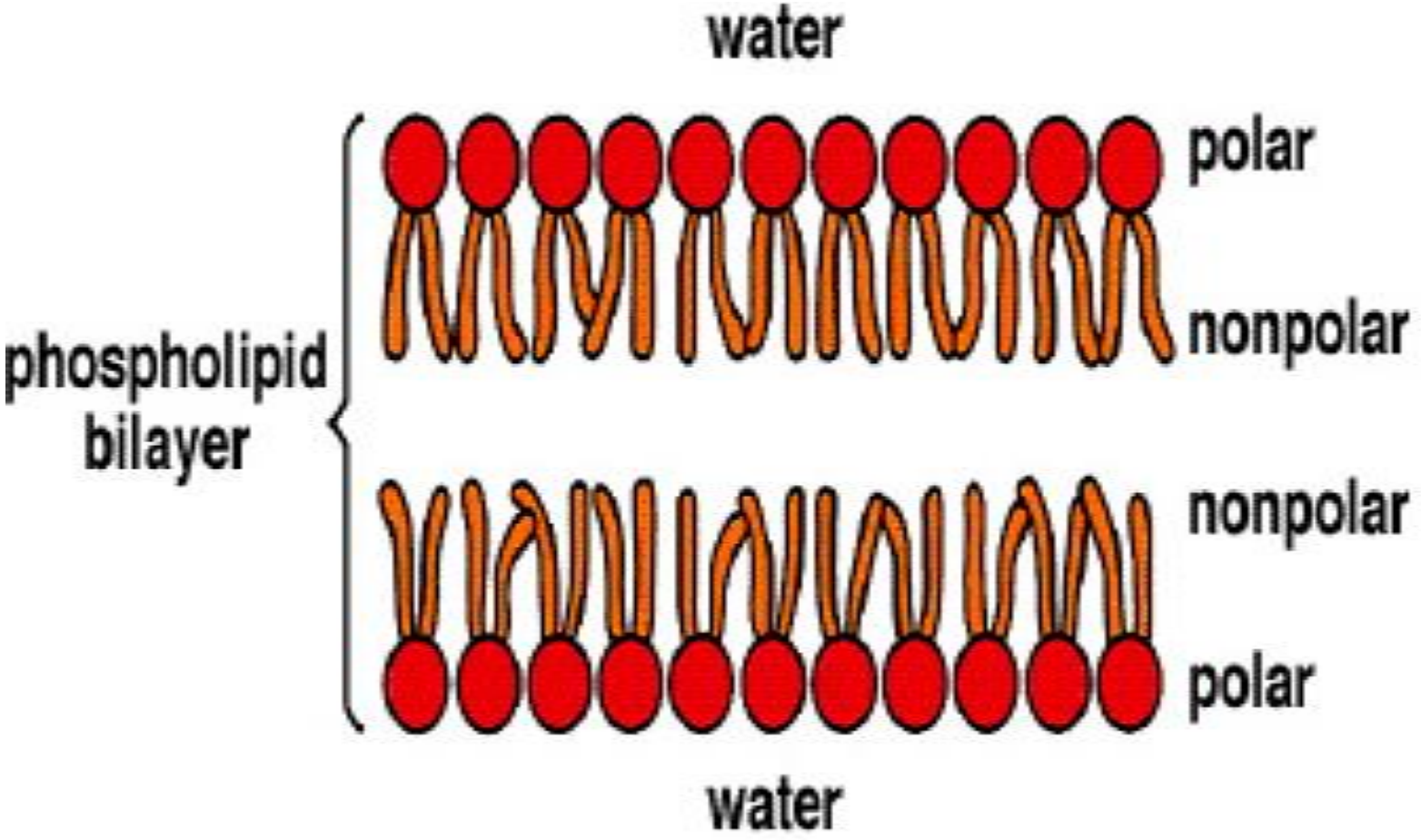
Generalized gangliosidoses	**Beta-galactosidase**	**Ganglioside (GM1)**	Mental retardation, hepatomegaly, skeletal deformities. Foam cells in bone marrow. Cherry red spot in the retina.
Lactosyl ceramidoses	**Beta-galactosidase**	**Lactosyl ceramide**	Mainly CNS and reticulo-endothelial system affected.
Sandhoff's disease	**Hexosaminidase A and B**	**Globoside**	Neurological deficit, mental retardation.

Disorders of Neutral Fats

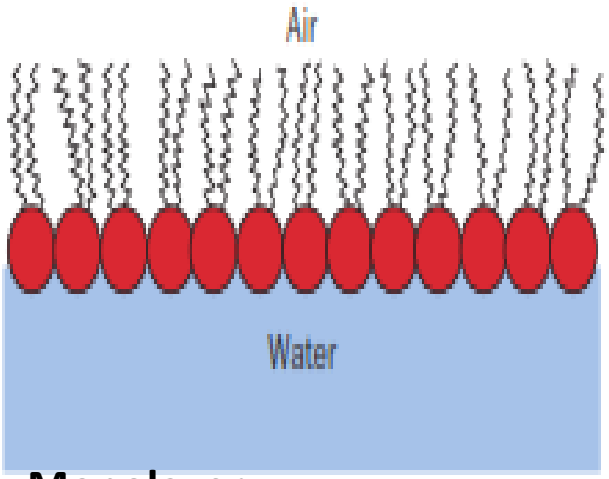
- Wolman disease
- Cholesterol ester storage disease

BIOLOGICAL MEMBRANE

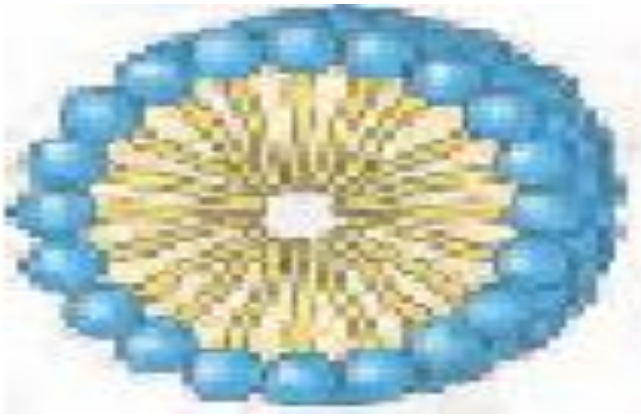
- Biological membranes are selectively permeable barriers composed of proteins associated with a lipid bilayer matrix


water
polar
nonpolar
phospholipid
bilayer
nonpolar
polar
water

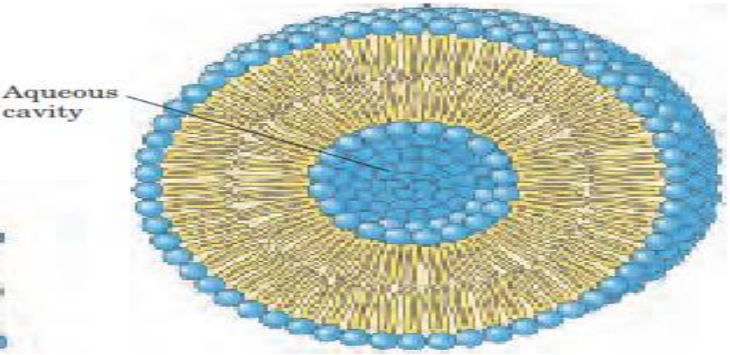
Aggregates of Lipids in water



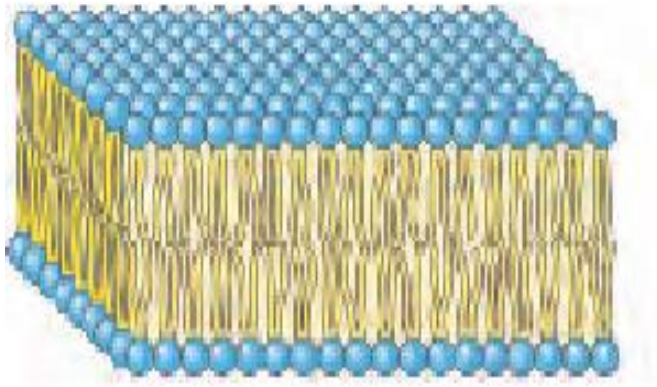
Monolayer



Micelles



Liposome

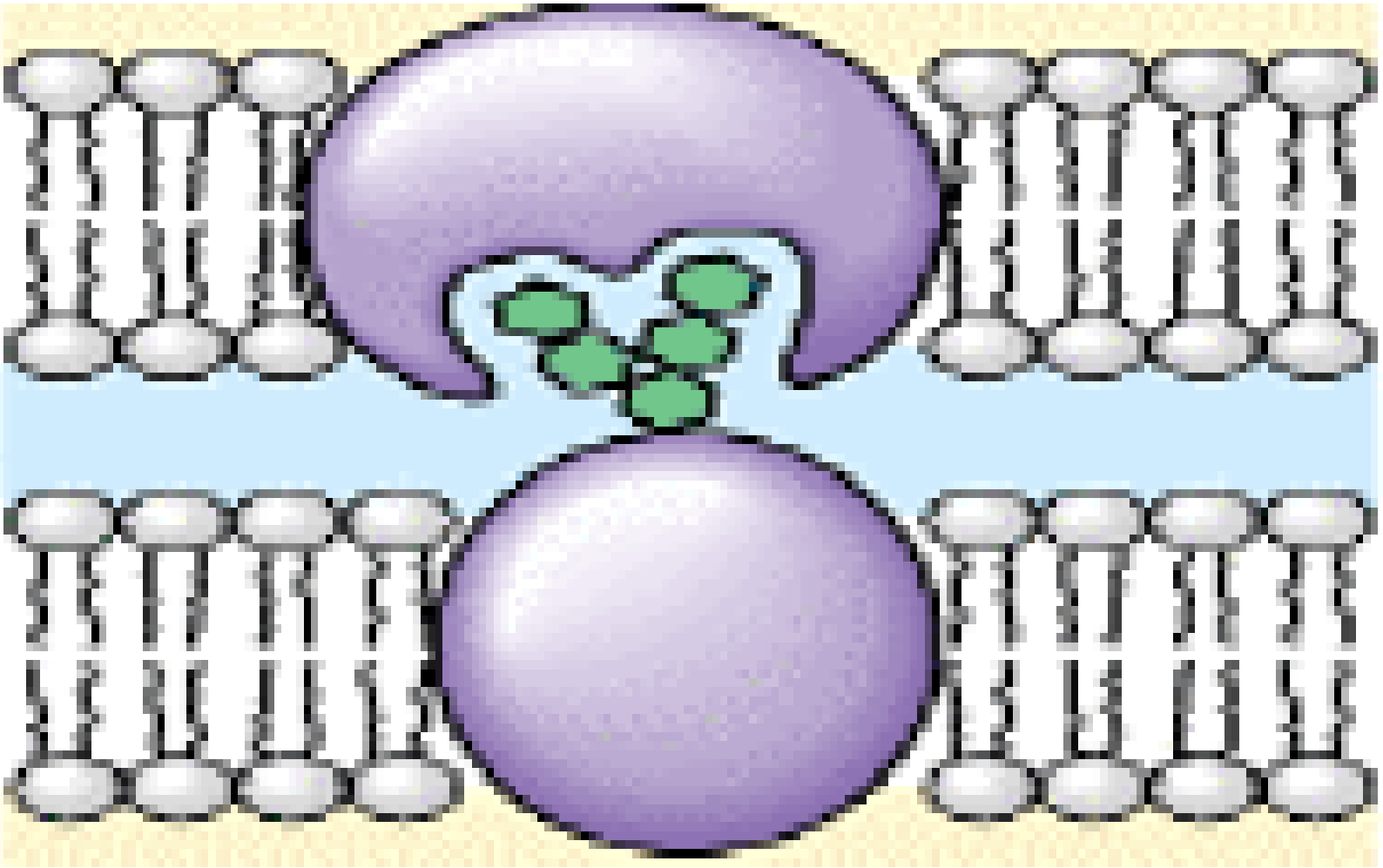


Bilayer

MEMBRANE FUNCTION

- Compartmentalization and Protective barrier
- Regulate transport in and out of cell
- Allow cell recognition e.g. cell recognition protein (MHC)
- Provide anchoring sites for filaments of cytoskeleton and scaffold for biochemical reactions
- Provide a binding site for enzymes (receptor)
- Intercellular interaction (interlocking surface or junctions connector)
- Contains the cytoplasm
- Signal transduction
- Enzymatic activity

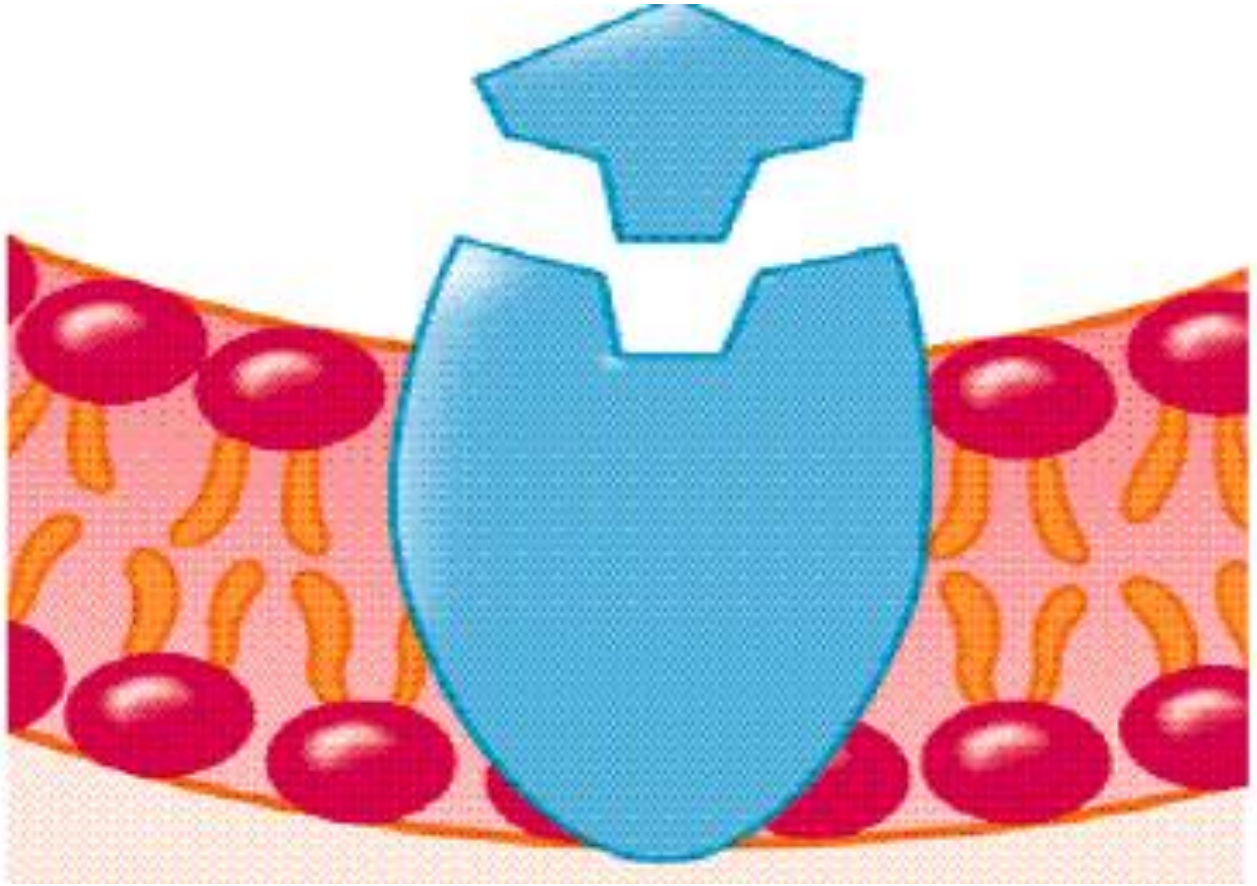
Cell recognition



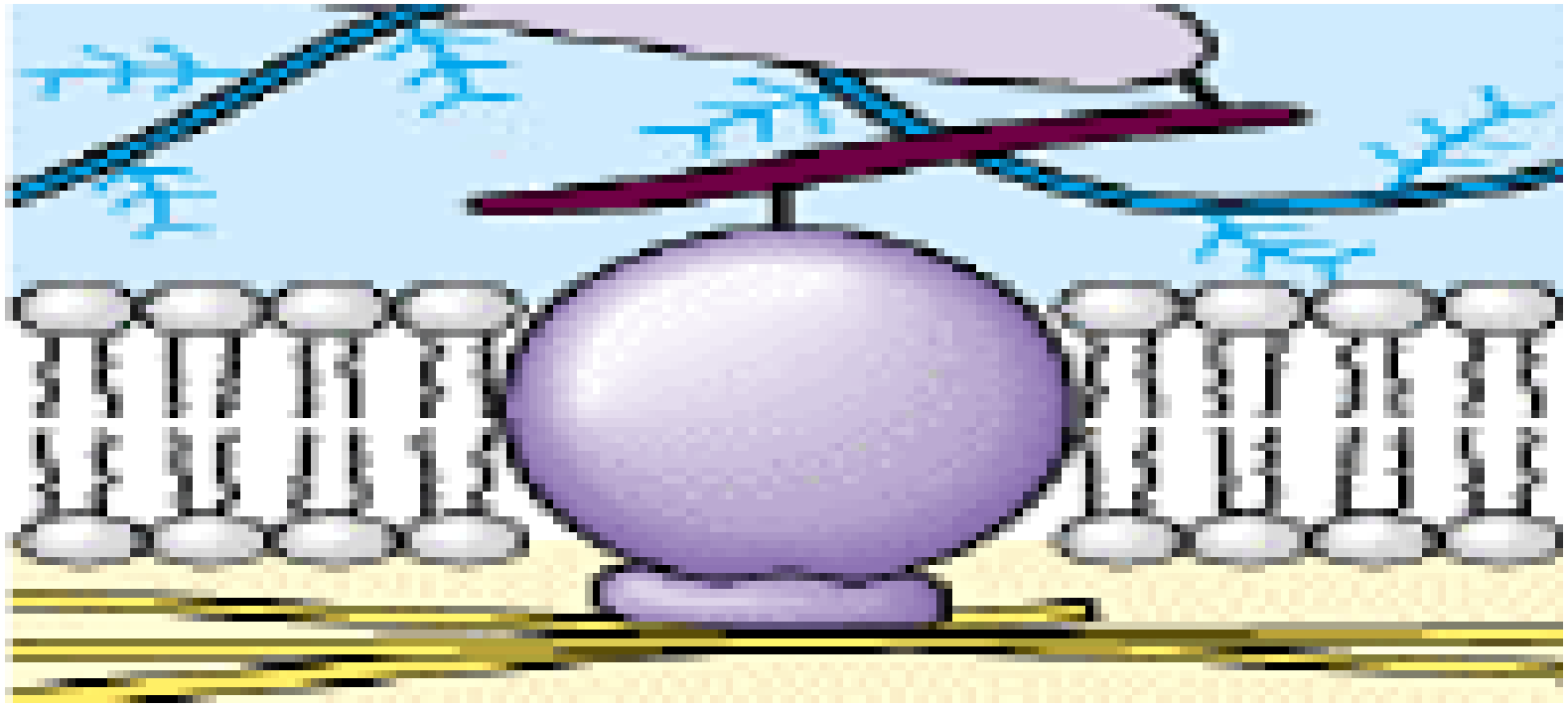
Membrane Transport

Membrane transport may be mediated by the carrier proteins e.g GLUT 2

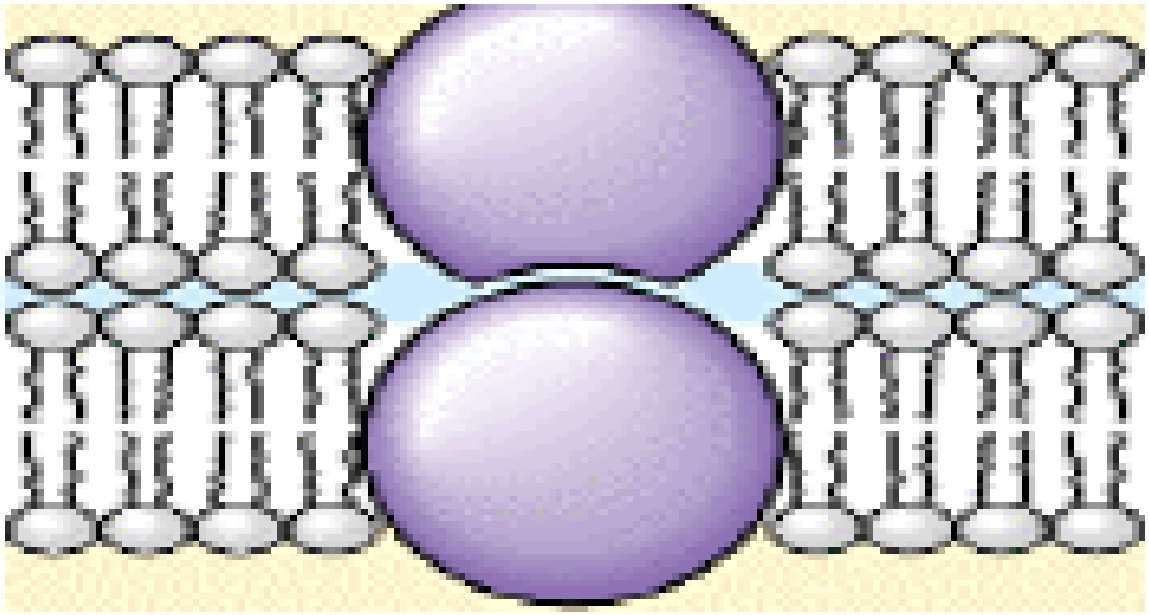
Binding site for enzyme



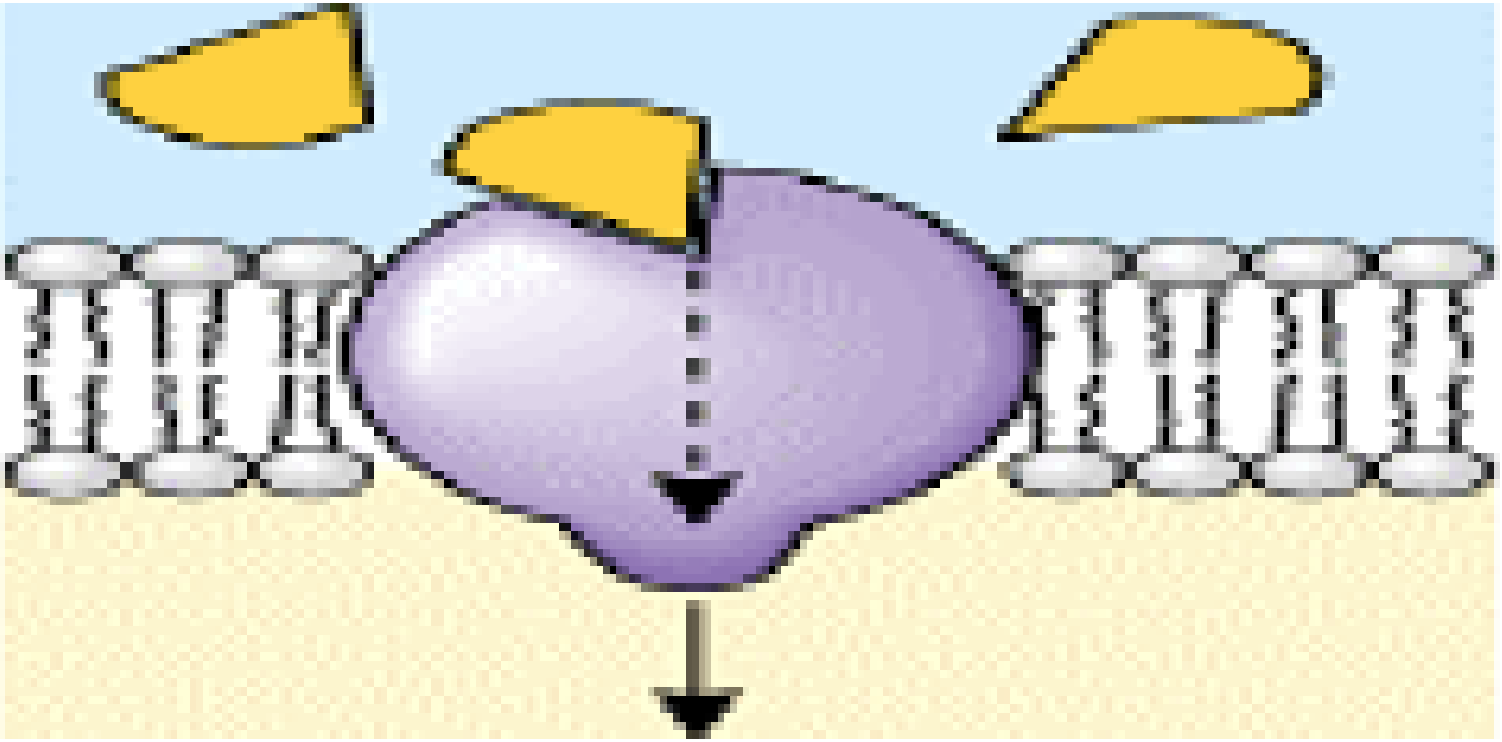
Anchoring and scaffold



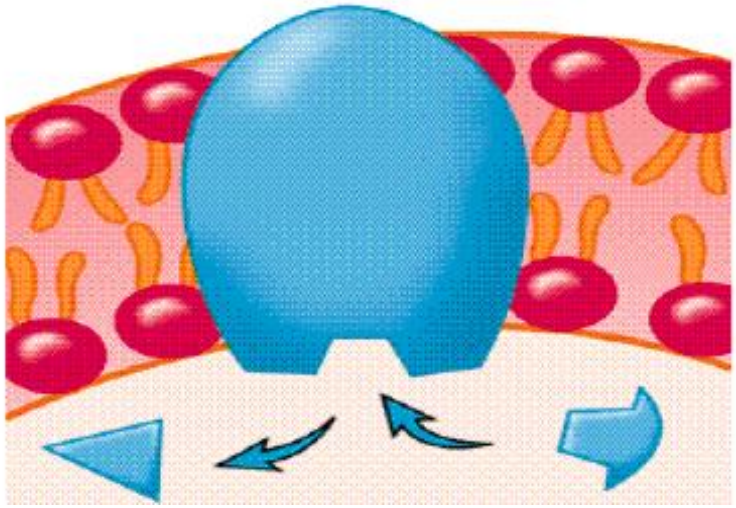
Intercellular interaction



Signal transduction



Enzymatic Activity



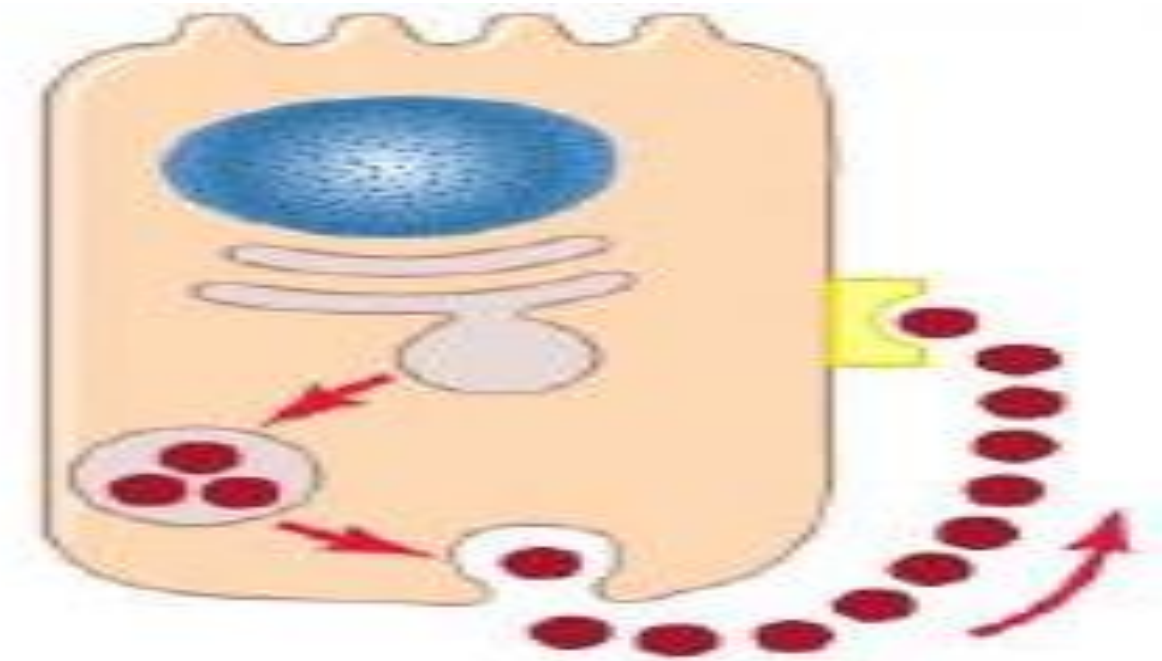
- For example, the membrane protein, adenylyl cyclase, is involved in ATP metabolism.

- Cholera bacteria release a toxin that interferes with the proper functioning of adenylyl cyclase, thus making sodium ion and water leave intestinal cells and the individual dies from severe diarrhea and dehydration.

CELL COMMUNICATION

- Cell communication is very essential for multicellular organisms. For instance, response to pain signals by the muscle cells.
- Why do cells communicate?
- How do cell communicate?
- Cells communicate through any of four basic mechanisms, depending primarily on the distance between the signaling and responding cells.
- In addition, some cells send signals that bind to specific receptors on their own plasma membrane. This is called autocrine signaling which is believed to play an important role in reinforcing developmental process.

Autocrine signaling



- External signals on the cell surface are converted into cellular responses by signal transduction pathways.
- These signals are in form of chemical messengers.
- A hormone is a chemical released by a cell in one part of the body, that sends out messages that affect cells in other parts of the organism.
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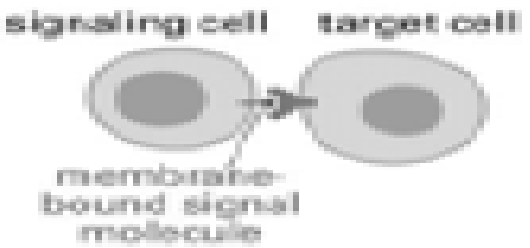
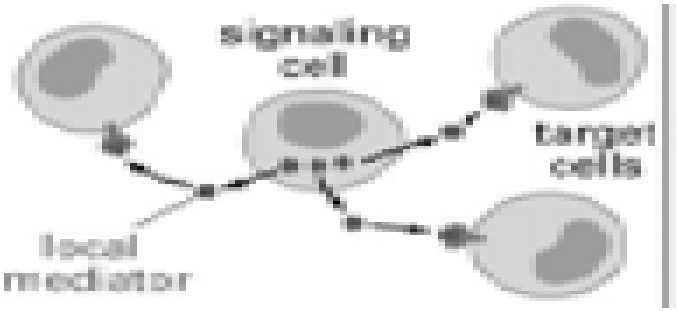
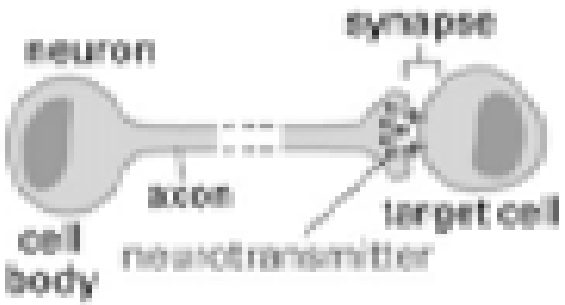
Types of cell signaling



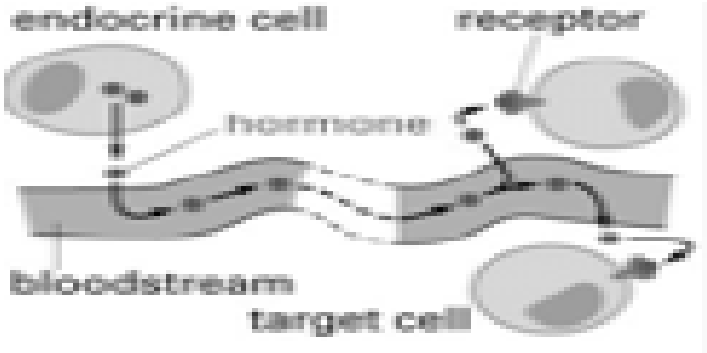
Direct contact



Paracrine signaling



Synaptic signaling



Endocrine signaling

- **Paracrine signaling**

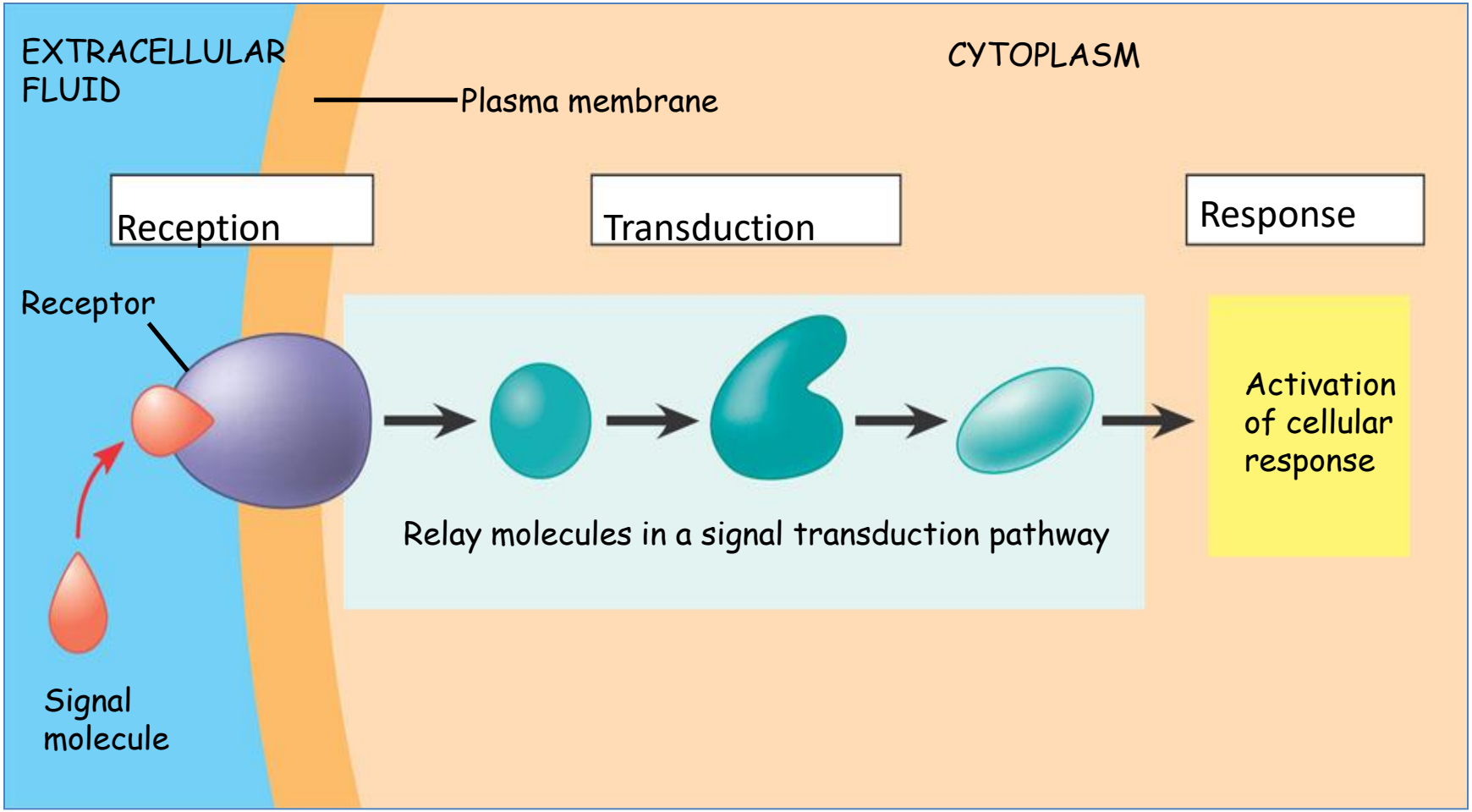
- Paracrine signals are released by cells into the extracellular fluid in their neighborhood and act locally (short distant). E.g. PGE1

- **Endocrine signaling**: hormone produced in endocrine glands are secreted into the bloodstream and are often distributed widely throughout the body.

- **Direct contact**: Cells that maintain an intimate membrane-to-membrane interface can engage in contact-dependent signaling.

- **Synaptic signals** are transmitted along axons to remote target cells.

Overview of cell signaling



- **Reception** occurs when a signal molecule binds to a receptor protein, causing a conformational change to occur.
- **Transduction:** The binding of the signal molecule alters the receptor protein in some way
- The signal usually starts a cascade of reactions known as a signal transduction pathway
- Multistep pathways can amplify a signal

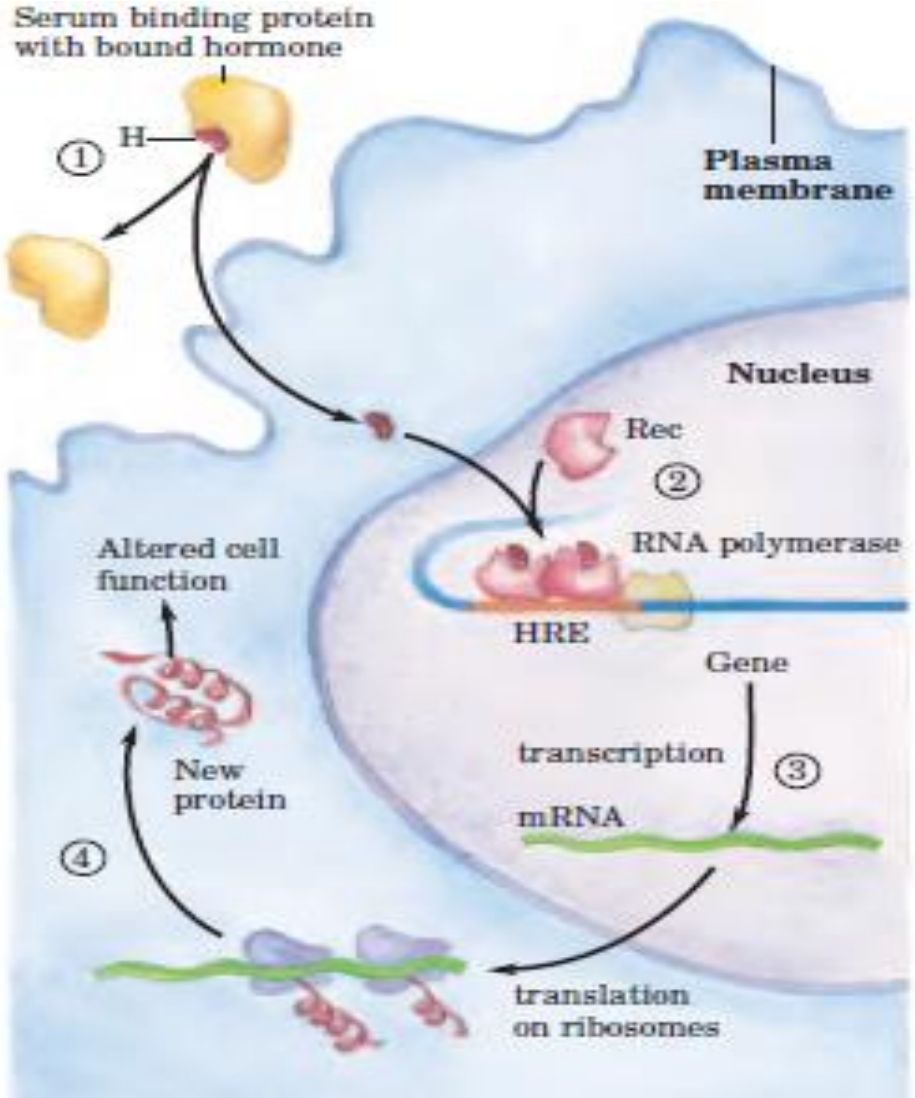
Response

- Cell signaling leads to regulation of cytoplasmic activities or transcription
  - Signaling pathways regulate a variety of cellular activities

Hormone Receptor

- Nuclear receptor: estrogen
- Cytoplasmic receptors: testosterone and thyroid hormones
- Cell surface receptor: peptide hormone and catecholamines

NUCLEAR RECEPTOR



① Hormone (H), carried to the target tissue on serum binding proteins, diffuses across the plasma membrane and binds to its specific receptor protein (Rec) in the nucleus.

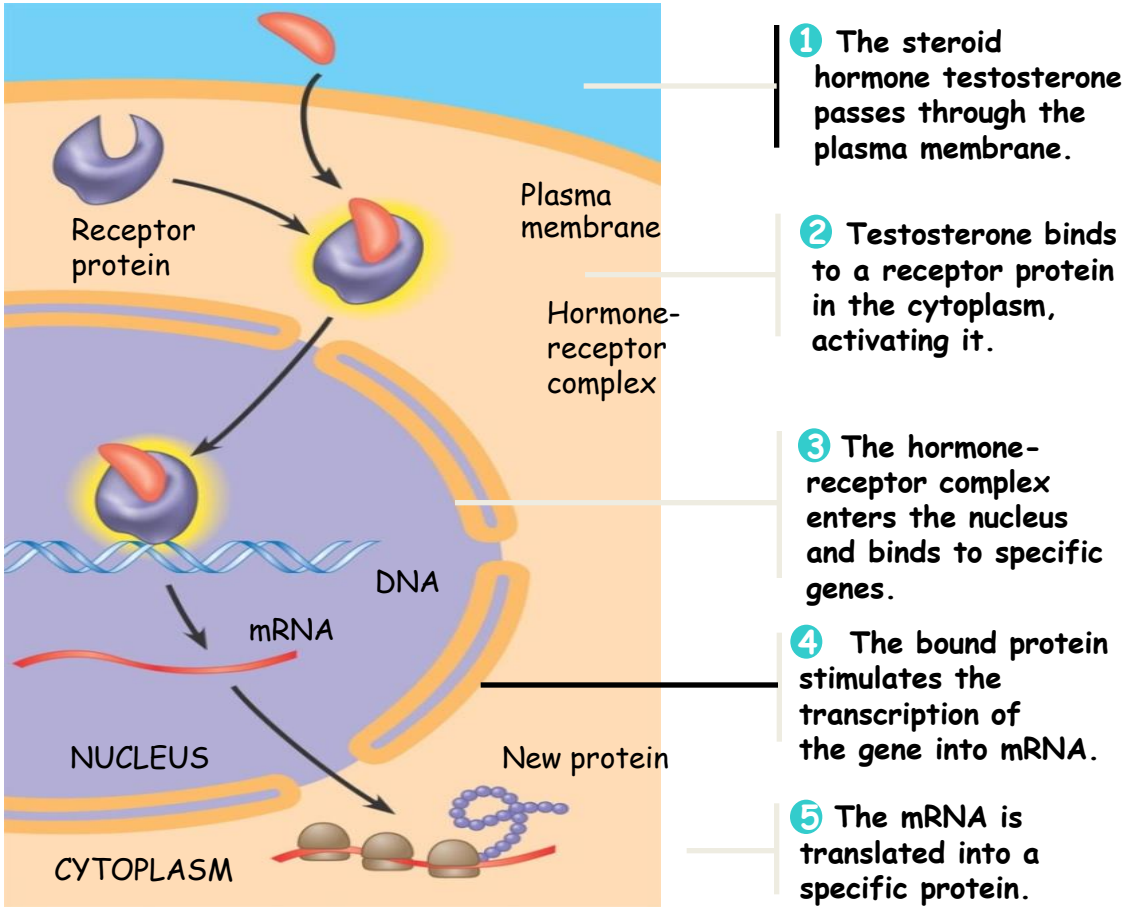
② Hormone binding changes the conformation of Rec; it forms homo- or heterodimers with other hormone-receptor complexes and binds to specific regulatory regions called hormone response elements (HREs) in the DNA adjacent to specific genes.

③ Binding regulates transcription of the adjacent gene(s), increasing or decreasing the rate of mRNA formation.

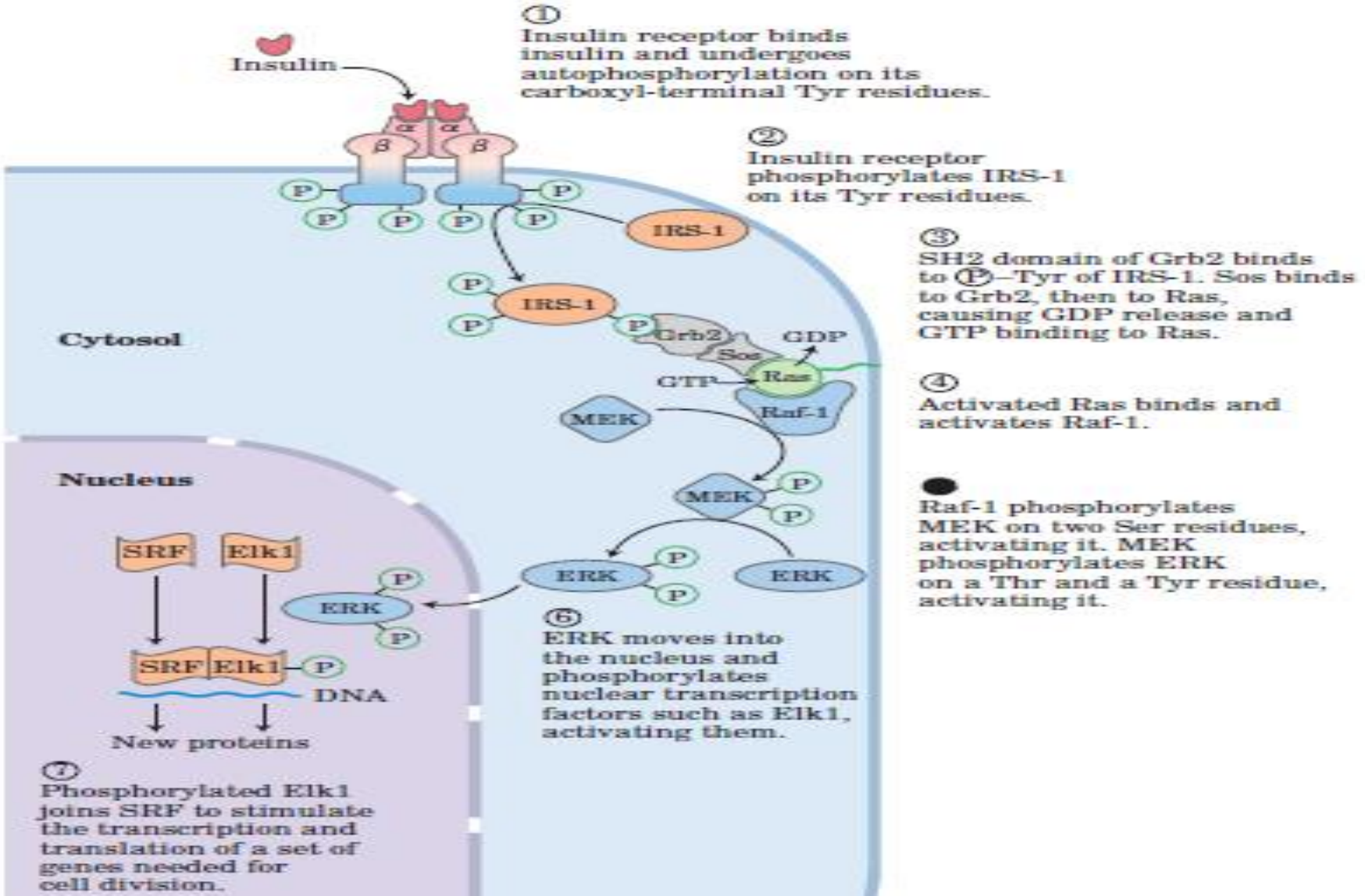
④ Altered levels of the hormone-regulated gene product produce the cellular response to the hormone.

CYTOPLASMIC RECEPTOR

Steroid hormones bind to intracellular receptors

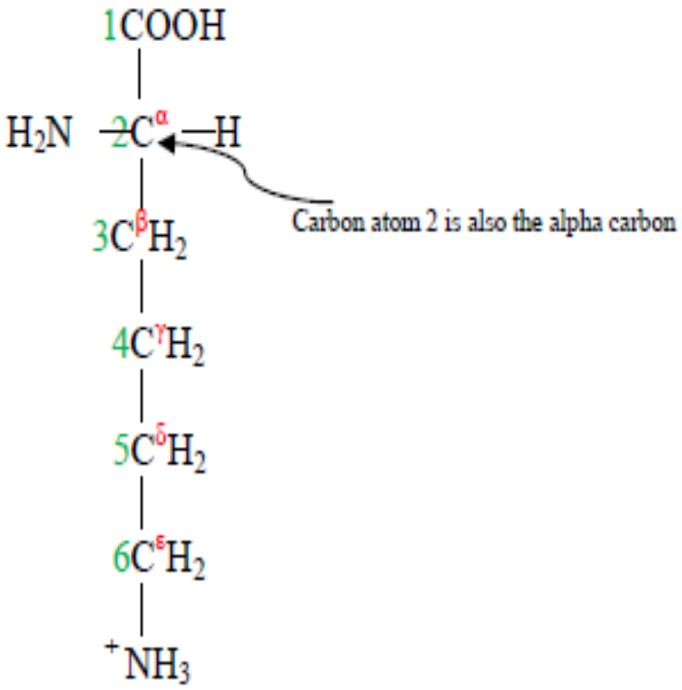


CELL SURFACE RECEPTOR: Receptor Tyrosine Kinase



Signal Molecule	Site of Origin	Chemical Nature	Some Actions
Hormones			
Adrenaline	adrenal gland	derivative of the amino acid tyrosine	increases blood pressure, heart rate, and metabolism
Cortisol	adrenal gland	steroid (derivative of cholesterol)	affects metabolism of proteins, carbohydrates, and lipids in most tissues
Estradiol	ovary	steroid (derivative of cholesterol)	induces and maintains secondary female sexual characteristics
Glucagon	alpha cells of pancreas	peptide	stimulates glucose synthesis, glycogen breakdown, and lipid breakdown in, e.g., liver and fat cells
Insulin	beta cells of pancreas	protein	stimulates glucose uptake, protein synthesis, and lipid synthesis in, e.g., liver cells
Testosterone	testis	steroid (derivative of cholesterol)	induces and maintains secondary male sexual characteristics
Thyroid hormone	thyroid gland	derivative of the amino acid tyrosine	stimulates metabolism of many cell types

Numbering of carbon atoms in amino acids



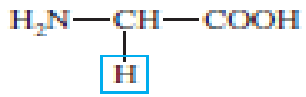
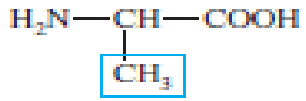
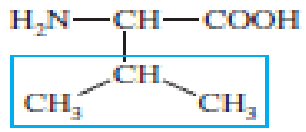
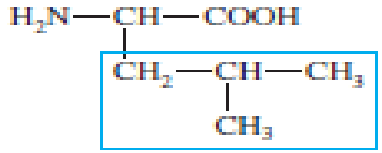
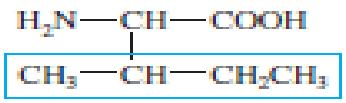
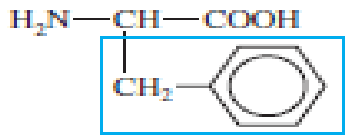
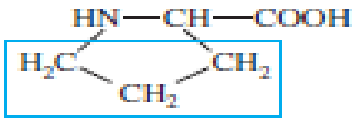
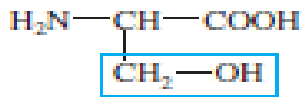
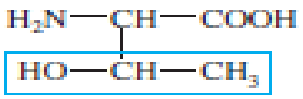
Stereochemistry of amino acids

- Stereochemistry of proteins explains the three-dimensional arrangement of the constituent atoms of the molecule in space.
- The configuration of simple sugar and amino acids are specified by L, D system.
- Various compounds formed from the different spatial arrangement of the compound are called its stereoisomers.
- Stereoisomers that are mirror images of each other are called enantiomers. If otherwise, they are called diastereomers

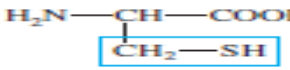
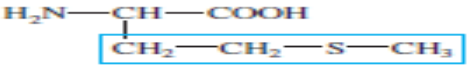
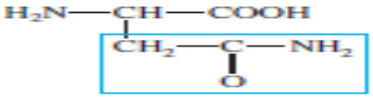
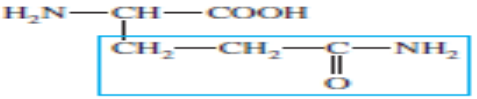
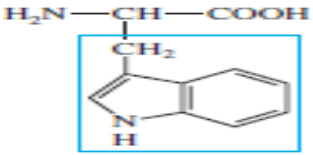
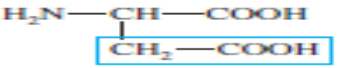
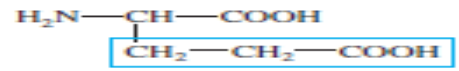
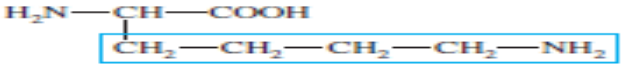
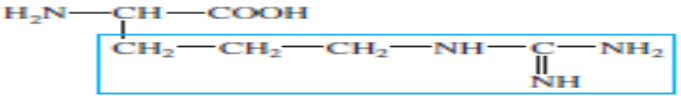
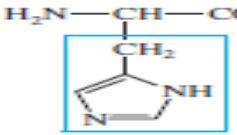
Standard amino acids

- These are the common amino acids found in proteins and they are essentially 20

The Standard Amino Acids

Name	Symbol	Abbreviation	Structure	Functional Group in Side Chain
side chain is nonpolar, H or alkyl				
glycine	G	Gly		none
alanine	A	Ala		alkyl group
*valine	V	Val		alkyl group
*leucine	L	Leu		alkyl group
*isoleucine	I	Ile		alkyl group
*phenylalanine	F	Phe		aromatic group
proline	P	Pro		rigid cyclic structure
side chain contains an —OH				
serine	S	Ser		hydroxyl group
*threonine	T	Thr		hydroxyl group

The Standard Amino Acids (*continued*)

Name	Symbol	Abbreviation	Structure	Functional Group in Side Chain
tyrosine	Y	Tyr		phenolic —OH gro
side chain contains sulfur				
cysteine	C	Cys		thiol
*methionine	M	Met		sulfide
side chain contains nonbasic nitrogen				
asparagine	N	Asn		amide
glutamine	Q	Gln		amide
*tryptophan	W	Trp		indole
side chain is acidic				
aspartic acid	D	Asp		carboxylic acid
glutamic acid	E	Glu		carboxylic acid
side chain is basic				
*lysine	K	Lys		amino group
*arginine	R	Arg		guanidino group
*histidine	H	His		imidazole ring

*essential amino acid

Classification based on polarity

- **Amino Acids with Nonpolar Side Chains**
- Examples are Glycine, Alanine, Valine, Leucine, Isoleucine, Methionine, Proline, Phenylalanine and Tryptophan
- **Amino Acids with Polar Side Chains**
- **Uncharged polar R groups**: e.g. **Serine** and **Threonine** - are polar because of their hydroxyl groups.

- **Asparagine** and **Glutamine** – the polarity is due to the presence of amide-bearing R groups.

- **Tyrosine** – has an OH functional group attached to benzene ring. This OH is hydrophilic.

- **Cysteine** – its thiol or (SH) group is responsible for its polarity

➢ Charged polar R groups

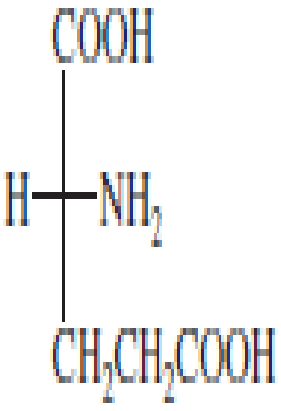
- At physiological pH, **Lysine**, **Arginine** and **Histidine** are positively charged due to their terminal ammonium, guanidinium, and the imidazolium groups respectively
- **Aspartic acid** and **Glutamic acid** are negatively charged above pH 3

Classification based on nutritional requirements

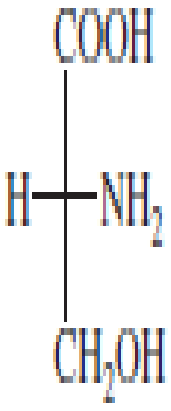
- **Essential amino acids**: Examples include Arg, Val, Met, Leu, Thr, Phe, His, Ile, Lys, and Trp.
- Dietary proteins that contain all the essential amino acids in the right proportion is said to be complete proteins e.g. fish, meat and egg.
- The proteins that are seriously deficient in one or several amino acids are called incomplete proteins e.g. plant proteins.

Rare and unusual amino acids

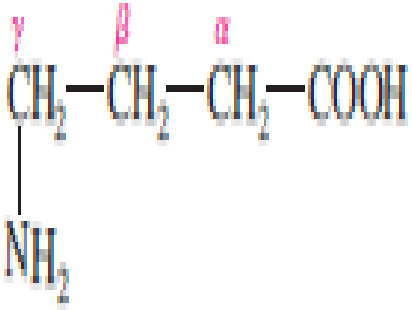
- For example, 4-hydroxyproline and 5-hydroxylysine, GABA (γ-amino butyric acid), β-alanine, D-glutamic acid, Ornithine, citrulline, homoserine are unusual amino acids.
-



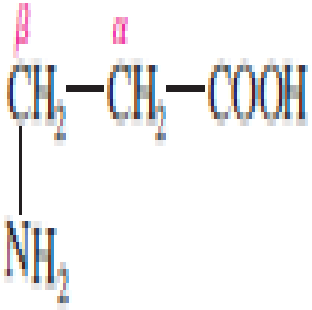
D-glutamic acid



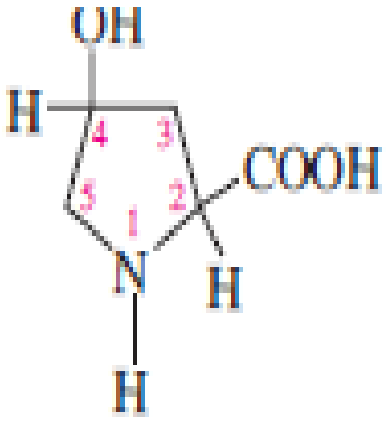
D-serine



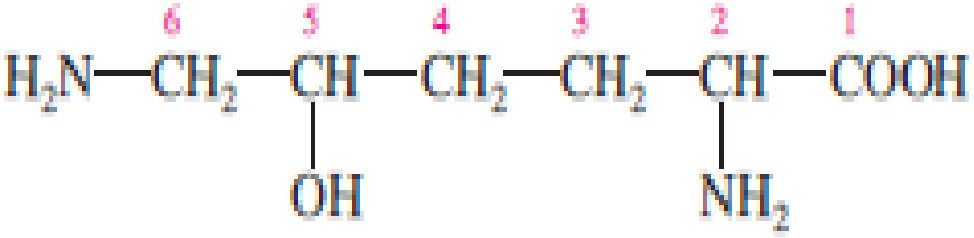
γ-aminobutyric acid



β-alanine



4-hydroxyproline



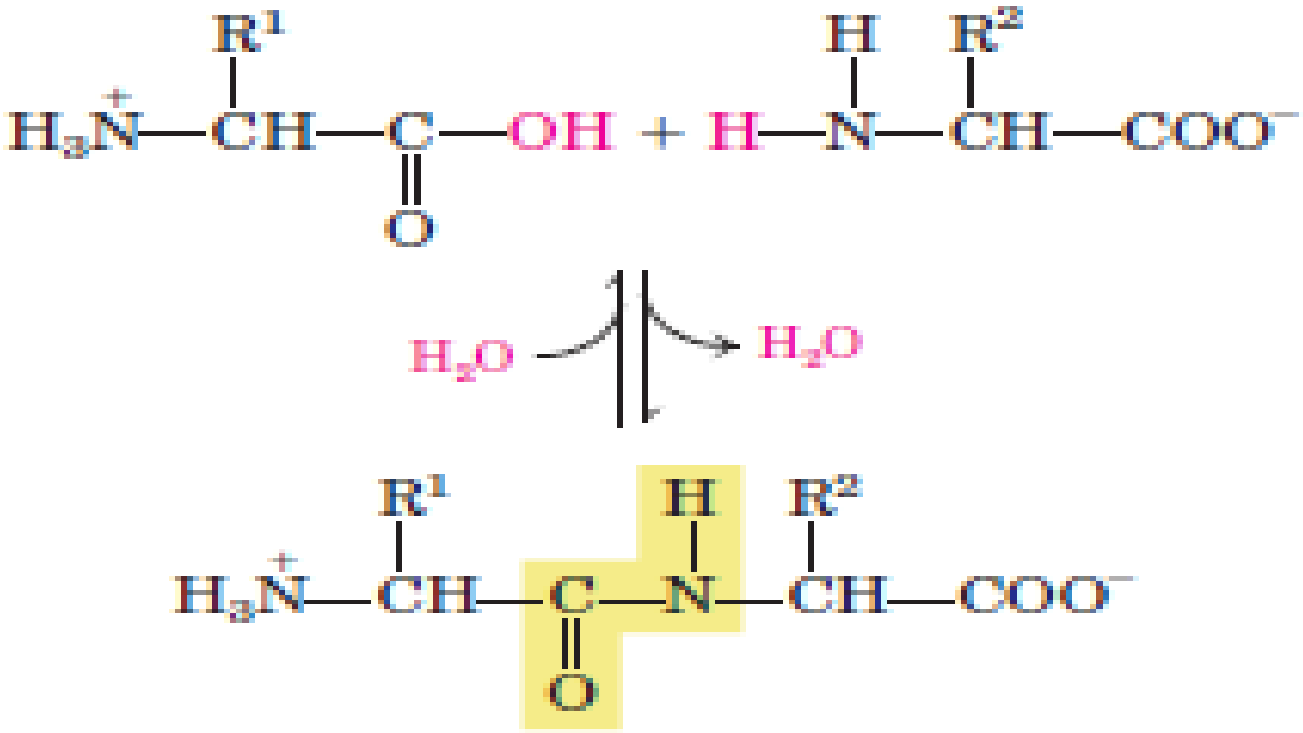
5-hydroxylysine

Classificaition of protein based on shape and size

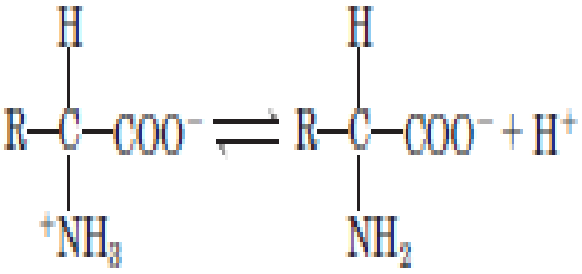
- **Fibrous proteins**
- These are proteins that exist as long fibres. They are tough and water-insoluble. Examples involve alpha keratin found in hair, skin; beta-keratin
- **Globular proteins**
- These are mostly water-soluble and fragile in nature. Examples include enzymes, haemoglobin, hormones and antibodies

Structural organization of proteins

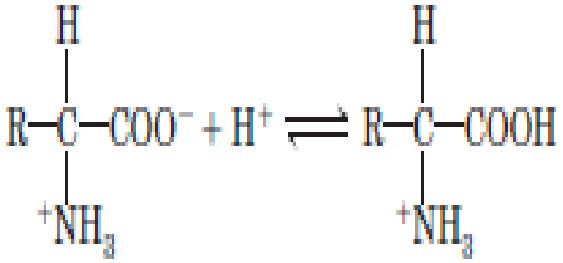
- Primary structure: The primary structure of protein is the linear order of amino acid or its sequence in a given protein.
- Proteins are linear polymers formed by covalent linkage of α-carboxyl group of an amino acid and α-amino group of another amino acid by a peptide bond.


R1
H3N+—CH—C—OH + H—N—CH—COO−
H
R2
O
H2O
H2O
R1
H
R2
H3N+—CH—C—N—CH—COO−
O

- **Amphoteric nature of amino acids**: This is the ability of amino acid in aqueous solution to exist either as acid or base.
- This amino acid is said to be dipolar ion or zwitterion.



Zwitterion



Zwitterion

- **Secondary structures**
- These are the interactions of about tens amino acid residues to give rise to regular repeating structures.
- Each of these regular repeats is called a helix.
- The two main types of secondary structure are the α-helix and the ß-sheet.

- **The α-helix** is a right-handed coiled strand.
- Some amino acids have high helix forming tendencies. These include methionine, alanine, leucine, glutamate, and lysine.
- While others such as proline, glycine, and aspartate are negatively disposed to α-helix formation.
- **Beta strands:** these are the most fundamental helix, having essentially a 2D backbone of folds like pleating skirt.

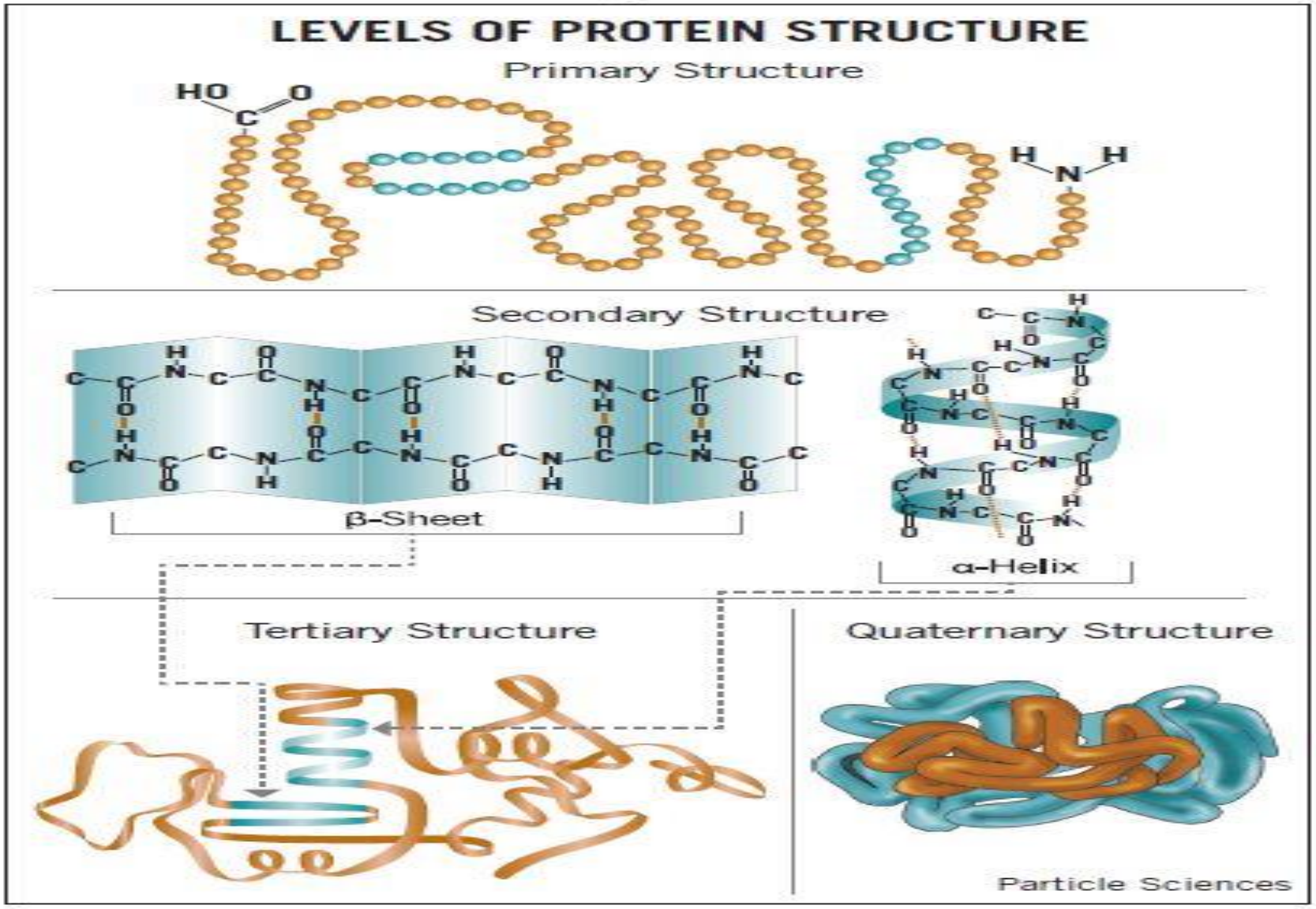
Tertiary Structure

- The overall three-dimensional shape of an entire protein molecule is the tertiary structure.
- It is the overall folding pattern of a single covalently linked molecule.
- The characteristic bond type are: hydrophobic and others- hydrogen, ion pair, van der Waals, and disulphide.

Quaternary Structure

- This is the association of two or more independent proteins via non-covalent forces to form a multimeric protein. That is, many protein subunits come together to form the quaternary structure.
- This subunits may be homodimers or heterodimers.
- The quaternary structure refers to how these protein subunits interact with each other and arrange themselves to form a larger aggregate protein complex
- The final shape of the protein complex is also stabilized by various interactions, like hydrogen-bonding, disulfide-bridges and salt bridges.

Figure 2


LEVELS OF PROTEIN STRUCTURE
Primary Structure
Secondary Structure
β-Sheet
α-Helix
Tertiary Structure
Quaternary Structure
Particle Sciences