

# **BCM 225 LECTURE**

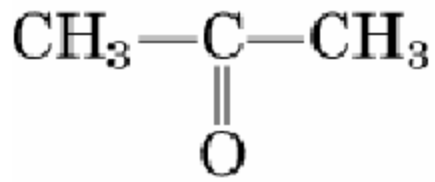
**SALEMCITY, A.J**

# KETOSIS AND KETONE BODIES

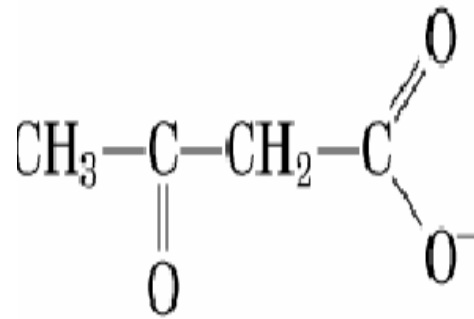
- What is ketosis?
- This is a condition in which the level of ketone bodies in the urine and the blood are elevated, conditions known as ketonuria and ketonemia respectively.
- This condition can result in ketoacidosis commonly experienced in diabetes mellitus.

# Ketone Bodies

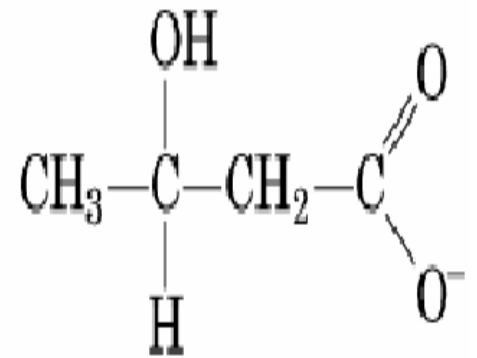
- These are the chemicals produced when fatty acids are broken down in excess.
- They include acetoacetic acid,  $\beta$ -hydroxy butyric acid and acetone.
- The ketone bodies are usually utilized in the heart and brain during starvation when glucose is not available.
- The synthesis of these compounds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



Acetone

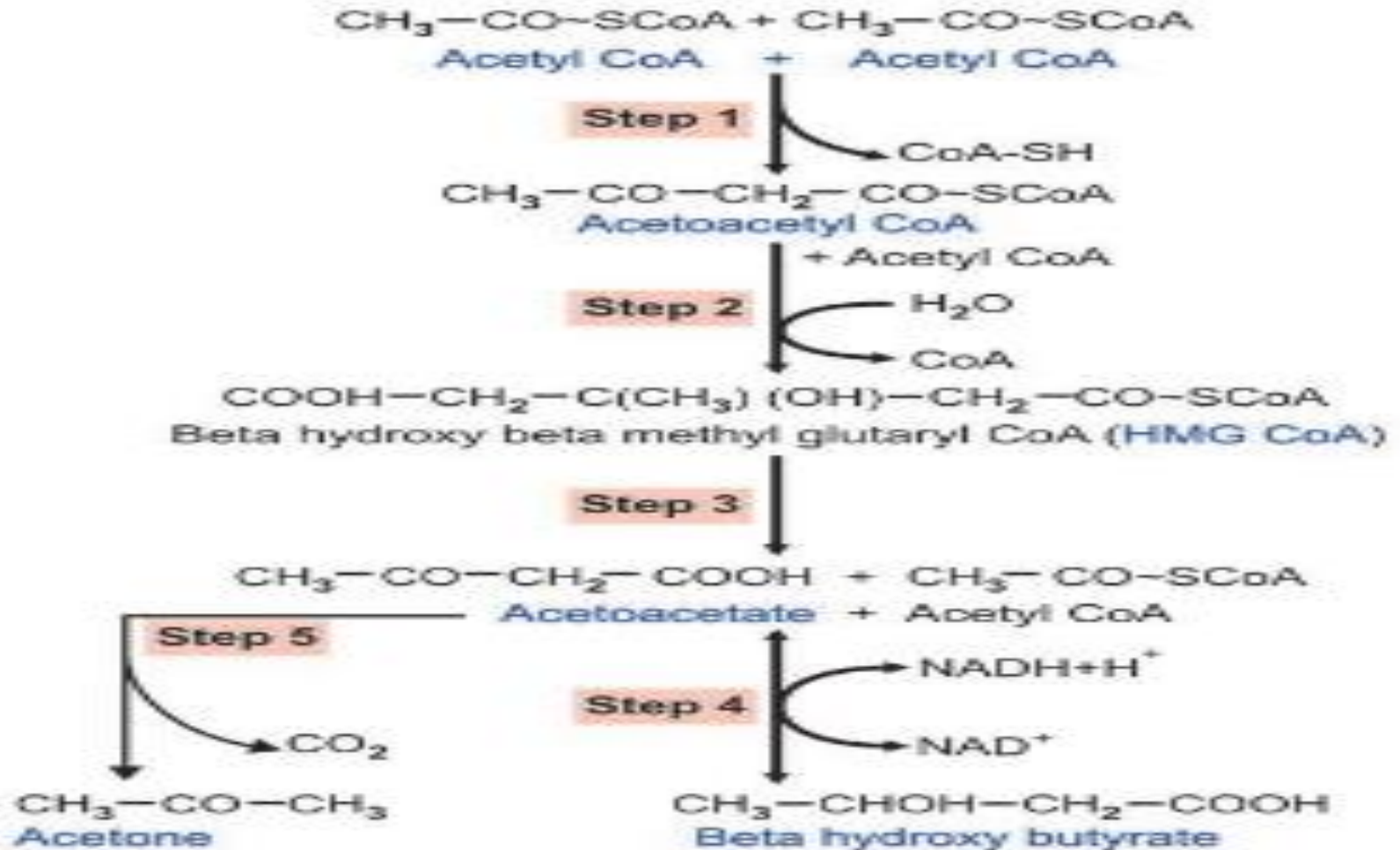


Acetoacetate

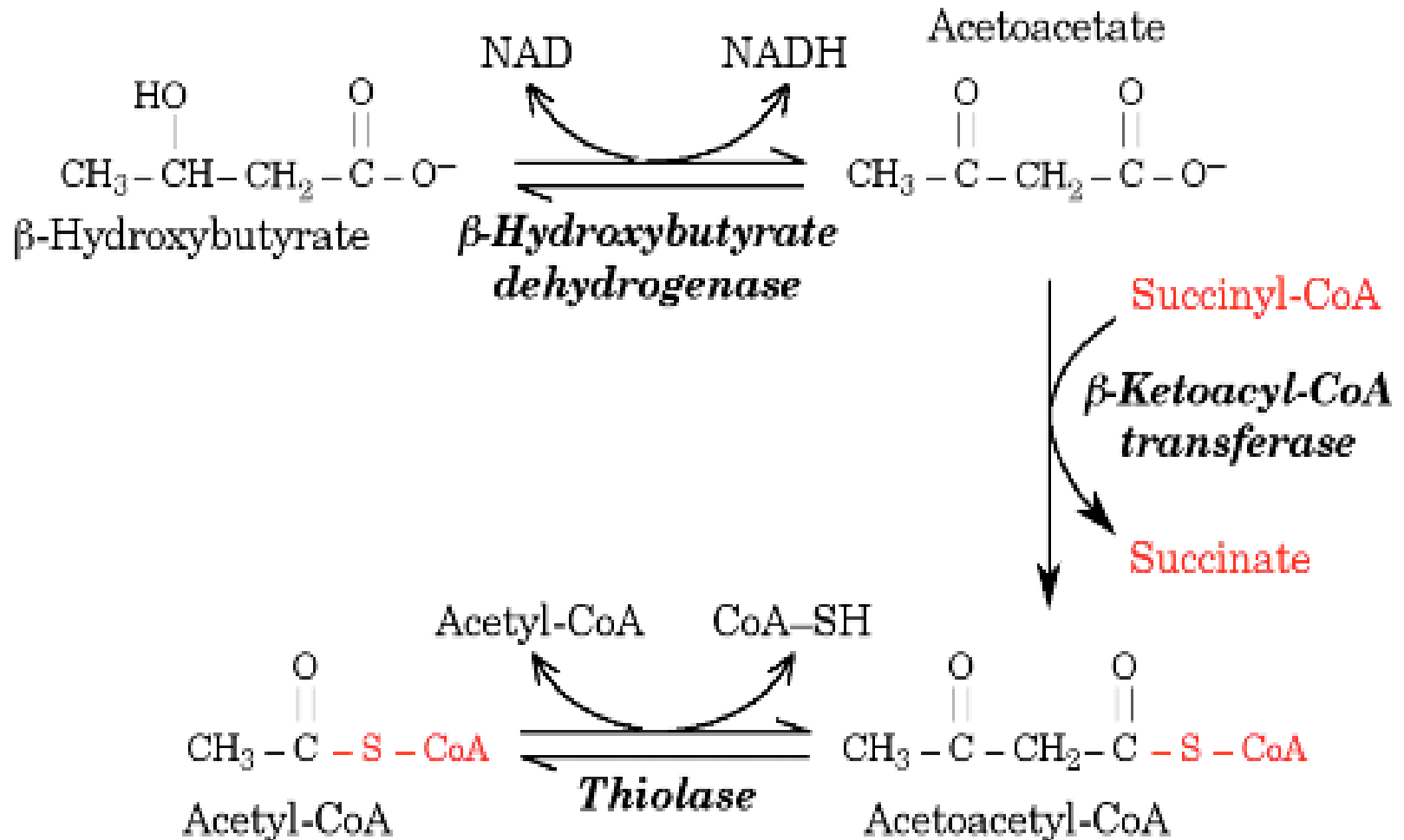


$\beta$  - Hydroxybutyrate

# 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.

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

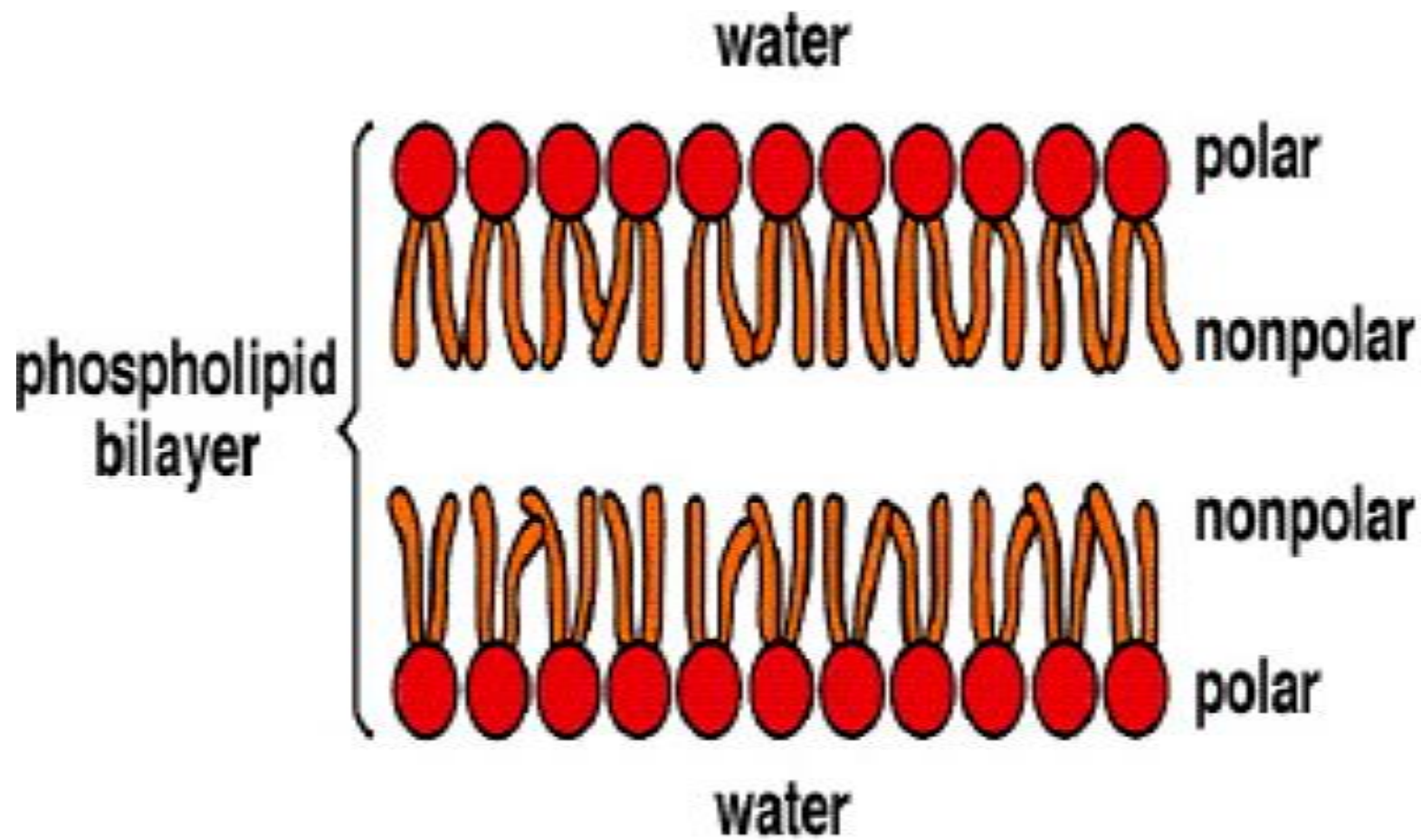
<b>Generalized gangliosidoses</b>	<b>Beta-galactosidase</b>	<b>Ganglioside (GM1)</b>	Mental retardation, hepatomegaly, skeletal deformities. Foam cells in bone marrow. Cherry red spot in the retina.
<b>Lactosyl ceramidoses</b>	<b>Beta-galactosidase</b>	<b>Lactosyl ceramide</b>	Mainly CNS and reticulo-endothelial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

# Disorders of Neutral Fats

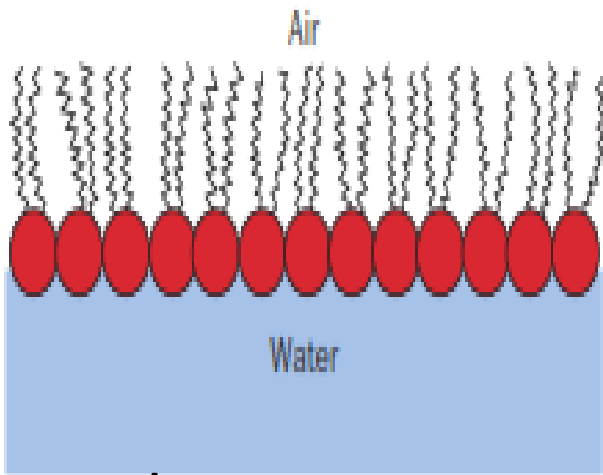
- Wolman disease
- Cholesterol ester storage disease

# BIOLOGICAL MEMBRANE

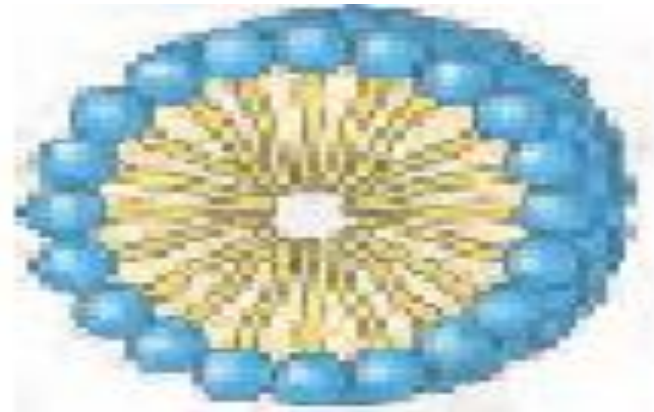
- Biological membranes are selectively permeable barriers composed of proteins associated with a lipid bilayer matrix



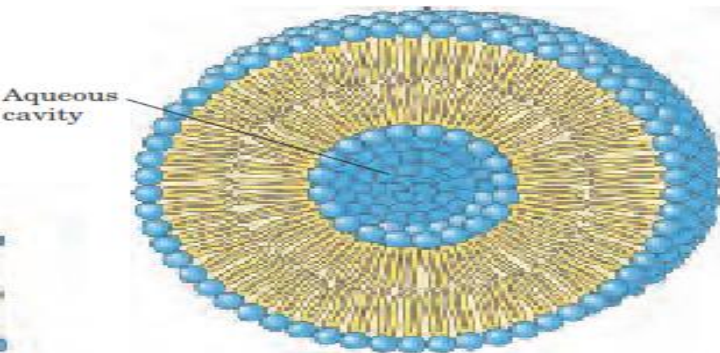
# Aggregates of Lipids in water



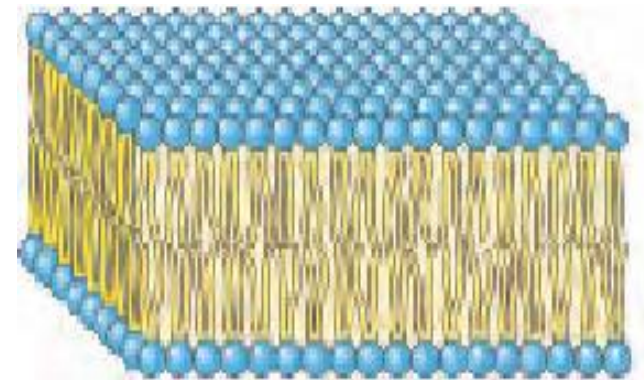
**Monolayer**



**Micelles**



**Liposome**



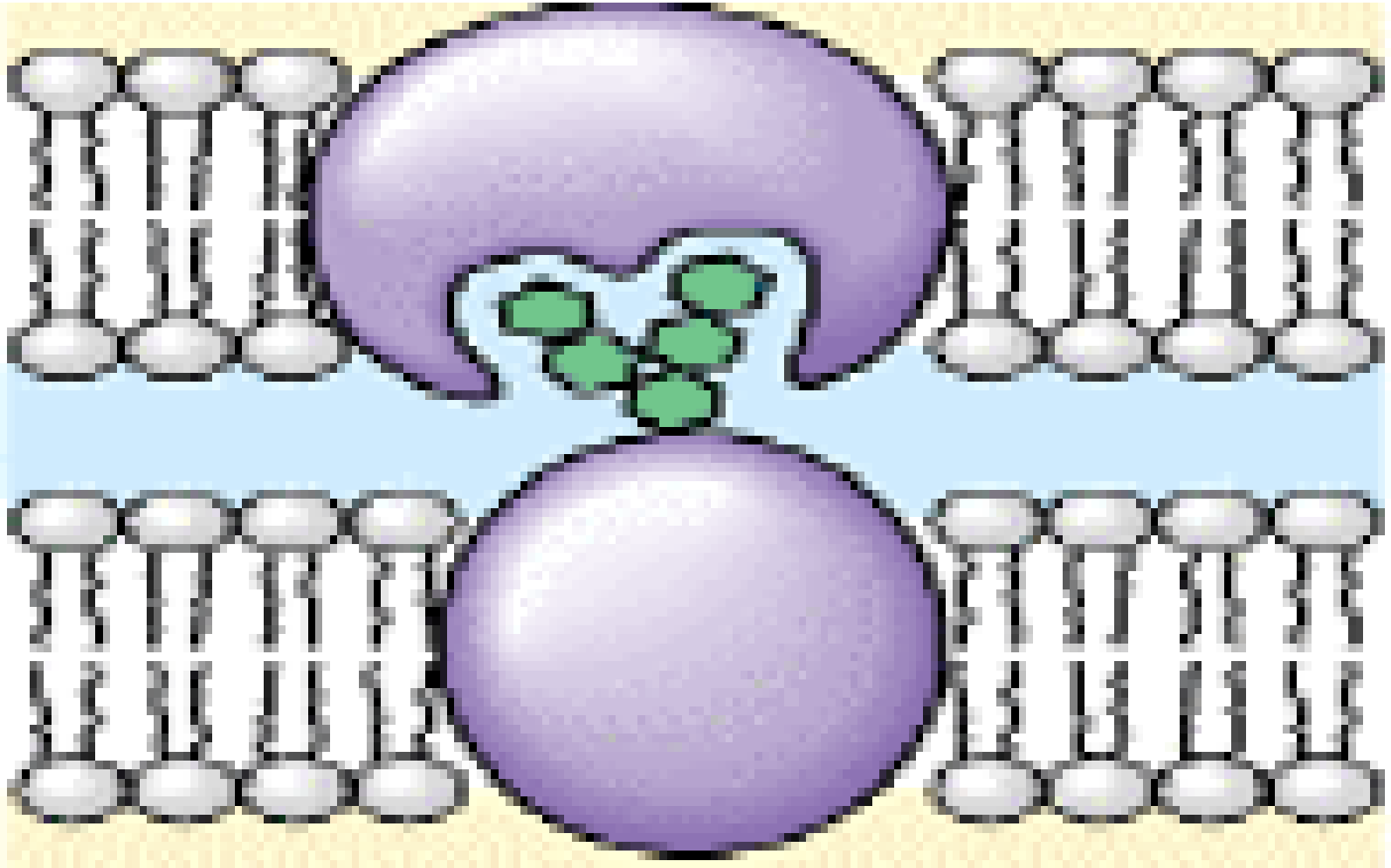
**Bilayer**



# 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

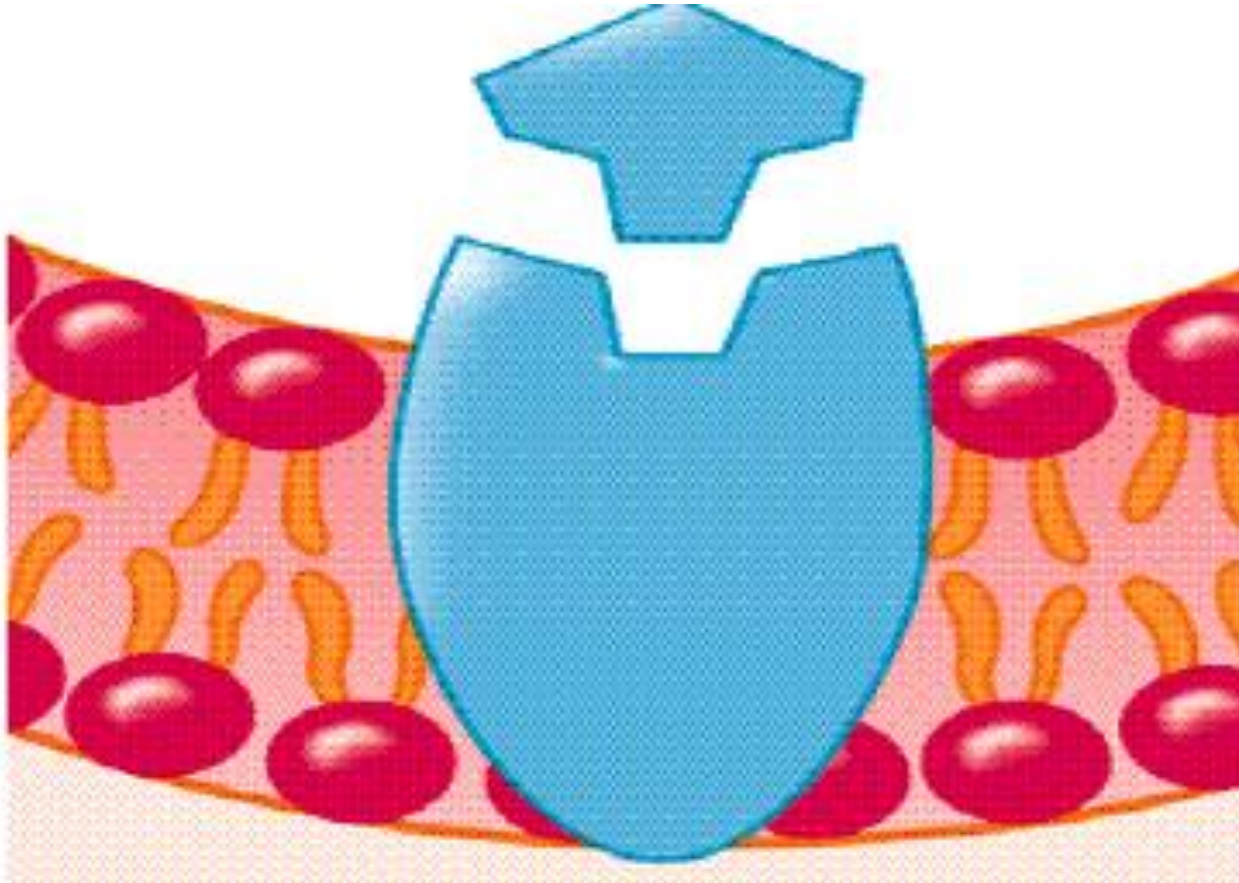


# Membrane Transport

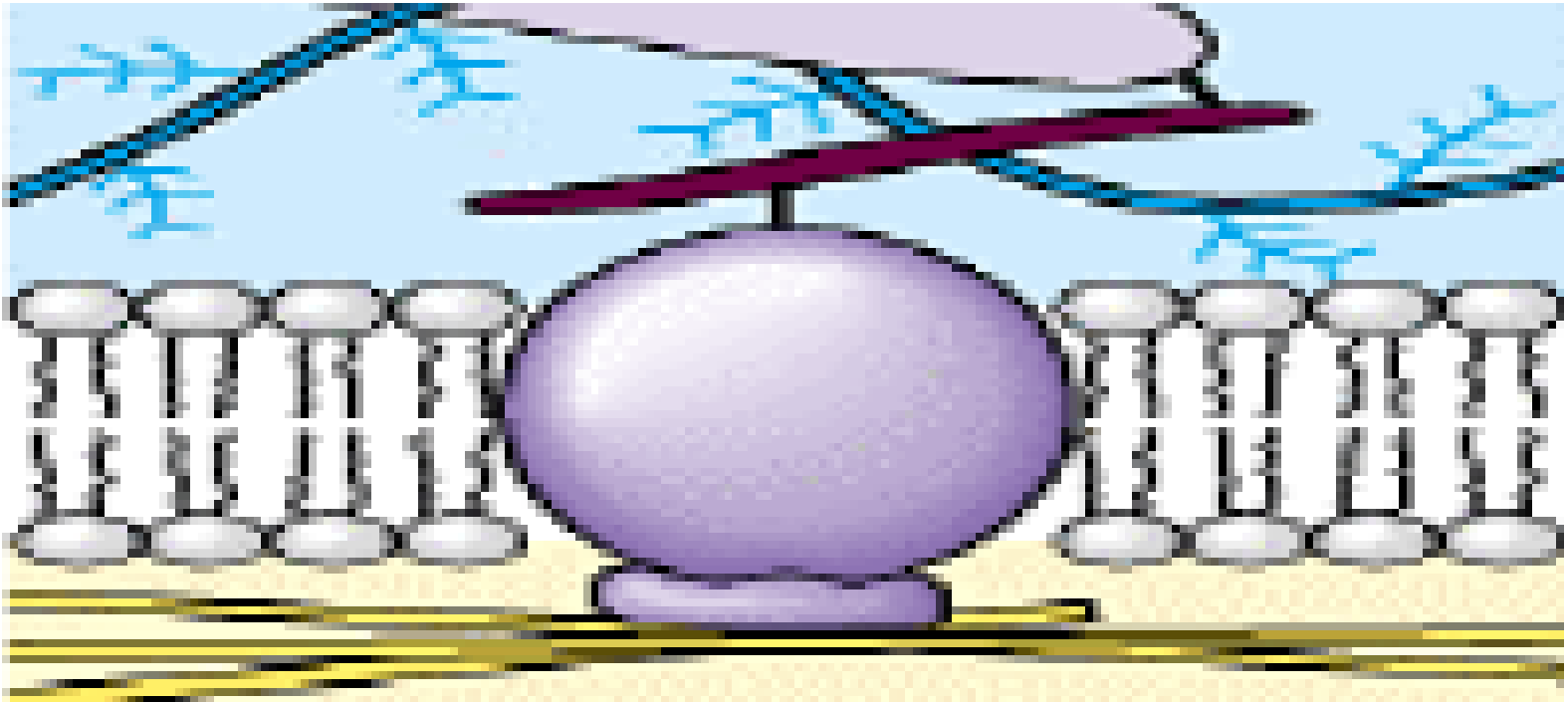


Membrane transport may be mediated by the carrier proteins e.g GLUT 2

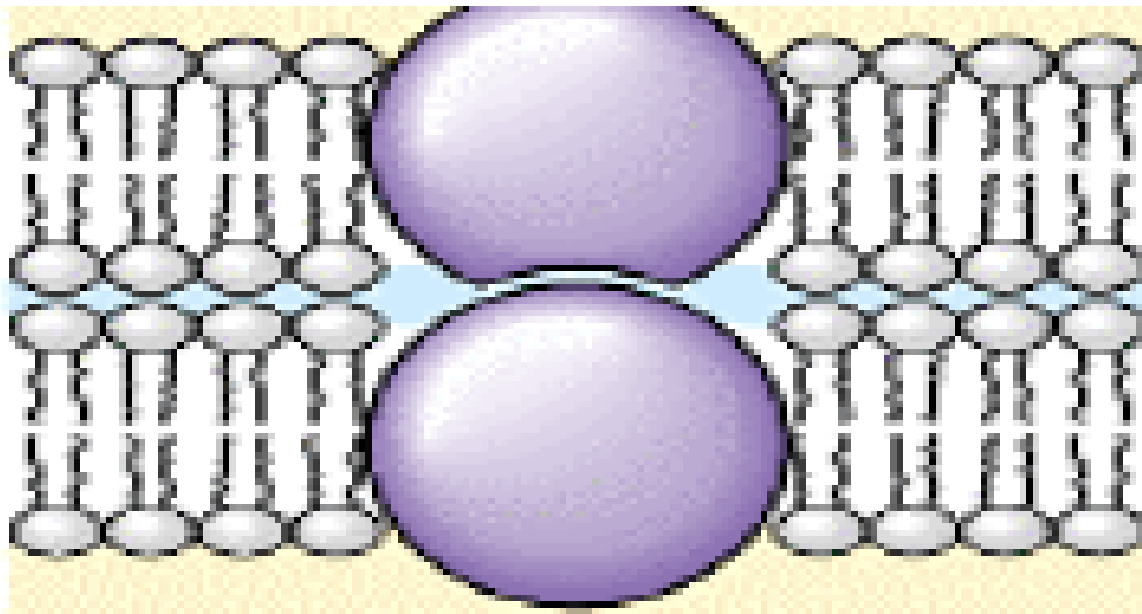
# Binding site for enzyme



# Anchoring and scaffold

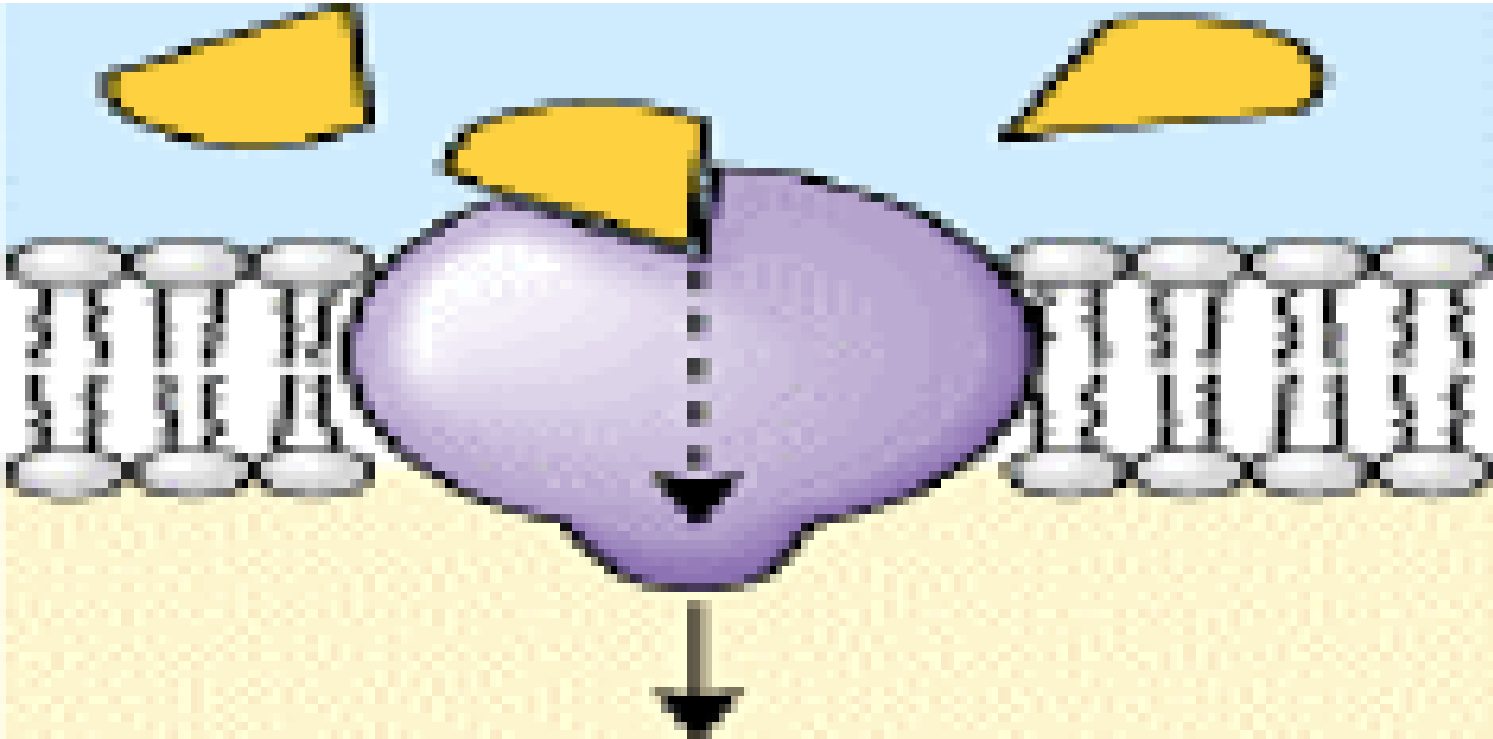


# Intercellular interaction

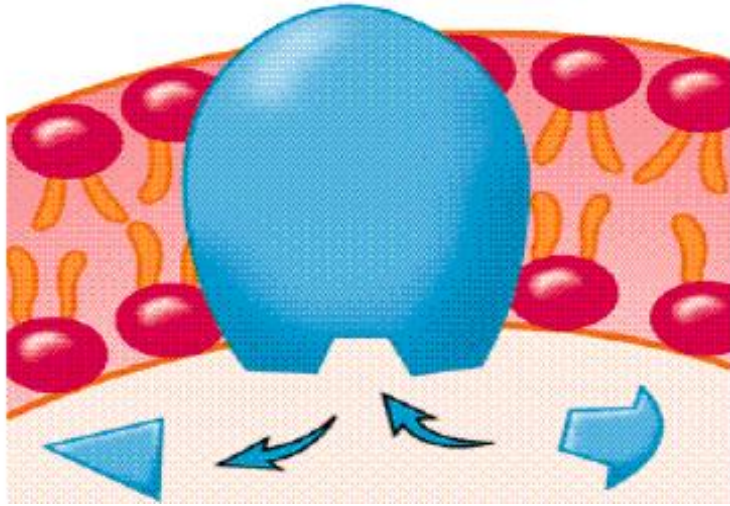


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# Signal transduction



# Enzymatic Activity



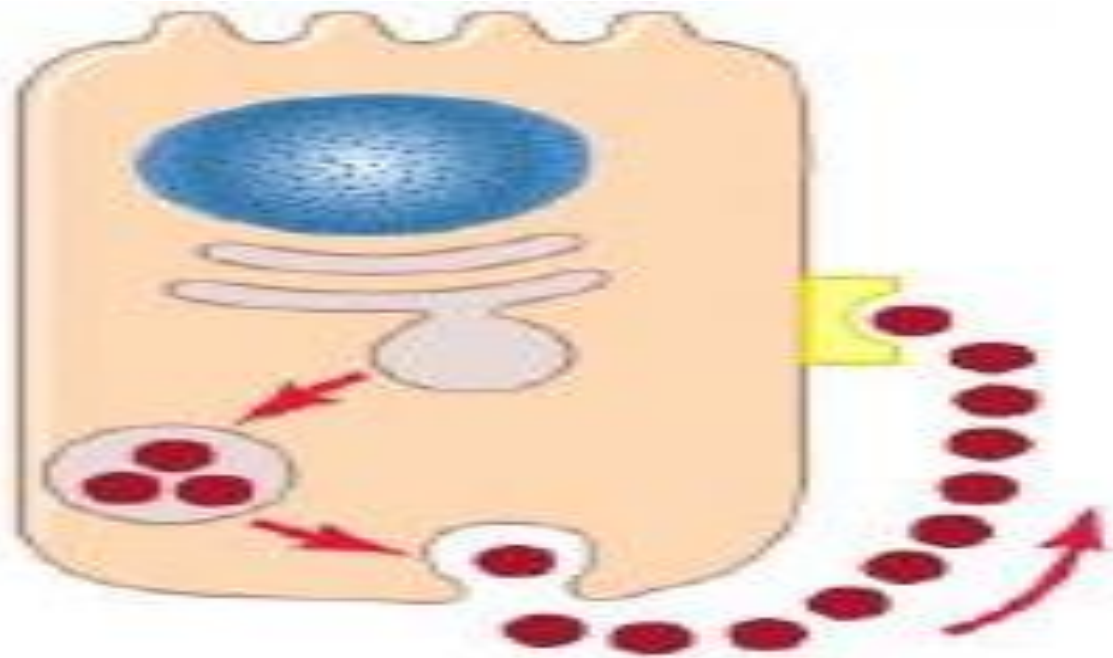
- For example, the membrane protein, adenylyl cyclase, is involved in ATP metabolism.
- Cholera bacteria release a toxin that interferes with the proper functioning of adenylyl cyclase, thus making sodium ion and water leave intestinal cells and the individual dies from severe diarrhea and dehydration.



# 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.

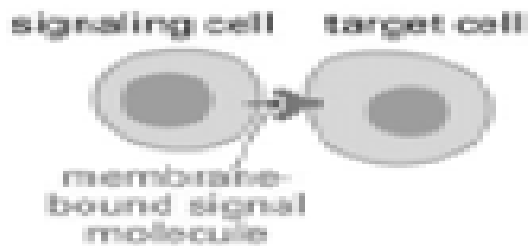
# Autocrine signaling



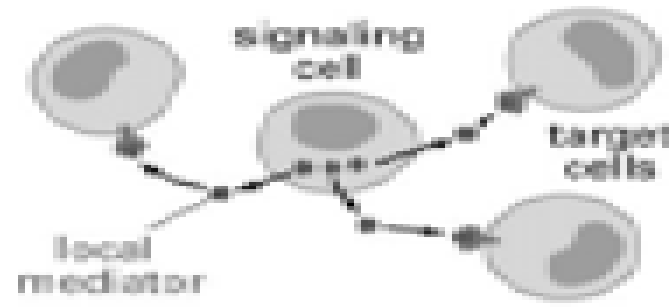
- External signals on the cell surface are converted into cellular responses by signal transduction pathways.
- These signals are in form of chemical messengers.
- A hormone is a chemical released by a cell in one part of the body, that sends out messages that affect cells in other parts of the organism.

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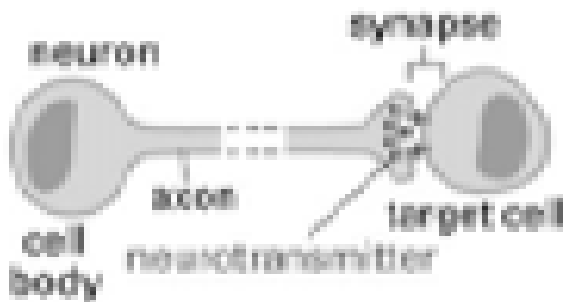
# Types of cell signaling



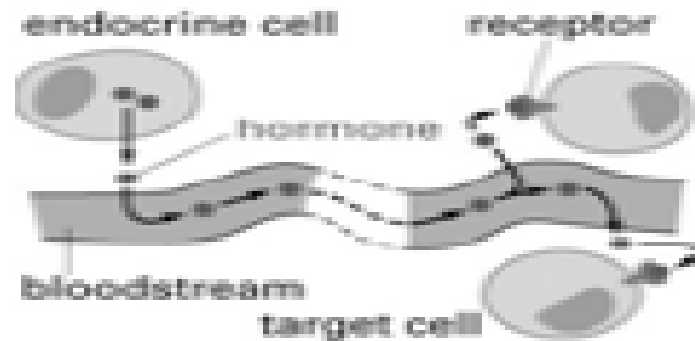
Direct contact



Paracrine signaling



Synaptic signaling



Endocrine signaling

## ➤ **Paracrine signaling**

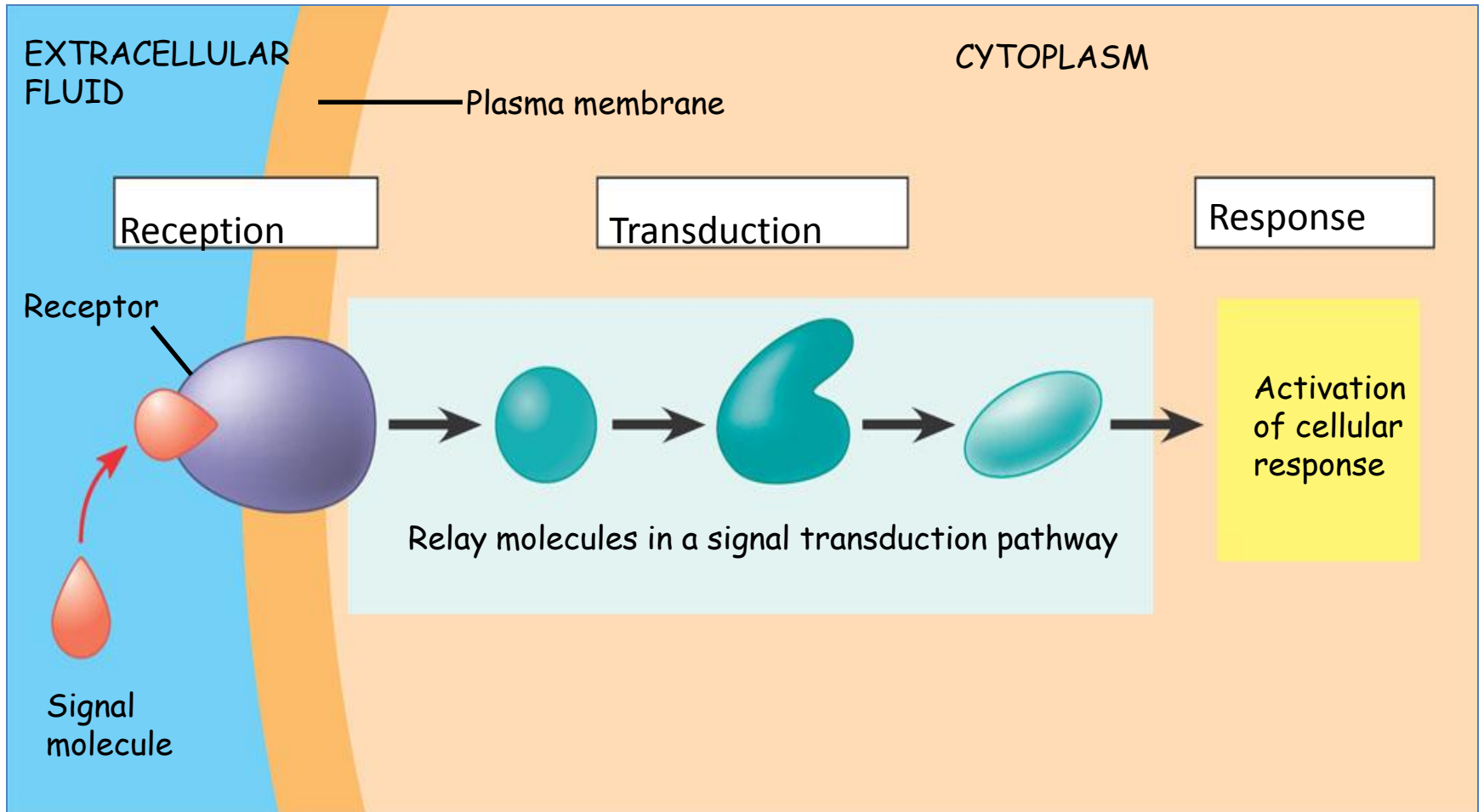
- Paracrine signals are released by cells into the extracellular fluid in their neighborhood and act locally (short distant). E.g. PGE1

➤ **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

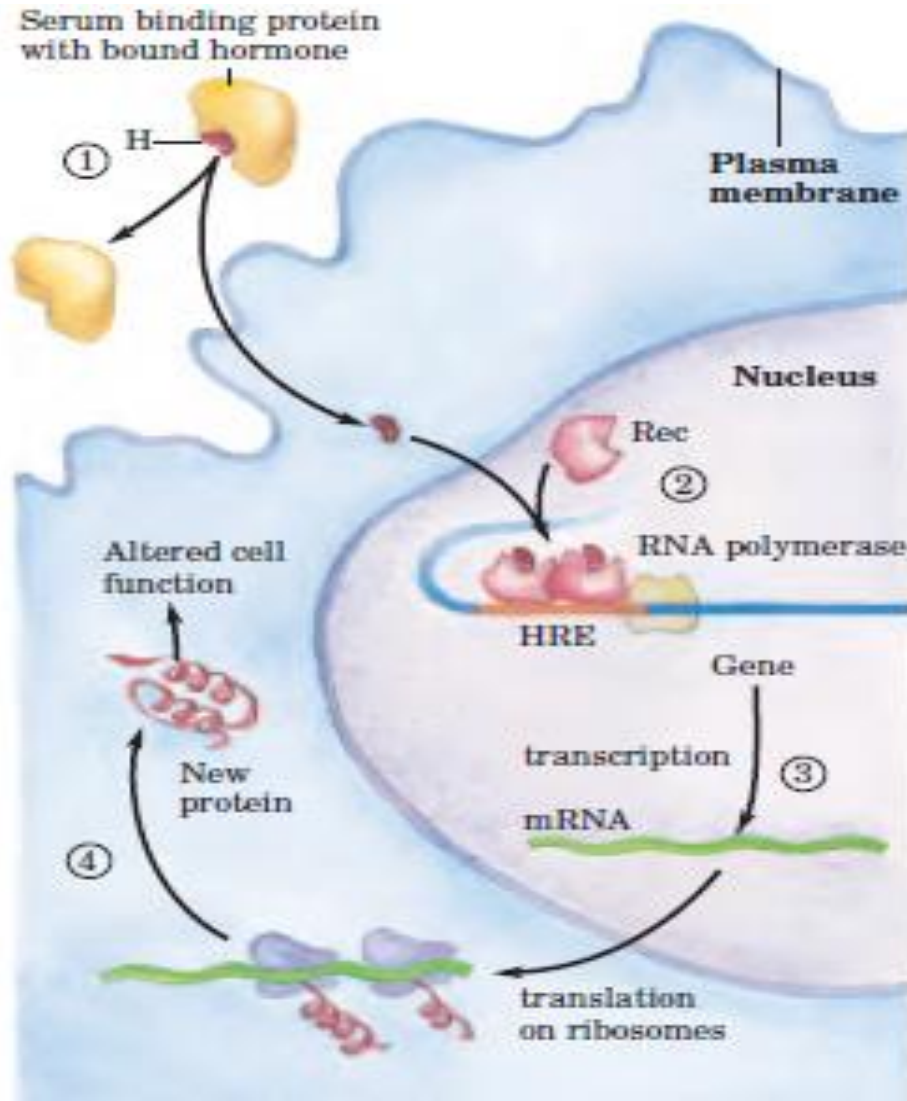
- Cell signaling leads to regulation of cytoplasmic activities or transcription
  - Signaling pathways regulate a variety of cellular activities



# Hormone Receptor

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

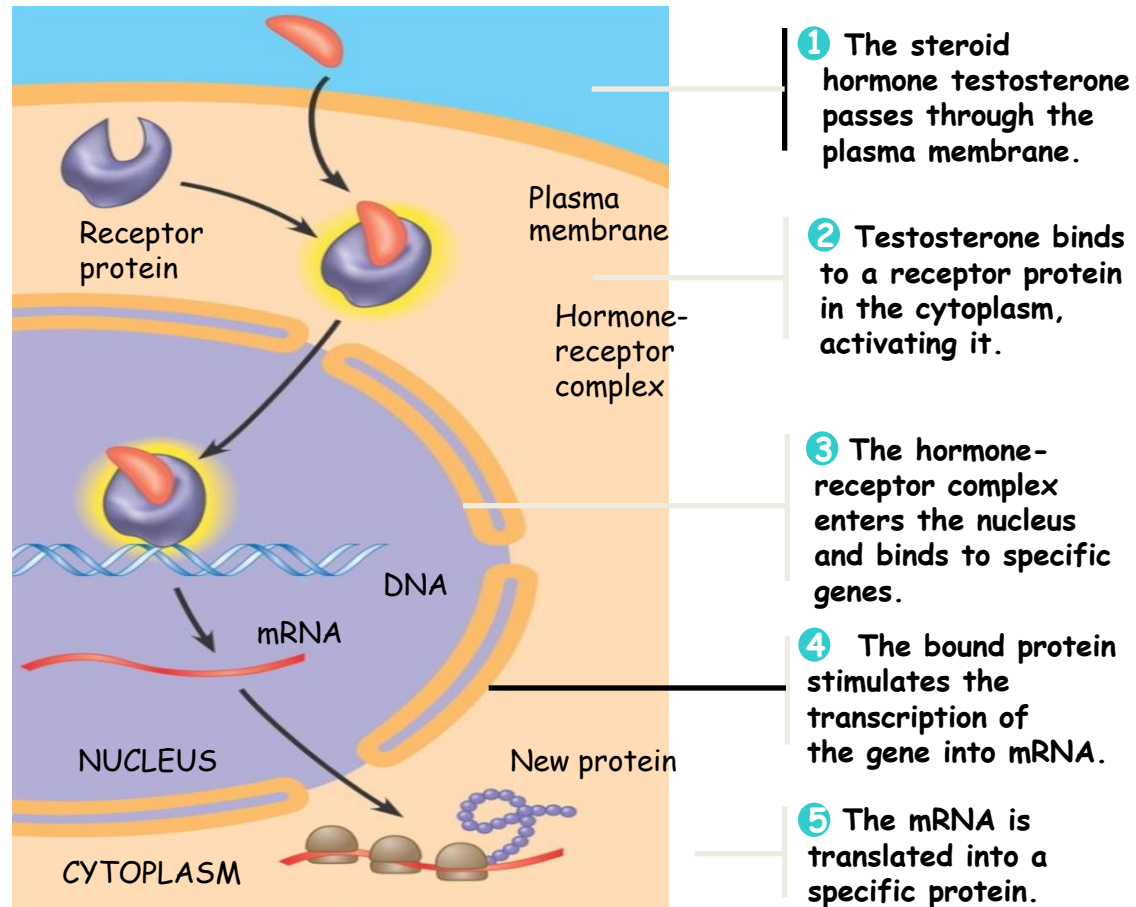
# NUCLEAR RECEPTOR



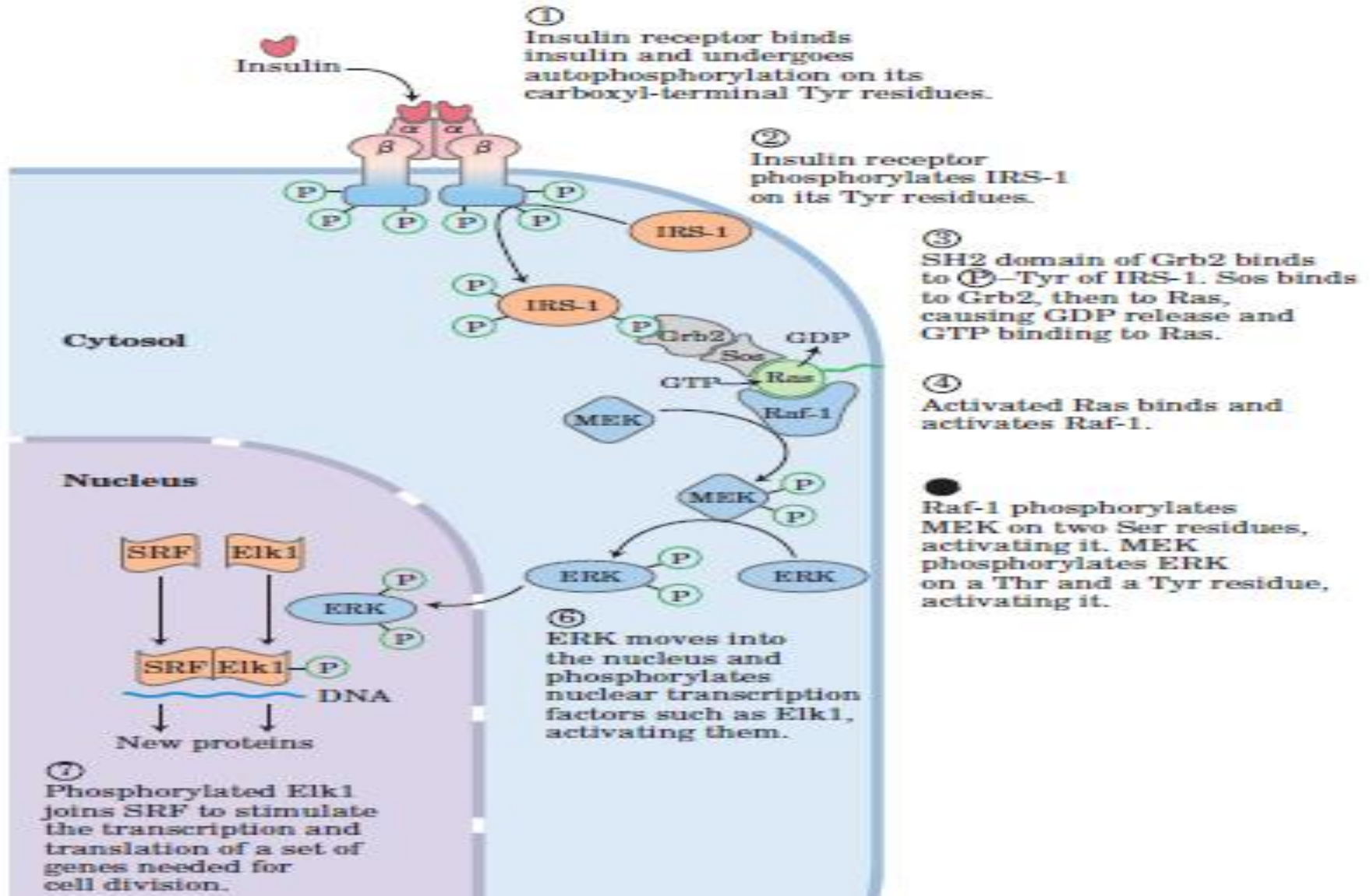
- ① Hormone (H), carried to the target tissue on serum binding proteins, diffuses across the plasma membrane and binds to its specific receptor protein (Rec) in the nucleus.
- ② Hormone binding changes the conformation of Rec; it forms homo- or heterodimers with other hormone-receptor complexes and binds 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

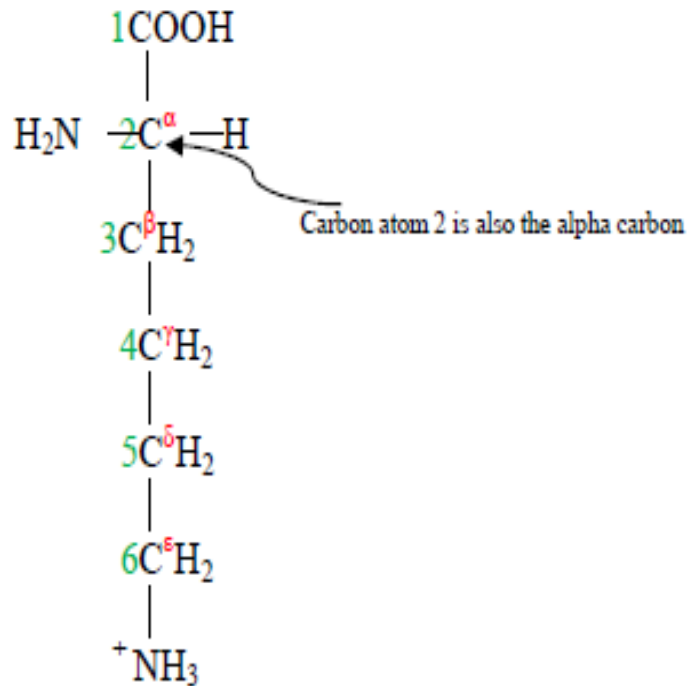


# CELL SURFACE RECEPTOR: Receptor Tyrosine Kinase



Signal Molecule	Site of Origin	Chemical Nature	Some Actions
<b>Hormones</b>			
<i>Adrenaline</i>	adrenal gland	derivative of the amino acid tyrosine	increases blood pressure, heart rate, and metabolism
<i>Cortisol</i>	adrenal gland	steroid (derivative of cholesterol)	affects metabolism of proteins, carbohydrates, and lipids in most tissues
<i>Estradiol</i>	ovary	steroid (derivative of cholesterol)	induces and maintains secondary female sexual characteristics
<i>Glucagon</i>	alpha cells of pancreas	peptide	stimulates glucose synthesis, glycogen breakdown, and lipid breakdown in, e.g., liver and fat cells
<i>Insulin</i>	beta cells of pancreas	protein	stimulates glucose uptake, protein synthesis, and lipid synthesis in, e.g., liver cells
<i>Testosterone</i>	testis	steroid (derivative of cholesterol)	induces and maintains secondary male sexual characteristics
<i>Thyroid hormone</i>	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
<b>side chain is nonpolar, H or alkyl</b>				
glycine	G	Gly	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{H} \end{array}$	none
alanine	A	Ala	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH}_3 \end{array}$	alkyl group
*valine	V	Val	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH} \\ / \quad \backslash \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$	alkyl group
*leucine	L	Leu	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH}_2-\text{CH}-\text{CH}_3 \\   \\ \text{CH}_3 \end{array}$	alkyl group
*isoleucine	I	Ile	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH} \\ / \quad \backslash \\ \text{CH}_3 \quad \text{CH}_2\text{CH}_3 \end{array}$	alkyl group
*phenylalanine	F	Phe	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH}_2-\text{C}_6\text{H}_5 \end{array}$	aromatic group
proline	P	Pro	$\begin{array}{c} \text{HN}-\text{CH}-\text{COOH} \\ / \quad \backslash \\ \text{H}_2\text{C} \quad \text{CH}_2 \\   \\ \text{CH}_2 \end{array}$	rigid cyclic structure
<b>side chain contains an —OH</b>				
serine	S	Ser	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH}_2-\text{OH} \end{array}$	hydroxyl group
*threonine	T	Thr	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH} \\ / \quad \backslash \\ \text{HO} \quad \text{CH}_3 \end{array}$	hydroxyl group

The Standard Amino Acids (continued)

Name	Symbol	Abbreviation	Structure	Functional Group in Side Chain
tyrosine	Y	Tyr	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH}_2-\text{C}_6\text{H}_4-\text{OH} \end{array}$	phenolic—OH gro
<b>side chain contains sulfur</b>				
cysteine	C	Cys	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH}_2-\text{SH} \end{array}$	thiol
*methionine	M	Met	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_3 \end{array}$	sulfide
<b>side chain contains nonbasic nitrogen</b>				
asparagine	N	Asn	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH}_2-\text{C}-\text{NH}_2 \\    \\ \text{O} \end{array}$	amide
glutamine	Q	Gln	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH}_2-\text{CH}_2-\text{C}-\text{NH}_2 \\    \\ \text{O} \end{array}$	amide
*tryptophan	W	Trp	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH}_2 \\   \\ \text{Indole ring} \end{array}$	indole
<b>side chain is acidic</b>				
aspartic acid	D	Asp	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH}_2-\text{COOH} \end{array}$	carboxylic acid
glutamic acid	E	Glu	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH}_2-\text{CH}_2-\text{COOH} \end{array}$	carboxylic acid
<b>side chain is basic</b>				
*lysine	K	Lys	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2 \end{array}$	amino group
*arginine	R	Arg	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}-\text{C}-\text{NH}_2 \\    \\ \text{NH} \end{array}$	guanidino group
*histidine	H	His	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}-\text{COOH} \\   \\ \text{CH}_2 \\   \\ \text{Imidazole ring} \end{array}$	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**

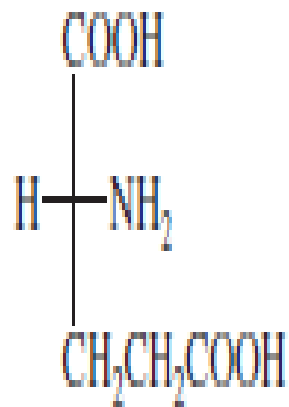
- At physiological pH, **Lysine**, **Arginine** and **Histidine** are positively charged due to their terminal ammonium, guanidinium, and the imidazolium groups respectively
- **Aspartic acid** and **Glutamic acid** are negatively charged above pH 3

# Classification based on nutritional requirements

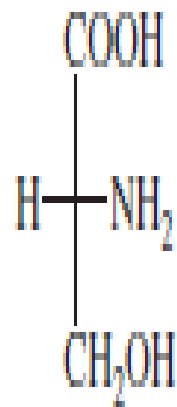
- **Essential amino acids:** Examples include Arg, Val, Met, Leu, Thr, Phe, His, Ile, Lys, and Trp.
- Dietary proteins that contain all the essential amino acids in the right proportion is said to be complete proteins e.g. fish, meat and egg.
- The proteins that are seriously deficient in one or several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

# Rare and unusual amino acids

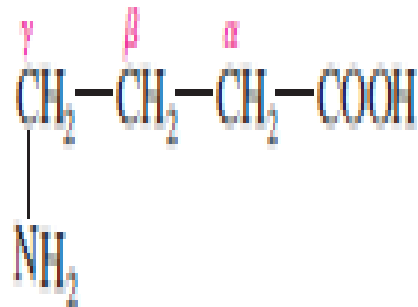
- For example, 4-hydroxyproline and 5-hydroxylysine, GABA ( $\gamma$ -amino butyric acid),  $\beta$ -alanine, D-glutamic acid, Ornithine, citrulline, homoserine are unusual amino acids.
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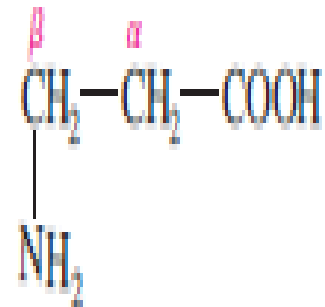
D-glutamic acid



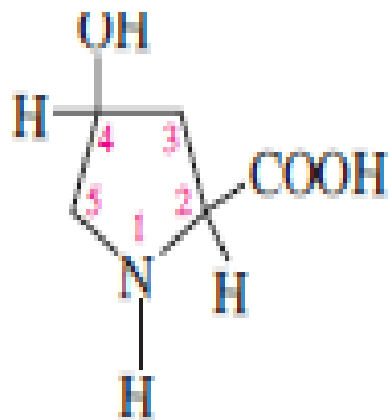
D-serine



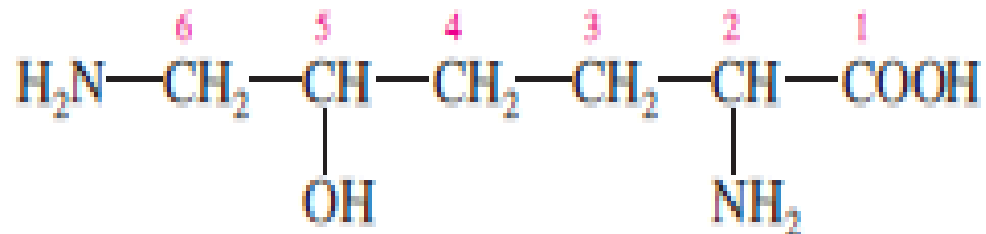
$\gamma$ -aminobutyric acid



$\beta$ -alanine



4-hydroxyproline



5-hydroxylysine

# Classification 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

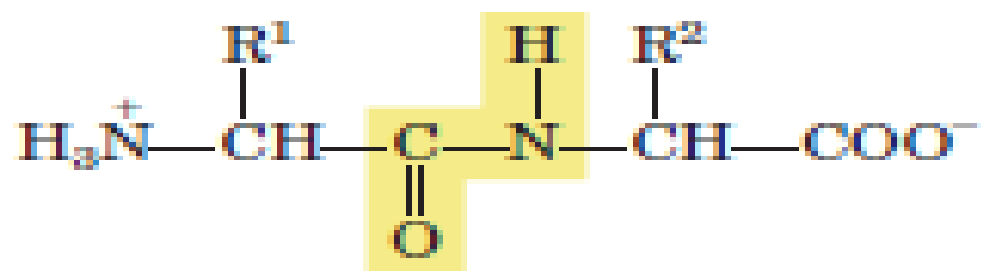
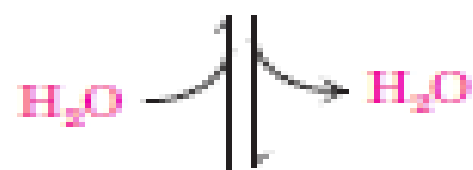
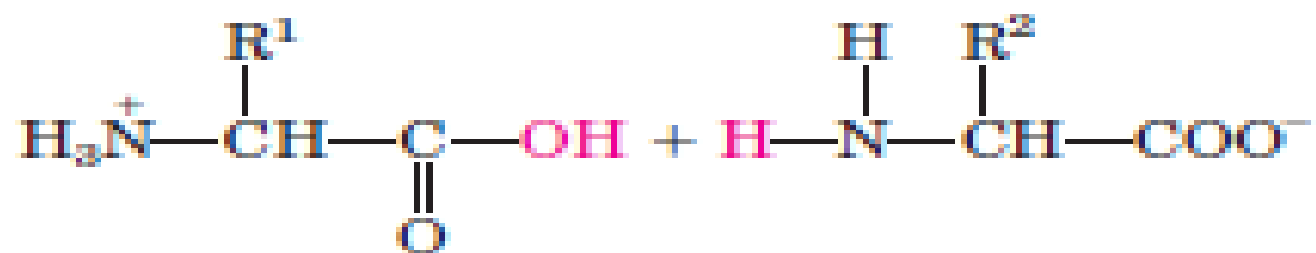
## ➤ **Globular proteins**

- These are mostly water-soluble and fragile in nature. Examples include enzymes, haemoglobin, hormones and antibodies

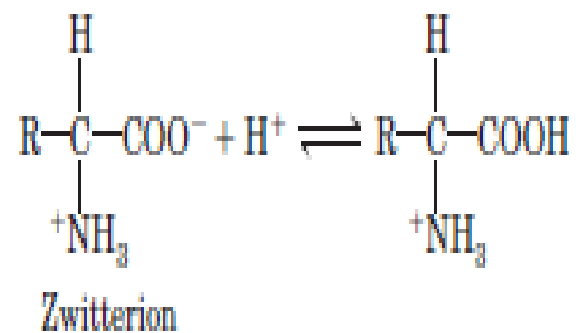
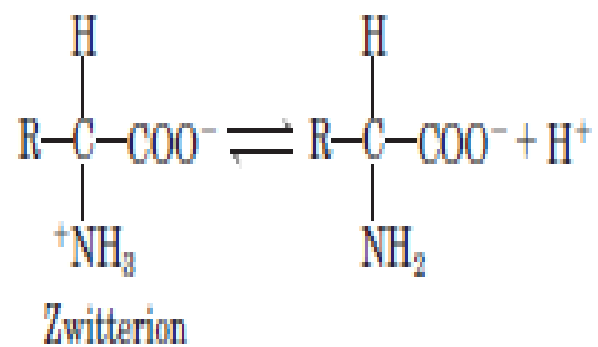


# Structural organization of proteins

- 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  $\alpha$ -carboxyl group of an amino acid and  $\alpha$ -amino group of another amino acid by a peptide bond.



- **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.



- **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  $\alpha$ -helix and the  $\beta$ -sheet.

- **The  $\alpha$ -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  $\alpha$ -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

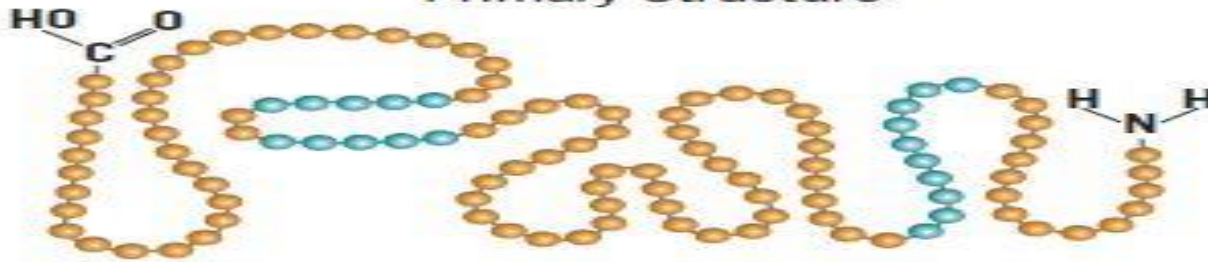
- This is the association of two or more independent proteins via non-covalent forces to form a multimeric protein. That is, many protein subunits come together to form the quaternary structure.
- These subunits may be homodimers or heterodimers.
- The quaternary structure refers to how these protein 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.



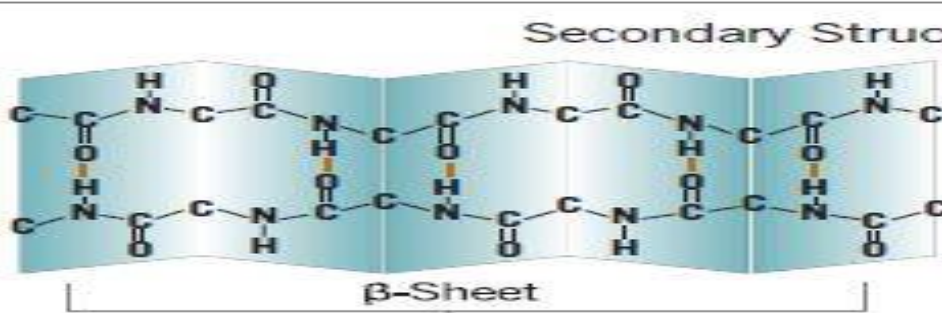
Figure 2

# LEVELS OF PROTEIN STRUCTURE

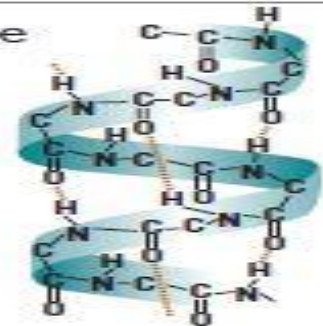
## Primary Structure



## Secondary Structure



$\beta$ -Sheet



$\alpha$ -Helix

## Tertiary Structure



## Quaternary Structure

