5 marks

Biological Membranes and Transport

The plasma membrane is an envelope surrounding the cell. It separates and protects the cell from the external hostile environment. Beside being a protective barrier, plasma membrane provides a connecting system between the cell and its environment.

Chemical composition :-

The membrances are composed of lipids protein and carbohydrates.

Structure of Membrane :-

1. Extrinsic (peripheral) membrane protein.
2. Intrinsic (integral) membrane.

Transport across membrances :-

1. Passive diffusion
2. Facicipated diffusion
3. Active transport.

Transport systems :-

1. Uniport system
2. Symport system
3. Antiport system
4. Cotransport system.

Carbohydrates

Definition:

Carbohydrates are broadly defined as polyhydroxy aldehydes or ketones & their derivatives or as substances that yields one of these compounds.

Composed of carbon, hydrogen, oxygen, $C_6H_{12}O_6$ classification.

Carbohydrates are classified into four major groups.

(i) Monosaccharids (ii) Disaccharids

(iii) Oligosaccharids (iv) Polysaccharides

(i) Monosaccharids

Monosaccharides contain only one molecule of sugar & they cannot be broken into simpler substances by hydrolysis. They are further subdivided according to the number of carbon atoms contained in their structure as indicated below:

i) Diose → has 2 carbon atoms.

Molecular formula: $C_2H_4O_2$

Eg. glycolaldehyde.

ii) Triose → has 3 carbon atoms.

Molecular formula: $C_3H_6O_3$

Eg. a) glyceraldehyde

b) Dihydroxyacetone.

iii) Tetrose → has 4 carbon atoms. Molecular formula: $C_4H_8O_4$

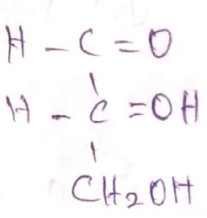
Eg: a) Erythrose b) Threose

(iv) Pentose → has 5 carbon atoms.
Molecular formula : ~~$C_4H_8O_4$~~ $C_5H_{10}O_5$
Eg : a) Ribose b) Deoxyribose c) xylose

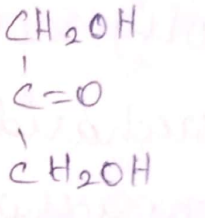
(v) Xenose → has 6 carbon atoms,
Molecular formula : $C_6H_{12}O_6$
Eg :- a) Glucose b) Fructose c) Galactose
d) Mannose.

(vi) Heptose → has 7 carbon atoms.
Molecular formula : $C_7H_{14}O_7$
Eg :- a) Sedoheptulose b) glucoheptose.

Triose :-

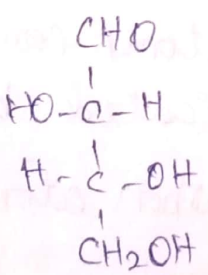


Glyceraldehyde

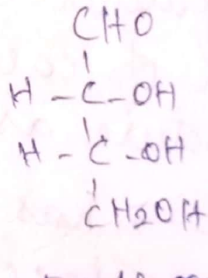


Dihydroxyacetone

Tetroses :-

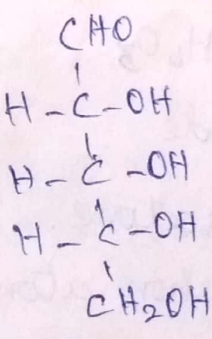


Threose

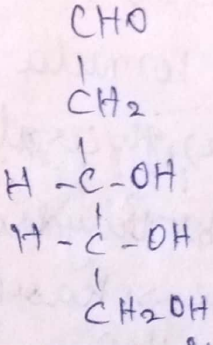


Erythroose

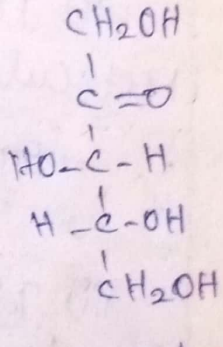
Pentose :-



Ribose

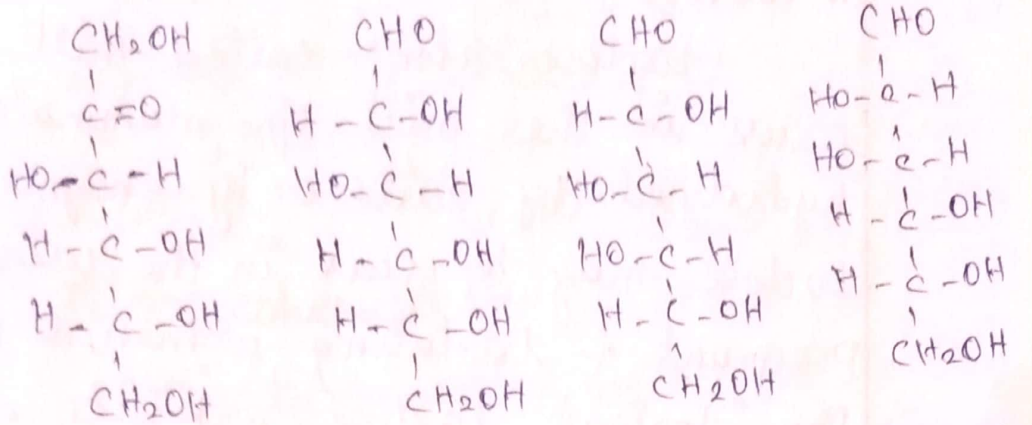


Deoxyribose



xylose

Hexose :-



Fructose Glucose Galactose Mannose

(ii) Disaccharides :-

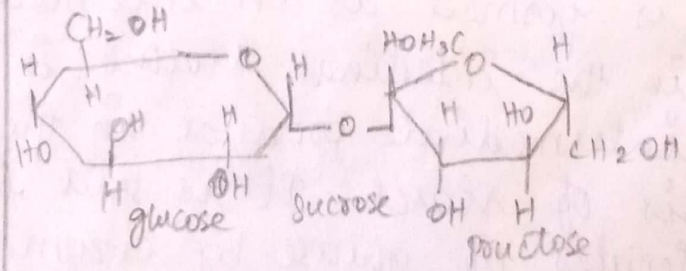
Disaccharides yield two molecules of monosaccharides on hydrolysis. They have a molecular formula of $C_{12}H_{22}O_{11}$

Eg (i) Sucrose (ii) Lactose (iii) Maltose.

(i) Sucrose :-

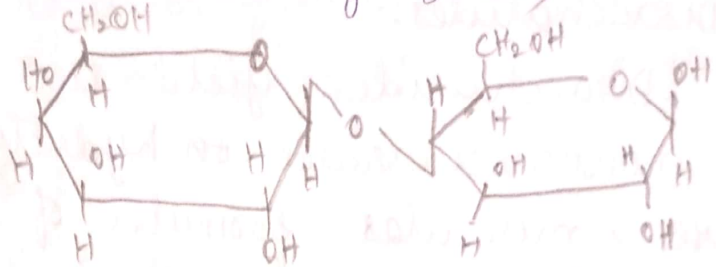
Sucrose is cane sugar. It is the most commonly & extensively used sugar in the food. It is widely distributed in plants & is obtained, from sugar cane, beetroot, pineapple, honey, fruits & certain plants.

An important property of sucrose is that, it is a non-reducing sugar & this is due to its structural peculiarity which is rather unusual.



(ii) Lactose :-

(Lactose also called milk sugar occurs in the milk of mammals. When hydrolysed by acids or by enzyme lactose) Lactose may be occur in the urine of pregnant & lactating women) & this is physiological. lactose exhibits an the reactions of reducing sugars. (It is not fermented by yeast.)

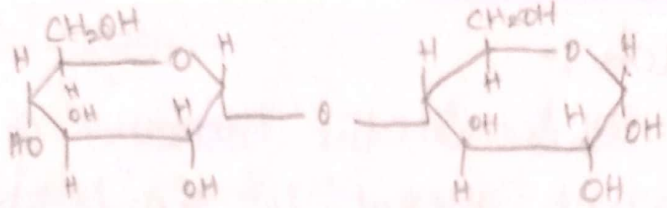


Galactose Lactose Glucose

(iii) Maltose :-

Maltose is composed of two glucose units, combined in glucosidic linkage. Condensation between the hydroxyl group of glucose 1 at carbon - 1 & hydroxyl group of glucose 2 at carbon - 1 results in the liberation of one molecule of H_2O.

Maltose is the end product of digestion of starch by the action of salivary amylose ptyalin, in the molecules pancreatic amylase in the intestines. Maltose is formed as an intermediate product in the intestines. Maltose is formed as an intermediate product in the acid hydrolysis of starch. It is split into two molecules of glucose by enzyme maltose of the intestinal juice before absorption.



glucose Maltose glucose

(iii) **Oligosaccharides :-**

Oligosaccharides yield two to ten monosaccharide units on hydrolysis. Strictly speaking disaccharides also come under this group.

Eg:-

a) Raffinose - Trisaccharide

b) Stachyose - Tetra saccharide

c) Verbascose - Penta saccharide

(iv) **Polysaccharides :-**

Polysaccharides yield more than ten molecules of monosaccharides on hydrolysis. They have a molecular formula of $(C_6H_{10}O_5)_n$.

Eg. Starch, glycogen

Dextrin, cellulose

These are 2 types

↓

i) Homopolysaccharides

ii) Heteropolysaccharides

(i) Starch :-

This is the storage of carbohydrate present in plants, being abundantly found in roots, tubers, stem, vegetables, fruits & cereals.

The bulk of our diet which consists mainly of rice, wheat & vegetables is a good source of starch, Starch occurs in the form of grains which may be spherical or oval in shape.

Starch which is composed of several glucose molecules is a mixture of two types of molecules namely, amylose, in which glucose molecules are arranged in a linear form & amylopectin, in which the glucose molecules are arranged in a highly branched form. Amylose forms the inner portion of the starch grain & is soluable in water. Amylopectin forms the outer covering of the starch grain & is insoluble in water. Starch as a whole is insoluble in cold water. When it is heated with water the amlopectin absorbs water, swens up & bursts to form a paste, with amylose diffusing into the water, at a temperature between 60° & 80°C. The amylopectin, being insoluble settles down. The mixture of amylose & amylopectin in water is called starch paste. The amylopectin can be separated by centrifuga-tion.

(ii) Glycogen :-

Glycogen or animal starch is the storage form of carbohydrate in animals. It is found in large amounts in liver & muscles & in smaller amounts in other tissues like kidney's & heart. Glycogen plays an important role in the metabolism of carbohydrate.

Glycolysis :-

The anaerobic phase of carbohydrate metabolism where by glucose or glycogen is oxidised to pyruvic acid & lactic acid is known as glycolysis

Glycogenesis :-

Glycogenesis is the process of glycogen synthesis, in which glucose molecules are added to chains of glycogen for storage.

This reaction is common as the first reaction in the pathway of glycolysis from glucose & as the first reaction in glycogenesis.

Glycogenolysis :-

Glycogen formed thus may be stored in liver, muscles & tissues. This process of breakdown of liver glycogen to glucose is called glycogenolysis.

Gluconeogenesis:

When the supply of glucose from dietary sources is not available in adequate amount for the varied metabolic reactions. The requirements are met by synthesis of glucose from non-carbohydrates sources. The formation of glucose or glycogen from non-carbohydrate sources is known as gluconeogenesis.

— × — × — ×

GLYCOLYSIS

GLYCOLYSIS

Glycolysis comes from a merger of two Greek words:

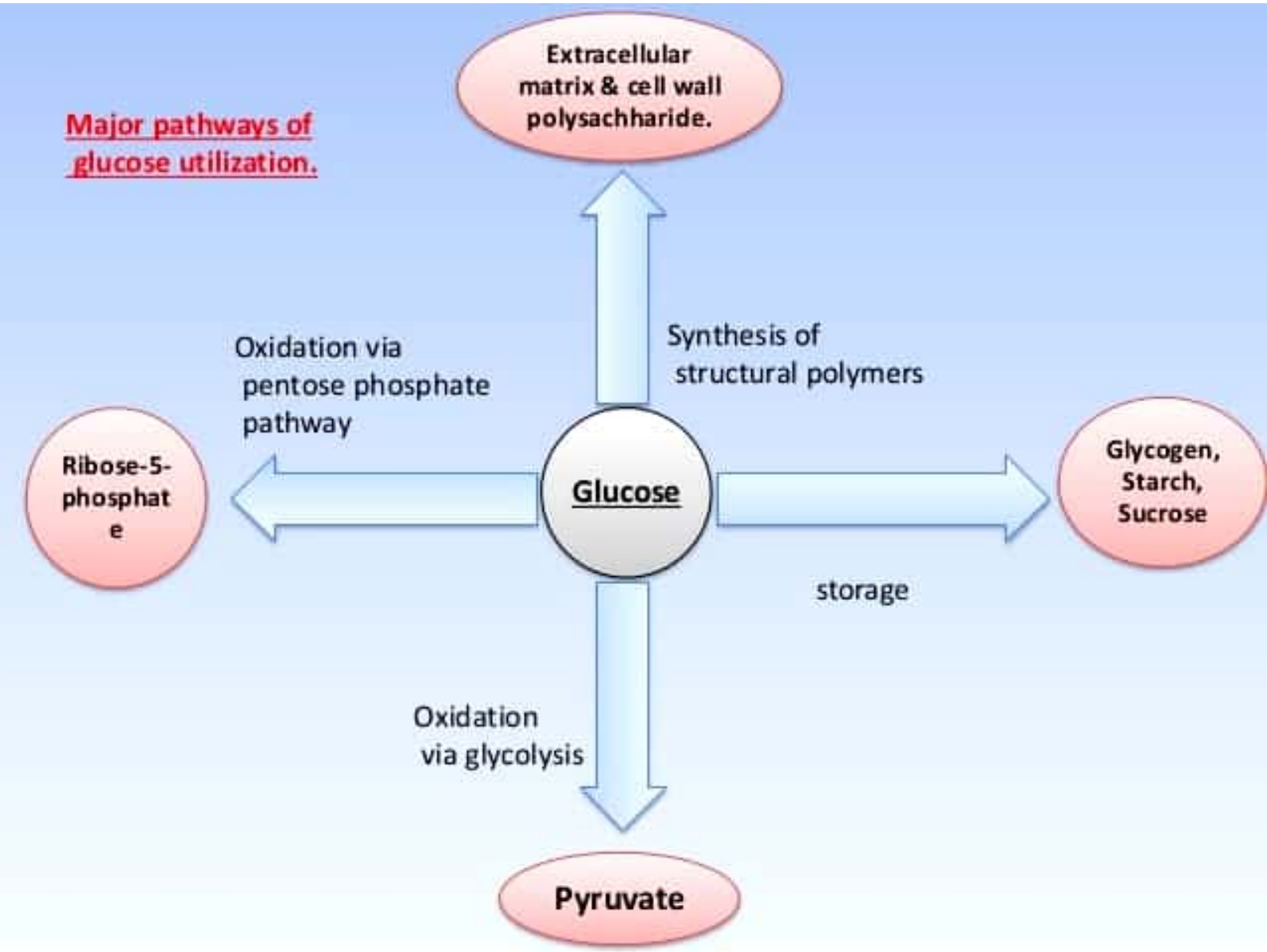
- **Glykys = sweet**
- **Lysis = breakdown/ splitting**

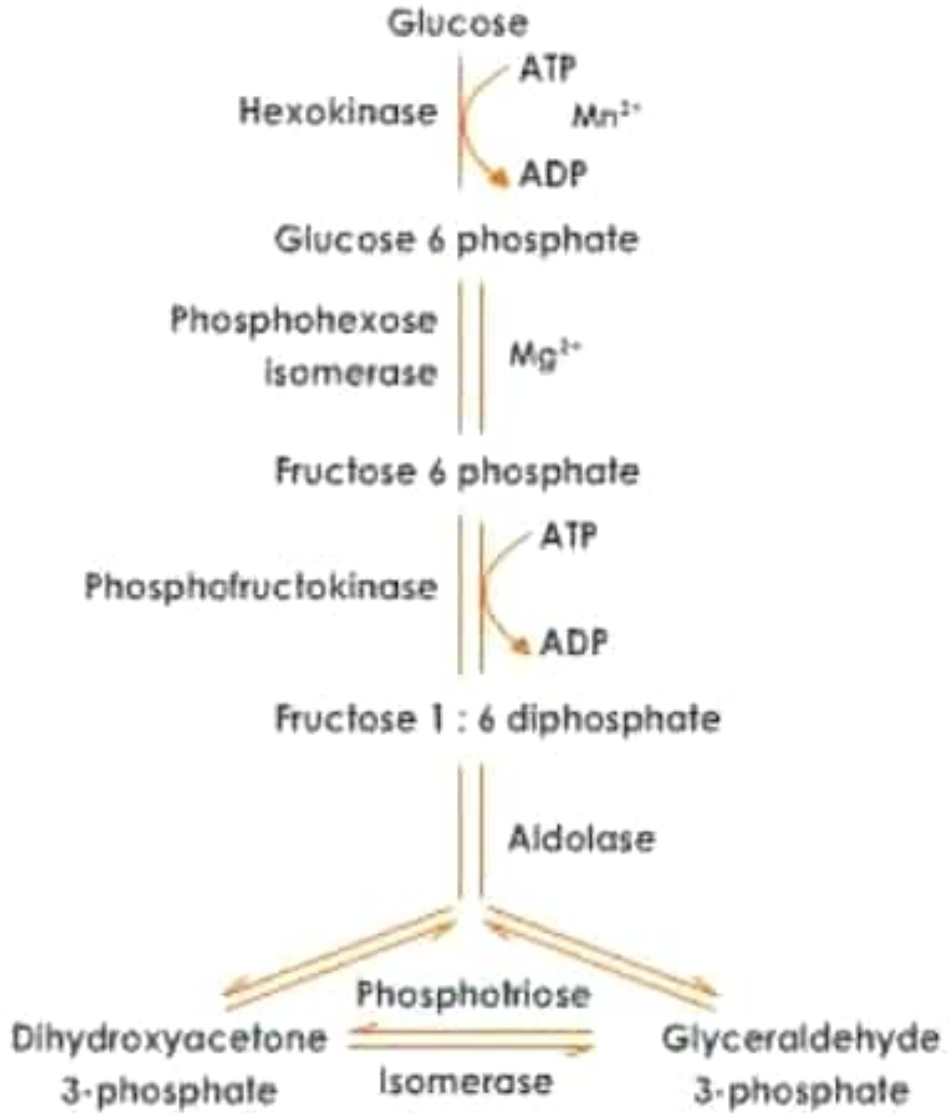
It is also known as Embden-Meyerhof-Parnas pathway or EMP pathway.

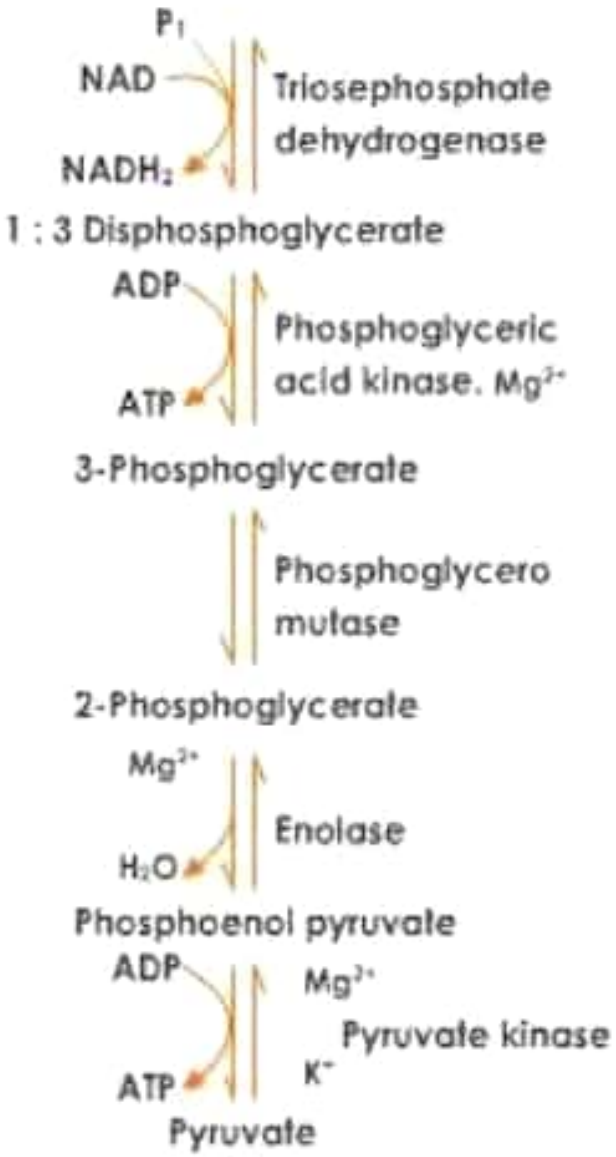
INTRODUCTION

- GLYCOLYSIS is the sequence of 10 enzyme-catalyzed reactions that converts glucose into pyruvate with simultaneous production on of ATP.
- In this oxidative process, 1mol of glucose is partially oxidised to 2 moles of pyruvate.
- This major pathway of glucose metabolism occurs in the cytosol of all cell.
- This unique pathway occurs **aerobically** as well as **anaerobically & doesn't involve molecular oxygen.**

- It also includes formation of Lactate from Pyruvate.
- The glycolytic sequence of reactions differ from species to species only in the mechanism of its regulation & in the subsequent metabolic fate of the pyruvate formed.
- In aerobic organisms, glycolysis is the prelude to Citric acid cycle and ETC.
- Glycolysis is the central pathway for Glucose catabolism.

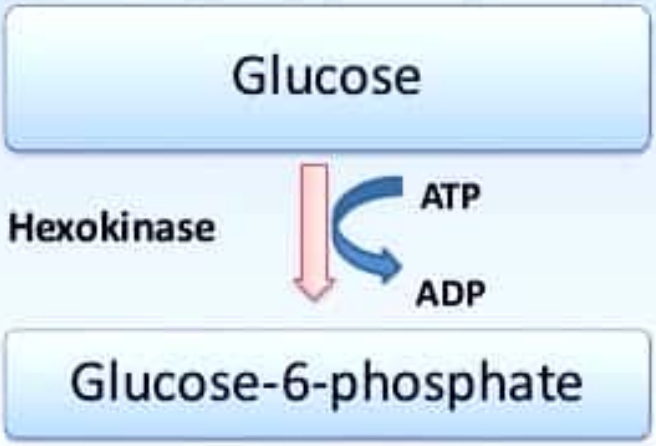






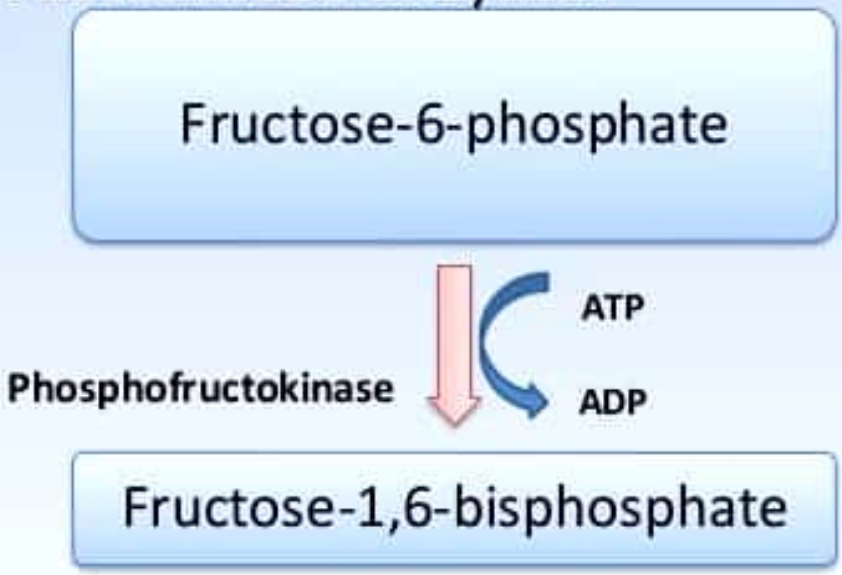
STEP 1: PHOSPHORYLATION

- Glucose is phosphorylated by ATP to form sugar phosphate.
- This is an irreversible reaction & is catalyzed by ***hexokinase.***
- Thus the reaction can be represented as follows:



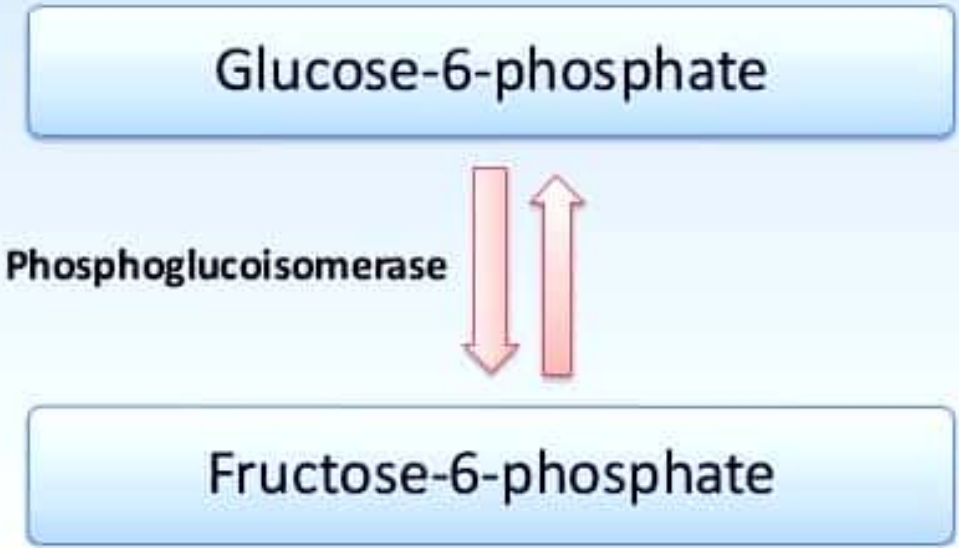
STEP 3: PHOPHORYLATION

- Here the ***Fructose-6-phosphate*** is phosphorylated by ATP to ***fructose-1,6-bisphosphate.***
- This is an ***irreversible reaction*** and is catalyzed by ***phosphofructokinase*** enzyme.



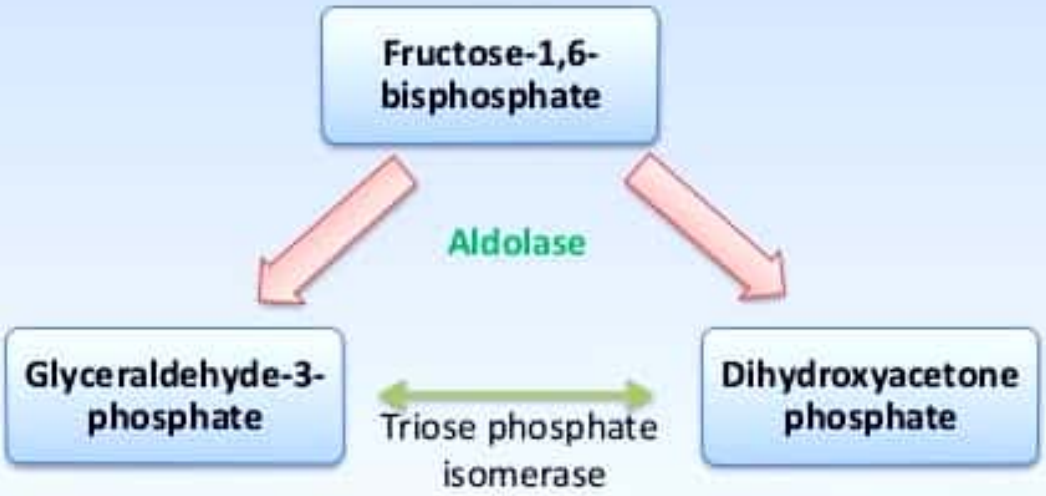
STEP 2: ISOMERIZATION

- It is a reversible rearrangement of chemical structure of carbonyl oxygen from C1 to C2, forming a Ketose from the Aldose.
- Thus, isomerization of the aldose Glucose6-phosphate gives the ketose, Fructose-6-phoshphate.



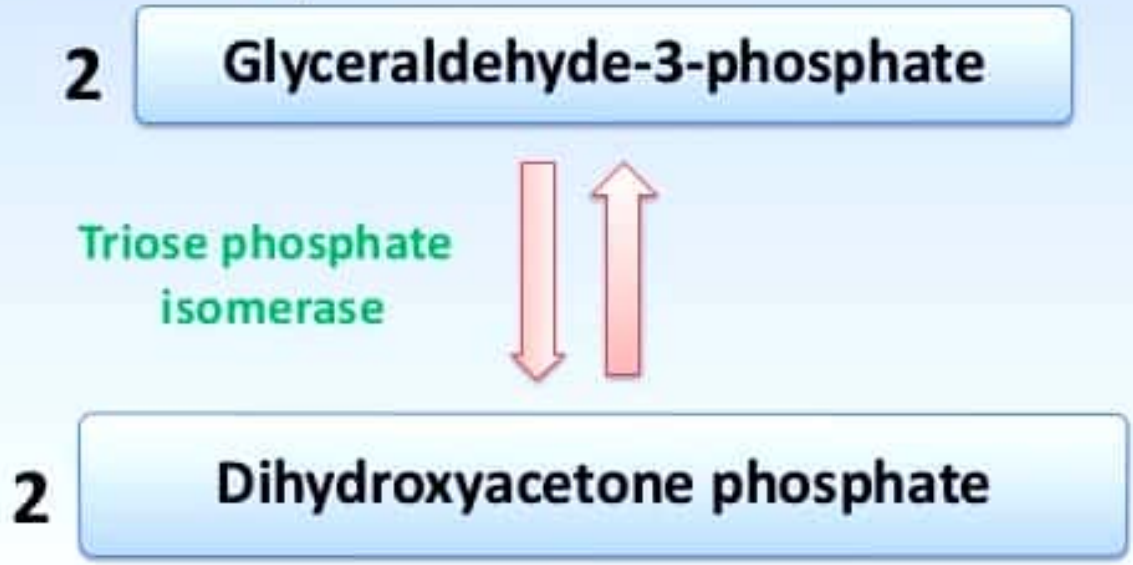
STEP 4: BREAKDOWN

- This six carbon sugar is cleaved to produce two 3-C molecules: ***glyceradldehyde-3-phosphate (GAP)*** & ***dihydroxyacetone phosphate(DHAP).***
- This reaction is catalyzed by ***Aldolase.***



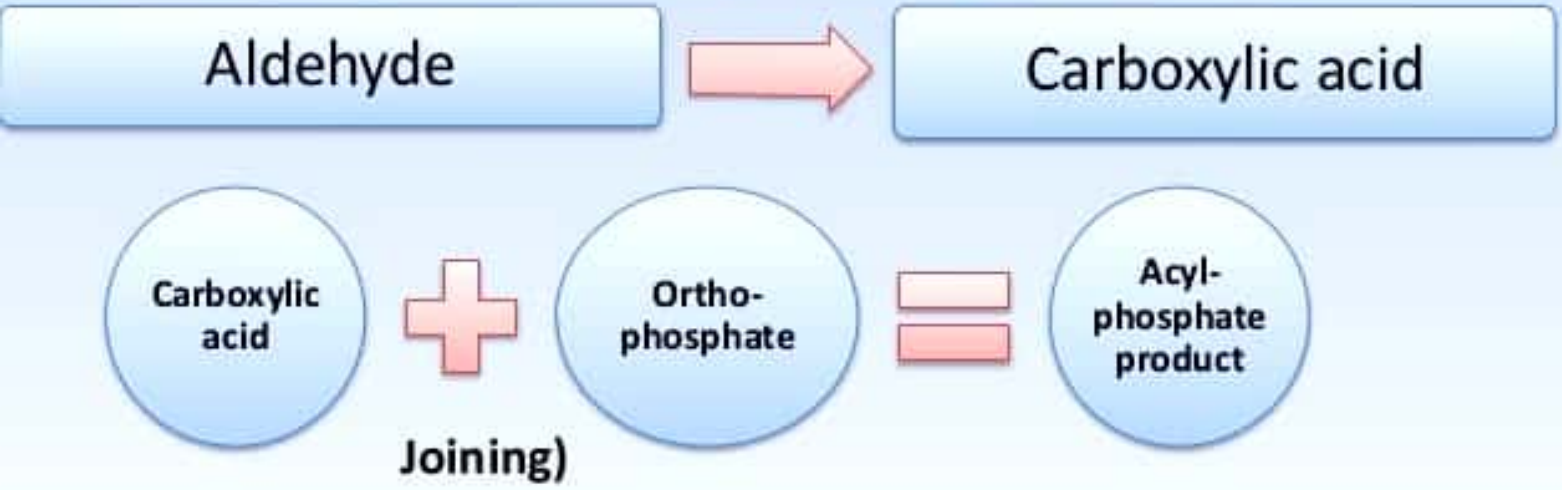
STEP 5: ISOMERIZATION

- Dihydroxyacetone phosphate is oxidized to form Glyceraldehyde-3-phosphate.
- This reaction is catalyzed by ***triose phosphate isomerase*** enzyme.



STEP 6

- 2 molecules of Glyceraldehyde-3-phosphate are oxidized.
- ***Glyceraldehyde-3-phosphate dehydrogenase*** catalyzes the conversion of Glyceraldehyde3-phosphate into ***1,3-bisphosphoglycerate.***

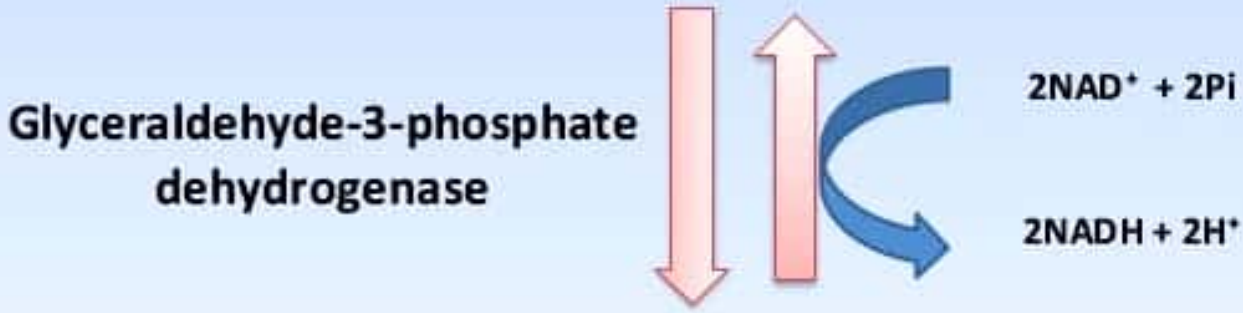


STEP 7

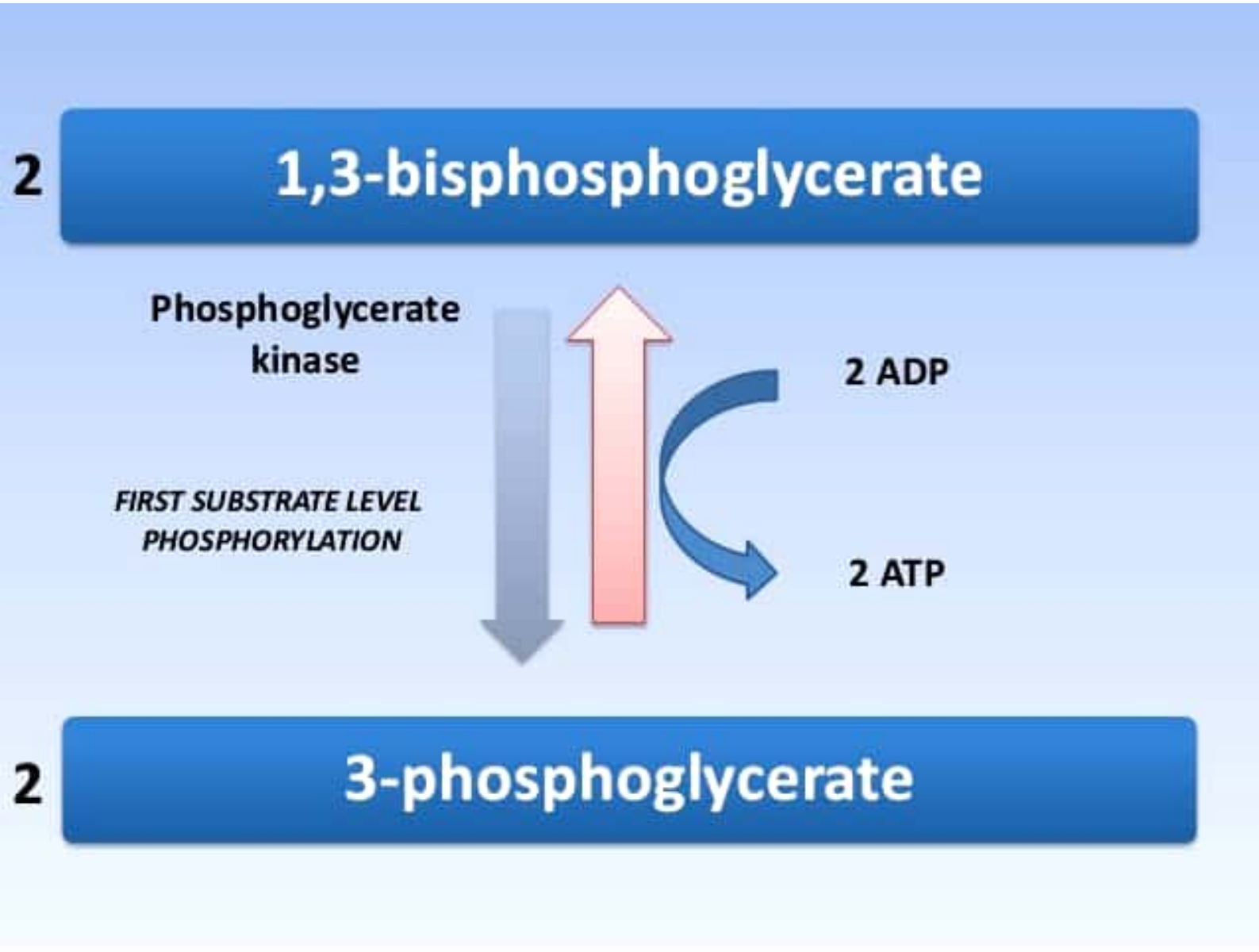
- The transfer of high-energy phosphate group that was generated earlier to ADP, form ATP.
- This phosphorylation i.e. addition of phosphate to ADP to give ATP is termed as ***substrate level phosphorylation*** as the phosphate donor is the substrate ***1,3-bisphosphoglycerate (1,3-BPG).***
- The product of this reaction is 2 molecules of ***3-phosphoglycerate.***

Resultant reaction

2 **Glyceraldehyde-3-phosphate**

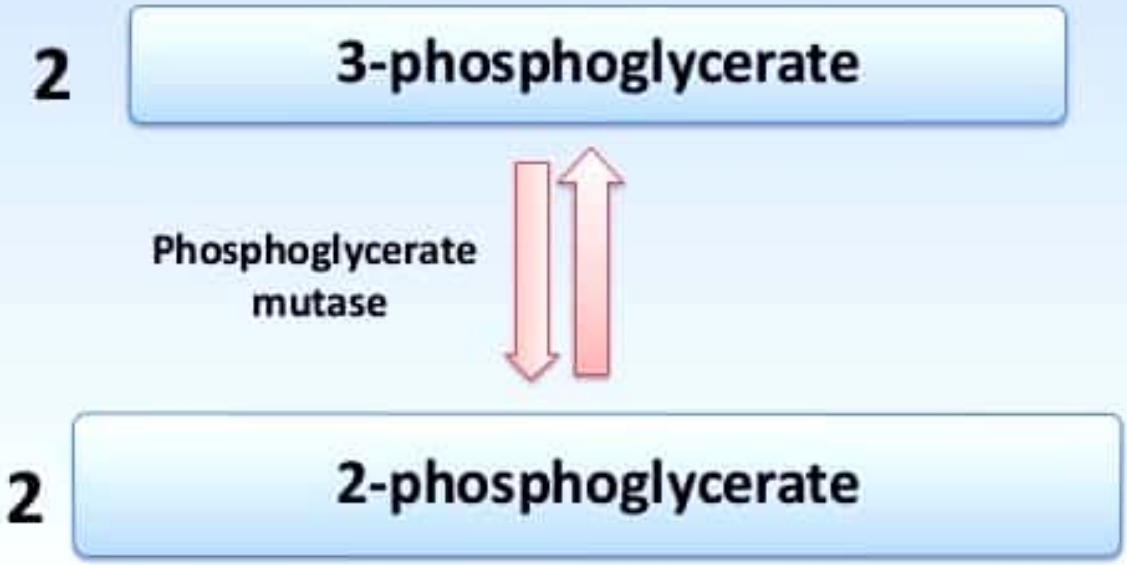


2 **1,3-bisphosphoglycerate**



STEP 8

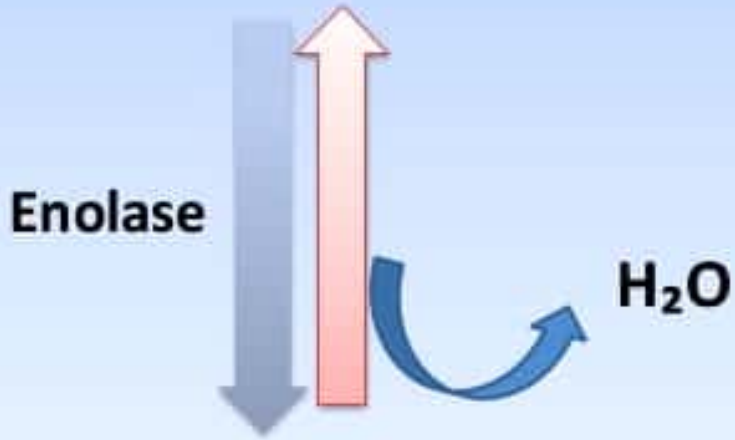
- The remaining phosphate-ester linkage in 3-phosphoglycerate, is moved from carbon 3 to carbon 2 ,because of relatively low free energy of hydrolysis, to form ***2-phosphoglycerate*(2-PG).**



STEP 9: DEHYDRATION OF 2-PG

- This is the second reaction in glycolysis where a high-energy phosphate compound is formed.
- The 2-phosphoglycerate is dehydrated by the action of ***enolase*** to ***phosphoenolpyruvate(PEP)***. This compound is the phosphate ester of the enol tautomer of pyruvate.
- This is a reversible reaction.

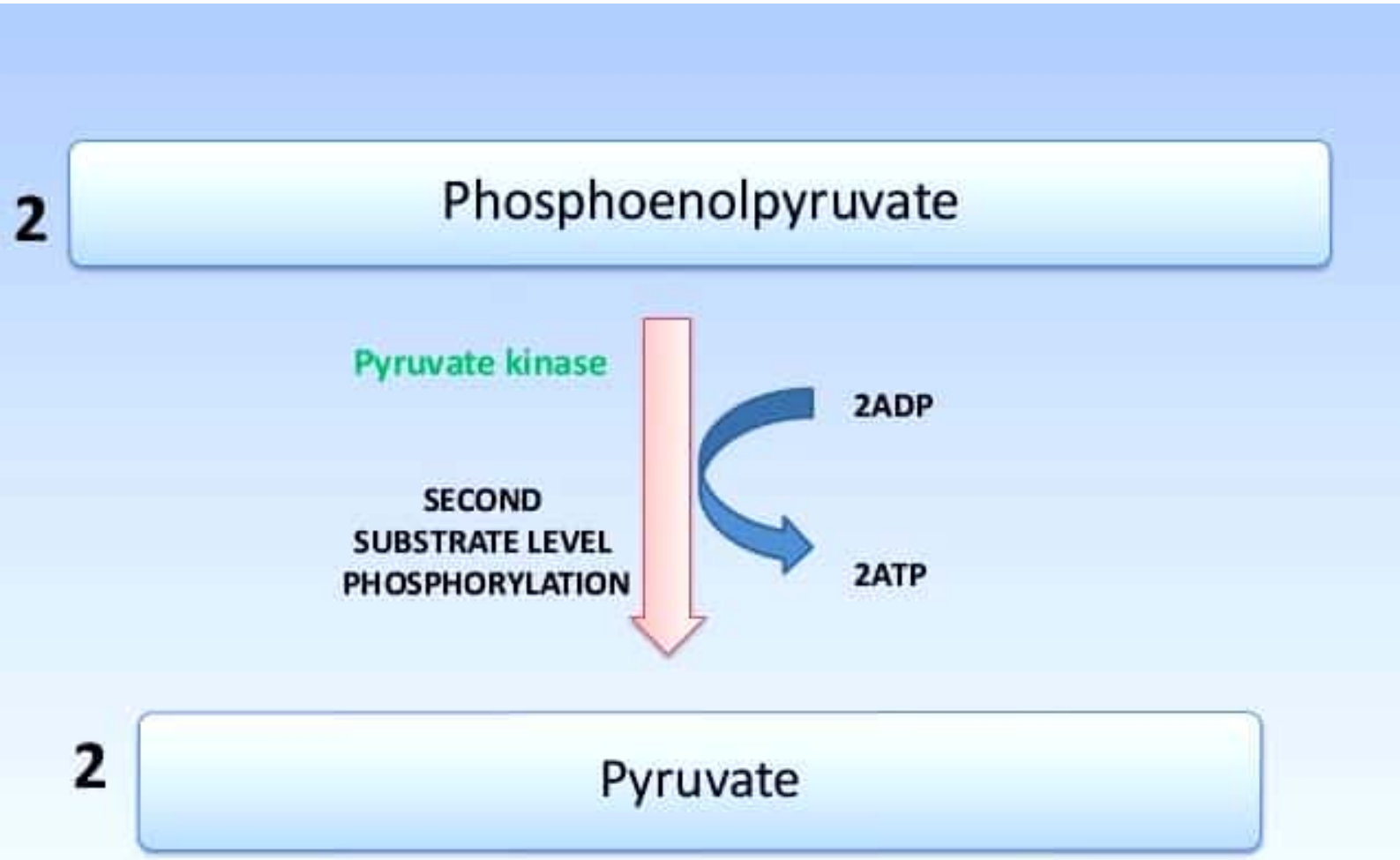
2 2-phosphoglycerate



2 Phosphoenol pyruvate

STEP 10: TRANSFER OF PHOSPHATE FROM PEP to ADP

- This last step is the irreversible transfer of high energy phosphoryl group from phosphoenolpuruvate to ADP.
- This reaction is catalyzed by ***pyruvate kinase.***
- This is the ***2nd substrate level phosphorylation*** reaction in glycolysis which yields ATP.
- This is a non-oxidative phosphorylation reaction.



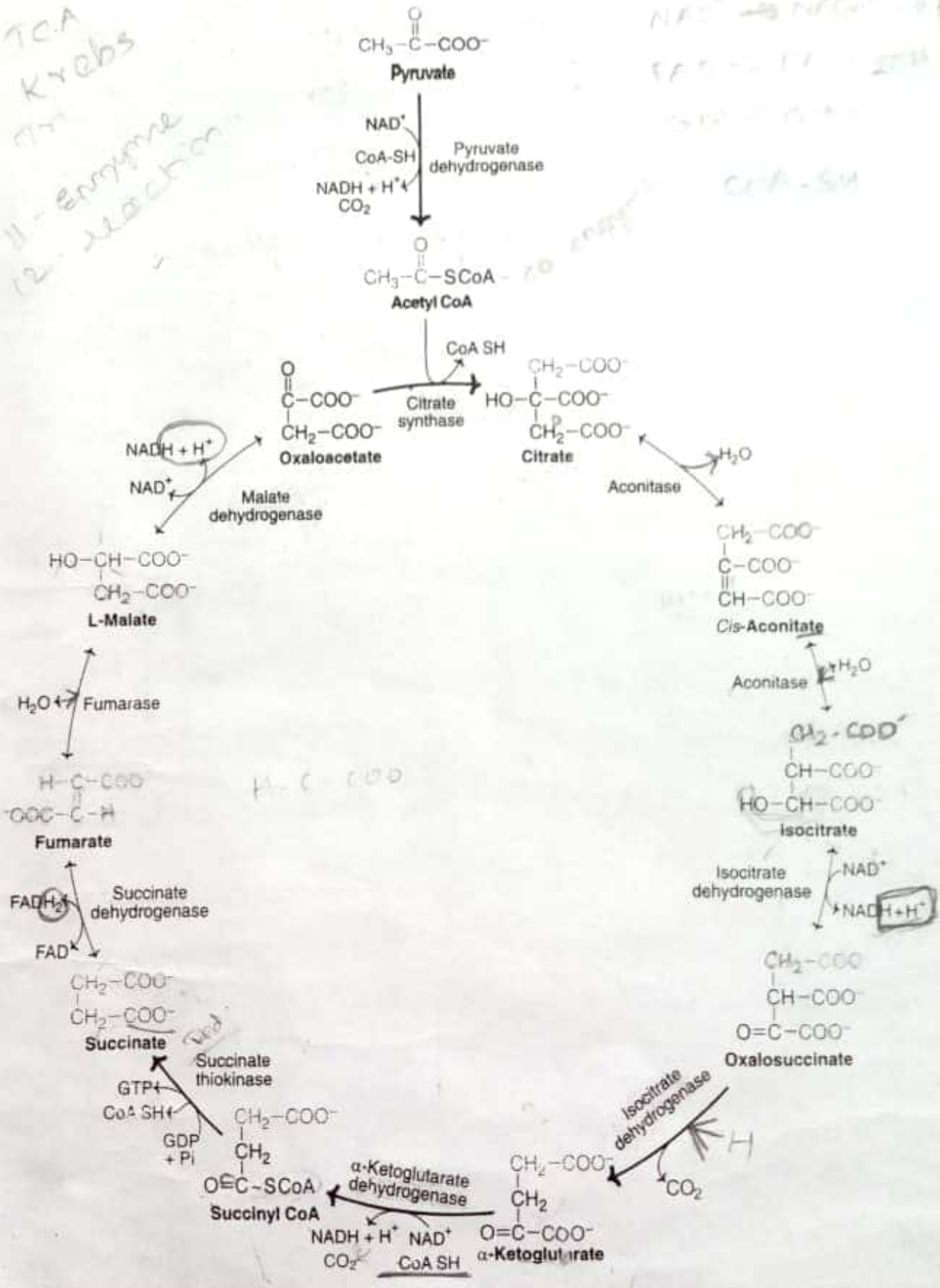


Fig.13.5 : The citric acid (Krebs) cycle. (Irreversible reactions shown by thick arrows)

Reactions of citric acid cycle

1) Formation of citrate:
condensation of acetyl CoA and oxaloacetate → catalysed by citrate synthase

2) & 3) citrate is isomerized to isocitrate → aconitase (two steps).

4) & 5) Formation of α-ketoglutarate:
enzyme isocitrate dehydrogenase.

6) conversion of α-ketoglutarate to succinyl CoA:
through oxidative decarboxylation, catalysed by α-ketoglutarate dehydrogenase complex.

7) Formation of succinate:
enzyme succinate thiokinase
GTP + ADP ⟷ ATP + GDP (nucleoside diphosphate kinase)

8) conversion of succinate to fumarase:
enzyme succinate dehydrogenase

9) Formation of malate: enzyme fumarase

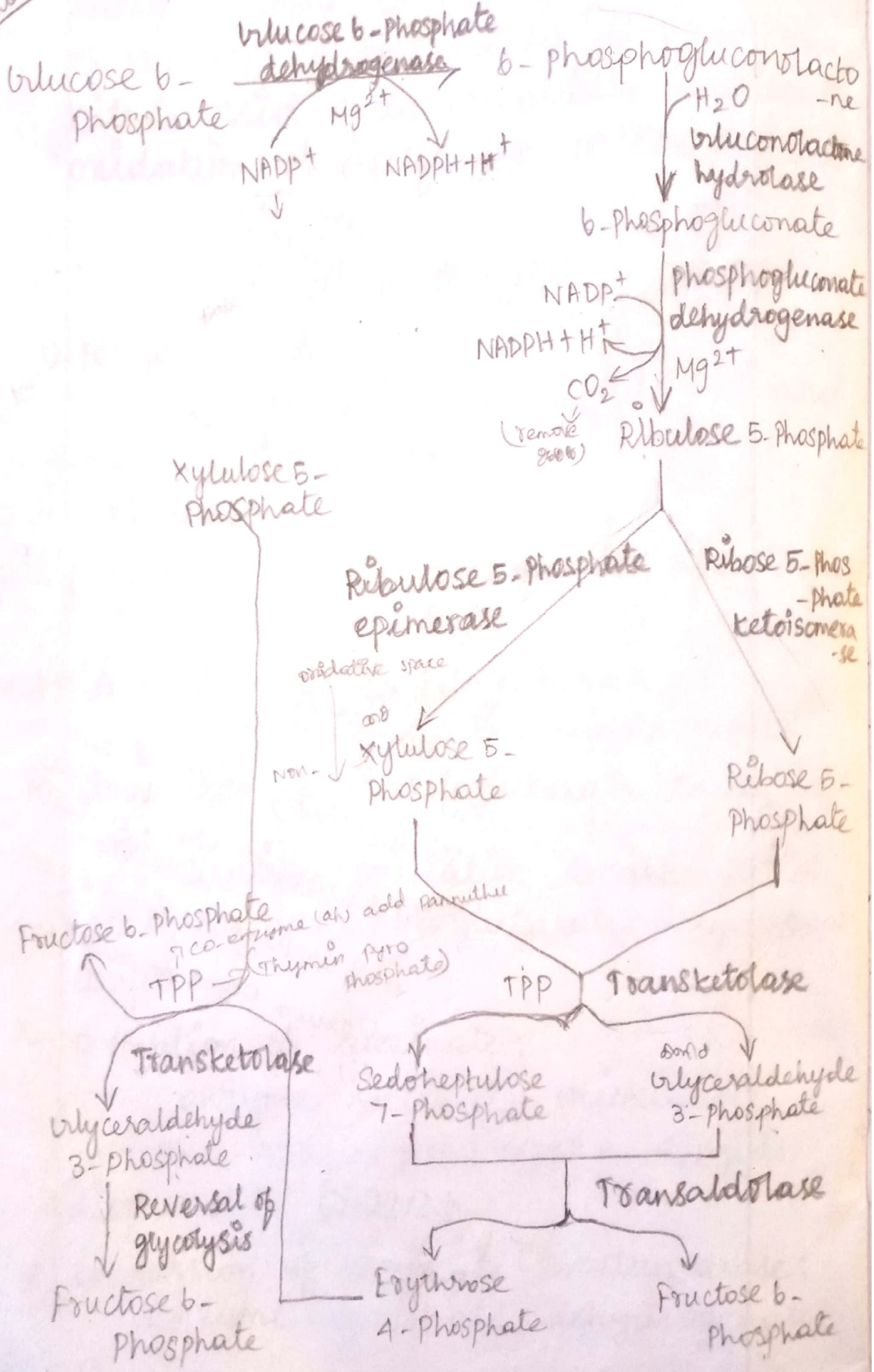
10) conversion of malate to oxaloacetate:
enzyme malate dehydrogenase

~~Citric acid cycle~~

: The hexose monophosphate Shunt

(H.M.S.)

Shunt (pentose phosphate pathway)



Introduction :- (Lipids)

*. The word lipid is derived from a greek word "lipos" which means FAT.

*. These are heterogenous group of compounds

*. Unlike proteins, nucleic acids, polysaccharides, lipids are not polymers rather they are small molecules.

*. They are the chief storage form of energy, besides their role in cellular structure and other biochemical functions.

Definition :-

*. Lipids may be regarded as organic substances relatively insoluble in water, soluble in organic solvents, actually or potentially related to fatty acids and utilized by the living cells.

Functions :-

*. Fat is stored in adipose tissue, where it also serves as a thermal insulator in the subcutaneous tissues.

*. Fatty acid derivatives serve as vitamins (A, D, E & K) or hormones.

*. It act as energy / food reservior (Triacylglycent).

*. Serveral proteins are covalently modified by fatty acids.

*. Structural components of biological membranes (lipoprotein, phospholipids & sphingomyelins).

*. Lipids act as important cellular metabolic regulators (PGs & steroid hormones)

*. Lipids are compounds in inner mitochondrial membrane and participate in Electron transport chain.

Classification :-

*. Lipids are broadly classified into 5 types which are the following :-

I. Simple lipids
II. Complex lipids
III. Derived lipids
IV. Neutral lipids and
V. Miscellaneous lipids.

I. Simple Lipids :-

*. Esters of fatty acids with ~~glycerol~~ Alcohols.

*. Mainly of two types.

(i) Fats and oils :-

- These are ~~the~~ esters of fatty acids and glycerol.

- difference b/w fats and oils is physical.

(ii) Waxes :-

- Esters of fatty acids + alcohol other than glycerol.

- cetyl alcohol is most commonly used.

II

Complex or compound Lipids:-

*. Esters of fatty acids + Alcohol + other groups like phosphate, Nitrogenous base, carbohydrate, protein, etc...

*. Based on the group present they are further classified into:-

i. Phospholipids:-

*. F.A + Alcohol + phosphoric acid as nitrogenous base.

*. Based on the type of alcohol present they are again divided into.

*. Glycerophospholipids:- contain Glycerol as alcohol. Eg: lecithin & cephalin

*. Sphingophospholipids:- Contain sphingosine as alcohol. Eg: Sphingomyelin

ii) Glycolipids:-

*. Fatty acids + alcohol + carbohydrate as nitrogenous base.

*. They contain sphingosine as alcohol and hence also known as Glycosphingolipids

*. Eg. cerebrosides and Gangliosides.

iii) Lipoproteins:- (Protein உடன் lipids attach ஆகுறது தான்)

*. Macromolecular complexes of lipids with proteins. (Lipoproteins)

*. Eg: LDL, VLDL, Chylomicrons, HDL, etc...

iv) Other complex lipids:-

*. Sulfolipids, Aminolipids and other Lipopolysaccharides come under this.

III Derived Lipids :-

*. These are the derivatives of hydrolysis of simple and complex lipids which possess the characteristics of lipids.

*. These include :-

*. Lipid soluble vitamins

*. Steroid hormones

*. Hydrocarbons

*. Ketone bodies

*. Mono and diacylglycerol, etc..

IV Neutral Lipids :-

*. These are the lipids which are unchanged and are reffered to as neutral lipids.

*. These are mono, di and triacylglycerols, cholestrol and cholesteryl esters.

V Miscellaneous Lipids :-

*. A large number of compounds possess characteristics of lipids, such compounds come under this category.

*. Example :- carotenoids, squalene, hydrocarbons like pentacosone and terpenes etc.

properties of lipids :-

Did you know?
(The long hydrocarbon chain is quite resistant, barely reacts in any chemical reaction)

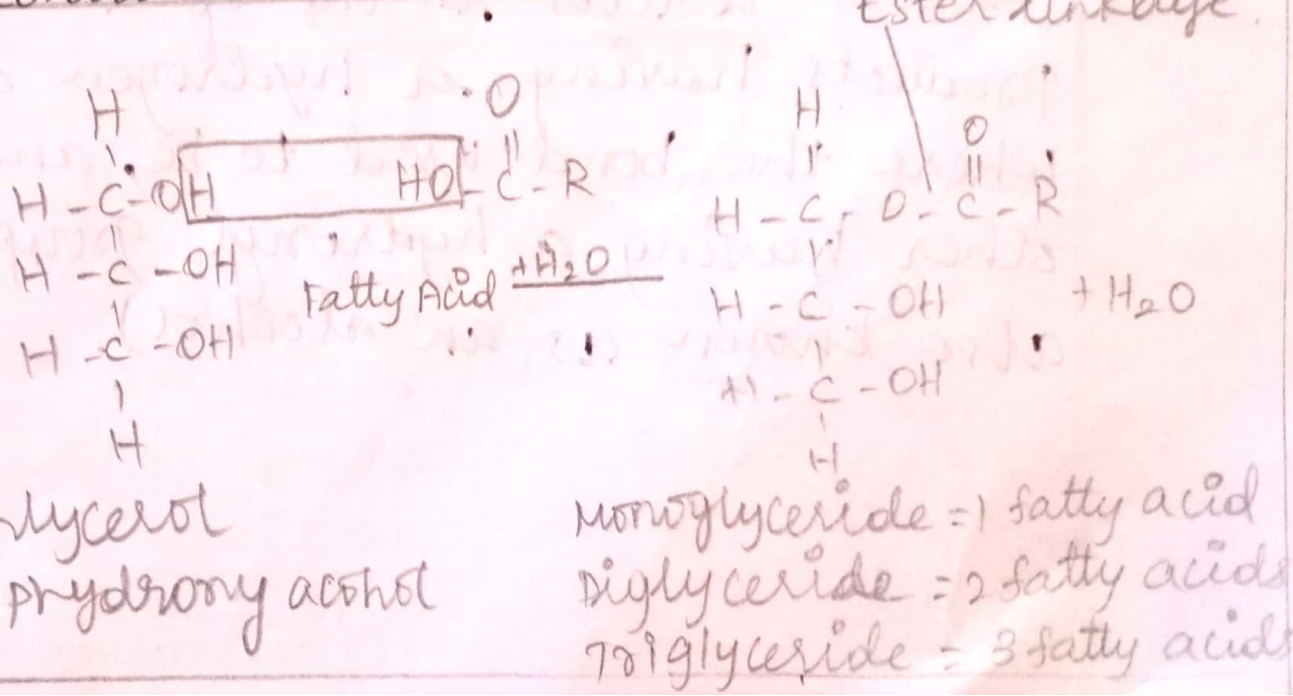
S. Mary

chemical properties of lipids :-

Essential components that define fatty acids :-

* Hydrocarbon chain (1s)
* Saturated (pure C-C bonds) or unsaturated (contains one or more C=C bonds)
* carboxylic acid.

chemical properties of a substance depend upon its active group. In lipids these are because of carbonyl group (which react with alcohols (R'OH) to form esters).



carboxyl part participating in Reaction of Fatty Acid

Some chemical properties are:-

* Hydrolysis → நீராற்பகுப்பு
* Saponification → சவர்க்காரமாக்கல்.
* Hydrogenation → ஐதரசனேற்றம்
* Rancidity
* Ester formation
* prostaglandin formation

1. Hydrolysis:-

"Hydrolysis is the process wherein a covalent bond within a molecule is broken down by the addition of water"

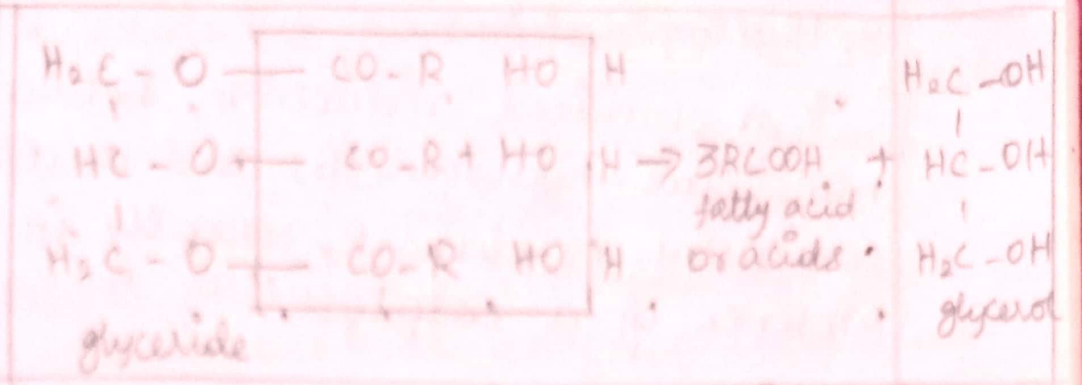
The Fats may be hydrolyzed with the following:-

* Super heated steam.
* By acids, or alkalis.
* By the specific fat splitting enzymes lipases.

Lipases are hydrolyzing enzymes found in

* saliva
* gastric juice
* Pancreatic juice

process results in one of the reaction products having a hydrogen atom where the bond used to be, and the other having a hydroxyl group (-OH, also known as an alcohol).



Hydrolysis of triglycerides

2. Saponification:

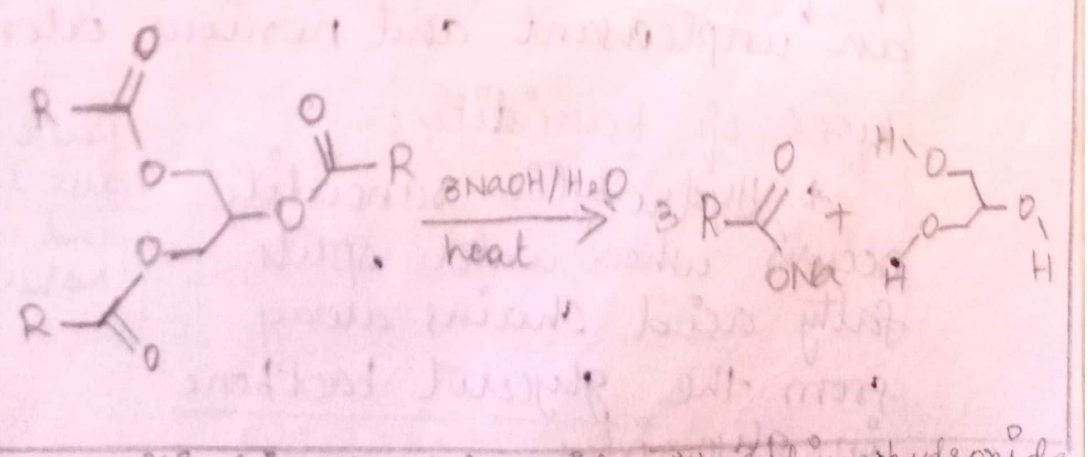
"Triglycerides (soap) are reacted with strong alkali (sodium or potassium hydroxide) to produce glycerol and a fatty acid salt, called soap".

* Triglycerides, are mixtures derived from diverse fatty acids.

* For soap making, the triglycerides are highly purified.

* Soap formed by this process is precipitated by salting it out with saturated sodium chloride.

* Saponification value: The number of milligrams of potassium hydroxide required to sponify 1g of fat under the conditions specified.



Saponification of a triglyceride with sodium hydroxide to give soap and glycerine

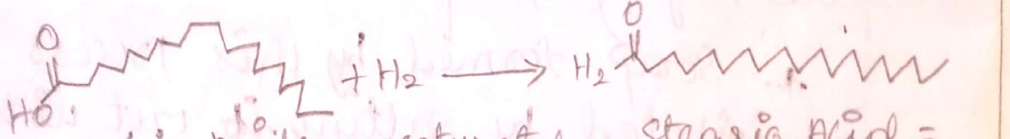
3. Hydrogenation :-

["A chemical reduction, between molecular hydrogen (H_2) and another compound or element, usually in the presence of a catalyst."]

*. The catalysts used are : Platinum, palladium, rhodium, and ruthenium and Raney nickel and Urushibara nickel

*. Unsaturated fatty acids may be converted to saturated fatty acids by the relatively simple hydrogenation reaction.

[Oleic Acid - unsaturated + H_2 ----> Stearic Acid - Saturated]



Hydrogenation of Oleic Acid - Unsaturated

4. Rancidity :

"Rancidity is the chemical decomposition of fats, oils and other lipids yielding on an unpleasant and noxious odor."

Types of Rancidity :-

*. Hydrolytic rancidity occurs when water splits fatty acid chains away from the glycerol backbone in glycerides. (1 Mark)

Rancidity is due to oxidative and Hydrolytic nature.

*. oxidative rancidity occurs when the double bonds of an unsaturated fatty acid react chemically with oxygen.

*. Microbial rancidity refers to a process in which microorganisms such as bacteria use their enzymes, including lipases, to breakdown chemical structures in the fat.

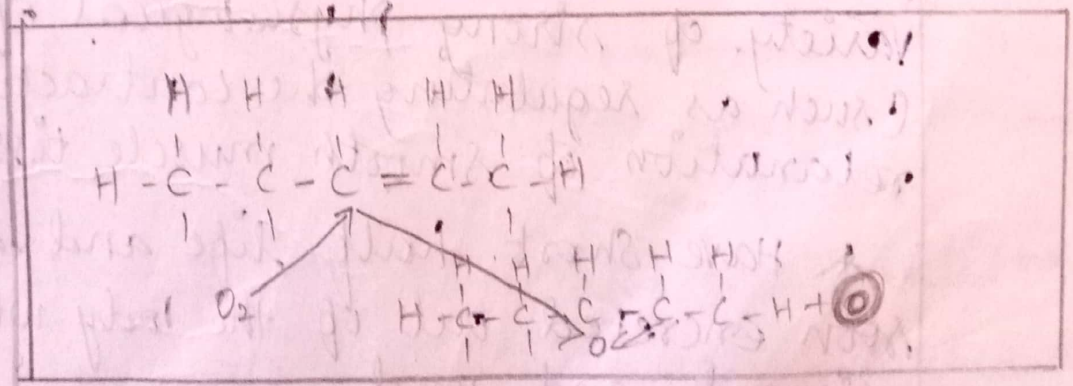
It results in formation of aldehydes and ketones which occurs in contact with air at room temperature which gives undesirable odor and flavor.

Factors affecting oxidation → A cause of Rancidity :-

*. Light, heat, metals (iron and copper), oxidizer as chlorophyll, hemoglobin, and certain synthetic dyes.

*. Another factor affecting the oxidation rate is the amount of oxygen, the degree of unsaturated of fatty acids in oils etc.

*. And the presence of antioxidants.

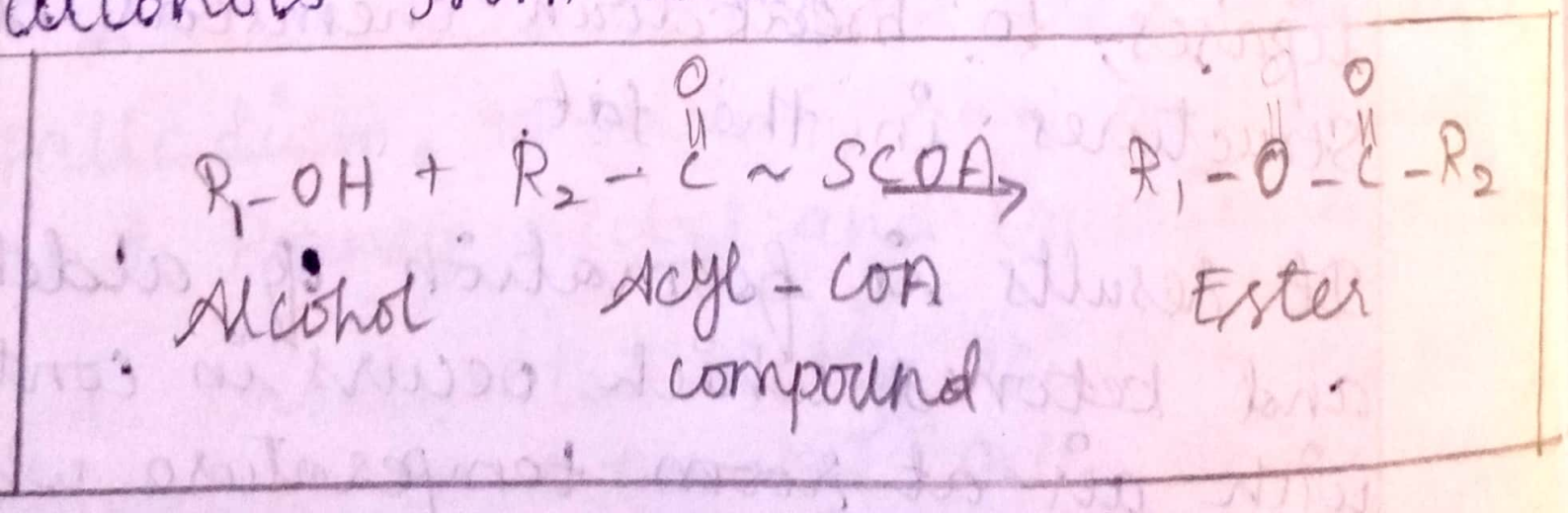


Process of oxidization of Lipids - Rancidity

5. Ester Formation :-

Fatty acids in combination with alcohols form esters.

Examples with glycerol from mono-, di- and tri- glycerides and with other alcohols from waxes.



physical properties of lipids :-

* colorless
* odorless
* tasteless

hydrofilic - like

* Hydrophobic (like) (repel water and so insoluble in water) and soluble in only organic solvents (such as ether, hexane or chosoform) because of the non-polar hydrocarbon chain
* specific gravity is less than 1.0
* Are saturated and unsaturated

* Saturated : NO double bonds in structure of any fatty acid chain.. like fat and butter..
* Unsaturated : Having double or Triple bond in the structure of their fatty acid chain like olive oil.

* Emulsified when shaken with water.
* High solubility with increasing number of double bonds of its long hydrophobic fatty acid chain.
* Melting point of lipids increase with increasing number of carbon atoms in the fatty acid chain.

glutathione is important for many of its biological functions. In a steady state, the cells generally

etc. are the gastrointestinal peptides which serve as hormones.

15 METABOLISM OF AMINO ACIDS

Proteins are the ***most abundant organic compounds*** and constitute a major part of the body dry weight (10-12 kg in adults). They perform a wide variety of static (structural) and dynamic (enzymes, hormones, clotting factors, receptors etc.) functions. About half of the body protein (predominantly collagen) is present in the supportive tissue (skeleton and connective) while the other half is intracellular.

The proteins on degradation (proteolysis) release individual amino acids. Amino acids are not just the structural components of proteins. Each of the 20 naturally occurring amino acids undergoes its own metabolism and performs specific functions. Some of the amino acids also serve as precursors for the synthesis of many biologically important compounds (e.g. melanin, serotonin, creatine etc.), ***Protein metabolism is more appropriately learnt as metabolism of amino acids.***

AMINO ACID POOL

An adult has about 100 g of free amino acids which represent the amino acid pool of the body. The amino acid pool may be an oversimplification of the facts, since there is no single compartment—rather, several compartments exist.

Glutamate and ***glutamine*** together constitute **about 50%**, and essential amino acids about 10% of the body pool (100 g). The concentration of intracellular amino acids is always higher than the extracellular amino acids. Amino acids enter the cells against a concentration gradient by active transport.

The amino acid pool (100 g) of the body is maintained by the sources that contribute (input) and the metabolic pathways that utilize (output) the amino acids (***Fig. 15.1***).

I. Sources of amino acid pool

Turnover of body protein, intake of dietary protein and the synthesis of non-essential amino acids contribute to the body amino acid pool.

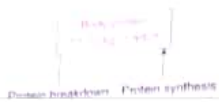
(a) **Protein turnover :** The protein present in the body is in a dynamic state. It is estimated that about ***300-400 g of protein per day*** is constantly degraded and synthesized which represents body protein turnover.

(b) **Dietary protein :** There is a regular loss of nitrogen from the body due to degradation of amino acids. In healthy adults, it is estimated that about 30-50 g of protein is lost everyday from the body. This amount of protein (30-50 g/day) must, therefore, be supplied daily in the diet to maintain nitrogen balance. The RDA for protein is 1 g/kg body weight/day.

(c) **Synthesis of non-essential amino acids :** Ten out of the 20 naturally occurring amino acids can be synthesized by the body which contributes to the amino acid pool.

II. Utilization of amino acids from body pool

(a) Most of the body proteins (300-400 g/day) degraded are synthesized from the amino acid pool. These include enzymes, hormones, immunoproteins, contractile proteins etc.



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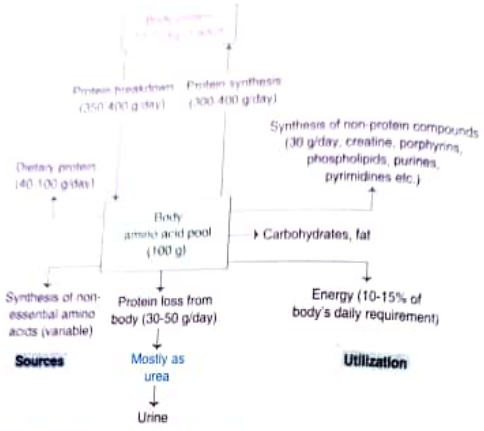

Fig.15.1 : Overview of body's amino acid pool—sources and utilization.

(b) Many important nitrogenous compounds (porphyrins, purines, pyrimidines, etc.) are produced from the amino acids.

(c) Generally, about 10-15% of body energy requirements are met from the amino acids.

(d) The amino acids are converted to carbohydrates and fats.

METABOLISM OF AMINO ACIDS—GENERAL ASPECTS

The amino acids undergo certain common reactions like ***transamination*** followed by ***deamination*** for the liberation of ***ammonia***. The amino group of the amino acids is utilized for the formation of ***urea*** which is an excretory end product of protein metabolism. The carbon skeleton of the amino acids is first converted to keto acids (by transamination) which meet one or more of the following fates.

1. Utilized to generate energy.
2. Used for the synthesis of glucose.
3. Diverted for the formation of fat or ketone bodies.
4. Involved in the production of non-essential amino acids.

A general picture of amino acid metabolism is depicted in ***Fig.15.2***.

TRANSAMINATION

The ***transfer of an amino (—NH_2) group from an amino acid to a keto acid*** is known as transamination (***Fig.15.3***). This process involves the interconversion of a pair of amino acids and a pair of keto acids, catalysed by a group of enzymes called ***transaminases*** (recently, ***aminotransferases***).

Salient features of transamination

1. All transaminases require ***pyridoxal phosphate*** (PLP), a coenzyme derived from vitamin B_6.
2. There is no free NH_3 liberated, only the transfer of amino group occurs.
3. Transamination is ***reversible***.
4. It involves both catabolism (degradation) and anabolism (synthesis) of amino acids. Transamination is ultimately responsible for the ***synthesis of non-essential amino acids***.
5. Transamination diverts the excess amino acids towards ***energy generation***.

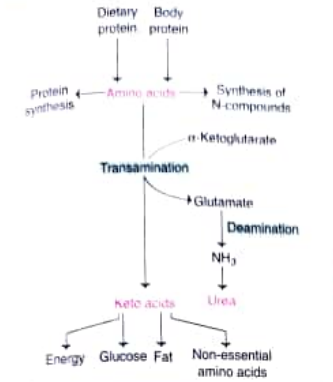

Fig.15.2 : An overview of amino acid metabolism.

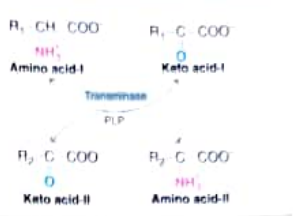

Fig.15.3 : Transamination reaction.

6. The amino acids undergo transamination to finally concentrate nitrogen in glutamate. ***Glutamate*** is the only amino acid that undergoes oxidative deamination to a significant extent to liberate free NH_3 for urea synthesis.

I. Oxidative deamination

Oxidative deamination is the liberation of free ammonia from the amino group of amino acids coupled with oxidation. This takes place mostly in liver and kidney. The purpose of oxidative deamination is to provide NH_3 for urea synthesis and α-keto acids for a variety of reactions, including energy generation.

Role of glutamate dehydrogenase : In the process of transamination, the amino groups of most amino acids are transferred to α-ketoglutarate to produce glutamate. Thus, ***glutamate*** serves as a '***collection centre' for amino groups*** in the biological system.

(d) The amino acids are converted to carbohydrates and fats.

METABOLISM OF AMINO ACIDS—GENERAL ASPECTS

The amino acids undergo certain common reactions like ***transamination*** followed by ***deamination*** for the liberation of ***ammonia***. The amino group of the amino acids is utilized for the formation of ***urea*** which is an excretory end product of protein metabolism. The carbon skeleton of the amino acids is first converted to keto acids (by transamination) which meet one or more of the following fates.

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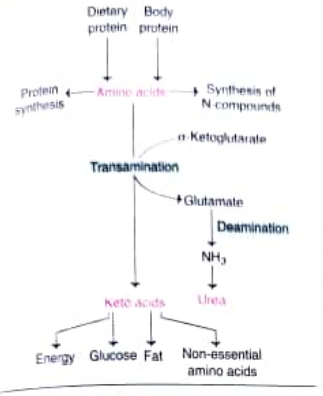

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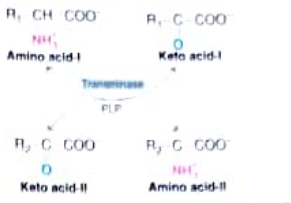

Fig.15.3 : Transamination reaction

6. The amino acids undergo transamination to finally concentrate nitrogen in glutamate. ***Glutamate*** is the only amino acid that undergoes oxidative deamination to a significant extent to liberate free NH_3 for urea synthesis.

7. All amino acids except lysine, threonine, proline and hydroxyproline participate in transamination.

DEAMINATION

The ***removal of amino group*** from the amino acids as NH_3 is deamination. It results in the liberation of ammonia for urea synthesis. Deamination may be either oxidative or non-oxidative.

I. Oxidative deamination

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Role of glutamate dehydrogenase : In the process of transamination, the amino groups of most amino acids are transferred to α-ketoglutarate to produce glutamate. Thus, ***glutamate*** serves as a '***collection centre' for amino groups*** in the biological system. Glutamate rapidly undergoes oxidative deamination, catalysed by glutamate dehydrogenase (GDH) to liberate ammonia. This enzyme is unique in that it can utilize either NAD^+ or $NADP^+$ as a coenzyme. Conversion of glutamate to α-ketoglutarate occurs through the formation of an intermediate, α-iminoglutarate (***Fig.15.4***).

Oxidative deamination by amino acid oxidases : L-Amino acid oxidase and D-amino acid oxidase are flavoproteins, possessing FMN and

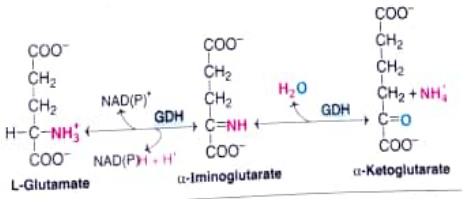
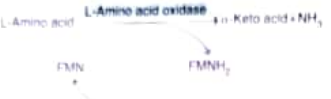


Fig.15.4 : Oxidation of glutamate by glutamate dehydrogenase (GDH).



II. Disposal of ammonia

The organisms, during the course of evolution have developed different mechanisms for the disposal of ammonia from the body. The animals in this are of three different types

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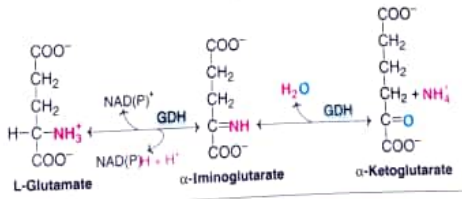


Fig.15.4 : *Oxidation of glutamate by glutamate dehydrogenase (GDH).*

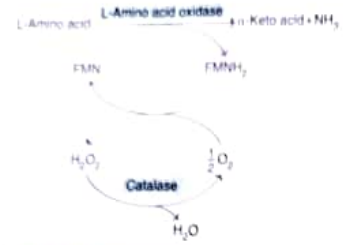


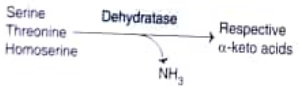
Fig.15.5 : *Oxidative deamination of amino acids.*

FAD, respectively. They act on the corresponding amino acids (L or D) to produce α-keto acids and NH_3. In this reaction, oxygen is reduced to H_2O_2, which is later decomposed by catalase (***Fig.15.5***).

II. Non-oxidative deamination

Some of the amino acids can be deaminated to liberate NH_3 without undergoing oxidation

(a) **Amino acid dehydrases :** Serine, threonine and homoserine are the hydroxy amino acids. They undergo non-oxidative deamination catalysed by PLP-dependent dehydrases (dehydratases).



(b) **Deamination of histidine :** The enzyme histidase acts on histidine to liberate NH_3 by a non-oxidative deamination process.

METABOLISM OF AMMONIA

Ammonia is constantly being liberated in the metabolism of amino acids (mostly) and other nitrogenous compounds. At the physiological pH, ***ammonia exists as ammonium (NH_4^+) ion.***

I. Formation of ammonia

The production of NH_3 occurs from the amino acids (transamination and deamination), biogenic amines, amino group of purines and pyrimidines and by the action of intestinal bacteria (urease) on urea.

II. Disposal of ammonia

The organisms, during the course of evolution, have developed different mechanisms for the disposal of ammonia from the body. The animals in this regard are of three different types

(a) **Ammoniotelic :** The aquatic animals excrete off NH_3 into the surrounding water.

(b) **Uricotelic :** Ammonia is converted mainly to uric acid e.g. reptiles and birds.

(c) **Ureotelic :** The mammals including man convert NH_3 to urea. Urea is a non-toxic and neutral compound, hence easily excreted.

UREA CYCLE

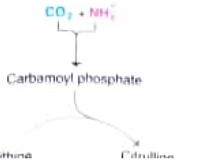
Urea is the end product of protein metabolism (amino acid metabolism). The nitrogen of amino acids converted to ammonia (as described above) is toxic to the body. It is converted to urea and detoxified. As such, urea accounts for 80-90% of the nitrogen containing substances excreted in urine.

Urea is ***synthesized in liver*** and transported to kidneys for excretion in urine. Urea cycle is the ***first metabolic cycle*** that was elucidated by Hans Krebs and Kurt Henseleit (1932), hence it is known as ***Krebs-Henseleit cycle.*** The individual reactions, however, were described in more detail later on by Ratner and Cohen.

Urea has ***two amino ($-NH_2$) groups,*** one derived ***from NH_3*** and the other ***from aspartate.*** Carbon atom is supplied by CO_2. Urea synthesis is a five-step cyclic process, with five distinct enzymes. The first ***two enzymes*** are present in ***mitochondria*** while the ***rest*** are localized in ***cytosol.*** The details of urea cycle are described next (***Figs. 15.6*** and ***15.7***).

1. **Synthesis of carbamoyl phosphate :** Carbamoyl phosphate synthase I (CPS I) of mitochondria catalyses the condensation of NH_3 ions with CO_2 to form carbamoyl phosphate. This step consumes two ATP and is ***irreversible,*** and ***rate-limiting.*** CPS I requires ***N-acetylglutamate*** for its activity.

2. **Formation of citrulline :** Citrulline is synthesized from carbamoyl phosphate and ornithine by ornithine transcarbamoylase. Ornithine is regenerated and used in urea cycle

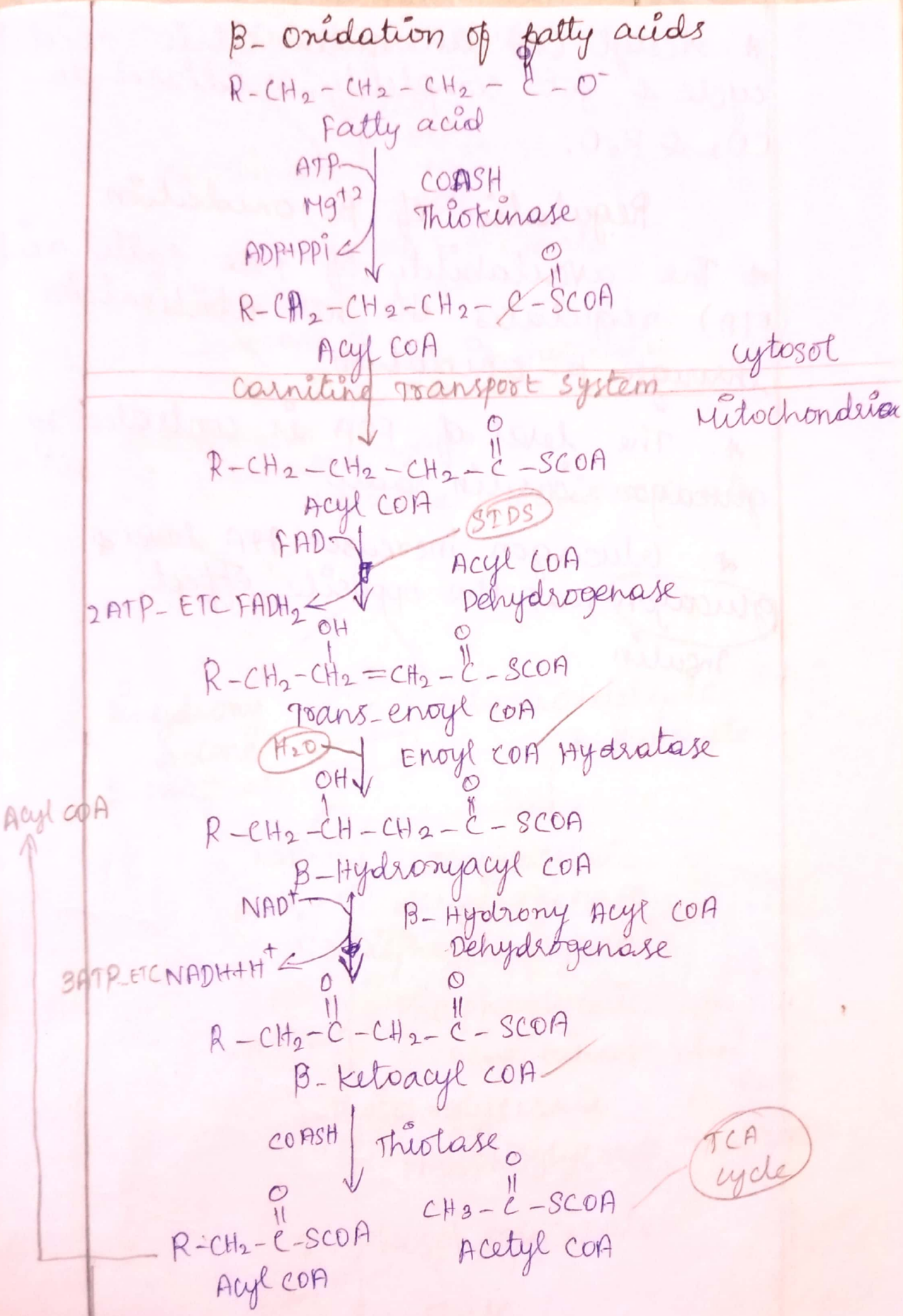


is allosterically activated by N-acetylglutamate (NAG).

Metabolic disorders of urea cycle

Metabolic defects associated with each of the five enzymes of urea cycle have been reported (***Table 15.1***). All the disorders invariably lead to a

β- oxidation of fatty acids



Beta Oxidation Of Fatty Acid

Definition

* Beta-Oxidation may be defined as the oxidation of fatty acid on the β-carbon atom.

* This result in the sequential removal of a two carbon fragment, acetyl CoA.

Stages and tissues

* Three stages

* Activation of fatty acids - in the Cytosol.

* Transport of fatty acids into mitochondria.

* Beta-oxidation proper in the mitochondrial matrix.

* Fatty acids are oxidized by most of the tissue in the body.

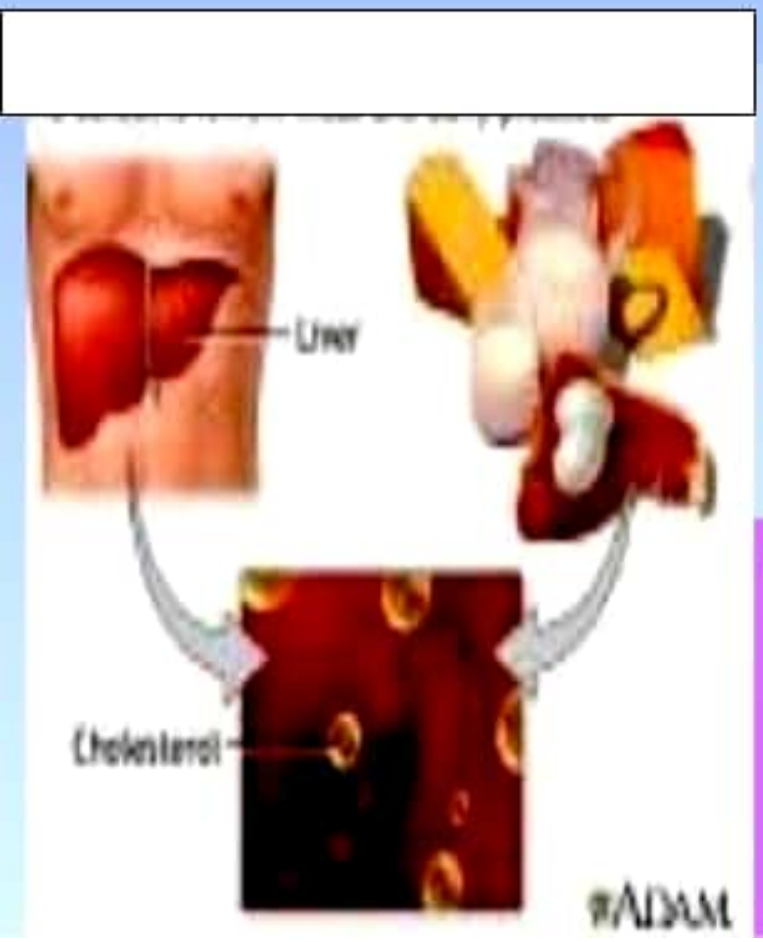
* Brain, erythrocytes & adrenal medulla cannot utilize fatty acids for energy requirment.

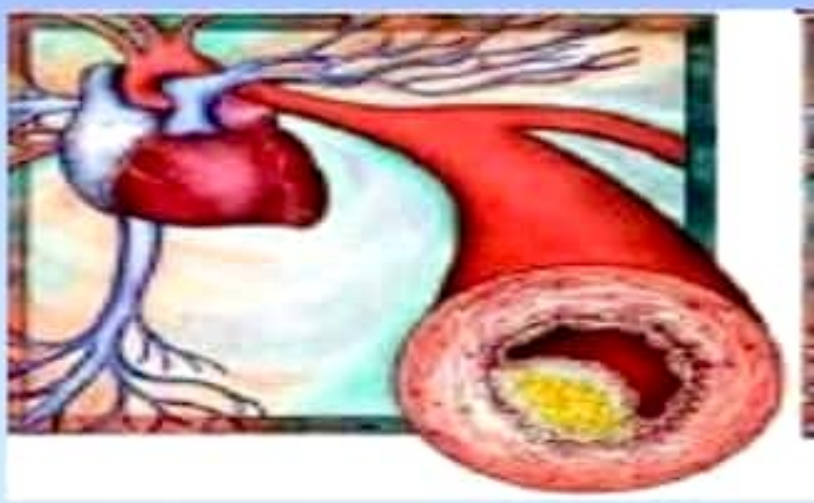
* Two high energy phosphates are utilized. Since ATP is converted to Pyrophosphate (ppi)

* The enzyme inorganic pyrophosphatase hydrolase ppi to phosphate.

* The immediate elimination of pi makes this reaction totally irreversible

Cholesterol Metabolism





- Dr. V. Siva Prabodh MD
  Professor
  Dept. of Biochemistry
  NRI Medical College

CHOLESTEROL

→ Cholesterol is a **light yellow crystalline solid**

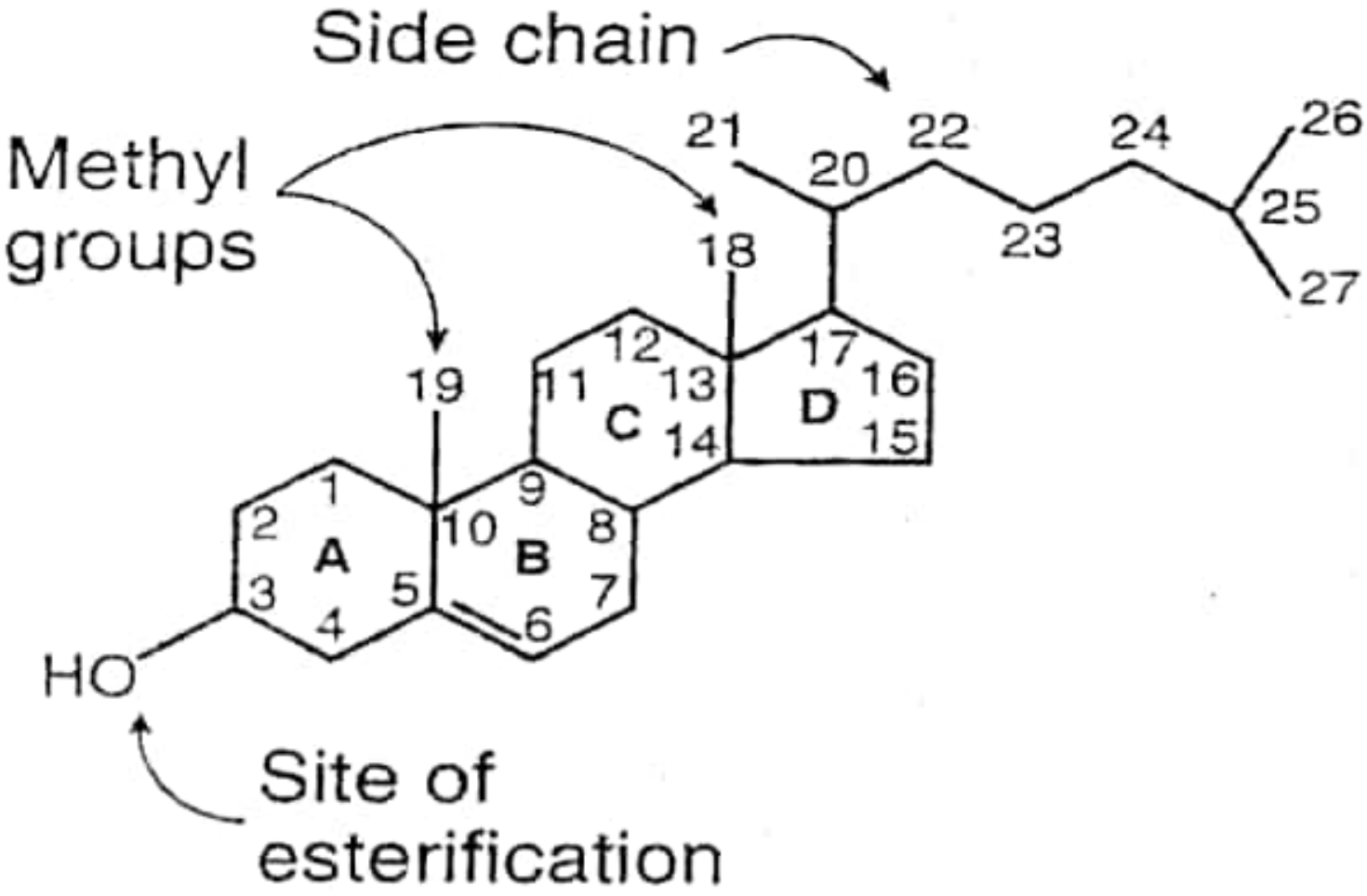
→ It is a **27 Carbon compound**

→ contains ***cyclopentano perhydro phenanthrene*** ring

→ **One hydroxyl group (OH) at 3rd position**

→ **Double bond** between **5 & 6 Carbons**

→ **8 Carbon side chain** at 17th Carbon



Cholesterol

Significance of Cholesterol

1) Normal level ***150 – 200 mg/dl*** . Increased levels increases the risk for ***Atherosclerosis***
2) Important ***component of cell membranes*** which affects fluid state of membrane
3) It is used to ***Insulate Nerve fibers***.
4) ***Bile acids*** (24 Carbon) are derived from Cholesterol
5) ***Steroid hormones*** (21 'C' glucocorticoids, 19 'C' androgens and 18 'C' estrogens) are produced from cholesterol
6) ***Vitamin D*** formed from Cholesterol

Biosynthesis of Cholesterol

Major sites – ***Liver, Adrenal Cortex, testis, ovaries*** and ***Intestine***

80% by Liver

The enzymes involved in synthesis are located partly in ***cytoplasm*** and ***endoplasmic reticulum.***

Requirements:

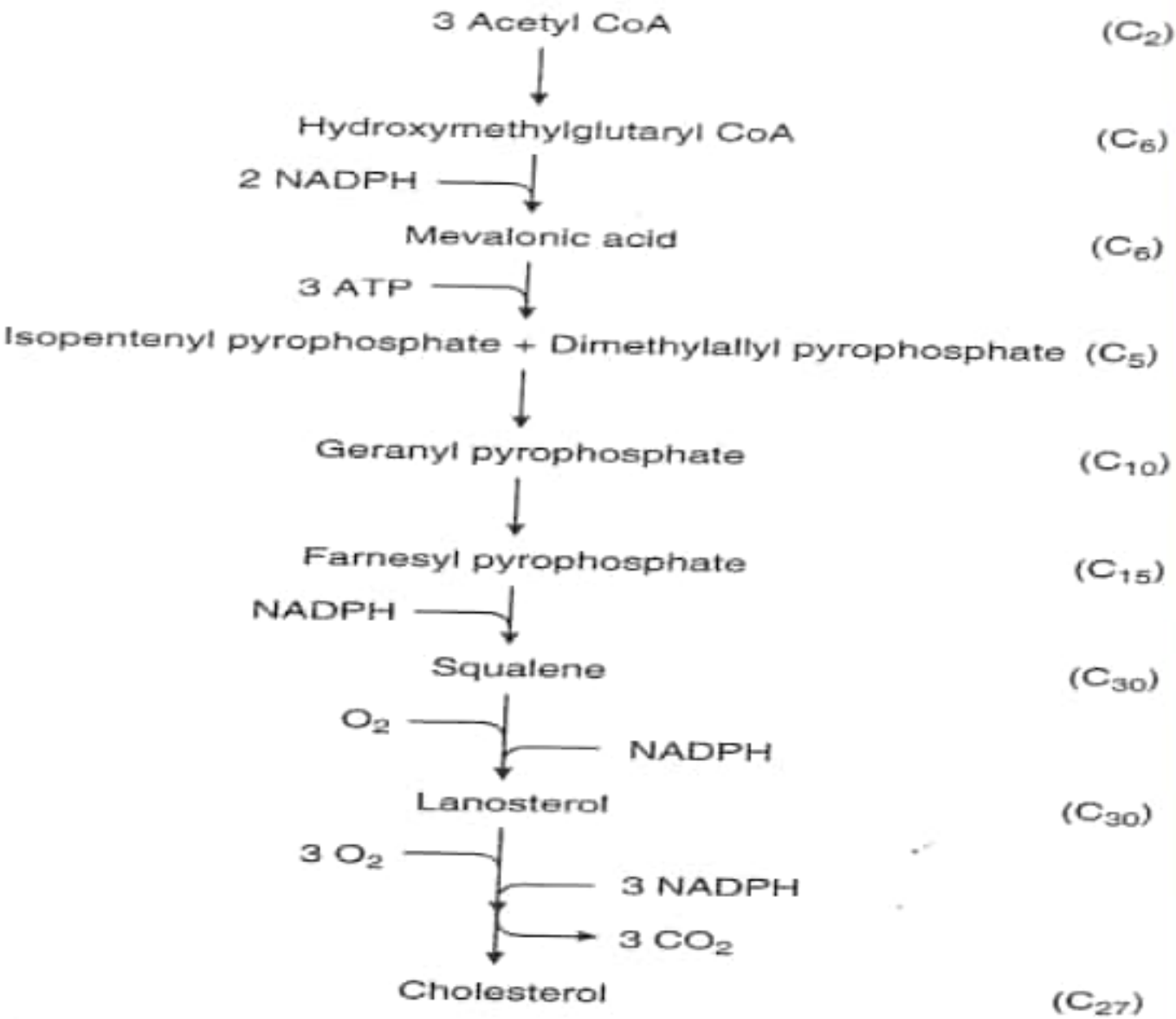
1) Acetate of **acetyl CoA** provides all the carbon atoms of cholesterol
2) Reducing equivalents by **NADPH**
3) Energy from **ATP.**

De novo Synthesis of Cholesterol

- Primary site: liver (~1g/d)
  - Secondary sites: adrenal cortex, ovaries, testes
- Overall equation:

$$18\ \text{Acetyl CoA} + 18\ \text{ATP} + 16\ \text{NADPH} + 4\ O_2 \longrightarrow$$

$$\text{cholesterol} + 9\ CO_2 + 16\ NADP^+ + 18\ \text{ADP} + 18\ P_i$$



Cholesterol Synthesis in 5 stages

1) Synthesis of **HMG CoA (6 c)**
2) Formation of **mevalonate (6 C)**
3) Production of **Isoprenoid Units (5 C)**
4) Synthesis of **squalene (30 C)**
5) Conversion of **Squalene to cholesterol (27 C)**

2C ▶ 6C ▶ 6C ▶ 5C ▶ 10C ▶ 15C ▶ 30C ▶ 27C

Step I : Condensation

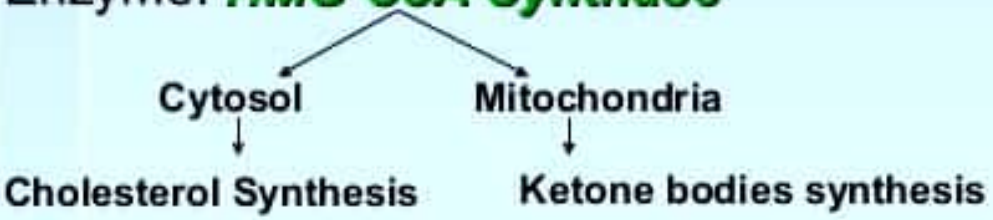
Two molecules of Acetyl CoA condense to form **Acetoacetyl CoA**

Enzyme: ***Acetoacetyl CoA Synthase***

Step II : *Production of HMG CoA*

One acetyl CoA condenses with Acetoacetyl CoA to form ***β-hydroxy β-methyl glutaryl CoA*** (HMG CoA)

Enzyme: ***HMG CoA Synthase***



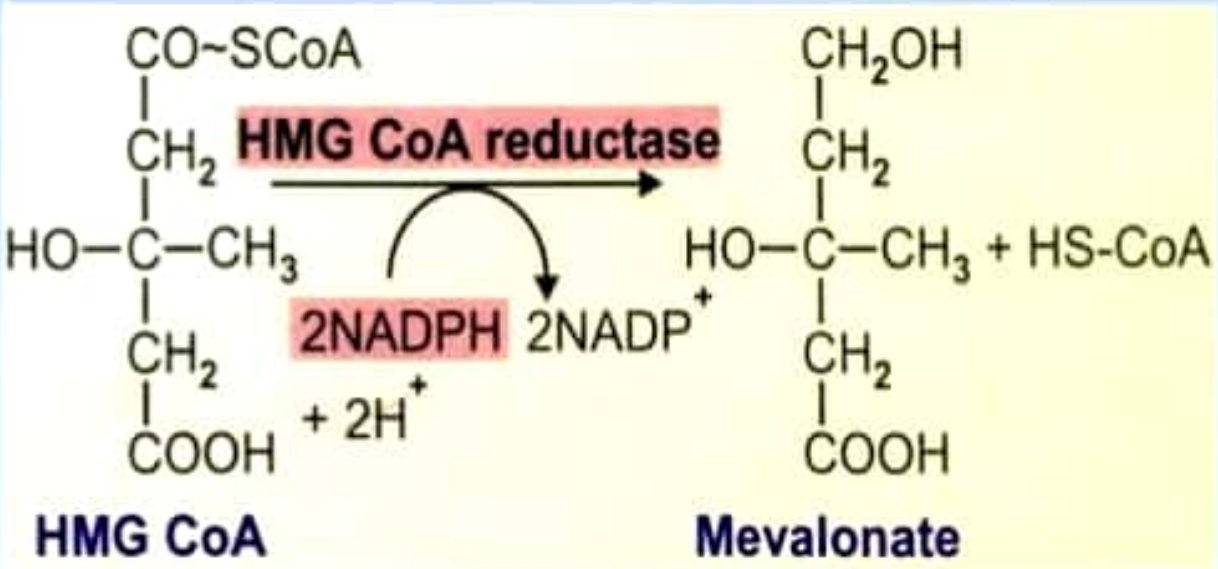
Step III – Regulating Step

Formation of **Mevalonate**

Reduction of HMG CoA to Mevalonate

Enzyme: ***HMG CoA reductase***

requires 2 NADPH



Step 3 of cholesterol synthesis

Step 4 : Formation of Isoprenoid Unit (5 C)

Mevalonate is ***phorphorylated*** three times to form ***3" phospho 5" pyrophospho mevalonate***, requires 3 ATP.

This undergoes **decarboxylation** to form ***Isopentanyl Pyrophosphate*** (5 C)

Step 5: Synthesis of Squalence (30 C)

Isopentanyl pyrophosphate Isomerizes to form

Di methyl allyl pyrophosphate

One molecule of **IPP** (5 C) condenses with **DMP** (5 C) to form **Geranyl pyrophosphate** (10 C)

One molecule of **IPP** (5 C) condenses with **GP** (10 C) to form **Farnesyl pyrophosphate (15 C)**

Two molecules of **Farnesyl pyrophosphate (15 C)** condenses to form **Squalene (30 C)**

Regulation of Cholesterol Synthesis

HMG CoA reductase is the regulating Enzyme

1. **Feed back Inhibition:**

   The end product cholesterol in excess inhibits the gene which is responsible for production of HMG CoA reductase

2. **Hormonal regulation:**

   Glucogon & Glucocorticoids favor the formation of Inactive HMG CoA reductase, thus decreases the cholesterol synthesis

   Insulin increases cholesterol synthesis by enhancing the formation of active HMG CoA reductase.

3. **Inhibition by drugs:**

Compactive

Lovastatin

Competitive Inhibitors for HMG CoA reductase.

Bile acids:

24 Carbon compounds with steroid ring.

Helps in digestion & absorption of lipids.

Synthesis takes place in **Liver**

7-hydroxylase is the regulating Enzyme

Primary Bile acids –

cholic acid, chenodeoxy cholic acid

Secondary Bile acids –

deoxycholic acid, Lithocholic acid

KETONE BODIES

Tapeshwar Yadav
)Lecturer(
, BMLT, DNHE
M.Sc. Medical Biochemistry

Ketone Bodies

They are;

- Acetoacetic acid CH_3-CO-CH_2-COOH
- β(3)-hydroxybutyric acid CH_3-CHOH-CH_2-COOH
- Acetone CH_3-CO-CH_3

Ketogensesis

Definition:

It means Synthesis of ketone bodies.

Site.

Mitochondrial matrix of liver cells.

Ketoacidosis (Ketosis)

Definition

It is a metabolic disorder characterized by a triad of :

1. Ketonemia (increase ketone bodies in blood).
2. ketonuria (increase ketone bodies in urine).
3. acetone (fruity) odor of breath.

There are also dehydration, acidosis, coma, and death (if untreated).

Causes of Ketosis

1. Prolonged starvation.
2. Severe dieting.
3. Uncontrolled diabetes mellitus.