CHAPTER 5

Carbohydrates Metabolism

INTRODUCTION TO METABOLISM

- Humans and all living organisms are in a steady dynamic state.
- This is maintained by the free energy obtained from the oxidation of nutrients through the different metabolic pathways.

- The objectives of this chapter are:
  1. To understand the **different forms of energy**.
  2. To know the **amount of energy stored in different types of chemical bonds**.
  3. To know **how chemical energy is generated, transferred and stored** by living cells.

METABOLISM

Metabolism means the series of biochemical reactions that occur for biomolecules in living organisms.

It is classified into: anabolism and catabolism.

ANABOLISM

- Means synthesis of macromolecules from simple one. Anabolism is usually endergonic (consumes energy).

Examples

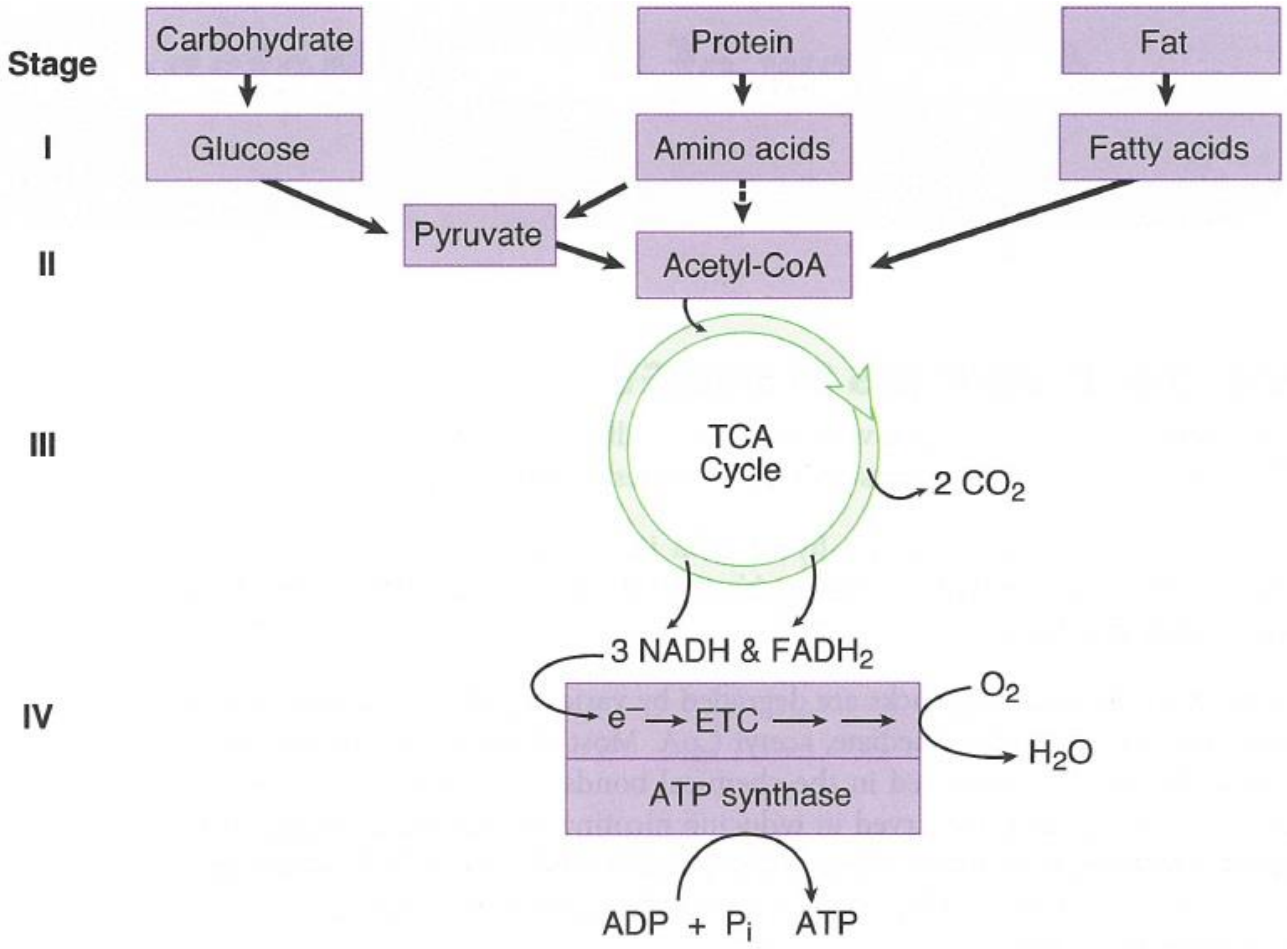
- Synthesis of polysaccharides from monosaccharides.
- Synthesis of triacylglycerol from glycerol and fatty acids.
- Synthesis of proteins from amino acids.

CATABOLISM

Means breakdown of macromolecules into simplest components. It is usually exergonic (release energy).

- Catabolism of the main metabolites occurs in **4 stages:**

- In stage 1, metabolic fuels are hydrolyzed in the gastrointestinal tract to a diverse set of monomeric building blocks (glucose, amino acids, and fatty acids) and absorbed.
- In stage 2,
  - **THE** building blocks are degraded by various pathways in tissues to a common metabolic intermediate, **ACETYL-COA**.
  - Most of the energy contained in metabolic fuels is conserved in the chemical bonds (electrons) of acetyl-CoA.
  - A smaller portion is conserved in reducing nicotinamide adenine dinucleotide (NAD) to **NADH+H** or flavin adenine dinucleotide (FAD) to **$FADH_2$**.
  - Reduction indicates the addition of electrons that may be free, part of a hydrogen atom (H), or a hydride ion.
- In stage 3, the **citric acid** (Krebs, or tricarboxylic acid 'TCA') cycle oxidizes acetyl-CoA to CO_2. The energy released in this process is primarily conserved by reducing (NAD) to **NADH+H** or (FAD) to **$FADH_2$**.
- The final stage is **oxidative phosphorylation**, in which the energy of **NADH+H** and **$FADH_2$** is released via the **electron transport chain** (ETC) and used by an ATP synthase to produce **ATP**. This process requires O_2.



METABOLIC ENERGY STORAGE

- ATP is a form of circulating energy currency in cells. It is formed in **catabolic pathways** by phosphorylation of ADP and may provide energy for biosynthesis (**anabolic pathways**). There is a limited amount of ATP in circulation.
- Most of the excess energy from the diet is stored as **glycogen** and **fatty acids**. Although **proteins** can be mobilized for energy in a prolonged fast, they are normally more important for other functions (contractile elements in muscle, enzymes, etc.).

LOW AND HIGH-ENERGY BONDS

LOW-ENERGY BONDS yields < 7.3 Kcal/mol on hydrolysis.	HIGH-ENERGY BONDS yields > 7.3 Kcal/mol.
Examples of low energy bonds • Ester bonds (Phosphate ester) • Glycosidic bonds (oligo, polysaccharides) • Peptide bonds.	**1- Phosphate bonds** • Phosphoenolpyruvate. • Carbamoyl phosphate • Creatine phosphate • Pyrophosphate as ADP and ATP • 1,3 Bisphosphoglycerate **2- Sulfur bonds** • Active methionine: SAM • Thioester as acetyl COA • B-Ketoacyl-CoA as: **Acetoacetyl-Co**

REDOX REACTION

Oxidation accompanied by reduction called redox reaction

OXIDATION	REDUCTION
1- Addition of oxygen 2. Removal of hydrogen 3. Loss of electron increase in positive charge. .	1. Removal of oxygen 2. Addition of hydrogen 3. Addition of electrons

Redox potential

Electron Affinity

Hydrogen is transferred through different component of redox chain so energy liberated is gradual

DEFINITION

Affinity of a substance for electron (its electronegativity) compared with hydrogen.

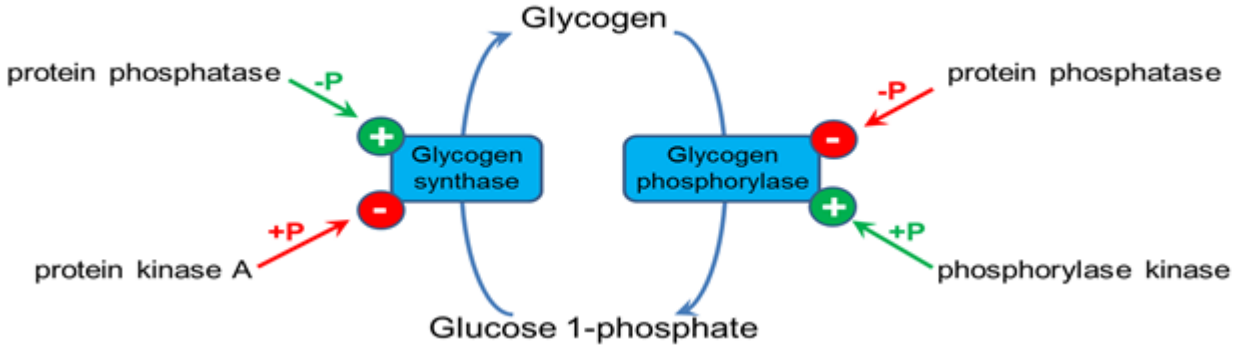
- Hydrogen has lowest electron affinity
- Oxygen has highest electron affinity.
- All other substances lie between O_2 and H^+.

NB. Hydrogen atom formed of one electron and one proton

REGULATION OF FUEL METABOLISM

- The pathways that are operational in fuel metabolism **depend on** the **nutritional status** of the organism. Shifts between storage and mobilization of a particular fuel, as well as shifts among the types of fuel being used, are very pronounced in going from the well-fed state to an overnight fast, and finally to a prolonged state of starvation. The shifting metabolic patterns are regulated mainly by the **insulin/glucagon** ratio.
- Insulin is an anabolic hormone that promotes fuel storage. Its action is opposed by a number of hormones (anti insulin hormones), including (glucagon, epinephrine, cortisol, and growth hormone).
- The major function of glucagon is to respond rapidly to decreased blood glucose levels by promoting the synthesis and release of glucose into the circulation.
- **Anabolic and catabolic pathways are controlled at three important levels:**
  - **Allosteric** inhibitors and activators of rate-limiting enzymes.
  - **Feedback inhibition.**
  - **Feedback regulation** "Control of gene expression" by **insulin, glucagon** and **substrate**.

Phosphorylation by (**glucagon**) through (**Kinase**) and de



FATE OF GLUCOSE

Oxidation احرقه لو محتاج		***Storage*** أو أخزنه في التلاجات	***Conversion*** أو أحوله لحاجات
Major pathway	Minor pathway	As glycogen by glycogenesis in Liver and Muscles	e.g. - To lipid by lipogenesis or - To ptn
Glycolysis ↓ Pyruvate ↓ Acetyl Co-A ↓ Krebs cycle ↓ R. chain	- pentose phosphate pathway ***Or*** - Uronic acid pathway		

CHAPTER MAP

Glucose Metabolism		***Galactose Metabolism***	***Fructose Metabolism***
Feeding state واحنا واكلين هيكون في انسولين	**Fasting state** واحنا صايمين		
1- Glycolysis Glucose → pyruvate **2- Pyruvate → A. Co-A** **3- Krebs cycle** $NADH+H^+$ & $FADH_2$ **4- Respiratory chain** ATP **5- Minor pathways** PPP &UAP **6- Glycogenesis** **7- Lipogenesis** See lipid Metabolism	**1- Glycogenolysis** 2- **Gluco*neo*genesis**	**1- Conversion of Glucose to Galactose** **2- Conversion of Galactose to Glucose** **3- Lactose synthesis** ~~**4- Ds**~~	**1- Catabolism** **2- Conversion of Fructose to Glucose** ~~**3- Ds**~~

GLYCOLYSIS (EMBDEN MEYERHOF PATHWAY)

DEFINITION

Breakdown of glucose into **2** molecules of **pyruvate** **aerobically** (in the presence O_2)
or **2** molecules of **lactate** **an aerobically** (in the absence of O_2).

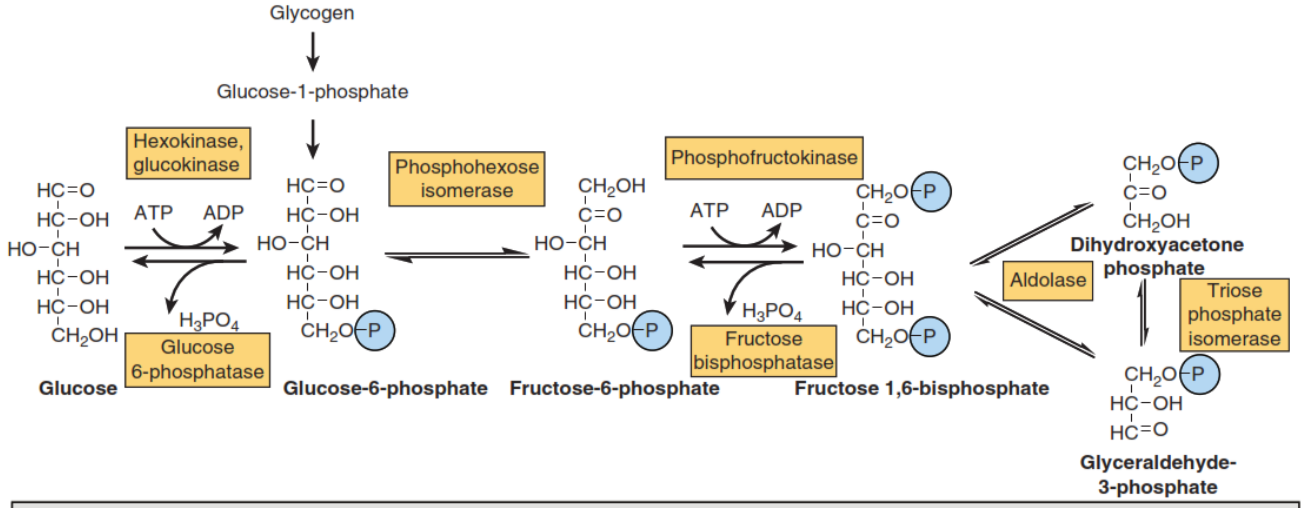
SITE

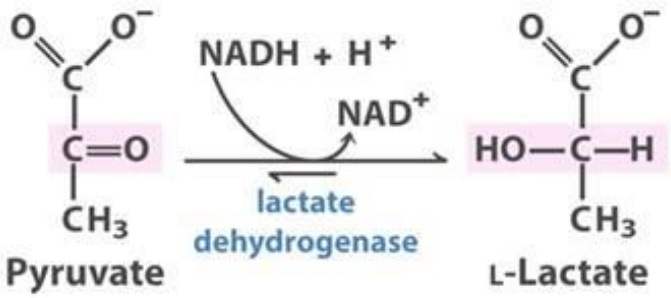
Cytosol of all tissue cells

STAGES OF GLYCOLYSIS

1. **Stage one (the energy requiring stage):**
   a) One molecule of glucose is converted into two molecules of glyceraldehyde-3- phosphates
   b) This step requires **2** molecules of ATP (energy loss)
2. **Stage two (the energy producing stage):**
   a) The **2** molecules of glyceraldehyde-3-phosphate are converted into **pyruvate** (aerobic glycolysis) or **lactate** (anaerobic glycolysis)

STEPS





BIOLOGICAL IMPORTANCE (FUNCTIONS) OF GLYCOLYSIS

1. **Energy (ATP) production of glycolysis:**

ATP production = ATP produced - ATP utilized.

	ATP produced	*ATP utilized*	*Net*
In absence of oxygen (anaerobic glycolysis)	**4 ATP by (Substrate level phosphorylation)** • **2ATP** from **1,3** BPG. • **2ATP** from phosphoenol pyruvate	**2 ATP** • From glucose to glucose-6-p. • From fructose-6 to fructose1,6 bis p.	**2 ATP**
In presence of oxygen (aerobic glycolysis)	**4 ATP by (Substrate level phosphorylation)** • **2ATP** from **1,3** BPG. • **2ATP** from Phosphoenol pyruvate **6 ATP or 4 ATP** (From oxidation of **2** $NADH+H^+$ in mitochondria). See later	**2ATP** • From glucose to glucose-6-p. • From fructose-6- p to fructose 1, 6 bisphosphates.	**6 Or 8 ATP**

2. **Oxygenation of tissues:**
Through formation **2, 3 bisphosphoglycerate**, this **decreases** the affinity of Hemoglobin to O^2.

3. **Provides important intermediates:**
a) Dihydroxyacetone phosphate: may give glycerol-3-phosphate, which is used for **synthesis of triacylglycerols and phospholipids** (lipogenesis).
b) 3-Phosphoglycerate: which may be used for **synthesis of** serine**.**
c) Pyruvate: which may be used in **synthesis of amino acid** alanine**.**

4. **Aerobic glycolysis provides the mitochondria with pyruvate,** which gives **acetyl CoA →** Krebs' cycle.

5. **very important in: (**because the glucose is the most dependent source of energy**)**
- **Tissues with no mitochondria:** mature RBCs, cornea and lens
- **Tissues with few mitochondria:** Testes, leucocytes, medulla of the kidney, retina, skin and gastrointestinal tract.
- **Tissues undergo frequent oxygen lack:** skeletal muscles especially during exercise

6. **Functions of glycolysis in RBC:**
1. Mature RBCs contain **no mitochondria thus:**
a) They depend only upon glycolysis for energy production (=2 ATP).
b) Lactate is always the end product.
2. Glucose uptake by RBCs is insulin **in**dependent.
3. **Reduction of met-hemoglobin: Met-hemoglobin** binds oxygen irreversibly. Glycolysis produces NADH+H, which used for reduction of met-hemoglobin in red cells, into hemoglobin. This reaction is catalyzed by "**cytochrome b_5-met-haemoglobin reductase**" system (cyt b5).

Met-HB —NADH+H→ HB

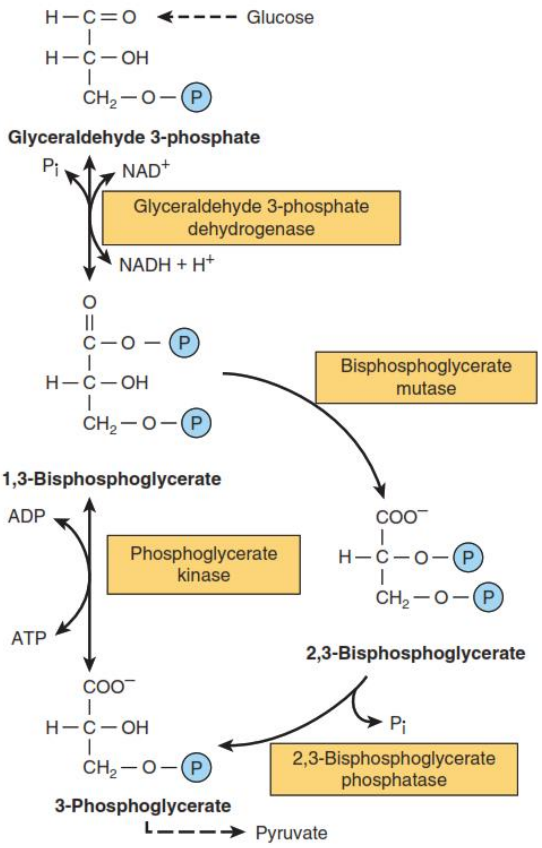
4. **2,3 Bisphosphoglycerate (2,3 BPG):**

a) The RBCs have the ability to form **2, 3** bisphosphoglycerate **(2, 3** BPG) through what is called: (**Rapoport-Luebering cycle**) or (**2, 3 b**isphosphoglycerate cycle).

2, 3 BPG ↓ affinity of hemoglobin to **O_2** → Good oxygenation of tissues.

b) **Mechanism:**

In the erythrocytes of many mammalian species the reaction



DIFFERENCES BETWEEN AEROBIC AND ANAEROBIC GLYCOLYSIS

	Aerobic	Anaerobic
End product	Pyruvate	Lactate
Energy	**6** or **8** ATP	**2** ATP
Regeneration of NAD	Through respiratory chain in mitochondria	Through lactate formation
Availability to TCA in mitochondria	Available and **2** pyruvate can oxidize to give **30** ATP	Not available as lactate is cytosolic substrate

IMPORTANCE OF LACTATE PRODUCTION IN ANAEROBIC GLYCOLYSIS:

- In absence of oxygen, $NADH+H^+$ is not oxidized by the respiratory chain, thus: **The conversion of pyruvate to lactate is the mechanism for regeneration of NAD.**

This helps continuity of glycolysis, as the generated NAD will be used once more for oxidation of another glucose molecule.

Regulation of glycolysis

The rate of glycolysis is regulated by controlling of the **three irreversible enzymes** (key enzymes). These enzymes catalyze what is called committed reactions of the pathway.

These enzymes are: **Glucokinase (Hexokinase), phosphofructokinase-1** and **pyruvate kinase.**

	Glucokinase	*Hexokinase*
Site	Liver only	All tissue cells
Affinity to glucose	Low affinity (high km) i.e. it acts only in the presence of high Glucose blood concentration.	High affinity (low km) i.e. it acts even in the presence of low blood Glucose concentration.
Substrate	Glucose only	Glucose, galactose and fructose
Effect of insulin	Induces synthesis of Glucokinase	No effect
Effect of glucose-6-phosphate	No effect	Allosterically inhibits Hexokinase
Function	Acts in liver after meals. It removes glucose coming in portal circulation, converting it into glucose-6-phosphate	It phosphorylates glucose inside the body cells. This makes glucose concentration more in blood than inside the cells This leads to continuous supply of glucose for the tissues even in the presence of low blood glucose

- **Hormonal regulation:**
  a) Insulin: **Stimulates** synthesis of all key enzymes of glycolysis. It is secreted after meal (in response to high blood glucose level).
  b) **Glucagon:** **Inhibits** the activity of all key enzymes of glycolysis. It is secreted in response to low blood glucose level.
- **Energy regulation:**
  a) High level of ATP inhibits PFK-1 and pyruvate kinase.
  b) High level of ADP and AMP stimulate PFK-1.

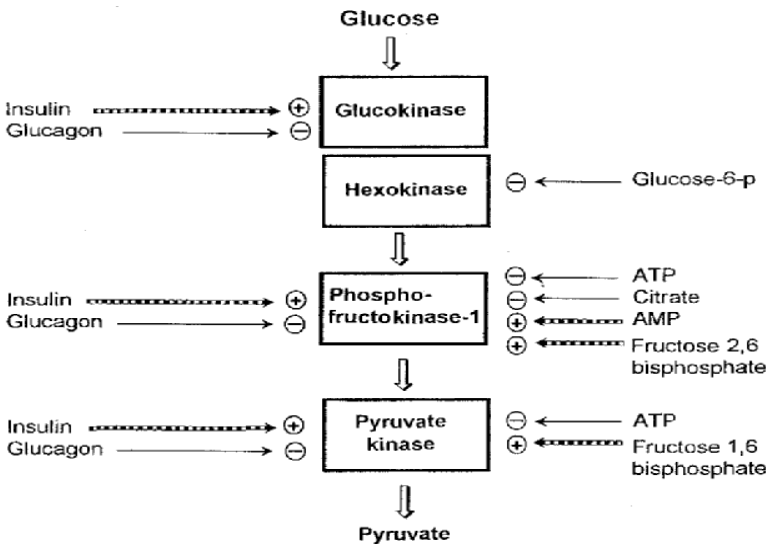
Substrate regulation:

a) Glucose-6-phosphate inhibits Hexokinase (and not Glucokinase).

b) Fructose 2, 6 bisphosphate stimulates PFK-1.

c) Citrate inhibits PFK-1.

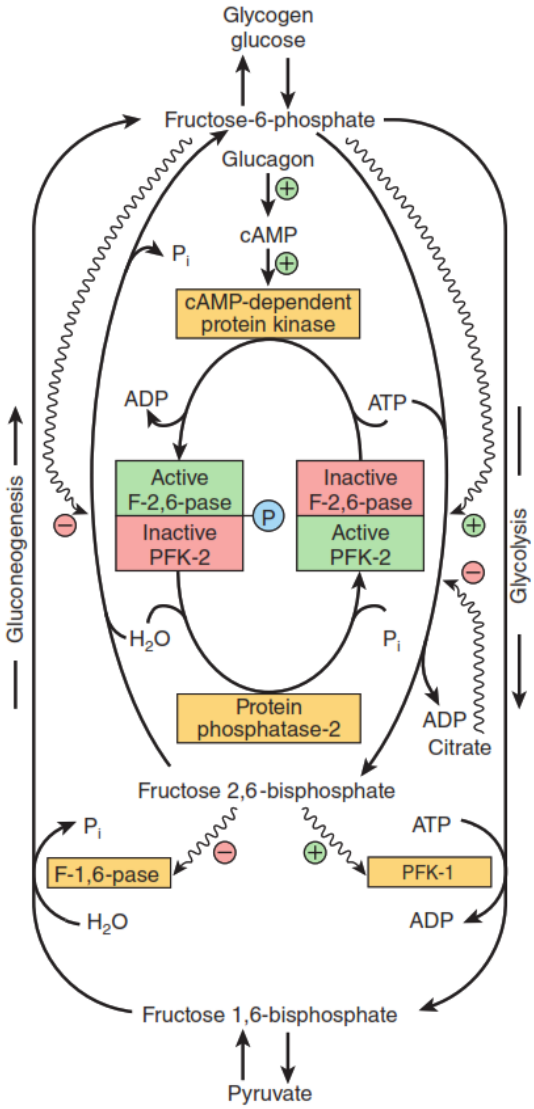
d)Fructose 1,6 bisphosphate stimulates pyruvate kinase.



- **Fructose 2, 6 bisphosphate:**

a) This substrate is produced from **fructose-6-phosphate** by reaction catalyzed by: phosphofructokinase-2 (PFK-2) enzyme.

b) Fructose 2, 6 bisphosphate stimulates glycolysis by allosteric stimulation of PFK-1. It also inhibits gluconeogenesis by inhibiting fructose 1, 6 bisphosphatase enzyme.



Clinical aspects of glycolysis:

There are many diseases associated with impaired glycolysis they include:

- **Pyruvate kinase (PK) deficiency:**

a) This leads to excessive **hemolysis** of RBCs → leading to hemolytic anemia.

b) Genetic deficiency of PK enzyme causes decrease the rate of glycolysis and decrease production of ATP.

c) ATP is required for Na-K ATPase, which is important for stability of RBCs.

- **Hexokinase deficiency:**

It leads to hemolytic anemia due to decrease ATP production.

The mechanism is similar to that of PK deficiency.

- **Lactic acidosis:**

Definition: It is the lowered blood pH and bicarbonate levels due to increased blood lactate above normal level.

Mechanism: This depletes bicarbonate → ↓pH of blood → Lactic acidosis may lead to coma.

Causes: **It** results from increased formation OR decreased utilization of lactate.

1) Increased formation of lactate: as in severe muscular exercises.
2) Decreased utilization of lactate in tissues: if occurs in cases of anoxia or lack of oxygen e.g. myocardial infarction, respiratory disorders and anemia.
3) Phenformin: is oral hypoglycemic drug causing excessive anaerobic oxidation of glucose and excess lactate production.

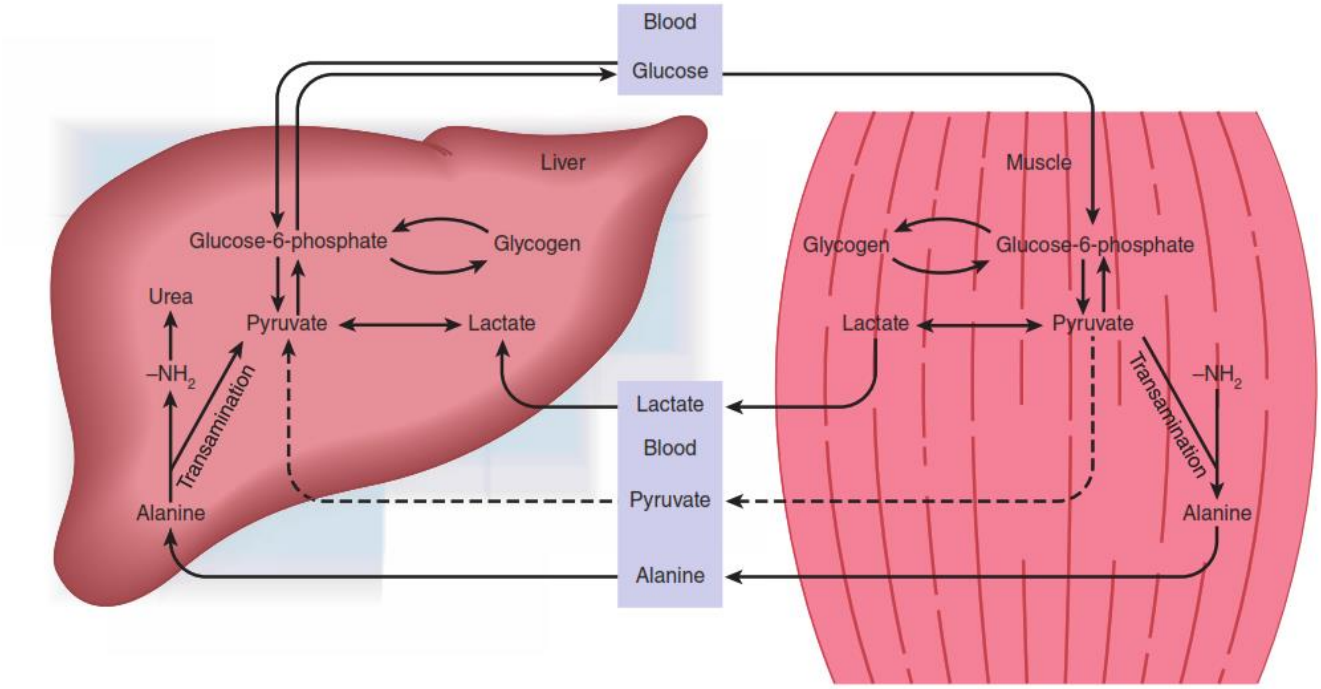
Lactate

a) Sources: From glycolysis especially in RBCs due to absence of mitochondria and Muscle during exercises due to oxygen lack

b) Fate:

1) Glucose formation: [**through lactic acid cycle (Cori cycle)**]:
   - Lactate formed in muscles and RBCs may diffuse to the blood then to the liver.
   - In the liver, lactate is converted to glucose by gluconeogenesis. Glucose may diffuse back to the blood, then to red cells or muscles to be used for production of energy.
2) Conversion into pyruvate: If oxygen gets available, lactate is converted into pyruvate, which proceeds into **Kreps cycle**
3) Lactate may be accumulated in muscles causing muscle fatigue.
4) Lactate is excreted in urine and sweat

Definition of Cori cycle: It is the conversion of glucose into lactate in **peripheral tissues**.
Followed by conversion of lactate into glucose in **liver**.



Lactate dehydrogenase

1. It is an enzyme which catalyzes the reaction: **Lactate ↔ Pyruvate**
2. This reaction helps the re-oxidation of NADH+H into NAD.
3. It has 5 isoenzymes: LD1, LD2, LD3, LD4 and LD5.
4. **Medical importance:**

Estimation of the activity of lactate dehydrogenase enzyme in plasma helps the diagnosis of heart and liver diseases:

a) LD1: Elevated in some heart diseases e.g. myocardial infarction.
b) LD5: Elevated in some liver diseases as acute viral hepatitis.

In vitro inhibition of glycolysis

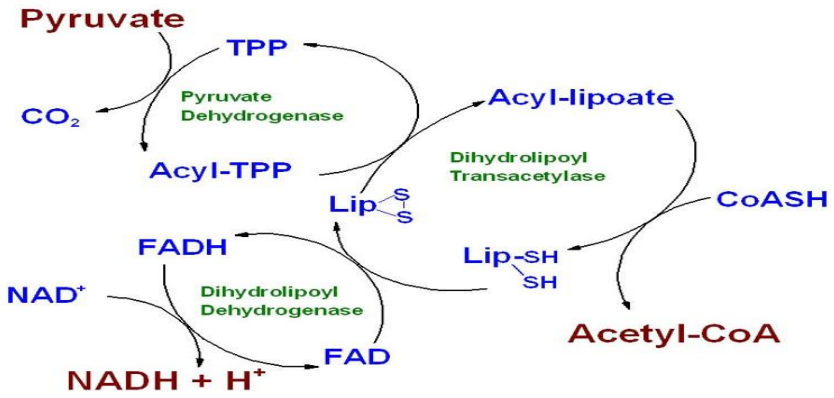
1- Arsenate: by competing with inorganic phosphate in the reaction:
glyceraidhyde-3 -p → 1,3 bisphosphoglycerate
2. Iodoacetate: by inhibiting glyceraldhyde-3-p dehydrogenase.
3. Fluoride: Inhibits enolase enzyme. Clinical laboratories use fluoride to inhibit glycolysis by adding it to the blood before measuring blood glucose.

MITOCHONDRIAL PATHWAY FOR GLUCOSE OXIDATION

- Complete oxidation of glucose occurs in both Cytosol (glycolysis) and mitochondria (Krebs' cycle).
- In the presence of O_2, pyruvate (the end product of glycolysis) passes by special pyruvate transporter into mitochondrion which proceeds as follows:
  Oxidative decarboxylation of pyruvate to Acetyl-COA.
  Acetyl CoA is then oxidized completely to CO_2, H_2O through Krebs' cycle

OXIDATIVE DECARBOXYLATION OF PYRUVATE TO ACETYL COENZYME A (= ACETYL COA)

- **Enzyme:** Pyruvate dehydrogenase (PDH) complex:
  - **a) Structure:** contains 3 subunits, which catalyzes the reaction in 4 steps. These subunits are: pyruvate decarboxylase, dihydrolipoyl transacetylase and dihydrolipoyl dehydrogenase.
  - **b) Coenzymes:** needs 5 coenzymes (all are vitamin B complex derivatives):
    1) Vitamin B1 = Thiamin pyrophosphate = TPP.
    2) Lipoic acid
    3) Coenzyme A = CoASH.
    4) Flavin adenine dinucleotide = FAD.
    5) Nicotinamide adenine dinucleotide = NAD+.
  - **c) Location:** PDH is located within the mitochondrial matrix.
- **Reactions:**



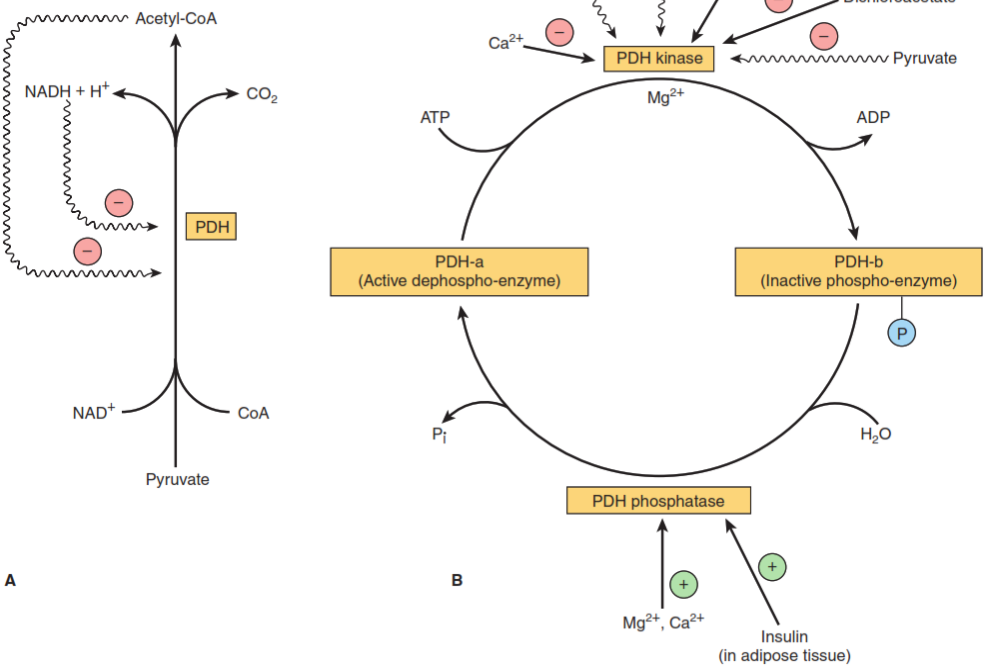
- **Energy production:** → **NADH+H** (through respiratory chain) →**3ATP**
- **Regulation of oxidative decarboxylation (PDH):**

a) PDH exists in two forms: Phosphorylated (inactive) and dephosphorylated (activated).
- PDH kinase enzyme converts active into inactive PDH enzyme.

In vitro inhibition of PDH:

a) Arsenic.

b) Thiamin (B1) deficiency



MCQ

1. **The product of glycolysis in erythrocytes is:**
   a- NADPH b- Lactate c- Pyruvate d- Carbon dioxide
2. **Glucokinase is more active after a meal, because:**
   a- It is an inducible enzyme. b- It has more affinity to glucose than hexokinase
   c- It is present in all tissues d- Can act on all monosaccharides
3. **An example of substrate level phosphorylation is:**
   a- Isocitrate Dehydrogenase b- Enolase
   c- Pyruvate kinase d- Glyceraldehyde-3-phosphate dehydrogenase
4. **Which enzyme catalysis an irreversible reaction?**
   a- Transketolase b- Phospho fructokinase
   c- Aldolase d- Glyceraldehyde-3-phosphate dehydrogenase
5. **Which enzyme in glycolytic pathway is inhibited by fluoride ions?**
   a- Hexokinase b- phosphofructokinase c- Aldolase d- Enolase
6. **During anaerobic glycolysis NAD+ is regenerated from NADH by:**
   a- Glyceraldehyde-3-phosphate dehydrogenase b- Oxygen
   c- Glutamate dehydrogenase d- Lactate dehydrogenase
7. **All the enzymes listed below are regulatory enzymes, EXCEPT:**
   a- Glycogen phosphorylase b- Glucose-6-phosphate dehydrogenase
   c- Pyruvate kinase d- Lactate dehydrogenase
8. **ATP is generated in all the following reactions EXCEPT:**
   a- Glyceraldehyde-3-phosphate dehydrogenase b- I ,3-bisphosphoglycerate kinase
   c- Pyruvate kinase d- Hexokinase
9. **The key enzyme of glycolysis is:**
   a- Glucose-6-phosphatase b- Glyceraldehyde-3-phosphate dehydrogenase
   c- Phosphohexose isomerase d- Phosphofructokinase
10. **Catalytic activity of phosphofructokinase is increased by:**
    a- AMP c- ATP b- Fructose-I ,6-bisphosphate d- Fructose-I -phosphate
11. **Complete Oxidation of one molecule of glucose yields how many ATPs?**
    a- 12 b- 24 c. 38 d. 129
12. **All the following coenzymes are involved in the pyruvate dehydrogenase reaction EXCEPT:**
    a. Thiamine pyrophosphate (TPP) b- Biotin c- NAD^+ d- FAD
13. **There is no net synthesis of glucose from fatty acids, because of the irreversible nature of the reaction:**
    a- Pyruvate to oxaloacetate b- Pyruvate to acetyl COA
    c- Phosphoenol pyruvate to pyruvate d- Oxaloacetate to Phosphoenol pyruvate
14. **Pyruvate is converted to acetyl COA by:**
    a- Pyruvate dehydrogenase b- Pyruvate carboxylase
    c- Pyruvate kinase d- Lactate dehydrogenase
15. **In glycolysis, the following reactions are irreversible, EXCEPT that catalyzed by:**
    a- Glucokinase. b- Phosphoglycerate kinase. c- PFK-1 d- Pyruvate kinase.
16. **Phosphoglycerate kinase catalyzes conversion of BPG into:**
    a-2,3 BPG. b- 2-phosphoglycerate. c- 3-phosphoglycerate. d- Non of the above.

KREBS' CYCLE

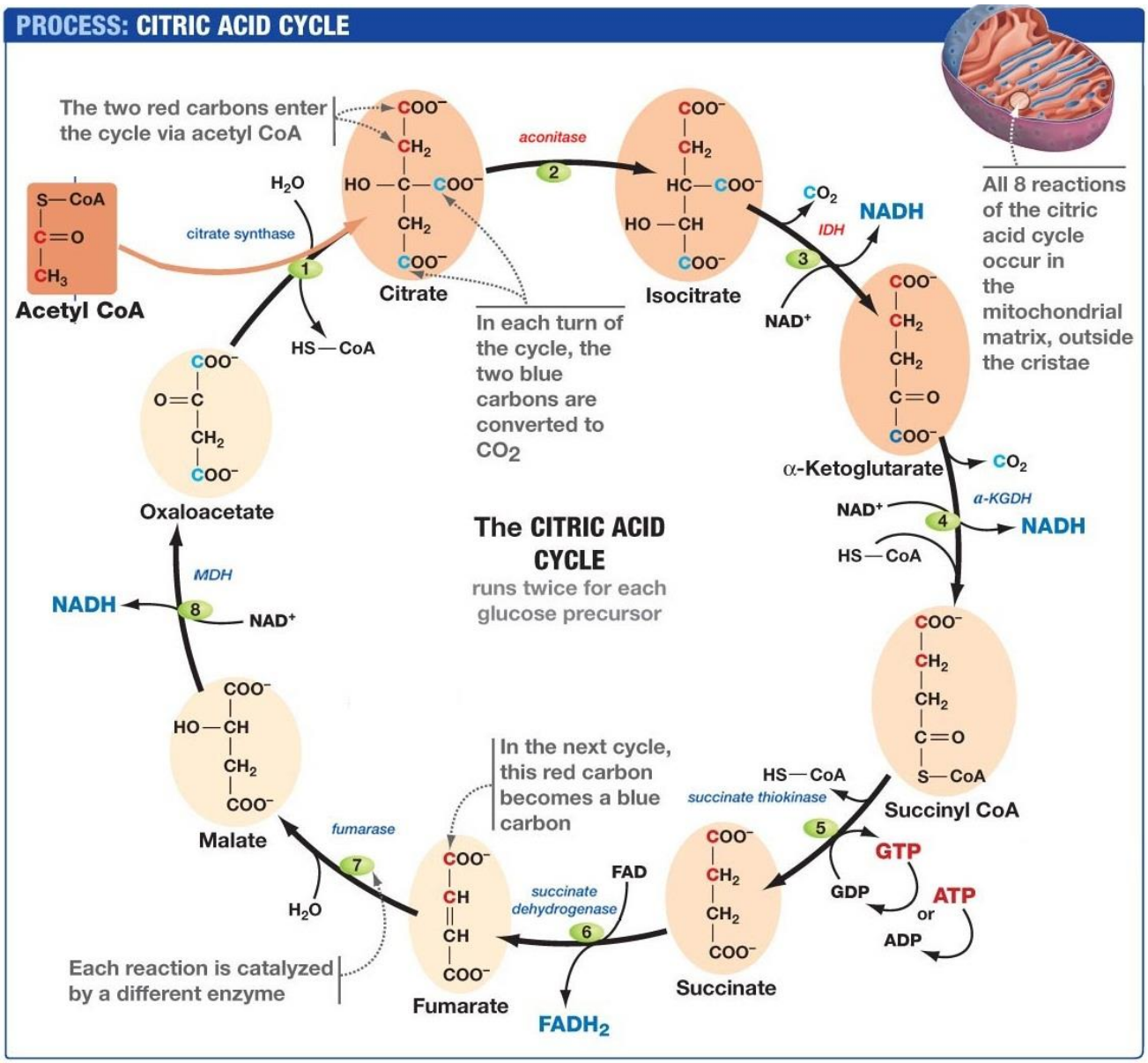
Citric acid cycle (CAC), tricarboxylic acid cycle (TCA) or Catabolism of acetyl CoA

DEFINITION series of reactions in which acetyl CoA is oxidized into CO2, H2O and energy.

LOCATION Mitochondria

STEPS

Citrate Is Krebs' Starting Substrate For Making Oxaloacetate.



ENERGY PRODUCTION OF TCA:

Enzyme	*Method of ATP production*	*No. of ATP*
Isocitrate dehydrogenase	Oxidation of $NADH+H^+$ by respiratory chain	**3 ATP**
α-Ketoglutarate DH	Oxidation of $NADH+ H^+$ by respiratory chain	**3 ATP**
Succinyl CoA thiokinase	Substrate level phosphorylation	**1 ATP**
Succinate dehydrogenase	Oxidation of $FADH_2$ by respiratory chain	**2 ATP**
Malate dehydrogenase	Oxidation of $NADH+H^+$ by respiratory chain	**3 ATP**
Total =		**12 ATP**

FUNCTIONS (SIGNIFICANCE) OF TCA: TCA CYCLE IS AMPHIBOLIC

I.e. it has catabolic (breakdown) and anabolic (formation) functions.

- **Energy:** 12 ATP
- **Catabolic functions:** Oxidation of carbohydrate, lipids and proteins.
- **Anabolic functions:** Formation of:
  - ✓ **Amino acids:** α-Ketoglutarate —Transamination→ Glutamate.
  - ✓ **Glucose:** α-Ketoglutarate —Gluconeogenesis→ Glucose.
  - ✓ **Heme synthesis:** Succinyl CoA → Heme.
  - ✓ **Fatty acid and cholesterol.**
  - ✓ **CO_2:** is used in the (CO_2 fixation reactions) (carboxylation reactions) :
- **Requirements:** 1- Enzyme: carboxylase. 2- Co-enzyme: Biotine
  3- CO_2 4- ATP
- **Important Reactions:**

- **CHO:** Pyruvate + CO_2 → Oxaloacetate —Gluconeogenesis→ Glucose
- **Lipid:** Acetyl COA + CO_2 → Malonyl CoA → Fatty acids.
- **Ptn:** Ammonia + ATP + CO_2 → Carbamoyl phosphate → Urea and pyrimidines.
- Propionyl CoA + CO_2 → Methyl malonyl CoA → Succinyl CoA → Intermediate of citric acid cycle.
- Formation of C6 of purines.

IN VITRO INHIBITION OF TCA CYCLE:

a) Fluoroacetate (F_1- CH_2-COSCoA): inhibits **aconitase** enzyme.
b) Arsenate: inhibits α-Ketoglutarate dehydrogenase enzyme.
c) Malonic acid: inhibits Succinate dehydrogenase enzyme (competitive inhibition.

REGULATION OF CITRIC ACID CYCLE

TCA is regulated through the key enzymes (citrate synthase, Isocitrate DH and α-Ketoglutarate DH) and the availability of **CO_2**

a) Citrate synthase

1) Stimulated by: acetyl CoA, oxaloacetate, ADP and NAD.
2) Inhibited by: long chain acyl CoA, citrate, Succinyl CoA, ATP and $NADH+H^+$

b) Isocitrate dehydrogenase and α-Ketoglutarate dehydrogenase:

1) Stimulated by: NAD, ADP.
2) Inhibited by: $NADH+H^+$ and ATP.

c) Availability of Oxygen: Citric acid cycle needs oxygen to proceed. This is because in absence of oxygen, respiratory chain is inhibited leading to increase **$NADH+H^+$** → inhibition of TCA cycle.

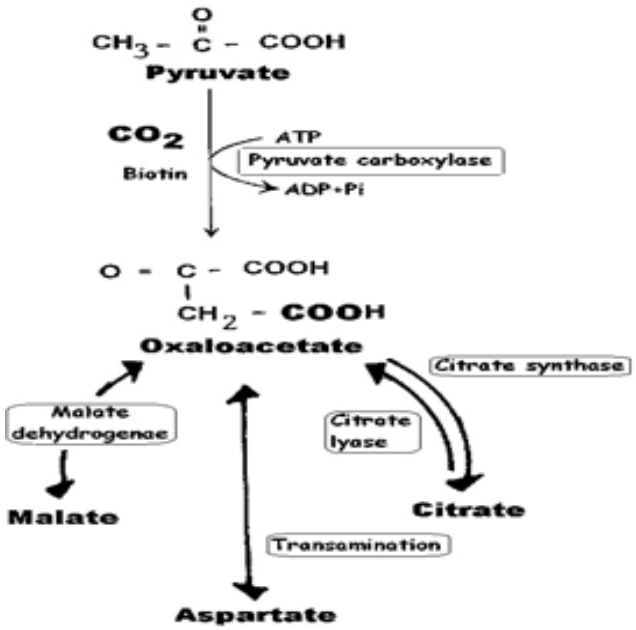
SOURCES AND FATE OF OXALOACETATE

a) Sources of oxaloacetate:

1) **Oxidation of Malate.**
2) **Transamination of Aspartate:**
3) **Carboxylation of pyruvate**
4) **Cleavage of citrate**

b) Fate of oxaloacetate:

1) **Formation of citrate:**
2) **Reduction to Malate.**
3) **Transamination into aspartate**



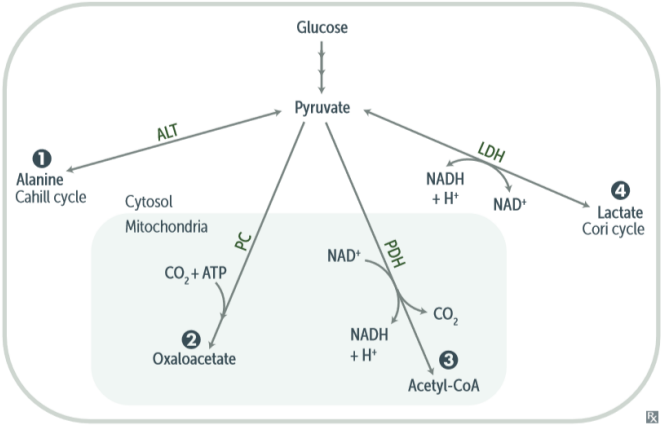
SOURCES AND FATE OF PYRUVATE

Sources

1. **Glucose:** glycolysis.
2. **Lactate:** by lactate DH
3. **Malate:** by malic enzyme.
4. **Alanine:** by transamination.
5. **Serine:** by non-oxidative deamination.
6. **Other amino acids:** methionine

Fate

1. **Glucose formation:** gluconeogenesis.
2. **Lactate formation:** by lactate DH.
3. **Malate formation:** by malic enzyme.
4. **Alanine formation:** by transamination.
5. **Oxaloacetate formation:** by pyruvate carboxylase.



MCQ

17. How many ATPs are generated per one rotation of the citric acid cycle?
a- 2 b- 8 c- 12 d- 15

18. The following reaction produces ATP at the substrate level:
a- PFK-1 b. Aldolase. c. Phosphoglycerate kinase. d- Glycaaldehyde-3P dehydrogenase.

19. Oxidation of glucose in RBCs gives:
a- 2ATP. b- 3 ATP. c- 8 ATP. d. None of the

20. PFK-1 is inhibited by all. EXCEPT:
a- ATP b- Citrate. c. Glucagon. d- AMP

21. Conversion of glucose phosphate to fructose-1,6 bisphosphate requires:
a- Phosphoglucomutases and phosphorylase. b-Phosphoglucomutases and aldolase.
c. Phosphohexose and phosphofructokinase
d. Phosphoglucomutases and phosphofructokinase- 1

22. Pyruvate can be converted to :
a- Lactate b- Nanine c- Oxaloacetate. d. All of the above.

23. Pyruvate dehydrogenase complex, requires all,
a- NAD. b- COA. C- ATP d- Pyruvate.

24. All the following correctly pairs coenzyme with its enzyme, EXCEPT:
a- Succinate dehydrogenase, FAD. b- Malate dehydrogenase NAD.
c- Acetyl COA carboxylase, biotin. d- Pyruvate dehydrogenase PLP.

25. Oxidative decarboxylation of a-ketoglutarate requires an, EXCEPT:
a- FAD b- COASH. c. PLP. d- Lipoate

26. In TCA cycle the only enzyme which requires FAD is:
a- Iso-citrate dehydrogenase. b- a-ketoglutarate dehydrogenase.
c- Succinate dehydrogenase. d- Malate dehydrogenase.

27. All of the following are Krebs' cycle intermediates, EXCEPT:
a- Acetoacetate. b- Cis aconitate. c. Succinate d- Fumarate.

28. The release or carbon dioxide results from the following reaction of the citric acid cycle:
a- Citrate to isocitrate. b-Fumarate to malate.
c- Malate to oxaloacetate. d- Isocitrate to a-ketoglutarate.

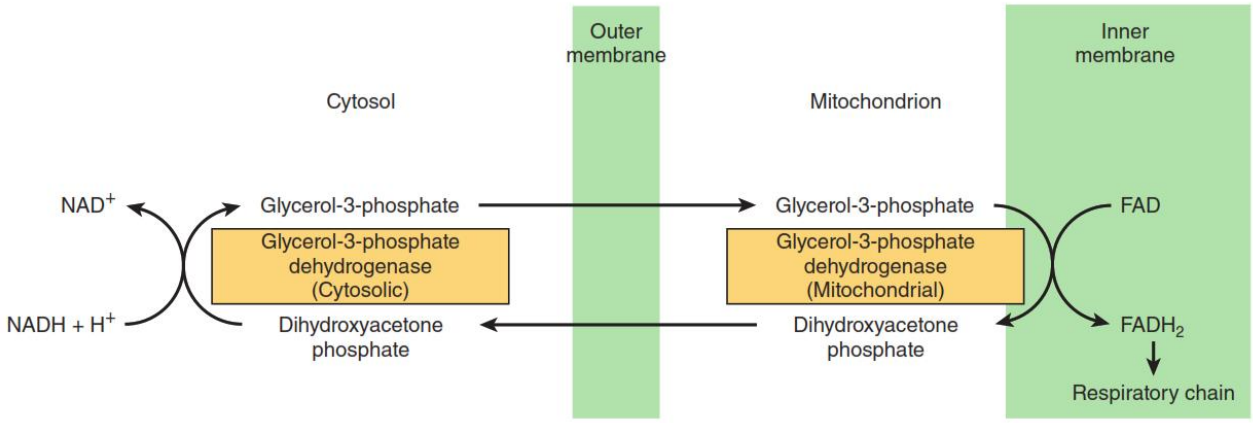
29. In pyruvate kinase (PK) deficiency, hemolysis of red cells occurs primarily because of increased intracellular levels of:
a- Lactate. b- Pyruvate.
c- ADP to ATP ratio. d- 2,3-diphosphoglycerate.

OXIDATION OF EXTRA MITOCHONDRIAL NADH+H$^+$

1. The molecules of cytosolic NADH+H$^+$ cannot penetrate mitochondrial membrane; however, they can be used to produce energy by respiratory chain phosphorylation in the mitochondria.
2. This can be done by using special carriers for hydrogen of NADH+H$^+$ these carriers are either (Glycerophosphate shuttle) or (Aspartate - Malate shuttle).

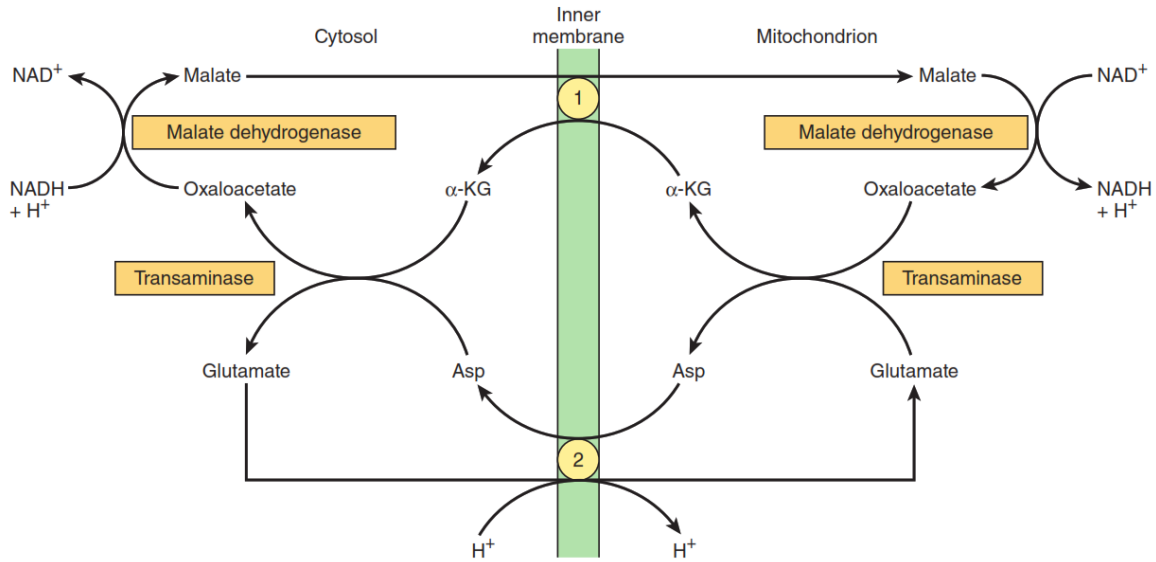
GLYCEROPHOSPHATE SHUTTLE

- It is important in certain muscles and nerve cells.
- The final energy produced is **2** x **2** ATP → **4** ATP.
- **Mechanism:**
  - The coenzyme of cytosolic (glycerol -3- phosphate DH) is NAD$^+$.
  - The coenzyme of mitochondrial (glycerol -3- phosphate DH) is FAD.



MALATE - ASPARTATE SHUTTLE

- It is important in tissues particularly liver and heart.
- The final energy produced is **2 x 3** ATP → **6** ATP
- Mechanism:
  - The coenzyme of cytosolic and mitochondrial (Malate dehydrogenase) is NAD$^+$



RESPIRATORY CHAIN (ELECTRON TRANSPORT CHAIN)

DEFINITION

It is the final common pathway in aerobic cells by which electrons derived from various substances are transferred to oxygen to form water.

SITE

Mitochondria in all over body cells except: (RBC, cornea).

ORGANIZATION OF THE RESPIRATORY CHAIN

- The inner mitochondrial membrane contains 5 **fixed enzyme complexes**, called complex I, II, Ill, IV and V. **Complex V catalyses ATP synthesis**.

a) Each complex accepts or donates electrons to relatively 2 **mobile electron carriers** such as **coenzyme Q** and **cytochrome C**.

b) Each carrier of electron transport chain can receive electrons from the more electronegative donor to the next more electropositive carrier in the chain.

- Finally electrons combine with **oxygen** and protons to form water.

COMPONENT

a) Complex I: Contains an enzyme called (NADH dehydrogenase)
   (i) Its coenzyme is FMN.
   (ii) It contains several iron and sulfur atoms.
   (iii) It oxidizes NADH+H into NAD. And converts its coenzyme FMN into $FMNH^2$.

b) Complex II: Contains an enzyme called: (flavoprotein dehydrogenase) e.g. Succinate dehydrogenase of TCA **and** acyl COA dehydrogenase of fatty acid oxidation.
   (i) Its coenzyme is FAD.
   (ii) It contains iron and sulfur atoms.

c) Complex Ill: contains an enzyme cytochrome b.

d) Complex IV: contains cytochromes a + a3

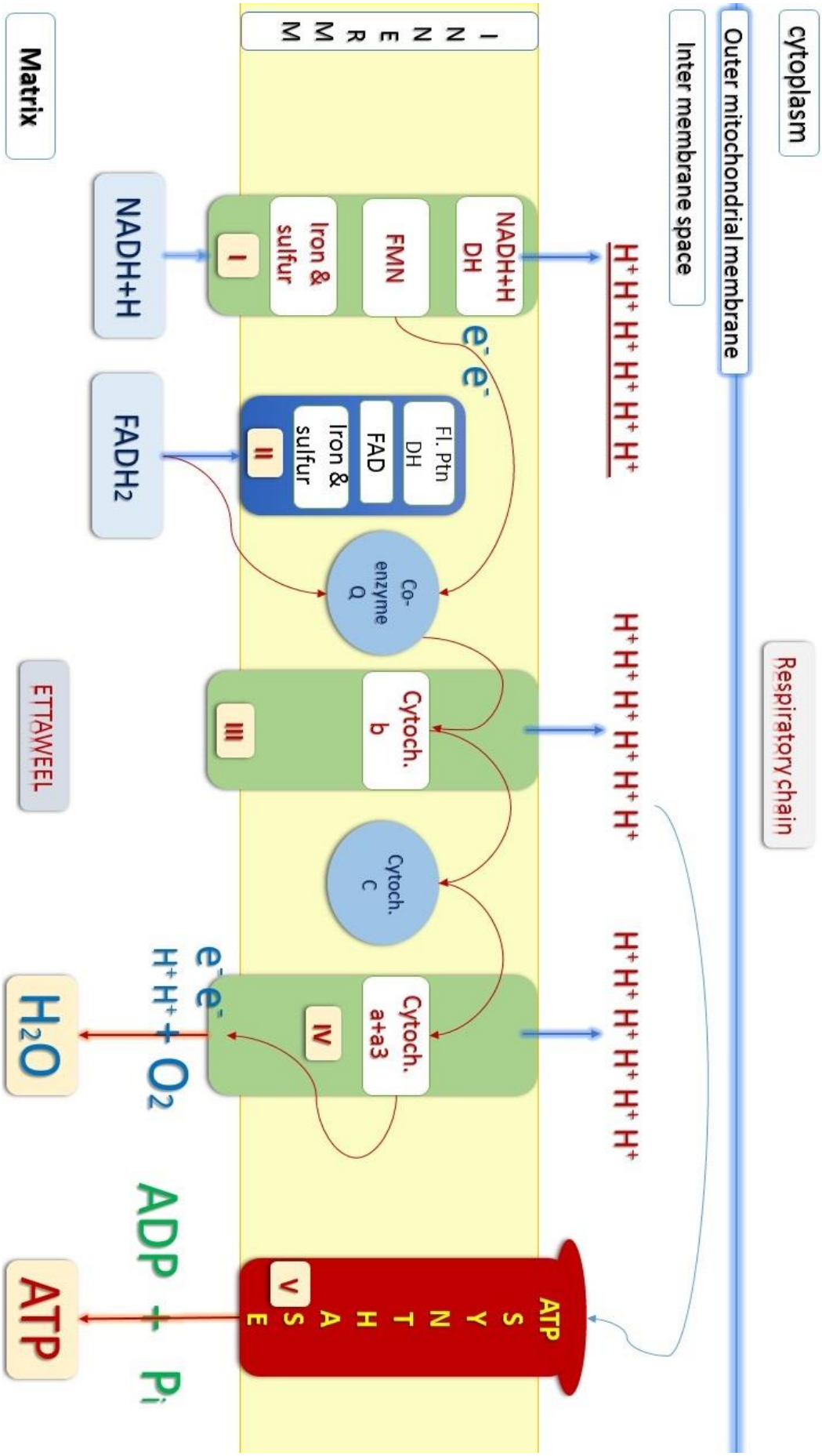
e) Complex V: catalysis ATP synthesis

REACTIONS OF RESPIRATORY CHAIN

1. Entry via NADH + H^+: NADH + H^+ obtained from reactions catalyzed by dehydrogenase enzymes e.g. dehydrogenase of TCA can join the chain giving electrons to FMN of complex I to coenzyme Q, to cytochrome b, cytochrome c to cytochrome a + a3 to the final acceptor O_2.

2. Entry via $FADH_2$: $FADH_2$ obtained from reactions catalyzed by flavoprotein dehydrogenase e.g. Succinate dehydrogenase can join the chain directly giving electrons to coenzyme Q, then to cytochrome b, c, a + a3 to the final acceptor O_2.

STEPS



OXIDATIVE PHOSPHORYLATION

A. Introduction:

1. Electrons are transferred down the respiratory chain from NADH to oxygen. This is because **NADH** is a strong electron donor, while **oxygen** is a strong electron acceptor.
2. The flow of electrons from NADH to oxygen (oxidation) results in ATP synthesis by phosphorylation of ADP by inorganic phosphate "Pi" (phosphorylation). Therefore, there is a coupling between oxidation and phosphorylation.

Two theories explain the ATP synthesis, (chemiosmotic hypothesis) and (membrane transport system).

B. Chemiosmotic hypothesis: (Mitchell hypothesis).

- This hypothesis is one form of oxidative phosphorylation. It can be summarized as follows:

1. Proton pump:

a. The transport of electrons down the respiratory chain → Gives energy.
b. This energy is used to transport H+ from the mitochondrial matrix → across inner mitochondrial membrane → inter membrane space.
c. This is done by complexes I, lll and IV.
d. This process creates across the inner mitochondrial membrane:
   - **i. An electrical gradient:** (with more positive charges on the outside of the Membrane than on the inside)
   - **ii. A pH gradient:** (the outside of the membrane is at lower pH than the inside).
e. The energy generated by Hits proton gradient is sufficient for ATP synthesis.

2. ATP synthase (complex V):

In the inner mitochondrial membrane, there is a phosphorylating enzyme complex: **ATP synthase (or complex V).**

a) It is formed of 2 subunits:
   (I) F_1 subunit which protrude into matrix.
   (ii) F_o subunit which present in the membrane.
b) The protons outside the inner mitochondrial membrane can re-enter the mitochondrial matrix by passing through channel (F_o - F1 complex) to pass by ATP synthase enzyme which is present in F_1 subunit. This results in the synthesis of ATP from ADP + Pi. At the same time decrease the pH and electrical gradients.

❖ **Evidences support chemiosmotic theory:**

a) Addition of protons (acid) to the external medium of intact mitochondria leads to the generation of ATP.
b) ATP synthesis does not occur in soluble Cytosol system where there is no ATP synthase. A closed membrane as mitochondria must be present in order to obtain oxidative phosphorylation.
C) The component of respiratory chain is organized in a sided manner as required by chemiosmotic theory.

❖ **P/O ratio:** It is the ratio **between** numbers of ADP mole changed into ATP **to** the number of oxygen atom (1/2 O_2) utilized by respiratory chain.

- It is **3:1** if electrons enter through **NAD-coenzyme Q** .
- And it is **2:1** if electrons join the chain **directly** at the level of coenzyme Q.

INHIBITORS OF RESPIRATORY CHAIN

- **Definition:** Are compounds preventing the passage of electrons by binding to a component of the chain, blocking the oxidation, reduction reaction.

Complexes	*Inhibited by*
Complex I (site 1)	Barbiturates, "piericidin A" antibiotic and by the insecticide and fish poison "rotenone"
Complex II	Carboxin
Complex III (site 2)	Antimycin A and dimercaprol.
Complex IV (site 3)	H2S, cyanide (CN-), carbon monoxide and sodium azide.
Complex V	Oligomycin

UNCOUPLERS OF RESPIRATORY CHAIN

- **Definition:** These are substances that **allow** oxidation to proceed but **prevent** phosphorylation. So energy released by electron transport will be lost in the form of **heat**. This explains the cause of hotness after intake of these substances.

Uncoupler	*Mechanism*
Thermogenin Thyroxin	In brown adipose tissues
Oligomycin	Binds to the stalk of the ATP synthase. Closes the H+ channel, and prevent re-entry of protons to the mitochondrial matrix.
2,4 dinitrophenol	It increases the permeability of the inner mitochondrial membrane to proton causing decrease proton gradient.
Calcium and high doses of aspirin:	This explains the fever that accompanies toxic overdoses of these drugs.
Ionophores : e.g. antibiotic "valinomycin"	They have the ability to make a complex with cations as "K+" and facilitate their transport into mitochondria and other biological membranes. They inhibit phosphorylation because they decrease both electrical and pH gradient.

PENTOSE PHOSPHATE PATHWAY

DEFINITION

It is an alternative pathway for glucose oxidation **where:**

1. ATP (energy) is **neither** produced **nor** utilized.
2. Its main function is to produce **NADPH+H$^+$** and **pentoses**.

LOCATION

1. **Intracellular location:** Cytosol.
2. **Organ location:**
   a) **It is active in tissues where NADPH+H$^+$ is needed for fatty acids synthesis.**
      1- **Adipose tissue and liver.** 2- **Adrenal cortex and gonads.**
      3- **Red cells** 4- **Retina**
   b) **In many tissues:** It supplies **pentoses** for synthesis of nucleotides.

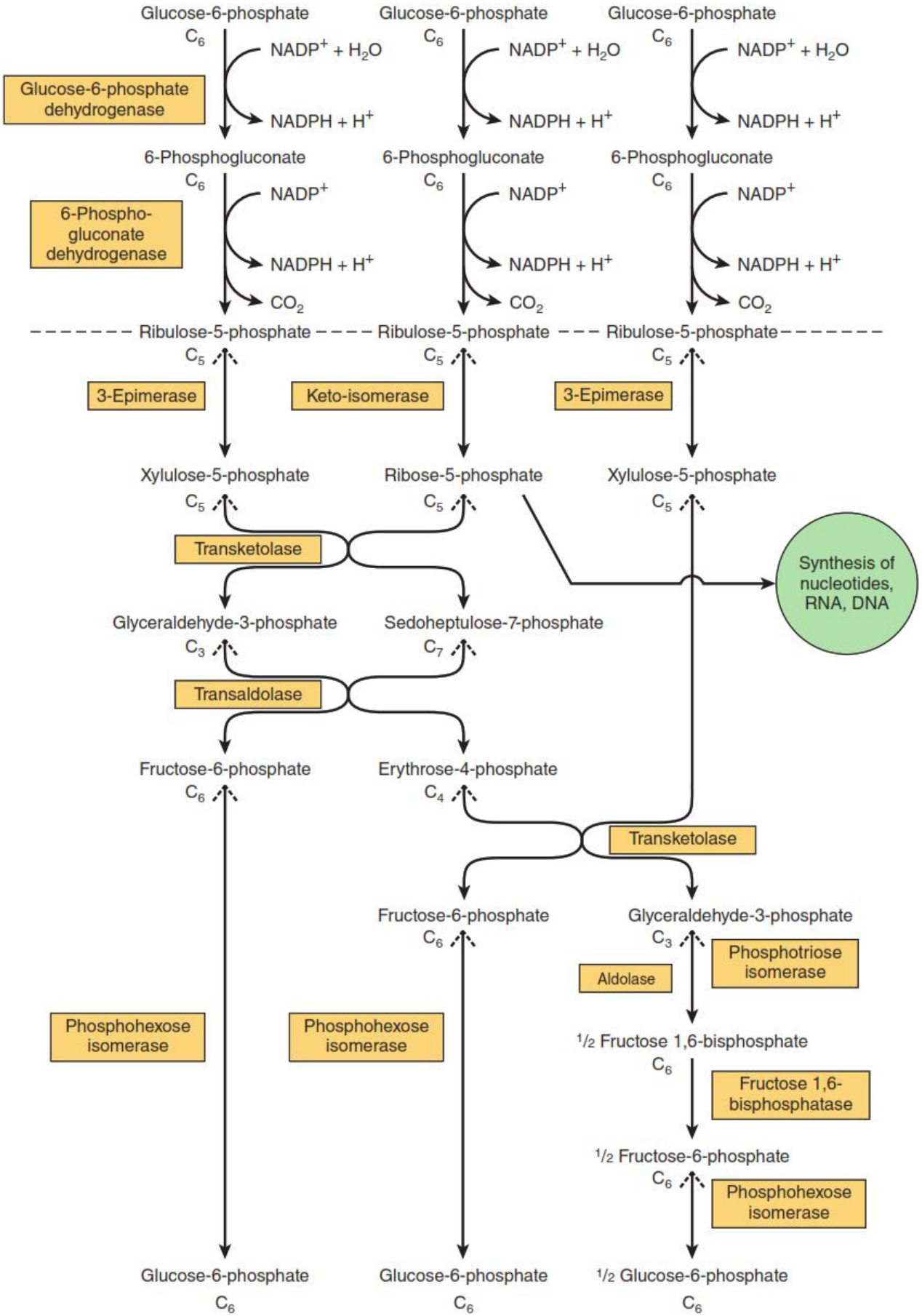
FUNCTIONS OF HMP PATHWAY

1. **Production of pentoses:**
   Which are essential for synthesis of nucleic acids (RNA and DNA), nucleotides as (ATP, GTP) and coenzymes as (NAD, NADP, FAD).
2. **Production of NADPH+H+:**
   A. **Sources :**
      1. **Pentose phosphate pathway.**
      2. **Malic enzyme** (Malate ⟶ pyruvate).
      3. **Isocitrate dehydrogenase** (cytoplasmic).
   B. **Fate:**
      1- Reductive biosynthesis.
         a) CHO: uronic acid
         b) Lipids: (Fatty acids, cholesterol, steroids, Bile salts).
         c) Proteins: non-essential amino acids.
      2- Reduction of Glutathione.
      3- Reduction of retinal. 4- Reduction of Cyt P450
      5- N.O synthesis 6- sphingosine & galactolipids.
      7- Non-essential amino acid 8- Phagocytosis
      - **Phagocytosis by white blood cells (respiratory burst):**

      Def: It is the rapid consumption of molecular oxygen that accompanies the formation of superoxide by **NADPH oxidase**.
      - Superoxide is then converted into H_2O_2 by **superoxide dismutase** enzyme.
      - **H_2O_2** by **myeloperoxidase** enzyme in the presence of **HCL** is converted into hypochlorite ($HOCL^-$), which kills bacteria.

REACTIONS (STEPS)

- two phases: **oxidative** and **non-oxidative**:
  1. **Oxidative (irreversible) phase:**
     Where **3** molecules of "**glucose-6-phosphate**" are converted into **3** molecules of "**Ribulsose-5-phosphate**" with production of **NADPH+H$^+$** and **CO2**.
  2. **Non-oxidative (reversible) phase:**
     Where the **3** molecules of "**ribulose-5-phosphate**" are interacted and converted into **2** molecules of "**glucose-6-phosphate**" and one molecule of "**glyc-3-phosphate**".



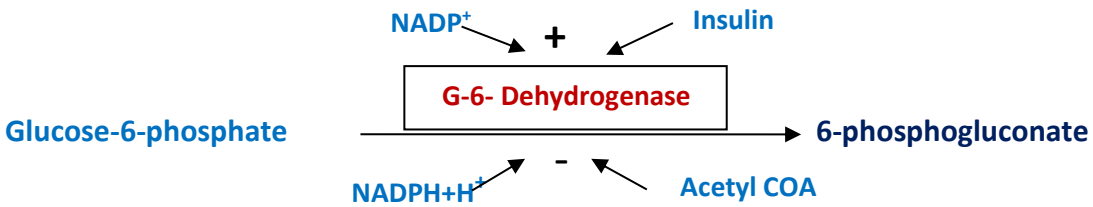
PENTOSE PHOSPHATE PATHWAY IN SKELETAL MUSCLES

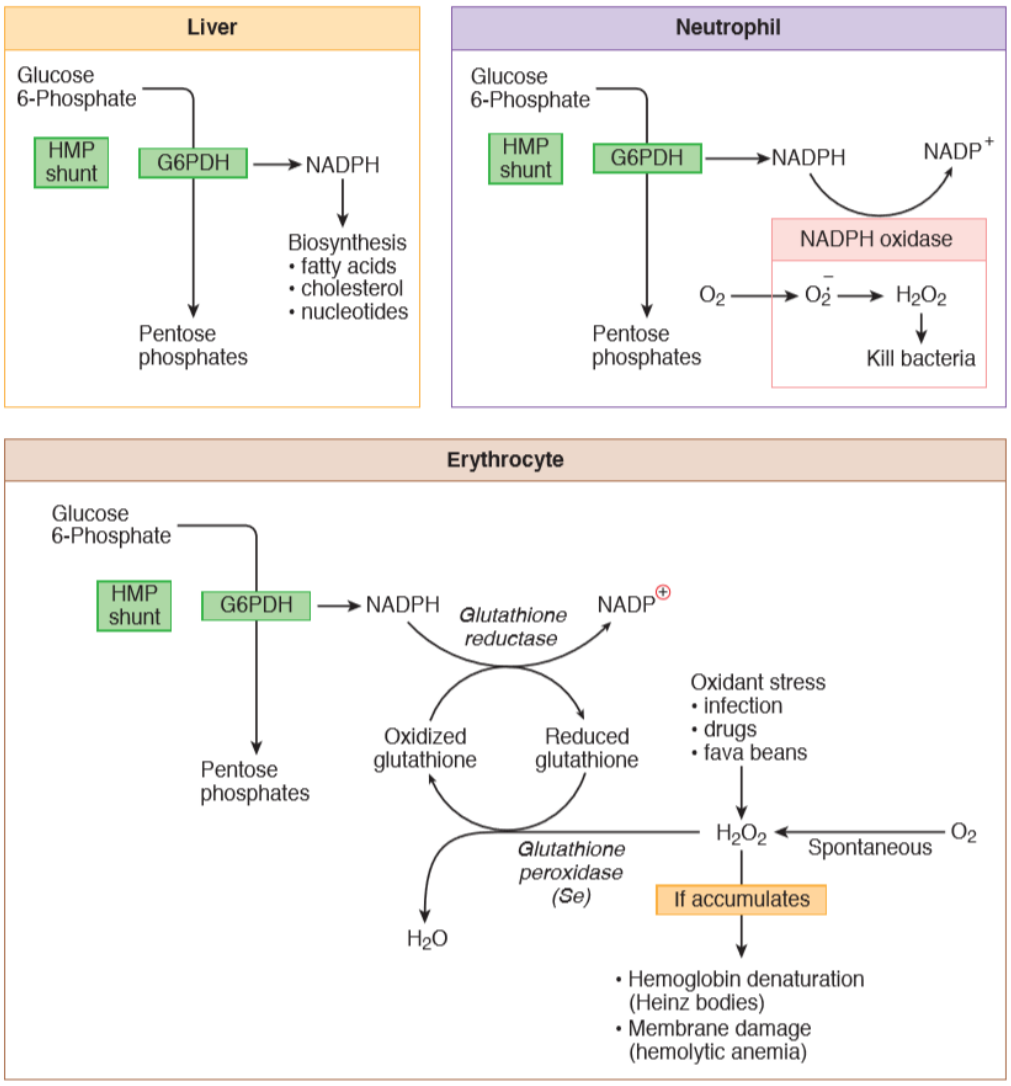
- Skeletal muscles obtain their pentose requirement by reversible reactions of pentose phosphate pathway, using **fructose-6-phosphate** and **glyceraldehyde-3-p** and the enzymes transketolase and transaldolase. As they are poor in **G-6-PDH.**

DIFFERENCES BETWEEN HMP SHUNT AND GLYCOLYSIS

	HMP pathway	Glycolysis
Location	In certain cells	In all cells
Oxidation of glucose	Oxidation occurs in the first reaction.	Phosphorylation occurs first then oxidation.
Coenzyme	NADP	NAD^+
Energy	No energy production	2 or 8 ATP
CO2	Produced	Not produced
Pentoses	Produced	Not produced

REGULATION



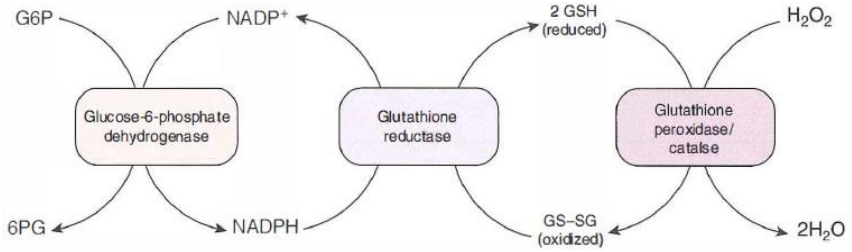


DEFECT OF PENTOSE PHOSPHATE PATHWAY: "FAVISM"

- **Definition:**
  It is type of a **hemolytic anemia** (excessive destruction of RBCs) results after ingestion of **fava beans** and some other compounds (sulfonamide, primaquine, anti-tuberculosis).
- **Cause:** Deficiency of glncose-6-phosphate dehydrogenase enzyme.
- **CCC:** "Heinz bodies"- oxidized Hemoglobin precipitated within RBCs.
- **Mechanism:**
  a) Deficiency of glucose-6-P dehydrogenase 4 Decreased NADPH+H+ production (which is essential to reduce glutathione in RBCs)
  b) Reduced glutathione (G-SH) is needed to remove hydrogen peroxide (H202) which is toxic to the cell.

SIGNS AND SYMPTOMS OF FAVISM

Hemolytic anemia in the form of severe jaundice and decreased hemoglobin.



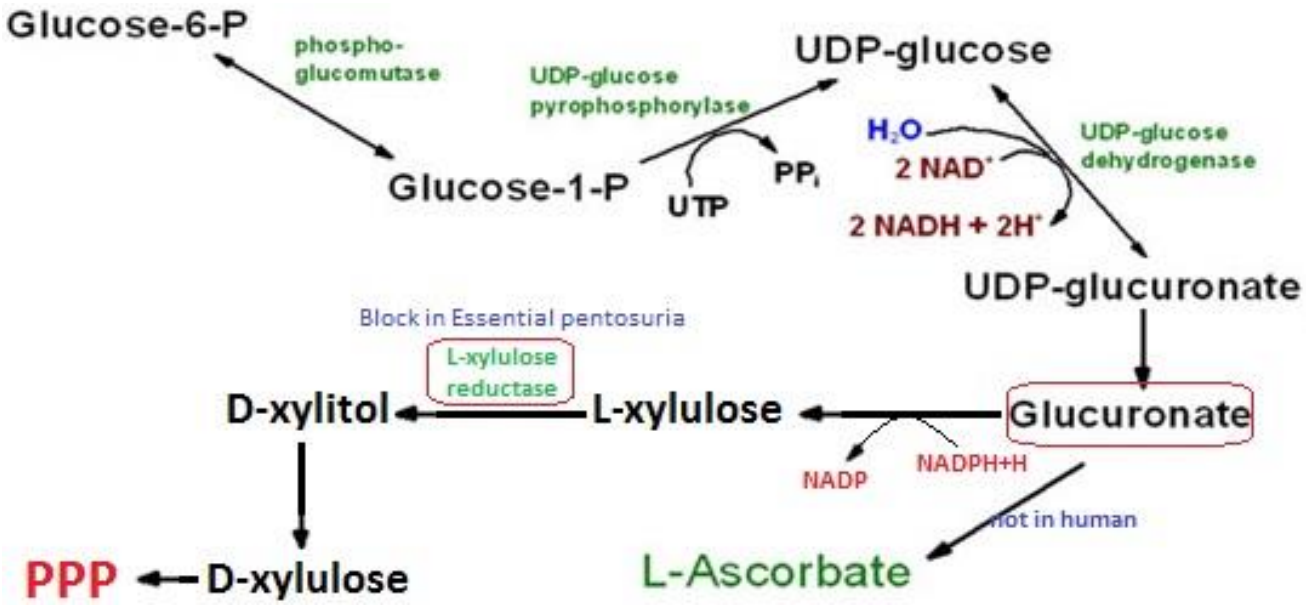
URONIC ACID PATHWAY

Definition It is a minor pathway, in which glucose is converted into glucuronic acid.

LOCATION OF THE PATHWAY:

- **Intracellular location:** Cytosol.
- **Organ location:** Mainly liver.

STEPS



FUNCTIONS (IMPORTANCE) OF URONIC ACID PATHWAY

This pathway produces glucuronic acid, which is important for:

A. Synthesis of substrates:

1. Glycosaminoglycans.

B. Conjugation reactions:

UPD-glucuronic acid is used for conjugation with many body compounds to make them more soluble before excretion e.g. steroid hormones and bilirubin.

C. Detoxification reactions:

UDP-glucuronic acid is used for conjugation with toxic compounds to make them less toxic e.g. phenols.

FATE OF GLUCURONIC ACID:

UDP-glucuronate is converted to glucuronate then → L-xylulose —> D-xylitol → D-xylulose → which then joins **pentose phosphate pathway** to be completely oxidized.

DEFECTS OF URONIC ACID PATHWAY = ESSENTIAL PENTOSURIA:

1. **Definition:** It is benign rare hereditary disease
2. **Cause:** failure of conversion of L-xylulose into D-xylulose (due to deficiency of **L-xylulose reductase**)
3. **Manifestation:** L-xylulose will accumulate and excreted in urine.

Give +ve Bendict test.

MCQ

30. All the dehydrogenases listed below are NAD^+ dependent, EXCEPT:

a. Lactate dehydrogenase
b- Glucose-6-phosphate dehydrogenase
c- Pyruvate dehydrogenase
d- Glyceraldehyde-3-phosphate dehydrogenase

31. The following statements on glucuronic acid pathway are true EXCEPT:

a- It can be synthesized in the human body from active glucose.
b- It can be used in the synthesis of L- ascorbic acid in human body.
c- It is used in detoxication of benzoate.
d- It conjugates with bilirubin in the liver.

32. Which enzyme generates NADPH?

a- Pyruvate carboxylase
b- Pyruvate dehydrogenase
c- Glucose-6-phosphate dehydrogenase
d- Lactate dehydrogenase

33. Transketolase activity is decreased in the deficiency of:

a- Thiamine pyrophosphate (TPP)
b- Nicotinamide adenine dinucleotide
c- Flavin adenine dinucleotide
d- Pyridoxal phosphate

34. The HMP shunt pathway is important for all the following

a- Generation Of ATP
b- Fatty acid biosynthesis
c- Synthesis of reduced glutathione
d- Synthesis of ribose

35. HMP pathway occurs in the cytosol of:

a- Liver.
b- Adipose tissue.
c- Testis.
d- All of the above.

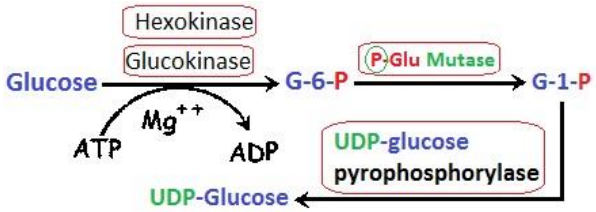
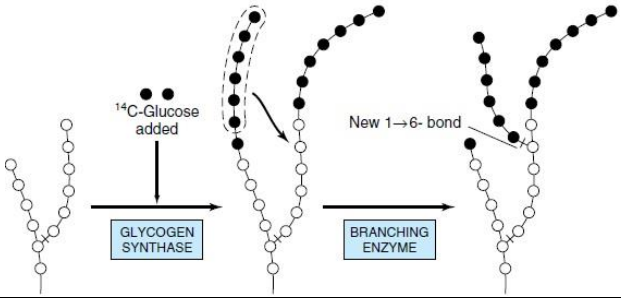
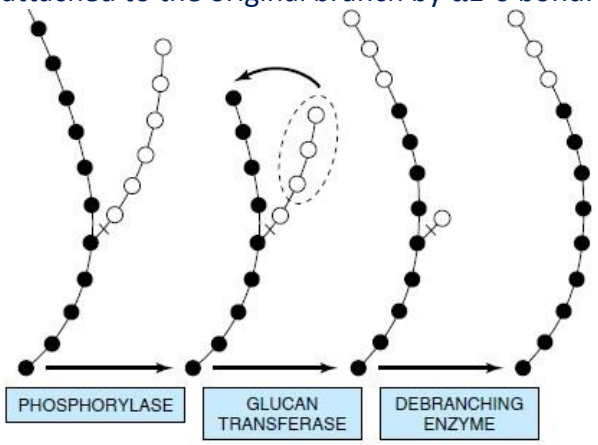
36. NADPH is important FOR ALL Except:

a- Fatty acid synthesis.
b-Hydroxylation reactions.
c- Gluconeogenesis.
d- Steroid synthesis.

37. Favism is due to deficiency of:

a- Glucose -6- phosphatase.
b- Pyruvate kinase.
c- G-6-P-dehydrogenase.
d- Aldolase B.

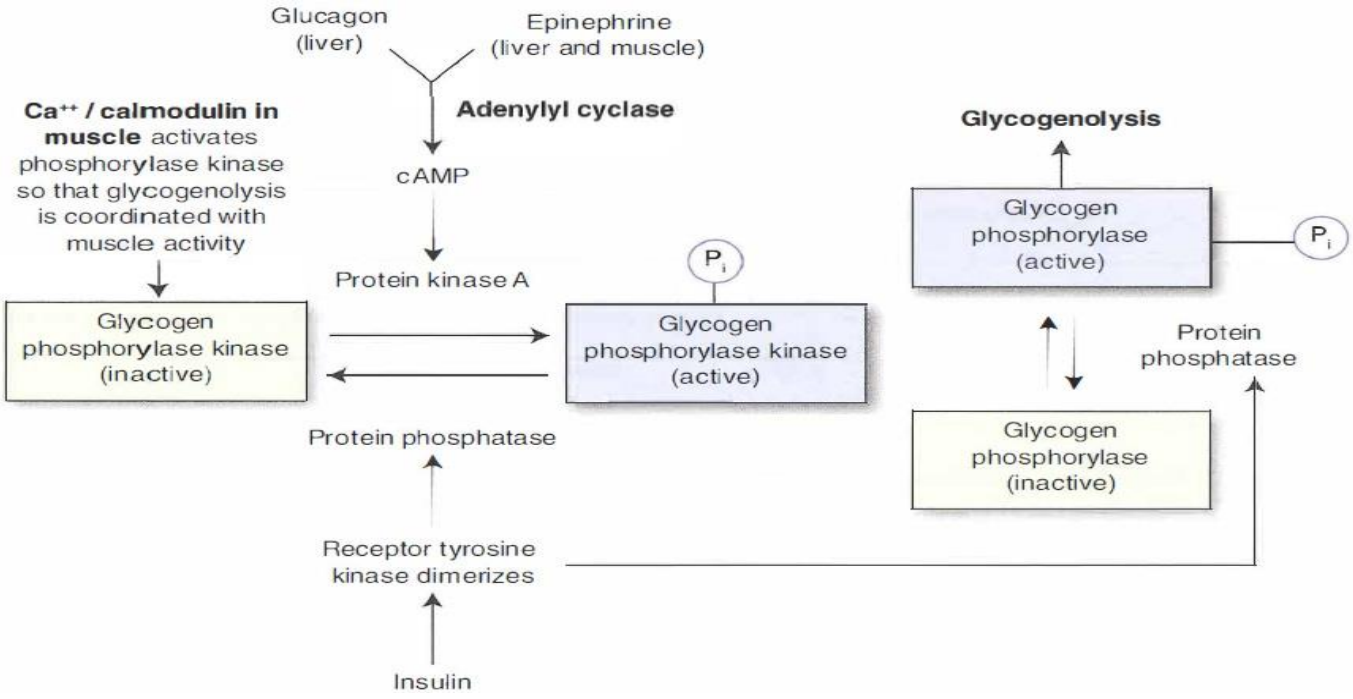
Glycogen Metabolism

	GLYCOGENESIS	GLYCOGENOLYSIS
Def	Formation of glycogen in liver and muscle.	Breakdown of glycogen into glucose (in liver) and lactate (in muscles)
Site	Cytoplasm in liver and muscle	Cytoplasm in liver and muscle
Steps	**1. Activation of Glucose to (UDP-Glucose):**  **2. Formation of glycogen primer which:** - Few molecules of glucose react with OH of tyrosine of a protein called glycogenin. **3. Glycogen synthase "Key enz."** - UDP-G molecules are added to glycogen primer causing elongation of the α1-4 branches up to 12-14 glucose units. **4. Branching enzyme:** -Transfers parts of the elongated chains (5-8 glucose residues) to the next chain forming a new α1-6 glycosidic bond. 	**1. Phosphorylase "Key enz.".** - Acts on α1-4 bonds, breaking it down by phosphorolysis. - It removes glucose units in the form of glucose-1-phosphate. - It acts on the branches containing more than 4 glucosyl units. **2. Transferase:** - When the branch contains 4 glucose units, **3** of them are transferred to a next branch by transferase enzyme leaving the last one. **3.Debranching enzyme:** Removes the last glucose unit that is attached to the original branch by α1-6 bond. 

Liver Glycogen	Muscle Glycogen
From bl. glucose, other Hexose & lactate	From blood only
120 gm. = 6%	350gm. = 1%
Correct blood glucose	ATP for muscle only
Contain G-6-phosphatase	NO G-6-phosphatase
Stimulated by Glucagon	NO effect

REGULATION OF GLYCOGENESIS AND GLYCOGENOLYSIS

There is a **coordinated** regulation of glycogenesis and glycogenolysis **i.e.** conditions **stimulate** glycogenolysis, **inhibit** glycogenesis at the same time and vise versa.



GLYCOGEN STORAGE DISEASES

Glycogen storage diseases	12 types, all resulting in abnormal glycogen metabolism and an accumulation of glycogen within cells.		**V**ery **P**oor **C**arbohydrate **M**etabolism.
Disease	**Findings**	**Deficient enzyme**	**Comments**
Von Gierke's disease (type I)	Severe fasting hypoglycemia, ↑↑ glycogen in liver, ↑ blood lactate, hepatomegaly, **Gout**	Glucose-6-phosphatase	
Pompe's disease (type II)	Cardiomegaly and systemic findings leading to early death	Lysosomal α-1,4-glucosidase (acid maltase)	**P**ompe's trashes the **P**ump (heart, liver, and muscle).
Cori's disease (type III)	Milder form of type I with normal blood lactate levels	Debranching enzyme (α-1,6-glucosidase)	Gluconeogenesis is intact.
McArdle's disease (type V)	↑ glycogen in muscle, but cannot break it down, leading to painful muscle cramps, myoglobinuria with strenuous exercise	Skeletal muscle glycogen phosphorylase	**M**cArdle's = **M**uscle.

GLUCONEOGENESIS

DEFINITION

Gluconeogenesis is the formation of **glucose** from **non-carbohydrate** sources.

These sources include:

- Lactate.
- Pyruvate.
- Glycerol.
- Some amino acids.
- Propionate (in ruminants only).

SITE

A. Intracellular location: Cytosol & mitochondria.

B. Organ location: 1. Liver (90%).
2. Kidney (10%).

STEPS

The steps of gluconeogenesis are mainly the reversal of glycolysis, except for the three irreversible kinases which are replaced by the following enzymes:

Glycolysis	Gluconeogenesis
Glucokinase.	Glucose-6-phosphatase.
Phosphofructokinase -1.	Fructose 1, 6 bisphosphatase.
Pyruvate kinase.	Pyruvate carboxylase.
	Phosphoenol pyruvate carboxykinase.

1. Pyruvate to phosphoenol pyruvate:

- This conversion is done by dicarboxylic acid shuttle and needs 2 enzymes:
  - **a) Pyruvate carboxylase:** present in mitochondria.
  - **b) Phosphoenol pyruvate carboxykinase:** present in Cytosol.
- Pyruvate should pass first **from** Cytosol **to** mitochondria by special transporter.
- Pyruvate is then converted into oxaloacetate by pyruvate carboxylase (in the presence of biotin, CO_2 and ATP).
- The mitochondrial membrane is **im**permeable to oxaloacetate. So, oxaloacetate is converted to Malate by **(Malate dehydrogenase)**.
- Malate is transported to Cytosol, where it is converted again into oxaloacetate **(by Cytosolic Malate dehydrogenase)**.
- Oxaloacetate is converted into phosphoenol pyruvate by **(phosphoenol pyruvate carboxykinase)**.

N.B. : Pyruvate **never goes** in the course of citric acid pathway to reach Malate, **Because** this pathway needs **insulin** and **other factors**.

2. Fructose 1,6 bisphosphate to fructose-6-phosphate:

This reaction is catalyzed by the enzyme **(fructose 1, 6 bisphosphatase)**.

3. Glucose-6-phosphate to glucose:

This reaction is catalyzed by the enzyme **(glucose-6-phosphatase).**

PATHWAYS FOR DIFFERENT SOURCES OF GLUCONEOGENESIS

A. gluconeogenesis from lactate:

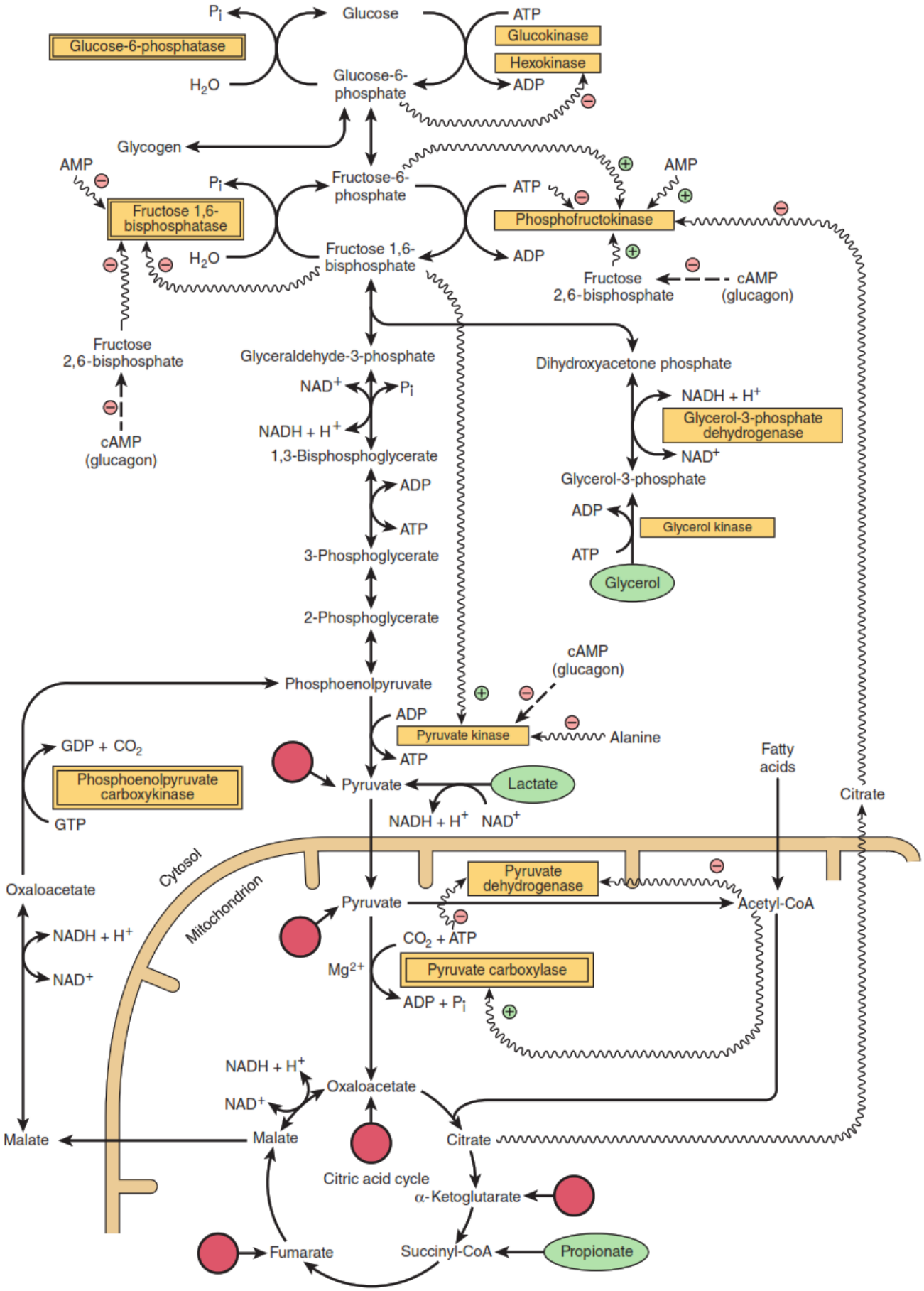
B. Gluconeogenesis from glutamate:

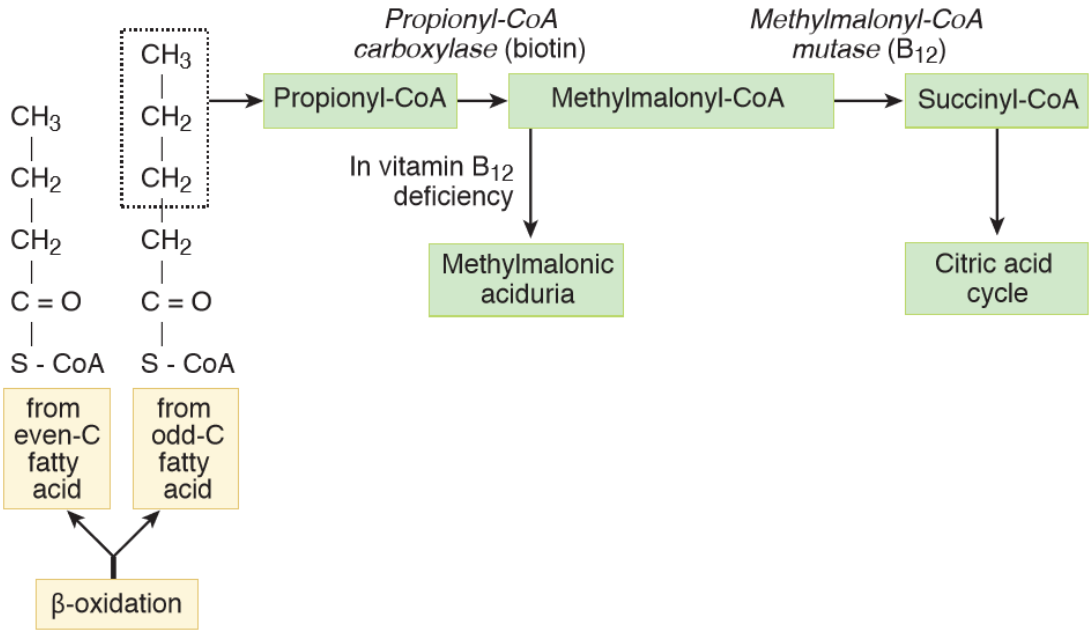
Glutamate is converted into **α-Ketoglutarate** by **transamination** reaction → **krebs**

D. Gluconeogenesis from Glycerol:

C. Gluconeogenesis from Propionic acid:

- This occurs only in **ruminants** and not in human.
- Propionic acid is converted into **Succinyl CoA** → **Malate** → common pathway.





REGULATION OF GLUCONEOGENESIS

gluconeogenesis& glycolysis are reciprocally regulated

A. Hormonal regulation:

Glucagon (+)
- -Secreted in response to hypoglycemia
- - ↑ synthesis of gluconeogenesis enz.
- - inhibit glycolysis.
- - stimulate insulin secretion.

Cortisol (+)
- - ↑ synthesis of gluconeogenesis enz.
- -↑ protein catabolism
- -↑glycogenic amino acids
- - inhibit glycolysis.

Insulin (-)
- - Secreted in response to hyperglycemia.
- - inhibit of gluconeogenesis enzymes
- - stimulate glycolysis.

B. Substrate regulation: Acetyl CoA and ATP

1. **Stimulate gluconeogenesis** by **inhibiting glycolysis** (through inhibiting **PFK-1**) and stimulate gluconeogenesis (by stimulating **fructose1, 6 bisphosphatase**).
2. Acetyl CoA also stimulates **pyruvate carboxylase** (gluconeogenesis)
   And inhibit **pyruvate dehydrogenase** (oxidation).

MCQ

38. Gluconeogenesis is inhibited by:

a- Glucagon b- Growth hormone c- Insulin d- Glucocorticoids

39. All the following are key gluconeogenic enzymes EXCEPT:

a- Pyruvate carboxylase b- Phosphoenol pyruvate carboxykinase

c- Phosphofructokinase d- Glucose-6-phosphatase

40. How many ATP molecules are required to convert 2 molecules of pyruvate into glucose?

a- Two b- three c- Six d- Eight

41. All the following are substrates for gluconeogenesis Except

a- palmitic acid b- Lactic acid c- Alanine d- Glycerol

42. The hormone activating the enzyme glycogen phosphorylase is:

a- Epinephrine b- Insulin c- Growth hormone d- Glucocorticoids

43. Von Gierk's disease is characterized by the deficiency Of:

a- Glucose-6-phosphatase b- Glyceraldehyde-3-phosphate dehydrogenase

c- Phosphofructokinase d- Phosphorylase

44. As regards glycogen:

a- It is a highly branched polymer of aD glucose.

b. The glucose residues are united by a, and a, glucosidic bonds.

c- Glycogen stores in muscles are more than that of liver.

d- All of the above.

45. Glycogen phosphorylase is:

a- The key enzyme of glycogenesis. b- Activated by lcAMP.

c- Allosterically inhibited by ATP. d- Activated by insulin.

46. As regards Von Gierk's disease, all are correct, EXCEPT:

a- It is due to deficiency of G-6-phosohatase in the liver and kidneys.

b-There is fasting hypoglycemia.

c- There is hyperlipidemia and ketosis.

d- There is hypouricemia.

47. All gluconeogenic enzymes are present in cytosol, EXCEPT:

a- G-6-phosphatase.

b-Pyruvate carboxylase.

c- PEP carboxykinase.

d- Aldolase A.

48. One of the following cannot act as a precursor for gluconeogenesis

a- Lactate. b- Glycerol c- Alanine. d. Acetyl COA.

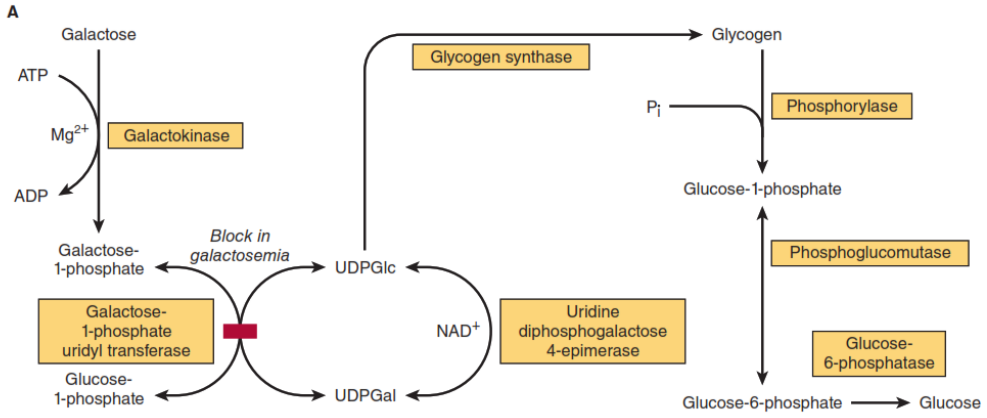
GALACTOSE METABOLISM

IMPORTANCE OF GALACTOSE: IN THE FORM OF UDP-GALACTOSE

A. Synthesis of lactose (= Milk sugar).
B. Synthesis of glycolipids (cerebrosides).
C. Synthesis of glycoproteins and proteoglycans.
D. Synthesis of glycosaminoglycans.

CONVERSION OF GALACTOSE INTO GLUCOSE

A. Site: Liver.
B. Steps:



GALACTOSEMIA

Definition: It is increase blood galactose concentration due to inability to metabolize galactose.
Causes: Inherited enzyme deficiency of:

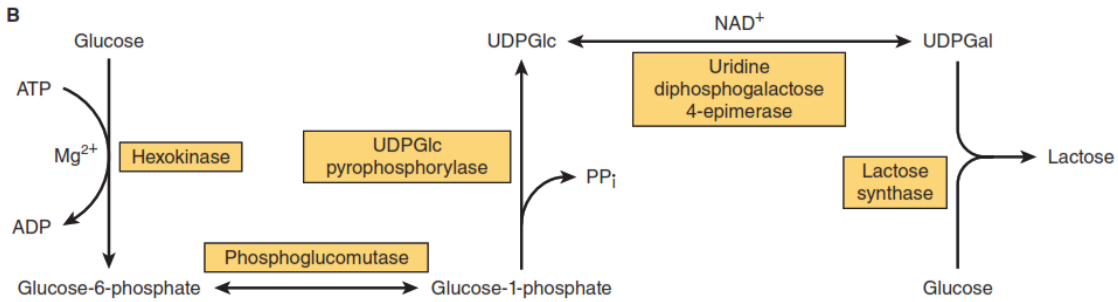
1. Galactokinase.
2. Galactose-1-P uridyl transferase:
3. Epimerase.

Effect: **a) Infantile Cataract** = opacity of eye lens:
Galactose in the eye is reduced by an enzyme called **Aldose reductase** into galacticol, which accumulates causing cataract.
b) Liver failure.
c) Mental retardation.
d) Galactosuria: excretion of galactose in urine.

CONVERSION OF GLUCOSE INTO GALACTOSE IN MAMMARY GLAND AND LACTOSE SYNTHESIS

Lactose is a disaccharide formed of **β -galactose** attached to **α-glucose** by **β1-4 bonds**. It is called **milk sugar**

Steps: **1.** Glucose is first converted into UDP-galactose.
2. UPD-Galactose reacts with a molecule of glucose in the presence of enzyme to form lactose.



FRUCTOSE METABOLISM

DIETARY SOURCES OF FRUCTOSE

- **Sucrose:** (table sugar): Hydrolysis of sucrose → glucose and Fructose
- **In honey and in many fruits and vegetables** as a monosaccharide.

IMPORTANCE OF FRUCTOSE

A. Energy production: 15% of daily energy is derived from fructose.

B. Fructose is the major energy source for **spermatozoa** in the **seminal vesicle**.

METABOLISM OF FRUCTOSE

A. In the liver:

1. Liver contains **fructokinase** enzyme, which phosphorylates fructose into fructose-1-phosphate.
2. Fructose-1-phosphate by **aldoase B** enzyme → Dihydroxyacetone phosphate + glyceraldehyde.
3. Glyceraldehyde → glyceraldehydes-3-phosphate.
4. Glyceraldehyde-3-p + Dihydroxyacetone may undergo:
   a) **Glucose formation** (gluconeogenesis) main pathway.
   b) **Oxidation to pyruvate** (glycolysis).

B. In extra-hepatic tissues:

1. Because fructokinase is not available in muscles and adipose tissue, fructose is metabolized by Hexokinase and other enzymes into pyruvate → oxidation

C. In the testis (seminal vesicle, lens, peripheral nerves and renal glomeruli:

1. Glucose is converted into fructose through sorbitol formation:
2. Fructose is the main nutrient for sperms.
3. Deficiency of fructose in semen correlates with male infertility.

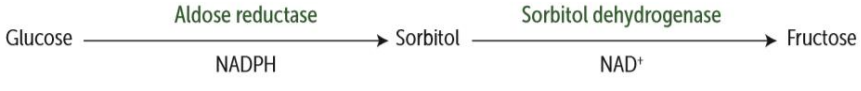
GENETIC DISORDERS OF FRUCTOSE METABOLISM

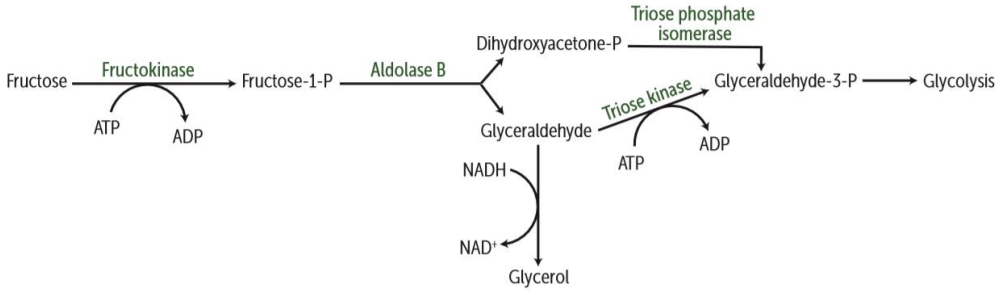
1- Essential fructosuria:

1. **Cause:** Due to deficiency of **Fructokinase** enzyme.
2. **Effect:** Not serious condition. The excess accumulated fructose is lost in urine.

2- Hereditary fructose intolerance.

1. **Cause:** Due to deficiency of **Aldolase-B enzyme**. This leads to accumulation of Fructose-1-phosphate.
2. **Effect:** the accumulation of Fructose-1-phosphate leads to:
   a) Damage of liver and kidney tissues → Liver and kidney failure.
   b) Inhibition of Phosphorylase enzyme. This leads to inhibition of glycogenolysis and fasting hypoglycemia.





MCQ

49. All are true as regards fructose intolerance

a- Defective enzyme is aldolase-B
b- Fructose-I-phosphate accumulates
c- Glycogen phosphorylase is inhibited
d- Urine is free from fructose

50. Features of galactosemia include the following

a- Cataract
b- Hepatosplenomegaly
c- Mental retardation
d- Hemolytic anemia

51. The commonest deficient enzyme in Galactosemia is:

a- Galactokinase
b- Galactose -1- P uridyl transferase
c- UDP transferase
d- Galactose -l phosphatase.

52. Hereditary fructose intolerance is a condition caused by a deficiency of:

a- Phosphofructokinase.
b- Fructokinase.
c- Aldolase B.
d- Fructose 6-phosphatase.

BLOOD GLUCOSE

PLASMA GLUCOSE LEVELS

A. Fasting level = 65-110 mg/dl (3.6-6.1 mmol/L)
B. One hour after carbohydrate meal = 120-150 mg/dl (6.7-8.3 mmol/L).
C. Two hours after carbohydrate meal (PP) = 65-140 mg/dl (3.6-7.8 mmol/L).

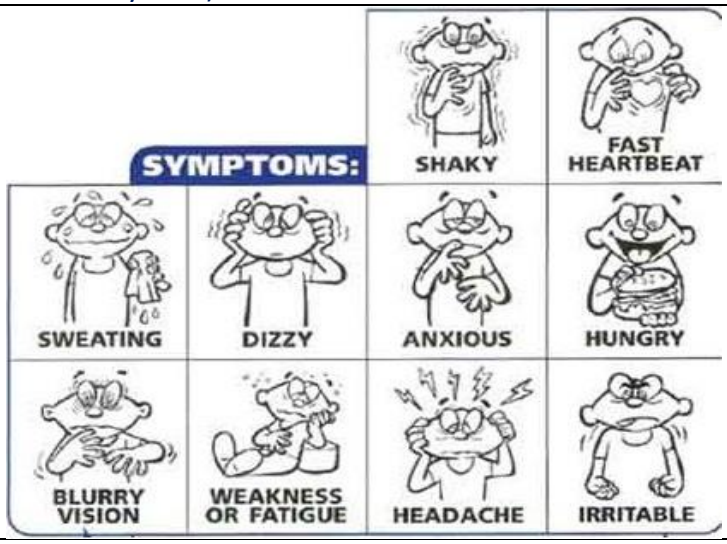
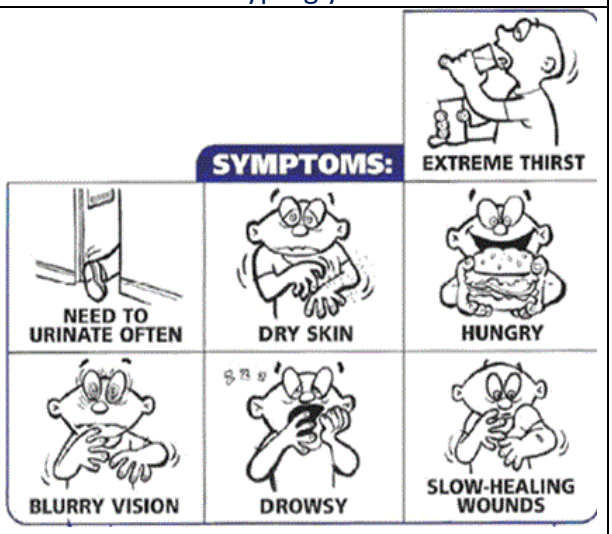
REGULATION OF BLOOD GLUCOSE LEVEL

<table>
<tr><th>Hormonal regulation</th><th>Organ regulation</th></tr>
<tr><td>Insulin
the only hormone which reduces blood glucose level through:
Stimulation of: - Glucose uptake by cell.
- Glucose oxidation.
- Glycogenesis.
- Lipogenesis.

Inhibition of: - Glycogenolysis.
- Gluconeogenesis.</td><td rowspan="5">Liver
During fasting:
- Glycogenolysis.
- Gluconeogenesis.
- Ketogenesis.
After carbohydrate meal:
60% of glucose is taken up by liver, and converted into glucose-6-phosphate, by Glucokinase enzyme:
- Glucose-6-phosphate will undergo one of the following fate in the liver:
- (Glycogenesis)
- (lipogenesis).

Kidney
- Glucose is completely reabsorbed by kidney until reaching renal threshold (Average 180 mg/dl).
- Then appears in urine (glycosuria).
Low renal threshold:
- Normally in some persons due to defective tubular enzymes for Glucose reabsorption (diabetes innocence).
- In 20% of pregnant females.
High renal Threshold:
- In Elderly people due to reduced glomerular filtration rate.
- In cases of diabetes with renal damage.</td></tr>
<tr><td>Glucagon
Stimulation of: - Glycogenolysis
- Gluconeogenesis.</td></tr>
<tr><td>Catecholamines
Stimulation of: - Glycogenolysis</td></tr>
<tr><td>Glucocorticoids
Stimulation of: - Gluconeogenesis.
- ↑ Ptn catabolism→↑a.a.</td></tr>
<tr><td>Growth hormone
Inhibition of: glucose uptake by cells.
Blocks: insulin action at cell membranes.</td></tr>
</table>

VARIATIONS IN BLOOD GLUCOSE

<table>
<tr><th>Hypoglycemia</th><th>Hyperglycemia</th></tr>
<tr><td>Definition:
Decrease of blood glucose concentration below normal fasting average concentration: less than 65 mg/dl.</td><td>Definition:
It is the rise of blood glucose above normal average level.</td></tr>
<tr><td>Mechanism:
Hypoglycemia activates:
1- α- Cells of islets of Langerhans → ↑Glucagon + ↑Glycogenolysis →↑Blood glucose.
2- Receptors in hypothalamus: This stimulates Secretion of epinephrine (mediated by autonomic nervous system).</td><td>Causes:
1. Diabetes mellitus: CC
2. In patients receiving intravenous fluid containing glucose.
3. Temporarily in severe stress.
4. After cerebro-vascular accidents.
5. Disturbance in hyperglycemic hormones.</td></tr>
<tr><td> 
</td><td> 
</td></tr>
<tr><td>Types and causes of hypoglycemia:
<table>
<tr><th>Types</th><th>Organ or cause</th><th>Examples</th></tr>
<tr><td rowspan="3">Fasting</td><td>- Pancreas</td><td>Insulinoma.</td></tr>
<tr><td>- Other endocrine gland</td><td>Adrenocortical hypofunction.</td></tr>
<tr><td>Liver</td><td>Prolonged starvation.</td></tr>
<tr><td rowspan="3">Stimulative</td><td>-Drugs and Poisons</td><td>↑insulin or ↑sulphonylurea.
- Liver poisons</td></tr>
<tr><td>-Postgastrectomy
- Leucine
- hypersensitivity</td><td></td></tr>
<tr><td>- Inborn errors of metabolism</td><td>- Galactosemia
- fructosemia
- Von Gerkie’s D</td></tr>
</table></td><td></td></tr>
</table>

CHO DISEASE

	DISEASE	DEFICIENCY OF	EFFECT
LACTOSE	**1. Lactose intolerance** Maybe: 1- congenital (Rare) 2- Acquired (Common	**Lactase enzyme**	**1-** Osmotic pressure → Dehydration & causing diarrhea. **2-** ↑ fermentation of lactose by bacteria → Abdominal cramps.
GLYCOLYSIS	**1- Hemolytic anemia**	Pyruvate kinase Hexokinase	↓rate of Glycolysis → ↓production of ATP
	2-Lactic acidosis	**Causes** of lactic acidosis: **a-** Increase formation of lactate **b-** Decrease utilization of lactate.	
HEXOSE PHOSPHATE PATHWAY OR (PPP)	**1- Favism:** (Hemolytic anemia) In the form of severe jaundice & ↓HB conc. **Precipitating factors:** **a-** Oxidant drugs e.g. sulpha & Primaquine Anti-malarial, **b-** Fava beans.	Glucose -6-phosphate dehydrogenase	**a-** ↓NADPH+H→↓ reduced glutathone→ accumulation of H_2O_2 →Hemolysis of RBCs. **b-** H_2O_2 conversion HB into Met-hemoglobin → the RBC membrane fragility.
	2- Chronic bacterial infection	NADPH+H^+ oxidase	
URONIC ACID PATHWAY	**Essential pentosuria**	L- xylulose reductase	pentosuria
GLYCOGEN STORAGE DISEASES	**Von Gerkie's disease (type I)**	Glucose-6-phosphatase (# gluconeogenesis)	Severe fasting hypoglycemia, ↑ glycogen in liver, ↑ blood lactate, hepatomegally, Guat
	Pompe's disease (type II)	Lysosomal α-1,4-glucosidase (acid maltase)	Cardiomegaly and systemic findings leading to early death
	Cori's disease (type III)	Debranching enzyme (α-1,6-glucosidase)	Milder form of type I with normal blood lactate levels **Gluconeogenesis is intact**.
	McArdle's disease (type V) **m**uscle	Skeletal muscle glycogen Phosphorylase	↑ glycogen in muscle, but cannot break it down, leading to painful muscle cramps, myoglobinuria with strenuous exercise
FRUCTOSE	**Essential**	Fruktokinase	fructosuria
	Fructose intolerance	Aldolase-B	- Liver and kidney failure - fasting hypoglycemia

CHAPTER 6

Lipid Metabolism

CHAPTER MAP

Lipids Metabolism

Feeding state واحنا واكلين هيكون في انسولين	Fasting state واحنا صايمين
1- Fatty acid synthesis 2- Lipogenesis 3- Cholesterol synthesis 4- Conjugated lipid synthesis	1- Lipolysis 2- Fatty acid oxidation 3- Ketogenesis 4- Ketolysis

FATE OF ABSORBED LIPIDS

A. After fatty meal plasma shows a **milky appearance**. This due to venous blood contains excess **chylomicrons** after absorption.

- Excess chylomicrons stimulate **mast cells** to produce **heparin**. Heparin then stimulates the lining epithelium of blood vessels of **heart**, **lungs**, **spleen** and **adipose tissue** to produce an enzyme called: **lipoprotein lipase** (plasma clearing factor).
- Lipoprotein lipase enzyme will act on **triacylglycerols** of chylomicrons, converting them into glycerol and free fatty acids.

B. Glycerol and **fatty acids** are taken up by different tissues for the following fate:

1. Formation of depot fat (adipose tissue).

a) It is formed mainly of Triacylglycerols **b)** It is present in fat cells of adipose tissue.

2. Oxidation for production of energy:

a) Fatty acids: Converted into **acetyl CoA** that is oxidized in **citric acid cycle**.

b) Glycerol: Converted into **glycerol-3-phosphate** (by glycerol kinase). This is then converted into **DHAP**. The later will undergo oxidation in **glycolysis.**

3. Glucose formation by gluconeogenesis:

a) Glycerol → Glucose.

b) Odd number fatty acids oxidation → Propionyl CoA → Glucose.

4. Synthesis of biologically active compounds: e.g. different **steroids** and **eicosanoids**

5. Synthesis of tissue fats (structural cellular fats).

STORAGE AND MOBILIZATION

- Body lipids are of 4 types: tissue lipids, adipose tissue (depot fat), plasma lipoproteins and bone marrow lipids.

Tissue lipids

- These lipids enter in the structure of body cells as cell membrane and mitochondria.
- Tissue lipids never oxidized to give energy.

Adipose tissue (depot fat)

White adipose tissue

a) Composition:

1) Triacyiglycerols: main content that contain saturated and unsaturated fatty acids. This makes depot fat in a fluid state at body temperature.

2) Little phospholipids and cholesterol.

b) Site:

1) Under skin and in the breast.

2) Around important organs e.g. kidney.

3) In the omentum and mosentry.

c) Sources:

1) Absorbed fat. **2)** Carbohydrate.

d) Functions: depot fat is important for:

1) Energy production: During fasting, the triacylglycerols stored in depot fat provide the body with free fatty acids that oxidize to give energy.

2) Fixation of some organs e.g. kidney.

Heat insulator around the body.

4) Production of vitamin D_3: by exposure of skin to ultraviolet rays

Brown adipose tissue

a) Certain areas of adipose tissue appear **brown** as they contain high content of **mitochondria, cytochromes** and well developed **blood supply**.

b) Function:

Production of heat. They contain a protein called Thermogenin. This protein acts as **Uncoupler** of oxidative phosphorylation → ↓ATP production and ↑heat generation.

c) Site: common in animals exposed to cold atmosphere for warmness: It is little in human, especially in obese persons.

LIPOLYSIS

DEFINITION hydrolysis of Triacylglycerols in adipose tissue into glycerol and fatty acids.

STEPS

Lipolysis is carried out by a number of lipase enzymes, which are present in adipose tissue. These are

1. Hormone sensitive triacylglycerol lipase.
2. Diacylglycerol lipase.
3. Monoacylglycerol lipase.

FATE OF PRODUCTS OF LIPOLYSIS

1. **Fate of fatty acids**
   - **a)** Oxidation by tissue to give energy.
   - **b)** Fatty acids may remain in adipose tissue to be re-esterified into TAG again.
2. **Fate of glycerol:** Glycerol may diffuse to blood and then taken up by the liver to give:
   1) Glucose by gluconeogenesis. 2) Pyruvate by glycolysis.
   3) Triacylglycerols by lipogenesis.

Regulation of Lipolysis

The key enzyme controlling Lipolysis is the Hormone sensitive triacylglycerol lipase. It exists in 2 forms: active (**Phosphorylated**) and inactive (**dephosphorylated**)

Causes of excessive Lipolysis: In conditions where the need for energy is increased (low insulin and high glucagon):

1. Starvation.
2. Diabetes mellitus.
3. Low carbohydrate diet.
4. In certain infectious diseases as in tuberculosis (due to high catabolic state)

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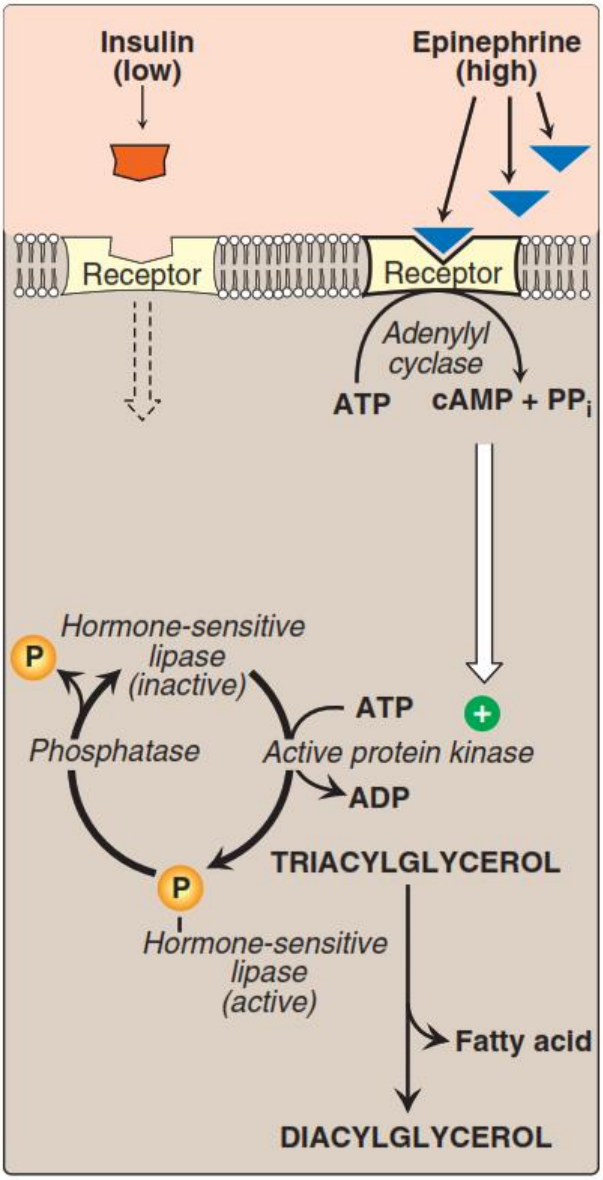


Fatty acids oxidation

- 3 Different pathways for fatty acid oxidation are present: α, β and ω

β-OXIDATION

Site

1. Intracellular location: Mitochondria

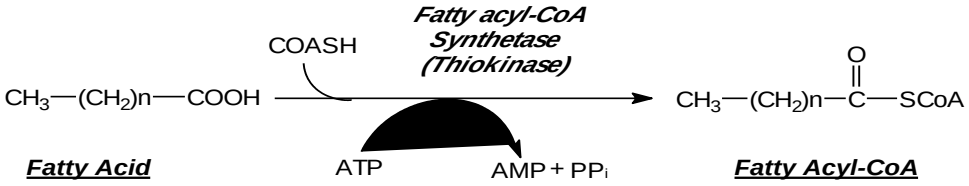
2. Organ location:

a) Liver, kidney, heart and skeletal muscles.

b) β-Oxidation **never occur** in **brain** (*can't pass BBB*) and **RBCs** (*no mitochondria*).

Mechanism

1- Activation of Fatty Acids.



Activation Of A Fatty Acid.

2- Transport of Acyl-CoA from Cytosol into Mitochondria by Carnitine Shuttle:

a) Structure of Carnitine:

Carnitine is β-hydroxy-γ-trimethyl ammonium butyric acid. It is derived from lysine amino acid.

b) Function of Carnitine:

It transports long chain acyl CoA inside the mitochondrial matrix where enzymes for β-oxidation are present.

c) Steps of shuttle three enzymes are involved

1. Carnitine acyl transferase I (Carnitine palmitoyl transferase I)

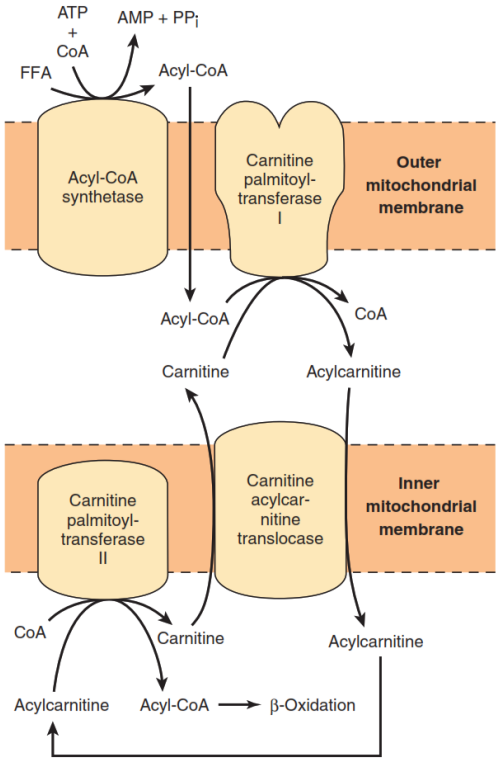
- It is present in the outer mitochondrial membrane.
- It transfers the **acyl group** from acyl CoA to Carnitine to form **acyl Carnitine**.

2. Carnitine acylcarnitine translocase:

- It is present in the inner mitochondrial membrane.
- It transports acyl Carnitine across inner mitochondrial membrane (in exchange with Carnitine).

3. Carnitine acylcarnitine transferase II (Carnitine palmitoyl transferase II).

- It is present in the inner mitochondrial membrane.
- It transfers the acyl group from acyl Carnitine to form **acyl CoA** again.

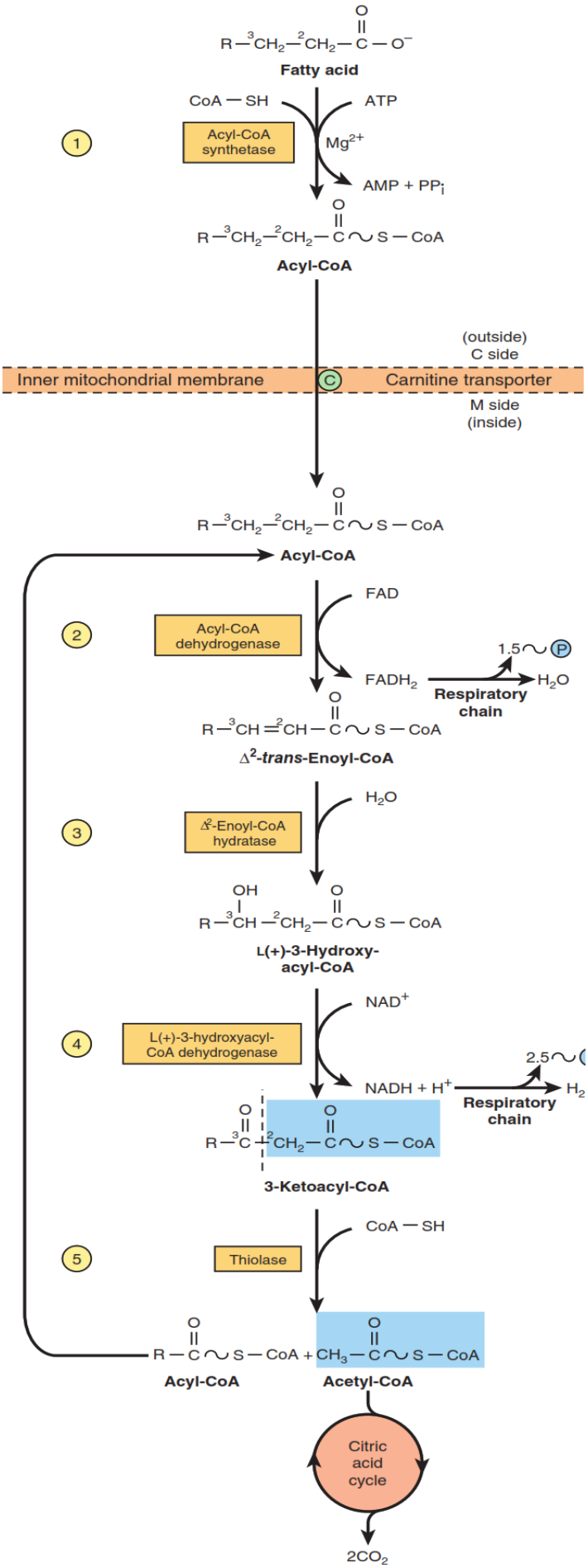


3. Unsaturation of fatty acids: Catalyzed by fatty acyl CoA dehydrogenase enzyme.

4. Hydration: Catalyzed by enoyl CoA hydratase enzyme.

5. Oxidation: Catalyzed by β-hydroxy acyl CoA dehydrogenase enzyme.

6. Splitting (Cleavage) step: Catalyzed by Acyl CoA acyl transferase (thiolase) enzyme.



ENERGY PRODUCTION OF β -OXIDATION

- Calculation formula of energy production of oxidation of any fatty acids:
- Oxidation of one molecule of acetyl CoA in citric acid cycle gives 12 ATP.
- In each turn: **1 $FADH_2$** → 2ATP **1 NADH+H** → 3 ATP = **5 ATP**

= **{(N/2 - 1) x 5 ATP} + {N/2 x 12 ATP} - 2 ATP**

-Two high energy phosphate bonds are utilized in the first reaction. Catalyzed by (acyl CoA synthetase) which occurs for one time only.

e.g. **palmitic acid** (16 carbons):

= **{(16/2 - 1) x 5 ATP} + {16/2 x 12 ATP} - 2 ATP**

= **{(35 ATP} + {96ATP} - 2 ATP =** 129 ATP

IMPORTANCE (FUNCTIONS) OF β -OXIDATION:

1. **Energy production** e.g. palmitic acid produces 129 ATP.
2. **Production of acetyl CoA:** which enter in many pathways.
3. **Ketone bodies formation:** Acetoacetyl CoA is the last 4 carbons product in the course of β-oxidation of even numbered fatty acids. It may be converted into acetoacetate; one of ketone bodies (see later).

OXIDATION OF ODD NUMBER FATTY ACIDS:

1. They are oxidized by **α-oxidation** till a **Propionyl CoA**, (3 carbons) is produced. Then Propionyl CoA is converted to **Succinyl CoA**

UNSATURATED FATTY ACIDS

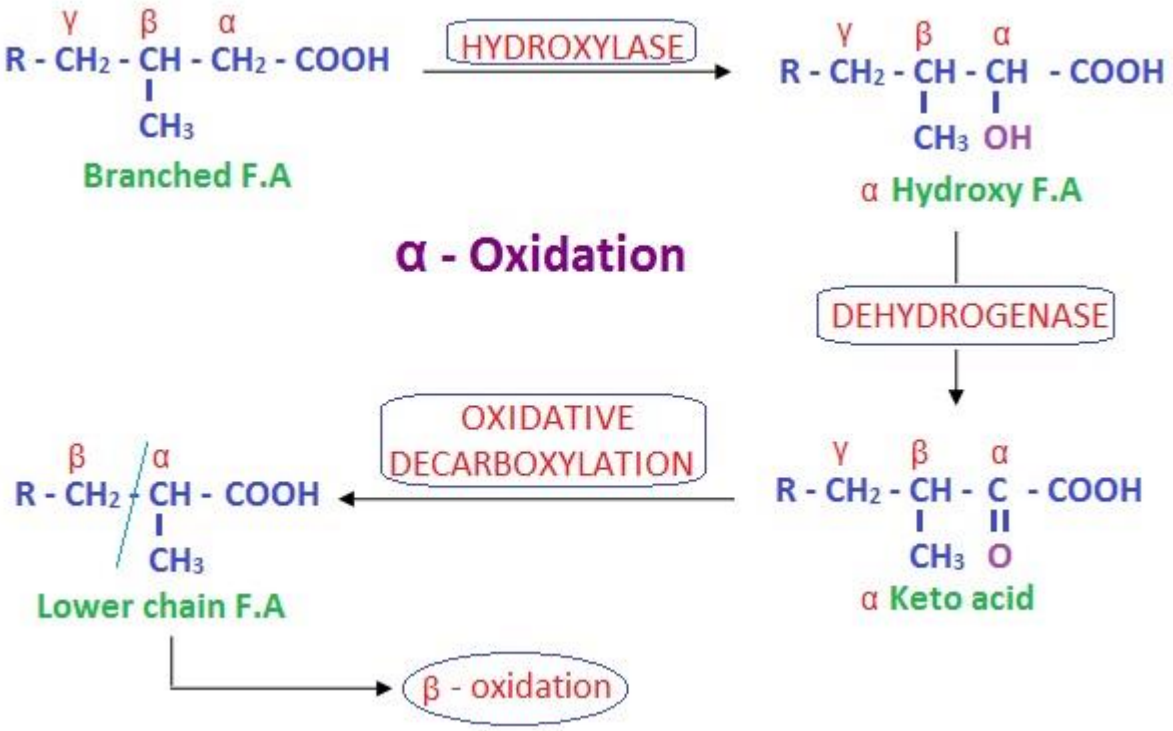
- Their oxidation requires **new** enzymes in addition to the four enzymes.
- The pathways differ depending on the position in which the double bond is located.
  a. **For fatty acids that contain a double bond at an odd carbon number** (e.g., between carbons 9 and 10), b-oxidation occurs until the double bond of the unsaturated fatty acid reaches position 3 of the acyl CoA. At this point, an isomerase will convert the cisD3 double bond to a transD2double bond. The normal steps of b-oxidation can then proceed.
  b. **For fatty acids that contain a double bond at an even carbon position** (e.g., between carbons 12 and 13), b-oxidation occurs until the double bond of the unsaturated acid reaches position 4 of the acyl CoA.
  After the acyl CoA dehydrogenase creates the trans double bond between carbons 2 and 3, the enzyme 2,4-dienoyl CoA reductase reduces the two double bonds into one, generating a trans D3 double bond. The trans D3 double bond is then isomerized to transD2,so that the normal steps of b-oxidation can then proceed.

α-OXIDATION

- This type of oxidation occurs in α- position and characterized by:
  1. It is a mechanism mainly for oxidation of branched chain fatty acid, which are methylated at β position.
  2. It is specific for oxidation of Phytanic acid (3, 7, 11, 15 tetramethyl palmitic acid), present in plant foodstuffs.
  3. It is minor pathway for fatty acid oxidation, occurs mainly in brain and nervous tissues.
- In α-oxidation, there is **one carbon** atom removed at a time from α position
- It does not **require CoASH** and does **not** generate high energy phosphate.

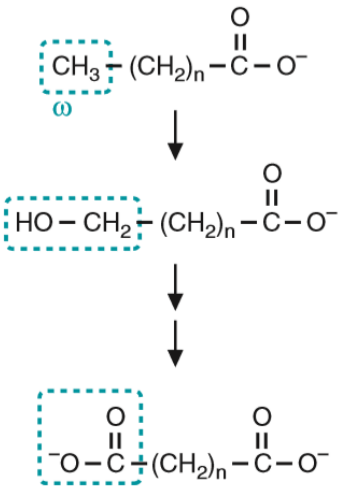
REFSUM'S DISEASE:

- **Def:** inherited deficiency of enzymes responsible for α-oxidation of Phytanic acid.
- **Manifestation:** accumulation of Phytanic acid in nervous tissue and produce nervous damage e.g. **deafness** and **blindness**.



ω-OXIDATION

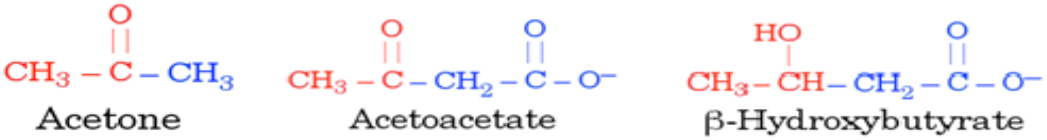
- It is oxidation of terminal **CH_3** group (ω carbon) of fatty acid.
- This produces **dicarboxylic fatty** acids. By **β**-oxidation they are converted to adipic acid (6 carbons) and suberic acid (8 carbons).
- ω-Oxidation is a minor pathway for fatty acid oxidation and catalyzed by hydroxylase enzymes of **cytochrome P_{450}**



KETONE BODIES

Definition

these are 3 compounds formed by the liver and include:



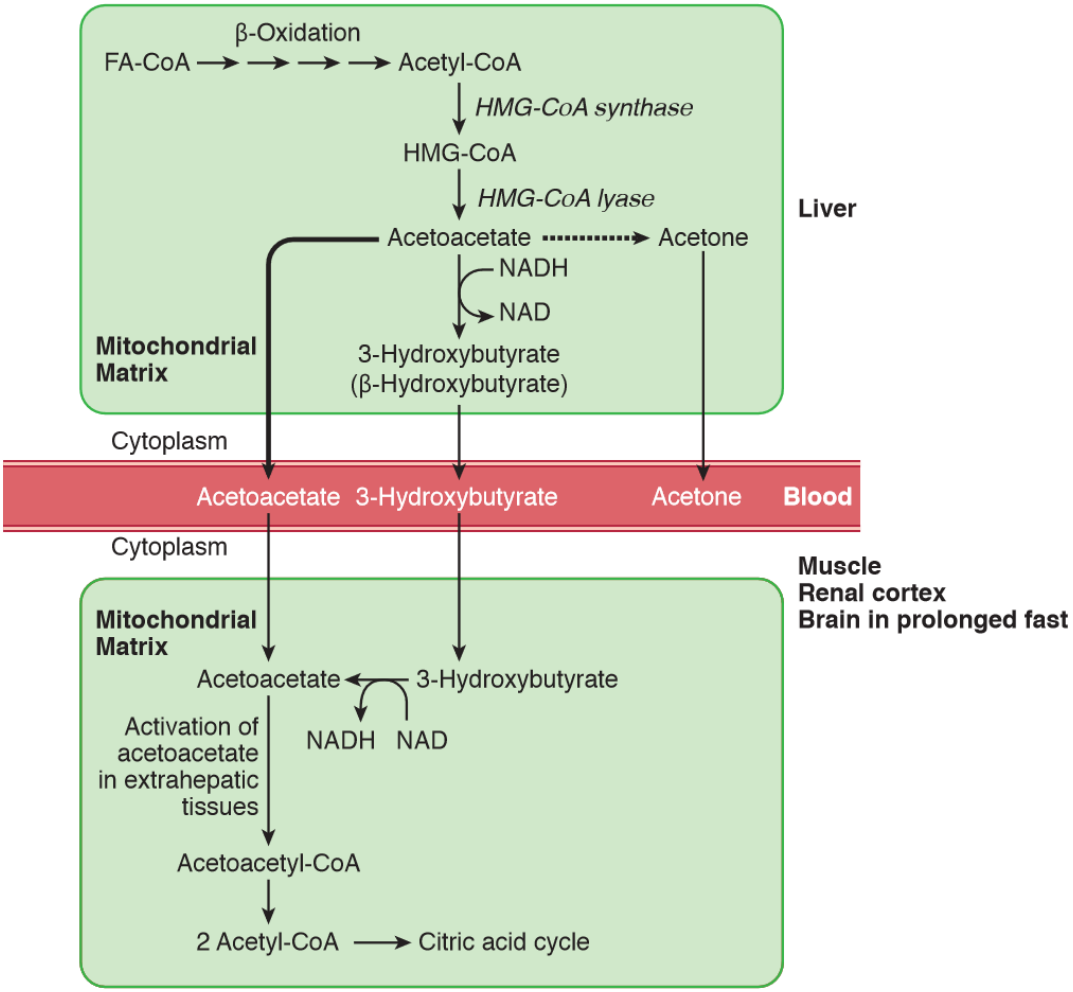
FUNCTIONS OF KETONE BODIES

- **Source of energy:** They are converted into acetyl-CoA which is oxidized in tricarboxylic acid (TCA) cycle.
- Skeletal muscles, cardiac muscles, kidneys and most of tissues can use ketone bodies as a source of energy in **prolonged fasting** and **starvation**.
- **Brain tissue** can also oxidize ketone bodies within 5 to 6 days of starvation.
  Note: brain never oxidizes fatty acids.
- **Liver** does not contain enzymes for ketone bodies oxidation (**ketolysis**). Thus liver cannot oxidize them.

	Ketogenesis	Ketolysis
location	Organ: Liver (partial oxidation)	Extra-hepatic tissues
	Intracellular: Mitochondria	
Precursor	Acetyl CoA from: (F.A oxidation & Ketogenic a.a)	
Steps	**1.** Formation of **acetoacetyl CoA**: **a)** From condensation of 2 acetyl CoA. **b)** Acetoacetyl CoA may also be derived from β-oxidation of F.A **2.** Formation of **HMG-CoA** By condensation of third molecule of **acetyl CoA** in the presence of HMG CoA synthase **3.** Formation of **acetoacetate** by HMG CoA lyase. **4.** Acetoacetate is either: a) Spontaneously decarboxylated into **acetone** b) Reduced by hydroxybutyrate dehydrogenase into **β-hydroxybutyrate.**	- **Acetone** is volatile and removed in the expired air. - **β-Hydroxybutyrate** is converted into acetoacetate by hydroxybutyrate dehydrogenase - **Acetoacetate** is then activated into Acetoacetyl CoA by: a) **Thiophorase** in the presence of Succinyl CoA. **b) Acetoacetate synthetase** in the presence of ATP. - **Acetoacetyl CoA** is split into two molecules of **acetyl CoA** which are oxidized in TCA
Regulation	**1. After meal:** insulin is secreted, and this inhibits Lipolysis and in turn inhibit Ketogenesis. **2. During fasting:** glucagon. This stimulates Lipolysis and in turn Ketogenesis.	

Conditions that increase Ketogenesis:

1. Fasting and starvation. 2. Carbohydrate poor diet. 3. High fat diet. 4. Diabetes mellitus
5. ↑ muscular exercise. 6. pregnancy



BLOOD KETONE BODIES AND KETOSIS

- **Blood ketone bodies** concentration is less than **3** mg/dl.
- **Ketonemia:** is the increase of blood ketone bodies above normal concentration.

1. It occurs when the rate of **Ketogenesis** is greater than the rate of **ketolysis**.

- **Urine ketone bodies:** is less than **40** mg/day.
- **Ketonuria:** is the increase of urine ketone bodies above normal concentration.

1. It usually occurs with Ketonemia. 2. Concentration may reach 5000 mg/day.

CAUSES OF KETONEMIA AND KETONURIA

1. Starvation. **2.** Severe diabetes mellitus. **3.** Hypercatabolic states e.g. diarrhea

KETOSIS = (KETOACIDOSIS)

- **Definition:** It is a condition of metabolic acidosis results from Ketonemia.
- **Mechanism: a)** An increase of ketone bodies in the blood is neutralized by blood buffers mainly bicarbonate (HCO3).

b) Bicarbonate will be depleted and this leads to decreased blood pH (acidosis).

- **Effects of acidosis:**

a) Acidosis causes dizziness, loss of concentration...etc.

b) Acidosis causes transfer of **potassium** (K^+) ions from intracellular fluid to blood leading to (↑ K^+) hyperkalemia.

- **Ketotic coma:** In severe cases of ketosis as in uncontrolled diabetes mellitus, coma may be developed and the condition may be fatal.

Lipogenesis

FATTY ACID SYNTHESIS

- There are 2 mechanisms for fatty acids synthesis: cytoplasmic and microsomal.

❖ CYTOPLASMIC SYSTEM (extra-mitochondrial) or (de novo)

- The main product of this pathway is **palmitate** (16_C).

SITE

1. Intracellular location: Cytosol.

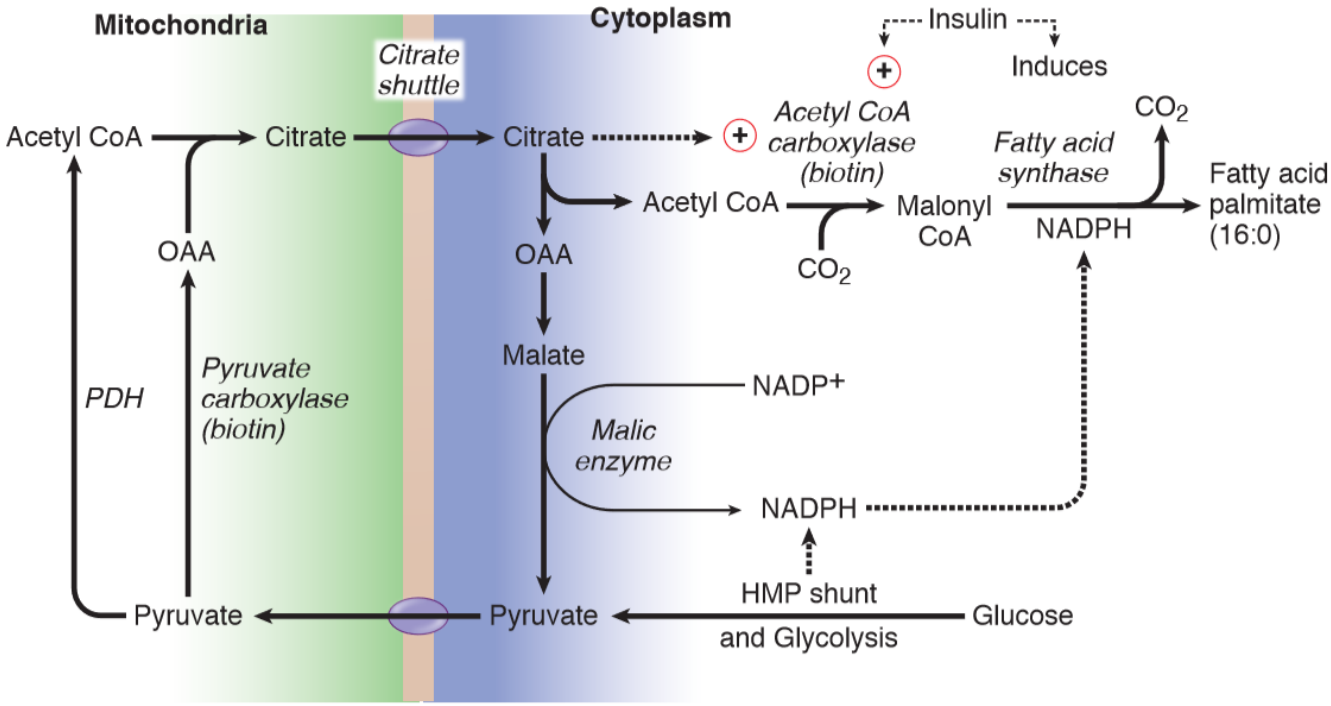
2. Organ location: Many tissues including liver, adipose tissue, lung and kidney.

REQUIREMENTS

❖ This pathway needs the following substrates: **acetyl CoA**, **NADPH+H** and group of enzymes called **fatty acid synthase complex**.

1. Acetyl CoA:

- It is provided mainly by glucose through pyruvate (glycolysis).
- Acetyl CoA is formed in mitochondria and fatty acid synthesis occurs in cytosol.
- The acetyl CoA cannot diffuse to cytosol because mitochondrial membrane is impermeable to it.



2. NADPH+H: It is provided by 3 sources:

a) Pentose phosphate pathway.

b) Action of cytoplasmic (Isocitrate dehydrogenase) on Isocitrate. It is similar to mitochondrial one but it uses $NADP^+$ as hydrogen carrier.

c) Action of malic enzyme on malate to produce pyruvate.

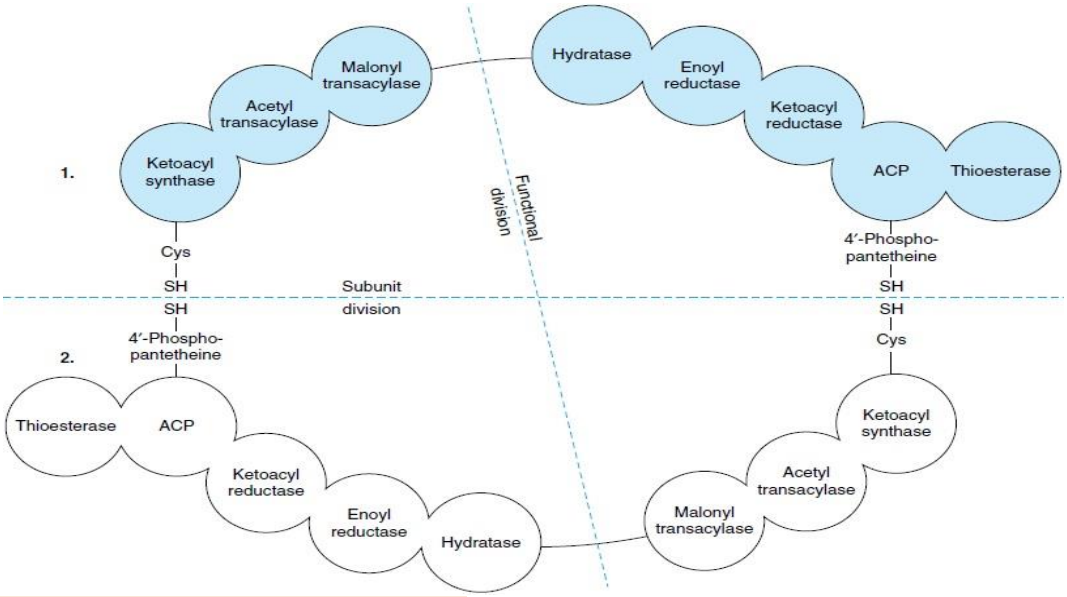
3. Fatty acid synthase complex:

a) This enzyme is a dimer i.e. formed of 2 subunits.

b) Each unit, which is called monomer, contains 7 enzymes and a terminal protein called acyl carrier protein (ACP).

c) Each monomer contains 2 -SH groups, one provided by **phosphopantotheine** and attached to ACP. The other is provided by **cysteine** and attached to the enzyme 3-ketoacyl synthase.

d) The 2 monomers are arranged head to tail, so the -SH group of ACP of one monomer is very close to the - SH group provided by 3-ketoacyl synthase of the other monomer.



REGULATION OF FATTY ACID SYNTHESIS

The key enzyme of cytoplasmic pathway is acetyl CoA carboxylase enzyme.

1- Insulin: Stimulates fatty acid synthesis through:

a) Insulin activates both acetyl CoA carboxylase and pyruvate dehydrogenase [PDH]

b) Insulin stimulates also the transport of glucose into cells.

c) Insulin inhibits Lipolysis.

2- Glucagon and epinephrine: Inhibits fatty acid synthesis through cyclic AMP

- and it also stimulates Lipolysis

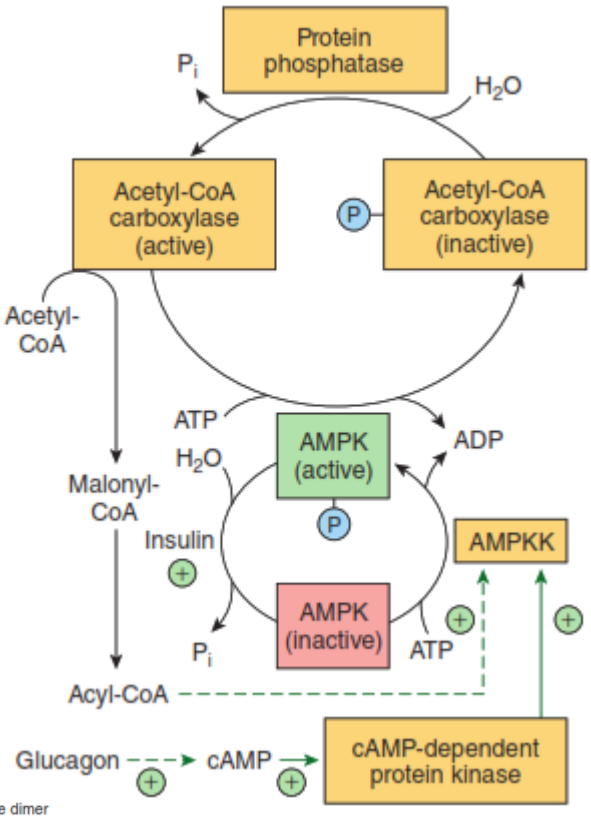
3- Long chain acyl CoA: Inhibits Fatty acid synthesis through:

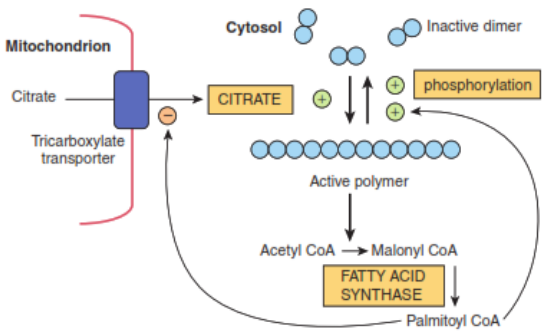
a) It inhibits allosterically acetyl CoA carboxylase.

b) It inhibits transport of citrate from mitochondria to cytosol.

c) It inhibits pyruvate dehydrogenase (PDH).

4- Citrate: stimulates fatty acid synthesis through stimulation of acetyl CoA carboxylase.

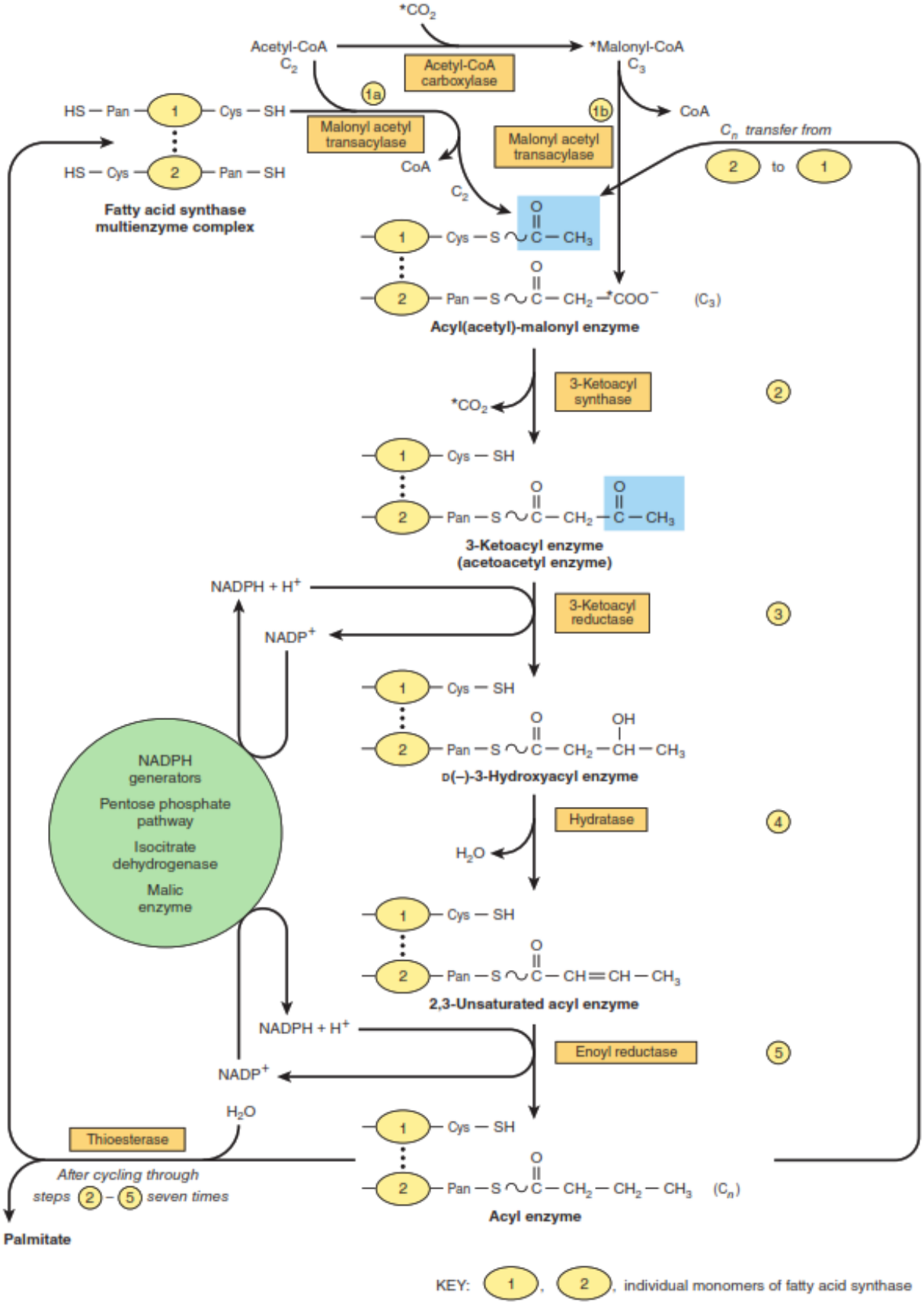




STEPS OF CYTOPLASMIC PATHWAY

- **Carboxylation of acetyl CoA to form malonyl CoA:** (committed step in the pathway).

a) Malonyl CoA is synthesized from acetyl CoA by acetyl CoA carboxylase in the presence of biotin and ATP.



	F.A synthesis	F.A oxidation
Organ location	Mainly liver	Mainly liver and muscles
Intracellular location	Cytosol	Mitochondria
Nutritional state	After meals	Fasting
Hormonal stimulation	Insulin	Glucagon
Carrier of acetyl acyl group between cytosol and mitochondria	Citrate (mitochondria to cytosol).	Carnitin (cytosol to mitochondria)
Active carriers	> Acyl carrier protein > CoASH	> CoASH
Coenzyme	$NADP^+$	NAD^+
Two carbon donor	Malonyl CoA	Acetyl CoA
Activator	Citrate	
Inhibitor	Fatty acyl CoA (inhibits acetyl CoA carboxylase)	Malonyl CoA (inhibits Carnitine acyl transferase)
Product of pathway	Palmitate	Acetyl CoA

MICROSOMAL PATHWAY FOR F.A. SYNTHESIS

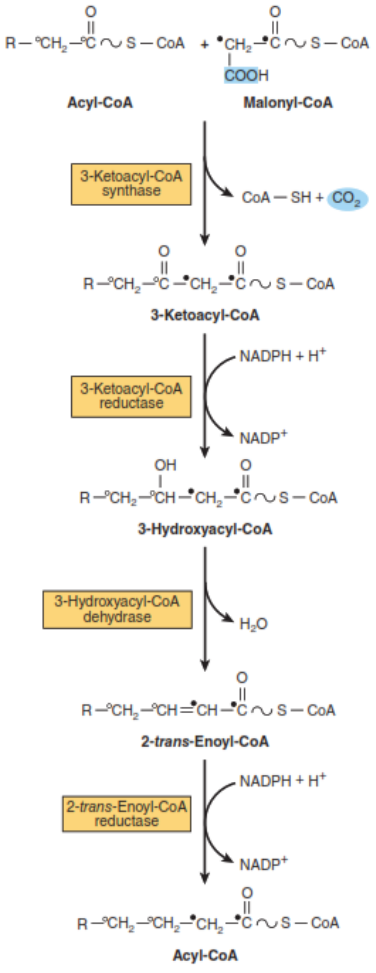
- This is probably the main site for the **elongation** of existing long chain fatty acid molecules i.e. production of fatty acids longer than 16 carbon atoms.

A. The elongated molecules (C10-C16) are derived from:

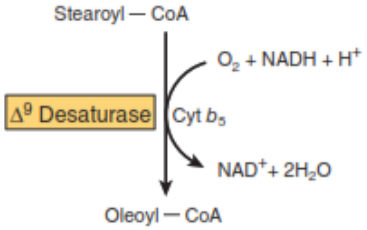
1. **Palmitate:** by cytoplasmic pathway.
2. **Fatty acids of diet.**

B. The microsomal pathway needs malonyl CoA as acetyl donor and $NADPH+H^+$ as coenzyme.

C. Function: This system becomes active during **myelination** of nerves in order to provide C22 and C24 fatty acids which are present in sphingolipids.



SYNTHESIS OF UNSATURATED F.A



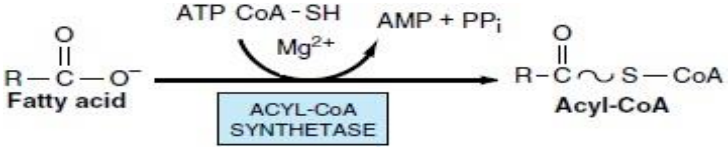
Lipogenesis

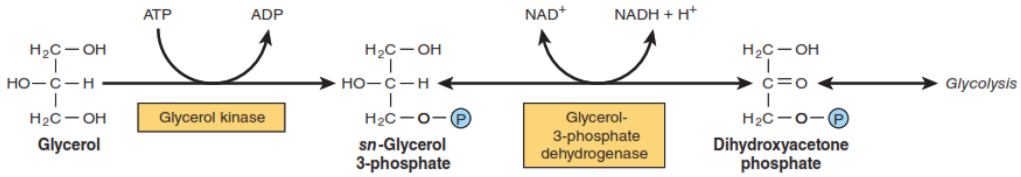
DEFINITION

synthesis of triacylglycerols from fatty acids (acyl CoA) and glycerol (glycerol-3-phosphate).

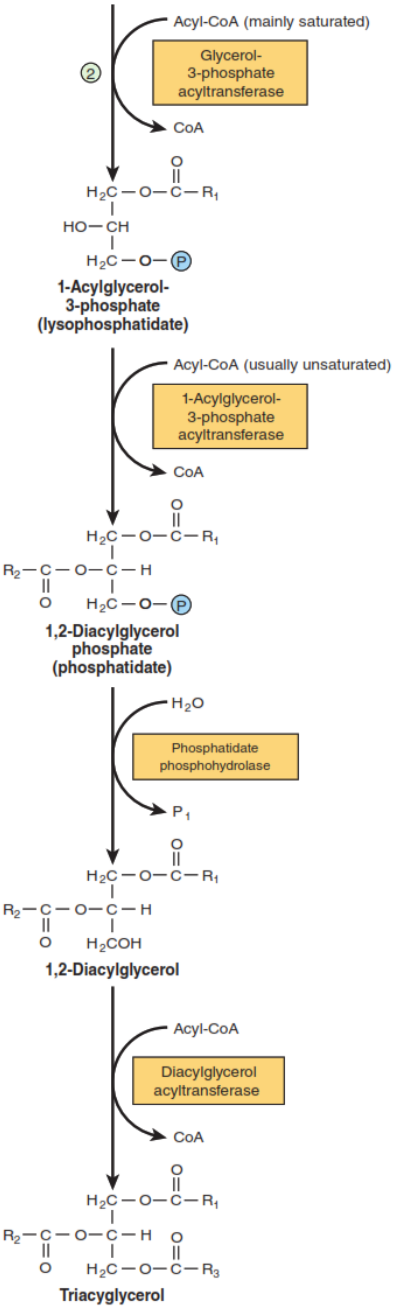
STEPS

1. Activation of fatty acids into fatty acyl CoA





2. Synthesis of glycerol phosphate
   a) In liver, kidney, intestine, and lactating mammary glands:
      Glycerol phosphate is formed from
      Glycerol by glycerokinase or from glucose through glycolysis.
   b) In muscles and adipose tissue:
      glycerokinase is deficient. In these tissues glycerol phosphate is formed from glucose (through glycolysis).
3. Synthesis of triacylglycerol: by reaction between acyl CoA and glycerol phosphate.



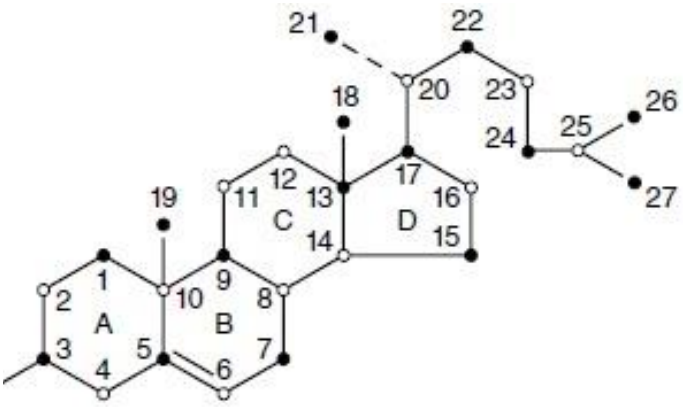
REGULATION OF LIPOGENESIS

1. After meal, lipogenesis is stimulated: Insulin is secreted which stimulates glycolysis. Glycolysis supplies dihydroxyacetone phosphate that converted into glycerol phosphate in adipose tissue.
2. During fasting lipogenesis inhibited: as anti-insulin hormones e.g. glucagon is secreted. These inhibit lipogenesis and stimulate Lipolysis.

METABOLISM OF CHOLESTEROL

STRUCTURE

- Cholesterol is an animal sterol.
- It is a solid alcohol having group at C_3



SOURCES OF CHOLESTEROL

A. Endogenous: Cholesterol is formed in the body almost in all nucleated cells from Acetyl-COA (about 700 mg/day).

B. Exogenous: Cholesterol occurs only in food of animal origin such as egg yolk, meat, liver and brain. Diet supplies about 400 mg/day.

SYNTHESIS OF CHOLESTEROL

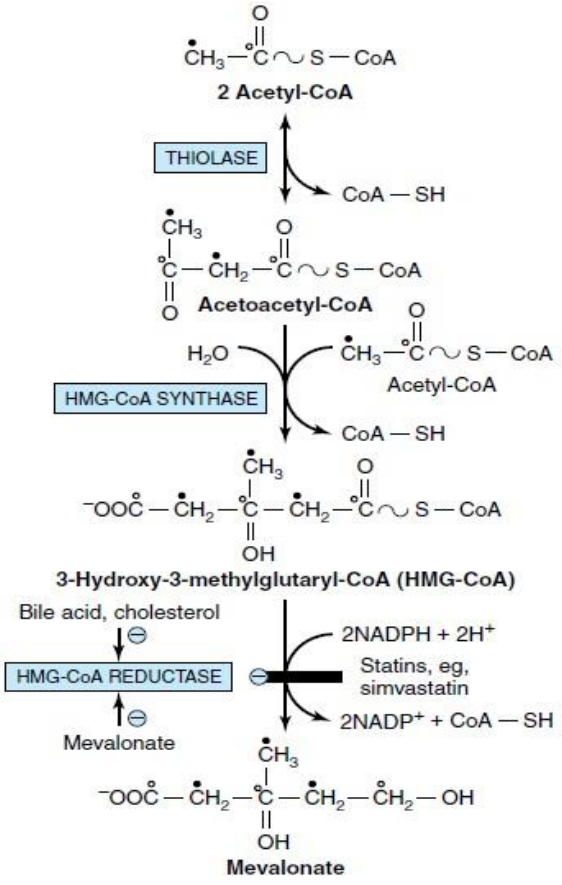
A. Location:

1. Intracellular location: Cytosol.
2. Organ location: a) Liver is the major
   b) Other tissues e.g. intestine, adrenal cortex, gonads and skin.

B. Precursor: Acetyl CoA.

C. Steps:

1. Formation of acetoacetyl CoA: by condensation of two molecules acetyl CoA:
2. Conversion of acetoacetyl CoA to mevalonate
3. Conversion of mevalonate to cholesterol.

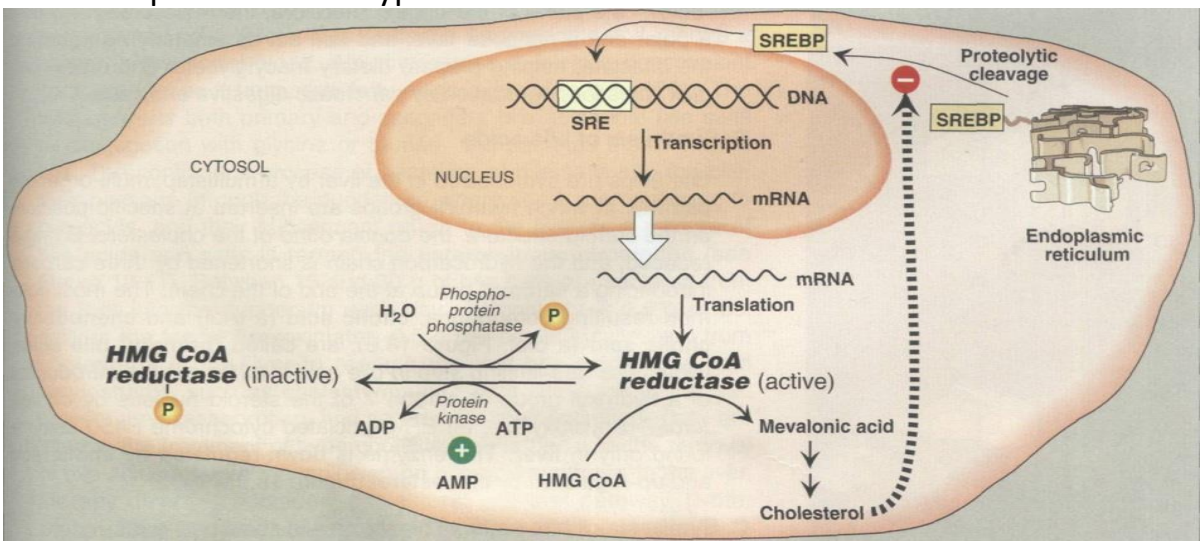


REGULATION OF CHOLESTEROL SYNTHESIS

HMG COA reductase the key enzymes for cholesterol synthesis. It is present in two forms: **active dephosphorylated** and **inactive Phosphorylated**. It is Regulated through:

1. Feedback inhibition: Cholesterol acts as feedback inhibitor of HMG COA reductase enzyme. Thus, it decreases more cholesterol synthesis.
2. Feedback regulation: Cholesterol (either synthesized by the cell or reaching it from diet) inhibits HMG COA reductase gene. this **decreases** transcription and synthesis of HMG CoA reductase.
3. Hormonal regulation:
   - **a) Glucagon:** Inhibits HMG CoA reductase.
   - **b) Insulin:** Stimulates HMG CoA reductase.
4. Inhibition by drugs:

   Lovastatin and **mevastatin** are drugs, which inhibit HMG CoA reductase by reversible competitive inhibition. They are used to decrease plasma cholesterol levels in patients with hypercholesterolemia.



FUNCTIONS OF CHOLESTEROL

it is important for:

1. **It enters in the structure of everybody cell particularly:**
   a) Cell membranes.
   b) In nervous tissue.
2. **Synthesis of steroid hormones.**
3. **Synthesis of bile salts.**
4. **Synthesis of vitamin D3.**

EXCRETION

- **One** gram daily → - ½ as such with bile. - ½ converted to bile.
- Some cholesterol is synthesized by intestinal cells and modified by bacteria before excretion. Bacterial enzymes reduce cholesterol into **coprostanol**, excreted in feces

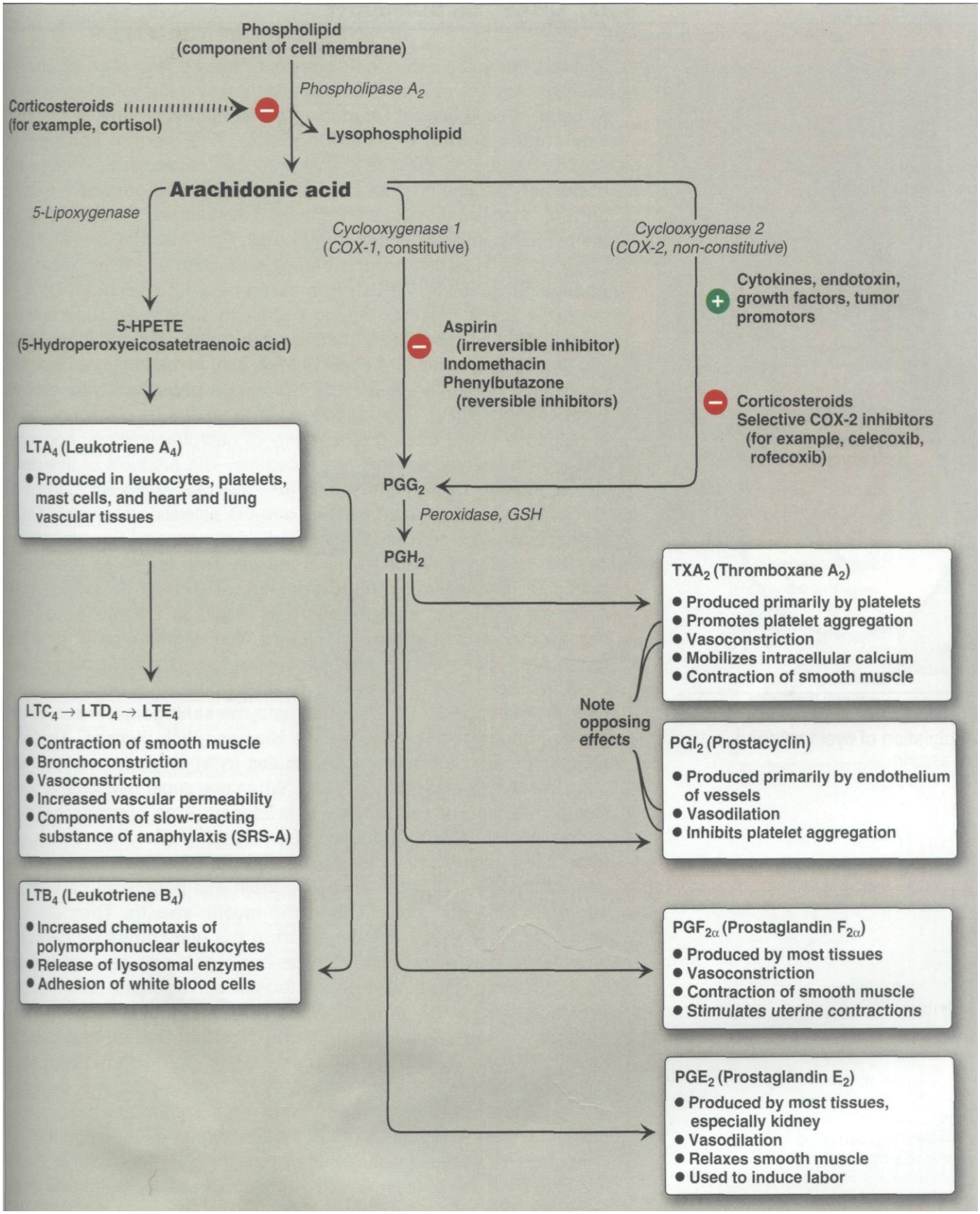
PLASMA CHOLESTEROL

A. Cholesterol present in plasma is either free or esterified (cholesteryl ester).

1. **Total** plasma cholesterol: 140 —220 mg/dl.
2. **Free** plasma cholesterol: 26 — 126 mg/dl.

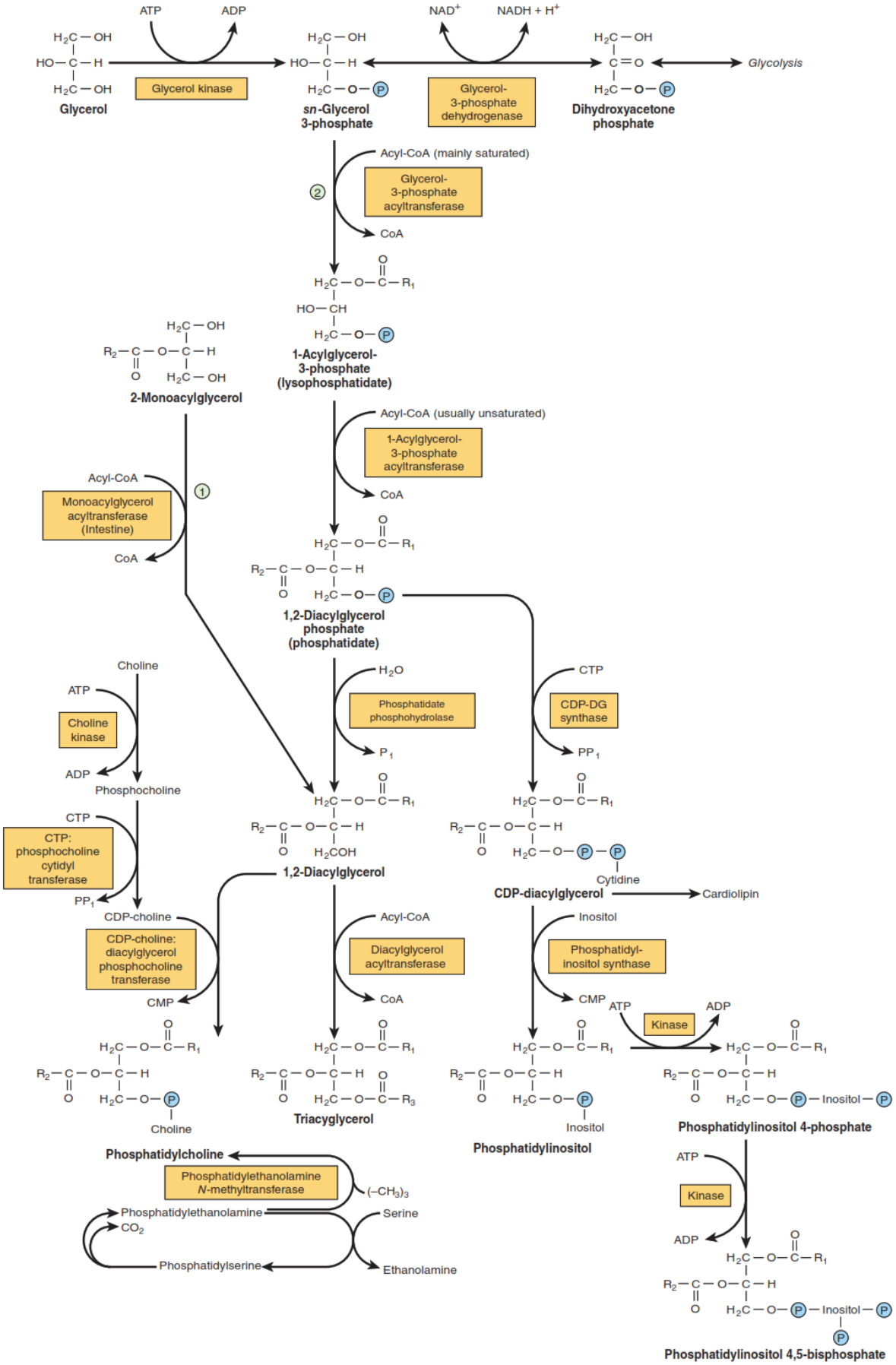
Hypercholesterolemia	Hypocholesterolemia
Definition: It is increased plasma cholesterol concentration above 220 mg/dl.	**Definition:** It is decreased plasma cholesterol concentration below 140 mg/dl
- Diet rich in carbohydrate, cholesterol - diabetes mellitus - Obesity - Kidney affection (nephrotic syndrome) - Hypothyroidism as thyroxin stimulates conversion of cholesterol to bile acids. - Obstructive jaundice - familial Hypercholesterolemia	- Fasting → ↓ insulin - Unsaturated fatty acid diet - Liver diseases. - Hyperthyroidism - Chronic infection

EICOSANOIDS

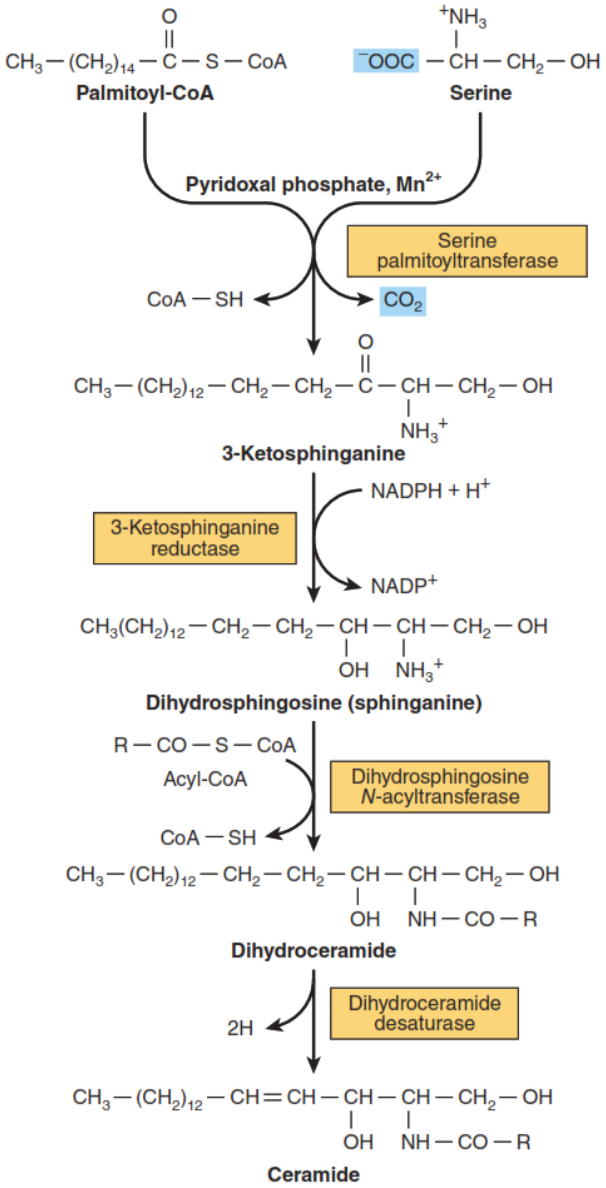


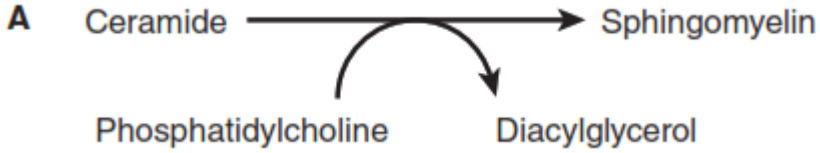
METABOLISM OF CONJUGATED LIPIDS

SYNTHESIS OF GLYCEROL PHOSPHOLIPIDS



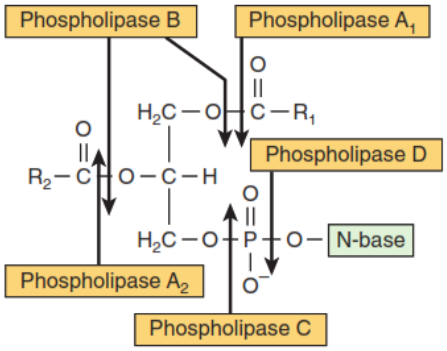
SYNTHESIS OF SPHINGOPHOSPHOLIPIDS





Degradation of phospholipids

- **Phosphoglycerides** are degraded by Phospholipases A1, A2, C and D.



- **Sphingomyelin** is degraded by lysosomal enzymes, sphingomyelinase its deficiency leads to a disease called Niemann Pick disease.
  - It is characterized by **enlarged liver and spleen** and **death at early life**
- **Plasma enzyme called LCAT** (lecithin cholesterol acyl transferase) can act upon second fatty acyl CoA of converting it into lysolecithin.

Lecithin + Cholesterol —LCAT→ **Cholesterol ester + lysolecithin**

FUNCTIONS OF PHOSPHOLIPIDS

- Phospholipids enter in the structure of cell membrane.
- Phospholipids containing Choline (e.g. lecithin) act as neurotransmitters. They also act as methyl donors in transmethylation reaction.
- Phospholipids act as **lipotropic factors** i.e. prevent accumulation of fat in liver and hence prevent fatty liver.
- Dipalmityl lecithin acts as **surfactant** in the lungs. It prevents adherence of alveolar wall. Its deficiency leads to respiratory distress syndrome in premature babies
- Cephalin has a role in **coagulation** mechanism.
- Lipositol (Phosphatidyl Inositol) acts as precursor for **Inositol triphosphate**. That acts as **2nd messenger**, mediating action of some hormones inside target cells.
- Phospholipids in bile make cholesterol **soluble**. Their deficiency leads to cholesterol gallstones.

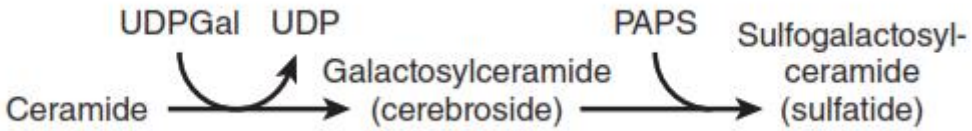
METABOLISM OF GLYCOLIPIDS (SPHINGOLIPIDS):

- Glycolipids are lipid containing carbohydrates
- They also contain sphingosine and one fatty acid. They differ from each other according to the type of carbohydrate content.

SYNTHESIS OF CEREBROSIDES

They Contain galactose.

1. Synthesis of sphingosine 2. Formation of ceramide. 3. Activation of galactose



DEGRADATION OF CEREBROSIDES

is by glucocerebrosidase its deficiency leads to a disease called Gaucher's disease.

- It is characterized by **mental retardation** and **enlarged liver and spleen** in children,

LIPIDOSIS:

- Errors of phospholipids and sphingolipids metabolism:
- These are a group of diseases in which there is abnormal accumulation of Phospholipids and glycolipids in nervous tissue. They are common in children.

They are characterized by:

1. Deficiency of specific lysosomal enzymes responsible for degradation of sphingolipids
2. Accumulation of sphingolipids in tissues leads to their enlargement e.g. liver and spleen enlargement
3. Mental retardation is present in many diseases
4. The most common diseases are Gaucher's disease and Niemann Pick diseases.

Disease	Enzyme Deficiency	Lipid Accumulating[1]	Clinical Symptoms
Tay-Sachs disease	Hexosaminidase A	Cer—Glc—Gal(NeuAc)—GalNAc G_{M2} Ganglioside	Mental retardation, blindness, muscular weakness.
Fabry's disease	α-Galactosidase	Cer—Glc—Gal—Gal Globotriaosylceramide	Skin rash, kidney failure (full symptoms only in males; X-linked recessive).
Metachromatic leukodystrophy	Arylsulfatase A	Cer—Gal—OSO_3 3-Sulfogalactosylceramide	Mental retardation and psychologic disturbances in adults; demyelination.
Krabbe's disease	β-Galactosidase	Cer—Gal Galactosylceramide	Mental retardation; myelin almost absent.
Gaucher's disease	β-Glucosidase	Cer—Glc Glucosylceramide	Enlarged liver and spleen, erosion of long bones, mental retardation in infants.
Niemann-Pick disease	Sphingomyelinase	Cer—P—choline Sphingomyelin	Enlarged liver and spleen, mental retardation; fatal in early life.
Farber's disease	Ceramidase	Acyl—Sphingosine Ceramide	Hoarseness, dermatitis, skeletal deformation, mental retardation; fatal in early life.

LIPOPROTEINS

CHYLOMICRONS METABOLISM

1-Site of synthesis: intestinal mucosal cells

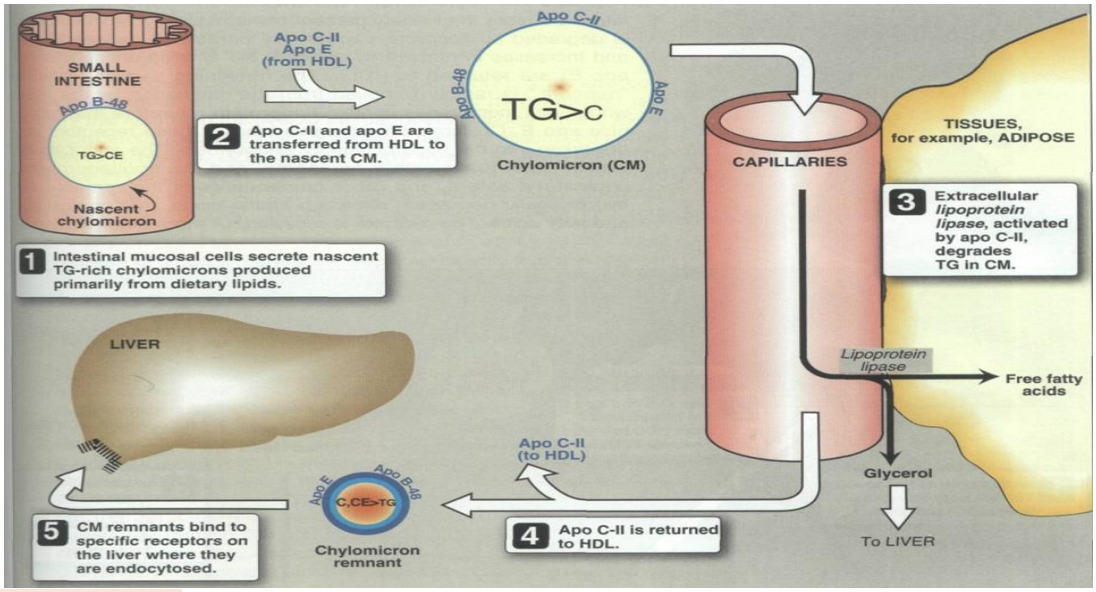
2-Functions: transport dietary lipids from intestine to peripheral tissues.

3-Structure:

a- Main lipids: triacylglycerols. Chylomicrons contain also cholesterol, phospholipids and fat soluble vitamins.

b- Proteins: (2%), apo B_{48} and receives apo CII and apo E from **HDL**.

4-catabolism: TG are hydrolyzed by lipoprotein lipase (which is activated by apo CII). The remaining parts are **chylomicron remnants**, which are then taken up by the liver. Hepatocyte receptors can recognize apo B_{48} and apo E.



VLDL METABOLISM

1- Site of synthesis: Liver.

2- Functions: transport lipids mainly TG from liver to peripheral tissues.

3- Structure:

a- Main lipids: triacylglycerols. It contains also cholesterol, phospholipids.

b- Proteins: (12%), apo B_{100} and receives apo CII and apo E from **HDL**.

5- **Catabolism:** TG are hydrolyzed by lipoprotein lipase (that is activated by apo CII). The remaining parts are IDL, which are then converted into LDL by transferring phospholipids, apo CII and apo E to HDL.

LDL METABOLISM

1-SITE OF SYNTHESIS: circulation from VLDL.

2-FUNCTION: LDL particles provide cholesterol to peripheral tissues.

3-STRUCTURE:

a- Lipid contents: cholesterol, cholesterol esters and phospholipids.

b- Protein contents: (22%), apo B_{100}

4-CATABOLISM:

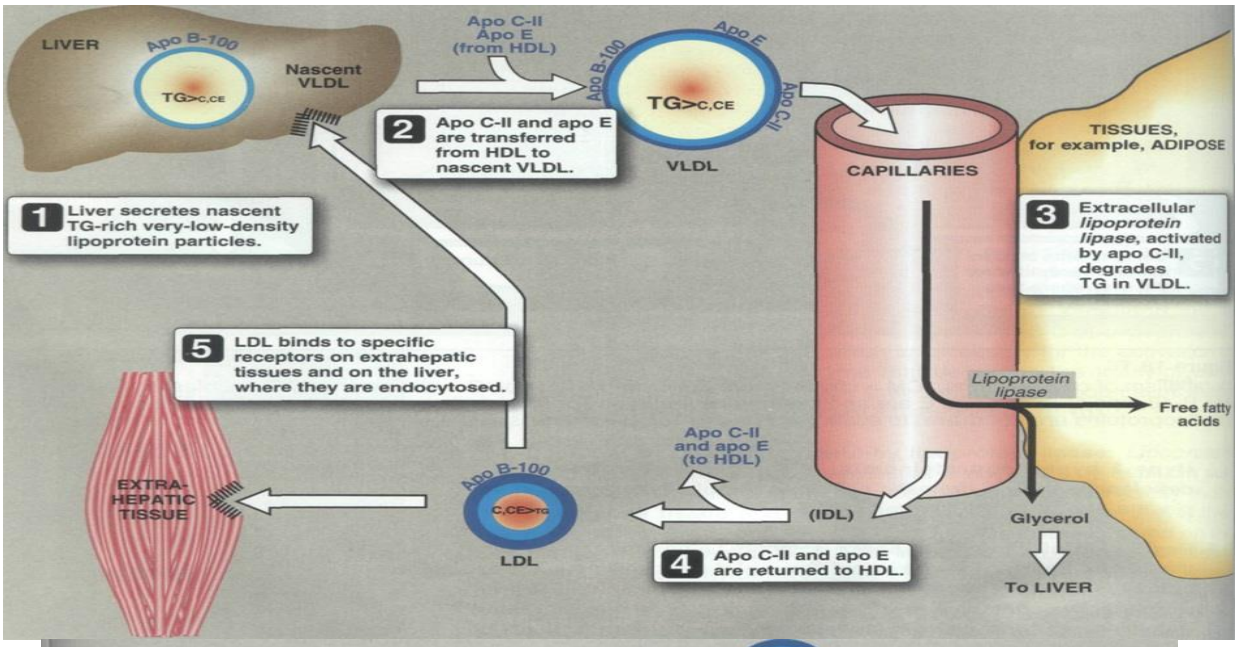
LDL apo B_{100} are recognized by tissue receptors. After binding with receptors, the LDL are internalized by endocytosis. Inside cells LDL are separated from receptors and hydrolyzed by lysosomal enzymes releasing cholesterol, amino acids, fatty acids and phospholipids.

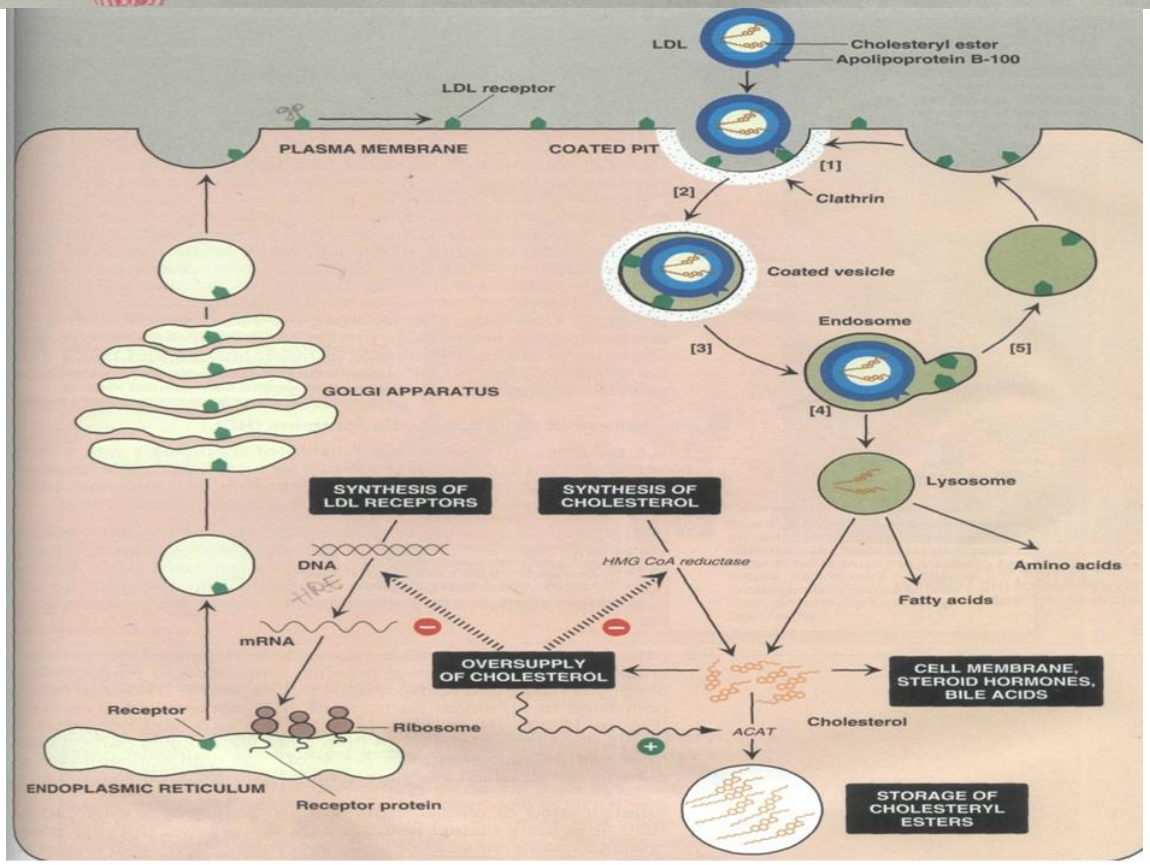
***If the cell contains oversupply of cholesterol from LDL, HDL or chylomicron remnants, the cholesterol amount can be decreased by:**

a- Inhibition of HMG-CoA reductase → Inhibition of cholesterol synthesis.

b- Stimulation of **ACAT** enzyme → Cholesterol ester.

c- Inhibition of synthesis of **LDL receptors** → inhibition of LDL uptake by cells





HDL METABOLISM

1-Site of HDL synthesis: Liver.

2-Functions:

a- Contain Apo CII, which activates **lipoprotein lipase** that hydrolyzes TG.

b- Remove cholesterol from peripheral tissues and esterified it by **LCAT** enzyme → Cholesterol esters.

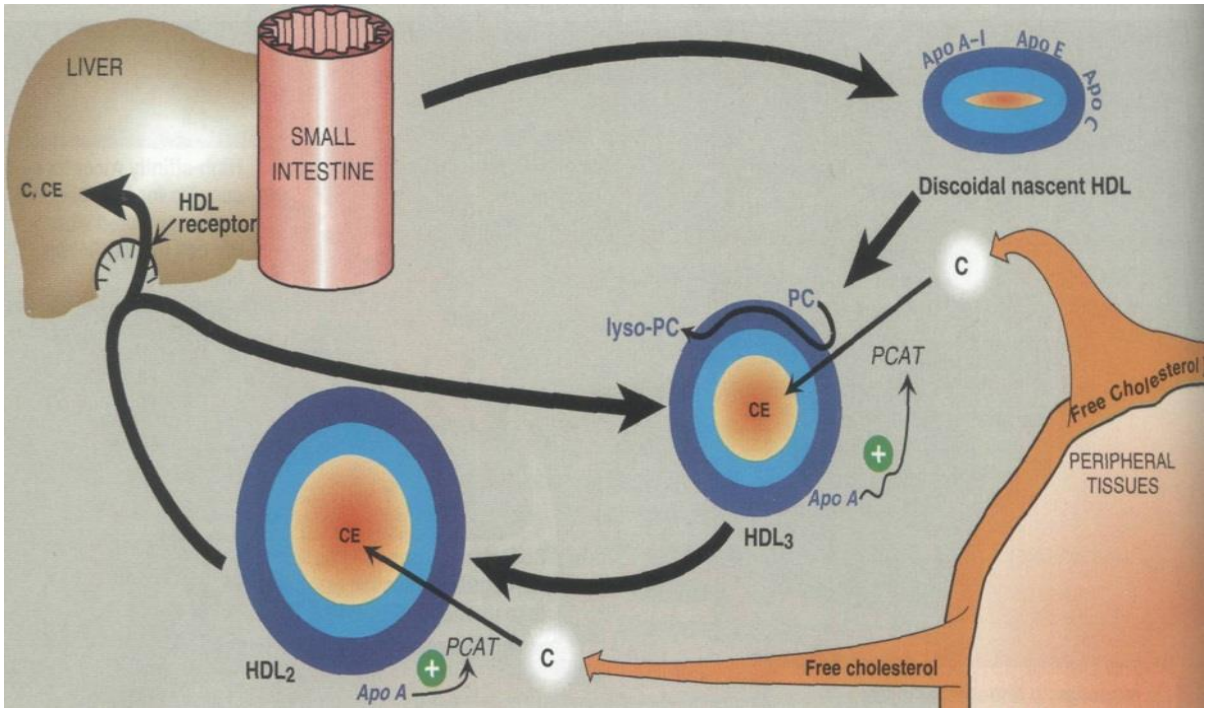
c- Carry cholesterol esters to VLDL & chylomicrons to the liver.

3-Structure:

a- Main lipids: cholesterol (free and esterified) and phospholipids, mainly lecithin.

b- Proteins: (50%), apo A-1 (which activates **LCAT**), apo CII (which activates **lipoprotein lipase** and E (which is recognized by hepatic receptors)

4-Catabolism: HDL accepts unesterified cholesterol from peripheral tissues. Then HDL particles (by **LCAT** enzyme) esterify cholesterol into cholesterol esters. Then HDL is taken up by the liver cells where Cholesterol esters are released inside them to be utilized in the formation of lipoproteins or excreted in bile.



APOPROTEINS (APOLIPOPROTEINS)

- **Definition:** These are proteins (globulins) present in association with plasma lipids to form lipoproteins.
- **Functions**:
  1. Apolipoproteins form with lipids water-soluble compounds, so they help transport of lipids between tissues.
  2. Some apoproteins activate certain enzymes e.g. ***Apo C II*** activates lipoprotein lipase and ***Apo-A1*** activates LCAT.
  3. They act as liganda (connection) for interaction of lipoprotein with their receptors in tissues i.e. receptors of lipoproteins in tissues can recognize lipoproteins through their apoproteins e.g. apo B100 for LDL receptors

Classification

	LIPOPROTEIIIS	COMMEIIT
Apo A-I	HD L	*Activator of LCAT *Legend for HDL-receptors
Ape B- 100	LDL-YLDL-IDL	*synthesized by liver *Legend for LDL-receptcrs
Ape B- 48	Chylomicrons - chylomicron remnants	*Synthesized by intestine *Legend for chylomicron remnant receptors in Liver.
Ape C II	Chylomicrons-VLDL-HDL	Activator of lipoprotein lipase
Ape D	HDL	May act as lipid transfer protein.
Ape E	Chylomicrons - Chylomicron remnants – VLDL - HDL	* Legend for chylomicron remnant receptors in liver. * Legend for LDL receptors in tissues.

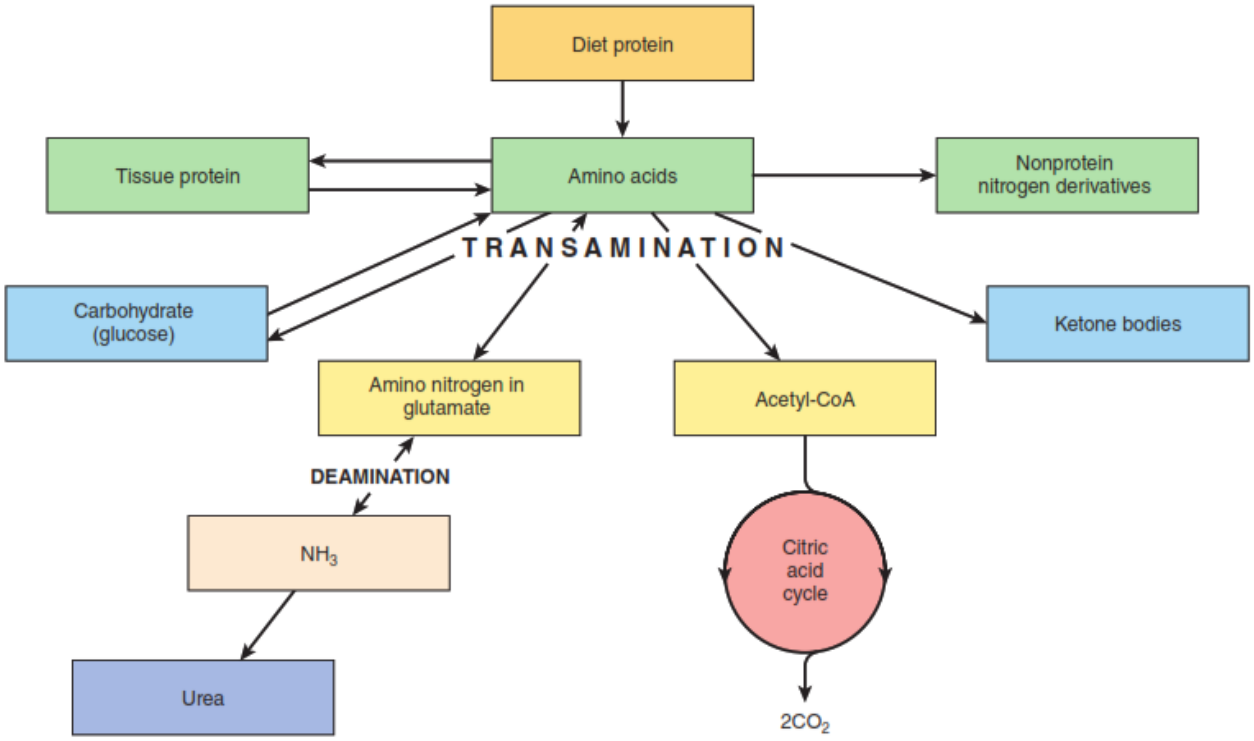
CHAPTER 7

Proteins Metabolism

CHAPTER MAP

ptn Metabolism

CATABOLIC PATHWAYS	Ammonia And Urea	Amino Acid Metabolism
1- Transamination. 2- Deamination 3- Transdeamination 4- Decarboxylation.	1- Source and fate of ammonia. 2- Ammonia intoxication 3- Urea cycle	1- Glycine 2- Phenyl alanine 3- Tyrosine 4- Tryptophan 5- Rest of A.A



GENERAL CATABOLIC PATHWAYS OF AMINO ACIDS

In human, the end products of protein and amino acids catabolism are ammonia and urea. They are produced through the following catabolic pathways.

- Transamination.
- Deamination: Oxidative - Non oxidative - Hydrolytic.
- Transdeamination: i.e. transamination followed by deamination.
- Decarboxylation.

DEAMINATION

DEFINITION

It is the removal of amino group from amino acids in the form of ammonia (NH_3).

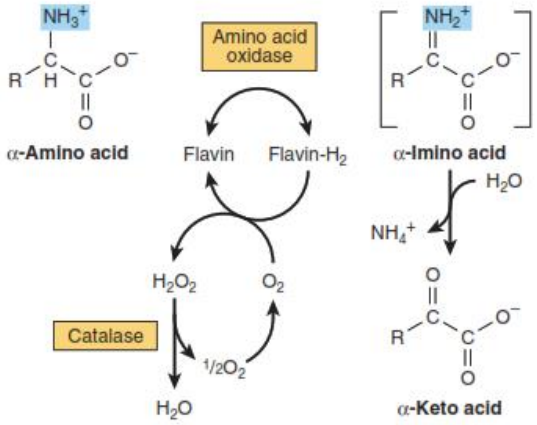
SITE

Mostly liver and kidney.

TYPES

1- Oxidative, 2-NON-Oxidative, 3-hydrolytic deamination.

1- Oxidative



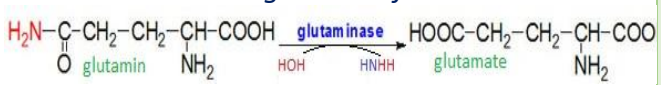
	L. a.a oxidase	D.a.a oxidase	L-glutamate dehydrogenase
Carrier	FMN	FAD	NAD or NADP.
Site	Liver & kidney	Liver & kidney	Most tissues.
Activity	Low	highly active	highly active
Reversibility	Irreversible	irreversible	Reversible

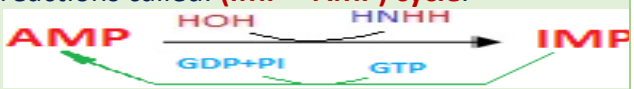
2- Non-oxidative deamination

- For **hydroxy** amino acids e.g. serine, threonine, without removal of (H^+)
- Its coenzyme is: pyridoxal phosphate (**PLP**).

3- Hydrolytic deamination

For glutamine and asparagine	For adenosine monophosphate (AMP):
- Enz → glutaminase & asparaginase *- Glutaminase is present in kidney.* *- It produces ammonia (NH_3), which is used in regulation of acid base balance*	- In **muscles**, AMP is hydrolytically deaminated into inosine monophosphate Producing (**NH_3**). This occurs by a series of reactions called: **(IMP – AMP) cycle**.





TRANSAMINATION

DEFINITION

- It is the transfer of amino group from α-amino acid to α-ketoacid to form a new α-amino acid and a new α-ketoacid.

MECHANISM

1. By enzymes called transaminases (or amino transferases) catalyze transamination.
2. Pyridoxal phosphate (PLP = active vitamin B6) is the coenzyme of all transaminases.
3. For all amino acids except: (lysine, threonine, proline and hydroxyproline).
4. All transamination reactions are reversible.
5. Present either in cytosol or in both cytosol and mitochondria of most tissues.
6. Among all transaminases, 3 are present in most mammalian tissues and they are of clinical importance. These are: ALT, AST and glutamate transaminase.

Enzymes	Site	Function
Alanine transaminase (ALT): **or** Glutamate pyruvate transaminase (GPT).	cytosol	ALT is an enzyme that catalysis the transfer of amino group from Alanine to α-Ketoglutarate to form glutamate and pyruvate.
Alanine + α-Ketoglutarate ⟷ (ALT, PLP) **pyruvate + glutamate**		
Aspartate transaminase (AST): **or** Glutamate oxaloacetate transaminase (GOT).	cytosol and mitochondria	catalysis the transfer of amino group from Aspartate to α-Ketoglutarate to form Glutamate and oxaloacetate.
Aspartate + α-Ketoglutarate ⟷ (AST, PLP) **oxaloacetate + glutamate**		
Glutamate transaminase:		Catalysis the transfer of amino group from any amino acid to α-Ketoglutarate.

Role of pyridoxal phosphate in transamination

Acts as an **intermediate** carrier of amino group.

Functions of transamination

1. **Transfer** of amino group (-NH2) from most amino acids to α-Ketoglutarate to form **glutamate** then deaminated to give **ammonia**.
2. Transamination is important for formation of **non-essential amino acids**.

Diagnostic importance of transaminases (ALT and AST): normally intracellular

↑ **ALT** → liver diseases

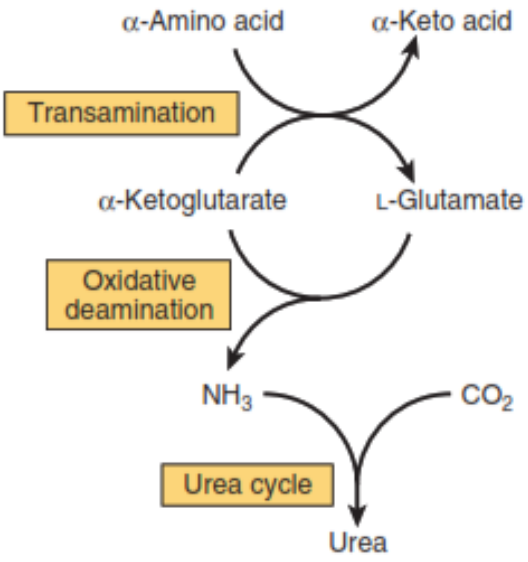
↑ **AST** → heart muscle (myocardial infarction), skeletal muscle or kidney.

↑ **Both** → damage of liver cells with escape of hepatic enzymes into blood.

TRANSDEAMINATION

Definition:

- It is **transamination** of most amino acids with α-Ketoglutarate to form glutamate, Then glutamate is **deaminated** to give ammonia (NH_3).
- It is the main pathway by which amino group (NH_2) of most amino acids is released in the form of ammonia (NH_3).



DECARBOXYLATION

Definition:

removal of **CO_2** of amino acids produces the corresponding amines.

Functions:

- Some amines have important biologic functions: e.g.

1. Histamine (from histidine) is vasodilator.

2. γ-Amino butyric acid (from glutamate) is neurotransmitter.

Destruction of amines

- The resulting amines are further oxidized -after carrying out their functions by amine oxidase enzymes.
- Amine oxidase enzymes are two types: monoamine oxidase and diamine oxidase. Both contain **Pyridoxal phosphate** and **copper** as prosthetic groups.

e.g. ??

AMMONIA (NH_3)

DEFINITION

- Ammonia is a toxic substance especially to the **central nervous system**.
- Any ammonia formed in the peripheral tissue must be moved to the liver to be converted into **urea**.
- This maintains ammonia at low level in circulating blood.

BLOOD AMMONIA

- Blood contains traces of ammonia: 10- 80 ug/dI.

Sources and fate of ammonia

SOURCES	FATE
1. Transdeamination of amino acids: In Many tissues, particularly liver 2- Glutamine: The kidneys form ammonia from glutamine by glutaminase enzyme. Most of this ammonia is used in regulation of Acid base balance. 3. Purines and pyrimidines metabolism. 4. Various nitrogenous compounds e.g.: monoamines that act as neurotransmitters. 5. In intestine: ammonia is produced by the action of bacterial enzymes on: a) Dietary amino acids. b) Urea secreted into the intestine.	1. Formation of non-essential amino acids: Through Transdeamination. 2. Formation of glutamine: a) Glutamine synthetase is a mitochondrial enzyme present in many tissues as kidney and brain. b) Glutamine has the following functions: 1) Regulation of acid base balance: glutamine is deaminated by glutaminase, releasing ammonia again. Ammonia is used in regulation of acid base balance by the kidneys. 2) Removes the toxic effect of ammonia In brain: Ammonia + Glutamate → Glutamine. 3) Glutamine is the source of: N_3 and N_9 of purines bases. 4) Glutamine is used in detoxication of phenyl acetic acid (a toxic substance). 3. Formation of urea: It is the main pathway by which the body can get rid of ammonia. 4. Excretion in urine

UREA

DEFINITION

- Urea (H_2N-CO-NH_2) is the main end product of protein (amino acids) metabolism.
- Urea formation is the pathway through which the liver can convert toxic ammonia into non-toxic urea.

SITE OF UREA FORMATION

1. Liver is the only site for urea formation.
2. Then urea is transported in the blood to the kidney to be excreted in urine (urine urea is 20-40 g/day).

PLASMA UREA

1. Plasma urea: is 20-50 mg/dl.
2. **Diagnostic importance** of plasma urea determination:
   a) Measurement of plasma urea is one of the **kidney function tests**.
   b) In kidney diseases as in renal failure, kidney fails to excrete urea → High blood urea concentration (uremia).

UREA FORMATION

It is also called **Krebs'** Henseleit cycle.

SITE: Liver.

1. The first two reactions occur in mitochondria where other reactions occur in cytosol.
2. **Six amino acids share in urea cycle**: ornithine, citrulline, arginosuccinate, Aspartate. And Arginine. The **6th** one is **N-acetyl glutamate** that acts as allosteric activator of Carbamoyl phosphate synthase I.

STEPS

1. Formation of Carbamoyl phosphate:

a) This reaction occurs in mitochondria.

b) It needs **CO_2** (a product of citric acid cycle), ammonia (a product of deamination of glutamate) and phosphate (from ATP).

c) This reaction is catalyzed by **Carbamoyl phosphate synthase I.** It needs magnesium (Mg) ions, manganese (Mn^{++}) and N-acetyl glutamate as activators.

d) 2 ATP molecules are used in this reaction, one to provide phosphate and the other to supply energy.

2. Formation of citrulline:

a) This reaction also occurs in mitochondria.

b) Carbamoyl phosphate reacts with **ornithine**, in the presence of ornithine **transcarbamoylase** enzyme producing citrulline.

c) Citrulline then passes to **cytosol.**

d) Ornithine is regenerated with each turn of urea cycle**.**

3. Formation of arginosuccinate:

a) Citrulline reacts with **Aspartate** in the **cytosol** to form **arginosuccinate.**

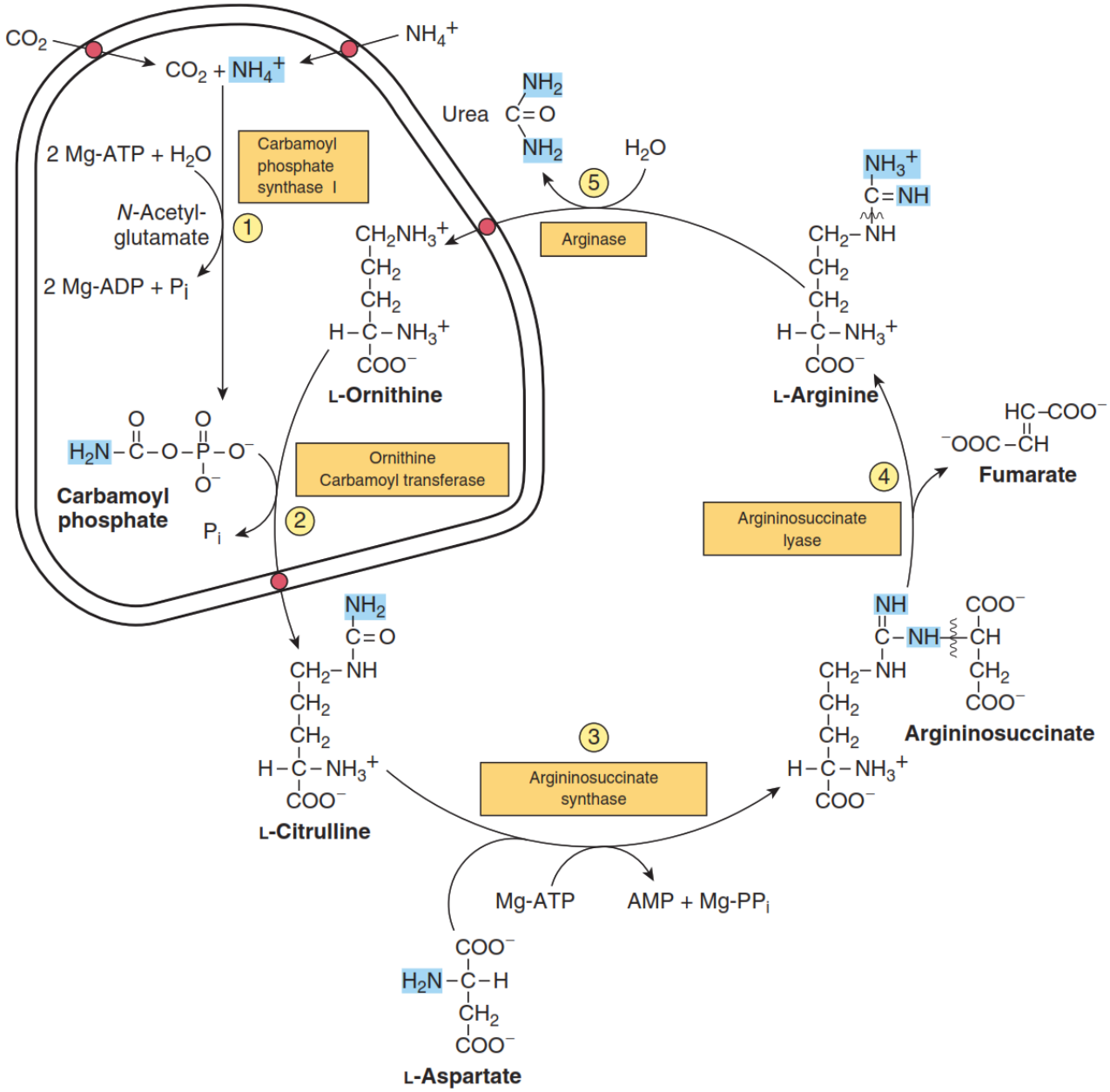
4. Cleavage of arginosuccinate:

a) It is cleaved into **Arginine** and **Fumarate.**

5. Cleavage of Arginine into ornithine and urea:

a) Ornithine then passes to the **mitochondria** to start a new cycle**.**

b) Urea passes to the blood to be excreted by the kidney in urine**.**



- **Three ATP molecules** and **four high-energy phosphate bonds** are utilized in the reactions.
- **Sources of different atoms of urea (H_2N-CO-NH_2):**
  1. **1st Nitrogen atom:** from ammonia.
  2. **Carbon atom:** from CO_2.
  3. **2nd Nitrogen atom:** from Aspartate.

AMMONIA INTOXICATION

Definition: Excess ammonia which is toxic to the central nervous system.

Symptoms: Include:

A. Flapping tremors, slurring speech, blurring vision and vomiting in infancy.

B. High concentration of ammonia may cause **coma** and **death**.

Types and causes of hyperammonemia

Acquired hyperammonemia

1- **Liver cell failure**: The diseased liver cells cannot convert ammonia into urea.
2- **Renal failure**
3- **Shunt operation** between portal and systemic circulation.
4- **Collaterals** between portal and systemic circulation due cirrhosis of liver by bilharziasis , hepatitis etc.

Inherited hyperammonemia

Result from genetic deficiency of one of five enzymes of urea cycle → Failure to synthesize urea → Hyperammonemia during the first week after birth → Mental retardation.

Type I	Car. Ph. synthetase I.
Type II	Transcarbamoylase.
Ctrullinemia	Arg.succ.synthetase
Argininosuccinuria	Arginosuccinase
Argininemia	Arginase

Mechanism of ammonia intoxication:

- At normal blood ammonia level, any ammonia reaches the brain incorporated into glutamine formation by glutamine synthetase enzyme.
- In cases of hyperammonemia, ammonia reacts not only with glutamate, but also with **α-Ketoglutarate** by **glutamate dehydrogenase** enzyme. This depletes **α-Ketoglutarate** which is an essential intermediate of citric acid cycle → Decrease in **ATP** and **energy** production → symptoms of ammonia intoxication → **coma**.

FATE OF α -KETO-ACIDS

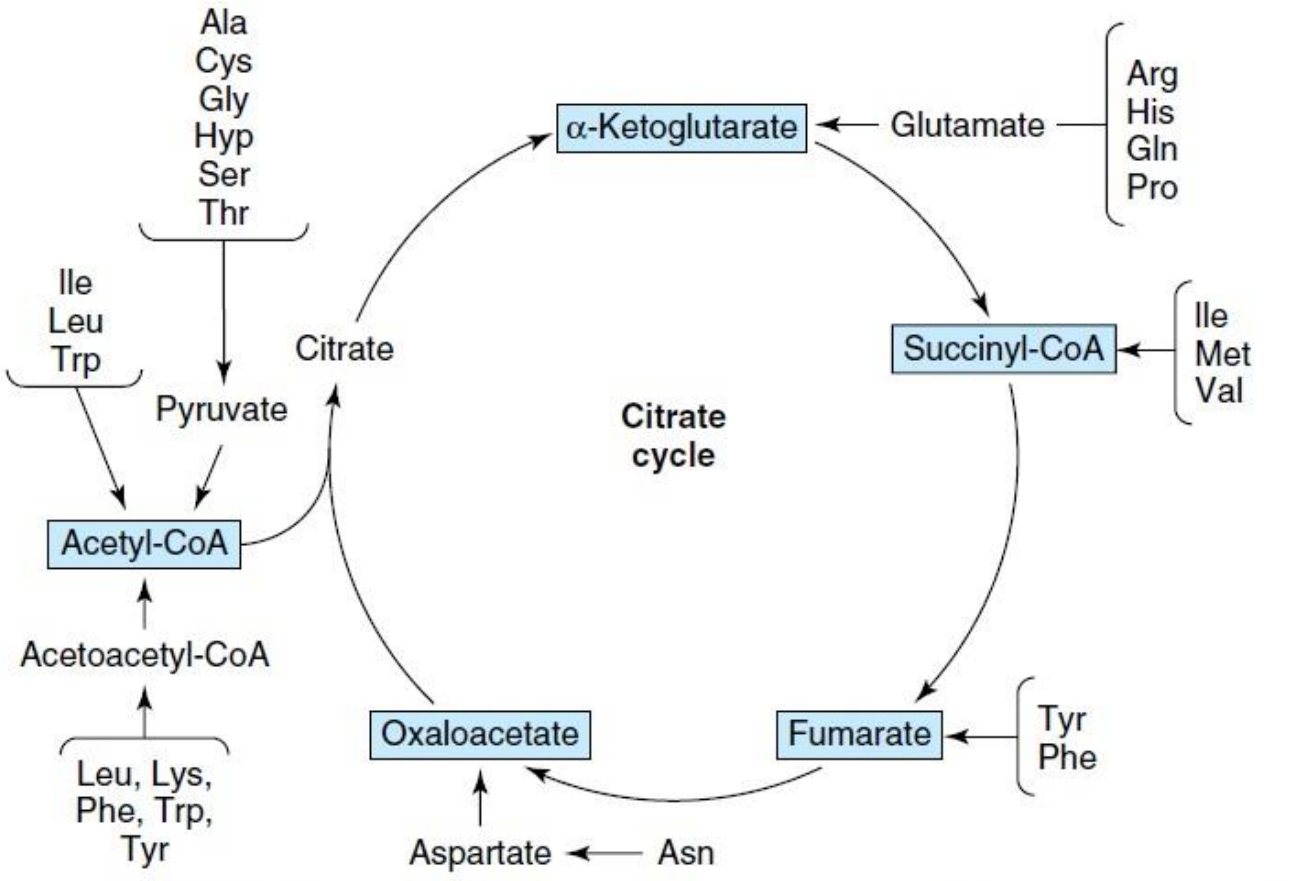
- The α-ketoacid (the carbon skeleton) remaining after the removal of the amino group **(NH_2)** by transamination and deamination of amino acids may undergo:

A. Reamination: by ammonia (**NH_3**) to form again the corresponding amino acid (by **glutamate dehydrogenase**).

B. Catabolized to form seven products: pyruvate, acetyl CoA, acetoacetyl CoA, Fumarate, oxaloacetate, α-Ketoglutarate and Succinyl CoA.

C. These products enter different pathways which lead to:

1. Synthesis of **glycogen** or **glucose.**
2. Synthesis of **lipids.**
3. Complete oxidation into **CO_2** and **H_2O**.

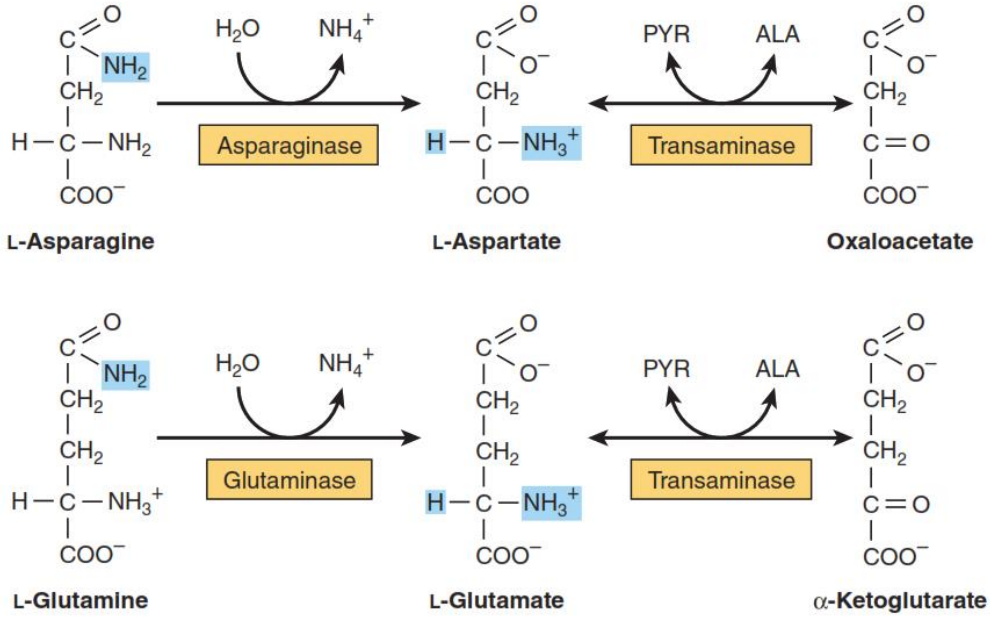


Amphibolic intermediates formed from the carbon skeletons of amino acids.

METABOLIC CLASSIFICATION OF AMINO ACIDS

	Glucogenic	Glucogenic and Ketogenic	Ketogenic
Nonessential	Alanine Arginine Asparagine Aspartate Cysteine Glutamate Glutamine Glycine Proline Serine	Tyrosine	
Essential	Histidine Methionine Threonine Valine	Isoleucine Phenyl-alanine Tryptophan	Leucine Lysine

Note



CONVERSION OF AMINO ACIDS TO SPECIALIZED PRODUCTS

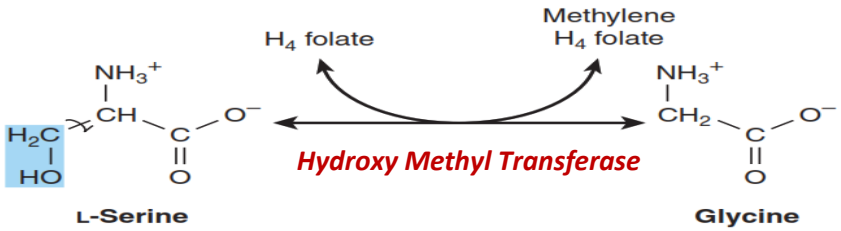
GLYCINE

- **Glycine** is **non-essential** - **glycogenic** amino acid.

SYNTHESIS AND FATES

1- **DENOVO:** **CO2 + NH2 + H2O** ⟶ (*Glycine synthase*; ⟵ *Glycine cleavage system*) **GLYCINE**

2- **SERINE:**



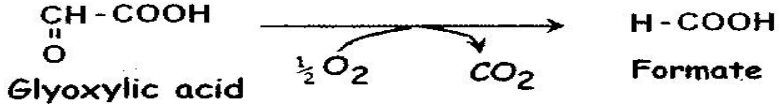
3- **THERIONINE:** **THERIONINE** ⟶ (*Threonine aldolase*) **GLYCINE + Acetaldehyde**

4- **GLYOXILIC ACID:** **BY REAMINATION**

Functions Glycine is the precursor for:

- Heme - Hippuric acid - Glutathione - Glyoxylic acid
- Purine bases - Bile salts - Collagen -Creatine - Serine - Neurotransmitter

1. **Heme:** is the pigment, which combines with globin protein to form hemoglobin.
   - Glycine reacts with Succinyl CoA to form a substance called amino levulonic acid (**ALA**) a reaction needs pyridoxal phosphate. ALA is finally converted to heme.
2. **Hippuric acid:**
   - Glycine conjugates with the toxic compounds like **benzoate** (an additive used to preserve foods) to form the **non-toxic** hippuric acid. This occurs in the **liver**.
3. **Glyoxylic acid**
   - **Synthesis:** Glyoxylic acid is formed from glycine by 2 mechanisms:
     oxidative deamination and **transamination**:
   - **Fate of Glyoxylic acid:**
     a) Formation of formate: (by **oxidative decarboxylation**).



     b) Formation of glycine: By Reamination (**transamination**).

- Primary hyperoxaluria:

- **Def:** It is a metabolic disease **ccc** by excessive excretion of **Oxalate** unrelated to dietary intake of oxalate. This leads to formation of urinary oxalate stones.
- **Complication:** This condition usually ends by death in early life from either renal failure or hypertension.
- **Causes:** failure of conversion of Glyoxylic a. into formate or glycine. leads to **oxalate** formation.

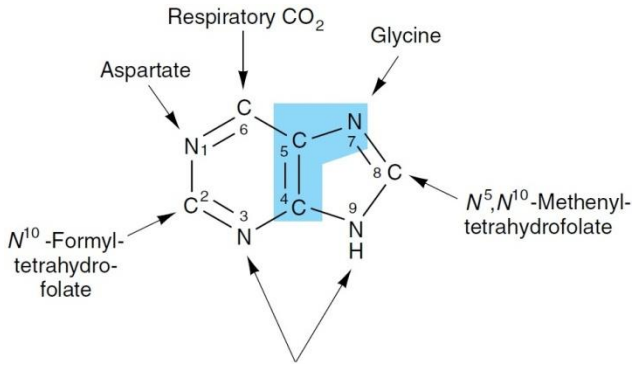
- Glycinuria

- **Def:** It is a rare **dominant x-linked disease ccc** by excess urinary excretion of glycine.
- **Complication:** It leads to formation of **oxalate renal stones**.
- **Causes:** is due to defect in renal tubular reabsorption of glycine.

4. **Glutathione:** It is also called "**γ-glutamyl, cysteinyl glycine"**.

- **Structure:** Glutathione is a **Tripeptide** formed of three amino acids: glutamate, cysteine and glycine.
- **Synthesis:** It is synthesized in two Glutathione steps catalyzed by (γ-glutamyl cysteine synthetase and glutathione synthetase).
- **Forms of glutathione:**
  - **Two** Forms are present: **reduced** (G-SH) and **oxidized** (G-S).
  - *-**SH** group indicates the sulfhydryl group of the cysteine and it is the most active part of the molecule.
- **Functions of glutathione:**
  1. **Defense mechanism** against certain toxic compounds (Detoxification).
  2. **Absorption of amino acid:** glutathione has a role in transport of amino acids across intestinal cell membrane..
  3. **Protect against cell damage and hemolysis of RBCs:** Glutathione breakdown the hydrogen peroxide (H_2O_2) which causes cell damage and hemolysis.
  4. **Activation of some enzymes.**
  5. **Inactivation of insulin hormone.**

5. **Bile salts:**
   - These are sodium and potassium salts of glycocholic acid.
   - Glycine is conjugated to cholic acid to form glycocholic acid.
6. **Purine bases:**
   - Carbon atoms NO. **4, 5** and nitrogen atom NO. **7** are derived from glycine.



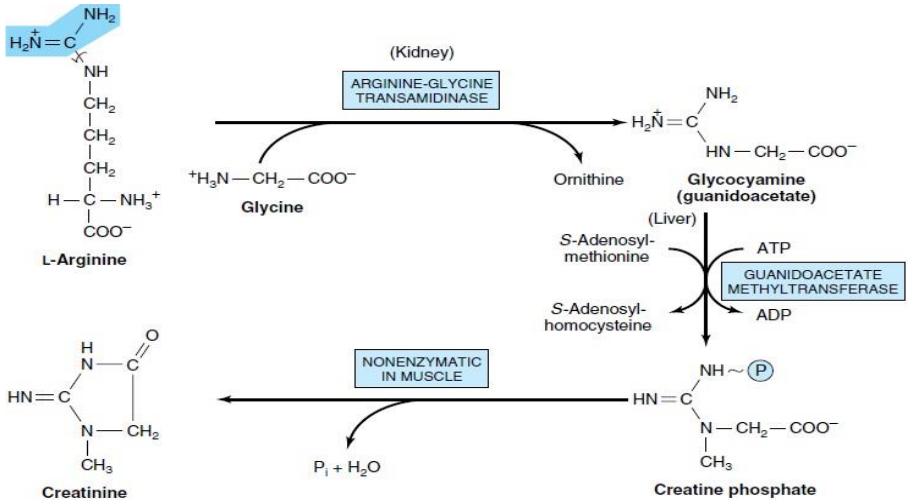
7. **Collagens:**
   - Collagens are the main proteins of **connective tissue**.
   - All collagen types have a **triple helical structure**.
   - Each helix is formed of **3** amino acids.
   - **Glycine** is present at every third position.

8. Creatine (N-methyl-guanidoacetate):

- Synthesis of Creatine: It is synthesized from three amino acids: glycine, arginine, and methionine. This occurs by two reactions in **kidney** and **liver**.

a) In kidney: the first reaction is **transamdination** i.e. transfer of **guanido** group, H_2N-[C=NH]-NH_2 from Arginine to glycine to form guanidoacetate.

b) In liver: the second reaction is **Transmethylation** i.e. transfer of **methyl** group from **S-adenosyl-methionine** to guanidoacetate to form methyl guanidoacetate



- Functions of Creatine:

- Creatine is phosphorylated to Creatine phosphate this occurs in muscles.
- **Creatine phosphate** acts as a **store** of high energy phosphate in muscles and used during muscle exercise (as it can give phosphate to ADP to form **ATP**).

- Creatine kinase enzyme (CK): Also called **Creatine phospho kinase (CPK):**

- This enzyme catalyses the formation of creatine phosphate. Present in **3** isoenzymes

1) CK-MM: from **skeletal muscles** and its serum level is elevated in muscle disease
2) CK-MB: mainly from **heart muscle** and its serum level is elevated in recent myocardial infarction.
3) CK-BB: derived from **brain** and its serum level is elevated in damage of brain cells.

- Degradation of Creatine phosphate → (gives creatinine):

a) Creatine phosphate loses water and phosphate molecules to form a substance called creatinine (= **anhydrous Creatine**).

b) Creatinine is the end product of Creatine metabolism and is normally rapidly removed from the blood and **excreted by the kidney** in urine.

- Diagnostic importance of determination of plasma creatinine:

a) Estimation of plasma creatinine (0.6 - 1.2 mg/dl) is used as kidney function test.

b) High blood creatinine (and urea) levels are sensitive indicators of renal failure.

9. Serine:

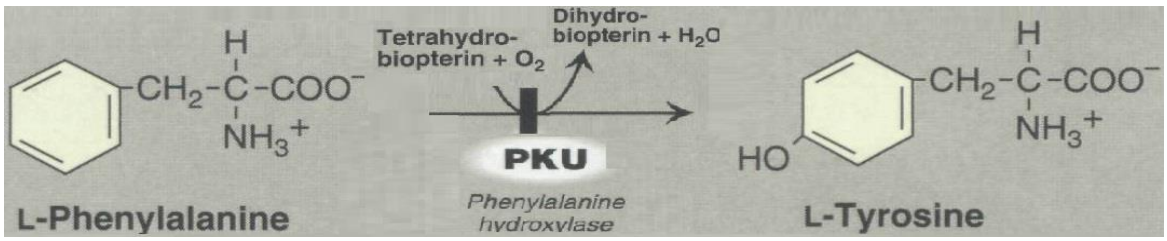
- Methylene H_4 folate is used as **donor** of **one carbon** fragment (-CH_2OH).
- It gives this carbon to glycine to form serine. The reaction is reversible.

10. Neurotransmitter: acts as an inhibitory transmitter in spinal cord and medulla

11. Catabolism of glycine: by enzyme called: glycine **cleavage** system

PHENYLALANINE

- **Phenylalanine** is a **Ketogenic and glycogenic essential** amino acid.
- **Functions:** phenylalanine is the precursor for **Tyrosine**. In liver as follows:



- This reaction needs phenylalanine hydroxylase enzyme and tetrahydrobiopterin as coenzyme. This results in the formation of dihydrobiopterin (DHB) which must be regenerated by dihydrobiopterin reductase enzyme with NADPH + H as coenzyme.
- Deficiency of either **phenylalanine hydroxylase** or **dihydrobiopterin reductase** results in a disease called: **PHENYLKETONURIA.**

- **Definition:** It is inherited deficiency of phenylalanine hydroxylase enzyme.
  Atypical phenylketonuria: deficiency of dihydrobiopterin reductase enzyme.
- **Effects (**signs and symptoms):
  1) Mental retardation. (By inhibit of pyruvate translocase enzyme)
  2) Increased blood phenylalanine: due to inability to hydroxylate phenylalanine to tyrosine. & converted it to phenylpyruvate and phenyllactate, which excreted in urine.
  3) Failure to walk and talk. **4)** Hyperactivity and tremors.
  5) Failure to grow. **6)** An Intelligence Quotient (IQs) **7)** Skin lesion e.g. eczema.
- **Frequency of phenylketonuria:** is 1 in 10,000 live births.
- **Diagnosis of phenylketonuria:**
  a) Infants are screened at birth (4th day) by measuring blood phenylalanine by a test called **Guthrie test**, a bacterial assay for phenylalanine.
  - **Prevention of phenylketonuria:**
  a) Any infant proved to have abnormal high level of blood phenylalanine, should feed milk containing **very low** amount of phenylalanine.
  b) This regimen of diet is maintained up to 6 years of age when a high concentration of phenylalanine has no longer effect on brain cells.

TYROSINE

- **Tyrosine** is a **Ketogenic and glycogenic non-essential** amino acid.
- **Tyrosine** becomes essential in case of deficiency of **phenylalanine hydroxylase.**

Functions Tyrosine is the precursor for: **CMT**

1- Catecholamines. **2- M**elanin pigments. **3- T**hyroid hormones.

CATECHOLAMINES

These are dopamine, nor-epinephrine and epinephrine.

SYNTHESIS OF CATECHOLAMINES:

They are synthesized from tyrosine at storage sites: **adrenergic neurons** and **adrenal medulla**.

- In neurons: nor-epinephrine and dopamine are synthesized from tyrosine as follows:

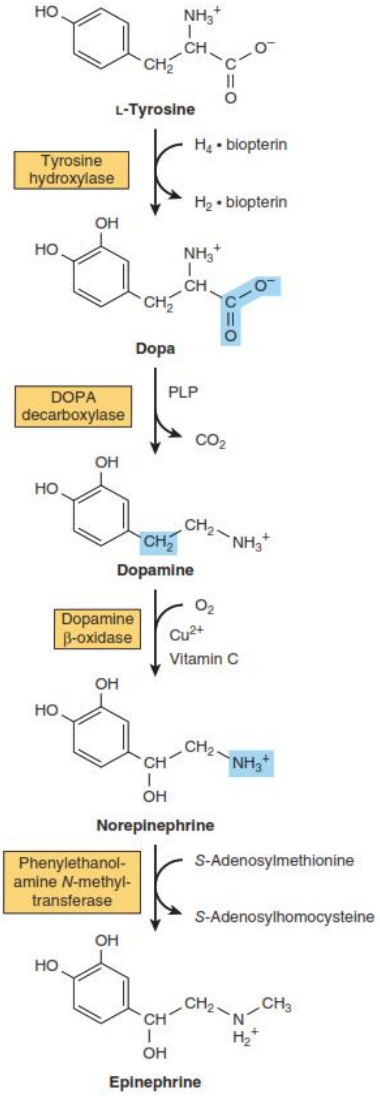
1) Tyrosine is first **hydroxylated** to form 3, 4 dihydrophenylalanine (DOPA).

2) DOPA is then **decarboxylated** to dopamine, which is **hydroxylated** to nor-epinephrine by dopamine hydroxylase.

- In adrenal medulla:

1) Synthesis of catecholamines is similar to synthesis in neurons.

2) In addition adrenal medullary cells, contain phenylethanolamine N-methyltransferase (PNMT). This enzyme catalyzes the conversion of nor-epinephrine to epinephrine [by **Transmethylation**].



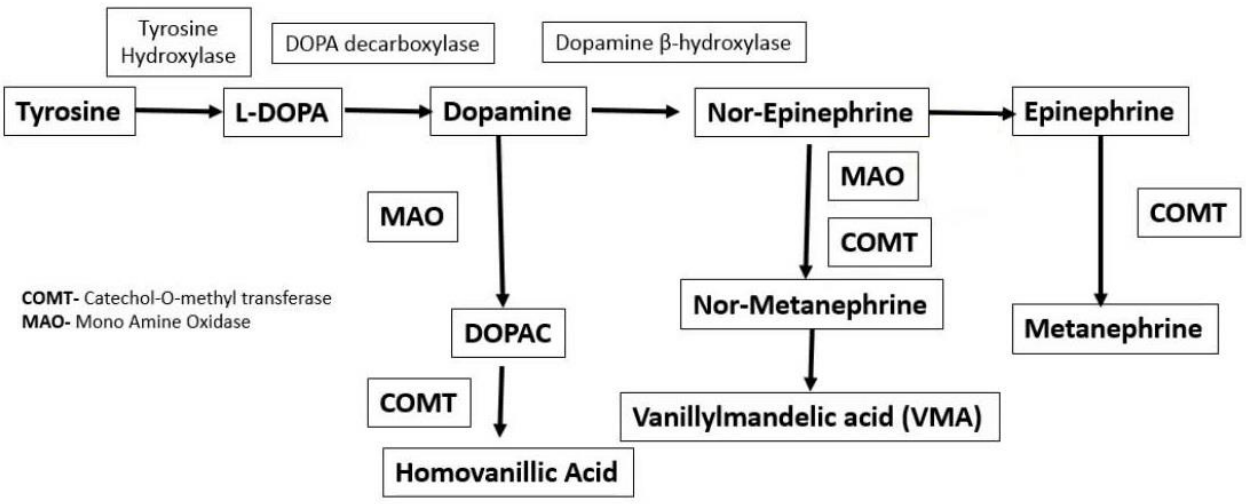
REGULATION OF SYNTHESIS:

Tyrosine hydroxylase is the key enzyme. It is inhibited by feedback inhibition by either **dopamine** or **nor-epinephrine**.

CATABOLISM OF CATECHOLAMINES: by 2 enzymes:

1) Monoamine oxidase (MAO): present mainly in the mitochondria of adrenergic nerve

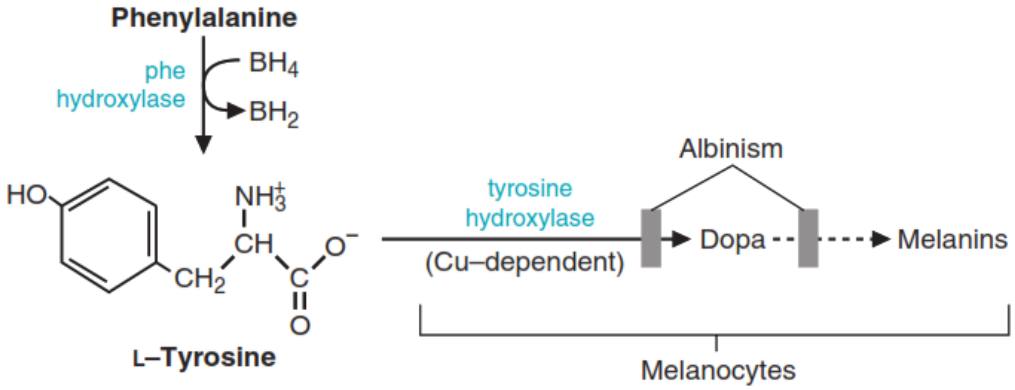
2) Catechol-ortho-methyl transferase (COMT): which is present in all tissues, with high concentration in the liver and kidney, but not found in the nerve endings.



2-MELANIN PIGMENTS

SYNTHESIS OF MELANIN

In the skin, melanins are synthesized in melanocytes (pigment forming cells) by **tyrosine hydroxylase** (tyrosinase) enzyme.



FUNCTIONS OF MELANIN

a) Melanins are pigments present in many tissues particularly in the iris, hair and skin.

b) Melanins are synthesized to protect underlying cells from the harmful effects of sunlight.

3. THYROID HORMONES

SYNTHESIS OF THYROID HORMONES

a) Synthesis and release of T3 and are stimulated by (TSH).

b) TSH secretion is under control of thyrotropin releasing hormone (TRH) which is a Tripeptide hormone produced in the hypothalamus.

- By feedback mechanism: Increased levels of plasma T_3 and T_4 inhibit the secretion of TRH from hypothalamus and TSH from pituitary gland.

STEPS OF THYROID HORMONES SYNTHESIS

1) The thyroid gland contains many follicles, each composed of a shell of single layered cells surrounding a central space filled with glycoprotein called: thyroglobulin (TG).

2) Thyroglobulin contains about 150 tyrosine residues.**3)** Iodide ions (I^-) can be taken up by thyroid cells and oxidized into higher value state (positive ions, I^+). This needs H_2O_2 and thyroid peroxidase enzyme.

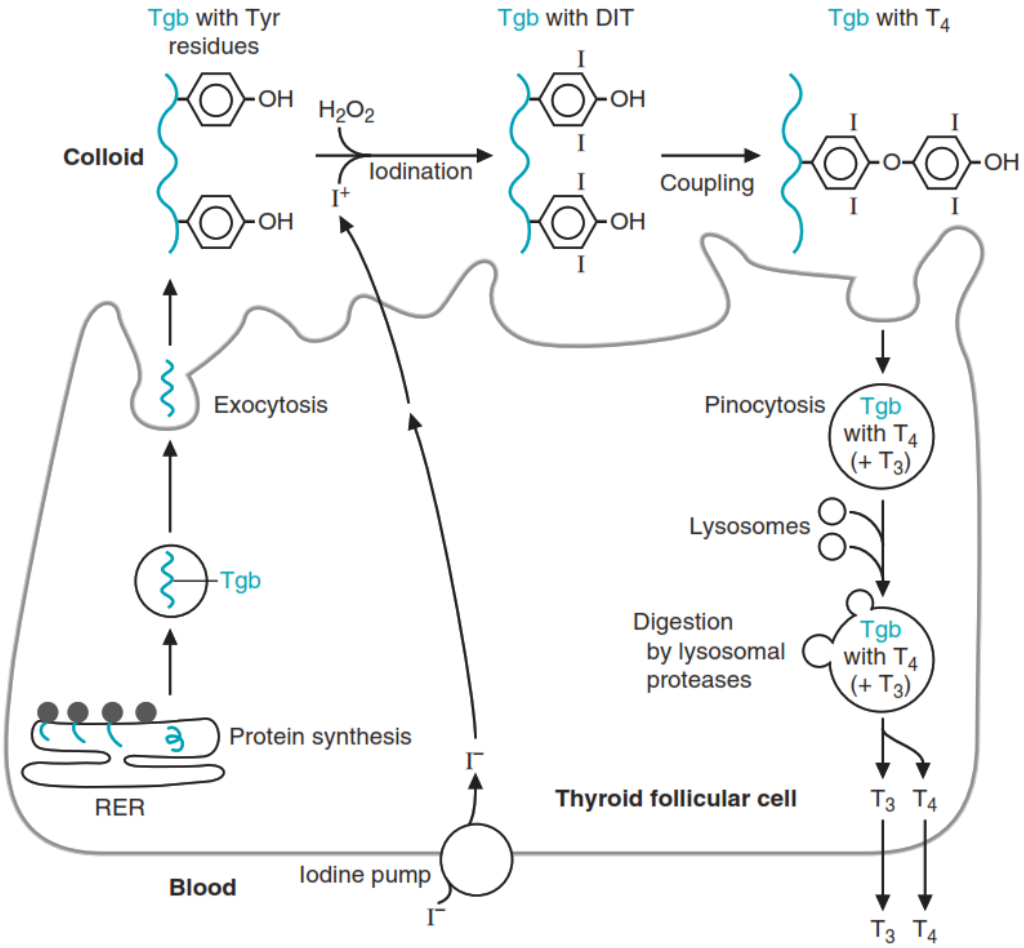
4) I^+ is then incorporated into the tyrosine residues of TG.

5) The resulting Monoiodotyrosine and Diiodotyrosine residues react together to give one of the following compounds:

a. Tetraiodotyrosine {thyroxin, T4}. b. Triiodotyrosine {T3}. c. Reverse {rT}.

6) Both T_3 and T_4 are biologically active, while rT_3 is biologically **in**active.

7) Enzyme hydrolysis of thyroglobulin releases free T_3 and T_4 into the plasma.



FUNCTIONS OF THYROID HORMONES:

a) They increase heat production and oxygen consumption in most tissues through stimulation of ATPase activity.

b) They regulate the growth of long bones (together with growth hormone).

c) They affect protein synthesis through stimulation of DNA in the nucleus of cells.

d) They increase catecholamine effect.

- **Plasma T_3 and T_4:**

a) In the plasma 99.95% of T_3 and T_4 are transported in association with 2 proteins:

1) Thyroxin binding globulin (TBG). **2) Thyroxin binding prealbumin**.

b) About 0.05 % of T_3 and T_4 are Free T3 and T4 "active" hormones in the plasma

Hypothyroidism

- Def: ↓ amounts of free T_3 or T_4.

- Cause: thyroid failure

can be due to disease of the pituitary or hypothalamus.

- The thyroid hormones insufficiency during intrauterine fetal life results in a disease shows **abnormal physical** development and **mental retardation** (cretinism).

Measurement of T3, T4 and TSH must be done for every newly born infant

- If the disease occurs later in life, it is called: (myxodema),

Hyperthyroidism

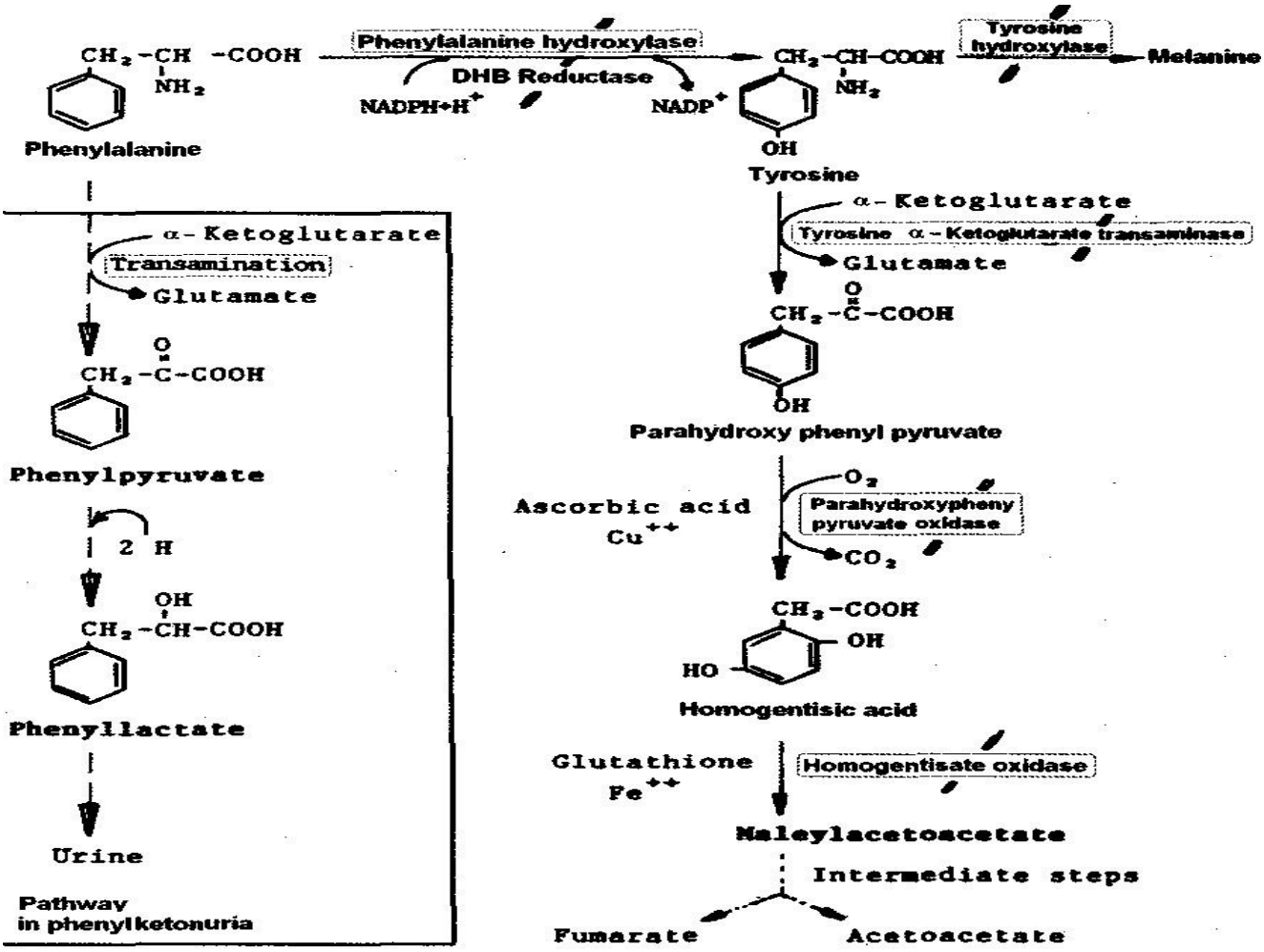
(thyrotoxicosis)

- Def: ↑production of T_3 or T_4

- Cause: Most cases are due to Graves disease which results from the production of antibodies that activate TSH production and in turn produces excessive amounts of T_3 and T_4. These antibodies are called: Thyroid-stimulating IgG (TSI).

CATABOLISM OF PHENYLALANINE AND TYROSINE

The carbon skeletons that have left after the removal of amino groups of both phenylalanine and tyrosine may catabolize to form Fumarate (glycogenic) or acetoacetate (Ketogenic).



INBORN ERRORS OF TYROSINE METABOLISM

1- Hereditary tyrosinemia (tyrosinosis):

- **Def:** It is inability to metabolise **tyrosine** and **p-hydroxy phenylpyruvate**.
- **Cause:** deficiency of tyrosine **α-Ketoglutarate transaminase** and **p-hydroxy-phenylpyruvate oxidase** enzymes
- **Forms of tyrosinemia:**

a) **Acute:** where there is diarrhea, vomiting and failure to grow. Death from liver failure occurs within **7** months.

b) **Chronic:** occurs later in life. **Liver cirrhosis** and **hepatic carcinoma** are common. There is also a mild mental retardation. **For unknown cause methionine level may be high**.

- **Prevention and treatment:**
- Feeding the affected infant and children a diet containing very low levels of tyrosine and phenylalanine (precursor of tyrosine).

2. Alkaptonuria:

- **Def:** benign disease resulting from deficiency of homogentisate oxidase enzyme.
- **Effects:** Homogentisate increases and causes:

a) Deposition in joints causing **arthritis**.

b) Deposition in connective tissue causing generalized pigmentation (**ochronosis**).

c) Excreted in large amounts in urine, that is oxidized in the air giving the **dark urine**

3. Albinism:

- **Def:** hereditary deficiency of tyrosine hydroxylase enzyme in melanocytes. **- Effects:** defective synthesis of melanin pigments. Eye, skin and hair are affected.
- **Types of albinism:** according to the site affected:

a) Eye: ocular albinism. **b) Skin:** cutaneous albinism.

c) Eye and skin: oculo-cutaneous albinism.

Tryptophan

- It is **glycogenic and ketogenic essential** amino acid.
- **Functions:** Tryptophan is the precursor of: **SMNI**

1. Serotonin. **2. M**elatonin. **3. N**iacin (nicotinic acid) **4.**Indole and skatole.

SEROTONIN

Also called 5-hydroxytryptamine.

SYNTHESIS OF SEROTONIN

- Tryptophan is hydroxylated in a reaction similar to that of phenylalanine. The product **5-hydroxytryptophan** is decarboxylated to **serotonin**.

- **Storage sites of secretion & Functions of serotonin::**

a) Hypothalamus and brain stem → Neurotransmitter: it is stimulatory one.

b) Pineal gland (body) → regulate circadian rhythm.

C) Argentaffin cells in intestinal mucosa→ Contraction of smooth muscle fibers.

d) Platelets → Vasoconstriction.

CATABOLISM OF SEROTONIN

- Serotonin undergoes oxidative deamination by monoamine oxidase (MAO). The resulting compound, 5-hydroxyindol acetic acid is excreted in urine.
- Certain substances can inhibit MAO enzyme e.g. iproniazide drugs. This causes increase of serotonin, a stimulatory transmitter in brain. These drugs are used in treatment of psychic conditions as **depression.**

Argentaffinoma (carcinoid syndrome):

- **Def:** **malignant disease characterized by excessive production of serotonin**
- **Complication:** **↓niacin synthesis → signs of pellagra developed, diarrhea and broncho-spasm**
- **Diagnosis:** **Urinary excretion of 5-hydroxyindol acetic acid is increased.**

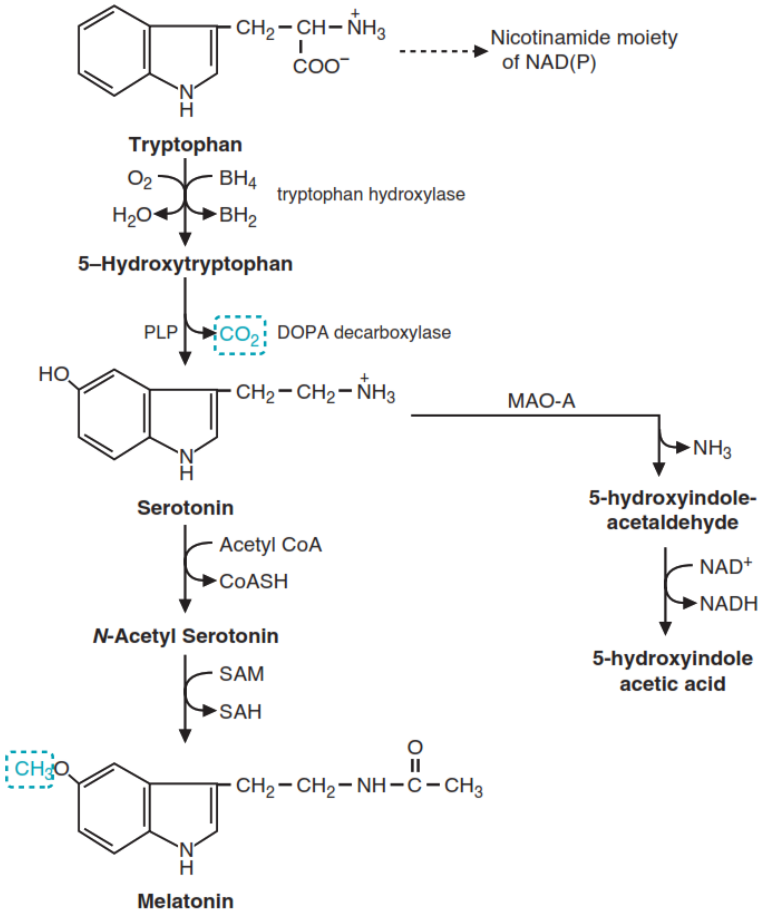
Melatonin

SITE OF SECRETION: pineal gland

SYNTHESIS OF MELATONIN:

a) It is synthesized in pineal gland, as the **acetyl transferase** needed for melatonin synthesis is present in pined gland. Melatonin is synthesized from serotonin by acetylation followed by methylation.

b) Melatonin is secreted only at night (dark). This is because the release of melatonin **is inhibited by light entering the eye and transmitted to the pineal gland by way of the CNS.**



FUNCTIONS OF MELATONIN

a) It inhibits gonadal functions.

b) It has sleep inducing effect.

c) It inhibits synthesis and secretion of other neurotransmitters: dopamine and GABA.

d) Regulation of circadian rhythm, being synthesized mostly at night.

NIACIN (NICOTINIC ACID)

SYNTHESIS OF NIACIN

a) It is synthesized in the course of tryptophan catabolism.

b) Every **60** mg tryptophan are converted into **1** mg niacin.

FUNCTIONS OF NIACIN

Niacin is a member of **vitamin B complex**, being synthesized in liver.

a) It is essential for synthesis of **NAD** and **NADP** coenzymes, which act as hydrogen carriers in varieties of metabolic reactions.

b) Niacin lowers plasma cholesterol. This is because it inhibits the flow of free fatty acids (FFA) from adipose tissue, which provides acetyl CoA essential for cholesterol synthesis.

PELLAGRA

a) This is a disease resulting from deficiency of niacin formation.

b) It results from deficiency of either niacin tryptophan, or pyridoxine.

c) It is the disease of 4Ds. These are diarrhea, dermatitis, dementia and death.

INDOLE AND SKATOLE

1. These are putrefactive products of tryptophan produced by bacteria in large intestine.
2. Indole and skatole give the characteristic odor of stool.
3. Indole and skatole may be absorbed and go to the liver to be hydroxylated and conjugated with sulphate and excreted in urine as salt forms:

- Potassium skatolxyl
- Sulphate and potassium indoxyl sulphate (=**indican**).

HARTNUP'S DISEASE:

- **Def:** hereditary abnormality in tryptophan metabolism where the intestinal absorption and renal tubular reabsorption of this amino acid are impaired.
- **Characters:** by pellagra skin rashes, psychiatric changes and mental retardation.
- There is excess excretion of tryptophan together with lysine and histidine in urine (aminoaciduria).
- **ttt:** Administration of Nicotinamide usually relieves all symptoms except aminoaciduria.

GLUTAMIC ACID

- **Glutamic acid** in **nonessential glycogenic** amino acid.
- **Functions of glutamic acid:** **Remove GEFN**

1. Removal of amino group of most amino acids.
2. Glutathione synthesis
3. Glutamine synthesis
4. Gamma amino butyric acid (GABA).
5. Enzyme activator.
6. Folic acid synthesis.
7. Neurotransmitter.

- **Removal of amino group of most amino acids:** in the form of **ammonia** through Transdeamination.
- **Glutathione synthesis:** (See glycine metabolism).
- **Glutamine synthesis:** (See fate of ammonia).
- **Enzyme activator:**

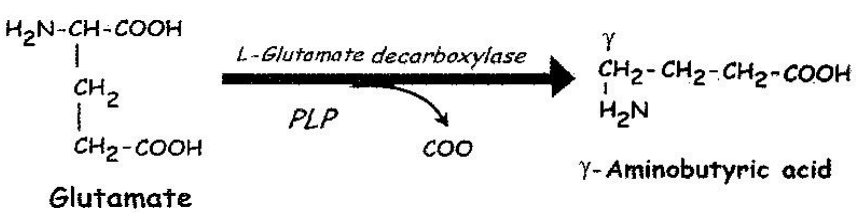
  N-Acetyl glutamate activates Carbamoyl phosphate synthase **I** enzyme (see urea biosynthesis).
- **Folic acid synthesis:**

  - Folic acid is a member of vitamin B-complex being composed of pteridine base, Para-amino benzoic acid (PABA), and one or more glutamic acid residues.

  - Function: acts as a carrier of one carbon units, which has important role in amino acid metabolism and Purine and pyrimidines synthesis.
- **Neurotransmitter:**

  Glutamate acts as excitatory neurotransmitter in all CNS neurons.
- **Gamma amino butyric acid (GABA):**
  - **Synthesis of GABA:**

    - It is synthesized from L-glutamate by L-glutamate decarboxylase in the presence of pyridoxal phosphate as coenzyme.



- **Functions of GABA:**

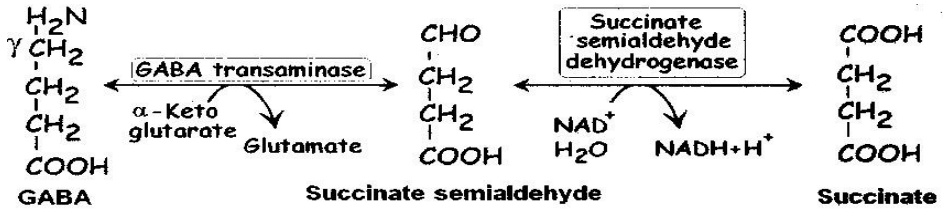
  - It is an inhibitory transmitter in brain and spinal cord.

  a) In the brain, GABA is a postsynaptic inhibitory transmitter.

  b) In the spinal cord, GABA is pre-synaptic inhibitory transmitter.

- **Catabolism of GABA:**

  - It is metabolized within the neurons to Succinate:



- **Deficiency of GABA:**

  a) It may be due to deficiency of either: L-glutamate decarboxylase or pyridoxal phosphate.

  b) It causes convulsions especially in children.

ASPARTATE

- It is **non-essential glycogenic** amino acid.
- **Functions of Aspartate: papun β**

• **P**urine formation • **A**sparagine • **P**yrimidines formation • **U**rea formation
• **N**eurotransmitter • β-Alanine

➢ **Purine formation:**

Aspartate is the source of N_1 of Purine.

➢ **Pyrimidines formation:**

Aspartate is the source of N_1, C_4, C_5 and C_6 of pyrimidines.

➢ **Urea formation:**

Aspartate reacts with citrulline to form arginosuccinate.

➢ **Asparagine formation:**

- **Functions:**

a) It enters in the structure of some proteins e.g. **oxytocin** hormone.

b) It is a source of ammonia especially in plants.

➢ **Neurotransmitter:**

Aspartate acts as an excitatory transmitter on all CNS neurons.

➢ **β-Alanine:**

- In bacteria, decarboxylation of aspartic acid produces β-Alanine.
- In mammalian tissues β-alanine arises during catabolism of cytosine base.
- β-Alanine enters in the structure of: pantothenic acid, coenzyme A, carnosine, anserine and homocarnosine.

ARGININE

- It is **glycogenic, semi-essential amino** acid i.e. formed in amount not sufficient for body especially in children and pregnant females.

- Functions of Arginine: CANU

- **Creatine formation:** see glycine metabolism.
- **Arginine phosphate** (**Arginine — P**): it is present in muscles and acts as a source of energy in animals (invertebrate).
- **Urea formation:** see urea cycle.
- **Nitric oxide:** L-Arginine serves as a precursor of nitric oxide (NO).

1. NO is an **intracellular** signaling molecule and functions as neurotransmitter, smooth muscle relaxant and vasodilator (through **cGMP**).

- **NO synthase** is a complex enzyme using 5 cofactors: *NAD*, *FAD*, *FMN*, *heme* and *tetrahydrobiopterin*

2. Nitroglycerine (glyceryl trinitrate) is a powerful coronary vasodilator through increasing **NO** formation.

3. Sildenafil (Viagra) is a drug that **inhibits phosphodiesterase** enzyme that converts **cGMP** into **GMP**. This maintains the action of **cGMP** as smooth muscle relaxant and vasodilator and used as a drug that maintains penile erection.

ORNITHINE

- It is a **glycogenic, non-essential** amino acid.

- Functions: Ornithine is important for:

- **Urea formation.**
- **Detoxication:**

  Ornithine + Phenyl acetyl CoA (Toxic) → Phenyl acetyl ornithine (non-toxic).
- **Spermidine and spermine formation:** These are polyamines formed in prostate by ornithine and methionine.

- **Functions:**

a) Cell proliferation (division) and growth.

b) Stabilization of intact cells, cell membrane and sub-cellular organelles.

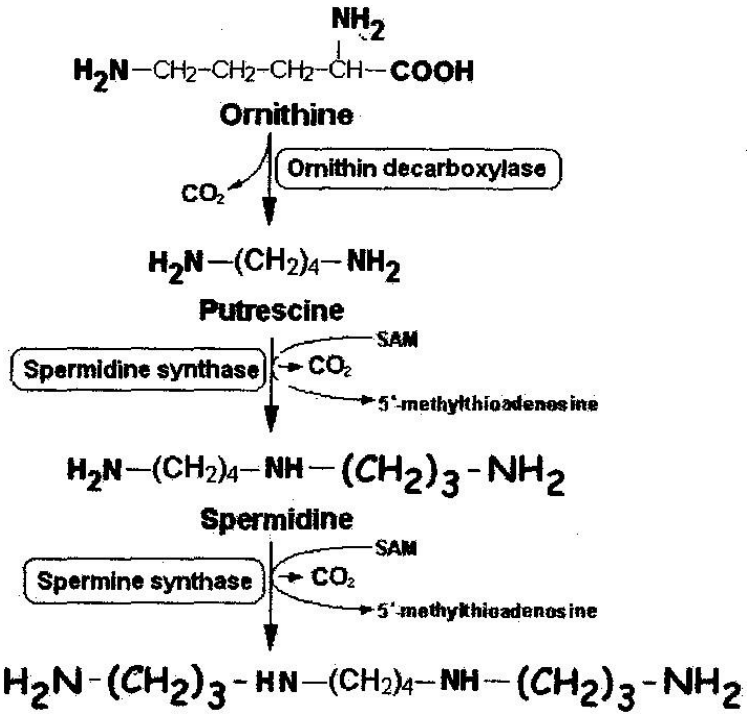
c) They give the characteristic odor of **semen**.

d) Stimulation of **DNA** and **RNA** biosynthesis.

e) Inhibition of protein kinase enzyme.

f) In pharmacological doses, polyamines cause decrease in both blood pressure (hypotension) and body temperature (hypothermia).

- **Biosynthesis:**



- **Catabolism:**

  a) Spermine is oxidized to **Spermidine** and **putrescine**.

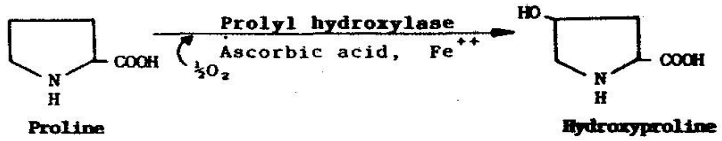
  b) Both are either excreted in urine or converted to **CO_2** and **NH_3**.

PROLINE ANT HYDROXYPROLINE

- These are **non-essential glycogenic** imino acids.

- Functions of proline:

➢ **Hydroxyproline synthesis:**



➢ **Collagen synthesis:**

1. Proline and hydroxyproline are very rich in collagen.
2. Ascorbic acid deficiency leads to a weak collagen (scurvy).

- **Catabolism of proline:** gives glutamate.

CYSTEINE

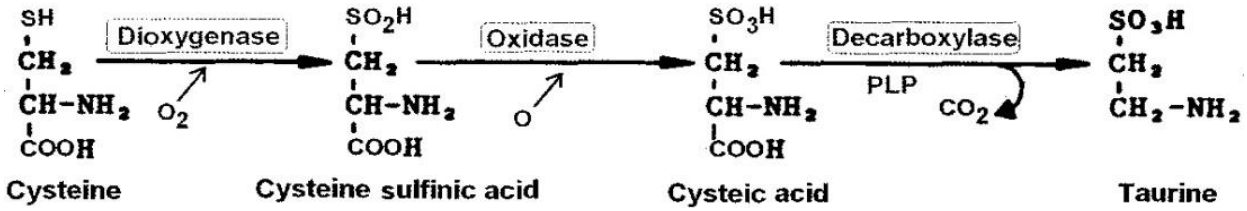
- Cysteine is glycogenic, non-essential amino acid.

- Functions: It enters in the synthesis of:

- **G**lutathione
- **T**aurine
- **T**hioethylamine
- **P**roteins
- **D**etoxication

➢ **Taurine:**

- **Synthesis:**



- **Functions:**

It combines with cholic acid to form taurocholic acid. Its sodium salt (sodium taurocholate) is one of bile salts, which are Important for digestion, and absorption of lipids.

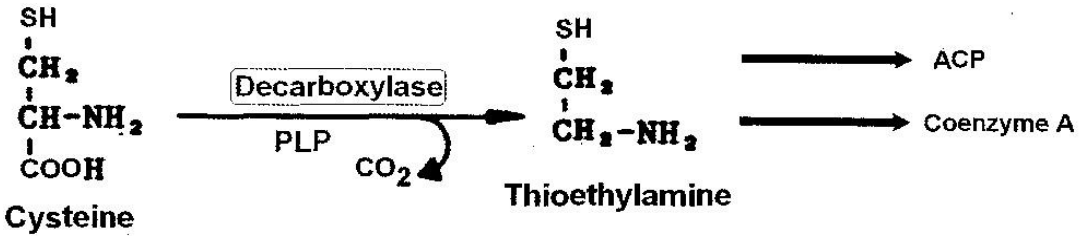
➢ **Thioethylamine:** A part of the vitamin: Pantothenic acid.

- **Functions: it enters in the structure of:**

a) Coenzyme A: It is a coenzyme, which is important in carbohydrates and lipids metabolism.

b) Acyl carrier protein (ACP): This is a component of fatty acid synthase enzyme.

- **Synthesis:**



➢ **Protein synthesis:** Cysteine is very important amino acid for some proteins as:

1. Keratins: simple proteins that are present in hair, nail, skin etc. Keratins are very rich in cysteine.

2. Many enzymes: e.g. **glyceraldhyde-3-phosphate dehydrogenase** contains in its active center **-SH** group derived from cysteine.

➢ **Detoxication:** Cysteine is important for the detoxication of some aromatic compounds e.g. bromobenzene.

CYSTINE

- **Cystine** (di-cysteine) is glycogenic, non-essential amino acid.
- **Functions:**

➢ **A. Protein structure:** The -S-S- group of cystine is important for tertiary and quaternary structure of proteins e.g. insulin hormone has two -S-S- groups.

Cystinuria (cystine - lysinuria):

- Def: hereditary disease characterized by amino aciduria (excessive excretion of cystine together with basic amino acids; lysine, Arginine, and ornithine.

- Cause: defective renal tubular reabsorption of these 4 amino acids. Cystine may precipitated in renal tubules forming renal stones.

HOMOCYSTEINE

- Homocysteine test measures the amount of the amino acid in the blood.
- Homocysteine may get high levels when cholesterol, white blood cells, calcium, and other substances (plaque) build up in blood vessels. This build-up may lead to a heart attack. Stroke. And blood clots in the lungs (pulmonary embolism) or deep veins of the legs (deep venous thrombosis).

METHIONINE

i. Methionine is glycogenic, essential amino acid.

ii. Function: It enters in the synthesis of:

A. Cysteine synthesis: Through formation of Homocysteine, this reacts with **serine** to give **cysteine**.

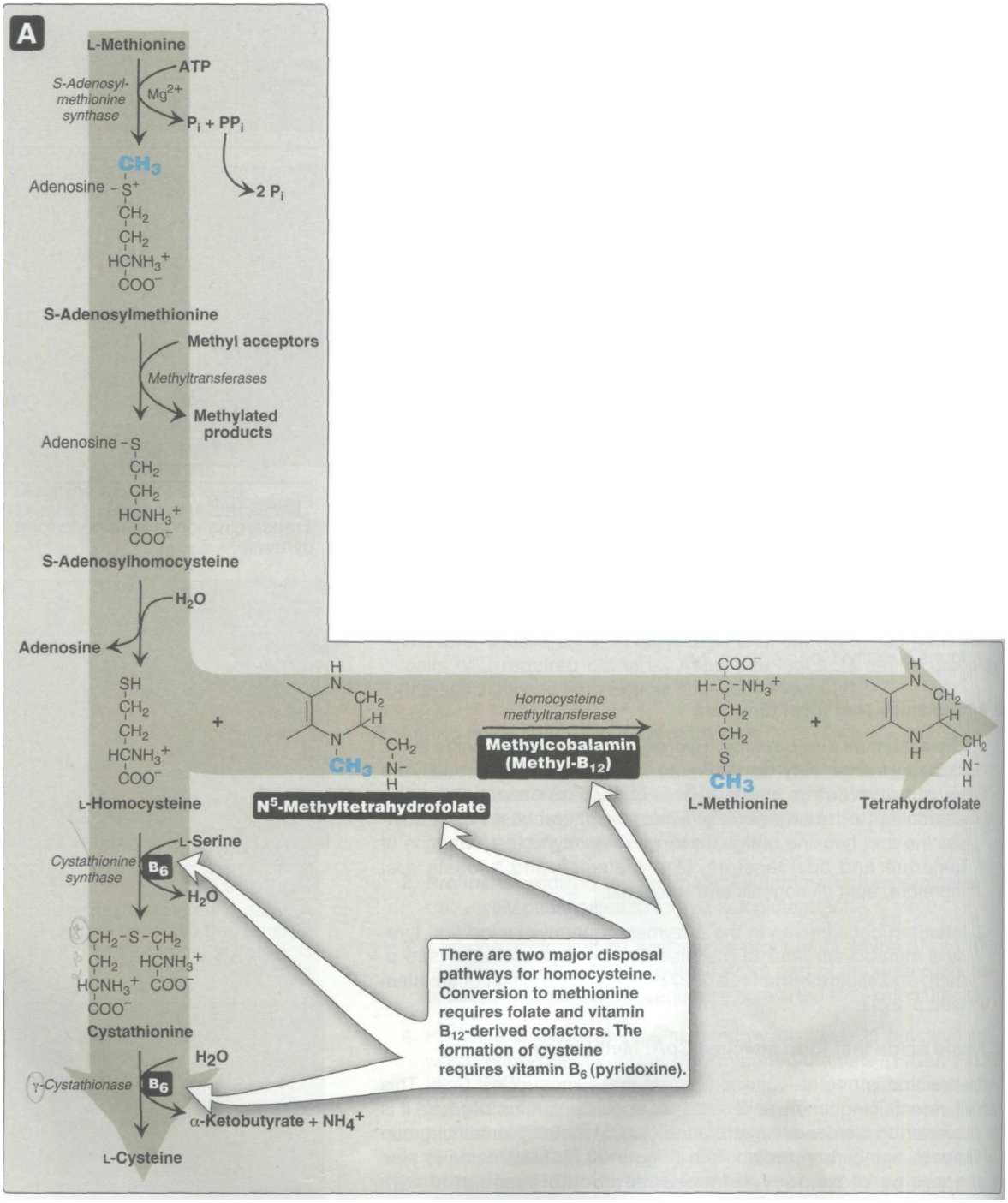
B. Lipotropic factor: Methionine is one of lipotropic factors, which prevent **fatty liver**.

C. Spermidine and spermine: see ornithine metabolism.

D. S-Adenosyl methionine (SAM): The main **methyl donor**, used in Transmethylation reactions.

Transmethylation reactions.

- **Def:** the transfer of **active methyl group** from a **methyl donor** to a **methyl acceptor**.
- **Formation:** SAM is a high energy compound resulting from a condensation of **methionine** with **ATP** with hydrolysis of **all** phosphate bonds in **ATP**.



- **Catabolism:** - After giving the **methyl group** to a methyl acceptor, **SAM** is converted to S-adenosyl Homocysteine, which is then hydrolyzed to **Homocysteine** & **adenosine**.

- Homocysteine has two fates:

1) Synthesis of cysteine:

i- Homocysteine can combine with serine forming cystathionine by **cystathionine synthtase**

ii- Cystathionine is hydrolyzed to L-Homoserine and cysteine by **cystathionase**.

iii- Homoserine → α-Keto butyrate → oxidatively decarboxylated to form → Propionyl COA → Succinyl CoA → glucose.

2) Re-Synthesis of methionine:

i- Homocysteine can accept a methyl group from **methyl tetrahydro-folate** (Me-H4-Folate) in a reaction requiring cobalamine (B12) as an intermediate cofactor.

- Examples:

	SAM		SAH
1. Nor-epinephrine	→	methyl-transferase	epinephrine.
2. N-acetyl serotonin	→		melatonin.
3. Ethanolamine	→		Choline.
4. Guanido acetate	→		Creatine.
5. Pyridine	→		N methyl pyridine.

HOMOCYSTANURIA:

* This is a hereditary disease due to deficiency of **cystathionine β-synthase**
* Plasma methionine levels are elevated.
* There is excessi ve urinary excretion of **Homocysteine** and **SAM**
*sig and symptoms include: mental retardation, thromboses, osteoporosis and dislocation of eye lenses.
***Treatment:** feeding a diet low in methionine high in cysteine.

HISTIDINE

I. It is essential, glycogenic amino acid.

It is used for synthesis of: **A. HISTAMINES**

1. Functions: Histamine is secreted by **mast cells** as a result of allergic reactions or trauma. It has the following functions: a) Vasodilatation. b) Contraction of smooth muscles of bronchi. c) Stimulation of gastric secretions.

2. Synthesis:

Histamine is derived from histidine by **decarboxylation**. This reaction is catalyzed by either 2 different enzymes: **a)** Aromatic L-amino acid decarboxylase or **b)** Histidine decarboxylase.

B. Ergothionine:

1. It is N-trimethyl, thiol histidine. 2. Ergothionine is an intracellular antioxidant naturally occurring in plants and animals.

C. Carnosine and Anserine:

1. Carnosine is a substance results from conjugation of **histidine** with **β-alanine**.
2. **Anserine** is produced by **methylation** of **carnosine**.
3. Both are present in skeletal muscles and not in cardiac muscle.

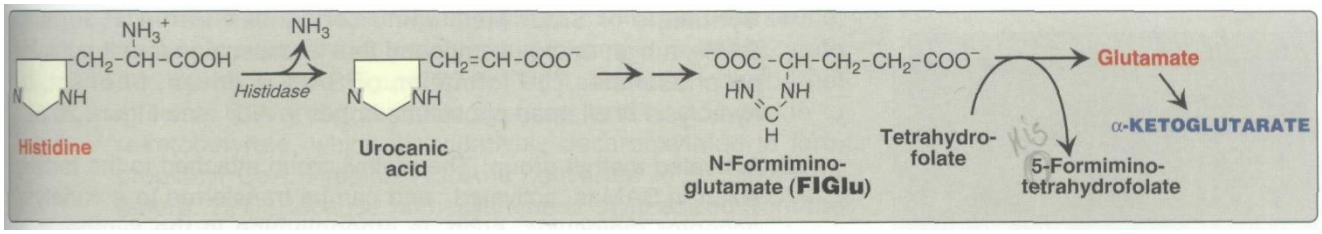
4. Functions:

a) Anserine and carnosine activate myosin ATPase enzyme.

b) They have antioxidant activity and have a role in copper metabolism.

- **Catabolism of Hisidine:** is deaminated to **urocanic** acid, which is converted to **4-imidazolone 5-propionate**. Hydrolysis of the later, **gives N-formiminoglutamate (FIGlU)** , which donates its formimino group to **tetrahydro-folate** , leaving glutamate which is then converted to a-Ketoglutarate.

a) FIGLU excretion test: Deficiency of folic acid + excretes increased amount of FIGIU in urine. It is useful test of **folic** acid deficiency.



HISTIDINEMIA:

* This is a hereditary disease due to deficiency of **histidase** enzyme.

* It is characterized by mental retardation and speech defects.

SERINE

I. Serine is non-essential, glycogenic amino acid.

II. Serine is used for the synthesis of:

A. Phosphoprotein: The -OH group of serine residues present in proteins is the site of etherification of phosphate to form phosphoprotein.

B. Sphingosine base: Serine reacts with palmityl CoA to form sphingosine base. It enters in the structure of **Sphingomyelin**

C. Cysteine: Serine reacts with Homocysteine (derived from Adenosyl methionine) to form cysteine.

D. Purine bases: n-carbon of serine enters in the formation of C_2 and C_5 of Purine

E. Glycine: Through the action of serine hydroxy methyl transferase.

F. Ethanolamine and choline: Serine, ethanolamine and choline are important constituents of phospholipids.

Alanine and β-alanine

I. These are non-essential, glycogenic amino acid

ii. Alanine is important for:

A. Alanine -together with glycine- forms a major fraction of **plasma amino acids**.

B: Alanine is the main amino acid that is converted into glucose in liver through **alanine-glucose cycle**.

G. Alanine is a major component of bacterial cell wall.

- β-Alanine is important for the synthesis of:

A. Pantothenic acid, anserine acid carnosine.

B. -Alanine does not enter in the formation of proteins.

Threonine

I. It is essential, glycogenic amino acid.

II. Threonine is used for the synthesis of:

A. Phosphoproteins: Like serine, the -OH group of threonine is important for. the **synthesis of** Phospho-proteins.

B. Glycine: Through the action of threonine aldolase enzyme.

LYSINE AND HYDROXYLYSINE

I. Lysine is an essential, ketogenic & glucogenic amino acid.

II. Lysine is important for Hydroxylysine synthesis:

A. Collagen synthesis: Lysine and hydroxylysine are very rich in collagen.

B. Carnitine synthesis: 1. It is 3-hydroxy, y-trimethyl amino butyric acid.

2. It is synthesized from lysine, at first by **methylation** (using S-**adenosyl methionine**), then **deamination** and finally by **removal of 2** carbons to give Carnitine.

3. Functions: Carnitine acts as a carrier, transporting long chain acyl CoA across inner mitochondrial membrane. This is essential for fatty acid oxidation

BRANCHED CHAIN AMINO ACIDS

Valine - Leucine – Iso-Leucine

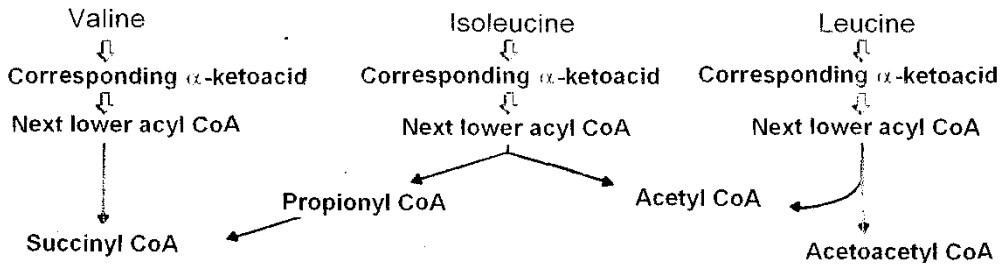
1. All are essential amino acids.
2. Valine is glycogenic, Leucine is Ketogenic and Isoleucine is glycogenic and Ketogenic.
3. All enter in the formation of body proteins.

- Catabolism:

- The **transamination** of the branched chain amino acids occurs mainly in muscle, brain and adipose tissue. Liver is deficient in transaminase required for their transamination.
- The **α-ketoacid**, which result from the transamination reactions are **oxidatively decarboxylated** by α- **ketoacid decarboxylase** to give **acyl CoA** that is less than a-keto acid by one carbon atom. This reaction is similar to that catalyzed by pyruvate dehydrogenase complex.
- The acyl CoA will be oxidized through several steps to give:

a) Succinyl CoA: this is for valine (glycogenic).

b) Acetyl CoA, acetoacetyl CoA: this is for Leucine (Ketogenic).



Summary of catabolism of branched chain amino acids

MAPLE SYRUP URINE DISEASE:

a) Definition: It is accumulation of α-ketoacid of branched chain amino acids and their excretion in urine.

b) Cause: it results from deficiency of oxidative decarboxylation of α-ketoacid.

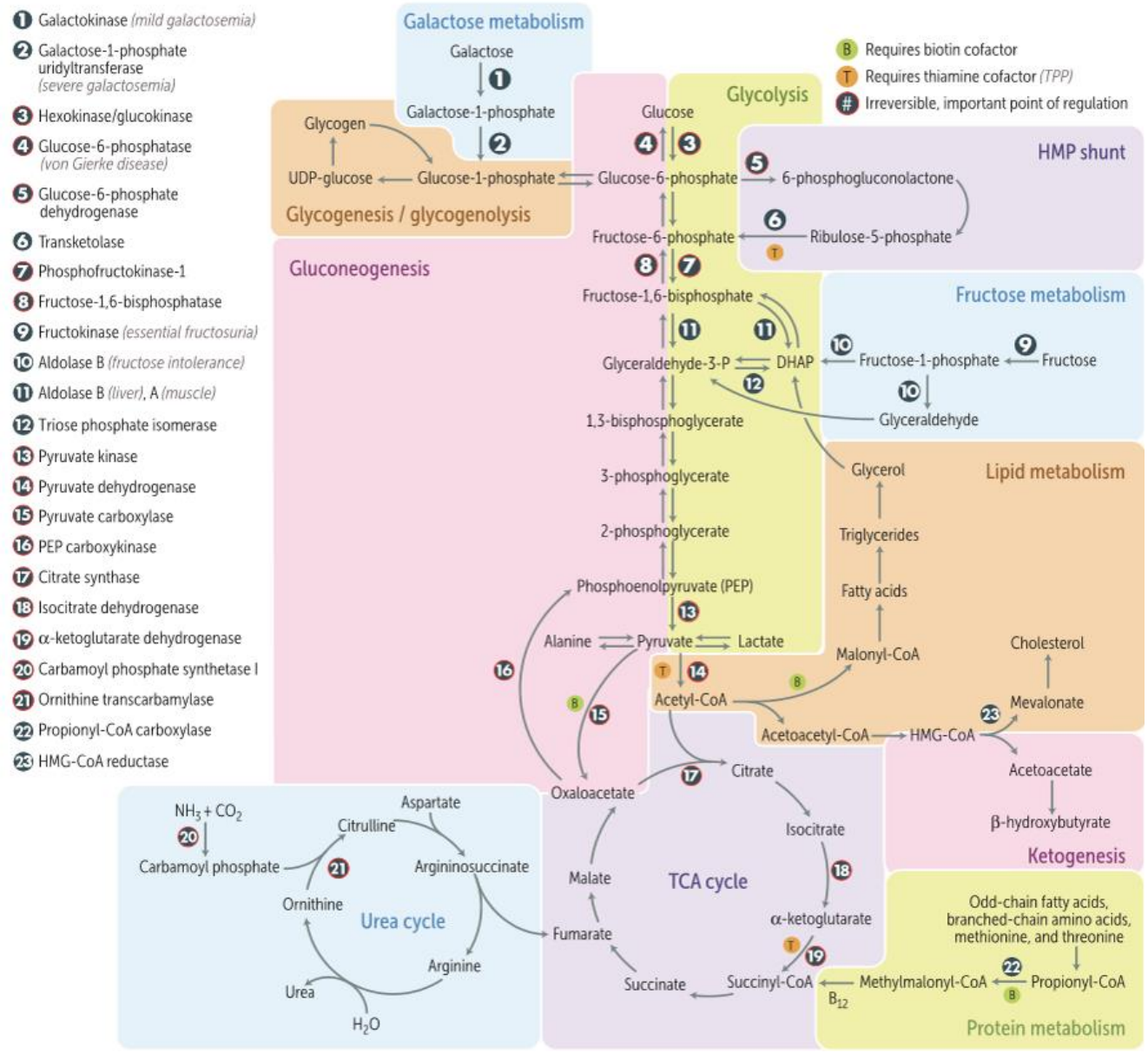
c) Effects: 1. Mental retardation. 2. Urine has a maple syrup odor or burnt sugar.

3. Children do not usually live more than 1 year.

PROTEIN DISEASE

	DISEASE	DEFICIENCY OF	EFFECT
GLYCINE	**GLYCINURIA**	- ↓renal reabsorption of glycine - dominant x-linked disease	- oxalate renal stones
	PRIMARY HYPEROXALURIA	failure of conversion of Glyoxylic acid into formate or glycine	- renal failure or - Hypertension. - death in early life
METHIONINE	**HOMOCYSTANURIA**	cystathionine β-synthase	- mental retardation, - thromboses, - osteoporosis and
PHENYLALANINE	**PHENYLKETONURIA**	- phenylalanine hydroxylase or - dihydrobiopterin reductase	- Mental retardation - Failure to walk and talk. - Hyperactivity and tremors - An Intelligence Quotient (IQs) -Skin lesion e.g. eczema
TYROSINE	**TYROSINOSIS**	- tyrosine α-Ketoglutarate transaminase and - p-hydroxy-phenylpyruvate oxidase	- Liver cirrhosis and - hepatic carcinoma - mental retardation
	ALKAPTONURIA	Homogentisate oxidase	- arthritis - ochronosis - dark urine
	ALBINISM	- tyrosine hydroxylase	Defective synthesis of melanin pigments. Eye, skin and hair are affected
TRYPTOPHAN	**HARTNUP'S DISEASE**	- intestinal absorption - renal tubular reabsorption	- pellagra skin rashes, - psychiatric changes and mental retardation
BRANCHED CHAIN AMINO ACIDS	**MAPLE SYRUP URINE DISEASE**	oxidative decarboxylation of α-ketoacid	- Mental retardation. - Urine has a maple syrup odor or burnt sugar
CYSTINE	**CYSTINUREA**	↓ renal reabsorption of cystine	- Crystaluria - stone formation
	CYSTINOSIS	Defect of transport system of tyrosine.	

Summary of pathways



CHAPTER 8

Vitamins

Vitamins

❖ Definitions:

- **Vitamins:** Are organic compounds that:
  1. **Essential** for many biochemical reactions.
  2. Many of them act as **coenzymes.**
  3. They **do not enter** in the structure of the tissues or **oxidized** by them.
  4. They are needed in **very small amounts.**
- **Provitamins:**
  - These are **precursors** of vitamins that converted into vitamins inside the body e.g. **carotenes** are **Provitamin A.**
- **Vitamers:**
  - These are different forms of one vitamin e.g. Vitamin **D** has **2 Vitamers**; D_2 and D_3.

❖ CLASSIFICATION OF VITAMINS: According to the solubility, vitamins are classified into:

- **A. Fat soluble vitamins:** These are vitamins: **A, D**, **E**, and **K**.
  1. They are **soluble** in **fat** solvents.
  2. They need **bile** salts for absorption.
  3. They can be **stored** in the body.
- **B. Water soluble vitamins:** These are vitamins: **C** and **B complex** group.
  1. They are **soluble** in **water**.
  2. Most of them are **not stored** in the body.