Aminoacids Metabolism

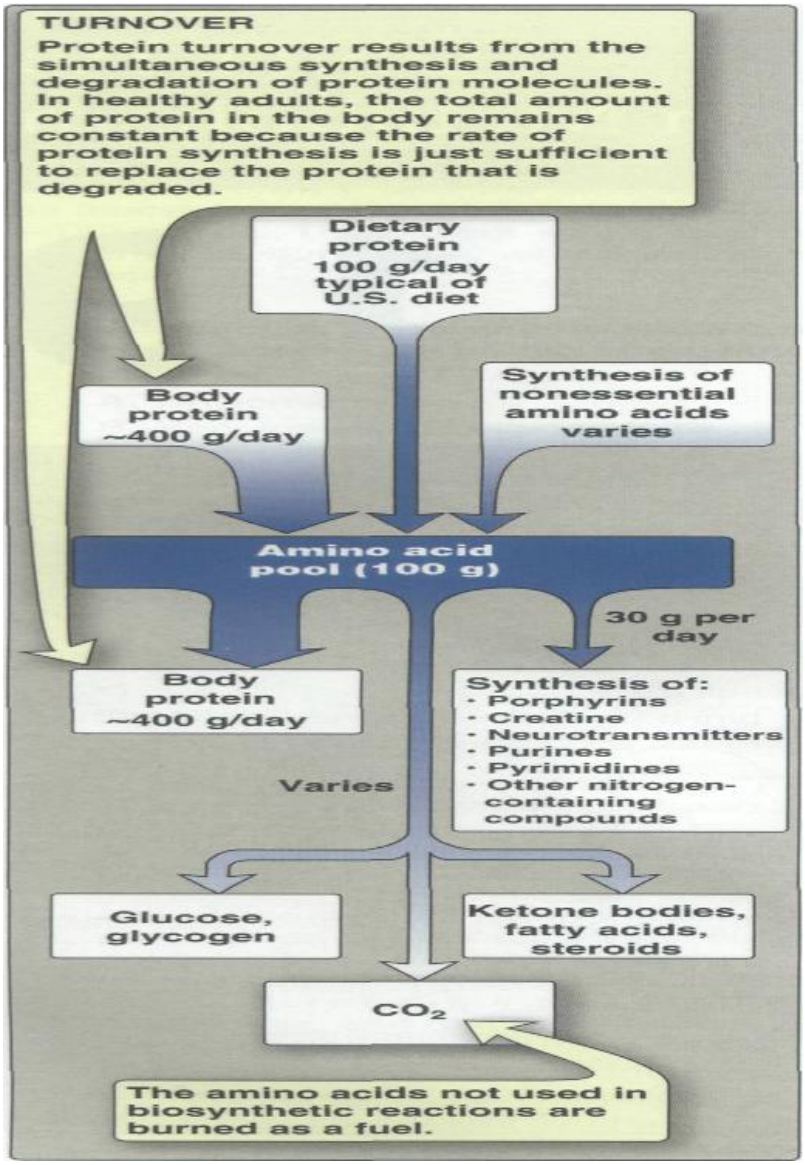
المحاضره الأولى

Objectives:

The students are learned to understand the Catabolism of amino acids including aminoacids pool and removal of amino group by transamination

Catabolism of amino acids

free a.as are derived from dietary proteins or from degradation of endogenous proteins are metabolized in identical ways .



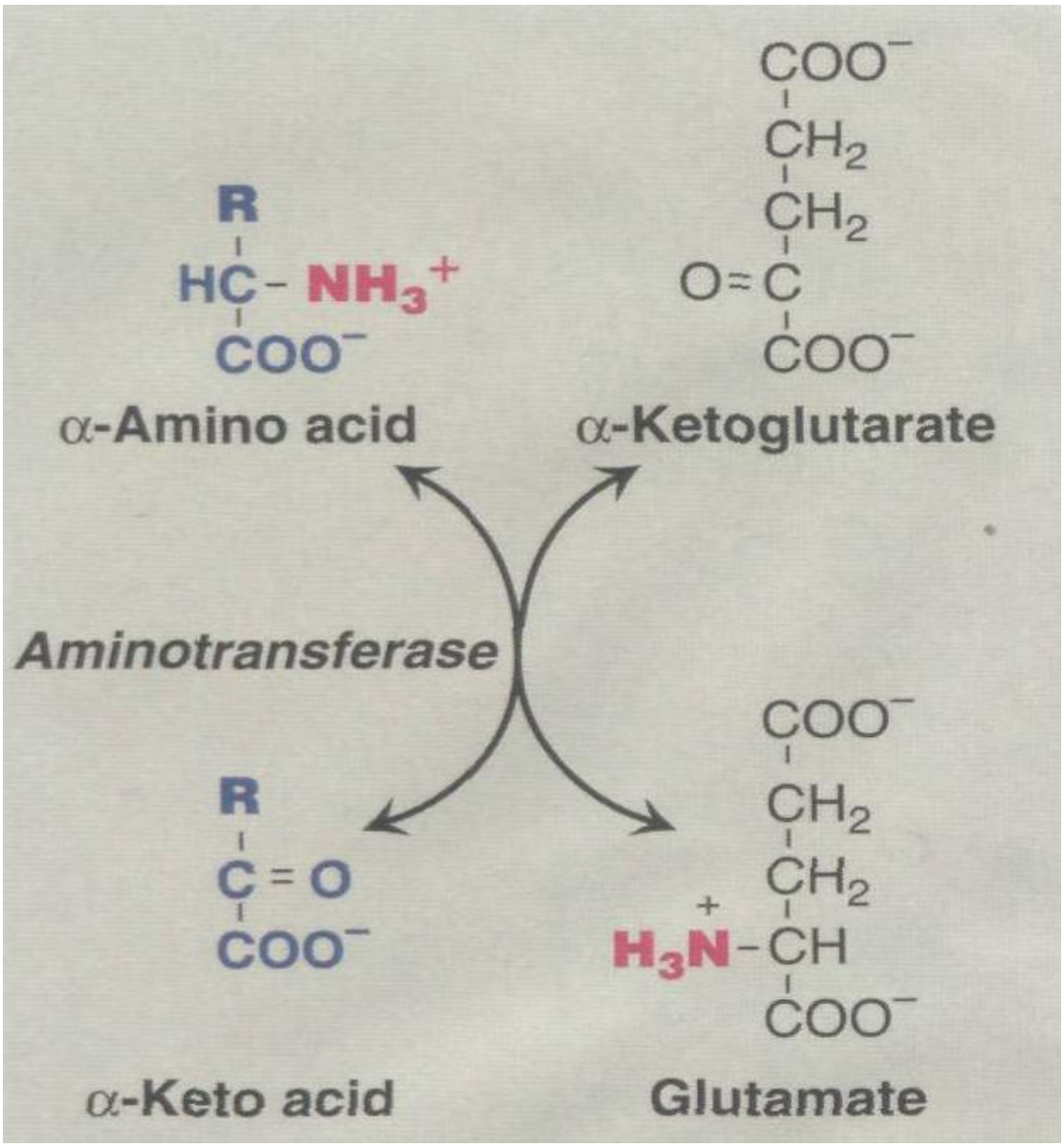
Their alpha amino nitrogen is first removed either by transamination or by oxidative & nonoxidative deamination . The resulting carbon skeleton is then degraded .

Transamination

It is the most general & predominant mode of nitrogen removal , which involve a reversible transfer of the alpha amino group from a.a toalpha ketoglutarate

a.a + alpha ketoglutarate ↔↔↔ keto acid + glut.

(keto acid) (a.a)



all a.a except threonine , lysine , proline , & hydroxyproline can undergo transamination with alpha ketoglutarate.These reactions are catalyzed by **transaminases (aminotransferases**)

Tow transaminases are present in most mammalian tissues catalyze the transfer of amino group from most a.as & are of clinical importance

1-GOT or AST

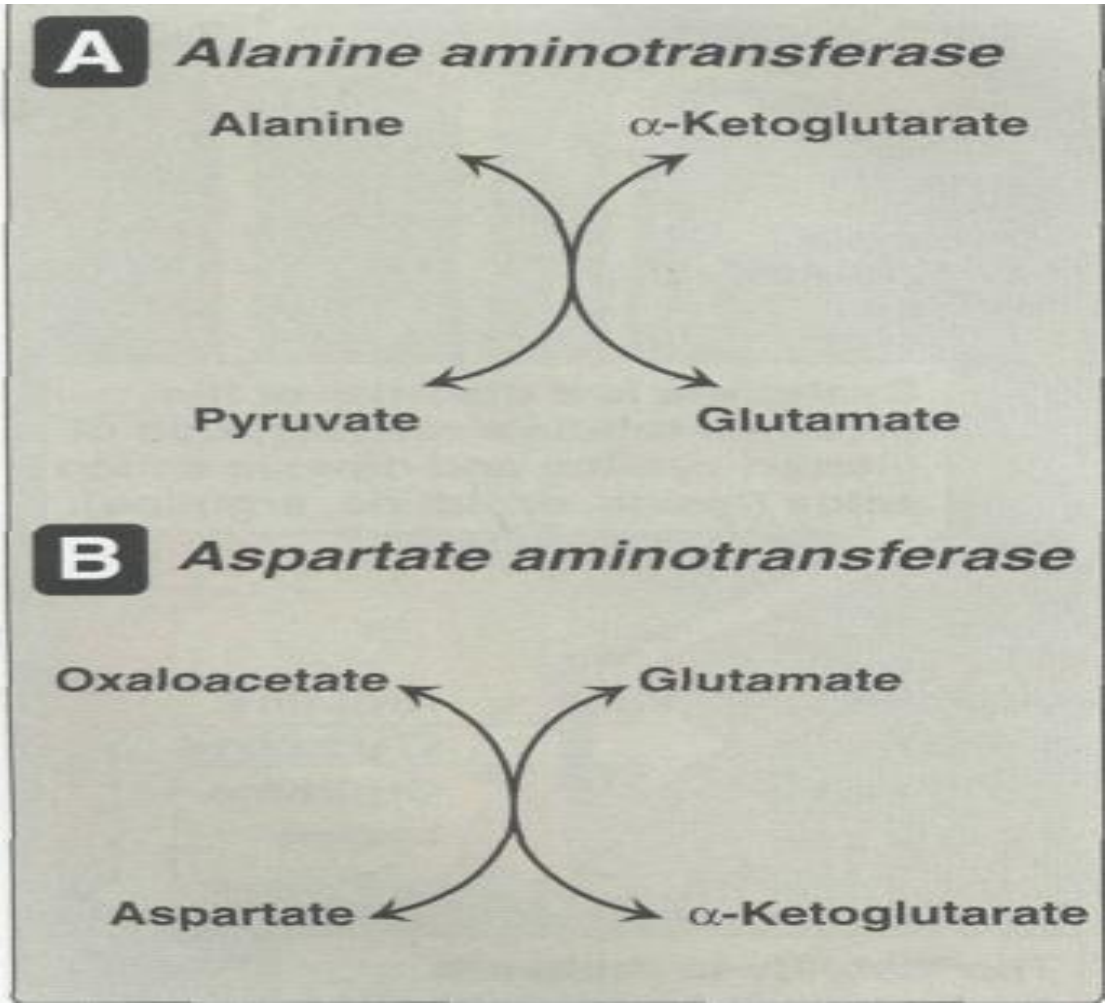
(glutamate oxaloacetate transaminase or aspartate aminotransferase)

glu. + oxal.↔↔↔alpha ketoglutarate + aspartate

2-GPT or ALT

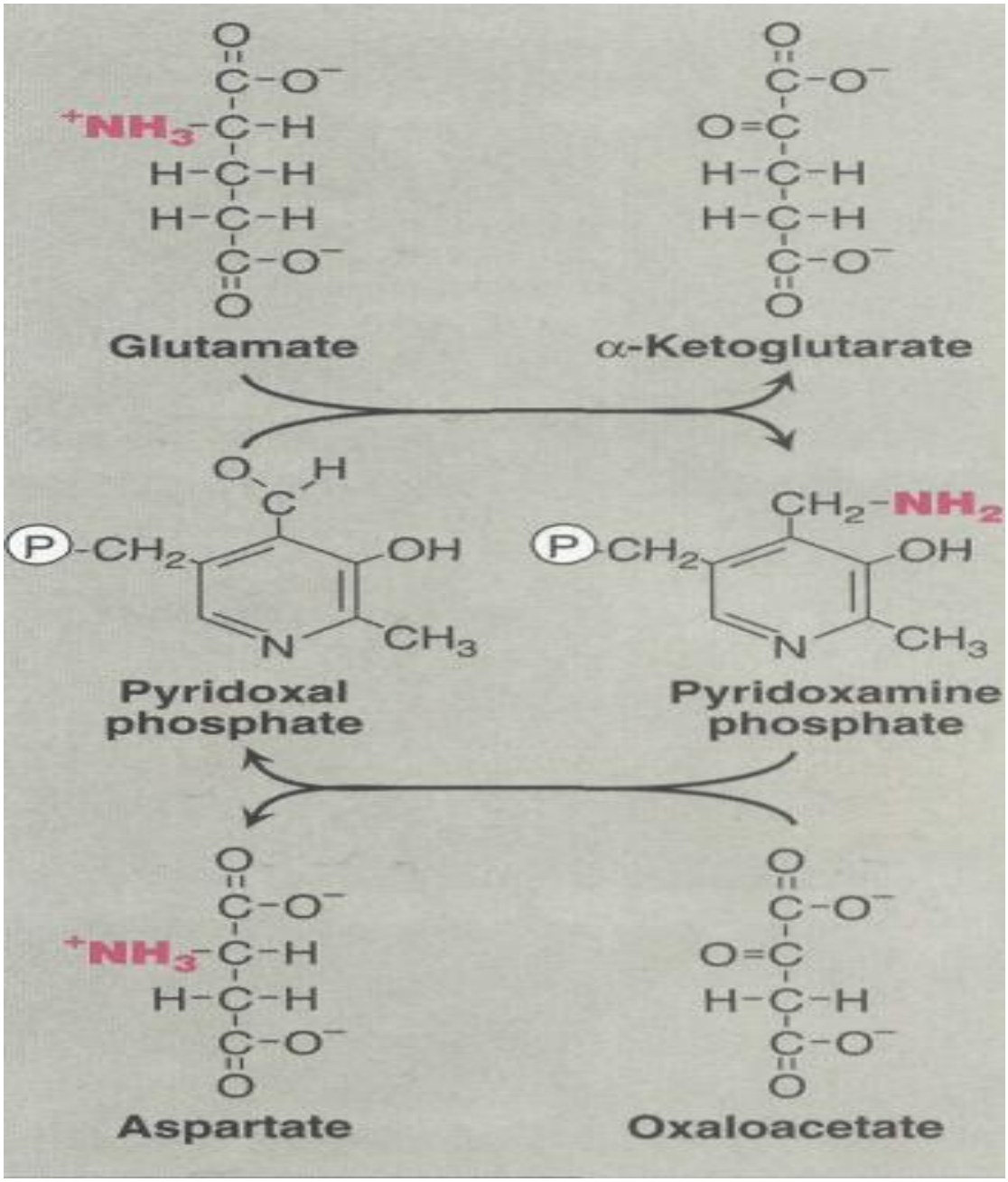
(glu. pyruvate transaminase or alanine aminotransferase)

glu. + pyruvate ↔↔↔alpha ketoglu. + alanine



¤ all transaminases have pyridoxal phosphate as coenzyme

¤Transaminases are specific for only one pair of alpha amino & alpha ketoacids .



¤Since the reactions are freely reversible , they can serve to form a.as from the corresponding keto - acid. So transaminases reactions are central to both the degradation and the synthesis of a.as .

¤Since these reactions involve the Interconversion of amino acid with pyruvate or alpha ketoglutarate, they function as a bridge between the metabolism of amino acids & CHO.

المحاضره الثانية

Objectives:

The students are learned to understand the following points:

- Deamination reaction

- **Oxidative deamination**
- **Nonoxidative deamination**

- Ammonia metabolism

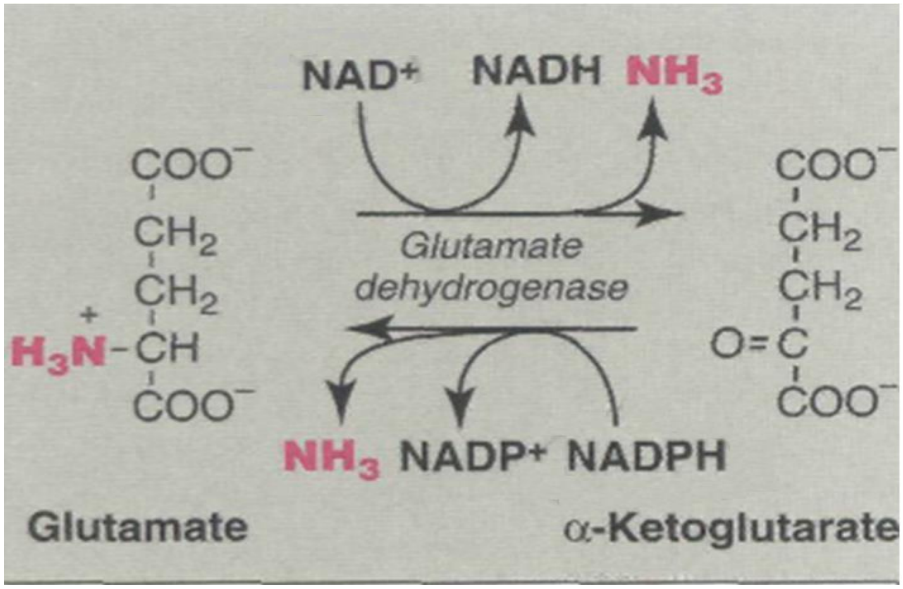
Deamination reaction

Some a.as can be converted directly to their corresponding ketoacids by the oxidative deamination nonoxidative deamination

Oxidative deamination :

the most important of these reactions is the oxidation of glutamate to alpha ketoglutarate which is catalyzed by NAD linked enzyme called glutamate dehydrogenase

Glu.+NAD+H2O↔↔↔alpha ketoglu. +NADH+ + NH3



The glutamate dehydrogenase reaction can be visualized as a link in the general process in which a.a are converted to ketoacid by transamination with alpha ketoglu. The glutamate that is formed can be reoxidized by glutamate dehydrogenase to regenerate the alpha ketoglutarate .

The reverse reaction can function to provide glutamate from alpha ketoglutarate . The glutamate can then be utilized for the biosynthesis of a.as from the corresponding ketoacids by transamination reaction

Another type of oxidative deamination is catalyzed by L – amino acid oxidases

a.a + flavoprotein (FMN or FAD) →→→ ketoacid + NH_3 +

reduce flavoprot.

reduce flavoprot. + O_2→→→ flavoprot. + H_2O_2

↓

catalase ↓

↓

$H_2O + O_2$

The activity of L – a.a oxidase is comparatively low & probably not play a major role in a.as catabolism .

Nonoxidative deamination :

certain a.a ex. serine , threonine, & cysteine are deaminated by specific lyases that require pyridoxal phosphate .

CH_2OH CH_3

| serine |

$CHNH_2$ →→→→ C = O + NH_3 + H_2O

| dehydratase |

COOH COOH

serine pyruvate

Ammonia metabolism

The transfer of amino group from most a.as to alpha ketoglutarate by transamination & the action of glutamate dehydrogenase on theresultant glutamate , leads to the release of considerable amount of ammonia. Smaller amounts of ammonia **also arise from :**

1-action of amino acid oxidase

2-nonoxidative deamination

3-hydrolysis of ketoglutaramic & ketosuccinamic acid

4-hydrolysis of glutamine by Glutaminase

Glutamine + H_2O →→→ glutamate + NH_3

There are three mechanisms for the disposal of potentially toxic NH_3 :

1-interaction with alpha ketoglutarate to form glutamate by the action of glutamate dehydrogenase.

2- Synthesis of glutamine from glutamate

glutamine synthetase

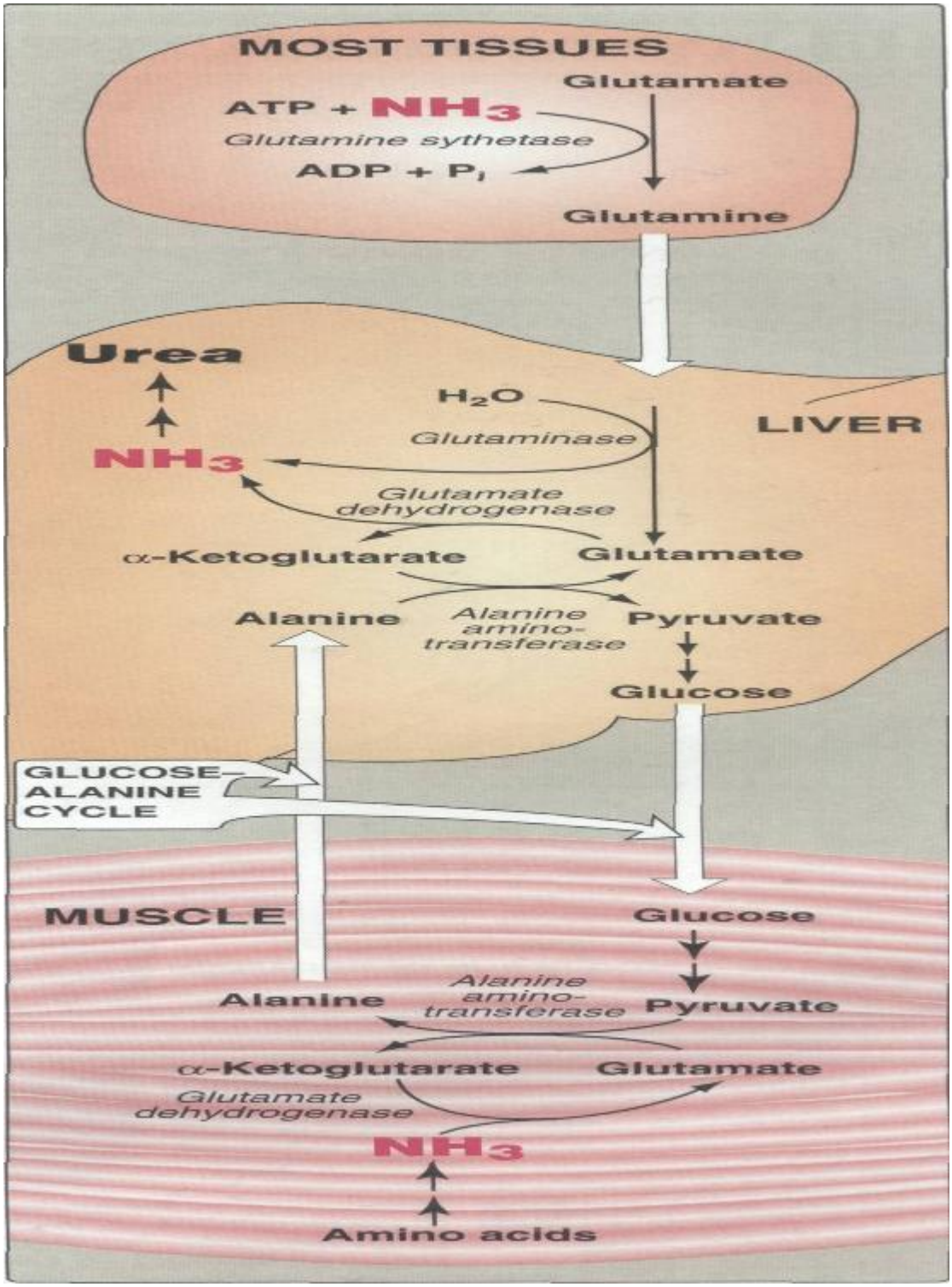
glutamate + NH_3 + ATP→→→glutamine + ADP + Pi

3- Synthesis of carbamoyl phosphate

car. Phosphate synthetase

$CO_2 + NH_3 + 2ATP \rightarrow\rightarrow\rightarrow$ carbamoyl phosphate + 2ADP + Pi

Formed mainly in liver & principally utilized for urea synthesis .



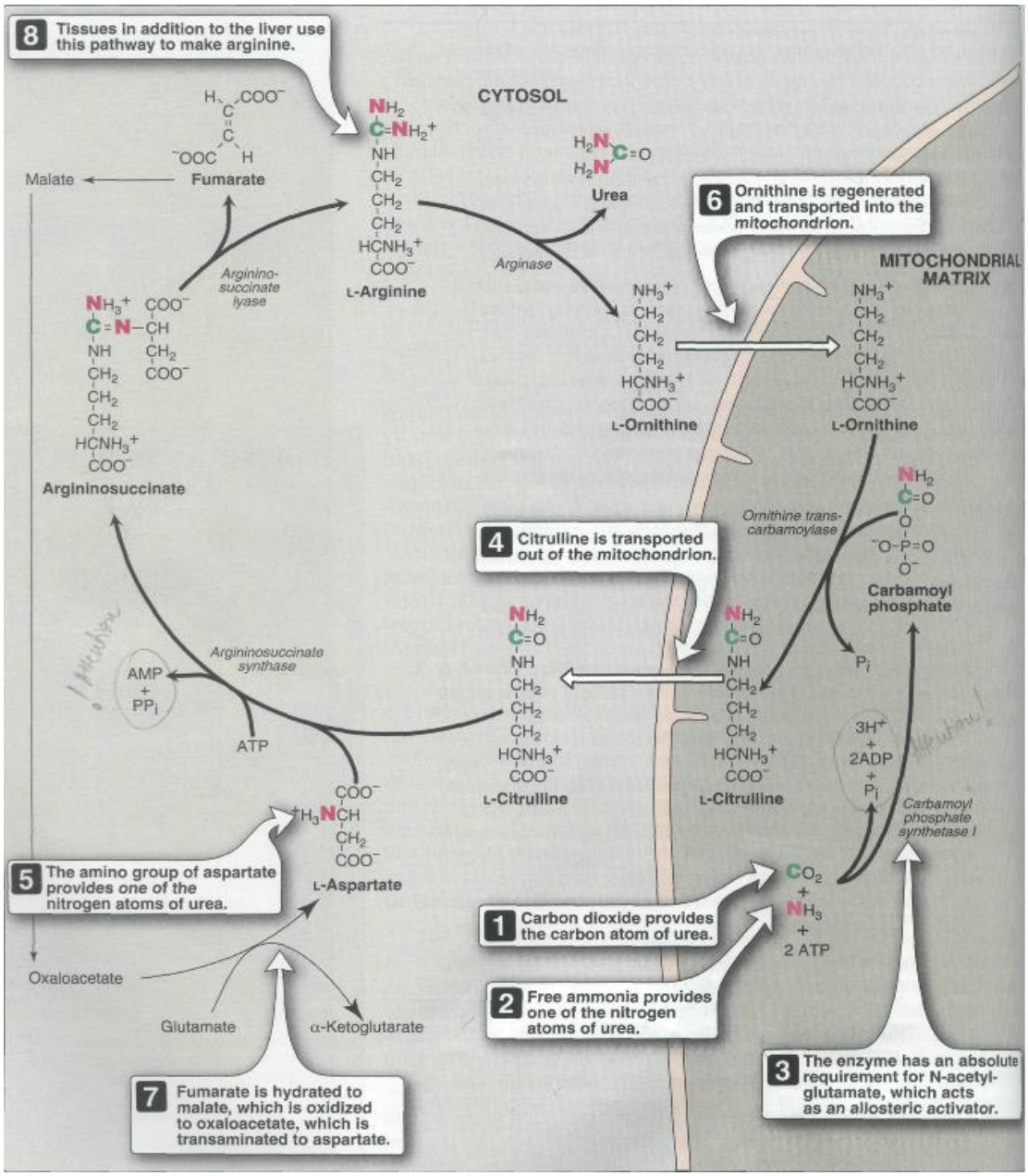
المحاضره الثالثة

Objectives

The students are learned to understand the following points:

- Urea cycle
- Catabolism of the carbon skeleton
- Transmethylation reaction including creatine metabolism

UREA CYCLE



net reaction of urea cycle

carb. phosphate +aspartate+ 4 ATP →→→ urea + fumarate+ 2ADP +

AMP+ PPi

Urea is the principle end product of protein metabolism which is finally excreted in urine . normally the amount formed is dependent on protein intake . Urea cycle occur only in the liver because the enzyme **Arginase** not present in other tissue .

The rate limiting step appear to be those catalyzed by the following enzyme :

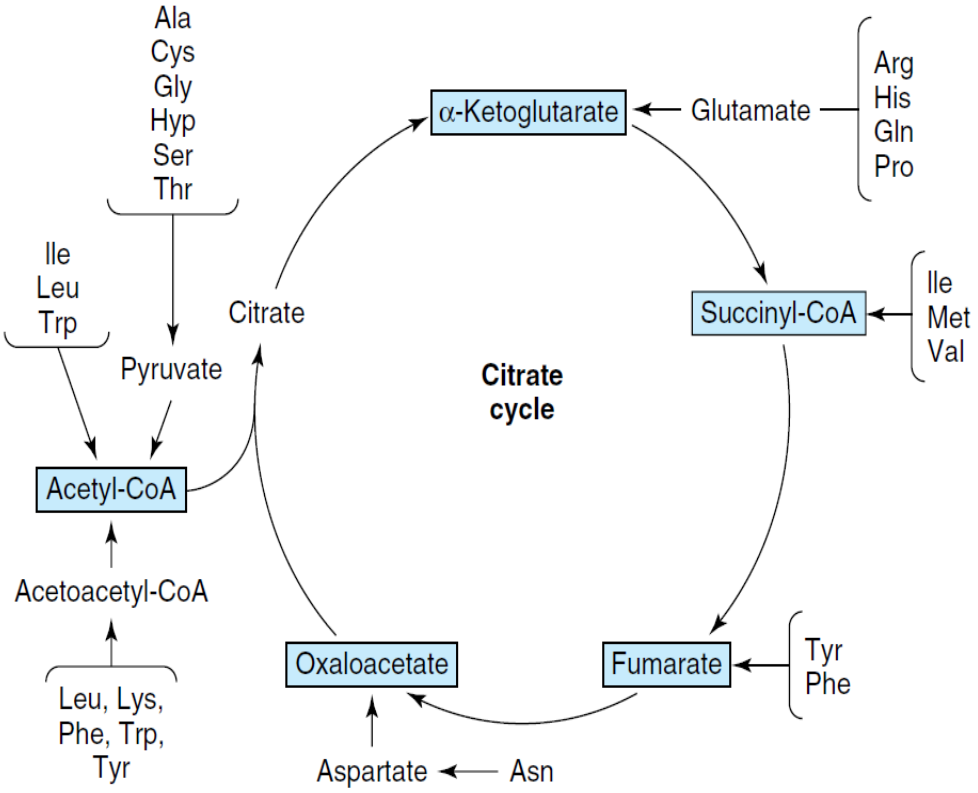
-Carbamoyl phosphate synthetase

-Ornithine transcarbamoylase

-Arginase

Catabolism of the carbon skeleton of amino acids

The hydrocarbon portion of a.as can be carried through a wide variety of pathways& utilized in the synthesis of numerous intermediates . All a.as are ultimatelyconvertible to either acetyl CoA , pyruvate, or intermediates of citric acid cycle .



In addition, these metabolic intermediates ex. pyruvate , oxaloacetate , alpha ketoglutarate ,succinate & fumarate can be utilized for the synthesis of glucose by gluconeogenesis . These a.as called **glucogenic a.as**. Other a.as which ultimately form acetoacetate or acetyl CoA are called **ketogenic a.as** . Some a.as are both glucogenic & ketogenic .

Glucogenic		Ketogenic	Glucogenic and Ketogenic
Ala	Hyp	Leu	Ile
Arg	Met		Lys
Asp			Phe
Asn	Pro		Trp
Cys	Ser		Tyr
Glu	Thr		
Gln	Val		
His			

Transmethylation :

Transmethylation involve the transfer of an intact methyl group from one intermediate to another . The source of such methyl group is methionine . At first the methionine should be converted to **S – adenosyl methionine**

Methyl Adenosyl Transferase

Methionine + ATP →→→ S - adenosyl meth. +PPi+ Pi

The methyl group attached to the sulpher atom of S-adenosyl meth. can be transferred to various acceptor by specific methyl transferases

Acceptor compounds of such methyl group include:

1- phosphatidyle ethanolamine→→→phosph.choline.

2- guanidinoacetic acid→→→→→ creatine

3- nicotinamide →→→→
N – methylnicotinamide

4- norepinephrine →→→→ epinephrine

5- carnosine →→→→ anserine

Creatine metabolism

Creatine is vital to muscles metabolism because it serves as energy store . It is synthesize as follow

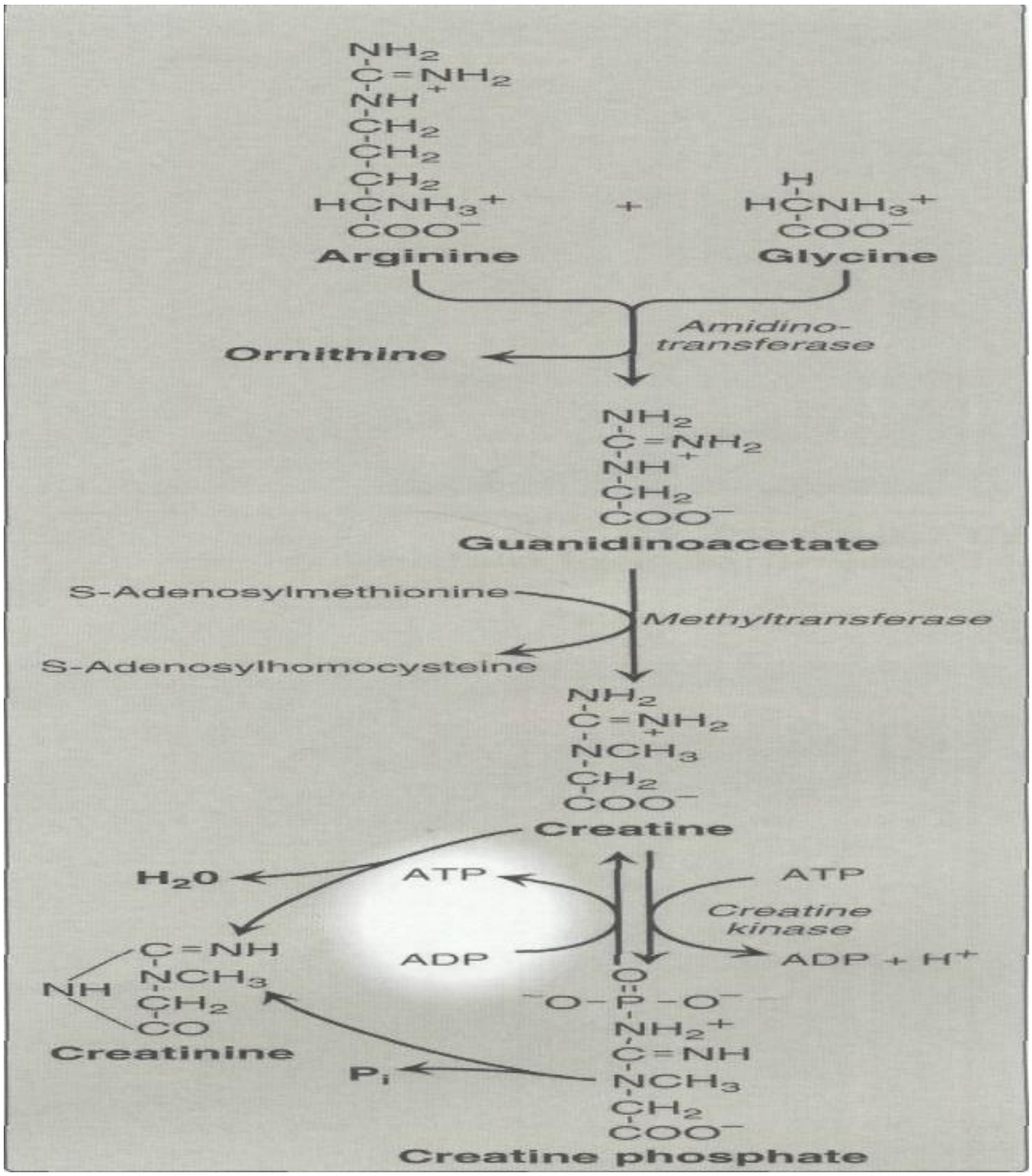
transamidinase
1- Arg. + gly. →→→→ ornithine + guanidinoacetic acid
this reaction occurs in kidney , liver , & pancreas

transmethylase
2- guanid. + S-adenosyl meth.→→→ creatine + S – adenosyl-homocystein

creatine kinase

3- creatine + ATP ↔↔↔ phosphocreatine + ADP

Phosphocreatine has a large negative free energy of hydrolysis (- 9 Kcal / mole) similar to that of ATP . So it serve as storage energy in muscles .



Its availability allows for the rapid conversion of ADP to ATP and the utilization of the latter for muscle contraction . Muscle contain about 40 micromole / gram or 0.5% . phosphocreatine has limited stability and easily transformed to creatinine .

phosphocreatine→→→→→ creatinine + Pi

Creatinine diffuse to blood and excreted in urine . A regulatory mechanism in creatine metabolism is the inhibition of synthesis of guanidinoacetic Acid by creatine .

المحاضره الرابعة

Objectives

The students are learned to understand the Single carbon transfers other than methylation and Biosynthesis of nonessential amino acids

Single carbon transfers other than methylation :

The single carbon carrier in such process is THFA , which can accept one carbon units from various a.as or their metabolites ex.

Serine + THFA ↔↔↔ glycine + N^5 - N^{10} - Methylene THFA

The single carbon unites carried by THFA may be utilized in nucleotides synthesis. Other example of single carbon transfer include the formation of serine from glycine (by reverse of above reaction) & of methionine from homocysteine .

Biosynthesis of nonessential amino acids :

A number of a.as can be synthesized from components of glycolytic pathway and the CAC . In addition several of the a.as can be formed from other a.as. These a.as called nonessential a.as i.e. they can be made available to the cells even though they are not included in the diet.

Essential amino acids	Nonessential amino acids
Arg*	Ala Ser
His*	Asp Tyr
Leu	Asn
Ile	Cys
Lys	Glu
Met	Gln
Phe	Gly
Thr	Pro
Val	Hyp
Trp	Hylys

***Alanine** from pyruvate by transamination

pyruvate + glu. ↔↔↔ alanine + alpha – ketoglut.

***Aspartate** from oxaloacetate by transamination

oxaloacetate + glu.↔↔↔ aspartate + alpha - ketoglutarate

***Glutamate** is formed by transamination when the above reaction is reversed. Glutamate also formed from alpha- ketoglutarate by glutamate dehydrogenase reaction**.**

Aspartate & glutamate also formed as a result of the hydrolysis asparagine & glutamine by the enzyme Asparaginase & Glutaminase

***Glutamine** is synthesized as follow

glutamine synthetase

glutamate + ATP + NH_3 →→→→ glutamine + ADP + Pi

***Asparagine**

Asparagine synthetase

aspartate +glutamine + ATP →→→→→ Asparagine + ADP + Pi

***Proline** can be formed from glutamate

***Serine** is formed from 3 – phospho - glycerate (glycolytic intermediate)

*G**lycine** is generated by a single carbon transfer from serine to THFA

***Cysteine** can be synthesized from the carbon skeleton of serine

Cystathionine Synthase

homocysteine + serine →→→ cystathionine

Cystathionase

Cystathionine →→→→→ cysteine + alpha – ketobutyrate

***Tyrosine** is formed from phenylalanine & oxygen by the NADPH dependent enzyme called **phenylalanine hydroxylase** which require the coenzyme **tetrahydrobiopterin**

phenylalanine + NADPH + H+ + O2→→ tyrosine + NADP + H2O

Tyrosine and cysteine are formed from an essential amino acid and, is therefore, nonessential only in the presence of adequate dietary phenylalanine and methionine.

المحاضره الخامسة

Objectives:

The students are learned to understand the conversion of amino acids to specialized products including Glycine, Serine, Methionine, Histidine, Arginine, Tryptophan, Tyrosine, and Glutamate.

Conversion of amino acids to specialized products:

Glycine

-synthesis of heme

-synthesis of purine nucleotides

-synthesis of creatine

-formation of glycine conjugates ex.

cholic acid + glycine→→ glycocholic acid

Serine

-phosphatidyl serineinvolved in the synthesis of sphingosine

- involved in the synthesis of purine & pyrimidine nucleotide

Methionine

S-adenosyl methionine is the methyl donor in various synthetic reactions. S-adenosyl methionine also serve as precursor for the synthesis of 1,3 – diaminopropan portions of the polyamines : spermine & spermidine (growth factors)

Histidine

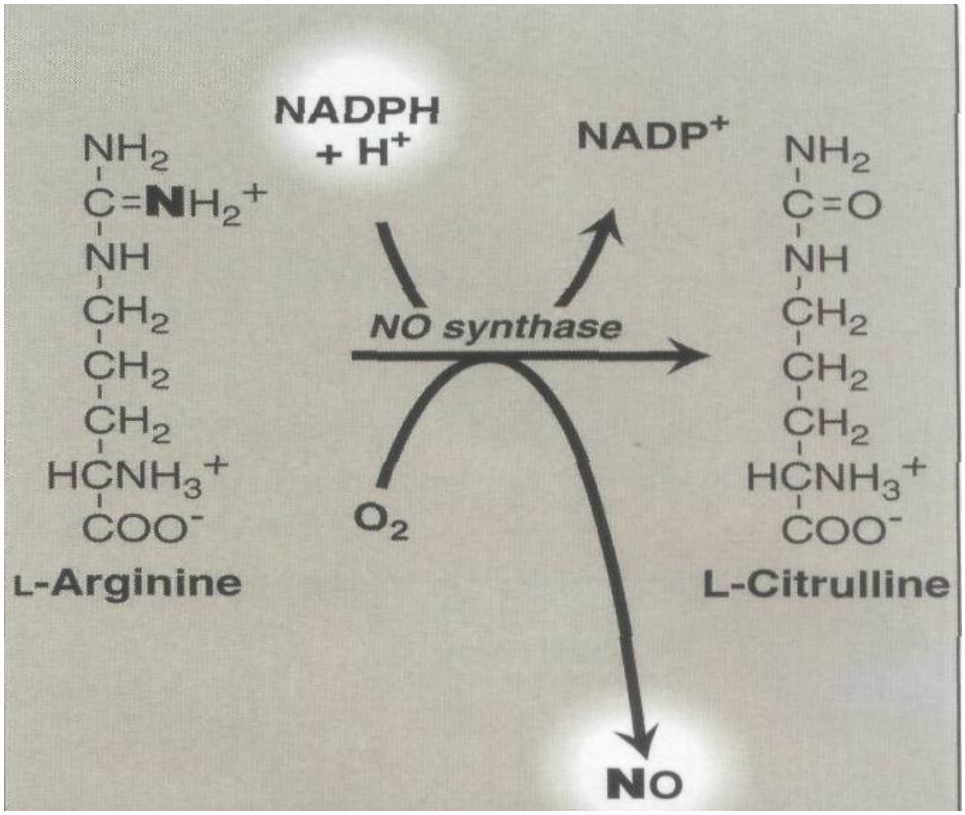
Decarboxylation of histidine yield thehistamine

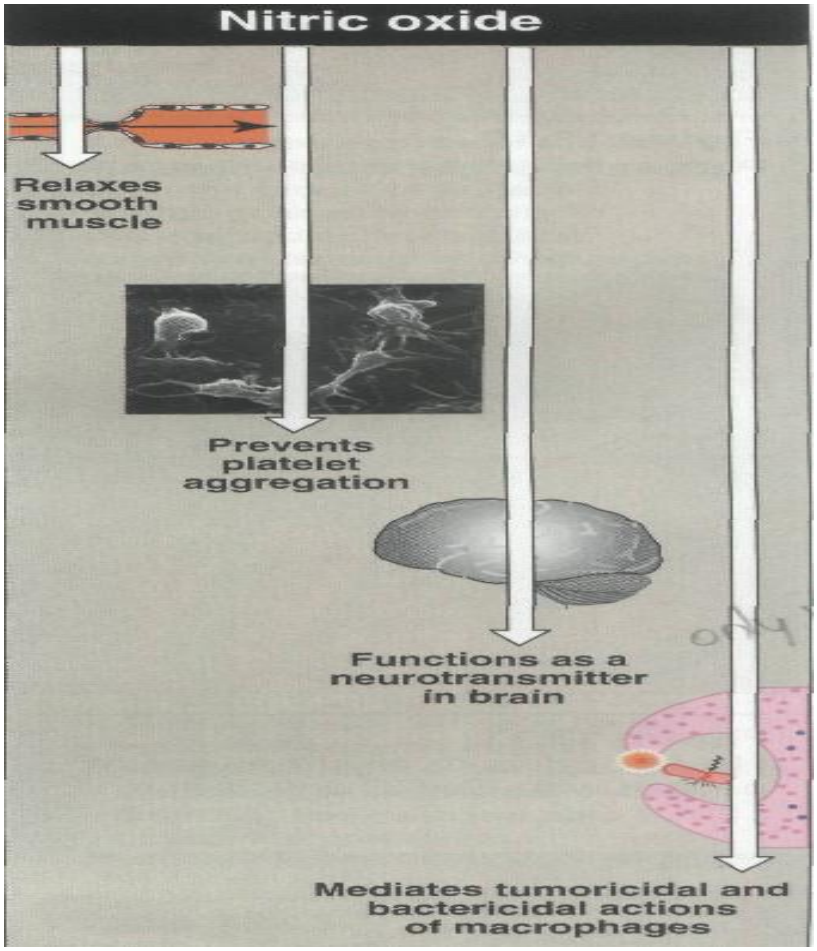
Arginine

-Creatine synthesis

-Spermine & spermidine synthesis

-precursor for nitric oxide





Tryptophan

- Serotonin

hydroxylation

tryptophan →→→ 5-hydroxytryptophan

↓

decarboxylation ↓

↓

5-hydroxytryptamine

(serotonin)

-Melatonin (formed in pineal body)

Serotonin →→ N- acetyl serotonin

↓

↓

melatonin

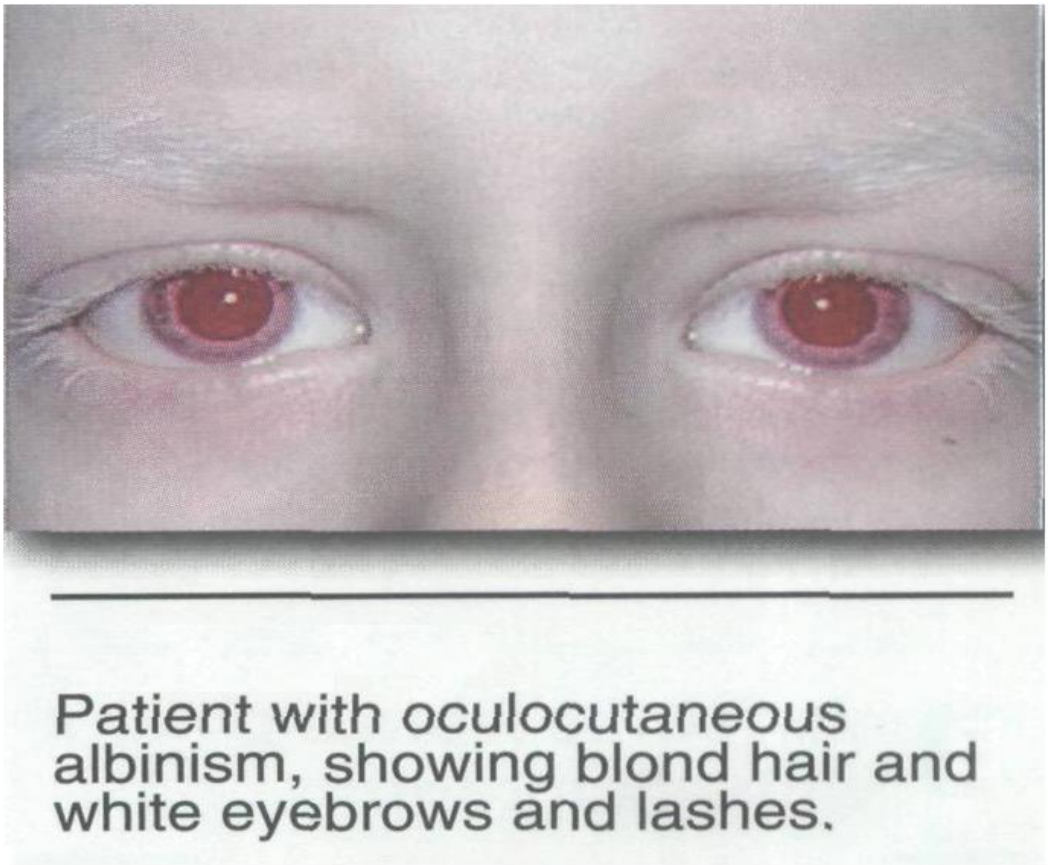
Tyrosine

-melanin synthesis

albinism : deficiency in tyrosinase in melanocytes .

-epinephrine & norepinephrine

-thyroid hormones



Patient with oculocutaneous albinism, showing blond hair and white eyebrows and lashes.

Glutamate

- ỳ - aminobutyrate (GABA)

glutamate decarboxylase

glutamate →→→→→→ ỳ - aminobutyrate

-glutathione formed from glutamate, cysteine , glycine

المحاضره السادسة

Objectives:

The students are learned to understand the Inborn error of aminoacids metabolism including Cystinuria, Cystinosis, Homocystinuria, Hyperhydroxyprolinemia, Hyperprolinemia, Histidinemia, the Inborn error of Tyrosine metabolism, Phenylketonuria, and Maple syrup urine disease

Inborn error of aminoacids metabolism:

Cystinuria

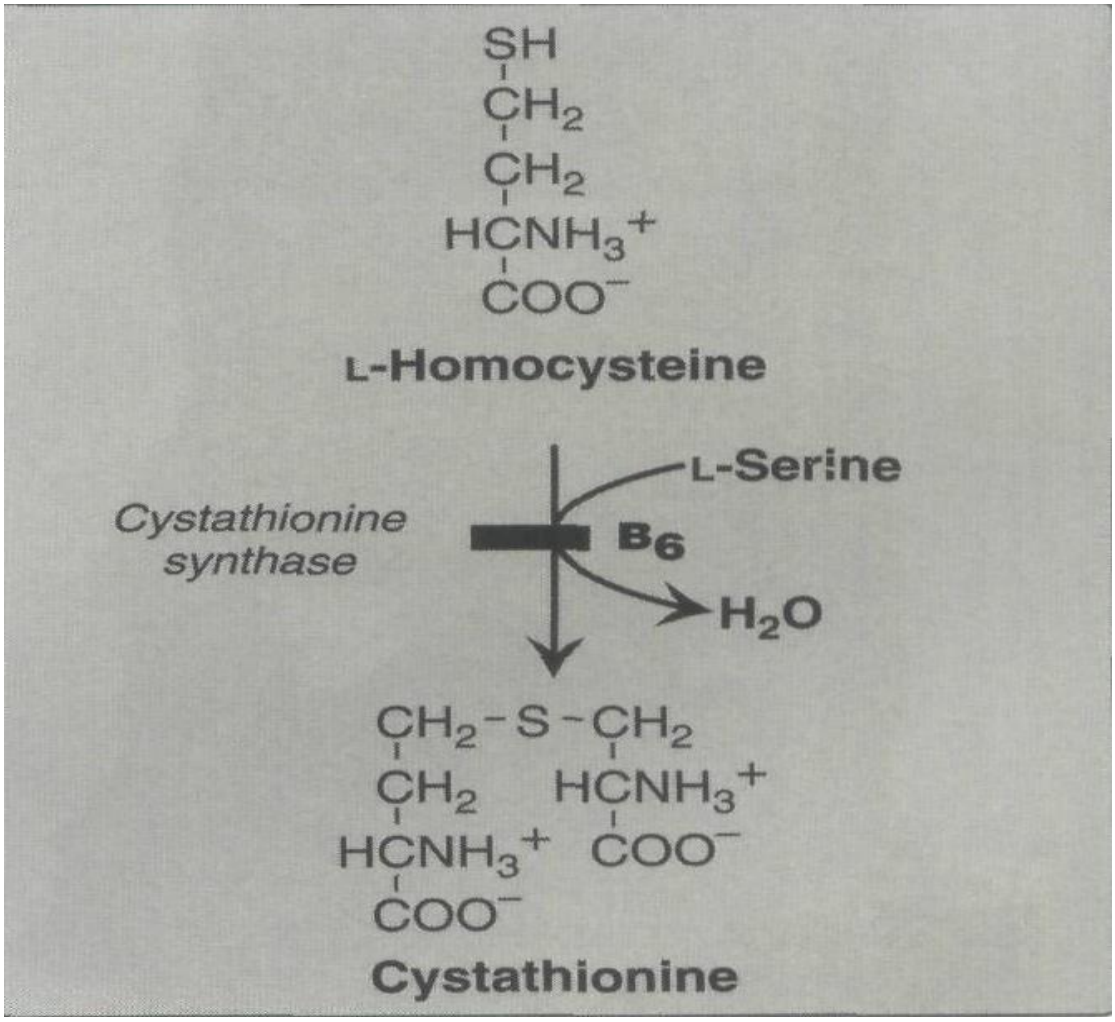
inherited metabolic disorder. Urinary excretion of cystine is 20 – 30 times above normal . Excretion of lysine , arginine , & ornithine is also increased suggesting a defect in the renal reabsorption for these four a.as. The disease expresses itself clinically by the precipitation of cystine to form kidney stones

Cystinosis

Inherited disorder results from defective carrier -mediated transport of cystine in which cystine crystals deposited in many tissues .

Homocystinuria

A group of disorders involving defects in the metabolism of homocysteine. The diseases are inherited as autosomal recessive illnesses, characterized by high plasma and urinary levels of homocysteine and methionine and low levels of cysteine.



The most common cause of homocystinuria is a defect in the enzyme *cystathionine synthase, which converts homocysteine to cystathionine*

Hyperhydroxyprolinemia

High plasma level of 4 – hydroxyproline due to deficiency 4 – hydroxyproline dehydrogenase .

Hyperprolinemia

High plasma level of proline due to deficiency of proline dehydrogenase

Histidinemia

Increased level of histidine in blood & urine due to impaired the activity of liver histidase

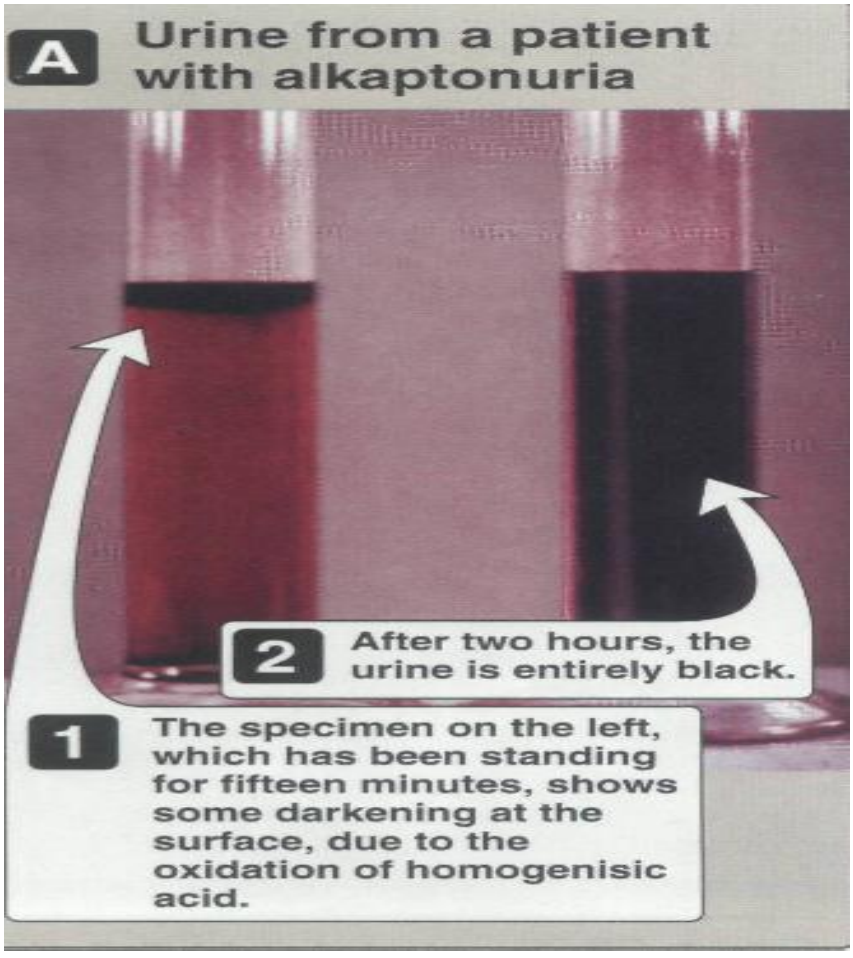
Tyrosine

-Tyrosinemia type I :defect in the fumaryl acetoacetate hydroxylase

-Tyrosinemia type II : defect in hepatic tyrosine transaminase

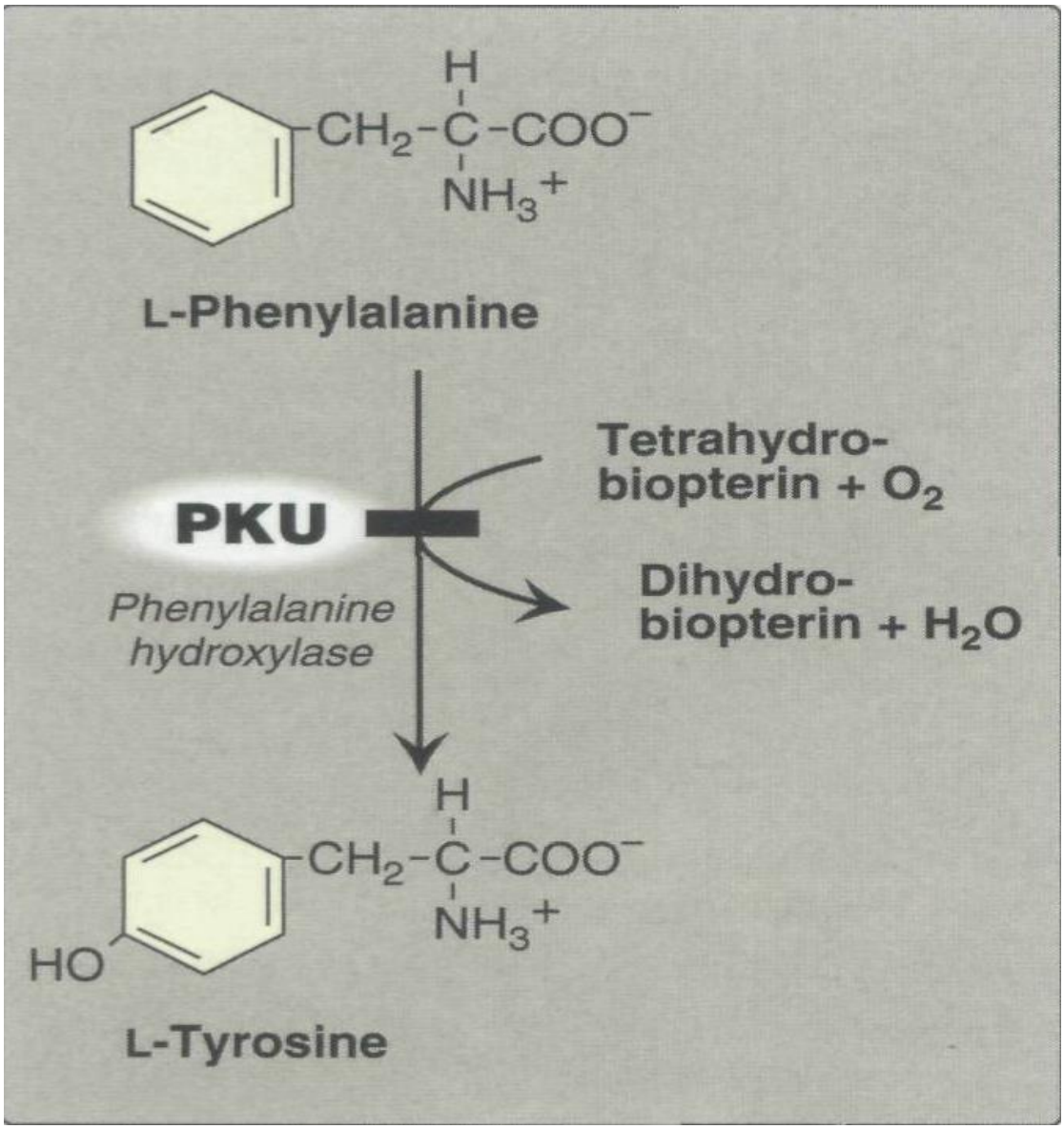
-Alkaptonuria : due to lack of homogentisate oxidase . Homogentisate is excreted in urine where it is oxidized in air to a brownish black pigment

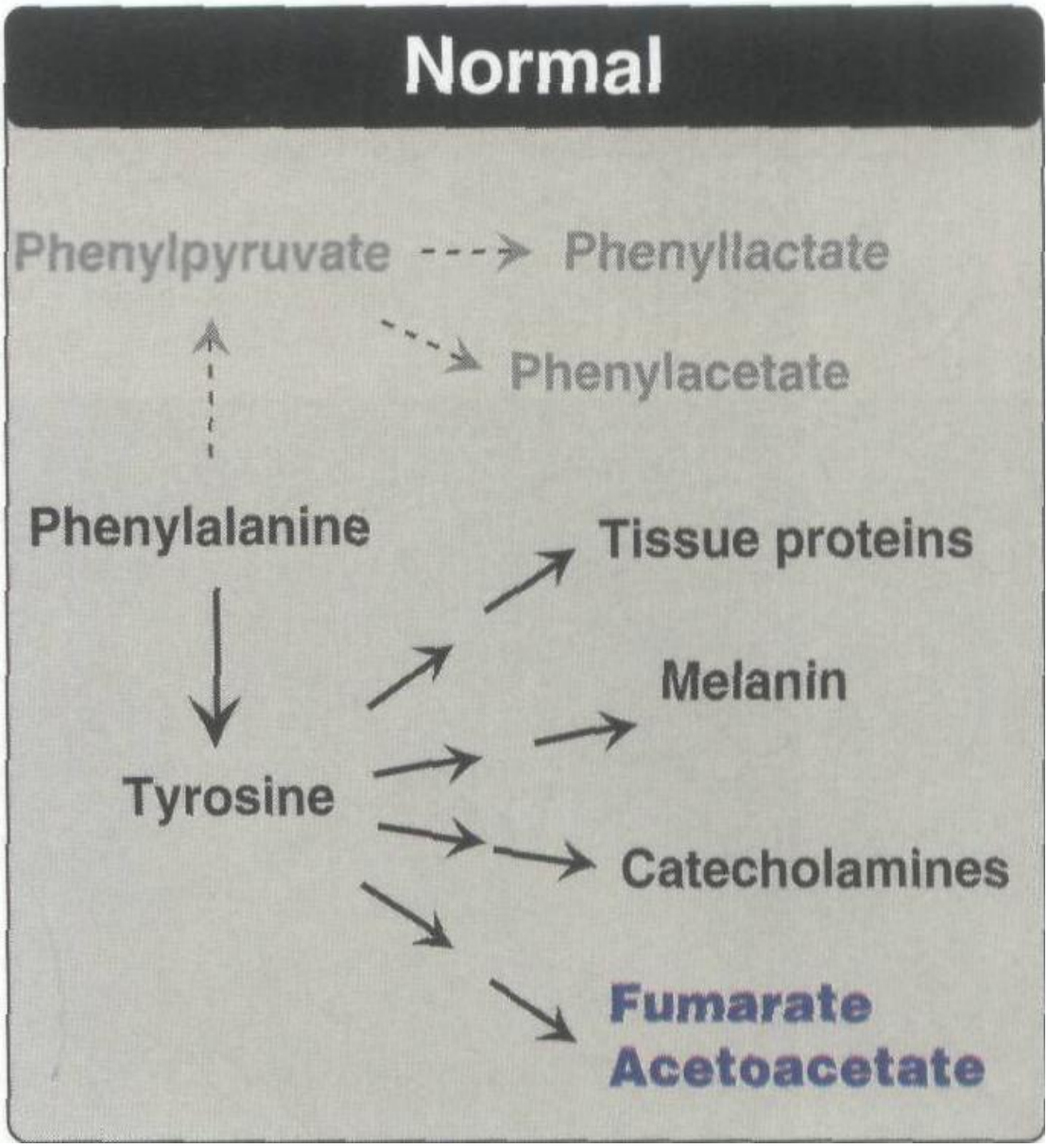
- **Albinism**

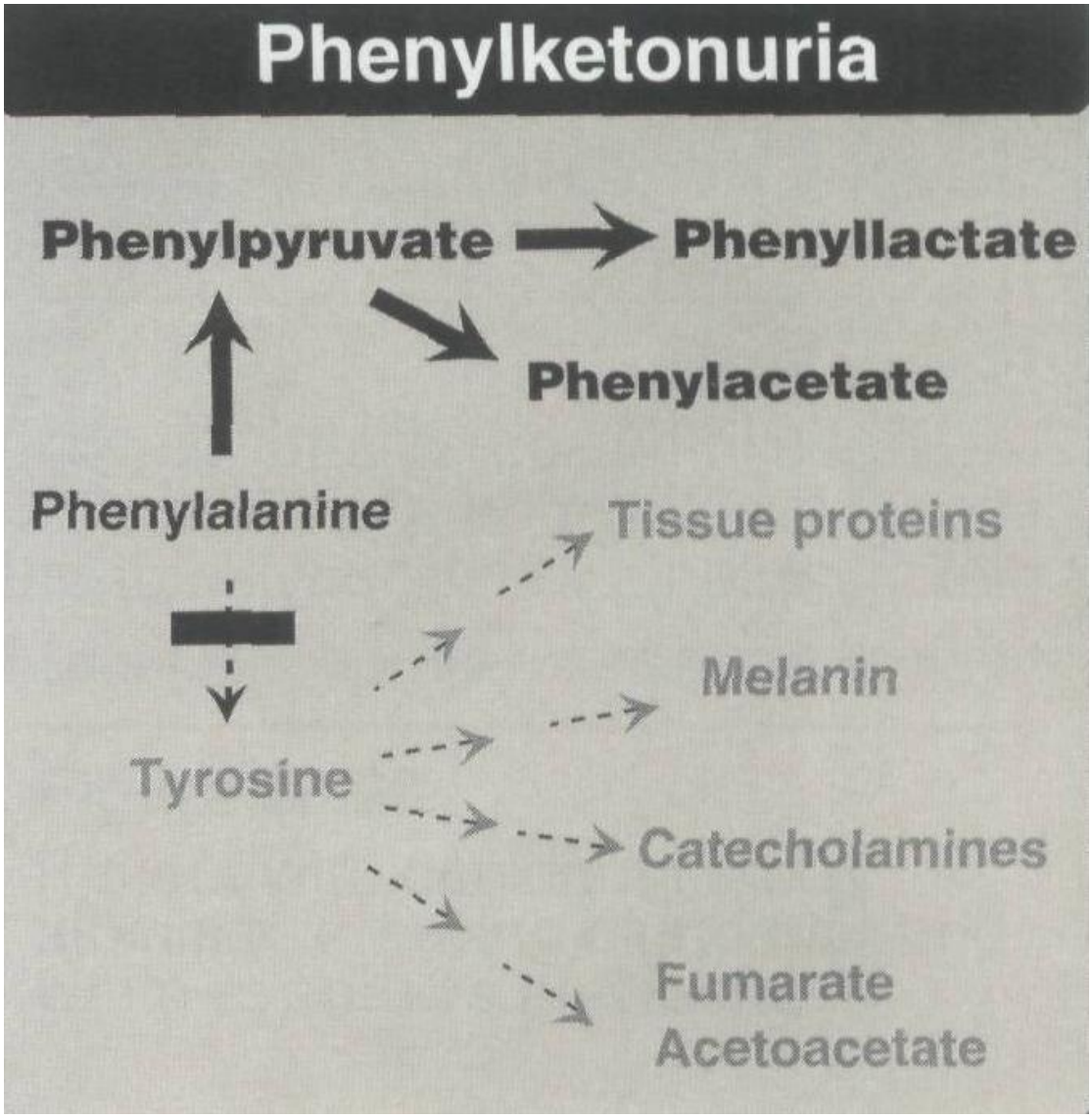


Phenylketonuria

Impaired ability to convert phenylalanine to tyrosine due to deficiency of *phenylalanine hydroxylase. It is the most common clinically encountered inborn error of amino acid metabolism. Hyperphenylalaninemia* may also be caused by deficiencies in the enzymes that synthesize or reduce the coenzyme Tetrahydrobiopterin.




Normal
Phenylpyruvate
Phenyllactate
Phenylacetate
Phenylalanine
Tissue proteins
Melanin
Tyrosine
Catecholamines
Fumarate
Acetoacetate



Maple syrup urine disease

characteristically the odor of urine resembles that of maple syrup. Plasma & urinary levels of leucine, isoleucine, valine & their alpha ketoacid metabolites are greatly elevated. It due to absence or greatly reduce activity of the branched-chain alpha – keto acid Dehydrogenase that catalyzed the decarboxylation of all 3 branched chain amino acids