الكلية : كلية الطب العام

القسم او الفرع : فرع الكيمياء والكيمياء الحياتية

المرحلة : الاولى

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اسم المحاضرة السادسة باللغة الانكليزية: Protein and amino acid Metabolism


Protein and amino acid
Metabolism

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* Amino acids classification and general properties of protein.
* Metabolism of amino acid and Protein .
*Catabolism of amino acid.
* Ammonia formation.
* Urea Cycle.
* Conversion of amino acid in to special products.
* Disorders of amino acid.

INTRODUCTION

Proteins are present in every cell of humans, animals, plant tissues.

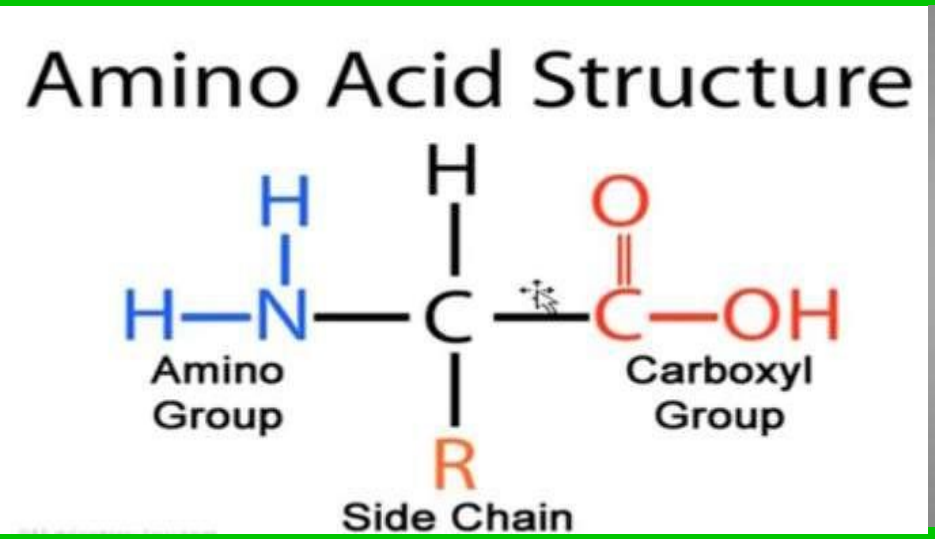
Proteins a large molecule composed of one or more chains of amino acids.

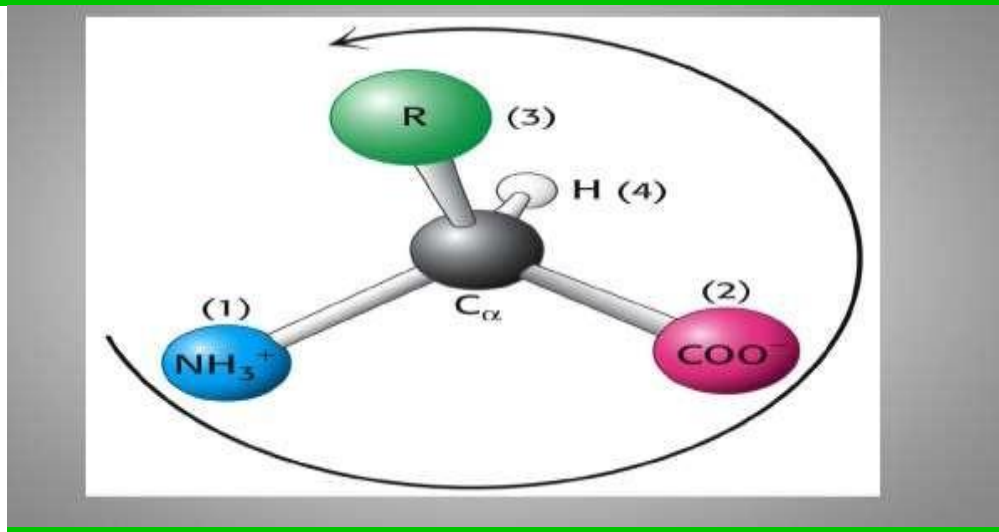
They account for about 50% of the dry weight of a cell.

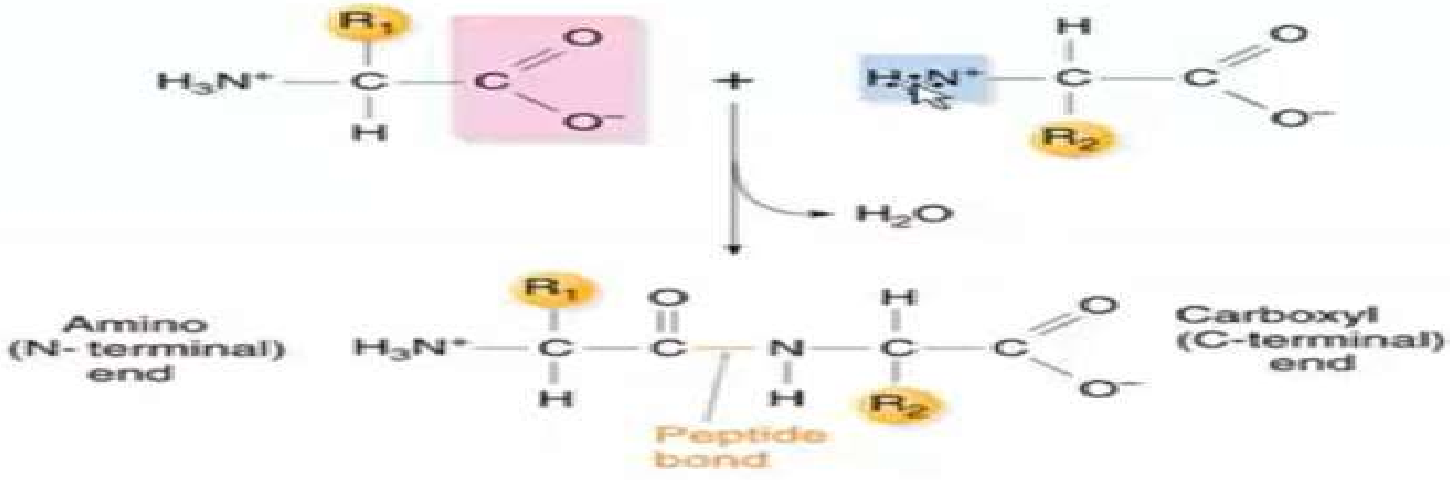
All proteins are polymers of amino acids. The amino acids in proteins are united through "Peptide" linkage. Sometimes proteins are also called as polypeptides because they contain many peptide bonds.

Structure of amino acids:

Each amino acid has 4 different groups attached to α- carbon (which is C-atom next to COOH). These 4 groups are: amino group, COOH group, Hydrogen atom and side Chain (R).







Peptide bond formation

Each polypeptide chain starts on the **left side by free **amino group** of the first amino acid enter in chain formation, it is termed **(N-terminus).***

Each polypeptide chain ends on the **right side by free **carboxylic group** of the last amino acid termed **(C-terminus).***

SUBCLASSIFICATION OF AMINO ACIDS:|

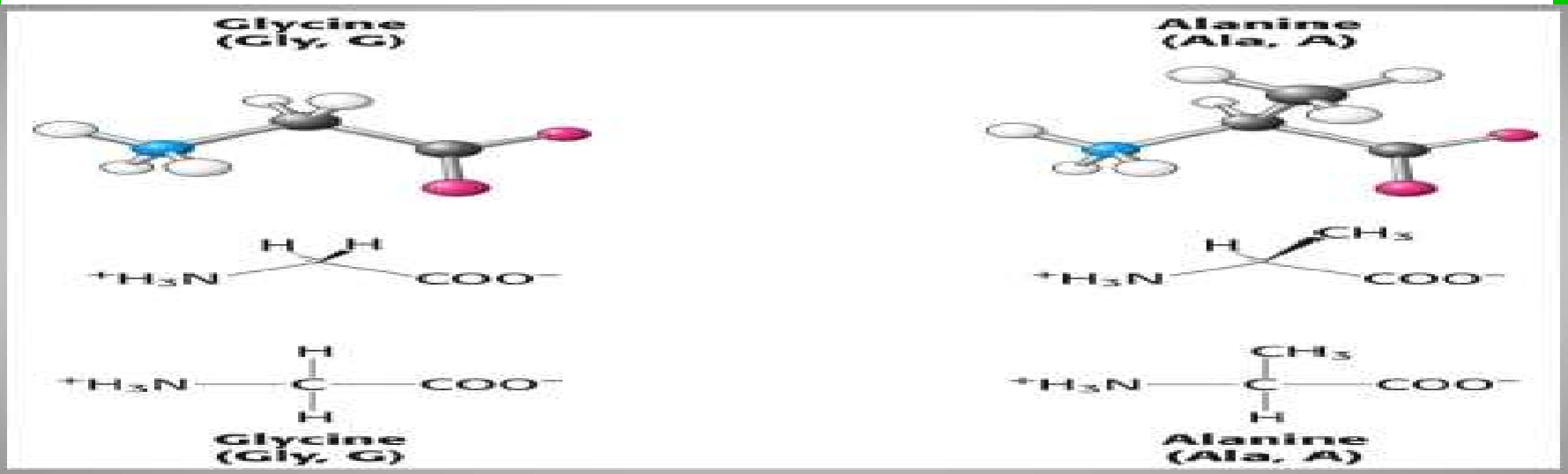
I- According to net charge on amino acid. A-NEUTRAL AMINO ACIDS:

A- NUTRAL AMINO ACIDS:

All structures are required

1- Glycine (Gly) R=H

2- Alanine (Ala) $R=CH_3$



3- Branched chain amino acids:

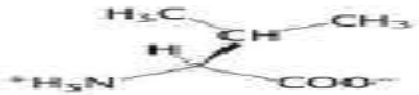
R is branched such as in:

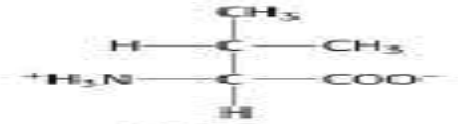
a – Valine — R= isopropyl gp

b- Leucine — R= isobutyl gp

c- Isoleucine — R = is isobutyl

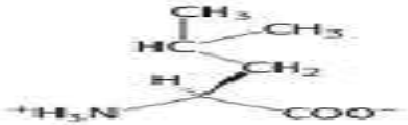
Valine (Val, V)

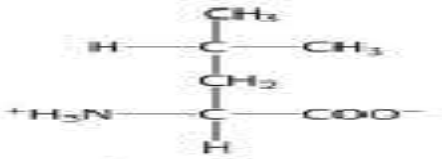




Valine (Val, V)

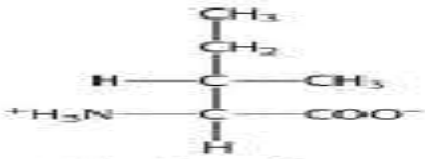
Leucine (Leu, L)





Leucine (Leu, L)

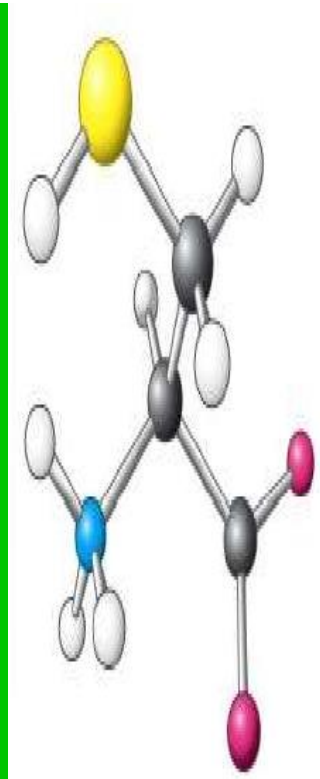
Isoleucine (Ile, I)

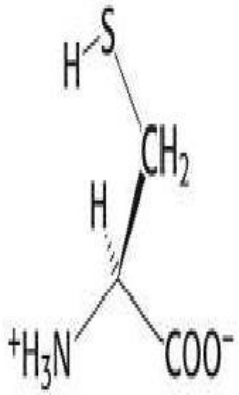


Isoleucine (Ile, I)

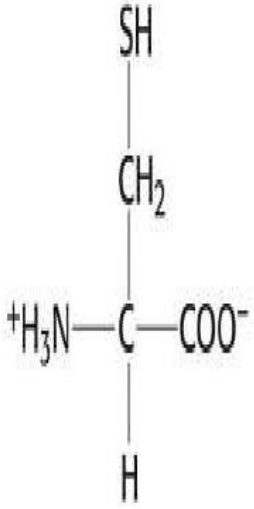
4- Neutral Sulfur containing amino acids:

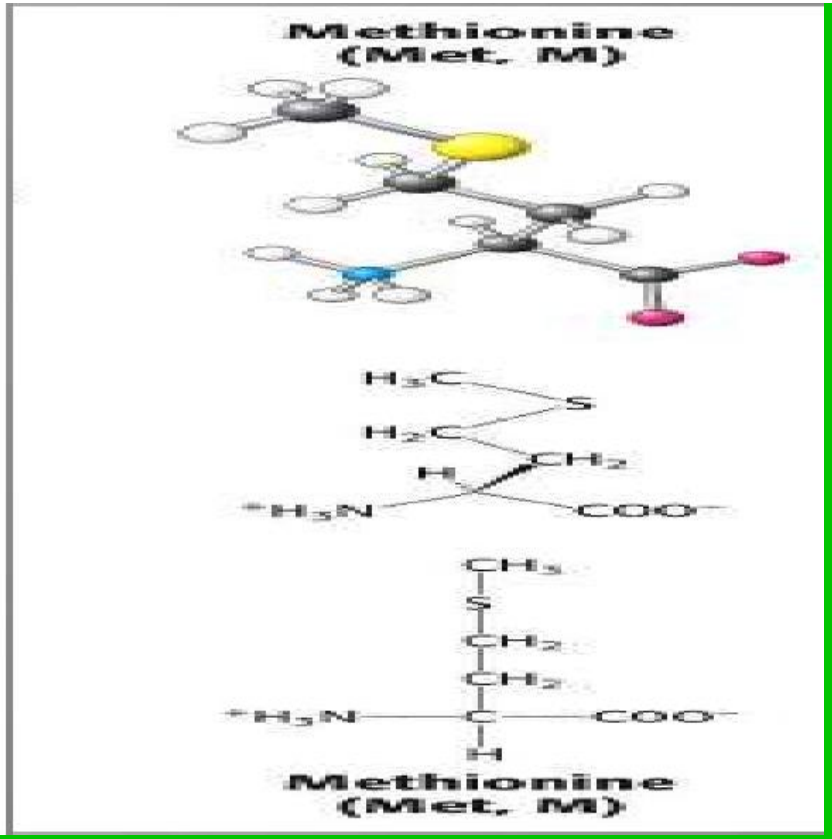
Cysteine and Methionine .





Cysteine
(Cys, C)

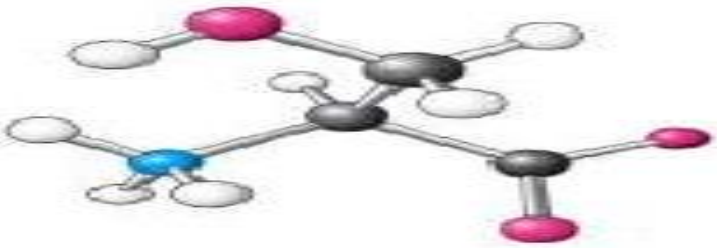


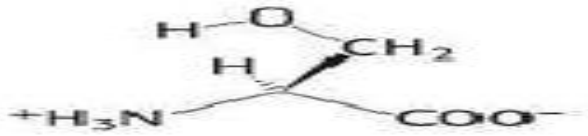


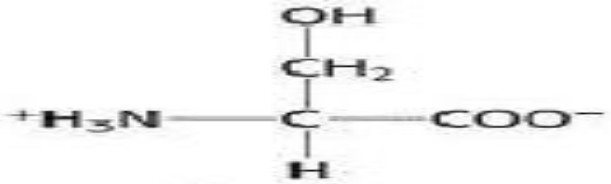
5- Neutral, hydroxyl amino acids:

E.G. : Serine and Threonine.

Serine
(Ser, S)

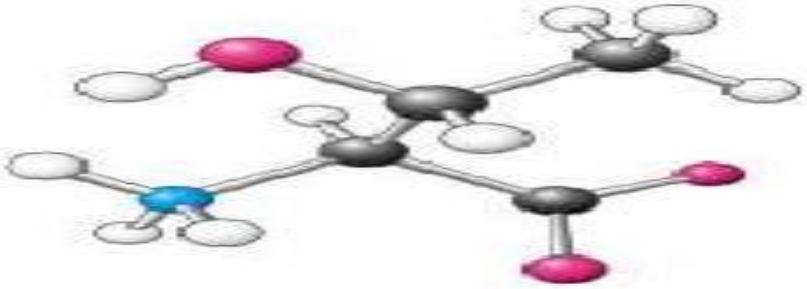


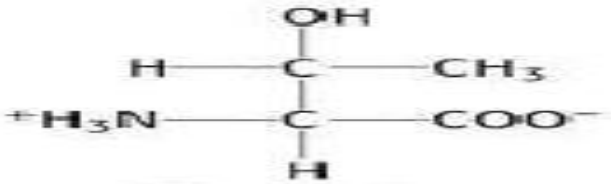




Serine
(Ser, S)

Threonine
(Thr, T)





Threonine
(Thr, T)

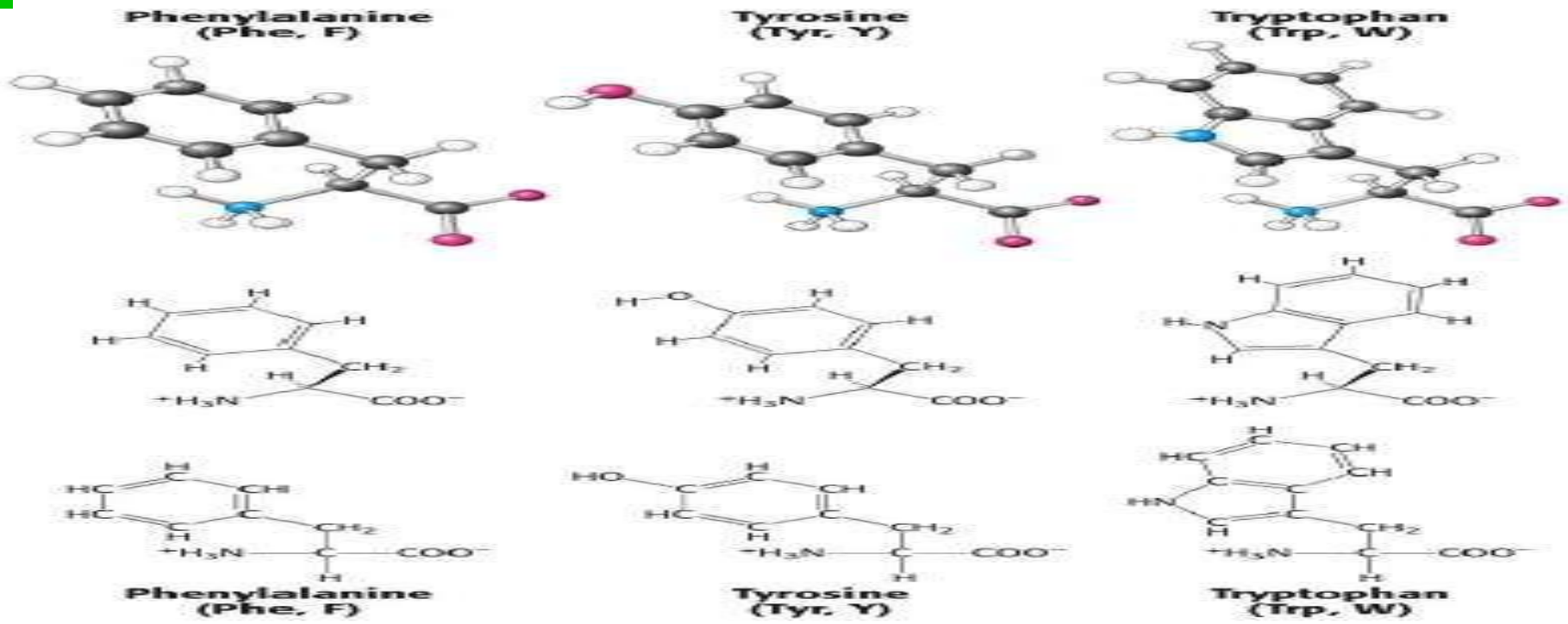
6- Neutral aromatic amino acids:

a- ***Phenyl alanine :*** It's alanine in which one hydrogen of CH_3 is substituted with phenyl group. So it's called phenyl alanine

b- ***- Tyrosine:*** - it is P- hydroxy phenyl alanine

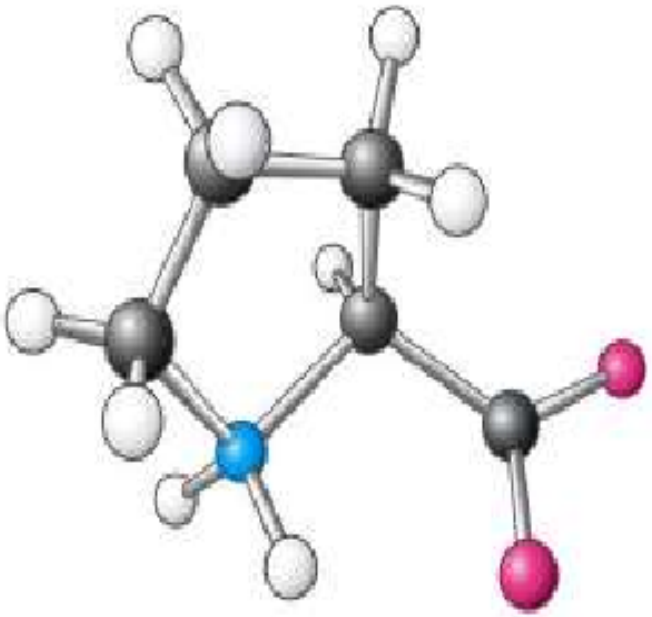
it is classified as phenolic amino acid

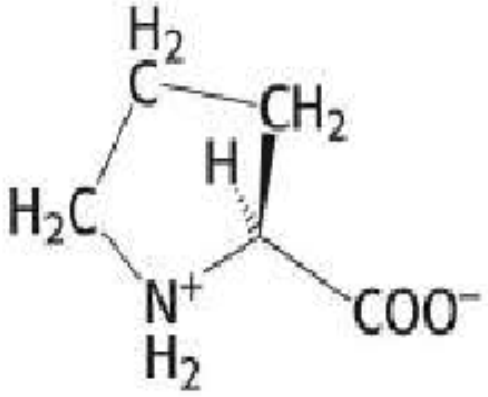
c- ***Tryptophan:*** as it contains indole ring so it is classified as heterocyclic amino acid.



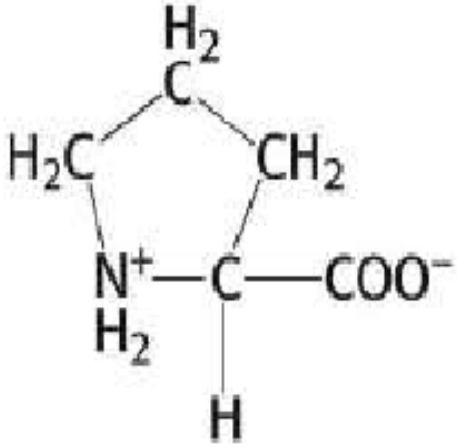
7- Neutral heterocyclic amino acids:

Proline: In proline, amino group enters in the ring formation being α imino gp so proline is an α-imino acid rather than α amino acid .





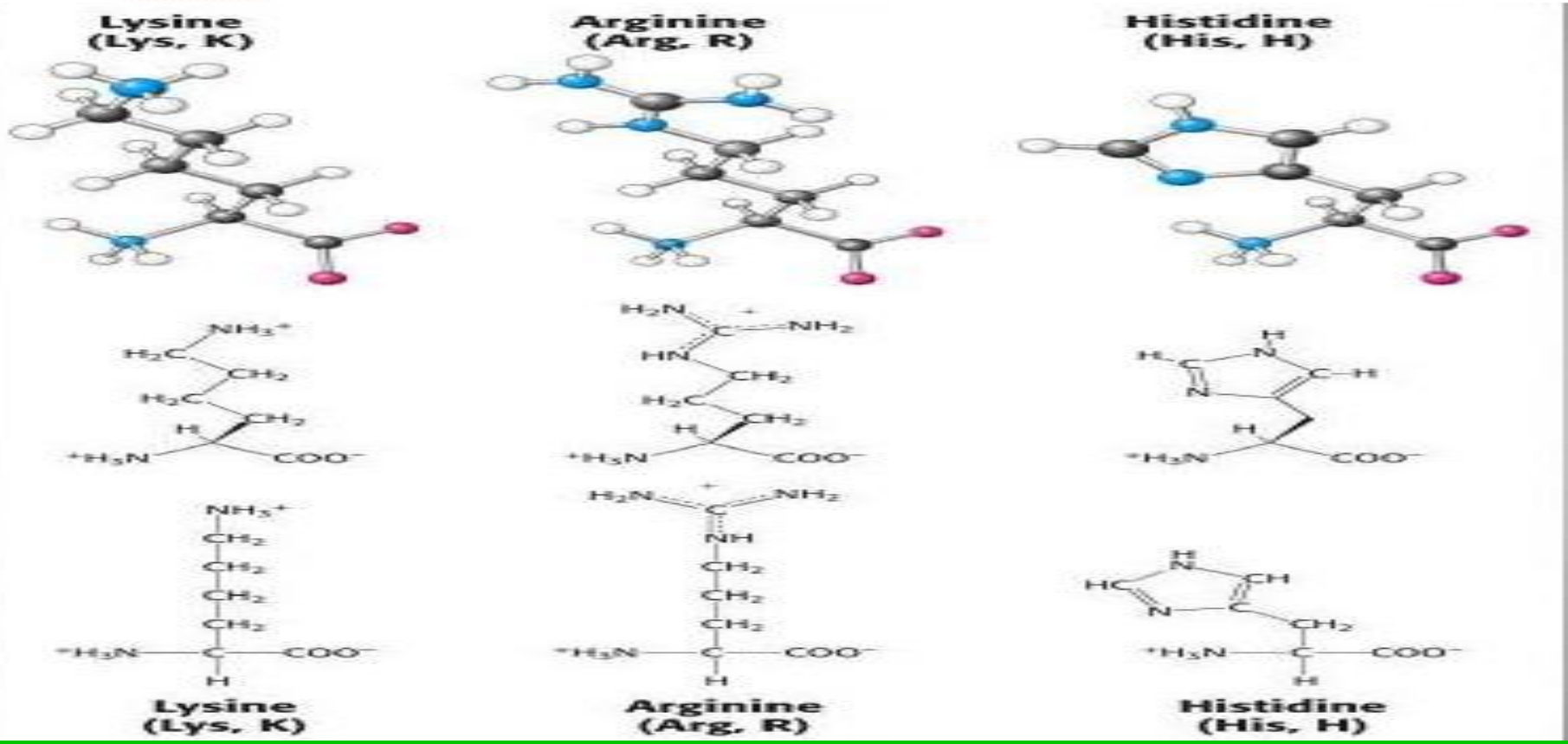
Proline
(Pro, P)



B- BASIC AMINO ACIDS:

Contain two or more NH2 groups or nitrogen atoms that act as base i.e. can bind proton. At physiological pH, basic amino acids will be positively charged.

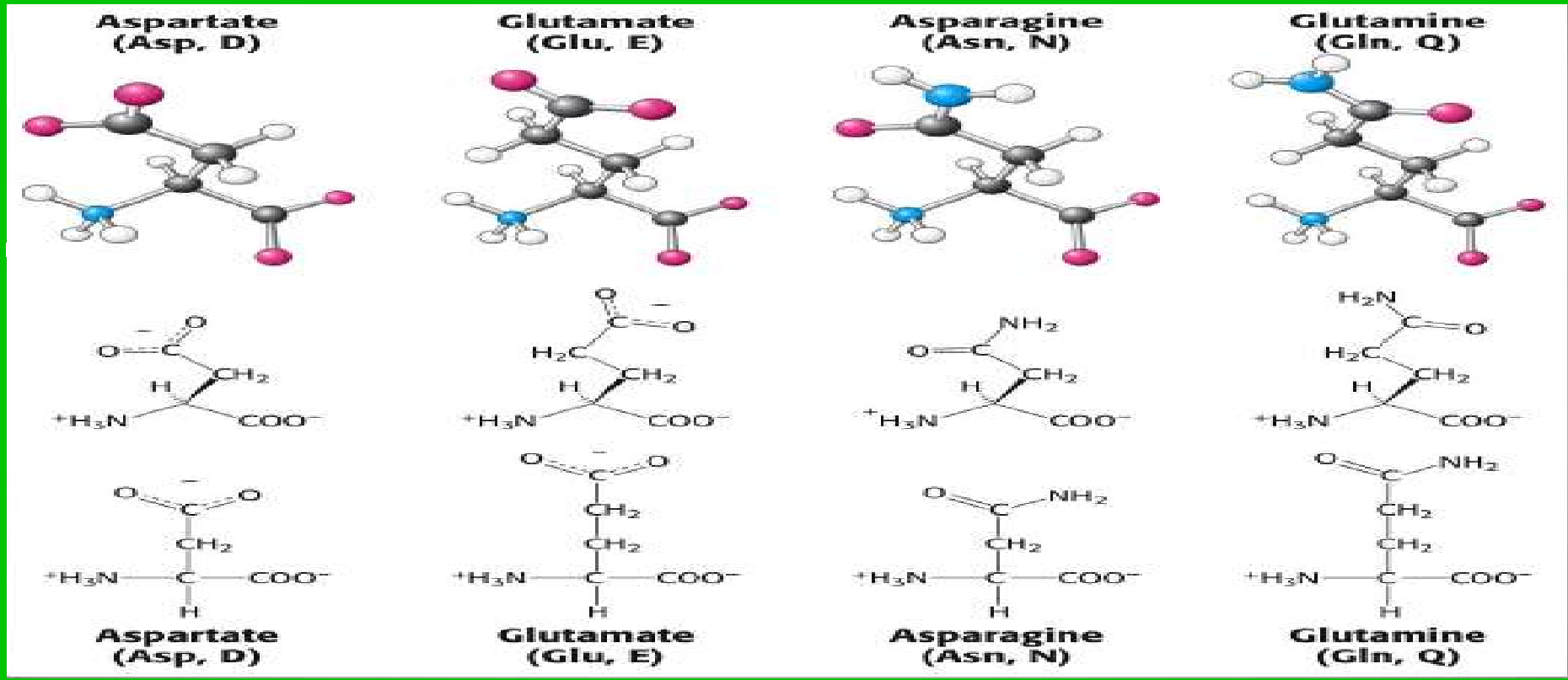
a- *Lysine*
b- *Arginine: contains guanido group*
c- *Histidine: is an example on basic heterocyclic amino acids.*



C- ACIDIC AMINO ACIDS : *at physiological pH will carry negative charge.*

E.G. Aspartic acid (aspartate) and Glutamic acid (glutamate). see structures in hand out.

Aspargine and Glutamine: They are amide forms of aspartate and glutamate in which side chain COOH groups are amidated. They are classified as neutral amino acids



Nutritional classification:

1- Essential amino acids: *These amino acids can't be formed in*

the body and so, it is essential to be taken in diet. Their deficiency affects growth, health and protein synthesis. Half of the amino acids listed cannot be made by human body. These eight are called essential amino acids (Val, Leu, Ilo, Phe, Trp, Thr, Lys,, Met). They are indicated by an asterisk in the Table

2- Semiessential amino acids: *These are formed in the body but not in sufficient amount for body requirements especially in children.*

** Semi-essential amino acids (Arg, His). These amino acids must be obtained from the food we eat.*

3- Non essential amino acids: *These are the rest of amino acids*

that are formed in the body in amount enough for adults and children. They are the remaining 10 amino acids.

Classification of Amino Acids

Nonessential	Essential
Alanine	Arginine*
Asparagine	Histidine*
Aspartate	Valine
Cysteine	Lysine
Glutamate	Isoleucine
Glutamine	Leucine
Glycine	Phenylalanine
Proline	Methionine
Serine	Threonine
Tyrosine	Tyrptophan

Metabolic fate classification:

according to metabolic or degradation products of amino acids they may be:

1- Ketogenic amino acids: which give ketone bodies. Lysine and Leucine are the only pure ketogenic amino acids.

2- Mixed ketogenic and glucogenic amino acids: which give both ketonbodies and glucose. These are: isoleucine, phenyl alanine, tyrosine and tryptophan.

3- Glucogenic amino acids: Which give glucose. They include the rest of amino acids. These amino acids by catabolism yields products that enter in glycogen and glucose formation.

Fate of Amino Acids (Metabolic pathways)

A. Anabolic pathways:

Protein synthesis (tissue proteins, plasma proteins, enzymes, some hormones, milk, repair/maintenance, etc.).

B. Catabolic pathways:

(Transamination and Deamination), amino acids are catabolized i.e. amino group is separated from the carbon skeleton (keto acid).

Carbon skeleton is used as a source of energy & Ammonia (NH3) for urea synthesis or other synthetic

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.

Biological Significance of Transamination

1. First step of catabolism

In this first step, ammonia is removed, and the carbon skeleton of the amino acid enters into catabolic pathway.

2. Synthesis of nonessential amino acids

By means of transamination, all nonessential amino acids can be synthesized by the body from keto acids available from other sources. For example, pyruvate can be transaminated to synthesize alanine. Similarly oxaloacetate produces aspartic acid. Alpha keto glutarate is transaminated to form glutamic acid. Those amino acids, which cannot be synthesized in this manner, are therefore essential: they should be made available in the food.

3. Interconversion of amino acids

If amino acid no.1 is high and no.2 is low; the amino group from no.1 may be transferred to a keto acid to give amino acid no. 2 to equalize the quantity of both. This is called equalization of quantities of nonessential amino acids.

PROTEIN AND AMINO ACID METABOLISM

General Metabolism of Amino Acids

1. ***The anabolic reactions*** where proteins are synthesized.

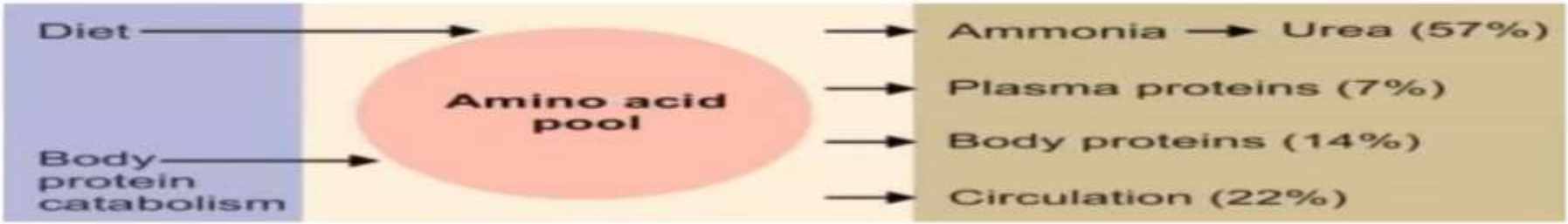
2. Synthesis of specialized products such as ***heme, creatine, purines and pyrimidines.***

3. ***The catabolic reactions*** ***where dietary proteins and body proteins are broken down to amino acids.***

4. Transamination: amino group is removed to produce the carbon skeleton (keto acid). The amino group liberated as ammonia is detoxified and excreted as urea.

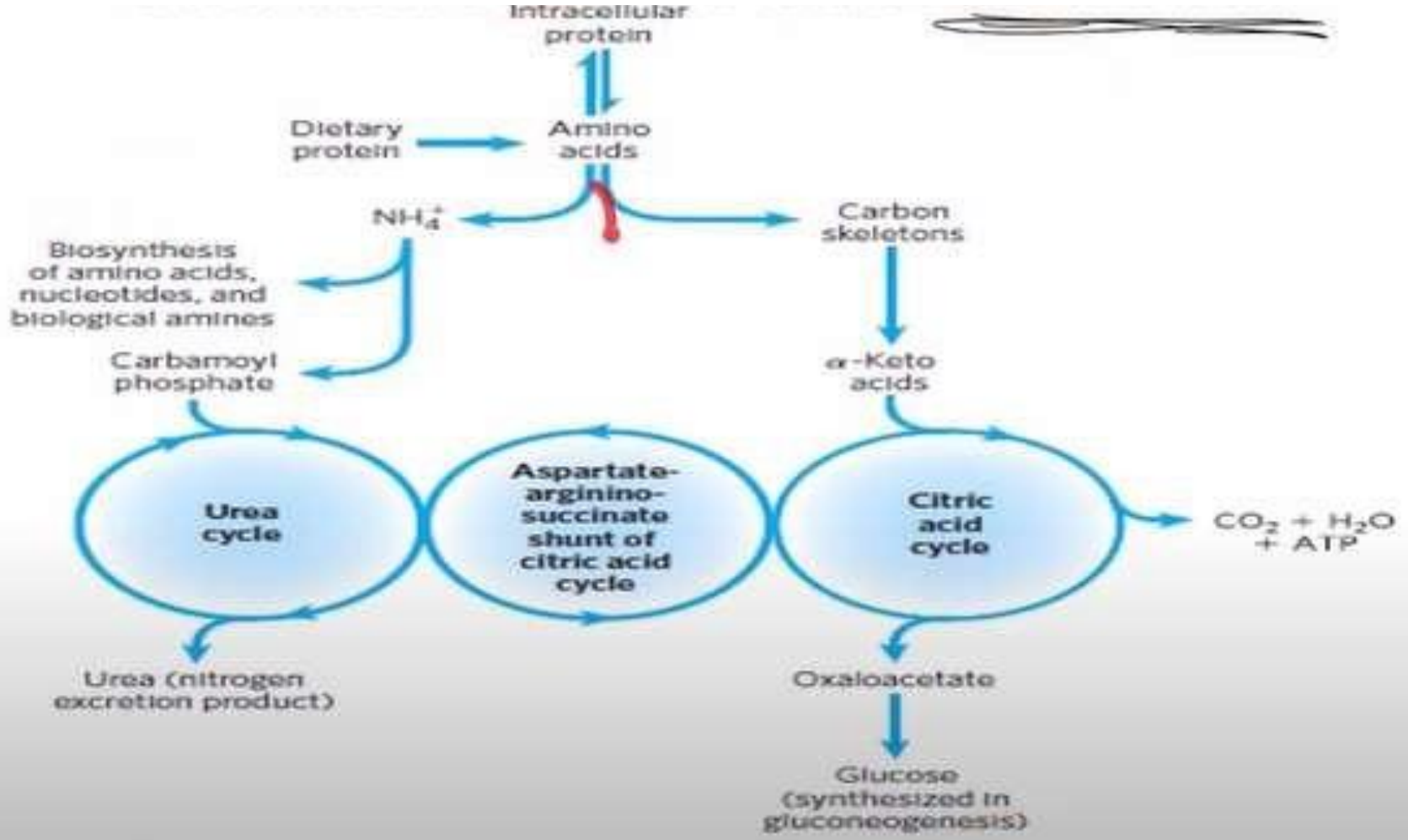
5. The carbon skeleton is used for synthesis of nonessential amino acids.

6. It is also used for gluconeogenesis or for complete oxidation.



Overview of amino acid catabolism

Intracellular protein



Catabolic pathways of Amino acids

1. Transamination:

The transfer of an amino (NH2) group from an amino acid, to an a- keto acid (carbon skeleton of a.a) => reversible reaction. the original amino acid is converted to the corresponding a-keto acid and vice versa.

It is Catalyzed by aminotransferases (transaminases):

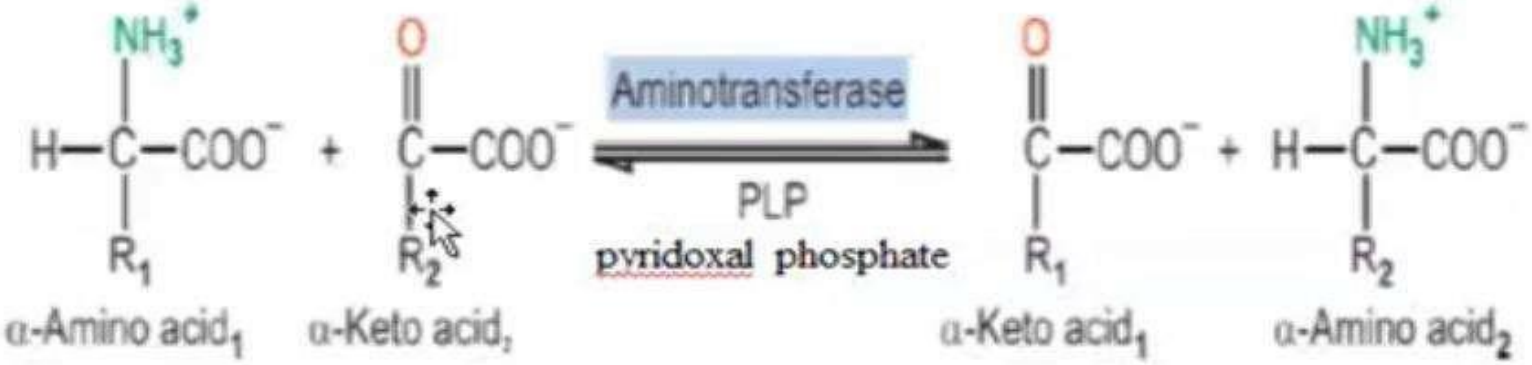
1) Alanine aminotransferase (ALT).

2) Aspartate aminotransferase (AST).

**** Enzymes/Co-enzymes involved are:***

Vitamin B6 (pyridoxal phosphate, PLP) is an essential component of the transamination reactions.

1. Transamination: it is the transfer of amino group from an α-amino acid to α-keto acid.



L-Alanine + α-Ketoglutarate ⇌ (ALT or GPT, PLP) Pyruvate + L-Glutamate

L-Aspartate + α-Ketoglutarate ⇌ (AST or GOT, PLP) Oxaloacetate + L-Glutamate

Biological importance and clinical significance of Transamination

**Synthesis of new non-essential amino acids.*

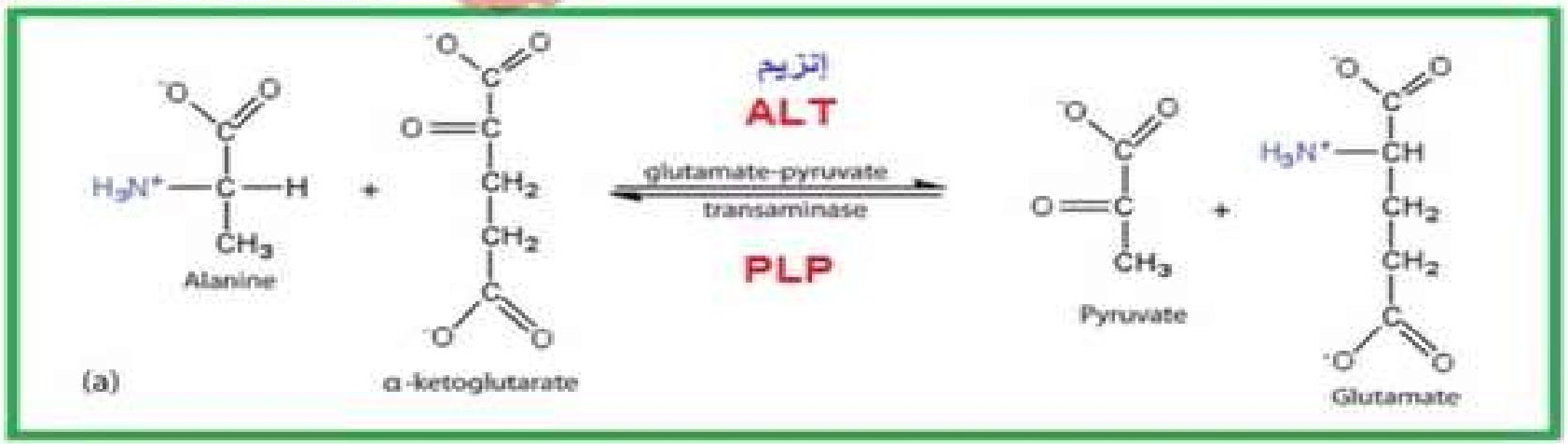
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are important in the diagnosis of heart and liver damage caused by heart attack, drug toxicity, or infection.

** AST increases in myocardial infarction, lung embolism, in liver disease.*

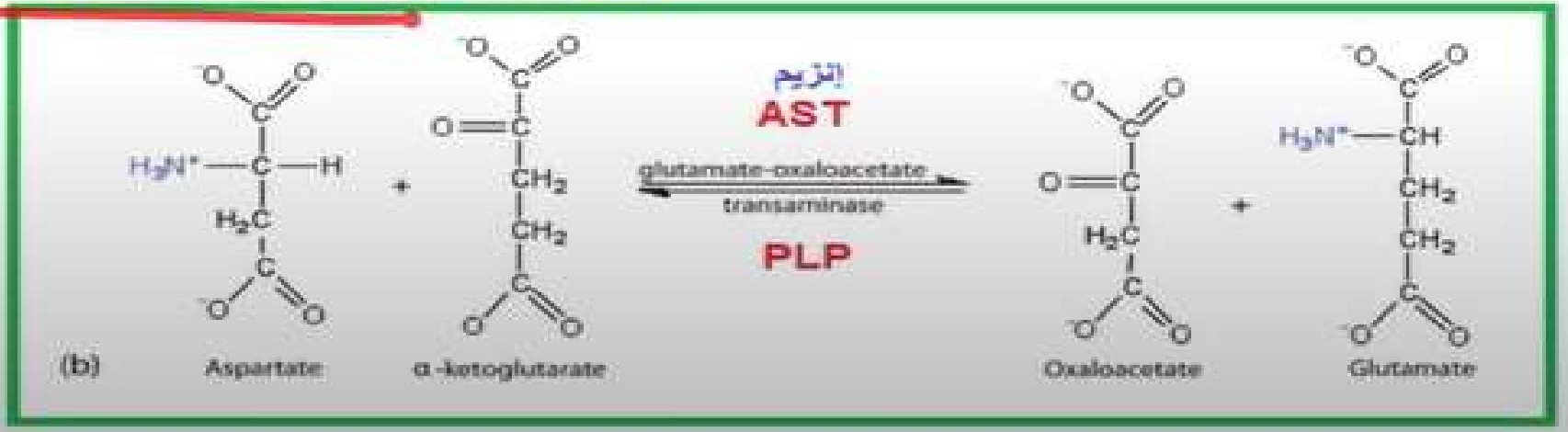
**ALT increases in liver disease (hepatitis, tumor).*

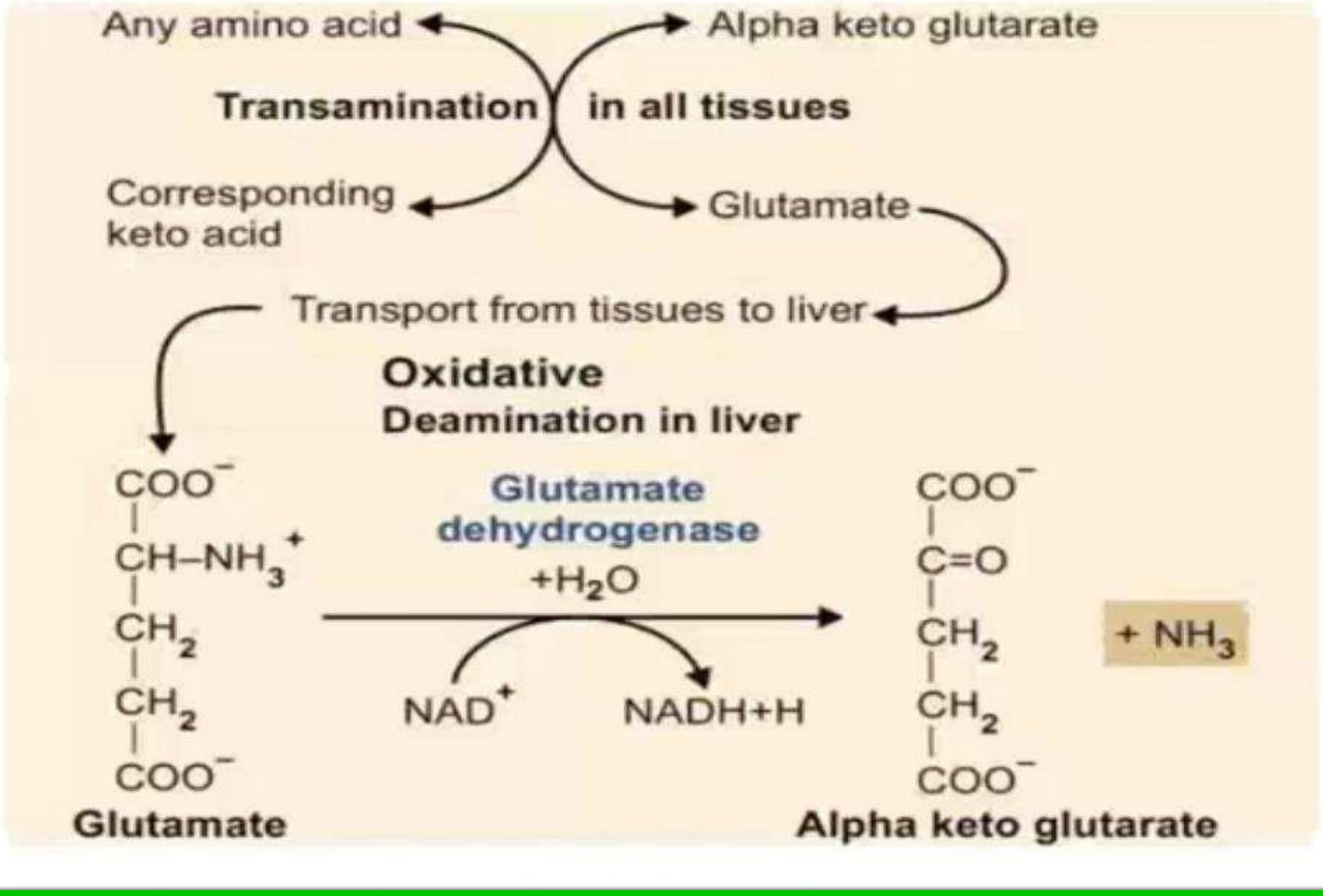
**The AST and ALT tests are also important in occupational medicine, to determine whether people exposed to carbon tetrachloride, chloroform, or other industrial solvents have suffered from liver damage.*

1. Alanine transaminase (ALT)



2. Aspartate transaminase (AST)

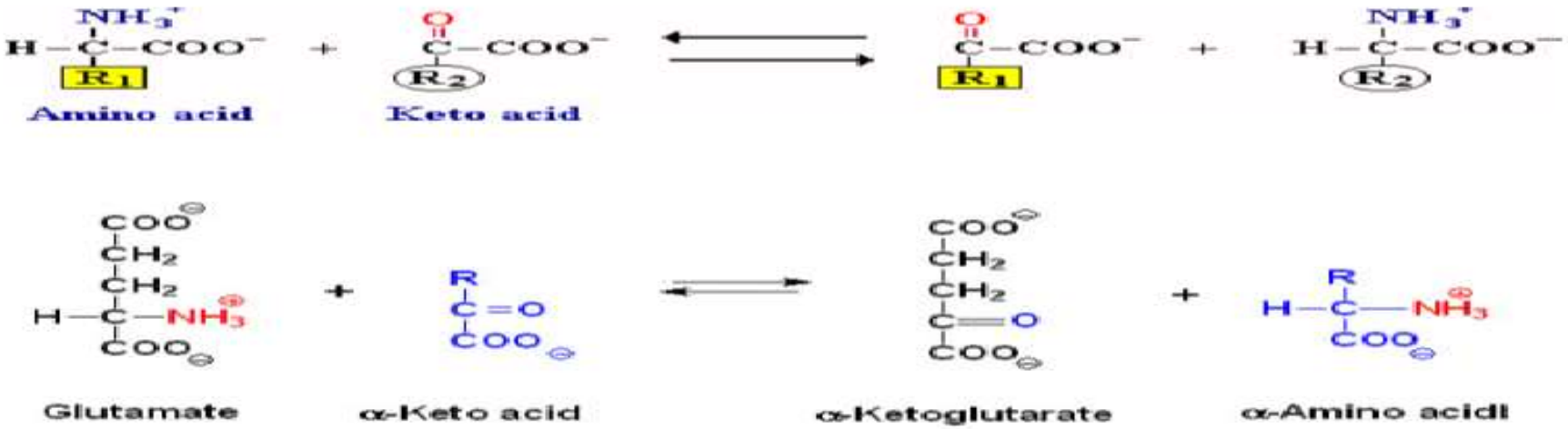



Any amino acid
Alpha keto glutarate
Transamination
in all tissues
Corresponding keto acid
Glutamate
Transport from tissues to liver
Oxidative
Deamination in liver
Glutamate dehydrogenase
+H2O
NAD+
NADH+H
+ NH3
Glutamate
Alpha keto glutarate

PROTEIN AND AMINO ACID METABOLISM

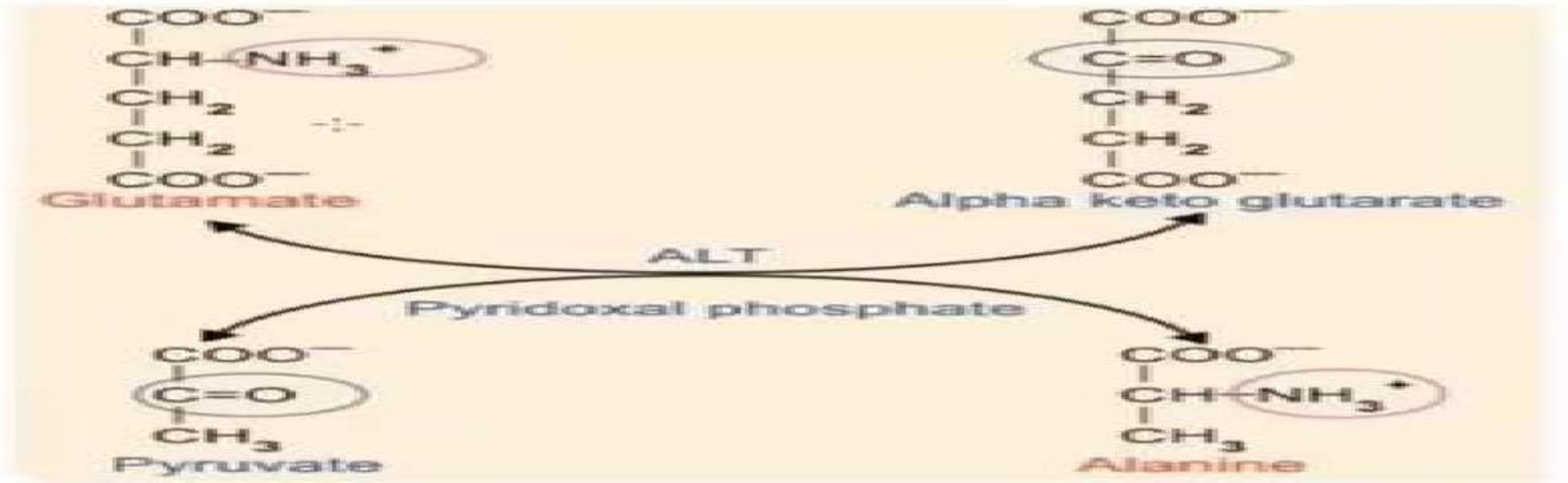
A. Transamination

1. Transamination is the exchange of the alpha amino group between one alpha amino acid and another alpha keto acid, forming a new alpha amino acid.



2. As an example, amino group is interchanged between alanine and glutamic acid . In almost all cases, the amino group is accepted by alpha ketoglutaric acid so that glutamic acid is formed.

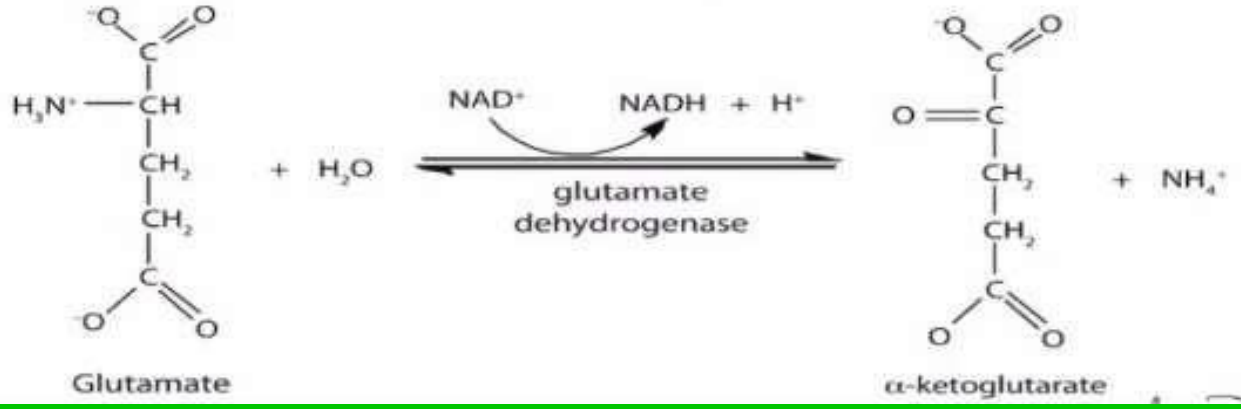
3. The enzymes catalysing the reaction as a group are known as amino transferases.



Transamination reaction. In this example, enzyme is Alanine aminotransferase (ALT) and pyridoxal phosphate is the coenzyme.

2. Oxidative deamination:

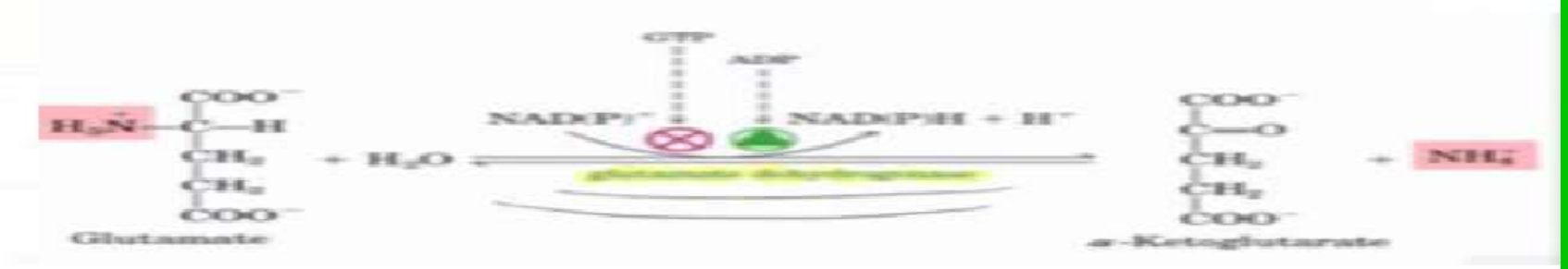
- The removal of an amino (NH2) group from an amino acid, producing an α- keto acid (carbon skeleton of a.a) and ammonia.
- It is Catalyzed by L-amino acid oxidase and L-glutamate dehydrogenase (deaminases).



2. Oxidative deamination:(Glutamate Dehydrogenase)

*In the liver, once the amino groups are transferred to a- ketoglutarate to make L-Glutamate.

*L-glutamate is transported to the mitochondria for oxidative deamination as follows:



***L-Glutamate- dehydrogenase uses NAD^+ or $NADP^+$ (cofactor) to accept reducing equivalents.

***The a-ketoglutarate formed is fed into the citric acid cycle or glucose synthesis (gluconeogenesis).

3. Nonoxidative deamination

requires dehydratase & vitamin B6 (PLP), deaminates the OH containing-amino acids:

Serine → pyruvate + NH_4^+

Threonine → a-ketobutyrate + NH_4^+

B. Trans-deamination

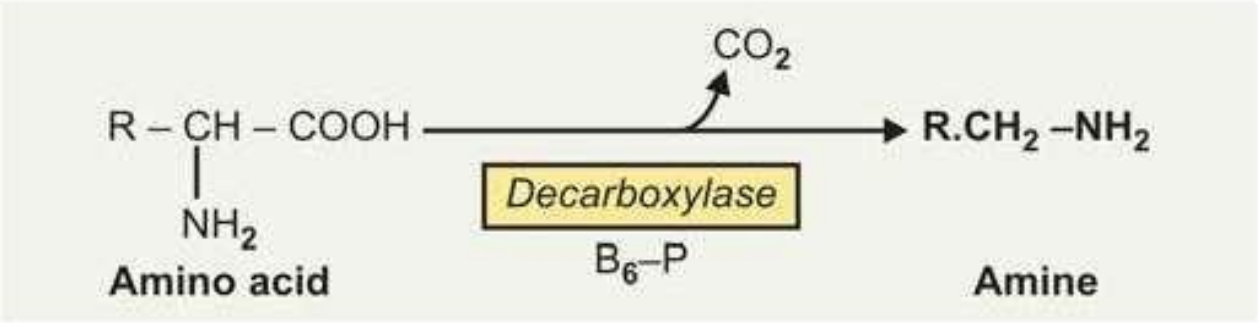
1. The amino group of most of the amino acids is released by a coupled reaction, transdeamination, that is transamination followed by oxidative deamination.

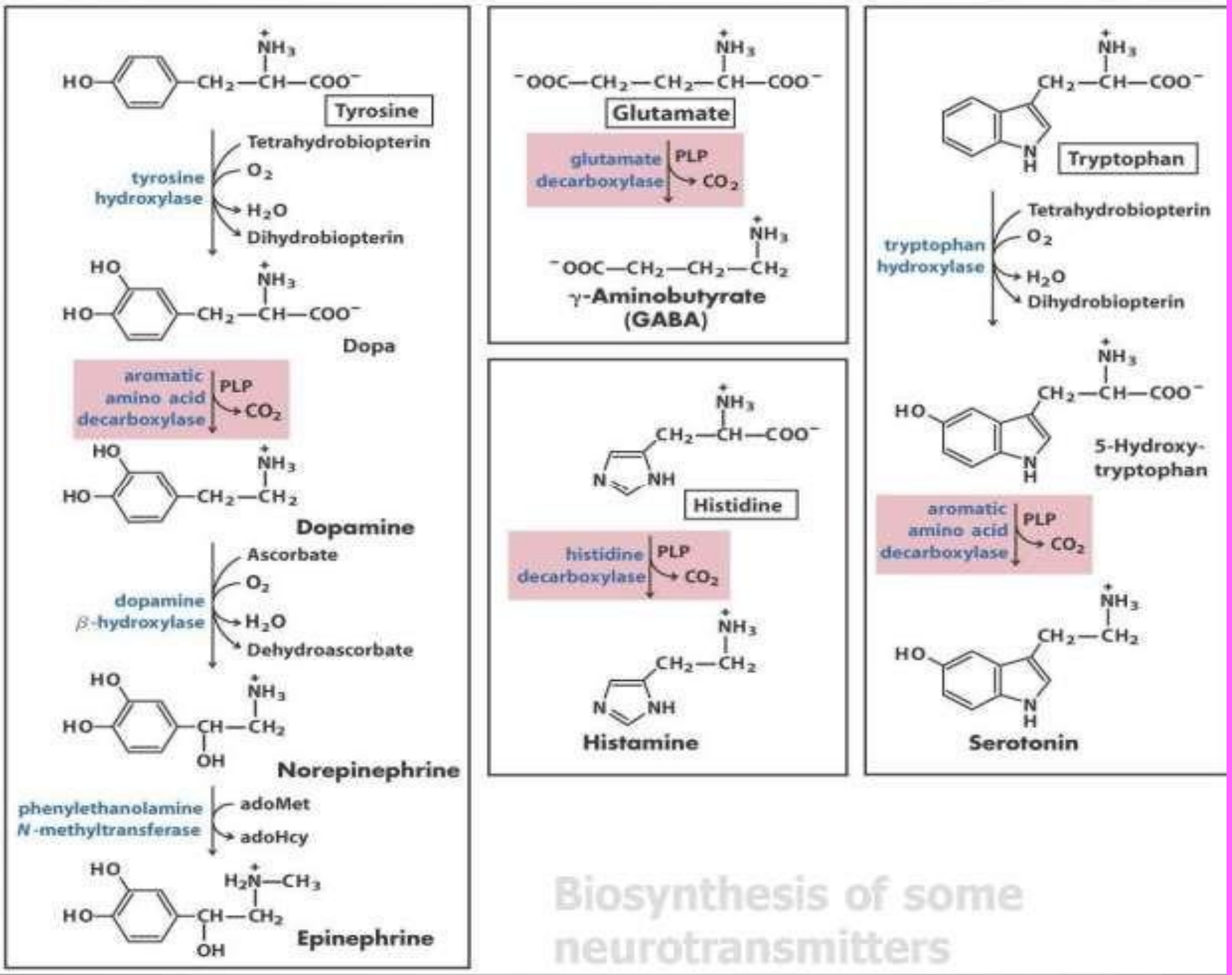
2. Transamination takes place in the cytoplasm of all the cells of the body; the amino group is transported to liver as glutamic acid which is finally oxidatively deaminated in the mitochondria of hepatocytes.

DECARBOXYLATION REACTION AND BIOGENIC AMINES

Decarboxylation

Decarboxylation is the reaction by which CO2 is removed from the COOH group of an amino acid as a result ***an amine is formed.*** The reaction is catalysed by the enzyme ***decarboxylase,*** which requires pyridoxal-P (B6-PO4) as coenzyme. Tissues like liver, kidney, brain possess the enzyme *decarboxylase* and also by microorganisms of intestinal tract. The enzyme removes CO2 from COOH and converts the amino acid to corresponding amine.





Biosynthesis of some neurotransmitters

MEDICAL AND BIOLOGICAL IMPORTANCE

The main role of amino acids is in the synthesis of structural and functional proteins. Unlike carbohydrates and fats, there is no storage form of proteins in the body. The non-essential amino acids are either derived from the diet or synthesized in the body. The essential amino acids are obtained from the diet. Even if one is deficient, protein synthesis cannot take place. The body amino acid pool is always in a dynamic steady state. In an adult, the rate of synthesis of proteins balances the rate of degradation, so that nitrogen balance is maintained

MEDICAL AND BIOLOGICAL IMPORTANCE

1. A 70 kg human adult body contains about 12 kg of protein.

2. Body proteins have life times. They undergo degradation and re-synthesis. About 400 gm of body protein is synthesized and degraded per day i.e., about 6 gm of protein is synthesized and broken down per kg body weight per day.

3. Aged proteins damaged or modified proteins and non-functional proteins of the body undergo degradation. Further degradation is one way of controlling enzyme activity. Hence, continuous re-synthesis and degradation of proteins is a quality control mechanism.

4. Protein degradation may play important role in shaping tissues and organs during pregnancy and development.

MEDICAL AND BIOLOGICAL IMPORTANCE

5. In starvation, diabetes and tissue injury, protein degradation is more.

6. Protein synthesis and degradation is an integral part of cellular adaptation to changed environment.

7. Plasma free amino acid concentration ranges from 40 to 60 mg%. Excess amino acids cannot be stored in the body. First amino group is extracted as ammonia and then carbon skeleton is oxidized to produce energy. In starvation carbon skeletons are used for glucose formation. Carbon skeletons of some amino acids produce acetyl-CoA as end product.

MEDICAL AND BIOLOGICAL IMPORTANCE

8. Ammonia, which is toxic to cells is converted to urea in the liver. Conversion of ammonia to urea is impaired in some inherited diseases and liver disease.

9. Amino acids are needed for the formation of specialized products like hormones, purines, pyrimidines, porphyrins, vitamins, amines, creatine and glutathione.

10. Amino acid degradation is impaired in several inherited diseases due to lack of enzymes.

11. Amino acid degradation is more in starvation, diabetes and high protein diet.

12. Some cancer cells have high amino acid (aspargine) requirement.

Fate of the carbon skeletons of amino acids

Amino acids can be classified as glucogenic or ketogenic or Glucogenic and Ketogenic according to the nature of their metabolic end products.

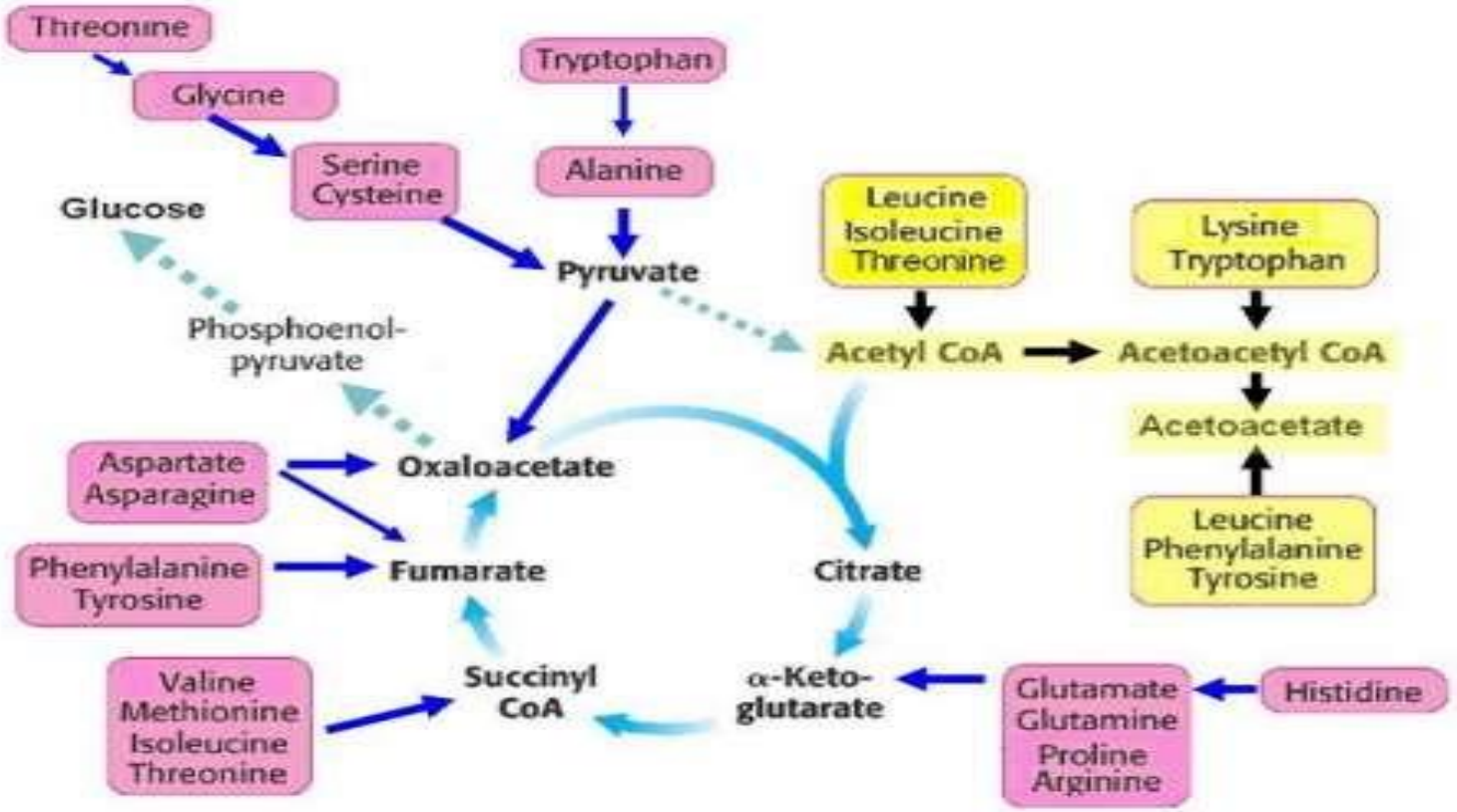
A- Glucogenic amino acids: Which give glucose. They include the rest of amino acids. These amino acids by catabolism yields products that enter in glycogen and glucose formation. And the amino acids results (after catabolism) pyruvate or one of the intermediate of citric acid cycle.These intermediates are substrates for gluconeogenesis and therefore can give rise to the formation of glycogen or glucose in liver and muscle.

B. Ketogenic amino acids: which give ketone bodies. Lysine and Leucine are the only pure ketogenic amino acids and the amino acids gives (after catabolism) either acetoacetate, acetoacetyl CoA or acetyl CoA.

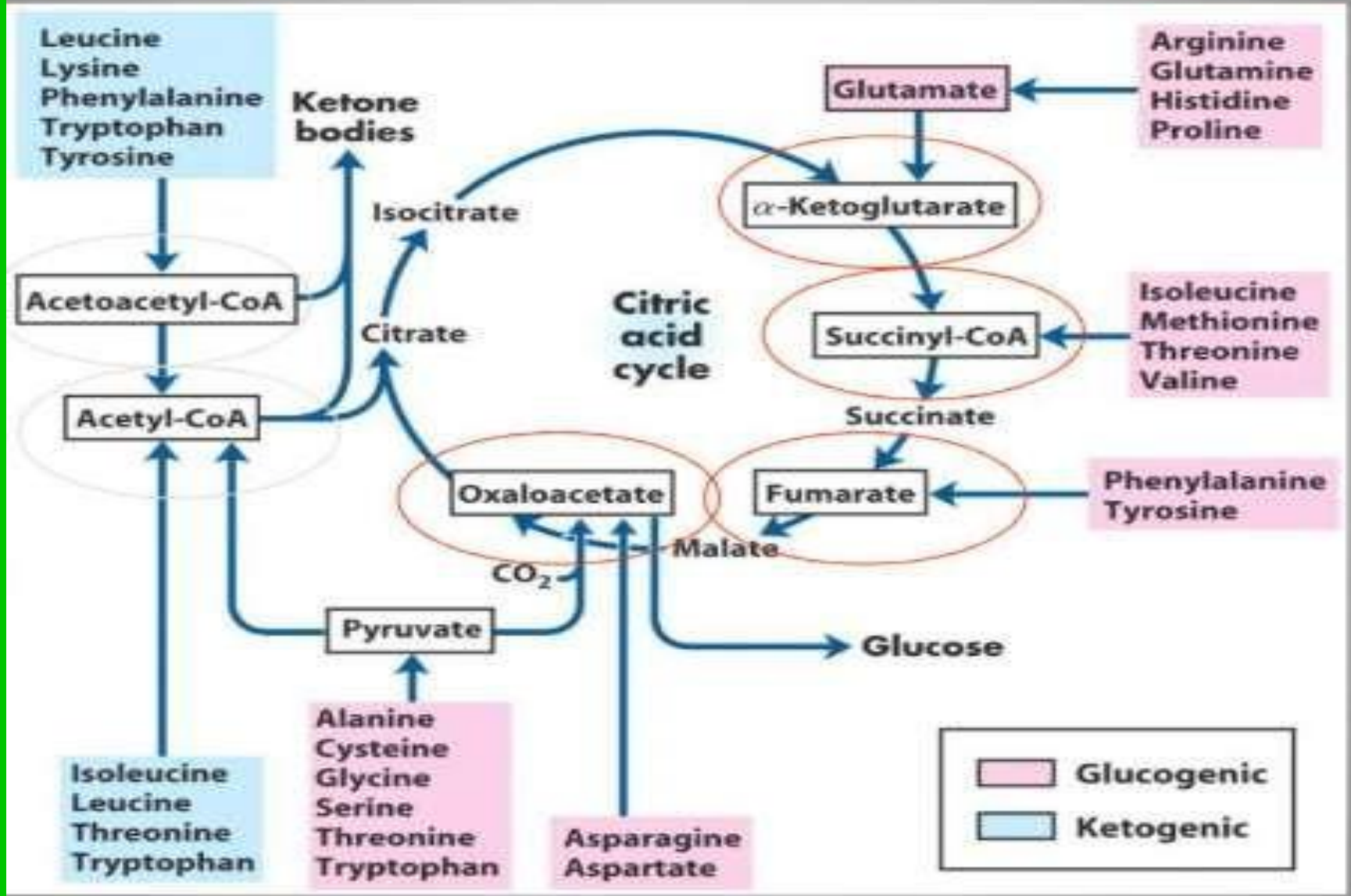
C. Glucogenic and Ketogenic amino acids: which give ketone bodies. Lysine and Leucine are the only pure ketogenic amino acids.And the amino acids gives (after catabolism) gives either glucose or lipid intermediates.

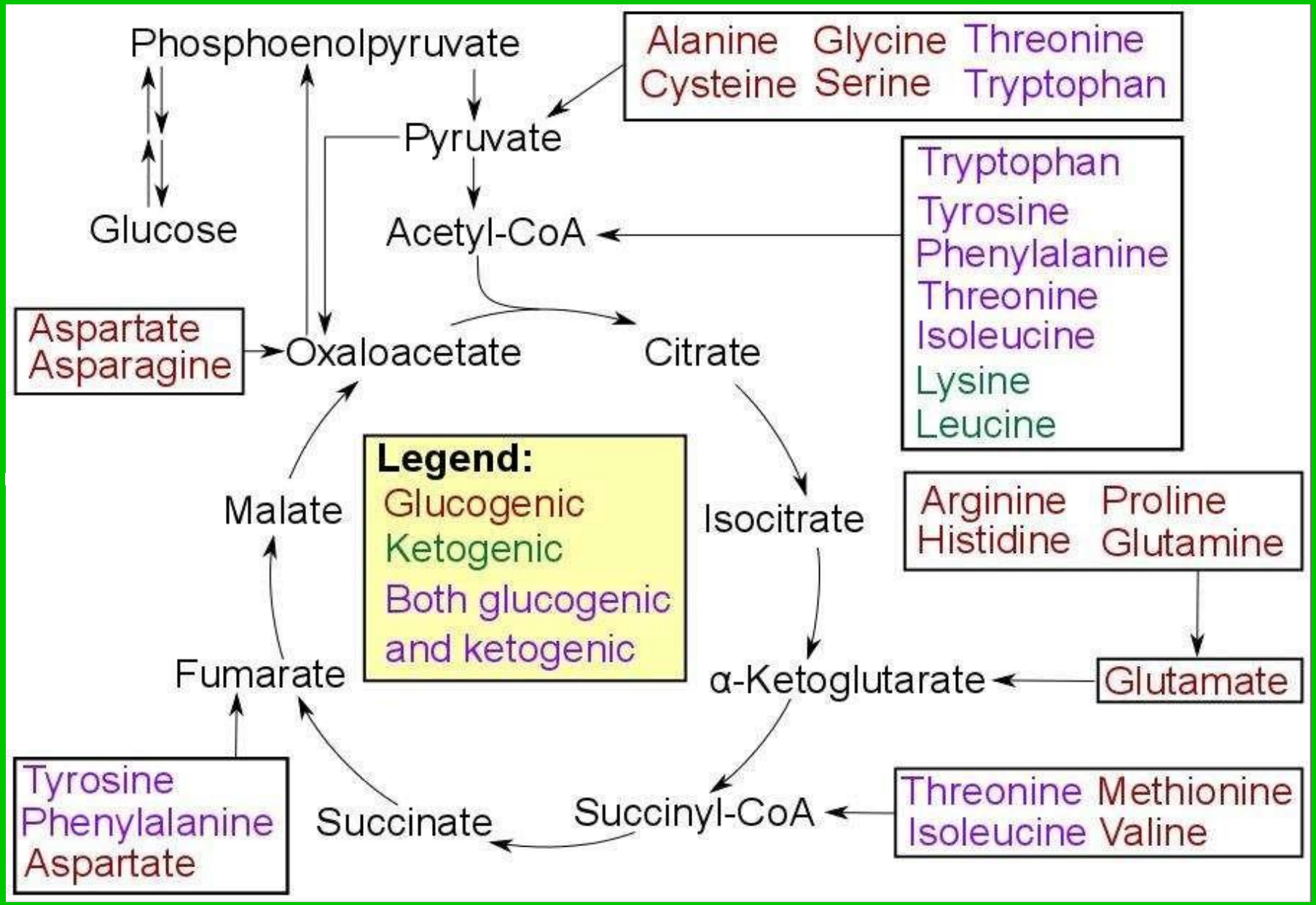
Glucogenic	Glucogenic and Ketogenic	Ketogenic
Alanine Arginine Asparagine Aspartate Cysteine Glutamate Glutamine Glycine Proline Serine	Tyrosine	
Histidine Methionine Threonine Valine	Isoleucine Phenyl-alanine Tryptophan	Leucine Lysine

Glucogenic and ketogenic amino acids



Catabolism

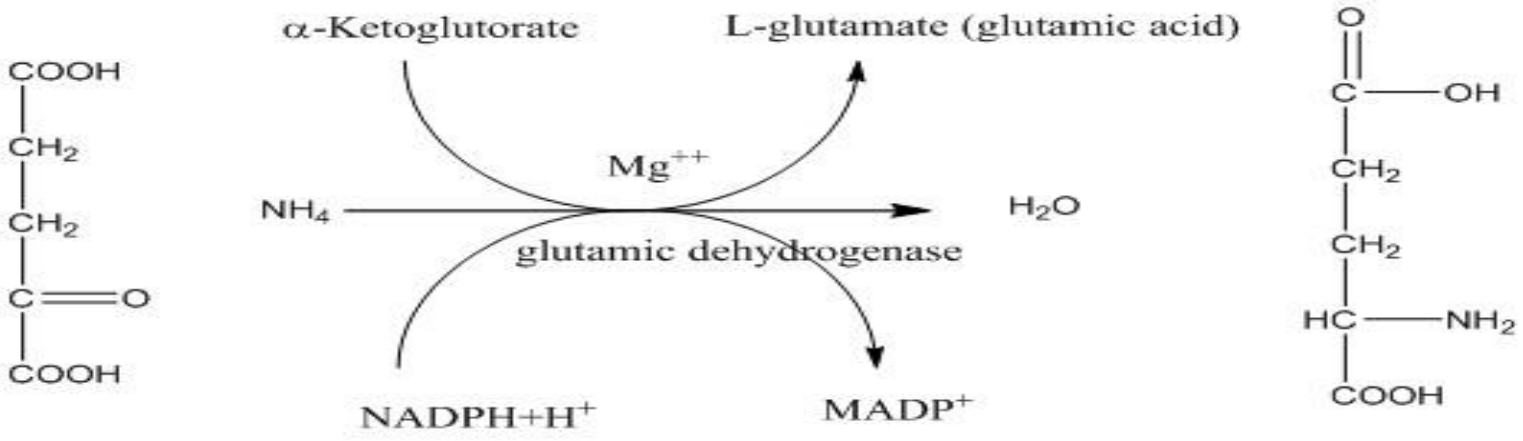

Leucine
Lysine
Phenylalanine
Tryptophan
Tyrosine
Ketone bodies
Isocitrate
Glutamate
Arginine
Glutamine
Histidine
Proline
α-Ketoglutarate
Acetoacetyl-CoA
Citrate
Citric acid cycle
Succinyl-CoA
Isoleucine
Methionine
Threonine
Valine
Acetyl-CoA
Succinate
Oxaloacetate
Fumarate
Phenylalanine
Tyrosine
Malate
CO_2
Pyruvate
Glucose
Alanine
Cysteine
Glycine
Serine
Threonine
Tryptophan
Isoleucine
Leucine
Threonine
Tryptophan
Asparagine
Aspartate
Glucogenic
Ketogenic


Phosphoenolpyruvate
Alanine Glycine Threonine
Cysteine Serine Tryptophan
Pyruvate
Glucose
Acetyl-CoA
Tryptophan
Tyrosine
Phenylalanine
Threonine
Isoleucine
Lysine
Leucine
Aspartate
Asparagine
Oxaloacetate
Citrate
Legend:
Glucogenic
Ketogenic
Both glucogenic
and ketogenic
Malate
Isocitrate
Arginine Proline
Histidine Glutamine
Fumarate
α-Ketoglutarate
Glutamate
Tyrosine
Phenylalanine
Aspartate
Succinate
Succinyl-CoA
Threonine Methionine
Isoleucine Valine

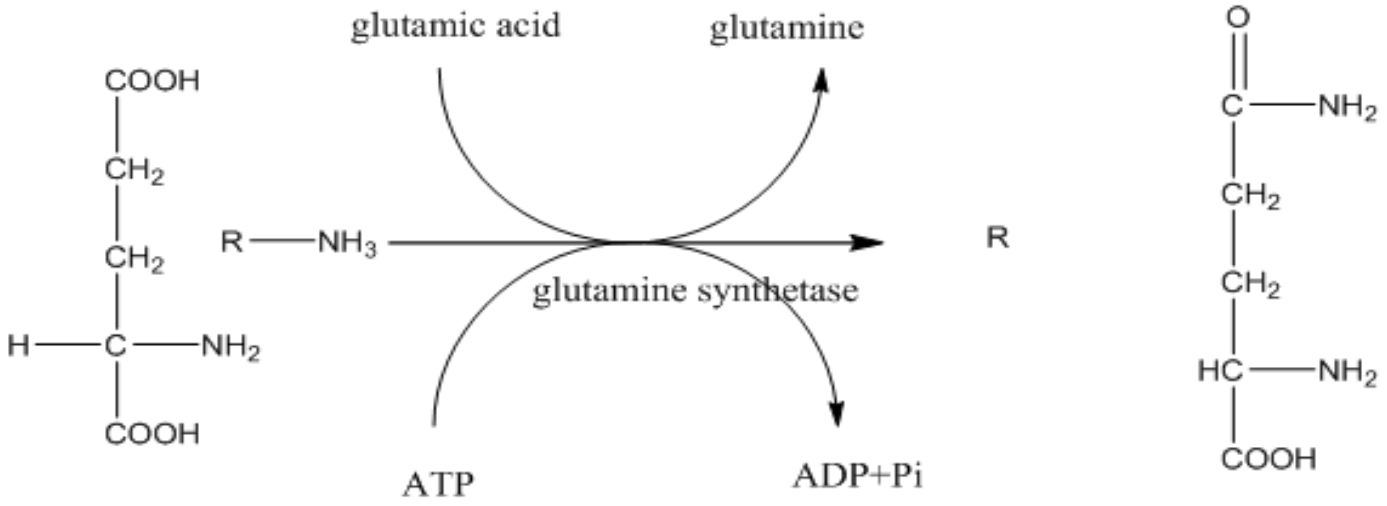
A- Synthesis of non-essential amino acids from compounds Intermediate metabolism:

1- Synthesis of glutamic acid and clotamine from a-ketoglutarate

The methods of biosynthesis of these amino acids are simple where Glutamic acid consists of ammonia and alpha-ketochloric acid, which is one of the intermediate compounds In the cycle of TCA tricarboxylic acid and with the help of Glutamic enzyme dehydrogenos



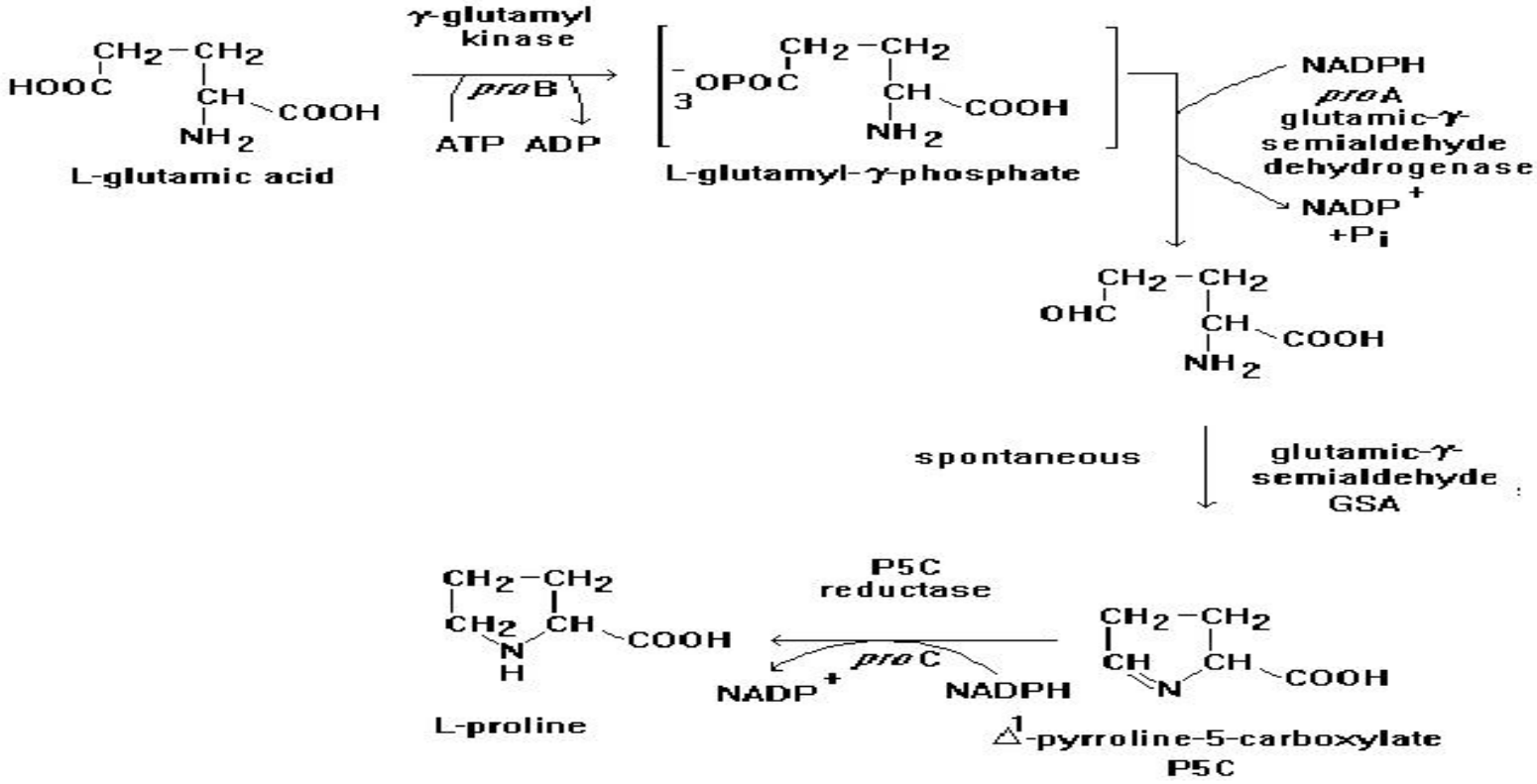
This reaction is of paramount importance in the biosynthesis of all amino acids and in all living organisms because it is the main way in the formation of the group Alpha amino directly from ammonia and consists of glutamic acid formed by that donates the group Amino in the synthesis of most other amino acids, where the derivative of glutamic acid is formed A component called glutamine with the help of the enzyme glutamine synthetase



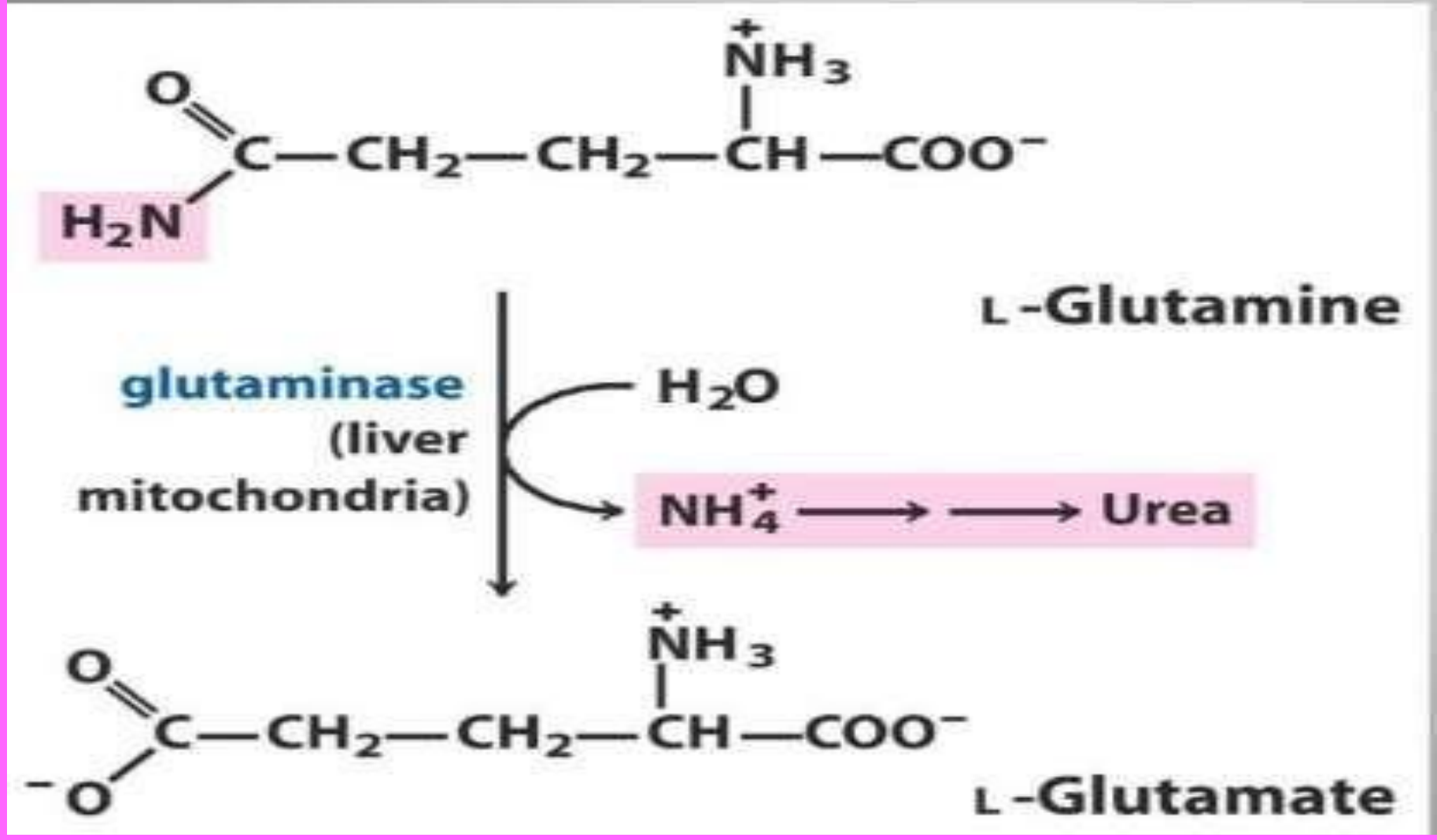
B- Synthesis of non-essential amino acids from acids Other Amini:

- Synthesis of Proline from glutamate

In mammals and some other forms of life proline creates glutamate through a number of reversible biocatering reactions:

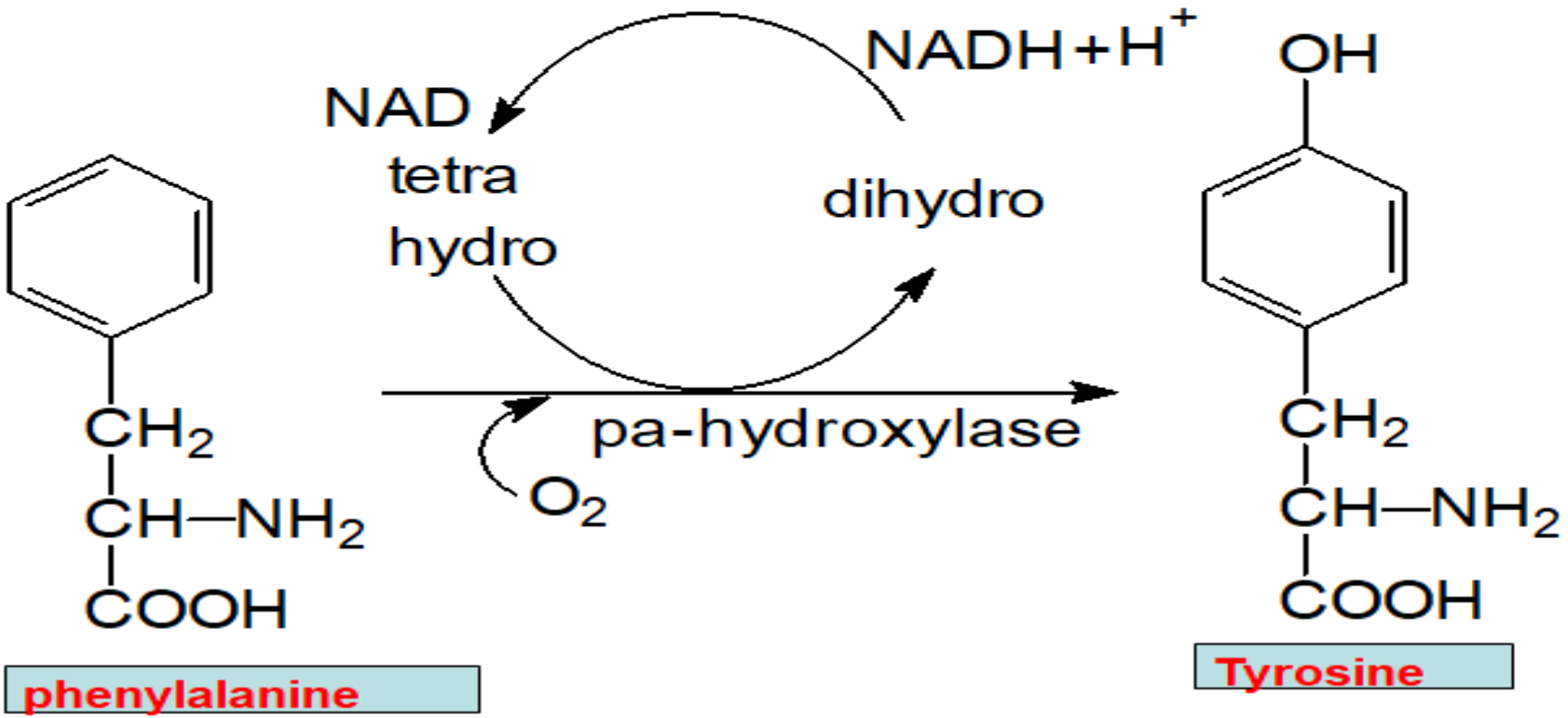


Action of glutamina



Tyrosine

Tyrosine is a non essential Amino Acid synthesized from hydroxylation of phenylalanine by the phenylalanine hydroxylase



The end result of tyrosine metabolism are

1.Fumarate ..... Citric Acid cycle

2.Acetoacetate& Acetate.....Fatty Acid Synthesis

Tyrosine is both glucogenic & Ketogenic

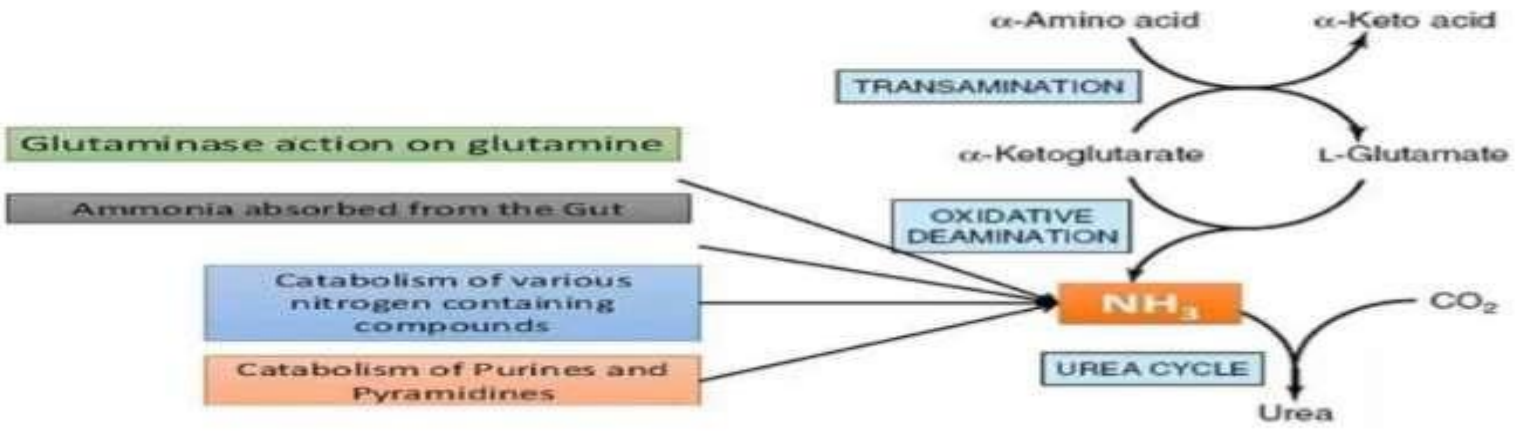
Fumarate ⟶ Glucogenic

Acetoacetate ⟶ Ketogenic

Formation of Ammonia

The first step in the catabolism of amino acids is to remove the amino group as ammonia. This is the major source of ammonia. However, small quantities of ammonia may also be formed from catabolism of purine and pyrimidine bases.

Ammonia is highly toxic especially to the nervous system. Detoxification of ammonia is by conversion to urea and excretion through urine.



Sources and fate of ammonia

Formation of ammonia

Ammonia is formed from amino acids by a combination of two reactions:

Transamination and Deamination.

****Transamination takes place in the cytoplasm of all the cells of the body.***

****Amino group is transported to liver as glutamic acid which is finally oxidatively deaminated in the mitochondria of hepatocytes.***

Transport of ammonia to the liver (and kidney):

This ammonia is excreted into the urine as ammonium ion (NH4+), an important mechanism for maintaining whole-body acid-base balance.

Hepatic glutaminase levels rise in response to high protein intake while renal glutaminase increases in metabolic acidosis.

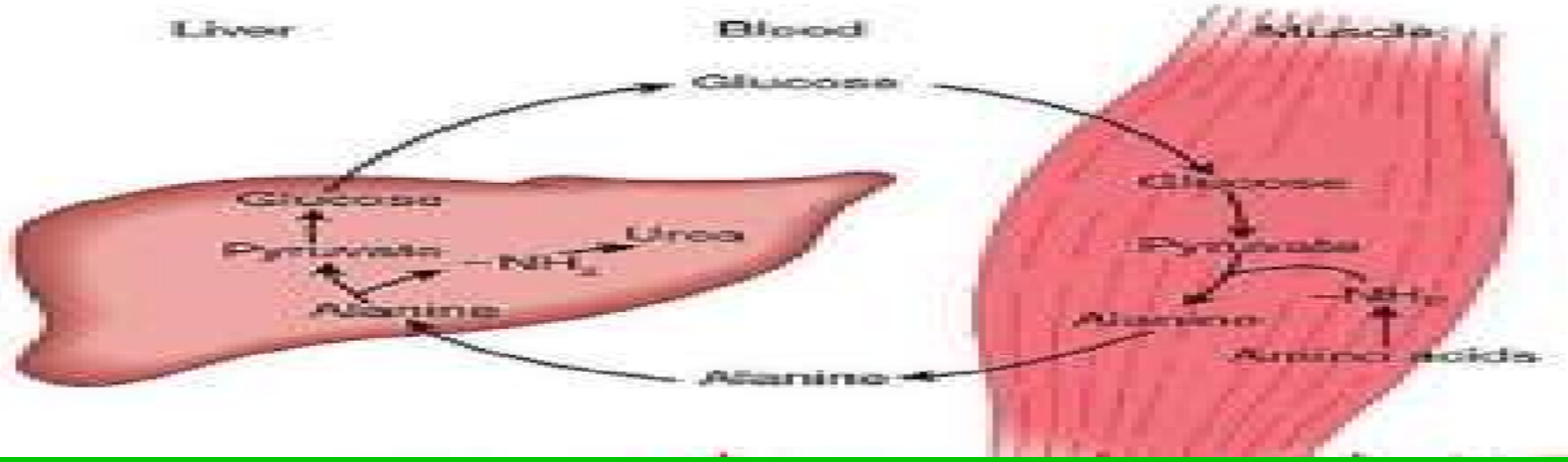
(Glucose – alanine cycle):

****The second mechanism involves the glucose-alanine cycle.*

****Amino acids derived from skeletal muscle protein breakdown, in the post absorptive state, are converted to alanine, which is transported to liver where it is deaminated to form pyruvate.*

****Waste NH3 groups enter the urea cycle, while pyruvate is used for gluconeogenesis.*

Alanine is synthesized in muscle by transamination of glucose-derived pyruvate, released into the bloodstream, and taken up by the liver. In the liver, the carbon skeleton of alanine is reconverted to glucose and released into the bloodstream, where it is available for uptake by muscle and resynthesis of alanine.



Urea Cycle

*Formation of urea by "Kreb's Henseleit urea cycle" is an ultimate route for the metabolic disposal of ammonia.

*Urea has no physiological function. Hence it is transported to kidneys where it is excreted in urine.

*It is major end product of protein catabolism in humans. About 10-25 gm of urea is excreted in urine per day which makes up to 80-90% of total

*nitrogen excreted per day. However, blood also contains some urea.

Significance of urea cycle

**The toxic ammonia is converted into the harmless nontoxic urea.

**It disposes of two waste products, ammonia and CO_2.

Urea is synthesized in the liver and transported to the kidney for excretion in urine.

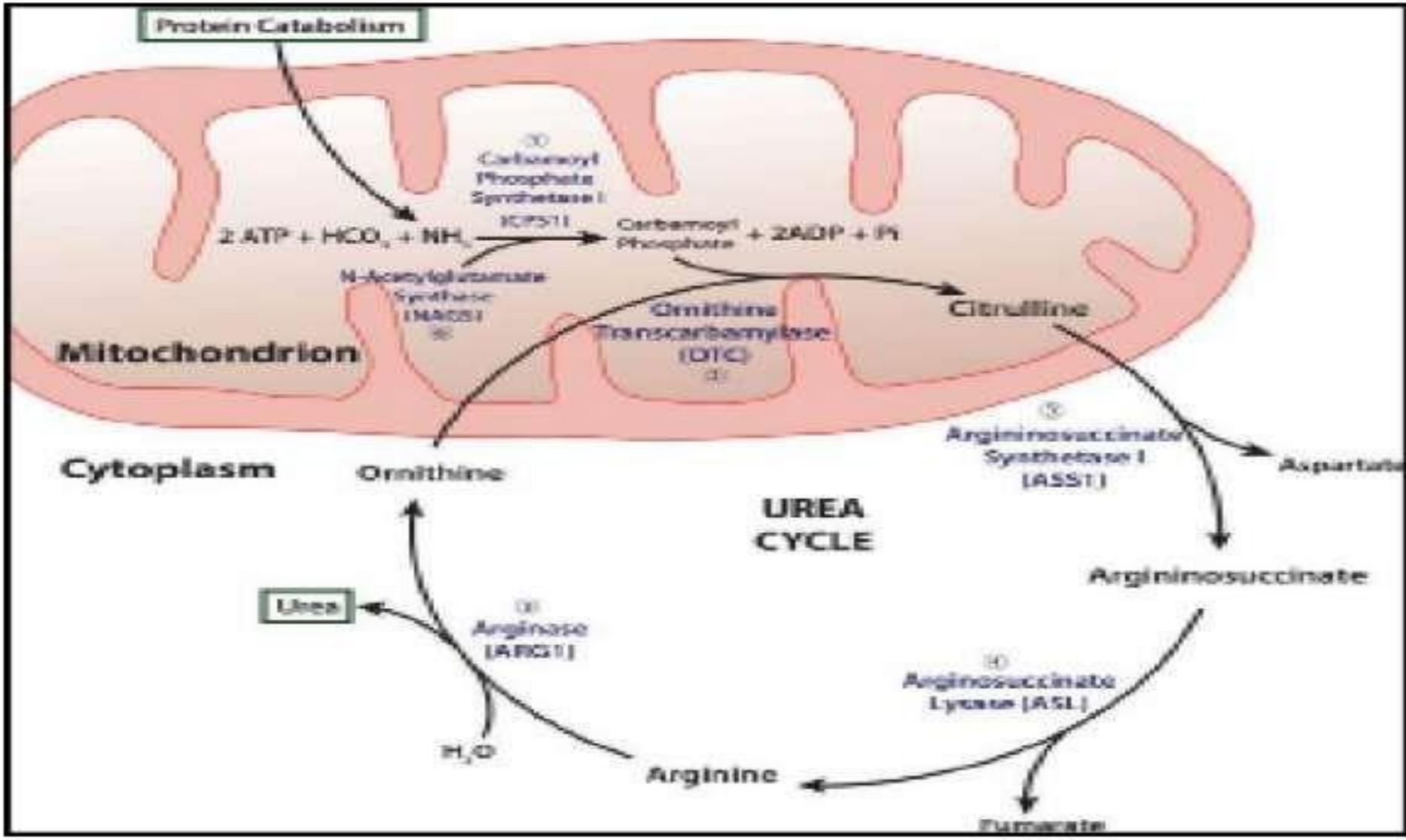
Urea cycle is the first metabolic cycle Urea synthesis is a five steps with five distinct enzymes.

The first two steps are mitochondrial, while the rest are localized in the cytoplasm.

The urea cycle:

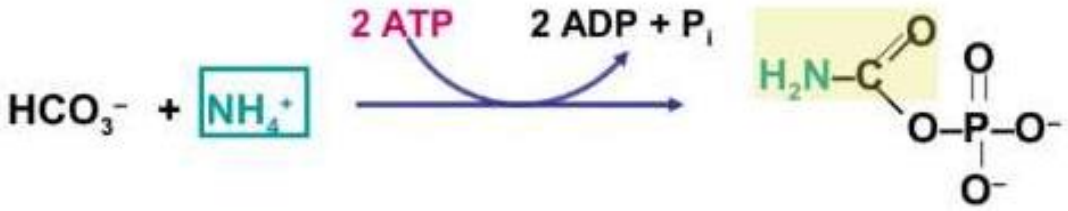
-Detoxifies ammonium ion from amino acid degradation.

Converts ammonium ion to urea in the liver.


Protein Catabolism
Carbamoyl Phosphate Synthetase I (CPS1)
2 ATP + HCO3 + NH3
Carbamoyl Phosphate + 2ADP + Pi
N-Acetylglutamate Synthase (NAGS)
Ornithine Transcarbamylase (OTC)
Citrulline
Mitochondrion
Cytoplasm
Ornithine
Argininosuccinate Synthetase I (ASS1)
Aspartate
UREA CYCLE
Argininosuccinate
Urea
Arginase (ARG1)
Argininosuccinate Lyase (ASL)
H2O
Arginine
Fumarate

Urea is synthesized in five steps:

1 Synthesis of carbamoyl phosphate in the mitochondrial matrix

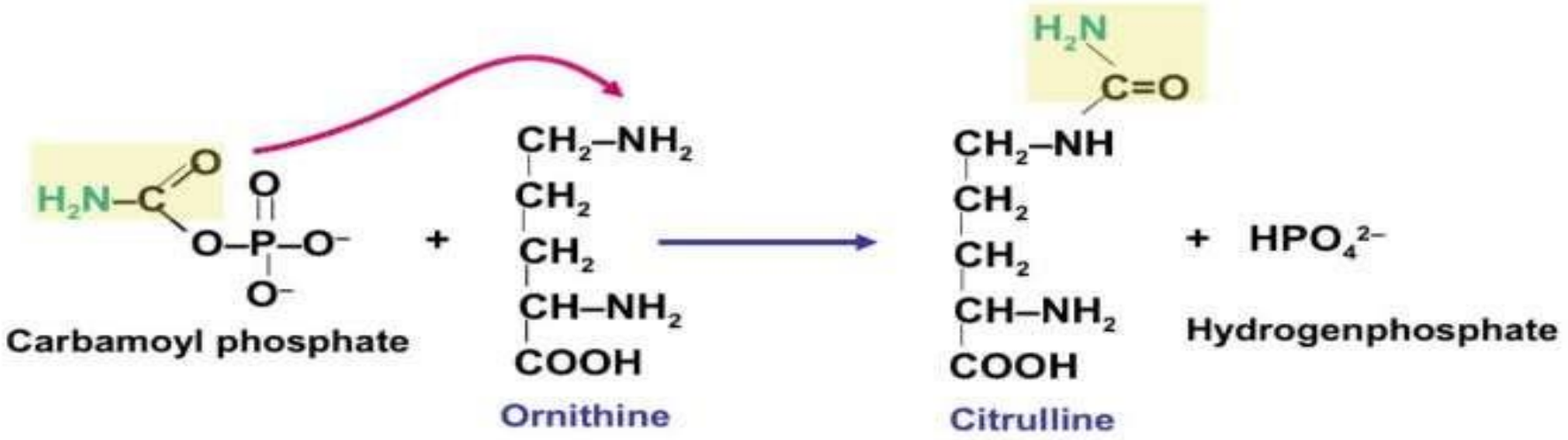


Carbamoyl phosphate
(a mixed anhydride,
a high-energy compound)

The reaction is catalysed by **carbamoyl phosphate synthetase I** which requires essentially the allosteric activator – ***N*-acetylglutamate**.

The cytosolic form of the enzyme – carbamoyl phosphate synthetase II – utilizes glutamine instead of ammonia and catalyses the first step of the pyrimidine base synthesis.

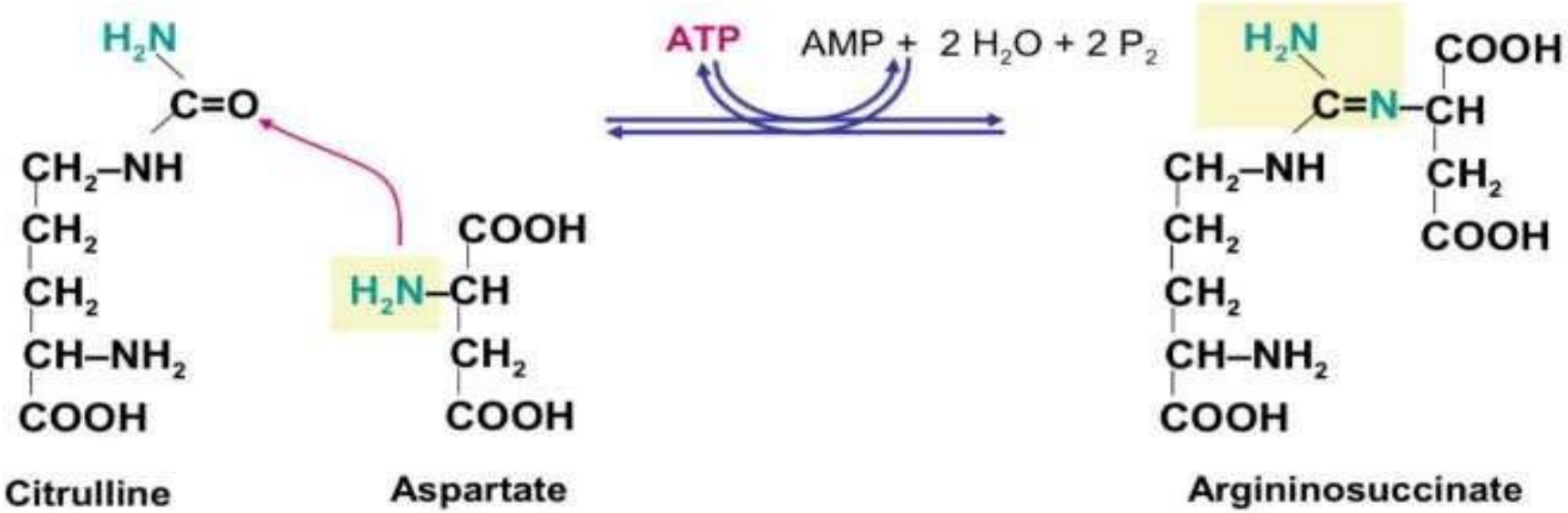
2 The transfer of carbamoyl to ornithine



The reaction is catalysed by **ornithine transcarbamoylase** to form citrulline.
Both ornithine and citrulline are amino acids, but they are not used as building blocks of proteins.

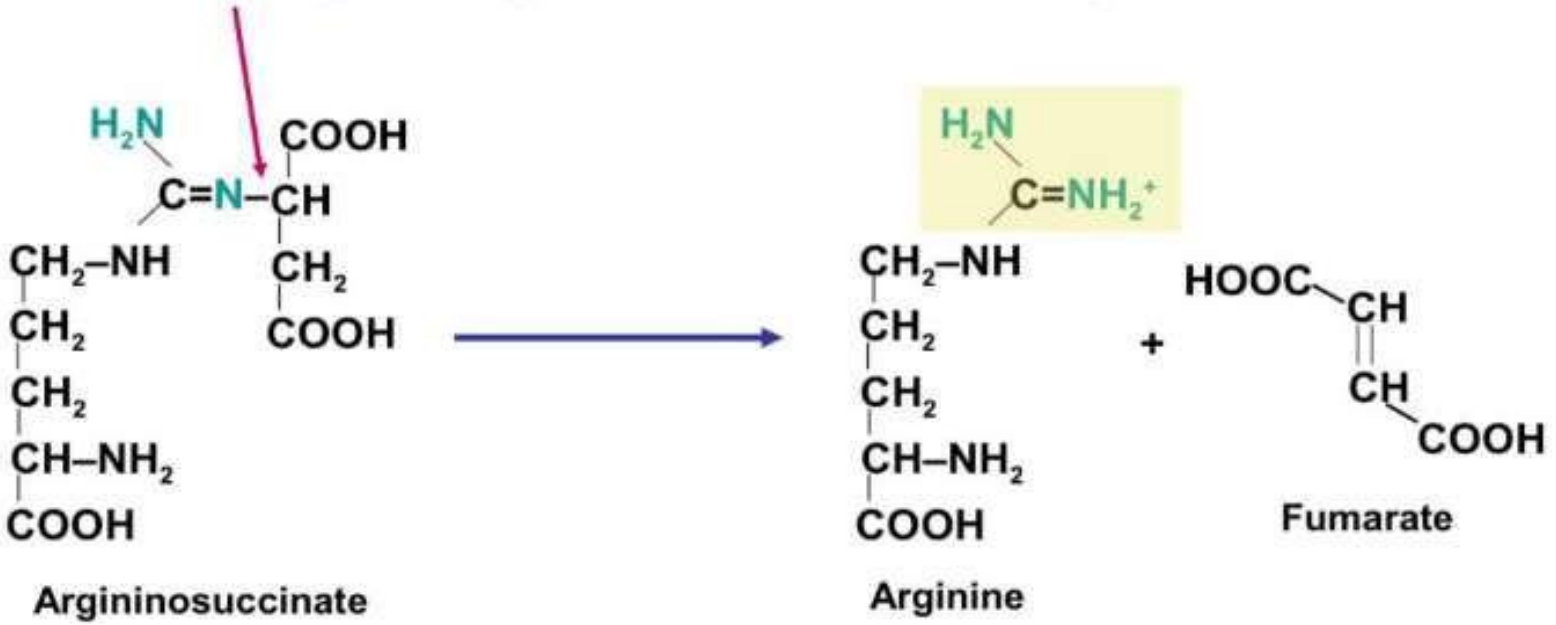
The next three reaction of the cycle také place in the cytoplasma.

3 The transport of citrulline to the cytoplasma and condensation with aspartate



The reversible reaction is catalysed by **argininosuccinate synthetase** and is driven by the cleavage of ATP into AMP and diphosphate and by the subsequent hydrolysis of diphosphate.

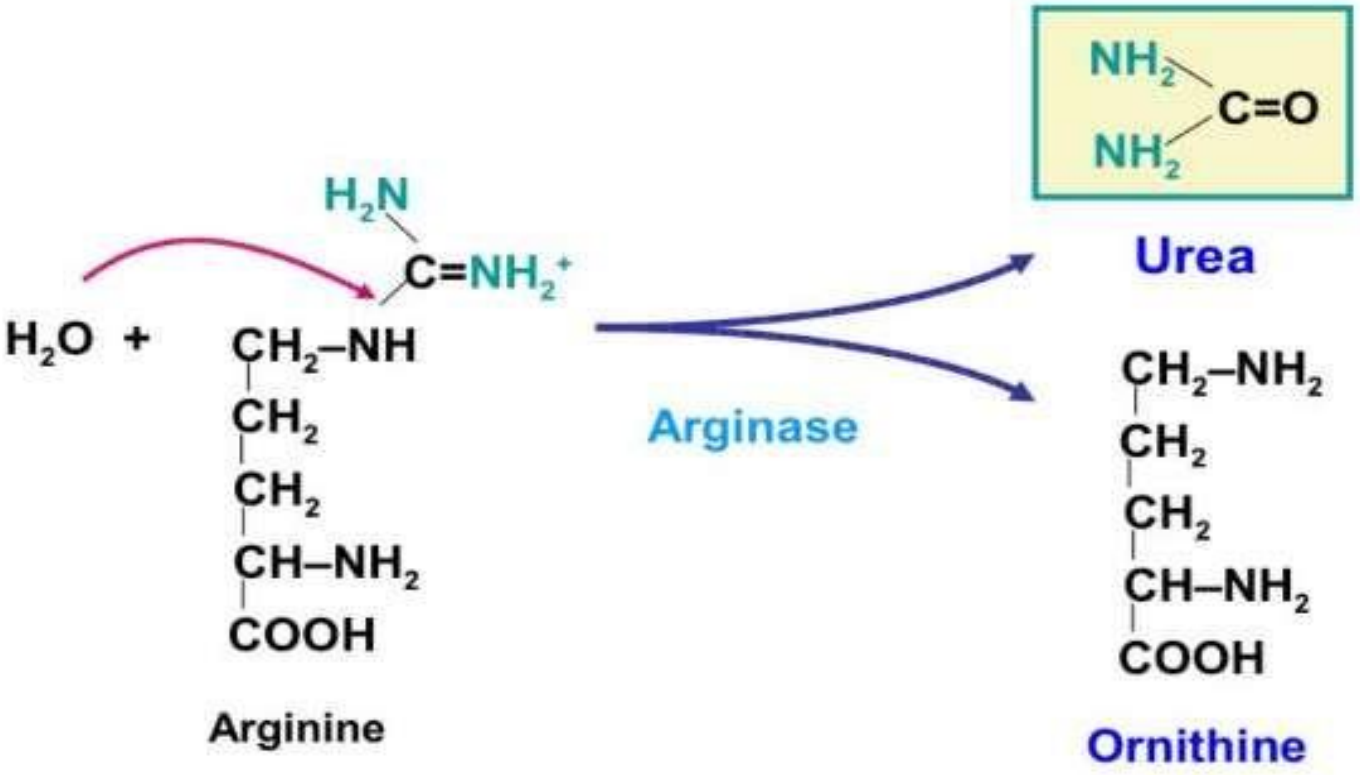
4 The cleavage of argininosuccinate into arginine and fumarate

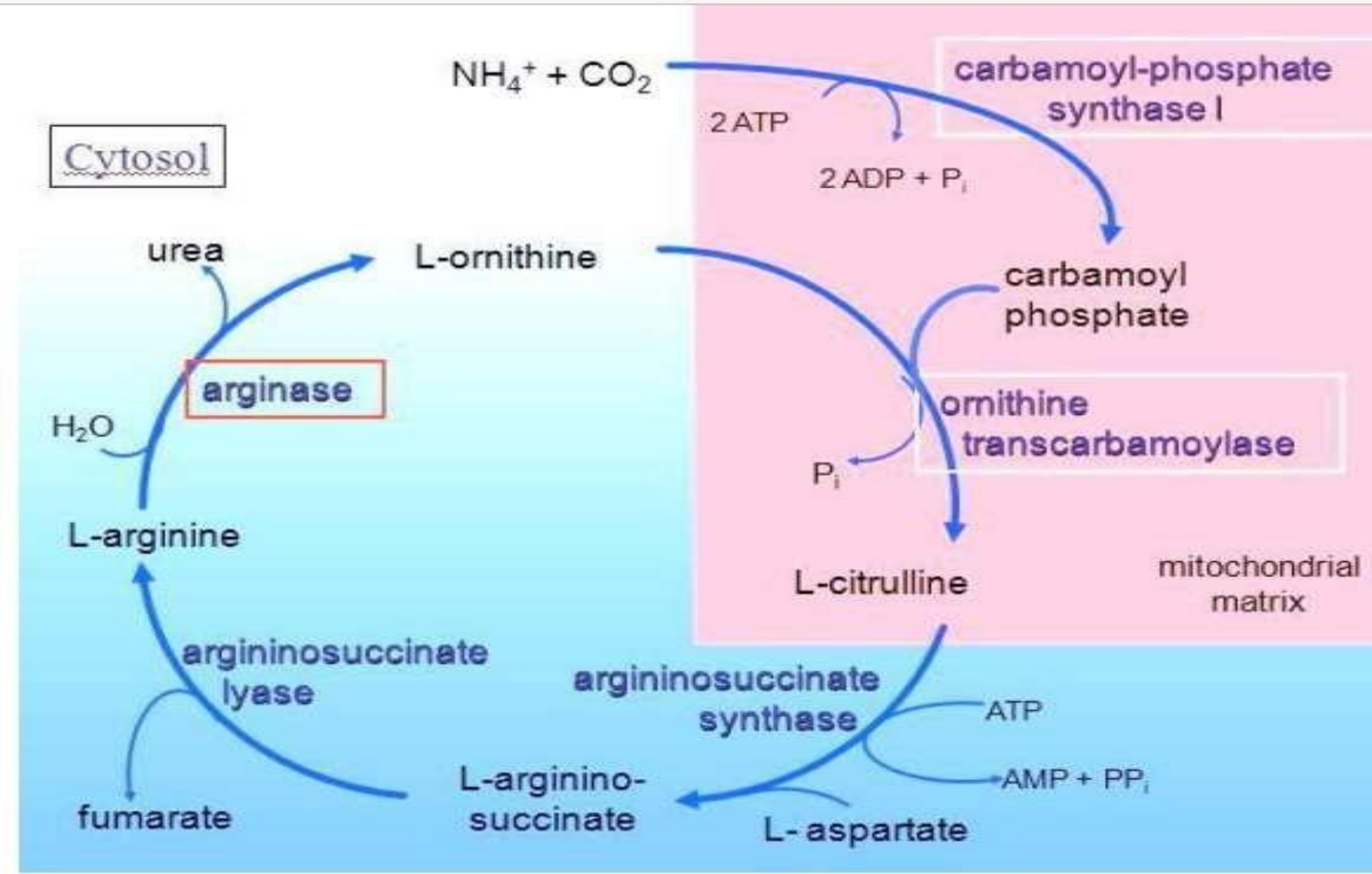


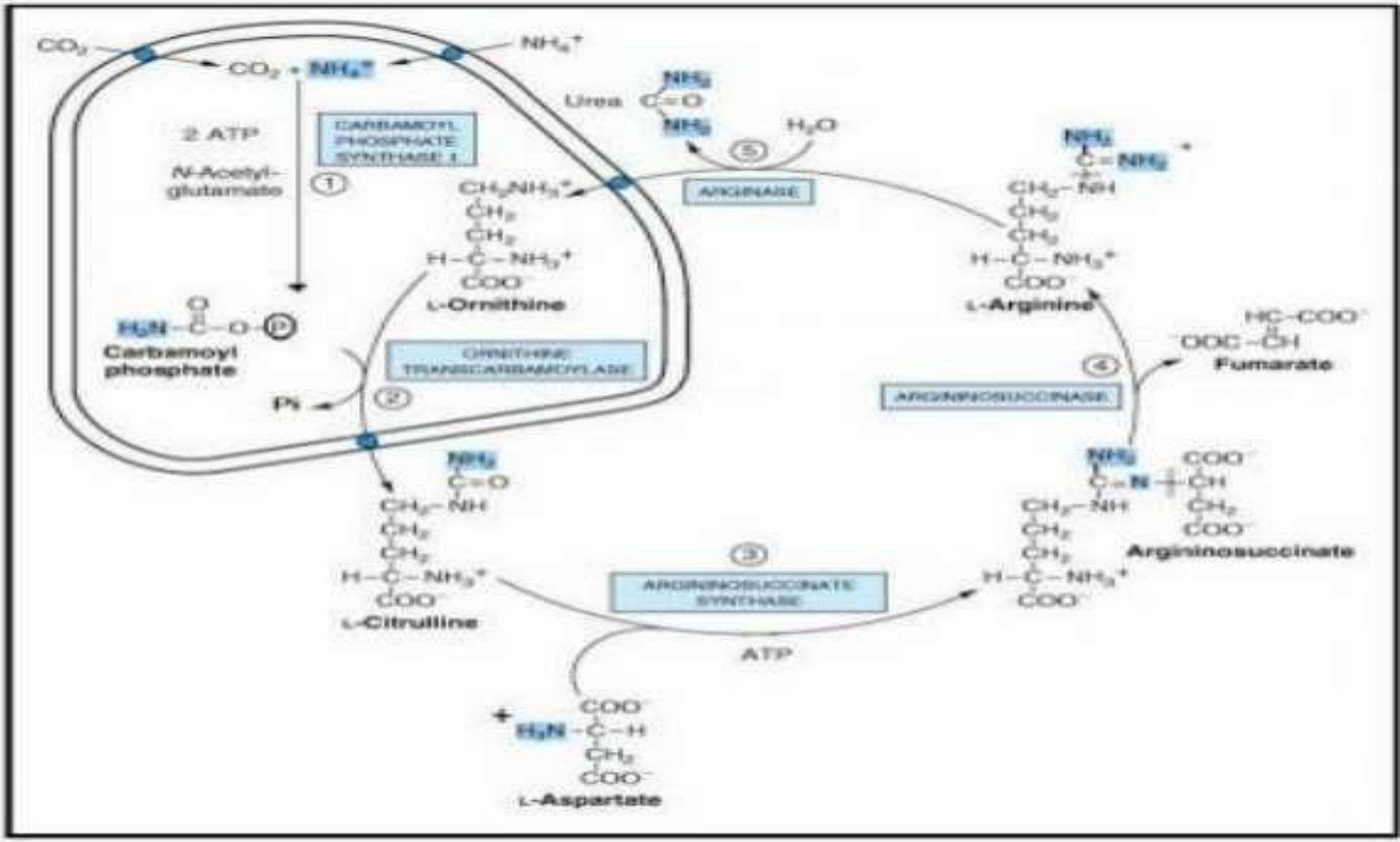
Argininosuccinase cleaves argininosuccinate into arginine and fumarate. The carbon skeleton of aspartate is preserved in the form of fumarate.

The synthesis of fumarate by the urea cycle is important because it **links the urea cycle and the citric acid cycle:** Fumarate after hydratation to malate may enter mitochondrion and be oxidized to oxaloacetate, which can undergo transamination to aspartate. .

5 The hydrolysis of arginine generates urea and ornithine




$NH_4^+ + CO_2$
2 ATP
2 ADP + P_i
carbamoyl-phosphate synthase I
Cytosol
urea
L-ornithine
carbamoyl phosphate
arginase
ornithine transcarbamoylase
H_2O
P_i
L-arginine
L-citrulline
mitochondrial matrix
argininosuccinate lyase
argininosuccinate synthase
ATP
AMP + PP_i
L-arginino-succinate
fumarate
L-aspartate

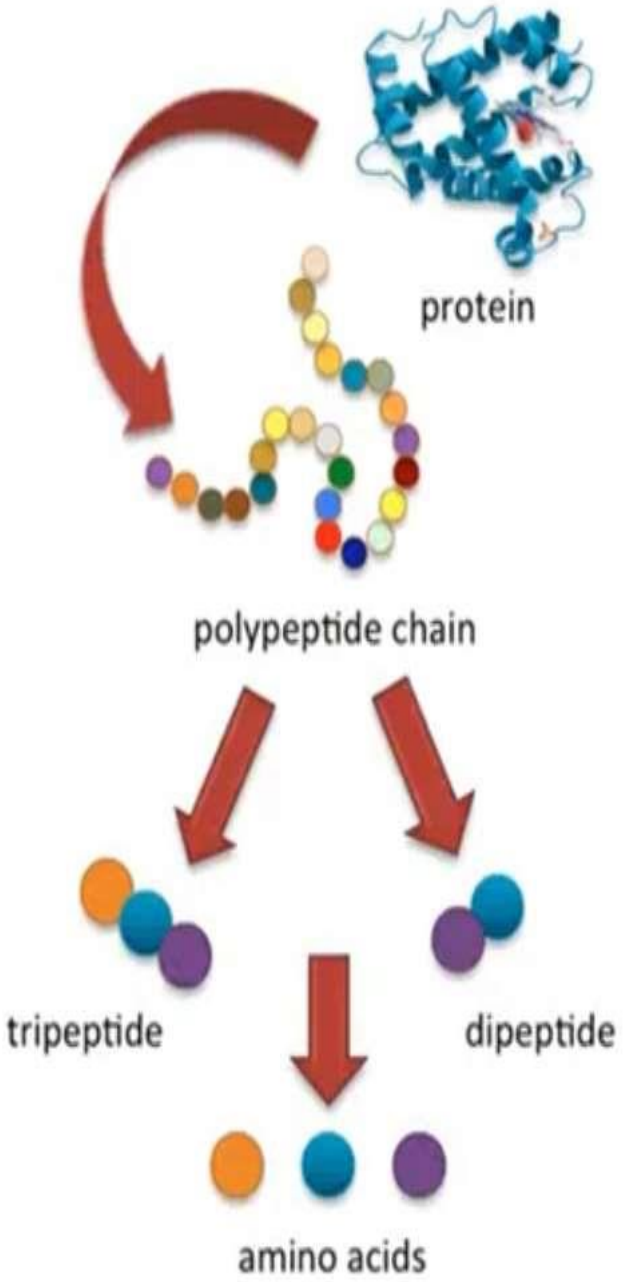

2 ATP
N-Acetyl-glutamate
Carbamoyl phosphate
Pi
L-Ornithine
L-Citrulline
L-Aspartate
ATP
Urea
H_2O
L-Arginine
Fumarate
Argininosuccinate

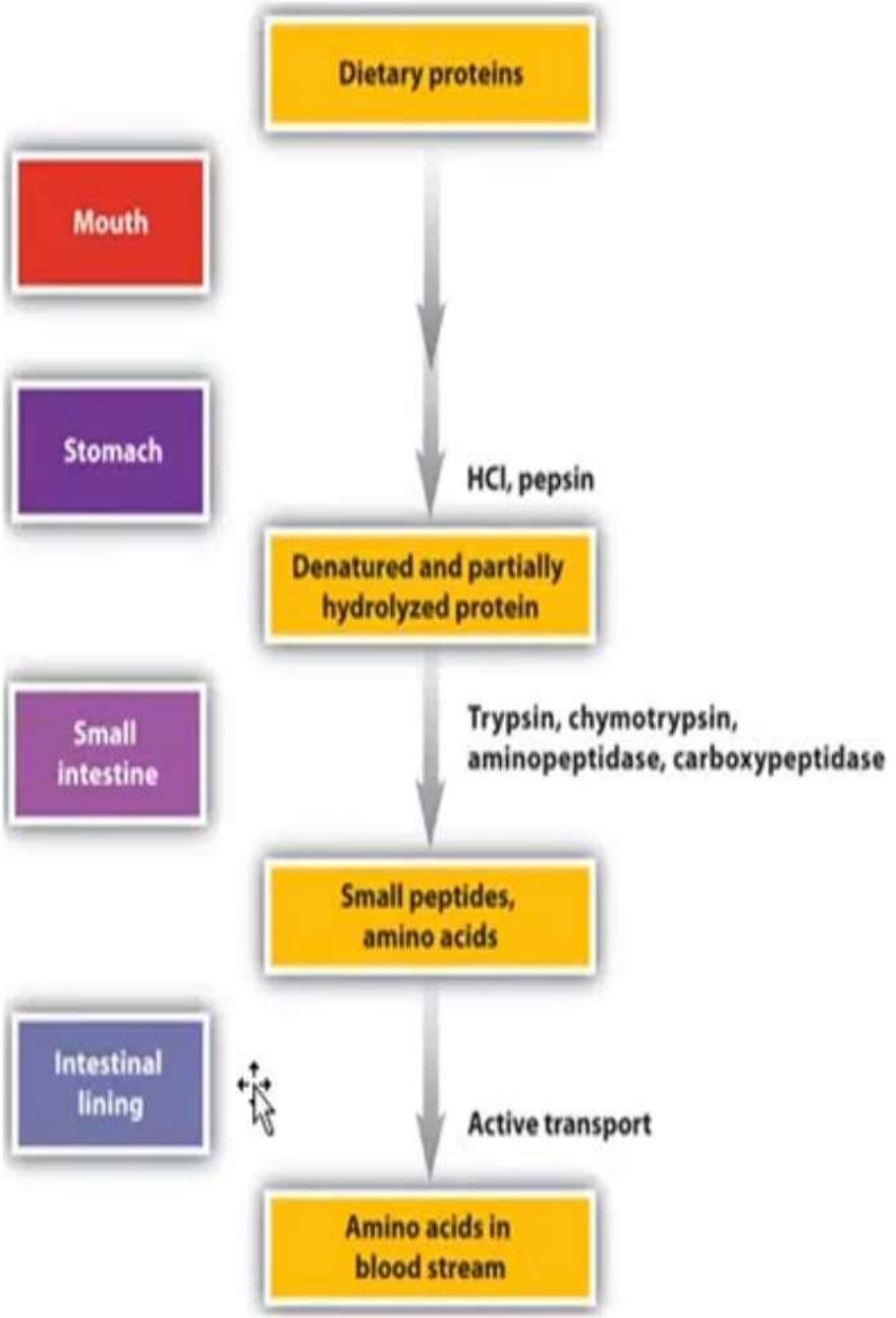
Digestion and absorption of proteins

**Proteolytic enzymes (also called proteases) break down dietary proteins into amino acids.

**Proteases are produced by three different organs:

1. The stomach.
2. The pancreas.
3. The small intestine.


protein
polypeptide chain
tripeptide
dipeptide
amino acids


Dietary proteins
Mouth
Stomach
HCl, pepsin
Denatured and partially hydrolyzed protein
Small intestine
Trypsin, chymotrypsin, aminopeptidase, carboxypeptidase
Small peptides, amino acids
Intestinal lining
Active transport
Amino acids in blood stream

Digestion in Mouth

*There is no protein digestion in the mouth.

*The digestion of proteins starts in the stomach.

Digestion in Stomach

When protein enters the stomach, it stimulates the secretion of the hormone gastrin.

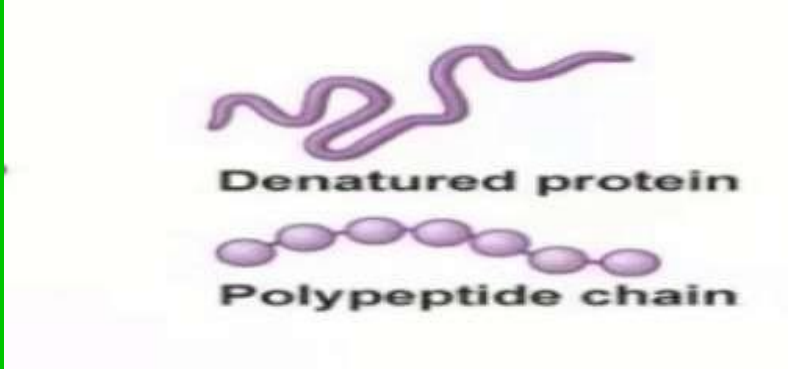
*Gastrin then stimulates the release of gastric juice.

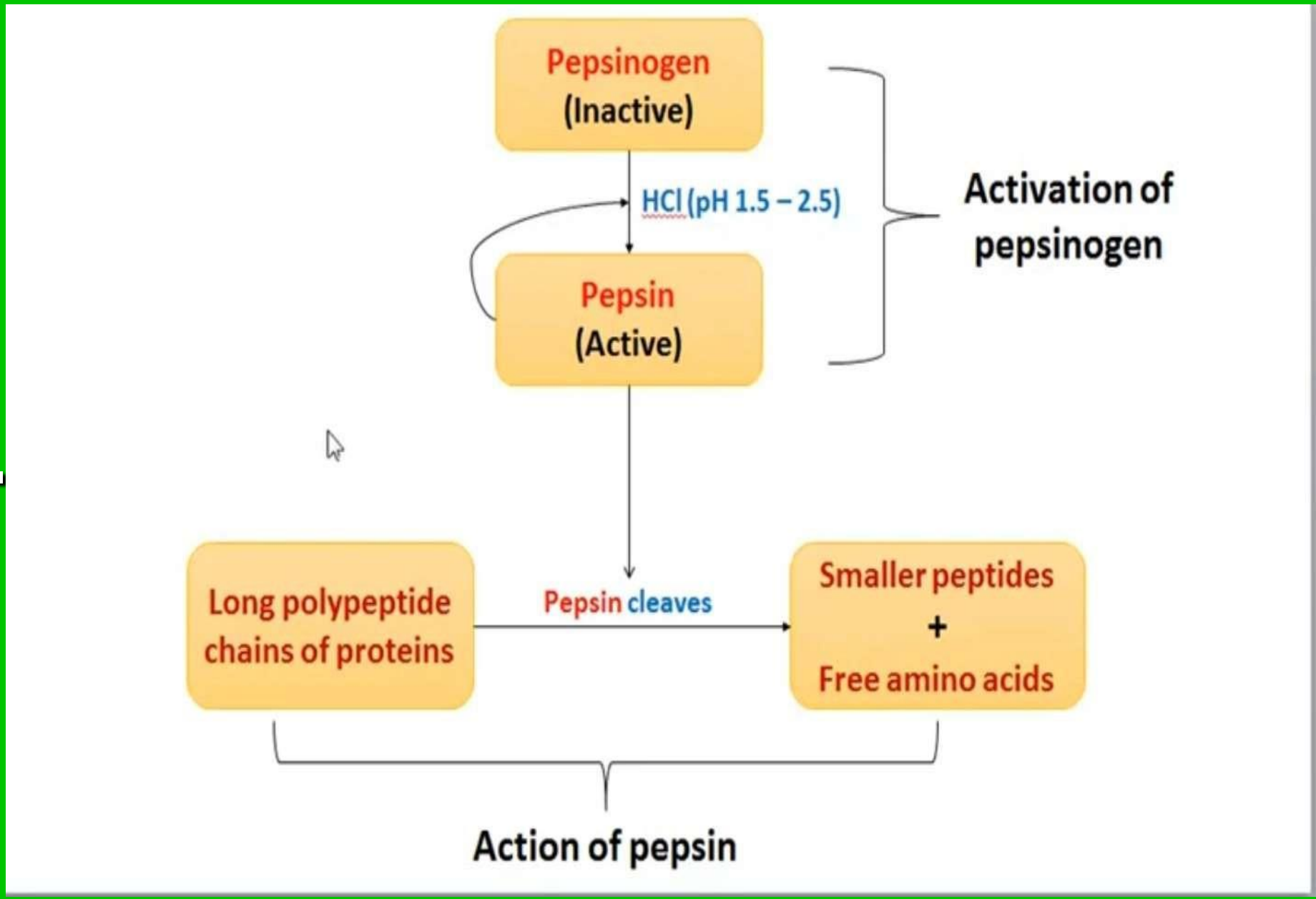
*Gastric juice contains:

1. Hydrochloric acid.
2. Pepsinogen (zymogen).
3. Rennin (in infants).

Hydrochloric acid denatures protein and activates pepsinogen to form pepsin. Pepsin breaks the polypeptide chain into smaller polypeptides.

.

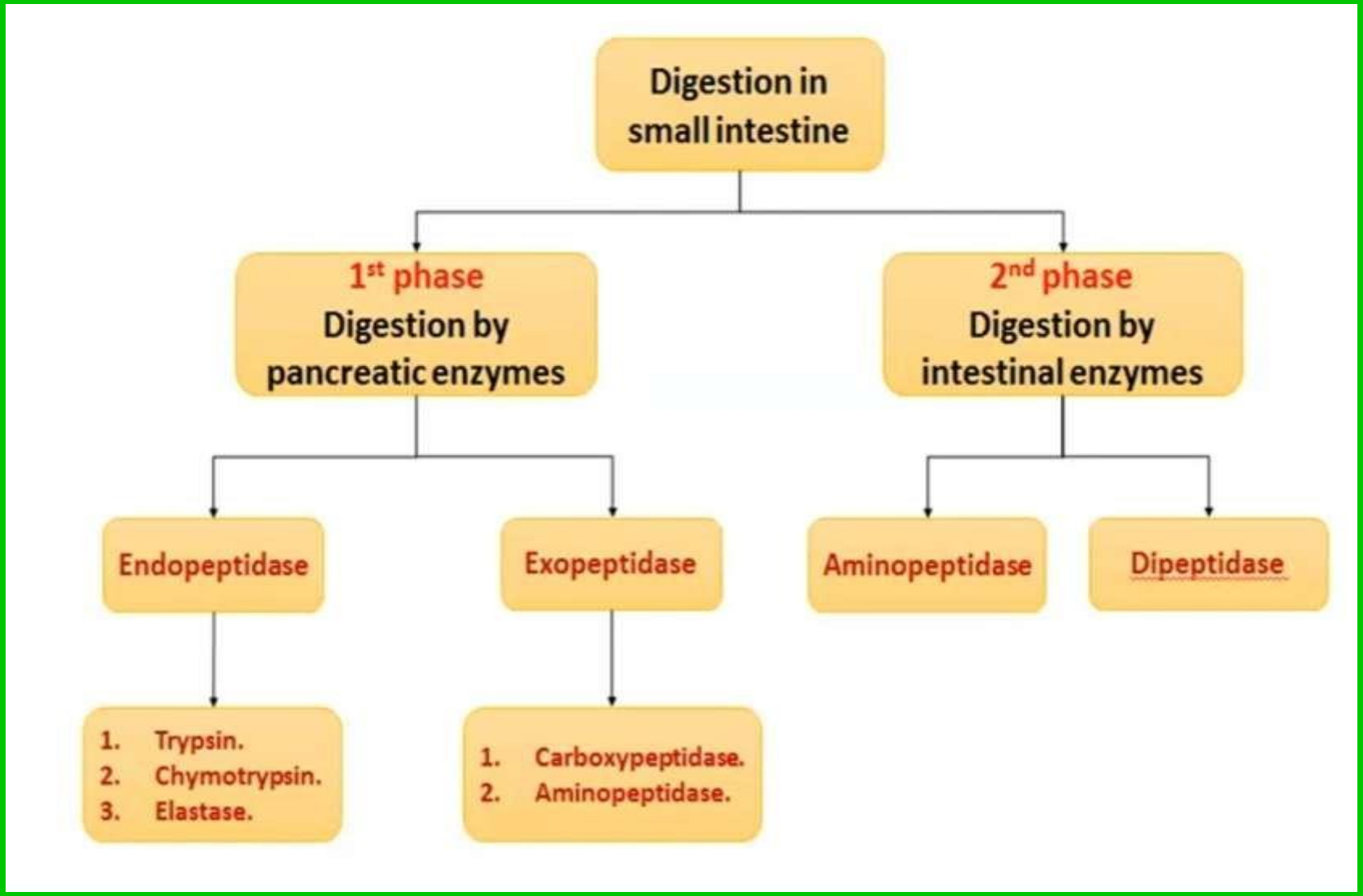



Pepsinogen
(Inactive)
HCl (pH 1.5 – 2.5)
Pepsin
(Active)
Activation of
pepsinogen
Long polypeptide
chains of proteins
Pepsin cleaves
Smaller peptides
+
Free amino acids
Action of pepsin

Digestion in small intestine

Digestion of proteins in the small intestine occurs in two phases:

1. The first phase (1st phase) is digestion by pancreatic enzymes.
2. The second phase (2nd phase) is digestion by intestinal enzymes.


Digestion in small intestine
1st phase Digestion by pancreatic enzymes
2nd phase Digestion by intestinal enzymes
Endopeptidase
Exopeptidase
Aminopeptidase
Dipeptidase
1. Trypsin.
2. Chymotrypsin.
3. Elastase.
1. Carboxypeptidase.
2. Aminopeptidase.

Small intestine and pancreas

Enzymes from the pancreas enter the small intestine and continue to cleave peptide bonds, resulting in dipeptides, tripeptides, and single amino acids.

(Trypsin – chymotrypsin)

Small intestine lining Tripeptidases and dipeptidases on thesurface of the small intestinal cells finishthe digestion to yield single amino acids,which can then be absorbed.Single amino acids

.

Amino Acid Absorption

*Amino acids are absorbed in the small intestine .

*Amino acids are transported to the liver from the intestines via the portal vein.

In the liver, amino acids are:

1 Used to synthesize new proteins

2 Converted to energy, glucose, or fat

3 Released to the bloodstream and transported to cells throughout the body.

Metabolism of amino

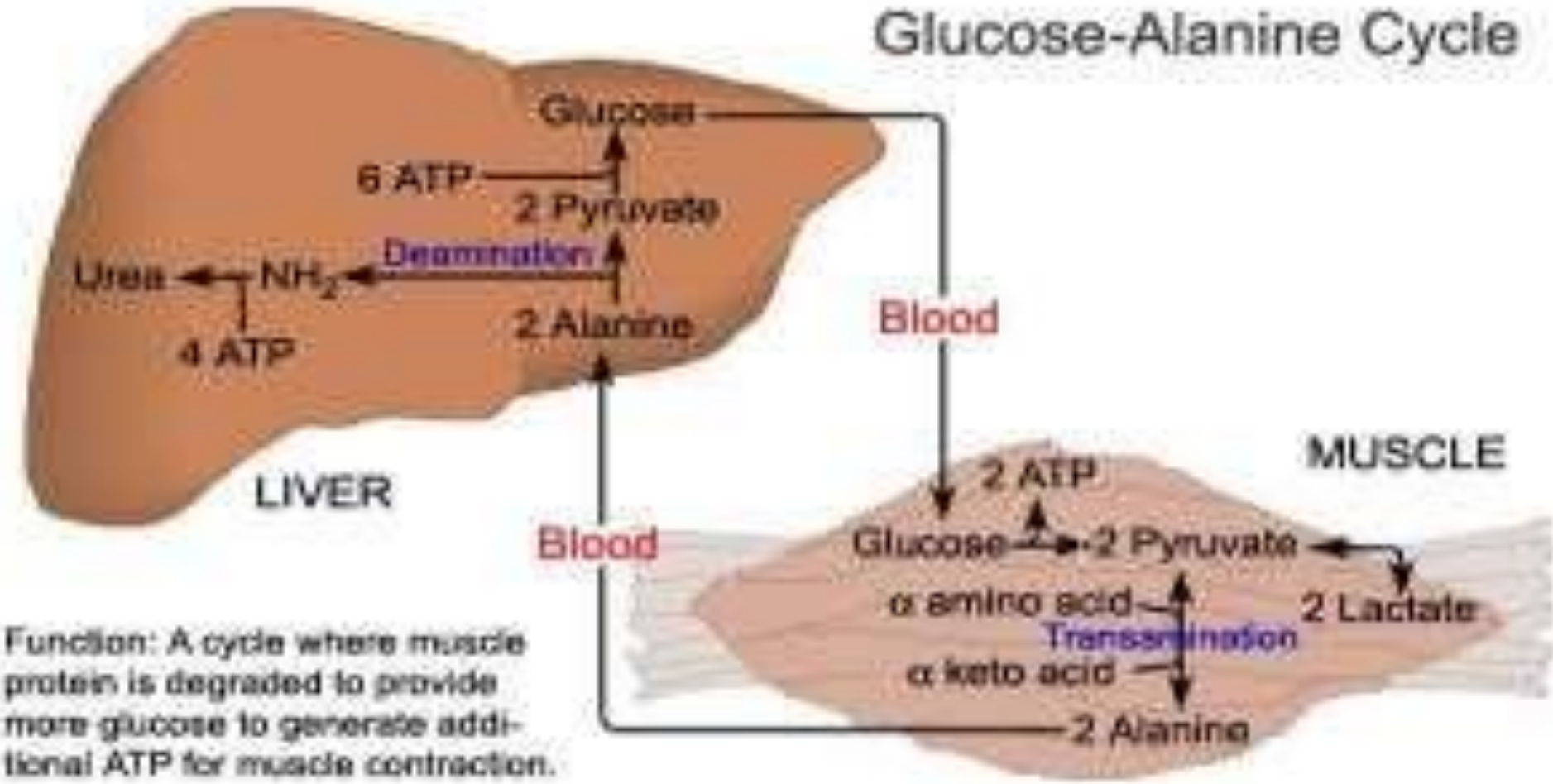
**Liver metabolizes amino acids, depending on bodily needs.

##Most amino acids are sent into the blood to be used by the cells.

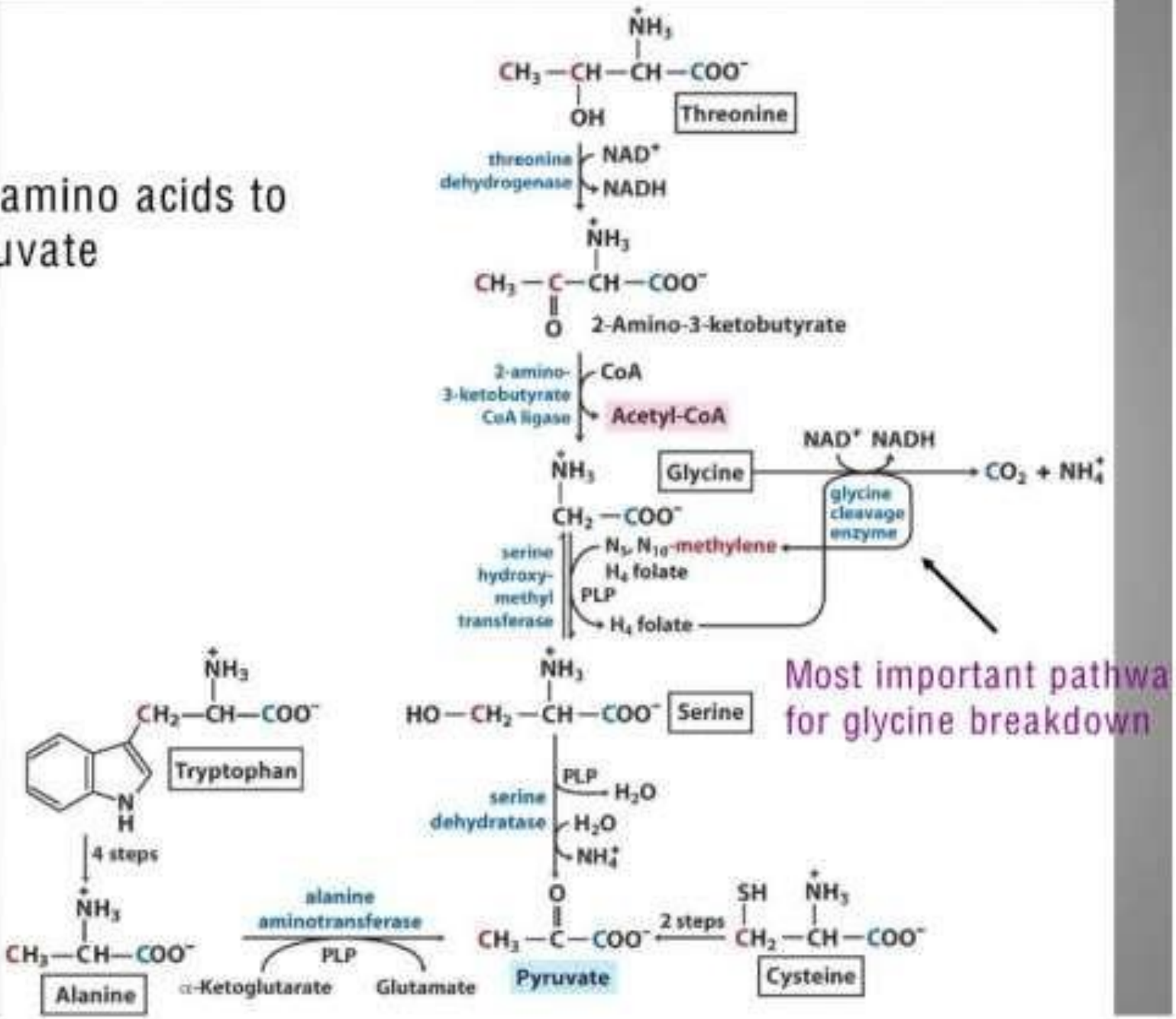
##Amino acid pool is limited but has many uses.

##Protein turnover - the continuall degradation and synthesizing of protein

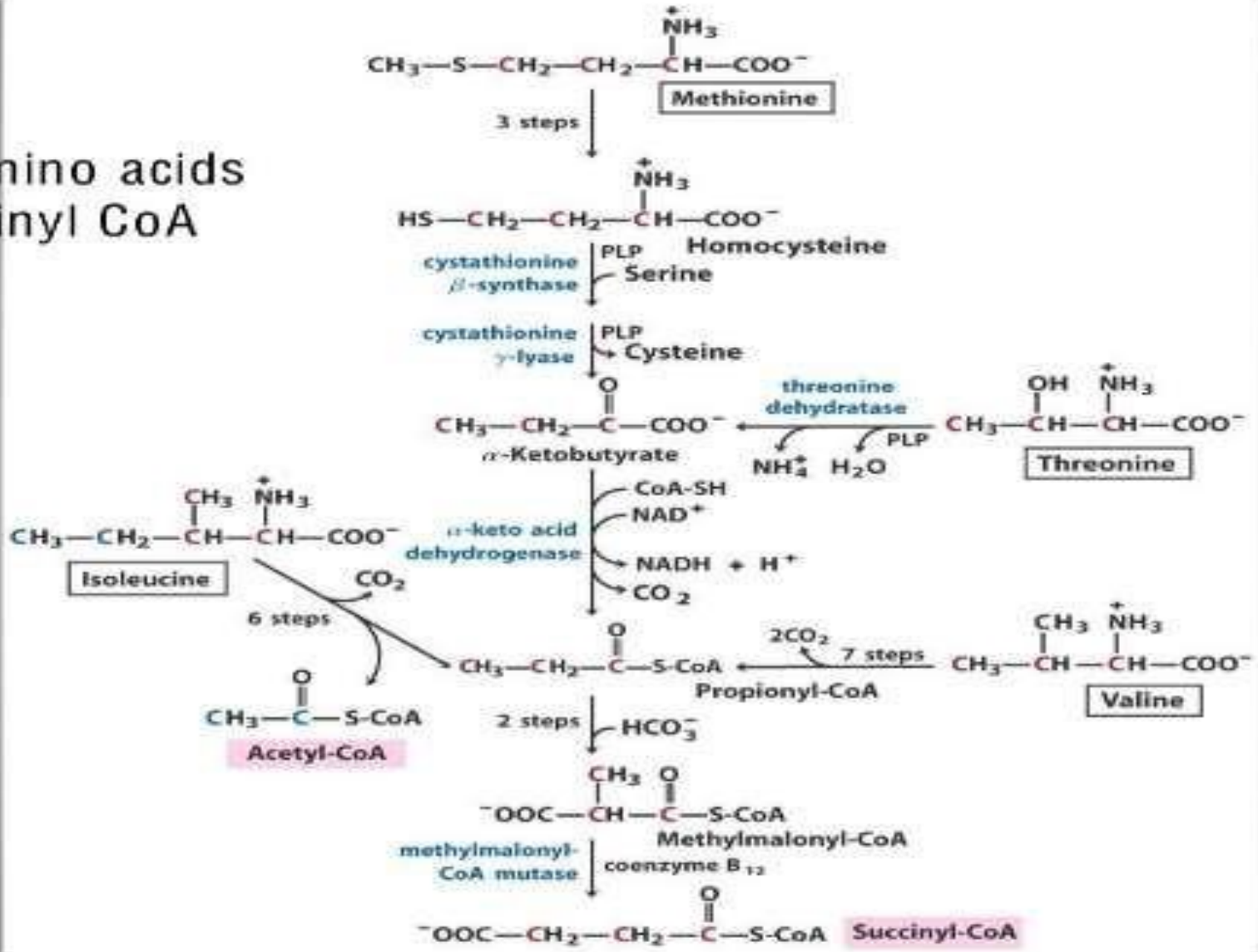
Catabolism of Alanine to Pyruvate



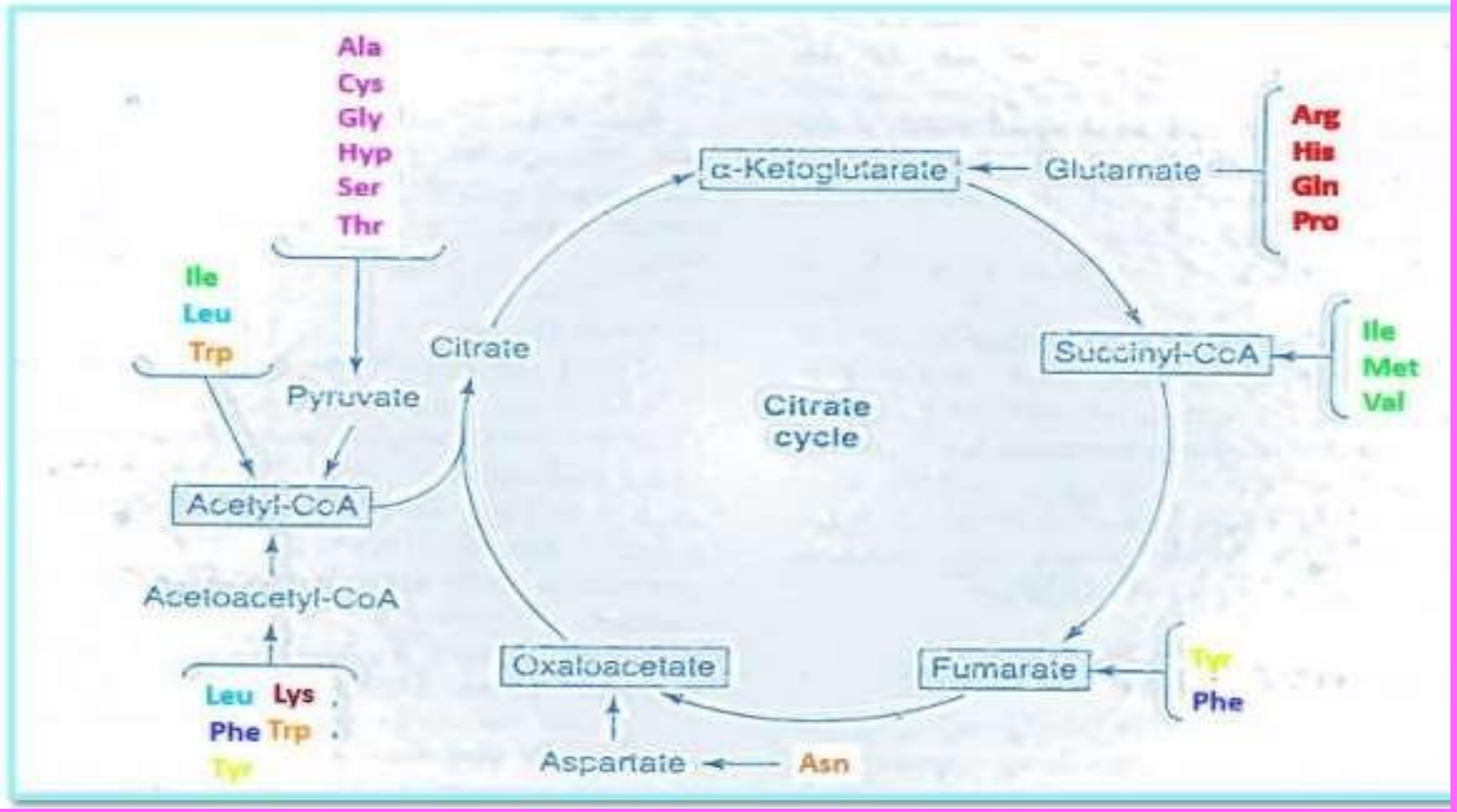
Six amino acids to pyruvate



Four amino acids to succinyl CoA



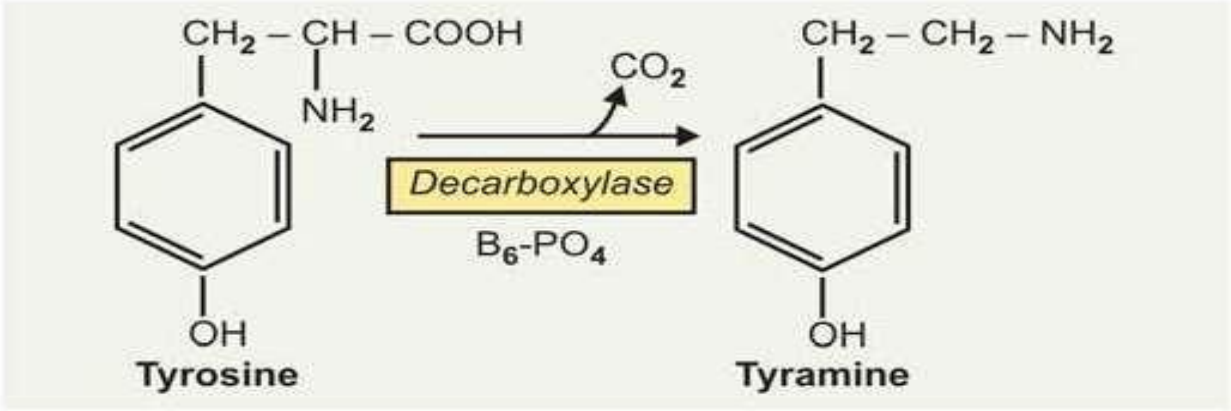
Amphibolic intermediates formed from the carbon skeletons of AAs:



SOME OF THE IMPORTANT BIOGENIC AMINES

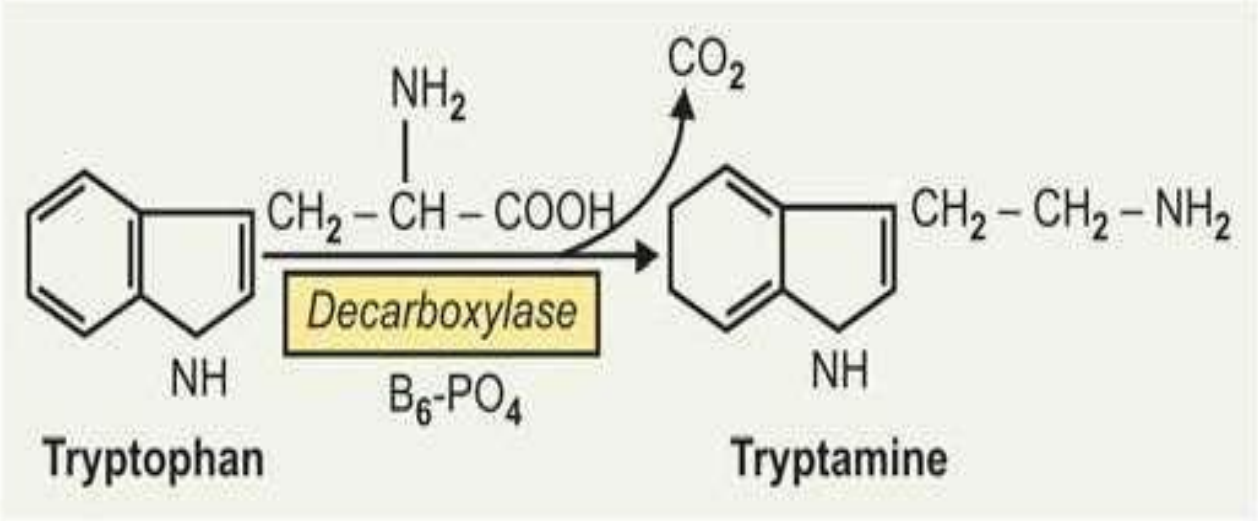
1. Tyramine

Decarboxylation of tyrosine forms tyramine. This occurs in the gut as a result of bacterial action. Also this reaction takes place in kidney. The ***reaction is favoured by O2-deficiency.*** In the presence of sufficient O2, tissue deaminates tyrosine. Tyramine elevates blood pressure.



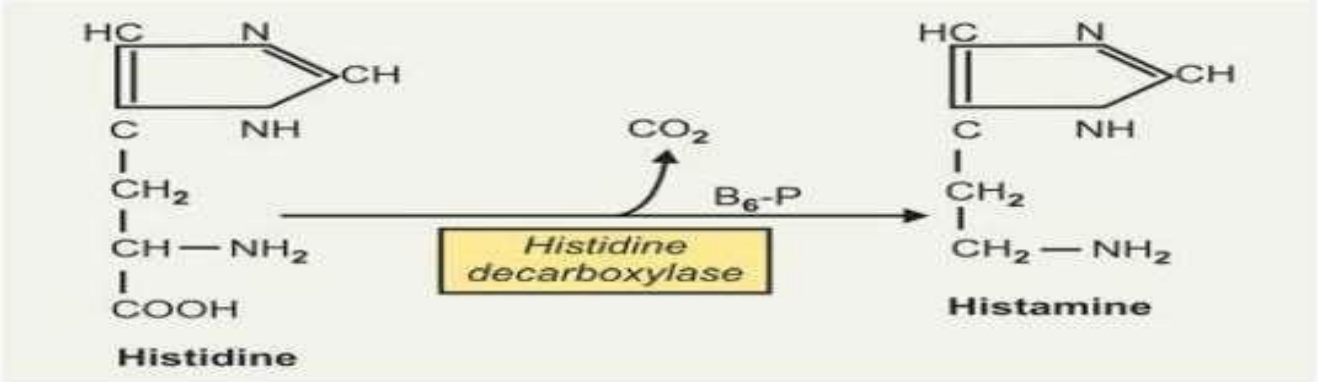
2. Tryptamine

Mammalian kidney, liver and bacteria of gut can decarboxylate the amino acid, tryptophan to form the amine ***tryptamine***. Tryptamine also elevates blood pressure. Hydroxylation at 5-position produces 5-OHtryptamine- 5-HT (Serotonin).

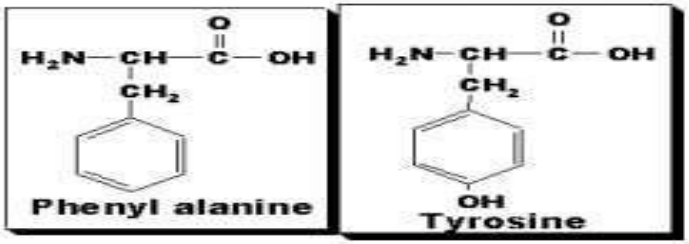


Histamine

Histamine is formed by decarboxylation of amino acid "Histidine" by the enzyme ***Histidine decarboxylase*** or aromatic L-amino acid decarboxylase in presence of B6-PO4.



A-Metabolism of Aromatic amino acids



Points to remember

- Phenyl alanine is nutritionally an essential amino acid. It cannot be synthesized in humans, hence must be provided in diet.

- Tyrosine is not essential, as it can be formed in the body from phenyl alanine.

- Tyrosine possesses an additional –OH group at para position of benzene ring
- Phenyl alanine is readily converted to tyrosine, but the reaction is NOT reversible.
- The feeding of tyrosine decreases the need of phenyl alanine in the diet ("sparing action").
- In phenyl ketonuria patient, where phenyl alanine cannot be converted to tyrosine in the body due to inherited deficiency of the enzyme, tyrosine becomes essential amino acid to the patient.
- Both amino acids are 'glucogenic' and 'ketogenic'.
- Both can participate in transamination reaction.

Note:

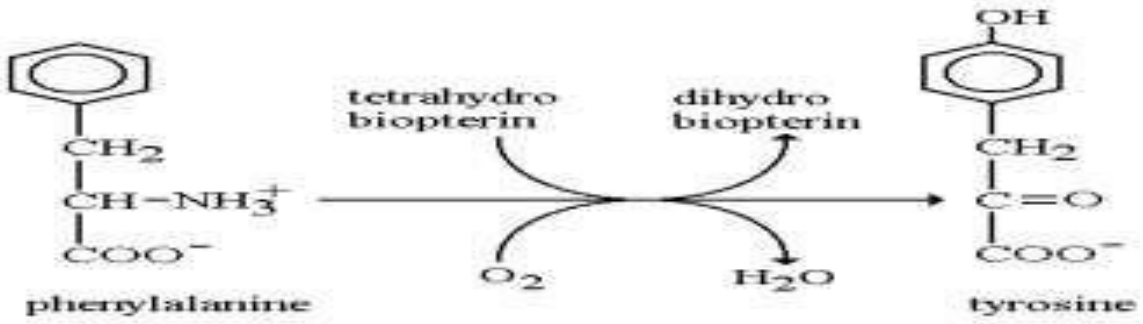
-Amino acids which give rise to pyruvic acid or one of the intermediates of Krebs cycle are **glucogenic.**

-Amino acids which give acetyl CoA are **Ketogenic** amino acids. Leucine and lysine are the only pure ketogenic amino acids.

A- Metabolic Fate:

(1) Conversion of phenyl alanine to tyrosine.

The reaction involves hydroxylation of phenyl alanine at p-position in benzene ring by phenyl alanine hydroxylase which present in the liver. The enzyme requires coenzymes and cofactors for its activity: Molecular oxygen, NADPH, Fe^{++} and Ptreidine (folic acid) coenzyme: Tetrahydrobiopterin- FH_4]



(2) Metabolic Fate of Tyrosine.

1-Tyrosine is degraded to produce as end products Fumarate and acetoacetate.

2-Fumarate is glucogenic, whereas acetoacetate is ketogenic.

3-Phenyl alanine is catabolized via tyrosine. Hence both phenyl alanine and tyrosine are glucogenic and ketogenic.

B-Metabolic Role of Tyrosine:

Tyrosine though it is non- essential, but it is of great importance in human body. Many biological compounds of importance are synthesized from tyrosine like:

1 -Synthesis of thyroid hormones: Thyroxine (T_4) and tri-iodo thyroxine (T_3)

2 -Synthesis of catecholamine's: epinephrine (adrenaline), nor epinephrine (nor-adrenaline) and dopamine. All three are synthesized from tyrosine and acts as "neurotransmitters"

Steps of synthesis:

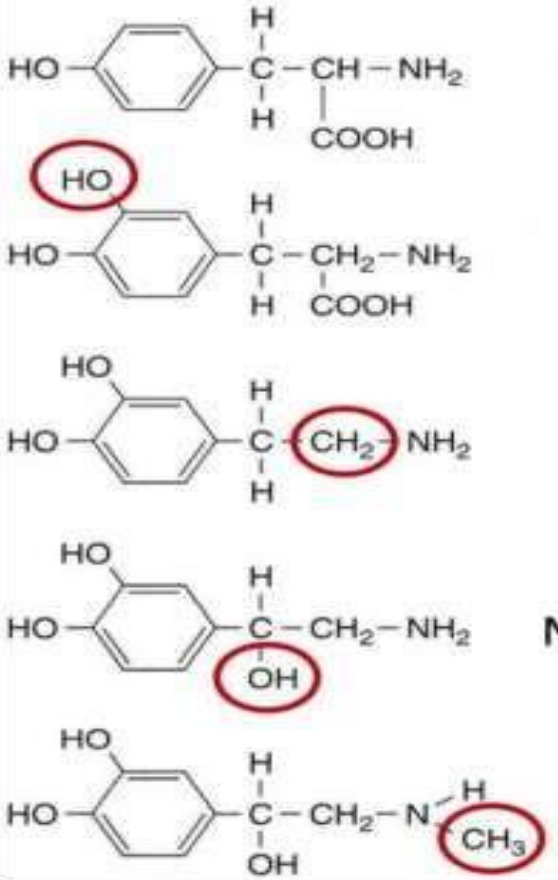
a- Conversion of tyrosine to DOPA (3,4-di-hydroxy phenyl alanine)(in mitochondrion).

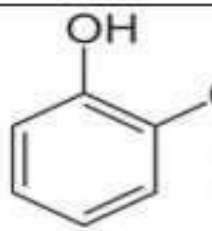
b- Conversion of DOPA to dopamine (in cytoplasm).

c- Conversion of dopamine to nor-epinephrine (in granules / vesicles).

d- Conversion of nor-epinephrine to epinephrine (in cytosol).

Structure of Catecholamines





Catechol Structure

Note benzene ring with two OH groups

Synthesis of norepinephrine from tyrosine occurs in four steps:

1) Hydroxylation
2) Decarboxylation
3) Hydroxylation
4) Methylation

Substitution mutations of these core molecules are the basis fo numerous therapeutic drugs.

You *do* need to know these structures

Clinical aspect: Inherited Disorders

Following disorders are associated with phenylalanine and tyrosine metabolism.

1-Phenyl Ketonuria

2- Albinism

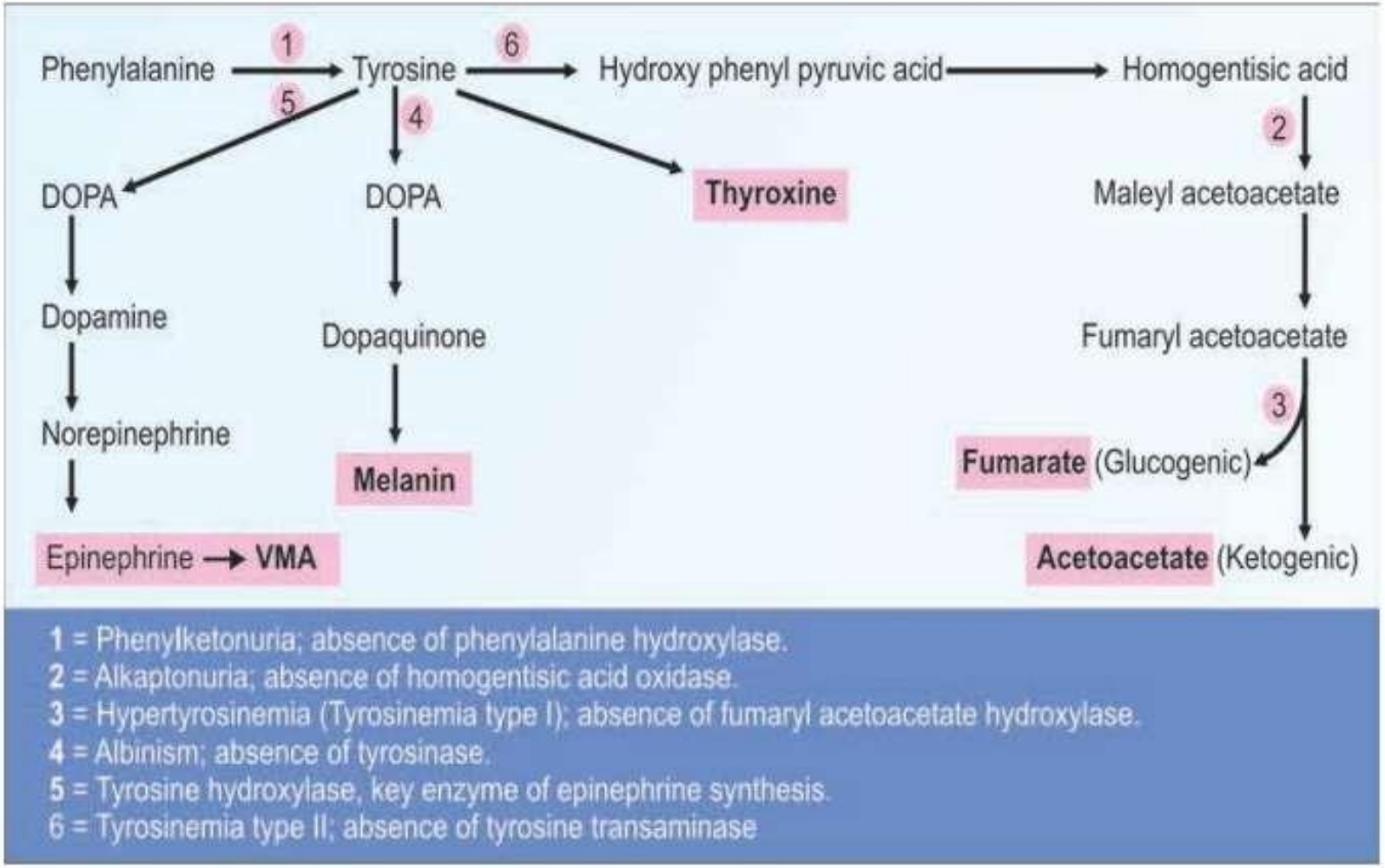
3- Tyrosinaemia Type I

4-Tyrosinaemia Type II

5- Neonatal Tyrosinaemia

6-Hereditary Tyrosinaemia

7- Alkaptonuria


Phenylalanine
1
Tyrosine
6
Hydroxy phenyl pyruvic acid
Homogentisic acid
5
4
2
DOPA
DOPA
Thyroxine
Maleyl acetoacetate
Dopamine
Dopaquinone
Fumaryl acetoacetate
3
Norepinephrine
Fumarate (Glucogenic)
Melanin
Epinephrine → VMA
Acetoacetate (Ketogenic)
1 = Phenylketonuria; absence of phenylalanine hydroxylase.
2 = Alkaptonuria; absence of homogentisic acid oxidase.
3 = Hypertyrosinemia (Tyrosinemia type I); absence of fumaryl acetoacetate hydroxylase.
4 = Albinism; absence of tyrosinase.
5 = Tyrosine hydroxylase, key enzyme of epinephrine synthesis.
6 = Tyrosinemia type II; absence of tyrosine transaminase

Albinism

Albinism refers to a group of conditions in which a defect in tyrosine metabolism results in a deficiency in the production of melanin (hypomelanosis). These defects result in partial or full absence of pigment from skin, hair and eyes.

3- Synthesis of melanin pigment:

Melanins are synthesized from tyrosine in " melanosomes", membrane bound particles within melanocytes in skin which are cells of neural crest origin. Melanins function is to protect underlying cells from the harmful effects of sunlight.

Albinism.

#Deficiency of tyrosinase enzyme of melanocytes.
#Failure of melanocyte to form melanin pigments.
#Whitish skin, Whitish eye lashes, whitish hair
#Intolerance to sunlight.

2-Alkaptonuria:

A rare inborn error or hereditary defect in metabolism of phenyl alanine and tyrosine. This is based on the observation that the urine becomes black on standing when it becomes alkaline. Enzyme deficiency: lack of the enzyme homogentisate oxidase resulting in the accumulation of homogentisic acid (one of many derivatives of tyrosine).

Diagnosis of Alkaptonuria

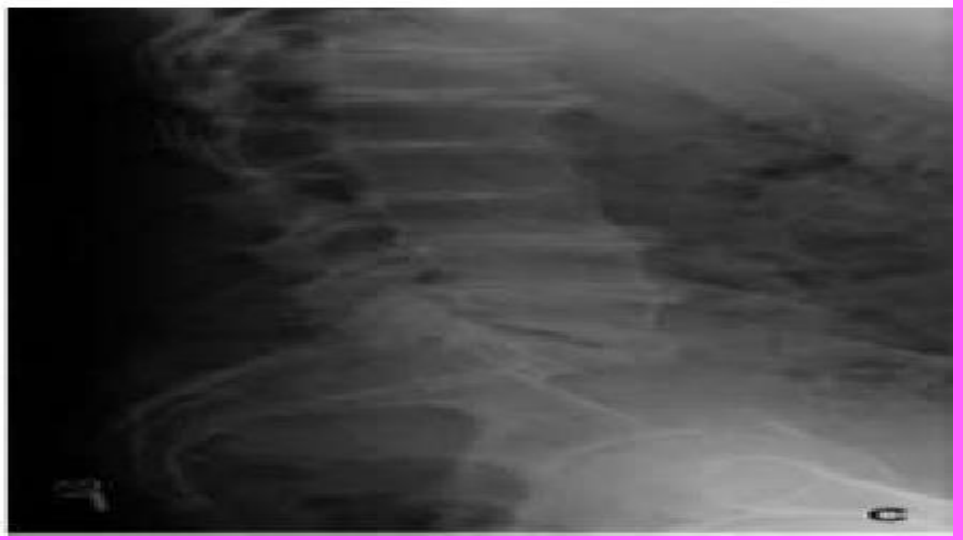
1. Urine becomes black on standing when it becomes alkaline. Blackening is accelerated on exposure to sunlight and oxygen. The urine when kept in a test tube will start to blacken from the top layer.

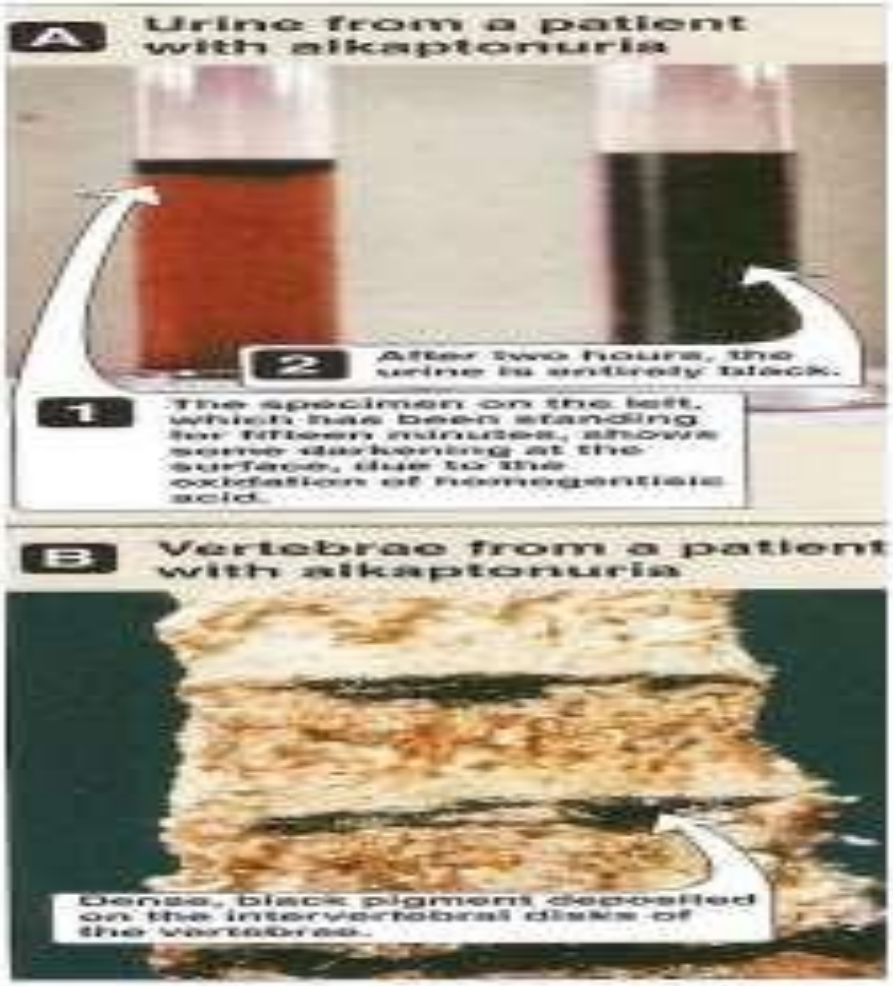
2. Ferric chloride test will be positive for urine.

3. Benedict's test is strongly positive. Therefore, alkaptonuria comes under the differential diagnosis of reducing substances in urine

Alkaptonuria

#Autosomal recessive.
#Deficiency of homogentisic acid oxidase.
#Increase homogentisic acid in blood and urine.
#Homogentisic acid on standing become black pigment. .(Alkapotonuria)
#It may be precipitate in the cartilage specially in the ear.
#Harmless.
#Diagnosis: Black color urine.
#Ferric chloride test is positive.




A
Urine from a patient with alkaptonuria
2
After two hours, the urine is entirely black.
1
The specimen on the left, which has been standing for fifteen minutes, shows some darkening at the surface, due to the oxidation of homogentisic acid.
B
Vertebrae from a patient with alkaptonuria
dense, black pigment deposited on the intervertebral disks of the vertebrae.

Phenyl Ketonuria:

Classical type of phenyl Ketonuria (PKU):

An inherited disorder with incidence of 1 in 10,000 live births.Enzyme deficiency: phenyl alanine hydroxylase is absent. Metabolic changes: phenyl alanine cannot be converted to tyrosine, as a result alternative catabolites are produced, phenyl alanine accumulates in the blood; phenyl alanine undergoes transamination to form phenyl pyruvic acid and its products as phenyl lactic acid and phenyl acetic acid are produced. Phenyl acetic acid is conjugated with glutamine and excreted as phenyl acetyl glutamine in urine (responsible for "mousy odour "of urine).

:Phenylketonuria

Deficiency of Ph. Hydroxylase enzyme

-autosomal recessive .1/10000

*Treatable disease with early diagnosis.

Late diagnosis lead to mental retardation. if diagnose after 2 weeks


Thank
You
For your Attention