Biochemistry course

Part 02: metabolic biochemistry

Chapter 02: **PROTEIN METABOLISM**

Dr. BENHIZIA Selma

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PROTEIN METABOLISM

1/INTRODUCTION

The catabolism of amino acids is always accompanied by the removal of amino nitrogen, either by transamination, or by deamination. Nitrogen, whose simple mineral form of NH_4^+ is toxic (especially for the central nervous system), is eliminated from the body:

- In the form of urea (major route: hepatic ureogenesis, 4/5 of nitrogen excreted).
- In the form of NH_4 (minor pathway: renal ammoniagenesis, 1/5).

Amino acid catabolism begins in the tissues where proteolysis takes place (intestine and muscles), and in the liver which receives amino acids from these tissues.

In animals, the source of amino acids is mainly dietary. Unlike carbohydrates and lipids, excess AA cannot be stored, so they are quickly degraded by transamination or deamination to give an ammonium ion NH_4^+ and a carbon skeleton. The ammonium ion is eliminated by excretion or by ureogenesis (urea cycle) or recycled for the synthesis of another amino acid. The carbon skeleton can also be reused to reform the corresponding amino acid or serve as precursors either for the synthesis of carbohydrates (glucoforming amino acids) or for the synthesis of fatty acids (ketogenic amino acids). Amino acid metabolism in animals serves two main purposes: maintain the amino acid pool, and ensure protein turnover.

The amino acid pool is formed by the hydrolysis of dietary and cellular proteins.

It represents approximately 100 g for a 70 kg individual and is sufficient to ensure the renewal of the body's proteins. Unfortunately, only 75% is recovered and recycled for protein renewal and 25% serves as precursors for the synthesis of other amino compounds. This explains the need for dietary protein to compensate for this deficit. Amino acid metabolism is therefore part of an organism's nitrogen metabolism.

2/DIGESTION OF FOOD PROTEINS

Amino acids normally enter the body from food in the form of polymers, i.e., in the form of proteins. The hydrolysis of proteins into peptides and isolated amino acids begins in the stomach. However, the residence time there is too short for complete hydrolysis. Shorter peptides thus reach into the epithelial cells of the intestine (mucosa) through transport systems and are completely broken down into amino acids in their cytoplasm. The mucosal cells supply the amino acids to the blood, through which they are transported for further processing.

Food ⇒ dietary proteins (plant and animal) ⇒ amino acids (by the action of proteases).

2.1/CATABOLISM OF AMINO ACIDS

Removal of amino nitrogen is done either by:

- Transamination common to all amino acids except lysine.
- Oxidative deamination, glutamate.
- Non-oxidative deamination, serine, cysteine and threonine.

This leads to the production of a compound toxic to the central nervous system, ammonia (NH3). This is eliminated by the body's detoxification systems either in the form of NH4+ (renal ammoniogenesis which represents 1/5 of the nitrogen eliminated; minor way), either in the form of urea *via* the ornithine cycle or urea cycle or Krebs-Henseleit cycle (ureogenesis; major hepatic pathway which represents 4/5 of the nitrogen eliminated).

2.1.1/Transamination

Transamination reactions, catalyzed by aminotransferases (ASAT and ALAT), ensure nitrogen exchanges between amino acids and α-keto acids: the amino acid, donor of the amine group, becomes an α-keto acid while the acceptor α-keto acid becomes an α-amino acid.

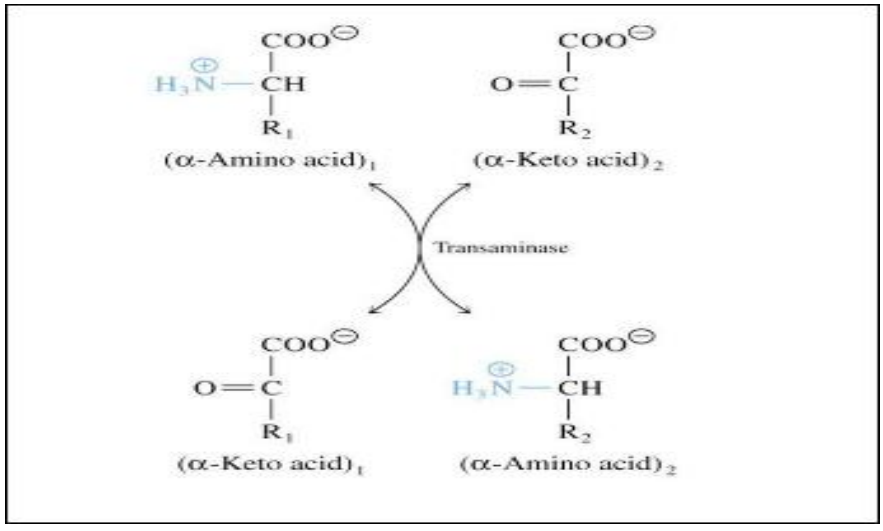


Fig. 1. General diagram of the reaction catalyzed by an aminotransferase

The transamination reaction requires a coenzyme, pyridoxal phosphate (PPal), intermediate transporter of the amine function, and takes place in two stages. Transamination reactions take place in the intestine, liver and muscles; they are reversible reactions.

- In the intestine and in the muscles; the reaction is catalyzed by ALAT.
- In the liver; the reaction is catalyzed by ASAT

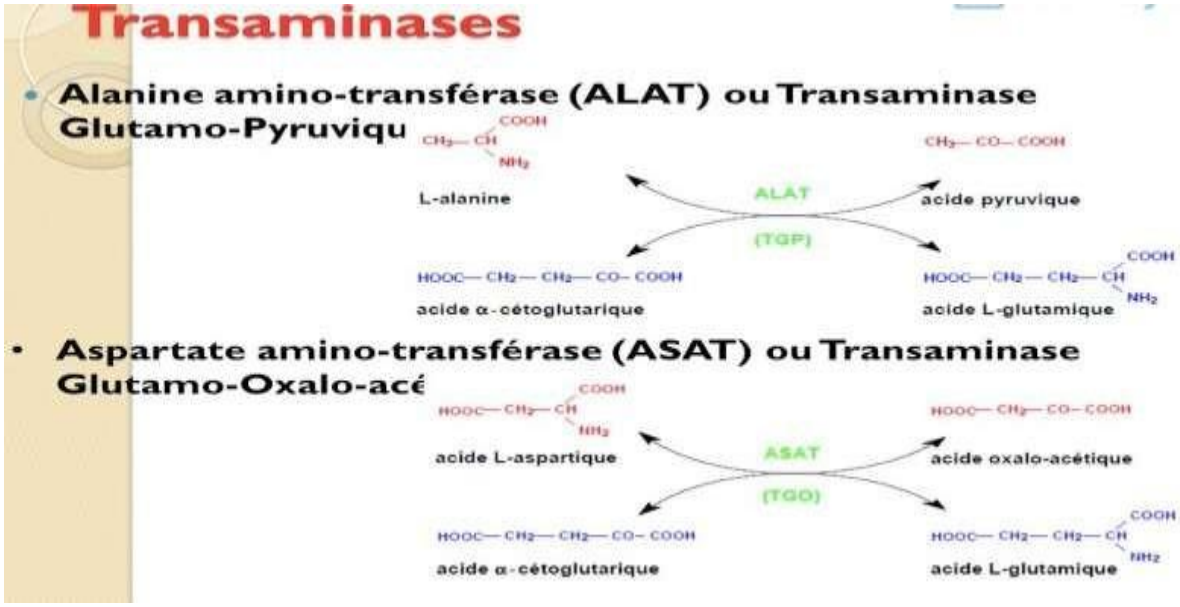


Fig. 2. Transamination patterns by ALAT and ASAT

2.1.2/Oxidative desamination

It occurs in muscles and liver. L-glutamate, produced by transamination reactions, is transported from the cytosol to the mitochondria, where it undergoes oxidative deamination, catalyzed by L-glutamate dehydrogenase, which will ultimately eliminate the α-amino group in the form of NH3. In mammals, ammonia, toxic to the cell, will be incorporated into the urea cycle and then excreted. The oxidative transamination-deamination coupling of glutamate is the major pathway for ammonia production by cells.

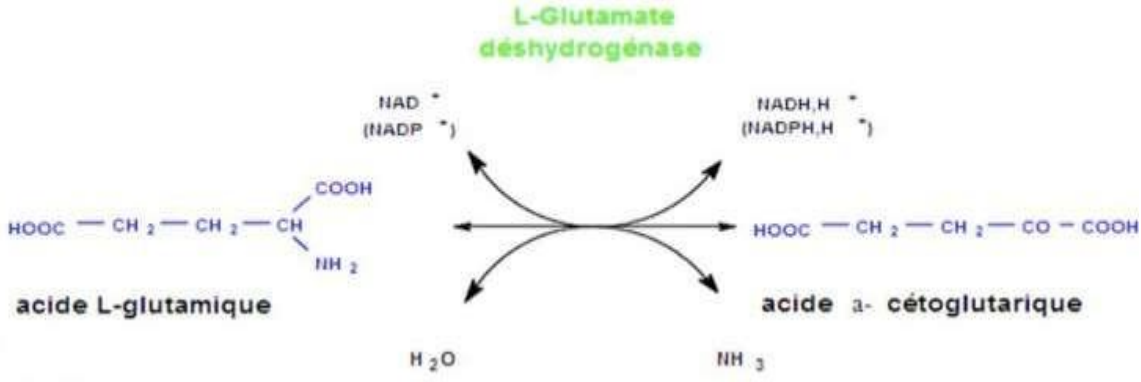


Fig 3. Principle of oxidative deamination

2.1.3/Decarboxylation

This is the release of CO2 by a decarboxylase, we obtain an amine.

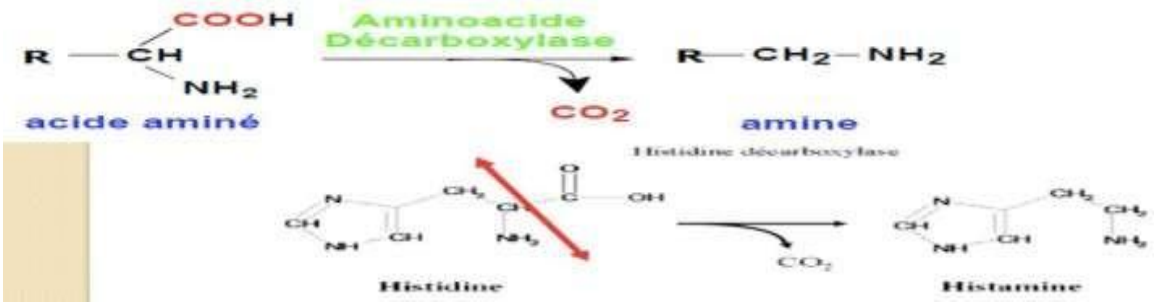


Fig 4. Principle of decarboxylation

2.1.4/Catabolism of the carbon skeleton

After the α-amino group leaves in the form of ammonia, the 20 amino acids found in proteins each release the corresponding α-ketoacid (carbon skeleton). The degradation of the 20 carbon skeletons leads to the formation of seven compounds, namely : α-ketoglutarate, oxaloacetate, fumarate, acetoacetyl-CoA, succinyl-CoA, pyruvate and acetyl-CoA.

They enter the intermediate metabolism for the production of energy or for the synthesis of carbohydrates or lipids. Depending on the fate of the carbon skeletons, amino acids are classified into three groups:

1- The glucoforming amino acids (glucogenic) whose degradation of the carbon skeleton releases one of the following intermediates: α-ketoglutarate, oxaloacetate, fumarate, succinyl- CoA and pyruvate. This class covers among the non-essential amino acids: alanine, asparagine, aspartate, glutamate, glutamine, proline, glycine, serine, cysteine; and among the essential amino acids: arginine, histidine, methionine, threonine and valine.

2- The ketogenic (or ketonic) amino acids whose degradation of the carbon skeleton provides the acetyl-CoA or the acetoacetyl-COA. Here we find 2 essential amino acids: leucine and lysine.

3-Amino acids that are both glucoforming and ketogenic: tyrosine (non-essential), phenylalanine, tryptophan and isoleucine (all 3 essential).

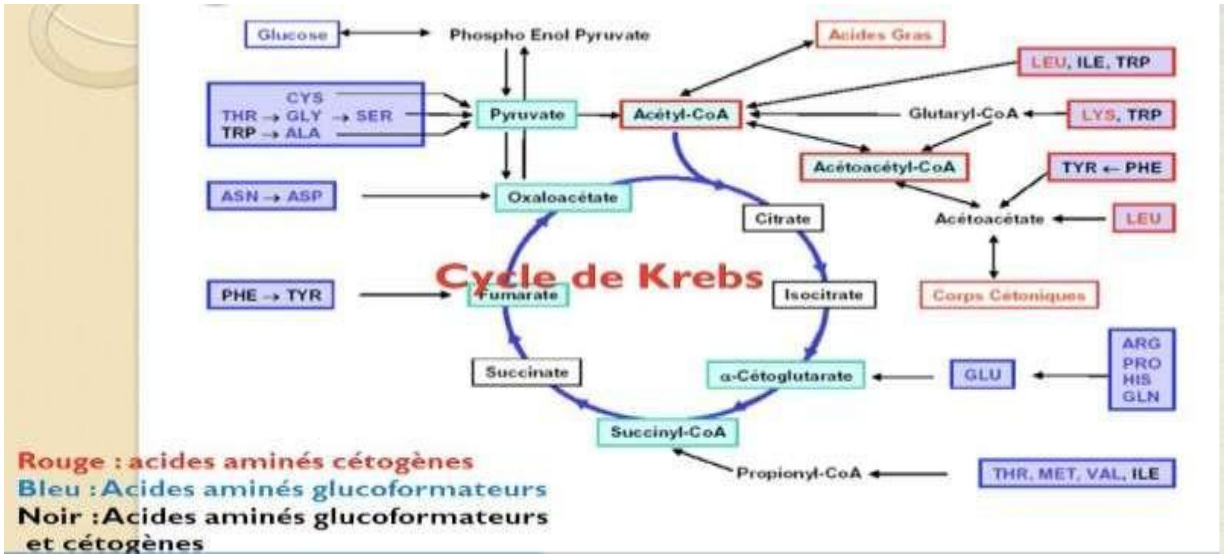
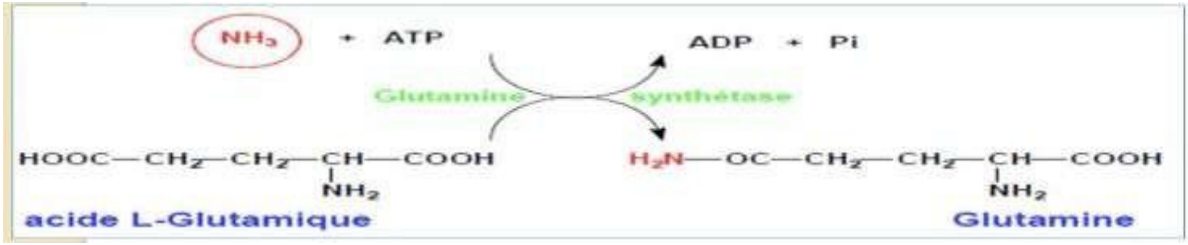


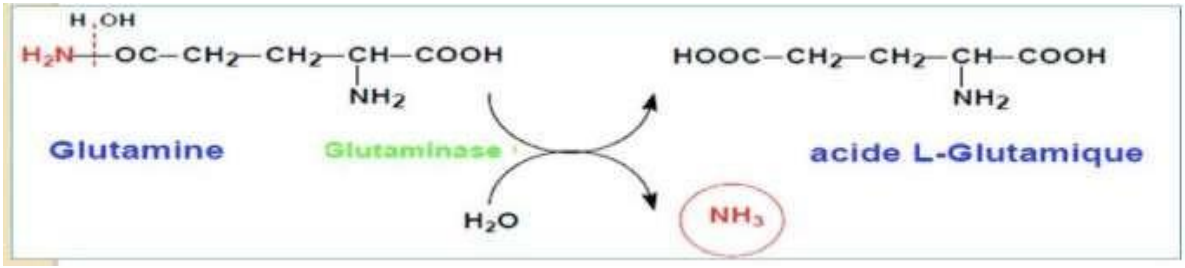
Fig 5. Catabolism of the carbon skeleton of amino acids.

2.1.5.Fate of NH3 (ammonia) from deamination

In the liver, it is, along with aspartate, a substrate for ureogenesis. And in the muscles, it reacts with glutamate (a reaction catalyzed by glutamine synthetase) to form glutamine going to the intestines and kidneys.



- In the kidneys, glutamine successively releases its 2 nitrogen atoms in the form of NH4+ eliminated in the urine (renal ammoniogenesis).
- In the intestine, glutamine ishydrolyzedinglutamate, the NH3 leaving for the liver.



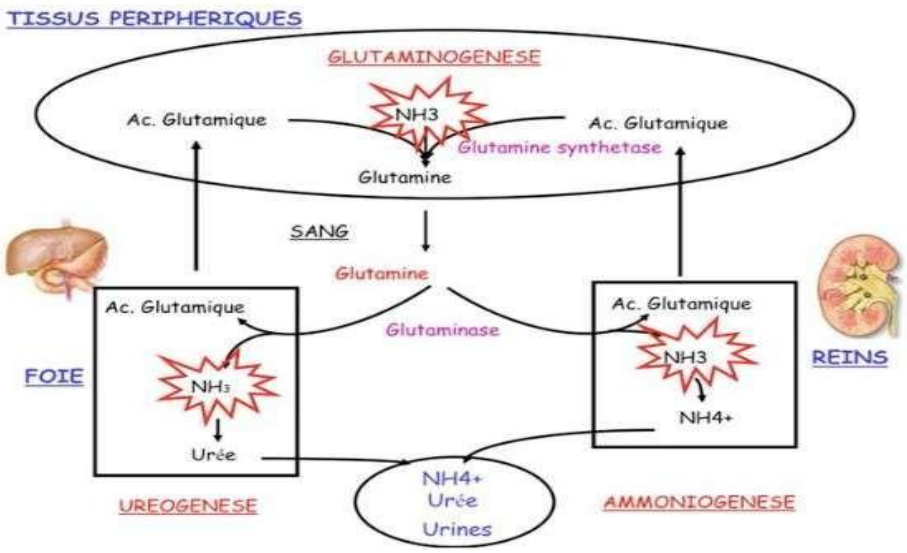


Fig. 6. Fate of ammonia from deamination.

- **Ammoniogenesis**

In the kidney, the NH3 released from glutamine will combine with H+ protons to form the ammonium ion NH4+ which will be eliminated in the urine.

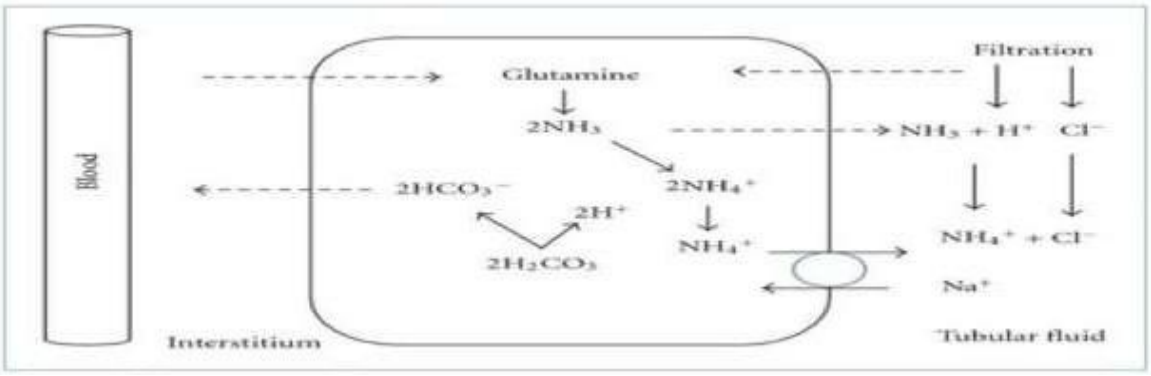


Fig. 7. Ammonigenesis

- **Ureogenesis or urea cycle**

The urea cycle is the hub of ammonia detoxification in urotelic species. It takes place in the liver. This is where glutamate accumulates as the end product of various AA catabolic pathways. Ammonia is released into the mitochondria during deamination reactions. In the form of ammonium ion, it condenses with hydrogen carbonate to produce carbamoyl phosphate. To synthesize urea, which contains two nitrogen atoms, another nitrogen atom must enter the reaction cycle. This comes from aspartate, which

is itself obtained by transamination from glutamate and oxaloacetate.

Non-proteinogenic amino acid ornithine (1) reacts with the carbamoyl phosphate formed from glutamate to give citrulline (2). There citrulline is transported from the mitochondria to the cytoplasm and forms there with the aspartate of the argininosuccinate (3). The argininosuccinate lyase releases it from fumarate (4), which gives back oxaloacetate by transamination. This results in the proteinogenic amino acid arginine (5). This can enter into protein synthesis or be transformed into ornithine by the arginase by releasing some urea (6). As soon as ornithine returns to the mitochondria by active transport, the urea cycle reaction sequence is completed.

A total of five enzymatic reactions are involved in urea biosynthesis. Two of them take place in the mitochondria and three in the cytoplasm. Carbamoyl phosphate synthetase (CPS) is the key enzyme that regulates the urea cycle. Two isoforms of this enzyme are distinguished. The CPS I isoform (7) is mitochondrial and is involved in the urea cycle. In contrast, the CPS II isoform is cytoplasmic and is involved in the synthesis of pyrimidines. Furthermore, they differ in the choice of substrate: CPS I condenses the ammonium ion and the hydrogen carbonate ion, and CPS II has glutamine as its substrate.

Physiologically relevant, urea biosynthesis is related to the amino acid concentration in the portal blood flowing to the liver. There is an approximately linear relationship between plasma nitrogen concentration and urea synthesis. CPS I responds very quickly to changes in N-acetyl glutamate concentration. If this signaling substance is lacking, CPS I is completely inactivated. To synthesize N-acetylglutamate, an increase in blood glutamate concentration, obtained with protein intake, is required.

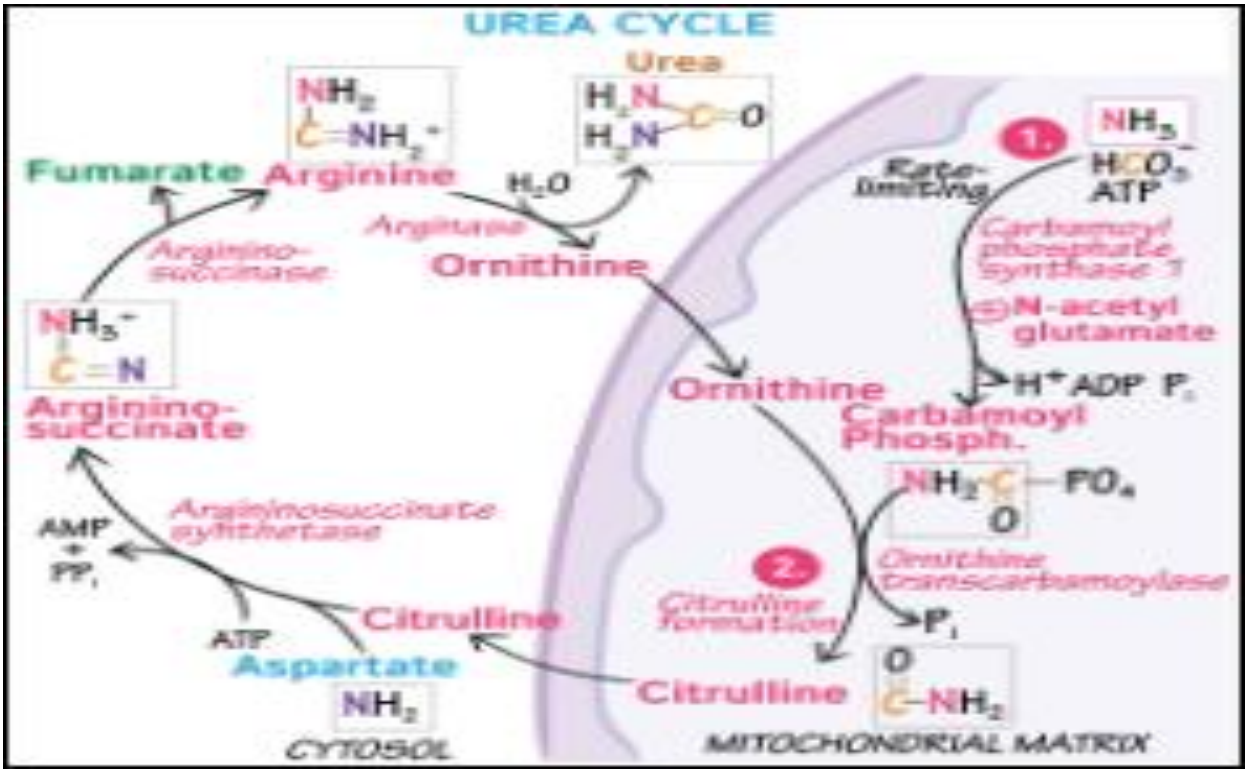


Fig. 8. Urea cycle

2.2/SYNTHESIS OF AMINO ACIDS

The body cannot synthesize the so-called essential amino acids; they must be provided by food: Lys, Met, Thr, Ile, Val, Leu, Phe, Trp.

Non-essential amino acids can be synthesized by the body through simple reactions using metabolic precursors. Amino acid biosynthetic pathways are diverse, but they all have one important common characteristic: the carbon skeleton of amino acids comes from intermediates of glycolysis, the pentose phosphate pathway, or the citric acid cycle. There are only06 biosynthetic families.

1. α-Ketoglutarate leads to the glutamate family: glutamate, glutamine, proline, arginine and lysine.
2. Oxaloacetate gives the aspartate family: aspartate, asparagine, methionine, threonine and isoleucine.
3. Glycerate-3-phosphateleads to the serine family: serine, glycine, cysteine.
4. Pyruvate provides the alanine family: alanine, valine and leucine.
5. Phosphoenolpyruvate and erythrose-4-phosphateare the starting point of phenylalanine, tyrosine and tryptophan.
6. Ribose-5-phosphateis the precursor of histidine.

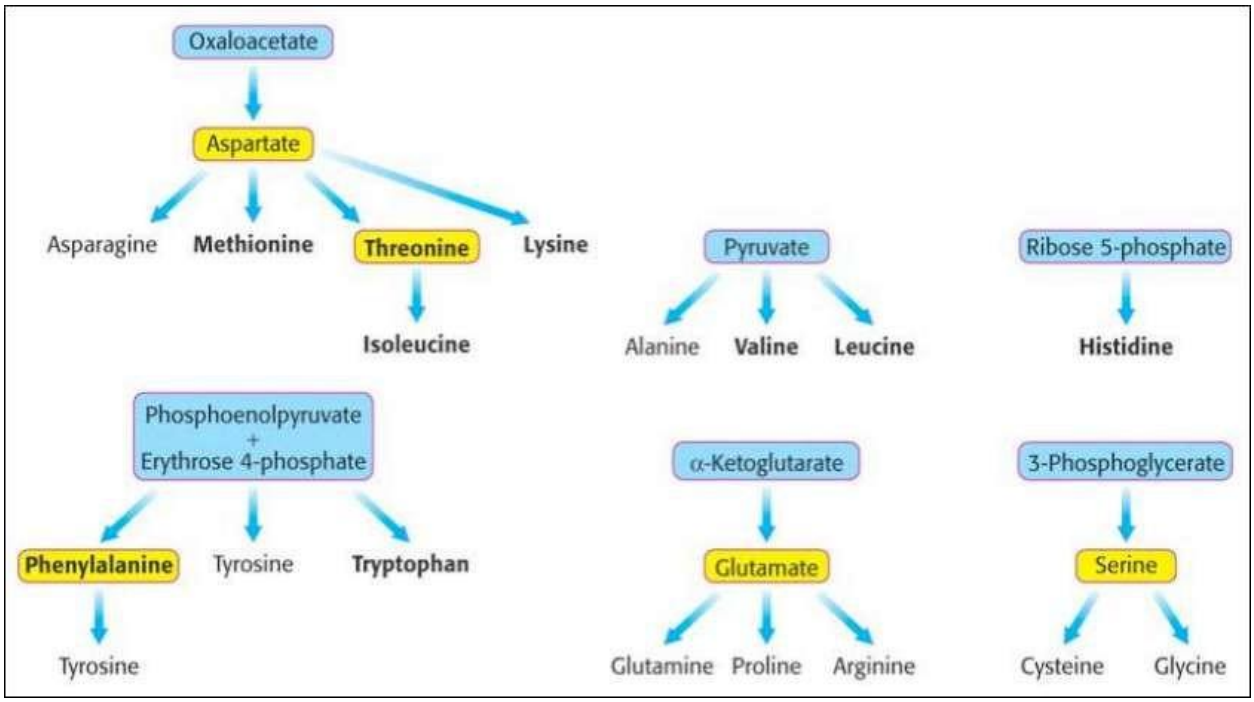


Fig. 9. Amino acid biosynthetic pathways