Proteins and amino acids metabolism

Amino acids are used for protein synthesis and as N and C donors for the synthesis of other types of macromolecule, e.g. the nucleic acids as well as numerous small molecular compounds. After deamination, i.e. removal of the amino group, the carbon skeleton may be used for the formation of glucose or even fats or it may be oxidized to CO_2 and water with the production of metabolic energy. Decarboxylation, i.e. removal of the carboxyl group of certain of the amino acids, leads to the production of biogenic amines such as histamine, serotonin and γ-aminobutyrate.

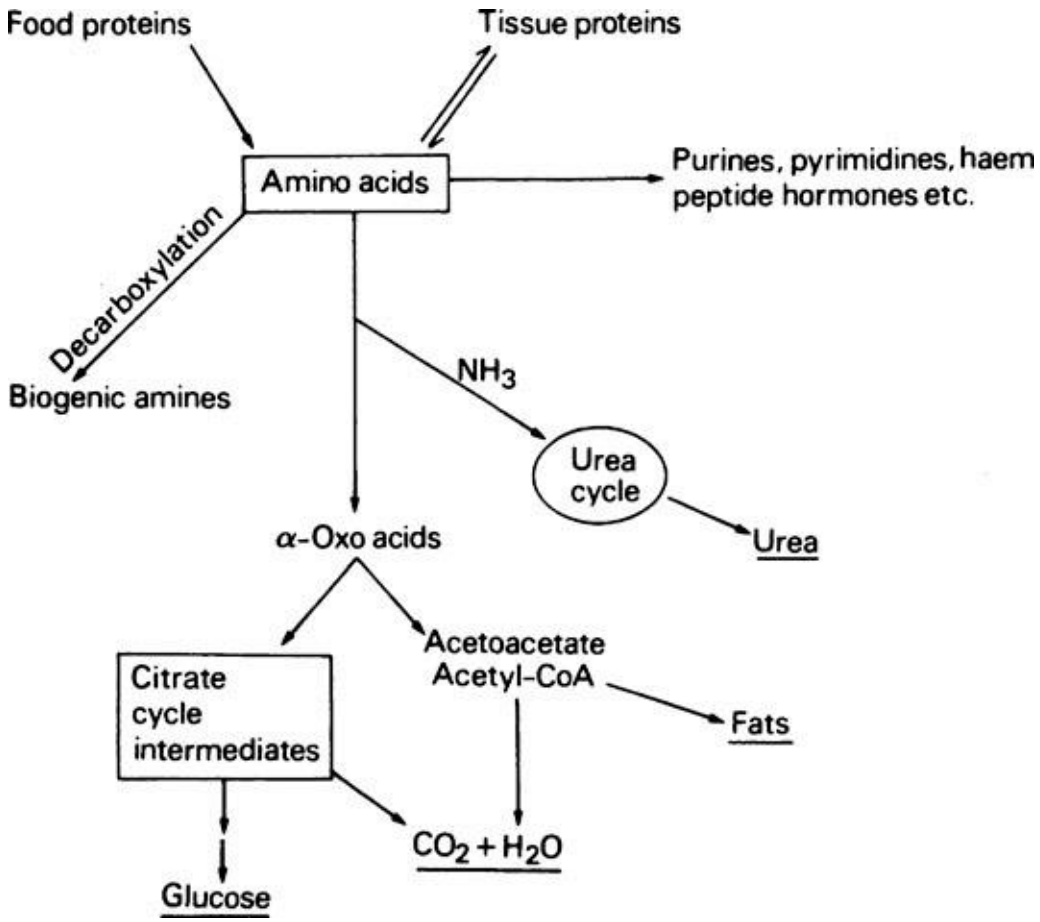


Figure 1: Amino acid metabolism

Urea cycle

The urea cycle (also known as the ornithine cycle) is a cycle of biochemical reactions that produces urea $(NH_2)_2CO$ from ammonia (NH_3).

The urea cycle converts highly toxic ammonia to urea for excretion.[1] This cycle was the first metabolic cycle to be discovered (**Hans Krebs and Kurt Henseleit, 1932**), five years before the discovery of the TCA cycle. This cycle was described in more detail later on by Ratner and Cohen. The urea cycle takes place primarily in the liver and, to a lesser extent, in the kidneys.

Functions

Amino acid catabolism results in waste ammonia. All animals need a way to excrete this product. Most aquatic organisms, or ammonotelic organisms, excrete ammonia without converting it. Organisms that cannot easily and safely remove nitrogen as ammonia convert it to a less toxic substance, such as urea, via the urea cycle, which occurs mainly in the liver. Urea produced by the liver is then released into the bloodstream, where it travels to the kidneys and is ultimately excreted in urine. The urea cycle is essential to these organisms, because if the nitrogen or ammonia is not eliminated from the organism it can be very detrimental. In species including birds and most insects, the ammonia is converted into uric acid or its urate salt, which is excreted in solid form. Further, the urea cycle consumes acidic waste carbon dioxide by combining it with the basic ammonia, helping to maintain a neutral pH.

Reactions

The entire process converts two amino groups, one from NH_4^+ and one from aspartate, and a carbon atom from HCO_3^-, to the relatively nontoxic excretion product urea. This occurs at the cost of four "high-energy" phosphate bonds (3 ATP hydrolyzed to 2 ADP and one AMP). The conversion from ammonia to urea happens in five main steps. The first is needed for ammonia to enter the cycle and the following four are all a part of the cycle itself. To enter the cycle, ammonia is converted to carbamoyl

phosphate. The urea cycle consists of **four enzymatic reactions**: **one mitochondrial** and **three cytosolic**.

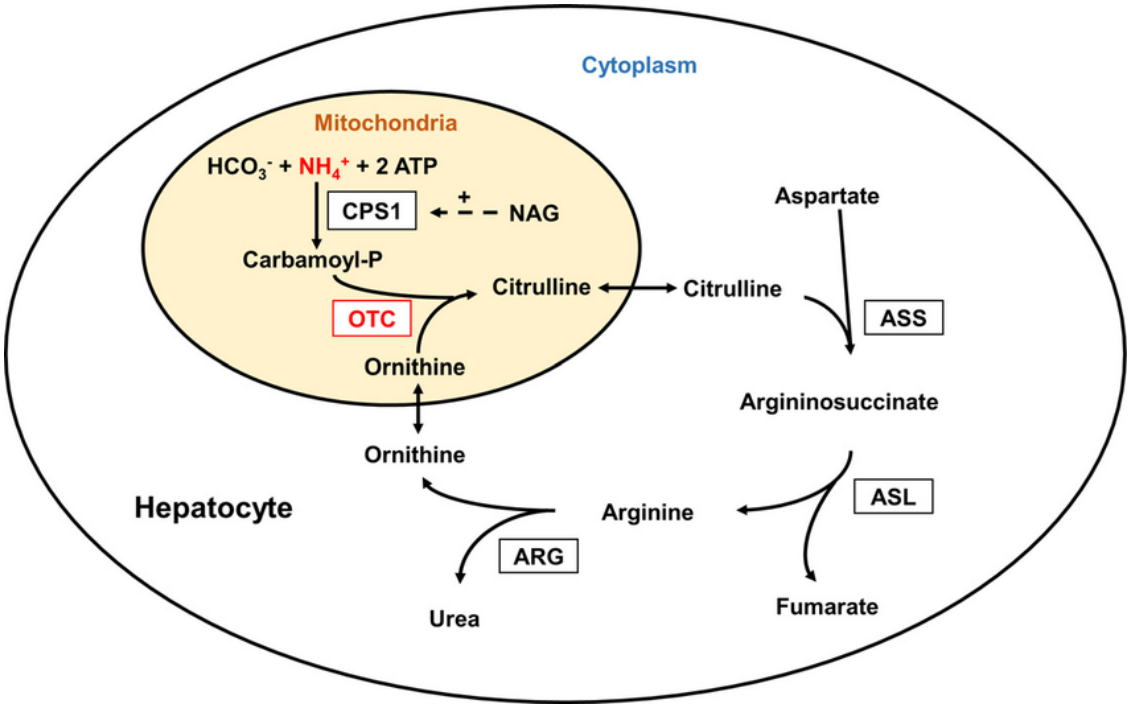


Figure 1: Urea cycle

CPS1= Carbamoyl phosphate synthetase I

OTC= Ornithine transcarbamylase,

ASS= Argininosuccinate synthase

ASL=Argininosuccinate lyase

ARG= Arginase

First reaction: entering the urea cycle

Before the urea cycle begins ammonia is converted to carbamoyl phosphate. The reaction is catalyzed by carbamoyl phosphate synthetase I and requires the use of two ATP molecules. The carbamoyl phosphate then enters the urea cycle.

Steps of the urea cycle

1. Carbamoyl phosphate is converted to citrulline. With catalysis by ornithine transcarbamylase, the carbamoyl phosphate group is donated to ornithine and releases a phosphate group.
2. A condensation reaction occurs between the amino group of aspartate and the carbonyl group of citrulline to form argininosuccinate. This reaction is ATP dependent and is catalyzed by argininosuccinate synthetase.
3. Argininosuccinate undergoes cleavage by argininosuccinase to form arginine and fumarate.
4. Arginine is cleaved by arginase to form urea and ornithine. The ornithine is then transported back to the mitochondria to begin the urea cycle again.

Products of the urea cycle

As stated above many vertebrates use the urea cycle to create urea out of ammonium so that the ammonium does not damage the body. Though this is helpful, there are other effects of the urea cycle. For example: consumption of two ATP, production of urea, generation of H^+, the combining of HCO^{-3} and NH_4^+ to forms where it can be regenerated, and finally the consumption of NH_4^+.

Overall reaction and energetics

The urea cycle is irreversible and consumes 4 ATP. Two ATP are utilized for the synthesis of carbamoyl phosphate. One ATP is converted to AMP and PPi to produce arginosuccinate which equals to 2 ATP. Hence **4 ATP** are actually consumed.

$NH4_+$ + CO2 + Aspartate + 3ATP →Urea+ Fumarate + 2 ADP + 2 Pi + AMP + PPi

Regulation

- **N-Acetylglutamic acid**

The synthesis of carbamoyl phosphate and the urea cycle are dependent on the presence of N-acetylglutamic acid (NAcGlu), which allosterically **activates CPS1**. NAcGlu is an obligate activator of carbamoyl phosphate synthetase1 (CPS1). Synthesis of NAcGlu by N-acetylglutamate synthase (NAGS) is stimulated by both Arg, allosteric stimulator of NAGS, and Glu, a product in the transamination reactions and one of NAGS's substrates, both of which are elevated when free amino acids are elevated. So Glu not only is a substrate for NAGS but also serves as an activator for the urea cycle.

- **Substrate concentrations**

The remaining enzymes of the cycle are controlled by the concentrations of their substrates. Thus, inherited deficiencies in cycle enzymes other than ARG1 do not result in significant decreases in urea production (**if any cycle enzyme is entirely missing, death occurs shortly after birth**). Rather, the deficient enzyme's substrate builds up, increasing the rate of the deficient reaction to normal.

The anomalous substrate buildup is not without cost, however. The substrate concentrations become elevated all the way back up the cycle to NH_4^+, resulting in **hyperammonemia.**

Link with the citric acid cycle

The urea cycle and the citric acid cycle are independent cycles but are linked. **One of the nitrogen atoms** in the urea cycle is obtained from the **transamination of oxaloacetate to aspartate**. The **fumarate** that is produced in step three is also an intermediate in the citric acid cycle and is returned to that cycle.

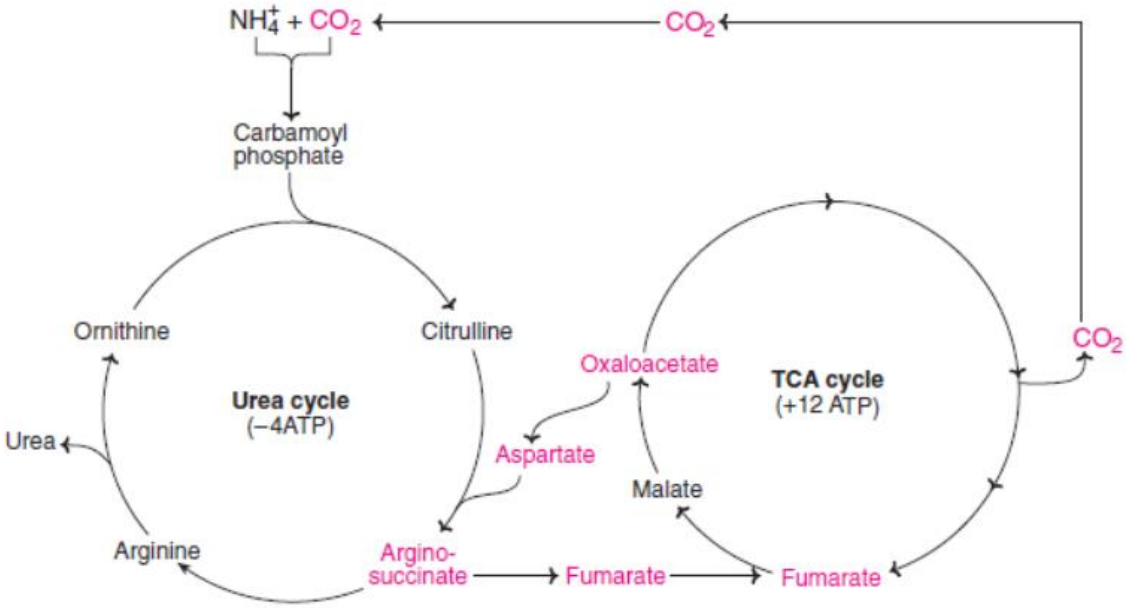


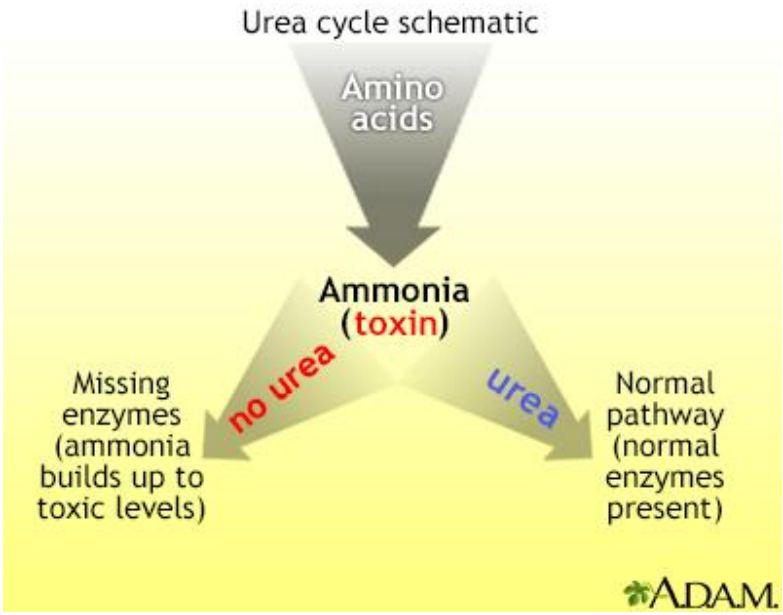
Figure 2: The relationship between the urea cycle and the Krebs cycle

Metabolic disorders of urea cycle

Metabolic defects associated with each of the five enzymes of urea cycle have been reported are given below. All the disorders invariably lead to a build-up in blood ammonia **(hyperammonemia)**, leading to toxicity. Other metabolites of urea cycle also accumulate which, however, depends on the specific enzyme defect. The clinical symptoms associated with defect in urea cycle enzymes include vomiting, lethargy, irritability, ataxia and mental retardation.

Defect	*Enzyme involved*
Hyperammonemia type I	Carbamoyl phosphate synthase I
Hyperammonemia type II	Ornithine transcarbamoylase
Citrullinemia	Arginosuccinate synthase
Arginosuccinic aciduria	Arginosuccinase
Hyperargininemia	Arginase

Hereditary urea cycle abnormality is an inherited condition. It can cause problems with the removal of waste from the body in the urine.



Several inherited conditions can cause problems with this waste-removal process. People with a urea cycle disorder have a defective gene that makes the enzymes needed to break down ammonia in the body.