Urea Cycle

Ammonia toxicity

Ammonia '*passes* freely through body barriers, e.g. hematoencephalic barrier. When "increasing" its concentration in the body, the balance of many important reactions is disturbed.

Glutamate + NAD^+ → α-ketoglutarate + NH_4^+

Glutamate + NH_4^+ + ATP → glutamine + ADP + P_i

With an excess of ammonia, the concentration of glutamine slowly increases, but its production simultaneously consumes α-ketoglutarate from the Krebs cycle - the speed of this important pathway gradually decreases and thus energy production in cells. The plasma concentration of ammonia should not exceed the value of *35 µmol/l*. In the human body, most of the toxic ammonia is converted by the reactions of the urea cycle '*to urea*.

Urea cycle reaction

Urea, a non-toxic compound, is transported through the bloodstream to the kidneys, where it is excreted from the body in the urine. The urea cycle, located both in the matrix of mitochondria and in the cytosol of liver cells, represents an energy-demanding process into which three substrates enter:

- ammonia;
- carbon dioxide (bicarbonate);
- aspartate (its amino group).

The regulatory enzyme is mitochondrial carbamoyl phosphate synthetase I.

The **ornithine cycle'** communicates with the **Krebs cycle** through oxaloacetate and fumarate.

The formation of urea takes place during five reactions:

1. Formation of carbamoyl phosphate

- catalyzed by mitochondrial carbamoyl phosphate synthase I;

  $NH_4^+ + HCO_3^- + 2ATP \rightarrow$ carbamoyl phosphate + 2 ADP + P_i

2. Formation of citrulline

- catalyzed by ornithine transcarbamoylase;

  Ornithine + carbamoyl phosphate → citrulline + P_i

  Citrulline is transported into the cytosol.

3. Formation of arginine succinate

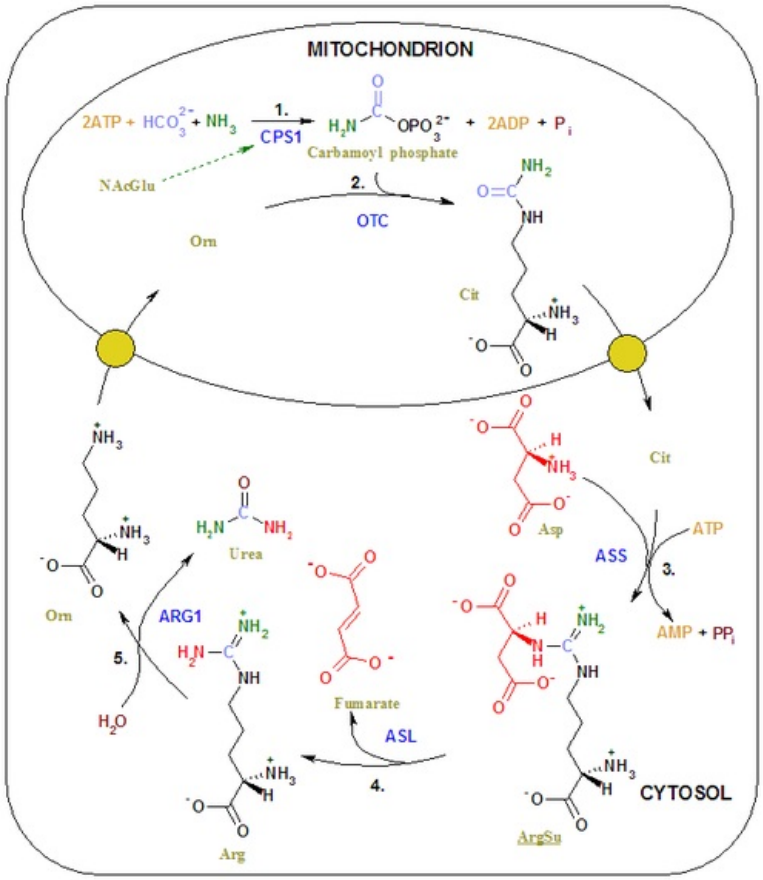
- catalyzed by arginine succinate synthase;

  Citrulline + Asp + ATP → arginine succinate + AMP + PP_i

4. Breakdown of arginine succinate

- catalyzed by arginine succinate lyase;

  Arginine succinate → arginine + fumarate



Uric acid cycle

5. Hydrolysis of arginine

- arginase catalyzed;

  Arginine + H_2O → ornithine + urea

This is followed by the transfer of ornithine to the mitochondrial matrix.

The **urea cycle** is closely connected with the Krebs cycle - the resulting fumarate becomes aspartate. Fumarate is first hydrated to malate, the oxidation of which produces oxaloacetate. This is transaminated with **glutamate'** by means of the enzyme aspartate aminotransferase, resulting in **aspartate** entering the ornithine cycle. *Glutamate is obtained by* transamination *of degraded amino acids, which transfer their amino groups to α-ketoglutarate molecules.*

Regulation of the ornithine cycle

Carbamoyl phosphate synthase I is the master regulatory enzyme of the ornithine cycle. It is activated through N-acetylglutamate, which is formed by the reaction of Acetyl-CoA and glutamate catalyzed by N-acetylglutamate synthetase. Its activity is increased by the amino acid arginine.

Transcription of enzymes of the urea cycle is *increased* with a high-protein diet or with increasing proteocatabolism (e.g. during starvation), i.e. in states of increased supply of amino acids. Since the urea cycle is one of the proton-producing reactions, its attenuation occurs when the pH drops - acidosis.

Urea cycle disorders

1. **Hyperammonemia type I** - carbamoyl synthase enzyme is missing
2. **Hyperammonemia type II** - the enzyme ornithine transcarbamoylase is missing
3. **Citrullinemia** - the enzyme arginine succinate synthase is missing
4. **Arginine succinatria** - the enzyme arginine succinate lyase is missing
5. **Hyperargininemia** - lack of arginase enzyme

All of these disorders are extremely rare, but very serious. Hyperammonemias are the most important of the mentioned disorders due to the fact that in the other disorders part of the ammonia has already been covalently bound to the carbon chain. The symptoms of all the listed diseases correspond to ammonia intoxication.

- ws: Močovinový cyklus (FBLT)