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Urea Cycle

Introduction

As we discussed under amino acids metabolism section, produced ammonia is toxic to the body. Hence, if it is not reused to synthesize new amino acids or other nitrogen containing compounds, it is excreted out of the body as urea. This process of formation of urea occurs via the urea cycle for most animals, also known as ureotelic species. There are exceptions to this, like aquatic species which excrete ammonia directly into the surrounding, and ammonia then is diluted with water and these species are called ammonotelic species. Also, certain species like birds and reptiles excrete ammonia as uric acid and hence are known as uricotelic species. Once the urea produced, it is excreted out by the kidneys in the urine. Urea is also called carbamide and when dissolved in water it has a neutral pH.

Urea cycle

Ammonia is converted to urea in the hepatocytes in five steps via urea cycle- in the mitochondria (first 2 steps) and cytosol (last 3 steps). The urea then travels through the blood stream to the kidney and is excreted in the urine. The urea cycle was discovered by Hans Krebs (who also discovered Citric acid or Krebs cycle).

Steps of Urea Cycle

Urea cycle is a series of five reactions catalyzed by several key enzymes. The first two steps in the cycle take place in the mitochondrial matrix and the rest of the steps take place in the cytosol. Thus, urea cycle is carried out in two cellular compartments of the liver cell.

- In the first step, ammonia produced in the mitochondria is converted to carbamoyl phosphate by an enzyme called carbamoyl phosphate synthetase I. The reaction can be given as follows:

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

- The second step involves the transfer of the carbamoyl group from carbamoyl phosphate to ornithine to form citrulline. This step is catalyzed by the enzyme ornithine transcarbamoylase (OTC) . The reaction is given as follows:

Carbamoyl phosphate + ornithine → citrulline + Pi

Citrulline thus formed is released into the cytosol for usage in the rest of the steps of the cycle.

- The third step is catalyzed by an enzyme called argininosuccinate synthetase, which uses citrulline and ATP to form a citrullyl-AMP intermediate, which reacts with an amino group from aspartate to produce argininosuccinate. This reaction can be given as follows:

Citrulline + ATP + aspartate → argininosuccinate + AMP + PPi

- The fourth step involves the cleavage of argininosuccinate to form fumarate and arginine. Argininosuccinate lyase is the enzyme catalyzing this reaction, which can be represented as follows:

Argininosuccinate → arginine + fumarate

- In the fifth and last step of the urea cycle, arginine is hydrolyzed to form urea and ornithine. This is catalyzed by arginase and can be given as follows:

Arginine → urea + ornithine

The overall reaction can be given as follows:

2NH3 + CO2 + 3ATP = urea + 2ADP + AMP + PPi + 2Pi

Energetics of urea cycle

On considering only, the urea cycle, and not considering the other biopathways linked, to produce one urea molecule, 4 ATP molecules are used up as shown below:

NH_4^+ ions to carbamoyl phosphate- utilization of 2ATP. Citrulline to arginosuccintae- breakdown of 1 ATP to AMP + PPi which is equivalent to 2 Pi

Therefore, the entire energetic reaction can be summarised as follows:

$2NH_4^+ + HCO_3^- + H_2O + 3ATP + Aspartate \rightarrow Urea + 2ADP + 4Pi + AMP + 2H^+ +$ Fumarate

Rate limiting steps of urea cycle

The conversion of ammonium ions to carbamoyl phosphate catalyzed by carbamoyl synthetase I is the rate limiting step. This enzyme (carbamoyl synthetase I) is activated by N-acetylglutamate (NAG) which is formed by a reaction between acetyl CoA and glutamate catalyzed by the enzyme N-acetylglutamate synthase (activated by arginine). Thus, concentrations of glutamate and acetyl CoA as well as levels of arginine determine the steady state levels of N-acetylglutamate (NAG) which in turn regulates the concentration of urea. When a high protein diet is consumed, levels of NAG increases and in turn urea levels increase. Also during starvation, when muscle proteins start breaking down to source out energy, urea levels increase in response. The rest of all enzymes participating in the urea cycle are mostly regulated by the concentrations of their respective substrates.

Diagnosis of urea cycle defects

A blood aminogram is routinely used in the diagnosis of urea cycle disorders. The concentration of the nitrogen-carrying amino acids, glutamine and asparagine, in plasma is elevated in cases of ornithine transcarbamylase deficiency (OTC). In babies, elevated levels of orotic acid in the urine may be an indicator of OTC deficiency. Increased levels of blood citrulline and argininosuccinate are also seen in cases of citrullinemia.

In older children, these disorders may present in the form of growth failure, psychomotor retardation and behavioral abnormalities. Hence, blood ammonia and urinary orotic acid monitoring and quantitation are crucial in patients with unexplained neurological symptoms.