

Urea Cycle

BIOCHEMISTRY

- Urea is the major disposal form of amino groups derived from amino acids, and accounts for about 90% of the nitrogen-containing components of urine. One nitrogen of the urea molecule is supplied by free NH_3 , and the other nitrogen by aspartate.

- [Note: Glutamate is the immediate precursor of both ammonia (through oxidative deamination by glutamate dehydrogenase) and aspartate nitrogen (through transamination of oxaloacetate by AST).]

- The carbon and oxygen of urea are derived from CO_2 . Urea is produced by the liver, and then is transported in the blood to the kidneys for excretion in the urine.

Reactions of the cycle

- The first two reactions leading to the synthesis of urea occur in the mitochondria, whereas the remaining cycle enzymes are located in the cytosol

- Formation of carbamoyl phosphate:
Formation of carbamoyl phosphate by carbamoyl phosphate synthetase I is driven by cleavage of two molecules of ATP.

- Ammonia incorporated into carbamoyl phosphate is provided primarily by the oxidative deamination of glutamate by mitochondrial glutamate dehydrogenase

- Carbamoyl phosphate synthetase I requires N-acetylglutamate as a positive allosteric activator

Formation of citrulline

- Ornithine and citrulline are basic amino acids that participate in the urea cycle.
- (They are not incorporated into cellular proteins, because there are no codons for these amino acids)
- Ornithine is regenerated with each turn of the urea cycle, much in the same way that oxaloacetate is regenerated by the reactions of the citric acid cycle

Synthesis of argininosuccinate

- Citrulline condenses with aspartate to form argininosuccinate. The α -amino group of aspartate provides the second nitrogen that is ultimately incorporated into urea.
- ATP to adenosine monophosphate (AMP) and pyrophosphate. This is the third and final molecule of ATP consumed in the formation of urea

Cleavage of argininosuccinate

- Argininosuccinate is cleaved to yield arginine and fumarate. The arginine formed by this reaction serves as the immediate precursor of urea.

- Fumarate produced in the urea cycle is hydrated to malate, providing a link with several metabolic pathways.

- For example, the malate can be transported into the mitochondria via the malate shuttle and reenter the tricarboxylic acid cycle. Alternatively, cytosolic malate can be oxidized to oxaloacetate, which can be converted to aspartate

Cleavage of arginine to ornithine and urea

- Arginase cleaves arginine to ornithine and urea, and occurs almost exclusively in the liver.

Fate of urea:

- Urea diffuses from the liver, and is transported in the blood to the kidneys, where it is filtered and excreted in the urine. A portion of the urea diffuses from the blood into the intestine, and is cleaved to CO_2 and NH_3 by bacterial urease.

- This ammonia is partly lost in the feces, and is partly reabsorbed into the blood. In patients with kidney failure, plasma urea levels are elevated, promoting a greater transfer of urea from blood into the gut.

- The intestinal action of urease on this urea becomes a clinically important source of ammonia, contributing to the hyperammonemia often seen in these patients. Oral administration of neomycin¹ reduces the number of intestinal bacteria responsible for this NH_3 production.

- Four high-energy phosphates are consumed in the synthesis of each molecule of urea:
- two ATP are needed to restore two ADP to two ATP, plus two to restore AMP to ATP.
Therefore, the synthesis of urea is irreversible, with a large, negative ΔG

Regulation of the urea cycle

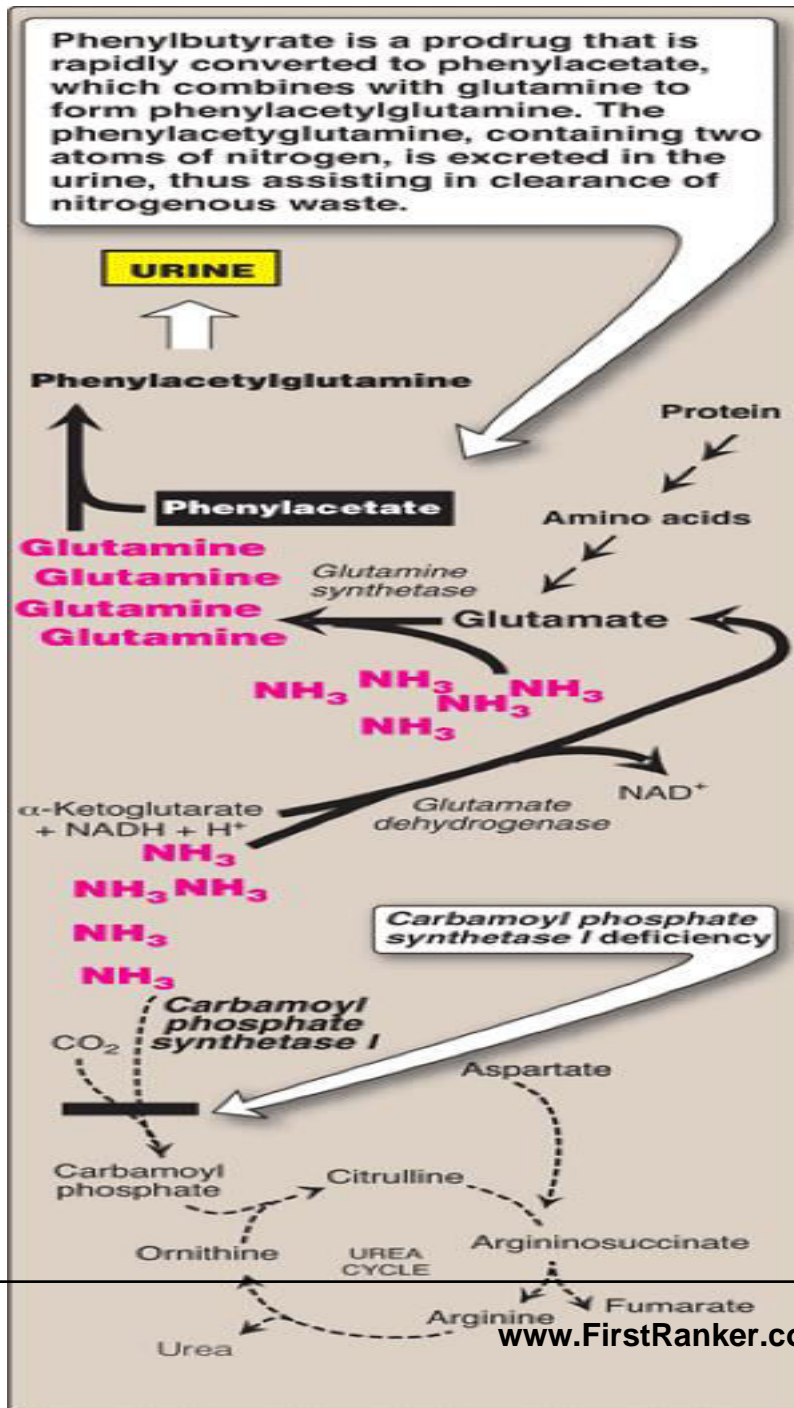
- N-Acetylglutamate is an essential activator for carbamoyl phosphate synthetase I—the rate-limiting step in the urea cycle
- N-Acetylglutamate is synthesized from acetyl coenzyme A and glutamate by N-acetylglutamate synthase in a reaction for which arginine is an activator.

- Therefore, the intrahepatic concentration of N-acetylglutamate increases after ingestion of a protein-rich meal, which provides both the substrate (glutamate) and the regulator of N-acetylglutamate synthesis. This leads to an increased rate of urea synthesis.

Metabolism of Ammonia

- **Transport of ammonia** to liver(glucose-alanine cycle)
- **Sources of ammonia:**
 1. Liver(Transdeamination)
 2. Renal/Intestinal (glutaminase)
 3. Bacterial urease
 4. Amines (hormones/neurotransmitters)
 5. Purines/Pyrimidines
- **Transport of ammonia in circulation**
(urea)(glutamine)

- **Hyperammonia** (5-50umol/L)
 1. Acquired (liver diseases + symptoms)
 2. Hereditary (enzyme deficiencies)



Ammonia Intoxication Is Life-Threatening

- The ammonia produced by enteric bacteria and absorbed into portal venous blood and the ammonia produced by tissues are rapidly removed from circulation by the liver and converted to urea.
- Only traces (10–20 μ g/dL) thus normally are present in peripheral blood.
- This is essential, since ammonia is toxic to the central nervous system.

- Ammonia may be toxic to the brain in part because it reacts with α -ketoglutarate to form glutamate.
- The resulting depleted levels of α -ketoglutarate then impair function of the tricarboxylic acid (TCA) cycle in neurons

- All defects in urea synthesis result in ammonia intoxication. Intoxication is more severe when the metabolic block occurs at reactions 1 or 2

- Clinical symptoms common to all urea cycle disorders include vomiting, avoidance of high-protein foods, intermittent ataxia, irritability, lethargy, and mental retardation.

- Significant improvement and minimization of brain damage accompany a low-protein diet ingested as frequent small meals to avoid sudden increases in blood ammonia levels.

- **Hyperammonemia Type 1.** A consequence of carbamoyl phosphate synthase I deficiency
- **Hyperammonemia Type 2.** A deficiency of ornithine transcarbamoylase

- **Citrullinemia** --argininosuccinate synthase
- **Argininosuccinicaciduria** –argininosuccinase
- **Hyperargininemia** --- arginase

- **Gene Therapy Offers Promise for Correcting Defects in Urea Biosynthesis**