

Urea Formation (Krebs-Henseleit cycle)

Ammonia is highly toxic to the central nervous system. It is converted to urea, which is much less toxic, water soluble and easily excreted in urine. The liver is the site of Urea biosynthesis. Urea biosynthesis occurs by urea cycle (Krebs Henseleit cycle) in five steps. The first 2 steps occur in mitochondria, while the last 3 steps occur in cytoplasm. It is catalyzed by five enzymes. Any defect in one of these enzymes leads to ammonia intoxication. The two nitrogen atoms of urea are derived from two different sources, one from ammonia and the other directly from the alpha amino group of aspartic acid.

Note

Other Organs

- **Kidneys:** Urea cycle operates in a limited extent. Kidney can form up to arginine but cannot form urea,

as enzyme arginase is absent in kidney tissues.

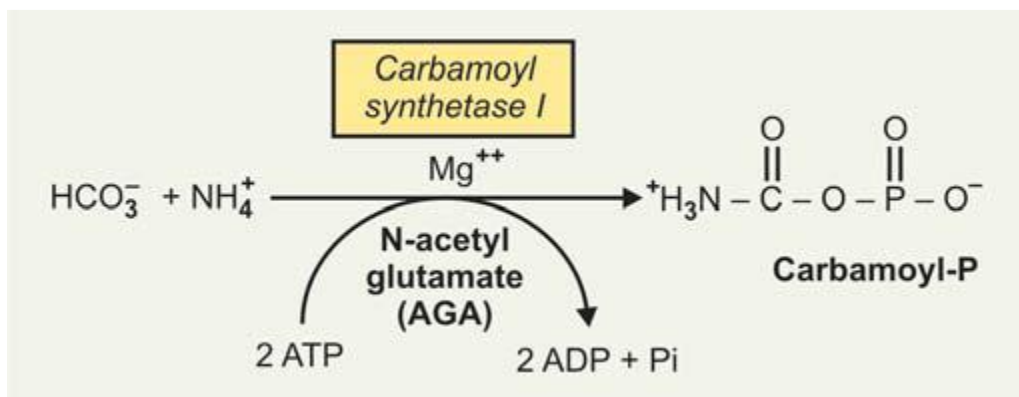
- **Brain:** Brain can synthesis urea from citrulline, but lacks the enzyme for forming citrulline from ornithine.

Thus, neither the kidneys nor the brain can form urea in significant amounts.

Steps of urea biosynthesis

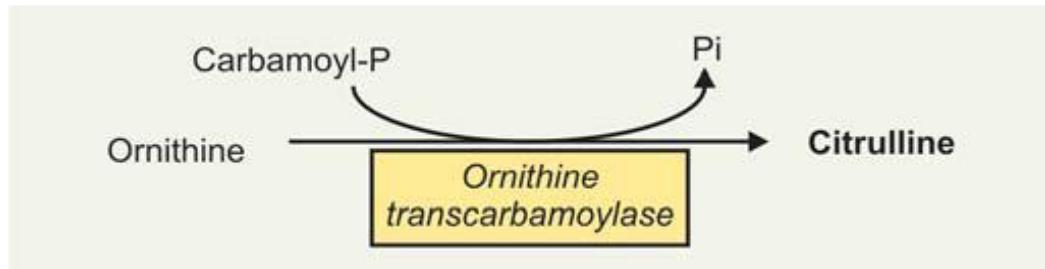
1- Biosynthesis of carbamoyl phosphate

One molecule of ammonia condenses with CO₂ in the presence of **two molecules of ATP** to form carbamoyl phosphate. The reaction is catalyzed by the mitochondrial enzyme **carbamoyl phosphate synthetase-I**



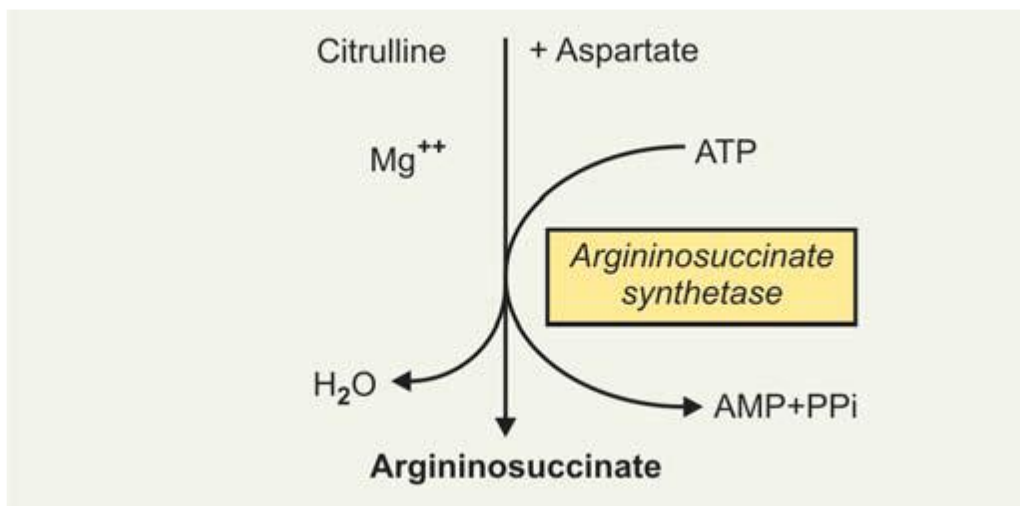
2- Formation of citrulline

The second reaction is also **mitochondrial**. The carbamoyl group is transferred to the NH₂ group of ornithine by **ornithine transcarbamoylase**.



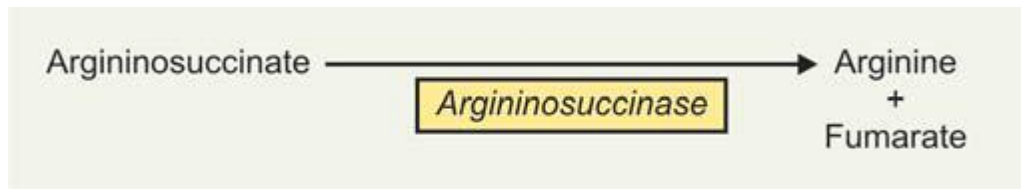
3-Formation of argininosuccinate

One molecule of aspartic acid adds to citrulline forming a carbon to nitrogen bond, which provides the 2nd nitrogen atom of urea. **Argininosuccinate synthetase** catalyzes the reaction. This needs hydrolysis of ATP to AMP level, so **two high energy phosphate bonds** are utilized. The PPi is an inhibitor of this step.



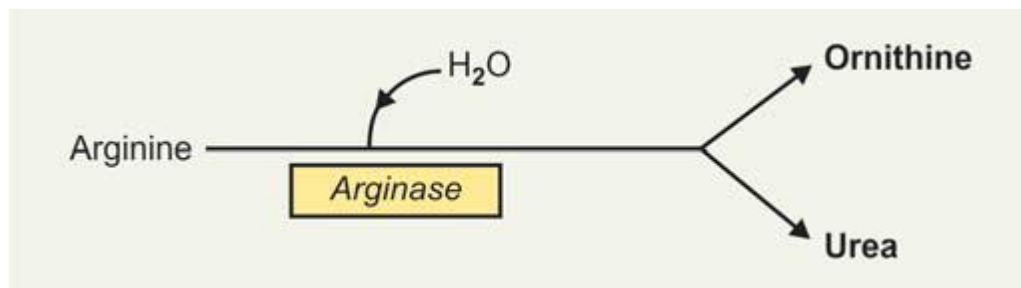
4-Cleavage of argininosuccinate

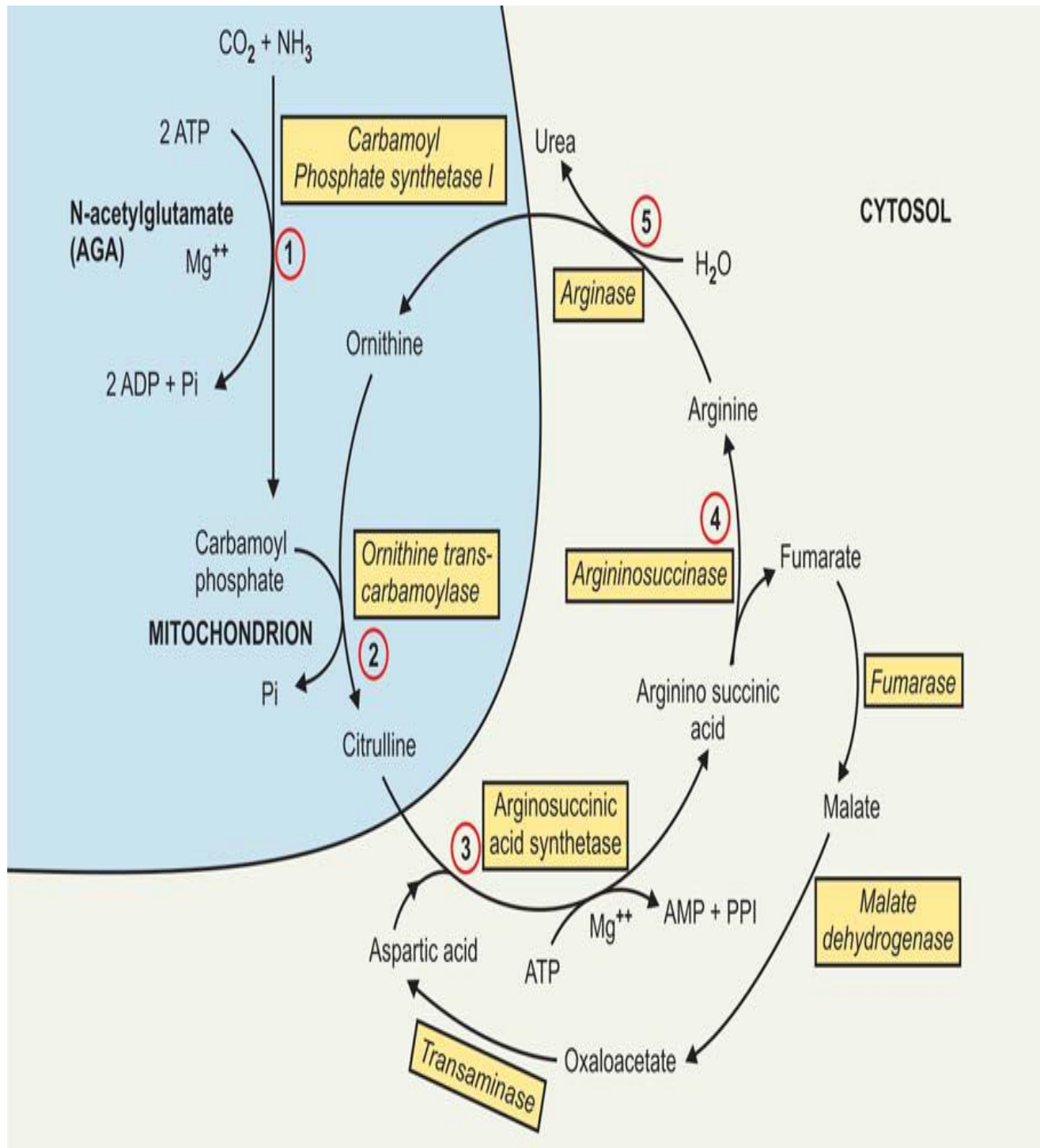
Argininosuccinate is cleaved by **argininosuccinate lyase** (argininosuccinase) to arginine and fumarate. Fumarate produced is used to regenerate aspartic acid again.



5- Cleavage of arginine

The final reaction of the cycle is the hydrolysis of arginine to urea and ornithine by arginase.

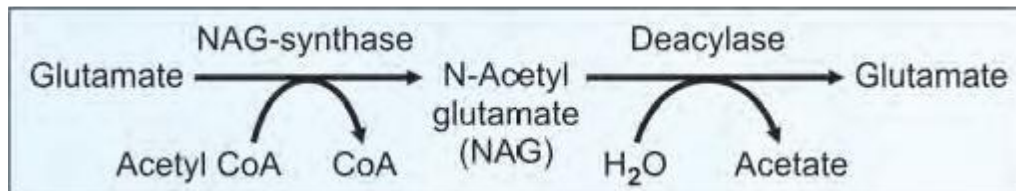




Biosynthesis of urea or ornithine—urea cycle

Regulation of urea cycle

The major regulatory step is catalyzed by CPS-I where the positive effector is **N-acetyl glutamate (NAG)**. It is formed from glutamate and acetyl CoA. Arginine is an activator of NAG synthase.



Disorders of Urea Cycle

Deficiency of any of the urea cycle enzymes would result in **hyperammonemia**. When the block is in one of the earlier steps, the condition is more severe, since ammonia itself accumulates. Deficiencies of later enzymes result in the accumulation of other intermediates, which are less toxic and hence symptoms are less. As a general description, disorders of urea cycle is characterized by hyperammonemia, encephalopathy and respiratory alkalosis. Clinical symptoms include vomiting, irritability, lethargy and severe mental retardation. Infants appear normal at birth, but within days progressive lethargy.

Clinical significance of urea:

1-Normal level: the normal concentration of blood plasma in healthy adult ranges from 20-40 mg/dl

2- Increase levels Increases in blood urea may occur in a number of diseases in addition to those in which the kidneys are primarily involved. The causes can be classified as:

- Prerenal,
- Renal, and
- Postrenal

(a) Prerenal

most important are conditions in which plasma vol / body-fluid are reduced:

- Salt and water depletion,
- Severe and protracted vomiting as in pyloric and intestinal obstruction,
- Severe and prolonged diarrhea,
- Pyloric stenosis with severe vomiting,
- Haematemesis,
- Haemorrhage and shock; shock due to severe burns,
- Ulcerative colitis with severe chloride loss,
- In crisis of Addison's disease (hypoadrenalism).

(b) Renal

The **blood urea** can be **increased in all forms of kidney diseases** like:

- In acute glomerulonephritis.
- In early stages of type II nephritis (nephrosis) the blood urea may not be increased, but in later stages with renal failure, blood urea rises.
- Other conditions are malignant nephrosclerosis, chronic pyelonephritis and mercurial poisoning.
- In diseases such as hydronephrosis, renal tuberculosis; small increases are seen but depends on extent of kidney damage.

(c) Postrenal Diseases

These lead to increase in blood urea, when there is obstruction to urine flow. This causes retention of urine and so reduces the effective filtration pressure at the glomeruli; when prolonged, produces irreversible kidney damage.

Causes:

- Enlargement of prostate,
- Stones in urinary tract,
- Stricture of the urethra,

- Tumours of the bladder affecting urinary flow.

Note

Increase in blood urea above normal is called ***uraemia***.

3- Decreased levels: are rare, but may be seen in:

- Some cases of severe liver damage.
- Physiological condition: blood urea is lower in pregnancy than in normal non pregnant women.

GLUCOSE-ALANINE CYCLE

1. Skeletal muscle transports NH_3 to the Liver in the form of the amino acid 'alanine'. The alanine is formed in the muscle tissue by a transamination reaction between pyruvate (PA) and glutamate.
2. The alanine is transported through the bloodstream to the liver, where it reacts with α -ketoglutarate to reform Pyruvate and glutamate. This reaction is catalyzed by *alanine transaminase*.
3. The nitrogen originating from the glutamate is processed by the urea cycle.
4. When the blood glucose is low, the Pyruvate resulting from alanine transamination is used to make glucose via the gluconeogenesis pathway.
5. The glucose can be returned to the skeletal muscle to supply quick energy.

Thus, the transport of alanine from muscle to Liver results in a reciprocal transfer of glucose to muscle. The entire cyclical process is referred to as the "glucosealanine cycle".

Its importance is proportional to the muscular activity of the organism. It is to be noted that active muscle tissue operates anaerobically, producing large quantities of Pyruvate (PA) and consuming large quantities of glucose.

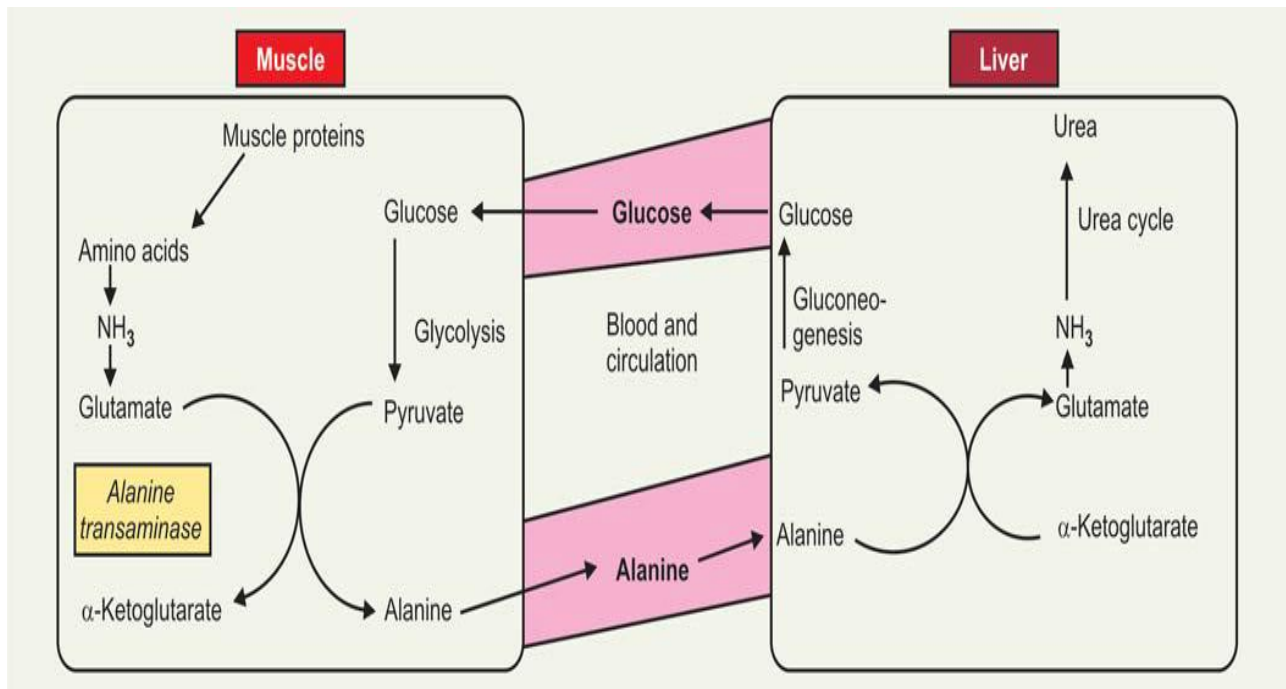


Fig.: Glucose-alanine cycle