

Urea cycle: Urea cycle is discovered by Krebs and Hanseleit (1932).

Urea cycle is the removal excess of NH₂ derived from amino acids catabolism in the tissues and excreted in urine.

Site of synthesis: urea formation, take place in liver in mammals and the enzymes isolated from liver tissues.

Urea cycle is incomplete in kidney and brain, why?

Because absence of enzyme arginase in kidney.

- Sources of ammonia:**
1. NH₂----- from oxidative deamination.
 2. NH₂ ----- from aspartate.

Significance of urea cycle:

1. detoxification of ammonia : toxic ammonia is converted into a nontoxic substance called urea excreted in urine.
2. biosynthesis of arginine: used for synthesis of protein.

Overall stoichiometry of the urea cycle:

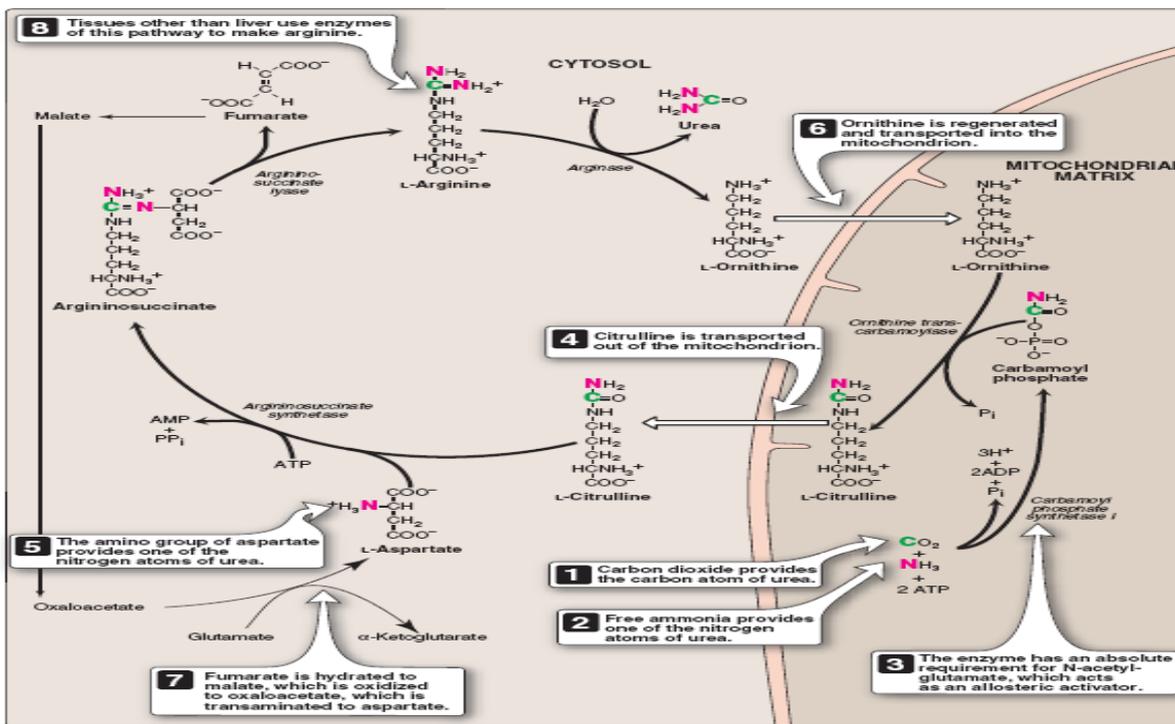
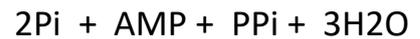


Figure 19.14 Reactions of the urea cycle.

Kidney Functions:

Kidney functions are measure of 1. glomerular filtration rate 2. study tubular function.

Kidney functions test are:

1. blood urea.
2. serum creatinine
3. creatinine clearance.

1. Blood Urea

Urea is the end product of protein metabolism. It consist of 2NH_3 and CO_2 .



Normal blood urea in healthy fasting adult = 15- 40 mg/dl

Uremia: increase in blood urea above normal value .

Increase in blood urea occur in:

severe burns , hemorrhage , obstruction to urine flow, acute glomerulonephritis , renal tuberculosis.

Decrease in blood urea:

Severe liver damage , in pregnancy (physiological condition).

Fate of urea : Urea diffuses from liver transport to the blood then to the kidney (filtered and excreted in urine).

A portion of urea diffuse from blood to the intestine also.

Ammonia(NH_3):

Normal blood level = 40-70 microgram/ dl

Transportation of ammonia:

1. The final deamination and production of ammonia is taking place in liver.
2. **Glutamic acid** the major transport of ammonia from the tissues to the liver.
3. The concentration of **glutamic acid** in the blood **is 10 times more** than other amino acids.
4. **glutamine and asparagine** are the transport forms of ammonia in brain.

(They are the first line of defense against ammonia toxicity).

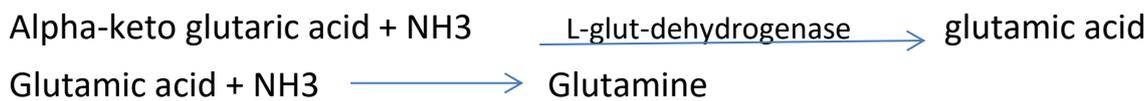
Hyperammonaemia: increase level of ammonia in the blood more than normal value.

Ammonia increase in :

1. hepatic disease (liver cirrhosis) cause severe reducing in urea synthesis.
2. genetic defects in urea cycle enzymes cause decrease in urea level and increase in NH_3 concentration.

Why ammonia is toxic?

1. it raise intracellular PH.
2. in mitochondria excess of NH_3 will favor the reverse reaction of L- glutamate dehydrogenase .



In brain the toxicity is due to:

low level of alpha keto glutarate cause depletion in CAC cause inhibition in respiration of brain Fatal (high level of NH₃ in tissues and blood).

NH₃ is removed from the body by several methods:

- 1. Amination of keto acid.
- 2. Amidation of glutamic acid to form glutamine.
- 3. formation of urea cycle.

Toxicity affect CNS(central nervous system) cause:

- 1. weakness 2. unsteadiness 3. tremors 4. Seizures 5. decerabrate rigidity
 7. coma 8. death**

2. serum creatine and creatinine:

Creatine: is normal constituent of the body, consist of amino acids glycine , arginine and methionine.

Creatine present: 1- 2 % in liver , blood , brain.

98% is present in muscle, as free and phosphorylated.

(phosphorylated creatine in muscle equal to 80%.

In whole blood : normal creatine level varies from 2- 7 mg/ dl

In male : 0.2- 0.6 mg/dl

In female: 0.35- 0.9 mg/dl

Urinary excretion:

- In healthy people, creatine is excreted as creatinine form in urine.
- In male: 1.5- 2.0 mg in 24 hrs in urine.
- In female: 0.8- 1.5 mg in 24 hrs in urine.

Increase in urine in case of

- 1. muscular persons. 2. after severe exercise. 3. pregnancy 4. myopathese disease. 5. children: reason probably lack of ability to convert creatine to creatinine 6. in wasting disease, malignancies.**

3. Uric acid:

It is the chief end product of purine metabolism.

The ingestion of food high in nucleoproteins such as glandular organs produces a marked increase in urinary uric acid and red meat .

Diets like milk , eggs , cheese, low purine contents, cause no increase in urinary uric acid.

Uric acid present in body water. In normal subjects about 1130 mg of uric acid is present.

Plasma contains higher concentration of uric acid compared to other compartment contain water.

Normal range of uric acid: in male: 3- 7 mg/dl

• in female: 2- 6 mg/dl

- Normally 500- 600 mg of uric acid is synthesized. Some is excreted in urine ,some is excreted in bile and some is converted to ammonia and urea by the intestinal bacteria.

Clinical disorder:

Gout: Gout is chronic disorder characterized by excess of uric acid in blood (hyperuricemia).

This occur due to deposition of **sodium monourate** in **tophi structure**.

Recurring attacks of acute arthritis; These are due to deposition of **monosodiumurate** in and around the affected joints