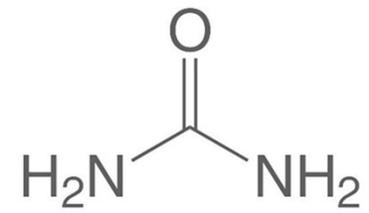


UREA CYCLE



What is urea cycle??

Subhadipa 2020

- **Deamination of amino acids** produce large amounts of NH_3 which is toxic for a animal body.
- The urea cycle mediates the **removal of ammonia as urea** in the amount of 10 to 20 g per day in the healthy adult.
- When this process is not working efficiently, toxic ammonia (NH_3) **accumulates within the body** and may elicit clinical manifestations such as **lethargy, slurred speech, cerebral edema, and asterixis**.
- **Teleost** are **ammonotelic** and directly **excrete NH_3 through the gills**.
- **Reptiles and birds** convert ammonia into uric acid for excretion through kidneys and they are **uricotelic**.
- **Mammals amphibians and elasmobranch** fishes **convert NH_3 into urea** for renal excretion and they are called **ureotelic**.
- Urea is formed **mainly in liver** and very small extent in kidneys and brain.
- This **energy-dependent process** occurs only within the **liver's mitochondria and cytoplasm**.

Also known as **arginine urea pathway** or **Krebs-Hanseleit ornithine cycle**.

Symptoms of **Hyperammonemia**

General

- Growth retardation
- Hypothermia

Muscular/Neurologic

- Poor coordination
- Dysdiadochokinesia
- Hypotonia or hypertonia
- Ataxia
- Tremor
- Seizures
- Decorticate or decerebrate posturing

Central

- Combativeness
- Lethargy
- Coma

Eyes

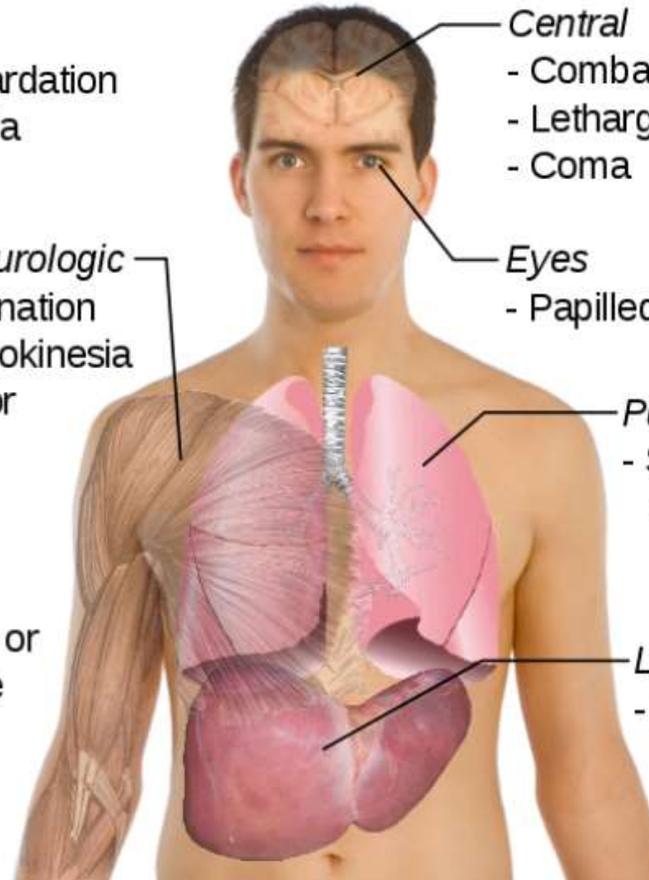
- Papilledema

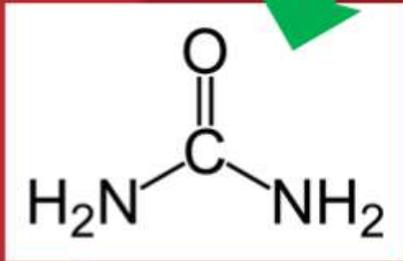
Pulmonary

- Shortness of breath

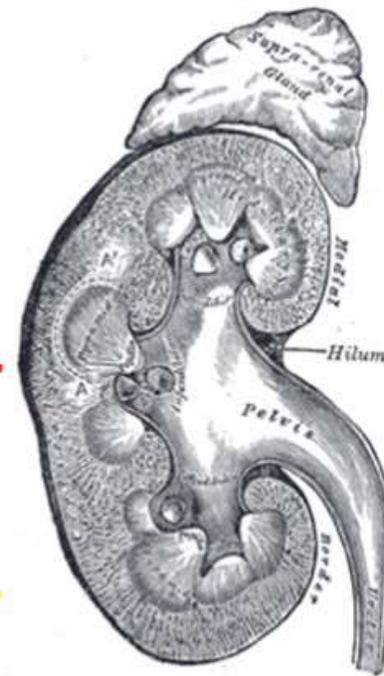
Liver

- Enlargement





Urea



Kidney

The net reaction



Summary of the Steps in the Urea Cycle

Subhadipa 2020

The mitochondrial stage

Carbamoyl phosphate is formed from ammonia and bicarbonate, by CPS.

OTC condenses carbamoyl phosphate and ornithine to form citrulline.

Citrulline is then transported to the cytosol by SLC25A15.

The cytosolic stage

AS condenses citrulline and aspartate to form argininosuccinate.

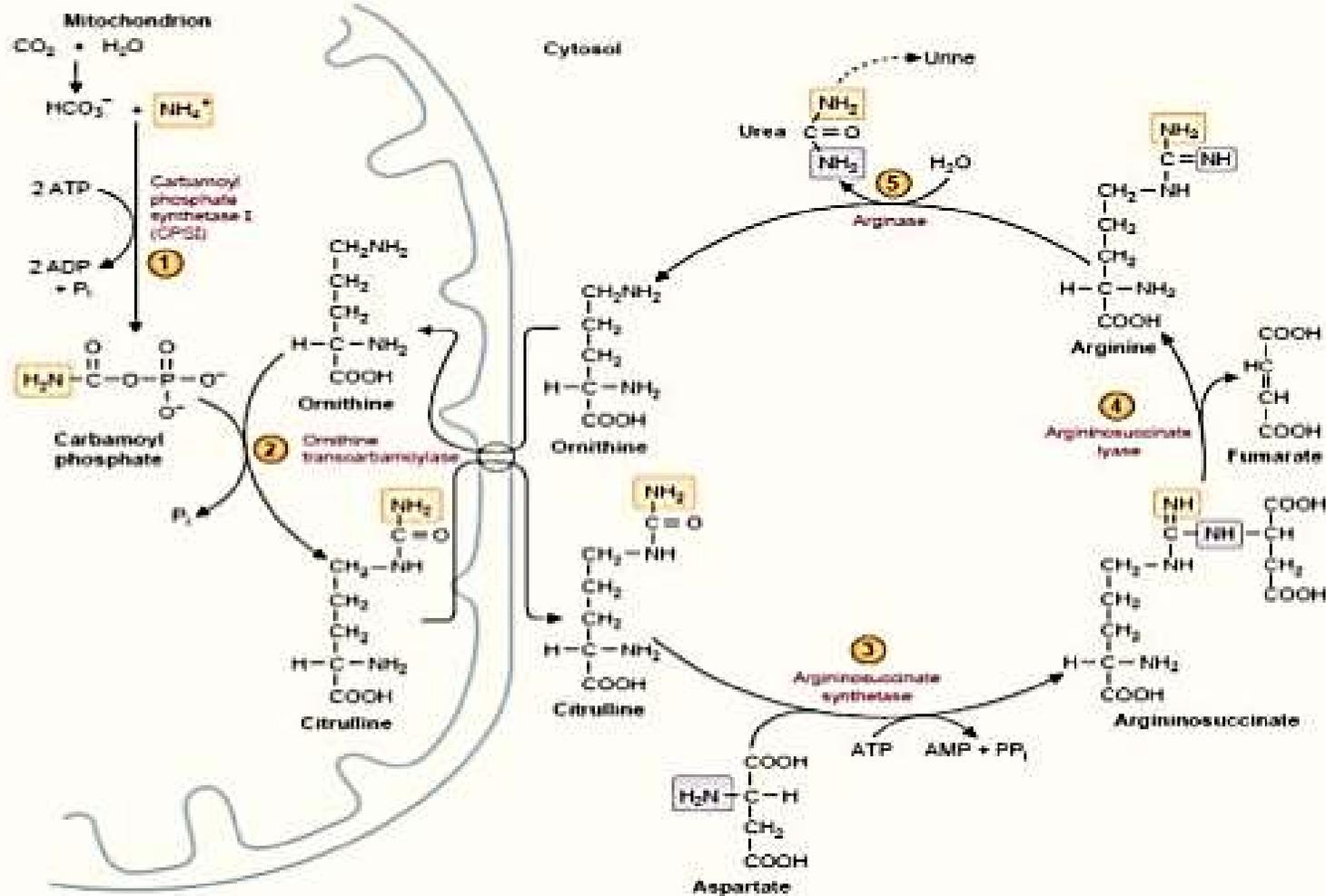
Argininosuccinate is broken down into arginine and fumarate by AL.

Arginine is broken down into urea and ornithine by arginase.

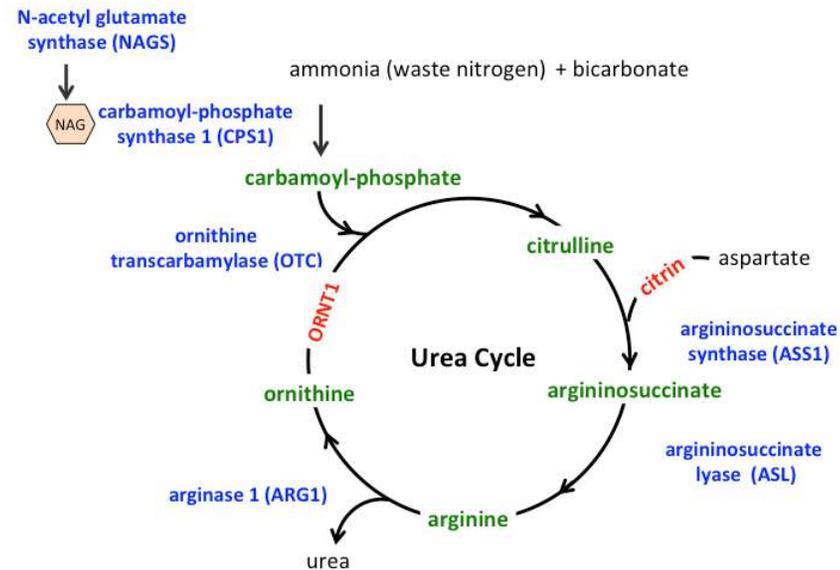
Ornithine translocase transports ornithine into the mitochondria.

Pathway of Urea Cycle

Subhadipa 2020



The Mitochondrial Stage



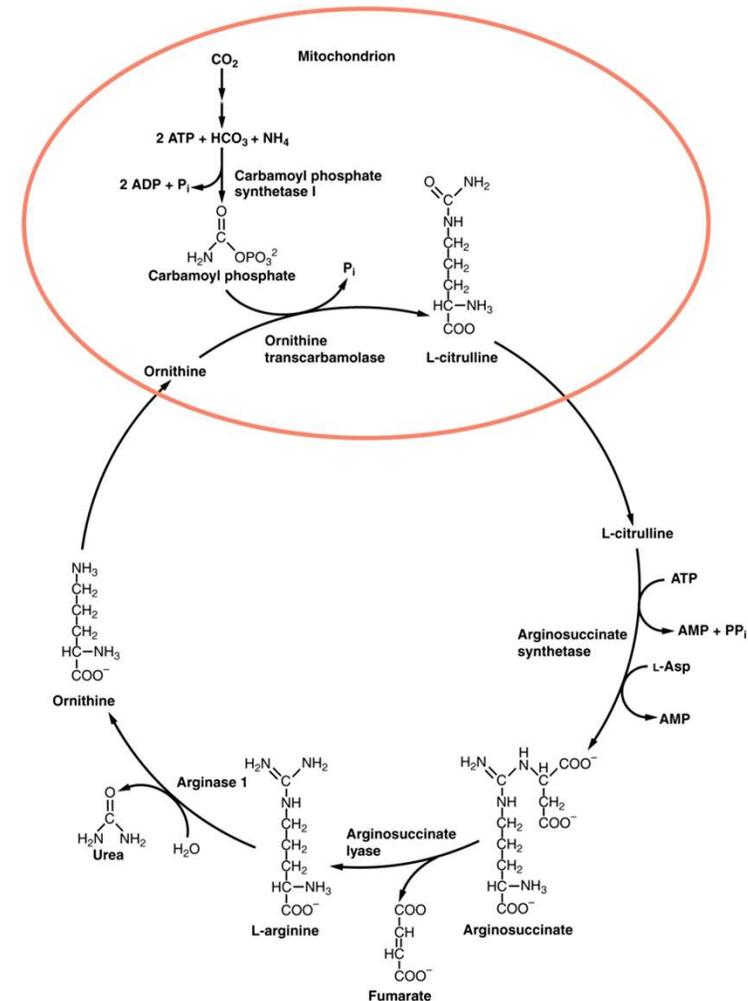
First, the enzyme **carbamoyl phosphate synthetase (CPS)** takes ammonia and bicarbonate, and forms carbamoyl phosphate with the **use of ATP**. This is the step in the cycle which determines how fast the cycle progresses. **N-acetylglucosamine is also required for CPS to function, and functions as a regulator for the formation of urea.**

Ornithine transcarbamoylase (OTC) then condenses carbamoyl phosphate and ornithine, which forms citrulline.

This **citrulline** is then moved out of the mitochondria into the cytosol of the cell by the transporter **SLC25A15**.

The Cytosolic Stage

- **Argininosuccinate synthetase (AS)** takes the **citrulline formed in the mitochondrial stage**, and condenses it with aspartate to form argininosuccinate. This occurs by the formation of an intermediate, citrulline-AMP.
- Argininosuccinate is then **broken into arginine and fumarate by argininosuccinate lyase (AL)**. Fumarate is then incorporated into another metabolic cycle, the TCA cycle. The TCA cycle can then reform aspartate, which is used by AS.
- **Arginine is then further broken down into urea and ornithine by arginase**. Arginine can also be acquired from the diet, and this can also be taken in by the liver cells and broken down into urea and ornithine by arginase.
- **The ornithine is then transported into the mitochondria by ornithine translocase**. There, it is used by **OTC** again, to form citrulline. The citrulline is then processed to form urea and ornithine again, and the cycle continues. During the cycle, urea is the only new product which is formed, while all other molecules used in the cycle are recycled.



Significance

- The toxic ammonia is converted into nontoxic urea. It disposes off two waste products, ammonia and CO₂.
- It forms semi essential amino acid, arginine. It participates in the regulation of blood pH, which is depends upon the ratio of dissolved CO₂, e.g H₂CO₃ to HCO₃.
- Ornithine is a precursor for the formation of polyamines like, spermidine and spermin .

Regulation

- Carbamoyl phosphate synthetase-I is an allosteric regulatory enzyme of urea cycle, which is activated by N-acetylglutamate (NAG). NAG is synthesized from acetyl-CoA and glutamate by NAG-synthase to activate CPS-I.