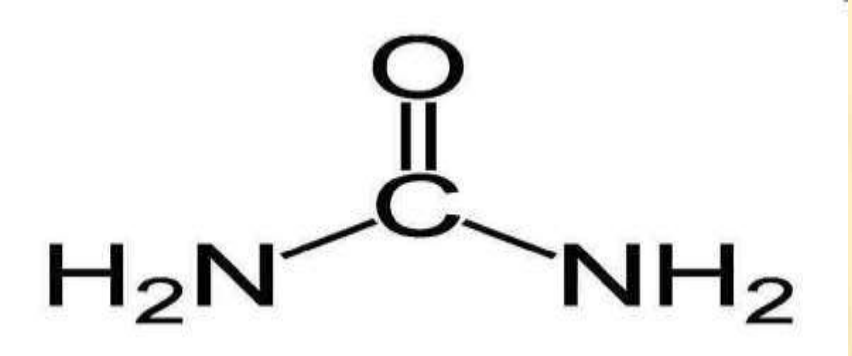


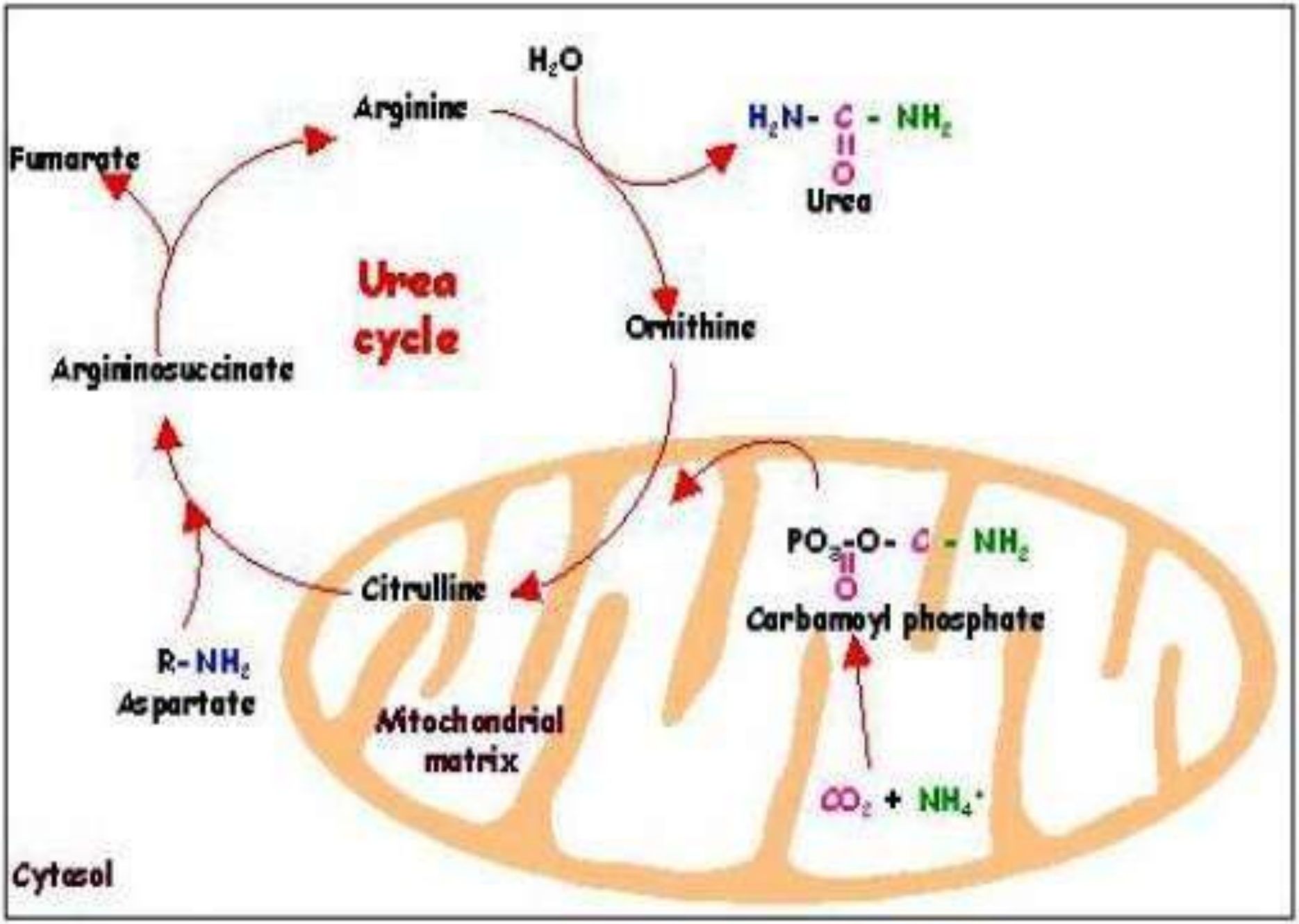
UREA CYCLE

BIOSYNTHESIS OF UREA

- Urea is the major end product in Nitrogen metabolism in humans and mammals.
- NH_3, the product of oxidative deamination reaction, is toxic in even small amount and must be removed from the body.
- Urea cycle a.k.a Ornithine cycle is the conversion reactions of NH_3 into urea.

- This reaction occur in liver (certain occur in cytosol and mitochondria)
- The urea is transported to the kidney where it is excreted.
- The overall urea formation reaction is :-

$$2\,NH_3 + CO_2 + 3ATP \text{ ---> } urea + H_2O + 3\,ADP$$


H_2O
Arginine
$H_2N-C(=O)-NH_2$
Urea
Fumarate
Urea cycle
Ornithine
Argininosuccinate
$PO_3-O-C(=O)-NH_2$
Carbamoyl phosphate
Citrulline
$R-NH_2$
Aspartate
Mitochondrial matrix
$CO_2 + NH_4^+$
Cytosol

- One amine group comes from oxidative deamination of glutamic acid.
- While, the other amino group come from aspartic acid.-Aspartic acid is generated from fumaric acid produced by the urea cycle
- The fumaric acid first undergoes reactions through a portion of citric acid cycle (krebs cycle) to produce oxaloacetic acid which is then changed by transamination into aspartic acid.

STEPS IN UREA CYCLE

1. Synthesis of carbamoyl phosphate :

Carbamoyl phosphate synthase I (CPS I) of mitochondria catalyses the condensation of NH_4^+ ions with CO_2 to form carbamoyl phosphate. This step consumes 2 ATP and is **irreversible**, and **rate-limiting**. CPS I requires **N-acetylglutamate** for its activity. Another enzyme, carbamoyl phosphate synthase II (CPS II)- involved in pyrimidine synthesis-is present in cytosol. It accepts amino group from glutamine and does not require N-acetylglutamate for its activity.

STEPS IN UREA CYCLE

2. Formation of citrulline : Citrulline is synthesized from carbamoyl phosphate and ornithine by ornithine transcarbamoylase. Ornithine is regenerated and used in urea cycle. Therefore, its role is comparable to that of oxaloacetate in citric acid cycle. Ornithine and citrulline are basic amino acids. (They are never found in protein structure due to lack of codons). Citrulline produced in this reaction is transported to cytosol by a transporter system.

STEPS IN UREA CYCLE

3. Synthesis of arginosuccinate :

Arginosuccinate synthase condenses citrulline with aspartate to produce arginosuccinate. The second amino group of urea is incorporated in this reaction. This step requires ATP which is cleaved to AMP and pyrophosphate (PPi). The latter is immediately broken down to inorganic phosphate (Pi).

STEPS IN UREA CYCLE

4. Cleavage of arginosuccinate :

Arginosuccinase cleaves arginosuccinate to give arginine and fumarate. Arginine is the immediate precursor for urea. Fumarate liberated here provides a connecting link with TCA cycle, gluconeogenesis etc.

STEPS IN UREA CYCLE

5. Formation of urea : Arginase is the fifth and final enzyme that cleaves arginine to yield urea and ornithine. Ornithine, so regenerated, enters mitochondria for its reuse in the urea cycle. Arginase is activated by Co^{2+} and Mn^{2+} Ornithine and lysine compete with arginine (competitive inhibition). ***Arginase*** is mostly found in the liver, while the rest of the enzymes (four) of urea cycle are also present in other tissues. For this reason, Arginine synthesis may occur to varying degrees in many tissues. But only the liver can ultimately produce urea.