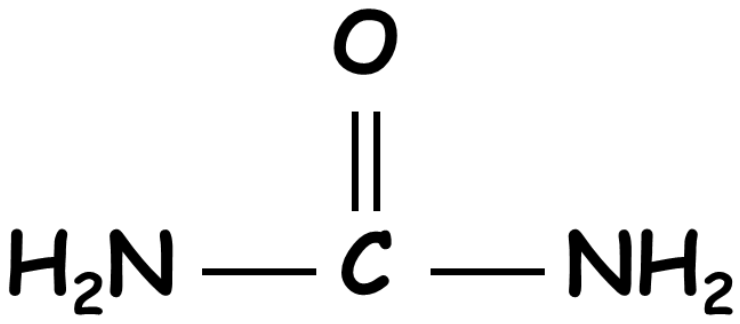
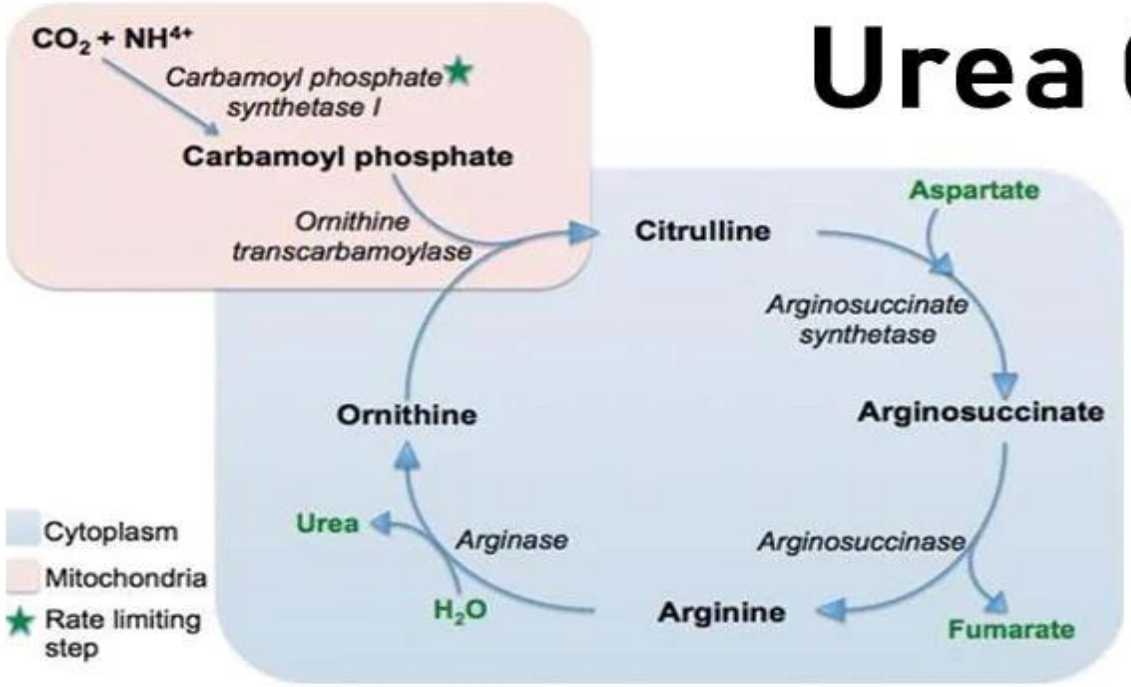


Urea Cycle



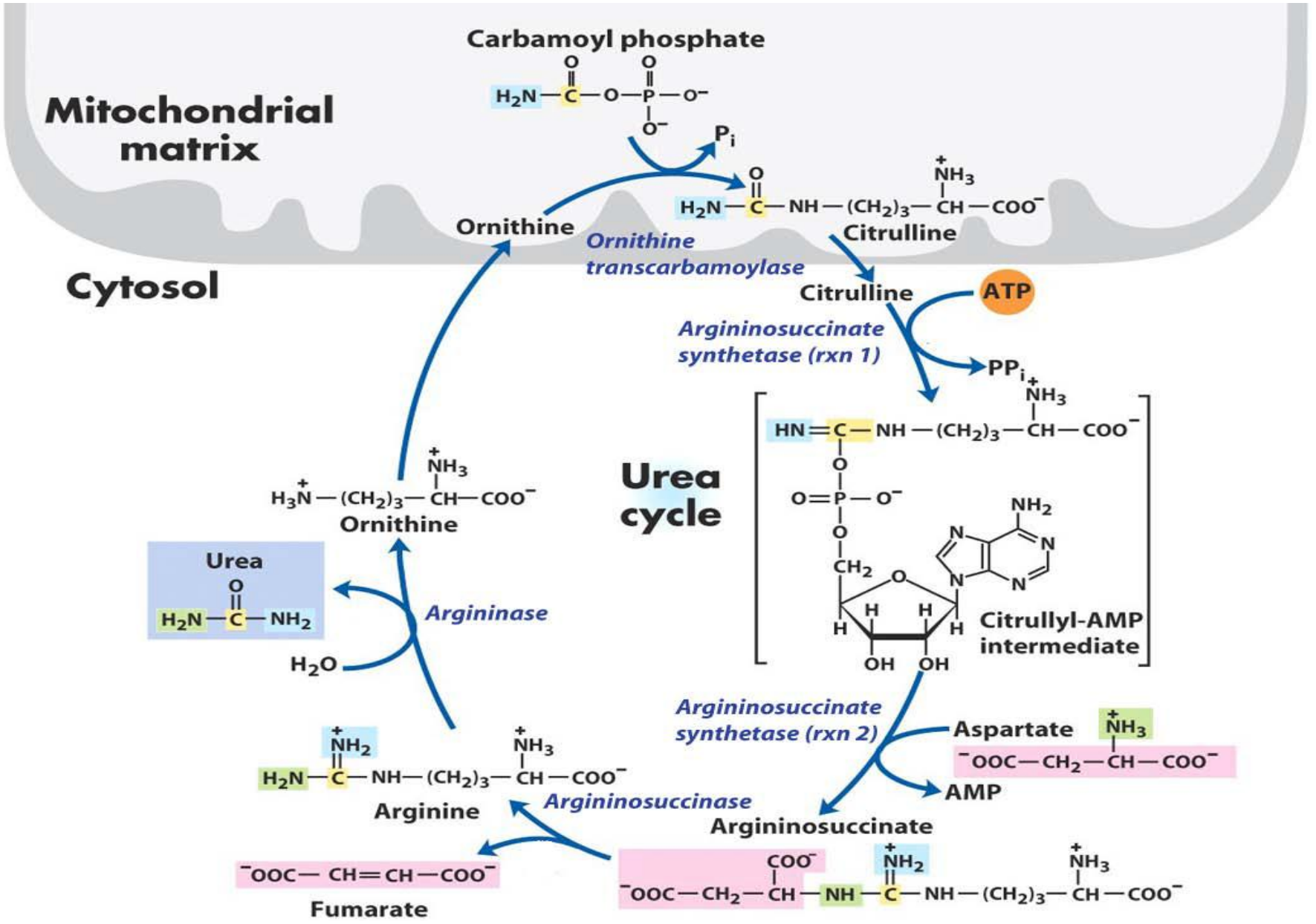
Enzymes & Steps

The urea cycle

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 ammonia, and the other nitrogen by aspartate. [Note: Glutamate is the immediate precursor of both ammonia (through oxidative deamination by glutamatedehydrogenase) and aspartate nitrogen (through transamination of oxaloacetate by AST). (Aspartate transaminase).

The carbon and oxygen of urea are derived from CO2. Urea is produced by the liver, and then is transported in the blood to the kidneys for excretion in the urine.
Most of our nitrogenous waste comes from the breakdown of amino acids. This occurs by deamination. Deamination of amino acids results in the production of ammonia (NH3) Ammonia is an extremely toxic base and its accumulation in the body would quickly be fatal.

However, the liver contains a system of carrier molecules and enzymes which quickly converts the ammonia (and carbon dioxide) into urea. One turn of the cycle:
- consumes 2 molecules of ammonia. - consumes 1 molecule of carbon dioxide
- creates 1 molecule of urea ((NH2)2CO


Mitochondrial matrix
Cytosol
Carbamoyl phosphate
Ornithine
Ornithine transcarbamoylase
Citrulline
Citrulline
ATP
Argininosuccinate synthetase (rxn 1)
PPi
Urea cycle
Citrullyl-AMP intermediate
Argininosuccinate synthetase (rxn 2)
Aspartate
AMP
Argininosuccinate
Argininosuccinase
Arginine
Fumarate
Argininase
Urea
H2O
Ornithine

The urea cycle is linked to the citric acid cycle

The synthesis of fumarate by the urea cycle is important because it links the urea cycle and citric acid cycle . Fumarate is hydrated to malate, which is in turn oxized to oxaloacetate.

Oxaloacetate has several possible fates:

1-Transamination to aspartate

2-Conversion into glucose by the gluconeogenic pathway

3-Condesation with acetyl CoA to form citrate 4- Conversion into pyruvate.

Fate of Urea

Urea diffuses from the liver, and is transported in the blood to the kidney , where it is filtered and excreted in the urine. A portion of urea diffuses from the into the intestine, and is cleaved to CO2 and NH3 by bacterial urease. This NH3 is partly lost in feces, and is partly reabsorbed into the blood.

In patient with kidney failure, the plasma urea levels are elevated promoting a greater transfer of urea from blood into gut. The intestinal action of urease on this urea becomes a clinically important source of NH3, contributing to the hyperammonemia often seen in these patients.

Overall stoichiometry of urea cycle :-

Aspartate + NH_3 + CO_2 + 3ATP → Urea + fumarate + 2ADP + AMP + 2PI + PPI + $3H_2O$

Significance of Urea cycle

- Detoxification of NH_3:- major biological role in the pathway is the detoxication of NH_3, toxic ammonia is converted into a nontoxic substance urea and excreted in urine.

-Biosynthesis of Arginine:- the urea cycle also serves for biosynthesis of arginine from ornithine in liver, kidney and intestinal mucosa. Kidney and intestinal mucosa probably contribute most of the body arginine because they possess all the urea cycle enzymes except arginase .

Hence they can form up to arginine and cannot form urea. The arginine is used for protein synthesis.

Regulation of Urea synthesis

Two major points of regulation:

1- concentration of urea cycle enzymes

2- CPS activity

- Achieved by linkage of mitochondrial glutamate dehydrogenase with carbamoyl-P-synthetase-I. Carbamoyl-P-synthetase –I is thought to act in conjunction with mitochondrial glutamate dehydrogenase to channelize nitrogen from glutamate and, therefore, from all amino acids as NH3 and then through carbamoyl-p and thus finally to urea.

-Though the equilibrium constant of the glutamate dehydrogenase reaction favors glutamate formation rather than formation of NH3, but removal of NH3 by carbamoyl-p-synthetase-I reaction and oxidation of α-ketoglutarate by TCA cycle favor the glutamate .

-The above effect is favored by the presence of ATP, which in addition to being a requirement for carbamoyl-p-synthetase-I reaction, it also stimulates glutamate dehydrogenase activity unidirectional in the direction of NH3 formation .

Clinical significance of urea

A moderately active man consuming about 300 gm of carbohydrates, 100 gm of fat and 100 gm of proteins daily must excrete about 16.5 gm of N daily . Almost 95% is eliminated by the kidneys and the remaining 5% for the most part as N, in the feces

1- Normal level :- The concentration of urea in normal blood plasma from a healthy fasting adult ranges from 20 to 40% mg.

2- Increased 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 *Postrenal

Medical Importance

Urea formation is impaired in several inherited diseases. They are due to deficiency of enzymes of urea cycle. The rate of incidence of urea cycle disorders is one in 2500. Most of these inherited diseases are due to defective genes and are fatal. Since the urea cycle converts ammonia to urea these disorders of urea cycle cause ammonia intoxication. Some common clinical symptoms seen in these diseases are vomiting, irritability, lethargy, seizures, mental retardation, coma and early death. They are

1. Hyper ammonemia Type I

It is due to deficiency of enzyme carbamoyl phosphate synthetase-I. Mental retardation is the main symptom of this condition.

2. Hyper ammonemia Type II

It is most common among others. It is due to deficiency of enzyme ornithine trans carbamoylase. So, in this condition carbamoyl phosphate accumulates and diverted to pyrimidine formation. This results in excretion of oroticacid and uracil in urine. Glutamate also accumulates in this condition.

3. Citrullinemia

This condition is due to the absence of enzyme argininosuccinate synthetase. Hence citrulline accumulates in blood and excreted in urine.

4. Argininosuccinicaciduria

Argininosuccinase is absent in this condition. So, argininosuccinate accumulates in blood and excreted in urine.

5. Hyper argininemia

This condition is due to low arginase activity. Hence, arginine accumulates and excreted in urine. However some urea may be excreted in urine due to kidney arginase.

6. N-acetyl glutamate synthetase deficiency

It is a rare disorder. N-acetyl glutamate synthetase is involved in formation of N-acetyl glutamate from acetyl-CoA and glutamate. Hyper ammonemia and aminoacid uria occurs in this condition. Since carbamoyl glutamate is an analog of acetyl glutamate administration of carbamoyl glutamate can lower symptoms.