Urea Cycle

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Formation of Urea

- Urea is the end product of protein metabolism. The nitrogen of amino acids removed in the form of ammonia is detoxified by converting it to urea.

- Formation of urea by “Kreb’s Henseleit urea cycle” is an ultimate route for the metabolic disposal of ammonia.

- Urea is produced exclusively by the liver and then is transported through blood to the kidneys for excretion in the urine.

• Urea is formed from ammonia, carbon dioxide and α-amino nitrogen of aspartate, which requires ATP.

• Enzymes catalyzing the urea cycle reactions are distributed between the mitochondria and the cytosol of the liver

The first two reactions of urea cycle occur in the mitochondria, whereas the remaining reactions occur in the cytosol.

UREA CYCLE

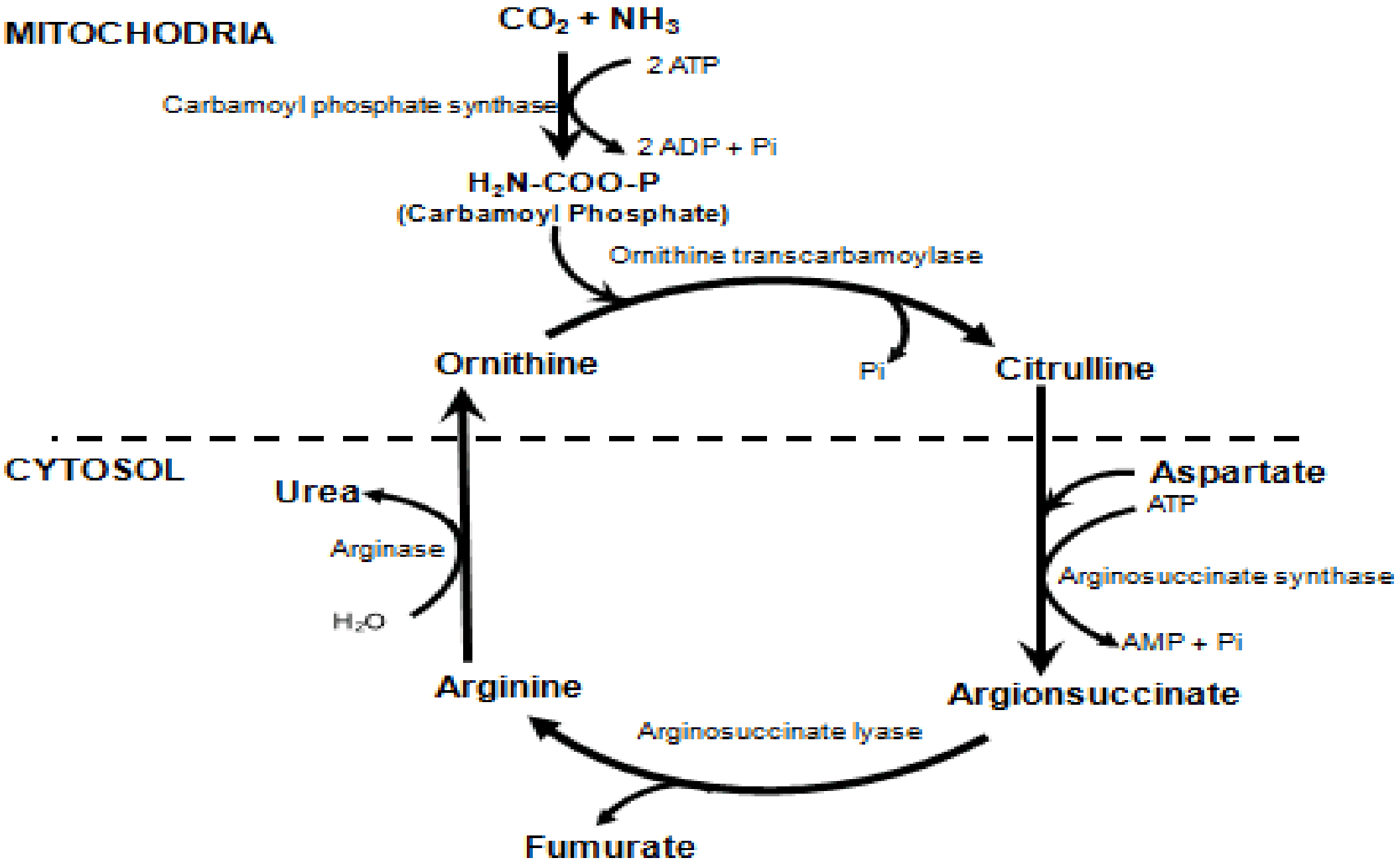
The sequence of reactions involved in the biosynthesis of urea, summarized in five steps as follows:

1 Formation of Carbamoyl Phosphate: The biosynthesis of urea begins with the condensation of carbon dioxide, ammonia and ATP to form carbamoyl phosphate, a reaction catalyzed by mitochondrial carbamoyl phosphate synthase-I (CPS-I).

- Formation of carbamoyl phosphate requires **2 molecules of ATP**. One ATP serves as a source of phosphate and second ATP is converted to ADP and Pi.

2 Formation of Citrulline: Carbamoyl phosphate donates its carbamoyl group to ornithine to form citrulline and release phosphate, in a reaction catalyzed by ornithine transcarbamoylase, a Mg^{2+} requiring mitochondrial enzyme.

- The citrulline so formed now leaves the mitochondria and passes into the cytosol of the liver cell.


MITOCHODRIA
$CO_2 + NH_3$
2 ATP
Carbamoyl phosphate synthase
2 ADP + Pi
H_2N-COO-P
(Carbamoyl Phosphate)
Ornithine transcarbamoylase
Ornithine
Pi
Citrulline
CYTOSOL
Urea
Arginase
H_2O
Aspartate
ATP
Arginosuccinate synthase
AMP + Pi
Arginine
Argionsuccinate
Arginosuccinate lyase
Fumurate

- **3 Formation of Arginosuccinate:** The transfer of the second amino group (from aspartate) to citrulline occurs by a condensation reaction between the amino group of aspartate and citrulline in the presence of ATP to form arginosuccinate.
- This needs hydrolysis of ATP to AMP and PPi, so two high energy phosphate bonds are utilized.

- • This reaction is catalyzed by arginosuccinate synthase of the liver cytosol, a Mg 2+ dependent enzyme.

4 Formation of Arginine and Fumarate: Arginosuccinate is cleaved by arginosuccinate lyase (arginosuccinase) to form free arginine and fumarate.

- The fumarate so formed returns to the pool of citric acid cycle intermediates.
- Though fumarate urea cycle is linked with the citric acid cycle, the two Kreb's cycles together have been referred to as the Kreb's bi cycle.

5 Formation of Urea and Ornithine: In the last reaction of urea cycle the liver hydrolytic enzyme arginase, cleaves arginine to yield urea and ornithine.

- Ornithine is thus regenerated and can enter mitochondria again to initiate another round of the urea cycle.

The urea thus formed is excreted in the urine.

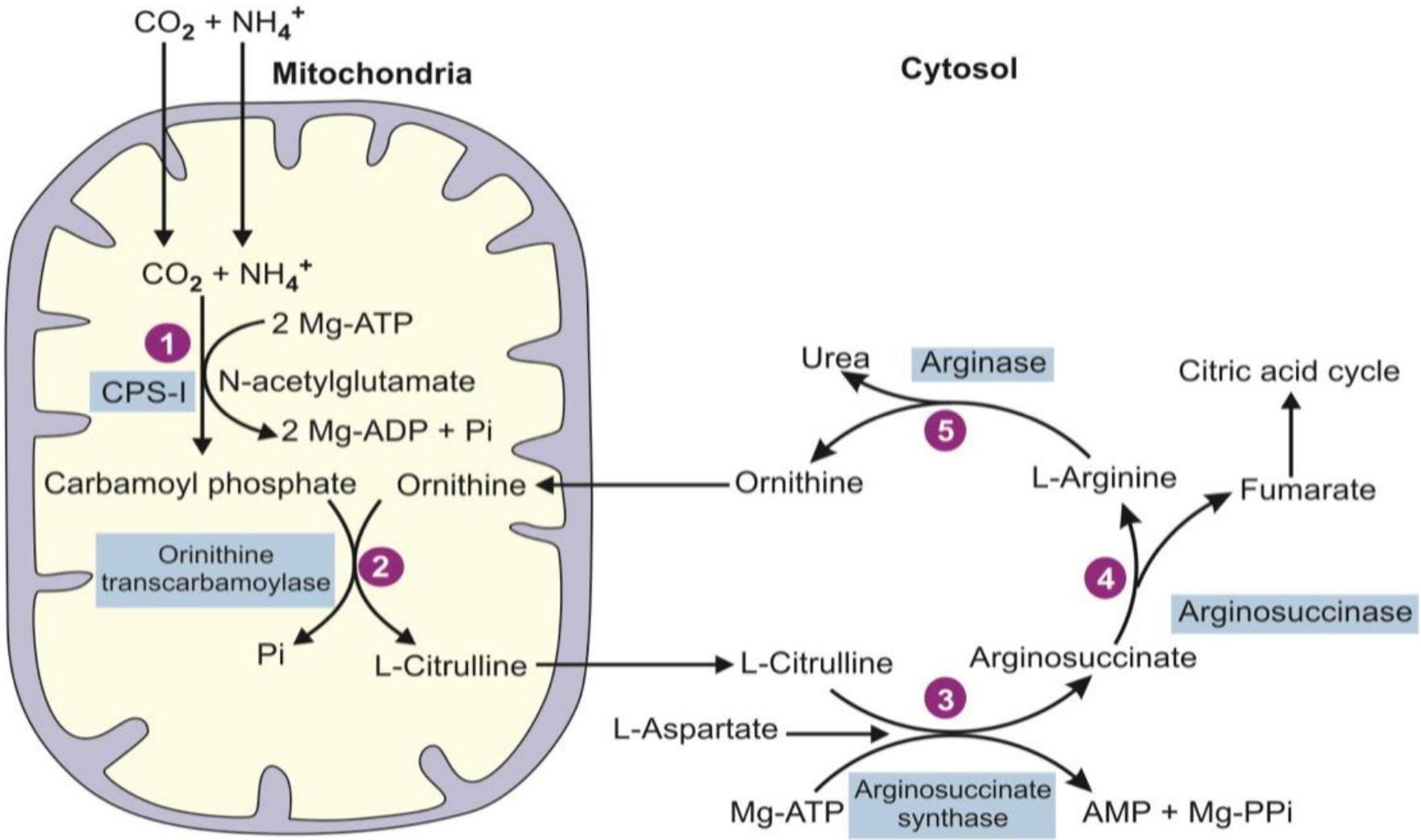


Figure 14.10: Reactions of urea cycle
where, CPS-I: Carbamoyl phosphate synthase-I

The Energy Cost of Urea Cycle

NH 3 + CO 2 + Aspartate → Urea + Fumarate

In the urea cycle 2 ATPs are used in the first reaction. Another ATP is converted to AMP and PPi,which is equivalent to 2 ATPs.The urea cycle consumes 4 high energy phosphate bonds.

The urea cycle and TCA cycle are interlinked, and so, it is called as "urea bicycle".

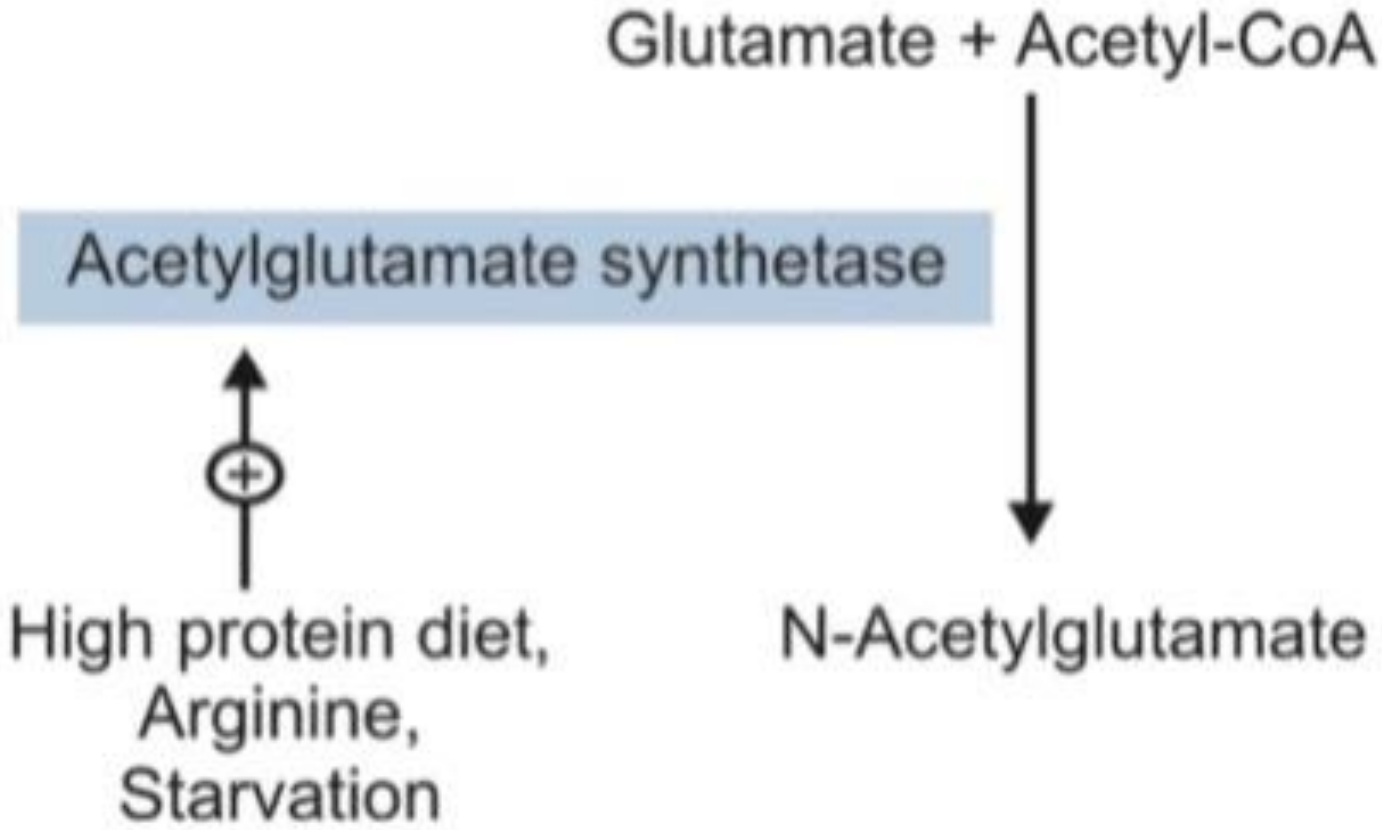
Significance of Urea Cycle

- The toxic ammonia is converted into the harmless 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
- Ornithine which is formed in urea cycle can form nonessential amino acid proline .

Regulation of Urea Cycle

- Carbamoyl phosphate synthetase-I is an allosteric regulatory enzyme of urea cycle, which is allosterically activated by N-acetylglutamate (NAG). NAG is synthesized from acetyl-CoA and glutamate by NAG-synthase to activate CPS-I. It has no other function.

- The synthesis of NAG increases after intake of protein rich diet, by arginine and during starvation, which ultimately increases the urea formation.


Glutamate + Acetyl-CoA
Acetylglutamate synthetase
High protein diet,
Arginine,
Starvation
N-Acetylglutamate

Metabolic Inborn Errors of Urea Cycle

- Five disorders associated with each of the five enzymes of urea cycle have been reported

Since urea synthesis converts toxic ammonia to non-toxic urea, all defects in urea synthesis result in hyperammonemia and ammonia intoxication.

- This intoxication is more severe when the metabolic block occurs at reaction I or II, since it accumulates ammonia itself.

- Deficiency of later enzymes result in the accumulation of other intermediates of the urea cycle, which are less toxic and therefore severity of symptoms is less.

Table 14.2: Disorders caused by genetic defects of urea cycle enzymes

Disorders	*Defective enzyme*	*Products accumulated*
Hyperammonemia type-I	Carbamoyl phosphate synthase-I	Ammonia
Hyperammonemia type-II	Ornithine transcarbamoylase	Ammonia
Citrullinemia	Arginosuccinate synthase	Citrulline
Argininosuccinic aciduria	Argininosuccinate lyase	Argininosuccinate
Argininemia	Arginase	Arginine

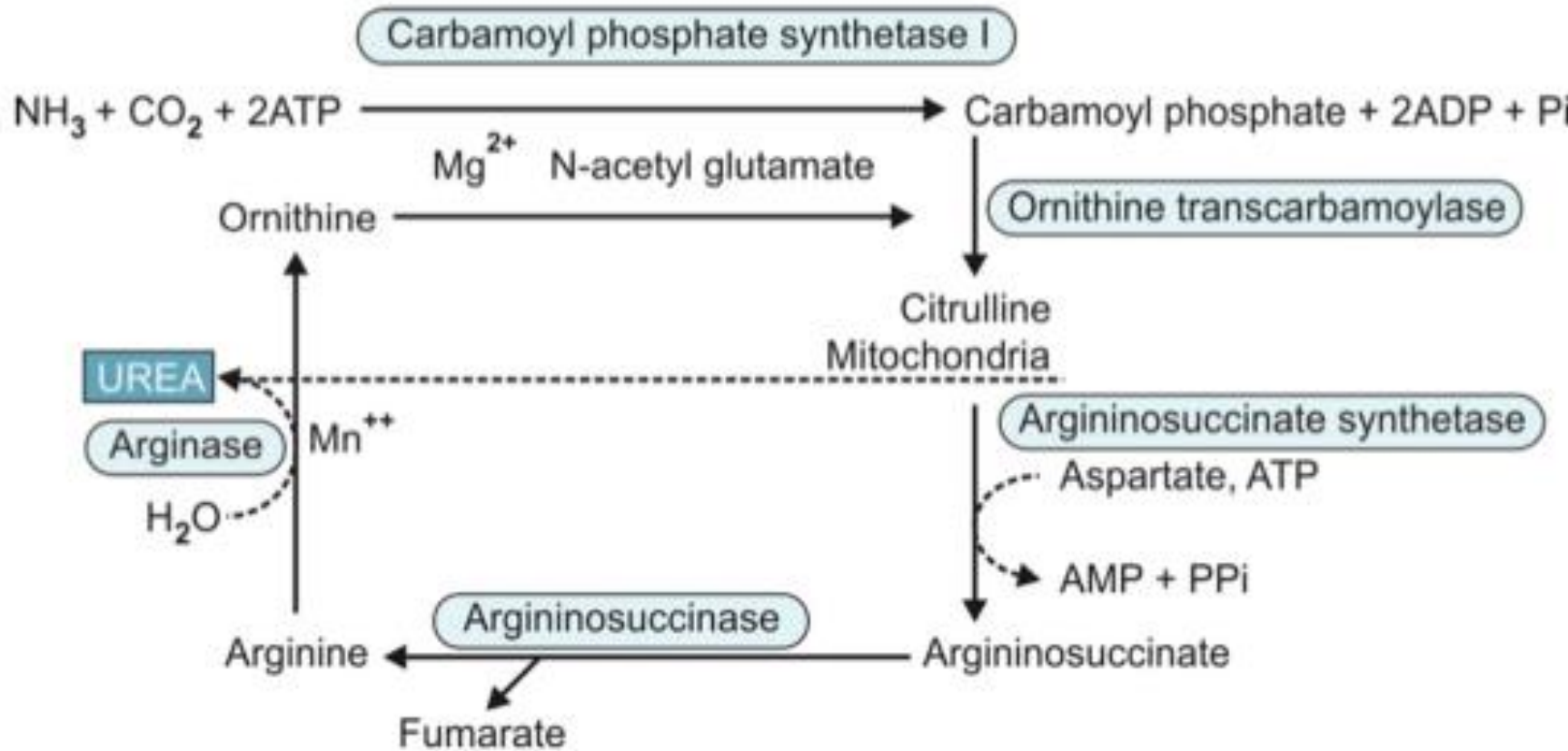


Figure 5.3: Schematic view of urea cycle

Treatment of hyperammonemia

- Low protein diet

- small meals to avoid sudden increase in blood ammonia levels.

Urea and its Clinical Significance

Blood Urea

- Normal range of blood urea for a healthy adult is 20 to 40 mg/dL. High protein diet shows increase in level of blood urea concentration.

- In clinical practice, blood urea level is taken as an indicator of renal function.

- The term uremia is used to indicate increased blood urea levels. For convenience, the causes of high blood urea are subdivided into three classes.

Table 14.3: Causes of high blood urea (Uremia)

Types	*Causes*
Prerenal uremia	High protein diet Any cause of increased protein catabolism, e.g. trauma, surgery, starvation, diabetes mellitus. Any cause of impaired renal perfusion, e.g. cardiac failure
Renal uremia	Any cause that leads to reduced GFR and leads to urea retention
Postrenal uremia	Any cause of obstruction to urine outflow, e.g. benign prostatic hypertrophy, malignant stricture or obstruction, stone

Thank you