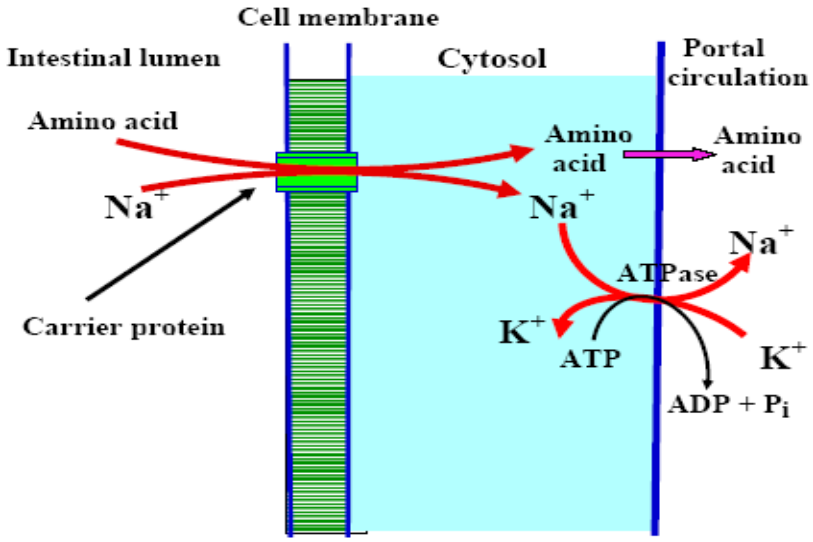
Protein Metabolism

Digestion: Dietary proteins must be digested to small simple molecules (amino acids), which are easily absorbed from the intestine. Protein digestion begins in the stomach by gastric juice, pepsin, and rennin. Digestion of proteins is completed in the small intestine by proteolytic enzymes (as trypsin, chymotrypsin, and aminopeptidase) present in pancreatic and intestinal juices.

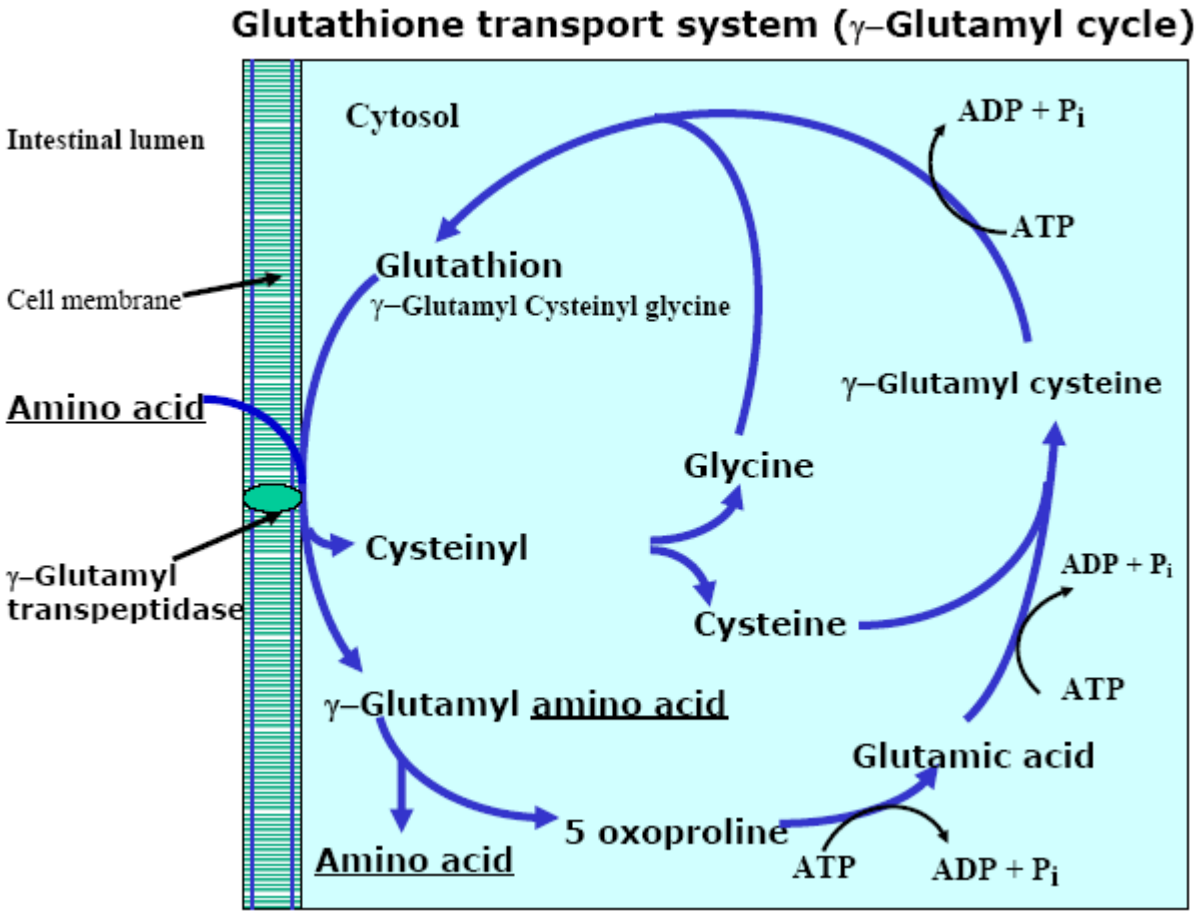
Absorption: It occurs in the small intestine. Absorption of amino acids is rapid in the duodenum and jejunum but slow in the ileum. There are two mechanisms for amino acids absorption.

1- **Carrier proteins transport system**: It is the main system for amino acid absorption. Absorption of one amino acid molecule needs one ATP molecule. There are seven carrier proteins, one for each group of amino acids. Each carrier protein has to sites one for amino acid and one for Na+. It co-transports amino acid and Na^+ from intestinal lumen to cytosol of intestinal mucosa cells. The absorbed amino acid passes to the portal circulation, while Na^+ is extruded out of the cell in exchange with K^+ by sodium pump.



Carrier Protein Transport System

2- **Glutathione transport system (γ−Glutamyl cycle):** Glutathione is used to transport amino acids from intestinal lumen to cytosol of intestinal mucosa cells. Absorption of one amino acid molecule needs 3 ATP molecules. Glutathione reacts with the amino acid in the presence of γ−glutamyl transpeptidase to form γ−glutamyl amino acid. γ−glutamyl amino acid releases amino acid in the cytosol of intestinal mucosa cells with formation of 5-oxoproline that is used for regeneration of glutathione to begin another turn of the cycle.



Sources of amino acid:

1- Dietary protein.

2- Breakdown of tissue proteins.

3- Biosynthesis of nonessential amino acids.

The fate of amino acid:

1- Biosynthesis of structural proteins e.g. tissue proteins

2- Biosynthesis of functional proteins e.g. hemoglobin, myoglobin, protein hormones and enzymes.

3- Biosynthesis of small peptides of biological importance e.g. glutathione.

4- Biosynthesis of non-protein nitrogenous compounds (NPN) as urea, uric acid, creatine, creatinine, and ammonia.

5- Catabolism of amino acids to give α-keto acids and ammonia. The α- keto acids that remain after removal of ammonia from amino acids are called the carbon skeleton. Ammonia is transformed mainly into urea.

The fate of Carbon Skeleton:

1- Biosynthesis of nonessential amino acids by transamination with glutamic acid.

2- Amino acids which give acetyl CoA are Ketogenic amino acids. Leucine is the only pure ketogenic amino acid.

3- Amino acids which give rise to pyruvic acid or one of the intermediates of Krebs cycle are glucogenic e.g. glycine, alanine, and cysteine.

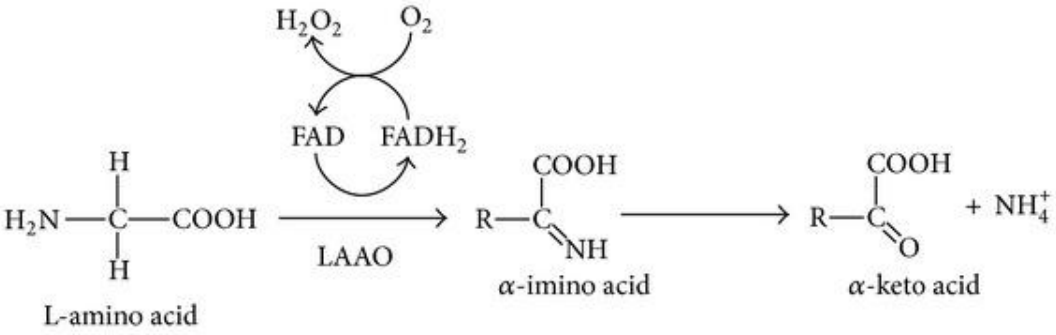
4- Oxidation via the Krebs cycle to give carbon dioxide, water, and energy.

Ammonia

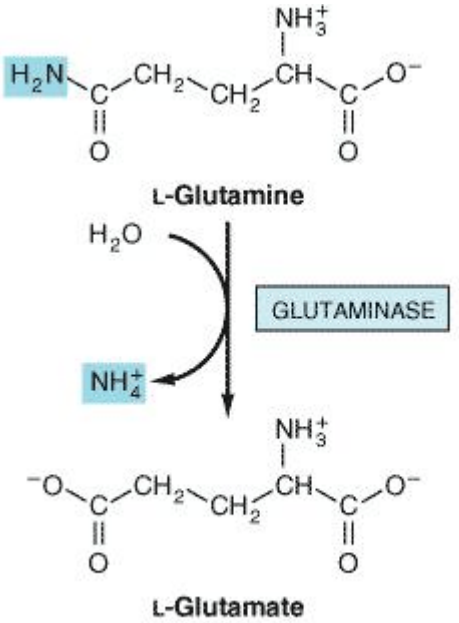
Ammonia is toxic to the central nervous system and its accumulation in the body is fatal. Once formed in the body, ammonia must be removed from the blood**.** It is removed by the liver that converts it to urea, which is less toxic, water-soluble and easily excreted in the urine.

Sources of ammonia:

1- Deamination of amino acids with the formation of α-keto acids and ammonia.

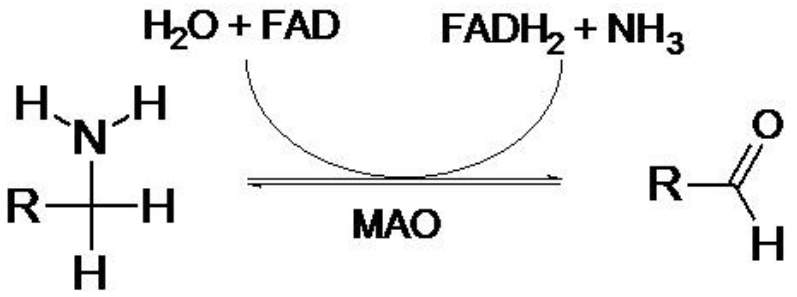


2- Glutamine in the kidney by glutaminase enzyme gives glutamic acid and ammonia which is used by the kidney to regulate the acid-base balance

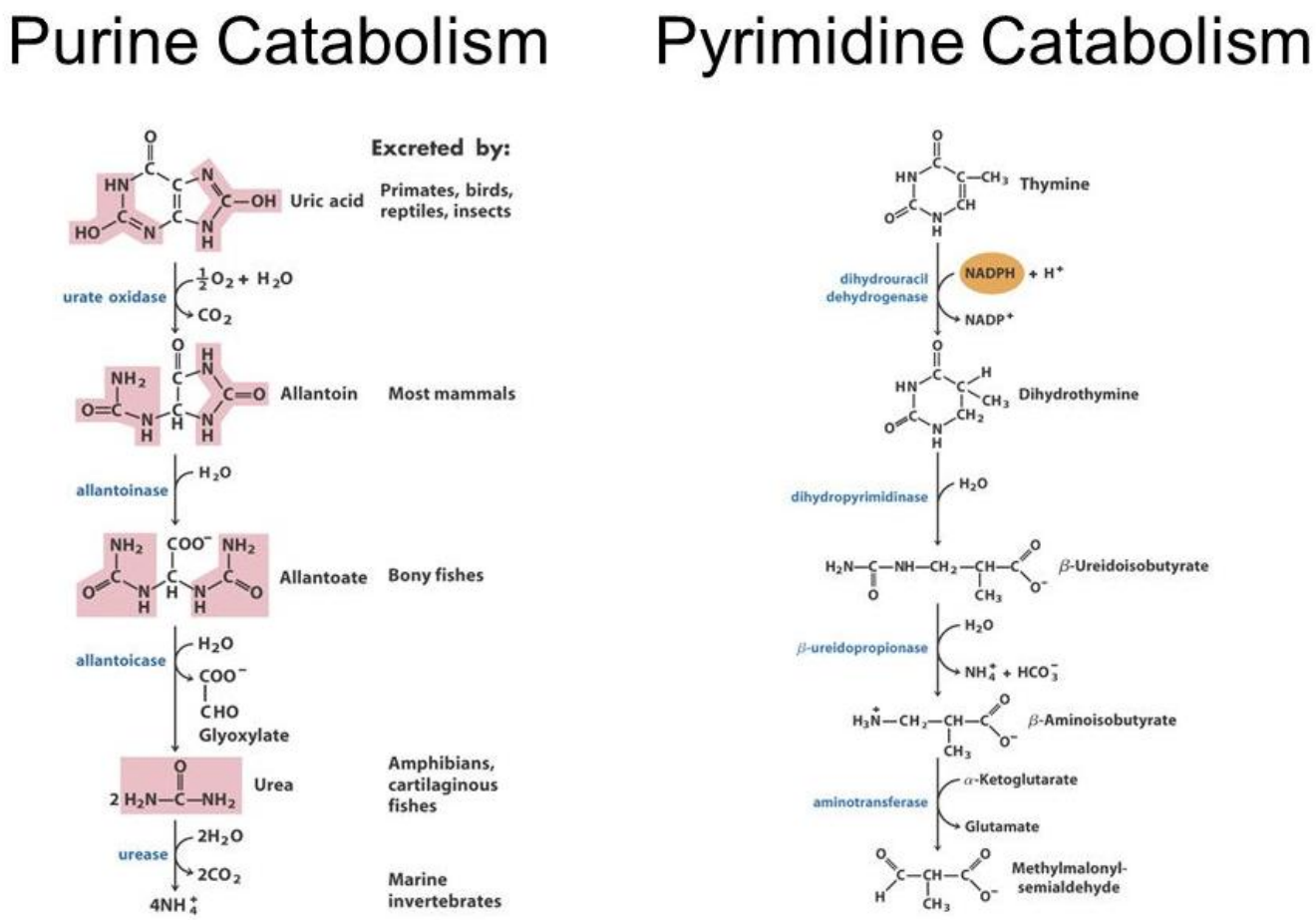


4-Ammonia produced by the action of intestinal bacteria on the non-absorbed dietary amino acids.

5-Ammonia is released from monoamines (e.g. epinephrine, norepinephrine, and dopamine) by the action of monoamine oxidase (MAO) enzyme.



6- Ammonia is released during purine and pyrimidine catabolism.



The fate of ammonia:

1- Biosynthesis of urea is the main fate of ammonia.

2- Small amounts of ammonia are excreted in urine.

3- Biosynthesis of glutamic acid, nonessential amino acids and glutamine.

Urea Biosynthesis

Ammonia is highly toxic to the central nervous system. It is converted to urea, which is much less toxic, water soluble and easily excreted in urine. The liver is the site of Urea biosynthesis. Urea biosynthesis occurs by urea cycle.

Steps of urea biosynthesis:

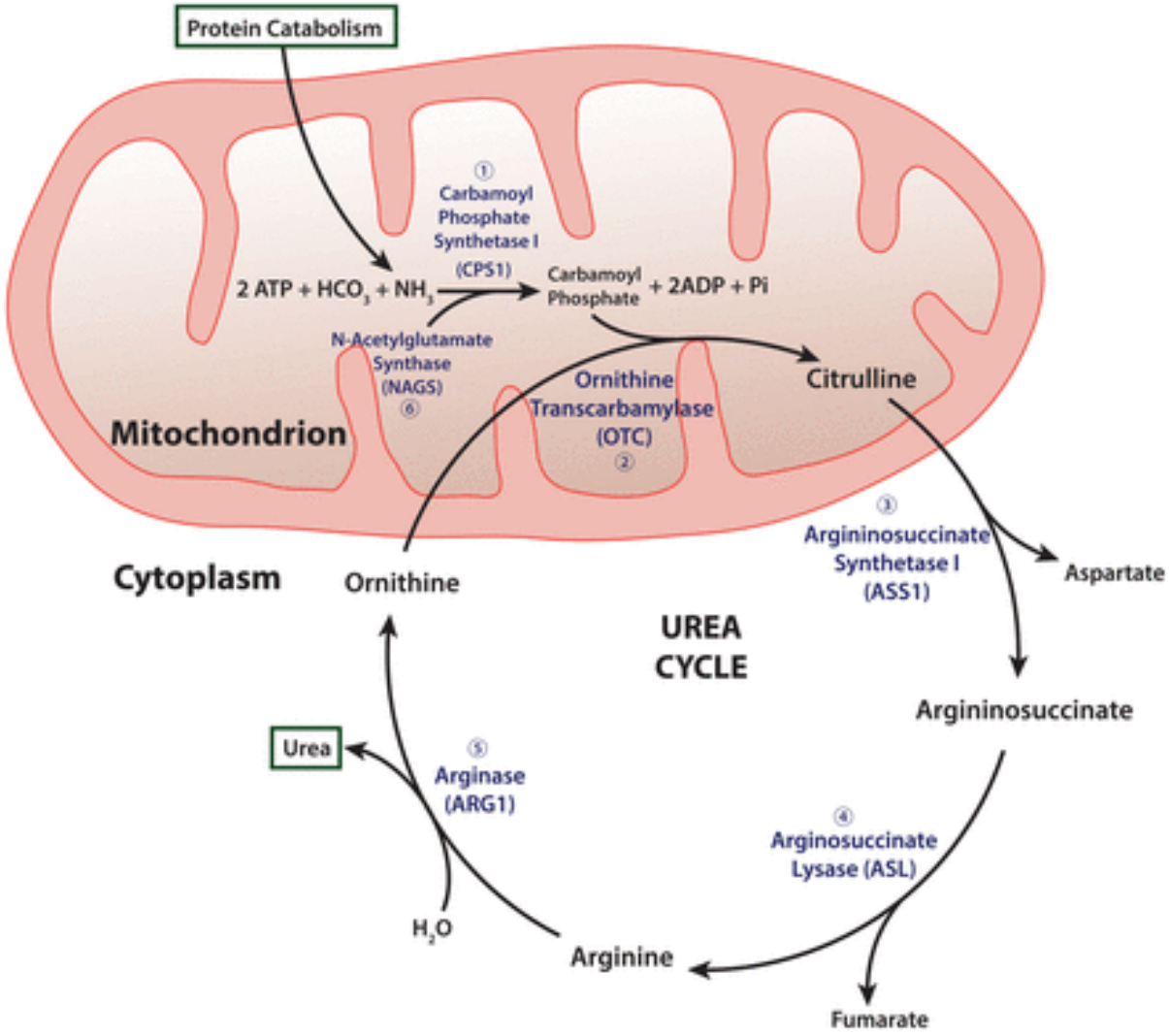
The conversion from ammonia to urea happens in five main steps: a)The first 2 steps occur in mitochondria, b) The last 3 steps occur in the cytoplasm.

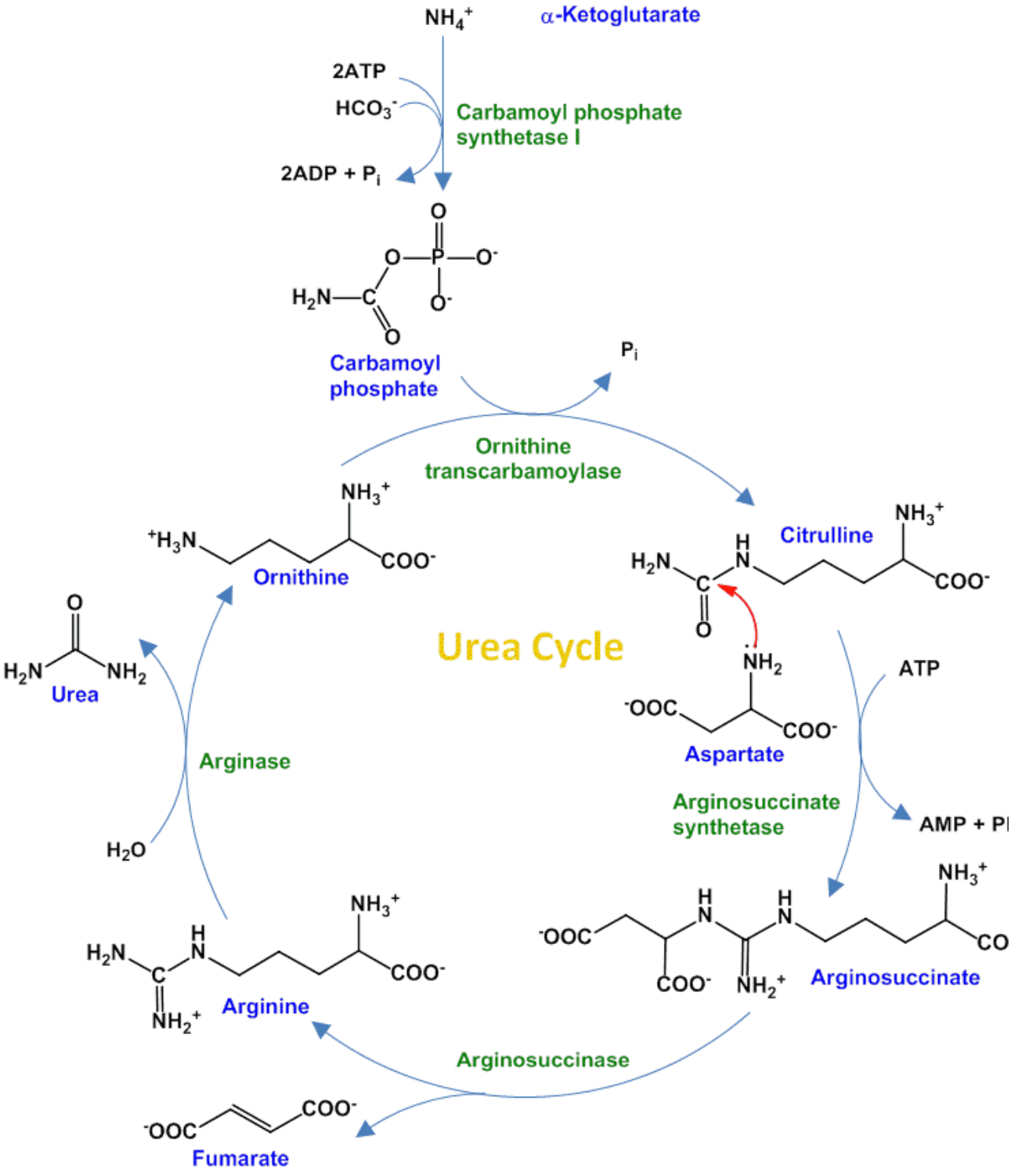
Reactions of the urea cycle

Step	Reactants	Products	Catalyzed by	Location
1	$NH_3 + HCO_3^- + 2ATP$	carbamoyl phosphate + 2ADP + P_i	CPS1	mitochondria
2	carbamoyl phosphate + ornithine	citrulline + P_i	OTC, zinc, biotin	mitochondria
3	citrulline + aspartate + ATP	argininosuccinate + AMP + PP_i	ASS	cytosol
4	argininosuccinate	arginine + fumarate	ASL	cytosol
5	arginine + H_2O	ornithine + urea	ARG1, manganese	cytosol

The entire process converts two amino groups, one from NH_4^+ and one from Aspartate, and a carbon atom from HCO_3^-, to the relatively nontoxic excretion product urea at the cost of four "high-energy" phosphate bonds (3 ATP hydrolyzed to 2 ADP and one AMP).

$2NH4^{+}$ + HCO3– + H2O + 3ATP + Aspartate → Urea + 2ADP + 4Pi + AMP + $2H^{+}$ + Fumarate




NH4+
α-Ketoglutarate
2ATP
HCO3-
Carbamoyl phosphate synthetase I
2ADP + Pi
Carbamoyl phosphate
Pi
Ornithine transcarbamoylase
Ornithine
Citrulline
Urea Cycle
Urea
Aspartate
ATP
Arginase
Arginosuccinate synthetase
AMP + PI
H2O
Arginine
Arginosuccinate
Arginosuccinase
Fumarate