FATE OF AMMONIA

NH_4^+

Ammonia (as ammonium ion)

Ammonotelic animals: most aquatic vertebrates, such as bony fishes and the larvae of amphibia

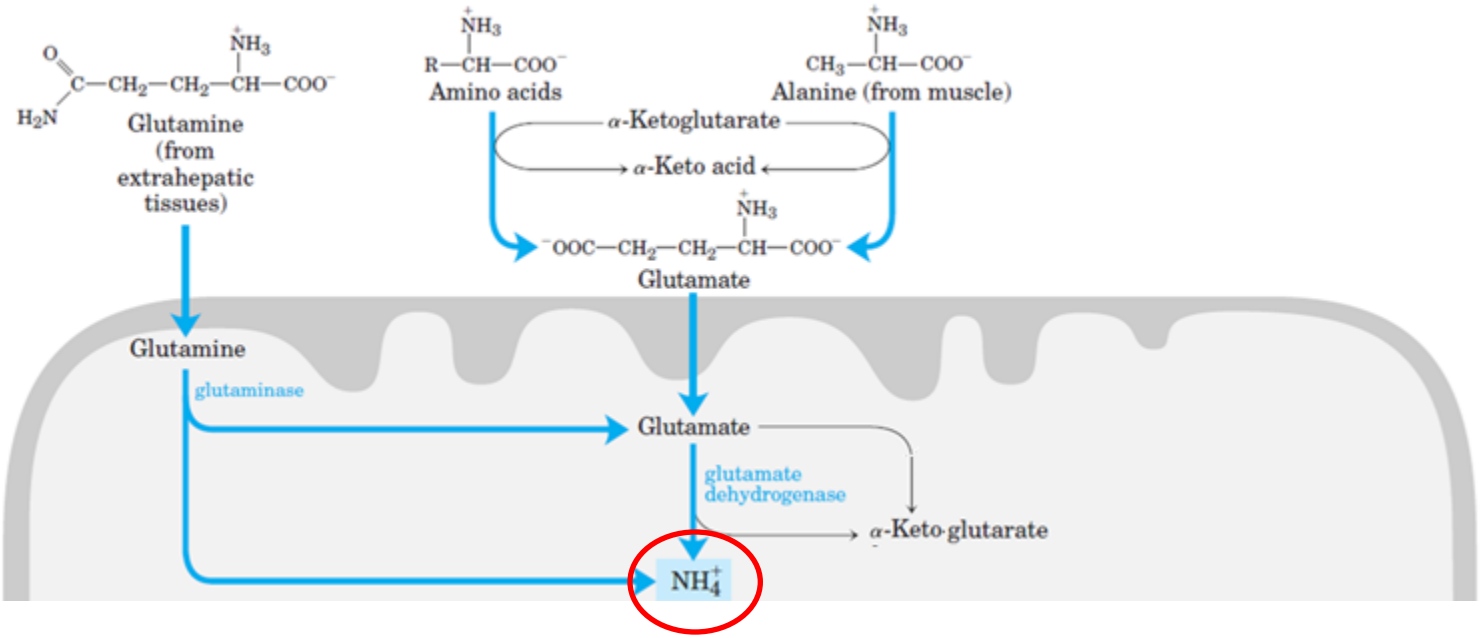
Ammonia is toxic and must be quickly excreted or transformed into a non-toxic compound as soon as it is formed.

1. Heart: direct toxic action of ammonium ion + hyperkalemia (tachyarrhythmias, fibrillation, arrest).

2. Central Nervous System: direct action of ammonium ion on motor neurons (reduction of postsynaptic inhibition due to alteration of ionic exchanges) with convulsive activity.

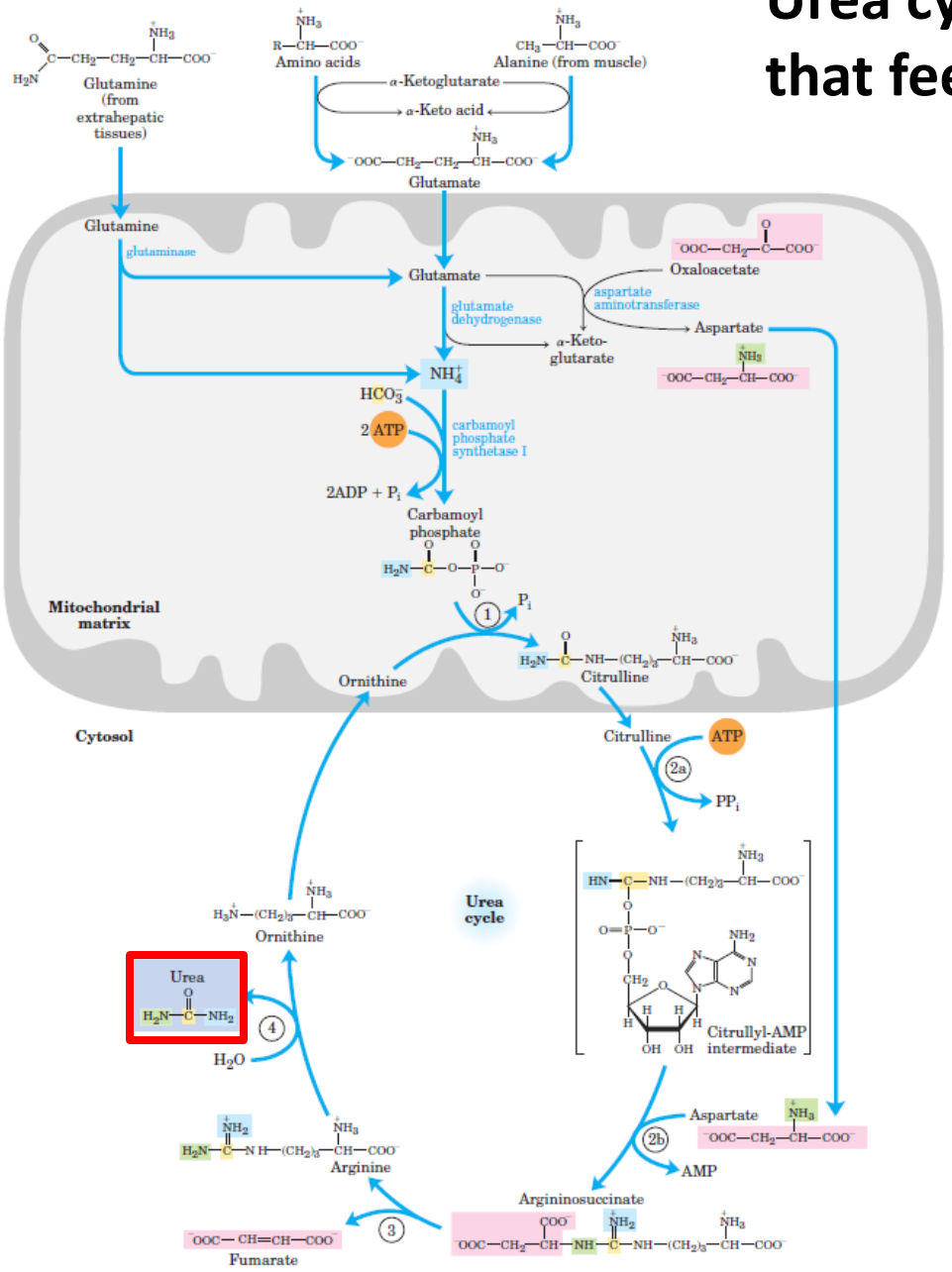
3. Lungs: pulmonary edema (increased capillary permeability following autonomic reflex stimuli) + polypnea (edema and acidosis)

Liver



Liver mitochondria

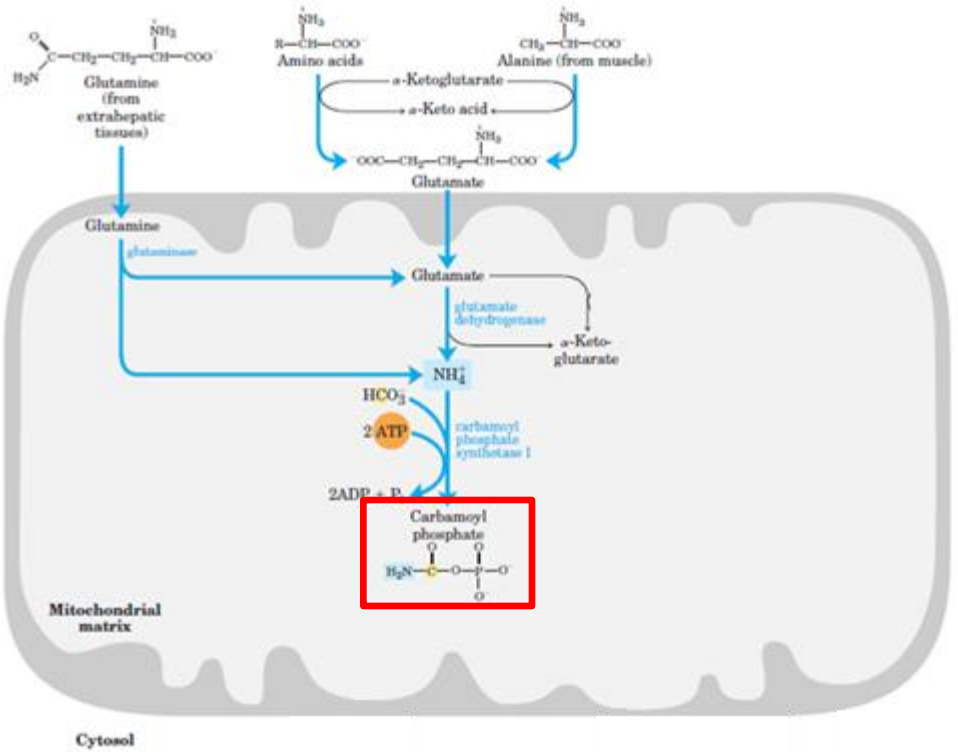
Urea cycle and reactions that feed amino groups

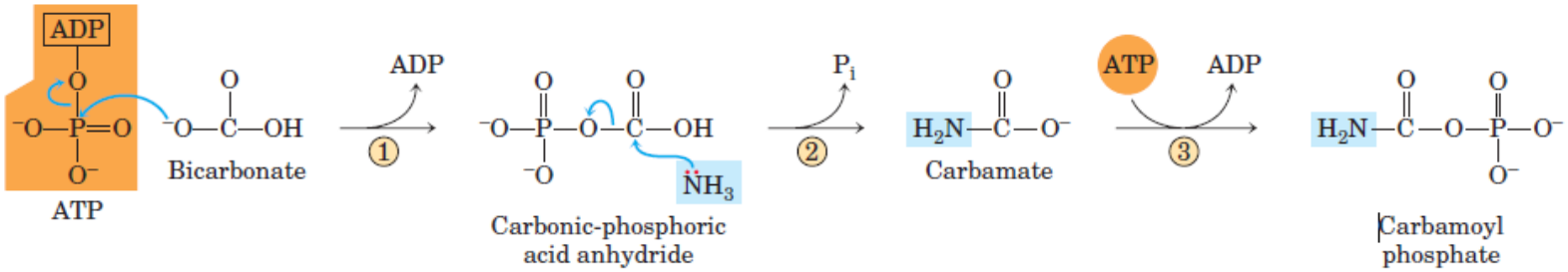


Whatever its source, the NH_4^+ generated in liver mitochondria is immediately used, together with CO_2 (as HCO_3^-) produced by mitochondrial respiration, to form carbamoyl phosphate in the matrix.

This ATP-dependent reaction is catalyzed by carbamoyl phosphate synthetase I, a regulatory enzyme.

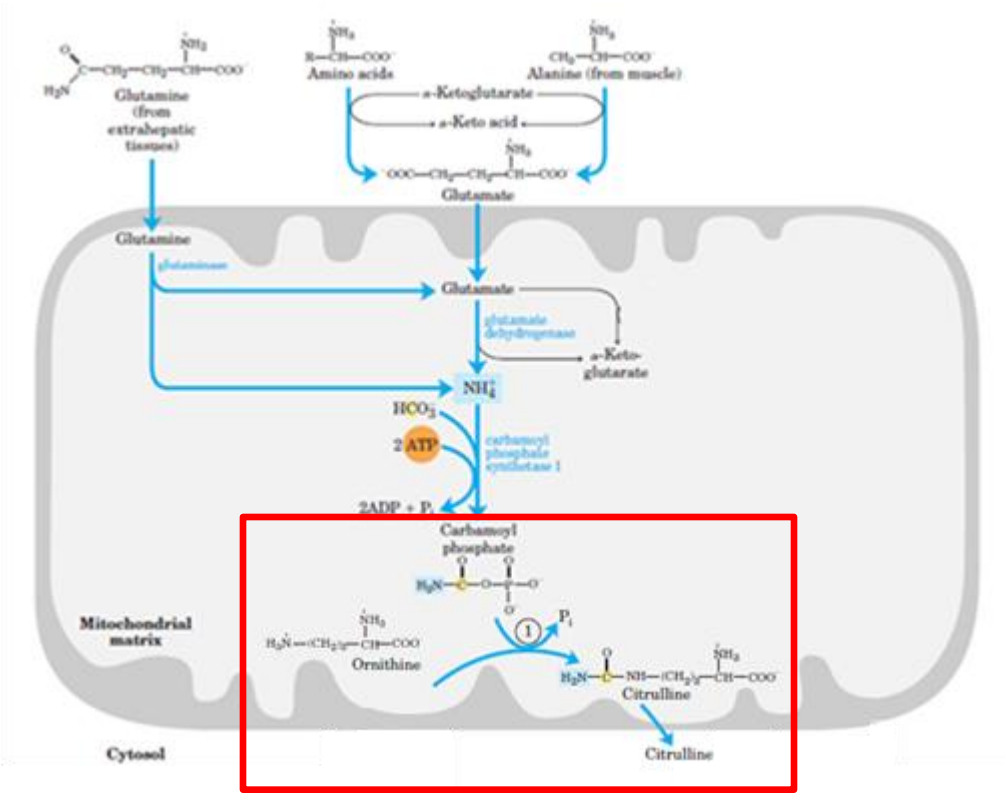
Note that the mitochondrial form of this enzyme is distinct from a cytosolic (II) form, which has a separate function in pyrimidine biosynthesis.





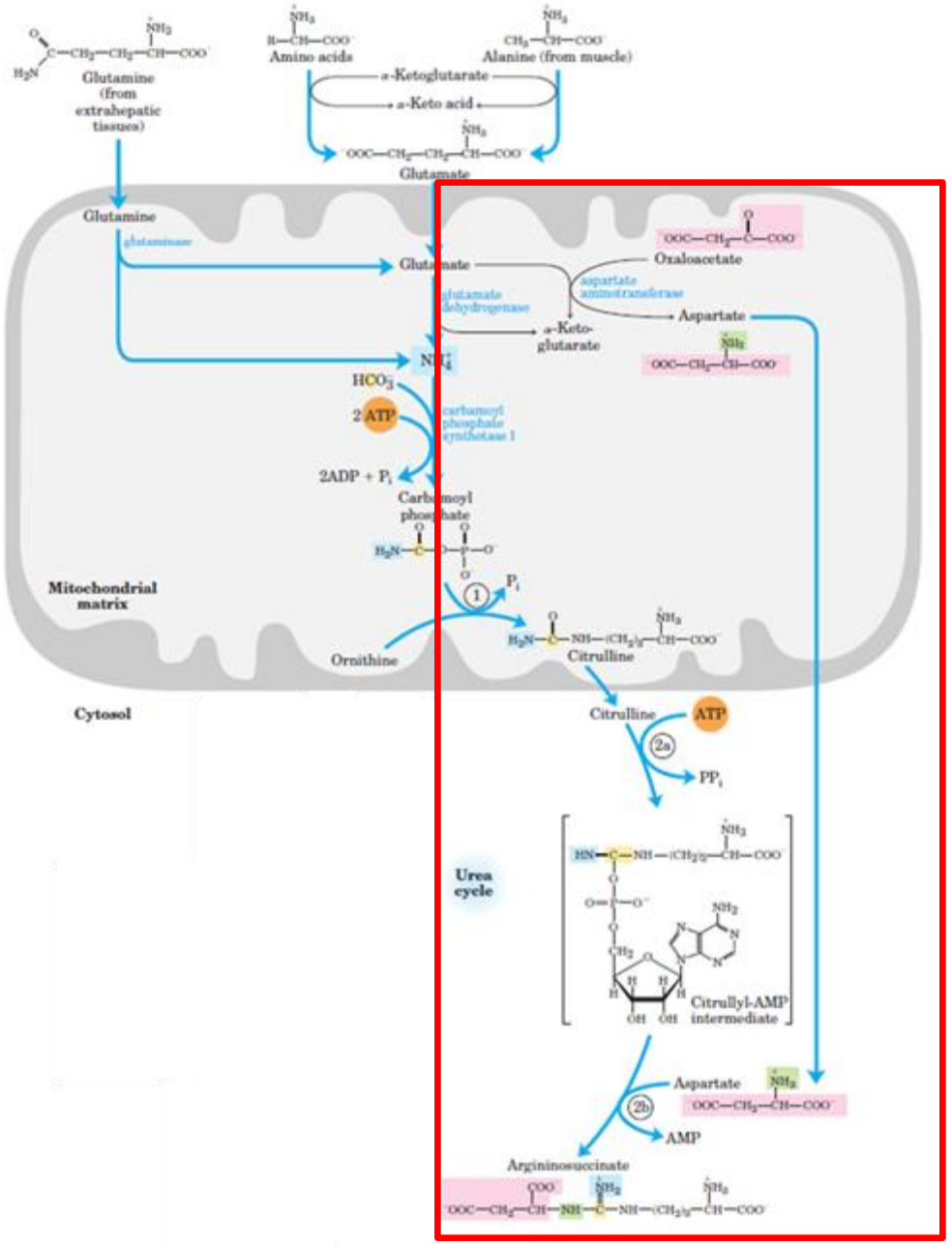
In the reaction catalyzed by carbamoyl phosphate synthetase I, a nitrogen enters from ammonia. The terminal phosphate groups of **two molecules of ATP are used** to form one molecule of carbamoyl phosphate. In other words, this reaction has two activation steps (1 and 3).

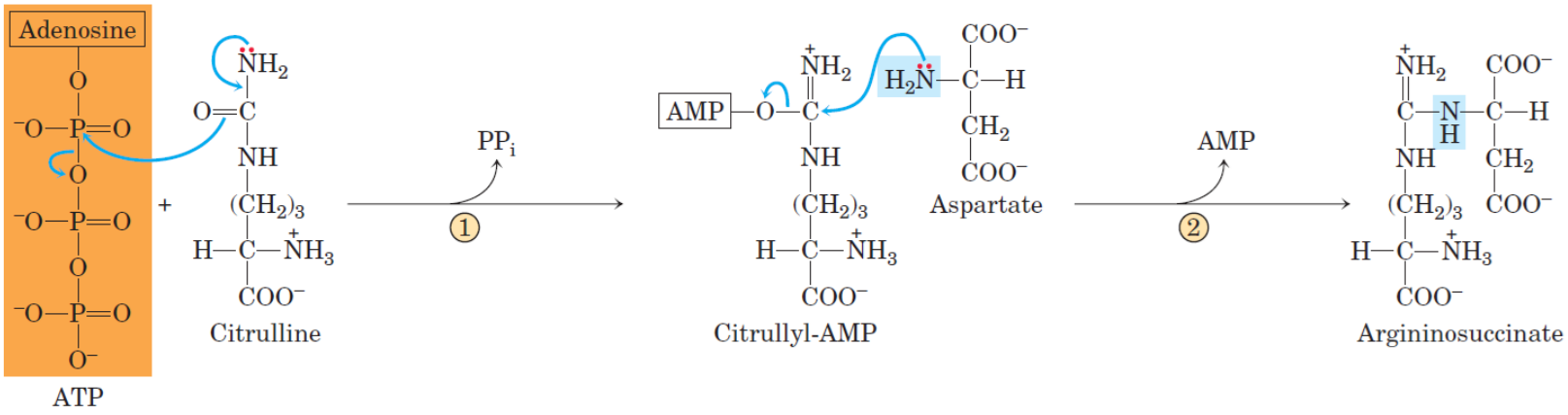
Carbamoyl phosphate donates its carbamoyl group to ornithine to form citrulline, with the release of Pi. Ornithine plays a role resembling that of oxaloacetate in the citric acid cycle, accepting material at each turn of the cycle. The reaction is catalyzed by **ornithine transcarbamoylase,** and the citrulline passes from the mitochondrion to the cytosol.



The second amino group now enters from aspartate (generated in mitochondria by transamination and transported into the cytosol) by a condensation reaction between the amino group of aspartate and the ureido (carbonyl) group of citrulline, forming argininosuccinate.

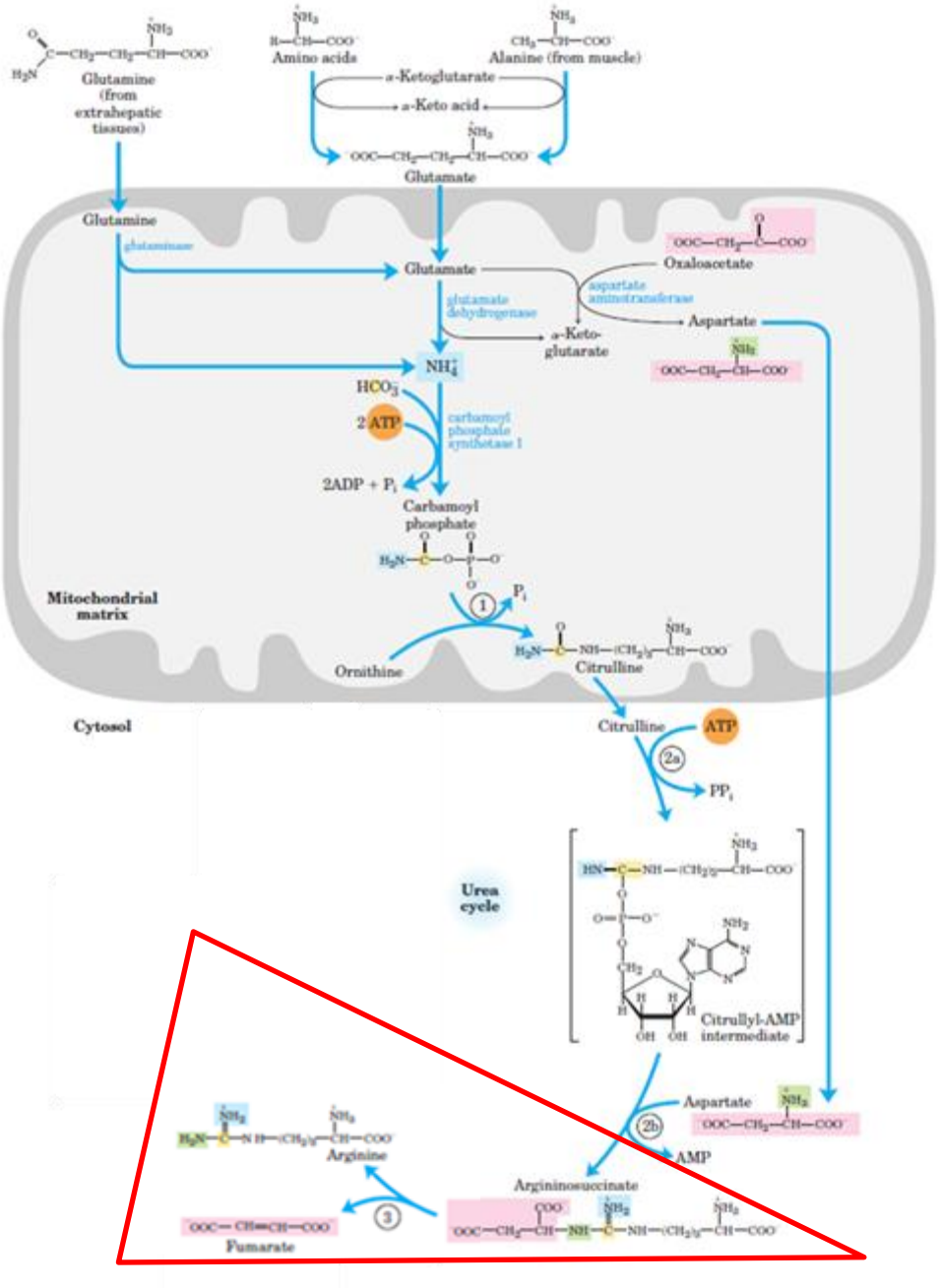
This cytosolic reaction, catalyzed by **argininosuccinate synthetase**, requires ATP and proceeds through a citrullyl-AMP intermediate.



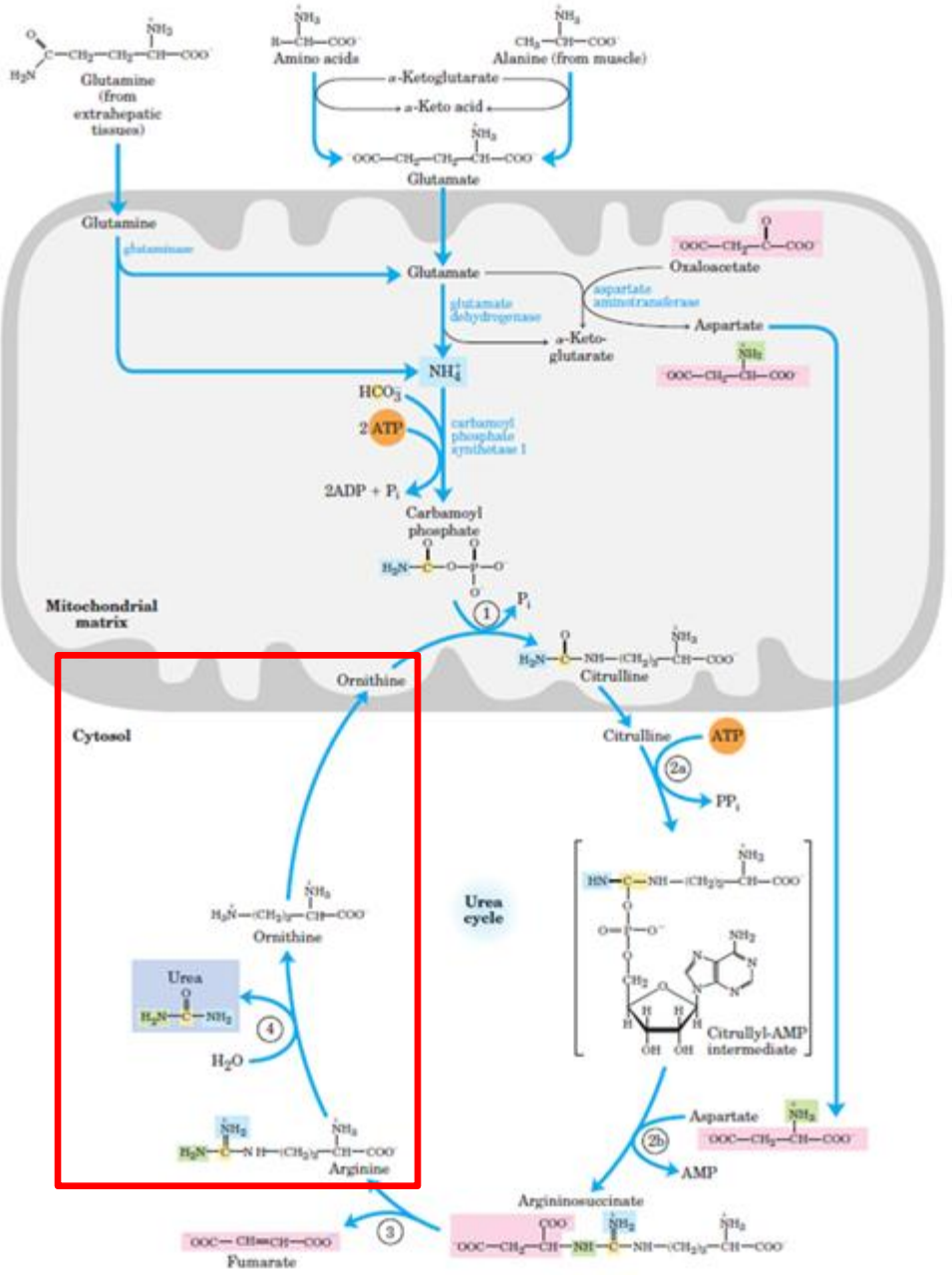


In the reaction catalyzed by argininosuccinate synthetase, the second nitrogen enters from aspartate. The ureido oxygen of citrulline is activated by the addition of AMP in step 1 ; this sets up the addition of aspartate in step 2 , with AMP (including the ureido oxygen) as the leaving group.

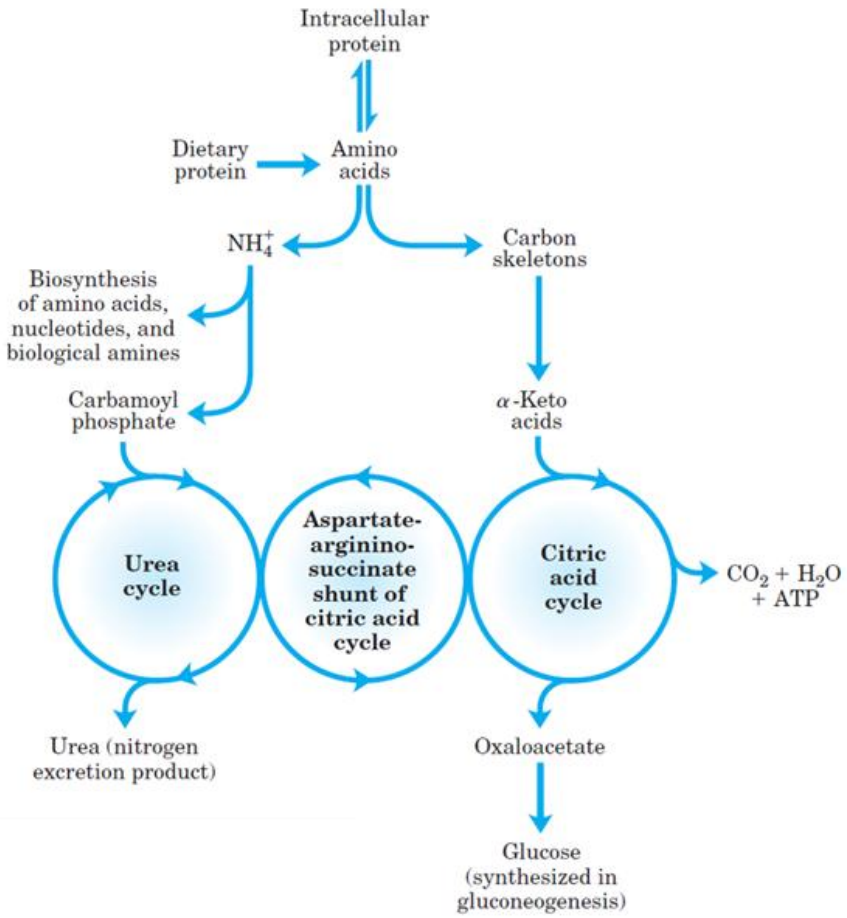
The argininosuccinate is then cleaved by **argininosuccinase** to form free arginine and fumarate, the latter entering mitochondria to join the pool of citric acid cycle intermediates. This is the only reversible step in the urea cycle.



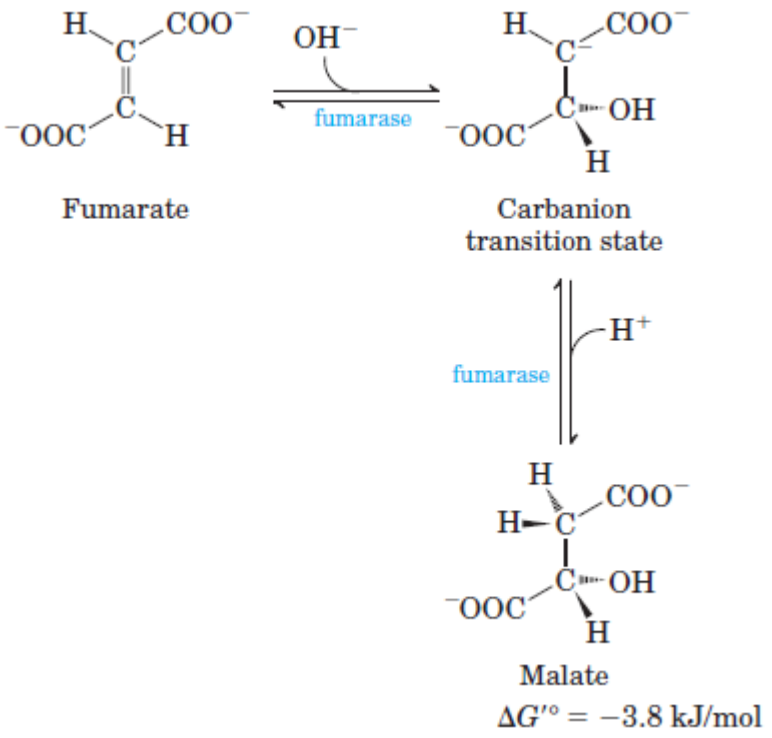
In the last reaction of the urea cycle, the cytosolic enzyme **arginase** cleaves arginine to yield urea and ornithine.
Ornithine is transported into the mitochondrion to initiate another round of the urea cycle.



Because the fumarate produced in the argininosuccinase reaction is also an intermediate of the citric acid cycle, the cycles are, in principle, interconnected. However, each cycle can operate independently and communication between them depends on the transport of key intermediates between the mitochondrion and cytosol. Several enzymes of the citric acid cycle, including fumarase (fumarate hydratase) and malate dehydrogenase, are also present as isozymes in the cytosol. The fumarate generated in cytosolic arginine synthesis can therefore be converted to malate in the cytosol, and these intermediates can be further metabolized in the cytosol or transported into mitochondria for use in the citric acid cycle. Aspartate formed in mitochondria by transamination between oxaloacetate and glutamate can be transported to the cytosol, where it serves as nitrogen donor in the urea cycle reaction catalyzed by argininosuccinate synthetase. These reactions, making up the **aspartate-argininosuccinate shunt,** provide metabolic links between the separate pathways by which the amino groups and carbon skeletons of amino acids are processed.



The fumarate generated in cytosolic arginine synthesis can therefore be converted to malate in the cytosol, and these intermediates can be further metabolized in the cytosol or transported into mitochondria for use in the citric acid cycle.



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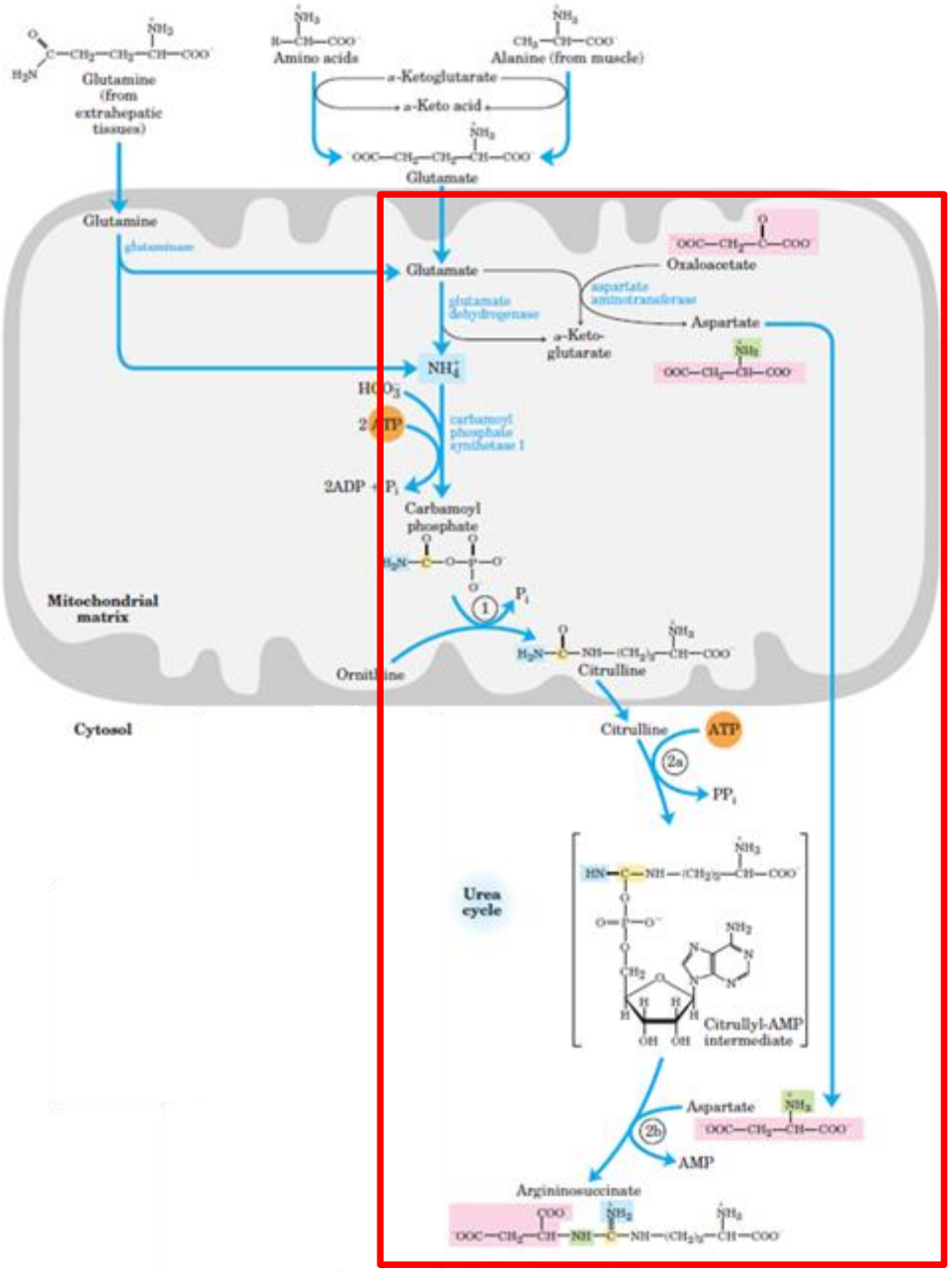
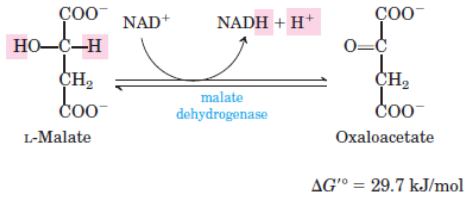
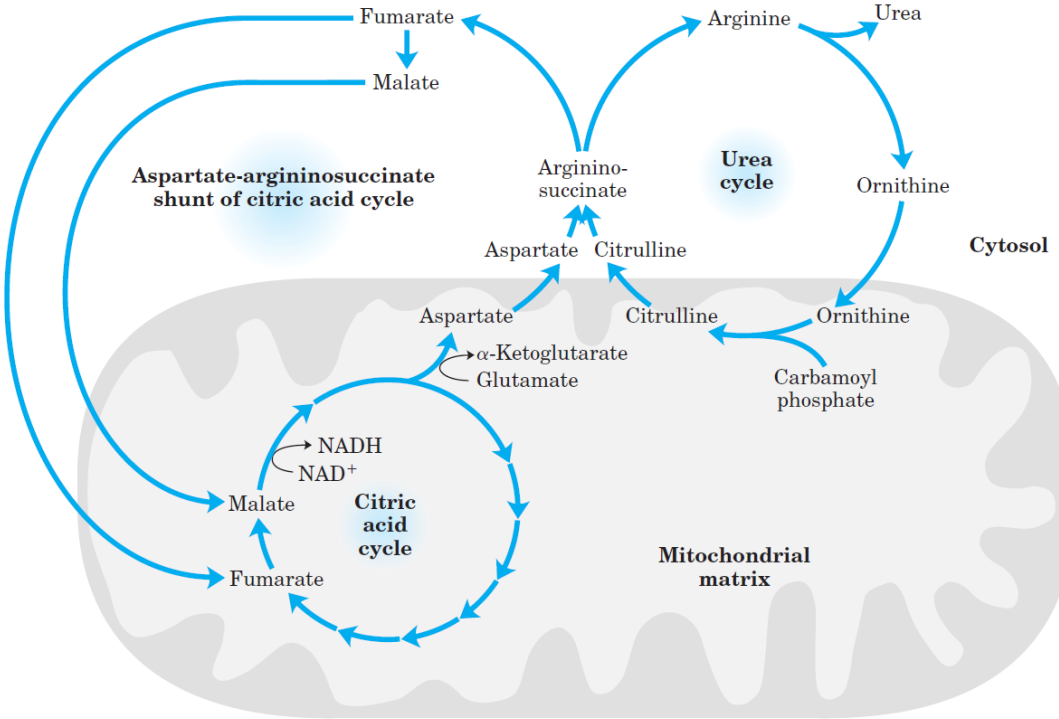


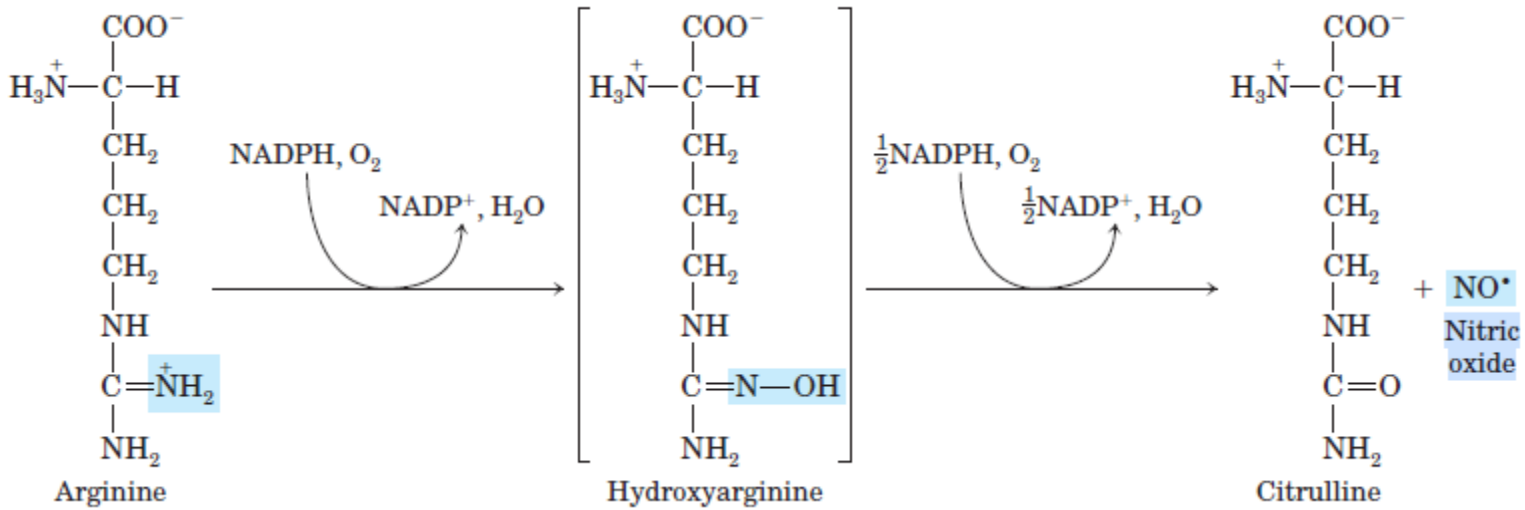
Links between the urea cycle and citric acid cycle



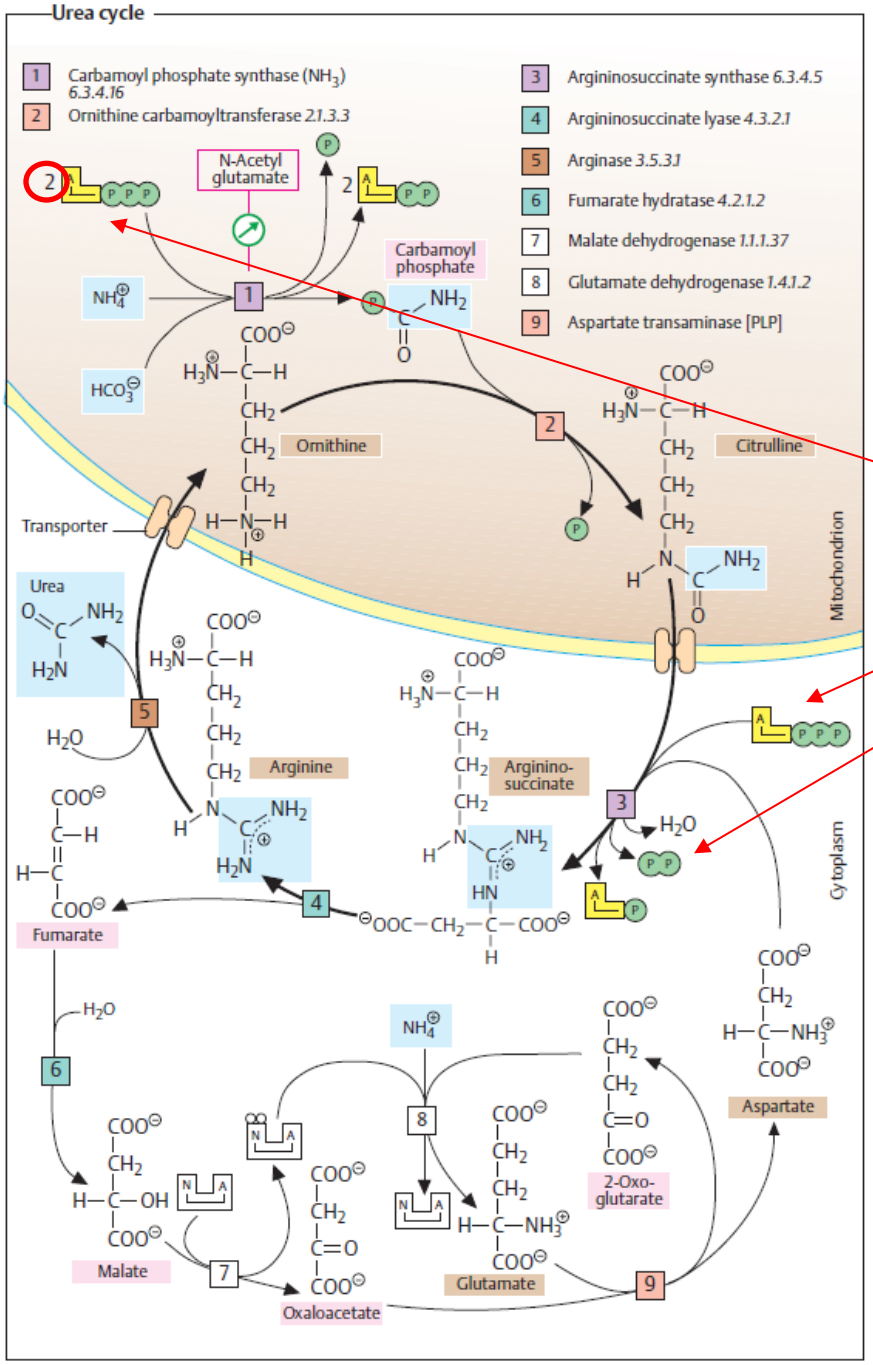


The pathways linking the citric acid and urea cycles are called the aspartate-argininosuccinate shunt; these effectively link the fates of the amino groups and the carbon skeletons of amino acids. The interconnections are even more elaborate than the arrows suggest. For example, some citric acid cycle enzymes, such as fumarase and malate dehydrogenase, have both cytosolic and mitochondrial isozymes. Fumarate produced in the cytosol — whether by the urea cycle, purine biosynthesis, or other processes—can be converted to cytosolic malate, which is used in the cytosol or transported into mitochondria (via the malate-aspartate shuttle) to enter the citric acid cycle.

Biosynthesis of nitric oxide



Arginine is the precursor of nitric oxide, a biological messenger. The nitrogen of the NO is derived from the guanidino group of arginine. Both steps are catalyzed by nitric oxide synthase. This enzyme is found in many tissues and cell types: neurons, macrophages, hepatocytes, myocytes of smooth muscle, endothelial cells of the blood vessels, and epithelial cells of the kidney. Nitric oxide is a relatively stable free radical NO acting near its point of release, entering the target cell and activating the cytosolic enzyme guanylyl cyclase, which catalyzes the formation of the second messenger cGMP.



1 molecule of urea *costs* 4 high-energy phosphate groups

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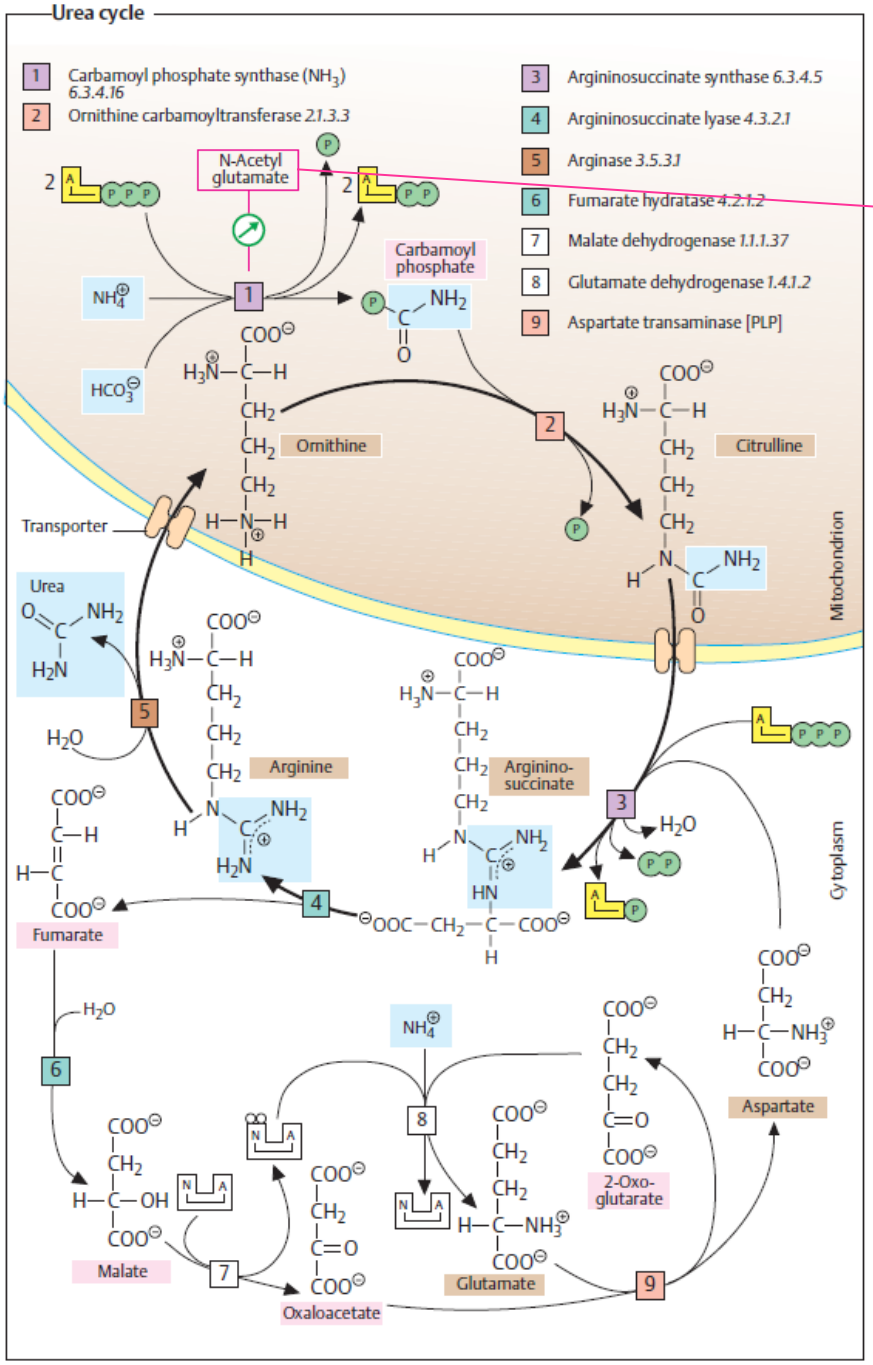

allosteric activation

The rate of urea formation is mainly controlled by reaction 1 . N-acetyl glutamate, as an allosteric effector, activates carbamoylphosphate synthase.

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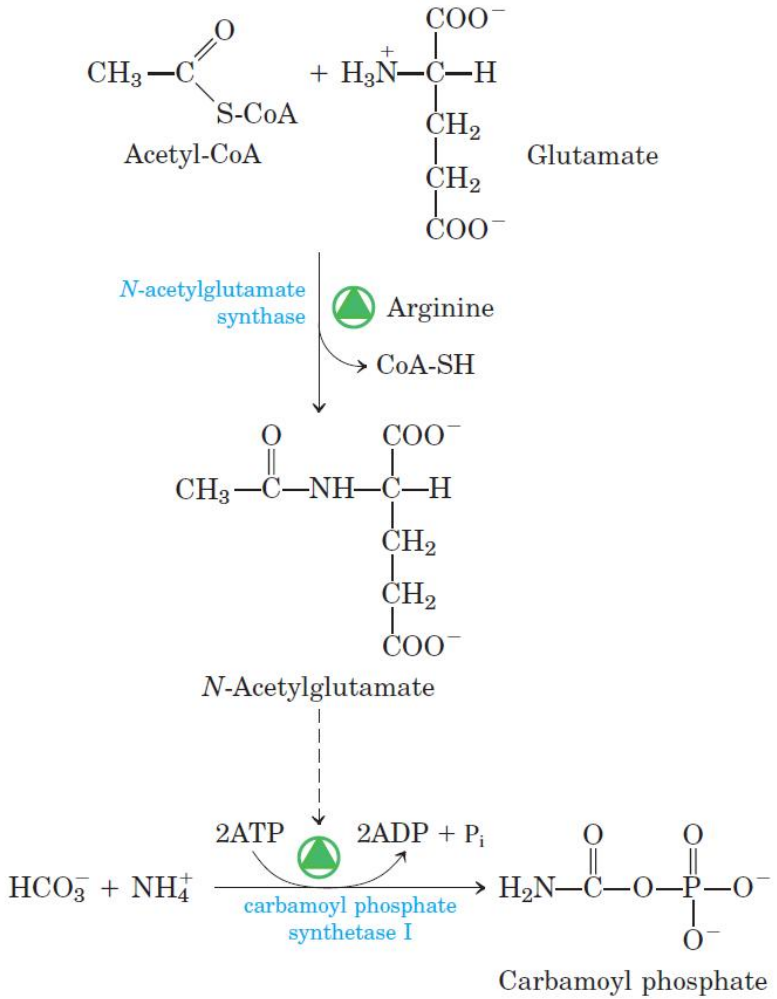
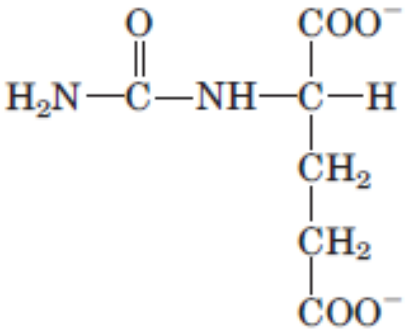
Synthesis of *N*-acetylglutamate and its activation of carbamoyl phosphate synthetase I



Deficiency of N-acetylglutamate synthase results in the absence of the normal activator of carbamoyl phosphate synthetase I. This condition can be treated by administering carbamoyl glutamate, an analog of N-acetylglutamate that is effective in activating carbamoyl phosphate synthetase I.



Carbamoyl glutamate

Nonessential and Essential Amino Acids for Humans

Nonessential	*Conditionally essential**	*Essential*
Alanine	Arginine	Histidine
Asparagine	Cysteine	Isoleucine
Aspartate	Glutamine	Leucine
Glutamate	Glycine	Lysine
Serine	Proline	Methionine
	Tyrosine	Phenylalanine
		Threonine
		Tryptophan
		Valine

*Required to some degree in young, growing animals, and/or sometimes during illness.

Treatment for deficiencies in urea cycle enzymes

The aromatic acids benzoate and phenylbutyrate, administered in the diet, are metabolized and combine with glycine and glutamine, respectively. The products are excreted in the urine.

Subsequent synthesis of glycine and glutamine to replenish the pool of these intermediates removes ammonia from the bloodstream.