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Urea Cycle

Urea Cycle Biochemistry

All tissues have some capability for synthesis of the non-essential amino acids, amino acid by remodeling, and the conversion of non-amino acid carbon skeletons into amino acids and other derivatives that contain nitrogen. However, the liver is the major site of nitrogen metabolism in the body. In times of dietary surplus, the potentially toxic nitrogen of amino acids is eliminated via transaminations, deamination, and urea formation; the carbon skeletons are generally conserved as carbohydrate, via gluconeogenesis, or as fatty acid via fatty acid synthesis pathways. In this respect amino acids fall into three categories: glucogenic, ketogenic, or glucogenic and ketogenic.

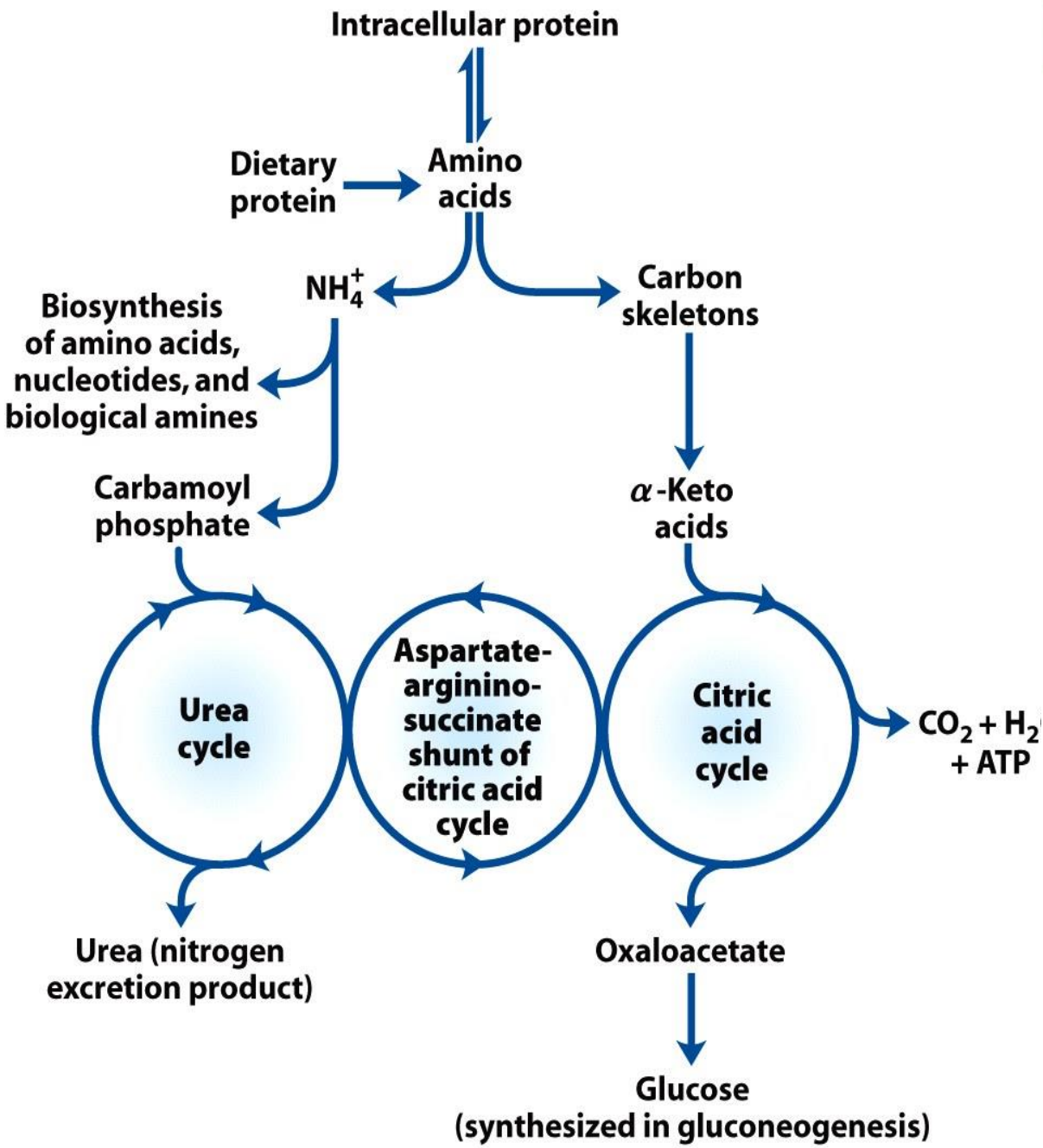


Figure 18-1
Lehninger Principles of Biochemistry, Fifth Edition

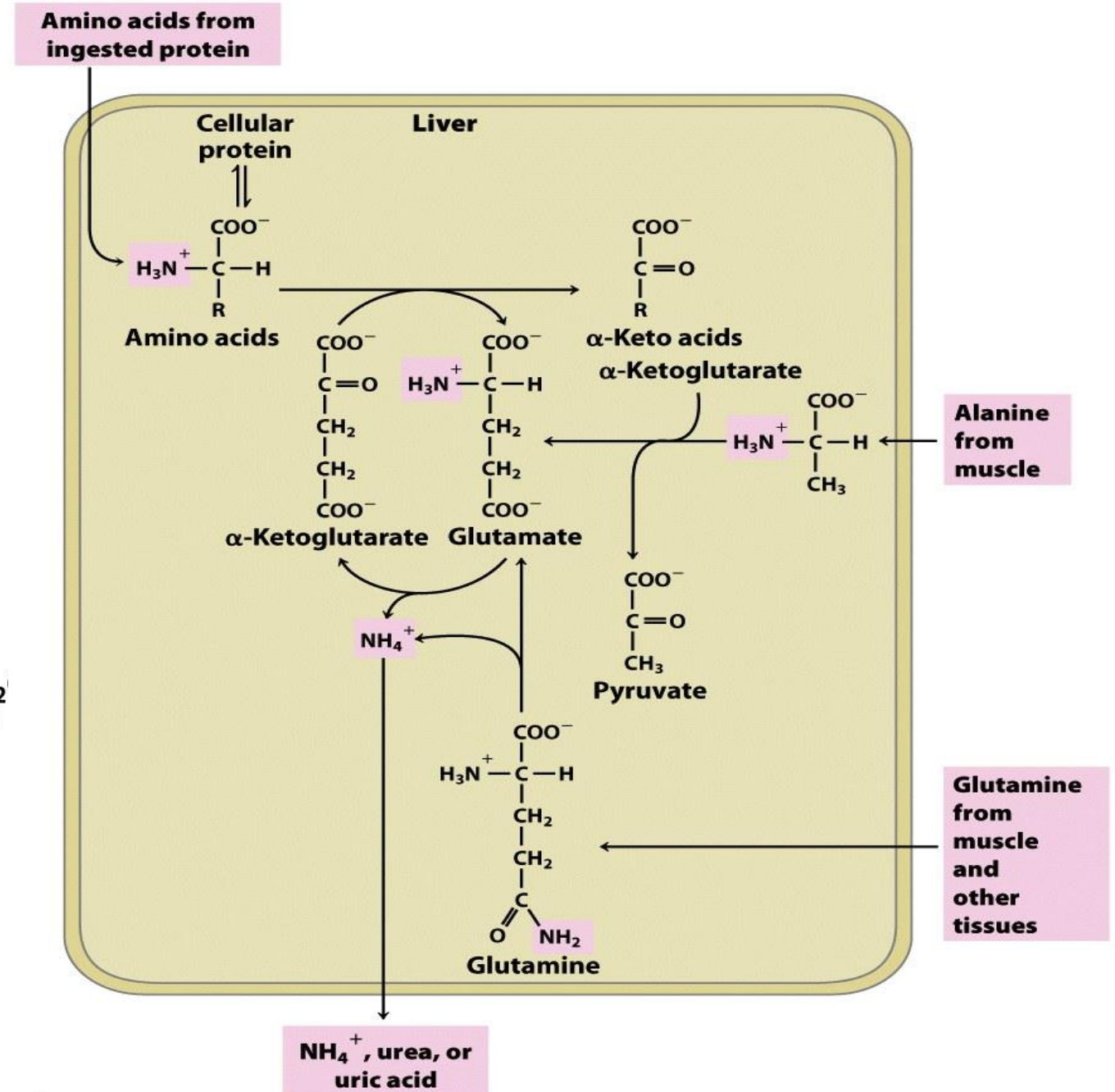
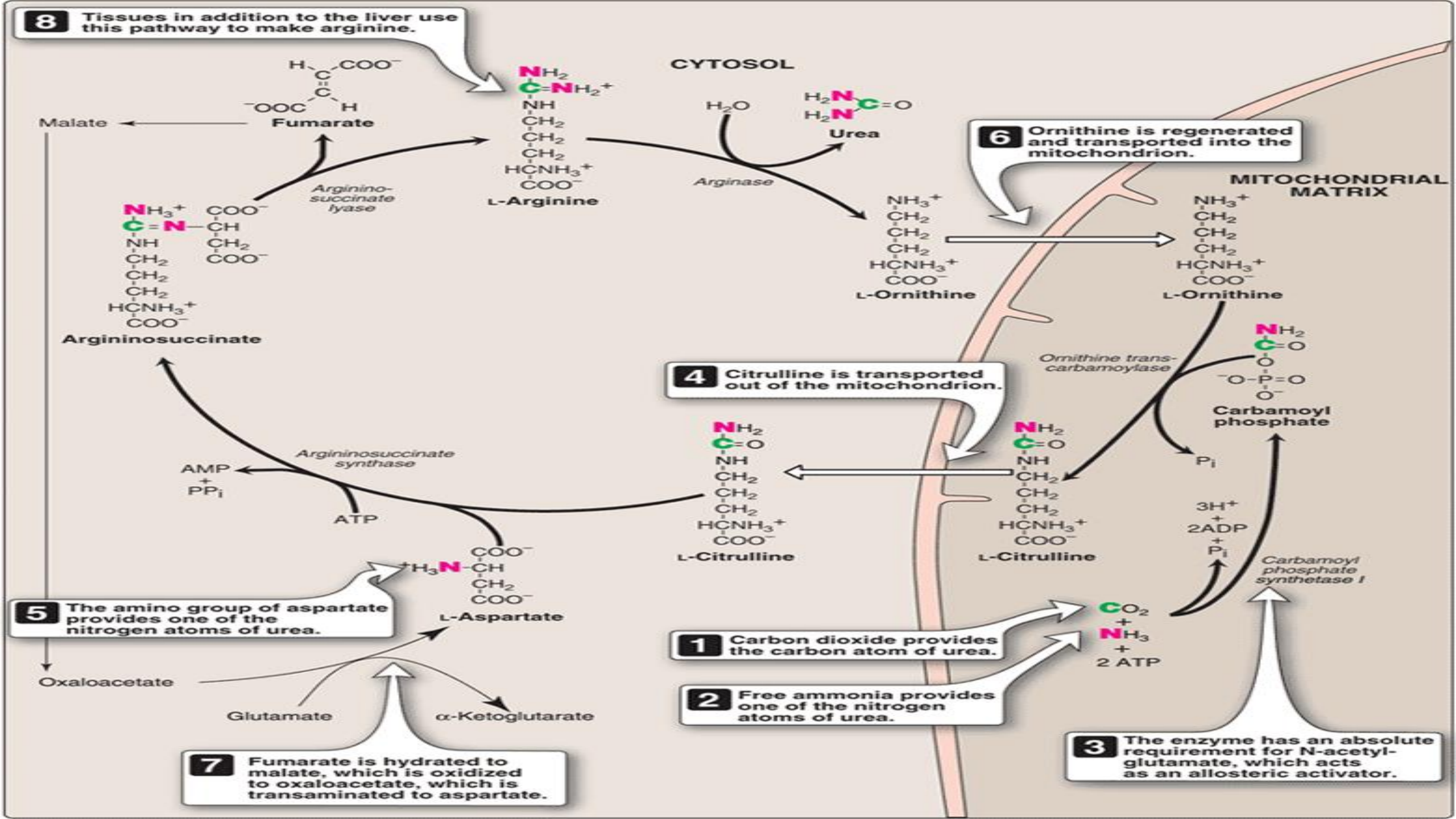
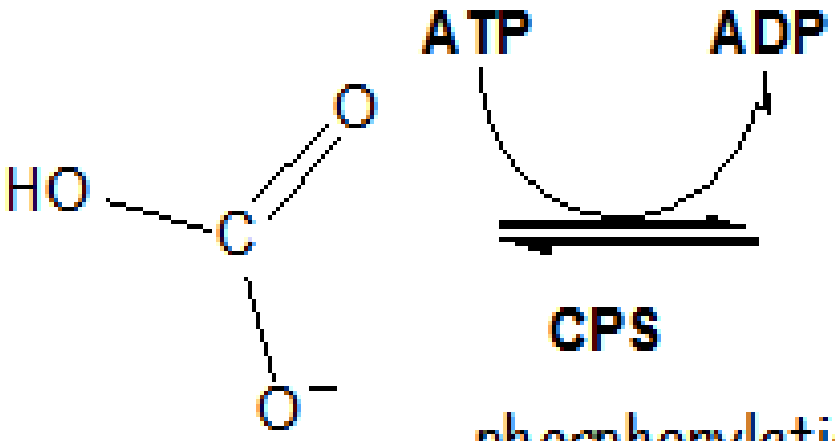


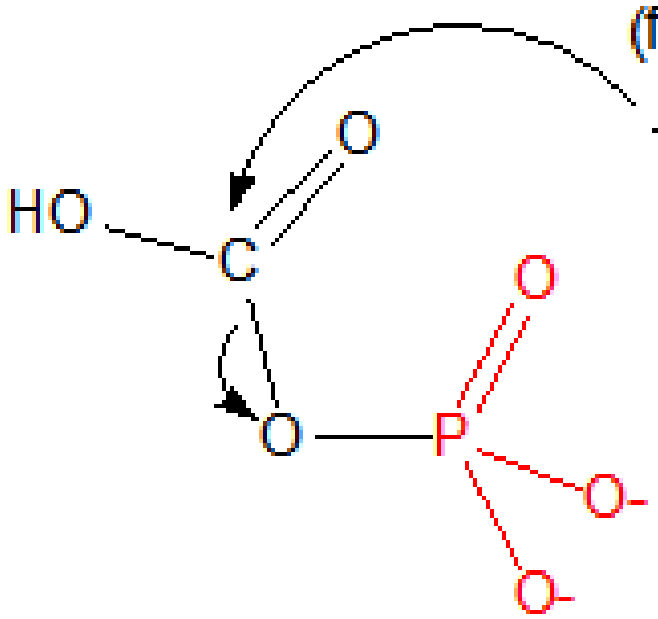
Figure 18-2a
Lehninger Principles of Biochemistry, Fifth Edition


8 Tissues in addition to the liver use this pathway to make arginine.
CYTOSOL
Fumarate
Malate
L-Arginine
Urea
Arginase
Arginino-succinate lyase
Argininosuccinate
6 Ornithine is regenerated and transported into the mitochondrion.
MITOCHONDRIAL MATRIX
L-Ornithine
L-Ornithine
Ornithine trans-carbamoylase
Carbamoyl phosphate
4 Citrulline is transported out of the mitochondrion.
Argininosuccinate synthase
AMP + PPi
ATP
L-Citrulline
L-Citrulline
Pi
3H+ + 2ADP + Pi
Carbamoyl phosphate synthetase I
5 The amino group of aspartate provides one of the nitrogen atoms of urea.
L-Aspartate
CO2 + NH3 + 2 ATP
1 Carbon dioxide provides the carbon atom of urea.
2 Free ammonia provides one of the nitrogen atoms of urea.
3 The enzyme has an absolute requirement for N-acetyl-glutamate, which acts as an allosteric activator.
Oxaloacetate
Glutamate
α-Ketoglutarate
7 Fumarate is hydrated to malate, which is oxidized to oxaloacetate, which is transaminated to aspartate.

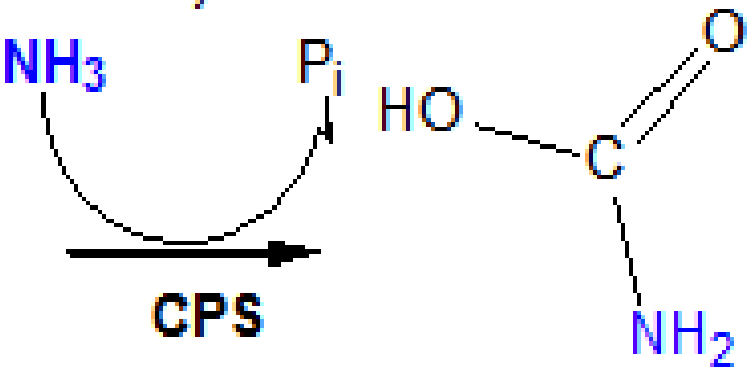


phosphorylation of bicarbonate

Bicarbonate

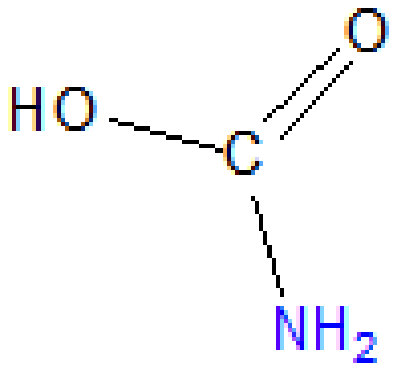


Carboxyphosphate

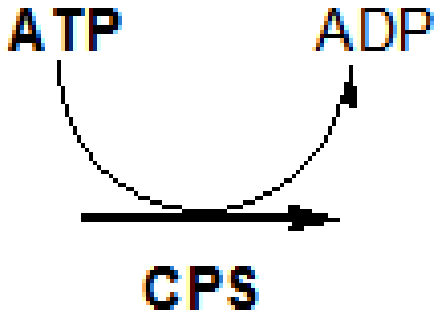


ammonia displaces the phosphate

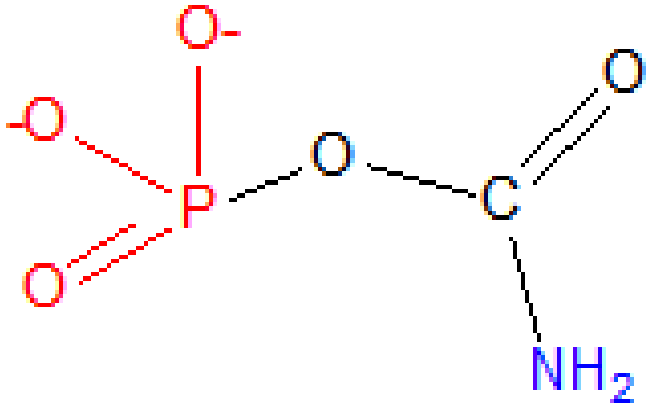
Carbamic acid



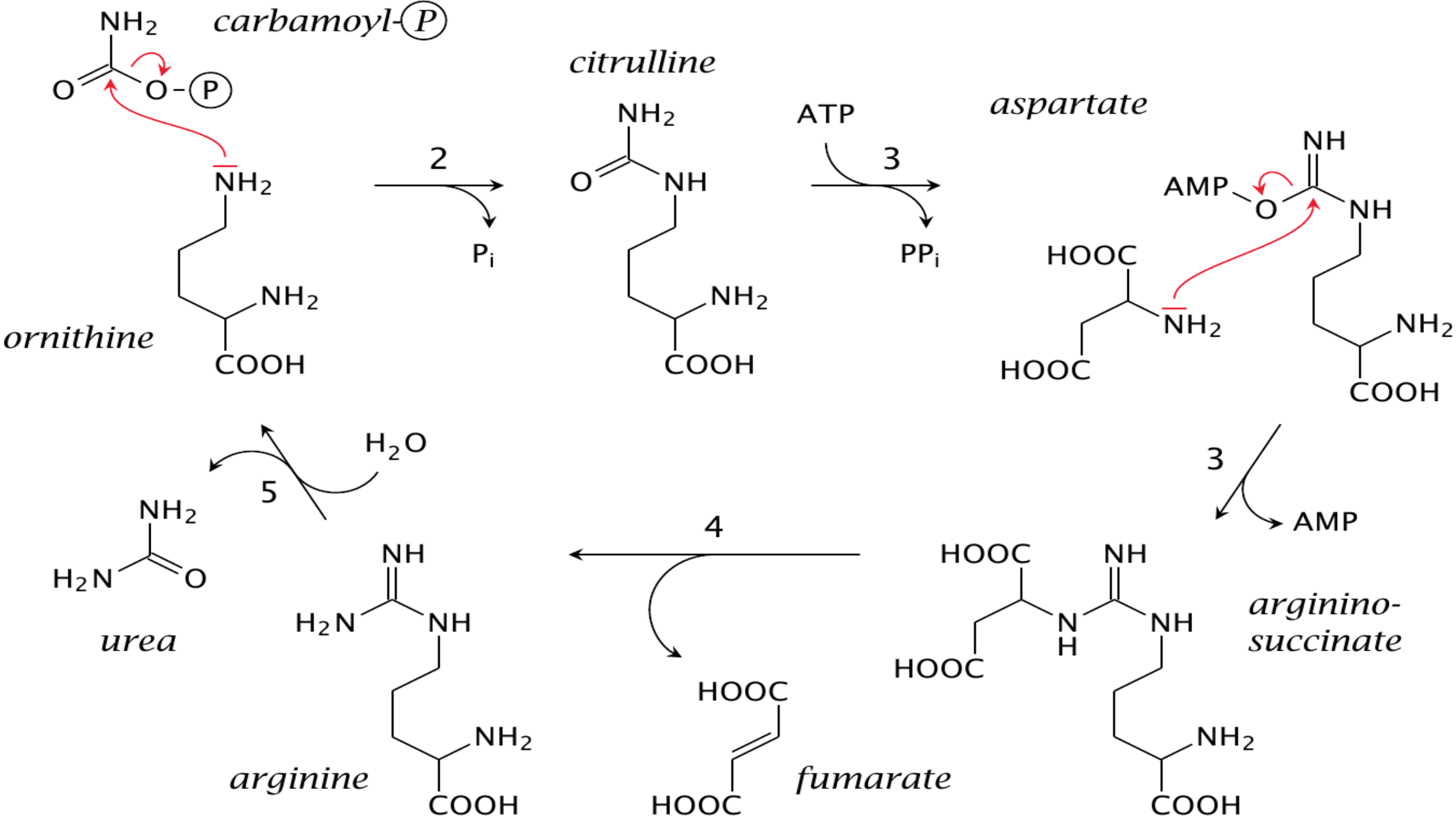
Carbamic acid



phosphorylation



Carbamoyl phosphate


carbamoyl-P
ornithine
2
Pi
citrulline
ATP
3
PPi
aspartate
AMP
3
AMP
arginino-
succinate
4
fumarate
arginine
5
H2O
urea

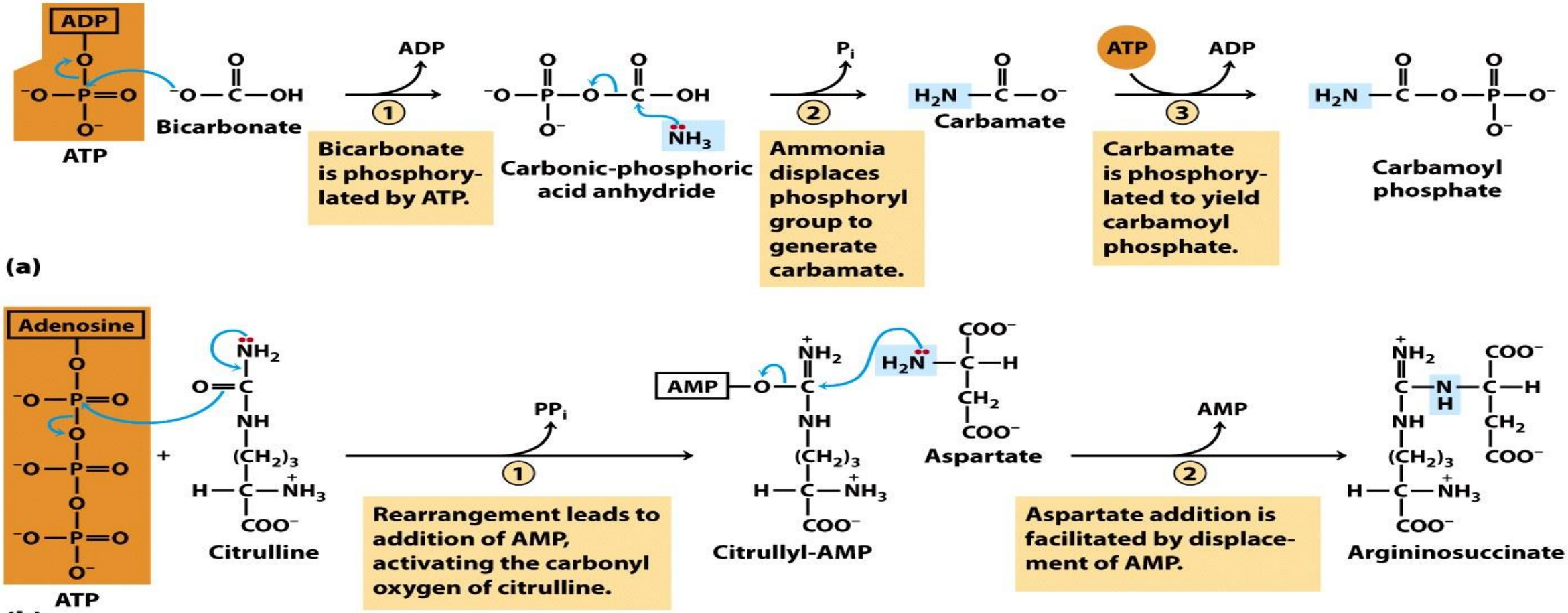
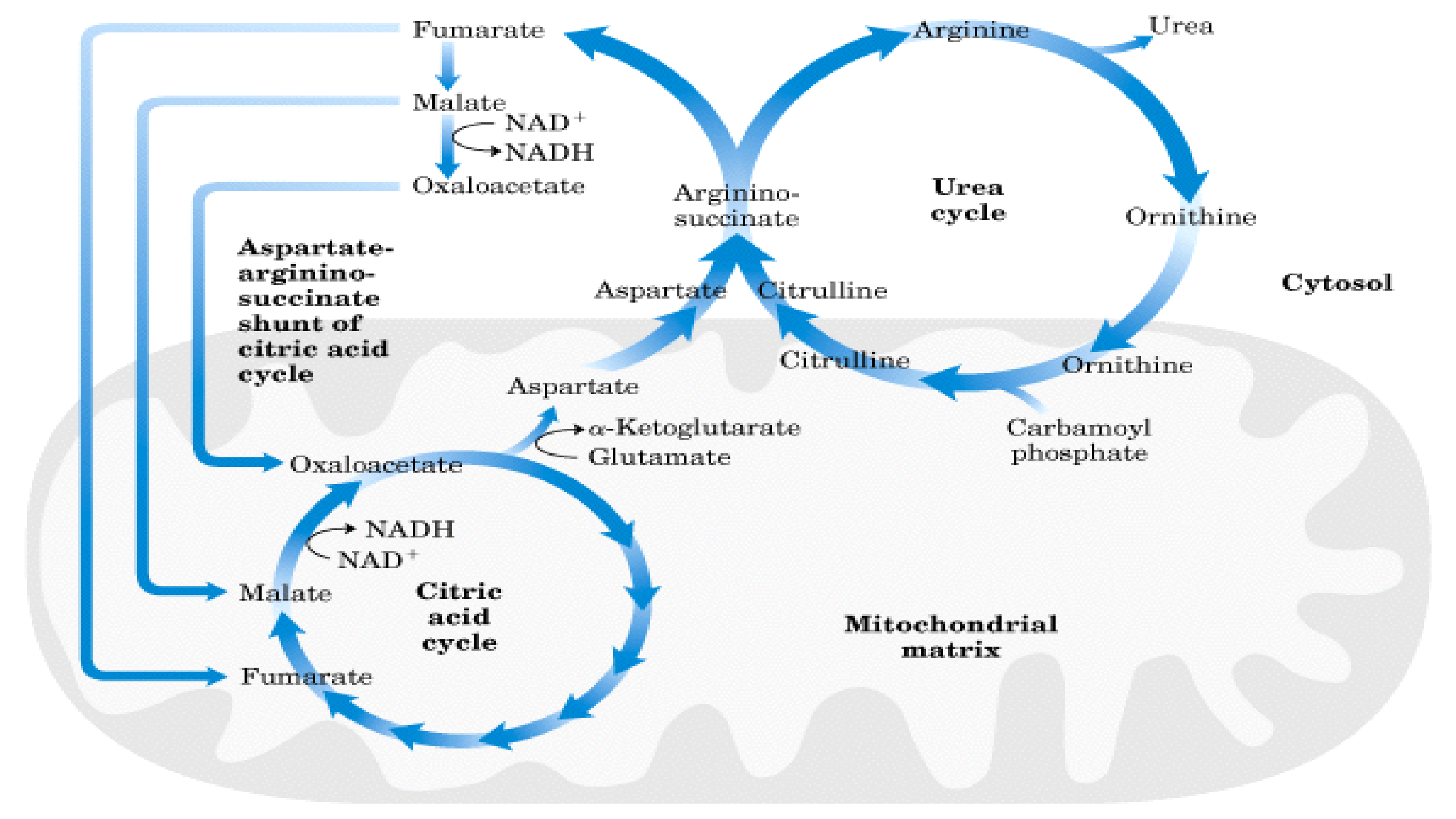
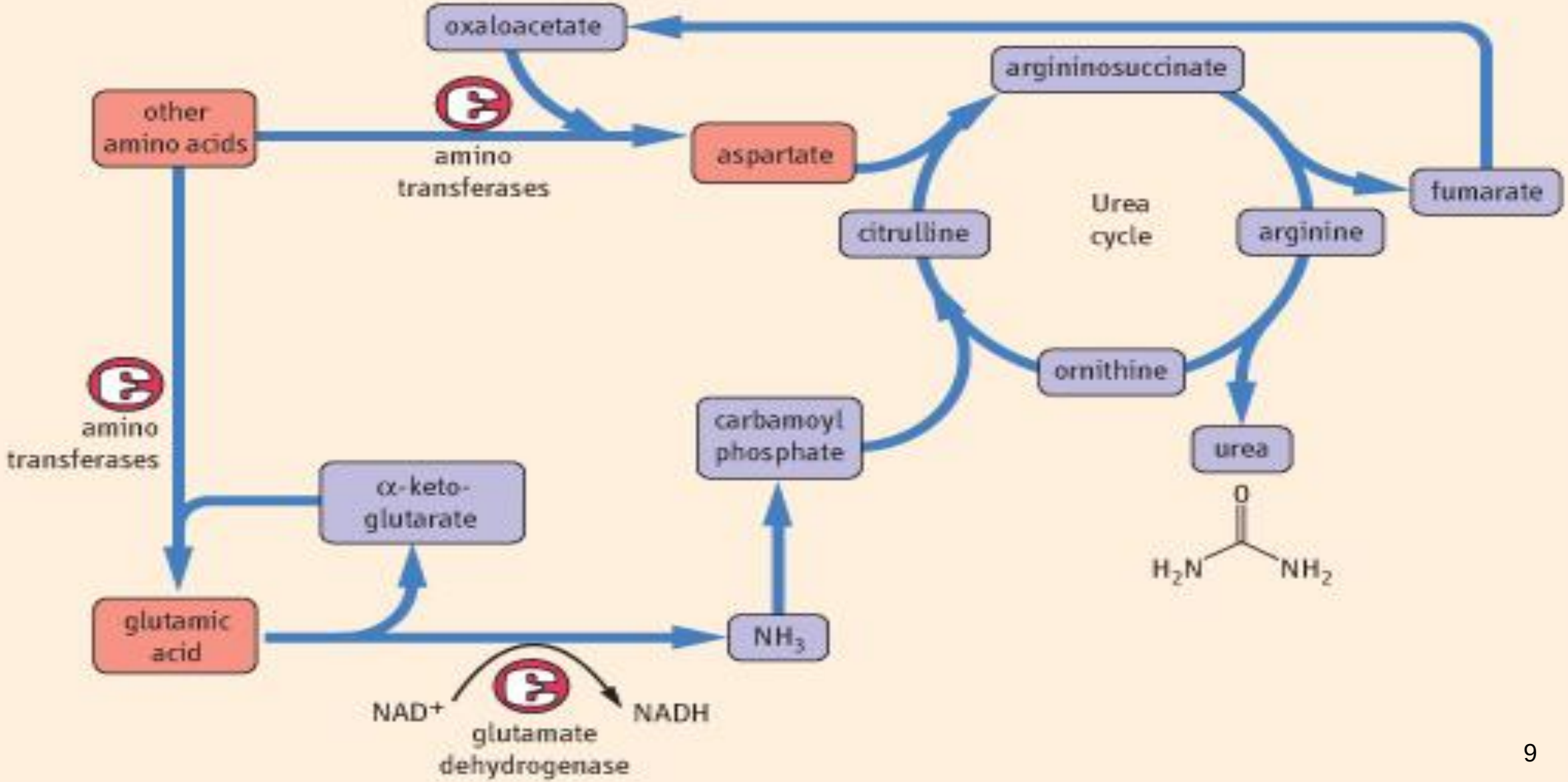


Figure 18-11
Lehninger Principles of Biochemistry, Fifth Edition

Nitrogen-acquiring reactions in the synthesis of urea. The urea nitrogens are acquired in two reactions, each requiring ATP. (a) In the reaction catalyzed by carbamoyl phosphate synthetase I, the first 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). (b) In the reaction catalyzed by argininosuccinate synthetase, the second nitrogen enters from aspartate. Activation of the ureido oxygen of citrulline in step 1 sets up the addition of aspartate in step 2.


Fumarate
Malate
NAD+
NADH
Oxaloacetate
Arginine
Urea
Arginino-
succinate
Urea
cycle
Ornithine
Aspartate-
arginino-
succinate
shunt of
citric acid
cycle
Aspartate
Citrulline
Cytosol
Citrulline
Ornithine
Aspartate
α-Ketoglutarate
Glutamate
Carbamoyl
phosphate
Oxaloacetate
NADH
NAD+
Malate
Citric
acid
cycle
Mitochondrial
matrix
Fumarate

Sources of nitrogen atoms for 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 NH_3, and the other nitrogen by aspartate.

[Note: Glutamate is the immediate precursor of both ammonia (through oxidative deamination by glutamate dehydrogenase) and aspartate nitrogen (through transamination of oxaloacetate by AST).]

- The carbon and oxygen of urea are derived from CO_2. Urea is produced by the liver, and then is transported in the blood to the kidneys for excretion in the urine.

Reactions of the cycle

- The first two reactions leading to the synthesis of urea occur in the mitochondria, whereas the remaining cycle enzymes are located in the cytosol

- Formation of carbamoyl phosphate: Formation of carbamoyl phosphate by carbamoyl phosphate synthetase I is driven by cleavage of two molecules of ATP.

Ammonia incorporated into carbamoyl phosphate is provided primarily by the oxidative deamination of glutamate by mitochondrial glutamate dehydrogenase

- Carbamoyl phosphate synthetase I requires N-acetylglutamate as a positive allosteric activator

Formation of citrulline

- Ornithine and citrulline are basic amino acids that participate in the urea cycle.
- (They are not incorporated into cellular proteins, because there are no codons for these amino acids)
- Ornithine is regenerated with each turn of the urea cycle, much in the same way that oxaloacetate is regenerated by the reactions of the citric acid cycle

Synthesis of argininosuccinate

Citrulline condenses with aspartate to form argininosuccinate. The α-amino group of aspartate provides the second nitrogen that is ultimately incorporated into urea. ATP to adenosine monophosphate (AMP) and pyrophosphate. This is the third and final molecule of ATP consumed in the formation of urea

Cleavage of argininosuccinate

Argininosuccinate is cleaved to yield arginine and fumarate. The arginine formed by this reaction serves as the immediate precursor of urea.

- Fumarate produced in the urea cycle is hydrated to malate, providing a link with several metabolic pathways.

- For example, the malate can be transported into the mitochondria via the malate shuttle and reenter the tricarboxylic acid cycle. Alternatively, cytosolic malate can be oxidized to oxaloacetate, which can be converted to aspartate

Cleavage of arginine to ornithine and urea

Arginase cleaves arginine to ornithine and urea, and occurs almost exclusively in the liver.

Fate of urea:

Urea diffuses from the liver, and is transported in the blood to the kidneys, where it is filtered and excreted in the urine. A portion of the urea diffuses from the blood into the intestine, and is cleaved to CO_2 and NH_3 by bacterial urease.

- This ammonia is partly lost in the feces, and is partly reabsorbed into the blood. In patients with kidney failure, plasma urea levels are elevated, promoting a greater transfer of urea from blood into the gut.

The intestinal action of urease on this urea becomes a clinically important source of ammonia, contributing to the hyperammonemia often seen in these patients. Oral administration of neomycin[1] reduces the number of intestinal bacteria responsible for this NH_3 production.

- **Four high-energy phosphates are consumed in the synthesis of each molecule of urea:**

two ATP are needed to restore two ADP to two ATP, plus two to restore AMP to ATP. Therefore, the synthesis of urea is irreversible, with a large, negative ΔG

Regulation of the urea cycle

N-Acetylglutamate is an essential activator for carbamoyl phosphate synthetase I—the rate-limiting step in the urea cycle N-Acetylglutamate is synthesized from acetyl coenzyme A and glutamate by N-acetylglutamate synthase in a reaction for which arginine is an activator.

- Therefore, the intrahepatic concentration of N-acetylglutamate increases after ingestion of a protein-rich meal, which provides both the substrate (glutamate) and the regulator of N-acetylglutamate synthesis. This leads to an increased rate of urea synthesis.

Metabolism of Ammonia

Transport of ammonia to liver(glucose-alanine cycle)

Sources of ammonia:

Liver(Transdeamination)

Renal/Intestinal (glutaminase)

Bacterial urease

Amines (hormones/neurotransmittors)

Purines/Pyrimidines

Transport of ammonia in circulation (urea)(glutamine)


Thank you for attention