UREA CYCLE

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AMINO ACID OXIDATION AND THE PRODUCTION OF UREA

- In animals, amino acids undergo oxidative degradation in three different metabolic circumstances:

- 1. some amino acids that are released from protein breakdown and are not needed for new protein synthesis undergo oxidative degradation.

- 2. When a diet is rich in protein and the ingested amino acids exceed the body's needs for protein synthesis, the surplus is catabolized; amino acids cannot be stored.

- 3. During starvation or in uncontrolled diabetes mellitus, cellular proteins are used as fuel.

- Under all these metabolic conditions, amino acids lose their amino groups to form -keto acids, the "carbon skeletons" of amino acids.
- The -keto acids undergo oxidation to CO٢

and H2O or,

can be converted by gluconeogenesis into glucose, the fuel for brain, skeletal muscle, and other tissues.

- every amino acid contains:
- an amino group, and
- the carbon skeleton
- the -amino group is separated from carbon skeleton and shunted into the pathways of amino group metabolism

Metabolic Fates of Amino Groups

- Amino acids derived from dietary protein are the source of most amino groups.
- Most amino acids are metabolized in the liver.
- Some of the ammonia generated in this process is recycled and used in a variety of biosynthetic pathways;
- the excess is either excreted directly or converted to urea for excretion

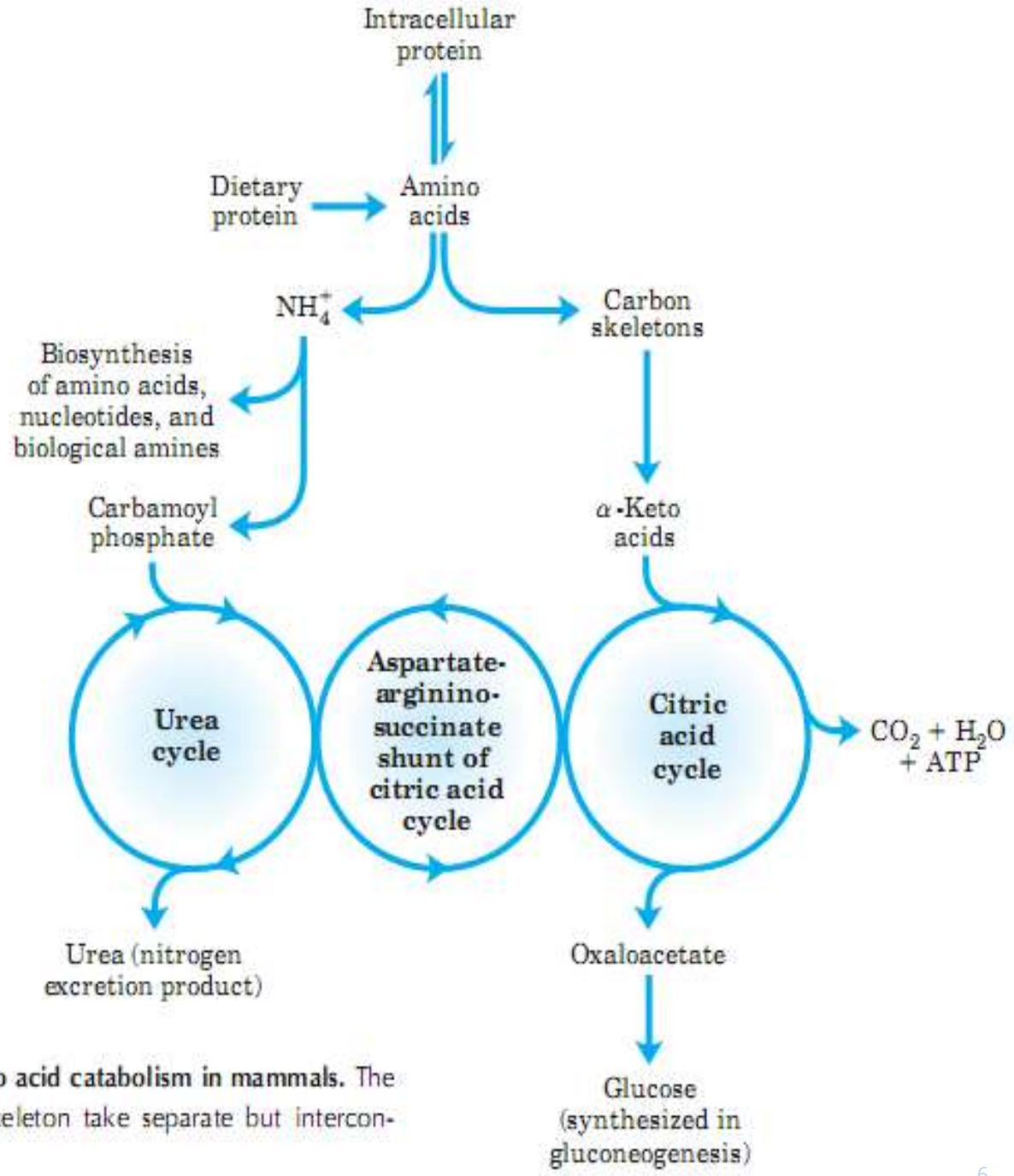
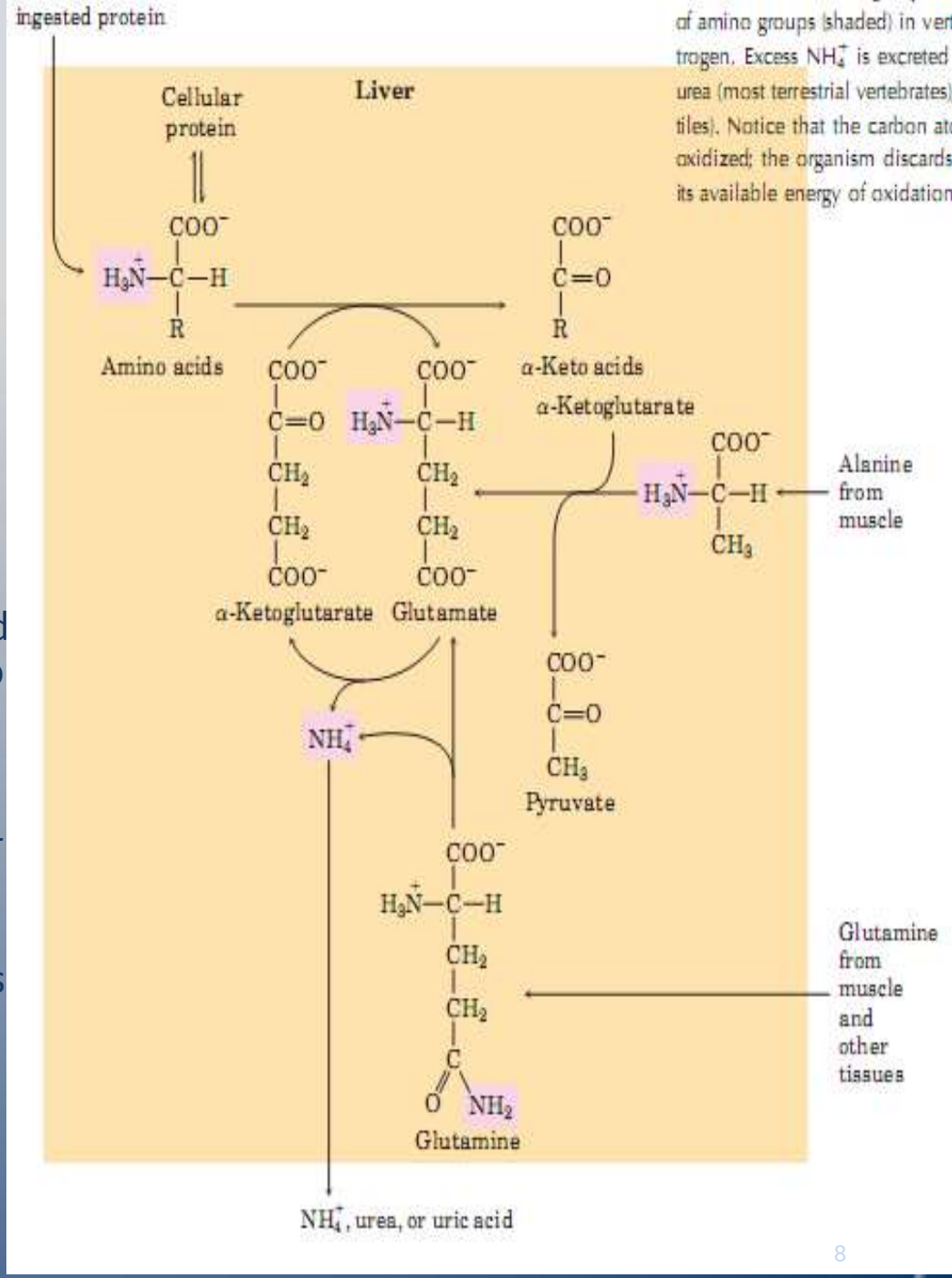


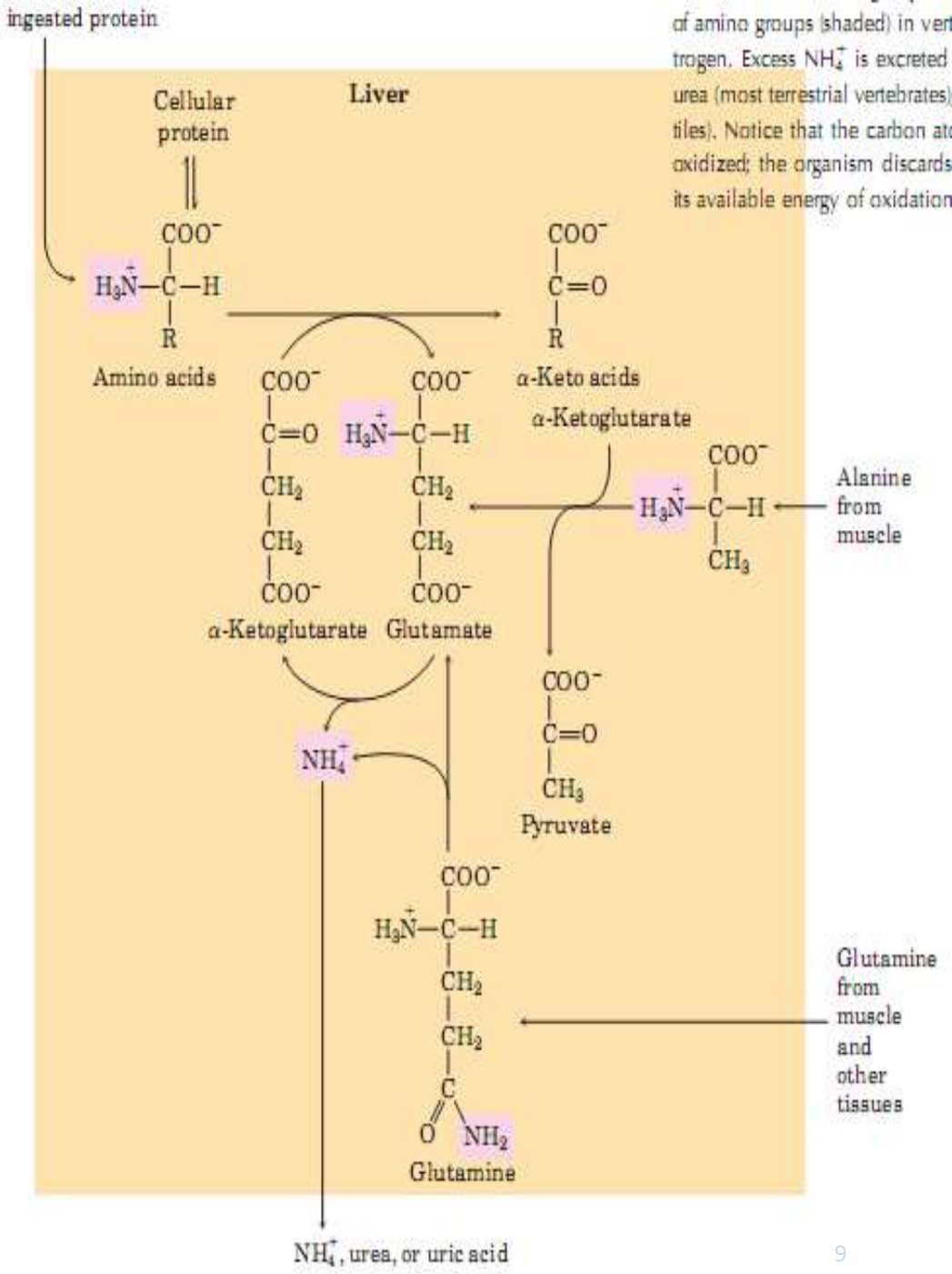
FIGURE 18–1 Overview of amino acid catabolism in mammals. The amino groups and the carbon skeleton take separate but interconnected pathways.

- Excess ammonia generated in other (extrahepatic) tissues travels to the liver (in the form of amino groups, for conversion to the excretory form.
- Glutamate and glutamine play especially critical roles in nitrogen metabolism, acting as a kind of general collection point for amino groups.

- In the cytosol of hepatocytes, amino groups are transferred to -ketoglutarate to form glutamate, which enters mitochondria and gives up its amino group to form NH_4
- Excess ammonia generated in most other tissues is converted to the amide nitrogen of glutamine, which passes to the liver, then into liver mitochondria



- In skeletal muscle, excess amino groups are generally transferred to pyruvate to form alanine, another important molecule in the transport of amino groups to the liver.



Glutamate Releases Its Amino Group as Ammonia in the Liver

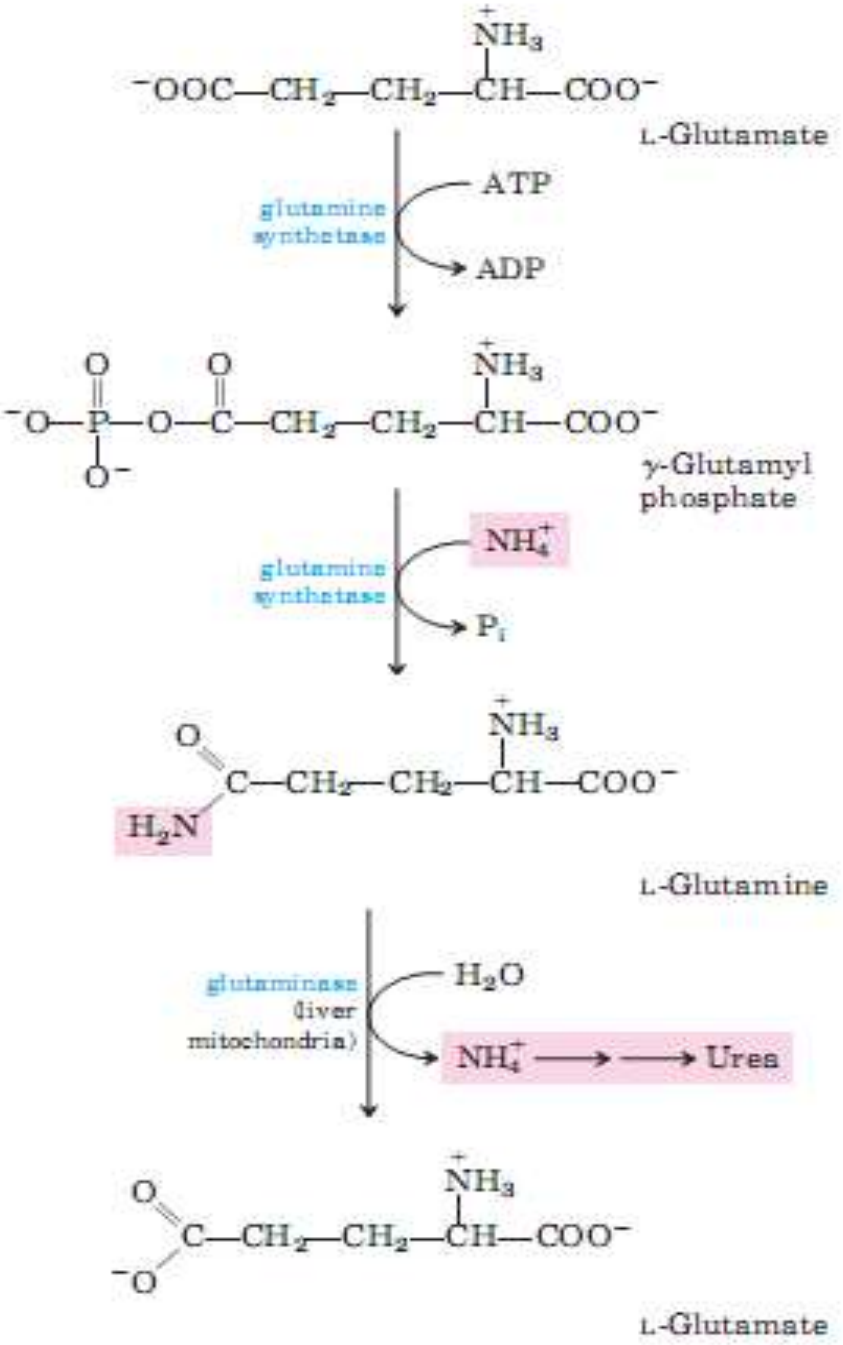
- the amino groups from many of the -amino acids are collected in the liver in the form of the amino group of L-glutamate molecules.
- In hepatocytes, glutamate is transported from the cytosol into mitochondria, where it undergoes **oxidative deamination catalyzed by Lglutamate dehydrogenase**
- The -ketoglutarate formed from glutamate deamination can be used in the citric acid cycle and for glucose synthesis.

Glutamine Transports Ammonia in the Bloodstream

In many tissues, including the brain, some processes such as nucleotide degradation generate free ammonia.

The free ammonia produced in tissues is combined with glutamate to yield glutamine by the action of **glutamine synthetase.**

First, glutamate and ATP react to form ADP and a -glutamyl phosphate intermediate, which then reacts with ammonia to produce glutamine and inorganic phosphate



Alanine Transports Ammonia from Skeletal Muscles to the Liver

- In muscle and certain other tissues that degrade amino acids for fuel, amino groups are collected in the form of glutamate by transamination

- In the cytosol of hepatocytes, alanine aminotransferase transfers the amino group from alanine to -ketoglutarate, forming pyruvate and glutamate. Glutamate can then enter mitochondria, where the glutamate dehydrogenase reaction releases NH_4

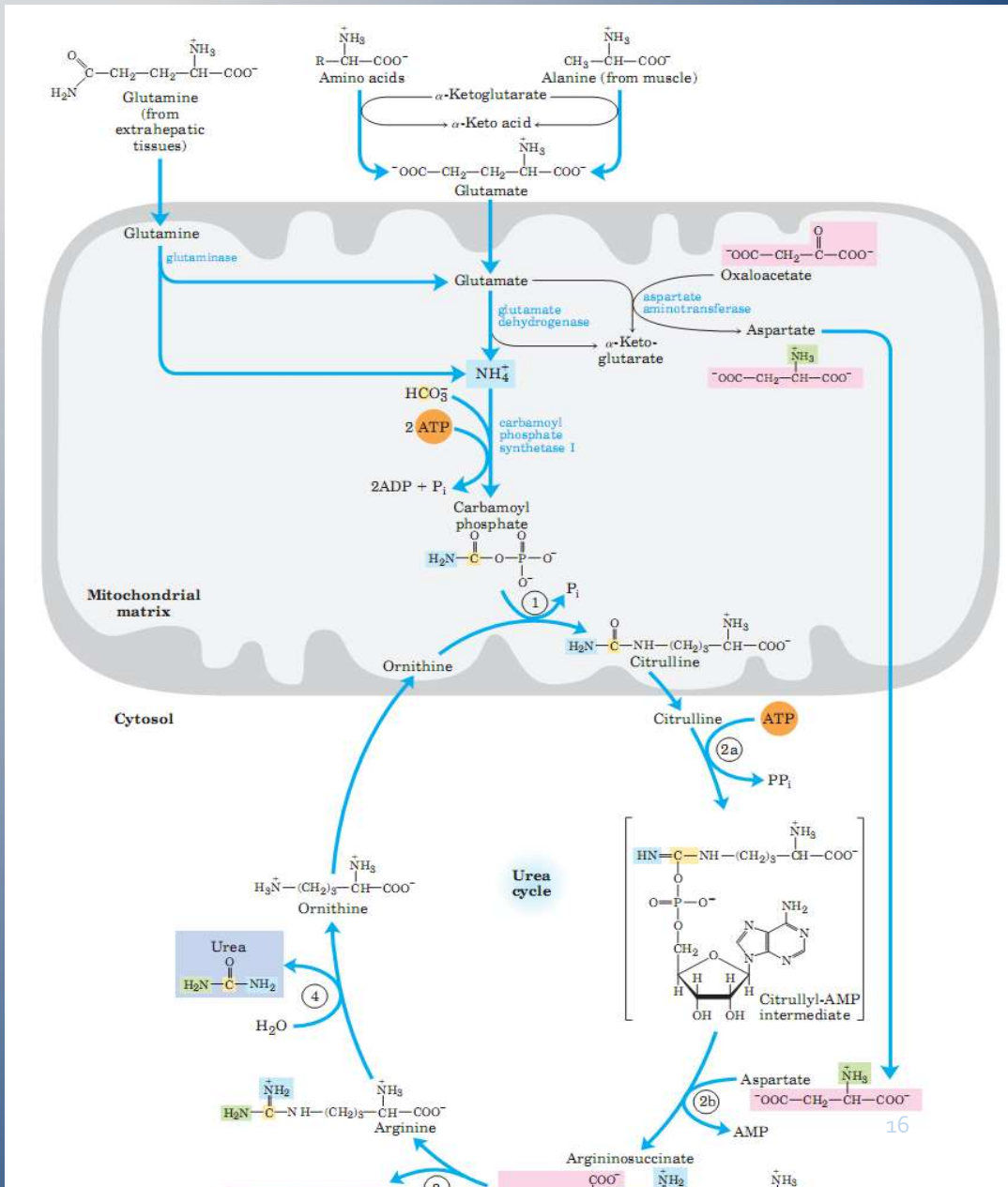
Nitrogen Excretion and the Urea Cycle

- If not reused for the synthesis of new amino acids or other nitrogenous products, amino groups are channeled into a single excretory end product .
- In ureotelic organisms, the ammonia deposited in the mitochondria of hepatocytes is converted to urea in the **urea cycle.**

- This pathway was discovered in 1932 by Hans Krebs (who later also discovered the citric acid cycle) and a medical student associate, Kurt Henseleit.
- Urea production occurs almost exclusively in the liver and is the fate of most of the ammonia channeled there. The urea passes into the bloodstream and thus to the kidneys and is excreted into the urine.

Urea Is Produced from Ammonia in Five Enzymatic Steps

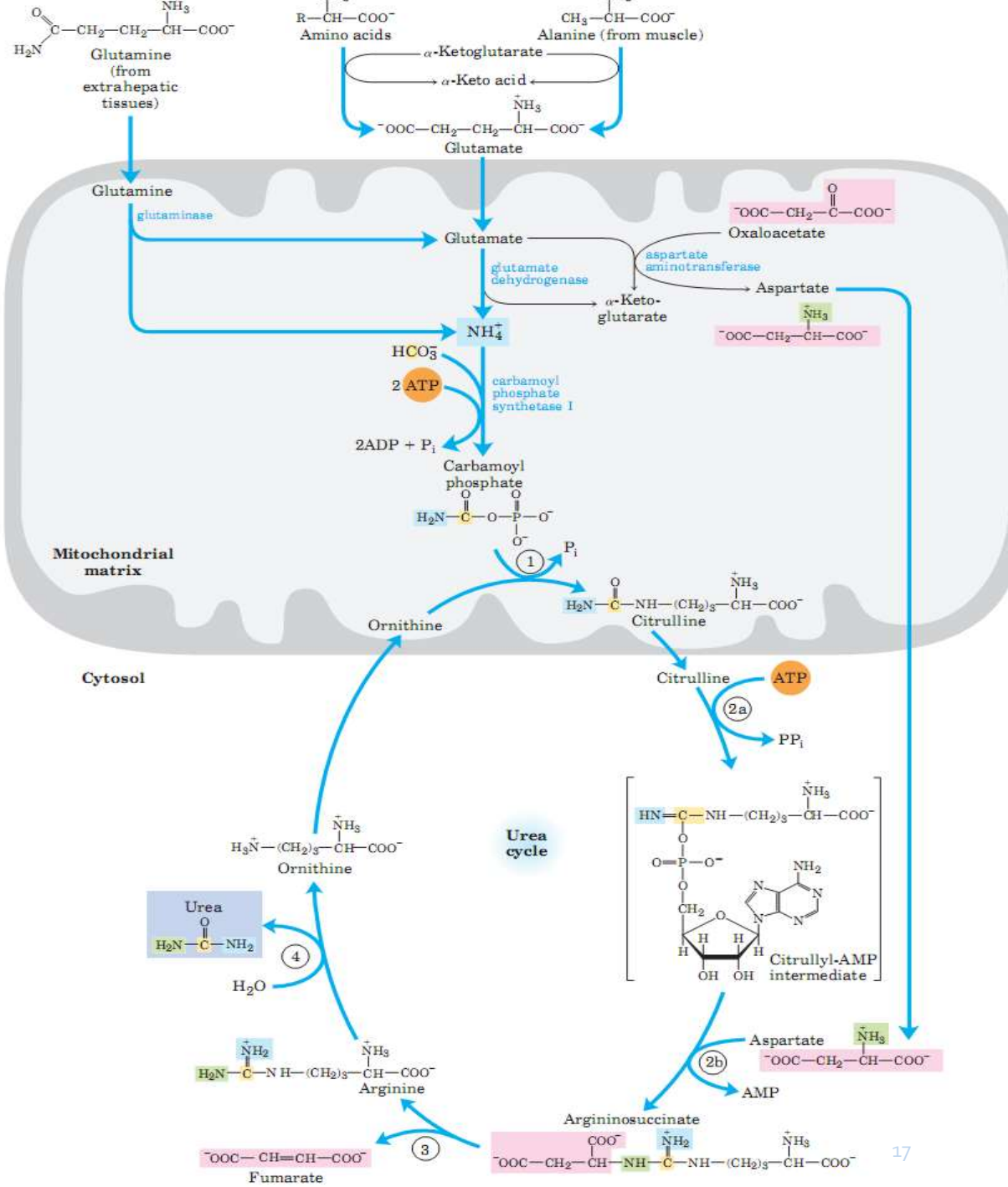
- The urea cycle begins inside liver mitochondria, but three of the subsequent steps take place in the cytosol
- The first amino group to enter the urea cycle is derived from ammonia in the mitochondrial
- The liver also receives some ammonia via the portal vein from the intestine, from the bacterial oxidation of amino acids.
- 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,**



The cycle has four enzymatic steps.

step 1 : carbamoyl phosphate donates its carbamoyl group to ornithine to form citrulline, with the release of P

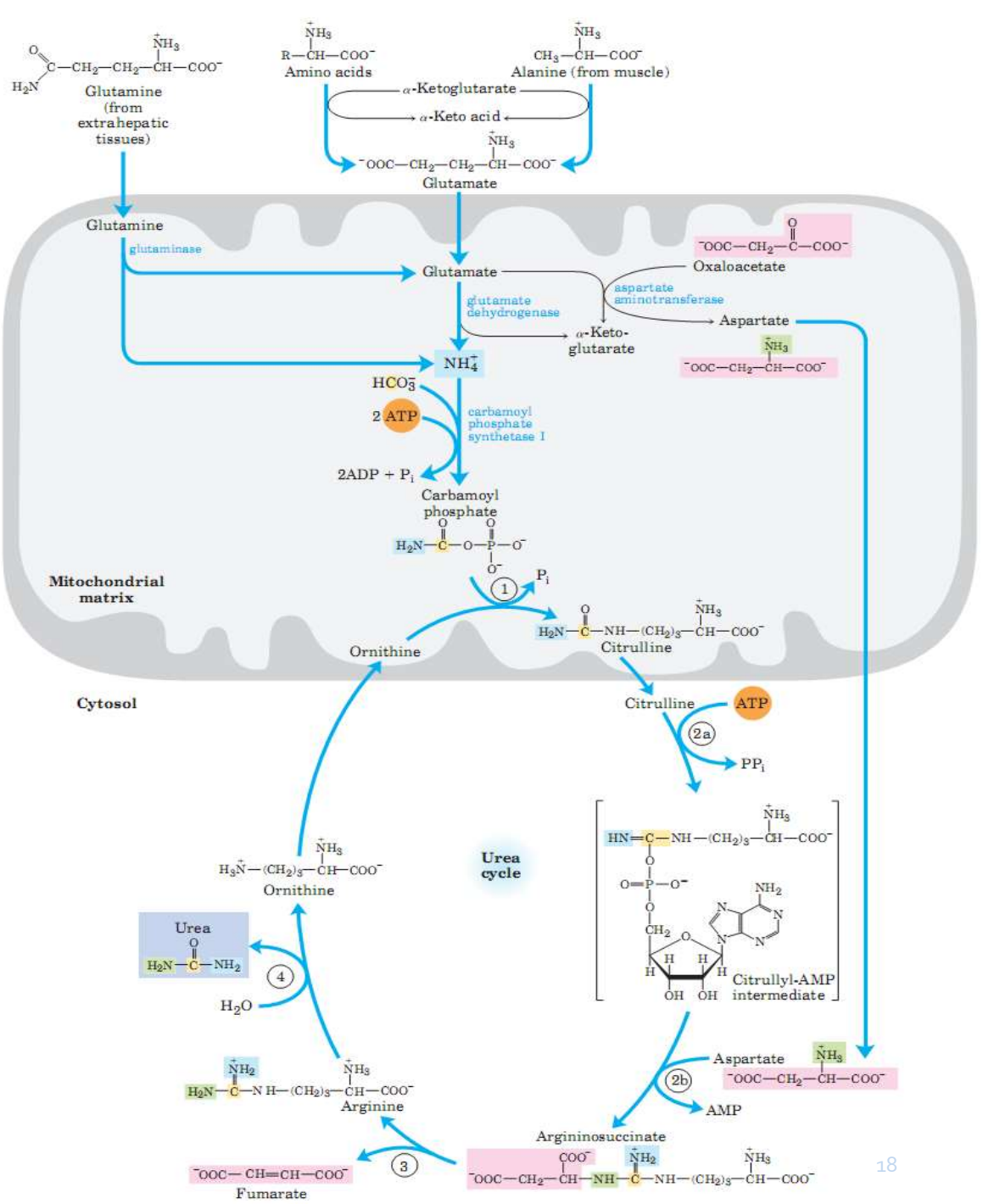
The reaction is catalyzed by **ornithine transcarbamoylase, and the citrulline passes from the mitochondrion to the cytosol.**



step 2: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 (carbonyl) group of citrulline, forming argininosuccinate

catalyzed by **argininosuccinate** synthetase



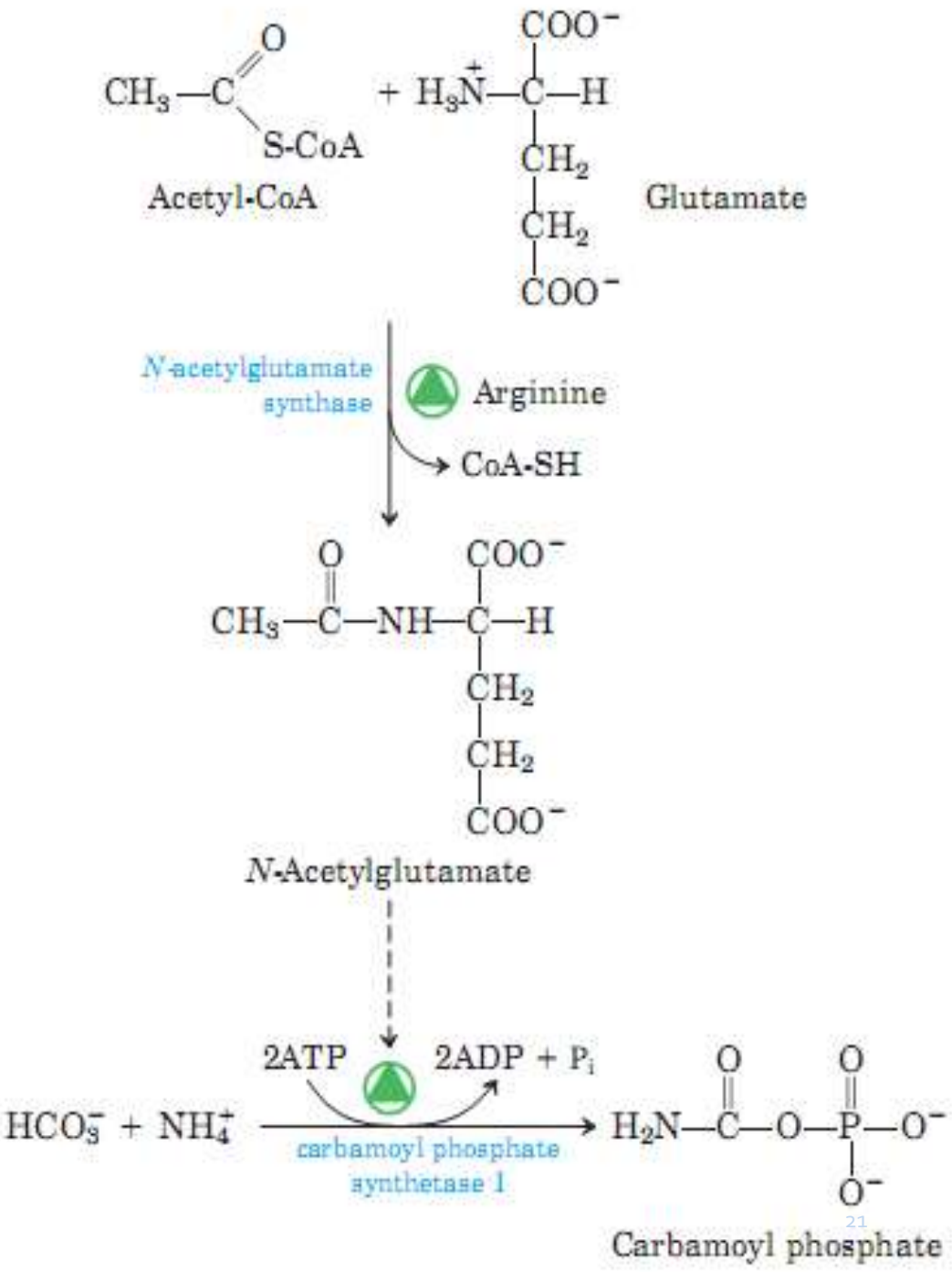
- **step 3:**The argininosuccinate is then cleaved by **argininosuccinase to form free arginine and fumarate,**
- (step 4),: **arginase cleaves arginine to yield urea and ornithine.**
- **Ornithine is transported into the mitochondrion to initiate another round of the urea cycle.**

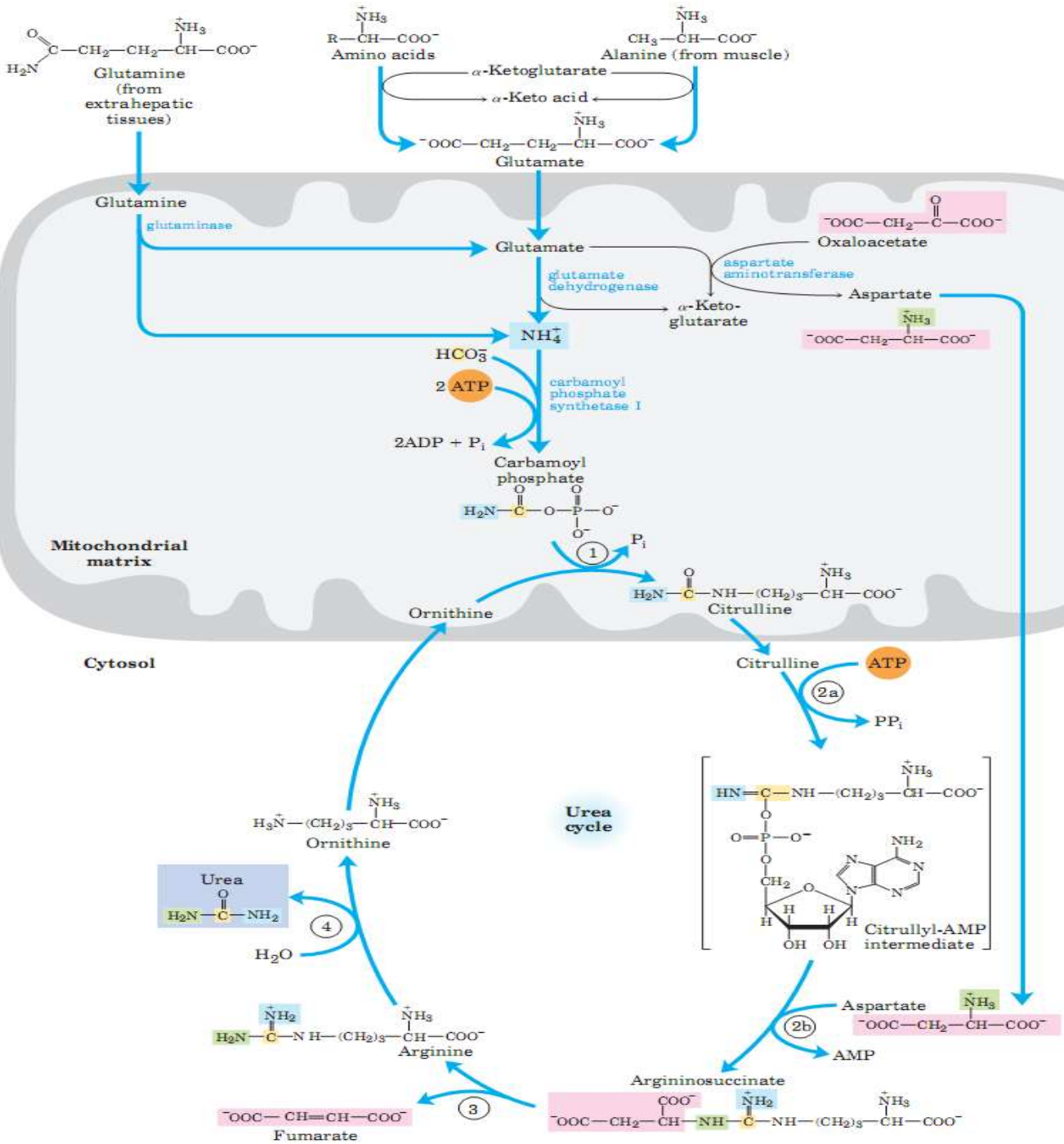
- The citrulline transported out of the mitochondrion is not diluted into the general pool of metabolites in the cytosol but is passed directly to the active site of argininosuccinate synthetase. This channeling between enzymes continues for argininosuccinate, arginine, and ornithine. Only urea is released into the general cytosolic pool of metabolites.

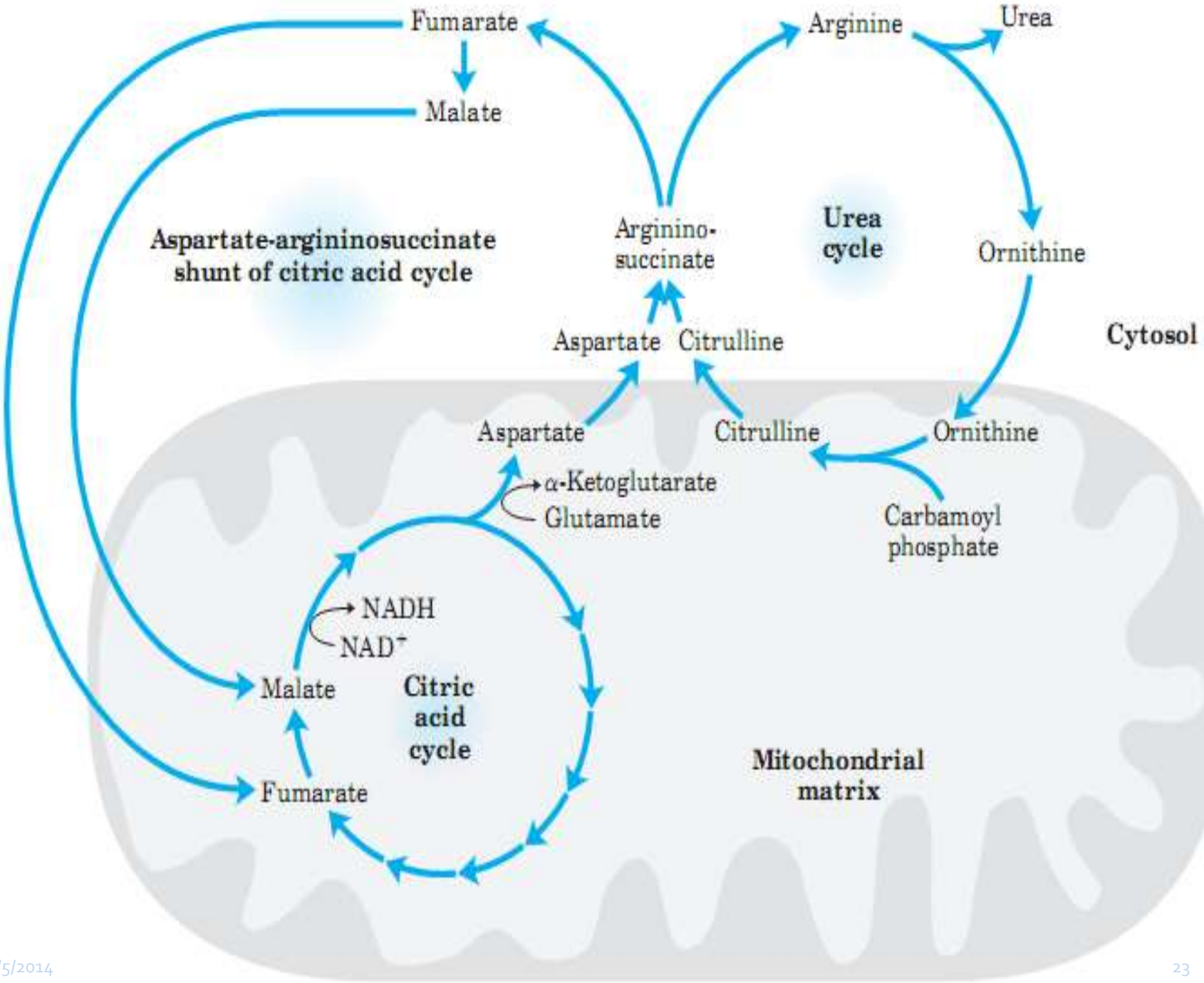
The Activity of the Urea Cycle Is Regulated at Two Levels

The first enzyme in the pathway, carbamoyl phosphate synthetase I, is allosterically activated by ***N-acetylglutamate, which is synthesized from acetylCoA and glutamate by N-acetylglutamate synthase***

arginine (an activator of *N-acetylglutamate synthase, and thus an activator of the urea cycle).*




Glutamine
(from extrahepatic tissues)
Amino acids
α-Ketoglutarate
α-Keto acid
Alanine (from muscle)
Glutamate
Glutamine
glutaminase
Glutamate
Oxaloacetate
aspartate aminotransferase
glutamate dehydrogenase
α-Keto-glutarate
Aspartate
NH4+
HCO3−
2 ATP
carbamoyl phosphate synthetase I
2ADP + Pi
Carbamoyl phosphate
Mitochondrial matrix
1
Pi
Ornithine
Citrulline
Cytosol
Citrulline
ATP
2a
PPi
Urea cycle
Citrullyl-AMP intermediate
Ornithine
Urea
4
H2O
Aspartate
2b
AMP
Arginine
Argininosuccinate
3
Fumarate


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

Urea toxicity

- Ammonia increases the transport of tryptophan across the bloodbrain barrier,
- leads to an increased production and release of serotonin.
- glutamine can also be shown to accumulate at high concentrations
- cellular swelling and cerebral oedema.