CHAPTER 18
Amino Acid Oxidation and the Production of Urea

p695

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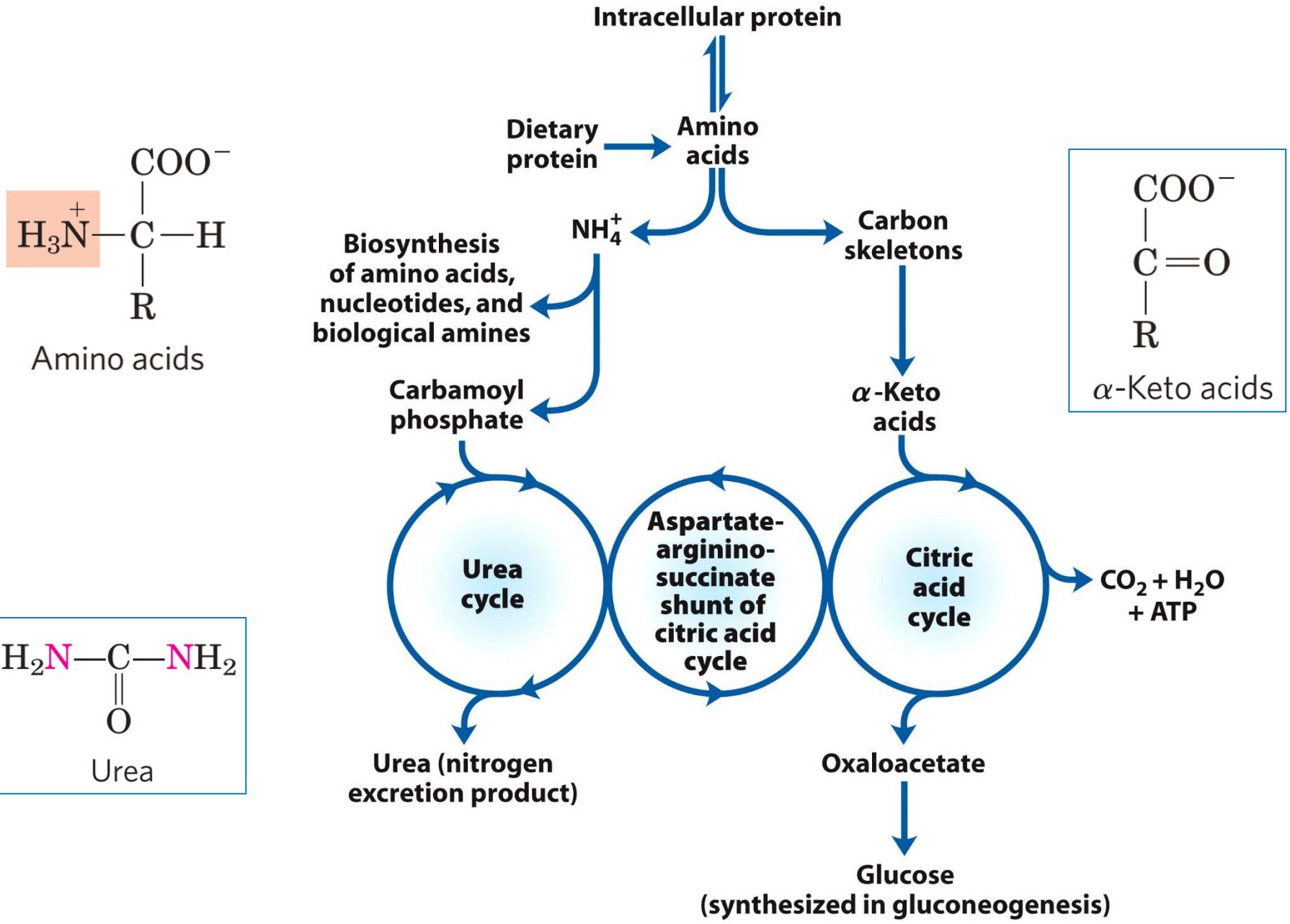
• Oxidative degradation of amino acids occurs-

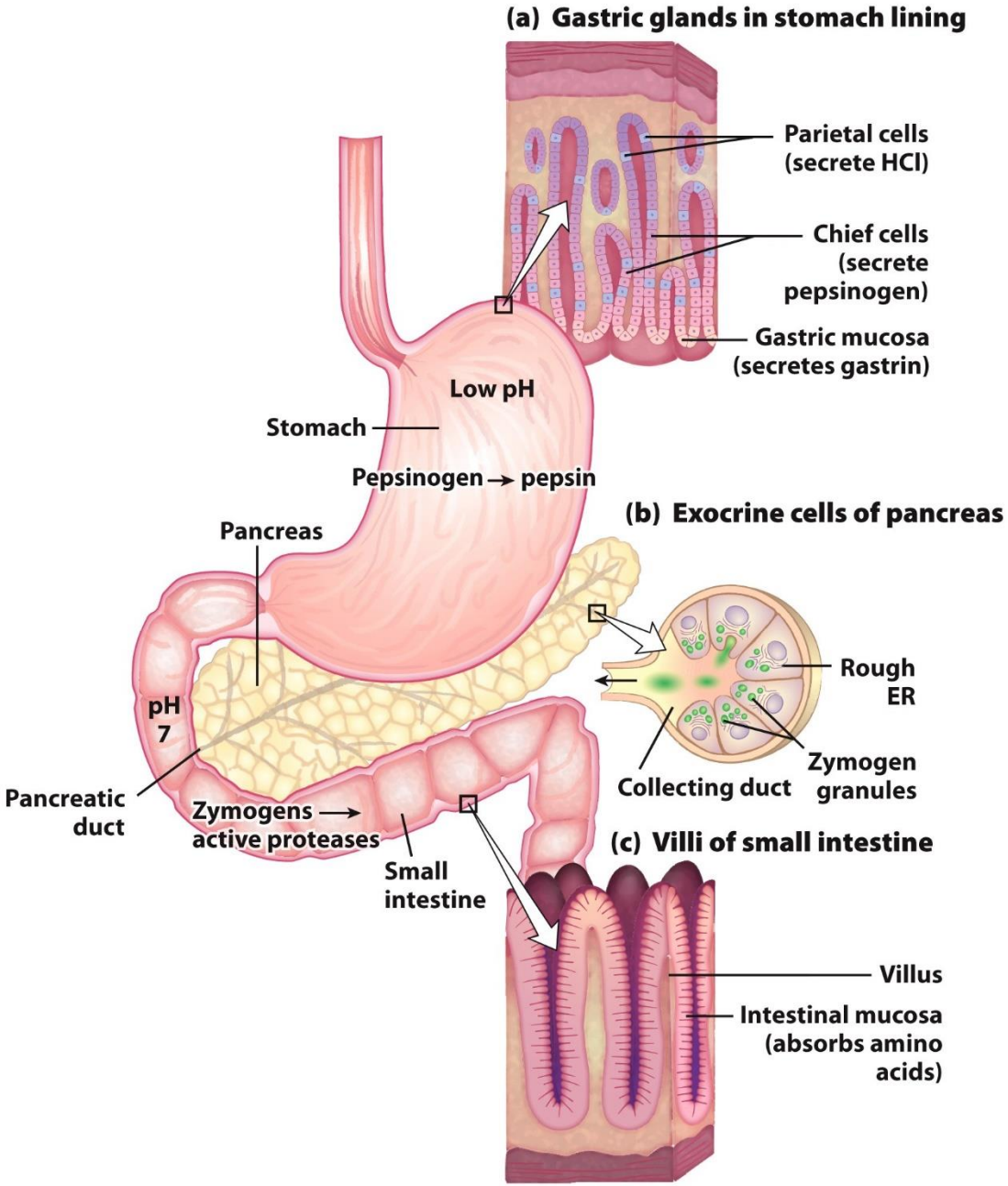
- During the normal synthesis and degradation of cellular proteins, some amino acids that are released from protein breakdown and are not needed for new protein synthesis undergo oxidative degradation.
- When a diet is rich in protein and the ingested amino acids exceed the body's needs for protein synthesis, the surplus is catabolized; amino acids cannot be stored.
- During starvation or in uncontrolled diabetes mellitus, when carbohydrates are either unavailable or not properly utilized, cellular proteins are used as fuel.

- **Overview of amino acid catabolism in mammals.**



18.1 Metabolic Fates of Amino Groups

• Dietary Protein Is Degraded to Amino Acids



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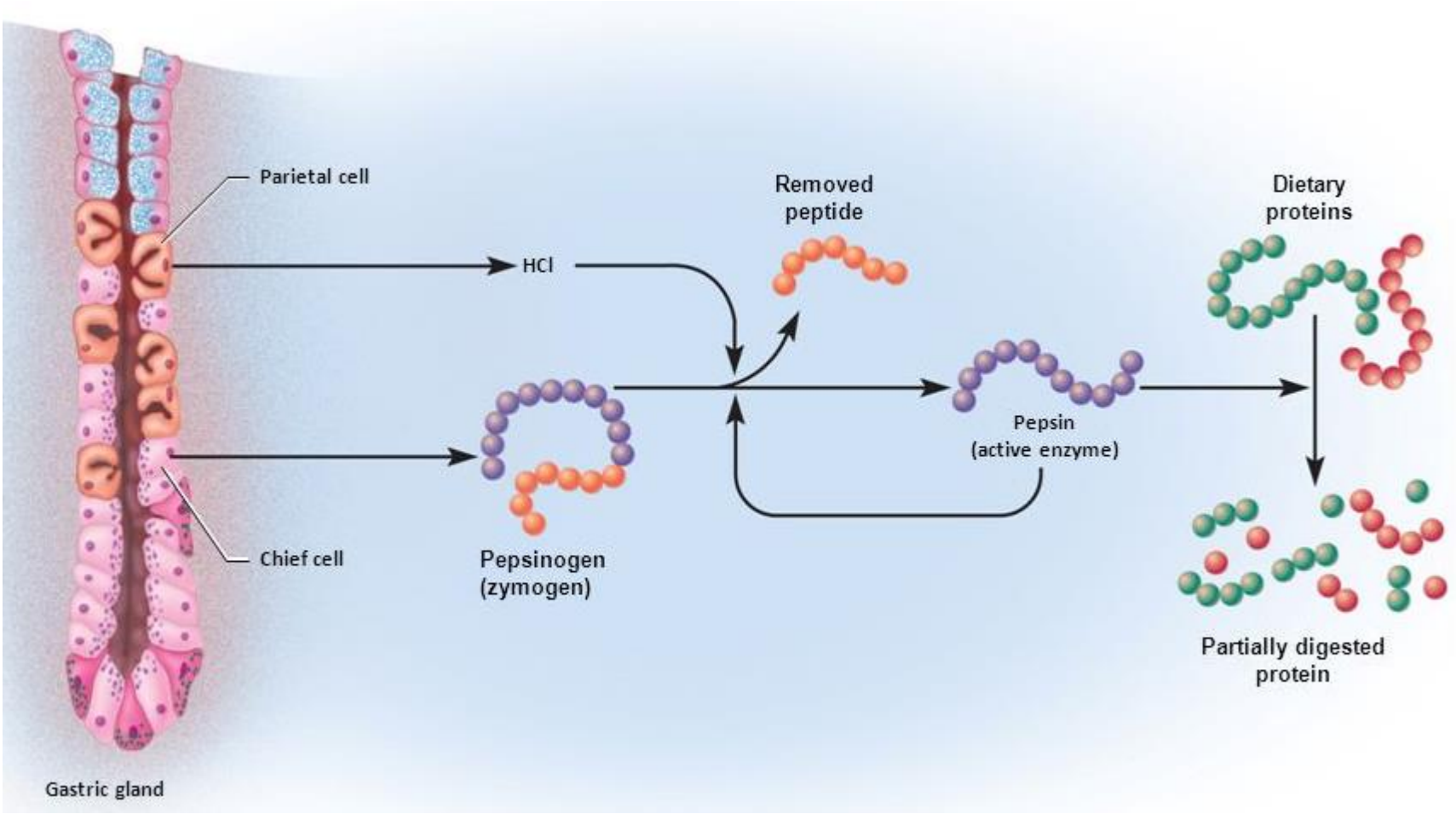

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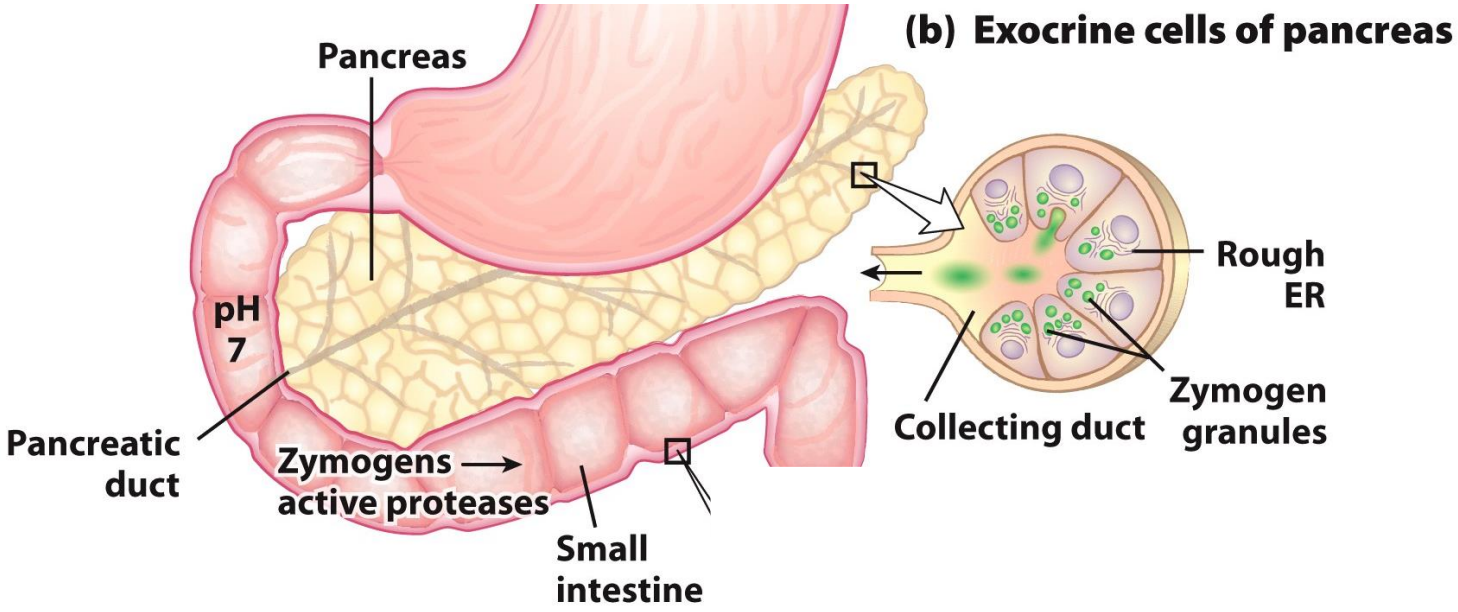


Secretin

↓

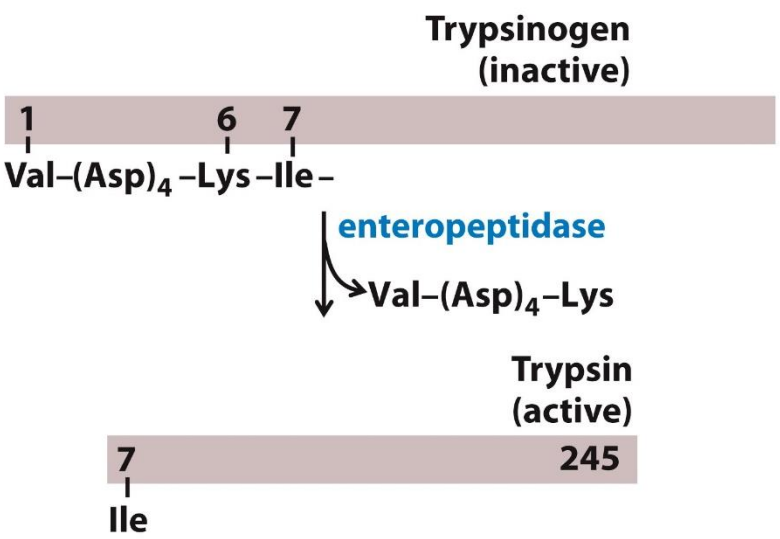
bicarbonate

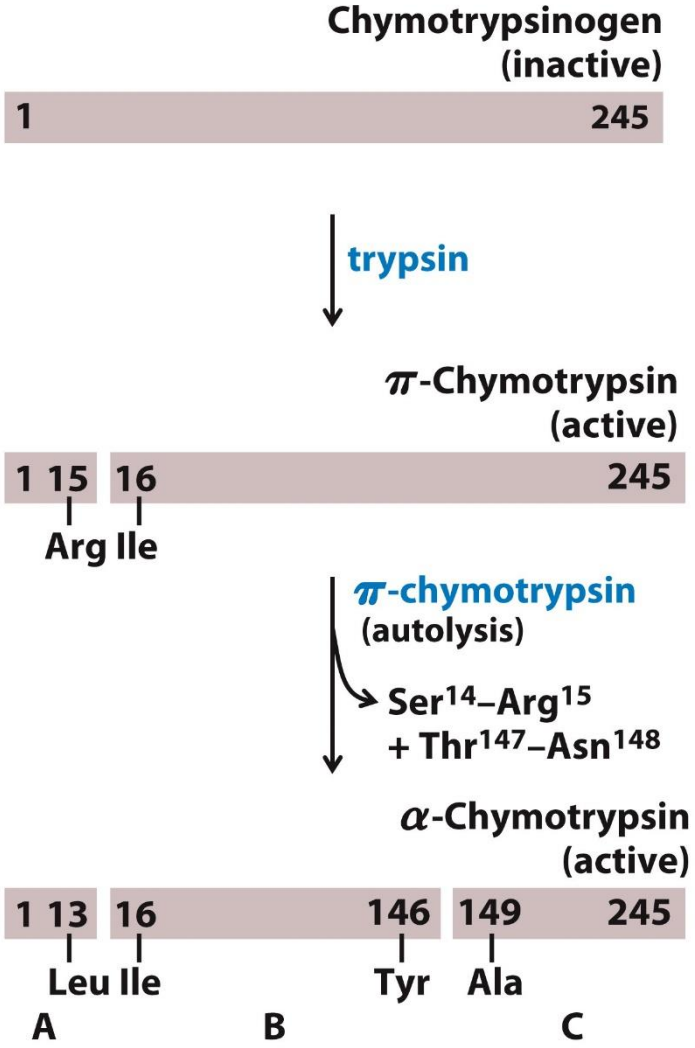
cholecystokinin

↓

Trypsinogen, chymotrypsinogen, procarboxypeptidases A and B

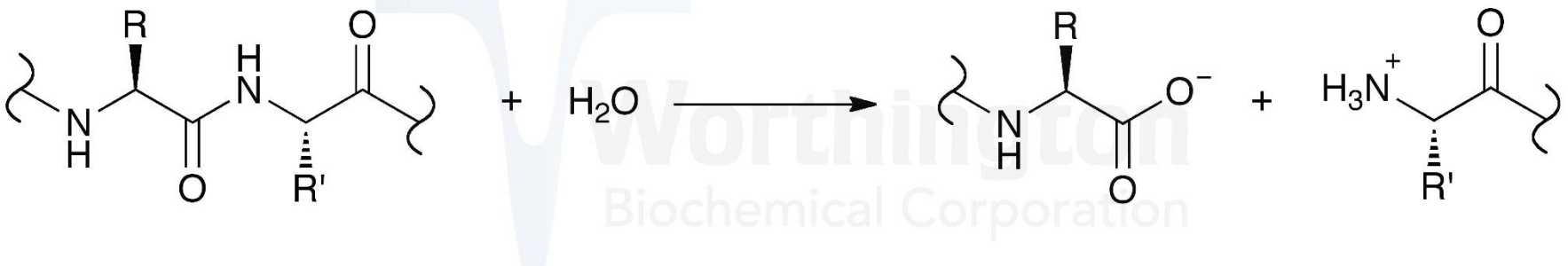
• Activation of zymogens by proteolytic cleavage





Acute pancreatitis

• amino acid specificities of proteases



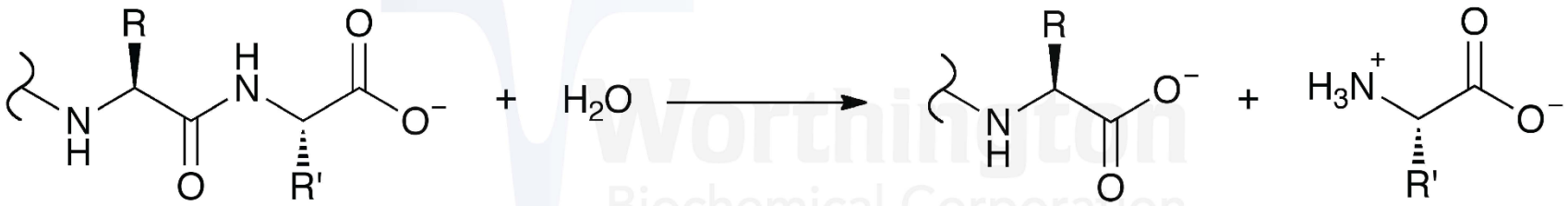
Polypeptide

Polypeptide fragments

Pepsin: R’ = Leu, Phe, Trp, and Tyr

Trypsin: R = Arg and Lys

Chymotrypsin: R=Phe, Trp, Tyr; R’ ≠ Pro



Polypeptide (**n** residues)

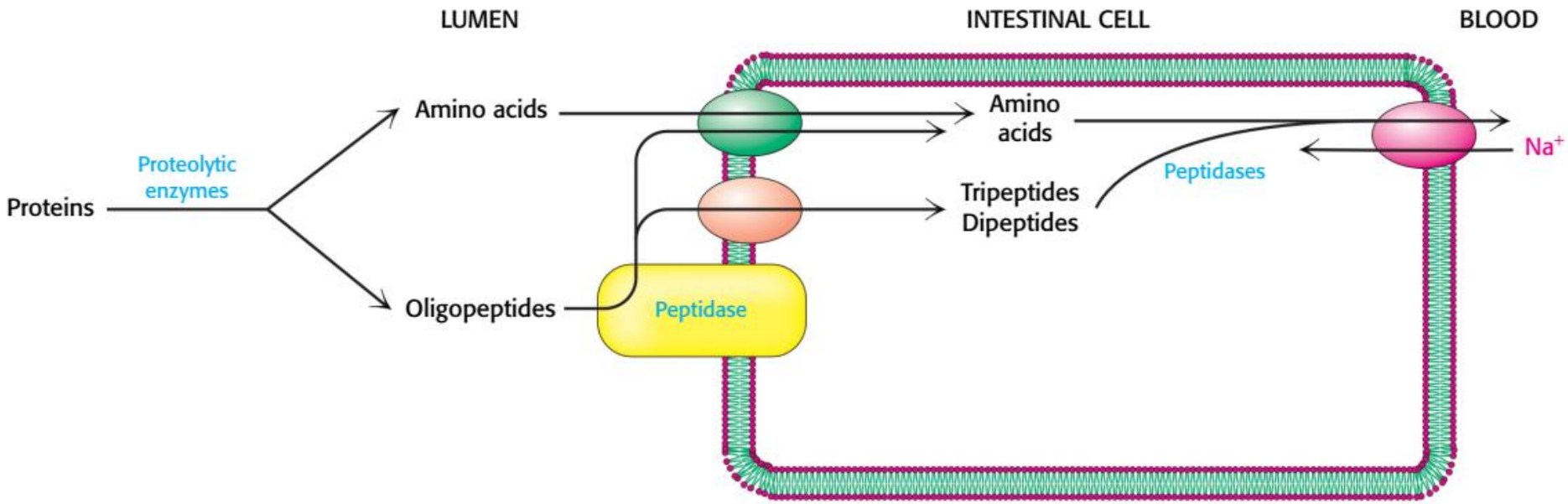
Polypeptide (**n-1** residues)

Amino Acid

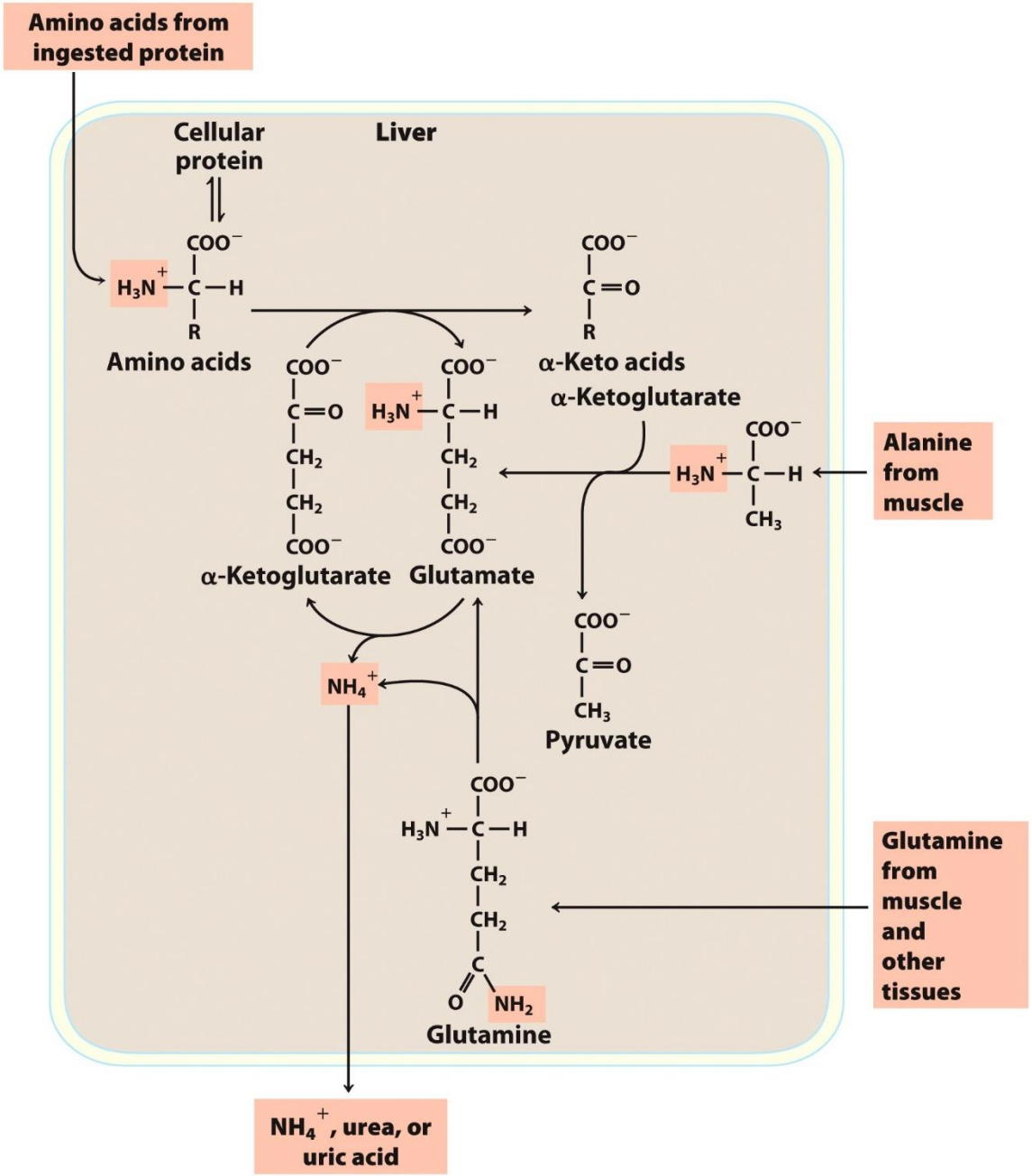
Carboxypeptidase A: R’ = All except Arg, Pro, Lys

Carboxypeptidase B: R’ = Arg and Lys

• Dietary Protein Is Degraded to Amino Acids



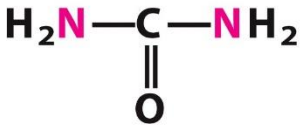
• Amino group catabolism



Aminotransferase
or Transaminase

• Excretory forms of nitrogen

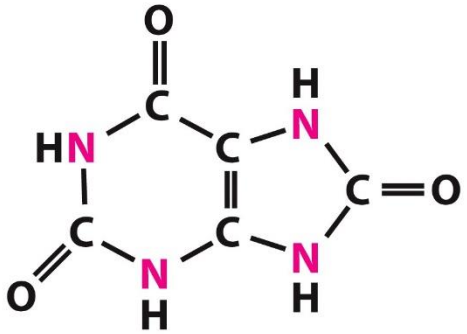
Ammonia (as ammonium ion)



Urea

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

Ureotelic animals: many terrestrial vertebrates; also sharks



Uric acid

Uricotelic animals: birds, reptiles

Figure 18-2b
Lehninger Principles of Biochemistry, Sixth Edition

• Enzyme-catalyzed transamination

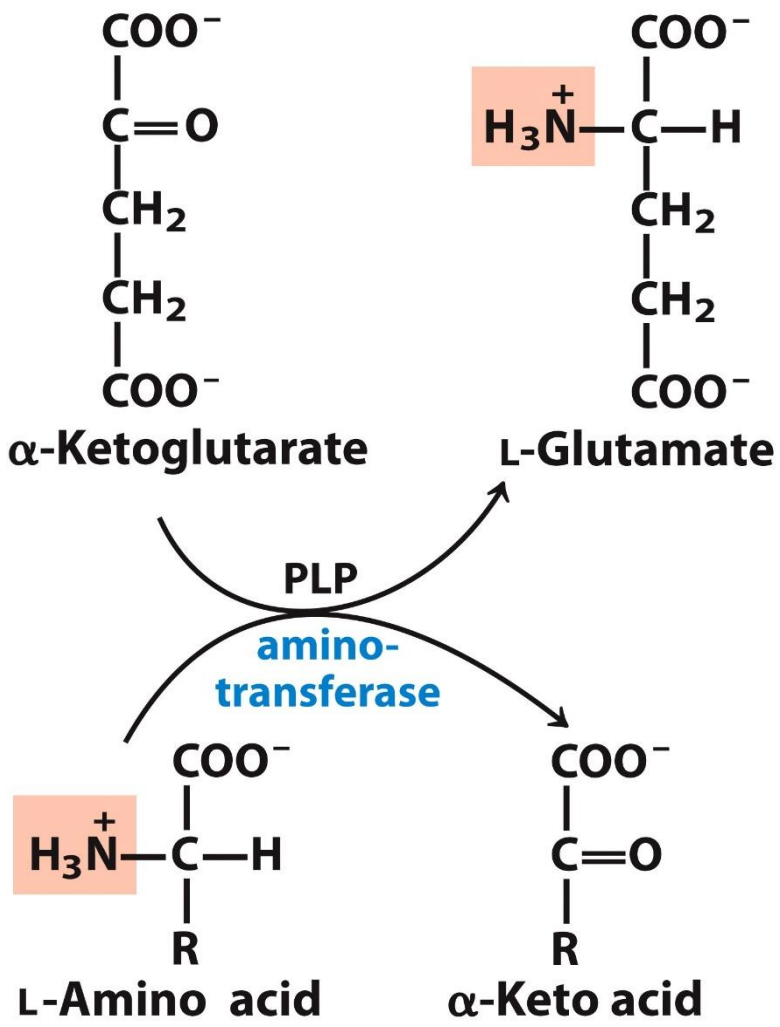


Figure 18-4
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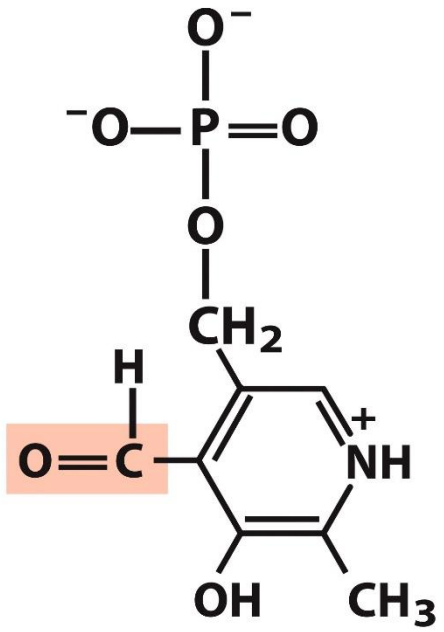
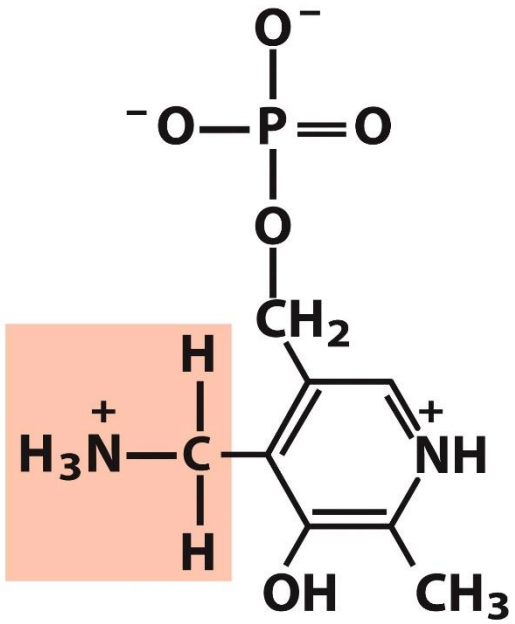
- **All aminotransferases have PLP as cofactor**



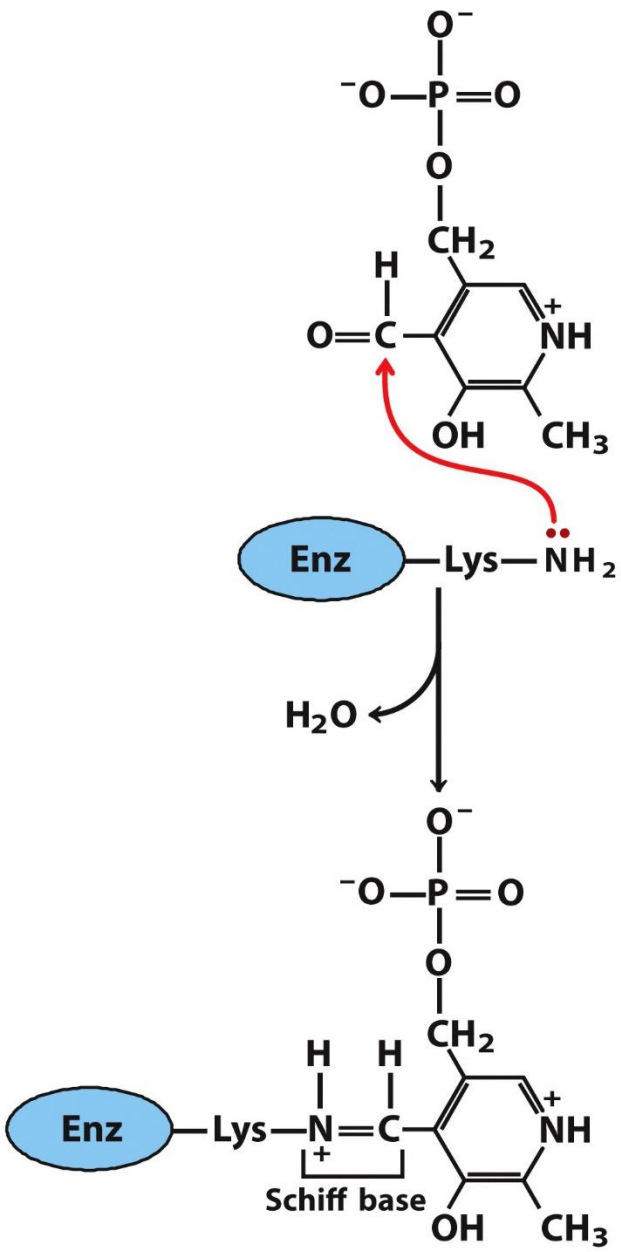
Pyridoxal phosphate (PLP)

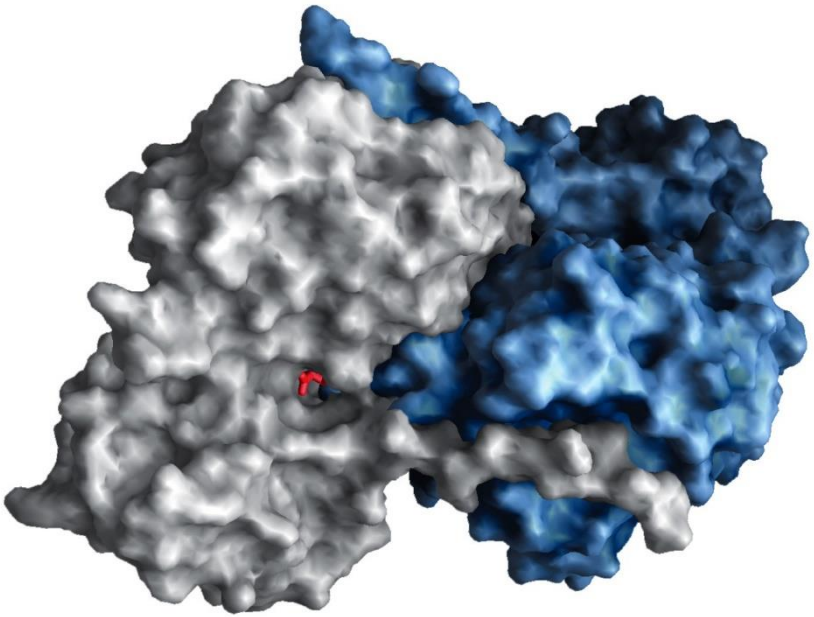


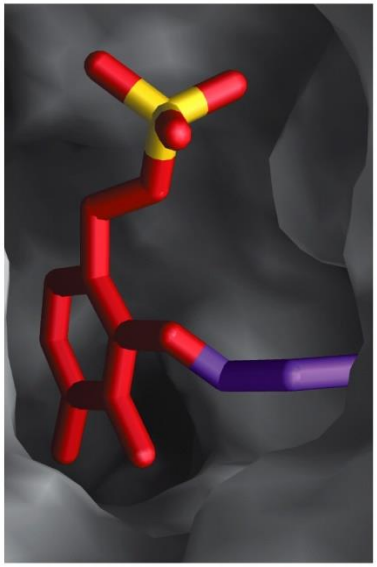
Pyridoxamine phosphate

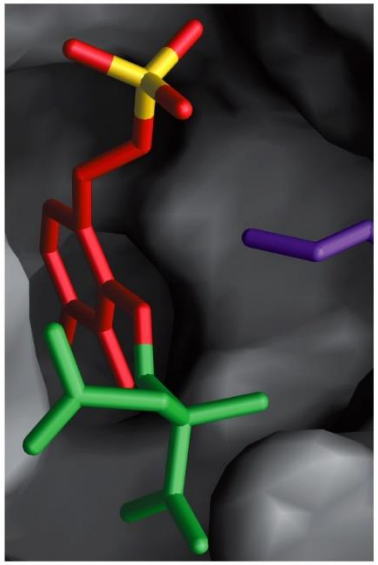
Figure 18-5a
Lehninger Principles of Biochemistry, Sixth Edition

- **All aminotransferases have PLP as cofactor**

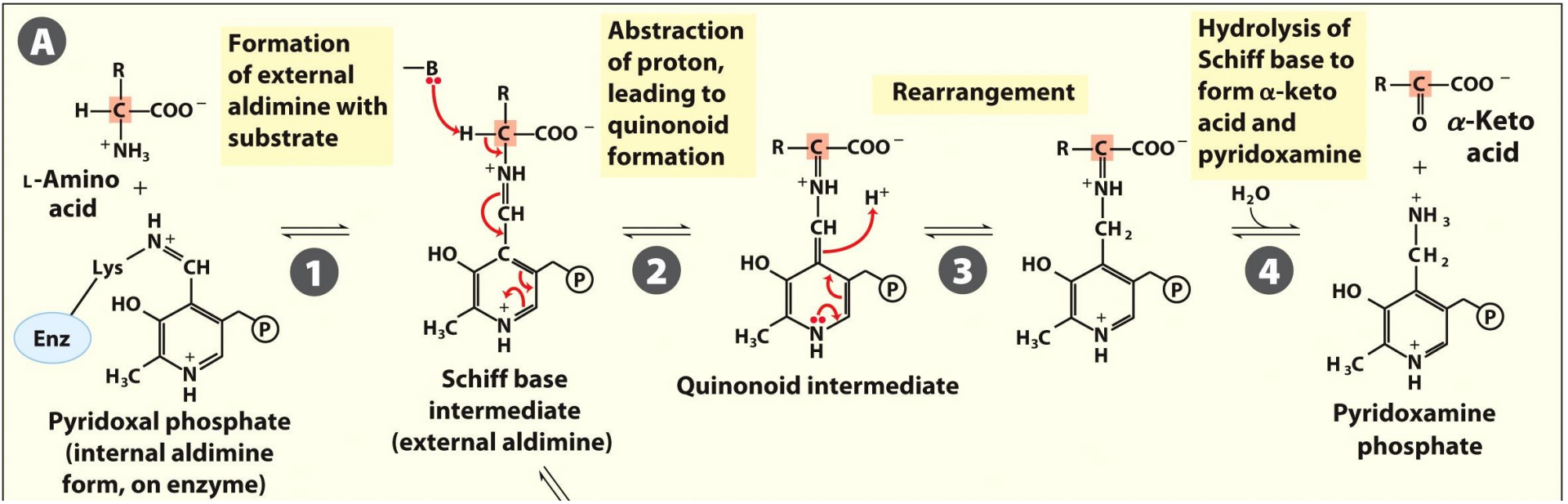






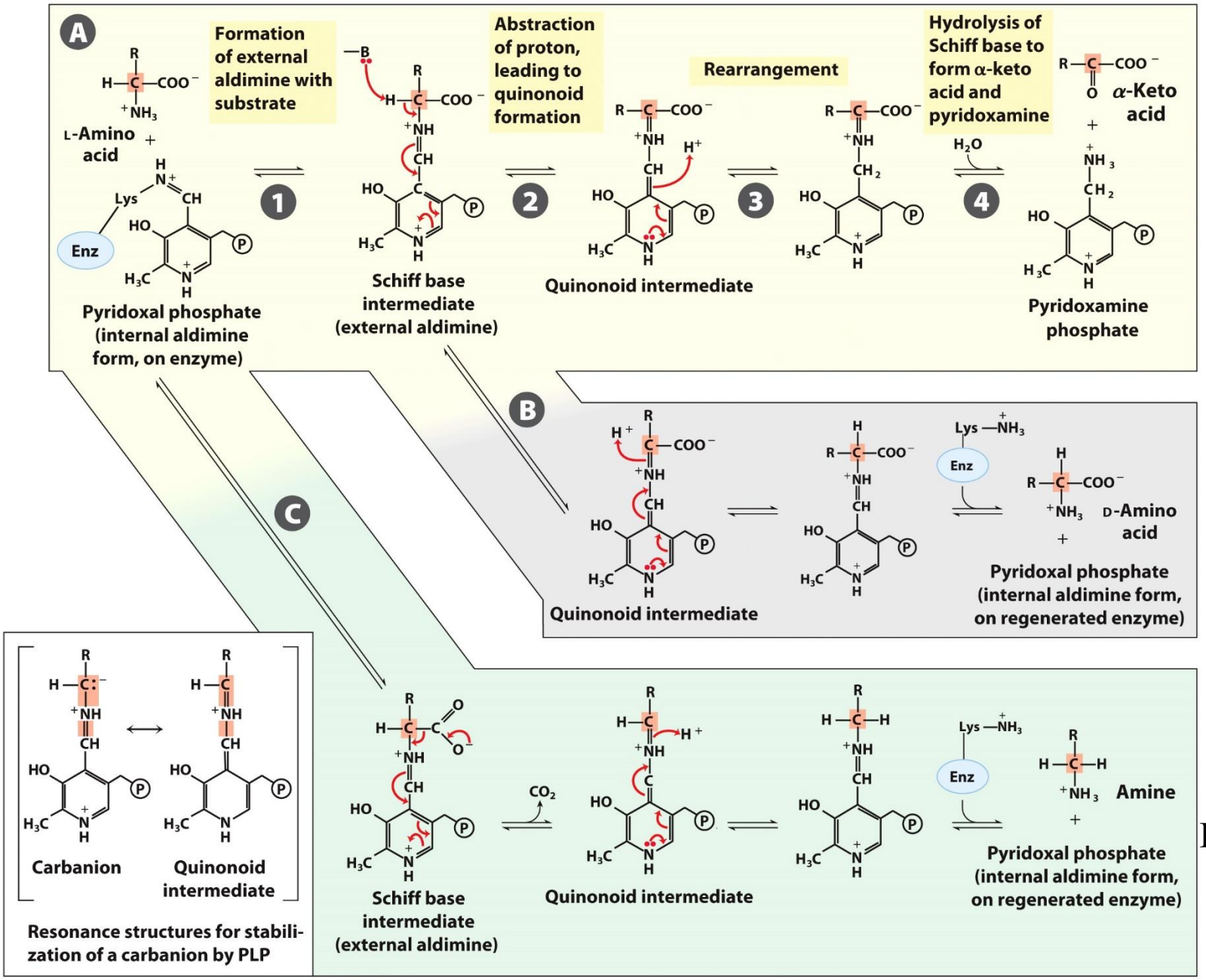


• PLP participates in aminotransferation



Ping-Pong reactions

• PLP participates in a variety of reactions of amino acids



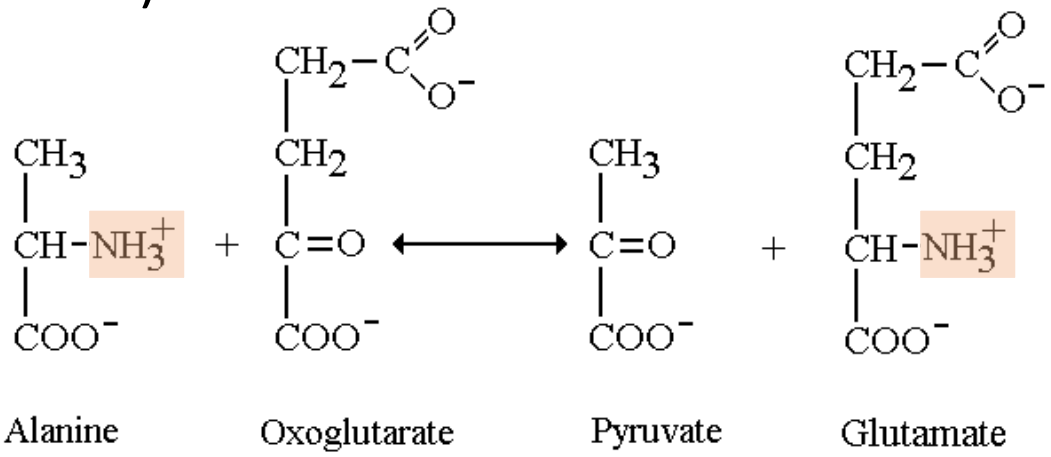
Transamination

Racemization

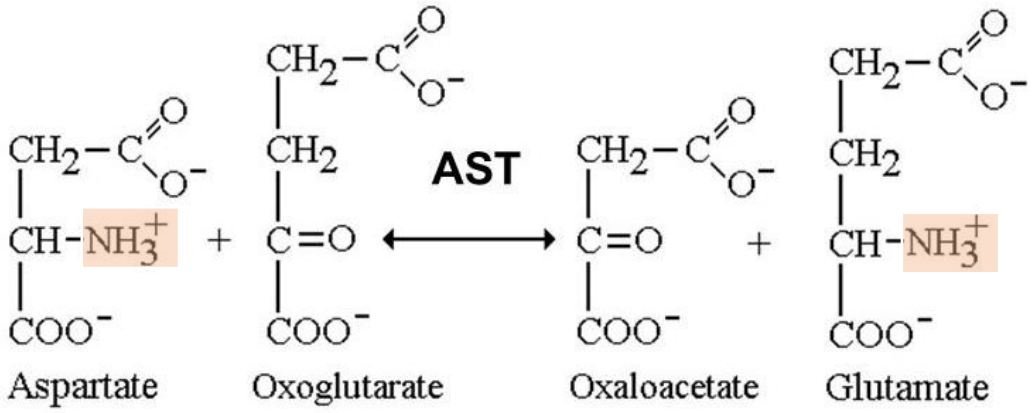
Decarboxylation

• Aminotransferase are named for the amino group donor

- ALT (alanine aminotransferase) or GPT (glutamate-pyruvate transaminase)



- AST (aspartate aminotransferase) or GOT (glutamate-oxaloacetate transaminase)



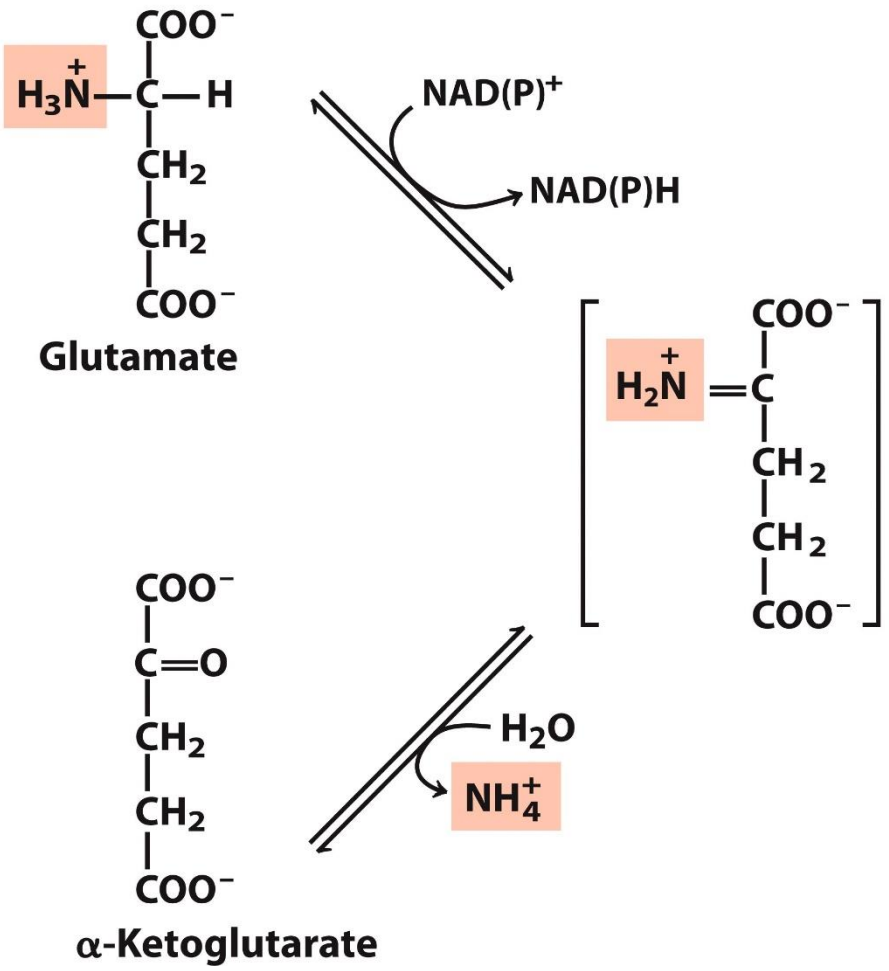
• Assays for Tissue Damage

The concentration of AST and ALT in different organs.

organs	AST（U/g）	ALT（U/g）
heart	156000	7100
liver	142000	44000
Skeletal muscle	99000	4800
kidney	91000	19000
spleen	14000	1200
lung	10000	700
serum	20	16

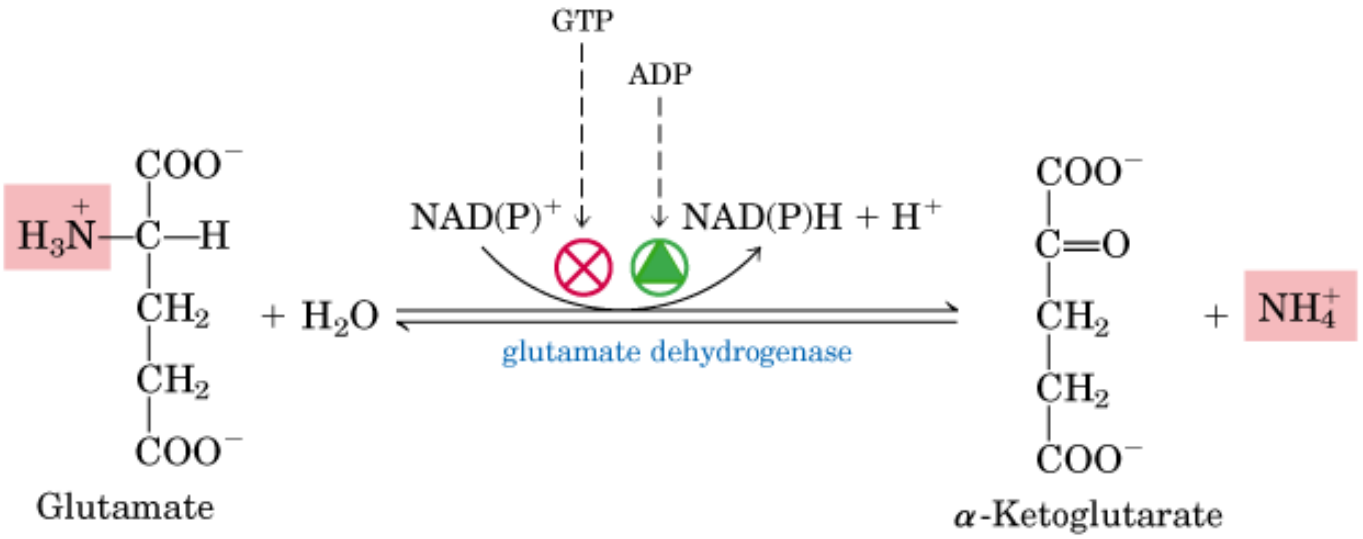
AST and ALT are important in the diagnosis of heart and liver damage caused by heart attack, drug toxicity, or infection.

• Oxidative deamination in the Liver



In hepatocytes, glutamate is transported from the cytosol into mitochondria, where it undergoes **oxidative deamination** catalyzed by **L-glutamate dehydrogenase (GDH).**

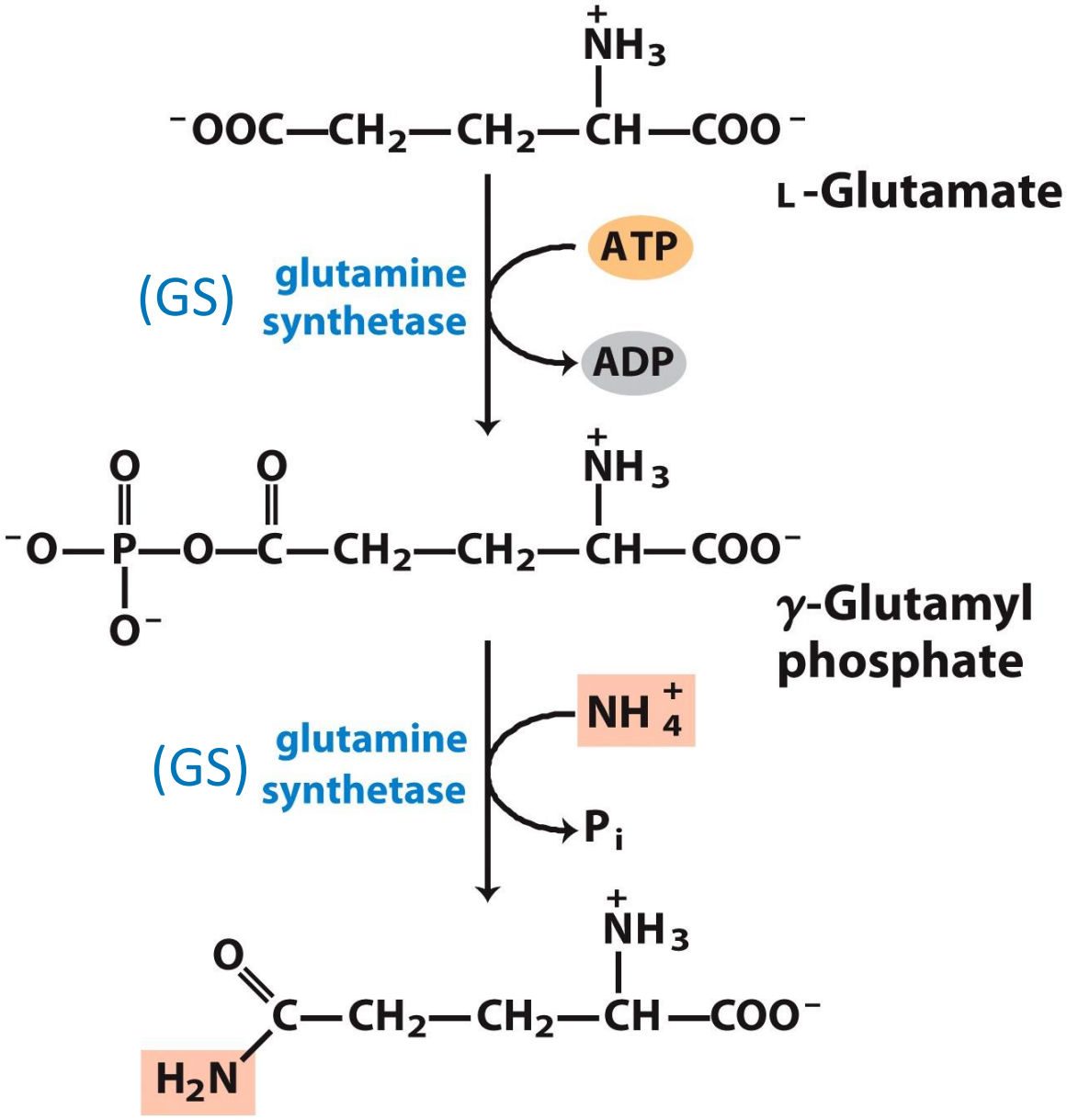
• Oxidative deamination in the Liver



- GDH is allosterically negatively regulated by GTP and positively regulated by ADP.
- GDH is the only enzyme that can use either NAD^+ or $NADP^+$ as the acceptor of reducing equivalents.

- Transdeamination: combined action of an aminotransferase and glutamate dehydrogenase

• Glutamine Transports Ammonia in the Bloodstream



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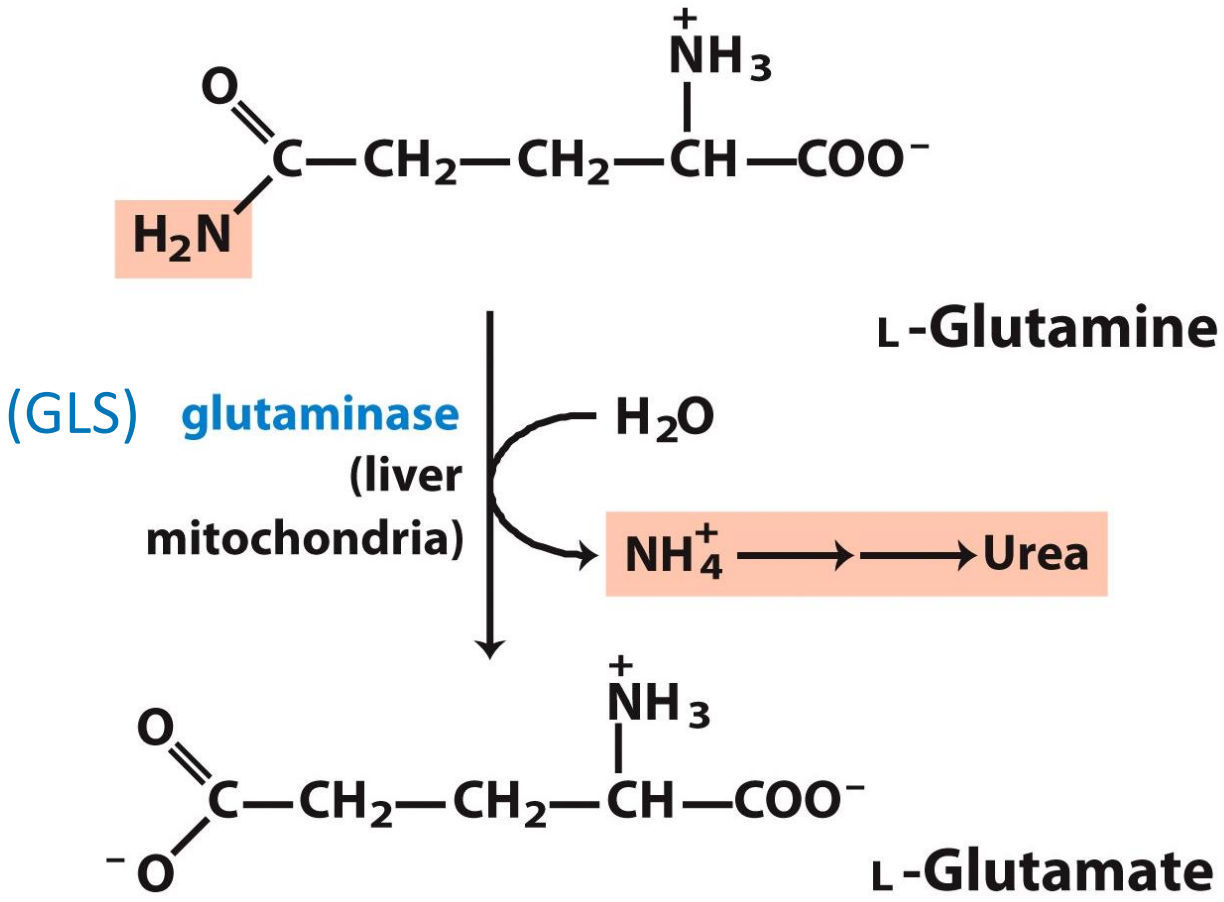
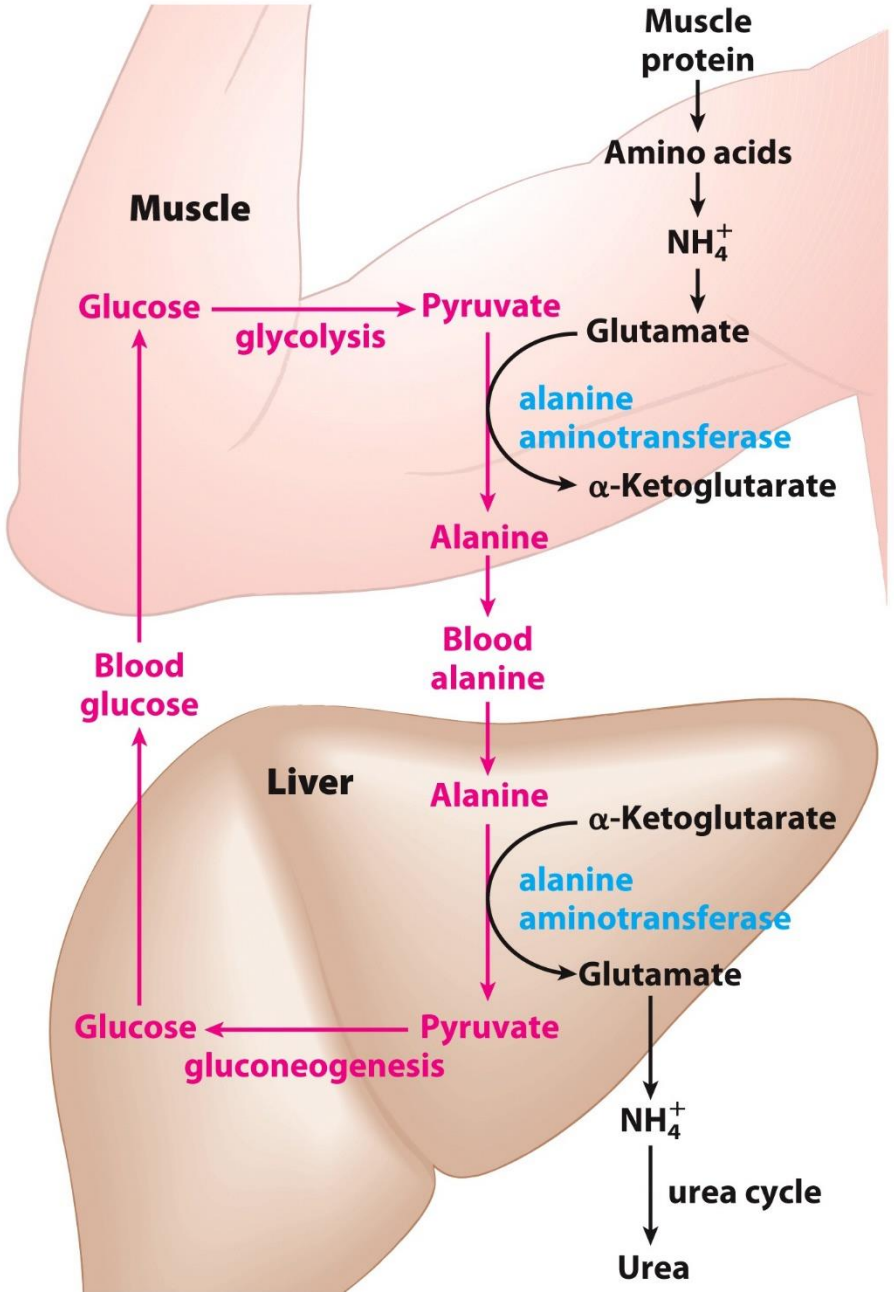


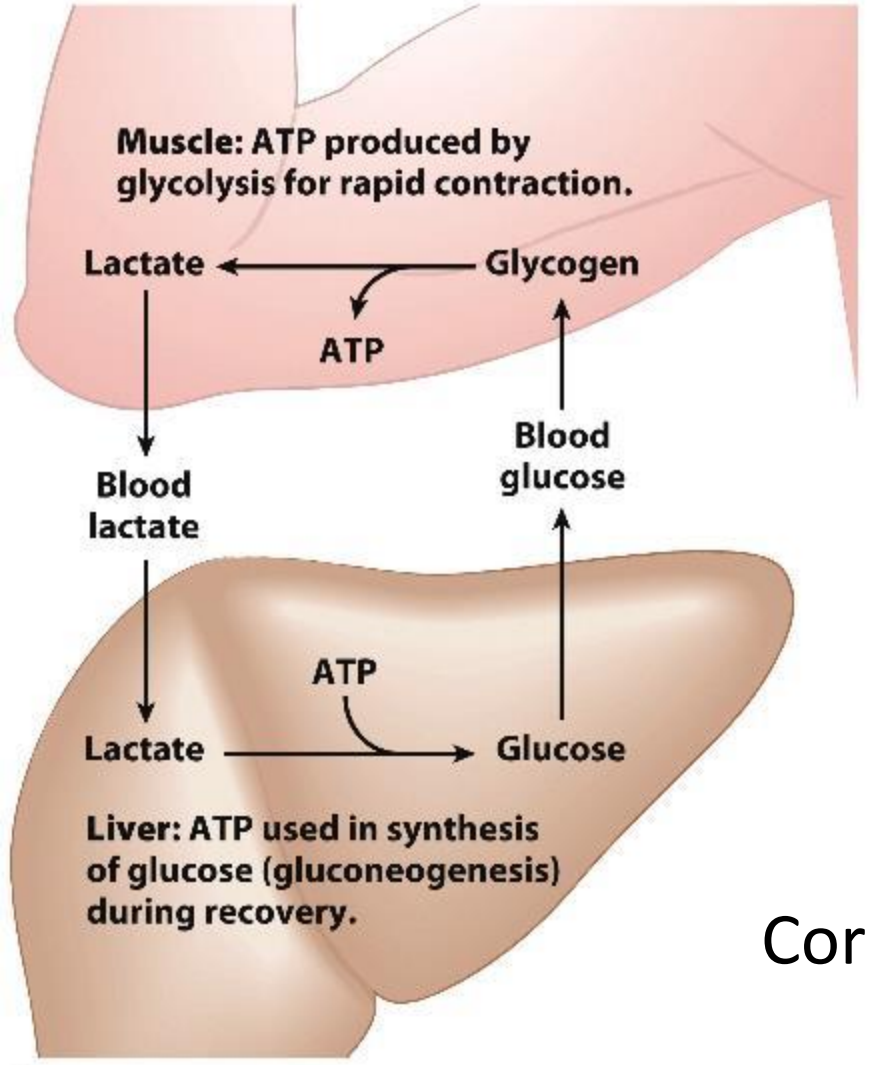
Glutamine is a nontoxic transport form of ammonia, it is normally present in blood in much higher concentration than other amino acids.

• Alanine Transports Ammonia from Skeletal Muscles



glucose-alanine cycle

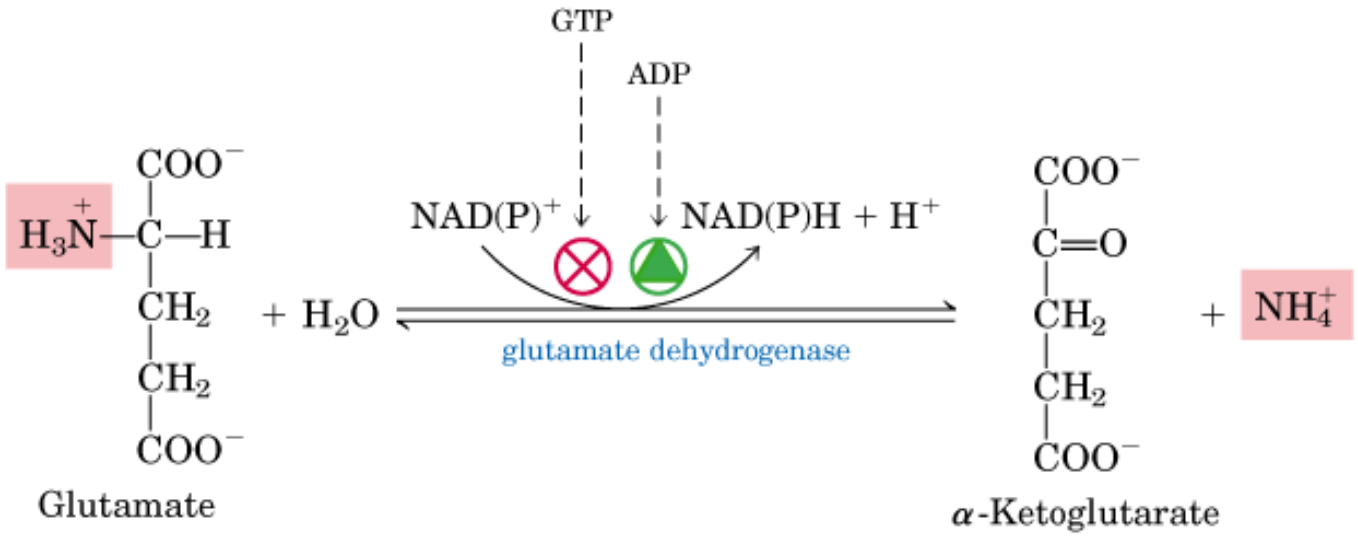
• Alanine Transports Ammonia from Skeletal Muscles

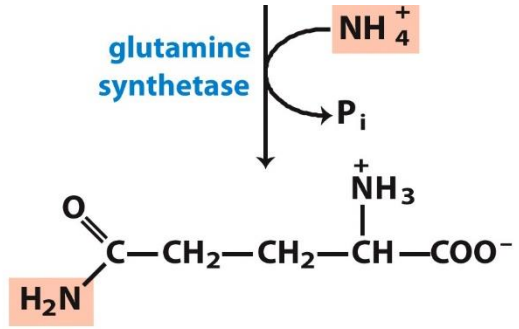


Cori cycle

• Ammonia Is Toxic to Animals

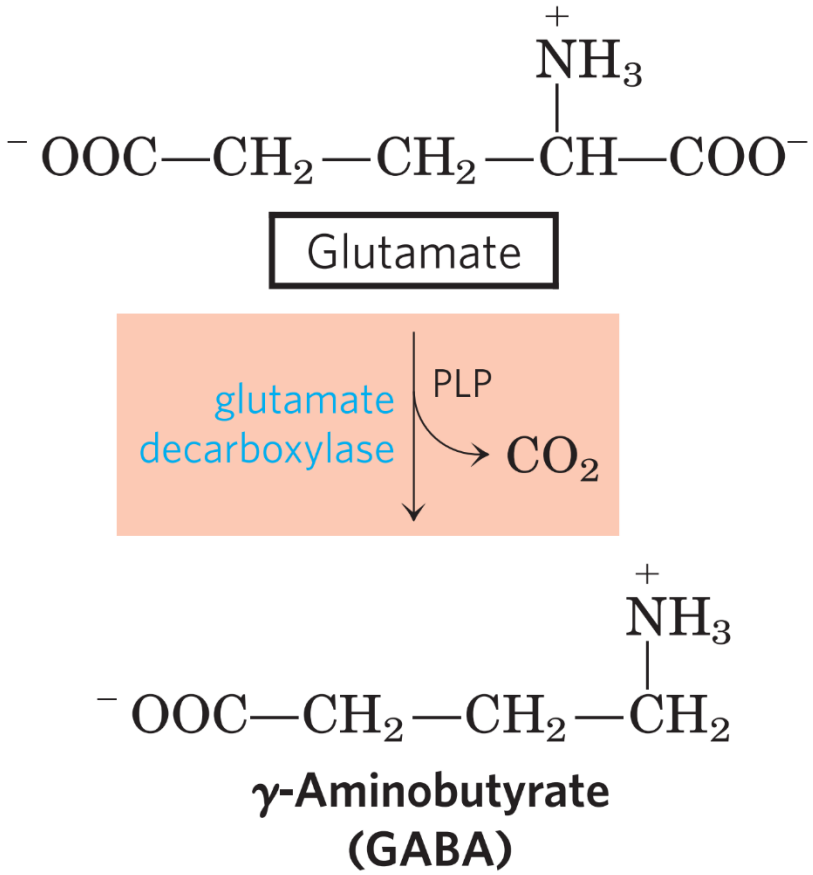
- The terminal stages of ammonia intoxication in humans are characterized by onset of a comatose state (昏迷) accompanied by cerebral edema (脑水肿) from the depletion of ATP and uptake of water.





• Ammonia Is Toxic to Animals

- neurotransmitters



• SUMMARY 18.1

- Humans derive a small fraction of their oxidative energy from the catabolism of amino acids. Amino acids are derived from the normal breakdown (recycling) of cellular proteins, degradation of ingested proteins, and breakdown of body proteins in lieu of other fuel sources during starvation or in uncontrolled diabetes mellitus.
- Proteases degrade ingested proteins in the stomach and small intestine. Most proteases are initially synthesized as inactive zymogens.
- An early step in the catabolism of amino acids is the separation of the amino group from the carbon skeleton. In most cases, the amino group is transferred to α-ketoglutarate to form glutamate. This transamination reaction requires the coenzyme pyridoxal phosphate (PLP).

• SUMMARY 18.1

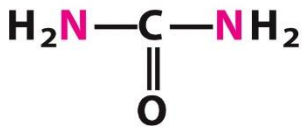
- Glutamate is transported to liver mitochondria, where glutamate dehydrogenase (GDH) liberates the amino group as ammonium ion (NH_4^+). Ammonia formed in other tissues is transported to the liver as the amide nitrogen of glutamine or, in transport from skeletal muscle, as the amino group of alanine.

- The pyruvate produced by deamination of alanine in the liver is converted to glucose, which is transported back to muscle as part of the glucose-alanine cycle.

18.2 Nitrogen Excretion and the Urea Cycle

• Excretory forms of nitrogen

Ammonia (as ammonium ion)



Urea

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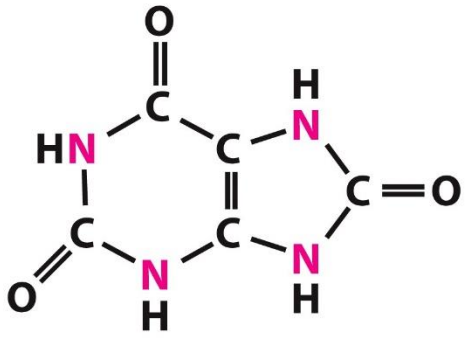
Ureotelic animals: many terrestrial vertebrates; also sharks

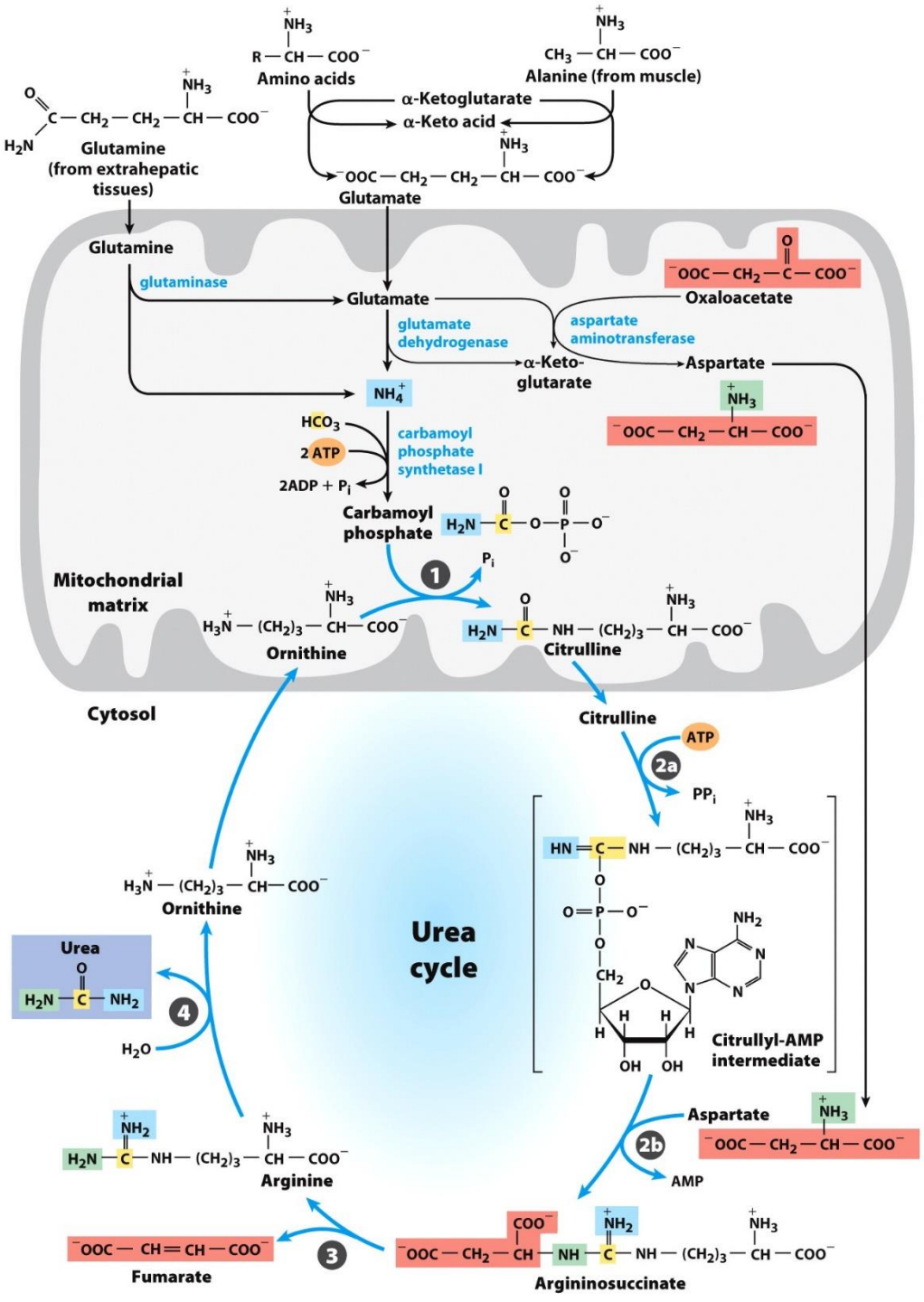


Uric acid

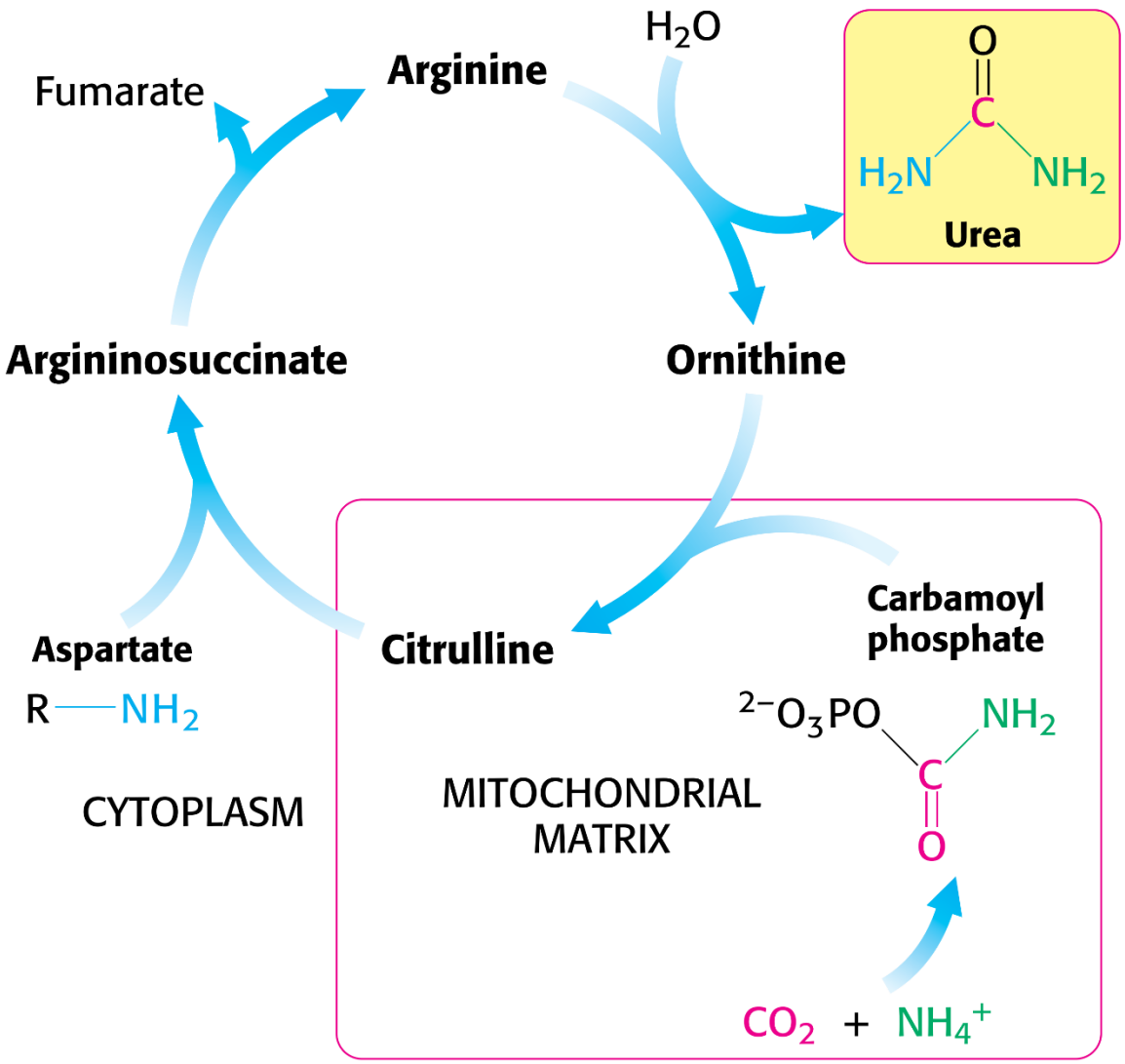
Uricotelic animals: birds, reptiles

The carbon atoms of urea and uric acid are highly oxidized.

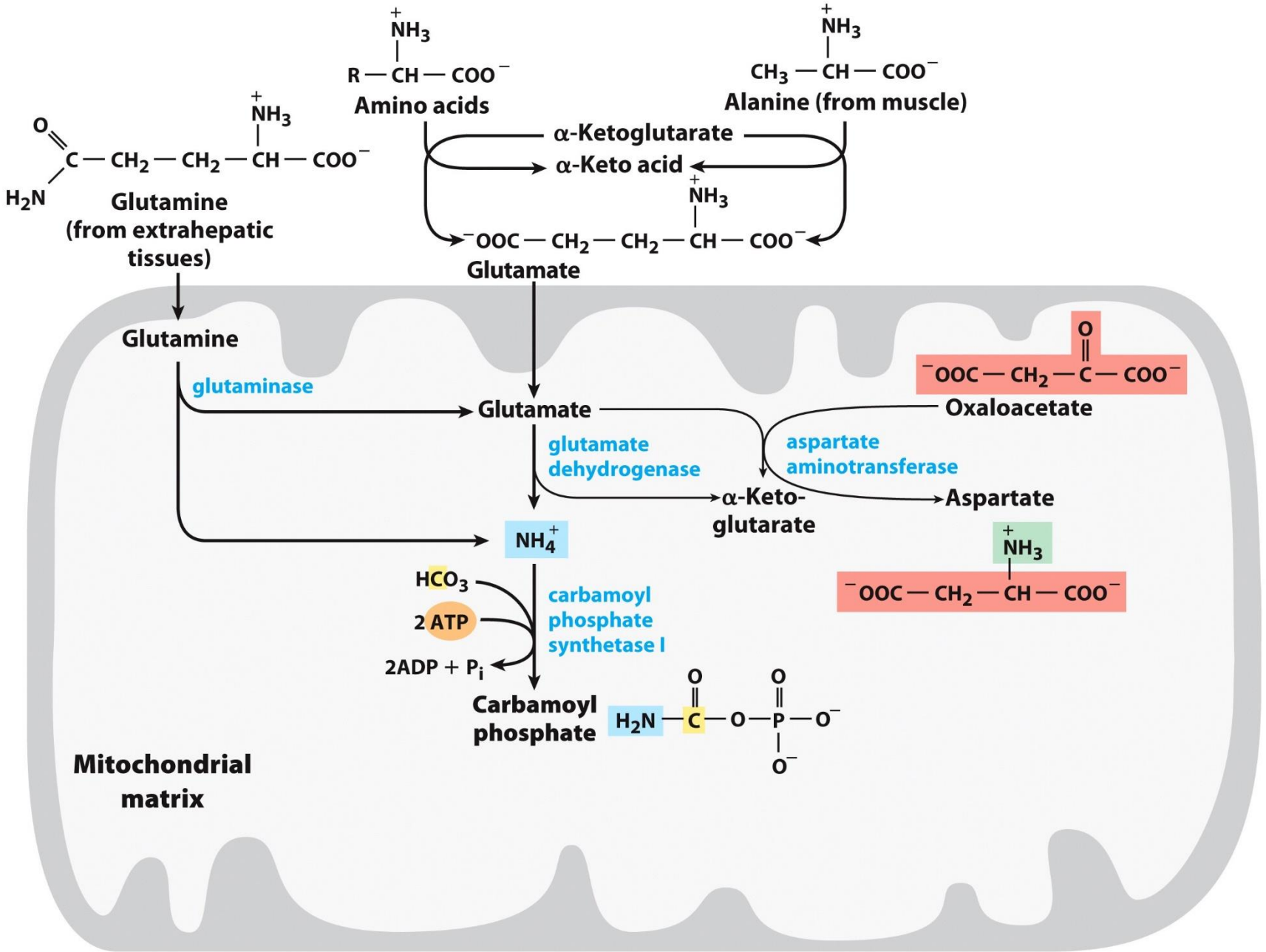
- **Urea Cycle**


Amino acids
Alanine (from muscle)
α-Ketoglutarate
α-Keto acid
Glutamate
Glutamine (from extrahepatic tissues)
Glutamine
glutaminase
Glutamate
Oxaloacetate
glutamate dehydrogenase
aspartate aminotransferase
α-Keto-glutarate
Aspartate
NH_4^+
HCO_3
2 ATP
2ADP + P_i
carbamoyl phosphate synthetase I
Carbamoyl phosphate
Mitochondrial matrix
1
P_i
Ornithine
Citrulline
Cytosol
Citrulline
ATP
2a
PP_i
Citrullyl-AMP intermediate
Aspartate
2b
AMP
Argininosuccinate
3
Fumarate
Arginine
Urea
4
H_2O
Ornithine
Urea cycle

• Urea Cycle


Fumarate
Arginine
H_2O
O
C
H_2N
NH_2
Urea
Argininosuccinate
Ornithine
Aspartate
R—NH_2
Citrulline
Carbamoyl phosphate
$^{2-}O_3PO$
NH_2
C
O
CYTOPLASM
MITOCHONDRIAL MATRIX
CO_2 + NH_4^+

• Synthesis of Carbamoyl Phosphate



• Carbamoyl Phosphate Synthetase I (CPS1) Mechanism

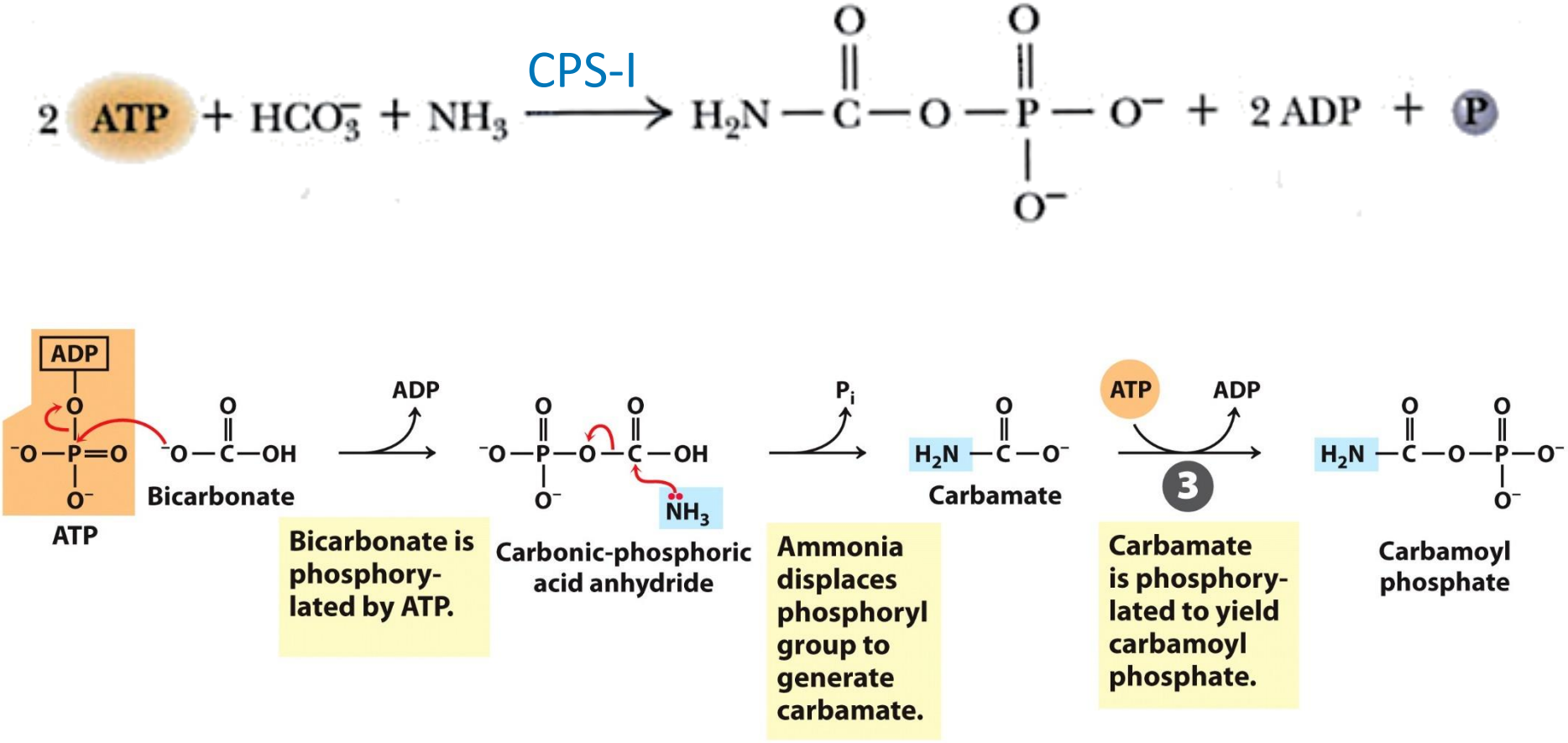
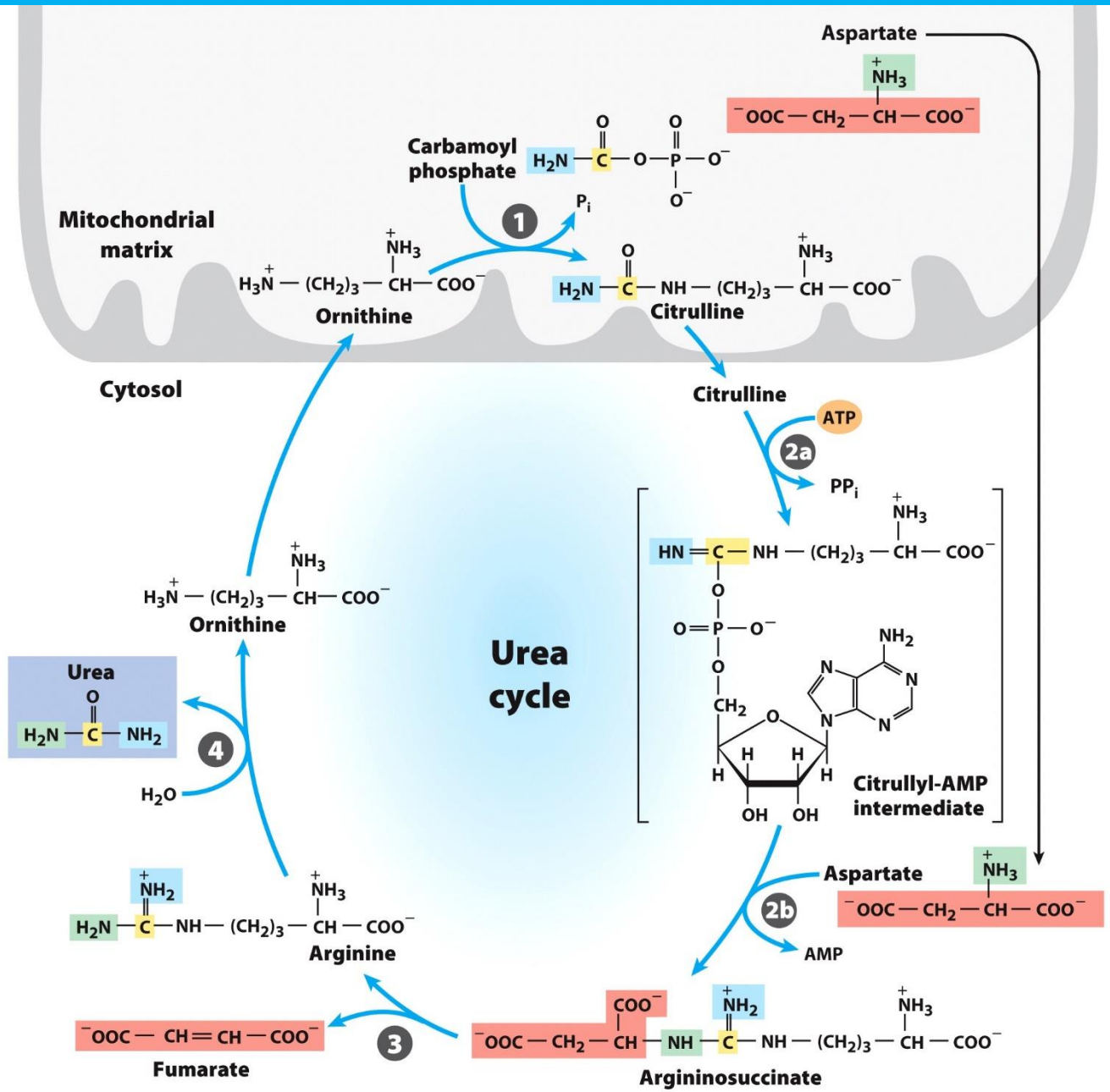
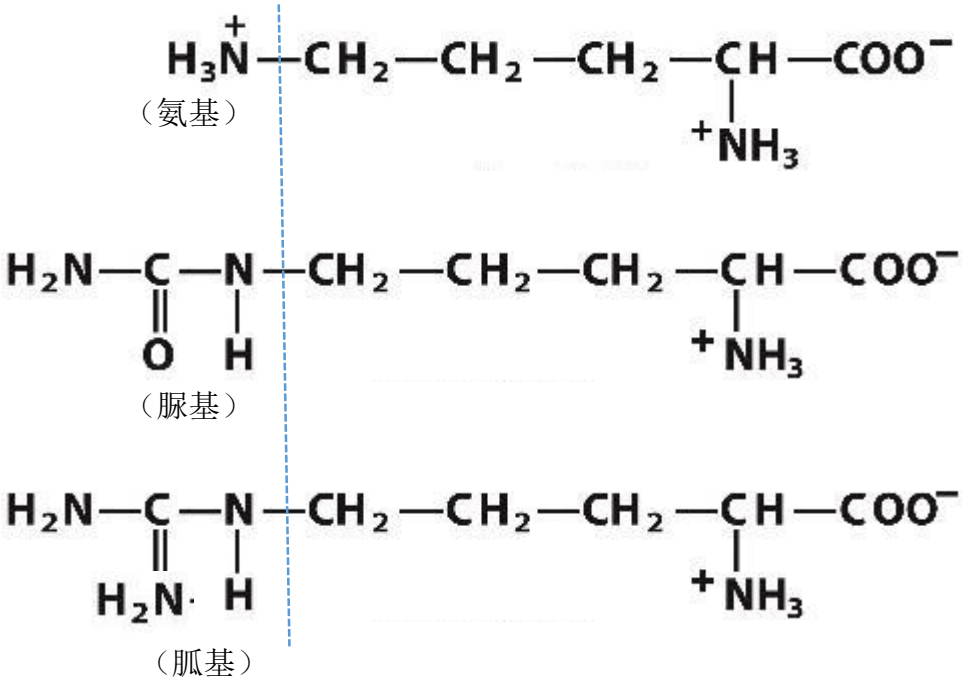


Figure 18-11a
Lehninger Principles of Biochemistry, Sixth Edition

• Urea Cycle


Aspartate
Carbamoyl phosphate
Mitochondrial matrix
Ornithine
Citrulline
Cytosol
Citrulline
ATP
2a
PPi
Urea cycle
Citrullyl-AMP intermediate
Aspartate
2b
AMP
Urea
4
H2O
Ornithine
Arginine
3
Fumarate
Argininosuccinate

• Amino Acids in Urea Cycle

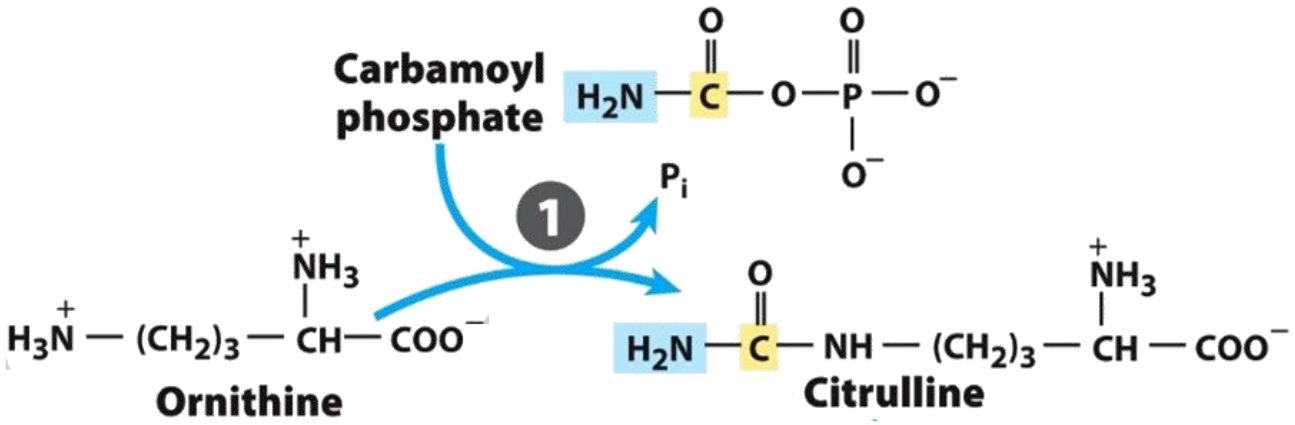


(Ornithine)

(Citrulline)

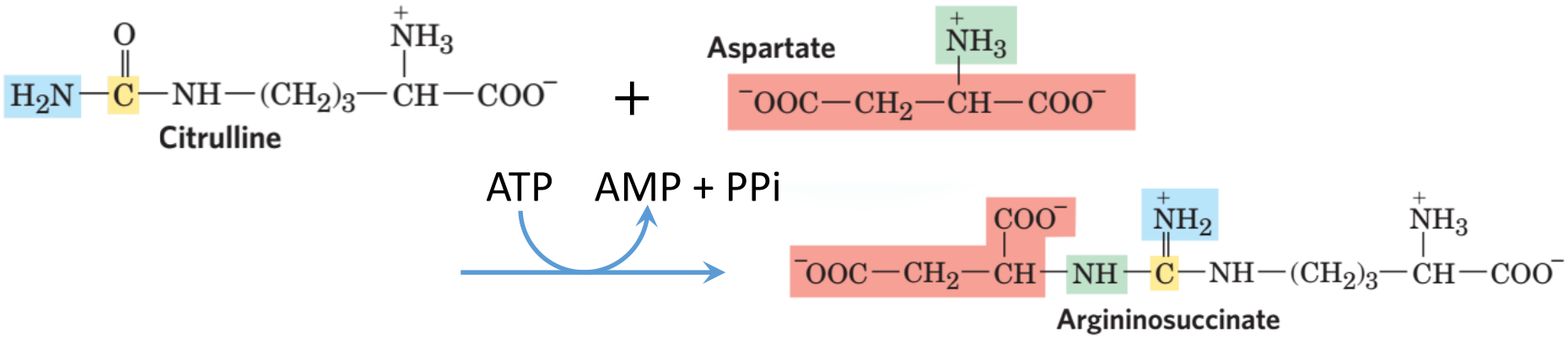
(Arginine)

• ① Citrulline formation in mitochondrial matrix

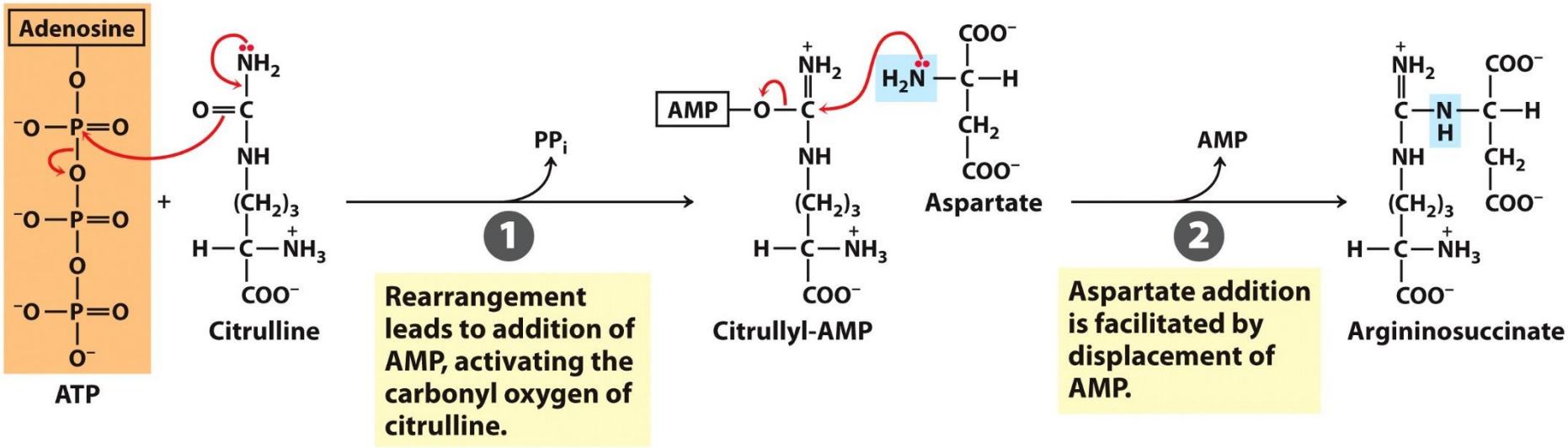


ornithine transcarbamoylase (OTC)

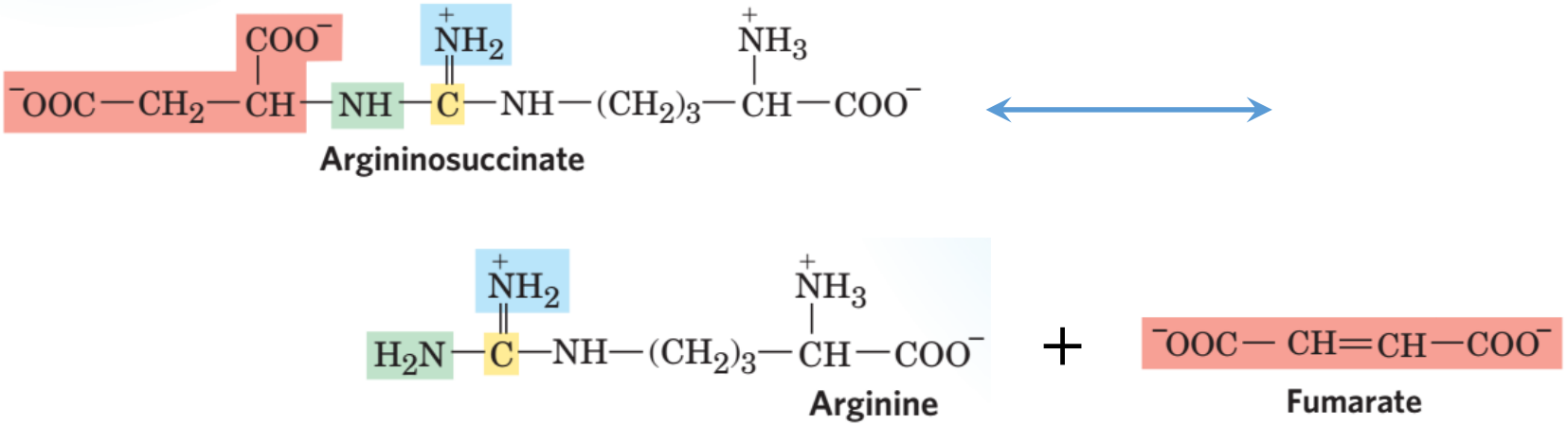
• ② argininosuccinate formation in cytosol



argininosuccinate synthetase (ASS)



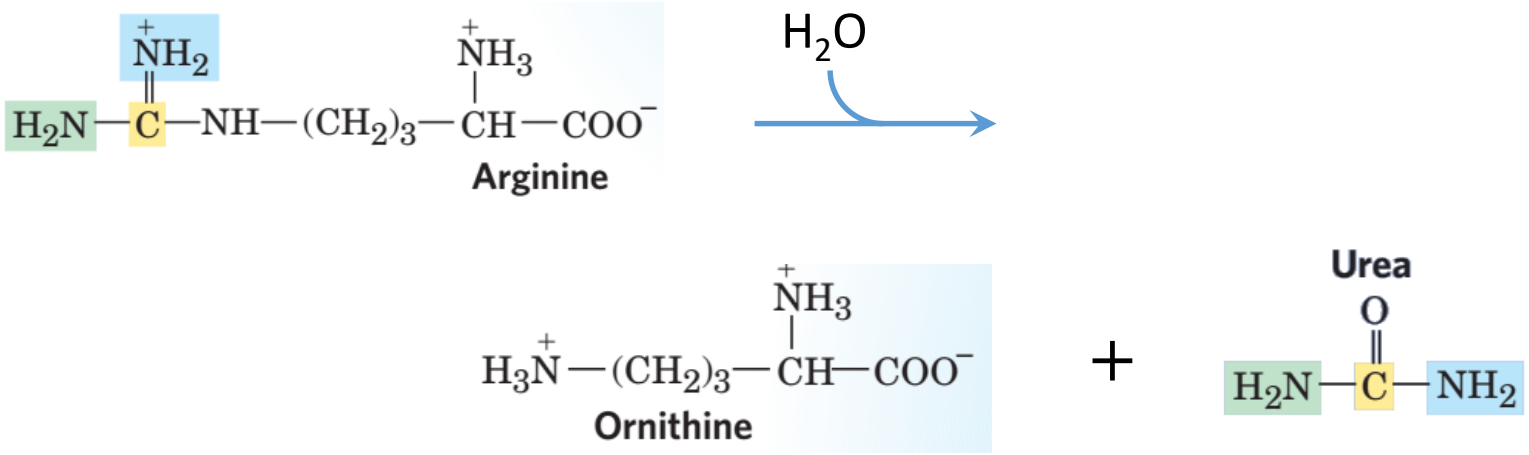
• ③ arginine and fumarate formation in cytosol



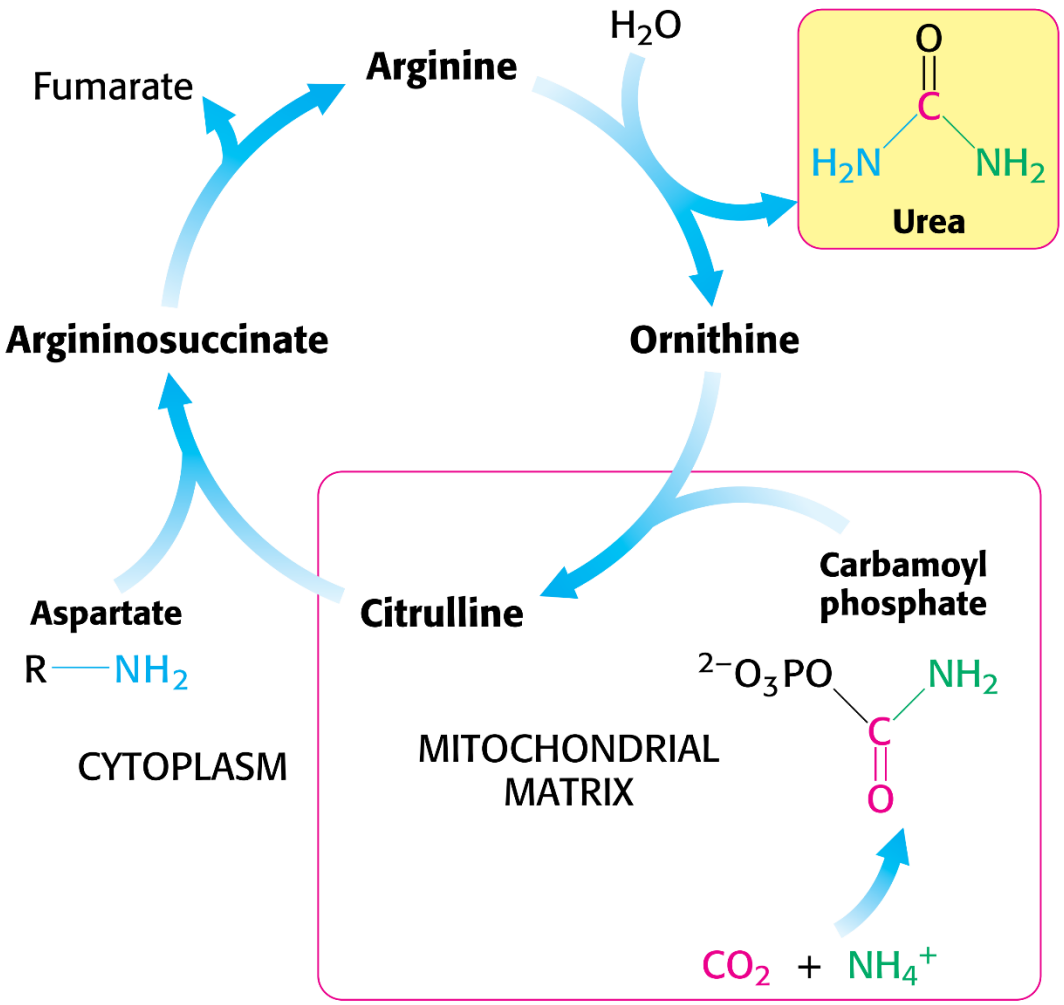
Argininosuccinase (argininosuccinate lyase, ASL)

- This is the only reversible reaction in urea cycle.

• ④ Urea and ornithine formation in cytosol

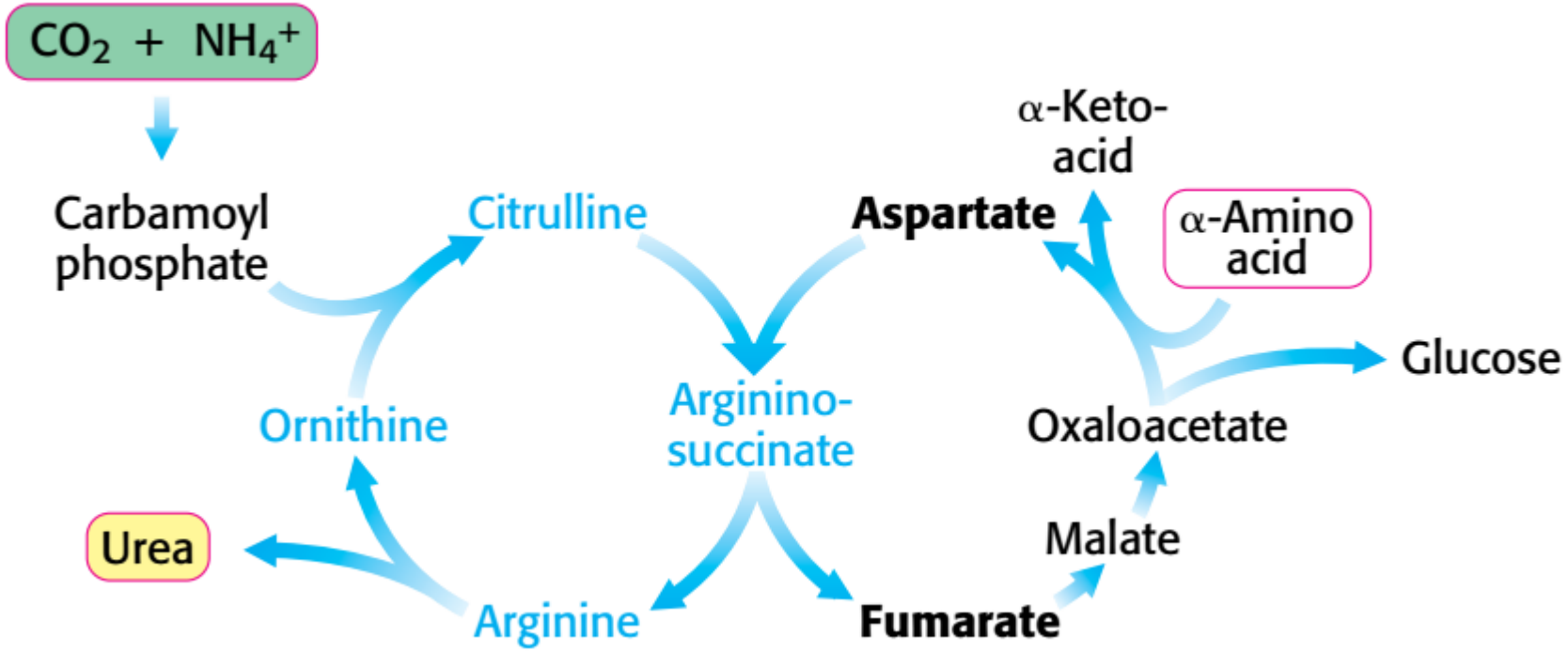


• Urea Cycle

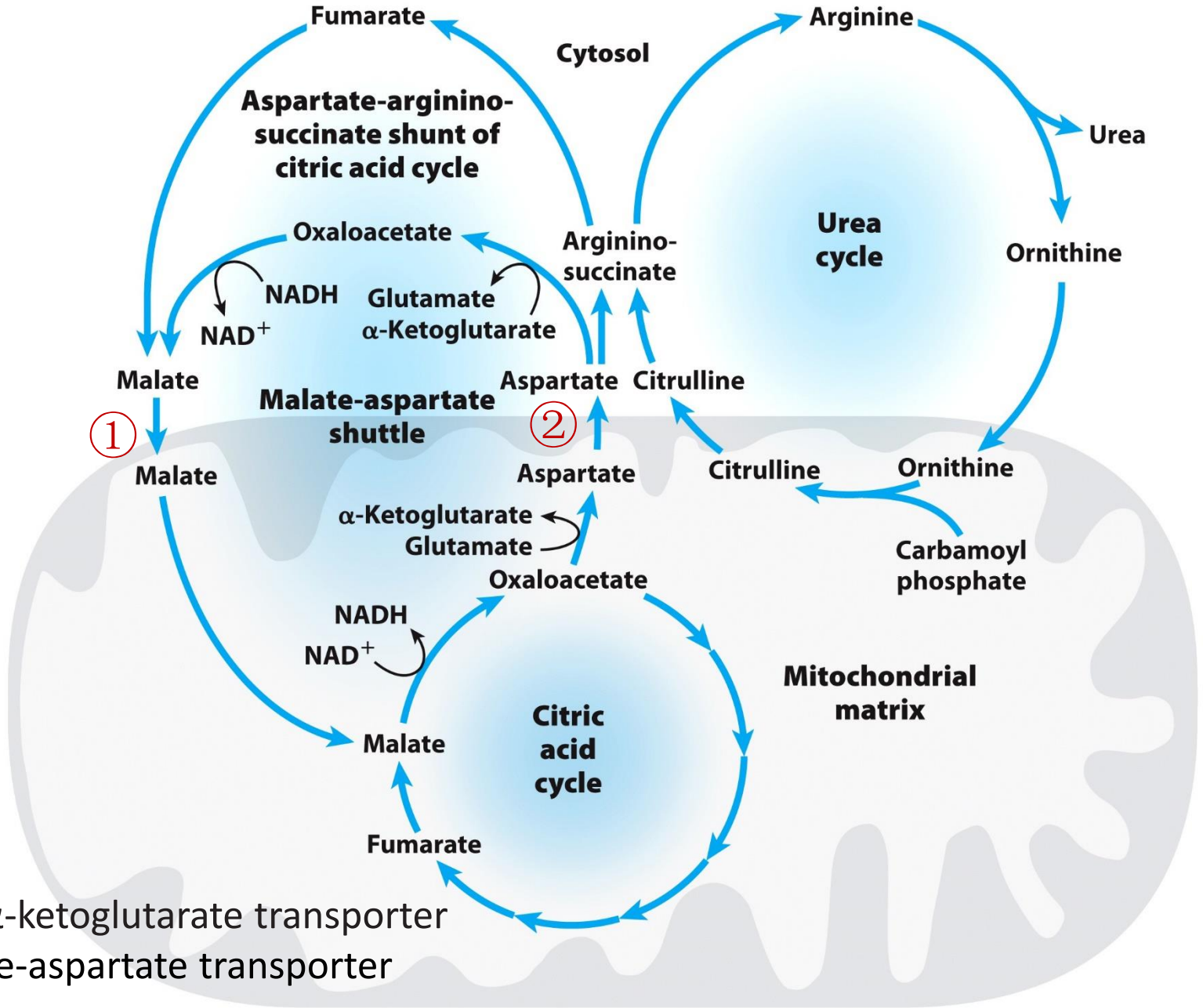


$$CO_2 + NH_4^+ + 3\,ATP + aspartate + 2\,H_2O \longrightarrow urea + 2\,ADP + P_i + AMP + PP_i + fumarate$$

• The Citric Acid and Urea Cycles Can Be Linked

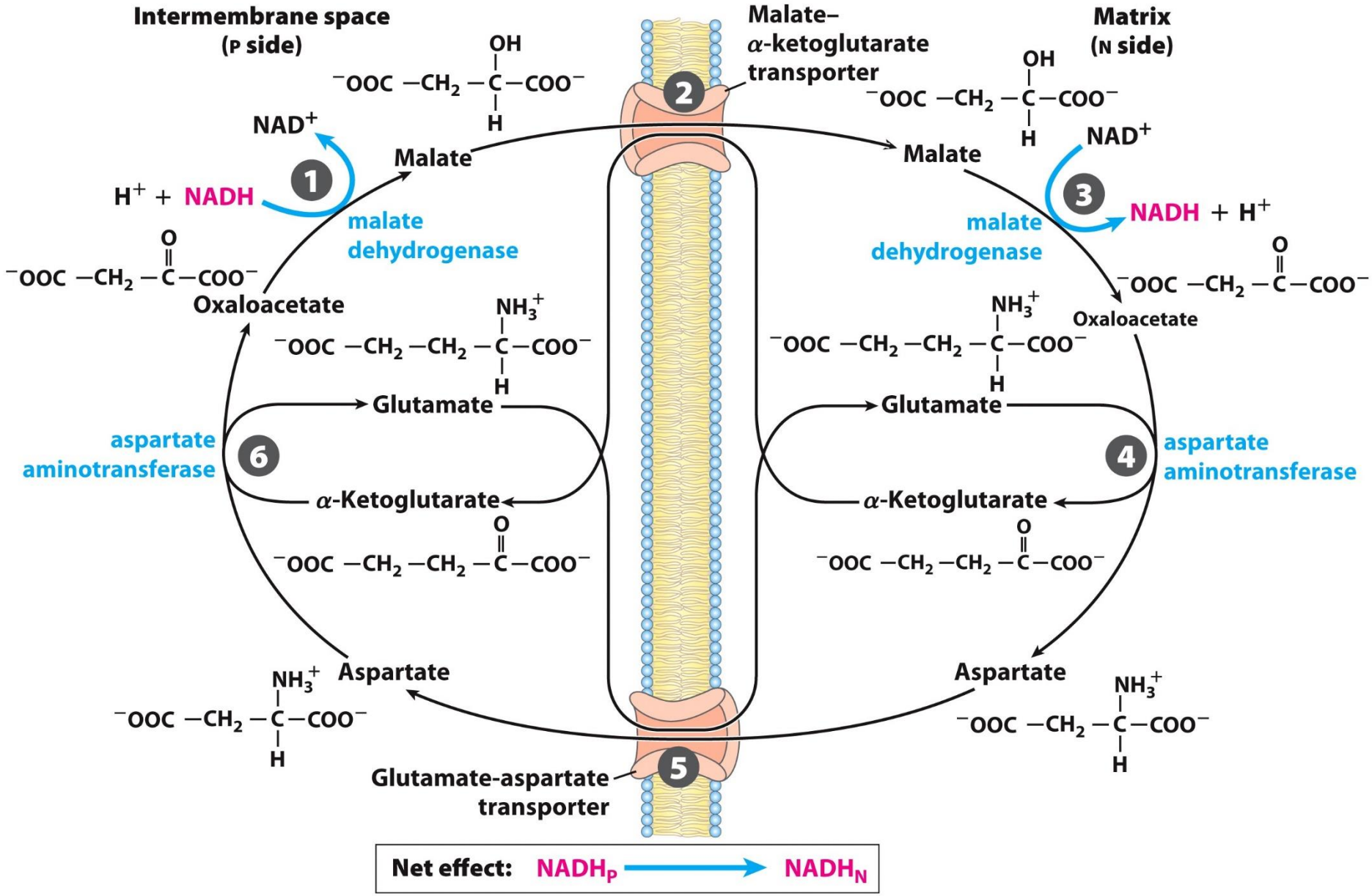


• “The Krebs bicycle”

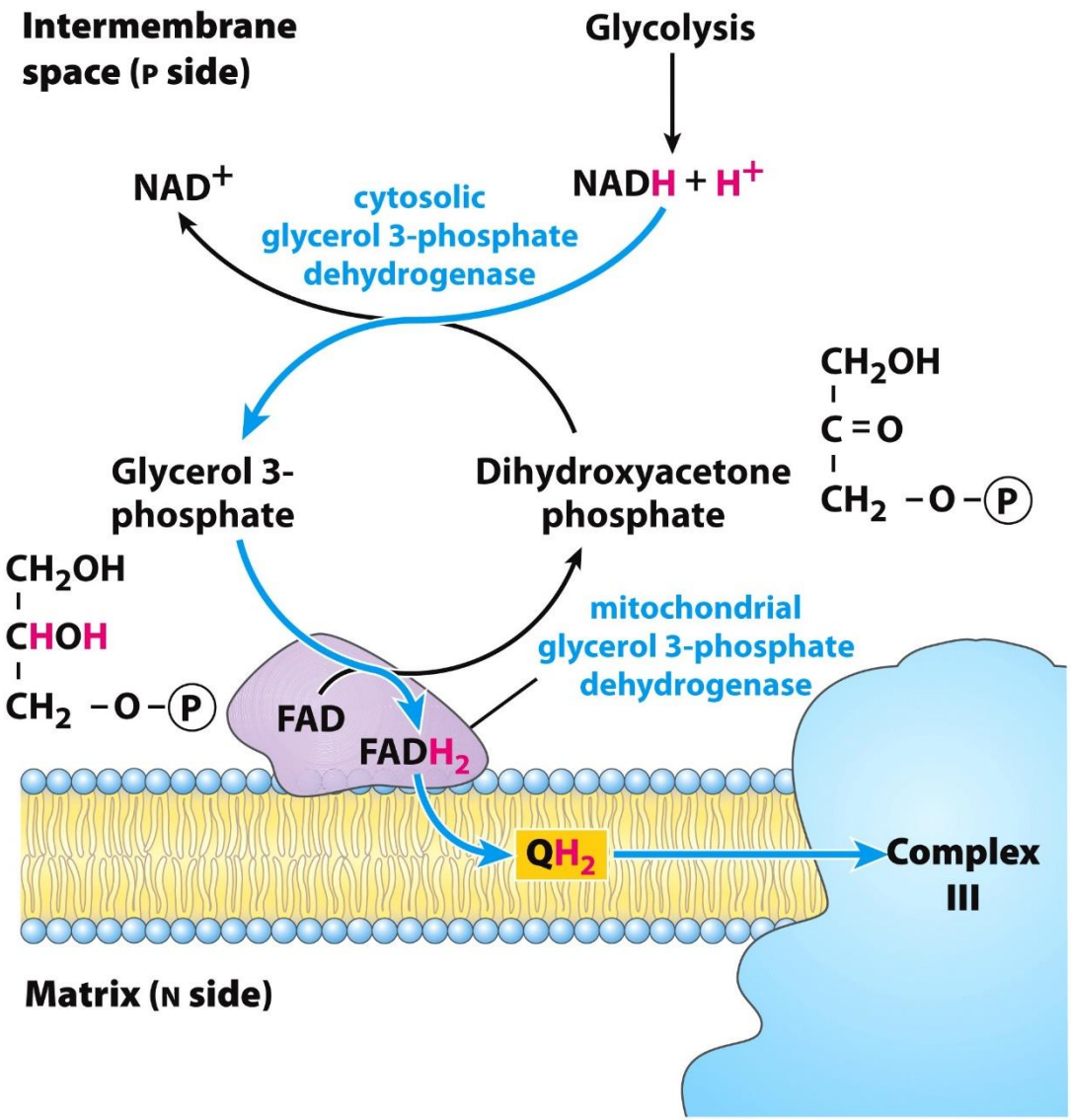


① malate–α-ketoglutarate transporter
② glutamate-aspartate transporter

- malate-aspartate shuttle in liver, kidney and heart



• Glycerol 3-phosphate shuttle in muscle and brain



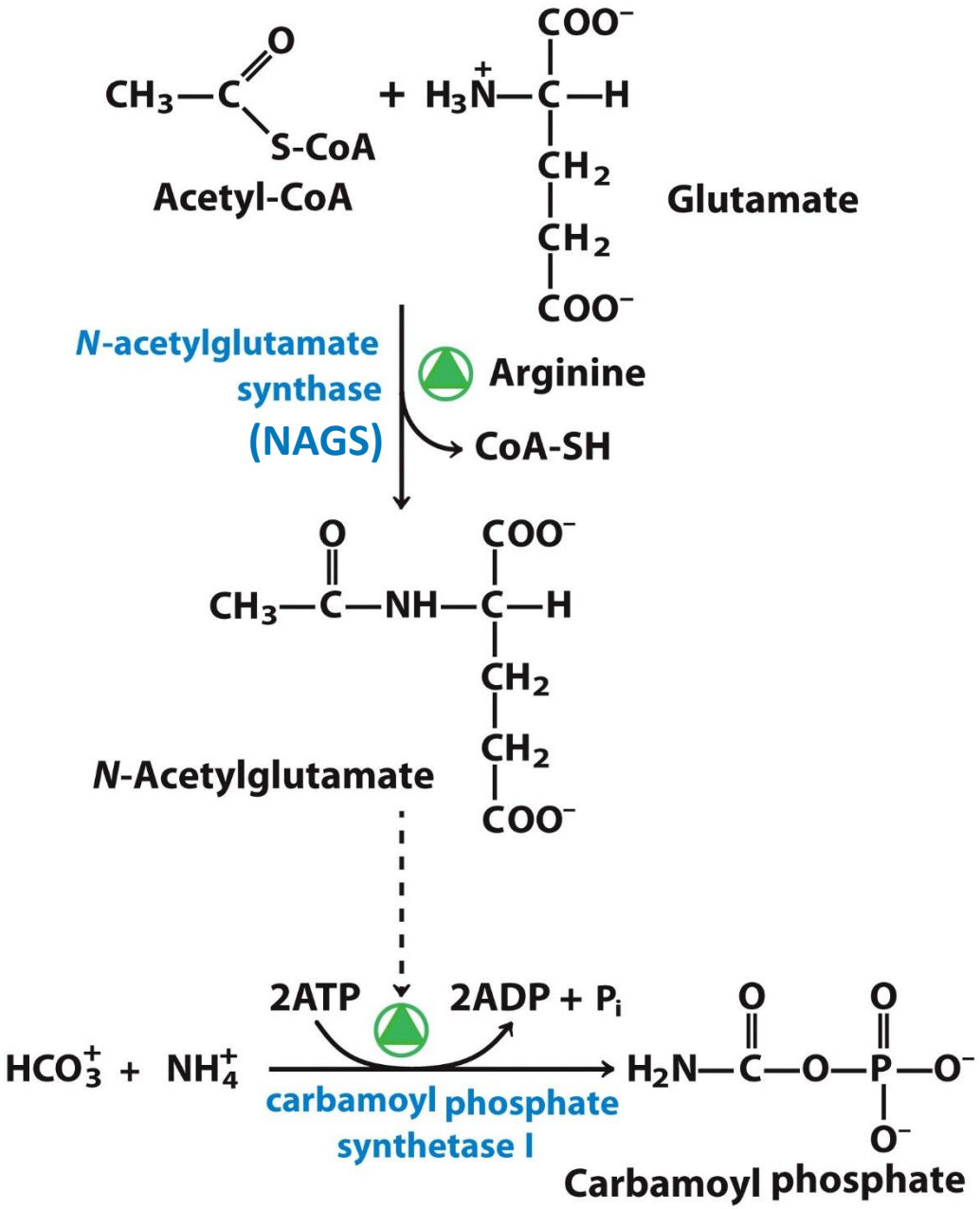
Net effect: $NADH_p \rightarrow FADH_{2\ N}$

• Regulation of Urea Cycle

- Long-term Regulation
  - All five enzymes are synthesized at higher rates in starving animals and in animals on very-high-protein diets than in well-fed animals eating primarily carbohydrates and fats. Animals on protein-free diets produce lower levels of urea cycle enzymes.

- Short-term Regulation
  - allosteric regulation of CPS1

• Allosteric Regulation of CPS1



• Genetic Defects in the Urea Cycle Can Be Life-Threatening

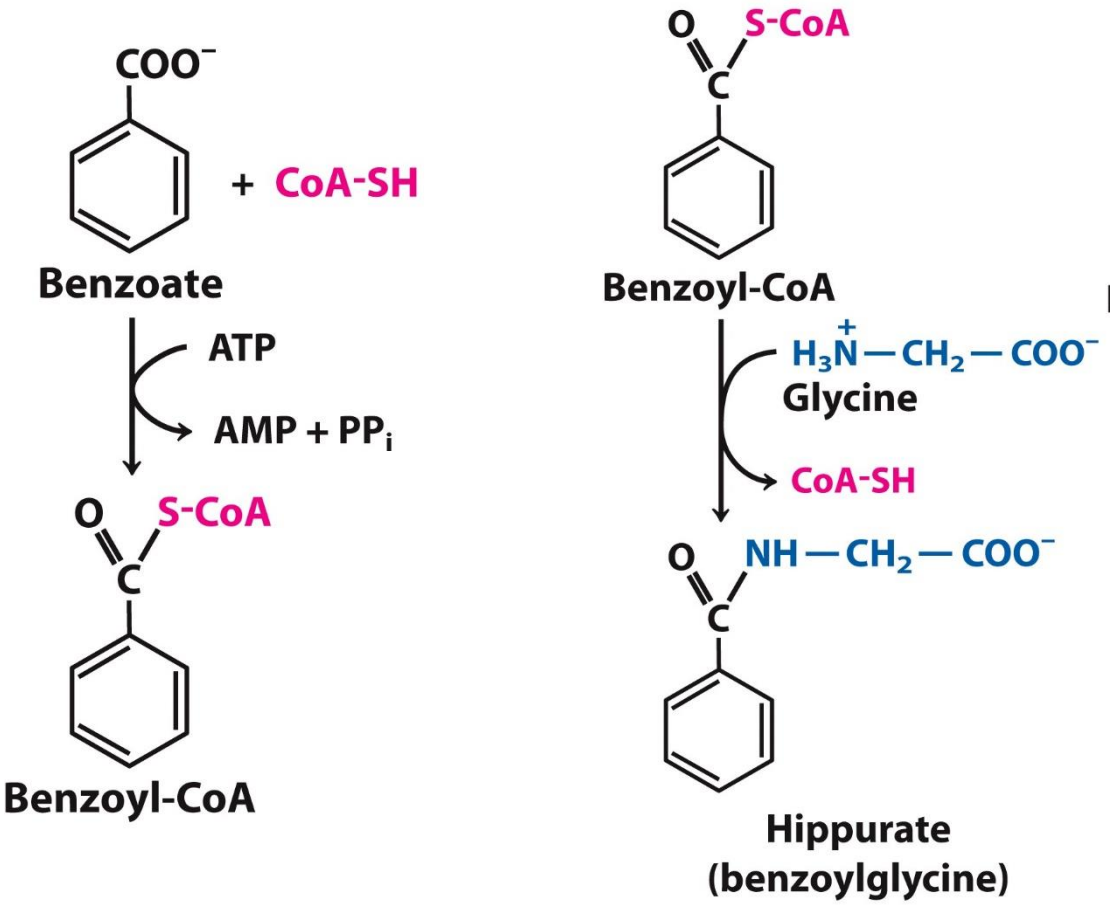
- The absence of a urea cycle enzyme can result in hyperammonemia (高血氨症) or in the buildup of one or more urea cycle intermediates.
- a protein-free diet is not a treatment option.

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.

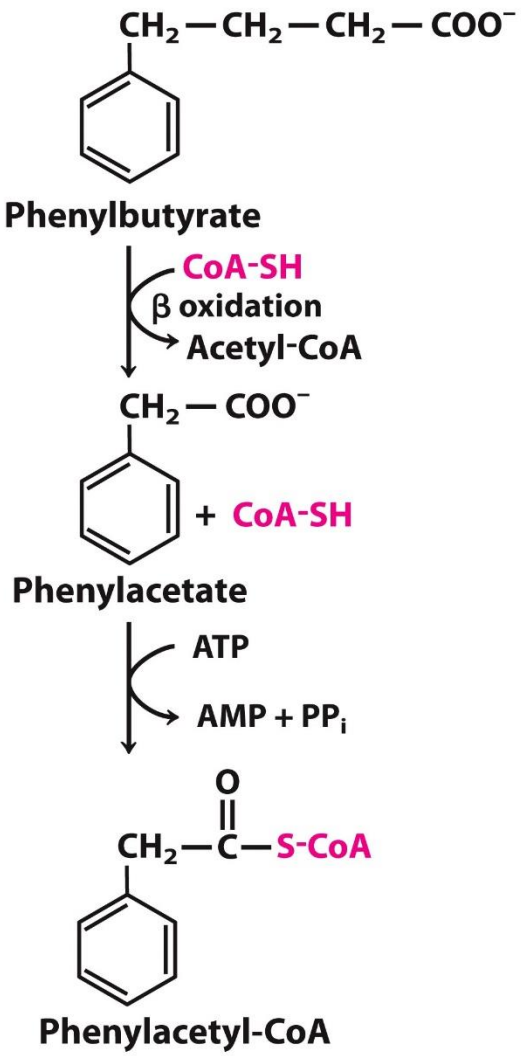
• Treatment for deficiencies in urea cycle enzymes

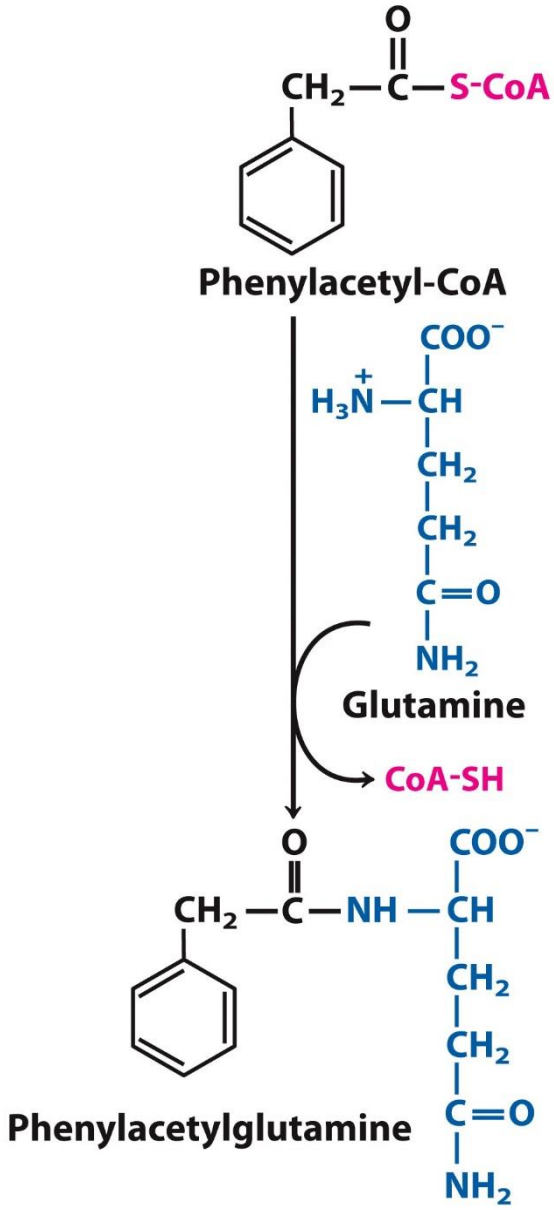
- Benzoate (苯甲酸) treatment



- **Treatment for deficiencies in urea cycle enzymes**

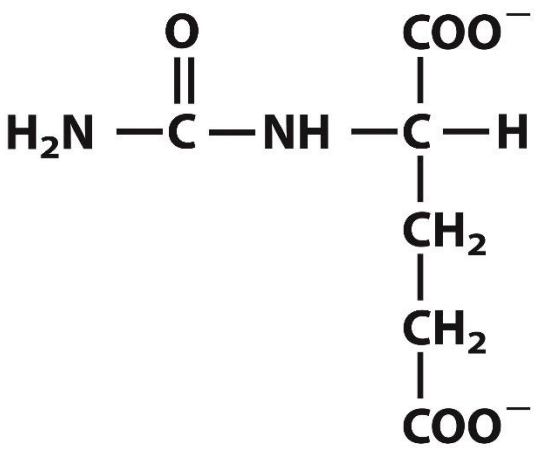
Phenylbutyrate (苯丁酸)



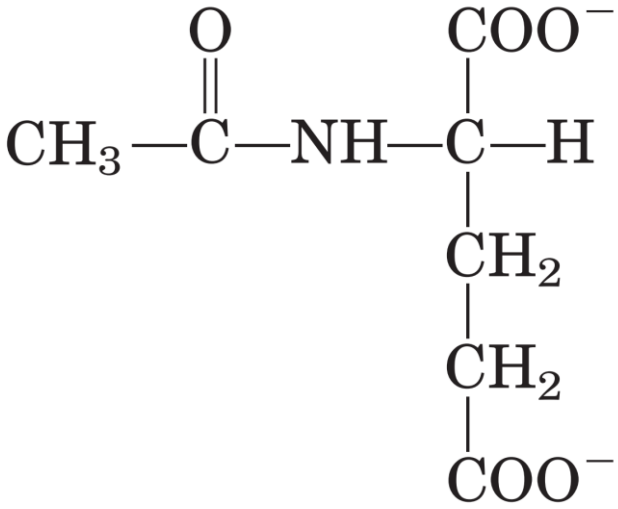


• Treatment for deficiencies in urea cycle enzymes

Carbamoyl glutamate



Carbamoyl glutamate

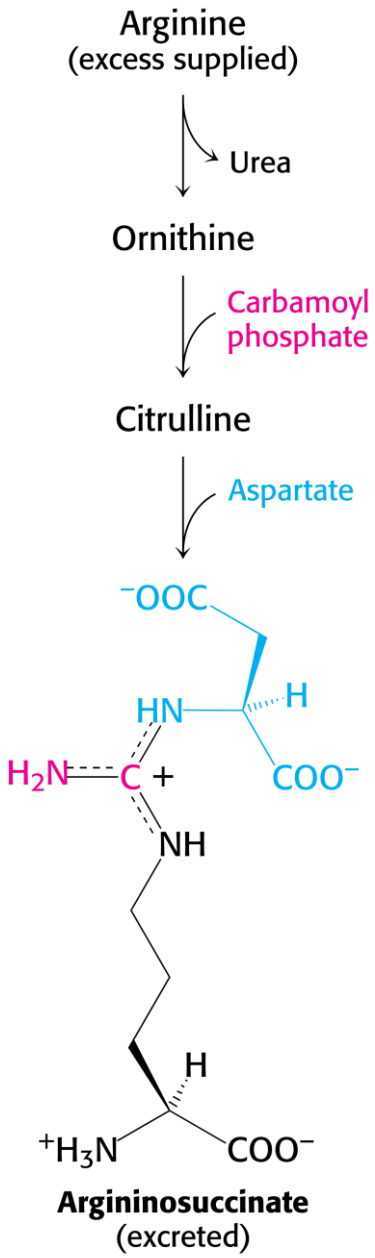


N-Acetylglutamate

- Only for deficiency of *N*-acetylglutamate synthase (NAGS) .

• Treatment for deficiencies in urea cycle enzymes

- Treatment of argininosuccinase (ASL) deficiency.



• SUMMARY 18.2

- Ammonia is highly toxic to animal tissues. In the urea cycle, ornithine combines with ammonia, in the form of carbamoyl phosphate, to form citrulline. A second amino group is transferred to citrulline from aspartate to form arginine—the immediate precursor of urea. Arginase catalyzes hydrolysis of arginine to urea and ornithine; thus ornithine is regenerated in each turn of the cycle.

- The urea cycle results in a net conversion of oxaloacetate to fumarate, both of which are intermediates in the citric acid cycle. The two cycles are thus interconnected.

• SUMMARY 18.2

- The activity of the urea cycle is regulated at the level of enzyme synthesis and by allosteric regulation of the enzyme that catalyzes the formation of carbamoyl phosphate.