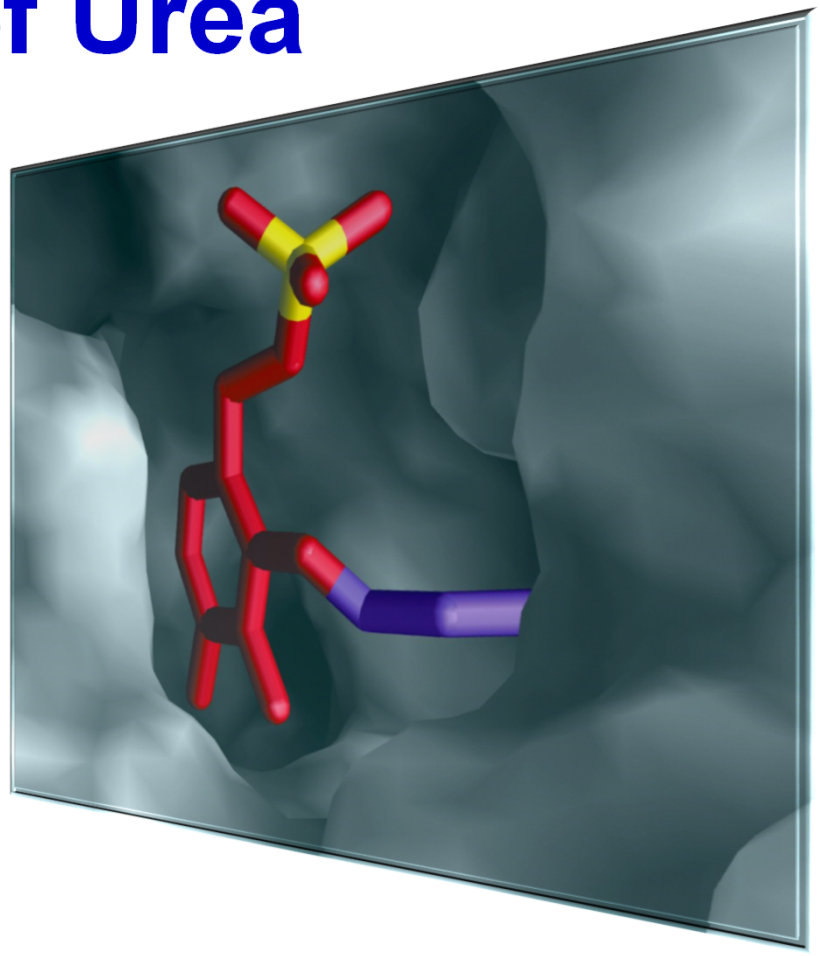
Chpt. 18

Amino acid oxidation and the production of Urea



1. Metabolic fates of amino group
2. Nitrogen excretion and the urea cycle
3. Pathways of amino acid degradation

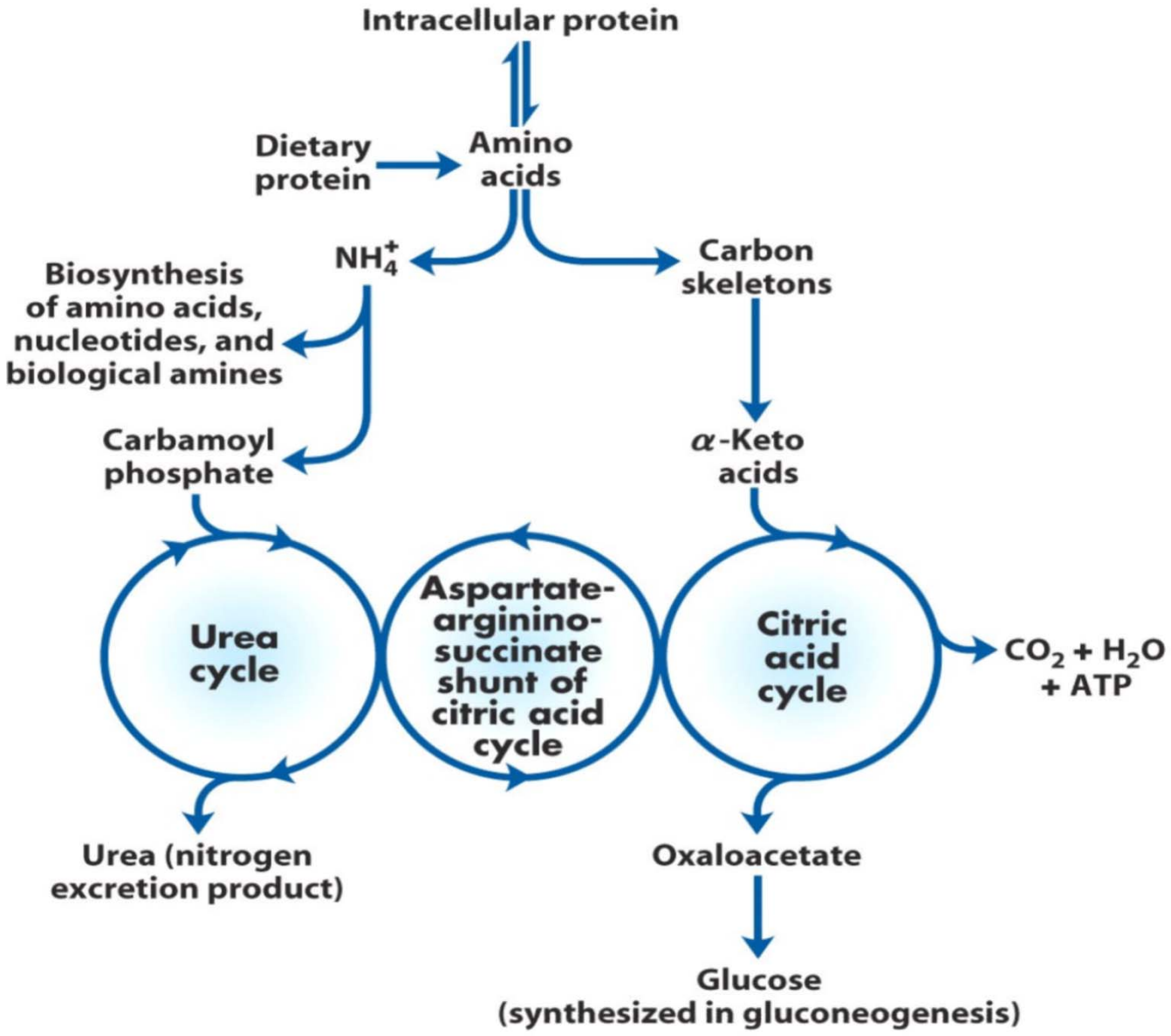
Amino acids undergo oxidative degradation in different metabolic circumstances

1. 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.

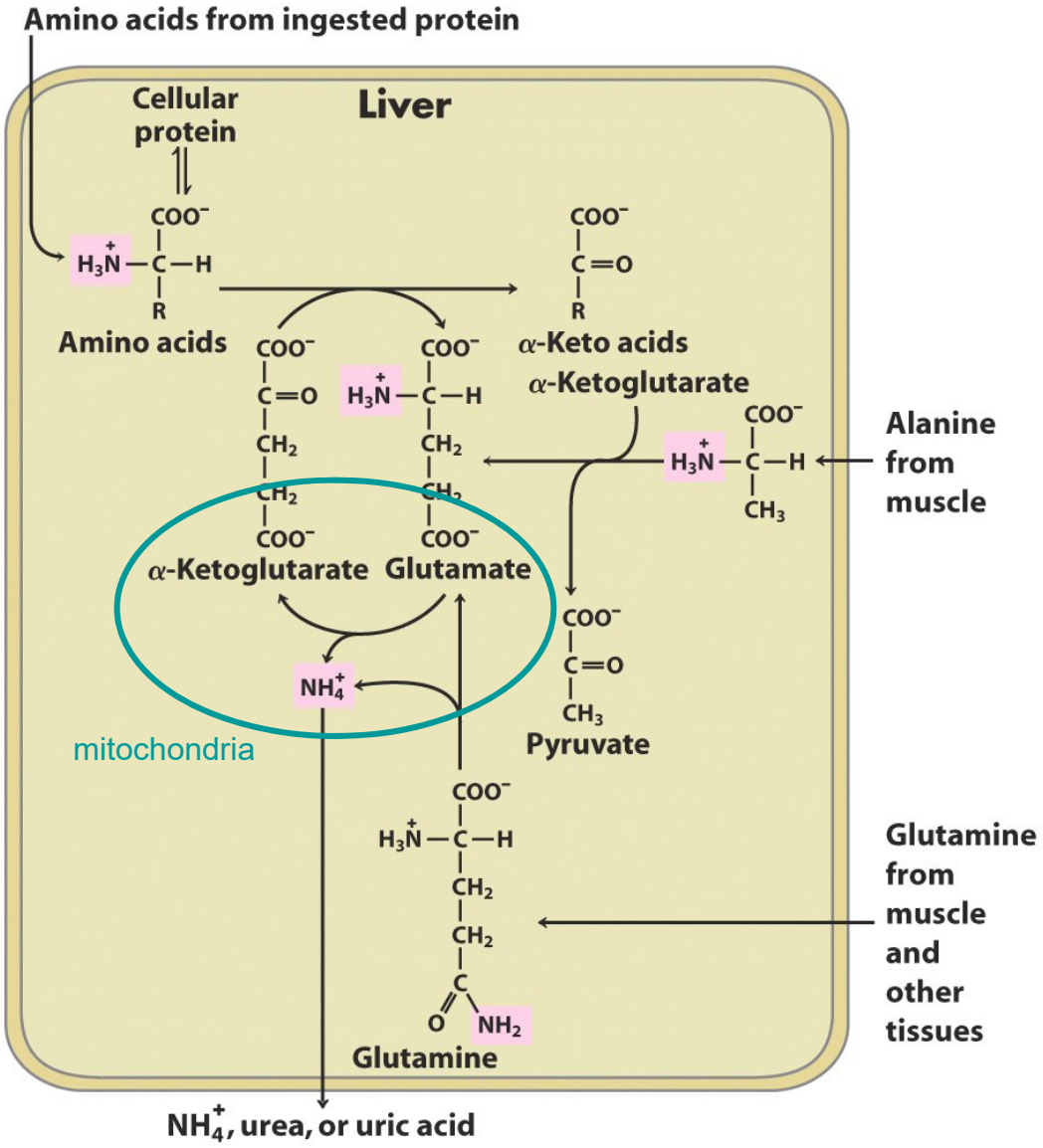
2. When a diet is rich in protein and the ingested amino acids exceed the body's needs for protein synthesis, the surplus is catabolized; *amino acids cannot be stored.*

3. During starvation or in uncontrolled diabetes melitus, when carbohydrates are either unavailable or not properly utilized, cellular proteins used as fuel.

Overview of amino acid catabolism in mammals



Metabolic fates of amino groups



NH_4^+

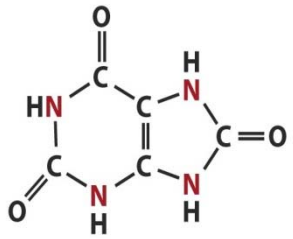
Ammonia (as ammonium ion)

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

$H_2N-C(=O)-NH_2$

Urea

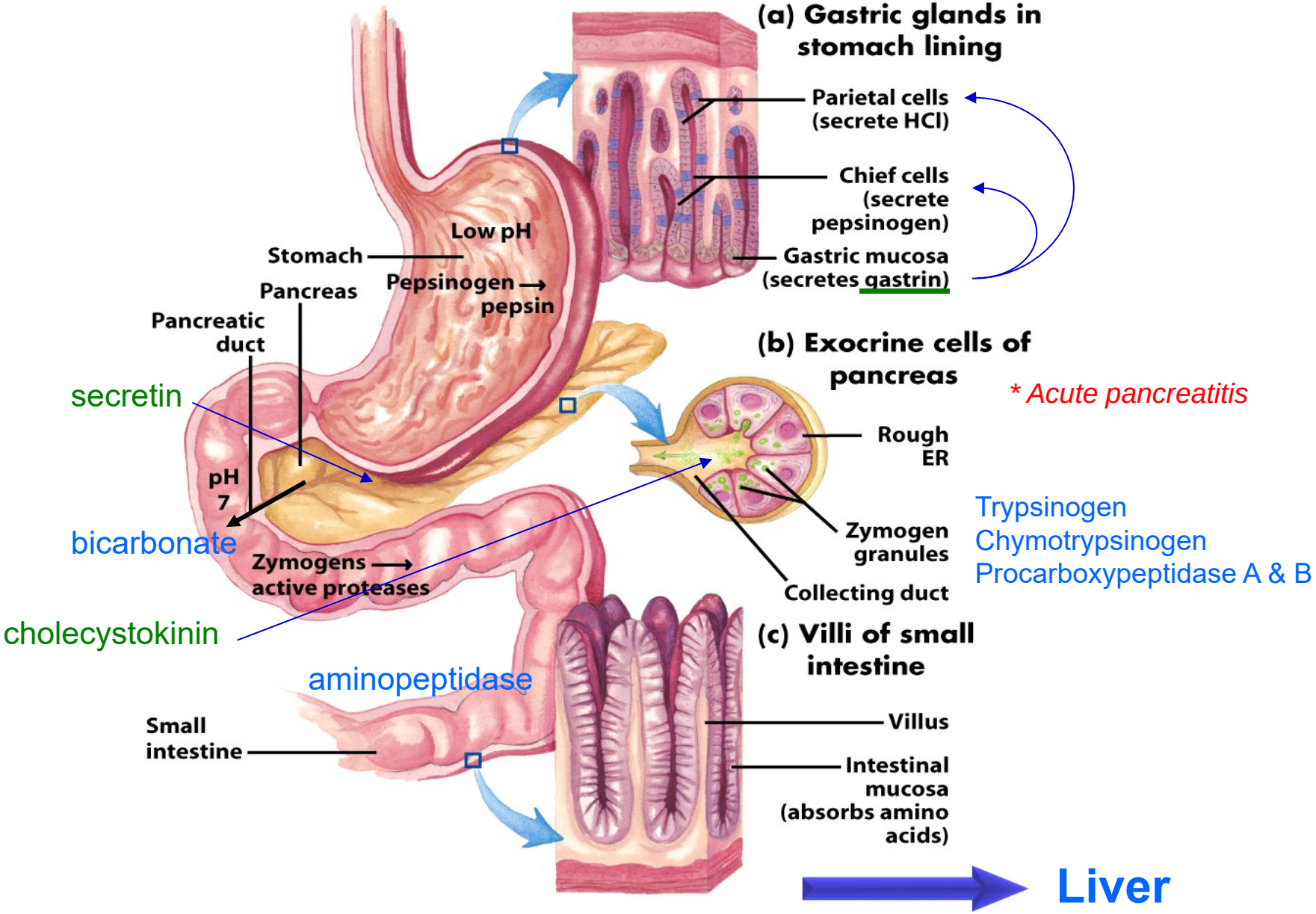
Ureotelic animals: many terrestrial vertebrates; also sharks



Uric acid

Uricotelic animals: birds, reptiles

Part of human digestive (gastrointestinal) tract



** Acute pancreatitis*

Activation of zymogens by proteolytic cleavage

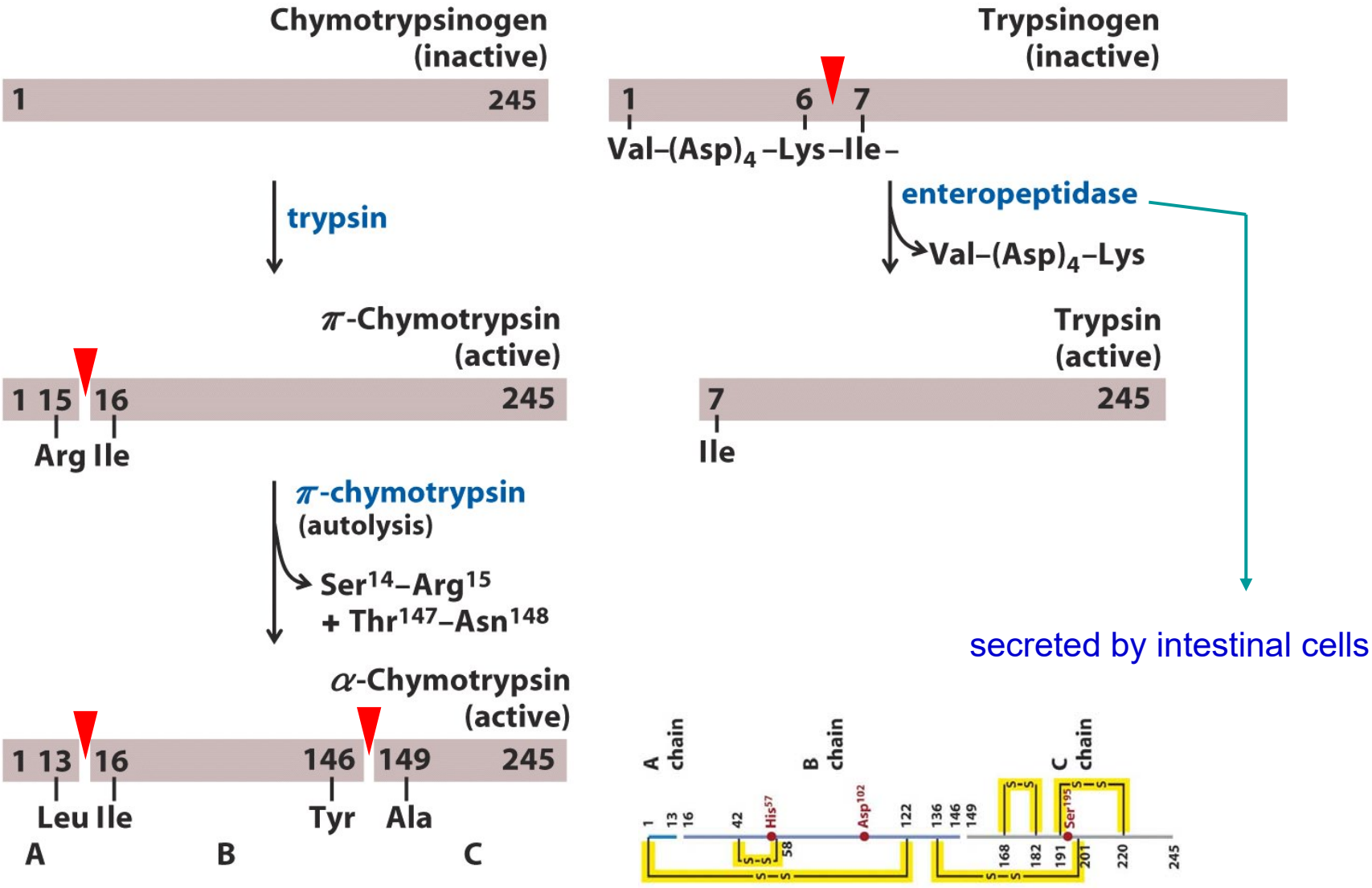


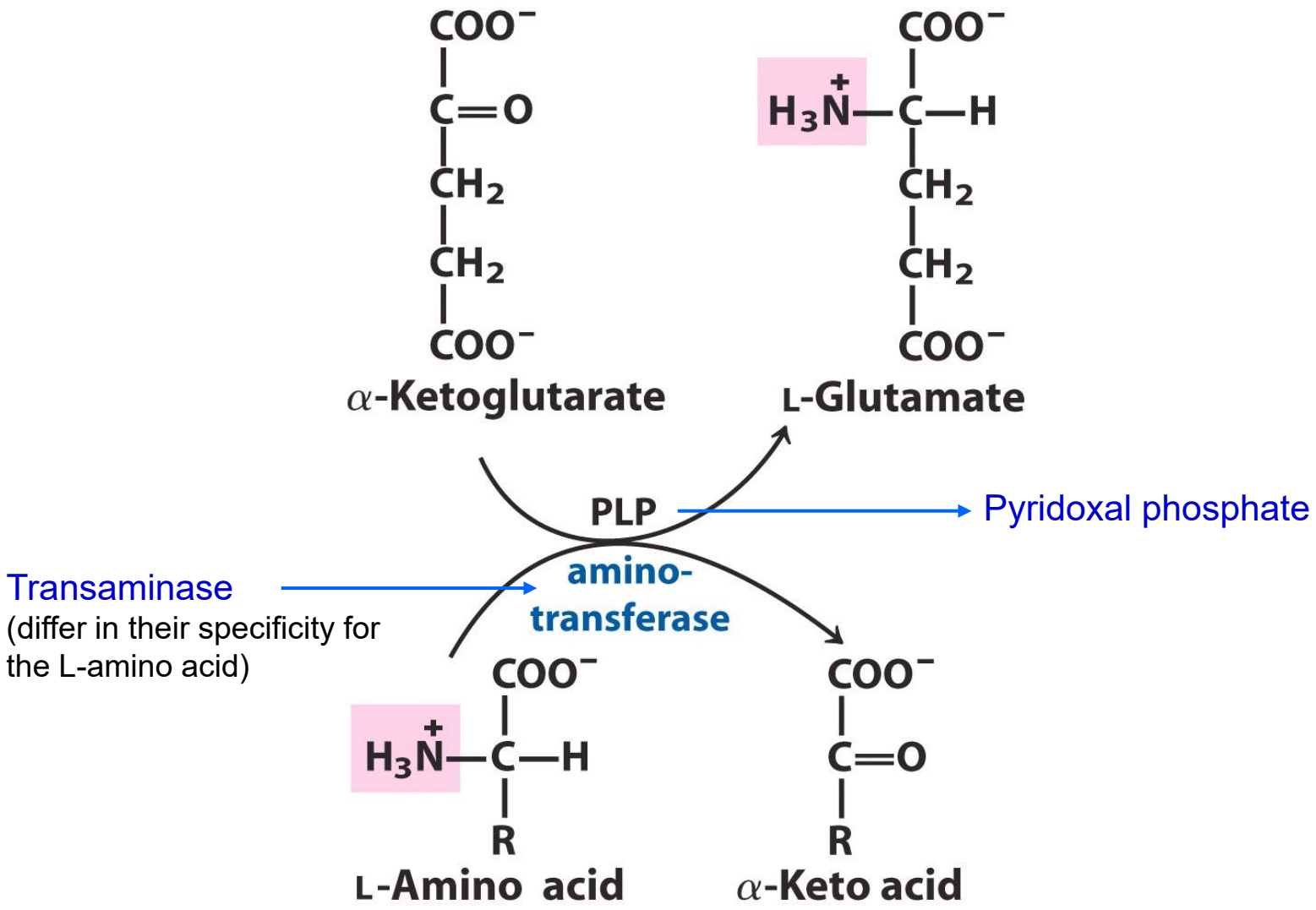
TABLE 3–7 The Specificity of Some Common Methods for Fragmenting Polypeptide Chains

*Reagent (biological source)**	*Cleavage points*[†]
Trypsin (bovine pancreas)	Lys, Arg (C)
Submaxillarus protease (mouse submaxillary gland)	Arg (C)
Chymotrypsin (bovine pancreas)	Phe, Trp, Tyr (C)
Staphylococcus aureus V8 protease (bacterium *S. aureus*)	Asp, Glu (C)
Asp-*N*-protease (bacterium *Pseudomonas fragi*)	Asp, Glu (N)
Pepsin (porcine stomach)	Phe, Trp, Tyr (N)
Endoproteinase Lys C (bacterium *Lysobacter enzymogenes*)	Lys (C)
Cyanogen bromide	Met (C)

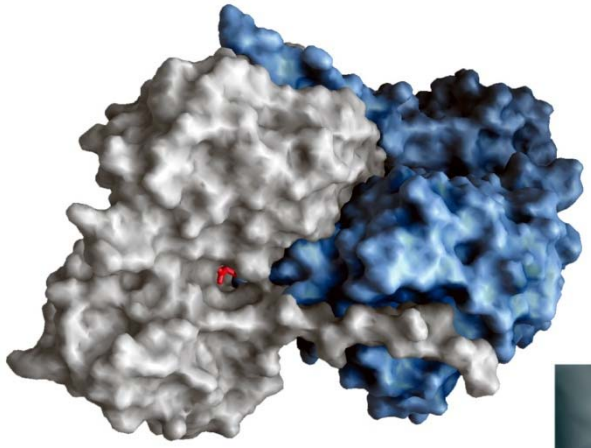
*All reagents except cyanogen bromide are proteases. All are available from commercial sources.

[†]Residues furnishing the primary recognition point for the protease or reagent; peptide bond cleavage occurs on either the carbonyl (C) or the amino (N) side of the indicated amino acid residues.

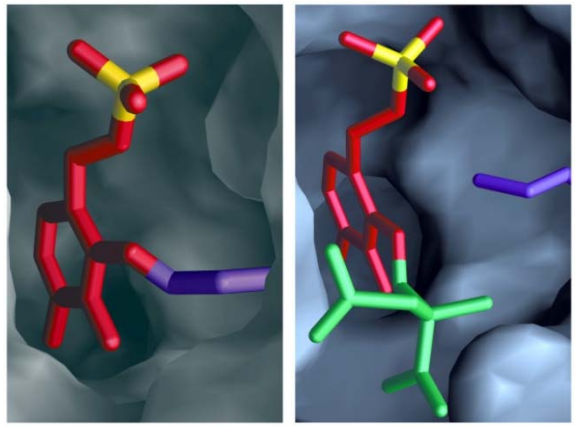
Enzyme-catalyzed transaminations

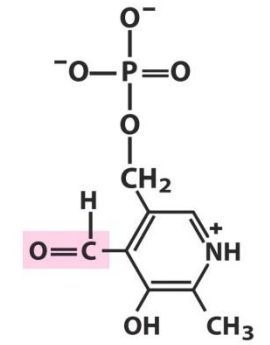


Pyridoxal phosphate, the prosthetic group of aminotransferase

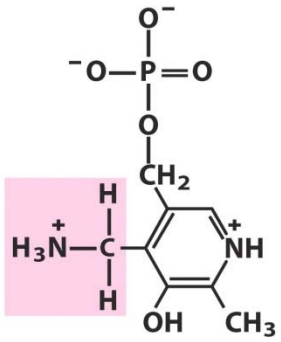


Asp aminotransferase

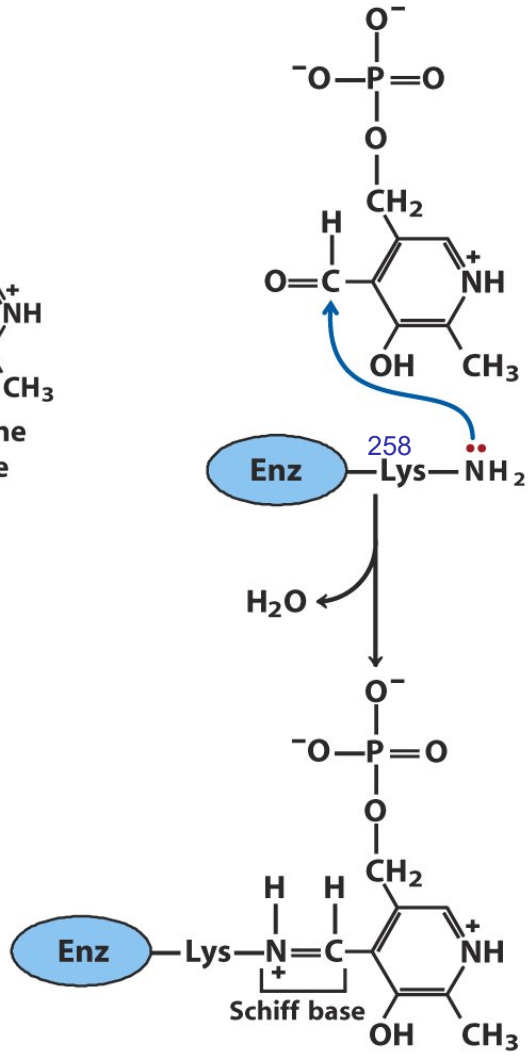




Pyridoxal phosphate (PLP)

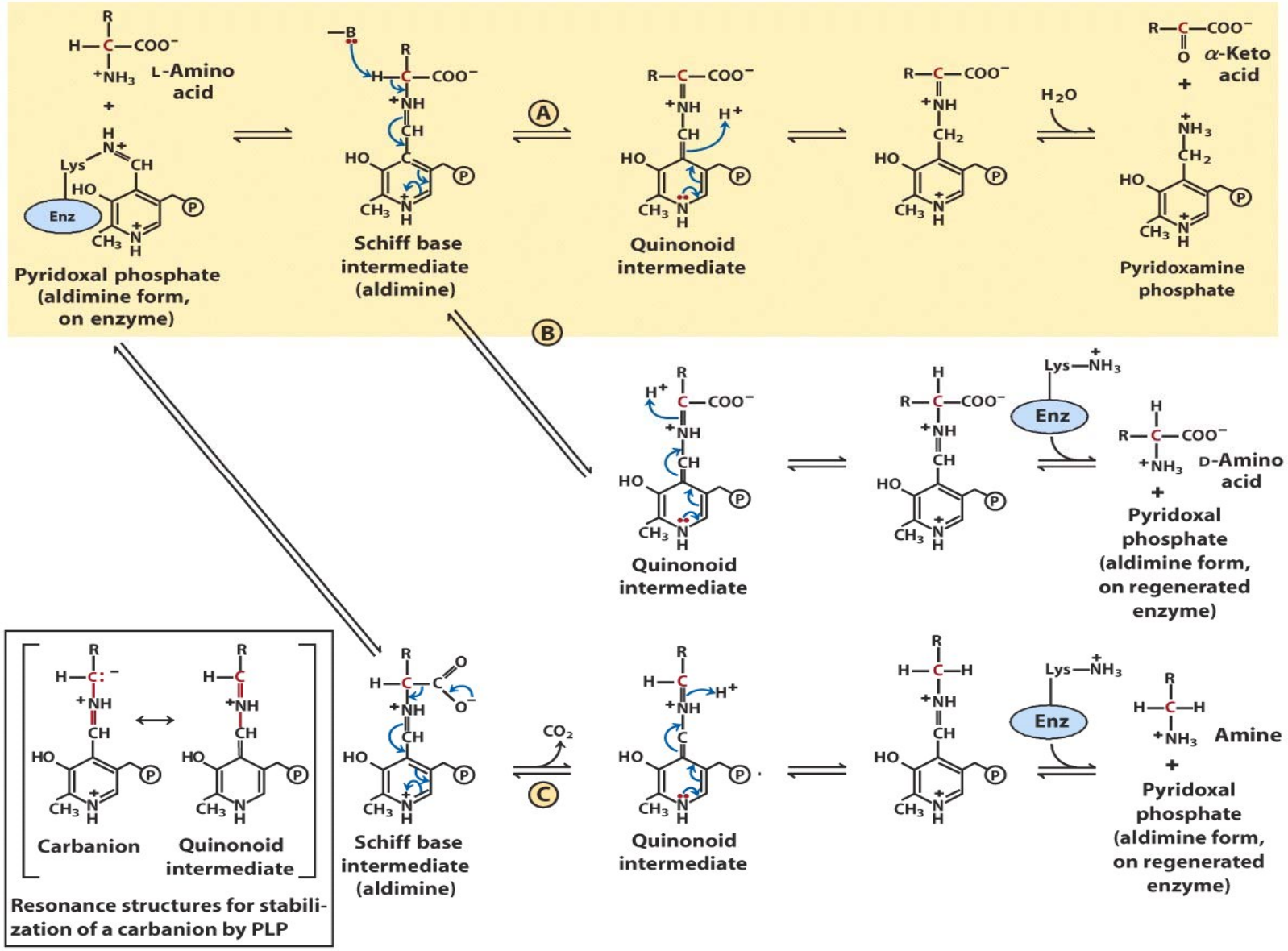


Pyridoxamine phosphate

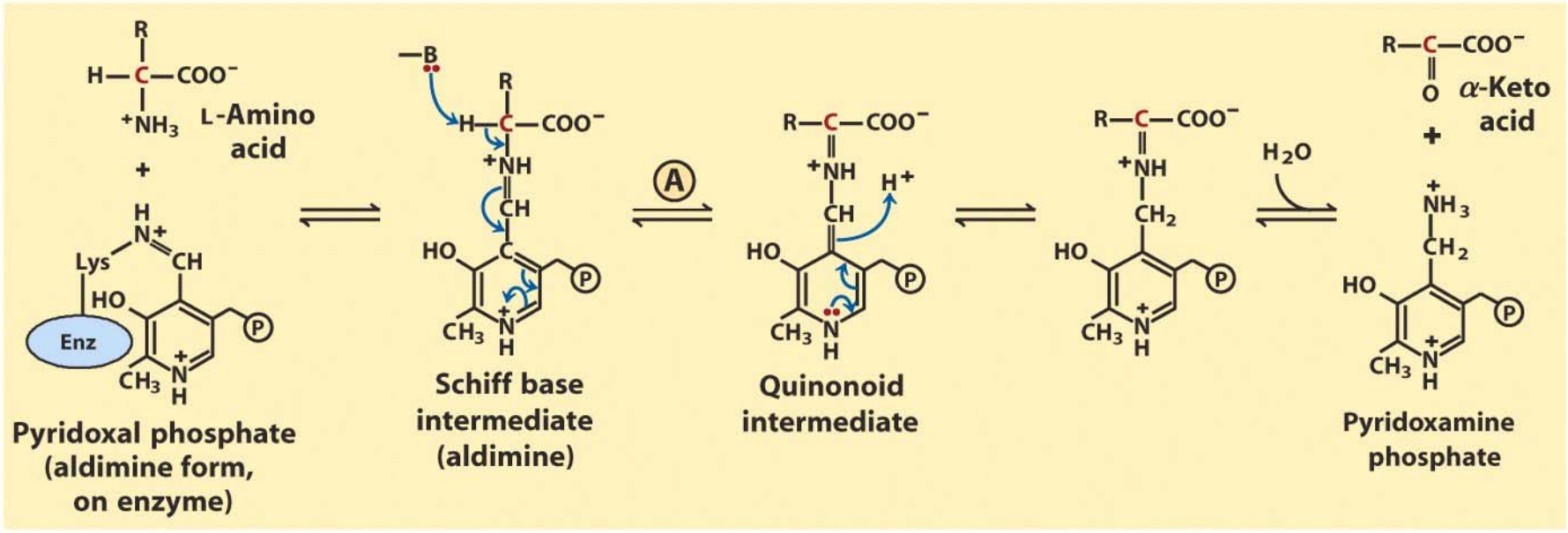


aldimine linkage

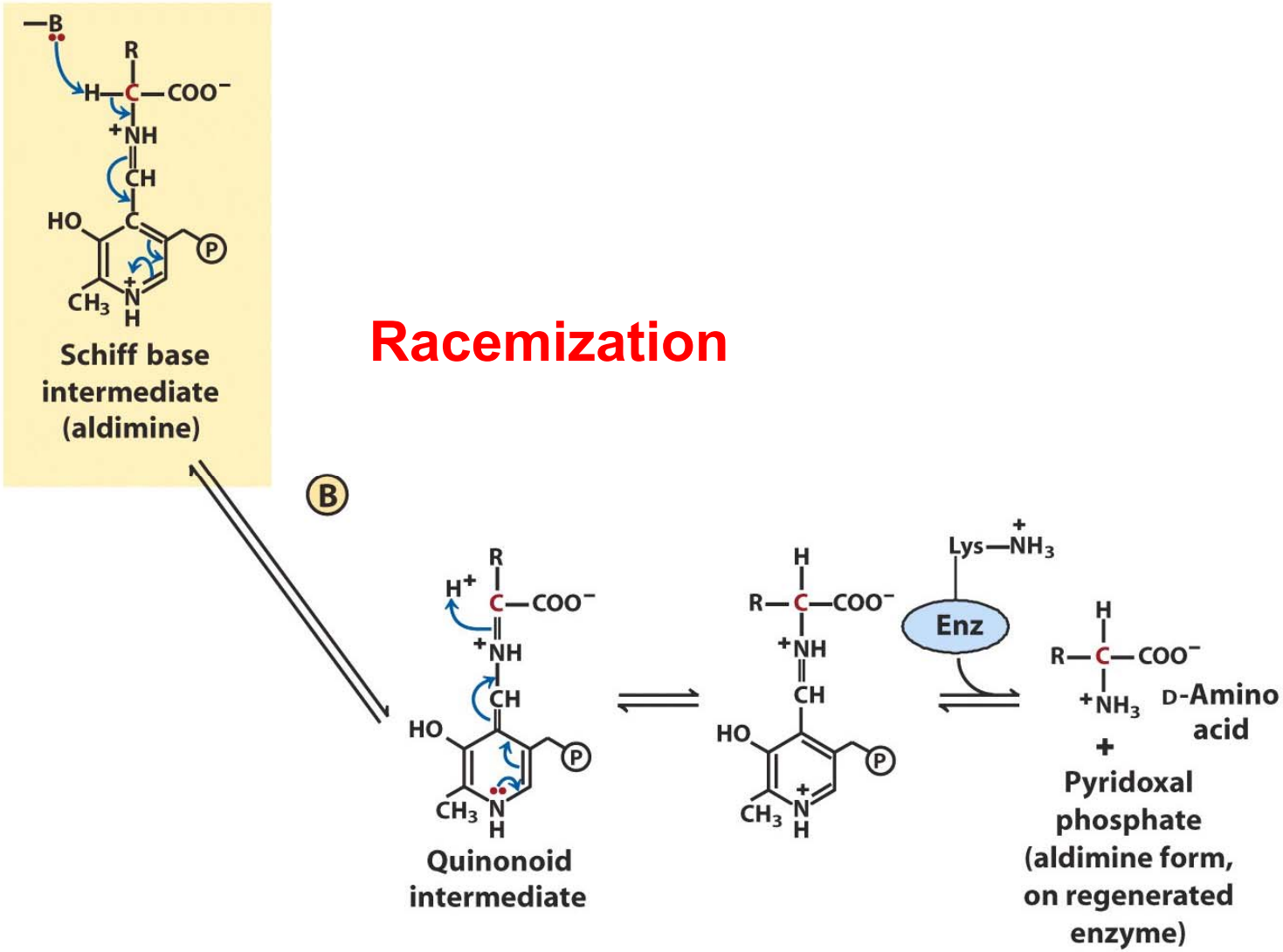
Some amino acid transformations at the α carbon that are facilitated by pyridoxal phosphate

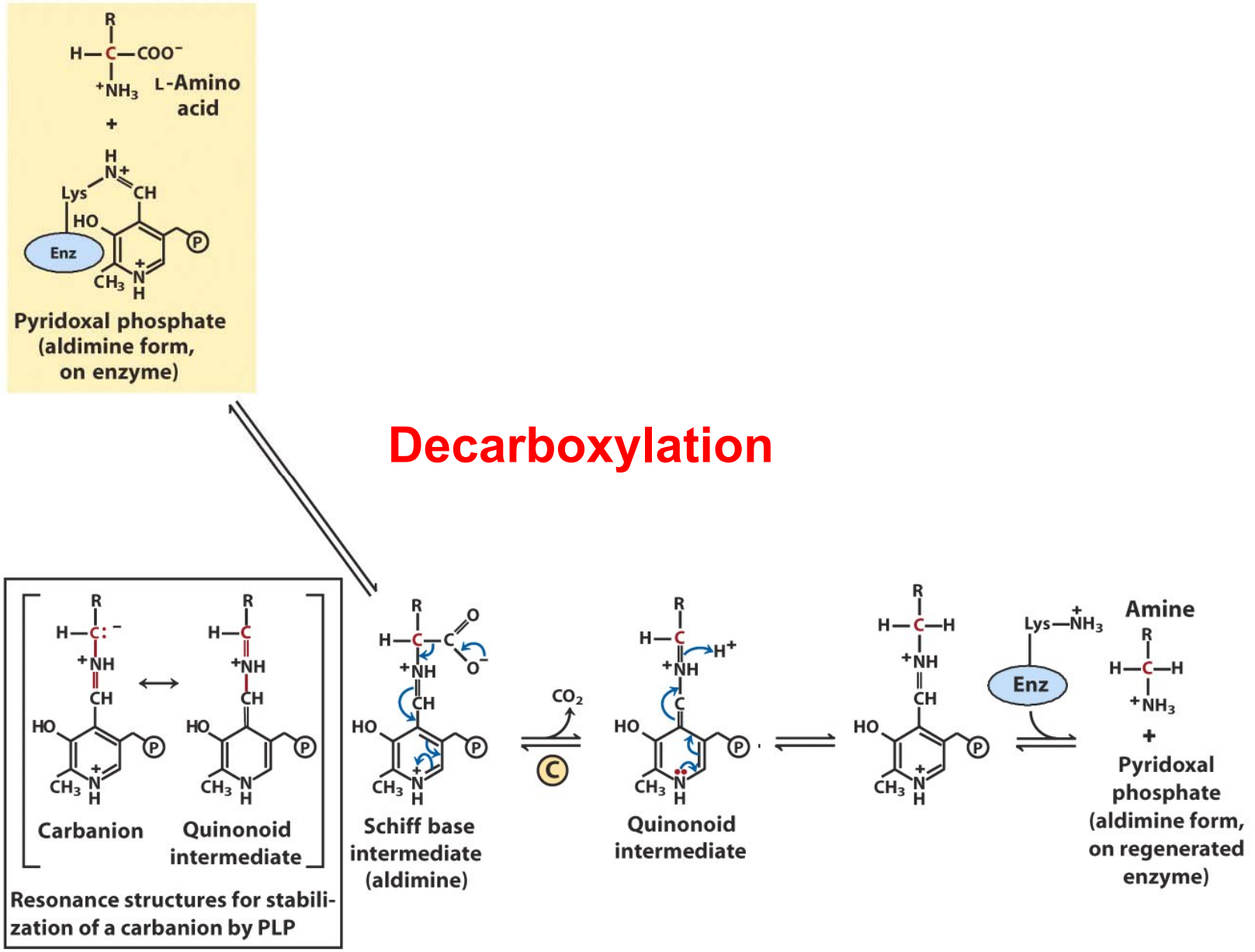


Transamination

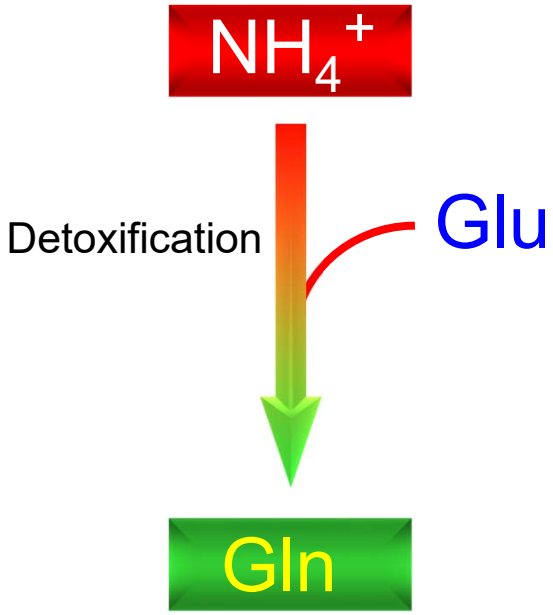


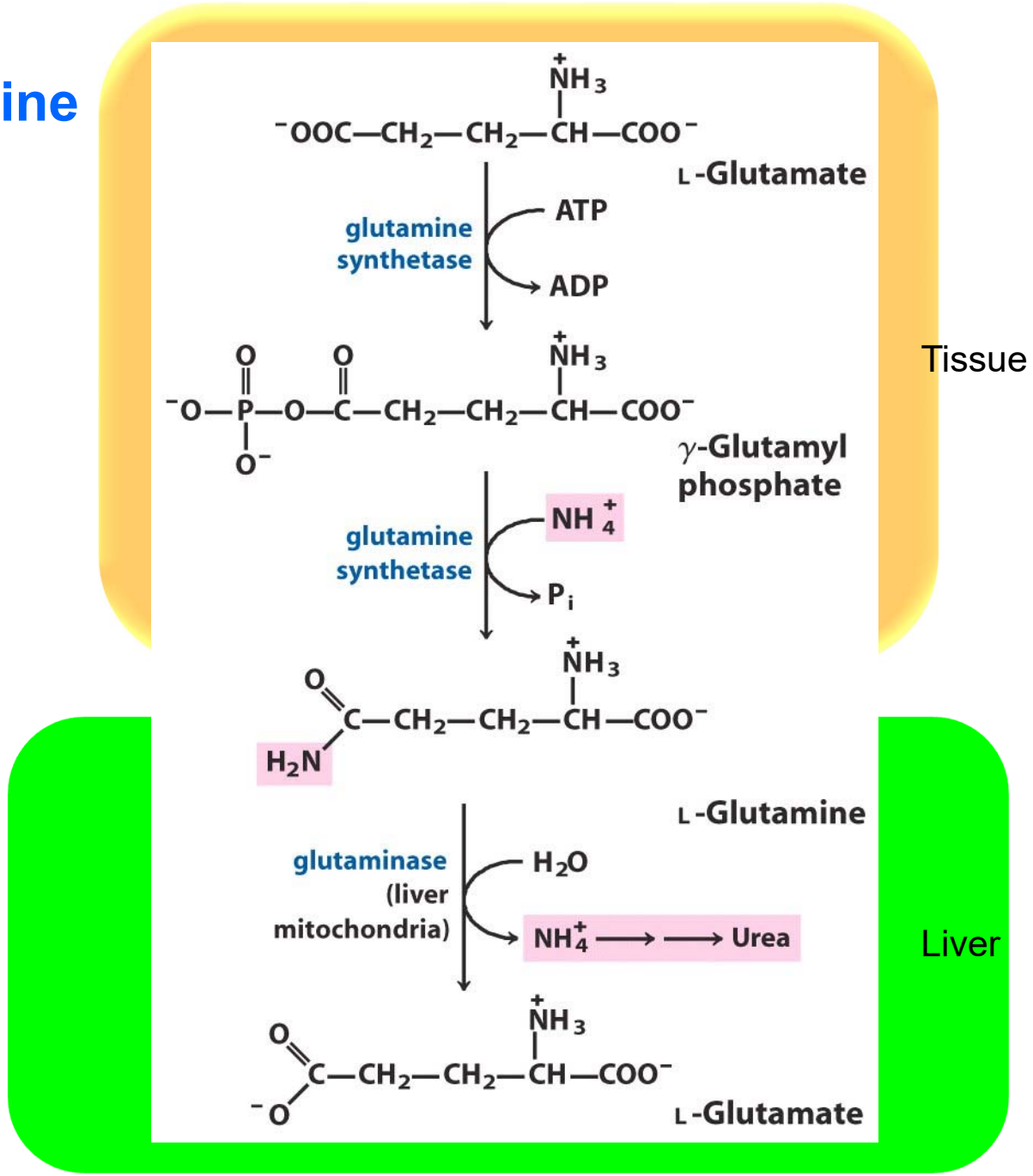
Racemization




L-Amino acid
Pyridoxal phosphate (aldimine form, on enzyme)
Decarboxylation
Carbanion
Quinonoid intermediate
Resonance structures for stabilization of a carbanion by PLP
Schiff base intermediate (aldimine)
Quinonoid intermediate
Amine
Pyridoxal phosphate (aldimine form, on regenerated enzyme)

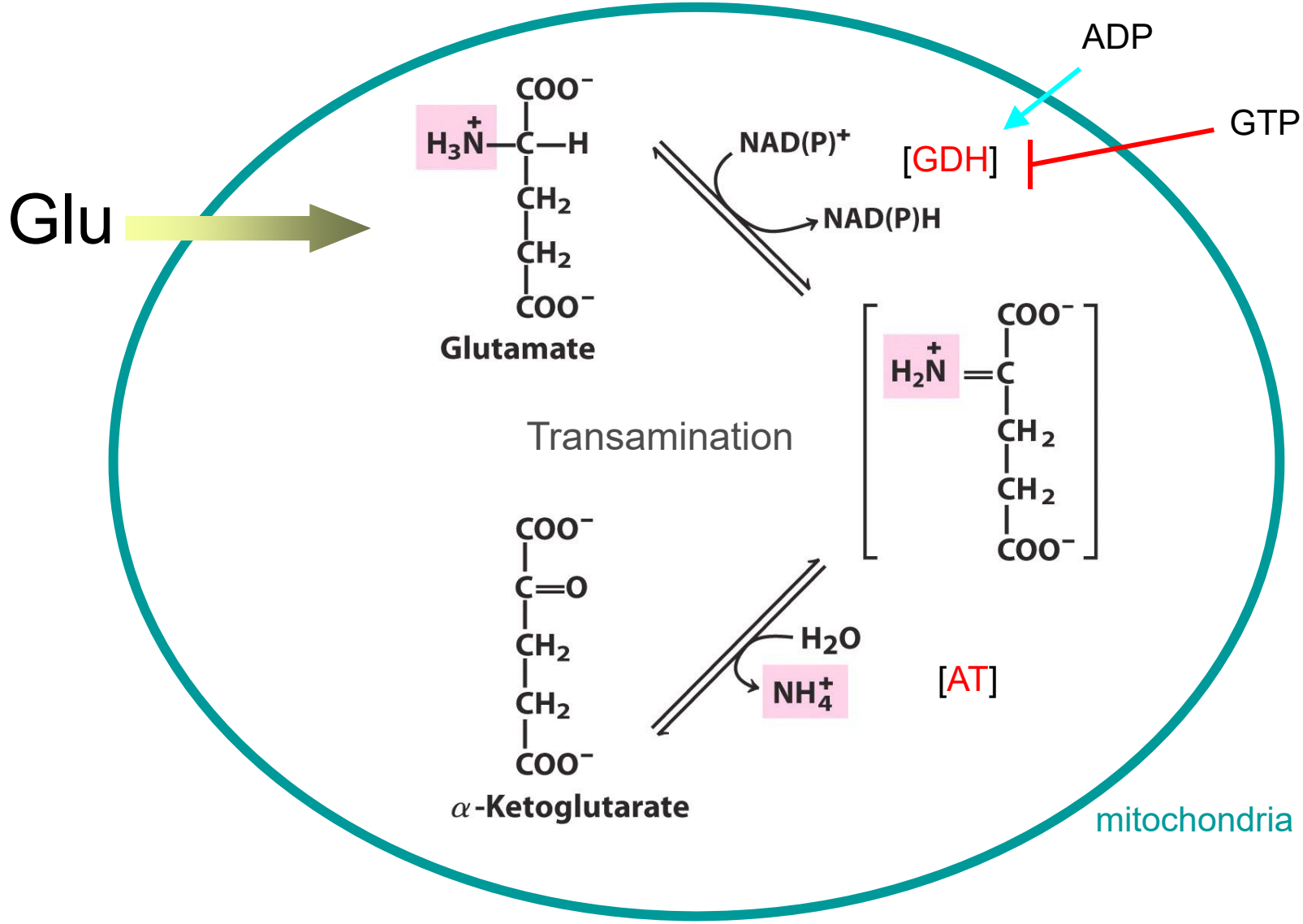
Ammonia transport in the form of glutamine



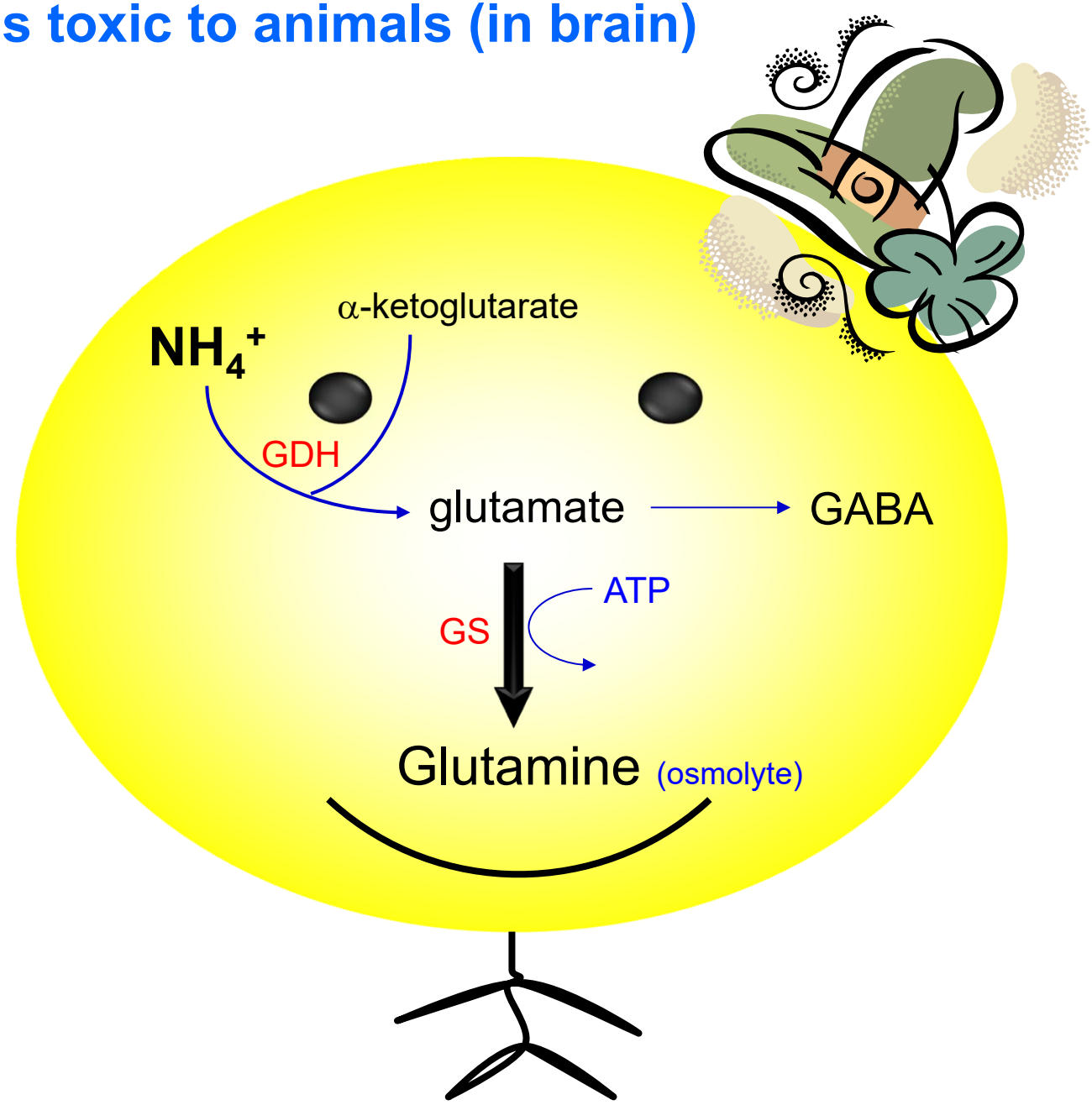


Reaction catalyzed by glutamate dehydrogenase

(Glutamate releases its amino group as ammonia in the liver)

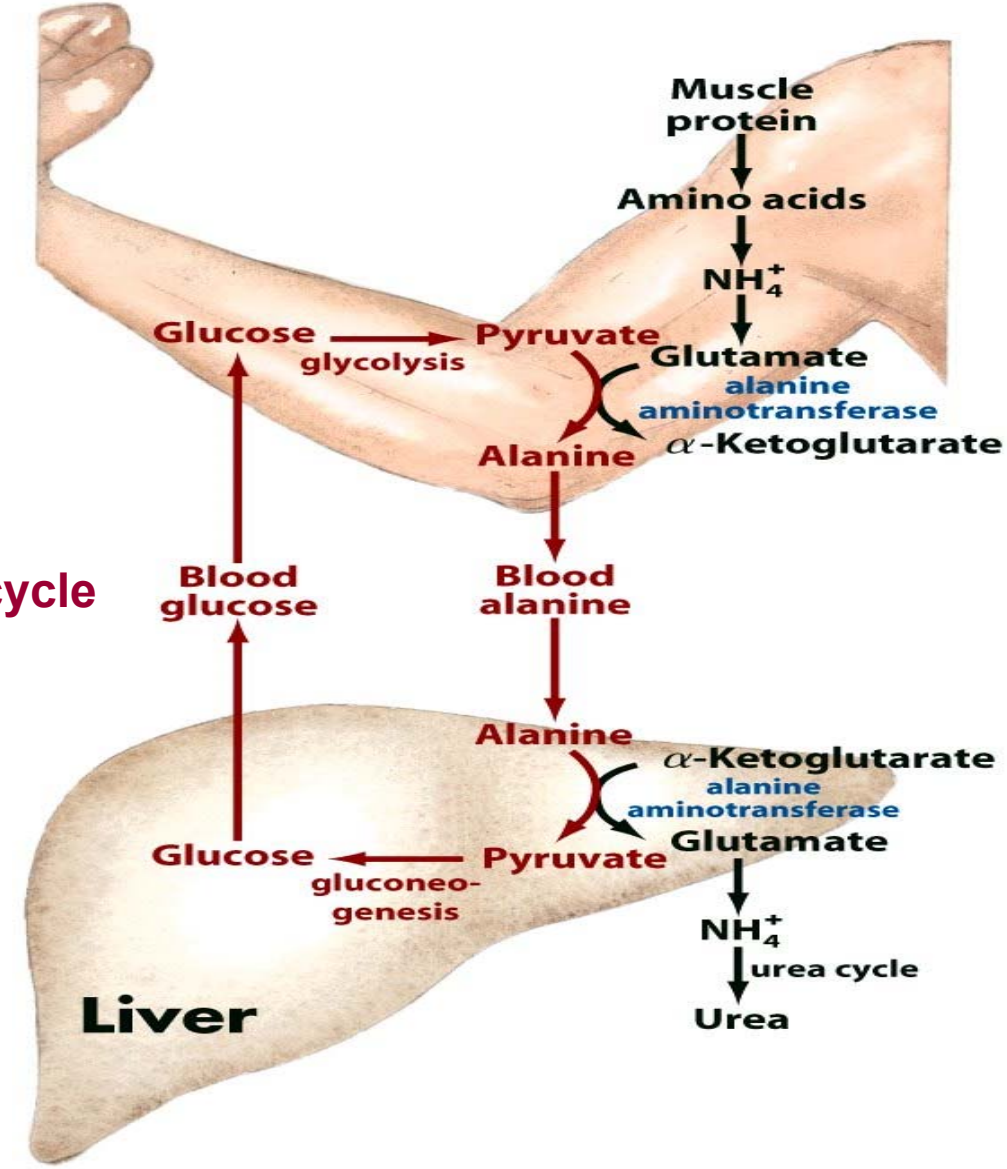


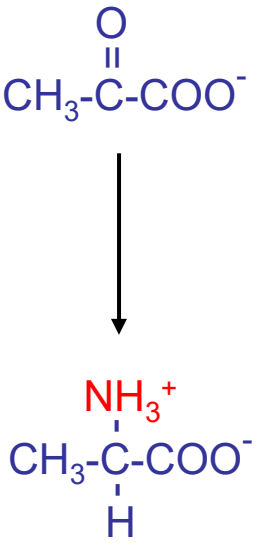
Ammonia is toxic to animals (in brain)



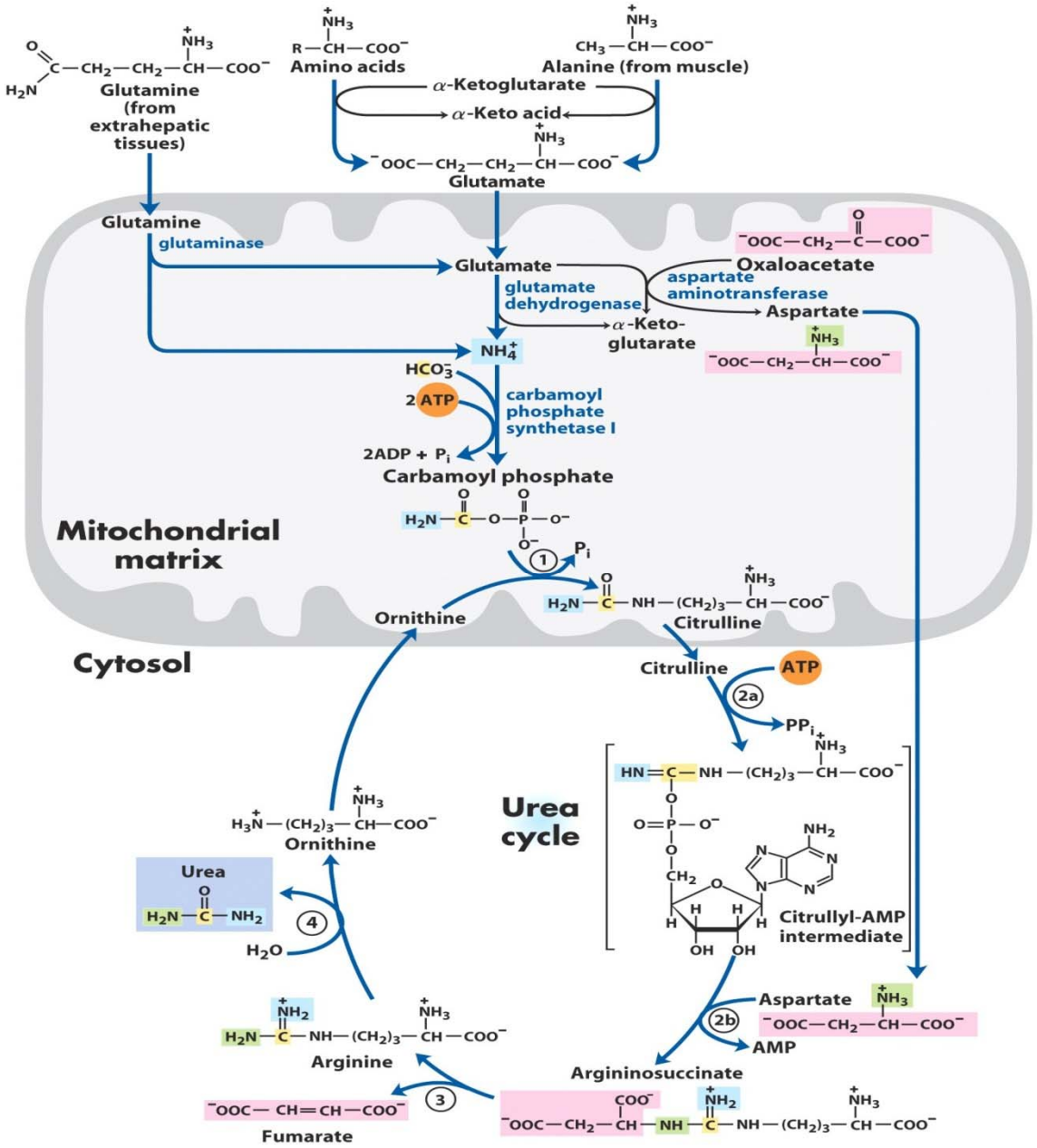
Alanine transports ammonia from skeletal muscle to the liver

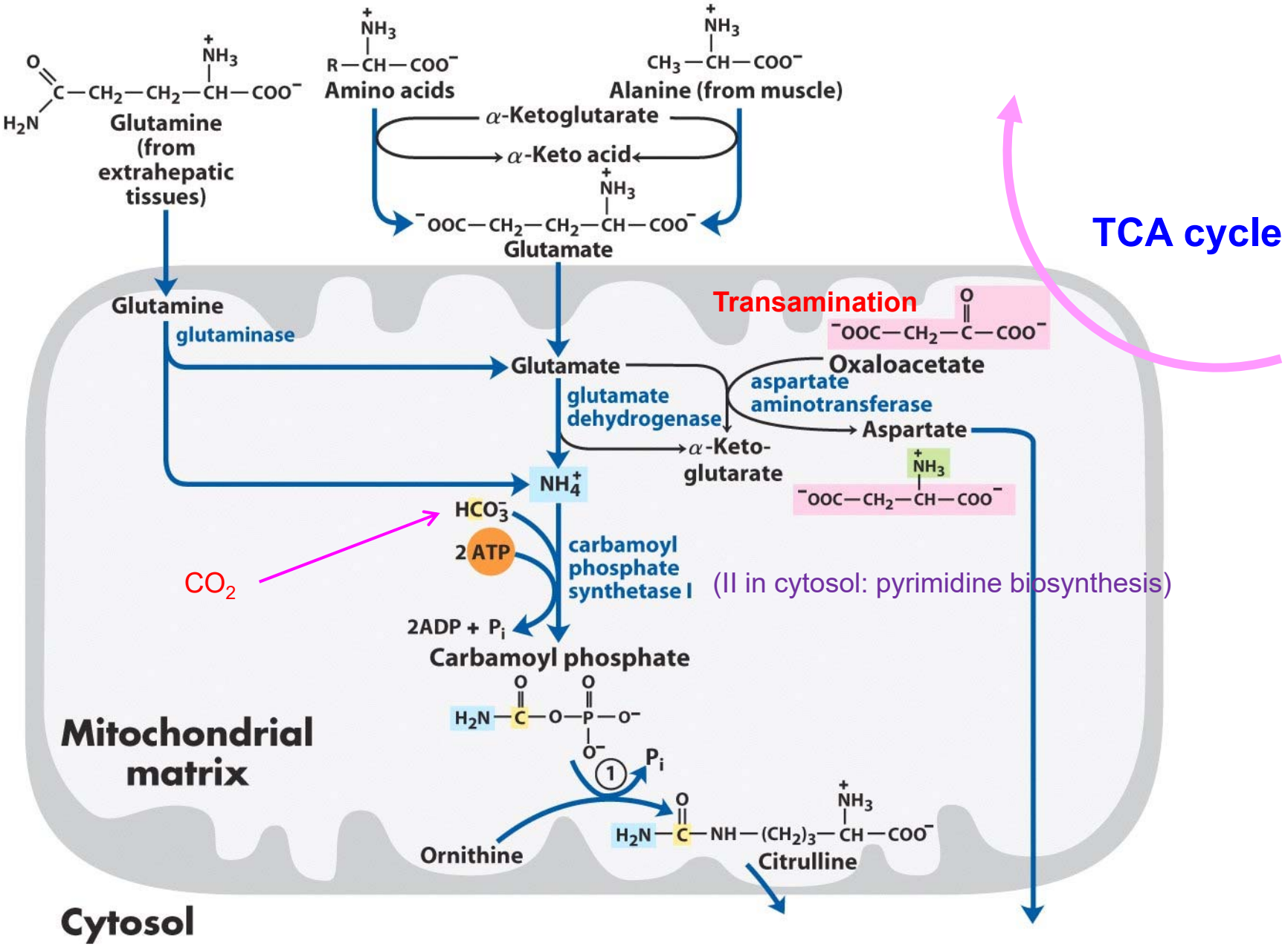
Glucose-alanine cycle

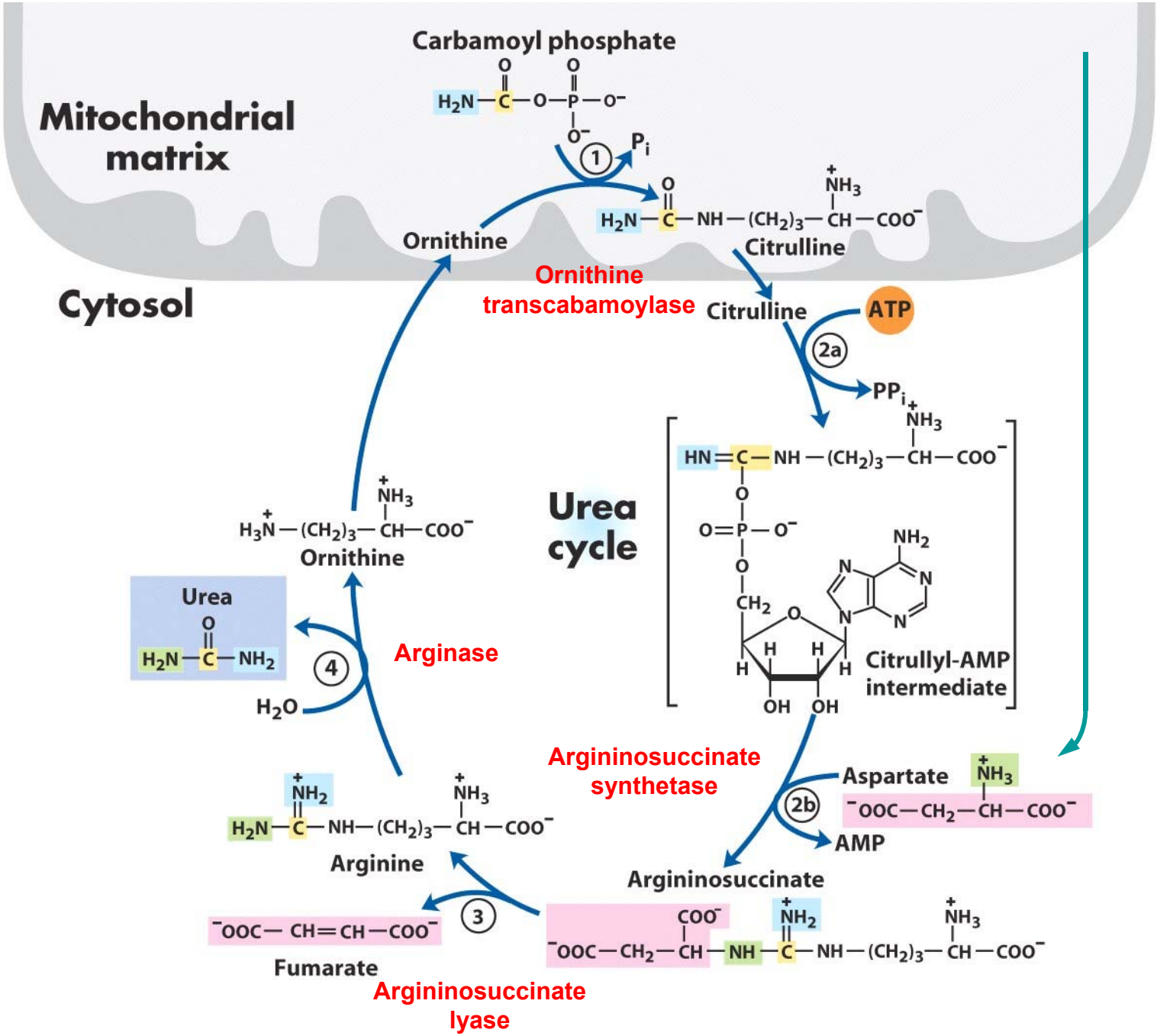




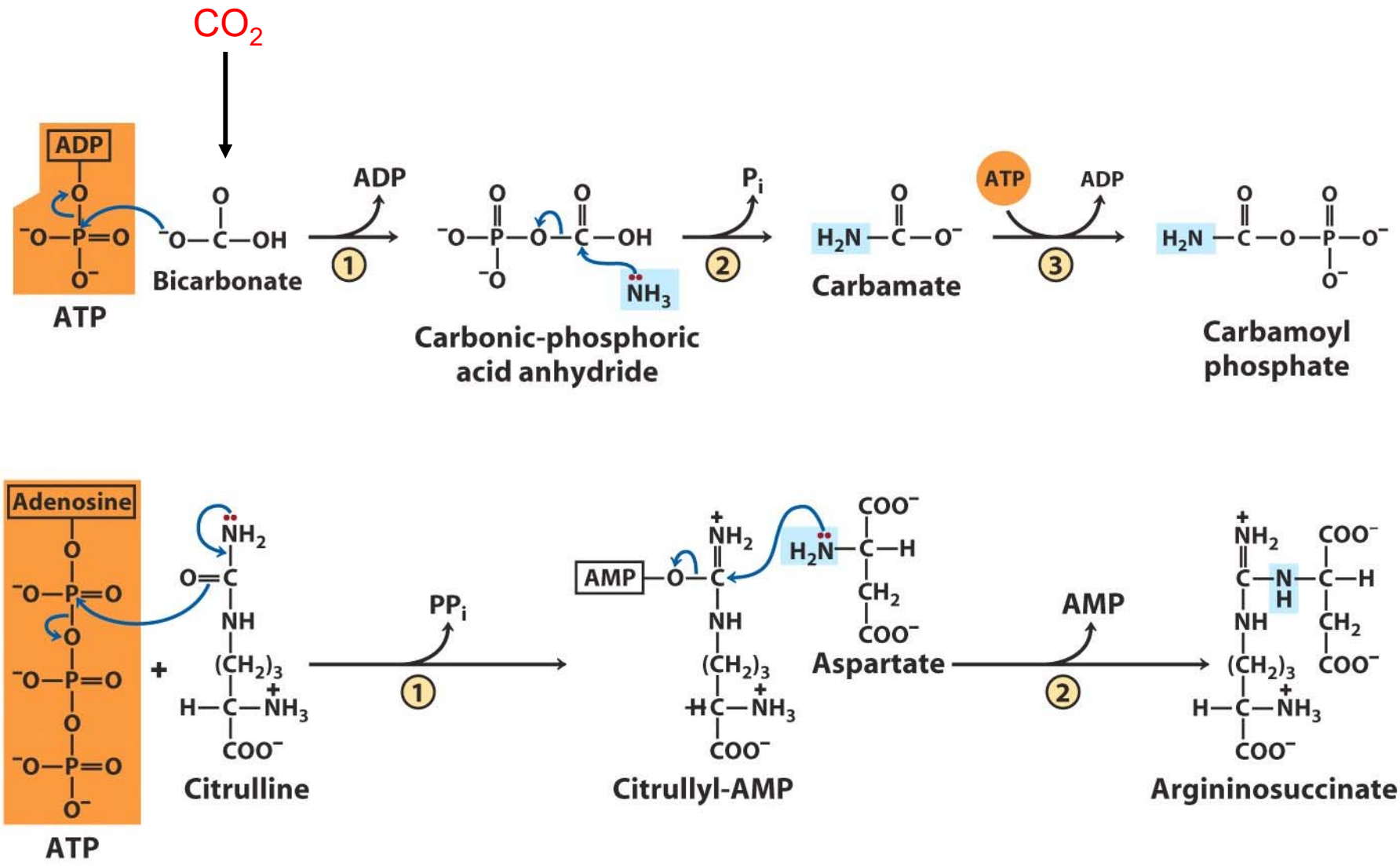
Urea cycles and reactions that feed amino groups into the cycle



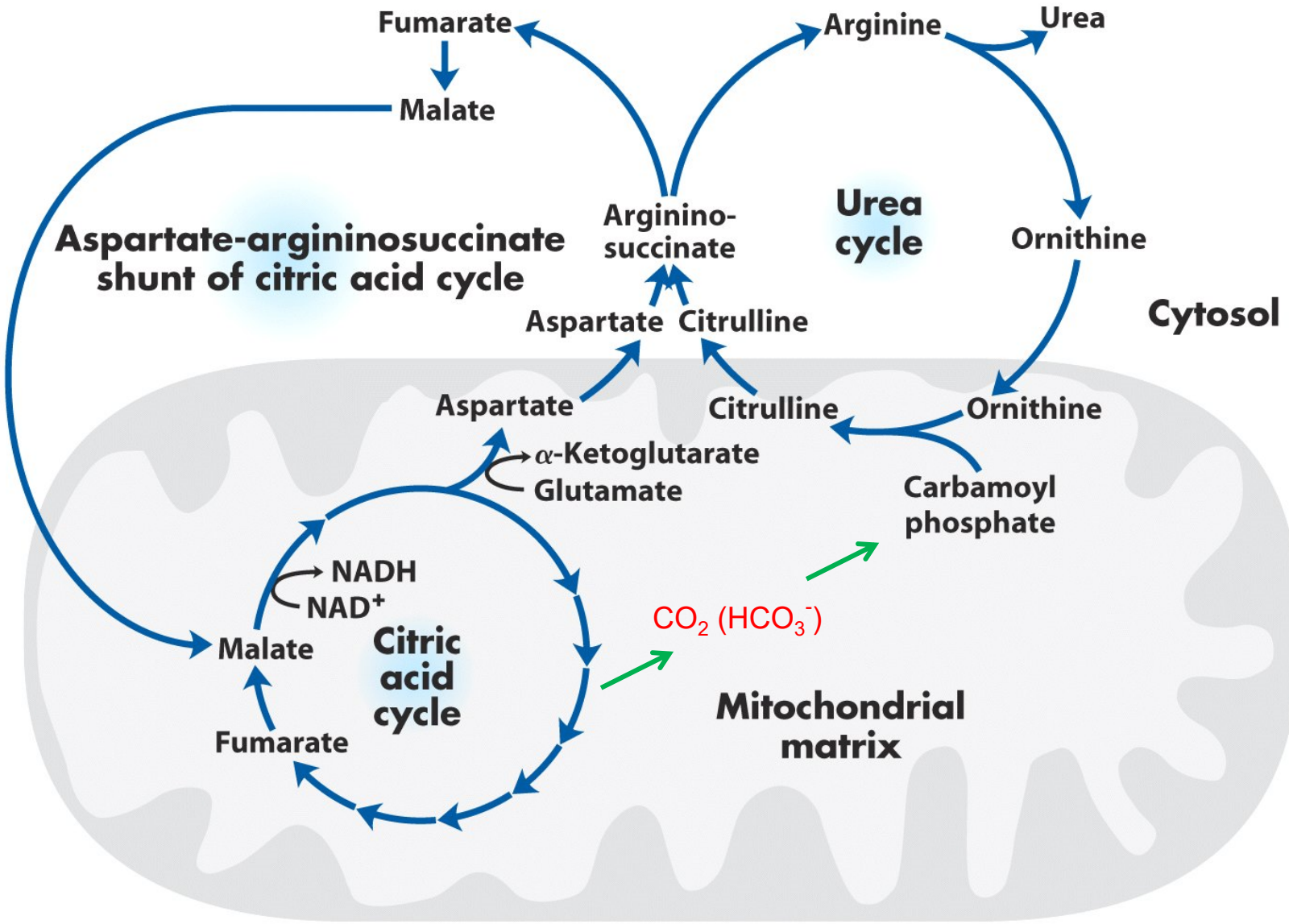

Glutamine
(from
extrahepatic
tissues)
Amino acids
Alanine (from muscle)
α-Ketoglutarate
α-Keto acid
Glutamate
TCA cycle
Transamination
Oxaloacetate
aspartate
aminotransferase
Aspartate
Glutamine
glutaminase
Glutamate
glutamate
dehydrogenase
α-Keto-
glutarate
NH4+
HCO3−
2 ATP
carbamoyl
phosphate
synthetase I
CO2
(II in cytosol: pyrimidine biosynthesis)
2ADP + Pi
Carbamoyl phosphate
Mitochondrial
matrix
Pi
Ornithine
Citrulline
Cytosol


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

Nitrogen-acquiring reactions in the synthesis of urea



Links between the urea cycle and citric acid cycle



The activity of the urea cycle is regulated

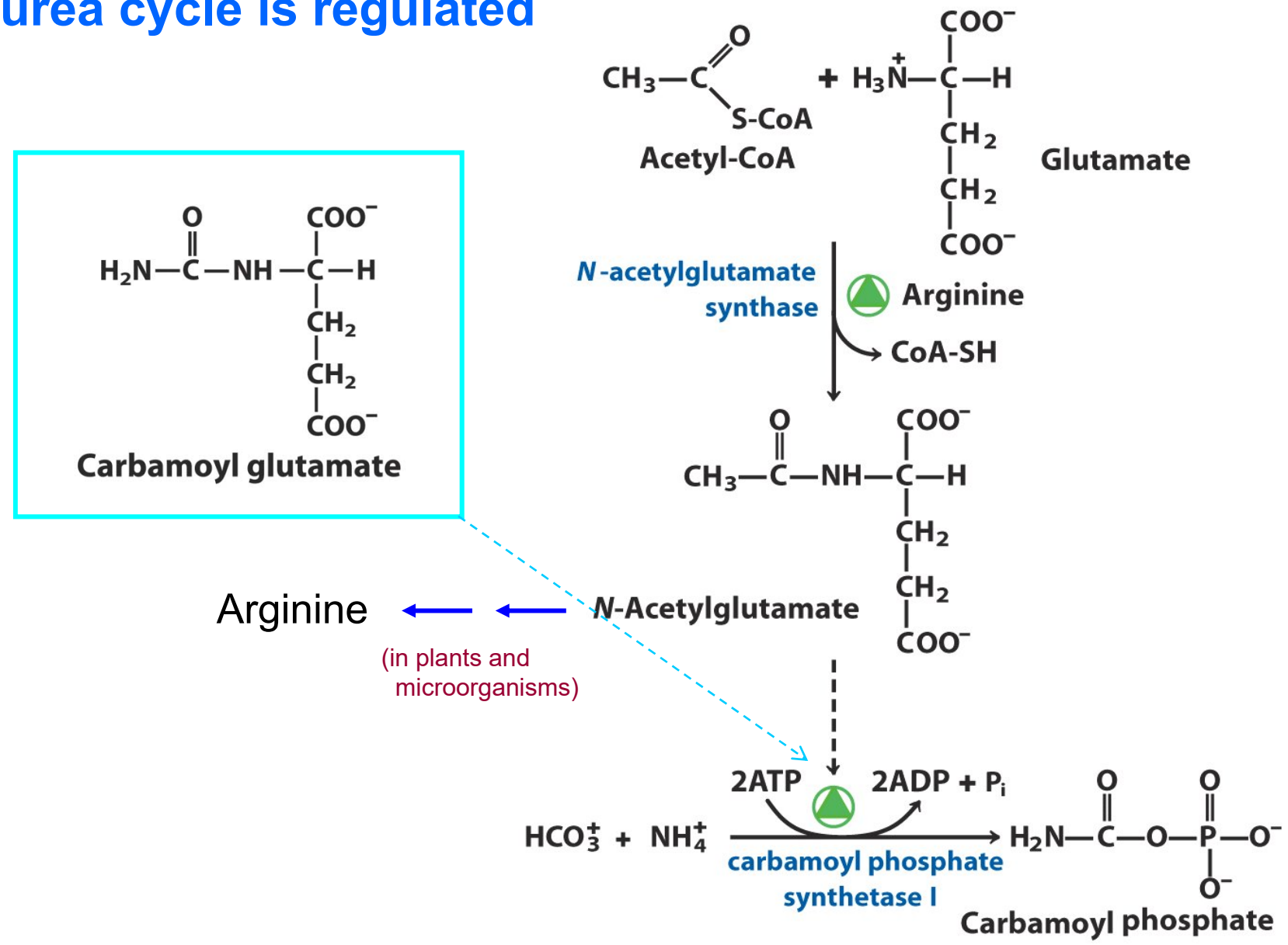
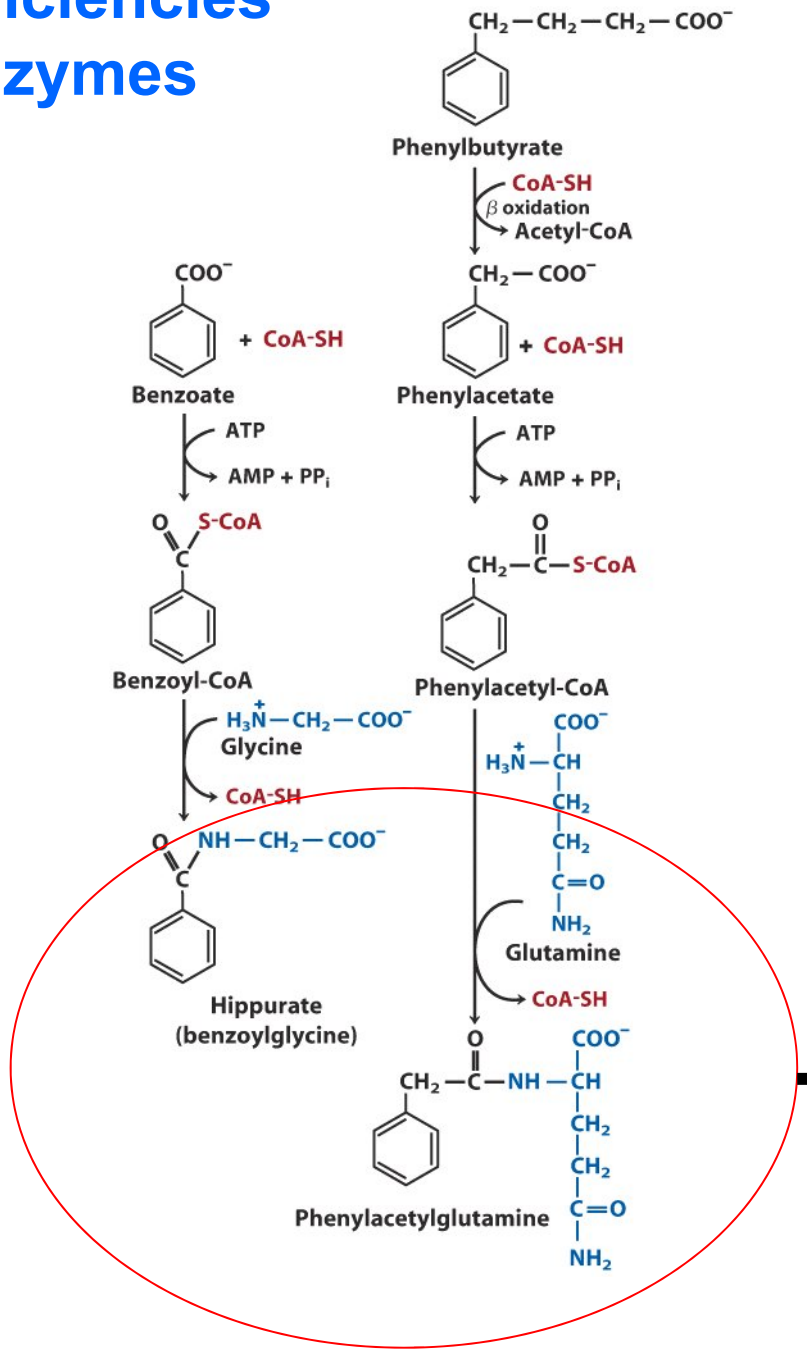


TABLE 18–1 Nonessential and Essential Amino Acids for Humans and the Albino Rat

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.

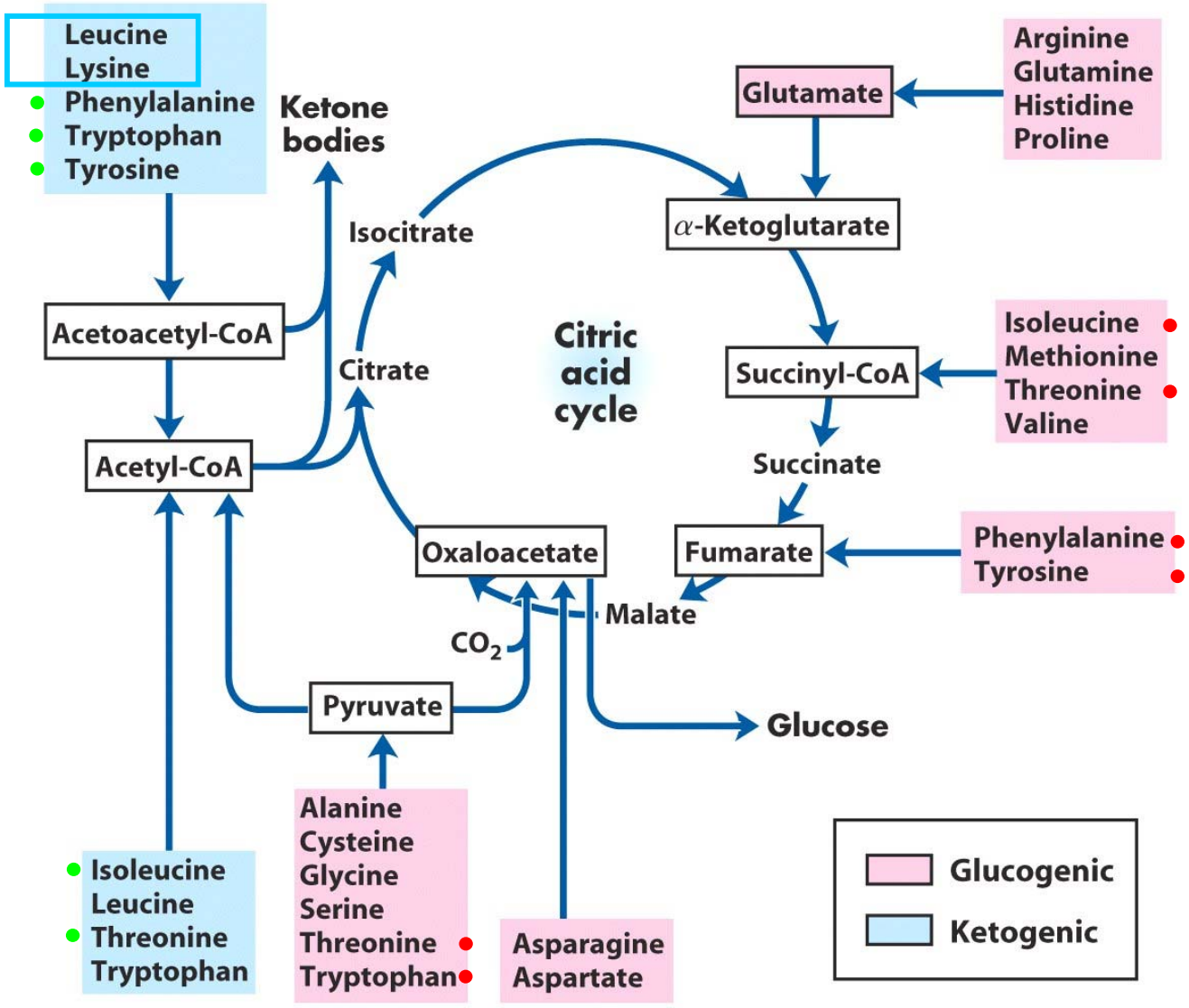
Treatment of deficiencies in urea cycle enzymes



excreted in the urine

Summary of amino acid catabolism

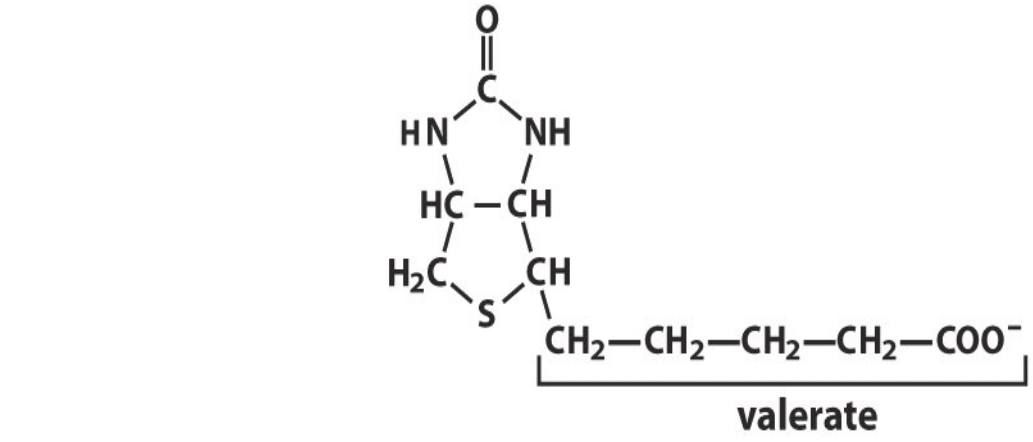
(account for only 10 ~ 15% of the human body's energy production)



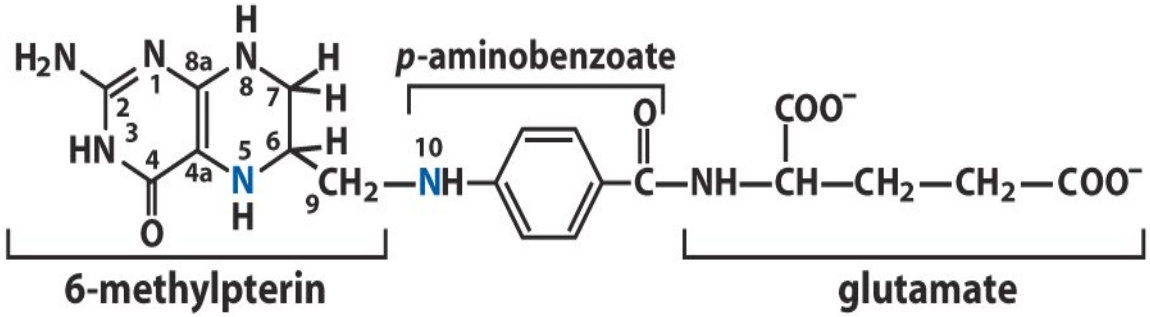
Some enzyme cofactors important in one-carbon transfer reactions

(* transamination: PLP)

Amino acid catabolism: transamination
one-carbon transfer

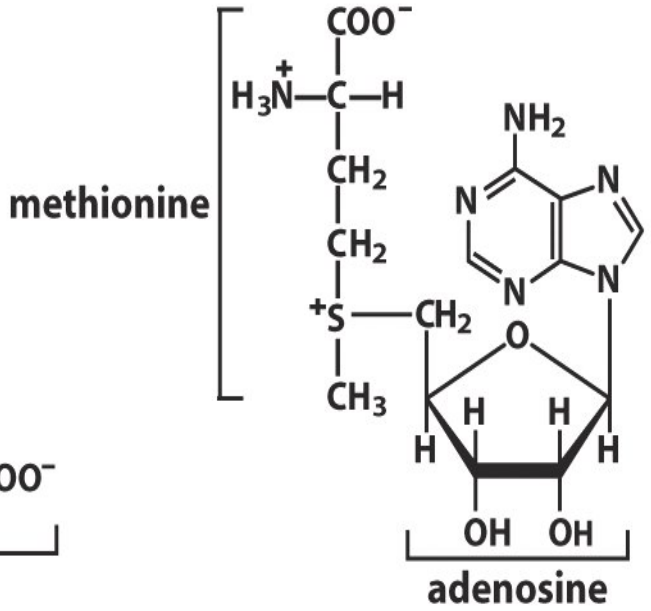


Biotin



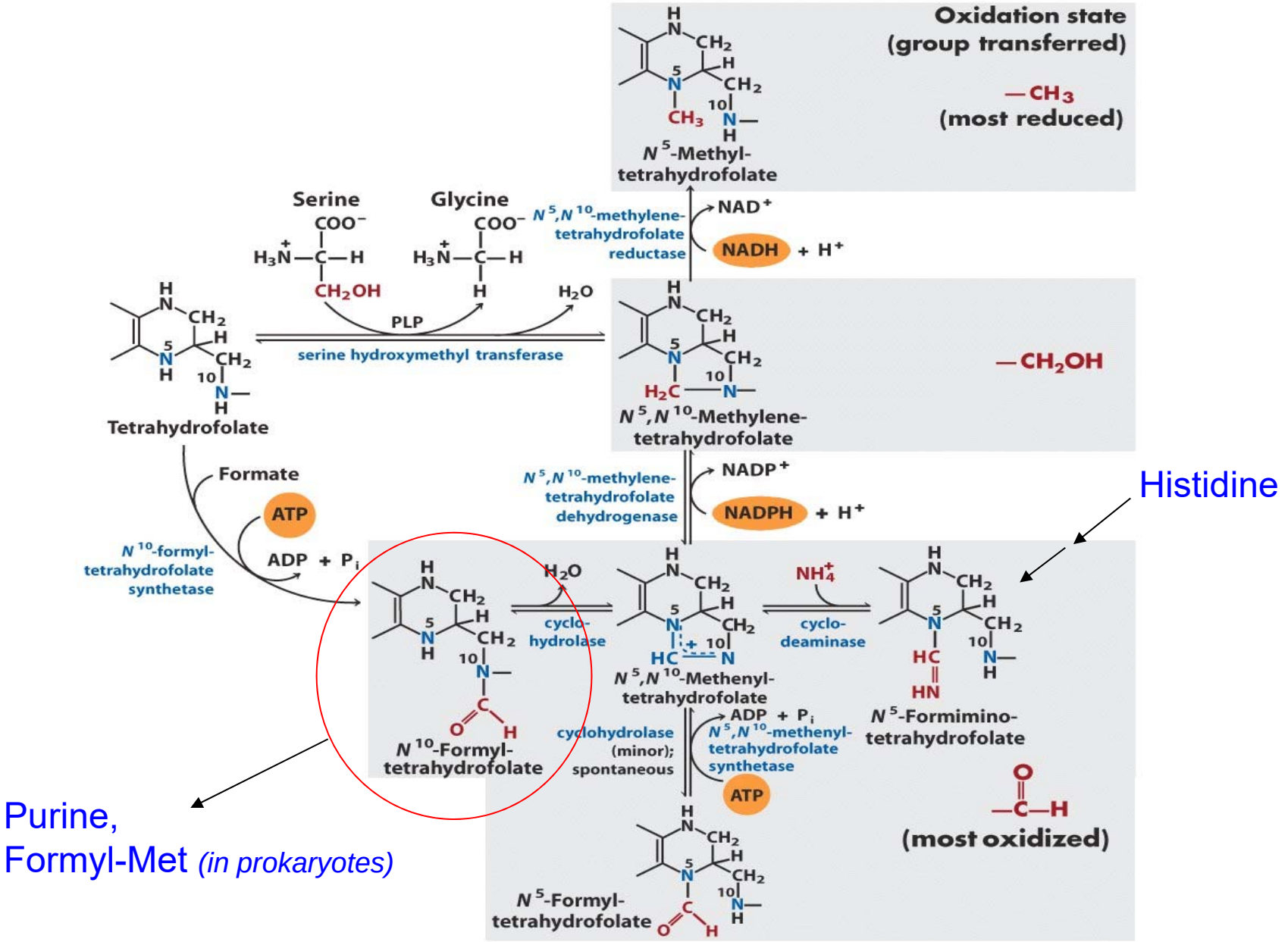
Tetrahydrofolate (H_4 folate)

(synthesized in bacteria)

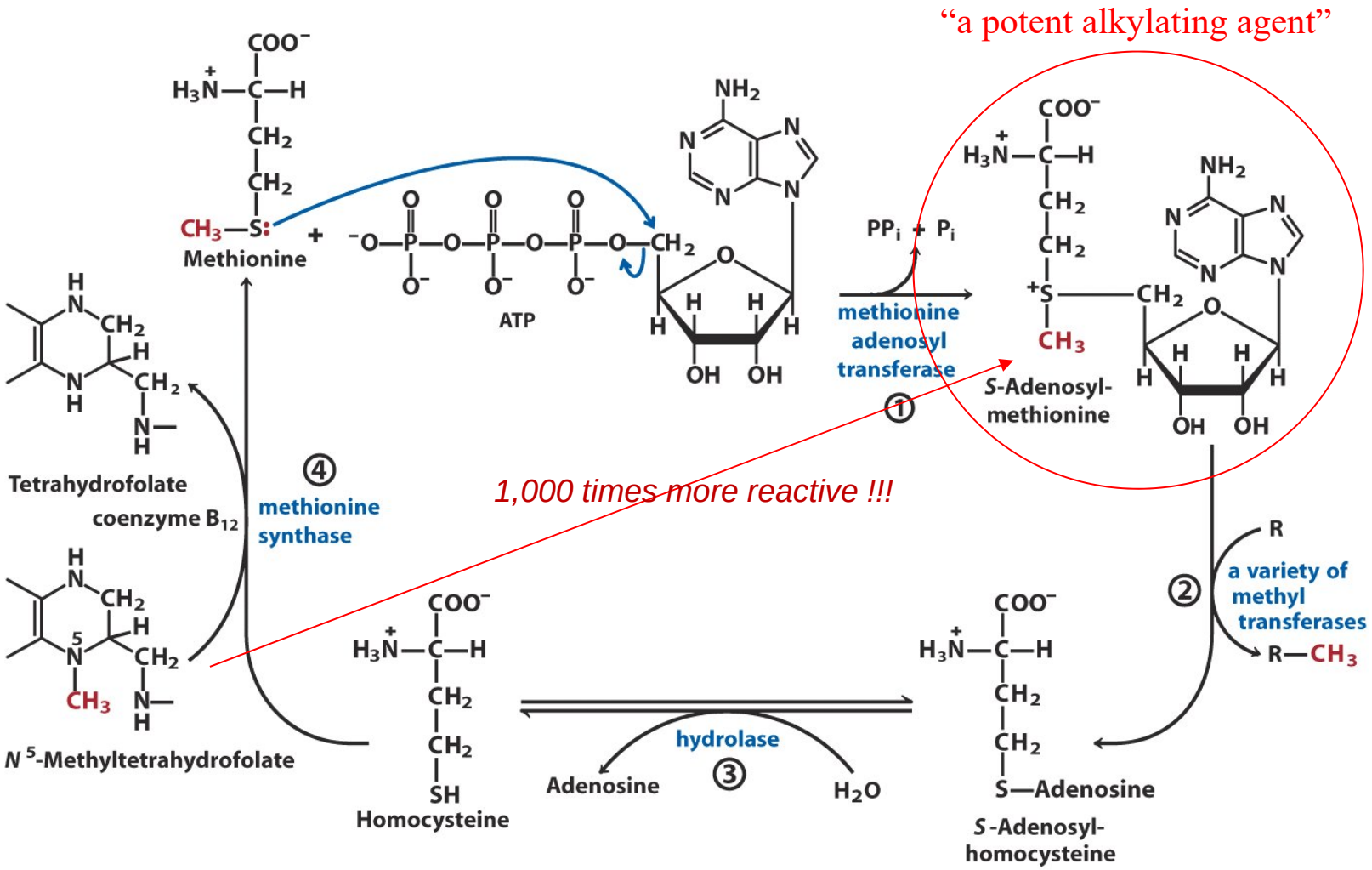


S-Adenosylmethionine (adoMet)

Conversion of one-carbon units on tetrahydrofolate



Synthesis of Met and s-adenosyl-Met in an activated-methyl cycle



Catabolic pathways for:

Ala, Gly, Ser, Cys, Trp, Thr

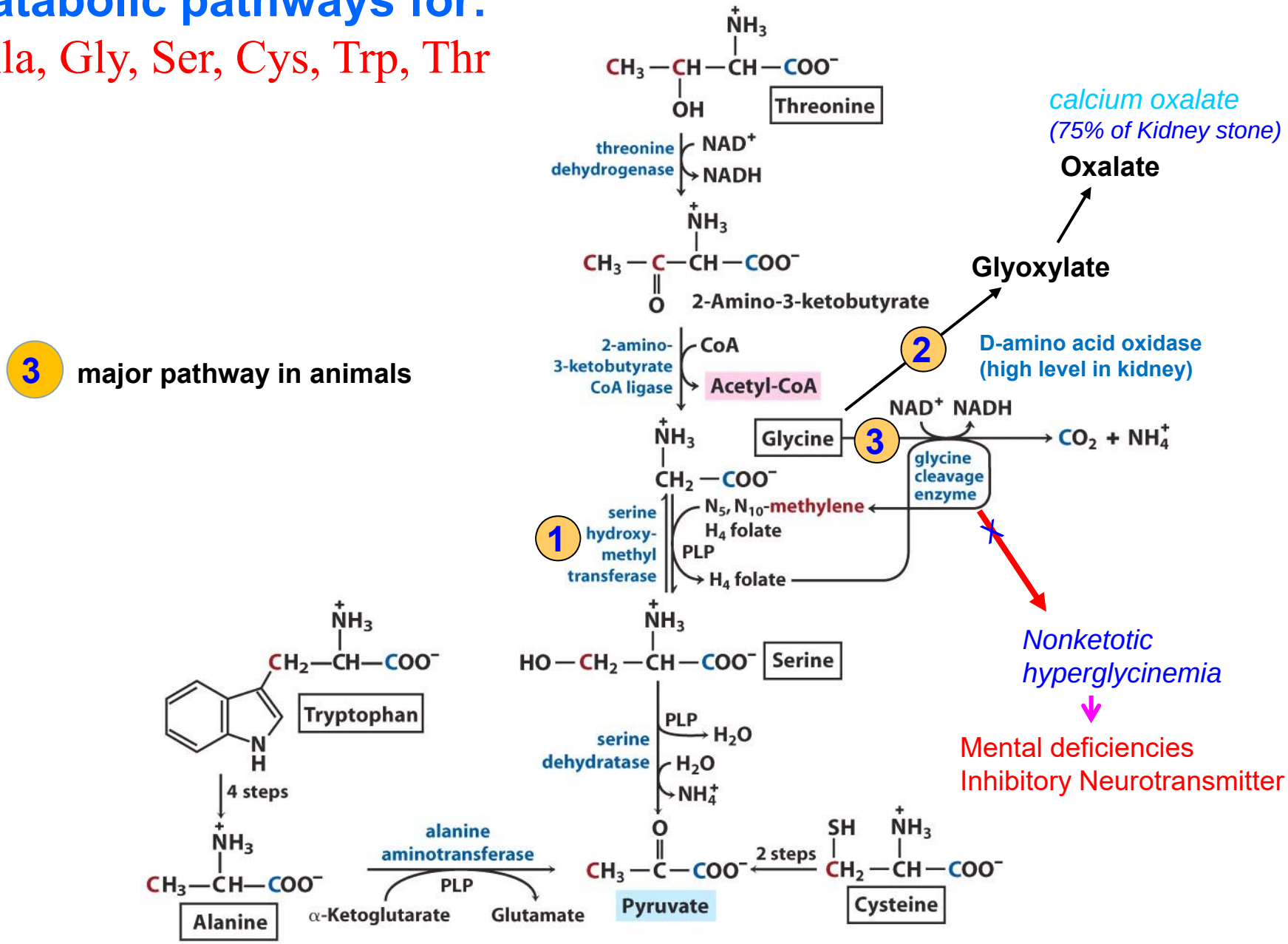
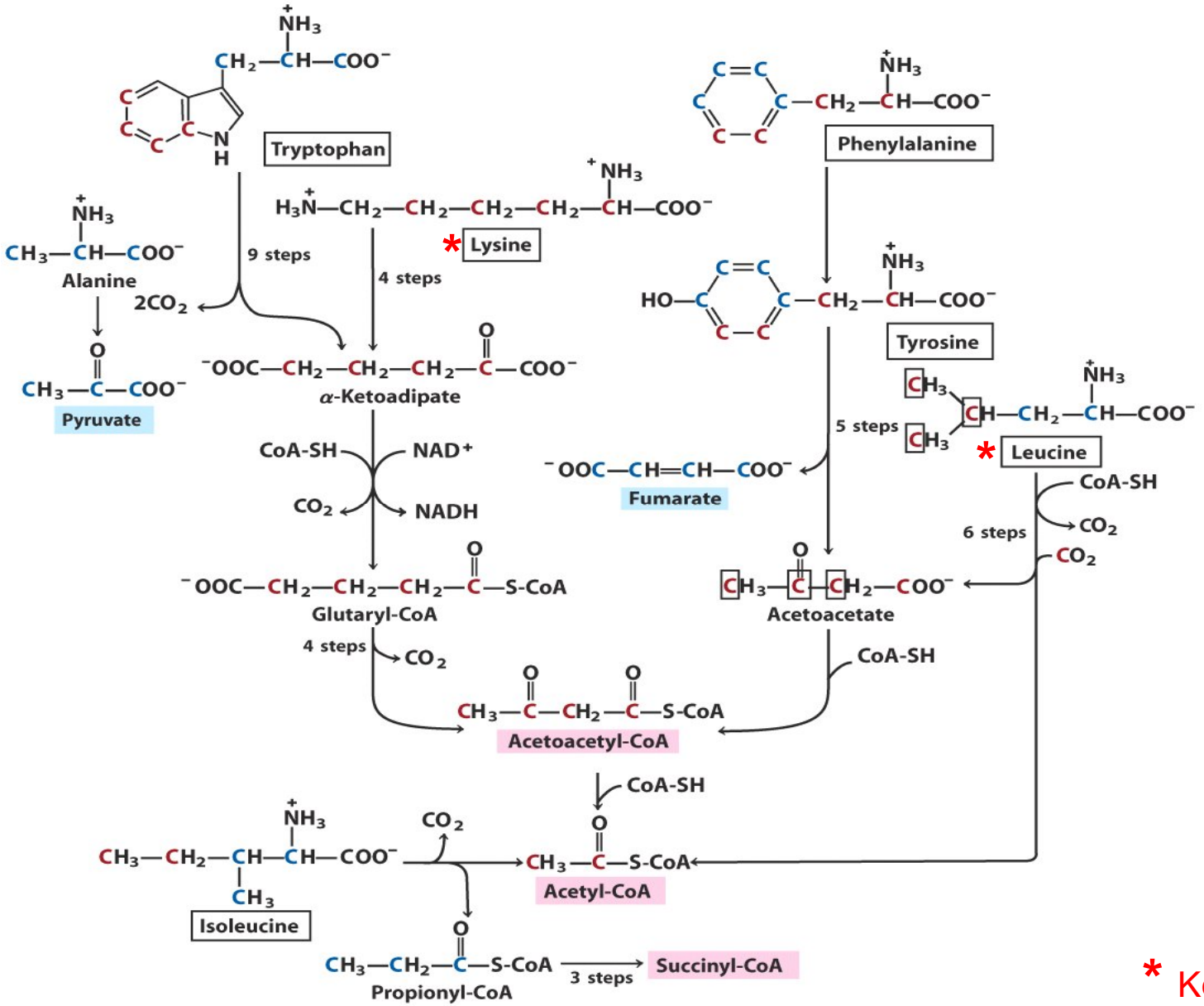


TABLE 18–2 Some Human Genetic Disorders Affecting Amino Acid Catabolism

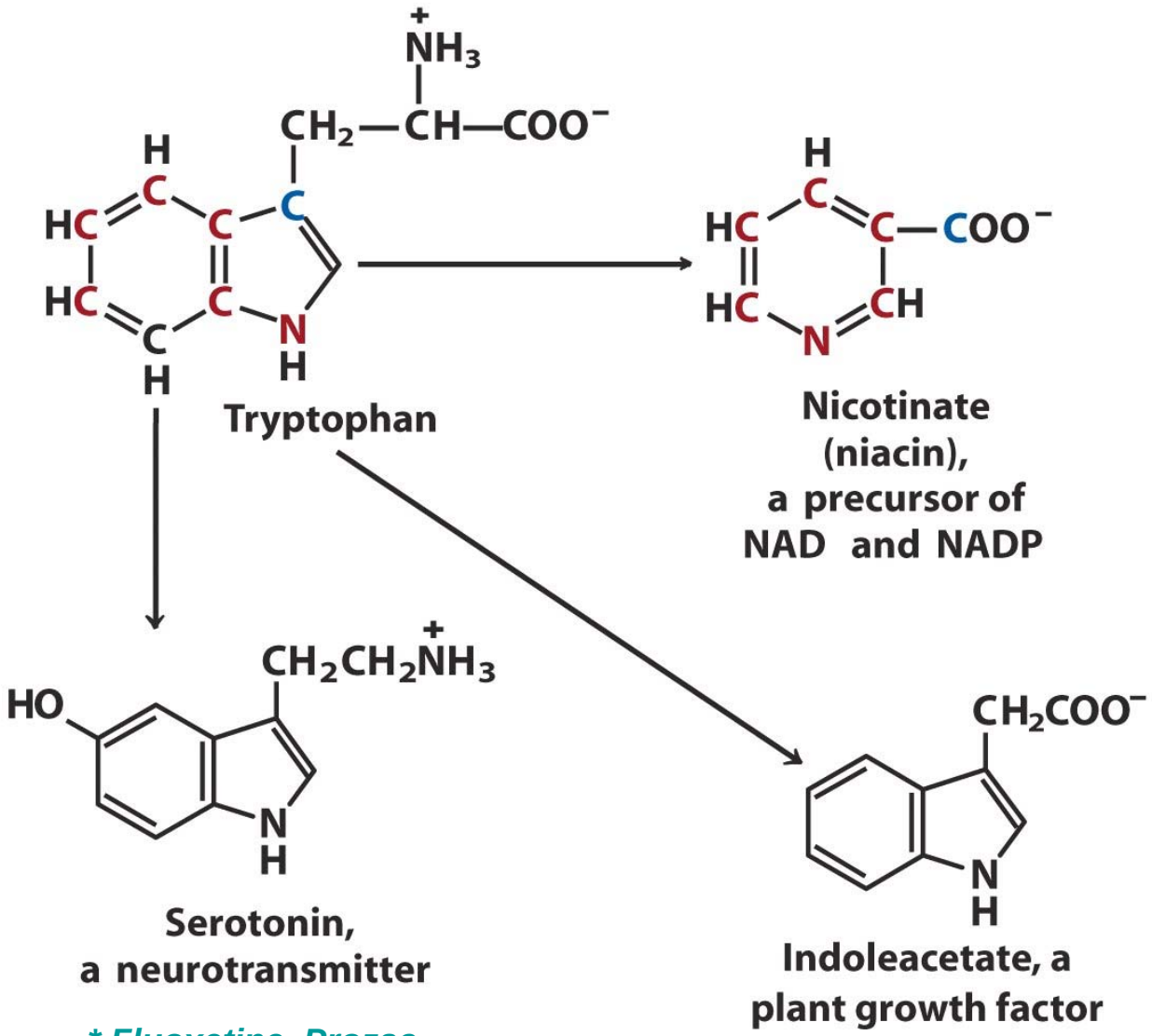
Medical condition	*Approximate incidence (per 100,000 births)*	*Defective process*	*Defective enzyme*	*Symptoms and effects*
Albinism	<3	Melanin synthesis from tyrosine	Tyrosine 3-monooxygenase (tyrosinase)	Lack of pigmentation: white hair, pink skin
Alkaptonuria	<0.4	Tyrosine degradation	Homogentisate 1,2-dioxygenase	Dark pigment in urine; late-developing arthritis
Argininemia	<0.5	Urea synthesis	Arginase	Mental retardation
Argininosuccinic acidemia	<1.5	Urea synthesis	Argininosuccinase	Vomiting; convulsions
Carbamoyl phosphate synthetase I deficiency	<0.5	Urea synthesis	Carbamoyl phosphate synthetase I	Lethargy; convulsions; early death
Homocystinuria	<0.5	Methionine degradation	Cystathionine β-synthase	Faulty bone development; mental retardation
Maple syrup urine disease (branched-chain ketoaciduria)	<0.4	Isoleucine, leucine, and valine degradation	Branched-chain α-keto acid dehydrogenase complex	Vomiting; convulsions; mental retardation; early death
Methylmalonic acidemia	<0.5	Conversion of propionyl-CoA to succinyl-CoA	Methylmalonyl-CoA mutase	Vomiting; convulsions; mental retardation; early death
Phenylketonuria	<8	Conversion of phenylalanine to tyrosine	Phenylalanine hydroxylase	Neonatal vomiting; mental retardation

Catabolic pathways for: Trp, Lys, Phe, Tyr, Leu, Ile



* Ketogenic

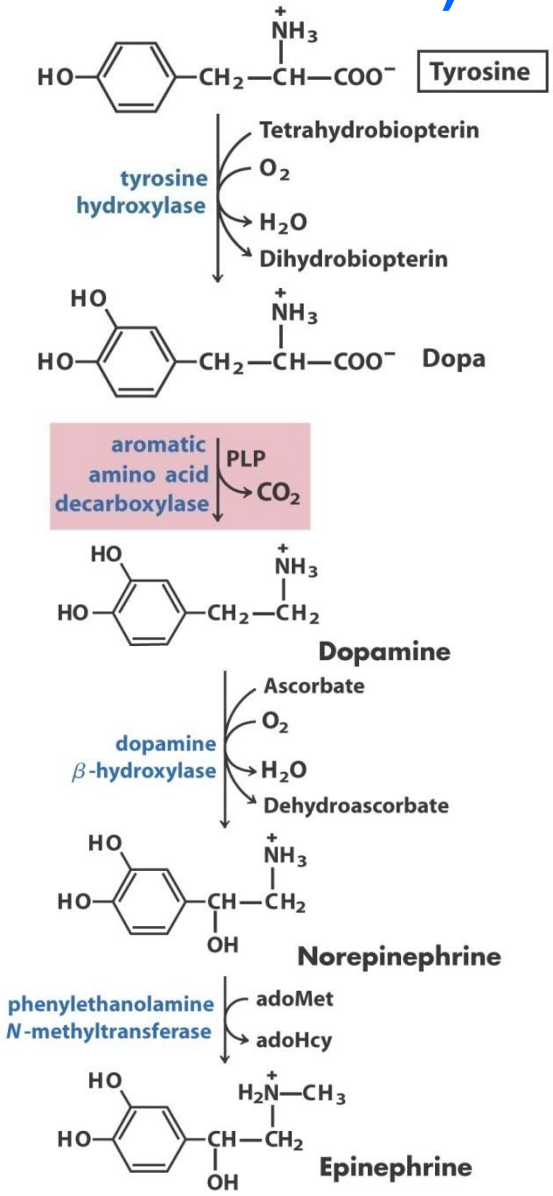
Tryptophan as precursor

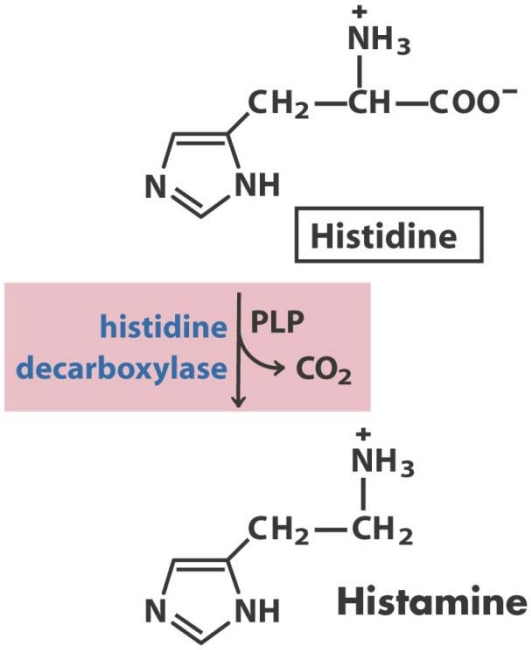


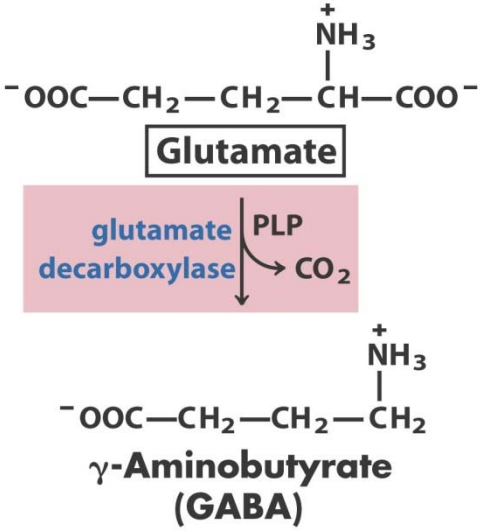
** Fluoxetine, Prozac*

lysergic acid diethylamide (LSD)

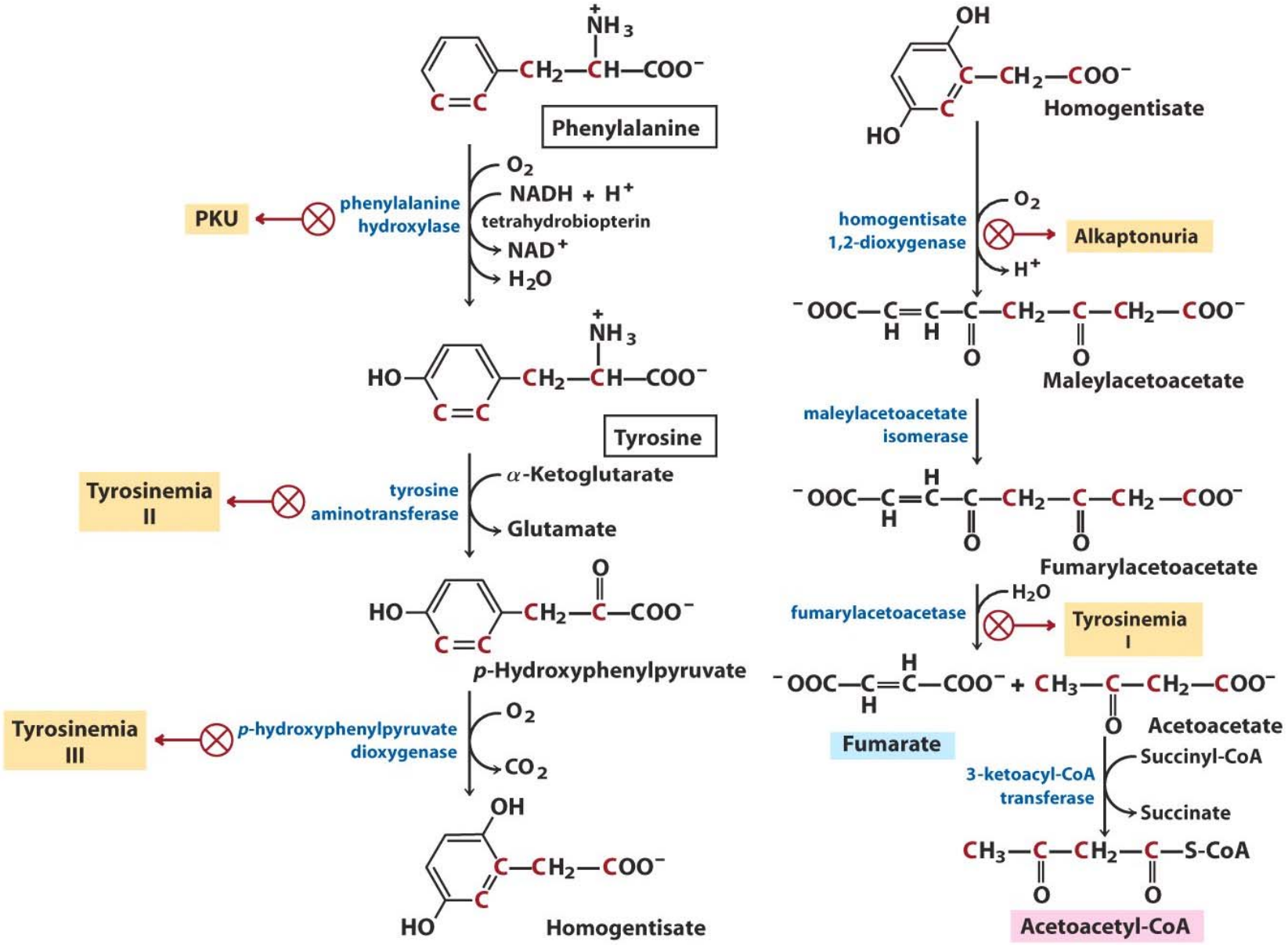
Biosynthesis of some neurotransmitters from amino acids (Catecholamines)



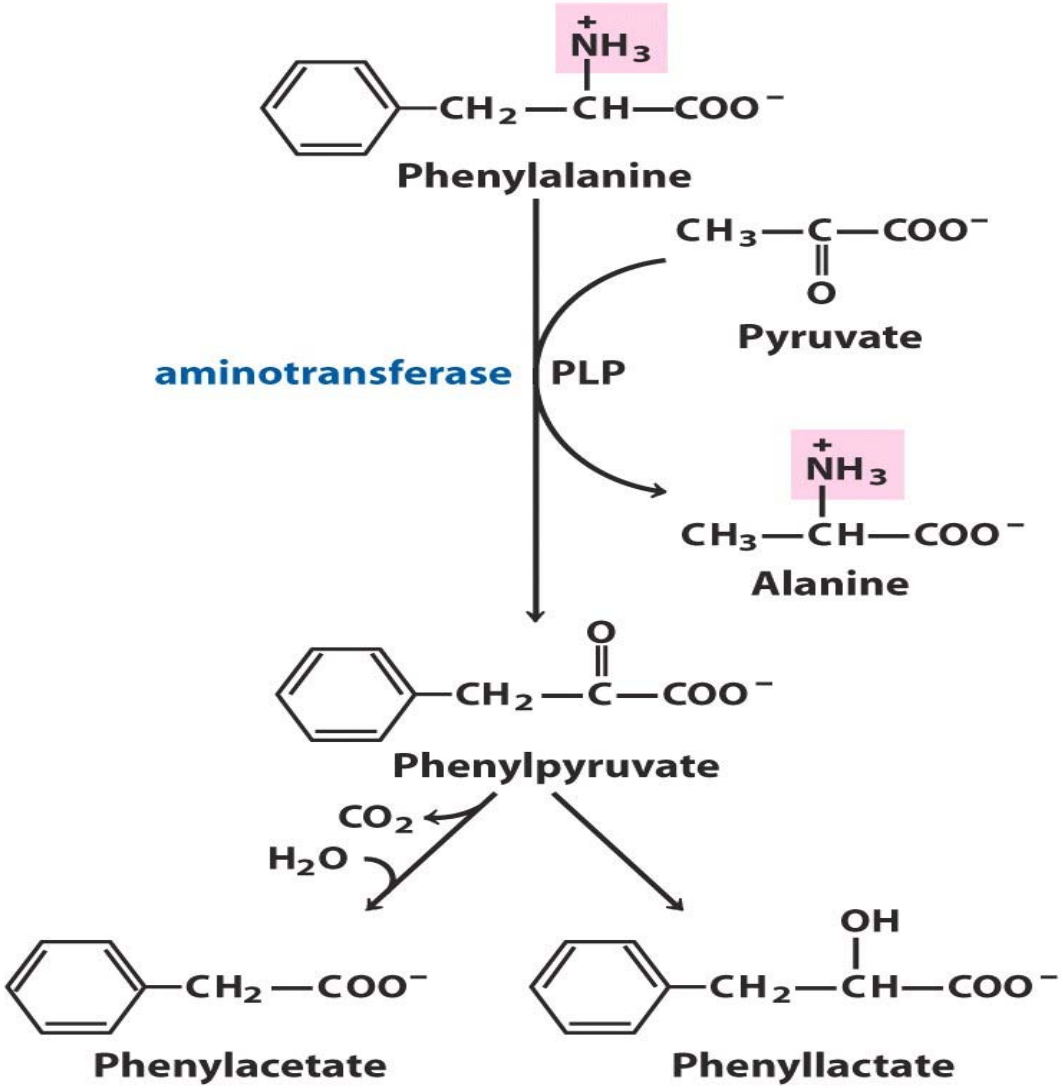




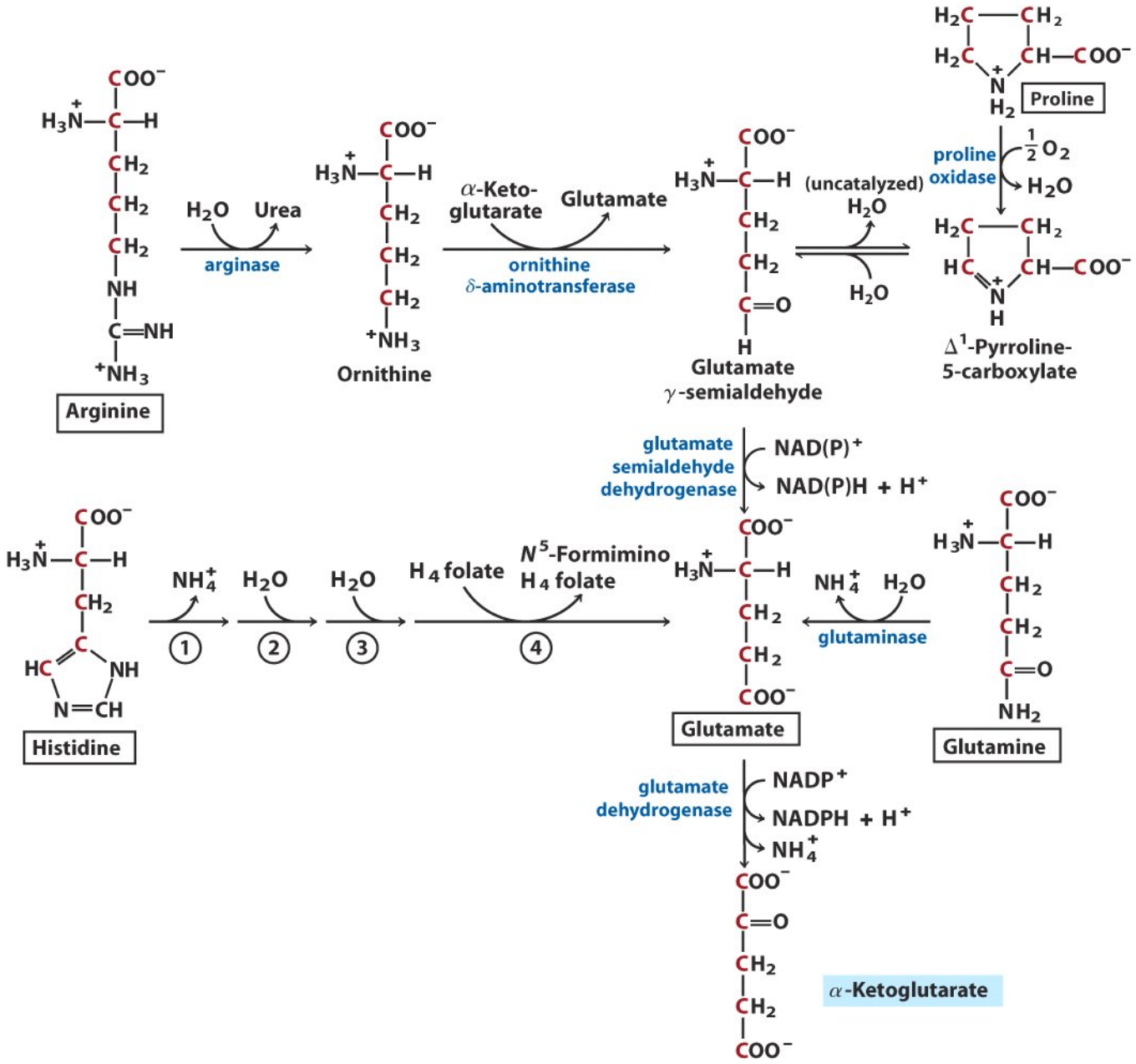
Catabolic pathways for: Phe, Tyr



Alternative pathways for catabolism of Phenylalanine in phenylketonuria

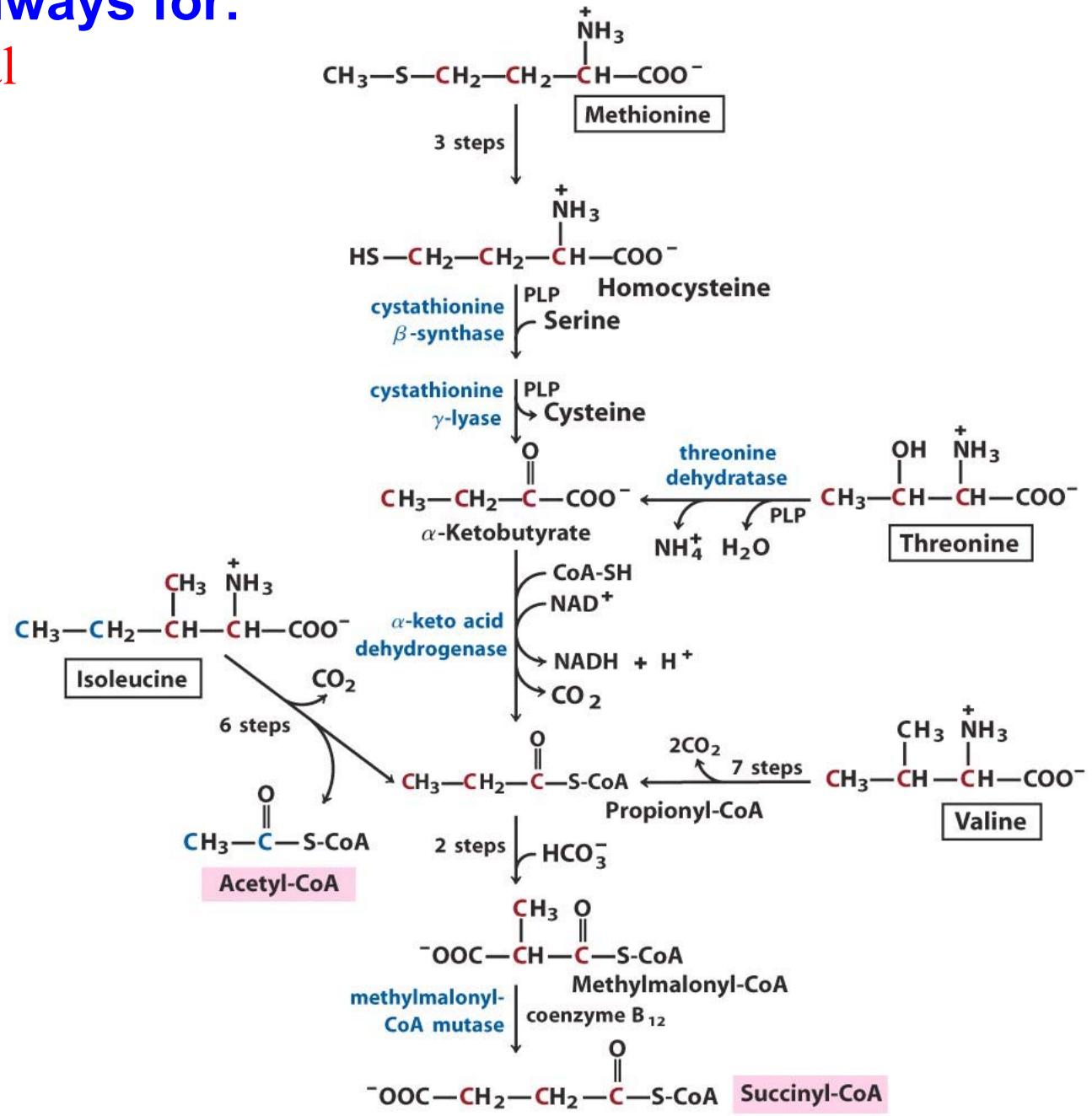


Catabolic pathways for: Arg, His, Glu, Gln, Pro



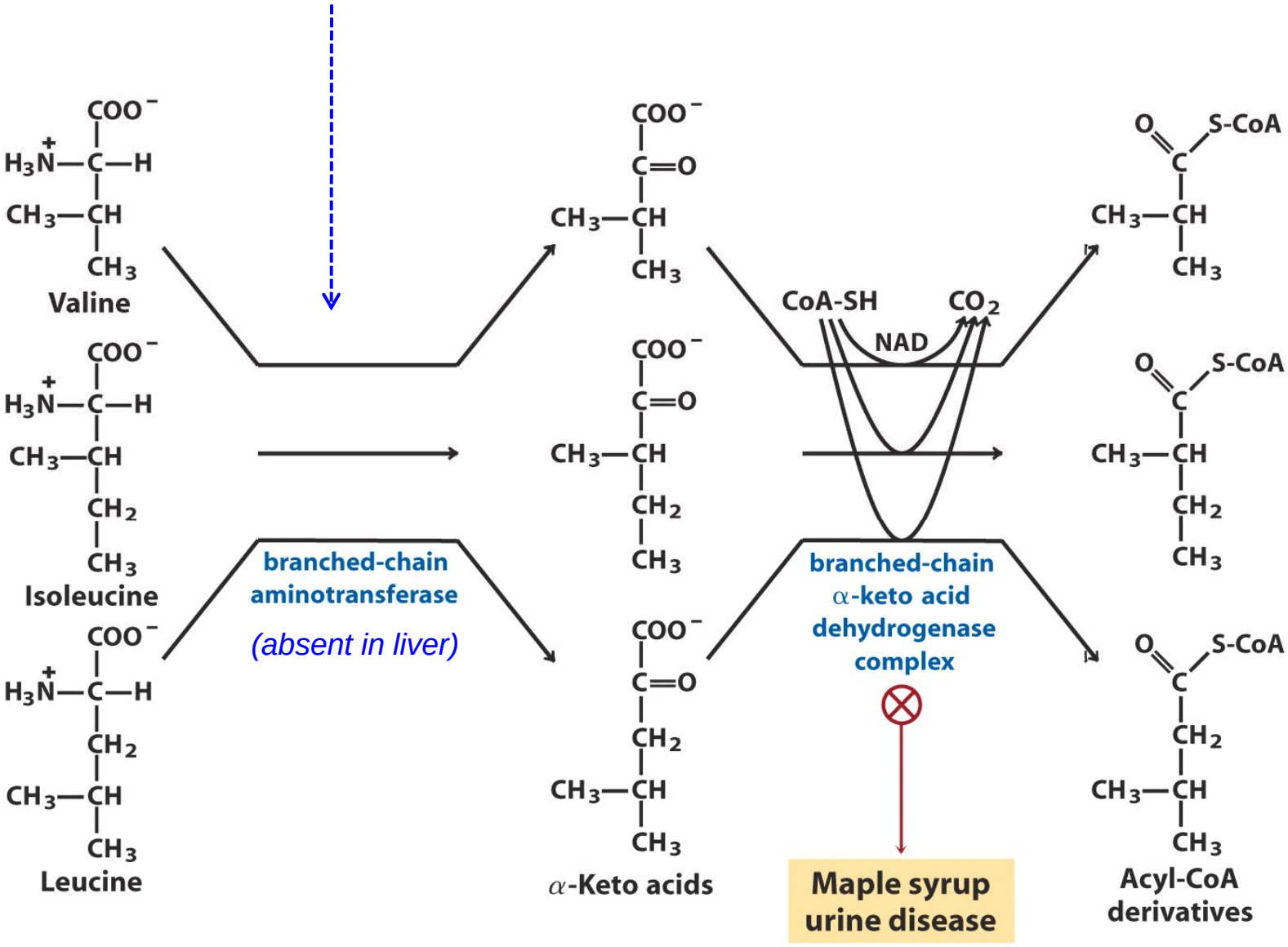
Catabolic pathways for:

Met, Ile, Thr, Val



Catabolic pathways for three-branched amino acids:

Val, Ile, Leu (are oxidized as fuels primarily in muscle, adipose, kidney, and brain tissue)



Catabolic pathways for:

Asn, Asp