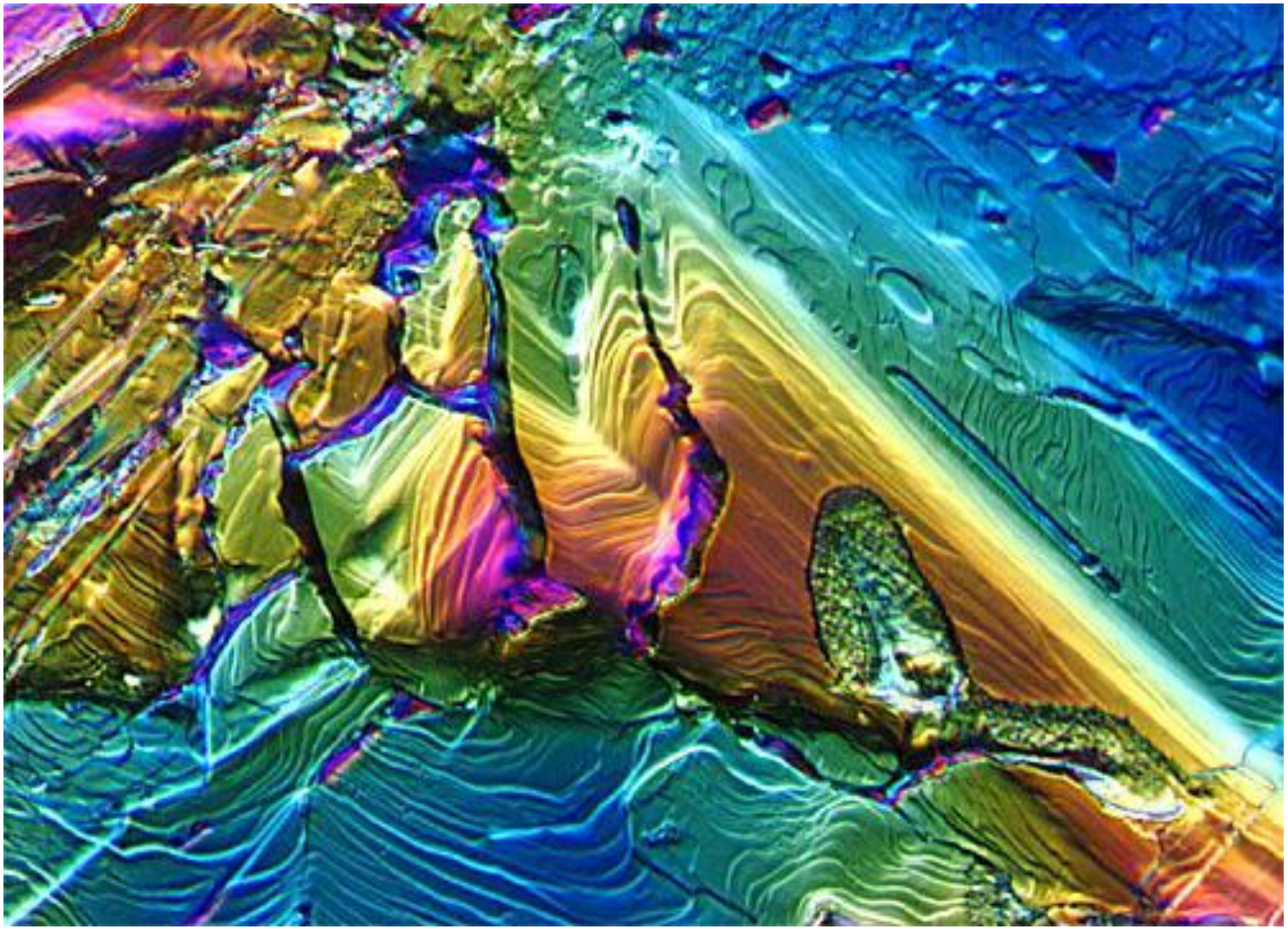
Amino Acid Metabolism

Amino Acid Oxidation and the Production of Urea



❖Amino acids through their oxidative degradation, make a significant contribution to the generation of metabolic energy.

❖The fraction of metabolic energy obtained from amino acids, whether they are derived from dietary protein or from tissue protein, varies greatly with the type of organism and with metabolic conditions.

❖Carnivores can obtain (immediately following a meal) up to 90% of their energy requirements from amino acid oxidation, whereas herbivores may fill only a small fraction of their energy needs by this route.

❖Most microorganisms can scavenge amino acids from their environment and use them as fuel when required by metabolic conditions.

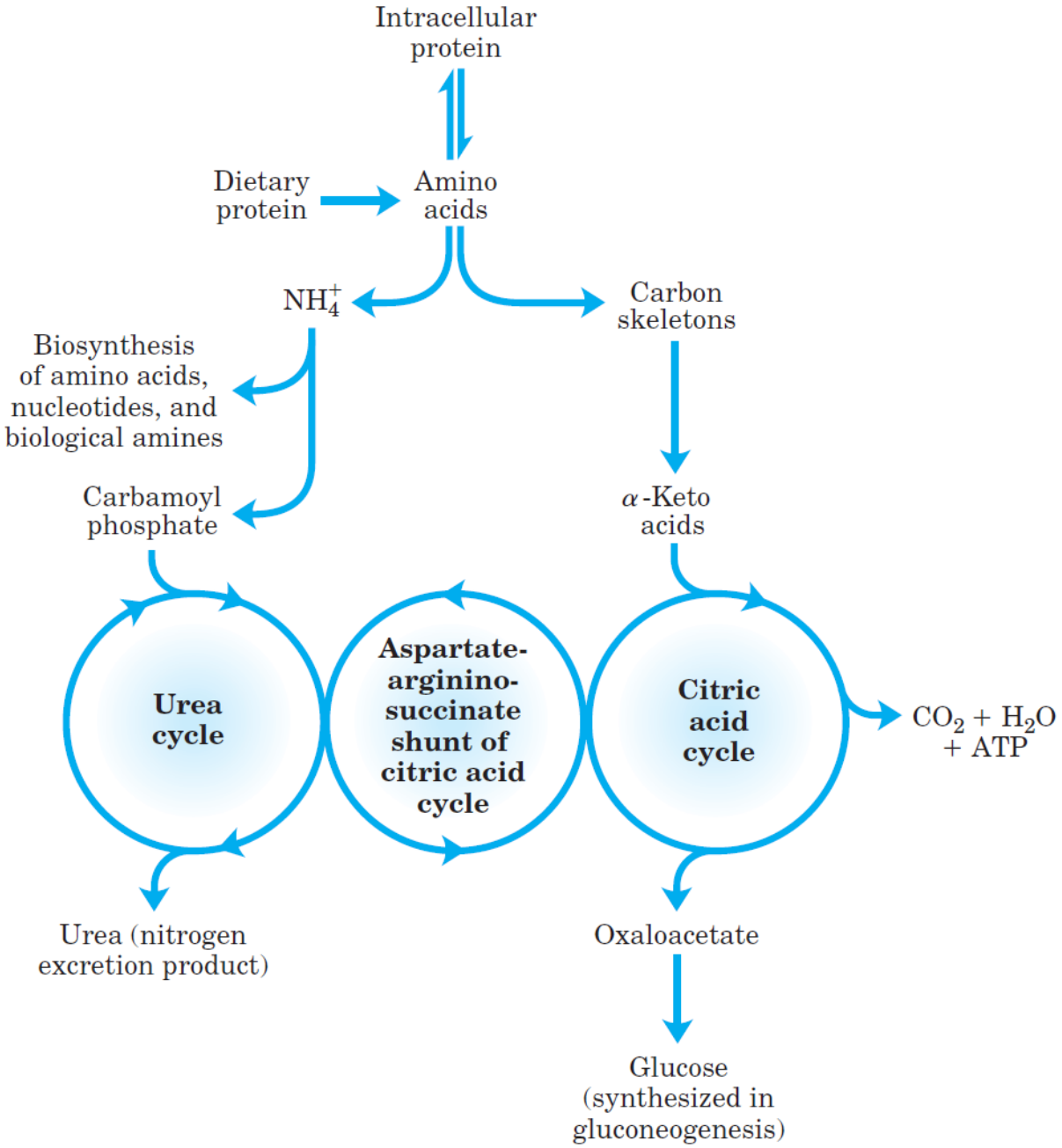
❖Plants, however, rarely if ever oxidize amino acids to provide energy; the carbohydrate produced from CO_2 and H_2O in photosynthesis is generally their sole energy source. Amino acid catabolism does occur in plants, but its purpose is to produce metabolites for other biosynthetic pathways.

❖In animals, amino acids undergo oxidative degradation in three 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 mellitus, when carbohydrates are either unavailable or not properly utilized, cellular proteins are used as fuel.



❖Under all these metabolic conditions, amino acids lose their amino groups to form α-keto acids, the "carbon skeletons" of amino acids.

❖The α-keto acids undergo oxidation to CO_2 and H_2O or, often more importantly, provide three- and four-carbon units that can be converted by gluconeogenesis into glucose, the fuel for brain, skeletal muscle, and other tissues

❖Nitrogen, N_2, is abundant in the atmosphere but is too inert for use in most biochemical processes. Because only a few microorganisms can convert N_2 to biologically useful forms such as NH_3, amino groups are carefully husbanded in biological systems.

❖For vertebrates, 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 or uric acid for excretion, depending on the organism.

❖Glutamate and glutamine play especially critical roles in nitrogen metabolism, acting as a kind of general collection point for amino groups.

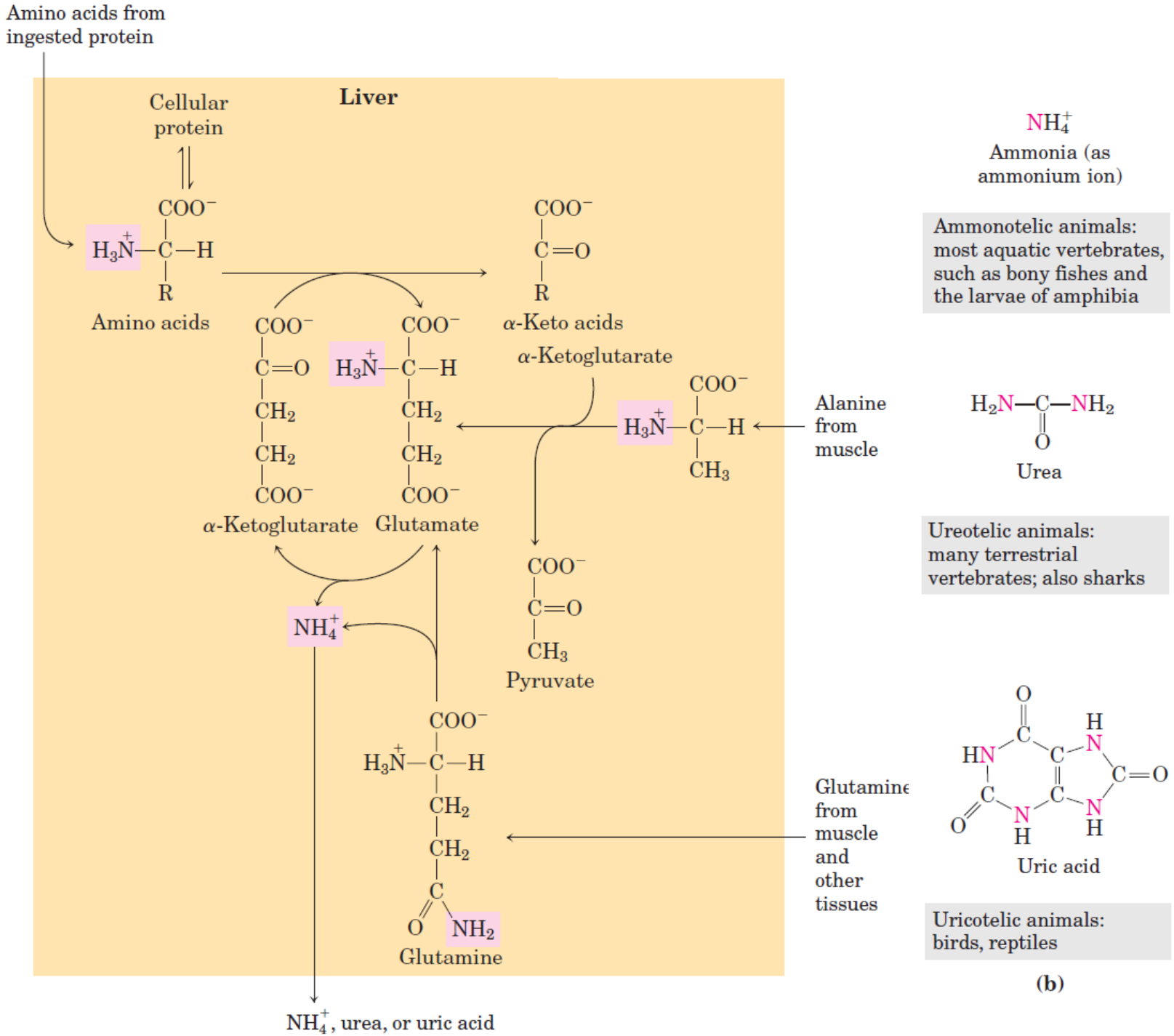
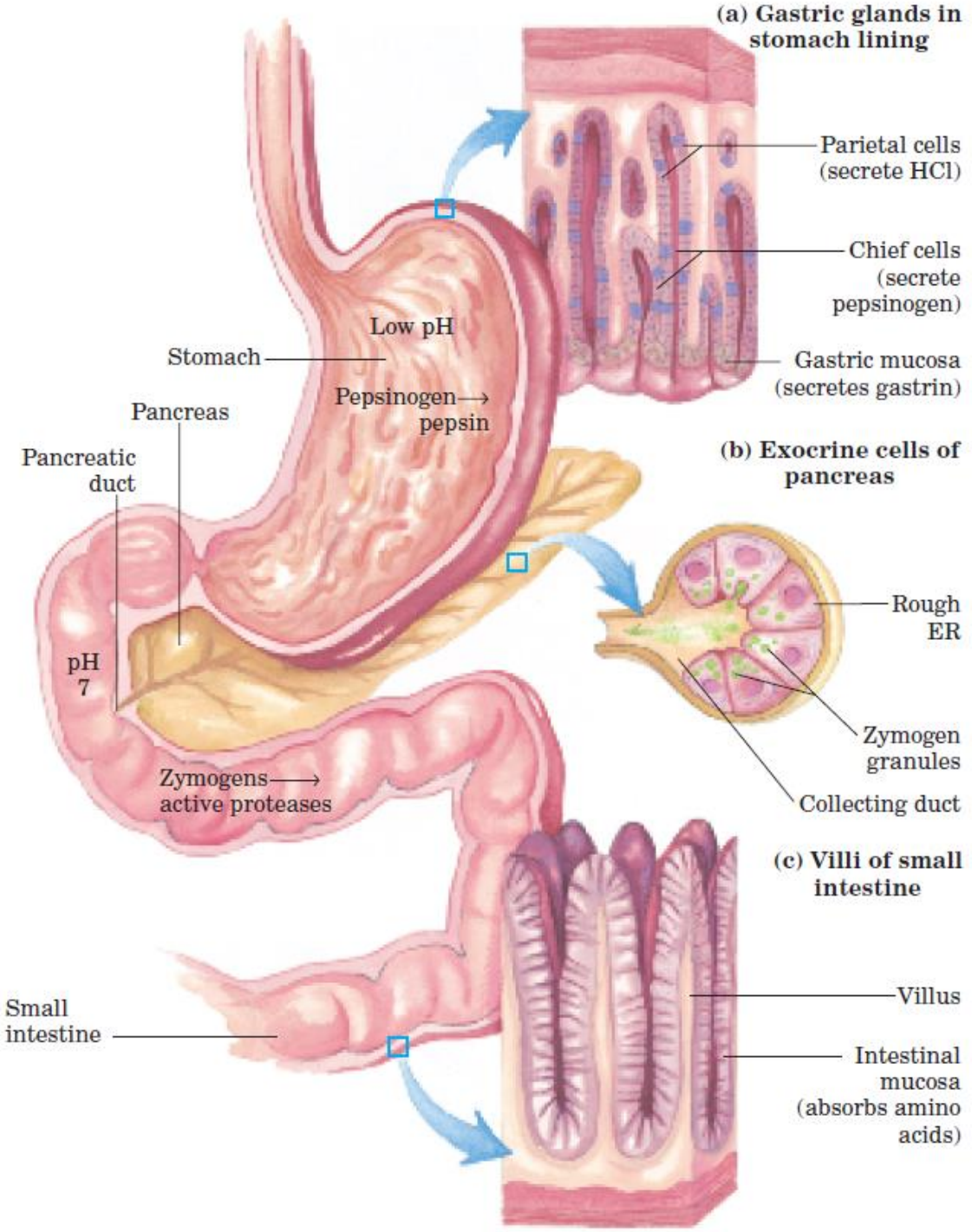

Amino acids from ingested protein
Liver
Cellular protein
Amino acids
α-Keto acids
α-Ketoglutarate
α-Ketoglutarate
Glutamate
Alanine from muscle
Pyruvate
NH4+
Glutamine
Glutamine from muscle and other tissues
NH4+, urea, or uric acid
NH4+
Ammonia (as ammonium ion)
Ammonotelic animals: most aquatic vertebrates, such as bony fishes and the larvae of amphibia
Urea
Ureotelic animals: many terrestrial vertebrates; also sharks
Uric acid
Uricotelic animals: birds, reptiles
(b)

FIGURE 18–3 Part of the human digestive (gastrointestinal) tract. **(a)** The parietal cells and chief cells of the gastric glands secrete their products in response to the hormone gastrin. Pepsin begins the process of protein degradation in the stomach. **(b)** The cytoplasm of exocrine cells is completely filled with rough endoplasmic reticulum, the site of synthesis of the zymogens of many digestive enzymes. The zymogens are concentrated in membrane-enclosed transport particles called zymogen granules. When an exocrine cell is stimulated, its plasma membrane fuses with the zymogen granule membrane and zymogens are released into the lumen of the collecting duct by exocytosis. The collecting ducts ultimately lead to the pancreatic duct and thence to the small intestine. **(c)** Amino acids are absorbed through the epithelial cell layer (intestinal mucosa) of the villi and enter the capillaries. Recall that the products of lipid hydrolysis in the small intestine enter the lymphatic system after their absorption by the intestinal mucosa (see Fig. 17–1).



❖In humans, the degradation of ingested proteins to their constituent amino acids occurs in the gastrointestinal tract.

❖Entry of dietary protein into the stomach stimulates the gastric mucosa to secrete the hormone gastrin, which in turn stimulates the secretion of hydrochloric acid by the parietal cells and pepsinogen by the chief cells of the gastric glands.

❖The acidic gastric juice (pH 1.0 to 2.5) is both an antiseptic, killing most bacteria and other foreign cells, and a denaturing agent, unfolding globular proteins and rendering their internal peptide bonds more accessible to enzymatic hydrolysis.

❖Pepsinogen (Mr 40,554), an inactive precursor, or zymogen, is converted to active pepsin (Mr 34,614) by the enzymatic action of pepsin itself.

❖In the stomach, pepsin hydrolyzes ingested proteins at peptide bonds on the amino-terminal side of the aromatic amino acid residues Phe, Trp, and Tyr, cleaving long polypeptide chains into a mixture of smaller peptides.

❖As the acidic stomach contents pass into the small intestine, the low pH triggers secretion of the hormone secretin into the blood.

❖Secretin stimulates the pancreas to secrete bicarbonate into the small intestine to neutralize the gastric HCl, abruptly increasing the pH to about 7. The digestion of proteins now continues in the small intestine.

❖Arrival of amino acids in the upper part of the intestine (duodenum) causes release into the blood of the hormonecholecystokinin, which stimulates secretion of several pancreatic enzymes with activity optima at pH 7 to 8.

❖Trypsinogen, chymotrypsinogen, and procarboxypeptidases A and B, the zymogens of trypsin, chymotrypsin, and carboxypeptidases A and B, are synthesized and secreted by the exocrine cells of the pancreas.

❖Trypsinogen is converted to its active form, trypsin, by enteropeptidase, a proteolytic enzyme secreted by intestinal cells. Free trypsin then catalyzes the conversion of additional trypsinogen to trypsin. Trypsin also activates chymotrypsinogen, the procarboxypeptidases, and proelastase.

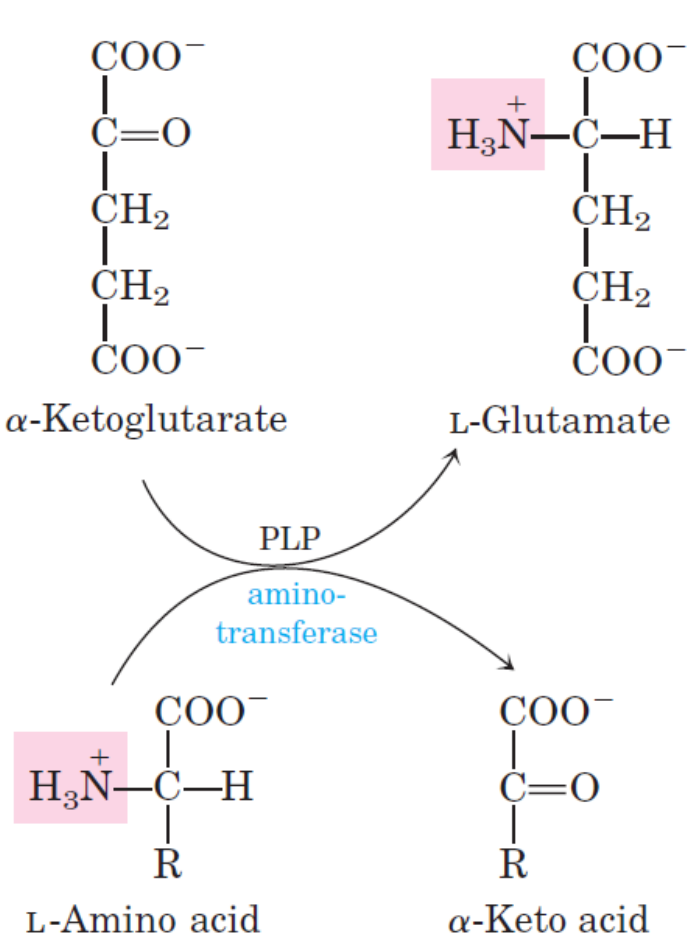
❖Degradation of the short peptides in the small intestine is then completed by other intestinal peptidases.

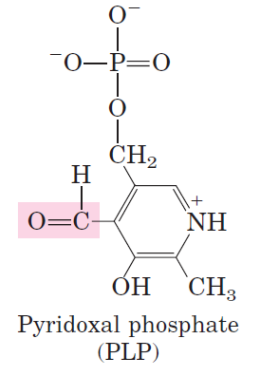
❖The resulting mixture of free amino acids is transported into the epithelial cells lining the small intestine, through which the amino acids enter the blood capillaries in the villi and travel to the liver.

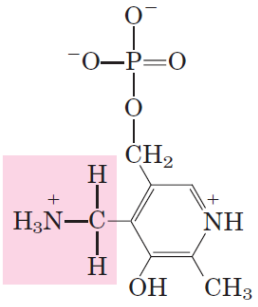
❖The first step in the catabolism of most L-amino acids, once they have reached the liver, is removal of the α-amino groups, promoted by enzymes called aminotransferases or transaminases. In these transamination reactions, the α-amino group is transferred to the α-carbon atom of α-ketoglutarate, leaving behind the corresponding α-keto acid analog of the amino acid

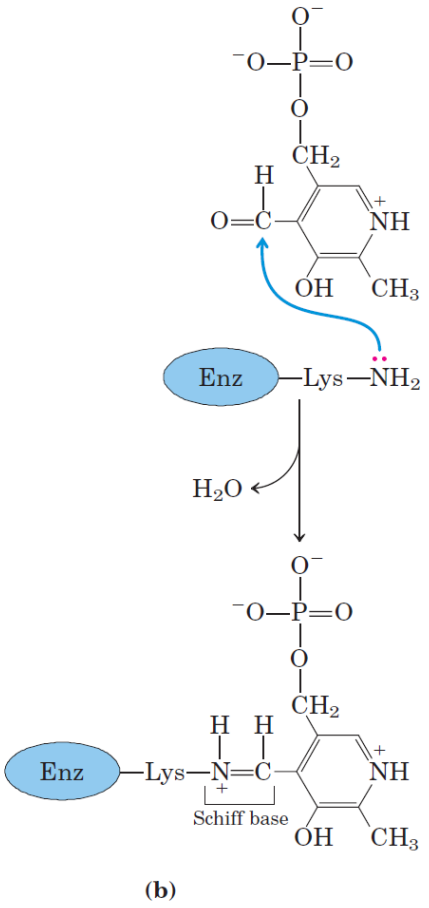
❖There is no net deamination (loss of amino groups) in these reactions, because the α-ketoglutarate becomes aminated as the α-amino acid is deaminated.

❖The effect of transamination reactions is to collect the amino groups from many different amino acids in the form of L-glutamate.









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

❖The combined action of an aminotransferase and glutamate dehydrogenase is referred to as transdeamination.

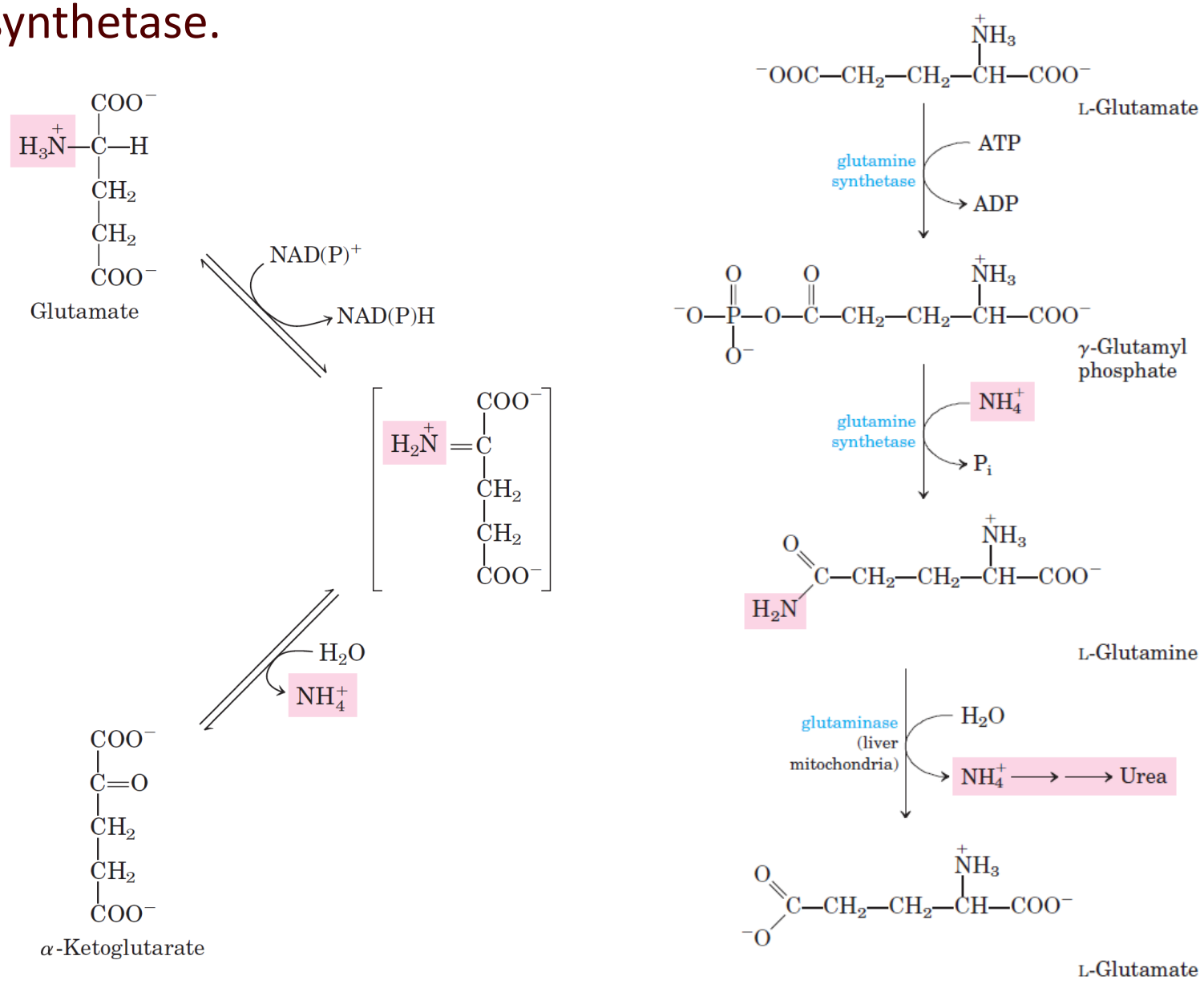
❖A few amino acids bypass the transdeamination pathway and undergo direct oxidative deamination.

❖The α-ketoglutarate formed from glutamate deamination can be used in the citric acid cycle and for glucose synthesis..

❖Ammonia is quite toxic to animal tissues, and the levels present in blood are regulated.

❖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.



❖This reaction requires ATP and occurs in two steps.

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

❖Glutamine also serves as a source of amino groups in a variety of biosynthetic reactions.

❖In most terrestrial animals, glutamine in excess of that required for biosynthesis is transported in the blood to the intestine, liver, and kidneys where the enzyme glutaminase converts glutamine to glutamate and NH_4^+.

❖The NH_4^+ from intestine and kidney is transported in the blood to the liver.

❖Alanine also plays a special role in transporting amino groups to the liver in a nontoxic form, via a pathway called the glucose-alanine cycle.

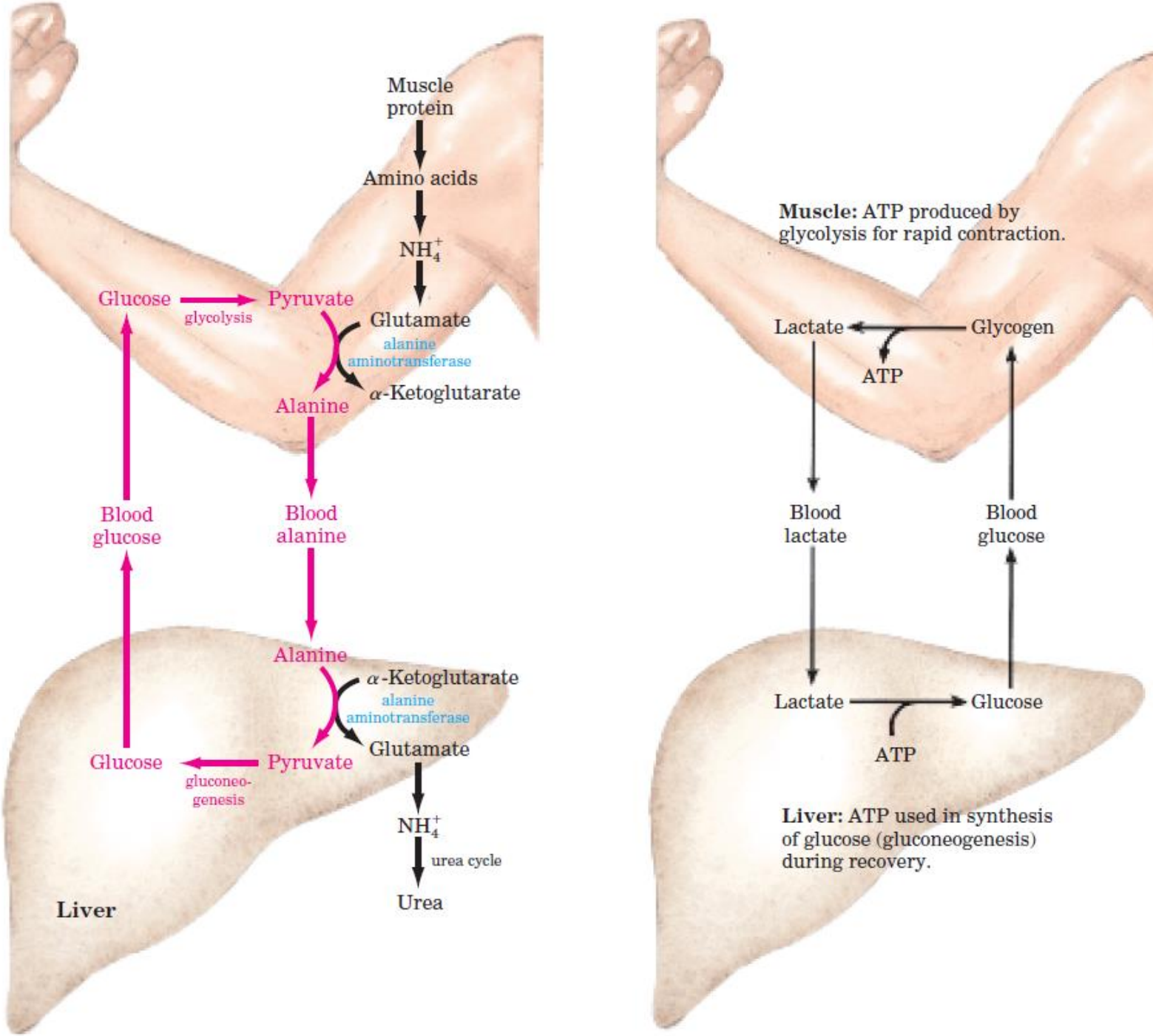
❖In muscle and certain other tissues that degrade amino acids for fuel, amino groups are collected in the form of glutamate by transamination.

❖Glutamate can be converted to glutamine for transport to the liver, as described above, or it can transfer its α-amino group to pyruvate, a readily available product of muscle glycolysis, by the action of alanine aminotransferase.

❖The alanine so formed passes into the blood and travels to the liver.

❖In the cytosol of hepatocytes, alanine aminotransferase transfers the amino group from alanine to α-ketoglutarate, forming pyruvate and glutamate.

❖Glutamate can then enter mitochondria, where the glutamate dehydrogenase reaction releases NH_4^+.


Muscle protein
Amino acids
NH_4^+
Glucose
glycolysis
Pyruvate
Glutamate
alanine aminotransferase
α-Ketoglutarate
Alanine
Blood glucose
Blood alanine
Alanine
α-Ketoglutarate
alanine aminotransferase
Glutamate
Glucose
gluconeo-genesis
Pyruvate
NH_4^+
urea cycle
Urea
Liver
Muscle: ATP produced by glycolysis for rapid contraction.
Lactate
Glycogen
ATP
Blood lactate
Blood glucose
Lactate
Glucose
ATP
Liver: ATP used in synthesis of glucose (gluconeogenesis) during recovery.

❖The use of alanine to transport ammonia from skeletal muscles to the liver is another example of the intrinsic economy of living organisms.

❖Vigorously contracting skeletal muscles operate anaerobically, producing pyruvate and lactate from glycolysis as well asammonia from protein breakdown.

❖These products must find their way to the liver, where pyruvate and lactate are incorporated into glucose, which is returned to the muscles, and ammonia is converted to urea for excretion.

❖The glucose-alanine cycle, in concert with the Cori cycle, accomplishes this transaction.

❖The energetic burden of gluconeogenesis is thus imposed on the liver rather than the muscle, and all available ATP in muscle is devoted to muscle contraction.

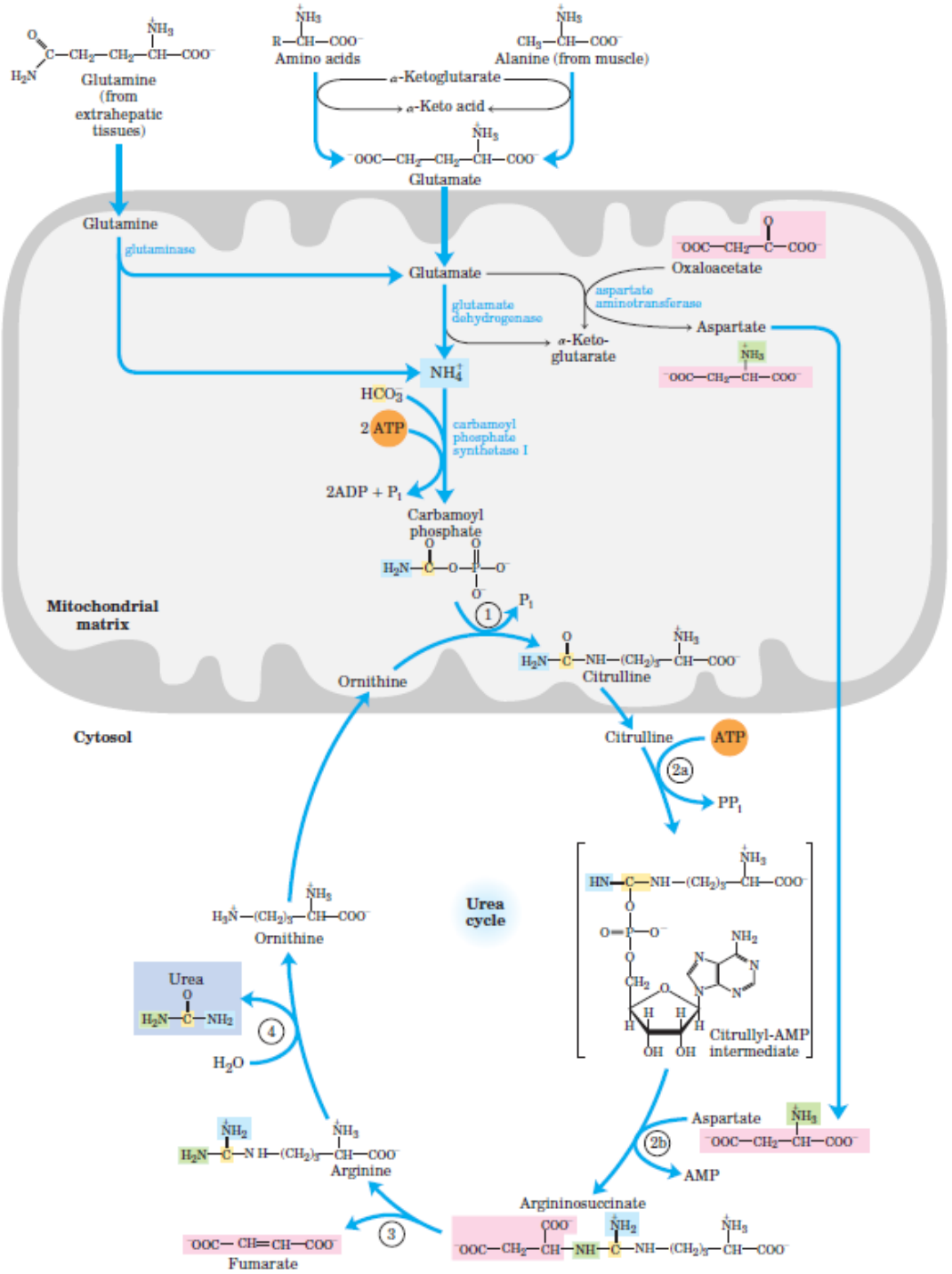
❖If not reused for the synthesis of new amino acids or other nitrogenous products, amino groups are channeled into a single excretory end product.

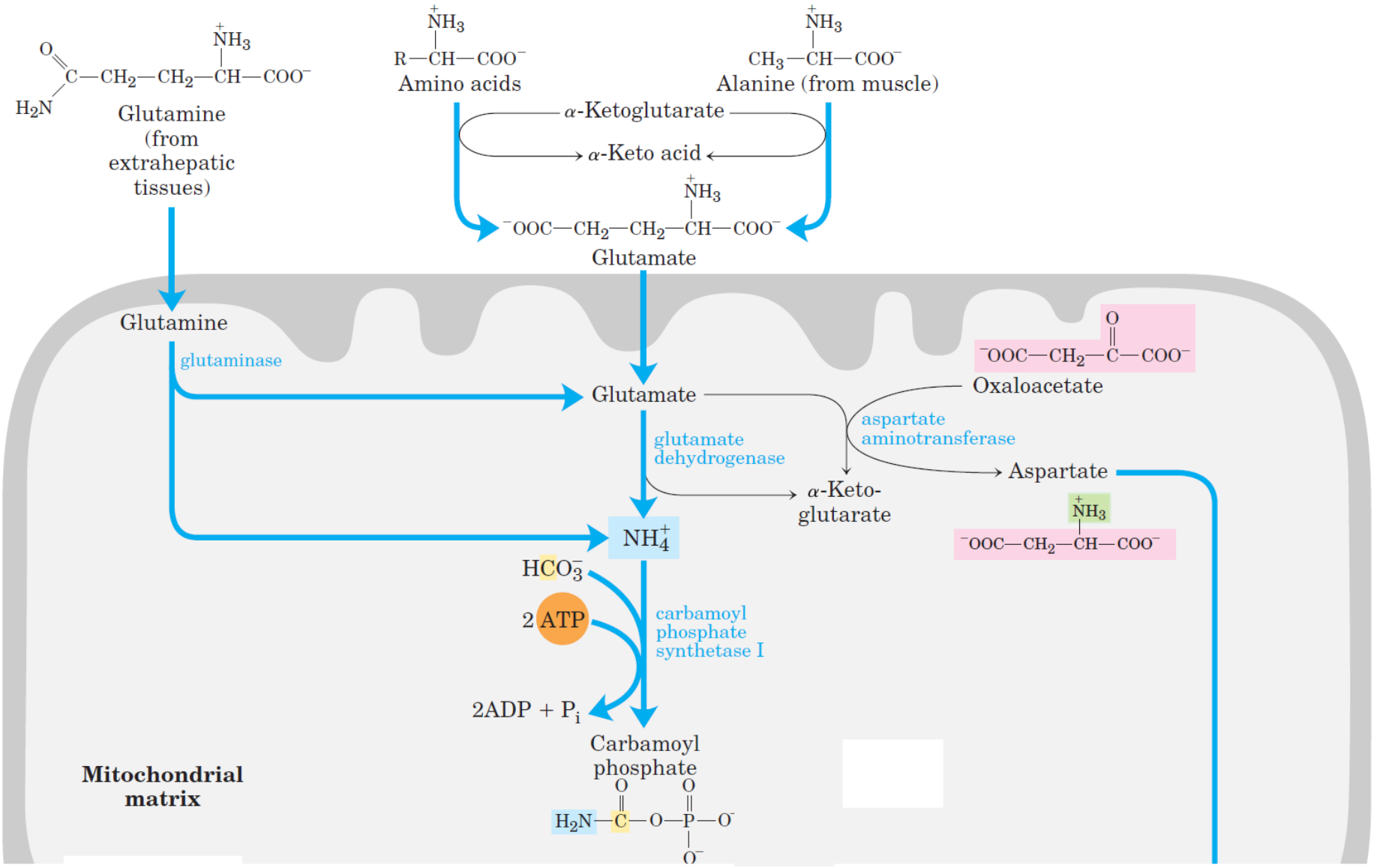
❖Most aquatic species, such as the bony fishes, are ammonotelic, excreting amino nitrogen as ammonia. The toxic ammonia is simply diluted in the surrounding water.

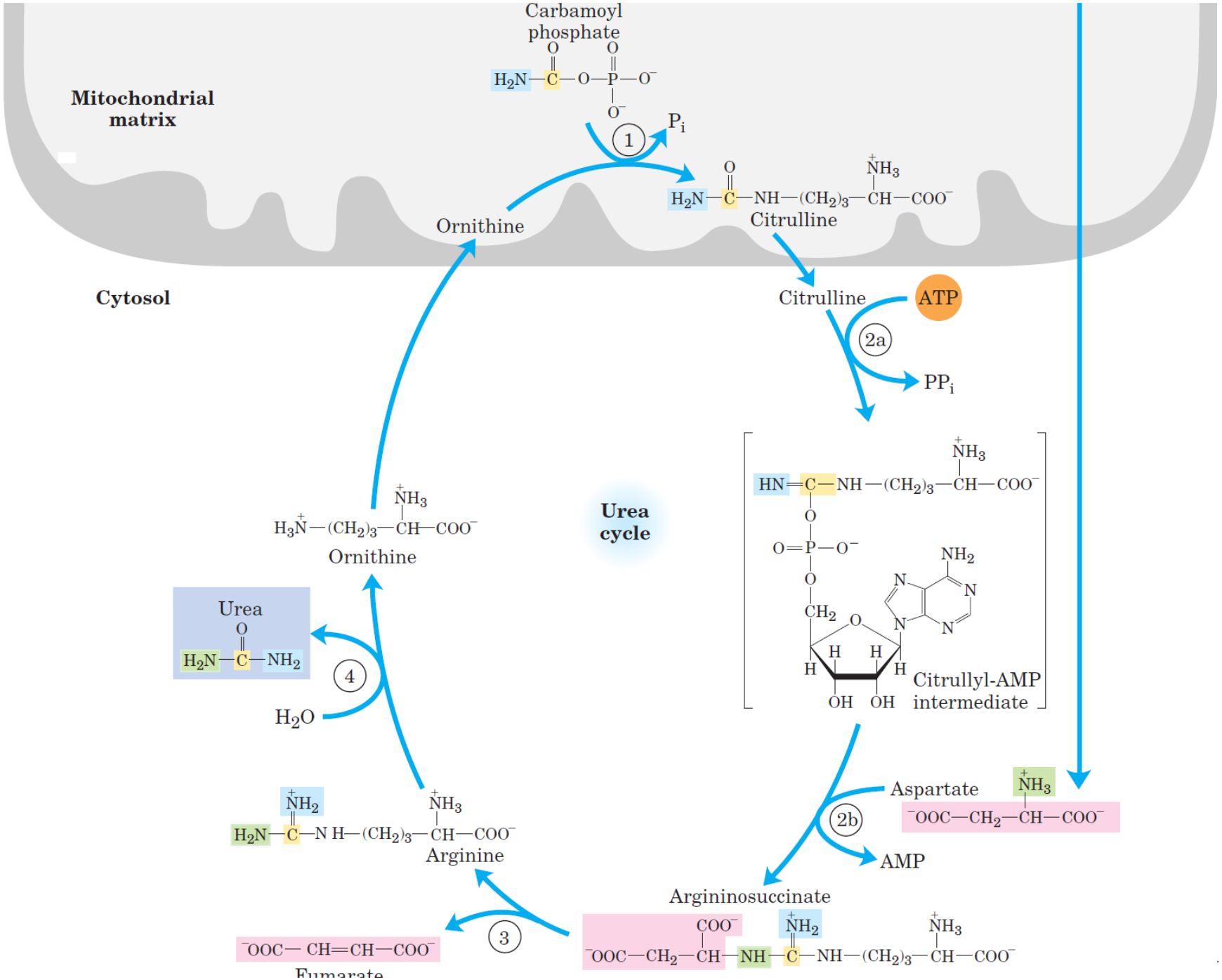
❖Terrestrial animals require pathways for nitrogen excretion that minimize toxicity and water loss. Most terrestrial animals are ureotelic, excreting amino nitrogen in the form of urea; birds and reptiles are uricotelic, excreting amino nitrogen as uric acid.

❖Plants recycle virtually all amino groups, and nitrogen excretion occurs only under very unusual circumstances.

❖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.


Glutamine (from extrahepatic tissues)
Amino acids
Alanine (from muscle)
α-Ketoglutarate
α-Keto acid
Glutamate
Glutamine
glutaminase
Glutamate
Oxaloacetate
aspartate aminotransferase
Aspartate
glutamate dehydrogenase
α-Keto-glutarate
NH4+
HCO3−
2 ATP
carbamoyl phosphate synthetase I
2ADP + P1
Carbamoyl phosphate
Mitochondrial matrix
P1
Ornithine
Citrulline
Cytosol
Citrulline
ATP
2a
PPi
Urea cycle
Citrullyl-AMP intermediate
Ornithine
Urea
4
H2O
Aspartate
2b
AMP
Arginine
Argininosuccinate
3
Fumarate


Glutamine
(from
extrahepatic
tissues)
Amino acids
Alanine (from muscle)
α-Ketoglutarate
α-Keto acid
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


Mitochondrial matrix
Cytosol
Carbamoyl phosphate
$H_2N-C(=O)-O-P(=O)(O^-)-O^-$
1
P_i
Ornithine
Citrulline
Citrulline
ATP
2a
PP_i
Urea cycle
Citrullyl-AMP intermediate
Aspartate
$^-OOC-CH_2-CH(NH_3^+)-COO^-$
2b
AMP
Argininosuccinate
Arginine
3
$^-OOC-CH=CH-COO^-$
Fumarate
4
H_2O
Urea
$H_2N-C(=O)-NH_2$
Ornithine

❖The urea cycle begins inside liver mitochondria, but three of the subsequent steps take place in the cytosol; the cycle thus spans two cellular compartments

❖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 .

❖The carbamoyl phosphate, which functions as an activated carbamoyl group donor, now enters the urea cycle.

❖Carbamoyl phosphate donates its carbamoyl group to ornithine to form citrulline.

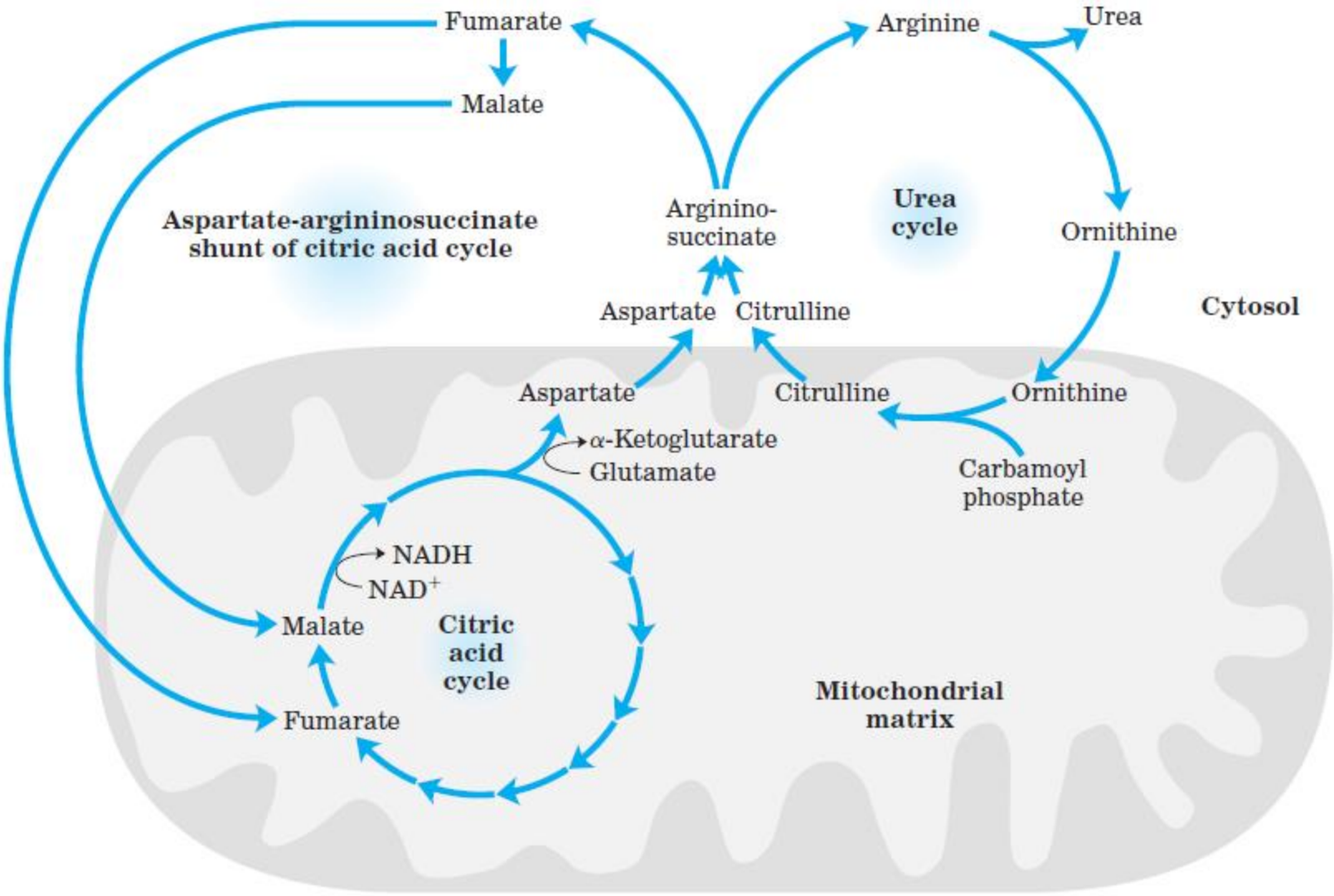
❖The second amino group now enters from aspartateby a condensation reaction between the amino group of aspartate and the ureido(carbonyl) group of citrulline, forming argininosuccinate.

❖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.

❖In the last reaction of the urea cycle (step 4), 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—in a process dubbed the “Krebs bicycle”


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

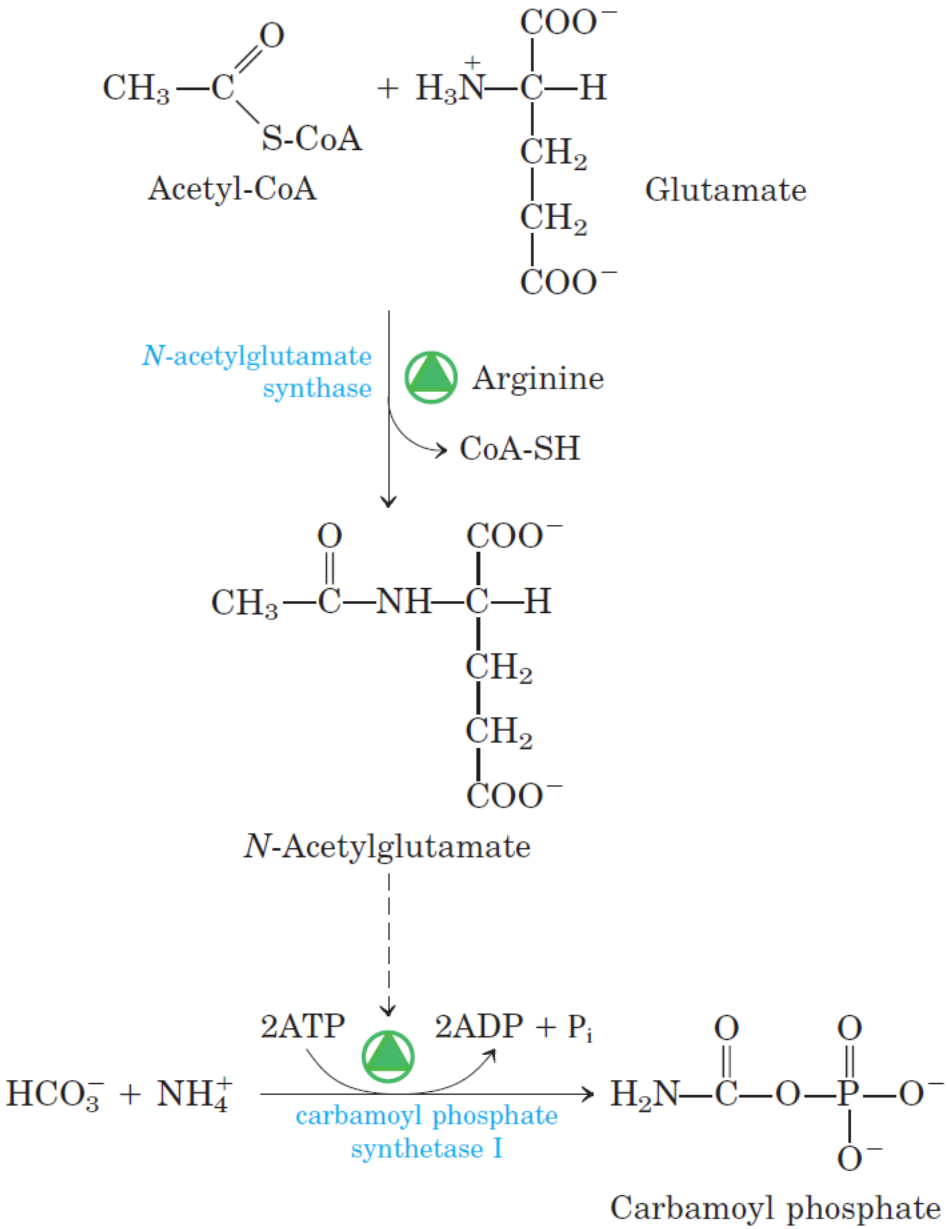
❖The flux of nitrogen through the urea cycle in an individual animal varies with diet.

❖When the dietary intake is primarily protein, the carbon skeletons of amino acids are used for fuel, producing much urea from the excess amino groups.

❖During prolonged starvation, when breakdown of muscle protein begins to supply much of the organism's metabolic energy, urea production also increases substantially.

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

❖Thus elevated levels of glutamate increase the rate of urea cycle.


Acetyl-CoA
Glutamate
N-acetylglutamate synthase
Arginine
CoA-SH
N-Acetylglutamate
2ATP
2ADP + Pi
carbamoyl phosphate synthetase I
Carbamoyl phosphate

❖The overall equation of the urea cycle is:

$$2NH_4^+ + HCO_3^- + 3ATP^{4-} + H_2O \longrightarrow \text{urea} + 2ADP^{3-} + 4P_i^{2-} + AMP^{2-} + 2H^+$$

❖If we consider the urea cycle in isolation, we see that the synthesis of one molecule of urea requires four high energy phosphate groups. Two ATP molecules are required to make carbamoyl phosphate, and one ATP to make argininosuccinate—the latter ATP undergoing a pyrophosphate cleavage to AMP and PPi, which is hydrolyzed to two Pi.

❖However, the urea cycle also causes a net conversion of oxaloacetate to fumarate (via aspartate), and the regeneration of oxaloacetate produces NADH in the malate dehydrogenase reaction.

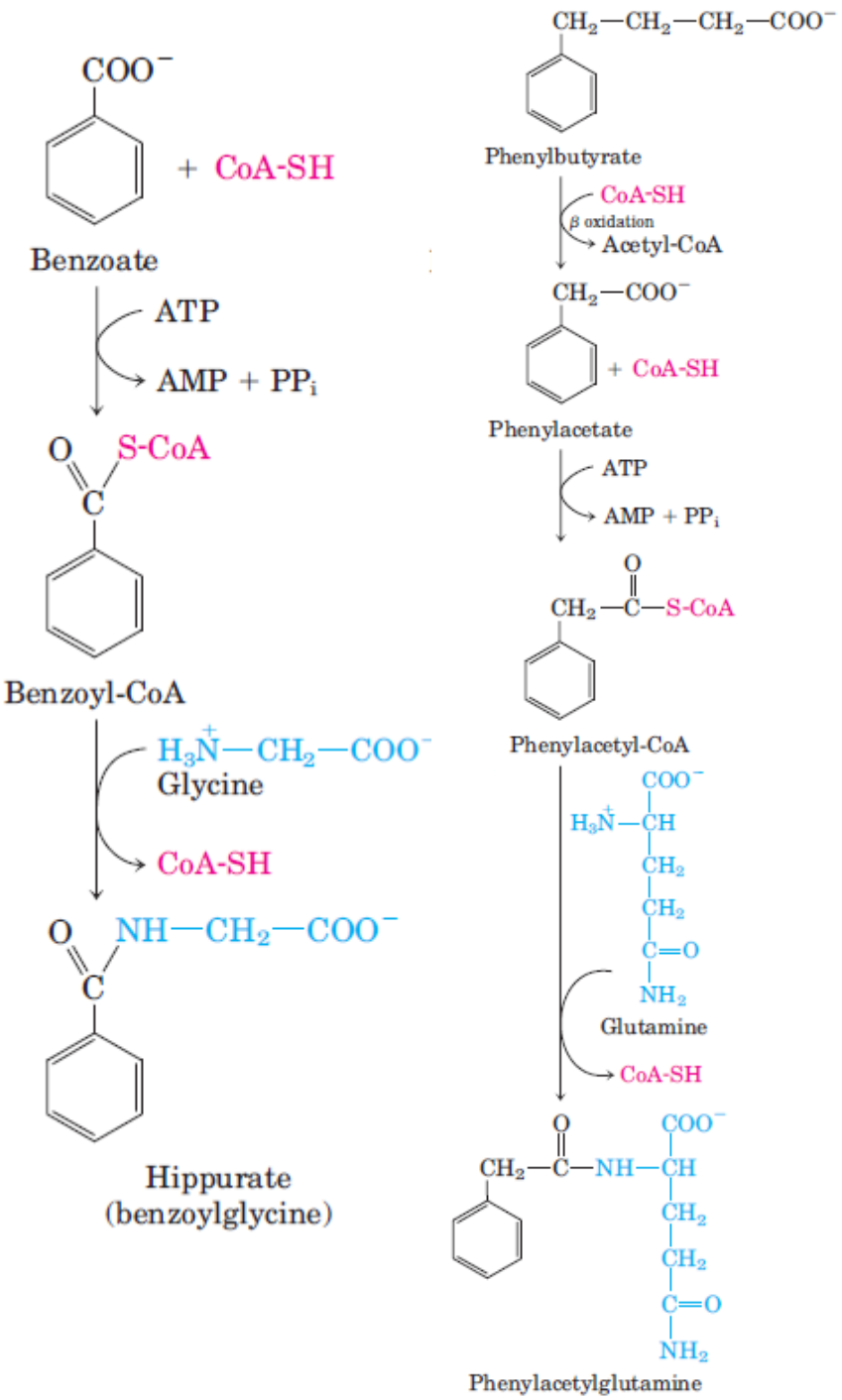
❖Each NADH molecule can generate up to 2.5 ATP during mitochondrial respiration, greatly reducing the overall energetic cost of urea synthesis..

❖People with genetic defects in any enzyme involved in urea formation cannot tolerate proteinrich diets.

❖Amino acids ingested in excess of the minimum daily requirements for protein synthesis are deaminated in the liver, producing free ammonia that cannot be converted to urea and exported into the bloodstream, and, as we have seen, ammonia is highly toxic.

❖The absence of a urea cycle enzyme can result in hyperammonemia or in the build-up of one or more urea cycle intermediates, depending on the enzyme that is missing.

❖Although the breakdown of amino acids can have serious health consequences in individuals with urea cycle deficiencies, a protein-free diet is not a treatment option. Humans are incapable of synthesizing half of the 20 common amino acids, and these essential amino acids must be provided in the diet.

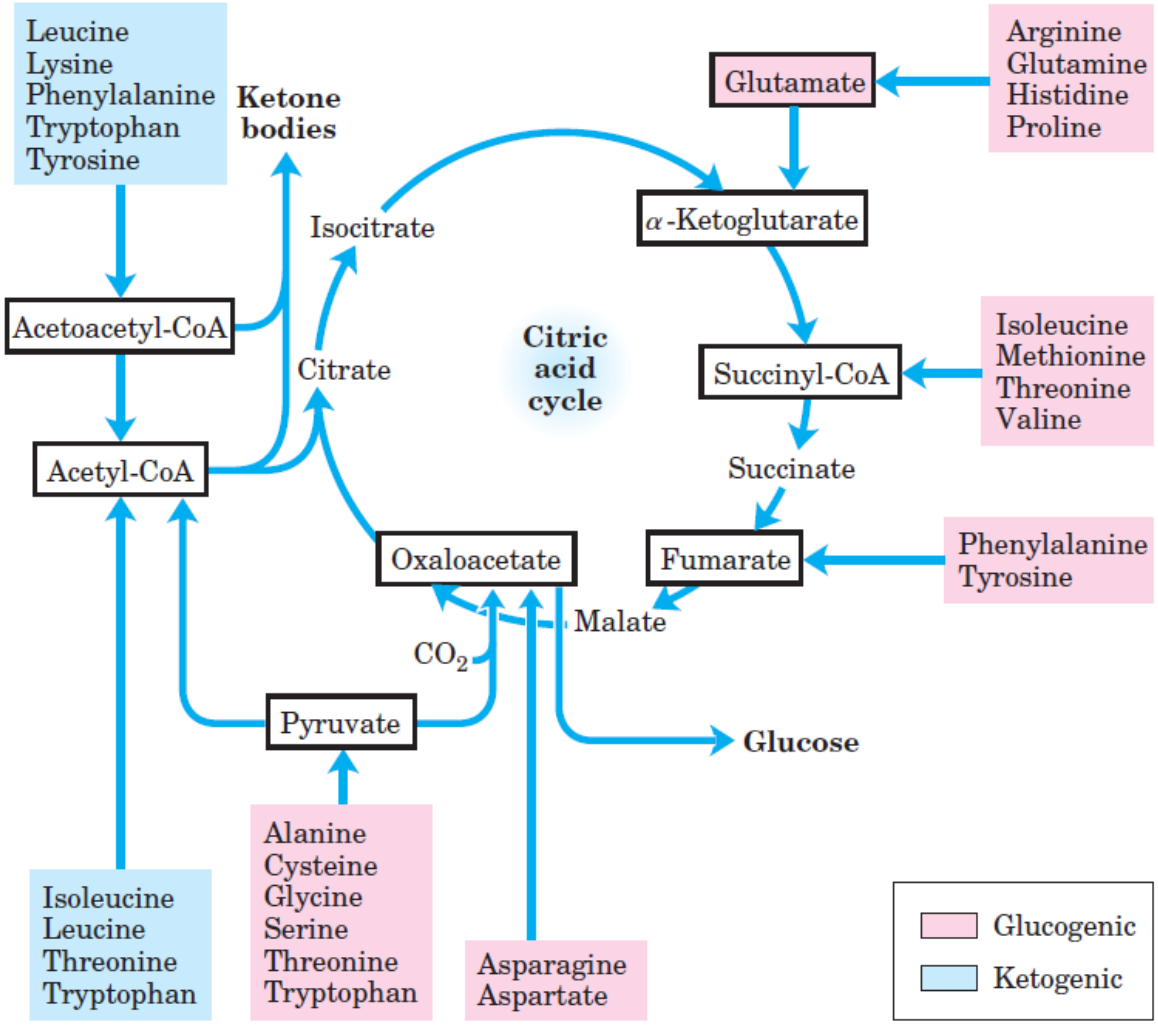


❖A variety of treatments are available for individuals with urea cycle defects.

❖Careful administration of the aromatic acids benzoate or phenylbutyrate in the diet can help lower the level of ammonia in the blood.

Amino Acid Catabolism

❖The pathways of amino acid catabolism, taken together, normally account for only 10% to 15% of the human body's energy production; these pathways are not nearly as active as glycolysis and fatty acid oxidation.



❖The 20 catabolic pathways converge to form only six major products, all of which enter the citric acid cycle.

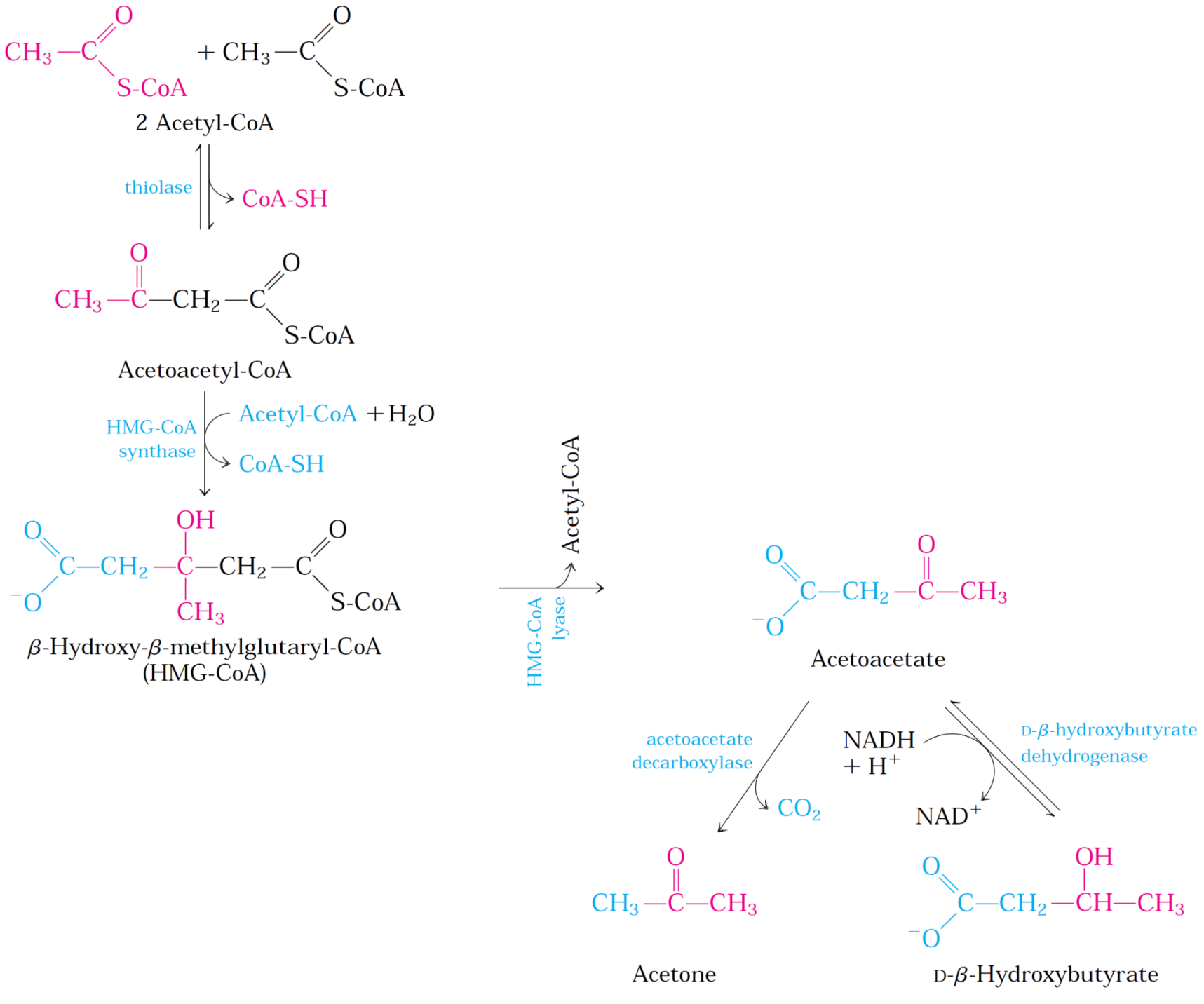
❖From here the carbon skeletons are diverted to gluconeogenesis or ketogenesis or are completely oxidized to CO_2 and H_2O.

❖The seven amino acids that are degraded entirely or in part to acetoacetyl-CoA and/or acetyl-CoA—phenylalanine, tyrosine, isoleucine, leucine, tryptophan, threonine, and lysine—can yield ketone bodies in the liver, where acetoacetyl-CoA is converted to acetoacetate and then to acetone and β-hydroxybutyrate.

❖These are the **ketogenic** amino acids

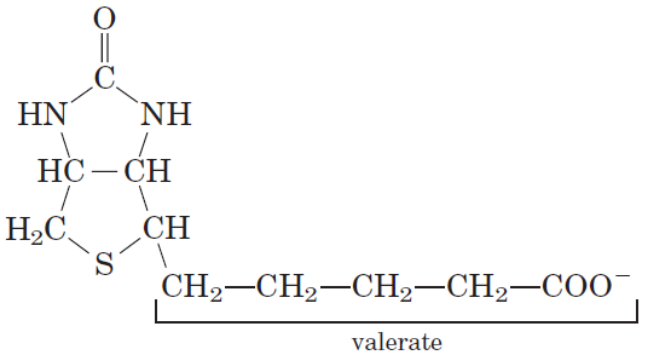
❖The amino acids that are degraded to pyruvate, α-ketoglutarate, succinyl-CoA, fumarate, and/or oxaloacetate can be converted to glucose and glycogen.

❖They are the **glucogenic** amino acids.

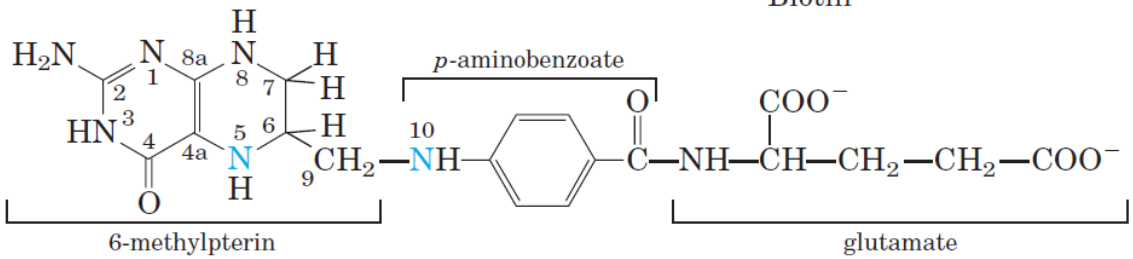

2 Acetyl-CoA
thiolase
CoA-SH
Acetoacetyl-CoA
HMG-CoA synthase
Acetyl-CoA + H2O
CoA-SH
β-Hydroxy-β-methylglutaryl-CoA (HMG-CoA)
HMG-CoA lyase
Acetyl-CoA
Acetoacetate
acetoacetate decarboxylase
CO2
NADH + H+
NAD+
D-β-hydroxybutyrate dehydrogenase
Acetone
D-β-Hydroxybutyrate

❖The division between ketogenic and glucogenic amino acids is not sharp; five amino acids—tryptophan, phenylalanine, tyrosine, threonine, and isoleucine—are both ketogenic and glucogenic.

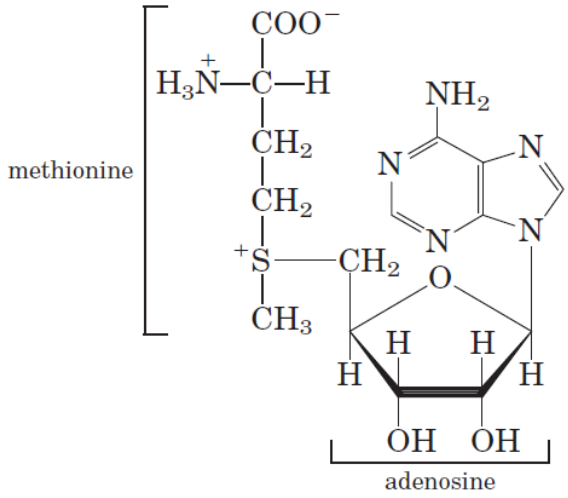
❖Pyridoxal phosphate, biotin, tetrahydrofolate and S-adenosyl methionine are the cofactors involved in amino acid catabolisn.



Biotin



Tetrahydrofolate (H_4 folate)

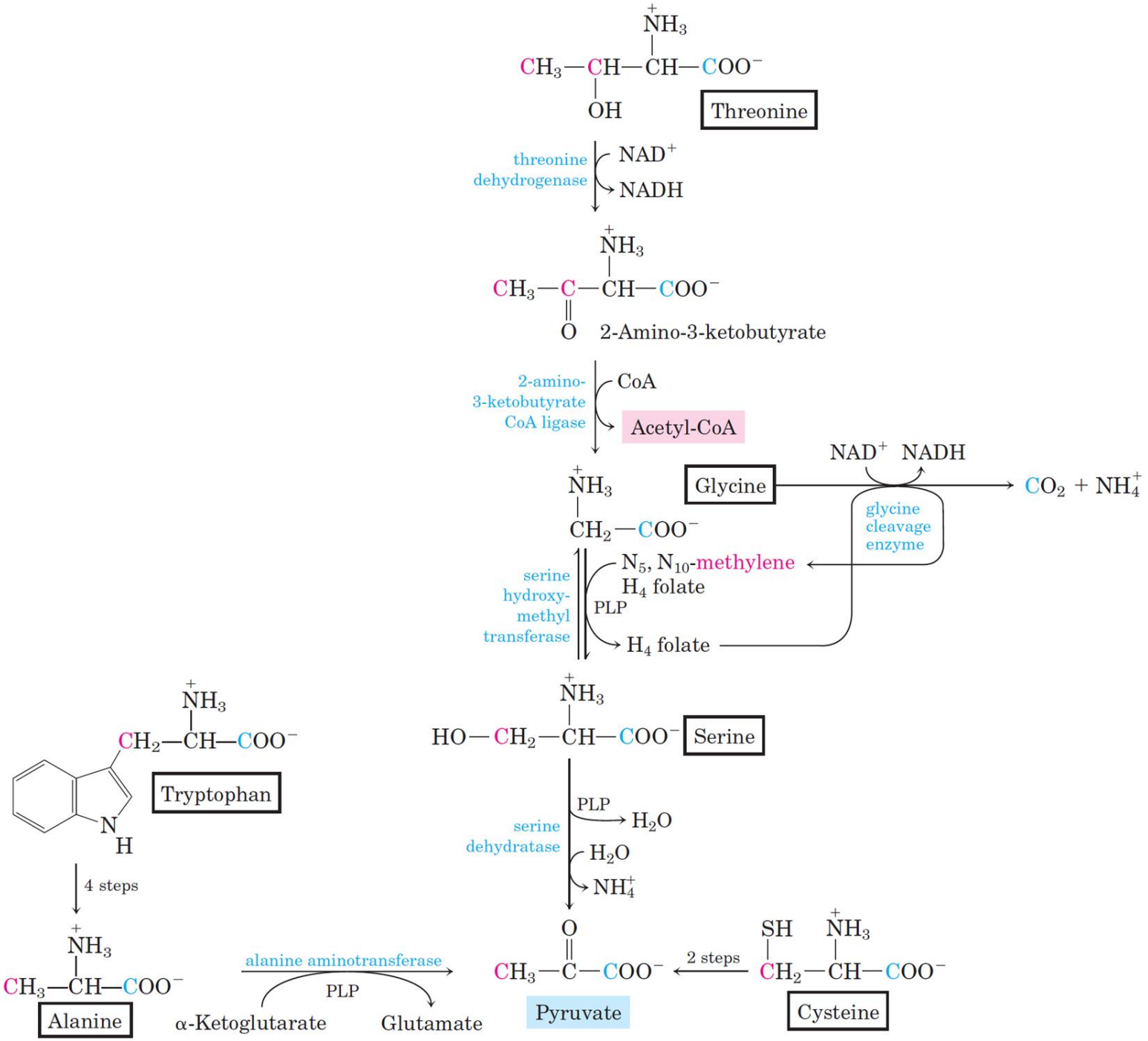


S-Adenosylmethionine (adoMet)

❖The carbon skeletons of six amino acids (alanine, tryptophan, cysteine, serine, glycine, and threonine) are converted in whole or in part to pyruvate.

❖The pyruvate can then be converted to either acetyl-CoA (a ketone body precursor) or oxaloacetate (a precursor for gluconeogenesis).

❖Thus amino acids catabolized to pyruvate are both ketogenic and glucogenic.

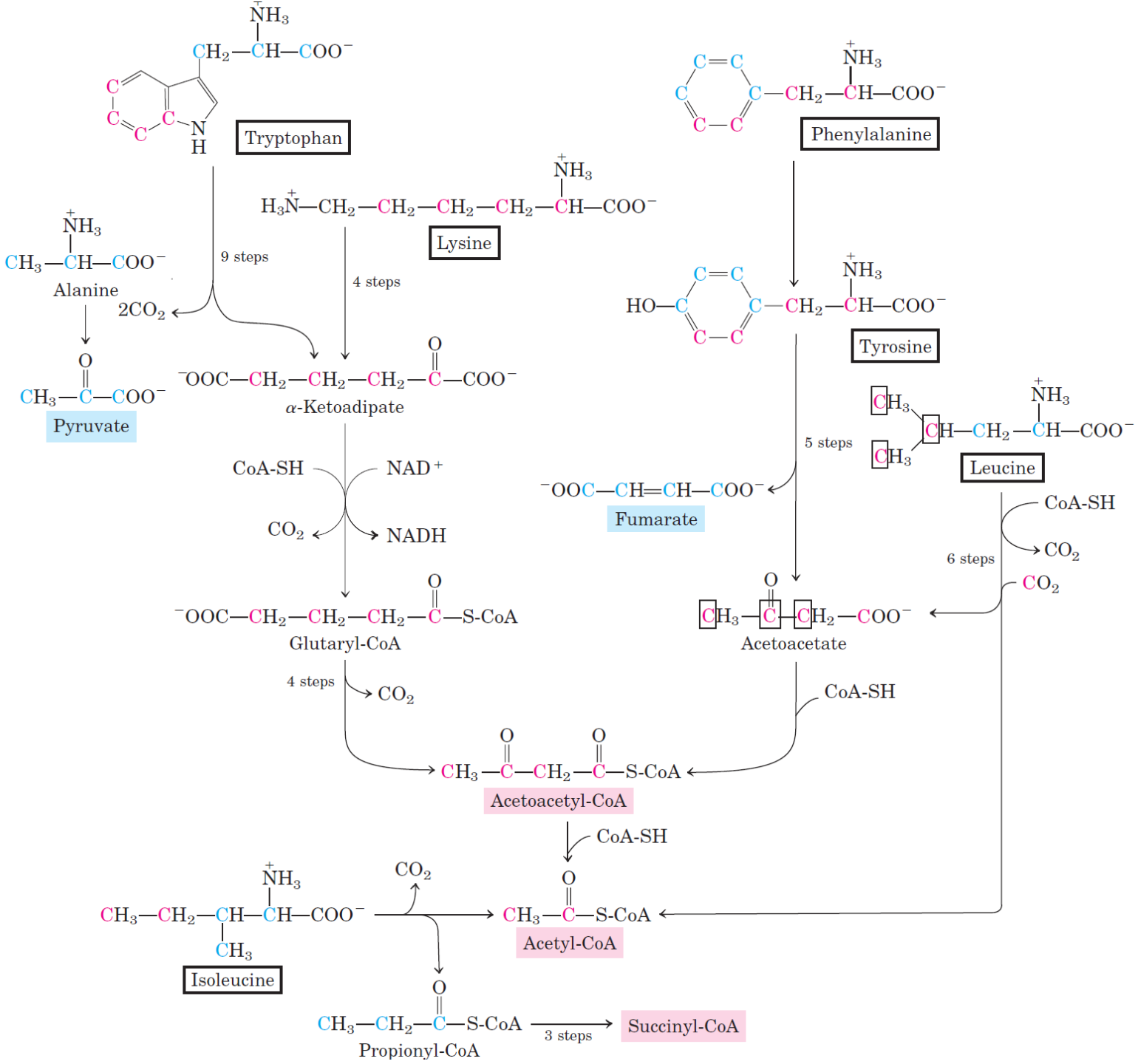

Threonine
threonine dehydrogenase
NAD+
NADH
2-Amino-3-ketobutyrate
2-amino-3-ketobutyrate CoA ligase
CoA
Acetyl-CoA
Glycine
NAD+ NADH
CO2 + NH4+
glycine cleavage enzyme
serine hydroxy-methyl transferase
N5, N10-methylene H4 folate
PLP
H4 folate
Serine
PLP
H2O
serine dehydratase
H2O
NH4+
Tryptophan
4 steps
Alanine
alanine aminotransferase
PLP
α-Ketoglutarate
Glutamate
Pyruvate
2 steps
Cysteine

❖Portions of the carbon skeletons of seven amino acids— tryptophan, lysine, phenylalanine, tyrosine, leucine, isoleucine, and threonine— yield acetyl-CoA and/or acetoacetyl-CoA, the latter being converted to acetyl-CoA.

❖The degradative pathways of two of these seven amino acids deserve special mention. Tryptophan breakdown is the most complex of all the pathways of amino acid catabolism in animal tissues; portions of tryptophan (four of its carbons) yield acetyl-CoA via acetoacetyl-CoA.

❖Some of the intermediates in tryptophan catabolism are precursors for the synthesis of other biomolecules, including nicotinate, a precursor of NAD and NADP in animals; serotonin, a neurotransmitter in vertebrates; and indoleacetate, a growth factor in plants.

❖The breakdown of phenylalanine is noteworthy because genetic defects in the enzymes of this pathway lead to several inheritable human diseases.

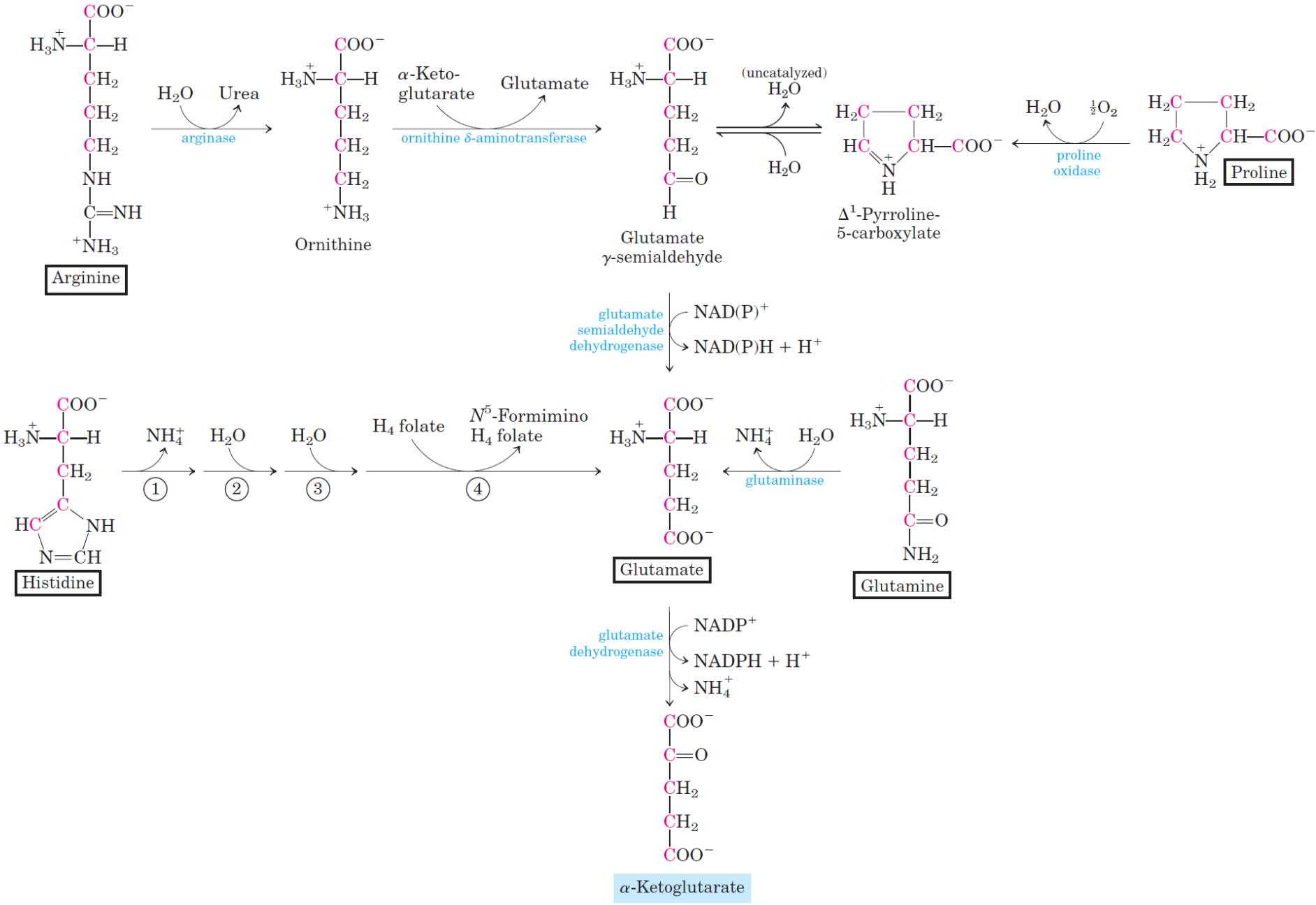

Tryptophan
Phenylalanine
Lysine
Alanine
9 steps
4 steps
2CO2
Tyrosine
Pyruvate
α-Ketoadipate
5 steps
Leucine
CoA-SH
NAD+
CO2
NADH
Fumarate
6 steps
CO2
Glutaryl-CoA
Acetoacetate
4 steps
CO2
CoA-SH
Acetoacetyl-CoA
CoA-SH
CO2
Acetyl-CoA
Isoleucine
Propionyl-CoA
3 steps
Succinyl-CoA

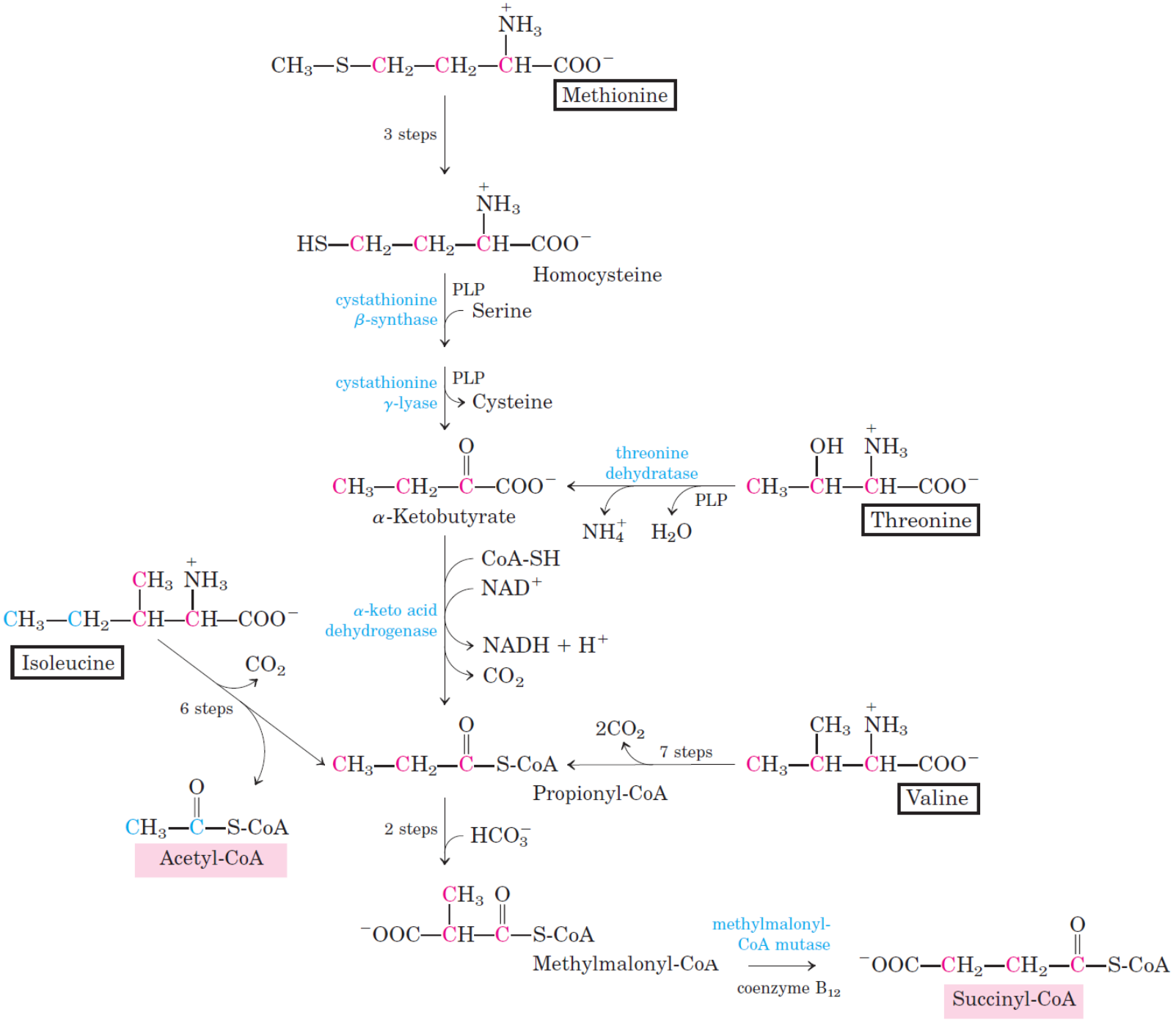
❖The carbon skeletons of five amino acids (proline, glutamate, glutamine, arginine, and histidine) enter the citric acid cycle as α-ketoglutarate.

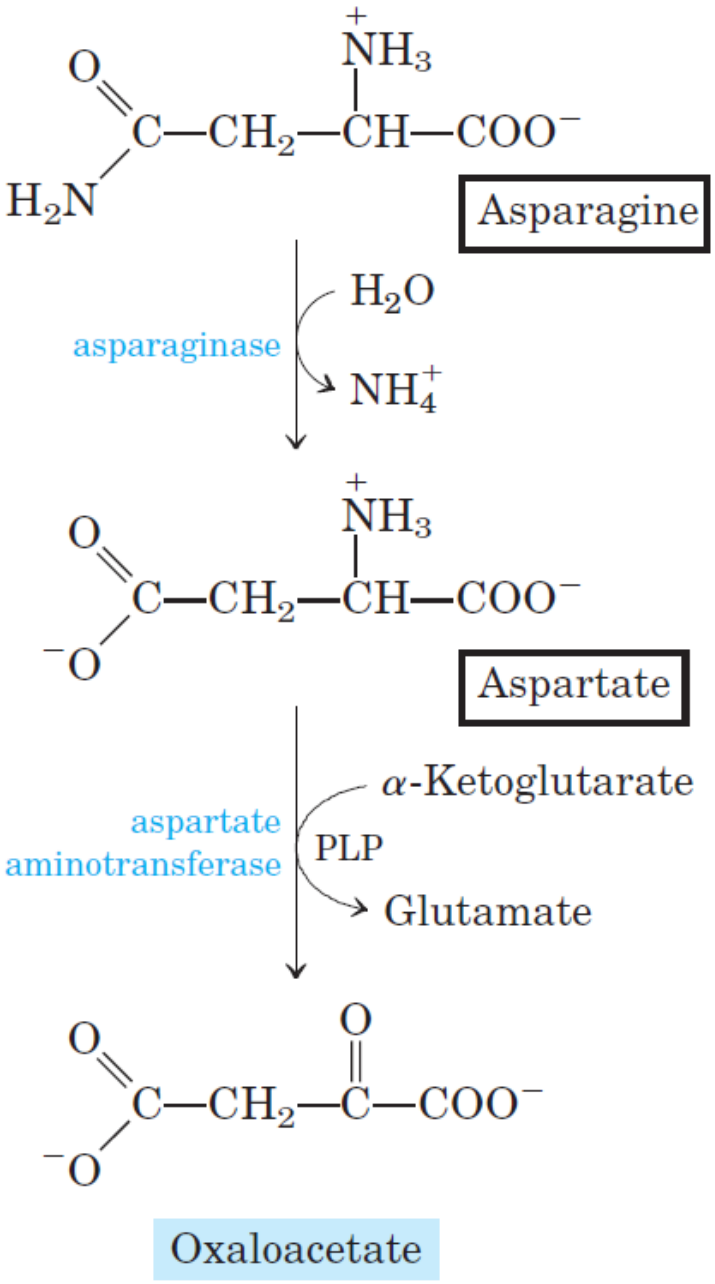
❖The carbon skeletons of methionine, isoleucine, threonine, and valine are degraded by pathways that yield succinyl-CoA.

❖Although much of the catabolism of amino acids takes place in the liver, the three amino acids with branched side chains (leucine, isoleucine, and valine) are oxidized as fuels primarily in muscle, adipose, kidney, and brain tissue.

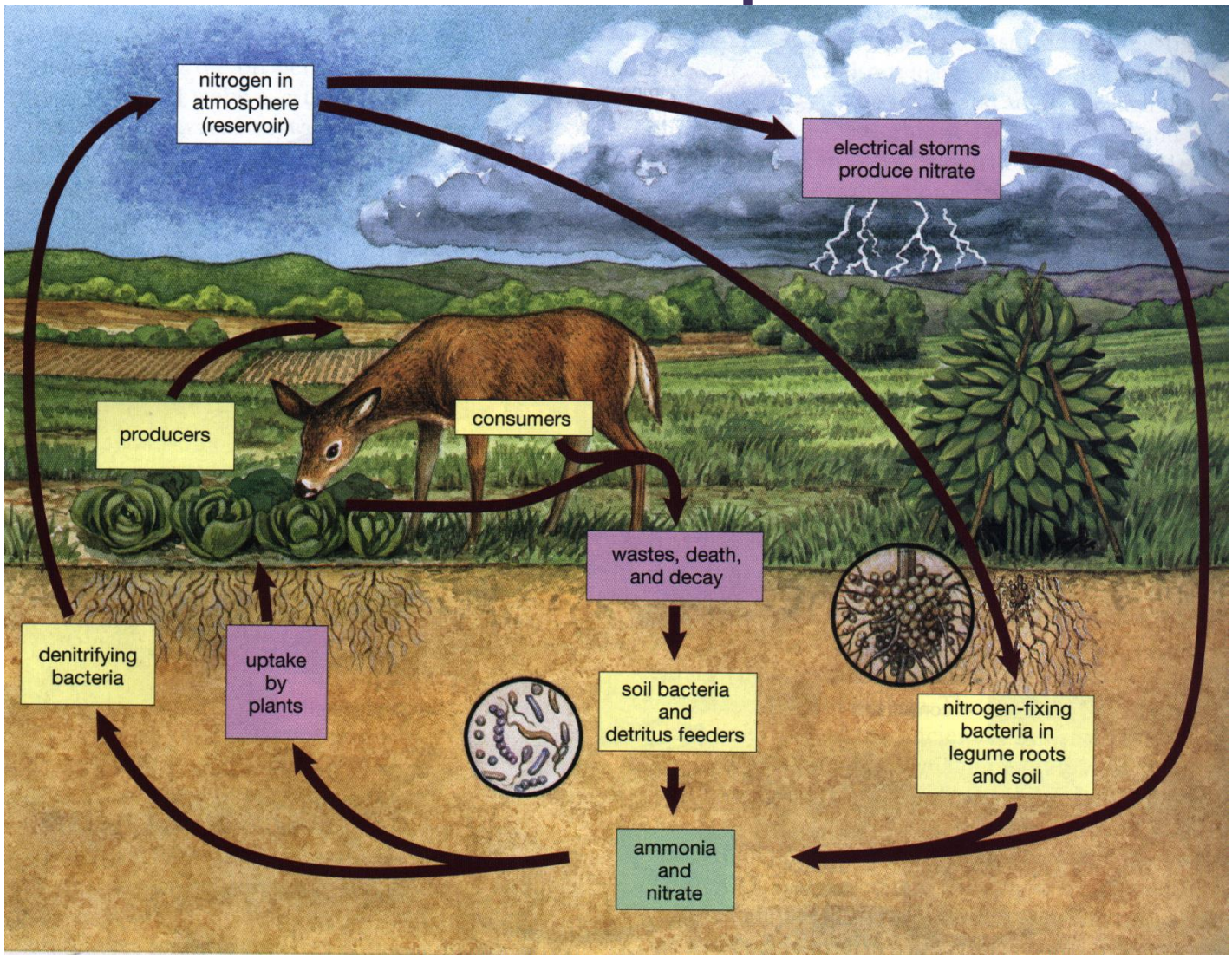
❖The carbon skeletons of asparagine and aspartate ultimately enter the citric acid cycle as oxaloacetate.


Arginine
H_2O
Urea
arginase
Ornithine
α-Keto-glutarate
Glutamate
ornithine δ-aminotransferase
Glutamate γ-semialdehyde
(uncatalyzed)
H_2O
H_2O
Δ^1-Pyrroline-5-carboxylate
H_2O
$\frac{1}{2}O_2$
proline oxidase
Proline
glutamate semialdehyde dehydrogenase
$NAD(P)^+$
$NAD(P)H + H^+$
Histidine
NH_4^+
H_2O
H_2O
H_4 folate
N^5-Formimino H_4 folate
1
2
3
4
Glutamate
NH_4^+
H_2O
glutaminase
Glutamine
glutamate dehydrogenase
$NADP^+$
$NADPH + H^+$
NH_4^+
α-Ketoglutarate


Methionine
3 steps
Homocysteine
cystathionine β-synthase
PLP
Serine
cystathionine γ-lyase
PLP
Cysteine
α-Ketobutyrate
threonine dehydratase
PLP
NH4+
H2O
Threonine
CoA-SH
NAD+
α-keto acid dehydrogenase
NADH + H+
CO2
Isoleucine
CO2
6 steps
2CO2
7 steps
Propionyl-CoA
Valine
Acetyl-CoA
2 steps
HCO3−
Methylmalonyl-CoA
methylmalonyl-CoA mutase
coenzyme B12
Succinyl-CoA


Asparagine
asparaginase
H_2O
NH_4^+
Aspartate
aspartate aminotransferase
PLP
α-Ketoglutarate
Glutamate
Oxaloacetate

Biosynthesis of Amino Acids and Related Compounds



- Nitrogen ranks behind only carbon, hydrogen, and oxygen in its contribution to the mass of living systems.

- Most of this nitrogen is bound up in amino acids and nucleotides.

- Although Earth's atmosphere is four-fifths molecular nitrogen (N_2), relatively few species can convert this atmospheric nitrogen into forms useful to living organisms.

- In the biosphere, the metabolic processes of different species function interdependently to salvage and reuse biologically available nitrogen in a vast nitrogen cycle.

- The first step in the cycle is fixation (reduction) of atmospheric nitrogen by nitrogen-fixing bacteria to yield ammonia (NH3 or NH_4^+).

- Although ammonia can be used by most living organisms, soil bacteria that derive their energy by oxidizing ammonia to nitrite (NO_2^-) and ultimately nitrate (NO_3^-) are so abundant and active that nearly all ammonia reaching the soil is oxidized to nitrate.

- This process is known as **nitrification**.

- Plants and many bacteria can take up and readily reduce nitrate and nitrite to ammonia through the action of nitrate and nitrite reductases.

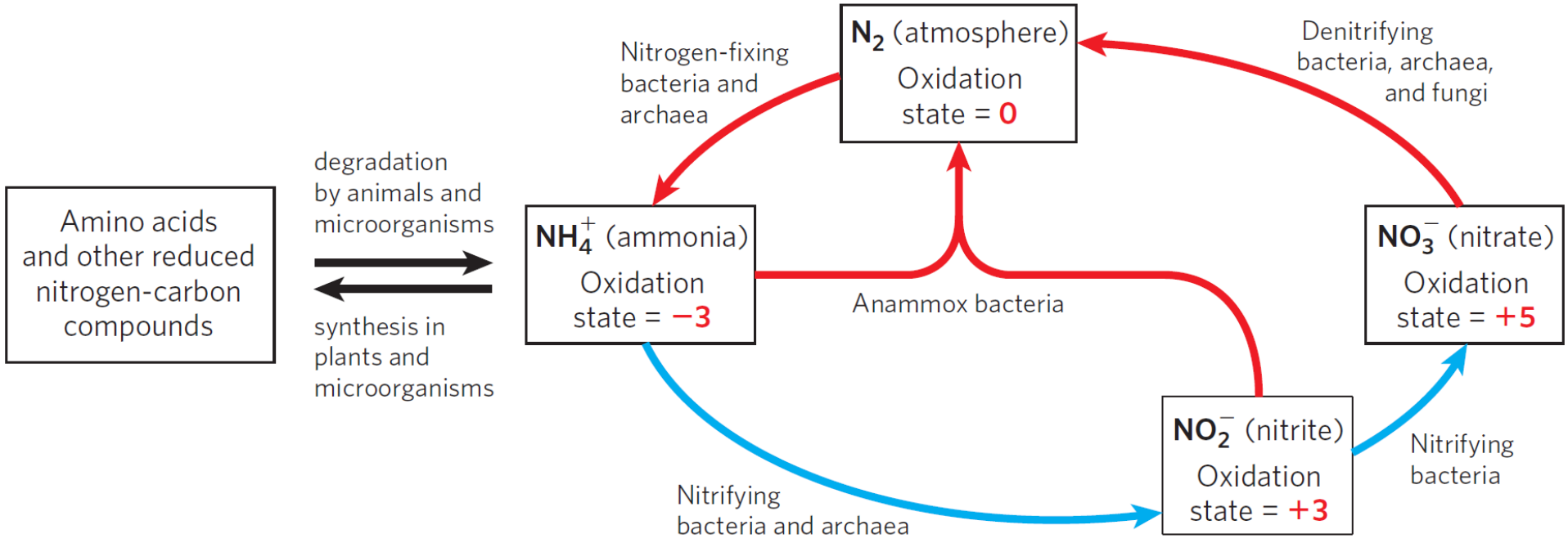
- This ammonia is incorporated into amino acids by plants.

- Animals then use plants as a source of amino acids, both nonessential and essential, to build their proteins.

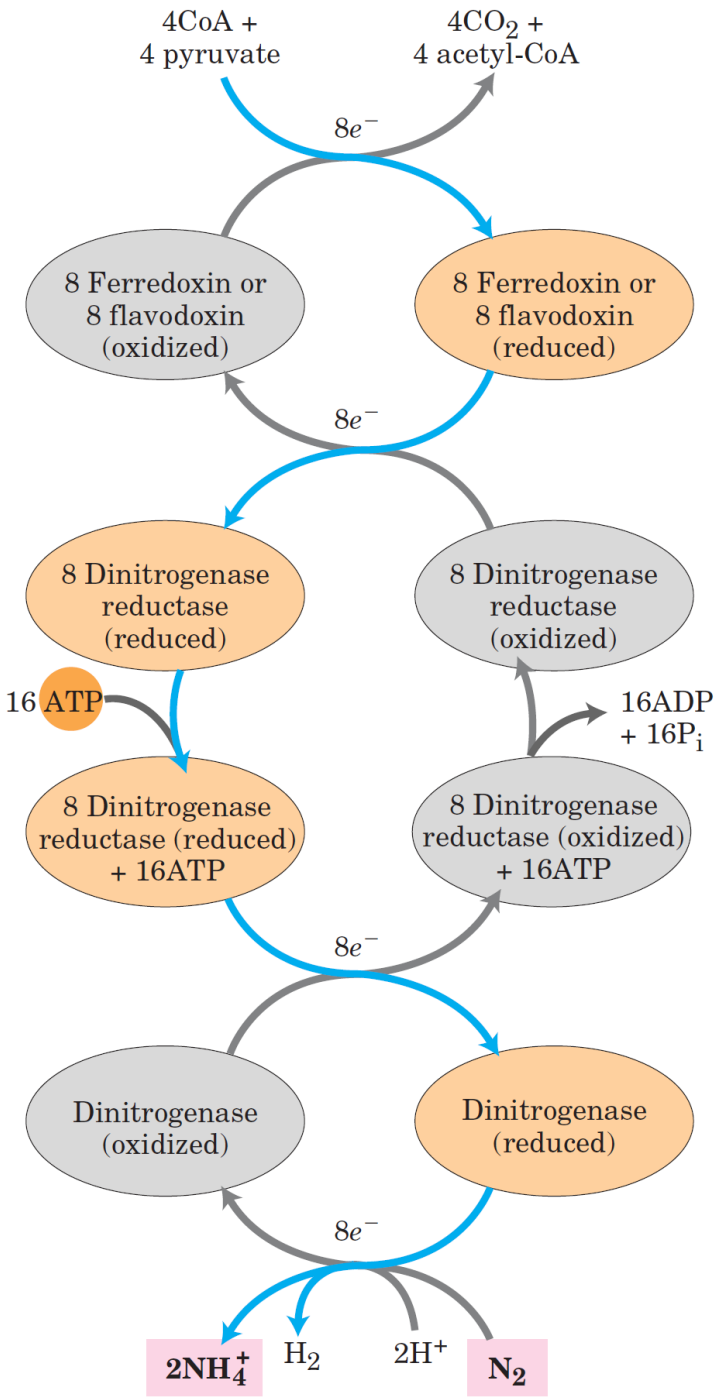
- When organisms die, microbial degradation of their proteins returns ammonia to the soil, where nitrifying bacteria again convert it to nitrite and nitrate.

- A balance is maintained between fixed nitrogen and atmospheric nitrogen by bacteria that reduce nitrate to N_2 under anaerobic conditions, a process called **denitrification**.

- Only certain bacteria and archaea can fix atmospheric N_2. The first important product of nitrogen fixation is ammoniawhich can be used by all organisms either directly or after its conversion to other soluble compounds such as nitrites, nitrates, or amino acids.


Amino acids and other reduced nitrogen-carbon compounds
degradation by animals and microorganisms
synthesis in plants and microorganisms
N_2 (atmosphere) Oxidation state = 0
Nitrogen-fixing bacteria and archaea
Denitrifying bacteria, archaea, and fungi
NH_4^+ (ammonia) Oxidation state = −3
Anammox bacteria
NO_3^- (nitrate) Oxidation state = +5
NO_2^- (nitrite) Oxidation state = +3
Nitrifying bacteria and archaea
Nitrifying bacteria

- Biological nitrogen fixation is carried out by a highly conserved complex of proteins called the nitrogenase complex.
- The nitrogenase complex is remarkably unstable in the presence of oxygen.
- Free-living bacteria that fix nitrogen cope with this problem in a variety of ways.
- Some live only anaerobically or repress nitrogenase synthesis when oxygen is present.
- Some aerobic species, partially uncouple electron transfer from ATP synthesis so that oxygen is burned off as rapidly as it enters the cell.



- Reduced nitrogen in the form of NH_4^+ is assimilated into amino acids and then into other nitrogen-containing biomolecules.

- Two amino acids, glutamate and glutamine provide the critical entry point.

- Glutamate is the source of amino groups for most other amino acids, through transamination reactions.

- The amide nitrogen of glutamine is a source of amino groups in a wide range of biosynthetic processes.

- The most important pathway for the assimilation of NH_4^+ into glutamate requires two reactions.

- First, glutamine synthetase catalyzes the reaction of glutamate and NH_4^+ to yield glutamine.

glutamine synthetase reaction

(1) Glutamate + ATP $\longrightarrow$ γ-glutamyl phosphate + ADP

(2) γ-Glutamyl phosphate + NH_4^+ $\longrightarrow$ glutamine + P_i + H^+

Glutamate + NH_4^+ + ATP $\longrightarrow$ glutamine + ADP + Pi + H^+

glutamate synthase reaction

α-Ketoglutarate + glutamine + NADPH + H^+ $\longrightarrow$ 2 glutamate + $NADP^+$

The net reaction of glutamine synthetase and glutamate synthase

α-Ketoglutarate + NH_4^+ + NADPH + ATP $\longrightarrow$ L-glutamate + $NADP^+$ + ADP + P_i

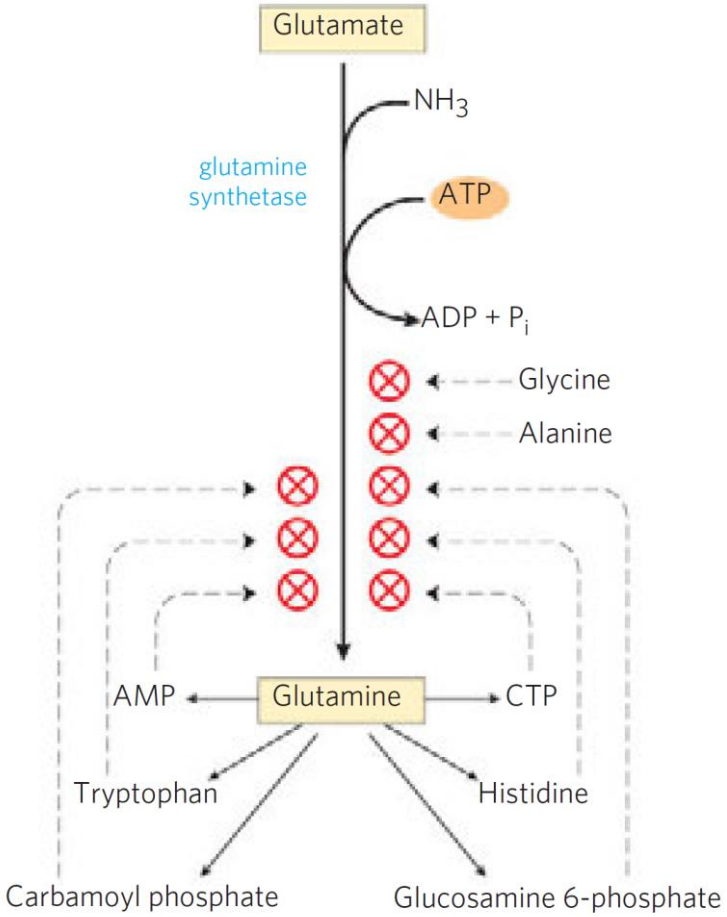
---

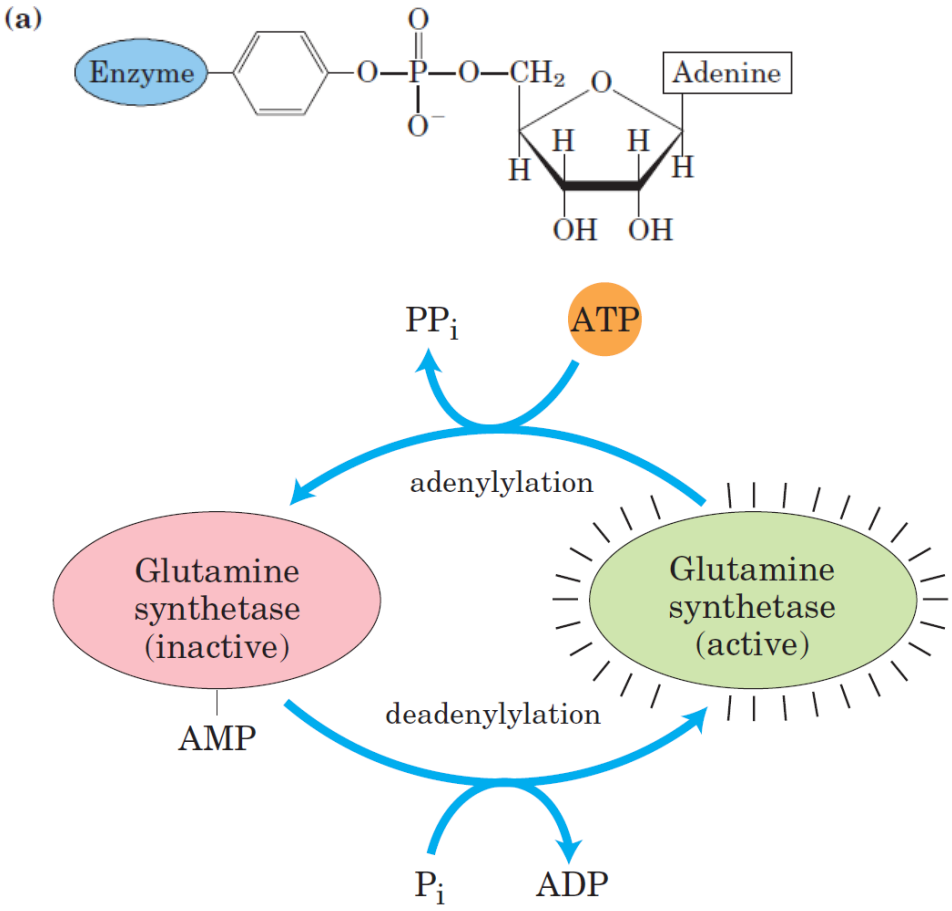
minor pathway : L-glutamate dehydrogenase reaction

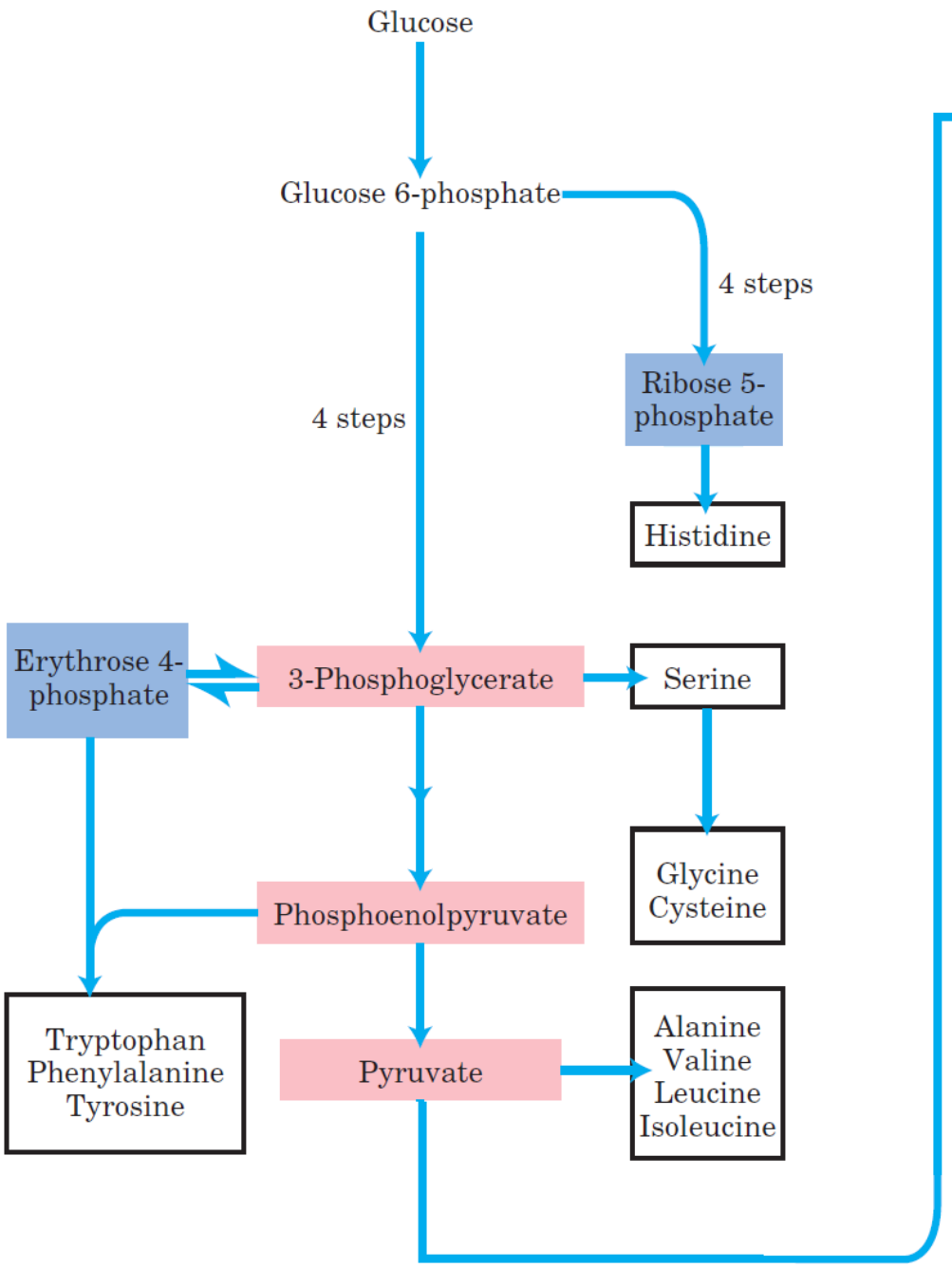
α-Ketoglutarate + NH_4^+ + NADPH $\longrightarrow$ L-glutamate + $NADP^+$ + H_2O

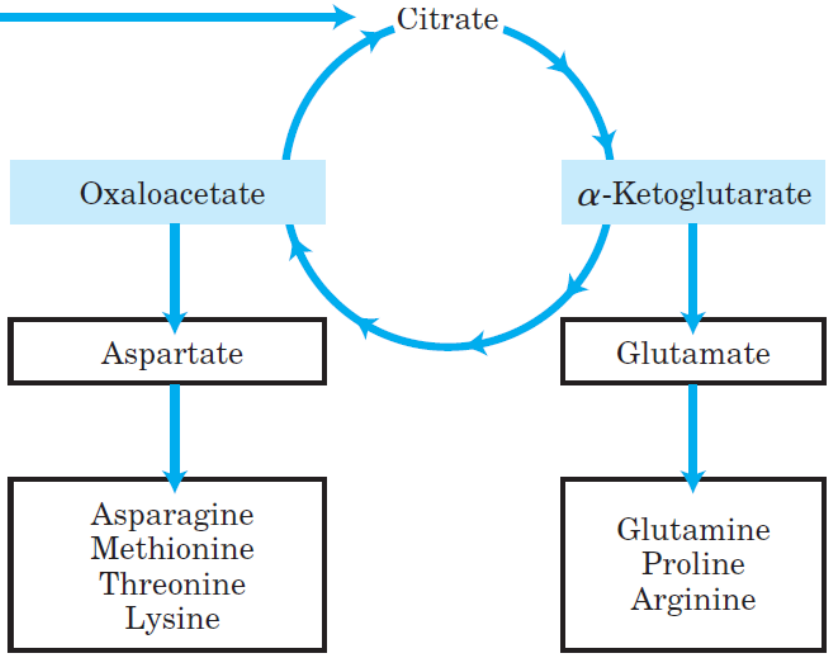
- The activity of glutamine synthetase is regulated in virtually all organisms—as expected, given its central metabolic role as an entry point for reduced nitrogen.

- In enteric bacteria such as E. coli, the regulation is unusually complex. Type I enzyme (from bacteria) has 12 identical subunits of Mr 50,000 and is regulated both allosterically and by covalent modification.









- All amino acids are derived from intermediates in glycolysis, the citric acid cycle, or the pentose phosphate pathway.
- Nitrogen enters these pathways by way of glutamate and glutamine.

- Organisms vary greatly in their ability to synthesize the 20 common amino acids.

- Whereas most bacteria and plants can synthesize all 20, mammals can synthesize only about half of them—generally those. with simple pathways. These are the **nonessential amino acids**, not needed in the diet.

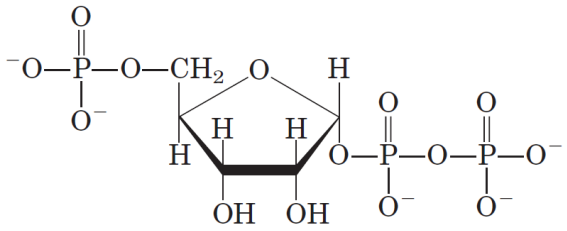
- The remainder, the **essential amino acids**, must be obtained from food.

- Yiyecekler ile birlikte dışarıdan alınması zorunlu olan, organizmada sentezlenemeyen amino asitler ise esansiyel amino asitler olarak adlandırılırlar.

- A useful way to organize these biosynthetic pathways is to group them into six families corresponding to their metabolic precursors.

- In addition to these six precursors, there is a notable intermediate in several pathways of amino acid and nucleotide synthesis: 5-phosphoribosyl-1-pyrophosphate (PRPP).

5-phosphoribosyl-1- pyrophosphate (PRPP):



Ribose 5-phosphate + ATP ⟶ 5-phosphoribosyl-1-pyrophosphate + AMP

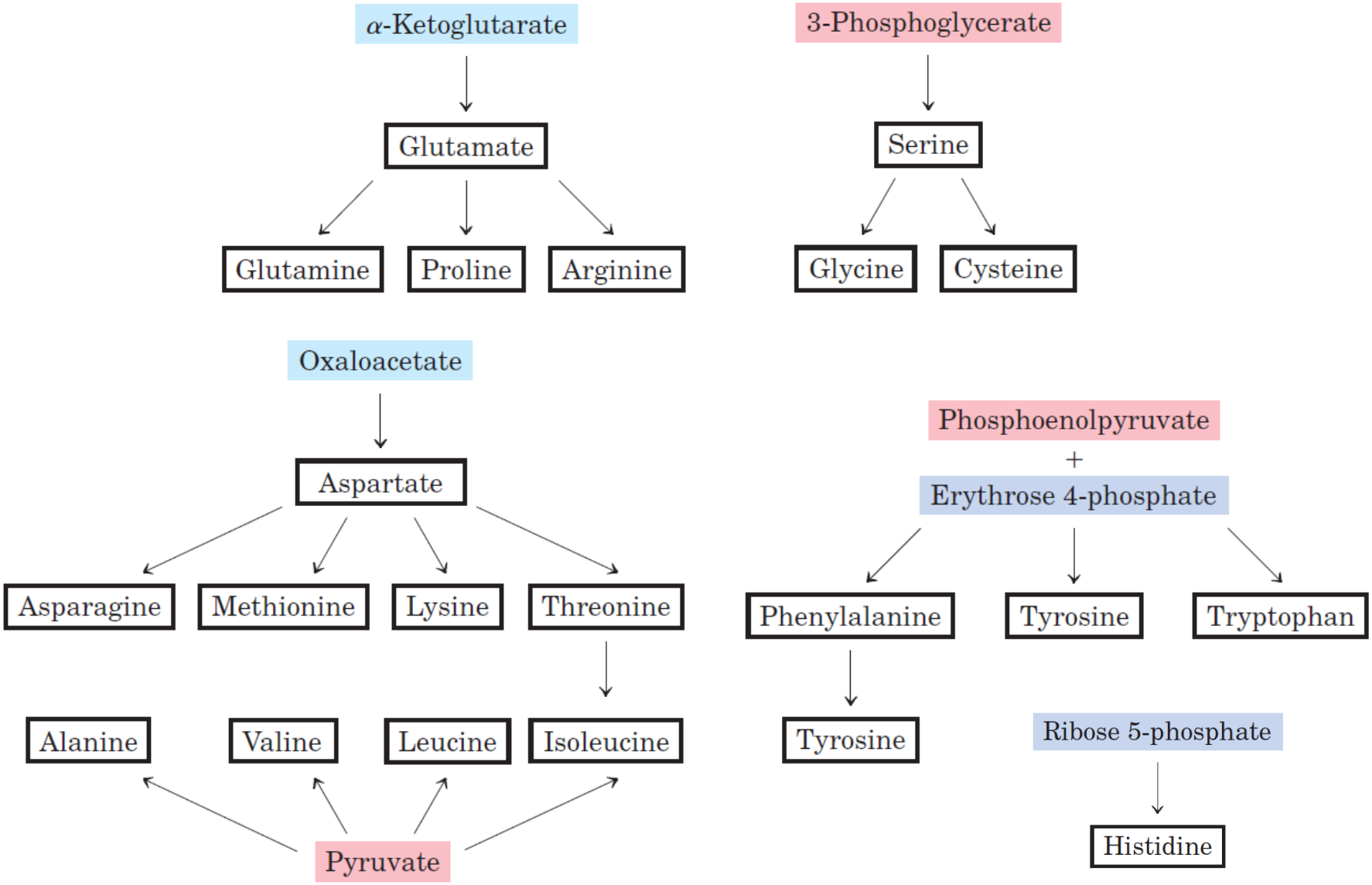
ribose phosphate pyrophosphokinase

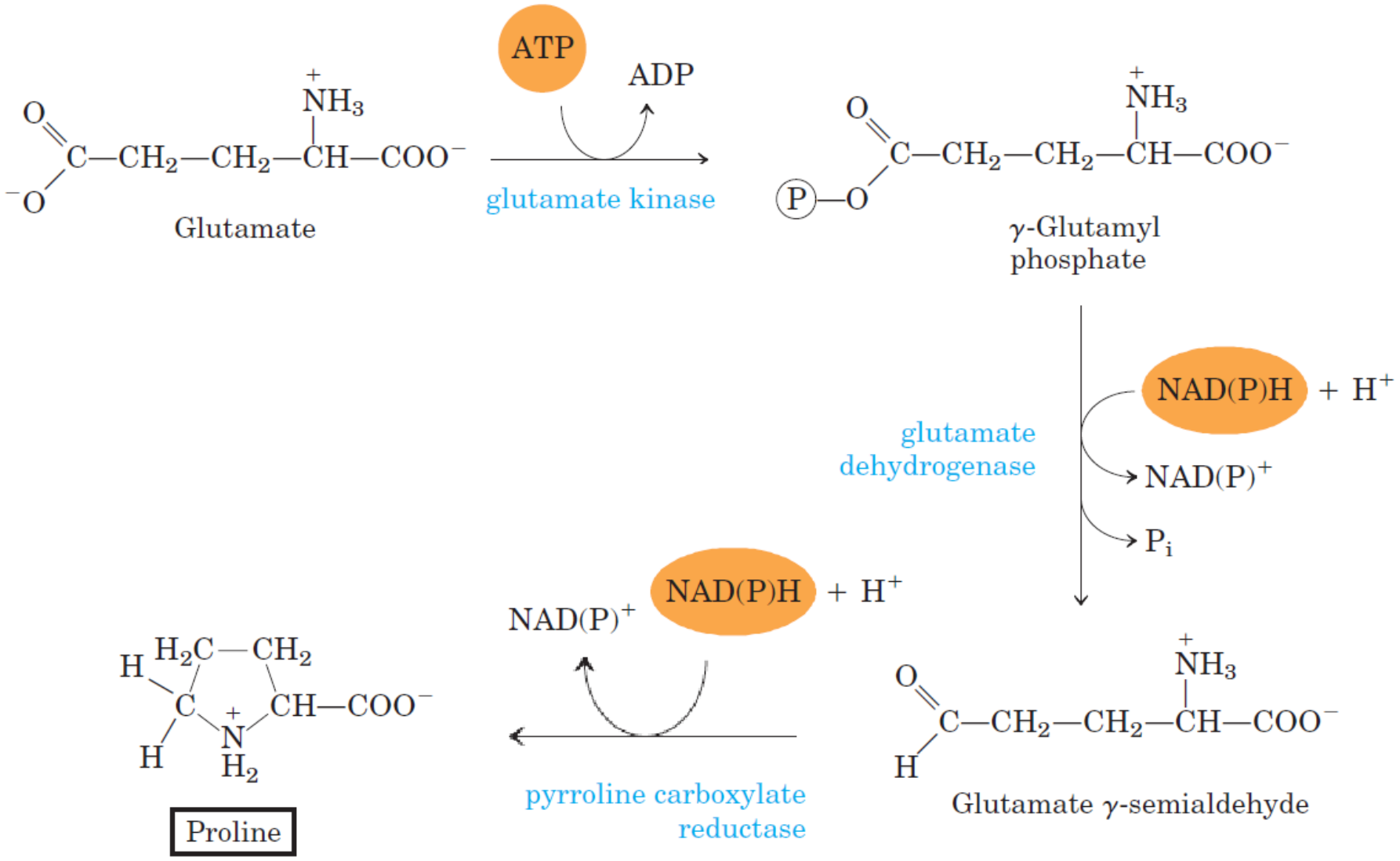
TABLE 22–1 Amino Acid Biosynthetic Families, Grouped by Metabolic Precursor

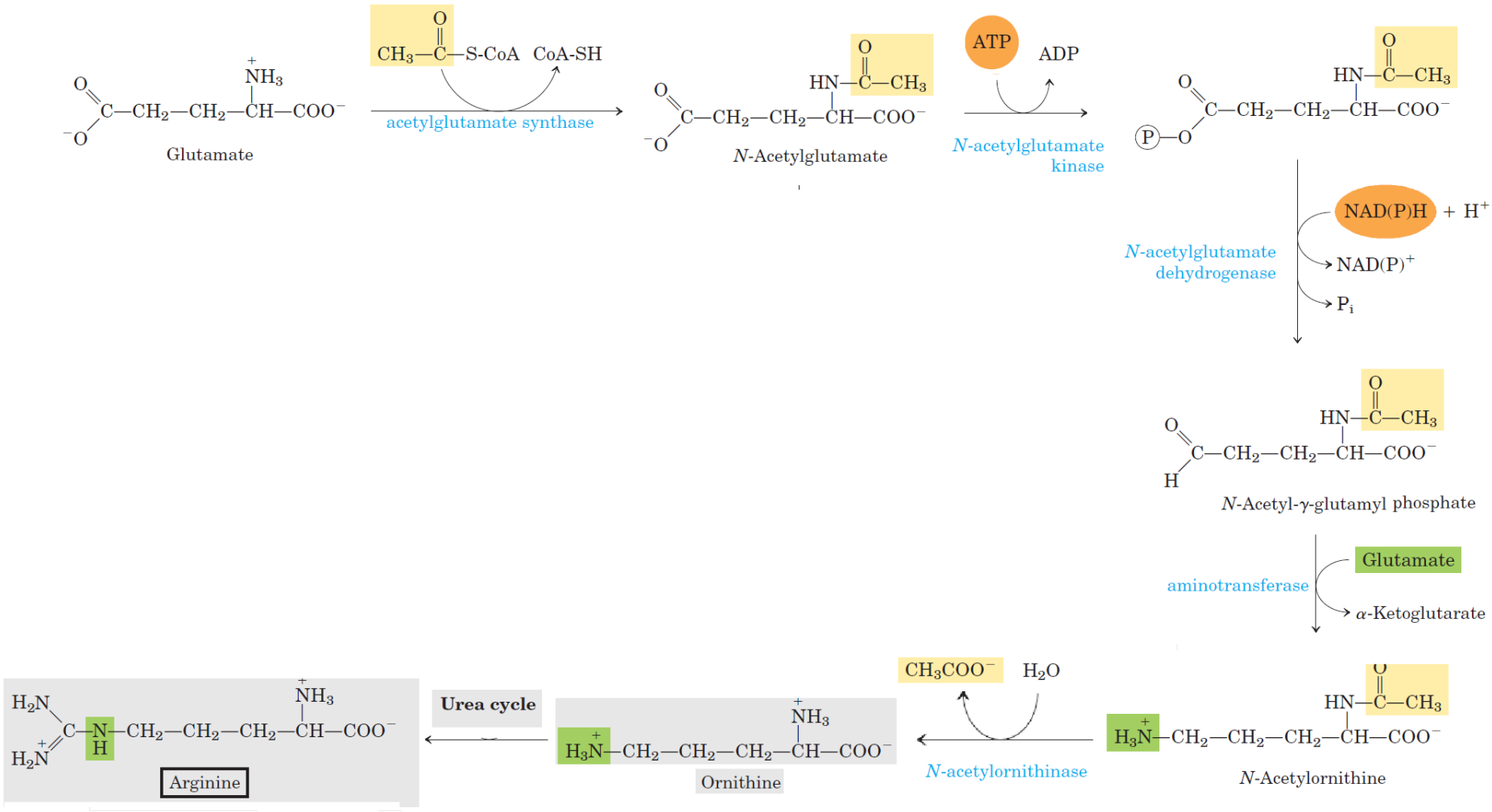
α-Ketoglutarate	**Pyruvate**
Glutamate	Alanine
Glutamine	Valine*
Proline	Leucine*
Arginine	Isoleucine*
3-Phosphoglycerate	**Phosphoenolpyruvate and erythrose 4-phosphate**
Serine	
Glycine	
Cysteine	Tryptophan*
Oxaloacetate	Phenylalanine*
Aspartate	Tyrosine†
Asparagine	**Ribose 5-phosphate**
Methionine*	Histidine*
Threonine*	
Lysine*	

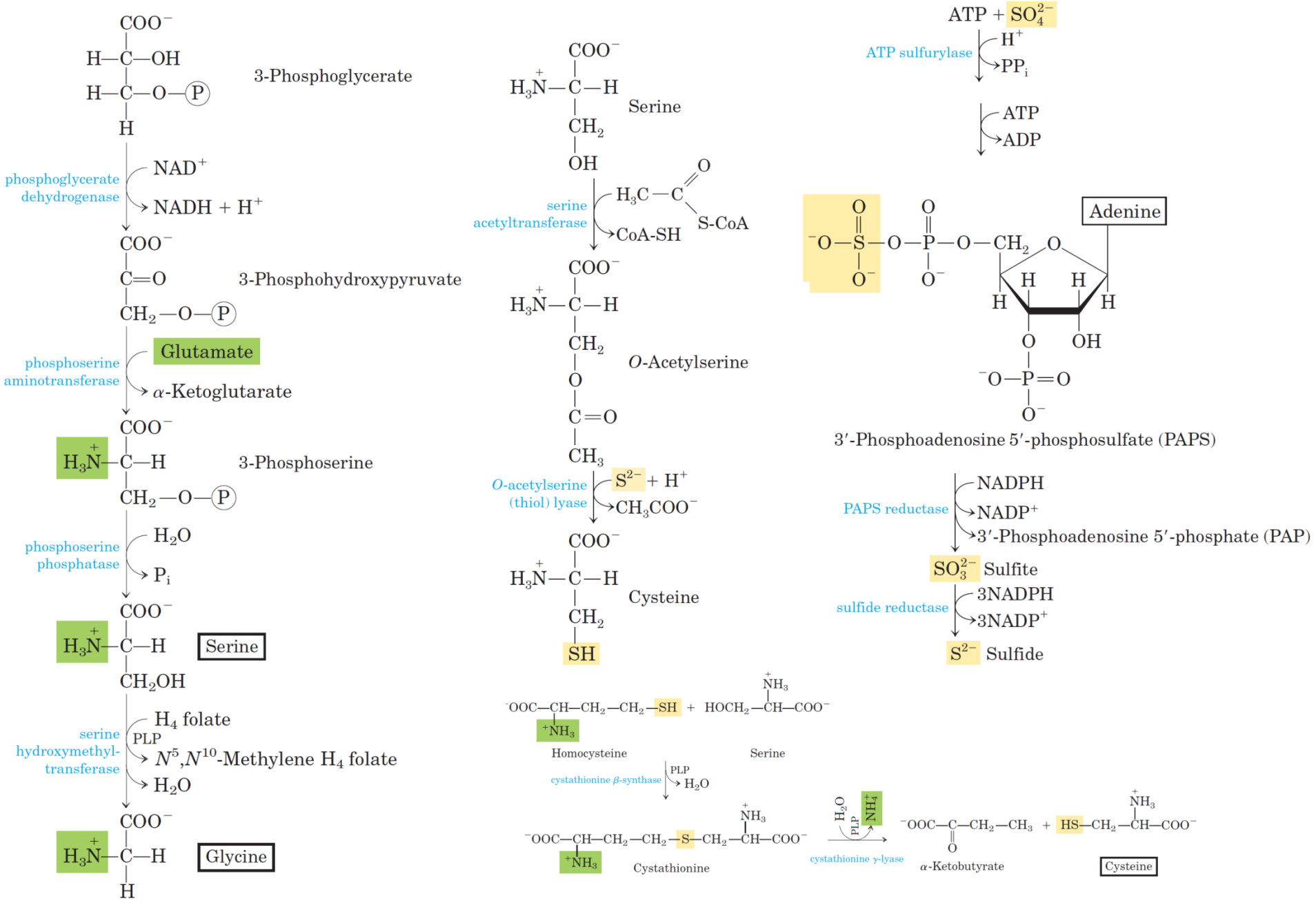
*Essential amino acids in mammals.

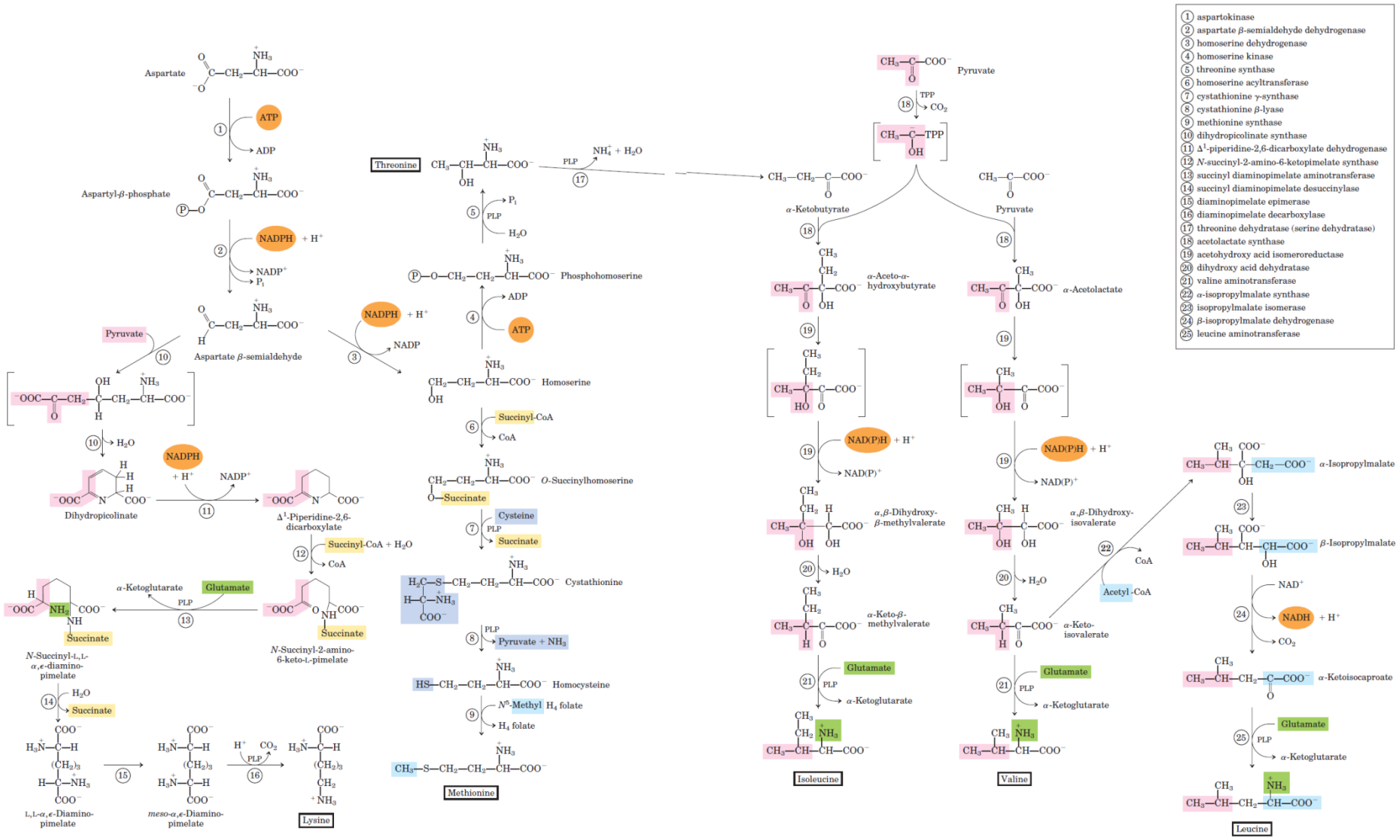
†Derived from phenylalanine in mammals.

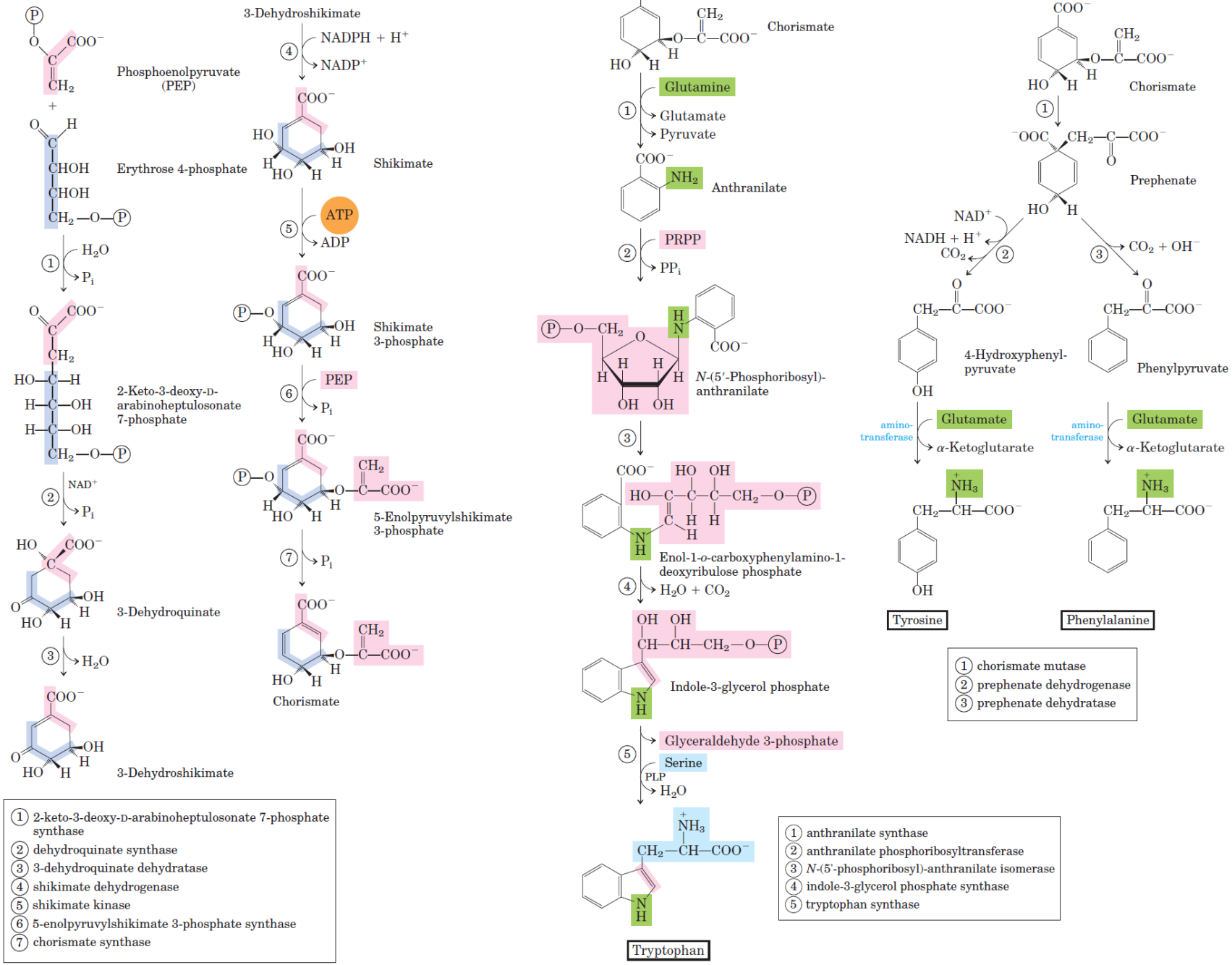

α-Ketoglutarate
Glutamate
Glutamine
Proline
Arginine
3-Phosphoglycerate
Serine
Glycine
Cysteine
Oxaloacetate
Aspartate
Asparagine
Methionine
Lysine
Threonine
Alanine
Valine
Leucine
Isoleucine
Pyruvate
Phosphoenolpyruvate
+
Erythrose 4-phosphate
Phenylalanine
Tyrosine
Tryptophan
Tyrosine
Ribose 5-phosphate
Histidine

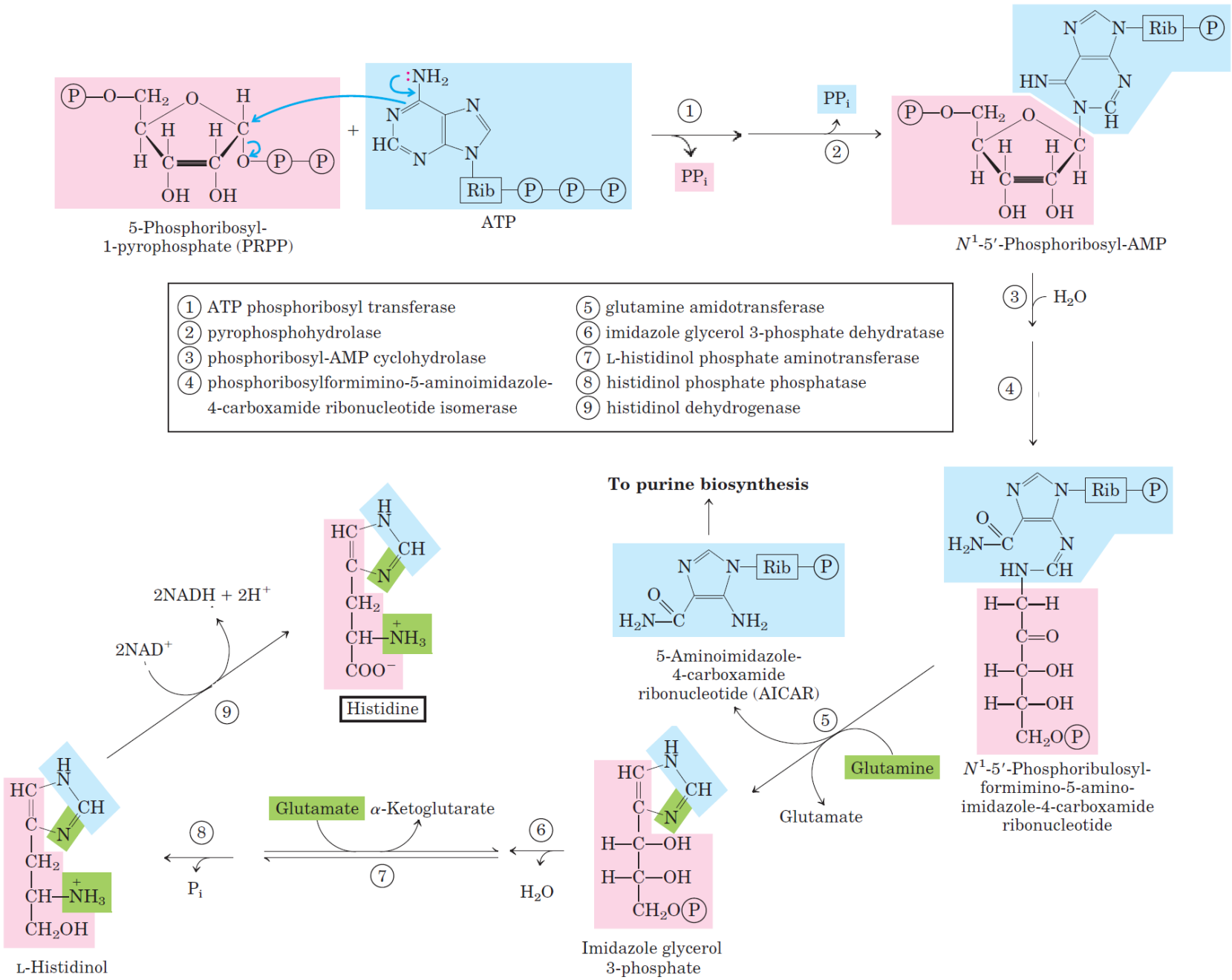

ATP
ADP
glutamate kinase
Glutamate
γ-Glutamyl phosphate
glutamate dehydrogenase
NAD(P)H + H+
NAD(P)+
Pi
NAD(P)H + H+
NAD(P)+
pyrroline carboxylate reductase
Glutamate γ-semialdehyde
Proline


Glutamate
CH3—C—S-CoA
CoA-SH
acetylglutamate synthase
N-Acetylglutamate
ATP
ADP
N-acetylglutamate kinase
NAD(P)H + H+
N-acetylglutamate dehydrogenase
NAD(P)+
Pi
N-Acetyl-γ-glutamyl phosphate
Glutamate
aminotransferase
α-Ketoglutarate
N-Acetylornithine
CH3COO−
H2O
N-acetylornithinase
Ornithine
Urea cycle
Arginine


3-Phosphoglycerate
phosphoglycerate dehydrogenase
NAD+
NADH + H+
3-Phosphohydroxypyruvate
Glutamate
phosphoserine aminotransferase
α-Ketoglutarate
3-Phosphoserine
H2O
phosphoserine phosphatase
Pi
Serine
H4 folate
PLP
serine hydroxymethyl-transferase
N5,N10-Methylene H4 folate
H2O
Glycine
Serine
serine acetyltransferase
CoA-SH
S-CoA
O-Acetylserine
O-acetylserine (thiol) lyase
S2− + H+
CH3COO−
Cysteine
ATP + SO4 2−
ATP sulfurylase
H+
PPi
ATP
ADP
Adenine
3′-Phosphoadenosine 5′-phosphosulfate (PAPS)
PAPS reductase
NADPH
NADP+
3′-Phosphoadenosine 5′-phosphate (PAP)
SO3 2− Sulfite
sulfide reductase
3NADPH
3NADP+
S2− Sulfide
Homocysteine
Serine
cystathionine β-synthase
PLP
H2O
Cystathionine
cystathionine γ-lyase
H2O
PLP
NH4+
α-Ketobutyrate
Cysteine


1 aspartokinase
2 aspartate β-semialdehyde dehydrogenase
3 homoserine dehydrogenase
4 homoserine kinase
5 threonine synthase
6 homoserine acyltransferase
7 cystathionine γ-synthase
8 cystathionine β-lyase
9 methionine synthase
10 dihydropicolinate synthase
11 Δ1-piperidine-2,6-dicarboxylate dehydrogenase
12 N-succinyl-2-amino-6-ketopimelate synthase
13 succinyl diaminopimelate aminotransferase
14 succinyl diaminopimelate desuccinylase
15 diaminopimelate epimerase
16 diaminopimelate decarboxylase
17 threonine dehydratase (serine dehydratase)
18 acetolactate synthase
19 acetohydroxy acid isomeroreductase
20 dihydroxy acid dehydratase
21 valine aminotransferase
22 α-isopropylmalate synthase
23 isopropylmalate isomerase
24 β-isopropylmalate dehydrogenase
25 leucine aminotransferase
Aspartate
ATP
ADP
Aspartyl-β-phosphate
NADPH
+ H+
NADP+
Pi
Aspartate β-semialdehyde
Pyruvate
Dihydropicolinate
H2O
NADPH
+ H+
NADP+
Δ1-Piperidine-2,6-dicarboxylate
Succinyl-CoA + H2O
CoA
N-Succinyl-2-amino-6-keto-L-pimelate
α-Ketoglutarate
Glutamate
PLP
Succinate
N-Succinyl-L,L-α,ε-diamino-pimelate
H2O
Succinate
L,L-α,ε-Diamino-pimelate
meso-α,ε-Diamino-pimelate
H+
CO2
PLP
Lysine
Threonine
NH4+ + H2O
PLP
Pi
PLP
H2O
Phosphohomoserine
ADP
ATP
Homoserine
Succinyl-CoA
CoA
O-Succinylhomoserine
Cysteine
PLP
Succinate
Cystathionine
PLP
Pyruvate + NH3
Homocysteine
N5-Methyl H4 folate
H4 folate
Methionine
Pyruvate
TPP
CO2
α-Ketobutyrate
α-Aceto-α-hydroxybutyrate
NAD(P)H + H+
NAD(P)+
α,β-Dihydroxy-β-methylvalerate
H2O
α-Keto-β-methylvalerate
Glutamate
PLP
α-Ketoglutarate
Isoleucine
Pyruvate
α-Acetolactate
NAD(P)H + H+
NAD(P)+
α,β-Dihydroxy-isovalerate
H2O
α-Keto-isovalerate
Glutamate
PLP
α-Ketoglutarate
Valine
CoA
Acetyl-CoA
α-Isopropylmalate
β-Isopropylmalate
NAD+
NADH + H+
CO2
α-Ketoisocaproate
Glutamate
PLP
α-Ketoglutarate
Leucine


Phosphoenolpyruvate (PEP)
Erythrose 4-phosphate
2-Keto-3-deoxy-D-arabinoheptulosonate 7-phosphate
3-Dehydroquinate
3-Dehydroshikimate
3-Dehydroshikimate
Shikimate
Shikimate 3-phosphate
5-Enolpyruvylshikimate 3-phosphate
Chorismate
1 2-keto-3-deoxy-D-arabinoheptulosonate 7-phosphate synthase
2 dehydroquinate synthase
3 3-dehydroquinate dehydratase
4 shikimate dehydrogenase
5 shikimate kinase
6 5-enolpyruvylshikimate 3-phosphate synthase
7 chorismate synthase
Chorismate
Anthranilate
N-(5′-Phosphoribosyl)-anthranilate
Enol-1-o-carboxyphenylamino-1-deoxyribulose phosphate
Indole-3-glycerol phosphate
Tryptophan
1 anthranilate synthase
2 anthranilate phosphoribosyltransferase
3 N-(5′-phosphoribosyl)-anthranilate isomerase
4 indole-3-glycerol phosphate synthase
5 tryptophan synthase
Chorismate
Prephenate
4-Hydroxyphenyl-pyruvate
Phenylpyruvate
Tyrosine
Phenylalanine
1 chorismate mutase
2 prephenate dehydrogenase
3 prephenate dehydratase


5-Phosphoribosyl-
1-pyrophosphate (PRPP)
ATP
PPi
PPi
N1-5′-Phosphoribosyl-AMP
1 ATP phosphoribosyl transferase
2 pyrophosphohydrolase
3 phosphoribosyl-AMP cyclohydrolase
4 phosphoribosylformimino-5-aminoimidazole-4-carboxamide ribonucleotide isomerase
5 glutamine amidotransferase
6 imidazole glycerol 3-phosphate dehydratase
7 L-histidinol phosphate aminotransferase
8 histidinol phosphate phosphatase
9 histidinol dehydrogenase
H2O
To purine biosynthesis
5-Aminoimidazole-
4-carboxamide
ribonucleotide (AICAR)
N1-5′-Phosphoribulosyl-
formimino-5-amino-
imidazole-4-carboxamide
ribonucleotide
Glutamine
Glutamate
2NADH + 2H+
2NAD+
Histidine
L-Histidinol
Glutamate
α-Ketoglutarate
Pi
H2O
Imidazole glycerol
3-phosphate

- In the case of amino acid synthesis, regulation takes place in part through feedback inhibition of the first reaction by the end product of the pathway.

- This first reaction is often catalyzed by an allosteric enzyme that plays an important role in the overall control of flux through that pathway.

- In addition to their role as the building blocks of proteins, amino acids are precursors of many specialized biomolecules, including hormones, coenzymes, nucleotides, alkaloids, cell wall polymers, porphyrins, antibiotics, pigments, and neurotransmitters.

- The biosynthesis of porphyrins, for which glycine is a major precursor, is our first example because of the central importance of the porphyrin nucleus in heme proteins such as hemoglobin and the cytochromes.

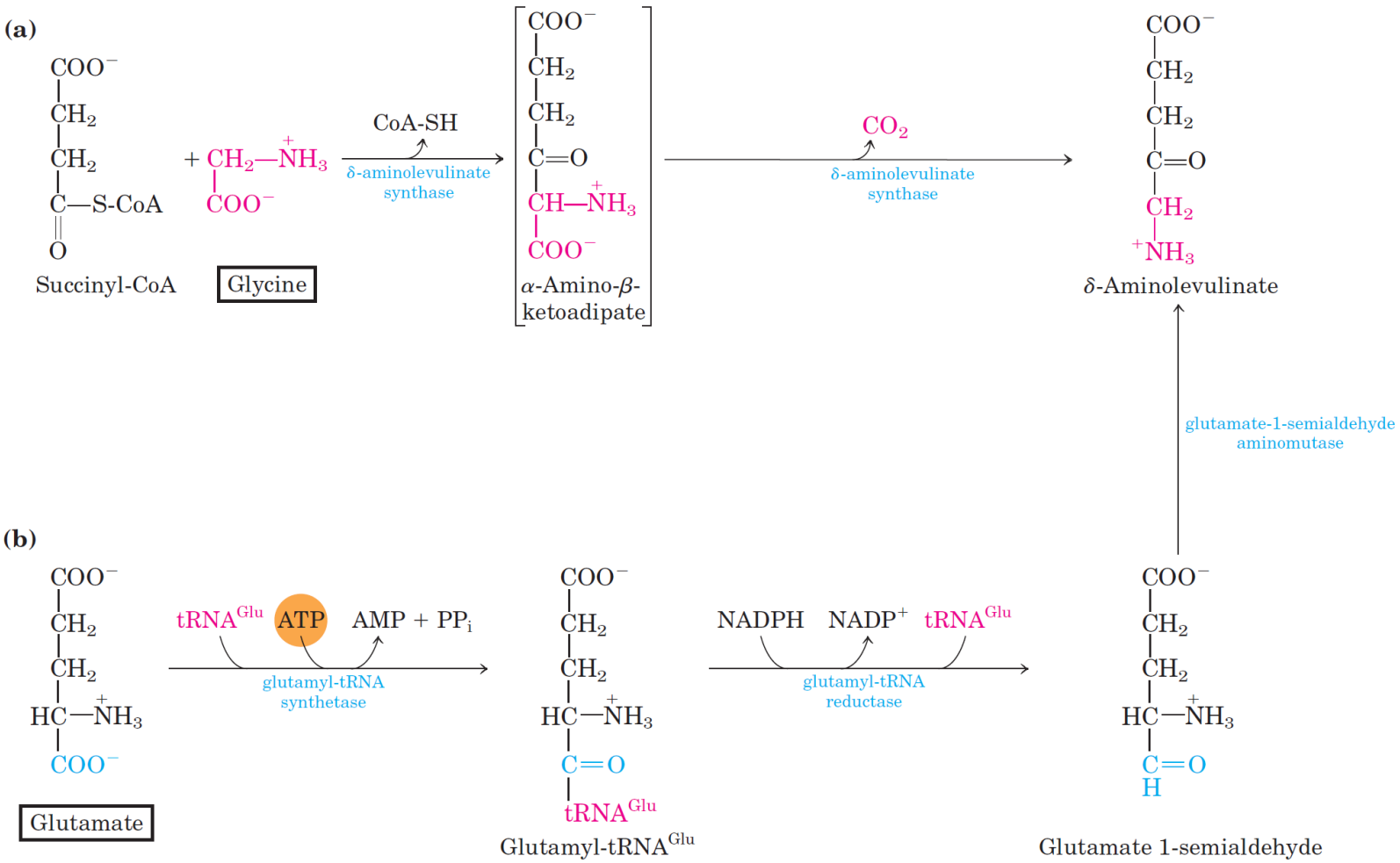


FIGURE 22–23 Biosynthesis of δ-aminolevulinate. (a) In mammals and other higher eukaryotes, δ-aminolevulinate is synthesized from glycine and succinyl-CoA. The atoms furnished by glycine are shown in red. **(b)** In bacteria and plants, the precursor of δ-aminolevulinate is glutamate.

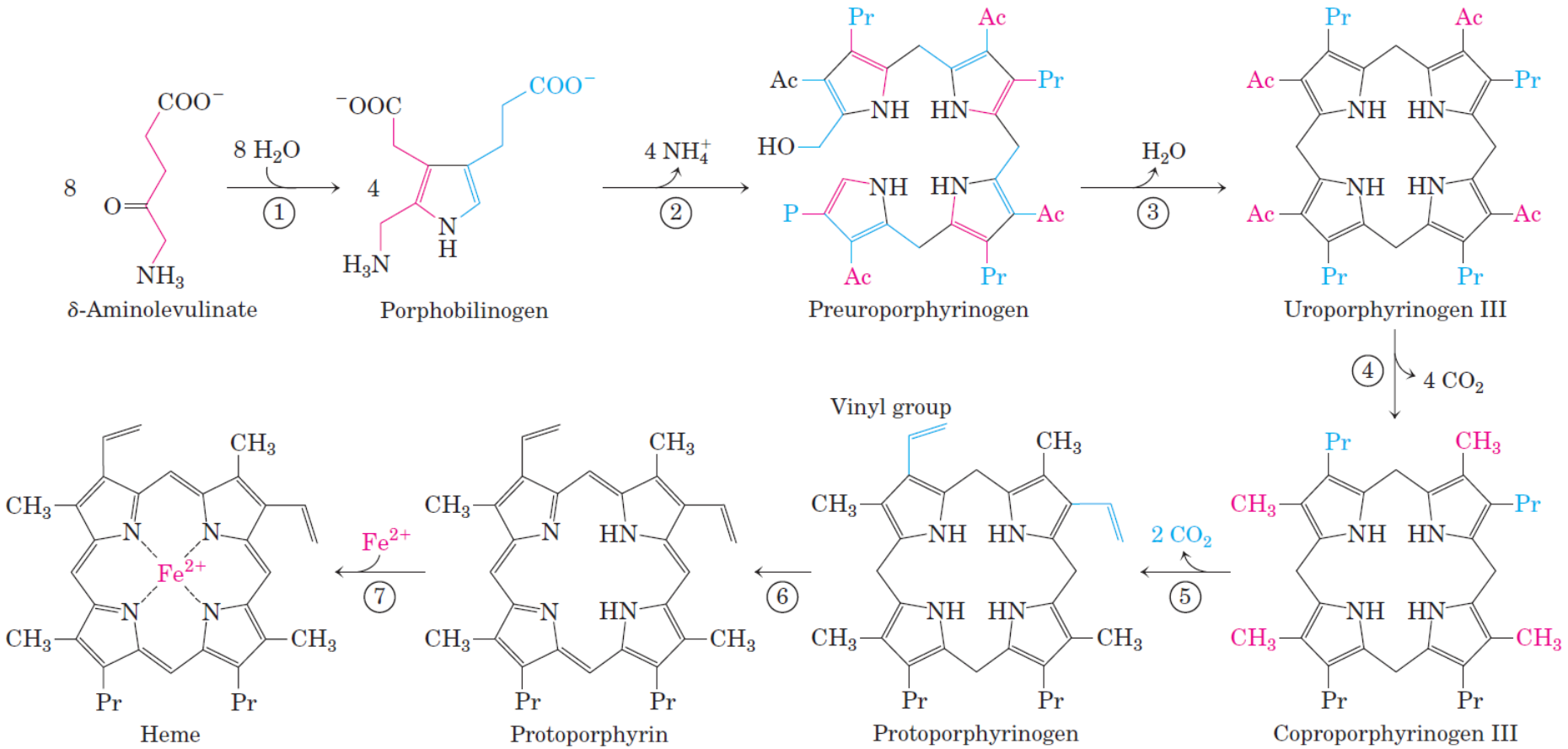


FIGURE 22–24 **Biosynthesis of heme from δ-aminolevulinate.** Ac represents acetyl (—CH_2COO^-); Pr, propionyl (—$CH_2CH_2COO^-$).

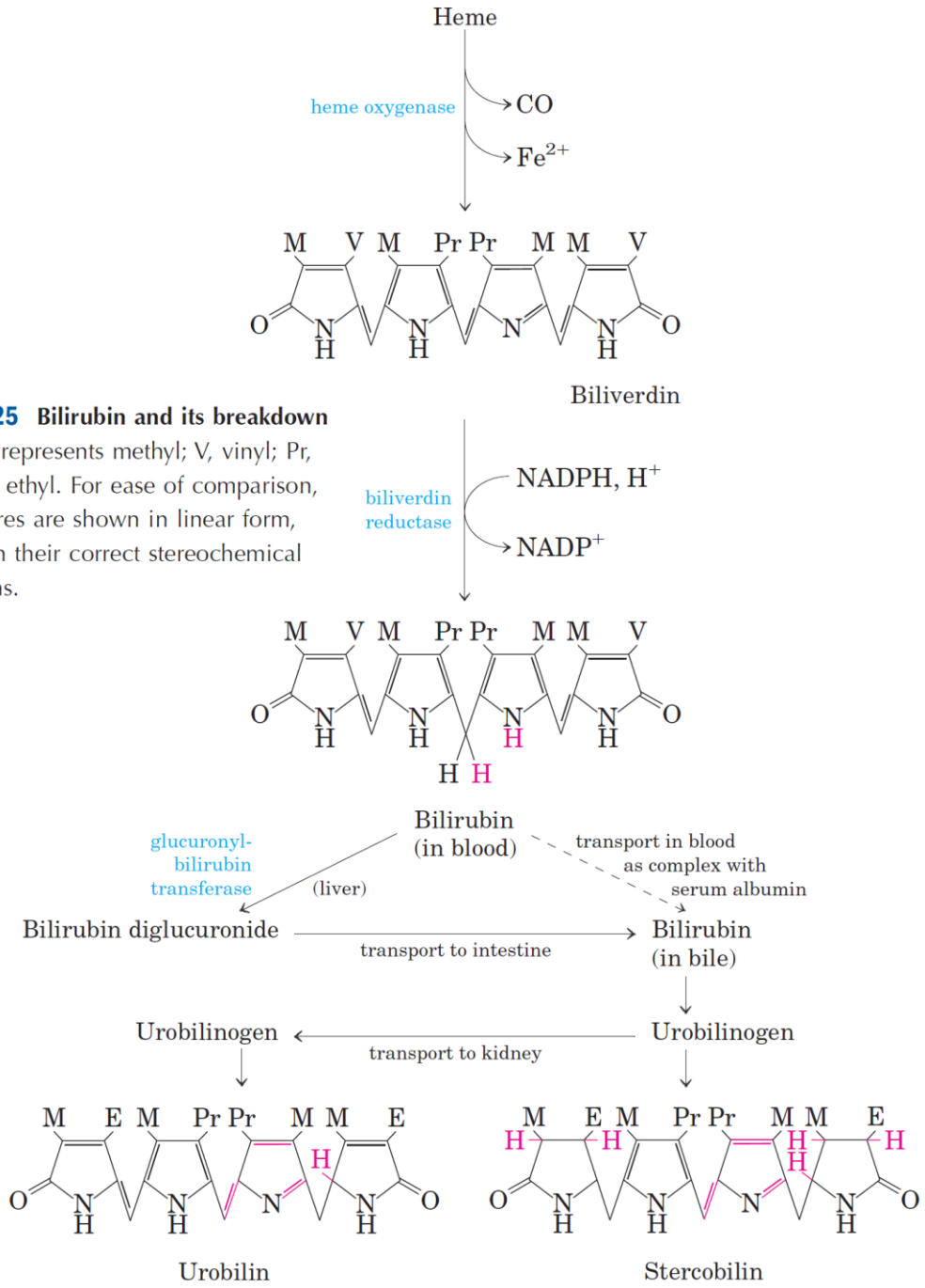
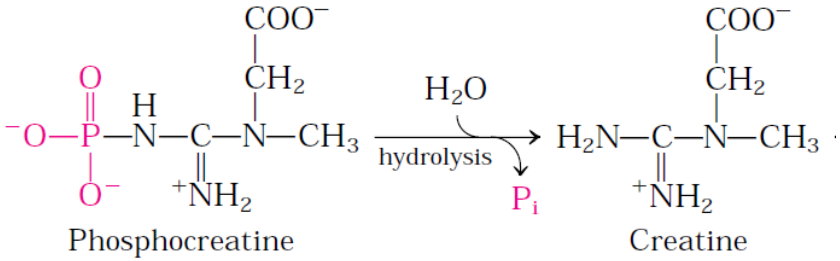


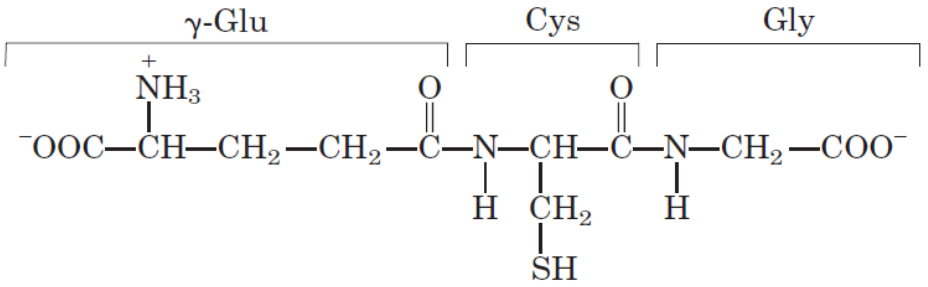
FIGURE 22–25 Bilirubin and its breakdown products. M represents methyl; V, vinyl; Pr, propionyl; E, ethyl. For ease of comparison, these structures are shown in linear form, rather than in their correct stereochemical conformations.

- Phosphocreatine, derived from creatine, is an important energy buffer in skeletal muscle. Creatine is synthesized from glycine and arginine.

- Glutathione (GSH), present in plants, animals, and some bacteria, often at high levels, can be thought of as a redox buffer. It is derived from glutamate, cysteine, and glycine.

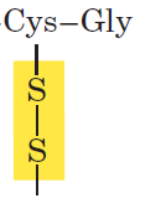


Phosphocreatine Creatine

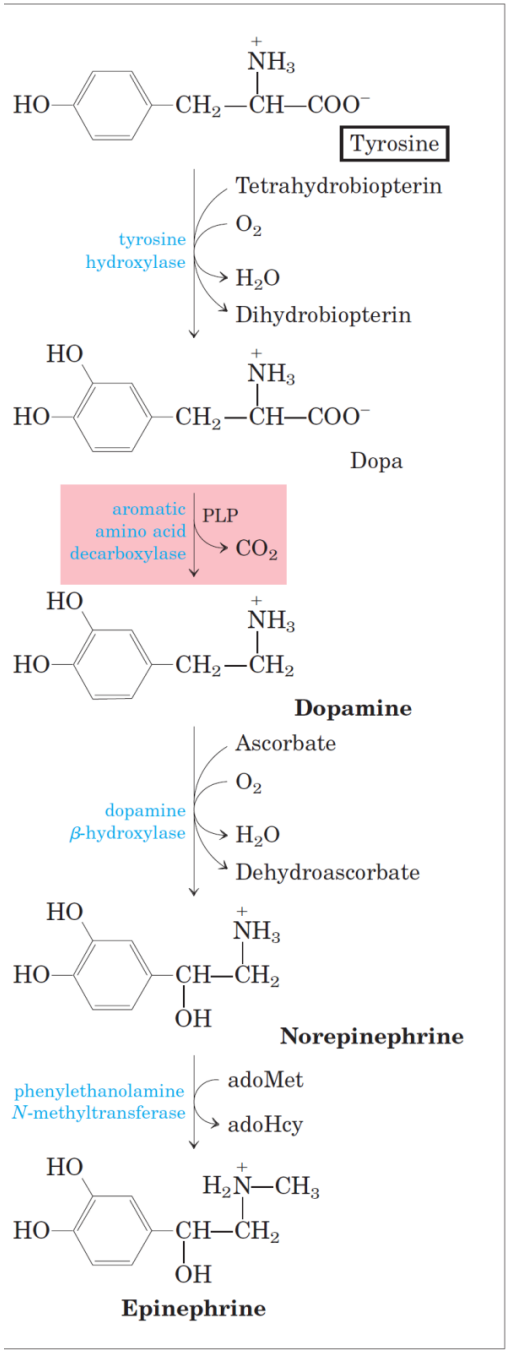


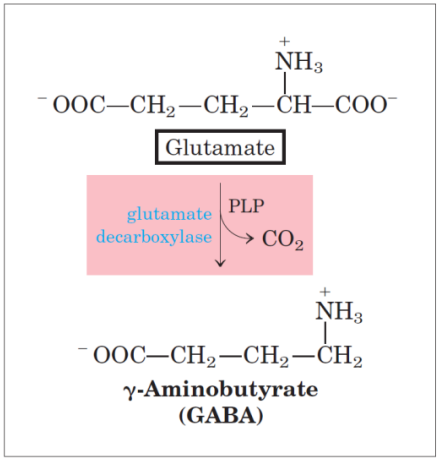
Glutathione (GSH)
(reduced)

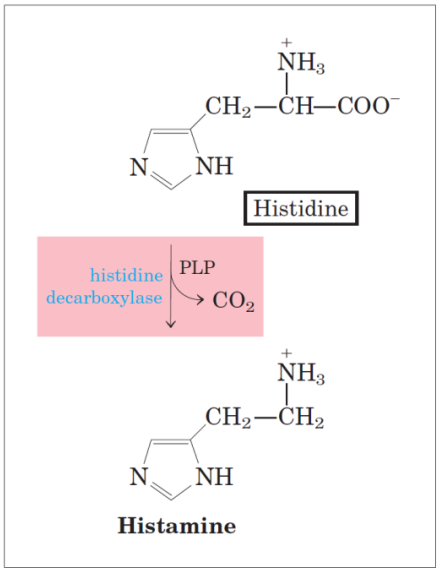
(b)



Glutathione (GSSG)
(oxidized)







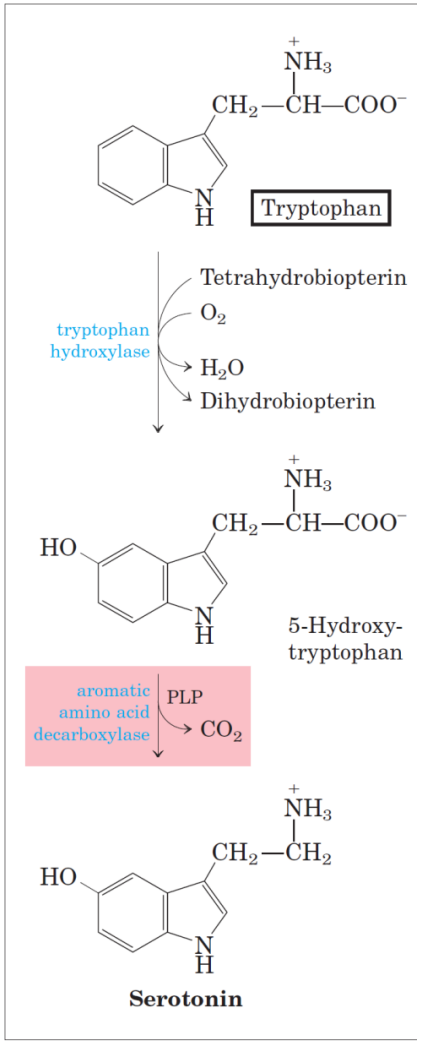


FIGURE 22–29 Biosynthesis of some neurotransmitters from amino acids. The key step is the same in each case: a PLP-dependent decarboxylation (shaded in pink).

- Aromatic amino acids are precursors of many plant substances.
- Biological amines are products of amino acid decarboxylation

- Nucleotides have a variety of important functions in all cells. They are the precursors of DNA and RNA.

- They are essential carriers of chemical energy—a role primarily of ATP and to some extent GTP. They are components of the cofactors NAD, FAD, adenosylmethionine, and coenzyme A, as well as of activated biosynthetic intermediates.

- Some, such as cAMP and cGMP, are also cellular second messengers.

- Two types of pathways lead to nucleotides: the de novo pathways and the salvage pathways.

- De novo synthesis of nucleotides begins with their metabolic precursors: amino acids, ribose 5-phosphate, CO_2, and NH_3.

- Salvage pathways recycle the free bases and nucleosides released from nucleic acid breakdown.

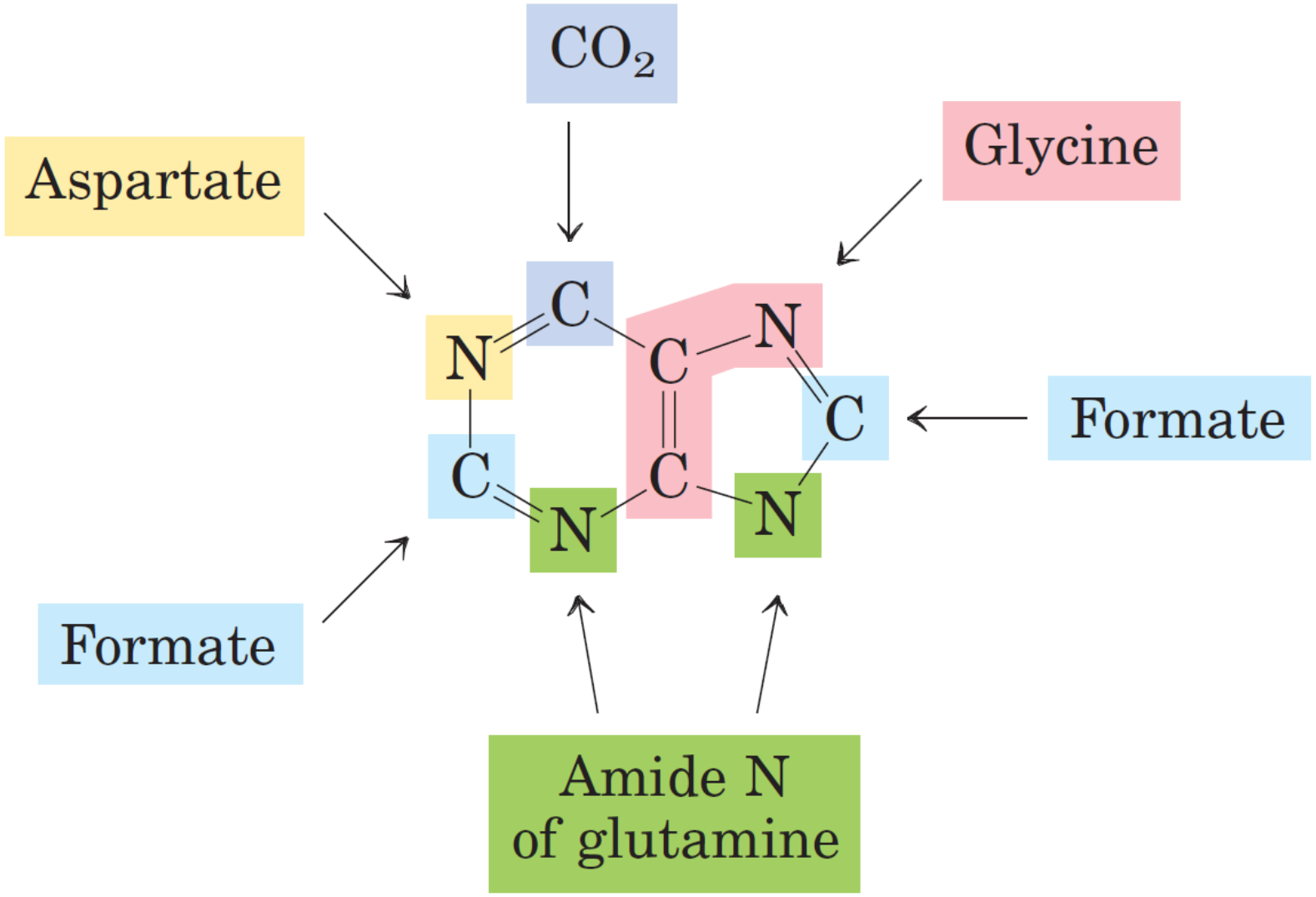
- The de novo pathways for purine and pyrimidine biosynthesis seem to be nearly identical in all living organisms.

- Notably, the free bases guanine, adenine, thymine, cytidine, and uracil are not intermediates in these pathways; that is, the bases are not synthesized and then attached to ribose, as might be expected.

- The purine ring structure is built up one or a few atoms at a time, attached to ribose throughout the process.

- The pyrimidine ring is synthesized as orotate, attached to ribose phosphate, and then converted to the common pyrimidine nucleotides required in nucleic acid synthesis.

- Although the free bases are not intermediates in the de novo pathways, they are intermediates in some of the salvage pathways.


CO_2
Aspartate
Glycine
Formate
Formate
Amide N
of glutamine
C
N
C
N
C
C
N
C
N

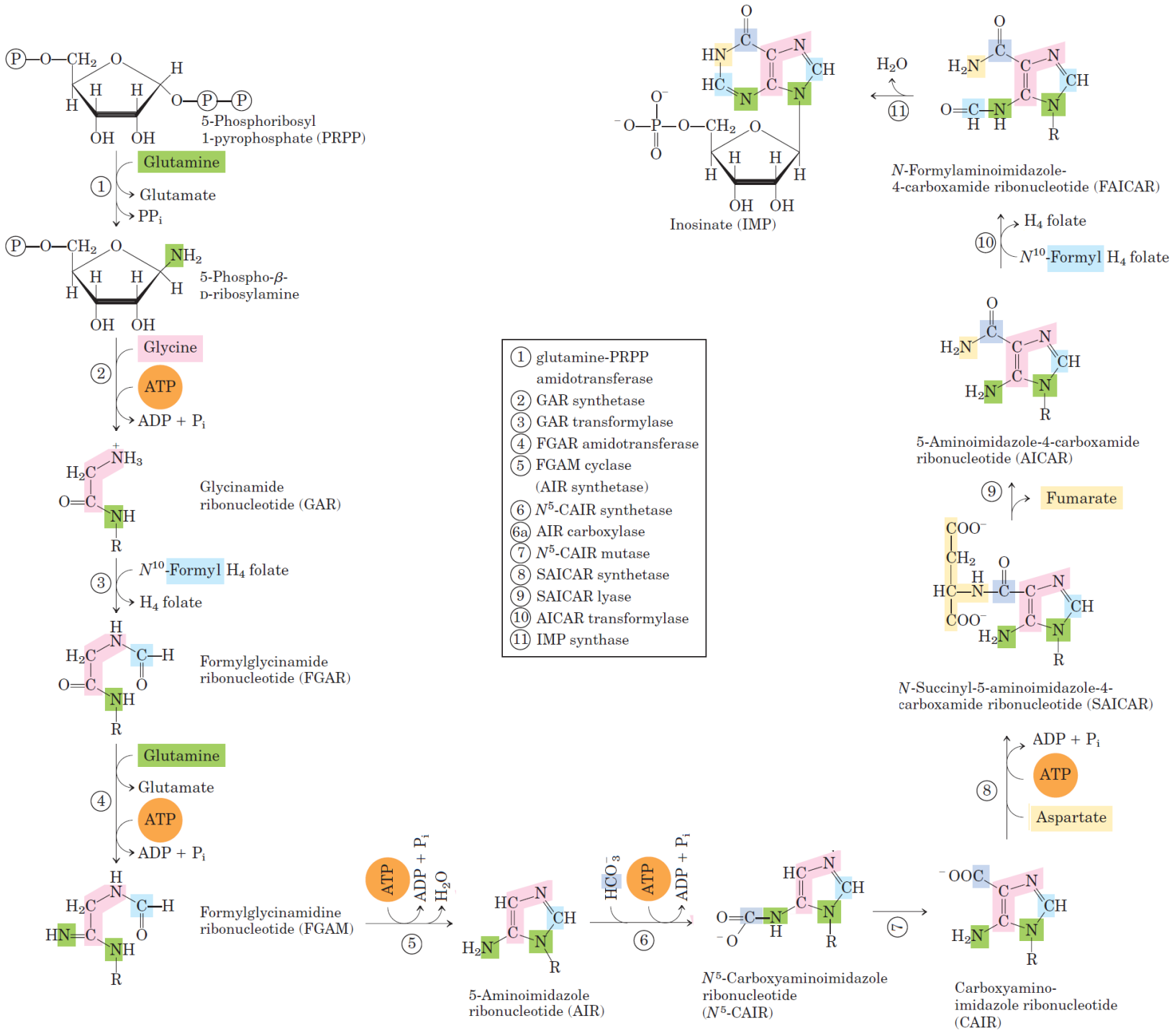
- The two parent purine nucleotides of nucleic acids are adenosine 5′-monophosphate (AMP; adenylate) and guanosine 5′-monophosphate (GMP;guanylate), containing the purine bases adenine and guanine.

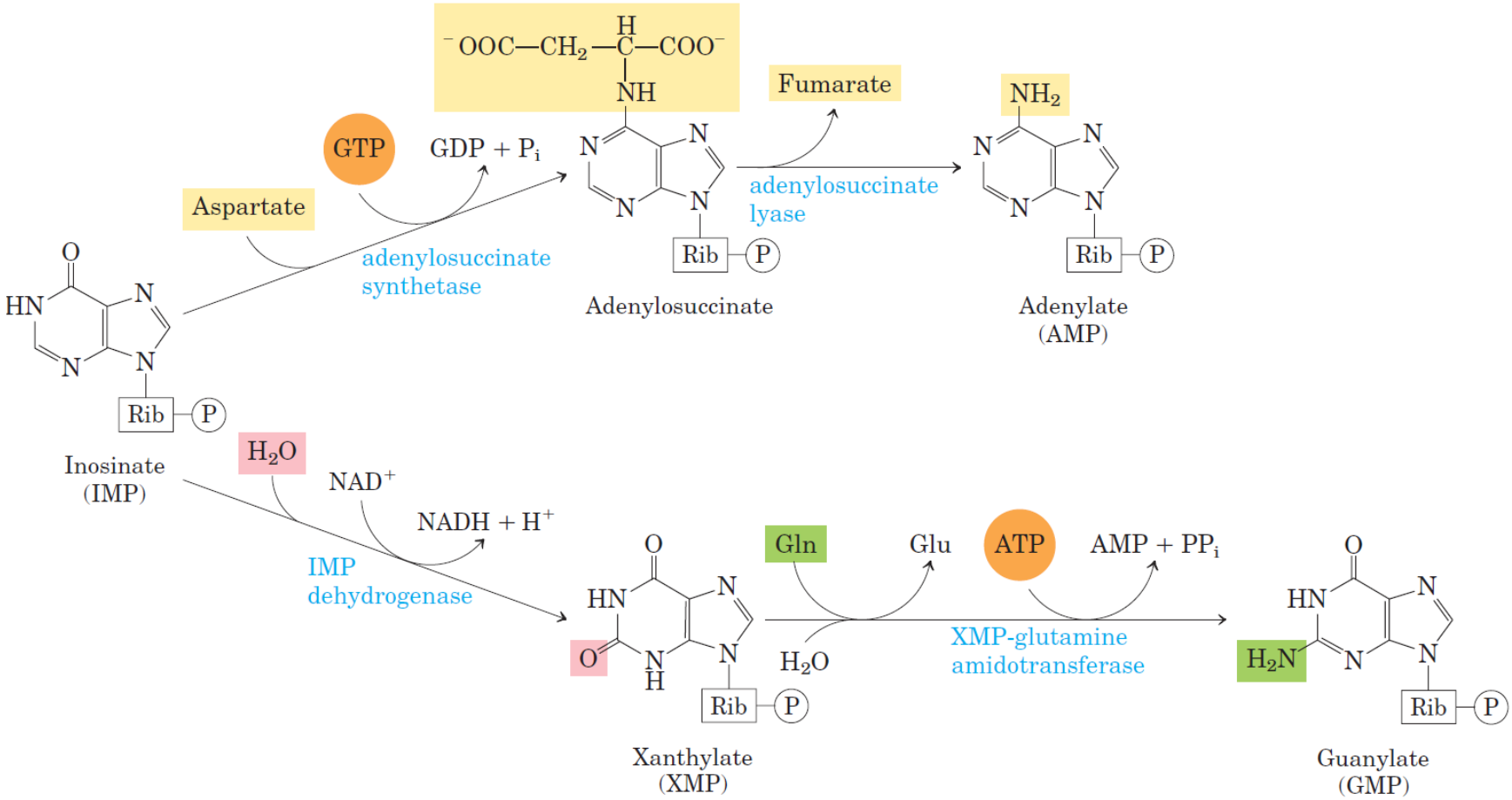
- In the first committed step of the pathway, an amino group donated by glutamine is attached at C-1 of PRPP.

- The resulting 5- phosphoribosylamine is highly unstable, with a half-life of 30 seconds at pH 7.5.

- The purine ring is subsequently built up on this structure.

- The pathway described here is nearly identical in all organisms.


5-Phosphoribosyl 1-pyrophosphate (PRPP)
Glutamine
Glutamate
PPi
5-Phospho-β-D-ribosylamine
Glycine
ATP
ADP + Pi
Glycinamide ribonucleotide (GAR)
N10-Formyl H4 folate
H4 folate
Formylglycinamide ribonucleotide (FGAR)
Glutamine
Glutamate
ATP
ADP + Pi
Formylglycinamidine ribonucleotide (FGAM)
ATP
ADP + Pi
H2O
5
5-Aminoimidazole ribonucleotide (AIR)
HCO3−
ATP
ADP + Pi
6
N5-Carboxyaminoimidazole ribonucleotide (N5-CAIR)
7
Carboxyamino-imidazole ribonucleotide (CAIR)
ADP + Pi
ATP
Aspartate
8
N-Succinyl-5-aminoimidazole-4-carboxamide ribonucleotide (SAICAR)
9
Fumarate
5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR)
10
H4 folate
N10-Formyl H4 folate
N-Formylaminoimidazole-4-carboxamide ribonucleotide (FAICAR)
H2O
11
Inosinate (IMP)
1 glutamine-PRPP amidotransferase
2 GAR synthetase
3 GAR transformylase
4 FGAR amidotransferase
5 FGAM cyclase (AIR synthetase)
6 N5-CAIR synthetase
6a AIR carboxylase
7 N5-CAIR mutase
8 SAICAR synthetase
9 SAICAR lyase
10 AICAR transformylase
11 IMP synthase

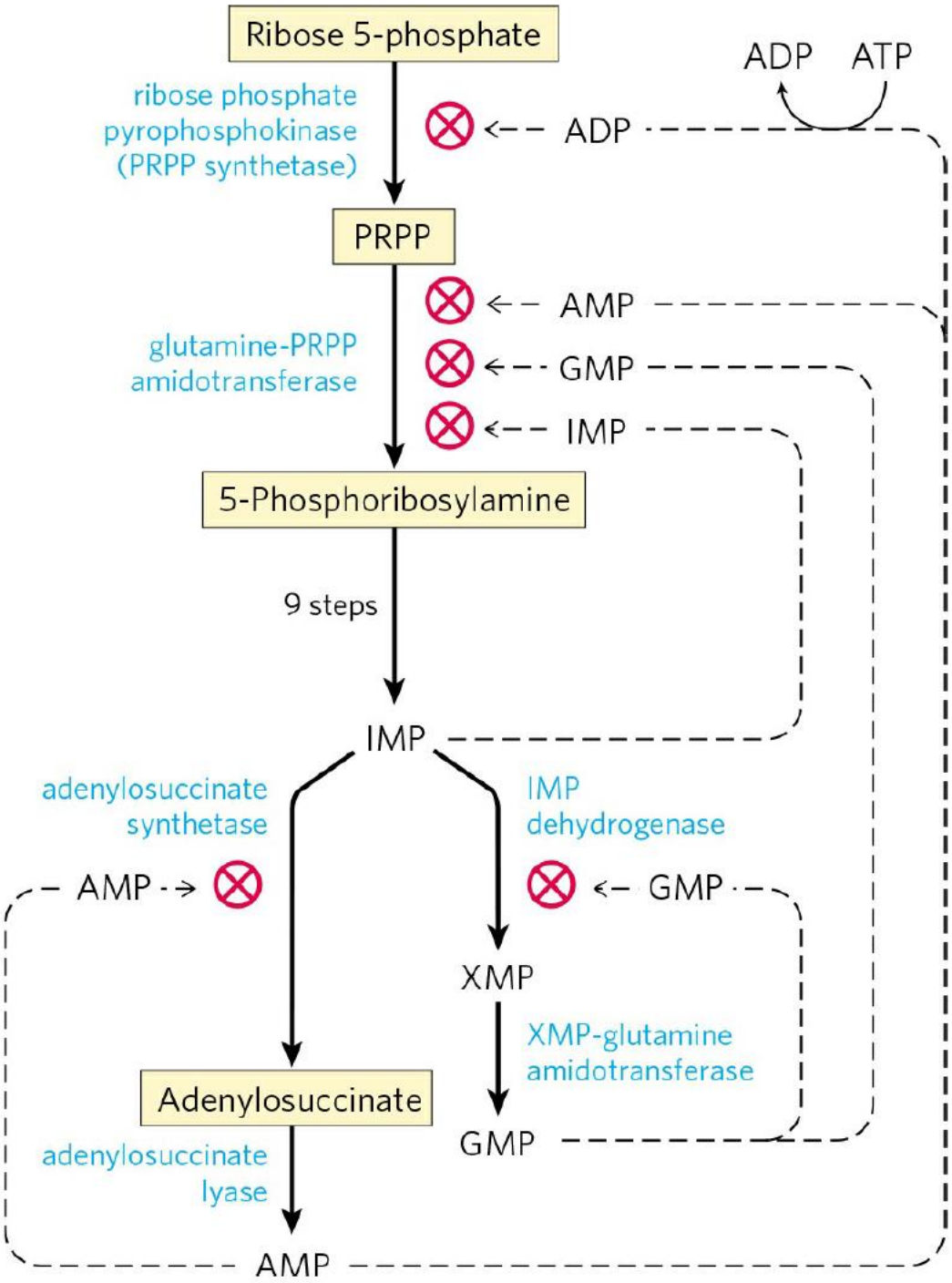

⁻OOC—CH2—C(H)—COO⁻
NH
GTP
GDP + Pi
Aspartate
adenylosuccinate synthetase
Fumarate
adenylosuccinate lyase
NH2
Rib
P
Adenylosuccinate
Adenylate (AMP)
Inosinate (IMP)
H2O
NAD+
NADH + H+
IMP dehydrogenase
Gln
Glu
ATP
AMP + PPi
XMP-glutamine amidotransferase
H2N
Xanthylate (XMP)
Guanylate (GMP)

- Three major feedback mechanisms cooperate in regulating the overall rate of de novo purine nucleotide synthesis and the relative rates of formation of the two end products, adenylate and guanylate.

- The first mechanism is exerted on the first reaction that is unique to purine synthesis: transfer of an amino group to PRPP to form 5-phosphoribosylamine.

- In the second control mechanism, exerted at a later stage, an excess of GMP in the cell inhibits formation of xanthylate from inosinate by IMP dehydrogenase, without affecting the formation of AMP.

- Conversely, an accumulation of adenylate inhibits formation of adenylosuccinate by adenylosuccinate synthetase, without affecting the biosynthesis of GMP.

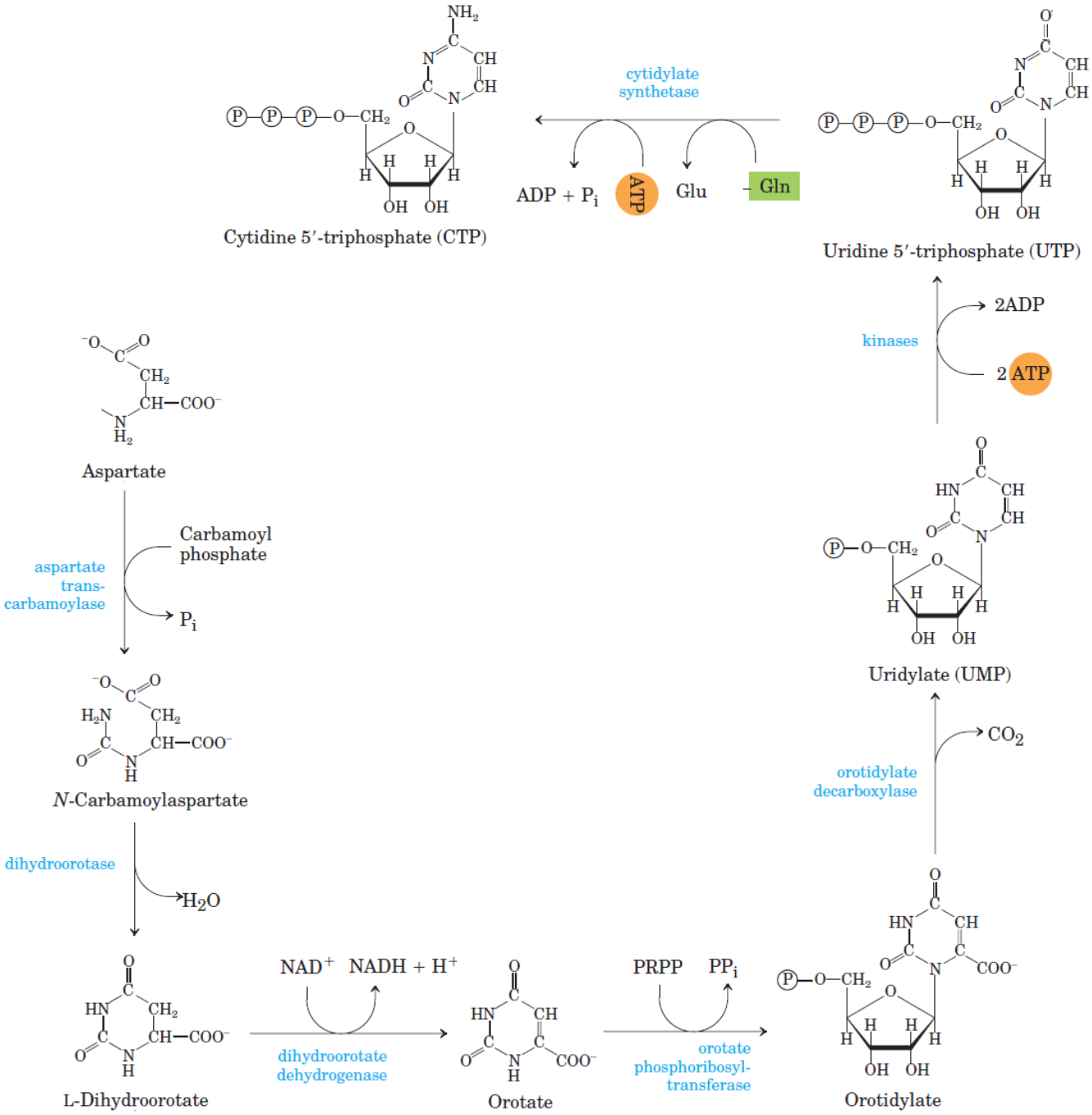

Ribose 5-phosphate
ADP
ATP
ribose phosphate pyrophosphokinase (PRPP synthetase)
ADP
PRPP
AMP
glutamine-PRPP amidotransferase
GMP
IMP
5-Phosphoribosylamine
9 steps
IMP
adenylosuccinate synthetase
IMP dehydrogenase
AMP
GMP
XMP
XMP-glutamine amidotransferase
Adenylosuccinate
GMP
adenylosuccinate lyase
AMP

- The common pyrimidine ribonucleotides are cytidine 5′-monophosphate (CMP; cytidylate) and uridine 5′-monophosphate (UMP; uridylate), which contain the pyrimidines cytosine and uracil.

- De novo pyrimidine nucleotide biosynthesis proceeds in a somewhat different manner from purine nucleotide synthesis; the six-membered pyrimidine ring is made first and then attached to ribose 5-phosphate.

- Required in this process is carbamoyl phosphate, also an intermediate in the urea cycle.

- However, in animals the carbamoyl phosphate required in urea synthesis is made in mitochondria by carbamoyl phosphate synthetase I, whereas the carbamoyl phosphate required in pyrimidine biosynthesis is made in the cytosol by a different form of the enzyme, carbamoyl phosphate synthetase II.


Cytidine 5′-triphosphate (CTP)
cytidylate synthetase
ADP + Pi
ATP
Glu
Gln
Uridine 5′-triphosphate (UTP)
kinases
2ADP
2 ATP
Aspartate
aspartate trans-carbamoylase
Carbamoyl phosphate
Pi
Uridylate (UMP)
N-Carbamoylaspartate
dihydroorotase
H2O
orotidylate decarboxylase
CO2
NAD+ NADH + H+
dihydroorotate dehydrogenase
PRPP PPi
orotate phosphoribosyl-transferase
L-Dihydroorotate
Orotate
Orotidylate

- Regulation of the rate of pyrimidine nucleotide synthesis in bacteria occurs in large part through aspartate transcarbamoylase (ATCase), which catalyzes the first reaction in the sequence and is inhibited by CTP, the end product of the sequence.

- Nucleotides to be used in biosynthesis are generally converted to nucleoside triphosphates.

- The conversion pathways are common to all cells.

- Phosphorylation of AMP to ADP is promoted by adenylate kinase, in the reaction;

$$\mathbf{ATP} + \mathbf{AMP} \rightleftharpoons \mathbf{2ADP}$$

- The ADP so formed is phosphorylated to ATP by the glycolytic enzymes or through oxidative phosphorylation.

- ATP also brings about the formation of other nucleoside diphosphates by the action of a class of enzymes called nucleoside monophosphate kinases.

- These enzymes, which are generally specific for a particular base but nonspecific for the sugar (ribose or deoxyribose), catalyze the reaction;

$$\mathbf{ATP + NMP \rightleftharpoons ADP + NDP}$$

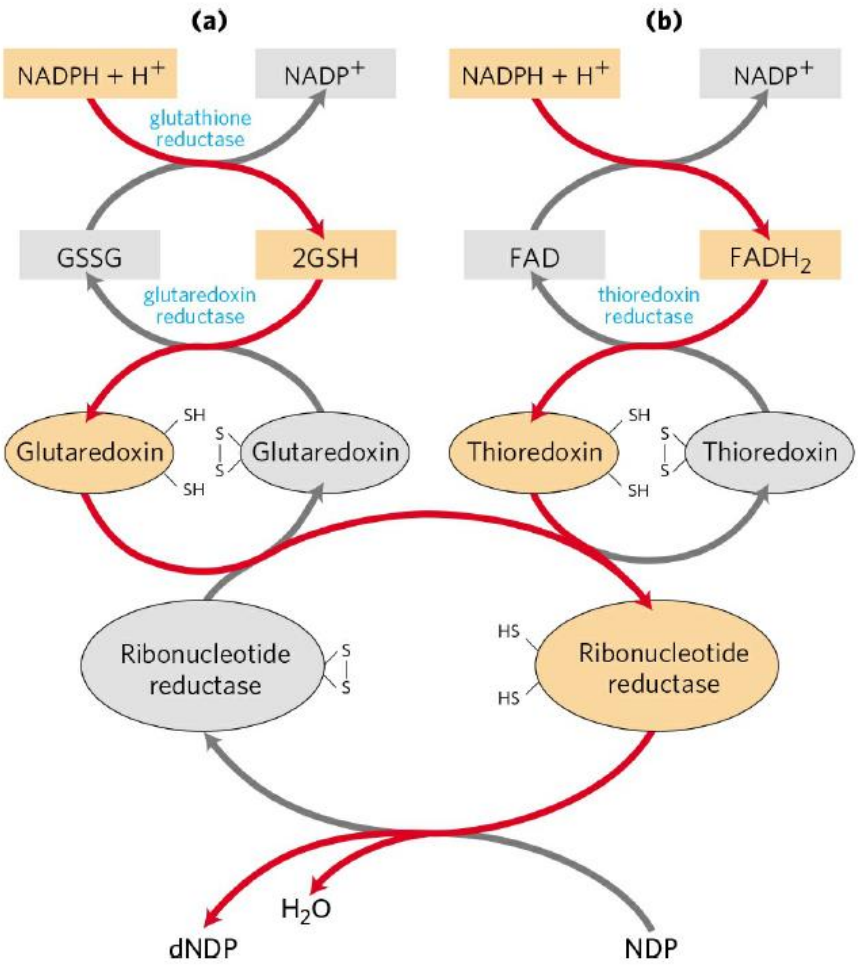
- Nucleoside diphosphates are converted to triphosphates by the action of a ubiquitous enzyme, nucleoside diphosphate kinase, which catalyzes the reaction;

$$\mathbf{NTP_D + NDP_A \rightleftharpoons NDP_D + NTP_A}$$

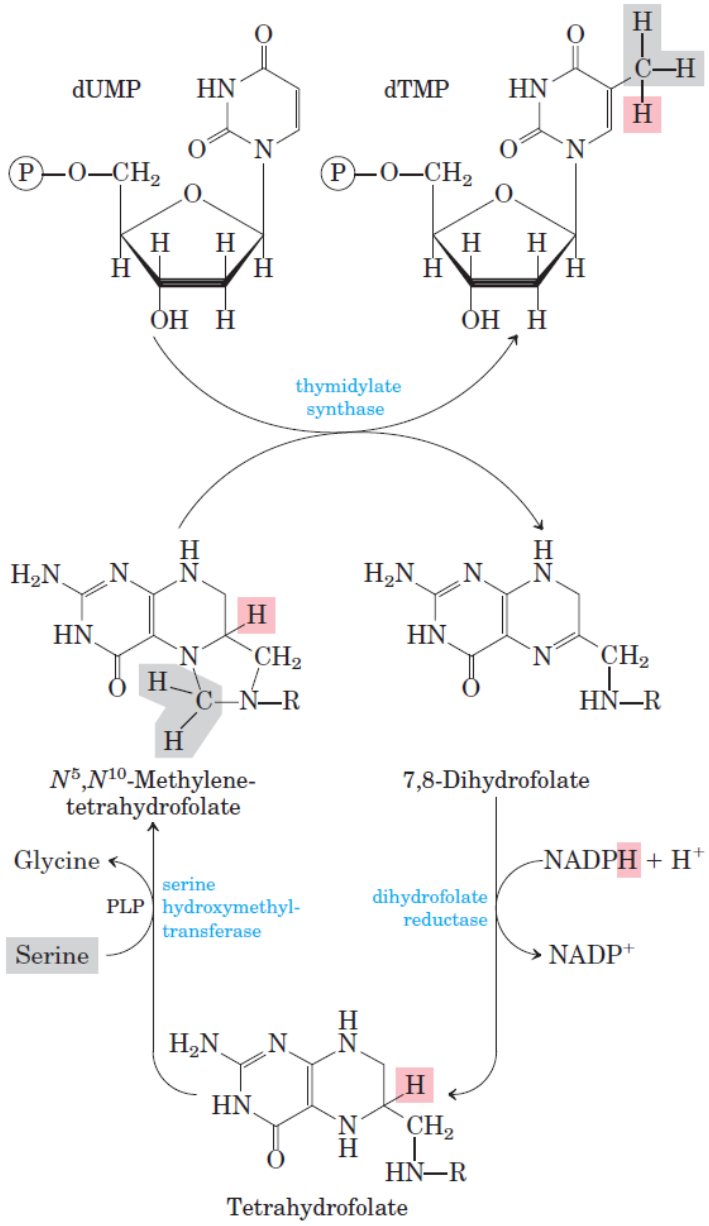
- Deoxyribonucleotides,are derived from the corresponding ribonucleotides by direct reduction at the 2′-carbon atom of the D-ribose to form the 2′-deoxy derivative.

- This reaction is somewhat unusual in that the reduction occurs at a nonactivated carbon; no closely analogous chemical reactions are known.

- The reaction is catalyzed by ribonucleotide reductase.



- DNA contains thymine rather than uracil, and the de novo pathway to thymine involves only deoxyribonucleotides.
- The immediate precursor of thymidylate (dTMP) is dUMP.
- Conversion of dUMP to dTMP is catalyzed by thymidylate synthase.



- Purine nucleotides are degraded by a pathway in which they lose their phosphate through the action of 5′-nucleotidase.

- Adenylate yields adenosine, which is deaminated to inosine by adenosine deaminase, and inosine is hydrolyzed to hypoxanthine (its purine base) and D-ribose.

- Hypoxanthine is oxidized successively to xanthine and then uric acid by xanthine oxidase, a flavoenzyme with an atom of molybdenum and four iron-sulfur centers in its prosthetic group.

- Molecular oxygen is the electron acceptor in this complex reaction.

- GMP catabolism also yields uric acid as an end product.

- GMP is first hydrolyzed to guanosine, which is then cleaved to free guanine.

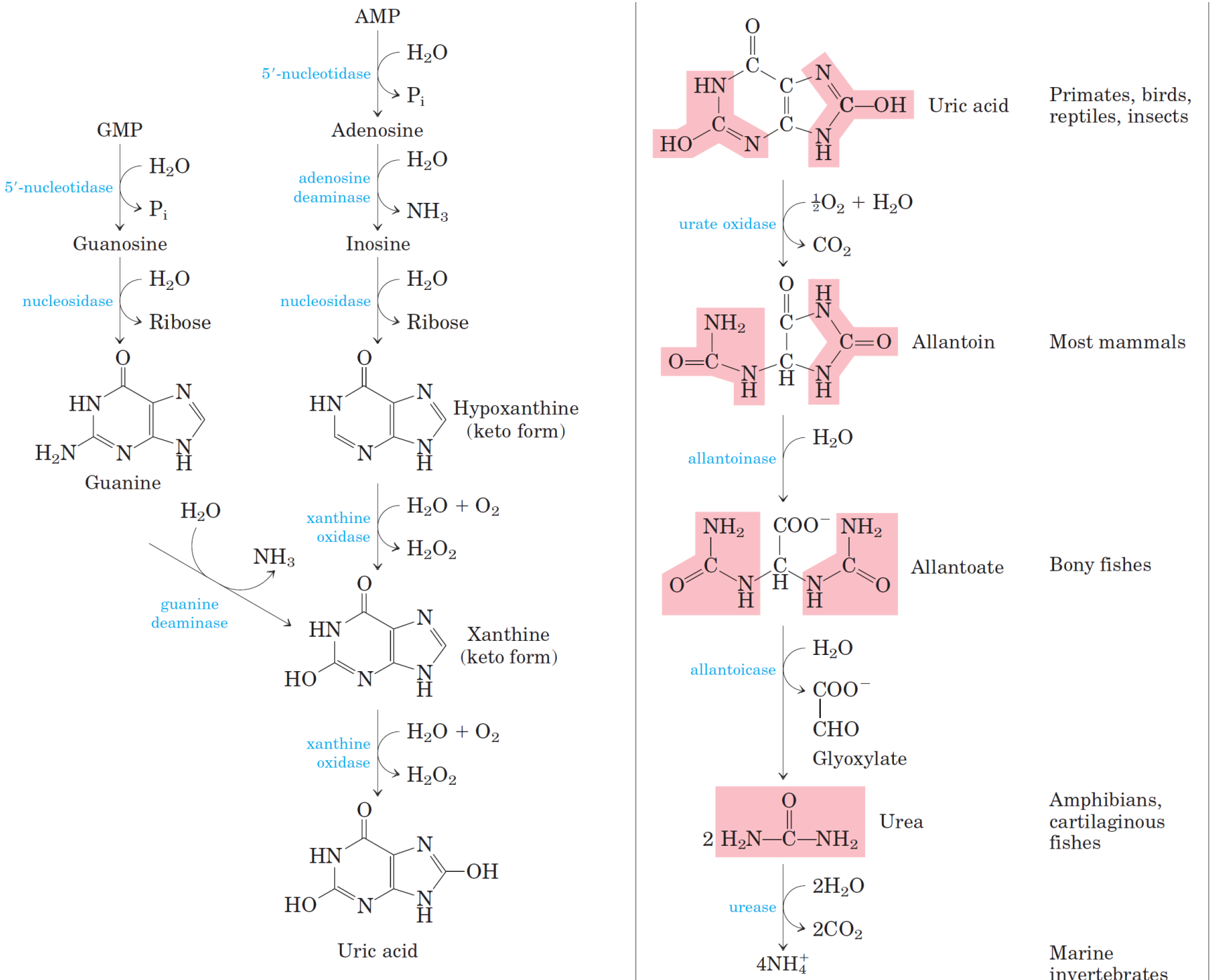
- Guanine undergoes hydrolytic removal of its amino group to yield xanthine, which is converted to uric acid by xanthine oxidase.

- Uric acid is the excreted end product of purine catabolism in primates, birds, and some other animals.

- A healthy adult human excretes uric acid at a rate of about 0.6 g/24 h; the excreted product arises in part from ingested purines and in part from turnover of the purine nucleotides of nucleic acids.

- In most mammals and many other vertebrates, uric acid is degraded to allantoin by the action of urate oxidase.

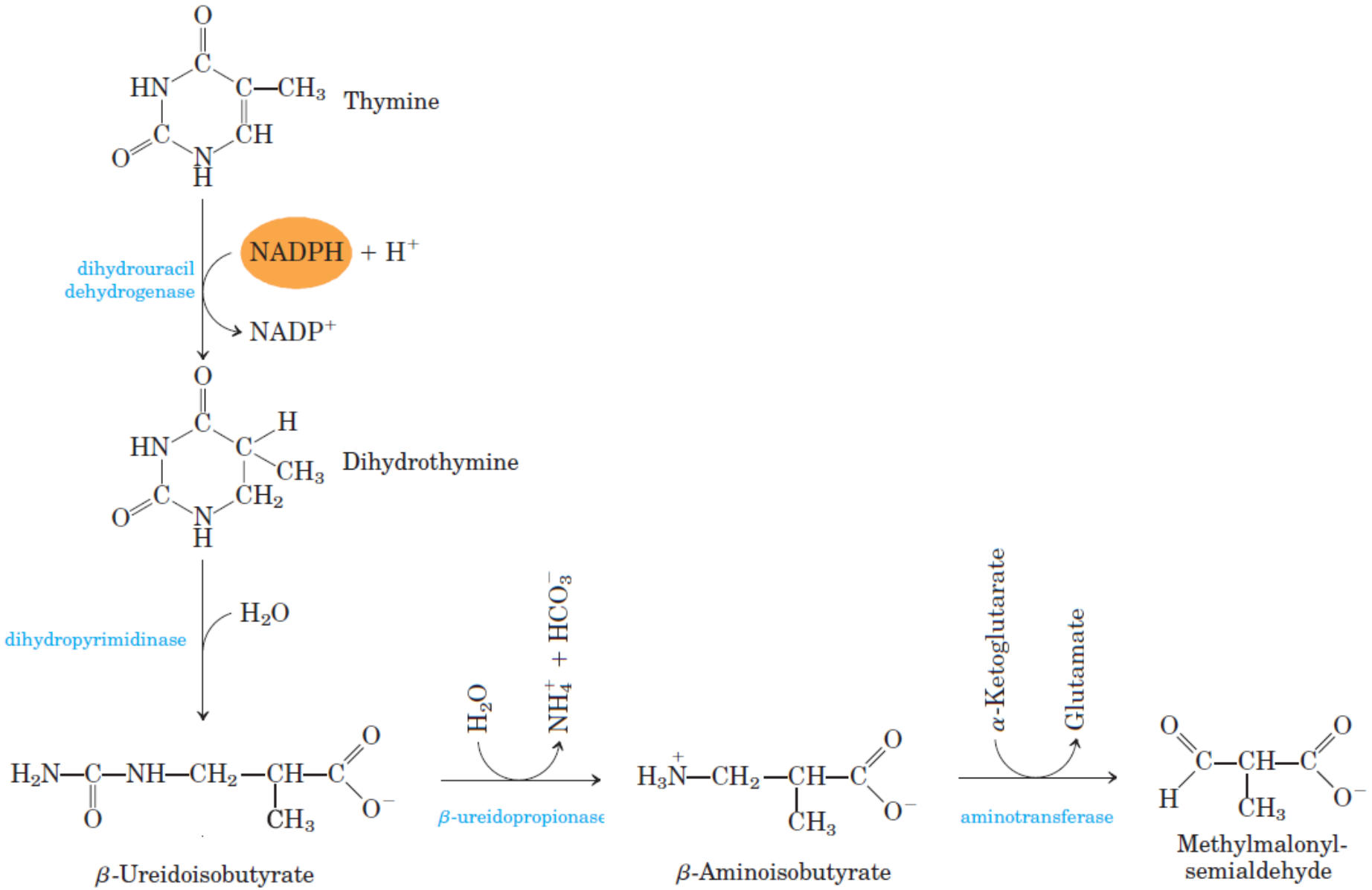
- In other organisms the pathway is further extended.


AMP
H2O
5′-nucleotidase
Pi
GMP
Adenosine
H2O
adenosine deaminase
NH3
5′-nucleotidase
H2O
Pi
Guanosine
Inosine
H2O
nucleosidase
Ribose
H2O
nucleosidase
Ribose
Hypoxanthine (keto form)
Guanine
H2O
xanthine oxidase
H2O + O2
H2O2
NH3
guanine deaminase
Xanthine (keto form)
xanthine oxidase
H2O + O2
H2O2
Uric acid
Uric acid
Primates, birds, reptiles, insects
urate oxidase
½O2 + H2O
CO2
Allantoin
Most mammals
allantoinase
H2O
Allantoate
Bony fishes
allantoicase
H2O
COO⁻
CHO
Glyoxylate
Urea
Amphibians, cartilaginous fishes
urease
2H2O
2CO2
4NH4+
Marine invertebrates

- The pathways for degradation of pyrimidines generally lead to production and thus to urea synthesis.

- Thymine, for example, is degraded to methylmalonylsemialdehyde, an intermediate of valine catabolism.

- It is further degraded through propionyl-CoA and methylmalonyl-CoA to succinyl-CoA.


Thymine
NADPH + H+
dihydrouracil dehydrogenase
NADP+
Dihydrothymine
H2O
dihydropyrimidinase
β-Ureidoisobutyrate
H2O
NH4+ + HCO3−
β-ureidopropionase
β-Aminoisobutyrate
α-Ketoglutarate
Glutamate
aminotransferase
Methylmalonyl-semialdehyde

- Free purine and pyrimidine bases are constantly released in cells during the metabolic degradation of nucleotides.

- Free purines are in large part salvaged and reused to make nucleotides, in a pathway much simpler than the de novo synthesis of purine nucleotides described earlier.

- One of the primary salvage pathways consists of a single reaction catalyzed by adenosine phosphoribosyltransferase, in which free adenine reacts with PRPP to yield the corresponding adenine nucleotide:

$$\mathrm{Adenine} + \mathrm{PRPP} \rightarrow \mathrm{AMP} + \mathrm{PP_i}$$

- Free guanine and hypoxanthine (the deamination product of adenine; are salvaged in the same way by hypoxanthine-guanine phosphoribosyltransferase.

- A similar salvage pathway exists for pyrimidine bases in microorganisms, and possibly in mammals.