18 Amino Acid Oxidation and the Production of Urea

P1 Principle 1 (1 of 7)

The many paths for amino acid catabolism have two broad parts, one involving the amino groups and the other involving the carbon skeletons. All of the pathways for amino acid degradation include a key step, always involving a pyridoxal phosphate cofactor, in which the *α*-amino group is separated from the carbon skeleton and shunted into the pathways of amino group metabolism. The carbon skeletons are broken down to citric acid cycle intermediates.

P2 Principle 2 (1 of 4)

Four amino acids—alanine, glutamate, glutamine, and aspartate—play key roles in the transport and distribution of amino groups. All are present in relatively high concentrations in one or many mammalian tissues. All are readily converted to key citric acid cycle intermediates.

P3 Principle 3 (1 of 5)

Metabolic pathways are not distinct. The various pathways for amino acid catabolism are elaborately intertwined with other catabolic and anabolic pathways.

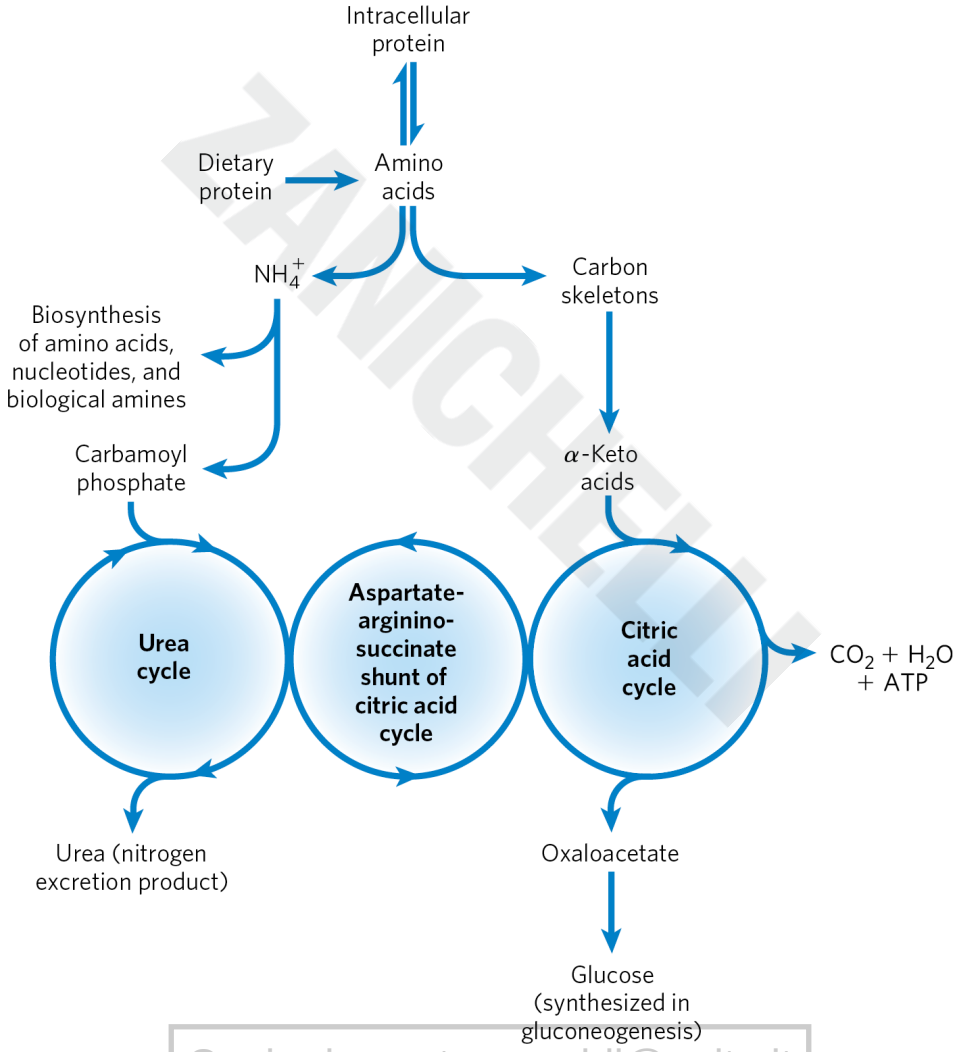
P4 Principle 4 (1 of 3)

Free ammonia is toxic. Excess amino groups must be safely excreted. In mammals, the urea cycle serves this purpose.

P5 Principle 5 (1 of 6)

Each amino acid has a different catabolic fate. The varied carbon skeletons of amino acids are broken down via equally varied pathways. All can be oxidized to generate ATP. All but leucine and lysine can contribute to gluconeogenesis when needed.

Overview of Amino Acid Catabolism in Mammals



Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

Metabolic Circumstances of Amino Acid Oxidation

- amino acids undergo oxidative degradation when:
  - amino acids released during protein turnover are not needed for new protein synthesis
  - ingested amino acids exceed the body's needs for protein synthesis
  - cellular proteins are used as fuel because carbohydrates are either unavailable or not properly utilized

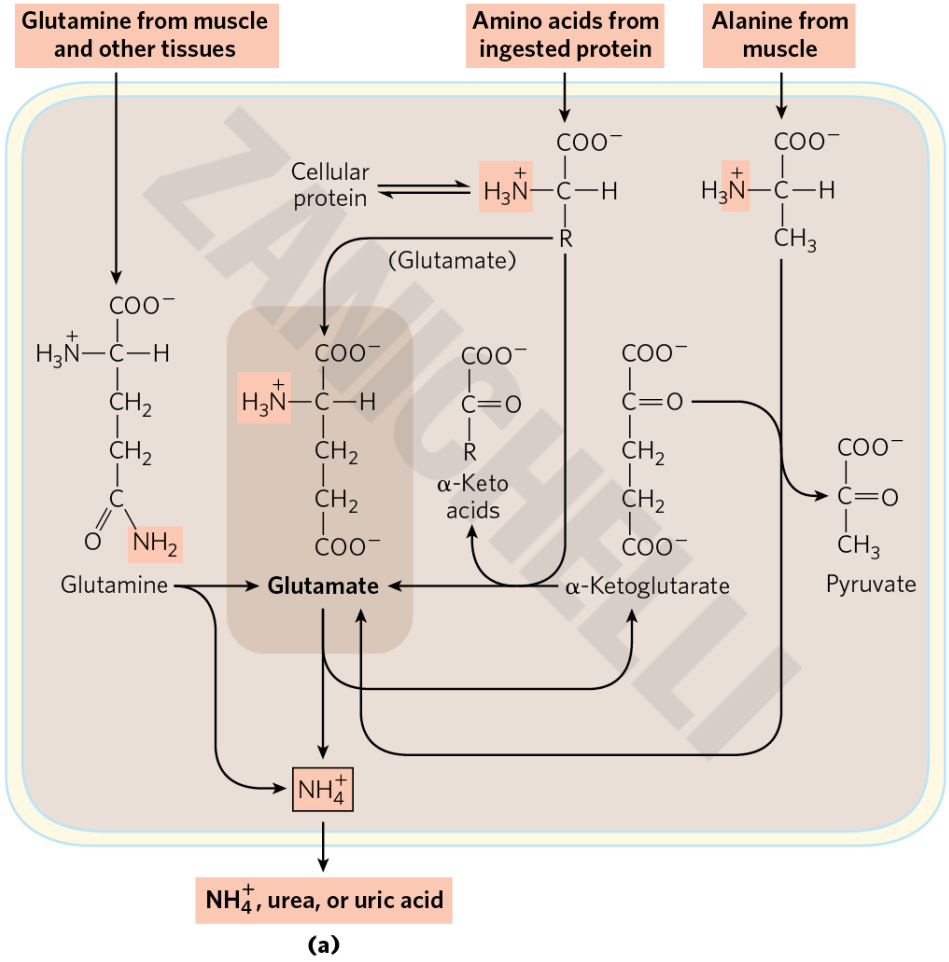
18.1 Metabolic Fates of Amino Groups

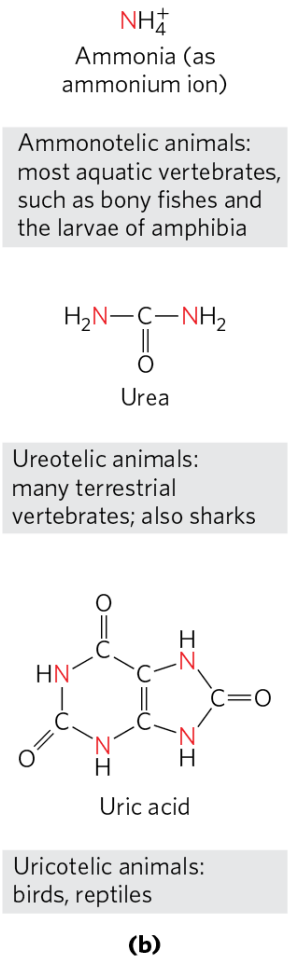
P4 Principle 4 (2 of 3)

Free ammonia is toxic. Excess amino groups must be safely excreted. In mammals, the urea cycle serves this purpose.

Amino Group Catabolism

- unless reused, amino groups are channeled into a single excretory end product





Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

Ammonotelic, Ureotelic, and Uricotelic Animals

- **ammonotelic** animals = excrete amino nitrogen as ammonia
  - most aquatic species

- **ureotelic** animals = excrete amino nitrogen as urea
  - most terrestrial animals

- **uricotelic** animals = excrete amino nitrogen as uric acid
  - birds and reptiles

P2 Principle 2 (2 of 4)

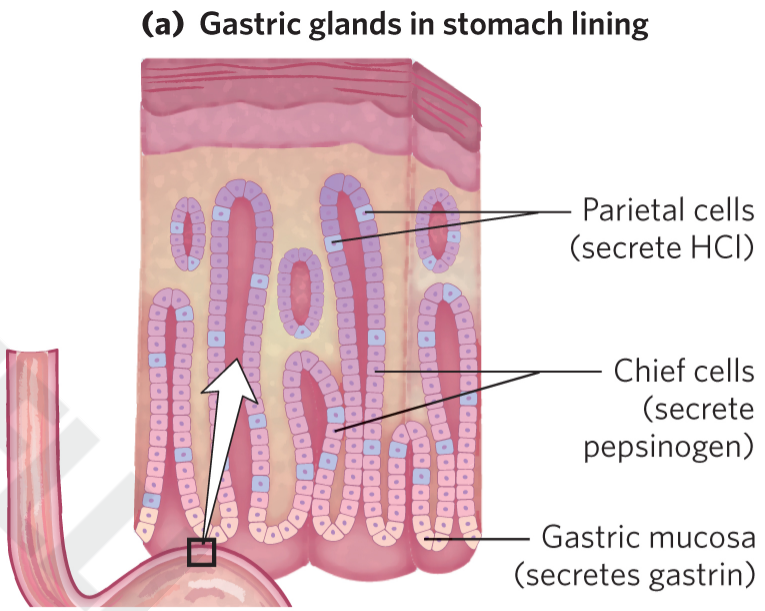
Four amino acids—alanine, glutamate, glutamine, and aspartate—play key roles in the transport and distribution of amino groups. All are present in relatively high concentrations in one or many mammalian tissues. All are readily converted to key citric acid cycle intermediates.

Amino Acids Involved in Nitrogen Metabolism

- glutamate, glutamine, alanine, and aspartate are most easily converted into citric acid cycle intermediates:
  - glutamate to *α*-ketoglutarate
  - glutamine to *α*-ketoglutarate
  - alanine to pyruvate
  - aspartate to oxaloacetate

Dietary Protein Is Enzymatically Degraded to Amino Acids

- degradation occurs in the gastrointestinal tract
- **gastrin** = hormone secreted when dietary protein enters the stomach
  - stimulates the secretion of HCl and pepsinogen
- **pepsinogen** = zymogen that is converted to active pepsin by autocatalytic cleavage at low pH

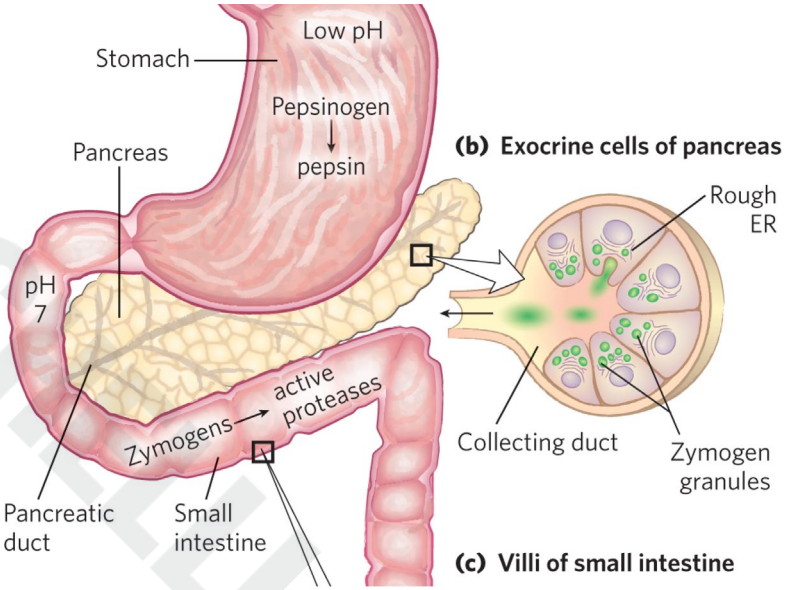


Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

Pepsin and Secretin

- pepsin = cleaves long polypeptide chains into a mixture of smaller peptides

- **secretin** = hormone secreted into the blood in response to low pH in the small intestine
  - stimulates the pancreas to secrete bicarbonate into the small intestine



Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

Zymogens Are Secreted by the Exocrine Cells of the Pancreas

- **cholecystokinin** = hormone secreted into the blood in response to the arrival of peptides in the duodenum
  - stimulates secretion of several pancreatic proteases:
    - trypsinogen is the zymogen of **trypsin**
    - chymotrypsinogen is the zymogen of **chymotrypsin**
    - procarboxypeptidases A and B are the zymogens of **carboxypeptidases A** and **B**

Trypsin and Pancreatic Trypsin Inhibitor

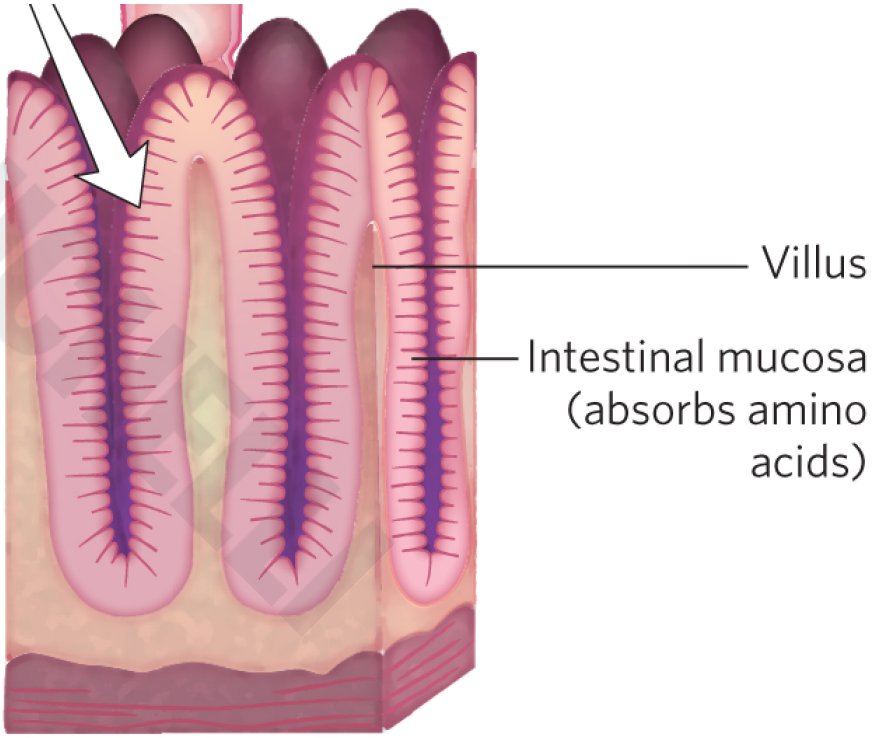
- **enteropeptidase** = a proteolytic enzyme that converts trypsinogen to trypsin

- **trypsin** = activates additional trypsinogen, chymotrypsinogen, the procarboxypeptidases, and proelastase

- **pancreatic trypsin inhibitor** = protein inhibitor that further protects the pancreas against self-digestion

The Intestinal Mucosa Absorbs Amino Acids

- free amino acids are transported into the epithelial cells lining the small intestine, enter the blood capillaries in the villi, and travel to the liver



Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

Acute Pancreatitis

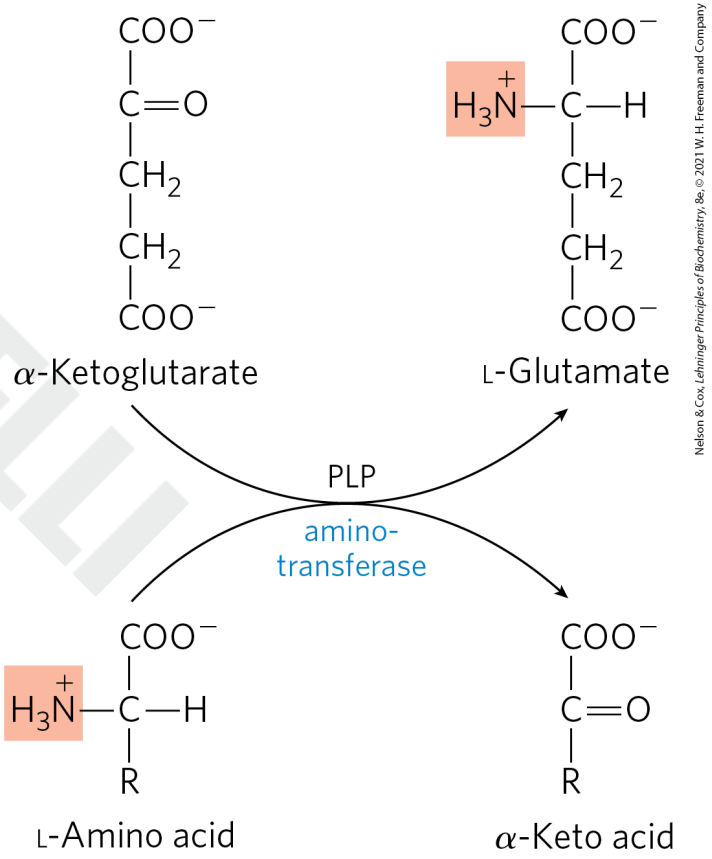
- **acute pancreatitis** = caused by obstruction of the pathway by which pancreatic secretions enter the intestine
  - zymogens are prematurely converted to their active forms inside the pancreatic cells and attack the pancreatic tissue

P1 Principle 1 (2 of 7)

The many paths for amino acid catabolism have two broad parts, one involving the amino groups and the other involving the carbon skeletons. All of the pathways for amino acid degradation include a key step, always involving a pyridoxal phosphate cofactor, in which the *α*-amino group is separated from the carbon skeleton and shunted into the pathways of amino group metabolism. The carbon skeletons are broken down to citric acid cycle intermediates.

Pyridoxal Phosphate Participates in the Transfer of α-Amino Groups to α-Ketoglutarate

- **aminotransferases (transaminases)** = catalyze the removal of the α-amino groups
  - cells contain different types that differ in their specificity for the L-amino acid
  - many are specific for α-ketoglutarate as the amino group acceptor



P2 Principle 2 (3 of 4)

Four amino acids—alanine, glutamate, glutamine, and aspartate—play key roles in the transport and distribution of amino groups. All are present in relatively high concentrations in one or many mammalian tissues. All are readily converted to key citric acid cycle intermediates.

Transamination Reactions

- **transamination** reactions = transfer the *α*-amino group to the *α*-carbon atom of *α*-ketoglutarate, yielding an *α*-keto acid analog of the amino acid
  - reactions are freely reversible ($\Delta G' \approx 0$ kJ/mol)
  - effectively collect the amino groups from many amino acids in the form of L-glutamate

P1 Principle 1 (3 of 7)

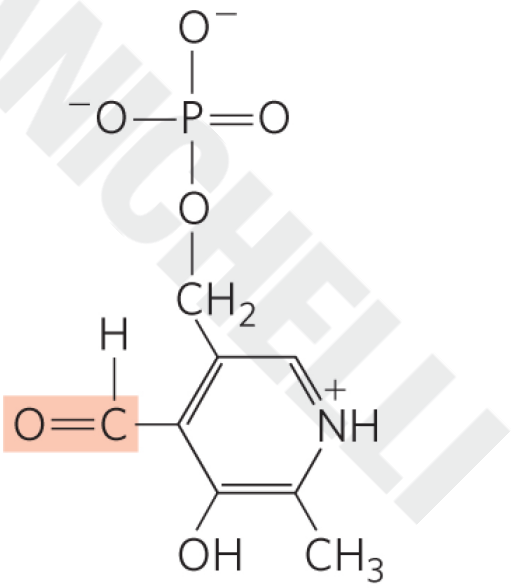
The many paths for amino acid catabolism have two broad parts, one involving the amino groups and the other involving the carbon skeletons. All of the pathways for amino acid degradation include a key step, always involving a pyridoxal phosphate cofactor, in which the *α*-amino group is separated from the carbon skeleton and shunted into the pathways of amino group metabolism. The carbon skeletons are broken down to citric acid cycle intermediates.

Pyridoxal Phosphate (PLP)

- **pyridoxal phosphate (PLP)** = the coenzyme form of pyridoxine or vitamin B_6
  - used as a prosthetic group by all aminotransferases
  - carries amino groups at the active site

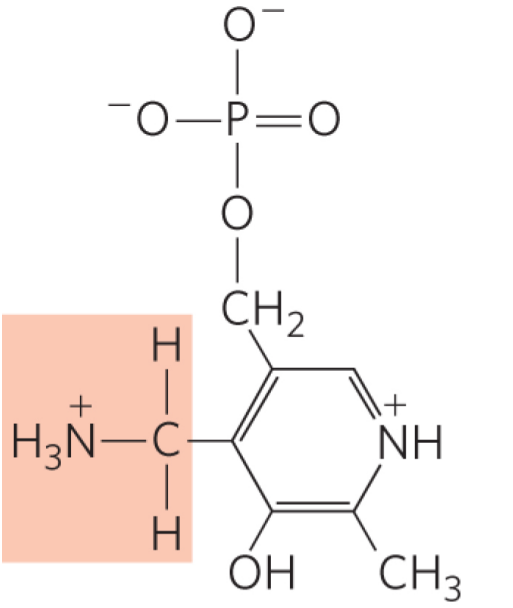
The Structure of Pyridoxal Phosphate and Pyridoxamine Phosphate

- PLP (aldehyde form) = accepts an amino group
- pyridoxamine phosphate (aminated form) = donates its amino group to an *α*-keto acid



Pyridoxal phosphate (PLP)

Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

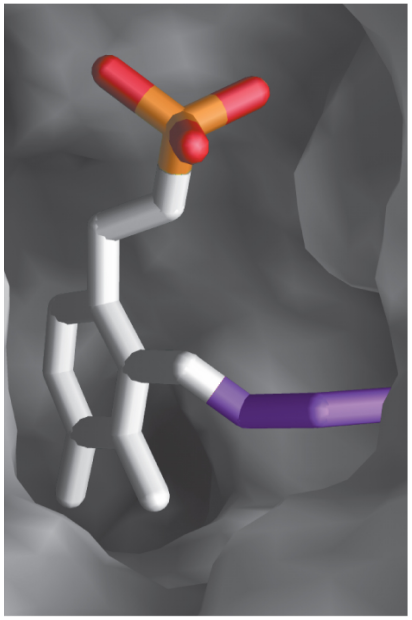


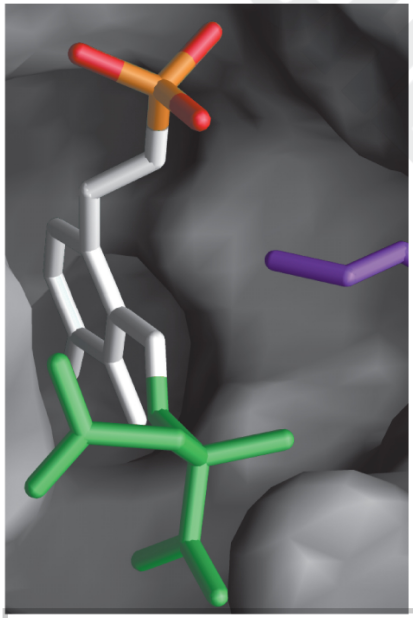
Pyridoxamine phosphate

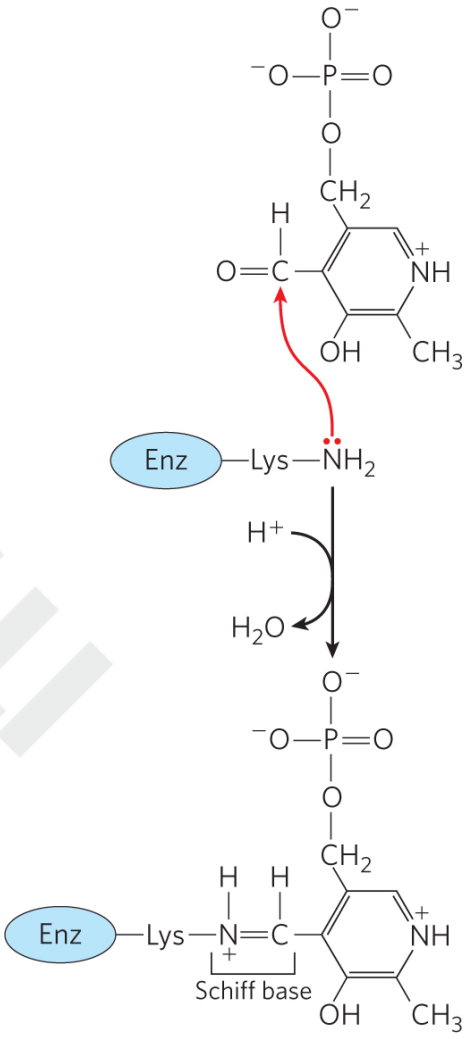
Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

Pyridoxal Phosphate Is Covalently Linked to the Enzyme

- covalently linked through an aldimine (Schiff base) linkage to the ε-amino group of a Lys residue





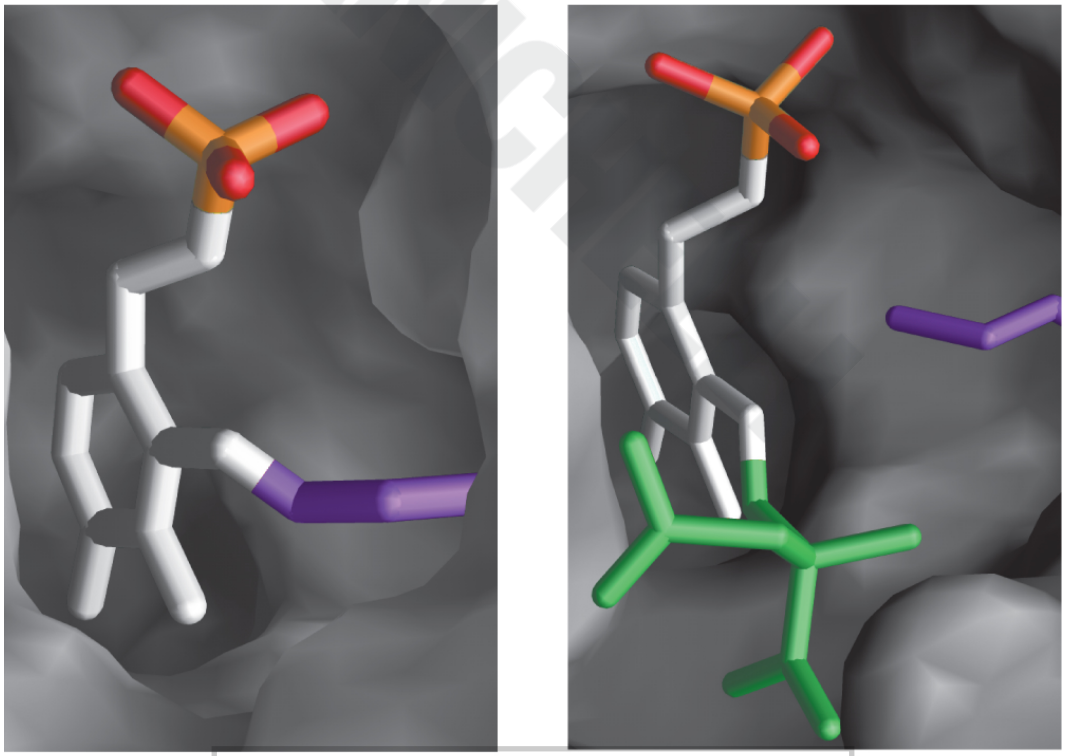


Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

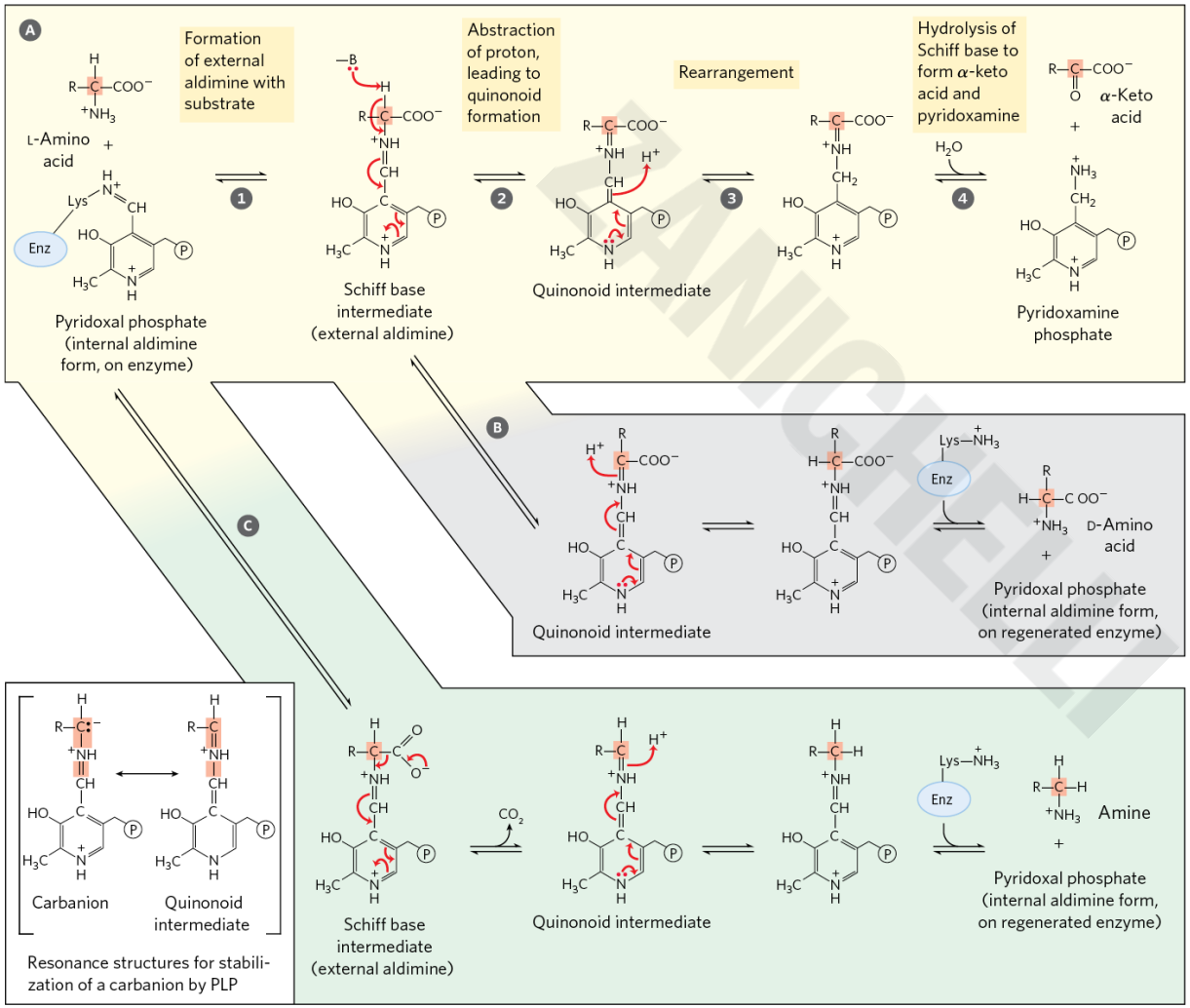
Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

The Aldimine Linkage Is Replaced by the Amino Group

- the aldimine linkage is replaced by the amino group of the amino acid as the first step in most PLP-catalyzed reactions



Some Reactions Facilitated by PLP



Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W.H. Freeman and Company

transamination

racemization

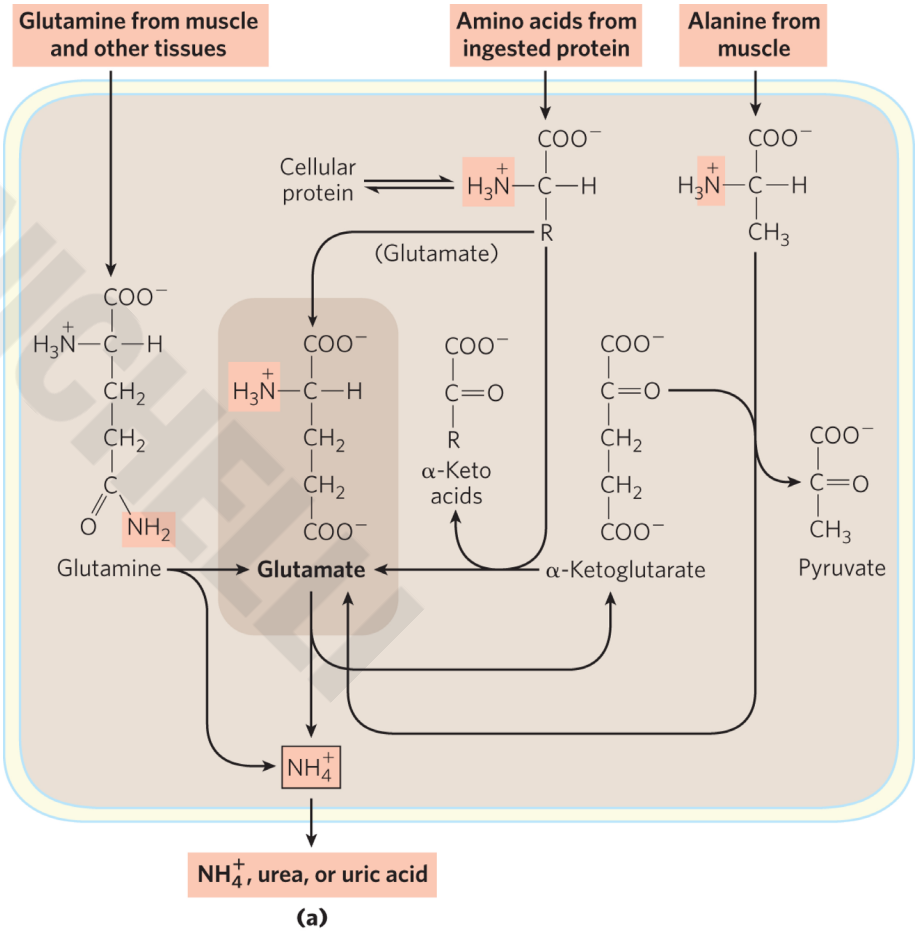
decarboxylation

P1 Principle 1 (4 of 7)

The many paths for amino acid catabolism have two broad parts, one involving the amino groups and the other involving the carbon skeletons. All of the pathways for amino acid degradation include a key step, always involving a pyridoxal phosphate cofactor, in which the *α*-amino group is separated from the carbon skeleton and shunted into the pathways of amino group metabolism. The carbon skeletons are broken down to citric acid cycle intermediates.

Glutamate Releases Its Amino Group as Ammonia in the Liver

- NH_4^+ in the mitochondria comes from many different α-amino acids in the form of:
  - the amino group of L-glutamate
  - the amide nitrogen of glutamine



Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

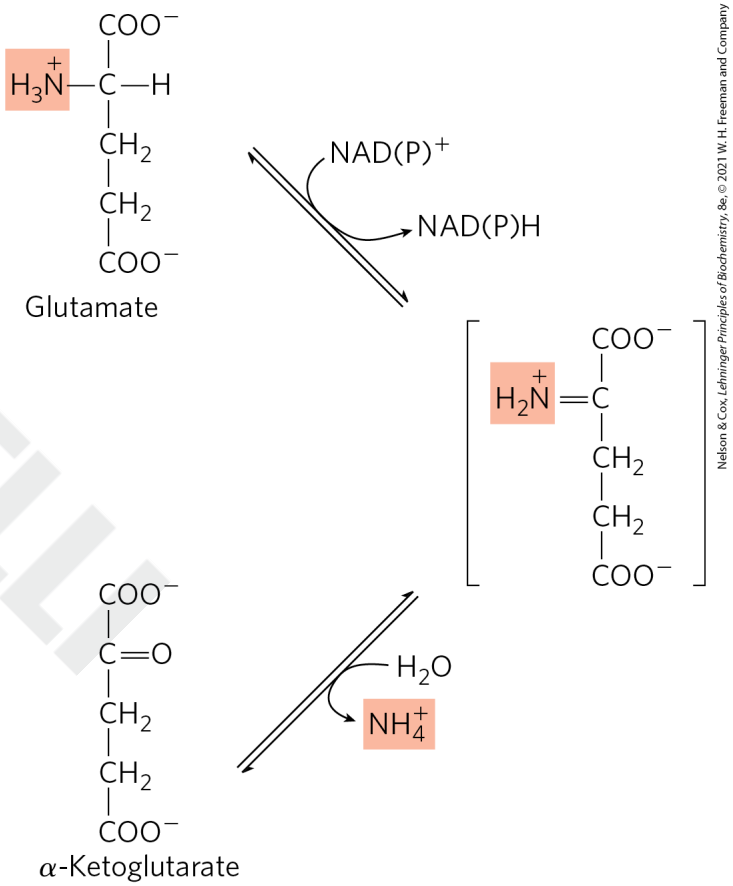
P3 Principle 3 (2 of 5)

Metabolic pathways are not distinct. The various pathways for amino acid catabolism are elaborately intertwined with other catabolic and anabolic pathways.

L-Glutamate Dehydrogenase

- **L-glutamate dehydrogenase** = catalyzes the **oxidative deamination** of glutamate to produce NH_4^+ and α-ketoglutarate
  - present in the mitochondrial matrix
  - can use either NAD^+ or $NADP^+$

- α-ketoglutarate can enter the citric acid cycle or be used for glucose synthesis



Transdeamination Reactions

- **transdeamination** reactions = result from the combined action of an aminotransferase and glutamate dehydrogenase

P1 Principle 1 (5 of 7)

The many paths for amino acid catabolism have two broad parts, one involving the amino groups and the other involving the carbon skeletons. All of the pathways for amino acid degradation include a key step, always involving a pyridoxal phosphate cofactor, in which the *α*-amino group is separated from the carbon skeleton and shunted into the pathways of amino group metabolism. The carbon skeletons are broken down to citric acid cycle intermediates.

P2 Principle 2 (4 of 4)

Four amino acids—alanine, glutamate, glutamine, and aspartate—play key roles in the transport and distribution of amino groups. All are present in relatively high concentrations in one or many mammalian tissues. All are readily converted to key citric acid cycle intermediates.

P3 Principle 3 (3 of 5)

Metabolic pathways are not distinct. The various pathways for amino acid catabolism are elaborately intertwined with other catabolic and anabolic pathways.

Glutamate Dehydrogenase Operates at an Important Intersection in Carbon and Nitrogen Metabolism

- *α*-ketoglutarate product can be oxidized as fuel or serve as a glucose precursor in gluconeogenesis

- glutamate dehydrogenase is:
  - positively modulated by ADP (signals low glucose levels)
  - negatively modulated by GTP (signals high levels of *α*-ketoglutarate)

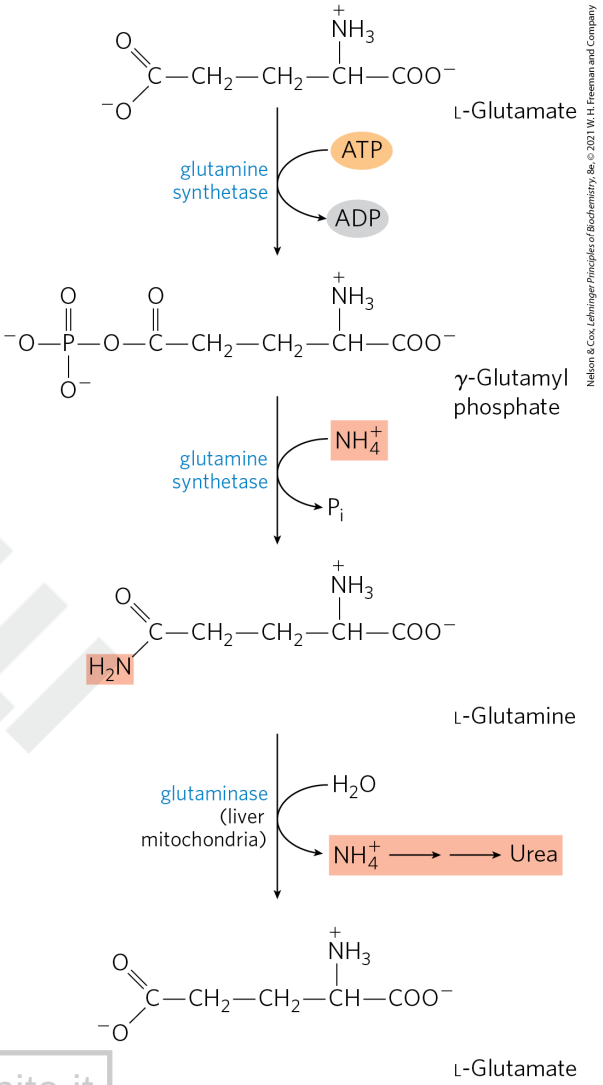
P4 Principle 4 (3 of 3)

Free ammonia is toxic. Excess amino groups must be safely excreted. In mammals, the urea cycle serves this purpose.

Glutamine Transports Ammonia in the Bloodstream

- **glutamine synthetase** = catalyzes the combination of free ammonia with glutamate to yield glutamine
  - requires ATP
  - critical to transport toxic ammonia to the liver

- **glutaminase** = catalyzes the conversion of glutamine to glutamate and NH_4^+



Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

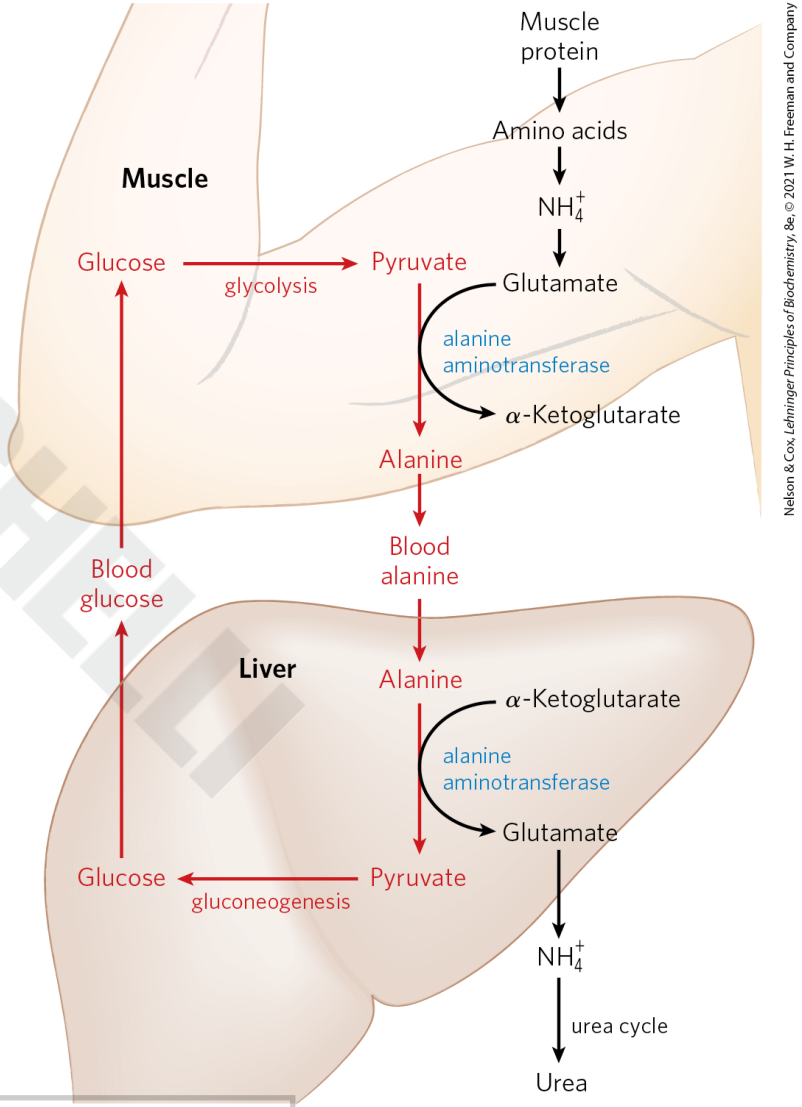
Alanine Transports Ammonia from Skeletal Muscles to the Liver

- skeletal muscles produce pyruvate, lactate, and ammonia

- **alanine aminotransferase** = interconverts pyruvate and alanine via transamination with glutamate

The Glucose-Alanine Cycle

- **glucose-alanine cycle** = pathway by which alanine carries ammonia and the carbon skeleton from pyruvate to the liver
  - ammonia is excreted
  - pyruvate is used to produce glucose, which is returned to the muscle



Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

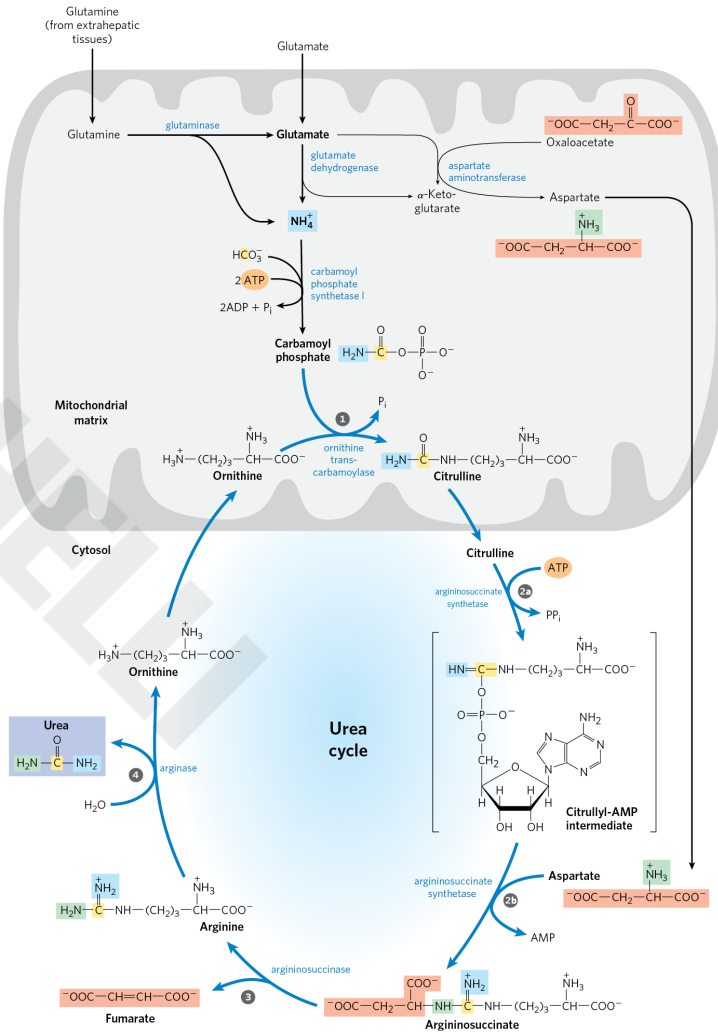
Ammonia Is Toxic to Animals

- free ammonia is toxic, especially to the brain
- NH_4^+ competes with K^+ for transport into astrocyte cells through Na^+K^+ ATPase
  - results in elevated extracellular $[K^+]$
- **Na^+-K^+-2Cl^- cotransporter 1 (NKCC1)** = symporter that transports Na^+, K^+, and Cl^-
  - excess Cl^- from the excess K^+ alters neuronal response to the neurotransmitter GABA

18.2 Nitrogen Excretion and the Urea Cycle

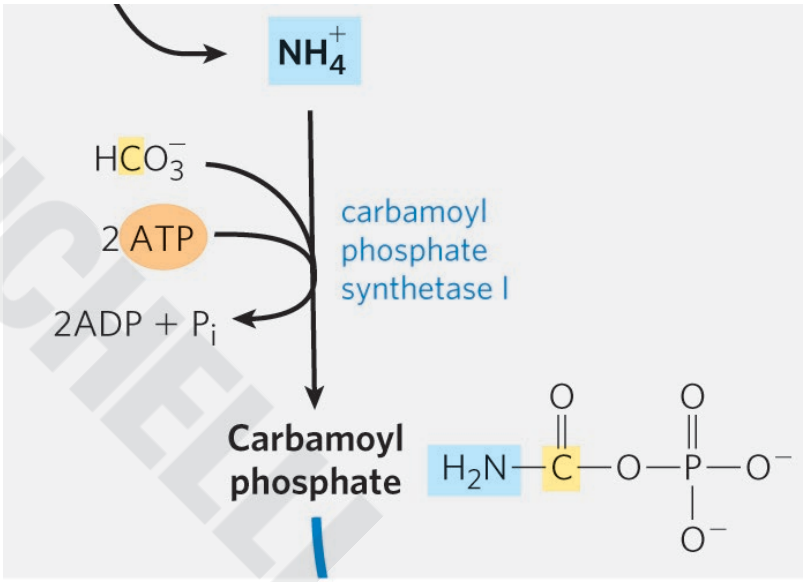
The Urea Cycle

- **urea cycle** = pathway by which the ammonia deposited in the mitochondria of hepatocytes is converted to urea
  - urea enters the bloodstream and is excreted into the urine
  - enzymes are clustered in metabolons



Urea Is Produced from Ammonia in Five Enzymatic Steps

- **carbamoyl phosphate synthetase I** = catalyzes the formation of carbamoyl phosphate from NH_4^+ and CO_2 (as HCO_3^-)
  - requires 2 ATP
  - occurs in the mitochondrial matrix

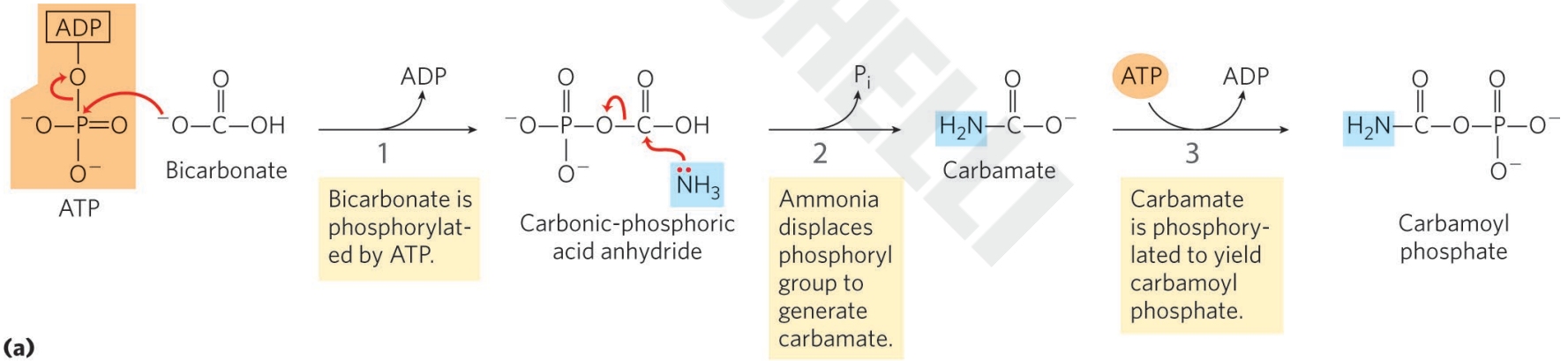


Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

The Carbamoyl Phosphate Synthetase I Reaction

- the first nitrogen enters from ammonia in the reaction catalyzed by carbamoyl phosphate synthetase I

- the reaction has two activation steps that require ATP

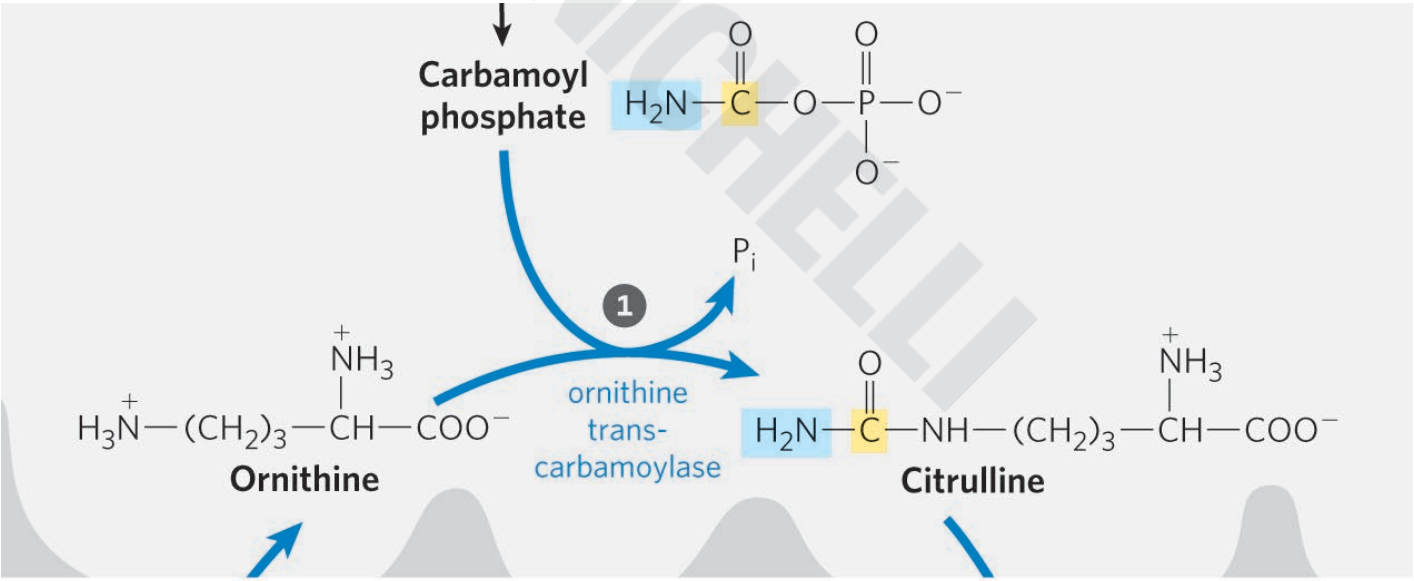


(a)

Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

The Formation of Citrulline

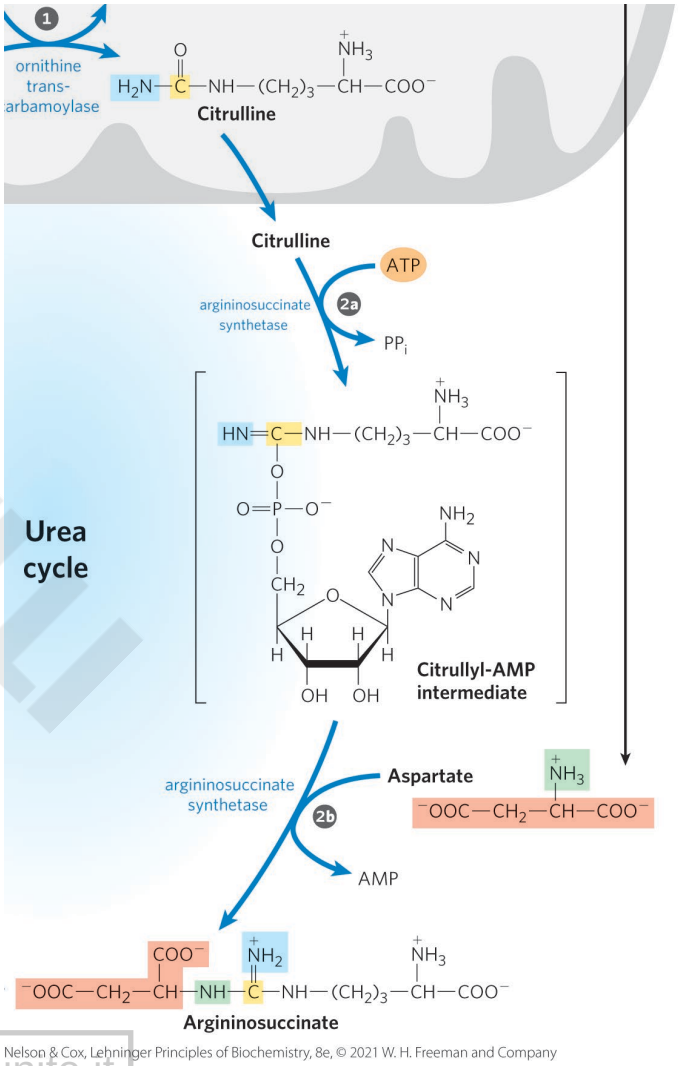
- **ornithine transcarbamoylase** = catalyzes the formation of citrulline and P_i from ornithine and carbamoyl phosphate



Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

The Formation of Argininosuccinate

- citrulline passes from the mitochondrion to the cytosol
- **argininosuccinate synthetase** = catalyzes the condensation of the amino group of aspartate and the ureido group of citrulline to form argininosuccinate
  - requires ATP
  - uses a citrullyl-AMP intermediate

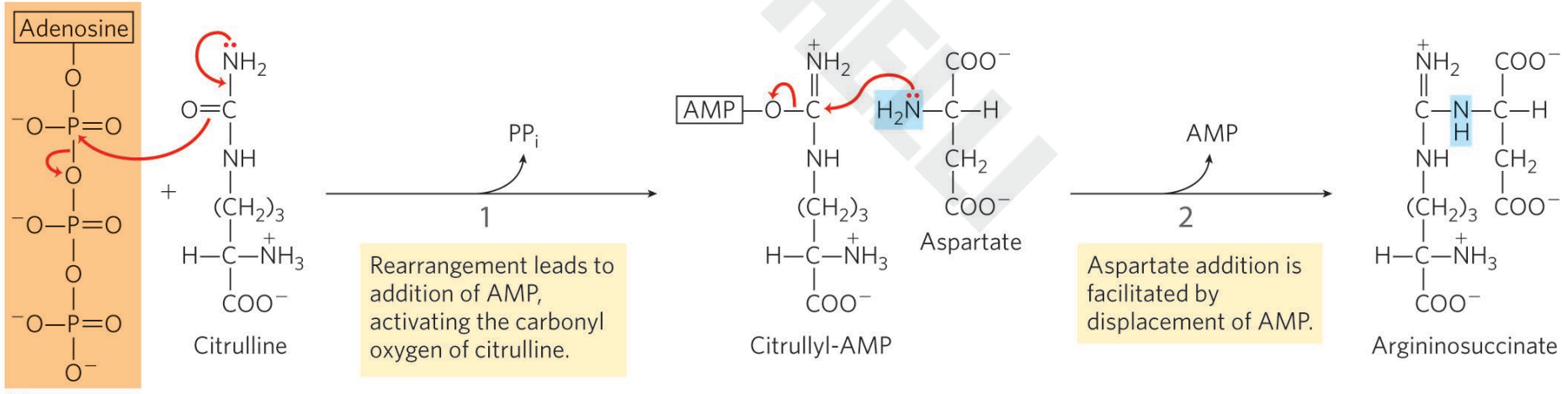


Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

The Argininosuccinate Synthetase Reaction

- the second nitrogen enters from ammonia in the reaction catalyzed by argininosuccinate synthetase

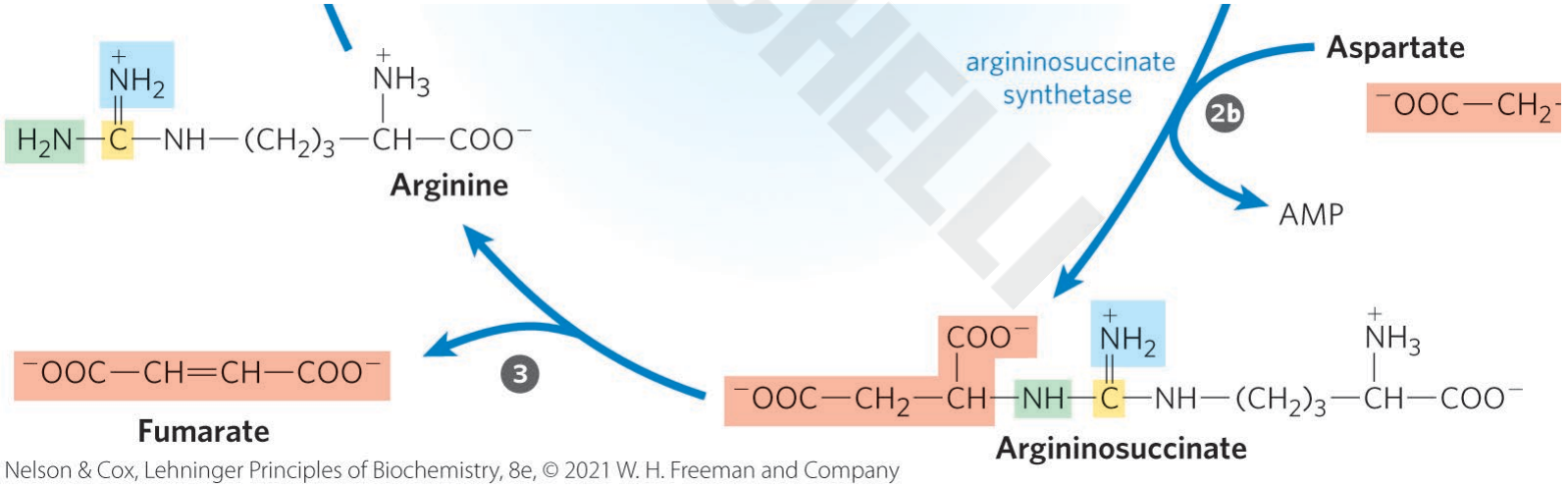
- the reaction has two activation steps



Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

The Formation of Arginine

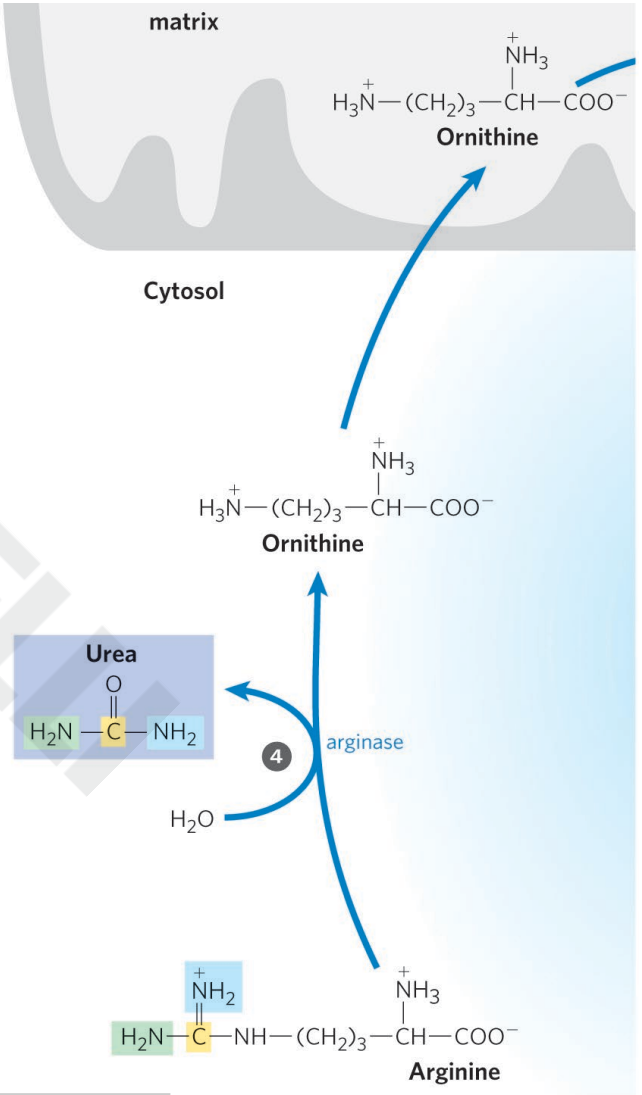
- **argininosuccinase** = catalyzes the reversible cleavage of argininosuccinate to form arginine and fumarate
  - fumarate is converted to malate and joins the pool of citric acid cycle intermediates



Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

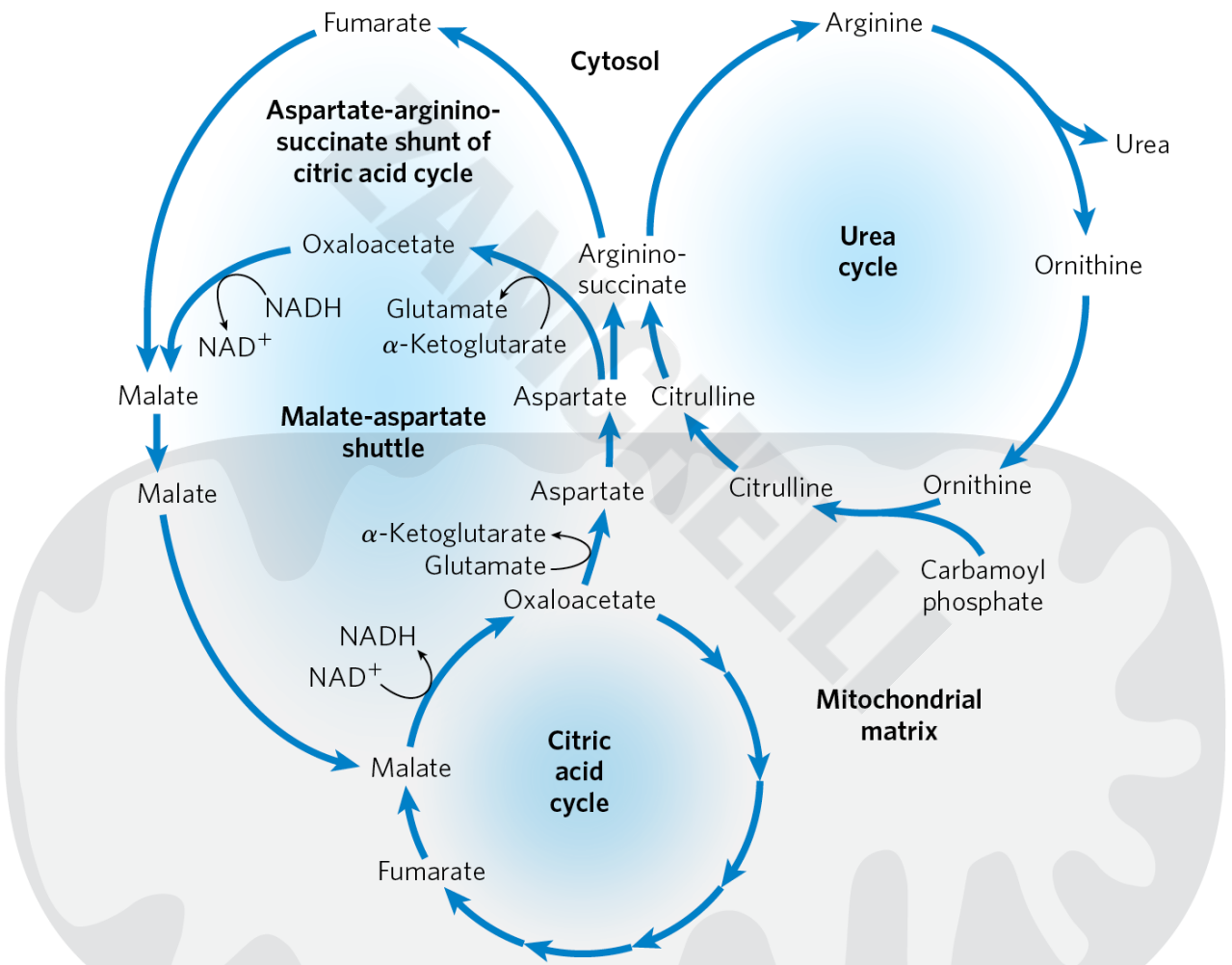
The Formation of Urea

- **arginase** = catalyzes the cleavage of arginine to form **urea** and ornithine
  - ornithine is transported into the mitochondrion to initiate another round



Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

The Citric Acid and Urea Cycles Can Be Linked



Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

Communication Between the Citric Acid and Urea Cycles

- communication depends on the transport of key intermediates between the mitochondrion and cytosol:
  - malate–*α*-ketoglutarate transporter
  - glutamate-aspartate transporter
  - glutamate-OH^- transporter

The Aspartate-Argininosuccinate Shunt

- **aspartate-argininosuccinate shunt** = pathways linking the citric acid and urea cycles
  - link the fates of the amino groups and the carbon skeletons of amino groups

P3 Principle 3 (4 of 5)

Metabolic pathways are not distinct. The various pathways for amino acid catabolism are elaborately intertwined with other catabolic and anabolic pathways.

Aspartate as a Nitrogen Donor

- this pathway for nitrogen incorporation is one of the two common ways to introduce amino groups into biomolecules

- the urea and citric acid cycles are closely tied to an additional process that brings NADH, in the form of reducing equivalents, into the mitochondrion

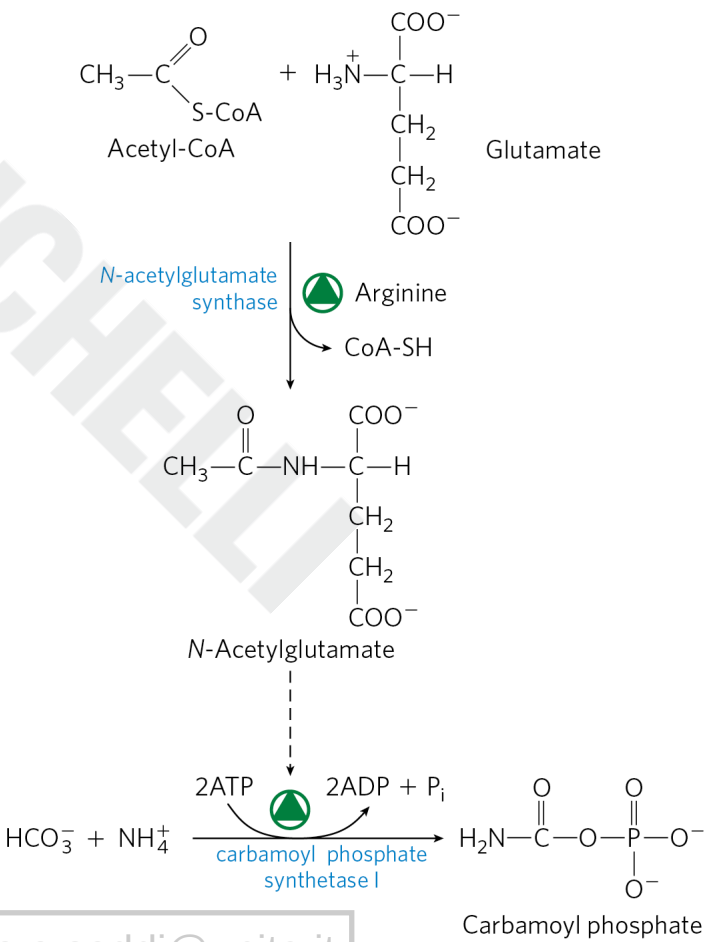
The Activity of the Urea Cycle Is Regulated at Two Levels

- the urea cycle is regulated:
  - at the level of enzyme synthesis for:
    - the four urea cycle enzymes
    - carbamoyl phosphate synthetase I
  - by allosteric regulation of carbamoyl phosphate synthetase I

Synthesis of *N*-Acetylglutamate and Its Activation of Carbamoyl Phosphate Synthetase I

- ***N*-acetylglutamate synthase** = catalyzes the formation of ***N*-acetylglutamate** from acetyl-CoA and glutamate

- ***N*-acetylglutamate** = allosterically activates carbamoyl phosphate synthetase I



Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

Pathway Interconnections Reduce the Energetic Cost of Urea Synthesis

- in isolation, the urea cycle requires four high-energy phosphate groups

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

- the energetic cost of the urea cycle is reduced by cycle interconnections

Genetic Defects in the Urea Cycle Can Be Life-Threatening

- protein-free diets are not a treatment option for individuals with defects in urea cycle enzyme
- **essential amino acids** = amino acids that cannot be synthesized by humans and must be obtained in the diet

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

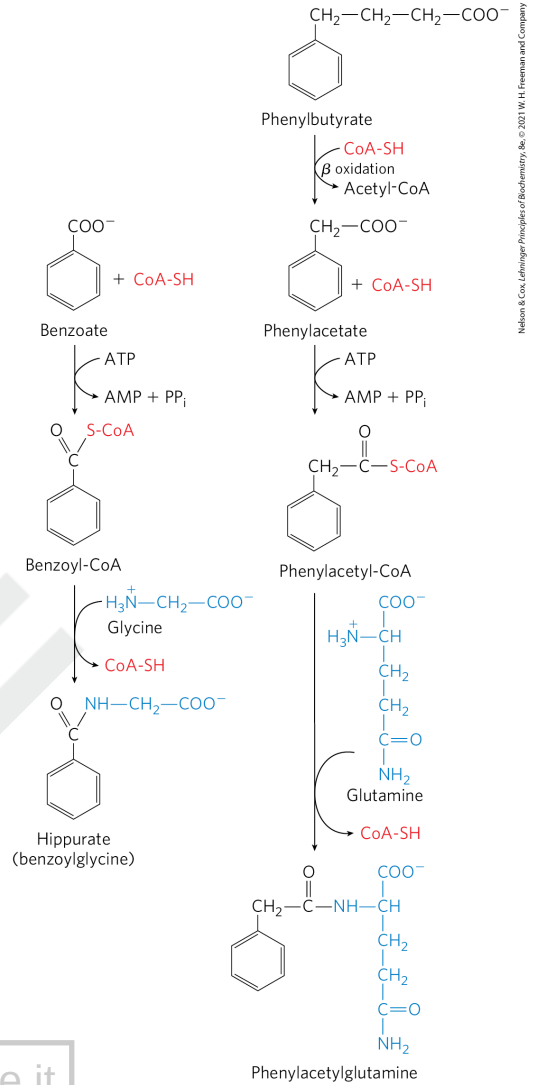
Nonessential	Conditionally essential[a]	Essential
Alanine	Arginine	Histidine
Asparagine	Cysteine	Isoleucine
Aspartate	Glutamine	Leucine
Glutamate	Glycine	Lysine
Serine	Proline	Methionine
	Tyrosine	Phenylalanine
		Threonine
		Tryptophan
		Valine

[a]Required to some degree in young, growing animals and/or sometimes during illness.

Treatments for Urea Cycle Enzyme Deficiencies

- the aromatic acid benzoate is metabolized and combines with glycine

- the aromatic acid phenylbutyrate is metabolized and combines with glutamine



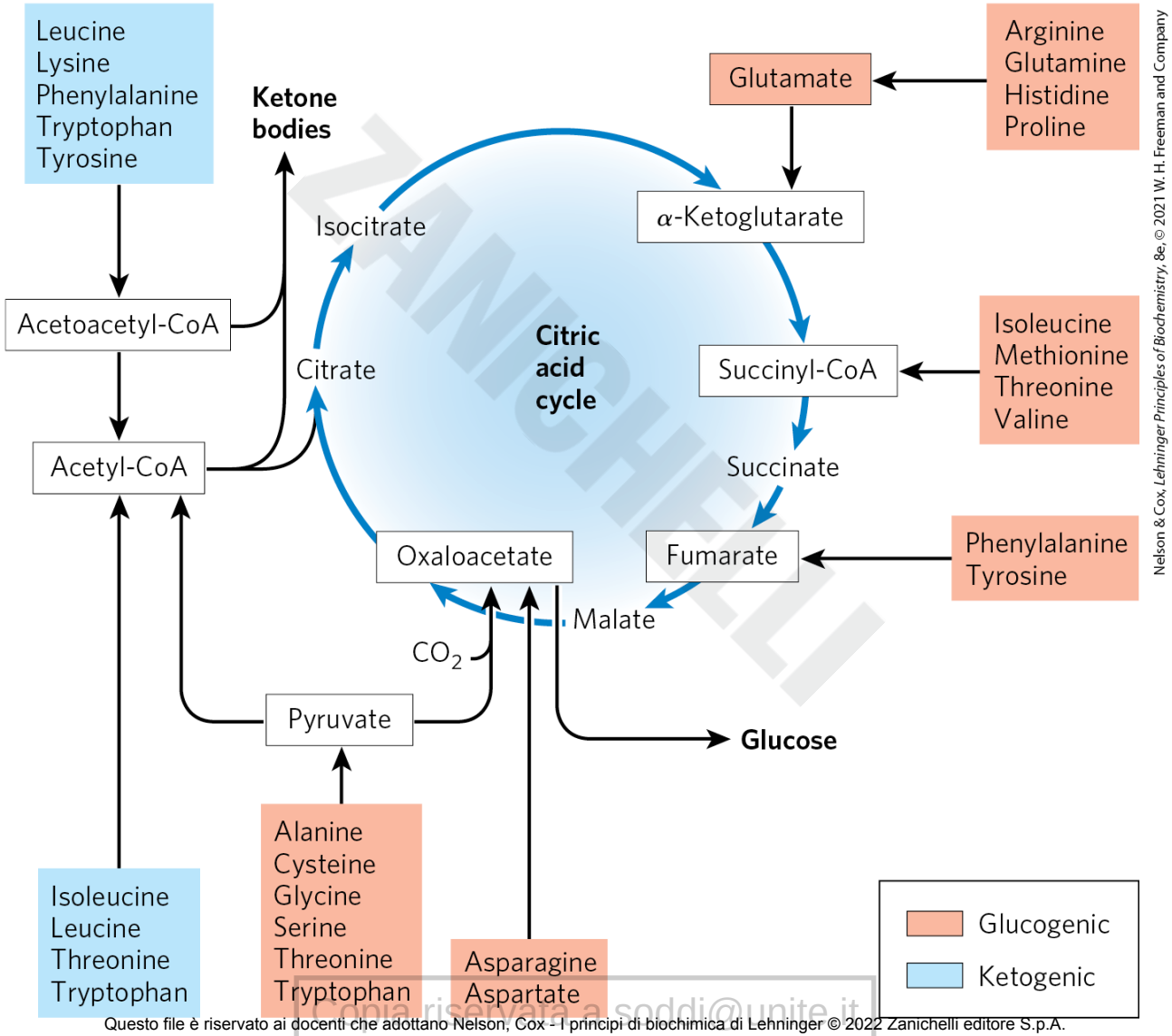
18.3 Pathways of Amino Acid Degradation

Amino Acid Catabolism

- accounts for 10-15% of human energy production

- the 20 catabolic pathways converge to form six major products (all of which enter the citric acid cycle):
  - pyruvate
  - acetyl-CoA
  - *α*-ketoglutarate
  - succinyl-CoA
  - fumarate
  - oxaloacetate

Summary of Amino Acid Catabolism



P5 Principle 5 (2 of 6)

Each amino acid has a different catabolic fate. The varied carbon skeletons of amino acids are broken down via equally varied pathways. All can be oxidized to generate ATP. All but leucine and lysine can contribute to gluconeogenesis when needed.

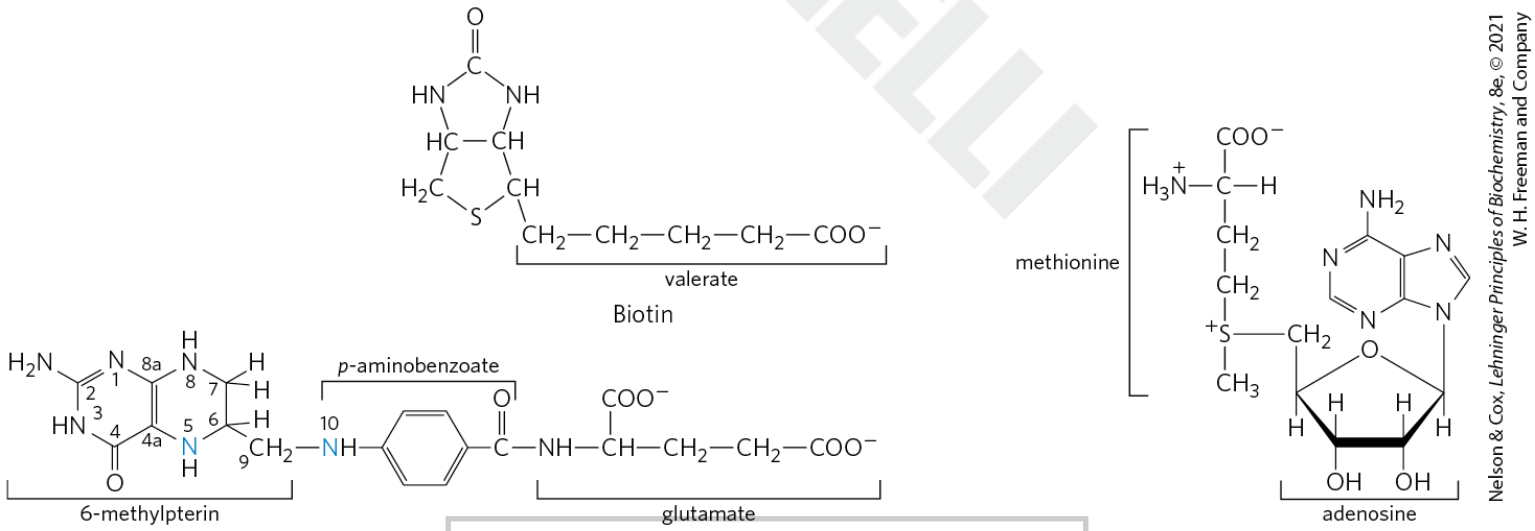
Some Amino Acids Can Contribute to Gluconeogenesis, Others to Ketone Body Formation

- **ketogenic** amino acids = can yield ketone bodies in the liver
  - phenylalanine, tyrosine, isoleucine, leucine, tryptophan, threonine, and lysine

- **glucogenic** amino acids = can be converted to glucose and glycogen
  - all amino acids except lysine and leucine

Several Enzyme Cofactors Play Important Roles in Amino Acid Catabolism

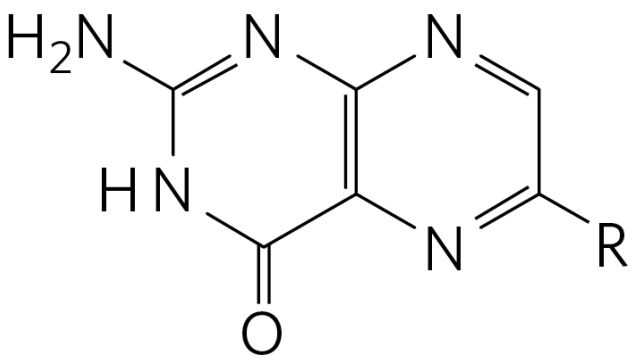
- one-carbon transfers usually involve one of three cofactors:
  - biotin (transfers CO_2)
  - tetrahydrofolate (transfers intermediate oxidation states)
  - *S*-adenosylmethionine (transfers methyl groups)



Tetrahydrofolate (H_4 Folate)

- **tetrahydrofolate (H_4 folate)** = consists of substituted pterin (6-methylpterin), *p*-aminobenzoate, and glutamate moieties
  - synthesized in bacteria

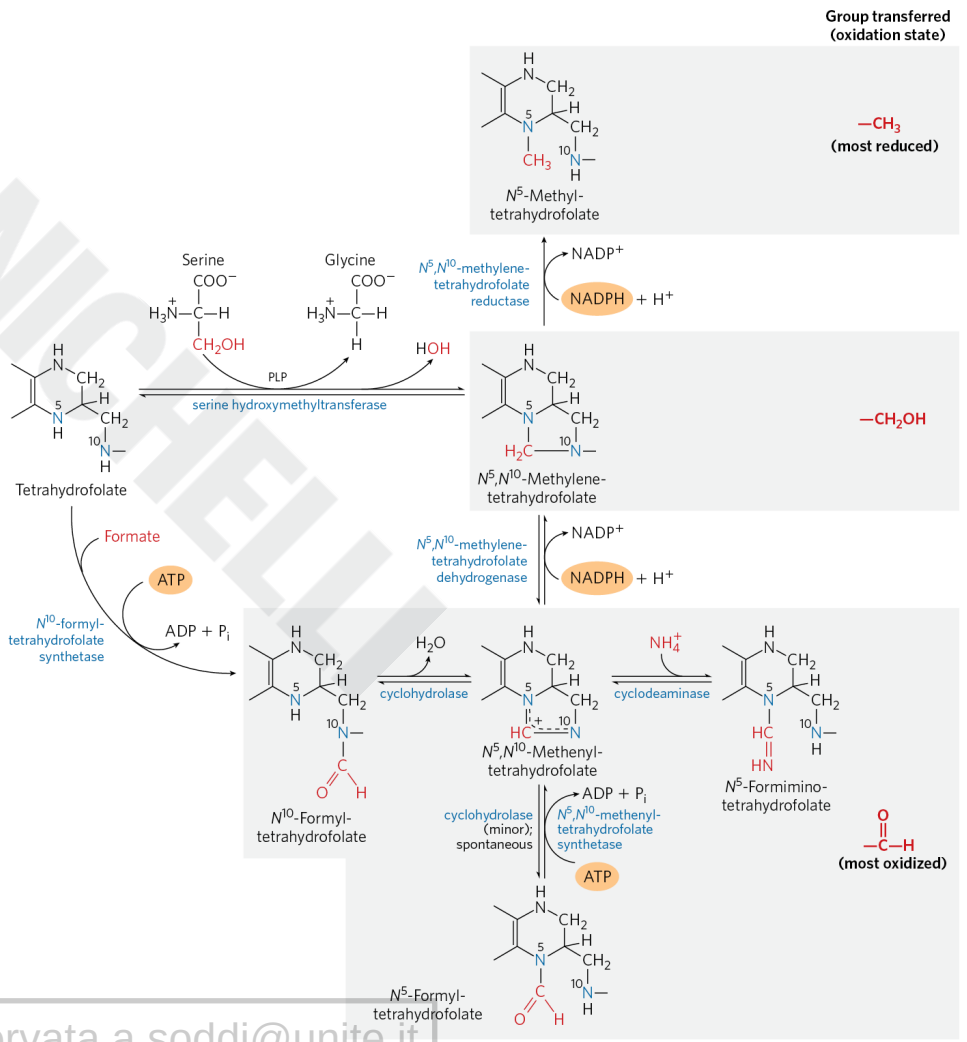
- folate = the oxidized form of tetrahydrofolate
  - converted to tetrahydrofolate in two steps by dihydrofolate reductase



Pterin

Conversions of One-Carbon Units on Tetrahydrofolate

- the one-carbon group is bonded to N-5, N-10, or both



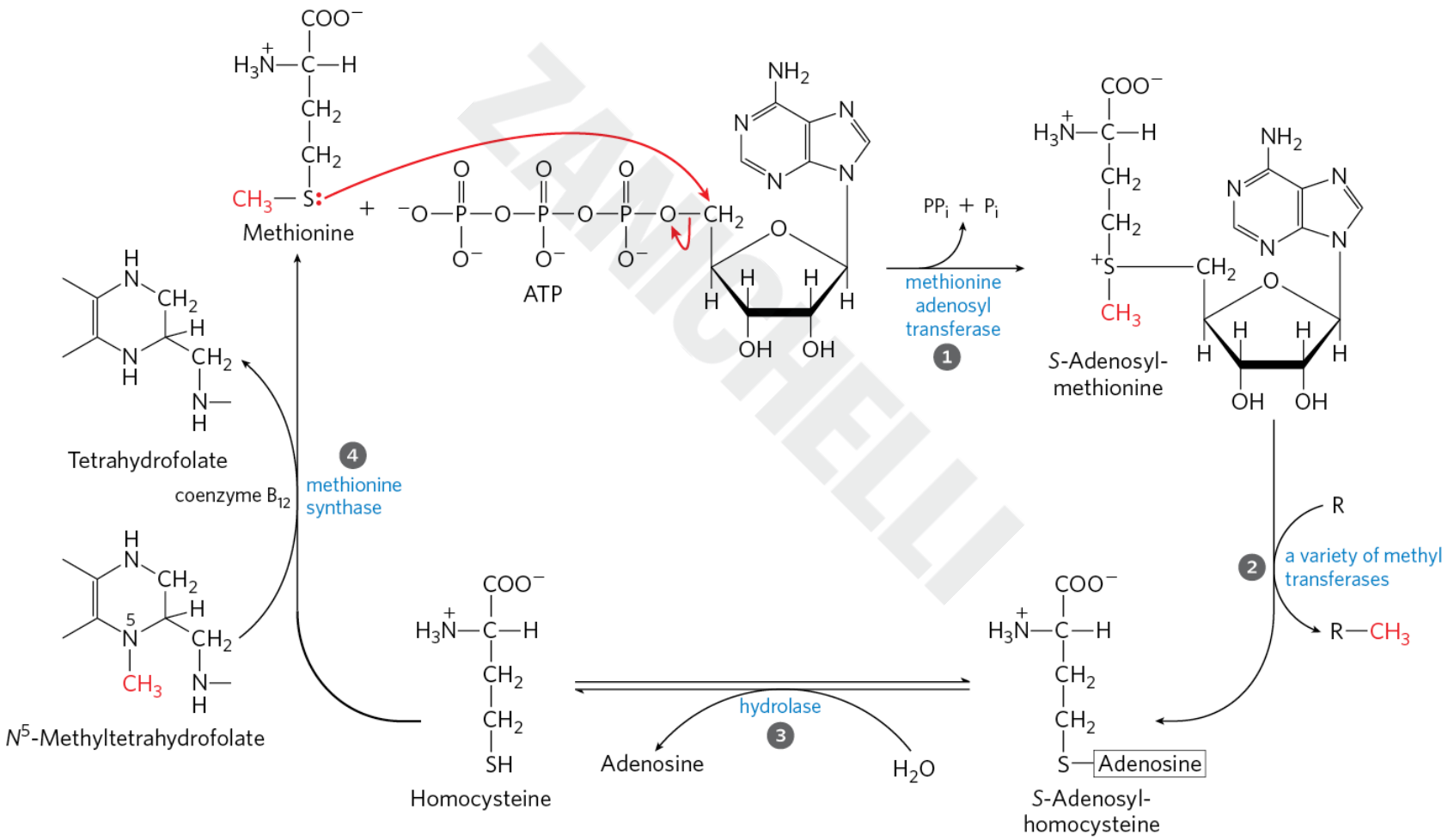
S-Adenosylmethionine (adoMet)

- ***S*-adenosylmethionine (adoMet)** = preferred cofactor for biological methyl group transfers
  - Its methyl group is ~ 1000x more reactive than the methyl group of N^5-methyltetrahydrofolate

- **methionine adenosyl transferase** = catalyzes the synthesis of *S*-adenosylmethionine from ATP and methionine

- ***S*-adenosylhomocysteine** = formed when the methyl group from *S*-adenosylmethionine is transferred to an acceptor

Synthesis of Methionine and *S*-Adenosylmethionine



Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

Pernicious Anemia

- **pernicious anemia** = observed in B_{12} deficiency disease
  - traced to the methionine synthase reaction

Megaloblatic Anemia

- **megaloblastic anemia** = observed in vitamin B_{12} deficiency
  - decline in the production of mature erythrocytes
  - appearance of immature precursor cells, or **megaloblasts,** in the bone marrow
  - replacement of erythrocytes with a smaller number of abnormally large erythrocytes (**macrocytes)**

- erythocyte defects are due to the depletion of the N^5,N^{10}-methylenetetrahydrofolate

Tetrahydrobiopterin

- **tetrahydrobiopterin** = cofactor of amino acid catabolism
  - similar to the pterin moiety of tetrahydrofolate
  - participates in oxidation reactions

P1 Principle 1 (6 of 7)

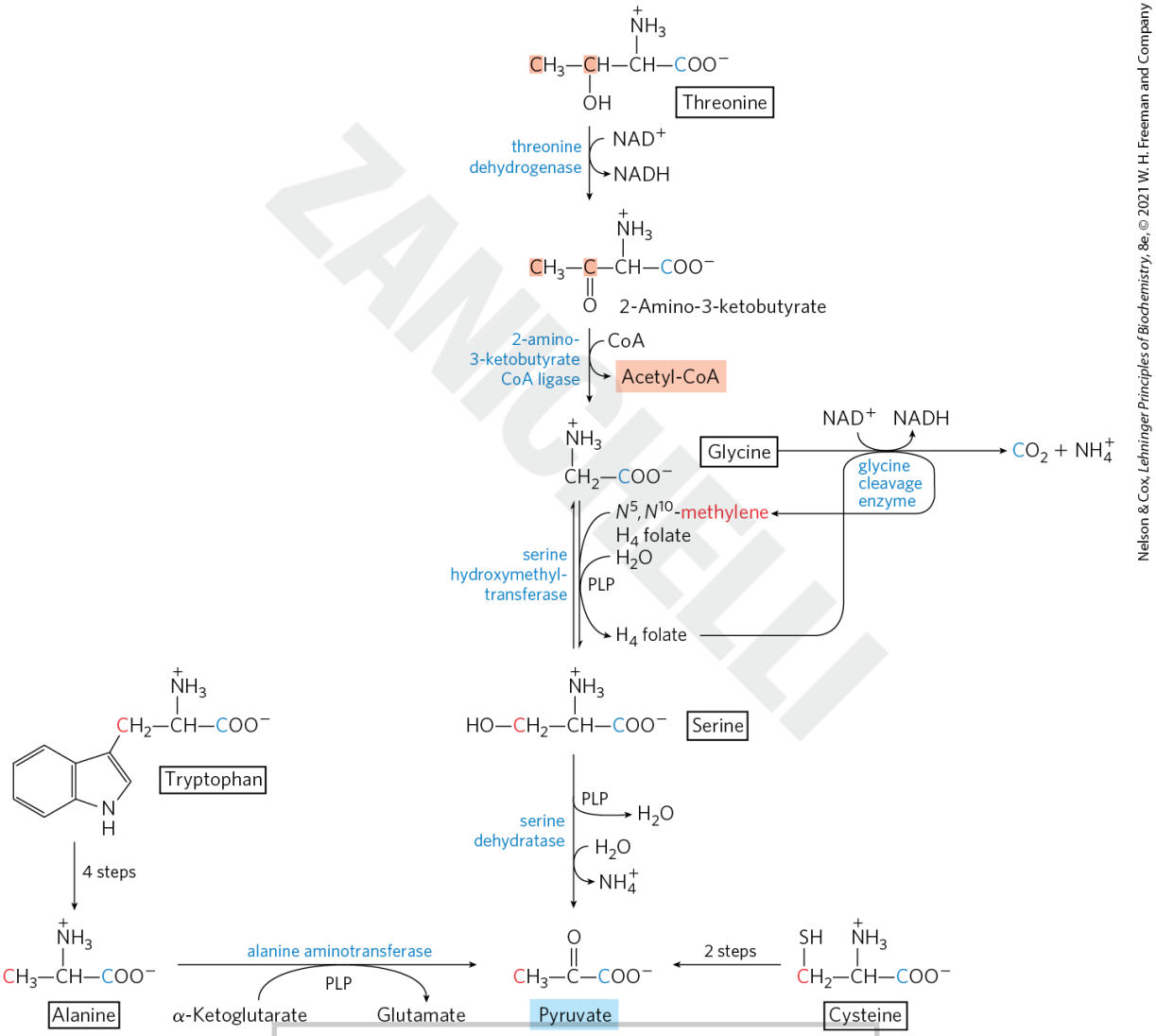
The many paths for amino acid catabolism have two broad parts, one involving the amino groups and the other involving the carbon skeletons. All of the pathways for amino acid degradation include a key step, always involving a pyridoxal phosphate cofactor, in which the *α*-amino group is separated from the carbon skeleton and shunted into the pathways of amino group metabolism. The carbon skeletons are broken down to citric acid cycle intermediates.

Six Amino Acids Are Degraded to Pyruvate

- **alanine**, **tryptophan**, **cysteine**, **serine**, **glycine**, and **threonine** are converted in whole or in part to pyruvate

- pyruvate is either converted to:
  - acetyl-CoA for oxidation via the citric acid cycle
  - oxaloacetate to enter gluconeogenesis

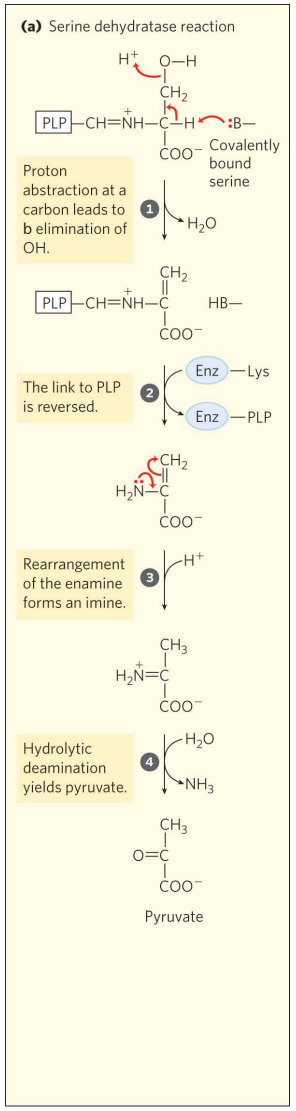
Amino Acid Degradation to Pyruvate



Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

Serine Dehydratase

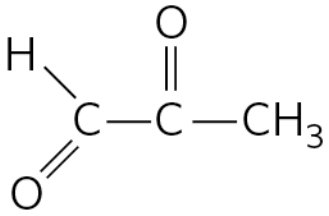
- serine dehydratase = catalyzes the conversion of serine to pyruvate
  - removes both the β-hydroxyl and the α-amino groups of serine
  - pyridoxal phosphate–dependent reaction



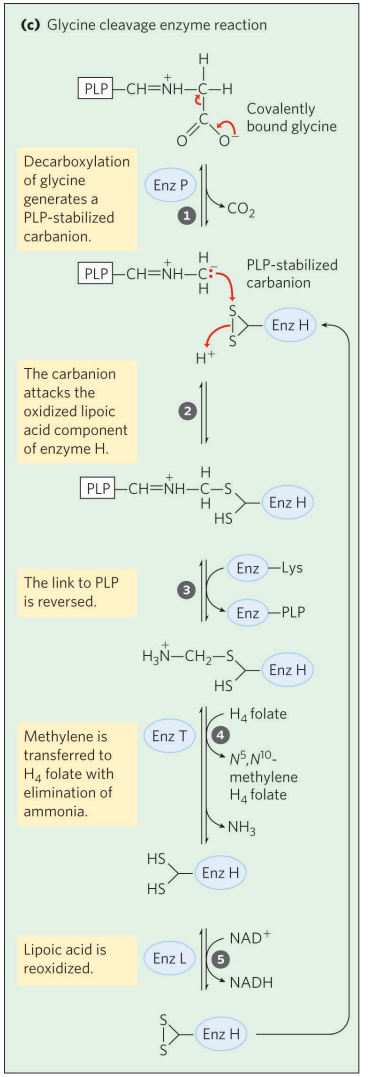
Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

Glycine Degradation by Glycine Cleavage Enzyme

- **glycine cleavage enzyme =** catalyzes the reversible oxidative cleavage of glycine to CO_2, NH_4^+, and a methylene group
  - requires tetrahydrofolate
  - enzymatic defects causes the formation of **methylglyoxal**, which modifies proteins and DNA



Methylglyoxal

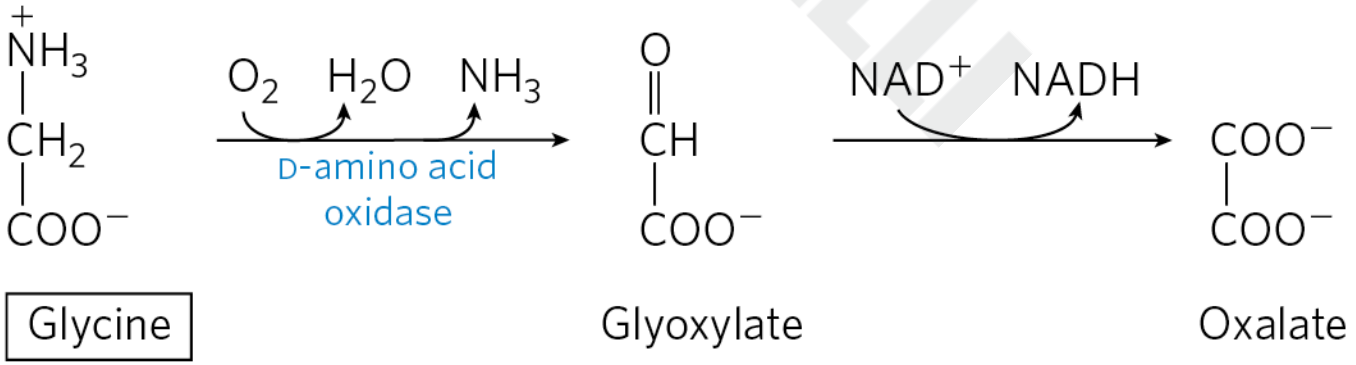


Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

Glycine Degradation by D-Amino Acid Oxidase

- D-amino acid oxidase = catalyzes the conversion of glycine to glyoxylate, which is oxidized to oxalate

- calcium oxalate crystals account for up to 75% of all kidney stones



P1 Principle 1 (7 of 7)

The many paths for amino acid catabolism have two broad parts, one involving the amino groups and the other involving the carbon skeletons. All of the pathways for amino acid degradation include a key step, always involving a pyridoxal phosphate cofactor, in which the *α*-amino group is separated from the carbon skeleton and shunted into the pathways of amino group metabolism. The carbon skeletons are broken down to citric acid cycle intermediates.

P5 Principle 5 (4 of 6)

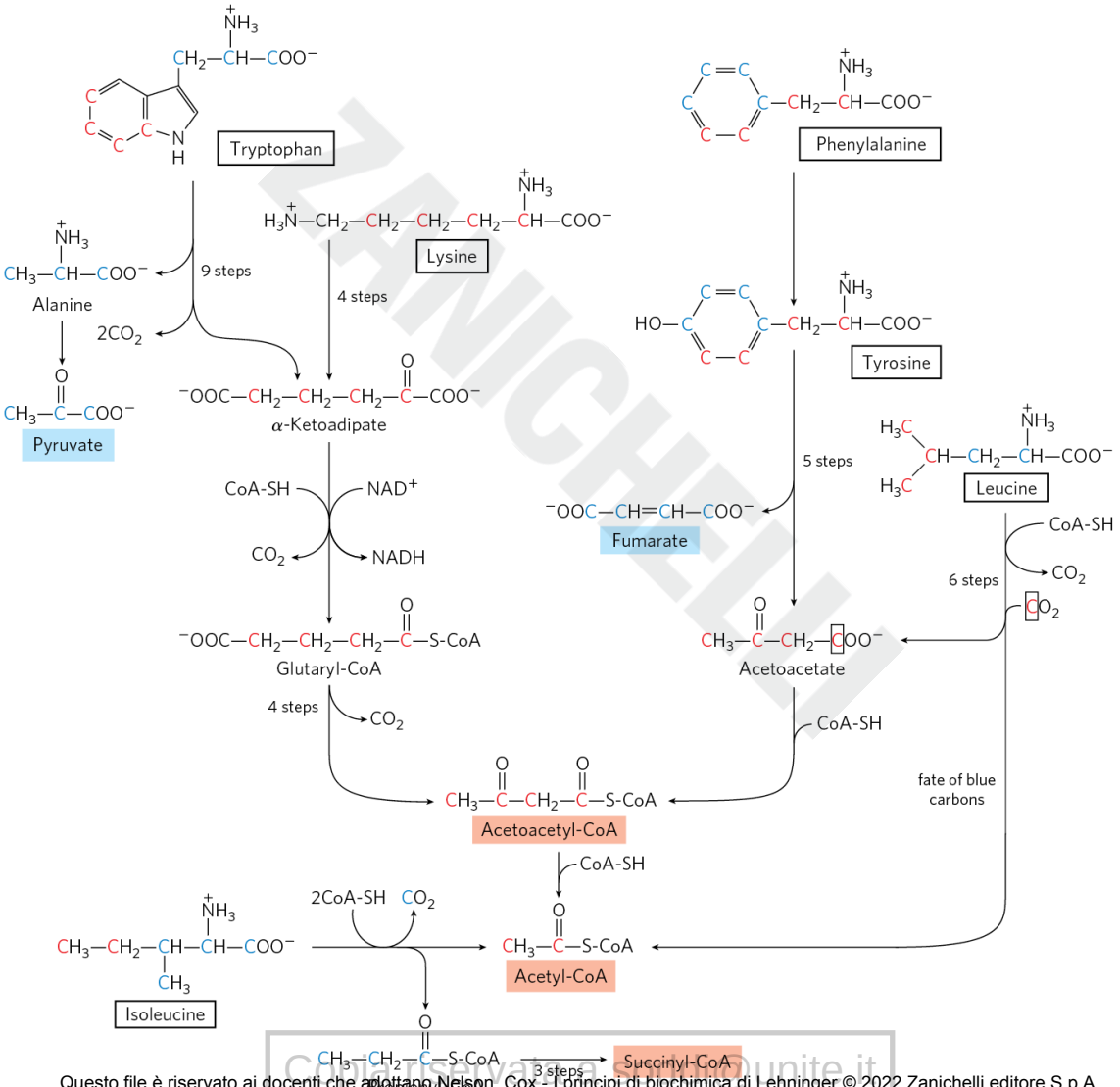
Each amino acid has a different catabolic fate. The varied carbon skeletons of amino acids are broken down via equally varied pathways. All can be oxidized to generate ATP. All but leucine and lysine can contribute to gluconeogenesis when needed.

Seven Amino Acids Are Degraded to Acetyl-CoA

- **leucine**, **lysine**, **phenylalanine**, **tyrosine**, and **tryptophan** yield acetyl-CoA via acetoacetyl-CoA

- **isoleucine**, leucine, **threonine**, and tryptophan form acetyl-CoA directly

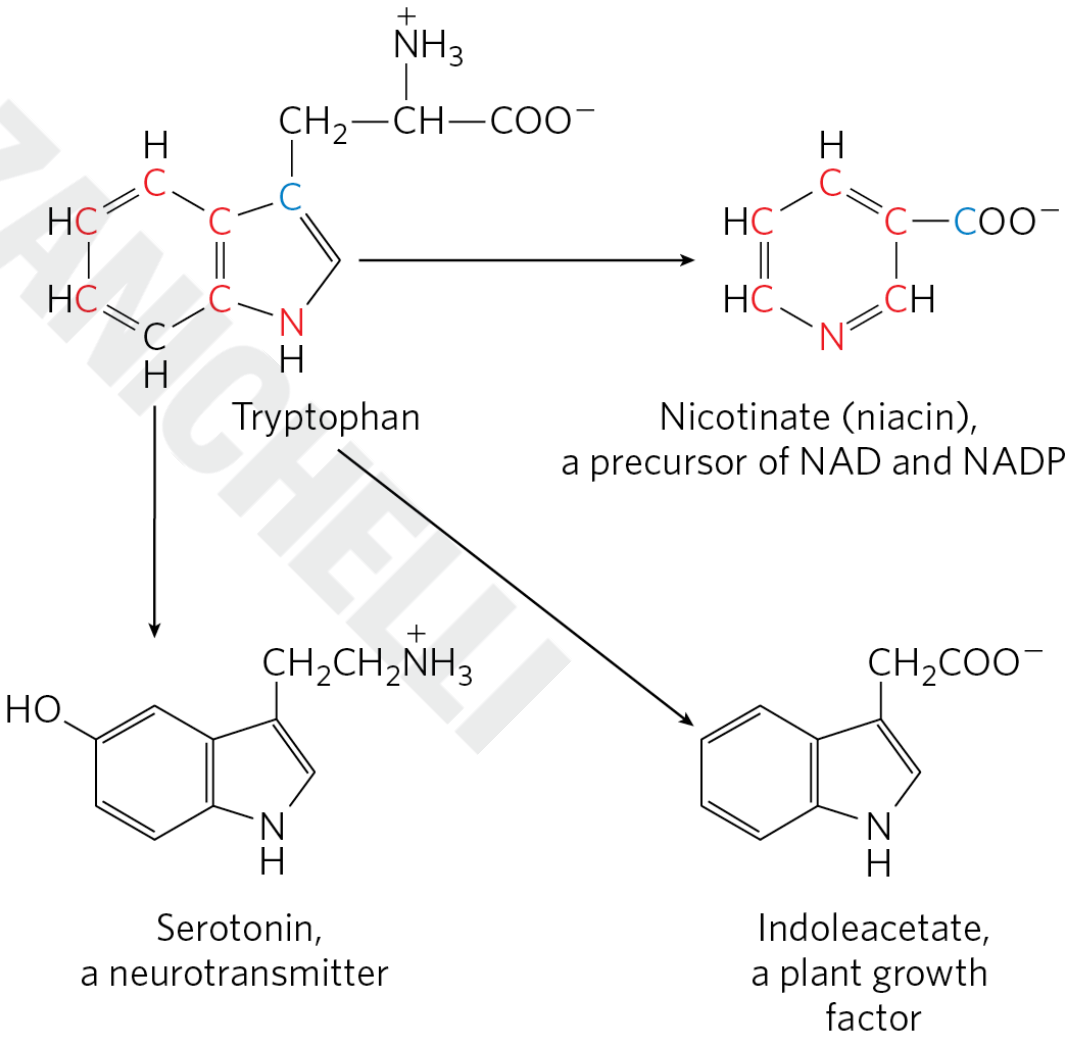
Amino Acid Degradation to Acetyl-CoA



Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

Tryptophan Breakdown

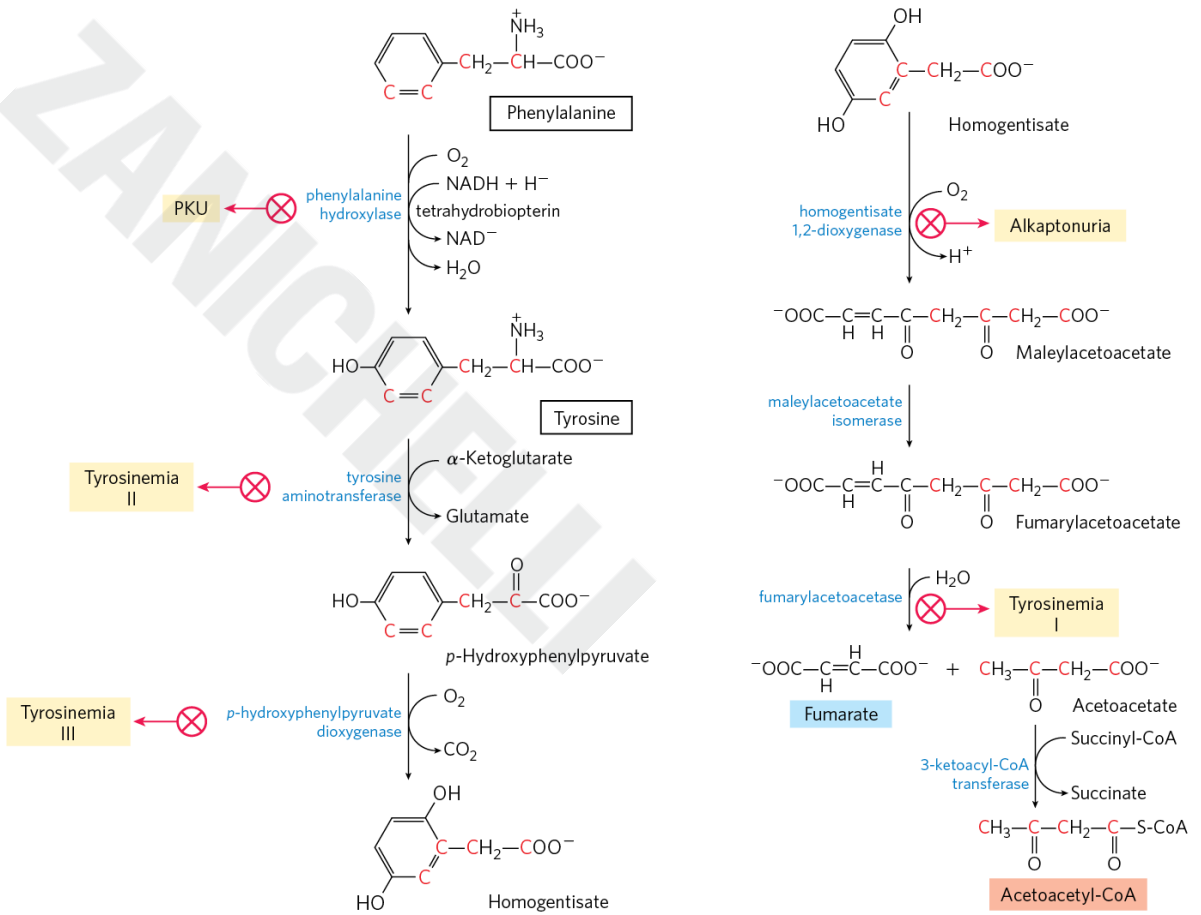
- most complex of all the pathways of amino acid catabolism
- some catabolic intermediates are precursors for the synthesis of other biomolecules



Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

Catabolic Pathways for Phenylalanine and Tyrosine

- phenylalanine and tyrosine are degraded into acetoacetyl-CoA (and thus acetyl-CoA) and fumarate
- genetic defects in pathway enzymes lead to inheritable diseases



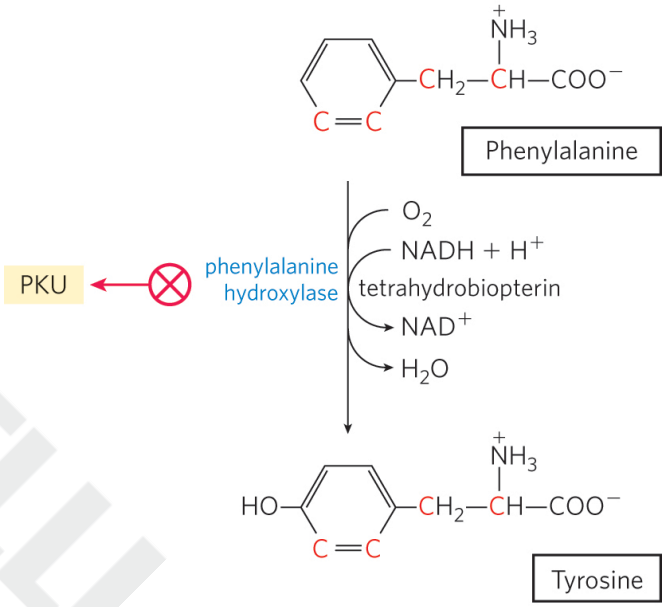
Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

Phenylketonuria (PKU)

- **phenylketonuria (PKU)** = disease caused by a genetic defect in **phenylalanine hydroxylase**
  - most common cause of elevated levels of phenylalanine in the blood
  - treated with dietary intervention

Phenylalanine Hydroxylase

- **phenylalanine hydroxylase** = the first enzyme in the catabolic pathway for phenylalanine
  - requires the cofactor tetrahydrobiopterin
  - part of the **mixed-function oxygenase** enzyme class (catalyzes hydroxylation of a substrate by an oxygen atom of O_2 and reduction of the other oxygen atom to H_2O)

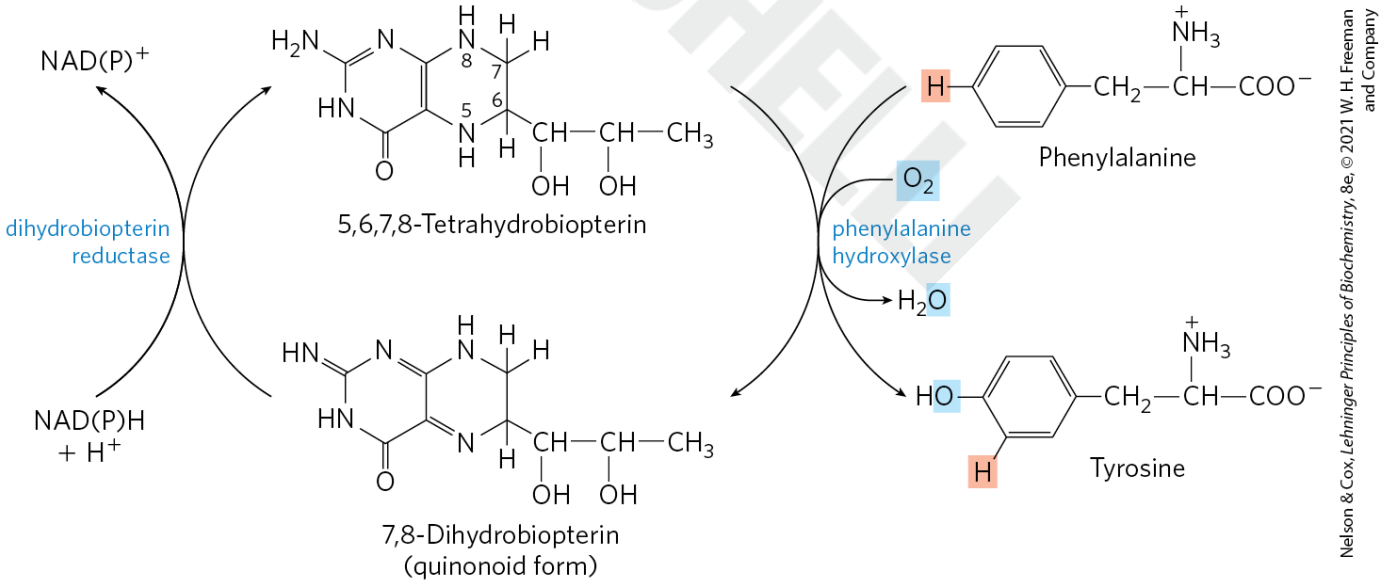


Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

Role of Tetrahydrobiopterin in the Phenylalanine Hydroxylase Reaction

- tetrahydrobiopterin carries electrons from NADPH to O_2 and becomes oxidized to dihydrobiopterin

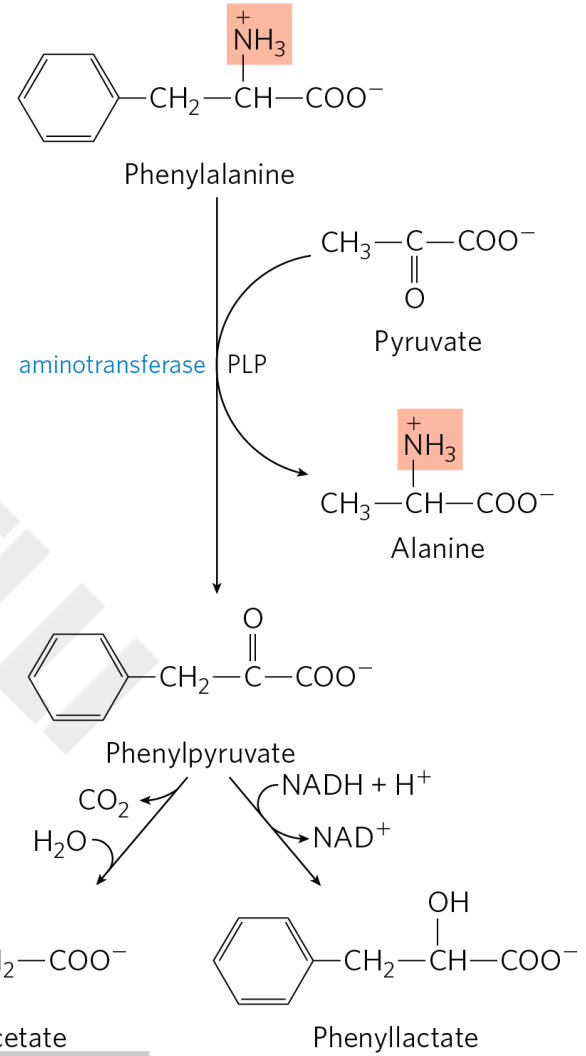
- **dihydrobiopterin reductase** = catalyzes the reduction of dihydrobiopterin to tetrahydrobiopterin



Alternative Pathways for Catabolism of Phenylalanine in PKU

- aminotransferase = catalyzes the transamination of phenylalanine with pyruvate to form **phenylpyruvate**

- phenylpyruvate is decarboxylated or reduced

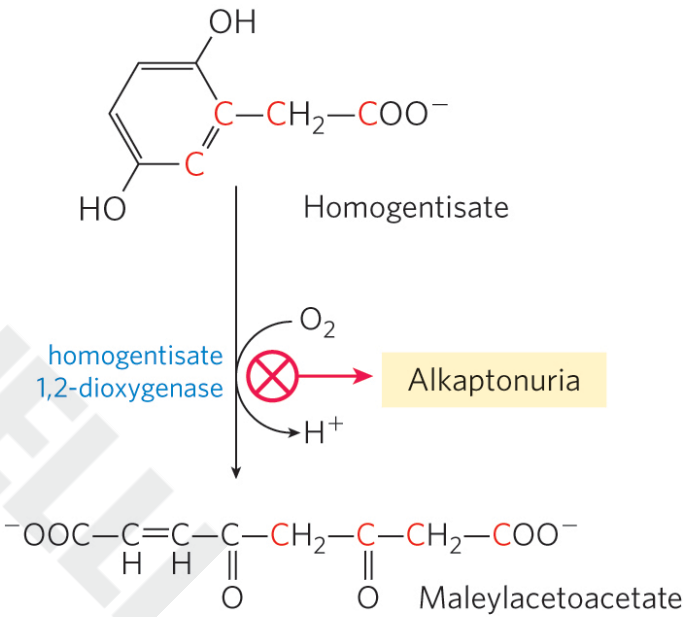


Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

Alkaptonuria

- **alkaptonuria** = disease caused by a genetic defect in **homogentisate dioxygenase**

- large amounts of homogentisate are excreted, and its oxidation turns urine black



Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021
W. H. Freeman and Company

P5 Principle 5 (5 of 6)

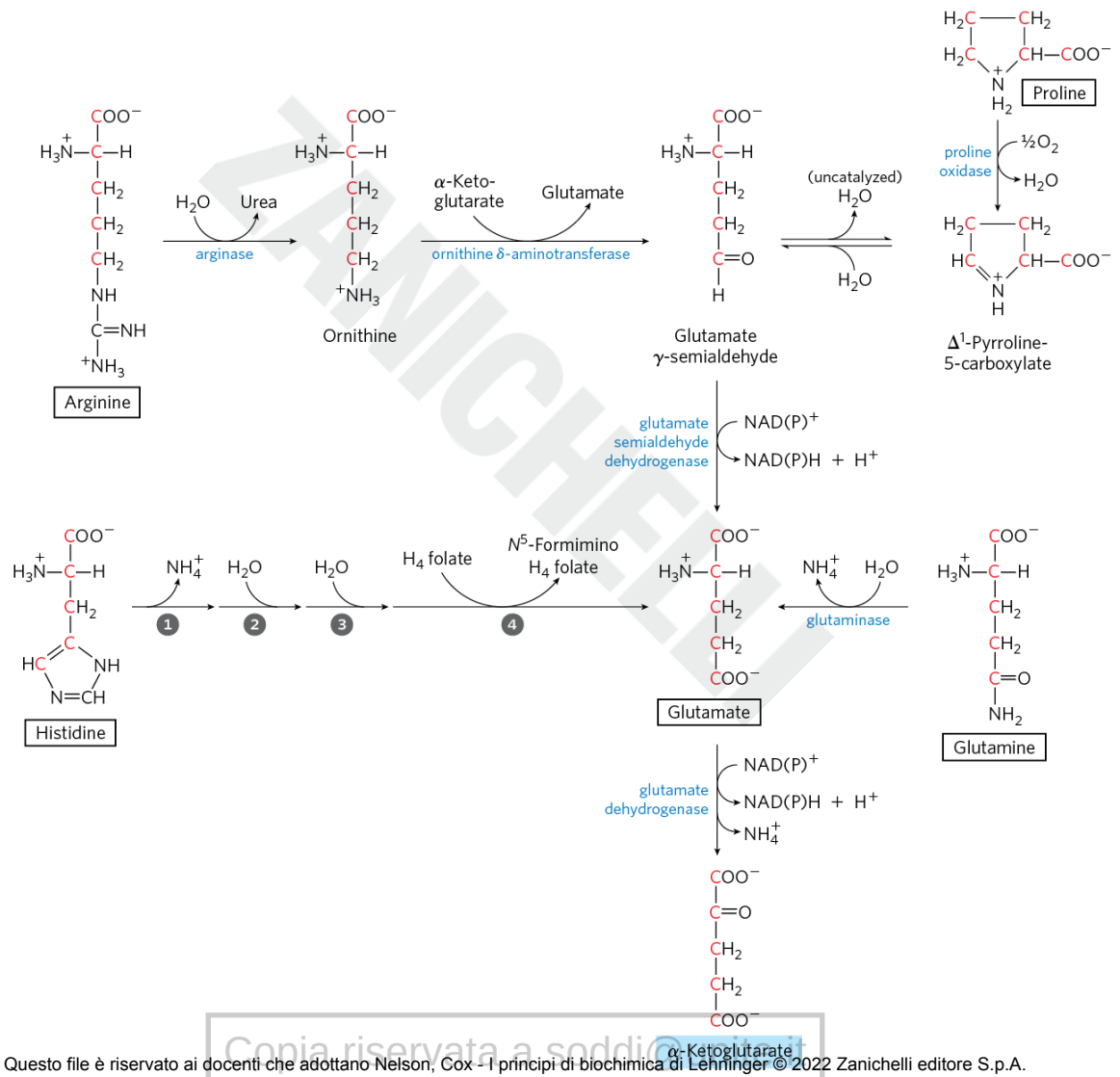
Each amino acid has a different catabolic fate. The varied carbon skeletons of amino acids are broken down via equally varied pathways. All can be oxidized to generate ATP. All but leucine and lysine can contribute to gluconeogenesis when needed.

Five Amino Acids Are Converted to α-Ketoglutarate

- **arginine**, **glutamate**, **glutamine**, **histidine**, and **proline** are degraded to α-ketoglutarate
- proline, arginine, histidine, and glutamine are all converted to glutamate
- glutamate is deaminated to α-ketoglutarate

Amino Acid Degradation to α-Ketoglutarate

arginine degradation is part of the urea cycle



Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

P5 Principle 5 (6 of 6)

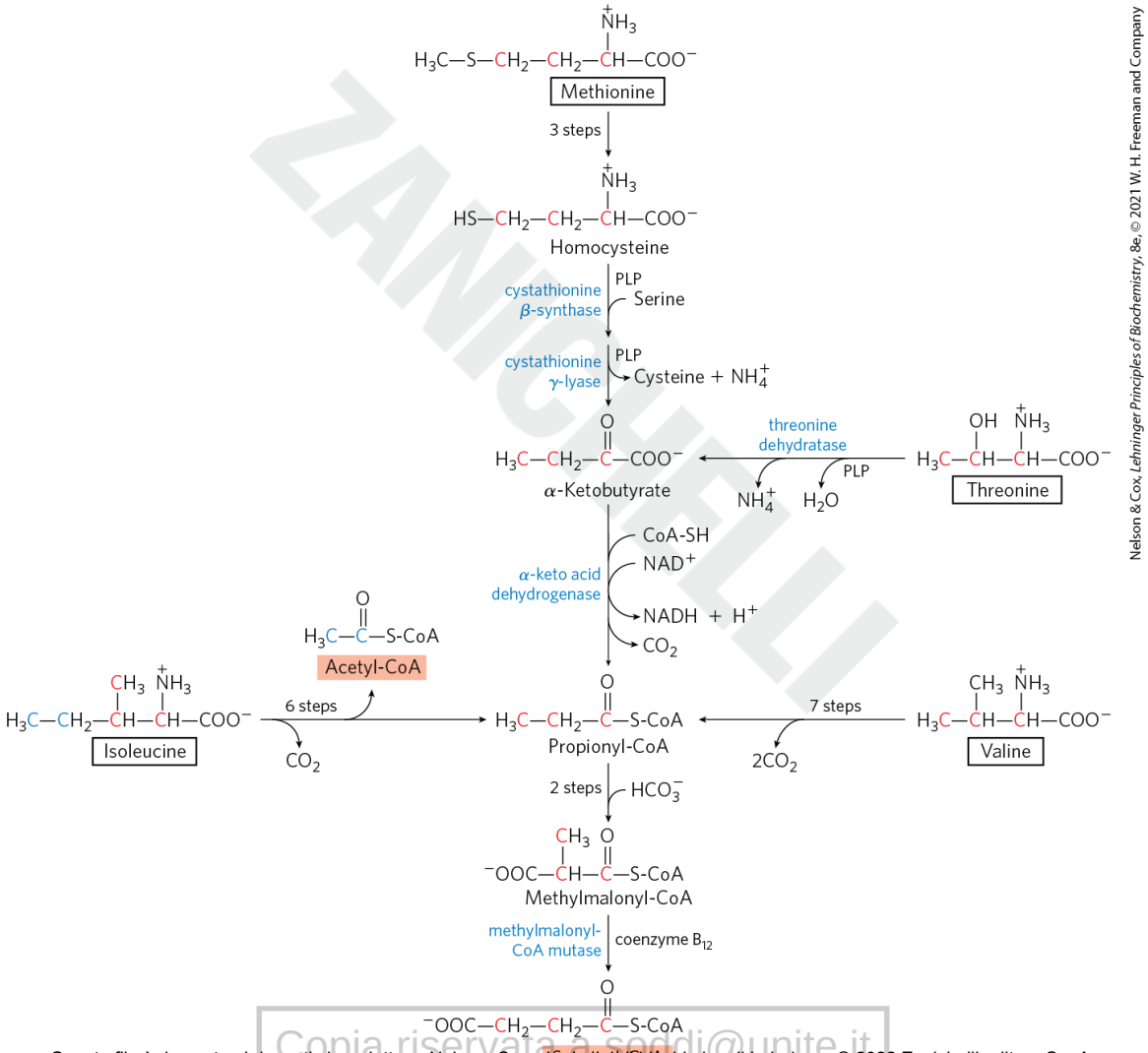
Each amino acid has a different catabolic fate. The varied carbon skeletons of amino acids are broken down via equally varied pathways. All can be oxidized to generate ATP. All but leucine and lysine can contribute to gluconeogenesis when needed.

Four Amino Acids Are Converted to Succinyl-CoA

- **isoleucine**, **methionine**, **threonine**, and **valine** are degraded to succinyl-CoA

- succinyl-CoA is an important intermediate of the citric acid cycle

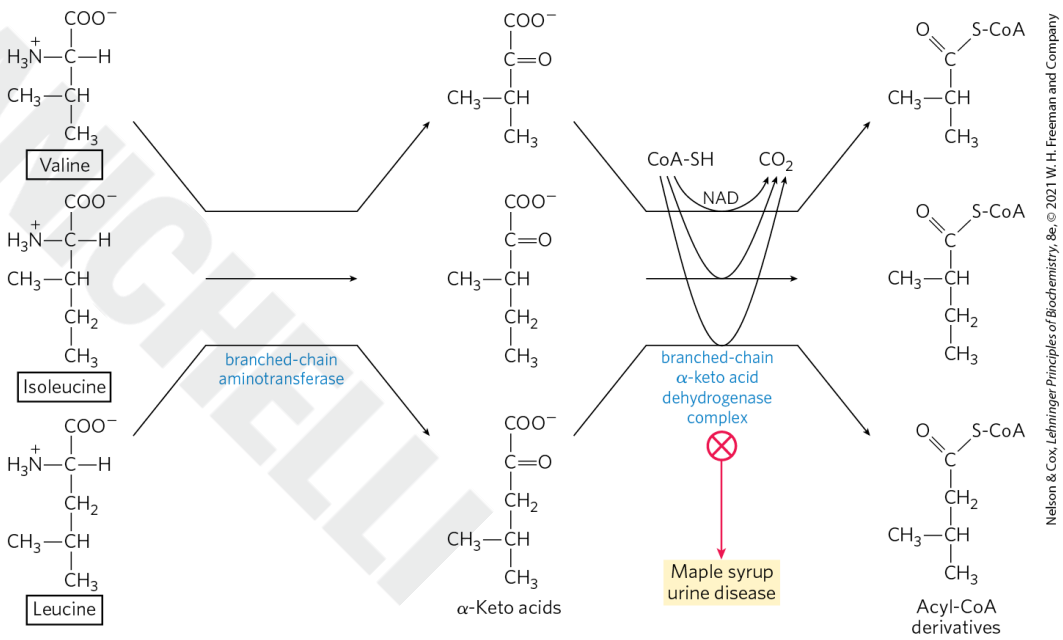
Amino Acid Degradation to Succinyl-CoA



Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

Branched-Chain Amino Acids Are Not Degraded in the Liver

- unlike other amino acids, the branched-chain amino acids (isoleucine, leucine, and valine) are degraded only in extrahepatic tissues (muscle, adipose, kidney, brain)
  - the aminotransferase is absent in liver

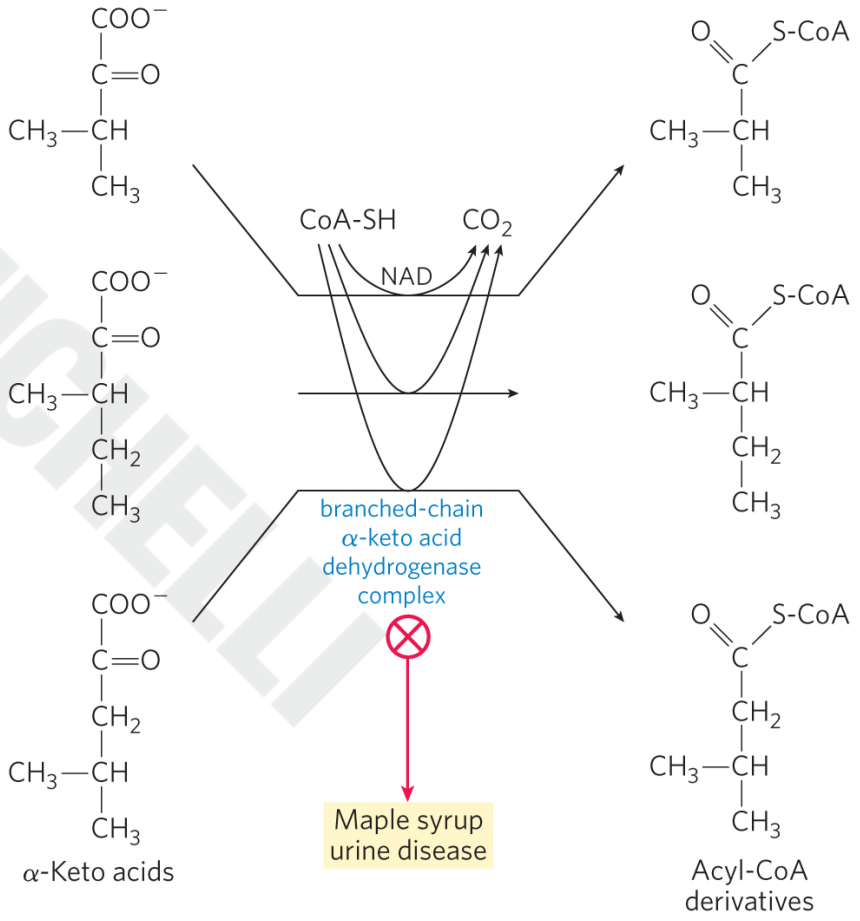


Branched-Chain α-Keto Acid Dehydrogenase Complex

- **branched-chain α-keto acid dehydrogenase complex** = catalyzes oxidative decarboxylation of all three α-keto acids, releasing CO_2 and producing the acyl-CoA derivative
  - regulated by covalent modification in response to the content of branched-chain amino acids in the diet
  - inactive when phosphorylated

Maple Syrup Urine Disease

- **maple syrup urine disease** = condition in which the three branched-chain α-keto acids and their precursor amino acids accumulate in the blood and "spill over" into the urine
  - treated by rigid control of the diet



Nelson & Cox, Lehninger Principles of Biochemistry, 8e, © 2021 W. H. Freeman and Company

Asparagine and Aspartate Are Degraded to Oxaloacetate

- **asparagine** and **aspartate** are degraded to oxaloacetate
- **asparaginase** = catalyzes the hydrolysis of asparagine to aspartate
- **aspartate aminotransferase** = catalyzes the transamination of aspartate with *α*-ketoglutarate to yield glutamate and oxaloacetate