Catabolism of the Carbon Skeletons of Amino Acids

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BIOMEDICAL IMPORTANCE

This chapter considers conversion of the carbon skeletons of the common L-amino acids to amphibolic intermediates and the metabolic diseases or "inborn errors of metabolism" associated with these processes. Left untreated, they can result in irreversible brain damage and early mortality. Prenatal or early postnatal detection and timely initiation of treatment thus are essential. Many of the enzymes concerned can be detected in cultured amniotic fluid cells, which facilitates early diagnosis by amniocentesis. Treatment consists primarily of feeding diets low in the amino acids whose catabolism is impaired. While many changes in the primary structure of enzymes have no adverse effects, others modify the three-dimensional structure of catalytic or regulatory sites, lower catalytic efficiency (lower V_{max} or elevate K_m), or alter the affinity for an allosteric regulator of activity. A variety of mutations thus may give rise to the same clinical signs and symptoms.

TRANSAMINATION TYPICALLY INITIATES AMINO ACID CATABOLISM

Removal of α-amino nitrogen by transamination (see Figure 28–3) is the first catabolic reaction of amino acids except in the case of proline, hydroxyproline, threonine, and lysine. The residual hydrocarbon skeleton is then degraded to amphibolic intermediates as outlined in Figure 30–1.

Asparagine, Aspartate, Glutamine, and Glutamate. All four carbons of asparagine and aspartate form **oxaloacetate** (Figure 30–2, top). Analogous reactions convert glutamine and glutamate to **α-ketoglutarate** (Figure 30–2, bottom). Since the enzymes also fulfill anabolic functions, no metabolic defects are associated with the catabolism of these four amino acids.

Proline. Proline forms dehydroproline, glutamate-γ-semialdehyde, glutamate, and, ultimately, **α-ketoglutarate** (Figure 30–3, top). The metabolic block in **type I hyperprolinemia** is at **proline dehydrogenase.**

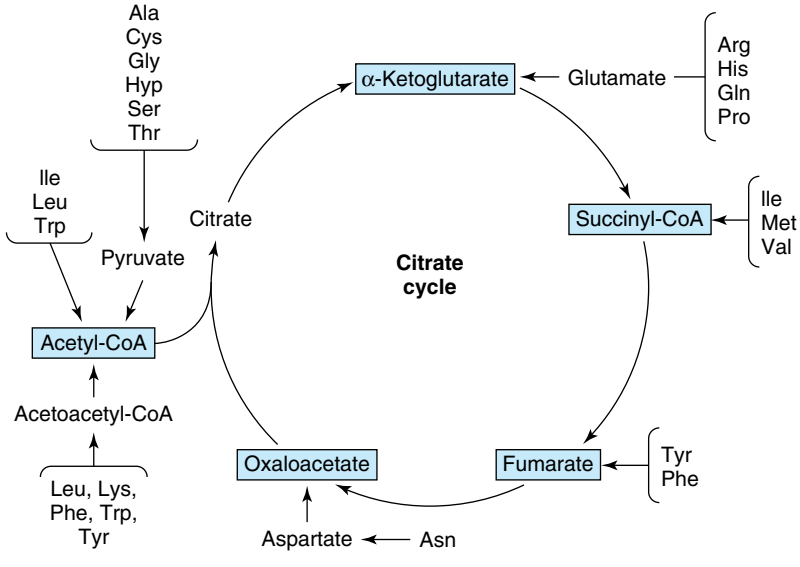

Figure 30–1. Amphibolic intermediates formed from the carbon skeletons of amino acids.

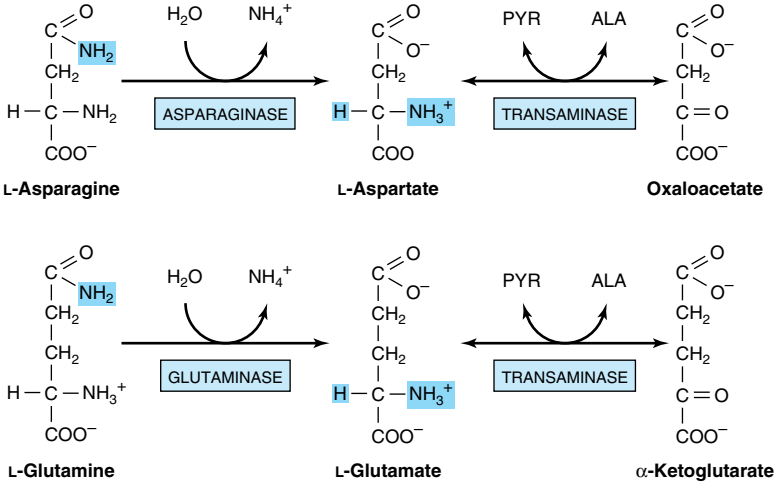

Figure 30–2. Catabolism of L-asparagine (*top*) and of L-glutamine (*bottom*) to amphibolic intermediates. (PYR, pyruvate; ALA, L-alanine.) In this and subsequent figures, color highlights portions of the molecules undergoing chemical change.

There is no associated impairment of hydroxyproline catabolism. The metabolic block in **type II hyperprolinemia** is at **glutamate-γ-semialdehyde dehydrogenase,** which also functions in hydroxyproline catabolism. Both proline and hydroxyproline catabolism thus are affected and Δ^1-pyrroline-3-hydroxy-5-carboxylate (see Figure 30–10) is excreted.

Arginine and Ornithine. Arginine is converted to ornithine, glutamate γ-semialdehyde, and then **α-ketoglutarate** (Figure 30–3, bottom). Mutations in **ornithine δ-aminotransferase** elevate plasma and urinary ornithine and cause **gyrate atrophy of the retina.** Treatment involves restricting dietary arginine. In **hyperornithinemia-hyperammonemia syndrome,** a defective mitochondrial **ornithine-citrulline antiporter** (see Figure 29–9) impairs transport of ornithine into mitochondria for use in urea synthesis.

Histidine. Catabolism of histidine proceeds via urocanate, 4-imidazolone-5-propionate, and *N*-formiminoglutamate (Figlu). Formimino group transfer to tetrahydrofolate forms glutamate, then **α-ketoglutarate** (Figure 30–4). In folic acid deficiency, group transfer is impaired and Figlu is excreted. Excretion of Figlu following a dose of histidine thus has been used to detect folic acid deficiency. Benign disorders of histidine catabolism include **histidinemia** and **urocanic aciduria** associated with impaired **histidase.**

SIX AMINO ACIDS FORM PYRUVATE

All of the carbons of glycine, serine, alanine, and cysteine and two carbons of threonine form pyruvate and subsequently acetyl-CoA.

Glycine. The **glycine synthase complex** of liver mitochondria splits glycine to CO_2 and NH_4^+ and forms N^5,N^{10}-methylene tetrahydrofolate (Figure 30–5).

Glycinuria results from a defect in renal tubular reabsorption. The defect in **primary hyperoxaluria** is the failure to catabolize glyoxylate formed by deamination of glycine. Subsequent oxidation of glyoxylate to oxalate results in urolithiasis, nephrocalcinosis, and early mortality from renal failure or hypertension.

Serine. Following conversion to glycine, catalyzed by **serine hydroxymethyltransferase** (Figure 30–5), serine catabolism merges with that of glycine (Figure 30–6).

Alanine. Transamination of alanine forms pyruvate. Perhaps for the reason advanced under glutamate and aspartate catabolism, there is no known metabolic defect of alanine catabolism. **Cysteine.** Cystine is first reduced to cysteine by **cystine reductase** (Figure 30–7). Two different pathways then convert cysteine to pyruvate (Figure 30–8).

There are numerous abnormalities of cysteine metabolism. Cystine, lysine, arginine, and ornithine are excreted in **cystine-lysinuria (cystinuria),** a defect in renal reabsorption. Apart from cystine calculi, cystinuria is benign. The mixed disulfide of L-cysteine and L-homocysteine (Figure 30–9) excreted by cystinuric patients is more soluble than cystine and reduces formation of cystine calculi. Several metabolic defects result in vitamin B_6-responsive or -unresponsive **homocystinurias.** Defective carrier-mediated transport of cystine results in **cystinosis (cystine storage disease)** with deposition of cystine crystals in tissues and early mortality from acute renal failure. Despite

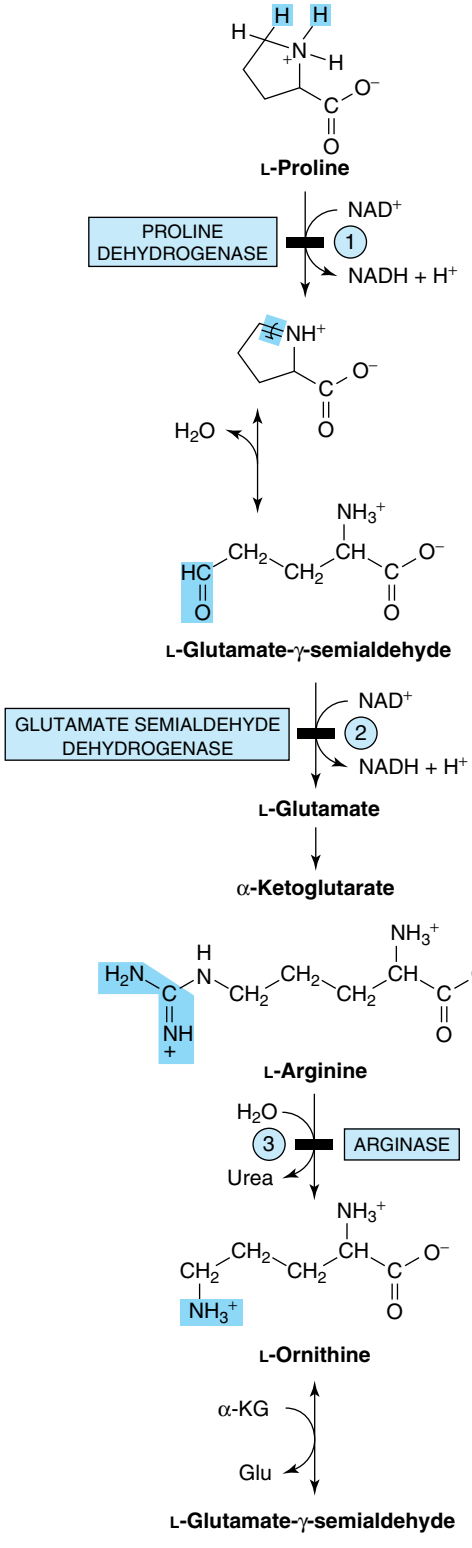

Figure 30–3. **Top:** Catabolism of proline. Numerals indicate sites of the metabolic defects in ① type I and ② type II hyperprolinemias. **Bottom:** Catabolism of arginine. Glutamate-γ-semialdehyde forms α-ketoglutarate as shown above. ③, site of the metabolic defect in hyperargininemia.

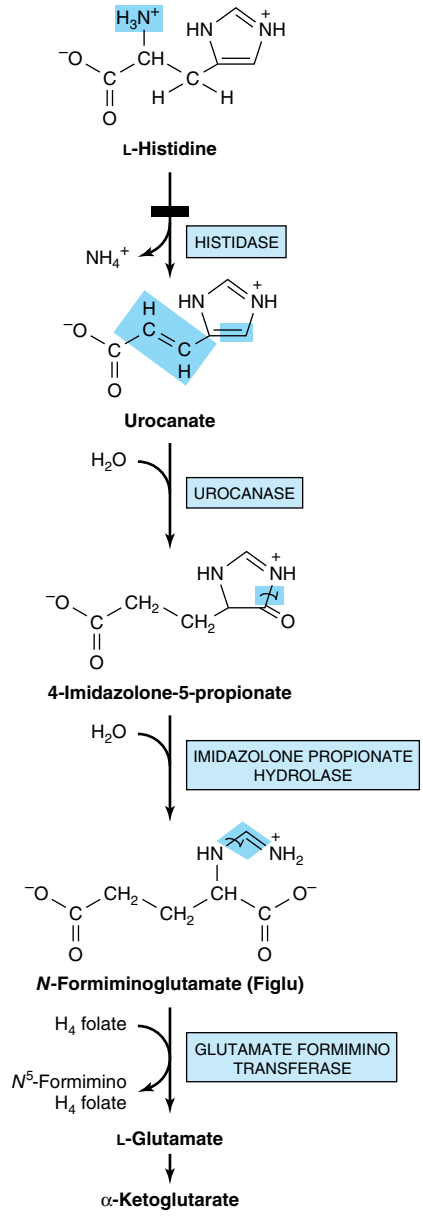

Figure 30–4. Catabolism of L-histidine to α-ketoglutarate. (H_4 folate, tetrahydrofolate.) Histidase is the probable site of the metabolic defect in histidinemia.

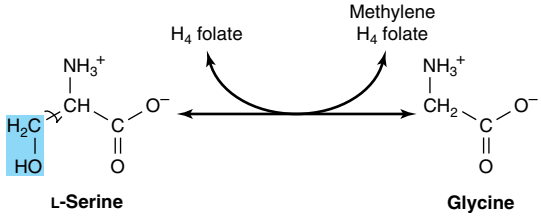

Figure 30–5. Interconversion of serine and glycine catalyzed by serine hydroxymethyltransferase. (H_4 folate, tetrahydrofolate.)

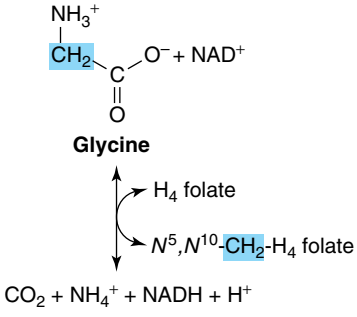

Figure 30–6. Reversible cleavage of glycine by the mitochondrial glycine synthase complex. (PLP, pyridoxal phosphate.)

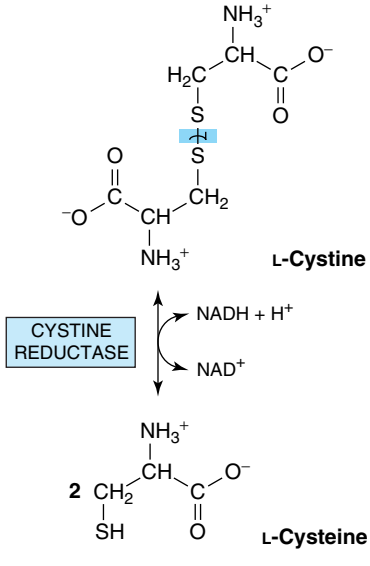

Figure 30–7. The cystine reductase reaction.

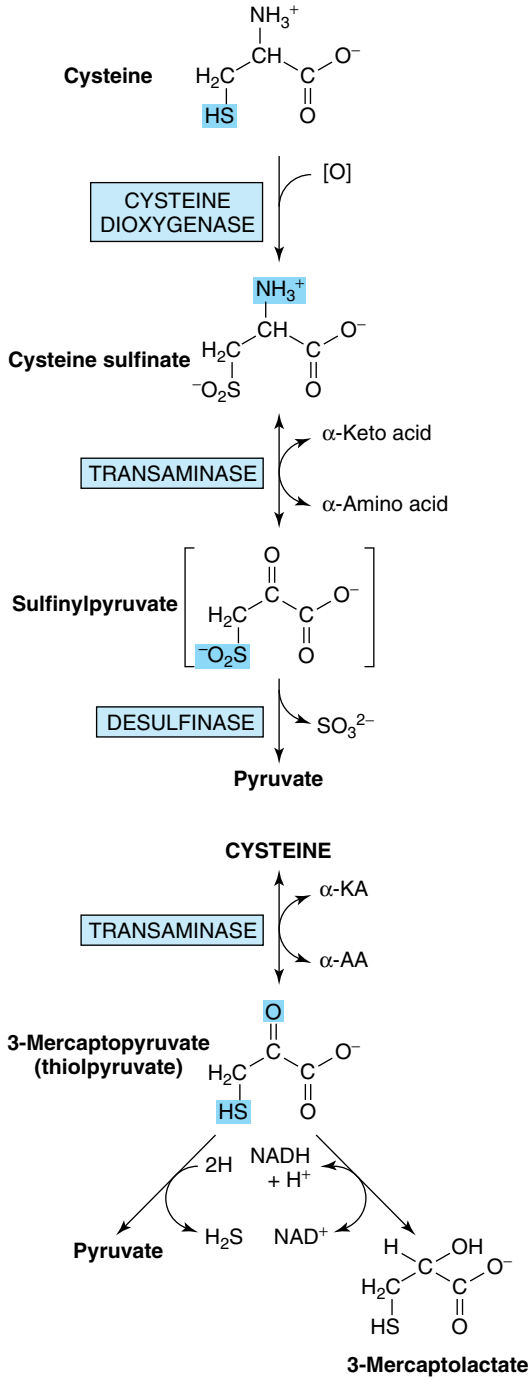

Figure 30–8. Catabolism of L-cysteine via the cysteine sulfinate pathway *(top)* and by the 3-mercaptopyruvate pathway *(bottom)*.

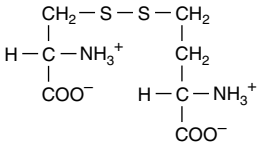

Figure 30–9. Mixed disulfide of cysteine and homocysteine.

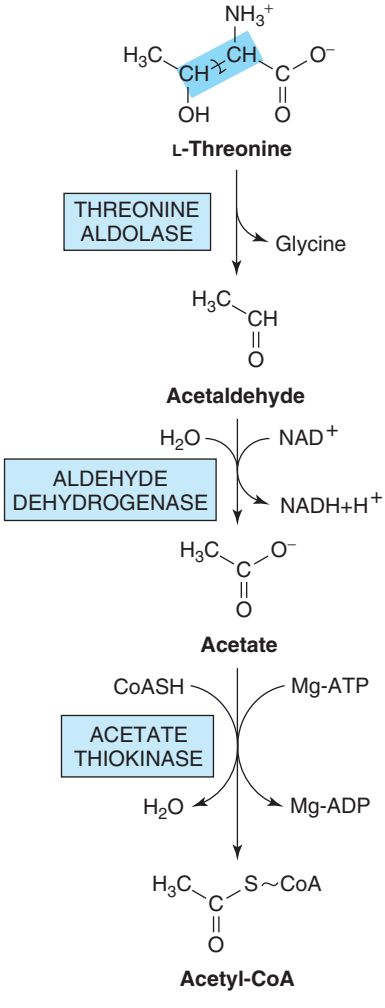

Figure 30–10. Conversion of threonine to glycine (see Figure 30–6) and acetyl-CoA.

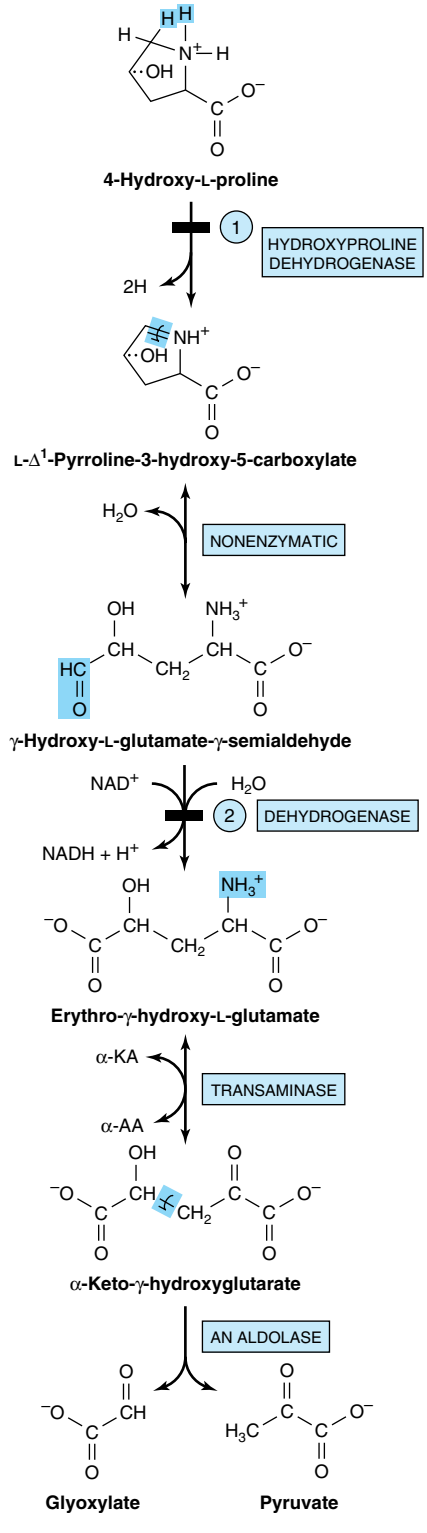

Figure 30–11. Intermediates in L-hydroxyproline catabolism. (α-KA, α-keto acid; α-AA, α-amino acid.) Numerals identify sites of metabolic defects in ① hyperhydroxyprolinemia and ② type II hyperprolinemia.

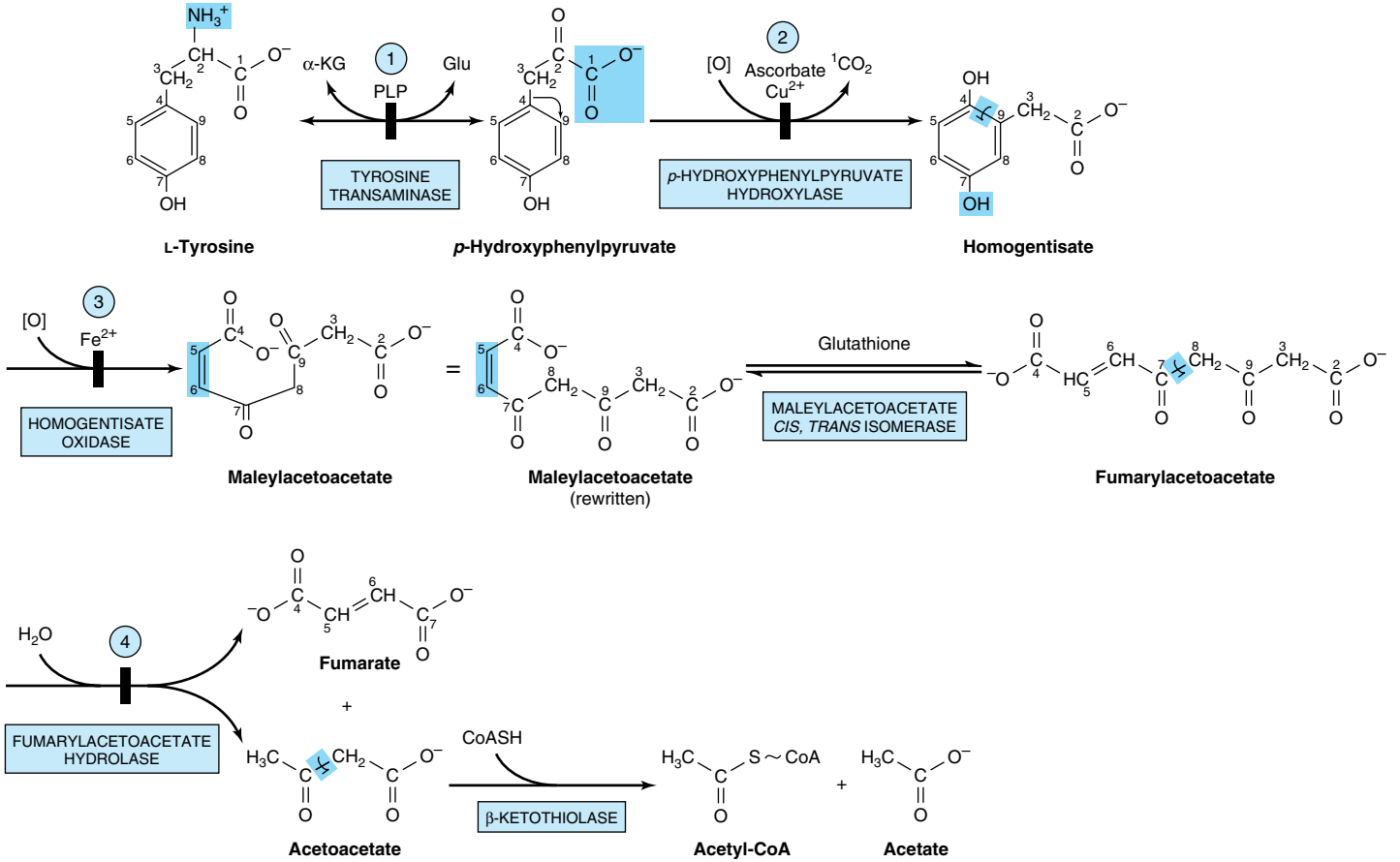

Figure 30–12. Intermediates in tyrosine catabolism. Carbons are numbered to emphasize their ultimate fate. (α-KG, α-ketoglutarate; Glu, glutamate; PLP, pyridoxal phosphate.) Circled numerals represent the probable sites of the metabolic defects in ① type II tyrosinemia; ② neonatal tyrosinemia; ③ alkaptonuria; and ④ type I tyrosinemia, or tyrosinosis.

epidemiologic data suggesting a relationship between plasma homocysteine and cardiovascular disease, whether homocysteine represents a causal cardiovascular risk factor remains controversial.

Threonine. Threonine is cleaved to acetaldehyde and glycine. Oxidation of acetaldehyde to acetate is followed by formation of acetyl-CoA (Figure 30–10). Catabolism of glycine is discussed above.

4-Hydroxyproline. Catabolism of 4-hydroxy-L-proline forms, successively, L-Δ^1-pyrroline-3-hydroxy-5-carboxylate, γ-hydroxy-L-glutamate-γ-semialdehyde, erythro-γ-hydroxy-L-glutamate, and α-keto-γ-hydroxyglutarate. An aldol-type cleavage then forms glyoxylate plus pyruvate (Figure 30–11). A defect in **4-hydroxyproline dehydrogenase** results in **hyperhydroxyprolinemia,** which is benign. There is no associated impairment of proline catabolism.

TWELVE AMINO ACIDS FORM ACETYL-CoA

Tyrosine. Figure 30–12 diagrams the conversion of tyrosine to amphibolic intermediates. Since ascorbate is the reductant for conversion of *p*-hydroxyphenylpyruvate to homogentisate, scorbutic patients excrete incompletely oxidized products of tyrosine catabolism. Subsequent catabolism forms maleylacetoacetate, fumarylacetoacetate, fumarate, acetoacetate, and ultimately **acetyl-CoA.**

The probable metabolic defect in **type I tyrosinemia (tyrosinosis)** is at **fumarylacetoacetate hydrolase** (reaction 4, Figure 30–12). Therapy employs a diet low in tyrosine and phenylalanine. Untreated acute and chronic tyrosinosis leads to death from liver failure. Alternate metabolites of tyrosine are also excreted in **type II tyrosinemia (Richner-Hanhart syndrome),** a defect in **tyrosine aminotransferase** (reaction 1, Figure 30–12), and in **neonatal tyrosinemia,** due to lowered *p*-hydroxyphenylpyruvate hydroxylase activity (reaction 2, Figure 30–12). Therapy employs a diet low in protein.

Alkaptonuria was first described in the 16th century. Characterized in 1859, it provided the basis for Garrod's classic ideas concerning heritable metabolic disorders. The defect is lack of **homogentisate oxidase** (reaction 3, Figure 30–12). The urine darkens on exposure to air due to oxidation of excreted homogentisate. Late in the disease, there is arthritis and connective tissue pigmentation (ochronosis) due to oxidation of homogentisate to benzoquinone acetate, which polymerizes and binds to connective tissue.

Phenylalanine. Phenylalanine is first converted to tyrosine (see Figure 28–10). Subsequent reactions are those of tyrosine (Figure 30–12). **Hyperphenylalaninemias** arise from defects in phenylalanine hydroxylase itself (**type I, classic phenylketonuria** or **PKU**), in dihydrobiopterin reductase (**types II and III**), or in dihydrobiopterin biosynthesis (**types IV and V**) (Figure 28–10). Alternative catabolites are excreted (Figure 30–13). DNA probes facilitate prenatal diagnosis of defects in phenylalanine hydroxylase or dihydrobiopterin reductase. A diet low in phenylalanine can prevent the mental retardation of PKU (frequency 1:10,000

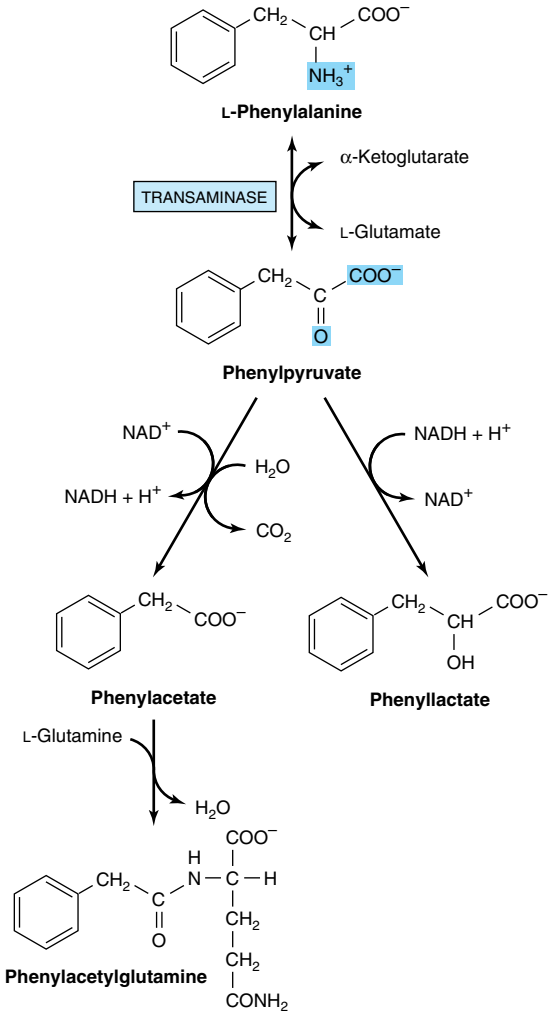

Figure 30–13. Alternative pathways of phenylalanine catabolism in phenylketonuria. The reactions also occur in normal liver tissue but are of minor significance.

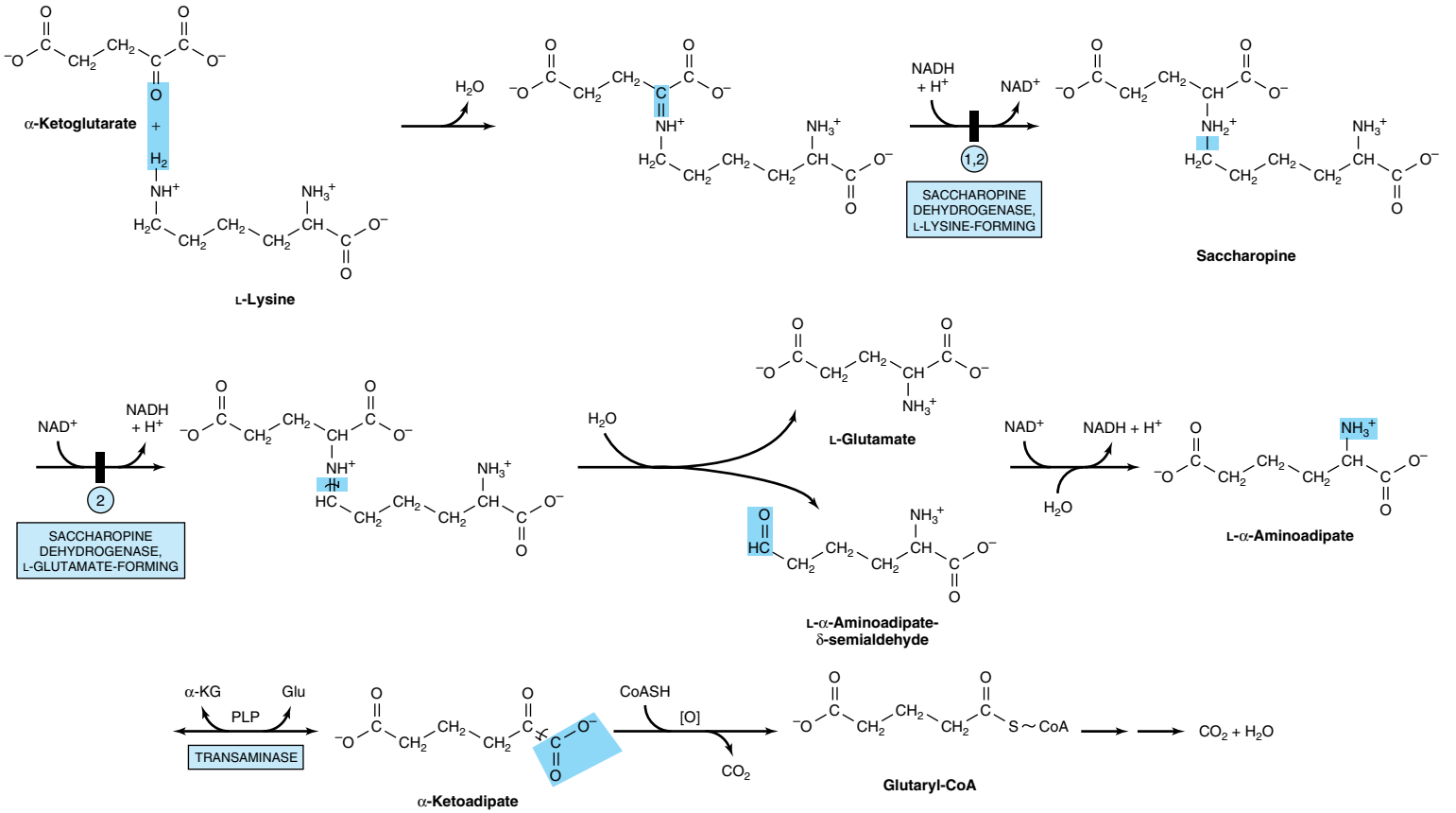

Figure 30–14. Catabolism of L-lysine. (α-KG, α-ketoglutarate; Glu, glutamate; PLP, pyridoxal phosphate.) Circled numerals indicate the probable sites of the metabolic defects in ① periodic hyperlysinemia with associated hyperammonemia; and ② persistent hyperlysinemia without associated hyperammonemia.

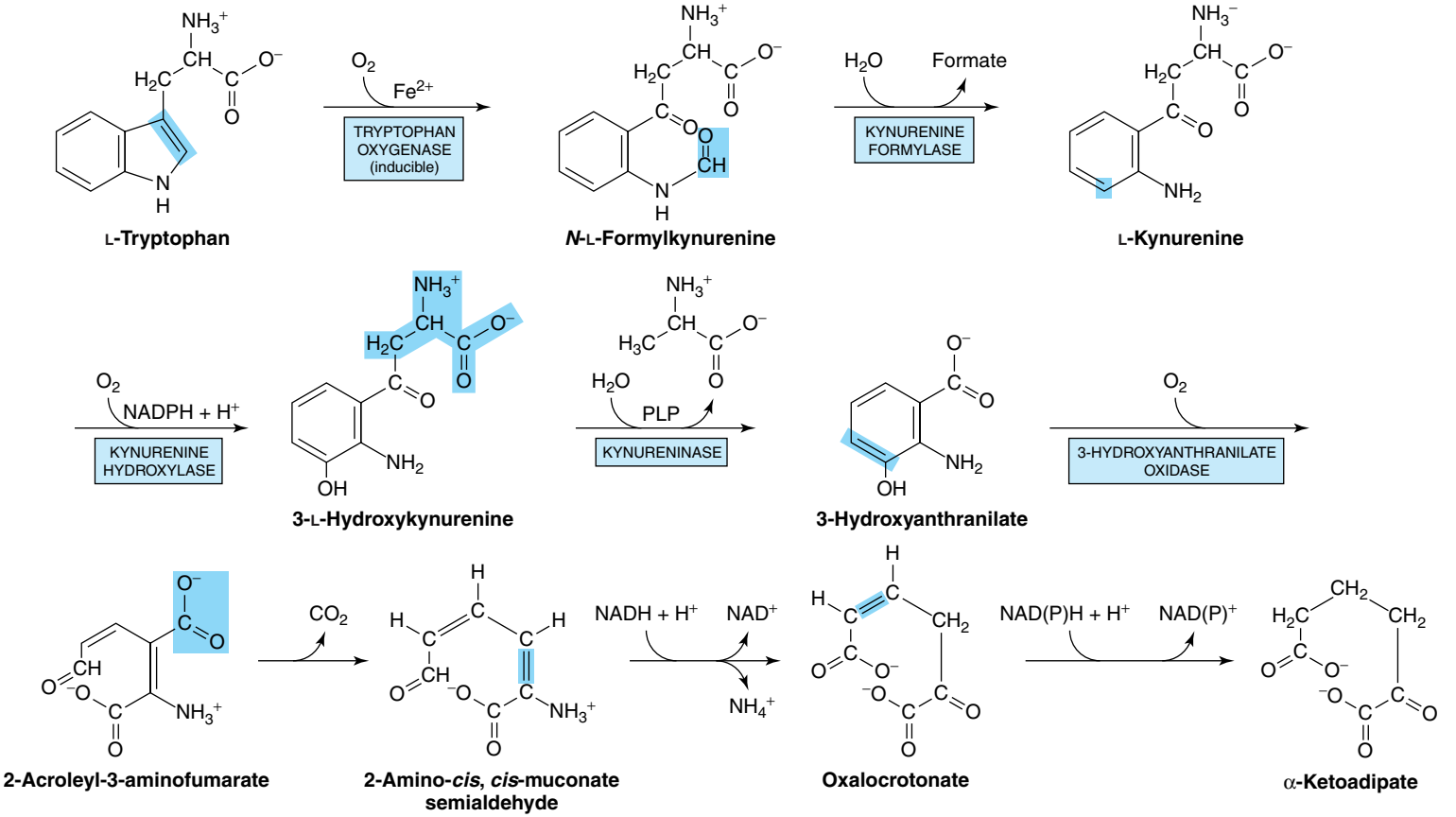

Figure 30–15. Catabolism of L-tryptophan. (PLP, pyridoxal phosphate.)

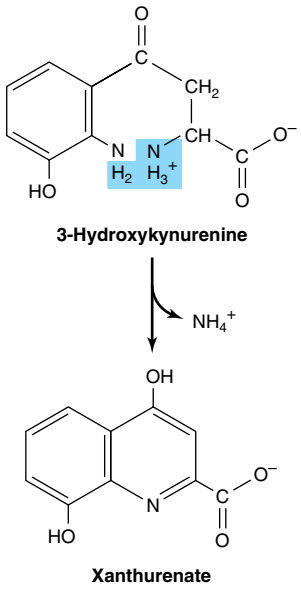

Figure 30–16. Formation of xanthurenate in vitamin B_6 deficiency. Conversion of the tryptophan metabolite 3-hydroxykynurenine to 3-hydroxyanthranilate is impaired (see Figure 30–15). A large portion is therefore converted to xanthurenate.

births). Elevated blood phenylalanine may not be detectable until 3–4 days postpartum. False-positives in premature infants may reflect delayed maturation of enzymes of phenylalanine catabolism. A less reliable screening test employs $FeCl_3$ to detect urinary phenylpyruvate. $FeCl_3$ screening for PKU of the urine of newborn infants is compulsory in the United States and many other countries.

Lysine. Figure 30–14 summarizes the catabolism of lysine. Lysine first forms a Schiff base with α-ketoglutarate, which is reduced to **saccharopine.** In one form of **periodic hyperlysinemia**, elevated lysine competitively inhibits liver **arginase** (see Figure 29–9), causing hyperammonemia. Restricting dietary lysine relieves the ammonemia, whereas ingestion of a lysine load precipitates severe crises and coma. In a different **periodic hyperlysinemia,** lysine catabolites accumulate, but even a lysine load does not trigger hyperammonemia. In addition to impaired synthesis of saccharopine, some patients cannot cleave saccharopine.

Tryptophan. Tryptophan is degraded to amphibolic intermediates via the kynurenine-anthranilate pathway (Figure 30–15). **Tryptophan oxygenase (tryptophan pyrrolase)** opens the indole ring, incorporates molecular oxygen, and forms *N*-formylkynurenine. An iron porphyrin metalloprotein that is inducible in liver by adrenal corticosteroids and by tryptophan, tryptophan oxygenase is feedback-inhibited by nicotinic acid derivatives, including NADPH. Hydrolytic removal of the formyl group of *N*-formylkynurenine, catalyzed by **kynurenine formylase,** produces kynurenine. Since **kynureninase** requires pyridoxal phosphate, excretion of xanthurenate (Figure 30–16) in response to a tryptophan load is diagnostic of vitamin B_6 deficiency. **Hartnup disease** reflects impaired intestinal and renal transport of tryptophan and other neutral amino acids. Indole derivatives of unabsorbed tryptophan formed by intestinal bacteria are excreted. The defect limits tryptophan availability for niacin biosynthesis and accounts for the pellagra-like signs and symptoms.

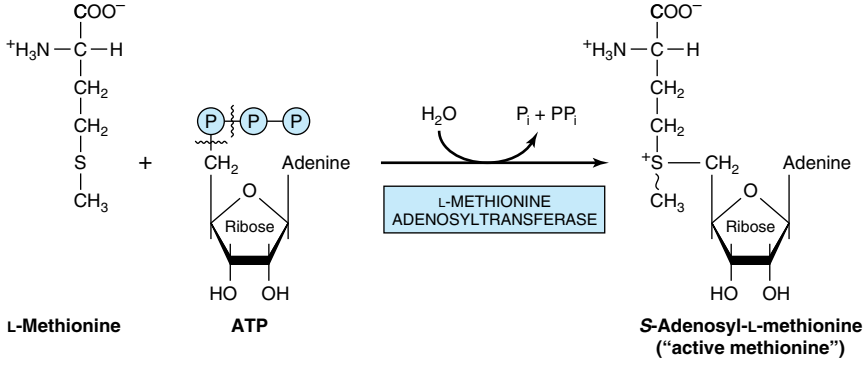

Figure 30–17. Formation of *S*-adenosylmethionine. ~CH_3 represents the high group transfer potential of "active methionine."

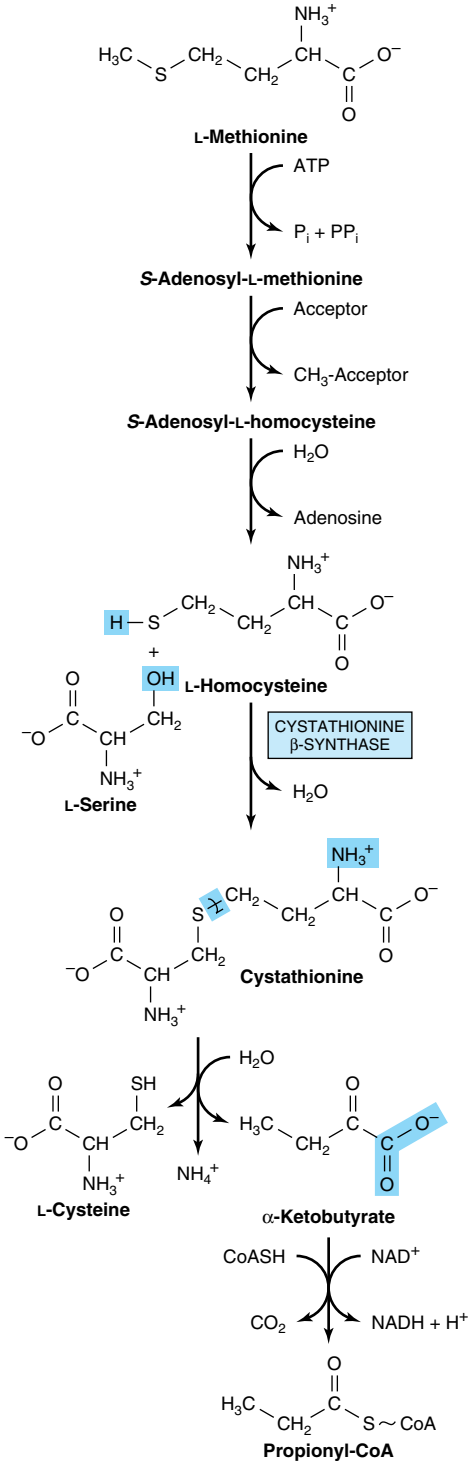

Figure 30–18. Conversion of methionine to propionyl-CoA.

Methionine. Methionine reacts with ATP forming *S*-adenosylmethionine, "active methionine" (Figure 30–17). Subsequent reactions form propionyl-CoA (Figure 30–18) and ultimately succinyl-CoA (see Figure 19–2).

THE INITIAL REACTIONS ARE COMMON TO ALL THREE BRANCHED-CHAIN AMINO ACIDS

Reactions 1–3 of Figure 30–19 are analogous to those of fatty acid catabolism. Following transamination, all three α-keto acids undergo oxidative decarboxylation catalyzed by mitochondrial **branched-chain α-keto acid dehydrogenase.** This multimeric enzyme complex of a decarboxylase, a transacylase, and a dihydrolipoyl dehydrogenase closely resembles pyruvate dehydrogenase (see Figure 17–5). Its regulation also parallels that of pyruvate dehydrogenase, being inactivated by phosphorylation and reactivated by dephosphorylation (see Figure 17–6).

Reaction 3 is analogous to the dehydrogenation of fatty acyl-CoA thioesters (see Figure 22–3). In **isovaleric acidemia,** ingestion of protein-rich foods elevates isovalerate, the deacylation product of isovaleryl-CoA. Figures 30–20, 30–21, and 30–22 illustrate the subsequent reactions unique to each amino acid skeleton.

METABOLIC DISORDERS OF BRANCHED-CHAIN AMINO ACID CATABOLISM

As the name implies, the odor of urine in **maple syrup urine disease (branched-chain ketonuria)** suggests maple syrup or burnt sugar. The biochemical defect involves the **α-keto acid decarboxylase complex** (reaction 2, Figure 30–19). Plasma and urinary levels of leucine, isoleucine, valine, α-keto acids, and α-hydroxy acids (reduced α-keto acids) are elevated. The mechanism of toxicity is unknown. Early diagnosis, especially prior to 1 week of age, employs enzymatic analysis. Prompt replacement of dietary protein by an amino acid mixture that lacks leucine, isoleucine, and valine averts brain damage and early mortality.

Mutation of the dihydrolipoate reductase component impairs decarboxylation of branched-chain α-keto acids, of pyruvate, and of α-ketoglutarate. In **intermittent branched-chain ketonuria,** the α-keto acid decarboxylase retains some activity, and symptoms occur later in life. The impaired enzyme in **isovaleric acidemia** is **isovaleryl-CoA dehydrogenase** (reaction 3, Figure 30–19). Vomiting, acidosis, and coma follow ingestion of excess protein. Accumulated

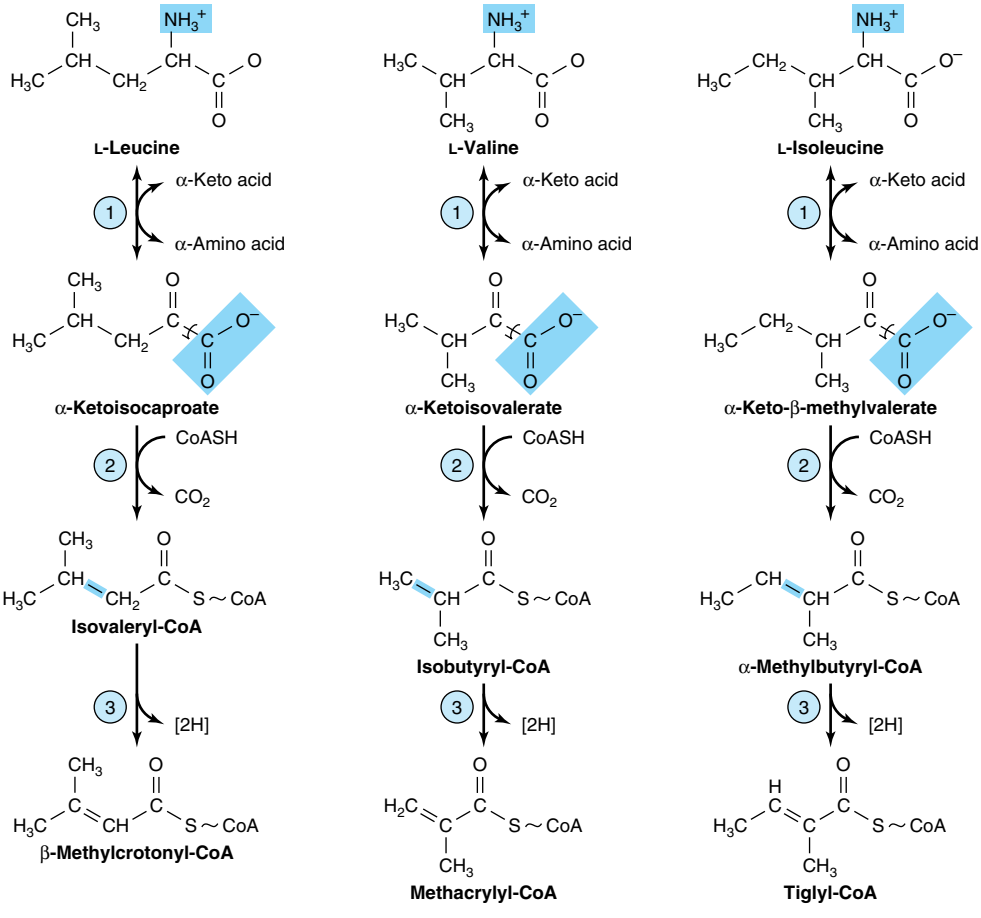

Figure 30–19. The analogous first three reactions in the catabolism of leucine, valine, and isoleucine. Note also the analogy of reactions ② and ③ to reactions of the catabolism of fatty acids (see Figure 22–3). The analogy to fatty acid catabolism continues, as shown in subsequent figures.

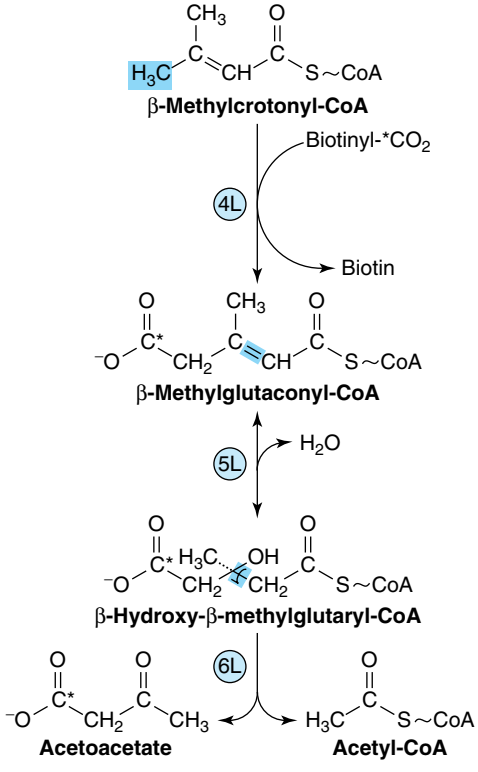

Figure 30–20. Catabolism of the β-methylcrotonyl-CoA formed from L-leucine. Asterisks indicate carbon atoms derived from CO_2.

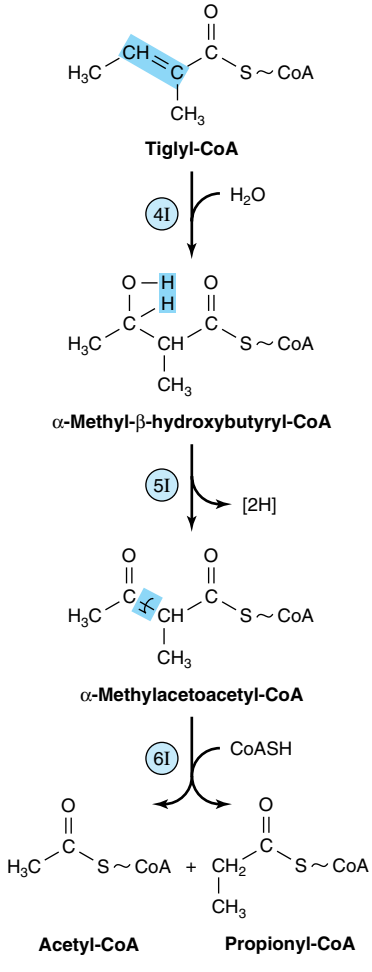

Figure 30–21. Subsequent catabolism of the tiglyl-CoA formed from L-isoleucine.

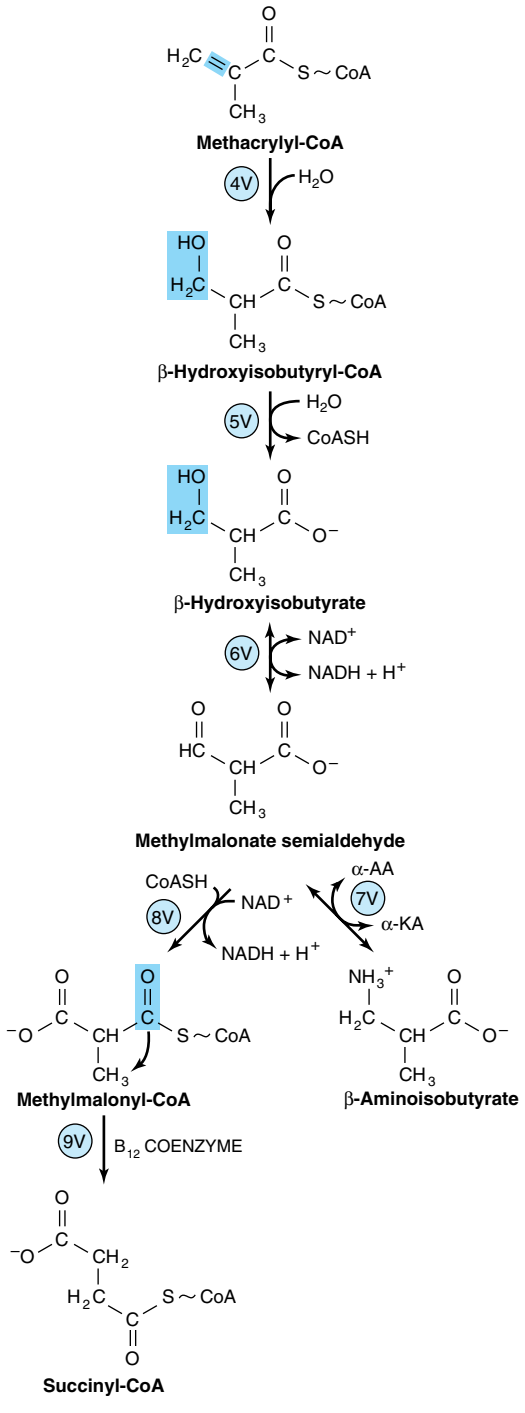

Figure 30–22. Subsequent catabolism of the methacrylyl-CoA formed from L-valine (see Figure 30–19). (α-KA, α-keto acid; α-AA, α-amino acid.)

isovaleryl-CoA is hydrolyzed to isovalerate and excreted.

SUMMARY

- Excess amino acids are catabolized to amphibolic intermediates used as sources of energy or for carbohydrate and lipid biosynthesis.
- Transamination is the most common initial reaction of amino acid catabolism. Subsequent reactions remove any additional nitrogen and restructure the hydrocarbon skeleton for conversion to oxaloacetate, α-ketoglutarate, pyruvate, and acetyl-CoA.
- Metabolic diseases associated with glycine catabolism include glycinuria and primary hyperoxaluria.
- Two distinct pathways convert cysteine to pyruvate. Metabolic disorders of cysteine catabolism include cystine-lysinuria, cystine storage disease, and the homocystinurias.
- Threonine catabolism merges with that of glycine after threonine aldolase cleaves threonine to glycine and acetaldehyde.
- Following transamination, the carbon skeleton of tyrosine is degraded to fumarate and acetoacetate. Metabolic diseases of tyrosine catabolism include tyrosinosis, Richner-Hanhart syndrome, neonatal tyrosinemia, and alkaptonuria.
- Metabolic disorders of phenylalanine catabolism include phenylketonuria (PKU) and several hyperphenylalaninemias.
- Neither nitrogen of lysine undergoes transamination. Metabolic diseases of lysine catabolism include periodic and persistent forms of hyperlysinemia-ammonemia.
- The catabolism of leucine, valine, and isoleucine presents many analogies to fatty acid catabolism. Metabolic disorders of branched-chain amino acid catabolism include hypervalinemia, maple syrup urine disease, intermittent branched-chain ketonuria, isovaleric acidemia, and methylmalonic aciduria.

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