

39 Synthesis and Degradation of Amino Acids



As a general rule, genetic codons exist for 20 amino acids. Only these 20 common amino acids are incorporated into proteins during the process of protein synthesis. Modifications to these amino acids occur after they are incorporated into proteins (such as the synthesis of hydroxyproline in collagen). The major exception to this rule is selenocysteine, which is an essential component of enzymes involved in scavenging free radicals (such as glutathione peroxidase-1; see Chapter 24). Selenocysteine has a selenium atom in the place of the oxygen atom in serine and is synthesized enzymatically in a reaction that requires adenosine triphosphate (ATP), selenium, and serine attached to a tRNA specific for selenocysteine. This reaction uses two high-energy bonds. The codon recognized by the tRNA-selenocysteine is a stop codon in the mRNA (UGA). The secondary structure of the mRNA allows the ribosomes and tRNA to understand which UGA is a stop codon and which requires the insertion of selenocysteine.

Because each of the 20 common amino acids has a unique structure, their metabolic pathways differ. Despite this, some generalities do apply to both the synthesis and degradation of all amino acids. These are summarized in the following sections. Because a number of the amino acid pathways are clinically relevant, we present most of the diverse pathways occurring in humans. However, we will be as succinct as possible.

Important coenzymes: *Pyridoxal phosphate* (derived from vitamin B6) is the quintessential coenzyme of amino acid metabolism. In degradation, it is involved in the removal of amino groups, principally through **transamination reactions** and in donation of amino groups for various amino acid biosynthetic pathways. It is also required for certain reactions involving the carbon skeleton of amino acids.

Tetrahydrofolate (FH₄) is a coenzyme used to transfer one-carbon groups at various oxidation states. FH₄ is used both in amino acid degradation (e.g., serine and histidine) and biosynthesis (e.g., glycine). **Tetrahydrobiopterin (BH₄)** is a cofactor required for ring hydroxylation reactions (e.g., phenylalanine to tyrosine).

Synthesis of the amino acids: *Eleven of the twenty common amino acids can be synthesized in the body (Fig. 39.1). The other nine are considered “essential” and must be obtained from the diet. Almost all of the amino acids that can be synthesized by humans are amino acids used for the synthesis of additional nitrogen-containing compounds. Examples include glycine, which is used for porphyrin and purine synthesis; glutamate, which is required for neurotransmitter and purine synthesis; and aspartate, which is required for both purine and pyrimidine biosynthesis.*

Nine of the eleven “nonessential” amino acids can be produced from glucose plus, of course, a source of nitrogen, such as another amino acid or ammonia. The other two nonessential amino acids, tyrosine and cysteine, require an essential amino acid for their synthesis (phenylalanine for tyrosine, and methionine for cysteine). The carbons for cysteine synthesis come from glucose; the methionine only donates the sulfur.

The carbon skeletons of the 10 nonessential amino acids derived from glucose are produced from intermediates of glycolysis and the tricarboxylic acid (TCA) cycle (see Fig 39.1). Four amino acids (serine, glycine, cysteine, and alanine) are produced from glucose through components of the glycolytic pathway. TCA cycle intermediates (which can be produced from glucose) provide carbon for synthesis of the six remaining nonessential amino acids. α -Ketoglutarate is the precursor for the synthesis of glutamate, glutamine, proline, and arginine. Oxaloacetate provides carbon for the synthesis of aspartate and asparagine.

The regulation of individual amino acid biosynthesis can be quite complex, but the overriding feature is that the pathways are feedback regulated such that as the concentration of free amino acid increases, a key biosynthetic enzyme is allosterically or transcriptionally inhibited. Amino acid levels, however, are

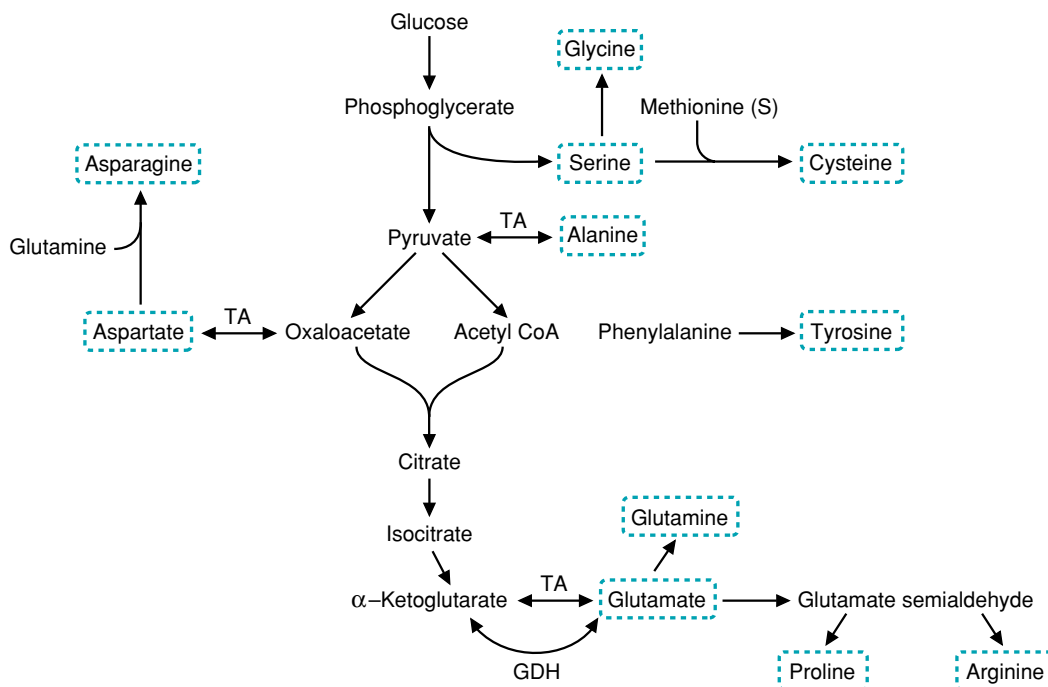


Fig. 39.1. Overview of the synthesis of the nonessential amino acids. The carbons of 10 amino acids may be produced from glucose through intermediates of glycolysis or the TCA cycle. The 11th nonessential amino acid, tyrosine, is synthesized by hydroxylation of the essential amino acid phenylalanine. Only the sulfur of cysteine comes from the essential amino acid methionine; its carbons and nitrogen come from serine. Transamination (TA) reactions involve pyridoxal phosphate (PLP) and another amino acid/ α -keto acid pair.

always maintained at a level such that the aminoacyl-tRNA synthetases can remain active, and protein synthesis can continue.

Degradation of amino acids: The *degradation pathways* for amino acids are, in general, **distinct from biosynthetic pathways**. This allows for separate regulation of the anabolic and catabolic pathways. Because protein is a fuel, almost every amino acid will have a degradative pathway that can generate NADH, which is used as an electron source for oxidative phosphorylation. However, the energy-generating pathway may involve direct oxidation, oxidation in the TCA cycle, conversion to glucose and then oxidation, or conversion to **ketone bodies**, which are then oxidized.

The fate of the carbons of the amino acids depends on the physiologic state of the individual and the tissue where the degradation occurs. For example, in the liver during fasting, the carbon skeletons of the amino acids produce glucose, ketone bodies, and CO_2 . In the fed state, the liver can convert intermediates of amino acid metabolism to glycogen and triacylglycerols. Thus, the **fate of the carbons of the amino acids parallels that of glucose and fatty acids**. The liver is the only tissue that has all of the pathways of amino acid synthesis and degradation.

As amino acids are degraded, their **carbons** are converted to (a) CO_2 , (b) compounds that produce **glucose** in the liver (pyruvate and the TCA cycle intermediates α -ketoglutarate, succinyl CoA, fumarate, and oxaloacetate), and (c) **ketone bodies** or their precursors (acetoacetate and acetyl CoA) (Fig. 39.2). For simplicity, amino acids are considered to be **glucogenic** if their carbon skeletons can be converted to a precursor of glucose and **ketogenic** if their carbon skeletons can be directly converted to acetyl CoA or acetoacetate. Some amino acids contain carbons that produce a glucose precursor and other carbons that produce acetyl CoA or acetoacetate. These amino acids are both glucogenic and ketogenic.

The amino acids synthesized from intermediates of glycolysis (**serine, alanine, and cysteine**) plus certain other amino acids (**threonine, glycine, and tryptophan**)

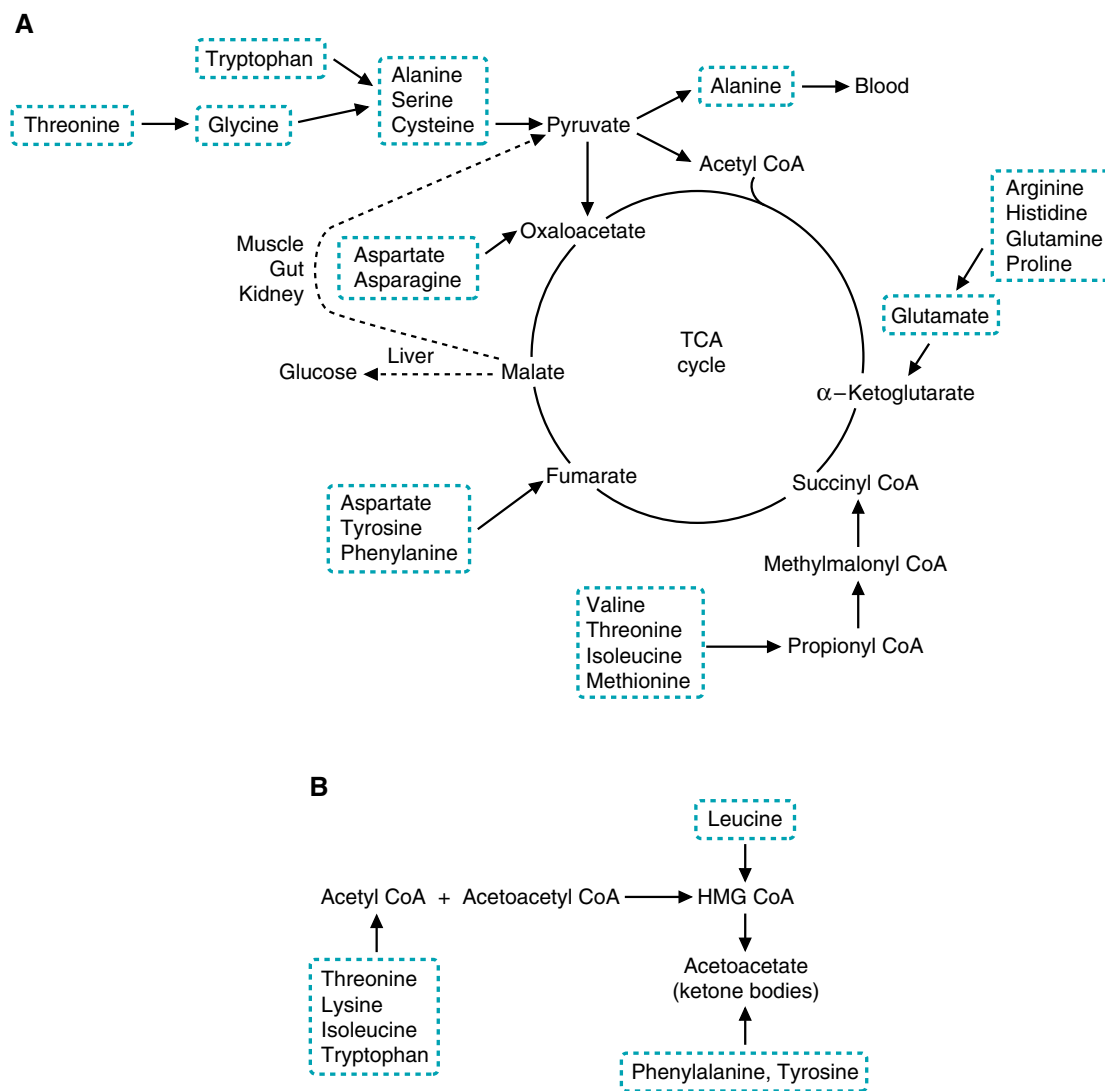


Fig. 39.2. Degradation of amino acids. A. Amino acids that produce pyruvate or intermediates of the TCA cycle. These amino acids are considered glucogenic because they can produce glucose in the liver. The fumarate group of amino acids produces cytoplasmic fumarate. Potential mechanisms whereby the cytoplasmic fumarate can be oxidized are presented in section III.C.1. B. Amino acids that produce acetyl CoA or ketone bodies. These amino acids are considered ketogenic.

produce **pyruvate** when they are degraded. The amino acids synthesized from TCA cycle intermediates (**aspartate, asparagines, glutamate, glutamine, proline, and arginine**) are reconverted to these intermediates during degradation. **Histidine** is converted to **glutamate** and then to the TCA cycle intermediate **α -ketoglutarate**. **Methionine, threonine, valine, and isoleucine** form **succinyl CoA**, and **phenylalanine** (after conversion to **tyrosine**) forms **fumarate**. Because pyruvate and the TCA cycle intermediates can produce glucose in the liver, these amino acids are glucogenic.

Some amino acids with carbons that produce glucose also contain other carbons that produce ketone bodies. **Tryptophan, isoleucine, and threonine** produce **acetyl CoA**, and **phenylalanine and tyrosine** produce **acetoacetate**. These amino acids are both glucogenic and ketogenic.

Two of the essential amino acids (**lysine and leucine**) are strictly **ketogenic**. They do not produce glucose, only acetoacetate and acetyl-CoA.



THE WAITING ROOM



Piquet Yuria, a 4-month-old female infant, emigrated from the Soviet Union with her French mother and Russian father 1 month ago. She was normal at birth but in the last several weeks was less than normally attentive to her surroundings. Her psychomotor maturation seemed delayed, and a tremor of her extremities had recently appeared. When her mother found her having gross twitching movements in her crib, she brought the infant to the hospital emergency room. A pediatrician examined Piquet and immediately noted a musty odor to the baby's wet diaper. A drop of her blood was obtained from a heel prick and used to perform a Guthrie bacterial inhibition assay using a special type of filter paper. This screening procedure was positive for the presence of an excess of phenylalanine in Piquet's blood.



Homer Sistine, a 14-year-old boy, had a sudden grand mal seizure (with jerking movements of the torso and head) in his eighth grade classroom. The school physician noted mild weakness of the muscles of the left side of Homer's face and of his left arm and leg. Homer was hospitalized with a tentative diagnosis of a cerebrovascular accident involving the right cerebral hemisphere, which presumably triggered the seizure.

Homer's past medical history was normal, except for slight mental retardation requiring placement in a special education group. He also had a downward partial dislocation of the lenses of both eyes for which he had had a surgical procedure (a peripheral iridectomy).

Homer's left-sided neurologic deficits cleared spontaneously within 3 days, but a computerized axial tomogram (CAT) showed changes consistent with a small infarction (damaged area caused by a temporary or permanent loss of adequate arterial blood flow) in the right cerebral hemisphere. A neurologist noted that Homer had a slight waddling gait, which his mother said began several years earlier and was progressing with time. Further studies confirmed the presence of decreased mineralization (decreased calcification) of the skeleton (called osteopenia if mild and osteoporosis if more severe) and high methionine and homocysteine but low cystine levels in the blood.

All of this information, plus the increased length of the long bones of Homer's extremities and a slight curvature of his spine (scoliosis), caused his physician to suspect that Homer might have an inborn error of metabolism.

I. THE ROLE OF COFACTORS IN AMINO ACID METABOLISM

Amino acid metabolism requires the participation of three important cofactors. Pyridoxal phosphate is the quintessential coenzyme of amino acid metabolism (see Chapter 38). All amino acid reactions requiring pyridoxal phosphate occur with the amino group of the amino acid covalently bound to the aldehyde carbon of the coenzyme (Fig. 39.3). The pyridoxal phosphate then pulls electrons away from the bonds around the α -carbon. The result is transamination, deamination, decarboxylation, β -elimination, racemization, and γ -elimination, depending on which enzyme and amino acid are involved.

The coenzyme FH_4 is required in certain amino acid pathways to either accept or donate a one-carbon group. The carbon can be in various states of oxidation. Chapter 40 describes the reactions of FH_4 in much more detail.

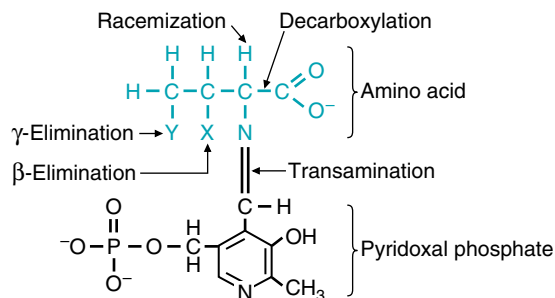


Fig. 39.3. Pyridoxal phosphate covalently attached to an amino acid substrate. The arrows indicate which bonds are broken for the various types of reactions in which pyridoxal phosphate is involved. The X and Y represent leaving groups that may be present on the amino acid (such as the hydroxyl group on serine or threonine).

The coenzyme BH_4 is required for ring hydroxylations. The reactions involve molecular oxygen, and one atom of oxygen is incorporated into the product. The second is found in water (see Chapter 24). BH_4 is important for the synthesis of tyrosine and neurotransmitters (see Chapter 48).

II. AMINO ACIDS DERIVED FROM INTERMEDIATES OF GLYCOLYSIS

Four amino acids are synthesized from intermediates of glycolysis: serine, glycine, cysteine, and alanine. Serine, which produces glycine and cysteine, is synthesized from 3-phosphoglycerate, and alanine is formed by transamination of pyruvate, the product of glycolysis (Fig. 39.4). When these amino acids are degraded, their carbon atoms are converted to pyruvate or to intermediates of the glycolytic/gluconeogenic pathway and, therefore, can produce glucose or be oxidized to CO_2 .

A. Serine

In the biosynthesis of serine from glucose, 3-phosphoglycerate is first oxidized to a 2-keto compound (3-phosphohydroxypyruvate), which is then transaminated to form phosphoserine (Fig. 39.5). Phosphoserine phosphatase removes the phosphate, forming serine. The major sites of serine synthesis are the liver and kidney.

Serine can be used by many tissues and is generally degraded by transamination to hydroxypyruvate followed by reduction and phosphorylation to form 2-phosphoglycerate, an intermediate of glycolysis that forms PEP and, subsequently, pyruvate. Serine also can undergo β -elimination of its hydroxyl group, catalyzed by serine dehydratase, to form pyruvate.

Regulatory mechanisms maintain serine levels in the body. When serine levels fall, serine synthesis is increased by induction of 3-phosphoglycerate dehydrogenase and by release of the feedback inhibition of phosphoserine phosphatase (caused by higher levels of serine). When serine levels rise, synthesis of serine decreases because synthesis of the dehydrogenase is repressed and the phosphatase is inhibited (see Fig. 39.5).

B. Glycine

Glycine can be synthesized from serine and, to a minor extent, threonine. The major route from serine is by a reversible reaction that involves FH_4 and pyridoxal phosphate (Fig. 39.6). Tetrahydrofolate is a coenzyme that transfers one-carbon groups at different levels of oxidation. It is derived from the vitamin folate and is discussed in more detail in Chapter 40. The minor pathway for glycine production involves threonine degradation (this is an aldolase-like reaction because threonine contains a hydroxyl group located two carbons from the carbonyl group).

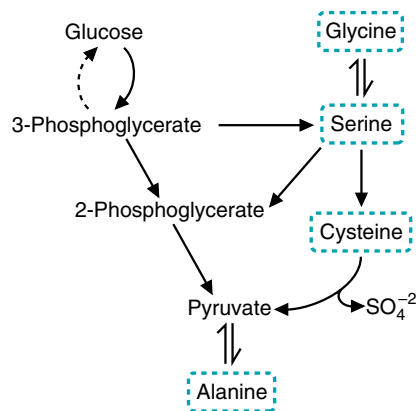


Fig. 39.4. Amino acids derived from intermediates of glycolysis. These amino acids can be synthesized from glucose. Their carbons can be reconverted to glucose in the liver.

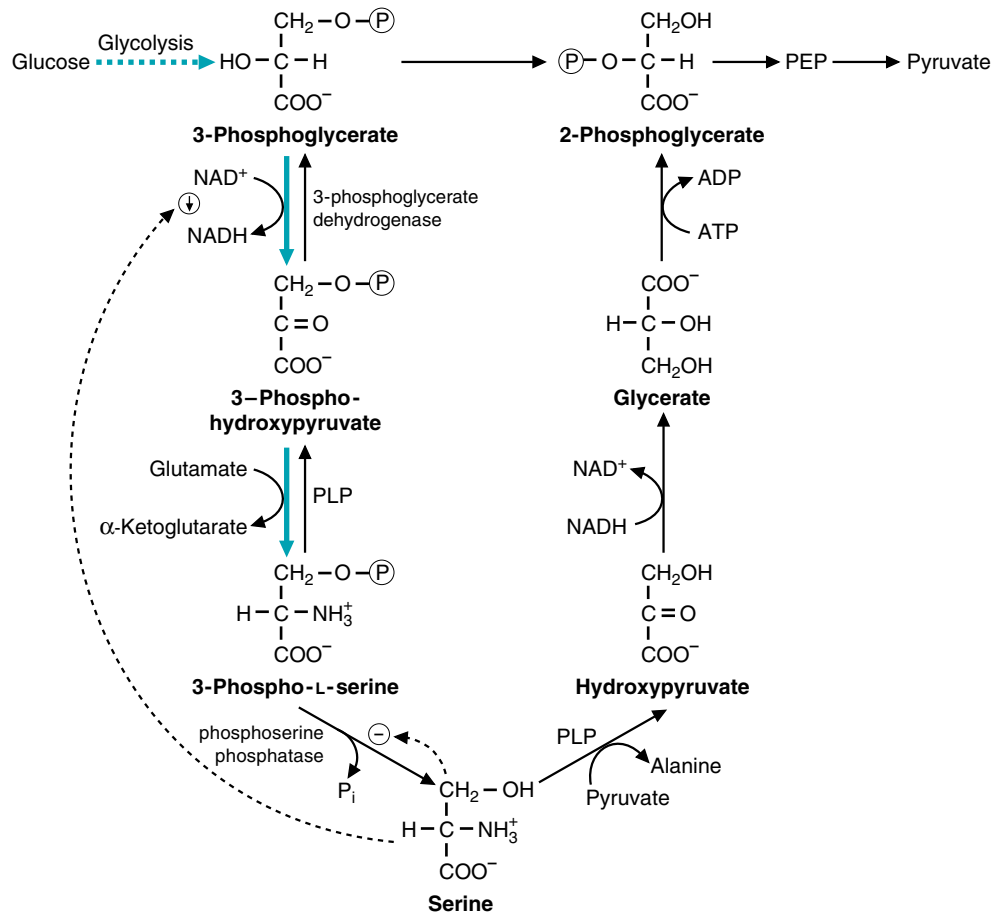


Fig. 39.5. The major pathway for serine synthesis from glucose is on the left, and for serine degradation on the right. Serine levels are maintained because serine causes repression (circled \downarrow) of 3-phosphoglycerate dehydrogenase synthesis. Serine also inhibits (circled $-$) phosphoserine phosphatase.

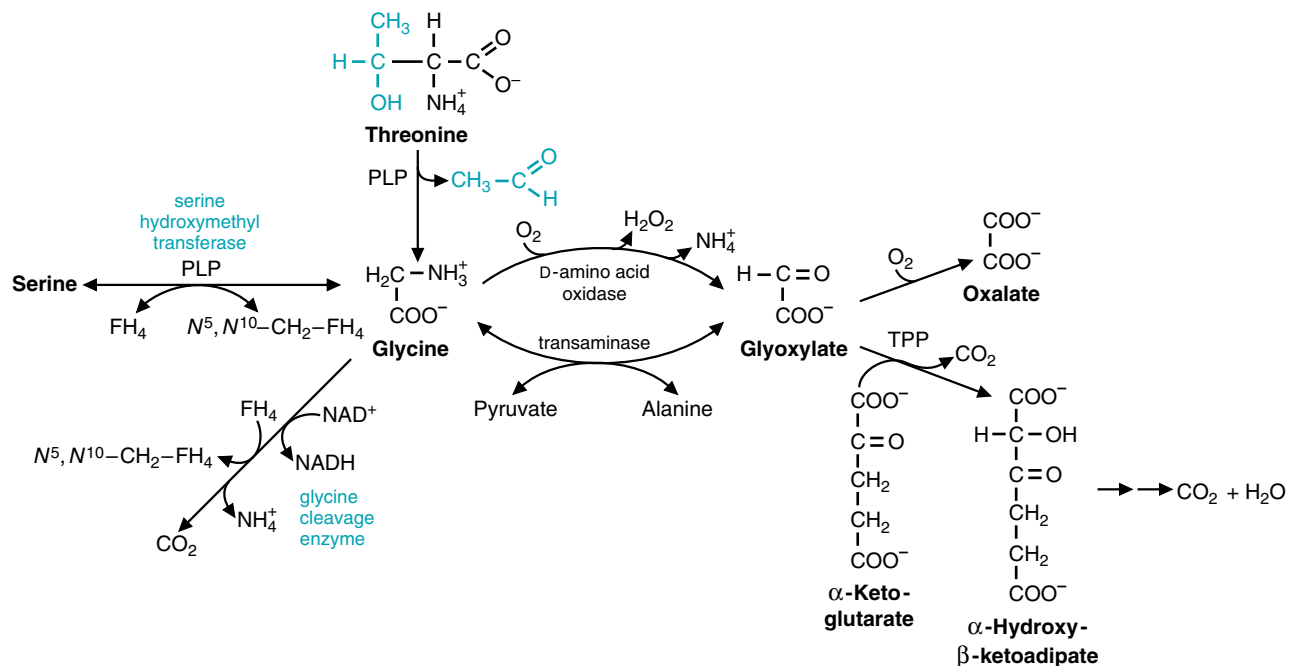


Fig. 39.6. Metabolism of glycine. Glycine can be synthesized from serine (major route) or threonine. Glycine forms serine or CO_2 and NH_4^+ by reactions that require tetrahydrofolate (FH_4). Glycine also forms glyoxylate, which is converted to oxalate or to CO_2 and H_2O .



Oxalate, produced from glycine or obtained from the diet, forms precipitates with calcium. Kidney stones (renal calculi) are often composed of calcium oxalate. A lack of the transaminase that can convert glyoxylate to glycine (see Fig 39.6) leads to the disease primary oxaluria type I (PH 1). This disease has a consequence of renal failure attributable to excessive accumulation of oxalate in the kidney.



Cystathionuria, the presence of cystathionine in the urine, is relatively common in premature infants. As they mature, cystathionase levels rise, and the levels of cystathionine in the urine decrease.

In adults, a genetic deficiency of cystathionase causes cystathionuria. Individuals with a genetically normal cystathionase can also develop cystathionuria from a dietary deficiency of pyridoxine (vitamin B6), because cystathionase requires the cofactor pyridoxal phosphate. No characteristic clinical abnormalities have been observed in individuals with cystathionase deficiency, and it is probably a benign disorder.



Cystinuria and cystinosis are disorders involving two different transport proteins for cystine, the disulfide formed from two molecules of cysteine. Cystinuria is caused by a defect in the transport protein that carries cystine, lysine, arginine, and ornithine into intestinal epithelial cells and that permits resorption of these amino acids by renal tubular cells. Cystine, which is not very soluble in the urine, forms renal calculi (stones). **Cal Kulis**, a patient with cystinuria, developed cystine stones (see Chapter 37).

Cystinosis is a rare disorder caused by a defective carrier that normally transports cystine across the lysosomal membrane from lysosomal vesicles to the cytosol. Cystine accumulates in the lysosomes in many tissues and forms crystals, impairing their function. Children with this disorder develop renal failure by 6–12 years of age.



Alanine aminotransferase (ALT) and aspartate amino transferase (AST) are released from the liver when liver cells are injured. Measurement of these two transaminases in the serum (ALT and AST) is one of the standard laboratory tests for liver damage caused by a variety of conditions.

The conversion of glycine to glyoxylate by the enzyme D-amino acid oxidase is a degradative pathway of glycine that is medically important. Once glyoxylate is formed, it can be oxidized to oxalate, which is sparingly soluble and tends to precipitate in kidney tubules, leading to kidney stone formation. Approximately 40% of oxalate formation in the liver comes from glycine metabolism. Dietary oxalate accumulation has been estimated to be a low contributor to excreted oxalate in the urine because of poor absorption of oxalate in the intestine.

Although glyoxylate can be transaminated back to glycine, this is not really considered a biosynthetic route for “new” glycine, because the primary route for glyoxylate formation is from glycine oxidation.

Generation of energy from glycine occurs through a dehydrogenase (glycine cleavage enzyme) that oxidizes glycine to CO_2 , ammonia, and a carbon that is donated to FH_4 .

C. Cysteine

The carbons and nitrogen for cysteine synthesis are provided by serine, and the sulfur is provided by methionine (Fig. 39.7). Serine reacts with homocysteine (which is produced from methionine) to form cystathionine. This reaction is catalyzed by cystathionine β -synthase. Cleavage of cystathionine by cystathionase produces cysteine and α -ketobutyrate, which forms succinyl CoA via propionyl CoA. Both cystathionine β -synthase (β -elimination) and cystathionase (γ -elimination) require PLP.

Cysteine inhibits cystathionine β -synthase and, therefore, regulates its own production to adjust for the dietary supply of cysteine. Because cysteine derives its sulfur from the essential amino acid methionine, cysteine becomes essential if the supply of methionine is inadequate for cysteine synthesis. Conversely, an adequate dietary source of cysteine “spares” methionine; that is, it decreases the amount that must be degraded to produce cysteine.

When cysteine is degraded, the nitrogen is converted to urea, the carbons to pyruvate, and the sulfur to sulfate, which has two potential fates (see Fig. 39.7; see also Chapter 43). Sulfate generation, in an aqueous media, is essentially generating sulfuric acid, and both the acid and sulfate need to be disposed of in the urine. Sulfate is also used in most cells to generate an activated form of sulfate known as PAPS (3'-phosphoadenosine 5'-phosphosulfate), which is used as a sulfate donor in modifying carbohydrates or amino acids in various structures (glycosaminoglycans) and proteins in the body.

The conversion of methionine to homocysteine and homocysteine to cysteine is the major degradative route for these two amino acids. Because this is the only degradative route for homocysteine, vitamin B6 deficiency or congenital cystathionine β -synthase deficiency can result in homocystinemia, which is associated with cardiovascular disease.

D. Alanine

Alanine is produced from pyruvate by a transamination reaction catalyzed by alanine aminotransferase (ALT) and may be converted back to pyruvate by a reversal of the same reaction (see Fig. 39.4). Alanine is the major gluconeogenic amino acid because it is produced in many tissues for the transport of nitrogen to the liver.

III. AMINO ACIDS RELATED TO TCA CYCLE INTERMEDIATES

Two groups of amino acids are synthesized from TCA cycle intermediates; one group from α -ketoglutarate and one from oxaloacetate (see Fig. 39.2). During degradation, four groups of amino acids are converted to the TCA cycle intermediates α -ketoglutarate, oxaloacetate, succinyl CoA, and fumarate (see Fig. 39.3A).

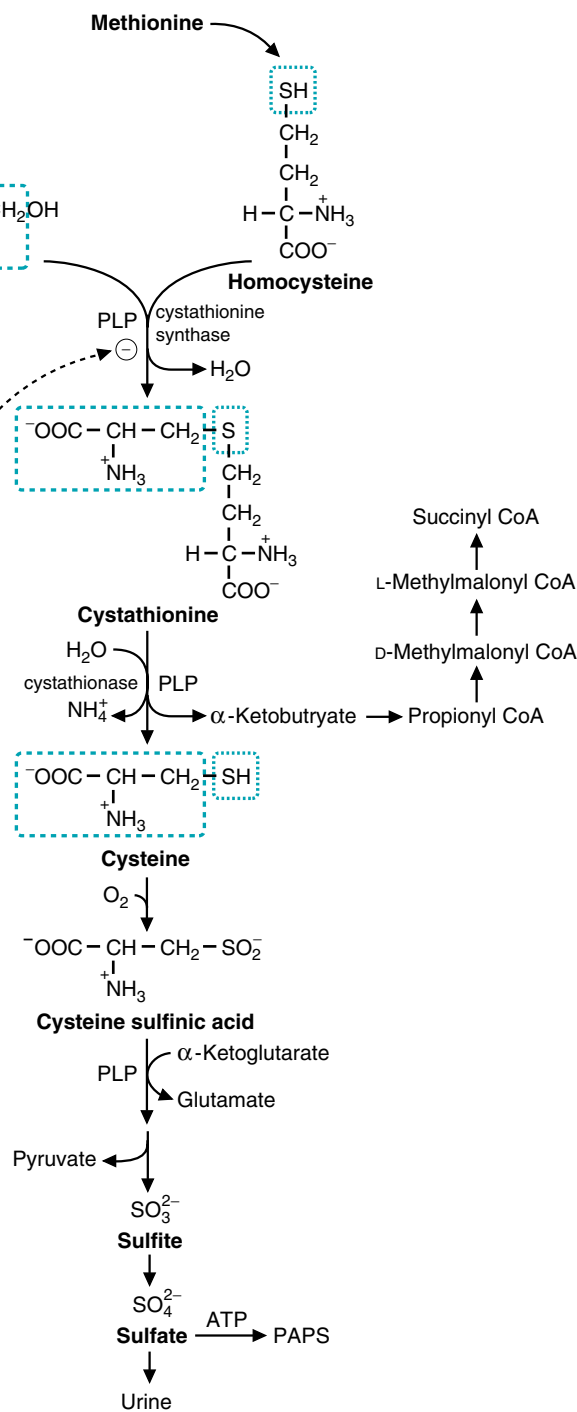
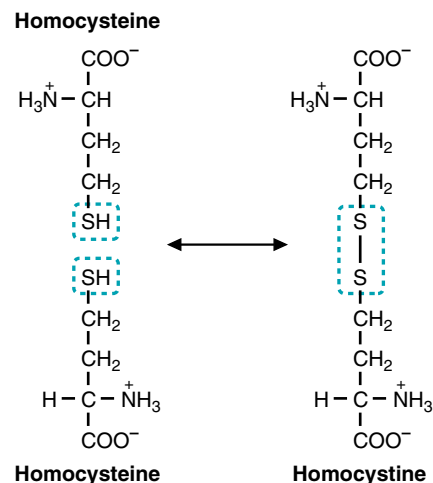


Fig. 39.7. Synthesis and degradation of cysteine. Cysteine is synthesized from the carbons and nitrogen of serine and the sulfur of homocysteine (which is derived from methionine). During the degradation of cysteine, the sulfur is converted to sulfate and either excreted in the urine or converted to PAPS (universal sulfate donor; 3'-phosphoadenosine 5'-phosphosulfate), and the carbons are converted to pyruvate.

Q: Homocysteine is oxidized to a disulfide, homocystine. To indicate that both forms are being considered, the term *homocyst(e)ine* is used.



Because a colorimetric screening test for urinary homocysteine was positive, the doctor ordered several biochemical studies on **Homer Sistine's** serum, which included tests for methionine, homocyst(e)ine (both free and protein-bound), cystine, vitamin B12, and folate. The level of homocysteine in a 24-hour urine collection was also measured.

The results were as follows: the serum methionine level was 980 μM (reference range, <30); serum homocyst(e)ine (both free and protein bound) was markedly elevated; cystine was not detected in the serum; the serum B12 and folate levels were normal. A 24-hour urine homocysteine level was elevated.

Based on these measurements, **Homer Sistine's** doctor concluded that he had homocystinuria caused by an enzyme deficiency. What was the rationale for this conclusion?

A: If the blood levels of methionine and homocysteine are very elevated and cystine is low, cystathionine β -synthase could be defective, but a cystathionase deficiency is also a possibility. With a deficiency of either of these enzymes, cysteine could not be synthesized, and levels of homocysteine would rise. Homocysteine would be converted to methionine by reactions that require B12 and tetrahydrofolate (see Chapter 40). In addition, it would be oxidized to homocystine, which would appear in the urine. The levels of cysteine (measured as its oxidation product cystine) would be low. A measurement of serum cystathionine levels would help to distinguish between a cystathionase or cystathionine β -synthase deficiency.

A. Amino Acids Related through α -Ketoglutarate/ Glutamate

1. GLUTAMATE

The five carbons of glutamate are derived from α -ketoglutarate either by transamination or by the glutamate dehydrogenase reaction (see Chapter 38). Because α -ketoglutarate can be synthesized from glucose, all of the carbons of glutamate can be obtained from glucose (see Fig. 39.2). When glutamate is degraded, it is likewise converted back to α -ketoglutarate either by transamination or by glutamate dehydrogenase. In the liver, α -ketoglutarate leads to the formation of malate, which produces glucose via gluconeogenesis. Thus, glutamate can be derived from glucose and reconverted to glucose (Fig. 39.8).

Glutamate is used for the synthesis of a number of other amino acids (glutamine, proline, ornithine, and arginine) (see Fig. 39.8) and for providing the glutamyl moiety of glutathione (γ -glutamyl-cysteinyl-glycine; see Biochemical Comments of Chapter 37). Glutathione is an important antioxidant, as has been described previously (see Chapter 24).

2. GLUTAMINE

Glutamine is produced from glutamate by glutamine synthetase, which adds NH_4^+ to the carboxyl group of the side chain, forming an amide (Fig. 39.9). This is one of only three human enzymes that can fix free ammonia into an organic molecule; the other two are glutamate dehydrogenase and carbamoyl-phosphate synthetase I (see Chapter 38). Glutamine is reconverted to glutamate by a different enzyme, glutaminase, which is particularly important in the kidney. The ammonia it produces enters the urine and can be used as an expendable cation to aid in the excretion of metabolic acids ($\text{NH}_3 + \text{H}^+ \rightarrow \text{NH}_4^+$).

3. PROLINE

In the synthesis of proline, glutamate is first phosphorylated and then converted to glutamate 5-semialdehyde by reduction of the side chain carboxyl group to an

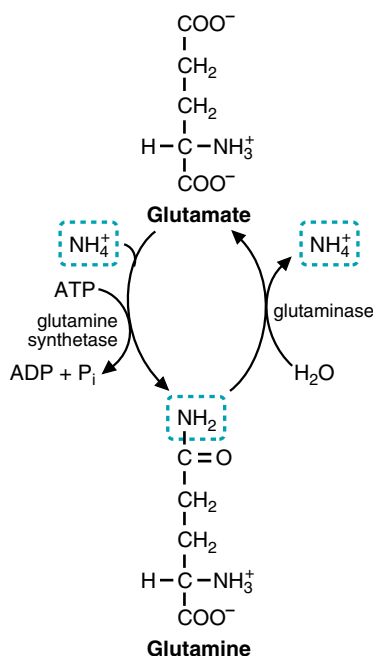


Fig. 39.9. Synthesis and degradation of glutamine. Different enzymes catalyze the addition and the removal of the amide nitrogen of glutamine.

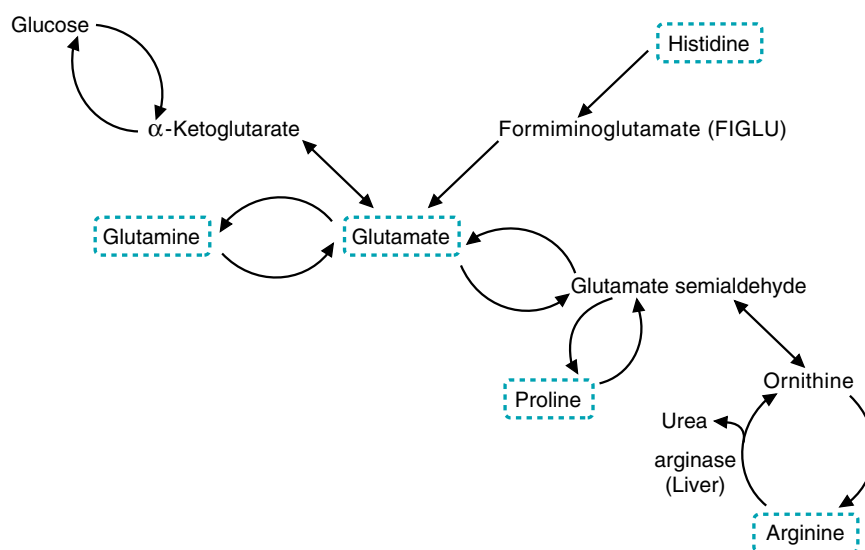


Fig. 39.8. Amino acids related through glutamate. These amino acids contain carbons that can be reconverted to glutamate, which can be converted to glucose in the liver. All of these amino acids except histidine can be synthesized from glucose.

aldehyde (Fig. 39.10). This semialdehyde spontaneously cyclizes (forming an internal Schiff base between the aldehyde and the α -amino group). Reduction of this cyclic compound yields proline. Hydroxyproline is only formed after proline has been incorporated into collagen (see Chapter 49) by the prolyl hydroxylase system, which uses molecular oxygen, iron, α -ketoglutarate, and ascorbic acid (vitamin C).

Proline is converted back to glutamate semialdehyde, which is reduced to form glutamate. The synthesis and degradation of proline use different enzymes even though the intermediates are the same. Hydroxyproline, however, has an entirely different degradative pathway (not shown). The presence of the hydroxyl group in hydroxyproline will allow an aldolase-like reaction to occur once the ring has been hydrolyzed, which is not possible with proline.

4. ARGININE

Arginine is synthesized from glutamate via glutamate semialdehyde, which is transaminated to form ornithine, an intermediate of the urea cycle (see Chapter 38 and Fig. 39.11). This activity (ornithine aminotransferase) appears to be greatest in the epithelial cells of the small intestine (see Chapter 42). The reactions of the urea cycle then produce arginine. However, the quantities of arginine generated by the urea cycle are adequate only for the adult and are insufficient to support growth. Therefore, during periods of growth, arginine becomes an essential amino acid. It is important to realize that if arginine is used for protein synthesis, the levels of ornithine will drop, thereby slowing the urea cycle. This will stimulate the formation of ornithine from glutamate.

Arginine is cleaved by arginase to form urea and ornithine. If ornithine is present in amounts in excess of those required for the urea cycle, it is transaminated to glutamate semialdehyde, which is reduced to glutamate. The conversion of an aldehyde to a primary amine is a unique form of a transamination reaction and requires pyridoxal phosphate (PLP).

5. HISTIDINE

Although histidine cannot be synthesized in humans, five of its carbons form glutamate when it is degraded. In a series of steps, histidine is converted to formiminoglutamate (FIGLU). The subsequent reactions transfer one carbon of FIGLU to the FH_4 pool (see Chapter 40) and release NH_4^+ and glutamate (Fig. 39.12).

B. Amino Acids Related to Oxaloacetate (Aspartate and Asparagine)

Aspartate is produced by transamination of oxaloacetate. This reaction is readily reversible, so aspartate can be reconverted to oxaloacetate (Fig. 39.13).

Asparagine is formed from aspartate by a reaction in which glutamine provides the nitrogen for formation of the amide group. Thus, this reaction differs from the synthesis of glutamine from glutamate, in which NH_4^+ provides the nitrogen. However, the reaction catalyzed by asparaginase, which hydrolyzes asparagine to NH_4^+ and aspartate, is analogous to the reaction catalyzed by glutaminase.

C. Amino Acids That Form Fumarate

1. ASPARTATE

Although the major route for aspartate degradation involves its conversion to oxaloacetate, carbons from aspartate can form fumarate in the urea cycle (see Chapter 38). This reaction generates cytosolic fumarate, which must be converted to malate (using cytoplasmic fumarase) for transport into the mitochondria for oxidative or anaplerotic purposes. An analogous sequence of reactions occurs in the purine nucleotide cycle. Aspartate reacts with inosine monophosphate (IMP) to

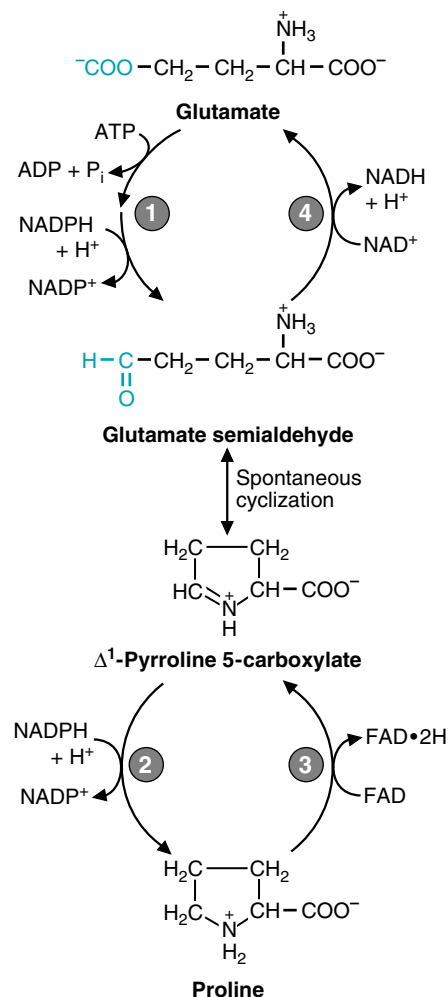


Fig. 39.10. Synthesis and degradation of proline. Reactions 1, 3, and 4 occur in mitochondria. Reaction 2 occurs in the cytosol. Synthesis and degradation involve different enzymes. The cyclization reaction (formation of a Schiff base) is nonenzymatic, i.e., spontaneous.



Certain types of tumor cells, particularly leukemic cells, require asparagine for their growth. Therefore, asparaginase has been used as an anti-tumor agent. It acts by converting asparagine to aspartate in the blood, decreasing the amount of asparagine available for tumor cell growth.

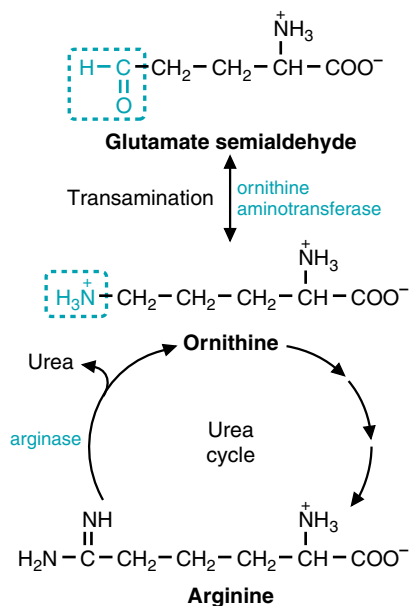


Fig. 39.11. Synthesis and degradation of arginine. The carbons of ornithine are derived from glutamate semialdehyde, which is derived from glutamate. Reactions of the urea cycle convert ornithine to arginine. Arginase converts arginine back to ornithine by releasing urea.

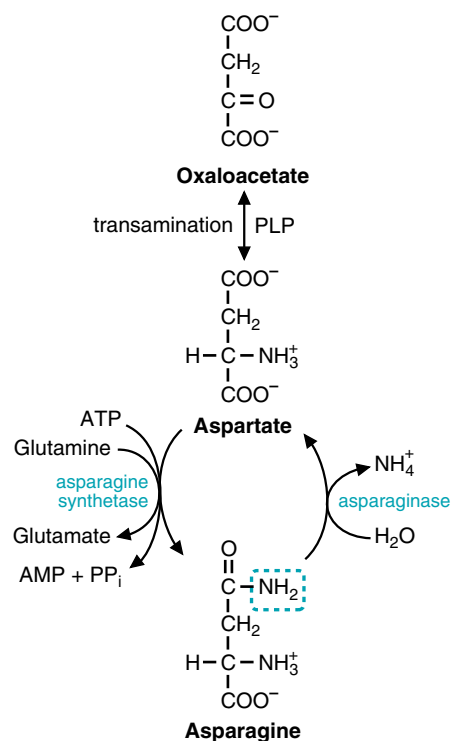


Fig. 39.13. Synthesis and degradation of aspartate and asparagine. Note that the amide nitrogen of asparagine is derived from glutamine. (The amide nitrogen of glutamine comes from NH_4^+ , see Fig. 39.9.)

form an intermediate (adenylosuccinate) which is cleaved, forming adenosine monophosphate (AMP) and fumarate (see Chapter 41).

2. PHENYLALANINE AND TYROSINE

Phenylalanine is converted to tyrosine by a hydroxylation reaction. Tyrosine, produced from phenylalanine or obtained from the diet, is oxidized, ultimately forming acetoacetate and fumarate. The oxidative steps required to reach this point are, surprisingly, not energy-generating. The conversion of fumarate to malate, followed by the action of malic enzyme, allows the carbons to be used for gluconeogenesis. The conversion of phenylalanine to tyrosine and the production of acetoacetate are considered further in section IV of this chapter.

D. Amino Acids That Form Succinyl CoA

The essential amino acids methionine, valine, isoleucine, and threonine are degraded to form propionyl-CoA. The conversion of propionyl CoA to succinyl CoA is common to their degradative pathways. Propionyl CoA is also generated from the oxidation of odd-chain fatty acids.

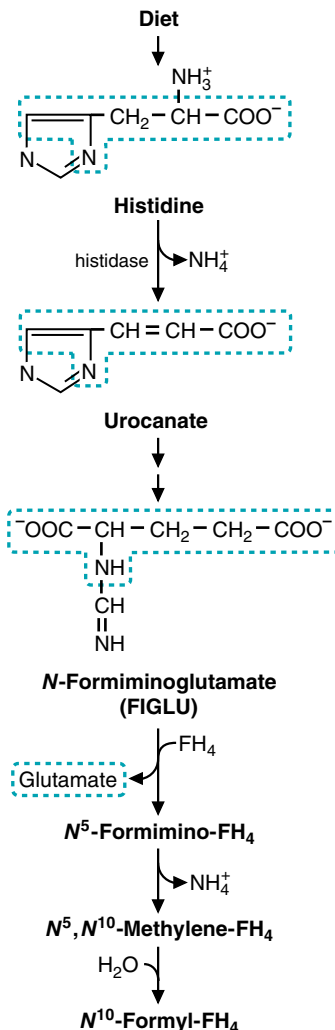


Fig. 39.12. Degradation of histidine. The highlighted portion of histidine forms glutamate. The remainder of the molecule provides one carbon for the tetrahydrofolate (FH₄) pool (see Chapter 40) and releases NH_4^+ .

Propionyl CoA is carboxylated in a reaction that requires biotin and forms D-methylmalonyl CoA. The D-methylmalonyl CoA is racemized to L-methylmalonyl CoA, which is rearranged in a vitamin B12-requiring reaction to produce succinyl CoA, a TCA cycle intermediate (see Fig. 23.11).

1. METHIONINE

Methionine is converted to *S*-adenosylmethionine (SAM), which donates its methyl group to other compounds to form *S*-adenosylhomocysteine (SAH). SAH is then converted to homocysteine (Fig. 39.14). Methionine can be regenerated from homocysteine by a reaction requiring both FH_4 and vitamin B12 (a topic that is considered in more detail in Chapter 40). Alternatively, by reactions requiring PLP, homocysteine can provide the sulfur required for the synthesis of cysteine (see Fig. 39.7). Carbons of homocysteine are then metabolized to α -ketobutyrate, which undergoes oxidative decarboxylation to propionyl-CoA. The propionyl-CoA is then converted to succinyl CoA (see Fig. 39.14).

2. THREONINE

In humans threonine is primarily degraded by a PLP-requiring dehydratase to ammonia and α -ketobutyrate, which subsequently undergoes oxidative decarboxylation to form propionyl CoA, just as in the case for methionine (see Fig. 39.14).

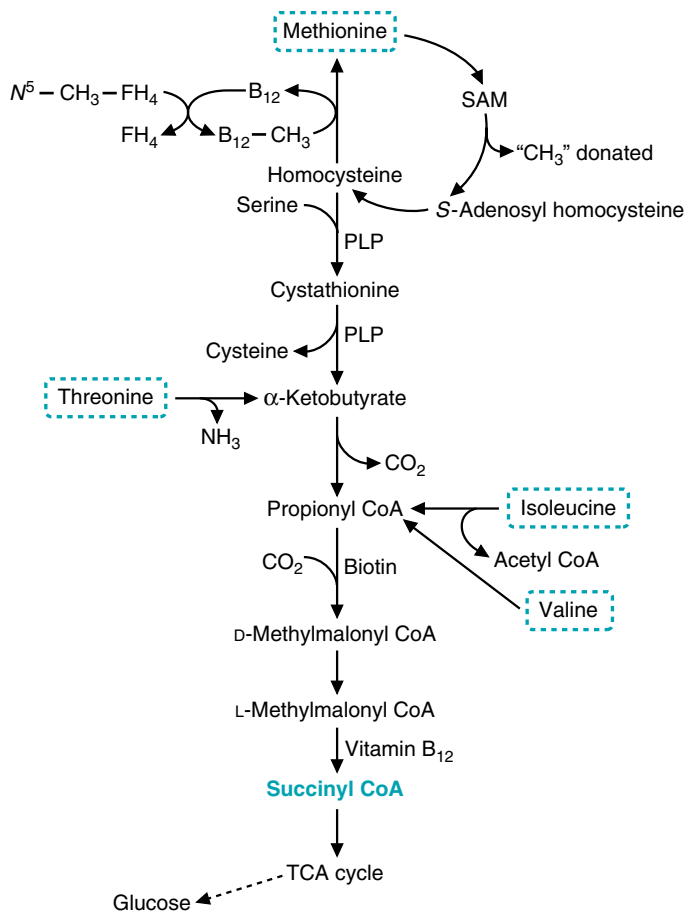


Fig. 39.14. Conversion of amino acids to succinyl CoA. The amino acids methionine, threonine, isoleucine, and valine, all of which form succinyl CoA via methylmalonyl CoA, are essential in the diet. The carbons of serine are converted to cysteine and do not form succinyl CoA by this pathway. SAM = *S*-adenosylmethionine.



The conversion of α -ketobutyrate to propionyl-CoA is catalyzed by either the pyruvate or branched-chain α -keto dehydrogenase enzymes.



Homocystinuria is caused by deficiencies in the enzymes cystathionine β -synthase and cystathionase as well as by deficiencies of methyltetrahydrofolate ($\text{CH}_3\text{-FH}_4$) or of methyl-B12. The deficiencies of $\text{CH}_3\text{-FH}_4$ or of methyl-B12 are due either to an inadequate dietary intake of folate or B12 or to defective enzymes involved in joining methyl groups to tetrahydrofolate (FH_4), transferring methyl groups from FH_4 to B12, or passing them from B12 to homocysteine to form methionine (see Chapter 40).

Is **Homer Sistine's** homocystinuria caused by any of these problems?

A: **Homer Sistine's** methionine levels are elevated, and his B12 and folate levels are normal. Therefore, he does not have a deficiency of dietary folate or B12 or of the enzymes that transfer methyl groups from tetrahydrofolate to homocysteine to form methionine. In these cases, homocysteine levels are elevated but methionine levels are low.

A biopsy specimen from **Homer Sistine's** liver was sent to the hospital's biochemistry research laboratory for enzyme assays. Cystathionine β -synthase activity was reported to be 7% of that found in normal liver.

V: Thiamine deficiency will lead to an accumulation of α -keto acids in the blood because of an inability of pyruvate dehydrogenase, α -ketoglutarate dehydrogenase, and branched-chain α -keto acid dehydrogenase to catalyze their reactions (see Chapter 8). **Al Martini** had a thiamine deficiency resulting from his chronic alcoholism. His ketoacidosis resulted partly from the accumulation of these α -ketoacids in his blood and partly from the accumulation of ketone bodies used for energy production.

Q: What compounds form succinyl CoA via propionyl CoA and methylmalonyl CoA?

V: In maple syrup urine disease, the branched-chain α -keto acid dehydrogenase that oxidatively decarboxylates the branched-chain amino acids is defective. As a result, the branched-chain amino acids and their α -keto analogs (produced by transamination) accumulate. They appear in the urine, giving it the odor of maple syrup or burnt sugar. The accumulation of α -keto analogs leads to neurologic complications. This condition is difficult to treat by dietary restriction, because abnormalities in the metabolism of three essential amino acids contribute to the disease.

3. VALINE AND ISOLEUCINE

The branched-chain amino acids (valine, isoleucine, and leucine) are a universal fuel, and the degradation of these amino acids occurs at low levels in the mitochondria of most tissues, but the muscle carries out the highest level of branched-chain amino acid oxidation. The branched-chain amino acids make up almost 25% of the content of the average protein, so their use as fuel is quite significant. The degradative pathway for valine and isoleucine has two major functions, the first being energy generation and the second to provide precursors to replenish TCA cycle intermediates (anaplerosis). Valine and isoleucine, two of the three branched-chain amino acids, contain carbons that form succinyl CoA. The initial step in the degradation of the branched-chain amino acids is a transamination reaction. Although the enzyme that catalyzes this reaction is present in most tissues, the level of activity varies from tissue to tissue. Its activity is particularly high in muscle, however. In the second step of the degradative pathway, the α -keto analogs of these amino acids undergo oxidative decarboxylation by the α -keto acid dehydrogenase complex in a reaction similar in its mechanism and cofactor requirements to pyruvate dehydrogenase and α -ketoglutarate dehydrogenase (see Chapter 20). As with the first enzyme of the pathway, the highest level of activity for this dehydrogenase is found in muscle tissue. Subsequently, the pathways for degradation of these amino acids follow parallel routes (Fig. 39.15). The steps are analogous to those for β -oxidation of fatty acids so NADH and FAD(2H) are generated for energy production.

Valine and isoleucine are converted to succinyl CoA (see Fig. 39.14). Isoleucine also forms acetyl CoA. Leucine, the third branched-chain amino acid,

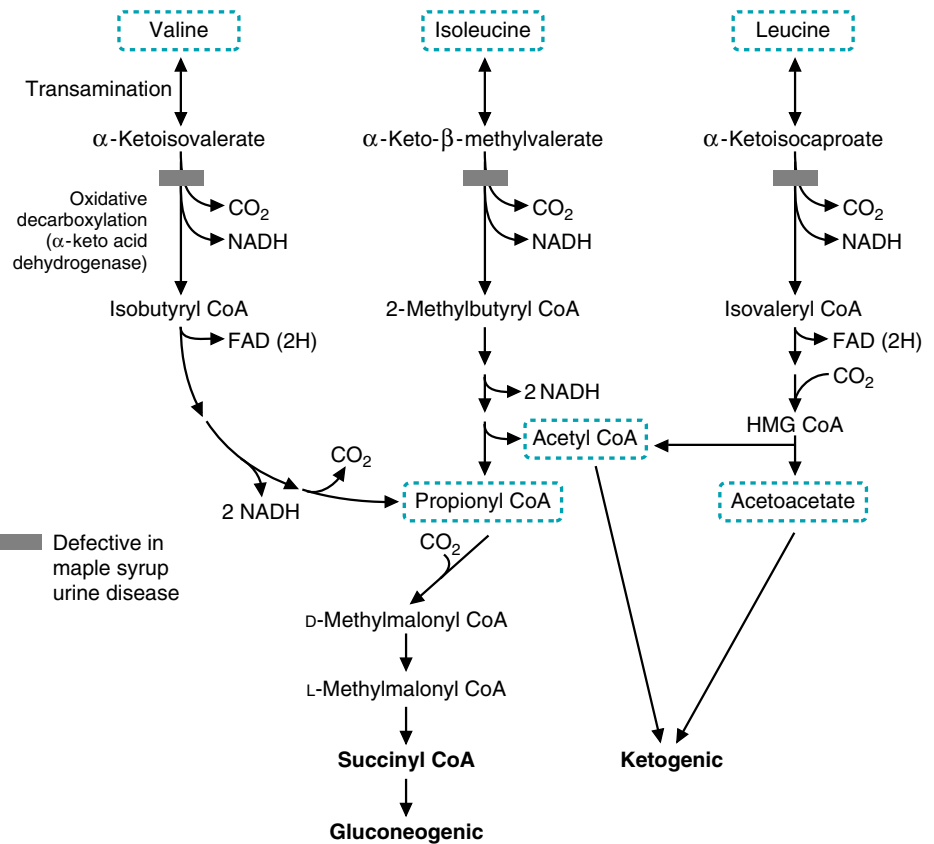


Fig. 39.15. Degradation of the branched-chain amino acids. Valine forms propionyl CoA. Isoleucine forms propionyl CoA and acetyl CoA. Leucine forms acetoacetate and acetyl CoA.

does not produce succinyl CoA. It forms acetoacetate and acetyl CoA and is strictly ketogenic.

IV. AMINO ACIDS THAT FORM ACETYL CoA AND ACETOACETATE

Seven amino acids produce acetyl CoA or acetoacetate and therefore are categorized as ketogenic. Of these, isoleucine, threonine, and the aromatic amino acids (phenylalanine, tyrosine, and tryptophan) are converted to compounds that produce both glucose and acetyl CoA or acetoacetate (Fig. 39.16). Leucine and lysine do not produce glucose; they produce acetyl CoA and acetoacetate.

A. Phenylalanine and Tyrosine

Phenylalanine is converted to tyrosine, which undergoes oxidative degradation (Fig. 39.17). The last step in the pathway produces both fumarate and the ketone body acetoacetate. Deficiencies of different enzymes in the pathway result in phenylketonuria, tyrosinemia, and alcaptonuria.

Phenylalanine is hydroxylated to form tyrosine by a mixed function oxidase, phenylalanine hydroxylase (PAH), which requires molecular oxygen and tetrahydrobiopterin (Fig. 39.18). The cofactor tetrahydrobiopterin is converted to quinoid dihydrobiopterin by this reaction. Tetrahydrobiopterin is not synthesized from a vitamin; it can be synthesized in the body from GTP. However, as is the case with other cofactors, the body contains limited amounts. Therefore, dihydrobiopterin must be reconverted to tetrahydrobiopterin for the reaction to continue to produce tyrosine.

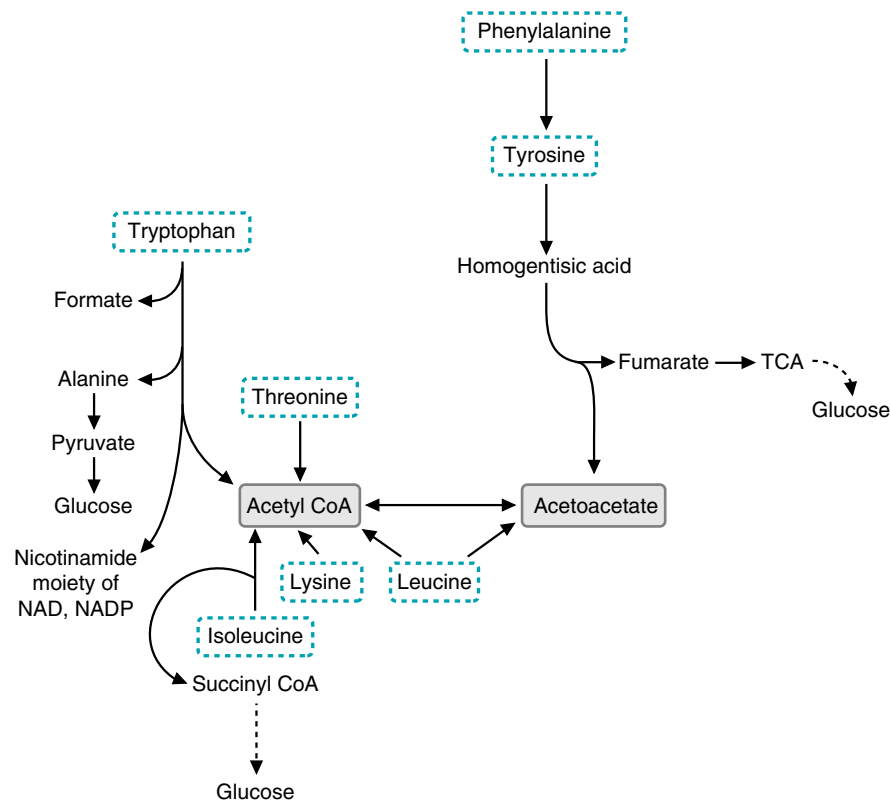


Fig. 39.16. Ketogenic amino acids. Some of these amino acids (tryptophan, phenylalanine, and tyrosine) also contain carbons that can form glucose. Leucine and lysine are strictly ketogenic; they do not form glucose.



Alcaptonuria occurs when homogentisate, an intermediate in tyrosine metabolism, cannot be further oxidized because the next enzyme in the pathway, homogentisate oxidase, is defective. Homogentisate accumulates and auto-oxidizes, forming a dark pigment, which discolors the urine and stains the diapers of affected infants. Later in life, the chronic accumulation of this pigment in cartilage may cause arthritic joint pain.



Transient tyrosinemia is frequently observed in newborn infants, especially those that are premature. For the most part, the condition appears to be benign, and dietary restriction of protein returns plasma tyrosine levels to normal. The biochemical defect is most likely a low level, attributable to immaturity, of 4-hydroxyphenylpyruvate dioxygenase. Because this enzyme requires ascorbate, ascorbate supplementation also aids in reducing circulating tyrosine levels.

Other types of tyrosinemia are related to specific enzyme defects (see Fig. 39.17). Tyrosinemia II is caused by a genetic deficiency of tyrosine aminotransferase (TAT) and may lead to lesions of the eye and skin as well as neurologic problems. Patients are treated with a low-tyrosine, low-phenylalanine diet.

Tyrosinemia I (also called tyrosinosis) is caused by a genetic deficiency of fumarylacetoacetate hydrolase. The acute form is associated with liver failure, a cabbage-like odor, and death within the first year of life.



A: In addition to methionine, threonine, isoleucine, and valine (see Fig. 39.14), the last three carbons at the ω -end of odd-chain fatty acids, form succinyl CoA by this route (see Chapter 23)



A small subset of patients with hyperphenylalaninemia show an appropriate reduction in plasma phenylalanine levels with dietary restriction of this amino acid; however, these patients still develop progressive neurologic symptoms and seizures and usually die within the first 2 years of life (“malignant” hyperphenylalaninemia). These infants exhibit normal phenylalanine hydroxylase (PAH) activity but have a deficiency in dihydropteridine reductase (DHPR), an enzyme required for the regeneration of tetrahydrobiopterin (BH_4), a cofactor of PAH (see Fig. 39.18). Less frequently, DHPR activity is normal but a defect in the biosynthesis of BH_4 exists. In either case, dietary therapy corrects the hyperphenylalaninemia. However, BH_4 is also a cofactor for two other hydroxylations required in the synthesis of neurotransmitters in the brain: the hydroxylation of tryptophan to 5-hydroxytryptophan and of tyrosine to L-dopa (see Chapter 48). It has been suggested that the resulting deficit in central nervous system neurotransmitter activity is, at least in part, responsible for the neurologic manifestations and eventual death of these patients.



If the dietary levels of niacin and tryptophan are insufficient, the condition known as pellagra results. The symptoms of pellagra are dermatitis, diarrhea, dementia, and, finally, death. In addition, abnormal metabolism of tryptophan occurs in a vitamin B6 deficiency. Kynurenine intermediates in tryptophan degradation cannot be cleaved because kynureninase requires PLP derived from vitamin B6. Consequently, these intermediates enter a minor pathway for tryptophan metabolism that produces xanthurenic acid, which is excreted in the urine.

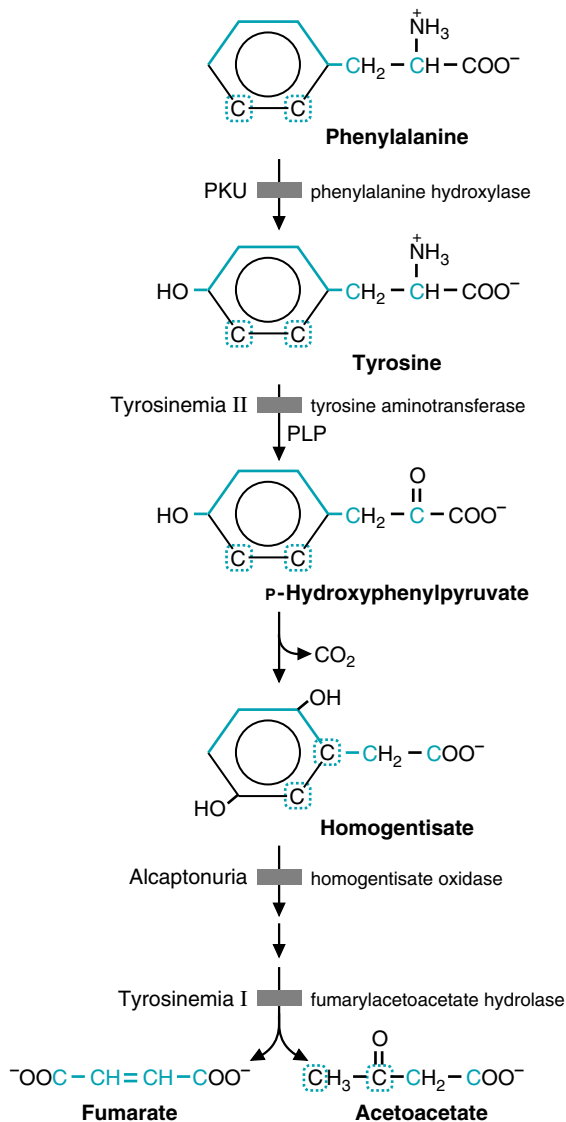


Fig. 39.17. Degradation of phenylalanine and tyrosine. The carboxyl carbon forms CO_2 , and the other carbons form fumarate or acetoacetate as indicated. Deficiencies of enzymes (gray bars) result in the indicated diseases. PKU = phenylketonuria.

B. Tryptophan

Tryptophan is oxidized to produce alanine (from the non-ring carbons), formate, and acetyl CoA. Tryptophan is, therefore, both glucogenic and ketogenic (Fig. 39.19).

NAD and NADP can be produced from the ring structure of tryptophan. Therefore, tryptophan “spares” the dietary requirement for niacin. The higher the dietary levels of tryptophan, the lower the levels of niacin required to prevent symptoms of deficiency.

C. Threonine, Isoleucine, Leucine, and Lysine

As discussed previously, the major route of threonine degradation in humans is by threonine dehydratase (see section III.D.2.). In a minor pathway, threonine degradation by threonine aldolase produces glycine and acetyl CoA in the liver.

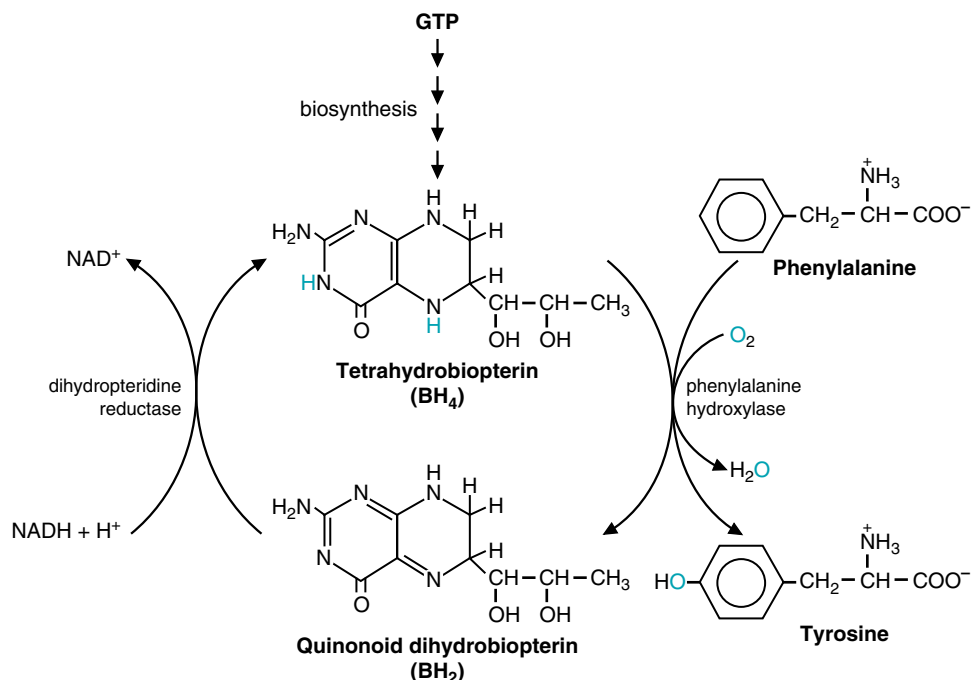


Fig. 39.18. Hydroxylation of phenylalanine. Phenylalanine hydroxylase (PAH) is a mixed-function oxidase; i.e., molecular oxygen (O₂) donates one atom to water and one to the product, tyrosine. The cofactor, tetrahydrobiopterin (BH₄), is oxidized to dihydrobiopterin (BH₂), and must be reduced back to BH₄ for the phenylalanine to continue forming tyrosine. BH₄ is synthesized in the body from GTP. PKU results from deficiencies of PAH (the classic form), dihydropteridine reductase, or enzymes in the biosynthetic pathway for BH₄.

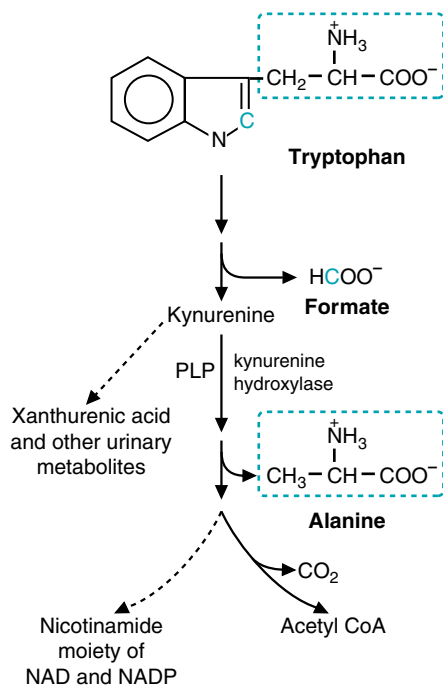
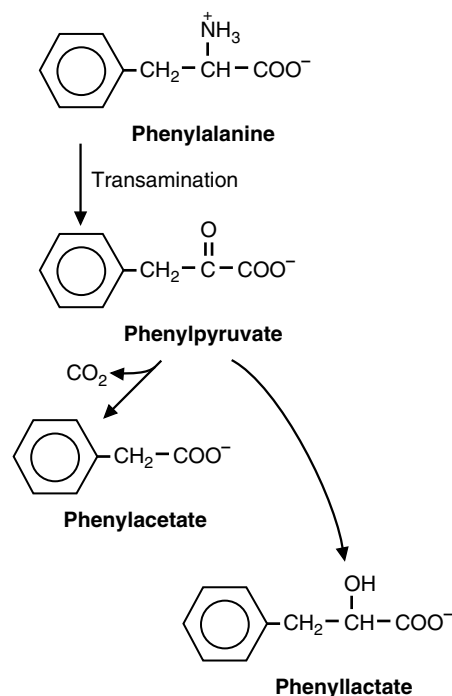


Fig. 39.19. Degradation of tryptophan. One of the ring carbons produces formate. The non-ring portion forms alanine. Kynurenine is an intermediate, which can be converted to a number of urinary excretion products (e.g., xanthurenate), degraded to CO₂ and acetyl CoA, or converted to the nicotinamide moiety of NAD and NADP, which also can be formed from the vitamin niacin.



On more definitive testing of **Piquet Yuria's** blood, the plasma level of phenylalanine was elevated at 18 mg/dL (reference range, <1.2). Several phenyl ketones and other products of phenylalanine metabolism, which give the urine a characteristic odor, were found in significant quantities in the baby's urine.



A liver biopsy was sent to the special chemistry research laboratory, where it was determined that the level of activity of phenylalanine hydroxylase (PAH) in Piquet's blood was less than 1% of that found in normal infants. A diagnosis of "classic" phenylketonuria (PKU) was made.

Until gene therapy allows substitution of the defective PAH gene with its normal counterpart *in vivo*, the mainstay of therapy in classic PKU is to maintain levels of phenylalanine in the blood between 3 and 12 mg/dL through dietary restriction of this essential amino acid.

Isoleucine produces both succinyl CoA and acetyl CoA (see section III.D.3.).

Leucine is purely ketogenic and produces hydroxymethylglutaryl CoA (HMG-CoA), which is cleaved to form acetyl CoA and the ketone body acetoacetate (see Figs. 39.15 and 39.16). Most of the tissues in which it is oxidized can use ketone bodies, with the exception of the liver. As with valine and isoleucine, leucine is a universal fuel, with its primary metabolism occurring in muscle.

Lysine cannot be directly transaminated at either of its two amino groups. Lysine is degraded by a complex pathway in which saccharopine, α -ketoacid, and crotonyl CoA are intermediates. During the degradation pathway NADH and FADH_2 are generated for energy. Ultimately, lysine generates acetyl CoA (see Fig. 39.16) and is strictly ketogenic.

CLINICAL COMMENTS



Piquet Yuria. The overall incidence of hyperphenylalaninemia is approximately 100 per million births, with a wide geographic and ethnic variation. PKU occurs by autosomal recessive transmission of a defective PAH gene, causing accumulation of phenylalanine in the blood well above the normal concentration in young children and adults (less than 1–2 mg/dL). In the newborn, the upper limit of normal is almost twice this value. Values above 16 mg/dL are usually found in patients, such as **Piquet Yuria**, with "classic" PKU.

Patients with classic PKU usually appear normal at birth. If the disease is not recognized and treated within the first month of life, the infant gradually develops varying degrees of irreversible mental retardation (IQ scores frequently under 50), delayed psychomotor maturation, tremors, seizures, eczema, and hyperactivity. The neurologic sequelae may result in part from the competitive interaction of phenylalanine with brain amino acid transport systems and inhibition of neurotransmitter synthesis. These biochemical alterations lead to impaired myelin synthesis and delayed neuronal development, which result in the clinical picture in patients such as **Piquet Yuria**. Because of the simplicity of the test for PKU (elevated phenylalanine levels in the blood), all newborns in the United States are required to have a PKU test at birth. Early detection of the disease can lead to early treatment, and the neurologic consequences of the disease can be bypassed.

To restrict dietary levels of phenylalanine, special semisynthetic preparations such as Lofenalac or PKUaid are used in the United States. Use of these preparations reduces dietary intake of phenylalanine to 250–500 mg/day while maintaining normal intake of all other dietary nutrients. Although it is generally agreed that scrupulous adherence to this regimen is mandatory for the first decade of life, less consensus exists regarding its indefinite use. Evidence suggests, however, that without lifelong compliance with dietary restriction of phenylalanine, even adults will develop at least neurologic sequelae of PKU. A pregnant woman with PKU must be particularly careful to maintain satisfactory plasma levels of phenylalanine throughout gestation to avoid the adverse effects of hyperphenylalaninemia on the fetus.

Piquet's parents were given thorough dietary instruction, which they followed carefully. Although her pediatrician was not optimistic, it was hoped that the damage done to her nervous system before dietary therapy was minimal and that her subsequent psychomotor development would allow her to lead a relatively normal life.



Homer Sistine. The most characteristic biochemical features of the disorder affecting **Homer Sistine**, a cystathionine β -synthase deficiency, are the presence of an accumulation of both homocyst(e)ine and methionine in the blood. Because renal tubular reabsorption of methionine is highly efficient, this

amino acid may not appear in the urine. Homocystine, the disulfide of homocysteine, is less efficiently reabsorbed, and amounts in excess of 1 mmol may be excreted in the urine each day.

In the type of homocystinuria in which the patient is deficient in cystathionine β -synthase, the elevation in serum methionine levels is presumed to be the result of enhanced rates of conversion of homocysteine to methionine, caused by increased availability of homocysteine (see Fig. 39.14). In type II and type III homocystinuria, in which there is a deficiency in the synthesis of methyl cobalamin and of N⁵-methyltetrahydrofolate, respectively (both required for the methylation of homocysteine to form methionine), serum homocysteine levels are elevated but serum methionine levels are low (see Fig. 39.14).

Acute vascular events are common in these patients. Thrombi (blood clots) and emboli (clots that have broken off and traveled to a distant site in the vascular system) have been reported in almost every major artery and vein as well as in smaller vessels. These clots result in infarcts in vital organs such as the liver, the myocardium (heart muscle), the lungs, the kidneys, and many other tissues. Although increased serum levels of homocysteine have been implicated in enhanced platelet aggregation and damage to vascular endothelial cells (leading to clotting and accelerated atherosclerosis), no generally accepted mechanism for these vascular events has yet emerged.

Treatment is directed toward early reduction of the elevated levels of homocysteine and methionine in the blood. In addition to a diet low in methionine, very high oral doses of pyridoxine (vitamin B6) have significantly decreased the plasma levels of homocysteine and methionine in some patients with cystathionine β -synthase deficiency. (Genetically determined “responders” to pyridoxine treatment make up approximately 50% of type I homocystinurics.) PLP serves as a cofactor for cystathionine β -synthase; however, the molecular properties of the defective enzyme that confer the responsiveness to B6 therapy are not known.

The terms *hypermethioninemia*, *homocystinuria* (or *-emia*), and *cystathioninuria* (or *-emia*) designate biochemical abnormalities and are not specific clinical diseases. Each may be caused by more than one specific genetic defect. For example, at least seven distinct genetic alterations can cause increased excretion of homocystine in the urine. A deficiency of cystathionine β -synthase is the most common cause of homocystinuria; more than 600 such proven cases have been studied.



The pathologic findings that underlie the clinical features manifested by **Homer Sistine** are presumed (but not proved) to be the consequence of chronic elevations of homocysteine (and perhaps other compounds, e.g., methionine) in the blood and tissues. The zonular fibers that normally hold the lens of the eye in place become frayed and break, causing dislocation of the lens. The skeleton reveals a loss of bone ground substance (i.e., osteoporosis), which may explain the curvature of the spine. The elongation of the long bones beyond their normal genetically determined length leads to tall stature.

Animal experiments suggest that increased concentrations of homocysteine and methionine in the brain may trap adenosine as S-adenosylhomocysteine, diminishing adenosine levels. Because adenosine normally acts as a central nervous system depressant, its deficiency may be associated with a lowering of the seizure threshold as well as a reduction in cognitive function.

BIOCHEMICAL COMMENTS



Phenylketonuria. Many enzyme deficiency diseases have been discovered that affect the pathways of amino acid metabolism. These deficiency diseases have helped researchers to elucidate the pathways in humans, in whom experimental manipulation is, at best, unethical. These spontaneous mutations (“experiments” of nature), although devastating to patients, have resulted in an understanding of these diseases that now permit treatment of inborn errors of metabolism that were once considered to be untreatable.

Classic PKU is caused by mutations in the gene located on chromosome 12 that encodes the enzyme phenylalanine hydroxylase (PAH). This enzyme normally catalyzes the hydroxylation of phenylalanine to tyrosine, the rate-limiting step in the major pathway by which phenylalanine is catabolized.

In early experiments, sequence analysis of mutant clones indicated a single base substitution in the gene with a G to A transition at the canonical 5' donor splice site of intron 12 and expression of a truncated unstable protein product. This protein lacked the C-terminal region, a structural change that yielded less than 1% of the normal activity of PAH.

Table 39.1. Genetic Disorders of Amino Acid Metabolism

Amino Acid Degradation Pathway	Missing Enzyme	Product That Accumulates	Disease	Symptoms
Phenylalanine	Phenylalanine hydroxylase	Phenylalanine	PKU (classical)	Mental retardation
	Dihydropteridine reductase	Phenylalanine	PKU (non-classical)	Mental retardation
	Homogentisate oxidase	Homogentisic acid	Alcaptonuria	Black urine, arthritis
Tyrosine	Fumarylacetoacetate hydrolase	Fumarylacetoacetate	Tyrosinemia I	Liver failure, death early
	Tyrosine aminotransferase	Tyrosine	Tyrosinemia II	Neurologic defects
Methionine	Cystathionase	Cystathionine	Cystathioninuria	Benign
	Cystathionine β -synthase	Homocysteine	Homocysteinemia	Cardiovascular complications and neurologic problems
Glycine	Glycine transaminase	Glyoxylate	Primary oxaluria type I	Renal failure due to stone formation
Branched-chain amino acids (leucine, isoleucine, valine)	Branched-chain α -keto acid dehydrogenase	α -Keto acids of the branched chain amino acids	Maple syrup urine disease	Mental retardation

Since these initial studies, DNA analysis has shown over 100 mutations (missense, nonsense, insertions, and deletions) in the PAH gene, associated with PKU and non-PKU hyperphenylalaninemia. That PKU is a heterogeneous phenotype is supported by studies measuring PAH activity in needle biopsy samples taken from the livers of a large group of patients with varying degrees of hyperphenylalaninemia. PAH activity varied from below 1% of normal in patients with classic PKU to up to 35% of normal in those with a non-PKU form of hyperphenylalaninemia (such as a defect in BH_4 production; see Chapter 48).

The genetic diseases affecting amino acid degradation that have been discussed in this chapter are summarized in Table 39.1.

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REVIEW QUESTIONS—CHAPTER 39

- If an individual has a vitamin B6 deficiency, which of the following amino acids could still be synthesized and be considered nonessential?
 - Tyrosine
 - Serine
 - Alanine
 - Cysteine
 - Aspartate

2. The degradation of amino acids can be classified into families, which are named after the end product of the degradative pathway. Which of the following is such an end product?
- (A) Citrate
 - (B) Glyceraldehyde-3-phosphate
 - (C) Fructose-6-phosphate
 - (D) Malate
 - (E) Succinyl-CoA
3. A newborn infant has elevated levels of phenylalanine and phenylpyruvate in her blood. Which of the following enzymes might be deficient in this baby?
- (A) Phenylalanine dehydrogenase
 - (B) Phenylalanine oxidase
 - (C) Dihydropteridine reductase
 - (D) Tyrosine hydroxylase
 - (E) Tetrahydrofolate synthase
4. Pyridoxal phosphate is required for which of the following reaction pathways or individual reactions?
- (A) Phenylalanine \rightarrow tyrosine
 - (B) Methionine \rightarrow cysteine + α -ketobutyrate
 - (C) Propionyl CoA \rightarrow succinyl-CoA
 - (D) Pyruvate \rightarrow acetyl-CoA
 - (E) Glucose \rightarrow glycogen
5. A folic acid deficiency would interfere with the synthesis of which of the following amino acids from the indicated precursors?
- (A) Aspartate from oxaloacetate and glutamate
 - (B) Glutamate from glucose and ammonia
 - (C) Glycine from glucose and alanine
 - (D) Proline from glutamate
 - (E) Serine from glucose and alanine