SECTION III
Metabolism of Proteins & Amino Acids

Biosynthesis of the Nutritionally Nonessential Amino Acids

28

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BIOMEDICAL IMPORTANCE

All 20 of the amino acids present in proteins are essential for health. While comparatively rare in the Western world, amino acid deficiency states are endemic in certain regions of West Africa where the diet relies heavily on grains that are poor sources of amino acids such as tryptophan and lysine. These disorders include kwashiorkor, which results when a child is weaned onto a starchy diet poor in protein; and marasmus, in which both caloric intake and specific amino acids are deficient.

Humans can synthesize 12 of the 20 common amino acids from the amphibolic intermediates of glycolysis and of the citric acid cycle (Table 28–1). While *nutritionally* nonessential, these 12 amino acids are not "nonessential." All 20 amino acids are *biologically* essential. Of the 12 nutritionally nonessential amino acids, nine are formed from amphibolic intermediates and three (cysteine, tyrosine and hydroxylysine) from nutritionally essential amino acids. Identification of the twelve amino acids that humans can synthesize rested primarily on data derived from feeding diets in which purified amino acids replaced protein. This chapter considers only the biosynthesis of the twelve amino acids that are synthesized in human tissues, not the other eight that are synthesized by plants.

NUTRITIONALLY NONESSENTIAL AMINO ACIDS HAVE SHORT BIOSYNTHETIC PATHWAYS

The enzymes glutamate dehydrogenase, glutamine synthetase, and aminotransferases occupy central positions in amino acid biosynthesis. The combined effect of those three enzymes is to transform ammonium ion into the α-amino nitrogen of various amino acids.

Glutamate and Glutamine. Reductive amination of α-ketoglutarate is catalyzed by glutamate dehydrogenase (Figure 28–1). Amination of glutamate to glutamine is catalyzed by glutamine synthetase (Figure 28–2).

Alanine. Transamination of pyruvate forms alanine (Figure 28–3).

Aspartate and Asparagine. Transamination of oxaloacetate forms aspartate. The conversion of aspartate

Table 28–1. Amino acid requirements of humans.

Nutritionally Essential	Nutritionally Nonessential
Arginine[1]	Alanine
Histidine	Asparagine
Isoleucine	Aspartate
Leucine	Cysteine
Lysine	Glutamate
Methionine	Glutamine
Phenylalanine	Glycine
Threonine	Hydroxyproline[2]
Tryptophan	Hydroxylysine[2]
Valine	Proline
	Serine
	Tyrosine

[1]"Nutritionally semiessential." Synthesized at rates inadequate to support growth of children.
[2]Not necessary for protein synthesis but formed during post-translational processing of collagen.

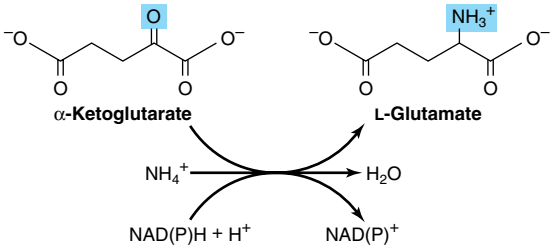

Figure 28–1. The glutamate dehydrogenase reaction.

to asparagine is catalyzed by asparagine synthetase (Figure 28–4), which resembles glutamine synthetase (Figure 28–2) except that glutamine, not ammonium ion, provides the nitrogen. Bacterial asparagine synthetases can, however, also use ammonium ion. Coupled hydrolysis of PP_i to P_i by pyrophosphatase ensures that the reaction is strongly favored.

Serine. Oxidation of the α-hydroxyl group of the glycolytic intermediate 3-phosphoglycerate converts it to an oxo acid, whose subsequent transamination and dephosphorylation leads to serine (Figure 28–5).

Glycine. Glycine aminotransferases can catalyze the synthesis of glycine from glyoxylate and glutamate or alanine. Unlike most aminotransferase reactions, these strongly favor glycine synthesis. Additional important mammalian routes for glycine formation are from choline (Figure 28–6) and from serine (Figure 28–7).

Proline. Proline is formed from glutamate by reversal of the reactions of proline catabolism (Figure 28–8).

Cysteine. Cysteine, while not nutritionally essential, is formed from methionine, which is nutritionally essential. Following conversion of methionine to ho-

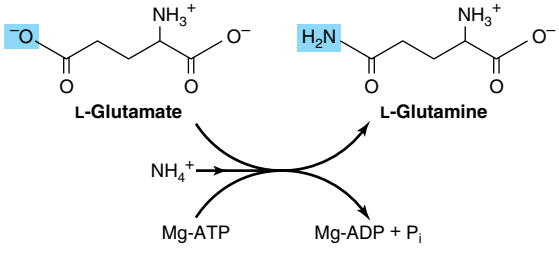

Figure 28–2. The glutamine synthetase reaction.

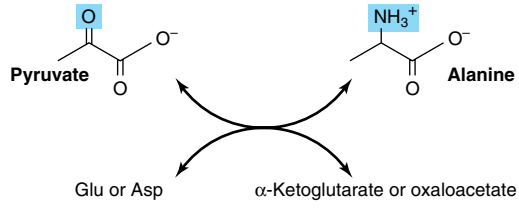

Figure 28–3. Formation of alanine by transamination of pyruvate. The amino donor may be glutamate or aspartate. The other product thus is α-ketoglutarate or oxaloacetate.

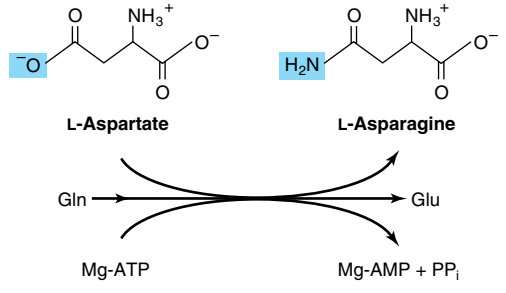

Figure 28–4. The asparagine synthetase reaction. Note similarities to and differences from the glutamine synthetase reaction (Figure 28–2).

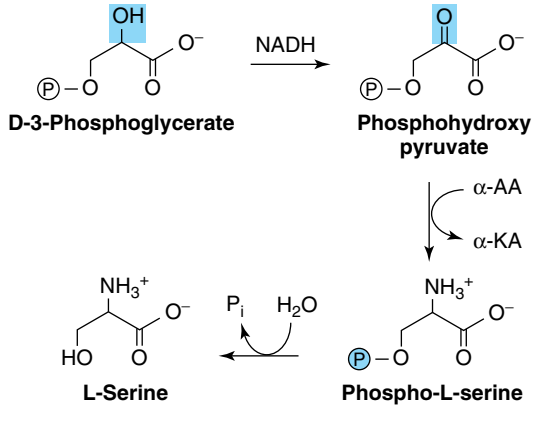

Figure 28–5. Serine biosynthesis. (α-AA, α-amino acids; α-KA, α-keto acids.)

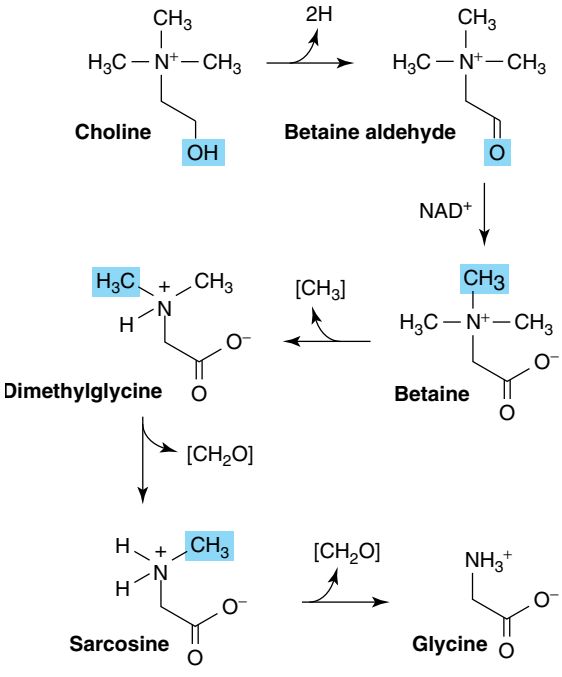

Figure 28–6. Formation of glycine from choline.

mocysteine (see Chapter 30), homocysteine and serine form cysteine and homoserine (Figure 28–9).

Tyrosine. Phenylalanine hydroxylase converts phenylalanine to tyrosine (Figure 28–10). Provided that the diet contains adequate nutritionally essential phenylalanine, tyrosine is nutritionally nonessential. But since the reaction is irreversible, dietary tyrosine cannot replace phenylalanine. Catalysis by this mixed-function oxygenase incorporates one atom of O_2 into phenylalanine and reduces the other atom to water. Reducing power, provided as tetrahydrobiopterin, derives ultimately from NADPH.

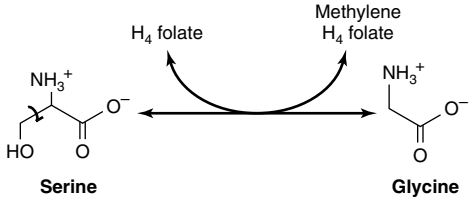

Figure 28–7. The serine hydroxymethyltransferase reaction. The reaction is freely reversible. (H_4 folate, tetrahydrofolate.)

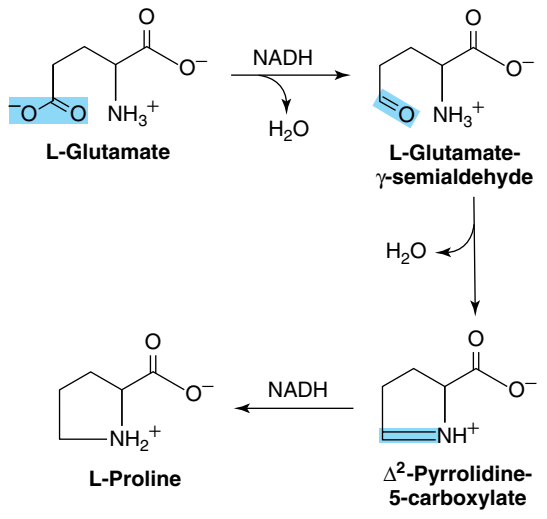

Figure 28–8. Biosynthesis of proline from glutamate by reversal of reactions of proline catabolism.

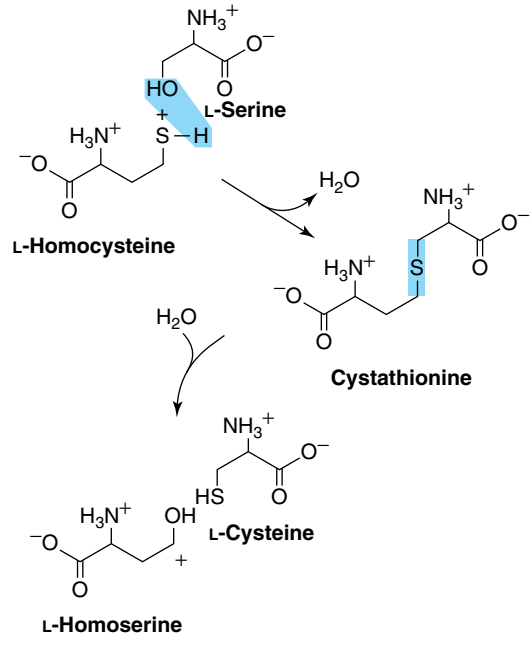

Figure 28–9. Conversion of homocysteine and serine to homoserine and cysteine. The sulfur of cysteine derives from methionine and the carbon skeleton from serine.

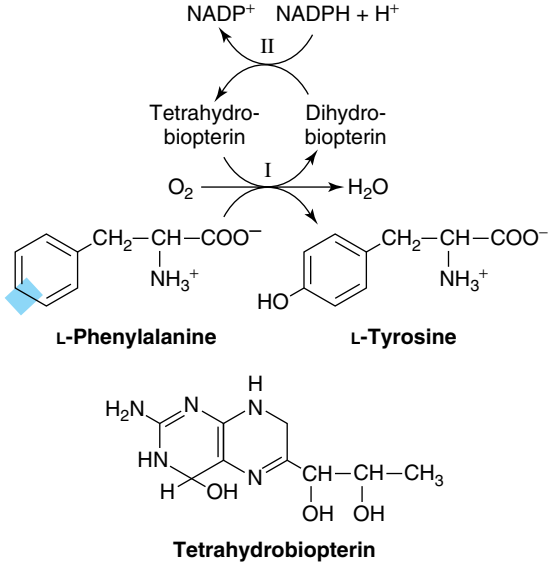

Figure 28–10. The phenylalanine hydroxylase reaction. Two distinct enzymatic activities are involved. Activity II catalyzes reduction of dihydrobiopterin by NADPH, and activity I the reduction of O_2 to H_2O and of phenylalanine to tyrosine. This reaction is associated with several defects of phenylalanine metabolism discussed in Chapter 30.

Hydroxyproline and Hydroxylysine. Hydroxyproline and hydroxylysine are present principally in collagen. Since there is no tRNA for either hydroxylated amino acid, neither dietary hydroxyproline nor hydroxylysine is incorporated into protein. Both are completely degraded (see Chapter 30). Hydroxyproline and hydroxylysine arise from proline and lysine, but only after these amino acids have been incorporated into peptides. Hydroxylation of peptide-bound prolyl and lysyl residues is catalyzed by prolyl hydroxylase and lysyl hydroxylase of tissues, including skin and skeletal muscle, and of granulating wounds (Figure 28–11). The hydroxylases are mixed-function oxygenases that require substrate, molecular O_2, ascorbate, Fe^{2+}, and α-ketoglutarate. For every mole of proline or lysine hydroxylated, one mole of α-ketoglutarate is decarboxylated to succinate. One atom of O_2 is incorporated into proline or lysine, the other into succinate (Figure 28–11). A deficiency of the vitamin C required for these hydroxylases results in scurvy.

Valine, Leucine, and Isoleucine. While leucine, valine, and isoleucine are all nutritionally essential

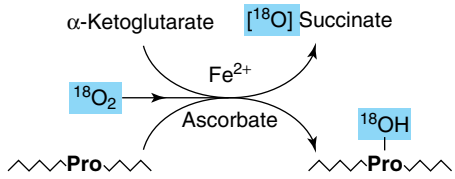

Figure 28–11. The prolyl hydroxylase reaction. The substrate is a proline-rich peptide. During the course of the reaction, molecular oxygen is incorporated into both succinate and proline. Lysyl hydroxylase catalyzes an analogous reaction.

amino acids, tissue aminotransferases reversibly interconvert all three amino acids and their corresponding α-keto acids. These α-keto acids thus can replace their amino acids in the diet.

Selenocysteine. While not normally considered an amino acid present in proteins, selenocysteine occurs at the active sites of several enzymes. Examples include the human enzymes thioredoxin reductase, glutathione peroxidase, and the deiodinase that converts thyroxine to triiodothyronine. Unlike hydroxyproline or hydroxylysine, selenocysteine arises co-translationally during its incorporation into peptides. The UGA anticodon of the unusual tRNA designated $tRNA^{Sec}$ normally signals STOP. The ability of the protein synthetic apparatus to identify a selenocysteine-specific UGA codon involves the selenocysteine insertion element, a stem-loop structure in the untranslated region of the mRNA. Selenocysteine-$tRNA^{Sec}$ is first charged with serine by the ligase that charges $tRNA^{Ser}$. Subsequent replacement of the serine oxygen by selenium involves selenophosphate formed by selenophosphate synthase (Figure 28–12).

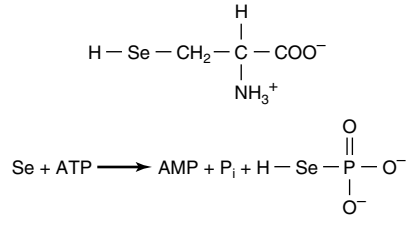

Figure 28–12. Selenocysteine *(top)* and the reaction catalyzed by selenophosphate synthetase *(bottom)*.

SUMMARY

- All vertebrates can form certain amino acids from amphibolic intermediates or from other dietary amino acids. The intermediates and the amino acids to which they give rise are α-ketoglutarate (Glu, Gln, Pro, Hyp), oxaloacetate (Asp, Asn) and 3-phosphoglycerate (Ser, Gly).
- Cysteine, tyrosine, and hydroxylysine are formed from nutritionally essential amino acids. Serine provides the carbon skeleton and homocysteine the sulfur for cysteine biosynthesis. Phenylalanine hydroxylase converts phenylalanine to tyrosine.
- Neither dietary hydroxyproline nor hydroxylysine is incorporated into proteins because no codon or tRNA dictates their insertion into peptides.
- Peptidyl hydroxyproline and hydroxylysine are formed by hydroxylation of peptidyl proline or lysine in reactions catalyzed by mixed-function oxidases that require vitamin C as cofactor. The nutritional disease scurvy reflects impaired hydroxylation due to a deficiency of vitamin C.
- Selenocysteine, an essential active site residue in several mammalian enzymes, arises by co-translational insertion of a previously modified tRNA.

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