Biosynthesis of non-essential amino acids

Department of Biochemistry

Specific Learning Objectives

1. Biosynthesis of non-essential amino acids (body can synthesize them from other proteins so not essential to eat them)

Essential and non-essential amino acids

- Essential aa: Cannot be synthesize in body so "essential" to eat them from dietary food.
- Non-essential: Body can synthesize them from other proteins so not essential to eat them

TABLE 27-1 Amino Acid Requirements of Humans

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

Table 27.1. Harper's Illustrated Biochemistry 30th Edition

Overview of amino acid biosynthesis

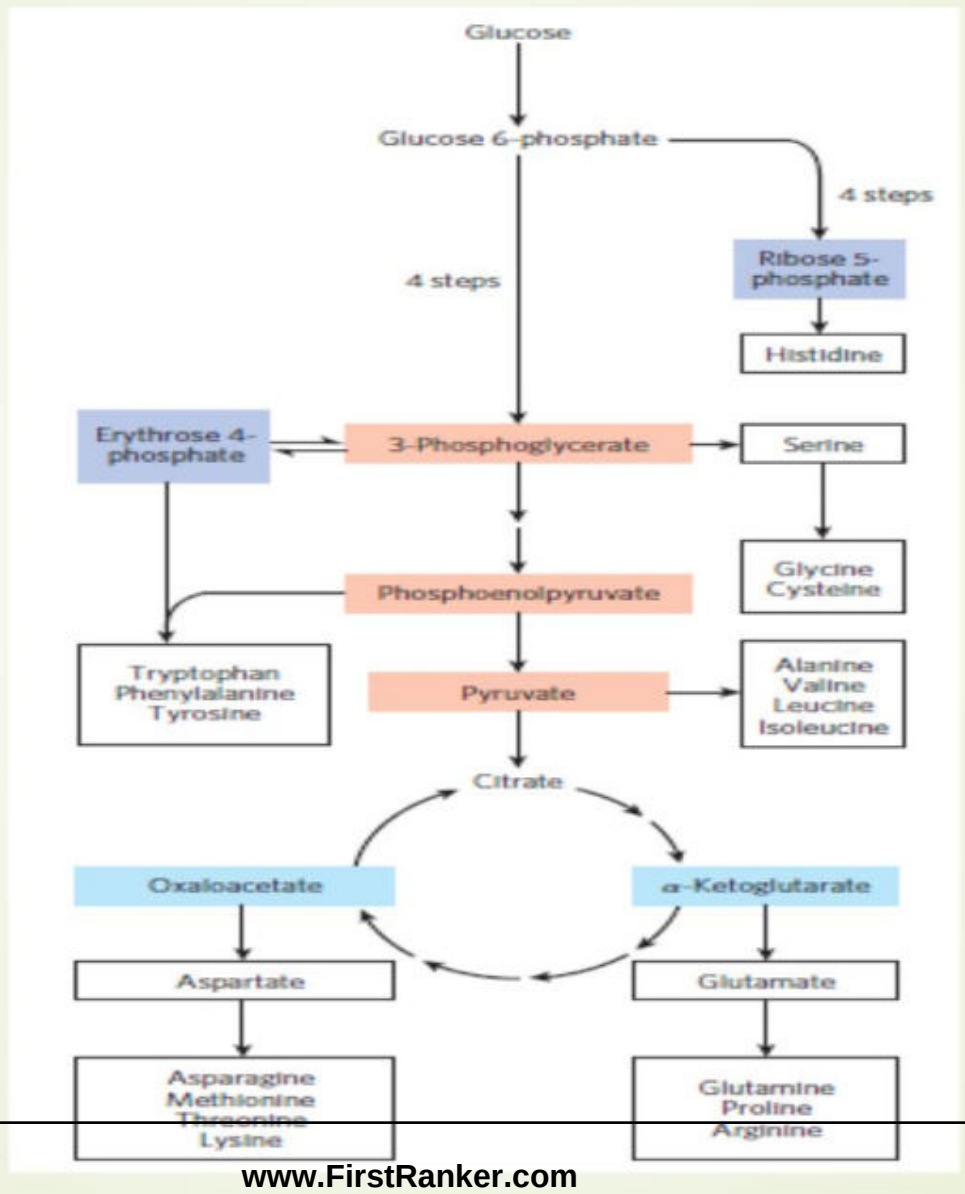

Fig22.11: Lehninger Principles of Biochemistry by David L Nelson, 6th Ed.

Glutamate

- Glutamate, is formed by the amidation of α-ketoglutarate, catalyzed by mitochondrial glutamate dehydrogenase
- It require NADPH as a reducing agent
- The reaction strongly favors glutamate synthesis, which lowers the concentration of cytotoxic ammonium ion.

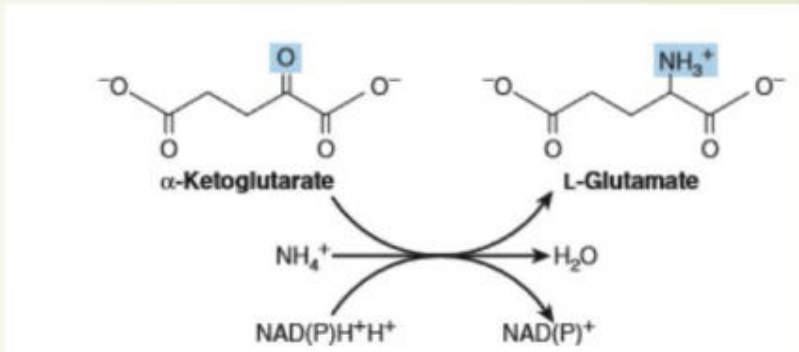

FIGURE 27–1 The reaction catalyzed by glutamate dehydrogenase (EC 1.4.1.3).

Glutamine

- Amidation of glutamate to glutamine catalyzed by glutamine synthetase, involves intermediate formation of γ-glutamyl phosphate
- In Binding of glutamate and ATP, glutamate attacks γ-phosphorus of ATP, forming γ-glutamyl phosphate and ADP
- NH4+ binds, and uncharged NH_3 attacks γ-glutamyl phosphate
- Release of Pi and of a proton from γ-amino group of tetrahedral intermediate then allows release of product, glutamine

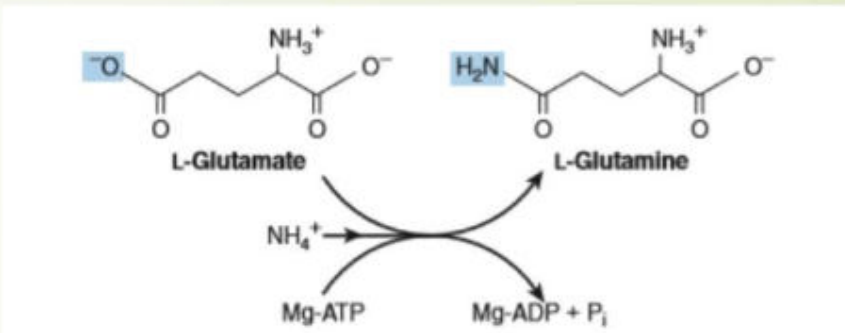

FIGURE 27–2 The reaction catalyzed by glutamine synthetase (EC 6.3.1.2).

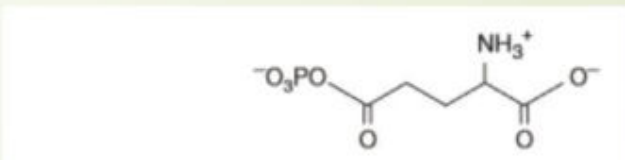
FIGURE 27–3 γ-Glutamyl phosphate.

Alanine & Aspartate

- Transamination of pyruvate forms alanine
- Similarly, transamination of oxaloacetate forms aspartate

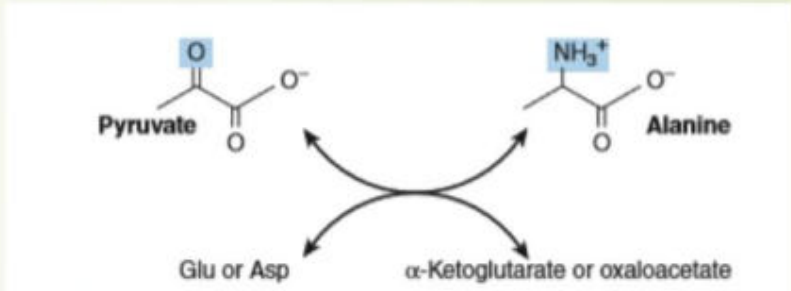

FIGURE 27–4 Formation of alanine by transamination of pyruvate. The amino donor may be glutamate or aspartate. The other product thus is α-ketoglutarate or oxaloacetate.

Asparagine

- Conversion of aspartate to asparagine, catalyzed by asparagine synthetase
- Reaction involves intermediate formation of aspartyl phosphate
- Coupled hydrolysis of PPi to Pi by pyrophosphatase, ensures that reaction is strongly favored

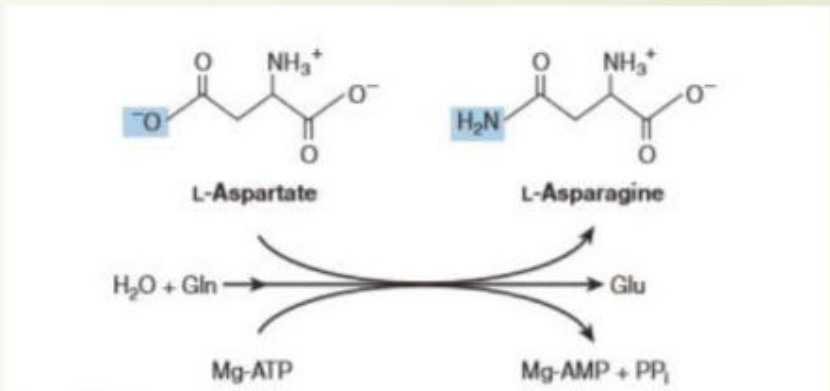

FIGURE 27–5 The reaction catalyzed by asparagine synthetase (EC 6.3.5.4). Note similarities to and differences from the glutamine synthetase reaction (Figure 27–2).

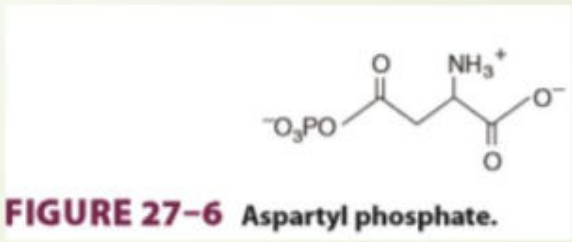

FIGURE 27–6 Aspartyl phosphate.

Serine

- Oxidation of α-hydroxyl group of glycolytic intermediate 3-phosphoglycerate, catalysed by 3-phosphoglycerate dehydrogenase, converts it to 3-phosphohydroxypyruvate

- Transamination and subsequent dephosphorylation then form serine

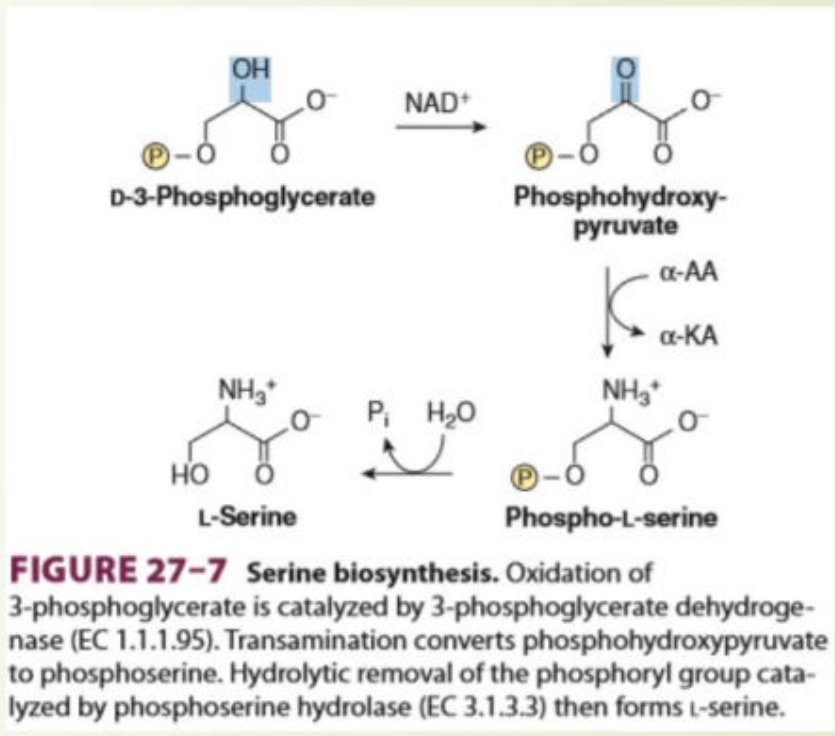

FIGURE 27–7 **Serine biosynthesis.** Oxidation of 3-phosphoglycerate is catalyzed by 3-phosphoglycerate dehydrogenase (EC 1.1.1.95). Transamination converts phosphohydroxypyruvate to phosphoserine. Hydrolytic removal of the phosphoryl group catalyzed by phosphoserine hydrolase (EC 3.1.3.3) then forms L-serine.

Glycine

- Glycine aminotransferases can catalyze synthesis of glycine from glyoxylate and glutamate or alanine.

- Unlike most aminotransferase reactions, these strongly favor glycine synthesis

- Important mammalian routes for glycine formation are from choline

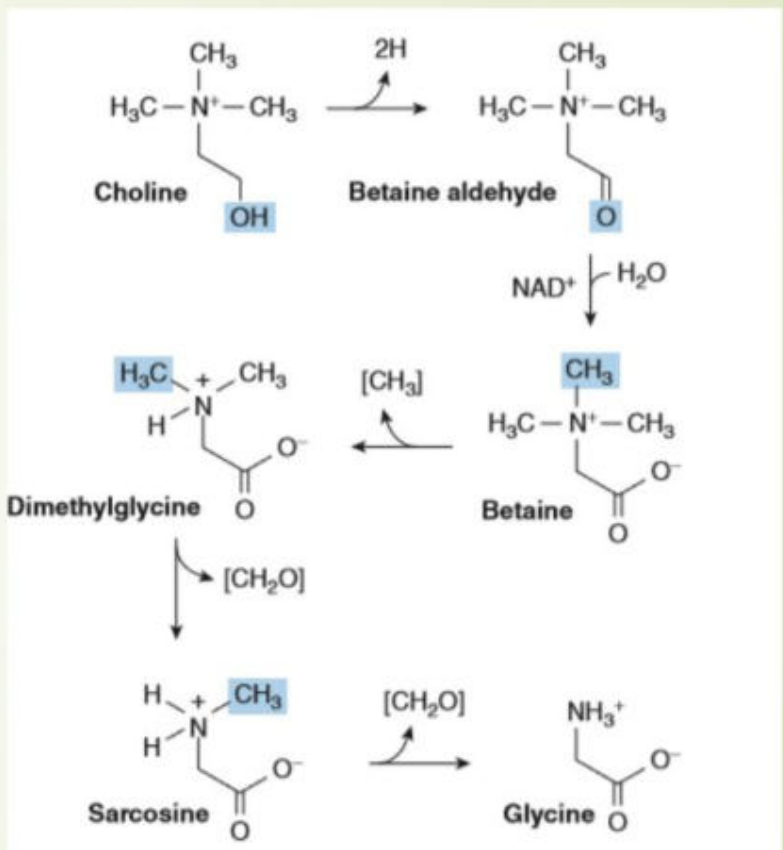

FIGURE 27–8 **Formation of glycine from choline.** Catalysts include choline dehydrogenase (EC 1.1.91.1), betaine dehydrogenase (EC 1.2.1.8), betaine-homocysteine *N*-methyltransferase, sarcosine dehydrogenase (EC 1.5.8.3), and dimethylglycine dehydrogenase (EC 1.5.99.2).

Cont--

- Glycine formation are from serine

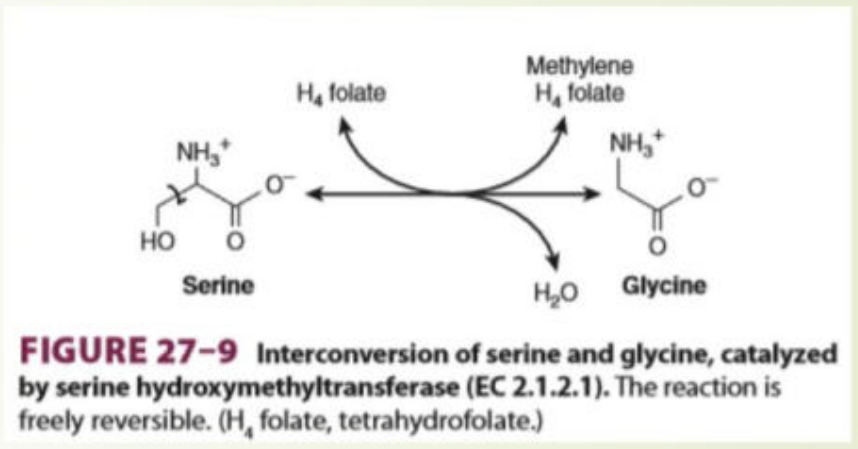

FIGURE 27–9 **Interconversion of serine and glycine, catalyzed by serine hydroxymethyltransferase (EC 2.1.2.1).** The reaction is freely reversible. (H_4 folate, tetrahydrofolate.)

Proline

- Initial reaction of proline biosynthesis converts γ-carboxyl group of glutamate to mixed acid anhydride of glutamate γ-phosphate

- Subsequent reduction forms glutamate γ-semialdehyde, which following spontaneous cyclization is reduced to proline

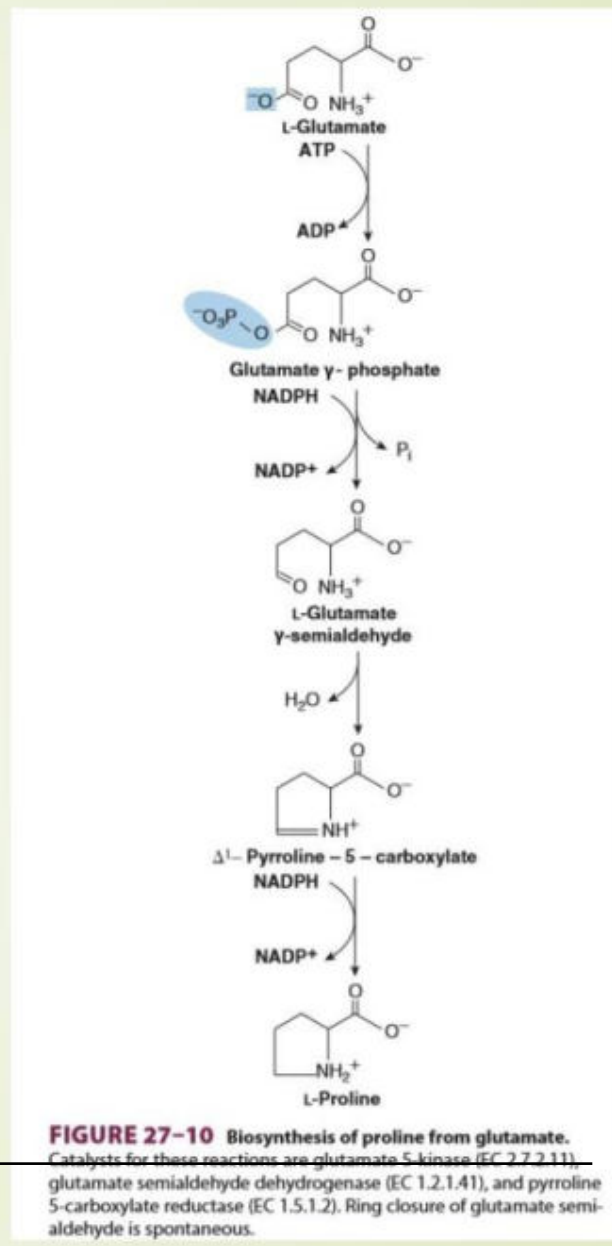

FIGURE 27–10 **Biosynthesis of proline from glutamate.** Catalysts for these reactions are glutamate 5-kinase (EC 2.7.2.11), glutamate semialdehyde dehydrogenase (EC 1.2.1.41), and pyrroline 5-carboxylate reductase (EC 1.5.1.2). Ring closure of glutamate semialdehyde is spontaneous.

Cysteine

- While not nutritionally essential, cysteine is formed from methionine, which is nutritionally essential
- Following conversion of methionine to homocysteine, homocysteine and serine form cystathionine, whose hydrolysis forms cysteine and homoserine

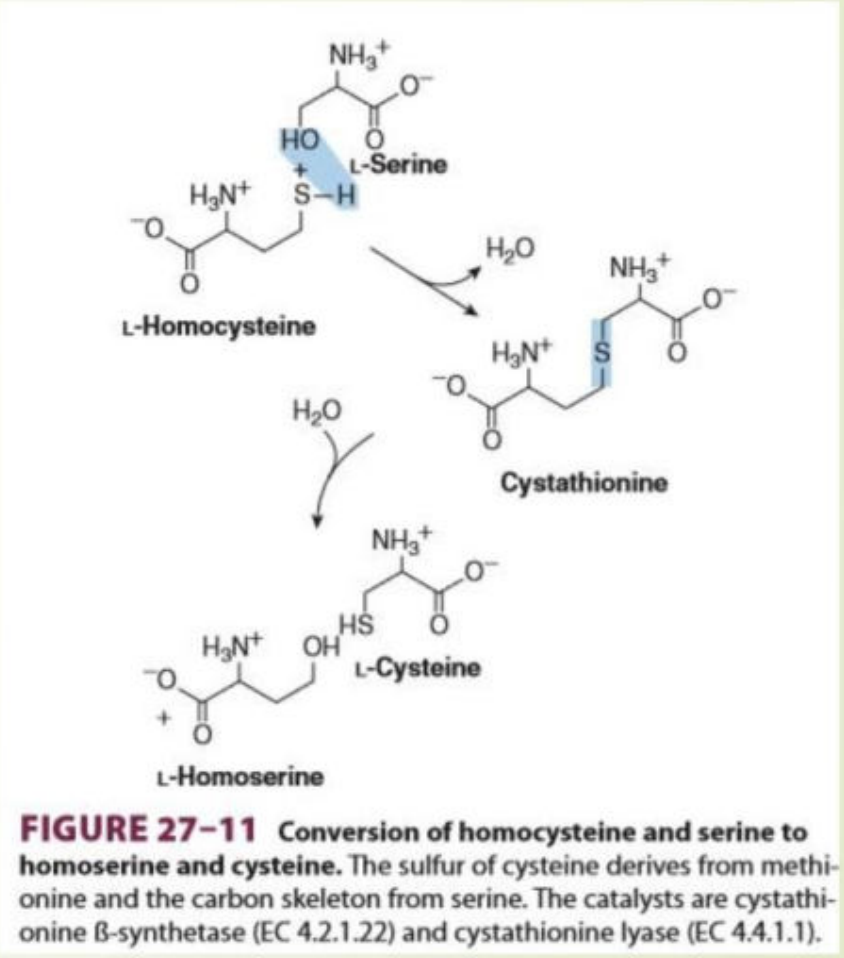

FIGURE 27–11 Conversion of homocysteine and serine to homoserine and cysteine. The sulfur of cysteine derives from methionine and the carbon skeleton from serine. The catalysts are cystathionine ß-synthetase (EC 4.2.1.22) and cystathionine lyase (EC 4.4.1.1).

Tyrosine

- Phenylalanine hydroxylase converts phenylalanine to tyrosine
- Phenylalanine hydroxylase reaction is irreversible, dietary tyrosine cannot replace phenylalanine
- Catalysis by this mixed-function oxidase incorporates one atom of O_2 into para position of phenylalanine and reduces other atom to water
- Reducing power, provided as tetrahydrobiopterin derives ultimately from NADPH

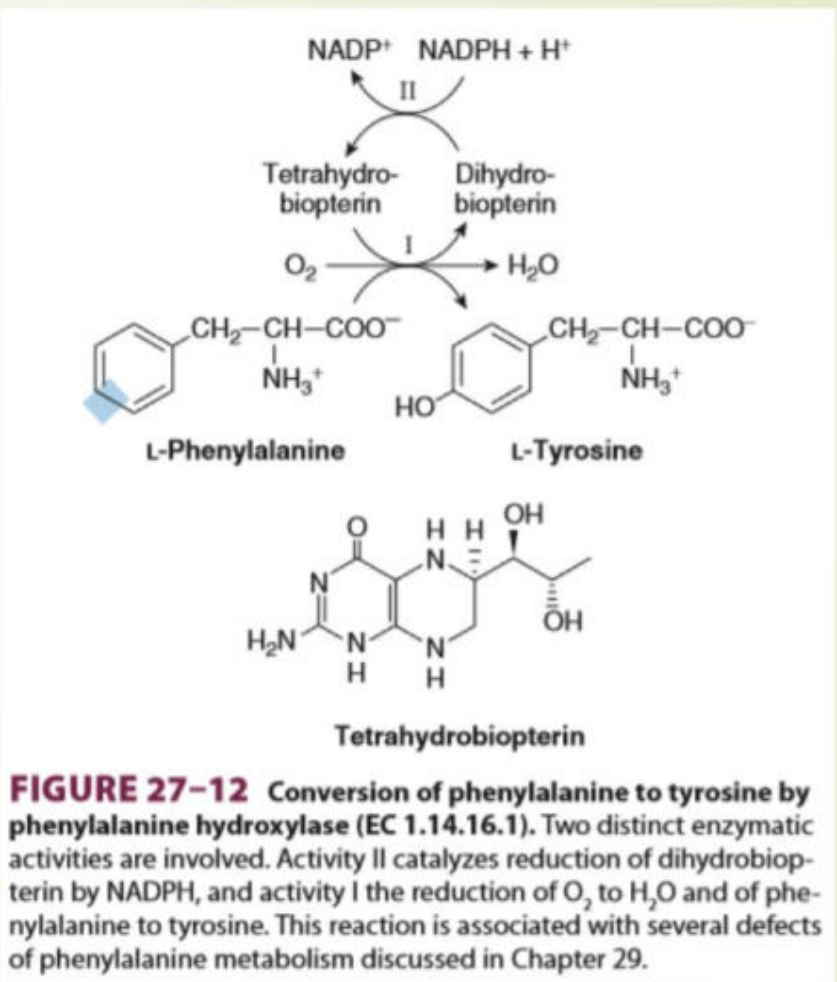

FIGURE 27–12 Conversion of phenylalanine to tyrosine by phenylalanine hydroxylase (EC 1.14.16.1). Two distinct enzymatic activities are involved. Activity II catalyzes reduction of dihydrobiopterin by NADPH, and activity I the reduction of O_2 to H_2O and of phenylalanine to tyrosine. This reaction is associated with several defects of phenylalanine metabolism discussed in Chapter 29.

Valine, Leucine, & Isoleucine

- While leucine, valine, and isoleucine are all nutritionally essential 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 diet

Hydroxyproline & Hydroxylysine

- Peptidyl hydroxyproline and hydroxylysine arise from proline and lysine
- Hydroxylation of peptidyl prolyl and peptidyl lysyl residues, catalyzed by prolyl hydroxylase and lysyl hydroxylase of skin, skeletal muscle, and granulating wounds requires, in addition to the substrate, molecular O2, ascorbate, Fe2+, and α-ketoglutarate
- For every mole of proline or lysine hydroxylated, one mole of α-ketoglutarate is decarboxylated to succinate
- A deficiency of the vitamin C required for these two hydroxylases results in scurvy

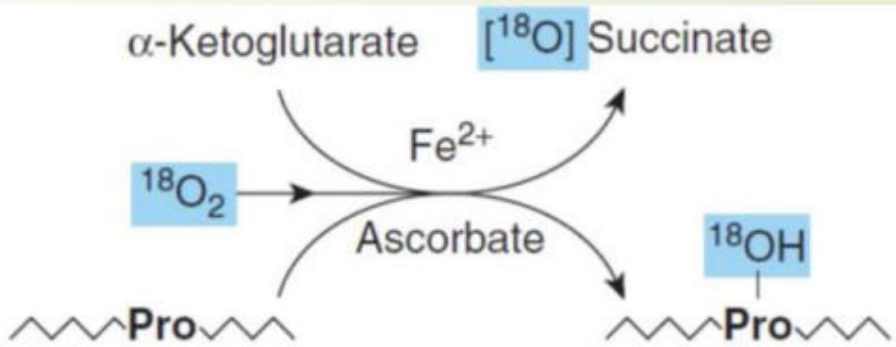

FIGURE 27–13 Hydroxylation of a proline-rich peptide. Molecular oxygen is incorporated into both succinate and proline. Peptidyl prolyl 4-hydroxylase (EC 1.14.11.2) thus is a mixed function oxidase. Lysyl 5-hydroxylase (EC 1.14.11.4) catalyzes an analogous reaction.

Two Clinical-cases discussed

Group Discussion and Rivision

- Subtopics of previous and today's class discussed in groups.

Reference Books

1) Lehninger Principles of Biochemistry, 6th Ed.
2) Harper's Illustrated Biochemistry-30th edition
3) Biochemistry, Lippincott's Illustrated Reviews, 6th Ed
4) Gregory S. Ducker and Joshua D Rabinowitz. Cell Metab. 2017 Jan 10;25(1):27-42

Thank you