Department of Biochemistry

Learning Objectives

1. Biosynthesis of non-essential amino acids:

- Alanine
- Asparagine & Aspartate
- Cysteine
- Glutamate
- Glutamine
- Glycine
- Proline
- Serine
- Tyrosine
- Hydroxyproline and Hydroxylysine

Biosynthesis of non-essential amino acids

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

Glutamate

- Glutamate, is formed by amidation of α-ketoglutarate, catalyzed by mitochondrial glutamate dehydrogenase

- It require NADPH as a reducing agent

- This reaction strongly favors glutamate synthesis, which lowers the concentration of cytotoxic ammonium ion.

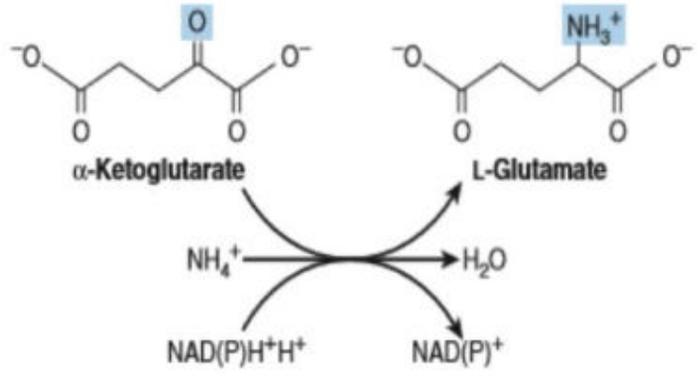

FIGURE 27–1 The reaction catalyzed by glutamate dehydrogenase (EC 1.4.1.3).

Fig 27.1. Harper's Illustrated Biochemistry 30th Edition

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- NH4+ binds, and uncharged NH_3 attacks γ-glutamyl phosphate

- Release of Pi and of a proton from the γ-amino group of the tetrahedral intermediate then allows release of the product, glutamine

Glutamine

- Amidation of glutamate to glutamine catalyzed by glutamine synthetase

- Glutamine, is amino group donor in formation of many biosynthetic products, as well as being a storage form of ammonia

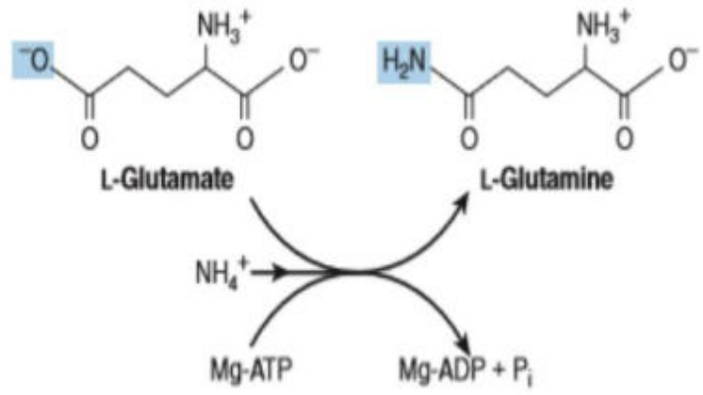

FIGURE 27–2 The reaction catalyzed by glutamine synthetase (EC 6.3.1.2). Fig 27.2. Harper's Illustrated Biochemistry 30th Edition

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- Mammalian Glutamine synthetases are activated by α-ketoglutarate, the product of glutamate's oxidative deamination

- This prevents the accumulation of the ammonia produced by that reaction

Alanine

- Transamination of pyruvate forms alanine by aminotransferase

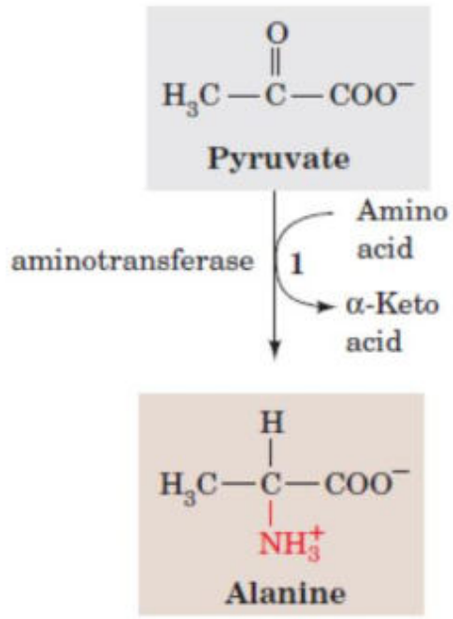

Fig.26.54. Biochemistry. 4th edition by Donald Voet and Judith G. Voet

Aspartate

- Transamination of oxaloacetate forms aspartate by aminotransferase

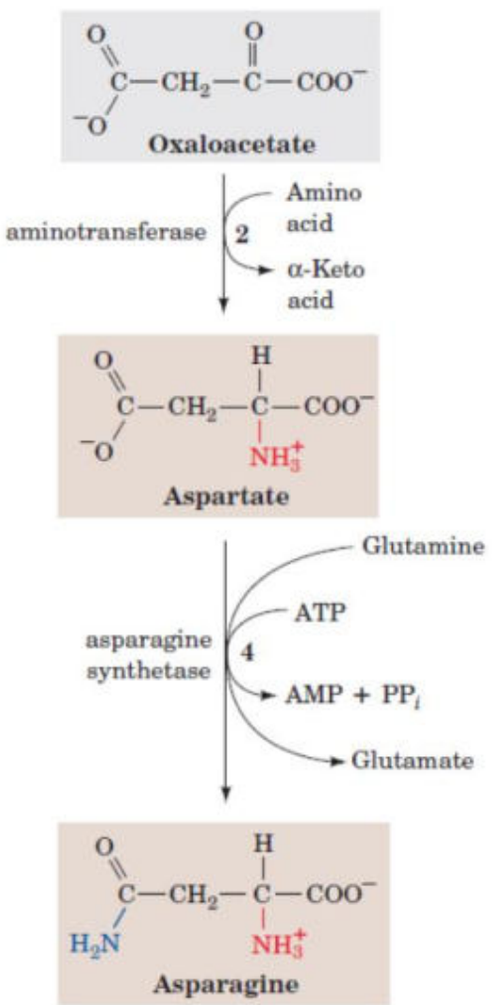

Fig.26.54. Biochemistry. 4th edition by Donald Voet and Judith G. Voet

Asparagine

- Conversion of aspartate to asparagine, by amidation reaction and catalyzed by asparagine synthetase

- ATP is needed to activate the receptor a carboxyl group

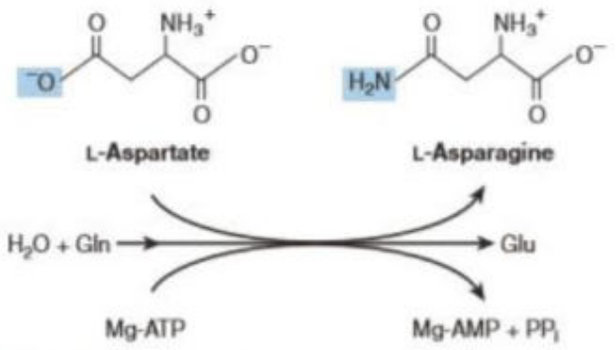

FIGURE 27–5 **The reaction catalyzed by asparagine synthetase (EC 6.3.5.4).** Note similarities to and differences from the glutamine synthetase reaction (Figure 27–2).

Fig 27.5. Harper's Illustrated Biochemistry 30th Edition

- Asparagine is readily synthesized in most cells, but some leukemic cells lost this ability

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- Therapeutic approach for patients with asparagine synthetase deficient tumors is treatment with exogenous asparaginase to hydrolyze the bloodborne asparagine on which these cells rely

- Normal cells synthesize and degrade asparagine.

Serine

The pathway enzymes are:

- 3-phosphoglycerate dehydrogenase
- PLP-dependent aminotransferase
- Phosphoserine phosphatase.

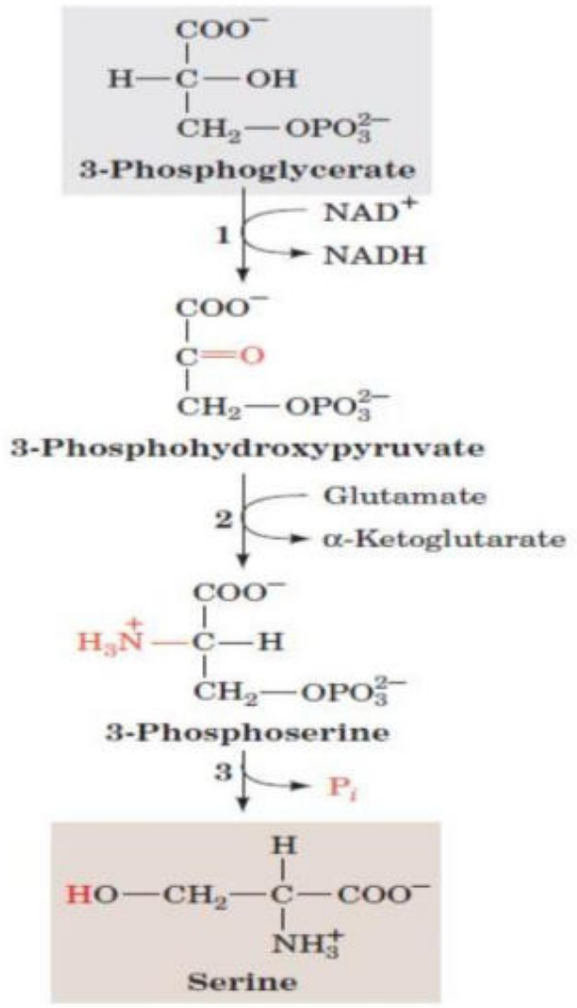

Fig.26.58. Biochemistry. 4th edition by Donald Voet and Judith G. Voet

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

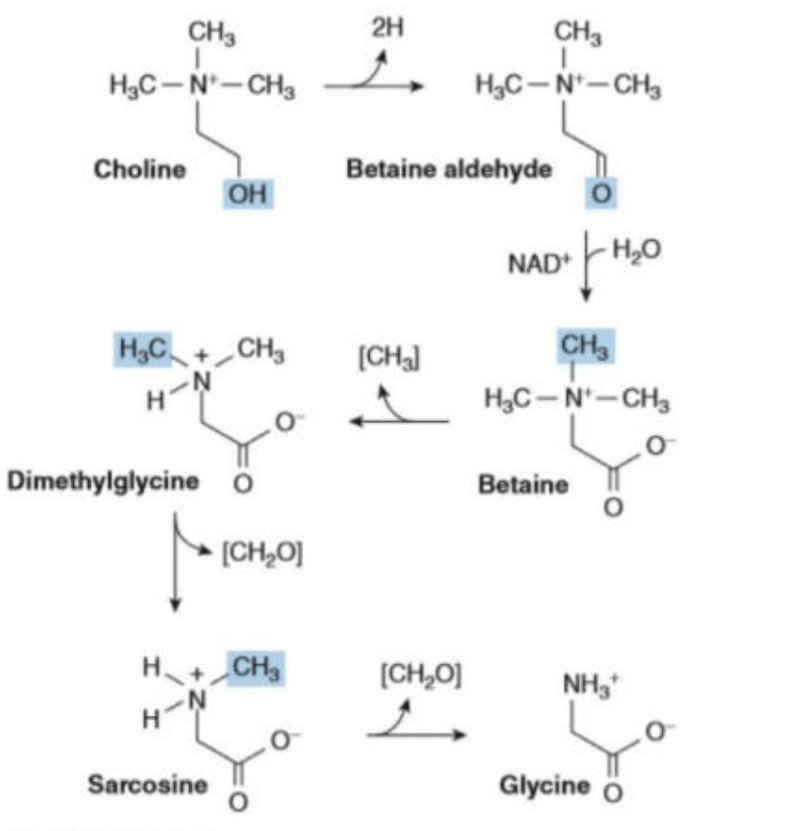

FIGURE 27–8 Formation of glycine from choline. Catalysts include choline dehydrogenase (EC 1.1.91.1), betaine dehydrogenase (EC 1.2.1.8), betaine-homocysteine *N*-methyltransferase, sarcosine dehydrogenase (EC 1.5.8.3), and dimethylglycine dehydrogenase (EC 1.5.99.2). Fig 27.8. Harper's Illustrated Biochemistry 30th Edition

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Serine participates in glycine synthesis in two ways:

1. Direct conversion of serine to glycine by serine hydroxymethyl transferase in a reaction that also yields N5,N10-methylene-THF

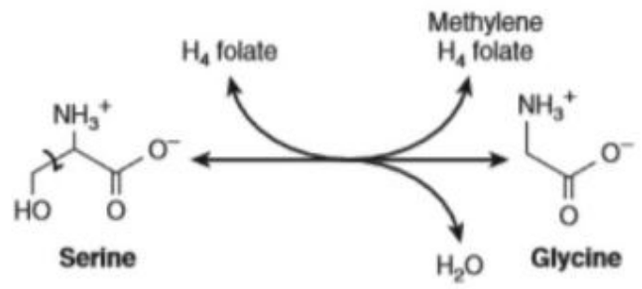

FIGURE 27–9 Interconversion of serine and glycine, catalyzed by serine hydroxymethyltransferase (EC 2.1.2.1). The reaction is freely reversible. (H_4 folate, tetrahydrofolate.)

Fig 27.9. Harper's Illustrated Biochemistry 30th Edition

2. Condensation of the N5,N10-methylene-THF with CO2 and by the glycine cleavage system

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

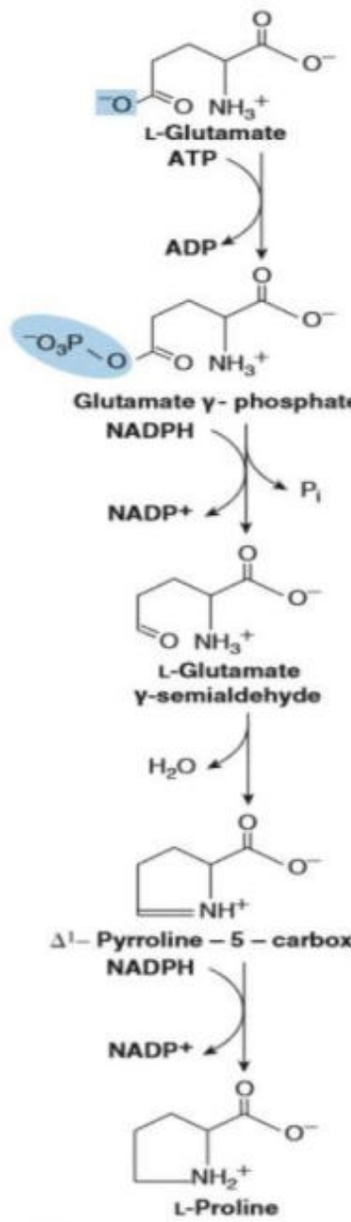

FIGURE 27–10 Biosynthesis of proline from glutamate. Catalysts for these reactions are glutamate 5-kinase (EC 2.7.2.11), glutamate semialdehyde dehydrogenase (EC 1.2.1.41), and pyrroline 5-carboxylate reductase (EC 1.5.1.2). Ring closure of glutamate semialdehyde is spontaneous.

Fig 27.10. Harper's Illustrated Biochemistry 30th Edition

Cysteine

- While not nutritionally essential, cysteine is formed from methionine
- Require for formation of glutathione, which is imp for transport of aa
- Homocystinuria occur due to deficiency of cystathionine β-synthase

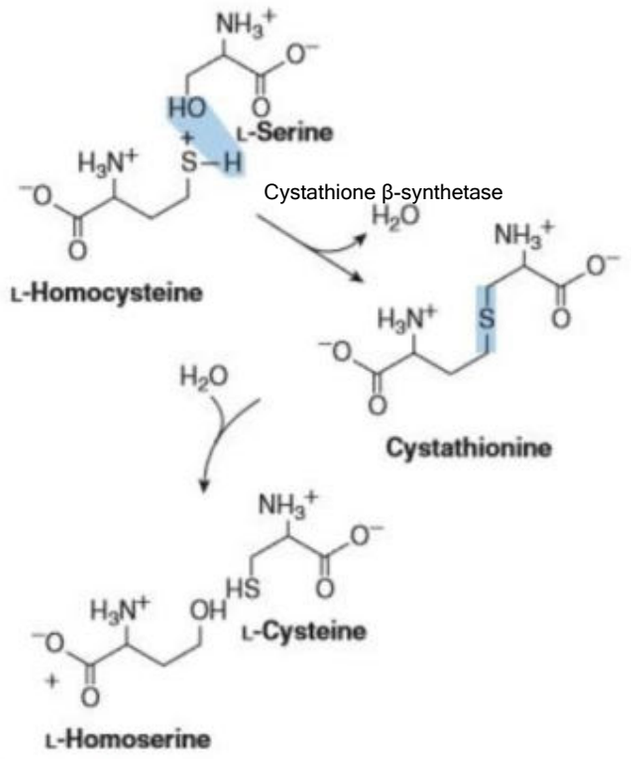

FIGURE 27–11 Conversion of homocysteine and serine to homoserine and cysteine. The sulfur of cysteine derives from methionine and the carbon skeleton from serine. The catalysts are cystathionine ß-synthetase (EC 4.2.1.22) and cystathionine lyase (EC 4.4.1.1).

Fig 27.11. Harper's Illustrated Biochemistry 30th Edition

Tyrosine

- Phenylalanine hydroxylase converts phenylalanine to tyrosine
- Its irreversible reaction, dietary tyrosine cannot replace phenylalanine

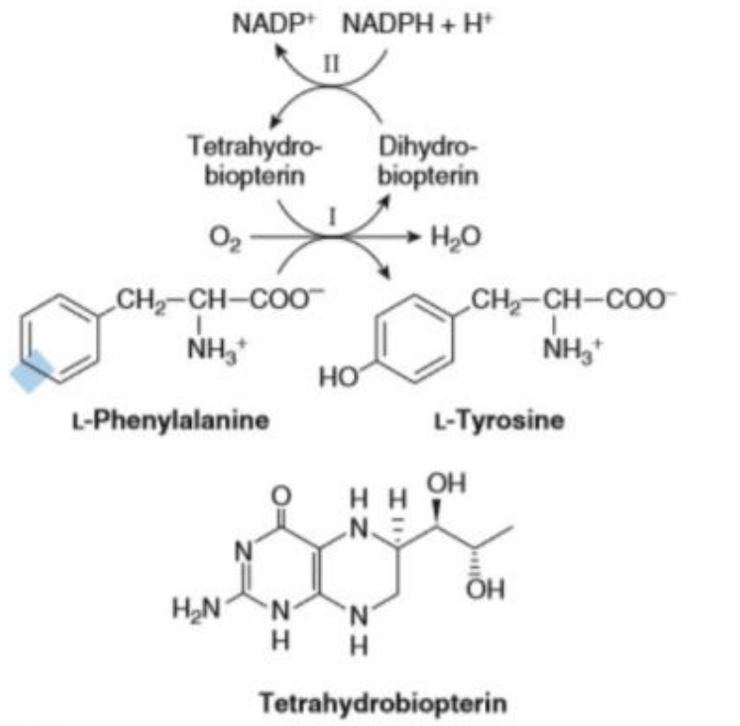

FIGURE 27–12 Conversion of phenylalanine to tyrosine by phenylalanine hydroxylase (EC 1.14.16.1). Two distinct enzymatic activities are involved. Activity II catalyzes reduction of dihydrobiopterin by NADPH, and activity I the reduction of O_2 to H_2O and of phenylalanine to tyrosine. This reaction is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

Fig 27.12. Harper's Illustrated Biochemistry 30th Edition

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- 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 from NADPH

Branched chain aa (Valine, Leucine, & Isoleucine)

- While leucine, valine, and isoleucine are all nutritionally essential aa , tissue aminotransferases reversibly interconvert all three aa and their corresponding α-keto acids.

- These α-keto acids can replace their aa 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

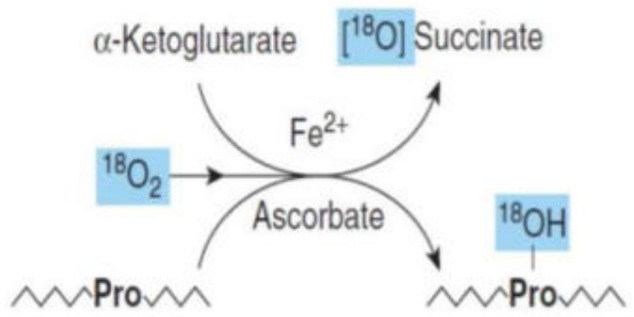

FIGURE 27–13 Hydroxylation of a proline-rich peptide. Molecular oxygen is incorporated into both succinate and proline. Peptidyl prolyl 4-hydroxylase (EC 1.14.11.2) thus is a mixed function oxidase. Lysyl 5-hydroxylase (EC 1.14.11.4) catalyzes an analogous reaction. Fig 27.13. Harper's Illustrated Biochemistry 30th Edition

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- 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

Amino acid degradation and related disorders

Summary of Amino acid Catabolism

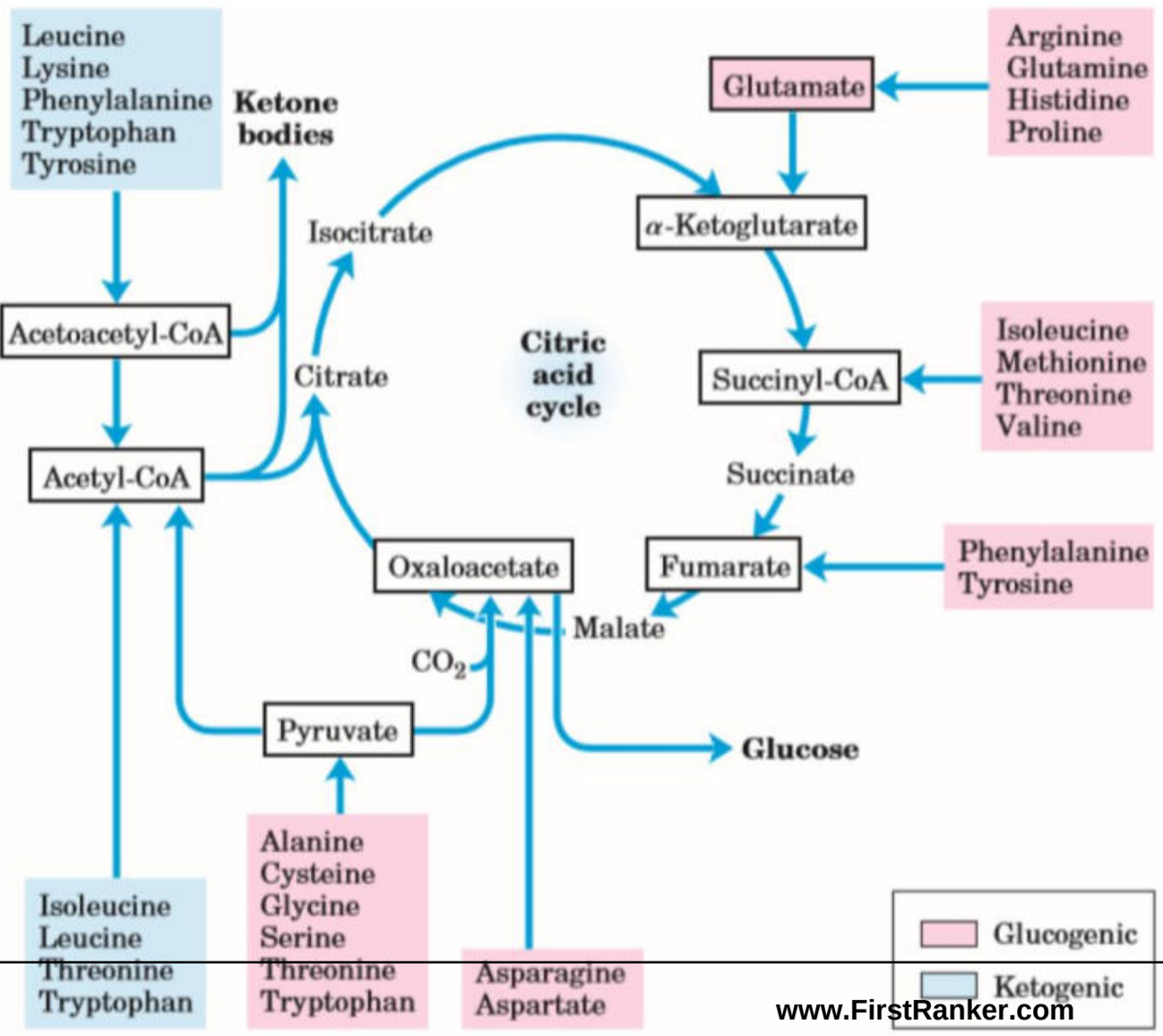

FIGURE 18–15 Summary of amino acid catabolism. Amino acids are grouped according to their major degradative end product. Some amino acids are listed more than once because different parts of their carbon skeletons are degraded to different end products. The figure shows the most important catabolic pathways in vertebrates, but there are minor variations among vertebrate species. Threonine, for instance, is degraded via at least two different pathways (see Figs 18–19, 18–27), and the importance of a given pathway can vary with the organism and its metabolic conditions. The glucogenic and ketogenic amino acids are also delineated in the figure, by color shading. Notice that five of the amino acids are both glucogenic and ketogenic. The amino acids degraded to pyruvate are also potentially ketogenic. Only two amino acids leucine and lysine, are exclusively ketogenic

Fig18.15: Lehninger Principles of Biochemistry by David L Nelson

Genetic disorders related to Amino-acid catabolism

TABLE 18–2 Some Human Genetic Disorders Affecting Amino Acid Catabolism

Medical condition	*Approximate incidence (per 100,000 births)*	*Defective process*	*Defective enzyme*	*Symptoms and effects*
Albinism	<3	Melanin synthesis from tyrosine	Tyrosine 3-monooxygenase (tyrosinase)	Lack of pigmentation: white hair, pink skin
Alkaptonuria	<0.4	Tyrosine degradation	Homogentisate 1,2-dioxygenase	Dark pigment in urine; late-developing arthritis
Argininemia	<0.5	Urea synthesis	Arginase	Mental retardation
Argininosuccinic acidemia	<1.5	Urea synthesis	Argininosuccinase	Vomiting; convulsions
Carbamoyl phosphate synthetase I deficiency	<0.5	Urea synthesis	Carbamoyl phosphate synthetase I	Lethargy; convulsions; early death
Homocystinuria	<0.5	Methionine degradation	Cystathionine β-synthase	Faulty bone development; mental retardation
Maple syrup urine disease (branched-chain ketoaciduria)	<0.4	Isoleucine, leucine, and valine degradation	Branched-chain α-keto acid dehydrogenase complex	Vomiting; convulsions; mental retardation; early death
Methylmalonic acidemia	<0.5	Conversion of propionyl-CoA to succinyl-CoA	Methylmalonyl-CoA mutase	Vomiting; convulsions; mental retardation; early death
Phenylketonuria	<8	Conversion of phenylalanine to tyrosine	Phenylalanine hydroxylase	Neonatal vomiting; mental retardation

Table 18.2: Lehninger Principles of Biochemistry by David L Nelson

Interaction with students

- Distributed subtopics of class to students for participate in group discussion in next class.

Reference Books

1) Lehninger Principles of Biochemistry
2) Harper's Illustrated Biochemistry-30th Ed
3) Biochemistry, Lippincott's Illustrated Reviews, 6th Ed
4) Text Book of Medical Biochemistry by Chatterjee & Rana Shinde, 8th Ed
5) Biochemistry, Donald Voet and Judith G. Voet, 4th Ed.

Thank you