Catabolism of Carbon Skeletons of amino acids and related disorders-III

Specific Learning Objectives

- Integrate aa synthesis with specific precursors from glycolysis, citric acid cycle and pentose phosphate pathway
- List which aa are precursors to citric acid cycle intermediates and identify specific intermediates (in addition to Acetyl-CoA and Acetoacetyl-CoA)
- Catabolic pathways of seven aa to Acetyl-CoA

Summary of Amino acid Catabolism

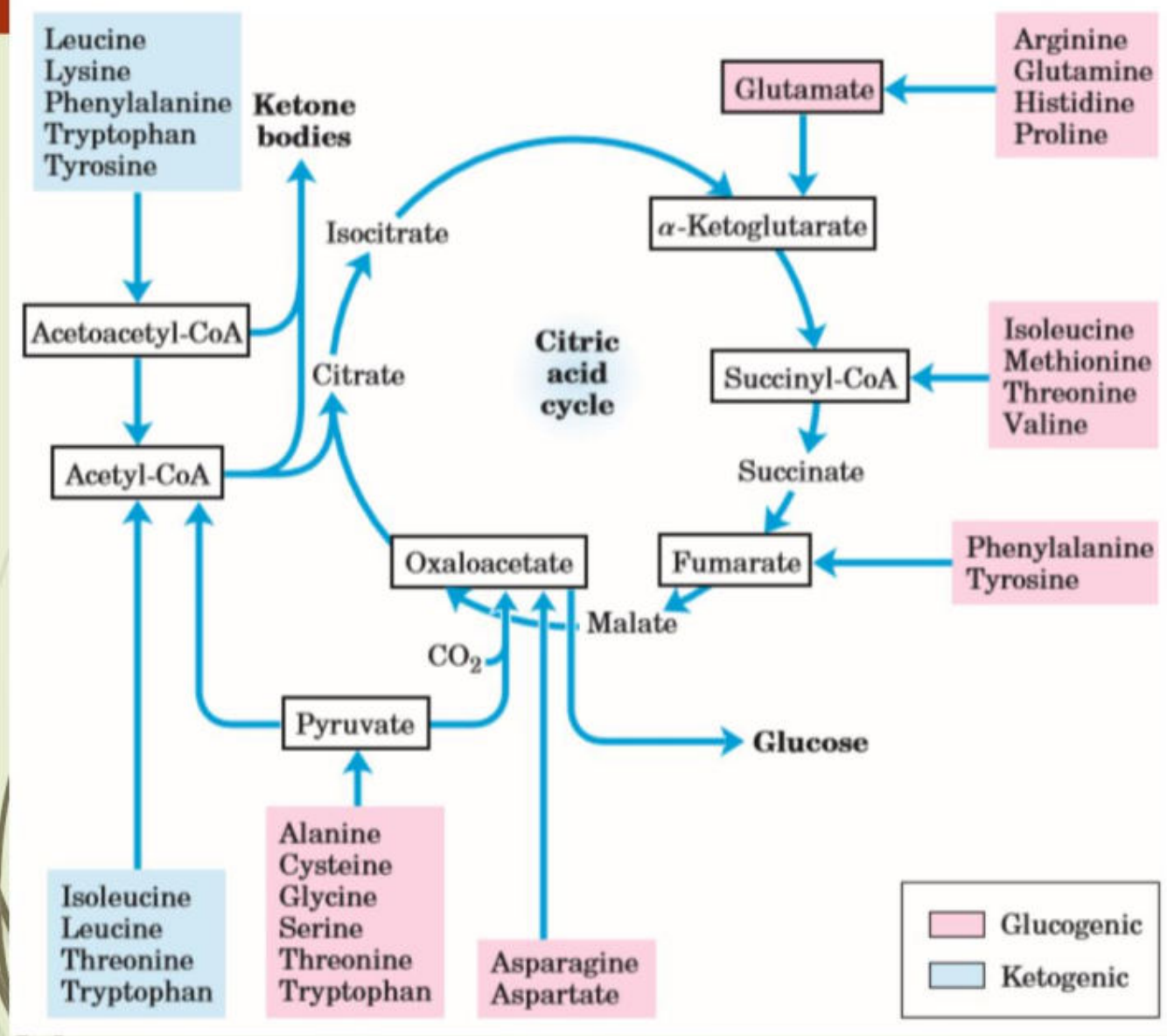

FIGURE 18–15 Summary of amino acid catabolism. Amino acids are grouped according to their major degradative end product. Some amino acids are listed more than once because different parts of their carbon skeletons are degraded to different end products. The figure shows the most important catabolic pathways 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

Introduction

Carbon skeletons are generally conserved as:

- Carbohydrate, via gluconeogenesis
- Fatty acid via fatty acid synthesis pathways

These pathways converge to form seven intermediate products:

- Oxaloacetate, α-ketoglutarate, pyruvate, fumarate, succinyl coenzyme A (CoA) , acetyl CoA, and acetoacetate

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These products directly enter pathways of intermediary metabolism:

- Resulting either in synthesis of glucose or lipid or in production of energy through their oxidation to CO_2 and water by citric acid cycle

Catabolic pathways of six aa to Pyruvate

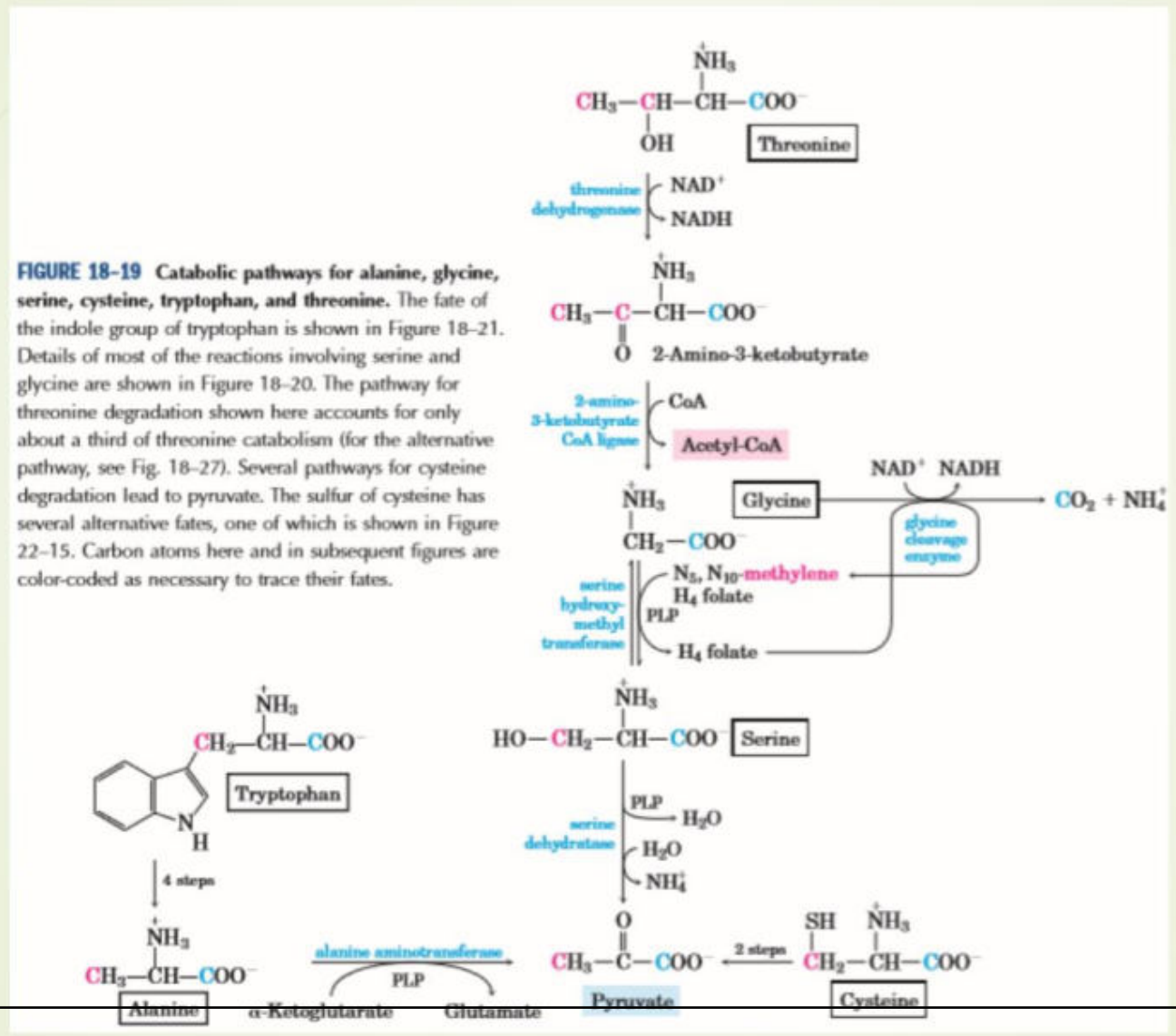

FIGURE 18–19 Catabolic pathways for alanine, glycine, serine, cysteine, tryptophan, and threonine. The fate of the indole group of tryptophan is shown in Figure 18–21. Details of most of the reactions involving serine and glycine are shown in Figure 18–20. The pathway for threonine degradation shown here accounts for only about a third of threonine catabolism (for the alternative pathway, see Fig. 18–27). Several pathways for cysteine degradation lead to pyruvate. The sulfur of cysteine has several alternative fates, one of which is shown in Figure 22–15. Carbon atoms here and in subsequent figures are color-coded as necessary to trace their fates.

Fig18.19: Lehninger Principles of Biochemistry, by David L Nelson

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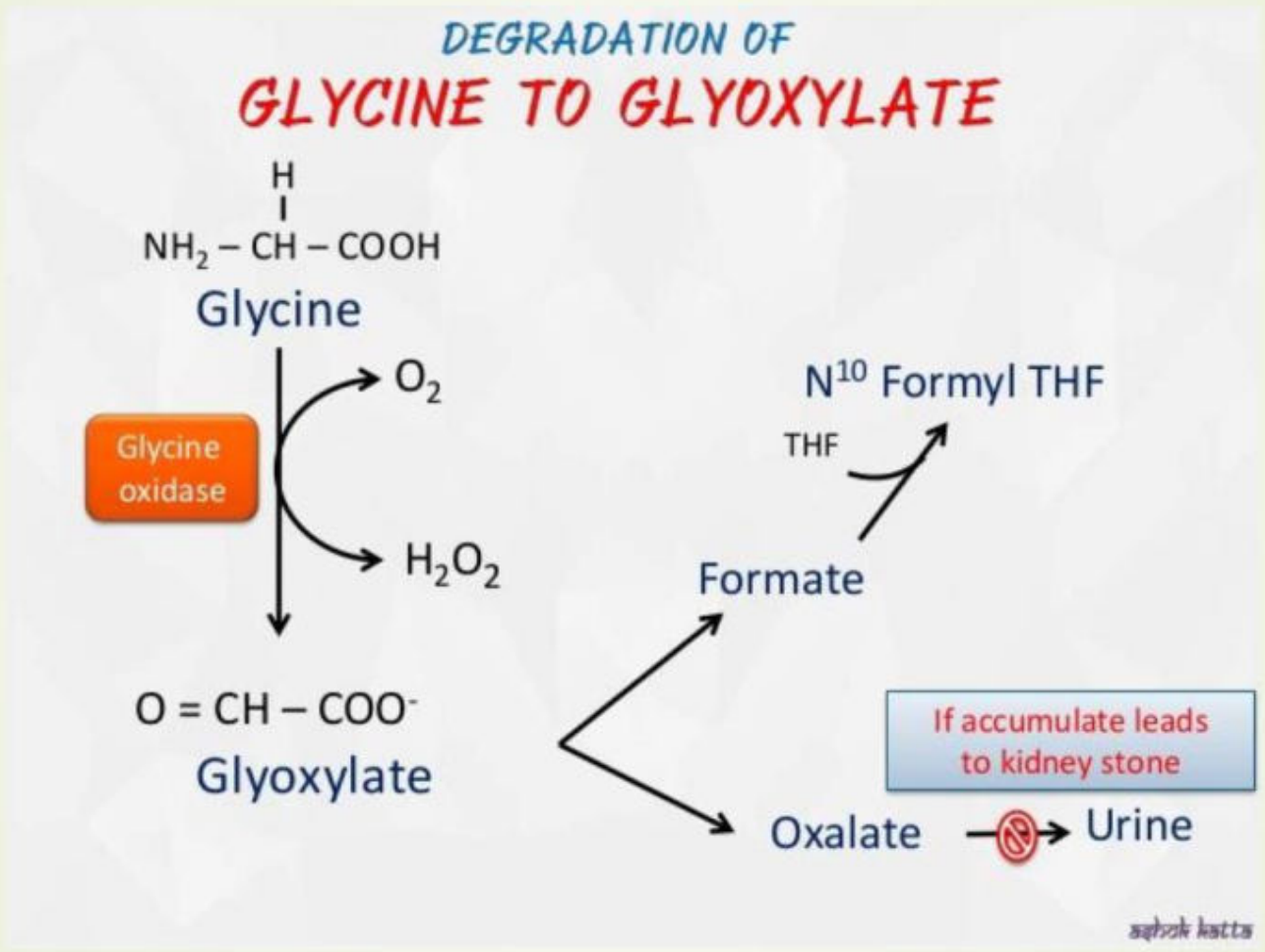
Glycine cleavage system is multienzyme complex: It consists of four proteins:

1. PLP-dependent glycine decarboxylase (P-protein)
2. Lipoamide-containing aminomethyl carrier (H-protein), which carries aminomethyl group remaining after glycine decarboxylation
3. N5,N10-methylene-THF synthesizing enzyme aminomethyltransferase (AMT) (T-protein), which accepts a methylene group from aminomethyl carrier, amino group is released as ammonia
4. NAD^+-dependent, FAD-requiring dihydrolipoyl dehydrogenase (L-protein), a protein shared by and known as E3 in pyruvate dehydrogenase complex



https://www.slideshare.net/ashokktt/metabolism-of-glycine

Disorder related to glycine

Non-ketotic hyperglycinemia (NKH)

- Humans with serious defects in glycine cleavage system activity due to absence of one of components of glycine cleavage system
- Elevated serum levels of glycine, leading to mental retardation and death in very early childhood

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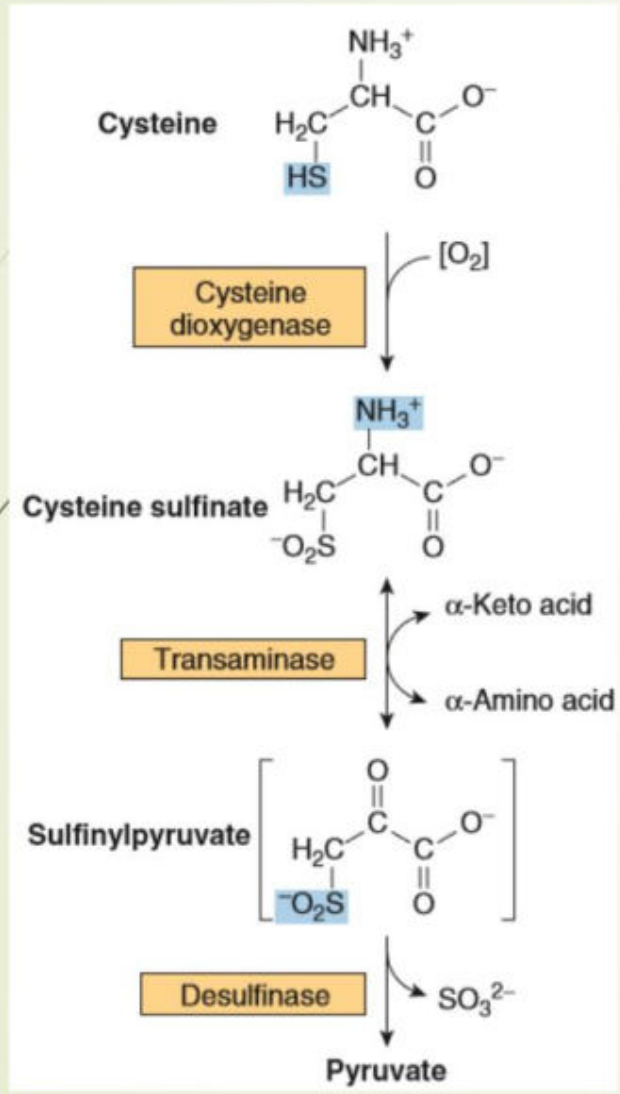
- In one of glycine degradation pathway, glycine is converted into glyoxylate by D-amino acid oxidase
- Glycine is precursor of glyoxalate, which can be transaminated back to glycine or oxidized to oxalate by lactate dehydrogenase
- Excessive production of oxalate forms the insoluble calcium oxalate salt, lead to kidney stones.

Two pathways catabolize cysteine



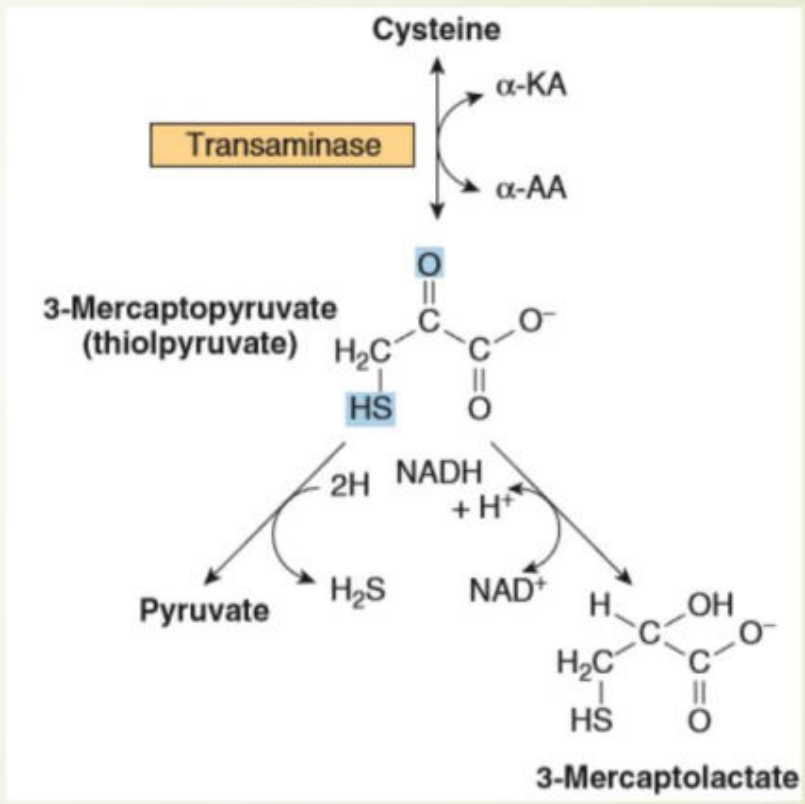


Fig 29.9: Harper's Illustrated Biochemistry 30th Edition

Disorders related to Cysteine

- Cystinuria is caused by mutations in SLC3A1 and SLC7A9 genes.
- These defects prevent reabsorption of basic positively charged aa (Cysteine, lysine, ornithine and arginine)
- Under normal condition, these proteins allow certain aa including cysteine to be reabsorbed into blood from filtered fluid that will become urine
- Mutations in either of these genes disrupt ability of this transporter protein exist in kidney tubules to reabsorb these aa, allowing them to excretion of these aa in urine

Cystinosis

- Cystinosis is a lysosomal storage disease in which abnormal accumulation of cystine, leads to intracellular crystal formation throughout body. Cystine: It is formed from oxidation of two cysteine molecules, via formation of a disulfide bond)

- Cystinosis is most common cause of Fanconi syndrome in pediatric age group

- Fanconi syndrome occurs when function of cells in renal tubules is impaired, leading to abnormal amounts of carbohydrates and amino acids in urine, excessive urination, and low blood levels of potassium and phosphates

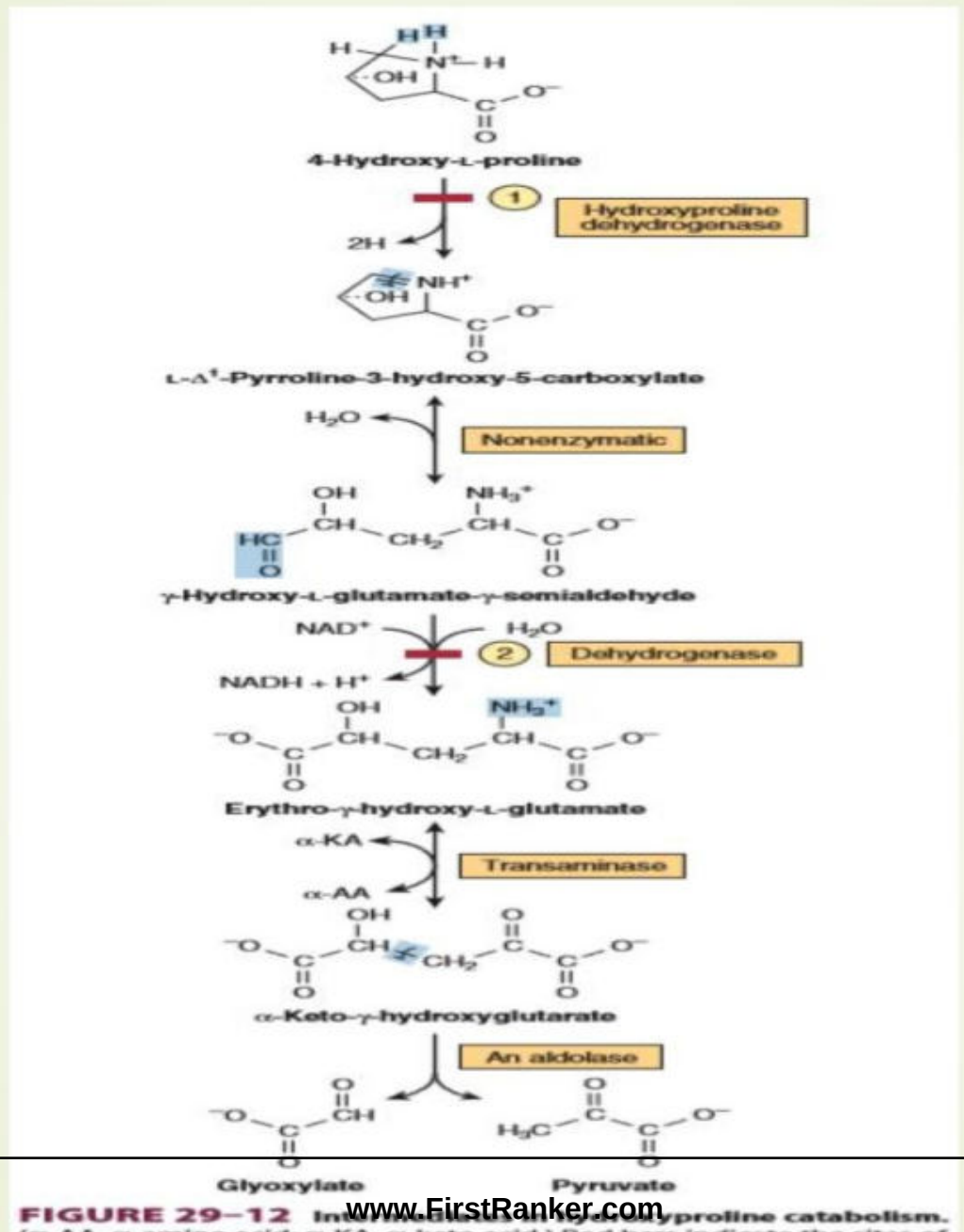


FIGURE 29–12 Intermediate steps in hydroxyproline catabolism. (α-AA, α-amino acid; α-KA, α-keto acid.) Red bars indicate the sites of the inherited metabolic defects in ① hyperhydroxyprolinemia and ② type II hyperprolinemia.

Harper's Illustrated Biochemistry 30th Edition

Disorders related to Hydroxyporoline

Type II hyperprolinemia: A defect in 4-hydroxyproline dehydrogenase results in hyperhydroxyprolinemia, an excess of free hydroxyproline in plasma and urine

- Associated with mental retardation

Type II hyperprolinemia: A defect in glutamate-γ-semialdehyde dehydrogenase/ 1-pyrroline-3-hydroxyl-5-carboxylate dehydrogenase

- Type II hyperprolinemia is a rare form of disorder may appear benign at time but often involves seizures, convulsions and intellectual disability

Catabolic pathways of seven aa to Acetyl-CoA

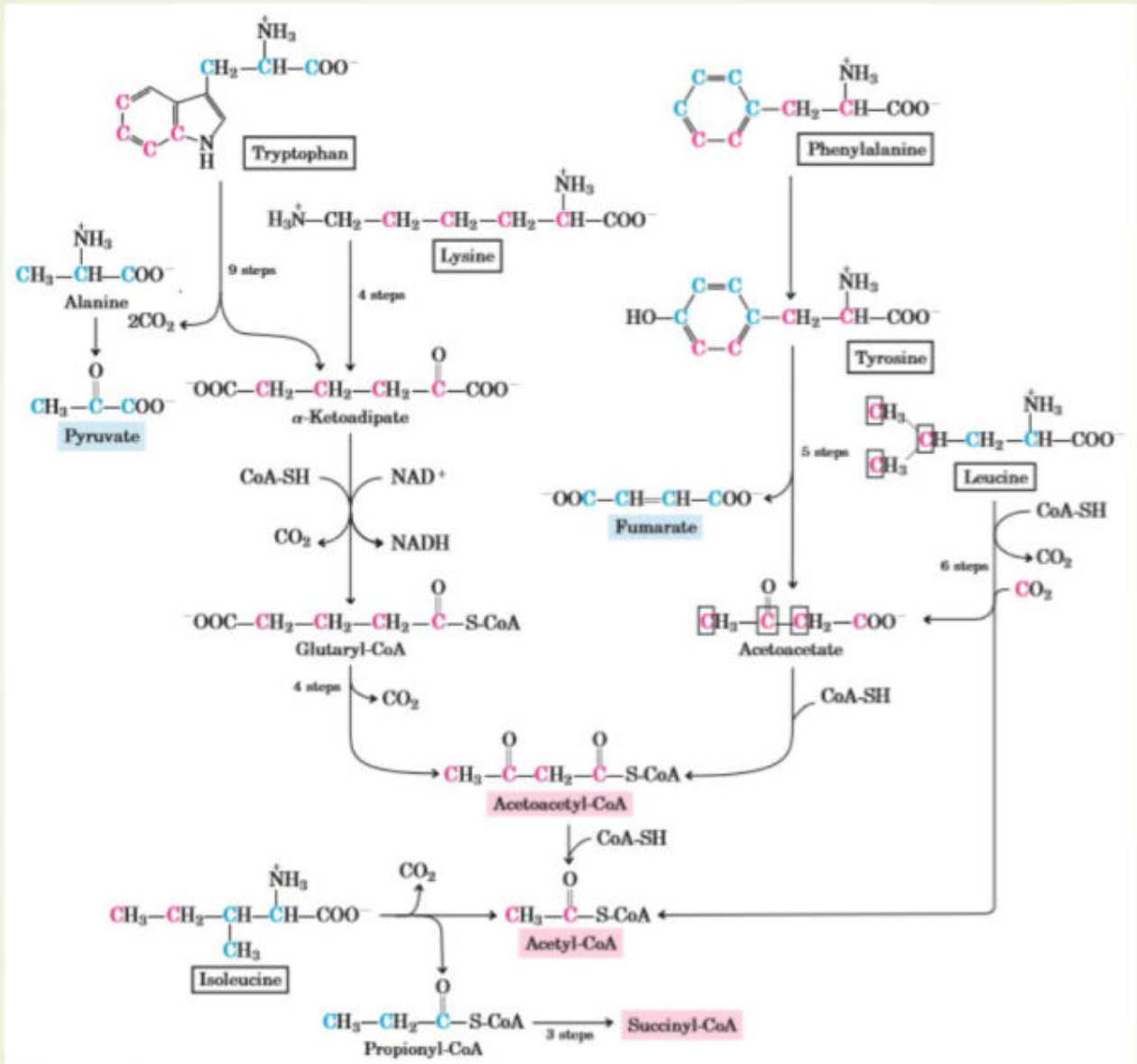


FIGURE 18–21 Catabolic pathways for tryptophan, lysine, phenylalanine, tyrosine, leucine, and isoleucine. These … some of their carbons (red) to acetyl-CoA. Tryptophan, phenylalanine, tyrosine, and isoleucine also contribute carbons (blue) to pyruvate or citric acid cycle intermediates. The phenylalanine pathway is de… re detail in Figure 18–23. The fate of nitrogen atoms is not traced in this scheme; in most cases they are transferred to α-ketoglutarate to form glutamate.

Fig18.21: Lehninger Principles of Biochemistry by David L Nelson

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- Tryptophan breakdown is most complex of all pathways of aa catabolism in animal tissues
- Portions of tryptophan (four of its carbons) yield acetyl-CoA via acetoacetyl CoA
- Some of intermediates in tryptophan catabolism are precursors for tsynthesis of other biomolecules, including nicotinate, a precursor of NAD and NADP, serotonin

Catabolism of Tryptophan to α-Ketoadipate

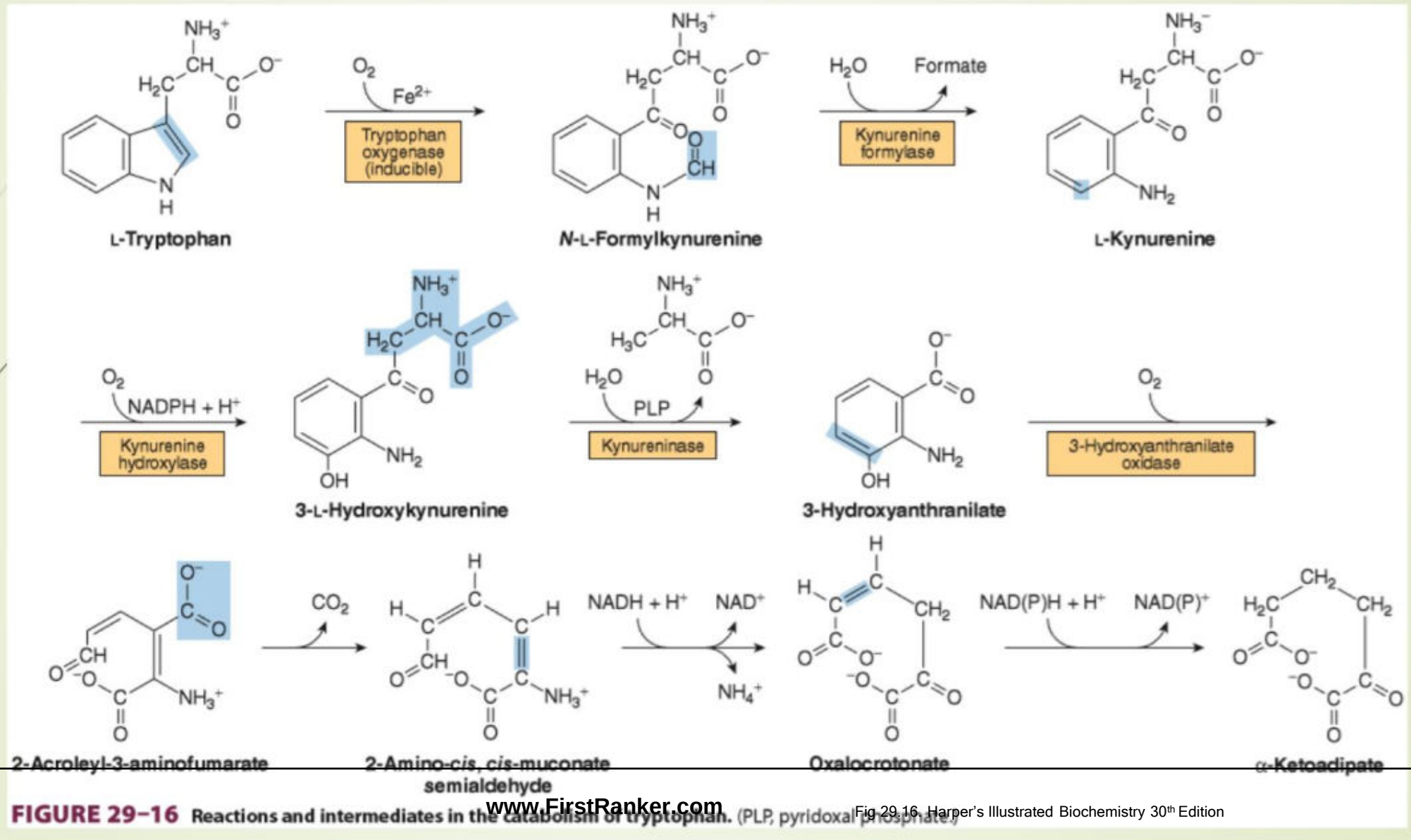

FIGURE 29–16 Reactions and intermediates in the catabolism of tryptophan. (PLP, pyridoxal phosphate.)

Fig 29.16, Harper's Illustrated Biochemistry 30th Edition

Disorder related to Tryptophan

Hartnup disease: In catabolism of Typ, kynureninase requires PLP (active form of vit B6), acts on 3-L hydroxylkynurenine

- Defect in kynureninase limits tryptophan availability for niacin biosynthesis, cause reduced synthesis of NAD^+ and $NADP^+$ leads to pellagra-like signs and symptoms.

- Due to lack of PLP, Kynureninase reaction blocked and 3-L hydroxylkynurenine is diverted and form xanthurenate catalyzed by Kynurenine transferases

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- Elevated levels of xanthurenate shows vit B6 deficiency

- Hartnup disease reflects impaired intestinal and renal transport of tryptophan and other neutral aa

- Indole derivatives of unabsorbed tryptophan formed by intestinal bacteria are excreted

Catabolic pathways of seven aa to Acetyl-CoA

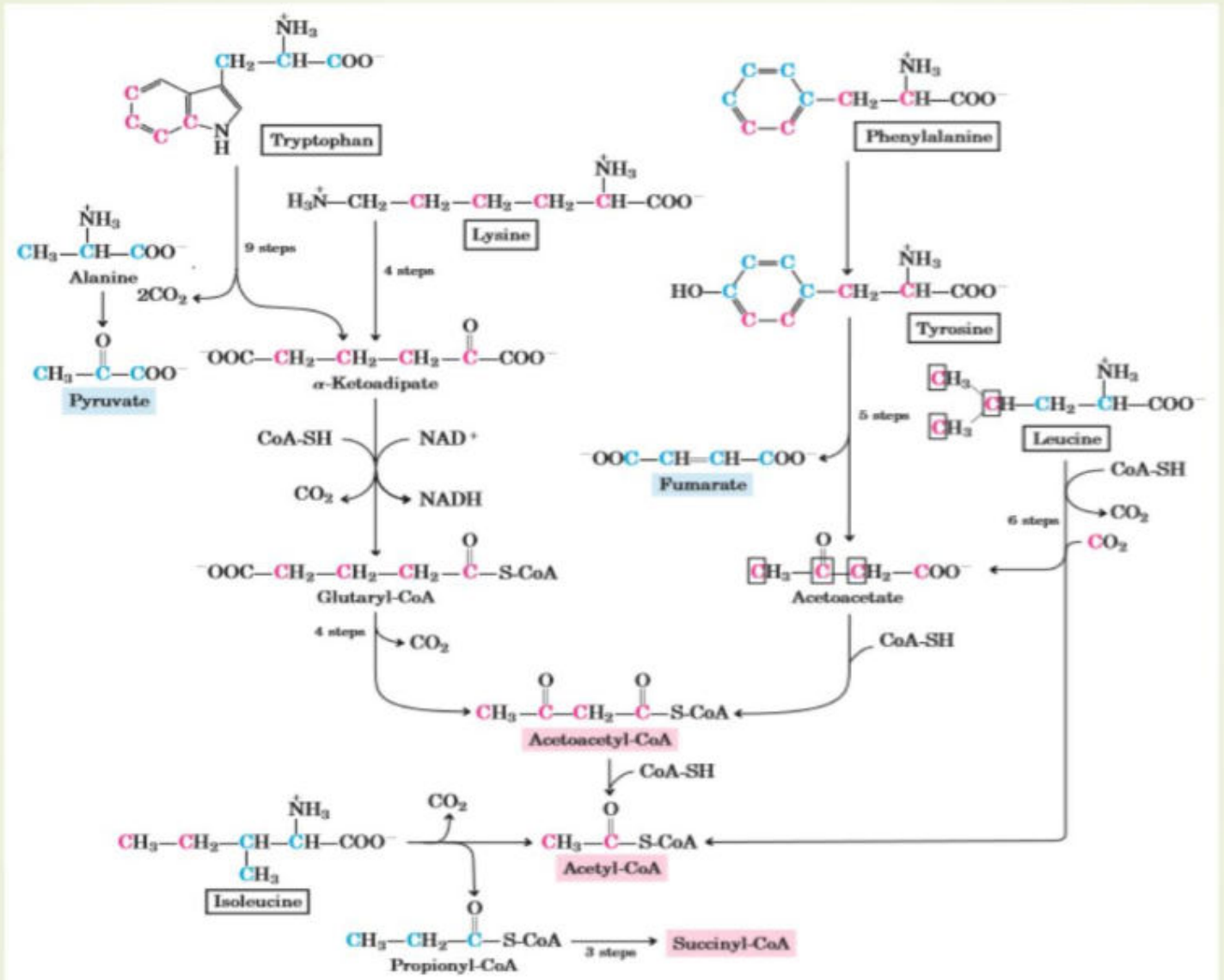


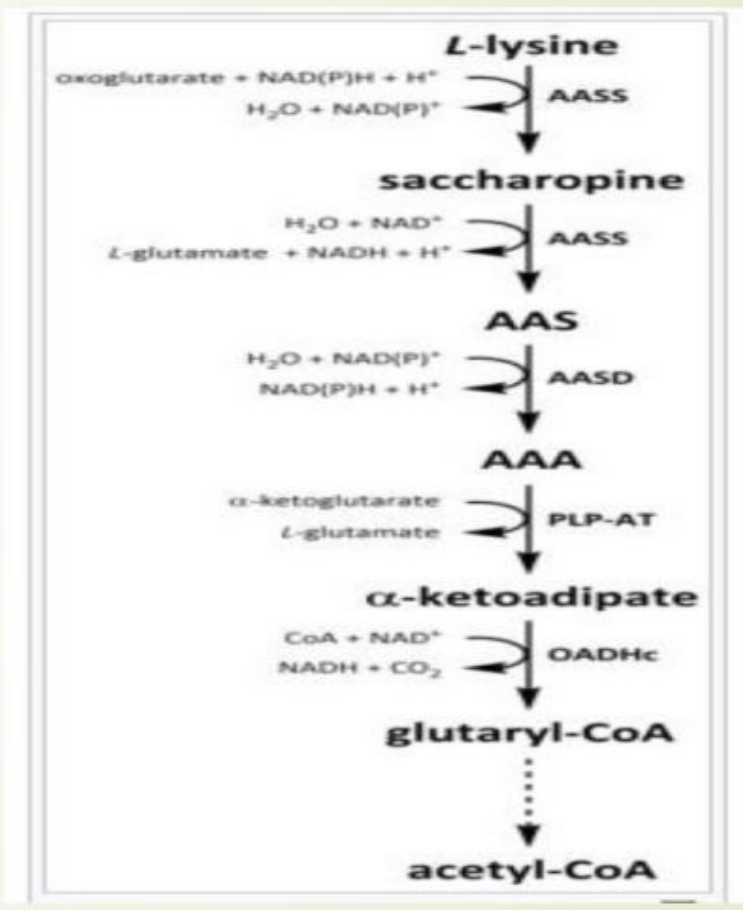
FIGURE 18–21 Catabolic pathways for tryptophan, lysine, phenylalanine, tyrosine, leucine, and isoleucine. These amino acids donate some of their carbons (red) to acetyl-CoA. Tryptophan, phenylalanine, tyrosine, and isoleucine also contribute carbons (blue) to pyruvate or citric acid cycle intermediates. The phenylalanine pathway is described in more detail in Figure 18–23. The fate of nitrogen atoms is not traced in this scheme; [illegible] α-ketoglutarate to form glutamate.

Threonine yield some acetyl CoA also

Fig18.21: Lehninger Principles of Biochemistry by David L Nelson

Saccharopine lysine catabolism pathway

First two steps of saccharopine pathway are catalysed by bifunctional enzyme,α-aminoadipic semialdehyde synthase (AASS), which possess both lysine-ketoglutarate reductase (LKR) and saccharopine dehydrogenase (SDH) activities



https://en.wikipedia.org/wiki/Lysine

Disorder related to Lysine

Hyperlysinemia: is an autosomal recessive inborn error of L-lysine degradation in liver and production of acetyl-CoA

- lysine and α-ketoglutarate are converted into saccharopine by lysine-ketoglutarate reductase
- Saccharopine is then oxidized to α-aminoadipic semialdehyde and glutamate by saccharopine dehydrogenase
- Both enzyme activities are catalyzed by a single mitochondrial bifunctional enzyme named α-aminoadipic semialdehyde synthase (AASS) which is encoded by gene AASS
- One mutation in AASS, cause hyperlysinemia, along with mental and physical retardation

Catabolism of Asparagine and Aspartate to Oxaloacetate

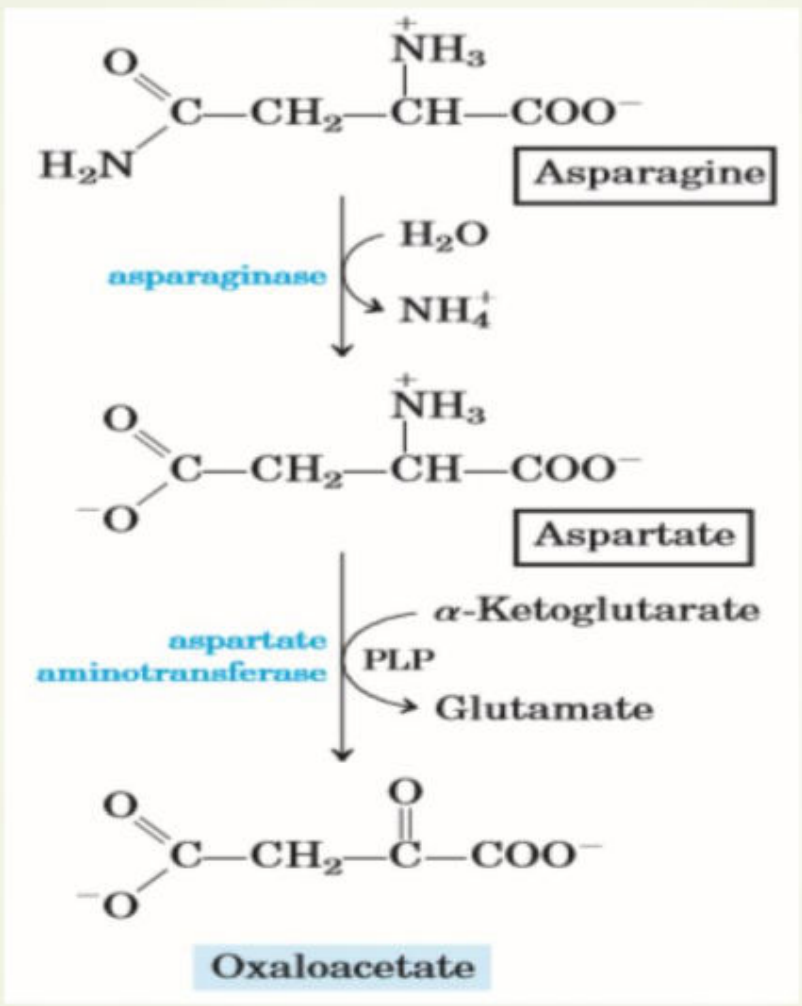


Fig18.29: Lehninger Principles of Biochemistry by David L. Nelson

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- L-asparaginase is an effective chemotherapeutic agent in treatment of cancers that must obtain asparagine from blood, particularly acute lymphoblastic leukemia

Reference Books

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

Two Clinical-cases discussed

Thank you