Department of Biochemistry

# Learning Objectives

Catabolism of the Carbon Skeletons of amino acids and related disorders:

- Catabolism of Phenylalanine and Tyrosine with genetic disorders
- Arginine, Histidine, glutamate, glutamine and proline to α-ketoglutarate
- Methionine, isoleucine, threonine and valine to Succinyl CoA
- Degradation of branched chain aa (Leucine to Acetoacetate and Acetyl-CoA, Valine to β-Aminoisobutyrate and Succinyl-CoA and Isoleucine to Acetyl-CoA and Propionyl-CoA)
- Asparagine and Aspartate to Oxaloacetate

## Conversion of amino acids to Specialized products

# Catabolism of Phenylalanine and Tyrosine with genetic disorders

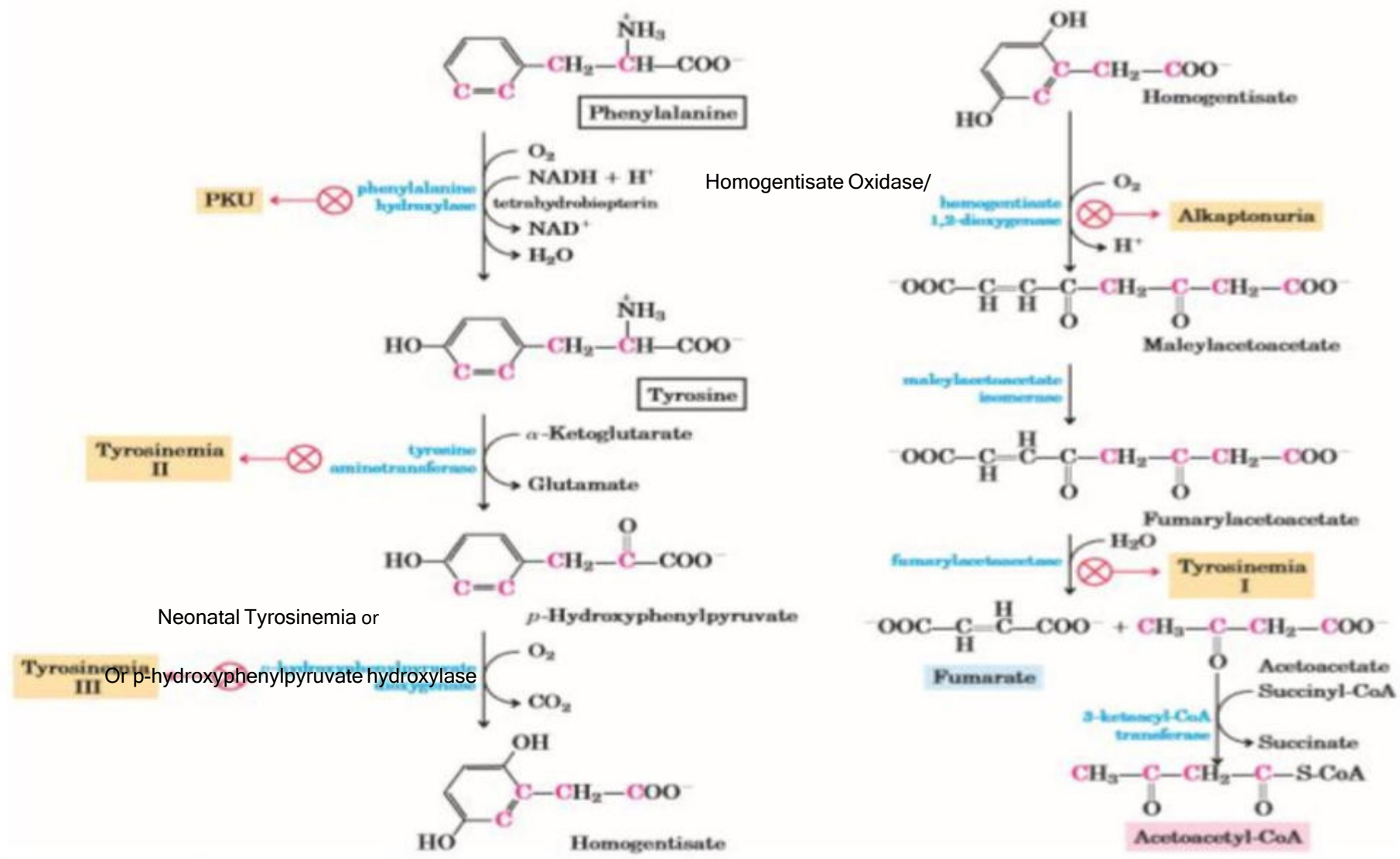



FIGURE 18–23 Catabolic pathways for phenylalanine and tyrosine. In humans these amino acids are normally converted to acetoacetyl-CoA and fumarate. Genetic defects in many of these enzymes cause inheritable human diseases (shaded yellow).

Fig18.23: Lehninger Principles of Biochemistry by David L Nelson

# Disorder related to phenylalanine catabolism

## Phenylketonuria (PKU)

- Genetic defect in phenylalanine hydroxylase, first enzyme in catabolic pathway for phenylalanine, is responsible for disease phenylketonuria (PKU),most common cause of elevated levels of phenylalanine (hyperphenylalaninemia)
- Excess phenylalanine is transaminated to Phenylpyruvate
- The “spillover” of Phenylpyruvate (a phenylketone) into urine
- High concentration of phenylalanine itself gives rise to brain dysfunction.

Cont--

- Phenylalanine hydroxylase requires the cofactor tetrahydrobiopterin, which carries electrons from NADH to O2 and becomes oxidized to dihydrobiopterin

- It is subsequently reduced by enzyme dihydrobiopterin reductase in a reaction that requires NADH

- Diet low in phenylalanine can prevent the mental retardation of PKU

## Disorder related to Tyrosine catabolism

Alkaptonuria

- Metabolic defect in alkaptonuria is a defective homogentisate oxidase the enzyme that catalyzes homogentisate to Maleylacetoacetate

- Large amounts of homogentisate are excreted and urine darkens on exposure to air due to oxidation of excreted homogentisate

- This autooxidizes to the corresponding quinone, which polymerizes to form an intensely dark color

- Late in the disease, there is arthritis and connective tissue pigmentation (ochronosis) due to oxidation of homogentisate to benzoquinone acetate, which polymerizes and binds to connective tissue

## Type I Tyrosinemia

- Several metabolic disorders are associated with the tyrosine catabolic pathway
- Probable metabolic defect in type I tyrosinemia (tyrosinosis) is at fumarylacetoacetate hydrolase
- Untreated acute and chronic tyrosinosis leads to death from liver failure, renal tubular dysfunction, rickets and polyneuropathy

## Type II Tyrosinemia

- Alternate metabolites of tyrosine are also excreted in type II tyrosinemia (Richner-Hanhart syndrome), a defect in tyrosine aminotransferase produces accumulation and excretion of tyrosine and metabolites
- Leads to eye and skin lesions and mental retardation

# Type III Tyrosinemia

- Neonatal Tyrosinemia or type III tyrosinemia, due to lowered activity of p-hydroxyphenylpyruvate dioxygenase/ p-hydroxyphenylpyruvate hydroxylase

- It can cause learning problems, seizures, and loss of balance

- Therapy employs a diet low in protein, tyrosine and phenylalanine

## Catabolic pathways of five aa to α-ketoglutarate

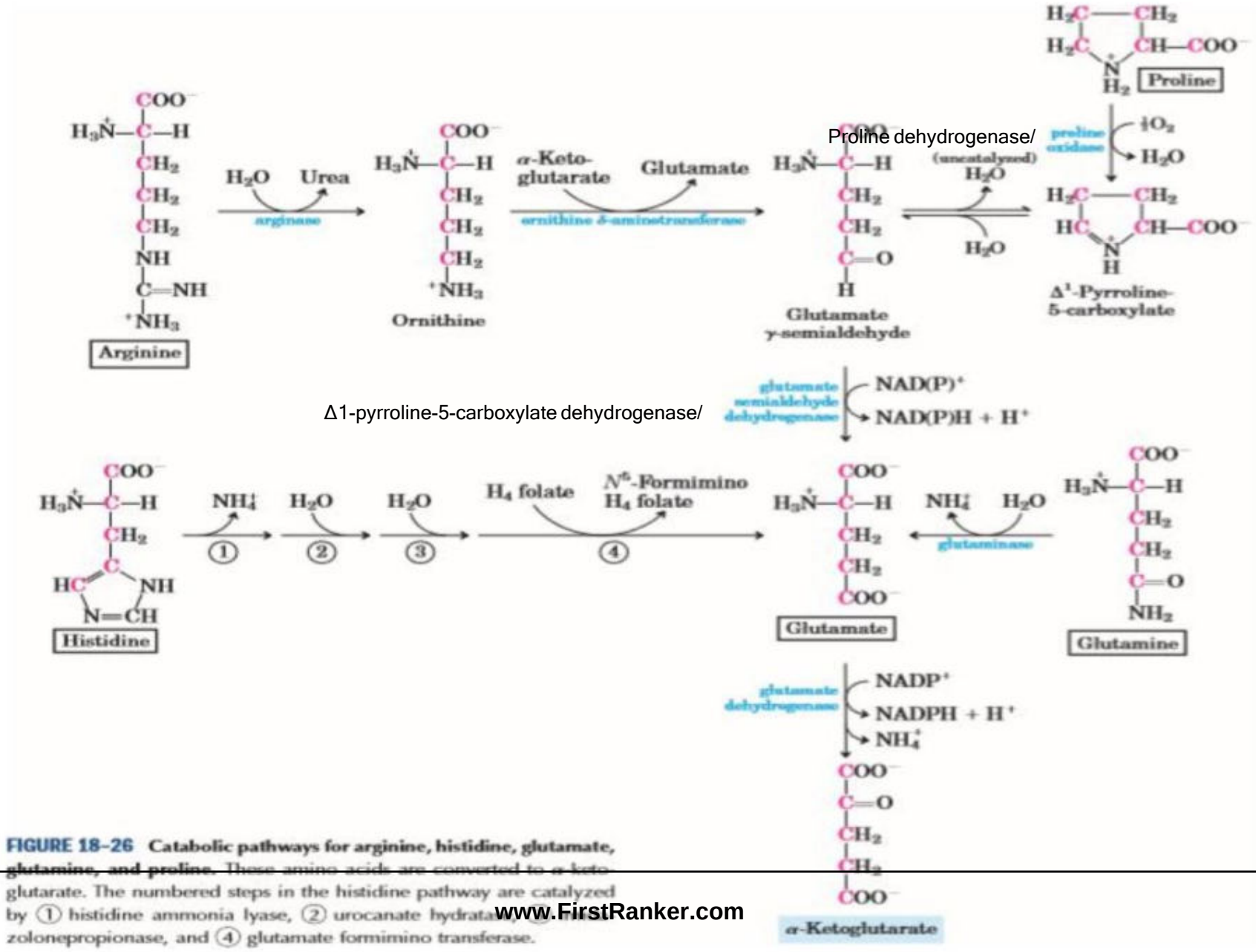



**FIGURE 18–26 Catabolic pathways for arginine, histidine, glutamate, glutamine, and proline.** These amino acids are converted to α-ketoglutarate. The numbered steps in the histidine pathway are catalyzed by ① histidine ammonia lyase, ② urocanate hydratase, ③ N-formiminozoloneproprionase, and ④ glutamate formimino transferase.



Fig18.26: Lehninger Principles of Biochemistry by David L Nelson

# Disorder related to Proline catabolism

## Type I hyperprolinemia

- The metabolic block in type I hyperprolinemia is at proline dehydrogenase/proline oxidase
- Some individuals with hyperprolinemia type I exhibit seizures, intellectual disability, or other neurological or psychiatric problems

## Type II hyperprolinemia

- The metabolic block in type II hyperprolinemia is at Δ1-pyrroline-5-carboxylate dehydrogenase, which also participates in the catabolism of arginine, ornithine, and hydroxyproline
- It leads to seizures or intellectual disability.

# Catabolic pathways of four aa to Succinyl-CoA

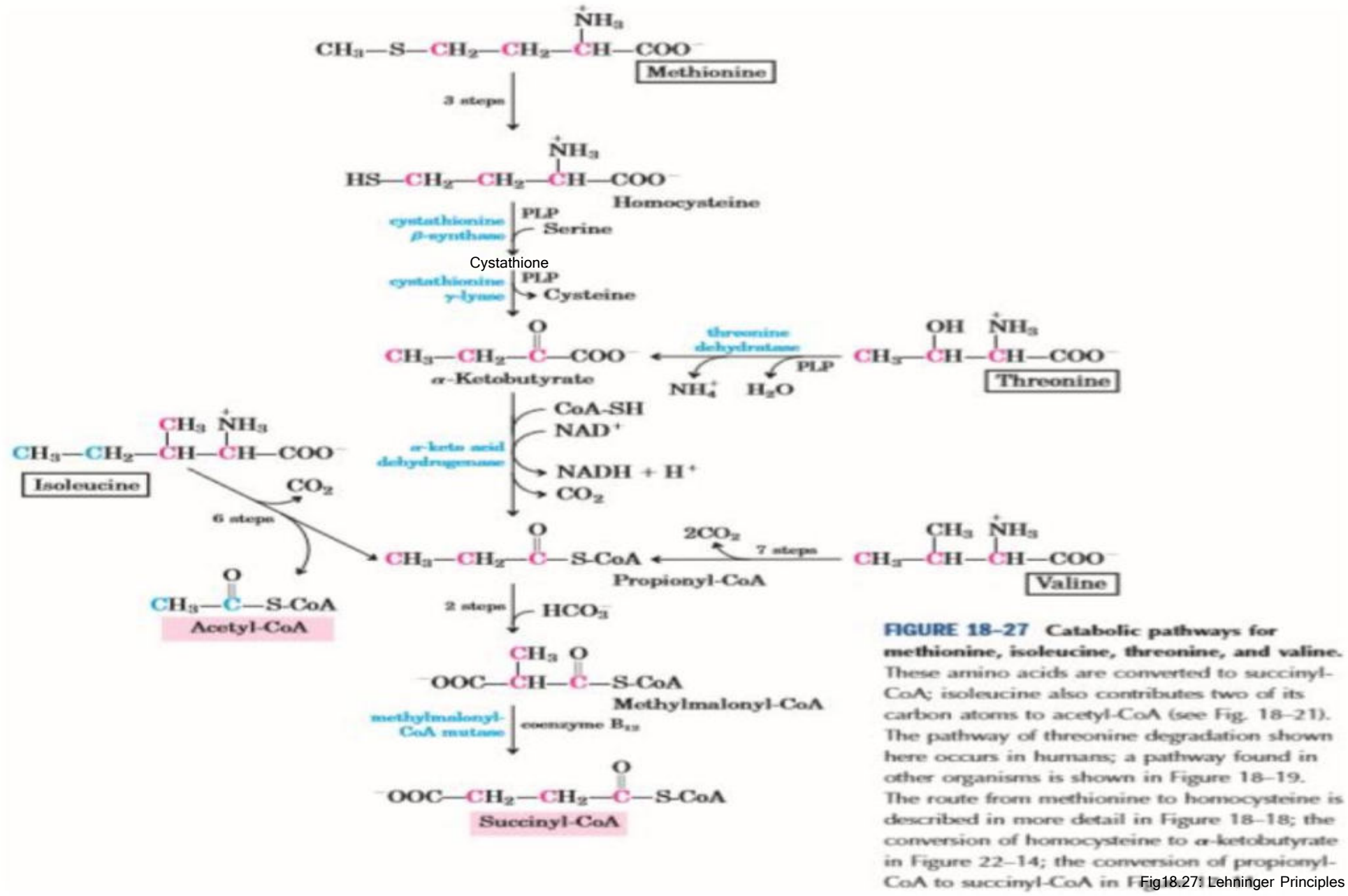



**FIGURE 18–27 Catabolic pathways for methionine, isoleucine, threonine, and valine.** These amino acids are converted to succinyl-CoA; isoleucine also contributes two of its carbon atoms to acetyl-CoA (see Fig. 18–21). The pathway of threonine degradation shown here occurs in humans; a pathway found in other organisms is shown in Figure 18–19. The route from methionine to homocysteine is described in more detail in Figure 18–18; the conversion of homocysteine to α-ketobutyrate in Figure 22–14; the conversion of propionyl-CoA to succinyl-CoA in Fig

Fig18.27: Lehninger Principles of Biochemistry by David L Nelson

## Cont--

- Catabolism of isoleucine, methionine, and valine to propionyl-CoA

- Propionyl-CoA, product of odd-chain fatty acid degradation, is converted, to succinyl-CoA by a series of reactions involving the participation of biotin and coenzyme B12

# Degradation and Resynthesis of Methionine

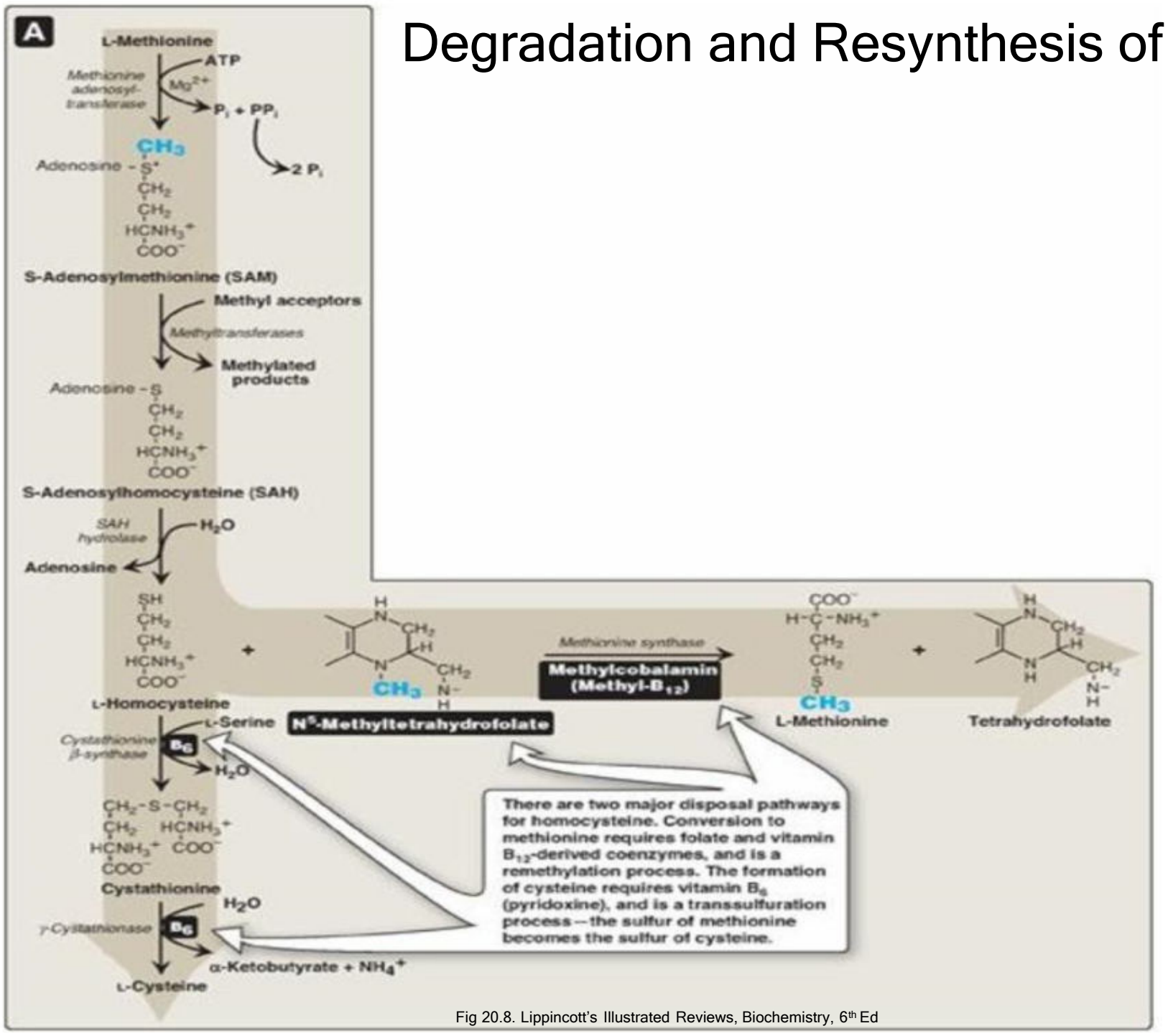
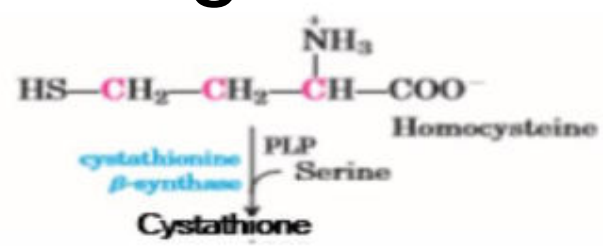



Fig 20.8. Lippincott's Illustrated Reviews, Biochemistry, 6th Ed

Biosynthesis of S-adenosylmethionine from methionine and ATP is catalyzed by methionine adenosyltransferase (MAT)

# Disorder related to Methionine degradation

## Hyper Homocysteinemia




- Elevations in plasma homocysteine (Hcy) as a result of rare deficiencies in cystathionine β-synthase of the transsulfuration pathway causes homocysteine to accumulate and remethylation leads to high levels of methionine in patients

- Elevated homocysteine and decreased folic acid levels in pregnant women are associated with increased incidence of neural tube defects (improper closure, as in spina bifida) in fetus

## Cont--

- The lens of eye is frequently dislocated after the age of 3, and other ocular abnormalities occur
- Mental retardation is frequently the first indication of this deficiency
- Attempts at treatment include restriction of methionine intake and feeding of betaine (or its precursor, choline)
- In some cases significant improvement by feeding pyridoxine (vit B6)
- Supplementation with folate reduces the risk of such defects

# Degradation of Branched chain amino acids

- Mitochondrial branched-chain α-keto acid dehydrogenase complex consists of five components:

E1: thiamin pyrophosphate (TPP)-dependent branched chain α-ketoacid decarboxylase
E2: dihydrolipoyl transacylase (contains lipoamide)
E3: dihydrolipoamide dehydrogenase (contains FAD)
Protein kinase
Protein phosphatase

Catabolism of Leucine to Acetoacetate and Acetyl-CoA

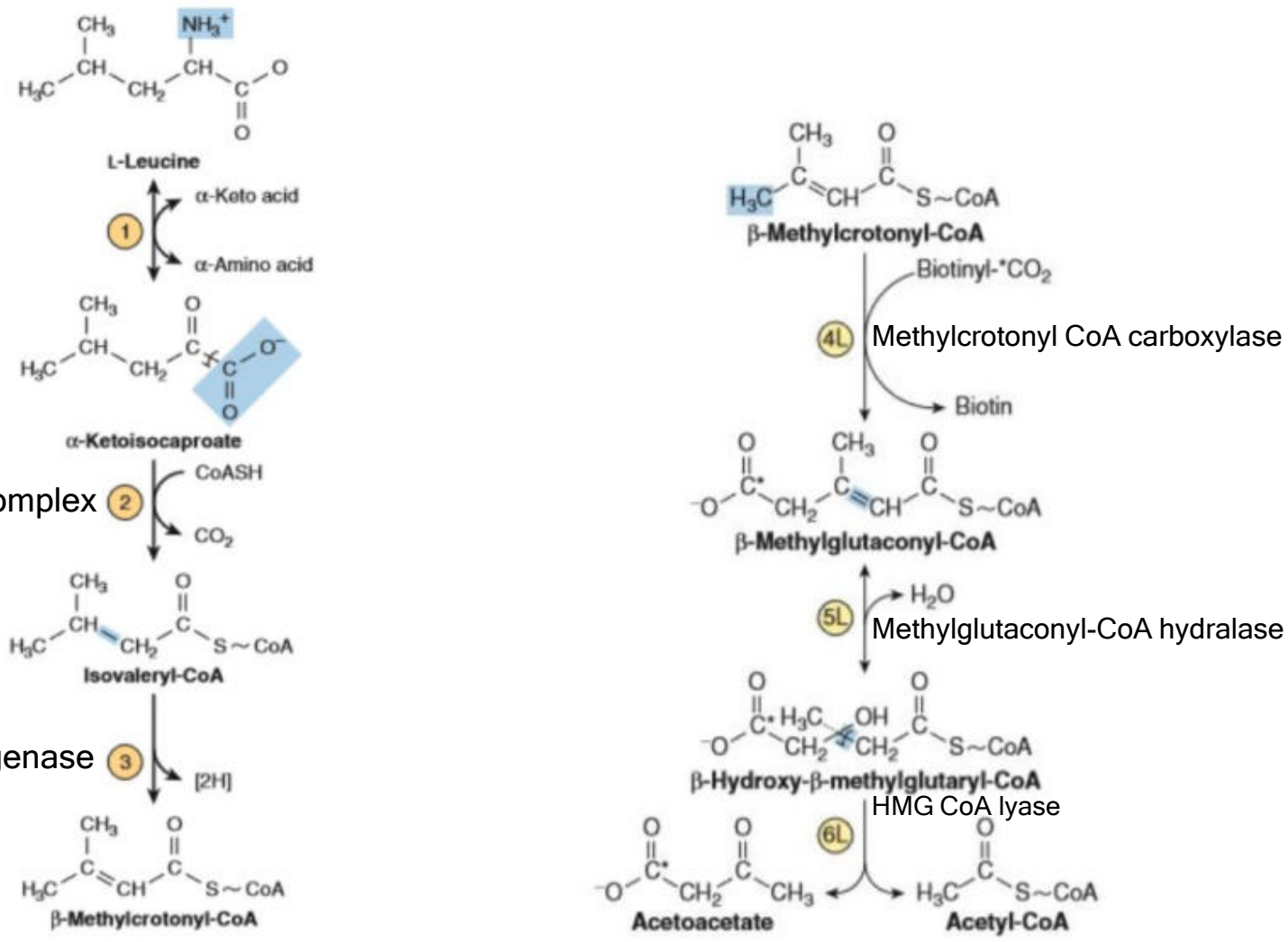
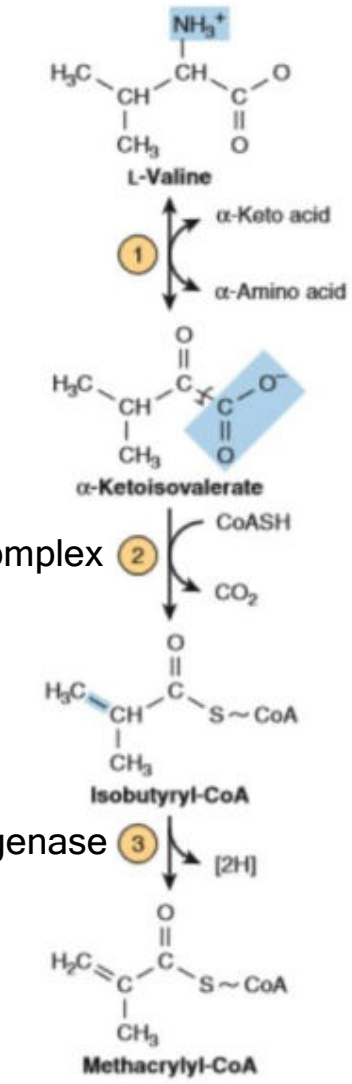


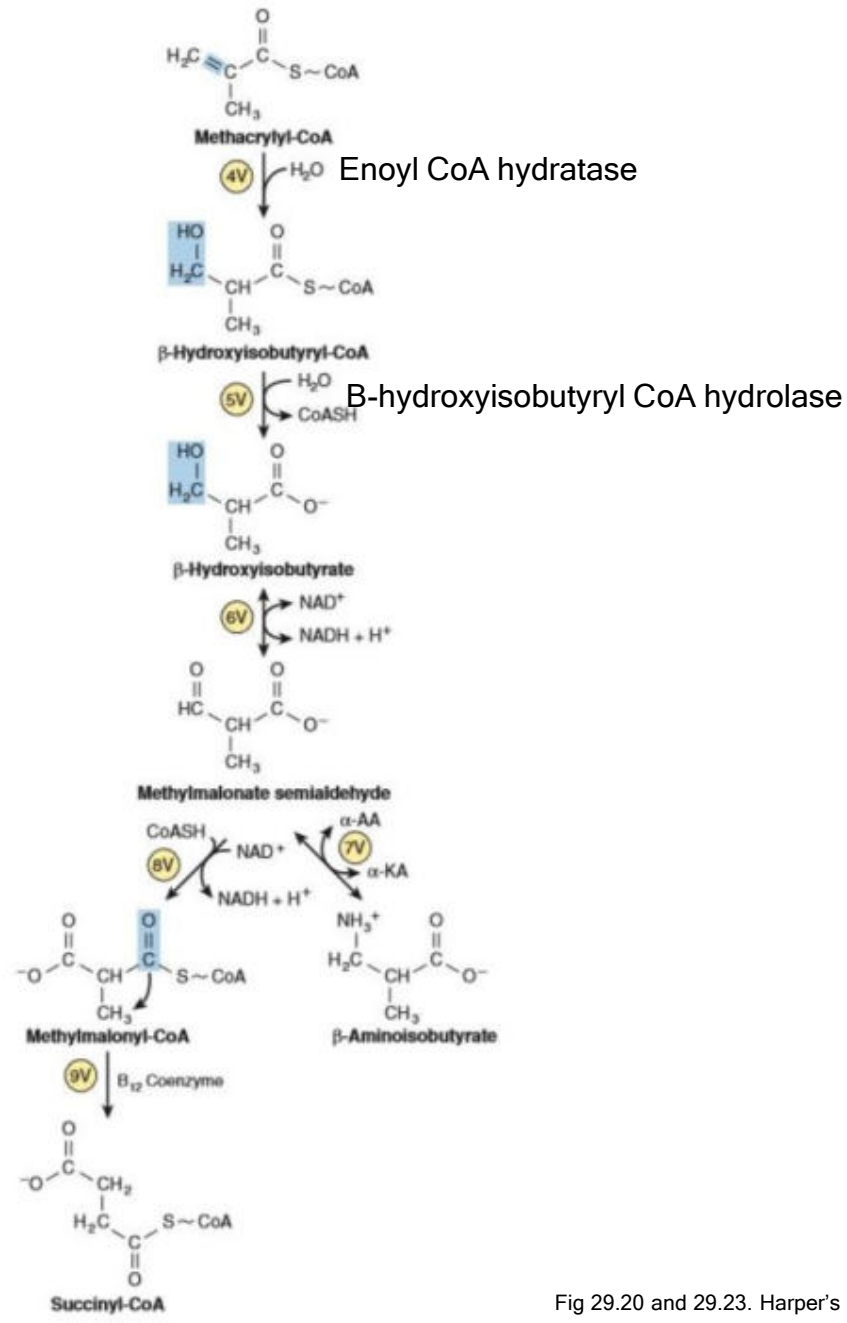

Fig 29.20 and 29.21. Harper's Illustrated Biochemistry 30th Edition

# Catabolism of Valine to β-Aminoisobutyrate and Succinyl-CoA




α-keto acid decarboxylase complex

A Methacrylyl CoA dehydrogenase

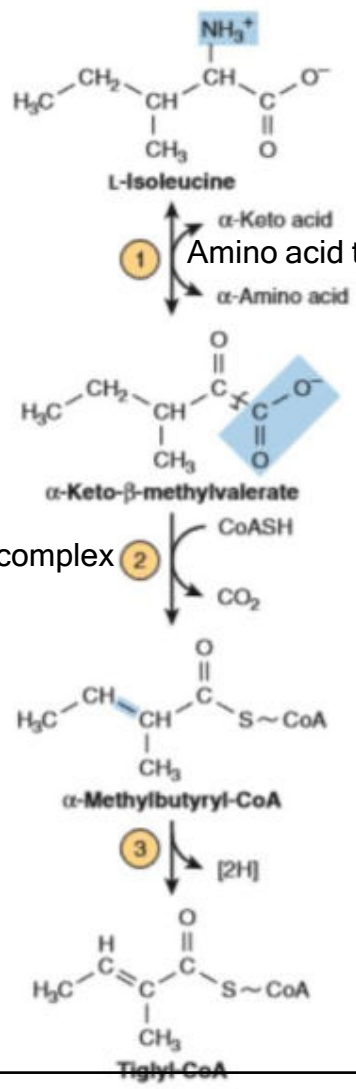



Enoyl CoA hydratase

B-hydroxyisobutyryl CoA hydrolase

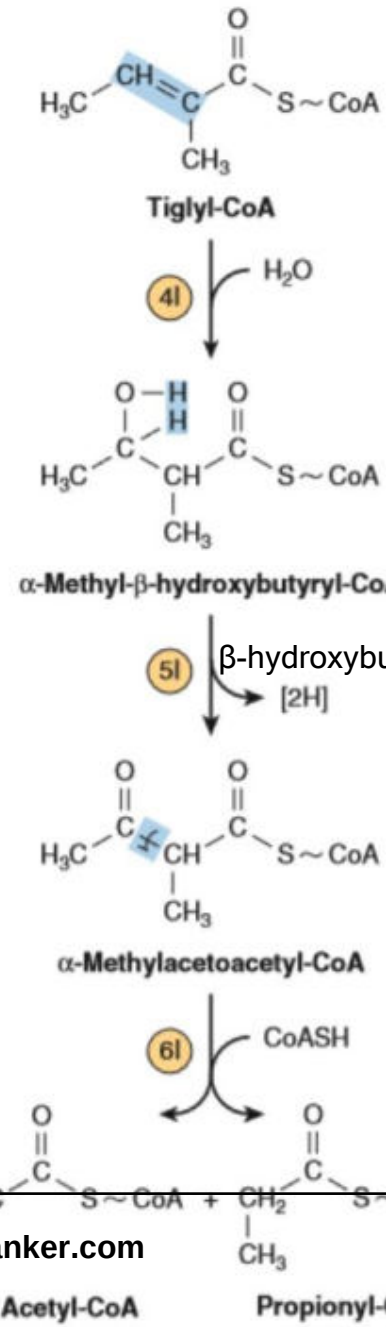
Fig 29.20 and 29.23. Harper's Illustrated Biochemistry 30th Edition

# Catabolism of Isoleucine to Acetyl-CoA and Propionyl-CoA




Amino acid transaminase

α-keto acid decarboxylase complex




β-hydroxybutyryl CoA dehydrogenase



Fig 29.20 and 29.22. Harper's Illustrated Biochemistry 30th Edition

# Disorder related to Branch chain aa degradation

- Biochemical defect in maple syrup urine disease (MSUD) involves α-keto acid decarboxylase complex (thiamine pyrophosphate, FAD, NAD, lipoate and CoA)

- Plasma and urinary levels of leucine, isoleucine, valine, and their α-keto acids and α-hydroxy acids (reduced α-keto acids) are elevated and accumulated in blood and spill over into the urine

- This condition is called MSUD or branched-chain ketonuria suggests maple syrup, or burnt sugar.

- Signs and symptoms of MSUD include fatal ketoacidosis, neurological derangements, mental retardation, and a maple syrup odor of urine

- Early diagnosis by enzymatic analysis is essential to avoid brain damage and early mortality by replacing dietary protein by an aa mixture that lacks leucine, isoleucine, and valine

# Catabolism of Asparagine and Aspartate to Oxaloacetate

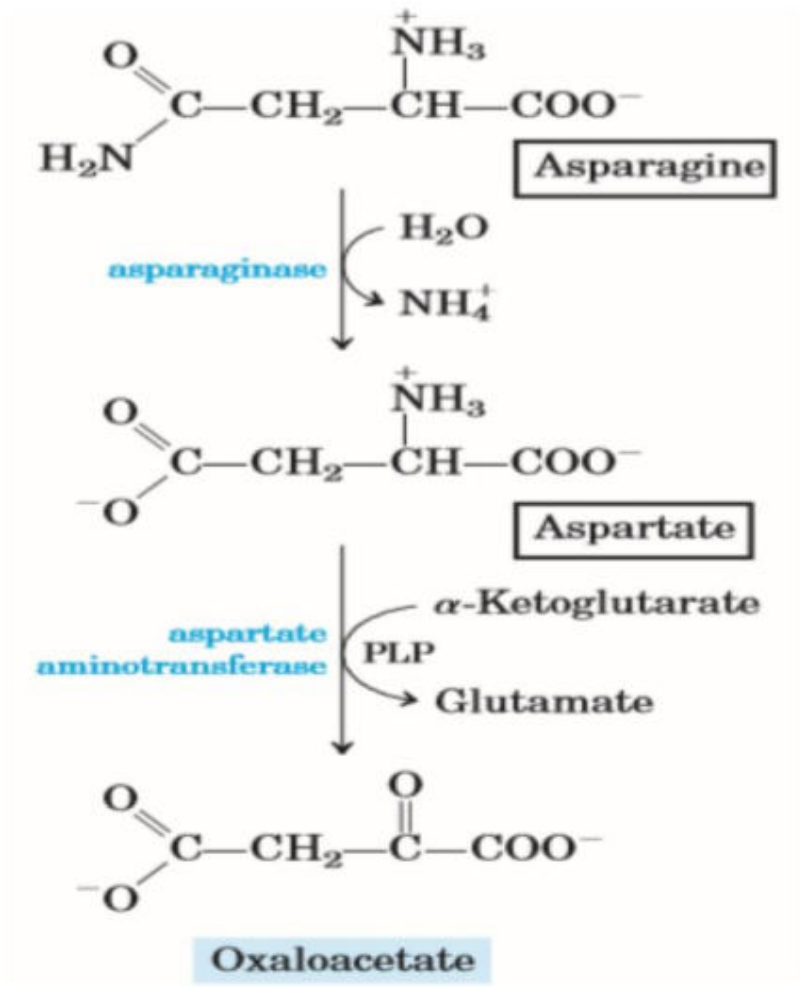



Fig18.29: Lehninger Principles of Biochemistry by David L Nelson

## Cont--

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

# Conversion of amino acids to Specialized products

## Introduction

- In addition to serving as building blocks for proteins, amino acids are precursors of many nitrogen-containing compounds that have important physiologic functions

- These molecules include porphyrins (involved in heme biosynthesis), hormones, purines, and pyrimidines, neurotransmitters.

# Conversion of arginine, ornithine and proline to specialized products

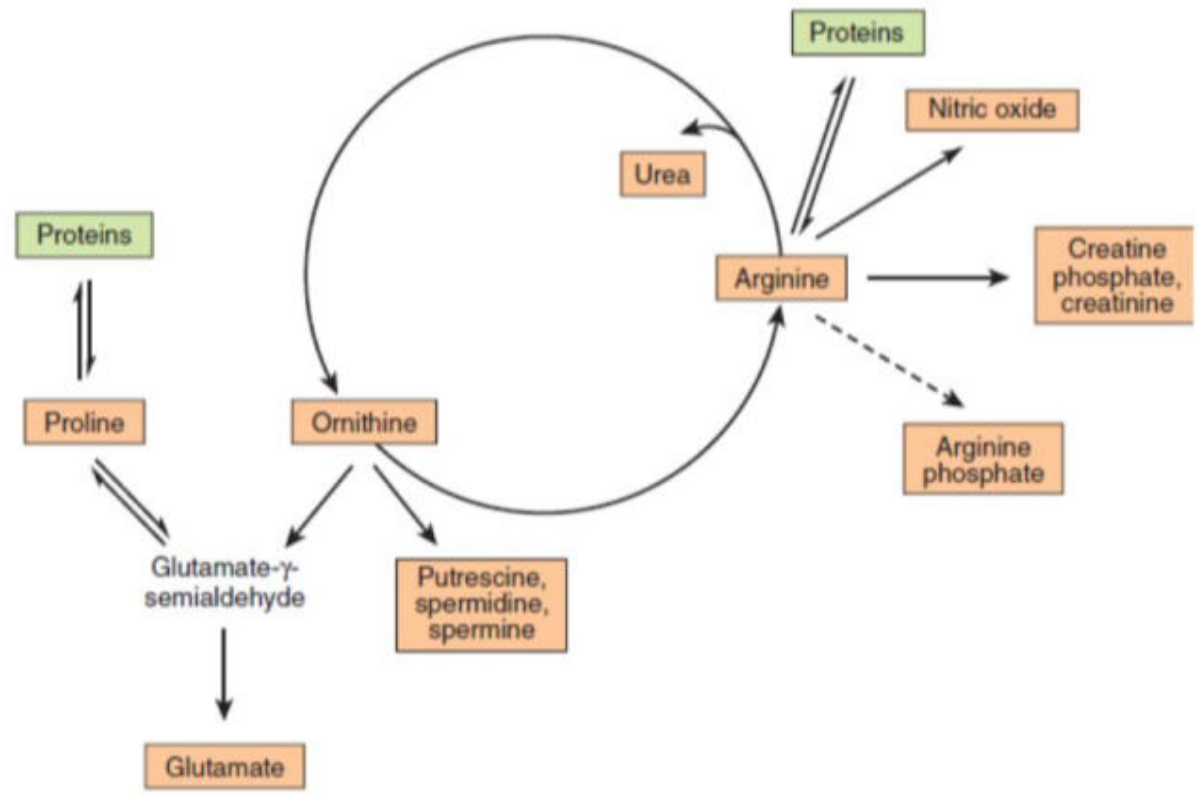



**FIGURE 30–1 Arginine, ornithine, and proline metabolism.** Reactions with solid arrows all occur in mammalian tissues. Putrescine and spermine synthesis occurs in both mammals and bacteria. Arginine phosphate of invertebrate muscle functions as a phosphagen analogous to creatine phosphate of mammalian muscle. Fig 30.1. Harper's Illustrated Biochemistry 30th Edition

## Creatine & Creatinine

- Creatinine is formed in muscle from creatine phosphate by irreversible, non-enzymatic dehydration, and loss of phosphate

- Glycine, arginine, and methionine all participate in creatine biosynthesis

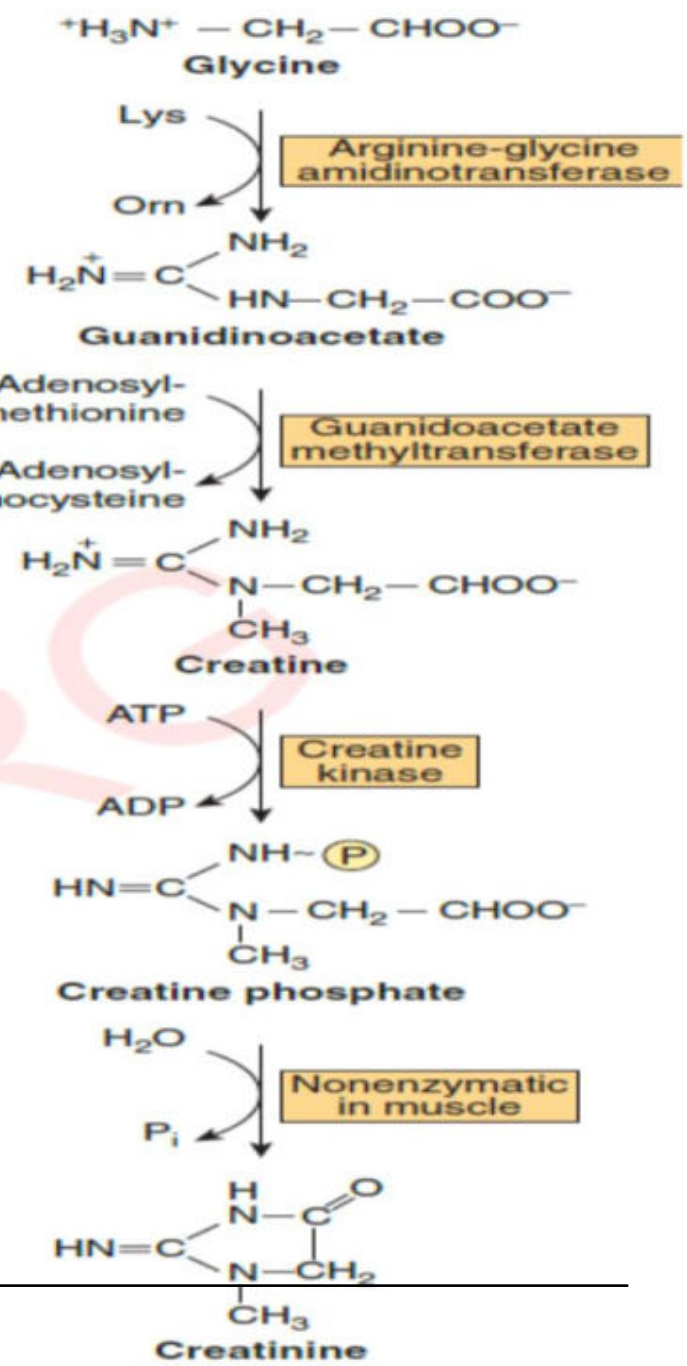



Fig 30.13. Harper's Illustrated Biochemistry 30th Edition

# Cont--

- Creatine converted into creatine phosphate by creatine kinase using ATP as a phosphate donor

- Presence of creatine kinase in the plasma is indicative of heart damage and is used in the diagnosis of myocardial infarction

# Conversion of cysteine to Taurine

- Three enzyme catalyzed reactions convert cysteine to taurine

- Taurine displace the coenzyme A moiety of cholyl-CoA to form the bile acid taurocholic acid

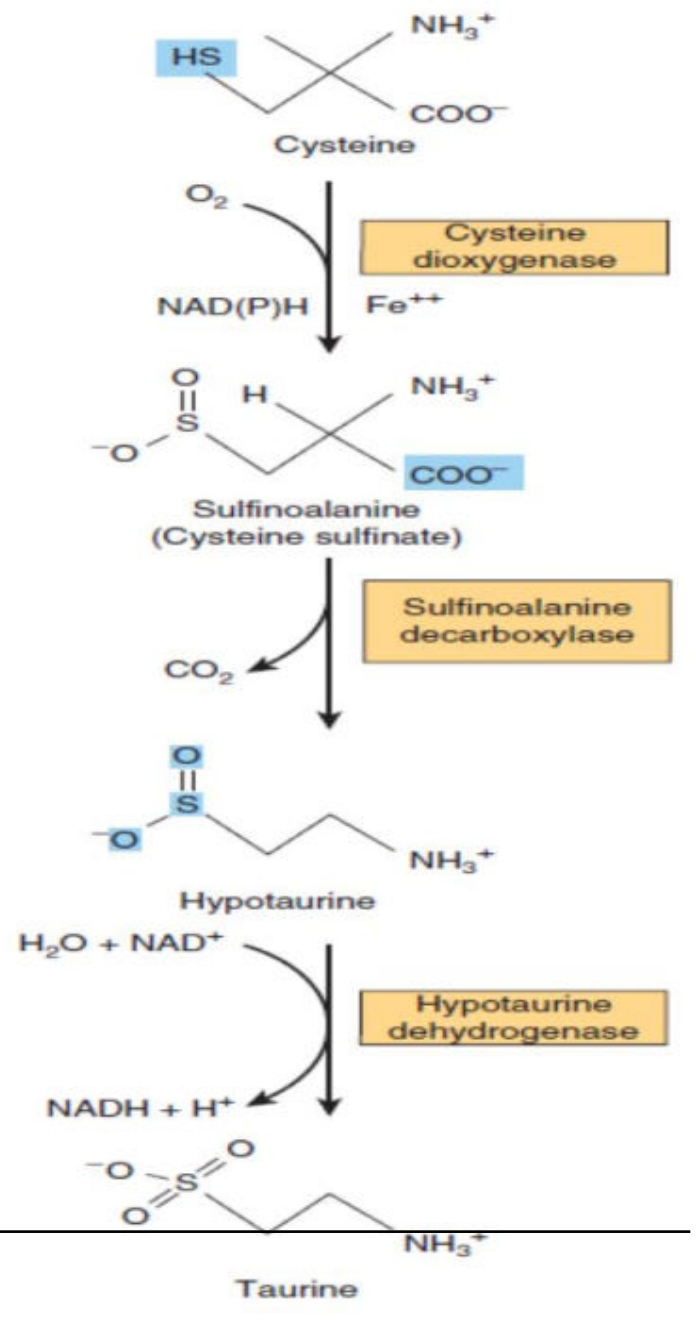


Fig 30.4. Harper's Illustrated Biochemistry 30th Edition

# Biosynthesis of hippurate from glycine

- Many metabolites and pharmaceuticals are excreted as water soluble glycine conjugates
- Ex. include glycocholic acid and hippuric acid formed from the food additive benzoate
- Many drugs, drug metabolites, and other compounds with carboxyl groups are conjugated with glycine, which makes them more water-soluble and thereby facilitates their excretion in urine

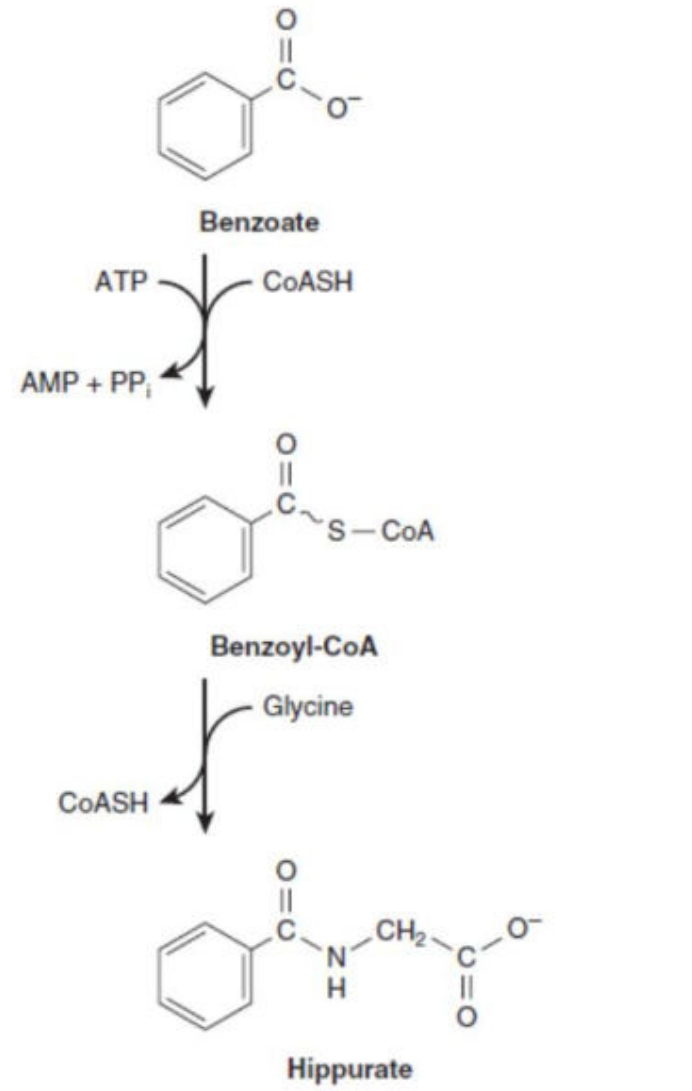



Fig 30.5. Harper's Illustrated Biochemistry 30th Edition

# Derivatives of Histidine

- Decarboxylation of histidine to histamine is catalyzed by the pyridoxal 5′-phosphate-dependent enzyme histidine decarboxylase
- Histamine functions in allergic reactions and gastric secretion

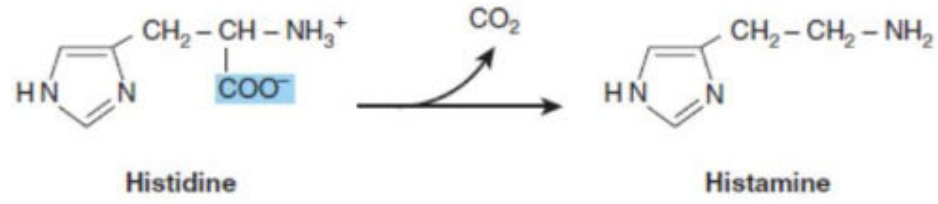



**FIGURE 30–6** The reaction catalyzed by histidine decarboxylase.

Fig 30.6. Harper's Illustrated Biochemistry 30th Edition

# Derivatives of Methionine

- These polyamines function in cell proliferation and growth, are growth factors for cultured mammalian cells, and stabilize intact cells, subcellular organelles, and membranes

- They bear multiple positive charges, polyamines readily associate with DNA and RNA

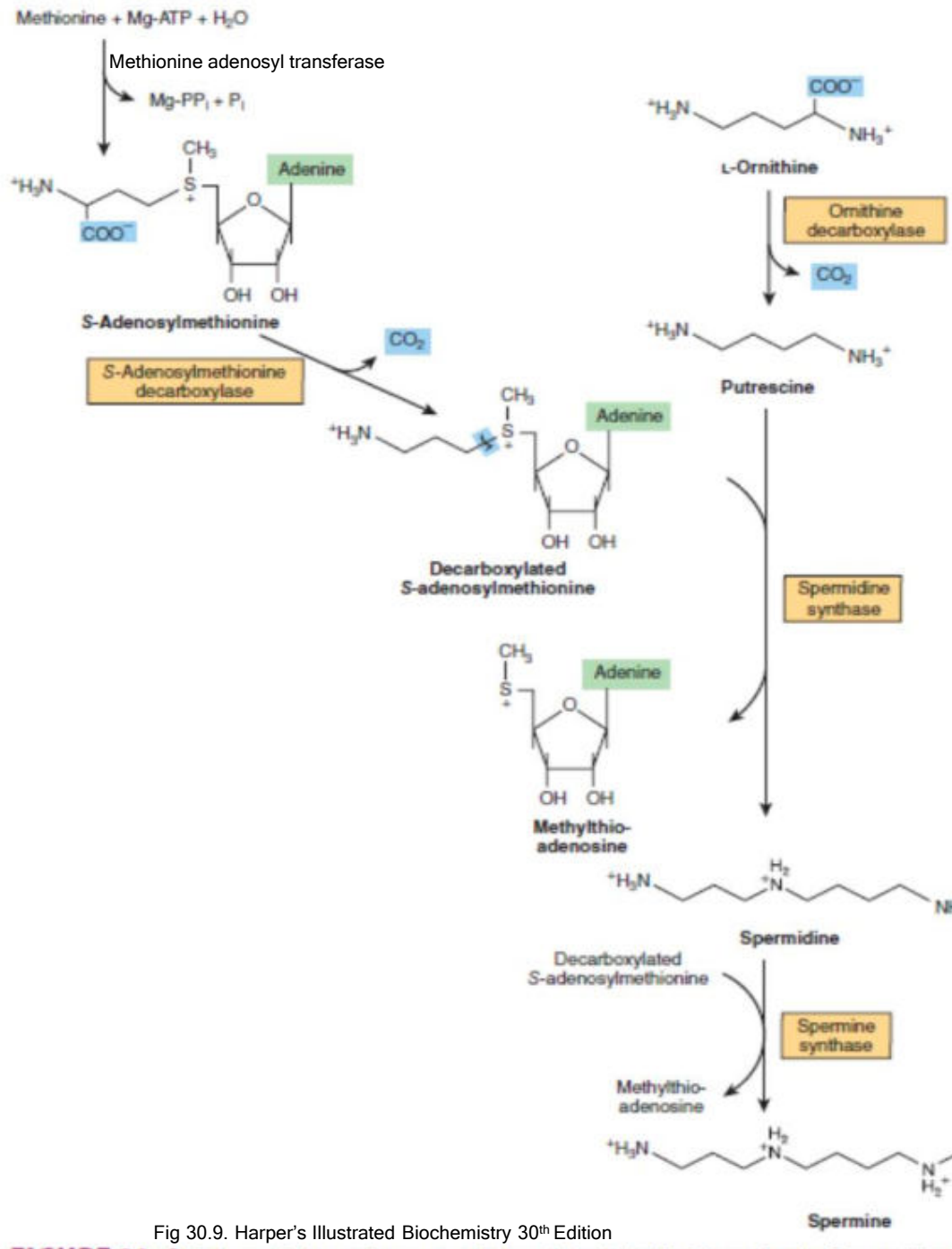



Fig 30.9. Harper's Illustrated Biochemistry 30th Edition

**FIGURE 30–9** Intermediates and enzymes that participate in the biosynthesis of spermidine and spermine.

# Derivatives of Tryptophan

- Hydroxylation of tryptophan to 5-hydroxytryptophan by liver tryptophan hydroxylase subsequent decarboxylation forms serotonin a potent vasoconstrictor and stimulator of smooth muscle contraction.

- Catabolism of serotonin is initiated by deamination to 5-hydroxyindole-3-acetate, a reaction catalyzed by monoamine oxidase

# Cont--

- N-Acetylation of serotonin, followed by its O-methylation in the pineal body, forms melatonin

- Kidney tissue, liver tissue, and fecal bacteria all convert tryptophan to tryptamine, then to indole 3-acetate

- The principal normal urinary catabolites of tryptophan are 5-hydroxyindoleacetate and indole 3-acetate.

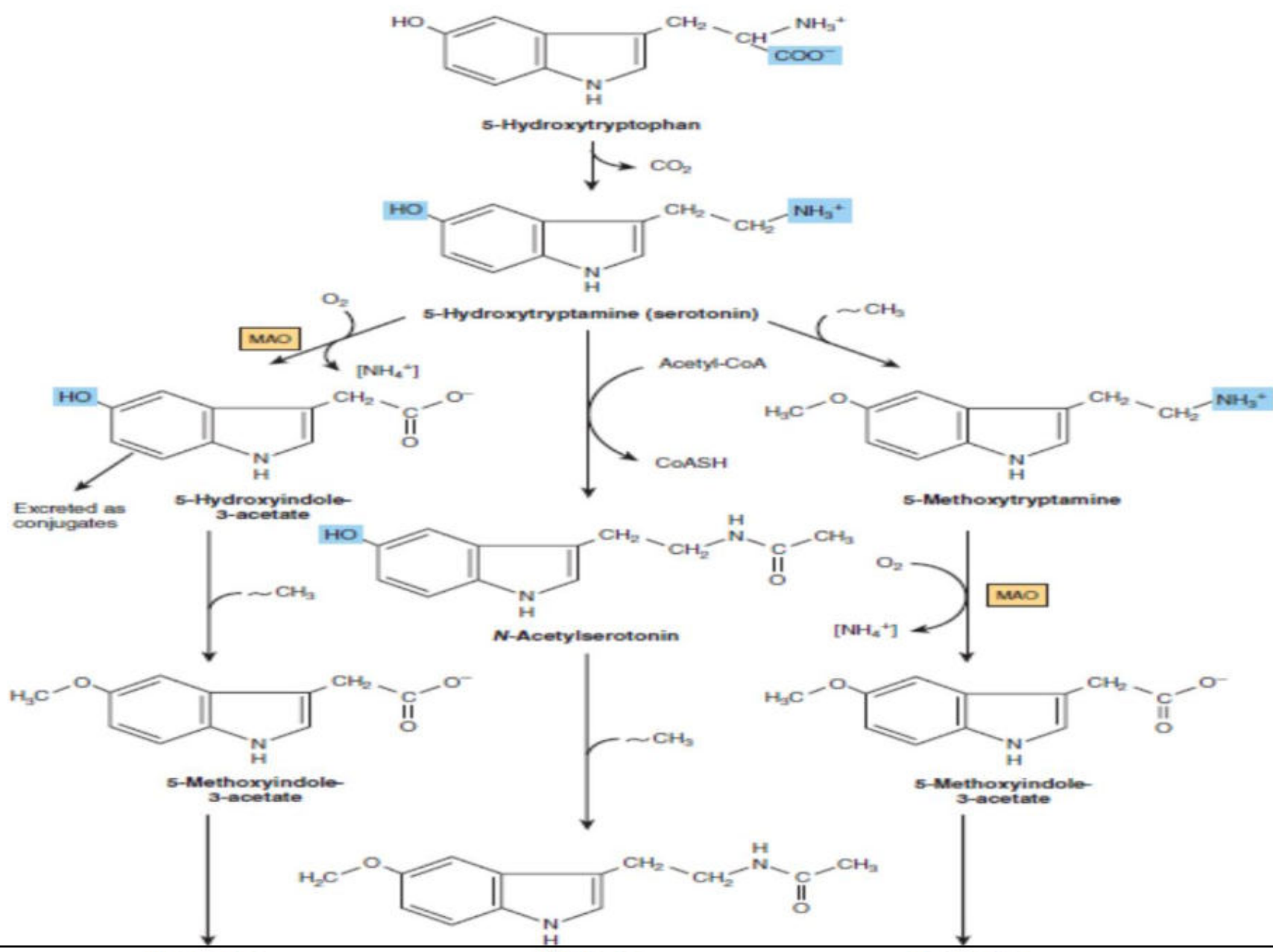





**FIGURE 30–11 Biosynthesis and metabolism of serotonin and melatonin.** ([$NH_4^+$], by transamination; MAO, monoamine oxidase; ~$CH_3$, from *S*-adenosylmethionine.) Fig 30.11. Harper's Illustrated Biochemistry 30th Edition

# Derivatives of Tyrosine

- Neural cells convert tyrosine to epinephrine and norepinephrine
- Dopa is also an intermediate in the formation of melanin, different enzymes hydroxylate tyrosine in melanocytes
- Dopa decarboxylase, a PLP-dependent enzyme, forms dopamine.

## Cont--

- Subsequent hydroxylation, catalyzed by dopamine β-oxidase forms norepinephrine
- In adrenal medulla, phenylethanolamine-N-methyltransferaseutilizes S-adenosylmethionine to methylate the primary amine of norepinephrine, forming epinephrine
- Tyrosine is also a precursor of triiodothyronine and thyroxine

# Derivatives of Tyrosine: Epinephrine

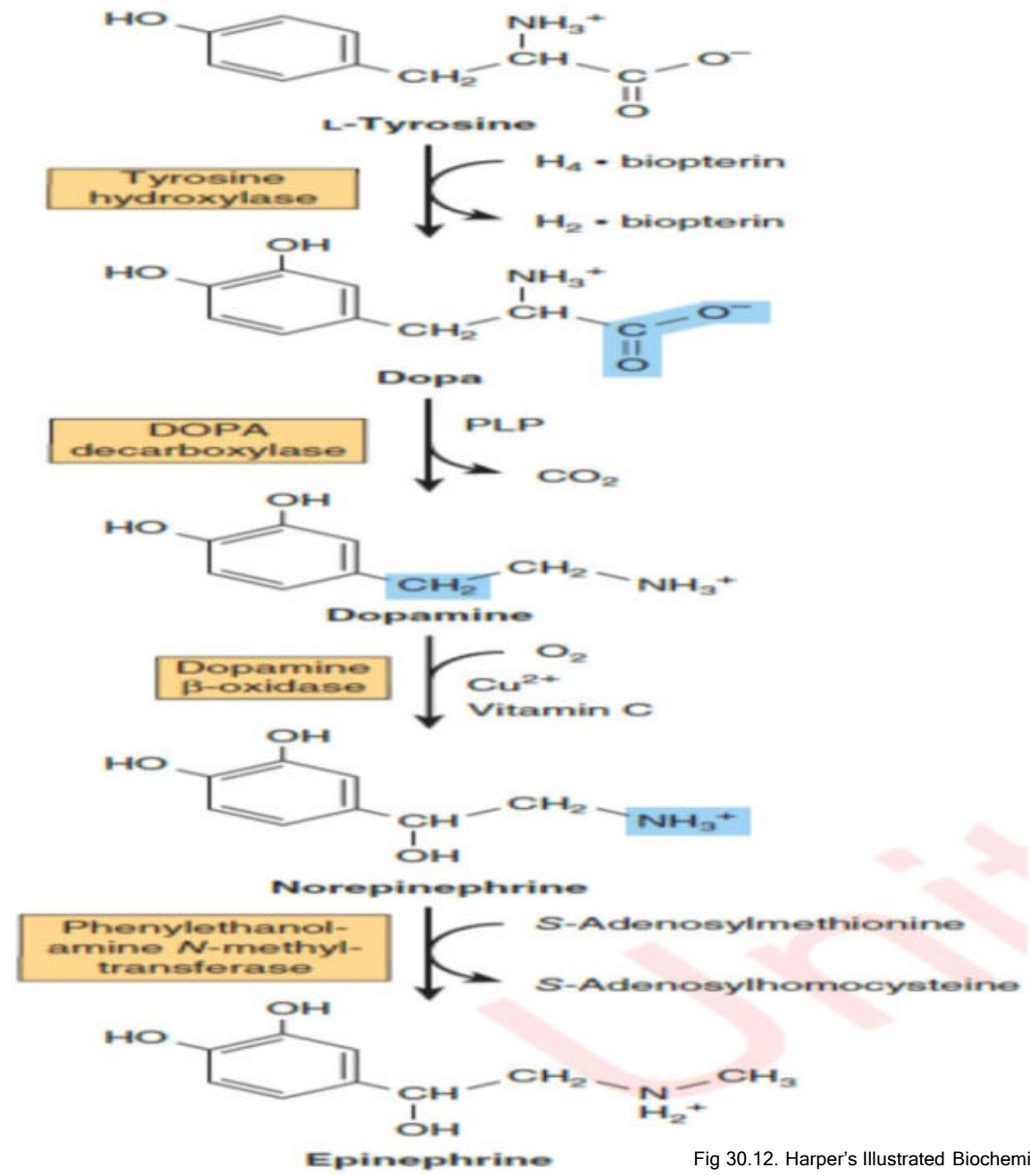



Fig 30.12. Harper's Illustrated Biochemistry 30th Edition

# Derivatives of Tyrosine: Melanin






Fig. 15.20 : Metabolism of tyrosine—biosynthesis of melanin (Defect in tyrosinase causes albinism).

DM Vasudevan' s Textbook of Biochemistry for Medical Students-6th Ed

# Derivatives of Tyrosine: T3 and T4

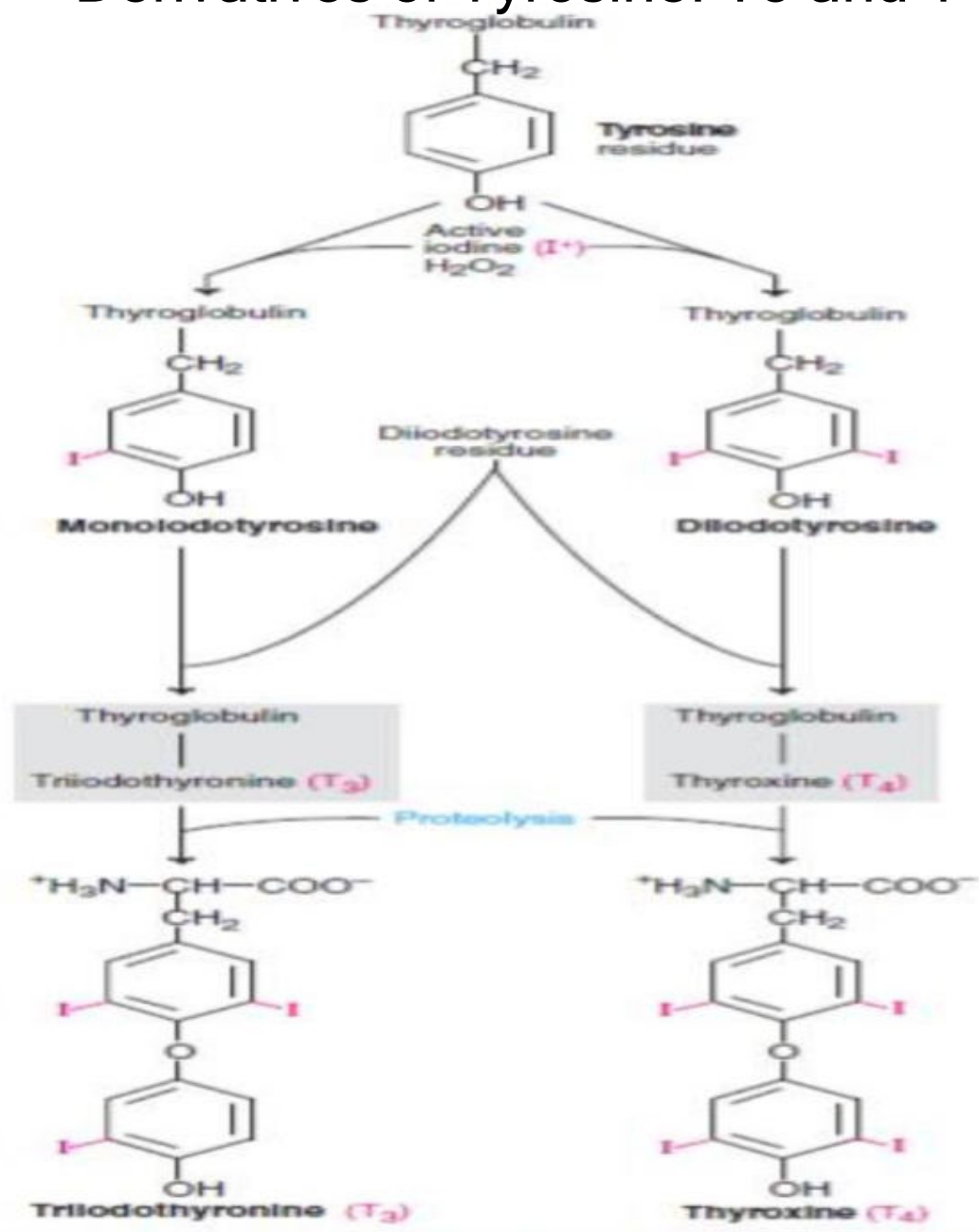



*Fig. 15.21 : Metabolism of tyrosine-synthesis of thyroid hormones.*

DM Vasudevan' s Textbook of Biochemistry for Medical Students-6th Ed

# Disorder related to Tyrosine derivative

## Albinism

- A deficiency of tyrosinase in melanocytes causes one form of albinism; it is inherited as an autosomal recessive disorder
- Pigmentation of the skin, hair and iris is reduced and the eyes may appear pink
- Reduced pigmentation of the iris causes photosensitivity, and decreased skin pigmentation is associated with an increased incidence of certain skin cancers
- The tyrosinase involved in catecholamine synthesis is a different isoenzyme, controlled by a different gene; consequently, adrenaline (epinephrine) metabolism is normal

# Metabolism of γ-AminoButyrate (GABA)

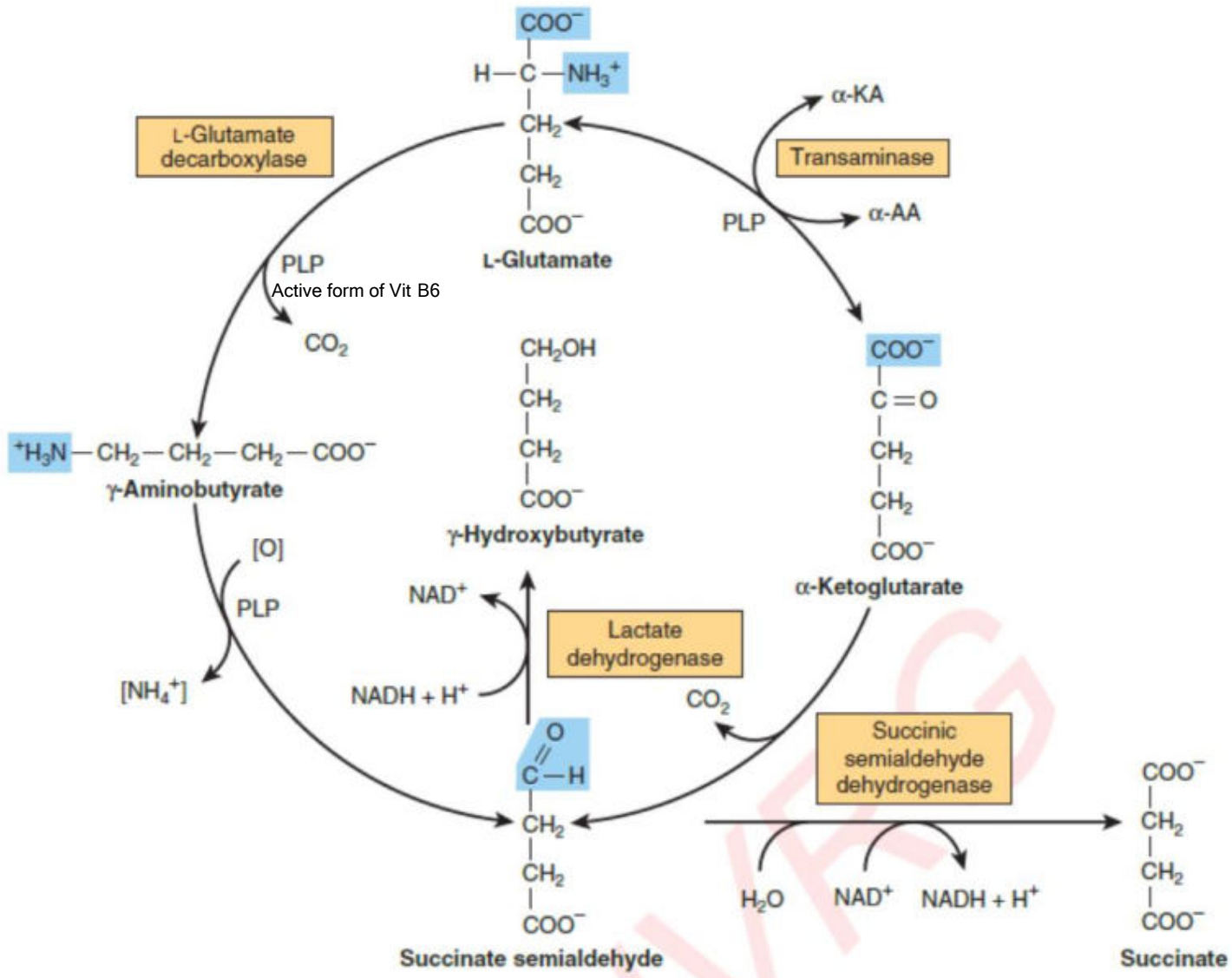



**FIGURE 30–14** **Metabolism of γ-aminobutyrate.** (α-AA, α-amino acids; α-KA, α-keto acids; PLP, pyridoxal phosphate.) Fig 30.14. Harper's Illustrated Biochemistry 30th Edition

# Disorder related to GABA

## 4-hydroxybutyric aciduria

- Defects in succinic semialdehyde dehydrogenase, are responsible for 4-hydroxybutyric aciduria a rare metabolic disorder of γ-aminobutyrate catabolism
- Characterized by the presence of 4-hydroxybutyrate in urine, plasma and cerebrospinal fluid
- No present treatment is available for the accompanying mild to severe neurologic symptoms.

# Group Discussion

- Subtopics of previous and today's class discussed in groups.
- Next integrated class on Protein metabolism by me and from department of Pediatrics (discussed inborn error of metabolism case studies).

**Thank you**