Catabolism of Carbon Skeletons of aa and related disorders-II

Specific Learning Objectives

- Catabolic pathways of four aa to Succinyl-CoA
- Degradation and Resynthesis of Methionine
- Disorder related to Methionine degradation
- Degradation of Branched chain amino acids
- Disorder related to Branch chain aa degradation

Summary of Amino acid Catabolism

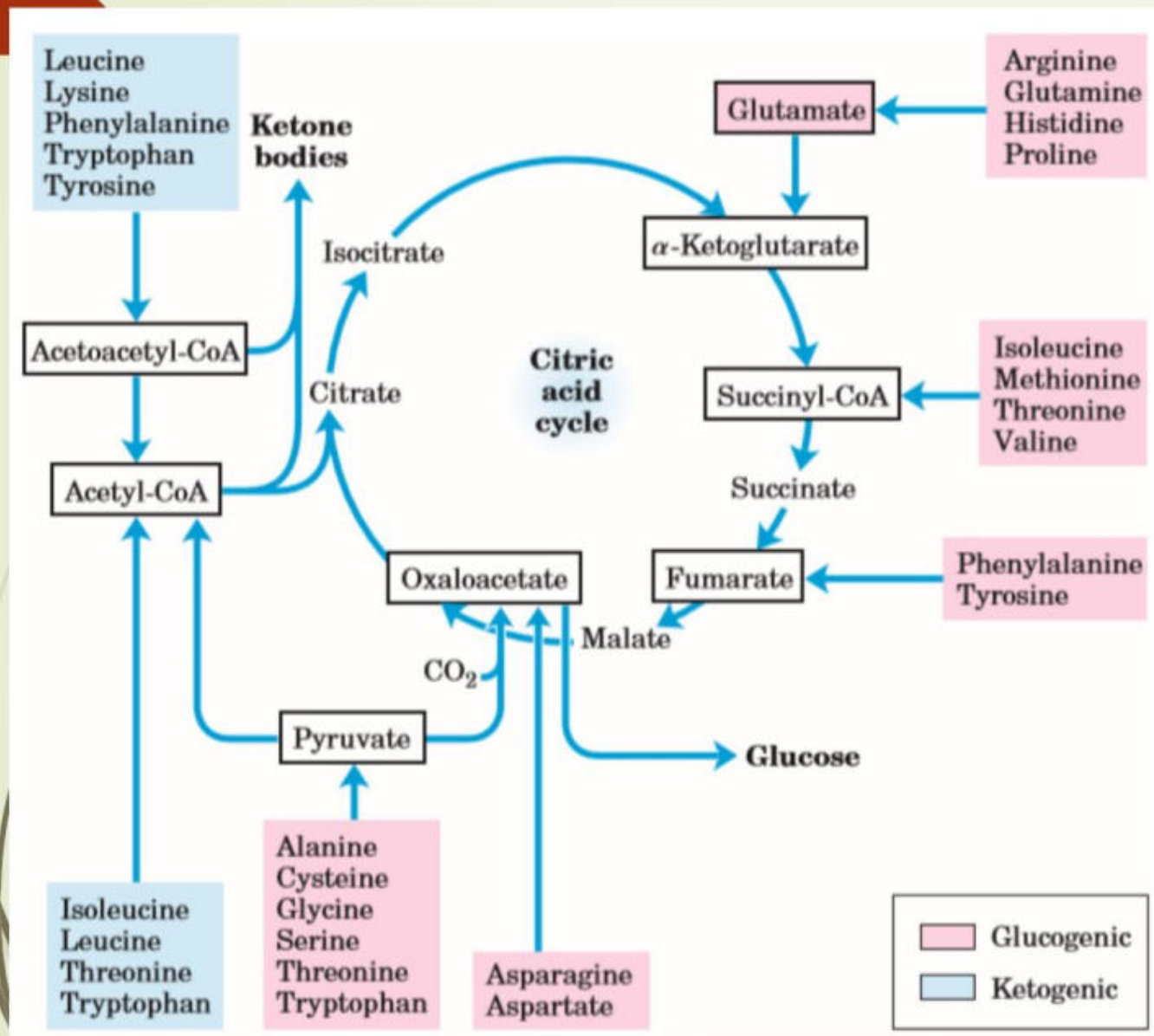

FIGURE 18–15 Summary of amino acid catabolism. Amino acids are grouped according to their major degradative end product. Some amino acids are listed more than once because different parts of their carbon skeletons are degraded to different end products. The figure shows the most important catabolic pathways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

Catabolic pathways of four aa to Succinyl-CoA

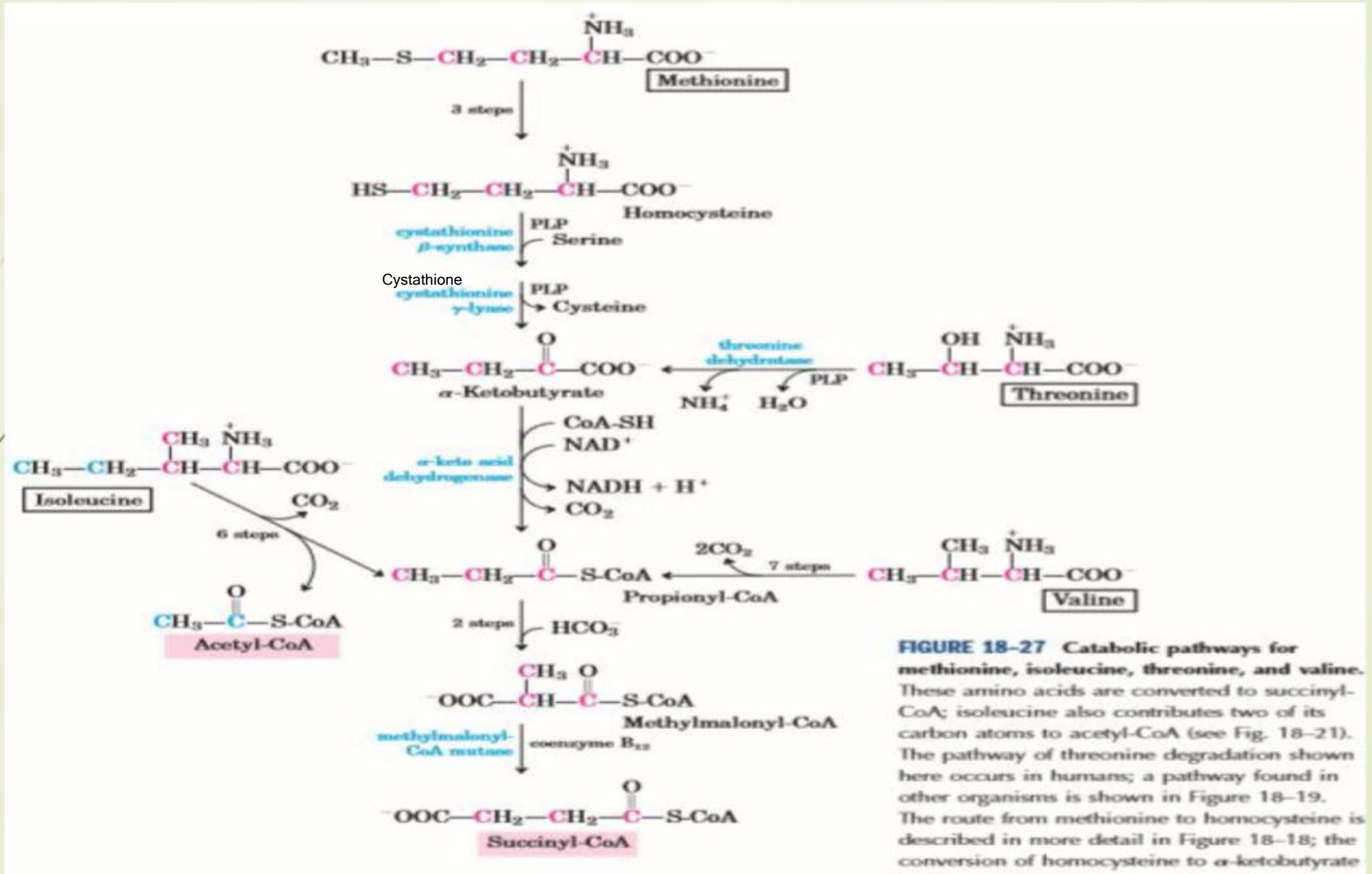

FIGURE 18–27 Catabolic pathways for methionine, isoleucine, threonine, and valine. These amino acids are converted to succinyl-CoA; isoleucine also contributes two of its carbon atoms to acetyl-CoA (see Fig. 18–21). The pathway of threonine degradation shown here occurs in humans; a pathway found in 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 Figure 17–11.

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

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- 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 participation of biotin and coenzyme B12

Degradation and Resynthesis of Methionine

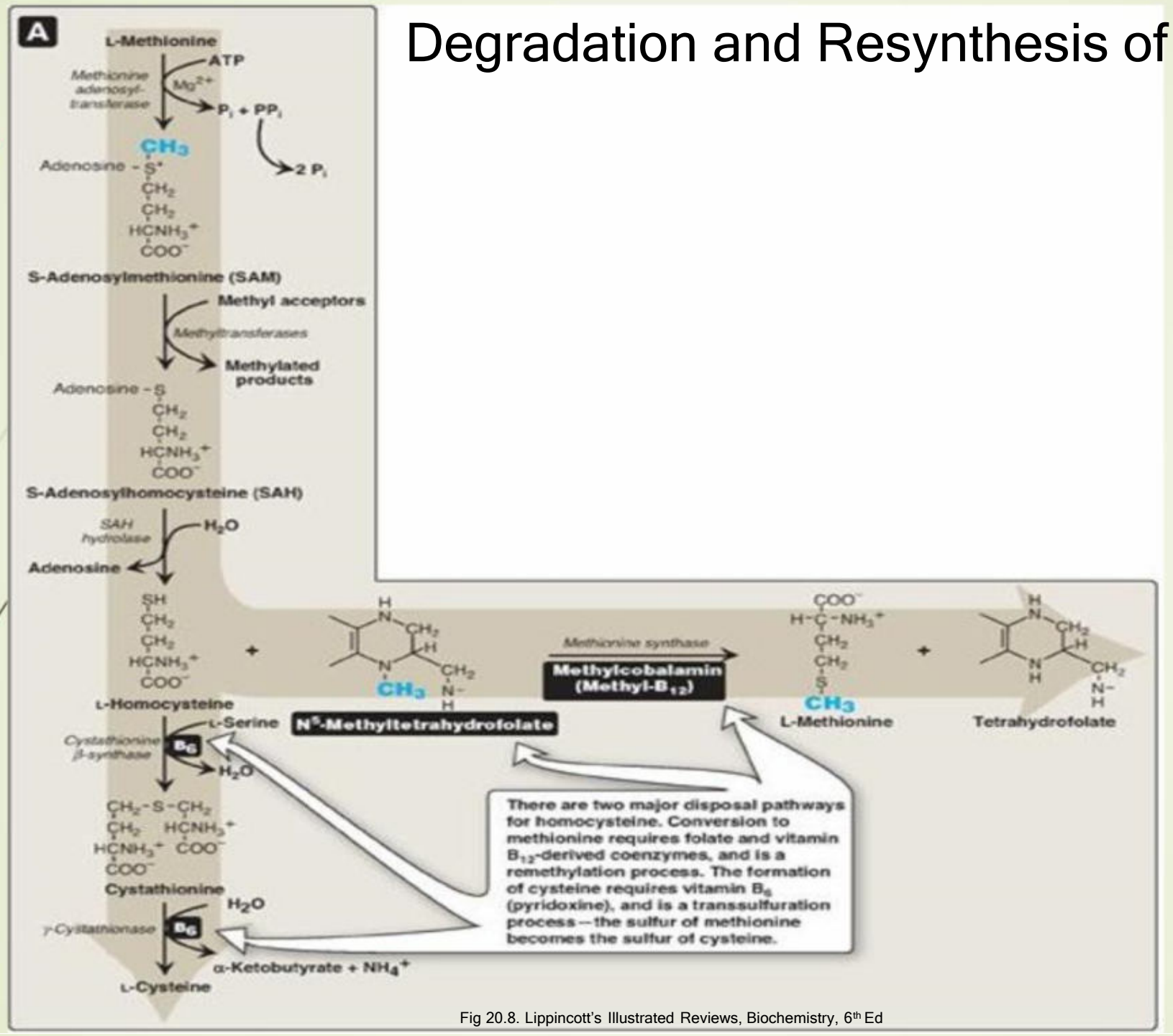
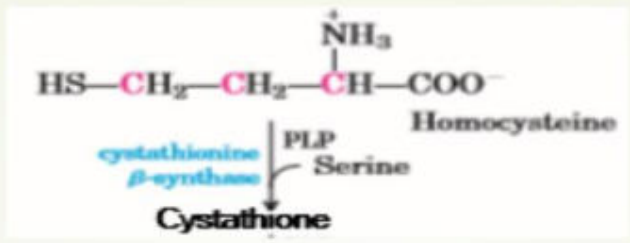


Fig 20.8. Lippincott's Illustrated Reviews, Biochemistry, 6th Ed

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 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--

- Lens of eye is frequently dislocated after age of 3, and other ocular abnormalities occur
- Mental retardation is frequently 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 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

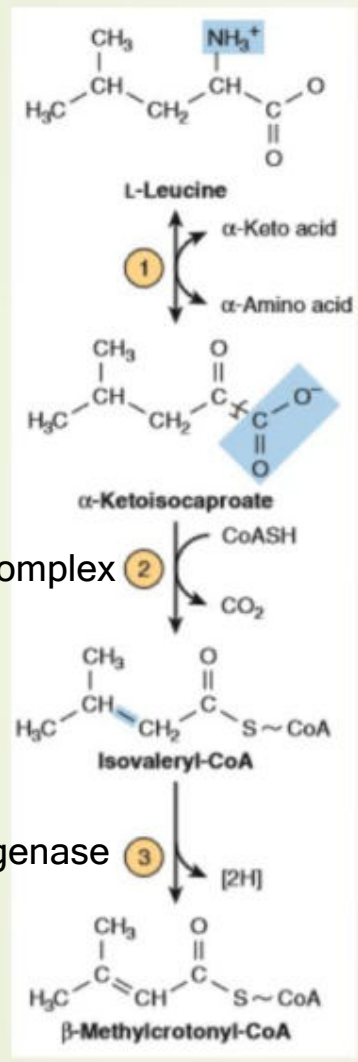
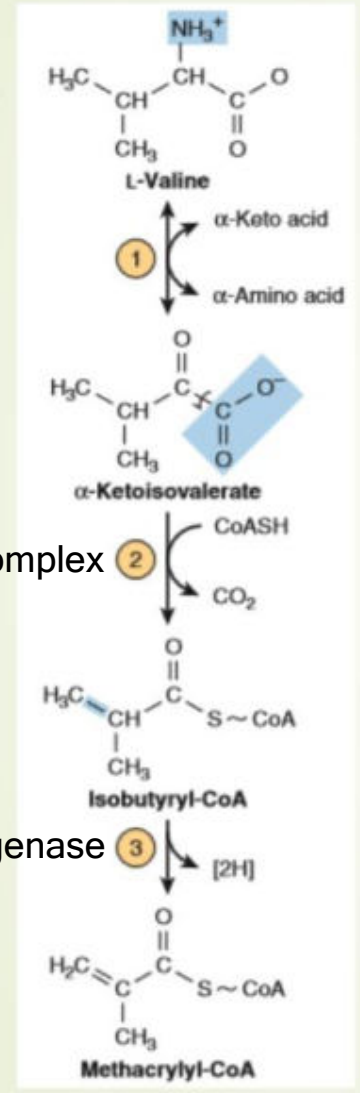


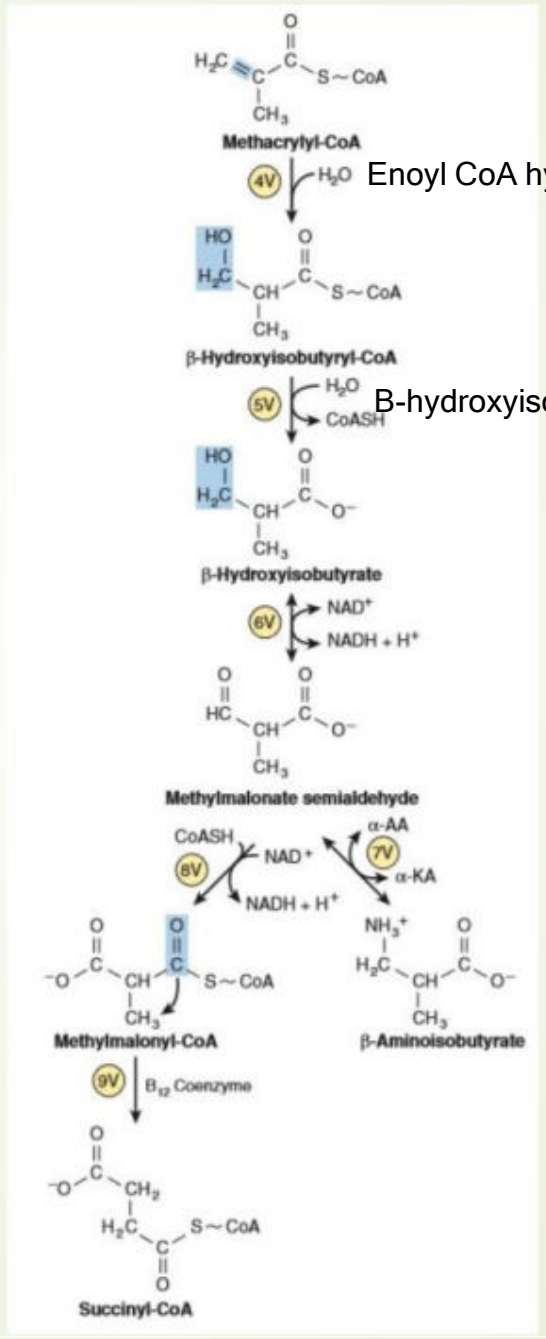
Fig 29.20 and 29.21. Harper's Illustrated Biochemistry 30th Edition

Catabolism of Valine to β-Aminoisobutyrate and Succinyl-CoA



α-keto acid decarboxylase complex

A Methacrylyl CoA dehydrogenase

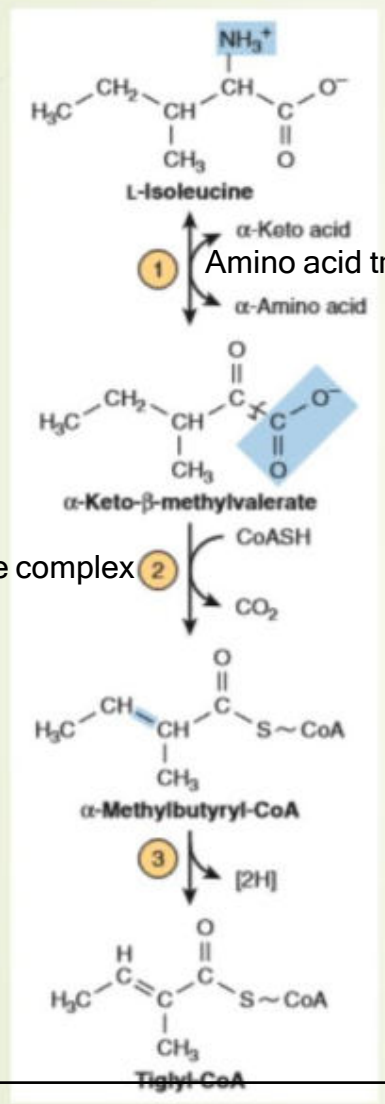


Enoyl CoA hydratase

B-hydroxyisobutyryl CoA hydrolase

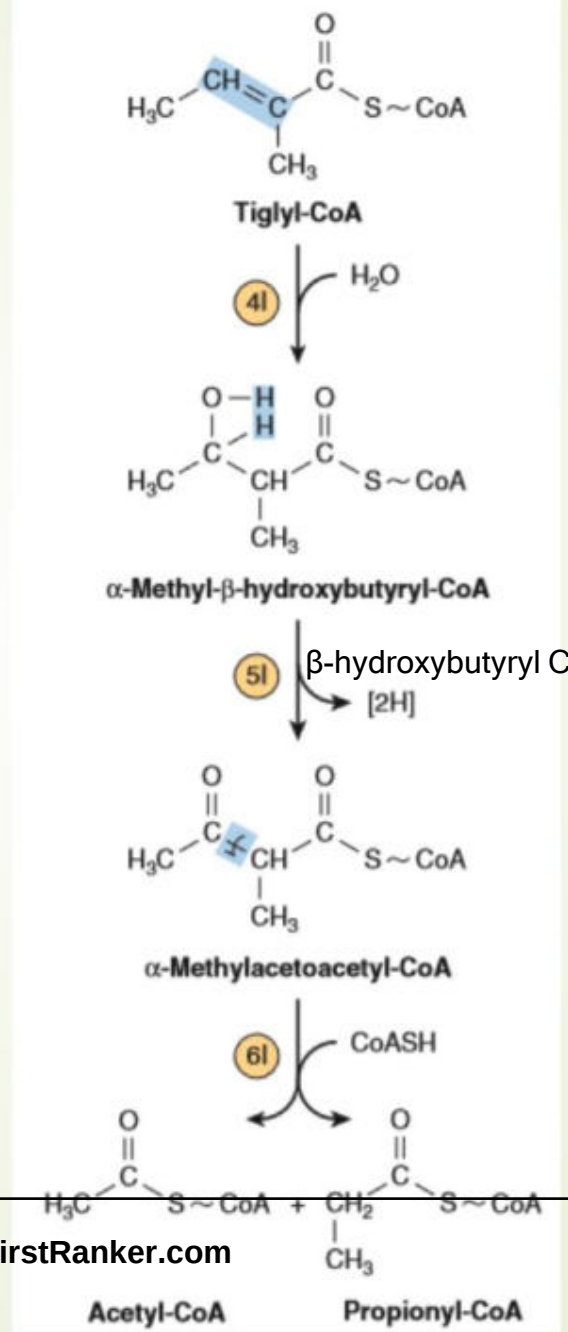
Fig 29.20 and 29.23. Harper's Illustrated Biochemistry 30th Edition

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 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

Two Clinical-cases discussed

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) Text Book of Medical Biochemistry by Chatterjee & Rana Shinde, 8th Ed
5) DM Vasudevan' s Textbook of Biochemistry for Medical Students, 6th Ed
6) Gregory S. Ducker and Joshua D Rabinowitz. Cell Metab. 2017 Jan 10;25(1):27-42

Thank you