Catabolism of Carbon Skeletons of aa and related disorders-I

Department of Biochemistry

Specific Learning Objectives

- Catabolism of Carbon Skeletons of aa and related disorders:
- Distinguish following disease states associated with Inborn Errors of Metabolism, including deficient enzyme, relation of deficiency to build-up of secondary metabolites, and clinically relevant information related to disease state (vitamin deficiencies, symptoms, diagnosis, pathology and treatments:

- Cystinuria
- Histidinemia
- Phenylketonuria (PKU)
- Methylmalonyl CoA mutase deficiency e. Albinism
- Homocystinuria
- Alkaptonuria
- Maple syrup urine disease
- Cystathioninuria
- Tyrosinemia

- Catabolism of Phenylalanine and Tyrosine with genetic disorders
- Catabolic pathways of five aa to α-ketoglutarate and associated disorders

Summary of Amino acid Catabolism

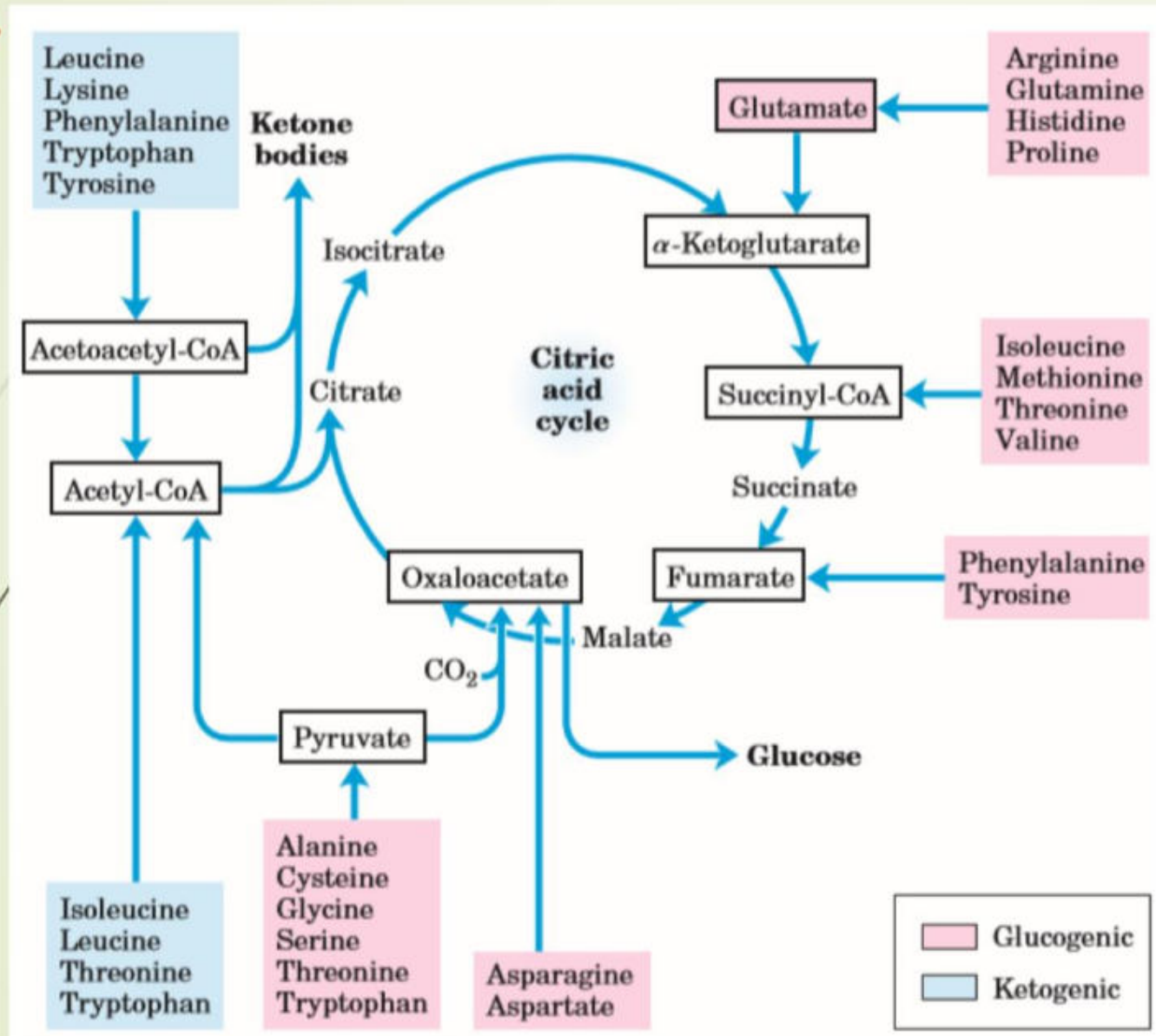

FIGURE 18–15 **Summary of amino acid catabolism.** Amino acids are grouped according to their major degradative end product. Some amino acids are listed more than once because different parts of their carbon skeletons are degraded to different end products. The figure shows the most important catabolic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

Catabolism of Phenylalanine and Tyrosine with genetic disorders

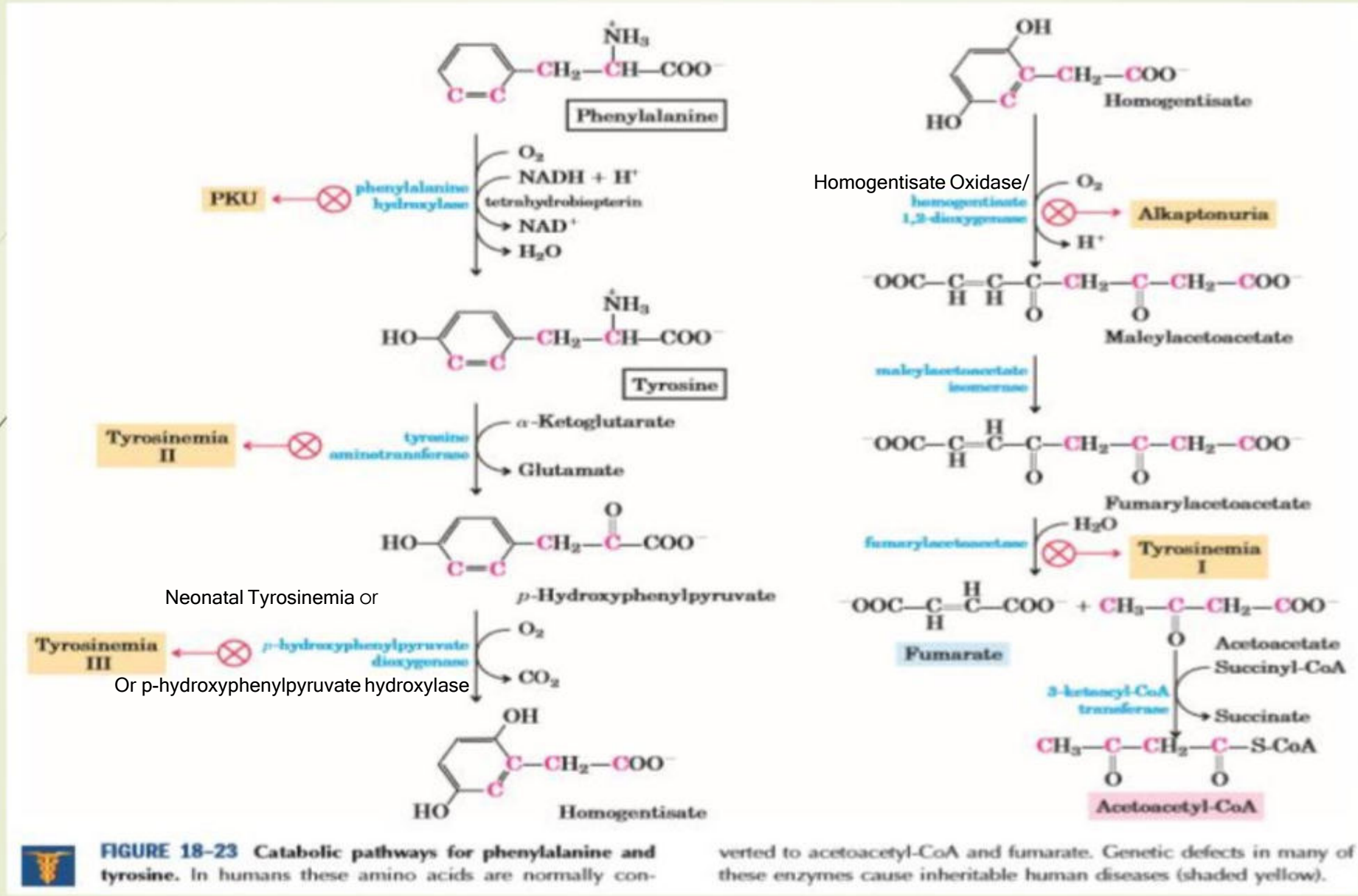

FIGURE 18–23 Catabolic pathways for phenylalanine and tyrosine. In humans these amino acids are normally converted to acetoacetyl-CoA and fumarate. Genetic defects in many of these enzymes cause inheritable human diseases (shaded yellow).

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

Alternative pathways for catabolism of phenylalanine in PKU

- Phenylalanine and phenylpyruvate accumulate in blood and tissues and are excreted in urine–hence name “phenylketonuria”
- Phenylpyruvate, excreted as either decarboxylated to phenylacetate or reduced to phenyllactate
- Phenylacetate gives a characteristic odor to urine, (for detection of PKU in infants)

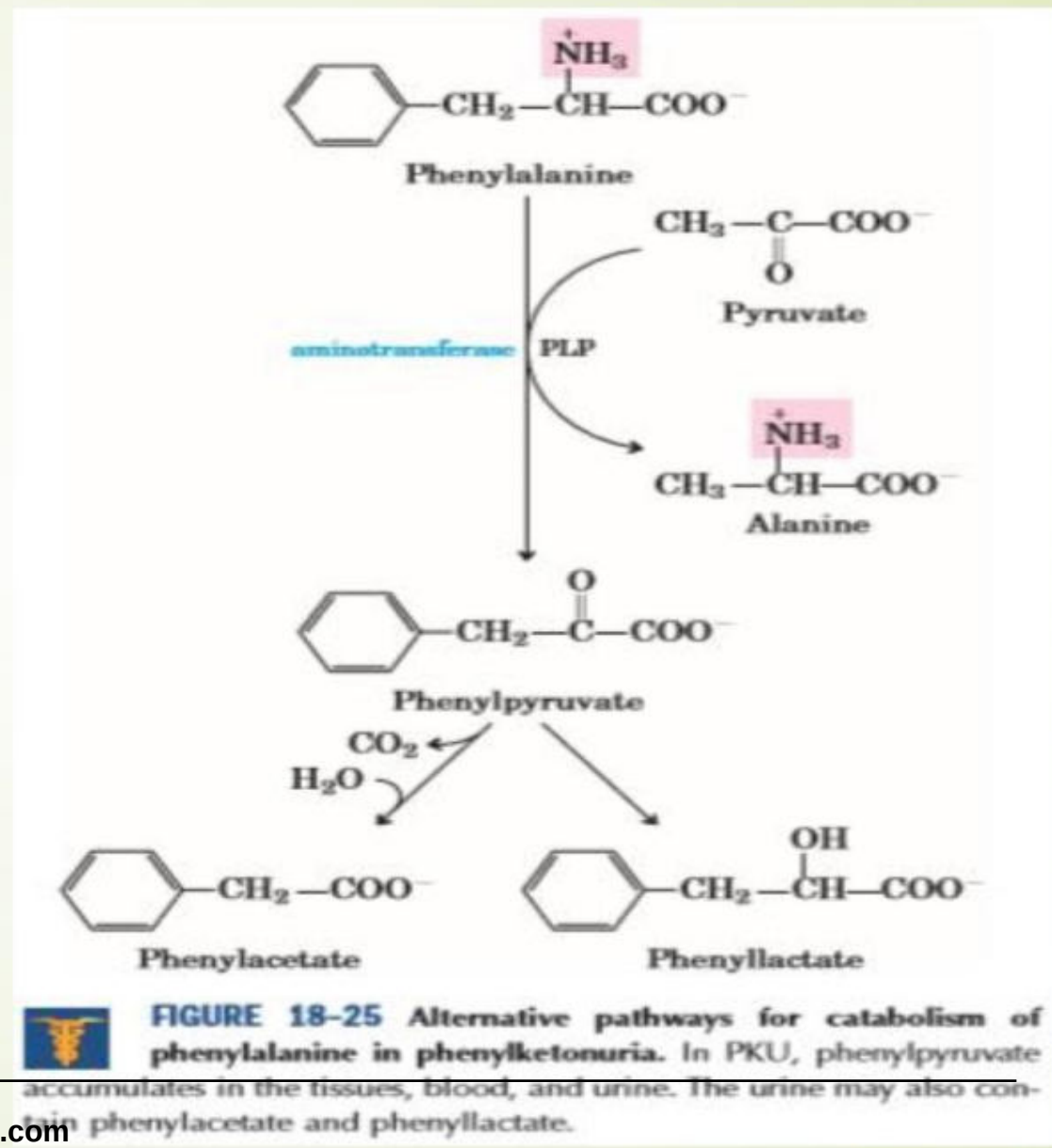

FIGURE 18–25 Alternative pathways for catabolism of phenylalanine in phenylketonuria. In PKU, phenylpyruvate accumulates in the tissues, blood, and urine. The urine may also contain phenylacetate and phenyllactate.

Fig18.25: Lehninger Principles of Biochemistry by David L Nelson, 6th Ed.

Disorder related to phenylalanine catabolism

Phenylketonuria (PKU): Genetic defect in phenylalanine hydroxylase, first enzyme in catabolic pathway for phenylalanine, is responsible for 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 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 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 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 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

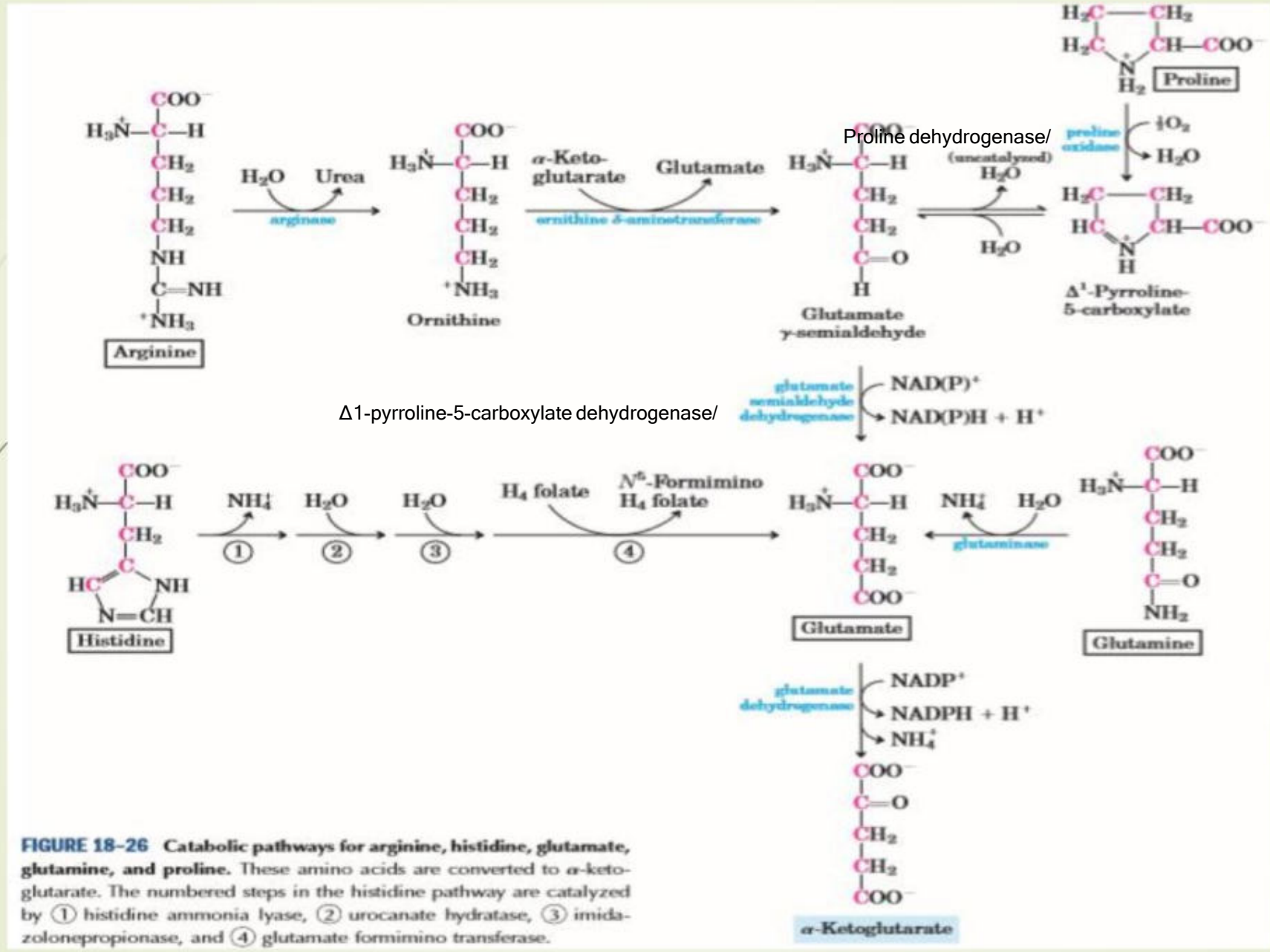

FIGURE 18–26 Catabolic pathways for arginine, histidine, glutamate, glutamine, and proline. These amino acids are converted to α-ketoglutarate. The numbered steps in the histidine pathway are catalyzed by ① histidine ammonia lyase, ② urocanate hydratase, ③ imidazolonepropionase, and ④ glutamate formimino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

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

Disorder related to Proline catabolism

Type I hyperprolinemia

- 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

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

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

Thank you