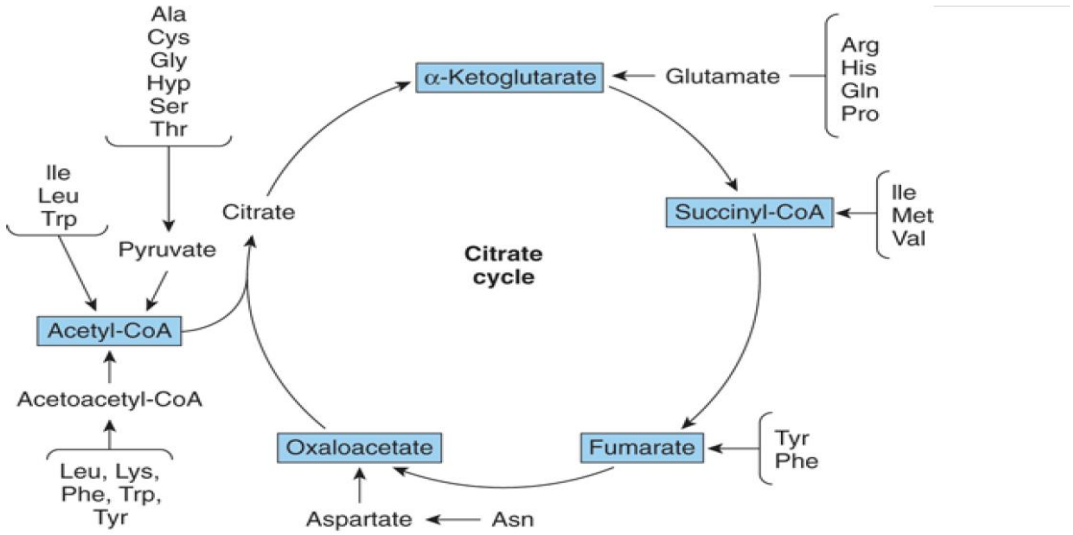
TRANSAMINATION TYPICALLY INITIATES AMINO ACID CATABOLISM

Removal of -amino nitrogen by transamination is the first catabolic reaction of amino acids except for proline, hydroxyproline, threonine, and lysine. The hydrocarbon skeleton that remains is then degraded to amphibolic intermediates as outlined in Figure.



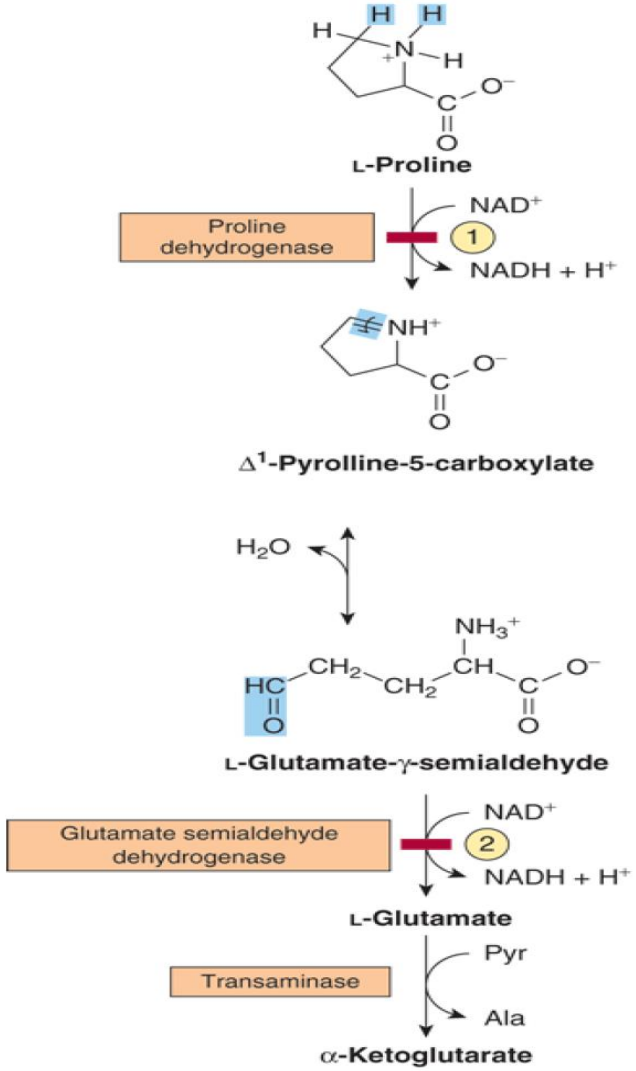
Asparagine, Aspartate, Glutamine, and Glutamate

All four carbons of asparagine and aspartate form **oxaloacetate** .Analogous reactions convert glutamine and glutamate to **–ketoglutarate.** No metabolic defects are associated with the catabolism of these four amino acids

Proline

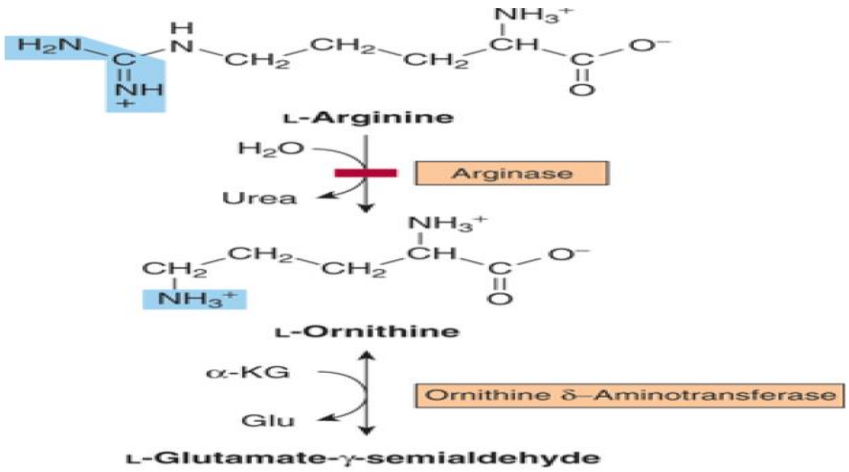
The catabolism of proline takes place in mitochodria. Since proline does not participate in transamination, the nitrogen of this amino acid is retained throughout its oxidation to 1 -pyrolline-5-carboxylate, ring opening to glutamate- -semialdehyde, and oxidation to glutamate, and is only removed during transamination of glutamate to-ketoglutarate. There are two metabolic disorders of proline catabolism. Both types are inherited as autosomal recessive traits, and are consistent with a normal adult life. The metabolic block in **type I hyperprolinemia** is at **proline dehydrogenase.** There is no associated impairment of hydroxyproline catabolism.

The metabolic block in **type II hyperprolinemia** is at **glutamate- -semialdehyde dehydrogenase,** an enzyme that also functions in hydroxyproline catabolism. Both proline and hydroxyproline catabolism thus are affected, and both 1 -pyroline-5-carboxylate and 1 -pyroline-3-hydroxy-5-carboxylate are excreted.



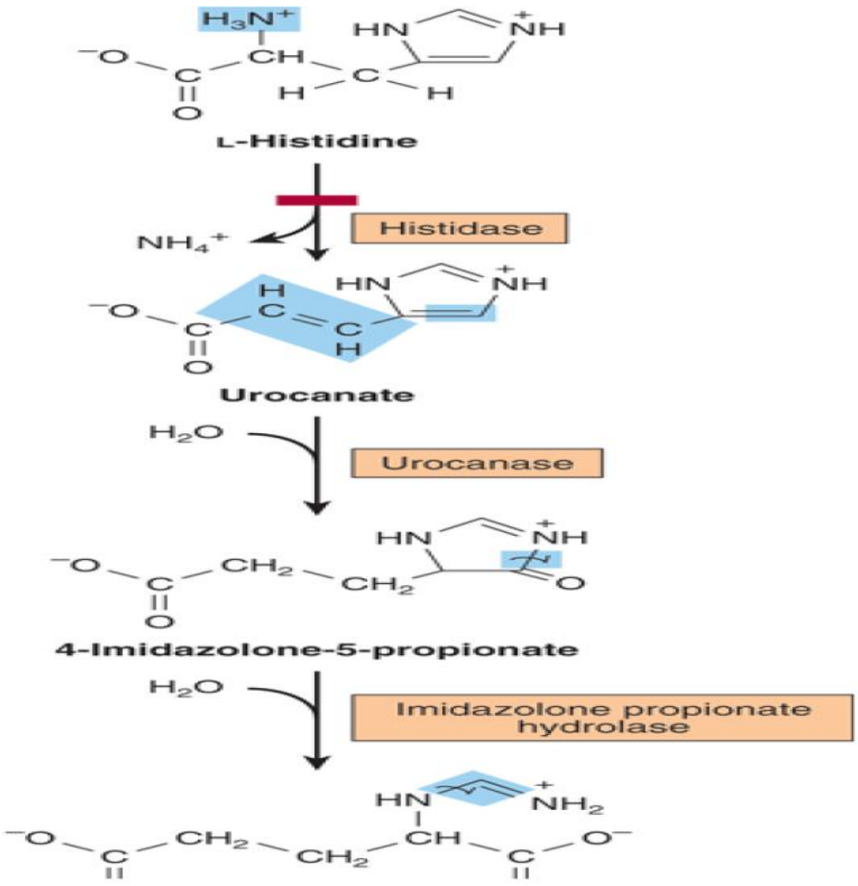
Arginine and Ornithine

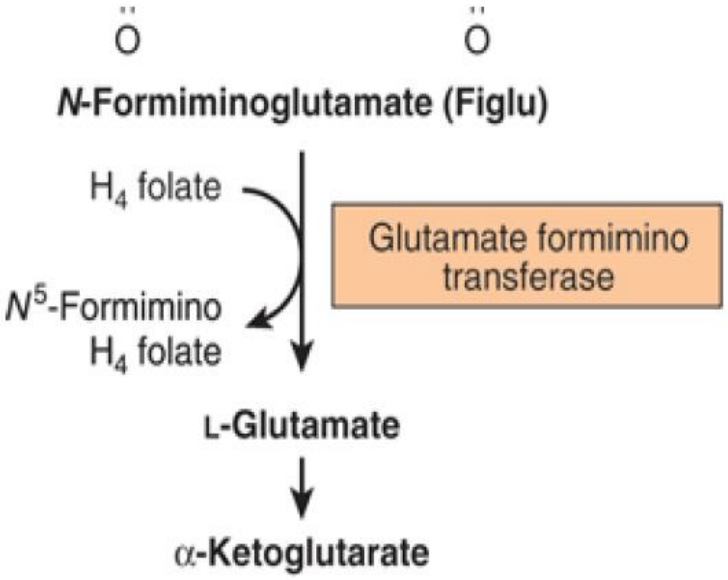
Arginine is converted to ornithine then to glutamate– -semialdehyde. Subsequent catabolism to **-ketoglutarate** occurs as described above for proline . Mutations in **ornithine -aminotransferase** elevate plasma and urinary ornithine and cause **gyrate atrophy of the retina.** Treatment involves restricting dietary arginine. In **hyperornithinemia-hyperammonemia syndrome,** a defective mitochondrial **ornithine-citrulline antiporter** impairs transport of ornithine into mitochondria for use in urea synthesis.



Histidine

Catabolism of histidine proceeds via urocanate, 4-imidazolone-5-propionate, and *N* -formiminoglutamate (Figlu). Formimino group transfer to tetrahydrofolate forms glutamate, then -**ketoglutarate**. In folic acid deficiency, group transfer of the formimino group is impaired, and Figlu is excreted. Excretion of Figlu following a dose of histidine thus can be used to detect folic acid deficiency. Benign disorders of histidine catabolism include **histidinemia** and **urocanic aciduria** associated with impaired **histidase.**





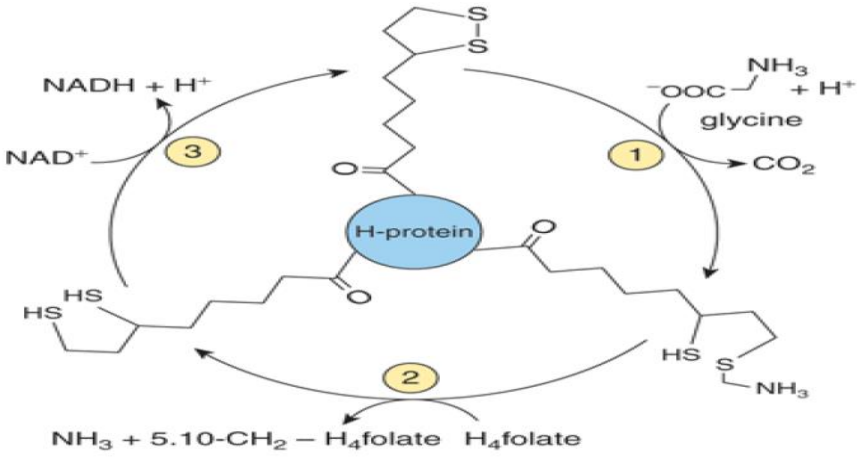
Catabolism of glycine, serine, alanine, cysteine, threonine and 4-hydroxyproline

Glycine

The **glycine cleavage complex** of liver mitochondria splits glycine to CO2 and NH4 + and forms *N* 5 ,*N* 10 - methylene tetrahydrofolate.

Glycine + H4 folate+ NAD+ CO2 + NH3 + 5,10-CH2 -H4 folate + NADH + H+

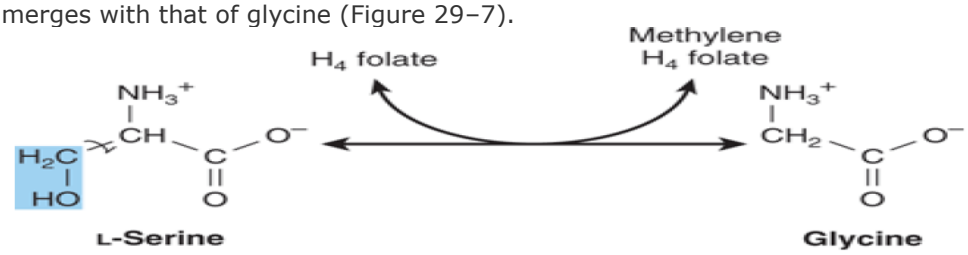
In **nonketotic hyperglycinemia,** a rare inborn error of glycine degradation presently known only in Finland, glycine accumulates in all body tissues including the central nervous system. The defect in **primary hyperoxaluria** is the failure to catabolize glyoxylate formed by the deamination of glycine. Subsequent oxidation of glyoxylate to oxalate results in urolithiasis, nephrocalcinosis, and early mortality from renal failure or hypertension. **Glycinuria** results from a defect in renal tubular reabsorption.



The glycine cleavage system of liver mitochondria. The complex consists of three enzymes and an "H-protein" that has ovalently attached dihyrolipoate. Catalysts for the numbered reactions are glycine dehydrogenase (decarboxylating), an ammonia-forming aminomethyltransferase, and dihydrolipoamide dehydrogenase. (H4 folate, tetrahydrofolate).

Serine

Following conversion to glycine, catalyzed by **serine hydroxymethyltransferase,** serine catabolism merges with that of glycine (Figure 29–7).



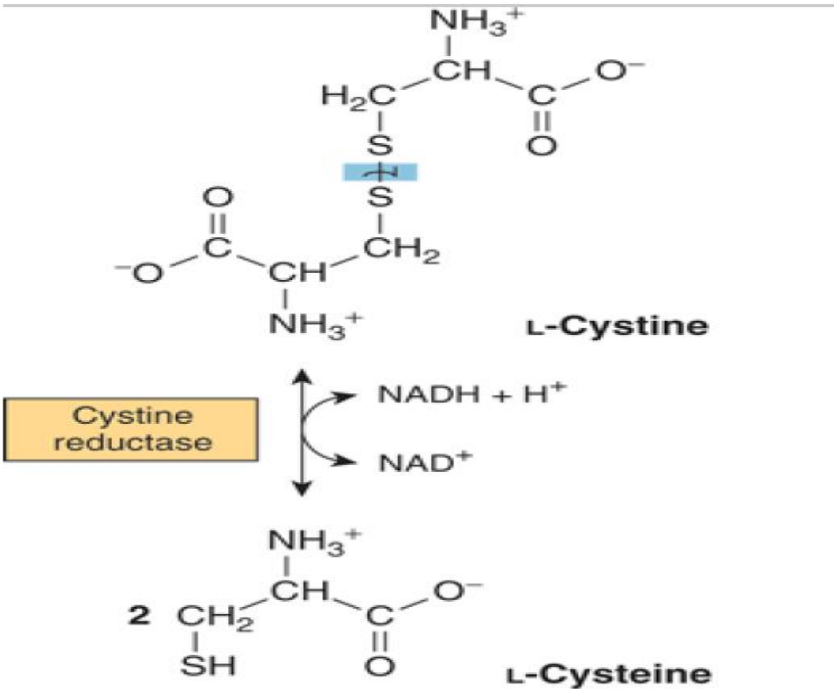
Interconversion of serine and glycine by serine hydroxymethyltransferase (H_4 folate, tetrahydrofolate).

Alanine

Transamination of -alanine forms pyruvate. Probably on account of its central role in metabolism there is no known metabolic defect of -alanine catabolism.

Cysteine

Cystine is first reduced to cysteine by **cystine reductase** (Figure 29–8). Two different pathways then convert cysteine to pyruvate (Figure 29–9). There are numerous abnormalities of cysteine metabolism. Cystine, lysine, arginine, and ornithine are excreted in **cystine-lysinuria (cystinuria),** a defect in renal reabsorption of these amino acids. Apart from cystine calculi, cystinuria is benign. The mixed disulfide of L -cysteine and L -homocysteine excreted by cystinuric patients is more soluble than cystine and reduces formation of cysteine calculi.



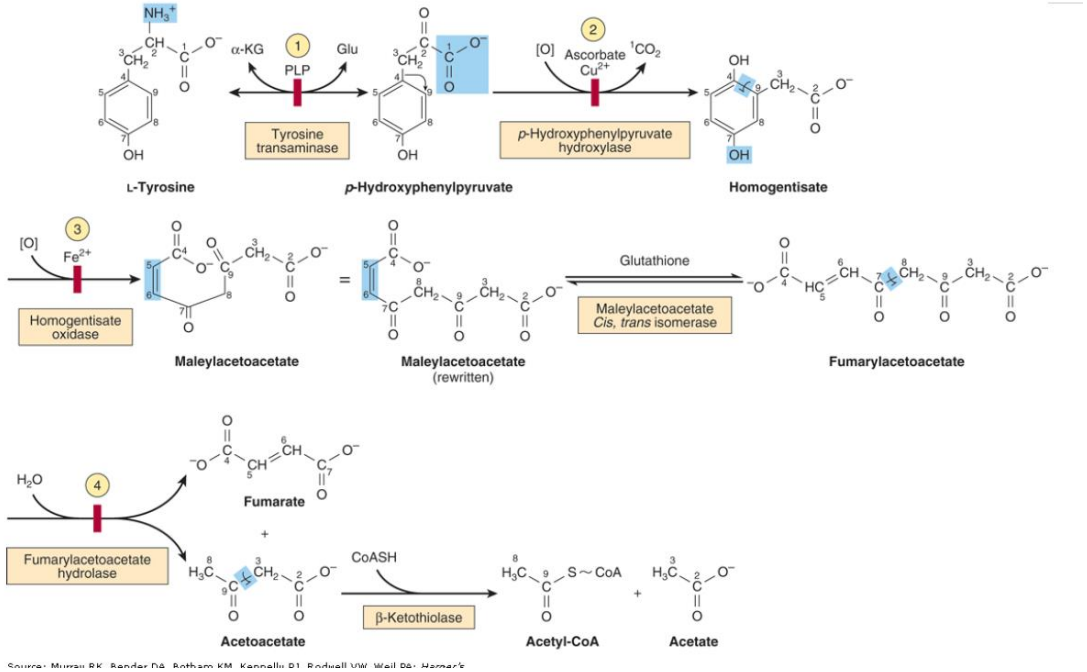
Threonine

Threonine aldolase cleaves threonine to acetaldehyde and glycine. Oxidation of acetaldehyde to acetate is followed by formation of acetyl-CoA .

ADDITIONAL AMINO ACIDS THAT FORM ACETYL-COA

Tyrosine

The diagrams show the conversion of tyrosine to amphibolic intermediates. Since ascorbate is the reductant for conversion of *p* -hydroxyphenylpyruvate to homogentisate, scorbutic patients excrete incompletely oxidized products of tyrosine catabolism. Subsequent reactions form maleylacetoacetate, fumarylacetoacetate, fumarate, acetoacetate, and ultimately acetyl-CoA.



Intermediates in tyrosine catabolism. Carbons are numbered to emphasize their ultimate fate. (-KG, -ketoglutarate; Glu, glutamate; PLP, pyridoxal phosphate.) Circled numerals represent the probable sites of the metabolic defects in type II tyrosinemia; neonatal tyrosinemia; alkaptonuria; and type I tyrosinemia, or tyrosinosis.

The probable metabolic defect in **type I tyrosinemia (tyrosinosis)** is at **fumarylacetoacetate hydrolase** (Figure 29–13). Therapy employs a diet low in tyrosine and phenylalanine. Untreated acute and chronic tyrosinosis leads to death from liver failure. Alternate metabolites of tyrosine are also excreted in **type II tyrosinemia (Richner-Hanhart syndrome),** a defect in **tyrosine aminotransferase** (reaction 1, Figure 29–13), and in **neonatal tyrosinemia,** due to lowered *p* -hydroxyphenylpyruvate hydroxylase activity (reaction 2, Figure 29–13). Therapy employs a diet low in protein.

Alkaptonuria was first recognized and described in the 16th century. Characterized in 1859, it provided the basis for Garrod's classic ideas concerning heritable metabolic disorders. The defect is lack of **homogentisate oxidase**

(reaction 3, Figure 29–13). The urine darkens on exposure to air due to oxidation of excreted homogentisate. 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.

Phenylalanine

Phenylalanine is first converted to tyrosine (see Figure 27–10). Subsequent reactions are those of tyrosine (Figure

29–13). **Hyperphenylalaninemias** arise from defects in phenylalanine hydroxylase itself (**type I, classic phenylketonuria** or **PKU,** frequency 1 in 10,000 births), in dihydrobiopterin reductase **(types II and III),** or in dihydrobiopterin biosynthesis **(types IV and V)** (see Figure 27–10). Alternative catabolites are excreted (Figure 29–14). A diet low in phenylalanine can prevent the mental retardation of PKU.

DNA probes facilitate prenatal diagnosis of defects in phenylalanine hydroxylase or dihydrobiopterin reductase. Elevated blood phenylalanine may not be detectable until 3–4 days postpartum. False-positives in premature infants may reflect delayed maturation of enzymes of phenylalanine catabolism. An older and less reliable screening test employs $FeCl_3$ to detect urinary phenylpyruvate. $FeCl_3$ screening for PKU of the urine of newborn infants is compulsory in many countries, but in the United States has been largely supplanted by tandem mass

spectrometry.

Lysine

The first six reactions of L-lysine catabolism in human liver form crotonyl-CoA, which is then degraded to acetyl- CoA and CO_2 by the reactions of fatty acid catabolism (see Figure 22–3). In what follows, circled numerals refer to the corresponding numbered reactions of Figure 29–15. Reactions 1 and 2 convert the Schiff base formed between -ketoglutarate and the -amino group of lysine to L - - aminoadipate- -semialdehde. Both reactions are catalyzed by a single bifunctional enzyme, aminoadipate semialdehde synthase (also called lysine 2-oxoglutarate reductasesaccharopine dehydrogenase). Reduction of L - -aminoadipate- -semialdehde to L - -aminoadipate (reaction 3) is followed by transamination to - ketoadipate (reaction 4). Conversion to the thioester glutaryl-CoA (reaction 5) is followed by the decarboxylation of glutaryl-CoA to crotonyl-CoA (reaction 6). The subsequent reactions are those of the catabolism of -unsaturated fatty acids with an odd number of carbons. Reactions and intermediates in the catabolism of L-lysine. (-KG, -ketoglutarate; Glu, L -glutamate.) Shown on the left are the reactions, and on the right the structures, of the intermediates. The numbered reactions and the metabolic defects associated with lysine catabolism are discussed in the accompanying text.

Metabolic defects associated with reactions of the lysine catabolic pathway include hyperlysinemias. Hyperlysinemia can result from a defect in activity 1 or 2 of the bifunctional enzyme aminoadipate semialdehde synthase.

Hyperlysinemia is accompanied by elevated levels of blood saccharopine only if the defect involves activity 2. A metabolic defect at reaction 6 results in an inherited metabolic disease that is associated with striatal and cortical degeneration, and characterized by elevated concentrations of glutarate and its metabolites, glutaconate and 3-hydroxyglutarate. The challenge in management of these metabolic defects is to restrict dietary intake of L-lysine without accompanying malnutrition.

Tryptophan

Tryptophan is degraded to amphibolic intermediates via the kynurenine-anthranilate pathway (Figure 29–16) **Tryptophan oxygenase (tryptophan pyrrolase)** opens the indole ring, incorporates molecular oxygen, and forms *N* -formylkynurenine. Tryptophan oxygenase, an iron porphyrin metalloprotein that is inducible in liver by adrenal corticosteroids and by tryptophan, is feedback-inhibited by nicotinic acid derivatives, including NADPH.

Hydrolytic removal of the formyl group of *N* -formylkynurenine, catalyzed by **kynurenine formylase,** produces kynurenine. Since **kynureninase** requires pyridoxal phosphate, excretion of xanthurenate (Figure 29–17) in response to a tryptophan load is diagnostic of vitamin B6 deficiency. **Hartnup disease** reflects impaired intestinal and renal transport of tryptophan and other neutral amino acids. Indole derivatives of unabsorbed tryptophan formed by intestinal bacteria are excreted. The defect limits tryptophan availability for niacin biosynthesis and accounts for the pellagra-like signs and symptoms.

Formation of xanthurenate in vitamin B6 deficiency. Conversion of the tryptophan metabolite 3-hydroxykynurenine to 3-hydroxyanthranilate is impaired (see Figure 29–16). A large portion is therefore converted to xanthurenate.

Methionine

Methionine reacts with ATP forming *S* -adenosylmethionine, "active methionine" (Figure 29–18). Subsequent reactions form propionyl-CoA (Figure 29–19) and ultimately succinyl-CoA (see Figure 20–2).

Figure 29–18.

Formation of *S* -adenosylmethionine. CH_3 represents the high group transfer potential of "active methionine."

Figure 29–19.

Conversion of methionine to propionyl-CoA.