AMINO ACID OXIDATION

Proteins are polymers of amino acids, joined by peptide bond. All 20 of the common amino acids are α-amino acids. They have a carboxyl group and an amino group bonded to the same carbon atom (the α- carbon). They differ from each other in their side chains, or **R groups,** which vary in structure, size, and electric charge, and which influence solubility of amino acids in water. The fraction of metabolic energy obtained from amino acids, whether they are derived from dietary protein or from tissue protein, varies greatly with the type of organism and with metabolic conditions. Thus carnivores can obtain (immediately following a meal) up to 90% of their energy requirements from amino acid oxidation, whereas herbivores may fill only a small fraction of their energy needs by this route. Plants, however, rarely if ever oxidize amino acids to provide energy; the carbohydrate produced from CO_2 and H_2O in photosynthesis is generally their sole energy source. Amino acid concentrations in plant tissues are carefully regulated to just meet the requirements for biosynthesis of proteins, nucleic acids, and other molecules needed to support growth.

Protein turnover is the balance between protein synthesis and protein degradation. More synthesis than breakdown indicates an anabolic state that builds lean tissues, more breakdown than synthesis indicates a catabolic state that burns lean tissues.

Protein turnover is believed to decrease with age in all senescence organisms including humans. This results in an increase in the amount of damaged protein within the body. The damaged

protein results in a slower protein turnover which then results in more damaged protein causing an exponential increase in damage to all protein within the body and to aging.

Amino acids pool is the amount of free amino acids distributed throughout the body, it tend to increase in fed state and decrease in the post absorptive state.

Sources of Amino acid pool

1. Dietary proteins
2. Breakdown of tissue proteins.
3. Biosynthesis of nonessential amino acids

Fate of Amino Acid pool

1. Biosynthesis of structural proteins e.g Tissue proteins
2. Biosynthesis of functional proteins e.g Haemoglobin, myoglobin, protein hormones and enzymes
3. Biosynthesis of small peptides of biological importance e.g glutathione, endorphins and enkephalins.
4. Biosynthesis of non protein nitrogenous compounds (NPN) as urea, uric acid, creatine, creatinine and ammonia.
5. Catabolism of amino acids to give ammonia and α-keto acids.

In animals, amino acids undergo oxidative degradation in three different metabolic circumstances:

1. During normal synthesis and degradation of cellular proteins, some amino acids that are released from protein breakdown and are not needed for new protein synthesis undergo oxidative degradation.

2. When diet is rich in protein and the ingested amino acids exceed the body's needs for protein synthesis, the surplus is catabolized; amino acids cannot be stored.

3. During starvation or in uncontrolled diabetes mellitus, when carbohydrates are either unavailable or not properly utilized, cellular proteins are used as fuel.

In these metabolic conditions, amino acids lose their amino groups to form α-keto acids, the "carbon skeletons" of amino acids. The α-keto acids undergo oxidation to CO_2 and H_2O or, often more importantly, provide three- and four-carbon units that can be converted by gluconeogenesis into glucose, the fuel for brain, skeletal muscle, and other tissues.

One important feature distinguishes amino acid degradation from other catabolic processes described to this point: every amino acid contains an amino group, and the pathways for amino acid degradation therefore include a key step in which the α-amino group is separated from the carbon skeleton and shunted into the pathways of amino group metabolism such as urea cycle.

Metabolic Fates of Amino Groups

Most amino acids are metabolized in the liver. Some of the ammonia generated in this process is recycled and used in a variety of biosynthetic pathways; the excess is either excreted directly or converted to urea or uric acid for excretion, depending on the organism. Excess ammonia generated in other (extrahepatic) tissues is transported to the liver in the form of amino groups, for conversion to the excretory form.

In the cytosol of hepatocytes, amino groups from most amino acids are transferred to α-ketoglutarate to form glutamate, which enters mitochondria and gives up its amino group to form NH_4^+. Excess ammonia generated in most other tissues is converted to the amide nitrogen of glutamine, which is transported into the cytosol and subsequently to liver mitochondria.

Glutamine, glutamate or both are present in higher concentrations than other amino acids in most tissues due to their role in scavenging amino groups from all other amino acids. In skeletal muscle, excess amino groups are generally transferred to pyruvate to form alanine, another important molecule in the transport of amino groups to the liver.

Overview of Amino Acid Catabolism

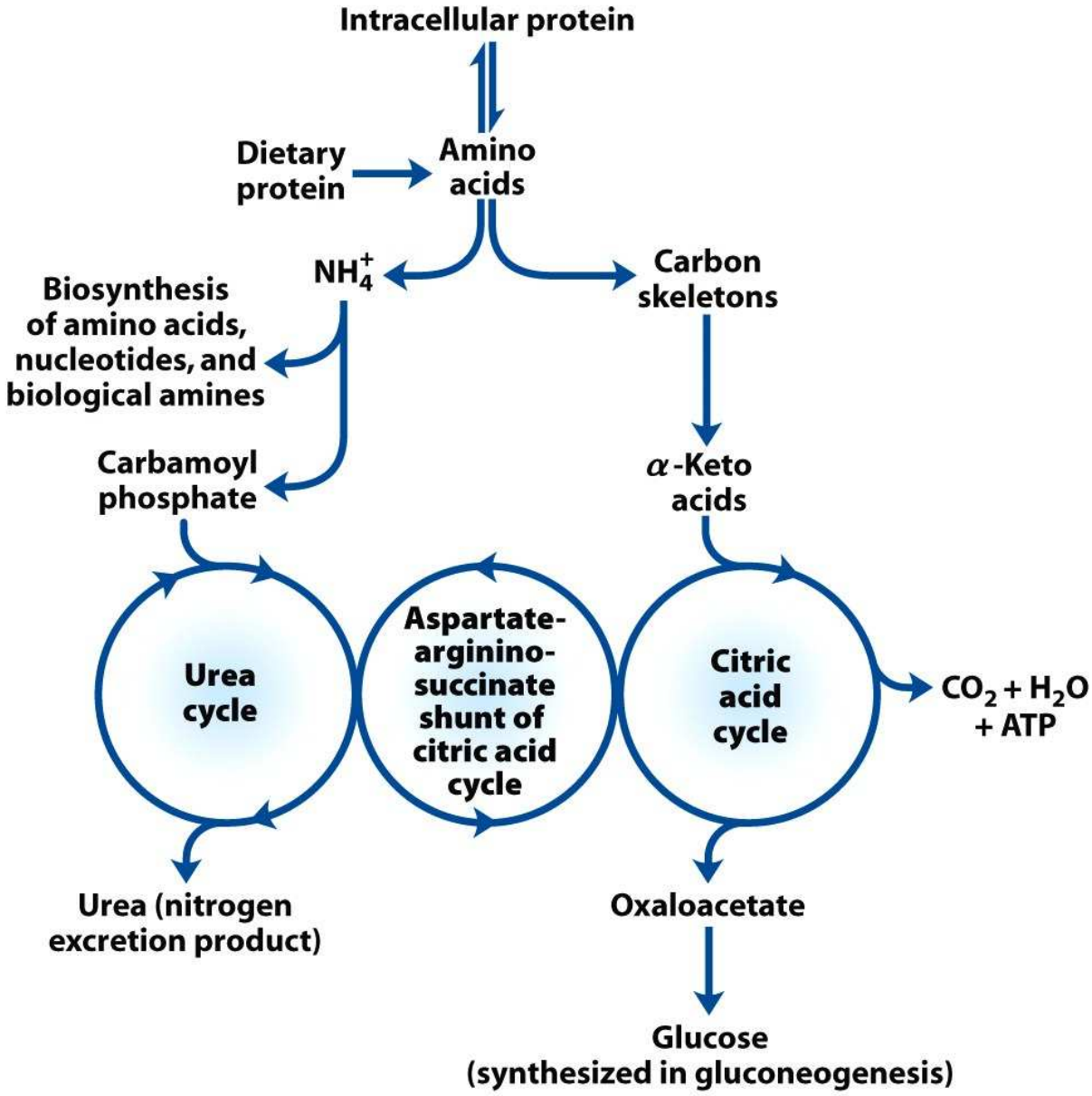

Figure 18-1
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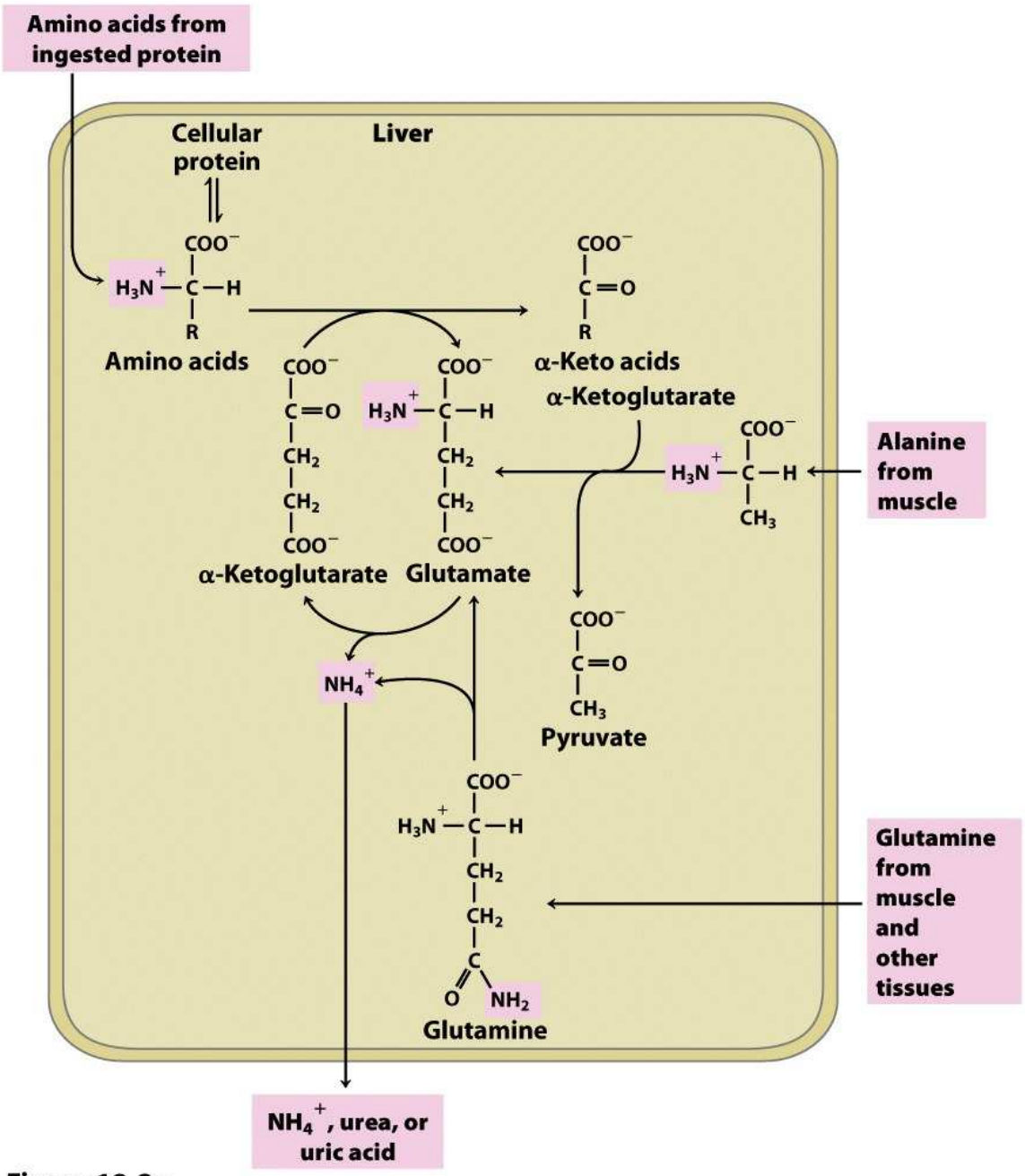

Figure 18-2a
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Schematic Diagram of Metabolic Fates of Amino Groups

Enzymatic Degradation of Dietary Protein to Amino Acids

Entry of dietary protein into the stomach stimulates the gastric mucosa to secrete the hormone **gastrin,** which in turn stimulates secretion of hydrochloric acid by the parietal cells and pepsinogen by the chief cells of the gastric glands. The acidic gastric juice (pH 1.0 to 2.5) is both an antiseptic, killing most bacteria and other foreign cells, and a denaturing agent, unfolding globular proteins and rendering their internal peptide bonds more accessible to enzymatic hydrolysis. **Pepsinogen**, an inactive precursor, or zymogen, is converted to active pepsin by the enzymatic action of pepsin itself. In the stomach, pepsin hydrolyzes ingested proteins at peptide bonds on the amino-terminal side of the aromatic amino acid residues Phe, Trp, and Tyr , cleaving long polypeptide chains into a mixture of smaller peptides.

As the acidic stomach contents pass into the small intestine, the low pH triggers secretion of the hormone **secretin** into blood. Secretin stimulates the pancreas to secrete bicarbonate into the small intestine to neutralize the gastric HCl, abruptly increasing the pH to about 7. (All pancreatic secretions pass into the small intestine through the pancreatic duct.). Digestion of proteins now continues in the small intestine. Arrival of amino acids in the upper part of the intestine (duodenum) causes release into the blood of the hormone **cholecystokinin,** which stimulates secretion of several pancreatic enzymes with optimal activity at pH 7 to 8.

Trypsinogen, chymotrypsinogen, and **procarboxypeptidases A** and **B,** the zymogens of **trypsin, chymotrypsin,** and **carboxypeptidases A** and **B,** are synthesized and secreted by the exocrine cells of the pancreas. Trypsinogen is converted to its active form, trypsin, by **enteropeptidase,** a proteolytic enzyme secreted by intestinal cells. Free trypsin then catalyzes conversion of additional trypsinogen to trypsin. Trypsin also activates chymotrypsinogen, the procarboxypeptidases, and proelastase.

Why this elaborate mechanism for getting active digestive enzymes into the gastrointestinal tract?

Synthesis of enzymes as inactive precursors protects the exocrine cells from destructive proteolytic attack. The pancreas further protects itself against self-digestion by making a specific inhibitor, a protein called **pancreatic trypsin inhibitor**, that effectively prevents premature production of active proteolytic enzymes within the pancreatic cells.

Trypsin and chymotrypsin further hydrolyze the peptides that were produced by pepsin in the stomach. This stage of protein digestion is accomplished efficiently, because pepsin, trypsin, and chymotrypsin have different amino acid specificities. Degradation of the short peptides in the small intestine is then completed by other intestinal peptidases. These include carboxypeptidases A and B (both of which are zinc-containing enzymes), which remove successive carboxyl-terminal residues from peptides, and an **aminopeptidase** that hydrolyzes successive amino-terminal residues from short peptides. The resulting mixture of free amino acids is transported into the epithelial cells lining the small intestine, through which the amino acids enter blood capillaries in the villi and are transported to the liver.

Clinical Case

Acute pancreatitis is a disease caused by obstruction of the normal pathway by which pancreatic secretions enter the intestine. The zymogens of the proteolytic enzymes are converted to their catalytically active forms prematurely inside the pancreatic cells, and attack pancreatic tissue. This causes excruciating pain and damage to the organ that can prove fatal.

Pyridoxal Phosphate as a coenzyme/prosthetic group in the Transfer of α-Amino Groups to α-Ketoglutarate.

The first step in catabolism of most L-amino acids, once they have reached the liver, is removal of the α-amino groups, promoted by **aminotransferases** or **transaminases.** In these **transamination** reactions, the α-amino group is transferred to the α-carbon atom of α-ketoglutarate, leaving behind the corresponding α-keto acid analog of the amino acid. There is no net deamination (loss of amino groups) in these reactions, because the α-ketoglutarate becomes aminated as the α-amino acid is deaminated. The glutamate then functions as an amino group donor for biosynthetic pathways or for excretion pathways that lead to the elimination of nitrogenous waste products.

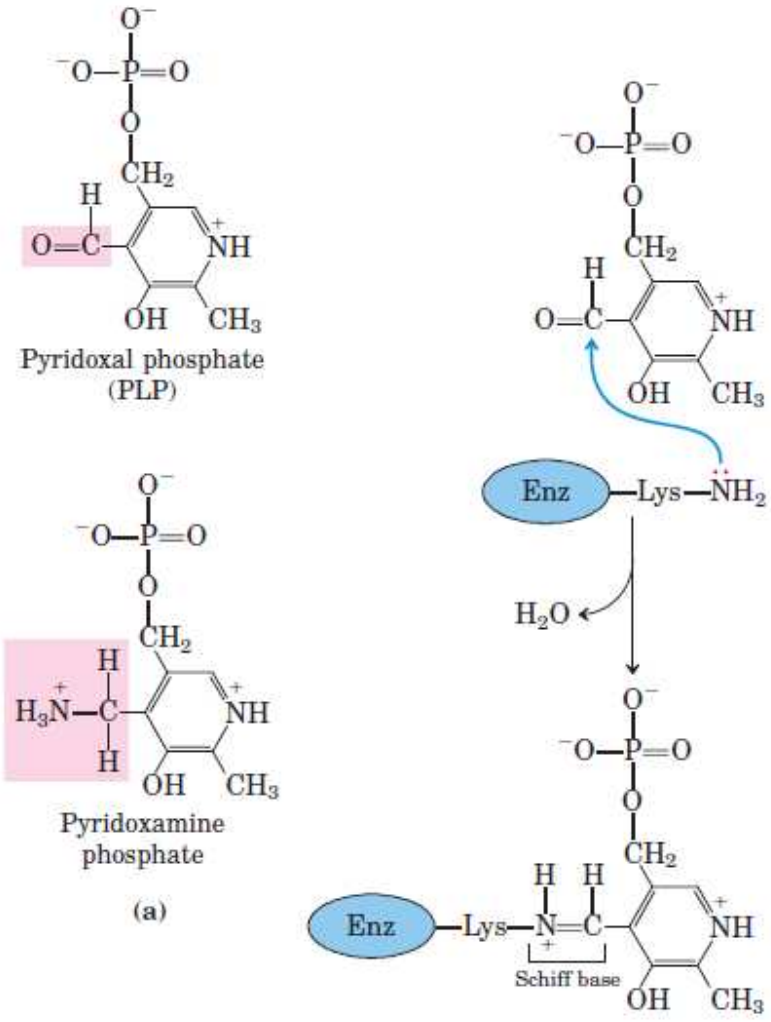
Cells contain different types of aminotransferases. Many are specific for α-ketoglutarate as the amino group acceptor but differ in their specificity for the L-amino acid. All aminotransferases have the same prosthetic group and the same reaction mechanism. The prosthetic group is **pyridoxal phosphate (PLP),** the coenzyme form of pyridoxine, or vitamin B6.

Pyridoxal phosphate functions as an intermediate carrier of amino groups at the active site of aminotransferases. It undergoes reversible transformations between its aldehyde form, pyridoxal phosphate, which accepts an amino group, and its aminated form, pyridoxamine phosphate, which donates its amino group to an α-keto acid. Pyridoxal phosphate is generally covalently bound to the enzyme's active site through an aldimine (Schiff base) linkage to the α-amino group of a Lys residue.

Aminotransferases are classic examples of enzymes catalyzing bimolecular Ping-Pong reactions, in which the first substrate reacts and the product must leave the active site before the second substrate can bind. Thus the incoming amino acid binds to the active site, donates its

amino group to pyridoxal phosphate, and departs in the form of an α-keto acid. The incoming α-keto acid then binds, accepts the amino group from pyridoxamine phosphate, and departs in the form of an amino acid.

Pyridoxal phosphate, the prosthetic group of aminotransferases.



Enzyme-catalyzed transaminations by amino-transferase

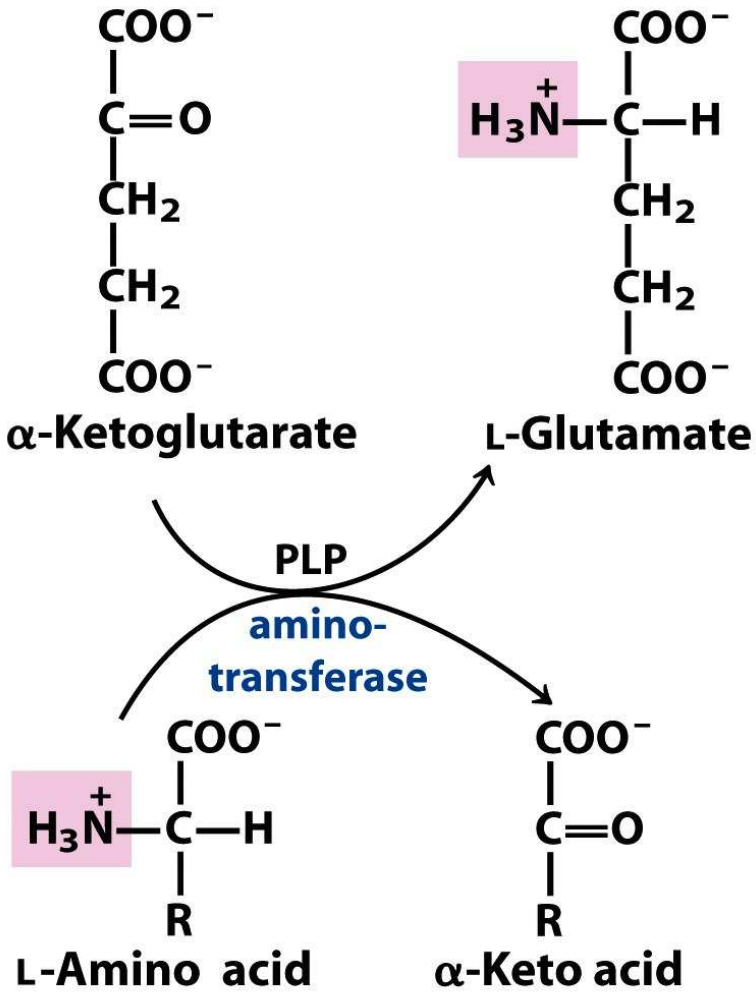


Figure 18-4
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Glutamate Releases Its Amino Group as Ammonia in the Liver

The amino groups from many of the α-amino acids are collected in the liver in the form of the amino group of L-glutamate molecules. These amino groups must then be removed from glutamate to prepare them for excretion. In hepatocytes, glutamate is transported from the cytosol into mitochondria, where it undergoes **oxidative deamination** catalyzed by **L-glutamate Dehydrogenase.** The combined action of an aminotransferase and glutamate dehydrogenase is referred to as **transdeamination.** The α-ketoglutarate formed from glutamate deamination can be used in the citric acid cycle and for glucose synthesis.

Glutamate dehydrogenase operates at an important intersection of carbon and nitrogen metabolism. An allosteric enzyme with six identical subunits, its activity is influenced by a complicated array of allosteric modulators. The best-studied of these are the positive modulator ADP and the negative modulator GTP. The metabolic rationale for this regulatory pattern has not been elucidated in detail. Mutations that alter the allosteric binding site for GTP or otherwise cause permanent activation of glutamate dehydrogenase lead to a human genetic disorder called hyperinsulinism-hyperammonemia syndrome, characterized by elevated levels of ammonia in the bloodstream and hypoglycemia.

Reaction catalyzed by glutamate dehydrogenase

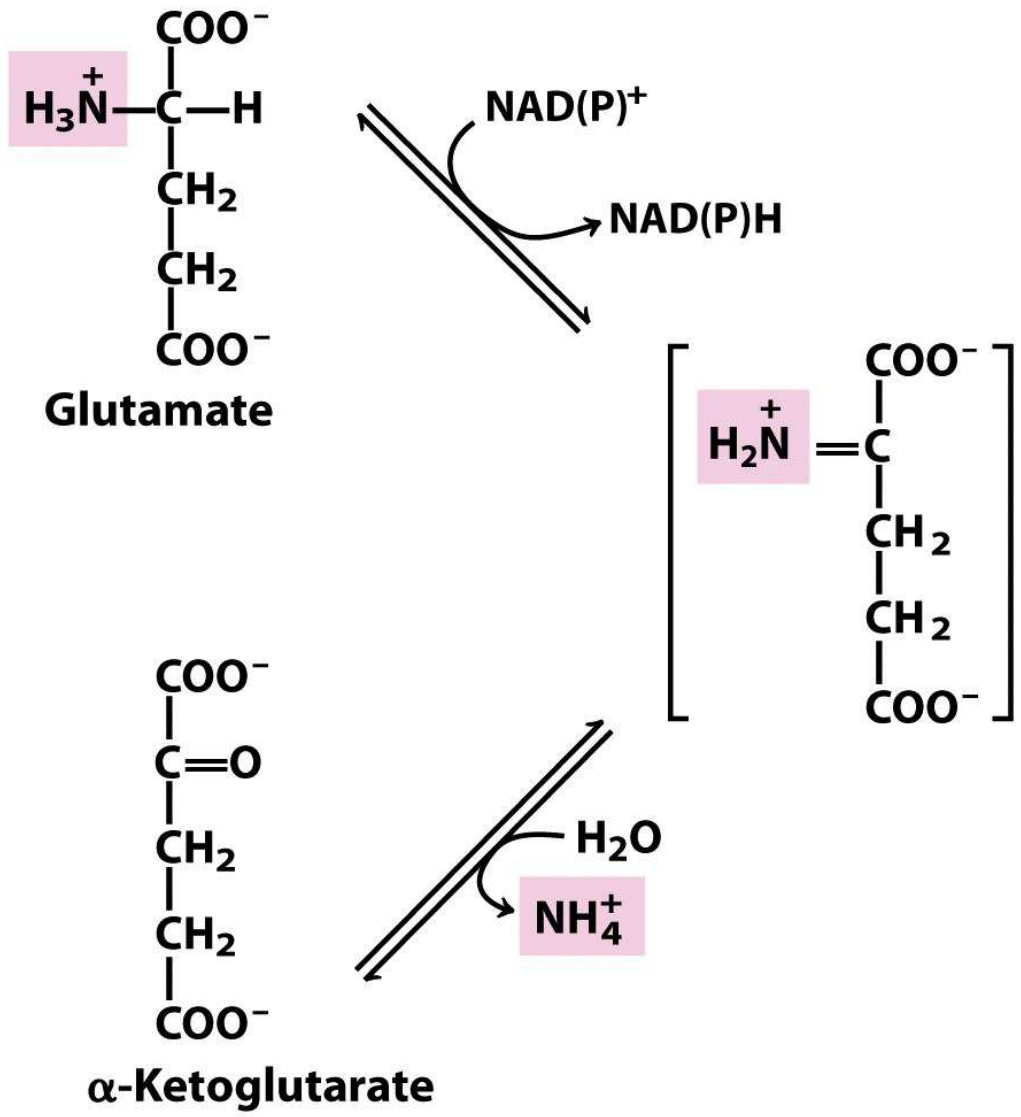

Figure 18-7
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Glutamine Transports Ammonia in the Bloodstream

Ammonia is toxic to animal tissues, and the levels present in blood must be regulated. In many tissues, including the brain, some processes such as nucleotide degradation generate free ammonia. The terminal stages of ammonia intoxication in humans are characterized by onset of a comatose state accompanied by cerebral edema (an increase in the brain's water content) and increased cranial pressure. Both Glutamate dehydrogenase and Glutamine synthetase enzymes are present at high levels in the brain, although the glutamine synthetase reaction is almost certainly the more important pathway for removal of ammonia.

In most animals much of the free ammonia is converted to a nontoxic compound before export from the extrahepatic tissues into the liver or kidneys. The free ammonia produced in tissues is combined with glutamate to yield glutamine by the action of **glutamine synthetase.** This reaction requires ATP and occurs in two steps. First, glutamate and ATP react to form ADP and a γ-glutamyl phosphate intermediate, which then reacts with ammonia to produce glutamine and inorganic phosphate.

In most terrestrial animals, glutamine in excess of that required for biosynthesis is transported in blood to intestine, liver, and kidneys for processing. In these tissues, the amide nitrogen is released as ammonium ion in the mitochondria, where the enzyme **glutaminase** converts glutamine to glutamate and NH_4^+ . The NH_4^+ from intestine and kidney is transported in blood to the live where ammonia from all sources is disposed of by urea synthesis. Some of the glutamate produced in the glutaminase reaction may be further processed in the liver by glutamate dehydrogenase, releasing more ammonia and producing carbon skeletons for metabolic fuel. However, most glutamate enters the transamination reactions required for amino acid biosynthesis and other processes.

Ammonia transport in the form of glutamine

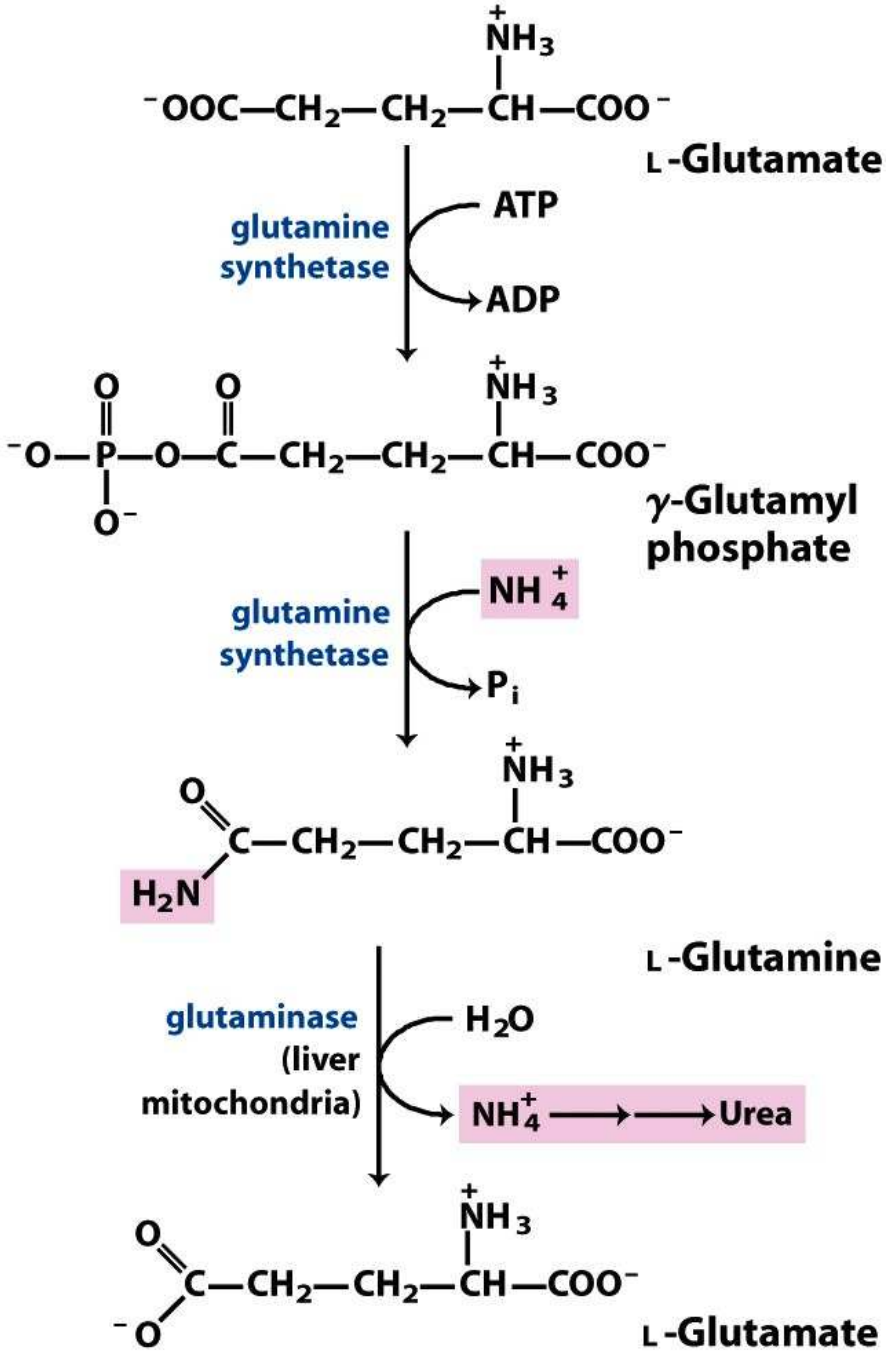

Figure 18-8
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Clinical use of SGPT and SGOT In Diagnoses of Tissue Damage

Analyses of certain enzyme activities in blood serum give valuable diagnostic information for a number of disease conditions. Alanine aminotransferase (ALT; also called glutamate-pyruvate transaminase, GPT) and aspartate aminotransferase (AST; also called glutamate oxaloacetate transaminase, GOT) are important in diagnosis of heart and liver damage caused by heart attack, drug toxicity, or infection. After a heart attack, a variety of enzymes, including aminotransferases, leak from the injured heart cells into the bloodstream. Measurements of the blood serum concentrations of the two aminotransferases by the SGPT and SGOT tests (S for serum)—and of another enzyme, **creatine kinase,** by the Serum Creatine Kinase test(SCK test) can provide information about severity of damage. Creatine kinase is the first heart enzyme to appear in the blood after a heart attack; it also disappears quickly from blood. GOT is the next to appear, and GPT follows later. Lactate dehydrogenase also leaks from injured or anaerobic heart muscle.

The SGOT and SGPT tests are also important in occupational medicine, to determine whether people exposed to carbon tetrachloride, chloroform, or other industrial solvents have suffered liver damage. Liver degeneration caused by these solvents is accompanied by leakage of various enzymes from injured hepatocytes into blood. Aminotransferases are most useful in monitoring people exposed to these chemicals, because these enzyme activities are high in liver and can be detected in very small amounts.

Alanine Transports Ammonia from Skeletal Muscles to the Liver

Alanine also plays a special role in transporting amino groups to the liver in a nontoxic form, via a pathway called the **glucose-alanine cycle**. In muscle and certain other tissues that degrade amino acids for fuel, amino groups are collected in the form of glutamate by transamination.

Glutamate can be converted to glutamine for transport to the liver, or it can transfer its α-amino group to pyruvate, a readily available product of muscle glycolysis, by action of **alanine aminotransferase**. The alanine so formed passes into blood and is transported to the liver. In the cytosol of hepatocytes, alanine aminotransferase transfers the amino group from alanine to α-ketoglutarate, forming pyruvate and glutamate. Glutamate can then enter mitochondria, where the glutamate dehydrogenase reaction releases NH_4^+, or can undergo transamination with oxaloacetate to form aspartate, another nitrogen donor in urea synthesis. Vigorously contracting skeletal muscles operate anaerobically, producing pyruvate and lactate from glycolysis as well as ammonia from protein breakdown. These products must find their way to the liver, where pyruvate and lactate are incorporated into glucose, which is returned to the muscles, and ammonia is converted to urea for excretion.

The glucose-alanine cycle, in concert with the Cori cycle, accomplishes this transaction. The energetic burden of gluconeogenesis is thus imposed on the liver rather than the muscle, and all available ATP in muscle is devoted to muscle contraction.

Glutamate can Donate Ammonia to Pyruvate to Make Alanine.

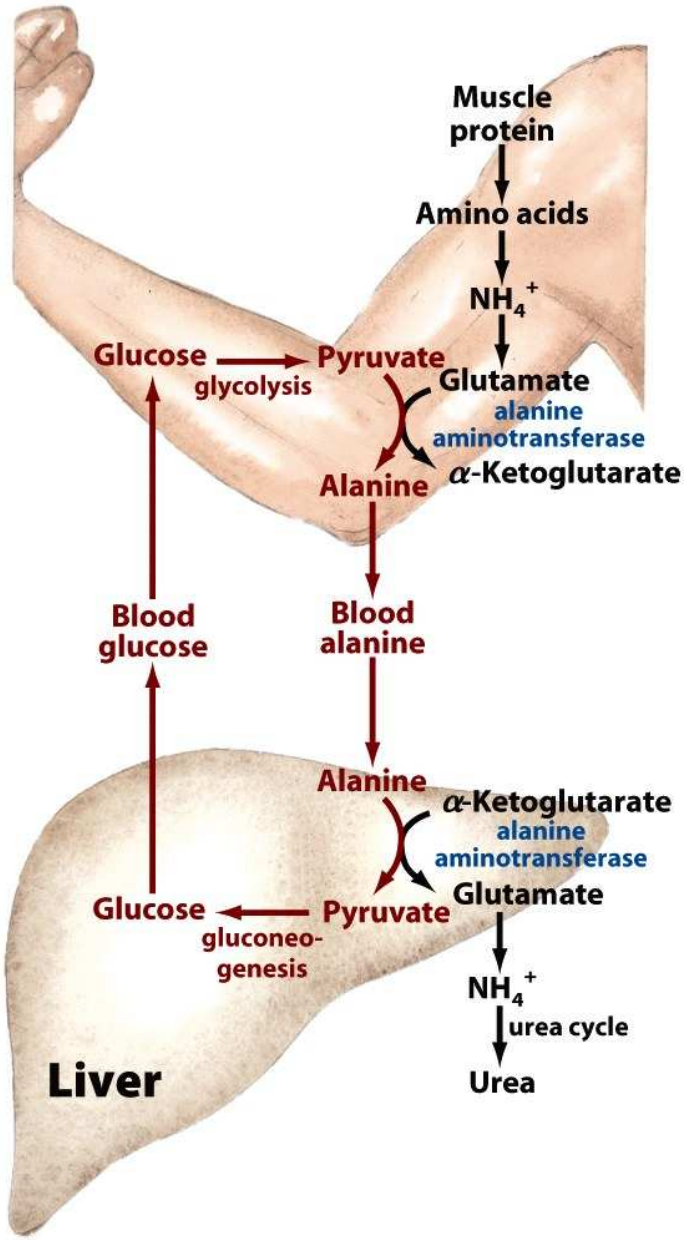

Figure 18-9
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Nitrogen Excretion and the Urea Cycle

If not reused for the synthesis of new amino acids or other nitrogenous products, amino groups are channeled into a single excretory end product. Most aquatic species, such as bony fishes, are **ammonotelic,** excreting amino nitrogen as ammonia. Toxic ammonia is simply diluted in the surrounding water. Terrestrial animals require pathways for nitrogen excretion that minimize toxicity and water loss. Most terrestrial animals are **ureotelic,** excreting amino nitrogen in form of urea; birds and reptiles are **uricotelic,** excreting amino nitrogen as uric acid. In ureotelic organisms, the ammonia deposited in the mitochondria of hepatocytes is converted to urea in the **urea cycle**

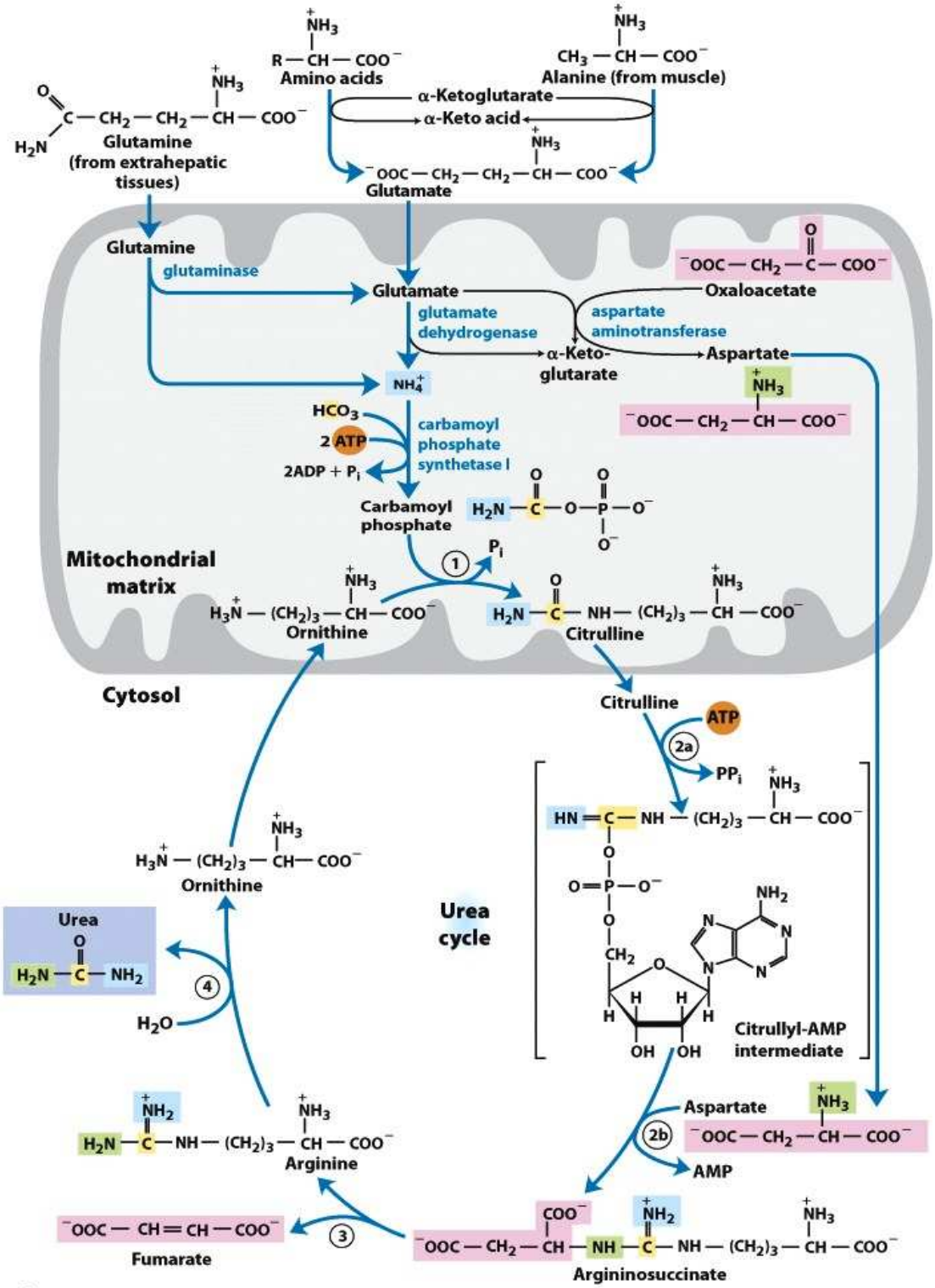

Figure 18-10

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Amino Acid Oxidation and the Production of Urea

The urea cycle begins inside liver mitochondria, but three of the subsequent steps take place in the cytosol; the cycle thus spans two cellular compartments. The first amino group to enter the urea cycle is derived from ammonia in the mitochondrial matrix—$NH4^+$ arising by the pathways described above. The liver also receives some ammonia via the portal vein from the intestine, from the bacterial oxidation of amino acids. Whatever its source, the $NH4^+$ generated in liver mitochondria is immediately used, together with CO_2 (as HCO_3^-) produced by mitochondrial respiration, to form carbamoyl phosphate in the matrix. This ATP-dependent reaction is catalyzed by **carbamoyl phosphate synthetase I,** a regulatory enzyme.

The carbamoyl phosphate, which functions as an activated carbamoyl group donor, now enters the urea cycle. The cycle has four enzymatic steps. First, carbamoyl phosphate donates its carbamoyl group to ornithine to form citrulline, with the release of Pi. Ornithine plays a role resembling that of oxaloacetate in the citric acid cycle, accepting material at each turn of the cycle. The reaction is catalyzed by **ornithine transcarbamoylase,** and the citrulline passes from the mitochondrion to the cytosol. The second amino group now enters from aspartate (generated in mitochondria by transamination and transported into the cytosol) by a condensation reaction between the amino group of aspartate and the ureido (carbonyl) group of citrulline, forming argininosuccinate. This cytosolic reaction, catalyzed by **argininosuccinate synthetase,** requires ATP and proceeds through a citrullyl-AMP intermediate. The argininosuccinate is then cleaved by **argininosuccinase** to form free arginine and fumarate, the latter entering mitochondria to join the pool of citric acid cycle intermediates. This is the only reversible step in the urea cycle. In the last reaction of the urea cycle, the cytosolic enzyme **arginase** cleaves arginine to yield **urea** and

ornithine. Ornithine is transported into the mitochondrion to initiate another round of the urea cycle.

Genetic Defects in the Urea Cycle Can Be Life-Threatening

People with genetic defects in any enzyme involved in urea formation cannot tolerate protein rich diets. Amino acids ingested in excess of the minimum daily requirements for protein synthesis are deaminated in the liver, producing free ammonia that cannot be converted to urea and exported into the bloodstream, yet ammonia is highly toxic. Absence of a urea cycle enzyme can result in hyperammonemia or in the build-up of one or more urea cycle intermediates, depending on the enzyme that is missing. Given that most urea cycle steps are irreversible, the absent enzyme activity can often be identified by determining which cycle intermediate is present in elevated concentration in blood and/or urine. Although the breakdown of amino acids can have serious health consequences in individuals with urea cycle deficiencies, a protein-free diet is not a treatment option. Humans are incapable of synthesizing half of the 20 common amino acids, and these **essential amino acids** must be provided in the diet. Careful administration of the aromatic acids benzoate or phenylbutyrate in diet can help lower the level of ammonia in the blood. Other therapies are more specific to a particular enzyme deficiency eg Carefull administration of carbamoyl glutamate, an analog of *N*-acetylglutamate is effective in activating carbamoyl phosphate synthetase I.

Nonessential	*Conditionally essential**	*Essential*
Alanine	Arginine	Histidine
Asparagine	Cysteine	Isoleucine
Aspartate	Glutamine	Leucine
Glutamate	Glycine	Lysine
Serine	Proline	Methionine
	Tyrosine	Phenylalanine
		Threonine
		Tryptophan
		Valine

Pathways of Amino Acid Degradation

The 20 catabolic pathways converge to form only six major products, all of which enter the citric acid cycle. The carbon skeletons of amino acids are diverted to gluconeogenesis or ketogenesis or are completely oxidized to CO_2 and H_2O.

All or part of the carbon skeletons of seven amino acids are ultimately broken down to acetyl-CoA. Five amino acids are converted to α-ketoglutarate, four to succinyl-CoA, two to fumarate, and two to oxaloacetate. Parts or all of six amino acids are converted to pyruvate, which can be converted to either acetyl-CoA or oxaloacetate.

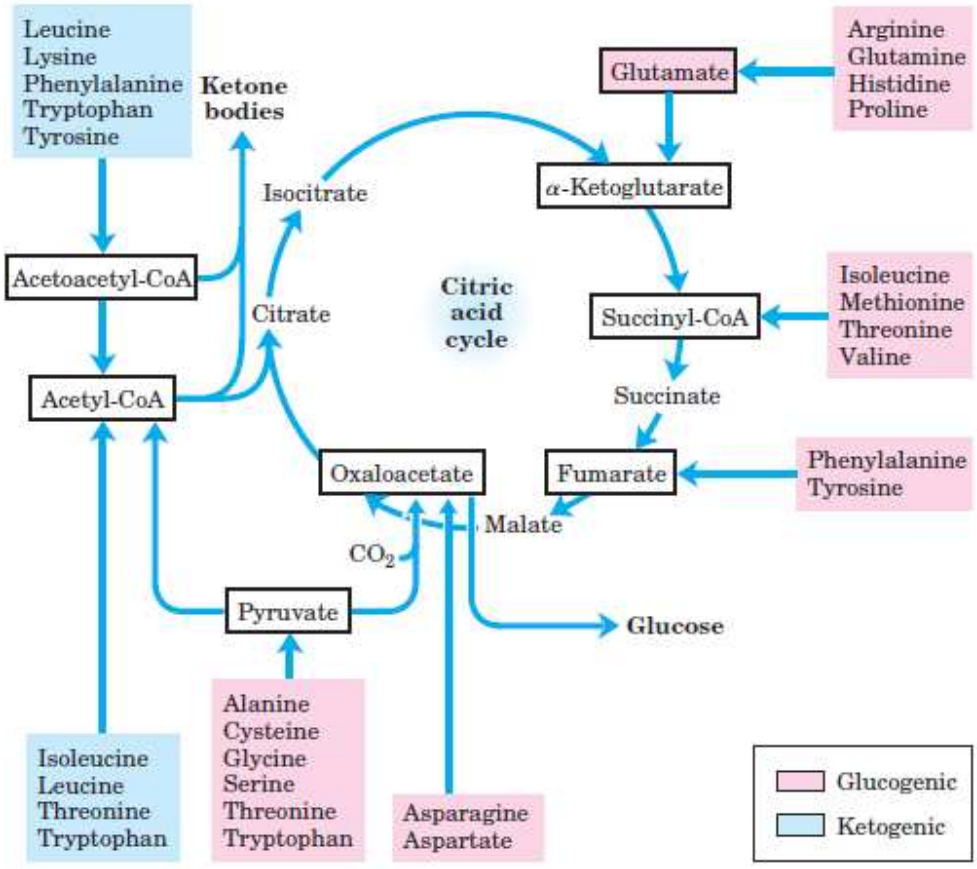
Some Amino Acids Are Converted to Glucose, Others to Ketone Bodies

The seven amino acids that are degraded entirely or in part to acetoacetyl-CoA and/or acetyl CoA—phenylalanine, tyrosine, isoleucine, leucine, tryptophan, threonine, and lysine—can yield ketone bodies in the liver, where acetoacetyl-CoA is converted to acetoacetate and then to acetone and β-hydroxybutyrate. These are the **ketogenic** amino acids.

Their ability to form ketone bodies is particularly evident in uncontrolled diabetes mellitus, in which the liver produces large amounts of ketone bodies from both fatty acids and the

ketogenic amino acids. The amino acids that are degraded to pyruvate, α-ketoglutarate, succinyl-CoA, fumarate, and/or oxaloacetate can be converted to glucose and glycogen, They are the **glucogenic** amino acids. Five amino acids—tryptophan, phenylalanine, tyrosine, threonine, and isoleucine—are both ketogenic and glucogenic. Only two amino acids, leucine and lysine, are exclusively ketogenic.

Summary of amino acid catabolism.



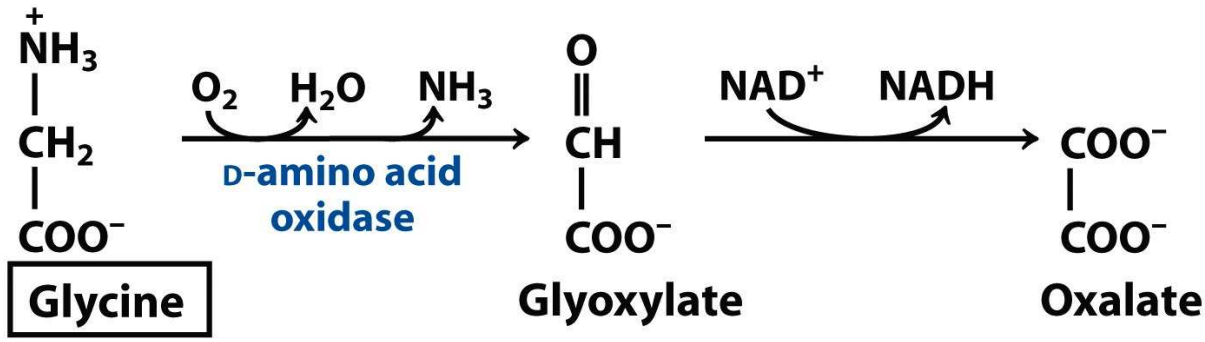
Six Amino Acids Are Degraded to Pyruvate

The carbon skeletons of six amino acids are converted in whole or in part to pyruvate. The pyruvate can then be converted to either acetyl-CoA (a ketone body precursor) or oxaloacetate (a precursor for gluconeogenesis). Thus amino acids catabolized to pyruvate are both ketogenic

and glucogenic. The six are alanine, tryptophan, cysteine, serine, glycine, and threonine. **Alanine** yields pyruvate directly on transamination wit α-ketoglutarate, and the side chain of **tryptophan** is cleaved to yield alanine and thus pyruvate. **Cysteine** is converted to pyruvate in two steps; one removes the sulfur atom, the other is a transamination. **Serine** is converted to pyruvate by serine dehydratase. Both the β-hydroxyl and the α-amino groups of serine are removed in this single pyridoxal phosphate–dependent reaction. **Glycine** is degraded via three pathways, only one of which leads to pyruvate. Glycine is converted to serine by enzymatic addition of a hydroxymethyl group. This reaction is catalyzed by **serine hydroxymethyl transferase.**

The second pathway, which predominates in animals, glycine undergoes oxidative cleavage to CO_2, NH_4^+ and a methylene group (-CH2-). This readily reversible reaction is catalyzed by **glycine cleavage enzyme.** Humans with serious defects in glycine cleavage enzyme activity suffer from a condition known as nonketotic hyperglycinemia. The condition is characterized by elevated serum levels of glycine, leading to severe mental deficiencies and death in very early childhood.

The third and final pathway of glycine degradation, the achiral glycine molecule is a substrate for the enzyme D-amino acid oxidase and glycine is converted to glyoxylate.



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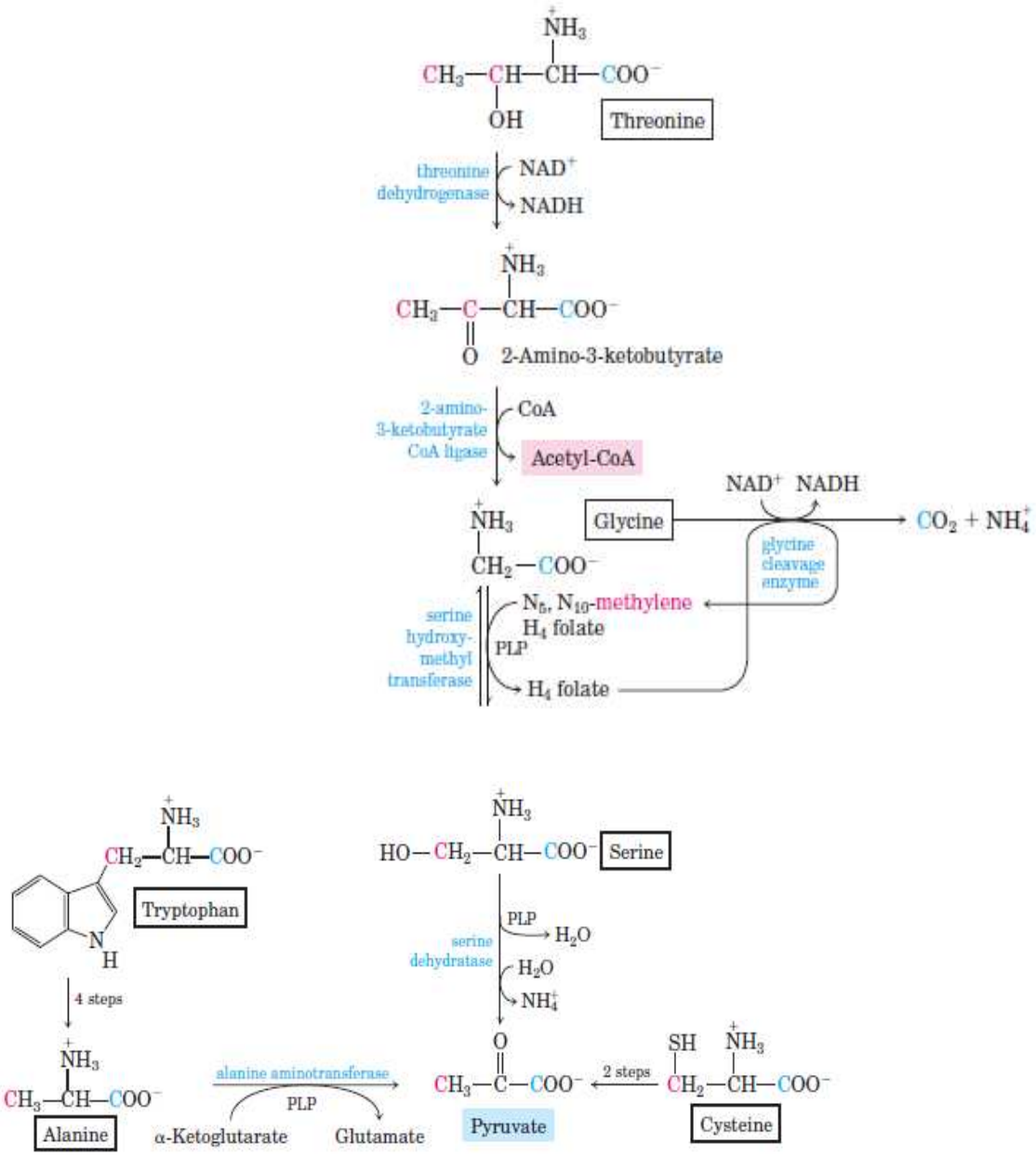
Threonine
threonine dehydrogenase
NAD+
NADH
2-Amino-3-ketobutyrate
2-amino-3-ketobutyrate CoA ligase
CoA
Acetyl-CoA
Glycine
NAD+ NADH
CO2 + NH4+
glycine cleavage enzyme
N5, N10-methylene H4 folate
PLP
H4 folate
serine hydroxy-methyl transferase
Tryptophan
4 steps
Alanine
alanine aminotransferase
PLP
α-Ketoglutarate
Glutamate
Serine
PLP
H2O
serine dehydratase
H2O
NH4+
Pyruvate
2 steps
Cysteine

Seven Amino Acids Are Degraded to Acetyl-CoA

Portions of the carbon skeletons of seven amino acids—**tryptophan, lysine, phenylalanine, tyrosine, leucine,isoleucine,** and **threonine**—yield acetyl-CoA and/or acetoacetyl-CoA, the latter being converted to acetyl-CoA. Some of the final steps in the degradative pathways for leucine, lysine, and tryptophan resemble steps in the oxidation of fatty acids. Threonine yields some acetyl-CoA. Some of the intermediates in tryptophan catabolism are precursors for the synthesis of other biomolecules, including nicotinate, a precursor of NAD and NADP in animals; serotonin, a neurotransmitter in vertebrates; and indoleacetate, a growth factor in plants.

The breakdown of phenylalanine is noteworthy because genetic defects in the enzymes of this pathway lead to several inheritable human diseases. Phenylalanine, after its hydroxylation to tyrosine, is also the precursor of dopamine, a neurotransmitter, and of norepinephrine and epinephrine, hormones secreted by the adrenal medulla. Melanin, the black pigment of skin and hair, is also derived from tyrosine.

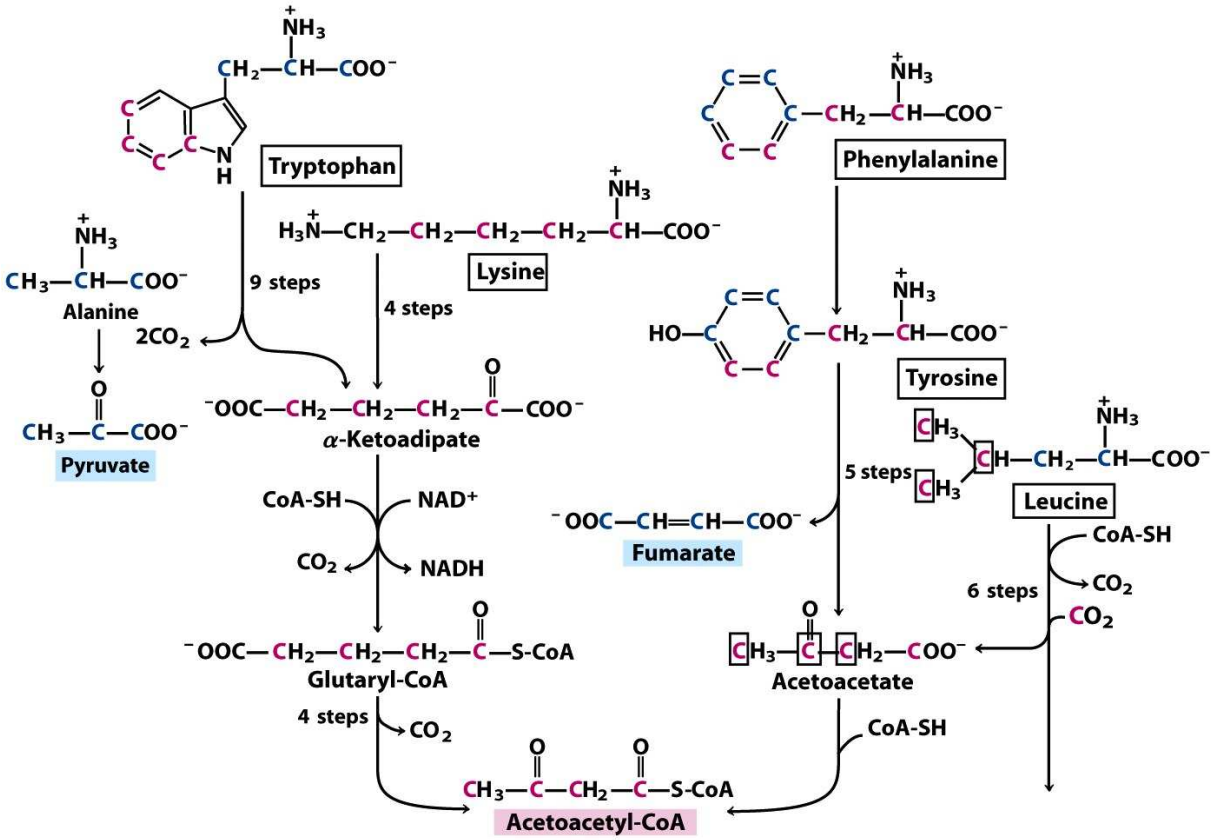

Figure 18-21 part 1
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Phenylalanine Catabolism Is Genetically Defective in Some People

Given that many amino acids are either neurotransmitters or precursors or antagonists of neutrotransmitters, genetic defects of amino acid metabolism can cause defective neural development and mental retardation. In most such diseases specific intermediates accumulate. For example, a genetic defect in **phenylalanine hydroxylase,** the first enzyme in the catabolic pathway for phenylalanine , is responsible for the disease **phenylketonuria (PKU),** the most common cause of elevated levels of phenylalanine (hyperphenylalaninemia).

Accumulation of phenylalanine or its metabolites in early life impairs normal development of the brain, causing severe mental retardation. This may be caused by excess phenylalanine competing with other amino acids for transport across the blood-brain barrier, resulting in a

deficit of required metabolites. When this condition is recognized early in infancy, mental retardation can largely be prevented by rigid dietary control. The diet must supply only enough phenylalanine and tyrosine to meet the needs for protein synthesis.

Catabolic pathways for phenylalanine and Tyrosine.

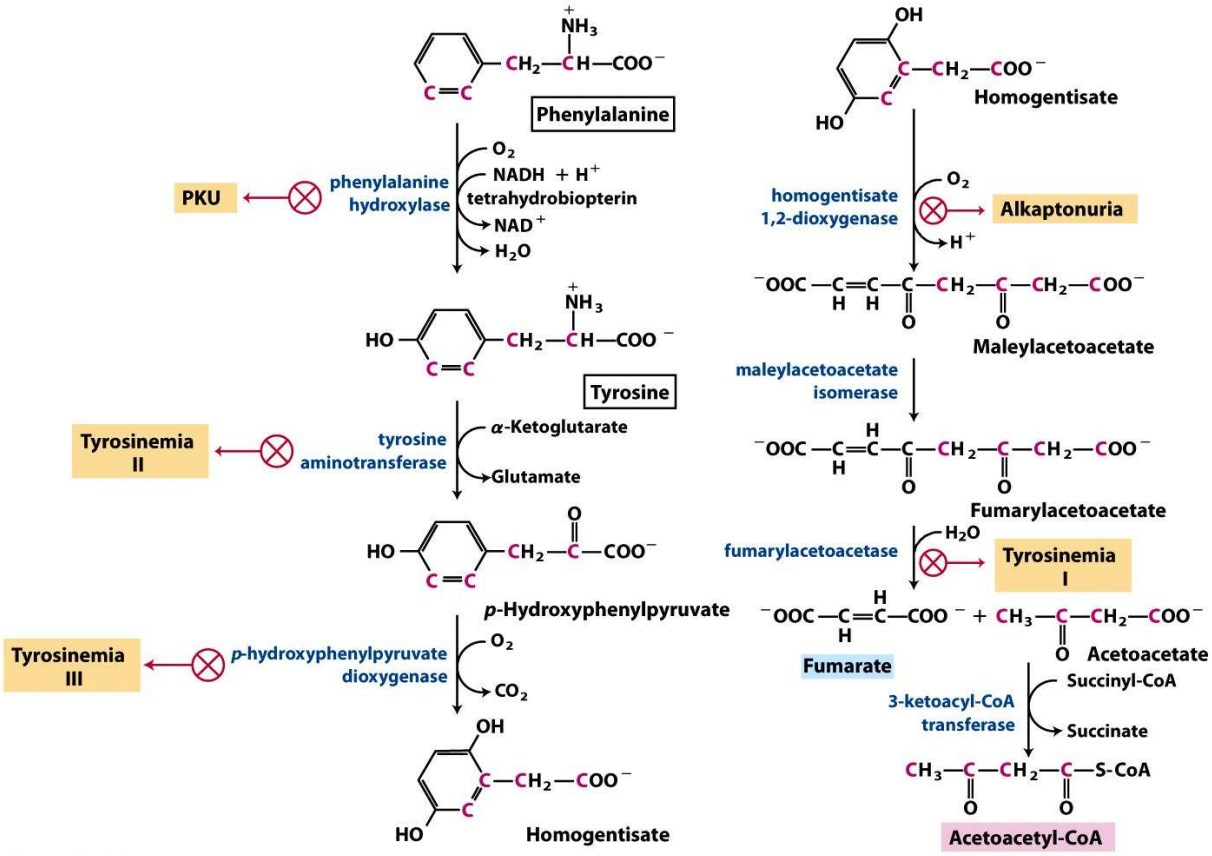

Figure 18-23
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Five Amino Acids Are Converted to α-Ketoglutarate

The carbon skeletons of five amino acids (proline, glutamate, glutamine, arginine, and histidine) enter the citric acid cycle as α-ketoglutarate.

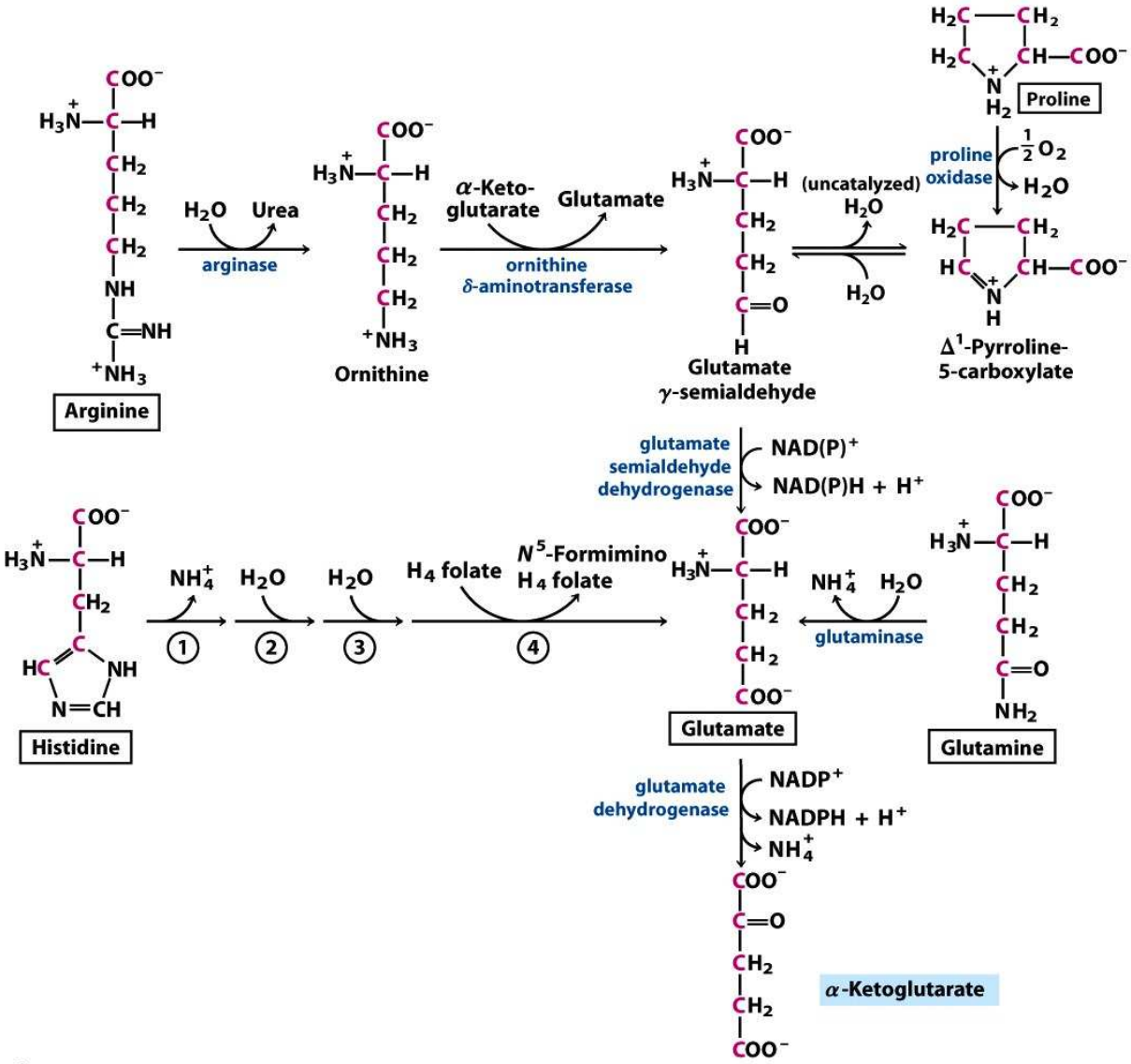

Figure 18-26
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Four Amino Acids Are Converted to Succinyl-CoA

Carbon skeletons of methionine, isoleucine, threonine, and valine are degraded by pathways that yield succinyl- CoA. **Methionine** donates its methyl group to one of several possible acceptors through *S*-adenosylmethionine, and three of its four remaining carbon atoms are converted to the propionate of propionyl-CoA, a precursor of succinyl-CoA. **Isoleucine** undergoes transamination, followed by oxidative decarboxylation of the resulting α-keto acid. The remaining five-carbon skeleton is further oxidized to acetyl-CoA and propionyl-CoA. **Valine** undergoes transamination and decarboxylation, then a series of oxidation reactions that convert the remaining four carbons to propionyl-CoA. Some parts of the valine and isoleucine degradative pathways closely parallel steps in fatty acid degradation. In human tissues, **threonine** is also converted in two steps to propionyl- CoA. This is the primary pathway for threonine degradation in humans for the alternative pathway). The mechanism of the first step is analogous to that catalyzed by serine dehydratase, and the serine and threonine dehydratases may actually be the same enzyme. The propionyl-CoA derived from these three amino acids is converted to succinyl-CoA.

Asparagine and Aspartate Are Degraded to Oxaloacetate.

The carbon skeletons of **asparagine** and **aspartate** ultimately enter the citric acid cycle as oxaloacetate. The enzyme **asparaginase** catalyzes the hydrolysis of asparagine to aspartate, which undergoes transamination with α-ketoglutarate to yield glutamate and oxaloacetate.

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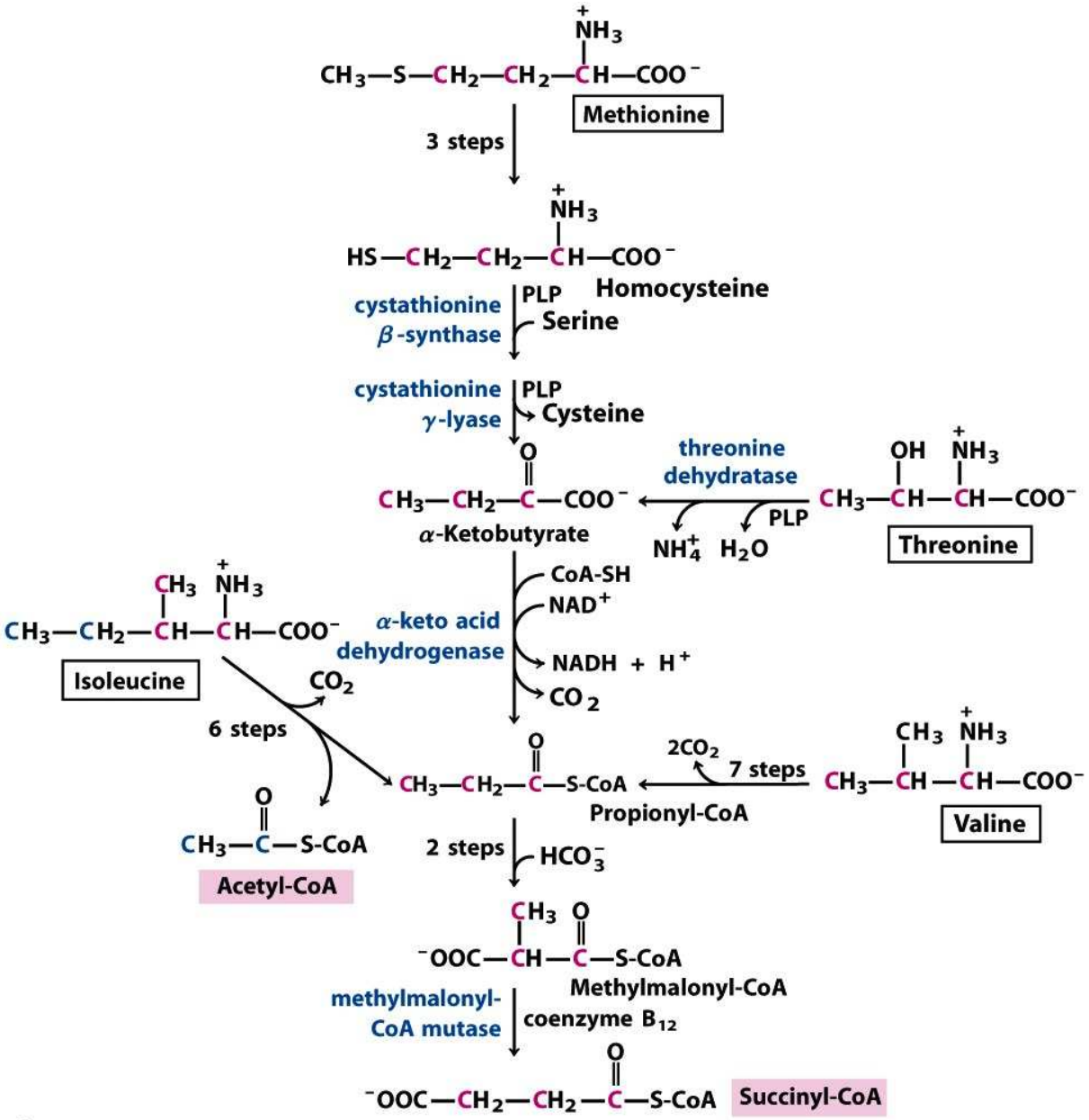

Figure 18-27
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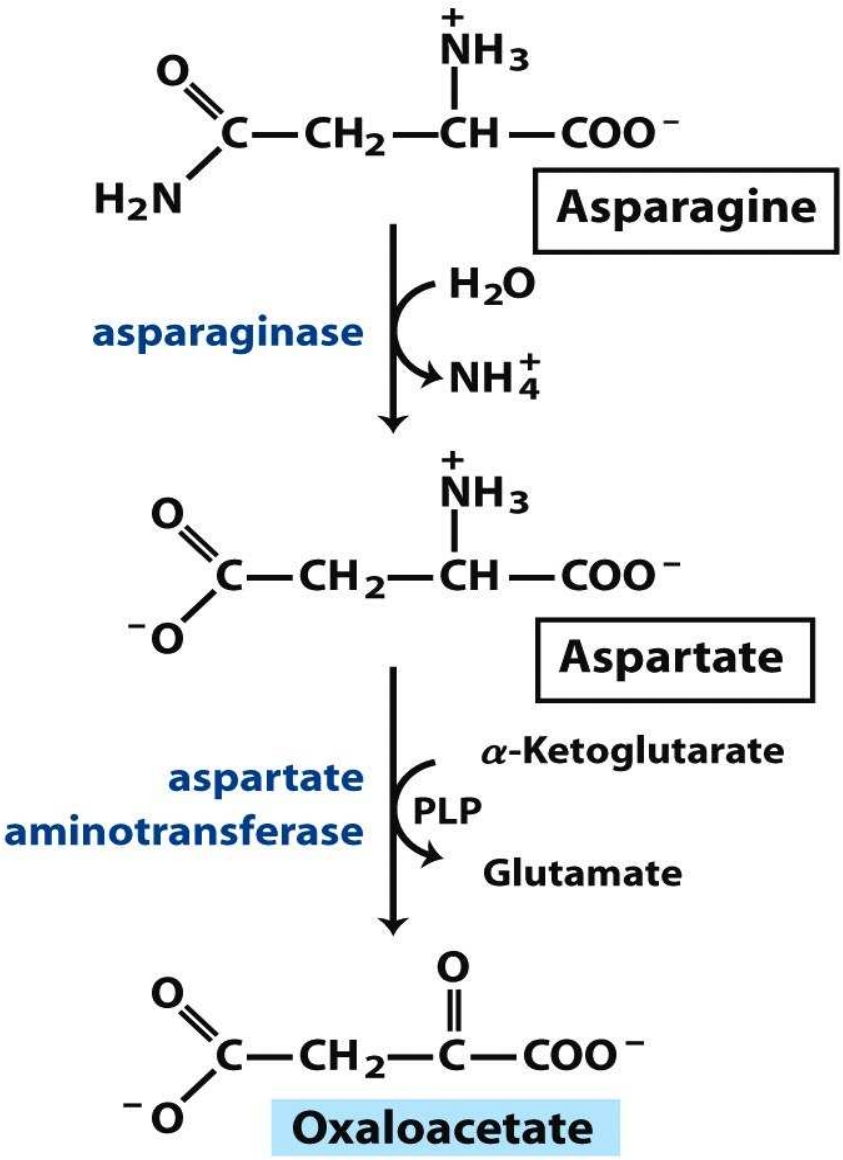

Figure 18-29
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Catabolic pathway for asparagine and aspartate.

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