NITROGEN METABOLISM

Amino Acids: Disposal of Nitrogen

I. Overview

Unlike fats and carbohydrates, amino acids are not stored by the body, i.e., no protein exists whose sole function is to maintain a supply of amino acids for future use. Therefore, amino acids must be obtained from the diet, synthesized de novo, or produced from normal protein degradation.

Any amino acids in excess of the biosynthetic needs of the cell are rapidly degraded.

The first phase of catabolism involves the removal of the α-amino groups (usually by transamination and subsequent oxidative deamination), forming ammonia and the corresponding α-keto acid—the “carbon skeletons” of amino acids.

- A portion of the free ammonia is excreted in the urine, but most is used in the synthesis of urea, which is quantitatively the most important route for disposing of nitrogen from the body.
- In the second phase of amino acid catabolism, described in Chapter 20, the carbon skeletons of the α-ketoacids are converted to common intermediates of energy producing, metabolic pathways.
- These compounds can be metabolized to CO_2 and water, glucose, fatty acids, or ketone bodies by the central pathways of metabolism.

II. Overall Nitrogen Metabolism

- Amino acid catabolism is part of the larger process of the metabolism of nitrogen-containing molecules.
- Nitrogen enters the body in a variety of compounds present in food, the most important being amino acids contained in dietary protein.
- Nitrogen leaves the body as urea, ammonia, and other products derived from amino acid metabolism.
- The role of body proteins in these transformations involves two important concepts: the amino acid pool and protein turnover.

A. Amino acid pool :

- Free amino acids are present throughout the body, for example, in cells, blood, and the extracellular fluids.
- For the purpose of this discussion, envision all these amino acids as if they belonged to a single entity, called the amino acid pool.
- This pool is supplied by three sources:

1) amino acids provided by the degradation of body proteins,

2) amino acids derived from dietary protein, and

3) synthesis of nonessential amino acids from simple intermediates of metabolism (Figure 19.2).

In healthy, well fed individuals, the input to the amino acid pool is balanced by the output, that is, the amount of amino acids contained in the pool is constant. The amino acid pool is said to be in a steady state.

- Conversely, the amino pool is depleted by three routes:

1) synthesis of body protein,

2) amino acids consumed as precursors of essential nitrogen-containing small molecules, and

3) conversion of amino acids to glucose, glycogen, fatty acids or CO_2 (Figure 19.2).

- Although the amino acid pool is small (comprised of about 90–100 g of amino acids) in comparison with the amount of protein in the body (about 12 kg in a 70-kg man), it is conceptually at the center of whole-body nitrogen metabolism.

B. Protein turnover

- Most proteins in the body are constantly being synthesized and then degraded, permitting the removal of abnormal or unneeded proteins.
- For many proteins, regulation of synthesis determines the concentration of protein in the cell, with protein degradation assuming a minor role.
- For other proteins, the rate of synthesis is constitutive, that is, relatively constant, and cellular levels of the protein are controlled by selective degradation.

2. Protein degradation:

- There are two major enzyme systems responsible for degrading damaged or unneeded proteins:
- the energy-dependent ubiquitin-proteasome mechanism, and
- the non-energy-dependent degradative enzymes (acid hydrolases) of the lysosomes.
- Proteasomes mainly degrade endogenous proteins, that is, proteins that were synthesized within the cell.
- Lysosomal enzymes degrade primarily extracellular proteins, such as plasma proteins that are taken into the cell by endocytosis, and cell-surface membrane proteins that are used in receptor-mediated endocytosis.

Digestion of Dietary Proteins :

Most of the nitrogen in the diet is consumed in the form of protein, typically amounting to 70–100 g/day in the American diet (see Figure 19.2).
Proteins are generally too large to be absorbed by the intestine. [Note: An example of an exception to this rule is that newborns can take up maternal antibodies in breast milk.]
They must, therefore, be hydrolyzed to yield their constituent amino acids, which can be absorbed.
Proteolytic enzymes responsible for degrading proteins are produced by three different organs: the stomach, the pancreas, and the small intestine (Figure 19.4).

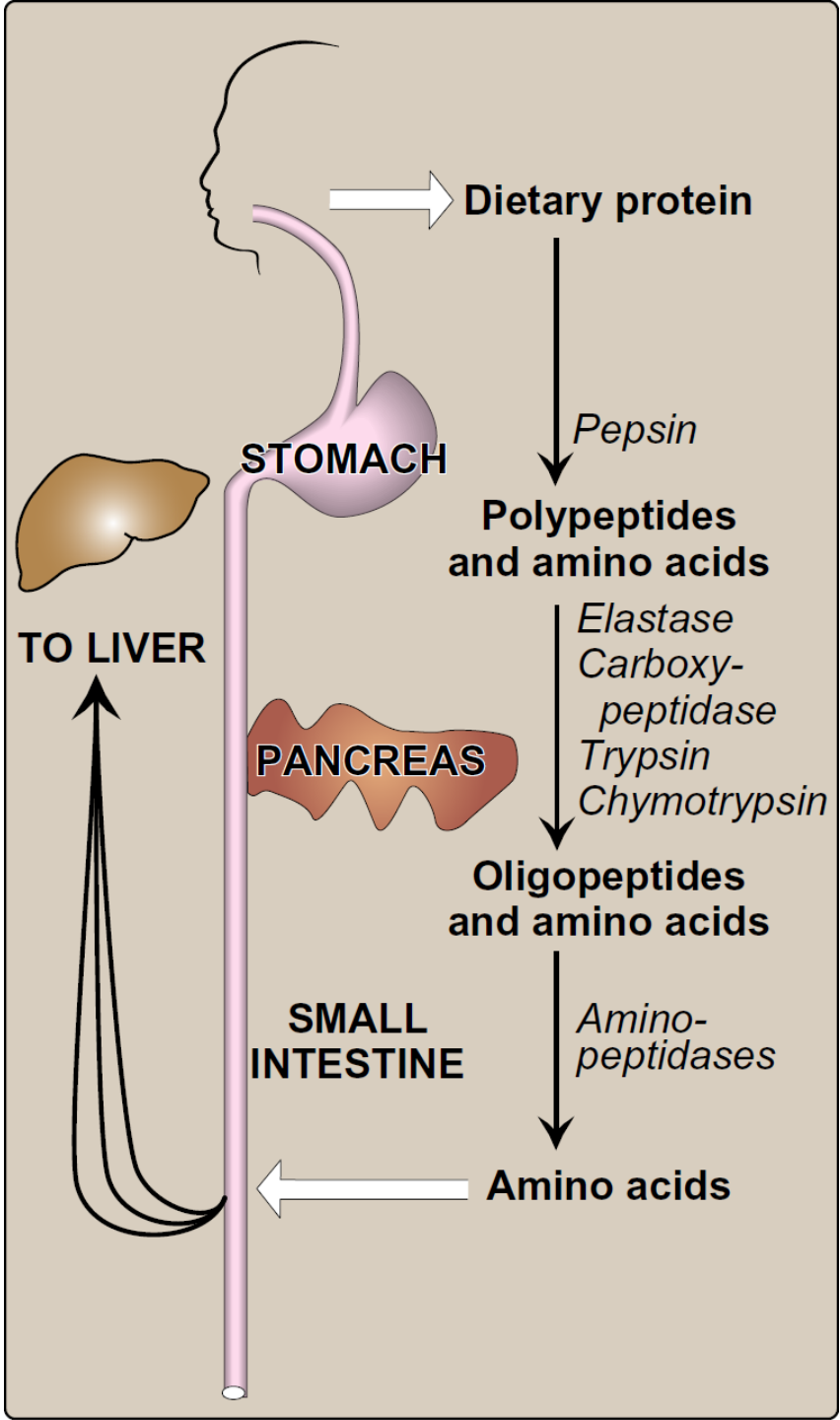


Figure 19.4 Digestion of dietary proteins by the proteolytic enzymes of the gastrointestinal

A.Digestion of proteins by gastric secretion:

The digestion of proteins begins in the stomach, which secretes gastric juice—a unique solution containing hydrochloric acid and the proenzyme, pepsinogen.

1. Hydrochloric acid: Stomach acid is too dilute (pH 2–3) to hydrolyze proteins. The acid functions instead to kill some bacteria and to denature proteins, thus making them more susceptible to subsequent hydrolysis by proteases.

2. Pepsin: This acid-stable endopeptidase is secreted by the serous cells of the stomach as an inactive zymogen (or proenzyme), pepsinogen.

In general, zymogens contain extra amino acids in their sequences, which prevent them from being catalytically active.

[Note: Removal of these amino acids permits the proper folding required for an active enzyme.]
Pepsinogen is activated to pepsin, either by HCl, or autocatalytically by other pepsin molecules that have already been activated.
Pepsin releases peptides and a few free amino acids from dietary proteins.

B. Digestion of proteins by pancreatic enzymes :

On entering the small intestine, large polypeptides produced in the stomach by the action of pepsin are further cleaved to oligopeptides and amino acids by a group of pancreatic proteases.

1. Specificity:

- Each of these enzymes has a different specificity for the amino acid R-groups adjacent to the susceptible peptide bond (Figure 19.5).
- For example, trypsin cleaves only when the carbonyl group of the peptide bond is contributed by arginine or lysine.
- These enzymes, like pepsin described above, are synthesized and secreted as inactive zymogens.

2. Release of zymogens:

The release and activation of the pancreatic zymogens is mediated by the secretion of cholecystokinin and secretin, two polypeptide hormones of the digestive tract (see p. 176).

3. Activation of zymogens:

Enteropeptidase (formerly called enterokinase)— an enzyme synthesized by and present on the luminal surface of intestinal mucosal cells of the brush border membrane—converts the pancreatic zymogen trypsinogen to trypsin by removal of a hexapeptide from the NH_2-terminus of trypsinogen.
Trypsin subsequently converts other trypsinogen molecules to trypsin by cleaving a limited number of specific peptide bonds in the zymogen.
Enteropeptidase thus unleashes a cascade of proteolytic activity, because trypsin is the common activator of all the pancreatic zymogens (see Figure 19.5).

4. Abnormalities in protein digestion:

In individuals with a deficiency in pancreatic secretion (for example, due to chronic pancreatitis, cystic fibrosis, or surgical removal of the pancreas), the digestion and absorption of fat and protein is incomplete.
This results in the abnormal appearance of lipids (called steatorrhea, see p. 177) and undigested protein in the feces.

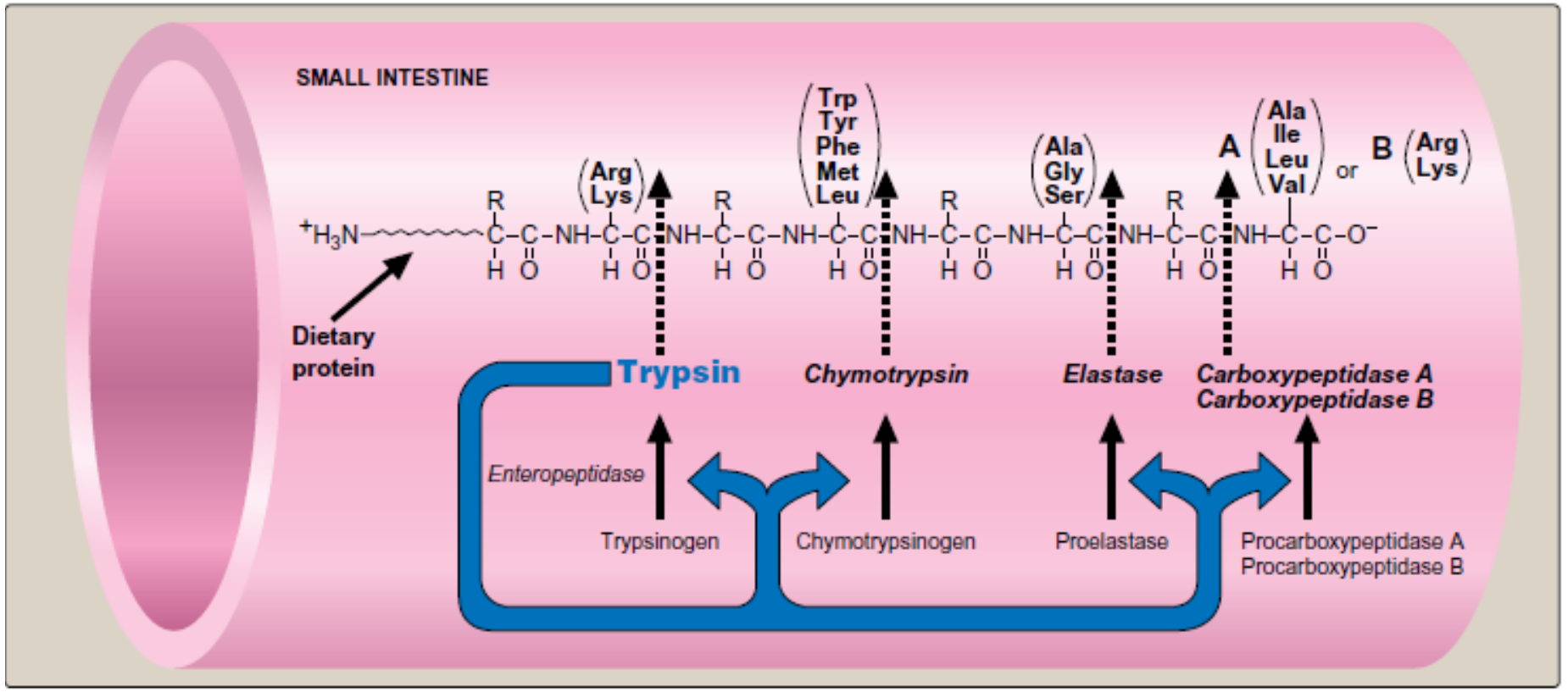


Figure 19.5 Cleavage of dietary protein by proteases from the pancreas. The peptide bonds susceptible to hydrolysis are shown for each of the five major pancreatic proteases. [Note: Enteropeptidaseis synthesized in the intestine.]

C. Digestion of oligopeptides by enzymes of the small intestine:

The luminal surface of the intestine contains aminopeptidase—an exopeptidase that repeatedly cleaves the N-terminal residue from oligopeptides to produce free amino acids and smaller peptides.

D. Absorption of amino acids and dipeptides :

Free amino acids are taken into the enterocytes up by a Na+-linked secondary transport system.
Di- and tripeptides, however, are taken up by a H+-linked transport system.
There, the peptides are hydrolyzed in the cytosol to amino acids before being released into the portal system.
Thus, only free amino acids are found in the portal vein after a meal containing protein.
These amino acids are either metabolized by the liver or released into the general circulation.
[Note: Branched-chain amino acids are important examples of amino acids that are not metabolized by the liver, but instead are sent from the liver into the blood.]

Transport of Amino Acids into Cells:

The concentration of free amino acids in the extracellular fluids is significantly lower than that within the cells of the body.
This concentration gradient is maintained because active transport systems, driven by the hydrolysis of ATP, are required for movement of amino acids from the extracellular space into cells.
At least seven different transport systems are known that have overlapping specificities for different amino acids.

The small intestine and the proximal tubule of the kidney have common transport systems for amino acid uptake; therefore, a defect in any one of these systems results in an inability to absorb particular amino acids into the gut and into the kidney tubules.

For example, one system is responsible for the uptake of cystine and the dibasic amino acids, ornithine, arginine, and lysine (represented as “COAL”).

In the inherited disorder cystinuria, this carrier system is defective, and all four amino acids appear in the urine (Figure 19.6).

Cystinuria occurs at a frequency of 1 in 7,000 individuals, making it one of the most common inherited diseases, and the most common genetic error of amino acid transport.

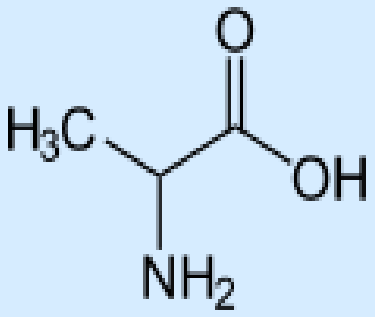
The disease expresses itself clinically by the precipitation of cystine to form kidney stones (calculi), which can block the urinary tract.
Oral hydration is an important part of treatment for this disorder.
[Note: Defects in the transport of tryptophan (and other neutral amino acids) can result in Hartnup disorder and pellagra-like (see p. 380) dermatologic and neurologic symptoms.

Essential and non essential amino acid

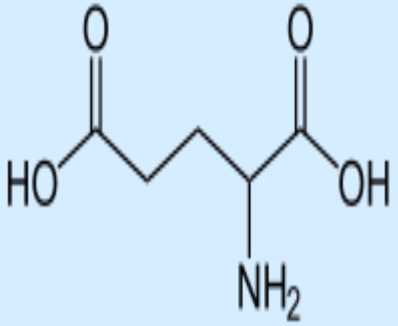
essential	Non essential
*Arginine	Alanine
Histidine	Asparagine
Isoleucine	Aspartate
Leucine	Cysteine
Lysine	Glutamate
Methionine*	Glutamine
Phenylalanine*	Glycine
Threonine	Proline
Tryptophan	Serine
valine	Tyrosine

Central role of glutamate

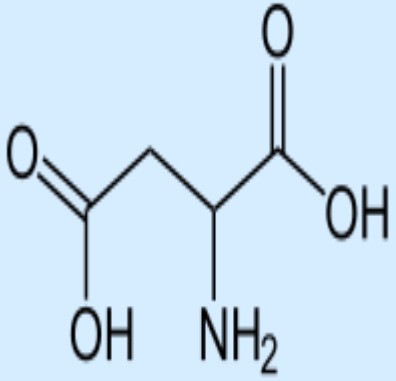
- Four of the amino acids :glutamate,aspartate,alanine and glutamine are present in cells at much higher concentration than the others 16 . All four have major metabolic function in addition to their roles in proteins but glutamate occupies the prime position .



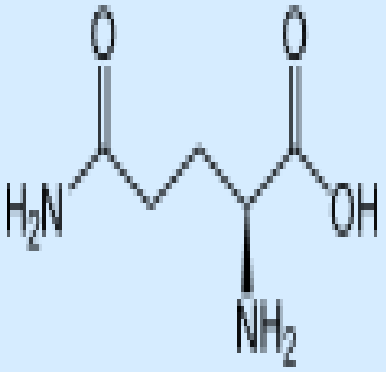
Alanine



Glutamic acid



Aspartic acid



Glutamine

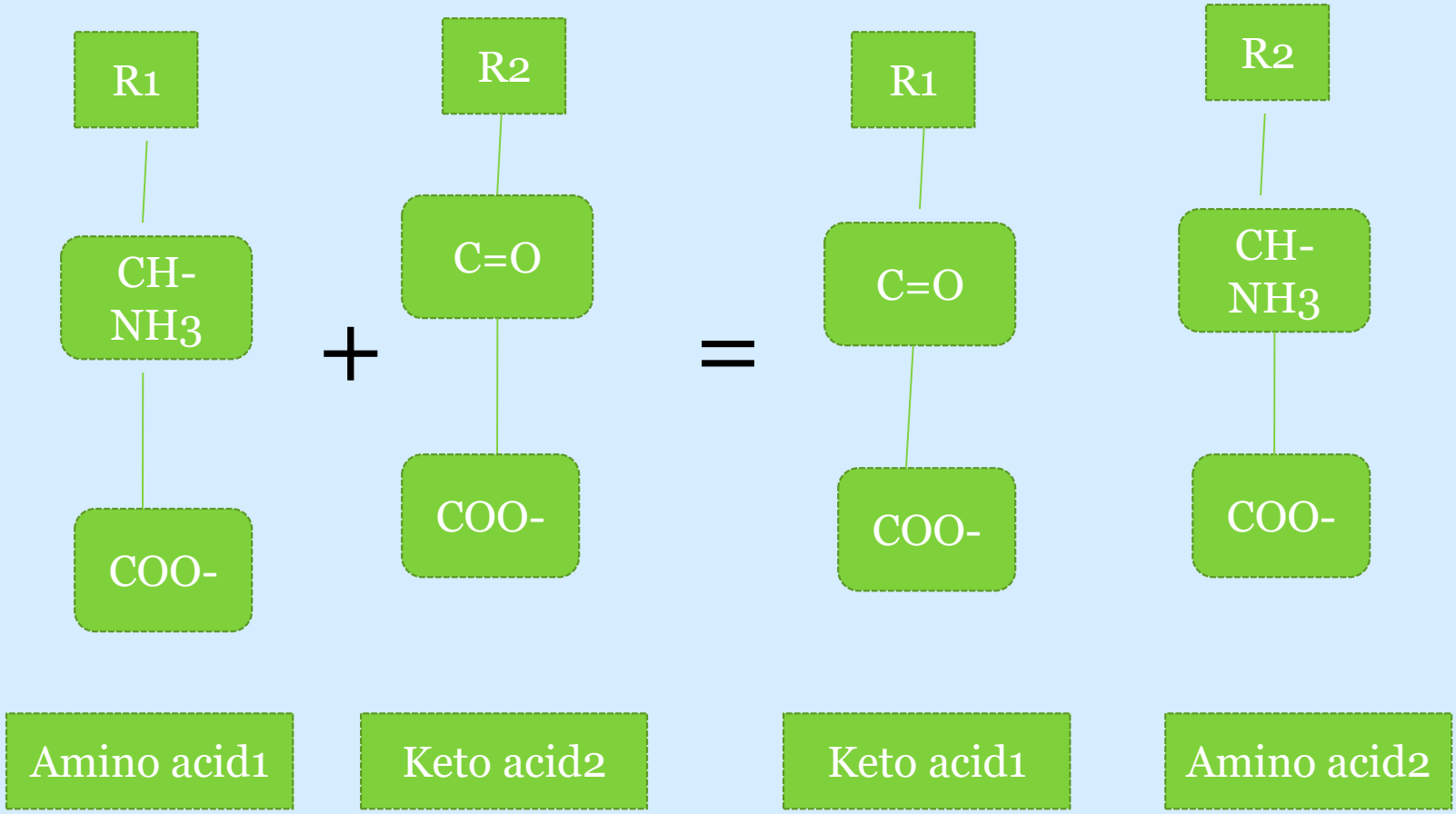
Function of four amino acids

- Glutamate and aspartate function as excitory neurotransmtters in the CNS
- Glutamate is partly responsible for the flavor of food .
- Glutamine also occupies especial position in amino acids breakdown ,and most of the nitrogen from dietary protein is ultimately excreted from the body via glutamate pool.

- Glutamate is a special because it is chemically related to 2-oxoglutarate which is a key intermediate in the citric acid cycle .
- Glutamate can be reversibly into oxoglutarate by transaminases or by glutamate dehydrogenase.
- Glutamate can be converted into glutamine , an important nitrogen carrier ,and the most common free amino acid in human blood plasma.

Transamination: the funneling of amino groups to glutamate

- The first step in the catabolism of most amino acids is the transfer of their α-amino group to α-ketoglutarate.
- The products are an α-keto acid (derived from the original amino acid) and glutamate.
- α-Ketoglutarate plays a pivotal role in amino acid metabolism by accepting the amino groups from other amino acids, thus becoming glutamate.
- Glutamate produced by transamination can be oxidatively deaminated (see below), or used as an amino group donor in the synthesis of nonessential amino acids.


R1
CH-NH3
COO-
+
R2
C=O
COO-
=
R1
C=O
COO-
R2
CH-NH3
COO-
Amino acid1
Keto acid2
Keto acid1
Amino acid2

- This transfer of amino groups from one carbon skeleton to another is catalyzed by a family of enzymes called aminotransferases (formerly called transaminases).
- These enzymes are found in the cytosol and mitochondria of cells throughout the body—especially those of the liver, kidney, intestine, and muscle.
- All amino acids, with the exception of lysine and threonine, participate in transamination at some point in their catabolism.
- These two amino acids lose their α-amino groups by deamination.

Aspartate aminotransferase (AST):

- AST formerly called glutamate-oxaloacetate transaminase, AST is an exception to the rule that aminotransferases funnel amino groups to form glutamate.
- During amino acid catabolism, AST transfers amino groups from glutamate to oxaloacetate, forming aspartate, which is used as a source of nitrogen in the urea cycle .

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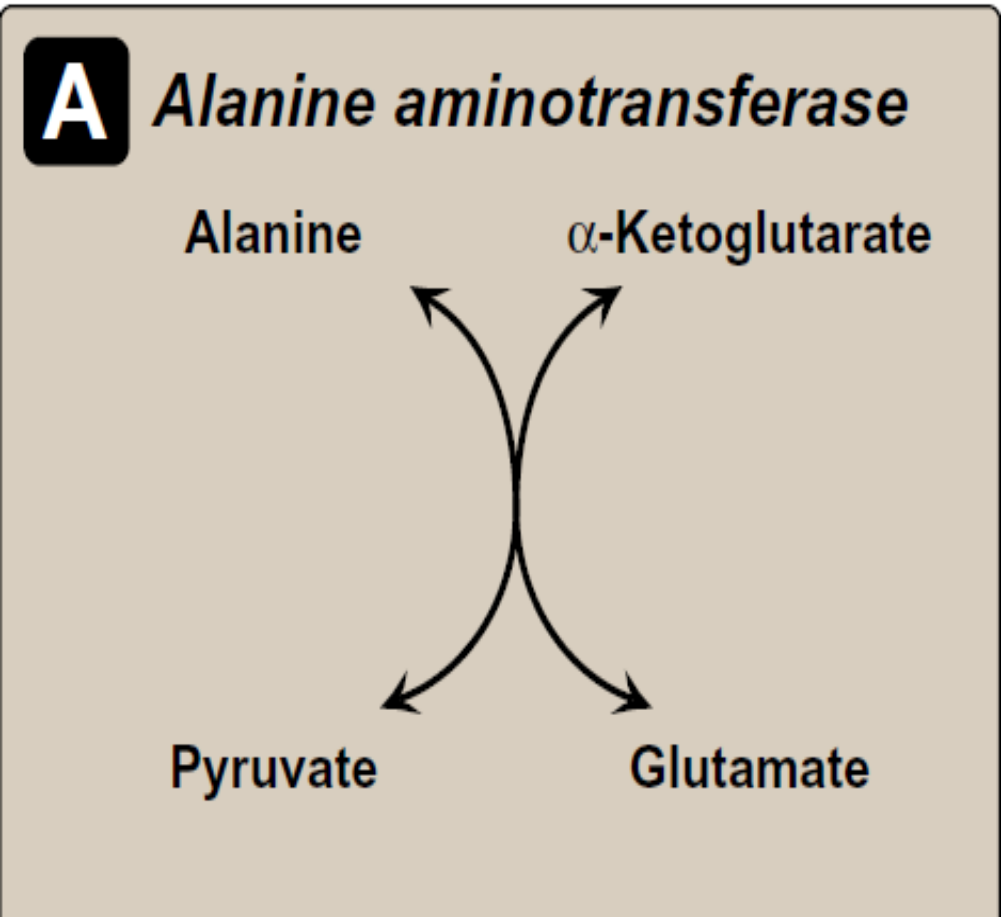
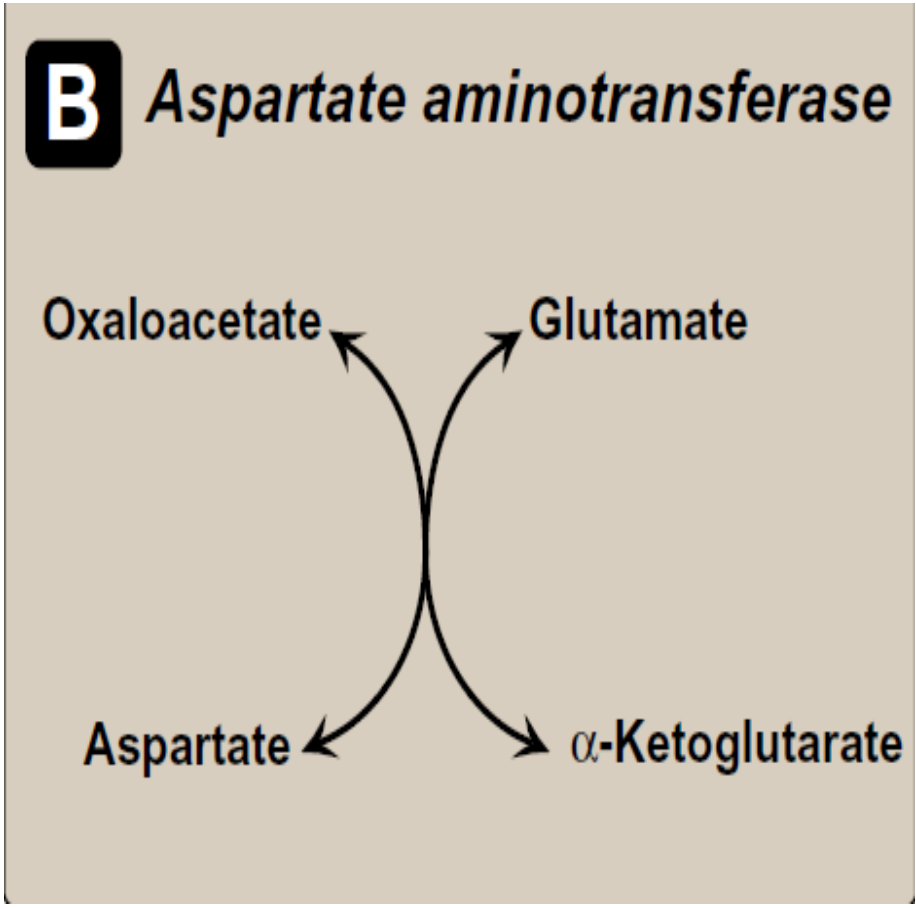
Alanine aminotransferase (ALT):

- Formerly called glutamate-pyruvate transaminase, ALT is present in many tissues.
- The enzyme catalyzes the transfer of the amino group of alanine to α-ketoglutarate, resulting in the formation of pyruvate and glutamate.
- The reaction is readily reversible. However, during amino acid catabolism, this enzyme (like most aminotransferases) functions in the direction of glutamate synthesis.
- Thus, glutamate, in effect, acts as a “collector” of nitrogen from alanine.





Reactions catalyzed during amino acid catabolism. A. Alanine aminotransferase (ALT). B. Aspartate aminotransferase (AST).

Diagnostic value of plasma aminotransferases:

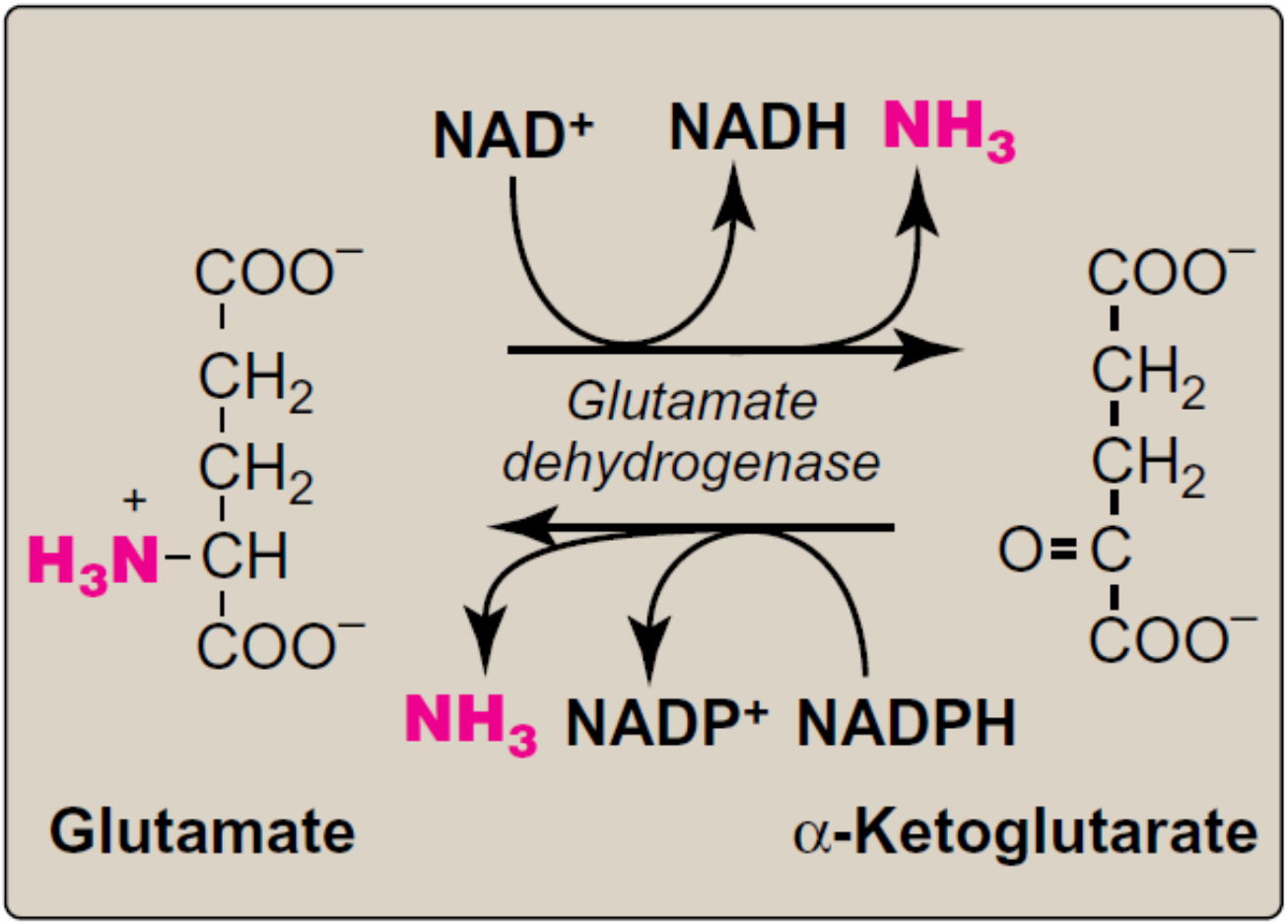
Aminotransferases are normally intracellular enzymes, with the low levels found in the plasma representing the release of cellular contents during normal cell turnover.

The presence of elevated plasma levels of aminotransferases indicates damage to cells rich in these enzymes.

For example, physical trauma or a disease process can cause cell lysis, resulting in release of intracellular enzymes into the blood. Two aminotransferases—AST and ALT—are of particular diagnostic value when they are found in the plasma.

Glutamate dehydrogenase: the oxidative deamination of amino acids

- In contrast to transamination reactions that transfer amino groups, oxidative deamination by glutamate dehydrogenase results in the liberation of the amino group as free ammonia .
- These reactions occur primarily in the liver and kidney.
- They provide α-keto acids that can enter the central pathway of energy metabolism, and ammonia, which is a source of nitrogen in urea synthesis.



Oxidative deamination by glutamate dehydrogenase.

1-Glutamate dehydrogenase:

As described above, the amino groups of most amino acids are ultimately funneled to glutamate by means of transamination with α-ketoglutarate.
Glutamate is unique in that it is the only amino acid that undergoes rapid oxidative deamination—a reaction catalyzed by glutamate dehydrogenase .
Therefore, the sequential action of transamination (resulting in the collection of amino groups from other amino acids onto α-ketoglutarate to produce glutamate) and the oxidative deamination of that glutamate (regenerating α-ketoglutarate) provide a pathway whereby the amino groups of most amino acids can be released as ammonia.

2. D-Amino acid oxidase:

D-Amino acids are found in plants and in the cell walls of microorganisms, but are not used in the synthesis of mammalian proteins.
D-Amino acids are, however, present in the diet, and are efficiently metabolized by the kidney and liver.
D-Amino acid oxidase is an FAD-dependent peroxisomal enzyme that catalyzes the oxidative deamination of these amino acid isomers.
The resulting α-keto acids can enter the general pathways of amino acid metabolism, and be reaminated to L-isomers, or catabolized for energy.

Transport of ammonia to the liver

Two mechanisms are available in humans for the transport of ammonia from the peripheral tissues to the liver for its ultimate conversion to urea.

The first, found in most tissues, uses glutamine synthetase to combine ammonia with glutamate to form glutamine—a nontoxic transport form of ammonia .

The glutamine is transported in the blood to the liver where it is cleaved by glutaminase to produce glutamate and free ammonia

The second transport mechanism, used primarily by muscle, involves transamination of pyruvate (the end product of aerobic glycolysis) to form alanine .
Alanine is transported by the blood to the liver, where it is converted to pyruvate, again by transamination.
In the liver, the pathway of gluconeogenesis can use the pyruvate to synthesize glucose, which can enter the blood and be used by muscle—a pathway called the glucose-alanine cycle.

Urea Cycle

Urea is the major disposal form of amino groups derived from amino acids, and accounts for about 90% of the nitrogen-containing components of urine.
One nitrogen of the urea molecule is supplied by free NH_3, and the other nitrogen by aspartate.
[Note: Glutamate is the immediate precursor of both ammonia (through oxidative deamination by glutamate dehydrogenase) and aspartate nitrogen (through transamination of oxaloacetate by AST).]
The carbon and oxygen of urea are derived from CO_2.
Urea is produced by the liver, and then is transported in the blood to the kidneys for excretion in the urine.

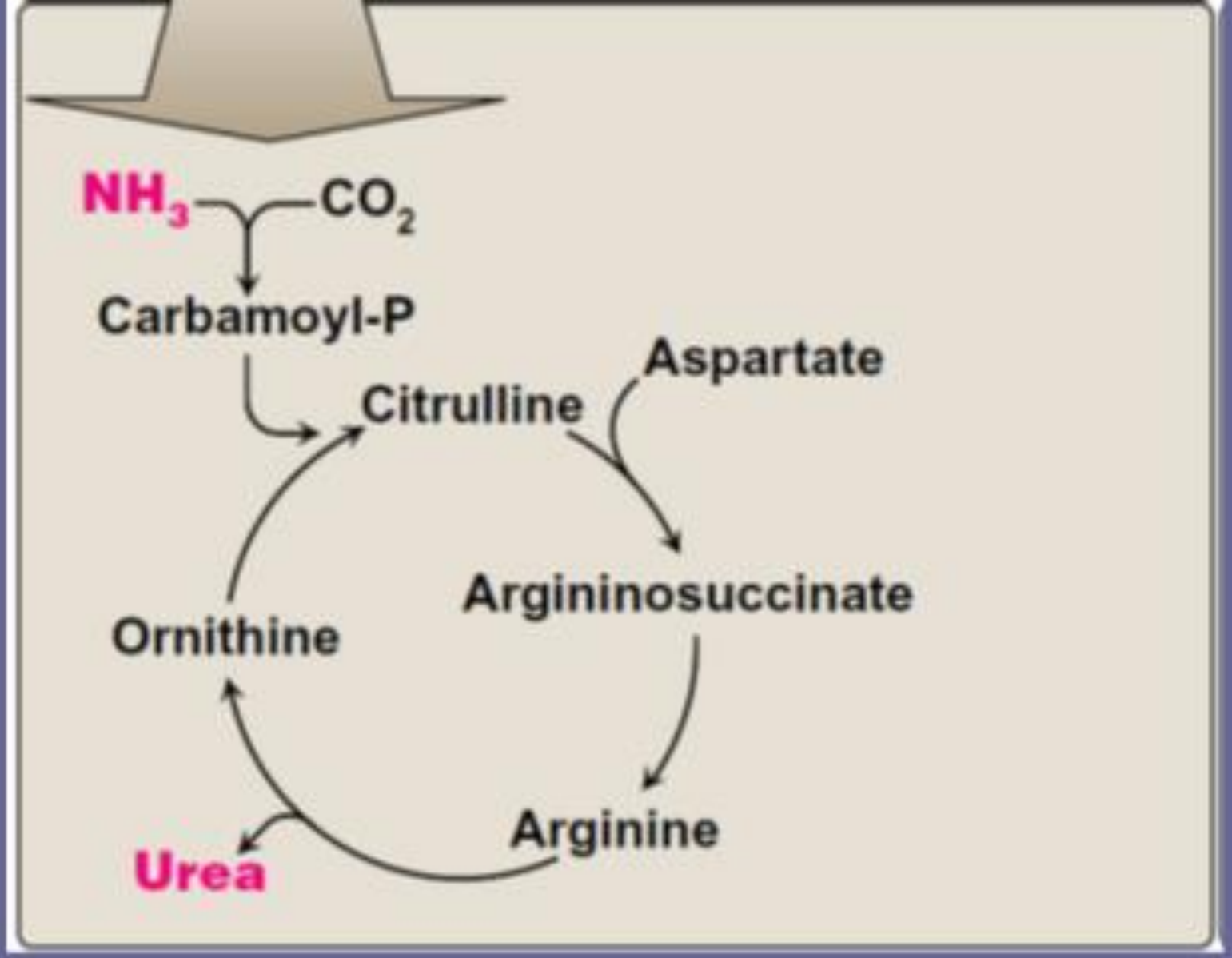


Figure 19.1 Urea cycle shown as part of the essential reactions of energy metabolism.

. Reactions of the cycle

The first two reactions leading to the synthesis of urea occur in the mitochondria, whereas the remaining cycle enzymes are located in the cytosol .

Formation of carbamoyl phosphate:

Formation of carbamoyl phosphate by carbamoyl phosphate synthetase I is driven by cleavage of two molecules of ATP.

Ammonia incorporated into carbamoyl phosphate is provided primarily by the oxidative deamination of glutamate by mitochondrial glutamate dehydrogenase .

Ultimately, the nitrogen atom derived from this ammonia becomes one of the nitrogens of urea.

Carbamoyl phosphate synthetase I requires N-acetylglutamate as a positive allosteric activator .
[Note: Carbamoyl phosphate synthetase II participates in the biosynthesis of pyrimidines .It does not require N-acetylglutamate, and occurs in the cytosol.]

2. Formation of citrulline:

Ornithine and citrulline are basic amino acids that participate in the urea cycle.
[Note: They are not incorporated into cellular proteins, because there are no codons for these amino acids.]
Ornithine is regenerated with each turn of the urea cycle, much in the same way that oxaloacetate is regenerated by the reactions of the citric acid cycle .
The release of the high-energy phosphate of carbamoyl phosphate as inorganic phosphate drives the reaction in the forward direction.
The reaction product, citrulline, is transported to the cytosol.

3. Synthesis of argininosuccinate:

Citrulline condenses with aspartate to form argininosuccinate. The α-amino group of aspartate provides the second nitrogen that is ultimately incorporated into urea.

The formation of argininosuccinate is driven by the cleavage of ATP to adenosine monophosphate (AMP) and pyrophosphate. This is the third and final molecule of ATP consumed in the formation of urea.

4. Cleavage of argininosuccinate:

Argininosuccinate is cleaved to yield arginine and fumarate.

The arginine formed by this reaction serves as the immediate precursor of urea.

Fumarate produced in the urea cycle is hydrated to malate, providing a link with several metabolic pathways.

For example, the malate can be transported into the mitochondria via the malate shuttle and reenter the tricarboxylic acid cycle.

Alternatively, cytosolic malate can be oxidized to oxaloacetate, which can be converted to aspartate or glucose .

5. Cleavage of arginine to ornithine and urea:

Arginase cleaves arginine to ornithine and urea, and occurs almost exclusively in the liver.

Thus, whereas other tissues, such as the kidney, can synthesize arginine by these reactions, only the liver can cleave arginine and, thereby, synthesize urea.

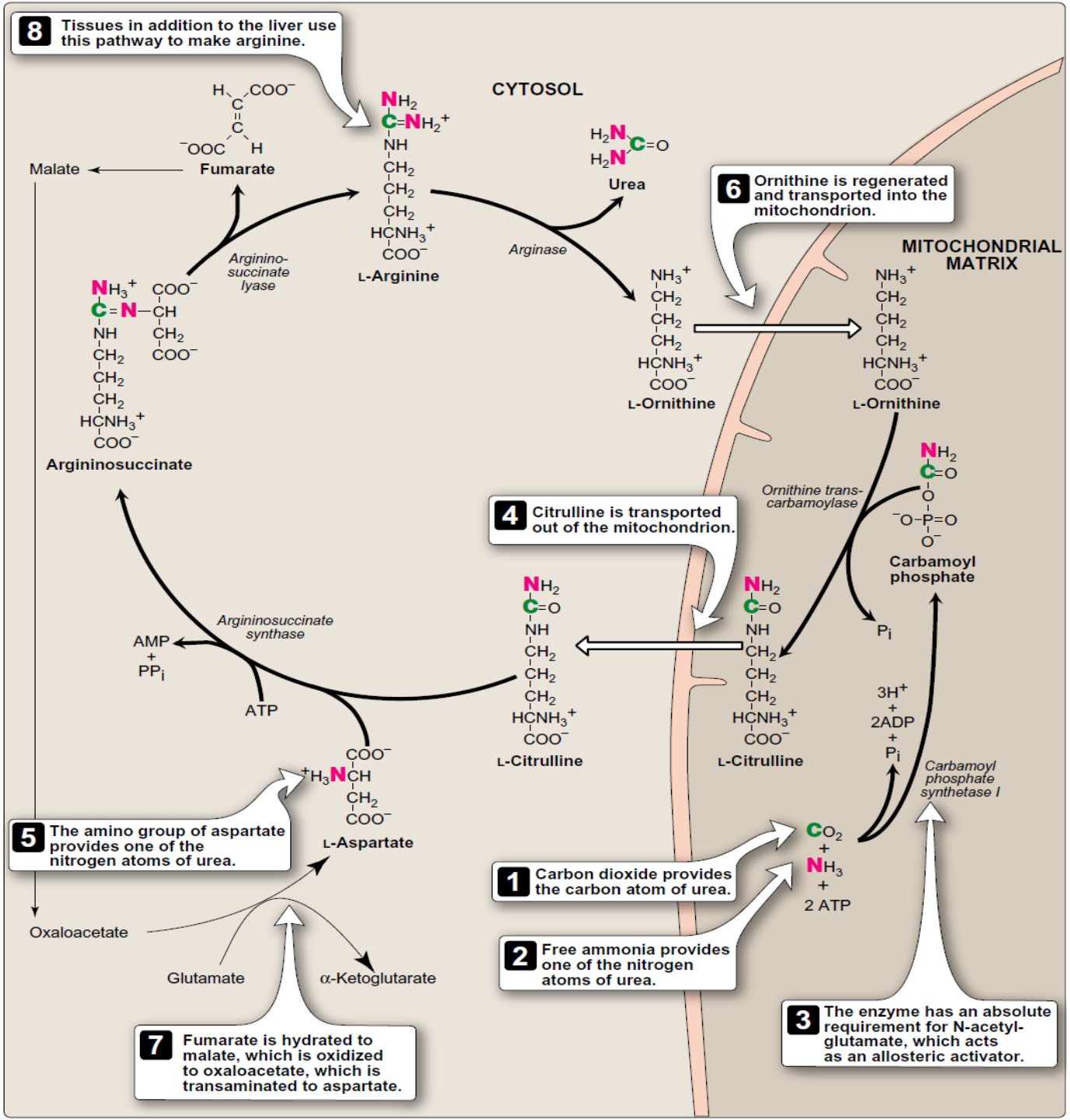
. Fate of urea:

Urea diffuses from the liver, and is transported in the blood to the kidneys, where it is filtered and excreted in the urine.
A portion of the urea diffuses from the blood into the intestine, and is cleaved to CO_2 and NH_3 by bacterial urease.
This ammonia is partly lost in the feces, and is partly reabsorbed into the blood.
In patients with kidney failure, plasma urea levels are elevated, promoting a greater transfer of urea from blood into the gut.
The intestinal action of urease on this urea becomes a clinically important source of ammonia, contributing to the hyperammonemia often seen in these patients.
Oral administration of neomycin reduces the number of intestinal bacteria responsible for this NH_3 production.

. Overall stoichiometry of the urea cycle

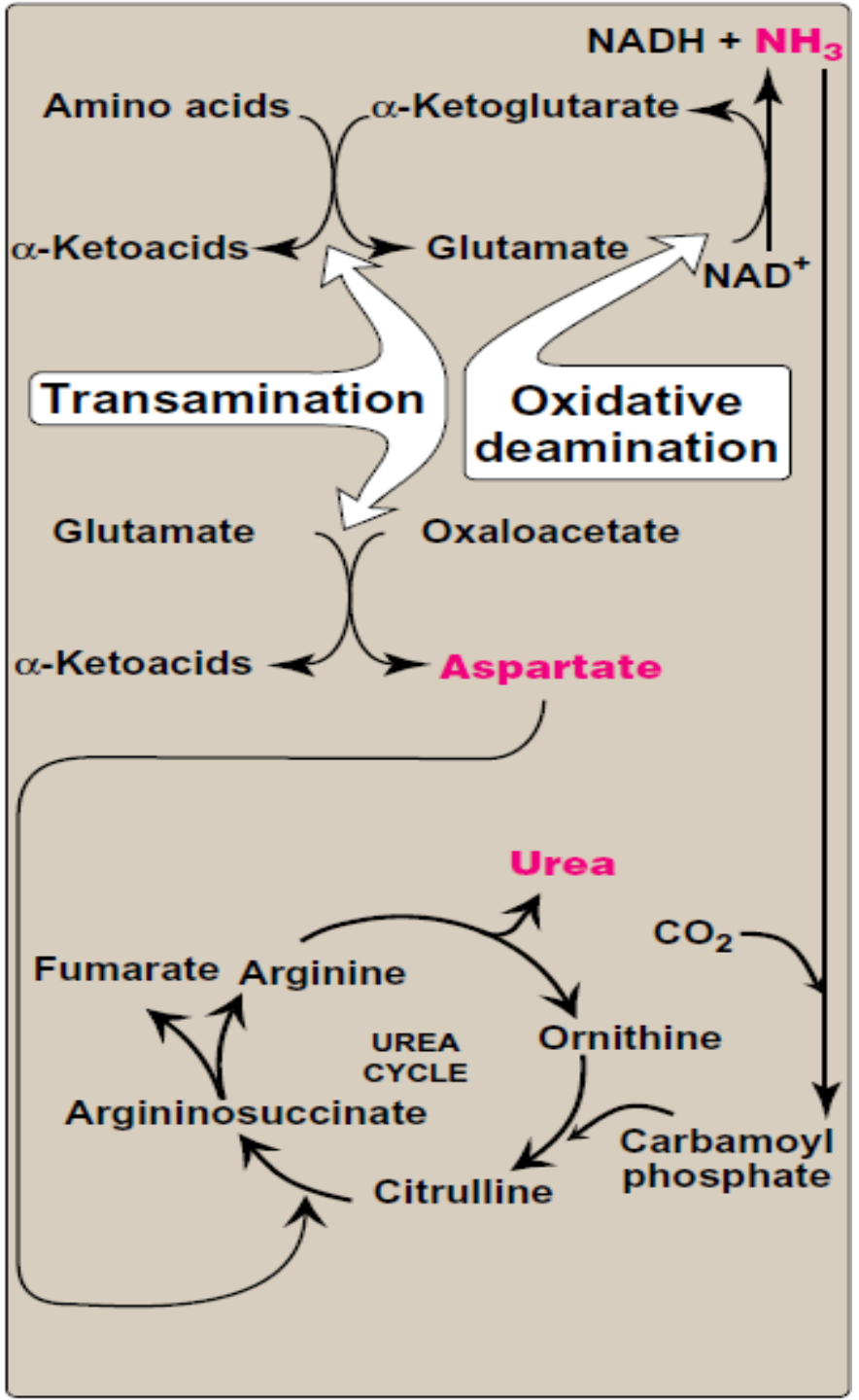
$$\text{Aspartate} + NH_3 + CO_2 + 3\,\text{ATP} \rightarrow$$

$$\text{urea} + \text{fumarate} + 2\,\text{ADP} + \text{AMP} + 2\,P_i + PP_i + 3\,H_2O$$


8 Tissues in addition to the liver use this pathway to make arginine.
CYTOSOL
MITOCHONDRIAL MATRIX
Fumarate
Malate
Arginino-succinate lyase
L-Arginine
Urea
Arginase
6 Ornithine is regenerated and transported into the mitochondrion.
L-Ornithine
L-Ornithine
Argininosuccinate
Ornithine trans-carbamoylase
Carbamoyl phosphate
Pi
4 Citrulline is transported out of the mitochondrion.
Argininosuccinate synthase
AMP + PPi
ATP
L-Citrulline
L-Citrulline
3H+ + 2ADP + Pi
Carbamoyl phosphate synthetase I
5 The amino group of aspartate provides one of the nitrogen atoms of urea.
L-Aspartate
CO2 + NH3 + 2 ATP
1 Carbon dioxide provides the carbon atom of urea.
2 Free ammonia provides one of the nitrogen atoms of urea.
3 The enzyme has an absolute requirement for N-acetyl-glutamate, which acts as an allosteric activator.
Oxaloacetate
Glutamate
α-Ketoglutarate
7 Fumarate is hydrated to malate, which is oxidized to oxaloacetate, which is transaminated to aspartate.

Four high-energy phosphates are consumed in the synthesis of each molecule of urea:
two ATP are needed to restore two ADP to two ATP, plus two to restore AMP to ATP.
Therefore, the synthesis of urea is irreversible, with a large, negative ΔG.
One nitrogen of the urea molecule is supplied by free NH_3, and the other nitrogen by aspartate.
Glutamate is the immediate precursor of both ammonia (through oxidative deamination by glutamate dehydrogenase) and aspartate nitrogen (through transamination of oxaloacetate by AST).
In effect, both nitrogen atoms of urea arise from glutamate, which, in turn, gathers nitrogen from other amino acids .

Flow of nitrogen from amino acids to urea. Amino groups for urea synthesis are collected in the form of ammonia and aspartate



Regulation of the urea cycle

N-Acetylglutamate is an essential activator for carbamoyl phosphate synthetase I—the rate-limiting step in the urea cycle

N-Acetylglutamate is synthesized from acetyl coenzyme A and glutamate by N-acetylglutamate synthase ,in a reaction for which arginine is an activator.

Therefore, the intrahepatic concentration of N-acetylglutamate increases after ingestion of a protein-rich meal, which provides both the substrate (glutamate) and the regulator of N-acetylglutamate synthesis.

This leads to an increased rate of urea synthesis.

Metabolism of Ammonia

Ammonia is produced by all tissues during the metabolism of a variety of compounds, and it is disposed of primarily by formation of urea in the liver.
However, the level of ammonia in the blood must be kept very low, because even slightly elevated concentrations (hyperammonemia) are toxic to the central nervous system (CNS).
There must, therefore, be a metabolic mechanism by which nitrogen is moved from peripheral tissues to the liver for ultimate disposal as urea, while at the same time low levels of circulating ammonia must be maintained.

Sources of ammonia

Amino acids are quantitatively the most important source of ammonia, because most Western diets are high in protein and provide excess amino acids, which are deaminated to produce ammonia. However, substantial amounts of ammonia can be obtained from other sources.

1.From amino acids: Many tissues, but particularly the liver, form ammonia from amino acids by transdeamination—the linking of aminotransferase and glutamate dehydrogenase reactions previously described.

2.From glutamine: The kidneys form ammonia from glutamine by the actions of renal glutaminase (and glutamate dehydrogenase.

Most of this ammonia is excreted into the urine as NH_4^+, which provides an important mechanism for maintaining the body's acid-base balance.

Ammonia is also obtained from the hydrolysis of glutamine by intestinal glutaminase. The intestinal mucosal cells obtain glutamine either from the blood or from digestion of dietary protein.

[Note: Intestinal glutamine metabolism produces citrulline, which travels to the kidney and is used to synthesize arginine.]

3. From bacterial action in the intestine: Ammonia is formed from urea by the action of bacterial urease in the lumen of the intestine. This ammonia is absorbed from the intestine by way of the portal vein and is almost quantitatively removed by the liver via conversion to urea.

4. From amines: Amines obtained from the diet, and monoamines that serve as hormones or neurotransmitters, give rise to ammonia by the action of amine oxidase for the degradation of catecholamines).

5. From purines and pyrimidines: In the catabolism of purines and pyrimidines, amino groups attached to the rings are released as ammonia.

Transport of ammonia in the circulation

Although ammonia is constantly produced in the tissues, it is present at very low levels in blood.

This is due both to the rapid removal of blood ammonia by the liver, and the fact that many tissues, particularly muscle, release amino acid nitrogen in the form of glutamine or alanine, rather than as free ammonia .

1.Urea: Formation of urea in the liver is quantitatively the most **.1** important disposal route for ammonia.

Urea travels in the blood from the liver to the kidneys, where it passes into the glomerular filtrate.

2. Glutamine: This amide of glutamic acid provides a nontoxic storage and transport form of ammonia .
The ATP-requiring formation of glutamine from glutamate and ammonia by glutamine synthetase occurs primarily in the muscle and liver, but is also important in the nervous system, where it is the major mechanism for the removal of ammonia in the brain.

Glutamine is found in plasma at concentrations higher than other amino acids—a finding consistent with its transport function.

Circulating glutamine is removed by the liver and the kidneys and deaminated by glutaminase.

. Hyperammonemia

The capacity of the hepatic urea cycle exceeds the normal rates of ammonia generation, and the levels of serum ammonia are normally low (5–50 μmol/L).
However, when liver function is compromised, due either to genetic defects of the urea cycle, or liver disease, blood levels can rise above 1,000 μmol/L.
Such hyperammonemia is a medical emergency, because ammonia has a direct neurotoxic effect on the CNS.
For example, elevated concentrations of ammonia in the blood cause the symptoms of ammonia intoxication, which include tremors, slurring of speech, somnolence, vomiting, cerebral edema, and blurring of vision.
At high concentrations, ammonia can cause coma and death. The two major types of hyperammonemia are:

1. Acquired hyperammonemia:

Liver disease is a common cause of hyperammonemia in adults. It may be a result of an acute process, for example, viral hepatitis, ischemia, or hepatotoxins.
Cirrhosis of the liver caused by alcoholism, hepatitis, or biliary obstruction may result in formation of collateral circulation around the liver.
As a result, portal blood is shunted directly into the systemic circulation and does not have access to the liver.
The detoxification of ammonia (that is, its conversion to urea) is, therefore, severely impaired, leading to elevated levels of circulating ammonia.

2. Hereditary hyperammonemia:

Genetic deficiencies of each of the five enzymes of the urea cycle have been described, with an overall prevalence estimated to be 1:30,000 live births.

Ornithine transcarbamoylase deficiency, which is X-linked, is the most common of these disorders, predominantly affecting males, although female carriers may become symptomatic.

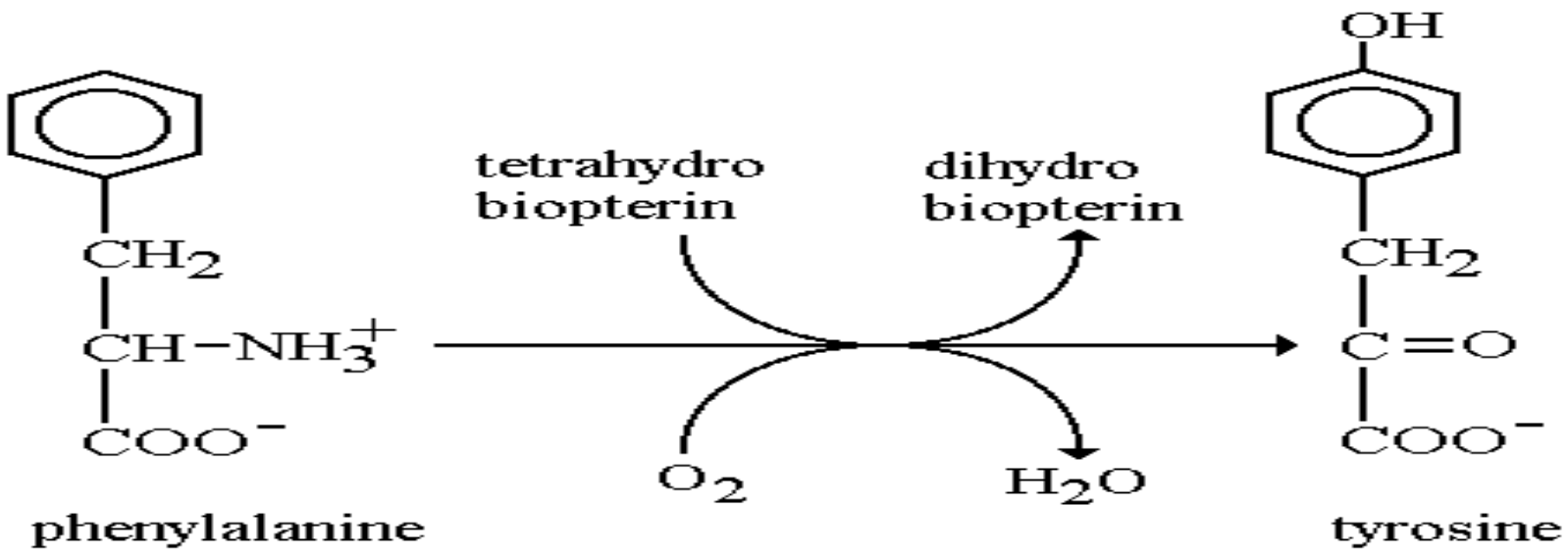
All of the other urea cycle disorders follow an autosomal recessive inheritance pattern.

In each case, the failure to synthesize urea leads to hyperammonemia during the first weeks following birth.

All inherited deficiencies of the urea cycle enzymes typically result in mental retardation.
Treatment includes limiting protein in the diet, and administering compounds that bind covalently to amino acids, producing nitrogen-containing molecules that are excreted in the urine.
For example, phenylbutyrate given orally is converted to phenylacetate. This condenses with glutamine to form phenylacetylglutamine, which is excreted .

Phenylketonuria

Phenylalanine is normally metabolised by conversion to tyrosine. The enzyme responsible for this conversion is phenylalanine hydroxylase, a mixed function oxygenase with a tetrahydrobiopterin cofactor:



Tyrosine is the only aromatic amino acid made in animals.

Phenylalanine + Dihydrobiopterin + O2 <=> Tyrosine + Tetrahydrobiopterin + H2O

Deficiency of phenylalanine hydroxylase is responsible for Phenylketonuria (PKU), an
Autosomal recessive disease that results in the accumulation of too much phenylalanine,
because the synthesis of tyrosine is blocked. When untreated, this metabolic defect leads to
excessive urinary excretion of phenyl pyruvate and phenyl lactate, followed by severe mental
retardation, seizure, psychosis and eczema. Clear cur diagnosis requires measurement of
plasma phenylalanine, which may be raised above 300mg/d. (normal 30mg/d).