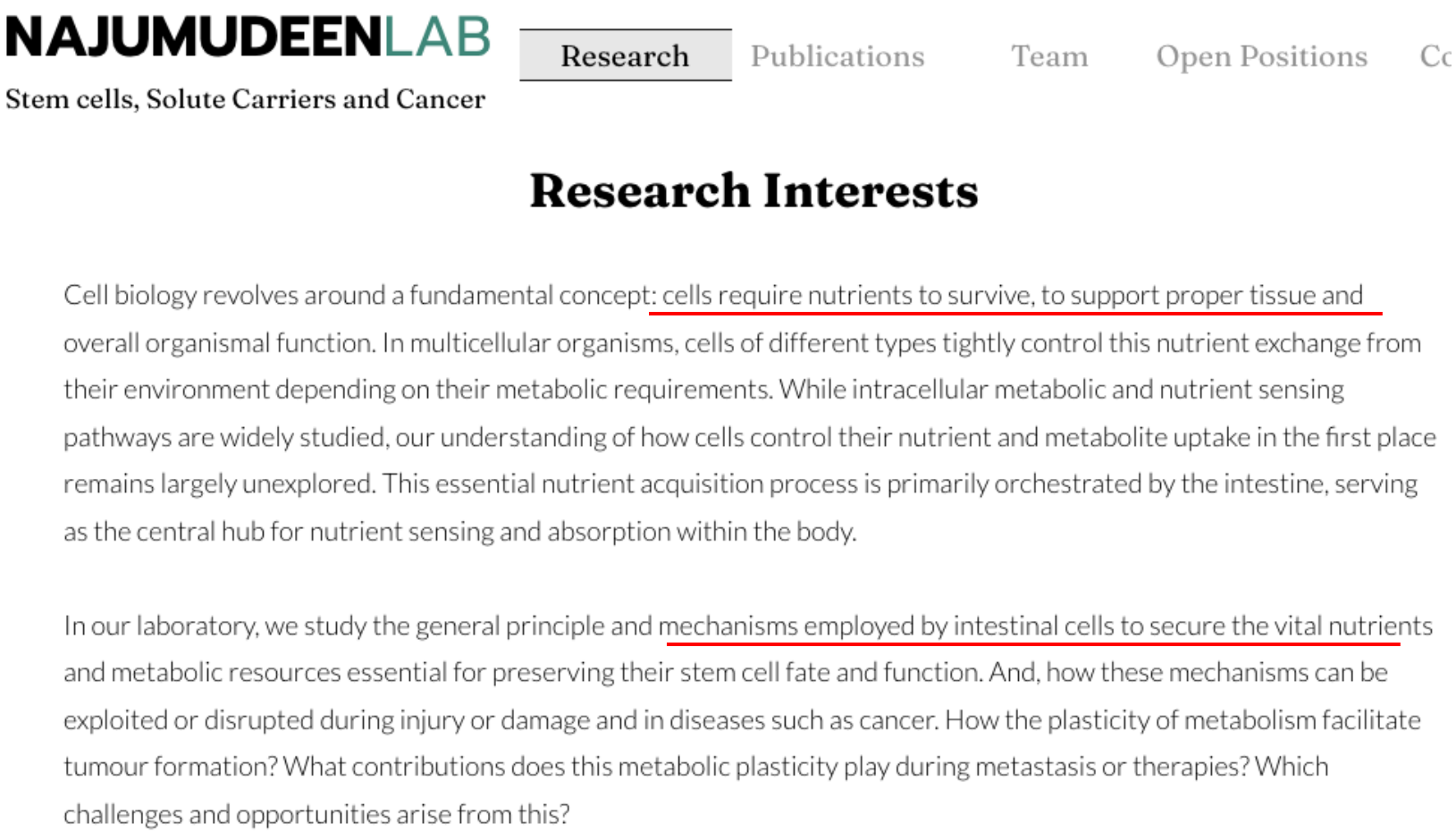
Amino acid metabolism

MOLE-203 | Metabolism

Rafa Najumudeen, FIMM, Helsinki Institute of Life Science

Who am I? What do I do?

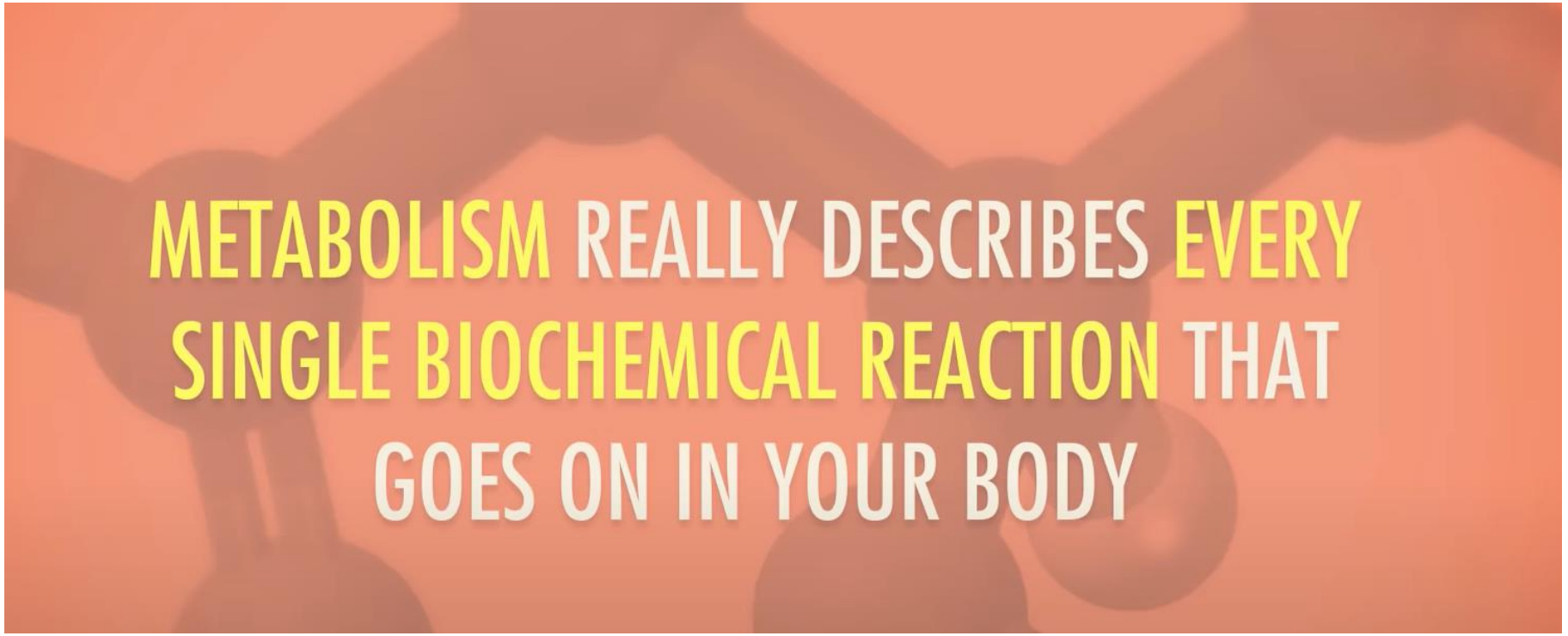


Intended outcomes:

What is amino acid metabolism?

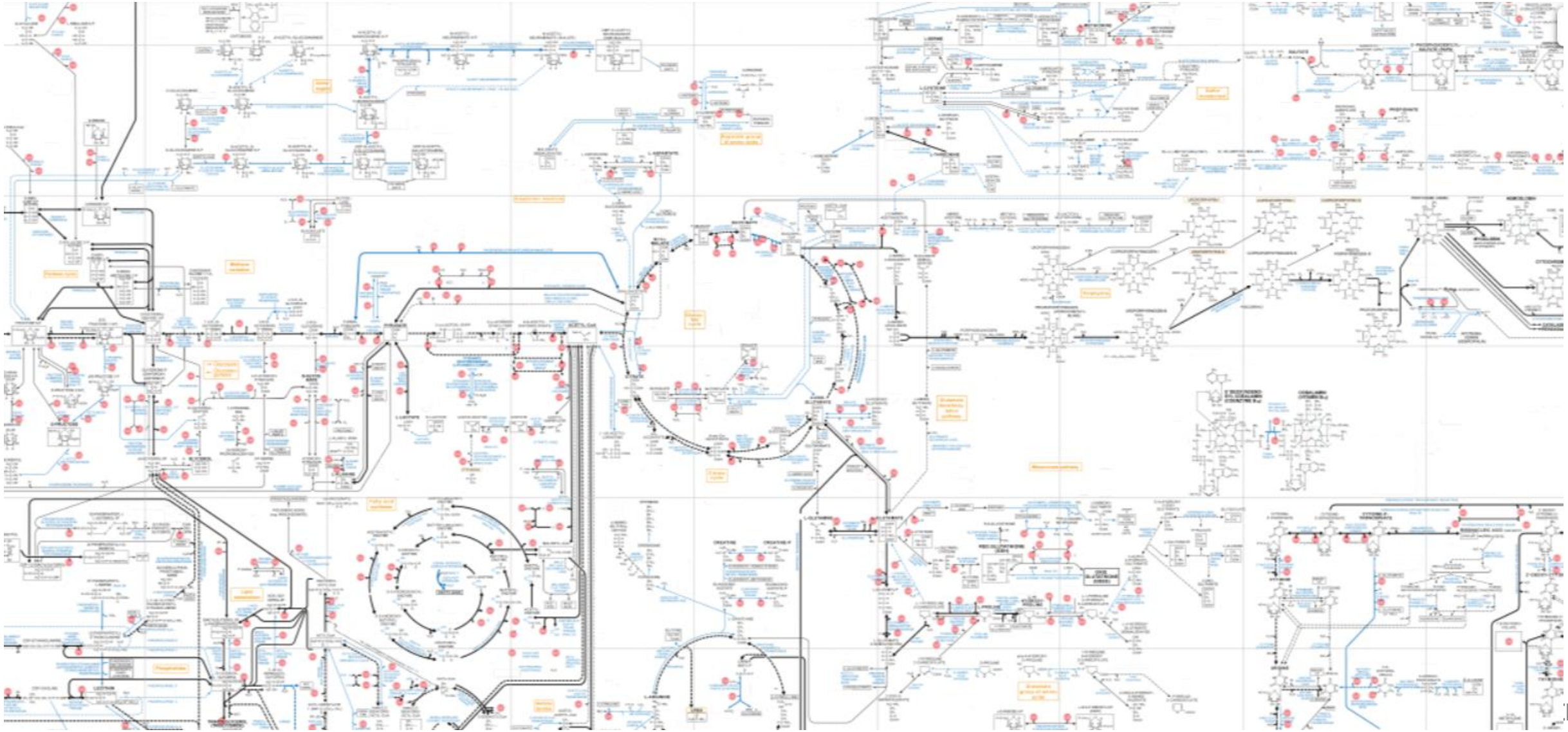
Different ways the cells use and generate amino acids

Role of amino acid metabolism in cellular signaling, health and disease

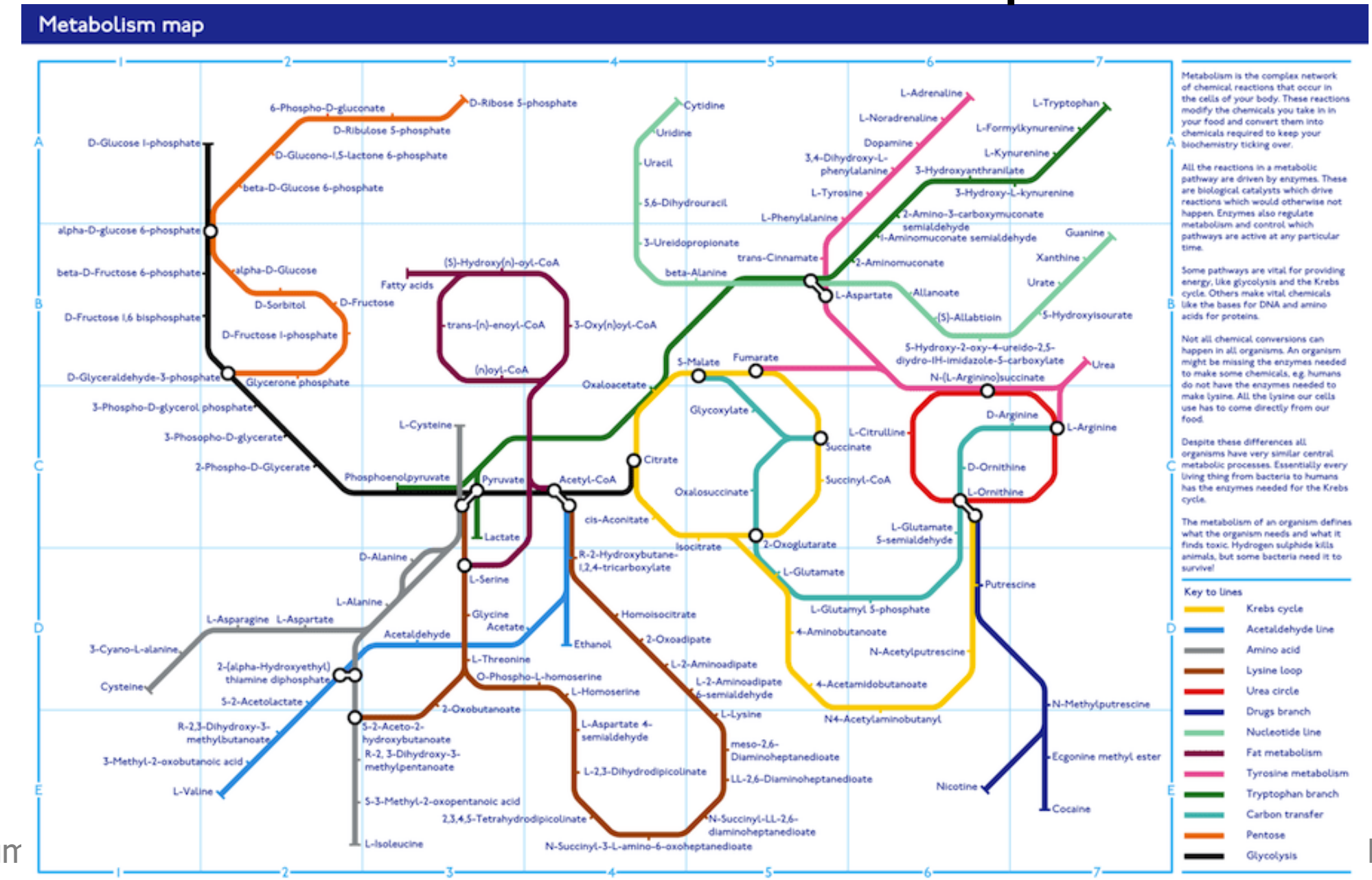

METABOLISM REALLY DESCRIBES EVERY
SINGLE BIOCHEMICAL REACTION THAT
GOES ON IN YOUR BODY

Two important and conflicting processes

Metabolic Complexity



Metabolic Metro Map



David L. Nelson & Michael M. Cox,

authors of *Lehninger Principles of Biochemistry*:

"The metabolism of amino acids is a key component in the regulation of energy production, cellular growth, and detoxification."

Overview

Main Features of Amino acid metabolism

Transamination - Central to both synthesis and breakdown of amino acids.

Essential and Non-Essential Amino Acids

Amino Acid Biosynthesis

Amino Acid Breakdown

Carbon Skeleton Utilization: Amino acids can be converted into glucose (glucogenic) or ketone bodies (ketogenic) for energy metabolism or used in biosynthesis.

Amino Nitrogen Removal: Ammonia is converted to urea in the liver for excretion.

Carbamyl Phosphate Synthesis and the Urea Cycle

Amino Acid Derivatives

NOTE: Following not covered and will not be asked in exam: Synthesis of essential amino acids, breakdown of food and proteins (covered in MOLE-204)

A bit of background

Amino Acids Function:

- **Building Blocks:** Proteins and peptides
- **Precursors:** Nucleotides, enzyme cofactors, other nitrogen-containing biomolecules (e.g., neurotransmitters, pigments).
- **Energy Sources:** Used when there are no better sources (ie., no fats or sugars available).

Sources of Amino Acids:

- **Breakdown of Food:** Digestion of dietary proteins
- **Body's Own Proteins:** Recycling of cellular proteins
- **Synthesis:** From available metabolites

Transamination: A central reaction in the metabolism of amino acids

- First step in the catabolism of L-amino acids
- Removal of the amino group and transferred to acceptors
- **Key Enzymes:** Aminotransferases (e.g., alanine aminotransferase, aspartate aminotransferase).
- **Common Keto Acids:** α-ketoglutarate, oxaloacetate.
- **Reaction:** Oxaloacetate + Glutamate → Aspartate + α -ketoglutarate (enzyme: Aspartate aminotransferase)
- **Reversible –** easily, depending on the concentrations of the substrates

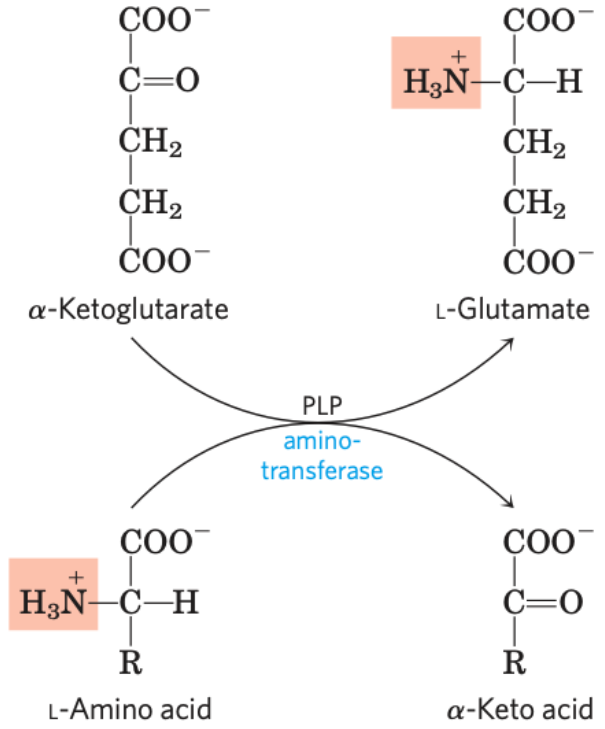


FIGURE 18–4 **Enzyme-catalyzed transaminations.** In many aminotransferase reactions, α-ketoglutarate is the amino group acceptor. All aminotransferases have pyridoxal phosphate (PLP) as cofactor. Although the reaction is shown here in the direction of transfer of the amino group to α-ketoglutarate, it is readily reversible.

Nitrogen metabolism

1. **NAD(P)+/NAD(P)H**: These coenzymes are crucial in redox reactions and help remove nitrogen from amino acids.
2. **Glutamate Dehydrogenase (GDH)**: This enzyme, along with glutamine synthetase, helps incorporate ammonium nitrogen into amino acids.
3. **Reverse Reaction**: In humans and other vertebrates, GDH often works in reverse, converting glutamate into α-ketoglutarate and ammonium (NH4+).

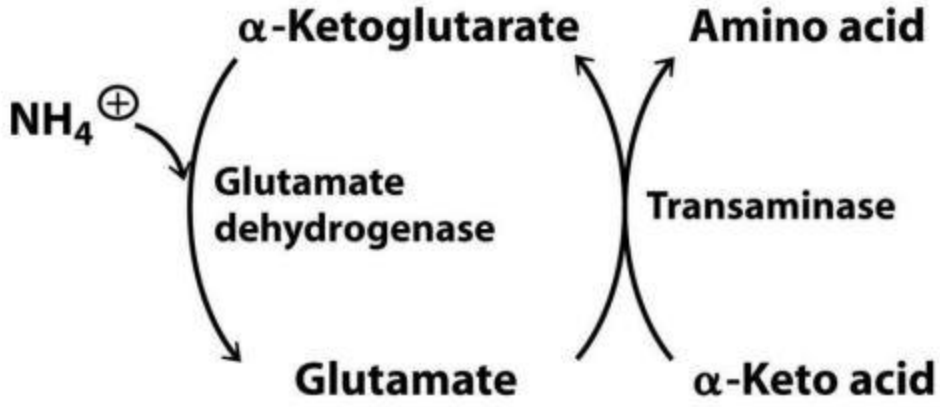


Figure 17-8a Principles of Biochemistry, 4/e
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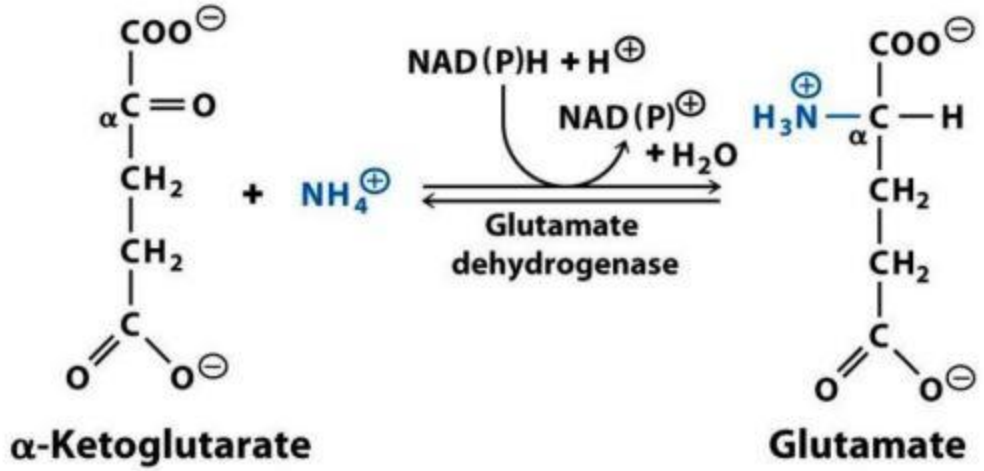

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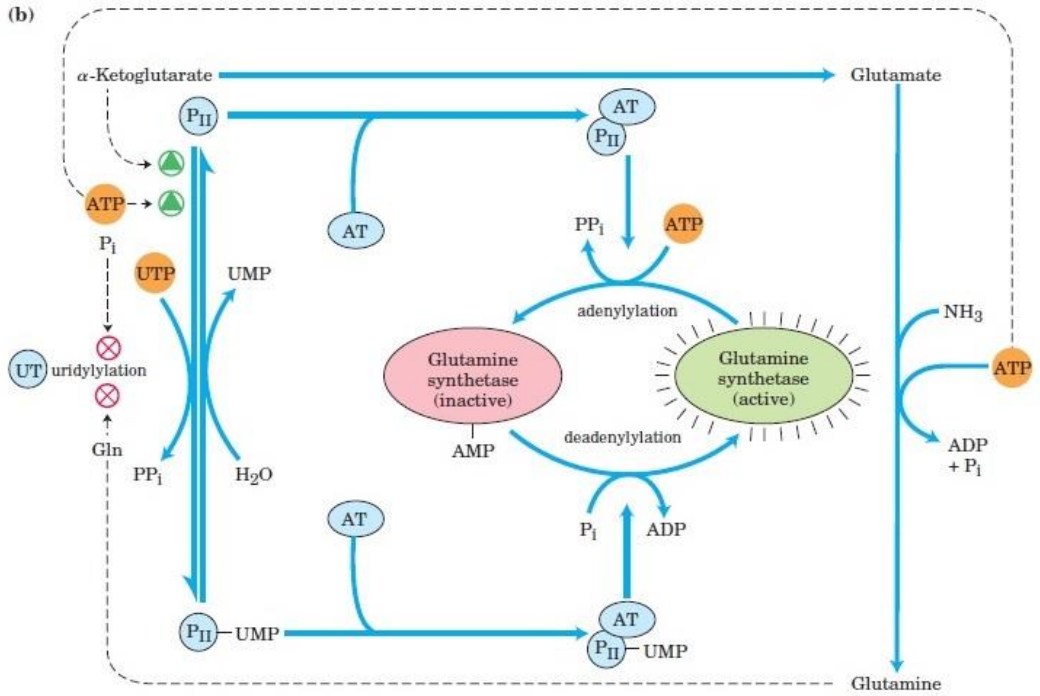
Ammonium nitrogen is incorporated into amino acids in reactions catalyzed GS and glutamine synthetase

Glutamine Synthetase (GS)

- The enzyme Glutamine Synthetase (GS) catalyzes the conversion of glutamate to glutamine in two steps:
- 1. activation of the carboxylate group by ATP
- 2. Binding of ammonium ion (NH4+)
- The reaction is practically irreversible, with the reverse reaction involving hydrolysis catalyzed by glutaminase.
- The enzyme is tightly regulated, with α-Ketoglutarate (α-KG) activating it and glutamine inhibiting it. Additionally, the enzyme and its regulatory proteins undergo covalent modifications.



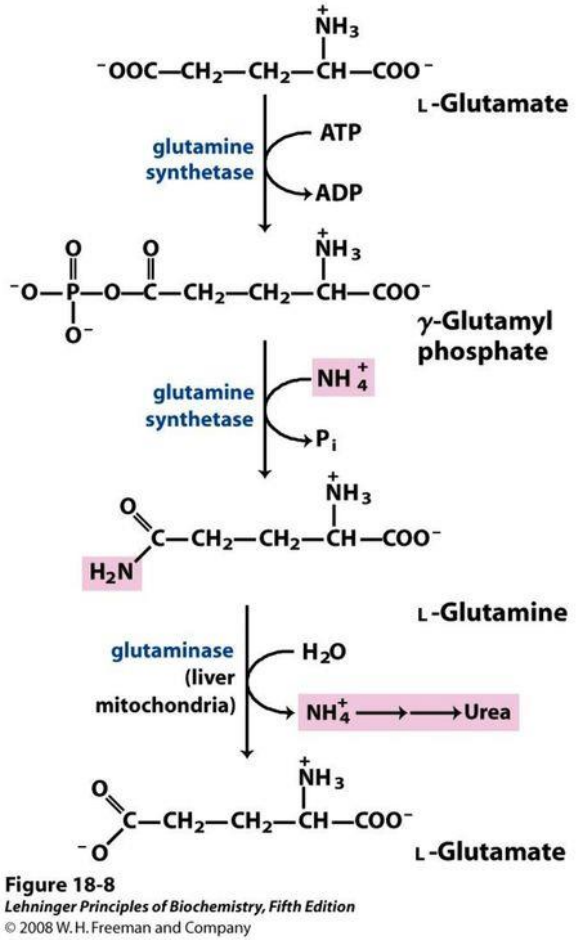


Figure 18-8
Lehninger Principles of Biochemistry, Fifth Edition

Pyridoxal phosphate (PLP) as a cofactor for transaminases

1. PLP is the active form of vitamin B6.
- Functions in transamination and decarboxylation of amino acids.

2. Binding to Transaminase:
- PLP binds to transaminase, forming a Schiff's base with the amino acid.

3. Electron Sink:
- PLP's structure acts as an electron sink, weakening bonds and aiding reactions.

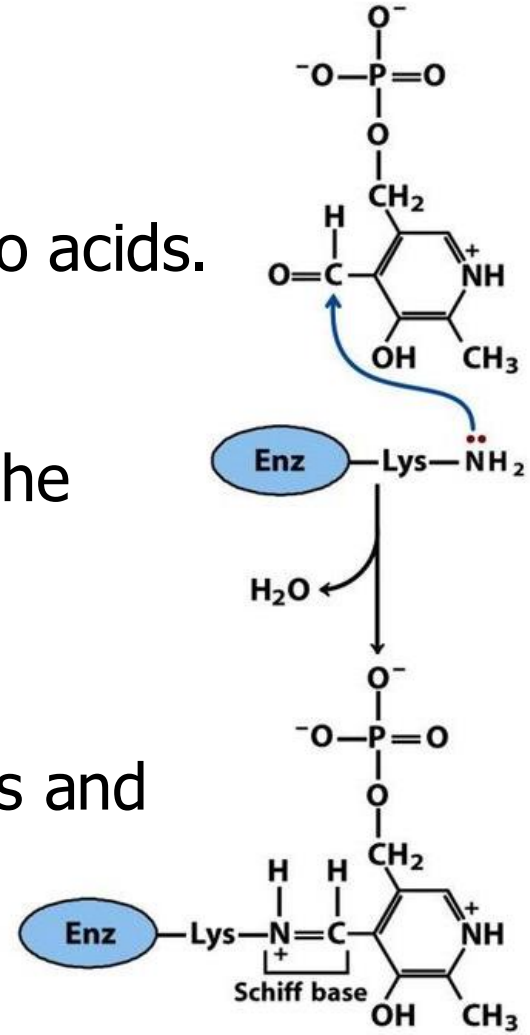


Figure 18-5b
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Activity of PLP in transamination

1. **Release of α-Keto Acid**: When an amino acid enters the reaction, it loses its amino group and is converted into an α-keto acid. This means the amino acid is now missing its amino group.
2. **Binding of a New α-Keto Acid**: In the next step, a different α-keto acid comes into the reaction. This new α-keto acid binds to pyridoxamine phosphate (a form of PLP that has already accepted an amino group from the first amino acid).
3. The reactions that happened in the first step now occur in reverse.
4. The amino group from the first amino acid is now attached to the second α-keto acid, turning it into a new amino acid.

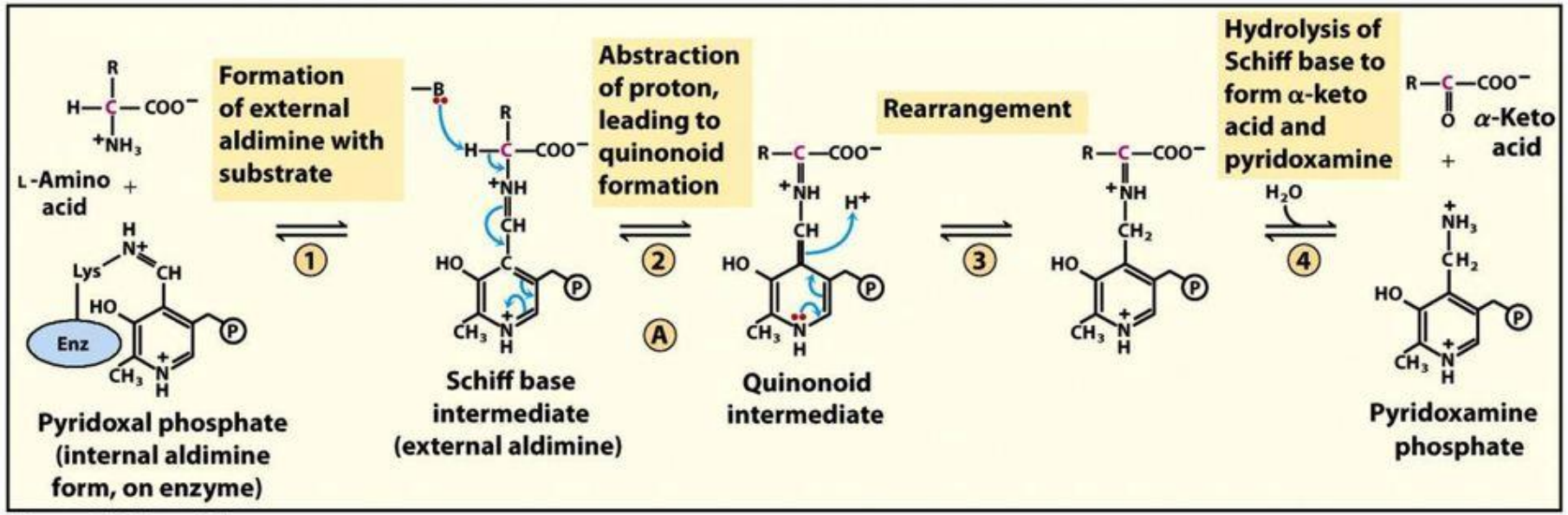

Figure 18-6 part 1
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Biosynthesis of amino acids

Non-essential amino acids

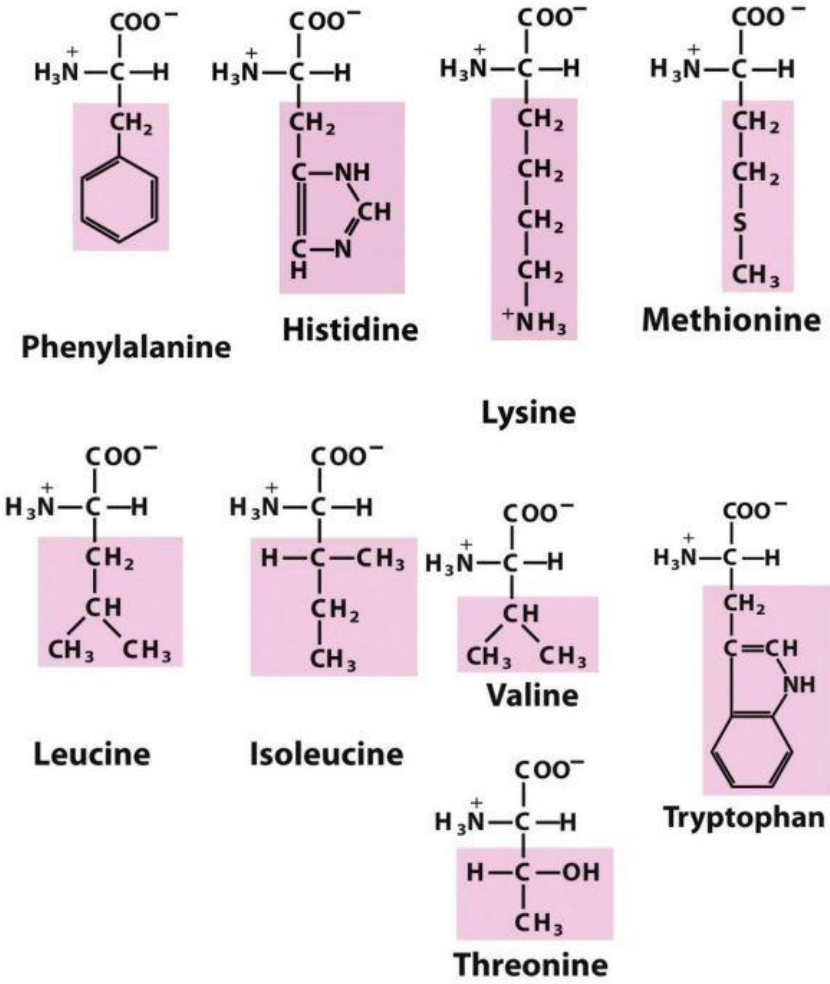
Can be synthesized by the human body even if not obtained from the diet.

Amino Acid	Precursor	Mechanism
Alanine	Pyruvate	Transamination of pyruvate
Asparagine	Aspartate	Amidation of aspartate
Aspartic Acid	Oxaloacetate	Transamination of oxaloacetate
Glutamic Acid	α-Ketoglutarate	Reductive amination of α-ketoglutarate
Glutamine	Glutamate	Amidation of glutamate
Glycine	Serine	Conversion of serine
Proline	Glutamate	Reduction and cyclization of glutamate
Serine	3-Phosphoglycerate	Oxidation and transamination of 3-phosphoglycerate
Tyrosine	Phenylalanine	Hydroxylation of phenylalanine
Cysteine	Serine and Methionine	Conversion of serine using sulfur from methionine

Essential amino acids (in humans)

- Cannot be synthesized by the human body
- Must be obtained through diet
- synthesis ability usually only by microbes and plants
- the chemical structure of the side chain is demanding in terms of synthesis

Amino Acid	Side Chain Nature
Histidine	Basic, Imidazole
Isoleucine	A branched aliphatic chain ,Nonpolar
Leucine	A branched aliphatic chain
Lysine	Primary amino group ,Basic
Methionine	Thioether,Nonpolar
Phenylalanine	Aromatic ring (benzene)
Threonine	Secondary alcohol group,Polar, Uncharged
Tryptophan	Aromatic ring (indole)
Valine	A branched aliphatic chain, Nonpolar

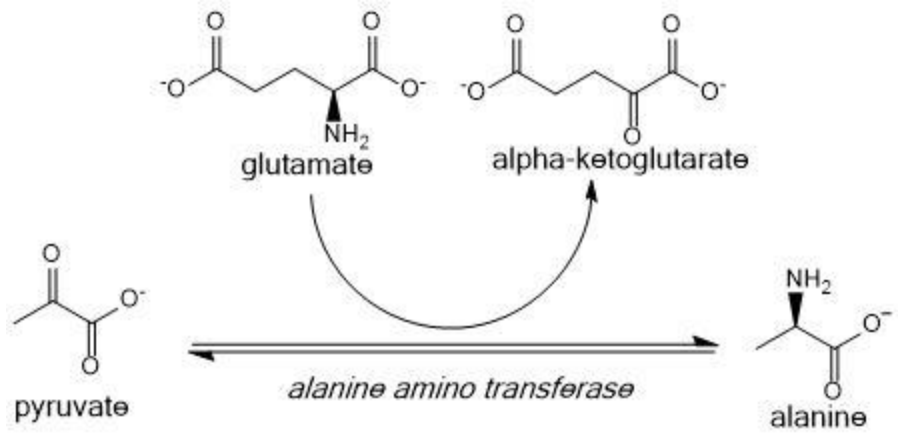


Biosynthesis of non-essential amino acids in mammals

Alanine, aspartate and asparagine biosynthesis

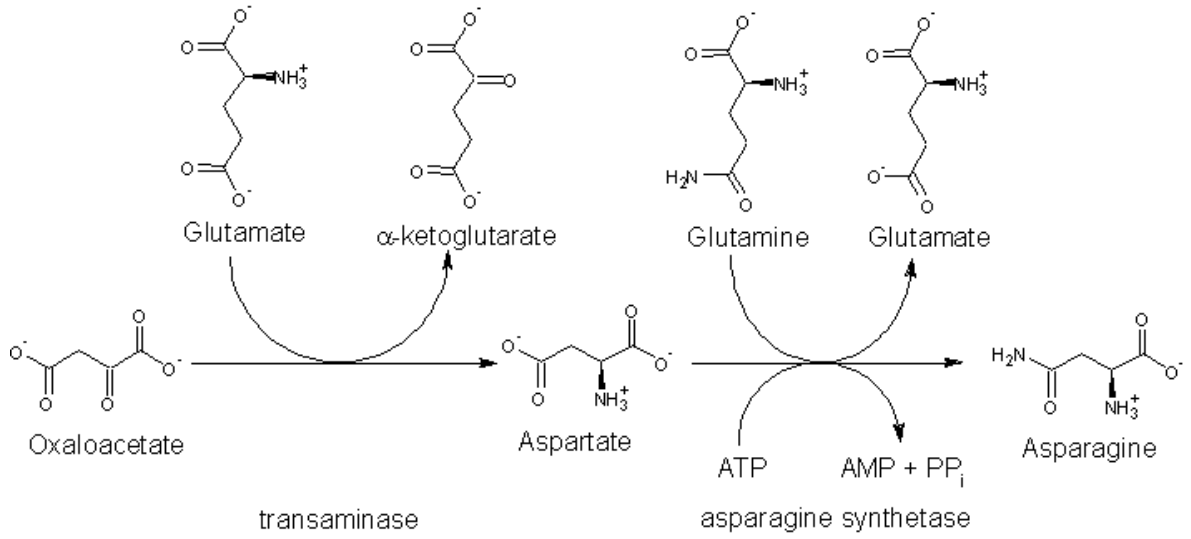
Alanine: Formed by transamination from pyruvate.

Aspartate: Formed by transamination from oxaloacetate.



Asparagine Synthesis:

- Catalyzed by Asparagine Synthase:
- The amide group of glutamine is transferred to the side chain of aspartate.
- Glutamine is converted to glutamate in the process.



Glutamate and Glutamine biosynthesis

- Glutamate is a precursor for glutamine
- Catalysis by glutamine synthetase
- Activation by phosphorylation: The -carboxylate group of glutamate is activated by phosphorylation.
- Ammonium ion displacement: The ammonium ion displaces the phosphoryl group → the formation of glutamine

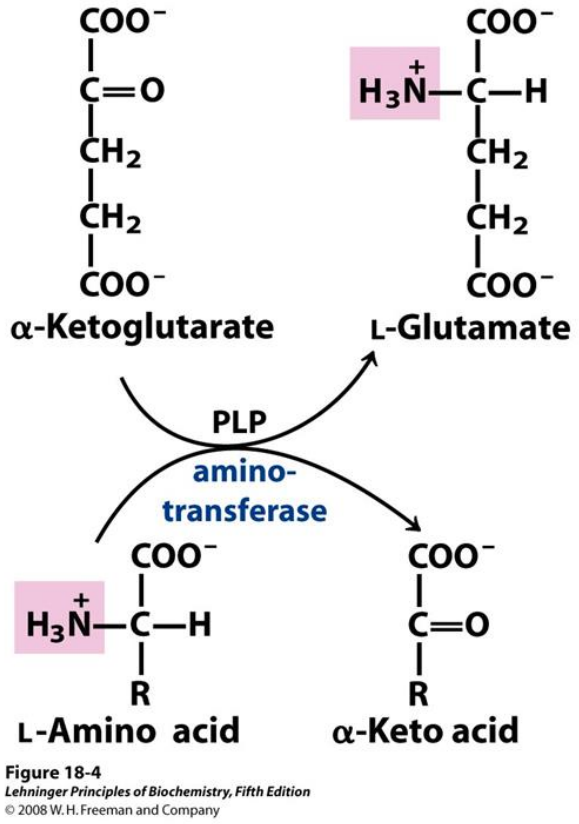


Figure 18-4
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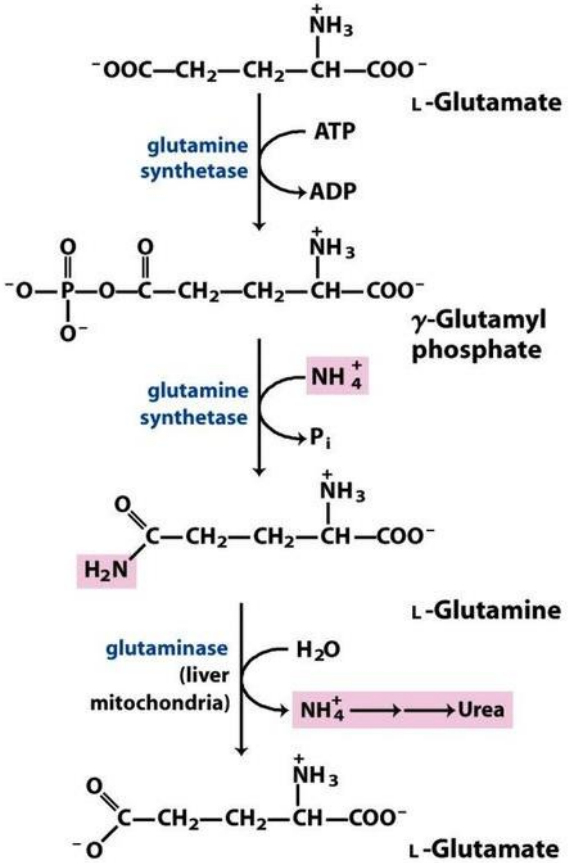
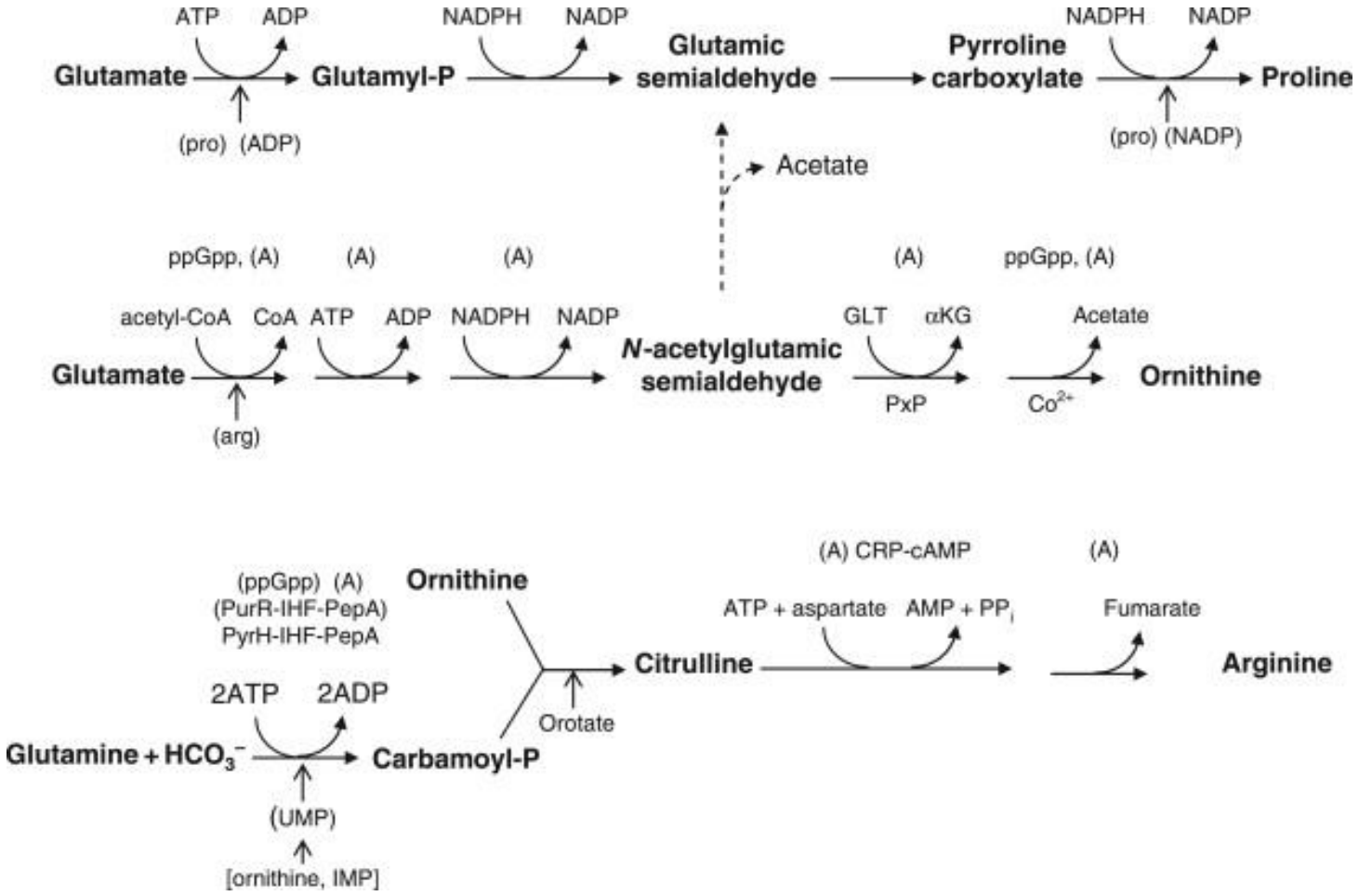


Figure 18-8
Lehninger Principles of Biochemistry, Fifth Edition

Proline and arginine

- **Starting Material**: Glutamate
- **Glutamate as precursor for Ornithine**:
- Non-protein amino acid
- Important intermediate in amino acid metabolism
- Key role in the urea cycle

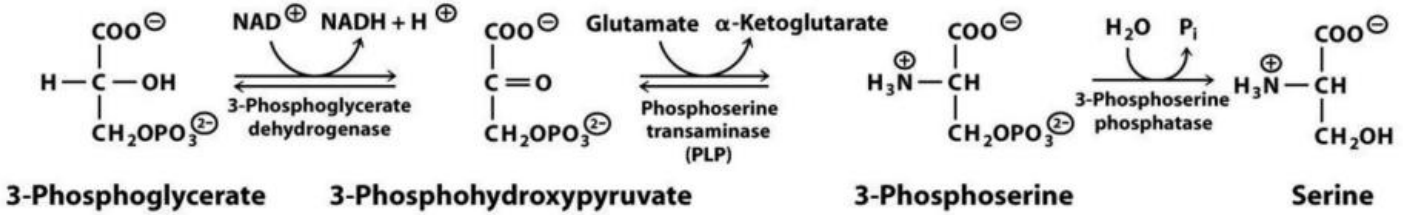


Serine and Glycine

Serine and glycine are synthesized from glycolysis intermediates.

- 3-Phosphoglycerate

Precursor for serine and glycine.



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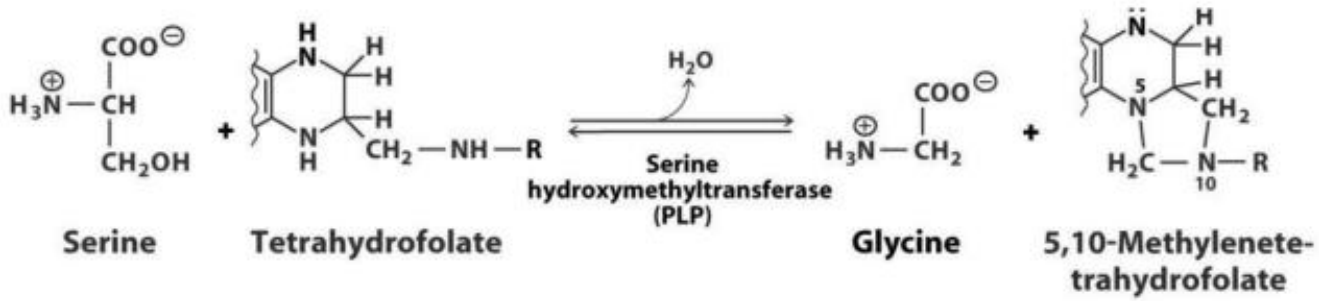
- Tetrahydrofolate (THF):

Derivative of folic acid (vitamin B group).

Cofactor/cosubstrate in one-carbon unit transfers.

Essential in amino acid and nucleotide metabolism.



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Cysteine

- Synthesized from serine

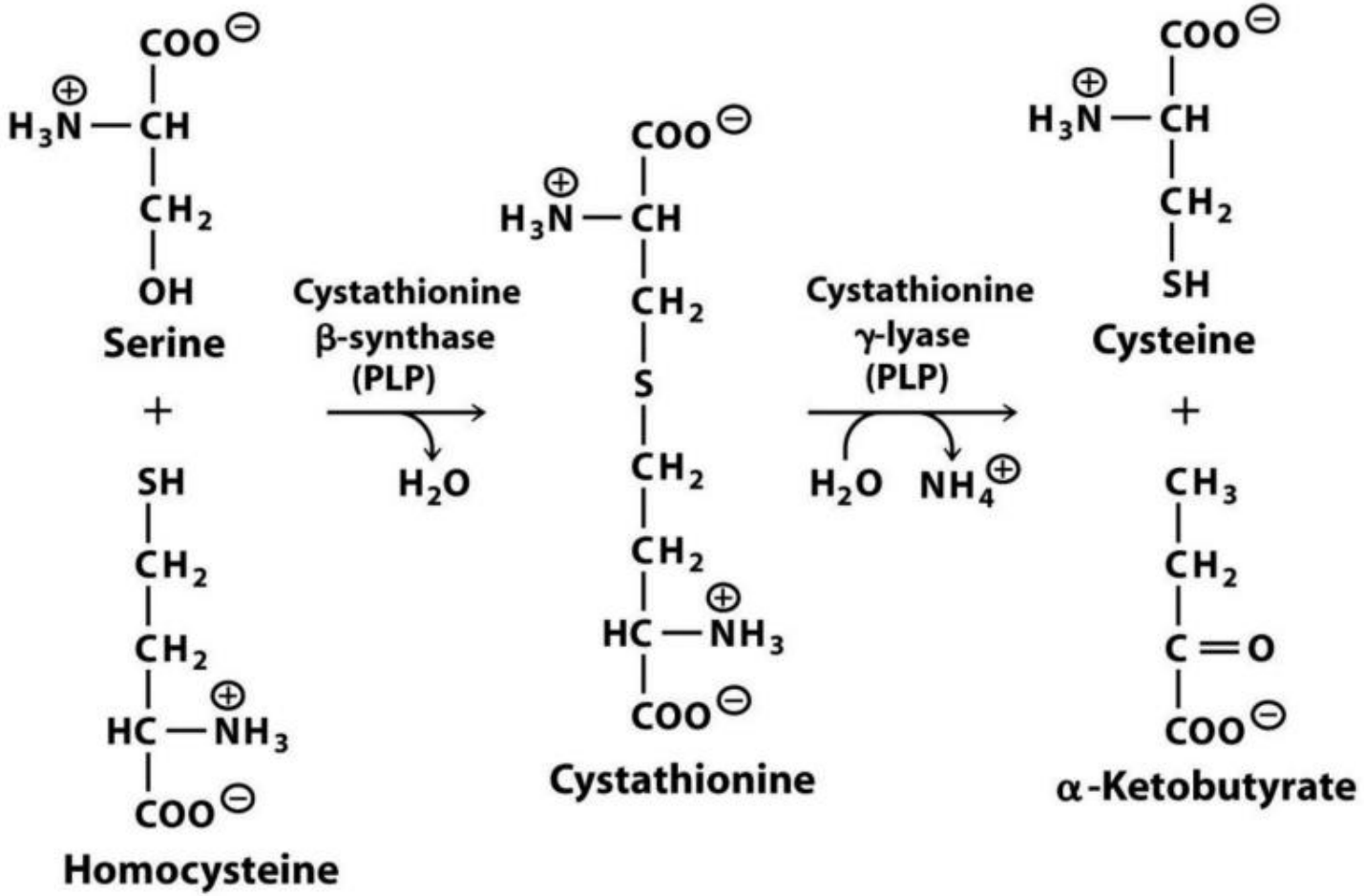
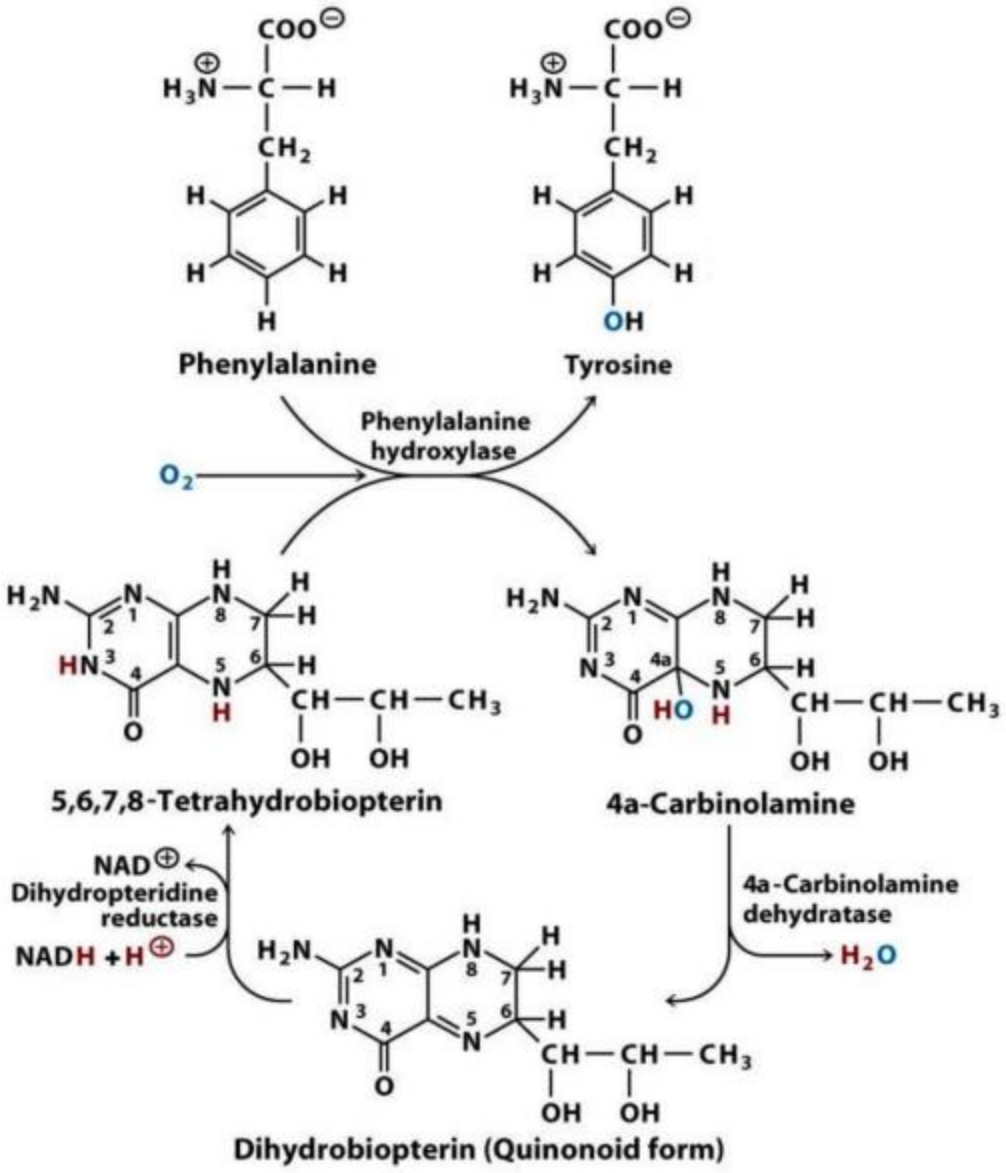


Figure 17-17 Principles of Biochemistry, 4/e

Tyrosine

- Phenylalanine Hydroxylase Enzyme: catalyzes the conversion of **phenylalanine** to tyrosine.
- Hydroxylation Reaction:This reaction involves the hydroxylation of the benzene ring in phenylalanine, adding a hydroxyl group (-OH) to form tyrosine.
- The enzyme requires a cofactor called tetrahydrobiopterin (BH4) to facilitate the hydroxylation process.
- Molecular oxygen (O2) is also involved, with one oxygen atom being incorporated into the hydroxyl group and the other is used to regenerate BH4.
- enzyme deficiency => phenylketonuria



Catabolism of amino acids

Amino acid breakdown: Catabolism

- Primarily in the **liver**: starts with transamination.
- Amino nitrogen of amino acids is transported to the liver, especially via alanine (from muscles) and glutamine (from muscles and other tissues).
- Amino nitrogen is directed to the urea cycle via glutamate.
- **Basic plot of catabolism:**
- The amino group is separated from the carbon skeleton (transamination; oxidative deamination).
- The carbon frame is utilized as a substrate for energy metabolism or biosynthesis.
- Amino nitrogen is removed from cells (and the body) in the form of urea or used in nitrogen-demanding biosynthesis.

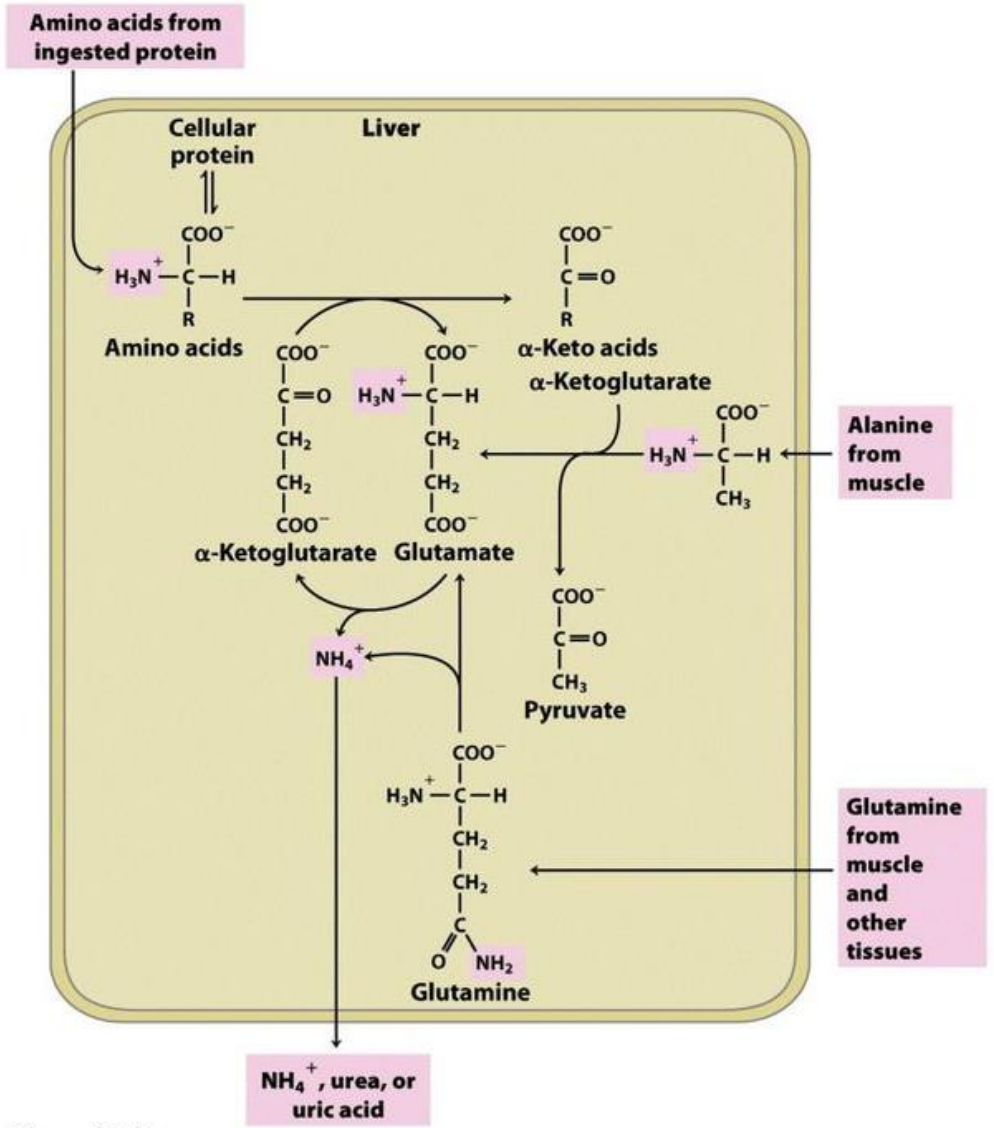


Figure 18-2a
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Amino acid breakdown: deamination

1.Transamination:

1. Amino groups of amino acids are transferred to α-ketoglutarate or oxaloacetate, producing glutamate and aspartate.
2. Glutamate (and glutamine) and aspartate can donate amino nitrogen to the urea cycle.

2.Oxidative Deamination:

1. Catalyzed by glutamate dehydrogenase with NAD(P)+ as a coenzyme.
2. The amino group of glutamate is cleaved off, resulting in α-ketoglutarate, reduced coenzyme [NAD(P)H], and free NH4+ ion.
3. Two mechanisms: glutamate is oxidized (donates electrons), hence "oxidative" deamination.

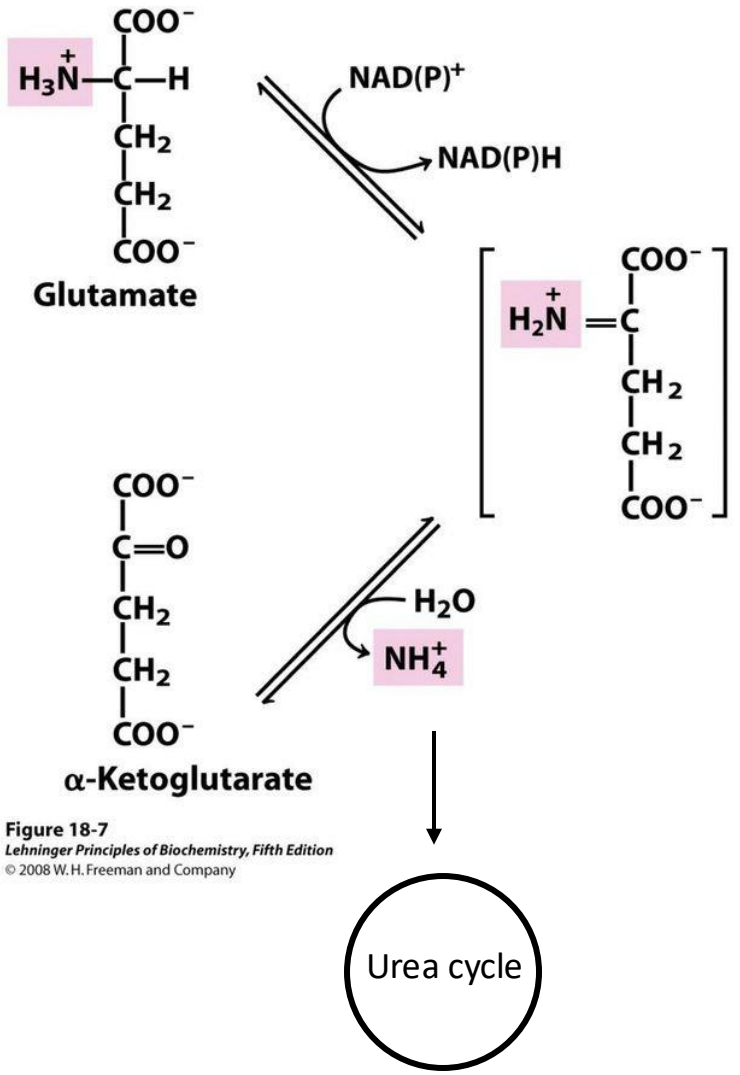

Figure 18-7
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Breakdown of amino acids: Glucogenic and ketogenic amino acids

Glucogenic Amino Acids:

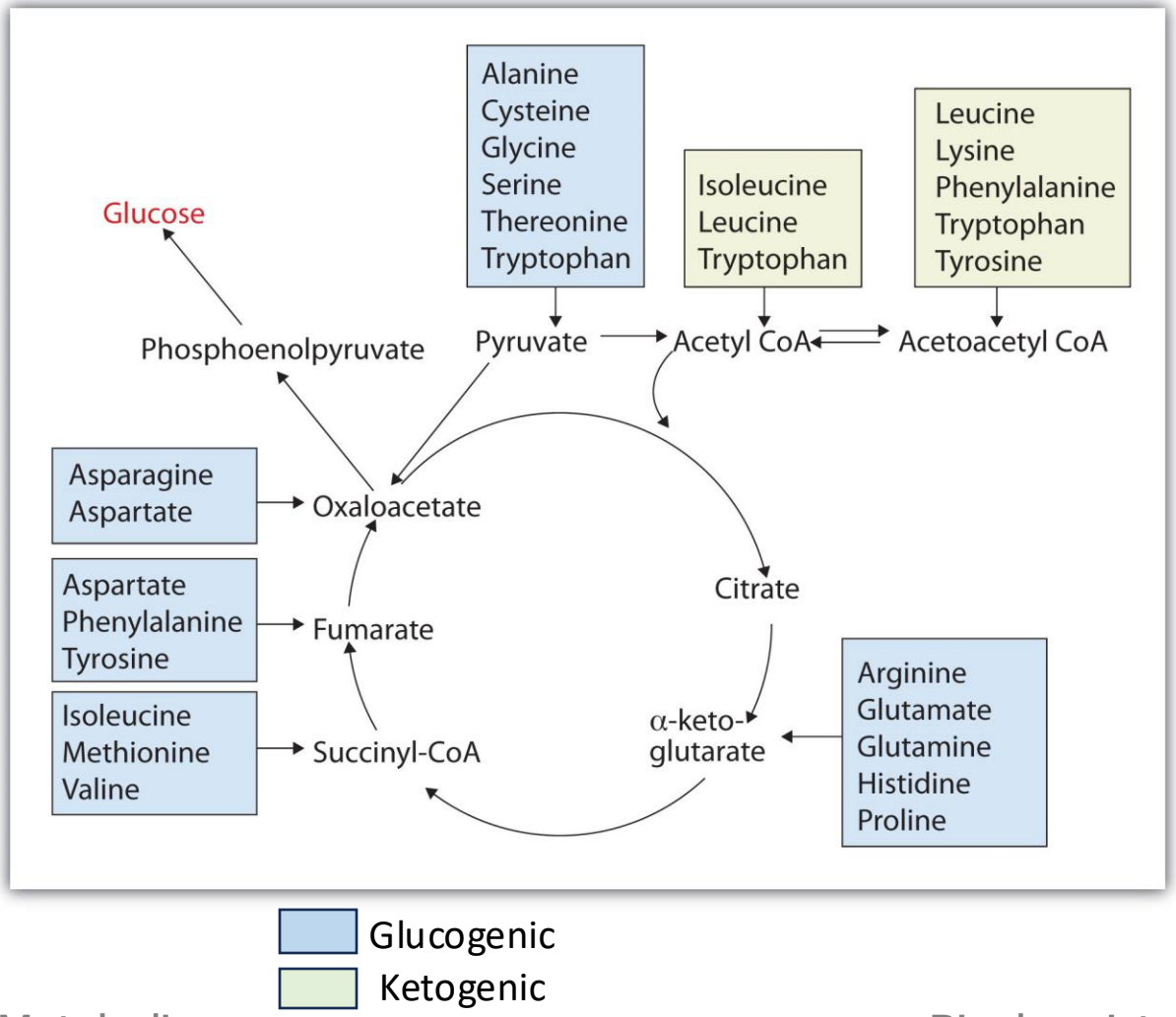
- Broken down into pyruvate or citric acid cycle intermediates.
- These intermediates can be used to produce glucose through gluconeogenesis.

Ketogenic Amino Acids:

- Converted into acetoacetate or acetyl-CoA.
- These compounds are used to produce ketone bodies or fats, not glucose.

- Some amino acids are both glucogenic and ketogenic.
- Their carbon skeletons split into parts with different metabolic fates.

- Acetyl-CoA and acetoacetate cannot be used to make glucose because they are fully oxidized in the citric acid cycle.

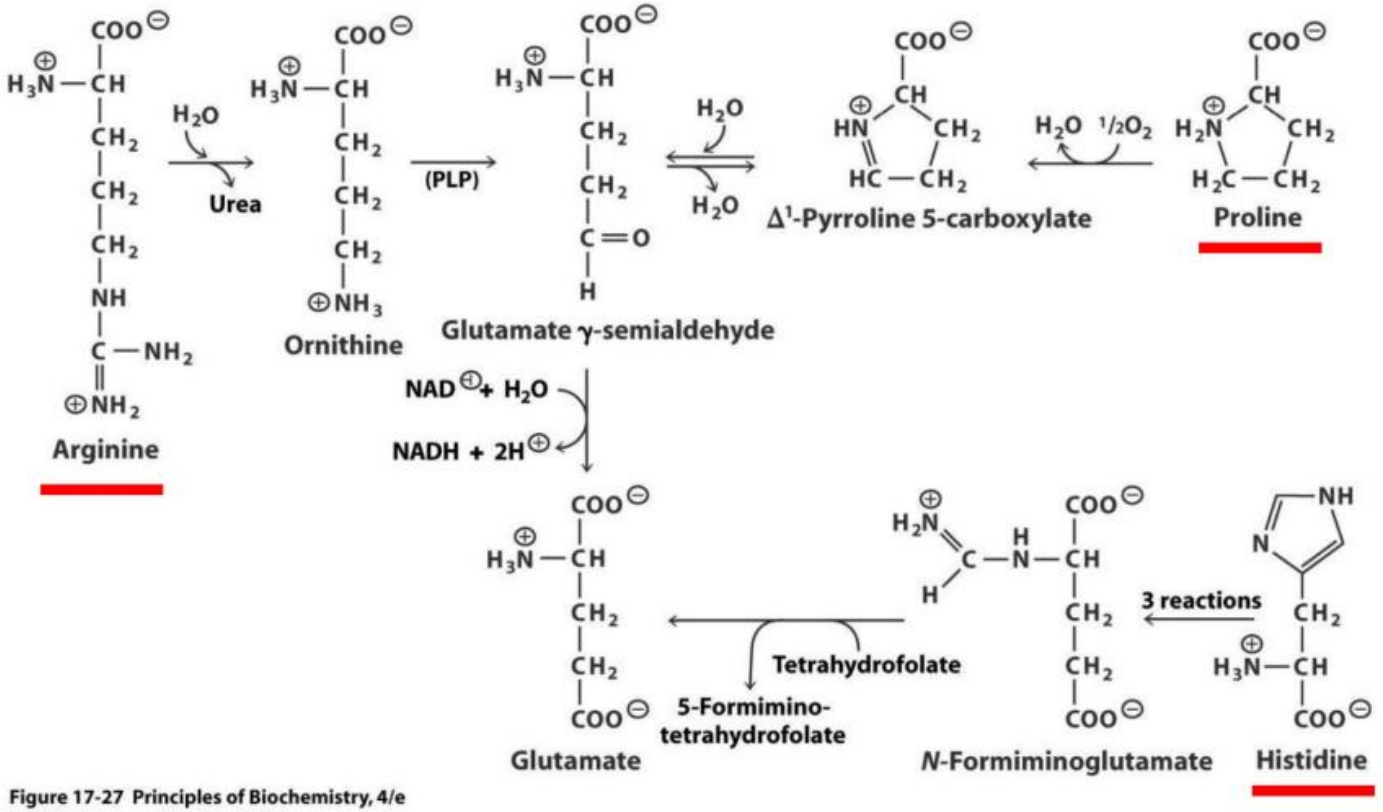


Arginine, Proline, and Histidine Catabolism

These amino acids are glucogenic and are metabolized into glutamate.

Common Intermediate

The breakdown pathways of arginine and proline end in a common intermediate, glutamate semialdehyde.



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Branched-chain amino acids (BCAAs)

Leucine, isoleucine, and valine.

- A transaminase specific for leucine, valine, and isoleucine.
- A decarboxylase specific for the corresponding keto acids.
- The first steps of decomposition produce three different acyl groups.
- These acyl groups are further metabolized into acetyl-CoA and/or succinyl-CoA.

Pathways:

- Leucine: Converted to acetyl-CoA (ketogenic).
- Valine: Converted to succinyl-CoA (glucogenic).
- Isoleucine: Converted to both acetyl-CoA and succinyl-CoA (both ketogenic and glucogenic).

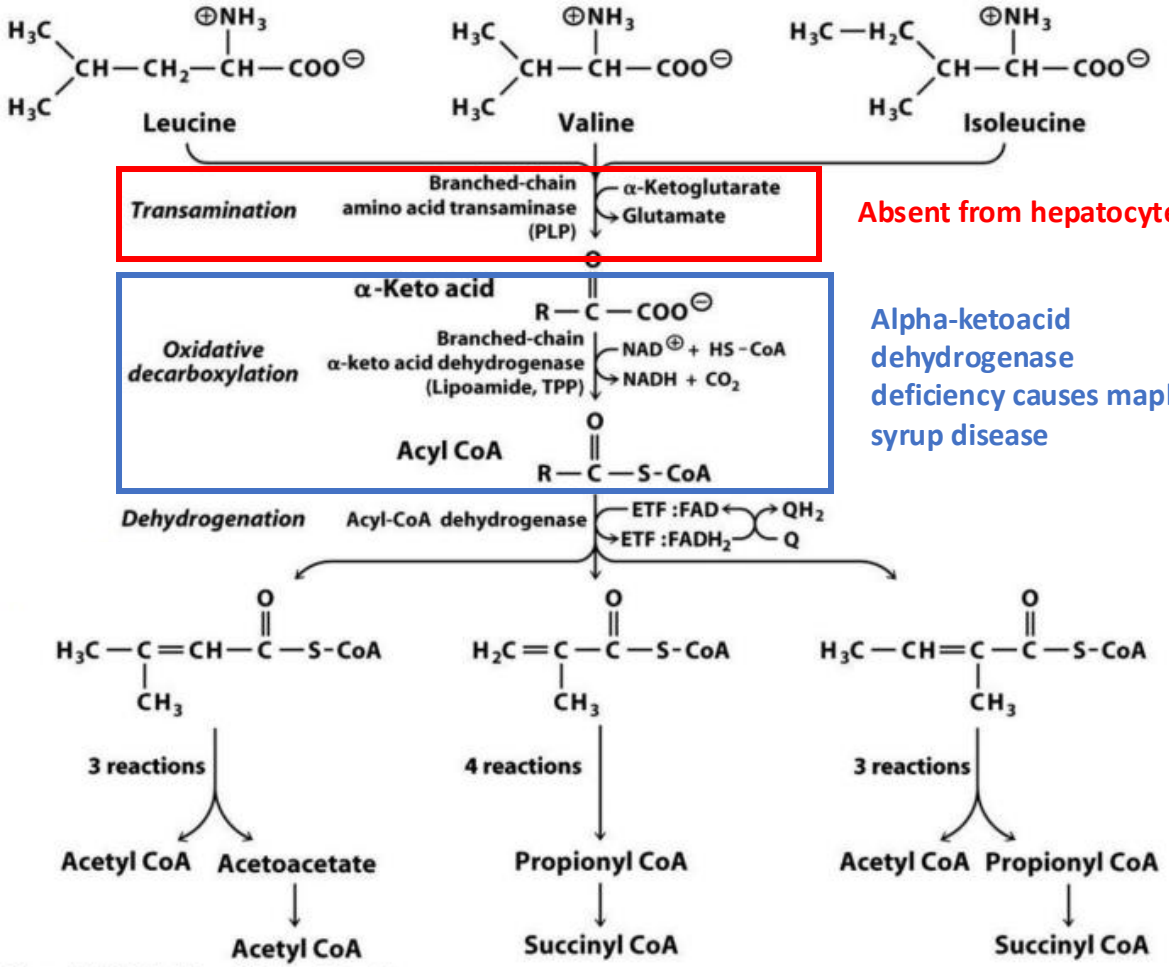
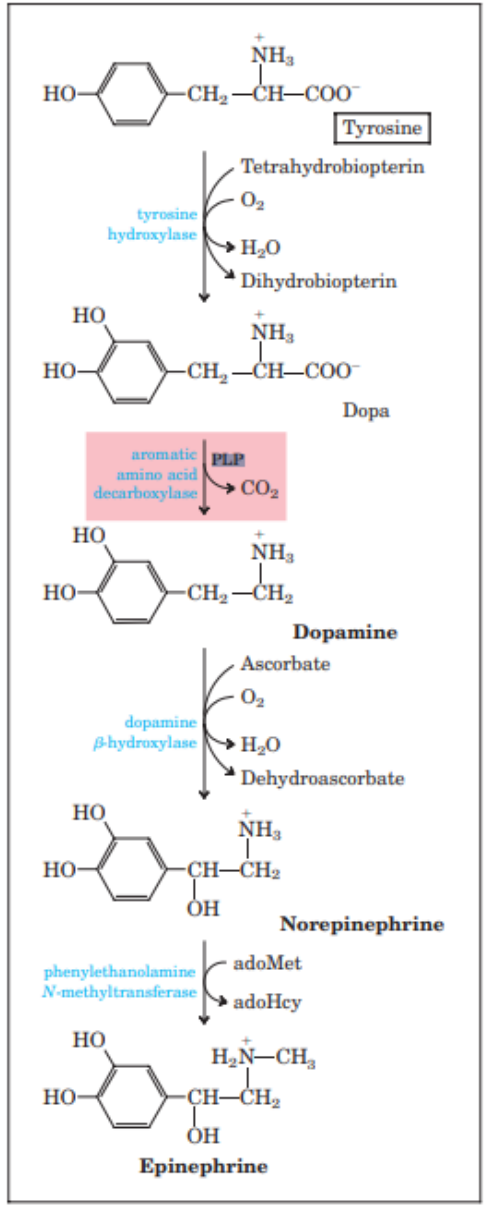


Figure 17-30 Principles of Biochemistry, 4/e

Pyridoxal phosphate (PLP)

- As a cofactor for amino acid decarboxylases
- Removal of a carboxyl group, resulting in the formation of amines.
- PLP forms a Schiff base (aldimine) with the amino group of the amino acid substrate.

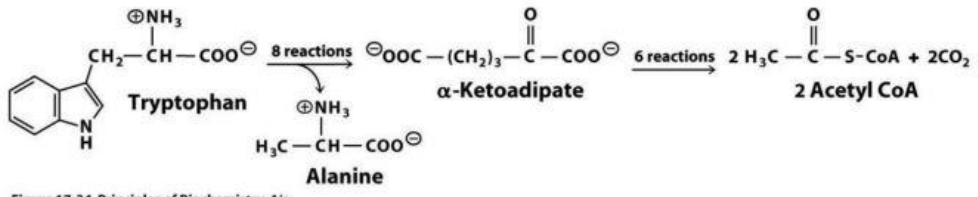
- This intermediate facilitates the removal of the carboxyl group, leading to the production of the corresponding amine and CO2.



Catabolism of phenylalanine, tyrosine and tryptophan

- Glucogenic and Ketogenic:
-
- - Phenylalanine and Tyrosine Degradation:
- - Phenylalanine is degraded via tyrosine.
- - The first step is catalyzed by phenylalanine hydroxylase (deficiency causes phenylketonuria).
- - Alkaptonuria is caused by a deficiency in the homogentisate-degrading enzyme.
- - End products are fumarate and acetoacetate.

- Tryptophan Breakdown:
- Multi-step breakdown of tryptophan results in alanine and acetyl-CoA as end products.



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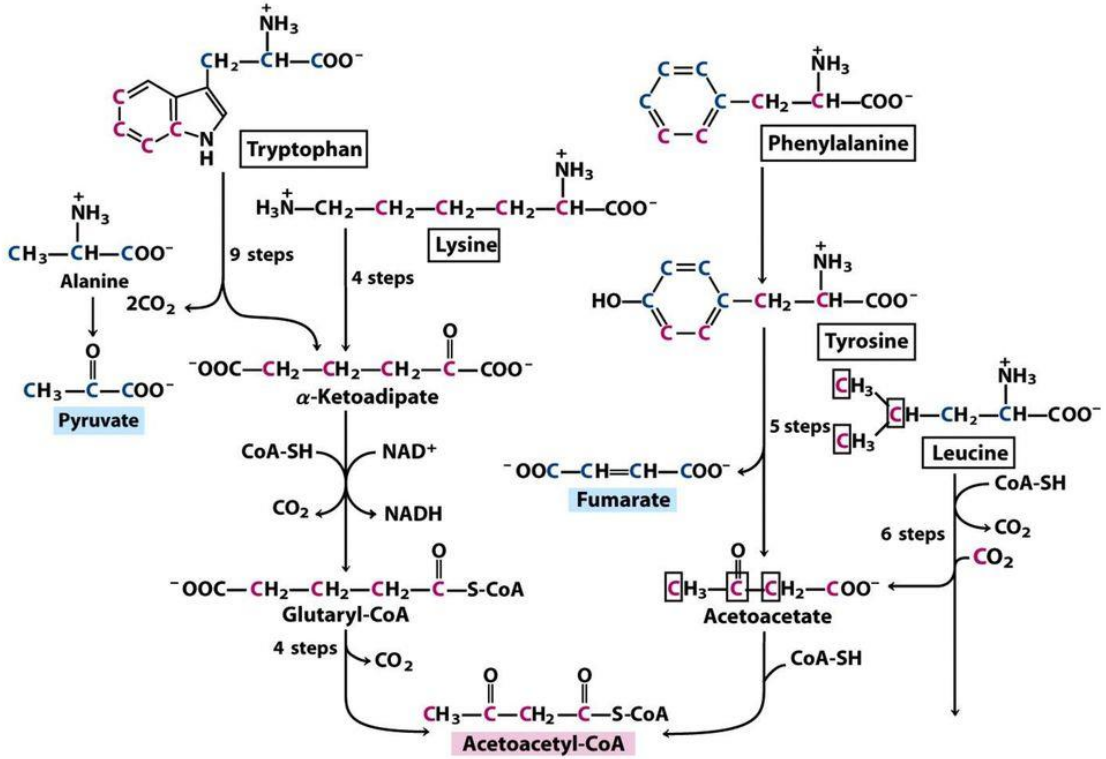

Figure 18-21 part 1
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TABLE 18–2 Some Human Genetic Disorders Affecting Amino Acid Catabolism

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 1 deficiency	<0.5	Urea synthesis	Carbamoyl phosphate synthetase 1	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
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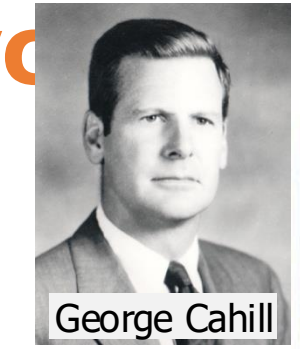
Glucose-Alanine cycle (Cahill Cyc


George Cahill

- Alanine from muscle to liver, glucose from liver to muscle

- proteolysis of muscle proteins produces excess ammonium nitrogen, which is bound (via glutamate) to pyruvate in transamination → alanine; released into the bloodstream
- **Muscle**: waste product called ammonia is produced.
- Converted to alanine to be transferred to the liver.
- **Liver:** liver converts alanine into pyruvate (a key molecule in energy production) and ammonia. Ammonia is converted to Urea and excreted from the body.
- Gluconeogenesis: liver uses the pyruvate, is used as a substrate in gluconeogenesis (2 pyruvate → 1 glucose)
- Produce glucose which will be sent to muscles for energy

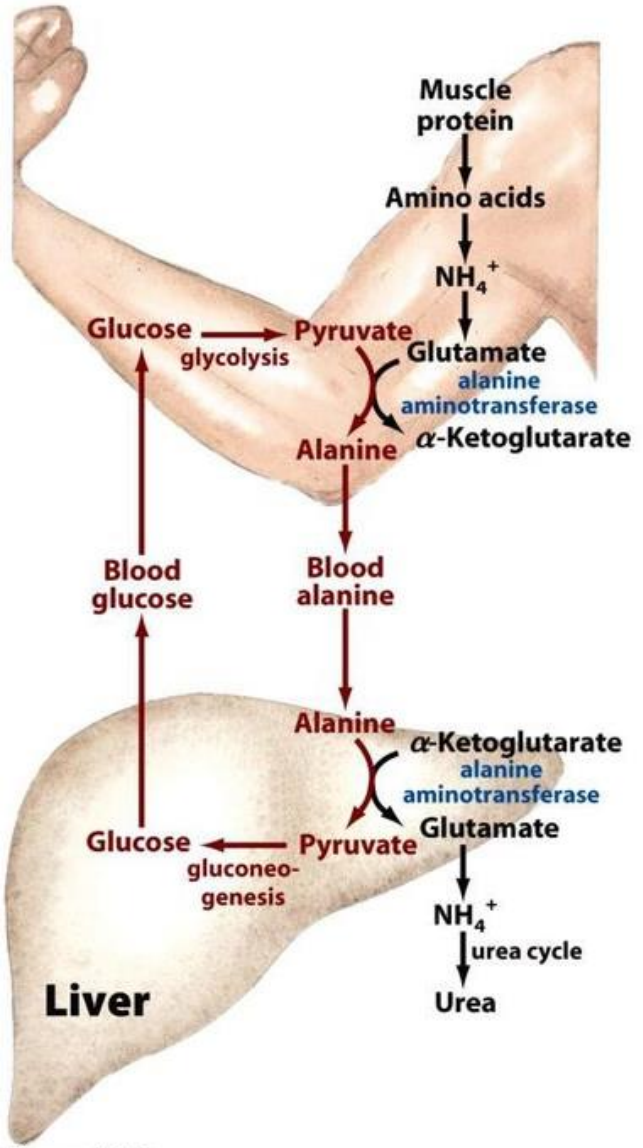


Figure 18-9
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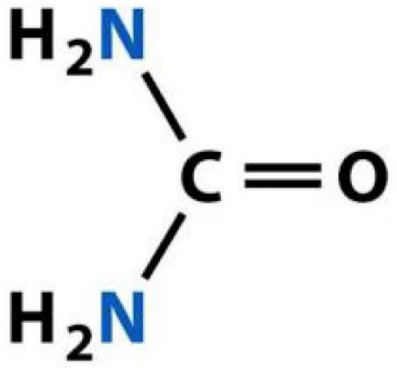
Nitrogen removal and the urea cycle



Urea

Urea cycle

Converts nitrogen from amino acids into urea for excretion.

1. **Nitrogen Transfer**: Nitrogen from amino acids is transferred to arginine.

2. **Hydrolysis**: Arginine is hydrolyzed into ornithine and urea (catalyzed by arginase).

Nitrogen Sources:

Carbamyl Phosphate: Attached to ornithine (catalyzed by carbamyl phosphate synthetase).
Aspartate: Combined with citrulline (catalyzed by argininosuccinate synthetase) to form argininosuccinate.
Mitochondria: Synthesis of carbamyl phosphate.
Cytosol: Other reactions.

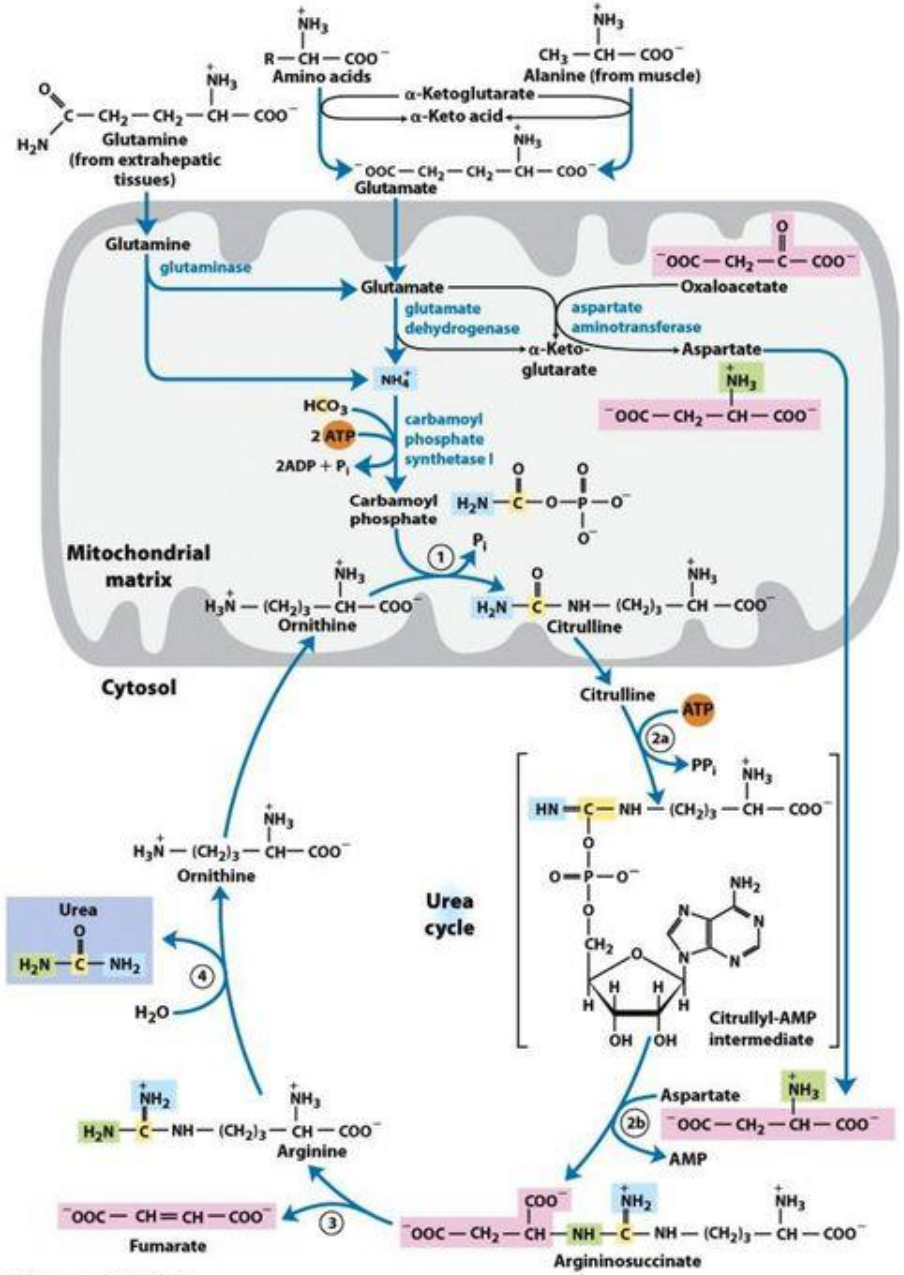


Figure 18-10
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Nitrogen input to the urea cycle

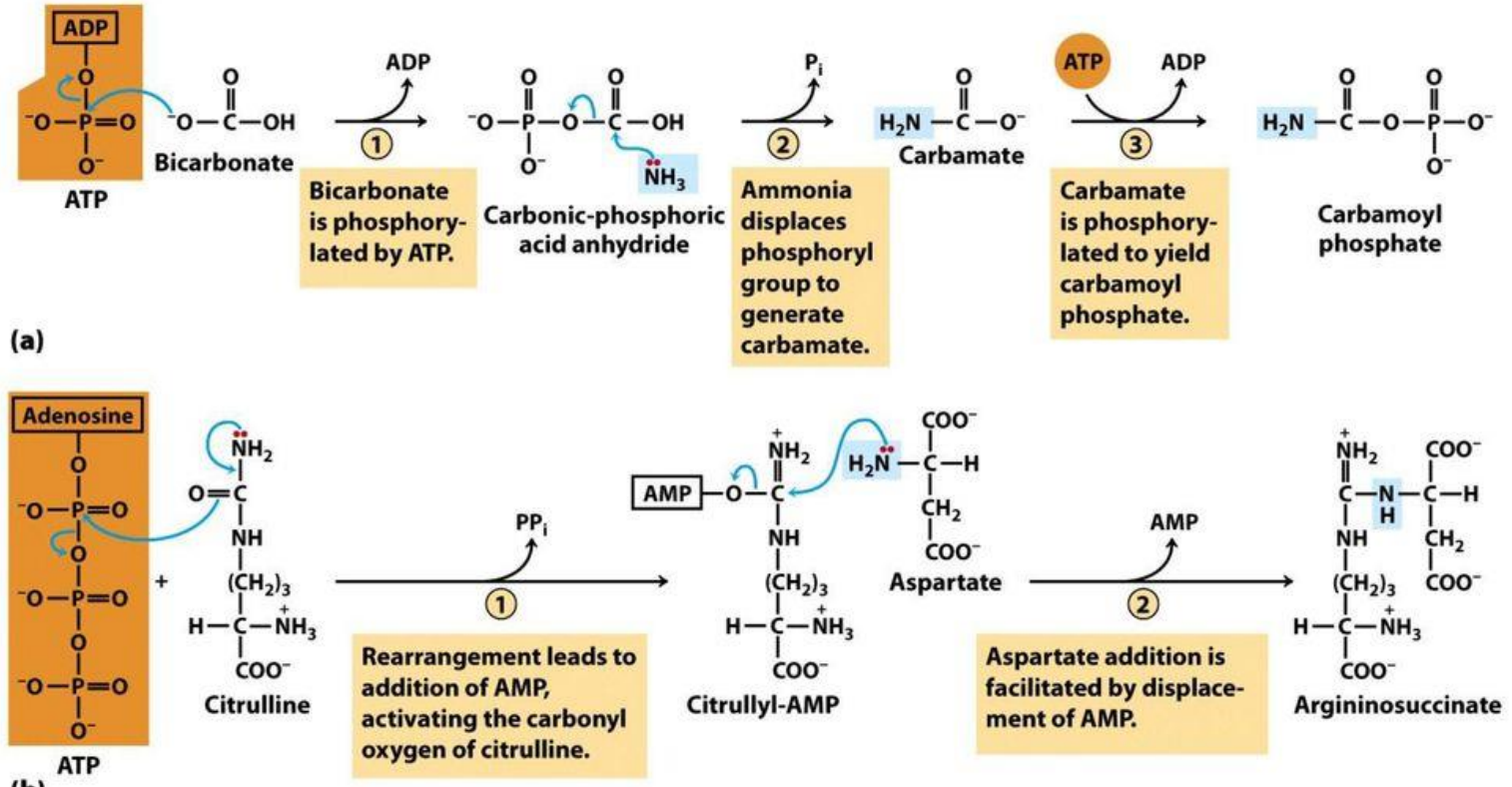

Figure 18-11
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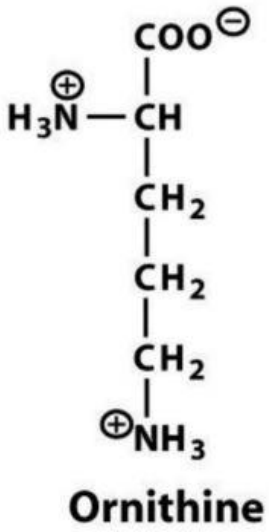
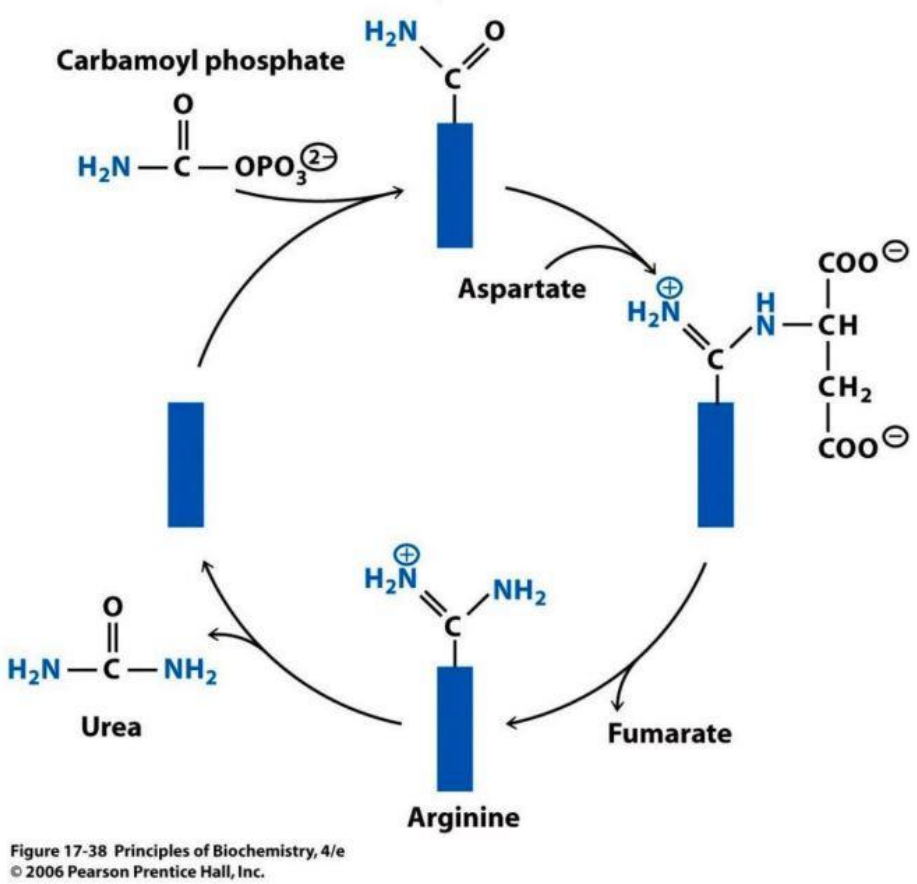
The role of ornithine in the function of the urea cycle

- Acts as a carrier of reacting structures in the urea cycle.
- Regenerates within the cycle (blue bar).
- Similar to the role of oxaloacetate in the citric acid cycle.





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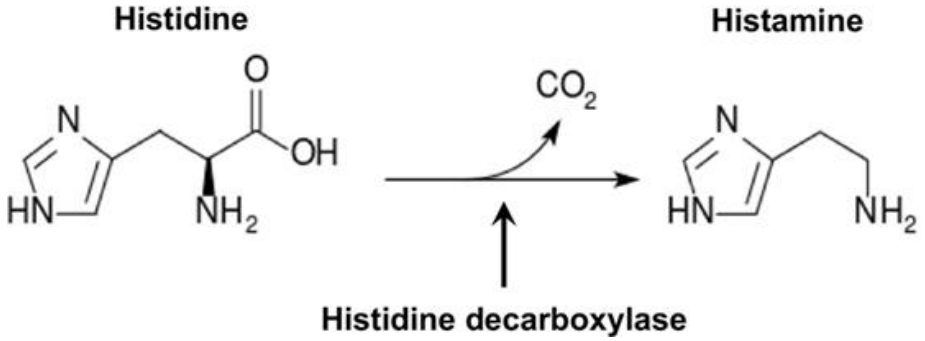
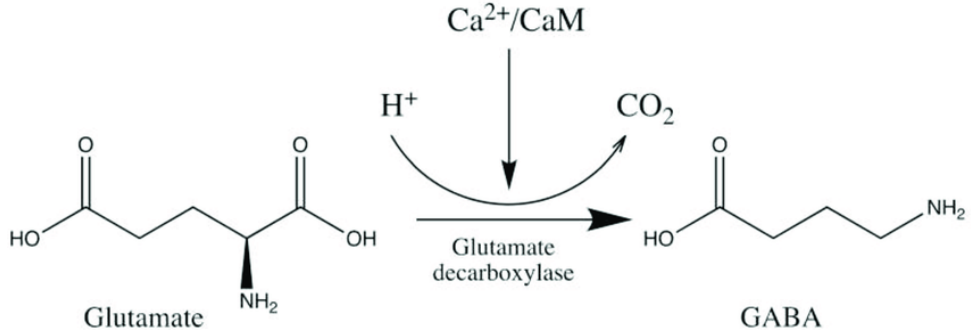
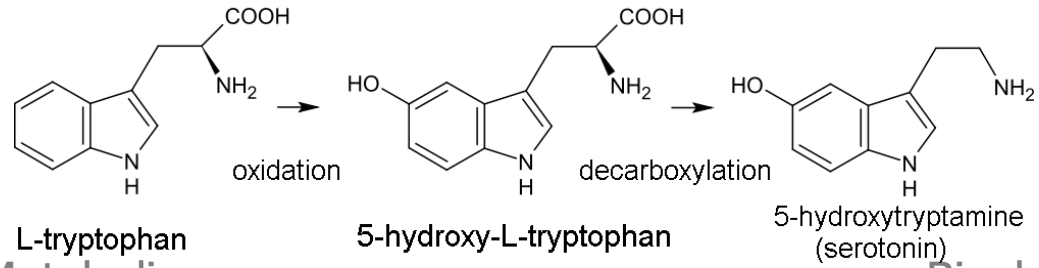
Amino acid derivatives

Serotonin, GABA and histamine

- Decarboxylation of amino acids, make important neurotransmiters:
- **Histidine**: Converts to histamine.
- **Tryptophan**: Converts to serotonin.
- **Glutamate**: Converts to gamma-aminobutyric acid (GABA).
- **Glutamate**: Main excitatory neurotransmitter in the central nervous system.
- **GABA**: Main inhibitory neurotransmitter in the central nervous system.







Catecholamines

- A group of hormones and neurotransmitters that include **dopamine**, **adrenaline (epinephrine)**, and **noradrenaline (norepinephrine)**.

- Derived from the amino acids phenylalanine and tyrosine

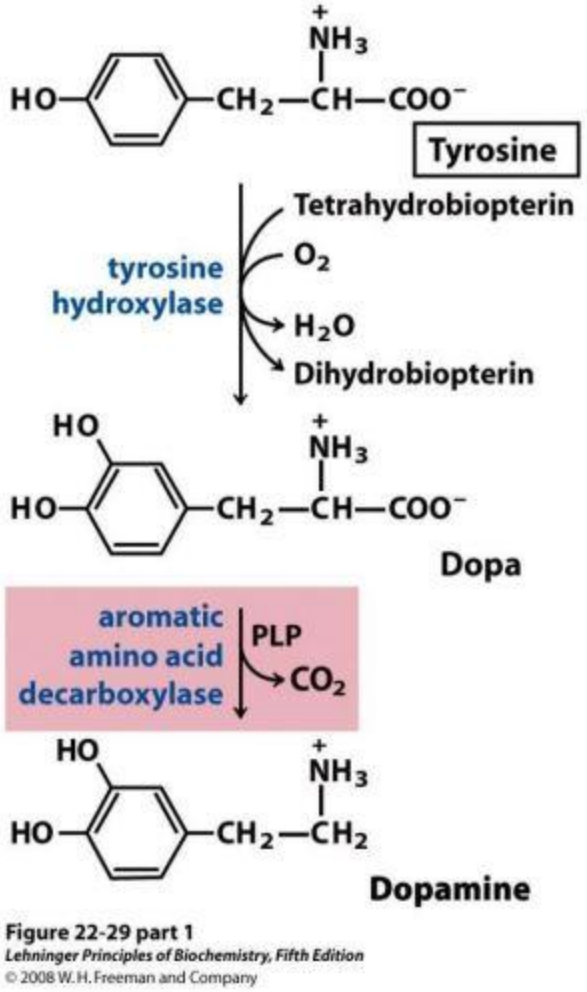


Figure 22-29 part 1
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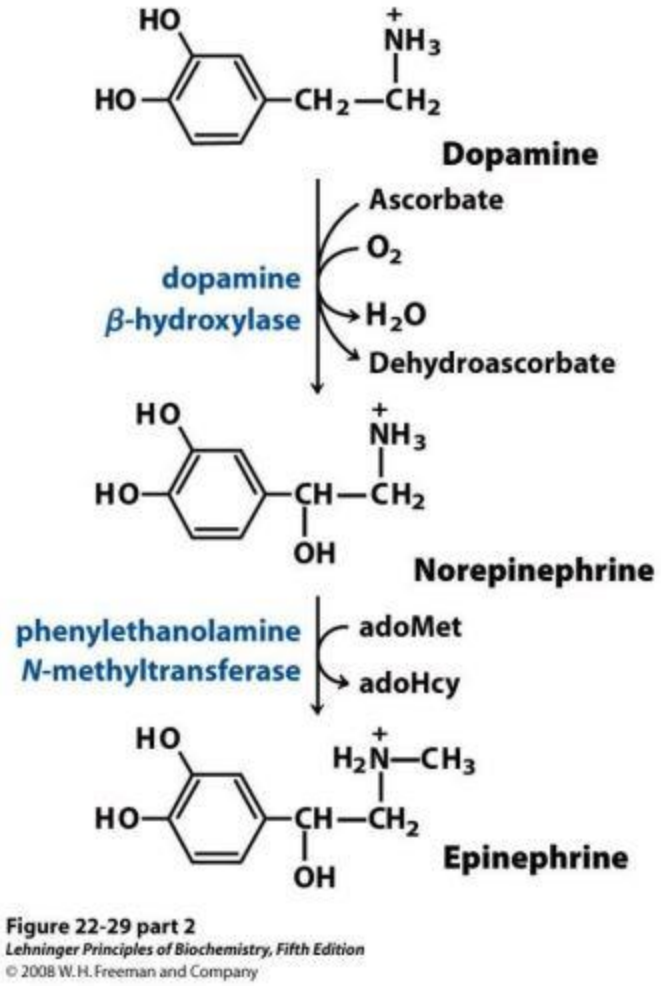

Figure 22-29 part 2
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Glutathione (GSH)

- A tripeptide synthesized enzymatically from glutamate, cysteine and glycine
- Protects cells from oxidative damage by neutralizing ROS.
- Two forms: reduced (GSH) and oxidized (GSSG)

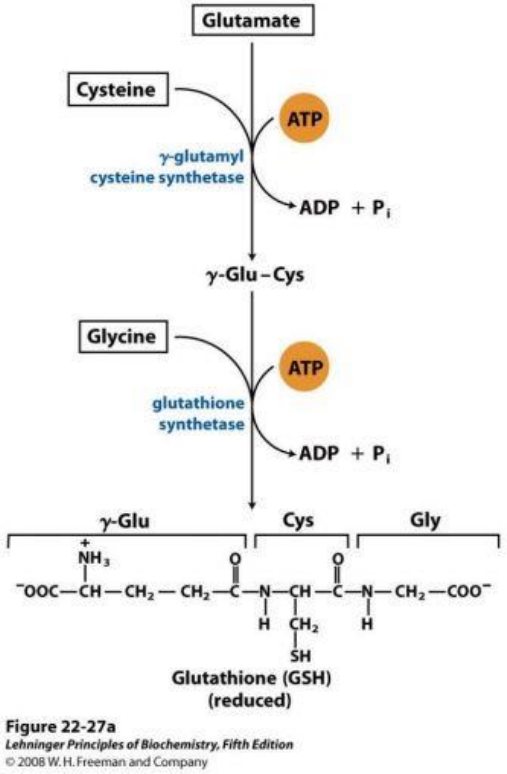

Figure 22-27a
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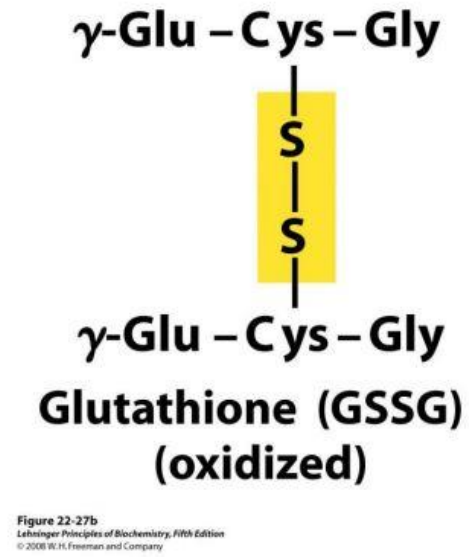

Figure 22-27b
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Summary

- **Amino Acid Synthesis in Humans**: Humans can synthesize about half of the protein amino acids; the rest (9-10 essential amino acids) must be obtained from food.
- **Amino Acid Synthesis in Plants and Microbes**: Capable of synthesizing all 20 protein amino acids.
- **Amino Acid Catabolism:** Begins with transaminations, breaking down proteins.
- **Transamination:** Converts amino acid carbon backbone to corresponding α-keto acid, which breaks down into metabolites for energy metabolism or biosynthesis (e.g., TCA cycle intermediates, pyruvate, acetyl-CoA).
- **Pyridoxal Phosphate:** Key cofactor in amino acid metabolism, especially in transamination and decarboxylation.
- **Glutamate Dehydrogenase:** Catalyzes oxidative deamination, releasing ammonia.
- **Nitrogen Excretion:** Nitrogen from amino acid breakdown is converted to urea (urea cycle) and excreted as ammonium ion from glutamate.