Biological Chemistry Department

Biological Chemistry

General Amino Acid Pathways

Speciality: Pharmacy for foreign students (Language of instructions – English)

Lecturer: ass. prof. Kravchenko G.B.

Lecture Plan

1. *Hemoprotein metabolism in healthy state and under pathology.*

1.1. Iron and hemoprotein digestion and absorption.

1.2. Heme biosynthesis. Porphyrias.

1.3. Heme degradation. Types of Jaundice.

2. Nucleoprotein Metabolism in Healthy State and under Pathology.

2.1. Nucleoprotein digestion and absorption.

2.2. Nucleotide biosynthesis.

2.3. Nucleotide catabolism. Gout and its treatment.

<u>Individual work</u>

1. *Lesch-Nyhan syndrome.*
2. *Acute intermittent porphyria.*
3. *Eriythropoietic porphyria.*
4. *Hereditary coproporphyria.*

Information Resources

1. Biological Chemistry: Textbook / A.L. Zagayko, L.M. Voronina, G.B. Kravchenko, K.V. Strel`chenko. – Kharkiv: NUPh; Original, 2011. – 120-139 p.
2. Training Journal for Licensed Exam "KROK-1": Study Material in Biological Chemistry. – Kharkiv: NUPh, 2017. – 81-98 p.
3. Laboratory Manual on Biochemistry. Kharkiv: NUPh, 2017. - 53-58 p.
4. Amino Acid Metabolism: The Medical Biochemistry Page. Available on: **https://themedicalbiochemistrypage.org/amino-acid-metabolism.php.**
5. Nitrogen Metabolism and the Urea Cycle: The Medical Biochemistry Page. Available on: **https://themedicalbiochemistrypage.org/nitrogen-metabolism.php.**

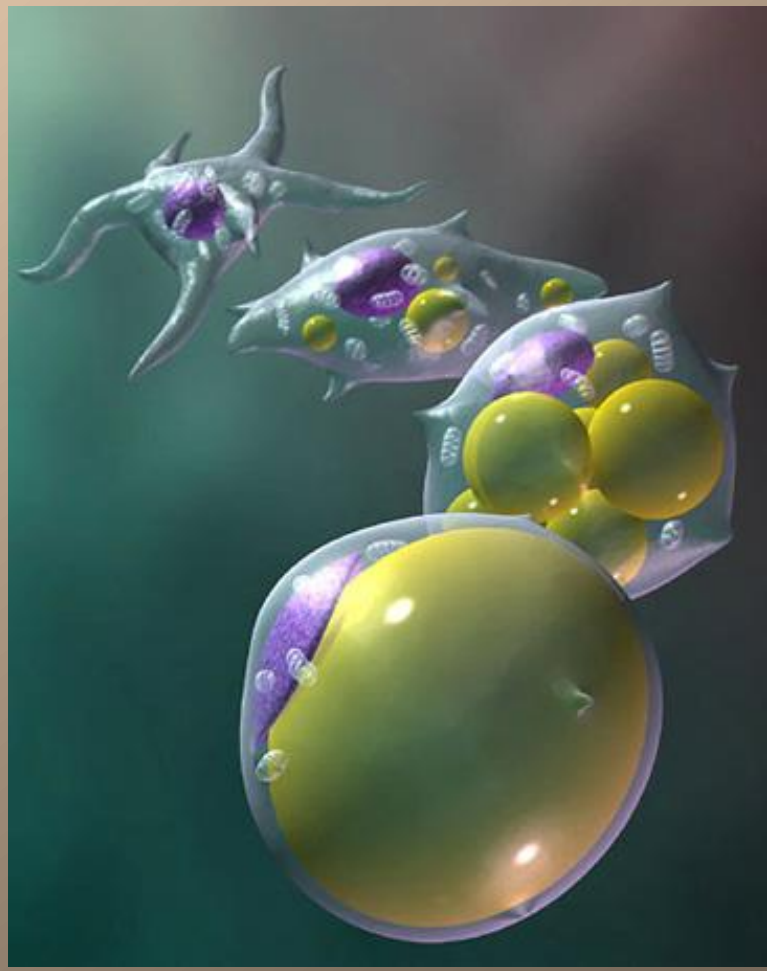
Organic nitrogenous compounds are formed by the incorporation of NH_4^+ into carbon skeletons. Ammonium can be formed from oxidized inorganic percursors by reductive reactions: ***nitrogen fixation*** *reduces N_2 to NH_4^+;* ***nitrate assimilation*** *reduces NO_3^- to NH_4^+.*

Nitrifying bacteria can oxidize NH_4^+ back to NO_3^- and obtain energy for growth in the process of ***nitrification.*** ***Denitrification*** *is a form of bacterial respiration whereby nitrogen oxides serve as electron acceptors in the place of O_2 under anaerobic conditions.*

Whereas carbohydrates and lipids can be stored and mobilized as needed for biosynthetic reactions or for energy generation, there is no nitrogen-storing molecule. (One exception to this rule is the storage proteins in seeds).

Consequently, organisms must constantly replenish their supply of usable nitrogen to replace organic nitrogen that is lost in catabolism.

Animals must have a steady supply of amino acids in their diets to replace the nitrogen that is excreted as urea, uric acid, and other nitrogenous waste products.



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Because there is no significant storage form of nitrogen or amino compounds in humans, nitrogen metabolism is quite dynamic. A careful balance is maintained between nitrogen ingestion and secretion.

Nitrogen Balance - the difference between the amount of nitrogen taken in and the amount excreted or lost.

The concept of nitrogen balance reminds us of the continuous turnover in the normal human body of amino acids, proteins, and some nucleic acids.

In an average, healthy diet the amount of nitrogen excreted is approximately equal to that taken in. Such a healthy adult would be said to be "in nitrogen balance".

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When there is a need to increase protein synthesis, such as in recovering from trauma or in a rapidly growing child, the amount of nitrogen excreted is less than that consumed in the diet, and the individual would be in "positive nitrogen balance".

The converse is true in protein malnutrition: because of the need to synthesize essential body proteins, other proteins, such as muscle protein or hemoglobin, are degraded and more nitrogen is lost than is consumed in the diet. Such an individual would be said to be in "negative nitrogen balance". Fasting, starvation and poorly controlled diabetes are also characterized by negative nitrogen balance, as body protein is degraded to amino acids and their carbon skeletons are used for gluconeogenesis.

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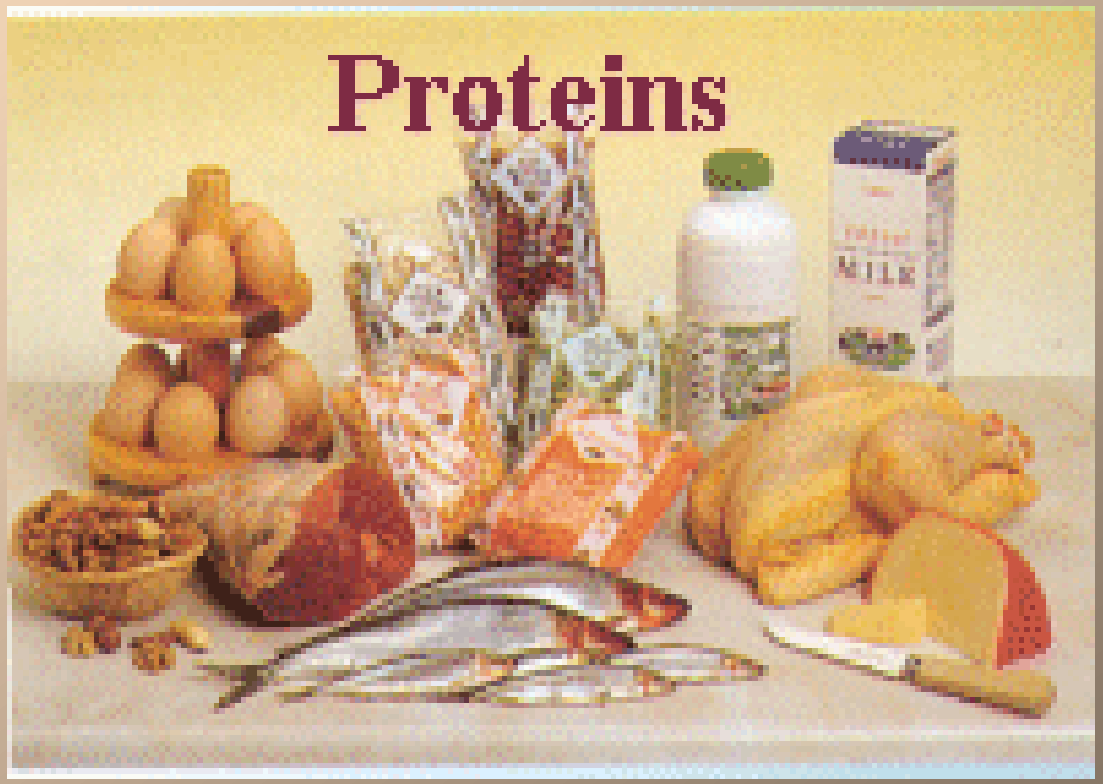
PROTEIN DIGESTION



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Essential and Nonessential Amino Acids in Mammals

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

*Arginine and histidine are essential in the diets of juveniles, not adults.

†Tyrosine is classified as nonessential only because it is readily formed from essential phenylalanine.

ESSENTIAL AMINO ACIDS

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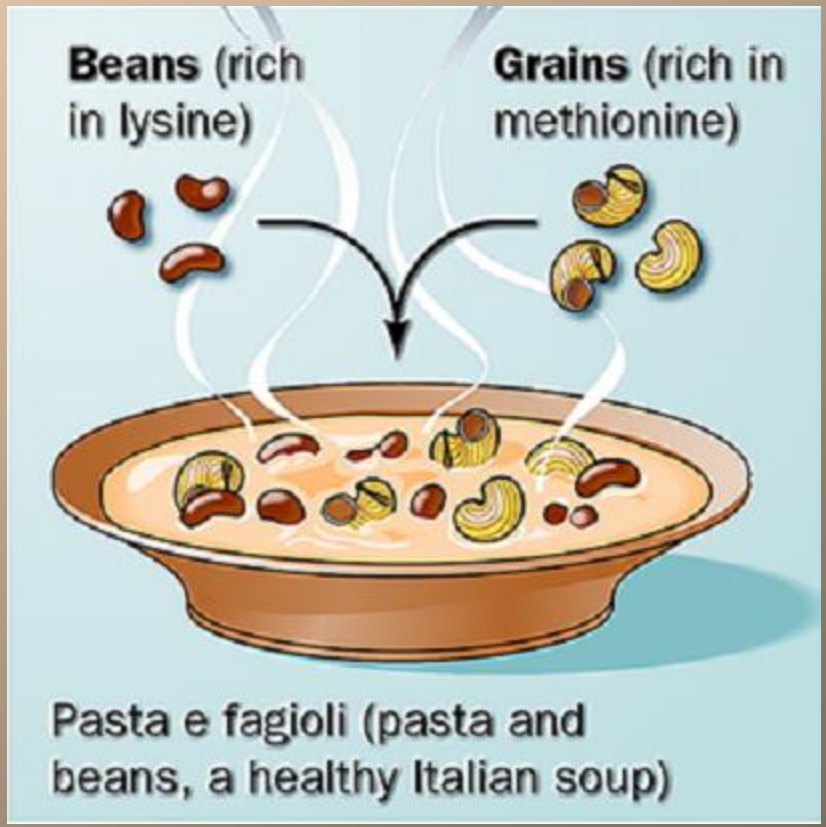

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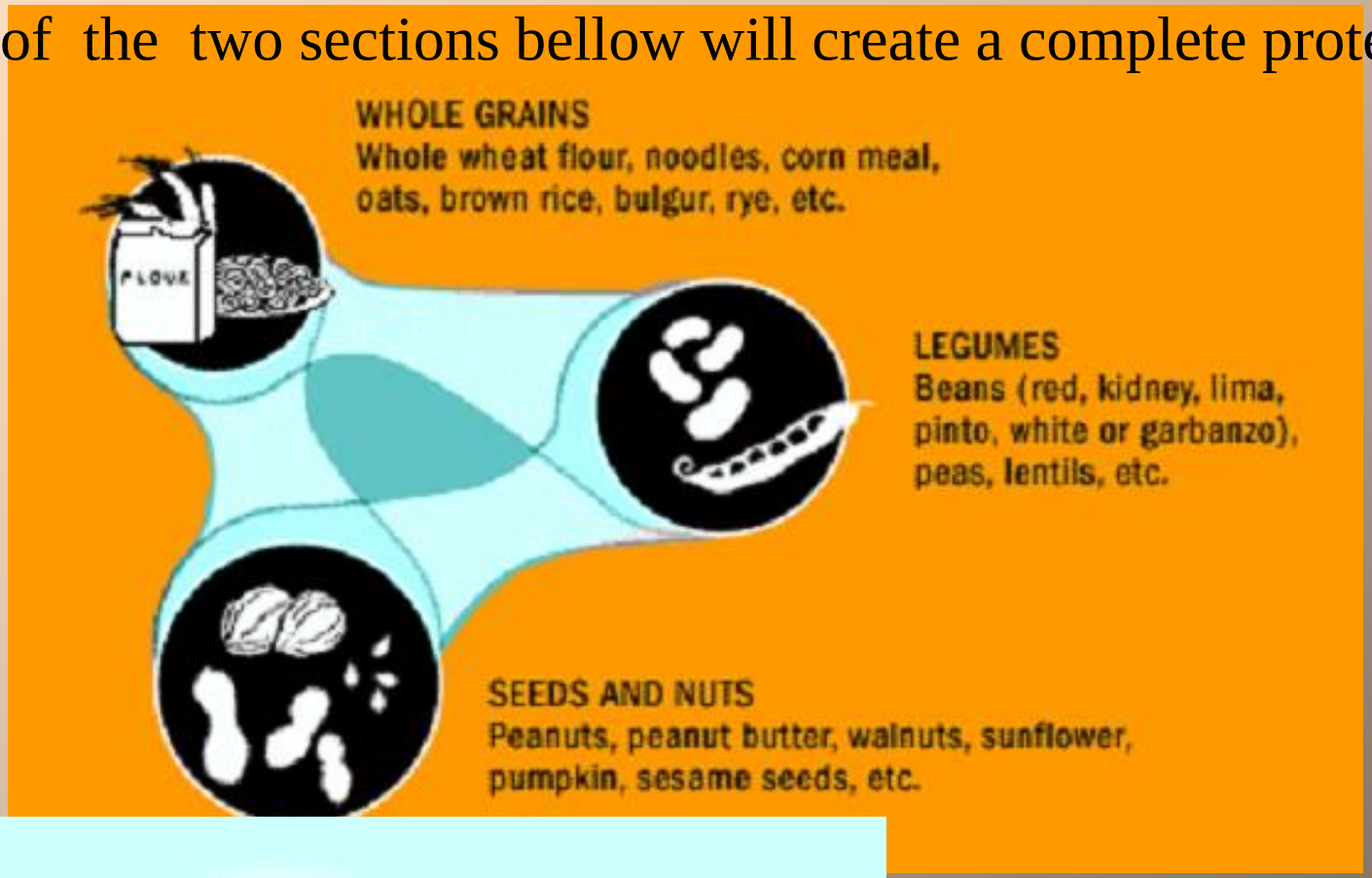
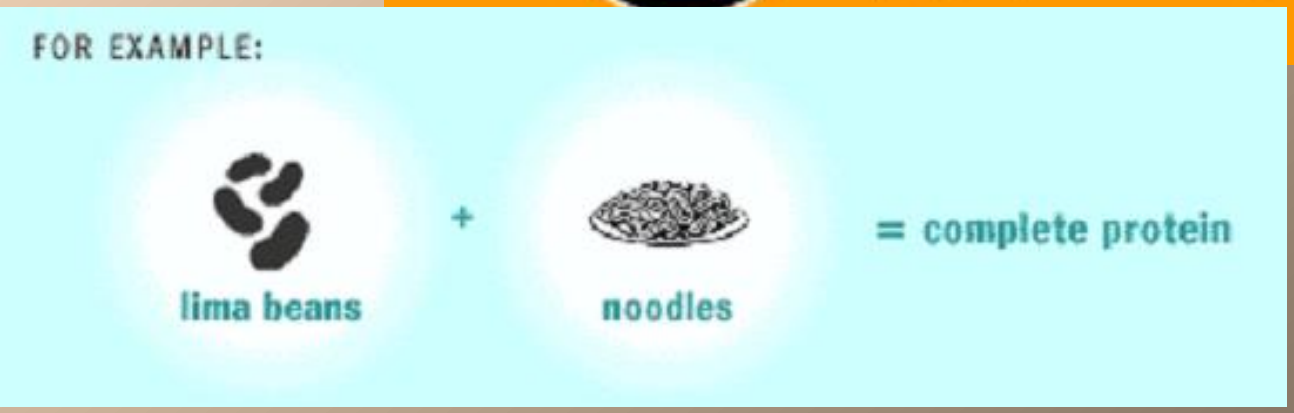
Complete Protein Combination

(combination of the two sections bellow will create a complete protein)





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Dietary Protein Is Enzymatically Degraded to Amino Acids

Proteins are broken down by hydrolysis of peptide bonds and hence the enzymes involved are termed "peptidases". These enzymes can either cleave internal peptide bonds (endopeptidases) or cleave off one amino acid at a time from either the –COOH or $–NH_2$ terminal of the polypeptide (exopeptidases subclassified into carboxypeptidases and aminopeptidases, respectively).

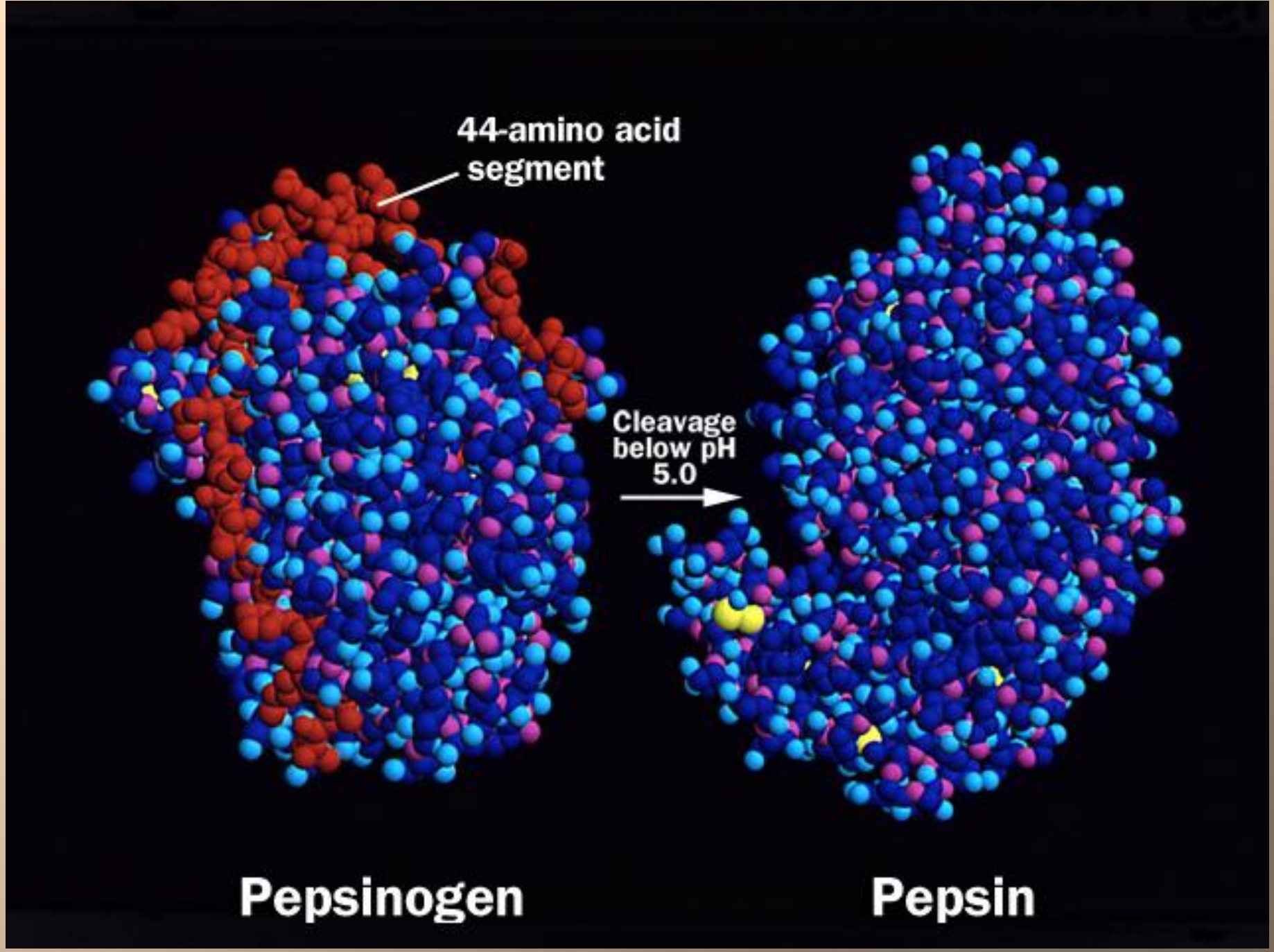
The endopeptidases cut the large polypeptides to smaller oligopeptides, which can be acted upon by the exopeptidases to produce the final products of protein digestion, di- and tripeptides and amino acids, which are then absorbed by the enterocytes.

Most Digestive Enzymes in the Gut are Secreted as Inactive Precursors

- Digestive enzymes secreted into the gut lumen are present as inactive precursors termed zymogens.

- Enzymes involved in protein digestion (proteases) are synthesized as inactive zymogens and are only activated on their release to the gut lumen.

- In general, these enzymes, once in their active form, can activate their own precursors. Activation of their precursors can occur by their change in pH (e.g. pepsinogen in the stomach is converted at pH below 4.0 to the active enzyme, pepsin), or by the action of specific enteropeptidases bound to the mucosal membrane of the duodenum.



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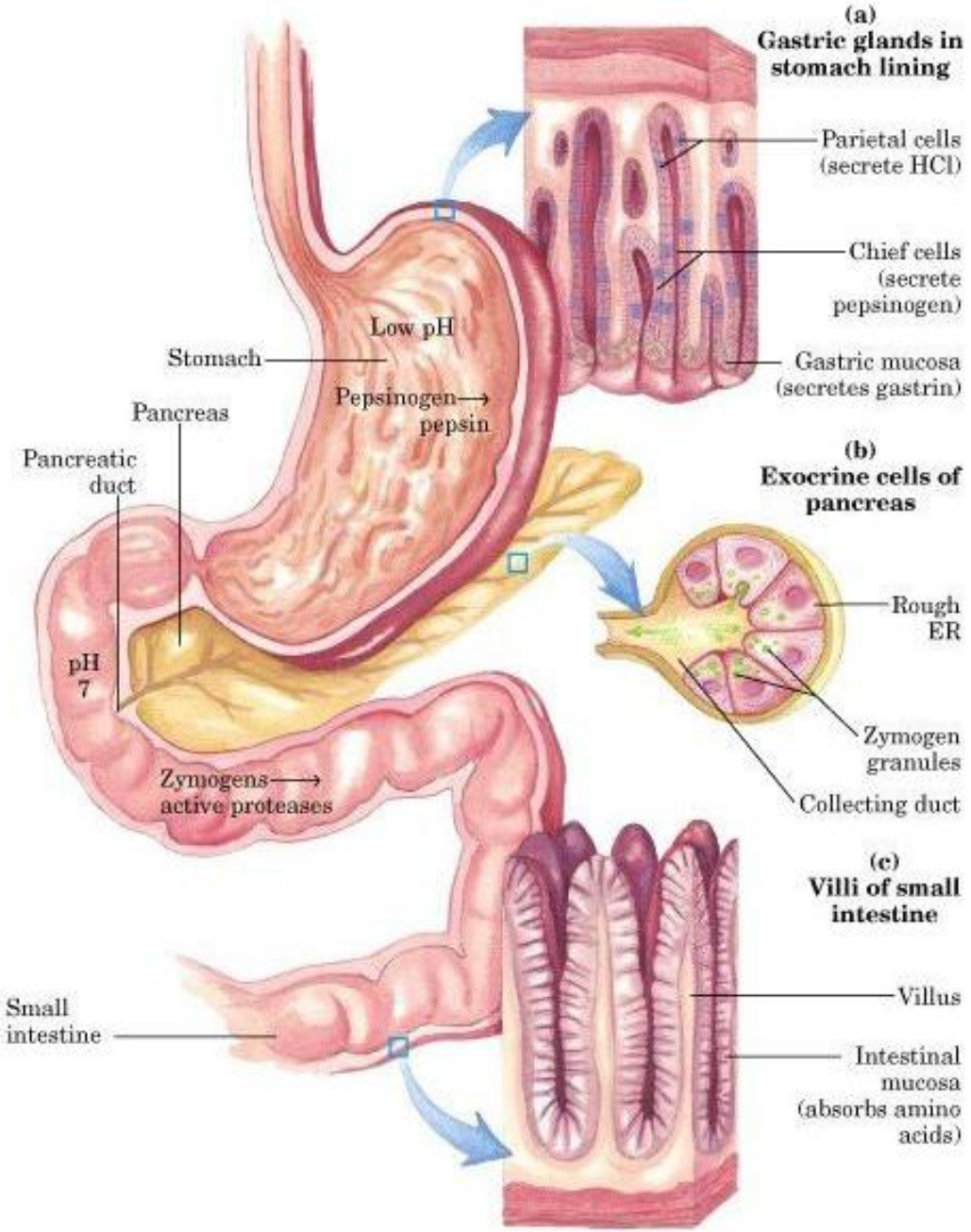
Depending on the source of the peptidases, protein digestion can be divided into

- ***gastric,***
- ***pancreatic and***
- ***intestinal phases.***



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Protein digestion begins in stomach

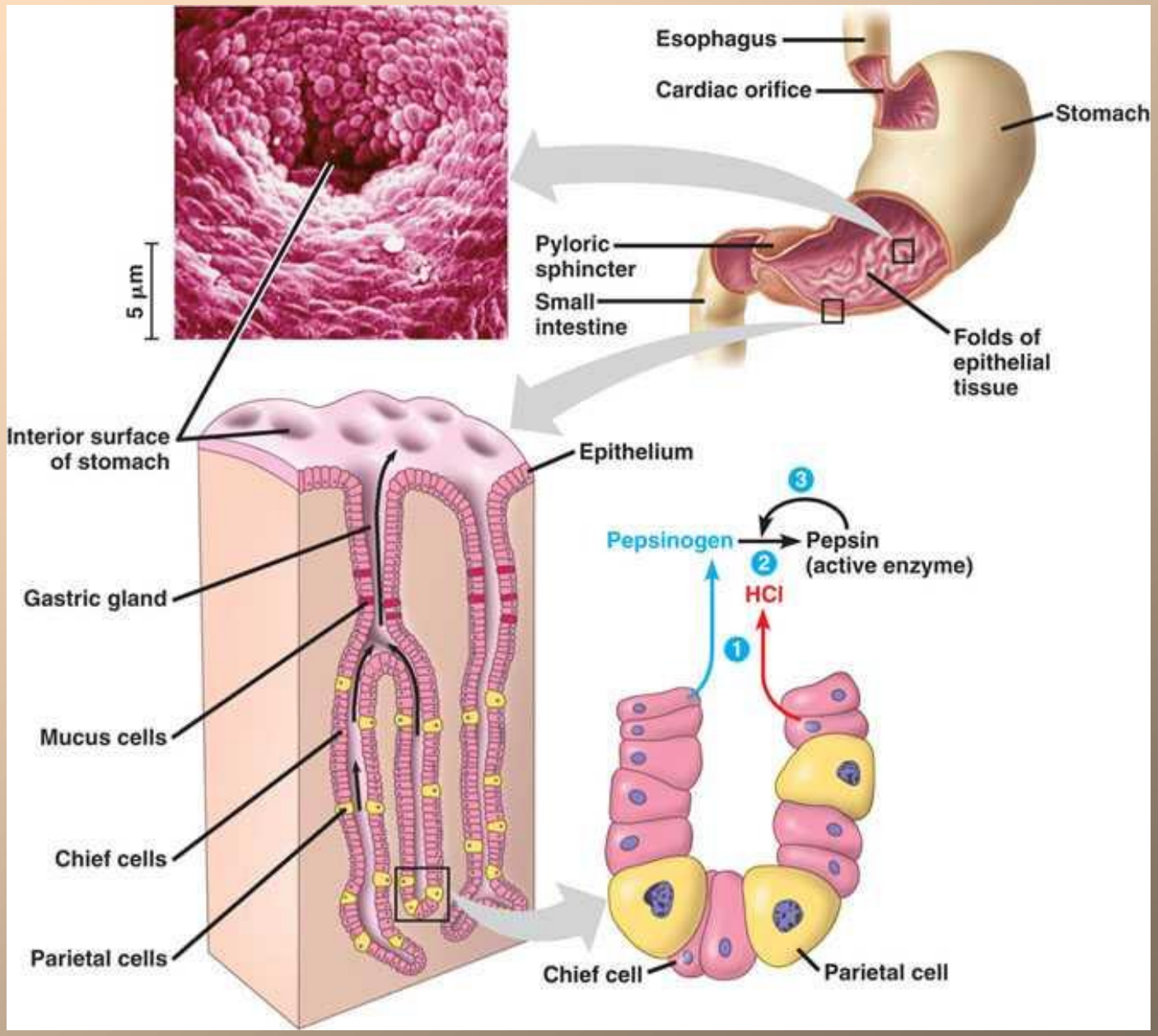
In the stomach, secreted HCl (by parietal or oxyntic cells) reduces the pH to 1-2. Most proteins are denaturated in the acidic environment. The acidity of the stomach also has an antibacterial action.

Pepsins are secreted by the Chief cells (zymogenic or peptic cells) of the gastric mucosa. These proteases are released as the inactive precursors, pepsinogenes A and B, and are activated by either an intramolecular reaction (autoactivation) at a pH below 5 or by active pepsin (autocatalysis). It is activated by hydrolysis of a single peptide bond, releasing a 44-amino acid peptide and the active enzyme.

Pepsin has pH optimum around 2. It acts preferentially on peptide bonds in the middle of peptide chains, to the C-terminal side of aromatic amino acids.

The major products of pepsin digestion of proteins are large peptide fragments and some free amino acids.

Human Stomach



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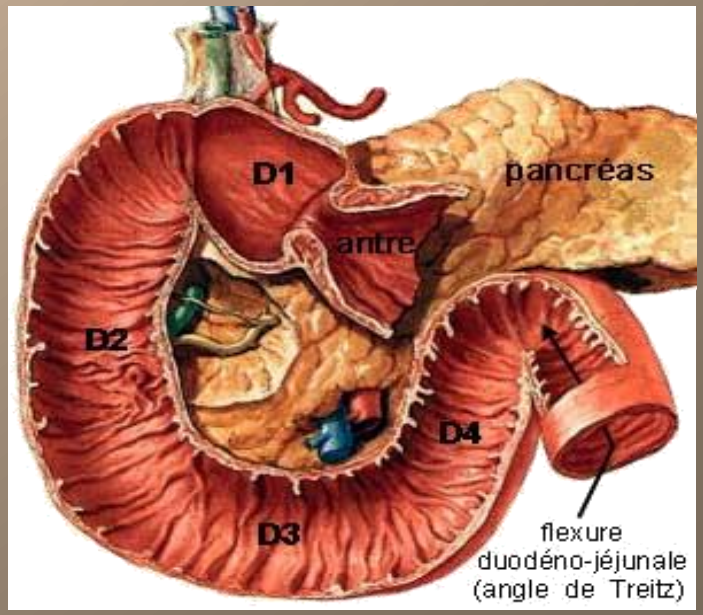
Digestive Process in the Small Intestine

The pancreatic juice contains a number of enzymes with proteolytic activity. The most important of these are trypsin (secreted as trypsinogen), chymotrypsin (secreted as chymotrypsinogen), carboxypeptidases (the precursor procarboxypeptidase is activated to produce carboxypeptidases A and B) and elastase secreted as proelastase).

The enzyme trypsin is derived from trypsinogen by the action of an "enterokinase" associated with the brush border membrane; trypsin then catalyses the activation of the other zymogens.



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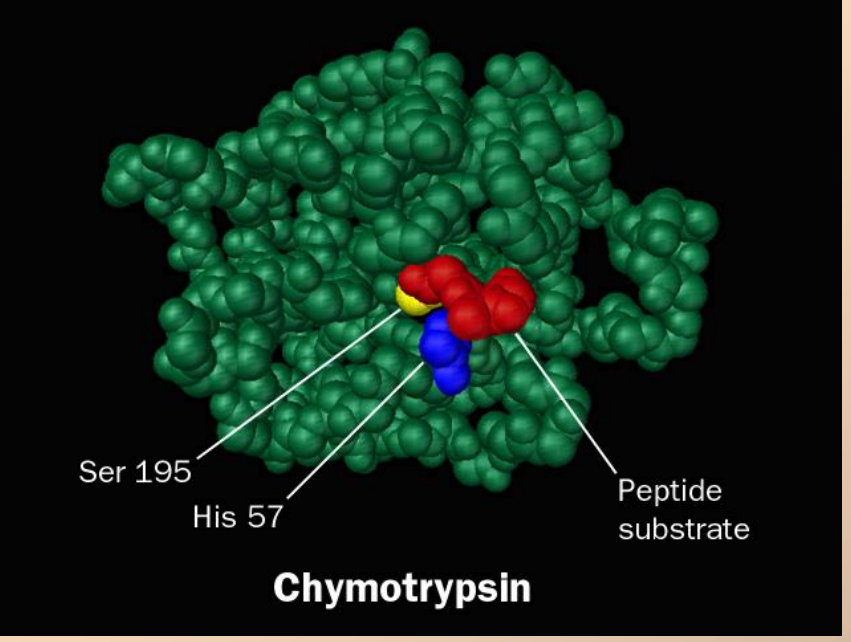

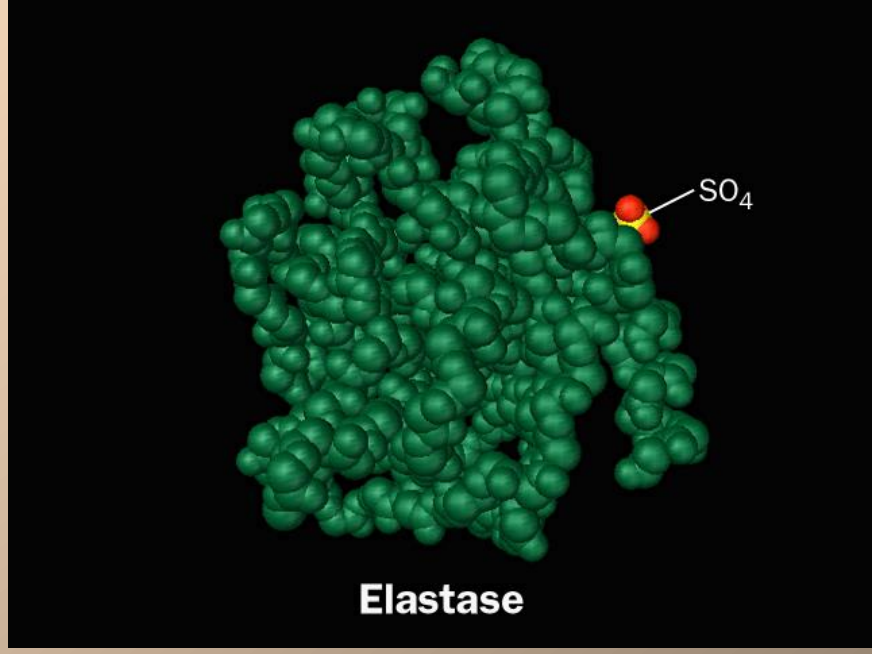

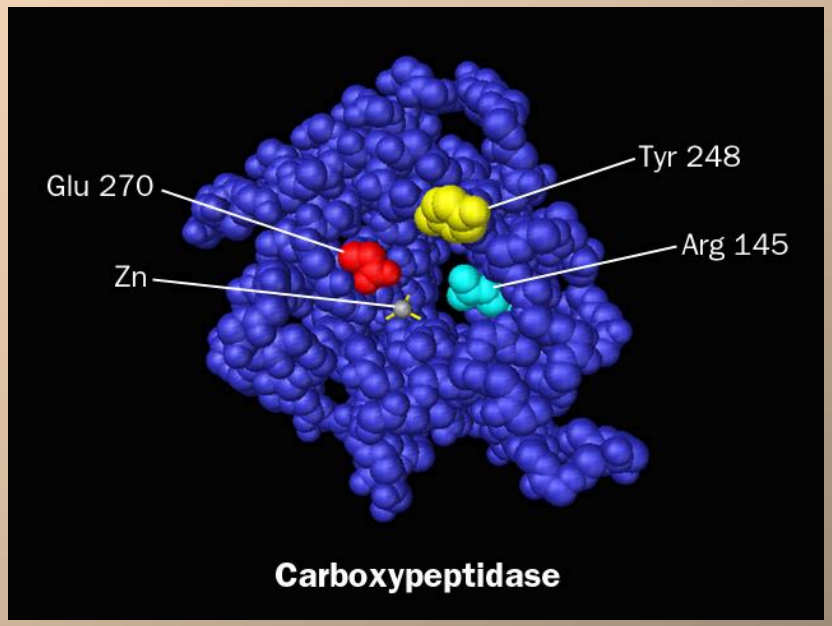

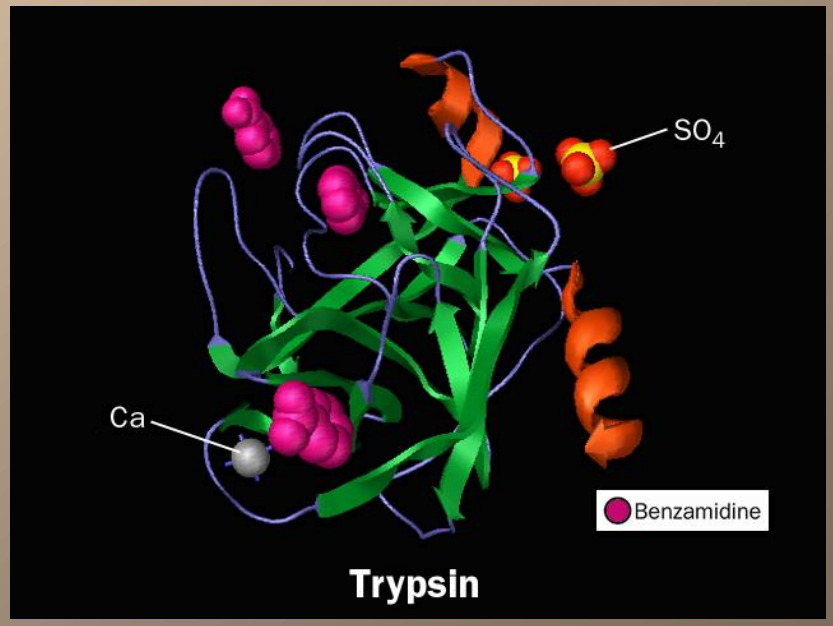

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Pancreatic proteases have different substrate specificity with respect to peptide bond cleavage

***Trypsin** cleaves proteins at lysine and arginine residues.*
***Chymotripsin** at aromatic amino acids.*
***Elastase** at smaller hydrophobic amino acids.*

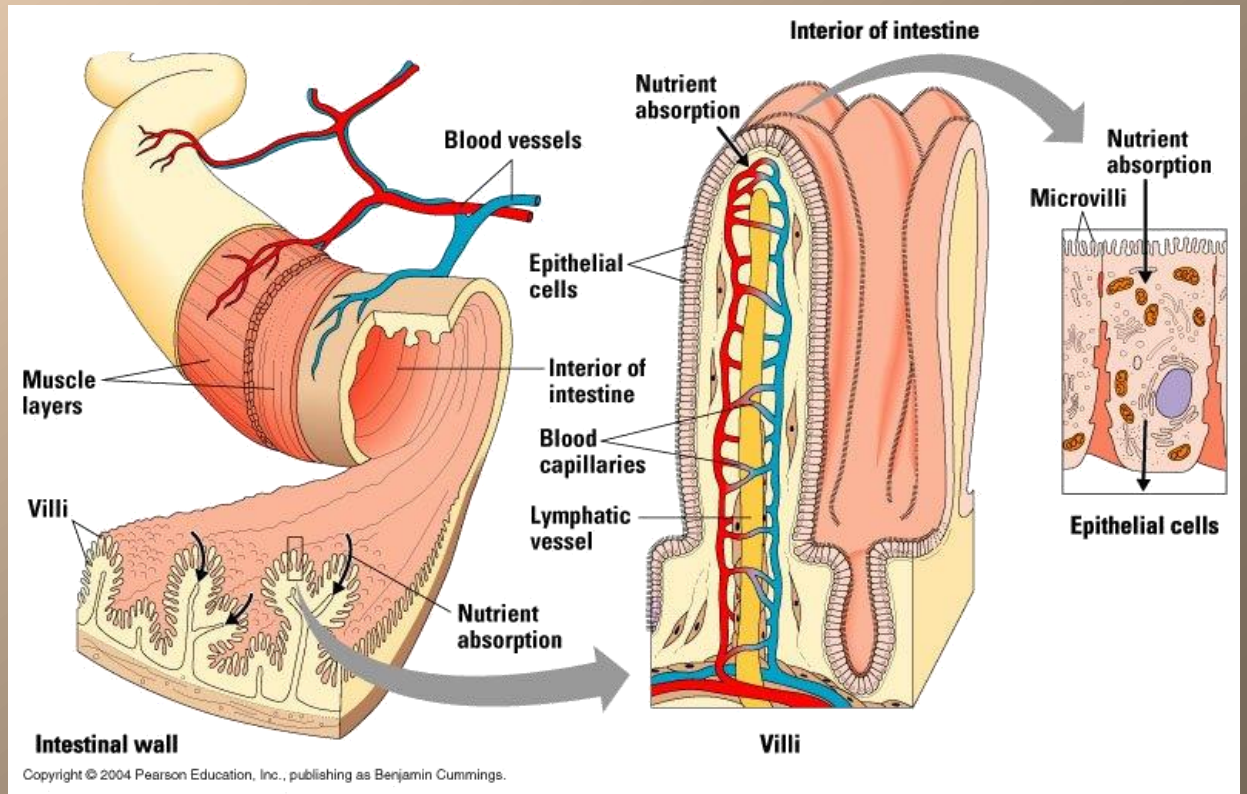
The combined effect of this pancreatic enzymes is to produce an abundance of free amino acids and small molecular weight peptides of two to eight residues in length.

This may be further hydrolysed by membrane-bound enzymes to tri- and dipeptides and amino acids for absorbtion.

Active transport of amino acids into intestinal epithelial cells

At the brush border membrane Na^+-dependent symporters (membrane transporters which transport two substances in the same direction) for amino acid uptake are linked to ATP-dependent pumping out of Na^+ at the contraluminal membrane.

A similar H^+-dependent symporter is present on the brush-border surface for di- and tripeptide active transport into the cell.



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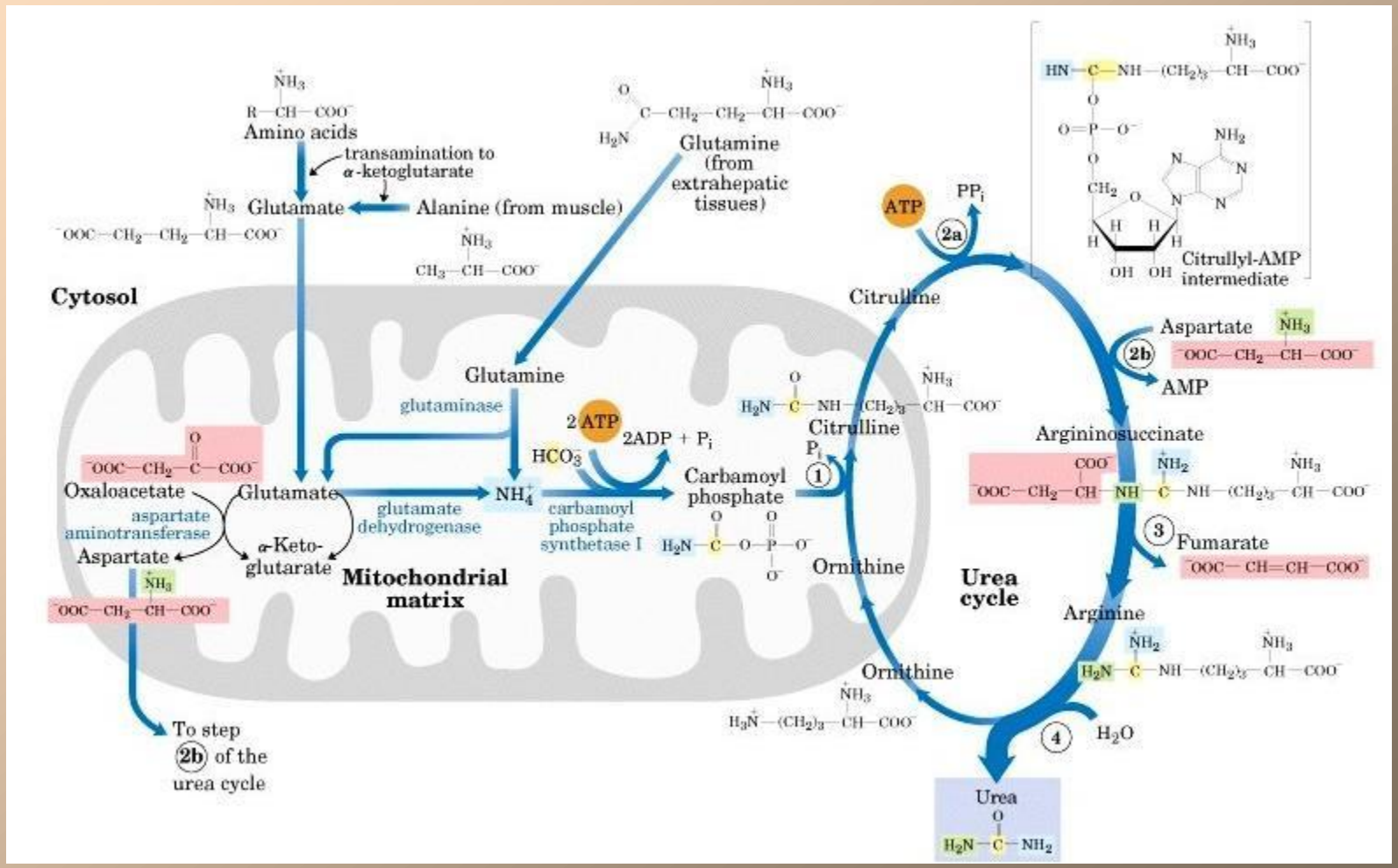
Na^+-independent transporters are present on the contraluminal surface, thus allowing the facilitated transport of amino acids to the hepatic portal system.

From both genetic and transporter studies, at least six specific symporter systems have been identified for the uptake of L-amino acids from the intestinal lumen:

- *neutral amino acid symporter for amino acids with short or polar side-chains (Ser, Thr, Ala);*
- *neutral amino acid symporter for aromatic or hydrophobic side-chains (Phe, tyr, Met, Val, Leu, Ileu);*
- *imino acid sympoter (Pro, OH-Pro);*
- *basic amino acid symporter (Lys, Arg);*
- *acidic amino acid symporter (Asp, Glu);*
- *β-amino acid symporter (β-Ala, Tau).*

Amino Acid



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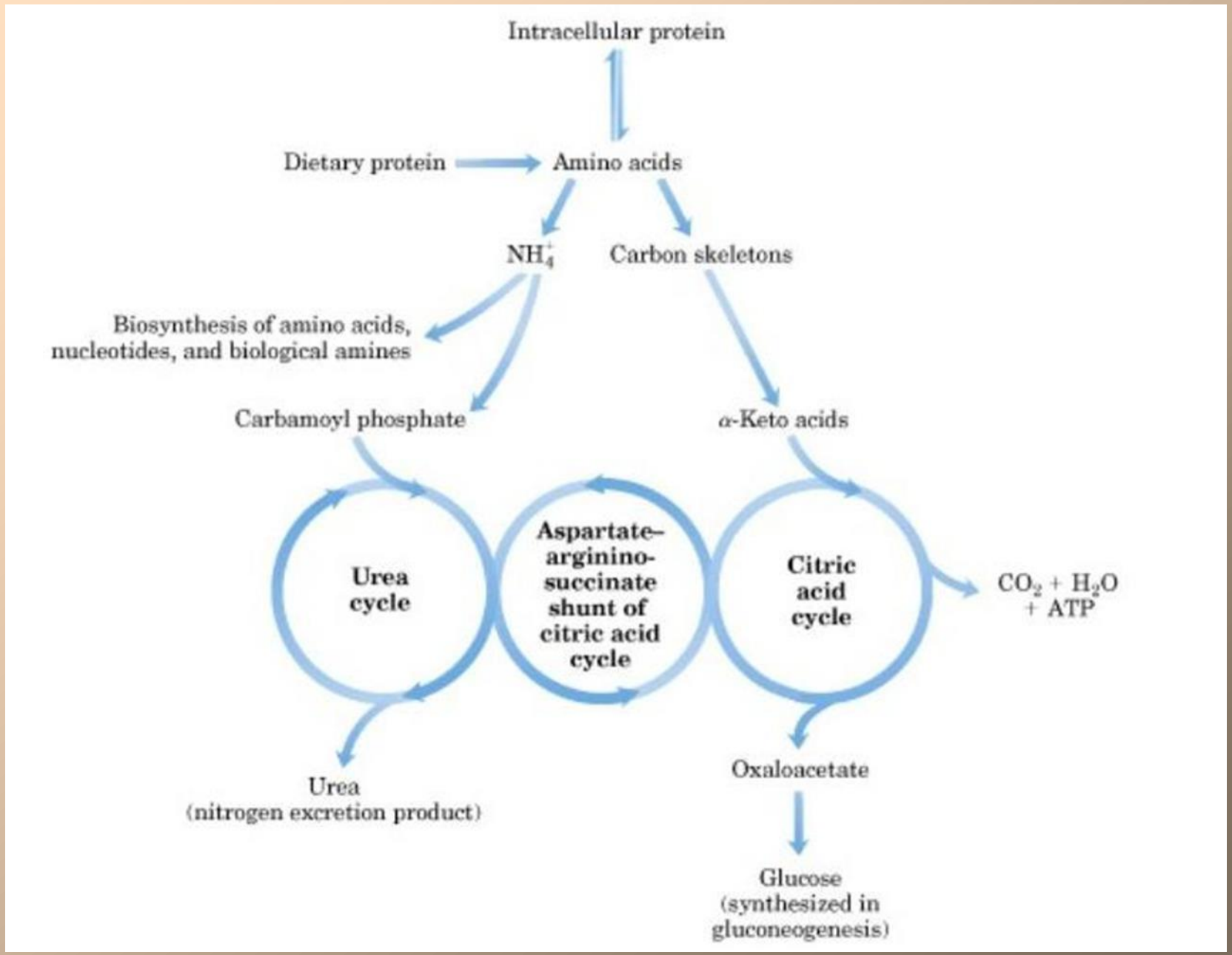

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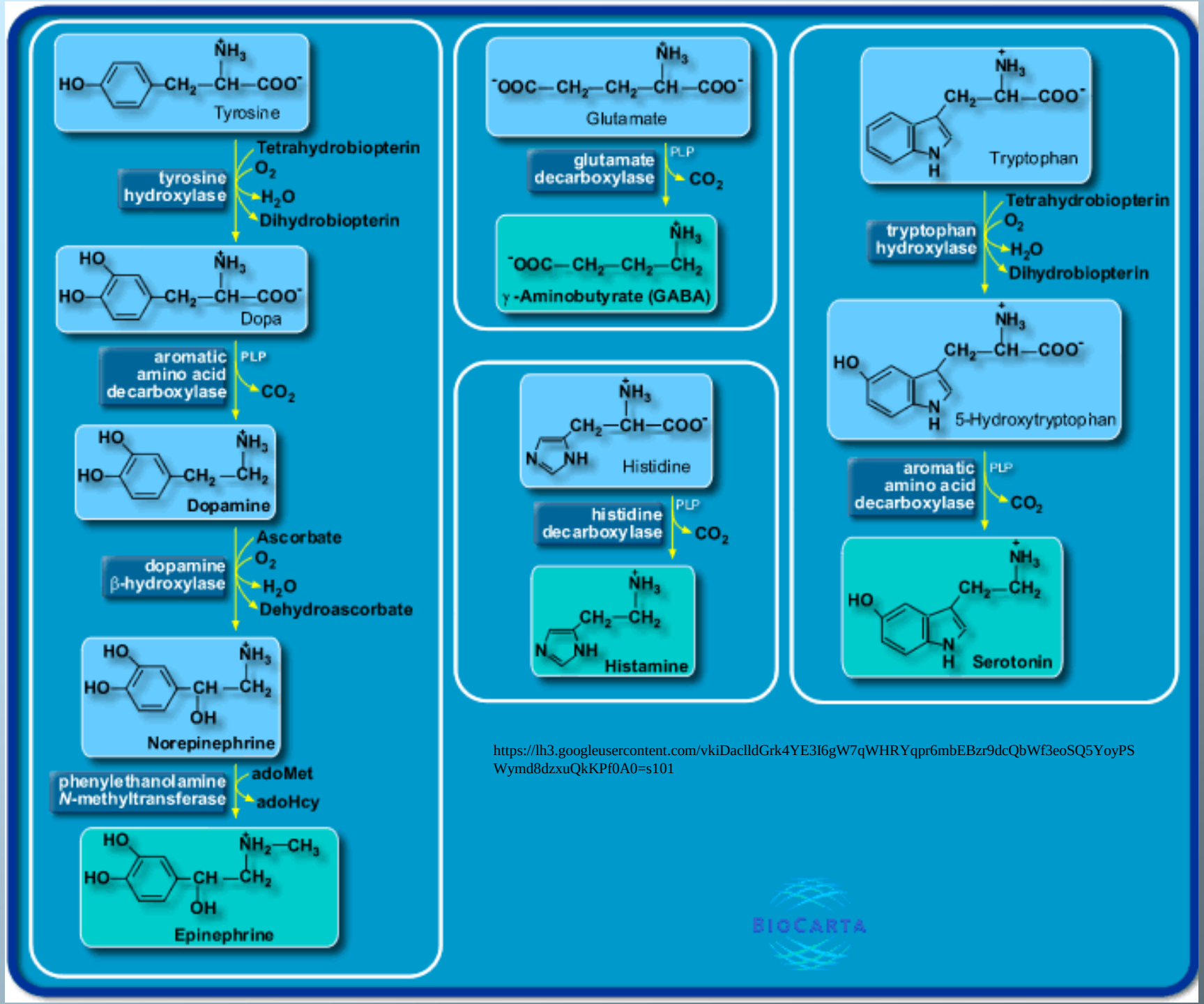
Biogenic Amines

- a group of naturally occurring amines derived by enzymatic decarboxylation of the natural amino acids. many have powerful physiological effects (e.g., histamine, serotonin, epinephrine, tyramine). Those derived from aromatic amino acids, and also their synthetic analogs (e.g., amphetamine), are of use in pharmacology.



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Histamine

- an amine that produced in numerous tissues throughout the body, has complex physiological effects. It is a mediator of allergic and inflammatory reactions, a stimulator of gastric acid production, and a neurotransmitter in several areas of the brain.

Histamine is formed by the decarboxylation of L-histidine in a reaction catalyzed by histidine decarboxylase, a pyridoxal phosphate-requiring enzyme.

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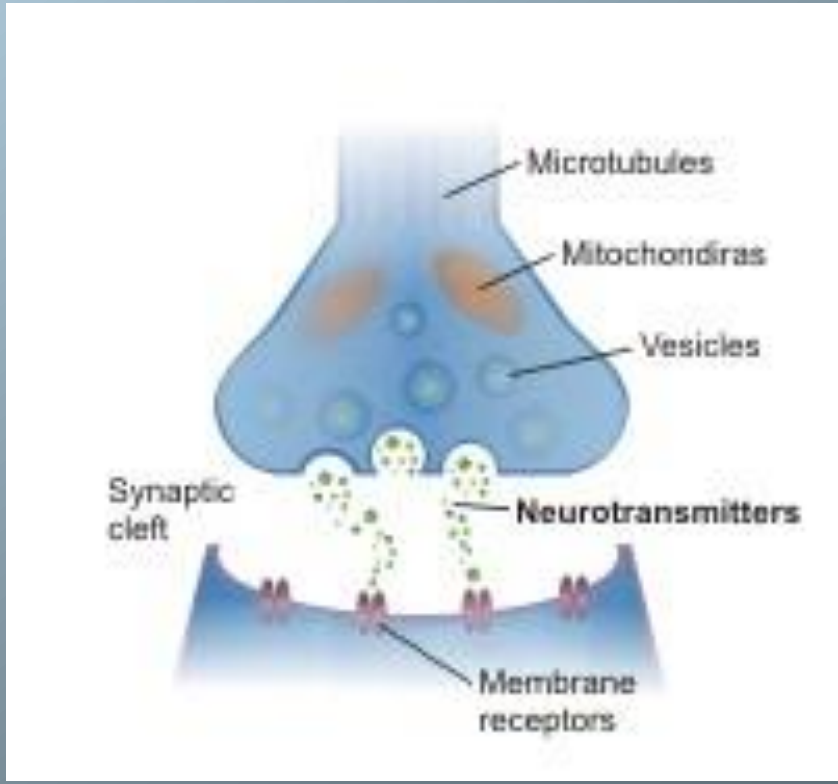
Serotonin

***Tryptophan hydroxilase** uses O_2 and the electron donor **dihydrobiopterin** (oxidized form, BH_2) to hydroxylate C^5 of tryptophan.*

The product called 5-hydroxytryptophan , then undergoes a decarboxylation catalyzed by 5-hydroxytryptophan decarboxylase, a pyridoxal phosphate-requiring enzyme. Serotonin is often referred to as 5-hydroxytriptamine.



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Serotonin is found in various cells within the central nervous system, where it excretes an inhibitory effect on feeding behavior.

Serotonin has been implicated in human eating disorders such as anorexia nervosa, bulimia, and the carbohydrate craving associated with seasonal affective disorder (SAD). SAD is clinical depression triggered by the decreased daylight in autumn and winter.

Additionally, serotonin appears to affect mood, temperature regulation, pain perception, and sleep. The hallucinogenic drug LSD (lysergic acid diethylamide) apparently competes with serotonin for specific brain receptors. Serotonin is also found in the gastrointestinal tract, blood platelets, and mast cells.

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γ-Aminobutyric acid ***(GABA) acts as an inhibitory neurotransmitter in the central nervous system. The binding of GABA to its receptor results in an increase in the nerve cell membrane`s permeability to chloride ions. The benzodiazopines, a class of tranquilizers that alleviates anxiety and aggressive behavior, have been shown to enhance GABA`s ability to increase membrane conductance of chloride.***

GABA is produced by decarboxylation of glutamate. The reaction is catalyzed by glutamate decarboxylase, which is a pyridoxal phosphate-requiring enzyme.

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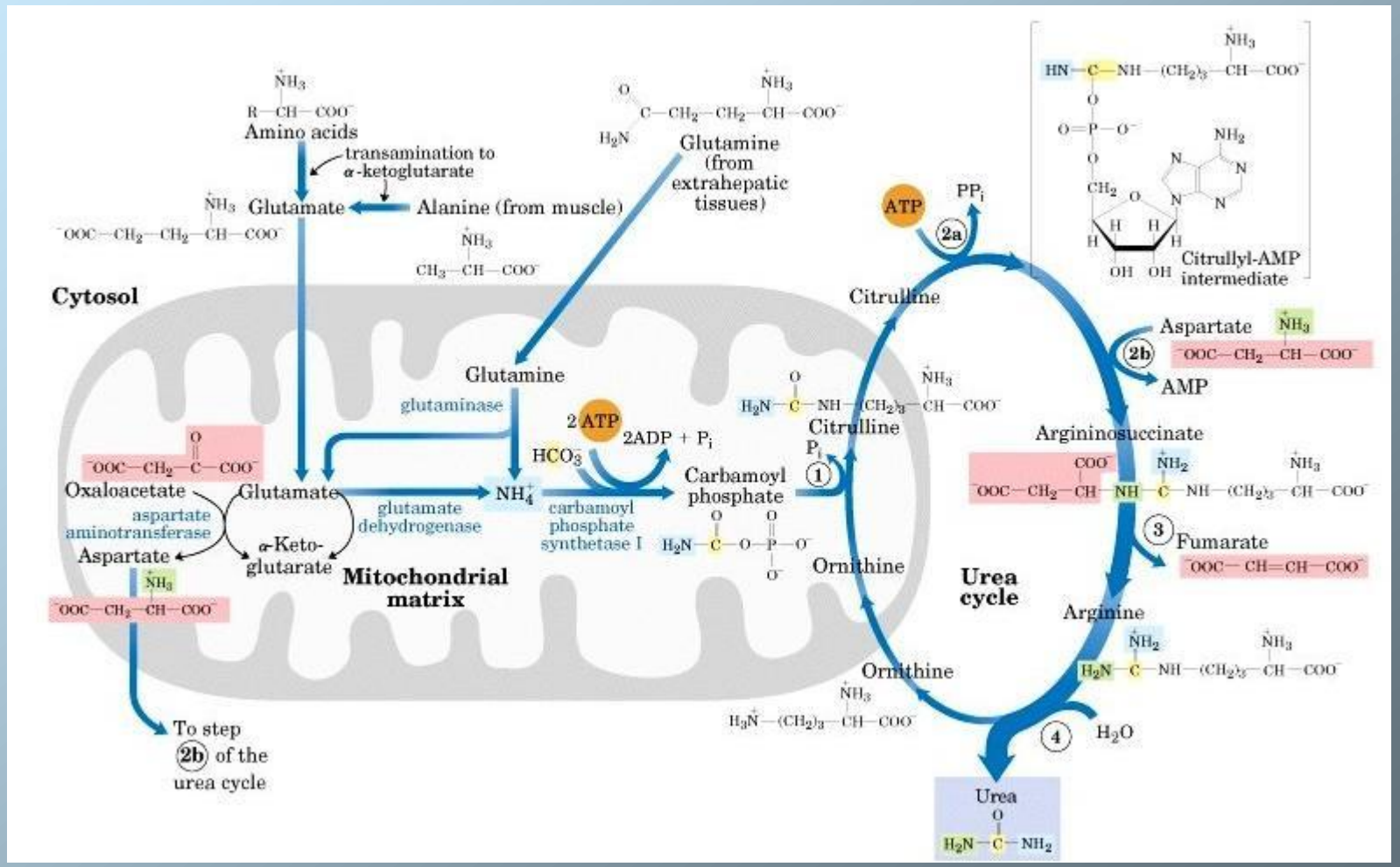
Amino Acid Oxidation and the Production of Urea



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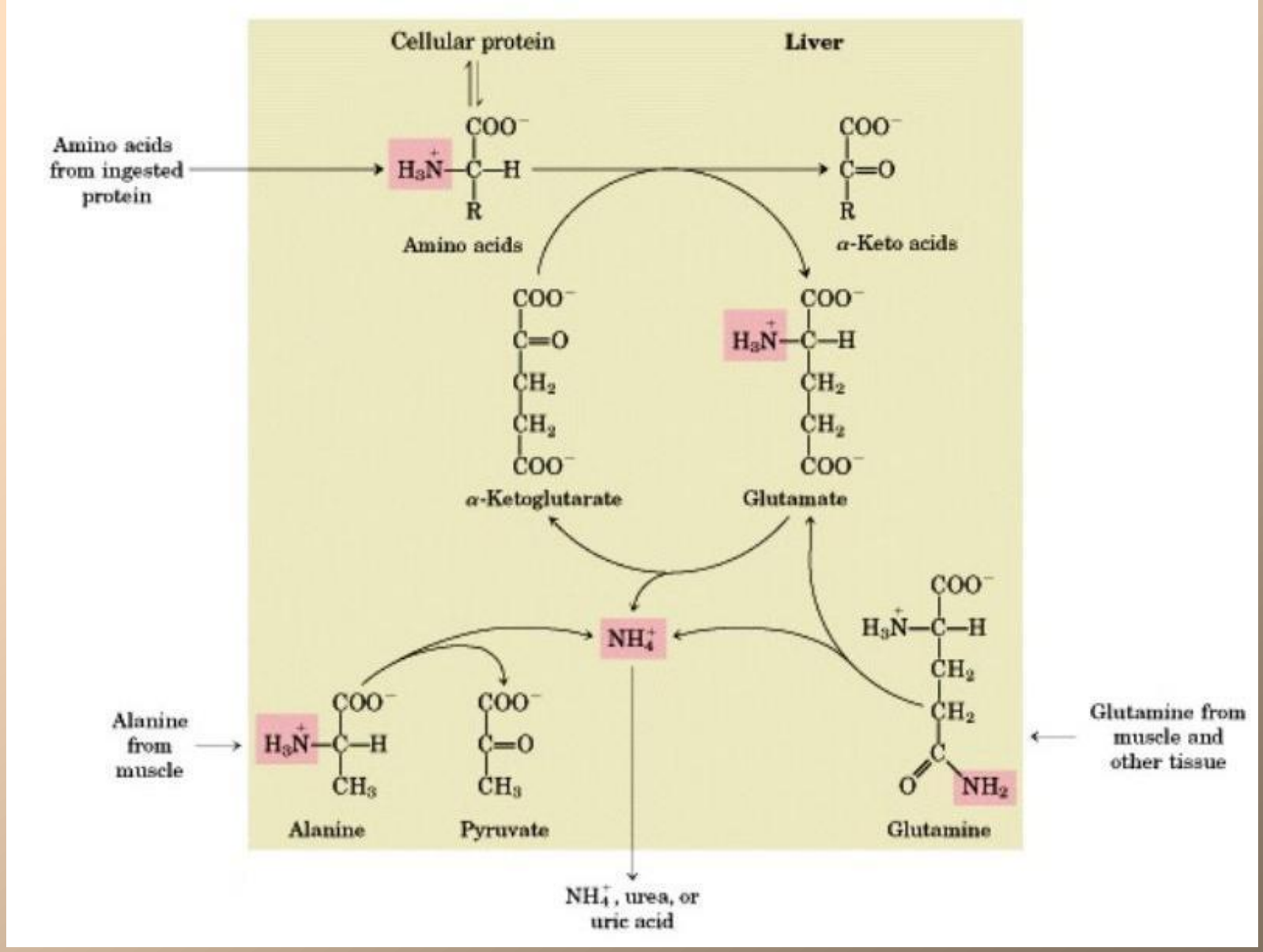
Metabolic Fates of Amino Groups

Amino acids derived from dietary proteins are the source of most amino groups. Most of the amino acids are metabolized in the liver. Some of the ammonia that is generated is recycled and used in a variety of biosynthetic processes; the excess is either excreted directly or converted to uric acid or urea 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 appropriate excreted form.



Overview of amino group catabolism in the vertebrate liver (shaded). Excess NH_4^+ is excreted as urea or uric acid.

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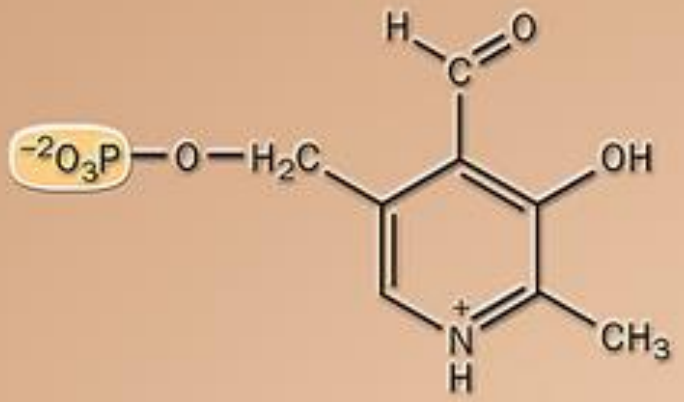
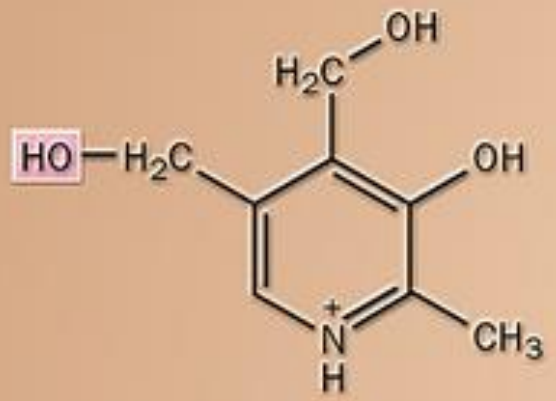
Transamination and Deamination

***Transamination** involves transfer of an α-amino group from an amino acid to the α-keto position of an α-keto acid. In the process, the amino donor becomes an α-keto acid while the α-keto acid acceptor becomes an α-amino acid.*

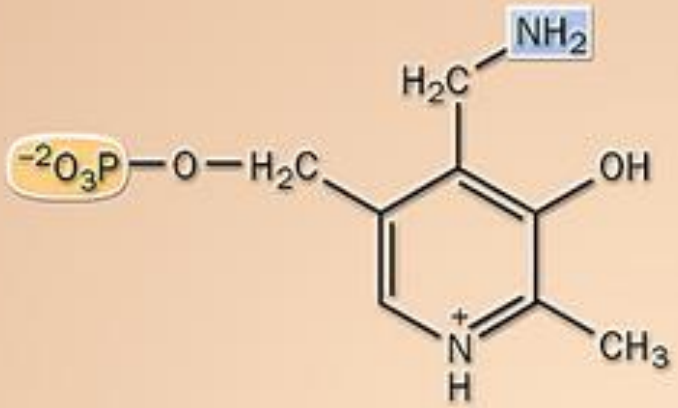
*Transamination reactions are catalyzed by **aminotransferases**. (coenzyme is **pyridoxal phosphate**). Aminotransferases are prime examples of enzymes that catalyze double displacement (ping-pong) - type bisubstrate reactions.*



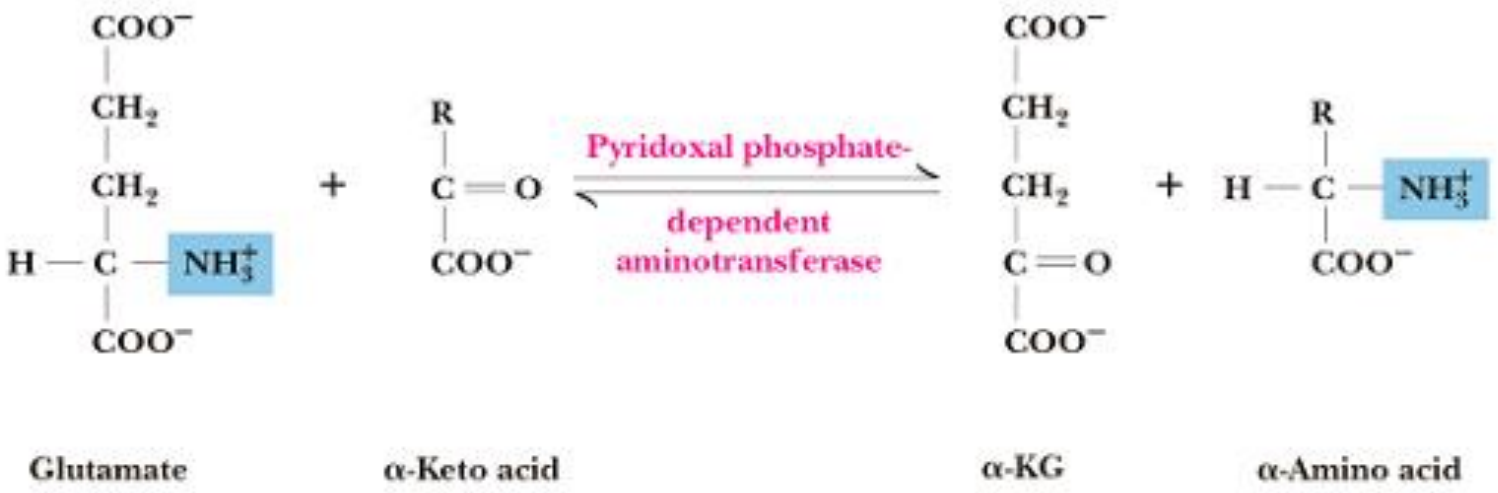
Pyridoxal phosphate

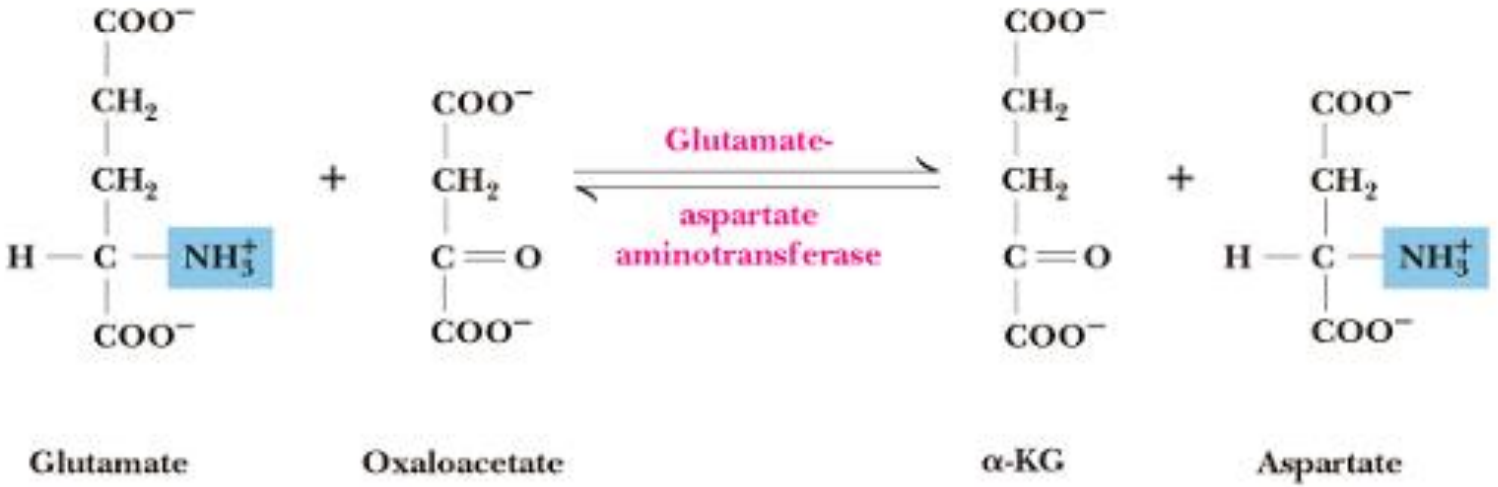


Pyridoxine (Vitamin B_6)



Pyridoxamine phosphate





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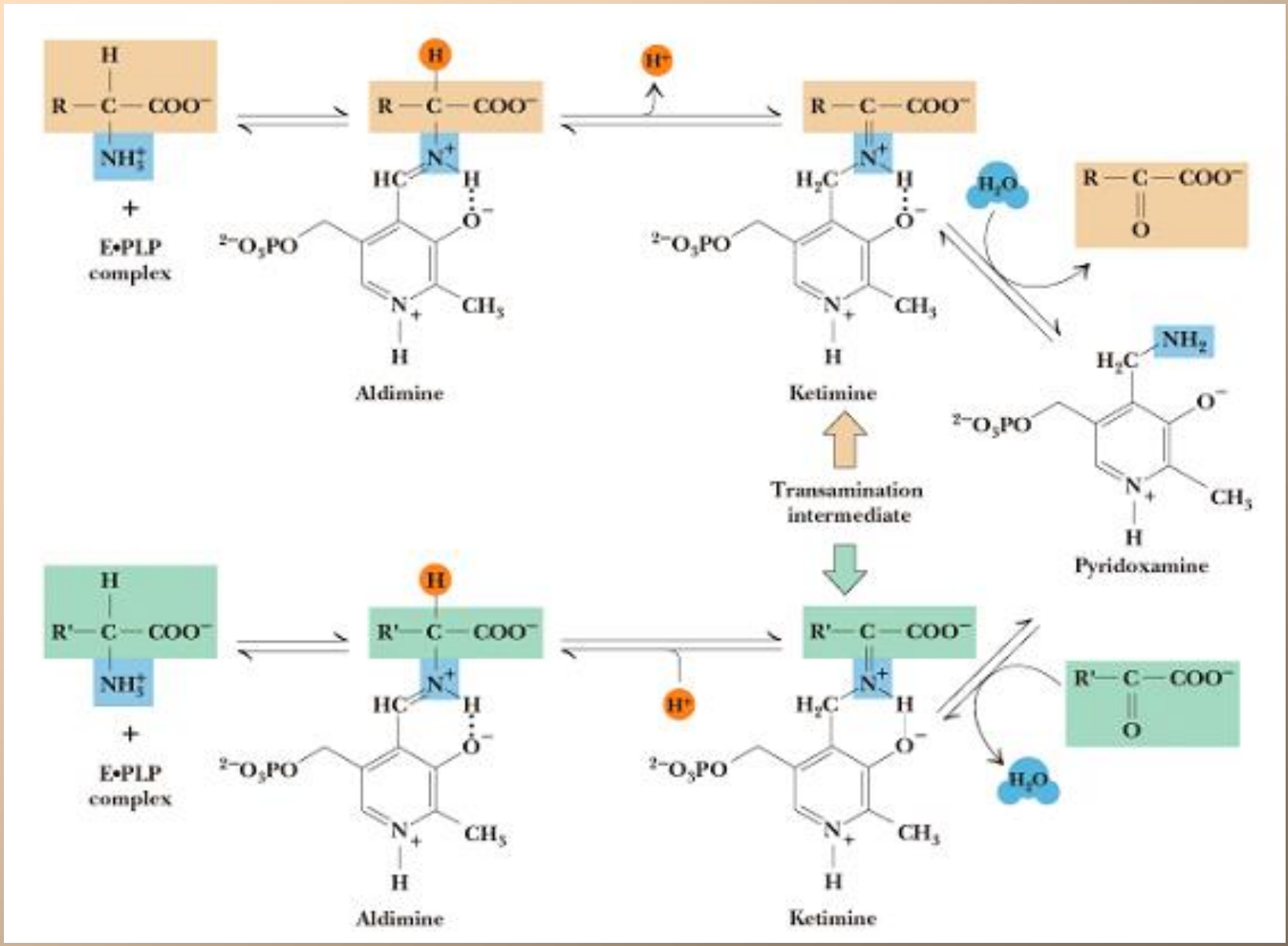

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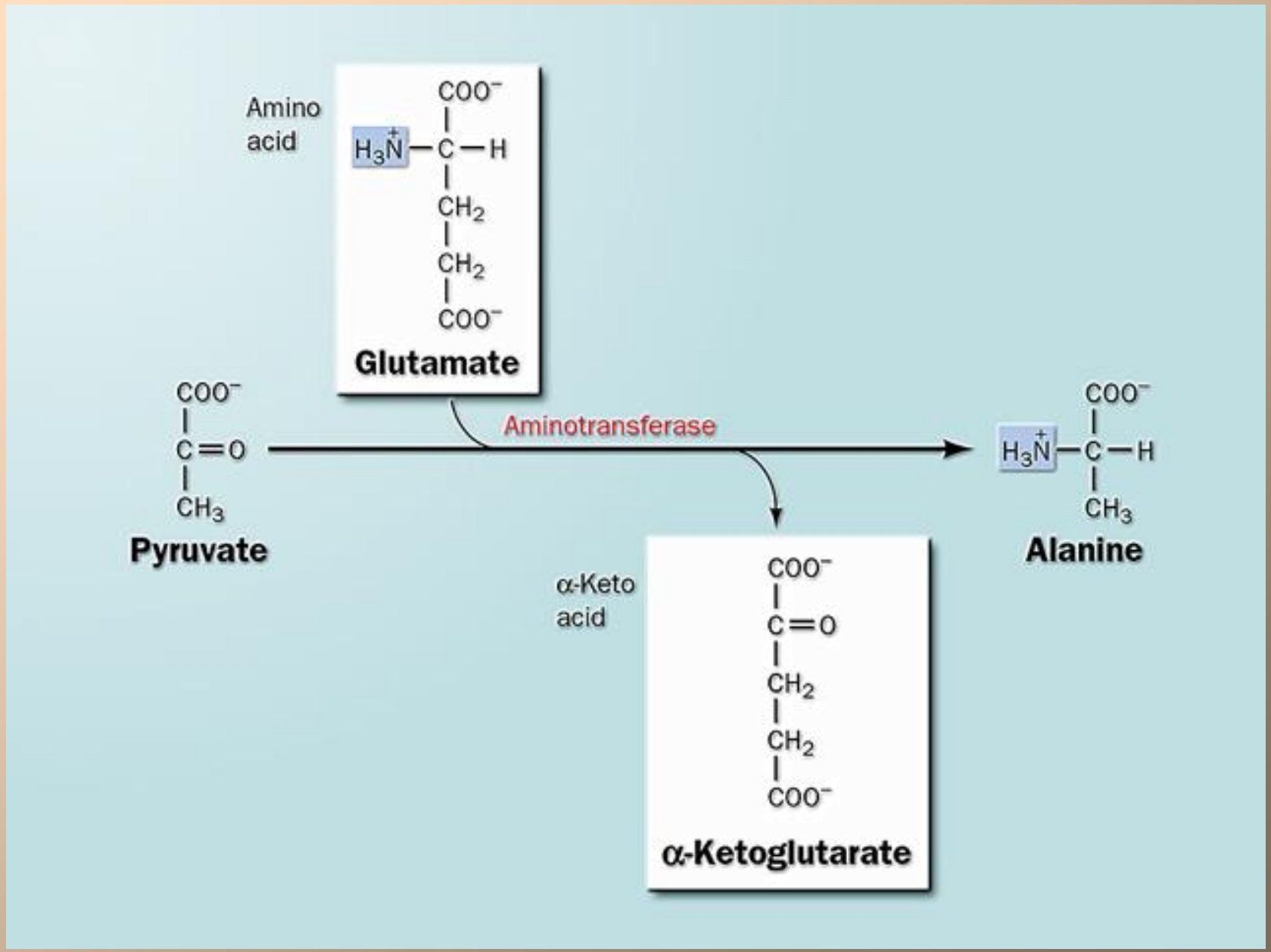
Ammonia Is Formed from Glutamate

Glutamate is transported from the cytosol to the mitochondria, where it undergoes oxidative deamination catalyzed by L-glutamate dehydrogenase. This enzyme, which is present only in the mitochondrial matrix, requires NAD^+ (or $NADP^+$) as the acceptor of the reducing equivalents.

The combined action of the aminotransferases and glutamate dehydrogenase is referred to as transdeamination. A few amino acids bypass the transdeamination pathway and undergo direct oxidative deamination.



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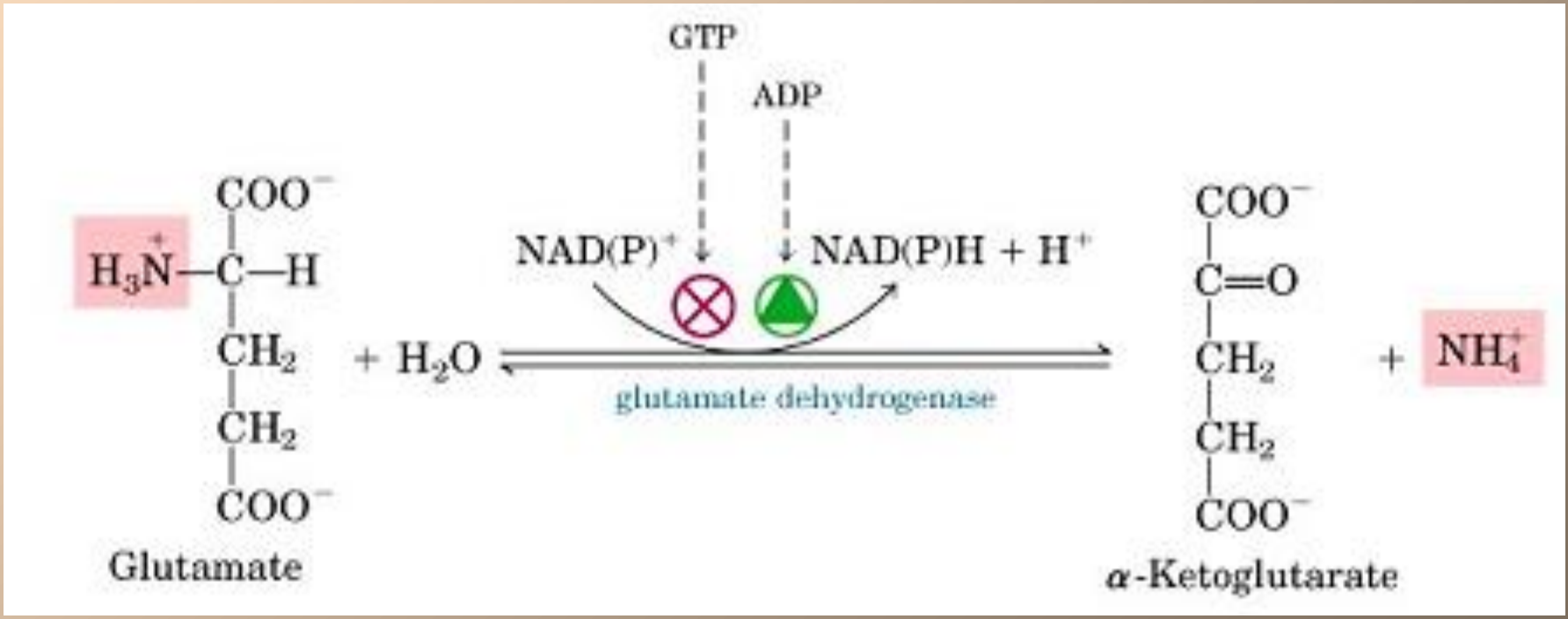
The reaction catalyzed by glutamate dehydrogenase. This enzyme can employ either NAD^+ or $NADP^+$ as cofactor, and is allosterically regulated by GTP and ADP.



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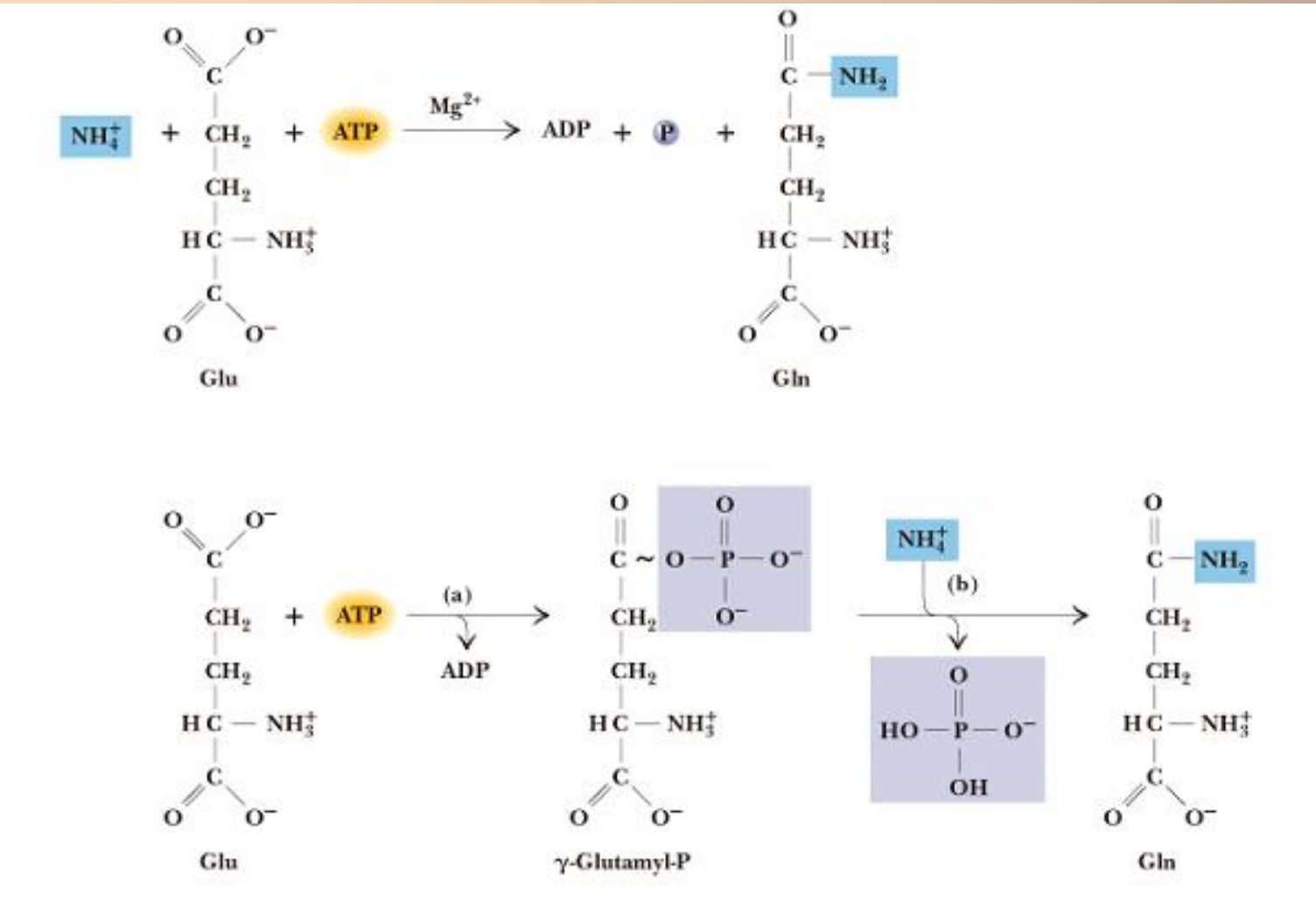
Glutamine Carries Ammonia to the Liver



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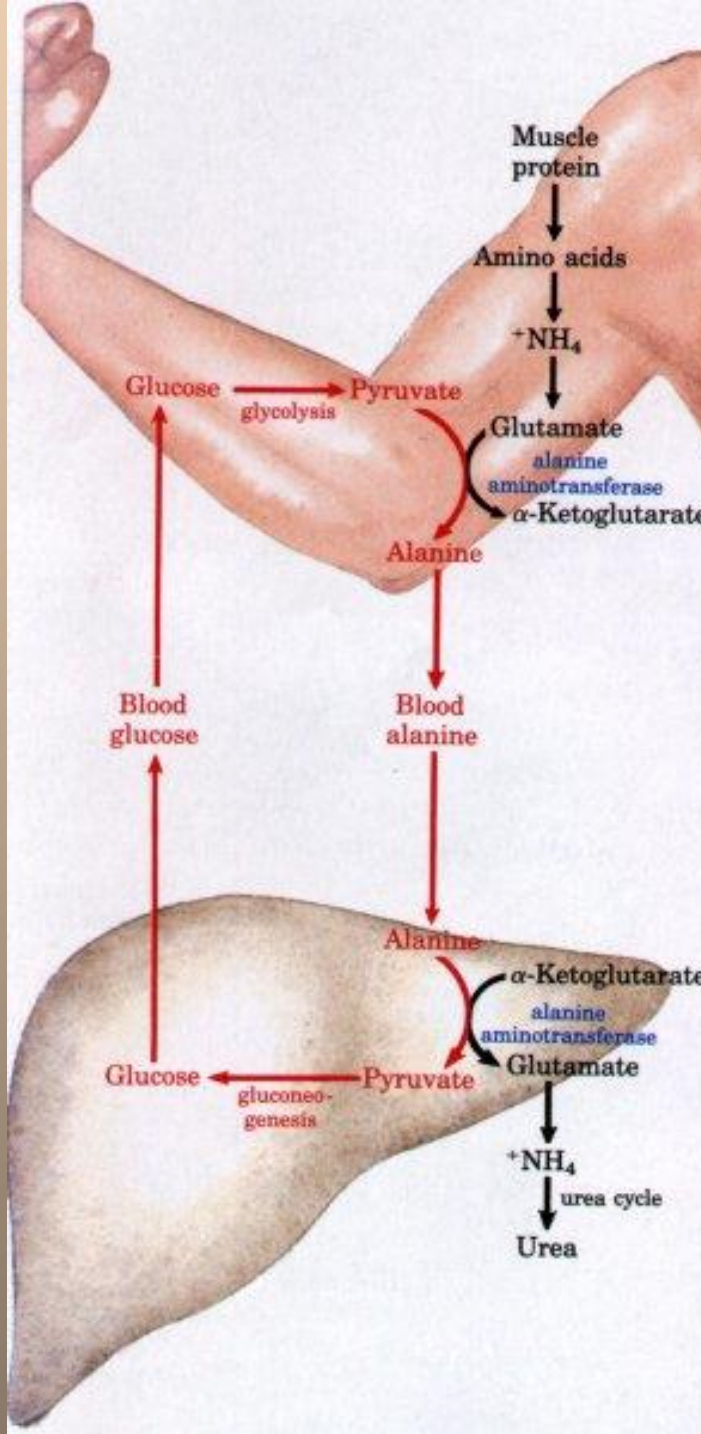
Alanine Carries Ammonia from Muscles to the Liver

Alanine serves as a carrier of ammonia equivalents and of the carbon skeleton of pyruvate from muscle to liver. The ammonia is excreted, and the pyruvate is used to produce glucose, which is returned to the muscle.



The glucose-alanine cycle

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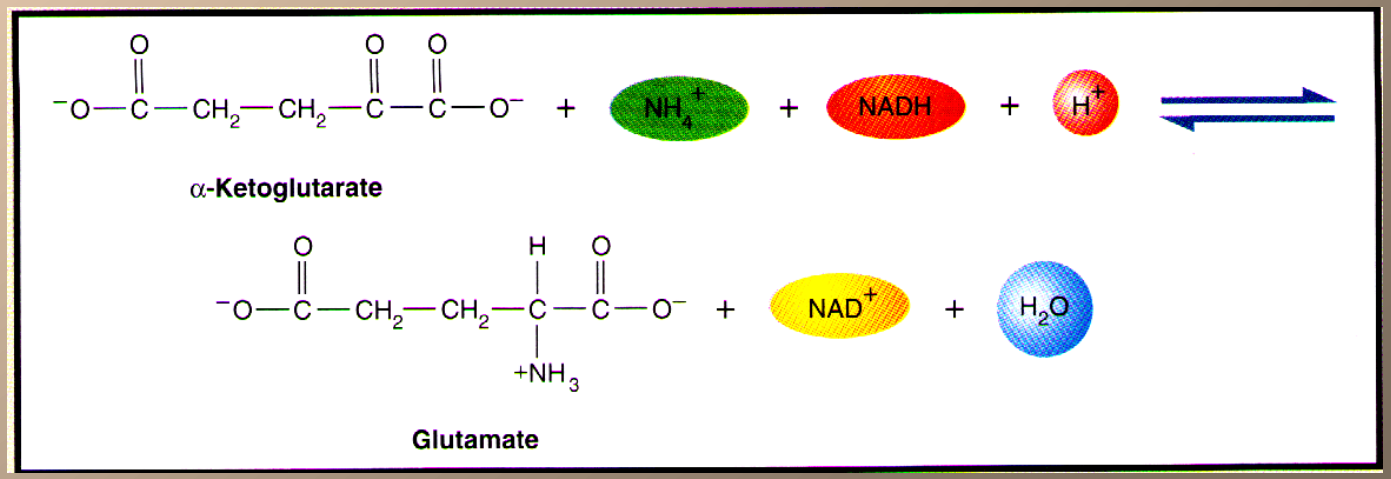
Ammonia Is Toxic to Animals

Ammonia readily traverses the brain blood barrier and in the brain is converted to glutamate via glutamate dehydrogenase, depleting the brain of a-ketoglutarate. As the a-ketoglutarate is depleted, oxaloacetate falls correspondingly, and ultimately TCA cycle activity comes to a halt. In the absence of aerobic oxidative phosphorylation and TCA cycle activity, irreparable cell damage and neural cell death ensue.



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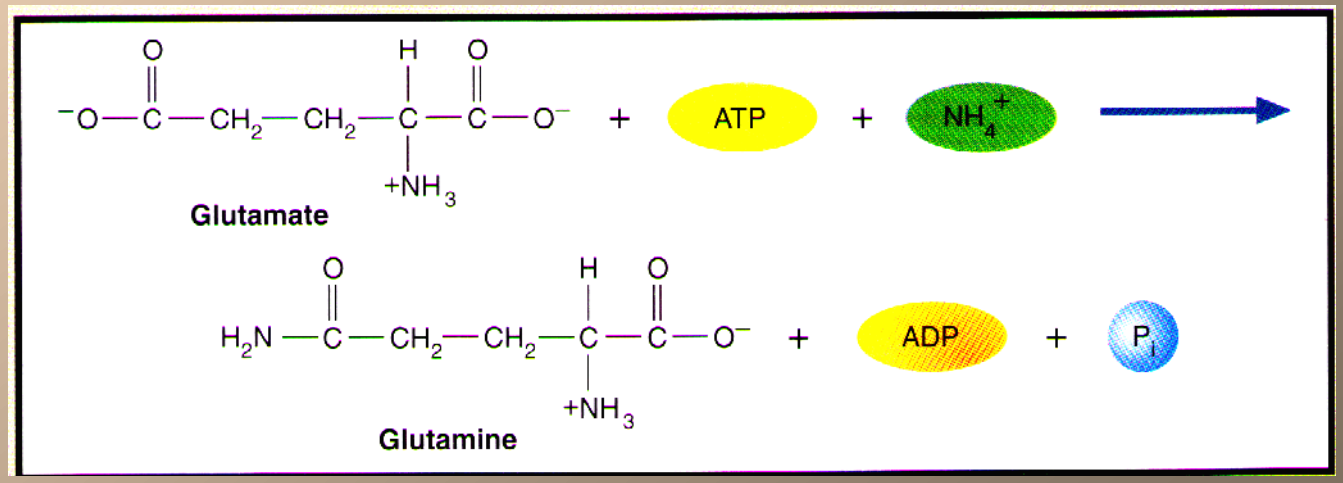
The increased glutamate leads to glutamine formation. Elevated levels of glutamine formed from NH_4^+ and glutamate produce osmotic effects that lead directly to brain swelling. This depletes glutamate stores which are needed in neural tissue since glutamate is both a neurotransmitter and a precursor for the synthesis of g-aminobutyrate, GABA, another neurotransmitter. Therefore, reductions in brain glutamate affect energy production as well as neurotransmission.



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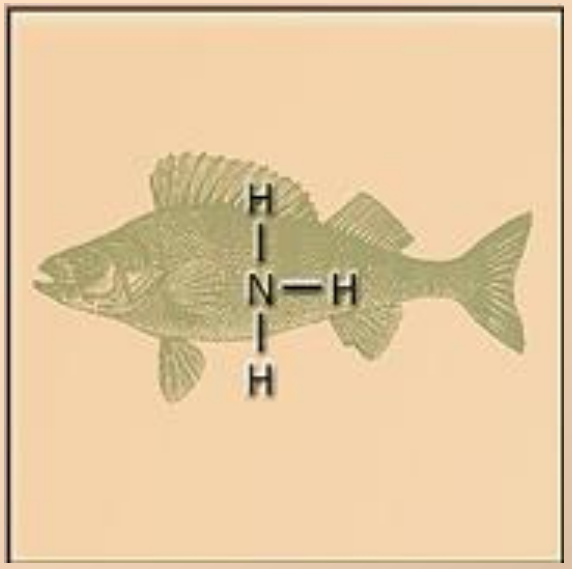
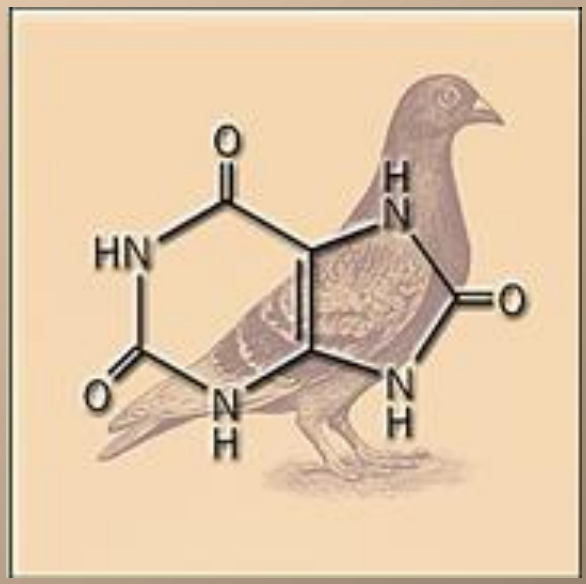
Excreted Forms of Nitrogen



Ammonia

Urea



Uric acid

Ammonotelic animals: most aquatic vertebrates, such as bony fishes and larvae of amphibia

Ureotelic animals: many terrestrial vertebrates; also sharks

Uricotelic animals: birds, reptiles

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The Fate of Ammonium

Three major reactions in all cells

- ***Carbamoyl-phosphate synthetase I***
  - ***two ATP required - one to activate bicarb, one to phosphorylate carbamate***
- ***Glutamate dehydrogenase***
  - ***reductive amination of alpha-ketoglutarate to form glutamate***
- ***Glutamine synthetase***
  - ***ATP-dependent amidation of gamma-carboxyl of glutamate to glutamine***

The Urea Cycle

In ureotelic organisms the urea cycle disposes of approximately 90% of surplus nitrogen. Urea is formed from ammonia, CO_2, and aspartate in a cyclic pathway referred to as the urea cycle.

The urea cycle is a mechanism designed to convert NH_4^+ to urea, a less toxic molecule. Note that citrulline is transported across the inner membrane by a carrier for neutral amino acids. Ornithine is transported in exchange for H^+ or citrulline. Fumarate is transported back into the mitochondrial matrix.

Because the urea cycle was discovered by Hans Krebs and Kurt Henseleit, it is often referred to as the Krebs urea cycle or the Krebs-Henseleit cycle.

Hans Krebs

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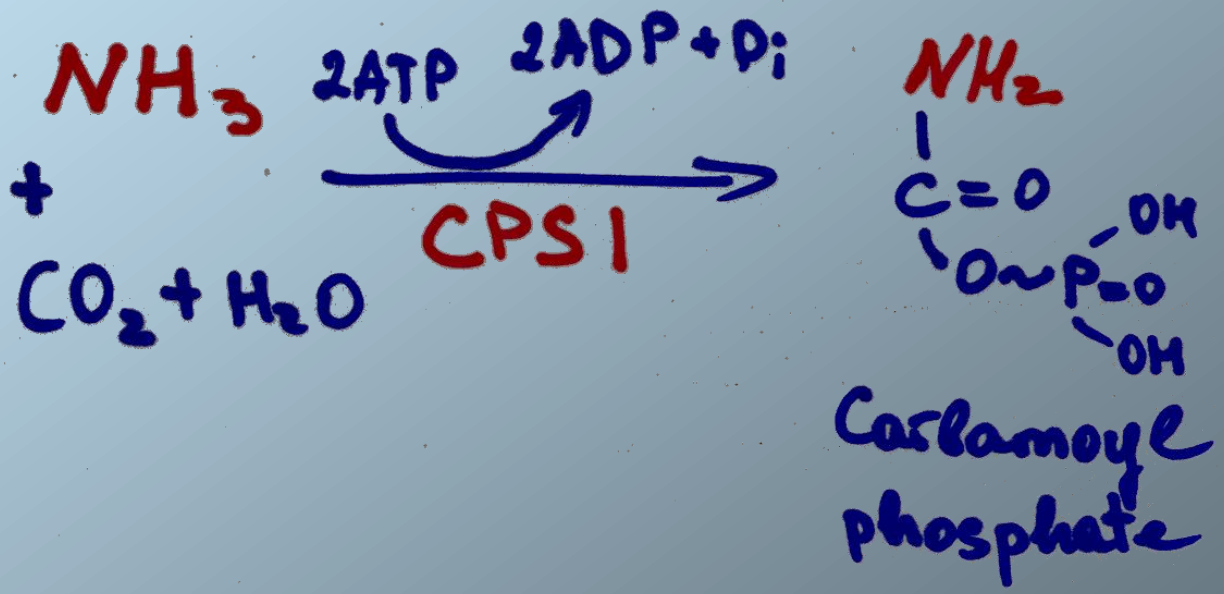
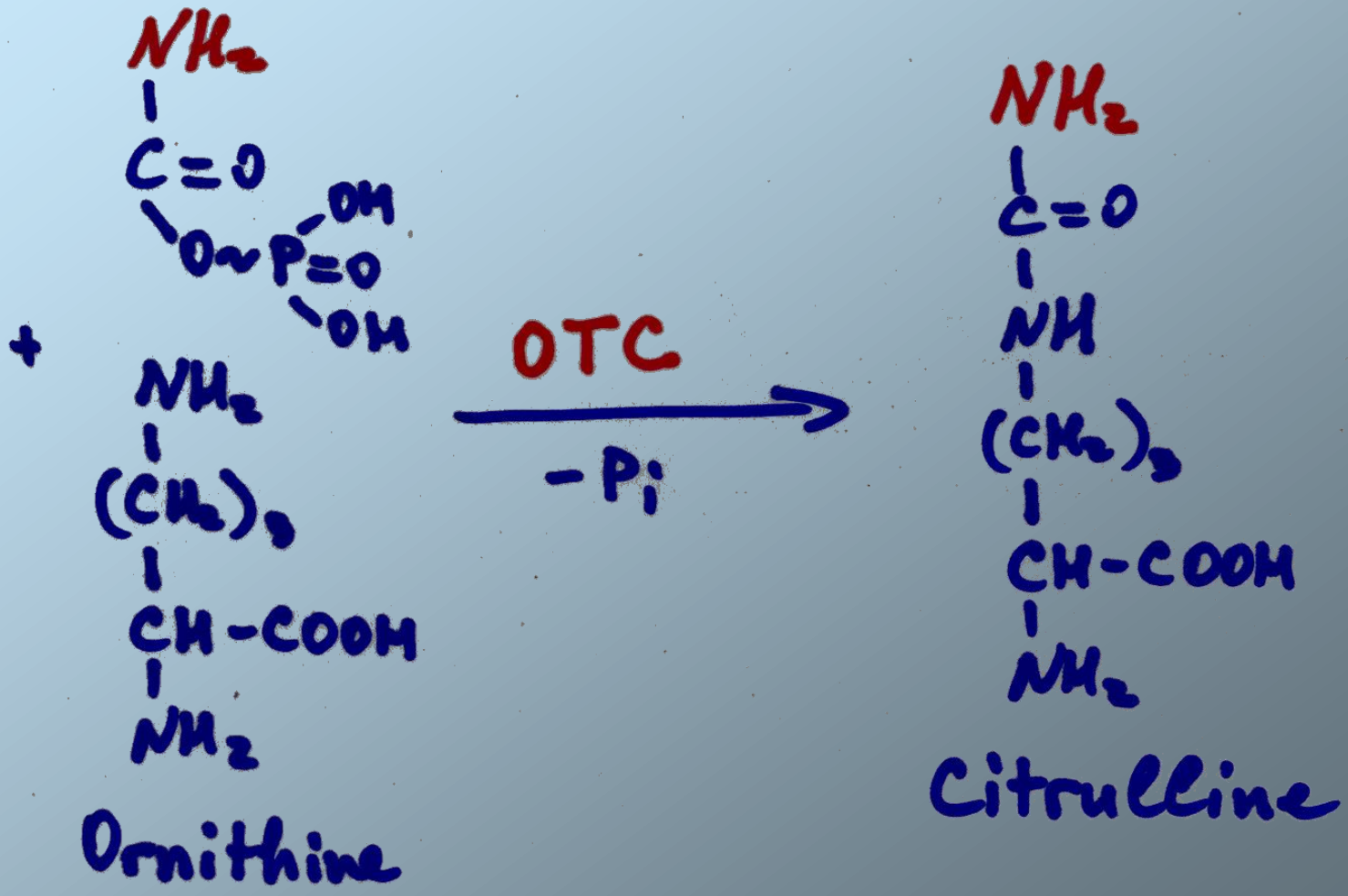
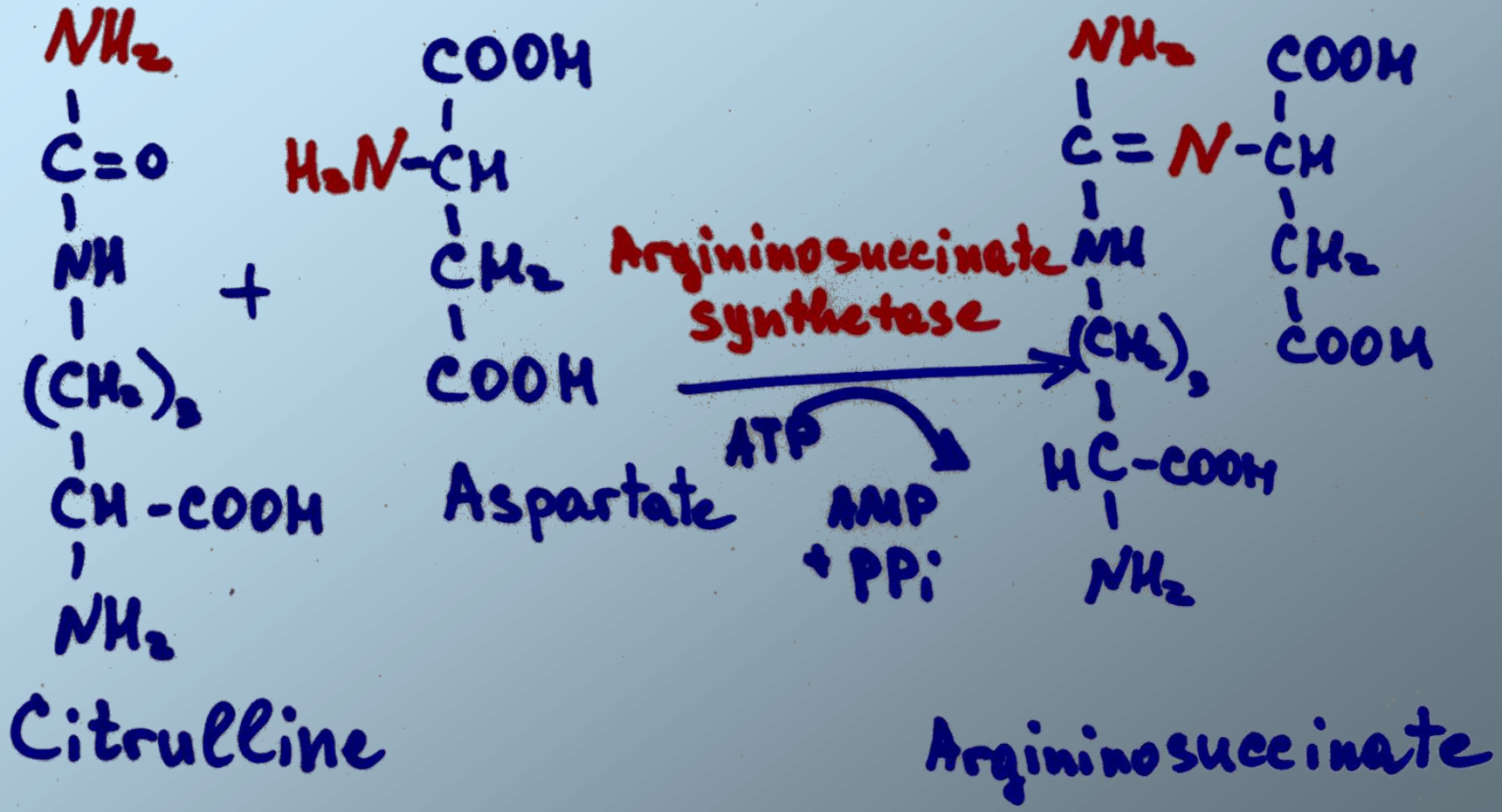
Urea synthesis begins with the formation of carbamoyl phosphate. The substrates for this reaction, which catalyzed by carbamoyl phosphate synthetase I, are NH_4^+ and HCO^- . Because two molecules of ATP are required in carbamoyl phosphate synthesis, this reaction is essentially irreversible.



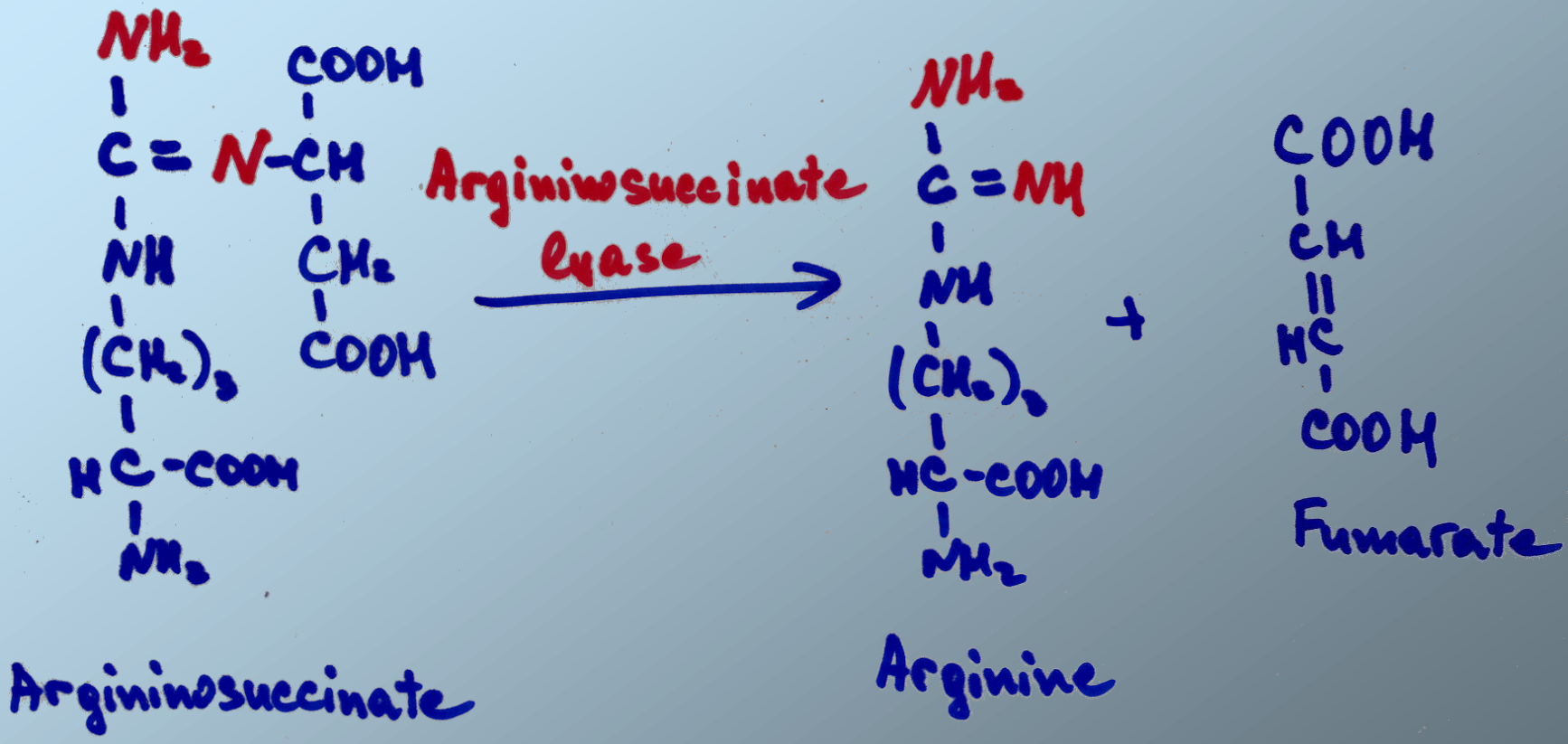
Carbamoyl phosphate subsequently reacts with ornithine to form citrulline. This reaction, which catalyzed by ornithine transcarbamoylase, is driven to completion because of the release of phosphate from carbamoyl phosphate.



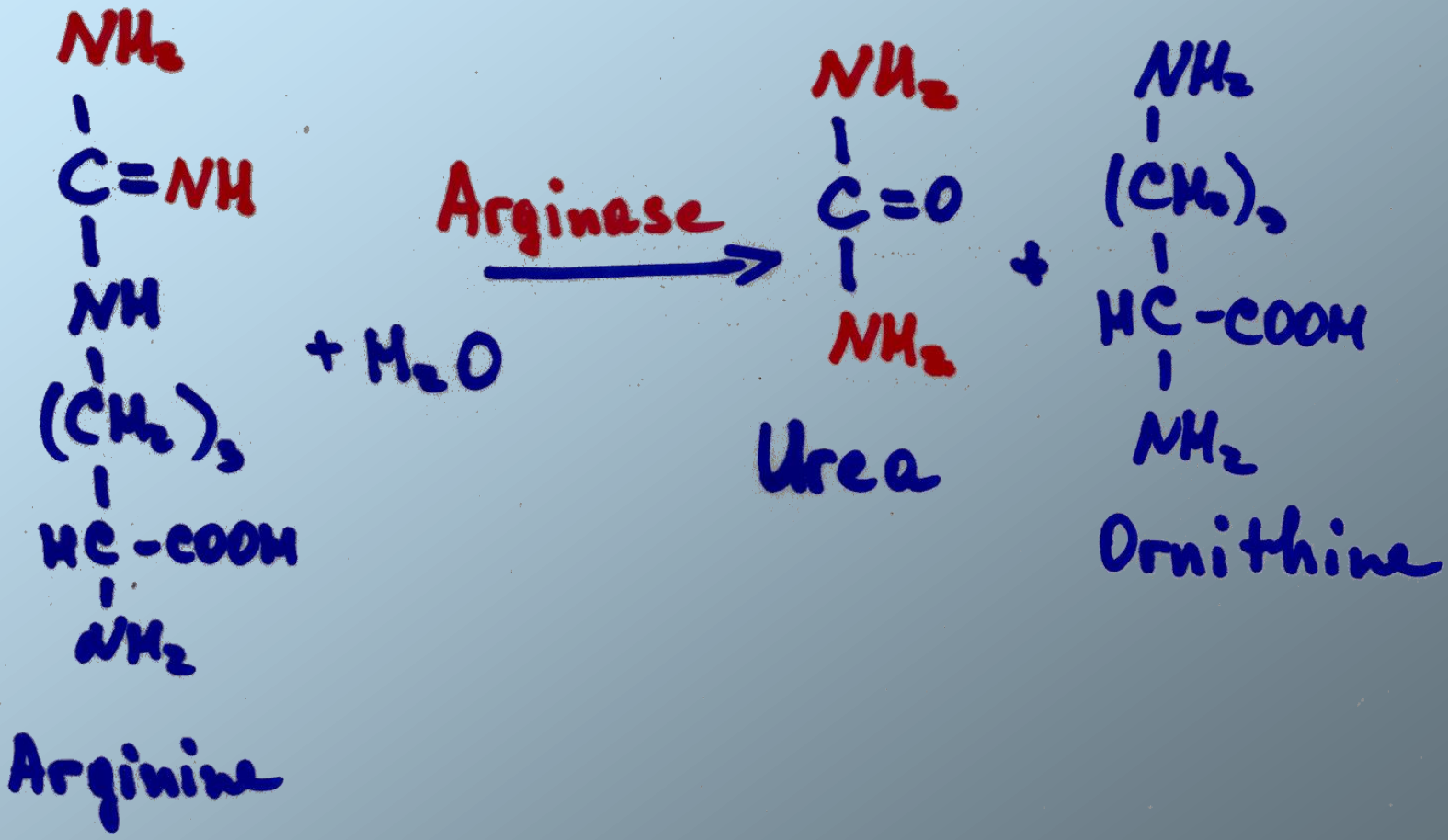
Citrulline is transported to the *cytoplasm*, where it reacts with *aspartste*. The amino group of aspartste provides the second nitrogen that is ultimately incorporated into urea. This reaction is catalyzed by *argininosuccinate synthase*.

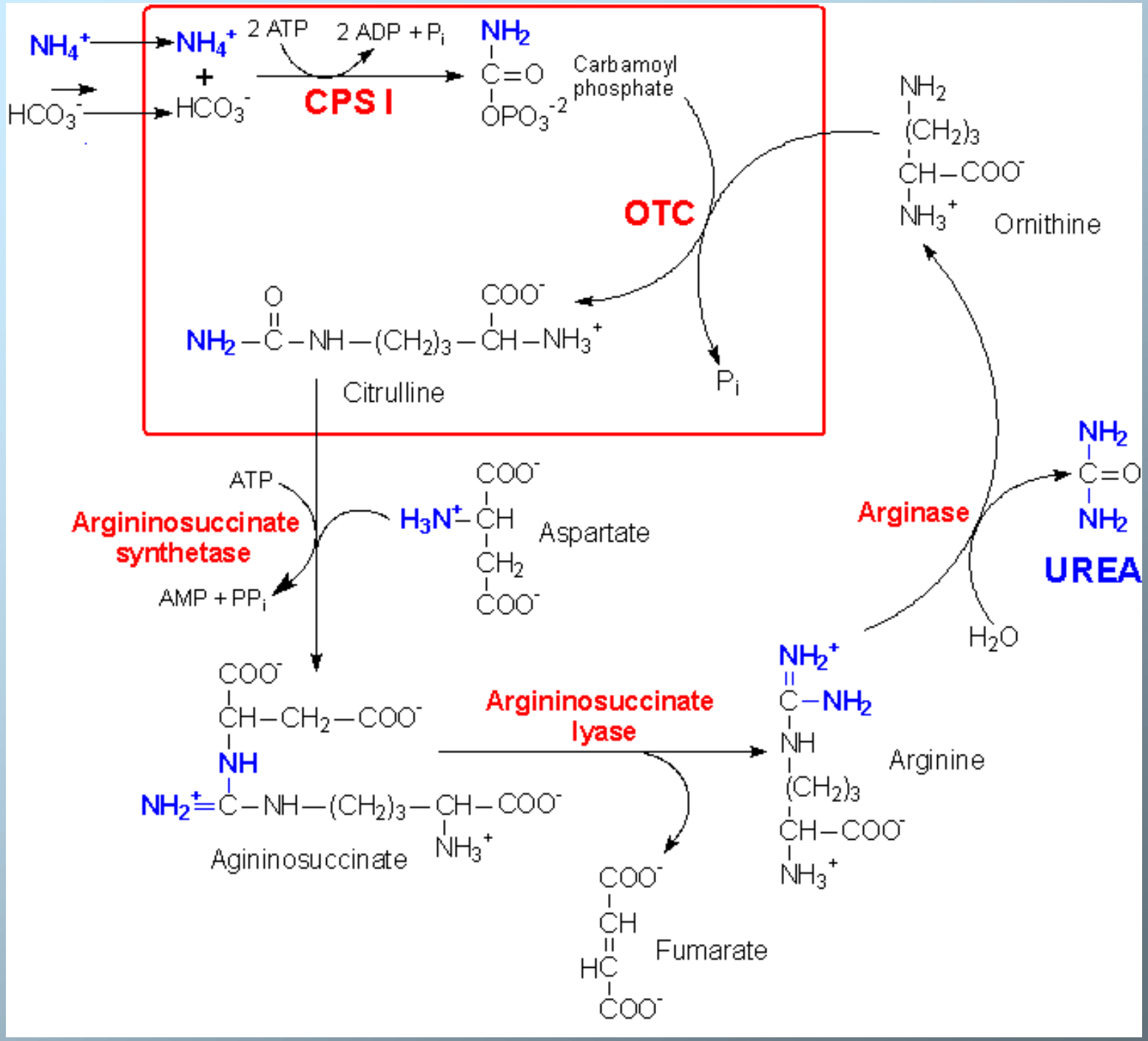


***Argininosuccinate lyase** subsequently cleaves arginosuccinate to form **arginine** (the immidiate precursor of urea) and **fumarate**.*



In the final reaction of the urea cycle, arginase catalyzes the synthesis of urea. Ornithine, the other product of this reaction, is transported into the mitochondrial matrix, thus enabling the urea cycle to continue.





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The Urea Cycle Is Energetically Expensive

The overall equation of the urea cycle is

$$2NH_4^+ + HCO_3^- + 3ATP^{4-} + H_2O \longrightarrow urea + 2ADP^{3-} + 4P_i^{2-} + AMP^{2-} + 5H^+$$

The synthesis of one molecule of urea requires four high-energy phosphate groups.

Two ATPs are required to make carbamoyl phosphate, and one ATP is required to make argininosuccinate. In the latter reaction, however, the ATP undergoes a pyrophosphate cleavage to AMP and pyrophosphate, which may be hydrolyzed to yield two Pi.

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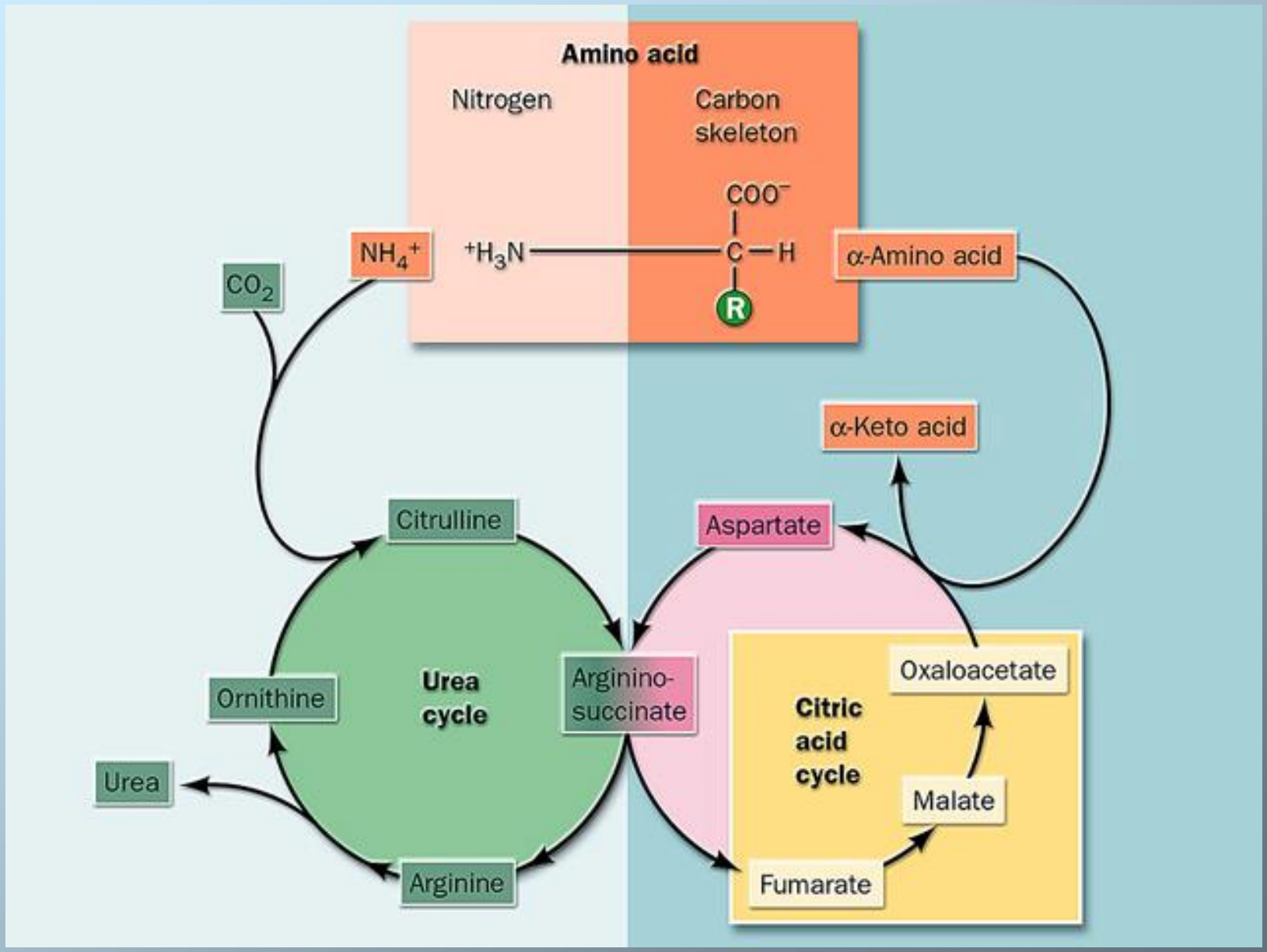
After its transport back into the mitochondrial matrix, fumarate is hydrated to form malate, a component of the citric acid cycle. The oxaloacetate product of the citric acid cycle can subsequently be used in energy generation, or it can be converted to glucose or aspartate. The relationship between the urea cycle and citric acid cycle, often referred to as Krebs bicycle.



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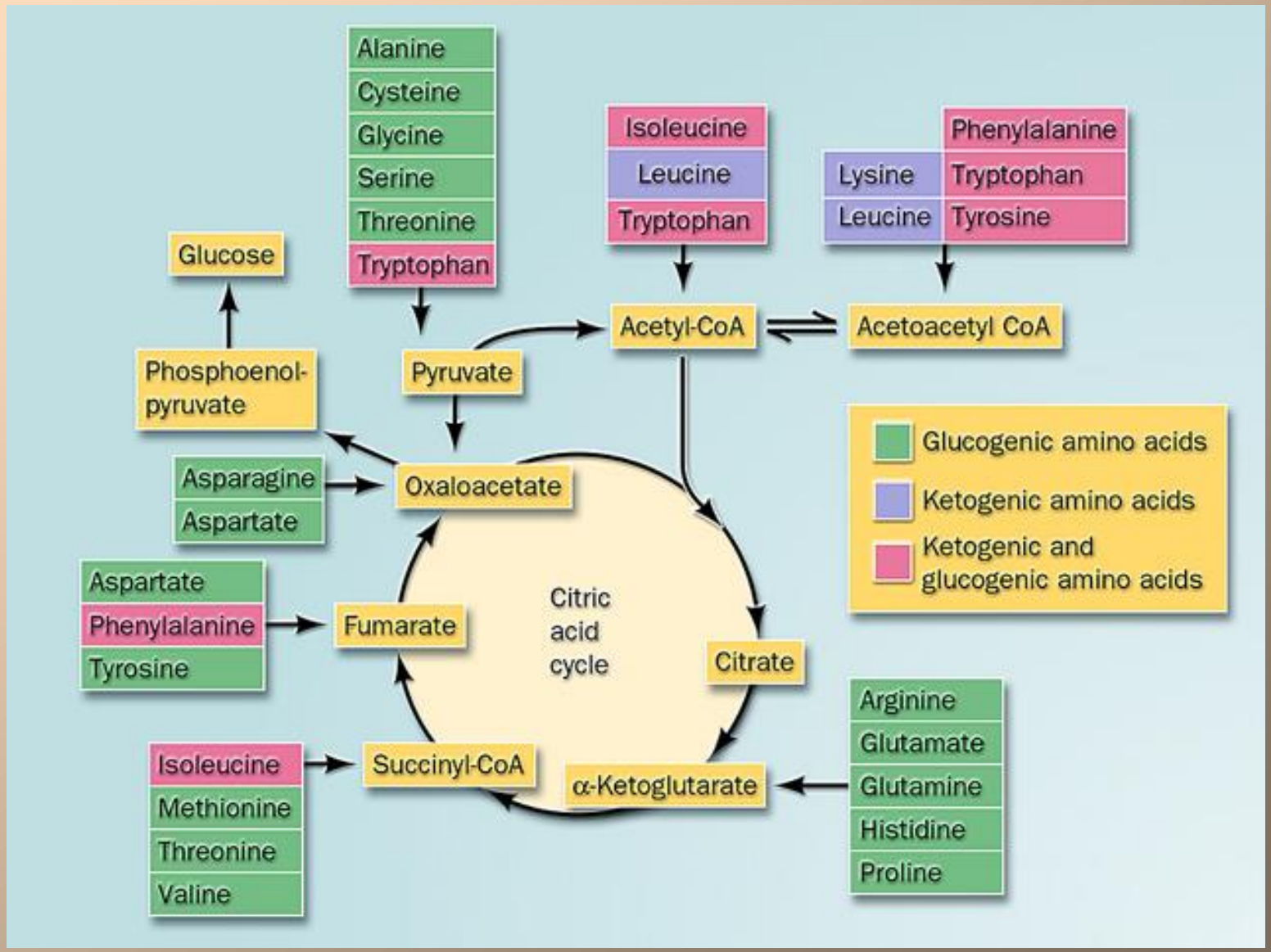
Degradation of Amino Acids

The 20 amino acids are degraded to produce (mostly) TCA intermediates



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Disorders of Amino acid Catabolism

Alkaptonuria *caused by a deficiency of homogentisate oxidase. Large quontaties of homogentisate, the substrate for defective enzyme, are excreted in urine.Homogentisate turns black when it is oxydized as the urine is exposed to air.*

Alkaptonuria is not innocuous, since alkaptonic patients developartritis in later life. In addition, pigment accumulates gradually and evenly darkens the skin.

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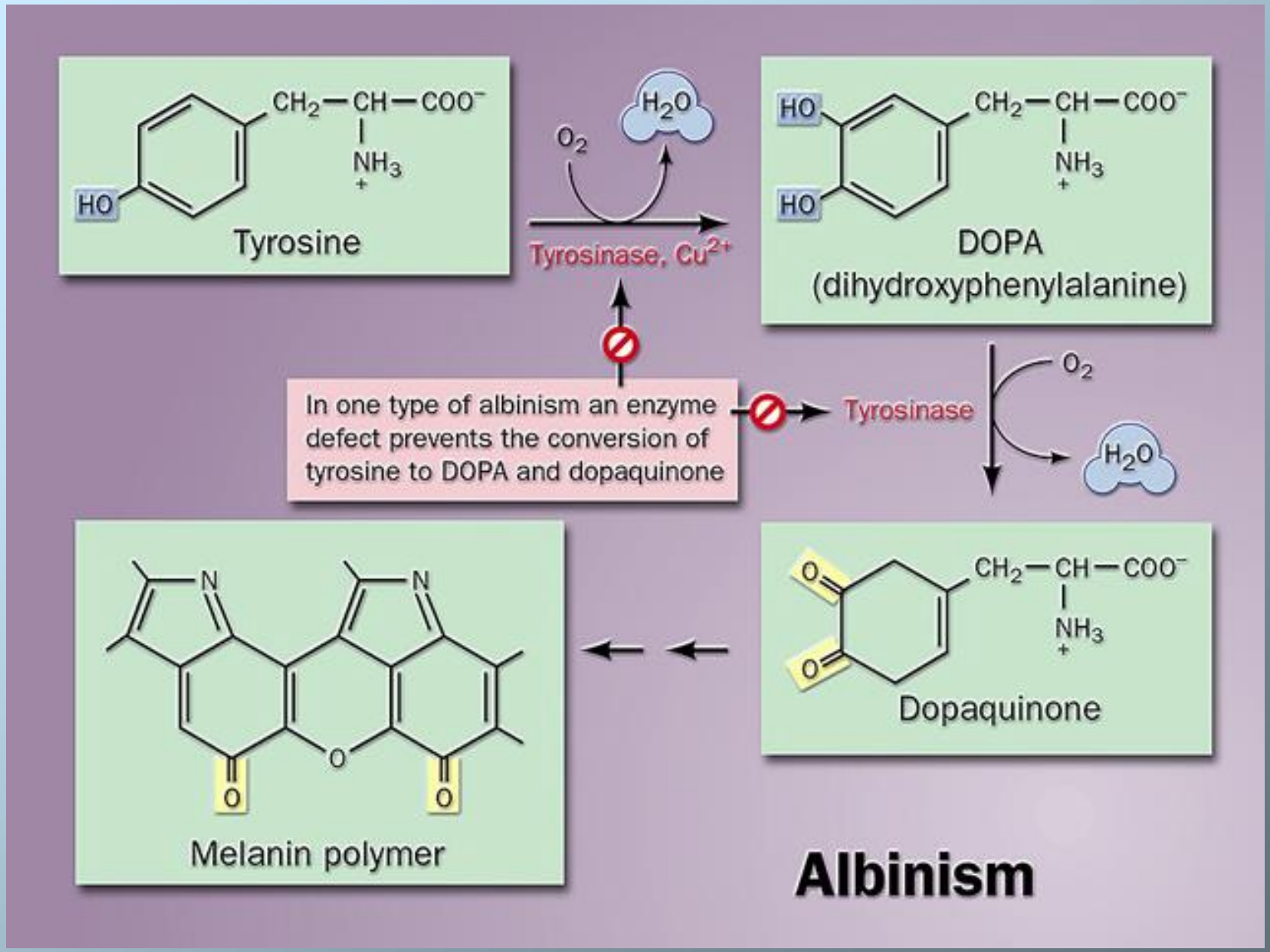

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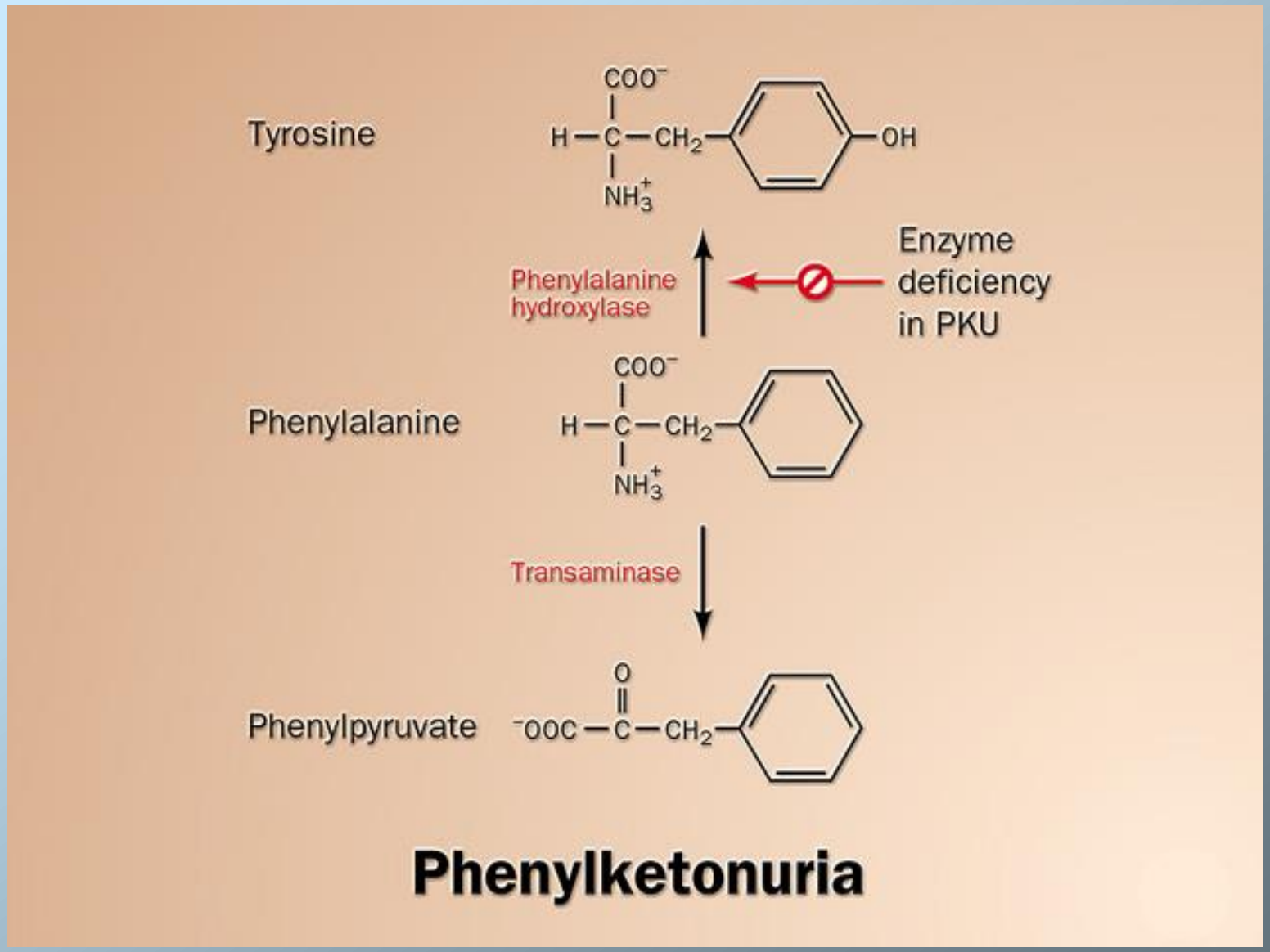
Phenylketonuria *is caused by deficiency of phenylalanine hydroxylase. If this condition is not treated immediately after berth, mental retardation and other forms of irreversible brain damage occur.*

This damage results from the accumulation of phenylalanine. When it present in excess, phenylalanine undergoes transamination to form phenylpyruvate, which is also subsequently converted to phenyllactate and phenylacetate. Large amounts of these molecules are excreted in the urine. Phenylacetate gives the urine its characteristic musty odor. Phenylketonuria is treated with a low phenylalanine diet.



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In **marple syrup urine disease**, *also called* ***branched chain ketoaciduria***, *the keto acids derived from leucine, isoleucine, and valine accumulate in large quantaties in blood. Their presence in urine imparts a characteristic odor that gives the malady its name.*

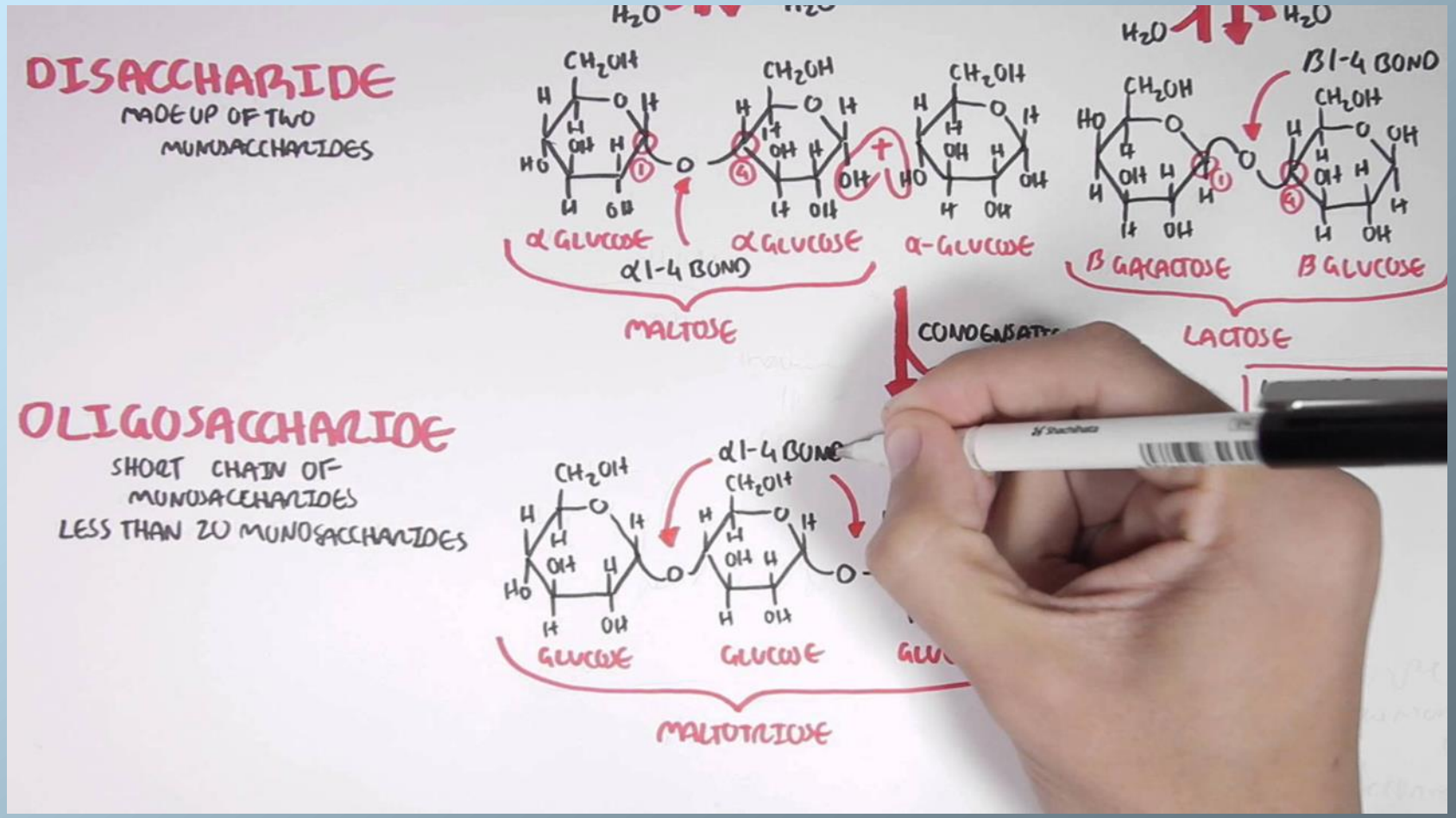
All tree keto acids accumulate because of a ***deficient branched chain keto acid dehydrogenese complex****. If left untreatedaffected individuals experience vomiting, convalsions,severe brain damage, and mental retardation. Death than occurs befor one year of age. Treatment consists of rigid dietary control.*

Conclusions

1. Organisms are very wide in there ability to synthesize amino acids.
2. Proteins are broken down by hydrolysis of peptide bonds and hence the enzymes involved are termed "peptidases".
3. Amino acids are absorbed by intestinal epithelial cells and released into the blood by two types of transport system: sodium-amino acid carrier system and γ-glutamyl cycle.
4. Amino acids that re immediately available for utilization in metabolic process are referred to as the amino acid pool.
5. The removal of the α-amino group from the amino acid involves two types of biochemical reactions: transamination and oxidative deamination.
6. Urea is formed from ammonia, CO2, and aspartate in a cyclic pathway referred to as the urea cycle. In ureotelic organisms the urea cycle disposes of approximately 90% of surplus nitrogen.
7. A significant percentage of neurotransmitter molecules are either amino acid or amino acid derivatives (due to decarboxylation). The latter class is often referred to as the biogenic amines.

Do you have any questions?

Thank you for your attention!



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