Protein Metabolism

ZOO 630

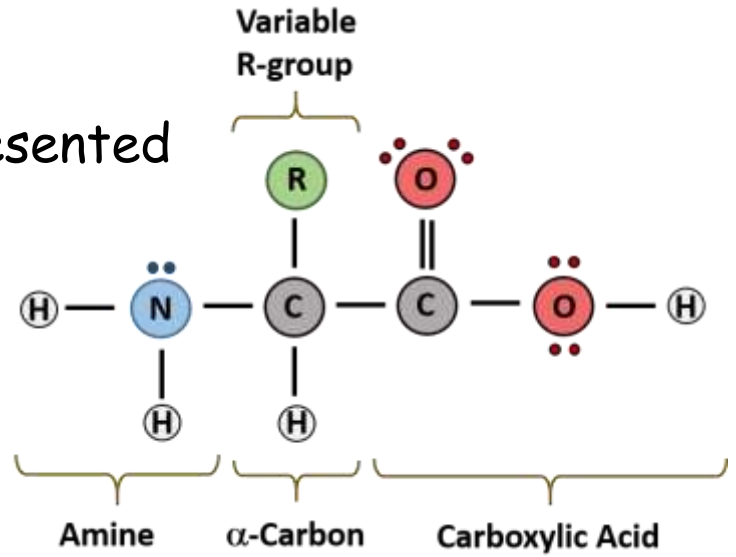
Outline

- Basic Properties of Proteins.
- Transport and Storage of Amino Acids.
- Functional Roles of the Plasma Proteins.
- Use of Proteins for Energy.
  - Transamination.
  - Deamination.
  - Urea Formation.
- Obligatory Degradation of Proteins.

- About three quarters of the body solids are proteins.
- These proteins include structural proteins, enzymes, nucleoproteins, proteins that transport oxygen, proteins of the muscle that cause muscle contraction, and many other types that perform specific intracellular and extracellular functions throughout the body.
- The basic chemical properties that explain the diverse functions of proteins are so extensive that they constitute a major portion of the entire discipline of biochemistry. For this reason, the current discussion is confined to a few specific aspects of protein metabolism that are important as background for other discussions in this text.

Basic Properties of Proteins

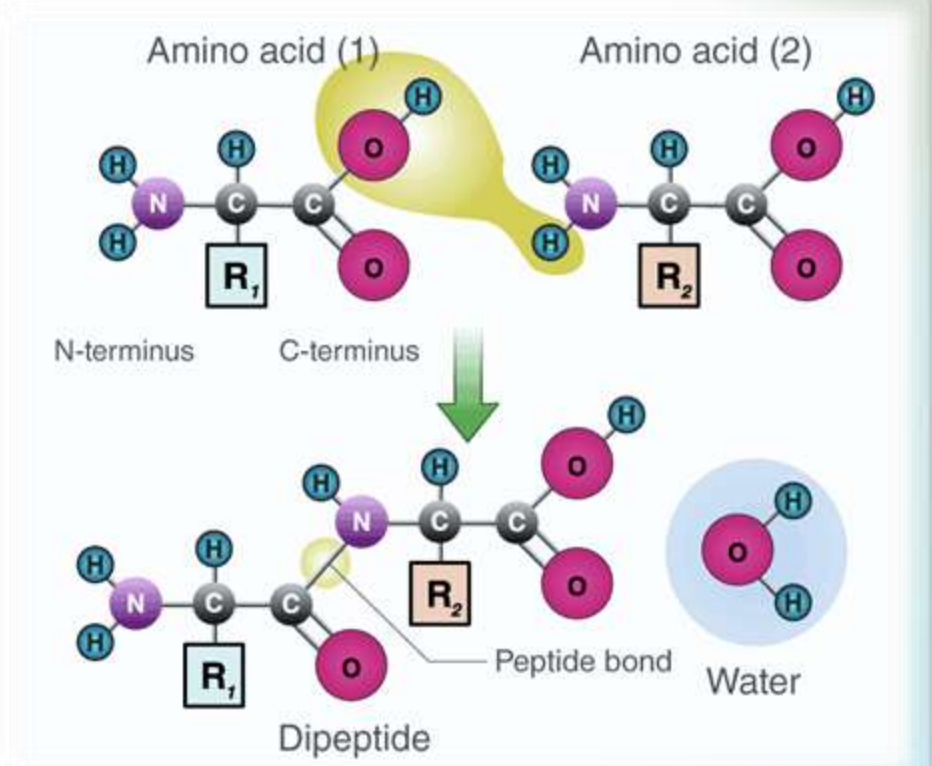
- The principal constituents of proteins are amino acids. Twenty of these amino acids are present in the body proteins in significant quantities.
- **The chemical formulas of these 20 amino acids, demonstrates that they all have two features in common:**
  - An acidic group (–COOH).
  - A nitrogen atom attached to the molecule, usually represented by the amino group (–NH2).



Peptide Linkages and Peptide Chains.

- The amino acids of proteins are aggregated into long chains by means of peptide linkages. The chemical nature of this linkage is demonstrated by the following reaction.

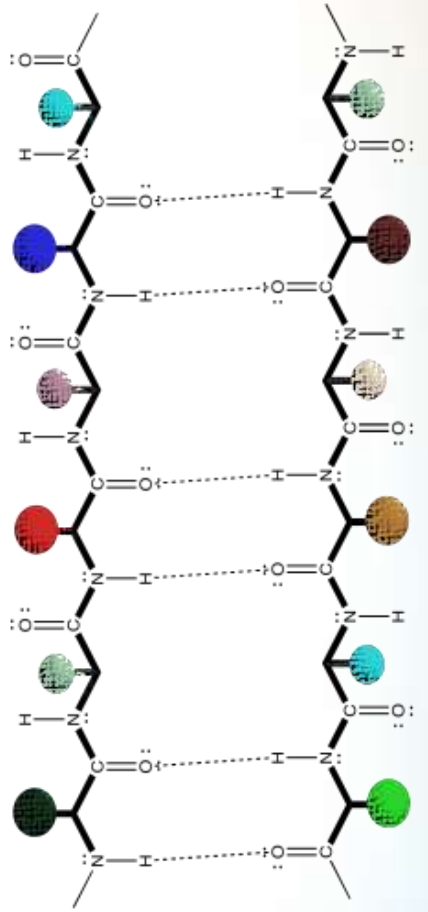
- Note in this reaction that the nitrogen of the amino radical of one amino acid bonds with the carbon of the carboxyl radical of the other amino acid.
- A hydrogen ion is released from the amino radical, and a hydroxyl ion is released from the carboxyl radical; these two ions combine to form a molecule of water.
- After the peptide linkage has been formed, an amino radical and a carboxyl radical are still at opposite ends of the new, longer molecule.
- Each of these radicals is capable of combining with additional amino acids to form a peptide chain.



- Each of these radicals is capable of combining with additional amino acids to form a peptide chain. Some complicated protein molecules have many thousands of amino acids combined by peptide linkages, and even the smallest protein molecule usually has more than 20 amino acids combined by peptide linkages. The average is about 400 amino acids

Other Linkages in Protein Molecules.

- Some protein molecules are composed of several peptide chains rather than a single chain, and these chains are bound to one another by other linkages, often by hydrogen bonding between the CO and NH radicals of the peptides, as follows:
- Many peptide chains are coiled or folded, and the successive coils or folds are held in a tight spiral or in other shapes by similar hydrogen bonding and other forces



Transport and Storage of Amino Acids

- The normal concentration of amino acids in the blood is between 35 and 65 mg/dl, which is an average of about 2 mg/dl for each of the 20 amino acids, although it varies.
- Because the amino acids are relatively strong acids, they exist in the blood principally in the ionized state, as a result of the removal of one hydrogen atom from the NH2 radical.
- They actually account for 2 to 3 milliequivalents of the negative ions in the blood.
- The precise distribution of the different amino acids in the blood depends to some extent on the types of proteins eaten, but the concentrations of at least some individual amino acids are regulated by selective synthesis in the different cells.

Fate of Amino Acids Absorbed From the Gastrointestinal Tract

- The products of protein digestion and absorption in the gastrointestinal tract are almost entirely amino acids;
- Only rarely are polypeptides or whole protein molecules absorbed from the digestive tract into the blood.

- Soon after a meal, the amino acid concentration in a person's blood rises the increase is usually only a few milligrams per deciliter, for two reasons:
  - First, protein digestion and absorption are usually extended over 2 to 3 hours, which allows only small quantities of amino acids to be absorbed at a time
  - Second, after entering the blood, the additional amino acids are absorbed within 5 to 10 minutes by cells throughout the body, especially by the liver.
- Therefore, large concentrations of amino acids almost never accumulate in the blood and tissue fluids.
- The turnover rate of the amino acids is so rapid that many grams of proteins can be carried from one part of the body to another in the form of amino acids each hour

Active Transport of Amino Acids Into the Cells

- The molecules of all the amino acids are much too large to diffuse readily through the pores of the cell membranes.
- Therefore, amino acids can move either inward or outward through the membranes only by facilitated transport or active transport using carrier mechanisms.

Renal Threshold for Amino Acids:

- In the kidneys, the different amino acids can be reabsorbed through the proximal tubular epithelium by secondary active transport.
- Which removes them from the glomerular filtrate and returns them to the blood as they filter into the renal tubules through the glomerular membranes.
- However, there is an upper limit to the rate at which each type of amino acid can be transported.
- For this reason, when the concentration of a particular type of amino acid becomes too high in the plasma and glomerular filtrate, the excess that cannot be actively reabsorbed is lost into the urine.

Storage of Amino Acids as Proteins in the Cells

- After entry into tissue cells, amino acids combine with one another by peptide linkages, under the direction of the cell's messenger RNA and ribosomal system, to form cellular proteins.
- Therefore, the concentration of free amino acids inside most cells usually remains low, and storage of large quantities of free amino acids does not occur in the cells;
- Instead, they are stored mainly in the form of actual proteins. However, many of these intracellular proteins can be rapidly decomposed again into amino acids under the influence of intracellular lysosomal digestive enzymes. These amino acids can then be transported back out of the cell into the blood.

- Special exceptions to this reversal process are the proteins in the chromosomes of the nucleus and the structural proteins such as collagen and muscle contractile proteins. These proteins do not participate significantly in this reverse digestion and transport back out of the cells.
- Some tissues of the body participate in the storage of amino acids to a greater extent than do others.
- For instance, the liver, which is a large organ and has special systems for processing amino acids, can store large quantities of rapidly exchangeable proteins, which is also true of the kidneys and the intestinal mucosa to a lesser extent.

Release of Amino Acids From the Cells as a Means of Regulating Plasma Amino Acid Concentration.

- Whenever plasma amino acid concentrations fall below normal levels, the required amino acids are transported out of the cells to replenish their supply in the plasma.
- In this way, the plasma concentration of each type of amino acid is maintained at a reasonably constant value.

Reversible Equilibrium Between the Proteins in Different Parts of the Body

- Because cellular proteins in the liver (and, to a much less extent, in other tissues) can be synthesized rapidly from plasma amino acids, and because many of these proteins can be degraded and returned to the plasma almost as rapidly,
- constant interchange and equilibrium occurs between the plasma amino acids and labile proteins in virtually all cells of the body.
- For instance, if a particular tissue requires proteins, it can synthesize new proteins from the amino acids of the blood; in turn, the blood amino acids are replenished by degradation of proteins from other cells of the body, especially from the liver cells.
- These effects are particularly noticeable in relation to protein synthesis in cancer cells. Cancer cells are often prolific users of amino acids; therefore, the proteins of the other cells can become markedly depleted.

Upper Limit for the Storage of Proteins:

- Each particular type of cell has an upper limit with regard to the amount of proteins it can store.
- After all the cells have reached their limits, the excess amino acids still in the circulation are degraded into other products and used for energy, or they are converted to fat or glycogen and stored in these forms.

Functional Roles of the Plasma Proteins

The major types of protein present in the plasma are albumin, globulin, and fibrinogen:

Name of Amino Acid	Function
Albumin	to provide colloid osmotic pressure in the plasma, which prevents plasma loss from the capillaries.
Globulins	• Perform several enzymatic functions in the plasma. • They are principally responsible for both the natural and acquired immunity of the body against invading organisms
Fibrinogen	polymerizes into long fibrin threads during blood coagulation, thereby forming blood clots that help repair leaks in the circulatory system.

Formation of the Plasma Proteins:

- Essentially all the albumin and fibrinogen of the plasma proteins, as well as 50 to 80 percent of the globulins, are formed in the liver.
- The remaining globulins, which are formed almost entirely in the lymphoid tissues, are mainly the gamma globulins that constitute the antibodies used in the immune system.
- The rate of plasma protein formation by the liver can be extremely high as much as 30 g/day.

- Certain disease conditions cause rapid loss of plasma proteins;
  - severe burns that denude large surface areas of the skin can cause the loss of several liters of plasma through the denuded areas each day. The rapid production of plasma proteins by the liver is valuable in preventing death in such states.
  - Occasionally, a person with severe renal disease loses as much as 20 grams of plasma protein in the urine each day for months, and this plasma protein is continually replaced mainly by liver production of the required proteins.
  - In persons with cirrhosis of the liver, large amounts of fibrous tissue develop among the liver parenchymal cells, causing a reduction in their ability to synthesize plasma proteins. As discussed in Chapter 25, this phenomenon leads to decreased plasma colloid osmotic pressure, which causes generalized edema.

Plasma Proteins as a Source of Amino Acids for the Tissues

- When the tissues become depleted of proteins, the plasma proteins can act as a source of rapid replacement.
- Indeed, whole plasma proteins can be imbibed in toto by tissue macrophages through the process of pinocytosis;
- once in these cells, they are split into amino acids that are transported back into the blood and used throughout the body to build cellular proteins wherever they are needed.
- In this way, the plasma proteins function as a labile protein storage medium and represent a readily available source of amino acids whenever a particular tissue requires them.

Reversible Equilibrium Between the Plasma Proteins and the Tissue Proteins:

- A constant state of equilibrium exists among the plasma proteins, the amino acids of the plasma, and the tissue proteins.
- It has been estimated that normally about 400 grams of body protein are synthesized and degraded each day as part of the continual state of flux of amino acids, which demonstrates the general principle of reversible exchange of amino acids among the different proteins of the body.
- Even during starvation or severe debilitating diseases, the ratio of total tissue proteins to total plasma proteins in the body remains relatively constant at about 33 : 1.

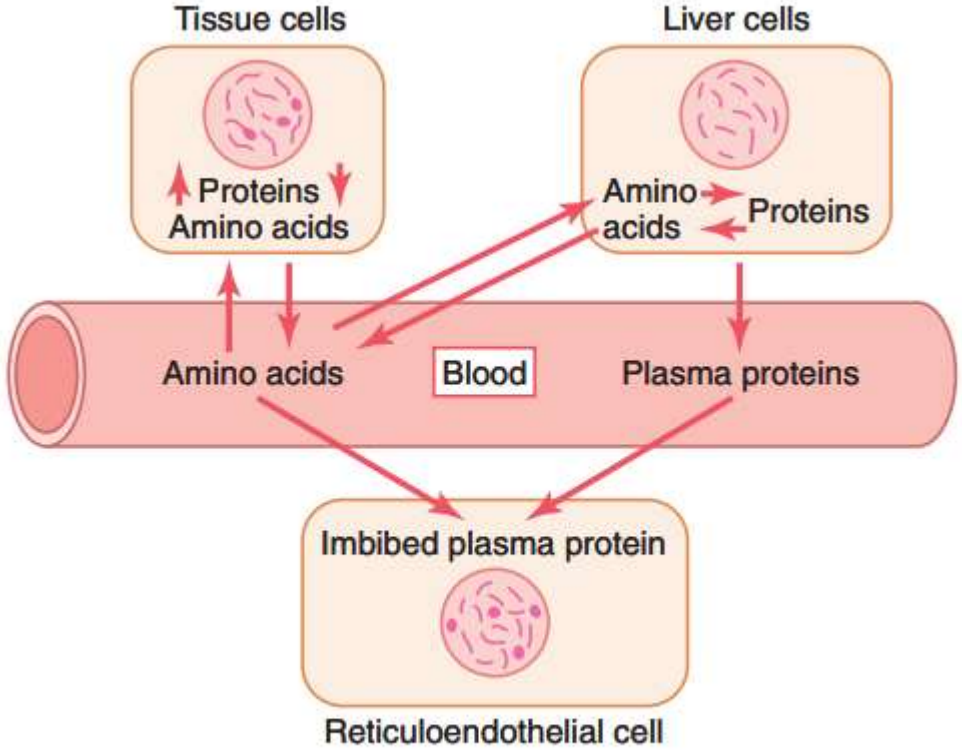


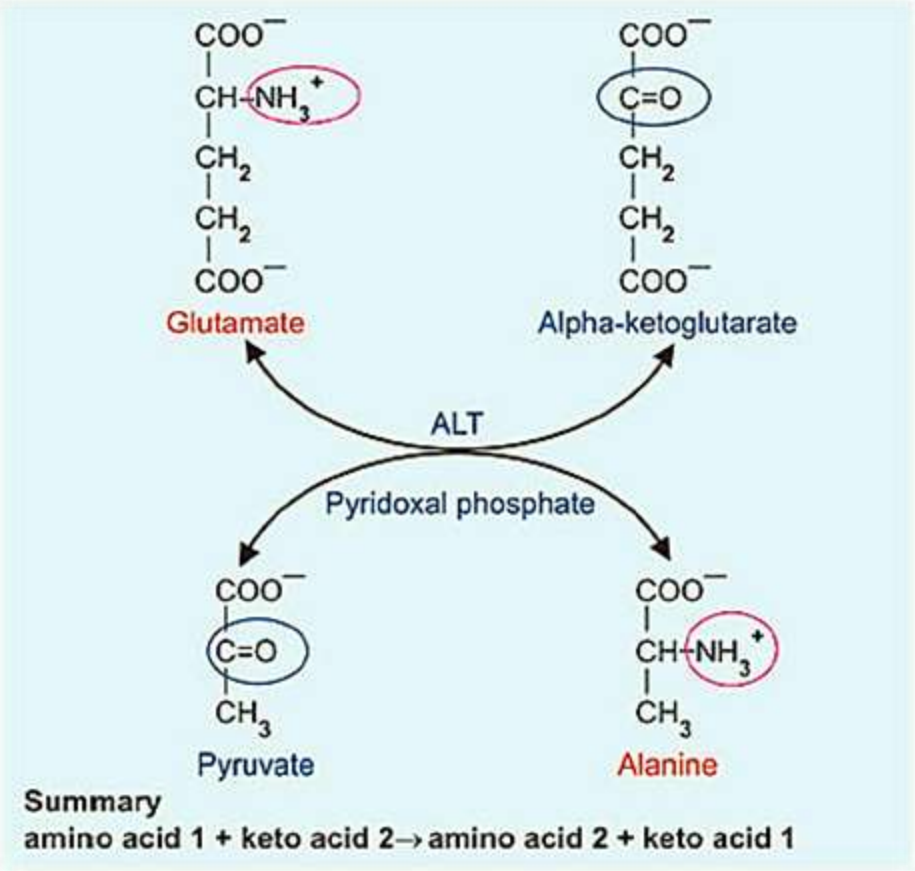
Figure 70-2. Reversible equilibrium among the tissue proteins, plasma proteins, and plasma amino acids.

Essential and Nonessential Amino Acids

- Ten of the amino acids normally present in animal proteins can be synthesized in the cells.
- Whereas the other 10 either cannot be synthesized or are synthesized in quantities too small to supply the body's needs.
  - This second group of amino acids that cannot be synthesized is called the essential amino acids. Use of the word "essential" does not mean that the other 10 "nonessential" amino acids are not required for the formation of proteins but only that the others are not essential in the diet because they can be synthesized in the body.
- Synthesis of the nonessential amino acids depends mainly on the formation of appropriate α-keto acids, which are the precursors of the respective amino acids.
- For instance, pyruvic acid, which is formed in large quantities during the glycolytic breakdown of glucose, is the keto acid precursor of the amino acid alanine.

Transamination

- The process of transamination, an amino radical is transferred to the a-keto acid, and the keto oxygen is transferred to the donor of the amino radical. Note that the amino radical is transferred to the pyruvic acid from another chemical that is closely allied to the amino acids—glutamine.
- Glutamine is present in the tissues in large quantities, and one of its principal functions is to serve as an amino radical storehouse. In addition, amino radicals can be transferred from asparagine, glutamic acid, and aspartic acid.
- Transamination is promoted by several enzymes, among which are the aminotransferases, which are derivatives of pyridoxine, one of the B vitamins (B6). Without this vitamin, the amino acids are poorly synthesized and protein formation cannot proceed normally.



Use of Proteins for Energy

- Once the cells are filled to their limits with stored protein, any additional amino acids in the body fluids are degraded and used for energy or are stored mainly as fat or secondarily as glycogen. This degradation occurs almost entirely in the liver, and it begins with deamination, which is explained in the following section.

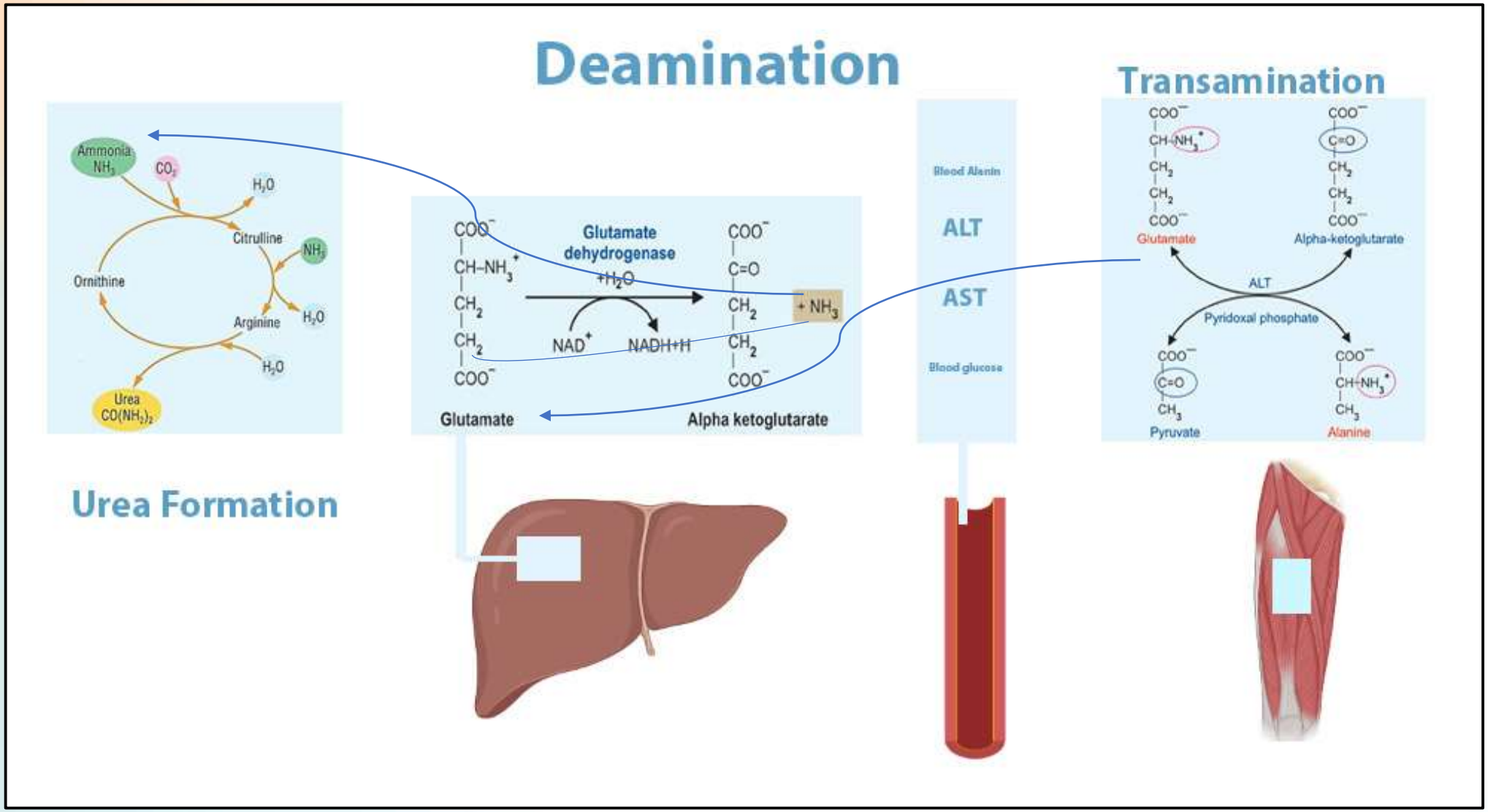
Deamination—the Removal of Amino Groups From Amino Acids:

- Deamination occurs mainly by transamination, which means transfer of the amino group to some acceptor substance. This process is the reverse of transamination, which was explained earlier in relation to the synthesis of amino acids..

Deamination

- The greatest amount of deamination occurs according to the following transamination schema:
- Note from this schema that the amino group from the amino acid is transferred to a-ketoglutaric acid, which then becomes glutamic acid. The glutamic acid can then transfer the amino group to other substances or release it in the form of ammonia (NH3). In the process of losing the amino group, the glutamic acid once again becomes a-ketoglutaric acid, so the cycle can be repeated again and again. To initiate this process, the excess amino acids in the cells, especially in the liver, induce activation of large quantities of aminotransferases, the enzymes responsible for initiating most deamination

Deamination Transamination Mind Map

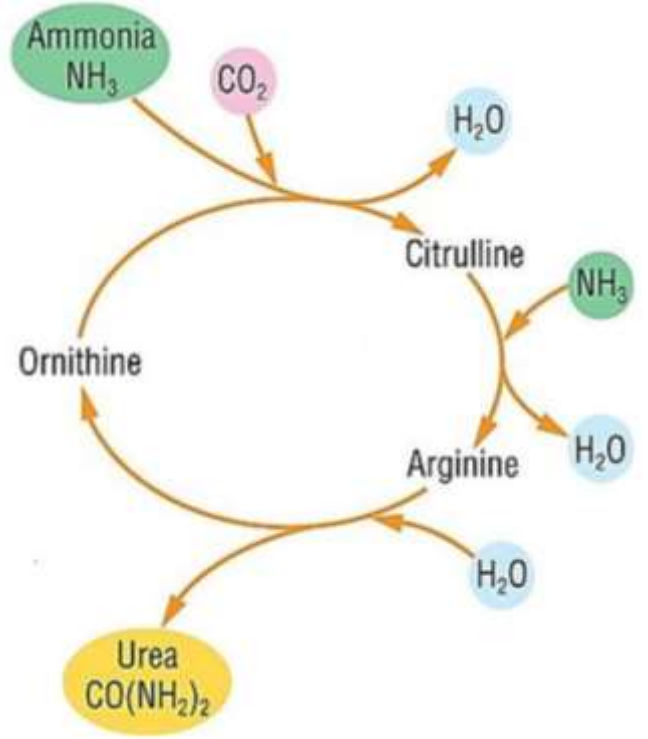


Urea Formation by the Liver:

- The ammonia released during deamination of amino acids is removed from the blood almost entirely by conversion into urea. Two molecules of ammonia and one molecule of carbon dioxide combine in the following net reaction:

$$2NH_3 + CO_2 \rightarrow H_2N{-}\underset{\underset{O}{\|}}{C}{-}NH_2 + H_2O$$

- Essentially all urea formed in the human body is synthesized in the liver. In the absence of the liver or in persons with serious liver disease, ammonia accumulates in the blood. This accumulation of ammonia is extremely toxic, especially to the brain, and can lead to a state called hepatic coma. The stages in the formation of urea are essentially the following:
- After its formation, the urea diffuses from the liver cells into the body fluids and is excreted by the kidneys



Oxidation of Deaminated Amino Acids:

Once amino acids have been deaminated, the resulting keto acids can, in most instances, be oxidized to release energy for metabolic purposes. This oxidation usually involves two successive processes:

(1) The keto acid is changed into an appropriate chemical substance that can enter the citric acid cycle,

(2) This substance is degraded by the cycle and used for energy in the same manner that acetyl coenzyme A (acetyl-CoA) derived from carbohydrate and lipid metabolism is used. In general, the amount of adenosine triphosphate formed for each gram of protein that is oxidized is slightly less than that formed for each gram of glucose that is oxidized.

Gluconeogenesis and Ketogenesis

- Certain deaminated amino acids are similar to the substrates normally used by the cells, mainly the liver cells, to synthesize glucose or fatty acids. For instance, deaminated alanine is pyruvic acid, which can be converted into either glucose or glycogen. Alternatively, it can be converted into acetyl-CoA, which can then be polymerized into fatty acids.
- Also, two molecules of acetyl-CoA can condense to form acetoacetic acid, which is one of the ketone bodies. The conversion of amino acids into glucose or glycogen is called gluconeogenesis, and the conversion of amino acids into keto acids or fatty acids is called ketogenesis. Of the 20 deaminated amino acids, 18 have chemical structures that allow them to be converted into glucose, and 19 of them can be converted into fatty acids.

Obligatory Degradation of Proteins

- When a person eats no proteins, a certain proportion of body proteins is degraded into amino acids and then deaminated and oxidized.
- This process involves 20 to 30 grams of protein each day, which is called the obligatory loss of proteins.
- Therefore, to prevent net loss of protein from the body, the average person must ingest a minimum of 20 to 30 grams of protein each day, although this amount depends on multiple factors, including muscle mass, activity, and age; to be on the safe side, a minimum of 60 to 75 grams is usually recommended.

- The ratios of the different amino acids in the dietary protein must be about the same as the ratios in the body tissues if the entire dietary protein is to be fully usable to form new proteins in the tissues.
- If one particular type of essential amino acid is low in concentration, the others become unusable because cells synthesize either whole proteins or none at all. The unusable amino acids are deaminated and oxidized.
- A protein that has a ratio of amino acids different from that of the average body protein is called a partial protein or an incomplete protein, and such a protein is less valuable for nutrition than is a complete protein.

Effect of Starvation on Protein Degradation

- Except for the 20 to 30 grams of obligatory protein degradation each day, the body uses almost entirely carbohydrates or fats for energy, as long as they are available.
- However, after several weeks of starvation, when the quantities of stored carbohydrates and fats begin to run out, the amino acids of the blood are rapidly deaminated and oxidized for energy. From this point on, the proteins of the tissues degrade rapidly—as much as 125 grams daily and, as a result, cellular functions deteriorate precipitously. Because carbohydrate and fat utilization for energy normally occurs in preference to protein utilization, carbohydrates and fats are called protein sparers.

Hormonal Regulation of Protein Metabolism

1

Growth Hormone

Increases the Synthesis of Cellular Proteins it is believed to result mainly from increased transport of amino acids through the cellmembranes, acceleration of the DNA and RNA transcription and translation processes for protein synthesis, a decreased oxidation of tissue proteins

2

Insulin

lack of insulin reduces protein synthesis to almost zero. Insulin accelerates the transport of some amino acids into cells which could be the stimulus for protein degradation and increases the availability for energy is correspondingly reduced of glucose to the cells, so the need for amino acids

3

Glucocorticoids

The glucocorticoids secreted by the adrenal cortex decrease the quantity of protein in most tissues while increasing the amino acid concentration in the plasma as well as increasing liver proteins and plasma proteins

It is believed that the glucocorticoids act by increasing the rate of breakdown of extrahepatic proteins, thereby making increased quantities of amino acids available in the body fluids. this allows the liver to synthesize increased quantities if hepatic cellular proteins and plasma proteins

4

Testosterone

it causes incresed deposition of protein in tissues throughout the body especially the contractile protiens of the muscles. testosterone causes the muscles and, to a much lesser extent, some other protein tissues to enlarge for only several months

Once the muscles and other protein tissues have reached a maximum further protein deposition .ceases

5

Estrogen

,Estrogen, the principal female sex hormone also causes some deposition of protein, but the effect of estrogen is much less compared .with that of testosterone

6

Thyroxine

Thyroxine indirectly affects protein metabolism by increasing metabolism of the cells. If insufficient ,carbohydrates and fats are available for energy thyroxine causes rapid degradation of proteins and uses them for energy conversely if they are available it can increase the protein synthesis

In growing animals or human beings, deficiency of thyroxine causes growth to be greatly inhibited because of .lack of protein synthesis

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