St. Philomena's College
Department of Biochmeistry
Amino acid Metabolism_001

Proteins are nitrogen-containing macromolecules consisting of L-α-amino acids as the repeating units. Of the 20 amino acids found in proteins, half can be synthesized by the body (non-essential) while the rest have to be provided in the diet (essential amino acids).

The proteins on degradation (proteolysis) release individual amino acids. Amino acids are not just the structural components of proteins. Each one of the 20 naturally occurring amino acids undergoes its own metabolism and performs specific functions. Some of the amino acids also serve as precursors for the synthesis of many biologically important compounds (e.g melanin, serotonin, creatine etc.). Certain amino acids may directly act as neurotransmitters (e.g. glycine aspartate, glutamate). Protein metabolism is more appropriately learnt as metabolism of amino acids

AMINO ACID POOL

An adult has about 100 g of free amino acids which represent the amino acid pool of the body. The amino acid pool may be an oversimplification of the facts, since there is no single compartment—rather, several compartments exist.

Glutamate and glutamine together constitute about 50%, and essential amino acids about 10% of the body pool (100 g). The concentration of intracellular amino acids is always higher than the extracellular amino acids. Amino acids enter the cells against a concentration gradient by active transport.

The amino acid pool of the body is maintained by the sources that contribute (input) and the metabolic pathways that utilize (output) the amino acids

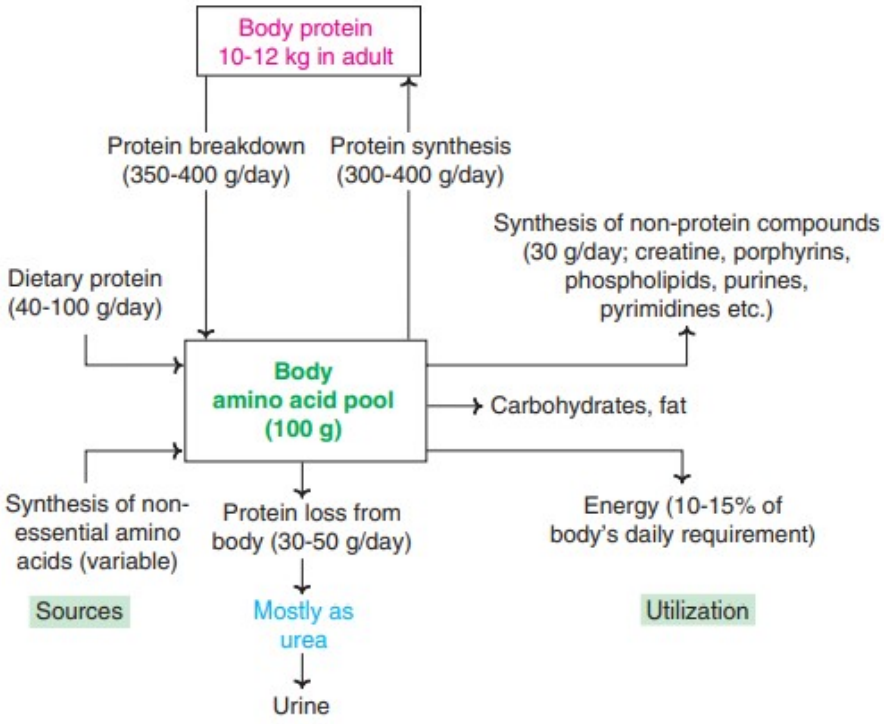


Fig. 15.1 : *Overview of body's amino acid pool—sources and utilization.*

I. Sources of amino acid pool

Turnover of body protein, intake of dietary protein and the synthesis of non-essential amino acids contribute to the body amino acid pool

(a) **Protein turnover** : The protein present in the body is in a dynamic state. It is estimated that about 300-400 g of protein per day is constantly degraded and synthesized which represents body protein turnover. There is a wide variation in the turnover of individual proteins. For instance, the plasma proteins and digestive enzymes are rapidly degraded, their half-lives being in hours or days. The structural proteins (e.g. collagen) have long half-lives, often in months and years

Control of protein turnover : The turnover of the protein is influenced by many factors. A small polypeptide called ubiquitin (mol. wt. 8,500) tags with the proteins and facilitates degradation. Certain proteins with amino acid sequence proline, glutamine (one letter code E), serine and threonine (PEST sequence) are rapidly degraded.

(b) **Dietary protein** : There is a regular loss of nitrogen from the body due to degradation of amino acids. In healthy adults, it is estimated that about 30-50 g of protein is lost everyday from the body. This amount of protein (30-50 g/ day) must, therefore, be supplied daily in the diet to maintain nitrogen balance. The

purpose of dietary protein is to supply amino acids (particularly the essential ones) for the synthesis of proteins and other nitrogen compounds.

There is no storage form of amino acids as is the case for carbohydrates (glycogen) and lipids (triacylglycerols). The excess intake of amino acids are metabolized—oxidized to provide energy, converted to glucose or fat. The amino groups are lost as urea and excreted. The protein consumption in developed countries is much higher than the recommended dietary allowance (i.e. 1g/kg body weight/day). The daily protein intake by an adult in most countries is 40-100 g. Protein is digested by proteolytic enzymes to amino acids which are absorbed in the intestine and enter the body pool of amino acids.

(c) **Synthesis of non-essential amino acids** : Ten out of the 20 naturally occurring amino acids can be synthesized by the body which contribute to the amino acid pool.

II. Utilization of amino acids from body pool

(a) Most of the body proteins (300-400 g/day) degraded are synthesized from the amino acid pool. These include enzymes, hormones, immunoproteins, contractile proteins etc

(b) Many important nitrogenous compounds (porphyrins, purines, pyrimidines, etc.) are produced from the amino acids. About 30 g of protein is daily utilized for this purpose.

(c) Generally, about 10-15% of body energy requirements are met from the amino acids.

(d) The amino acids are converted to carbohydrates and fats. This becomes predominant when the protein consumption is in excess of the body requirements.

METABOLISM OF AMINO ACIDS —GENERAL ASPECTS

The amino acids undergo certain common reactions like transamination followed by deamination for the liberation of ammonia. The amino group of the amino acids is utilized for the formation of urea which is an excretory end product of protein metabolism. The carbon skeleton of the amino acids is first converted to keto acids (by transamination) which meet one or more of the following fates.

1. Utilized to generate energy.

2. Used for the synthesis of glucose.

3. Diverted for the formation of fat or ketone bodies.

4. Involved in the production of non-essential amino acids.

A general picture of amino acid metabolism is depicted in

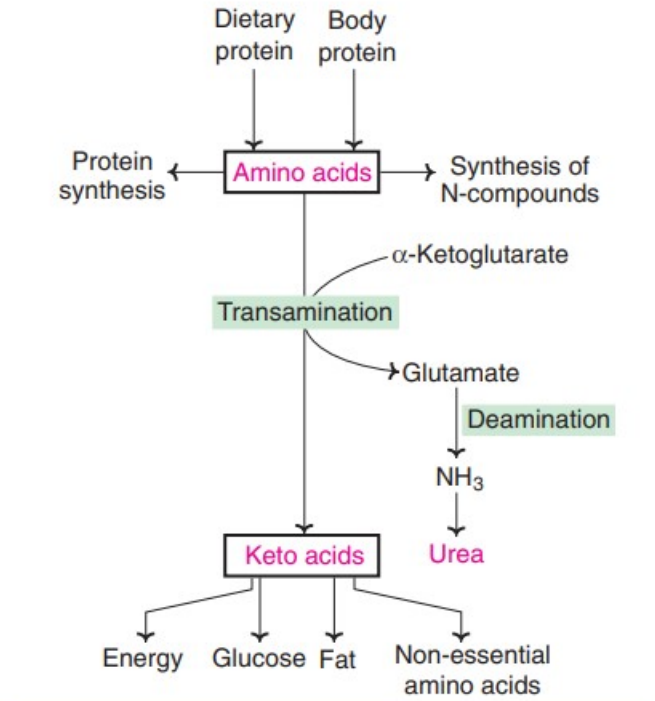


***Fig. 15.2 :** An overview of amino acid metabolism.*

(The details of general and specific metabolic reactions of amino acids are described in the following)

TRANSAMINATION

The transfer of an amino ($-NH_2$) group from an amino acid to a keto acid is known as transamination. This process involves the interconversion of a pair of amino acids and a pair of keto acids, catalysed by a group of enzymes called transaminases (recently, aminotransferases)

Salient features of transamination

1. All transaminases require pyridoxal phosphate (PLP), a coenzyme derived from vitamin B6.

2. Specific transaminases exist for each pair of amino and keto acids. However, only two—namely, aspartate transaminase and alanine transaminase—make a significant contribution for transamination.

3. There is no free NH_3 liberated, only the transfer of amino group occurs.

4. Transamination is reversible

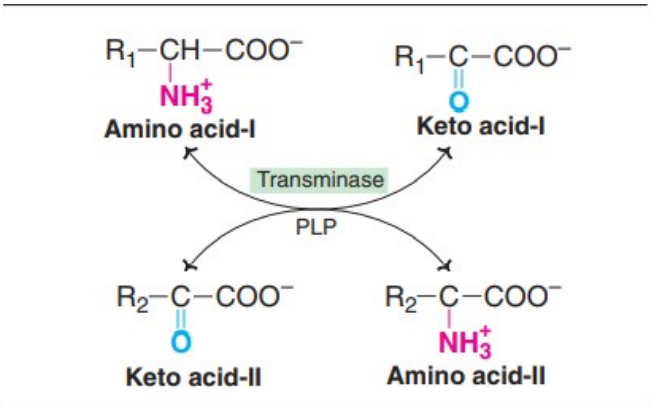


Fig. 15.3 : *Transamination reaction.*

5. Transamination is very important for the redistribution of amino groups and production of non-essential amino acids, as per the requirement of the cell. It involves both catabolism (degradation) and anabolism (synthesis) of amino acids.

6. Transamination diverts the excess amino acids towards energy generation.

7. The amino acids undergo transamination to finally concentrate nitrogen in glutamate. Glutamate is the only amino acid that undergoes oxidative deamination to a significant extent to liberate free NH_3 for urea synthesis.

8. All amino acids except lysine, threonine, proline and hydroxyproline participate in transamination.

9. Transamination is not restricted to α -amino groups only. For instance, δ -amino group of ornithine is transaminated.

10. Serum transaminases are important for diagnostic and prognostic purposes.

Mechanism of Transamination

Transamination occurs in two stages

1. Transfer of the amino group to the coenzyme pyridoxal phosphate (bound to the coenzyme) to form pyridoxamine phosphate.

2. The amino group of pyridoxamine phosphate is then transferred to a keto acid to produce a new amino acid and the enzyme with PLP is regenerated.

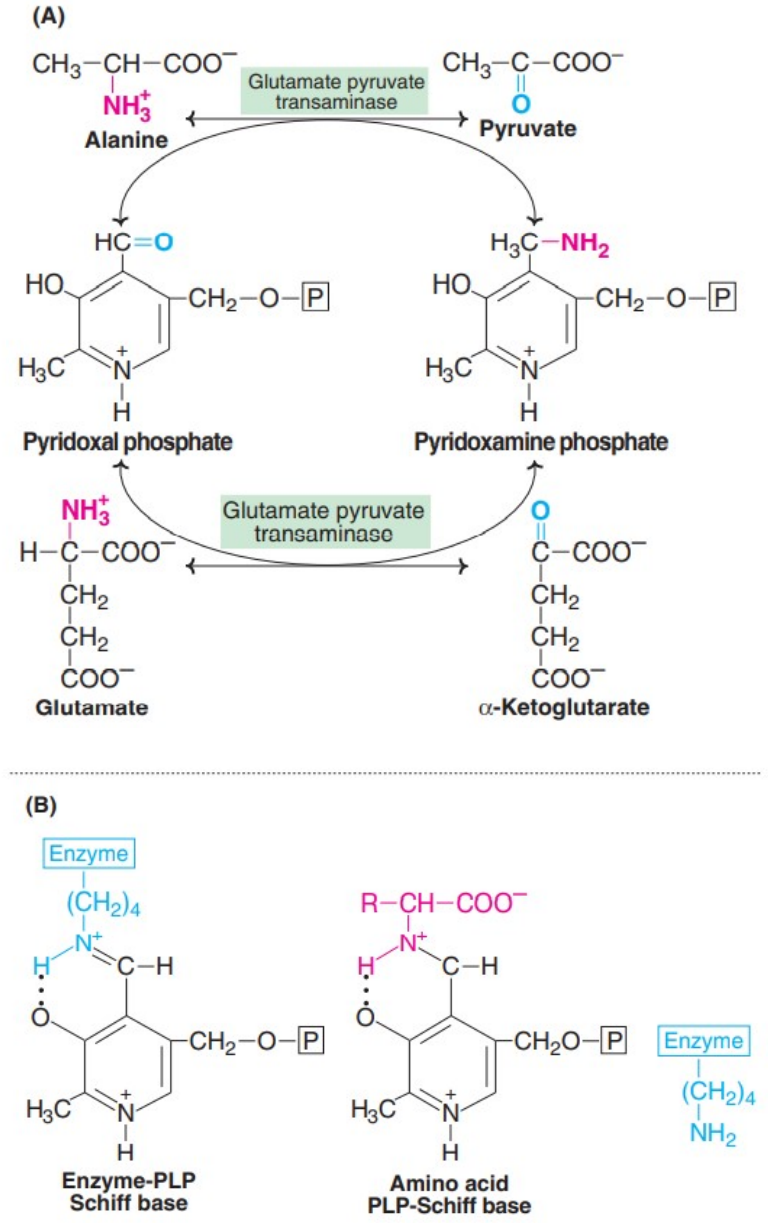


Fig. 15.4 : *Mechanism of transamination—(**A**) Involvement of pyridoxal phosphate (PLP) in the transfer of amino group, (**B**) Formation of enzyme-PLP-Schiff base and amino acid-PLP-Schiff base.*
Note that when the amino acid binds, enzyme separates.

- All the transaminases require pyridoxal phosphate (PLP), a derivative of vitamin B6.
- The aldehyde group of PLP is linked with ε-amino group of lysine residue, at the active site of the enzyme forming a Schiff base (imine linkage).

- When an amino acid (substrate) comes in contact with the enzyme, it displaces lysine and a new Schiff base linkage is formed. The amino acid-PLP-Schiff base tightly binds with the enzyme by noncovalent forces.

DEAMINATION

- The removal of amino group from the amino acids as NH_3 is deamination.
- deamination results in the liberation of ammonia for urea synthesis.
- Simultaneously, the carbon skeleton of amino acids is converted to keto acids
- . Deamination may be either oxidative or non-oxidative.

I. Oxidative deamination

Oxidative deamination is the liberation of free ammonia from the amino group of amino acids coupled with oxidation.
This takes place mostly in liver and kidney.
The purpose of oxidative deamination is to provide NH_3 for urea synthesis and α -keto acids for a variety of reactions, including energy generation.

Role of glutamate dehydrogenase : In the process of transamination, the amino groups of most amino acids are transferred to α -ketoglutarate to produce glutamate. Thus, glutamate serves as a 'collection centre' for amino groups in the biological system.

Glutamate rapidly undergoes oxidative deamination, catalysed by glutamate dehydrogenase (GDH) to liberate ammonia. This enzyme is unique in that it can utilize either NAD^+ or $NADP^+$ as a coenzyme. Conversion of glutamate to α -ketoglutarate occurs through the formation of an intermediate, α –iminoglutarate

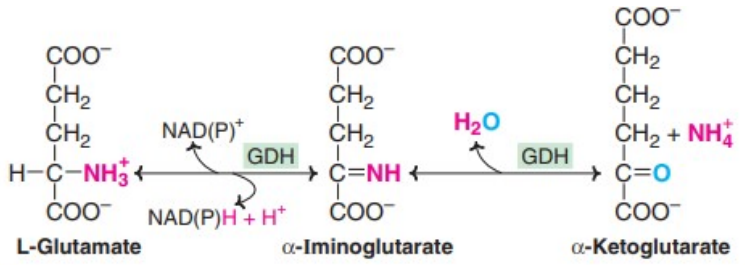


Fig. 15.5 : Oxidation of glutamate by glutamate dehydrogenase (GDH).

NOTE: Glutamate dehydrogenase catalysed reaction is important as it reversibly links up glutamate metabolism with TCA cycle through α -ketoglutarate. GDH is involved in both catabolic and anabolic reactions.

Regulation of GDH activity :

Glutamate dehydrogenase is a zinc containing mitochondrial enzyme. It is a complex enzyme consisting of six identical units with a molecular weight of 56,000 each. GDH is controlled by allosteric regulation. GTP and ATP inhibit— whereas GDP and ADP activate—glutamate dehydrogenase. Steroid and thyroid hormones inhibit GDH

After ingestion of a protein-rich meal, liver glutamate level is elevated. It is converted to α -ketoglutarate with liberation of NH_3. Further, when the cellular energy levels are low, the degradation of glutamate is increased to provide α -ketoglutarate which enters TCA cycle to liberate energy.

Oxidative deamination by amino acid oxidases :

L-Amino acid oxidase and D-amino acid oxidase are flavoproteins, possessing FMN and FAD, respectively. They act on the corresponding amino acids (L or D) to produce α -keto acids and NH_3. In this reaction, oxygen is reduced to H_2O_2, which is later decomposed by catalase.

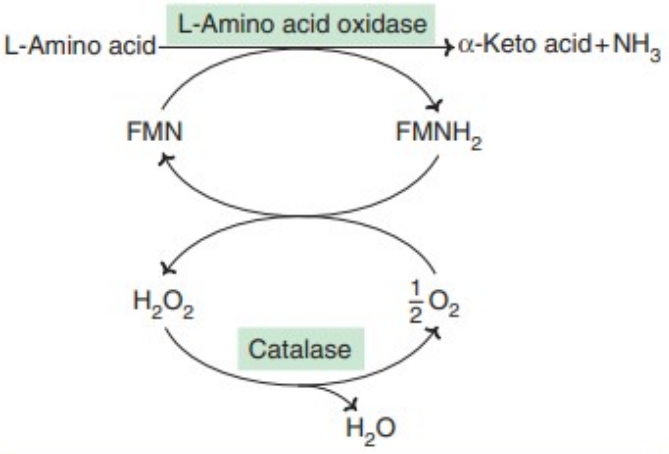


Fig. 15.6 : Oxidative deamination of amino acids.

The activity of L-amino acid oxidase is much low while that of D-amino acid oxidase is high in tissues (mostly liver and kidney). L-Amino acid oxidase does not act on glycine and dicarboxylic acids. This enzyme, due to its very low activity, does not appear to play any significant role in the amino acid metabolism.

Fate of D-amino acids : D-Amino acids are found in plants and microorganisms. They are, however, not present in the mammalian proteins. But D-amino acids are regularly taken in the

diet and metabolized by the body. D-Amino acid oxidase converts them to the respective α -keto acids by oxidative deamination. The α -keto acids so produced undergo transamination to be converted to L-amino acids which participate in various metabolisms. Keto acids may be oxidized to generate energy or serve as precursors for glucose and fat synthesis. Thus, D-amino acid oxidase is important as it initiates the first step for the conversion of unnatural D-amino acids to L-amino acids in the body

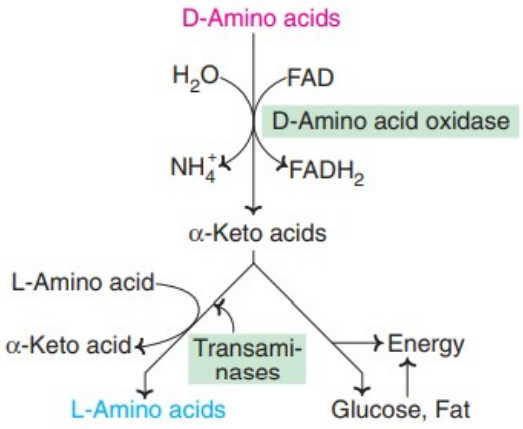
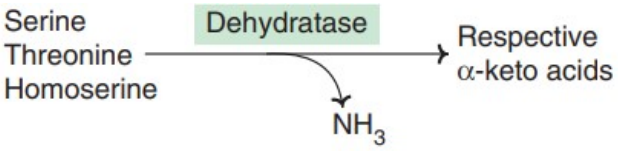


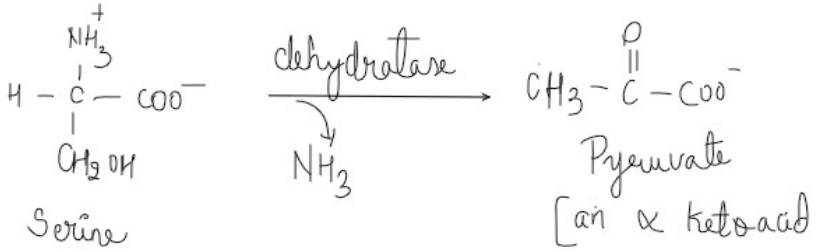
Fig. 15.7 : *Metabolic fate of D-amino acids.*

II. Non-oxidative deamination

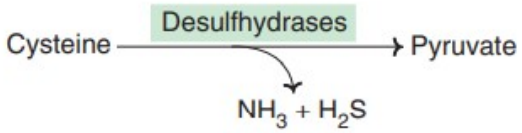
Some of the amino acids can be deaminated to liberate NH_3 without undergoing oxidation

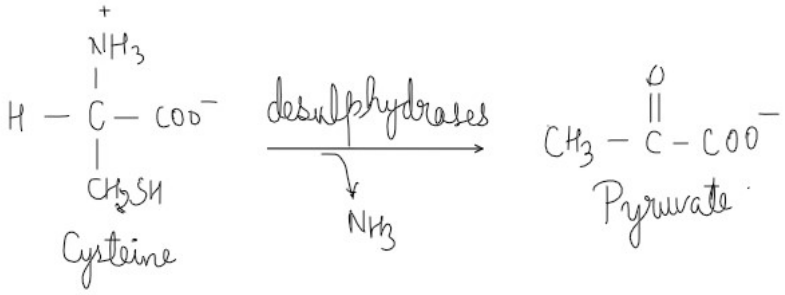
a) **Amino acid dehydrases** : Serine, threonine and homoserine are the hydroxy amino acids. They undergo non-oxidative deamination catalysed by PLP-dependent dehydrases (dehydratases).



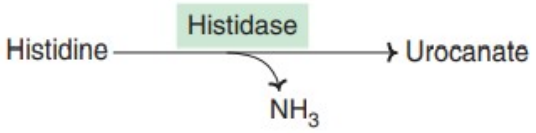


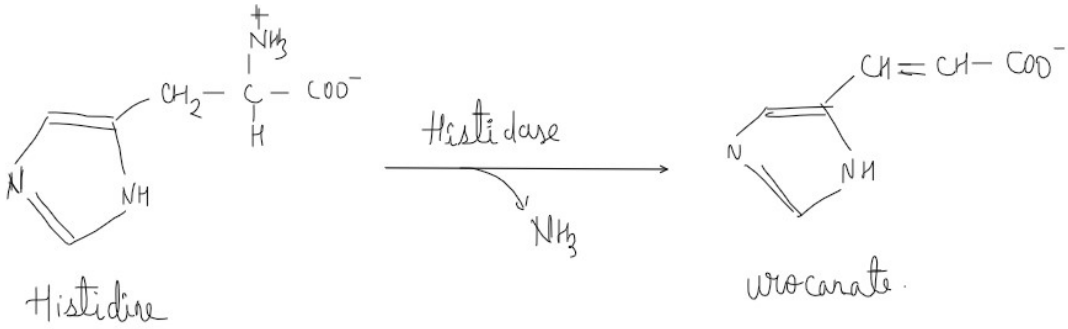
b) **Amino acid desulfhydrases** : The sulfur amino acids, namely cysteine and homocysteine, undergo deamination coupled with desulfhydration to give keto acids.





(d) **Deamination of histidine** : The enzyme histidase acts on histidine to liberate NH_3 by a non-oxidative deamination process.





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