Proteins part3

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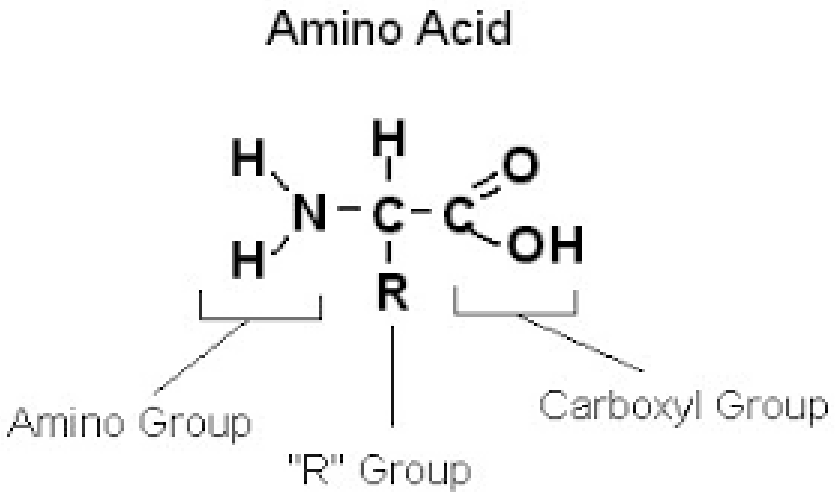
GENERAL CATABOLIC PATHWAYS OF AMINO ACIDS

In human, the end products of protein and amino acids catabolism are ammonia and urea. They are produced through the following catabolic pathways.



- Transamination.
- Deamination: Oxidative - Non oxidative
- Transdeamination: i.e. transamination followed by deamination.
- Decarboxylation.

Transamination

- Transamination involves the transfer of α-amino group of α-amino acid to an α-keto acid to form new amino acid and a new keto acid. The enzymes that catalyze these reactions are called aminotransferases or transaminases
- • Most transaminases use α-ketoglutarate (α-keto acid) as a common acceptor of amino groups.

- • All transaminases require pyridoxal phosphate (PLP) as a coenzyme. Some of the most important transaminases are alanine transaminase (ALT) and aspartate transaminase (AST)
- • Alanine transaminase (ALT) also called glutamate pyruvate transaminase (GPT), catalyzes the transfer of amino group of alanine to α-ketoglutarate resulting in the formation of pyruvate and L-glutamate.

- Aspartate transaminase (AST), also called glutamate oxaloacetate transaminase (GOT), catalyzes the transfer of the amino group of aspartate to αketoglutarate, resulting in the formation of oxaloacetate and L-glutamate.

Clinical significance of transaminase enzyme

Serum levels of some transaminases are elevated in some disease state and measurement of these are useful in medical diagnosis, e.g. ALT (GPT) and AST (GOT) are important in the diagnosis of liver and heart damage

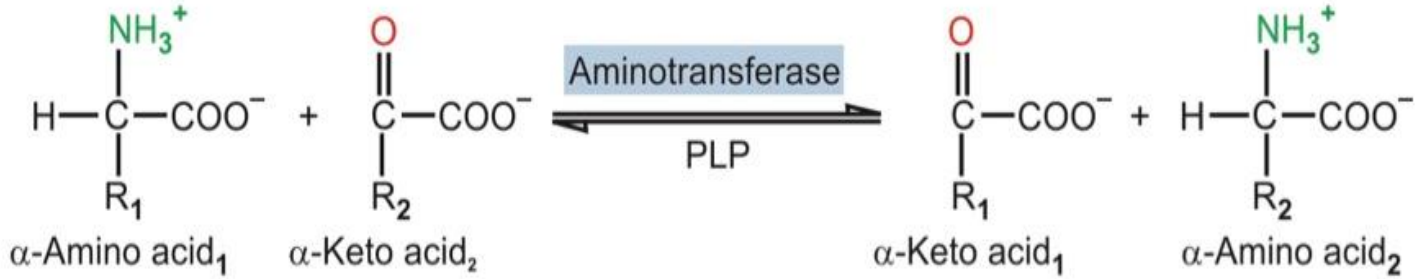


Figure 14.5: Transamination reaction

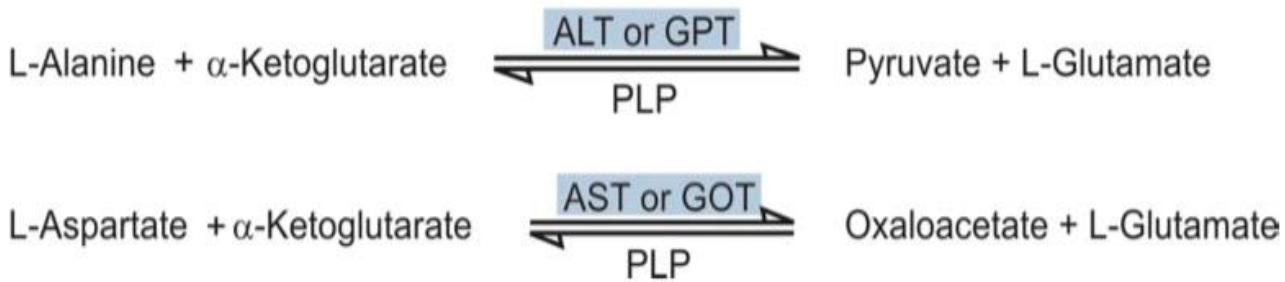


Figure 14.6: Reactions catalyzed by alanine transaminase and aspartate transaminase

Deamination

- Deamination: Since transamination involves only the transfer of an a-amino group from amino acid to a-keto acid and as such there is no net loss of the amino group, deamination is the actual process resulting in the removal of the a-amino group of an amino acid, which is released in the form of ammonia. Liver and kidney are the main organs involved in the deamination of an amino acid.

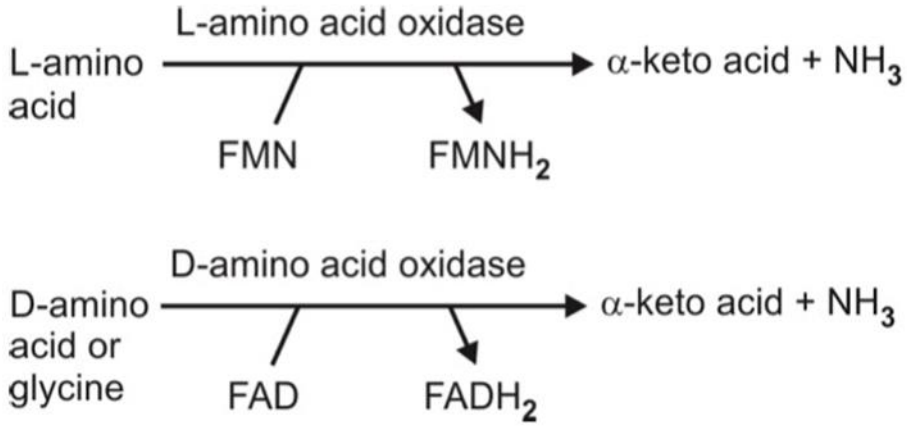
- There are two types of deamination reactions:

- 1. Oxidative deamination

- 2. Nonoxidative deamination.

Oxidative deamination

- Oxidative deamination: L-amino acid oxidase, D-amino acid oxidase and glutamate dehydrogenase are the main enzymes involved in the deamination of amino acids. These enzymes remove hydrogens from the amino acids.



Nonoxidative deamination

- The α-amino groups of serine and threonine can be directly deaminated into NH 4 + ion. These amino acids contains hydroxy group attached to its βcarbon atom.
- These direct deaminations are catalyzed by serine dehydratase and threonine dehydratase, in which pyridoxal phosphate (PLP) is the coenzyme

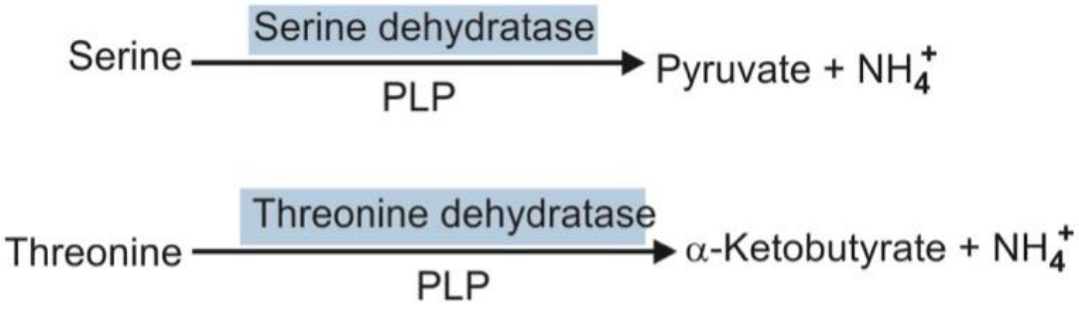
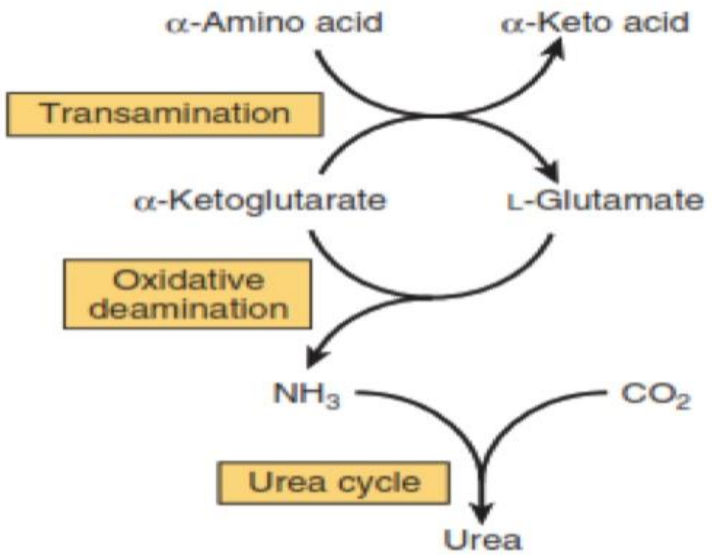


Figure 14.9: Nonoxidative deamination by amino acid dehydratase

TRANSDEAMINATION

- It is transamination of most amino acids with α-Ketoglutarate to form glutamate, Then glutamate undergoes oxidative deamination by the action of glutamate dehydrogenase.

- It is the main pathway by which amino group (NH2) of most amino acids is released in the form of ammonia (NH3).



DECARBOXYLATION

- removal of CO2 of amino acids produces the corresponding amines.

Functions:

Some amines have important biologic functions: e.g.

1. Histamine (from histidine) is vasodilator.

2. γ-Amino butyric acid (from glutamate) is neurotransmitter.

- The resulting amines are further oxidized after carrying out their functions- by amine oxidase enzymes.

METABOLIC FATE OF AMMONIA

- Ammonia is produced in most tissues. Since ammonia is extremely toxic, it is immediately converted to nontoxic metabolites such as, glutamate or glutamine or alanine and ultimately to urea. For the ultimate conversion of ammonia to urea, ammonia is transported to the liver.

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

Transport of Ammonia in the Form of Glutamine

- Since free ammonia is highly toxic, it is never transported in free form in blood.

- In many tissues (liver, kidney and brain), ammonia is enzymatically combined with glutamate to yield glutamine by the action of glutamine synthetase.

- The glutamine, so formed is a neutral nontoxic major transport form of ammonia. The glutamine is transported by blood to the liver, where it is cleaved by glutaminase to yield glutamate and free ammonia.
- The ammonia so formed is converted by the liver into urea.

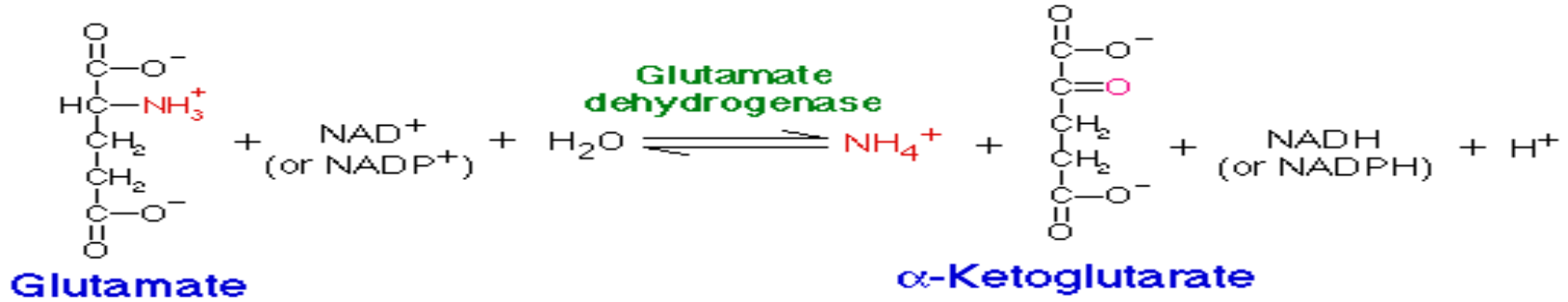
Transport of Ammonia in the Form of Alanine

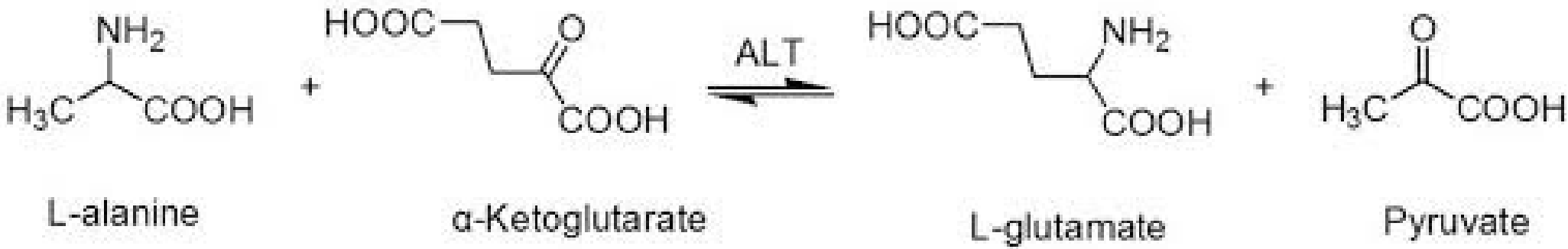
- Alanine transports ammonia from muscles to the liver through glucose alanine cycle
- In muscle, glutamate is formed from ammonia and α-ketoglutarate by reversal of the glutamate reversal of the glutamate dehydrogenase reaction

glutamate then transfers its α-amino group to pyruvate by transamination reaction to form alanine.

- Alanine so formed in muscle is transported to liver where it is converted to pyruvate and glutamate again by transamination reaction.

- In the liver, glutamate undergoes oxidative deamination to release free ammonia, which is converted to urea. Whereas, pyruvate is converted to glucose by gluconeogenesis.


Glutamate dehydrogenase
NAD+ (or NADP+)
H2O
NH4+
NADH (or NADPH)
H+
Glutamate
α-Ketoglutarate


ALT
L-alanine
α-Ketoglutarate
L-glutamate
Pyruvate

Sources of ammonia

1. Transdeamination of amino acids: In Many tissues, particularly liver

2- Glutamine: The kidneys form ammonia from glutamine by glutaminase enzyme. Most of this ammonia is used in regulation of Acid base balance.

3. Nitrogenous compounds : Purines and pyrimidines metabolism or amine metabolism as histamine.

4. Urea: by urease enzyme

Fate of ammonia

1. **Formation of non-essential amino acids:** Through Transdeamination.

2. **Formation of urea:** It is the main pathway by which the body can get rid of ammonia.

3. **Excretion in urine**

4. **Nucleotides formation**

5. **Formation of glutamine:** which has the following functions:

1) Regulation of acid base balance: In kidney, glutamine is deaminated by glutaminase enzyme, releasing ammonia again. Ammonia is used by the kidneys in regulation of acid base balance.

2) Removes the toxic effect of ammonia In brain

AMMONIA INTOXICATION

Definition: Excess ammonia which is toxic to the central nervous system.

Symptoms: Include:

- A. Flapping tremors, Ataxia, convulsions, slurring speech, blurring vision and vomiting.

B. High concentration of ammonia may cause coma and death.

Mechanism of ammonia intoxication:

- - At normal blood ammonia level, any ammonia reaches the brain incorporated into glutamine formation by glutamine synthetase enzyme.

- - In cases of hyperammonemia, ammonia reacts not only with glutamate, but also with αKetoglutarate by glutamate dehydrogenase enzyme. This depletes α-Ketoglutarate which is an essential intermediate of citric acid cycle → Decrease in ATP and energy production → symptoms of ammonia intoxication → coma.

Types of Hyperammonemia

a. Hereditary hyperammonemia

results from defects in urea cycle enzymes.

- Deficiencies of enzymes that are used in urea cycle (i.e., CPS I and ornithine transcarbamoylase) are associated with higher blood ammonia levels and more severe clinical manifestations than deficiencies of enzymes that are used later in the cycle (e.g., arginase).

b. Acquired hyperammonemia

1- Liver failure: The diseased liver cells cannot convert ammonia into urea

2- Renal failure

3- Shunt operation between portal and systemic circulation.

4- Collaterals between portal and systemic circulation due cirrhosis of liver by bilharziasis , hepatitis etc.

Thank you