Amino Acid Catabolism & Synthesis

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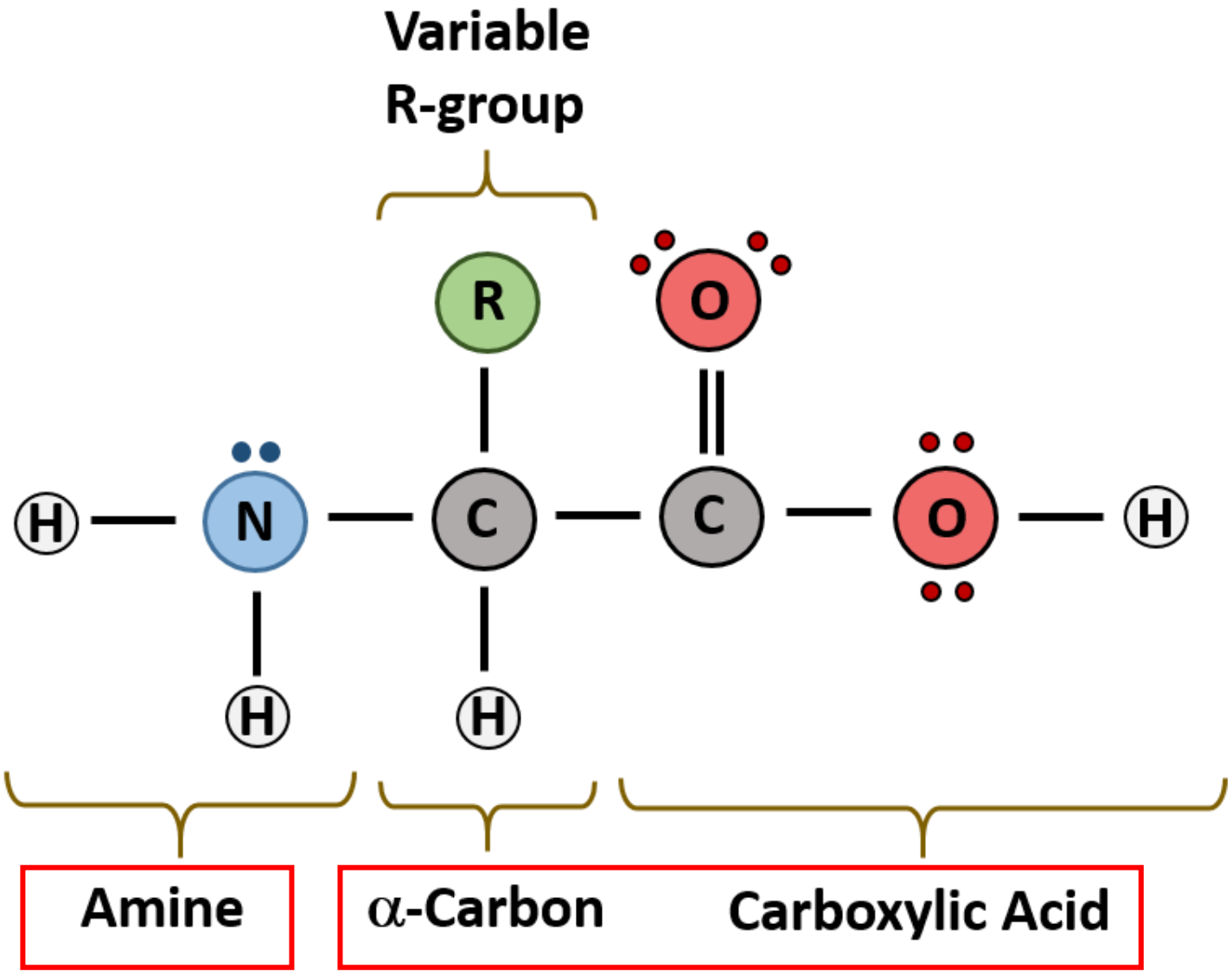
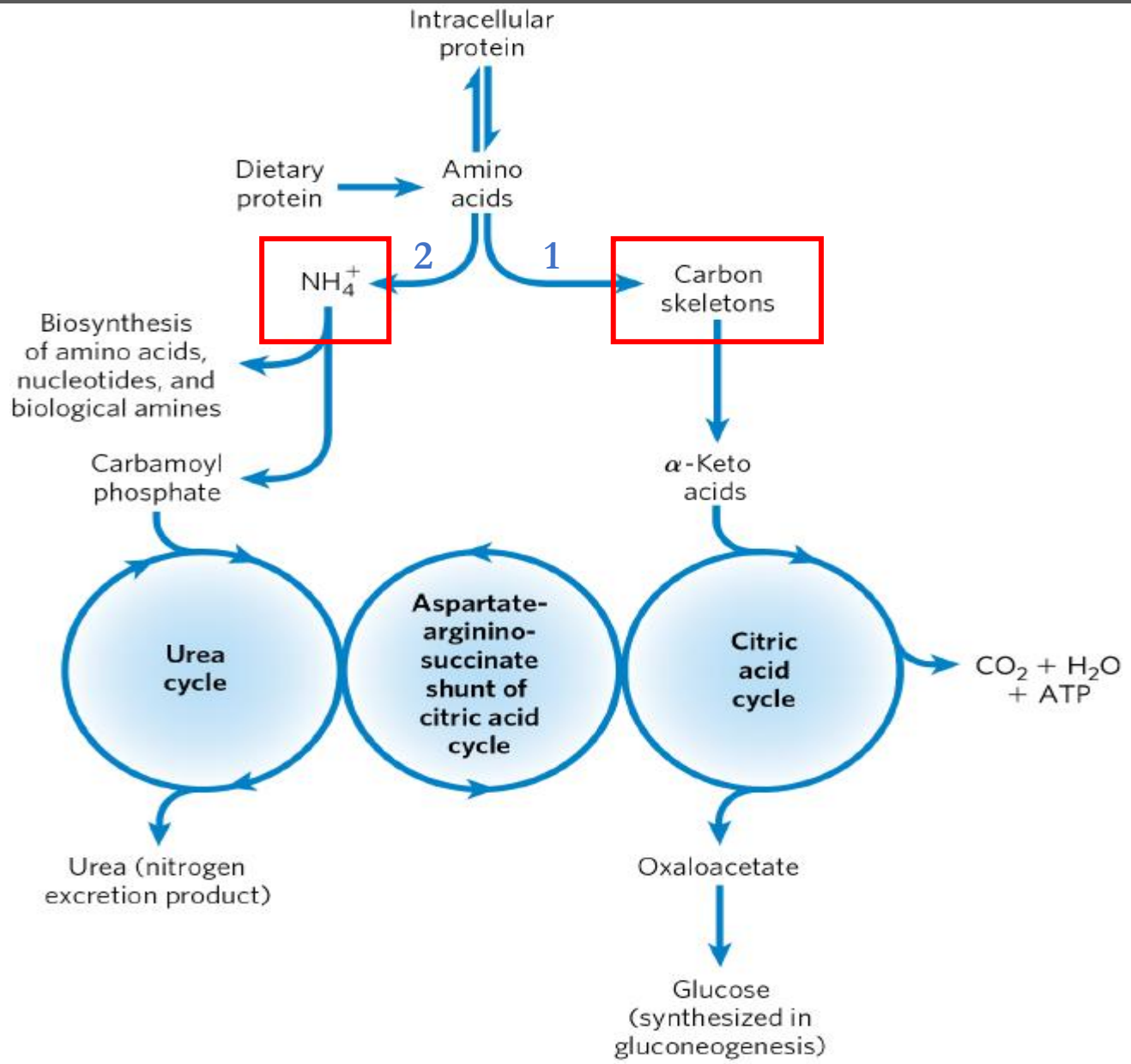
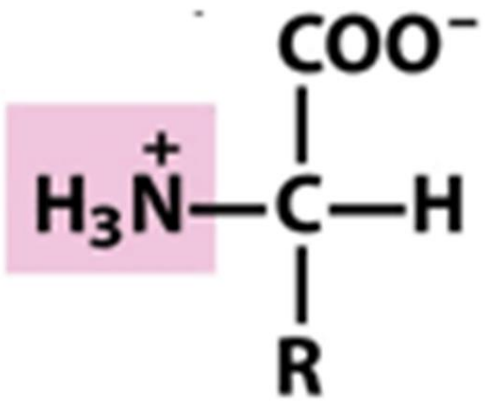
Inroduction

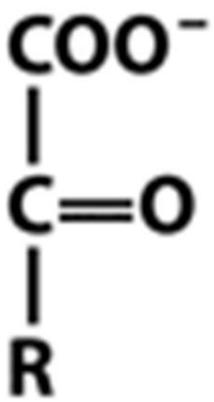
- Unlike fats and carbohydrates, amino acids are **not stored by the body.**
- Amino acids must be obtained from the diet, synthesized de novo, or produced from the degradation of body protein.
- Any amino acids in excess of the biosynthetic needs of the cell are rapidly degraded.


Variable
R-group
R
O
H
N
C
C
O
H
H
H
Amine
α-Carbon
Carboxylic Acid


Intracellular protein
Dietary protein
Amino acids
2
1
NH_4^+
Carbon skeletons
Biosynthesis of amino acids, nucleotides, and biological amines
Carbamoyl phosphate
α-Keto acids
Urea cycle
Aspartate-arginino-succinate shunt of citric acid cycle
Citric acid cycle
$CO_2 + H_2O$ + ATP
Urea (nitrogen excretion product)
Oxaloacetate
Glucose (synthesized in gluconeogenesis)



L-Amino acid



α-Keto acid

Amino Acid Catabolism

Amino acids undergo oxidative degradation in three different metabolic circumstances:

1. Amino acids released during normal protein turnover are **not needed** for new protein synthesis.

2. Ingested amino acids **exceed the body's needs** for protein synthesis.

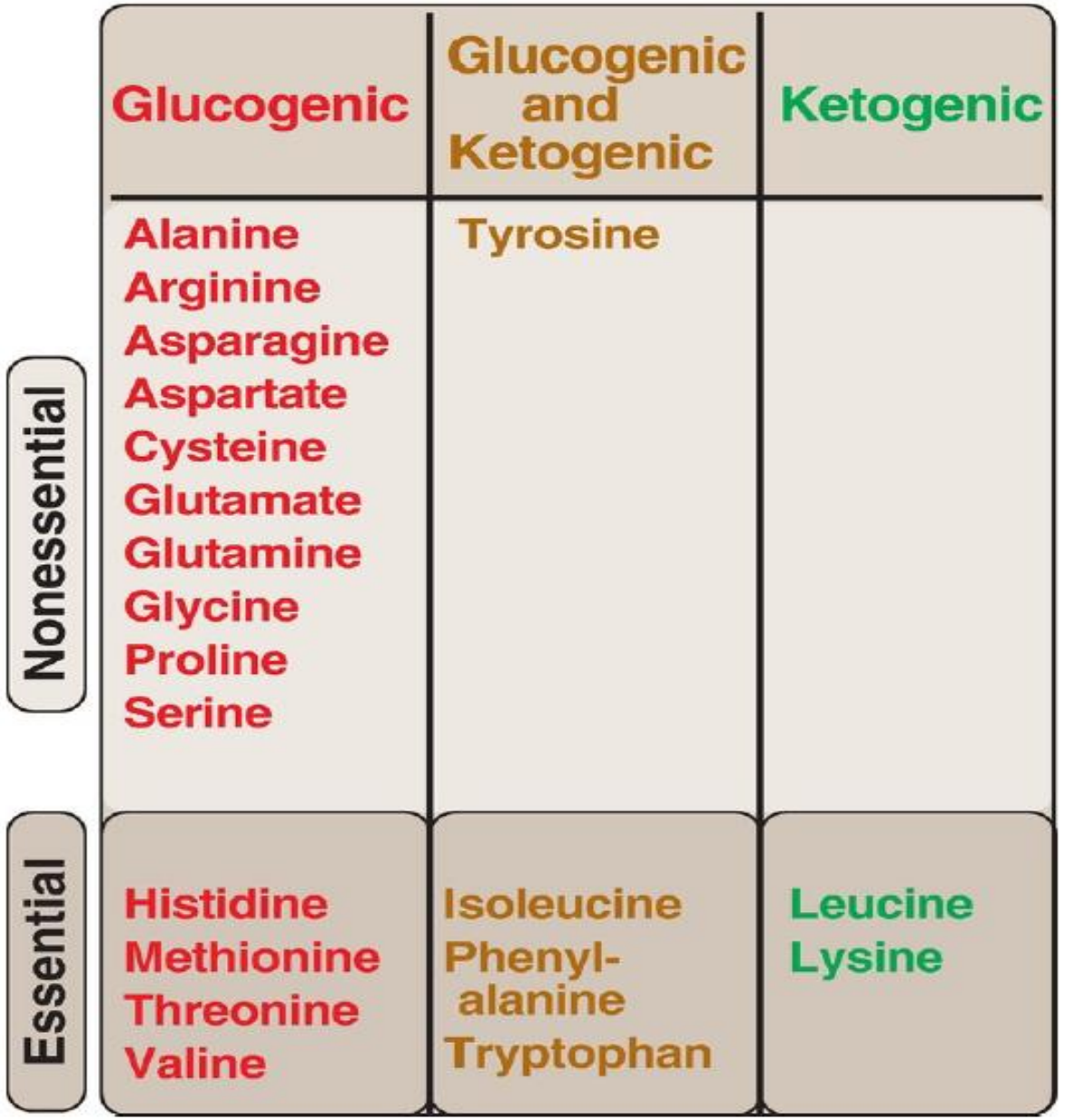
3. Cellular proteins are used as **fuel** because carbohydrates are either unavailable or not properly utilized due to **starvation** or **uncontrolled diabetes mellitus**.

First phase of AA catabolism

- Involves the **removal** of the **α-amino groups**, **forming ammonia** and the corresponding **α-keto acids**, the carbon skeletons of amino acids.
- A portion of the **free ammonia is excreted in the urine**, but most is used in the **synthesis of urea** which is quantitatively the most important route for disposing of nitrogen from the body.
- (next lecture)

Second phase of AA catabolism

- The **carbon skeletons of the α-keto acids** are converted to common **intermediates** of energy-producing metabolic pathways.
- These compounds can be **metabolized to carbon dioxide (CO_2)** and **water (H_2O), glucose, fatty acids, or ketone bodies** by the central pathways of metabolism.


Glucogenic
Glucogenic and Ketogenic
Ketogenic
Nonessential
Alanine
Arginine
Asparagine
Aspartate
Cysteine
Glutamate
Glutamine
Glycine
Proline
Serine
Tyrosine
Essential
Histidine
Methionine
Threonine
Valine
Isoleucine
Phenyl-alanine
Tryptophan
Leucine
Lysine

Principles of AA catabolism

- Four amino acids — **alanine**, **glutamate**, **glutamine**, and **aspartate** — play key roles in the **transport** and **distribution** of amino groups.

- All are present in relatively **high concentrations** in one or many tissues.

- All are **readily converted** to key **citric acid cycle intermediates**.

Principles of AA catabolism

- Metabolic pathways are not distinct. The various pathways for amino acid catabolism are elaborately **intertwined with other catabolic and anabolic pathways.**

- **Free ammonia is toxic**. Excess amino groups must be safely excreted. The **urea cycle** serves this purpose (next lecture).

Principles of AA catabolism

- Most amino acids are metabolized in the **liver.**
- Some of the ammonia generated in this process is recycled and used in **biosynthetic pathways** where glutamine, glutamate, and aspartate play major roles.
- Excess amino groups are either excreted directly or converted to urea or uric acid for excretion.
- Most excess ammonia generated in other (extrahepatic) tissues travels to the liver for conversion to urea.

Deamination of amino acids

- The first step in the catabolism of most L-amino acids, once they have reached the liver, is **removal of the α-amino groups**, promoted by enzymes called **aminotransferases** or **transaminases**.

- All amino acids can be transaminated, except **lysine**, **threonine**, **proline** & **hydroxyproline.**

Aminotransferase reactions

It is the transfer of an amino group from an α amino acid to an α keto acid, which is always α ketoglutarate (NH_2 acceptor).

- **Enzyme**: Aminotransferase (Transaminase)
- **Coenzyme**: Pyridoxal Phosphate (PLP) derived from vitamin B6, acts as intermediate-carrier of the amino group.
- **Site**: Present in the mitochondria and cytosol of all tissues, especially the liver.

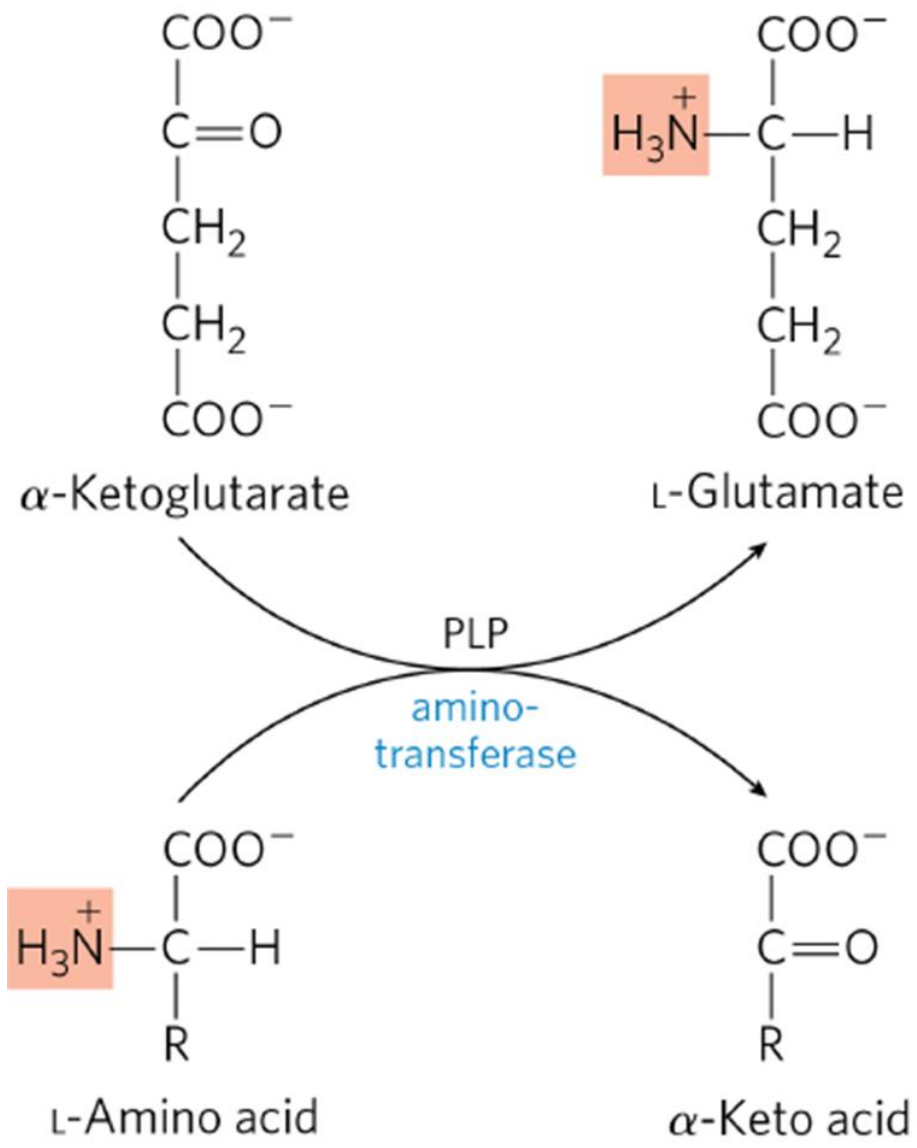
Properties of aminotransferase reactions

- The reaction is reversible.
- Several aminotransferases exist, each specific for one amino acid and the corresponding α keto acid.
- An aminotransferase is called after the amino acid to which it is specific.
- Two important aminotransferases are those that catalyze aminotransferase reactions involving **aspartic acid** and **alanine**, they are respectively called, aspartate aminotransferase (AST) and alanine aminotransferase (ALT).
- **α-Ketoglutarate** acts as an amino group acceptor in most reactions, forming glutamate.
- It involves **neither the uptake nor the release of free ammonia,** the ammonia removed is being transferred to another amino acid.

Funneling Amino Groups to Glutamate

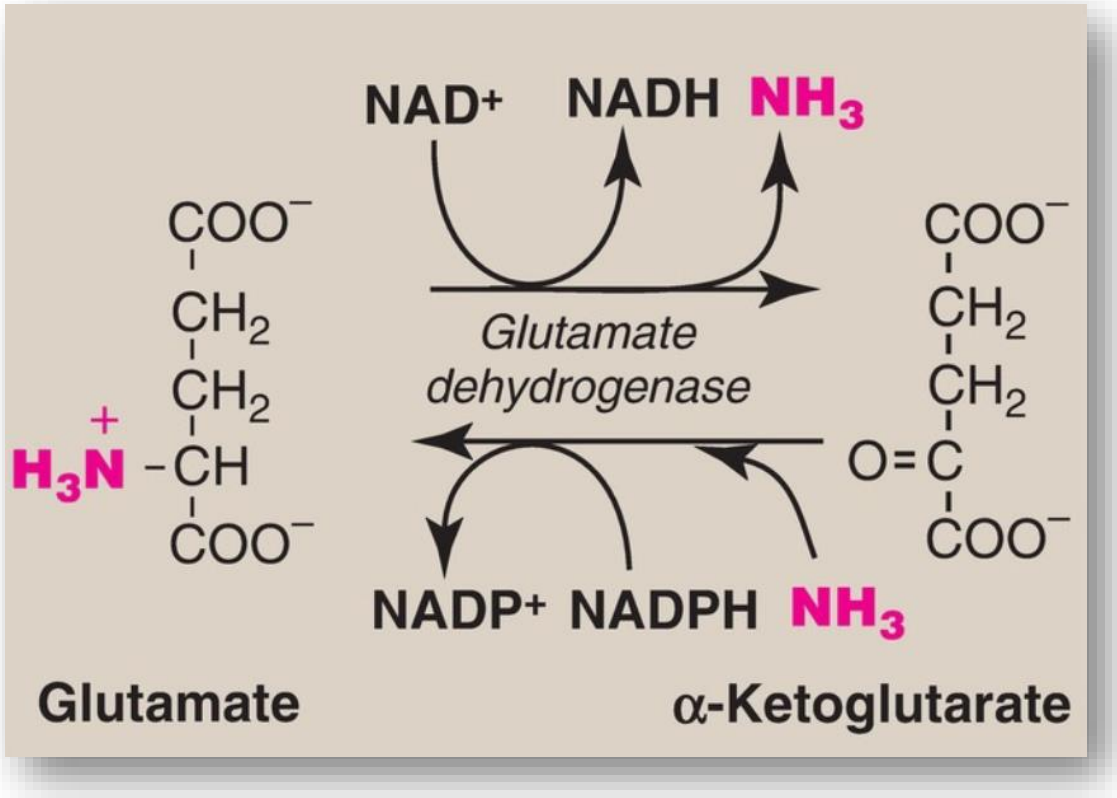
The first step in catabolism of most amino acids is the transfer of α-amino group to α-ketoglutarate, producing an α-keto acid (derived from the original amino acid) and glutamate.

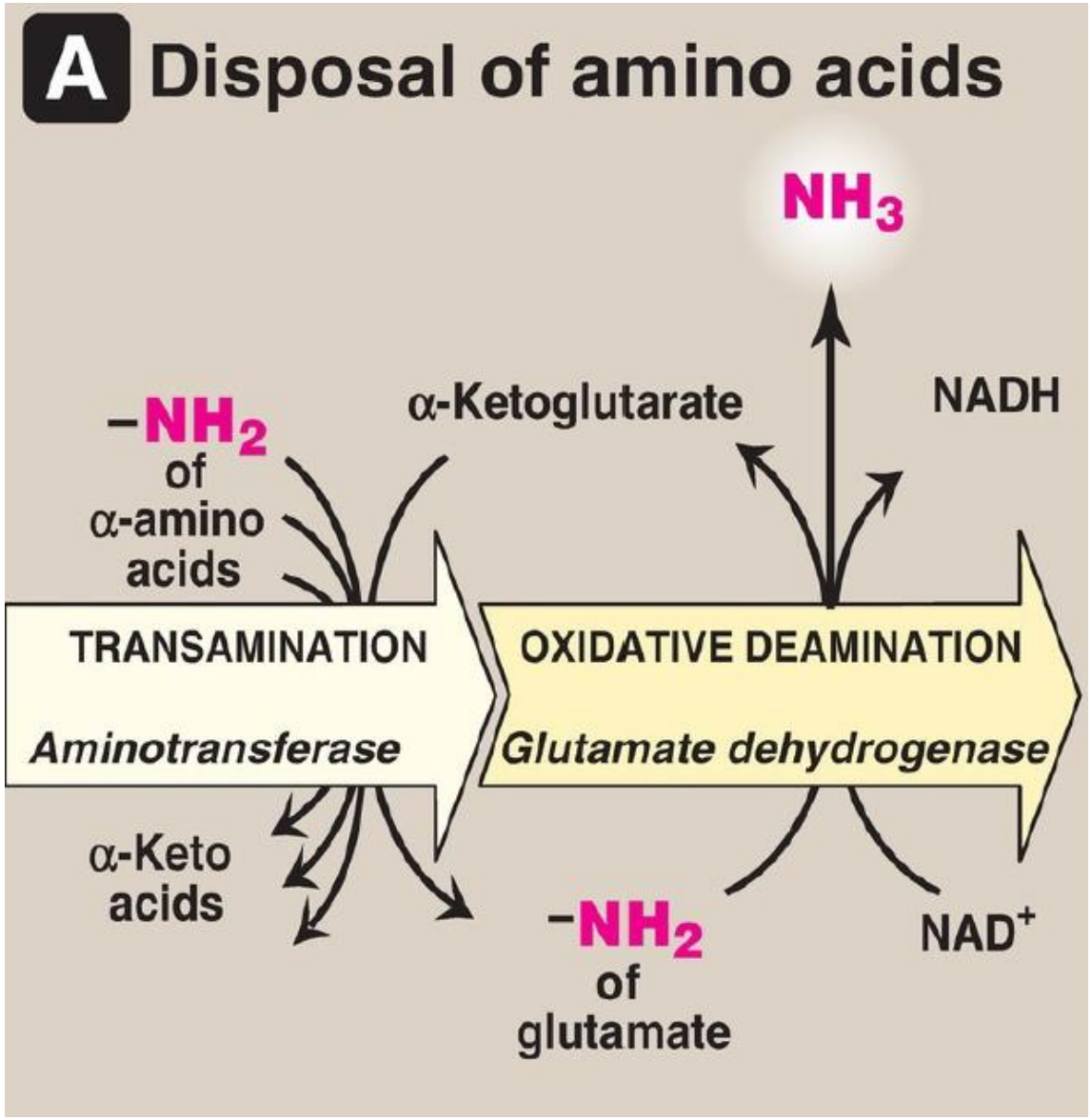
Glutamate produced by transamination can be **oxidatively deaminated** or used as an **amino group donor in the synthesis of nonessential amino acids.**



Oxidative deamination: Amino group removal

- In hepatocytes, glutamate is transported **from the cytosol into mitochondria**.
- Here, it undergoes oxidative deamination catalysed by **L-glutamate dehydrogenase** to produce NH^+_4 and **α-ketoglutarate.**
- **These reversible reactions occur primarily in the liver and kidney.**




A Disposal of amino acids
NH3
–NH2
of
α-amino
acids
α-Ketoglutarate
NADH
TRANSAMINATION
Aminotransferase
OXIDATIVE DEAMINATION
Glutamate dehydrogenase
α-Keto
acids
–NH2
of
glutamate
NAD+

Biological Significance of Transamination

1. **First step of catabolism**
   - In this first step, **ammonia** is removed (or actually transferred as will be removed in deamination) and the carbon skeleton of the amino acid enters into catabolic pathway.

2. **Synthesis of nonessential amino acids**
   - By means of transamination, **all**
   - **e.g. pyruvate → alanine; oxaloacetate → aspartic acid**
   - Those amino acids, which cannot be synthesized in this manner, are therefore essential; they should be made available in the food

Biological Significance of Transamination

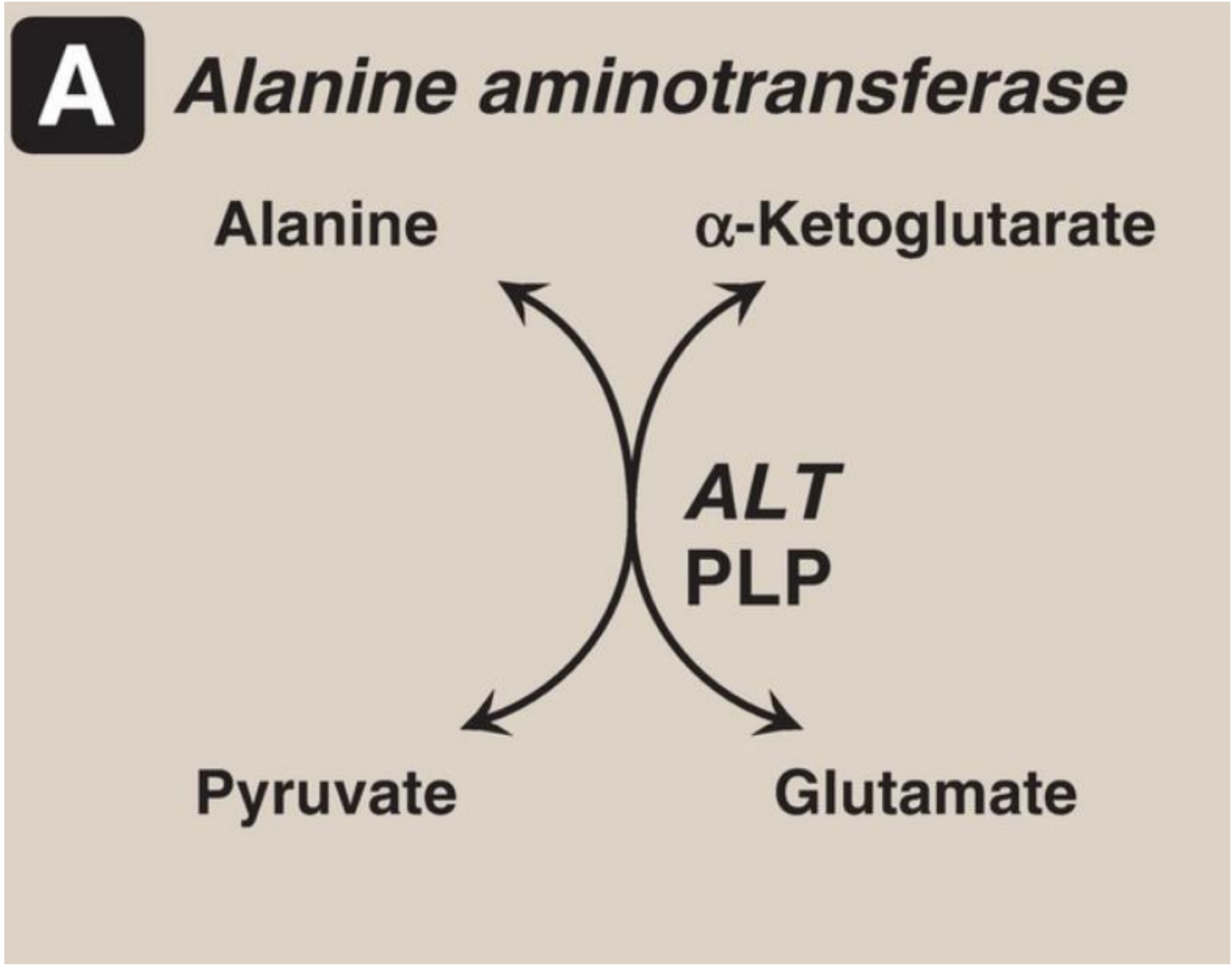
3. Interconversion of amino acids

- If amino acid number 1 is high and number 2 is low, the amino group from number 1 may be transferred to alpha keto acid to give amino acid number 2; equalizing the quantity for both amino acids.

- This is called equalization of quantities of nonessential amino acids.

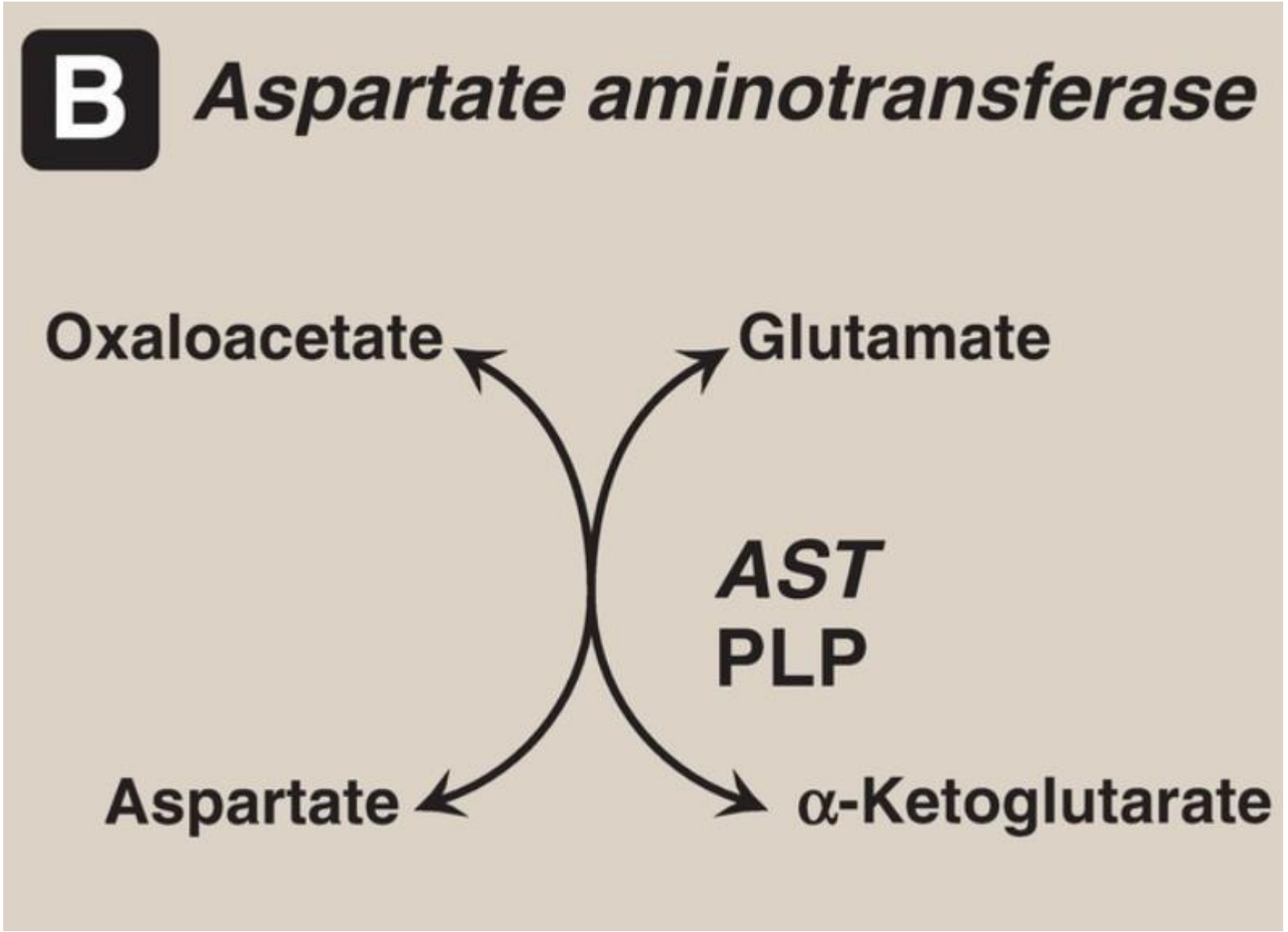
The most active transaminases are:

1. Alanine transaminase (ALT)



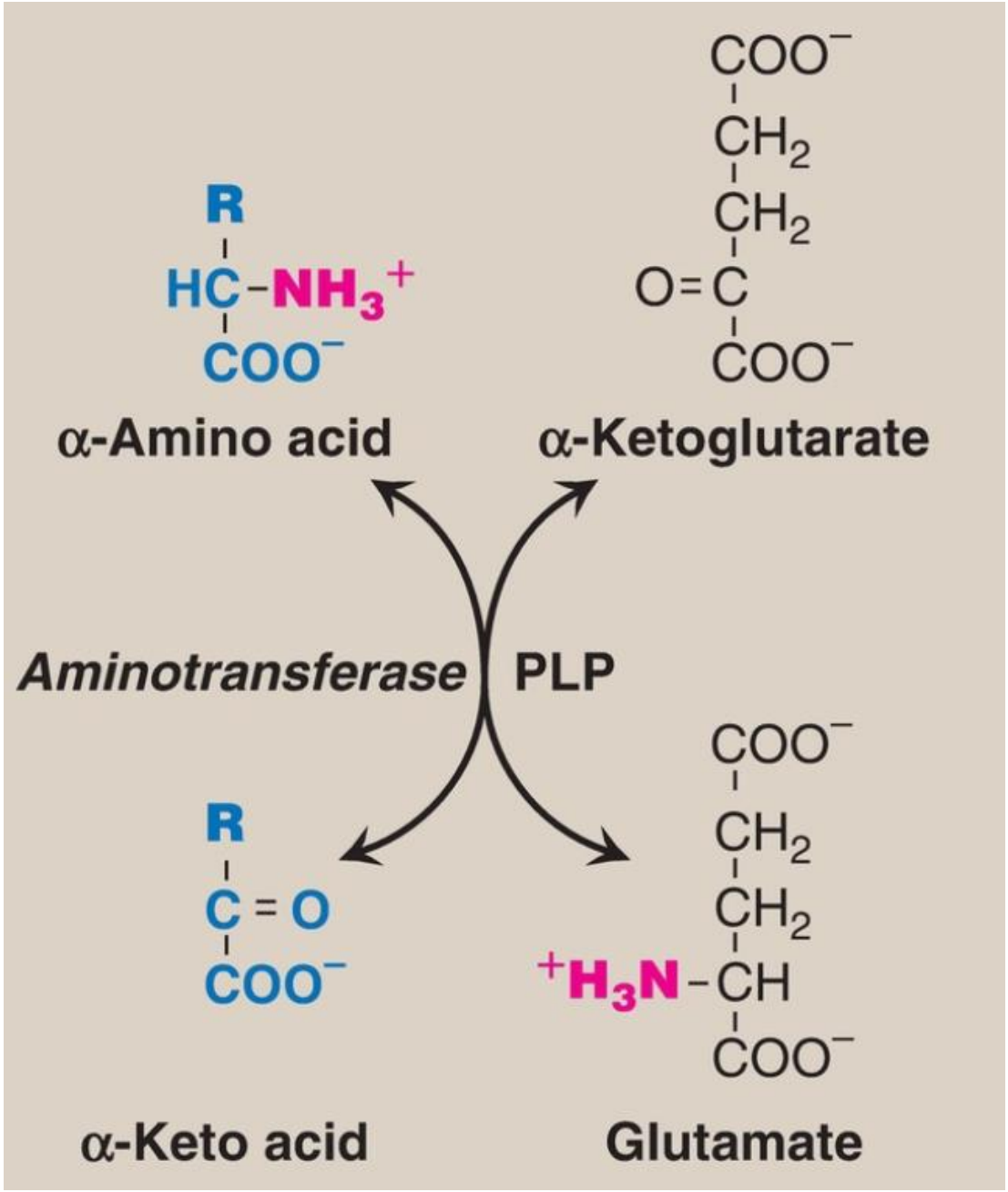
The most active transaminases are:

2. Aspartate transaminase (AST)



The most active transaminases are:

3. Glutamate transaminase (AST)

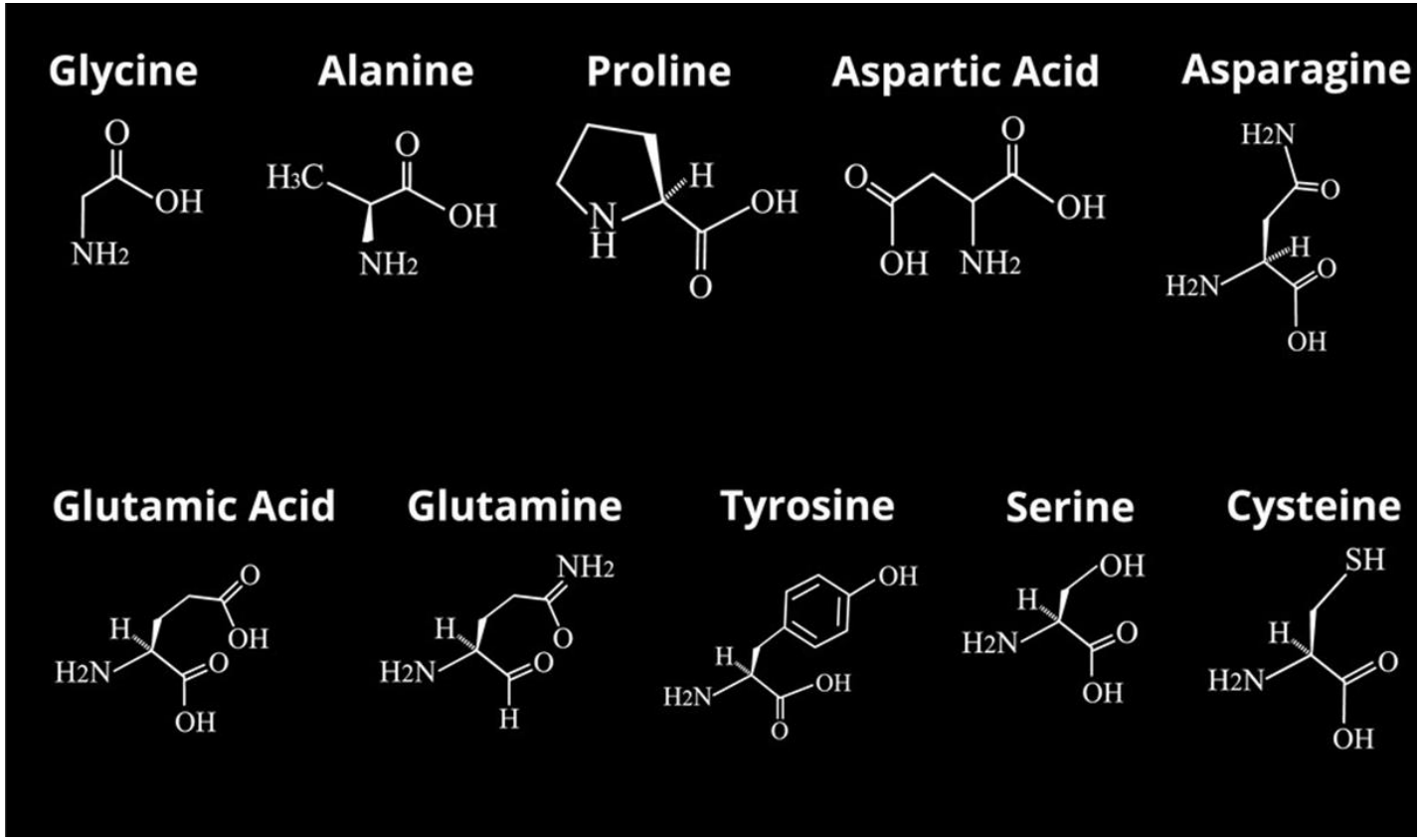


Clinical Significance of Transaminases

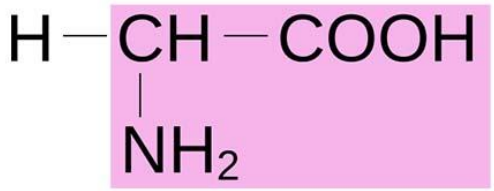
- Transaminases are intracellular enzymes; their levels in blood are **low** under **normal conditions**
- ALT and AST are **markers** of liver injury
- Elevated plasma levels of aminotransferases indicate damage to cells rich in these enzymes. For example, physical trauma or a disease process can cause cell lysis, resulting in release of intracellular enzymes into the blood.
- AST and ALT are induced by glucocorticoids which favors gluconeogenesis

Synthesis of non-essential amino acids

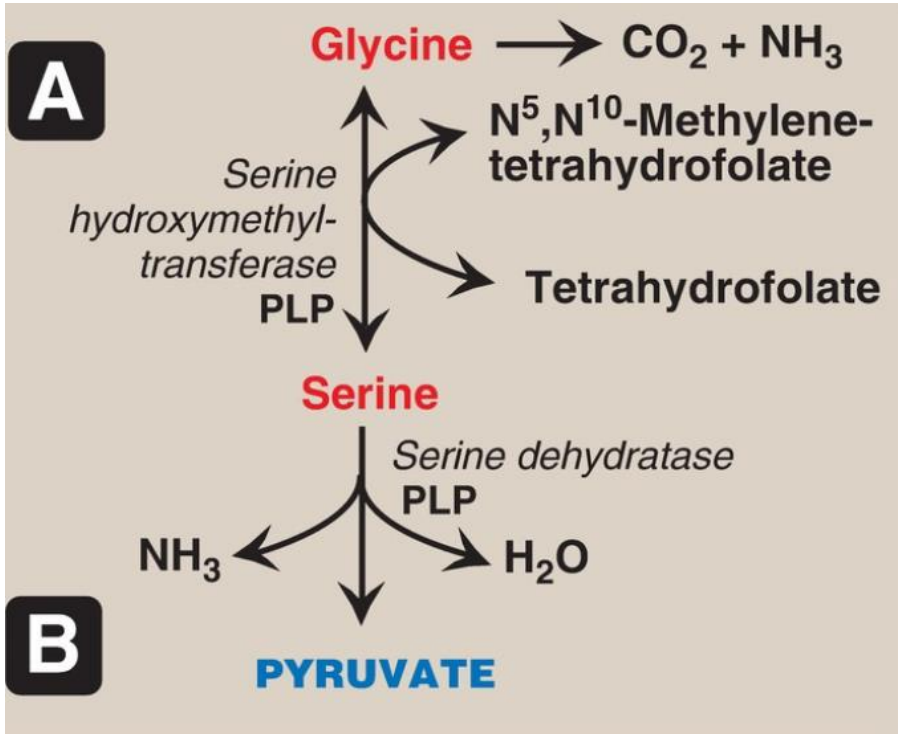
Non-essential amino acids are formed in the body in enough amounts for adults



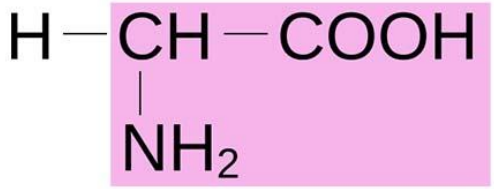
Glycine



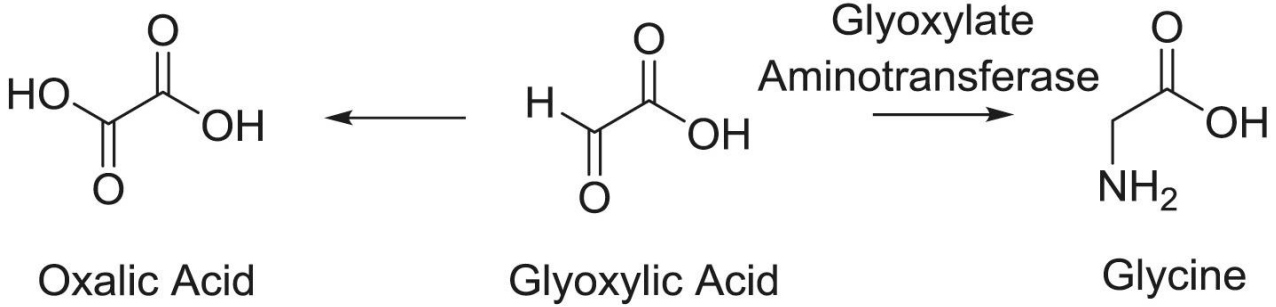
This amino acid is **synthesized** from **serine** by removal of a hydroxymethyl group, also by **serine hydroxymethyltransferase.**

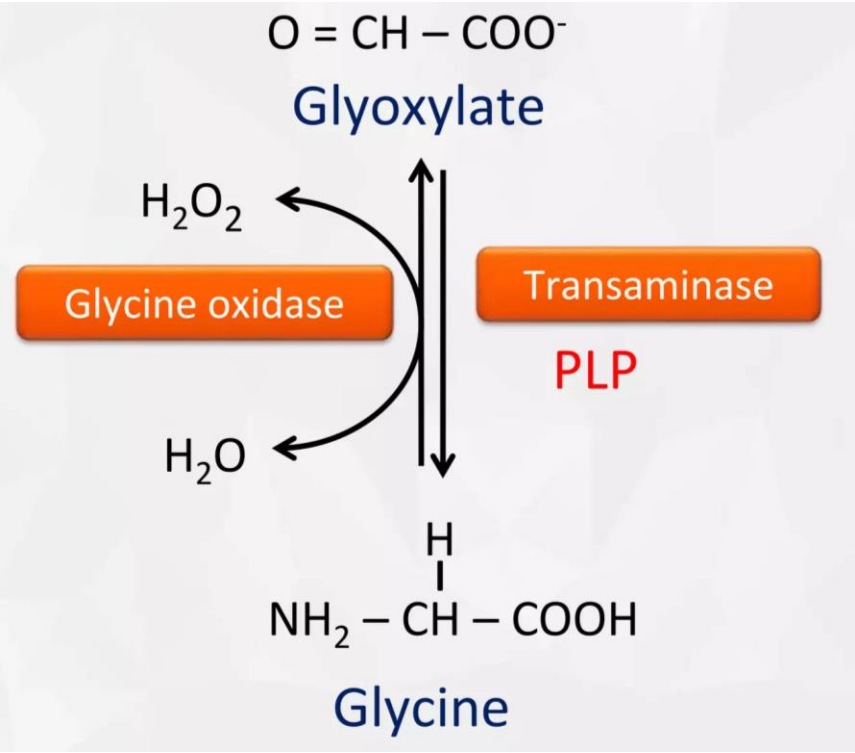


Glycine



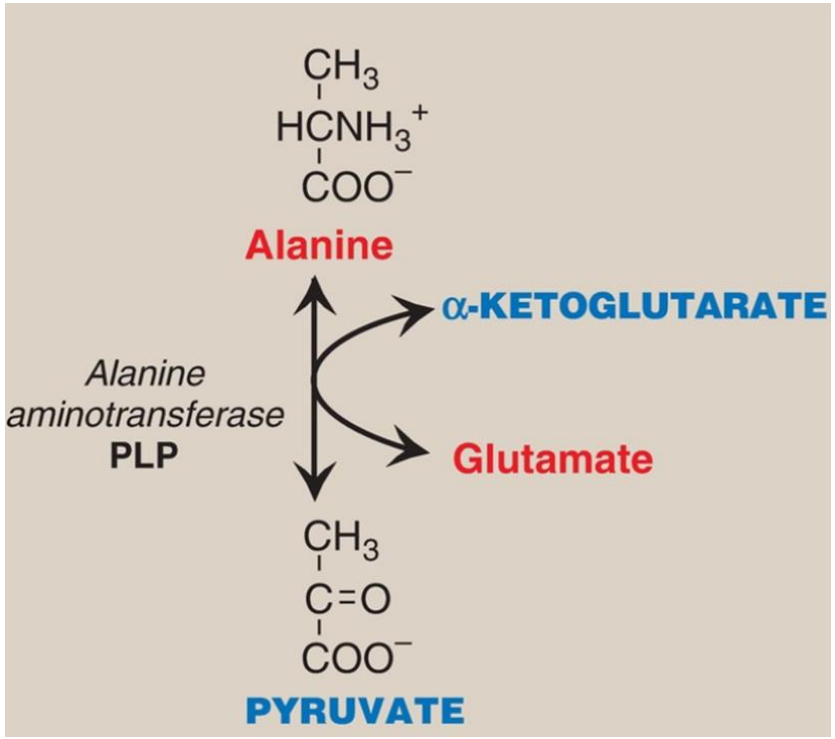
- Glycine can be deaminated to **glyoxylate**, which can be oxidized to **oxalate** or **transaminated to glycine**.
- Deficiency of the transaminase in liver peroxisomes causes **overproduction of oxalate**, the formation of oxalate stones, and kidney damage.

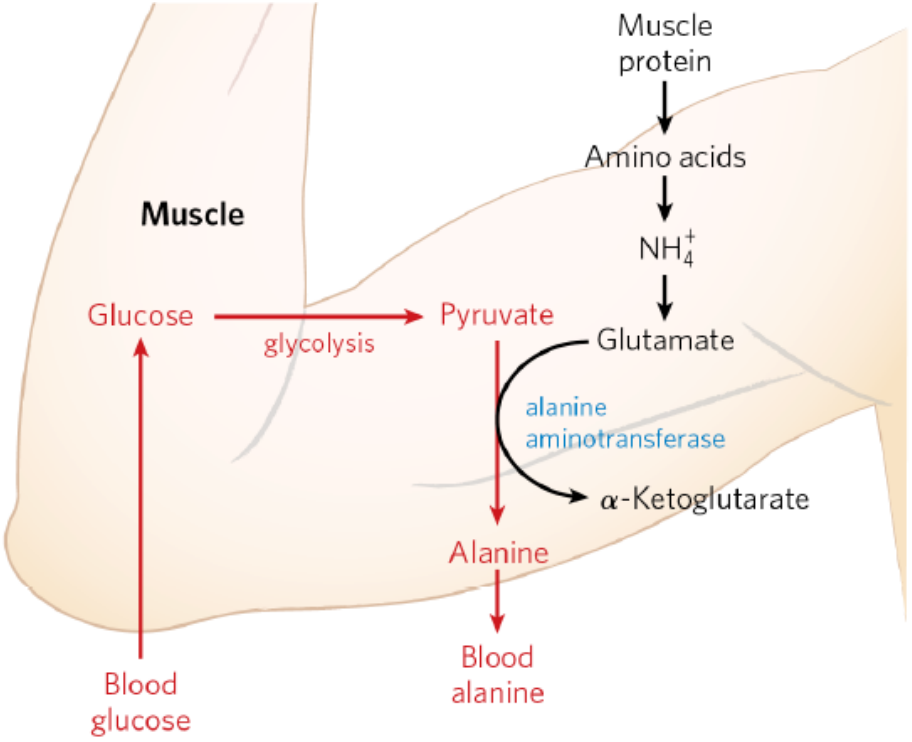




Alanine

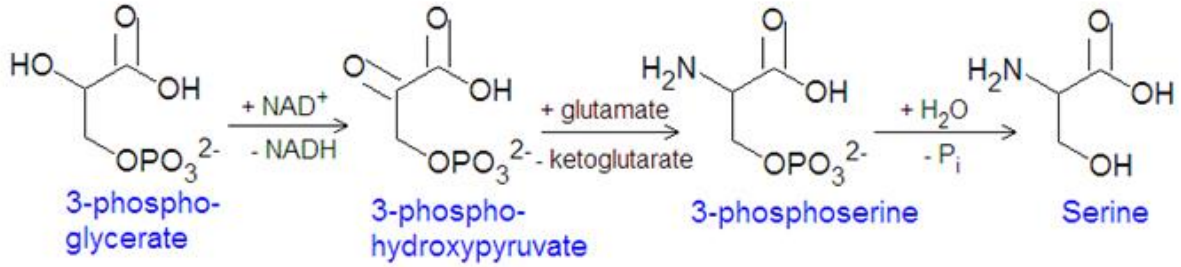
- This amino acid loses its amino group by transamination to **form pyruvate**.
- It is released from the muscles during starvation and changed to glucose in the liver by gluconeogenesis to supply blood glucose by glucose alanine cycle.

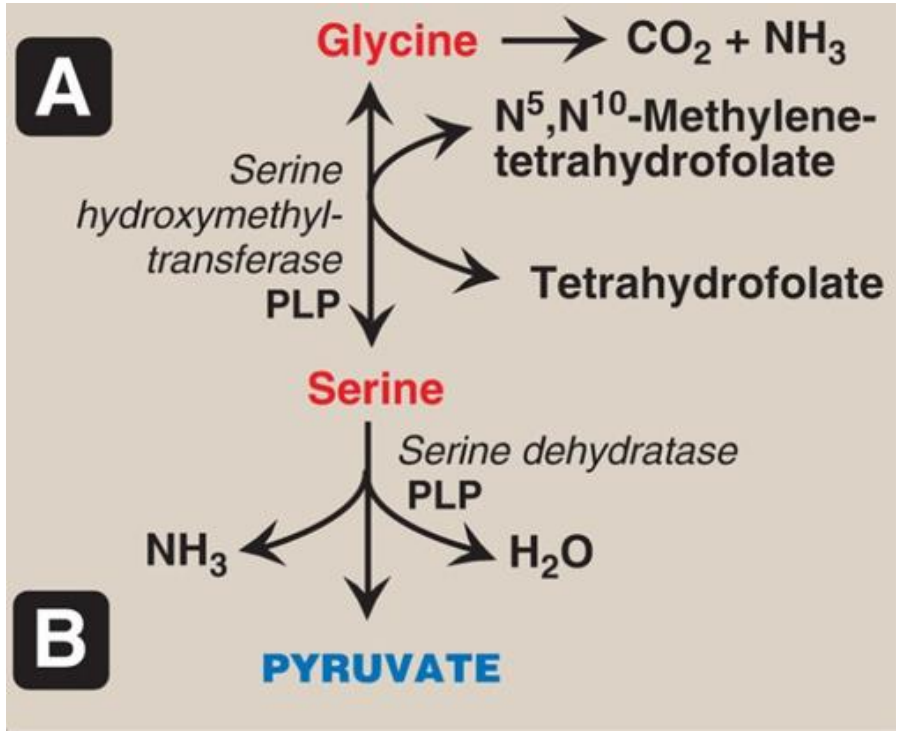




Serine

1. Formed from glycine through transfer of a hydroxymethyl group by serine **hydroxymethyl transferase**.
2. Formed from **3 phosphoglycerate** that is **oxidized to 3-phosphopyruvate**, and then **transaminated to 3 phosphoserine**.

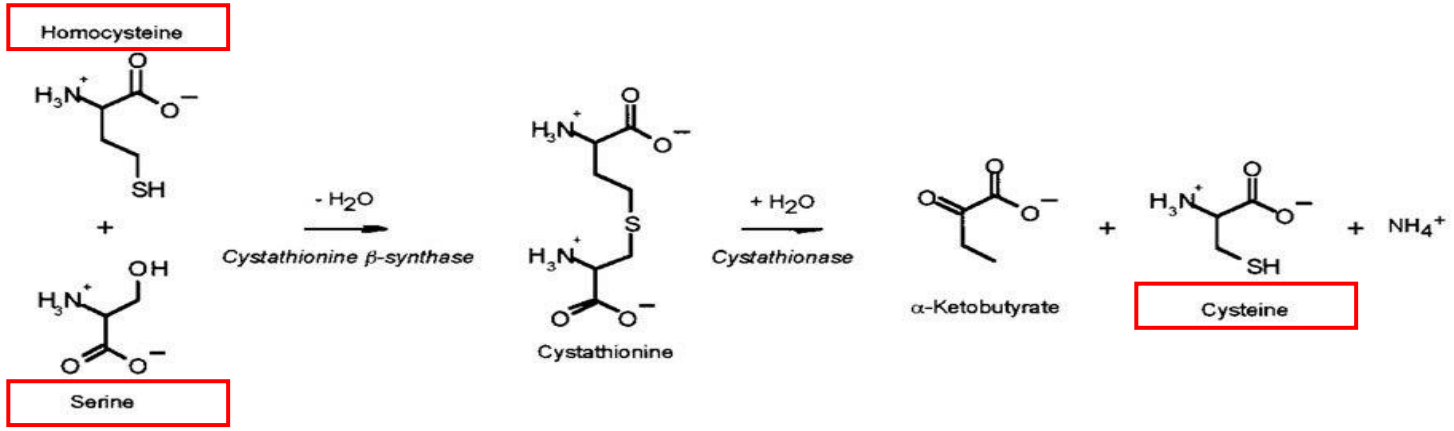




Cysteine

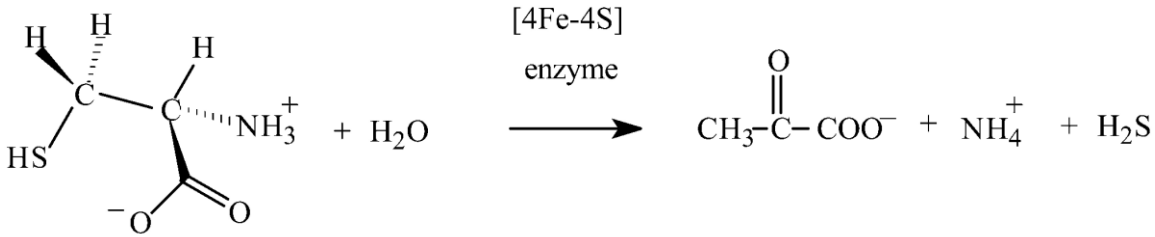
- It is formed from **serine** (provides the carbon skeleton) and **homocysteine** (provides the thiol group)
  - Homocysteine is formed from methionine

- Part of the dietary requirements for methionine is to **provide sulfur** for the biosynthesis of cysteine
  - If dietary methionine is inadequate, cysteine becomes essential



Importance of Cysteine

1. Synthesis of **glutathione** which is:
   - Powerful antioxidant
   - Used for removal of many toxic compounds
   - Acts as coenzyme for many enzymes
2. Synthesis of **thioethanolamine** which enters in the formation of:
   - phosphopantetheine of acyl carrier protein present in fatty acid synthase multienzyme complex coenzyme A
3. Synthesis of **cystine**; important in tertiary structure of proteins.
4. Cysteine desulfuration yields pyruvate (glucogenic).

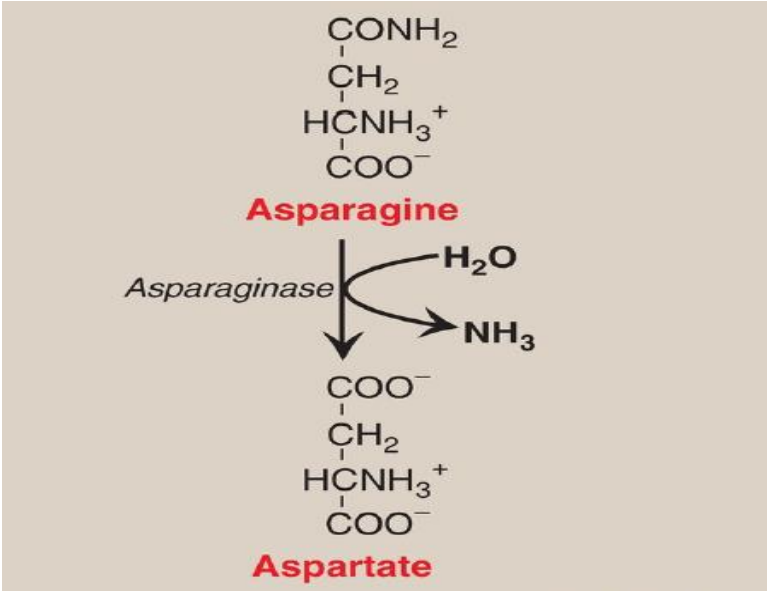


L-cysteine

pyruvate

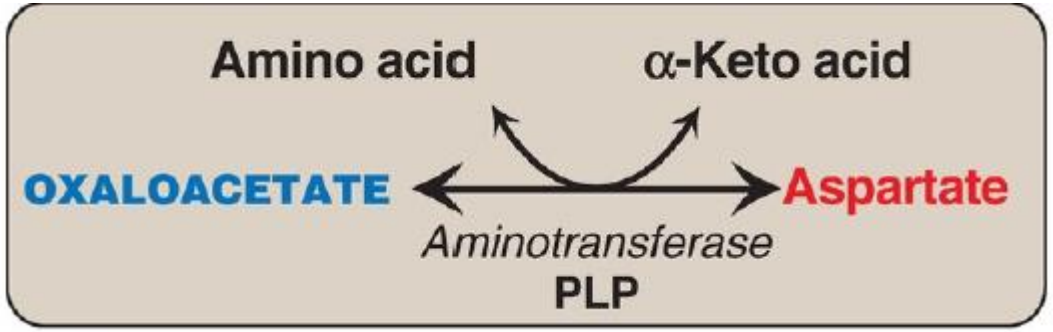
Aspartic acid

- It is formed from **oxaloacetic acid** by transamination, and also from asparagine by asparaginase enzyme.



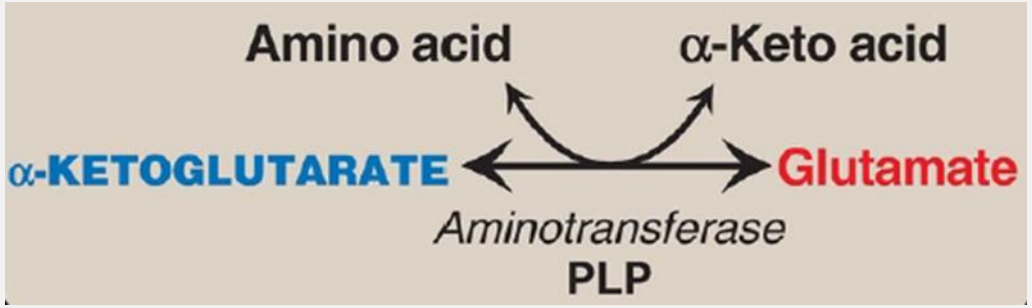
- **Importance:**

1. urea formation
2. purine synthesis
3. pyrimidine synthesis



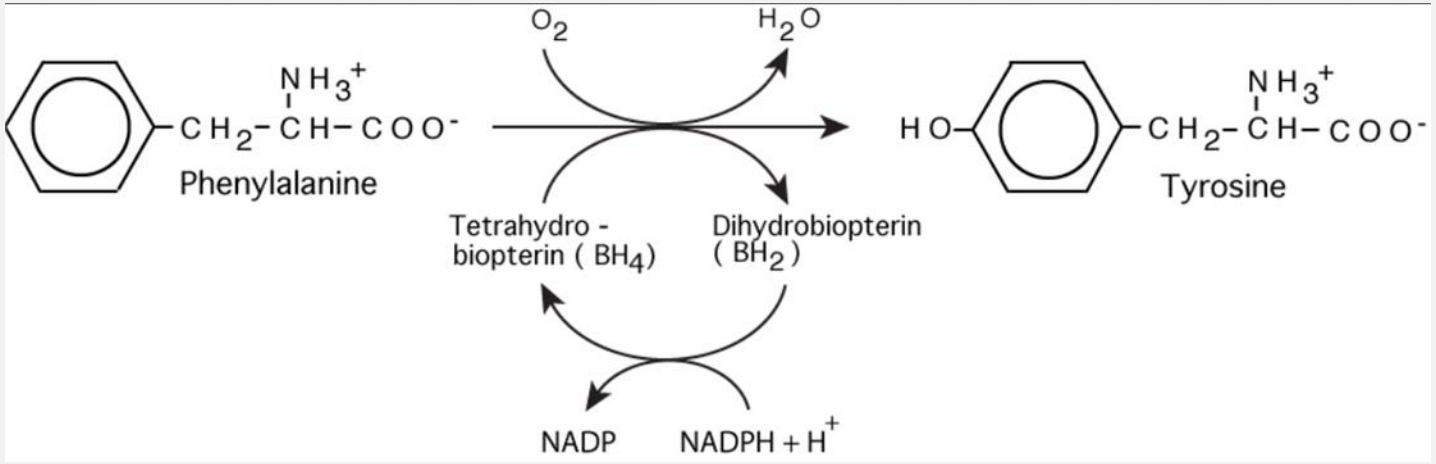
Glutamate

- Glutamate is unusual in that it can be synthesized by reversal of oxidative deamination, catalyzed by **glutamate dehydrogenase**, when ammonia levels are high.



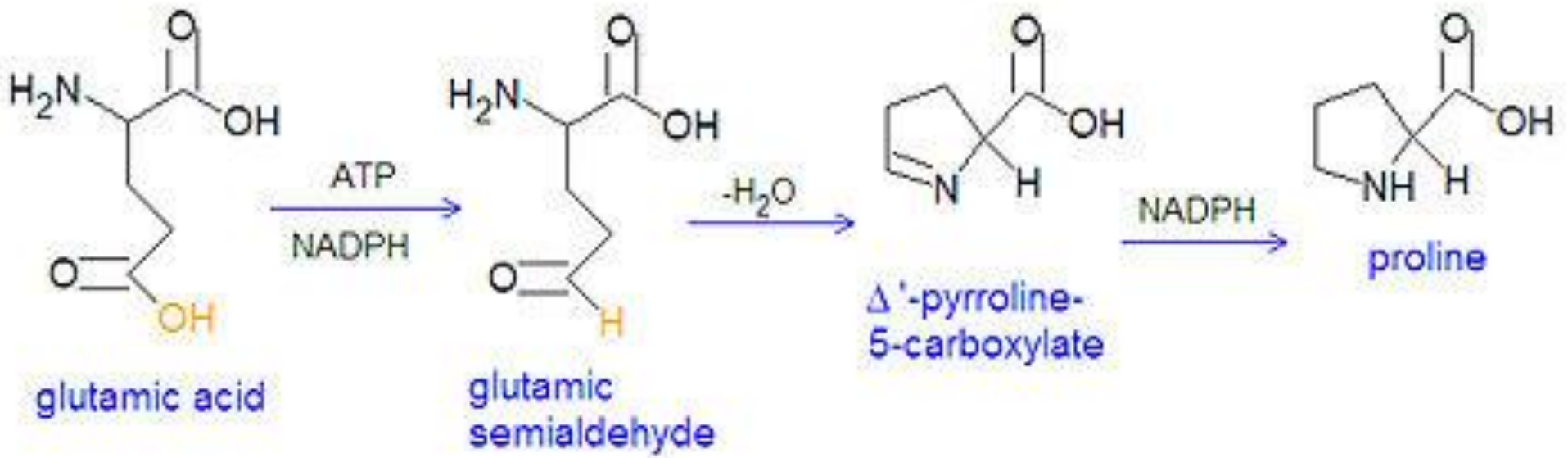
Tyrosine

- Tyrosine is formed **from phenylalanine,** by **phenylalanine hydroxylase**. The reaction requires molecular oxygen and the coenzyme tetrahydrobiopterin (BH4), which is synthesized from guanosine triphosphate.
- Tyrosine, like cysteine, is formed from an essential amino acid and is, therefore, nonessential only in the presence of adequate dietary phenylalanine.



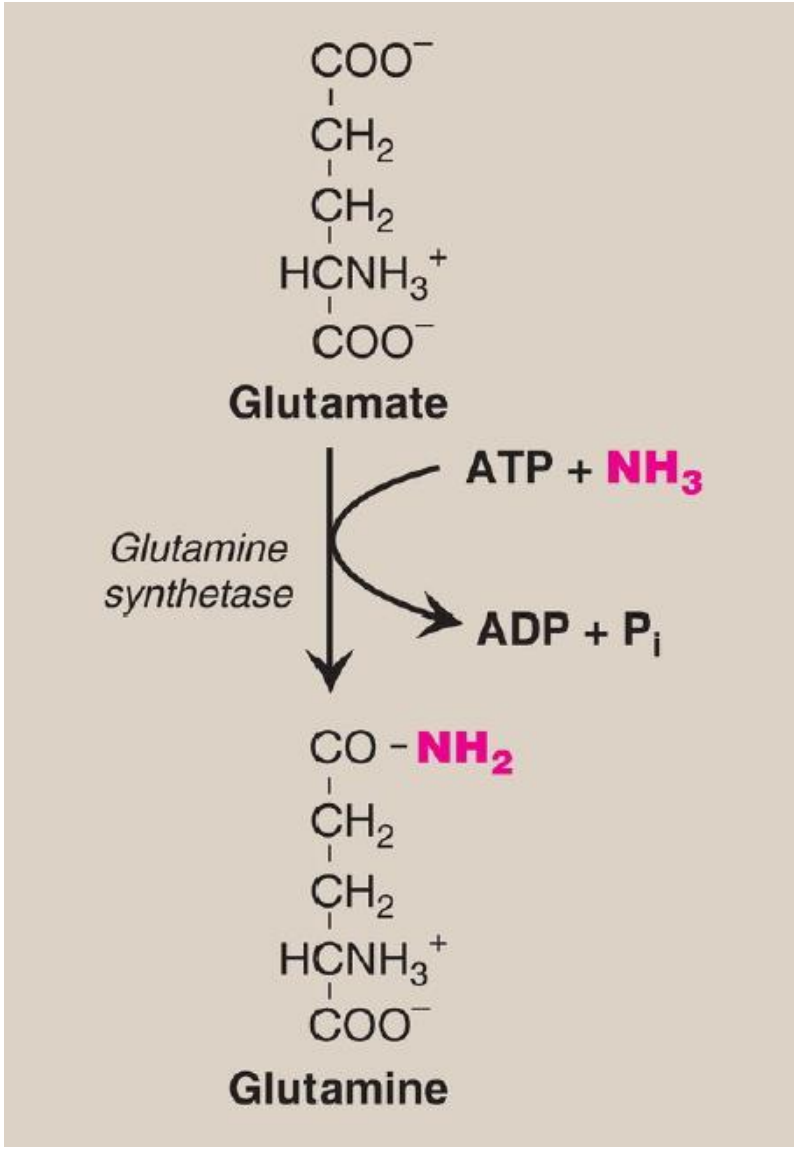
Proline

- **Glutamate via glutamate semialdehyde is converted to proline by cyclization and reduction reactions**



Glutamine

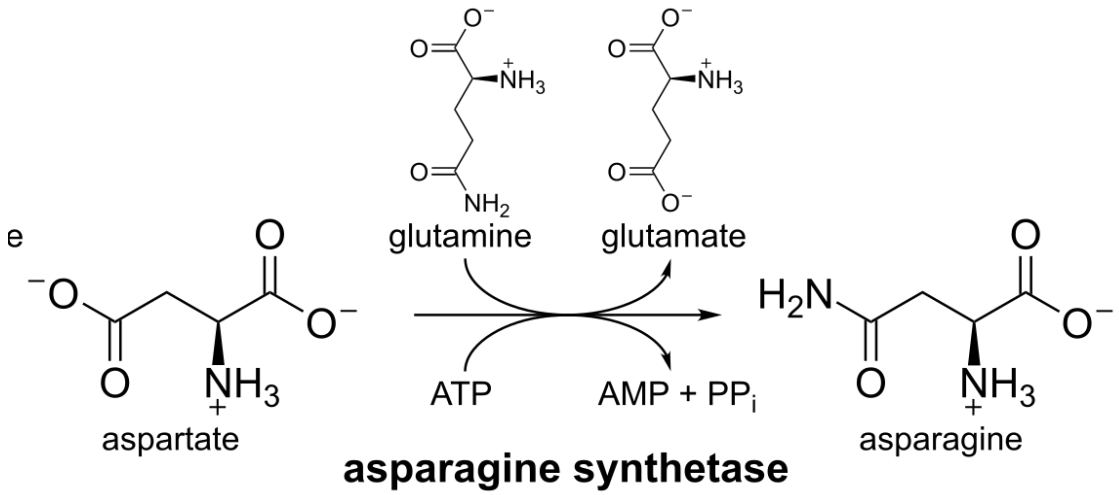
- Contains an amide linkage with ammonia at the γ-carboxyl, is formed from glutamate by glutamine synthetase.



Asparagine

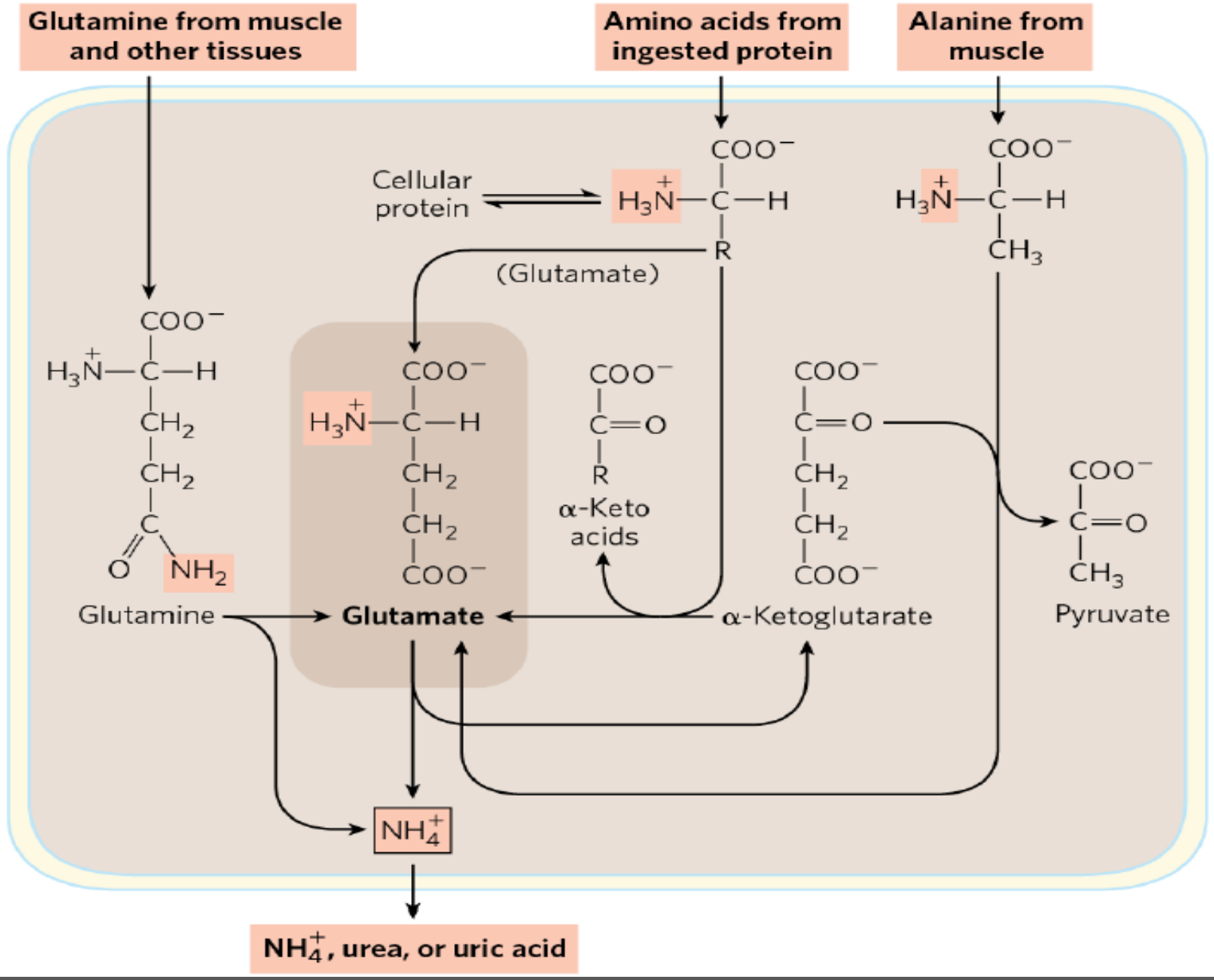
- Asparagine is hydrolyzed by **asparaginase**, liberating ammonia and aspartate.

- This amino acid, which contains an amide linkage with ammonia at the β-carboxyl, is **formed from aspartate by asparagine synthetase**, using glutamine as the amide donor.



Importance of Asparaginase

- Some rapidly dividing leukemic cells are unable to synthesize sufficient asparagine to support their growth. This makes asparagine an essential amino acid for these cells, which, therefore, require asparagine from the blood.
- Asparaginase, which hydrolyzes asparagine to aspartate, can be **administered systemically to treat leukemia**.
- Asparaginase lowers the level of asparagine in the plasma, thereby depriving cancer cells of a required nutrient


Glutamine from muscle and other tissues
Amino acids from ingested protein
Alanine from muscle
Cellular protein
(Glutamate)
α-Keto acids
Glutamine
Glutamate
α-Ketoglutarate
Pyruvate
NH_4^+
NH_4^+, urea, or uric acid