AMINO ACID METABOLISM

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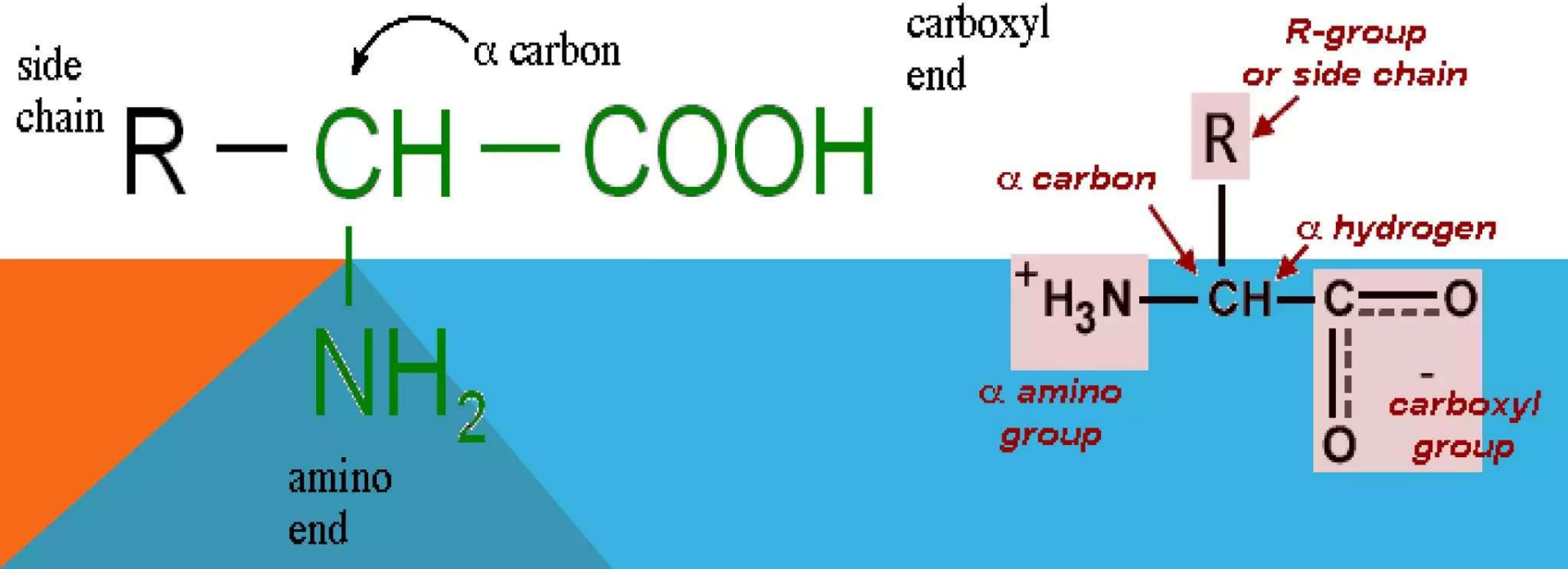
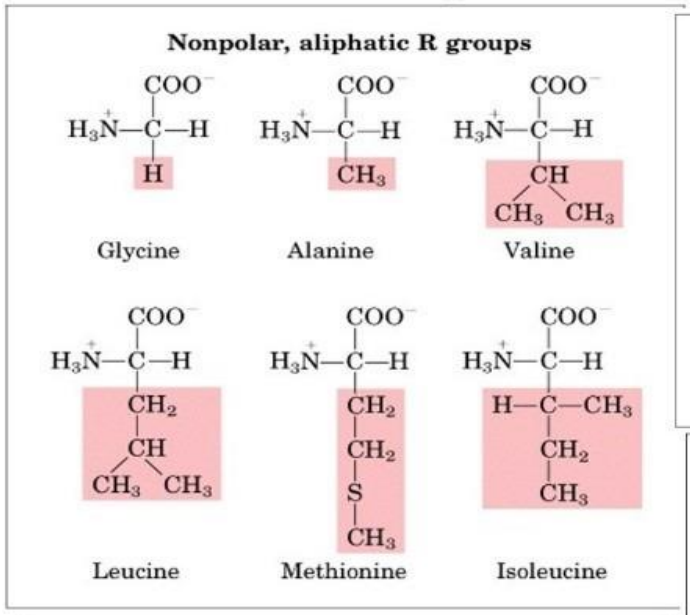
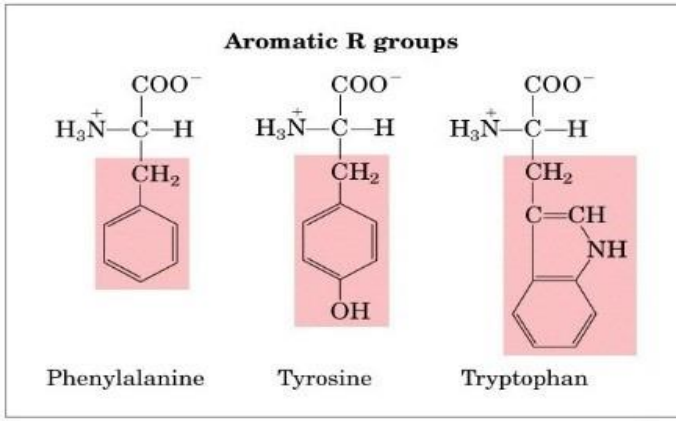
WHAT IS AMINO ACID?

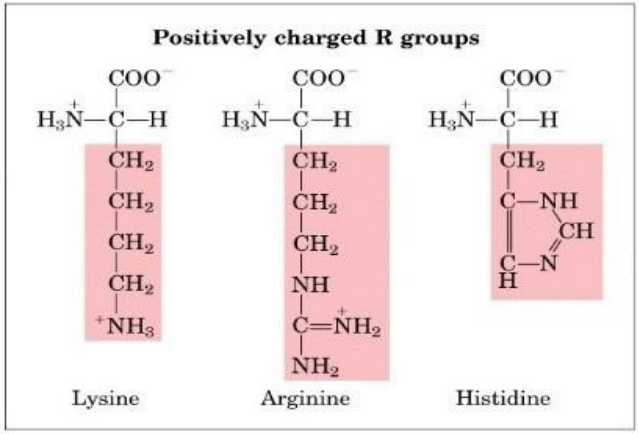
Amino acids are derivatives of carboxylic acids formed by substitution of α-hydrogen for amino functional group

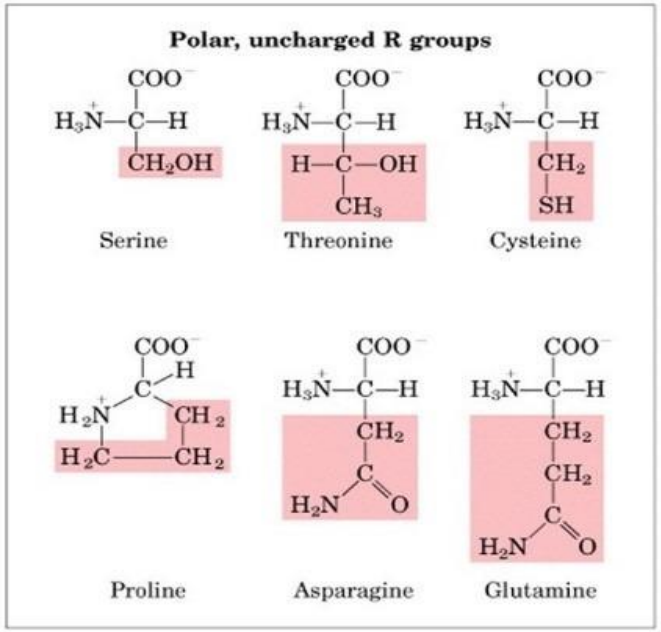


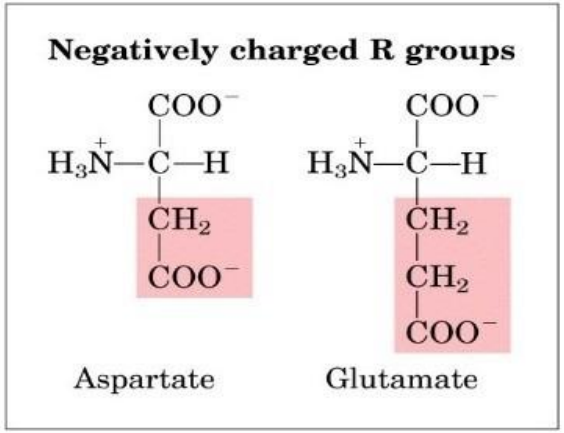
Classification of amino acids on SIDE CHAIN (R) groups











Nutritional classification of amino acids

Amino acids are classified nutritionally into three groups based on whether the human body can synthesize them:

Essential amino acids

These amino acids cannot be synthesized by the human body, so they must be obtained through diet.

Nonessential amino acids

These amino acids can be synthesized by the human body, so they are also called dispensable amino acids.

Conditionally essential amino acids

These amino acids are not normally required in the diet, but must be supplied when the body is not synthesizing them in adequate amounts.

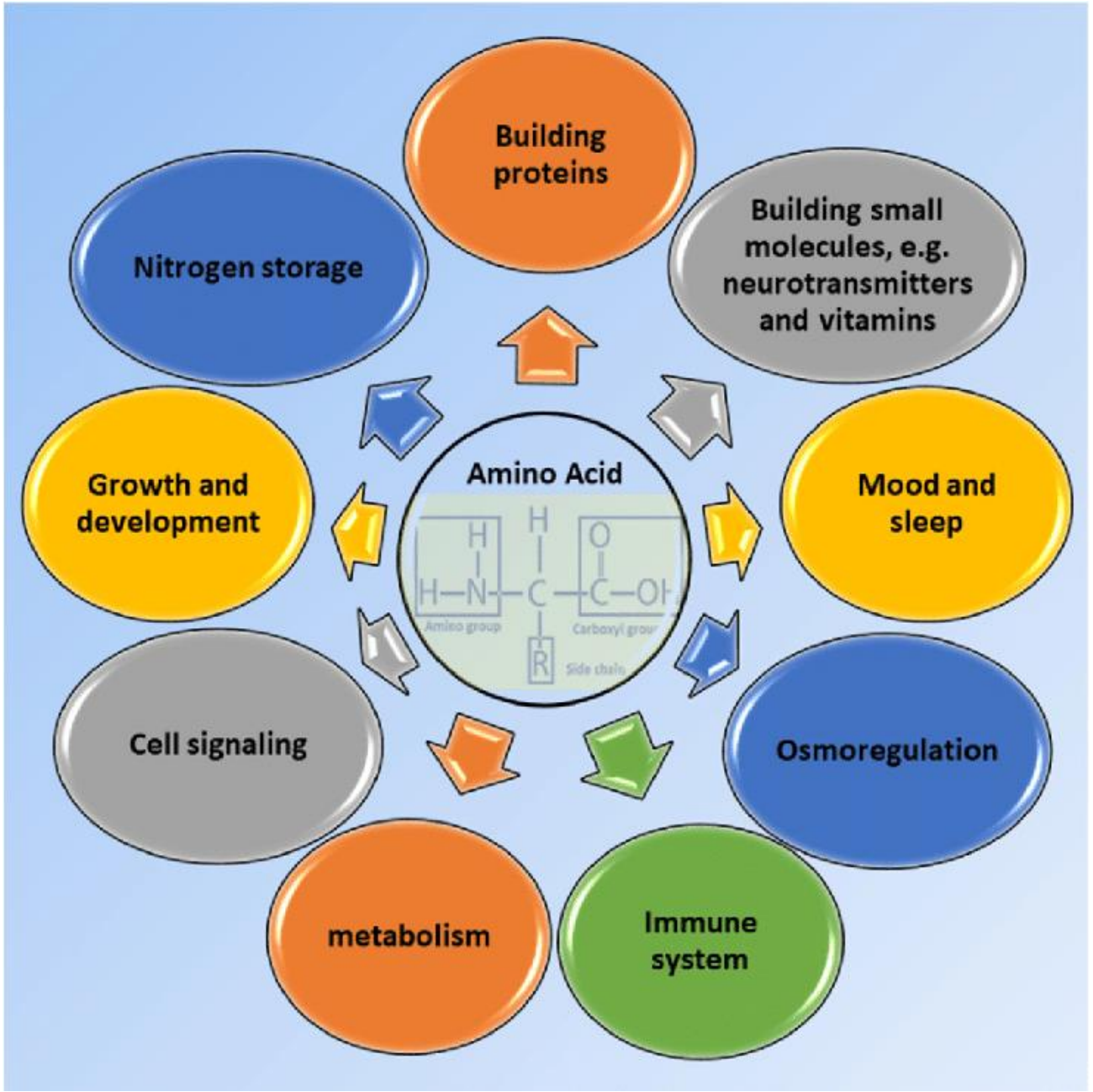
Essential	Conditionally Non-Essential	Non-Essential
Histidine	Arginine	Alanine
Isoleucine	Cystine	Asparagine
Leucine	Glutamine	Aspartate
Lysine	Glycine	Glutamate
Methionine	Proline	Serine
Phenylalanine	Tyrosine	
Threonine		
Tryptophan		
Valine		

Classification of amino acids ON FATE

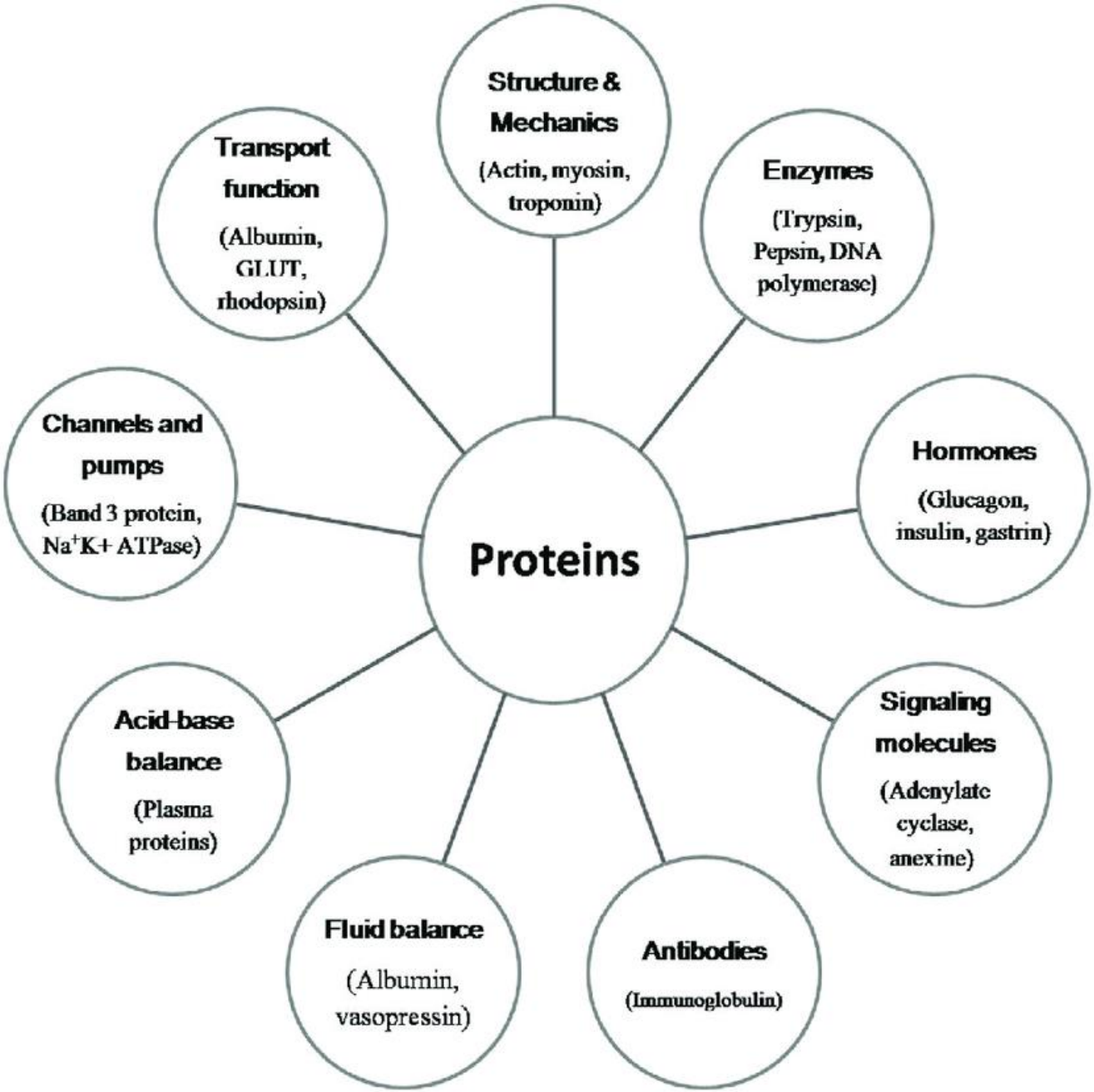
1. **Glucogenic amino acids**: These amino acids serve as precursors of gluconeogenesis for glucose formation. Glycine, alanine, serine, aspartic acid, asparagine, glutamic acid, glutamine, proline, valine, methionine, cysteine, histidine, and arginine.
2. **Ketogenic amino acids:** These amino acids break down to form ketone bodies. Leucine and Lysine.
3. **Both glucogenic and ketogenic amino acids:** These amino acids break down to form precursors for both ketone bodies and glucose. Isoleucine, Phenylalanine, Tryptophan, and tyrosine.

Glucogenic amino acids	Glucogenic and ketogenic	Ketogenic amino acids
Alanine, Arginine, Asparagine, Aspartate Asparagine, Cysteine, Methionine Glutamate, Glutamine, Glycine, Histidine Proline, Serine, Threonine,Valine	Tyrosine Isoleucine Phenylalanine Tryptophan	Leucine Lysine

Functions of amino acids



Functions of proteins



Amino acid pool

The amino acid pool is **the collection of free amino acids in the body that are available for metabolic processes**:

Composition

The amino acid pool is made up of amino acids from the diet, protein recycling, and non-essential amino acids produced by the body.

Function

The amino acid pool is critical for many metabolic processes, including protein synthesis, energy production, and regulating other cellular functions.

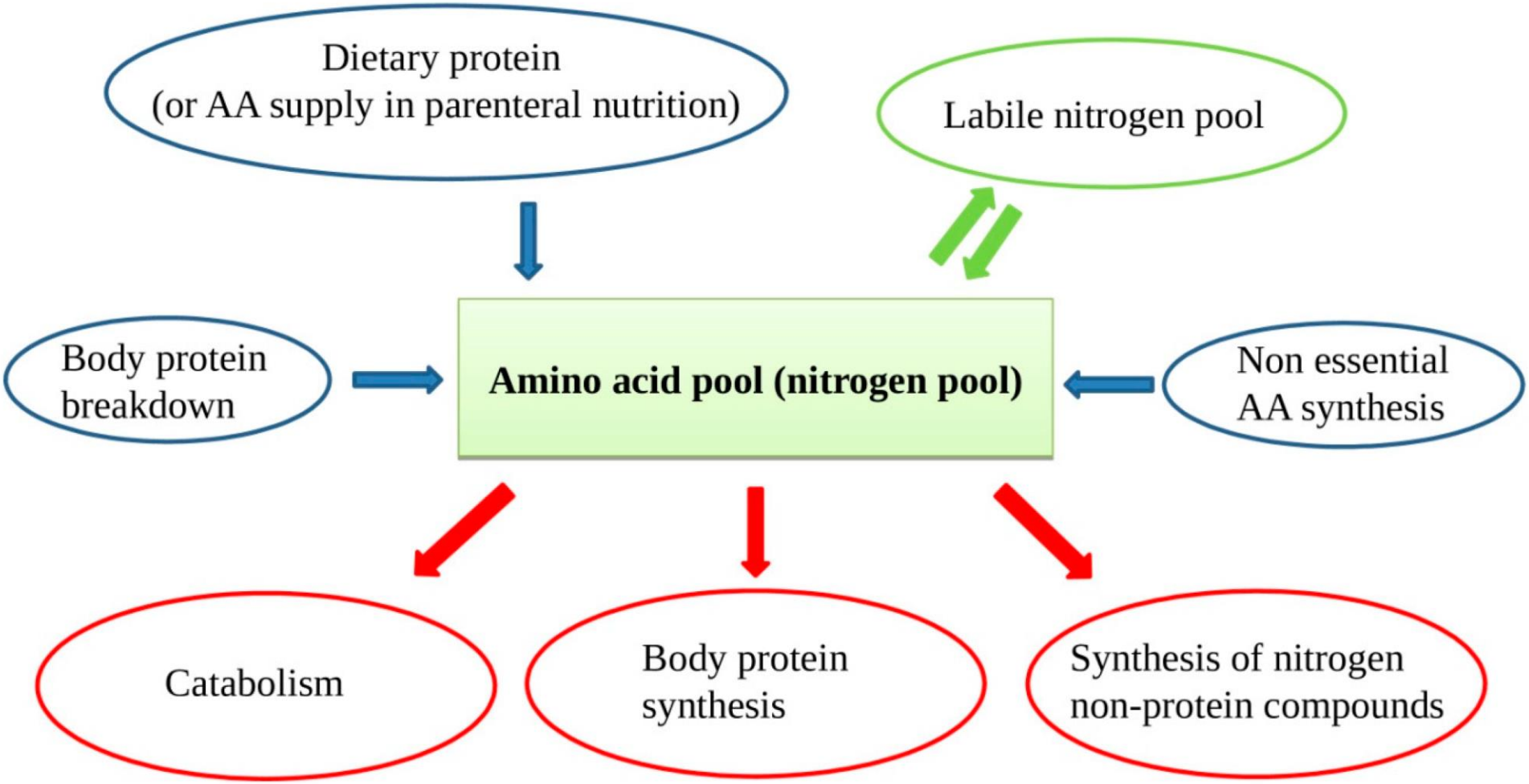
Location

The amino acid pool is found in cells, blood circulation, and extracellular fluid.

Storage

The human body does not store amino acids. If amino acids are not used for biological processes, they are degraded and the nitrogen is excreted in the urine as urea.

The amino acid pool is maintained by the balance of sources that provide amino acids and sources that use them.


Dietary protein
(or AA supply in parenteral nutrition)
Labile nitrogen pool
Body protein
breakdown
Amino acid pool (nitrogen pool)
Non essential
AA synthesis
Catabolism
Body protein
synthesis
Synthesis of nitrogen
non-protein compounds

Features of amino acid pool

The amino acid pool is the total amount of amino acids available to the body for protein synthesis and other functions. It has several key features, including:

Essential for proper functioning

The amino acid pool is vital for the proper functioning of an organism, as it's the primary source of amino acids for protein synthesis and other cellular processes.

Maintains balance

The amino acid pool helps maintain the balance between catabolism (breakdown of molecules) and anabolism.

Replenished by food and the body's own protein

The amino acid pool is replenished by the protein you eat and by your body's own protein.

Maintained in the blood

The body maintains a relatively large free amino acid pool in the blood, at approximately 35-65 mg/deciLiter.

Significance of amino acid pool

The amino acid pool is important for the proper functioning of an organism because **it's the primary source of amino acids for protein synthesis and other vital cellular processes**. The amino acid pool is made up of free amino acids in an organism's cells, tissues, and bloodstream. Here are some of its other significances:

Protein synthesis

The amino acid pool is used to build new proteins, replace damaged or degraded proteins, and maintain and repair tissues.

Nitrogen-containing compounds

The amino acid pool is used to synthesize DNA bases, neurotransmitters, and hormones.

Energy

The body can use amino acids as a source of energy under certain metabolic situations.

Catabolism and anabolism

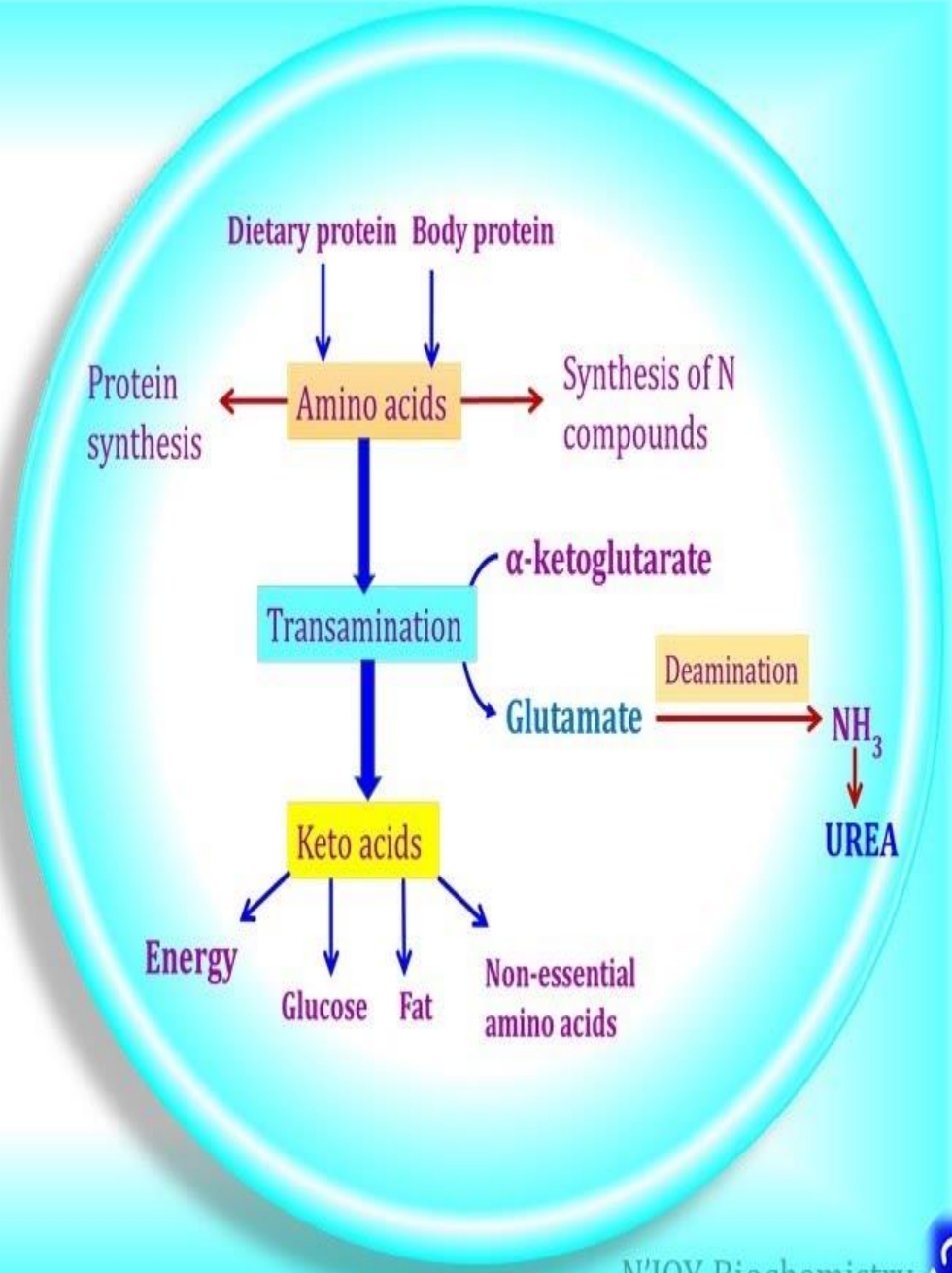
The amino acid pool helps maintain the balance between catabolism (breakdown of molecules) and anabolism (synthesis of molecules).

Immune system

Amino acid catabolism is important for the immune system, which depends on an adequate supply of amino acids.

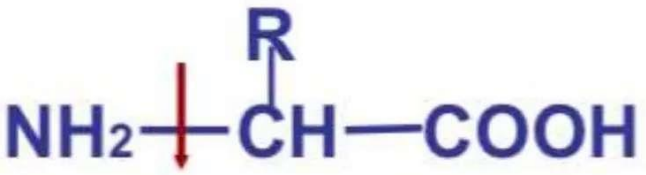
The amino acid pool is dynamic and constantly being replenished and utilized. Factors that can affect the size and composition of the amino acid pool include diet, exercise, stress, and illness.

Overview of Amino Acids Metabolism



N'JOY Biochemistry

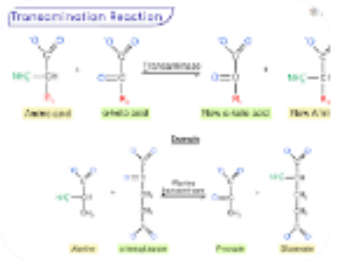
Metabolism OF AMINO ACIDS:



1. **Removal of amonia** by :
   - Deamination
     - **Oxidative deamination**
       1) glutamate dehydrogenase in mitochondria
       2) amino acid oxidase in peroxisomes
     - **Direct deamination (nonoxidative)**
       1) dea. by dehydration ($-H_2O$)
       2) dea. by desulhydration ($-H_2S$)
   - Transamination (GPT & GOT)
   - and transdeamination.
2. **Fate of carbon-skeletons of amino acids**
3. **Metabolism of ammonia**

Transamination

Transamination is **a chemical reaction that transfers an amino group from an amino acid to a keto acid to create new amino acids**. It's a reversible reaction that's a key part of amino acid biosynthesis and degradation.



Here are some things to know about transamination:

Enzymes

Transaminases, also known as aminotransferases, catalyze transamination reactions. These enzymes are found throughout the body, but are especially active in the heart, liver, skeletal muscle, and kidneys.

Process

Transamination involves two half-reactions:

1. The amino group is transferred from the amino acid to pyridoxal phosphate (PLP) to form PMP.
2. The PMP transfers the amino group to the carbon skeleton of the original oxoacid.

Importance

Transamination is a major pathway for degrading essential amino acids and converting them to non-essential amino acids.

Transamination Reaction

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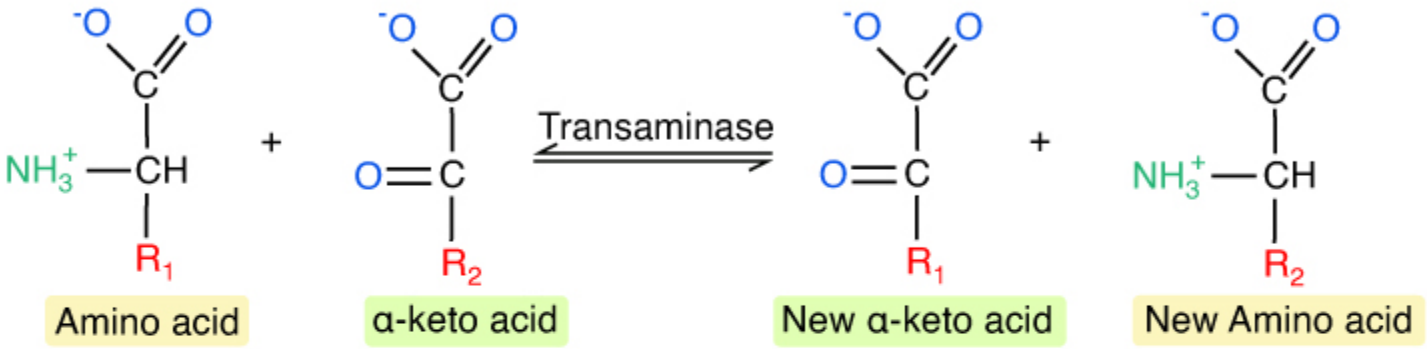
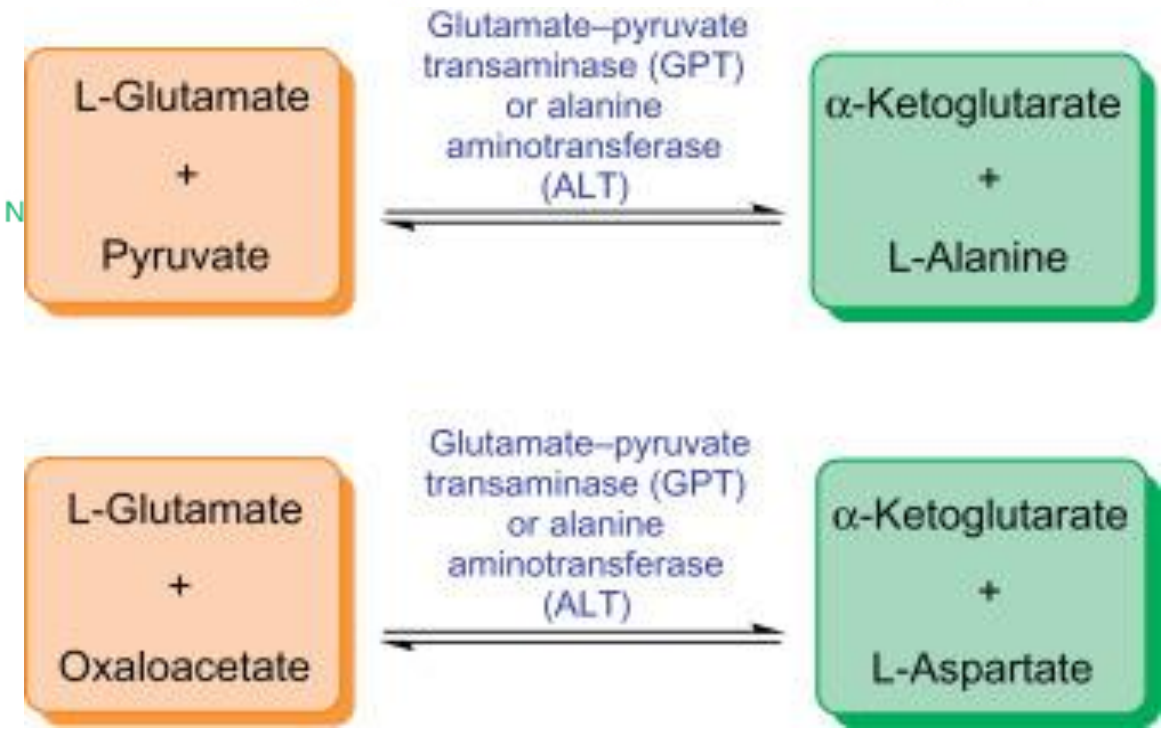


Example



Salient features of transamination

1. All transaminases require ***pyridoxal phosphate*** (PLP), a coenzyme derived from vitamin B_6.

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***).

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.

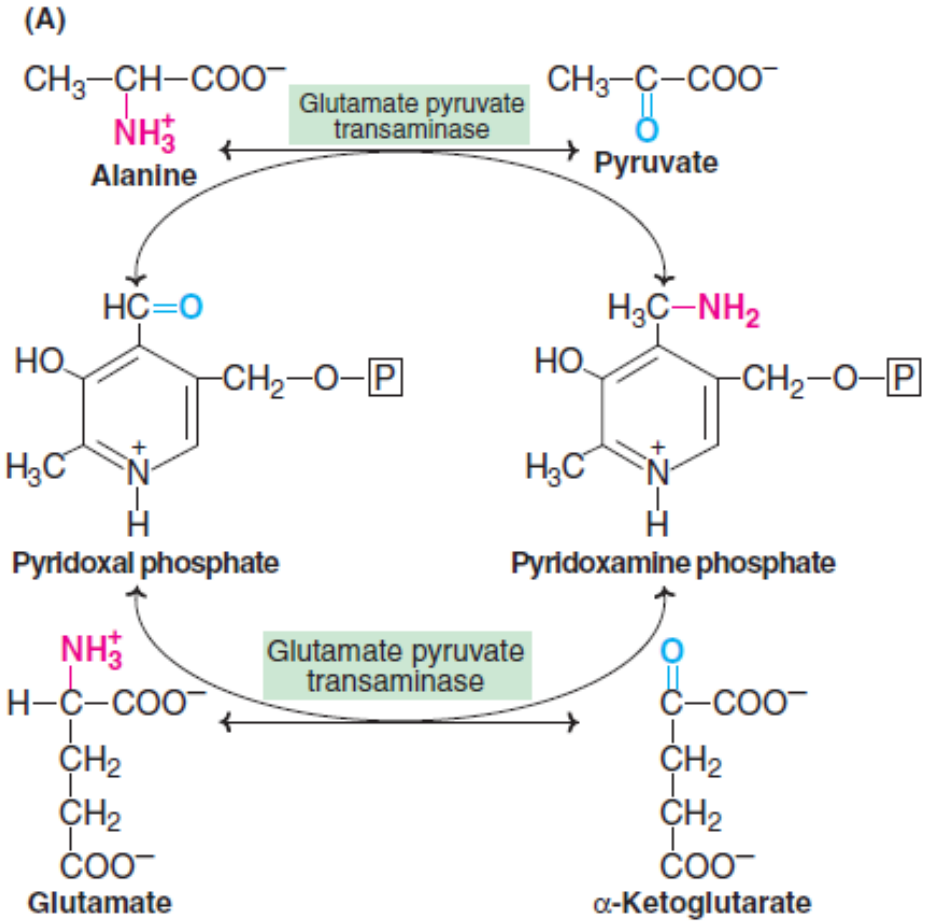
6. Transamination diverts the excess amino acids towards ***energy generation***.

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.

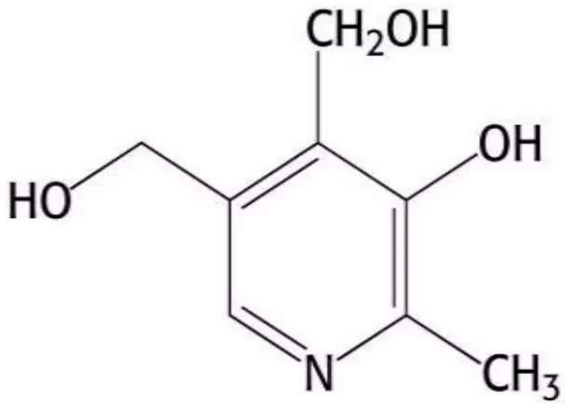
9. Transamination is not restricted to α-amino groups only. For instance, δ-amino group of ornithine is transaminated.

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



Mechanism of transamination

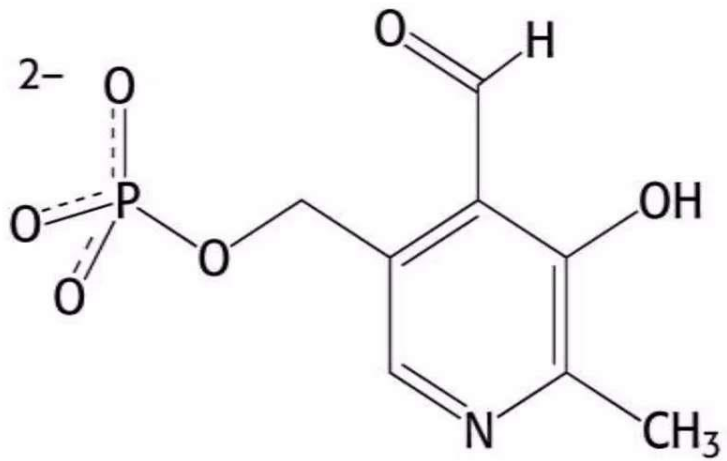
All aminotransferases require the prosthetic group ***pyridoxal phosphate (PLP),*** which is derived from ***pyridoxine (vitamin B_6).***



Pyridoxine (Vitamin B_6)

Ping-pong kinetic mechanism

First step: the amino group of amino acid is transferred to pyridoxal phosphate, forming pyridoxamine phosphate and releasing ketoacid.



Pyridoxal phosphate (PLP)

Second step: α-ketoglutarate reacts with pyridoxamine phosphate forming glutamate

Significance of Transamination

Transamination is a chemical reaction that's important for amino acid metabolism and has several significant roles, including:

Synthesis of nonessential amino acids

Transamination is responsible for converting essential amino acids into nonessential amino acids, which are amino acids that the body can synthesize on its own.

Metabolic adaptation

Transamination allows for the interconversion of amino acids, which is important for metabolic adaptation.

Production of metabolic intermediates

Transamination produces metabolic intermediates that are used in other pathways, such as the citric acid cycle and gluconeogenesis.

Transamination is catalyzed by enzymes called transaminases or aminotransferases.

Transaminases and their clinical significance

Transaminases are enzymes that are involved in transferring amino groups from one molecule to another. Some examples of transaminases include:

Aspartate aminotransferase (AST)

A transaminase that is often studied in conjunction with alanine aminotransferase (ALT) to diagnose liver dysfunction.

Alanine aminotransferase (ALT)

A transaminase that is commonly assayed in clinical practice. ALT is also known as serum glutamic pyruvate transaminase (SGPT).

Elevated levels of transaminases in the blood can be an early sign of liver stress or damage. This can be caused by a number of conditions, including:

Viral hepatitis

Hepatitis A and E viruses cause acute infections, while hepatitis B, C, and D are usually chronic.

Alcoholic liver disease

Patients with a history of alcohol use and abnormal transaminase levels may have alcoholic liver disease.

Hepatitis

Elevated transaminases can indicate hepatitis before other signs appear.

Other nonhepatic diseases

Abnormal transaminase levels can also indicate other diseases, such as Addison disease, hypothyroidism, and gluten-sensitive enteropathy.

Amino acids that don't participate in Transamination

- **The amino acids that do not participate in transamination reactions are lysine, threonine, proline, and hydroxyproline.**
- **A mnemonic for these amino acids is POLYTHENE, where PO stands for proline, LY stands for lysine, and THENE stands for threonine**

- **Lysine:** Lysine does not always undergo transamination because it uses a different pathway for degradation. A pathway that breaks down lysine into acetoacetate and carbon dioxide.
- **Proline and hydroxyproline:** These are actually imino acids and nitrogen is the part of ring.
- **Threonine:** doesn't undergo transamination because there are no in vivo aminotransferase reactions for threonine.

Deamination

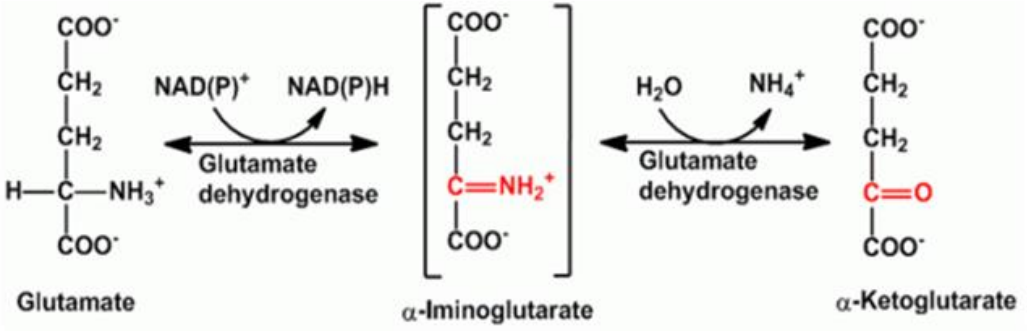
DEAMINATION

The ***removal of amino group*** from the amino acids as NH_3 is deamination. Transamination (discussed above) involves only the shuffling of amino groups among the amino acids. On the other hand, 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.

Although transamination and deamination are separately discussed, they occur simultaneously, often involving glutamate as the central molecule. For this reason, some authors use the term ***transdeamination*** while describing the reactions of transamination and deamination, particularly involving glutamate.

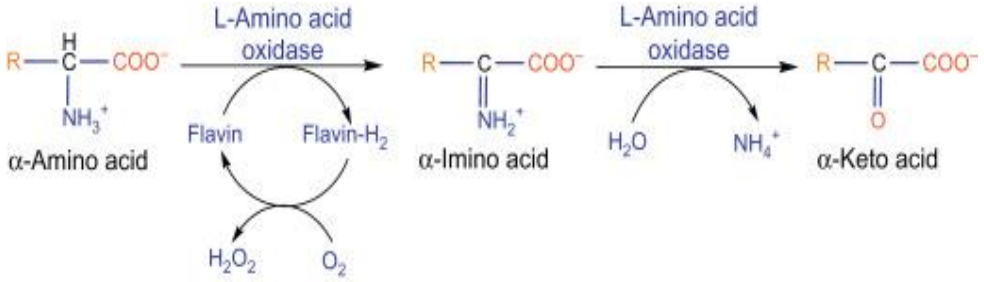
Oxidative Deamination

Oxidative Deamination by GLUTAMATE DEHYDROGENASE



Much of the oxidative deamination occurring in cells involves the amino acid glutamate, which can be oxidatively deaminated by the enzyme glutamate dehydrogenase (GDH), using NAD or NADP as a coenzyme. This reaction generates α-ketoglutarate (α-KG) and ammonia. This is a common pathway during amino acid catabolism.

Oxidative Deamination by L-amino acid oxidase



Another enzyme responsible for oxidative deamination is monoamine oxidase, which catalyses the deamination of monoamines via addition of oxygen. This generates the corresponding ketone- or aldehyde-containing form of the molecule, and generates ammonia. Monoamine oxidases MAO-A and MAO-B play vital roles in the degradation and inactivation of monoamine neurotransmitters such as serotonin and epinephrine.

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-keto-glutarate 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***).

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

Regulation of GDH activity : Glutamate dehydrogenase is a zinc containing mito-chondrial 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 oxi-dases : 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***).

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

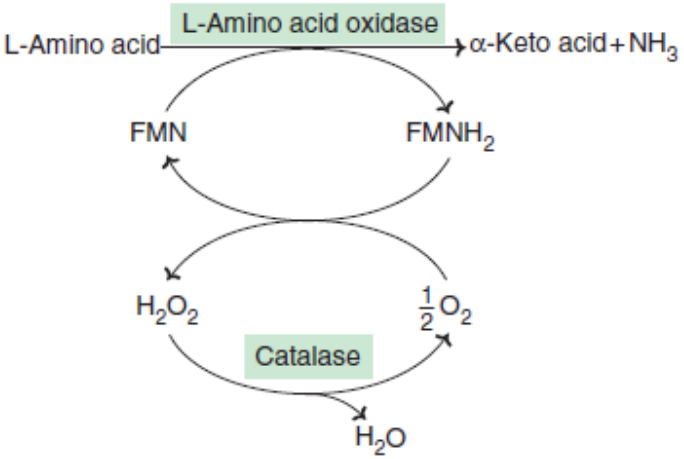


Fig. 15.6 : Oxidative deamination of amino acids.

acids. This enzyme, due to its very low activity, does not appear to play any significant role in the amino acid metabolism.

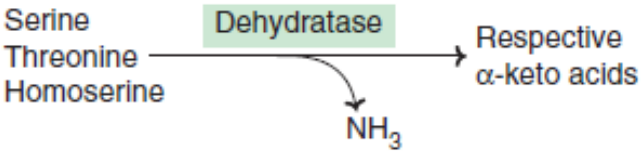
Fate of D-amino acids : D-Amino acids are found in plants and microorganisms. They are, however, not present in the mammalian proteins. But D-amino acids are regularly taken in the diet and metabolized by the body. D-Amino acid oxidase converts them to the respective α-keto acids by oxidative deamination. 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***).

Non-Oxidative deamination

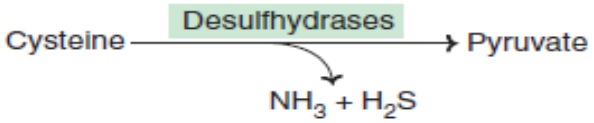
II. Non-oxidative deamination

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

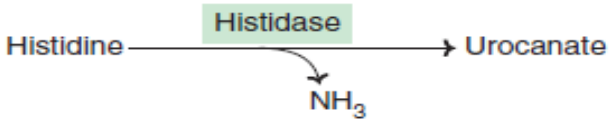
(a) **Amino acid dehydrases :** Serine, threonine and homoserine are the hydroxy amino acids. They undergo non-oxidative deamination catalysed by PLP-dependent dehydrases (dehydratases).



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



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



Non-Oxidative deamination

Reduction deamination:

$$\text{R-CH(NH}_2\text{)-COOH} + 2H^+ \rightarrow \text{R-CH}_2\text{-COOH} + \text{NH}_3$$

amino acid — *fatty acid*

Hydrolytic deamination:

$$\text{R-CH(NH}_2\text{)-COOH} + \text{H}_2\text{O} \rightarrow \text{R-CH(OH)-COOH} + \text{NH}_3$$

amino acid — *hydroxyacid*

Intramolecular deamination:

$$\text{R-CH(NH}_2\text{)-COOH} \rightarrow \text{R-CH-CH-COOH} + \text{NH}_3$$

amino acid — *unsaturated fatty acid*

Types of Deamination

OXIDATIVE DEAMINATION	NON-OXIDATIVE DEAMINATION
Process occurs via oxidation (of amino group amino acids)	Process occurs via other reactions which are not oxidation reactions (mainly hydrolysis, reduction or intramolecular reactions).
Main enzymes that are involved are glutamate dehydrogenase and monoamine oxidase.	Main enzymes that are involved include dehydratases, lyases, and amide hydrolases.
Only occurs in the liver and kidney,	Occurs in the other types of organisms.

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THE FATE OF CARBON-SKELETONS OF AMINO ACIDS

a) Simple degradation:

(amino acid → Common metabolic intermediate)

Alanine → Pyruvate

Glutamate → α-ketoglutarate

Aspartate → Oxaloacetate

b) Complex degradation:

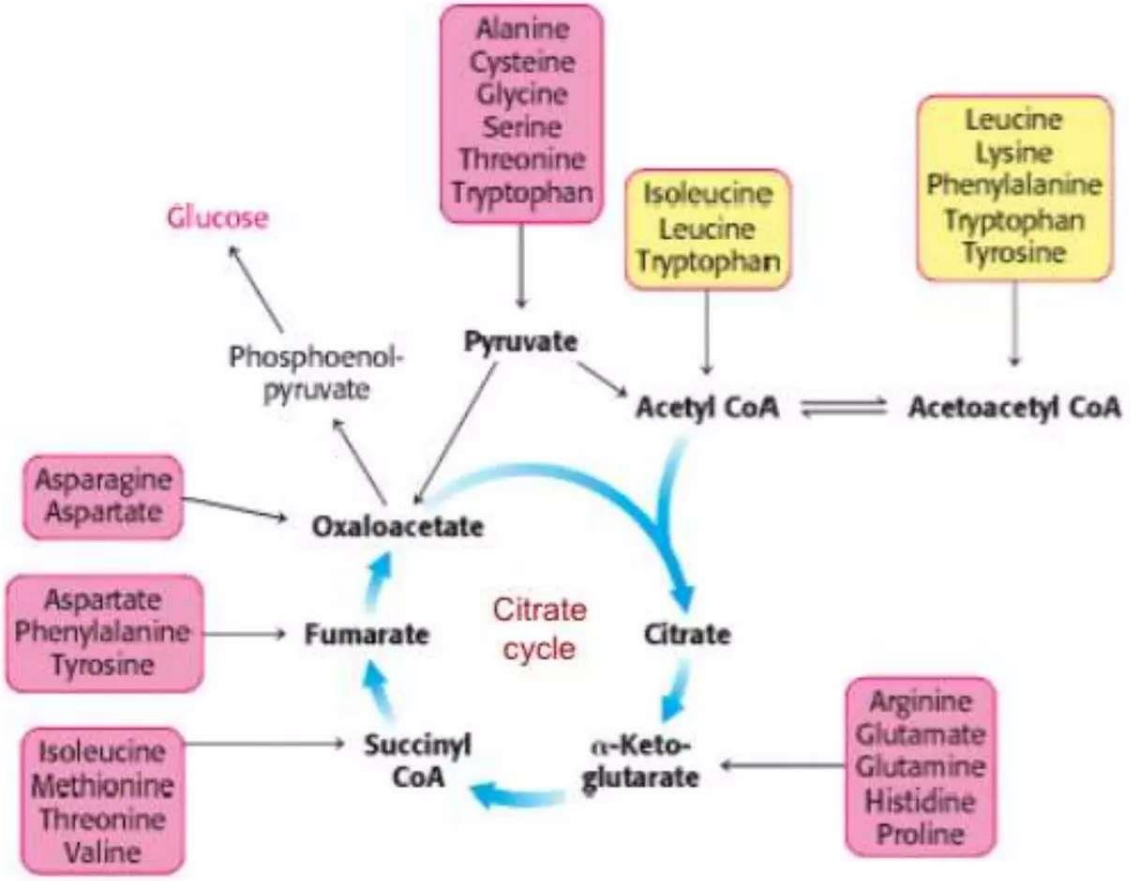
(amino acid--- Keto acid----- **complex** pathway---- Common metabolic intermediate)

Amino acids whose ketoacids are metabolized via **more complex** pathway **e.g. Tyrosine, Lysine, Tryptophan**

c) Conversion of one amino acid into another amino acid before degradation:

Phenylalanine is converted to **tyrosine** prior to its further degradation.

The common metabolic intermediates that arised from the degradations of amino acids are: acetyl CoA, pyruvate, one of the krebs cycle intermediates (α-ketoglutarate, succinyl CoA, fumarate& oxaloacetate)



Fates of the Carbon Skeletons of Amino Acids. Glucogenic amino acids are shaded red, and ketogenic amino acids are shaded yellow. Most amino acids are both glucogenic and ketogenic.

Metabolism of the Common Intermediates

1. ***Oxidation:*** all amino acids can be oxidized in **TCA** cycle with **energy** production
2. ***Fatty acids synthesis:*** some amino acids provide **acetyl CoA** e.g. leucine and lysine (ketogenic amino acids).
3. ***Gluconeogenesis:*** ketoacids derived from amino acids are used for synthesis of **glucose** (is important in starvation).

Glucogenic	***Ketogenic***	***Glucogenic&Ketogenic***
Ala, Ser, Gly, Cys, Arg, His, Pro, Glu, Gln, Val, Met, Asp, Asn.	Leu , Lys	Phe,Tyr,Trp,Ile,Thr

METABOLISM OF AMMONIA

Ammonia is formed in body from:

a) From amino acids: 1.Transdeamination in liver (NOT T.A.)

2.amino acid oxidases and amino acid deaminases in liver and kidney.

b) Deamination of physiological amines: by monoamine oxidase.

c) Deamination of purine nucleotides: especially adenine nucleotides

d) Pyrimidine catabolism.

e) From bacterial action in the intestine **on dietary protein & on urea in the gut.**

NH3 is also produced by glutaminase on glutamine .

Decarboxylation of amino acids

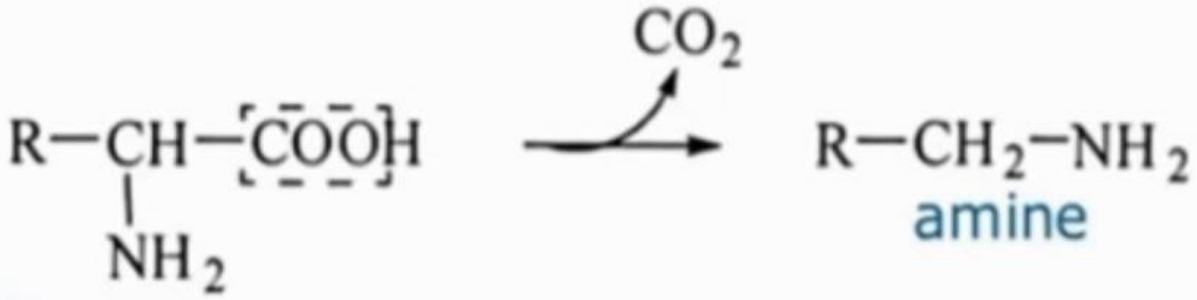
Decarboxylation of amino acids is a process that breaks the bond between the carboxylic group (-COOH) and the rest of the amino acid. This process results in the formation of an amine and carbon dioxide (CO_2):

Process	Result
Decarboxylation	Removal of the carboxyl group (-COOH) from the amino acid, resulting in an amine and CO_2

The decarboxylation process is catalyzed by enzymes called decarboxylases, which require pyridoxal phosphate (B6-PO4) as a coenzyme.

Decarboxylation of amino acids

Decarboxylation – removal of *carbon dioxide* from amino acid with formation of *amines*.



Usually amines have high physiological activity (hormones, neurotransmitters etc).

Amino acids	Amine	Biologic importance
Tyrosine	Tyramine	• Increases blood pressure (Vasoconstriction) • Contracts uterus
Tryptophan	Tryptamine 5-methoxy Tryptamine (Melatonin)	• Tissue hormone: a derivative of 5-OH Tryptamine (Serotonin) • Vasoconstriction • Increases blood pressure • Hormone of pineal gland
Histidine	Histamine	• Vasodilator, decreases blood pressure • HCl↑ • Pepsin ↑
Serine	Ethanolamine	• Forms choline by three methylations • Constituent of phospholipids like cephalin
Threonine	Propanolamine	• Constituent of vitamin B_{12}
Cysteine	β-mercaptoethanolamine	• Constituent of coenzyme A
Aspartic acid	β-alanine	• Constituent of pantothenic acid (coenzyme A) • As a constituent of dipeptide carnosine and anserine (they activate myocin, the muscle protein, ATP-ase activity and also enhance copper uptake)
Glutamic acid	γ-amino butyric acid (GABA)	• Presynaptic inhibitory neuro-transmitter in brain • Forms a bypass in citric acid cycle (GABA-shunt)
3,4,di-OH-phenylalanine (DOPA)	Dopamine	• Precursor of the hormones epinephrine and norepinephrine
Cysteine	Taurine	• Constituent of bile acid, taurocholic acid