The biochemical processes that form part of the amino acid metabolism all support the synthesis and breakdown of amino acids. In the following article, the three most important reactions of the metabolism, i.e. transamination, deamination and decarboxylation, are explained in a compact overview, providing you with the perfect preparation for your upcoming exams.

Definition of Amino Acids

Amino acids are a part of the building blocks that make up proteins. Amino acids form polymers with peptide bonds. These polymers are better known as proteins and represent, next to carbohydrates and fats, a main food and body component. Since amino acids, as suggested by their name, include a nitrogenous amino group in their base frame (NH2, NH, N), proteins are an important nitrogen donor. Nitrogen is essential for many
compounds and functions. This is why proteins, although they are an important food component, are only partially interesting for the energy supply (even though they still provide a significant part of the total energy amount); rather, the organism needs them as an amino acid supplier. With the amino acids supplied by proteins and those already present in the organism, new proteins can be built.

**Proteins**

**Functions of Proteins**

Proteins serve as:

- **Building material**: e.g., keratin in finger and toe nails, tissue, muscles, bones, skin hair.
- **Transport vehicles**: e.g., albumin in the blood circulation, they give cells their shape.
- **Signaling substances**: e.g., the G protein in signal transduction.
- **Instruments**: e.g., enzymes for synthesis and breakdown of structures.

Proteins are so elementary that their construction manual is codified in the DNA of our genetic makeup. It is only with their help that an organism can be built in a functioning and operative manner because the necessary tools and builders are always proteins. They make up at least 20% of the human body. Amino acids are so important that they must not be squandered. Therefore, the constant breakdown and rebuilding processes of the body require an ingenious recycling system: the amino acid metabolism.

**Synthesis of Proteinogenic Amino Acids**

At least 1,000 different proteins exist, but for the human organism, mainly proteinogenic amino acids are of importance. **Proteinogenic amino acids**, comprising 20 to 21 amino acids, form the basic modules of proteins. Sometimes, also the semi-essential amino acid selenocysteine is counted as a proteinogenic amino acid which makes for the number 21. The following table highlights the 20 proteinogenic amino acid with a major characteristic included:

<table>
<thead>
<tr>
<th>Protein</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysine</td>
<td>Positively charged</td>
</tr>
<tr>
<td>Arginine</td>
<td>Positively charged</td>
</tr>
<tr>
<td>Aspartate</td>
<td>Negatively charged</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Negatively charged</td>
</tr>
<tr>
<td>Amino Acid</td>
<td>Property</td>
</tr>
<tr>
<td>------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Serine</td>
<td>polar</td>
</tr>
<tr>
<td>Threonine</td>
<td>polar</td>
</tr>
<tr>
<td>Asparagine</td>
<td>polar</td>
</tr>
<tr>
<td>Glutamate</td>
<td>polar</td>
</tr>
<tr>
<td>Histidine</td>
<td>polar</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>polar</td>
</tr>
<tr>
<td>Alanine</td>
<td>hydrophobic</td>
</tr>
<tr>
<td>Valine</td>
<td>hydrophobic</td>
</tr>
<tr>
<td>Leucine</td>
<td>hydrophobic</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>hydrophobic</td>
</tr>
<tr>
<td>Proline</td>
<td>hydrophobic</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>hydrophobic</td>
</tr>
<tr>
<td>Tryptophane</td>
<td>hydrophobic</td>
</tr>
<tr>
<td>Cysteine</td>
<td>hydrophobic</td>
</tr>
<tr>
<td>Methionine</td>
<td>hydrophobic</td>
</tr>
<tr>
<td>Glycine</td>
<td>Does not have a side chain</td>
</tr>
</tbody>
</table>

Similar to the alphabet, where different combinations of letters form new words, those 21 amino acids can form many different proteins, which perform many different tasks. Amino acids find their way into the organism packed as proteins in, e.g., soy, milk or meat.

**Transport Proteins**

Through the mechanisms of digestion, the amino acids are cleaved and enter the blood circulation on specific transporters. Next, they are channeled into body cells, again with the help of transport proteins. Specific transport proteins facilitate diffusion or actively transport specific substances in the body through membranes. Transport proteins can be channel/pore that makes holes in membranes or carriers that open one side of the membrane. The metabolism of amino acids arriving postprandially occurs mainly in the liver and kidneys. Also, the regular breakdown of physiological structures (for example, muscle protein) constantly provides a supply of free amino acids so that a permanent pool of free amino acids is always present. For an amino acid in the amino acid pool, there are three travelling possibilities:
1. Integration into structural and tissue proteins for regeneration of tissue structures
2. Catabolism: deamination (removal of the amino group) and oxidation of the carbon frame releasing CO2 and ATP, or conversion into energy storages such as glycogen or lipids, and urea synthesis from the amino group
3. Anabolism: Synthesis of nitrogenous compounds such as purine bases, creatin, or adrenalin.

The **three most important reactions in the amino acid metabolism** are the **transamination**, **deamination** and **decarboxylation**. Depending on the current state of metabolism, the existing amino acids are either regrouped or broken down entirely.

**Transamination of Amino Acids**

One of the central reactions of the amino acid metabolism is transamination. As the name suggests, transamination refers to a **transfer of the amino group**. The process of transamination occurs through aminotransferase enzymes which can be specific for an amino acid or can cater to several amino acids that are similar in their chemical compositions. An amino acid that is currently not needed can be transformed into another amino acid that is currently needed. The reallocation of the amino group occurs via an alpha-keto acid, which basically has an analogous structure to **alpha-amino acids**. Alpha-keto acids only differ from alpha-amino acids in having a keto group, instead of an amino group.

![Image: "Aminotransfer Reaction Between an Amino Acid and an Alpha-Keto Acid." by Alcibiades. License: public domain]
Transamination turns the alpha-keto acid into a new amino acid available for metabolism. The responsible enzyme is called aminotransferase (or transaminase). The aminotransferase, however, needs an assistant to do its work: the pyridoxal phosphate (PLP). This is a coenzyme produced out of vitamin B6 (pyridoxine) by phosphorylation. PLP has an aldehyde group (H-C=O) that reacts in the transamination with the amino group of the amino acid (with elimination of H2O). With this, a Schiff base (R-NH2) is formed. This reaction destabilizes the amino acid and the hydrogen atom starts to migrate which, in turn, leads to a shift of the double bond and a ketamine (R-C=O) emerges from the former aldimin (H-C=O).

Then, water is added across this double bond which concludes the formation of the alpha-keto acid. PLP is reduced to PMP (pyridoxamine phosphate). The reverse reaction is also a common variation for generating another amino acid: pyridoxamine phosphate reacts with another alpha-keto acid and PLP is reconstituted.

The two most important transaminases are alanine transaminase (abbreviated as ALT or ALAT) and aspartate transaminase (abbreviated as AST or ASAT). ALAT catalyzes the transfer of an amino group from alanine to alpha-ketoglutarate, forming pyruvate and glutamate (which makes for its former name glutamate-pyruvate-transaminase, GPT). The ASAT transfers the amino group from aspartate to alpha-ketoglutarate, forming oxaloacetate and glutamate. Both transaminases are important diagnostic markers: increased values in a full blood count indicate a decay of cells in the liver (ALAT) and heart (ASAT and ALAT).

**Pyridoxal Phosphate**

The pyridoxal phosphate, or short PLP, is the most important coenzyme in the amino acid metabolism. PLP is the biological active form of pyridoxal, the aldehyde form of vitamin B6. Vitamin B6 also appears as amine (pyridoxamine) and alcohol (pyridoxine). The derivatives of vitamin B6 can be converted into each other. They are ingested and can be found in animal-based food (pyridoxal and pyridoxine), as well as in vegetable-based food (pyridoxine).
Relatively rich in vitamin B6 are wheat germs. PLP as a coenzyme is involved in the amino acid metabolism in the reactions of transamination, decarboxylation (for example, the formation of biogenous amines) and deamination. PLP links to a lysine residue of the according enzyme of the reaction, e.g., the alanine transaminase (ALT), and creates a Schiff base with the amino acid. The nitrogen of PLP contained in the pyrimidine ring, has a strong electrophilic effect which leads to the shifting of the bonds. This reaction forms toxic ammonia whose concentration requires being minimal at all time and it is unsuitable to dispose nitrogen thus urea cycle occurs. Leads to deamination of amino acids.

Deamination of Amino Acids

When an over-supply of nitrogen in the form of amino acids exists, it needs to be disposed of somewhere in the body. **Deamination** is the process that carries out this breakdown of amino acids. However, this process releases free cytotoxic ammoniac which has to be quickly metabolized to urea. This urea synthesis, which requires a lot of energy, takes place in the liver. For this to happen, the excess nitrogen needs to be transported from the periphery to the liver. Three central amino acids are involved in this transport: alanine (synthesized from pyruvate), glutamine (synthesized from aspartate) and aspartate (synthesized from oxaloacetate).

Deamination can be divided into three different reactions:

- Oxidative deamination
- Hydrolytic deamination
- Eliminative deamination

**Oxidative Deamination**

As in transamination, a Schiff base is formed with a dehydrogenase; more specifically, oxidation turns the amino group into an **imino group** (C=N). Electron acceptors are the
coenzymes NAD⁺ or NADP⁺ that are reduced in this process to NADH/H or NADPH/H respectively. By adding water, the imino group is converted into an alpha-keto group which releases ammoniac (NH₃).

**Example:** Glutamate dehydrogenase reaction with glutamate dehydrogenase: Glutamate - imino acid - alpha-ketoglutarate. In the liver, glutamate from the cytosol is taken into the mitochondrion, where oxidative deamination occurs, under the influence of enzyme **L-glutamatedehydrogenase**, located in the mitochondrial matrix.

**Hydrolytic Deamination**

In hydrolytic deamination, water reacts with the amino group. Thereby, a **hydroxyl group (OH-group)** is irreversibly attached and the amino group is eliminated in the form of ammoniac. In the glutaminase reaction from glutamine to glutamate, the responsible enzyme is glutaminase. The same reaction occurs from asparaginic amino acid to aspartate (the responsible enzyme is coincidently called asparaginase).

**Eliminative Deamination**

Small amino acids, such as serine or cysteine, can also be released through eliminative desamination of their nitrogen (in form of ammoniac) and by elimination of water, or hydrogen sulfide for sulfurous amino acids. For this reaction, once again PLP is necessary as a partner. This **hydratation** creates a double bond and, after the following **hydrolysis**, another alpha-keto acid.

**Decarboxylation of Amino Acids**

When a carboxyl group is cleaved from an amino acid, one amine and CO₂ are released as side products. The reaction is catalyzed by the enzyme **decarboxylase** using PLP as a partner. The resulting amines fulfill important functions in the body which is why they are called **biogenous amines**.

A well-known representative is **histamine** which is formed through decarboxylation from the basic amino acid histidine. The responsible enzyme is accordingly called histidine decarboxylase. Histamine is an important mediator and plays a vital role in, e.g., immediate hypersensitivity reactions. Further well-known biogenous amines relevant for metabolism are, for example, **GABA** (gamma-aminobutyric acid from glutamine acid) and **dopamine** (from 3,4-dihydroxyphenylalanine).

**Central Amino Acids**

There are four amino acids and their keto acids that can be described as the central hub of the amino acid metabolism, because they are of special significance and the most important metabolic pathways take place via these amino acids:

- Glutamate and alpha-ketoglutarate
- Glutamine and alpha-ketoglutarate
- Alanine and pyruvate
- Aspartate and oxaloacetate
Glutamine, Glutamate and Alpha-Ketoglutarate

Glutamine is the amino acid that is found most often in the blood plasma. Glutamine transports nitrogen to all the cells of the body that need it for, e.g., synthesis of purine and pyrimidine in the nucleotide biosynthesis. Glutamine is also needed as an amino acid donor: It is deaminated in the kidneys in order to gain free ammoniac.

The ammoniac is secreted in the proximal tubule and neutralizes acids in the urine, thereby forming ammonium ions (NH$_4^+$). In this process, alpha-ketoglutarate, which can be directly channeled into the citric acid cycle, is formed from glutamine via glutamate. This is killing two birds with one stone, as alpha-ketoglutarate refills the citric acid cycle when oxaloacetate has been pulled out of it for gluconeogenesis.

Alanine and Pyruvate

The amino acid alanine is the counterpart to the alpha-keto acid pyruvate, that is, to its salt (pyruvic acid, alpha-ketopropion acid). Via pyruvate and alanine, amino acids can be channeled into the citric acid cycle and decomposed into CO$_2$ and energy. Another possibility is the synthesis of glucose from pyruvate in gluconeogenesis, or metabolism of pyruvate to lactate under anaerobic conditions.

Alanine - Pyruvate

1) CO$_2$ + ATP
2) Glucose
3) Lactate

When alanine is broken down in the muscle, it first travels through the bloodstream to the liver. There, the synthesis of glucose in gluconeogenesis occurs, based on pyruvate obtained from transamination. The glucose travels through the bloodstream to the muscles and provides energy supply in the muscle cell through the breaking down of glucose in glycolysis.

This again yields pyruvate. Via the transamination reaction, pyruvate receives the amino
group of an amino acid from the breakdown of muscle protein. The alanine arrives in the liver where it is transaminated to pyruvate again, and is now available for glucose synthesis in gluconeogenesis. The enzyme that is responsible for the back and forth transfers of amino groups is called alanine aminotransferase (ALT, ALAT).

Aspartate and Oxaloacetate

A further important reactional pair is the amino acids aspartate and oxaloacetate (alpha-keto pyruvic acid). Their transformation is catalyzed by the enzyme aspartate aminotransferase (AST, ASAT) whose concentration can also be determined as diagnostic marker in the blood count. The ASAT catalyzes the transfer of the amino group from aspartate to alpha-ketoglutarate, forming oxaloacetate and glutamate. This is why this enzyme was formerly known under the name glutamate oxaloacetate transaminase (GOT).

Image: “Pathophysiology of Metabolic Disorders of Phenylalanine and Tyrosine” by LHcheM. License: CC BY-SA 3.0

An increase of ASAT in the blood can indicate diseases of liver and heart because this enzyme is present in large numbers in hepatocytes and heart muscle cells. So, when these cells are destroyed due to pathological changes, the ASAT presence in the blood increases. Oxaloacetate can participate in the citric acid cycle or in gluconeogenesis. Glutamate can be further transformed to alpha-ketoglutarate or, for instance, be used in oxidative deamination for ammoniac synthesis in the kidneys.

Serine Family

Two main paths lead to serine

1. From 3-phosphoglycerate (connection to glycolysis)
2. Exchanging carbon with glycine and folates (important for folate recycling)

Cysteine metabolism

<table>
<thead>
<tr>
<th>Cysteine metabolism</th>
<th>Multiple ways of making cysteine</th>
<th>Primary means tied to methionine catabolism</th>
</tr>
</thead>
</table>

Methionine catabolism
Cysteine metabolism & health

Homocystinuria is a genetic disease. It most commonly involves mutation of cystathionine β-synthase. Problems can include:

- Musculoskeletal anomalies
- Eye anomalies: cataracts, glaucoma, retinal detachment
- Intellectual disabilities
- Seizures
- Vascular disease
- Cystinuria — unrelated genetic disease
- Inability of kidneys to reabsorb cysteine leads to high levels of cysteine, ornithine, and arginine in urine
- Frequent kidney stones also occur

Other cysteine metabolisms
Selenocysteine metabolism

- Sometimes called 21st amino acid
- Not specified directly in genetic code
- Uses stop codon with unusual structure
- Synthesized from serine on tRNA

Aspartate Family

- All family members arise from aspartate
- Aspartate can be made from one of them — asparagine
- Numerous paths lead to aspartate

Asparagine metabolism

**Synthesis**

Aspartate + glutamate + ATP

Asparagine + α-ketoglutarate + AMP + PP

**Breakdown**

Asparagine + H₂O

Asparagine + NH₄⁺

Energetically costly, essentially not reversible
Methionine metabolism

- Breakdown overlaps with cysteine metabolism
- Complicated synthesis from aspartate

Steps to the process

1. Phosphorylation
2. Oxidation and dephosphorylation
3. Oxidation
4. Creates homoserine
5. Succinylation
6. Cysteine replacement of succinate
7. Loss of pyruvate & ammonium ion
8. This creates homocysteine
9. Methylation of homocysteine by a N5-methylfolate creates methionine (required vitamin B₁₂)

Homocysteine can be converted to methionine by the alternate path on the right.

- Methionine modified in bacteria for use in translation
- Occurs after methionine on initiator tRNA

Threonine Metabolism

First three steps are the same as methionine metabolism, creating homoserine

Lysine metabolism

- First two reactions same as threonine and methionine
- Nine steps total
- Lysine is one of most post-translationally modified amino acids, especially in histones
- Hydroxylation of lysine is important for making strong collagen
- Deficiency of one of the enzymes in the lysine degradation pathway, α-aminoadipic semialdehyde synthase, leads to hyperlysinemia — accumulation of lysine in the blood

Aromatic Family

![Aromatic Family Diagram]

- Tryptophan, phenylalanine, and tyrosine
- Each derived from phosphoenol-pyruvate and erythrose-4-phosphate
- Synthesis pathways complex
- Each involves shikimic acid and chorismic acid
- Phenylalanine and tyrosine pathways overlap
- Hormones and neurotransmitters are made from each

Tryptophan

- Interesting regulation of synthesis in bacteria
- Attenuation — all 5 genes on one operon
- When tryptophan high, transcription of operon aborts early
- When tryptophan low, transcription of operon continues through all genes

Molecules made from tryptophan

<table>
<thead>
<tr>
<th>Melatonin</th>
<th>Niacin</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Melatonin" /></td>
<td><img src="image" alt="Niacin" /></td>
</tr>
<tr>
<td>• Circadian rhythm sensing&lt;br&gt;• Affects mood, sleep, blood pressure&lt;br&gt;• Production affected by blue light</td>
<td>• Vitamin B₃&lt;br&gt;• Nicotinamind derived from it — part of NAD⁺/NADH &amp; NADP⁺/NADPH&lt;br&gt;• Deficiency leads to pellagra</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serotonin</th>
<th>Auxins</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Seroetonin" /></td>
<td><img src="image" alt="Auxins" /></td>
</tr>
</tbody>
</table>
Phenylalanine (PHE)

- An essential amino acid and precursor of tyrosine
- PHÉ hydroxylase catalyzes formation of tyrosine from PHE
- Deficiency of the enzyme PHE hydroxylase causes phenylketonuria
- High PHE levels cause damage to brain
- Treatable by reducing PHE levels
- Nutrasweet contains PHE

Tyrosine (TYR)

- Not essential if PHE present
- Precursor of catecholamines — L-dopa, L-dopamine, norepinephrine, and epinephrine
- Donates electrons to reduce chlorophyll in photosystem II
- Forms radical in ribonucleotide reductase

Tyrosine metabolism

<table>
<thead>
<tr>
<th>L-DOPA</th>
<th>Norepinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="L-DOPA structure" /></td>
<td><img src="image" alt="Norepinephrine structure" /></td>
</tr>
<tr>
<td>• Precursor to dopamine</td>
<td></td>
</tr>
<tr>
<td>• Crosses blood-brain barrier</td>
<td></td>
</tr>
<tr>
<td>• used to treat Parkinson’s disease</td>
<td></td>
</tr>
<tr>
<td>• Hormone and neurotransmitter</td>
<td></td>
</tr>
<tr>
<td>• Works through noradrenergic receptors</td>
<td></td>
</tr>
<tr>
<td>• Fight or flight response</td>
<td></td>
</tr>
<tr>
<td>• Increases heart rate and blood pressure</td>
<td></td>
</tr>
</tbody>
</table>

Dopamine | Epinephrine (adrenalin)
Tyrosine is a precursor of thyroid hormones:  

Tyrosine metabolism & disease

**Tyrosinemia — problems with tyrosine catabolism**
- Type I
- Type II
- Type III
- Alcaptonuria — black urine disease

**Treatments**
- Restricted TYR/PHE diet
- Liver transplant

**Pyruvate Family**

**Alanine metabolism**
- Most easily produced from pyruvate — transamination
- Byproduct of catabolism of valine, leucine, and isoleucine
- Glucose-alanine cycle

**Leucine (LEU)/ Valine (VAL)/ Isoleucine (ILE) metabolism**
- Branched-chain amino acids (BCAAs)
- Several common steps
- Start with decarboxylation and attachment of two carbon piece to TPP
- Valine and leucine pathways involve attachment of two carbon piece to pyruvate
- Isoleucine pathway involves attaching two carbon piece to α-ketoisobutyrate
- Penultimate products — α-ketoisocaproate (LEU), α-ketoisovalerate (VAL), and α-keto-β-methyl valerate (ILE) each is transaminated to make final amino acid
Breakdown of BCAAs occurs through the branched-chain α-keto acid dehydrogenase complex
- Mutations altering this complex can result in maple syrup urine disease

Histidine (HIS) metabolism
- Most complex of all the amino acids
- Overlaps nucleotide metabolism with ribose-5-phosphate & PRPP
- 10 steps in pathway
- Second enzyme of pathway (ATP-phosphoribosyltransferase) feedback inhibited by histidine

Disorders of the Amino Acid Metabolism

A relatively common genetic metabolic disorder is phenylketonuria, PKU (approx. 1 in 10,000 newborns is affected). Every newborn is tested for PKU (e.g., with the Guthrie test) because most effects of the disease can be avoided by keeping a strict diet.

Due to a defect of the enzyme phenylalanine hydroxylase, the amino acid phenylalanine accumulates in the tissue. Instead, the body turns phenylalanine into the keto acid phenylpyruvate. This product is partly exuded – which explains the name phenylketonuria – but partly metabolized further, building cytotoxic substrates. They cause damage, especially in the myelin sheaths of the CNS. This impairs normal development of the brain. It mainly facilitated by excess quantities of phenylalanine compared to concentration of other amino acids being transported across the blood-brain barrier, resulting in a deficit of required metabolites. The consequence of this disease is mental retardation. The newborn screening aims to identify affected persons, and give them a specific diet that is low phenylalanine and rich in tyrosine (tyrosine becoming the essential amino acid for the affected person). This way, damages can be prevented, or at least kept at bay.

Another genetically linked disease of phenylalanine catabolism is alkaptonuria, caused by the defective enzyme known as homogentisatedioxygenase. It is less fatal than PKU, this condition has less symptoms, although large amounts of homogentisate are excreted through urine and laboratory tests confirms its presence when the urine sample turns
black after oxidation. Alkaptonuria patients are also prone to develop a form of arthritis.

Review Questions

Solutions can be found below the references.

1. Which statement about aminotransferases is not correct?

A. Aminotransferases transfer amino groups between amino acids and alpha-keto acids.
B. During the reaction, the amino group of the amino acid is transferred to pyridoxal phosphate.
C. The aspartate aminotransferase (GOT) uses alpha-ketopropionic acid as alpha-keto acid.
D. The alanine aminotransferase (GPT) uses alpha-ketoglutaric acid as alpha-keto acid.
E. In phenylketonuria, the amino acid phenylalanine is increasingly transaminated to phenylpyruvate.

2. Histamine, a mediator of immediate hypersensitivity reactions, is enzymatically formed from histidine by...

A. ...decarboxylation.
B. ...deamination.
C. ...hydroxylation.
D. ...methylation.
E. ...transamination.

3. Ammoniac is toxic to the human organism, especially for the brain. Therefore, it is important to prevent a high concentration of ammoniac. The direct fixation of molecular ammoniac with a covalent bond onto a substrate molecule can be catalyzed by...

A. ...alanine aminotransferase.
B. ...aspartate aminotransferase.
C. ...glutamate dehydrogenase.
D. ...glutaminase.
E. ...transglutaminase.

References


Correct answers: 1C, 2A, 3C