THE METABOLISM OF AMINO ACIDS

Mirna Gavran[1], Vesna Gantner[1]

Short review

Summary

The building blocks of proteins, amino acids, play a crucial role in both animal and human metabolism and structure. In light of the fact that amino acids are crucial to life, the goal of this review was to analyze their metabolism. It is the liver that has the primary role in the metabolism of amino acids in humans and animals. It is possible to divide amino acids into essential and non-essential ones. Cell membranes in various tissues are the major route through which amino acids travel to the blood, primarily via cotransport systems dependent upon Na^+. In most land animals, the ammonium ion is converted to urea. Excess NH_4^+ is converted into urea. The process by which this takes place is called the urea cycle. During the process, glutamate dehydrogenase generates free $NH4^+$ previously transferred to α-ketoglutarate by transaminases. Fumarate, another product, links the urea cycle to the TCA cycle. The two input nitrogen atoms exit the cycle as urea, which the liver releases into the blood for disposal in the urine via the kidneys. Ammonia could be very toxic to the cells and tissues of all living beings. Therefore, knowing amino acid metabolism is crucial for human and animal nutrition to prevent the prevalence of numerous disorders or diseases.

Key words: *amino acids, metabolism, urea cycle*

Introduction

The building blocks of proteins, amino acids, play a crucial role in both animal and human metabolism and structure (Berg *et al.*, 2013; Li *et al.*, 2021). The amino acids necessary for optimal growth, reproduction, lactation, and maintenance are required by all animals (Kung and Rode, 1996). It is the liver that has the primary role in the metabolism of amino acids in humans and animals. As a result of its production, this organ synthesizes many amino acids (such as glutamate, glutamine, alanine, aspartate, asparagine, glycine, serine, and homoarginine), glucose, and glutathione (a major antioxidant) (Hou *et al.*, 2020). In order to create a common metabolic pool in the body, amino acids from the diet are added to those produced by the breakdown of endogenous proteins. The nitrogen balance refers to the balance between nitrogen intake (represented by the protein content of the diet) and nitrogen excretion through urine and feces. The amino acids found in the human body are used to synthesize proteins and

[1]University of J. J. Strossmayer in Osijek, Faculty of Agrobiotechnical Sciences Osijek, Department for animal production and biotechnology Osijek, Vladimira Preloga 1, 31000 Osijek, Croatia
*Correspondence: mgavran@fazos.hr

other nitrogenous compounds, or they are catabolized for energy. Amine groups are removed by transamination. During this reaction, the α-amino group of an amino acid is transferred to the α-keto group of an amino acid. A transaminase or aminotransferase catalyzes the reaction. Except for lysine and threonine, all amino acids engage in transamination processes with pyruvate, oxaloacetate, or α-ketoglutarate to produce the equivalent alanine, aspartate, glutamate, or α-keto acids. The amine groups of all amino acids converge to glutamate through the transamination of alanine and aspartate with α-ketoglutarate. Glutamate is deaminated to give rise to α-ketoglutarate and ammonia, which are then turned into urea. Another method of removing ammonia is the production of glutamine. The metabolic cycle in the liver produces urea, which is then excreted by the kidneys (Blanco and Blanco, 2017). Ammonia could be very toxic to the cells and tissues of all living beings. Therefore, knowing amino acid metabolism is crucial for human and animal nutrition to prevent the prevalence of numerous disorders or diseases.

Degradation of proteins in the gastrointestinal tract

Proteins that are ingested with food are broken down into amino acids that are absorbed, carried through the bloodstream, and absorbed by the cells of different tissues. Proteins and other molecules containing nitrogen are created using amino acids. The nitrogen in amino acids is transformed into urea and other nitrogen-containing molecules, which are excreted from the body, and the hydrocarbon skeleton of amino acids can also be oxidized to produce energy. The origin of proteins can be exogenous (from food) and endogenous (secretions of digestive tract glands, exfoliated epithelial cells, plasma proteins). Proteolytic enzymes are divided into:

endopeptidases - act in the middle of the polypeptide chain (pepsin, trypsin, and chymotrypsin); exopeptidases - which cleave the terminal amino acids of the peptide chain: carboxypeptidases act on the COOH end, while aminopeptidases act on the NH_2 end) (UCG, 2018).

Table 1. A list of essential and non-essential amino acids (Berg *et al*., 2013)

Essential	**Non-essential**
Histidine	Alanine
Isoleucine	Arginine
Leucine	Asparagine
Lysine	Aspartic acid
Methionine	Cysteine

Phenylalanine	Glutamic acid
Threonine	Glutamine
Tryptophan	Glycine
Valine	Proline
	Serine
	Tyrosine

Animals experience an oxidative breakdown of amino acids under three different metabolic conditions: 1. During the normal synthesis and breakdown of cellular proteins, some amino acids that are released from protein breakdown and are not required for new protein synthesis undergo oxidative degradation; 2. When a diet rich in protein exceeds the body's requirements for protein synthesis, the excess is catabolized; amino acids cannot be stored; 3. Throughout hunger or in unchecked diabetes mellitus, when carbohydrates are either inaccessible or insufficient, amino acids are catabolized (PMF, 2014, Mlinac Jerković, 2021). Proteins and nucleic acids, which include nitrogen, have a very different metabolism from carbohydrates and lipids. There is no nitrogen-storing molecule, whereas the latter molecules can be kept and mobilized as required for biosynthetic activities or energy production (one exception to this rule is storage protein in seeds). The organic nitrogen lost during catabolism must be replaced by an organism's steady supply of usable nitrogen. For example, to replace the nitrogen excreted as urea, uric acid, and other nitrogenous waste products, animals need a consistent supply of amino acids in their diets. Excess dietary amino acids are transformed into common metabolic intermediates including pyruvate, oxaloacetate, acetyl-CoA, and α -keto-glutarate since they are neither stored for later use nor excreted. As a result, amino acids are metabolic fuels since they are precursors to glucose, fatty acids, and ketone bodies (Mlinac Jerković, 2021). Through cell membranes in different organs, amino acids are delivered to the blood, predominantly by Na^+ dependent cotransport mechanisms. Therefore, amino acid transport is not the same as glucose transport. Amino acids from the blood can be concentrated in these tissues thanks to this method of amino acid transport in the liver, muscles, and other tissues. These transport proteins may differ in their genetic background, amino acid content, and substrate selectivity between various tissues. Multiple transport proteins can transport most amino acids (UCG, 2018).

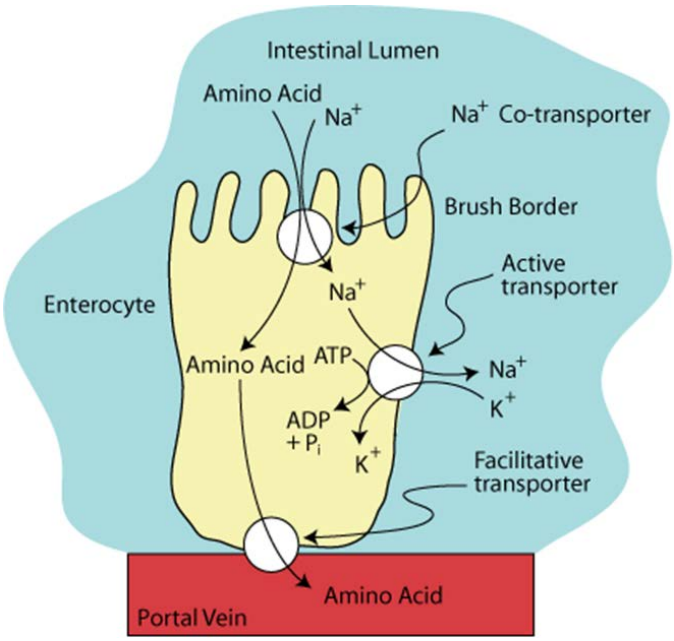

Figure 1. Absorption of amino acids and transport systems for amino acids (NYUSM, 2022)

As seen in Figure 1, a collection of transporters on the apical surface of enterocytes link the transport of amino acids and Na^+ ions, allowing amino acids to be absorbed from the intestinal lumen. Distinct classes of amino acids are transported through the enterocyte plasma membrane by at least seven different protein carriers. Low intracellular Na^+ concentration stimulates the cotransport of Na^+ from the outside of the apical membrane to the interior of the cell. Sodium-potassium ATPase on the basolateral membrane, which actively transports Na^+ out of the cell in exchange for K^+, maintains the low intracellular concentration of Na^+. Cells can concentrate amino acids from the intestinal lumen because of this transport, which keeps a Na^+ gradient in place. A cotransporter located on the basal-lateral surface of the enterocyte allows amino acids to exit the cell and travel to the blood. Na+-dependent cotransporters and, to a lesser extent, facilitative transporters are the principal mechanisms by which amino acids enter cells from the blood. The liver, muscle, and other tissues have Na+-dependent transport systems that enable these cells to concentrate amino acids from the blood. These transport proteins are different from those specified by the genes encoding the amino acid transporters of the luminal membrane of the intestinal epithelium in that they are encoded by different genes and have different specificities. Additionally, they vary slightly amongst tissues (e.g., the transport system for glutamine uptake is present in the liver or is not present in other tissues, or is present as an isoform with different properties) (NYUSM, 2022).

Amino acid nitrogen

Following a protein-rich meal, the liver receives the amino acids that are produced during digestion from the gut via the hepatic portal vein. In a typical diet, the liver and other tissues use the majority of the amino acids for protein synthesis. Excess amino acid carbon skeletons can be converted to fatty acids, oxidized for energy, or in specific physiological circumstances, glucose. Muscle protein is divided into amino acids while fasting, some of which are partially oxidized to provide energy. Alanine and glutamine are produced in part from these amino acids and are delivered into the bloodstream together with other amino acids. Several tissues, such as the kidneys and intestines, oxidize glutamine by converting some of the carbon and nitrogen into alanine. Alanine and other amino acids are transported to the liver, where nitrogen is changed into urea, which is then eliminated by the kidneys, and carbon is changed into glucose and ketone bodies. In order to remove nitrogen and interconvert amino acids so that carbon skeletons may be utilized, a number of enzymes are necessary. These comprise deaminases, transaminases, and glutamate dehydrogenases. Transaminases and glutamate dehydrogenase can provide amino groups for the synthesis of non-essential amino acids since the events they catalyze are reversible. The principal method for removing nitrogen from amino acids is called transamination. A transaminase transfers an amino group from one amino acid, which is transformed into its related α-keto acid, to another α-keto acid, which is then converted to its related α-amino acid (aminotransferase). Thus, nitrogen from one amino acid is present in another. The oxidative deamination of glutamate is catalyzed by glutamate dehydrogenase; as a result, $NH4^+$ is released, α-ketoglutarate is produced, and NAD^+ or $NADP^+$ is required. Some amino acids that have transaminases have their nitrogen released more frequently as $NH4^+$. Nitrogen is provided for urea synthesis through the urea cycle for the removal of nitrogen from the body in the urine. The ammonium ion is primarily produced directly from glutamate by glutamate dehydrogenase, and aspartate can be produced by the transamination of oxaloacetate with glutamate as an amino group donor (NYUSM, 2022). Deamination, which causes a -NH2 to be released as ammonia: Asparagine and glutamine are liberated by hydrolysis during hydrolytic deamination, while histidine and serine are degraded through elimination deamination. All three types of deamination are mediated by glutamate dehydrogenase (GDH). The mammalian liver's glutamate dehydrogenase has the rare ability to employ either NAD^+ or $NADP^+$ as a cofactor (Mlinac Jerković, 2021).

Urea cycle and ammonia detoxification

In most land animals, the ammonium ion is converted to urea. Excess NH_4^+ is converted into urea. The process by which this takes place is called the urea cycle. Organisms that remove excess NH_4^+ in the form of urea are called urothelial organisms. The urea cycle takes place in the liver (PMF, 2014). Ammonia must be expelled or detoxified since it is harmful to the central nervous system and is produced when amino acids break down.

While birds excrete ammonia as uric acid, most mammals detoxify ammonia and excrete it as urea in the urine (a white substance in excrement). The urea cycle involves two tissues in the detoxification of ammonia to produce urea. Throughout the urea cycle, ammonia in urea is detoxified. Ornithine and citrulline are two non-protein amino acids (amino acids not needed for protein synthesis) involved in the urea cycle. The liver's mitochondria condense ammonium ions with bicarbonate ions to produce carbamoyl phosphate, which is the first step in the urea cycle (Cherian, 2019). The daily intake of nitrogen, which comes primarily from protein from food, is equivalent to the daily output of nitrogen. Urea, which is formed in the liver and eliminated in the urine, is the major byproduct of nitrogen excretion. Since ammonia is toxic, especially to neural tissue, it must be transported to the liver in a nontoxic form so that it can be converted to urea, a nontoxic compound that is excreted by the kidneys. Ammonia is produced from the α-amino group of amino acids and other nitrogen-containing compounds in extrahepatic tissues. The two main amino acid transporters of nitrogen in the blood are alanine and glutamine. Transamination of pyruvate results in the metabolic process that yields alanine. In an ATP-dependent mechanism facilitated by glutamine synthetase, glutamate is converted to glutamine by adding an amide to the carboxyl group. In the liver, a sequence of transamination and deamination reactions convert amino acids into $NH4^+$ and aspartate, the forms of nitrogen that enter the urea cycle. A crucial enzyme in the process is glutamate dehydrogenase, which produces free $NH4^+$ from numerous amino acids that have previously been converted to α-ketoglutarate by transaminases. The concentration of urea cycle enzymes rises as dietary protein intake rises (high protein diet), indicating a controlled reaction to accommodate the increased need for nitrogen removal (NYUSM, 2022). Urea cycle reactions: as aspartate and $NH4^+$, two nitrogen atoms enter the urea cycle. The cycle's initial steps occur in the liver mitochondria, where $NH4^+$ and $HCO3^-$ mix to generate carbamoyl phosphate. Citrulline is created when carbamoyl phosphate combines with ornithine, a substance that is both an input and a product of the cycle. Citrulline then leaves the mitochondria and enters the cytosol, where the cycle's remaining events take place. The urea cycle produces the amino acid arginine as a byproduct intermediate. Another substance called fumarate connects the TCA cycle and urea cycle. The two nitrogen atoms that were added depart the cycle as urea, which the liver excretes into the circulation for kidney-mediated urination.

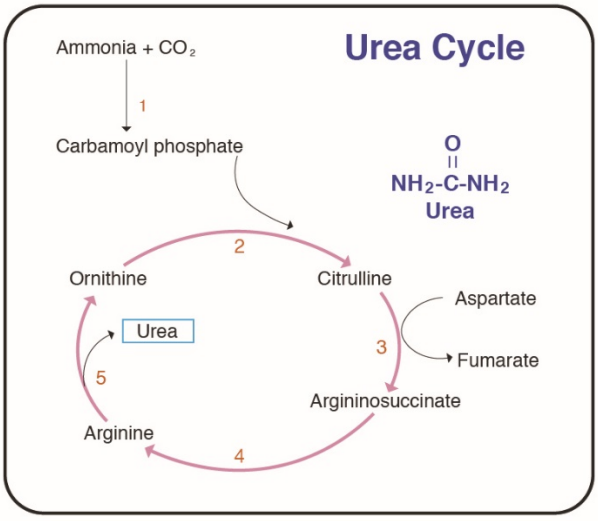

Figure 2. Urea Cycle (Cherian, 2019).

Urea synthesis and ornithine regeneration from arginine by arginase are depicted in Figure 3. About 90% of all bodily nitrogenous excretory products are urea, which enters the blood and is removed by the kidneys.

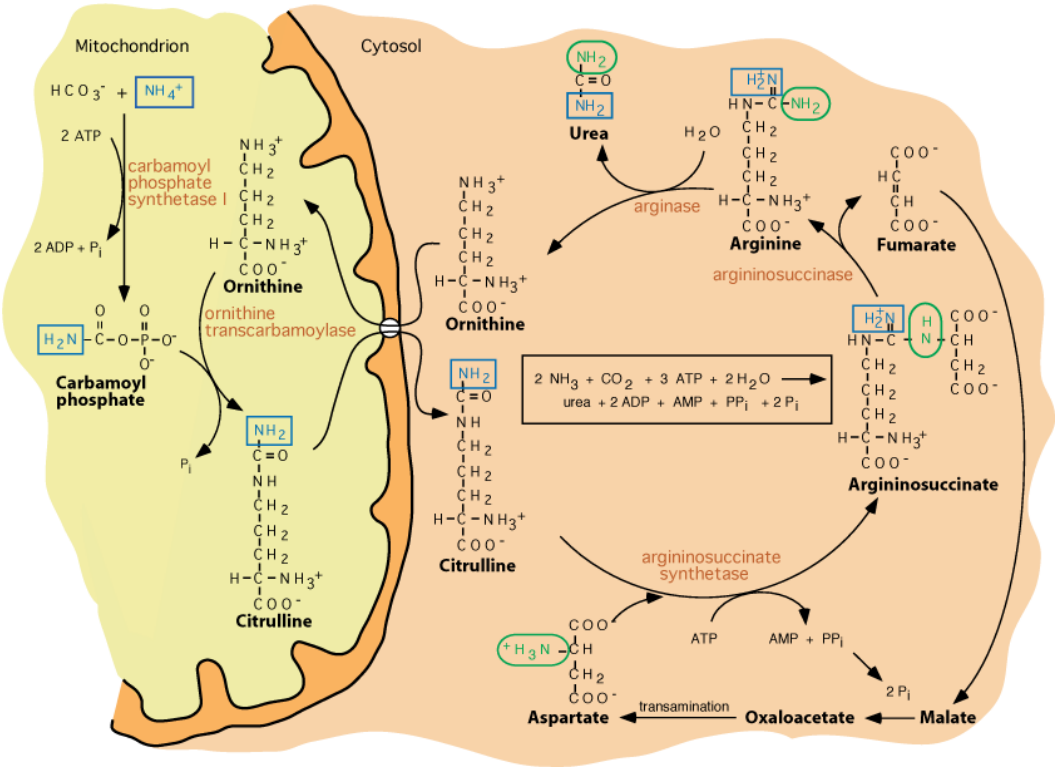

Figure 3. Formation of urea (NYUSM, 2022)

Because of the buildup of ammonia, a neurotoxic, urea cycle deficiencies pose a risk to health. Normally, glutamate dehydrogenase or glutamine synthetase fix free ammonia into either -keto glutarate or glutamine. Many different tissues can employ glutamine to contribute its amide nitrogen for the production of molecules that contain nitrogen. By transamination, the resultant glutamate largely contributes its amino group to pyruvate to create alanine, which transports the nitrogen to the liver. The first enzyme in the urea cycle, carbamoyl phosphate synthetase I, removes nitrogen from its carriers in the liver and fixes it to carbamoyl phosphate.

Conclusions

Since amino acids play a vital role in the existence of all living beings, this review aimed to analyze their metabolism. Based on the analyzed references it could be noticed that the consumed proteins broke down in the stomach and small intestine by proteases. An early step in the catabolism of amino acids is the separation of the amino group from the skeleton of carbon atoms performed by transamination reactions, so the corresponding a-ketoacids are formed from amino acids. In most cases, the amino group is converted to α-ketoglutarate, producing glutamate. The ammonium ion is mostly

produced directly from glutamate. Ammonia could be very toxic to the cells and tissues of all living beings. Therefore, knowing amino acid metabolism is crucial for human and animal nutrition to prevent the prevalence of numerous disorders or diseases.

References

Berg, J.M., Tymoczko, J.L., Stryer, L. (2013). Biokemija. Školska knjiga, Zagreb.

Blanco, A. and Blanco, G. (2017). Medical biochemistry, chapter 16 – Amino Acid Metabolism, 367-399. https://doi.org/10.1016/B978-0-12-803550-4.00016-1.

Cherian, G. (2019). A Guide to the Principles of Animal Nutrition. Oregon State University.

Hou, Y., Hu, S., Li, X., He, W., Wu, G. (2020). Amino Acid Metabolism in the Liver: Nutritional and Physiological Significance. Adv Exp Med Biol. 1265:21-37. doi: 10.1007/978-3-030-45328-2_2. PMID: 32761568.

Kung, L., Rode, L.M. (1996). Amino acid metabolism in ruminants, Animal Feed Science and Technology, Volume 59, Issues 1–3, 167-172. https://doi.org/10.1016/0377-8401(95)00897-7.

Li, P., He, W., Wu, G. (2021). Composition of Amino Acids in Foodstuffs for Humans and Animals. Adv Exp Med Biol. 1332:189-210. doi: 10.1007/978-3-030-74180-8_11. PMID: 34251645.

Mlinac Jerković, K. (2021). Amino acid degradation; urea cycle. Sveučilište u Zagrebu, Stomatološki fakultet, Zagreb. (chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.sfzg.unizg.hr/_download/repository/Lecture_Amino_acids_degradation_urea_cycle_KMJ.pdf)

NYU School of Medicine (NYUSM) (2022). Amino acid metabolism. (http://education.med.nyu.edu/mbm/aminoAcids/index.html)

Prirodoslovno-matematički fakultet (PMF) Sveučilišta u Zagrebu (2014). Razgradnja aminokiselina. (chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.pmf.unizg.hr/_download/repository/14obk-p30_razgradnja_aminokiselina-1.pdf)

Univerzitet Crne Gore (UCG) (2018). Metabolizam proteina (chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.ucg.ac.me/skladiste/blog_8726/objava_19720/fajlovi/MEDICINA%20katabolizam%20AK,%20purini%20i%20pirimidini%202018.pdf)

METABOLIZAM AMINOKISELINA

Rezime

Građevni blokovi proteina, aminokiseline, igraju ključnu ulogu u metabolizmu i strukturi životinja i ljudi. U svjetlu činjenice da su aminokiseline ključne za život, cilj ovog pregleda bio je analizirati njihov metabolizam. Jetra je ta koja ima primarnu ulogu u metabolizmu aminokiselina kod ljudi i životinja. Aminokiseline je moguće podijeliti na esencijalne i neesencijalne. Stanične membrane u različitim tkivima glavni su put kojim aminokiseline putuju u krv, prvenstveno putem kotransportnih sustava koji ovise o Na^+. Kod većine kopnenih životinja amonijev ion se pretvara u ureu. Višak $NH4^+$ se pretvara u ureu. Proces kojim se to odvija naziva se ciklus uree. Tijekom procesa glutamat dehidrogenaza stvara slobodni $NH4^+$ prethodno prenesen u α-ketoglutarat pomoću transaminaza. Fumarat, drugi proizvod, povezuje ciklus uree s ciklusom TCA. Dva ulazna atoma dušika izlaze iz ciklusa kao urea, koju jetra ispušta u krv za odlaganje u urinu putem bubrega. Amonijak bi mogao biti vrlo toksičan za stanice i tkiva svih živih bića. Stoga je poznavanje metabolizma aminokiselina ključno za prehranu ljudi i životinja kako bi se spriječila prevalencija brojnih poremećaja ili bolesti.

Ključne riječi: *aminokiseline, metabolizam, ciklus uree*