

Histidine

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summary

Histidine is an essential amino acid characterized by its unique imidazole side chain, which plays a crucial role in various biochemical processes and protein functions in living organisms. With a pKa of approximately 6.0, histidine can exist in both protonated and deprotonated forms, making it a key participant in acid-base catalysis within enzymes. This amino acid is particularly notable for its involvement in enzyme active sites, where it functions as a proton donor or acceptor, significantly influencing enzymatic reactions, including those related to metabolism and signal transduction-[\[1\]\[2\]](#).

The biosynthesis of histidine is a complex pathway consisting of multiple steps and key intermediates, reflecting its importance across different biological systems, including bacteria, archaea, and plants. In humans, histidine is categorized as a semi-essential amino acid, meaning it must be obtained through dietary sources, particularly from high-protein foods such as meat, fish, and dairy products[\[3\]\[4\]](#). A deficiency in histidine can lead to various health issues, including anemia and impaired cognitive functions, underscoring the significance of adequate dietary intake for maintaining optimal physiological health[\[4\]\[5\]](#).

Histidine also holds considerable clinical relevance, as its metabolism is implicated in several health conditions, including inflammation and cancer. Studies have suggested that histidine influences tumor metabolism and immune responses, highlighting its potential as a biomarker for disease monitoring and therapeutic interventions-[\[6\]\[7\]](#). Despite its essential role, excessive supplementation of histidine has been linked to adverse effects, prompting caution among healthcare providers regarding high doses, particularly for individuals with specific health concerns[\[8\]\[9\]](#).

In addition to its nutritional and metabolic importance, histidine's unique structural properties facilitate its use in various applications, including protein purification and as a supplement in sports nutrition aimed at enhancing athletic performance. As research continues to unfold, the multifaceted roles of histidine in health, metabolism, and clinical settings remain a significant area of interest within biochemistry and nutrition science[\[7\]\[10\]](#).

Structure

Histidine is an amino acid with a unique imidazole side chain that plays a critical role in its biochemical properties and interactions. The imidazole ring is characterized by its ability to exist in both protonated and deprotonated forms, which significantly

influences histidine's behavior in various environments. At neutral or physiological pH, the imidazole side chain is predominantly neutral, but it possesses a pKa of approximately 6.0. Therefore, below this pH, the imidazole ring is mostly protonated, carrying a positive charge (+1) and can be represented with two resonance structures, often denoted as Hip for the protonated form instead of His[1][2].

TIM-Barrel Structure

Histidine is often found in proteins that adopt a TIM-barrel (triose phosphate isomerase barrel) structure, which is composed of eight concatenated (²strand)-loop-(~~the~~ helix) units. In this configuration, the ²strands form the interior staves of the barrel, while the ~~the~~ helices surround them externally. This structure is essential for the function of enzymes such as HisA and HisF, which are involved in histidine biosynthesis[1]. The historical evolution of these proteins suggests that the ancestral forms may have originated from a series of gene duplications and elongations, leading to the current TIM-barrel structure that is capable of homo-dimerization to form functional enzymes[1].

Functional Implications

The imidazole side chain of histidine also serves as a ligand in metalloproteins, contributing to the coordination of metal ions crucial for enzymatic activity. For instance, in myoglobin and hemoglobin, the imidazole ring acts as an axial ligand to iron, which is vital for oxygen binding[2]. Furthermore, poly-histidine tags, which consist of several consecutive histidine residues, are widely utilized in protein purification due to their affinity for nickel or cobalt, highlighting the functional versatility of this amino acid[2].

Tautomerism and Catalytic Role

Histidine's acid-base properties are critical for its role in enzyme catalysis. In catalytic triads, the basic nitrogen of the imidazole ring can abstract a proton from serine or threonine, facilitating the reaction process. This property is further supported by studies demonstrating the preference for the N1-H tautomer over the N3-H form, influenced by hydrogen bonding interactions[2]. The tautomerism of histidine has been characterized using NMR spectroscopy, showing distinct chemical shifts that correlate with pH changes, thereby affecting its reactivity and function in enzymatic mechanisms[2].

Biosynthesis

Histidine biosynthesis is a complex and well-studied anabolic pathway found in a variety of organisms, including bacteria, archaea, and some lower eukaryotes, as well as in plants. This pathway consists of ten biochemical steps, leading to the production of L-histidine, a positively charged proteinogenic amino acid characterized by its imidazole side chain[3][4]. In humans, histidine is regarded as an essential amino acid that must be obtained through the diet[3].

Pathway Overview

The biosynthetic pathway of histidine involves several key intermediates and enzymes. The process is initiated from the precursor N'-(5'-phosphoribosyl)-formimino-5-aminoimidazol-4-carboxamide ribonucleotide (PRFAR), which is converted into 5'-(5-aminoimidazole-4-carboxamide) ribonucleotide (AICAR) and imidazole glycerol phosphate (IGP) via the action of the bifunctional enzyme imidazole glycerol phosphate (IGP) synthase[1]. This enzyme is a heterodimer composed of hisH and hisF gene products, with its activity linking histidine biosynthesis to purine metabolism[1].

The entire pathway is regulated by feedback inhibition, where the end product, L-histidine, inhibits the initial enzyme, thereby controlling the synthesis of this amino acid[11]. The genetic architecture of histidine biosynthesis genes is organized into compact operons, particularly in many Gram-negative and Gram-positive bacteria, though the gene order and operon content vary across different bacterial phyla[3]-[12].

Genetic and Biochemical Aspects

Histidine biosynthesis is one of the best-characterized metabolic pathways, with extensive genetic and biochemical information primarily derived from studies on *Escherichia coli* and *Salmonella enterica*[1][2]. In these organisms, the biosynthetic pathway is unbranched and consists of nine intermediates, with three genes coding for bifunctional enzymes involved in multiple steps of the synthesis[1].

The role of gene duplication and fusion is significant in the evolution of this metabolic pathway, as these mechanisms contribute to the assembly and optimization of the histidine biosynthetic genes[1]. Additionally, recent studies have highlighted the interplay between this biosynthetic pathway and other metabolic processes, particularly nitrogen metabolism and the de novo synthesis of purines, thereby underscoring the central role histidine plays in cellular metabolism[1][2].

Functions

Role in Protein Synthesis

Histidine is one of the 20 amino acids that are essential for the synthesis of proteins in living organisms.[13] It plays a critical role in the active site of various enzymes, particularly serine proteases such as trypsin, where it is involved in catalysis and substrate binding.[14][15][16] The unique imidazole side chain of histidine allows it to participate in proton transfer reactions, which is essential for the enzyme's activity and for maintaining the proper pH within the protein structure.[16]

Enzymatic Activity

Histidine is frequently found as a catalytic residue in enzymes, where it can act as a proton donor or acceptor. This functionality is particularly important in histidine

kinases, which are involved in cellular signal transduction. These kinases undergo autophosphorylation on a conserved histidine residue, facilitating the propagation of intracellular signals and regulating various cellular processes.[\[16\]](#)[\[1\]](#) Additionally, histidine's role in enzyme catalysis extends to metabolic pathways, including its involvement in nitrogen metabolism and the de novo synthesis of purines.[\[1\]](#)

Metabolic Interconnections

The biosynthesis of histidine is interconnected with multiple metabolic pathways, highlighting its significance beyond just protein synthesis. Histidine biosynthesis starts from ribose-5-phosphate, which is derived from glucose-6-phosphate, linking carbohydrate metabolism with amino acid synthesis. Furthermore, histidine metabolism overlaps with purine biosynthesis, illustrating its role as a metabolic crossroads.[\[1\]](#) The conversion of histidine and its degradation products also plays a role in nitrogen metabolism, where it contributes to nitrogen balance in cells.[\[1\]](#)

Nutritional Aspects

As a semi-essential amino acid, histidine must be obtained through dietary sources, especially in infants and young children, who have higher requirements for this amino acid.[\[13\]](#) It can be sourced from complete proteins, such as meat, eggs, and dairy products, which provide all essential amino acids necessary for proper bodily functions.[\[13\]](#) In the context of dietary intake, histidine is crucial for maintaining optimal health, supporting not only protein synthesis but also various metabolic functions in the body.

Dietary Sources

Histidine is an essential amino acid that plays a critical role in various physiological functions, including the synthesis of proteins and the production of histamine, a vital neurotransmitter.[\[17\]](#)[\[18\]](#) The body typically obtains histidine from a variety of dietary sources, which can be categorized into animal and plant-based foods.

Animal Sources

Animal proteins are considered the most effective sources of histidine due to their high bioavailability. Foods such as meat, poultry, and fish contain significant amounts of histidine, with concentrations ranging from 25 to 30 mg of histidine per gram of protein.[\[19\]](#)[\[13\]](#) Particularly rich sources include dried whale and seal meats, which provide nearly 3 g of histidine per 100 g serving.[\[18\]](#)[\[20\]](#) Eggs and dairy products, such as Greek yogurt, are also excellent sources, making them beneficial options for those seeking to increase their histidine intake.[\[17\]](#)

Plant Sources

While animal sources are predominant, certain plant-based foods can contribute to histidine intake. Foods such as apples, pomegranates, and a variety of vegetables

like spinach, garlic, and carrots provide lower yet valuable amounts of histidine.[\[17-21\]](#) Legumes, particularly soy products, are also notable sources, offering a good balance of amino acids for those following vegetarian or vegan diets.[\[17\]](#)

Recommended Intake

The recommended intake of histidine varies depending on age, health status, and dietary preferences. Generally, a well-balanced diet rich in both animal and plant proteins should suffice to meet the daily requirements of histidine and other essential amino acids.[\[17\]\[22\]](#) For individuals with specific dietary restrictions or health conditions, supplementation may be considered to ensure adequate intake, particularly in cases of increased demand, such as during illness or recovery from trauma.[\[17\]](#)

Health Implications

Nutritional Importance of Histidine

Histidine is an essential amino acid necessary for various physiological functions, including tissue growth and repair, red blood cell production, and the protection of tissues from damage due to radiation and heavy metals[\[23\]](#). It plays a crucial role in the formation of myelin sheaths that surround nerves, enabling efficient signal transmission to the brain[\[23\]](#). A deficiency in histidine may lead to several health issues, including anemia, skin lesions, and general feelings of unwellness[\[5\]](#). Long-term histidine deficiency can result in decreased hemoglobin levels, which may lead to anemia, and is characterized by low plasma levels of histidine[\[4\]\[24\]](#).

Clinical Studies and Observations

Research has shown that low levels of histidine are associated with increased inflammation and oxidative stress, particularly in populations with chronic kidney disease and obesity[\[25\]\[23\]](#). A clinical trial indicated that histidine depletion could adversely affect cognitive response processes[\[5\]](#). Moreover, a study found that individuals following a histidine-free diet experienced an 11% decrease in hemoglobin levels over a span of 48 days, potentially leading to anemia[\[5\]](#).

Recommended Intake and Supplementation Risks

Despite its essential role, histidine deficiency is relatively rare due to its presence in various protein sources[\[8\]](#). The recommended intake for histidine can generally be met through a balanced diet. However, excessive supplementation, particularly above 24 grams per day, has been linked to adverse effects such as gastrointestinal symptoms, headaches, and muscle weakness[\[8\]\[9\]](#). Additionally, single amino acid supplementation can lead to amino acid imbalances and may not be suitable for individuals with adequate dietary protein intake[\[8\]](#). Healthcare providers often advise against high doses of histidine supplements, especially for those with liver conditions, as complications such as liver enlargement may occur[\[8\]](#).

Implications for Special Populations

Certain populations, such as athletes and individuals engaging in regular physical activity, may benefit from monitoring their histidine levels due to its potential effects on muscle metabolism and recovery[7][23]. However, as histidine is produced by the liver in small quantities, ensuring adequate dietary intake is vital for maintaining optimal health and physiological functions[4]. Those with specific dietary restrictions or conditions that hinder protein absorption should discuss their histidine levels and supplementation needs with healthcare professionals.

Applications

Nutritional Supplementation

Histidine is recognized for its potential role in nutritional supplementation, particularly in the context of dietary needs and athletic performance. It is an essential amino acid that contributes to various physiological functions, including protein synthesis and the production of histamine, a crucial neurotransmitter.[10][8] Supplementation with L-histidine should be personalized and guided by healthcare professionals, such as registered dietitians or pharmacists, as it is not intended to treat, cure, or prevent diseases.[8] Inadequate levels of histidine may indicate deficiencies in dietary intake or digestive issues, which could warrant supplementation to restore balance and promote health.[10]

Health Monitoring and Laboratory Analysis

Healthmatters.io provides a platform for users to monitor and interpret their lab results, including histidine levels among other biomarkers. This service allows individuals to upload lab results, such as those obtained from various tests, and receive insights into their health status. Users can track changes over time, compare results, and gain a comprehensive understanding of their amino acid profiles, including histidine.[10] Additionally, professionals using this platform can customize reports to better communicate findings to their clients, thereby enhancing clinical outcomes through improved data visibility and trend monitoring.[10]

Clinical Implications

Research has suggested that histidine metabolism plays a significant role in various health conditions, including its impact on the immune system and cancer progression. For instance, recent studies indicate that histidine influences tumor metabolism and the immune microenvironment, which may affect patient prognosis and response to therapies.[6] By investigating histidine levels and metabolism, healthcare providers can gain valuable insights that may guide treatment decisions, particularly in oncology settings.[7] Thus, understanding histidine's role extends beyond nutrition into

clinical applications, where it may serve as a biomarker for disease monitoring and therapeutic interventions.[\[6\]](#)

Performance Enhancement

Histidine is increasingly recognized in the realm of sports nutrition for its potential benefits in enhancing athletic performance. Some studies suggest that supplementation may improve exercise capacity and recovery among athletes, particularly in conjunction with other amino acids.[\[7\]](#) By supporting metabolic functions and muscle repair, histidine may play a role in optimizing training outcomes for athletes engaged in intense physical activity.[\[7\]](#) As such, it is often included in formulations aimed at athletes and physically active individuals looking to maximize their performance and recovery.

History

Histidine was first identified in 1896 by the German chemist Hermann Emil Fischer, who isolated it from proteins using hydrolysis methods. This amino acid was later synthesized artificially in the early 20th century, leading to an increased understanding of its biochemical properties and physiological roles[\[4\]](#).

Evolutionary Significance

Research suggests that histidine's biosynthetic pathway has significant evolutionary implications. It is hypothesized that primitive catalysts may have required histidine, which imposed selective pressure on early organisms to develop the ability to synthesize this amino acid as prebiotic supplies became exhausted. This metabolic pathway likely began assembling long before the Last Universal Common Ancestor (LUCA), highlighting its importance in early biochemical processes[\[1\]](#). Furthermore, phylogenetic analyses have revealed that duplications and fusions of histidine biosynthesis genes have occurred throughout evolutionary history, contributing to the diversification of the pathways involved in its metabolism[\[1\]](#).

Contemporary Studies

In recent years, histidine has been the focus of various nutritional and health-related studies. Research has indicated that dietary histidine intake may correlate with various health outcomes, including energy metabolism and obesity. For instance, some studies have suggested that increased histidine intake might be associated with lower energy intake among specific populations, such as Japanese female students[\[26\]](#). Additionally, histidine's potential roles in managing conditions such as rheumatoid arthritis and its effects on cognitive functions in the elderly are being actively investigated[\[27\]](#).

References

- [1]: [The role of gene fusions in the evolution of metabolic pathways](#)

- [2]: [22.2: Biosynthesis of Amino Acids - Biology LibreTexts](#)
- [3]: [Evolution of transcriptional regulation of histidine metabolism in ...](#)
- [4]: [Histidine - Wikipedia](#)
- [5]: [MetaCyc L-histidine biosynthesis - BioCyc](#)
- [6]: [Histidine Biosynthesis - BioOne Complete](#)
- [7]: [Amino Acid: Benefits & Food Sources - Cleveland Clinic](#)
- [8]: [Histidine Metabolism and Function - PubMed](#)
- [9]: [Histidine Metabolism and Function - PMC - PubMed Central](#)
- [10]: [Understanding the Role of L-Histidine HCl in Protein Synthesis](#)
- [11]: [Essential Amino Acids: Definition, Benefits, and Food Sources](#)
- [12]: [Foods by Histidine content - Nutrition Value](#)
- [13]: [Histidine in Health and Disease: Metabolism, Physiological ...](#)
- [14]: [Histidine: A Systematic Review on Metabolism and Physiological ...](#)
- [15]: [-Histidine – What is it, Benefits and Properties HSN Blog](#)
- [16]: [9 Essential Amino Acids | Food Sources to Find Them - FoodUnfolded](#)
- [17]: [Histidine as a therapeutic supplement | EBSCO Research Starters](#)
- [18]: [10 Histidine Health Benefits: Function, Foods & Side Effects](#)
- [19]: [Histidine - Rupa Health](#)
- [20]: [Role of dietary histidine in the prevention of obesity and metabolic ...](#)
- [21]: [What Are the Benefits of L-Histidine? - Verywell Health](#)
- [22]: [Benefits and Adverse Effects of Histidine Supplementation](#)
- [23]: [Amino acids regulating skeletal muscle metabolism: mechanisms of ...](#)
- [24]: [Histidine - Lab Results explained - HealthMatters.io](#)
- [25]: [Histidine metabolism drives liver cancer progression via immune ...](#)
- [26]: [Histidine in Health and Disease: Metabolism, Physiological ... - MDPI](#)
- [27]: [Anserine, Balenine, and Ergothioneine: Impact of Histidine ... - MDPI](#)