alfa-Aminoadipic acid

Table of Contents

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summary

±Aminoadipic acid (2-AAA) is an alpha-amino acid notable for its critical role in various metabolic pathways, particularly in the biosynthesis and degradation of lysine. Its molecular formula is C6H11NO4, and it is characterized by the presence of a chiral carbon atom, which gives it a specific three-dimensional structure that is essential for its biochemical functions.[1][2] 2-AAA is not only involved in energy production via the tricarboxylic acid (TCA) cycle but also acts as an intermediary in the metabolism of branched-chain amino acids. Its significance extends beyond basic metabolism, as alterations in 2-AAA levels have been linked to various health conditions, including diabetes and renal failure.[3][4][5]

The biosynthesis of ±aminoadipic acid occurs primarily through the ±aminoadipate pathway, particularly in certain eukaryotic species such as fungi and yeasts, where it serves as a precursor for lysine synthesis. The pathway highlights the compound's unique metabolic role and positions it as a potential target for antifungal drug development due to its restricted distribution across organisms.[6][7] Additionally, 2-AAA plays a significant role in lysine degradation, illustrating its versatility in both catabolic and anabolic processes within biological systems.[3][8]

In clinical contexts, ±aminoadipic acid has emerged as a valuable biomarker for metabolic diseases, particularly diabetes and cardiovascular conditions. Studies have demonstrated that elevated levels of 2-AAA are associated with an increased risk of developing diabetes, making it a potential early indicator for individuals predisposed to metabolic dysregulation.[9][10] Its influence on glucose homeostasis and insulin sensitivity underscores its relevance in research focused on cardiometabolic health and the development of preventive strategies.[11][10] However, concerns about the implications of excessive 2-AAA levels on metabolic processes necessitate a cautious approach towards dietary supplementation, especially in at-risk populations.[12]

Overall, the multifaceted roles of ±aminoadipic acid in metabolism, its potential health implications, and its importance as a biomarker for disease highlight its significance in both basic biological research and clinical practice, warranting further exploration of its therapeutic potential and impact on health outcomes.

Chemical Properties

±Aminoadipic acid (2-AAA) is classified as an alpha-amino acid, characterized by the presence of an amino group, a carboxylic acid group, and a unique side chain, known as the R group, which imparts distinctive properties to this compound.[1] Its molecular formula is C6H11NO4, and it has a specific structure that includes a chiral carbon atom, giving it the L-configuration of the alpha-carbon atom[2].

The chemical structure of ±aminoadipic acid is defined by its functional groups, which are responsible for its biochemical roles and interactions. This compound participates in various metabolic pathways, particularly those involving branched-chain amino acids, where it undergoes transamination with ±ketoglutarate to yield 2-ketohexane-

dioic acid. This intermediate subsequently decarboxylates, catalyzed by a dehydrogenase enzyme, producing acetyl-CoA, which further integrates into the tricarboxylic acid (TCA) cycle, thus contributing to central energy production pathways[3][4].

Additionally, ±aminoadipic acid can exist in both its free form and as part of larger polypeptides or proteins, emphasizing its importance in both metabolic processes and protein synthesis. The biological significance of this amino acid is further highlighted by its roles in tissue growth, repair, and the potential implications of its levels in health conditions such as diabetes and renal failure[3][4][5].

Biosynthesis

±Aminoadipic acid plays a critical role as a metabolic precursor in the biosynthesis of lysine through the ±aminoadipate pathway. This pathway is especially notable in various eukaryotic species, including certain yeasts and higher fungi, where it is uniquely present[6]. The process begins with the condensation of acetyl-CoA and ±ketoglutarate, which results in the formation of homocitrate, a reaction catalyzed by homocitrate synthase[6][13]. Following this, homocitrate is converted to homoaconitate and then to homoisocitrate, with each step facilitated by specific enzymes such as homoaconitase and homoisocitrate dehydrogenase.

The pathway then leads to the formation of ±ketoadipate through decarboxylation of homoisocitrate. This intermediate is then transformed into ±aminoadipate by the incorporation of a nitrogen atom from glutamate, a reaction catalyzed by aminoadipate aminotransferase[6]. The ±aminoadipate can then undergo further enzymatic reduction to yield ±aminoadipate semialdehyde, which ultimately contributes to lysine synthesis via the action of saccharopine dehydrogenase, generating saccharopine that can be cleaved to produce lysine and ±ketoglutarate[6][7].

In addition to its biosynthetic role, ±aminoadipic acid is also involved in lysine degradation pathways, where lysine is converted to ±aminoadipate and subsequently metabolized to acetoacetate. This conversion involves a series of transamination and oxidation reactions, demonstrating the compound's versatility in metabolic processes[3][8-]. The distinctiveness of the ±aminoadipate pathway not only highlights its importance in amino acid metabolism but also presents potential therapeutic targets in antifungal drug development due to its limited distribution across organisms[6].

Biological Role

Metabolism and Pathways

±Aminoadipic acid (±AAA) is a significant intermediate in the lysine degradation pathway and plays a crucial role in various metabolic processes across different organisms. In humans, ±AAA is synthesized mainly through the catabolism of lysine, an essential amino acid that must be obtained from dietary sources such as meat, dairy, and legumes[14]. ±AAA is particularly noted for its involvement in the lysine and saccharopine pathways, and it acts as an acidogen, diabetogen, atherogen,

and metabotoxin, linking it to diseases like cancer, diabetes, and cardiovascular conditions[14].

The metabolism of ±AAA also interrelates with 2-aminoadipic acid (2-AAA), which is a stable oxidative byproduct of lysine metabolism. This relationship is vital as 2-AAA has emerged as a biomarker for diabetes risk, influencing glucose homeostasis and lipid metabolism[3]. The metabolic pathway begins in the liver, where lysine is transported, and enzymatic reactions convert it into 2-AAA, making it an integral component in understanding metabolic dysregulation[3].

Health Implications

Diabetes and Cardiometabolic Risk

Alfa-aminoadipic acid (2-AAA) has emerged as a significant biomarker in the study of diabetes and related cardiometabolic diseases. The rising prevalence of diabetes, affecting approximately 9.3% of the U.S. population, highlights the urgency of identifying early markers that predict individuals at high risk of developing dysregulated glycemic control and associated co-morbidities[9][8]. Elevated levels of 2-AAA have been linked to an increased risk of developing diabetes, with individuals exhibiting higher concentrations having a fourfold increase in diabetes risk over a 12-year period compared to those with lower levels[3]. This correlation suggests that 2-AAA may serve as a valuable early indicator for healthcare strategies aimed at prevention and intervention in at-risk populations[8].

Influence on Glucose Homeostasis

2-AAA plays a crucial role in glucose metabolism and homeostasis. Research indicates that it is positively correlated with insulin release and body mass index (BMI), while also being negatively associated with high-density lipoprotein (HDL) levels[3][11]. The implications of these relationships are significant, as persistent hyperglycemia, characteristic of diabetes, can lead to serious complications, including cardiovascular diseases[3]. Elevated plasma 2-AAA levels have been shown to correlate with increased fasting glucose and insulin levels, reinforcing its potential as a target for therapeutic intervention[10].

Population Variability

The impact of 2-AAA on health may vary across different populations. Studies suggest that plasma 2-AAA levels differ by sex and race, with men showing higher levels than pre-menopausal women, and Asian individuals exhibiting higher concentrations than other racial groups[10]. This variability underscores the importance of understanding the demographic differences in 2-AAA metabolism and its implications for personalized healthcare strategies aimed at preventing diabetes and cardiovascular diseases.

Nutritional Aspects

In addition to its metabolic roles, 2-AAA's regulation may be influenced by dietary factors. While most individuals obtain sufficient essential amino acids through a balanced diet, certain populations, including athletes, may benefit from amino acid supplementation to enhance performance and recovery[15]. However, it is crucial to approach supplementation with caution, as excessive intake could disrupt normal metabolic processes and exacerbate conditions like insulin resistance[12].

Clinical Relevance

Alfa-Aminoadipic acid (2-AAA) has garnered attention in clinical research due to its potential role as a biomarker for various cardiometabolic diseases. Studies have indicated that elevated levels of 2-AAA may correlate with increased risk factors for conditions such as diabetes and cardiovascular disease (CVD) [10][9]. The global prevalence of these diseases underscores the urgency for improved predictive markers, as they are significant contributors to mortality and healthcare costs [10].

Association with Diabetes and Cardiometabolic Risk

Recent research has explored the association between 2-AAA and other circulating markers in both healthy individuals and those with chronic conditions, such as treated human immunodeficiency virus (HIV) infection. This population is particularly relevant due to their heightened risk for cardiometabolic diseases [10]. The findings suggest that 2-AAA could serve as a valuable tool for early detection and intervention in diabetes management, helping to identify individuals at high risk before the onset of dysregulated glycemic control [3].

Impact on Treatment Strategies

The significance of understanding 2-AAA levels extends to therapeutic strategies as well. Current hypotheses propose that supplementation with vitamin B6 and alpha-ketoglutarate (ǂKG) may facilitate the conversion of alpha-aminoadipic acid to alpha-ketoadipic acid, potentially lowering 2-AAA levels [16]. This approach aims to modulate disease processes in individuals at risk of developing overt diabetes, thus having the potential to reduce morbidity and mortality associated with the disease [9].

Future Directions

While the correlation of 2-AAA with metabolic diseases shows promise, further investigation is necessary to establish its therapeutic potential and long-term safety. Strategies that inhibit DHTKD1, a key enzyme in the metabolism of 2-AAA, are being evaluated, but comprehensive studies will be essential to validate these findings and translate them into clinical practice [3]. As research continues, 2-AAA could emerge as an actionable target in metabolic medicine, enhancing the understanding and management of cardiometabolic disorders [3].

Applications

Clinical Use

Alpha-aminoadipic acid (AAA) has been identified as a metabolite of interest in various health conditions. It acts as a potential biomarker for insulin resistance, particularly in childhood obesity, suggesting its role in metabolic disorders[14][17]. Furthermore, clinical studies have indicated that elevated levels of AAA could predict the development of diabetes, highlighting its significance in glucose homeostasis regulation[10][18].

Treatment Approaches

In terms of treatment, supplementing with vitamin B6 and alpha-ketoglutarate (-±KG) has been suggested as a potential approach for managing elevated AAA levels[16][19]. This supplementation may facilitate the transamination conversion of ±aminoadipic to ±ketoadipic acid, thereby aiding metabolic processes related to AAA[20].

Laboratory Tracking

Healthmatters.io offers comprehensive solutions for healthcare professionals to track laboratory results, including those related to amino acids like AAA. Their platform allows for customizable reports and easy monitoring of patient data over time, which is particularly beneficial for practitioners managing conditions linked to amino acid imbalances[21][16]. With options for self-entry of lab reports or assistance from a data entry service, practitioners can efficiently manage and interpret their patients' results[16][20].

Research Applications

Research has also explored the role of AAA in the biosynthesis of ²lactam antibiotics. It serves as a precursor in the synthesis pathways of classical antibiotics, linking its metabolic functions to pharmaceutical applications[22][23]. This connection illustrates the broader implications of AAA in both clinical and research settings, particularly in developing therapeutic agents.

Research

Determinants of 2-Aminoadipic Acid Levels

Research into the determinants of 2-aminoadipic acid (2-AAA) has involved several studies, particularly focusing on its potential as a biomarker for insulin resistance and various metabolic disorders. One significant study conducted at Vanderbilt University Medical Center recruited 261 healthy adults aged 18-45 years, who completed a

single study visit and provided fasting blood samples for analysis of 2-AAA levels. Participants were excluded based on criteria including a body mass index (BMI) greater than 30 kg/m², active tobacco use, and certain medical conditions such as diabetes and cardiovascular diseases[10][24].

The HIV, Adipose Tissue Immunology, and Metabolism Study

Another pertinent study highlighted the relevance of 2-AAA in the context of obesity and metabolic dysfunction, especially in childhood. It was proposed that 2-AAA could serve as a potential biomarker for insulin resistance in this demographic[10]. The findings suggest that the level of 2-AAA may reflect underlying metabolic dysregulation associated with obesity, further establishing its significance in research related to cardiometabolic diseases.

Implications for Cardiometabolic Disease Research

The increasing prevalence of cardiometabolic diseases, including diabetes and cardiovascular disease, underscores the importance of identifying refined biomarkers such as 2-AAA. Known risk factors such as obesity and dysregulated glucose metabolism contribute to disease susceptibility; however, the variability in disease manifestation prompts the need for better predictive markers. By improving understanding of the underlying mechanisms of these diseases, 2-AAA may aid in identifying at-risk individuals and enhancing treatment strategies[10][24].

Funding and Ethical Considerations

The research involving 2-AAA has received support from various institutions, including the National Institute of Diabetes and Digestive and Kidney Diseases and the National Heart, Lung, and Blood Institute. All studies were conducted with appropriate ethical oversight, ensuring informed consent from participants[10][24]. The absence of commercial or financial conflicts of interest further strengthens the integrity of the findings reported in these studies.

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