Cystathionine

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summary

Cystathionine is a sulfur-containing amino acid that serves as a crucial intermediate in the transsulfuration pathway, a metabolic route essential for converting homocysteine into cysteine. Its chemical formula is $C7H14N2O4S$, and it plays a significant role in sulfur amino acid metabolism, influencing levels of critical biomolecules such as glutathione and hydrogen sulfide ($H2S$), which are vital for antioxidant defense and cellular functions.[1][2][3]. Cystathionine's metabolism is primarily facilitated by the enzymes cystathionine beta-synthase (CBS) and cystathionine gamma-lyase (CGL), both of which require the active form of vitamin B6, pyridoxal phosphate, for their catalytic activity.[4][5][3].

The biochemical significance of cystathionine extends to its potential implications in various health conditions. Elevated levels of cystathionine have been associated with hyperhomocysteinemia (HHcy), a condition linked to increased risks for cardiovascular diseases and neurodegenerative disorders.[6][7]. Moreover, deficiencies in CBS,

which lead to the accumulation of cystathionine, are implicated in homocystinuria—a genetic disorder characterized by an inability to properly metabolize homocysteine, resulting in systemic symptoms such as ocular and skeletal abnormalities.[8][9][10].

Cystathionine's role in metabolism and health has made it a focal point of research in nutritional science, with dietary influences noted for their impact on its levels in the body. Diets rich in sulfur amino acids, particularly methionine and cysteine, are crucial for maintaining optimal cystathionine metabolism, while restrictions on protein intake may be necessary for individuals with disorders related to its metabolism.[11][12]. Emerging therapeutic interventions, including dietary modifications and pharmacological approaches, are being explored to manage conditions associated with cystathionine and homocysteine, further underscoring its clinical relevance.[7][13][14].

As a biomarker for assessing methylation function and antioxidant capacity, cystathionine's levels can reflect metabolic health and are vital in the diagnosis and management of related disorders.[10][15]. Ongoing research continues to elucidate the multifaceted role of cystathionine in human health, suggesting its potential as a therapeutic target in various metabolic and degenerative diseases.[16][17].

Structure

Cystathionine, a key intermediate in the transsulfuration pathway, has the chemical formula C7H14N2O4S and an average molecular weight of 222.26 g/mol[1][2]. Structurally, it belongs to the class of organic compounds known as S-alkyl-L-cysteines[18].

Molecular Composition

The molecular structure of cystathionine consists of a central carbon atom attached to a hydrogen atom, a basic amino group, a carboxylic acid group, and a unique R group (side chain) that differentiates it from other amino acids[19]. The presence of sulfur in its structure is significant for its role in various biological processes.

3D Structure

The three-dimensional configuration of cystathionine is influenced by its interactions and the folding patterns resulting from its amino acid composition. This folding is critical as it facilitates the formation of specific functional groups necessary for enzymatic reactions in the body. In the context of enzymatic activity, cystathionine beta-lyase utilizes a pyridoxal phosphate (PLP) cofactor to cleave the S-C bond in cystathionine, highlighting its functional importance within the biochemical pathway[20].

Cofactors and Interactions

Cofactors play a significant role in the activity of enzymes that interact with cystathionine. For example, the enzyme cystathionine beta-synthase, which catalyzes the formation of cystathionine from homocysteine and serine, requires PLP for its activity, demonstrating how the structure of cystathionine is directly linked to its biochemical functions[4]. The intricate interplay of its structural components and cofactors underscores the importance of cystathionine in biological systems, particularly in amino acid metabolism and synthesis.

Biosynthesis

Cystathionine is a crucial intermediate in the metabolic pathway that synthesizes cysteine from homocysteine, known as the transsulfuration pathway. This pathway is vital for maintaining sulfur amino acid homeostasis in the body and involves a series of enzymatic reactions that convert homocysteine to cysteine through cystathionine.

Enzymatic Reactions

The biosynthesis of cystathionine is primarily facilitated by the enzyme cystathionine beta-synthase (CBS), which catalyzes the condensation of homocysteine and serine to form cystathionine. This reaction is dependent on the availability of the active form of vitamin B6, known as pyridoxal phosphate (PLP)[21][5]. Following the formation of cystathionine, the enzyme cystathionine gamma-lyase (CGL) then catalyzes its cleavage into cysteine and ±ketobutyrate, thus completing the conversion of homocysteine to cysteine[22].

Regulation and Function

The transsulfuration pathway plays a pivotal role in sulfur metabolism, allowing for the regulation of methionine and cysteine levels within the body. Hyperhomocysteinemia (HHcy), a condition characterized by elevated homocysteine levels, can result from mutations in the CBS enzyme, highlighting its critical function in amino acid metabolism[21][3]. Moreover, cystathionine serves not only as an intermediate in cysteine synthesis but also as a potential regulator of sulfur metabolism and related physiological processes.

Pathway Characteristics

The transsulfuration pathway includes both forward and reverse mechanisms, allowing for the interconversion of cysteine and homocysteine through cystathionine[3]. This flexibility is particularly significant in organisms like humans, which are unable to synthesize methionine and must rely on dietary sources. Consequently, the transsulfuration pathway becomes essential for maintaining adequate levels of cysteine from homocysteine, especially under conditions of dietary insufficiency or metabolic stress[5].

Function

Cystathionine plays a critical role in sulfur metabolism and the transsulfuration pathway, which interconverts homocysteine and cysteine through the formation of cystathionine as an intermediate[23][3]. This pathway is essential for synthesizing various biomolecules, including glutathione, taurine, and hydrogen sulfide (H2S), which are vital for cellular functions and antioxidant defense mechanisms[23][24].

Metabolic Significance

In the transsulfuration pathway, homocysteine can be converted into cystathionine by the action of cystathionine ^{2}synthase (CBS), a key enzyme in sulfur metabolism. Subsequently, cystathionine is cleaved by cystathionine lyase to yield cysteine, pyruvate, and ammonia[25][26]. This metabolic interconversion is particularly significant as elevated levels of homocysteine (hyperhomocysteinemia, HHcy) have been associated with various health risks, including cardiovascular disease and neurodegenerative disorders[6][27].

Role in Disease

Research has shown that elevated homocysteine levels can sensitize neurons to oxidative stress, potentially contributing to neurodegenerative diseases by activating NMDA receptors and generating free radicals like hydrogen peroxide[14]. Furthermore, HHcy is noted as a risk factor for cardiovascular disease (CVD), particularly in individuals with metabolic syndrome, as it may impair endothelial function and influence inflammatory processes within blood vessels[7][27][28].

Nutritional Implications

Cystathionine's role extends to nutrition as well, since it is influenced by dietary intake of sulfur amino acids such as methionine and cysteine. Adequate levels of these amino acids are crucial for maintaining optimal cystathionine and homocysteine metabolism[11][6]. The therapeutic implications of cystathionine metabolism highlight the importance of dietary management and supplementation, particularly for individuals with genetic disorders like homocystinuria or those with elevated cardiovascular risk profiles[29][27].

Clinical Significance

Cystathionine, an intermediate in the transsulfuration pathway, plays a critical role in the metabolism of homocysteine, which is associated with various clinical conditions. Elevated cystathionine levels often indicate a functional bottleneck in homocysteine clearance and sulfur metabolism, particularly due to deficiencies in vitamin B6 or inefficiencies in the enzymes cystathionine beta-synthase (CBS) and cystathionine gamma-lyase (CTH) [10][30].

Association with Hyperhomocysteinemia

High levels of homocysteine (Hcy) have been linked to multiple vascular diseases and conditions such as diabetes mellitus and insulin resistance (IR) [9][7]. The relationship between elevated cystathionine and high homocysteine levels suggests that cystathionine can serve as a marker for disruptions in sulfur amino acid metabolism.

Studies have demonstrated that cystathionine increases in conditions related to elevated total homocysteine (tHcy) levels, including folate and cobalamin deficiencies [15][10].

Implications in Disease Diagnosis

In clinical settings, the measurement of cystathionine can provide valuable insights into the functional status of the transsulfuration pathway and overall metabolic health. Elevated cystathionine levels may indicate vitamin B6 deficiency, a common cause of metabolic dysfunction [10][30]. Moreover, conditions such as homocystinuria, resulting from CBS deficiency, manifest with elevated cystathionine and are characterized by systemic symptoms including ocular and skeletal abnormalities [8].

Role as a Biomarker

Given its role as a metabolic bridge between homocysteine and cysteine, cystathionine can serve as a useful biomarker for assessing methylation function and antioxidant capacity [10]. Elevated levels of cystathionine may warrant further investigation into underlying metabolic disturbances, while low levels could suggest functional inefficiencies or dietary deficiencies impacting the transsulfuration pathway [15][10].

Dietary Sources and Nutritional Influence

Cystathionine is a key intermediate in the synthesis of L-cysteine, derived from methionine through the transsulfuration pathway. Its synthesis and availability can be influenced significantly by dietary choices. Individuals with homocystinuria (HCU), a condition associated with cystathionine metabolism, must carefully manage their intake of dietary protein since all protein sources contain methionine, which can exacerbate elevated homocysteine levels. Therefore, those affected by HCU are often advised to limit their consumption of high-protein foods such as milk, dairy products, and various meats[12][31].

Sources of Cysteine

Despite the restrictions on methionine intake, individuals can obtain cysteine from certain dietary sources. Foods such as chickpeas, lentils, oats, turkey, and walnuts are excellent options for enhancing cysteine levels in the diet[11]. Additionally, allium vegetables, which include garlic, onions, and leeks, are rich in sulfur and contribute to cysteine production and other metabolic processes[11].

Role of Sulfur in Diet

Dietary sulfur is critical for cystathionine and cysteine synthesis. Cruciferous vegetables like broccoli, cauliflower, and kale not only provide sulfur in the form of glucosinolates but are also high in fiber and linked to various health benefits, although conclusive clinical studies on their cancer risk reduction remain lacking[11].

Incorporating these vegetables into the diet can help meet sulfur needs, supporting the transsulfuration pathway that leads to cystathionine production[16].

Nutritional Strategies for HCU Management

Emerging dietary strategies are being explored to improve outcomes for patients with HCU. While traditional management relies on diet and nutrient supplementation, including betaine, the effectiveness can vary among individuals[13][32]. Betaine, in particular, has been shown to lower plasma homocysteine levels, which can be beneficial for individuals with hyperhomocysteinemia[7][27]. Such dietary interventions aim to optimize the balance between methionine, cysteine, and overall sulfur intake to manage homocysteine levels effectively.

Therapeutic Interventions

The management of hyperhomocysteinemia (Hcy) through therapeutic interventions focuses on dietary modifications and nutrient supplementation, which have shown varying degrees of effectiveness in patients with cystathionine-related disorders.

Nutritional Approaches

Current therapeutic strategies for homocystinuria (HCU) largely rely on dietary restrictions and the supplementation of essential nutrients. A diet low in methionine, combined with adequate intakes of vitamins B6, B12, and folate, can significantly reduce plasma Hcy levels in some patients[32][33]. Moreover, the enrichment of diets with specific amino acids or the exclusion of certain food groups can also lead to increased Hcy concentrations, highlighting the delicate balance required in dietary management[7][13].

Pharmacological Interventions

In addition to dietary management, several pharmacological agents are under investigation for their potential to modulate Hcy metabolism. Notably, common lipid-lowering drugs like fenofibrate and niacin have been shown to significantly elevate Hcy levels, while anti-epileptic medications such as phenytoin and valproic acid may also induce hyperhomocysteinemia (HHcy) as a side effect[7][27]. Conversely, medications that enhance the re-methylation of Hcy, such as rosiglitazone, have demonstrated a potential to lower total Hcy levels in specific populations[7].

Combination Therapies

Recent studies have explored the efficacy of combination therapies, particularly those incorporating a novel therapeutic cocktail of 5-methyltetrahydrofolate, methyl B12, betaine, and N-acetylcysteine (NAC). This multi-faceted approach aims to target various metabolic pathways involved in Hcy regulation, thereby facilitating substantial reductions in plasma Hcy levels and associated toxicities[14]. Such combinations may be particularly beneficial for individuals with genetic variants that impair Hcy metabolism[14].

Evidence of Efficacy

Research supports the notion that reducing Hcy levels can mitigate related pathologies. For instance, randomized controlled trials have indicated that B vitamin supplementation correlates with decreased brain atrophy in cognitively impaired elderly individuals[34]. Furthermore, large-scale studies, such as the China Stroke Primary Prevention Trial, have reported a significant reduction in the risk of stroke with folic acid supplementation[34].

Research

Overview of Cystathionine's Role in Health

Cystathionine, a sulfur-containing amino acid, plays a significant role in various physiological processes, particularly in the metabolism of homocysteine. High serum levels of cystathionine, along with homocysteine and L-cysteine, have been identified as risk factors for the progression of metastatic prostate cancer, highlighting its potential implications in oncogenesis and cancer progression[16]. Additionally, cystathionine has been implicated in the metabolic syndrome (MetS), with studies indicating that deficiencies in other micronutrients, such as vitamins A and D, prevalent in certain populations, may confound the associations observed with cystathionine levels[16].

Mechanisms of Action

Cystathionine-²synthase (CBS) is a key enzyme in the transsulfuration pathway that converts homocysteine into cystathionine. Alterations in CBS expression and activity have been linked to various diseases, including hyperhomocysteinemia and different forms of cancer[17]. In gastric cancer, for instance, CBS is identified as a novel metabolic regulator that may function as a tumor suppressor. The activation of the PI3K/AKT signaling pathway has been shown to promote CBS expression, thereby enhancing antioxidant responses and potentially mitigating cancer progression[17]. The role of CBS appears to be context-dependent, with evidence suggesting both tumor-promoting and tumor-suppressive functions across different cancer types[17].

Clinical Implications

The therapeutic targeting of homocysteine and its related metabolic pathways, including cystathionine metabolism, is being explored as a potential strategy for managing various pathologies. In clinical trials, B vitamin supplementation, which influences homocysteine metabolism, has demonstrated beneficial effects in cognitive health and stroke prevention[7]. For instance, the China Stroke Primary Prevention Trial indicated that folic acid supplementation significantly reduced the risk of stroke among participants, emphasizing the relevance of cystathionine's metabolic pathway in cardiovascular health[7].

Future Research Directions

Given the complexity of cystathionine's role in health and disease, future studies are encouraged to explore the biochemical mechanisms by which cystathionine and related metabolites affect disease progression and health outcomes. Moreover, investigations should consider potential confounders such as micronutrient deficiencies and other metabolic factors, particularly in diverse populations where such deficiencies may vary significantly[16]. Enhanced understanding of these interactions could lead to more effective therapeutic strategies targeting cystathionine and its metabolic pathways in clinical settings.

Citations

The study of cystathionine and its metabolic implications is well-documented in various scientific literature. Notably, Eckel et al. (2010) provide a comprehensive overview of the metabolic syndrome, which encompasses the pathways involving cystathionine and its role in homocysteine metabolism[16]. Additionally, the research presented in the article clarifies that the claims expressed are solely those of the authors, emphasizing the lack of commercial or financial conflicts of interest in the study[27]. For supplementary material related to this research, readers can refer to the online resource available at Frontiers in Endocrinology[4].

Further Reading

Cystathionine is a significant molecule in the metabolism of sulfur-containing amino acids and has been the subject of various research studies.

Key Studies and Reviews

Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. (2010) 375(9710):181–3. doi: 10.1016/S0140-6736(09)61794-3[16]. This foundational review discusses the metabolic syndrome, within which cystathionine's metabolic pathways are often implicated.

Additional research articles focusing on the synthesis and degradation pathways of cystathionine can provide deeper insights into its physiological significance and potential therapeutic targets.

Conflict of Interest and Funding

It is essential to note that some research may have associated funding or conflict of interest statements. For example, the authors of certain studies declare their research was conducted without commercial or financial relationships that could pose a conflict of interest, ensuring the integrity of the findings presented[21][14].

Supplementary Materials

For those interested in extended data and methodologies related to cystathionine studies, supplementary materials can often be found online, providing additional context and information relevant to ongoing research[27].

Engaging with these sources can enhance the understanding of cystathionine's role in human health and disease.

Relevant Databases

Gene Expression Data

Cystathionine, an important biomarker in metabolic pathways, has been extensively studied, and relevant RNA sequencing data can be found in public repositories. For instance, RNA sequencing data related to the effect of gene alterations in human fibroblasts have been deposited in the Gene Expression Omnibus (GEO) under accession code GSE200479[17]. This data includes various source files that provide insights into the expression levels of cystathionine and other related genes.

Molecular Characterization

The Broad Institute's Genome Data Analysis Center also provides comprehensive molecular characterization of conditions associated with cystathionine, such as gastric adenocarcinoma, contributing to the understanding of its role in disease contexts[17]. Researchers can access these databases for detailed insights into gene expression and associated biomarkers.

Data Management Features

For those looking to manage and analyze their laboratory test results, various platforms offer features like a table view that allows for a holistic display of biomarkers, facilitating easier comparison and analysis. Users can download their test results in CSV format or print their reports directly from the platform[10][8]. Additionally, a data entry service is available, allowing users to submit their lab results in various formats such as PDFs, JPGs, or Excel files, which are then entered into their private dashboard for personal tracking and analysis[10].

Educational Resources

Introduction to Cystathionine

Cystathionine is an important intermediate in the transsulfuration pathway, playing a crucial role in the metabolism of sulfur-containing amino acids. Understanding its biochemical functions and implications in health and disease is essential for students and researchers alike.

Key Resources

Academic Literature

Several foundational papers and reviews detail the role of cystathionine in metabolism and its physiological implications. Notable publications include comprehensive studies on its enzymatic pathways and associations with various health conditions.

Online Databases

Various online databases provide extensive information about cystathionine, including its chemical properties, metabolic pathways, and relevance in human health. Websites such as PubChem and KEGG offer accessible data for academic and research purposes.

Educational Institutions

Many universities and research institutions offer courses and resources focusing on amino acid metabolism, including cystathionine. Students can find lectures, seminars, and laboratory work that facilitate hands-on learning experiences.

Research Funding Opportunities

Researchers interested in studying cystathionine may find funding through various fellowships, such as the Kenneth A. Suarez Research Fellowship, which supports research in biochemistry and related fields[14].

Conflict of Interest Awareness

When engaging with educational materials and conducting research on cystathionine, it is crucial to be aware of potential conflicts of interest. It is recommended to review the affiliations and funding sources of research authors to ensure unbiased information is utilized[9].

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