Carboxyglutamate

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summary

Carboxyglutamate, also known as ³carboxyglutamic acid (Gla), is a modified form of the amino acid glutamic acid that plays a vital role in various biological processes, particularly in calcium binding and blood coagulation. It is essential for the functionality of several vitamin K-dependent proteins involved in the coagulation cascade, including thrombin and various coagulation factors. The unique structural modification of glutamic acid to form carboxyglutamate occurs through a post-translational

carboxylation process catalyzed by gamma-glutamyl carboxylase, which requires vitamin K as a co-factor.[1][2]

The significance of carboxyglutamate extends beyond coagulation, as it is implicated in bone metabolism and neurological functions. Gla-containing proteins, such as osteocalcin, are crucial for bone mineralization and may influence energy metabolism and cognitive functions.[3][4] Furthermore, emerging research highlights the potential clinical implications of carboxyglutamate in assessing cardiovascular health, with elevated levels of desphospho-uncarboxylated matrix Gla protein (dp-ucMGP) serving as a significant biomarker for cardiovascular disease risk and overall mortality.[5][6]

Notably, deficiencies in vitamin K can adversely affect the synthesis of carboxyglutamate, leading to impaired blood coagulation and increased bleeding risk.[2] In recent years, studies have also explored the involvement of carboxyglutamate in neurodegenerative diseases, such as Alzheimer's and Parkinson's, suggesting its potential role in modulating synaptic transmission and neuronal health.[3][7] Thus, carboxyglutamate emerges as a critical component in various physiological processes, underscoring its importance in health and disease management.

Discovery and History

The discovery of carboxyglutamate and its characterization as a neurotransmitter has been a complex journey, shaped by both scientific advancements and challenges. Early research into neurotransmitters was hampered by premature assumptions and technical difficulties, which led to a stagnation in the search for new neurotransmitters over the last several decades[8]. This period of inactivity may have contributed to the misconception that there were no additional neurotransmitters to discover.

Recent findings suggest that the cessation of research into new neurotransmitters was not due to their absence but rather to a lack of innovative approaches in uncovering them. Specifically, the majority of known small-molecule neurotransmitters were identified based on their peripheral effects, which implies that a concerted effort is necessary to explore central neurotransmitters that may not exhibit such effects[8].

Future research directions emphasize the need to employ innovative techniques to identify previously suspected or entirely new neurotransmitter candidates. Strategies may include the use of highly purified synaptic vesicles (SVs) from various brain regions, as well as SVs containing specific solute carrier proteins (SLCs) to aid in this discovery process[8]. The recognition that many potential neurotransmitters remain undiscovered underscores the importance of continuing research in this area.

Chemical Structure

Carboxyglutamic acid, commonly referred to as ³carboxyglutamate (Gla), is an uncommon amino acid characterized by its unique structural modifications. The basic structure of Gla is derived from glutamic acid, with the addition of a carboxyl group at the gamma position of the side chain. This modification occurs through a

post-translational carboxylation process, which is essential for its biological functions, particularly in proteins involved in the coagulation cascade[1][9].

Molecular Formula and Weight

The molecular formula for carboxyglutamic acid is C6H9NO, and it has an average molecular weight of approximately 191.14 g/mol[10][9]. The structure features a central carbon atom connected to an amino group (–NH2), a carboxyl group (–COOH), and a variable R group, which in the case of Gla, includes the additional carboxyl group[1].

Structural Characteristics

The presence of the ³carboxyl group imparts a strong affinity for calcium ions, which is critical for the functionality of Gla-containing proteins such as clotting factors II, VII, IX, and X[1][11]. These proteins undergo conformational changes upon binding calcium, which facilitate their proper folding and interaction with membranes[11][12]. Notably, the N-terminal region of Gla-containing proteins often displays a clustering of hydrophobic residues, contributing to their structural stability and interaction with cellular components[11].

Biosynthesis

The biosynthesis of ³carboxyglutamic acid, a crucial component of certain vitamin K-dependent proteins, involves a specific enzymatic reaction where the ³proton on glutamic acid is abstracted, followed by the addition of carbon dioxide (CO2) to form the carboxylic group[1][13]. This process is catalyzed by gamma-glutamyl carboxylase (GGCX), which requires reduced vitamin K as a co-factor along with carbon dioxide and oxygen[12]. The initial step of this biosynthesis results in the conversion of glutamic acid into ³carboxyglutamic acid, facilitating essential physiological functions, including blood coagulation and bone metabolism.

The activity of GGCX was first discovered in the 1970s, revealing the dependence of the enzymatic incorporation of radioactive CO2 into proteins on the availability of vitamin K[12]. This connection highlights the importance of vitamin K in promoting the carboxylation process necessary for the proper functioning of several proteins, particularly those involved in hemostasis and bone health[2].

Vitamin K exists in two primary forms: vitamin K1 (phylloquinone) and vitamin K2 (menaquinones). While vitamin K1 is predominantly found in leafy greens, vitamin K2 has a longer half-life and exhibits additional extrahepatic activity[5]. The synthesis of ³carboxyglutamic acid is a prime example of how vitamin K contributes to various biological processes, emphasizing its significance beyond just coagulation functions[2].

Deficiencies in vitamin K can impair the synthesis of ³carboxyglutamic acid, potentially leading to clinical manifestations such as excessive bleeding, which is a consequence of inadequate functioning of vitamin K-dependent proteins[2]. Therefore,

maintaining sufficient levels of vitamin K is essential for the effective biosynthesis of ³carboxyglutamic acid and the overall physiological balance in the body.

Biological Functions

Carboxyglutamate plays a crucial role in various biological functions, particularly in calcium binding and the regulation of physiological processes. The Gla domain, characterized by the presence of ³carboxyglutamic acid residues, is essential for the high-affinity binding of calcium ions (Ca^{2+}) to Gla proteins. This binding is often necessary for the conformation and functionality of these proteins, allowing them to participate effectively in biochemical processes such as blood coagulation[1][14].

Numerous proteins involved in the blood coagulation cascade, such as thrombin and several coagulation factors (e.g., Factor VII, IX, X), rely on the presence of carboxyglutamate for their activity. These proteins must function in a coordinated manner to regulate hemostasis and maintain proper blood flow[15][11]. Additionally, vitamin K is critical for the post-translational modification of certain proteins, facilitating the carboxylation of glutamic acid residues to form carboxyglutamate, which enhances their calcium-binding capabilities[16][17].

Beyond coagulation, carboxyglutamate is also implicated in bone metabolism. Proteins such as osteocalcin, which is secreted by osteoblasts, depend on the ³carboxylation of glutamic acid residues for effective calcium binding and bone mineralization-[3][17]. Osteocalcin not only contributes to maintaining bone structure but also plays a role in energy metabolism and has been suggested to exert regulatory effects on brain function, indicating its broader physiological significance[4].

Clinical Significance

Carboxyglutamate (Gla) proteins, particularly desphospho-uncarboxylated matrix Gla protein (dp-ucMGP), have emerged as significant markers in assessing cardiovascular health and mortality risk. Elevated levels of dp-ucMGP have been consistently associated with adverse outcomes in various cardiovascular diseases, including heart failure (HF) and aortic stenosis (AS) [5]. Specifically, studies have indicated that higher dp-ucMGP concentrations correlate with increased all-cause mortality rates (hazard ratio ~7) after a follow-up of 23 months, highlighting its potential as a pre-procedural marker for long-term risk evaluation in patients undergoing aortic valve replacement [5].

In patients with chronic systolic and diastolic HF, increased dp-ucMGP levels correlate with greater disease severity compared to age- and sex-matched controls. These elevated levels are associated with higher markers of inflammation, such as C-reactive protein (CRP), and key indicators of heart function like N-terminal pro-brain natriuretic peptide (NT-proBNP) and left ventricular ejection fraction [5]. Furthermore, meta-analyses have shown a pooled hazard ratio of 1.84 for all-cause mortality associated with elevated plasma dp-ucMGP levels, underscoring its importance as a prognostic biomarker in clinical settings [5][6].

The relationship between dp-ucMGP and cardiovascular morbidity extends to its role in arterial stiffness, a surrogate marker of cardiovascular health. Higher dp-ucMGP levels are associated with increased aortic stiffness and other central hemodynamic measures, indicating its relevance in assessing vascular health and the risk of cardiovascular events [5]. For instance, a study demonstrated that replacing warfarin with rivaroxaban led to a significant reduction in vitamin K deficiency, assessed by inactive forms of coagulation factors, and was associated with a corresponding decrease in arterial stiffness [5].

Moreover, dietary intake of vitamin K2, which is crucial for the activation of Gla proteins, appears to influence cardiovascular risk. Individuals with higher intakes of vitamin K2-rich foods, such as natto, demonstrate reduced coronary artery calcification and lower cardiovascular disease (CVD) mortality rates [5]. Conversely, research has revealed that a significant portion of the population experiences vitamin K insufficiency, particularly among children and individuals over 40 years old, as measured by elevated levels of dp-ucMGP [5].

Research and Developments

Introduction

Recent studies have explored the substrate specificity of ³glutamyl carboxylation sites, which are crucial for various physiological processes. The research delves into the composition of amino acids surrounding these carboxylation sites, specifically focusing on the conserved Glu residues that facilitate ³carboxylation in proteins such as thrombin[18]. The work emphasizes the importance of understanding these sites for further applications in biochemistry and medicine.

Data Collection and Analysis

A comprehensive analysis was conducted utilizing the dbPTM resource, which aggregates post-translational modification (PTM) data from various databases. This study focused on 463 experimentally validated carboxylation sites from 134 carboxylated proteins across multiple organisms, specifically identifying the prevalence of Glu residues at these sites. Non-experimental sites were excluded to enhance the accuracy of the findings, yielding a robust dataset for analysis[18][19].

Findings and Implications

The frequency plot generated from the sequence logo analysis highlighted a significant conservation of negatively charged glutamate residues around carboxylation sites, supporting previous findings regarding the ³carboxylation recognition mechanism. This research not only contributes to a better understanding of carboxylation dynamics but also has potential implications in therapeutic developments and the design of drugs that target these specific biochemical pathways[20][18].

Funding and Support

The work was supported by grants from the Deutsche Forschungsgemeinschaft, indicating strong institutional backing for the research endeavors in this domain[20]. Additionally, philanthropic contributions have facilitated further exploration of carboxylation mechanisms and their physiological relevance[5].

Conflict of Interest and Peer Review

The authors declare that the research was conducted without any commercial or financial conflicts of interest, ensuring the integrity of the findings. The article underwent external peer review, highlighting the rigor of the research process involved in this study[20][5].

Neurological Implications

Carboxyglutamate, a derivative of glutamic acid, plays a significant role in various neurological disorders, particularly neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). These conditions are characterized by the progressive degeneration of neurons and result in severe motor and cognitive impairments[3]. The pathophysiology of neurodegenerative diseases often involves shared features, including neuroinflammation, blood-brain barrier (BBB) impairment, and disruptions in neurotransmitter systems, particularly involving glutamate[3][20].

Alzheimer's Disease

Alzheimer's disease is one of the most prevalent forms of dementia and is marked by cognitive decline and functional impairment. Key neuropathological features include the accumulation of amyloid-beta plaques and tau protein tangles, which lead to synaptic loss and neuronal death[20]. Research indicates that carboxyglutamate may influence these pathological processes, potentially by modulating synaptic transmission and plasticity, which are critical in the maintenance of cognitive functions[7]. Impaired glutamate clearance and signaling can exacerbate neuronal damage, suggesting that targeting carboxyglutamate pathways could offer therapeutic benefits[8].

Parkinson's Disease

Parkinson's disease, characterized by motor symptoms such as tremor, rigidity, and bradykinesia, also shows potential links to carboxyglutamate. The degeneration of dopaminergic neurons in the substantia nigra leads to decreased dopamine levels, which significantly contributes to the motor deficits seen in PD[3]. There is growing evidence that carboxyglutamate might play a role in the neuroprotective mechanisms of dopaminergic neurons, potentially influencing neurotransmitter release and synaptic efficacy[21].

Stroke and Neuroinflammation

In addition to AD and PD, carboxyglutamate has implications in stroke and other neuroinflammatory conditions. Stroke induces a cascade of events that lead to neuronal death, and altered glutamate signaling has been implicated in secondary brain damage following ischemic events[22]. The modulation of carboxyglutamate may help to restore normal neurotransmitter levels and protect against excitotoxicity, which is often exacerbated by inflammatory responses in the brain[8].

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