

Phenylalanine

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summary

Phenylalanine is an essential amino acid, denoted by the chemical formula C_9H_9NO , known for its role in protein synthesis and as a precursor for key neurotransmitters such as dopamine, norepinephrine, and epinephrine.^{[1][2]} This amino acid is crucial for various biological processes, impacting mood regulation, metabolism, and overall health. It is obtained from dietary sources, particularly protein-rich foods, and is particularly notable for its involvement in conditions like phenylketonuria (PKU), a genetic disorder that impairs its metabolism, leading to severe neurological consequences if untreated.^{[3][4][5]}

Structurally, phenylalanine is characterized by a hydrophobic benzyl side chain, which contributes to its classification as a nonpolar amino acid. This unique structure allows it to participate in essential interactions that stabilize protein structures.^[3] The metabolism of phenylalanine primarily occurs through pathways that convert it into tyrosine, further facilitating the production of important neurotransmitters. Inadequate metabolism of phenylalanine can lead to significant clinical implications, including neurological disorders and mood-related issues, underscoring its importance in both biochemistry and health.^{[6][7]}

Notably, phenylalanine is also explored in biotechnological applications, particularly in protein engineering and synthetic biology, where its derivatives are utilized to modify protein functions and enhance therapeutic potential.^[3] Controversies surrounding phenylalanine mainly involve its role in PKU, where individuals with the condition must adhere to strict dietary restrictions to avoid toxic accumulation of the amino acid, raising concerns about the management and treatment of the disorder in affected populations.^{[8][7]}

In summary, phenylalanine is not only a vital building block for proteins and neurotransmitters but also a focal point of research concerning metabolic disorders and biotechnological innovations. Understanding its functions and metabolic pathways is essential for advancing therapeutic approaches and ensuring optimal health outcomes for individuals affected by conditions like PKU.^{[6][7][9]}

Chemical Structure

Phenylalanine (C_9H_9NO) is an essential amino acid characterized by a distinct molecular structure that includes a benzyl side chain and an alpha-amino group ($-NH_2$).

attached to a central carbon atom (α-carbon) [1][2]. The α-carbon is also bonded to a carboxyl group (-COOH) and a hydrogen atom [3]. This configuration allows phenylalanine to play a critical role in protein synthesis and metabolic processes.

Structural Components

The defining feature of phenylalanine is its hydrophobic benzyl group, which consists of a phenyl ring (C₆H₅...) attached to a methylene group (-CH₂-) [3]. This aromatic ring significantly contributes to the molecule's hydrophobicity and facilitates the stabilization of protein structures through interactions such as π - π stacking with other aromatic residues [3]. Phenylalanine is classified as neutral and nonpolar due to the inert nature of its benzyl side chain, which influences its behavior in biological systems [4][5].

Precursor Role

Phenylalanine is crucial for the biosynthesis of several important neurotransmitters, including dopamine, norepinephrine, and epinephrine, as it can be enzymatically converted into tyrosine [3][4]. This conversion underscores the importance of phenylalanine not only as a building block of proteins but also as a precursor for various signaling molecules in the body.

Chemical Properties

The molecular weight of phenylalanine is 165.19 g/mol, and its CAS Registry Number is 63-91-2 [2][8]. The IUPAC Standard InChIKey for phenylalanine is COLNVLDHVK-WLRT-MRVPVSSYSA-N, which aids in its identification in chemical databases [2]. As an amino acid, phenylalanine is involved in forming proteins coded for by DNA, highlighting its essentiality in biological processes [4].

Biological Role

Phenylalanine is an essential amino acid that plays a critical role in various biological processes within the body. It serves as a precursor for the synthesis of important neurotransmitters such as dopamine, norepinephrine, and epinephrine, which are crucial for regulating mood, attention, and response to stress [6][7]. Dysregulation of phenylalanine metabolism can lead to imbalances in these neurotransmitter levels, contributing to neurological disorders, including depression and Parkinson's disease [6][7].

Protein Synthesis

As a fundamental building block of proteins, phenylalanine is incorporated into polypeptide chains during protein synthesis, which is vital for various cellular functions, including enzyme activity and hormone regulation [9][10]. The body efficiently utilizes phenylalanine obtained from dietary sources—such as meat, dairy, and legumes—to meet its protein synthesis needs [11].

Metabolic Pathways

Phenylalanine metabolism primarily occurs through two pathways: the phenylalanine hydroxylase (PAH) pathway and the phenylalanine ammonia-lyase (PAL) pathway. The PAH pathway converts phenylalanine to tyrosine, which is then further metabolized into neurotransmitters. However, in certain conditions, such as phenylketonuria (PKU), PAH activity is deficient, leading to reliance on the PAL pathway, which alters the production of key neurotransmitters[7][10].

Moreover, phenylalanine can also be converted into phenylethylamine and other metabolites, impacting the metabolism of neurotransmitters such as serotonin and its derivatives, including melatonin[7]. The regulation of enzymes involved in these pathways is affected by the availability of phenylalanine, highlighting its importance in maintaining metabolic balance and overall health[7][12].

Applications in Biotechnology

Non-natural derivatives of phenylalanine have significant applications in biotechnology, particularly in protein engineering and synthetic biology. These derivatives allow for the incorporation of specific functional groups into proteins, enhancing their stability, altering their catalytic activity, and improving binding affinity to ligands[3]. This innovation has potential implications for the development of therapeutic proteins and industrial enzymes with tailored functionalities, demonstrating the versatile role of phenylalanine in modern biochemistry[3].

Sources

Phenylalanine is an essential amino acid that can be obtained from a variety of dietary sources. It is crucial for the synthesis of proteins and the production of neurotransmitters.

1. Protein-Rich Foods

Animal Sources

Animal-derived foods are among the richest sources of phenylalanine.

Meat: Beef, pork, and poultry provide significant amounts of this amino acid.

Fish: Various types of fish also contribute to dietary phenylalanine intake.

Dairy Products: Milk, cheese, and yogurt are important sources for many individuals[6][13].

Plant Sources

For those following a plant-based diet, several foods can supply phenylalanine:

Soy Products: Tofu, tempeh, and soy milk are excellent sources of phenylalanine.

Legumes: Beans, lentils, and chickpeas contribute to the overall intake.

Nuts and Seeds: Almonds, peanuts, and sunflower seeds are also beneficial[\[6\]](#)[\[13\]](#).

2. Whole Grains

Whole grains such as quinoa, brown rice, oats, and whole wheat bread contain smaller amounts of phenylalanine but can still contribute to the overall dietary intake[\[6\]](#)[\[13\]](#).

3. Supplements

Phenylalanine supplements are available but should be used under medical supervision, particularly for individuals with phenylketonuria (PKU) or hyperphenylalaninemia (HPA) to avoid excessive accumulation of this amino acid in the body[\[11\]](#)[\[6\]](#).

4. Balanced Diet

A well-balanced diet incorporating a variety of protein sources will generally meet the phenylalanine requirements for most individuals. The reference dietary intake (RDI) for phenylalanine and its precursor tyrosine is approximately 25 mg per kilogram of body weight[\[11\]](#)[\[13\]](#).

Individuals with specific metabolic conditions must carefully monitor their phenylalanine intake to maintain optimal health and prevent complications associated with high levels of this amino acid.

Metabolism

Phenylalanine metabolism is a crucial biochemical process involving a series of enzymatic reactions that convert phenylalanine into various metabolites, including tyrosine, neurotransmitters, and other important molecules essential for physiological functions[\[7\]](#)[\[6\]](#). As an essential amino acid, phenylalanine cannot be synthesized by the body and must be obtained through dietary sources such as meat, fish, eggs, dairy products, nuts, and seeds[\[6\]](#).

Pathways of Phenylalanine Metabolism

Conversion to Tyrosine

The primary metabolic pathway for phenylalanine involves its conversion to tyrosine, a process catalyzed by the enzyme phenylalanine hydroxylase (PAH). This reaction occurs predominantly in the liver and requires molecular oxygen, tetrahydrobiopterin (BH₄) as a cofactor, and ferrous iron (Fe²⁺)[\[6\]](#)[\[14\]](#). Tyrosine then serves as a precursor for the synthesis of various important neurotransmitters, including dopamine and norepinephrine, highlighting the significance of this metabolic pathway beyond mere protein synthesis[\[7\]](#)[\[6\]](#).

Phenylpropanoid Pathway

In addition to the conversion to tyrosine, phenylalanine metabolism also involves the phenylpropanoid pathway, where phenylalanine can be transformed into trans-cinnamate. This metabolic shift observed in conditions such as Parkinson's disease (PD) suggests a depletion in dopamine and norepinephrine production, which can have significant neurochemical implications[7]. The alteration in metabolite levels, such as the reduction of 3-hydroxyanthranilic acid—a metabolite linking phenylalanine to tryptophan metabolism—further emphasizes the interconnected nature of these metabolic pathways[7].

Further Metabolites

Beyond tyrosine and trans-cinnamate, phenylalanine can be further metabolized into other compounds such as phenylpyruvate, which can subsequently lead to the production of phenylacetate, phenyl lactate, and o-hydroxyphenylacetate. These metabolites play roles in various metabolic pathways, indicating the complex network of reactions influenced by phenylalanine metabolism[7][6].

Clinical Implications

Alterations in phenylalanine metabolism are linked to various clinical conditions, including metabolic disorders and neurodegenerative diseases. For instance, the decreased levels of key metabolites such as dopamine and norepinephrine due to impaired phenylalanine metabolism could contribute to the dopaminergic and adrenergic neurodegeneration seen in PD[7]. Understanding these metabolic pathways is crucial for developing therapeutic strategies to manage related health conditions and to enhance our comprehension of the disease processes involved[7][6].

Health Effects

Phenylalanine is an essential amino acid that plays a significant role in various physiological processes within the body. It is primarily involved in the synthesis of neurotransmitters and proteins, impacting mood, metabolism, and overall health.

Benefits of Phenylalanine

Phenylalanine is crucial for the production of several important brain chemicals, including dopamine, epinephrine, and norepinephrine. These neurotransmitters, known as catecholamines, are vital for proper nervous system functioning and play a role in managing stress responses, regulating blood pressure, heart rate, and digestion, as well as influencing mood and focus[15][16].

Supports Nervous System Functioning: By aiding in the production of neurotransmitters, phenylalanine contributes to mental alertness and emotional stability[15].

Improves Vitiligo Symptoms: Phenylalanine may help in the treatment of vitiligo, a condition characterized by skin depigmentation. When combined with ultraviolet (UV) light therapy, phenylalanine has been shown to aid melanin production, which is critical for skin pigmentation[\[15\]](#).

Mood Enhancement: Phenylalanine has been linked to improvements in mood, potentially benefiting individuals with mood disorders[\[17\]](#).

Weight Management: There is some evidence to suggest that phenylalanine may assist in maintaining ideal body weight[\[17\]](#).

Potential Risks and Side Effects

While phenylalanine is generally well-tolerated at standard dosages, it can cause side effects such as anxiety, headaches, insomnia, and gastrointestinal issues in some individuals, especially when taken in excessive amounts[\[15\]\[16\]](#). Specific populations, such as individuals with phenylketonuria (PKU), must be particularly cautious, as their bodies cannot properly metabolize phenylalanine. This can lead to a harmful accumulation of phenylalanine in the brain, resulting in severe neurological consequences including intellectual disabilities and seizures[\[15\]\[16\]](#).

Additionally, phenylalanine can interact with certain medications. For example, it may inhibit the absorption of baclofen and should be avoided by individuals taking levodopa for Parkinson's disease due to potential adverse effects[\[16\]\[18\]](#).

Phenylalanine Deficiency

Phenylalanine deficiency is rare, as it is typically obtained through adequate protein consumption, which is commonly found in foods such as meat, fish, eggs, dairy, nuts, seeds, and soy products[\[16\]](#). Symptoms of insufficient phenylalanine intake may include dry skin, hair loss, frequent illness, and muscle loss, but these are generally indicative of an overall protein deficiency rather than a specific lack of phenylalanine[\[15\]\[16\]](#).

Recommended Intake

The recommended daily intake of phenylalanine varies by age and other factors, generally ranging from 9.03 to 15.9 mg/kg/day for most individuals[\[16\]\[4\]](#). Maintaining a balanced diet that includes adequate protein is typically sufficient for achieving the necessary levels of phenylalanine.

Research and Studies

Phenylalanine (Phe) has been the subject of extensive research, particularly concerning its implications in metabolic disorders like phenylketonuria (PKU). Studies have explored various genetic and therapeutic approaches to manage and potentially correct the metabolic dysfunction associated with elevated levels of phenylalanine.

Genetic Approaches

Recent advancements in genetic research have introduced innovative methods such as prime editing and base editing for correcting genetic variants responsible for PKU. A study presented at the American Society of Human Genetics (ASHG) annual meeting highlighted the use of prime editing to address the c.1222C>T variant in the phenylalanine hydroxylase (PAH) gene, the most common variant causing PKU globally. Researchers demonstrated that this technique significantly lowered Phe buildup in animal models without adversely affecting liver function[\[19\]\[20\]](#).

Pharmacological Interventions

Current pharmacological strategies for PKU management include two FDA-approved agents: sapropterin dihydrochloride and pegvaliase. Sapropterin works by enhancing the residual activity of the PAH enzyme, while pegvaliase serves as an enzyme substitution therapy for individuals who do not achieve adequate Phe control with dietary modifications[\[21\]\[22\]](#). These treatments represent critical components of lifelong PKU therapy, which primarily involves dietary restrictions and careful monitoring of Phe levels[\[23\]\[24\]](#).

Innovative Screening Techniques

Researchers are also investigating non-invasive screening methods to identify PKU in newborns. These potential alternatives include analyzing saliva, urine, or breath samples, which could complement or even replace traditional blood tests, facilitating early detection and intervention[\[25\]](#).

Future Directions in Gene Therapy

The exploration of gene therapy for PKU is promising, with strategies focusing on gene addition and gene editing using techniques like CRISPR. Early results from animal studies have shown reductions in Phe levels and improvements in symptoms, paving the way for ongoing human clinical trials that may offer long-term solutions for affected individuals[\[25\]](#).

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