#### **Valine**

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### summary

Valine is an essential branched-chain amino acid (BCAA) vital for protein synthesis, energy production, and metabolic regulation in the human body. With the molecular formula C5H11NO2, valine is unique among amino acids due to its branched structure, which facilitates its role in various biological functions, including muscle metabolism, cognitive support, and nitrogen balance regulation.[1][2][3] Valine cannot be synthesized by the body and must be obtained through dietary sources, making it crucial for maintaining overall health and physical performance, particularly for athletes and those engaged in intense physical activity.[4][5]

Notably, valine is integral to metabolic processes, undergoing biosynthesis primarily in plants and microorganisms, while animals rely on dietary intake to meet their needs.[6] The catabolism of valine plays a significant role in energy generation and is linked to the metabolism of other branched-chain amino acids like leucine and isoleucine.[7][8] Disruptions in valine metabolism can lead to severe health conditions, including metabolic disorders such as maple syrup urine disease (MSUD) and insulin resistance, which are associated with obesity and type 2 diabetes.[9][10][11]

The significance of valine extends to supplementation, where it is commonly marketed to enhance muscle growth, athletic performance, and recovery. However, the efficacy of BCAA supplementation remains a topic of ongoing debate within the scientific community, with mixed results from clinical studies.[12][4] Research is increasingly focused on understanding the complex roles of valine in metabolic health, aging, and its interactions with other dietary components, highlighting the need for a nuanced approach to nutrition and supplementation strategies.[2][4][13]

### **Chemical Structure**

Valine is classified as one of the branched-chain amino acids (BCAAs), which include leucine and isoleucine. The term "branched-chain" refers to the specific chemical structure of these amino acids, characterized by a central carbon atom that is attached to three or more carbon atoms, creating a branched configuration[1][2].

#### Molecular Formula

The molecular formula of valine is C5H11NO2, indicating that it consists of five carbon atoms, eleven hydrogen atoms, one nitrogen atom, and two oxygen atoms. This composition is essential for its function in protein synthesis and metabolism within the body[4].

### Stereochemistry

Valine exists in two enantiomeric forms: L-valine and D-valine. The L-form is the biologically active isomer, which is utilized in protein synthesis, while the D-form is less common and does not play a significant role in human metabolism[3][7]. The presence of a chiral center in its structure allows valine to exhibit specific interactions with enzymes and receptors in biological systems[2].

#### Role in Protein Structure

As an essential amino acid, valine contributes to the structure and function of proteins. It participates in the formation of hydrophobic interactions within protein molecules, which are crucial for maintaining the stability and three-dimensional conformation of proteins. Valine's branched structure allows it to fit into protein pockets and influences protein folding, which is vital for biological activity[1][14].

## Biosynthesis

Valine is a branched-chain amino acid that plays a crucial role in energy generation and protein synthesis. The biosynthesis of valine primarily occurs in microorganisms and plants, as animals lack the enzymatic pathways necessary for its synthesis[6]. The biosynthetic pathway consists of four main enzymatic steps, starting with pyruvate, which is derived from the glycolytic pathway[6].

### **Enzymatic Steps in Valine Biosynthesis**

Formation of ±Acetolactate: In the first step, pyruvate is converted into ±acetolactate by the enzyme acetohydroxy acid synthase. This reaction represents the initial commitment of carbon skeletons towards valine production[6].

Conversion to  $\pm \cancel{B}$  ihydroxyisovalerate: The second step involves the action of acetohydroxy acid isomeroreductase, which catalyzes the conversion of  $\pm a$ cetolactate to  $\pm a$  ihydroxyisovalerate through an auto-displacement mechanism that transfers methyl groups [6].

Formation of ±Ketoisovalerate: The third step is catalyzed by dihydroxy-acid dehydratase, which converts ±Aihydroxyisovalerate into ±ketoisovalerate. Interestingly, this enzyme is inhibited by valine itself, which demonstrates a feedback regulation mechanism[6].

Synthesis of Valine: Finally, in the last step, branched-chain amino acid transaminase (BCAT) catalyzes the reaction of <u>#ke</u>toisovalerate to produce valine[6].

#### Industrial Production

In industrial applications, valine is commonly produced using mutant strains of microorganisms, particularly and (E. coli)[6][4]. These organisms have been genetically engineered to enhance the efficiency of valine biosynthesis, making them suitable platforms for large-scale production[3][7].

The regulation of valine metabolism is tightly controlled by various factors, including the phosphorylation state of the branched-chain ketoacid dehydrogenase (BCKDH) complex, which plays a pivotal role in the catabolism of branched-chain amino acids (BCAAs)[3][4].

#### Metabolism

#### Overview of Valine Catabolism

Valine, a branched-chain amino acid (BCAA), undergoes a series of metabolic processes primarily in the mitochondria. The initial step in its catabolism involves the removal of the amino group through transamination, producing alpha-ketoiso-valerate (KIV). This alpha-keto acid is subsequently converted into isobutyryl-CoA via oxidative decarboxylation, a reaction catalyzed by the branched-chain alpha-ketoacid dehydrogenase complex (BCKDH). The isobutyryl-CoA is then further oxidized and rearranged to succinyl-CoA, which can enter the citric acid cycle, providing direct fuel for muscle tissue metabolism[7][15][16].

### Pathway and Enzymatic Reactions

The degradation of valine shares common initial steps with the other BCAAs, leucine and isoleucine, which also undergo reversible transamination to yield their respective alpha-keto acids. Specifically, the transamination of valine produces KIV, while leucine generates alpha-ketoisocaproate (KIC), and isoleucine results in alpha-keto-ß-methylvalerate (KMV)[7][4]. This metabolic pathway not only generates energy but also produces critical intermediates for the tricarboxylic acid (TCA) cycle, such as acetyl-CoA and succinyl-CoA, and other metabolites like 3-hydroxyisobutyrate, which plays a role in fatty acid uptake[7].

### Interorgan Cycling and Regulation

Valine metabolism is tightly regulated and can be affected by various physiological conditions, including dietary intake and exercise. For instance, low glycogen availability during exercise has been shown to influence the serum levels of branched-chain amino acid metabolites, including those derived from valine[17]. Additionally, interorgan cycling of BCAAs and their ketoacids is essential for maintaining metabolic homeostasis, with the liver and muscle tissues playing key roles in this process[4][8].

### Medical Significance and Disorders

Disruptions in valine metabolism can lead to several metabolic diseases, including maple syrup urine disease (MSUD) and methylmalonic acidemia, which are characterized by an inability to properly degrade BCAAs[9]. Understanding the pathways of valine catabolism is crucial for developing therapeutic strategies for these conditions, as well as for enhancing metabolic health in the context of exercise and dietary practices[18][17].

## Functions in the Body

Valine, an essential branched-chain amino acid (BCAA), plays a crucial role in various physiological functions within the body. As one of the building blocks of proteins, valine is integral to protein synthesis, helping to maintain cellular structure and function, and promoting muscle repair and growth, especially in individuals engaged in regular physical activity such as athletes and bodybuilders[3][5].

### **Energy Supply**

One of the primary functions of valine is its ability to supply energy. It helps prevent the breakdown of muscle during periods of energy depletion, thus sustaining muscle energy supply [19][20]. Valine is involved in gluconeogenesis, particularly in the liver, contributing to glucose production which is a vital energy source for the body. This function is particularly significant during intense exercise when energy demands are elevated [5][20].

### Cognitive and Neurological Support

In addition to its metabolic roles, valine supports cognitive function by participating in the production of neurotransmitters. These are essential for maintaining mental clarity, memory, and concentration, potentially contributing to an improved mood[5][8].

### Wound Healing and Recovery

Valine also promotes wound healing by supporting tissue repair processes. This aspect is particularly important for individuals recovering from injuries or surgical procedures, as adequate valine levels can enhance recovery outcomes[5][20].

### Regulation of Nitrogen Metabolism

Valine plays a critical role in body nitrogen metabolism, which is essential for maintaining a positive nitrogen balance necessary for muscle growth and repair[21][3]. The metabolism of valine is closely linked with that of other BCAAs and is regulated by complex biochemical pathways that ensure its availability for various bodily functions[8][4].

## **Dietary Sources**

Valine, an essential branched-chain amino acid, is found in various animal- and plant-based foods, allowing most individuals to meet their daily requirements through a balanced diet. Major sources of valine include animal proteins, particularly meat, eggs, and poultry, which provide the highest concentrations of this amino acid[22][5].

#### **Animal Sources**

Animal-derived foods are considered the best sources of valine.

Meat: Beef, pork, and chicken are rich in valine and contribute significantly to overall protein intake.

Eggs: Eggs not only supply valine but also offer a complete amino acid profile and other essential nutrients.

Dairy Products: Milk, cheese, and yogurt are excellent sources of valine and provide additional vitamins and minerals, enhancing nutrient bioavailability[23].

#### **Plant Sources**

For those following a vegetarian or vegan diet, several plant-based foods are also high in valine:

Legumes: Foods such as lentils, beans, and peas are excellent sources of valine and provide substantial plant-based protein, making them ideal for vegetarians and vegans[5].

Nuts and Seeds: Almonds, peanuts, sunflower seeds, and pumpkin seeds not only provide valine but also offer healthy fats and fiber.

Whole Grains: Grains like quinoa and brown rice are good sources of valine and other essential amino acids, along with beneficial fiber and complex carbohydrates[5].

Soy Products: Soybeans, tofu, and other soy-derived foods are rich in valine and serve as important protein sources in plant-based diets[5].

#### Seaweed

Seaweed is another noteworthy source of valine, particularly in Asian cuisines, where it is commonly included in dishes like sushi and miso soup. Besides valine, seaweed provides a variety of essential minerals, including iodine[5].

By incorporating a diverse range of these foods into daily meals, individuals can effectively ensure adequate intake of valine and other essential amino acids necessary for overall health and well-being.

## **Deficiency and Health Implications**

Valine deficiency can lead to several metabolic disturbances and health complications. In various hypermetabolic states such as sepsis, burn injury, trauma, and cancer, the levels of branched-chain amino acids (BCAAs), including valine, may fluctuate inconsistently, leading to alterations in metabolism and systemic inflammatory response syndrome (SIRS) characterized by neuro-humoral abnormalities[8][4]. These conditions can result in insulin resistance, myofibrillar protein degradation, and significant lean body mass depletion, ultimately risking multisystem organ failure if the hypermetabolic state persists[8].

Additionally, individuals suffering from certain inherited metabolic disorders, such as maple syrup urine disease (MSUD), face severe consequences from impaired valine metabolism. In MSUD, defects in the branched-chain keto acid dehydrogenase (BCKDH) complex lead to toxic accumulation of valine and its byproducts, causing neurological symptoms and potential mortality if not properly managed through dietary restrictions and specialized amino acid supplementation[3][10].

Valine deficiency is also a concern in the context of chronic renal failure (CRF) and hyperammonemia, where altered amino acid metabolism can further exacerbate health issues. Individuals with urea cycle disorders (UCD) may experience low BCAA levels, indicating a need for therapeutic interventions involving valine supplementation, though such treatments remain underutilized in clinical practice[8][12][4].

Furthermore, chronic elevation of BCAAs, including valine, has been associated with metabolic diseases such as obesity, type 2 diabetes, and metabolic-associated fatty liver disease (MAFLD). The dysregulation of BCAA levels can contribute to insulin resistance, which is a key pathological feature of metabolic syndrome[11][10][2]. As such, maintaining appropriate levels of valine is crucial for metabolic health and the prevention of related disorders.

# Supplementation

L-valine is a branched-chain amino acid (BCAA) that plays a critical role in various bodily functions, including muscle metabolism and immune support. It is classified as an essential amino acid, meaning it cannot be synthesized by the body and must be obtained through dietary sources or supplementation[24][25]. While a normal diet typically provides sufficient L-valine, many individuals, particularly athletes and bodybuilders, choose to supplement this amino acid to enhance muscle growth, increase athletic performance, and improve recovery[26][12].

#### Forms of Supplementation

L-valine supplements are available in various forms, including capsules, powders, tablets, and liquid extracts. When selecting a valine supplement, it is essential to review the ingredient list, as some products may contain additional BCAAs like leucine and isoleucine, while others may include other components that cater to specific dietary needs, such as being gluten-free, vegan, or organic[12]. However, consumers should be cautious, as many valine supplements may derive from animal sources, and the capsules may contain gelatin, which is not suitable for vegans[12].

### Recommended Dosage

The recommended intake of valine can vary based on individual health status and activity level. A study proposed a mean requirement of approximately 17 mg of valine per kilogram of body weight per day for healthy adults[27]. However, athletes may require higher doses to support their intensive training regimens and recovery processes. It is advisable for individuals to consult healthcare professionals before beginning any new supplementation, particularly if they have pre-existing health conditions[24][25].

### Efficacy and Research

Despite the popularity of BCAA supplementation, including L-valine, research on their efficacy remains mixed. Some clinical trials have not provided strong evidence supporting the beneficial effects of BCAA supplements, and potential adverse effects, particularly concerning ammonia production during metabolism, have been noted[8-][2]. As a result, further research is needed to fully understand the role of L-valine and other BCAAs in muscle growth, exercise endurance, and overall metabolic health[4].

#### Research and Future Directions

Research on valine, a branched-chain amino acid (BCAA), has expanded significantly in recent years, focusing on its role in metabolic processes and its implications for health. Emerging evidence suggests that valine catabolism is intricately linked to lipid metabolism, indicating that dietary strategies that emphasize one macronutrient over others may not provide a comprehensive understanding of its effects on health outcomes[4].

### Valine and Protein Synthesis

Studies indicate that whole foods, such as whole eggs, can enhance myofibrillar protein synthesis more effectively than isolated protein sources like egg whites. This difference may be partially attributed to the amino acid profile, including valine, which plays a crucial role in stimulating protein synthesis, especially in response to resistance exercise [4]. Understanding the interplay between valine and other dietary components, particularly fatty acids, remains a critical area for future research.

### Implications for Aging and Insulin Resistance

Valine has also been implicated in the modulation of insulin resistance and longevity. Some studies suggest that increased valine levels may correlate with metabolic conditions associated with aging, such as insulin resistance[2]. The contradiction in the role of BCAAs, including valine, in lifespan and metabolic health highlights the need for further investigation into their complex roles within various populations, particularly the elderly[2].

### Nutrient Bioavailability and Dietary Interventions

Future research should also focus on nutrient bioavailability from complex foods and how different dietary interventions can optimize the intake and effectiveness of valine and other amino acids. There is a growing need to understand how food matrices and combinations of nutrients affect the absorption and utilization of valine, especially in populations requiring specialized nutritional support, such as athletes or individuals with metabolic disorders[23].

## Clinical Applications and Supplements

The potential clinical applications of valine supplementation in various health conditions, including metabolic syndromes and recovery from surgery or illness, warrant further exploration. Meta-analyses have shown positive outcomes with BCAA supplementation, indicating that valine might offer benefits in specific clinical settings, such as improving insulin sensitivity in obese individuals[13][8]. Continued research in this area could lead to targeted dietary recommendations and interventions that leverage the unique properties of valine.

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