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Review Article

The Physiological and Biochemical Aspects of Betaine in Athletes

Mehmet Alperen Ustüner and Muhammed Yildiz*

Department of Health Care Servıces, Artvin Çoruh University, Artvin, Türkiye

Abstract

Betaine is a derivative of amino acids that exhibits numerous beneficial effects on the organism. It is found in almost all tissues, with the highest concentrations in the liver, kidneys, and testes. Additionally, endogenous betaine synthesis occurs in the liver and kidneys from choline, which is an essential nutrient. Initially discovered as a natural by-product of sugar beet, its color arises from purple and yellow pigments collectively known as betalains (betacyanin and betaxanthin). These betaines possess potential antioxidant properties, and the antioxidant capacity of red beets has been reported to play a protective role against oxidative stress. Betaine is a zwitterion with a positively charged trimethylammonium group and a negatively charged carboxyl group at a physiological pH range; thus, it does not require any counter ions for electroneutrality in the cytoplasm. Betaine has gained popularity as a dietary supplement not only among bodybuilders but also among athletes from various disciplines due to its positive effects on body composition (muscle mass increase) and training performance. Studies indicate that betaine enhances muscle mass and endurance. In recent years, comprehensive summaries of some of the critical biological roles of betaine have emerged. Evidence has been identified that betaine effectively limits many diabetes-related conditions. Betaine treatment improves glucose tolerance and insulin action, strongly associated with changes in insulin-sensitive tissues such as skeletal muscle, adipose tissue, and the liver. Betaine supplementation positively influences multiple genes that are dysregulated in diabetes. In the liver, betaine synthesis and subsequent demethylation play a vital role in one-carbon metabolism. Betaine has become widely used as a pre-workout product designed to support muscle building among high-level athletes during periods of intense training.

Keywords: Betaine; Supplement; Sports; Metabolism

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***Corresponding author:** Muhammed Yildiz, Department of Health Care Servıces, Artvin Çoruh University, Artvin, Türkiye

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Introduction

Betaine

Betaine (N,N,N-trimethylglycine) is a derivative of amino acids that provides significant physiological benefits, including its essential roles in cellular homeostasis, methylation processes, and protection against environmental and metabolic stressors. As the trimethyl derivative of glycine, betaine is naturally present in human plasma due to endogenous synthesis in the liver and kidneys and can also be obtained through dietary sources such as whole grains, spinach, shrimp, and beets [1,2]. Betaine's critical function extends to cellular defense against universal stressors like high temperature and osmotic imbalance, acting as a methyl group donor in various biochemical pathways across microorganisms, plants, and animals [3]. In the United States, the average dietary intake of betaine is approximately 100-300mg/day, though endogenous synthesis from choline in the liver and kidneys also contributes significantly. Recent comprehensive summaries have highlighted the multifaceted biological roles of betaine [4,5].

Betaine primarily serves as both an osmolyte and a methyl group donor, playing a pivotal role in maintaining cellular osmotic balance and supporting systemic methylation processes. As an osmolyte, betaine preserves cell integrity under stress by stabilizing intracellular

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osmotic pressure. Concurrently, its role as a methyl donor facilitates critical biochemical pathways, such as the remethylation of homocysteine to methionine, which is fundamental for protein synthesis and epigenetic regulation. Its zwitterionic molecular structure featuring a positively charged trimethylammonium group and a negatively charged carboxyl group helps maintain intracellular osmotic equilibrium without requiring counter-ions [6-8].

Betaine biochemistry

Betaine, widely recognized as a methyl derivative of glycine, holds significant biochemical relevance due to its dual roles in osmotic regulation and methylation processes. The term "glycine betaine" distinguishes it from other derivatives such as proline betaine and alanine betaine. Betaine (CAS no. 107-43-7), also known as trimethylglycine or N,N,N-trimethylammonioacetate, is commercially marketed in its pharmaceutical form as Cystadane. Discovered as a natural byproduct of sugar beets (Beta vulgaris), sugar beets remain the primary commercial source of betaine. Table 1 provides an overview of its physical and chemical properties [1].

Table 1: Betaine physical and chemical properties.

Property	Description
CAS number	107-43-7
Molecular Formula	C5H11NO2
Molecular Weight	117.1
Color	White hygroscopic crystals
Taste	Sweet
pKa	1.83 at 0°C
Melting Point	293°C

At physiological pH, betaine exists as a zwitterion with a positively charged trimethylammonium group and a negatively charged carboxyl group (Figure 1). This zwitterionic nature eliminates the need for counter-ions to maintain cytoplasmic electroneutrality [9]. Betaine is stable, non-toxic, and highly water-soluble. In the presence of strong acids, anhydrous betaine forms salts such as betaine hydrochloride, which serves as a source of hydrochloric acid for individuals with hypochlorhydria. Once in the alkaline environment of the small intestine, betaine hydrochloride reverts to its original form [10,11].

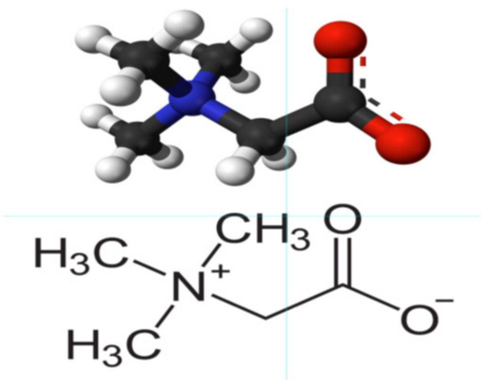

Figure 1: Structure of betaine [1].

When excreted or released into hypersaline environments, betaine undergoes microbial degradation through aerobic and anaerobic pathways, yielding products such as trimethylamine ($(CH_3)_3N$) and methylamine (CH_3NH_2). In the liver, betaine synthesis and subsequent demethylation are critical for one-carbon metabolism. Osmolytes like betaine-small organic compounds that cells accumulate under stressful external conditions-interact with macromolecules in non-disruptive ways, stabilizing their structures and functions. Unlike inorganic ions, which destabilize proteins and nucleic acids at high concentrations, osmolytes like betaine can be regulated without interfering with cellular processes [12-14].

Betaine's ability to stabilize proteins arises from its exclusion from the hydration layer surrounding macromolecules, promoting compact folding and structural integrity. Recent studies have underscored betaine's capacity to modulate water structure around macromolecules, further stabilizing their conformations [12,15]. Betaine's strong hydrogen bonding with water molecules-particularly its carboxylate and methyl groups-creates a dynamic hydration sphere that does not immobilize water, allowing it to influence the structural dynamics of surrounding biomolecules effectively [16-19]. Betaine has been shown to enhance albumin hydration, form a near-complete monolayer of water around proteins, and maintain hemoglobin solvency. In liver macrophages (Kupffer cells), betaine regulates immune responses by suppressing hyperosmolarity-induced tumor necrosis factor-α release and prostaglandin synthesis while inhibiting cyclooxygenase-2 expression [20,21].

Betaine's physiological roles are diverse and continually being elucidated. Both the kidneys and liver and potentially other organs express transport systems for betaine uptake and accumulation. In the kidney, betaine plays a vital role in osmoprotection within the inner medulla, where osmolarity is persistently high. Betaine accumulation through the Na+- and Cl^--dependent betaine-GABA transporter (BGT1) enables cells to maintain osmotic balance and normal volume under these conditions [22,23]. Its chaperone effect further protects intracellular proteins from the denaturing effects of urea and NaCl, which are present at high concentrations in the renal medulla. In the liver, betaine content exceeds that of other organs, supported by the abundance of BGT1 transport proteins. Betaine primarily serves as a methyl donor in one-carbon metabolism, where it facilitates remethylation of homocysteine to methionine. This process is crucial for DNA replication, repair, and epigenetic regulation. Betaine-homocysteine methyltransferase (BHMT), predominantly expressed in the liver and kidneys, catalyzes this reaction, with dimethylglycine as a byproduct. BHMT activity is tightly regulated by co-factors such as potassium ions [24,28-33].

Betaine's therapeutic relevance has been demonstrated in various contexts. In humans, it is effective for treating severe hyperhomocysteinemia caused by homocystinuria, a genetic disorder linked to neurodegenerative diseases and vascular complications. Betaine supplementation has also shown efficacy in lowering plasma homocysteine levels in individuals with mild hyperhomocysteinemia [5,34]. In livestock, betaine's use is well-documented for increasing lean muscle mass and reducing fat content. These effects are attributed to its methyl donor role in lipid metabolism, promoting phosphatidylcholine synthesis and reducing triglyceride accumulation. Betaine also enhances nutrient absorption and stabilizes cellular structures under stress, optimizing growth and muscle development [5,6]. Although studies on humans have yielded mixed results regarding its effects on body composition, betaine remains a focus of interest in sports nutrition and recovery [35-37].

Experimental Studies on Betaine

In recent years, pre-workout supplements have gained significant attention in the field of sports nutrition, particularly for their capacity to enhance acute exercise performance and facilitate recovery. These formulations typically consist of synergistic combinations of ingredients such as caffeine, creatine, beta-alanine, amino acids, and nitric oxide precursors. Among these components, betaine has emerged as a crucial ingredient both as a standalone supplement and as part of multi-component pre-workout products. Despite its growing prominence, research on the use of betaine as a dietary supplement in Turkey remains limited, which underscores the need for further investigation into its applications and efficacy. A systematic review conducted by Inés Guinaga et al. [38] examined the effects of various nutritional interventions on professional and semi-professional soccer players. By analyzing data from PubMed, Scopus, Web of Science, and clinical trial records, the authors identified 16 randomized clinical trials involving 310 participants. Their findings revealed that while no intervention significantly accelerated recovery, several nutritional strategies, including betaine supplementation, demonstrated notable improvements in performance metrics such as endurance, speed, agility, strength, and anaerobic capacity. The review highlighted the potential for betaine to optimize physical performance, positioning it as a valuable addition to athletes' dietary regimens. Moreover, the authors suggested that further exploration of the specific conditions under which betaine is most effective could broaden its applicability to a wider range of sports disciplines [38]. Leena and Thomas expanded the scope of betaine's research by investigating its role in neurological function, particularly its modulation of GABAergic and glycinergic neurotransmission. Their study underscored betaine's dual benefits, combining its enhancement of athletic performance with its therapeutic potential for neurological disorders such as epilepsy and neurodegenerative diseases. This duality positions betaine as a promising prophylactic agent against sports-related concussions. Additionally, their findings emphasized that betaine supplementation may bolster cognitive resilience in athletes, highlighting its importance not only for physical performance but also for mental health and well-being. These findings open avenues for further research into betaine's neuroprotective mechanisms and its broader implications for athlete care [39].

Emilia et al. [40] conducted a controlled trial to evaluate the effects of a three-week betaine supplementation protocol on body composition, CrossFit performance, and endocrine parameters. The study investigated the efficacy of two dosages (2.5g/day and 5.0g/day) and explored potential interactions with methylenetetrahydrofolate reductase (MTHFR) genotypes. Their findings indicated a significant increase in testosterone levels with both dosages, while no effects were observed on cortisol or insulin-like growth factor concentrations. Interestingly, the lack of interaction between betaine dosage and MTHFR genotype suggests that betaine's benefits are robust across genetic variations, underscoring its consistent efficacy as an ergogenic aid in high-intensity training scenarios. The study concluded that betaine supplementation not only enhances CrossFit performance but also positively impacts anabolic hormonal responses, which may have implications for long-term training adaptations [40]. Hadi Nobari et al. [41] investigated the long-term effects of a 14-week betaine supplementation regimen on young professional soccer players. Using a double-blind, position-matched design, the study administered 2g/day of betaine under a standardized nutritional protocol. Key performance metrics, including VO2max, sprint performance, muscular strength, and repeated sprint capacity, were assessed at three intervals: preseason (P1), midseason (P2), and postseason (P3). The results demonstrated significant improvements in aerobic capacity and repeated sprint performance, reaffirming betaine's role as a valuable nutritional strategy for maintaining and enhancing athletic performance throughout a competitive season. The findings also emphasized betaine's ability to sustain performance levels despite the cumulative physical demands of an intense soccer season, highlighting its utility for athletes in endurance-based sports [41].

Results

Methylation is a critical biological process that occurs billions of times per second in every cell of the human body, playing an indispensable role in maintaining overall health. This process involves the transfer of a methyl group to various amino acids, proteins, carbohydrates, lipids, and DNA within each tissue and cell. During methylation, the methyl group is transferred from one molecule to another, enabling the recipient molecule to become functional. One-carbon metabolism comprises interconnected metabolic pathways, including the folate and methionine cycles, which supply the 1C or methyl groups necessary for the synthesis of DNA, polyamines, amino acids, creatine, and phospholipids. Molecules receiving the methyl group undergo activation, and this process is also required to detoxify harmful substances for their excretion from the body.

Methylation is crucial for supporting immune function, reducing inflammation, synthesizing neurotransmitter hormones, and facilitating DNA synthesis and repair. Approximately half of the methylation process is supported by folate and vitamin B12, while the other half is facilitated by betaine and choline. S-adenosylmethionine (SAM) serves as a powerful aminopropyl and methyl donor within these methylation cycles. Betaine is essential for the remethylation of methionine, the precursor to SAM, which acts as the universal methyl donor in the body. Despite its critical role, the precise mechanisms underpinning betaine's effects and its long-term implications for human health remain to be fully elucidated. This study aims to present the evidence supporting the use of betaine as an ergogenic and aesthetic aid and to explore the potential mechanisms underlying these effects. Future research should focus on evaluating the impacts of betaine supplementation among athletes, particularly its effects on performance and recovery. Such investigations will provide valuable insights into the practical applications of betaine as a dietary supplement in sports nutrition and related fields.

Experimental studies consistently highlight betaine's versatility and multifaceted benefits as a dietary supplement. Beyond its well-documented effects on athletic performance, emerging research underscores its potential in therapeutic contexts, particularly in neuroprotection and hormonal optimization. Future studies should prioritize elucidating the precise pathways through which betaine exerts these effects, determining optimal dosages for diverse populations, and assessing its long-term impacts on both health and performance. These efforts will facilitate the seamless integration of betaine into evidence-based sports nutrition protocols, ensuring its effective application across a range of athletic and clinical settings.

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