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Creatine Supplementation and Cognitive Function: Mechanisms, Human Evidence, and Future Directions — A Narrative Review

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Abstract

Background.
Creatine is a widely used dietary supplement, mainly known for its role in sports performance and muscle energy metabolism. Recently, its potential role in brain function has gained increasing attention due to its involvement in the phosphocreatine system and ATP regeneration.

Aim.
The aim of this review was to summarize current evidence on the potential effects of creatine supplementation on cognitive function, including possible mechanisms, human studies, modifying factors, and safety aspects.

Material and methods.

This review analyzed scientific literature on creatine metabolism, brain bioenergetics, and cognitive outcomes in humans. Randomized controlled trials, systematic reviews, meta-analyses, narrative reviews, and relevant observational studies were included.

Results.
Current evidence suggests that creatine may support selected cognitive domains, especially memory, reasoning, processing speed, and mental fatigue. Benefits may be more evident in vegetarians, older adults, and individuals exposed to sleep deprivation or increased cognitive demand. However, findings remain inconsistent, particularly in healthy young adults.

Conclusions.
Creatine appears to be a promising but not fully confirmed nutritional strategy for supporting cognitive function. Further well-designed randomized controlled trials are needed to identify responsive populations, optimal protocols, and clinically meaningful effects.

Keywords: creatine supplementation; cognitive function; brain bioenergetics; phosphocreatine system; memory; mental fatigue; sleep deprivation; nutritional supplementation**.**

1. Introduction

Creatine is one of the most widely used dietary supplements, particularly among athletes and individuals engaged in resistance training or gym-based exercise. It is best known for its role in improving high-intensity exercise performance, increasing intramuscular phosphocreatine stores, and supporting training adaptations. Due to its relatively well-established efficacy and safety profile, creatine monohydrate is commonly regarded as one of the most extensively studied ergogenic supplements in sports nutrition [1]. Although creatine has traditionally been discussed mainly in the context of skeletal muscle metabolism and physical performance, recent research has increasingly focused on its potential effects beyond the muscular system, including its possible role in brain function and cognitive performance [2].

The biological rationale for investigating creatine in relation to cognition is based on its involvement in cellular energy metabolism. The brain is an organ with high energy demands, and adequate adenosine triphosphate availability is essential for processes such as attention, memory, information processing, and executive function. Creatine and phosphocreatine participate in the creatine kinase system, which helps buffer and rapidly regenerate ATP in tissues with fluctuating energy requirements. Since the brain also relies on efficient energy metabolism, creatine may theoretically support cognitive processes, especially under conditions of increased metabolic stress, such as sleep deprivation, aging, neurological disorders, or low baseline creatine availability [2, 3]. Importantly, oral creatine supplementation has been shown to increase total creatine concentration in the human brain, although the magnitude of this increase may vary between individuals [4].

Initial human studies suggested that creatine supplementation may positively influence selected cognitive domains. In a double-blind, placebo-controlled, crossover trial, Rae et al. observed improvements in working memory and intelligence-related tasks following creatine supplementation in young adult vegetarians [5]. These findings are particularly relevant because individuals consuming vegetarian or vegan diets may have lower dietary creatine intake compared with omnivores. Subsequent studies and reviews have examined whether creatine may improve memory, attention, reasoning, processing speed, and mental fatigue in different populations. A systematic review of randomized controlled trials suggested that oral creatine supplementation may improve short-term memory and reasoning in healthy individuals, although its effects on other cognitive domains remain less consistent [6].

More recent evidence continues to suggest potential cognitive benefits of creatine, but the overall conclusions remain cautious. A systematic review and meta-analysis reported that creatine monohydrate supplementation may have beneficial effects on cognitive function in adults, particularly in domains such as memory, attention time, and information processing speed [7]. However, not all studies have demonstrated significant improvements, and the heterogeneity of available research makes interpretation difficult. Differences in study design, supplementation dose, intervention duration, baseline diet, participant age, cognitive tests, and health status may partly explain the inconsistent findings. Moreover, the European Food Safety Authority concluded that, based on the available evidence, a cause-and-effect relationship has not been established between creatine supplementation and improvement in cognitive function [8].

Therefore, despite growing interest in creatine as a potential nutritional strategy for supporting brain function, its role in cognitive enhancement remains uncertain. Further evaluation of the current evidence is needed to clarify which cognitive domains may be most responsive to creatine supplementation, which populations are most likely to benefit, and what mechanisms could explain the observed effects. This review aims to summarize the available evidence on the relationship between creatine supplementation and cognitive function, with particular attention to brain energy metabolism, human intervention studies, potential modifying factors, and current limitations in the field.

Research Objective

The objective of this review is to summarize and critically analyze current evidence on the effects of creatine supplementation on cognitive function, with particular attention to brain energy metabolism, cognitive domains, and populations most likely to benefit.

Research Problems

This review addresses the following research problems:

1. What mechanisms may explain the relationship between creatine supplementation and cognitive function?
2. Which cognitive domains may be influenced by creatine?

3. Do the effects differ depending on age, diet, baseline creatine status, sleep deprivation, or health condition?
4. Why are findings from human studies inconsistent?
5. Is current evidence sufficient to support creatine as a strategy for improving cognitive function?

Research Hypotheses

Based on the available literature, the following hypotheses were formulated:

1. Creatine may support cognition by improving brain energy availability through the phosphocreatine system and ATP regeneration.
2. Its effects may be stronger in individuals with increased brain energy demand, such as older adults, sleep-deprived individuals, or people exposed to mental fatigue.
3. Individuals with lower dietary creatine intake, including vegetarians and those following predominantly plant-based diets, may respond more favorably than omnivores.
4. Creatine may mainly affect memory, attention, processing speed, and mental fatigue.
5. Inconsistent findings may result from differences in study design, supplementation protocols, cognitive tests, and participant characteristics.

2. Research Materials and Methods

2.1. Participants

As this is a review article, no participants were recruited. The research material consisted of previously published studies on creatine supplementation and cognitive function, including randomized controlled trials, systematic reviews, meta-analyses, narrative reviews, and observational studies.

The analyzed studies included healthy young adults, older adults, vegetarians, individuals following predominantly plant-based diets, omnivores, sleep-deprived individuals, and selected clinical populations. Particular attention was given to studies assessing cognitive outcomes after oral creatine supplementation.

2.2. Procedure / Measures / Instruments

A structured literature search was conducted using PubMed, Google Scholar, Scopus, Web of Science, and ScienceDirect. Search terms included: "creatine supplementation," "creatine monohydrate," "cognitive function," "cognition," "memory," "attention," "executive function," "processing speed," "mental fatigue," "brain function," "sleep deprivation," "older adults," "vegetarians," and "brain bioenergetics."

Included publications were English-language studies involving humans, studies evaluating creatine supplementation or dietary creatine intake in relation to cognition, and papers discussing mechanisms linking creatine with brain energy metabolism. Studies unrelated to cognition, focused only on athletic performance, animal-only studies, non-peer-reviewed sources, conference abstracts without full text, and papers with insufficient methodology were excluded.

The main outcomes considered were memory, working memory, attention, reasoning, processing speed, executive function, and mental fatigue. The relevance and quality of publications were assessed narratively.

2.3. Data Collection and Analysis / Statistical Analysis

Data were extracted from abstracts and full texts, including study design, population, sample size, creatine dose, supplementation duration, cognitive outcomes, main findings, and limitations. The data were analyzed using narrative synthesis and compared according to population, cognitive domain, supplementation protocol, and direction of effect.

Due to heterogeneity in study designs, populations, cognitive tests, and supplementation protocols, no quantitative meta-analysis was performed. Results were summarized descriptively to identify consistent findings, mechanisms, and research gaps.

2.3.1. Statistical Software

No statistical software was used, as this review did not include original data analysis or meta-analytical calculations. Literature organization was performed manually and, where applicable, with citation management tools.

2.3.2. Statistical Methods

No original statistical testing was conducted. The findings were analyzed descriptively and narratively. Greater emphasis was placed on systematic reviews, meta-analyses, and randomized controlled trials, while observational studies and narrative reviews were used mainly for context and discussion of mechanisms and research gaps.

3. Research results - literature findings

3.1. Creatine Metabolism and Brain Bioenergetics

Creatine is a nitrogen-containing compound that can be obtained from dietary sources, mainly meat and fish, and can also be synthesized endogenously from amino acids. Its synthesis involves arginine, glycine, and methionine, with the participation of key enzymes such as arginine:glycine amidinotransferase and guanidinoacetate methyltransferase [9-11]. Although creatine is widely known for its role in skeletal muscle metabolism, it is also present in the brain, where it contributes to cellular energy homeostasis [2].

The brain obtains creatine through both transport from the circulation and local synthesis within the central nervous system. Creatine transport across the blood–brain barrier is mediated mainly by the creatine transporter SLC6A8, although this process appears to be limited compared with other tissues [3, 12]. Therefore, local creatine synthesis in brain cells may be important for maintaining adequate cerebral creatine availability [13].

Creatine plays an important role in the phosphocreatine system, which supports rapid regeneration of adenosine triphosphate during periods of increased energy demand. Through the creatine kinase reaction, phosphocreatine acts as an energy buffer and helps stabilize intracellular ATP levels in tissues with high and fluctuating energy requirements, including the brain [14,15]. This mechanism may be particularly relevant for neuronal activity, as cognitive processes require continuous and efficient energy supply.

Oral creatine supplementation may increase total creatine concentration in the human brain, although the response appears to vary between individuals. Dechent et al. demonstrated that creatine supplementation increased cerebral creatine levels, supporting the hypothesis that dietary supplementation can influence brain creatine availability [4]. However, the magnitude of this effect is generally smaller than that observed in skeletal muscle, which may be related to the limited transport of creatine across the blood–brain barrier [2, 3].

The potential relationship between creatine and cognitive function is based mainly on its role in brain bioenergetics. By supporting ATP buffering and cellular energy stability, creatine may help maintain cognitive performance, especially under conditions of increased brain energy demand, such as sleep deprivation, aging, mental fatigue, or neurological conditions or other metabolically demanding states [2, 15]. These mechanisms provide a biological rationale for further investigation of creatine supplementation as a possible nutritional strategy for supporting selected cognitive domains.

3.2. Mechanisms Linking Creatine with Cognitive Function

The main mechanism linking creatine with cognitive function is its role in cellular energy metabolism. Creatine participates in the phosphocreatine system, which helps regenerate adenosine triphosphate during periods of increased energy demand. Since neuronal activity requires continuous energy supply, this system may support cognitive processes such as memory, attention, and executive function [2, 14, 15].

Creatine may also contribute to cognitive performance by supporting mitochondrial function and cellular energy stability. Efficient mitochondrial activity is essential for maintaining neuronal function, especially in conditions associated with aging, fatigue, or neurological conditions or other metabolically demanding states. By helping to stabilize energy availability, creatine may reduce the negative effects of impaired cellular bioenergetics on brain function [2, 3, 15, 16].

Another possible mechanism involves the neuroprotective properties of creatine. Some studies suggest that creatine may help reduce oxidative stress and support neuronal survival under metabolically demanding conditions. Although much of this evidence comes from experimental and mechanistic studies, it provides a rationale for investigating creatine in relation to brain health and cognitive function [3, 15, 16].

The cognitive effects of creatine may be more visible when the brain is exposed to increased energy demand, such as during sleep deprivation or mental fatigue. In such conditions, creatine may help maintain cognitive performance by supporting brain energy metabolism.

Previous studies have reported beneficial effects of creatine on mental fatigue and selected cognitive tasks under sleep deprivation or high cognitive load [17-19].

Creatine may also influence brain function through mechanisms related to neurotransmission and excitotoxicity. By supporting cellular energy balance, creatine may help protect neurons against excessive metabolic stress and disturbances in neuronal signaling. However, this mechanism remains less clearly established than its role in brain bioenergetics and requires further investigation in human studies [2, 16, 20].

3.3. Evidence from Human Studies

Evidence from studies in healthy young adults is mixed and often shows limited cognitive benefits. Rawson et al. reported that six weeks of creatine supplementation did not improve cognitive processing in non-sleep-deprived young adults [21]. Similarly, Moriarty et al. found no significant improvement in cognitive performance after six weeks of creatine supplementation at moderate or high doses [22]. A larger randomized controlled trial by Sandkühler et al. also suggested that cognitive effects in healthy adults may be small or inconsistent [23].

Some studies suggest that creatine may have stronger cognitive effects in individuals with lower dietary creatine intake, such as vegetarians. Rae et al. found that creatine supplementation improved working memory and intelligence-related tasks in young adult vegetarians [5]. Benton and Donohoe also reported that creatine supplementation improved memory mainly in vegetarians, while effects in omnivores were less evident [24].

Creatine may be more effective when the brain is exposed to increased energy demand. Watanabe et al. showed that creatine supplementation reduced mental fatigue during repeated cognitive tasks [17]. McMorris et al. reported beneficial effects of creatine on selected cognitive and psychomotor outcomes during sleep deprivation [18]. More recently, Gordji-Nejad et al. found that a single high dose of creatine improved cognitive performance during partial sleep deprivation, supporting the hypothesis that creatine may be particularly relevant under metabolic stress [19].

Findings in older adults are also inconsistent. Alves et al. found that creatine supplementation, with or without strength training, did not significantly improve cognitive function in older women [25]. However, a systematic review and meta-analysis by Prokopidis et al. suggested that creatine supplementation may improve memory performance in healthy individuals, especially in older adults [26]. These findings indicate that age and baseline cognitive or metabolic status may influence the response to supplementation.

Systematic reviews and meta-analyses generally suggest that creatine may have potential benefits for selected cognitive domains, particularly memory and reasoning, but the evidence remains heterogeneous. Avgerinos et al. concluded that creatine may improve short-term memory and intelligence or reasoning in healthy individuals, while effects on other cognitive domains are less clear [6]. Xu et al. reported that creatine supplementation may have potential beneficial effects on cognitive function in adults; however, the evidence remains heterogeneous and larger, well-designed randomized controlled trials are needed to confirm these findings [7]. In contrast, the European Food Safety Authority concluded that the available evidence is insufficient to establish a clear cause-and-effect relationship between creatine supplementation and improved cognitive function [8].

3.4. Factors Modifying the Effects of Creatine on Cognition

Age may be an important factor influencing the cognitive response to creatine supplementation. Some evidence suggests that older adults may benefit more from creatine, possibly due to age-related changes in brain energy metabolism and cognitive vulnerability. A meta-analysis reported that creatine supplementation may improve memory performance, particularly in older individuals [26]. However, not all studies support this effect, as Alves et al. found no significant improvement in cognitive function among older women after creatine supplementation [25].

Dietary habits may also modify the effects of creatine on cognition. Individuals following vegetarian or predominantly plant-based diets usually have lower dietary creatine intake than omnivores, which may influence their response to supplementation. Studies have suggested that individuals following vegetarian diets may respond more favorably to creatine supplementation, especially in memory and reasoning tasks [5, 24].

Creatine may be more effective under conditions of increased cognitive or energetic demand, such as sleep deprivation, mental fatigue, or high cognitive load. In these situations, the brain may rely more strongly on efficient ATP regeneration. Studies have shown that creatine supplementation can reduce mental fatigue and improve selected cognitive outcomes during sleep deprivation or cognitively demanding tasks [17-19].

The dose and duration of creatine supplementation may influence cognitive outcomes, although the optimal protocol remains unclear. Some studies using several weeks of supplementation in healthy young adults did not observe significant cognitive improvement [21, 22]. In contrast, a single high dose of creatine improved cognitive performance during partial sleep deprivation, suggesting that the effect may depend not only on dose, but also on the metabolic state of the brain [19].

The observed effects of creatine may differ depending on the cognitive domain and the type of test used. Previous reviews suggest that creatine may have more consistent effects on short-term memory and intelligence/reasoning than on other cognitive domains, while findings for attention, executive function, and processing speed remain less consistent [6, 7]. Differences in cognitive assessment tools may partly explain the heterogeneity of findings across studies.

Individual characteristics, including health status, baseline cognitive performance, diet, age, and brain creatine availability, may influence the response to supplementation. This may explain why some studies report cognitive benefits, while others show little or no effect. Overall, current evidence suggests that creatine may be most relevant in populations with lower creatine availability or increased brain energy demand, but further well-designed studies are needed to identify responders and optimal supplementation protocols [6-8].

3.5. Safety and Supplementation Strategies

Creatine monohydrate is considered one of the most extensively studied dietary supplements, with a generally favorable safety profile when used at recommended doses. It has been widely investigated in sports nutrition and is increasingly discussed in the context of health and brain function [1, 11]. Current evidence suggests that creatine supplementation is usually well tolerated in healthy individuals, although individual health status should always be considered before supplementation [27].

Concerns regarding kidney function, water retention, muscle cramps, dehydration, or other adverse effects are commonly discussed in relation to creatine use. However, available evidence does not support the view that recommended doses of creatine impair kidney function in healthy individuals [27, 28]. Nevertheless, individuals with pre-existing kidney disease or other chronic medical conditions should use creatine only under medical supervision.

The most commonly used supplementation strategy includes a loading phase of approximately 20 g/day for 5–7 days, followed by a maintenance dose of 3–5 g/day. An alternative approach is to use a lower daily dose without a loading phase, although this may require more time to increase tissue creatine stores [1]. In studies related to brain function and cognition, supplementation protocols vary considerably in dose, duration, and study population, which may partly explain inconsistent findings [2, 7].

Although creatine appears to be safe and biologically plausible as a supplement supporting brain energy metabolism, current evidence is not sufficient to recommend it universally for cognitive enhancement. Recent reviews suggest potential benefits for selected cognitive domains and specific populations, but results remain heterogeneous [7]. Moreover, the European Food Safety Authority concluded that a cause-and-effect relationship between creatine supplementation and improvement in cognitive function has not yet been established [8]. Therefore, creatine may be considered a promising but not yet fully confirmed nutritional strategy for supporting cognitive function.

4. Discussion, Limitations, and Future Directions

The available evidence suggests that creatine may have a potential role in supporting cognitive function, mainly through its involvement in brain energy metabolism and ATP regeneration. This mechanism may be particularly relevant in situations of increased brain energy demand, such as sleep deprivation, mental fatigue, or high cognitive load [2, 14, 17-19].

However, findings from human studies remain inconsistent. Positive effects have been reported in selected populations, including vegetarians, older adults, and individuals exposed to mental fatigue or sleep deprivation, suggesting that baseline creatine availability, age, diet, and increased brain energy demand may influence the response to supplementation [5, 17-19, 24, 26]. In contrast, studies in healthy young adults without additional cognitive or metabolic stress often show limited or no significant improvement in cognitive performance [21-23].

Several limitations should be considered when interpreting the current evidence. Available studies differ in participant characteristics, supplementation dose, intervention duration, cognitive tests, and outcome measures, which makes direct comparison difficult [6, 7]. In addition, many studies include relatively small sample sizes and do not directly measure brain creatine availability. Although oral creatine supplementation may increase cerebral creatine levels, individual responses appear to vary, and changes in brain creatine are not always assessed together with cognitive outcomes [2, 4].

Future research should include larger randomized controlled trials, standardized cognitive assessment methods, and clearly defined supplementation protocols. Studies should also consider factors such as age, dietary pattern, baseline creatine intake, sleep deprivation, mental fatigue, and health status. Whenever possible, future trials should include direct measures of brain creatine or phosphocreatine levels, for example using magnetic resonance spectroscopy. Such research is needed to identify populations most likely to benefit from creatine supplementation and to determine whether its cognitive effects are clinically meaningful.

5. Conclusions

Creatine is a well-studied dietary supplement with an established role in cellular energy metabolism. Although it is most commonly associated with sports performance, growing evidence suggests that creatine may also be relevant for brain function due to its involvement in the phosphocreatine system and ATP regeneration [1, 2].

Current human studies indicate that creatine supplementation may have potential benefits for selected cognitive domains, particularly memory, reasoning, and mental fatigue, with less consistent evidence for processing speed. However, these effects are not consistent across all populations or study designs. The available evidence suggests that creatine may be more beneficial in individuals with lower baseline creatine intake, older adults, or under conditions of increased brain energy demand, such as sleep deprivation or mental fatigue [6, 7, 26].

Overall, creatine appears to be a promising but not yet fully confirmed nutritional strategy for supporting cognitive function. Further well-designed randomized controlled trials are needed to determine optimal supplementation protocols, identify populations most likely to benefit, and clarify the mechanisms underlying its potential cognitive effects [8].

DISCLOSURE

Author's Contributions

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Declaration of generative AI and AI-assisted technologies in the writing process

In preparing this work, the authors used ChatGPT (OpenAI, San Francisco, CA, USA) for linguistic refinement, text organization, formatting support, and improvement of academic writing style. The authors critically reviewed, edited, and verified all generated content and accepted full responsibility for the final content of the manuscript.

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