WALCZAK, Kamil, KRASNOBORSKA, Julia, SAMOJEDNY, Sylwia, SUPERSON, Maciej, SZMYT, Katarzyna, SZYMAŃSKA, Katarzyna and WILK-TRYTKO, Klaudia. Effect of creatine supplementation on cognitive function and mood. Journal of Education, Health and Sport. 2024;73:51712. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.73.51712
https://apcz.umk.pl/JEHS/article/view/51712

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 25.04.2024. Revised: 10.05.2024. Accepted: 29.05.2024. Published: 03.06.2024.

Effect of creatine supplementation on cognitive function and mood

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Abstract

Background: Creatine, a naturally occurring compound plays a crucial role in cellular energy metabolism, particularly in tissues with high energy demands like muscles and the brain. Beyond its well-established role in physical performance enhancement, recent research has revealed its potential benefits for cognitive functions and mood regulation. This review paper aims to comprehensively analyze the existing literature on creatine supplementation's effects on cognitive functions and mood.

State of Knowledge: Findings suggest that creatine supplementation enhances memory, attention, and executive functions, especially under conditions of stress or sleep deprivation. Moreover, it exhibits mood-stabilizing effects, potentially offering relief for symptoms of depression and fatigue. Creatine's ability to augment brain energy metabolism, alongside its neuroprotective properties, underlies its cognitive and mood-enhancing effects. While generally safe, caution is advised, particularly in populations with kidney diseases or those using medications affecting kidney function.

Summary: Creatine emerges as a promising adjunct therapy for enhancing cognitive functions and promoting emotional well-being beyond its traditional role in physical performance.The review underscores the need for further research to elucidate the precise mechanisms of creatine's effects and explore its synergistic potential with other cognitive-enhancing supplements.

Keywords: Creatine; Cognitive function; Mood;

1. Introduction

Creatine is a naturally occurring nitrogenous organic acid that plays a critical role in energy metabolism within the body (1) . Approximately 95% of the body's creatine is stored in skeletal muscle, with the rest located in the brain, liver, and kidneys (2) (3). Creatine is synthesized endogenously from amino acids, but it can also be obtained exogenously through dietary sources and supplementation. The primary biological role of creatine is to facilitate the recycling of adenosine triphosphate (ATP), especially in tissues with high energy demands like muscles and the brain (3). Common dietary sources of creatine include red meat and fish. However, the concentration of creatine in these foods can vary significantly, leading many individuals, especially athletes and bodybuilders, to turn to creatine supplements to enhance physical performance and muscle growth (4). Beyond its well-known ergogenic effects, recent studies suggest that creatine supplementation may also have potential benefits for cognitive functions and mood regulation (5).

The purpose of this review paper is to analyze and sum up the current research regarding the impact of creatine supplementation on cognitive functions and mood. This review aims to assess the effectiveness of creatine supplementation in enhancing cognitive performance and improving mood states, as well as to understand the biological mechanisms underlying these effects, evaluate the safety and side effects associated with creatine use, and identify gaps in the current literature.

2. Methods

The literature search was conducted across several databases including PubMed, Scopus, and Google Scholar to ensure a comprehensive review of the available research concerning creatine supplementation's effects on cognitive functions and mood. The search employed specific keywords and phrases to refine the results, including "creatine supplementation," "cognitive functions," "mood, "creatine effects on the brain", "neuroprotection," and "exercise performance."

3. Creatine Supplementation

3.1 Metabolic role

Creatine plays main role in energy metabolism, particularly in the brain and muscles, where it's critical for maintaining high levels of physical and cognitive function (6) . This compound is produced in a two-step process: in the kidneys, arginine and glycine combine to form guanidinoacetate (GAA) through the action of the enzyme L-arginine:glycine amidinotransferase (AGAT). Then, in the liver via the enzyme guanidinoacetate methyltransferase (GAMT), GAA is methylated by S-adenosylmethionine (SAMe) to form creatine (7) (8). Once synthesized, creatine is transported in the bloodstream to other tissues, especially brain and muscle, a creatine transporter (CRT) encoded by the SLC6A8 gene is required for this (7) (9).

In tissues, creatine is phosphorylated to phosphocreatine (PCr) by the enzyme creatine kinase (CK). PCr has a key function in rapidly refilling ATP by attaching a phosphate group to ADP. This ATP is then available to drive cellular processes that require immediate energy, such as muscle contractions and rapid neuronal activation. The PCr system functions as an essential energy buffer, effectively maintaining ATP levels during moments when the energy demand temporarily surpasses what glycolysis and oxidative phosphorylation can provide. This capability is crucial within the brain, where a constant supply of energy is vital for processes such as neurotransmission, signal processing, and the maintenance of ionic gradients. Beyond serving as a rapid source of energy, the creatine-PCr system is integral to

cellular energy homeostasis, with significant implications for neuroprotection, cognitive enhancement, and physical performance (10).

3.2 Sources of creatine and supplementation

The primary dietary sources of creatine are animal products. Red meats (beef, pork) and fish (salmon, tuna) are particularly rich in creatine, providing approximately 2 grams of creatine per pound of uncooked meat (11). However, the amount of creatine obtained from the diet varies based on food preparation methods and individual dietary habits, with vegetarians and vegans typically having lower creatine stores due to the absence of meat in their diets (12) (13) (14). Creatine supplements are available in various forms, with creatine monohydrate being the most researched and widely used (15) (6) . Creatine monohydrate is praised for its safety, affordability, and efficacy in increasing muscular creatine levels. Other forms of creatine supplements include creatine ethyl ester, creatine hydrochloride (HCl), and buffered creatine, among others. These alternative forms claim to offer superior solubility, absorption, and efficacy, though scientific evidence supporting these claims is not as robust as for creatine monohydrate. Supplementation typically follows a loading phase of 20 grams per day (divided into 4 doses) for 5–7 days, followed by a maintenance phase of 3–5 grams per day (16) (6). This regimen is aimed at quickly saturating the muscles with creatine, leading to rapid increases in muscle creatine phosphate levels (17) (18).

The choice between dietary sources and supplementation forms of creatine depends on individual preferences, dietary restrictions, and specific health or performance goals. For cognitive and mood enhancement, the form of creatine might play a role in its efficacy, with ongoing research exploring the effects of various supplementation strategies.

4. Impact of Creatine Supplementation on Cognitive Functions

Cognitive functions are essential for day-to-day operations and overall mental health. They can be broadly categorized into several domains, including memory, attention, and executive function (19) (20). Recent studies provide empirical evidence explaining the effects of creatine supplementation on these cognitive domains (20). Short-term supplementation has been found to enhance memory and recall, particularly under conditions of sleep deprivation or stress (21), with some studies noting improvements in tasks requiring rapid memory recall

among individuals supplemented with creatine (22). Additionally, creatine supplementation may improve attention and processing speed, especially in tasks that require sustained mental effort over short periods (20). The benefits of creatine are not limited to the short term; long-term supplementation has shown promise in enhancing cognitive function in older adults, suggesting a potential role for creatine in mitigating age-related cognitive decline. Improvements have been noted in tasks measuring memory and executive function (23) (22). Moreover, the neuroprotective effects of long-term supplementation suggest that creatine could have a protective effect against neurodegenerative diseases, potentially through mechanisms related to energy metabolism and cellular homeostasis (24).

Moreover, creatine enhances the brain's energy availability by rephosphorylating ADP to ATP, thereby increasing energy capacity and potentially supporting more efficient brain function, particularly in tasks that demand significant mental effort (9). In addition, creatine supplementation may help protect neurons from damage due to oxidative stress, excitotoxicity, or energy depletion, contributing to improved cognitive function and resilience against neurodegenerative changes (25). There is also evidence to suggest that creatine can influence neurotransmitter systems, including serotonin and dopamine, which are critical for cognitive processes such as learning, memory, and attention (10).

5. Impact of Creatine Supplementation on Mood

Research into creatine's effects on mood has revealed promising findings, indicating not just broad benefits for the general population but also specific advantages for groups like the elderly (26). For the general populace, creatine supplementation has been associated with mood improvement, decreased symptoms of depression, reduced fatigue, and enhanced energy levels, contributing to better emotional well-being (27). Notably, a randomized controlled trial demonstrated that creatine, when used alongside standard depression treatments, facilitated quicker and more sustained alleviation of depressive symptoms than medication alone (28) (29).

The benefits of creatine extend to particular populations facing unique challenges related to mood and cognitive function. The elderly, for instance, might find creatine supplementation beneficial in counteracting age-related declines in mood and cognitive capabilities, thereby possibly protecting against mood disorders and cognitive deterioration—a growing concern given the increasing prevalence of these issues within the aging

demographic (26). Beyond improving physical performance, creatine has been shown to lessen mental fatigue and positively affect mood states post-exercise, aiding in recovery and performance (30) (31).

A key hypothesis about the mechanisms through which creatine influences mood revolves creatine's role in boosting energy metabolism; by increasing ATP availability in the brain, creatine could enhance the functioning of mood-regulating regions like the prefrontal cortex and limbic system. This boost in energy may support critical processes such as neurotransmitter synthesis, neuronal activity, and brain plasticity, essential for managing stress and regulating emotions. Additionally, creatine's neuroprotective properties, stemming from its ability to counteract oxidative stress and promote mitochondrial health, alongside its potential modulation of neurotransmitters like serotonin and dopamine, play vital roles in mood regulation (32).

Another significant aspect is creatine's capacity to alleviate mental fatigue, thereby indirectly influencing mood by improving cognitive function and stress resilience, particularly relevant in managing depression and anxiety symptoms (33).

6. Safety and Side Effects

Findings from numerous studies confirm that creatine supplementation is safe when adhered to recommended dosages (34). Research covering short-term to medium-term usage up to five years has consistently demonstrated its safety in healthy adults (35) (36). Among the common side effects, gastrointestinal distress, including symptoms like nausea, diarrhea, and cramping, has been noted, especially at higher intake levels(37) (38) . Additionally, creatine is associated with water retention during the initial phase of supplementation, which typically leads to temporary weight gain as the body adjusts to increased creatine stores (39). While these effects are generally mild, there have been reports of more serious concerns such as kidney stress or damage linked to excessive creatine consumption, often in the context of pre-existing kidney diseases or simultaneous use of multiple supplements (10) (40) . Moreover, creatine may interact with certain medications, particularly those that affect kidney function or water balance, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or diuretics (41). When NSAIDs are used concurrently with creatine, there's a theoretical risk that reduced kidney perfusion could be exacerbated, potentially leading to impaired kidney function, especially if hydration is not adequately maintained. Creatine and diuretics affect the

body's water balance but in opposite directions, combining them can put additional stress on the kidneys. While creatine promotes water retention within muscle cells, diuretics enhance water excretion, which can lead to dehydration and further concentrate the creatine in the body. This concentrated form may increase the workload on the kidneys as they filter blood, potentially leading to an increased risk of kidney damage in susceptible individuals (41).

Given these considerations, particular caution is advised for specific groups. Pregnant women are recommended to avoid creatine supplements due to the lack of definitive safety data during these critical periods (42). Individuals with existing kidney disease are cautioned against creatine use, as it may intensify renal stress through increased creatinine production, a byproduct processed by the kidneys (37). The safety of long-term creatine usage in children and adolescents remains under-researched, with current knowledge suggesting short-term safety but leaving questions about long-term effects open (35).

7. Discussion

Studies have repeatedly shown that creatine can improve memory, attention, and executive functions, particularly in situations that challenge cognitive performance, such as during sleep deprivation or under intense cognitive demand (42). This cognitive enhancement is attributed to creatine's ability to improve brain energy metabolism, which supports more robust cognitive processing and resilience in stressful situations (26). Moreover, creatine has emerged as a promising agent in mood regulation, offering potential relief for symptoms of depression and fostering overall emotional well-being (42) .

When placed alongside other supplements known for their cognitive and mood-enhancing properties—like omega-3 fatty acids, caffeine, and Ginkgo biloba—creatine's unique mechanism of action becomes apparent. It stands out by boosting ATP production and enhancing energy availability in the brain, unlike caffeine's stimulatory effects or omega-3s' contribution to membrane fluidity and anti-inflammatory benefits. This direct support for cellular energy mechanisms underlines creatine's distinct effectiveness in improving cognitive functions and mood, suggesting the exciting potential for creatine to work synergistically with other supplements to further enhance mental performance and mood regulation (32) (43) (44) (45) (46).

However, the existing literature on creatine's effects on cognition and mood, despite its promise, is not devoid of limitations. The research field is marked by studies with small

sample sizes and diverse design methodologies, including variations in creatine dosage, supplementation duration, and participant demographics. Moreover, the precise biological pathways through which creatine affects cognitive functions and mood are not fully understood, pointing to a clear need for more detailed biochemical and neurophysiological research (10) (31).

Looking ahead, future research efforts should aim to overcome the current limitations by conducting larger, more rigorously designed studies. Such studies could provide stronger evidence of creatine's benefits and clarify its mechanisms of action. Additionally, investigating how creatine might work in conjunction with other cognitive-enhancing supplements could reveal optimal strategies for mental health and performance interventions (27) (10).

8. Conclusion

Creatine supplementation has proven to offer a wide range of benefits that go beyond its well-known role in enhancing physical performance. Studies show that creatine significantly boosts cognitive functions such as memory, attention, and executive skills, while also stabilizing mood and showing potential as an adjunct therapy for depression. Its unique ability to enhance ATP production and optimize brain energy utilization distinguishes it from other cognitive and mood-enhancing supplements, suggesting the possibility of synergistic effects with other substances to further improve mental performance and emotional well-being.

Disclosures

Authors do not report any disclosures.

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Draft Preperation: Kamil Walczak, Julia Krasnoborska, Katarzyna Szmyt; Writing – Review & Editing: Maciej Superson, Katarzyna Szymańska, Klaudia Wilk-Trytko

All authors have read and agreed with the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

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