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The effects and benefits of creatine supplementation on brain health

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Abstract:

Introduction:

Creatine is a naturally occurring compound vital for energy metabolism, particularly in high-energy-demand tissues like muscles and the brain [1]. Traditionally, research on creatine has focused on its ergogenic effects in sports [2], but emerging research suggests it may also positively impact brain health. Studies are exploring creatine monohydrate's role in improving cognitive function [3], mitigating neurodegenerative processes [4], and supporting mental health [5]. This dual functionality highlights the compound's versatility as both a performance enhancer and a potential therapeutic agent for neurological health. By expanding the scope of creatine research beyond physical performance, we can better understand and utilize its full capabilities to enhance human health. This research review examines the growing evidence suggesting that creatine supplementation could significantly benefit brain health and the management of neurological diseases.

Aim of the study: This review aims to synthesize current findings on creatine's cognitive benefits and its therapeutic potential for neurological disorders, critically analyzing preclinical and clinical studies to identify gaps and suggest future research directions.

Materials and Methods: A comprehensive literature search was conducted using PubMed and Google Scholar databases, covering studies published between 2000 and 2024. Keywords such as creatine supplementation, brain health and neurodegeneration were used. Exclusion criteria included non-peer-reviewed articles, studies with insufficient data, and those not in English.

Conclusions: This review highlights the potential benefits of creatine supplementation for cognitive and neurodegenerative diseases, noting its positive effects on memory, alleviating depression, and anxiety, and offering neuroprotection. Future research should aim to standardize dosing, extend follow-up periods, and include larger, more diverse populations.

KEYWORDS: creatine; supplementation; brain health; depression; neurodegeneration

What is creatine

Creatine is naturally obtained from dietary sources, particularly animal products such as red meat and fish which serve as the primary dietary sources of creatine for humans [6]. Additionally, the human body synthesizes creatine from the amino acids glycine, arginine, and methionine [7], primarily occurring in the liver, kidneys, and pancreas. Once synthesized or ingested, creatine is mostly found in skeletal muscle and comes in two forms. About 60% is in the phosphorylated form of creatine phosphate (CP), and the remaining 40% is in the free creatine form (Crfree) [8]. Creatine phosphate is the main high-energy, phosphate-storage molecule of muscle. The most well-understood function of creatine in energy metabolism is that of an energy buffer. Through the creatine kinase process, creatine is transformed into phosphocreatine (PCr), which stores energy in a more stable form than adenosine triphosphate (ATP) [9].

Creatine exerts its effects through several mechanisms, primarily enhancing the phosphocreatine system, which boosts phosphocreatine levels in muscle, aiding rapid ATP regeneration via the phosphorylation of ADP to ATP during times of acute energy need/ high-intensity activities [10] thereby delaying fatigue [11]. It stimulates muscle protein synthesis via pathways like mTOR [11], essential for muscle growth, and promotes cellular hydration, drawing water into muscle cells to foster an anabolic environment [11]. Furthermore, creatine helps maintain ATP levels during intense muscle contractions through the energy-buffering role of creatine kinase [12]. Creatine functions as a "energy shuttle," moving energy along a concentration gradient more effectively from sites of synthesis (like mitochondria) to sites of utilization (like the neuronal membrane) due to its faster rate of intracellular diffusion than ATP . Higher activity brain regions like the hippocampus and cerebellum are where creatine kinase is most widely expressed [13]. Additionally creatine influences myogenic growth factors like IGF-1, enhancing muscle repair and hypertrophy by boosting satellite cell activity[11]. In the brain, creatine supports cognitive function by maintaining energy homeostasis and ensuring a stable ATP supply, crucial for synaptic transmission and plasticity [14].
Creatine monohydrate is the most supplemented form of creatine, owing to its proven efficacy, high bioavailability, and excellent safety profile[15]**.** Structurally, it is made of the amino acids glycine, arginine, and methionine and plays a vital role in energy production, particularly in muscle cells. Typically consumed in powder or capsule form, the standard dosing regimen involves an initial loading phase to rapidly saturate muscle stores, followed by a maintenance phase with lower, sustained doses [16]. It is predominantly used in the realm of sports and physical performance enhancement, where it is renowned for its ability to increase strength, boost muscle mass, and enhance overall athletic performance. However, its utility extends beyond sports, increasingly being investigated for its potential benefits in brain health.

Action on the brain

In the brain, creatine phosphate may be equally important in acting as a stabilizing energy source. The primary mechanism by which creatine promotes brain health is through its involvement in energy metabolism. The maintenance of ATP levels is facilitated by creatine and is essential for cellular energy. Given the high energy requirements of brain cells, this is very crucial. It has been suggested that high-energy phosphates help to maintain membrane potentials, participate in neurotransmitter release, contribute to calcium homeostasis, and play roles in neuronal migration, survival, and apoptosis [17]. Moreover, the antioxidant qualities of creatine aid in lowering oxidative stress, a major contributor to neurodegenerative illnesses [18].
Despite constituting only 2% of body mass, the brain consumes approximately 20% of the body's energy [19], highlighting its significant metabolic activity. Creatine, known for its role in energy regulation and bioenergetics, has emerged as a potential therapeutic agent for neurological and psychiatric conditions. Abnormalities in creatine metabolism are linked to various mental disorders and arise from an inability to synthesize or transport creatine [20]. The brain-specific isoform of creatine kinase (BB-CK) underscores creatine's role in maintaining CNS homeostasis and energy supply. Given the rapid ATP depletion during complex cognitive tasks, hypoxia, sleep deprivation, and certain neurological disorders, creatine metabolism is crucial for sustaining energy balance.

Additionally, brain creatine levels decline with age, correlating with decreased brain activity and the onset of neurodegenerative diseases. Experimental evidence from mice, showing impaired learning and brain plasticity upon deletion of brain-type CK, supports the involvement of the creatine-CK network in both brain metabolism and plasticity [21]. Increasing research suggests that creatine supplementation can elevate brain creatine levels, offering a promising intervention for age-related and metabolic brain conditions.

Mental health: Depression and Anxiety

The prevalence of mental health disorders is significant, affecting a considerable portion of the global population. Approximately 38.2% of the European Union (EU) population experiences a mental disorder each year [22]. Annually, around 19% of adults [23] and 13%-20% of children [24] in the United States experience mental health issues. Among these disorders, depression and anxiety rank at the forefront. Depression, characterized by persistent sadness, loss of interest and pleasure in activities, poor concentration, hopelessness, and changes in sleep and appetite, is a leading cause of disability and can result in suicide, particularly among young people. Globally, approximately 280 million people are affected by depression [25]. Anxiety disorders, which include generalized anxiety disorder, panic disorder, social anxiety disorder, and specific phobias, impact about 301 million people worldwide (people https://www.who.int/news-room/fact-sheets/detail/anxiety-disorders). These disorders are marked by excessive fear and worry, significantly impairing daily functioning and quality of life. The high prevalence of these conditions underscores the critical need for enhanced mental health awareness and resources.

Abnormal brain bioenergetics are common in mental health disorders like depression, associated with low brain creatine levels. Research indicates that reduced creatine function in the prefrontal cortex may be linked to a higher likelihood of experiencing depression and anxiety symptoms [26] In addition studies indicate that dietary creatine intake is inversely related to depression risk [27]. This has sparked interest in exploring creatine's potential for alleviating these symptoms. Studies have shown that creatine monohydrate supplementation, which increases phosphocreatine (PCr) content and the ratio of phosphocreatine to ATP, can have beneficial effects on mood disorders. Specifically, higher PCr levels are associated with lower depression scores, suggesting that enhancing creatine function through supplementation might help alleviate symptoms of mood disorders [5]. When combined with other treatments, such as selective serotonin reuptake inhibitors (SSRIs), creatine supplementation has shown an increase in PCr levels, leading to improvements in depression severity [28].

Despite high prevalence, treatment adherence is low, and medication success is limited. Human studies, including case studies and small clinical trials, indicate creatine monohydrate supplementation can improve depression symptoms, particularly as an adjunct to traditional medications [2928]. Consideration is necessary for certain subgroups, such as demonstrated by a group of depressed bipolar patients where hypomania/mania developed [30] moreover, some studies lead to inconclusive overall findings, demonstrating no statistically significant improvement [28]. Individual differences, including age, sex, clinical diagnosis, and symptom severity, may also influence the treatment response to creatine supplementation for mood disorders. Animal studies suggest creatine's antidepressant effects may be sex-dependent, with greater efficacy in females [31], though it also benefits males when combined with other antidepressants.

Creatine has shown antidepressant effects in models of epilepsy and Alzheimer's disease-related depression. It may activate mTORC1 pathway, akin to fluoxetine [32].
Overall evidence indicates that creatine supplementation can improve depression symptoms, particularly as an adjunct to traditional medications. This highlights creatine's potential as a complementary treatment for enhancing the efficacy of conventional antidepressant therapies nonetheless larger scale randomized controlled trials are needed to further explore its efficacy and the impact of dietary creatine intake.

Memory and cognitive function

Memory and cognitive functions are fundamental aspects of human cognition, enabling individuals to encode, store, retrieve, and utilize information. Memory refers to the processes involved in retaining and recalling past experiences [33], while cognitive functions encompass a broader range of mental processes including attention, perception, reasoning, and problem-solving [34]. These functions are essential for everyday activities, learning, and adaptation to new situations. Considering that memory, defined as the capacity to gather, store, and retrieve information, requires healthy mitochondrial respiration to function and given that creatine is a crucial regulator of energy status, increasing brain creatine levels may improve memory by changing the bioenergetics of the brain. Increased brain creatine content, particularly PCr, has been shown to maintain cell membrane integrity and stability, preserving structural stability and functional maintenance, and preventing cell apoptosis due to abnormal energy metabolism [35]. In vitro studies indicate that creatine enhances oxidative phosphorylation in synaptosomes and isolated brain mitochondria. In rats, creatine injected into the hippocampus improved spatial memory and object exploration [36]. Additionally, creatine injection upregulated cAMP-response element-binding protein (CREB), which influences memory, within 30 minutes [37]. Recent studies show that 4 weeks of creatine supplementation in mice enhanced hippocampal mitochondria and improved memory. Research should investigate whether daily dietary creatine intake can affect these mechanisms in humans. Evaluating several different research papers the outcomes of creatine's benefits on memory show significant differences concerning age. Amongst young adults (11–31 years) no differences following supplementation were observed, amidst the elderly study participants (66-76 years), a greater improvement in measure of memory was observed [35]. The following highlights clearer evidence of memory improvement in the elderly, while effects on younger individuals remain less conclusive, indicating a potential area for intensified future research.

Neurodegenerative diseases: Alzheimer's and Parkinson's

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and alterations in behavior. It is associated with significant alterations in cerebral metabolism and energy homeostasis. Creatine plays a vital role in this context. Increased levels of myo-inositol, a marker of glial activation, have been detected in the brains of individuals with Alzheimer's disease [38], indicating altered brain metabolism and inflammation. Scientific studies have shown that creatine and creatine kinase levels are altered in the brains of AD patients, with focal elevations of creatine observed in both animal models and human AD brain tissue [39]. These alterations suggest a potential compensatory mechanism or an attempt to maintain energy homeostasis.

Moreover, creatine has been shown to protect cultured hippocampal neurons against toxicity from glutamate and beta-amyloid, which are key pathological features of Alzheimer's disease [40]. By supporting mitochondrial function and enhancing cellular energy metabolism, creatine supplementation could potentially mitigate neuronal damage and slow the progression of Alzheimer's disease, highlighting its therapeutic potential in brain health. Creatine supplementation emerges as a promising neuroprotective approach that warrants further investigation for this condition.

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra region of the brain, leading to motor symptoms such as tremors, rigidity, and bradykinesia. In Parkinson's disease (PD), neurodegenerative alterations are caused by harmful processes such as inflammation, apoptosis, mitochondrial malfunction, and oxidative stress [41–44]. It has been demonstrated that oxidative stress severely damages lipids, proteins, and deoxyribonucleic acid (DNA), which leads to cell death through several pathways, including the activation of various apoptotic cell signaling molecules [41]. Due to oxidative stress playing a key factor in PDs pathophysiology, distorting the body's endogenous antioxidant systems, creatine supplementation may provide beneficial antioxidant properties and act as a neuroprotectant [18]. This neuroprotection is thought to be due to creatine's ability to enhance mitochondrial function and energy production [45,46], sustaining the brain's energy levels and reducing oxidative stress and neuronal damage. In addition to preventing damage from oxidative stress, excitotoxicity, and mitochondrial dysfunction—all of which are linked to the pathophysiology of several neurodegenerative disorders—creatine can help sustain brain energy levels [47]. By improving cellular energy metabolism, creatine can potentially modulate the disease mechanism of action in Parkinson's, providing a supportive environment for neuronal survival and function. Animal studies have demonstrated that creatine supplementation could be neuroprotective, as it has been shown to prevent the loss of dopaminergic neurons in models of PD [48].

Dosing

Creatine supplementation has shown potential benefits for brain health, including improved cognitive processing, brain function, and recovery from neurological conditions. Determining optimal dosages is crucial for maximizing these benefits. There is a wide range of dosing regimens when it comes to creatine. For a healthy individual, the recommended creatine supplementation involves a loading phase of 20 grams daily for 5-7 days, followed by a maintenance dose of 3-5 grams daily. This protocol effectively increases muscle creatine stores and enhances physical performance, with a well-established safety profile [49]. When it comes to the use of creatine outside the physical performance profile a general dosage for healthy individuals with some proven effects has been 4x5 g creatine monohydrate per day for four weeks. Higher doses were used for conditions such as Huntington's disease (8g/day for 16 weeks) with the effect of increased brain creatine levels and a reduced marker of oxidative injury[50]. A short-term supplementation has also been documented to provide improved cognitive performance and reduced mental fatigue when taking 8g/day for five days in a row [50]. Current research indicates that long-term creatine supplementation is generally safe for healthy individuals, with few serious adverse effects [51,52].

Common side effects, if any, are usually mild and include gastrointestinal discomfort and muscle cramping, which are infrequent [53]. Overall creatine is well tolerated at the recommended dosages, however, high doses and combined use with other supplements should be approached with caution. Regular monitoring is advised for those using creatine over extended periods.
The research suggests that creatine supplementation in doses ranging from 5 g/day to as high as 20g daily is beneficial and safe for brain health. However, optimal dosing protocols are yet to be fully established, and further research is necessary to refine these recommendations.

Discussion

The current body of research supports the potential benefits of creatine supplementation on brain health. Creatine appears to alleviate symptoms of mental health disorders such as depression and anxiety. Studies indicate that creatine can enhance mood and improve the efficacy of traditional antidepressants. The application of creatine in the treatment of cognitive and neurodegenerative diseases demonstrates an overall positive influence, with multiple studies indicating its potential benefits in improving cognitive function, especially in the elderly population and slowing disease progression. These findings suggest that creatine supplementation could be a valuable strategy for promoting brain health and preventing cognitive decline. Evidence proposes that creatine supplementation can be particularly beneficial in conditions such as Alzheimer's or Parkinson's disease, where it may support cellular energy metabolism, reduce oxidative stress, and provide neuroprotective effects.
Despite these promising findings, it is imperative to note that the current body of research is marked by variability in dosing regimens, study designs, and patient populations, which complicates the interpretation and generalization of results. Therefore, future research is essential to establish optimal dosing strategies and to ensure that findings are robust and reproducible. To achieve this, well-designed, controlled, and unanimous clinical trials are necessary. These trials should focus on standardized dosing protocols, longer follow-up periods, and larger, more diverse patient cohorts to verify the efficacy and safety of creatine in various cognitive and neurodegenerative contexts. Only through rigorous and systematic investigation can we solidify creatine's role in medical treatment and provide clear guidelines for its clinical application.

Conclusion

In conclusion, while the current evidence is encouraging, further research is crucial to fully understand and validate creatine's therapeutic potential in managing cognitive and neurodegenerative diseases.

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Author's contribution:

Conceptualization, Elena Sztemberg, and Dominik Lepecki; **Methodology**, Bartłomiej Grodziński, Robert Tomaszewski, Hanna Gruszczyńska; **Software**, Marta Kras, Aleksandra Cieślik; **Check**, Marcin Mikusek-Pham Van and Aleksandra Cieślik; **Formal analysis**, Marcin Mikusek van, Karolina Krawiel, and Marta Kras; **Investigation**, Elena Sztemberg, Dominik Lepecki and Hanna Gruszczyńska; **Resources**, Bartłomiej Grodziński, Aleksandra Cieślik, and Marek Król; **Data curation**, Dominik Lepecki, Robert Tomaszewski, and Marta Kras; **Writing - rough preparation**, Elena Sztemberg; **Writing - review and editing**, Elena Sztemberg, Dominik Lepecki, Bartłomiej Grodziński, Hanna Gruszczyńska, Robert Tomaszewski, Aleksandra Cieślik, Maricn Mikusek-Pham Van, Marta Kras, Karolina Krawiel and Marek Król; **Visualization**, Elena Sztemberg and Dominik Lepecki; **Supervision**, Hanna Gruszczyńsk**,** Aleksandra Cieślik and Karolina Krawiel; **Project administration**, Marta Kras, Robert Tomaszewski, Marek Król and Aleksandra Cieślik; **Receiving funding**, not applicable; All authors have read and agreed with the published version of the manuscript.

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