DOI: 10.4274/ejgg.galenos.2022.2022-9-9
Eur J Geriatr Gerontol 2023;5(1):1-5

The Potential and Challenges of Creatine Supplementation for Cognition/Memory in Older Adults

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Abstract

Creatine (Cr) has been proposed as an ergogenic resource and the adhesion to its therapeutic use has gained relevance in the last 2 decades. The role of Cr in the aging process has been highlighted, with many studies aiming to understand how aging affects the depletion of Cr resources in muscle and brain, especially because Cr is a natural regulator of energy homeostasis and plays a recognized role in brain function and development, justifying the rising hypothesis that Cr supplementation can help mitigate the effects of aging. Thus, we aimed to review the role of Cr (supplemented or obtained in daily diet) and its metabolism in the aging brain, with emphasis on cognition/memory. PubMed, PsychInfo, EBSCO, Medline, BioMed central and Science Direct, constituted the searched databases. Inclusion criteria specified peer-reviewed studies investigating creatine metabolism and/or creatine supplementation, and assessing cognition, and memory in old adults, and published between January, 2000 to September, 2022. The importance of creatine in the brain's energy metabolism is well established. The relationship between the decline of cognitive function and brain creatine storage still lacks stronger evidence. Evidence is also lacking on whether creatine supplementation is beneficial in mitigating the neural effects of aging, remaining an open field of studies that brings optimistic perspectives.

Keywords: Creatine, cognition, brain, memory, aging

Introduction

Creatine is a nitrogenous compound directly linked to energy metabolism in various organs and tissues. It is proposed as an ergogenic resource for a long time; however, its therapeutic use has gained relevance and adhesion in the last two decades. Interestingly, the role of this metabolite in the aging process has been highlighted, with many studies aiming to understand how aging affects creatine resource depletion (1-4), and how creatine supplementation could mitigate this event (2,5,6). Recent studies have risen the hypothesis that creatine supplementation can help mitigate the effects of aging, supported by the fact that creatine is a natural regulator of energy homeostasis, and plays a recognized role in brain function and development (7). Thus, this mini-review shows the state of the art in the role of creatine (supplemented or obtained in daily diet) and its metabolism in the aging brain, with emphasis on cognition/memory.

Methods

The following databases were searched: PubMed, PsychInfo, EBSCO, Medline, BioMed central, and Science Direct. Inclusion criteria specified peer-reviewed studies investigating creatine metabolism and/or creatine supplementation, and assessing cognition, and memory in old adults, and published between January, 2000 to September, 2022. Each author searched for articles separately based on the descriptors "creatine supplementation", "old people", "elderly", and "aging". After removing duplicate articles and abstracts that did not meet the inclusion criteria, only common articles selected by the authors were adopted.

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Received: 28.09.2022 **Accepted:** 14.11.2022

Cite this article as: Machado M, Pereira R. The Potential and Challenges of Creatine Supplementation for Cognition/Memory in Older Adults. Eur J Geriatr Gerontol 2023;5(1):1-5

Discussion

Creatine Metabolism and Energy Supply

Creatine (methyl guanidine-acetic acid) is derived and synthesized from reactions involving the amino acids arginine, glycine, and methionine in the kidneys and liver or can be ingested exogenously primarily from animal-based foods (i.e., red meat, seafood) or through dietary supplements (8-11). Ninety-five percent of creatine is found in skeletal muscle with the remaining 5% dispersed across the brain, liver, kidney, and testes (8,12). Once creatine is transported into the skeletal muscle, ~2/3 is converted to phosphocreatine (CrP) with the remainder stored as free creatine. Phosphocreatine can be rapidly catabolized via creatine kinase (CK) and acts as a metabolic intermediary of energy transfer by facilitating the rapid re-synthesis of adenosine triphosphate (ATP). The average amount of total creatine stored in the body is ~120 g (for a 70 kg human) and the rate of creatine degradation to creatinine is ~1.7% of the total body creatine pool per day (13,14). To compensate for this daily turnover, the average person requires ~2 g creatine per day, with about half of this daily requirement (1 g) synthesized endogenously and the remainder coming from dietary sources (10,12,15).

Creatine and Brain Metabolism

The brain is a metabolically active tissue, requiring ~20% of total energy consumption, despite only accounting for 2% of total body mass. Creatine content and metabolism impairments have been reported as associated with neurological and psychiatric disorders (7,16,17), rising the hypothesis that creatine intake, in the daily diet or as a supplement, could be of therapeutic value for treating neurologic/psychiatric illnesses (6,18,19).

Creatine is a natural regulator of energy homeostasis, playing a relevant role in brain bioenergetics (7), justifying the neurological disease's development and profound cognitive impairment due to the inability to synthesize or transport creatine (i.e., creatine deficiency syndrome) (6,18-20). Indeed, CK is expressed in a brain-specific isoform (BB-CK), suggesting that creatine plays a role in energy provision and homeostasis in the central nervous system (CNS) (12,20-22).

Complex cognitive tasks, hypoxia, sleep deprivation, and some neurological conditions are characterized by rapid brain metabolic activity and ATP depletion, where creatine metabolism could be essential for energy homeostasis (21-24). It is important to highlight that the brain creatine content may also decrease with age, and age-related decreases in brain creatine content could be associated with reduced brain activity or disease (22,25).

In addition, deletion of cytosolic brain-type CK in mice was shown to result in slower learning of a spatial task and diminished open-field habituation as well as increased intra- and infra-pyramidal hippocampal mossy fiber area, suggesting that the creatine-CK network is also involved in brain plasticity in addition to metabolism (26).

A growing body of literature shows that creatine supplementation can enhance brain creatine content (20,22). However, it is unclear if habitual dietary intake of creatine from food sources can be sufficient to maintain the brain's creatine stores as well and cognitive function.

Creatine and Brain Aging

The muscle creatine stores decrease with age, although it is not clear whether this reduction is due to aging or simply associated with declines in the amount of physical activity that elderly individuals engage (20). It is similarly thought that brain creatine levels may also decrease with age, and this may be due to general aging, or it may coincide with reductions in brain activity (22). Regardless of the mechanism, reductions in creatine content and its metabolites may be part of the cognitive capacity impairments, which are typically associated with aging (6). This is supported by data showing that older people with higher resting creatine concentrations tend to perform better in cognitively demanding tasks (6,21).

Aging, Obesity, and Cognition

Outside of aging, obesity may also play a role in cognition since obesity causes structural and functional cerebral microcirculation impairments, which play a crucial role in the pathogenesis of both cognitive impairment and major diseases such as Alzheimer's disease (27-29). Specifically pathophysiological consequences of cerebromicrovascular dysregulation in obesity have been associated with blood-brain barrier (BBB) disruption, neuroinflammation, exacerbation of neurodegeneration, microvascular rarefaction, and ischemic neuronal dysfunction and damage (27). These alterations are likely to have meaningful consequences on cognition. For example, overweight older women exhibit larger declines in perceptual speed over time than would be expected from normal aging (27). In fact, comparing overweight women to normal body weights ones, the observed decline in perceptual speed suggested an additional 2.4 years of aging (30). The hypothesized mechanism linking obesity and such brain alterations is related to the metabolic activity of adipose tissue, which secretes a variety of adipokines, which signal at both peripheral and central sites (27). Excessive adiposity can result in dysregulated adipokines secretion, many of them with pro-inflammatory effects, rendering the adipose tissue a major contributor to systemic inflammation (29). This low-grade inflammation, induced by circulating pro-inflammatory mediators secreted from adipocytes, is recognized as an important factor in impaired neuronal function and the pathogenesis of cognitive impairment (27).

Reduced selective attention and inhibitory function in overweight older adults affect autonomy, increasing the risk of other age-associated problems (28,29,31). Decreased ability to isolate central and flanked information can lead to postural instability and falls, while correctly discerning the surrounding environment increases autonomy. Previous studies (3,4,32-34) allow us to suggest that creatine intake in daily diet and supplementation can be an ally in maintaining the autonomy and health of old adults (33), not only due to the effects against sarcopenia but also in the maintenance of CNS activity (6,12,21).

Memory

One specific cognitive domain that appears critical in aging adults is memory. Memory is the ability to acquire, store and retrieve available information in the brain. It is also the stored information and facts, which were obtained through heard or lived experiences. The typical age-associated CNS function decline impairs the ability to store information and learn new tasks, impacting the quality of life in older adults (26,29-31,35).

Increased brain creatine content, specially CrP, has been shown to preserve the integrity and stability of the cell membrane, such as structural stability and functional maintenance, preventing cell apoptosis caused by abnormal energy metabolism (36). *In vitro*, creatine has been shown to increase oxidative phosphorylation in synaptosomes and isolated brain mitochondria (37). In rats, creatine injected into the hippocampus enhanced spatial memory and object exploration (38). In addition, cAMP-response element-binding protein (CREB) known to influence memory is upregulated 30 minutes after creatine injection (38). Recently, 4 weeks of creatine supplementation in mice enhanced isolated hippocampal mitochondria and improved memory (39). Further, creatine is important for neuronal protection (40). Future research is warranted to investigate whether creatine intake from a daily diet can alter these potential mechanisms in humans.

Neurodegenerative Diseases

Furthermore, creatine may play a role in the prevention of other neurodegenerative diseases such as Alzheimer's disease. Alzheimer's disease is associated with a reduction in brain creatine content and in a recent study using a 3xTg mouse model of Alzheimer's disease, creatine supplementation over 8-9 weeks exhibited beneficial preventative effects in females (41). It is described that the spatial memory impairments induced by beta-amyloid protein accumulation are greater in females (39,41), while Snow et al. (39,41) showed that the mitigating deleterious effects promoted by creatine supplementation are superior in females. It is important to note that the proposed underlying mechanism is not the decrease in plaque accumulation, but the greater availability of ATP/CrP, reducing the effects of neuronal apoptosis and necrosis, mainly in the hippocampus (39-41). Other proposed mechanistic effect is the down-regulation of the NF-κB inhibitor, IκB, induced by creatine (39). Notwithstanding, neuronal NF-κB regulates the expression of several genes involved in cognition and memory (39).

Creatine as a Needful Nutrient

Ostojic et al. (3) found a significant positive correlation between WAIS III Digit Symbol Substitution Test (DSS) scores and habitual dietary intake of creatine in a larger sample of older adults. Working memory for spatial locations activates the superior prefrontal cortex and posterior parietal cortex, and previous studies (6,42) showed a presence of BB-CK isoform and Cr/PCr in these brain areas, however, brain permeability to circulating creatine is limited due to the absence of creatine transporter expression in the astrocytes involved in crossing the BBB. Since the brain endogenously synthesizes creatine, it is unclear as to the importance of exogenous delivery of creatine, may differ in older adults (6,20). Thus, more specific studies on the association between daily dietary intake, biosynthesis, and creatine concentration in the CNS are needed.

Notwithstanding, the literature is conflicting on the effects of creatine supplementation on cognitive task performance in older adults (20). It is important to highlight that the difficulty in assessing brain creatine concentration is one of the main limitations of this kind of study. Despite the physiological plausibility of the proposed mechanisms for the success of creatine supplementation, added to the positive results. Some studies still show insufficient or contradictory results (15,43,44). The main challenge for the future is to measure the appropriate doses so that the results can be confirmed, increasing the strength of the evidence.

Approximately 1 g of creatine is converted to creatinine per day, suggesting that 1 g of creatine be ingested or synthesized to replenish reserves (8,10,32,33,45). It is quite common for older adults to have low protein intake, especially from meat (33), possibly due to difficulty in chewing. Older adults may need creatine supplementation beyond increasing dietary intake to help replenish reserves, regardless of whether they increase intracellular stores to improve some skill or competence.

Conclusion

The importance of creatine in the energy metabolism of the brain is already well established. The relationship between the decline of cognitive functions and creatine still lacks stronger evidence. Evidence is also lacking on whether creatine supplementation is beneficial in mitigating the neural effects of aging. Further studies should explore the scientific gaps in this field, as well as investigate the association between creatine supplementation and other interventions, such as exercise training, to minimize/ameliorate brain aging. In summary, it remains an open field of studies that brings plausible perspectives.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.M., R.P., Design: M.M., R.P., Analysis or Interpretation: M.M., R.P., Literature Search: M.M., R.P., Writing: M.M., R.P.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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