Review Article

Creatine Activity as a Neuromodulator in the Central Nervous System

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ABSTRACT

Creatine is a nutritional compound that potentially influences cognitive processing and neuroprotection. Recent evidence has demonstrated that similar to neurotransmitters, creatine is released in an excitotoxic and action potential-dependent manner and acts as a neuromodulator.
Creatine deficiency syndromes are characterized by severe mental and developmental disorders. Studies have reported that brain creatine content could be enhanced with creatine supplementation. Nevertheless, there is still limited knowledge about the effects of creatine on the central nervous system. However, ample evidence has proved the neuroprotective effects of creatine on various mental aspects, such as cognition, memory skills, and spatial memory. The present review aimed to review available experimental data and clinical observations confirming creatine roles in the central transmission process. A systematic search in the literature was performed in PubMed, Scopus, Embase, Cochrane Library, Web of Science, and Google Scholar database using all available MeSH terms for Creatine, Phosphocreatine, Bioenergetics, Nervous system, Brain, Cognition, and Neuroprotection. Electronic database searches were combined and duplicates were removed. Here, first, creatine and its potential influence on cognitive health and performance were briefly reviewed. Next, the existing experimental and clinical evidence was specifically explored to understand how creatine could interact as a neurotransmitter in the nervous system. Studies have revealed that exogenous creatine supplementation decreases neuronal cell loss in experimental paradigms of neurological diseases. It was observed that creatine could interact with the N-methyl-D-aspartate receptor, Na^+-K^+-ATPase enzyme, $GABA_A$ receptor, serotonin 1_A receptors, and presumably α_1-adrenoceptor and play critical roles in the central transmission process which implies that creatine can be considered a neuromodulator.

Keywords: Creatine, GABA, Neuroprotection, Neurotransmitter Agents; N-Methyl-D-Aspartate

1. Introduction

Creatine (N-aminoiminomethyl-N-methylglycine) is a nutritional compound produced endogenously and consumed exogenously through diet and supplements (1). Converging evidence indicates that creatine has neuroprotective effects on various mental aspects, such as cognition, memory skills, and spatial memory (2) through energy homeostasis, modulation of brain-derived neurotrophic factor, mitochondrial function, and protection against oxidative stress (3, 4).

In addition to its involvement in neuroprotection, recent evidence has suggested that creatine facilitates neuronal firing and acts as a neurotransmitter in the central nervous system (CNS) (5). Similar to other neurotransmitters, creatine is released in an excitotoxic and action potential-dependent manner. Moreover, it was enhanced by electrical stimulation and blocked by the absence of Ca^{2+} or by tetrodotoxin (6).

This evidence leads us to speculate that creatine might exert its neuroprotection at least by neuromodulatory effect; however, such examination has received less attention. Therefore, the present study aimed to review and investigate available evidence confirming creatine roles in the central transmission process.

For this goal, a systematic search in the literature was performed in PubMed, Scopus, Embase, Cochrane Library, Web of Science, and Google Scholar database using all available MeSH terms for Creatine, Phosphocreatine, Bioenergetics, Nervous system, Brain, Cognition, and Neuroprotection. Electronic database searches were combined and duplicates were removed.

The present review focused on the cellular mechanisms by which creatine may be involved in the modulation of neurotransmitters functions. Emphasis was laid on the possible role that creatine plays in the CNS. The basic and clinical evidence regarding creatine-based mechanisms of brain function were also highlighted.

2. Glutamate Excitotoxicity

Glutamate, the main excitatory neurotransmitter in the brain, has been implicated in the pathophysiology of various neurologic diseases, such as pain, anxiety, and depression (7, 8). It is believed that high concentrations of glutamate act as an excitotoxin and induce various impairments in CNS, such as mitochondrial dysfunction, intracellular adenosine triphosphate (ATP) insufficiency, oxidative damage, and subsequently neuronal apoptosis (9).

Oxidative agents (hydrogen peroxide) increase intracellular calcium levels through the activation of the N-methyl-D-aspartate receptor (NMDAR), leading to an increase in nitric oxide (NO) production (10, 11). In addition to oxidative stress, increases in calcium-glutamate-NO production are also neurotoxic and commonly involved in the pathophysiology of several neurological diseases and neuronal cell death (12).

Furthermore, NMDAR antagonists can counteract this glutamate excitotoxicity pathway. Creatine is a compound capable to act as an NMDAR antagonist target in the attenuates of glutamate excitotoxicity without causing side effects (10). A growing number of reports presented evidence for the protective effects of creatine against glutamate excitotoxicity (10-13). Creatine directly stimulates synaptic glutamate uptake to reduce extracellular glutamate by providing the energy of this very energy-demanding process (13).

In addition, creatine directly inhibits NMDAR-mediated calcium response and ATP depletion induced by glutamate (14) which leads to the prevention of excitotoxicity effect and cell survival (10). Moreover, creatine might also prevent the glutamate-induced increased levels of NO in neuron-glia cells (15). Similarly, a study reported that creatine supplementation completely restored NO to normal levels and stabilized intracellular calcium concentrations (12).

Another creatine target protein in neural transmembrane is NMDAR which plays a critical role in learning and memory through the activation of Na^+, K^+-ATPase enzyme. The Na^+, K^+-ATPase, a key enzyme in the cell membrane, which is activated by the calcineurin, plays a pivotal role in cellular ionic gradient maintenance and neural excitability (5). It is a critical process for neural functioning and its impairments are

associated with several neurological diseases (6). In accordance with this view, it was shown that Na^+, K^+-ATPase inhibition increased cellular Ca^{2+} and glutamate which could cause seizures in mice (16) and cell death in rat hippocampus (17).

Royes, Fighera (18) showed a direct stimulatory interaction of creatine with the NMDA receptor. In their study, creatine facilitated synaptic transmission and intracellular communication in the hippocampus which led to learning improvement. Furthermore, in the aforementioned study, 2-amino-5-phosphonopentanoic acid, the selective NMDA receptor antagonist, diminished the creatine enhancement effect on both the amplitude and the number of population spikes in the hippocampal CA1 subfield (18).

In a study performed by Rambo, Ribeiro (5), incubation of rat hippocampal slices with creatine increased Na^+, K^+-ATPase, voltage-gated Na^+ channels activity, and subsequent calcineurin pathway. It was assumed that depolarization produced an influx of Ca^{2+} and then subsequent release of creatine. If Ca^{2+} was not present or Na^+ channels were blocked, creatine was not released.

Hence, the stimulating effect of creatine on NMDA receptors must be mediated by cellular Ca^{2+} and Na^+ channels and subsequent calcineurin pathway activation (5, 6, 19, 20). These findings demonstrated that creatine supplementation improves learning and memory by a mechanism depending partially on the involvement of NMDA receptors and cellular ionic gradient maintenance (21, 22).

3. Effect of Creatine on γ-Aminobutyric Acid Receptors

It is estimated that 20-50% of all central synapses use γ-aminobutyric acid **(**GABA), one of the most important inhibitory neurotransmitters in the nervous system. The action of these receptors is mediated by two different receptor classes, namely $GABA_A$ and $GABA_B$ receptors (23). It has been indicated that creatine, as an agonist, exerts its effects by $GABA_A$, but not $GABA_B$ receptors (24, 25). Nonetheless, previous works have demonstrated that the hallmark feature of some psychiatric diseases is GABAergic impairment. Therefore, after post-traumatic epilepsy (26) and traumatic brain injury (TBI) (27), a substantial loss of GABA receptors in the hippocampus was observed.

However, creatine might protect the brain against neuronal loss and excitability by attenuating the loss of GABAergic interneurons (28)**.** In line with this finding, it has been shown that creatine stimulates synaptic glutamate uptake through the GABAergic system and thereby, reduces extracellular glutamate accumulation and excitotoxicity (6, 29, 30)**.**

In addition, the hippocampal enzyme glutamic acid decarboxylase 67, which is responsible for over 90% of GABA production in the CNS, was downregulated after TBI. Nevertheless, this effect was reversed by creatine supplementation (28). These reports declare that creatine is able to maintain the GABAergic tonus and maintain the GABA-mediated synaptic inhibition in the brain. Moreover, studies have revealed that chronic creatine supplementation treatment results in a moderate enhancement in the density of GABA neurons in spinal cord cultures (31).

4. Discussion

It has been reported that creatine is related to serotonin and dopamine activity in male and female rats and its supplementation attenuates the negative effects of forced swim stress by possibly interacting with the serotonergic system (32). In addition, Cunha, Pazini (33) demonstrated that acute creatine administration elicits an antidepressant-like effect dependent on, at least in part, activation of the α_1-adrenoceptor (dopaminergic activation).

Furthermore, Andres, Huber (34) identified creatine as a potent survival and neuroprotective factor for dopaminergic neurons, which protects them against neurotoxic and metabolic insults. It has been shown that the antidepressant-like effect of creatine appears to

be mediated via the activation of the post-synaptic serotonin 1_A (5-HT_{1A}) receptors and the suppression of presynaptic 5-HT_{1A} autoreceptors (35).

The antidepressant effect of creatine on the tail suspension test is suppressed by compounds that inhibit serotonin synthesis and increased by co-administration with selective serotonin reuptake inhibitors, like fluoxetine (35). Another study by Kanekar, Ettaro (36) showed that dietary oral creatine monohydrate supplementation can improve brain bioenergetic damage at altitude in rats of both genders and has gender-based effects on regional brain serotonin levels as well as antidepressant effects. They showed that creatine treatment improved serotonin deficits in female rats at altitude and has antidepressant efficacy. In male rats at altitude, creatine alone is not antidepressant, while creatine combined with the selective serotonin reuptake inhibitors fluoxetine enhances brain serotonin levels and is an antidepressant (36).

Parkinson's disease is one of the most common neurodegenerative diseases, especially in the elderly. It is a cognitive impairment characterized by progressive loss of dopaminergic neurons, with symptoms ranging from tremors, postural instability, and bradykinesia to loss of muscle mass and strength, increased susceptibility to fatigue, and movement disorders (37).

Human studies have shown that creatine responds better to dopaminergic therapy (38). Animal studies revealed that creatine supplementation may potentially be neuroprotective by preventing the loss of dopaminergic neurons (39). *In vivo* and *in vitro* investigations have suggested a protective role for creatine supplements against the cell damage induced by the dopaminergic neurotoxins 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and 1-methyl-4-phenylpyridinium ions (34, 40). Moreover, based on the results of a clinical trial study on creatine supplementation for 7 days, it was able to increase the plasma dopamine levels and enhance mood improvement (41).

Cunha, Machado (42) revealed that the antidepressant-like activity of creatine seems to be mediated by the activation of dopamine D_1 and D_2 receptors and probably a modulation of dopamine reuptake. Many studies have demonstrated that chronic stress causes dendritic atrophy and decreased spine density in neurons of the medial prefrontal cortex (43) and the hippocampus (44-46).

Several lines of evidence have shown that neuropeptides and neurotransmitters in the CNS could affect animal food intake and pain sensation (47-52). Wingless (Wnt) signaling is a key pathway that regulates glycogen synthase kinase 3β (GSK3β) activity (53). The Wnt receptors suppress proteasomal-dependent degradation of β-catenin, resulting in the aggregation of β-catenin in the nucleus (54). Evidence has shown that the GSK-3β/β-catenin pathway plays a pivotal role in the regulation of learning and memory (55).

Leem, Kato (56) showed that creatine supplementation through the canonical Wnt/GSK3β/β-catenin pathway prevented chronic stress-induced defects of hippocampal neurogenesis. Taken together, these findings confirm that creatine, by interaction with serotonergic and dopaminergic systems, is a potent endogenous survival and protective factor in the nervous system.

The present review aimed to summarize the available experimental data and clinical research reporting the neuromodulatory function of creatine in the nervous system. It can be concluded that creatine plays a critical role in the central transmission process through interaction with various receptors. This implies that creatine can be considered a neuromodulator.

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Authors' Contribution

Study concept and design: G. H. M.
Acquisition of data: G. H. M., G. P. G, B. H.
Analysis and interpretation of data: G. H. M.
Drafting of the manuscript: G. H. M.
Critical revision of the manuscript: G. H. M., G. P. G, B. H.

Conflict of Interest

The authors declare that they have no conflict of interest.

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