Review

Creatine as a Therapeutic Target in Alzheimer's Disease

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A B S T R A C T

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease, affecting approximately 6.5 million older adults in the United States. Development of AD treatment has primarily centered on developing pharmaceuticals that target amyloid-β (Aβ) plaques in the brain, a hallmark pathological biomarker that precedes symptomatic AD. Though recent clinical trials of novel drugs that target Aβ have demonstrated promising preliminary data, these pharmaceuticals have a poor history of developing into AD treatments, leading to hypotheses that other therapeutic targets may be more suitable for AD prevention and treatment. Impaired brain energy metabolism is another pathological hallmark that precedes the onset of AD that may provide a target for intervention. The brain creatine (Cr) system plays a crucial role in maintaining bioenergetic flux and is disrupted in AD. Recent studies using AD mouse models have shown that supplementing with Cr improves brain bioenergetics, as well as AD biomarkers and cognition. Despite these promising findings, no human trials have investigated the potential benefits of Cr supplementation in AD. This narrative review discusses the link between Cr and AD and the potential for Cr supplementation as a treatment for AD.

Keywords: Alzheimer's disease, creatine, brain, bioenergetics, mitochondria

Introduction

Adults aged 65+ represent the fastest-growing population and the most affected age segment for neurodegenerative diseases [1]. The most common neurodegenerative disease is Alzheimer's disease (AD), which currently affects about 6.5 million Americans and, by 2050, is expected to exceed 15 million [2]. This growth, combined with the lack of efficacious pharmacological treatments [3], constitutes a severe future risk to economic and social stability in the United States. Thus, there is a dire need for [1] effective preventive strategies that reduce AD risk and [2] therapeutic interventions that ameliorate symptoms

for those diagnosed with AD. For decades, the focus of the AD drug development pipeline for treatment and prevention has primarily targeted the amyloid-β (Aβ) plaques that accumulate as a hallmark pathological change in the progression toward symptomatic AD. Although novel Aβ antibody therapies have shown promise in recent clinical trials [4, 5], Aβ-centric approaches have had a poor track record of treatment development, leading to hypotheses that other AD pathology targets may be more appropriate for prevention and treatment [6].

One such target is brain energy metabolism, termed "brain bioenergetics." Along with the classic hallmark pathological signs

of AD, Aβ plaques and tau tangles, impaired brain metabolism is also observed before and after the onset of symptomatic AD [7]. Mitochondrial dysfunction and impaired glucose utilization have been consistently cited as contributing to AD progression [8], and it is hypothesized that bioenergetic decline is an essential upstream contributor to AD development [7]. Indeed, adenosine triphosphate (ATP), the body's primary energy-providing molecule, is decreased early in hippocampal and cortical neurons in AD pathogenesis [9]. Cellular levels of ATP are a critical factor in cellular survival [10], and reduced brain ATP is associated with altered Aβ processing [11] and cerebral accumulation of Aβ plaques [9]. Creatine (Cr) is an organic acid [12] important for maintaining ATP and energy homeostasis in organs with high energy flux, such as the brain [13]. Evidence suggests the brain Cr system is perturbed in AD [14] and represents a potential bioenergetic target for AD therapies.

Creatine monohydrate (CrM) is an oral nutritional supplement that safely and reliably increases intramuscular Cr levels and is commonly used as an ergogenic aid for sports and exercise [15]. Recent evidence suggests CrM supplementation may improve cognition in younger and older adults [13], and a few small-sample studies suggest brain Cr may increase after supplementation [16–23]. Dolan et al. [24] provide a detailed and up-to-date review of the studies that have investigated brain Cr and phosphorylated Cr (PCr) response to varying CrM interventions and demographics. However, it remains unclear how permissible the blood-brain barrier (BBB) is to peripheral Cr [25]. Emerging and promising evidence from AD rodent models suggest CrM supplementation may improve mitochondrial function and be neuroprotective [26–28]. Thus, CrM may be a feasible supplement for AD risk prevention and symptom treatment.

No clinical trials have investigated CrM supplementation as a potential treatment in individuals with AD. Therefore, the purpose of this review is to discuss the potential link between Cr and AD, existing evidence for CrM in AD animal models, potential beneficial mechanisms of CrM supplementation in AD, and the need for CrM clinical trials to investigate the potential benefit of CrM supplementation in treating humans with symptomatic and prodromal AD.

Brain Cr and AD

The Cr system is integral in supporting both peripheral and brain energy requirements. Its role may be especially vital in the brain as it is a highly metabolic organ, demanding approximately 20% of total body energy [29], and can locally synthesize Cr from its precursors [30]. In a 2-step process, nearly half of the body's Cr is synthesized from endogenous arginine, glycine, and s-adenosyl methionine (SAM) [12]. The first step involves the formation of guanidinoacetate (GAA) by glycine amidinotransferase, mitochondrial (GATM) activity, which is then used to synthesize Cr via guanidinoacetate N-methyltransferase (GAMT) activity. Cr can also access the brain from the periphery through the BBB via creatine transporter 1 (CRT1), though the rate of uptake and optimal peripheral concentration to facilitate increased uptake in the brain is not well understood [25]. Deficiency of either enzyme (GATM or GAMT) or CRT1 results in a cognitive disorder known as cerebral creatine deficiency syndrome (CCDS) [31].

To meet rapid energy demand and maintain energy homeostasis, Cr serves as the primary chaperone for transporting energy-producing phosphate groups generated by mitochondrial and cytosolic metabolism in muscle and brain cells [32, 33]. ATP generated by the tricarboxylic acid cycle and the ETC in mitochondria donate phosphate to Cr via mitochondrial Cr kinase (mtCK) activity to form PCr that then diffuses from the mitochondria into the cytosol. Likewise, brain-specific Cr kinase (BB-CK) [14] in the cytosol phosphorylates Cr to form a cytosolic pool of PCr. PCr is an important storage form of high energy phosphates that can be rapidly donated to adenosine diphosphate (ADP) to form ATP energy molecules to meet energy demand throughout the cell [34].

In individuals with AD, there is a recognized dysfunction in the brain's Cr system [35]. This dysfunction manifests in various ways. For instance, magnetic resonance spectroscopy imaging (MRSI) studies have revealed decreased levels of PCr in the brains of individuals with AD [36], and in the later stages of AD, there is a significant reduction in the levels of BB-CK [37]. Furthermore, nondemented older adults with at least one apolipoprotein E epsilon 4 (APOE4) allele, the strongest genetic risk factor for late-onset AD, had lower brain creatine levels than noncarriers and lower Cr levels were correlated with worse cognitive test performance [38]. This suggests Cr system impairments may be involved in early disease pathogenesis, preceding onset of AD symptoms.

Decreased brain Cr levels may be explained by brain hypometabolism and acute cognitive stress. In times of hypometabolism, brain PCr stores may be able to donate a phosphate to regenerate ATP as a compensatory mechanism, but this may only be effective for a limited time before PCr is depleted, eventually leading to decreased brain Cr stores. In other conditions where brain metabolism is impaired, such as in Down syndrome [39–42], where individuals are at high risk of developing AD at a young age [43, 44], and in schizophrenia [45, 46], it is similarly thought that PCr stores may be able to compensate for brain hypometabolism until PCr is diminished, resulting in decreased total brain Cr concentration. It remains unclear whether changes in the brain Cr system in AD are a downstream result of impaired energy metabolism or if dysfunction in the brain Cr system contributes to impaired brain energy metabolism and disease pathology. Nevertheless, brain Cr could be an important bioenergetic target for AD. Figure 1 illustrates transport, synthesis, bioenergetic roles, and potential mechanisms related to AD for Cr in the brain.

Animal models suggest Cr supplementation may be beneficial in AD

Evidence suggests there are potential benefits of CrM supplementation in various populations [47–51]. Though no reported trials have examined the effects of CrM supplementation in individuals with AD, CrM supplementation may benefit dysfunction of the brain Cr kinase system seen in humans with AD [52]. Two studies of CrM supplementation in rodent AD and mild cognitive impairment (MCI) models support this concept.

Snow et al. [27] demonstrated that between 8 and 9 wk of CrM supplementation in 7-mo old 3xTg mouse model, a mouse model of AD that expresses Aβ plaques and tau neurofibrillary tangles
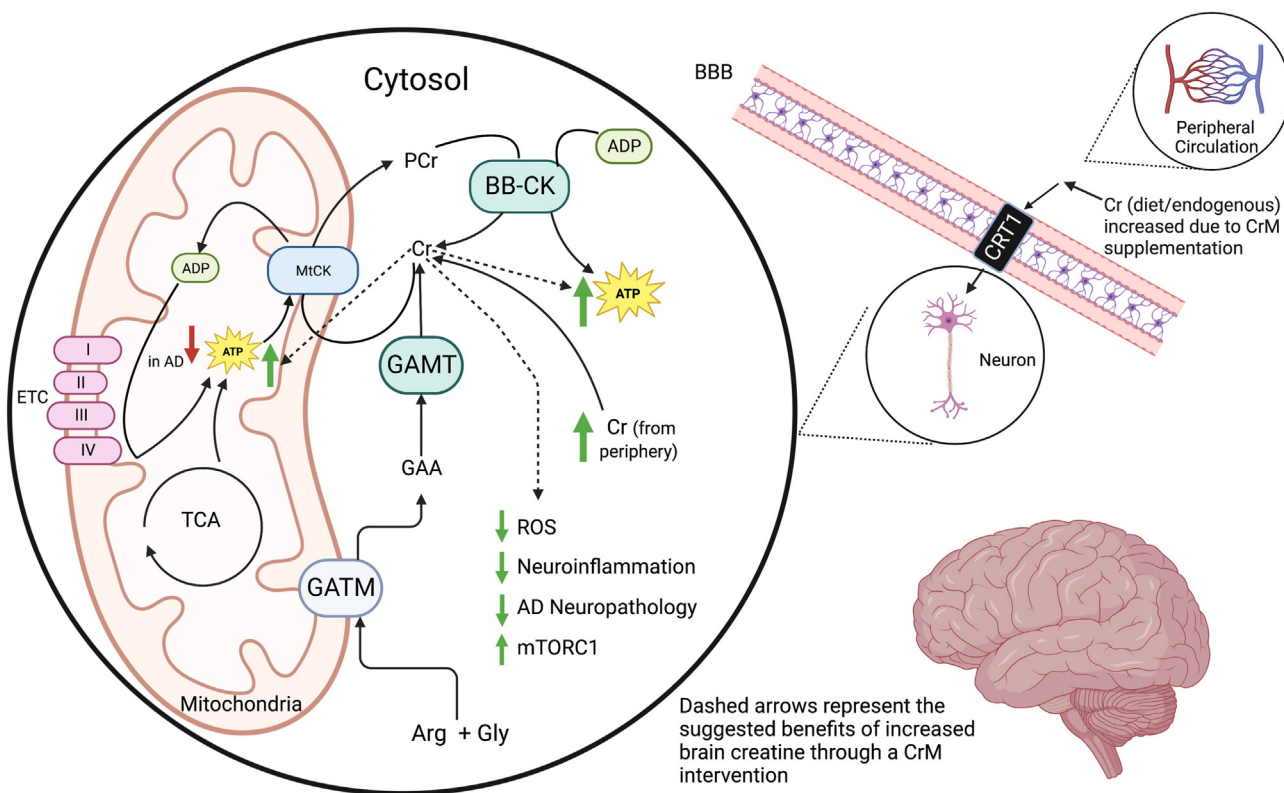
FIGURE 1. Creatine physiology in the brain and the proposed benefit of CrM in AD.

Cr in peripheral circulation is transported through the BBB via a Cr transporter, which may increase due to CrM supplementation. This Cr transporter is also expressed by neurons to allow Cr transport into the cell. Neurons also endogenously produce creatine from the amino acids Arg and Gly via a two-step process. The first step is the formation of GAA by GATM, which then forms Cr by GAMT activity. Cr helps maintain energy flux as a chaperone for energy-producing phosphate groups. ATP generated by the ETC and the TCA cycle donate phosphate to Cr via mtCK to form PCr. PCr is an important storage form of high energy phosphate that can meet energy demand throughout the cell. In the AD brain, ATP levels are decreased. Increased Cr levels in the brain may signal mitochondria to upregulate aerobic respiration by replenishing free Cr chaperones for the Cr Phosphate shuttle. Increased Cr levels in the brain may have several benefits: free Cr may have antioxidant properties and may be able to sequester ROS, decrease neuroinflammation, increase mTORC1 signaling, and decrease AD neuropathologies. This figure was created with BioRender (www.biorender.com).

Cr: creatine; CrM: creatine monohydrate; BBB: blood-brain barrier; CRT1: creatine transporter 1; Arg: arginine; Gly: glycine; GATM: glycine amidinotransferase, mitochondrial; GAA: guanidinoacetate; GAMT: guanidinoacetate N-methyltransferase; MtCK: mitochondrial Cr kinase; PCr: phosphorylated creatine; BB-CK: brain-specific Cr kinase; ATP: adenosine triphosphate; ADP: adenosine diphosphate; ETC: electron transport chain; TCA: tricarboxylic acid cycle; ROS: reactive oxygen species; mTORC1: mammalian target of rapamycin complex 1. BioRender.com

[53], improved several AD-related outcome measures. Mice in the experimental group consumed ad libitum unpurified diet containing 3% CrM by weight, whereas the control group's unpurified diet was unmodified. After 8 wk of their respective diets, all females had impaired Morris Water Maze (MWM) escape times, yet CrM supplemented females escaped more quickly and demonstrated improved spatial learning compared with control females. Males in both groups had similar MWM performance, with neither exhibiting impaired escape latency. Relative to control, CrM-fed females had increased hippocampal expression of proteins related to synaptic plasticity along with increased high-molecular weight Aβ oligomers and lower expression of low-weight Aβ oligomers, although amyloid precursor protein (APP) was unchanged. The investigators speculate that these sex differences were not likely due to sex differences in Cr metabolism, but likely due to sex differences in 3xTg mice. For instance, female 3xTg mice demonstrated worse initial cognitive impairment and learning ability than male mice at the time of study. Additionally, CrM supplementation in both males and

females improved hippocampal mitochondrial function respiration. These data suggest a possible role for CrM in supporting cognition and beneficially altering amyloidogenic processing in AD.

Mao et al. [54] investigated the effects of 6 wk of Cr supplementation (in unspecified supplemental form) on cognition and the mammalian target of rapamycin complex 1 (mTORC1) in an MCI rat model. Seven-wk-old female Wistar rats were allocated to 3 different groups: one group was injected with vehicle, whereas 2 groups were injected with lipopolysaccharide (LPS) to induce an MCI-like condition where one received Cr and the other received placebo. The Cr group received a loading dose of 1.542 g Cr/kg/d for the first wk and a maintenance dose of 0.385 g Cr/kg/d for the subsequent weeks. Compared with LPS-injected control rats, Cr-supplemented rats completed the Barnes maze test more quickly and spent more time observing objects during the novel object recognition test, suggesting Cr supplementation diminished expected LPS-induced cognitive deficits. These mice also had upregulated mTORC1 and synaptic

plasticity proteins in the dentate gyrus. In a second experiment from this study featuring rats that did not receive LPS injection, Cr-supplemented rats, similarly, had higher mTORC1 and synaptic protein expression in the dentate gyrus than the control mice. Unlike the LPS model, these rats did not have differing cognitive performance.

Evidence from these 2 studies in AD and MCI rodent models suggests CrM supplementation is potentially beneficial for cognition, bioenergetics, and AD-related biomarkers and may act in a sex-specific manner [27]. Clinical trials testing the effects of CrM on mechanisms and symptoms in AD are warranted and to determine if possible sex differences are directly related to sex or instead an advanced condition state.

Potential mechanisms for Cr in AD

The cause of AD is still not well understood, and many important etiological hypotheses attempt to explain its basis, including the leading hypothesis that Aβ initiates the disease cascade [55], as well as alternative hypotheses implicating impaired mitochondrial bioenergetics [7] or inflammation and oxidative stress [56]. CrM supplementation may be beneficial in AD as it is purported to influence each of the key components of these hypotheses as well as other potentially important mechanisms.

Decades prior to the development of histological and clinical manifestations of AD, brain mitochondrial bioenergetics and glucose metabolism are reduced [57]. Specifically, impairments have been found in the electron transport chain (ETC) complexes, including complex I [58], which is responsible for controlling a significant portion of mitochondrial respiration in synaptic mitochondria [59]. Evidence suggests mitochondrial respiration is partially regulated by the PCr/Cr ratio in human skeletal muscle [60], which could also be true in the brain. In mice, oral Cr supplementation increases mitochondrial respiration in the hippocampus. Specifically, Cr supplementation has been demonstrated to enhance the function of ETC complex I in healthy mice [26] and both ETC complexes I and III in mouse models of AD [27]. This suggests supplementing with CrM may signal mitochondria to upregulate respiration by increasing free Cr chaperones for the Cr Phosphate shuttle in the brain.

Brain insulin resistance is increasingly implicated in AD and may partially explain impaired brain glucose uptake in AD [61]. Therapies targeting brain insulin resistance have had mixed success [62, 63], yet this concept remains a reasonable bioenergetic target. In vitro and animal studies suggest Cr supplementation may improve peripheral insulin sensitivity [64, 65], though human trials have not affirmed these findings [66, 67]. Cr supplementation increases insulin-dependent GLUT-4 activity in muscle [68], a glucose transporter also expressed in the neurons of select brain regions [69], which facilitates increased glucose uptake [67]. Therefore, it is possible that Cr supplementation may enhance brain glucose uptake to provide key substrates for energy metabolism in the AD brain.

Oxidative stress is also implicated in the development and progression of AD [70, 71]. Oxidative stress is caused by excessive production of reactive oxygen species (ROS) due to aberrant mitochondrial and cytosolic energy metabolism [72, 73]. Free Cr may have direct effects as an antioxidant as it has been shown to

have ROS scavenging properties [74, 75]. Evidence suggests free Cr antioxidant activity may be particularly important for protecting mitochondria from ROS damage, which are susceptible to oxidative stress that can exacerbate mitochondrial impairment [76]. Furthermore, the BB-CK is a prime target of oxidative damage by free radicals and is perturbed in AD [77, 78]. Cr supplementation has been shown to attenuate the deleterious effects of oxidative stress on the CK isoforms [76, 79]; therefore, Cr supplementation may protect CK from oxidative damage in the brain, which is observed in cognitive decline [77].

Furthermore, CrM supplementation may be protective of neuroinflammation in AD. Aberrations to transcription factor nuclear factor kappa-b (NF-kB) have been found in AD, which may stimulate transcription of proinflammatory cytokines [80]. Although focus on NF-kB has been primarily on cancer and inflammation, it plays integral roles in memory and synaptic function [80]. NFk-B has been shown to target neurons and negatively affect APP and Aβ aggregation in AD [80]. Cr supplementation in rodents has been shown to decrease levels of NF-kB in the brain and is associated with enhanced learning, memory, and hippocampal mitochondrial function [26]. Cr supplementation has also been shown to augment synaptic proteins implicated in memory formation and learning with concurrent enhanced hippocampal-associated learning, memory, and mitochondrial function in a rodent model [81].

CrM supplementation may benefit patients with AD by modulating classical AD pathologies. Brain Aβ accumulation and bioenergetic impairment are cited as 2 of the first AD pathology changes [82] that are believed to cyclically influence each other [83]. Downstream of these initial changes, neurofibrillary tangles of phosphorylated tau (pTau) aggregate followed by frank neurodegeneration and onset of AD symptoms [82]. One preclinical study demonstrated that cultured hippocampal neurons treated with Cr were protected from neurotoxic effects from adding Aβ and glutamate to the cell cultures [28]. These effects coincided with a large increase in phosphorylation of Cr to form PCr and the ratio of PCr/ATP compared with the control, suggesting protection was conferred by increased neuronal energy potential and reserve. In female 3xTg mice, Cr supplementation altered Aβ processing by upregulating expression of high-molecular weight species and downregulating the low-molecular weight 12kDa mOC87 Aβ oligomer, the only Aβ species where higher concentration was correlated with worse cognitive impairment in this study [27]. In both sexes, 3xTg mice with higher Cr hippocampal concentration had a lower concentration of pTau/Tau [27]. These data suggest the potential bioenergetic effects of CrM in AD may influence processing and phosphorylation of the hallmark proteins, A-beta and tau.

The upregulation of mTORC1 signaling seen in mice represents another pathway Cr supplementation may provide benefit in AD [54, 84]. mTORC1 is an anabolic pathway that responds to feeding and stimulates protein synthesis [85]. Aside from its role in muscle hypertrophy, mTORC1 may play a role in memory formation [54]. For example, a rat study showed it has a role in regulating long-term potentiation in the hippocampus [86], a process that connects changes in synaptic strength to changes in long-term behavior. However, it is hypothesized perpetual activation of mTORC1 may negatively impact the aging brain [87]. Mice studies suggest chronically active mTORC1 may upregulate

Aβ accumulation and down-regulate autophagy, which both play a role in cognitive impairment in AD [87, 88]. Therefore, it may be prudent to selectively regulate mTORC1 in different phases of life. The aforementioned study by Mao et al. [54] supports the beneficial effects of Cr supplementation mediated through mTORC1 on the aging rodent brain.

CrM supplementation may have peripheral benefits outside of the brain. Specifically, Cr has the potential to enhance muscle protein synthesis by triggering signaling pathways activated through the osmotic effect of Cr in muscle cells [89]. In addition, Cr may promote muscle hypertrophy through various cellular mechanisms, including the inhibition of myostatin [90] and the activation of insulin-like growth factor/mTOR [54, 91]. Thus, CrM may be beneficial in AD because loss of lean body mass, primarily skeletal muscle, has been cross-sectionally associated with AD [92]. However, prospective studies show that muscle function and strength are better predictors for reducing risk of developing AD compared with maintenance of skeletal muscle mass volume [93–96]. Cr supplementation has been shown to increase muscle strength, lean body mass, and muscle function in diverse populations, although data are less conclusive in interventions without concomitant exercise [97–102]. Although speculative, Cr supplementation may help prevent and improve symptoms of AD through its effects on skeletal mass, muscle volume, and function [99, 103–107], which warrants future investigation.

Taken together, it is reasonable to hypothesize that Cr supplementation may offer benefits to humans in prevention as well as the early stages of AD through both brain bioenergetic and peripheral mechanisms. These mechanisms in brain health are summarized in Table 1.

Opportunities for Cr supplementation trials in humans

CrM supplementation trials in humans with AD are needed to glean essential knowledge regarding the utility of CrM as potential adjuvant therapy in AD. The mechanisms mentioned above about Cr in AD have not been tested in humans.

Currently, our group is conducting a single-arm proof-of-principle trial (NCT05383833) to determine if individuals with AD (n=20) can adhere to a 20 g/d CrM intervention for 8 wk. Our trial will generate preliminary data for key questions in AD, including change in the brain Cr levels, mitochondrial function, cognition, and muscle function and morphology to inform future, large-scale clinical trials. Our trial is a single-arm pilot trial; thus, all future results should be cautiously interpreted as preliminary, but our trial may serve as important justification for future investigation. Although this is a first step in the investigation of CrM for AD, other trials with larger sample size, a placebo control group, and an array of measures that interrogate different AD-related mechanisms and function will be necessary to determine efficacy and optimal dose in this population. For instance, since the ability of supplemental CrM to raise brain Cr levels still needs to be elucidated [13, 16, 17], future trials will be tasked with establishing optimal CrM dosing and interval required to effectively change brain Cr levels. Because the goal of AD therapies is to improve function and quality of life in individuals with AD, it will take large sample trials with an intervention interval of 1 y or longer to investigate whether CrM supplementation is beneficial for cognition and symptoms in AD.

Because bioenergetic decline is a progressive process that occurs early in AD's pathology physiology [7, 108], trials are also warranted to ascertain if CrM supplementation is valuable for AD prevention. In prodromal AD, there is a minor decrease in brain bioenergetics, but the brain may compensate until a threshold is exceeded, whereafter, a significant bioenergetic decline ensues, and AD symptoms are present [108]. Thus, a CrM intervention may be best suited early in AD pathophysiology to help delay the progression from preclinical or prodromal AD to symptomatic AD. Taken together, there is a strong rationale for Cr pilot trials in AD and those at high risk for AD.

Conclusions

It is imperative to identify effective, early treatments for AD. Cr is an important bioenergetic molecule, and the Cr system is shown to be dysfunctional in the brain of individuals with AD. Therefore, Cr may serve as a potential target for prevention and therapy and CrM supplementation may be beneficial in AD. To date, only rodent studies have investigated the use of CrM as a treatment for AD. Thus, clinical trials investigating the effects of CrM on cognition and CrM's mechanisms in humans with AD as well as its potential as a strategy to prevent cognitive decline in those with normal cognition, are needed. There is much to be learned about CrM intervention and brain health in different life and disease phases.

Author contributions

The authors' responsibilities were as follows—ANS and MKT wrote the first draft of the manuscript. All authors provided manuscript revisions and approved the final manuscript.

Conflicts of interest

The authors report no conflicts of interest.

TABLE 1
Putative roles for creatine in brain health

Putative role for creatine in brain health	References
Phosphate carrier	Wyss et al. [12]
	Hemmer et al. [14]
	Bonvento et al. [32]
	Bessman et al. [33]
ROS scavenging properties	Tarafdar et al. [73]
	Lawler et al. [74]
	Sestil et al. [75]
	Sestill et al. [76]
	Stachowiak et al. [79]
Improved energy metabolism	Snow et al. [26]
	Snow et al. [27]
	Brewer et al. [28]
	Snow et al. [80]
Protection against inflammation	Snow et al. [26]
	Snow et al. [80]
Modulation of AD neuropathology	Snow et al. [26]
	Snow et al. [27]
	Brewer et al. [28]
mTORC1 signaling	Mao et al. [54]
	Pazini et al. [84]

AD, Alzheimer's Disease; ROS, reactive oxygen species.

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Data availability

Not applicable. No data were analyzed.

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