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A Potential Role for Creatine in Drug Abuse?

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Abstract Supplemental creatine has been promoted for its positive health effects and is best known for its use by athletes to increase muscle mass. In addition to its role in physical performance, creatine supplementation has protective effects on the brain in models of neuronal damage and also alters mood state and cognitive performance. Creatine is found in high protein foods, such as fish or meat, and is also produced endogenously from the biosynthesis of arginine, glycine, and methionine. Changes in brain creatine levels, as measured using magnetic resonance spectroscopy, are seen in individuals exposed to drugs of abuse and depressed individuals. These changes in brain creatine indicate that energy metabolism differs in these populations relative to healthy individuals. Recent work shows that creatine supplementation has the ability to function in a manner similar to antidepressant drugs and can offset negative consequences of stress. These observations are important in relation to addictive behaviors as addiction is influenced by psychological factors such as psychosocial stress and depression. The significance of altered brain levels of creatine in drug-exposed individuals and the role of creatine supplementation in models of drug abuse have yet to be explored and represent gaps in the current understanding of brain energetics and addiction.

Keywords Creatine · Nutrition · Drug abuse · Depression · Stress · Magnetic resonance spectroscopy · Post-traumatic stress disorder · Traumatic brain injury

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Creatine monohydrate is one of the most popular dietary supplements on the market, with a 400-million-dollar industry promoting its use. Supplemental creatine is popular among athletes, who use it to boost performance in high-intensity physical activity like cycling or rowing, as well as to increase muscle mass and strength in resistance training. While creatine is more often associated with enhancing physical performance, it is also essential for the proper functioning of the brain. There is growing evidence that creatine may be of value in the treatment of neurological conditions, which are linked to dysfunctional energy metabolism such as age-related cognitive decline and neurodegenerative diseases [1, 2]. Moreover, creatine supplementation is beginning to attract attention as a complementary strategy in the treatment of psychiatric disorders such as depression and post-traumatic stress disorder [3–5]. Although there is virtually no research directly investigating the relationship between creatine supplementation and drug use, there is considerable evidence to support the role of creatine in both depression and stress, which are highly linked with drug use. Additionally, work examining the benefits of creatine in traumatic brain injury may be directly applicable to treating the types of neuronal damage seen with long-term drug use.

Creatine Intake, Synthesis, and Function

Creatine (*N*-aminoiminomethyl-*N*-methylglycine) is acquired from dietary intake of high protein foods, such as fish, eggs, or meat, or produced endogenously from the biosynthesis of arginine, glycine, and methionine in the liver, kidney, pancreas, and, to a lesser degree, the brain [1, 6, 7]. As it is synthesized endogenously, creatine itself is a non-essential nutrient. However, dietary intake of

creatine, or its precursors, is necessary because the reversible enzymatic conversion of creatine to phosphocreatine produces creatinine as a by-product, which is cleared from the body via the kidney. De novo creatine synthesis relies upon the one-carbon metabolism cycle, with guanidinoacetate receiving a methyl group from S-adenosylmethionine to form creatine (Fig. 1). Some estimates indicate that 70% of available S-adenosylmethionine is used to synthesize creatine [8], although these rates may be lower with high creatine intake [9]. Creatine is actively transported into the brain via a specific creatine transporter [6], and dietary supplementation with creatine increases brain levels of creatine [10].

The creatine–phosphocreatine system serves as a spatial and temporal energy buffer in tissues with significant and fluctuating energy requirements, including the brain [11–13]. Pools of cellular energy (ATP) are generated from the reaction: Phosphocreatine+ADP→Creatine+ATP and, conversely, energy is stored in the form of phosphocreatine: Creatine+ATP→Phosphocreatine+ADP [7, 14]. Creatine kinases, the catalysts of these reactions, are located in tissue where energy is needed, making this enzyme system a critical regulator of energy homeostasis [13, 15, 16]. Of importance to neuronal function, creatine improves the survival and differentiation of dopaminergic and GABAergic neurons [17–20].

Creatine is also important in imaging studies as a biomarker reflecting brain energetics. As an indication of neural energy requirements, the brain represents 2% of total body weight but uses approximately 20% of the body's energy. Peaks in regional brain creatine, which includes both creatine and phosphocreatine, represent a measurement of high-phosphate energy stores. Although historically the peak in phosphocreatine and creatine has been used as a reference point for changes in other metabolites such as *N*-acetyl aspartate (NAA) and myoinositol, emerging work suggests that fluctuations in the creatine peak may be an important measure of brain energetics. Changes in creatine resonance are indicative of fluctuations in energy use, and decreased total creatine suggests a decrease in available energy stores.

Depression

Results of a number of studies indicate that there is a relationship between creatine and depression, which is commonly comorbid with drug abuse. There is growing evidence that impairments in bioenergetic function within the brain, cellular resiliency, and neural plasticity are associated with the pathogenesis of depression. It has been hypothesized that by reversing these impairments, creatine could be useful in preventing or treating depression. In support of this hypothesis, chronic dietary intake of diets supplemented with 4% creatine decreased depressive-like behavior in a dose-dependent manner in female rats in the forced swim test, an animal model of depression. However, in male rats, intake of the creatine-supplemented diets failed to reduce depressive behavior [3].

Preliminary findings suggest that creatine supplementation can improve mood in humans [4, 5]. Individuals with treatment-resistant depression [5] or PTSD with and without comorbid depression [4] who were supplemented with 3–5 g/day of creatine monohydrate for 4 weeks reported elevated mood on the Hamilton Depression Rating Scale. This evidence is encouraging, but these studies are also methodologically limited and confounded by comorbidity, concurrent drug treatment, age, sex, and severity of depression. For instance, altered purine levels in depressed women, but not men, have been associated with treatment response [21], suggesting that creatine may be more beneficial for treating depressed females. Clinical trials are currently underway evaluating the ability of creatine to ameliorate symptoms of depression in young women (e.g., trials NCT00851006, NCT01175616, and NCT00313417).

Creatine supplementation has been widely investigated in neurodegenerative diseases linked with mitochondrial dysfunction such as Parkinson's disease, Huntington's disease, and ALS [1]. Creatine supplementation may be of particular relevance for psychiatric disorders in light of evidence that mitochondrial brain abnormalities are detected in depressed subjects [22, 23]. Creatine produces its neuroprotective effects by buffering ATP levels against neurotoxic assaults from 3-NP, MPTP, malonate, and high levels of glutamate [24–27].

Alterations in the creatine signal are seen in individuals with major depressive disorder [28]. More specifically, with respect to depression, alterations in high energy phosphate metabolism, particularly creatine and phosphocreatine levels, are associated with depression [14, 22, 29–33]. Moreover, some work has shown that there is a significant negative correlation between creatine metabolites and self-reported suicidal ideation in patients suffering from major depressive disorders [14]. More recently, it has been found that levels of brain creatine are inversely related to the severity of a depressive episode [34, 35]. Phosphorus magnetic resonance spectroscopy has shown increased phosphocreatine and decreased ATP values in the frontal lobe and basal ganglia of depressed subjects [32, 33, 36, 37].

Traumatic Brain Injury

Brain injury shares a number of common characteristics with long-term drug abuse. A recent review by Gold and colleagues [38] compares the types of cognitive and

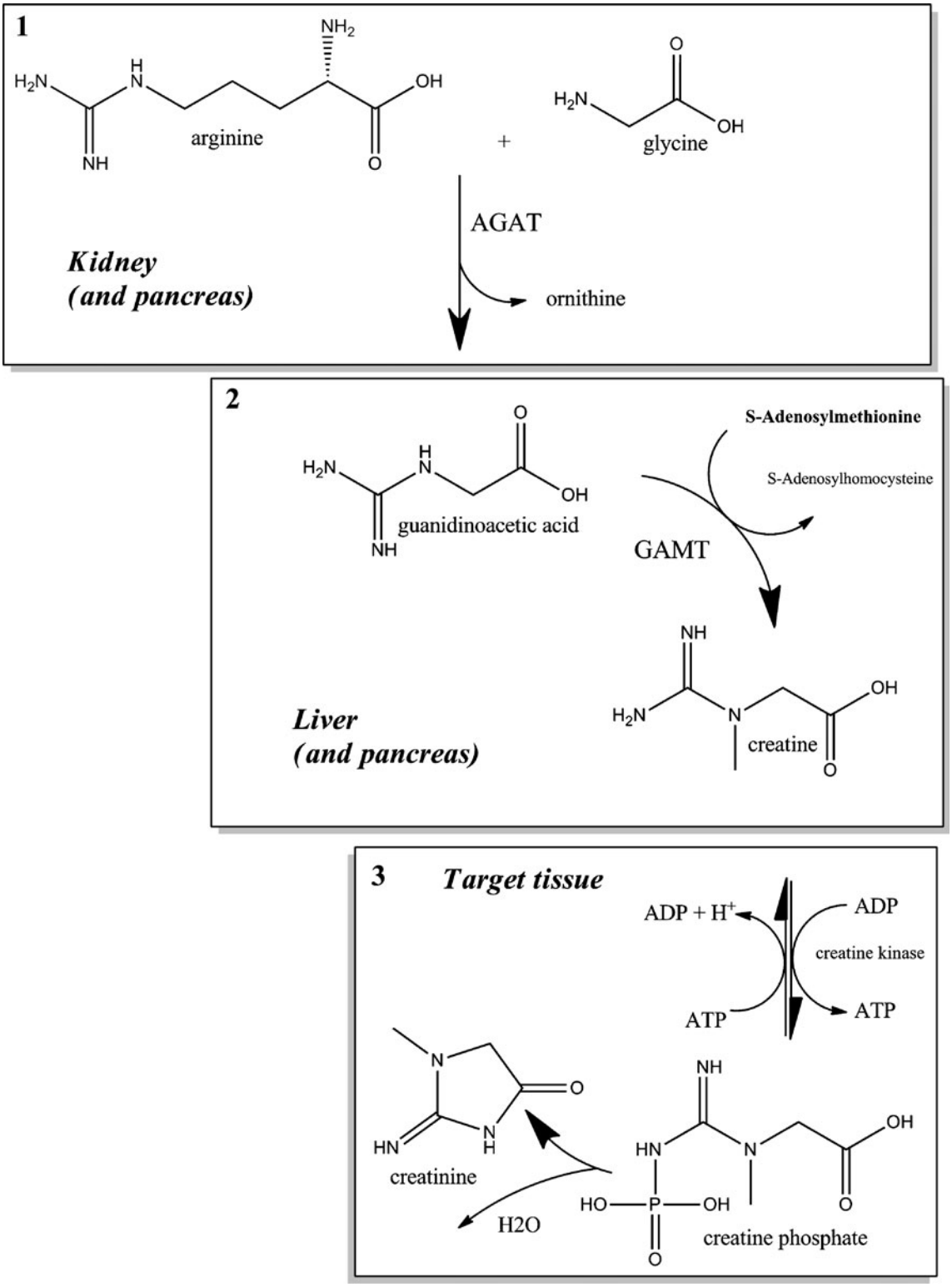

Fig. 1 Biosynthesis and metabolism of creatine. *1* The amino acids arginine and glycine are enzymatically converted by L-arginine: glycine amidinotransferase (AGAT) into guanidinoacetic acid (GAA) in the kidney. *2* GAA is methylated by guanidinoacetate methyltransferase (GAMT) in the liver producing creatine. *3* Creatine is transported to target tissue (e.g., brain or skeletal muscle) via the bloodstream. Creatine is enzymatically and reversibly converted to phosphocreatine via creatine kinase. Creatine is subsequently non-enzymatically converted into creatinine, which is excreted via the kidney

neuronal decrements seen in methamphetamine use with those seen in ischemic stroke and mechanical brain injury. Cognitive and neural deficits similar to those with traumatic brain injury are evident in those with histories of cocaine, opiate, ethanol, nicotine, and other addictive drugs [39]. It has been proposed that individuals addicted to methamphetamine might benefit from treatment with neuroprotective agents in a similar manner as those with mechanical brain injury [38]. Preliminary studies suggest that creatine supplementation may be useful in the treatment of the secondary symptoms of traumatic brain injury [40, 41]. On a short-term basis, children and adolescents given creatine spent less time in an intensive care unit and needed to be intubated for a shorter period of time than controls not given creatine. Additionally, when examined 3 and 6 months after injury, individuals who had received creatine supplementation displayed greater improvements in cognitive functioning, self-care, sociability, and communication skills than controls [40]. In a second study, the proportion of children having headaches, displaying dizziness, and reporting fatigue during a 6-month observation period was significantly lower in the creatine-supplemented group than in the control group [40].

Recent work in animals further underscores the potential for creatine supplementation in neuroprotection and recovery from brain injury. Sullivan and colleagues [42] demonstrated dose-related reductions in cortical damage following contusions in mice that had been given intraperitoneal injections of creatine for 1, 3, or 5 days before the induction of brain damage. Similarly, rats fed a standard rodent diet supplemented with creatine for 4 weeks before the induction of traumatic brain injury demonstrated a 50% reduction in cortical damage compared with rats fed only the standard diet. Moreover, creatine-treated rats displayed significantly increased mitochondrial membrane potentials, levels of mitochondrial calcium and ATP, and significantly decreased levels of reactive oxidative intermediaries, relative to rats not given creatine. In another work, rats fed a diet containing 1% creatine before experiencing controlled cortical contusions had significantly more sparing of cortical tissue and suppressed levels of lactate and free fatty acids than rats not given creatine [43]. Finally, creatine supplementation can also reduce (1) ischemia-mediated depletion of ATP and (2) caspace-3-activation and cytochrome *c* release, which are indicators of cell damage [44].

Drug Abuse

Studies demonstrating changes in brain creatine levels following drug use suggest drug-related changes in brain energetics, but the available data in both humans and animals are still limited. In many of the available studies, changes in creatine itself are not observed, but alterations in the ratio between NAA and creatine suggest increased neuronal dysfunction in individuals who have a history of abusing MDMA [45, 46], methamphetamine [47], cannabis [48], cocaine, alcohol, and polydrug use [49–51]. Very few studies report changes in creatine itself, perhaps because of its historical use as an internal reference point. In an animal model of attention deficit hyperactivity disorder, rats that were given therapeutic doses of methylphenidate during adolescence showed long-lasting increases in striatal creatine and decreases in nucleus accumbens creatine relative to controls [52]. Increases of striatal creatine in the methylphenidate-exposed animals were correlated with reduced impulsivity. In humans, one study showed decreased creatine in the basal ganglia of abstinent methamphetamine users relative to controls [53]. Children with early exposure to cocaine and males with a history of crack cocaine use show elevations of creatine in white matter [54, 55]. However, women with a history of crack cocaine use did not show significant changes in brain creatine [54]. Changes in creatine levels indicate that the brain cells of cocaine- and methamphetamine-exposed individuals may use energy differently. Similar to observations in individuals with depression, there are sex-related differences in brain creatine following drug use. However, the functional significance of these changes remains to be elucidated.

Conclusions

Drug abuse is linked with a number of long-term changes in brain, including cerebrovascular disease, decreased astrocyte and microglial activity, oxidative stress, metabolic abnormalities, increased risk for developing Parkinson's disease, and decreased neurogenesis [56, 57]. The therapeutic value of oral creatine supplementation to treat brain-related disorders is underscored by the ability of creatine to permeate the blood–brain barrier and increase cellular energy reserves [8, 58–61]. The beneficial effects of creatine are also connected to its role as a buffer in metabolic processes needed to prevent energy depletion and neuronal loss. Finally, recent work indicates that creatine prevents oxidative damage from the formation of reactive oxygen species through direct antioxidant activity [62].

The hypothesis that creatine will ameliorate some of the neurological consequences of drug abuse can be extrapolated from the current body of research examining the effects of creatine in brain trauma and in neurological disorders such as Huntington's disease and Parkinson's disease. Both Huntington's disease and Parkinson's disease have been linked with abnormalities in the creatine–phosphocreatine circuit and are accompanied by alterations in creatine kinase activity and mitochon-

drial dysfunction and oxidative damage [6, 63–66]. In human studies, creatine supplementation reduced levels of glutamate in cortex and lowered serum levels of 8-hydroxy-2-deoxyguanosine, which is a marker for oxidative damage in DNA, in patients with Huntington's disease [67, 68]. A randomized, placebo-controlled trial showed that individuals with Parkinson's disease who were supplemented with creatine for a total of 2 years reported elevated mood and required smaller increases in the amount of pharmacotherapy needed to treat symptoms in comparison to controls [69].

While research on the benefits of supplemental creatine in neurological disorders is in its infancy, emerging work indicates that creatine has potential in the treatment of a number of illnesses, including Parkinson's disease and Huntington's disease, and traumatic brain injury. The ability of dietary creatine to alter brain energetics, promote neurogenesis, and improve brain function safely and effectively also is opening up the possibility for creatine to provide a novel strategy for the treatment of mood and anxiety disorders. Given the high concordance between drug abuse and depression, creatine could moderate drug use through its beneficial effects in mood and stress-related disorders. Finally, the established similarities between drug use, traumatic brain injury, and neurodegenerative disease lead to a biologically plausible hypothesis for the ability of creatine to exert neuroprotective benefits in individuals with a history of drug use.

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