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Creatine as a treatment for depression: A brain bioenergetics perspective

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Creatine, a nitrogenous organic composed of the amino acids arginine, glycine and methionine, is a common and well-researched supplement used among athletes and bodybuilders to improve physical performance (Wyss and Kaddurah-Daouk, 2000). Beyond supplementation, it is derived from one's diet and is also produced by organs such as the liver and kidney. Through interaction with the enzyme creatine kinase, it gains a phosphoryl group, where it is stored as phosphocreatine largely in the muscles (approximately 95 %) with the remaining in the kidneys, liver and brain. Creatine's primary function is to facilitate the rapid regeneration of adenosine triphosphate (ATP), the cell's immediate energy currency, from adenosine diphosphate (ADP); when ATP releases energy to power cellular processes, it loses a phosphoryl group, converting it to ADP. Stored as phosphocreatine in tissues, creatine can rapidly donate its phosphoryl group to ADP, regenerating ATP for immediate energy needs. Because intense physical activity quickly depletes phosphocreatine reserves, supplementation enhances muscular storage capacity, providing greater energy availability for improved strength performance and accelerated recovery (Wyss and Kaddurah-Daouk, 2000). While creatine's role in muscle energetics is well-established, its equally crucial function in brain metabolism has recently gained scientific attention.

The brain, although only accounting for 2 % of body mass, utilizes approximately 20 % of energy consumption at rest (Kious et al., 2019). As such, there has been increasing interest in conceptualizing mental disorders, such as depression, through the lens of altered bioenergetics. In particular, depression represents a time of metabolic demand, related to mitochondrial pathology, including changes that affect oxidative phosphorylation and mitochondrial proliferation (Kious et al., 2019). The majority of ATP synthesis occurs during aerobic cellular respiration, which begins with glycolysis and culminates in oxidative phosphorylation, where ATP is formed from ADP using energy from the mitochondrial proton gradient. However, this metabolic pathway is complex and time-consuming. Whereas the creatine-creatine kinase-phosphocreatine circuit is able to quickly replenish ATP levels in the brain when there are significant metabolic demands, such as during depression. Yet when exposed to prolonged metabolic stress, brain phosphocreatine stores can become depleted, forcing cells to rely on the slower glycolysis pathway, potentially leading to mitochondrial dysfunction and brain pathology (Allen, 2012).

Dietary intake represents a significant source of creatine in humans. Red meat and fish provide particularly rich concentrations, while other animal products, fruits, and vegetables contain minimal amounts. As such, those that adhere to vegetarian or vegan diets have approximately 30 % lower creatine content than their meat-eating counterparts (Watt et al., 2004). A population-based study on 22,692 U.S. adults found an inverse, stepwise association between dietary creatine intake and depression, with the strongest effect in females and participants aged 20–39 years (Bakian et al., 2020). Although dietary creatine is important, one would need to eat approximately 3 pounds of beef in order to get the same amount of a single scoop (5 g) of creatine; as such it is not recommended to use meat as one's primary source of creatine.

Although creatine uptake in the brain is limited relative to skeletal muscle, it crosses the blood-brain barrier (BBB) via microcapillary endothelial cells expressing the sodium-dependent creatine transporter SLC6A8, albeit at a lower transport rate compared to peripheral tissues (Forbes et al., 2022). Therefore, total creatine ingestion may need to be higher (than what is feasibly possible by diet) and for prolonged periods of time to produce significant effects in the brain as compared to the muscle. Typically, when creatine is taken for physical performance, one starts a "loading phase" of 20–25 g for 7 days, followed by a "maintenance" of 3–5 g per day; the objective of this is to rapidly saturate the muscle creatine stores, leading to faster and more noticeable gains in strength and muscle mass. However, for brain benefits, perhaps the dose must be higher, and for a prolonged period of time.

Interestingly, creatine has been used as an adjunct to both selective serotonin reuptake inhibitors (SSRIs) and cognitive behavioural therapy (CBT) in the treatment of depression, with largely positive findings (Kious et al., 2019). In an 8-week double-blind placebo-controlled trial in participants with depression assigned to receive escitalopram in addition to creatine (5 g/day) or placebo, there were significantly

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greater improvements in depression score, as early as week 2 of treatment, which were maintained at weeks 4 and 8. This is in line with the literature that high phosphocreatine levels at baseline are associated with a subsequent positive treatment response to SSRIs (Lyoo et al., 2012). In an 8-week double-blind placebo-controlled trial in participants with depression assigned to receive CBT in addition to creatine (5 g/day) or placebo, there were similarly increases in the antidepressant efficacy. These observed benefits may be mediated by creatine's known benefits on cognition, allowing for increased active participation in therapy (Forbes et al., 2022). It is important to note that this is the first and only study which has combined creatine and CBT (Nogueira et al., 2025), and thus should be treated as preliminary evidence (De Giorgi et al., 2025).

Although these trials have paved the way for future creatine research, there is room for further optimization to maximize antidepressant efficacy. Firstly, as mentioned, although creatine is capable of crossing the BBB, higher doses (than 5 g/day) for a longer period of time (>8 weeks) remain largely unexplored and may be required for optimal efficacy. In particular, a recent trial administered a high single dose of creatine (0.35 g/kilogram of bodyweight; i.e., 35 g for a 100 kg person) among healthy, but sleep-deprived (a state of high metabolic demand) subjects, which partially reversed metabolic alterations and cognitive deterioration associated with sleep deprivation (Gordji-Nejad et al., 2024). Second, glycocyamine (GAA), a direct natural precursor to creatine, has demonstrated greater rise in brain creatine levels, than creatine itself. Therefore, GAA supplemented alone or with creatine may be a promising dietary strategy to alter the bioenergetics of the brain (Forbes et al., 2022). Third, as exercise has demonstrated equivalence in antidepressant effects amongst SSRIs and CBT, with impacts on brain bioenergetics, it is imperative that the combination of creatine and exercise be formally explored (Fabiano et al., 2025; Fabiano and Stubbs, 2025). In the real-world setting, this is extremely applicable given the high prevalence of creatine use among those who exercise. Overall, creatine remains a promising adjunctive intervention for the treatment of depression, which can be combined with many existing first-line options.

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Declaration of competing interest

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