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Review

Creatine metabolism and psychiatric disorders: Does creatine supplementation have therapeutic value?

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ABSTRACT

Athletes, body builders, and military personnel use dietary creatine as an ergogenic aid to boost physical performance in sports involving short bursts of high-intensity muscle activity. Lesser known is the essential role creatine, a natural regulator of energy homeostasis, plays in brain function and development. Creatine supplementation has shown promise as a safe, effective, and tolerable adjunct to medication for the treatment of brain-related disorders linked with dysfunctional energy metabolism, such as Huntington's Disease and Parkinson's Disease. Impairments in creatine metabolism have also been implicated in the pathogenesis of psychiatric disorders, leaving clinicians, researchers and patients alike wondering if dietary creatine has therapeutic value for treating mental illness. The present review summarizes the neurobiology of the creatine–phosphocreatine circuit and its relation to psychological stress, schizophrenia, mood and anxiety disorders. While present knowledge of the role of creatine in cognitive and emotional processing is in its infancy, further research on this endogenous metabolite has the potential to advance our understanding of the biological bases of psychopathology and improve current therapeutic strategies.

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1. Introduction

The prevalence and severity of psychiatric disorders are well substantiated by epidemiologic data, where an estimated 26–30% of the U.S. population is affected by at least one mental illness annually (Kessler et al., 1994, 2005). Compounding this issue, psychotropic medications have had limited treatment success owing to delayed onset of therapeutic activity, partial or no response, individual variability, poor tolerability, high cost, and stigma associated with use (Masand, 2003; Usala et al., 2008; Young et al., 2009). An array of possible side effects contribute to low adherence rates (28–44% discontinue use within 3 months), particularly impairments in memory, attention and executive processes, extrapyramidal effects, sexual dysfunction, weight gain, and sleep disturbances (Kennedy, 2006; Masand, 2003). With these concerns in mind, researchers, clinicians and patients alike are increasingly seeking out complementary and alternative medicines (CAM), or natural forms of therapy, to improve the speed and efficacy of relief, to reduce the occurrence of adverse events, and possibly to uncover innovative mechanisms of drug action. According to the 2007 National Health Interview Survey (Nahin et al., 2009), 38.3% of Americans reported using CAM annually and consumers spent more than $15 billion on non-vitamin/non-mineral products, which contain nutritional ingredients intended to supplement the diet.

Creatine monohydrate is one of the most popular of these naturally occurring compounds, with an estimated annual market value of $400 million (Metzl et al., 2001). The primary physiological function of creatine is to buffer energy concentrations in tissues with significant and fluctuating energy demands, especially in muscles and the brain (Wyss and Schulze, 2002). Interest in creatine has centered primarily on its use as an ergogenic aid to enhance sports performance (Benzi, 2000). Nevertheless, it is becoming increasingly evident that endogenous creatine plays a critical role in a range of cognitive functions, including learning, memory, attention, speech and language, and possibly emotion.

Impaired brain energy metabolism and alterations in neuronal plasticity are among the leading hypotheses in the pathogenesis of psychiatric disorders (Kondo et al., 2011a; Martin et al., 2009; Stork and Renshaw, 2005; Wood et al., 2009; Yildiz-Yesiloglu and Ankerst, 2006; Young et al., 2009). Logic would suggest that interventions like creatine that modulate energetic, oxidative and neurotrophic parameters would improve therapeutic efficacy in psychiatric patients. With this end in mind, it is important to know whether psychiatric disorders show reliable alterations in creatine metabolism, and if so, what the location and directionality of these changes are with respect to each disorder. Much of the recent evidence on changes in brain creatine metabolism in humans has been provided by studies using magnetic resonance spectroscopy (MRS), a neuroimaging tool that enables scientists to noninvasively measure major metabolites like creatine and phosphocreatine in various brain regions in vivo (for review, see Kondo et al., 2011a; Maddock and Buonocore, 2012).

Understanding the relationships between the creatine–phosphocreatine circuit, stress, and psychiatric disorders may inspire novel hypotheses for the biological bases of these disorders or provide insight for mechanisms of drug action for more rapid, effective treatment. Accordingly, the purpose of this article is to review studies linking endogenous creatine with psychopathology, to weigh available evidence for the use of dietary creatine to treat psychiatric symptoms, and to discuss plausible mechanisms of action relevant to these disorders. Specifically, this paper will (1) provide a comprehensive description of the neurobiology of creatine, (2) summarize reports on the bioavailability, safety, and tolerability of creatine supplementation in humans and animals, and (3) compare and contrast changes in creatine metabolism observed in schizophrenia, mood and anxiety disorders. The discussion will focus on whether there is value in dietary creatine for treating psychiatric disorders and clinical implications will be addressed, including sex differences in creatine metabolism and response to supplementation and the effects of psychotropic medications on creatine metabolism.

2. Neurobiology of creatine

2.1. Creatine synthesis, transport, and loss

Creatine is a constituent of a normal diet of protein-based foods, such as milk, meat, and nuts. It is not considered an essential nutrient because the kidneys, liver, pancreas, and possibly brain cells are able to synthesize this compound endogenously from the amino acids arginine, glycine, and methionine (Andres et al., 2008; Béard and Braissant, 2010; Wyss and Kaddurah-Daouk, 2000). It is estimated that approximately half of an individual's daily requirement comes from alimentary creatine, while the remainder is replenished by the body (Brosnan and Brosnan, 2007).

The synthesis of creatine is a simple, albeit metabolically demanding, two-step process that follows an inter-organ pathway (Fig. 1). Production of creatine begins in the kidney with L-arginine:glycine amidinotransferase (AGAT), an enzyme which catalyzes the conversion of arginine and glycine to form guanidinoacetate and ornithine. Evidence indicates that guanidinoacetate is then released from the kidney and taken up by the liver. In the liver, the second enzyme in this process, glycine N-methyltransferase (GAMT), recruits S-adenosylmethionine (SAMe) to methylate guanidinoacetate to form creatine and S-adenylhomocysteine (SAH). Creatine synthesis is estimated to consume between 40% and 70% of available methyl groups provided by SAMe, a considerable demand upon amino acid metabolism (Brosnan et al., 2007; Mudd and Poole, 1975; Stead et al., 2001; Wyss and Kaddurah-Daouk, 2000; Wyss and Wallimann, 1994).

Endogenous synthesis of creatine possibly occurs in the brain as AGAT and GAMT are expressed in most cell types, particularly neurons, oligodendrocytes, and astrocytes (Braissant et al., 2005). However, contrary findings raise uncertainty about whether central synthesis of creatine is possible, and if it is, whether it contributes