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Review Article

Carnitine: An ideal Physiological Marker or a Novel Neurotransmitter

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Abstract

There have been various documented health and possible therapeutic advantages of creatine, despite the fact that it has mostly been investigated as an ergogenic aid for exercise, training, and sport. This is due to the fact that creatine is essential for cellular metabolism, especially in situations where metabolism is under stress, and deficiencies in the capacity to transport and/or retain creatine might hinder metabolism. Additionally, increasing creatine availability in tissue may improve cellular metabolism, reducing the severity of damage and/or disease states, especially in situations when oxygen supply is limited. In the present review, the peer-reviewed scientific and medical literature on creatine's function in maintaining overall health has been evaluated. The present understanding on its physiological role and latest research on its possible role as a neurotransmitter make exploring Creatinine into its possible role in brain functions.

Keywords: Creatine; Neurotransmitter; CNS; Physiology; Disease

Introduction

Although it is scarce in plants, carnitine (β-hydroxy-γ-N-trimethylaminobutyric acid) is abundantly found in food derived from animals (Kendler, 1986). Dietary sources provide for 75% of carnitine intake in humans (De Vivo and Tein, 1990). Foods can be absorbed from either active or passive transport across enterocyte (intestinal cell) membranes to get L-carnitine, the physiologically active stereoisomer (Rebouche, 2004). The content of the food affects the bioavailability of carnitine. When people, like vegetarians, adjust to low-carb diets, their bioavailability of L-carnitine increases (66% to 86% of accessible carnitine) compared to normal red meat eaters who adjust to high-carb diets (54% to 72% of available carnitine) (Rebouche and Chenard, 1991). Lysine and methionine, two vital amino acids, are used by the body to naturally produce carnitine when it cannot be acquired from diet. Kidney, liver, and brain are affected by this (Cave et al., 2008). The largest quantities are seen in cardiac and skeletal muscle, which cannot produce their own carnitine and must instead obtain it from plasma. Microorganisms mostly break down unabsorbed carnitine in the large intestine (De Vivo and Tein,1990). Carnitine is intracellular in almost all cases (99%) (Cave

et al., 2008). Carnitine affects the metabolism of carbohydrates. Complications from diabetes mellitus, hemodialysis, trauma, malnutrition, cardiomyopathy, obesity, fasting, medication interactions, endocrine imbalances, and other illnesses are linked to abnormalities in the control of carnitine.

One of the most researched and successful ergogenic aids for athletes is creatine supplementation (Kreider et al., 2017) Increased anaerobic energy capacity, a reduction in protein breakdown, and an increase in muscle growth and athletic performance are just a few of the many ways that creatine works its magic (Kreider et al., 2017). Although creatine has well-established benefits for athletes, it may also be used as a clinical and therapeutic adjuvant to standard medical procedures (Gualono et al., 2012). In this regard, studies on the possible therapeutic effects of creatine supplementation on various health conditions pertaining to diabetes, sarcopenia, osteoporosis, cancer, rehabilitation, cognition, and cardiovascular health, among others, have been conducted in recent years. The use of creatine as a dietary approach to support the preservation of mental and functional ability, lower the risk of chronic illness as we age, and/or act as an adjuvant intervention to aid in the management of disease and/or aid in recovery has gained traction as a result of this study (Gualono et al., 2012).

Physiological role of Creatine in Diseases

a) Neurodegenerative Diseases and Muscular Dystrophy

A number of research studies have looked into the short- and long-term therapeutic benefits of creatine supplementation in individuals with a variety of neuromuscular diseases, including mitochondria-related diseases amyotrophic lateral sclerosis (ALS); spinal and bulbar muscular atrophy; and muscular dystrophies (MD) (Tarnopolsky et al., 1997; Gowayed et al., 2020). Numerous studies, mostly involving animal models, have documented better therapeutic results and/or increased exercise toleranceThere was evidence that creatine supplementation reduced brain shrinkage in HD patients, indicating a possible therapeutic effect in this group. The fact that individuals usually do not exhibit signs of neurodegenerative illnesses (e.g., ALS, HD, PD, etc.) until they have lost 70% or more of their alpha neurons may be the reason why animal research have shown more encouraging results. However, since the muscle is the main focus, outcomes in populations with muscular dystrophy have been more encouraging. In support of this claim, Kley and colleagues (2013) carried out a Cochrane systemic review of the literature and discovered that high-quality evidence from randomised clinical trials (RCTs) showed that functional performance in idiopathic inflammatory myopathy and muscular dystrophy and short- and medium-term creatine supplementation increases muscle strength in muscular dystrophies. Nonetheless, evaluation of high calibre RCTs revealed no appreciable increase in muscular strength in metabolic myopathies (Kley et al., 2013). Therefore, long-term, high-dose creatine supplementation in people with neurodegenerative diseases is currently equivocal, though promising, in patients with muscular dystrophy. This is despite the fact that creatine supplementation has been shown to have neuroprotective properties and improve muscle strength and endurance in patient populations.

b) Brain and Spinal Cord Neuroprotection

It is commonly recognised that supplementing with creatine boosts brain bioenergetics and has neuroprotective effects, especially when the body is responding to injury or ischemia. Thus, research on the impact of creatine supplementation on spinal cord injury (SCI), traumatic brain injury (TBI), cerebral ischemia, and stroke has been pursued. The

researchers discovered that feeding mice creatine led to a 25% decrease in the extent of brain damage and a considerable rise in the ratio of brain PCr to Pi (Pan and Takahashi, 2007; Ipsiroglu et al., 2001; Kley and Tarnopolsky, 2007).

c) *Pregnancy*

There has been interest in using creatine during pregnancy to promote neural development and lessen complications from birth asphyxia because it has been demonstrated to improve cellular bioenergetics during ischemic conditions and possess neuroprotective properties. The foetus depends on the placental transfer of maternal creatine until late in pregnancy, and as pregnancy goes on, there are substantial changes in creatine synthesis and excretion, which is the justification for creatine supplementation throughout pregnancy. As such, during pregnancy, there is a greater need for and use of creatine. In animals with birth asphyxia, maternal creatine supplementation has been shown to increase newborn survival and organ function. There is proof that a mother's creatine requirements rise during pregnancy in humans. Thus, research on the effects of creatine on foetal growth, development, and mother and child health during pregnancy has been pursued. The body of research reveals that the bioenergetics of successful reproduction may depend on creatine metabolism, and that supplementing with creatine may enhance the quality of perinatal and/or reproductive outcomes. It should be highlighted, nonetheless, that there is little data on the effects of creatine supplementation in expectant mothers. Further safety and tolerability studies in pregnant women and those attempting to conceive are required, even though creatine supplementation has been reported to be safe in a number of populations and there is no evidence that it poses a risk for women of reproductive age or preterm infants. Because of the scarcity of human research, care should be used before endorsing creatine supplementation during pregnancy, even though there is growing evidence that it may support the nutritional needs and health of the mother and child (Vallet et al., 2013; Ellery et al., 2013; Dickinson et al., 2013; Irelandet al., 2011; De Guingand et al., 2019).

d) *Immune Support*

The impact that creatine has on the immune system is among its most inventive possible applications. Numerous investigations conducted on animals and in vitro suggest that creatine has immunomodulatory properties. Regarding this, a number of research have revealed that taking supplements of creatine may change the expression and/or synthesis of molecules such as toll-like receptors (TLR) that are important in identifying infections. In a mouse macrophage cell line (RAW 254.7), creatine down-regulated the expression of TLR-2, TLR-3, TLR-4, and TLR-7. While TLR-4 downregulation may affect Parkinson's disease pathology and prevent neuronal death as the illness advances, it may also lessen the ability of immunocompromised persons to detect certain infections (Bassit et al., 2008; Deminice et al., 2013; Santos et al., 2004).

Additionally, there is evidence that creatine affects cytokines, growth factors, and/or receptors that can either favourably or adversely impact the immune response. These effects may be mediated through the NF-κB signalling system. A decrease in pro-inflammatory cytokines (like IL-6) and other inflammatory markers (like TNFα, PGE2) generated by creatine may account for some of the neuroprotective effects shown in individuals suffering from disorders connected to the central nervous system. It might also explain studies that, in response to severe exercise, creatine supplementation reduces inflammatory and/or muscle damage. However, a number of mouse studies have suggested that supplementing with creatine may reduce airway inflammation, which would exacerbate asthma brought on by exercise. The anti-inflammatory and immunomodulatory

effects of creatine are still unclear, however it is evident that creatine can influence these pathways. Therefore, there is evidence to support the possibility that supplements have immunomodulatory and anti-inflammatory properties (Bassit et al., 2008; Deminice et al., 2013; Santos et al., 2004).

*e) **Anticancer Properties***

The possible anticarcinogenic benefits of creatine supplements are another developing field. As previously mentioned, creatine and phosphagens are crucial for preserving energy availability, especially when it comes to the function of the CK/PRr system and the movement of ATP, ADP, and Pi into and out of the mitochondria for metabolic processes inside the cell. Previous research has demonstrated low levels of energy availability and creatine content in a variety of malignant cell types as well as T cells, which mediate the immunological responses against cancer. Furthermore, the expression of the creatine transport gene SLC6A8 significantly rises in immune cells that infiltrate tumours and produces a surface transporter that regulates creatine absorption into a cell. The anticancer effects of creatine and its related molecule cyclocreatine have been well-established. For instance, Patra et al (2012) also reported that administration of creatine, methylglyoxal, and ascorbic acid provided greater efficacy and eliminated visible signs of tumour growth.

The anticancer medication methylglyoxal (MG) is also significantly more effective when creatine is present. Furthermore, the concurrent regression of tumour cells was accompanied by a considerable elevation in creatine and CK, which were very low in sarcoma tissue. Similarly, Pal and colleagues (2016) found that co-administering creatine and ascorbic acid increased the efficacy of MG in muscle cells in vitro and in an animal model of sarcoma in vivo. This finding raises the possibility that creatine supplementation could be used in conjunction with MG as an adjuvant anticancer therapeutic intervention. Additionally, researchers found that while supplementing with creatine through dietary supplementation or direct administration significantly suppressed tumour growth in multiple mouse tumour models, CD8 T cell responses to antigen stimulation in vitro and tumour challenge in vivo were severely impaired. Furthermore, creatine's ability to cut down energy extends beyond only controlling CD8 T cells; decreased energy capacity in a variety of immune cells has also been shown in different mouse tumour models in creatine transporter mutant mice. The researchers came to the conclusion that supplementing with creatine may enhance T cell–based cancer immunotherapies and that creatine is a crucial metabolic regulator regulating antitumor T cell immunity. Taken together, these results suggest that supplementing with creatine may have anticancer effects. Based on the information that is now available, it is reasonable to assume that creatine plays a significant role as an energy source for immune cells, can aid in maintaining a healthy immune system, and may even possess some anticancer qualities (Patra et al, 2012; Soares et al., 2020; Cella et al., 2020; Pal et al., 2016).

*f) **Fertility***

There has been considerable curiosity in whether creatine supplementation and/or administration can increase fertility since sperm motility depends on ATP availability and CK activity has been linked to improved sperm quality and function. For instance, to improve sperm viability and the efficacy of fertility therapies, creatine has been added to the medium during intrauterine insemination. These results imply that creatine may be significant for fertility and reproductive health, while additional research is necessary (Sbracia, et al., 1996; Huszar et al., 1990; Fakih et al., 1986; Oehninger and Alexander, 1991; Gergely et al., 1999; Froman and Feltmann, 2010).

Creatine as Neurotransmitter

The role of creatine in the recycling of ATP in brain and muscle tissue has long been established (Wyss and Kaddurah-Daouk, 2000; Brosnan and Brosnan, 2007; Wallimann et al., 2011). It may also have additional roles in brain function, according to research conducted more recently (Ohtsuki et al., 2002; Braissant et al., 2011).

It was shown by Bian et al. (2023) that activated coronal brain slices produced creatine. It's interesting to note that slices from animals missing either the gene encoding the SLC6A8 creatine transporter or the gene encoding the enzyme AGAT, which is required for the synthesis of creatine, showed lower creatine release. Crucially, it was also noted that creatine inhibits a certain group of neurons. Additionally, they discovered that SLC6A8 is capable of delivering creatine into synaptosomes, which are isolated synaptic structures that house a device that aids in the release of neurotransmitters as well as a sizable number of synaptic vesicles. All of these findings point to creatine functioning as a neurotransmitter and AGAT and SLC6A8 assisting in that role (Figure 1).

Researches (Almeida et al., 2006; Peral et al., 2010; Bian et al., 2023) that suggested creatine could have characteristics similar to those of neurotransmitters. Still, there are unanswered questions requiring more research. Significantly, Bian et al. failed to find a particular postsynaptic receptor for creatine. According to the researchers' conjectures, creatine may bind to a metabotropic receptor (or receptors) (Figure 1). The fact that the majority of the creatine release following high potassium stimulation takes place in the absence of extracellular calcium remains a mystery. This contradicts the idea that the release's component included neurotransmitters. According to Bian et al., astrocytes may be to blame since they have large concentrations of the enzyme GAMT, which is necessary for the synthesis of creatine. Should this theory be true, astrocytic creatine may have a neuromodulatory function. The fact that SLC6A8 and AGAT are present in distinct brain cells presents one last mystery. Thus, if creatine were a neurotransmitter, this would imply a complicated paradigm in which creatine is first synthesised in one kind of cell and then transferred to another type of cell to be released (Figure 1).

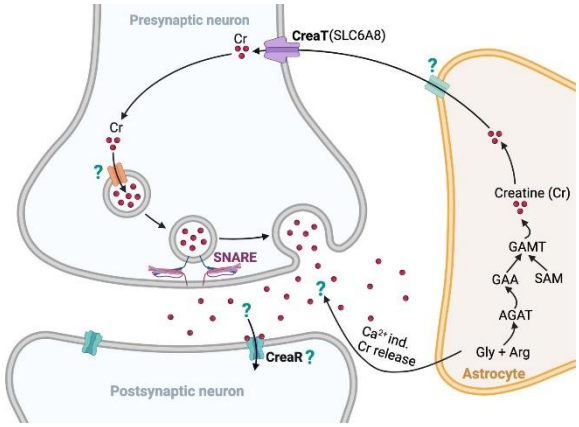

Figure 1: Mechanism of Creatinine synthesis, transport and release from the neuron

In conclusion, Bian et al. state that creatine satisfies many textbook requirements for a neurotransmitter (Kandel et al., 2021; Purves, 2018) and may be a neurotransmitter in the central nervous system. This is a potentially ground-breaking discovery with ramifications for our knowledge of neurotransmission and brain function. Additionally, it could shed light on previously undiscovered aspects of Creatine Transporter Deficiency, a neurological illness linked to faulty SLC6A8 that presents as a range of intellectual deficits, language delays, and other abnormalities (Salomons et al., 2003).

Conclusion:

Since the 1960s, there has been a push for carnitine as a dietary supplement to treat various conditions such as human carnitine deficiency and defective fatty acid oxidation. This suggests that carnitine supplements, whether pharmacological or nutritional, may be helpful in certain cases of these disorders [168]. It should be highlighted, nonetheless, that Stanley [168] claims that in the last 40

years, there have only been two distinct cases of illnesses directly related to carnitine deficiency that have demonstrated the unquestionable benefits of carnitine therapy.

Despite this, a lot of research has been done in a number of disease states about the effects of prophylactic amounts of carnitine; nevertheless, there is some debate and misunderstanding surrounding its usage in normal nutrition that needs to be cleared up. discussed. Carnitine is an organic substance that is devoid of poisoning when taken orally in amounts up to few grammes and supplements are therefore frequently advised in elementary and secondary shortcomings. Given that carnitine is widely excreted, further consumption is accepted with ease. Research on rats and humans has provided evidence that advantages for health when applied as a medicinal treatment.

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