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Review

Creatine supplementation and the role on oxidative stress, brain creatine level and inflammation. A brief review

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Abstract. One of the most important and popular nutritional ergogenic aids for athletes is creatine. Numerous scientific studies have shown that the constant supplementation of creatine favors the increase of its concentration in the muscles, and this could lead to an increase in physical performance, especially of high intensity exercises. Additionally, creatine supplementation appears to be related to improved post-exercise recovery, injury prevention, thermoregulation, rehabilitation, and neuroprotection of concussion and / or spinal cord. From these studies it is found that the intake of creatine, in addition to beneficial effects on sports performance, can have post-injury effects and improve injury-recovery, increasing the tolerance of athletes loaded with heavy training. Additionally, several studies have shown numerous potential beneficial effects of creatine supplementation. In this investigation was show that short and long-term supplementation (up to 30 g/day for 5 years) is safe and well-tolerated in healthy individuals and in a number of patient populations ranging from infants to the elderly. Moreover, significant health benefits may be provided by ensuring habitual low dietary creatine ingestion (e.g., 3 g/day) throughout the lifespan. The aim of this brief review is to provide an overview to the current literature regarding the role and safety of creatine supplementation in exercise, and the role on oxidative stress, brain creatine level and inflammation.

Key words: Creatine, supplementation, diet, oxidative stress, brain, inflammation

Introduction

In professional and amateur sport, athletes are constantly looking for solutions to improve performance, and, therefore, these subjects resort to particular nutritional strategies often to achieve the objectivesand to augment performance (i.e., enhanced muscular strength, power, and force) (1). One of the most commonly used and scientifically supported ergogenic aids is creatine monohydrate, commonly referred to as creatine (2,3). Creatine is an amino acid found in relatively high concentrations in skeletal muscle. The first studies in 1992 immediately highlighted the ability of creatine to increase the muscle reserves of phosphocreatine in the muscle (4), and later it was seen that these increases were linked to increased physical performance (5).

Creatine is currently one of the most popular supplements used by athletes. Furthermore, in addition to the sports world, creatine has been the subject of numerous scientific studies from which its ability to increase physical performance has emerged, all with minimal or no side effects in all age groups (6,7).

The showed ergogenic positive effect of creatine monohydrate include enhanced force output, augmented power output, increased strength, increased

anaerobic threshold, increased work capacity, enhanced recovery, and enhanced training adaptations (8,9).

In scientifi investigation several supplementation strategies have been explored to increase intramuscular creatine stores. In the first time, a loading phase was initially proposed (4,10) and has subsequently been used in a lot of of scientific investigations. This method requires the assumption of four separate doses of 5 g/day for five consecutive days and consistently leads to a 20%–40% increase in creatine content (11). Subsequently, other authors have experienced that smaller doses could support the muscle reserves of creatine (2-5 g per dose, 1 ×/giorno o 0,03 g/kg/dose). Although it has now been widely demonstrated that a loading phase is not necessary, this approach is still widely used to rapidly increase PCr levels in the muscle, and this has an impact on physical performance (12,13).

The aim of this brief review is to summarize the existing literature surrounding the efficacy of creatine supplementation on exercise and sports performance, and its invloving in brain and vascular health.

Creatine and oxidative stress

Creatine is a metabolite of three amino acids (arginine, glycine, and methionine) that are synthesized by the cooperation of various organs, including the liver, pancreas, and kidneys (14,15). As far as the sources of these amino acids are concerned, it should be remembered that there are foods such as beef that contain them in large quantities and food, mostly of vegetable origin, which contain low quantities (15,16). The synthesis of creatine starts from arginine; the guanidino group from arginine to glycine is transferred by glycine amidinotransferase, and produces guanidinoacetate and ornithine. It seems that the arginine–glycine aminotransferase is fundamentally expressed in the kidney tubules, pancreas, and a little in the liver and other organs. Thus, guanidineacetate is produced by renal components. The guanidinoacetate released by the kidneys is methylated by guanidinoacetate N-methyltransferase, which is mainly found in the liver, pancreas, and to a very small extent in the kidneys, and produces creatine (17).

Creatine synthesis is primarily regulated as follows: the changes in the renal arginine expression: glycine aminotransferase in rats and humans; and the the availability of substrates. Circulating growth hormone (GH) levels and creatine intake are critical for new creatine synthesis (17,18).

Studies have shown that creatine supplementation can have antioxidant properties. Early studies regarding the antioxidant properties of creatine suggested that its supplementation could protect rats from nitropropinic acid poisoning (13). Subsequently, in other studies using creatine as an integrator, a reduction in rotenone-induced mitochondrial osidative damage and neurotoxicity in Drosophila malanogaster was observed (19). Despite the studies carried out, the mechanism of action of creatine is still not definitively clear. However, creatine supplementation increases the activity of antioxidant enzymes and the elimination capacity of ROS and RONS (20,21).

Creatine protects two different and important cellular targets, mitochondrial deoxyribonucleic acid (mtDNA) and RNA against oxidative damage. Additionally, creatine supplementation has been shown to correlate with other effects that help the cell survive and function under oxidative stress. The functional function of creatine is also important is found at the level of the mitochondria, maintaining the integrity of organelles and preventing oxidative damage of RNA (22). Mitochondrial antioxidants have been proposed as a valuable tool to protect mitochondria against pathological changes (23,24). Studies have shown that creatine significantly protects mtDNA from oxidative damage (25,26). Creatine probably prevents damage through direct antioxidant activity. In this regard, different studies have shown that creatine supplementation protects mtDNA from oxidative damage, probably through a direct protective activity. Therefore, the integration of this substance can play a decisive role in the stability of the genome, which can regulate mitochondrial mutagenesis and intercept its functional consequences such as reduced oxygen consumption, mitochondrial membrane potential, ATP content and subsistence cellular (27,28).

Furthermore, it seems that the antioxidant properties of creatine are also related to the presence of arginine within its molecule (29).

Creatine supplementation on brain creatine levels

Muscles can rely on its intake or synthesis by the liver, kidneys and pancreas for the supply of creatine (30). On the other hand, the crevello is able to synthesize creatine as it is equipped with an enzymatic apparatus necessary for its synthesis within the nervous system. In addition, transporters are present in the blood-brain barrier, which suggests that brain creatine may not depend exclusively on endogenous production from organs or from alimentary numbness (31).

It would appear that brain creatine levels may be affected by aging (32), although comparable levels of brain PCr have been observed among healthy individuals of different ages (33). Beyond these aspects it seems that factors such as brain activity, physical activity, some pathologies such as depression and schizophrenia, are able to modify the conditions of creatine in the brain. The overlap between these factors may be misleading as to what might be identified as an age-related decline (34).

While a large number of studies are available on supplementation protocols aimed at increasing muscle creatine content (11,35), much less is known regarding the optimal supplementation strategy to increase brain creatine levels. There are currently twelve studies in scientific literature that have investigated the relationships between creatine supplementation and levels of creatine and PCr in the brain (36). Nine of these studies found a significant increase in brain creatine, on average about 5-10%, which is less than the increase in muscle creatine or CRP resulting from a similar supplementation protocol.

However, the differences in creatine uptake between muscle and brain have not yet been clarified.. The brain creatine content may rely less on exogenous creatine than muscle (30,37), which could theoretically involve a down-regulated response in brain creatine synthesis upon supplementation. Alternative to this hypothesis is the demonstration that the brain lacks the expression of creatine transporter in the astrocytes involved in the blood–brain barrier, thus implying a limited permeability of the brain to the circulating creatine (38), accordingly with the lack of increase in brain creatine following supplementation reported in scientific literature (39). It is therefore possible to hypothesize that high doses are needed to increase brain creatine levels, ie about 20 grams per day for 4 weeks. These hypotheses find confirmation in a study that evaluated creatine levels in muscle and brain in response to supplementation (33).

Creatine and inflammation

Inflammation, or the presence of chronic inflammatory markers, has been long associated with cardiovascular disease (40). Inflammatory processes can have harmful effects on the physiological functions of the organism by creating a favorable environment for the development of vascular pathologies. Although scientific reports evaluating the effect of creatine on levels are scarce, some studies have highlighted potential anti-inflammatory effects of creatine. In this regard, the first studies of the effects of creatine on inflammatory processes were conducted on rats (41). The injection of carrageenan into the paw causes an acute and local inflammatory response characterized by edema and the release of histamine, serotonin, bradykinin, prostaglandins, and cytokines such as interleukin-1beta (IL-1β), IL-6, IL-10, and tumor necrosis factor alpha (TNF-α). Using this model, the authors reported that those animals treated with an intraperitoneal injection of creatine showed significantly reduced paw swelling and edema (40). Subsequently, another study, using the same animal model, found that creatine treatment decreased the symptoms of inflammation similar to a non-steroidal anti-inflammatory (NSAID-phenylbutazone) (42). The same authors further investigated the application of creatine for defending against other edema including formaldehyde-induced arthritis, and analogous to previous findings, creatine proved again to be a beneficial anti-inflammatory effects (40).

In other studies, creatine has been shown to help decrease the inflammatory response linked to immune stressors, such as exercise-induced muscle damage. Santos et al. (43,44) investigated the effect of creatine supplementation (20 g/day) taken for five days before to a 30 km race event on inflammatory markers. The results showed that creatine supplementation decreased concentrations of E2 (PGE2) e TNF-α rispettivamente del 60,9% e del 33,7%, rispetto al gruppo

placebo che ha presentato aumenti significativi di tutti i marker.

Other authors, using a similar protocol five days before an Iron Man half event, reported that subjects who took creatine showed a minor increase in plasma levels of TNF-α, PGE2, interferon-α (INF-α) and IL-1β, compared to placebo at both 24 and 48 hours post-event (45). Moreover, in another study was showed that seven days of creatine supplementation (0.3 g/kg body weight) in young soccer players abolished the increase in TNF-α seen following a repeated sprint exercise, in comparison to placebo (46). Although in contrast other authors (47) descrived no reduction in inflammatory markers following eccentric contraction in rats, the majority of the above evidence suggests that creatine attenuates the pro-inflammatory response to exercise, therefore exhibiting potential anti-inflammatory properties.

Although there are few studies regarding the effect of creatine on vascular inflammation, the few findings suggest that it appears to have a link between creatine intake and level of harmful cytokine levels (40). However, further studies are needed to definitively clarify the role of creatine on the vascular system.

Conflicts of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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