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Supplementation of creatine and its role in brain function

Leila Abod[1*], Natalia Ilnicka[2], Daria Matyja[3], Maria Sadlik[4], Patrycja Zuziak[5]

[1]Jan Mikulicz-Radecki University Teaching Hospital Borowska 213, 50-556 Wrocław; leila.aboood@gmail.com; ORCID iD: 0000-0002-5895-0944

[2]Regional Specialist Hospital in Wroclaw, Research and Development Centre, H. Kaminski Street 73a, 51-124 Wroclaw, Poland; natalia.ilnicka@outlook.com; ORCID iD: 0000-0002-7149-8534

[3]J. Gromkowski Regional Specialist Hospital Koszarowa 5, 51 - 149 Wrocław; daria.matyja@gmail.com; ORCID iD: 0000-0002-9046-7821

[4]Jan Mikulicz-Radecki University Teaching Hospital Borowska 213, 50-556 Wrocław; sadlik.maria@gmail.com; ORCID iD: 0000-0001-8255-9200

[5]T. Marciniak Lower Silesian Specialist Hospital - Emergency Medicine Centre, Fieldorfa 2, 54-049 Wrocław; pat.zuziak@gmail.com; ORCID iD: 0000-0003-3612-0349

[*]Corresponding Author

ABSTRACT

Introduction and aim. In recent years growing awareness of the society regarding healthy lifestyle leads to increased interest in regular physical activity and usage of dietary supplements. Creatine supplementation is often used among athletes to improve muscle mass, performance and recovery. The aim of this paper is to present the effects of creatine

supplementation as well as its function in the body, forms and ways of intake, and potential benefits of its use.

Material and methods. A review of the available literature was performed by searching the PubMed and GoogleScholar databases using the following keywords: creatine, creatine supplementation, sports nutrition, brain function

Analysis of literature. Creatine is one of the most popular supplements recommended for athletes. It catalyzes transfer of phosphate groups into high energy compounds contributing in energy transportation and cellular energy buffering for cells and tissues with high energy demands. Its supplementation improves exercise performance, increases muscle mass and enhances recovery after training. In addition, there are indications that creatine shows promise in reducing symptoms associated with concussion, mild traumatic brain injury, and depression.

Conclusion. Creatine supplementation is used in sport mainly to improve exercise performance and muscle gain, however, it also plays an important role in brain function. In future it may be used in reducing symptoms associated with concussion, mild traumatic brain injury and depression.
Keywords. creatine; creatine supplementation; sports nutrition; brain function

Introduction

Creatine (Cr) is a chemical compound, an acid, which is made of three amino acids: arginine, glycine and methionine. Creatine kinase (CK) plays role as an enzyme catalyzing the reversible transfer of the gamma-phosphate group of ATP to the guanidino group of Cr to yield ADP and phosphocreatine (Figure 1).[1]

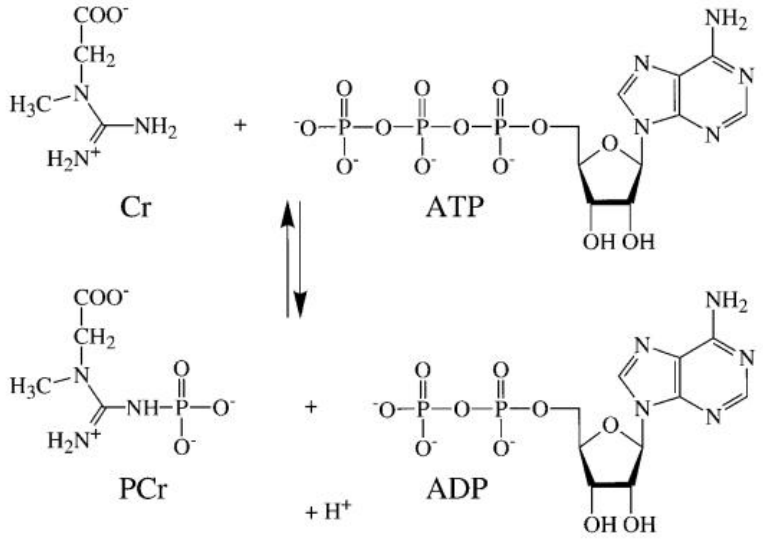

Fig. 1. The creatine kinase (CK) reaction. PCr, phosphorylcreatine; Cr, creatine.[1]

Aim

The aim of this paper is to present the effects of creatine supplementation as well as its function in the body, forms and ways of intake, and potential benefits of its use.

Material and methods

A review of the available literature was performed by searching the PubMed and GoogleScholar databases using the following keywords: creatine, creatine supplementation, sports nutrition, brain function

Analysis of literature

Metabolic function

Cr is found in human organisms mainly in cells and tissues where there is higher energy expenditure like skeletal or cardiac muscle, brain, retina and spermatozoa. There are four different types of CK subunits: two of them are cytosolic M-CK (M for muscle) and B-CK (B for brain), they form dimeric molecules and give rise to the MM-, MB-, and BB-CK isoenzymes, and two of them are mitochondrial CK isoforms, ubiquitous Mi-CK and sarcomeric Mi-CK. They are located in the mitochondrial intermembrane space as homodimeric and homooctameric molecules respectively. All of CK isoenzymes catalyze the same reaction.[1] In skeletal muscles, a large pool of phosphocreatine (PCr) is available for immediate regeneration of ATP hydrolyzed during short periods of intense work. Because of

the high cytosolic CK activity in these muscles, the CK reaction remains in a near-equilibrium state, keeps ADP and ATP almost constant (over several seconds), and thus "buffers" the cytosolic phosphorylation potential that seems to be crucial for the proper functioning of a variety of cellular ATPases. Heart, slow-twitch skeletal muscles, or spermatozoa, on the other hand, depend on a more continuous delivery of high-energy phosphates to the sites of ATP utilization. According to the "transport" ("shuttle") hypothesis for the CK system, distinct CK isoenzymes are associated with sites of ATP production (e.g., Mi-CK in the mitochondrial intermembrane space) and ATP consumption (e.g., cytosolic CK bound to the myofibrillar M line, the sarcoplasmic reticulum (SR), or the plasma membrane) and fulfill the function of a "transport device" for high-energy phosphates. To sum up - the creatine kinase/phosphocreatine system plays a key role in cellular energy buffering and energy transport, particularly in cells with high and fluctuating energy requirements.[1,2]

Creatine is taken up mainly from a diet containing fresh meat or fish. However, creatine can be also synthesized endogenously by the liver, kidney, pancreas, and to some extent in the brain.[3] By following a regular diet, we supply about 1-2 grams of creatine every day. This amount is only sufficient to replenish basic losses. Excretion of creatine is about 2 grams per day. It undergoes enzymatic breakdown in kidneys to form creatinine. Creatinine is a waste product that is then excreted from the body through urine.[15]

Supplementation effect

Creatine supplementation increases the concentration of creatine and phosphocreatine in the muscles. This results in an increase in performance during short-term, high-intensity exercise.[3] For this reason, creatine supplementation is especially recommended for athletes who practice disciplines in which short and intense effort is required. These include sprints and weightlifting. Studies have proven that, in addition to improving physical performance, creatine may contribute to better regeneration after exercise, preventing injuries or rehabilitation after injuries.[3] Creatine, through its osmotic properties, also increases the hydration of muscle cells, which results in a visible increase in their volume. In addition, creatine supplementation also supports the re-synthesis of muscle glycogen and contributes to the intensified rate of fast-twitch proteins synthesis, which is helpful in developing muscles.[3,4,5]

Forms and ways of intake

The modern supplement market offers many forms of creatine such as monohydrate, malate, hydrochloride, orotate or kre-alkalyn. Monohydrate is the best-investigated form of creatine.

In scientific studies, when creatine monohydrate was compared with other forms, monohydrate was better or as good as other forms in terms of muscle mass growth and exercise capacity.[6] In addition, the absorption of creatine monohydrate from the gastrointestinal tract is close to 100% and its conversion to creatinine during digestion is minimal (~ 2% per hour).[7] There are various creatine dosing regimens. One of the most popular protocols is the loading phase, which consists in taking very large amounts of creatine, doses ranging from 15 - 30g (saturation phase) for 3-6 days, after which dose is reduced to 2 - 5g per day (maintenance phase).[8] This method may be a suitable solution for athletes who are interested in rapid effects (increase in lean body mass in a relatively short time). However, creatine is an osmotically active substance. The intake of large doses of this compound at once may cause gastrointestinal problems (e.g. diarrhea), therefore, it is recommended to divide high doses into several small portions. In the light of scientific research, taking constant small doses of creatine (5g/day) for about 4 weeks is as effective in saturating muscles as supplementation with high doses (20-30g a day) for several days.[8] It is believed that creatine should be used periodically. The recommended duration of the creatine cycle is usually 4 to 8 weeks, after which it is suggested to take a monthly break. Factually, there are no contraindications to supplement creatine for a longer period of time with a maintenance dose (i.e. 3-5g per day) after reaching the maximum level of creatine in muscle cells.[9,10,11] Both short and long-term studies prove that creatine is a safe substance and does not pose risk in healthy individuals.[12,13] However, people with digestive problems should approach creatine supplementation with caution. Furthermore, it is contraindicated for those who suffer from renal failure.[14]

Creatine supplementation and brain function

While a significant amount of creatine is located in skeletal muscle, it is worth noting that the brain is also a highly active tissue that consumes about 20% of the body's energy.[16,17] In the ATP/CK/PCr system, which is crucial in energy production, there is a brain-specific form of creatine kinase (BB-CK).[18,19,20] This suggests that creatine may play a role in supplying energy to the central nervous system (CNS). In fact, conditions where the brain lacks sufficient creatine, known as creatine deficiency syndromes, are associated with significant mental and developmental disorders. These include mental retardation, learning delays, autism, and seizures.[21,22] Importantly, giving these individuals creatine supplements has shown to partially improve these symptoms.[23,24,25]

Several mental health disorders have been identified as having abnormalities in brain bioenergetics. For instance, depression, one of the common disorders, is linked to low levels

of creatine in specific brain regions.[26] These observations have sparked increasing interest in exploring the potential application of creatine monohydrate in treating various brain and neurological disorders, including mental and psychiatric conditions. The majority of studies have shown meaningful improvements and suggest further investigation into the use of creatine as an intervention for different forms of depression.[27-33] Researchers have explored the use of creatine in diverse clinical situations where depression often occurs as a result of an underlying disease or its treatment. For instance, in a study using mice with epilepsy, a diet supplemented with creatine not only reduced the severity of seizures but also decreased depressive-like behaviors.[34] In another study, antidepressant effects in mice treated with amyloid β1-40, a model of depression related to Alzheimer's disease were demonstrated.[35] Chronic corticosterone treatment, which can lead to depression-like symptoms, has also been investigated. One study found that a single dose of creatine resulted in changes in brain structure that improved depressive-like behaviors caused by formentioned treatment, similar to the effects of the commonly prescribed antidepressant fluoxetine.[36]

Moreover, when a person suffers a traumatic brain injury, one of the changes that occur is a disruption in the demand for ATP (a source of energy) due to reduced blood flow and lack of oxygen.[37] Brain creatine levels decrease after a mild traumatic brain injury (mTBI).[38] This makes creatine supplementation a potentially useful approach to lessen the severity of, or aid in the recovery from, mTBI or concussion by counteracting the negative impact on energy levels. Its efficacy was proven in a study by Sullivan et al.[39], where a significant reduction in brain damage was observed in both mice (36%) and rats (50%) with traumatic brain injury. However, it is important to note that while humans typically experience only around a 10% increase in brain creatine levels with supplementation, in certain animals a much larger increase of 30 to 50% can be seen.[40] Therefore, it is challenging to refer these results to the general population or athletes. Despite limited research in humans, the available studies show promising results. Creatine supplementation has demonstrated the ability to enhance cognition, communication, self-care, personality, and behavior, as well as reduce headaches, dizziness, and fatigue in children with mild traumatic brain injury (mTBI).[41,42]

Conclusion

Creatine is one of the most popular supplements recommended for athletes. It catalyzes transfer of phosphate groups into high energy compounds contributing in energy transportation and cellular energy buffering for cells and tissues with high energy demands. Its supplementation improves exercise performance, increases muscle mass and enhances

recovery after training. Although the majority of studies on creatine supplementation have primarily examined its impact on skeletal muscle, there is a growing body of research investigating the relationship between creatine and the brain. Initial findings suggest that supplementing with creatine can raise its levels in the human brain. Additionally, there are indications that creatine shows promise in reducing symptoms associated with concussion, mild traumatic brain injury and depression.

Declarations

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Author contributions

Conceptualisation, N.I.; Methodology, P.Z.; Software, M.S.; Validation, D.M.; Formal Analysis L.A.; Investigation, P.Z.; Resources, M.S.; Data Curation, D.M.; Writing – Original Draft Preparation, N.I.; Writing – Review & Editing, N.I., M.S.; Visualisation, P.Z.; Supervision, D.M.; Project Administration: N.I., L.A.

Conflicts of interest

Authors have no conflicts of interest to declare.

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