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Creatine in the brain

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Abstract  Since the 1990’s, creatine has become one of the most popular supplements in the world for the purpose of increasing skeletal muscle creatine, increasing skeletal muscle mass, and improving the amount of exercise training. The first patient with brain creatine deficiency was reported around the year 2000, and this patient’s severe clinical symptoms - such as impairment of brain function - drove researchers to start focusing more on the brain and related studies. Both in vitro and in vivo studies have shown creatine in the body to cover a wide range of roles including bioenergetic, anabolic, bone remodeling, anti-oxidant, anti-apoptotic, anti-excitotoxic and neuroprotective. In this short review, we introduce recent findings on the effects of creatine supplementation on brain function closely related to mental health, which directly influences the quality of life of elderly people.

Keywords: creatine, cognition, magnetic resonance spectroscopy

Introduction

Creatine and its phosphorylated form, phosphocreatine, are used as an energy reservoir by buffering ATP concentration via the creatine kinase (CK) reaction. This high-energy phosphate-buffering system is essential for maintaining adenosine triphosphate (ATP) levels in the body. The brain, that consumes 20% of the resting energy in the human body, maintains a high energy turnover rate by constant synthesis and degradation of ATP. Energy demand in the brain also further increases according to its activity status. For many years, the most important substrate, as an indirect energy source of the brain, has been thought to be glucose. However, since it shows a significant mental disability in patients exhibiting brain creatine deficiency2), the importance of the creatine/creatine phosphate/CK system in normal brain function is highlighted. It has been reported that the cerebral creatine level of the anterior cingulate cortex in patients with schizophrenia was 20% less than levels of healthy subjects3). The relationship between these clinical conditions and brain creatine level has not been fully understood in detail; however, creatine may play an important role in some mental diseases. Meanwhile, as far as the authors know, longitudinal studies on changes in age-related cerebral creatine in healthy subjects whose cognitive function declines with age have not been reported yet.

Role of creatine in the brain

Of the approximate 120 grams of creatine that exists in the human body, 95% is localized in the skeletal muscle, and only a few grams are localized in the brain. However, the role of creatine in the brain is essential and diverse for the human body. Energy synthesis in the brain via the creatine/phosphocreatine/CK system is thought to be involved in signal transduction in the central and peripheral nerves, and in maintenance of membrane potential4). In addition to indirect energy sources, creatine is also working as an osmotic regulator, neuromodulator and neuroprotective substrate5).

The effects of oral creatine supplementation on brain creatine levels

To date, a number of reports have been published regarding the effects of oral creatine supplementation on
The effect of creatine supplementation on cognitive function

Energy for cognitive function depends on ATP hydrolysis, and phosphocreatine is essential for resynthesis of ATP via a creatine kinase reaction. Creatine, phosphocreatine and CK are localized in brain regions such as the hippocampus and gray matter, and closely related to cognitive functions. While patients with creatine deficiency in the brain show a low intelligence quotient (IQ). As causes of deterioration of brain function accompanying aging, brain atrophy, decline of neurogenesis and neural networking, changes in neurotransmitters, and deterioration of energy metabolism are highly suspect. If we could increase cerebral creatine by oral creatine supplementation, it may be expected to improve cognitive function that normally deteriorates with aging (memory recall requires a lot of energy). In fact, a couple of previous studies demonstrated that an oral intake of creatine improved cognitive function. Hammett, et al. showed that auditory memory was improved after oral administration of 20 grams of creatine monohydrate daily for 5 consecutive days, followed by 5 grams per day for 2 days in eleven healthy volunteers\(^5\). Rae, et al. demonstrated that intelligence tests and working memory were enhanced due to 5 grams of creatine intake per day for 6 consecutive weeks in 45 young healthy vegetarians\(^6\). Watanabe, et al. revealed that oral supplementation of creatine at 8 grams a day for 5 consecutive days succeeded in reducing mental fatigue due to numerical calculation in 24 healthy young volunteers\(^7\). Another study reported by McMorris, et al. indicated that 20 grams of creatine supplementation daily for 7 consecutive days induced enhancement of all the cognitive tests other than counting recital memorization test in elderly with an average age of 76.4 years\(^8\). However, even though these studies showed an enhancement of cognitive function after oral creatine supplementation, they did not measure brain creatine levels before and after administration. Therefore, changes in brain creatine level due to creatine supplementation are unknown. For this reason, the amount of increase of brain creatine that is necessary/effective for improving cognitive function is not well understood. Further studies to answer these questions are needed.

In conclusion, creatine plays essential and various roles in the human brain. Creatine might be effective not only for maintenance and promotion of brain health in healthy individuals, but also in patients.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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