Sub-chronic administration of creatine produces antidepressant-like effect and modulates hippocampal neuroplasticity in mice: The role of the intracellular signaling pathway mediated by PGC1α/FNDC5/BDNF/Akt.

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Introduction: Creatine has been shown to play a significant role in the pathophysiology and treatment of depression. However, the mechanism of action of this compound is still not fully elucidated.

Objectives: Firstly, this study investigated the effect of creatine (p.o.) administered by 21 days in the tail suspension test (TST), predictive test of antidepressant activity. Taking into account that brain derived neurotrophic factor (BDNF) and its downstream intracellular pathway signaling mediated by Akt is involved in the action of several antidepressants, we investigated the involvement of the signalling pathway mediated by PGC1α/FNDC5, a signal transduction pathway widely correlated with hippocampal neuroplasticity and BDNF induction, as well as Akt phosphorylation, in the creatine antidepressant-like effect. We also investigated the antiapoptotic proteins Bcl2 and Bcl-xl, and the pro-apoptotic factors Bax and Bad in mice treated with creatine.

Materials and Methods: Female Swiss mice (30–40 g), maintained with free access to water and food, under a 12:12 h light: dark cycle were used. Creatine (0.1-10 mg/kg) or vehicle were administered by 21 days and behavioral tests were performed 24 hours after the last administration. In another set of the experiments mice were administered by 21 days with creatine (1 mg/kg) or vehicle and were killed by decapitation 24 hours after the last administration and hippocampi were collected for western blotting and quantitative RT-PCR analysis.

Results: Creatine reduced the immobility time in the TST (1-10 mg/kg), without affecting locomotor activity. Creatine increased the BDNF, FNDC5 and PGC1α gene expression. Creatine also increased the BDNF immunocontent and the phosphorylation of Akt in the hippocampus of mice. Furthermore, creatine supplementation increased the gene expression and immunocontent of the antiapoptotic protein Bcl2 in the hippocampus of mice.

Conclusions: These results indicate that the antidepressant-like effect of creatine is likely mediated by an modulation of PGC1α/FNDC5, BDNF and Akt phosphorylation, as well as Bcl2 translation.

Key Words: Antidepressant, BDNF, Creatine, FNDC5, Akt

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