Q - 045 - Creatine abolishes depressive-like behavior induced by chronic corticosterone treatment in mice through activation of PI3K/Akt/mTOR signaling pathway

Dayane Azevedo Padilha¹, Francis Leonardo Pazini¹, Maurício Pena Cunha¹, Julia Macedo Rosa¹, André Roberto da Silva Colla¹, Ana Lucia Severo Rodrigues¹
¹Universidade Federal de Santa Catarina, Bioquímica (SC, Brasil)

INTRODUCTION

Creatine plays an important role in the muscular and cerebral energy metabolism besides exhibiting antioxidant and neuroprotective effects as well as antidepressant activity in pre-clinical and clinical studies. A new therapeutic strategy for treatment-resistant depression consists in the use of ketamine, an NMDA receptor antagonist, which is a fast-acting antidepressant agent.

OBJECTIVES:

This study was aimed to investigate behavioral and biochemical similarity in the antidepressant-like effect of creatine and ketamine in mice.

MATERIALS AND METHODS

With due approval by the Ethics Committee of the Institution (CEUA/UFSC – PP00795), the antidepressant-like effects of creatine (10 mg/kg, p.o.) and ketamine (1 mg/kg, i.p.) was investigated in Swiss female mice (30-45g), and the participation of PI3K/Akt/mTOR pathway in this effect. In order to induce a depressive-like behavior, mice were administered (once a day for 21 days) with corticosterone (20 mg/kg, p.o).

DISCUSSION AND RESULTS

The increase in immobility time in the tail suspension test induced by corticosterone administration was prevented by the acute treatment with creatine or ketamine, but not with fluoxetine (10 mg/kg, p.o). Additionally, treatment of mice with wortmannin (an irreversible PI3K inhibitor, 0.1 µg/site, i.c.v) or rapamycin (an mTOR inhibitor, 0.2 nmol/site, i.c.v) abolished the anti-immobility effect of creatine or ketamine. None of the experimental groups caused changes in locomotor activity of animals in the open-field test. The effect of creatine and ketamine on the mTOR phosphorylation (Ser2481), in the hippocampus was also investigated. Ketamine or creatine treatments caused an increased p-mTOR/mTOR immunocontent as compared with vehicle-treated mice.

CONCLUSIONS

Moreover, these treatments were effective to abolish the corticosterone-induced reduction on p-mTOR/mTOR. The results indicate that creatine, similarly to ketamine, exerts an acute antidepressant-like effect in an animal model of depression responsive only to the chronic administration of conventional antidepressants through activation of PI3K/Akt/mTOR signaling pathway.

Keywords: creatine, depression, PI3K/Akt/mTOR pathway