INVolVEMENT OF AMPA/PI3K/AKT/GSK-3Β/MTOR PATHWAY IN THE ANTIDEPRESSANT-LIKE EFFECT OF AGMATINE IN THE TAIL SUSPENSION TEST

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Preclinical and clinical data have reported that agmatine exhibits antidepressant potential. In this context, the present study investigated the involvement of AMPA receptors, and PI3K/Akt/GSK-3β/mTOR pathway in its antidepressant-like effect in the tail suspension test (TST) in mice. The experiments were performed after approval of the protocol by the Ethics Committee of the Institution (PP00795 Protocol). Female Swiss mice were pretreated with agmatine (0.1 mg/kg, p.o.) and 45 min after, DNQX (2.5 μg/mouse, AMPA receptor antagonist), LY294002 (10 μg/mouse, i.c.v., reversible PI3K inhibitor), rapamycin (0.2 nmol/mouse, i.c.v., selective mTOR inhibitor), or vehicle was administered. The immobility time and locomotor activity were evaluated in the TST and open-field test (OFT), respectively. In another set of experiments, mice received sub-effective doses of agmatine (0.0001 mg/kg, p.o.) and lithium chloride (10 mg/kg, p.o., a non-selective GSK-3β inhibitor) or AR-A014418 (0.01 μg/mouse, i.c.v., a selective GSK-3β inhibitor) and 60 min latter the behavioral tests were performed. An independent group of mice treated with agmatine was used for the investigation of the immunocoutent of the synaptic proteins synapsin and PSD95 in the prefrontal cortex of mice. The antidepressant-like effect of agmatine in the TST was prevented by the pretreatment of mice with DNQX, LY294002 and rapamycin. The administration of sub-effective doses of lithium chloride or AR-A014418 in combination with a sub-effective dose of agmatine reduced the immobility time in the TST when compared with the control group. None of the treatments produced significant effects in the locomotor activity in the OFT. Moreover, agmatine administration increased the immunocoutent of PSD95, but not of synapsin. These results provide evidence that the antidepressant-like effect of agmatine in the TST involves the activation of AMPA receptors and PI3K/Akt /mTOR pathway as well as the inhibition of GSK-3β.

Keyword(s): depression; agmatine; TST


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