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1-Methyl-1,2,3,4-tetrahydroisoquinoline produces antidepressant-like effect in clonidine model of depression: behavioral and neurochemical studies

A Wasik, J Michaluk, E Mozdzen, I Romanska, L Antkiewicz-Michaluk. *Institute of Pharmacology PAS, Department of Neurochemistry 31-343 Krakow, Poland*

Dysfunction of monoaminergic transmission in the brain plays an important role in major depressive disorder (MDD). One of the basic forms of therapy in the clinic is the activation of of noradrenergic and/or serotoninergic transmission in the brain. Clonidine is an α_2-adrenoceptor agonist, so stimulation of this receptor leads to the reduction of noradrenaline concentration in the synaptic cleft, and produced depression-like behavior. The FST is the most widely used paradigm to assess depression and antidepressant-like behavior which takes advantage that rodents following initial escape-oriented movements, rapidly adopt and take the attitude of immobile posture in an inescapable cylinder filled with water. In the present study we tested antidepressant-like effects of 1-Methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ) in the model of depression caused by clonidine in the forced swimming test (FST) modified by Detke MJ et al., (1995) Psychopharmacology 121: 66-72 in male Wistar rat [n=28]. 1MeTIQ is an endogenous substance which is present in the mammalian brain and how it was demonstrated in our earlier papers exhibits neuroprotective, and MAO-inhibiting properties (Antkiewicz-Michaluk L et al., (2006) J Neurochem 97: 846-56). In the present neurochemical studies the rate of dopamine (DA), serotonin (5-HT) and noradrenaline (NA) metabolism were established after behavioral experiments in different brain structures (hypothalamus, striatum, frontal cortex) by HPLC methodology. The data were analyzed by means of a two-way ANOVA followed by Duncan's test. **Results:** The FST data has shown that 1MeTIQ in dose 25 mg/kg i.p evoked antidepressant-like effects, and significantly reduced the immobility time and concurrently produced an increase of a swimming time in rat. Acute administration of clonidine, (0.1 mg/kg i.p.) does not changes the behaviour of animals in FST to comparison of saline group. Co-administration of 1MeTIQ with clonidine causing significant decrease the immobility time, while the increase of climbing behaviour in FST. The neurochemical findings demonstrated that 1MeTIQ produced significant elevation the rate of noradrenaline, dopamine and serotonin metabolism in frontal cortex and hypothalamus. Acute clonidine administration induced significant increase the rate of dopamine and serotonin metabolism in investigated structures, and not significant decrease the rate of noradrenaline metabolism. Co-administration of both this drugs caused strongly elevation the rates of all monoamine metabolism in the brain.

Conclusions: As it demonstrated by behavioural and neurochemical studies, 1MeTIQ has shown antidepressant-like properties both in naive and treated with clonidine groups. 1MeTIQ reverses the effect of clonidine and increases the activation of catecholaminergic neurons in the brain. The present data strongly suggest that 1MeTIQ may be useful and safe drug in clinical practice but further studies are necessary to confirm this suggestion.

This work was supported by Project De-Me-Ter 3.5 Innovative Economy 2007-2013 Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland.