

**A STUDY FOR THE SCREENING OF POTENTIAL ANTIDEPRESSANT ACTION OF MIRTAZAPINE**

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Mirtazapine is a widely used antidepressant compound. The mechanism of action of mirtazapine is rather complex and it has been explained on the basis of its antagonistic activity at pre- and post-synaptic  $\alpha_2$ -adrenergic receptors and 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>3</sub> serotonergic receptors. Pre-synaptic  $\alpha_2$ -adrenergic receptors are localized in both adrenergic (autoreceptors) and non-adrenergic (heteroreceptors) terminals, where they play an inhibitory role on neurotransmitter release. Thus, their inhibition may result in an increased release of noradrenaline and other neurotransmitters. In particular, the inhibition of  $\alpha_2$ -autoreceptors in the locus coeruleus enhances the activity of the noradrenergic neurons which project to the dorsal raphe. This increased adrenergic input is sustained by the stimulation of  $\alpha_1$ -adrenoceptors located on dendrites of the serotonergic neurons which, in turn, project to the hippocampus. The resulting effect is an increased serotonergic transmission in hippocampus selectively sustained by 5-HT<sub>1A</sub> receptor stimulation, since mirtazapine is antagonistic at 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>3</sub> serotonergic receptors.

The aim of the present study was to characterize the effect of mirtazapine long-term treatment in a paradigm of unavoidable stress-induced transient hyporeactivity, (a paradigm of transient hyporeactivity induced by exposure to unavoidable stress), the acute Escape Deficit. Mirtazapine administered at the dose of 10 mg/kg i. p. once a day for 14 days completely protected rats from the behavioral sequelae induced by the acute exposure to unavoidable stress. We also studied both the dopaminergic and serotonergic transmission in the nucleus accumbens shell (NAcS) and medial prefrontal cortex (mPFC) in rats treated with mirtazapine (10 mg/kg i.p. once a day for 14 days) by microdialysis experiments. In the NAcS of rats chronically treated with mirtazapine, the basal levels of dopamine and serotonin are significantly lower than those of control group, while in the mPFC there are no differences between mirtazapine and control rats in dopamine and serotonin basal levels. Moreover, after the assessment of basal values, we measured dopaminergic and serotonergic output in the NAcS and mPFC in these rats after palatable food consummation. In the NAcS, the consummation of palatable food in mirtazapine group a much lower increase of dopamine release in respect of control group while in the mPFC there were not any differences. In the NAcS, the consummation of palatable food induced an increase in dopamine output which was lower in the mirtazapine group than in the control group. In the mPFC, no difference in the dopaminergic response to palatable food was observed between the 2 groups. Furthermore, the increase in serotonin levels in NAcS after palatable food consummation was significantly lower in the mirtazapine group than in the control group, while in the mPFC the mirtazapine group showed an increase in serotonin significantly higher than the control group.