EFFECT OF REPEATED TREATMENT WITH REBOXETINE ON THE CENTRAL $\alpha_1$-ADRENERGIC AND DOPAMINERGIC RECEPTORS

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Reboxetine (REB) is a member of a new class of antidepressant drugs, which selectively inhibit the neuronal reuptake of noradrenaline. It is devoid of any affinity for neurotransmitter receptors nor does it inhibit monoamine oxidases A or B. Since our earlier studies have shown that antidepressant drugs administered repeatedly increase the responsiveness of $\alpha_1$-adrenergic receptors and induce the up-regulation of postsynaptic dopamine D$_2$/D$_3$ receptors in the rat brain, we designed the present experiments to determine whether repeated administration of REB evokes similar effects.

The experiments were carried out on male Wistar rats. REB was administered at a dose of 10 mg/kg (or 30 mg/kg in some cases) once or repeatedly (twice daily for 14 days). The obtained results show that REB administered repeatedly increased exploratory behavior induced by phenylephrine and potentiated the hyperlocomotion induced by D-amphetamine. These behavioral effects indicate the hyperresponsiveness of $\alpha_1$-adrenergic receptors. Biochemical studies did not show any changes in the binding parameters of $[^{3}H]$prazosin ($B_{max}$ or $K_d$), but the ability of the $\alpha_1$-adrenergic receptor agonist, phenylephrine, to compete for these sites was significantly increased upon repeated administration of REB.

Locomotor activity induced by quinpirole was not changed, although there was a potentiation of 7-OH-DPAT-induced locomotor hyperactivity in rats receiving repeated administration of REB. At the same time no significant changes in the binding of $[^{3}H]$quinpirole and $[^{3}H]$7-OH-DPAT, or at the level of mRNA coding for dopamine D$_2$ receptors in the rat brain were observed. Enhanced responsiveness to 7-OH-DPAT observed in the behavioral studies might, therefore, result from alterations at the postreceptor level.

The above results indicate that repeated administration of REB induces the adaptive changes in the $\alpha_1$-adrenergic receptors, especially it enhances their functional responsiveness. However, the question whether this functional responsiveness is important for the clinical antidepressant efficacy, remains to be elucidated.

Key words: reboxetine, repeated treatment, adaptive changes, rats, noradrenergic and dopaminergic system

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