Repeated imipramine treatment enhances the 7-OH-DPAT-induced hyperactivity in rats: the role of dopamine D$_2$ and D$_3$ receptors.

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Previous studies have shown that antidepressant drugs with different pharmacological profiles, administered repeatedly, increase the locomotor hyperactivity induced by various dopaminomimetics, among others by (±)7-hydroxydipropylaminotetralin (7-OH-DPAT). Since, according to a recent study, this drug shows a high affinity for not only dopamine D$_3$ but also dopamine D$_2$ receptors, a question arises whether dopamine D$_3$ receptors are involved in the increase in 7-OH-DPAT-elicited locomotor hyperactivity induced by repeated treatment with antidepressant drugs. The aim of the present study was to investigate the effect of imipramine (IMI), administered repeatedly, on the hyperactivity induced by 7-OH-DPAT, a dopamine D$_3$ receptor-preferring agonist. Male Wistar rats were treated with IMI (10 mg/kg po) either acutely (single dose) or repeatedly (twice daily for 14 days). The locomotor hyperactivity induced by 7-OH-DPAT (3 mg/kg sc) was measured in photoresistor actometers. The influence of nafadotride (0.2 and 0.4 mg/kg ip), a dopamine D$_3$-preferring antagonist or sulpiride (10 and 25 mg/kg ip), a dopamine D$_2$/D$_3$ antagonist, on the 7-OH-DPAT-induced locomotor hyperactivity was studied. Nafadotride (in both doses used) or sulpiride (in the higher dose only) reduced (by about 50%) the hyperactivity induced by 7-OH-DPAT. Combined treatment with nafadotride (0.2 mg/kg) and sulpiride (25 mg/kg) completely abolished the effect of 7-OH-DPAT. IMI administered repeatedly (but not acutely) enhanced the 7-OH-DPAT-induced hyperactivity. Neither nafadotride, 0.2 mg/kg (or sulpiride, 10 mg/kg), given alone nor combined treatment with both these substances changed the hyperactivity induced by repeated treatment with IMI and 7-OH-DPAT (given 2 h after the last dose of IMI). Joint treatment with nafadotride, 0.2 mg/kg, and sulpiride, 25 mg/kg, completely abolished the enhancing effect of repeated treatment with IMI and 7-OH-DPAT.

The above results indicate that both types of dopamine receptors, D$_3$ and D$_2$, may play a substantial role in the mechanism of the 7-OH-DPAT-induced hyperactivity, as well as in the increase evoked by repeated treatment with IMI in rats.

Key words: imipramine, nafadotride, sulpiride, 7-OH-DPAT, locomotor activity, dopamine D$_2$ and D$_3$ receptors, rats