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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*

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INTRODUCTION

Our previous studies have shown that antidepressant drugs (ADs) with different pharmacological profiles, when administered repeatedly, enhance the behavioral stimulation (locomotor hyperactivity) induced by dopamine and various dopaminomimetics given systemically or locally into the nucleus accumbens [15, 18–22]. Similar findings were reported by other authors [23, 24]. Further study indicated that such effects result from the increased affinity of postsynaptic dopamine D_2 receptors in the rat mesolimbic system for their agonists [6, 14]. Among the different dopaminomimetic drugs tested were amphetamine, apomorphine, nomifensine as well as quinpirole or 7-hydroxydipropylaminotetralin (7-OH-DPAT). The latter drugs (quinpirole and 7-OH-DPAT) show affinity not only for dopamine D_3 receptors but also for dopamine D_2 receptors [e.g. 3, 7, 11, 29, 31, 32]. Therefore, it might be presumed that not only dopamine D_3 but also D_2 receptors are involved in the enhanced behavioral response to quinpirole or 7-OH-DPAT following repeated administration of ADs. Moreover, the biochemical studies (receptor autoradiography technique) indicated that ADs administered repeatedly increased the binding of [^{3}H]7-OH-DPAT in the islands of Calleja and in the shell part of the nucleus accumbens septi [12, 13], (brain regions with highly selective expression of dopamine D_3 receptors) [2]. The above results suggest that ADs administered repeatedly enhance the responsiveness of dopamine D_3 receptors, probably *via* an increase in the density of these receptors.

The aim of the present study was to investigate the effect of nafadotride (dopamine D_3-preferring antagonist) [10, 30] or sulpiride (dopamine D_2/D_3 antagonist) [e.g. 9, 31, 32] on the locomotor hyperactivity induced by repeated treatment with imipramine (IMI) and 7-OH-DPAT (a dopamine agonist with a strong preferences for dopamine D_3 receptors). IMI was administered repeatedly (twice a day, 14 days) and afterwards its effects on the 7-OH-DPAT-induced locomotor hyperactivity were evaluated.

MATERIALS and METHODS

Animals

The experiments were carried out on rats (male Wistar, weighing 250–280 g). The animals had free access to food and water before the experiment and were kept at a constant room temperature (22 ± 1°C), under a 12 hour light/dark cycle (the light on at 7 a.m.) with free access to food and water. The rats were divided into control and drug-treated groups and received either saline or IMI (10 mg/kg *po*), acutely (single dose) or repeatedly (twice daily for 14 days). The experimental protocols were approved by Ethics Committee at the Institute of Pharmacology, Polish Academy of Sciences in Kraków, and followed its guidelines.

Drugs

Imipramine (hydrochloride; IMI, Polfa, Poland), (±)7-hydroxydipropylaminotetralin (hydrobromide; 7-OH-DPAT, Research Biochemicals Int., USA), nafadotride (N-[(butyl-2-pyrrolidinyl)methyl]-1--methoxy-4-cyanonaphthalene-2-carboxamide; Dr. P. Sokoloff, Unite de Neurobiologie et Pharmacologie (U 109) de I'INSERM, Centre Paul Broca, Paris, France), S-(–)-sulpiride (Research Biochemicals Int., USA). All the drugs were dissolved in saline and administered in a volume of 2 ml/kg.

Locomotor activity in rats

The locomotor activity was measured in photoresistor actometers (two light beams) for 120 min at 10- or 30-min intervals, starting 5 min after administration of 7-OH-DPAT (*sc*). In experiments with animals treated with IMI, 7-OH-DPAT was given at a dose of 3 mg/kg *sc* 2 h after adminstration of IMI. Sulpiride (10 and 25 mg/kg *ip*) was injected at 60 min, and nafadotride (0.2 or 0.4 mg/kg *ip*) at 15 min before 7-OH-DPAT (3 mg/kg *sc*). Each group consisted of 8 rats.

RESULTS

7-OH-DPAT (3 mg/kg) increased the locomotor activity of rats. The effect was statistically significant between 30 and 120 min after 7-OH-DPAT administration (Tab. 1). A low dose (1 mg/kg) of 7-OH-DPAT did not change the basal locomotor activity of experimental animals (data not shown). Nafadotride in neither of the doses used (0.2 mg/kg and 0.4 mg/kg) altered the basal locomotor activity of experimental animals (data not shown), but significantly reduced (to a similar extent) the hyperactivity-evoking effect of 7-OH-DPAT at both the doses tested. Only the results obtained for nafadotride (0.2 mg/kg) are shown in Table 1.

Sulpiride (10 mg/kg) did not alter the locomotor activity of rats (data not shown), nor did change the hyperactivity effect of 7-OH-DPAT (Tab. 1). A higher dose (25 mg/kg) of sulpiride reduced (by about 50%) the locomotor activity of normal rats (data not shown) as well as the hyperactivity effect of 7-OH-DPAT of the rats (Tab. 1). Combined treatment with nafadotride (0.2 mg/kg) and sulpiride at a higher dose (25 mg/kg) completely abolished the 7-OH-DPAT-induced hyperactivity in rats (Tab.1).

IMI given acutely did not alter the locomotor activity of rats, nor did it change the hyperactivity induced by 7-OH-DPAT (data not shown).

IMI administered repeatedly did not alter the basal locomotor activity (data not shown), but significantly enhanced the 7-OH-DPAT-induced hyperactivity (Tab. 2 and 3). Neither nafadotride (0.2 mg/kg) or sulpiride (10 mg/kg) nor combined treatment with both these substances changed the hyperactivity induced by repeated treatment with IMI and 7-OH-DPAT in rats (Tab. 2).

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 (Tab. 3).

Table 1. Effect of nafadotride (NAF) and sulpiride (SUL) on the locomotor hyperactivity induced by 7-OH-DPAT (3 mg/kg *sc*) in rats

Compounds (mg/kg)	Activity counts (mean ± SEM)					
	10 min	20 min	30 min	60 min	90 min	120 min
Vehicle + vehicle	61.8 ± 5.1	80.1 ± 6.6	100.0 ± 11.1	120.4 ± 12.4	133.0 ± 11.4	162.6 ± 16.0
Vehicle + 7-OH-DPAT	64.3 ± 7.6	114.5 ± 9.4	188.8 ± 23.0*	333.3 ± 29.9*	521.4 ± 56.6*	696.3 ± 78.4*
NAF (0.2) + 7-OH-DPAT	77.5 ± 10.9	97.5 ± 9.2	122.6 ± 13.1	187.3 ± 44.7#	350.4 ± 60.7#	384.0 ± 58.9#
SUL (10) + 7-OH-DPAT	64.9 ± 16.9	76.9 ± 17.9	119.6 ± 22.3	241.1 ± 33.2	382.6 ± 33.6	464.4 ± 43.2
SUL (25) + 7-OH-DPAT	44.7 ± 9.5	60.6 ± 8.2	82.7 ± 7.2#	142.5 ± 8.4#	267.5 ± 21.5#	326.1 ± 54.8#
NAF (0.2) + SUL (10) + 7-OH-DPAT	45.1 ± 6.6	65.3 ± 10.0	88.5 ± 14.8	157.9 ± 31.9#	209.4 ± 51.6#	282.4 ± 49.2#
NAF (0.2) + SUL (25) + 7-OH-DPAT	42.5 ± 4.4	60.4 ± 10.6	69.5 ± 11.2	142.9 ± 30.4#	160.0 ± 17.2#	170.9 ± 23.5#

7-OH-DPAT was administered 5 min before the test. Nafadotride (NAF), 0.2 mg/kg *ip*, was given 15 min; sulpiride (SUL), 10 or 25 mg/kg *ip*, 60 min before the test. The rats were placed individually in actometers and their locomotor activity was measured for 2 h. Data represent the means ± SEM (n = 8). Dunnett's test (following ANOVA) was used to assess significance of differences between the treatment groups and the control. * $p < 0.001$ vs. vehicle, # $p < 0.001$ vs. 7-OH-DPAT

Table 2. Effect of nafadotride (NAF) and sulpiride (SUL, 10 mg/kg *ip*) on the hyperactivity induced by repeated treatment with imipramine (IMI, 10 mg/kg *po*) and 7-OH-DPAT (3 mg/kg *sc*, 2 h after the last dose of IMI) in rats

Compounds (mg/kg)	Activity counts (mean ± SEM)					
	10 min	20 min	30 min	60 min	90 min	120 min
Vehicle + vehicle	64.6 ± 6.9	92.0 ± 11.7	130.3 ± 16.4	165.1 ± 19.9	176.5 ± 21.4	187.6 ± 17.3
Vehicle + 7-OH-DPAT	66.1 ± 8.9	108.8 ± 13.5	189.5 ± 33.1	319.0 ± 50.9*	422.9 ± 62.9*	508.9 ± 62.8*
IMI + 7-OH-DPAT	218.8 ± 42.9#	372.0 ± 49.4#	435.3 ± 64.6#	599.6 ± 113.0#	995.5 ± 70.0#	1663.3 ± 203.9#
IMI + NAF (0.2) + 7-OH-DPAT	232.9 ± 35.9	367.6 ± 54.1	435.0 ± 63.8	732.4 ± 139.6	902.9 ± 163.9	1209.3 ± 217.4
IMI + SUL (10) + 7-OH-DPAT	156.3 ± 19.1	347.5 ± 39.5	475.5 ± 34.8	856.1 ± 102.9	1054.6 ± 125.8	1437.4 ± 154.8
IMI + NAF (0.2) + SUL (10) + 7-OH-DPAT	147.0 ± 16.8	224.4 ± 31.9	294.3 ± 33.8	577.3 ± 102.9	832.9 ± 89.9	1275.9 ± 104.7

The rats pretreated chronically (twice daily for 14 days) with imipramine (IMI) were injected with 7-OH-DPAT, 2 h after the last dose of IMI (and 5 min before the test). Nafadotride (NAF), 0.2 mg/kg *ip*, was given 15 min, sulpiride (SUL), 10 mg/kg *ip* – 60 min before the test. The rats were placed individually in actometers and their locomotor activity was measured for 2 h. Data represent the means ± SEM (n = 8). Dunnett's test (following ANOVA) was used to assess significance of differences between the treatment groups and the control. * $p < 0.001$ vs. vehicle, # $p < 0.001$ vs. 7-OH-DPAT

Table 3. Effect of nafadotride (NAF, 0.2 mg/kg *ip*) and sulpiride (SUL, 25 mg/kg *ip*) on the hyperactivity induced by repeated treatment with imipramine (IMI, 10 mg/kg *po*) and 7-OH-DPAT (3 mg/kg *sc*, 2 h after the last dose of IMI) in rats

Compounds (mg/kg)	Activity counts (mean ± SEM)					
	10 min	20 min	30 min	60 min	90 min	120 min
Vehicle + vehicle	77.1 ± 5.9	93.4 ± 7.9	113.6 ± 8.0	120.4 ± 12.4	131.5 ± 10.4	160.3 ± 10.8
Vehicle + 7-OH-DPAT	55.6 ± 13.9	86.0 ± 7.7	151.8 ± 14.6	309.1 ± 41.3*	435.7 ± 54.8*	532.5 ± 73.5*
IMI + 7-OH-DPAT	212.4 ± 26.2$^{\#}$	449.8 ± 46.1$^{\#}$	839.5 ± 61.2$^{\#}$	1329.9 ± 87.6$^{\#}$	1975.8 ± 163.5$^{\#}$	2399.0 ± 159.3$^{\#}$
IMI + NAF (0.2) + 7-OH-DPAT	180.3 ± 15.6	355.0 ± 39.5	548.0 ± 63.9	1014.0 ± 100.4	1477.9 ± 127.5	1710.4 ± 167.6
IMI + SUL (25) + 7-OH-DPAT	116.1 ± 15.6^{+}	187.0 ± 29.0^{+}	314.9 ± 64.9^{+}	537.6 ± 144.6^{+}	656.6 ± 199.3^{+}	874.3 ± 197.5^{+}
IMI + NAF (0.2) + SUL (25) + 7-OH-DPAT	90.3 ± 26.2^{+}	137.3 ± 30.3^{+}	180.1 ± 32.5^{+}	257.6 ± 41.8^{+}	325.6 ± 47.7^{+}	334.3 ± 50.4^{+}

The rats pretreated chronically (twice daily for 14 days) with imipramine (IMI) were injected with 7-OH-DPAT, 2 h after the last dose of IMI (and 5 min before the test). Nafadotride (NAF), 0.2 mg/kg *ip*, was given 15 min, sulpiride (SUL), 25 mg/kg *ip* – 60 min before the test. The rats were placed individually in actometers and their locomotor activity was measured for 2 h. Data represent the means ± SEM (n = 8). Dunnett's test (following ANOVA) was used to assess significance of differences between the treatment groups and the control. * $p < 0.001$ vs. vehicle, $^{\#}$ $p < 0.001$ vs. 7-OH-DPAT, $^{+}$ $p < 0.001$ vs. IMI + 7-OH-DPAT

DISCUSSION

Our previous studies showed that ADs given acutely or repeatedly did not change the locomotor activity of experimental animals [20]. However, D-amphetamine (0.5 mg/kg)-, apomorphine (0.3 mg/kg)-, quinpirole (0.3 mg/kg)-induced locomotor hyperactivity was significantly enhanced by repeated administration of ADs [15, 19, 20]. Also the 7-OH-DPAT (3 mg/kg)-evoked locomotor hyperactivity was enhanced by repeated administration of ADs such as, e.g. IMI, amitriptyline, citalopram, mianserin [12], and also venlafaxine, milnacipran, tianeptine [5, 16, 27].

The present study indicates that nafadotride, a dopamine D_3 receptor antagonist, which has been found to have a 10-fold greater preference for D_3 and D_2 [10, 30], at the tested doses does not change spontaneous locomotor activity in non-habituated rats; nevertheless, some authors observed an increase in locomotor activity in habituated rats or mice following a low dose of the drug in question [30, 34]. On the other hand, nafadotride partially inhibits the 7-OH-DPAT-induced locomotor hyperactivity and has no effect on the hyperactivity induced by D-amphetamine or quinpirole [17]. Sulpiride, a dopamine D_2/D_3 receptor antagonist [e.g. 9, 31, 32], at the higher dose used (25 mg/kg) reduced the locomotor activity of normal (non-habituated) rats, as well as the hyperactivity effect of 7-OH-DPAT. The effect of 7-OH-DPAT on locomotor activity have been extensively investigated by others authors. The results suggest that 7-OH-DPAT--induced hyperactivity is mediated principally *via* dopamine D_3 and D_2 receptors, since both sulpiride (20 mg/kg) or (+)-UH232 (10 mg/kg), a dopamine D_3 antagonist, inhibited that effect of 7-OH-DPAT [33]. Combined treatment with nafadotride and sulpiride (at the higher dose, 25 mg/kg) completely abolished the 7-OH-DPAT-induced hyperactivity. Also the enhancement by repeated administration of IMI of the 7-OH-DPAT-induced hyperactivity was not antagonized by nafadotride. However, blockade of that enhancement was produced by joint administration of nafadotride and sulpiride (25 mg/kg). The above results suggest that contribution of not only dopamine D_3, but also D_2 receptors to the mechanism of action of ADs should also be taken into account.

We found previously that 7-OH-DPAT at low dose (0.05 mg/kg) induced hypoactivity in rats; however, that effect was not modified by nafadotride [26]. ADs (IMI and citalopram) given repeatedly, but not acutely, reversed the effect of 7-OH-DPAT in a very similar manner as in the case of attenuation of the effect evoked by a low dose of apomorphine [4]. Indeed, recently Sanger et al. [28] showed that apomorphine and 7-OH-DPAT produced very similar discriminative stimuli in rats. Both the cueing and the response rate-decreasing effects of apomorphine and 7-OH-DPAT were antagonized by the autoreceptor selective dopamine antagonist amisul-

piride. This fact, together with other data presented in the present paper, suggest that these two compounds provide similar discriminative stimuli which may be mediated by presynaptically located dopamine D_3 receptors. Therefore, it may be concluded that repeated administration of ADs elicits the subsensitivity of presynaptic dopamine D_3 receptors.

On the other hand, up-regulation of both dopamine D_2 and D_3 receptors was shown by Rogoż and Dziedzicka-Wasylewska [25] in the forebrain following ADs administration, as well as by Lammers et al. [8] who found that common effect of repeated treatment with ADs was selective in dopamine D_3 receptor gene expression.

In the present study, behavioral up-regulation was observed after repeated treatment of rats with IMI, when locomotor hyperactivity was induced by 7-OH-DPAT (3 mg/kg) which was thought to act *via* dopamine D_3 as well as D_2 receptors. Moreover, the binding of [^{3}H]7-OH-DPAT was increased after repeated treatment with IMI and other ADs [12, 13] in the islands of Calleja and shell part of the nucleus accumbens septi, which are brain regions with a higher and selective expression of dopamine D_3 receptors. The functional role of these receptors in the islands of Calleja has not been fully understood so far. Studies by Barik and Beaurepaire [1] into local administration of dopamine D_3 receptor agonists indicate that these receptors mediate the decrease in the overall body temperature, but have no effect on the locomotor activity. Therefore, enhancement of 7-OH-DPAT-stimulated locomotor activity most probably results from activation of dopamine D_2 and D_3 receptors localized in the nucleus caudatus or a core region of the nucleus accumbens septi.

Summing up the above results, it may be concluded that – like other ADs – IMI administered repeatedly induces adaptive changes in the dopaminergic system. Enhancement of the functional effect of dopamine D_3 receptor agonist 7-OH-DPAT (locomotor hyperactivity) may possibly stem from an increase in the density of dopamine D_2 and D_3 receptors.

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