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Antidepressant drugs given repeatedly change the binding of the dopamine D_2 receptor agonist, [^{3}H]N-0437, to dopamine D_2 receptors in the rat brain

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Abstract

The effects of antidepressants given in a single dose or repeatedly (10 mg/kg p.o., twice daily, 14 days) on binding to dopamine D_2 receptors in the striatum and limbic forebrain of Wistar male rats were studied. [^{3}H]N-0437, (2-(*N*[2,3(n)-^{3}H]propyl-*N*-(2-thiofuranyl)-2′-ethylamino)-5-hydroxy-1,2,3,4-tetrahydronaphthalene), a dopamine D_2 receptor agonist, was used as a ligand. Already a single dose of imipramine and fluoxetine caused a statistically significant decrease in the affinity of the ligand for dopamine D_2 receptors in the striatum, but only at 72 h after drug administration. Also at 72 h after the single dose of mianserin a significant increase in the density of dopamine D_2 receptors was observed. Repeated imipramine, amitriptyline and mianserin increased the affinity for dopamine D_2 receptors in the striatum and in the limbic forebrain. Repeated fluoxetine increased that affinity in the striatum, but decreased it in the limbic forebrain. The density of dopamine D_2 receptors was increased by the repeated administration of the antidepressants studied in the limbic forebrain, but was not changed in the striatum. The results obtained in the present study are in good agreement with the previously reported enhancement of behavioural responsiveness to dopamine and dopamine stimulants (dopamine D_2 up-regulation) evoked by repeated treatment with antidepressants.

Keywords: Antidepressant; Repeated treatment; Dopamine D_2 receptor binding; [^{3}H]N-0437

1. Introduction

We found previously that many antidepressants given repeatedly but not in a single dose, which show a different pharmacological profile in acute experiments (imipramine, desipramine, clomipramine, amitriptyline, (+)- and (−)-oxaprotiline, mianserin, citalopram, iprindole), increased the locomotor hyperactivity induced by dopamine stimulants (D-amphetamine, nomifensine, apomorphine, quinpirole) (Maj et al., 1984, 1986, 1989, 1991; Maj, 1986, 1990; Klimek and Maj, 1989). Such an increase in behavioural stimulation after repeated antidepressants was also observed when dopamine or dopamine stimulants (D-amphetamine, quinpirole) were injected locally into the nucleus accumbens (Maj and Wędzony, 1985, 1988; Maj, 1986; Maj et al., 1987). Similar effects of some of the antidepressants mentioned above were reported by other authors (Spyraki and Fibiger, 1981; Martin-Iverson et al., 1983; Arnt et al., 1984; Płaźnik and Kostowski, 1987; Serra et al., 1990). Our above-cited results led to a hypothesis that repeated treatment with antidepressants increased the responsiveness of the dopamine system (or dopamine postsynaptic receptors), and especially the mesolimbic dopamine system, to its agonists, i.e. it induced dopamine receptor up-regulation. A similar possibility was also taken into account by some of the authors cited above.

Our biochemical studies indicated that antidepressants given repeatedly did not change the density (B_{max}) of brain dopamine D_2 receptors (measured by the binding of the dopamine D_2 receptor antagonist [^{3}H]spiperone) (Klimek and Nielsen, 1987; Klimek et al., 1990). However, our subsequent studies have shown that antidepressants given repeatedly increase the affinity (decrease the K_D) of quinpirole, a dopamine D_2 receptor agonist, for D_2 receptors in the limbic system (measured by displacement of [^{3}H]spiperone) (Klimek and Maj, 1989). It may therefore be concluded that the assumed functional (behavioural)

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dopamine receptor up-regulation is caused by an increase in the affinity of dopamine D_2 receptors for their agonists.

In the above-cited studies we used [^{3}H]spiperone, a dopamine D_2 receptor antagonist. Now a non-catecholic dopamine D_2 receptor agonist, [^{3}H]N-0437, is available, which has turned out to be both potent and selective (Van Oene et al., 1984; Van der Weide et al., 1986, 1987a). Therefore we used this ligand in the present study, which allowed us to measure the binding directly, i.e. not by displacing [^{3}H]spiperone by quinpirole.

We chose imipramine, amitriptyline, fluoxetine and mianserin as antidepressants. The drugs were administered repeatedly for 14 days, p.o., twice daily, as in our earlier studies cited above. The binding to dopamine D_2 receptors was measured in two rat brain regions, i.e.: the striatum and limbic forebrain.

2. Materials and methods

2.1. Animals

Male Wistar rats (180–220 g) were housed in groups of 10 on a natural day-night cycle at a room temperature of 19–21°C with free access to food and tap water. The animals (5–6 per group) were treated with antidepressants in a dose of 10 mg/kg p.o. twice daily, at 8 a.m. and 5 p.m. for 14 days. Apart from a control group which received saline, other groups of animals were treated with a single dose of antidepressant. Two or 72 h after the last dose, the animals were killed, the striata and limbic forebrains (containing the olfactory tubercle, nucleus accumbens and septum) were dissected and frozen for evaluation of [^{3}H]N-0437 binding.

2.2. [^{3}H]N-0437 binding

The tissues were prepared and the binding experiments were carried out according to a method originally described by Van der Weide et al. (1987a) with slight modifications. Briefly, rat striata and limbic forebrains were dissected and frozen; afterwards they were homogenized in 10 volumes of ice-cold 0.32 M saccharose. After initial centrifugation at $1000 \times g$ for 10 min, the supernatant was centrifuged at $20\,000 \times g$ for 20 min to yield a crude synaptosomal pellet. The final pellet was homogenized twice in 10 volumes of 50 mM Tris buffer containing 1 mM EDTA, 5 mM KCl, 1 mM $MgCl_2$, pH 7.4, and was centrifuged at $48\,000 \times g$ for 20 min. In order to remove endogenous ligands, the membranes were incubated for 30 min at 37°C, and were then washed twice by centrifugation for 15 min at $48\,000 \times g$. Binding assays were performed in triplicate by incubating 100 μl of [^{3}H]N-0437 (0.1–5.0 nM final concentration) with 2.5 mg of tissue ($\pm$0.12 mg protein) in the resuspension buffer (total volume of 1 ml). Incubation of the samples for 45 min at 25°C in a slowly agitated water bath was followed by rapid vacuum filtration through Whatman GF/B filters, which were then washed three times with 5 ml of ice-cold buffer, using a Brandell cell harvester. The non-specific binding was determined in the presence of (+)-butaclamol.

2.3. Drugs

As antidepressants the following drugs were used: imipramine HCl and amitriptyline HCl (both Polfa, Poland), fluoxetine HCl (Eli-Lilly, USA) and mianserin HCl (Sigma, Germany).

For binding experiments the radioligand [^{3}H]N-0437 (2-(*N*[2,3(*n*)-^{3}H]propyl-*N*-(2-thiofuranyl)-2′-ethylamino)-5-hydroxy-1,2,3,4-tetrahydronaphthalene) was obtained from Amersham (England) and (+)-butaclamol from Research Biochemicals International (USA).

2.4. Statistics

The results were statistically assessed by a one-way analysis of variance (ANOVA) and inter-group differences were analysed by Duncan's multiple range test.

3. Results

A typical Scatchard plot of the specific binding of [^{3}H]N-0437 to the rat striatal membranes is presented in the Fig. 1. Hill coefficients in all our experiments were not significantly different from unity, which indicates binding to a single binding site.

Parameters characteristic for the binding of [^{3}H]N-0437 to dopamine D_2 receptors in the striatum and limbic forebrain following single and repeated administration of imipramine are shown in Table 1. In the striatum there was no change in the B_{max} value in any of the groups studied, i.e. after neither single dose (10 mg/kg) nor repeated (10 mg/kg, twice daily, 14 days) treatment with imipramine, 2

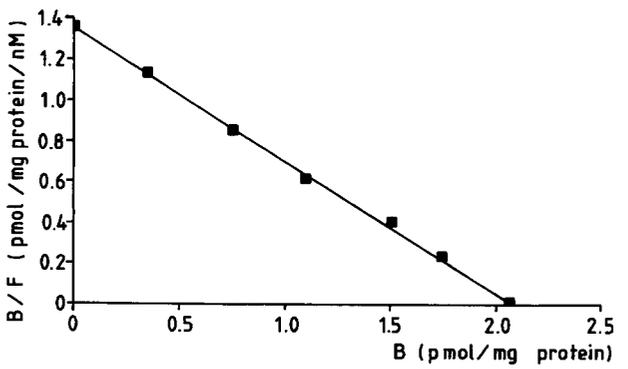

Fig. 1. Typical Scatchard plot of the specific binding of [^{3}H]N-0437 to rat striatal membranes. Binding assays were performed as described in Materials and methods. The Hill coefficient for this experiment was 0.99.

Table 1
The parameters of [^{3}H]N-0437 binding to the synaptosomal membranes of the rat striatum and limbic forebrain following administration of imipramine (IMI)

Treatment	B_{max} [pmol/mg protein]	K_D [nM]
Striatum		
–	2.08 ± 0.05	1.54 ± 0.2
IMI single, 2 h	2.07 ± 0.03	1.62 ± 0.18
IMI single, 72 h	1.97 ± 0.14	0.88 ± 0.09 [a]
IMI repeated, 2 h	1.97 ± 0.42	0.72 ± 0.05 [a]
IMI repeated, 72h	2.20 ± 0.15	0.68 ± 0.08 [a]
Limbic forebrain		
–	1.25 ± 0.09	1.38 ± 0.08
IMI single, 2 h	1.45 ± 0.15	1.48 ± 0.1
IMI single, 72 h	1.78 ± 0.15 [a]	1.61 ± 0.15
IMI repeated, 2 h	1.95 ± 0.11 [a]	1.20 ± 0.2
IMI repeated, 72 h	1.32 ± 0.09	0.82 ± 0.09 [a]

IMI was given p.o. in a dose of 10 mg/kg acutely (single dose) or repeatedly (twice daily, 14 days). The tissue for biochemical measurements was taken 2 or 72 h after the last dose of the drug. ANOVA followed by Duncan's test; [a] $P < 0.01$.

Table 3
The binding parameters of [^{3}H]-N0437 to the synaptosomal membranes of the rat striatum and limbic forebrain following administration of fluoxetine (FLU)

Treatment	B_{max} [pmol/mg protein]	K_D [nM]
Striatum		
–	2.08 ± 0.05	1.54 ± 0.2
FLU single, 2 h	2.10 ± 0.20	1.24 ± 0.13
FLU single, 72 h	2.35 ± 0.32	0.98 ± 0.09 [a]
FLU repeated, 2 h	1.98 ± 0.15	0.88 ± 0.05 [a]
FLU repeated, 72 h	1.88 ± 0.18	0.98 ± 0.08 [a]
Limbic forebrain		
–	1.25 ± 0.09	1.38 ± 0.08
FLU single, 2 h	1.42 ± 0.25	1.53 ± 0.20
FLU single, 72 h	1.37 ± 0.30	1.73 ± 0.18
FLU repeated, 2 h	1.62 ± 0.15 [a]	2.00 ± 0.15 [a]
FLU repeated, 72 h	1.58 ± 0.10 [a]	1.82 ± 0.20 [a]

FLU was given p.o. in a dose of 10 mg/kg acutely (single dose) or repeatedly (twice daily, 14 days). The tissue for biochemical measurements was taken 2 or 72 h after the last dose of the drug. ANOVA followed by Duncan's test; [a] $P < 0.01$

or 72 h afterwards. However, a significant decrease in the K_D value was observed after acute (after 72 h only) and repeated (after 2 and 72 h) imipramine administration.

In the limbic forebrain, the B_{max} value was increased following acute (after 72 h only) and repeated (after 2 h, but not after 72 h) treatment with imipramine (Table 1). The K_D was decreased in rats treated repeatedly with imipramine (after 72 h only).

Amitriptyline given in a single dose or repeatedly did not change the B_{max} value (measured after 2 or 72 h) of dopamine D_2 receptors in the striatum (Table 2). The K_D value was diminished only in the tissue obtained from rats treated repeatedly with amitriptyline (after 2 or 72 h).

Table 2
The parameters of [^{3}H]N-0437 binding to the synaptosomal membranes of the rat striatum and limbic forebrain following administration of amitryptyline (AMI)

Treatment	B_{max} [pmol/mg protein]	K_D [nM]
Striatum		
–	2.08 ± 0.05	1.54 ± 0.2
AMI single, 2 h	1.84 ± 0.15	1.44 ± 0.15
AMI single, 72 h	2.26 ± 0.22	1.72 ± 0.20
AMI repeated, 2 h	1.98 ± 0.23	1.26 ± 0.09 [a]
AMI repeated, 72 h	2.18 ± 0.25	1.19 ± 0.05 [a]
Limbic forebrain		
–	1.25 ± 0.09	1.38 ± 0.08
AMI single, 2 h	1.32 ± 0.15	1.36 ± 0.09
AMI single, 72 h	1.30 ± 0.09	1.60 ± 0.12
AMI repeated, 2 h	2.00 ± 0.25 [a]	0.98 ± 0.05 [a]
AMI repeated, 72 h	1.37 ± 0.20	1.00 ± 0.05 [a]

AMI was given p.o. in a dose of 10 mg/kg acutely (single dose) or repeatedly (twice daily, 14 days). The tissue for biochemical measurements was taken 2 or 72 h after the last dose of the drug. ANOVA followed by Duncan's test; [a] $P < 0.01$.

In the limbic forebrain, the B_{max} was increased only in rats treated repeatedly with amitriptyline (after 2 h; Table 2). The K_D value was diminished following repeated amitriptyline (after 2 and 72 h).

Single-dose or repeated treament with fluoxetine did not change the B_{max} of dopamine D_2 receptors in the striatum (Table 3). The K_D value was decreased after acute (after 72 h only) and repeated (at both the time points measured) treatment.

In the limbic forebrain, an increase in the B_{max} of dopamine D_2 receptors was observed after repeated (but not acute) fluoxetine administration (after 2 and 72 h; Table 3). Repeated (but not acute) treatment with fluoxetine increased the K_D value (at both the time points studied).

Mianserin given acutely or repeatedly did not affect the B_{max} value in the striatum (after 2 or 72 h; Table 4). The K_D was decreased only after repeated treatment (after 2 or 72 h).

In the limbic forebrain membranes the B_{max} value was increased after acute (after 72 h) and repeated (after 2 h) treatment with mianserin (Table 4). A decrease in the K_D value was found only following repeated mianserin administration (72 h after the last dose).

4. Discussion

Our results indicate that, when given repeatedly, the antidepressants tested in the present study increase the affinity of dopamine D_2 receptors for their agonist, [^{3}H]N-0437, in the rat striatum. Imipramine and fluoxetine were able to induce such an effect after 72 h also when they were given in a single dose. In the limbic forebrain, the

Table 4
The parameters of [^{3}H]N-0437 binding to the synaptosomal membranes of the rat striatum and limbic forebrain following administration of mianserin (MIA)

Treatment	B_{max} [pmol/mg protein]	K_D [nM]
Striatum		
–	2.08 ± 0.05	1.54 ± 0.20
MIA single, 2 h	2.20 ± 0.30	1.42 ± 0.17
MIA single, 72 h	2.00 ± 0.25	1.40 ± 0.25
MIA repeated, 2 h	1.92 ± 0.20	0.82 ± 0.09 [a]
MIA repeated, 72 h	1.98 ± 0.15	0.93 ± 0.01 [a]
Limbic forebrain		
–	1.25 ± 0.09	1.38 ± 0.08
MIA single, 2 h	1.37 ± 0.10	1.42 ± 0.15
MIA single, 72 h	1.68 ± 0.15 [a]	1.48 ± 0.15
MIA repeated, 2 h	1.72 ± 0.20 [a]	1.52 ± 0.20
MIA repeated, 72 h	1.27 ± 0.20	0.83 ± 0.10 [a]

MIA was given p.o. in a dose of 10 mg/kg acutely (single dose) or repeatedly (twice daily, 14 days). The tissue for biochemical measurements was taken 2 or 72 h after the last dose of the drug. ANOVA followed by Duncan's test; [a] $P < 0.01$.

affinity of [^{3}H]N-0437 was increased by repeated imipramine and mianserin (after 72 h only), and amitriptyline (2 and 72 h after the last dose). Unexpectedly, repeated fluoxetine decreased the affinity of this ligand for dopamine D_2 receptors.

The increase in the affinity of D_2 receptors described above was reported by us earlier for imipramine and mianserin in the limbic forebrain, but not in the striatum (Klimek and Maj, 1989). The cause of such a discrepancy seems to lie in the different method used in the present study, i.e.: direct binding of the radioligand of an agonistic nature to the receptor, instead of displacing [^{3}H]spiperone by quinpirole. Also the present binding study was conducted with synaptosomal membranes of the striatum or limbic forebrain, in contrast to our earlier studies which were carried out with a tissue homogenate.

In the striatum the density (B_{max}) of dopamine D_2 receptors was not modified by imipramine, amitriptyline, fluoxetine or mianserin (given repeatedly, as well as acutely), but in the limbic forebrain it was increased by repeated administration of these drugs. The above effect was evoked only by fluoxetine, at 2 or 72 h after drug administration, whereas in the case of the other antidepressants studied, it was observed after 2 h only. Imipramine and mianserin were also able to increase the density after the single-dose treatment (after 72 h).

In our earlier experiments we did not observe any increase in the B_{max} of dopamine D_2 receptors, caused by repeated administration of antidepressants, in the striatum or limbic forebrain, when [^{3}H]spiperone was used as a ligand (Klimek et al., 1990; Klimek and Nielsen, 1987). Similar results were reported by other authors (Peroutka and Snyder, 1980; Martin-Iverson et al., 1983). It seems that the method of using an agonist as a radioligand is more sensitive than that of using an antagonist. Some studies have already indicated that antagonists do not always provide full information concerning the native state of dopamine receptors, and the binding of agonists is necessary to elucidate more precisely any subtle but important alterations at the receptor level (Seeman and Grigoriadis, 1987). It seems to be interesting that some antidepressants given repeatedly do not change the binding of [^{3}H]prazosin (α_1-adrenoceptor antagonist) but increase the displacement of this ligand by phenylephrine (α_1-adrenoceptor agonist) (Menkes et al., 1983a). Concurrently functional α_1-adrenoceptor hypersensitivity is observed (Menkes et al., 1983b; Mogilnicka et al., 1987).

For biochemical determinations of the binding parameters we chose two time points following the last dose of antidepressants, i.e. 2 and 72 h. At 2 h after administration, the concentration of a drug is high, while it significantly decreases after 72 h, reaching a practically non-detectable level (Daniel et al., 1982). Our earlier studies showed that repeated treatment with antidepressants enhanced the behavioural action of D-amphetamine; this effect could be observed at both 2 and 72 h after antidepressants administration (e.g. Maj and Wędzony, 1985).

The reasons for the decrease in the affinity for dopamine D_2 receptors in the striatum and the increase in this parameter in the limbic forebrain following repeated fluoxetine administration are not clear. In the behavioural study we found that after repeated fluoxetine, the enhancement of the locomotor hyperactivity induced by D-amphetamine was relatively weak, or did not occur (unpublished data). A lack of effect of repeated fluoxetine on D-amphetamine-induced hyperlocomotion was also reported by Martin-Iverson et al. (1983). The effect of a single dose of fluoxetine on the dopamine system is not clear. The extracellular dopamine levels in the nucleus accumbens and striatum were reported to decrease (Ichikawa and Meltzer, 1995) or not to change (Fuller, 1994; Tanda et al., 1994). It was also demonstrated that 5-HT was able to increase the extracellular dopamine level in the striatum (e.g. Benloucif and Galloway, 1991; Blandina et al., 1988). Further study is needed to elucidate the reason for the opposite effects of fluoxetine found here. Fluoxetine is metabolized to norfluoxetine. The pharmacological profile of the latter in acute experiments is similar to that of fluoxetine; however, no data are available on its activity in chronic experiments.

A comparison between the obtained results indicates that an increase in the affinity of agonist for D_2 dopamine receptors is observed more often than an increase in D_2 dopamine receptors density.

In our experiments we used racemic [^{3}H]N-0437. Although there are some differences between (+) and (−) enantiomers in their action on pre- and postsynaptic dopamine D_2 receptors (Van der Weide et al., 1988), studies on the lesions induced by kainic acid and 6-hydroxydopamine show that the racemate has a preference

for postsynaptic receptors (Van der Weide et al., 1987b). Therefore it may be concluded that our results refer, above all, to postsynaptic receptors.

It has not been established whether N-0437 has affinity for dopamine D_3 and D_4 receptors. N-0434, another 2-aminotetralin derivate chemically related to N-0437 and with similar potency at D_2 receptors (Van der Weide et al., 1986), has been described as a ligand at human D_3 receptors (Freedman et al., 1984). Therefore it cannot be excluded that in our experiment we also measured binding to D_3 receptors, modified (or not) by repeated antidepressants. The effect of antidepressants on D_3 receptors has not been studied so far. We found previously that repeated antidepressants increased the behavioural stimulation induced by quinpirole (Maj et al., 1989). Since recently it is known that quinpirole shows high affinity for not only D_2, but also D_3 receptors (e.g. Levant et al., 1992). Hence participation of D_3 receptors in the activity of antidepressants on repeated administration requires further studies to be fully elucidated.

Our experiments were performed with normal rats. It is worthwhile to add that in chronic mild stress-induced anhedonia (a depression model in rats), dopamine D_2 receptor binding is decreased and this decrease is reversed by repeated imipramine (Papp et al., 1994).

In conclusion, repeated administration of the antidepressants studied here enhanced the affinity, as well as the density, of dopamine D_2 receptors, when the binding parameters were determined using an agonist as a radioligand. The results obtained in the present study are in good agreement with the formerly reported enhancement by repeated administration of different antidepressants of behavioural responsiveness to dopamine and dopamine stimulants, i.e. functional D_2 receptor up-regulation.

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