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# Effect of antidepressant drugs administered repeatedly on the dopamine $D_3$ receptors in the rat brain

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**Abstract**

Previous studies have indicated that antidepressant drugs displaying different pharmacological profiles, administered repeatedly, increase the locomotor hyperactivity induced by various dopaminomimetics, among others by quinpirole. As this drug, according to a recent study, shows high affinity not only for dopamine $D_2$ but also for dopamine $D_3$ receptors, the question arises if dopamine $D_3$ receptors are involved in the increase in quinpirole-elicited locomotor hyperactivity induced by repeated treatment with antidepressant drugs. In the present study we administered imipramine, amitriptyline, citalopram and mianserin (in a dose of 10 mg/kg p.o., twice a day, 14 days) to male Wistar rats and then (±)-7-OH-DPAT (7-hydroxy-dipropylaminotetralin), a dopamine $D_3$ receptor agonist, was given (3 mg/kg s.c.). Hyperlocomotion induced by (±)-7-OH-DPAT was significantly increased by repeated administration of antidepressant drugs. The receptor autoradiography technique with [$^3$H]7-OH-DPAT as a radioligand was applied to measure the effects of antidepressant drugs treatment on the dopamine $D_3$ receptors in the islands of Calleja and in the shell of the nucleus accumbens septi, which are brain regions with highly selective expression of dopamine $D_3$ receptors. The biochemical studies indicated that in both examined brain regions there was an increase in the binding of [$^3$H]7-OH-DPAT following the repeated administration of antidepressant drugs. In some cases this increase was also observed after the acute administration of antidepressants. The results obtained in the present study indicate that antidepressant drugs administered repeatedly enhance the responsiveness of dopamine $D_3$ receptors, probably via an increase in the density of these receptors. This mechanism is probably similar to that observed already in the case of dopamine $D_2$ receptors. Therefore it is hypothesized that dopamine $D_3$ receptors are also involved in the increased responsiveness to dopamine $D_3$ receptor agonists observed after antidepressants. 

*Keywords:* Antidepressant drug; Dopamine $D_3$ receptor autoradiography; (±)-7-OH-DPAT (7-hydroxy-dipropylaminotetralin); Hyperlocomotion; (Rat)

## 1. Introduction

Our previous studies have shown that antidepressant drugs 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 (Maj et al., 1984, 1987, 1989a,b; Maj and Wędzony, 1988). Similar findings were reported by other authors (Martin-Iverson et al., 1983; Płaźnik and Kostowski, 1987). 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 (Klimek and Maj, 1989; Maj et al., 1996). Among various dopaminomimetic drugs were the following: amphetamine, apomorphine, nomifensine as well as quinpirole. The latter drug shows affinity not only for dopamine $D_2$ receptors but also for the newly discovered dopamine $D_3$ receptors (e.g., Sokoloff et al., 1990; Levant et al., 1993; Kula et al., 1994). It has also been demonstrated that dopamine shows higher affinity for dopamine $D_3$ than for $D_2$ receptors (Sokoloff et al., 1990, 1992). Therefore it might be presumed that not only dopamine $D_2$ but also $D_3$ receptors are involved in the enhanced behavioral response to quinpirole following repeated administration of antidepressant drugs.

The present study was designed in order to examine whether antidepressant drugs administered repeatedly enhance the behavioral effects of the more selective dopamine $D_3$ receptor agonist, 7-hydroxy-dipropyloaminotetralin (7-OH-DPAT) (Sokoloff et al., 1992; Levesque et al., 1992;

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Damsma et al., 1993). Rats were treated with the following antidepressant drugs: imipramine, amitriptyline, citalopram and mianserin. Drugs were administered acutely (single dose) or repeatedly (twice a day, 14 days) and then the effects of antidepressant drugs on the (±)-7-OH-DPAT-induced locomotor hyperactivity were evaluated. The receptor autoradiography technique with [$^3$H]7-OH-DPAT as a radioligand was used to measure the effects of antidepressant drug treatment on the dopamine $D_3$ receptors in the islands of Calleja and in the shell of the nucleus accumbens septi, which are brain regions with highly selective expression of dopamine $D_3$ receptors (Bouthenet et al., 1991; Landwehrmeyer et al., 1993).

## 2. Materials and methods

### 2.1. Animals

Male Wistar rats weighing 200–250 g were kept in groups of 8 under standard laboratory conditions on a natural day–night cycle at room temperature (20°C) with free access to food and water. The animals were divided into control and drug treated groups and then received either saline or antidepressant drug (10 mg/kg p.o.) acutely (single dose) or repeatedly (twice a day for 14 days).

Following antidepressant drug administration the animals were used for behavioral experiments. Separate groups of rats were killed 2 or 72 h after the last administration of the appropriate drug, and the brains were removed and used for autoradiography procedures.

Experimental protocols were approved by the Ethics Committee and met the guidelines of the responsible Institute of Pharmacology agency.

### 2.2. Locomotor activity

The locomotor activity was measured in photoresistor actometers (two light beams) for 2 h starting 5 min after administration of various doses of (±)-7-OH-DPAT (given s.c.). In the experiments with animals receiving antidepressant drugs, (±)-7-OH-DPAT in a dose of 3 mg/kg s.c. was given 2 h after the single (acute experiment) or last dose (chronic experiment) of the appropriate antidepressant drug. In the chronic experiment locomotor activity was measured at 2 and 72 h after the last dose of antidepressant drug.

### 2.3. Autoradiographic procedure

Rat brains were carefully removed and rapidly frozen in dry ice liquid *n*-heptane. Consecutive coronal sections (12 μm) were cut at −19°C, using a cryostat Jung CM 3000 (Leica). The effect of the drug treatment on dopamine $D_3$ receptors was evaluated in the brain sections between the levels 1.0–1.7 mm from the Bregma and 10.0–10.7 mm from the Interaural lines including the shell part of the nucleus accumbens and islands of Calleja, according to the rat brain atlas (Paxinos and Watson, 1986).

The slices were sectioned and thaw-mounted on precleaned and gelatin-coated glass microscope slides. They were stored at −70°C. Immediately prior to use, the slide-mounted sections were dried at room temperature. For labelling of dopamine $D_3$ receptors with [$^3$H]7-OH-DPAT, binding was performed as described by Levesque et al. (1992). Briefly, tissue sections were first preincubated for 10 min at room temperature in 50 mM HEPES/NaOH buffer (pH 7.5), containing 1 mM EDTA and 0.1% bovine serum albumin. Sections were then incubated for 60 min at room temperature in the buffer described above with 0.5–1 nM of [$^3$H]7-OH-DPAT. To determine non-specific binding, parallel sections were incubated in the presence of 10 μM dopamine. Following incubation, tissue sections were washed four times in ice-cold 50 mM HEPES/NaOH buffer (pH 7.5) containing 100 mM NaCl, twice in distilled water and then dried in cool air.

After the experiment the sections were exposed together with tritiated standards (Amersham) for 6–8 weeks at 4°C to $^3$H-Hyperfilm (Amersham). Then the films were developed, fixed and washed under running water.

### 2.4. Drugs

Imipramine hydrochloride (Polfa), amitriptyline hydrochloride (Polfa), citalopram (Lundbeck), mianserin (Research Biochemicals), (±)-7-hydroxy-dipropyloaminotetralin hydrobromide ((±)-7-OH-DPAT, Research Biochemicals). All the drugs were dissolved in a physiological solution of saline and were administered in a volume of 2 ml/kg.

### 2.5. Radioligand

[$^3$H]7-OH-DPAT (specific activity 143 Ci/mmol) was purchased from Amersham (UK).

Other compounds for in vitro studies were of the highest commercially available purity.

### 2.6. Statistics

The data (locomotor activity) were evaluated using one-way analysis of variance (ANOVA), followed—when appropriate—by individual comparisons with the control, using Dunnett's test. The autoradiograms were analyzed by using a computer imaging system MCID-M1 (Canada) and quantified with the use of computer-generated curves derived from the standards. Film images of sections with non-specific binding were subtracted from those of adjacent sections with total binding, thus permitting the direct observation of images representing specific binding on screen. The regional densities of [$^3$H]7-OH-DPAT-labelled

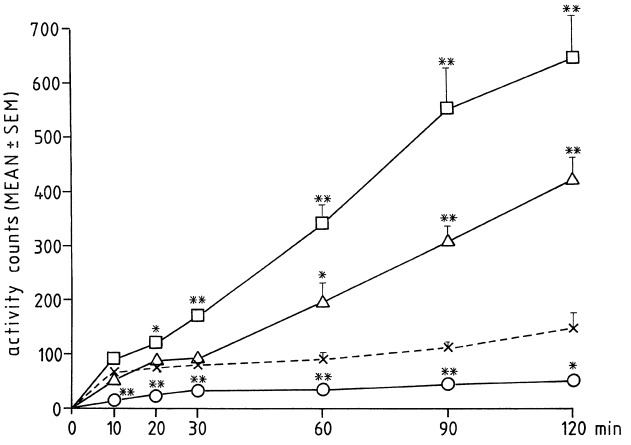


Fig. 1. Effect of (±)7-OH-DPAT on locomotor activity in untreated rats. (±)7-OH-DPAT was administered s.c. in the doses of 0.05 (– ○ –), 3 (△) and 10 (– □ –) mg/kg, 5 min before the test, (– × –) control locomotor activity. Locomotor activity was measured for 120 min at 10- or 30-min intervals. The results are means ± S.E.M., $n = 8$ rats per group. The statistical significance was calculated by using ANOVA, followed by Dunnett's test. $* P < 0.05$; $** P < 0.001$ vs. the control value.

receptors were compared by using ANOVA, followed by Fisher's test to compare each treatment with the appropriate control level.

## 3. Results

### 3.1. (±)-7-OH-DPAT-induced locomotor hyperactivity

To check the effects of (±)-7-OH-DPAT on rat locomotor activity various doses of the drug were administered s.c. and the effects were monitored for a period of 2 h. The results are presented in Fig. 1. A low dose (0.05 mg/kg) of (±)-7-OH-DPAT induced sedation, i.e., decrease in the locomotor activity of the rats by about 50%. A higher dose of the compound (3 mg/kg) increased the locomotor activity of the rats. The effect was significant between 60 and 120 min after its administration. Following this dose of (±)-7-OH-DPAT some episodes of stereotypy (sniffing) were also observed. A dose of 10 mg/kg of (±)-7-OH-DPAT induced strong hyperactivity already after 20 min and this lasted for the whole 2 h period of observation. Also more evident signs of stereotypy were apparent (sniffing but no licking or biting).

Imipramine, amitriptyline, citalopram and mianserin, given acutely or repeatedly, did not change the basal locomotor activity of the rats (data not shown).

Acute administration of the antidepressant drugs used did not change the (±)-7-OH-DPAT (3 mg/kg)-induced

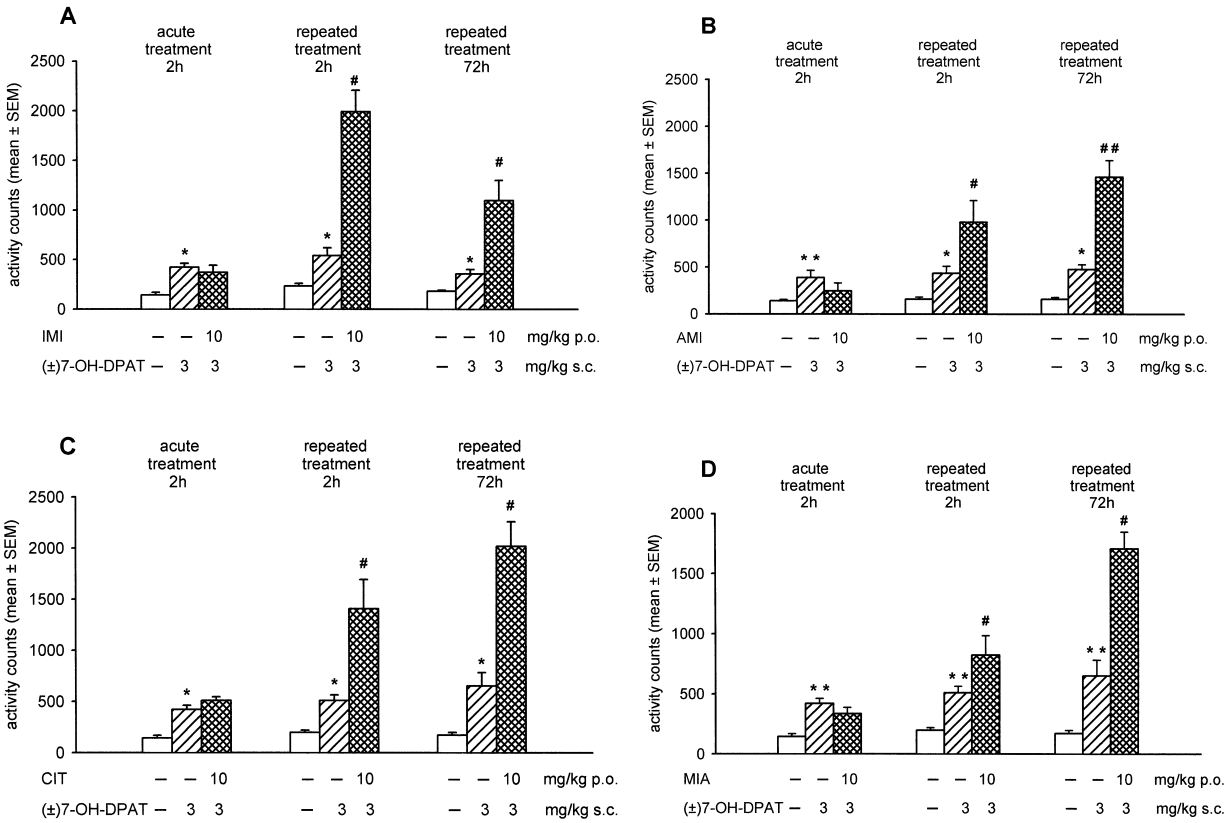


Fig. 2. (A–D). Effect of antidepressant drugs (10 mg/kg p.o.) administered acutely (single dose) or repeatedly (twice a day for 14 days) on the (±)-7-OH-DPAT-induced locomotor hyperactivity in rats. (±)-7-OH-DPAT (3 mg/kg s.c.) was given 2 h after the single administration of antidepressant drug and 2 or 72 h after the repeated treatment. Locomotor activity was measured at 5 min after administration of (±)-7-OH-DPAT for 120 min. (IMI, imipramine; AMI, amitriptyline; CIT, citalopram; MIA, mianserin). Results are means ± S.E.M., $n = 8$ animals per group. The statistical significance was calculated by using ANOVA, followed by Dunnett's test. $* P < 0.05$; $** P < 0.001$ vs. the control locomotor activity, $\#P < 0.05$; $\#\#P < 0.001$ vs. (±)-7-OH-DPAT-induced locomotor hyperactivity.

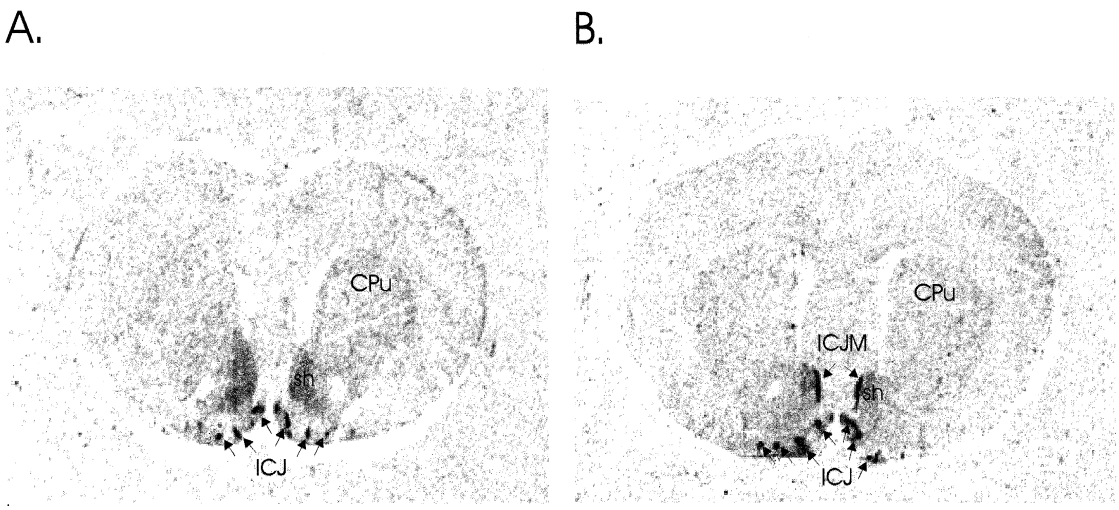


Fig. 3. Example photomicrograph of a brain section showing the specific binding of [$^3$H]7-OH-DPAT. ICj, islands of Calleja; ICjM, island of Calleja, major; sh, shell part of nucleus accumbens septi; CPu, caudate putamen. These areas were used for optical density measurements as described in Section 2. (A) 1.7 mm from Bregma, 10.7 mm from Interaural; (B) 1.2 from Bregma, 10.2 from Interaural, according to Paxinos and Watson (1986).

hyperactivity of the rats (Fig. 2A–D). Repeated administration of all antidepressant drugs enhanced the locomotor hyperactivity induced by (±)-7-OH-DPAT, 3 mg/kg, evaluated 2 or 72 h after the last dose of antidepressant. Also the signs of stereotypy were increased, i.e., ambulation and sniffing, but there was no biting.

### 3.2. Autoradiographic study

Fig. 3 represents a typical autoradiogram obtained with [$^3$H]7-OH-DPAT as a radioligand bound to coronal sections of the rat brain. At the concentration used, this radioligand labelled specifically and selectively the islands of Calleja (ICj) and the shell region of the nucleus accumbens septi (shell).

The effects of antidepressant drugs administered acutely or repeatedly on the binding of [$^3$H]7-OH-DPAT to the islands of Calleja are presented in Fig. 4. Imipramine given acutely induced a statistically significant increase in the binding of [$^3$H]7-OH-DPAT at 2 h but not 72 h after its administration. Following repeated administration of imipramine a significant increase in the binding of [$^3$H]7-OH-DPAT was observed both at 2 and 72 h after the last dose of the drug. Amitriptyline given acutely induced an increase in the binding of [$^3$H]7-OH-DPAT at 72 h after drug administration. Repeated administration of amitriptyline resulted in a significant increase in the density of dopamine $D_3$ receptors, but only 72 h after drug administration. Acute administration of citalopram increased the binding of [$^3$H]7-OH-DPAT after 2 h only. Repeated administration of citalopram induced a significant increase in the density of dopamine $D_3$ receptors after 2 and 72 h. Mianserin given acutely induced an increase in the binding of [$^3$H]7-OH-DPAT 72 h after drug administration. Also

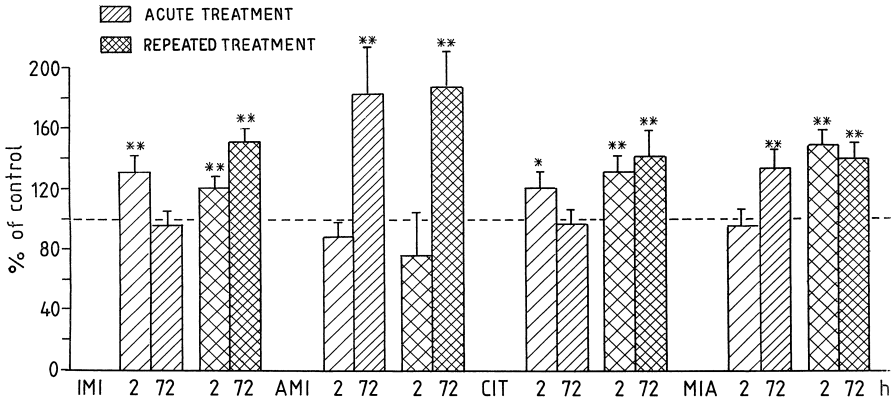


Fig. 4. Effect of antidepressant drugs (10 mg/kg p.o.) administered acutely (single dose) or repeatedly (twice a day for 14 days) on the binding of [$^3$H]7-OH-DPAT in the islands of Calleja of the rat. Rat brains were taken for autoradiographic analysis at 2 or 72 h after the last administration of antidepressant drug. (IMI, imipramine; AMI, amitriptyline; CIT, citalopram; MIA mianserin). Results are means ± S.E.M., $n = 6–8$ animals per group. Results are expressed as percentage of the control value ($B_{max} = 22.4 \pm 2.1$ fmol/mg protein)

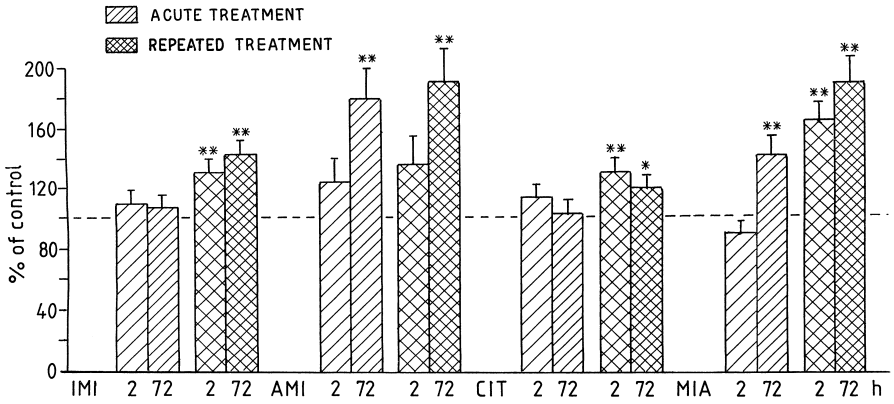


Fig. 5. Effect of antidepressant drugs (10 mg/kg p.o.) administered acutely (single dose) or repeatedly (twice a day for 14 days) on the binding of [$^3$H]7-OH-DPAT in the shell part of nucleus accumbens septi of the rat. Rat brains were taken for autoradiographic analysis at 2 or 72 h after the last administration of antidepressant drug. (IMI, imipramine; AMI, amitriptyline; CIT, citalopram; MIA, mianserin). Results are mean ± S.E.M., $n = 6–8$ animals per group. Results are expressed as percentage of the control value ($B_{max} = 7.6 \pm 0.6$ fmol/mg protein).

an increase in the density of dopamine $D_3$ receptors was observed following the repeated administration of mianserin, both at 2 and 72 h after the last dose of the drug.

In the shell part of the nucleus accumbens septi only repeated but not acute administration of imipramine and citalopram induced a significant increase in the binding of [$^3$H]7-OH-DPAT, both 2 and 72 h after the last dose of the drug (Fig. 5). Amitriptyline administered acutely or repeatedly induced a significant increase in the binding of [$^3$H]7-OH-DPAT in the shell part of the nucleus accumbens septi, but only 72 h after drug administration (Fig. 5). After 2 h the binding of [$^3$H]7-OH-DPAT was not changed. Mianserin given acutely induced an increase in the binding of [$^3$H]7-OH-DPAT at 72 h after drug administration (Fig. 5). Repeated administration of this drug resulted in a significant increase in the density of dopamine $D_3$ receptors at 2 and 72 h after the last dose of the drug.

## 4. Discussion

The results of our behavioral experiments indicate that antidepressant drugs administered repeatedly but not acutely enhance the motor hyperactivity induced by (±)-7-OH-DPAT, the dopamine $D_3$ receptor agonist. This enhancement is apparent not only after 2 h but also after 72 h following the last dose of the antidepressant drug. The observed effect was seen following the administration of antidepressant drugs displaying different pharmacological profiles: imipramine and amitriptyline, which are tricyclic drugs and inhibit noradrenaline and 5-hydroxytryptamine reuptake, citalopram, which is a selective inhibitor of 5-hydroxytryptamine reuptake, and mianserin, which does not have a significant effect on the reuptake of amines.

According to some authors, 7-OH-DPAT administered to naive rats induces a decrease in locomotor activity, which is thought to result from an action at the level of presynaptic or postsynaptic dopamine $D_3$ receptors (Daly and Waddington, 1993; Ahlenius and Salmi, 1994; Svensson et al., 1994; Gilbert and Cooper, 1995). Such an effect is observed following administration of low doses of 7-OH-DPAT. It has also been shown that treatment with higher doses of 7-OH-DPAT elicits signs of stimulation, i.e., an increase in locomotor activity or slight stereotypy manifested by sniffing and licking (Daly and Waddington, 1993; Ahlenius and Salmi, 1994; Kurashima et al., 1995; Khroyan et al., 1995, 1997). Also (±)-7-OH-DPAT given into the nucleus accumbens induces locomotor hyperactivity (Meyer, 1996). Weak stereotypy was also observed in the present study. It resembled the syndrome observed following administration of quinpirole, but not apomorphine or amphetamine, when—besides sniffing and enhanced ambulations—licking and biting are also observed.

Therefore, the antidepressant-induced increase in the locomotor hyperactivity elicited by (±)-7-OH-DPAT observed in the present study might be interpreted as the being due to an enhanced responsiveness of postsynaptic dopamine $D_3$ receptors.

Recently Collu et al. (1997) have shown an increase in quinpirole-induced hyperactivity following repeated administration of fluoxetine. A similar increase in quinpirole-induced hyperactivity has been shown by us following repeated imipramine, amitriptyline, citalopram, mianserin and (+)oxaprotiline (Maj et al., 1989a,b). Since quinpirole is a mixed dopamine $D_2/D_3$ receptor agonist, such an effect might result from the enhanced sensitivity of both types of dopamine receptors induced by repeated administration of fluoxetine (Collu et al., 1997).

In our autoradiographic experiments we studied the binding of [$^3$H]7-OH-DPAT to dopamine $D_3$ receptors in two rat brain regions, i.e., the islands of Calleja and the nucleus accumbens septi (shell), in which high expression of dopamine $D_3$ receptors has already been shown (Levesque et al., 1992; Hillefors-Berglund and Von Euler, 1994; Camacho-Ochoa et al., 1995).The results indicated that repeatedly administered antidepressant drugs signifi-

cantly increased the binding of [$^3$H]7-OH-DPAT in both of the examined brain regions. In some cases we also observed an increased binding of [$^3$H]7-OH-DPAT following acute treatment with antidepressant drugs. This effect might result from the influence of acute administration of antidepressant drugs on the fluidity of the neuronal membrane. It has already been shown that some antidepressant drugs given to rats in a single dose, in contrast to repeated administration, increase the fluidity of cortical membranes, since these drugs bind non-specifically to biological membranes, leading to phospholipid augmentation (Wesemann et al., 1988; Nocoń and Melzacka, 1991). In turn, changes in the membrane fluidity influence the binding of radioligands to their receptors, as has been described for serotonergic receptors, which may lead to misinterpretation of data (Heron et al., 1980). In our studies no enhancement of (±)-7-OH-DPAT-induced locomotor hyperactivity was observed after acute administration of antidepressant drugs. Therefore it is justified to conclude that the increase in the binding of [$^3$H]7-OH-DPAT observed shortly after the acute administration of antidepressant drugs results from the physical process unmasking receptors hidden in the cell membrane; however these receptors are not fully matured and do not transduce functional signals properly. It should be mentioned that changes in dopamine $D_1$, $D_2$ and $D_3$ receptor mRNA are also observed after 1 day of treatment with different antidepressants (Lammers et al., 1995).

The increase in the binding of [$^3$H]7-OH-DPAT seen following repeated administration of antidepressant drugs is an adaptive change most probably resulting from the increased biosynthesis of dopamine $D_3$ receptors. An increase in the level of mRNA coding for dopamine $D_2$ and $D_3$ receptors in the rat brain has already been observed after treatment with different antidepressants (Lammers et al., 1995). Similar effects have also been observed in our previous studies concerning the dopamine $D_2$ receptors (Dziedzicka-Wasylewska et al., 1997). Following repeated administration of antidepressant drugs not only was the binding of dopamine agonist, [$^3$H]*N*-0437 (2-*N*[2,3(*n*)-$^3$H]propyl-*N*-(2-thiofuranyl)-2′-ethylamino)-5-hydroxy-1,2,3,4-tetrahydronaphthalene), increased in the rat brain (Maj et al., 1996), but also the amount of mRNA coding for this dopamine receptor (Dziedzicka-Wasylewska et al., 1997).

More and more data have been reported which point to a role of the dopamine system in depression and in the activity of antidepressant drugs (e.g., Ebert and Lammers, 1997). Recently it has been reported that in depressive patients treated with fluoxetine, striatal $^{123}$I-iodobenzamide binding, measured by a SPECT method, is increased in responders and decreased in non-responders (Klimke et al., 1997).

Both behavioral and biochemical experiments performed in the present study indicate that antidepressant drugs administered repeatedly enhance the responsiveness of dopamine $D_3$ receptors in the rat brain, probably by increasing the density of these receptors. The obtained results are similar to those observed by us earlier for dopamine $D_2$ receptors (see Section 1). It may be hypothesized that for the action of antidepressants not only dopamine $D_2$ receptors but also dopamine $D_3$ receptors are important. The question arises whether the dopamine $D_3$ effects are involved in the clinical antidepressive activity.

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## References

Ahlenius, S., Salmi, P., 1994. Behavioral and biochemical effects of the dopamine $D_3$ receptor-selective ligand, 7-OH-DPAT, in the normal and reserpine-treated rat. Eur. J. Pharmacol. 260, 177–181.

Bouthenet, M.L., Souil, M.P., Martres, P., Sokoloff, P., Giros, B., Schwartz, J.C., 1991. Localization of dopamine $D_3$ receptor mRNA in the rat brain using in situ hybridization histochemistry: comparison with dopamine $D_2$ receptor mRNA. Brain Res. 564, 203–219.

Camacho-Ochoa, M., Walker, E.L., Evans, D.L., Piercey, M.F., 1995. Rat brain binding sites for pramipexole, a clinically useful $D_3$-preferring dopamine agonist. Neurosci. Lett. 196, 97–100.

Collu, M., Poggiu, A.S., Devoto, P., Serra, G., 1997. Behavioral sensitization of mesolimbic dopamine $D_2$ receptors in chronic fluoxetine-treated rats. Eur. J. Pharmacol. 322, 123–127.

Daly, S.A., Waddington, J.L., 1993. Behavioural effects of the putative $D_3$ dopamine receptor agonist 7-OH-DPAT in relation to other '$D_2$-like' agonists. Neuropharmacology 32, 509–510.

Damsma, G., Bottema, T., Westerink, B.H.C., Tepper, P.G., Dijkstra, D., Pugsley, T.A., MacKenzie, R.G., Heffner, T.G., Wikström, H., 1993. Pharmacological aspects of *R*-(+)-7-OH-DPAT, a putative dopamine $D_3$ receptor ligand. Eur. J. Pharmacol. 249, R9–R10.

Dziedzicka-Wasylewska, M., Rogoż, R., Klimek, V., Maj, J., 1997. Repeated administration of antidepressant drugs affects the levels of mRNA coding for $D_1$ and $D_2$ dopamine receptors in the rat brain. J. Neural Transm. 104, 515–524.

Ebert, D., Lammers, C.-H., 1997. Das zentralle dopamine sytem und die depression. Nervenarzt 68, 545–555.

Gilbert, D.B., Cooper, S.J., 1995. 7-OH-DPAT injected into the accumbens reduces locomotion and sucrose ingestion, $D_3$ autoreceptor-mediated effects. Pharmacol. Biochem. Behav. 52, 275–280.

Heron, D.S., Shinitzky, M., Samuel, D., 1980. Lipid fluidity markedly modulates binding of serotonin to mouse brain membranes. Proc. Natl. Acad. Sci. U.S.A. 77, 7453–7467.

Hillefors-Berglund, M., Von Euler, G., 1994. Pharmacology of dopamine $D_3$ receptors in the islands of Calleja of the rat using quantitative receptor autoradiography. Eur. J. Pharmacol. 261, 179–183.

Khroyan, T.V., Baker, D.A., Neisewander, J.L., 1995. Dose-dependent effects of the $D_3$-preferring agonist 7-OH-DPAT on motor behavior and place conditioning. Psychopharmacology 122, 351–357.

Khroyan, T.V., Fuchs, R.A., Baker, D.A., Neisewander, J.L., 1997. Effects of $D_3$-preferring agonists 7-OH-DPAT and PD-128, 907 on motor behaviors and place conditioning. Behav. Pharmacol. 8, 65–74.

Klimek, V., Maj, J., 1989. Repeated administration of antidepressants enhances agonist affinity for mesolimbic $D_2$ receptors. J. Pharm. Pharmacol. 41, 555–558.

Klimke, A., Larisch, R., Janz, A., Vosberg, H., Mueller-Gaertner, H., Gaebel, W., 1997. Dopamine $D_2$ receptor binding before and after

treatment of major depression measured by single photon emission computed tomography. Pharmacopsychiatry 30, 189.

Kula, N.S., Baldesarini, R.J., Kebabian, J.W., Neumeyer, J.S., 1994. *S*-(+)-aporphines are not selective for human $D_3$ dopamine receptors. Cell. Mol. Neurobiol. 14, 185–191.

Kurashima, M., Yamada, K., Nagashima, M., Shirakawa, K., Furukawa, T., 1995. Effects of putative dopamine $D_3$ receptor agonists, 7-OH-DPAT and quinpirole, on yawning, stereotypy and body temperature in rats. Pharmacol. Biochem. Behav. 52, 503–508.

Lammers, C.H., Diaz, G., Levesque, D., Griffon, N., Schwartz, J.C., Sokoloff, P., 1995. Regulation of dopamine receptor mRNA by antidepressants. Pharmacopsychiatry 28, 159.

Landwehrmeyer, B., Mengod, G., Palacios, M., 1993. Differential visualization of dopamine $D_2$ and $D_3$ receptor sites in rat brain. A comparative study using in situ hybridization histochemistry and ligand binding autoradiography. Eur. J. Pharmacol. 5, 145–153.

Levant, B., Grigoriadis, D.E., DeSouza, E.B., 1993. [$^3$H]Quinpirole binding to putative $D_2$ and $D_3$ dopamine receptors in rat brain and pituitary gland: a quantitative autoradiographic study. J. Pharmacol. Exp. Ther. 264, 991–1001.

Levesque, D., Diaz, J., Pilon, C., Martres, M.P., Giros, B., Souil, B., Schott, D., Morgat, J.L., Schwartz, Sokoloff, P., 1992. Identification, characterization and localization of the dopamine $D_3$ receptor in rat brain using 7-[$^3$H] hydroxy-*N*,*N*-di-*N*-propyl-2-aminotetralin. Proc. Natl. Acad. Sci. USA 89, 8155–8159.

Maj, J., Wędzony, K., 1988. The influence of oxaprotiline enantiomers given repeatedly on the behavioral effects of D-amphetamine and dopamine injected into the nucleus accumbens. Eur. J. Pharmacol. 145, 97–103.

Maj, J., Rogóż, Z., Skuza, G., Sowińska, H., 1984. Repeated treatment with antidepressant drugs increases the behavioral response to apomorphine. J. Neural Transm. 60, 273–282.

Maj, J., Wędzony, K., Klimek, V., 1987. Desipramine given repeatedly enhances behavioral effects of dopamine and D-amphetamine injected into the nucleus accumbens. Eur. J. Pharmacol. 140, 179–185.

Maj, J., Papp, M., Skuza, G., Bigajska, K., Zazula, M., 1989a. The influence of repeated treatment with imipramine, (+)- and (−)-oxaprotiline on behavioral effects of dopamine $D_1$ and $D_2$ agonists. J. Neural. Transm. 76, 29–38.

Maj, J., Rogóż, Z., Skuza, G., Sowińska, H., 1989b. Antidepressants given repeatedly increase the behavioral effect of dopamine $D_2$ agonists. J. Neural Transm. 78, 1–8.

Maj, J., Dziedzicka-Wasylewska, M., Rogoż, R., Rogóż, Z., Skuza, G., 1996. 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. Eur. J. Pharmacol. 304, 49–54.

Martin-Iverson, M.T., Leclere, J.F., Fibiger, H.C., 1983. Cholinergic–dopaminergic interactions and the mechanism of action of antidepressants. Eur. J. Pharmacol 94, 193–201.

Meyer, M.E., 1996. Mesolimbic 7-OH-DPAT affects locomotor activities in rats. Pharmacol. Biochem. Behav. 55, 209–214.

Nocoń, H., Melzacka, M., 1991. Effect of some cationic amphiphilic drugs on phospholipid methylation in the central nervous system of rats. J. Pharm. Pharmacol. 43, 107–110.

Paxinos, G., Watson, C., 1986. The Rat Brain Stereotaxic Coordinates. Academic Press, Sydney.

Płaźnik, A., Kostowski, W., 1987. The effects of antidepressants and electroconvulsive shock on the functioning of the mesolimbic dopaminergic system: a behavioral study. Eur. J. Pharmacol. 135, 389–396.

Sokoloff, P., Giros, B., Martres, M.P., Bouthenet, M.L., Schwartz, J.C., 1990. Molecular cloning and characterization of a novel dopamine receptor ($D_3$) as a target for neuroleptics. Nature 347, 146–151.

Sokoloff, P., Andrieux, M., Besancon, R., Pilon, C., Martres, M.P., Giros, B., Schwartz, J.C., 1992. Pharmacology of human dopamine $D_3$ receptor expressed in a mammalian cell line: comparison with $D_2$ receptor. Eur. J. Pharmacol. 225, 331–337.

Svensson, K., Carlsson, A., Waters, N., 1994. Locomotor inhibition by the $D_3$ ligand *R*-(+)-7-OH-DPAT is independent of changes in dopamine release. J. Neural Transm. Gen. Sect. 95, 71–74.

Wesemann, W., Melzacka, M., Lausch, R.O., Weiner, N., Mennel, H.D., Sontag, K.H., 1988. Age and drug-dependent changes of serotonin binding sites and membrane architecture. Abstr. XVIth C.I.N.P. Congress Psychopharmacol., Vol. 96, Suppl., pp. 165.