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Repeated administration of antidepressant drugs affects the levels of mRNA coding for D_1 and D_2 dopamine receptors in the rat brain

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Summary. The present study examined the effects of acute and repeated administration of three antidepressant drugs (imipramine, citalopram and (+)-oxaprotiline) on the levels of mRNA coding for dopamine D_1 and D_2 receptors in the rat brain. Quantitive in situ hybridization with ^{35}S-labelled oligonucleotide probes has been utilised. The level of mRNA coding for dopamine D_1 receptor (D_1 mRNA) is decreased following repeated administration of imipramine, both in the nucleus accumbens and in the striatum. On the other hand, the repeated administration of citalopram, the selective inhibitor of serotonin reuptake, resulted in an increase in the level of D_1 mRNA in the striatum and in the core region of nucleus accumbens. A similar tendency, i.e.: an increase in the level of D_1 mRNA was observed after repeated administration of (+)-oxaprotiline, a selective inhibitor of noradrenaline reuptake. The level of mRNA coding for dopamine D_2 receptors (D_2 mRNA) was increased in all the brain regions studied, both after administration of imipramine and citalopram. (+)-Oxaprotiline did not produce any statistically significant changes in the level of D_2 mRNA.

The results obtained in this study indicate that the levels of mRNA coding for dopamine D_1 and D_2 receptors are regulated by the antidepressant drugs. The changes concerning the dopamine D_2 receptors are more consistent and fit in with the previously described binding and behavioral effects and seem to be important for the mechanism of action of antidepressant drugs.

Keywords: Antidepressant drugs, D_1 and D_2 mRNA, striatum, nucleus accumbens, rat.

Introduction

Previous behavioural and neurochemical studies have shown that repeated antidepressant treatment influences the brain dopaminergic system. Repeated administration of antidepressant drugs increases locomotor hyperactivity induced by dopamine stimulants, possibly as a result of postsynaptic dopam-

inergic supersensitivity (Maj et al., 1984, 1987, 1989, 1991; Maj, 1986, 1990; Maj and Wędzony, 1985; Spyraki and Fibiger, 1981; Martin-Iverson et al., 1983; Arnt et al., 1984; Płaźnik and Kostowski, 1987; Serra et al., 1990). The hypothesis of supersensitivity of postsynaptic dopamine receptors, although well documented in behavioural studies, contrastes with the results of dopamine receptor binding studies, which suggest that after repeated treatment with antidepressant drugs dopamine D_2 receptor density as measured by [^{3}H]-spiperone binding is unchanged, whereas that of dopamine D_1 receptors, measured by [^{3}H]-SCH23390 binding, is decreased (Martin-Iverson et al., 1983; Klimek and Nielsen, 1987; De Montis et al., 1989). However, in further studies by Klimek and Maj (1989) it has been demonstrated that antidepressants given repeatedly increase the affinity of dopamine D_2 receptors for the agonist, evaluated by the displacement of [^{3}H]-spiperone by quinpirole. We have recently shown that antidepressants (imipramine, amitriptiline, fluoxetine and mianserin), administered repeatedly, increase the affinity and the density of dopamine D_2 receptors, measured by the binding of the D_2 agonist [^{3}H]-N-0437 (Maj et al., 1996). These findings are in line with the observation that repeated administration of antidepressants potentiates locomotor hyperactivity induced by dopamine agonists, among others by quinpirole (Maj, 1986, 1990).

Since clinical effects of antidepressant drugs are generally observed only after prolonged treatment, the biochemical changes underlying these effects may be secondary to alterations at the genomic level. Until recently, however, little was known about transcriptional and posttranscriptional factors regulated by chronic drug treatment, although long-term changes in neuronal synaptic function are known to be dependent upon selective regulation of gene expression (Karin, 1992). It has been recently shown that repeated treatment with lithium (Dziedzicka-Wasylewska and Wędzony, 1996) and also repeated but not acute electroconvulsive shock affects the level of mRNA coding for dopamine receptors in the rat nucleus accumbens (Smith et al., 1995).

The present study was therefore designed in order to obtain information on whether repeated administration of antidepressant drugs modifies the biosynthesis of postsynaptic dopamine D_1 and D_2 receptors. This aim was achieved by measuring the level of mRNA coding for dopamine D_1 and D_2 receptors in the rat striatum and the nucleus accumbens septi shell and core, using in situ hybridization.

Three antidepressant drugs with different pharmacological profiles have been used; imipramine – a noradrenaline and serotonin reuptake inhibitor, citalopram – a selective inhibitor of serotonin reuptake, and (+)-oxaprotiline – a selective noradrenaline reuptake inhibitor.

Methods

Animals

Male Wistar rats (180–220 g) were housed in groups of 10 on a natural day-night cycle at room temperature of 19–20°C with free access to food and tap water. The animals were

treated with antidepressant drugs at a dose of 10 mg/kg p.o., twice a day, at 8 a.m. and 5 p.m. for two weeks. Apart from the control groups, which received saline, there were groups of animals treated with a single dose of the appropriate drug. While not receiving the antidepressant drug, all rats were treated with saline p.o. All groups of animals, treated acutely or repeatedly with antidepressant drugs, were decapitated at the same time. This took place 2 or 72 h after the last dose. The brains of the rats were then rapidly removed and frozen on dry ice. The D_1 mRNA and D_2 mRNA measurements were carried out on the same groups of rats.

In situ hybridization

Coronal sections (12 μm thick) were made on a cryostat through the nucleus accumbens septi and the striatum (caudate-putamen). The sections were thaw-mounted onto chrome alum pretreated slides and processed for in situ hybridization using the method described previously (Dziedzicka-Wasylewska and Rogoż, 1995). Briefly, a mixture of 48-mer synthetic deoxyoligonucleotides (New England Nuclear) complementary to bases 4–51, 766–813 and 901–948 of the rat D_2 dopamine receptor (Bunzow et al., 1988) and complementary to bases 13–60, 520–567 and 664–711 of the rat D_1 dopamine receptor (Zhou et al., 1990) were labelled using [^{35}S]dATP (1,200 Ci/mmol, New England Nuclear) Tissue sections were thawed and fixed for 10 min in 4% paraformaldehyde in phosphate-buffered saline at 4°C. After three 5 min rinses in isotonic phosphate-buffered saline, sections were treated with 0.1 M triethanolamine (pH 8.0)/acetic anhydride (0.25%). The sections were then rinsed in 2 × SSC (300 mM NaCl/30 mM sodium citrate, pH 7.0) for 5 min, dehydrated through graded alcohols and allowed to air-dry. After this fixing and prehybridization, sections were treated with [^{35}S]dATP-labelled probes. Probes were diluted in hybridization buffer [50% (vol/vol) formanide, 10% (wt/vol) dextran sulfate, 4 × SSC (pH 7.0), 1 × Denhardt's solution (= 0.02% polivinylpyrrolidone/0.02% Ficoll/0.02% bovine serum albumine), yeast tRNA (0.25 mg/ml), sheared herring sperm DNA (0.2 mg/ml), 10 mM dithiothreitol] to result in a final concentration of 2×10^6 dpm/30 μl. All solutions were made up with autoclaved 0.1% diethylpyrocarbonate-treated water. Diluted probes (30 μl) were applied to sections, which were then covered with Parafilm. Hybridization occurred overnight in a humidified chamber at 39°C. Following hybridization, sections were washed in 1 × SSC for 10 min, then 4 times for 15 min each in 1 × SSC/50% formamide at 42°C, rinsed briefly in 1 × SSC and water at room temperature, then air-dried. Slides were then placed in X-ray cassettes, apposed to film (Amersham MP) for 20 days at −20°C. Different patterns of hybridization, found in the brain regions, fully agreed with the well known distribution of D_1 and D_2 receptors mRNAs (Mansour et al., 1991; Meador-Woodruff and Mansour, 1991) and provided support for the specificity of the probes under the present experimental conditions. The specificity of in situ hybridization was additionally assessed by pretreatment of some tissue sections with RNAase A (20 μg/ml) for 40 min at 30°C, which completely eliminated the hybridization signal with the cDNA probe.

Optical measurements were made from the autoradiograms corresponding to sections of the nucleus accumbens septi and the striatum, using an image analyzing system (Java: Jandel, Corte Madera CA, USA). The average optical density values were calculated after subtraction of the film background density. The mean optical density values were obtained by averaging out the measurements from autoradiograms of the 4–5 sections obtained from 5–6 animals per group.

Drugs

The following drugs were used as antidepressants: imipramine HCl (Polfa, Poland); citalopram (Lundbeck, Denmark) and (+)-oxaprotiline (Ciba-Geigy, Germany).

Statistics

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

Results

Figure 1 presents examples of photomicrographs of brain sections hybridized with probes against dopamine D_1 receptor mRNA (A) and dopamine D_2 receptor mRNA (B). On Fig. 1C the diagrammatic representation of the areas used in optical density analysis of specific brain regions is shown.

The effects of antidepressant drugs on the level of mRNA coding for D_1 receptor (D_1 mRNA) are presented in Table 1. Repeated but not acute treatment with imipramine (2h and 72h after the last dose) resulted in a significant decrease in the level of D_1 mRNA in all the brain regions studied.

The D_1 mRNA level in the striatum started to increase already after a single dose of citalopram (72h after the drug administration) but the effect was not statistically significant. Citalopram given repeatedly resulted in a significant increase in the level of D_1 mRNA in the core region of the nucleus accumbens septi and in the striatum. On the other hand, we did not see any significant effect of repeated citalopram on the level of D_1 mRNA in the shell region of nucleus accumbens septi.

Repeated administration of (+)-oxaprotiline resulted in a slight increase of the level of D_1 mRNA in nucleus accumbens, at 72h after drug withdrawal.

The effects of antidepressant drugs on the level of mRNA coding for D_2 receptors (D_2 mRNA) are presented in Table 2. Already a single dose of imipramine (2h after administration) resulted in a slight increase in the level of mRNA D_2 both in the striatum and core region of the nucleus accumbens, but the results did not reach statistical significance. At 72h after a single dose

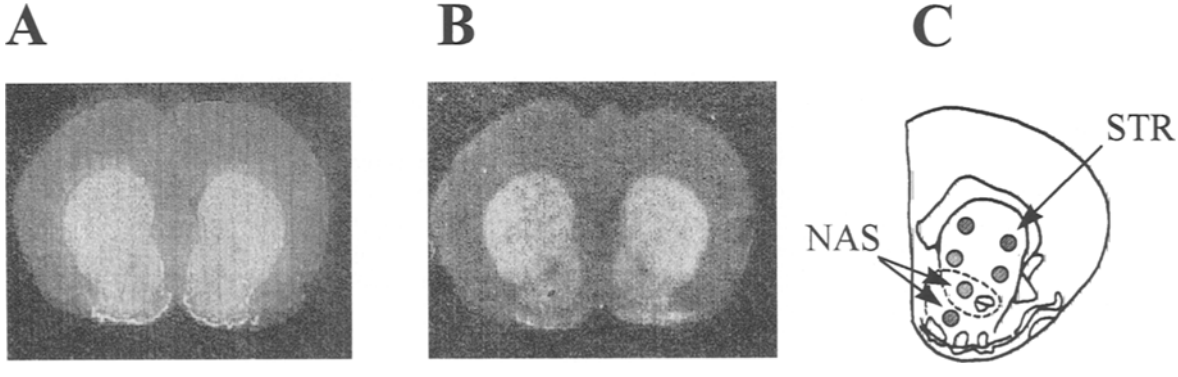

Fig. 1. Example photomicrographs of brain sections hybridised with probes against dopamine D_1 receptor mRNA (**A**) and dopamine D_2 receptor mRNA (**B**). **C** Shows diagrammatic representation of the areas used in optical density analysis of specific brain regions

Table 1. The effect of antidepressant drugs: imipramine (IMI), citalopram (CIT) and (+)-oxaprotiline (OXA) on the levels of mRNA [per cent of control level] coding for dopamine D_1 receptor in the striatum and nucleus accumbens septi (core and shell) of the rat

Treatment	Striatum	Nucleus accumbens	
		core	shell
IMI single, 2 h	104.5 ± 8.9	109.4 ± 4.6	112.5 ± 6.6
single, 72 h	114.5 ± 11.9	104.2 ± 7.8	92.3 ± 5.4
repeated, 2 h	72.6 ± 5.2*	76.8 ± 6.0*	72.3 ± 6.5*
repeated, 72 h	76.3 ± 6.6*	78.2 ± 6.4*	79.8 ± 7.5*
CIT single, 2 h	95.6 ± 2.9	102.7 ± 3.4	95.8 ± 7.3
single, 72 h	114.8 ± 4.9	105.2 ± 4.2	88.6 ± 4.2
repeated, 2 h	121.1 ± 7.5*	118.8 ± 6.8*	106.6 ± 5.8
repeated, 72 h	131.9 ± 3.3*	127.5 ± 5.6*	111.1 ± 7.0
OXA single, 2 h	96.2 ± 4.2	93.8 ± 6.4	89.9 ± 2.6
single, 72 h	105.9 ± 4.7	98.2 ± 3.7	90.3 ± 3.5
repeated, 2 h	105.6 ± 3.6	96.3 ± 4.1	108.0 ± 7.0
repeated, 72 h	111.5 ± 3.4	114.3 ± 4.2*	115.6 ± 3.2*

Imipramine (IMI), citalopram (CIT) and (+)-oxaprotiline (OXA) were administered in a single dose (single, 10 mg/kg p.o) or repeatedly (repeated, 10 mg/kg p.o. twice a day, for 14 days). Rats were killed 2 or 72 h after the last dose of the drug. The mean optical density values were obtained by averaging the measurements from autordiograms of the 4–5 sections obtained from 5–6 animals per group and recalculated as percentage of the level of D_1 receptor mRNA in control animals. Control level of D_1 mRNA for striatum was 100% ± 4.5; for core region of nucleus accumbens was 100% ± 3.4; for shell region of nucleus accumbens was 100% ± 4.9. ANOVA followed by Duncan's test, *$p < 0.05$ vs. the control level

of imipramine a significant increase in the level of D_2 mRNA was observed in all the brain regions examined. Repeated administration of imipramine caused an increase in the biosynthesis of D_2 receptor in all brain regions examined; the effect was statistically significant at both 2 and 72 h after the last dose of the drug.

Repeated (but not acute) administration of citalopram produced an increase of the level of D_2 mRNA in all the brain region studied. A similar tendency was observed already after a single dose of the drug, 72 h after the administration, but was not statistically significant.

(+)-Oxaprotiline did not produce any significant effects as far as the level of D_2 mRNA is concerned, neither after a single dose nor repeated administration, although generally the level of D_2 mRNA was lower than in the control group.

Discussion

Most recently it has become clear that long-term changes in neuronal synaptic function are correlated with, and in some cases shown to be dependent on, the

Table 2. The effect of antidepressant drugs: imipramine (IMI), citalopram (CIT) and (+)-oxaprotiline (OXA) on the levels of mRNA [per cent of control level] coding for dopamine D_2 receptors in the striatum and nucleus accumbens septi (core and shell) of the rat

Treatment	Striatum	Nucleus accumbens	
		core	shell
IMI single, 2 h	113.0 ± 5.9	114.9 ± 8.0	108.6 ± 3.6
single, 72 h	139.6 ± 8.2*	138.2 ± 6.8*	134.8 ± 5.2*
repeated, 2 h	129.3 ± 5.6*	132.8 ± 7.4*	136.2 ± 6.3*
repeated, 72 h	136.4 ± 3.8*	136.2 ± 5.2*	140.3 ± 6.4*
CIT single, 2 h	109.2 ± 4.3	106.3 ± 5.6	110.5 ± 4.1
single, 72 h	115.5 ± 7.0	113.2 ± 8.2	116.0 ± 4.8
repeated, 2 h	122.0 ± 3.2*	119.7 ± 6.4*	126.5 ± 6.3*
repeated, 72 h	129.6 ± 4.2*	122.5 ± 3.5*	128.6 ± 7.2*
OXA single, 2 h	92.8 ± 1.8	96.3 ± 2.3	92.0 ± 3.5
single, 72 h	92.0 ± 2.0	93.3 ± 2.4	95.2 ± 7.3
repeated, 2 h	95.6 ± 3.6	94.5 ± 3.2	88.7 ± 6.1
repeated, 72 h	96.7 ± 5.0	98.4 ± 2.4	87.9 ± 4.5

Imipramine (IMI), citalopram (CIT) and (+)-oxaprotiline (OXA) were administered in a single dose (single, 10 mg/kg p.o) or repeatedly (repeated, 10 mg/kg p.o. twice a day, for 14 days). Rats were killed 2 or 72 h after the last dose of the drug. The mean optical density values were obtained by averaging the measurements from autoradiograms of the 4–5 sections obtained from 5–6 animals per group and recalculated as percentage of the level of D_2 receptor mRNA in control animals. Control level of D_2 mRNA for striatum was 100% ± 5.2; for core region of nucleus accumbens was 100% ± 4.5; for shell region of nucleus accumbens was 100% ± 4.8. ANOVA followed by Duncan's test, *$p < 0.05$ vs. the control level

induction of new programs of gene expression (Karin, 1992; Sheng and Greenberg, 1990). Recent successful cloning of the genes coding for the dopamine receptors (Bunzow et al., 1988; Civelli et al., 1991; Zhou et al., 1990) offered the opportunity to study the modulation of the dopaminergic system at the level of receptor gene expression. It has also become apparent that receptor activity may be coupled to receptor biosynthesis, thus maintaining dopaminergic homeostasis in the brain. It has already been reported that dopamine receptor mRNA synthesis is affected by dopamine agonists, neuroleptics and 6-hydroxydopamine (Angulo et al., 1991; Chen et al., 1991, 1993; Coirini et al., 1990; Gerfen et al., 1990; Graham et al., 1990; Jongen-Rêlo et al., 1994; Le Moine et al., 1990; Savasta et al., 1988). Regulation of receptor expression by agonists has been recently described for other receptors (Hadcock and Malbon, 1991). The present study provides data indicating that antidepressant drugs, whose mechanism of action is not directly linked to dopaminergic neurotransmission, also profoundly influence the levels of mRNA coding for dopamine D_1 and D_2 receptors in the rat brain.

The results presented in this paper remain in line with our previous behavioural and receptor binding findings (see: Introduction), in-

dicating that antidepressants administered repeatedly affect the dopaminergic system.

The level of mRNA coding for dopamine D_1 receptors is decreased following repeated administration of imipramine, both in the nucleus accumbens and in the striatum. On the other hand, repeated administration of citalopram, the selective inhibitor of serotonin reuptake, resulted in an increase in the level of mRNA coding for dopamine D_1 receptor in the striatum and in the core region of nucleus accumbens. A similar tendency, i.e. an increase in the level of mRNA coding for dopamine D_1 receptors was observed after the repeated administration of (+)-oxaprotiline. The results reached statistical significance only in the nucleus accumbens, after 72h of repeated administration of the drug. Since in the previous studies a decrease in the binding sites of [^{3}H]SCH23390 was observed following the administration of antidepressant drugs (Klimek and Nielsen, 1987) – the results obtained at the level of mRNA coding for dopamine D_1 receptors following imipramine administration seem to match well with the binding studies. However, other antidepressants used in the present study, did not produce a similar effect. As it has been already discussed by others (Civelli et al., 1991; Jongen-Rêlo et al., 1994; Mansour et al., 1990), the precise relationship between receptor synthesis and the availability of the functional receptors in the neuronal membrane is not known. A complex series of events occurs, including post-transcriptional, translational and post-translational processes, the subsequent incorporation of the receptor protein into cell membrane, coupling through G proteins with the effector systems, and eventually degradation of the receptors. The precise relationships between the alterations in gene transcription, mRNA stability, translational processes and dopamine receptor binding remain to be clarified. For example, Jongen-Rêlo et al. (1994) found that following a 6-hydroxydopamine lesion, D_1 mRNA levels were decreased in the core and shell regions of the nucleus accumbens and in the striatum, whereas, in contrast, D_1 receptor density was increased in these three areas.

It may also well be that the changes at the level of dopamine D_1 receptors are less important for the mechanism of action of antidepressant drugs than are the changes concerning the dopamine D_2 receptors, which seem more consistent. It has been postulated (Serra et al., 1990) that chronic treatment with antidepressant drugs potentiates behavioral responses mediated by the stimulation of postynaptic D_2 receptors in the mesolimbic system and suggested that this behavioral supersensitivity is due to the enhanced neurotransmission at the D_1 receptor level. One may consider the down-regulation of the D_1 receptors as an adaptive change to the overstimulation of this receptor. Since not all antidepressant drugs are able to induce similar changes in the synaptic dopamine concentration at the same time, which in turn may influence the density of dopamine D_1 receptors, a variation in the effects is observed in the present study at the level of mRNA coding for D_1 receptor.

The level of mRNA coding for dopamine D_2 receptors is increased following the administration of imipramine and citalopram. The effect started to be statistically significant already 72h after a single dose of imipramine – what

may indicate that even a single dose of the drug is sufficient to trigger changes in the transcription of the gene encoding dopamine D_2 receptors, what may later result in the increase in the density of functionally mature D_2 receptors in the cell membrane. From our recently published binding studies (Maj et al., 1996) we know that, using an agonist for dopamine D_2 receptors ([^{3}H] N-0437) as a radioligand, we observed an increase in the density of D_2 receptors following the administration of imipramine and other antidepressant drugs. These results correspond with the previous behavioral studies showing an enhanced response to dopamine D_2 receptor stimulation following antidepressant drugs administration.

Although not all points can be fully clarified at present, it seems more apparent that alterations in the expression of genes coding for neurotransmitters receptors is the very level where one should search for the mechanism of action of drugs being therapeutically effective only after a prolonged administration.

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References

Angulo JA, Coirini H, Ledoux M, Schumacher M (1991) Regulation by dopaminergic neurotransmission of dopamine D_2 mRNA and receptor levels in the striatum and nucleus accumbens of the rat. Mol Brain Res 11: 161–166

Arnt J, Hyttel J, Fredrickson Overø K (1984) Prolonged treatment with the specific 5-HT-uptake inhibitor citalopram: effect on dopaminergic and serotonergic functions. Pol J Pharmacol Pharm 36: 221–230

Bunzow JR, Van Tol HHM, Grandy DK, Albert P, Salon J, Christie M, Machida CA, Neve KA, Civelli O (1988) Cloning and expression of a rat D_2 dopamine receptor cDNA. Nature 336: 783–787

Chen J, Qin ZH, Szele F, Bai G, Weiss B (1991) Neuronal localization and modulation of the D_2 dopamine receptor mRNA in brain of normal mice and mice lesioned with 6-hydroxydopamine. Neuropharmacology 30: 927–941

Chen JF, Aloyo VJ, Weiss B (1993) Continuous treatment with the D_2 dopamine receptor agonist quinpirole decreases D_2 dopamine receptors, D_2 dopamine receptor messenger RNA and proenkephalin messenger RNA, and increases mu opioid receptors in mouse striatum. Neuroscience 54: 669–680

Civelli O, Bunzow JR, Grandy DK, Zhou Q-Y, Van Tol HHM (1991) Molecular biology of the dopamine receptors. Eur J Pharmacol 207: 277–286

Coirini H, Schumacher M, Angulo JA, McEwen BS (1990) Increase in striatal dopamine D_2 receptor mRNA after lesions or haloperidol treatment. Eur J Pharmacol 186: 369–371

De Montis GM, Devoto P, Gessa GL, Meloni D, Porcella A, Saba P, Serra G, Tagliamonte A (1989) Chronic imipramine reduces [^{3}H]SCH 23390 binding and DA-sensitive adenylate cyclase in the limbic system. Eur J Pharmacol 167: 299–303

Dziedzicka-Wasylewska M, Rogoż R (1995) The effect of prolonged treatment with imipramine and electroconvulsive shock on the levels of endogenous enkephalins in

the nucleus accumbens and the ventral tegmentum of the rat. J Neural Transm [Gen Sect] 102: 221–228

Dziedzicka-Wasylewska M, Wędzony K (1996) The effect of prolonged administration of lithium on the level of dopamine D_2 receptor mRNA in the rat striatum and nucleus accumbens. Acta Neurobiol Exp 56: 29–34

Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Monsma FJ Jr, Sibley DR (1990) D_1 and D_2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science 250: 1429–1432

Graham WC, Crossman AR, Woodruff GN (1990) Autoradiographic studies in animal models of hemi-parkinsonism reveal dopamine D_2 but not D_1 receptor supersensitivity. I. 6-OHDA lesions of ascending mesencephalic dopaminergic pathways in the rat. Brain Res 514: 93–102

Hadcock JR, Malbon CC (1991) Regulation of receptor expression by agonists: transcriptional and post-transcriptional controls. Trends Neurosci 14: 242–247

Jongen-Rêlo AL, Docter GJ, Jonker AJ, Vreugdenhil E, Groenewegen HJ, Voorn P (1994) Differential effects of dopamine depletion on the binding and mRNA levels of dopamine receptors in the shell and core of the rat nucleus accumbens. Mol Brain Res 25: 333–343

Karin M (1992) Signal transduction from cell surface to nucleus in development and disease. FASEB J 6: 2581–2590

Klimek V, Nielsen M (1987) Chronic treatment with antidepressants decreases the number of ^{3}H-SCH 23390 binding sites in the rat striatum and the limbic system. Eur J Pharmacol 139: 163–169

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

Le Moine C, Normand E, Guitteny AF, Fouqe B, Teoule R, Bloch B (1990) Dopamine receptor gene expression by enkephalin neurons in rat forebrain. Proc Natl Acad Sci USA 87: 230–234

Maj J (1986) Repeated treatment with antidepressant drugs: responses mediated by brain dopamine receptors. In: Hippius H, Klerman GL, Matussek N (eds) New results in depression research. Springer, Berlin Heidelberg New York Tokyo, pp 90–98

Maj J (1990) Behavioural effects of antidepressant drugs given repeatedly on the dopaminergic system. In: Gessa GL, Serra G (eds) Advances in the biosciences 77. Pergamon Press, Oxford, pp 139–1

Maj J, Wędzony K (1985) Repeated treatment with imipramine or amitriptyline increases the locomotor response of rats to (+)-amphetamine given into the nucleus accumbens. J Pharm Pharmacol 37: 362–364

Maj J, Rogóż Z, Skuza G, Sowińska H (1984) Repeated treatment with antidepressant drugs potentiates the locomotor response to (+)-amphetamine. J Pharm Pharmacol 36: 127–130

Maj J, Wędzony K, Klimek V (1987) Desipramine given repeatedly enhances behavioural 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 (1989) The influence of repeated treatment with imipramine, (+)- and (−)-oxaprotyline on behavioural effects of dopamine D-1 and D-2 agonists. J Neural Transm 76: 29–38

Maj J, Klimek V, Rogóż Z, Skuza G, Sowińska H (1991) The effect of (+)- and (−)-oxaprotyline administered repeatedly on the dopamine system. J Neural Transm [Gen Sect] 86: 11–23

Maj J, Dziedzicka-Wasylewska M, Rogoż R, Rogóż Z, Skuza G (1996) Antidepressant drugs given repeatedly change the binding of the dopamine D_2 agonist, [^{3}H]-N-0437, to D_2 receptors in the rat brain. Eur J Pharmacol 304: 49–54

Mansour A, Meador-Woodruff JH, Bunzow JR, Civelli O, Akil H, Watson SJ (1990) Localization of dopamine D_2 receptor mRNA and D_1 and D_2 receptor binding in

the rat brain and pituitary: an in situ hybridization-receptor autoradiographic analysis. J Neurosci 10: 2587–2600

Mansour A, Meador-Woodruff JH, Zhou Q-Y, Civelli O, Akil H, Watson SJ (1991) A comparison of D_1 receptor binding and mRNA in rat brain using receptor autoradiographic analysis and in situ hybridization techniques. Neuroscience 45: 359–371

Martin-Iverson MT, Leclere J-F, Fibiger HC (1983) Cholinergic-dopaminergic interactions and the mechanisms of action of antidepressants. Eur J Pharmacol 94: 193–201

Meador-Woodruff JH, Mansour A (1991) Expression of the dopamine D_2 receptor gene in the brain. Biol Psychiatry 30: 985–1007

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

Savasta M, Dubois A, Benavidés J, Scatton B (1988) Different plasticity changes in D_1 and D_2 receptors in rat striatal subregions following impairment of dopaminergic transmission. Neurosci Lett 85: 119–124

Serra G, Collu M, D'Aquila PS, De Montis GM, Gessa GL (1990) Possible role of dopamine D_1 receptor in the behavioural supersensitivity to dopamine agonists induced by chronic treatment with antidepressants. Brain Res 527: 234–243

Sheng M, Greenberg ME (1990) The regulation and function of c-fos and other immediate early genes in the nervous system. Neuron 4: 477–485

Smith S, Linderfros N, Hurd Y, Sharp T (1995) Electroconvulsive shock increases dopamine D_1 and D_2 receptor mRNA in the nucleus accumbens of the rat. Psychopharmacology 120: 333–340

Spyraki Ch, Fibiger HC (1981) Behavioral evidence for supersensitivity of postsynaptic dopamine receptors in the mesolimbic system after chronic administration of desipramine. Eur J Pharmacol 74: 195–206

Zhou QY, Grandy DK, Thambi L, Kushner JA, Van Tol HHM, Cone R, Pribnow D, Salon J, Bunzow JR, Civelli O (1990) Cloning and expression of human and rat D_1 dopamine receptors. Nature 347: 76–80

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