ELSEVIER

European Journal of Pharmacology 337 (1997) 291–296

ejp

The effect of imipramine on the amount of mRNA coding for rat dopamine D_2 autoreceptors

Marta Dziedzicka-Wasylewska *

Institute of Pharmacology, Polish Academy of Sciences, 12 Smętna Str., PL-31-343 Kraków, Poland

Received 16 January 1997; revised 15 August 1997; accepted 19 August 1997

Abstract

Several reports have investigated the possibility that chronic antidepressant treatment alters dopamine autoreceptors. Since radioligand binding studies do not differentiate between presynaptic and postsynaptic dopamine D_2 receptors in the rat forebrain, we used the in situ hybridization technique to measure the amount of mRNA coding for dopamine D_2 autoreceptors in the dopaminergic cell bodies. The amount of mRNA coding for dopamine D_2 autoreceptors in the rat mesencephalon was analyzed following acute and repeated treatment with imipramine, the most widely used antidepressant drug. No significant changes in the amount of mRNA were observed in the substantia nigra of the rat, after acute or repeated treatment with imipramine. In the ventral tegmental area repeated treatment with imipramine (14 days, twice a day) increased the amount of dopamine D_2 autoreceptor mRNA in the lateral part of this brain region (containing nucleus paranigralis and n. parabrachialis pigmentosus), without there being any significant changes in the more medial part (n. interfascicularis and n. linearis). The increase in the amount of dopamine D_2 autoreceptor mRNA in the ventral tegmental area started to be significant 72 h after acute imipramine. Moreover, this increase was also observed after 14 drug-free days following the acute administration of the drug. The results indicate the different sensitivity of neurons synthesizing dopamine autoreceptors for imipramine. Another interesting finding is the observation that acute treatment with imipramine seems to be sufficient to trigger changes as a function of time regardless of whether imipramine is again administered, providing a possible explanation for the delayed therapeutic effect of the drug. © 1997 Elsevier Science B.V.

Keywords: Imipramine; Dopamine D_2 autoreceptor; mRNA; Ventral tegmental area; (Rat)

1. Introduction

The involvement of dopamine in depression and in the action of antidepressant drugs was first suggested by Randrup et al. (1975). Repeated administration of antidepressant drugs increases dopamine stimulant-induced locomotor activity (Maj, 1984). The hypothesis of supersensitivity of postsynaptic dopamine receptors, although well documented in behavioral studies, contrasted with the results of dopamine receptor binding studies which showed that after repeated administration of antidepressant drugs dopamine D_2 receptor density, as measured by [^{3}H]spiperone binding, was unchanged, whereas that of D_1 receptors, measured by [^{3}H]SCH 23390 (7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine) binding, was decreased (Martin-Iverson et al., 1983; Klimek and Nielsen, 1987; De Montis et al., 1989). However, in the further studies of Klimek and Maj (1989) it was demonstrated that antidepressants given repeatedly increase the affinity of dopamine D_2 receptors, evaluated by the displacement of [^{3}H]spiperone by quinpirole. Recently we have shown that imipramine, amitriptyline, fluoxetine and mianserin increase the affinity and the density of dopamine D_2 receptors, measured by the binding of the dopamine D_2 receptor agonist, [^{3}H]N0437 (Maj et al., 1996). We have also shown that imipramine and citalopram increase the amount of mRNA coding for dopamine D_2 receptors in the rat caudate putamen and nucleus accumbens (Dziedzicka-Wasylewska et al., 1997).

Several other reports have investigated the possibility that chronic antidepressant treatment alters dopamine autoreceptors (Serra et al., 1979, 1980; Waldmeier, 1984; Nielsen, 1986). Subsensitivity of dopamine autoreceptors has been proposed on the basis of the observation that repeated antidepressants not only potentiated the motor stimulant effect of apomorphine but also prevented the hypomotility and the inhibition of dopamine synthesis

* Tel.: (48-12) 637-4022; Fax: (48-12) 637-4500.

produced by small doses of the drug. Further support for this hypothesis was provided by Chiodo and Antelman (1980a,b), who observed that repeated treatment with typical and atypical antidepressants or electroconvulsive shock prevented the inhibitory effect of apomorphine on the firing rate of dopaminergic neurons in the substantia nigra. This effect was found to depend on the passage of time after the treatment rather than on daily drug administration.

The clinical effects of antidepressant drugs are generally observed only after prolonged treatment, thus the biochemical changes requiring such prolonged administration of a drug probably involve alterations at the genomic level. Until recently, however, little has been known about transcriptional and post-transcriptional factors regulated by chronic drug treatment, although long-term changes in neuronal synaptic function are known to depend upon selective regulation of gene expression.

The finding of mRNA coding for dopamine D_2 receptors in some dopamine-containing cell groups, i.e., the substantia nigra pars compacta and the ventral tegmental area (Mengod et al., 1989; Weiner and Brann, 1989; Najlerahim et al., 1989; Meador-Woodruff et al., 1991), suggests that dopamine D_2 receptors may have an autoreceptor function. Meador-Woodruff and Mansour (1991) have demonstrated additionally that cells in the substantia nigra and ventral tegmental area that express dopamine D_2 receptor mRNA are also positive for the presence of tyrosine hydroxylase, a biochemical marker for catecholamine synthesis. Since radioligand binding studies do not differentiate between presynaptic and postsynaptic dopamine D_2 receptors in the rat forebrain, we used the in situ hybridization technique to measure mRNA coding for dopamine D_2 autoreceptors in dopaminergic cell bodies. However, one should be aware that changes at the level of mRNA might not accurately reflect changes in receptor sensitivity.

The present studies were designed to obtain information about whether acute or repeated treatment with imipramine, the most widely used antidepressant drug, affects the amount of mRNA coding for dopamine D_2 autoreceptors in the rat substantia nigra and ventral tegmental area.

2. Materials and methods

2.1. Animals treatment

Male Wistar rats (180–220 g) were treated with imipramine (Polfa, Poland; 10 mg/kg p.o. twice daily at 8 a.m. and 5 p.m.) for 14 days. Apart from the control group that received saline (p.o.), some groups of animals were treated acutely with imipramine (10 mg/kg p.o. twice a day for 1 day). These groups of rats received two doses of imipramine followed by 2, 12, 24 and 72 h, or 14 days without drug. When not receiving imipramine, all rats were treated with saline p.o. All groups of animals, treated acutely or repeatedly with imipramine, were decapitated at the same time. So the animals were killed 2, 12, 24 and 72 h after acute and 2 or 72 h after repeated treatment with imipramine. For the in situ hybridization studies the brains of rats were rapidly removed and frozen on dry ice.

Experimental protocols were approved by the Ethics Committee and meet the guidelines of the responsible governmental agency.

2.2. In situ hybridization

Coronal sections (12 μm thick) were cut on a cryostat through the substantia nigra and ventral tegmental area at the level P 5700–P 6000, according to Palkovits and Brownstein (1988). The sections were thaw-mounted onto chrome alum-pretreated slides, postfixed in 4% paraformaldehyde for 10 min and processed for in situ hybridization by a method previously described (Dziedzicka-Wasylewska and Rogoż, 1995). Briefly, a mixture of 48-mer synthetic deoxyoligonucleotides complementary to bases 4–51, 766–813 and 901–948 of the rat dopamine D_2 receptor (Bunzow et al., 1988) was labelled using [^{35}S]dATP (1,200 Ci/mmol, NEN DuPont, UK) to obtain a specific activity of about 4×10^5 cpm/μl. The sections were hybridized with the labelled oligonucleotide for 20 h at 37°C in a humidified incubator. After being washed at 40°C, the sections were dried in a cool-air stream and exposed to a film (Amersham MP) for 20 days at -20°C. The different patterns of hybridization, found in the brain regions, fully agreed with the well known distribution of dopamine D_2 receptor mRNA, and provided support for the specificity of the probe under the present experimental conditions. The specificity of the probe 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.

The optical density of the autoradiograms corresponding to sections of the substantia nigra and ventral tegmental area was measured by using an image analyzing system (MCID, Imaging Research). In the densitometric application MCID computes optical density from the grey level values (256 grey levels) of all the pixels contained in the region of interest. This is called 'integrated optical density'. The system makes it possible to create and save a user-defined template to define the regions of interest. MCID integrates the pixel density values within the outline to report a single density value for each region. In the present study the same templates were used for all brain sections in order to ensure that the same regions were compared between experimental and control groups. For the purpose of the present study the option called Spatial Image Alignment, provided by the MCID system, was used in order to ascertain that the same areas were compared when comparing the sections from different brains. The average optical density values were calculated after subtraction of the film

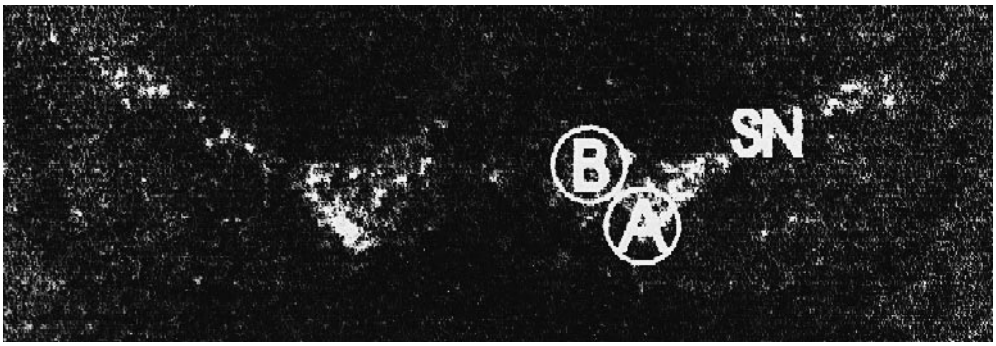

Fig. 1. Example photomicrograph of a brain section hybridized with probes against dopamine D_2 receptor mRNA. SN, Substantia nigra; ventral tegmental area was divided into more lateral (A) and more medial (B) regions. These areas were used for optical density analysis of the amount of mRNA coding for dopamine D_2 autoreceptors.

background density. The mean optical density values were obtained by averaging measurements from autoradiograms of 3–4 sections per brain obtained from 6–8 animals per group.

2.3. 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.

3. Results

Fig. 1 represents a typical autoradiogram of mRNA coding for dopamine D_2 autoreceptors in the pars compacta of substantia nigra and the ventral tegmental area of the rat brain. In this latter brain area two regions were discriminated on the basis of different density of dopamine D_2 autoreceptors mRNA: a more lateral region containing the nucleus paranigralis and n. parabrachialis pigmentosus (A) and a more medial region, containing the n. interfascicularis and n. linearis (B) (Oades and Halliday, 1987).

The amount of mRNA coding for dopamine D_2 autoreceptors in the substantia nigra of the rat is presented in Fig.

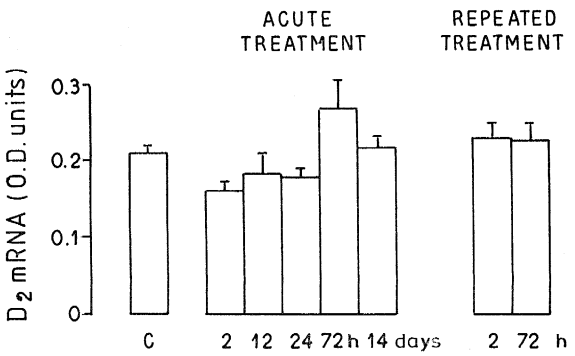

Fig. 2. The effect of imipramine on the amount of mRNA coding for dopamine D_2 autoreceptors in the rat substantia nigra pars compacta. Imipramine was administered for one day (10 mg/kg, p.o.; acute) or for 14 days (10 mg/kg, p.o., twice daily; repeated). Rats were killed at the indicated times after the last dose of the drug. Values are expressed as mean ± S.E.M. from autoradiograms of the sections obtained from 6–8 animals per group. Statistical significance was determined by ANOVA followed by Duncan's test. $P < 0.05$.

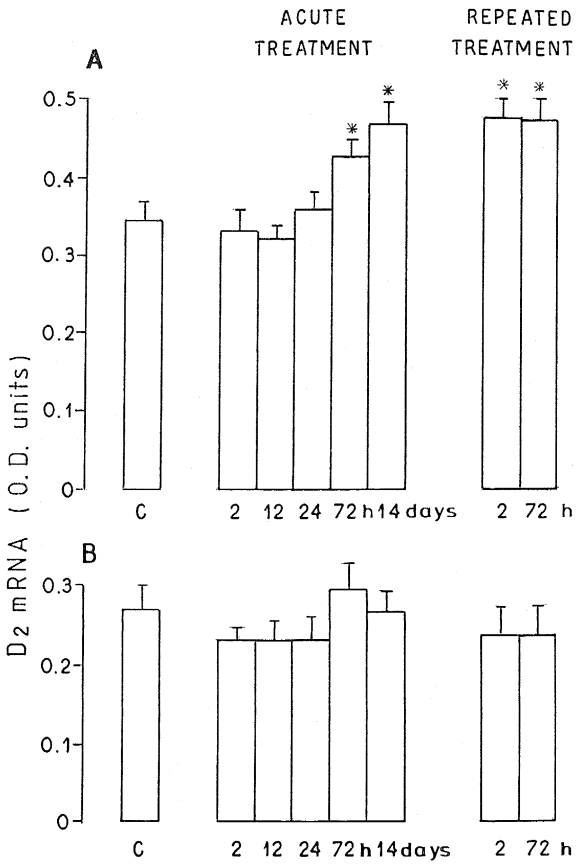

Fig. 3. The effect of imipramine on the amount of mRNA coding for dopamine D_2 autoreceptors in the rat ventral tegmental area. Imipramine was administered for one day (10 mg/kg, p.o.; acute) or for 14 days (10 mg/kg, p.o., twice daily; repeated). Rats were killed at the indicated times after the last dose of the drug. Values are expressed as mean ± S.E.M. from autoradiograms of the sections obtained from 6–8 animals per group. (A) Lateral and (B) medial region of the ventral tegmental area Statistical significance was determined by ANOVA followed by Duncan's test. $^{*}P < 0.05$.

2. No statistically significant changes in the amount of dopamine D_2 autoreceptor mRNA were observed in this brain region after imipramine administration.

The amount of mRNA coding for dopamine D_2 autoreceptors in the rat ventral tegmental area is presented in Fig. 3. Both acute and repeated administration of imipramine increased the amount of this mRNA in the more lateral region of the ventral tegmental area (Fig. 3A). Acute treatment with imipramine produced a statistically significant increase in the amount of mRNA coding for dopamine D_2 autoreceptors 72 h after drug administration and this increase was also observed after 14 drug-free days following the acute administration of imipramine. Repeated administration of imipramine also increased the amount of mRNA coding for dopamine D_2 autoreceptors in the lateral region of the ventral tegmental area and the effect was quantitatively similar at 14 days after the acute treatment with the drug.

In the medial region of the ventral tegmental area no statistically significant changes in the amount of mRNA coding for dopamine D_2 autoreceptors were observed following acute or prolonged treatment with imipramine (Fig. 3B).

4. Discussion

In 1979, Serra et al. proposed the hypothesis that chronic antidepressant treatment potentiates dopaminergic transmission by inducing subsensitivity of dopamine autoreceptors. This hypothesis was based on the observation that chronic antidepressant treatment prevented the hypomotility and the inhibition of dopamine synthesis produced by small doses of apomorphine.

The recent successful cloning of the genes coding for dopamine receptors (Bunzow et al., 1988; Zhou et al., 1990; Civelli et al., 1991) has provided the opportunity to study the modulation of the dopaminergic system at the level of receptor gene expression. It has become apparent that receptor activity may be coupled to receptor biosynthesis, thus maintaining dopaminergic homeostasis in the brain. We have recently shown that prolonged treatment with lithium (Dziedzicka-Wasylewska et al., 1996) as well as imipramine and citalopram (Dziedzicka-Wasylewska et al., 1997) increases the amount of mRNA coding for dopamine D_2 receptors in the rat striatum and the nucleus accumbens septi.

In the present study we observed an increase in the amount of mRNA coding for dopamine D_2 receptors following imipramine administration in the ventral tegmental area of the rat, but the effect was statistically significant only in the lateral part of this brain region. This finding indicates that dopaminergic neurons located within the nucleus paranigralis and nucleus parabrachialis pigmentosus display a sensitivity to imipramine different from that of neurons located in the more medial sector of the ventral tegmental area.

The results of most studies support generalizations about the crude topographic gradient in the mediolateral dimension: cells distributed more laterally in the ventral tegmental area region tend to project to more lateral structures, being the primary source of the mesolimbic afferents, and the more medial sector of the ventral tegmental area is thought to be the source of mesocortical innervation (Roth et al., 1987). Autoreceptors exist on most parts of dopamine cells, including soma, dendrites and nerve terminals (Roth, 1984). Stimulation of autoreceptors in the somatodendritic region slows the firing rate of dopamine neurons, whereas stimulation of autoreceptors located on dopamine nerve terminals results in the inhibition of dopamine synthesis and release (Wolf and Roth, 1990). Although the majority of the ventral tegmental dopamine neurons appear to possess somatodendritic and synthesis-modulating autoreceptors, the dopamine cells that project to the prefrontal and cingulate cortices appear either to have a greatly diminished number of these receptors or to lack them (Roth, 1984). The ventral tegmental area receives both serotonergic and noradrenergic afferents from brainstem monoamine neurons (Oades and Halliday, 1987). A number of reports suggest that these monoaminergic inputs to the ventral tegmental area may be of functional significance in regulating dopaminergic neurons. For example, dopamine utilization is relatively enhanced in the nucleus accumbens but decreased in the prefrontal cortex following electrolytic lesion of the median raphe (Herve et al., 1981). Lesion of the dorsal raphe reduces dopaminergic utilization in the prefrontal cortex but does not alter dopamine parameters in the nucleus accumbens (Herve et al., 1979). Furthermore, dopamine utilization is decreased in the prefrontal cortex but remains unaltered in the nucleus accumbens following 6-hydroxydopamine-induced degeneration of the noradrenergic fibers projecting to the ventral tegmental area (Herve et al., 1982). These results are consistent with the selective modulation of activity of mesolimbic and mesocortical dopamine neurons by serotonergic and noradrenergic afferents to the ventral tegmental area. It therefore seems likely that distinct afferents to different areas within the ventral tegmental area and substantia nigra may, in part, account for the selective responses of various dopamine systems to imipramine, the drug which inhibits serotonin and noradrenaline reuptake, rather than the presence or absence of somatodendritic and synthesis-modulating nerve terminal autoreceptors. It is not clear whether such regulation occurs at the level of the cell bodies of origin of these dopaminergic pathways or at the terminal field level. Clarification of this would require the specific delineation of the precise origin of chemically defined afferents innervating the ventral tegmental area, ruling out interactive effects occurring either through other afferent inputs or at the level of the terminal field.

The increase in the biosynthesis of dopamine D_2 autoreceptors following imipramine administration (manifested by the increase in the amount of mRNA coding for

dopamine D_2 autoreceptors) might be interpreted as an adaptive change to the attenuated sensitivity of these receptors observed in behavioral studies after chronic treatment with imipramine. This interpretation is further supported by the observation that the behavioral subsensitivity of dopamine D_2 autoreceptors is not observed after acute imipramine administration (Serra et al., 1979). However, acute treatment with imipramine was able to increase the amount of mRNA coding for dopamine D_2 autoreceptors, but the effect started to be statistically significant at 72 h after drug administration. It might well be that this time lag is necessary for a sort of feedback loop to start to operate between the nerve terminals and the cell nucleus.

Another interesting finding of our study is that acute treatment with imipramine induced changes at the level of the biosynthesis of dopamine D_2 receptors which persisted for a long period of time. In their pioneering work Antelman and coworkers (Chiodo and Antelman, 1980a,b; Antelman et al., 1982) found that long-term administration of several antidepressants attenuated the apomorphine-induced decrease in firing of dopamine neurons located in the zona compacta of the substantia nigra and that this effect was found to depend on the passage of time rather than on daily drug treatment. Our study also shows that short-term drug treatment seems to be sufficient to trigger changes as a function of time regardless of whether imipramine is administered again. The same data also provide a possible explanation for the delayed therapeutic effect of imipramine as well as other antidepressant drugs. We do not know at present whether the increased biosynthesis of dopamine autoreceptors is critical for the therapeutic efficacy of antidepressant drugs; however, it would be interesting to know whether the changes in noradrenaline and serotonin receptors induced by antidepressant drugs are also independent of repeated drug treatment. As has been already discussed by others (e.g. Mansour et al., 1990; Jongen-Rêlo et al., 1994), a complex series of events take place between receptor synthesis and availability of the functional receptors in the neuronal membrane, namely post-transcriptional, translational and post-translational processes, the subsequent incorporation of the receptor protein into the 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 remains to be clarified. Nevertheless, it seems that alterations in the expression of the genes coding for neurotransmitter receptors are the level at which one should search for the mechanism of action of drugs that are therapeutically effective only after prolonged administration.

Acknowledgements

The skillful technical assistance of Ms. Beata Adamczyk is highly appreciated. This research was partly supported by grant No 4P05A 007 13 from the Committee for Scientific Research, Poland.

References

Antelman, S.M., Chiodo, L.A., De Giovani, L.A., 1982. Antidepressants and dopamine autoreceptors: Implications for both a novel means of treating depression and understanding bipolar illness. In: Costa, E., Racagani, G. (Eds.), Typical and Atypical Antidepressants. Raven Press, New York, NY, pp. 121–146.

Bunzow, J.R., Van Tol, H.H.M., Grandy, D.K., Albert, P., Salon, J., Christie, M., Machida, C.A., Neve, K.A., Civelli, O., 1988. Cloning and expression of a rat D_2 dopamine receptor cDNA. Nature 336, 783–787.

Chiodo, L.A., Antelman, S.M., 1980a. Electroconvulsive shock: Progressive dopamine autoreceptor subsensitivity independent of daily drug treatment. Science 210, 799–801.

Chiodo, L.A., Antelman, S.M., 1980b. Repeated tricyclics induce a progressive dopamine autoreceptors subsensitivity independent of daily drug treatment. Nature 287, 451–454.

Civelli, O., Bunzow, J.R., Grandy, D.K., Zhou, Q., Van Tol, H.H.M., 1991. Molecular biology of the dopamine receptors. Eur. J. Pharmacol. 207, 277–286.

De Montis, G.M., Devoto, P., Gessa, G.L., 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 ventral tegmentum of the rat. J. Neural Transm. Gen. Sect. 102, 221–228.

Dziedzicka-Wasylewska, M., Maćkowiak, M., Fijał, K., Wędzony, K., 1996. Adaptive changes in the rat dopaminergic transmission following repeated lithium administration. J. Neural Transm. 103, 765–776.

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.

Herve, D., Simon, H., Blanc, G., Lisoprawski, A., Le Moal, M., Glowinski, J., Tassin, J.P., 1979. Increased utilization of dopamine in the nucleus accumbens but not in the cerebral cortex after dorsal raphe lesion in the rat. Neurosci. Lett. 15, 127–133.

Herve, D., Simon, H., Blanc, G., Le Moal, M., Glowinski, J., Tassin, J.P., 1981. Opposite changes in dopamine utilization in the nucleus accumbens and the frontal cortex after electrolytic lesion of the median raphe in the rat. Brain Res. 216, 422–428.

Herve, D., Blanc, G., Glowinski, J., Tassin, J.P., 1982. Reduction of dopamine utilization in the prefrontal cortex but not in the nucleus accumbens after selective destruction of noradrenergic fibers innervating the ventral tegmental area in the rat. Brain. Res. 237, 510–516.

Jongen-Rêlo, A.L., Docter, G.J., Jonker, A.J., Vreugdenhil, E., Groenewegen, H.J., 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.

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

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

Maj, J., 1984. Central effects following repeated treatment with antidepressant drugs. Pol. J. Pharmacol. Pharm. 36, 87–100.

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.

Mansour, A., Meador-Woodruff, J.H., Bunzow, J.R., Civelli, O., Akil, H., Watson, S.J., 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.

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.

Meador-Woodruff, J.H., Mansour, A., 1991. Expression of the dopamine D_2 receptor gene expression in brain. Biol. Psychiatry 30, 995–1007.

Meador-Woodruff, J.H., Mansour, A., Healy, D.J., Kuehn, R., Zhou, Q-Y., Bunzow, J.R., Akil, H., Civelli, O., Watson, S.J. Jr., 1991. Comparison of the distributions of D_1 and D_2 dopamine receptor mRNA in rat brain. Neuropsychopharmacology 5, 231–242.

Mengod, G., Martinez-Mir, M.I., Vilaro, M.Y., Palacios, J.M., 1989. Localization of the mRNA for the dopamine D_2 receptor in the rat brain by in situ hybridization histochemistry. Proc. Natl. Acad. Sci. USA 87, 6723–6727.

Najlerahim, A., Beston, A.J.L., Harrison, P.J., Heffernan, J., Pearson, R.C.A., 1989. Messenger RNA encoding the D_2 dopaminergic receptors detected by in situ hybridization histochemistry in rat brain. FEBS Lett. 255, 335–339.

Nielsen, J.A., 1986. Effects of chronic antidepressant treatment on nigrostriatal and mesolimbic dopamine autoreceptors in the rat. Neurochem. Int. 9, 61–67.

Oades, R.D., Halliday, G.M., 1987. Ventral tegmental (A 10) system: Neurobiology. 1. Anatomy and connectivity. Brain Res. Rev. 12, 117–165.

Palkovits, M., Brownstein, M.J., 1988. Maps and Guide to Microdissection of the Rat Brain. Elsvier, Amsterdam.

Randrup, A., Munkvad, I., Fog, R., Gerlach, J., Molander, L., Kjelberg, B., Scheel-Kruger, J., 1975. Mania, depression and brain dopamine. In: Essman, W.B., Valzelli, L. (Eds.), Current Developments in Psychopharmacology. Spectrum, New York, NY, pp. 206–248.

Roth, R.H., 1984. CNS dopamine autoreceptors: Distribution, pharmacology and function. Ann. N.Y. Acad. Sci. 430, 27–53.

Roth, R.H., Wolf, M.E., Deutch, A.Y., 1987. Neurochemistry of midbrain dopamine systems. In: Meltzer, H.Y. (Ed.), Psychopharmacology: The Third Generation of Progress. Raven Press, New York, NY, pp. 81–94.

Serra, G., Argiolas, A., Klimek, V., Fadda, F., Gessa, G.L., 1979. Chronic treatment with antidepressants prevents the inhibitory effect of small doses of apomorphine on dopamine synthesis and motor activity. Life Sci. 25, 415–424.

Serra, G., Argiolas, A., Fadda, F., Gessa, G.L., 1980. Hyposensitivity of dopamine 'autoreceptors' induced by chronic administration of tricyclic antidepressants. Pharmacol. Res. Commun. 12, 619–624.

Waldmeier, P.C., 1984. Effects of chronic antidepressant treatment on pre- and post-synaptic dopaminergic mechanisms. A short review of the literature and some complementary experiments. Pol. J. Pharmacol. Pharm. 36, 201–216.

Weiner, D.M., Brann, M.R., 1989. The distribution of a dopamine D_2 receptor mRNA in rat brain. FEBS Lett. 253, 207–213.

Wolf, M.E., Roth, R.H., 1990. Autoreceptors regulation of dopamine synthesis. Ann. N.Y. Acad. Sci. 604, 323–343.

Zhou, Q.Y., Grandy, D.K., Thambi, L., Kushner, J.A., Van Tol, H.H.M., Cone, R., Pribnow, D., Salon, J., Bunzow, J.R., Civelli, O., 1990. Cloning and expression of human and rat D_1 dopamine receptors. Nature 347, 76–80.