ELSEVIER

European Journal of Pharmacology 277 (1995) 139–144

ejp

Behavioural response to SKF 38393 and quinpirole following chronic antidepressant treatment

Karen Allison, Svetlana Ivanová, Andrew J. Greenshaw *

Neurochemical Research Unit, Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada T6G 2B7

Received 20 December 1994; accepted 20 January 1995

Abstract

The effects of chronic administration of antidepressant drugs (21–22 days s.c. via osmotic mini-pumps) on the behavioural responses of male Sprague-Dawley rats to (−)-quinpirole hydrochloride (0.05 mg kg^{-1} s.c., 5 min) and (±)-SKF 38393 hydrochloride (10 mg kg^{-1} s.c., 5 min) were investigated. Desipramine hydrochloride (10 mg kg^{-1} per day), phenelzine sulphate (10 mg kg^{-1} per day) and clorgyline hydrochloride (1 mg kg^{-1} per day) attenuated the suppression of locomotor activity induced by quinpirole, a dopamine D_2-like receptor agonist, while clomipramine hydrochloride (10 mg kg^{-1} per day) was without effect. Yawning elicited by quinpirole was absent in phenelzine- and clorgyline-treated rats, but unaffected in rats treated chronically with desipramine and clomipramine. SKF 38393, a dopamine D_1-like receptor agonist, significantly increased locomotor activity and time spent grooming in control animals. There were no significant effects of antidepressants on the behavioural responses to SKF 38393.

Keywords: Antidepressant; Dopamine receptor; Quinpirole; SKF 38393; Motor activity

1. Introduction

Several studies indicate a role for brain dopamine in antidepressant drug action (Spyraki and Fibiger, 1981; Martin-Iverson et al., 1983; Maj et al., 1989b; Serra et al., 1991; Brown and Gershon, 1993; Gessa, 1994). A variety of electrophysiological and neuropharmacological data indicate that chronic antidepressant treatment may decrease dopamine autoreceptor-mediated responses (Chiodo and Antelman, 1980a,b; Antelman and Chiodo, 1981; Nielsen, 1986). In addition, chronic antidepressant treatment may attenuate the suppression of locomotor activity induced by low doses of dopamine D_2-like receptor agonists (Serra et al., 1979; Maj et al., 1989a; Allison et al., 1993). These observations form the basis of the hypothesis that a decrease in the number or function of presynaptic dopamine receptors may play an important role in mediating the effects of chronic antidepressant treatment (Serra et al., 1979; Chiodo and Antelman, 1980a,b; Antelman and Chiodo, 1981; Nielsen, 1986). A decrease in uptake site density has also been proposed as a mechanism for antidepressant effects which have generally been attributed to changes in presynaptic dopamine receptors (Nomikos et al., 1991). This seems unlikely as chronic antidepressant treatment may not alter the affinity or density of [^{3}H]GBR 12935 dopamine uptake sites (Allison et al., 1993).

Data from several studies indicate that behavioural responses to high doses of dopamine D_2-like receptor agonists may be potentiated following chronic antidepressant treatment (Serra et al., 1990a; Spyraki and Fibiger, 1981). This potentiation may be attributable to the development of presynaptic dopamine receptor subsensitivity and/or postsynaptic dopamine receptor supersensitivity (Serra et al., 1979, 1990a; Spyraki and Fibiger, 1981; Gessa, 1994). Studies of chronic antidepressant effects on behavioural responses to dopamine D_1-like receptor agonists have so far not yielded any clear results (Chagraoui et al., 1990; Maj, 1990; Serra et al., 1990a; Wachtel et al., 1992).

The effects of chronic administration of monoamine oxidase inhibitor antidepressants have received very little attention in this context. Maj (1990) has reported that chronic administration of the selective, reversible

* Corresponding author. Tel. (403) 492-6550, fax (403) 492-6841.

0014-2999/95/$09.50 © 1995 Elsevier Science B.V. All rights reserved
SSDI 0014-2999(95)00059-3

type-A monoamine oxidase inhibitor moclobemide may result in decreased sedative effects of a low dose of apomorphine and may induce a potentiation of the stimulant effects of a high dose of this drug. Nevertheless, neither brofaromine nor moclobemide appear to alter the stimulant effects of (+)-amphetamine (Maj, 1990). In contrast to the effects of the irreversible monoamine oxidase inhibitor phenelzine (Paetsch and Greenshaw, 1992), brofaromine and moclobemide do not appear to alter the density or affinity of dopamine D_1- or D_2-like receptors (Klimek and Maj, 1990; Klimek et al., 1990).

In the present study, the effects of chronic tricyclic and irreversible monoamine oxidase inhibitor antidepressant treatment on the behavioural responses to both dopamine D_1-like (SKF 38393) and low-dose dopamine D_2-like (quinpirole: D2/D3) [Sokoloff et al., 1992] receptor agonists were compared. The antidepressants were chosen as compounds that respectively decrease dopamine D_1- and D_2-like receptor density (phenelzine: Paetsch and Greenshaw, 1992) or dopamine D_1-like receptor density following their chronic administration (desipramine: Klimek and Nielsen, 1987; Klimek and Maj, 1990; Paetsch and Greenshaw, 1992). Clorgyline was selected as a type-A monoamine oxidase inhibitor for comparison with the non-selective inhibitory actions of phenelzine on MAO. Clomipramine was also included in this study to more clearly assess its effects on dopamine receptor function in this context; in a previous study, chronic administration of clomipramine did not result in any changes in the locomotor-suppressant effects of the dopamine receptor agonist apomorphine (Allison et al., 1993).

2. Materials and methods

2.1. Animals and surgery

Male Sprague-Dawley rats weighing between 250 and 310 g at the time of surgery were used. Rats were housed two per cage on a 12-h light/dark cycle with food and water freely available. Animals were randomly allocated to one of five drug treatment groups ($n = 14$–15) that received either desipramine hydrochloride, clomipramine hydrochloride, phenelzine sulphate, clorgyline hydrochloride or the distilled water vehicle. Antidepressant drug doses were administered at salt doses of 10 mg kg^{-1} (desipramine, clomipramine and phenelzine) or 1 mg kg^{-1} (clorgyline). These drugs were obtained from Sigma (St. Louis, MO) except for clorgyline which was obtained from Research Biochemicals (Natick, MA). Animals were anaesthetized with the inhalant anaesthetic diethyl ether (BDH, Toronto, ONT) and implanted with 2ML4 Alzet (Alza Corp., Palo Alto, CA) osmotic mini-pumps under aseptic conditions. After recovery from surgery, the animals were returned to their home cages. Pump-filling concentrations were calculated according to the method of Greenshaw (1986). On the 28th day of drug administration, the rats were killed by guillotine decapitation. The brains were immediately removed and stored at −80° C until required for analysis of monoamine oxidase activity and determination of brain drug levels. These measurements were taken to ensure the efficacy of drug administration.

2.2. Drug levels and monoamine oxidase activity

Brain tissue concentrations of desipramine, clomipramine and desmethylclomipramine, the demethylated metabolite of clomipramine, were determined by gas chromatography using a modification of the procedure of Drebit et al. (1988) as described by Allison et al. (1993).

Monoamine oxidase activity was determined radiochemically using a modification of the procedure of Wurtman and Axelrod (1963) as described by Greenshaw et al. (1988). [^{14}C]5-HT and [^{14}C]2-phenylethylamine were used as substrates for determining monoamine oxidase-A and -B activity, respectively.

2.3. Behavioural testing

On days 21 and 22 of chronic drug or vehicle administration, the effects of either (−)-quinpirole hydrochloride (0.05 mg kg^{-1}), (±)-SKF 38393 hydrochloride (10 mg kg^{-1}) (Research Biochemicals, Natick, MA) or distilled water on spontaneous locomotor activity, grooming and yawning were measured. Doses of quinpirole and SKF 38393 are expressed as the free base. A procedure was followed in which half of the animals in each chronic drug treatment group were randomly chosen to receive the acute drug injection (quinpirole or SKF 38393) on day 21 while the other half received an injection of distilled water. On day 22, the acute treatments were reversed so that each animal received the alternate injection. As a result of this counterbalanced procedure, each subject served as its own control. Either quinpirole, SKF 38393, or distilled water was injected subcutaneously in a volume of 1 ml kg^{-1} 5 min prior to each behavioural test. Spontaneous locomotor activity was measured by placing animals individually in a computer-controlled infrared activity system for 30 min (Acadia Instruments, Saskatoon, Saskatchewan, Canada) in a quiet environment under conditions of reduced illumination. During this period, yawning and grooming were measured under blind conditions by two observers using a modification of the procedure of Molloy and Waddington (1987). Each animal was observed for 1 min at 5-min intervals, yielding 5 min of observation over each 30-min test.

The chosen doses of quinpirole (0.05 mg kg^{-1}) and SKF 38393 (10 mg kg^{-1}) were found in other studies to reliably elicit yawning and to increase grooming, respectively (Jackson et al., 1989; Longoni et al., 1987; Molloy and Waddington, 1987; Serra et al., 1987). Prior to this experiment, a pilot study was conducted with separate groups of subjects to confirm that these doses were effective. Since grooming is part of the neophobic behavioural repertoire elicited by a novel environment (Molloy and Waddington, 1987), all rats were habituated to the test environment for 15 min per day for the 6 days prior to behavioural test days.

2.4. Statistics

Effects of drug treatment on locomotor activity and time spent grooming were analysed using analysis of variance (ANOVA). In the case of a significant F-test, a Newman-Keuls multiple comparison test was used to determine significant differences between means ($\alpha = 0.05$) (Winer, 1971). A Kruskal-Wallis 1-way ANOVA was used to assess the effects of drug treatment on yawning and grooming. For these measures, the significance of differences between means was then assessed by Mann-Whitney U-tests using a Bonferroni correction for the α level (Krauth, 1988).

3. Results

3.1. Drug levels and monoamine oxidase activity

Concentrations of desipramine and clomipramine in the brain tissue of rats treated with these drugs were 1487.5 ± 215.8 and 844.5 ± 94.7 ng/g tissue, respectively. Brain levels of desmethylclomipramine, the metabolite of clomipramine, if present, were below the detectable limits of the assay (i.e. < 75 ng/g tissue). In the brain tissue of rats treated with clorgyline, inhibition of monoamine oxidase-A and -B was 88.1 ± 1.7% and 9.8 ± 2.0%, respectively. In phenelzine-treated rats, inhibition of monoamine oxidase-A and -B was 87.7 ± 1.2% and 93.9 ± 0.3%, respectively. These data are in accord with the results of previous experiments in this laboratory and confirm that the chronic drug administration procedure was effective.

3.2. Behavioural testing

Behaviours observed following quinpirole probe

Following the acute vehicle challenge, locomotor counts per 30 min (means ± S.E.M.) were as follows: vehicle, 2344.9 ± 276.3; desipramine, 1379.8 ± 244.1; clomipramine, 1543.8 ± 188.6; phenelzine, 1868.8 ± 239.7; clorgyline, 1309.2 ± 134.8. There was an effect of antidepressant treatment [$F(4,70) = 2.62$, $P < 0.05$],

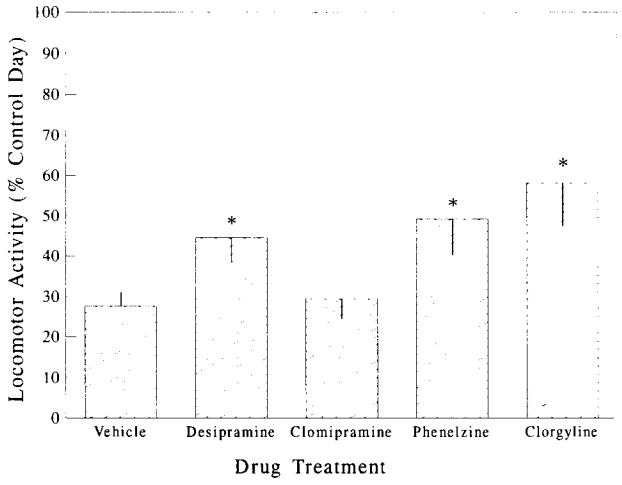

Fig. 1. Effects of quinpirole (0.05 mg kg^{-1}, s.c., 5 min) on spontaneous locomotor activity of rats following chronic (21/22 days) vehicle or antidepressant treatment (s.c. via osmotic mini-pump). Antidepressant drugs were administered at a salt dose of 10 mg kg^{-1} (desipramine, clomipramine and phenelzine) or 1 mg kg^{-1} (clorgyline). Desipramine, phenelzine and clorgyline attenuated the locomotor-suppressant effects of quinpirole relative to chronic vehicle-treated rats. Clomipramine did not alter the locomotor response to quinpirole. Data shown are means ± S.E.M. ($n = 15$). * Effects were significant at $P < 0.05$, relative to vehicle.

with desipramine and clorgyline significantly decreasing locomotor activity. The acute challenge with quinpirole induced a decrease in spontaneous locomotor activity [$F(1,70) = 224.20$, $P < 0.05$]: the activity of chronic vehicle-treated rats was reduced to 27.6 ± 3.1% of that seen following the distilled water injection (see Fig. 1). The locomotor-suppressant effect of quinpirole was attenuated [$F(4,70) = 5.75$, $P < 0.05$] following chronic treatment with each of the antidepressants tested except clomipramine, as illustrated in Fig. 1. The scattergram of Fig. 2 illustrates the distribution of yawning in each of the treatment groups following administration of quinpirole. Yawning was not observed in any of the animals following the acute distilled water injection. Following the administration of quinpirole, yawning was observed in vehicle-, desipramine- and clomipramine-treated animals but not in the phenelzine- and clorgyline-treated animals [$H = 34.18$, df = 4]. Statistical analysis of time spent grooming revealed no significant effect of either antidepressant treatment [$F(4,70) = 0.55$, $P > 0.05$] or quinpirole [$F(1,70) = 1.28$, $P > 0.05$]. There was also no effect of antidepressant treatment [$H = 3.65$, df = 4] or quinpirole [$H = -5.46$, df = 4] on the number of grooming bouts.

Behaviours observed following SKF 38393 probe

Following the acute vehicle challenge, locomotor counts per 30 min (mean ± S.E.M.) were as follows: vehicle, 1701 ± 267.7; desipramine, 1282.3 ± 184.5; clomipramine, 1387.6 ± 231.2; phenelzine, 1778.5 ±

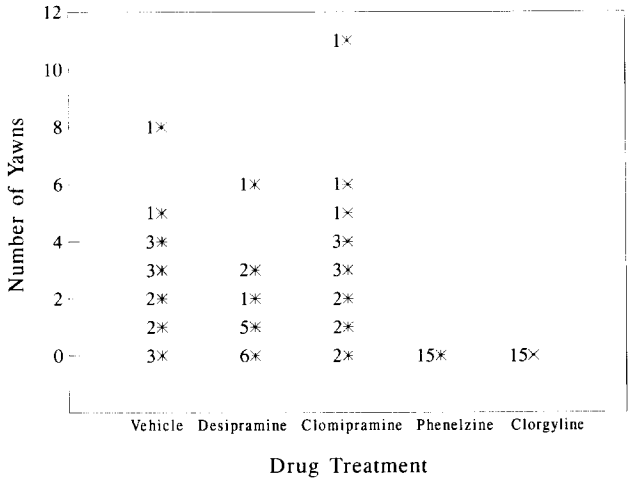

Fig. 2. Effects of quinpirole (0.05 mg kg^{-1}, s.c., 5 min) on the number of yawns observed in rats ($n = 15$) following chronic (21/22 days) vehicle or antidepressant treatment (s.c. via osmotic minipump). Antidepressant drugs were administered at a salt dose of 10 mg kg^{-1} (desipramine, clomipramine and phenelzine) or 1 mg kg^{-1} (clorgyline). Quinpirole induced yawning in chronic vehicle-treated rats. Yawning was observed in desipramine-, and clomipramine-treated rats but was absent in phenelzine- and clorgyline-treated rats ($P < 0.05$). Numbers beside asterisks indicate the number of rats exhibiting the specified number of yawns. See text for further details.

217.2; clorgyline, 1824.6 ± 286.8. There was no statistically significant effect of antidepressant treatment on locomotor activity [$F(4,69) = 1.47$, $P > 0.05$], although the activity of the desipramine and clomipramine groups appear to be decreased relative to controls. SKF 38393 increased locomotor activity [$F(1,69) = 19.18$, $P < 0.05$] and time spent grooming [$F(4,69) = 108.08$, $P < 0.05$]. In chronic vehicle-treated rats, this increase in locomotor activity was 125.7 ± 13.9% of the control level. Chronic antidepressant treatment had no effect on SKF 38393-induced hyperactivity [$F(4,69) = 1.94$, $P > 0.05$] or on the SKF 38393-induced increase in grooming [$F(4,69) = 1.60$, $P > 0.05$]. There was no significant effect of antidepressant treatment [$H = 0.79$, df = 4] or of the SKF 38393 probe [$H = 6.08$, df = 4] on the number of grooming bouts. Yawning was not exhibited by any of the rats following either the distilled water or SKF 38393 injection.

4. Discussion

In the present experiment, decreased sensitivity to quinpirole was observed following chronic administration of the tricyclic antidepressant desipramine and the monoamine oxidase inhibitors phenelzine and clorgyline. These results are consistent with a previous report of decreased locomotor-suppressant effects of apomorphine at 0.05 mg kg^{-1} following chronic treatment with desipramine or phenelzine (Allison et al., 1993).

Serra et al. (1990a,b observed an attenuation of the locomotor-suppressant effects of quinpirole at 0.05 mg kg^{-1}, but not at 0.01 mg kg^{-1} following chronic administration of the tricyclic antidepressant imipramine. They suggested that this dose-related effect indicates that chronic antidepressant treatment results in a postsynaptic dopamine receptor supersensitivity rather than a presynaptic autoreceptor subsensitivity. Serra et al. (1990a,b argued that the decreased locomotor suppressant effects of quinpirole were attributable to a shift to the left in the dose-response curve for postsynaptic dopamine receptor activation. The observations that the densities of dopamine D_2-like receptors may be reduced following chronic administration of irreversible monoamine oxidase inhibitors (Paetsch and Greenshaw, 1992), and that the locomotor-suppressant effects of quinpirole (this study) and of apomorphine (Allison et al., 1993) are decreased following chronic monoamine oxidase inhibition are inconsistent with this postsynaptic supersensitivity hypothesis.

It seems likely that a decreased density of dopamine D_2-like receptors resulting from chronic treatment with monoamine oxidase inhibitors (Paetsch and Greenshaw, 1992) contributed to the absence of quinpirole-induced yawning in phenelzine- and clorgyline-treated rats. In the present study, the tricyclic antidepressants did not alter quinpirole-induced yawning. This is consistent with the observation that chronic tricyclic antidepressant treatment does not result in a decrease in the density of dopamine D_2-like receptors (Klimek and Nielsen, 1987; Klimek and Maj, 1990; Paetsch and Greenshaw, 1992).

In this study, the control value for locomotor activity was increased following the administration of SKF 38393. The time spent grooming was also increased, however, the number of grooming bouts was not altered, in accord with the results of Wachtel et al. (1992). The lack of an interaction between chronic antidepressant treatment and the effects of SKF 38393 in the present study is in agreement with the results of Serra et al. (1990a). Maj et al. (1989a) have demonstrated that a SKF 38393-induced increase in grooming was attenuated at 2 but not 48 h following acute or chronic antidepressant administration. It is likely that this effect may be the result of a direct interaction between the effects of SKF 38393 and of primary antidepressant treatment effects, rather than emergent receptor changes. Chagraoui et al. (1990) reported that 2 days following chronic administration of amineptine or desipramine, there was a decrease in SKF 38393-induced locomotor activity, nevertheless, there were no changes in SKF-induced grooming. Decreases in dopamine D_1-like receptor density have been measured following chronic administration of tricyclic or monoamine oxidase inhibitor antidepressants (De

Montis et al., 1990a,b; Paetsch and Greenshaw, 1992). These biochemical changes do not correspond to changes in the present behavioural responses to a dopamine D_1-like receptor agonist.

The results of this study with respect to clorgyline reveal that selective type-A monoamine oxidase inhibition is a sufficient condition for changes in dopamine D_2-like receptor agonist responses. This is potentially an important result in view of the emergent interest in selective and reversible type-A monoamine oxidase inhibitor antidepressants (Callingham, 1993). This effect of clorgyline is in agreement with the observation of decreased apomorphine-induced sedation following chronic administration of the reversible type-A monoamine oxidase inhibitor moclobemide (Maj, 1990), although the degree and selectivity of monoamine oxidase inhibition was not reported in that study.

In the present study and that of Allison et al. (1993), the locomotor suppression induced by a low dose of quinpirole and of apomorphine was not attenuated by chronic administration of clomipramine, a potent serotonin (5-HT) uptake inhibitor ($IC_{50} = 1.5$ nM) (Hyttel, 1982). Clomipramine is not as selective for 5-HT uptake blockade as compounds such as fluoxetine. Nevertheless, in the present study, the demethylated metabolite of clomipramine, desmethylclomipramine, which is less selective for inhibiting 5-HT uptake ($IC_{50} = 41$ nM) (Hyttel, 1982) but more potent at inhibiting noradrenaline uptake ($IC_{50} = 0.46$ nM) (Hyttel, 1982), was not detected in the brain tissue of animals chronically treated with clomipramine. The absence of desmethylclomipramine in the brain tissue of rats treated with clomipramine in this and a previous study (Allison et al., 1993) suggests that clomipramine may not be metabolized in rats as extensively as it is in humans. In accord with the present clomipramine results, 5-HT uptake blockers such as citalopram, ifoxatine, fluoxetine and zimelidine may fail to affect either the stimulant effects of amphetamine or yawning induced by apomorphine (Martin-Iverson et al., 1983; Delini-Stula and Hunn, 1990; but see Pucilowski and Overstreet, 1993). The present clomipramine results and the observations described above suggest that, in contrast to monoamine oxidase inhibitors and desipramine, antidepressants which are potent inhibitors of 5-HT uptake may not mediate their effects by decreasing presynaptic dopamine autoreceptor function.

Acknowledgements

This research was supported by the Alberta Mental Health Research Fund. S. Ivanová was a visiting professor from the Bogomoletz Institute of Physiology in Kiev, Republic of the Ukraine. The authors would also like to thank Mrs. C.J. Kuefler, Mrs. G. Rauw, Mr. R. Strel and Mrs. J. van Muyden for their technical expertise and Ms. S. Omura for her assistance in the preparation of the manuscript.

References

Allison, K., P.R. Paetsch, G.B. Baker and A.J. Greenshaw, 1993, Chronic antidepressant drug treatment attenuates locomotor-suppressant effects of apomorphine without changing [^{3}H]GBR 12935 binding, Eur. J. Pharmacol. 249, 125.

Antelman, S.M. and L.A. Chiodo, 1981, Dopamine autoreceptor subsensitivity: a mechanism common to the treatment of depression and the induction of amphetamine psychosis?, Biol. Psychiatr. 16(8), 717.

Brown, A.S. and S. Gershon, 1993, Dopamine and depression, J. Neural Transm. [Gen. Sect.] 91, 75.

Callingham, B.A., 1993, Drug interactions with reversible monoamine oxidase-A inhibitors, Clin. Neuropharmacol. 16, Suppl. 2, S42.

Chagraoui, A., M. Vasse and Philippe Protais, 1990, Effects of chronic treatments with amineptine and desipramine on motor responses involving dopaminergic systems, Psychopharmacology 102, 201.

Chiodo, L.A. and S.M. Antelman, 1980a, Repeated tricyclics induce a progressive dopamine autoreceptor sensitivity independent of daily drug treatment, Nature 287(2), 451.

Chiodo, L.A. and S.M. Antelman, 1980b, Tricyclic antidepressants induce subsensitivity of presynaptic dopamine autoreceptors, Eur. J. Pharmacol. 64, 203.

Delini-Stula, A. and C. Hunn, 1990, Effects of single and repeated treatment with antidepressants on apomorphine-induced yawning in the rat: the implication of α-1 adrenergic mechanisms in the D-2 receptor function, Psychopharmacology 101, 62.

De Montis, M., P. Devoto, G.L. Gessa, D. Meloni, A. Porcella, P. Saba, G. Serra and A. Tagliamonte, 1990a, Central dopaminergic transmission is selectively increased in the limbic system of rats chronically exposed to antidepressants, Eur. J. Pharmacol. 180, 31.

De Montis, M., P. Devoto, G.L. Gessa, A. Porcella, G. Serra and A. Tagliamonte, 1990b, Possible role of DA receptors in the mechanism of antidepressants, in: Dopamine and Mental Depression, ed. G.L. Gessa and G. Serra (Pergamon Press, New York) p. 147.

Drebit, R., G.B. Baker and W.G. Dewhurst, 1988, Determination of maprotiline and desmethylmaprotiline in plasma and urine by gas chromatography with nitrogen-phosphorus detection, J. Chromatogr. Biomed. Appl. 432, 334.

Gessa, G.L., 1994, Dopaminergic system in antidepressant action, Neuropsychopharmacology 10 (3S), 47S.

Greenshaw, A.J., 1986, Osmotic mini-pumps: a convenient program for weight-adjusted filling concentrations, Brain Res. Bull. 16, 759.

Greenshaw, A.J., A.J. Nazarali, T.S. Rao, G.B. Baker and R.T. Coutts, 1988, Chronic tranylcypromine treatment induces functional α_2-adrenoceptor down-regulation in rats, Eur. J. Pharmacol. 154, 67.

Hyttel, J., 1982, Citalopram – pharmacological profile of a specific serotonin uptake inhibitor with antidepressant activity, Progr. Neuro-Psychopharmacol. Biol. Psychiatr. 6, 277.

Jackson, D.M., S.B. Ross and S.R. Edwards, 1989, Dopamine D2 agonist-induced behavioural depression is reversed by dopamine D1 agonists, J. Neural Transm. 75, 213.

Klimek, V. and J. Maj, 1990, The effect of antidepressant drugs given repeatedly on the binding of ^{3}H-SCH 23390 and ^{3}H-spiperone to dopaminergic receptors, in: Dopamine and Mental Depression, eds. G.L. Gessa and G. Serra (Pergamon Press, New York) p. 159.

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

Klimek, V., G. Nowak, J. Zak and J. Maj, 1990, The effect of repeated treatment with brofaromine, moclobemide and deprenyl on α_1-adrenergic and dopaminergic receptors in the rat brain, Neurosci. Lett. 108, 189.

Krauth, J., 1988, Distribution-Free Statistics: An Application-Oriented Approach, ed. J.P Huston (Elsevier Science Publishers, Amsterdam) p. 36.

Longoni, R., L. Spina and G. Di Chiara, 1987, Permissive role of D-1 receptor stimulation by endogenous dopamine for the expression of postsynaptic D-2 mediated behavioural responses. Yawning in rats, Eur. J. Pharmacol. 134, 163.

Maj, J., 1990, Behavioural effects of antidepressant drugs given repeatedly on the dopaminergic system, in: Dopamine and Mental Depression, eds. G.L. Gessa and G. Serra (Pergamon Press, New York), p. 139.

Maj, J., M. Papp, G. Skuza, K. Bigajska and M. Zazula, 1989a, The influence of repeated treatment with imipramine, (+)- and (−)-oxaprotiline on behavioural effects of dopamine D-1 and D-2 agonists, J. Neural Transm. 76, 29.

Maj, J., Z. Rogoz, G. Skuza and H. Sowinska, 1989b, Antidepressants given repeatedly increase the behavioural effect of dopamine D-2 agonist, J. Neural Transm. 78, 1.

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

Molloy, A.G. and J.L. Waddington, 1987, Assessment of grooming and other behavioural responses to the D-1 dopamine receptor agonist SK and F 38393 and its *R*- and *S*-enantiomers in the intact adult rat, Psychopharmacology 92, 164.

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

Nomikos, G.G., G. Damsma, D. Wenkstern and H.C. Fibiger, 1991, Chronic desipramine enhances amphetamine-induced increases in interstitial concentrations of dopamine in the nucleus accumbens, Eur. J. Pharmacol. 195, 63.

Paetsch, P.R. and A.J. Greenshaw, 1992, Effects of chronic antidepressant treatment on dopamine-related [^{3}H]-SCH 23390 and [^{3}H]-spiperone binding in the rat striatum, Cell. Mol. Neurobiol. 12, 597.

Pucilowski, O. and D.H. Overstreet, 1993, Effect of chronic antidepressant treatment on responses to apomorphine in selectively bred rat strains, Brain Res. Bull. 32, 471.

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

Serra, G., M. Collu, P.S. D'Aquila, G.M. De Montis and G.L. Gessa, 1990a, Possible role of dopamine D_1 receptor in the behavioural supersensitivity to dopamine agonists induced by chronic treatment with antidepressants, Brain Res. 527, 234.

Serra, G., M. Collu, P.S. D'Aquila, G.M. De Montis and G.L. Gessa, 1990b, On the mechanism involved in the behavioral supersensitivity to DA agonists induced by chronic antidepressants, in: Dopamine and Mental Depression, ed. G.L. Gessa and G. Serra (Pergamon Press, New York) p. 121.

Serra, G., M. Collu and G.L. Gessa, 1987, Yawning is elicited by D_2 dopamine agonists but is blocked by the D_1 antagonist, SCH 23390, Psychopharmacology 91, 330.

Serra, G., M. Collu, P.S. D'Aquila, G.M. De Montis and G.L. Gessa, 1991, Chronic imipramine "reverses" B-HT 920-induced hypomotility in rats, J. Neural Transm. 84, 237.

Sokoloff, P., M. Andrieus, R. Besançon, C. Pilon, M.-P. Martres, B. Giros and J.-C. Schwartz, 1992, Pharmacology of human dopamine D_3 receptor expressed in mammalian cell line: comparison with D_2 receptor, Eur. J. Pharmacol. 225, 331.

Spyraki, C. and H.C. Fibiger, 1981, Behavioral evidence for supersensitivity of postsynaptic dopamine receptors in the mesolimbic system after chronic administration of desipramine, Eur. J. Pharmacol. 74, 195.

Wachtel, S.R., R.J. Brooderson and F.J. White, 1992, Parametric and pharmacological analyses of the enhanced grooming response elicited by the D1 dopamine receptor agonist SKF 38393 in the rat, Psychopharmacology 109, 41.

Winer, B.J., 1971, Statistical Principles in Experimental Design (McGraw-Hill, New York) p.191.

Wurtman, R.J. and J. Axelrod, 1963, A sensitive and specific assay for the estimation of monoamine oxidase, Biochem. Pharmacol. 12, 1439.