Br. J. Pharmac. (1987), **91**, 747–752

Long-term imipramine treatment enhances locomotor and food intake suppressant effects of *m*-chlorophenylpiperazine in rats

Charanjit S. Aulakh, Robert M. Cohen, James L. Hill, Dennis L. Murphy & Joseph Zohar

Laboratory of Clinical Science, National Institute of Mental Health, NIH Clinical Center, 10/3D-41, Bethesda, MD 20892, U.S.A.

1 Administration of the 5-HT_{1B} receptor agonist *m*-chlorophenylpiperazine (m-CPP) to rats produces dose-dependent decreases in locomotor activity and food intake.

2 The locomotor suppressant effect of m-CPP was inhibited by the 5-hydroxytryptaminergic antagonist, metergoline, but not by phentolamine, propranolol, clonidine, or haloperidol.

3 The locomotor suppressant effects of m-CPP were enhanced following long-term (but not short-term) treatment with imipramine, possibly reflecting the postulated development of a functional supersensitivity of 5-HT_{1B} receptors mediating locomotion during longer-term antidepressant drug treatment.

4 The food intake suppressant effects of m-CPP were enhanced following both short (3–5 days) and longer-term (21 days) treatment with imipramine. Rapidly developing 5-hydroxytryptamine uptake inhibition may be responsible for this change, or it may represent an earlier adaptive change in the 5-HT_{1B} receptors mediating food intake compared to more complexly modulated motor responses.

Introduction

The therapeutic effects of various types of antidepressant drugs such as tricyclics or monoamine oxidase inhibitors are observed only after two or more weeks of their administration, while the uptake inhibition or enzymatic inhibition occurs within a few hours. Therefore, recent animal studies of molecular mechanisms pertinent to antidepressant efficacy have concentrated on the adaptive changes that occur following long-term administration of these drugs. Long-term but not short-term administration of various types of antidepressant drugs have been reported to cause a decrease in the density of β-adrenoceptors as well as a decrease in adrenoceptor-mediated cyclic adenosine 3:5-monophosphate (cyclic AMP) formation in the cerebral cortex (Sulser *et al.*, 1978; Sugrue, 1983).

In addition to the noradrenergic system induced alterations, adaptive changes have also been reported to occur in the 5-hydroxytryptaminergic (5-HT) system following chronic treatment with these drugs (Anderson, 1983). However, unlike the fairly consistent effects of antidepressant treatments on β-adrenoceptor function, their effects on the 5-HTergic system are variable. Although chronic treatment with most antidepressant drugs decreases 5-HT_2 receptor density in the frontal cortex (Peroutka & Snyder, 1980), chronic electroconvulsive treatment increases 5-HT_2 receptor density (Kellar *et al.*, 1981). Furthermore, some antidepressant drugs cause a decrease (Savage *et al.*, 1980) while the others cause no change (Bergstrom & Kellar, 1979) in the density of 5-HT_1 receptors following their chronic administration.

Recent ligand binding studies have demonstrated the existence of two subtypes of the 5-HT_1 receptor, designated 5-HT_{1A} and 5-HT_{1B} (Pedigo *et al.*, 1981). Indole-type 5-HT agonists, such as 5-methoxy-*N*, *N*-dimethyltryptamine (5-MeODMT) show a higher affinity for the 5-HT_{1A} receptor than for the 5-HT_{1B} subtype, whereas piperazine-type 5-HT agonists, such as *m*-chlorophenylpiperazine (m-CPP) show higher affinity for the 5-HT_{1B} receptor (Sills *et al.*, 1984). m-CPP, a metabolite of the antidepressant drug trazodone (Melzacka *et al.*, 1979) markedly reduces food intake in rats (Samanin *et al.*, 1979). This effect on food intake appears to result from postsynaptic 5-HT receptor stimulation since it is prevented by the 5-HT antagonist metergoline but not by mid-brain

raphe lesions (Samanin *et al.*, 1979). m-CPP also decreases locomotor activity in mice and rats (Vetulani *et al.*, 1982; Cohen *et al.*, 1983). The purposes of the present study were: (1) to investigate the dose-related effects of m-CPP on locomotor and feeding behaviour in rats; (2) to establish its specificity as a 5-HT agonist on these behaviours; and (3) using m-CPP as a challenge agent, to study possible functional adaptational changes in the 5-HTergic system following long-term imipramine treatment.

Methods

Male Wistar rats weighing approximately 250 g at the beginning of the study were used.

Locomotor study

The animals were housed six per cage and had free access to food and water. Imipramine hydrochloride (5 mg kg^{-1} daily) or saline was administered subcutaneously and continously by means of osmotic minipumps (Alza Corporation) for 28 days; the pumps were reimplanted at two weeks. Both the imipramine-treated and saline-treated animals were challenged with a 1 mg kg^{-1} dose of m-CPP on the 3rd, 14th and 21st days. In all the experiments, m-CPP was injected i.p. 30 min before the animals were placed in the activity boxes for locomotor assessment. For interaction studies, phentolamine, propranolol, haloperidol and clonidine were injected 10 min before the m-CPP injection whereas metergoline and ascorbic acid (1%) were injected 30 min before the m-CPP injection. All the drugs were dissolved in saline except metergoline which was dissolved in 1% ascorbic acid.

Locomotor activity of individual rats was recorded daily for a period of 40 min at the same time of the day in the same test cages (Coulbourn instruments, 30 cm × 25 cm × 29 cm) each equipped with four photocell detectors which were located 6 cm apart and 2 cm above the grid floor. The test cage was enclosed in a sound proof cubicle with a house light and a fan attached on the back side, and a small window for observation of the animal in the front. Interruptions of the photocell beams were recorded automatically by digital counters. Baseline activity was recorded for 5–7 days for all the animals before the start of drug treatment.

Food intake study

The animals were housed individually and had free access to water. The animals were trained to take their daily food (Purina food pellets) from 10 h 00 min to 14 h 00 min for 10 days before antidepressant drug treatment was begun. At the end of the first hour of food access the remaining food was weighed, and the difference from the original amount constituted the measure of food intake. In addition, total daily food intake (4 h), water intake (24 h) and body weight were also recorded for each animal. The animals were divided into control and antidepressant treatment groups with six rats in each group. Imipramine hydrochloride (5 mg kg^{-1} daily) or saline was subcutaneously administered continously by means of osmotic minipumps (Alza Corporation) for 28 days; the pumps were reimplanted at two weeks.

Each animal in both groups was challenged with saline or various doses of m-CPP with each dose separated by 48 h. m-CPP was injected intraperitoneally (i.p.) 10 min before placing the food cups into the cages. Food intake on days in between drug days was observed to return to baseline.

Statistics

Statistical analysis of main effects and interactions was conducted using repeated measures design analysis of variance (GLM Procedure, SAS Institute, Cary, NC). Detailed examination of significant effects were performed using either *a priori* designed contrasts or by *post-hoc* analysis using the Neuman-Keuls test or Student's *t* tests wherever appropriate. In the text, the drug effects are reported as % change from the baseline values. However, raw data were used for statistical analysis.

Results

Locomotor activity

m-CPP produced a dose-dependent decrease [$F(4, 20) = 54.8$, $P < 0.001$] in locomotor activity (Figure 1). The effect of the lowest dose (0.5 mg kg^{-1}) used was significantly ($P < 0.01$) different from the baseline control activity levels and furthermore was significantly different from the 1 mg kg^{-1} dose at $P < 0.05$ level. Clonidine suppressed locomotor activity when used alone (Student's *t* test, $P < 0.01$) and potentiated the effect of m-CPP when used in combination (Table 1). The effect of m-CPP was also significantly potentiated by propranolol and haloperidol. However, only metergoline significantly inhibited the locomotor suppressant effect of m-CPP (Table 1) while phentolamine and ascorbic acid were without effect (Table 1).

Long-term imipramine treatment did not affect baseline locomotor activity. m-CPP (1 mg kg^{-1}) decreased [$F(1, 22) = 9.02$, $P < 0.01$] locomotor activity in both the saline-treated controls and imipramine-treated animals, with no significant difference ($P > 0.05$) between the two groups on day 3 (Figure 2). However, after long-term imipramine

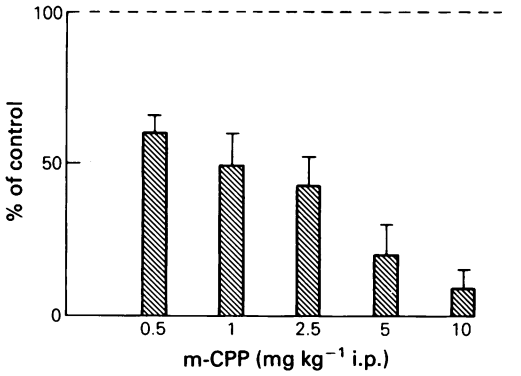

Figure 1 The effects of various doses of *m*-chlorophenylpiperazine (m-CPP) on locomotor activity in rats ($n = 6$). Drug effects were calculated as percentage change from the baseline values for each animal and are expressed as percentage of control (100%). The mean ± s.e.mean baseline locomotor counts were 1169 ± 219.

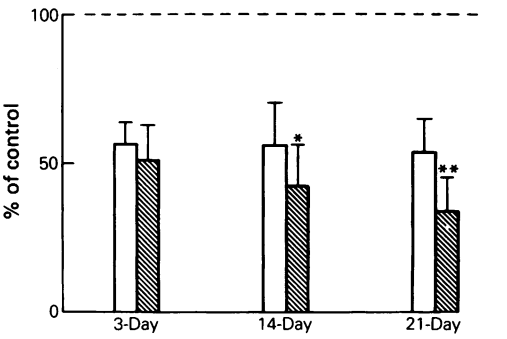

Figure 2 Effect of imipramine treatment (5 mg kg^{-1} daily) on *m*-chlorophenylpiperazine (m-CPP, 1 mg kg^{-1})-induced suppresion of locomotor behaviour in rats. The mean ± s.e.mean baseline locomotor counts for control and imipramine-treated animals were 1496 ± 269 and 1272 ± 206 respectively. Imipramine + m-CPP-treated rats ($n = 6$, hatched columns) were significantly different from m-CPP treated controls ($n = 6$, open columns) after 14 and 21 days of treatment, but not after 3 days of treatment. $^{*}P < 0.05$; $^{**}P < 0.01$.

treatment, the suppressant effect of m-CPP on motor activity was enhanced in imipramine-treated animals, with significant differences from the controls on day 14 ($P < 0.05$) and day 21 ($P < 0.01$) (Figure 2).

Food Intake

During 28 days of imipramine or saline treatment there was no significant difference between the two groups on daily baseline food intake [$F(1,10) = 1.62$, $P > 0.20$], water intake [$F(1,10) = 0.28$, $P > 0.60$] or body weight gain [$F(1,10) = 1.68$, $P > 0.20$] (Table 2). m-CPP induced dose-dependent decreases [$F(2,20) = 46.84$, $P < 0.001$] in 1 h food intake in both the saline-treated and imipramine-treated animals (Figure 3). However, the food intake suppressant effect of m-CPP (1.25 and 2.5 mg kg^{-1}) was significantly enhanced in both long-term and short-term [$F(1,10) = 9.66$, $P < 0.05$] imipramine-treated animals when compared to the controls and there was no significant difference between the short-term and long-term imipramine treatments (Figure 3). The lack of a significant difference at the highest dose of m-CPP apparently represented a 'ceiling' effect since this dose produced 70–85% inhibition of food intake under all three conditions.

Table 1 The effects of various drug treatments on *m*-chlorophenylpiperazine (m-CPP)-induced suppression of locomotor activity in rats

Effect of other drugs			
Drug and dose	*Effect*	*Effect of m-CPP* (1 mg kg^{-1})	*Interactive effect of m-CPP and other drugs combined*
Phentolamine (0.5 mg kg^{-1})	−2 ± 5 (6)	−47 ± 4 (6)	−49 ± 5 (6)
Ascorbic acid (10 mg ml^{-1})	−14 ± 8 (6)	−47 ± 4 (6)	−59 ± 4 (6)
Metergoline (1 mg kg^{-1})	−26 ± 6 (6)	−47 ± 4 (6)	−29 ± 4** (6)
Propranolol (5 mg kg^{-1})	−9 ± 6 (6)	−57 ± 7 (6)	−75 ± 2* (6)
Haloperidol (1 μg kg^{-1})	−12 ± 2 (6)	−49 ± 4 (6)	−77 ± 5** (6)
Clonidine (10 μg kg^{-1})	−51 ± 4 (6)	−49 ± 4 (6)	−79 ± 7** (6)

Drug effects are expressed as percentage change from baseline values (1010 ± 231). Effects of combination (m-CPP and interacting drug) treatment significantly different from m-CPP treatment alone in the same animals are represented by $^{*}P < 0.05$; $^{**}P < 0.01$.

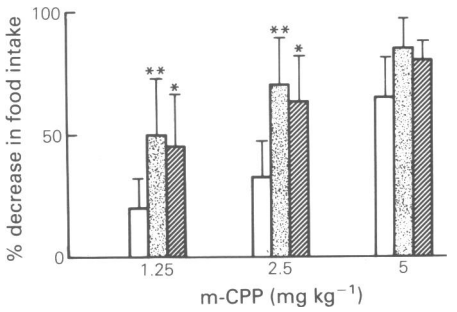

Figure 3 Effect of imipramine treatment (5 mg kg^{-1} daily for 28 days) on the suppression of food-intake by different doses of *m*-chlorophenylpiperazine (m-CPP) in rats. The mean ± s.e.mean baseline 1 h food intake (g) values for saline-treated, short-term imipramine-treated and long-term imipramine-treated animals were 11.3 ± 1.1, 10.5 ± 2.2 and 11.3 ± 2.1 respectively. Short-term (3–5 days) imipramine-treated rats ($n = 6$, stippled columns) and long-term (21–23 days) imipramine-treated rats ($n = 6$, hatched columns) were both significantly different from saline-treated rats ($n = 6$, open columns): $^*P < 0.05$; $^{**}P < 0.01$.

Discussion

The present study demonstrates a dose-dependent reduction in locomotor activity in rats treated with m-CPP. The motor activity changes are most probably attributable to stimulation of postsynaptic 5-HT receptors as they are inhibited by low concentrations (1 mg kg^{-1}) of the 5-HT receptor antagonist metergoline, but not by various noradrenoceptor or dopamine receptor blocking drugs.

At low doses (up to 2.5 mg kg^{-1}), m-CPP has been reported to decrease 5-hydroxyindoleacetic acid (5-HIAA) concentrations in various rat brain areas without any effect on brain homovanillic (HVA) or 3-methoxy-4-hydroxy-phenylethyleneglycol sulphate (MHPG) concentrations (Invernizzi *et al.*, 1981). However, at 3 mg and 10 mg kg^{-1} doses, m-CPP increases HVA and MHPG levels in addition to decreasing 5-HIAA levels (Invernizzi *et al.*, 1981). Therefore, a contribution of noradrenaline or dopamine to the locomotor suppressant effect of m-CPP at higher doses (above 2.5 mg kg^{-1}) cannot be ruled out. It is well known that the nucleus accumbens and the mesolimbic dopaminergic projections it receives from the midbrain are involved in the initiation of locomotor activity (Pijnenburg *et al.*, 1976; Costall & Naylor, 1975). Injection of dopamine itself or dopamine agonists directly into the nucleus accumbens have been reported to stimulate locomotor activity in unrestrained animals (Costall *et al.*, 1976; Pijnenburg *et al.*, 1976). The nucleus accumbens, however, also receives 5-HTergic projections from the raphe nuclei (Conrad *et al.*, 1974; Geyer *et al*, 1976). Lesioning of raphe nuclei produces hyperactivity (Costall *et al.*, 1976; Geyer *et al.*, 1976), which can be attenuated by 5-HT administration into the nucleus accumbens (Costall *et al.*, 1976). An inhibitory role of 5-HT on locomotor activity is further supported by the finding that dopamine-stimulated locomotor activity is attenuated by injecting 5-HT into the nucleus accumbens through the same cannula (Costall *et al.*, 1976; Jones *et al.*, 1980). Suppression of locomotor activity by m-CPP observed in the present study suggests that the 5-HT receptor involved is of 5-HT$_{1B}$ sub-type since ligand binding data has demonstrated that piperazine-type 5-HT agonists such as m-CPP show higher affinity for the 5-HT$_{1B}$ receptor than for the 5-HT$_{1A}$ subtype (Sills *et al.*, 1984). Differentiation between 5-HT$_{1A}$ and 5-HT$_{1B}$ subtypes have also been demonstrated in recent behavioural studies. Indole-type 5-HT agonists such as 5-MeODMT produce the 5-HT behavioural syndrome in rats (Sills *et al.*, 1985) and myoclonus in guinea-pigs (Luscombe *et al.*, 1982), whereas the piperazine-type agonists such as m-CPP do not produce this syndrome.

The present study further suggests that 5-HT receptors of the 5-HT$_{1B}$ subtype may become supersensitive after long-term treatment with the antidepressant drug imipramine. This is consistent with electrophysiological data demonstrating an increase in the inhibitory response of forebrain neurones to iontophoretic 5-HT following chronic administration of some tricyclic antidepressant drugs including desipramine, imipramine, and chlorimipramine (deMontigny & Aghajanian, 1978). In behavioural investigations, chronic administration of imipramine, desipramine, amitryptyline and mianserin led to enhanced 5-HT induced sleep in young chicks (Jones, 1980). Chronic electroconvulsive shock treatment also increased hyperthermic responses to m-CPP (Vetulani *et al.*, 1981).

Recently, Sills *et al.* (1985) have suggested that the 5-HT behavioural syndrome in rats is mediated by 5-HT$_{1A}$ receptors since it was produced by the 5-HT$_{1A}$ selective agonist 5-MeODMT but not by the 5-HT$_{1B}$ selective agonist m-CPP. These two subtypes of 5-HT$_1$ receptor might be affected differentially following chronic administration of antidepressant drugs. Such a differential effect might also explain why some antidepressant drugs cause a decrease while the others cause no change in the density of 5-HT$_1$ receptors following their chronic administration (Lucki & Frazer, 1982). Further ligand binding studies demonstrating specific changes in 5-HT$_{1A}$ vs 5-HT$_{1B}$ subtypes during antidepressant drug treatments will be necessary to clarify this. However, it is noteworthy that functional changes in the 5-HTergic system in the form of altered responses to a 5-HT agonist have been

Table 2 Effect of saline ($n = 6$) or imipramine ($n = 6$) treatment (5 mg kg^{-1} for 28 days) on daily food intake, water intake and body weight gain in rats

Treatment	*Food intake (g)*		*Water intake (ml)*		*Body weight (g)*	
days	*Saline*	*Imipramine*	*Saline*	*Imipramine*	*Saline*	*Imipramine*
0	18.2 ± 1.3	17.6 ± 2.0	28.9 ± 4.1	28.6 ± 3.4	268.7 ± 17.5	260.3 ± 15.8
7	19.0 ± 1.6	16.8 ± 2.7	31.6 ± 4.5	30.5 ± 5.2	292.5 ± 15.7	270.5 ± 20.7
14	17.9 ± 2.3	16.8 ± 3.0	30.6 ± 2.6	33.6 ± 8.8	317.7 ± 18.8	301.7 ± 30.9
21	18.3 ± 2.1	17.0 ± 3.9	27.6 ± 2.8	31.3 ± 11.1	336.3 ± 25.7	311.0 ± 37.9
28	18.0 ± 1.7	15.9 ± 2.0	29.5 ± 4.1	32.1 ± 8.6	349.7 ± 23.9	323.7 ± 34.7

Values are expressed as the raw data ± s.e.mean. There were no statistically significant differences between saline treated and imipramine treated rats on food intake, water intake or body weight gain.

reported to occur without parallel changes in the number of central [^{3}H]-5-HT binding sites (Samanin *et al.*, 1980).

Potentiation of food intake but not of the locomotor suppressant effect of m-CPP by short-term imipramine treatment demonstrates that these changes are not due to imipramine's effect on the metabolism of m-CPP or that the food intake decrements are not simply secondary to sedation or decreased locomotor activity. The earlier food intake changes raise the possibility that adaptational changes may occur earlier in some brain areas and later in other brain areas. Such phenomena, in fact, have previously been reported to occur in the 5-HTergic system (Samanin *et al.*, 1980). This would also be consistent with our neuroendocrine studies showing some potentiation of m-CPP's effect on plasma prolactin following short-term (3 day) imipramine treatment whereas more marked potentiation occurred following long-term (21 day) imipramine treatment (Aulakh *et al.*, unpublished observations).

Alternatively, potentiation of the effect of m-CPP on food intake folowing short-term imipramine treatment may be due to rapidly developing inhibition of 5-HT uptake by imipramine. Failure of short-term imipramine treatment to potentiate the locomotor suppressant effect of m-CPP may be due to the fact that uptake inhibition will increase the amount of 5-HT in the synapse and, therefore, will stimulate both 5-HT_{1A} as well as 5-HT_{1B} receptors. Since stimulation of 5-HT_{1A} receptors will produce hyperactivity (part of the classical '5-HT syndrome') on one hand and stimulation of 5-HT_{1B} receptors will cause hypoactivity on the other hand, the net effect may be no change in locomotor activity and therefore no potentiation of the effect of m-CPP on locomotion. This would also explain why imipramine treatment failed to affect baseline locomotor activity in the present study.

Enhanced net sensitivity to m-CPP following long-term imipramine treatment observed in the present study is of particular interest since m-CPP has been shown to be a metabolite of the antidepressant, trazodone (Caccia *et al.*, 1981) and may contribute to the pharmacological and therapeutic effects of trazodone (Fuller *et al.*, 1981; Rurak & Melzacka, 1983). However, the enhanced sensitivity of 5-HT_{1B} receptors observed in the present study cannot be related to a common mechanism for the therapeutic efficacy of all classes of antidepressant drugs, since in a previous study from this laboratory chronic administration of the monoamine oxidase type A (MAO-A) inhibiting antidepressant, clorgyline was shown to attenuate m-CPP-induced decreases in food intake and sedation (Cohen *et al.*, 1983). Nevertheless, the present findings may have therapeutic relevance, given the observations that the clinical characteristics of some patients who respond to MAO inhibitors may be different from those who generally respond to tricyclics (Robinson *et al.*, 1978; Quitkin *et al.*, 1979; Nies, 1983).

References

ANDERSON, J.L. (1983). Serotonergic receptor changes after chronic antidepressant treatments: ligand binding, electrophysiological and behavioral studies. *Life Sci.*, **32**, 1791–1801.

BERGSTROM, D.A. & KELLER, K.J. (1979). Effect of electroconvulsive shock on monoaminergic binding sites in rat brain. *Nature*, **278**, 464–466.

CACCIA, S., BALLABIO, M., SAMANIN, R., ZANINI, M.G. & GARATTINI, S. (1981). 1-m-chlorophenyl-piperazine, a central serotonin agonist, is a metabolite of trazodone. *J. Pharm. Pharmac.*, **33**, 477–478.

COHEN, R.M., AULAKH, C.S. & MURPHY, D.L. (1983). Long-term clorgyline treatment antagonizes the eating and motor function responses to m-chlorophenyl-piperazine. *Eur. J. Pharmac.*, **94**, 175–179.

CONRAD, L.C.A., LEONARD, C.M. & PFAFF, D.W. (1974).

Connections of the median and dorsal raphe nuclei in rat: An autoradiographic and degeneration study. *J. comp. Neurol.*, **156,** 179–206.

COSTALL, B. & NAYLOR, R.J. (1975). A comparison of circling models for the detection of anti-Parkinson activity. *Psychopharmacologia*, **45,** 57–64.

COSTALL, B., NAYLOR, R.J., MARSDEN, C.B. & PYCOCK, C.J. (1976). Serotonergic modulation of the dopamine response from the nucleus accumbens. *J. Pharm. Pharmac.*, **28,** 523–526.

DE MONTIGNY, C. & AGHAJANIAN, G.K. (1978). Tricyclic antidepressants: Long-term treatment increases responsivity of rat forebrain neurons to serotonin. *Science*, **202,** 1303–1305.

FULLER, R.W., SNODDY, H.D., MASON, N.R. & OWEN, J.E. (1981). Disposition and pharmacological effects of m-chlorophenyl-piperazine in rats. *Neuropharmacology*, **20,** 155–162.

GEYER, M.A., PUERTO, A., DAWSEY, W.J., KNAPP, S., BULLARD, W.P. & MANDELL, A.J. (1976). Histologic and enzymatic studies of the mesolimbic and mesostriatal serotonergic pathways. *Brain Res.*, **106,** 241–256.

INVERNIZZI, R., COTECCHIA, S., DEBLASI, A., MENNINI, T., PATACCINI, R. & SAMANIN, R. (1981). Effect of m-chlorophenylpiperazine on receptor binding and brain metabolism of monoamines in rats. *Neurochem. Int.*, **3,** 239–244.

JONES, D.L., MEGENSON, G.J. & WU, M. (1980). Injection of dopaminergic, cholinergic, serotonergic and gabaergic drugs into the nucleus accumbens: Effect on locomotor activity in the rat. *Neuropharmacology*, **20,** 29–37.

JONES, R.S.G. (1980). Enhancement of 5-hydroxytryptamine induced behavioral effects following chronic administration of antidepressant drugs. *Psychopharmacology*, **69,** 307–311.

KELLAR, K.J., CASCIO, C.S., BUTLER, J.A. & KURTZKF, R.N. (1981). Differential effects of electroconvulsive shock and antidepressant drugs on serotonin-2 receptors in rat brain. *Eur. J. Pharmac.*, **69,** 515–518.

LUCKI, I. & FRAZER, A. (1982). Prevention of the serotonin syndrome in rats by repeated administration of monoamine oxidase inhibitors but not tricyclic antidepressants. *Psychopharmacology*, **77,** 205–211.

LUSCOMBE, G., JENNER, P. & MARSDEN, C.D. (1982). Myoclonus in guinea pigs is induced by indole-containing but not piperazine-containing 5HT agonists. *Life Sci.*, **30,** 1487–1494.

MELZACKA, M., BOKSA, J. & MAJ., J. (1979). 1-(m-Chlorophenyl) piperazine: a metabolite of trazodone isolated from rat urine. *J. Pharm. Pharmac.*, **31,** 855–856.

NIES, A. (1983). Clinical applications of MAOI's. In *Drugs in Psychiatry*, Vol. 1. ed. Burrows, G.D., Norman, T.R. & Davies, B. pp. 219–247. Amsterdam: Elsevier.

PEDIGO, N.W., YAMAMURA, H.I. & NELSON, D.L. (1981). Discrimination of multiple [^{3}H]-5-hydroxytryptamine binding sites by the neuroleptic Spiperone in rat brain. *J. Neurochem.*, **36,** 220–226.

PEROUTKA, S.J. & SNYDER, S.H. (1980). Long-term antidepressant treatment decreases spiroperidol labeled serotonin receptor binding. *Science*, **210,** 88–90.

PIJNENBURG, A.J.J., HONIG, W.M.M., VAN DER HEYDEN, J.A.M. & VAN ROSSUM, J.M. (1976). Effects of chemical stimulation of the mesolimbic dopamine system upon locomotor activity. *Eur. J. Pharmac.*, **35,** 45–58.

QUITKIN, F., RIFKIN, A. & KLEIN, D.F. (1979). Monoamine oxidase inhibitors. *Archs Gen. Psychiatry*, **36,** 749–760.

ROBINSON, D.S., NIES, A., RAVARIS, C.L., IVES, J.O. & BARTLETT, D. (1978). Clinical pharmacology of phenelzine. *Archs Gen. Psychiatry*, **35,** 629–635.

RURAK, A. & MELZACKA, M. (1983). Effect of dosage and route of administration of trazadone on cerebral concentrations of 1-m-chlorophenylpiperazine in rats. Kinetics of trazodone biotransformation. *Pol. J. Pharac.*, **35,** 241–247.

SAMANIN, R., MENNINI, T., FERRARIS, A., BENDOTTI, C., BORSINI, F. & GARATTINI, S. (1979).m-Chlorophenylpiperazine: A central serotonin agonist causing powerful anorexia in rats. *Naunyn Schmiedebergs Arch. Pharmac.*, **308,** 159–163.

SAMANIN, R., MENNINI, T., FERRARIS, A., BENDOTTI, C. & BORSINI, F. (1980). Hyper- and hyposensitivity of central serotonin receptors: [^{3}H]serotonin binding and functional studies in the rat. *Brain Res.*, **189,** 449–457.

SAVAGE, D.D., MENDELS, J. & FRAZER, A. (1980). Monoamine oxidase inhibitors and serotonin uptake inhibitors: Differential effects on [^{3}H] serotonin binding sites in rat brain. *J. Pharmac. exp. Ther.*, **212,** 259–263.

SILLS, M.A., LUCKI, I. & FRAZER, A. (1985). Development of selective tolerance to the serotonin behavioral syndrome and suppression of locomotor activity after repeated administration of either 5-MeODMT or m-CPP. *Life Sci.*, **36,** 2463–2469.

SILLS, M.A., WOLFE, B.B. & FRAZER, A. (1984). Determination of selective and non-selective compounds for the 5-HT_{1A} and 5-HT_{1B} receptor subtypes in rat frontal cortex. *J. Pharmac. exp. Ther.*, **231,** 480–487.

SUGRUE, M.F. (1983). Chronic antidepressant therapy and associated changes in central monoaminergic receptor functioning. *Pharmac. Ther.*, **21,** 1–33.

SULSER, F., VETULANI, J. & MOBLEY, P. (1978). Mode of action of antidepressant drugs. *Biochem. Pharmac.*, **27,** 257–261.

VETULANI, J., LEBRECHT, U. & PILC. A. (1981). Enhancement of responsivenessof the central serotonergic system and serotonin-2 receptor density in rat frontal cortex by electroconvulsive treatment. *Eur. J. Pharmac.*, **76,** 81–85.

VETULANI, J., SANSONE, M., BEDNARCZYK, B. & HANO, J. (1982). Different effects of 3-chlorophenylpiperazine on locomotor activity and acquisition of conditioned avoidance response in different strains of mice. *Naunyn Schmiedebergs Arch. Pharmac.*, **319,** 271–274.

(Received November 25, 1986.
Revised March 17, 1987.
Accepted March 30, 1987.)