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Differential behavioural effect of quinpirole in neuroleptic-pretreated rats — role of α_1-adrenoceptor

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Abstract

This paper presents the effect of 14-day intraperitoneal (i.p.) neuroleptic treatment on the behavioural response of Wistar rats to (−)-quinpirole hydrochloride (3 mg/kg, i.p.) administered 24 h after the last neuroleptic dose. Chlorpromazine hydrochloride (10 mg/kg), haloperidol (2 mg/kg) or (±)-sulpiride (100 mg/kg) increased the effect of quinpirole; however, there were qualitative and quantitative differences between the neuroleptics. Chlorpromazine and haloperidol, but not sulpiride, pretreatment enhanced quinpirole-induced locomotor hyperactivity. Prazosin (0.5 mg/kg, i.p.) given to chlorpromazine-treated rats 1 h before quinpirole attenuated the quinpirole-induced hyperlocomotion. In chlorpromazine-pretreated rats, quinpirole elicited defensive aggressive behaviour with vocalization, copulatory attempts, intense rearing and head-down sniffing. When prazosin was given before quinpirole, head-down sniffing and object-directed oral activity were mainly observed. In haloperidol-pretreated rats, quinpirole induced intense head-down sniffing, rearing, grooming and object-directed oral activity. In sulpiride-pretreated rats, quinpirole induced intense head-down sniffing, grooming and object-directed oral activity. The results of the study suggest that differences in the behavioural expression of dopamine D_2 receptor supersensitivity induced by neuroleptics may be, at least in part, caused by concurrent stimulation of α_1-adrenoceptors.

Keywords: Neuroleptic-induced supersensitivity; Behaviour; Quinpirole; Prazosin

1. Introduction

Long-term neuroleptic treatment results in behavioural supersensitivity reflected by an enhanced response to endogenous dopamine and dopamine receptor agonists. This phenomenon has been investigated extensively, particularly after prolonged haloperidol treatment. For example, cessation of chronic haloperidol treatment increases spontaneous motor activity, apomorphine-induced hyperactivity and stereotypy (Antkiewicz-Michaluk et al., 1995), and enhances dopamine D_2/D_3 plus D_1 receptor agonist-induced stereotypy (LaHoste and Marshall, 1992) and dopamine D_1 receptor agonist-induced oral movements in rats (Ellison et al., 1988). It is generally presumed that neuroleptic behavioural supersensitivity results from an increase in the number of dopamine receptors, especially of D_2 receptors (Fleminger et al., 1983; Chipkin et al., 1987; LaHoste and Marshall, 1992). However, several recent studies have shown a dissociation between neuroleptic-induced behavioural supersensitivity and the up-regulation of dopamine receptors, suggesting that additional mechanisms are involved in the expression of behavioural supersensitivity. Chronic haloperidol and antimuscarinic treatment attenuated (Carvey et al., 1988), while haloperidol and monosialoganglioside treatment augmented (Schröder et al., 1994), behavioural supersensitivity; however, neither mode of treatment modified the haloperidol-induced up-regulation of dopamine D_2 receptors. Furthermore, coadministration of dopamine D_1 and D_2 receptor agonists diminished the enhanced apomorphine-induced stereotypy in haloperidol-pretreated rats but did not alter the increase in number of dopamine D_2 receptors induced by chronic haloperidol treatment (Marin and Chase, 1993). Therefore, it has been suggested that the increased dopamine D_2 receptor density is not solely responsible for the development and expression of neuroleptic-induced behavioural supersensitivity.

It has been well evidenced that long-term neuroleptic treatment alters not only dopaminergic but also non-dopaminergic transmission. In this study, we focused on

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the noradrenergic system because of the following reasons: (i) apart from their high affinity for dopamine receptors, many neuroleptics show high affinity for α_1-adrenoceptors (Leysen et al., 1993), and when given chronically, they increase the density of α_1-adrenoceptors (Cohen and Lipinski, 1986); (ii) a close relationship between noradrenergic and dopaminergic systems has been shown (Waldmeier et al., 1982; Grenhoff et al., 1993; Sommermeyer et al., 1995); and (iii) the noradrenergic system interacts with the dopaminergic system to modulate locomotor function (Rubinstein et al., 1989; Eshel et al., 1990; Darracq et al., 1998).

The present study was undertaken to compare the behavioural effects of quinpirole, a dopamine D_2/D_3 receptor agonist, in rats treated with chlorpromazine, haloperidol or sulpiride for 14 consecutive days. These neuroleptics were chosen because they differ in their abilities to block dopamine D_2-like and α_1-adrenoceptors. Chlorpromazine displays the highest affinity for the α_1-adrenoceptor and it also acts on dopamine D_2-like receptors; haloperidol is the most effective antagonist of dopamine D_2-like receptors with some activity against α_1-adrenoceptors; sulpiride preferentially binds to dopamine D_2-like receptors but with lower antagonistic potency than haloperidol or chlorpromazine and has no effect on α_1-adrenoceptors (Leysen et al., 1993). To test the hypothesis that an interaction between dopamine D_2 receptor and α_1-adrenoceptor is involved in the behavioural effects induced by stimulation of dopamine D_2 receptors in neuroleptic-pretreated rats, we evaluated the influence of the α_1-adrenoceptor antagonist, prazosin, on the behavioural response to quinpirole in chlorpromazine-pretreated rats.

2. Materials and methods

2.1. Subjects

Male Wistar rats (the Animal Farm of the Silesian University School of Medicine) initially weighing 190–240 g were housed in groups of six to seven per cage (55 cm × 32 cm × 18 cm) under standard conditions (22 ± 2°C, lights on: 0700–1900 h) with free access to standard pellet food and tap water. The animals were habituated to the conditions for 5 days before the experiments. All experiments were performed between 0900 and 1400 h. Each animal was used only once. This study was approved by the Bioethical Committee of the Silesian University School of Medicine.

2.2. Drugs

Chlorpromazine hydrochloride, haloperidol, (±)-sulpiride and prazosin hydrochloride were supplied by Sigma; (−)-quinpirole hydrochloride was supplied by Research Biochemical. Chlorpromazine was dissolved in 0.9% saline. Haloperidol was dissolved in a minimal volume (1 mg/50 μl) of glacial acetic acid (1% vol/vol). Sulpiride was dissolved in deionized water acidified with glacial acetic acid to pH 5.7. After dilution with an appropriate volume of deionized water, haloperidol and sulpiride solutions were adjusted to pH 6.2 with 1 M sodium hydroxide. Quinpirole was dissolved in 0.9% saline, prazosin was suspended in 1% Tween 80. The drug solutions were prepared just before use.

The rats were injected intraperitoneally (i.p.) with chlorpromazine (10 mg/kg), haloperidol (2 mg/kg) or sulpiride (100 mg/kg) for 14 consecutive days. The dopamine D_2/D_3 receptor agonist, quinpirole (3 mg/kg, i.p.), was administered 24 h after the last neuroleptic dose. In some chlorpromazine-treated groups, the α_1-adrenoceptor antagonist, prazosin (0.5 mg/kg, i.p.), was injected 1 h before quinpirole.

The doses of chlorpromazine, quinpirole and prazosin are expressed as the free base. The injection volume was 2 ml/kg. Control rats were given saline or 1% Tween, the latter in the case of prazosin treatment. Each experimental group included six to seven rats.

2.3. Behavioural assessment

2.3.1. Locomotor activity

Locomotor activity was measured in an LI-10-08 automated activity cage (the Center for Medical Technologies, Poland) (47 cm × 47 cm × 41 cm), the floor of which was composed of four copper plates separated from each other by 10-mm spaces. Every time the rat crosses such a space, the electrical circuit is closed and the resultant impulse is recorded by the counter. Twenty-four hours after the last neuroleptic or saline injection, the rats were placed individually in the actometers and were allowed to adapt to the new environment for 1 h. After quinpirole or saline injection, locomotor activity was recorded every 10 min for 2 h.

Table 1
Description of behavioural activities recorded during observation session

Activity	Description
Rearing	Rearing with the head up to cage walls (the head at least 12 cm above the floor)
Head-down sniffing	Sniffing of cage floor lasting at least 3 s
Grooming	Grooming of any body surface lasting at least 3 s
Object-directed oral activity	Includes gnawing and chewing shavings or feces while standing motionless
Aggression	Rats confront each other with their noses in close contact and make rhythmic movements with their front legs or the attacked rat adopts supine submissive posturing
Vocalization	
Copulation	

Table 2
Effect of quinpirole on locomotor activity of rats pretreated with chlorpromazine, haloperidol, (±)-sulpiride or saline
Data are means ± S.E.M. ($n = 6–7$ per group). Chlorpromazine hydrochloride (10 mg/kg), haloperidol (2 mg/kg), (±)-sulpiride (100 mg/kg) or saline was administered i.p. for 14 consecutive days. Rats adapted to actometers were given quinpirole (3 mg/kg, i.p.) or saline 24 h after cessation of neuroleptic or saline treatment.

Group	Locomotor activity (counts/2 h)
Saline + saline	30.7 ± 3.5
Saline + quinpirole	196.7 ± 40.4[a]
Chlorpromazine + quinpirole	882.7 ± 177.0[a,b]
Haloperidol + quinpirole	580.8 ± 144.2[a,b]
(±)-Sulpiride + quinpirole	140.2 ± 32.9[a]

[a] Different from the saline + saline group.
[b] Different from the saline + quinpirole group. Level of significance was set as at $P <$ (Student's *t*-test)

2.3.2. Behavioural observations

Observable behavioural activities (Table 1) were evaluated and recorded by two trained observers. Twenty-four hours after the last neuroleptic or saline injection, the rats were placed in pairs in glass boxes (40 cm × 25 cm × 25 cm) with shavings on the floor and were habituated to the new environment for 1 h. Both rats were from the same treatment group. Behavioural activities within 1-min periods were observed every 10 min for 3 h, starting 10 min after quinpirole or saline injection. The absolute frequency of each behaviour category was divided by the number of observation periods in order to obtain a relative value, which facilitated data interpretation. In addition, time spent on head-down sniffing, grooming, object-directed oral activity or aggressive behaviour and the number of rearing or copulation attempts was recorded. Since statistical analysis has shown that these data do not differ from the relative frequencies of particular behavioural activities, we have not included them in this paper.

2.4. Statistical analysis

The results were subjected to analysis of variance (ANOVA) followed by Student's *t*-test for locomotor activity and the Mann–Whitney *U*-test for behavioural observations. $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Effect of quinpirole on locomotor activity of neuroleptic- or saline-pretreated rats

During 1-h adaptation, which started 24 h after the last neuroleptic dose, spontaneous locomotor activity (data ob-

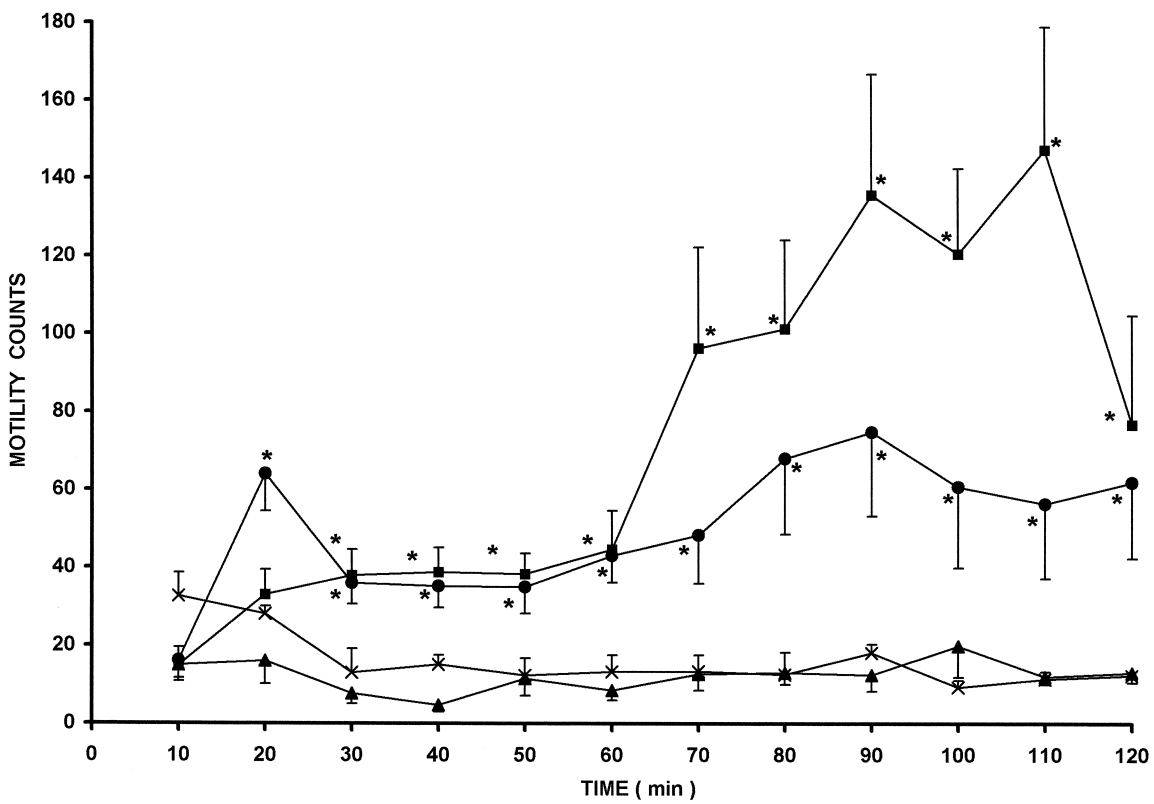

Fig. 1. The time course of the quinpirole effect on locomotor activity. Each value represents the mean ± S.E.M. for six to seven rats. Treatments were performed as described for Table 2. (*) Different from the saline + quinpirole group. Level of significance was set at $P < 0.05$ (Student's *t*-test). (-×-) Saline + quinpirole; (-■-) chlorpromazine + quinpirole; (-●-) haloperidol + quinpirole; (-▲-) (±)-sulpiride + quinpirole.

Table 3
Effect of prazosin on quinpirole-stimulated locomotor activity of rats pretreated with chlorpromazine or saline
Data are means ± S.E.M. ($n = 6–7$ per group). Rats adapted to actometers received prazosin (0.5 mg/kg, i.p.) 1 h before quinpirole (3 mg/kg, i.p.) injection given 24 h after cessation of chlorpromazine (10 mg/kg, i.p.) or saline 14-day treatment. As vehicle controls, some groups were given saline and/or 1% Tween.

Group	Locomotor activity (counts/2 h)
Saline + 1% Tween + saline	26.8 ± 4.1
Saline + prazosin + saline	10.0 ± 6.3[a]
Saline + prazosin + quinpirole	76.3 ± 19.1[a,b,c]
Saline + 1% Tween + quinpirole	180.1 ± 28.7[a]
Chlorpromazine + 1% Tween + quinpirole	1045.1 ± 173.4[a,c,d]
Chlorpromazine + prazosin + quinpirole	111.7 ± 20.0[a,b]

[a] Different from the saline + 1% Tween + saline group.
[b] Different from the saline + prazosin + saline group.
[c] Different from the saline + 1% Tween + quinpirole group.
[d] Different from the chlorpromazine + prazosin + quinpirole group.
Level of significance was set at $P < 0.05$ (Student's *t*-test).

tained between 20 and 60 min were analyzed statistically) increased only slightly in comparison with the controls [$F(2,95) = 0.06$, $P > 0.05$] (data not shown). As depicted in Table 2, quinpirole-induced locomotor activity was significantly higher than that of the controls. This locomotor hyperactivity was observed throughout the observation period (between 10 and 120 min). Chlorpromazine or haloperidol, but not sulpiride, pretreatment potentiated quinpirole-induced locomotor hyperactivity [$F(2,73) = 8.24$, $P < 0.01$]. For haloperidol, this effect appeared between 20 to 120 min, while for chlorpromazine, it appeared between 30 and 120 min. There was no significant difference between chlorpromazine- and haloperidol-pretreated groups (Fig. 1).

3.2. Effect of prazosin combined with quinpirole on locomotor activity of chlorpromazine- or saline-pretreated rats

Prazosin alone reduced spontaneous locomotor activity in rats, when compared to that of the controls, and attenuated the effect of quinpirole in saline-pretreated rats. In chlorpromazine-pretreated rats, prazosin given before quinpirole markedly attenuated locomotor hyperactivity between 20 and 120 min [$F(2,73) = 22.95$, $P < 0.01$]. The locomotor activity of the chlorpromazine + prazosin + quinpirole group was higher than that of the saline + prazosin + quinpirole group between 30 and 50 min after quinpirole injection (Table 3, Fig. 2).

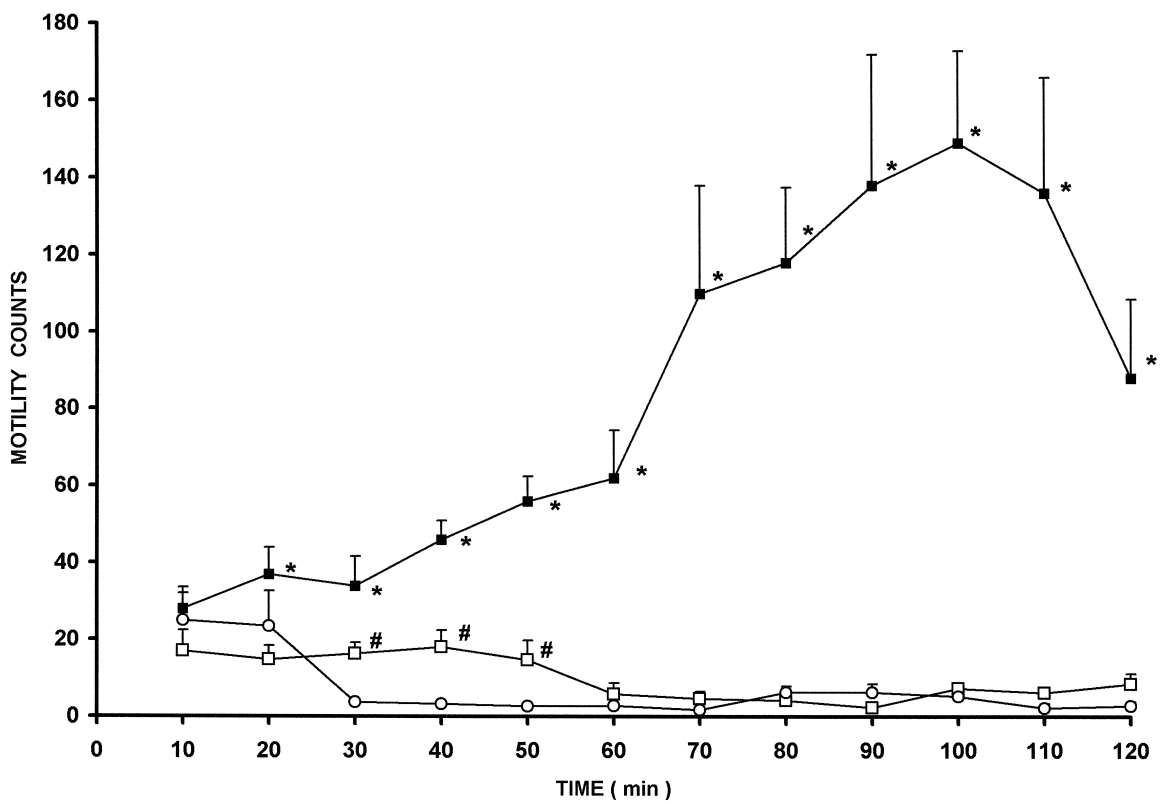

Fig. 2. The time course of the prazosin effect on locomotor activity induced by quinpirole in chlorpromazine- or saline-pretreated rats. Each value represents the mean ± S.E.M. for six to seven rats. Treatments were performed as described for Table 3. (*) Different from the chlorpromazine + prazosin + quinpirole group; (#) different from the saline + prazosin + quinpirole group. Level of significance was set at $P < 0.05$ (Student's *t*-test). (-■-) Chlorpromazine + 1% Tween + quinpirole; (-□-) chlorpromazine + prazosin + quinpirole; (-○-) saline + prazosin + quinpirole.

Table 4
Behavioural effects of quinpirole in rats pretreated with chlorpromazine, haloperidol, (±)-sulpiride or saline
Results are mean relative frequencies ± S.E.M. ($n = 6–7$ per group). Chlorpromazine hydrochloride (10 mg/kg), haloperidol (2 mg/kg), (±)-sulpiride (100 mg/kg) or saline was administered i.p. for 14 days. Rats were given quinpirole (3 mg/kg, i.p.) or saline 24 h after cessation of neuroleptic or saline treatment. Behavioural observations were made according to the schedule described in Section 2.3.2.

Behaviour	Relative frequency (%)				
	Saline + saline	Saline + quinpirole	Chlorpromazine + quinpirole	Haloperidol + quinpirole	(±)-Sulpiride + quinpirole
Rearing	10 ± 4	3 ± 2	50 ± 12[a,b]	46 ± 10[a,b]	12 ± 2[b]
Head-down sniffing	3 ± 2	28 ± 4[a]	48 ± 9[a]	100 ± 0[a,b]	87 ± 3[a,b]
Grooming	6 ± 3	9 ± 3	14 ± 6	45 ± 7[a,b]	27 ± 6[a,b]
Oral activity	0 ± 0	24 ± 8[a]	3 ± 1[b]	32 ± 4[a]	20 ± 5[a]
Aggression	0 ± 0	0 ± 0	76 ± 8[a,b]	0 ± 0	0 ± 0
Vocalization	0 ± 0	2 ± 1	55 ± 13[a,b]	6 ± 2[a,b]	3 ± 1
Copulation	0 ± 0	0 ± 0	60 ± 4[a,b]	0 ± 0	0 ± 0

[a] Different from the saline + saline group.
[b] Different from the saline + quinpirole group. Level of significance was set at $P < 0.05$ (Mann–Whitney U-test).

3.3. Effect of quinpirole on directly observable behavioural activities in neuroleptic- or saline-pretreated rats

During 1-h adaptation, which started 24 h after the last neuroleptic dose, behavioural activities (data obtained between 20 and 60 min were analyzed statistically) did not differ significantly from those of the controls. In haloperidol-pretreated rats, the time spent on head-down sniffing and the number of rearing episodes merely tended to decrease. Sulpiride-pretreated rats showed a tendency to an increased head-down sniffing and grooming. Object-directed oral activity was also observed in this group of rats (data not shown).

The behavioural effects of quinpirole are depicted in Table 4. Control rats were almost inactive for the entire 3-h observation period. We observed infrequent episodes of rearing, head-down sniffing and grooming. Quinpirole increased head-down sniffing, as compared with the saline-treated controls, and induced object-directed oral activity. The pattern of quinpirole-induced behaviour in neuroleptic-pretreated rats was markedly different from that in saline-pretreated rats. In chlorpromazine-pretreated rats, quinpirole induced aggressive behaviour with vocalization. Episodes of aggression appeared 10–20 min after quinpirole injection and continued for 5 h. (Fig. 3). In addition, frequent copulatory attempts, rearing and head-down sniffing were observed. The relative frequency of

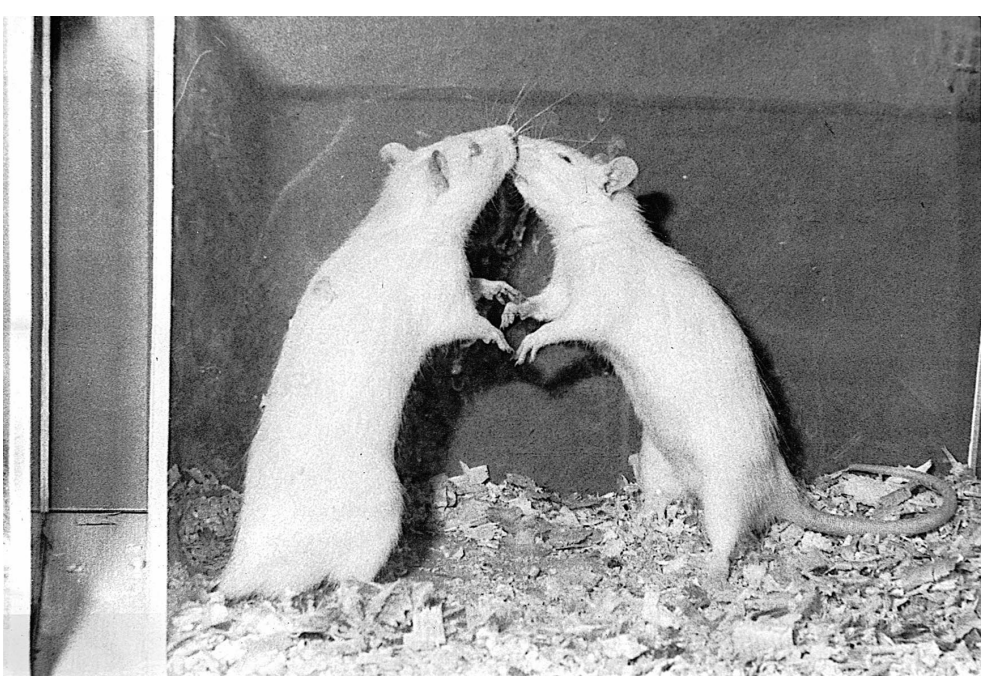

Fig. 3. Quinpirole (3 mg/kg, i.p.) injected 24 h after the last dose of chlorpromazine (10 mg/kg, i.p.) administered for 14 days induced aggressive behaviour in rats. This activity appeared 10–20 min after quinpirole injection and continued for 5 h.

Table 5
Influence of prazosin on quinpirole behavioural effects in rats pretreated with chlorpromazine or saline
Results are mean relative frequencies ± S.E.M. ($n = 6–7$ per group). Chlorpromazine hydrochloride (10 mg/kg, i.p.) was administered for 14 days. Prazosin (0.5 mg/kg, i.p.) or 1% Tween was given 1 h before quinpirole (3 mg/kg, i.p.) injection 24 h after the last dose of chlorpromazine or saline. Behavioural observations were made according to the schedule described in Section 2.3.2.

Behaviour	Relative frequency (%)				
	Saline + prazosin + saline	Saline + prazosin + quinpirole	Saline + 1% Tween + quinpirole	Chlorpromazine prazosin + quinpirole	Chlorpromazine + 1% Tween + quinpirole
Rearing	1 ± 1	3 ± 1	4 ± 2	8 ± 4	40 ± 8[a,b]
Head-down sniffing	0 ± 0	39 ± 8[c]	31 ± 5	62 ± 5[d]	32 ± 7[a]
Grooming	2 ± 1	10 ± 4	5 ± 3	4 ± 2	10 ± 3
Oral activity	0 ± 0	39 ± 3[c]	27 ± 7	34 ± 8	6 ± 1[a,b]
Aggression	0 ± 0	0 ± 0	0 ± 0	0 ± 0	80 ± 6[a,b]
Vocalization	0 ± 0	2 ± 1	0 ± 0	2 ± 1	65 ± 10[a,b]
Copulation	0 ± 0	0 ± 0	0 ± 0	9 ± 5	52 ± 4[a,b]

[a] Different from the chlorpromazine + prazosin + quinpirole group.
[b] Different from the saline + 1% Tween + quinpirole group.
[c] Different from the saline + prazosin + saline group.
[d] Different from the saline + prazosin + quinpirole group. Level of significance was set at $P < 0.05$ (Student's *t*-test).

object-directed oral activity in these rats was less than in saline-pretreated rats after quinpirole. In haloperidol-pretreated rats, the intensity of head-down sniffing, rearing and grooming after quinpirole was increased. Copulatory activity and aggression were not observed, but it should be mentioned that in our pilot study, aggressive behaviour was observed in two out of four haloperidol-treated rats in 7 out of 16 observation periods. In sulpiride-pretreated rats, quinpirole induced enhanced head-down sniffing, grooming and rearing. No significant differences in the relative frequency of object-directed oral activity were observed between haloperidol-, sulpiride- and saline-treated rats.

3.4. Effect of prazosin combined with quinpirole on directly observable behavioural activities in chlorpromazine- or saline-pretreated rats

The results of the experiment are depicted in Table 5. In saline-pretreated rats that were given prazosin before quinpirole, the frequencies of head-down sniffing and object-directed oral activity were higher than those in the saline + prazosin + saline group, but the behaviour of the former did not differ from that of the saline + 1% Tween + quinpirole group. In chlorpromazine-pretreated rats, prazosin injected before quinpirole increased the frequency of object-directed oral activity and head-down sniffing and markedly reduced the other behavioural components. When compared with the saline + prazosin + quinpirole group, the chlorpromazine + prazosin + quinpirole group showed increased head-down-sniffing and single copulatory attempts.

4. Discussion

In the present behavioural study, 14-day chlorpromazine, haloperidol or sulpiride treatment resulted in hypersensitivity of the dopamine system, which was reflected by an increased response to stimulation of dopamine D_2 postsynaptic receptors. This stimulation was induced with a high dose (3 mg/kg, i.p.) of the selective dopamine D_2/D_3 receptor agonist, quinpirole. Consistent with other reports, quinpirole induced hyperactivity in control rats, which was reflected by locomotor hypermotility, increased head-down sniffing and object-directed oral activity. These behavioural activities are considered to be exclusively or predominantly caused by the activation of dopamine D_2 postsynaptic receptors (e.g., Walters et al., 1987; Arnt et al., 1988; Meller et al., 1988, 1989). The quinpirole effects could be fully expressed, thanks to concurrent stimulation of dopamine D_1 receptors by endogenous dopamine, as D_1 and D_2 receptors have been proven to exert synergistic effects on stereotyped behaviour and locomotor activity in rats (e.g., Walters et al., 1987; Meller et al., 1988; White et al., 1988; Murray and Waddington, 1989). In this study, the behavioural effects of quinpirole in neuroleptic-withdrawn rats were more complex because they also resulted from the stimulation of other non-dopamine receptors by endogenous neurotransmitters.

Quinpirole-induced hyperlocomotion was potentiated by chlorpromazine or haloperidol but not sulpiride pretreatment. This finding is consistent with results of earlier studies that showed an increase in locomotor activity caused by the mixed dopamine D_1/D_2 receptor agonist, apomorphine, given to haloperidol-pretreated rats (e.g., Antkiewicz-Michaluk et al., 1995) or by quinpirole given to haloperidol — but not in sulpiride-pretreated rats (Prosser et al., 1989). In our study, the enhancement of the quinpirole locomotor effect was similar in both chlorpromazine- and haloperidol-pretreated groups (and even insignificantly higher in the chlorpromazine-group), whereas the most pronounced response should have been expected in the haloperidol-pretreated group because of the

greater up-regulation of dopamine D_2 receptors after the withdrawal of haloperidol, the most effective antagonist of dopamine D_2/D_1 receptors. This fact and the lack of effect of sulpiride pretreatment suggest that the increased response of neuroleptic-withdrawn rats to quinpirole is not caused by dopamine D_2 receptor supersensitivity only, but by a more complex mechanism. The unaltered quinpirole effect in sulpiride-pretreated rats cannot be explained by unchanged dopamine receptor sensitivity because recent reports have shown that chronic (21 days) sulpiride treatment (100 mg/kg, i.p.) significantly increases dopamine D_2 receptor expression in striatal and limbic structures involved in the control of locomotor activity (Hurley et al., 1996). Moreover, it seems that residual sulpiride remaining in the rat brain 24 h after drug withdrawal should be displaced from the binding sites by the high dose of quinpirole, the agonist with high affinity for the dopamine D_2 subfamily receptor (Piercey et al., 1996) because, of the neuroleptics studied, sulpiride shows the lowest binding affinity for dopamine D_2 receptors (K_i haloperidol 1.2; chlorpromazine 19; (±)-sulpiride 31; Leysen et al., 1993). The present study has shown that stimulation of α_1-adrenoceptors by endogenous noradrenaline may be a factor that potentiates the motility response to quinpirole because the α_1-adrenoceptor antagonist, prazosin, injected before quinpirole attenuated the effect of quinpirole in control rats and blocked the effect of quinpirole in chlorpromazine-pretreated rats (Table 3). One can therefore suppose that the effects of quinpirole on chlorpromazine-, haloperidol- or sulpiride-withdrawn rats differed as to intensity because of different levels of activation of dopamine D_2, D_1 receptors and α_1-adrenoceptors, resulting from adaptive changes induced by repeated administration of neuroleptics with different receptor affinities (see Section 1). To explain these differences, one should take into account not only the cooperative interaction between dopamine D_2 receptors and α_1-adrenoceptors but also a similar interaction between dopamine D_2 and D_1 receptors (e.g., Walters et al., 1987; Arnt et al., 1988; Eshel et al., 1990). Similarly, other authors reported an increased locomotor response to quinpirole when they used substances enhancing the activity of the noradrenegic system, such as the selective α_1-adrenoceptor agonist, ST587 (2-(2-chlor-5-trifluormethyl-phenyl-imino)-imidazoline) (Eshel et al., 1990; D'Aquila et al., 1992), the noradrenaline uptake inhibitor, (+)-oxaprotiline, but not the (−)-enantiomer, which has no effect on the noradrenergic system (Maj et al., 1989), the mixed α_1/α_2-adrenoceptor agonist, clonidine, given at high doses (Rubinstein et al., 1989; Eshel et al., 1990), and imipramine when given repeatedly (Maj et al., 1989; D'Aquila et al., 1992). This effect was blocked by prazosin (Rubinstein et al., 1989; Eshel et al., 1990; D'Aquila et al., 1992). Jackson et al. (1979) observed that the hyperkinetic syndrome seen in mice after cessation of chronic haloperidol treatment was antagonized by the α-adrenoceptor antagonist, phenoxybenzamine, but not by haloperidol. These data and the effects observed in our control or chlorpromazine-withdrawn rats indicate that stimulation of α_1-adrenoceptors may be an important factor to enhance dopamine D_2 receptor-induced locomotor hyperactivity.

Moreover, we observed that, in rats under supersensitive postsynaptic conditions induced by neuroleptic withdrawal, some quinpirole-elicited behavioural activities were enhanced or new activities occurred (Table 4). Some observable behaviours were mutually exclusive (e.g., aggression or copulatory attempts and increased object-directed oral activity or head-down sniffing). Enhanced rearing observed in chlorpromazine- or haloperidol-pretreated rats or intense head-down sniffing displayed mainly by haloperidol- or sulpiride-pretreated rats functionally confirm the up-regulation of the dopamine D_2 receptor. Grooming, a characteristic behavioural manifestation of dopamine D_1 receptor stimulation (e.g., Meller et al., 1988; Murray and Waddington, 1989), was intensified by haloperidol or sulpiride pretreatment. These differences in the quinpirole effect result, at least in part, from the different sensitivities of dopamine D_2 and D_1 receptors to quinpirole and endogenous dopamine, respectively, which are caused by repeated administration of neuroleptics with different antagonistic potency on dopamine receptors (see Section 1). The role of dopamine D_1 receptor stimulation is beyond question because numerous studies have shown a cooperative interaction between dopamine D_1 and D_2 receptors in the regulation of head-down sniffing, rearing and grooming (e.g., Meller et al., 1988; White et al., 1988; Murray and Waddington, 1989; Eshel et al., 1990).

In chlorpromazine-pretreated rats, quinpirole induced defensive aggressive behaviour with vocalization but without biting attack. The absence of aggression in rats injected with prazosin before quinpirole suggests that increased noradrenaline transmission at the α_1-receptor level is relevant for the effect observed. Similar aggression is caused by apomorphine, a powerful mixed dopamine D_1/D_2 receptor agonist (e.g., McKenzie, 1971), suggesting that α_1-adrenoceptor activation accompanied by strong concomitant dopamine D_2 receptor stimulation may compensate for the lack of high dopamine D_1 receptor activity. It has been evidenced that the activation of both dopamine D_1 and D_2 receptors induces aggression (Szczypka et al., 1998). The effect observed in our study was probably a result of increased noradrenaline transmission via α_1-adrenoceptors and of positive interaction between dopamine and noradrenaline systems, both of which excite general behavioural systems. It is known that slight activation of the central noradrenergic system stimulates aggression (Haller et al., 1998). This effect is mediated by postsynaptic α_2- (Haller et al., 1998) and α_1-adrenoceptors. The role of the latter is supported by reports in which aggression induced by high clonidine doses was markedly reduced by prazosin (e.g., Mogilnicka and Zazula, 1986). The well-evidenced postsynaptic adrenergic effect, in-

creased behavioural arousal (Robbins and Everitt, 1995), might be relevant for the observed quinpirole-induced aggression. Additionally, an excitatory adrenergic influence on dopamine midbrain transmission (Grenhoff et al., 1993; Sommermeyer et al., 1995; Darracq et al., 1998) was established.

The present study also showed that quinpirole-induced copulatory activity in chlorpromazine-pretreated rats results, at least partly, from increased noradrenaline transmission at α_1-adrenoceptors because prazosin given before quinpirole inhibited copulation. The mechanism of copulatory activity induced by stimulating the dopamine D_2 receptor in chlorpromazine-withdrawn rats seems to be complex. Results of studies on methoxamine (Clark et al., 1987) and prazosin (Clark et al., 1985), the former of which preferentially activates α_1-adrenoceptors, suggest that the noradrenergic system, via α_1-adrenoceptors, may play a facilitating or stimulating role in the regulation of male sexual behaviour, thus cooperating with dopamine system. It has been well-evidenced that increased dopamine neurotransmission stimulates rat sexual behaviour mainly by augmenting behavioural arousal (Agmo and Fernandez, 1989). It also cannot be excluded that enhanced noradrenergic system activity may increase dopaminergic tone. Biochemical and electrophysiological studies have revealed that the noradrenaline system stimulates, via postsynaptic α_1-adrenoceptors, dopamine neuron activity in some regions involved in the regulation of male sexual behaviour, namely in the nucleus accumbens, caudate–putamen (Sommermeyer et al., 1995), ventral tegmental area (Grenhoff and Svensson, 1993) and substantia nigra (Grenhoff et al., 1993). Increased dopamine system activity might be significant for this behaviour because the stimulatory impact of the dopamine system on rat sexual behaviour is known to be mediated not only via dopamine D_2 receptors (quinpirole effect) but also D_1 receptors (Szczypka et al., 1998). The increased copulatory activity may have been caused indirectly by rat locomotor hyperactivity as observed in the present study.

Moreover, in chlorpromazine-withdrawn rats treated with prazosin + quinpirole, the relative frequency of object-directed oral activity and head-down sniffing was higher than that in chlorpromazine-withdrawn rats treated with quinpirole alone (Table 5). One can suppose that α_1-adrenoceptor blockade increased the prevalence of dopamine-related behaviours because the frequency of other competing behaviours, such as aggression, copulatory activity and rearing, was decreased. It is also likely that a reduced level of behavioural arousal and motility or/and attenuated muscle tone induced by prazosin contributes to this effect. These changes are less likely to result from dopamine D_2/α_1-receptor interactions, though Kimura et al. (1996) reported an inhibitory effect of α_1-adrenoceptors on yawning induced by the selective dopamine D_2 receptor agonist, talipexole. The presence of such a dopamine D_2/α_1-adrenoceptor interaction would be supported by the fact that saline-pretreated rats injected with prazosin before quinpirole tended to show more head-down sniffing and object-directed oral activity than did those treated with quinpirole alone. Dickinson et al. (1988) and Eshel et al. (1990) also have shown that the noradrenaline system may modulate the expression and pattern of behaviour by influencing the function of the dopamine system. Dickinson et al. (1988) observed that prazosin pretreatment enhanced stereotyped gnawing and decreased sniffing and locomotion induced by a high dose of amphetamine or apomorphine. Eshel et al. (1990) observed that quinpirole plus a high dose of clonidine induced marked and long-lasting excitation (shaking and enhanced sniffing and rearing) in monoamine-depleted mice, while quinpirole alone induced a short-lasting increase in the intensity of sniffing and rearing.

Our results confirm indirectly the earlier suggestion that the noradrenergic system, via α_1-adrenoceptors, plays an important role in the manifestation of locomotor hyperactivity induced by stimulation of dopamine D_2 receptors. The profile of the behavioural supersensitivity induced by cessation of long-term neuroleptic treatment may depend on concurrent stimulation of dopamine D_2 receptors and α_1-adrenoceptors because α_1-adrenoceptor blockade markedly modifies the symptoms of dopamine D_2 receptor stimulation in rats pretreated with a neuroleptic that has high affinity for α_1-adrenoceptors.

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