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European Journal of Pharmacology 324 (1997) 31–37

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The behavioural effects of pramipexole, a novel dopamine receptor agonist

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Received 18 July 1996; revised 16 January 1997; accepted 17 January 1997

Abstract

Pramipexole (SND 919; 2-amino-4,5,6,7-tetrahydro-6-propyl-amino-benzthiazole-dihydrochloride) is a novel dopamine D_2 family receptor agonist with a predominant action on D_2 autoreceptors and with some D_3 vs. D_2 receptor preference. The central behavioural effects of pramipexole given subcutaneously to rats (male Wistar) and mice (Albino Swiss) are presented in this paper. Used in low doses (0.001–0.1 mg/kg), pramipexole induced locomotor hypoactivity which was antagonized by a low dose of spiperone; at higher doses (0.3, 1 mg/kg) it evoked hyperactivity which was inhibited by haloperidol, sulpiride and clozapine, but not by SCH 23390 (*R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride). Pramipexole (0.1–1.0 mg/kg) antagonized the akinesia induced by combined pretreatment with reserpine (5 mg/kg) and α-methyl-*p*-tyrosine (250 mg/kg). Pramipexole (0.1–1 mg/kg) potentiated the hyperkinetic effect of L-DOPA (L-3,4-dihydroxyphenylalanine) (50 and 200 mg/kg, together with benserazide, 50 mg/kg) in naive and monoamine-depleted (reserpine + α-methyl-*p*-tyrosine) rats. The higher doses of pramipexole (1 and 3 mg/kg) evoked stereotypy which was antagonized by pretreatment with sulpiride or clozapine. The catalepsy induced by haloperidol, spiperone or fluphenazine was antagonized by pramipexole (1–3 mg/kg). Pramipexole (1 mg/kg) induced hypothermia in mice, which was antagonized by sulpiride. The obtained results indicate that pramipexole: (i) at low doses stimulates the dopamine D_2 presynaptic autoreceptors; (ii) at higher doses stimulates dopamine D_2 postsynaptic receptors. An effect on the dopamine D_3 receptor cannot be excluded. At low doses pramipexole may have antipsychotic activity, and at higher ones antiparkinsonian activity.

Keywords: Pramipexole; Dopamine receptor agonist; Antipsychotic potential activity; Antiparkinsonian potential activity

1. Introduction

Pramipexole (SND 919; 2-amino-4,5,6,7-tetrahydro-6-propyl-amino-benzthiazole-dihydrochloride) is a novel, highly active dopamine receptor agonist with a preference for dopamine autoreceptors (Schneider and Mierau, 1987; Carter and Müller, 1991; Mierau and Schingnitz, 1992). This substance decreases brain extracellular concentrations of dopamine and its metabolites, these effects being reversed by sulpiride, but not by SCH 23390 (Carter and Müller, 1991). Pramipexole also inhibits the accumulation of L-DOPA and the α-methyltyrosine-induced reduction in dopamine, both these effects being antagonized by haloperidol, but not by SCH 23390 (Mierau and Schingnitz, 1992). Most recent binding and functional (e.g., stimulation of mitogenesis in CHO/Chinese hamster ovary/cells) studies indicate that pramipexole exhibits higher selectivity for dopamine D_3 than for D_2 and D_4 receptors (Mierau et al., 1995; Sautel et al., 1995).

Data on the behavioural effects of pramipexole show that the drug in question reduces locomotor activity and has a potent stimulating activity in dopamine-depleted animals (Mierau and Schingnitz, 1992; Svensson et al., 1994).

The present study was aimed at investigating the effects of pramipexole, in relation to its influence on the dopamine system.

2. Materials and methods

The experiments were carried out on rats (male Wistar, 250–280 g) and mice (Albino Swiss, 25–30 g), both from our breeding stock. The animals had free access to food

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0014-2999/97/$17.00
PII S0014-2999(97)00066-6

and water before the experiments and were kept at a constant room temperature (22 ± 1°C), under a natural day-night cycle. Pramipexole was dissolved in a physiological solution of saline; clozapine and L-DOPA were suspended in a 1% aqueous solution of Tween 80; all other substances were dissolved in distilled water and were injected in a volume of 2 ml/kg (rats) and 10 ml/kg (mice) i.p. Pramipexole, D-amphetamine and reserpine were given s.c. Control animals received vehicle only.

2.1. Locomotor activity in rats and mice

The locomotor activity was measured in photoresistor actometers (two light beams, two photoresistors). Pramipexole (0.01, 0.1, 0.3 and 1 mg/kg) was given 1 h before the test. Activity counts were recorded in single animals for 1 h. Each group consisted of 8 rats or 8–10 mice.

In a separate experiment the following substances were given 30 min before pramipexole (1 mg/kg): haloperidol (0.1, 0.25, 0.5 mg/kg), sulpiride (5, 25, 50 mg/kg), SCH 23390 (0.25, 0.5 mg/kg) and clozapine (3, 10, 30 mg/kg). Spiperone (1 μg/kg) was given 30 min before pramipexole (1, 10 μg/kg) injection. Activity counts were recorded 1 h after pramipexole administration for 1 h. SCH 23390 was injected also jointly with pramipexole and locomotion was measured 30 min after the injection. Each group consisted of 8 rats.

The influence of the drug on the joint action of L-DOPA + benserazide was also studied. Pramipexole (0.01, 0.1, 0.3 mg/kg) was given 30 min before L-DOPA (200 mg/kg) injection. Benserazide (25 mg/kg) was given 15 min before L-DOPA. Activity counts were recorded 30 min after L-DOPA administration for 1 h. Each group consisted of 8 rats.

2.2. Locomotor activity in monoamine-depleted rats

The influence of pramipexole (0.1, 0.3, 1 mg/kg), given alone or jointly with L-DOPA (50 mg/kg) + benserazide (100 mg/kg), on locomotor activity was also recorded in monoamine-depleted animals (reserpine, 5 mg/kg was given at 20 h and α-methyl-*p*-tyrosine (250 mg/kg) at 4 h before the experiment). Pramipexole and L-DOPA were given 1 h before the experiment; benserazide was administered 15 min before L-DOPA injection. Each group consisted of 8 rats.

2.3. Stereotypy in rats

Immediately after pramipexole (0.3, 1 and 3 mg/kg) injection, the rats were placed in wire cages. The intensity of the stereotyped behaviour was assessed according to an arbitrary 4-point scale (0 – normal, 1 – periodic sniffing, 2 – continuous sniffing, 3 – licking, 4 – gnawing and biting (according to the method of Costall and Naylor (1972)). The people scoring the behaviours were unaware of treatment. The stereotypy was evaluated every 30 or 60 min after pramipexole injection for 5 h. Sulpiride (5 and 25 mg/kg) and clozapine (10 and 30 mg/kg) were injected 30 min before pramipexole. Each group consisted of 8 rats.

2.4. Neuroleptic-induced catalepsy in rats

The catalepsy induced by neuroleptics (haloperidol, spiperone and fluphenazine) in rats was assessed according to the method of Delini-Stula and Morpurgo (1968). Each rat was tested with regard to its right and left front paws if it maintained an abnormal position for longer than 10 s. The original scoring system was doubled (the maximum response was 6 points, scored by a single rat). Pramipexole (0.3–3 mg/kg) was given 30 min after haloperidol (0.5 mg/kg), spiperone (0.3 mg/kg) or fluphenazine (0.4 mg/kg) injection.

2.5. Body temperature in mice

The rectal body temperature was measured with an Ellab T-3 thermometer every 15 min for 2 h, starting 15 min after pramipexole (0.1, 0.3 and 1 mg/kg) administration. The results are presented as the body temperature changes (Δt°C) in relation to the average temperature obtained from two preliminary measurements taken before the pramipexole treatment.

The body temperature was also measured in mice treated with sulpiride 5 mg/kg and pramipexole 1 mg/kg administered 60 and 30 min before the test respectively. Experiments were performed as described above. Each group consisted of 8 mice.

2.6. Substances used

D-Amphetamine sulphate (SmithKline and French), apomorphine hydrochloride (Sandoz), 3-(3,4-dihydroxyphenyl)-alanine (L-DOPA, Reanal), clozapine hydrochloride (Pharmaceutical Institute, Poland), fluphenazine (Byk-Gulden), haloperidol (Polfa), α-methyl-*p*-tyrosine (Sigma), pramipexole (SND 919; 2-amino-4,5,6,7-tetrahydro-6-propyl-amino-benzthiazole-dihydrochloride, Boehringer-Ingelheim), reserpine (Rausedyl, Richter), benserazide hydrochloride, *R*(+)-SCH 23390 hydrochloride (*R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride), spiperone hydrochloride and sulpiride (all Reaserch Biochemicals International).

2.7. Statistical evaluation

The data were evaluated by one-way analysis of variance (ANOVA), followed – when appropriate – by indi-

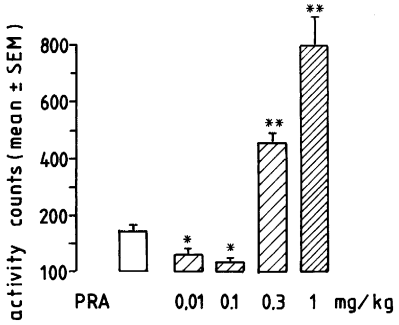

Fig. 1. Effects of pramipexole (PRA) on locomotor activity in rats. The locomotor activity was measured for 1 h, starting 1 h after s.c. injection of PRA. The data represent means ± S.E.M. ($n = 8$ rats/group). The statistical significance was calculated using ANOVA followed by Dunnett's test. * $P < 0.05$ vs. vehicle, * * $P < 0.001$ vs. vehicle.

vidual comparisons with the control, using Dunnett's test. In the case of catalepsy and stereotypy, Kruskal-Wallis ANOVA followed by Mann-Whitney *U*-test was used.

3. Results

3.1. Locomotor activity in rats and mice

Pramipexole (given 1 h before the test) in doses of 0.01 and 0.1 mg/kg inhibited locomotor activity, whereas doses of 0.3 and 1 mg/kg induced locomotor hyperactivity in rats (Fig. 1). Similar results were observed, when the locomotion was measured immediately after the injection of pramipexole (data not given).

The decrease in locomotor activity induced by pramipexole, 1 and 10 μg/kg, was reduced by spiperone, 1 μg/kg (Fig. 2).

The increase in locomotor activity, evoked by

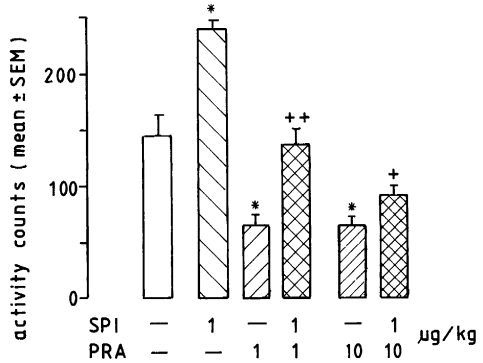

Fig. 2. Effects of spiperone (SPI) on pramipexole (PRA)-induced locomotor activity in rats. The locomotor activity was measured for 1 h, starting 1 h after s.c. injection of PRA. Spiperone (SPI, 1 μg/kg i.p.) was given 90 min before the experiment. The data are means ± S.E.M. ($n = 8$ rats/group). The statistical significance was calculated using ANOVA followed by Dunnett's test. * $P < 0.001$ vs. vehicle, + $P < 0.05$ vs. PRA 10 μg, ++ $P < 0.001$ vs. PRA 1 μg.

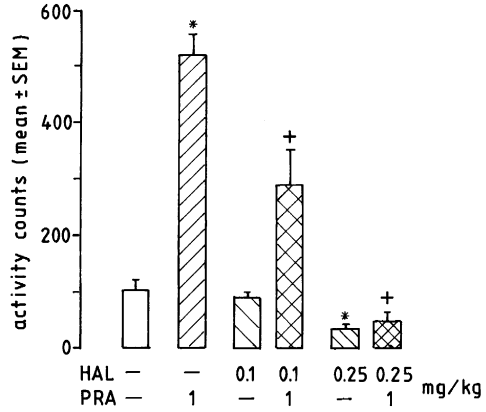

Fig. 3. Effects of haloperidol (HAL) on pramipexole (PRA)-induced locomotor hyperactivity in rats. PRA (1 mg/kg) was given s.c. at 1 h, and haloperidol (HAL, 0.1, 0.25, 0.5 mg/kg i.p.) at 90 min before the experiment. The data are means ± S.E.M. ($n = 8$ rats/group). The statistical significance was calculated using ANOVA followed by Dunnett's test. * $P < 0.001$ vs. vehicle, + $P < 0.001$ vs. PRA.

pramipexole, 1 mg/kg, was antagonized by haloperidol (0.1 and 0.25 mg/kg) and sulpiride (5, 25, 50 mg/kg) (Figs. 3 and 4). Clozapine given in doses of 10 and 30 mg/kg reduced the pramipexole (1 mg/kg)-induced locomotor hyperactivity by approx. 50% and approx. 80%, respectively (data not given). SCH 23390 (0.25 and 0.5 mg/kg, given 30 min before pramipexole or jointly with it) did not affect the pramipexole hyperlocomotion (data not shown).

The L-DOPA (200 mg/kg) + benserazide (25 mg/kg)-induced locomotor hyperactivity was increased by pramipexole (0.1 and 3 mg/kg) (Fig. 5).

In mice, pramipexole in doses of 0.01 and 0.1 mg/kg

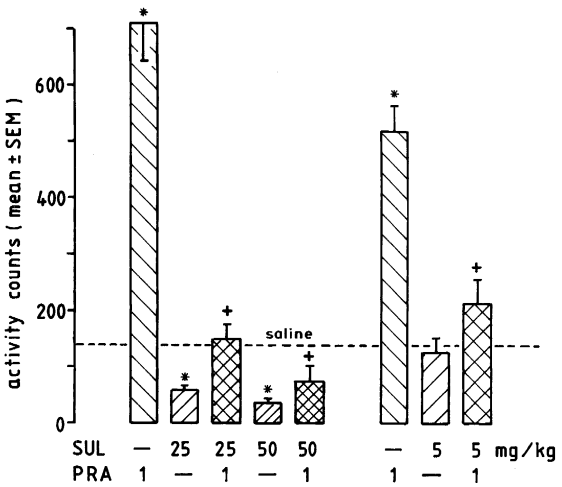

Fig. 4. Effects of sulpiride (SUL) on pramipexole (PRA)-induced locomotor hyperactivity in rats. PRA (1 mg/kg) was given s.c. at 1 h, and sulpiride (SUL, 5, 25, 50 mg/kg i.p.) at 90 min before the experiment. The data are means ± S.E.M. ($n = 8$ rats/group). The statistical significance was calculated using ANOVA followed by Dunnett's test. * $P < 0.001$ vs. vehicle, + $P < 0.001$ vs. PRA.

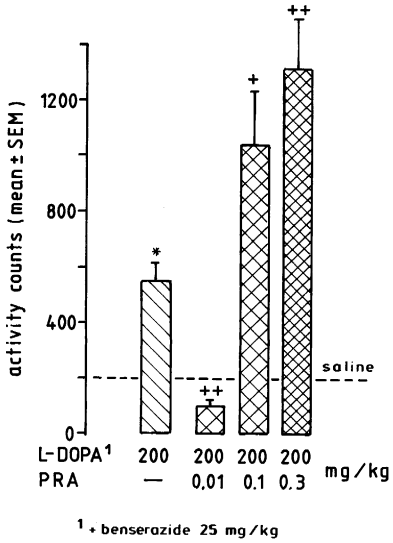

Fig. 5. Effects of pramipexole (PRA) on L-DOPA-induced locomotor hyperactivity in rats. PRA (0.01, 0.1, 0.3 mg/kg) was given s.c. at 1 h, L-DOPA (200 mg/kg i.p.) at 30 min before the experiment and benserazide (25 mg/kg i.p.) 15 min before L-DOPA). The results are presented as the means ± S.E.M. ($n = 8$ rats/group). The statistical significance was calculated using ANOVA followed by Dunnett's test. * $P < 0.001$ vs. vehicle, + $P < 0.05$ vs. L-DPOA (+benserazide), ++ $P < 0.001$ vs. L-DOPA (+benserazide).

reduced locomotor activity by 35% and 60%, respectively. The dose of 0.3 mg/kg was inactive, while the doses of 1 and 3 mg/kg increased locomotion by 160% and 120%, respectively.

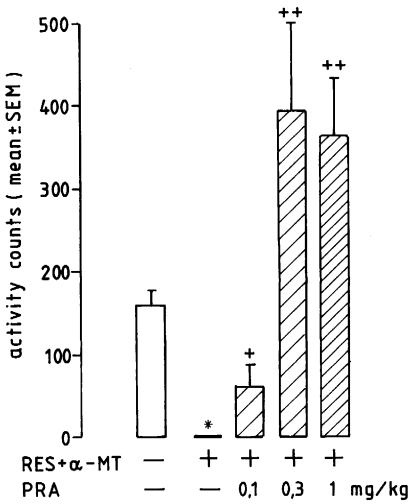

Fig. 6. Effects of pramipexole (PRA) on the locomotor activity of monoamine-depleted rats (reserpine (RES, 5 mg/kg s.c.) was given at 20 h, α-methyl-*p*-tyrosine (α-MT, 250 mg/kg i.p.) at 4 h before the experiment). PRA was injected s.c. at 1 h before the experiment. The locomotor activity was measured for 1 h. The data represent means ± S.E.M. ($n = 8$ rats/group). The statistical significance was calculated using ANOVA followed by Dunnett's test. * $P < 0.001$ vs. vehicle, + $P < 0.05$ vs. RES + α-MT, ++ $P < 0.001$ vs. RES + α-MT.

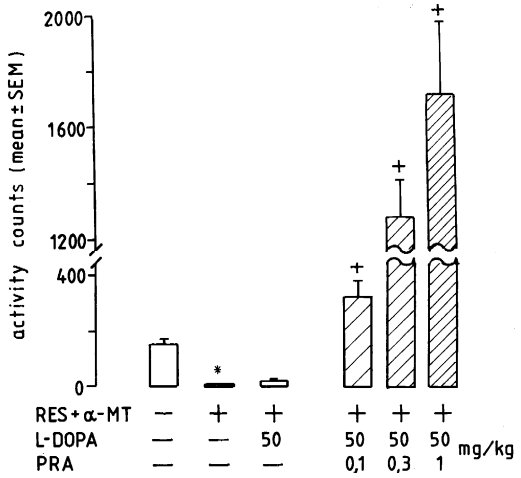

Fig. 7. Effects of combined treatment with L-DOPA + pramipexole (PRA) on the locomotor activity of monoamine-depleted rats (reserpine (RES, 5 mg/kg s.c.) was given at 20 h, α-methyl-*p*-tyrosine (α-MT, 250 mg/kg i.p.) at 4 h before the experiment). PRA (0.1, 0.3, 1 mg/kg) was given s.c. jointly with L-DOPA (50 mg/kg i.p.) 1 h before the experiment. The locomotor activity was measured for 1 h. The data represent means ± S.E.M. ($n = 8$ rats/group). The statistical significance was calculated using ANOVA followed by Dunnett's test. * $P < 0.001$ vs. vehicle, + $P < 0.001$ vs. RES + α-MT + L-DOPA.

3.2. Locomotor activity in monoamine-depleted rats

Pramipexole (0.1, 0.3 and 1 mg/kg) antagonized the akinesia induced by reserpine (5 mg/kg) + α-methyl-*p*-tyrosine (250 mg/kg) in rats (Fig. 6).

L-DOPA (50 mg/kg) + benserazide (100 mg/kg) did not influence the above-described akinesia in monoamine-depleted rats (Fig. 7) while joint administration of L-DOPA and benserazide with pramipexole (0.1, 0.3 and 1 mg/kg) induced potent locomotor hyperactivity (Fig. 7).

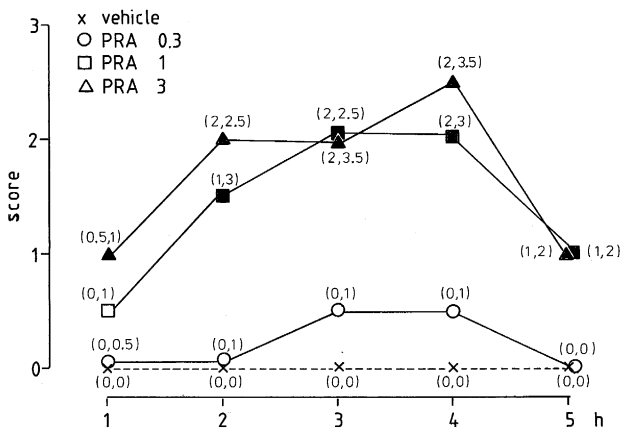

Fig. 8. Stereotypy induced by pramipexole (PRA) in rats. The stereotypy was evaluated every 60 min after s.c. injection of PRA (0.3, 1, 3 mg/kg) for 5 h. The results are presented as the median and semiquartiles (25 and 75% percentiles). Kruskal-Wallis non-parametric ANOVA followed by Mann-Whitney *U*-test were used. Solid symbols indicate results significantly different from control ($P < 0.05$ at least).

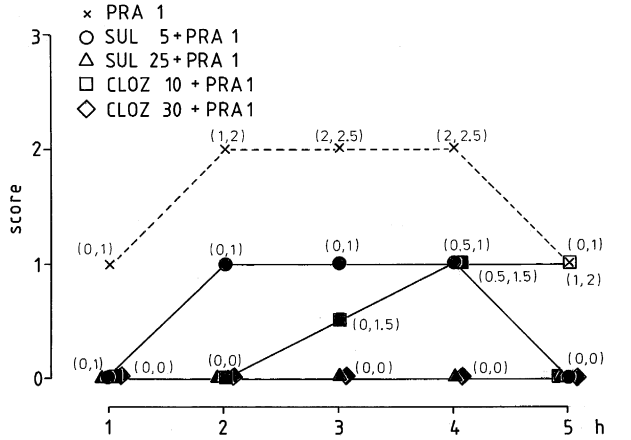

Fig. 9. Effects of sulpiride (SUL) and clozapine (CLOZ) on pramipexole (PRA)-induced stereotypy in rats. Sulpiride (SUL, 5, 25 mg/kg i.p.) or clozapine (CLOZ, 10, 30 mg/kg i.p.) was given at 30 min before pramipexole. Stereotypy was evaluated every 30 min after s.c. injection of PRA for 5 h. The results are presented as the median and semiquartiles (25 and 75% percentiles). Kruskal-Wallis non-parametric ANOVA followed by Mann-Whitney *U*-test was used. Solid symbols indicate results significantly different from control ($P < 0.05$ at least).

3.3. Stereotypy in rats

Pramipexole, 1 and 3 mg/kg, induced stereotypy in rats; however, no difference in the effects of the above doses was observed (Fig. 8). A dose of 0.3 mg/kg was inactive.

Sulpiride (5 and 25 mg/kg) and clozapine (10 and 30 mg/kg) antagonized the pramipexole (1 mg/kg)-induced stereotypy (Fig. 9).

3.4. Neuroleptic-induced catalepsy in rats

Haloperidol (0.5 mg/kg)-induced catalepsy in rats was antagonized by pramipexole at a dose of 3 mg/kg while a dose of 1 mg/kg produced no significant effect (Fig. 10). The catalepsy evoked by spiperone (0.3 mg/kg) was also antagonized by pramipexole at the high dose (3 mg/kg), but a lower dose (1 mg/kg) was ineffective (Fig. 10).

Pramipexole given in either of the three doses (0.3, 1, 3 mg/kg) abolished the catalepsy induced by fluphenazine, 0.4 mg/kg (Fig. 10).

3.5. Body temperature in mice

Pramipexole, 1 mg/kg, decreased body temperature in mice (Fig. 11); at lower doses (0.1, 0.3 mg/kg) it did not change this parameter (data not given). The hypothermia was reduced by sulpiride, 5 mg/kg (Fig. 11).

4. Discussion

Our results indicate that pramipexole in a low range of doses (0.001–0.1 mg/kg) inhibits the locomotor activity of rats and mice. In rats, this inhibition was antagonized by pretreatment with a low dose of spiperone (1 μg/kg). It is well known that apomorphine, a classical dopamine agonist, given in a low dose induces locomotor hypoactivity

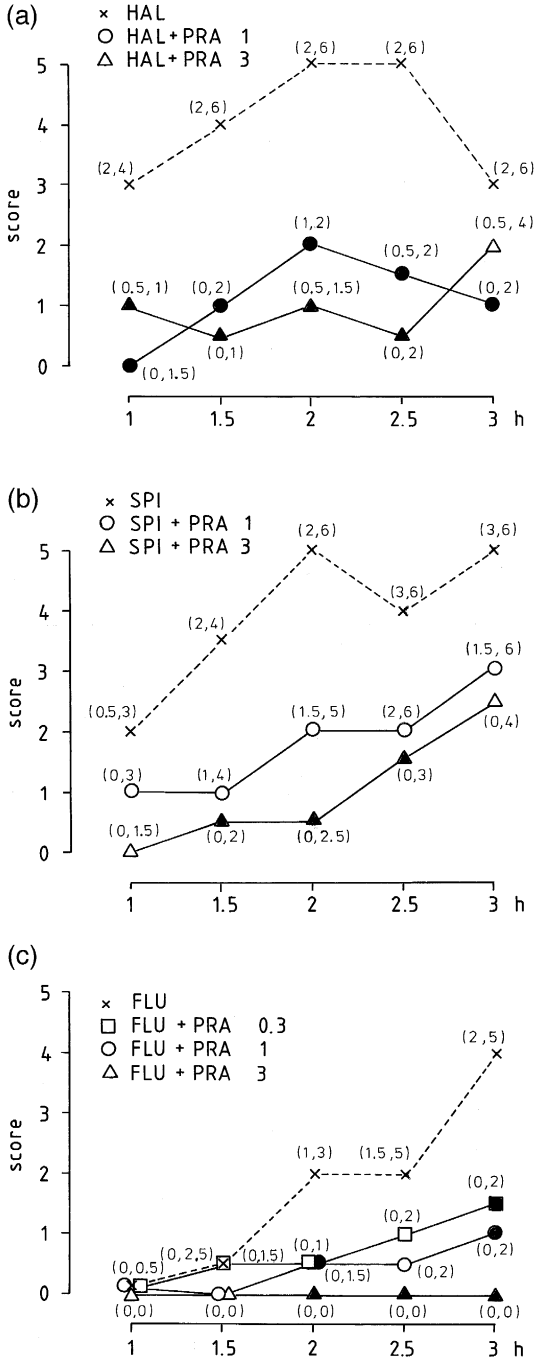

Fig. 10. Effects of pramipexole (PRA) on neuroleptic-induced catalepsy in rats. PRA (0.3, 1, 3 mg/kg) was given s.c. 30 min after haloperidol (HAL, 0.5 mg/kg i.p.), spiperone (SPI, 0.3 mg/kg i.p.) or fluphenazine (FLU, 0.4 mg/kg i.p.) injection. The catalepsy was assessed every 30 min, after neuroleptic administration, for 3 h. The results are presented as the median and semiquartiles (25 and 75% percentiles). Kruskal-Wallis non-parametric ANOVA followed by Mann-Whitney *U*-test was used. Solid symbols indicate results significantly different from control ($P <$ 0.05 at least).

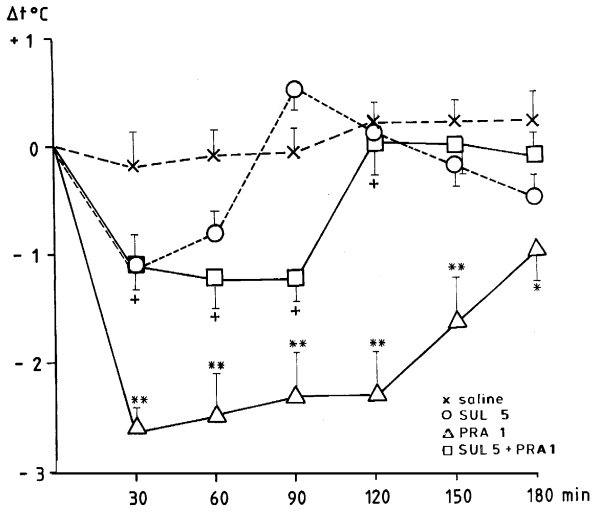

Fig. 11. Effects of sulpiride (SUL) on pramipexole (PRA)-induced hypothermia in mice. Sulpiride (SUL, 5 mg/kg i.p.) was given at 60 and PRA (1 mg/kg s.c.) at 30 min before the experiment. The rectal body temperature was measured for 3 h. The data represent means ± S.E.M. ($n = 8$ mice/group). The statistical significance was calculated using ANOVA followed by Dunnett's test. * $P < 0.05$ vs. vehicle, ** $P < 0.001$ vs. vehicle, $^{+}$ $P < 0.001$ vs. PRA 1.

which is antagonized by low doses of dopamine antagonists (e.g., spiperone) or lesion of the substantia nigra (e.g., Maj et al., 1977). Many other data also indicate the presynaptic action of low doses of apomorphine (e.g., Aghajanian and Bunney, 1974; Carlsson, 1975; Strömbom, 1976). Therefore it may be assumed that pramipexole decreases locomotor activity by stimulating presynaptic dopamine receptors. Pramipexole-induced locomotor hypoactivity was also reported by Mierau and Schingnitz (1992) and Svensson et al. (1994).

Pramipexole in higher doses (from 0.3 mg/kg upwards) increased the locomotor activity of rats and mice. This elevation is inhibited by haloperidol, sulpiride and clozapine, the two former drugs being used in doses which – when given alone – did not attenuate the locomotor activity. The pramipexole-induced hyperactivity was not inhibited by SCH 23390, a dopamine D_1 receptor antagonist. Hence it seems that pramipexole enhances locomotor activity by stimulating postsynaptic dopamine D_2 receptors. Some other authors (Svensson et al., 1994) also observed this locomotor hyperactivity.

Pramipexole in doses of 1 and 3 mg/kg produced stereotypy in rats, an effect which was inhibited by sulpiride and clozapine. It may be therefore concluded that pramipexole-induced stereotypy results from stimulation of postsynaptic dopamine D_2 receptors. Our other findings lead to a similar conclusion, as they indicate that pramipexole abolished the catalepsy evoked by neuroleptics (haloperidol, spiperone, fluphenazine).

A more potent stimulating activity was shown by pramipexole in monoamine-depleted rats. The drug antagonized the reserpine + α-methyl-*p*-tyrosine-induced locomotor sedation, exerting a stimulating effect already in doses which decreased this activiy in normal animals. In monoamine-depleted rats, these doses enhanced also the action of L-DOPA. A similar, more potent stimulating action of pramipexole was observed by Mierau and Schingnitz (1992) in monoamine-depleted monkeys (pretreated with *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)), or in rats with a unilateral lesion of the medial forebrain bundle. Thus the above results indicate that pramipexole, given alone or together with L-DOPA, may be a potential antiparkinsonian drug.

It is well known that apomorphine and other dopamine stimulants decrease body temperature in mice by stimulation of dopamine receptors. Our data show that pramipexole also caused hypothermia, which was inhibited by sulpiride. Therefore also the latter results indicate that pramipexole stimulates postsynaptic dopamine D_2 receptors.

Thus a number of the above findings show that pramipexole in higher doses stimulates postsynaptic dopamine D_2 receptors. A similar conclusion was also reached by Ferrari et al. (1993), who had found that pramipexole evoked penile erection, an effect blocked by sulpiride. A decrease in the prolactin level, reported by Domae et al. (1990), also points to an agonistic action on postsynaptic dopamine D_2 receptors.

According to Svensson et al. (1994), pramipexole reduces locomotion in rats via stimulation of postsynaptic dopamine D_3 receptors. The postsynaptic localization of dopamine D_3 receptors was suggested by Waters et al. (1993). The preference of pramipexole for dopamine D_3 vs. D_2 receptors has been reported (see Section 1). According to our results, the pramipexole-induced locomotor inhibition was reduced by low doses of spiperone, which block presynaptic dopamine D_2 receptors. It may therefore be concluded that pramipexole-induced locomotor inhibition is, at least in part, caused by stimulation of presynaptic dopamine D_2 receptors.

7-OH-DPAT (7-hydroxy-dipropylaminotetralin), another dopamine agonist with a preference for dopamine D_3 vs. D_2 receptors (Lévesque et al., 1992), induces hypothermia which is blocked by the putative D_3 receptor antagonist AJ 76 (*cis*-(+)-5-methoxy-1-methyl-2-(*n*-propylamino)tetralin) (Millan et al., 1994). Our results indicate that the pramipexole-induced hypothermia may also be reduced by sulpiride, a dopamine D_2 receptor antagonist.

In conclusion, our results indicate that both pre- and postsynaptic dopamine D_2 receptors are involved in the action of pramipexole on the dopamine system, low doses leading to sedation and high ones to stimulation. However, the above findings do not exclude participation of D_3 receptors, especially in the sedative action. The neuropharmacological profile of pramipexole shows that it may be an antiparkinsonian drug. When given in low doses, the drug is likely to exert an antipsychotic effect.

Acknowledgements

The authors wish to thank Boehringer-Ingelheim for the generous gift of pramipexole and the Pharmaceutical Institute, Poland, for the kind donation of clozapine.

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