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Dopamine D1 receptor agonists induce penile erections in rats

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Abstract

The dopamine receptor agonist apomorphine has been recently introduced in the treatment of erectile dysfunction. While it is well established that dopamine D2-like receptors play a crucial role in this effect, conflicting result are reported in the literature as for the role of dopamine D1-like receptors. The aim of this study was to determine the effect of systemic administration of dopamine D1-like receptor agonists on penile erection in rats. Male Wistar rats were treated with three different, and not structurally related, dopamine D1-like receptor agonists: the partial agonists SKF38393 ((+) 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine) and CY 208-243 ((−)-4,6,6*a*,7,8,12*b*-exahydro-7-methylindole [4,3-*ab*]fenantridine), and the full agonist A 77636 ((−)-(1*R*,3*S*)-3-Adamantyl-1-(aminomethyl)-3,4-dihydro-5,6-dihydroxy-1*H*-2-benzopyran hydrochloride). All three compounds dose-dependently increased the number of penile erections, with the full agonist A77636 showing a more pronounced effect with respect to the other two. Moreover, the dopamine D1-like receptor antagonist SCH 23390 ((*R*)-(+)-7-chloro-8-hydorxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine) dose-dependently antagonised A77636 effect. These results show that systemic administration of dopamine D1-like receptor agonists induce penile erection in rats. This observation suggests that dopamine D1-like receptor agonists might be considered as a possible alternative to apomorphine in the treatment of erectile dysfunction, thus avoiding the typical side effects related to the stimulation of dopamine D2-like receptors such as nausea.

Keywords: Penile erection; Dopamine D1-like receptor agonist; Erectile dysfunction

1. Introduction

The dopamine receptor agonist apomorphine has been recently introduced in the treatment of erectile dysfunction (Heaton et al., 1995; Padma-Nathan et al., 1999), showing to be particularly useful for those patients with cardiovascular problems which cannot be treated with sildenafil (Fagan et al., 2001). However, treatment with apomorphine induces nausea in about 10% of patients, especially at the beginning of treatment, due to stimulation of dopamine D2 receptors in the chemoreceptor trigger zone (Altwein and Keuler, 2001; Mulhall et al., 2001; Von Keitz et al., 2002).

The ability of dopamine receptor agonists to elicit penile erection has been described since 1975 (Baraldi and Benassi-Benelli, 1975) and successively confirmed by a number of studies (see Melis and Argiolas., 1999). The main neuroanatomical substrates of this effect appear to be the paraventricular nucleus and the medial pre-optic area of the hypothalamus (Melis et al., 1987; Argiolas et al., 1987; Pehek et al., 1989; Hull et al., 1993).

Both dopamine D1- and D2-like receptors seem to be involved in the control of this response: microinjection either of dopamine D1 receptor agonists into the medial pre-optic area (Hull et al., 1993; Pehek et al., 1989) or of dopamine D2 receptor agonists in the paraventricular nucleus (Melis et al., 1987) results in an increase of penile erection episodes. Less clear appears to be the picture emerging from studies examining the effect of systemic administration of dopamine receptor agonists. On the one hand, a number of studies show the ability of dopamine D2 receptor agonists to elicit penile erections, suggesting a positive role for this subtype of dopamine receptors (Doherty and Wisler, 1994; Ferrari and Giuliani, 1993; Ferrari et al., 1993). On the other hand, conflicting results are reported in the literature as for the role of dopamine D1 receptors, with some studies suggesting a stimulant effect (Dehpour et al., 1995; Ferrari and Giuliani, 1997; Hull, 1995), and others suggesting an inhibitory effect on this response (Zarrindast et al., 1992).

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To our knowledge, only one study reports the ability of systemic administration of a dopamine D1 receptor agonist to elicit penile erection (Serra et al., 1988): we have reported preliminary results showing that SKF 38393 increases penile erection episodes in rats and that this effect is antagonised by SCH 23390. In this study only one dopamine D1 receptor agonist and only one dose of the dopamine D1 receptor antagonist have been examined.

The aim of the present study was to determine the effect of systemic administration of dopamine D1-like receptor agonists on penile erection in rats. The potential ability of dopamine D1-like receptor agonists to induce penile erections might offer a possible alternative to apomorphine in the treatment of erectile dysfunction, thus avoiding the side effects of the stimulation of dopamine D2-like receptors, such as nausea.

To this end we examined the effect of three different, and not structurally related, dopamine D1-like receptor agonists: the partial agonists SKF38393 and CY 208-243, and the full agonist A77636. All three compounds elicited an increase in the number of penile erections, with the full agonist A 77636 showing a more pronounced effect. Finally, we studied the effect of the dopamine D1 receptor antagonist SCH 23390 on A 77636-induced erections.

2. Materials and methods

The present study was carried out in accordance to the Italian law, which allows experiments on laboratory animals only after submission of a research project to the competent authorities, and in accordance to the "Principles of laboratory animal care" (NIH publication no. 85-23, revised 1985).

2.1. Subjects

Male Wistar rats (Harlan, Italy) weighing initially 160–200 g were used as subjects. They were housed two to three per cage in air-conditioned rooms. The rooms were lit between 0800 and 2000 h and maintained at a temperature of 22 ± 2 °C and humidity 50–60%.

2.2. Drugs and treatments

The partial dopamine D1-like receptor agonist SKF38393 ((+) 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine, Sigma)(Setler et al., 1978) was dissolved in distilled water. Forty subjects were divided into four groups ($n = 10$) and treated with distilled water or SKF 38393 at doses of 2.5, 10 and 20 mg/kg intraperitoneally (i.p.).

The partial dopamine D1-like receptor agonist CY 208-243 ((−)-4,6,6*a*,7,8,12*b*-exahydro-7-methylindole [4,3-*ab*]fenantridine, Tocris)(Markstein et al., 1988) was dissolved in a few drops of glacial acetic acid and distilled water was added up to the final volume (20 μl in 6-ml water). Forty-one subjects were divided into five groups ($n = 8–9$) and treated with either vehicle or CY 208-243 at doses of 0.0625, 0.125, 0.25 and 0.5 mg/kg subcutaneously (s.c.).

The full dopamine D1-like receptor agonist A 77636 ((−)-(1*R*,3*S*)-3-Adamantyl-1-(aminomethyl)-3,4-dihydro-5,6-dihydroxy-1*H*-2-benzopyran hydrochloride, Sigma)(Kebabian et al., 1992) was dissolved in distilled water. Forty-one subjects were divided into five groups ($n = 8–9$) and treated with either distilled water or A 77636 at doses of 0.375, 0.75, 1.5 and 3 mg/kg s.c. In a subsequent experiment, 51 animals were divided into five groups ($n = 10–11$): four groups were treated with the dopamine D1-like receptor antagonist SCH 23390 ((*R*)-(+)-7-chloro-8-hydorxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, Sigma, dissolved in distilled water)(Iorio et al., 1983), at the doses of 0.025, 0.05 and 0.1 mg/kg s.c. or its vehicle, and immediately afterwards with A 77636 at the dose of 0.75 mg/kg s.c. The last group was treated with two injections of

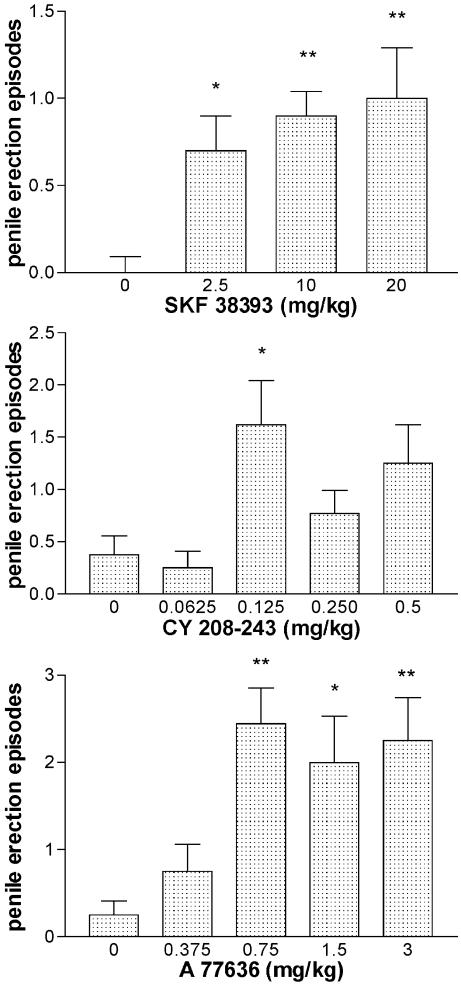

Fig. 1. Penile erection episodes induced by the dopamine D1 receptor agonists SKF 38393, CY 208-243 and A 77636. Each value represents mean ± S.E.M. from 8 to 10 subjects. Penile erections episodes have been recorded for 60 min, starting 5 min after agonist administration. *$P < 0.05$, **$P < 0.01$: effect of agonists with respect to the control group (ANOVA followed by Newman–Keuls test).

distilled water. A further experiment was performed to test the effect of SCH 233390 on its own: 20 rats were divided into four groups ($n=5$) and treated with SCH 23390 at the doses of 0.025, 0.05 and 0.1 mg/kg s.c. or its vehicle. Injection volume was 1 ml/kg for all drug solutions.

The doses of the drugs were chosen within a range known to show a reasonable selectivity, on the basis of their pharmacological effects described in the literature (Fenu et al., 2001; Serra et al., 1988; Wirtshafter and Asin, 2001; but see Foote et al., 1988).

2.3. Behavioural observation

The rats were individually placed into transparent Perspex cages (25 × 20 × 25 cm) and left for 60 min habituation to the new environment before starting the behavioural observation. Dopamine D1-like receptor agonists and the dopamine D1-like receptor antagonist SCH 23390 were administered 5 min before observation. The number of penile erection episodes was recorded for 60 min by experimenters unaware of the treatment received by the subjects. All experimental sessions were videotaped. Experiments were performed between 0900 and 1800 h in a soundproof room.

2.4. Statistics

The results were analysed by one-way analysis of variance (ANOVA), followed by Newman–Keuls test.

3. Results

The partial dopamine D1-like receptor agonist SKF 38393 [ANOVA: $F(3,36)=4.88$; $P=0.0059$] (Fig. 1, top panel) and the full dopamine D1-like receptor agonist A 77636 [$F(4,36)=5.79$; $P=0.01$] (Fig. 1, low panel) elicited a dose-dependent increase of penile erection episodes. The partial dopamine D1-like receptor agonist CY 208-243 induced a significant increase in penile erection episodes only at the dose of 0.125 mg/kg [$F(4,36)=4.0$; $P=0.0086$] (Fig. 1, mid panel). Treatment with the dopamine D1-like receptor antagonist SCH 23390 antagonised in a dose-dependent manner A 77636-induced penile erection episodes [$F(4,46)=10.06$; $P=6\times10^{-6}$] (Fig. 2). Administration of SCH 23390 on its own failed to affect the number of penile erections [number of penile erections, vehicle: 0.2 ± 0.2; SCH 23390 0.025 mg/kg: 0.2 ± 0.2; 0.05 mg/kg: 0.2 ± 0.2; 0.1 mg/kg: 0 ± 0; ANOVA: effect of treatment: $F(3,16)=0.333$, $P=0.8$].

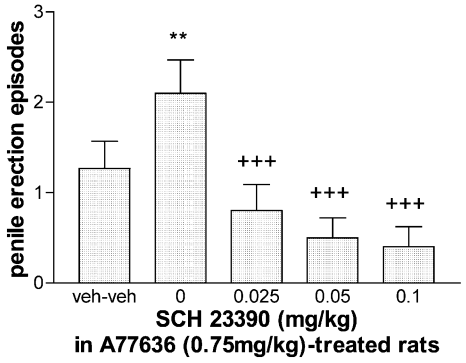

Fig. 2. Effect of the dopamine D1 receptor antagonist SCH 23390 on A 77636-induced penile erections. VEH = vehicle. Each value represents mean ± S.E.M. from 10 to 11 subjects. Penile erections episodes have been recorded for 60 min, starting 5 min after agonist administration. SCH 23390 was administered immediately before A 77636. *$P<0.05$, **$P<0.01$: effect of agonists with respect to the control group; $^{+++}P<0.001$: effect of SCH 23390 with respect to the group treated with A 77636 alone (ANOVA followed by Newman–Keuls test).

4. Discussion

The results show that systemic administration of three different and not structurally related dopamine D1-like receptor agonists induces an increased number of penile erection episodes. In particular, SKF 38393 and A 77636 induced a dose-dependent effect, with A 77636 effect reaching a *plateau* in a dose range including the three higher doses. CY 208-243 showed an inverted U-shaped dose–response curve. A 77636, which is a full agonist, resulted in a more pronounced effect than that observed with the partial agonists SKF 38393 and CY 208-243. Moreover, the dopamine D1-like receptor antagonist SCH 23390, which by itself did not affect the number of penile erections, dose-dependently antagonised the A 77636 effect. These observations suggest that the observed effects are due to the ability of these compounds to stimulate dopamine D1 receptors.

These results are consistent with the observation that blockade of dopamine D1 receptors results in a decreased number of penile erection episodes induced by apomorphine (Dehpour et al., 1995; Hull, 1995).

At variance with these observations, it has been reported that the stimulating effect on penile erection of low doses of apomorphine was antagonised not only by the dopamine D2 receptor antagonist L-sulpiride but also by the dopamine D1 receptor agonist SKF 38393. Conversely, the effect of high doses of apomorphine was potentiated by the dopamine D1 receptor antagonist SCH 23390 (Zarrindast et al., 1992). The authors of this study concluded that stimulation of dopamine D1 receptors exert an inhibitory effect on this response, as opposite to D2 receptor stimulation.

The observation of the inverted U-shaped dose–response curve of CY 208-343 in the present study may reconcile these apparently conflicting results. The inhibitory effect on penile erection of an excessive dopamine D1 receptor stimulation might explain both the inhibitory effect of the dopamine D1 agonist and the potentiating effect of the dopamine D1 antagonist on the effect of low and high doses of apomorphine, respectively.

However, the lack of effect of CY 208-243 at the higher doses might be explained also by its activity at 5-HT_{1A} receptors (Foote et al., 1988). Indeed, the 5-HT_{1A} receptor agonist 8-OH-DPAT was reported to decrease ex copula erections in rats (Rehman et al., 1999) and rhesus monkeys (Pomerantz et al., 1993).

Finally, the present results might lead to important clinical developments, suggesting that dopamine D1-like receptor agonists might be used in the treatment of erectile dysfunction as a possible alternative to apomorphine, thus avoiding the typical side effects related to the stimulation of dopamine D2-like receptors such as nausea (Altwein and Keuler, 2001; Mulhall et al., 2001; Von Keitz et al., 2002).

Acknowledgements

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