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Interactions of drugs acting on central dopamine receptors and cholinoceptors on yawning responses in the rat induced by apomorphine, bromocriptine or physostigmine

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1 Yawning was induced by subcutaneous (s.c.) injection of low doses of apomorphine to rats. This effect decreased with increasing doses of the drug.

2 Intraperitoneal (i.p.) pretreatment of animals with sulpiride (D_2-receptor blocker) reduced the frequency of the yawns induced by apomorphine, while SCH 23390 (D_1-receptor blocker, s.c.) pretreatment increased the small number of yawns which was induced by higher doses of apomorphine. Administration of SCH 23390 alone to rats also produced a low degree of yawning.

3 Apomorphine-induced yawning was decreased in animals treated with SK&F 38393 (D_1-agonist, i.p.), atropine (i.p.) or theophylline (i.p.).

4 Intraperitoneal injection of bromocriptine (D_2-agonist) in rats also induced dose-dependent yawning. The effect was decreased in animals pretreated with sulpiride, while SCH 23390 pretreatment did not change bromocriptine-induced yawning significantly. Pretreatment of animals with SK&F 38393, atropine or theophylline reduced the number of yawns induced by bromocriptine.

5 Physostigmine (i.p.) but not neostigmine (i.p.) also induced yawning. The effect was antagonized by atropine or theophylline but not by sulpiride. Administration of SK&F 38393 decreased yawning induced by physostigmine. This inhibitory influence of SK&F 38393 was reduced by SCH 23390 in pretreated animals. Treatment of animals with SCH 23390 or bromocriptine increased the frequency of yawns induced by physostigmine.

6 It is concluded that D_2-receptor activation elicits yawning through influence on cholinergic mechanisms, whereas D_1-receptor stimulation decreases yawning behaviour by a negative influence on the cholinergic system.

Introduction

Biochemical and pharmacological evidence indicate that two different dopamine receptors, termed D_1 and D_2 mediate the dopamine functions in brain (Garau *et al.*, 1978; Kebabian & Calne, 1979; Stoof & Kebabian, 1984; Onali *et al.*, 1985; Weiss *et al.*, 1985). These two categories of dopamine receptors are distinct molecular entities (Nielsen *et al.*, 1984; Dumbrille-Ross *et al.*, 1985) with different distributions (Altar *et al.*, 1985; Dawson *et al.*, 1985; Martres *et al.*, 1985; Scatton & Dubois, 1985).

Both D_1- and D_2-dopamine receptors, which exist in striatum, can stimulate and inhibit the striatal cyclic AMP formation respectively (Onali *et al.*, 1984; Stoof & Kebabian, 1981; 1984). Striatum contains the highest concentration of acetylcholine in the brain (Sethy *et al.*, 1973). Available evidence suggests that dopamine receptors have a regulatory role on striatal acetylcholine (Sethy & Van Woert, 1974). The opposing effects of D_1- and D_2-receptors on striatal cholinergic neurones have also been shown (Fage & Scatton, 1986).

Yawning can be induced in experimental animals by the dopamine receptor agonists apomorphine, norpropylnorapomorphine and lisuride (Mogilnicka & Klimek, 1977; Baggio & Ferrari, 1983). It has been proposed that stimulation of dopamine autoreceptors, and therefore inhibition of dopaminergic transmission in the brain, causes yawning (Yamada & Furukawa, 1980; Protais *et al.*, 1983; Baggio & Ferrari, 1983). This behaviour appears to be cen-

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trally mediated (Dourish *et al.*, 1985) and due to septal and striatal D_2-receptor activation (Yamada *et al.*, 1986), although results obtained by some workers (Morelli *et al.*, 1986) contradict the hypothesis that apomorphine produces yawning by acting on dopamine autoreceptors.

Some investigators have suggested that central cholinergic mechanisms are involved in yawning behaviour (Urbá-Holmgren *et al.*, 1977; Yamada & Furukawa, 1980; Ushijima *et al.*, 1984). Drugs acting on both cholinoceptors and dopamine receptors have been used to investigate the influence of D_1- and D_2-receptors on yawning behaviour.

Methods

Male albino rats weighing 200–250 g were used in these experiments. They were housed 10 per cage, in a room on a 12 h/12 h light-dark cycle at 20 ± 2°C. Food and water were freely available except during the time of experiments.

Behavioural observations

Rats were placed individually in a plastic cage at 20 ± 2°C during experiments and allowed to habituate for 15 min before injection of drugs. No more than two rats were observed simultaneously. Yawning was counted by direct observation after drug injection. The results were recorded and expressed as number of yawns in a 60 min period. The statistical analysis of the data was performed by ANOVA followed by Student's *t* test. Difference with $P < 0.05$ were considered statistically significant.

Drugs

The drugs used were apomorphine hydrochloride (MacFarlan Smith Ltd, England), bromocriptine (Sandoz, Switzerland), SCH 23390 (R-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol maleate; Schering, Italy), sulpiride (Delagrange, France), SK&F 38393 (1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride; R.B.Inc. Wayland, U.S.A.), atropine sulphate (E. Merck, Germany), physostigmine salicylate (Sigma, England), neostigmine methylsulphate (amp., Waldemar-Weimer, Germany) and theophylline (Sigma, England). Bromocriptine was dissolved in saline by the use of crystalline tartaric acid and a few drops of alcohol. Other drugs were dissolved in saline. The drugs were prepared immediately before use and were injected in a volume 1 ml kg^{-1}.

Results

Effects of drugs on yawning induced by apomorphine

Figure 1 illustrates the yawning induced by different doses of apomorphine and the effects of SCH 23390 or sulpiride on this behaviour. Subcutaneous (s.c.) injection of low doses of apomorphine (0.1, 0.3 and 0.6 mg kg^{-1}) induced yawning in rats. The maximal effect was observed at 0.1 mg kg^{-1}. It decreased with higher doses. Pretreatment of animals with sulpiride (10 mg kg^{-1}, i.p., 30 min) diminished the number of yawns induced by apomorphine (0.1–0.6 mg kg^{-1}, s.c.). SCH 23390 pretreatment (0.05 mg kg^{-1}, s.c., 30 min) potentiated the frequency of the small number of yawns elicited by higher doses (0.6 mg kg^{-1}, s.c.) of apomorphine. Administration of SCH 23390 alone (0.05 mg kg^{-1}, s.c.) also caused a low degree of yawning with a mean ± s.e. of 5.9 ± 2.1 (not shown). This effect of the drug was observed in 80% of animals.

SK&F 38393 (8 mg kg^{-1}, i.p.) reduced the number of yawns produced by apomorphine injection (Table

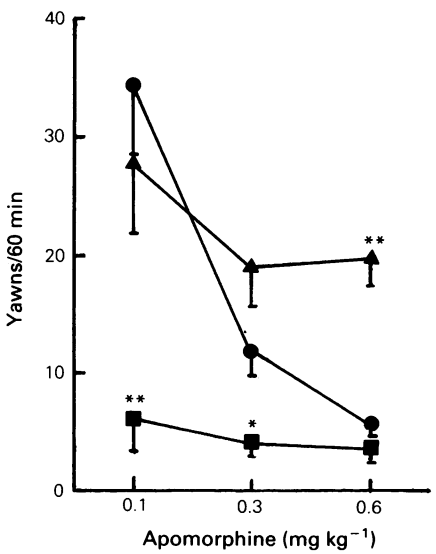

Figure 1 Yawning induced by administration of different doses of apomorphine in presence or absence of antagonists. Rats were injected subcutaneously with apomorphine alone (●) or with either SCH 23390 (▲) (0.05 mg kg^{-1}, s.c.) or sulpiride (■) (10 mg kg^{-1}, i.p.) 30 min before apomorphine injection. The number of yawns was counted immediately after administration of apomorphine for 60 min. Each point is the mean for minimum of 8 experiments; vertical bars show s.e.mean. * $P < 0.05$; ** $P < 0.001$: significantly different from apomorphine-treated group.

Table 1 Frequency of yawns induced by apomorphine (0.3 mg kg^{-1}) in rats in presence or absence of other drugs

Drug	mg kg^{-1}	Yawns/60 min Mean ± s.e.	n
Saline	1 ml	12.1 ± 2.3	8
SK&F 38393	8	2.8 ± 1.7*	6
Theophylline	25	0.2 ± 0.2**	6
Atropine	10	0.0 ± 0.0**	6

SK&F 38393 (i.p.), theophylline (i.p.) and atropine (i.p.) were injected respectively 0, 60 and 10 min before apomorphine injection (s.c.)
* $P < 0.01$; ** $P < 0.001$: significantly different from saline control group.

1). Yawning induced by apomorphine was abolished in animals pretreated with theophylline (25 mg kg^{-1}, i.p., 60 min) or atropine (10 mg kg^{-1}, i.p., 10 min).

Effects of drugs on bromocriptine-induced yawning

Dose-response curves for yawns induced by bromocriptine (2–16 mg kg^{-1}, i.p.) in the presence or absence of D_1- or D_2-receptor blockers are shown in Figure 2. Pretreatment of rats with sulpiride (10 mg kg^{-1}, i.p., 30 min) decreased the yawns induced by different doses of bromocriptine, while SCH 23390 did not change the frequency of yawns produced by the drug significantly. Administration of SK&F 38393 (4–16 mg kg^{-1}, i.p.) to rats decreased the yawning induced by bromocriptine (Figure 3). The influence of SK&F 38393 on bromocriptine-induced yawning was dose-dependent. The effect of bromocriptine was decreased by theophylline or atropine in pretreated animals (Table 2).

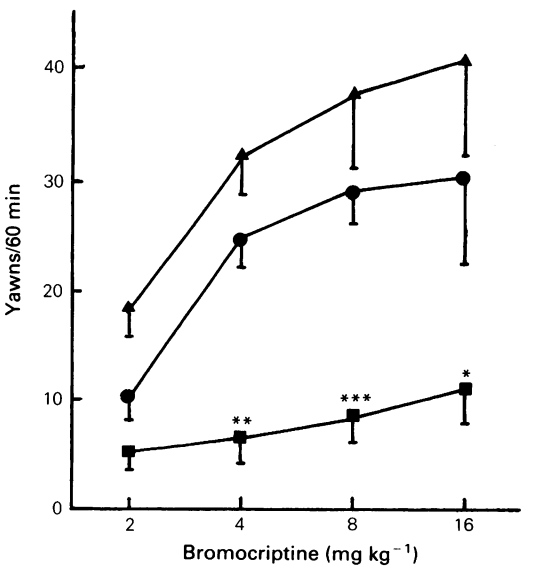

Figure 2 Yawning induced by administration of different doses of bromocriptine in presence or absence of antagonists. Rats were injected intraperitoneally with bromocriptine alone (●) or with either SCH 23390 (▲) (0.05 mg kg^{-1}, s.c.) or sulpiride (■) (10 mg kg^{-1}, i.p.) 30 min before bromocriptine injection. The number of yawns was recorded for 60 min. Each point is the mean for minimum of 8 animals; vertical bars show s.e.mean. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$: significantly different from bromocriptine-treated group.

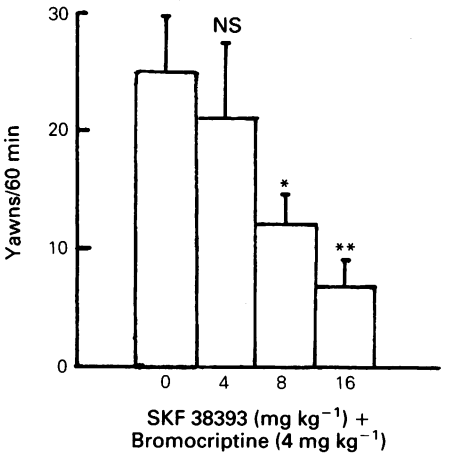

Figure 3 Yawning induced by bromocriptine (4 mg kg^{-1}, i.p.) alone or in combination with i.p. administration of different doses of SK&F 38393. Results are shown for total yawns induced during 60 min after bromocriptine injection. Each point is the mean for minimum of 8 experiments; vertical bars show s.e.mean. NS not significant; * $P < 0.05$; ** $P < 0.001$: significantly different from bromocriptine control group.

Table 2 Frequency of yawns induced by bromocriptine (8 mg kg^{-1}) in rats in presence or absence of theophylline or atropine

Drug	mg kg^{-1}	Yawns/60 min Mean ± s.e.	n
Saline	1 ml	29.1 ± 3.9	14
Theophylline	25	4.6 ± 1.6*	7
Atropine	10	0.0 ± 0.0*	6

Saline (i.p.), theophylline (i.p.) or atropine (i.p.) were injected respectively 30, 60 and 10 min before bromocriptine administration (i.p.).
* $P < 0.001$: significantly different from saline control group.

Table 3 Frequency of yawns induced by physostigmine (0.1 mg kg^{-1}) in rats in presence or absence of other drugs

Drug	mg kg^{-1}	Yawns/60 min Mean ± s.e.	n
Saline	1 ml	23.5 ± 4.4	6
Sulpiride	10	24.6 ± 11.5	6
SCH 23390	0.05	36.0 ± 6.2*	7
SK&F 38393	8	7.2 ± 2.8**	6
SCH 23390 + SK&F 38393	0.05 + 8	18.3 ± 3.0†	6
Bromocriptine	8	62.8 ± 11.0***	6
Theophylline	25	3.0 ± 1.5****	6
Atropine	10	0.0 ± 0.0****	6

Saline (i.p.), sulpiride (i.p.), SCH 23390 (s.c.), SK&F 38393 (i.p.), bromocriptine (i.p.), theophylline (i.p.) and atropine (i.p.) were administered 30, 30, 30, 0, 0, 60 and 10 min before physostigmine (i.p.) injection respectively.
* $P < 0.1$; ** $P < 0.02$; *** $P < 0.01$; **** $P < 0.001$ different from saline-treated rats.
† $P < 0.05$: different from SK&F 38393-treated animals.

Effects of drugs on physostigmine-induced yawning

As shown in Table 3, the yawns elicited by physostigmine (0.1 mg kg^{-1}, i.p.) were decreased by concomitant administration of SK&F 38393 (8 mg kg^{-1}, i.p.) and were antagonized by atropine (10 mg kg^{-1}, i.p., 10 min) or theophylline (25 mg kg^{-1}, i.p., 60 min) in pretreated animals. Neostigmine (0.1, 0.25 and 0.5 mg kg^{-1}, i.p.) did not induce yawning (data not shown). The inhibitory influence of SK&F 38393 on physostigmine-induced yawning was decreased in SCH 23390 pretreated rats; hence the number of yawns was increased. The effect of physostigmine was potentiated by concomitant administration of bromocriptine but less so by SCH 23390 pretreatment. Sulpiride had no influence on physostigmine-induced yawning.

Discussion

Apomorphine with D_1- and D_2-agonist properties (Seeman, 1980; Stoof & Kebabian, 1984) in small doses (0.1–0.6 mg kg^{-1}) induced yawning in rats. This syndrome was decreased by increasing the dose of the drug. Pretreatment of animals with sulpiride a D_2-dopamine receptor antagonist (Di Chiara *et al.*, 1976; Costall *et al.*, 1980; Kendler *et al.*, 1982; Stoof & Kebabian, 1984) reduced the ability of apomorphine to induce yawning. Our present results are in agreement with previous observations of others that apomorphine influences yawning biphasically in rats (Holmgren & Urbá-Holmgren, 1980; Yamada & Furukawa, 1980; Dubuc *et al.*, 1982; Protais *et al.*, 1983). Such a biphasic effect has been attributed to the successive involvement of D_2- and D_1-dopamine receptors; the lower doses of apomorphine stimulate D_2-receptors which decrease tonic dopaminergic transmission with a consequent induction of yawning, while the higher doses activate D_1-receptors and cause the abolition of yawning (Yamada & Furukawa, 1980; Urbá-Holmgren *et al.*, 1982). Pretreatment of animals with low doses of the specific D_1-receptor antagonist SCH 23390 (Hyttel, 1984) increased the ability of apomorphine to induce yawning. When dopamine activation of D_1-sites is impaired by SCH 23390, apomorphine activates only D_2-sites and therefore more frequent yawning can be observed. Administration of SCH 23390 alone also induced a low degree of yawning in rats, which may indicate inhibition of D_1- and unmasking of D_2-agonist properties of endogenous brain dopamine. These effects of SCH 23390 confirm the hypothesis that D_1-receptor stimulation can decrease the yawning episodes and contradict the suggestion of some investigators that autoreceptors are not involved, e.g. Morelli *et al.* (1986), who found SCH 23390 was able to antagonize yawning induced by apomorphine. For further evaluation of the opposite influences of D_1- and D_2- dopamine receptor activation on yawning, some studies were carried out with D_1- and D_2-agonists. Bromocriptine, a D_2-agonist (Di Chiara *et al.*, 1977; Gianutsos & Moore, 1980) has been reported to induce yawning through the stimulation of dopamine D_2-receptors in the rat striatum and septum (Yamada *et al.*, 1986). In the present study, bromocriptine caused yawning dose-dependently. The effect was decreased in animals pretreated with sulpiride. SCH 23390 did not alter the frequency of yawns induced by bromocriptine. These findings support the view that D_2-receptor stimulation may cause yawning.

SKF 38393 which does not induce yawning (Yamada *et al.*, 1986) is a D_1-receptor agonist devoid of D_2-receptor stimulation properties (Setler *et al.*, 1978; Tsuruta *et al.*, 1981; Stoof & Kebabian, 1982). This drug decreased yawning induced by both apomorphine and bromocriptine. These data may suggest that D_1-receptor stimulation exerts opposite influence on yawning. On the other hand, the ability of SKF 38393 to stimulate dopamine-sensitive adenylate cyclase has been shown (Setler *et al.*, 1978). It has been suggested that activation of D_1-receptors is associated with stimulation of adenylate cyclase (Kebabian & Calne, 1979) while D_2-receptor activation may cause inhibition of cyclic AMP formation in striatum (Onali *et al.*, 1984). Theophylline which increases cyclic AMP levels (Butcher & Sutherland,

1962), inhibits yawning induced by apomorphine, bromocriptine or physostigmine. Whether the opposite effects of D_1- and D_2-receptors on yawning behaviour are due to an increase or decrease of cyclic AMP levels is not clear and remains to be elucidated.

Previous investigations have pointed out the involvement of the cholinergic system in the induction of yawning syndrome (Urbá-Holmgren *et al.*, 1977; Yamada & Furukawa, 1980). The present data show that neostigmine, which is not able to enter the CNS, does not induce yawning behaviour and that atropine can antagonize episodes of yawning in rats treated with apomorphine, bromocriptine or physostigmine. This points to a possible central muscarinic component in the yawning induced by these drugs. These results are supported by the suggestion of Yamada & Furukawa (1980) who showed that apomorphine induced yawning through indirect activation of cholinergic neurones. Our results show that bromocriptine potentiates and SK&F 38393 decreases the frequency of yawns induced by physostigmine. It is therefore postulated that yawning may be induced through a cholinergic activation mechanism, while D_1- and D_2-receptor stimulation may have opposite effects on this behaviour.

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