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Theophylline-induced grooming: possible indirect dopaminergic mechanism

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Abstract

The ability of theophylline, an adenosine antagonist and phosphodiesterase inhibitor, to induce grooming was studied in rats. Grooming was induced by intraperitoneal (i.p.) injection of different doses (6–25 mg/kg) of theophylline to rats. The effect was dose-dependent. However, the response was decreased with increasing doses of the drug from 25–75 mg/kg. Administration of the dopamine D_1 receptor agonist SKF 38393 (1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride; 16 mg/kg i.p.) also caused grooming in a dose-dependent manner. The response induced by SKF 38393 (1–4 mg/kg i.p.) was decreased by the high doses of theophylline (50 and 75 mg/kg i.p.). The dopamine D_1 receptor antagonist SCH 23390 (*R*-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-benzazepine-7-ol maleate) decreased the theophylline and SKF 38393 response. Pretreatment of animals with reserpine (2.5 mg/kg i.p., 24 h) reduced the effect of theophylline (12.5 and 25 mg/kg i.p.) but not that of SKF 38393 (1 and 4 mg/kg i.p.). It is concluded that theophylline elicits grooming through an indirect D_1 dopaminergic mechanism.

Keywords: Theophylline; Dopamine receptor antagonist; Grooming; (Rat)

1. Introduction

The methylxanthine theophylline has a number of pharmacological properties. The drug is used clinically in the management of obstructive airway diseases. Theophylline has been shown to produce a variety of central nervous system side effects including headache, hyperactivity, emesis and seizures (Rall, 1985). It is also able to decrease body temperature in mice (Zarrindast and Heidari, 1994). The behavioural stimulant effects of the drug appear to involve blockade of adenosine receptors (Daly, 1982). However, there is evidence that theophylline functions as an adenosine receptor antagonist and also as a phosphodiesterase inhibitor (Choi et al., 1988). Our previous studies showed that theophylline can decrease the yawning induced by physostigmine or apomorphine in rats (Zarrindast and Poursoltan, 1989), morphine antinociception in mice (Zarrindast and Moghaddampour, 1989), pecking in chickens (Zarrindast and Nasir, 1991) and licking induced by apomorphine in rats (Zarrindast et al., 1992). Methylxanthines have been shown to cause the release of brain catecholamines (Berkowitz et al., 1970) and increase or decrease dopamine turnover (Waldeck, 1971; Corrodi et al., 1972). The drug may elicit direct dopaminergic effects (Watanabe et al., 1981; Herrera-Marschitz et al., 1988; Casas et al., 1989). Dopaminergic mechanisms may be involved in grooming behaviour (Van Wimersma Greidanus et al., 1989).

In the present work, the effect of theophylline on grooming and the mechanism involved were investigated.

2. Materials and methods

2.1. Animals

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 22–24°C. Food and water were freely available except during the experiments.

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2.2. Grooming measurement

Animals were placed individually in a glass cylinder (25 cm wide, 25 cm long) and allowed to habituate for 30 min before drug administration. Immediately after injection, each animal was placed into the cylinder and grooming behaviour was observed directly. The following elements of grooming were observed: head washing, body grooming, paw licking, anogenital grooming, tail licking and scratching. The bouts of grooming were recorded each 15 min for a period of 60 min. The results are expressed as the mean ± S.E.M. number of grooming episodes per treatment group (7 rats).

2.3. Statistical analysis

Analysis of variance (ANOVA) followed by Newman-Keuls tests were used to evaluate the significance of the results obtained.

2.4. Drugs

The following drugs were used: theophylline (Sigma, UK), SCH 23390 (*R*-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-benzazepine-7-ol maleate), sulpiride and SKF 38393 (1-phenyl-7-,8-dihydroxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride; Research Biochemicals, Wayland, USA) and reserpine (Ciba-Geigy). The drugs were prepared immediately before injection and were administered in a volume of 10 ml/kg. The pretreatment time and doses of antagonists used were as in our previous studies (Zarrindast and Nasir, 1991; Zarrindast and Amin, 1992). All the drugs were injected intraperitoneally (i.p.).

3. Results

3.1. Grooming behaviour induced by theophylline

I.p. injection of different doses of theophylline (6, 12.5, 25, 50 and 75 mg/kg) to rats caused grooming [$F(23,144) = 12.5$, $P < 0.01$]. The maximum effect was induced by 25 mg/kg of the drug. The response to theophylline (50 and 75 mg/kg) was decreased by increasing the dose of the drug (Fig. 1). Episodes of locomotor activity and sniffing were also observed with grooming during the experiments. Sniffing and locomotion were induced when grooming was decreased by increasing the dose of theophylline (data not shown).

3.2. Grooming behaviour induced by SKF 38393 in presence or absence of theophylline

Different doses of SKF 38393 (1, 2, 4, 8 and 16 mg/kg i.p.) also induced dose-dependent grooming [$F(5,36) = 83.2$, $P < 0.01$] (data not shown). When different doses of theophylline were challenged against SKF 38393 (1–4 mg/kg), a low dose of theophylline (25 mg/kg) potentiated, while high doses of the drug (50 and 75 mg/kg) reduced the grooming induced by SKF 38393 [$F(11,72) = 60.8$, $P < 0.01$] (Fig. 2).

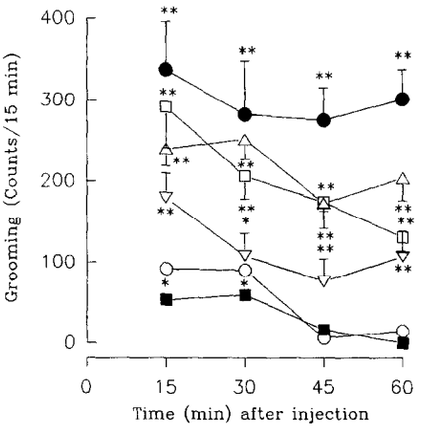

Fig. 1. Production of grooming behaviour in rats by different doses of theophylline. Groups of rats were injected with saline (○) or theophylline 6, (△) 12.5, (●) 25, (□) 50 or (■) 75 mg/kg. Grooming episodes were recorded immediately after administration of theophylline for 60 min. Each point is the mean ± S.E.M. for 7 experiments.

3.3. Effect of dopamine antagonists on SKF 38393- and theophylline-induced grooming

Pretreatment of animals with the dopamine D_1 receptor antagonist SCH 23390 (0.05 and 0.1 mg/kg i.p., 30 min) decreased the grooming [$F(19,120) = 43.0$, $P < 0.01$] induced by either theophylline (12.5 and 25 mg/kg i.p.) or SKF 38393 (1 and 4 mg/kg i.p.). However, sulpiride did not change the effects of SKF 38393 or theophylline (Fig. 3).

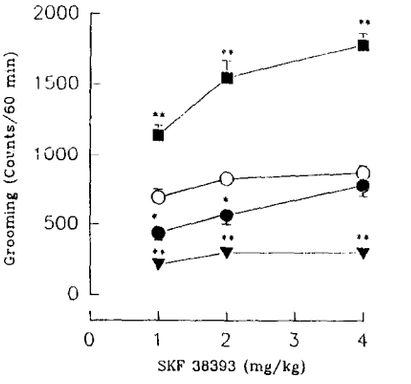

Fig. 2. Effects of high doses of theophylline on SKF 38393-induced grooming. Animals were injected (i.p.) with saline (○) or theophylline (■) 25, (●) 50 and (▼) 75 mg/kg, 60 min before SKF 38393 injection. The number of grooming episodes was counted for 60 min after SKF 38393 administration. Each point is the mean ± S.E.M of 7 experiments. * $P < 0.05$, ** $P < 0.01$ different from SKF 38393 treated animals.

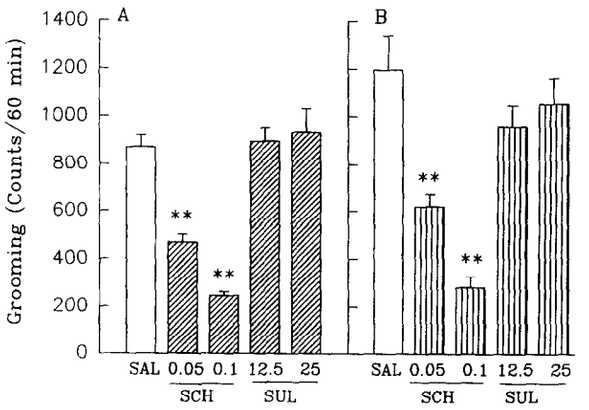

Fig. 3. Effect of dopamine antagonists on the SKF 38393 or theophylline-induced grooming. Rats were injected i.p. with either SKF 38393 (A; 4 mg/kg) or theophylline (B; 25 mg/kg) in the presence of either saline (SAL; 10 ml/kg) or SCH 23390 (SCH; 0.05 and 0.1 mg/kg) or sulpiride (SUL; 12.5 and 25 mg/kg) injection. SCH 23390 or sulpiride was injected (i.p.) 30 and 90 min before SKF 38393 or theophylline administration respectively. Other details as Fig. 1. * $P < 0.05$, ** $P < 0.01$ different from SKF 38393 or theophylline respective groups.

3.4. Effect of theophylline and SKF 38393 on reserpinized rats

Pretreatment of animals with reserpine (2.5 mg/kg i.p., 24 h) decreased the grooming induced by theophylline but not that induced by SKF 38393 [$F(7,48) = 16.9$, $P < 0.01$] (Table 1).

4. Discussion

In the present study, theophylline induced dose-dependent grooming. This effect decreased with increasing doses of the drug. The grooming induced by theophylline was decreased by the dopamine receptor antagonist SCH 23390 (Hyttel, 1984), which may indicate that the response of the drug is produced through dopaminergic mechanism(s). Theophylline has been shown to release dopamine in the brain (Lin et al., 1980) and to exert direct dopamine receptor agonist activity (Watanabe et al., 1981; Herrera-Marschitz et al., 1988; Casas et al., 1989). Dopamine acts at two pharmacologically different and distinct sites, which have been designated dopamine D_1 and D_2 receptors. Dopamine D_1 receptors stimulate adenylate cyclase while D_2 receptors inhibit it (Kebabian and Calne, 1979; Stoof and Kebabian, 1984). Since the dopamine D_1 receptor antagonist SCH 23390 (Hyttel, 1984) decreased the theophylline effect, the dopamine D_1 receptor mechanism may be involved in the drug effect. Pretreatment of animals with the dopamine D_2 receptor antagonist sulpiride (Di Chiara et al., 1976; Stoof and Kebabian, 1984) did not alter the theophylline effect. Thus the failure of the dopamine D_2 receptor antagonist sulpiride to decrease the theophylline effect excludes dopamine D_2 receptor involvement.

Table 1
Effects of reserpine on SKF 38393 or theophylline-induced grooming

Treatment (mg/kg)	Unreserpinized	Reserpinized
Theophylline (12.5)	866 ± 56	288 ± 34 [a]
Theophylline (25)	1196 ± 145	311 ± 38 [a]
SKF 38393 (1)	697 ± 60	588 ± 75
SKF 38393 (4)	873 ± 50	761 ± 28

A group of animals was injected with reserpine (2.5 mg/kg) 24 h before SKF 38393 or theophylline administration. Other details as Fig. 1. [a] $P < 0.01$ different from respective unreserpinized animals.

The present data showed that the dopamine D_1 receptor agonist SKF 38393 (Setler et al., 1978) also induced dose-dependent grooming. The response elicited by SKF 38393 also was reduced by the dopamine D_1 receptor antagonist SCH 23390 but not by the dopamine D_2 receptor antagonist sulpiride. The finding is in agreement with the suggestion of other investigators that dopamine D_1 receptors are involved in grooming behaviour (White et al., 1988; Van Wimersma Greidanus et al., 1989). Low doses of theophylline potentiated the grooming induced by the D_1 agonist SKF 38393. The results may further support that theophylline-induced grooming is mediated through a dopamine D_1 receptor mechanism. In reserpinized animals, the grooming induced by theophylline was decreased by reserpine pretreatment, which may indicate that reserpine causes the release of dopamine from the dopamine pool (Rebec, 1987). Some workers have proposed that methylxanthines have also direct dopamine agonist activity (Watanabe et al., 1981; Herrera-Marschitz et al., 1988; Casas et al., 1989). In the present work, the response of the dopamine D_1 receptor agonist SKF 38393 (Setler et al., 1978) was decreased by the high doses of theophylline, and high doses of theophylline induced less grooming than low doses. Methylxanthines are phosphodiesterase inhibitors and also competitive antagonists of adenosine receptors (Choi et al., 1988). One may suggest that the inhibitory response elicited by high doses of theophylline may be mediated by phosphodiesterase inhibition. Since SKF 38393 induces grooming, and dopamine D_1 receptor activation by the drug may increase cAMP levels, the decrease in the behaviour elicited by high doses of theophylline may not be mediated through this mechanism. This is in agreement with our previous experiments showing that inhibition of some behaviours, such as yawning in rats (Zarrindast and Poursoltan, 1989; Zarrindast et al., 1995), licking in rats (Zarrindast et al., 1992) and pecking in chickens (Zarrindast and Nasir, 1991), is not mediated through an increase in cAMP levels. Both adenosine A_1 and A_2 receptor subtypes may be blocked by theophylline (Choi et al., 1988); however, the drug may exert a greater A_2 antagonistic effect (Ferré et al., 1991). Blockade of adenoisine A_1 or A_2 receptors may be another explanation

for the response to the high dose of theophylline. It should be also considered that, since higher doses of theophylline induced sniffing and locomotion, this may mask the grooming induced by the drug. Drugs acting on dopamine D_1/D_2 receptors may have dual effects on grooming. It has been reported that a D_2 dopamine receptor mediated inhibition of grooming can occur, and even a dopamine D_1 receptor stimulation of grooming can be unmasked in the presence of a dopamine D_2 receptor antagonist (Molloy and Waddington, 1984; Starr and Starr, 1986). Therefore, the dopaminergic response to the drug may decrease the grooming through D_2 dopamine receptor activation. However, more experiments may be required to clarify the mechanism(s) involved in the inhibition of grooming elicited by higher doses of theophylline.

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