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# Chronic $D_1$-receptor blockade: effects on $D_2$-receptor agonist-induced yawning in rats

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**Abstract**—The effects of chronic treatment with the selective $D_1$ dopamine receptor antagonist SCH 23390 (0·25 mg $kg^{-1}$ s.c. twice daily for 18 days, 4 days withdrawal on yawning induced by the $D_2$-receptor agonist quinpirole has been investigated. Low doses of quinpirole (20 and 50 $\mu g\ kg^{-1}$ s.c.) induced dose-related yawning behaviour in rats. The yawning response to quinpirole was not significantly different in the presence or absence of SCH 23390 pretreatment. However, chronic treatment with SCH 23390 alone significantly suppressed yawning behaviour. The results suggest that chronic $D_1$-receptor blockade with SCH 23390 does not alter the function of the $D_2$-receptor population mediating yawning behaviour. However, after withdrawal it may result in behavioural activation as seen by suppression of yawning behaviour in the present study.

Low doses of selective $D_2$- or mixed $D_1/D_2$-receptor agonists are known to induce yawning behaviour in rodents (Mogilnicka & Klimek 1977; Yamada & Furukawa 1980; Serra et al 1987). The yawning syndrome is thought to be a behavioural consequence of dopamine autoreceptor activation and a subsequent decrease in dopaminergic activity in the central nervous system (Yamada & Furukawa 1980; Gower et al 1984; Dourish & Hutson 1985; Stoessl et al 1987). This autoreceptor hypothesis has been criticized as there is evidence suggesting that yawning may be mediated via a postsynaptic $D_2$-receptor population exceptionally sensitive to dopamine agonists (Morelli et al 1986; Serra et al 1986; Spina et al 1989). Regardless of the anatomical localization of the receptors mediating yawning behaviour, they belong to the $D_2$ category, because $D_2$-antagonists completely abolish dopamine agonist-induced yawning and selective $D_1$-agonists do not elicit that behaviour (Gower et al 1984; Yamada et al 1986). However, it has been shown that the selective $D_1$-receptor antagonist, SCH 23390 (Hyttel 1983; Iorio et al 1983), can also block $D_2$-agonist-induced yawning, suggesting that the $D_1$-receptor system may be involved in the modulation of yawning behaviour (Serra et al 1987; Longoni et al 1989). Therefore, since acute SCH 23390 blocks $D_2$-receptor-mediated yawning, we have tested whether $D_1$ supersensitivity after chronic $D_1$-receptor blockade (e.g. Creese & Chen 1985) increases yawning behaviour induced by the selective $D_2$-agonist, quinpirole (LY 171555).

## Materials and methods

Male Wistar rats, 200–240 g (ALAB, Sweden), were housed in groups of four under standard laboratory conditions (temperature 21°C, humidity 55 ± 5%, lights on from 0700 to 1900 h). Standard pelleted food (Ewos R3, Sweden) and tap water was available at all times. Rats were given subcutaneous (s.c.) injections of SCH 23390 (8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-7H-3-benzazepine-7-ol) hydrochloride (0·25 mg $kg^{-1}$) (Research Biochemicals Inc., USA) or an equal volume of vehicle (0·5% ethanol, 1 mL $kg^{-1}$) twice daily for 18 days. After a withdrawal period of four days rats were challenged with two doses of quinpirole hydrochloride (20 and 50 $\mu g\ kg^{-1}$ s.c.) (LY 171555, Lilly Co., USA); these were used because of the normal distribution of the dose-yawning curve for this $D_2$-agonist (Serra et al 1987; Longoni et al 1989). Doses of all drugs refer to the free base. Yawning behaviour was investigated (0830–1330 h) in a quiet room with similar illumination, humidity and temperature to that in the housing room. After the dose of quinpirole, yawning was quantitated as described by Serra et al (1987). The rats were placed in Perspex cages (floor area 22 × 37 cm) and after 5 min habituation the number of yawns were counted for 30 min by an observer who was unaware of the treatment status of the rats. A mirror was placed behind the cage to facilitate the counting. Statistical comparisons were made by two-way-analysis of variance followed by Newman-Keuls (NK) test for marginal means, as no significant interaction factor was observed (Andersen & McLean 1974). $P < 0.05$ was considered to be significant.

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## Results

Quinpirole induced dose-related yawning behaviour in rats (Fig. 1) sometimes associated with stretching of limbs. Both doses of quinpirole caused a peak effect in yawning about 10–20 min after the administration of the drug, indicating that most of the yawns were covered by the 30 min observation period. The appearance of the peak yawning effect for quinpirole was similar in SCH 23390- and vehicle-pretreated rats. Vehicle-challenged rats yawned only occasionally.

Two-way ANOVA on the yawning data showed that the challenge effect was very significant ($F = 49.32$, $P < 0.001$). The interaction factor (pretreatment × challenge), however, was not significant ($F = 1.30$, $P = 0.283$), suggesting that the dose-response curves for quinpirole in vehicle- and SCH 23390-treated rats are parallel (Fig. 1). As the interaction factor was negative, analysis was continued only for marginal means showing that both doses of quinpirole induced yawning behaviour significantly ($P < 0.01$, NK-test, both doses). The pretreatment effect was also significant ($F = 5.58$, $P = 0.02$) indicating that SCH 23390 treatment itself suppresses yawning behaviour in rats.

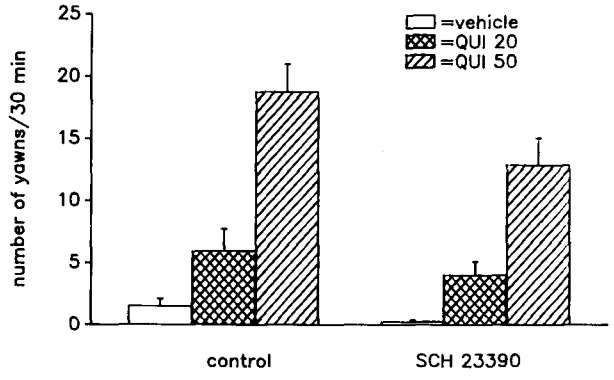


FIG. 1. The effects of chronic SCH 23390 or vehicle treatment on quinpirole (20 or 50 $\mu g\ kg^{-1}$ s.c.)-induced yawning in rats. Both doses of quinpirole induced significantly more yawning than saline challenged rats ($P < 0.05$ for the 20 $\mu g\ kg^{-1}$ dose and $P < 0.01$ for the 50 $\mu g\ kg^{-1}$ dose, NK-test for marginal means). The response to quinpirole was not different between vehicle- or SCH 23390-treated rats. Bars represent mean ± s.e.m. of 8 rats.

## Discussion

Low doses of the selective $D_2$-agonist, quinpirole, induced dose-related yawning in this study suggesting the involvement of a $D_2$-receptor population in this response. It has been previously demonstrated that acute administration of the selective $D_1$-receptor antagonist SCH 23390 (in doses up to 200 $\mu g\ kg^{-1}$, s.c.) unexpectedly blocks quinpirole-induced yawning (Serra et al 1987; Longoni et al 1989). The antagonism of $D_2$-receptor-mediated responses by SCH 23390 has been explained by a functional $D_1$–$D_2$-receptor interaction (see Clark & White 1987). In fact, it seems that several dopaminergic responses are essentially dependent on the activation of both $D_1$- and $D_2$-receptors. Despite the acute effects of SCH 23390 in the yawning model, our results suggest that chronic $D_1$-receptor blockade fails to modulate the function of the $D_2$-receptor population mediating quinpirole-induced yawning. We have previously demonstrated that this same chronic dose regimen of SCH 23390 is active biochemically and behaviourally, i.e. it decreases nigrostriatal and mesolimbic dopamine turnover in rat brain and is clearly cataleptic (Koulu et al 1988; Lappalainen et al 1989; Lappalainen et al 1990a). It appears that SCH 23390 treatment can differentially modulate $D_2$-receptor-mediated effects since chronic SCH 23390 treatment (0·5 mg $kg^{-1}$ $day^{-1}$ for 18–21 days) fails to modulate quinpirole-induced decrease in dopamine turnover, hypomotility and yawning (this study; Lappalainen et al 1990b), but enhances quinpirole-induced hypermotility and stereotypies (Hess et al 1986).

Chronic SCH 23390 treatment suppressed yawning behaviour. It has been demonstrated that rats are hyperactive after SCH 23390 treatment (Hess et al 1986; Lappalainen et al 1990b). This may explain the reduced yawning frequency in SCH 23390-treated rats since the expression of yawning is masked when the degree of behavioural activation increases. This phenomenon is seen as normal distribution dose-yawning curves after acute administration of $D_2$- or mixed $D_1/D_2$-agonists (e.g. Serra et al 1987; Longoni et al 1989) since behavioural activation (e.g. stereotypies and hyperlocomotion) is prominent with higher doses of dopamine agonists.

In conclusion, chronic treatment with SCH 23390 after a withdrawal period of four days suppresses yawning behaviour but fails to alter the function of the $D_2$-receptor population mediating yawning behaviour.

*Note added in proof.* Recent molecular biology studies (Sokoloff et al 1990) suggest the presence of a novel dopamine receptor subtype. The affinity of quinpirole for the $D_3$ receptor is relatively high in-vitro ($K_i$ 5·1 nM). Thus the effects of quinpirole in this study may, at least partly, be mediated via the $D_3$-receptor system.

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