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Effects of D1 and D2 Antagonists on Basal and Apomorphine Decreased Body Temperature in Mice and Rats

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CHIPKIN, R. E. *Effects of D1 and D2 antagonists on basal and apomorphine decreased body temperature in mice and rats.* PHARMACOL BIOCHEM BEHAV **30**(3) 683–686, 1988.—In these experiments representative selective antagonists at D1 (SCH 23390) and D2 (haloperidol) receptors were studied for their effects on basal and apomorphine decreased body temperature in mice and rats. In mice, SCH 23390 (up to 3 mg/kg SC) neither affected basal body temperature nor blocked apomorphine-induced hypothermia (AIH). On the other hand, haloperidol alone was hypothermic and paradoxically also blocked AIH in mice. In rats, SCH 23390 alone produced hyperthermia; the mechanism by which this occurred is not known. SCH 23390 also blocked AIH in rats. However, the inhibition of AIH only occurred at doses of SCH 23390 that were themselves hyperthermic. Haloperidol did not alter basal body temperature but did block AIH in rats. These data suggest that apomorphine-induced body temperature changes are D2 mediated.

SCH 23390 Haloperidol Apomorphine Body temperature D1 D2

THE ability of dopaminergic agonists and antagonists to affect body temperature is well-known [3,4]. However, the availability of selective D1 and D2 drugs provides new tools for understanding the receptor subtype responsible for these effects.

SCH 23390 is a D1 selective antagonist [1,7]. It has been reported [7] that SCH 23390 (up to 10 mg/kg IP) did not antagonize apomorphine-induced hypothermia in mice. In contrast, others have shown [2] that SCH 23390 blocked apomorphine- and ergot-induced hypothermia in the rat at low parenteral doses (0.025 mg/kg SC). Neither of these groups reported an effect of SCH 23390 on basal body temperature in either species.

To understand the reasons for the differences between these observations, the following studies were done. First, representative D1 (SCH 23390) and D2 (haloperidol) antagonists were tested for their ability to affect basal body temperature. Second, studies on the inhibition of apomorphine-induced hypothermia were also conducted using these selective antagonists. Collectively, these data were used to make hypotheses as to why different results were found and to speculate on the subtype of dopamine receptor involved in apomorphine-induced body temperature changes.

METHOD

Animals

Male CF1 mice (Charles Rivers, Kingston, NY, 20–25 g) and male Sprague-Dawley rats (Charles River, Wilmington, MA, 150–250 g) were used throughout. N=5–15 per group in all experiments. An animal was used for only one experiment and then sacrificed.

Drugs

Apomorphine HCl was purchased from Sigma Chemical Corp. (St. Louis). Haloperidol was a gift from McNeil Pharmaceuticals. SCH 23390 and SCH 23388 were synthesized at Schering Research (USA). All drugs were given subcutaneously (SC) and all doses refer to the free form of the drug. The vehicle was a 0.4% aqueous methylcellulose solution.

Measurement of Body Temperature

Body temperature was determined using a Cole-Palmer digital thermometer with a rectal probe. The probe was inserted into the animal's rectum (1.5 cm in the mouse and 3 cm in the rat) at 1 hr before and at specified times after drug treatments. The test times were determined by prior pilot studies showing that these were the peak times for the pharmacological effects. The experiments were done in non-temperature controlled rooms (range 21–23°C) in the afternoon (1–5 p.m.).

Statistics

Overall significance was determined using an analysis of variance (ANOVA) and individual comparisons were made using Duncan's Multiple Range Test. The criterion for significance was $p<0.05$.

RESULTS

Effect of D1 and D2 Antagonists on Basal Body Temperature in Mice

Body temperature was determined before and after

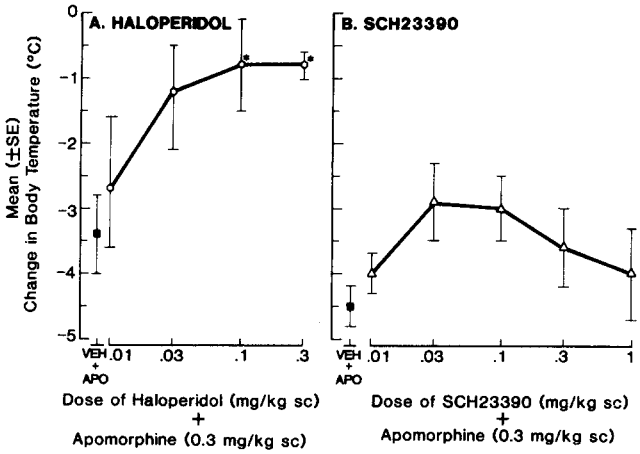

FIG. 1. Effect of (A) haloperidol or (B) SCH 23390 on apomorphine-induced hypothermia in mice. Haloperidol, SCH 23390 or vehicle (VEH) were given 30 min prior to apomorphine (APO). Testing took place 30 min after APO. The data are the mean (±SE) of five mice per group. *Significantly different from vehicle + apomorphine, $p<0.05$, Duncan's Multiple Range Test.

treatment with drugs. The change in body temperature (in °C) is the difference between these two values.

SCH 23390 given alone up to 3 mg/kg SC had no significant effect on basal body temperature of mice (Table 1). In contrast, haloperidol produced a dose-related hypothermia between 0.1 and 3 mg/kg SC. In a third experiment, lower doses were tested (<0.1 mg/kg SC) and these had no significant effects (data not presented). These doses of SCH 23390 and haloperidol are known to be pharmacologically relevant in mice based on their ability to block methamphetamine-induced aggregate toxicity (Chipkin, unpublished observations).

Effect of D1 and D2 Antagonists on Apomorphine-Induced Hypothermia in Mice

Apomorphine produced dose-related hypothermia in mice, with a peak effect at 0.3 mg/kg SC causing a roughly 4.0±0.5°C decrease in body temperature (data not presented). Haloperidol caused a dose-related inhibition of this dose of apomorphine (Fig. 1A). In contrast SCH 23390 had no significant effect on apomorphine induced hypothermia up to 1 mg/kg SC (Fig. 1B). Higher doses (up to 10 mg/kg SC) likewise had no effect when tested in a separate experiment (data not presented).

Effect of D1 and D2 Antagonists on Basal Body Temperature in Rats

SCH 23390 produced increases in the body temperature of rats at doses between 0.1 and 10 mg/kg SC (Fig 2). The dose-response curve for this effect is flat and the maximal increase in body temperature was roughly 1.0±0.3°C. In contrast, haloperidol up to 3 mg/kg SC had no effect on the basal body temperature of rats. These doses of SCH 23390 and haloperidol are equal or greater than behaviorally active doses in rats as seen by their effects on conditioned avoidance responding (Chipkin, unpublished observations).

Effect of D1 and D2 Antagonists on Apomorphine-Induced Hypothermia in Rats

Apomorphine produced dose-related hypothermia in rats

TABLE 1

EFFECT OF SCH 23390 OR HALOPERIDOL ON BASAL BODY TEMPERATURE IN MICE

Treatment	Dose (mg/kg SC)	Mean (±SE) Change in Body Temperature (°C) at 60 Min Posttreatment
Experiment No. 1		
Vehicle	—	+0.13 ± 0.09
SCH 23390	3	−0.58 ± 0.49
	1	+0.42 ± 0.17
	0.3	−0.02 ± 0.15
	0.1	+0.18 ± 0.31
Experiment No. 2		
Vehicle	—	+0.35 ± 0.10
Haloperidol	3	−0.95 ± 0.20*
	1	−0.70 ± 0.11*
	0.3	−0.80 ± 0.11*
	0.1	−0.17 ± 0.11*

*Significantly different from vehicle, $p<0.05$, Duncan's Multiple Range Test.

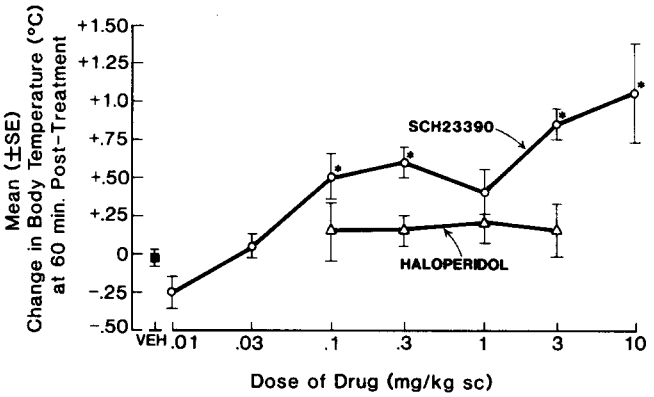

FIG. 2. Effect of SCH 23390, haloperidol or vehicle on basal body temperature of rats. Treatments were given 60 min prior to testing. The data are expressed as the mean (±SE) of the group. N=5/group for 0.01, 0.03 and 10 mg/kg SC; N=10 for 0.1 mg/kg SC; and, N=15 for 0.3, 1 and 3 mg/kg SC. The number of animals per group was varied to insure that at the critical doses sufficient animals were studied to adequately define the response. *Significantly different from vehicle, $p<0.05$, Duncan's Multiple Range Test.

with a peak effect between 0.3 and 1 mg/kg SC. The magnitude of the apomorphine-induced hypothermia in rats is substantially less than in mice; the maximal decrease in body temperature seen was approximately 0.9±0.1°C (data not presented). In the following experiments a dose of 0.3 mg/kg SC of apomorphine was used to induce hypothermia.

The ability of SCH 23390 to block apomorphine's effect in rats was tested. It was found that SCH 23390 did inhibit apomorphine-induced hypothermia (Fig. 3). However, this only occurred at doses that produced hyperthermia when given alone (see Fig. 2). Indeed, in general, the effects of SCH 23390 on apomorphine-induced hypothermia appear additive. This suggests that SCH 23390 is working via a separate mechanism which is opposite to the actions of apomorphine. This type of physiological antagonism also implies that the effects are occurring via different receptors.

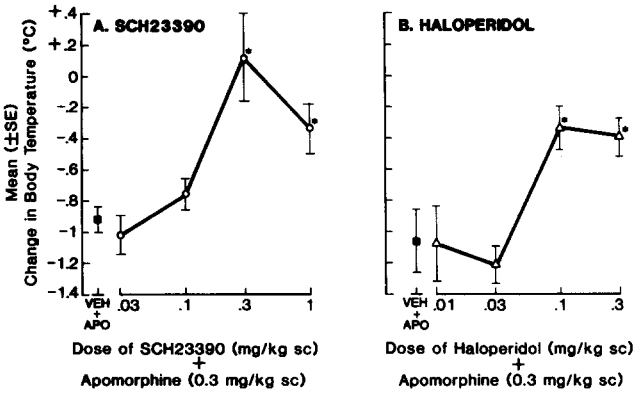

FIG. 3. Effects of (A) SCH 23390 or (B) haloperidol on apomorphine-induced hypothermia in rats. SCH 23390 or haloperidol were given 30 min prior to apomorphine. Testing took place 30 min after apomorphine. The data are expressed as the mean (±SE) of the group. N=5/group for all treatments except vehicle + apomorphine and haloperidol (0.3 mg/kg SC) + apomorphine where N=10/group. *Significantly different from vehicle, $p<0.05$, Duncan's Multiple Range Test.

Haloperidol was likewise tested for its effects on apomorphine-induced hypothermia. As in mice, haloperidol antagonized the effects of apomorphine in a dose-related manner (Fig. 3).

DISCUSSION

This discussion will take two issues into consideration. First, it will attempt to explain why other authors studying apomorphine-induced hypothermia found opposite effects with SCH 23390. Second, it will present a hypothesis for the role of D1 and D2 receptors in apomorphine's effects.

Carboni *et al.* [2] and Iorio *et al.* [7] both studied the effect of SCH 23390 on apomorphine-induced hypothermia (AIH). The results of the present studies may help to explain their discrepant observations. For example, these data agree with Iorio *et al.* [7] that in mice, D2 but not D1 antagonists block AIH. These studies also agree with Carboni *et al.* [2] since both D1 and D2 antagonists could be shown to block AIH in rats. Thus there appears to be a species specificity to the effect of SCH 23390 on AIH. Since Iorio *et al.* and Carboni *et al.* used different species, a difference in their results might be predicted and was observed. However, these data do not fully support Carboni *et al.* insofar as these authors reported actions of SCH 23390 at doses far below those used here. Indeed, we were unsuccessful in our attempts to replicate their experiments using apomorphine. The reasons for this are unclear. Furthermore, Carboni *et al.* speculated that the block of AIH by SCH 23390 was due to a direct receptor antagonism; our data do not support this conclusion. In contrast, however, we did fully replicate the results of Iorio *et al.*

These data can be used to evaluate the role of the different subtypes of dopamine receptors involved with apomorphine's effect on body temperature. It appears that the D2 receptor subtype is primarily involved in AIH, since it was blocked by haloperidol in both mice and rats at doses consistent with a receptor mediated pharmacological effect. D1 receptors are less involved since the doses of SCH 23390 needed to block AIH were in excess of those needed to block other effects. For example, the minimal effective dose (MED) for SCH 23390 to block apomorphine-induced stereotypy is ten times less than the MED for its ability to block AIH. In contrast, the MEDs for haloperidol to block either action of apomorphine are equivalent (Chipkin, unpublished observations). Furthermore, although AIH is qualitatively similar in both mice and rats and blocked equally well in both species by haloperidol, SCH 23390 only blocked AIH in the rat and only at hyperthermic doses. Moreover, it has been shown that the ability of dopamine agonists to produce hypothermia is correlated with their D2 binding affinities [5] and that D1 agonists (e.g., SKF 38393) do not produce hypothermia [2]. Therefore, the experimental results are consistent with the hypothesis that apomorphine-induced hypothermia is mediated via D2 receptors.

While this manuscript was in preparation, Faunt and Crocker [6] published their data on SCH 23390 and AIH. They reported identical results as ours and further showed that the initial hyperthermia induced by SCH 23390 is followed by a significant hypothermia. Based on their experiments with both D1 and D2 agonists and antagonists they reached the same conclusion discussed here, i.e., D2 receptors mediate AIH. However, they put forward the hypothesis that Carboni *et al.* and Iorio *et al.* differ because they administered their treatments at different times. From the results presented above, it is more likely that this discrepancy is related to the species tested.

The mechanism of action of SCH 23390 to produce hyperthermia is unknown. At present, the data are insufficient to either defend or rule out a specific D1 receptor mediated event. Further work is required to identify the exact mechanism.

In summary, SCH 23390 had no effect on basal or AIH in mice; SCH 23390 alone in the rat was hyperthermic and appeared to block AIH via a physiological (and not a receptor-mediated) mechanism. Haloperidol decreased mouse basal body temperature, and (at similar doses) blocked AIH. In rats, haloperidol had no significant effect on basal body temperature but blocked AIH at low doses. These data imply that apomorphine-induced changes in body temperature are primarily mediated via the D2 receptor.

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