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Importance of D-2 Mechanisms in the Reversal of Reserpine Hypothermia in the Mouse

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Abstract—The D-2 agonist LY 171555 (0·05, 0·1, 0·2 mg kg^{-1} s.c.) but not the D-1 agonist SK&F 38393 (5, 10, 20 mg kg^{-1} s.c.) reduced reserpine-induced hypothermia (RIH) in mice. This effect was antagonized by the D-2 antagonist (-)-sulpiride (50 mg kg^{-1} i.p.) but not by the D-1 antagonist SCH 23390 (0·1 mg kg^{-1} s.c.). SK&F 38393 (20 and 1 mg kg^{-1} s.c.) did not alter the effect of LY 171555 (0·1 and 0·2 mg kg^{-1}) on RIH, but administration of both LY 171555 (0·2 mg kg^{-1} s.c.) and SK&F 38393 (1 mg kg^{-1} s.c.) antagonized the reserpine-induced sedation.

There is evidence suggesting that some antidepressants (Fekete et al 1980), as well as apomorphine, reduce reserpine-induced effects such as hypothermia (Danielson et al 1985) and that dopamine is involved in the mechanism of action of antidepressants (Halaris et al 1975; Spyraki & Fibiger 1981; Borsini et al 1985; Plaznik & Kostowski 1987).

Since reversal of reserpine-induced hypothermia is commonly used to investigate antidepressant activity (Askew 1963; Maj et al 1976; Alhaider et al 1985; Astoin et al 1985) we thought it worthwhile to determine whether the selective D-1 agonist SK&F 38393 (O'Boyle et al 1984) and D-2 agonist LY 171555 (Stoof & Kebabian 1984) and antagonists, SCH 23390 (O'Boyle et al 1984) and (-)-sulpiride (Iorio et al 1983; Spano et al 1979) would affect reserpine-induced hypothermia (RIH) in the mouse.

Materials and Methods

Animals

Male Swiss albino mice (Nossan, Italy) 24–30 g, were housed under controlled temperature (22 ± 1°C) and humidity (60%), and a 12 h light dark cycle (lights on 0600 h) with free access to food and water.

Drugs

Reserpine (Serva, USA) was dissolved in 2% w/v L-ascorbic acid, LY 171555 (*trans*-(-)-4aR -4, 4a, 5, 6, 7, 8, 8a, 9-octahydro-5-propyl-1 H (or 2H)-pyrazolo-(3,4-g) quinoline, monohydrochloride, quinpirole hydrochloride) (Lilly laboratories, USA) and SK&F 38393 (2, 3, 4, 5-tetrahydro- 7,8-dihydroxy-1-phenyl-1 H-3-benzazepine HCl) (Smith, Kline and French, UK) in 0·9% NaCl saline, while SCH 23390 ((*R*)-(+)-8-chloro-2, 3, 4, 5-tetrahydro-3-methyl-5-phenyl-1 H-3-benzazepine-7-ol maleate) (Schering USA) and (-)-sulpiride (Ravizza, Italy) were dissolved in 0·1 M HCl and diluted in saline after neutralizing with $NaHCO_3$.

Injection volumes were 10 mL kg^{-1}. All drugs were injected subcutaneously except L-sulpiride which was administered intraperitoneally.

Experimental protocol

Reserpine, or its solvent, was administered 18–19 h before rectal temperature was recorded (Przegalinski et al 1980) to mice with a basal rectal temperature between 36·5–38·4°C. Experiments were carried out between 0900–1230 h in a controlled temperature (21 ± 1°C) room.

Drugs were administered at doses, routes, and times before recording rectal temperature previously reported to exert the maximum activity on dopaminergic systems. They were as follows: 1, 5, 10 and 20 mg kg^{-1} s.c. 25 min for SK&F 38393 (Starr & Starr 1985); 0·025, 0·05 and 0·1 mg kg^{-1} s.c. 30 min for SCH 23390 (Christensen et al 1984); 0·05, 0·1 and 0·2 mg kg^{-1} s.c. 60 min for LY 171555; 12·5, 25 and 50 mg kg^{-1} i.p. 90 min for L-sulpiride (Vasse et al 1985).

Reversal of reserpine-induced sedation was determined by assessing the presence or absence of locomotion.

Measurement of rectal temperature

Rectal temperature was measured by an Ellab digital recorder to the nearest 0·1°C by inserting a thermistor probe 2·5 cm into the rectum of manually restrained mice.

Statistical analysis

Each experimental group was chosen by a completely randomized schedule (Borsini 1985) and consisted of 8–11 mice. Values represent means ± s.e.m. Data were tested for homogeneity of variance before statistical evaluation. Factorial analysis of variance was used for evaluation of temperature results. Fisher's exact probability test was used for analysing data on locomotion.

Results

None of the compounds tested (SK&F 38393, SCH 23390, LY 171555 and L-sulpiride) reduced rectal temperature in non-reserpinized (normal) mice (Fig. 1) and only LY 171555, reduced reserpine-induced hypothermia. This effect was dose-dependent (Fig. 1C) and was antagonized by L-sulpiride (50 mg kg^{-1}) but unaffected by SCH 23390 (0·1 mg kg^{-1}) (Fig. 2A, B) or SK&F 38393 (1 mg kg^{-1}) (Fig. 3A). The concomitant administration of SK&F 38393 (20 mg kg^{-1}) and LY 171555 (0·1 mg kg^{-1}) did not modify the effect of the latter (Fig. 3B). Reserpine-induced sedation was reduced by SK&F 38393 (20 mg kg^{-1}) but not by LY 171555 (0·2 mg kg^{-1}). A dose of SK&F 38393 (1 mg kg^{-1}) inactive itself in

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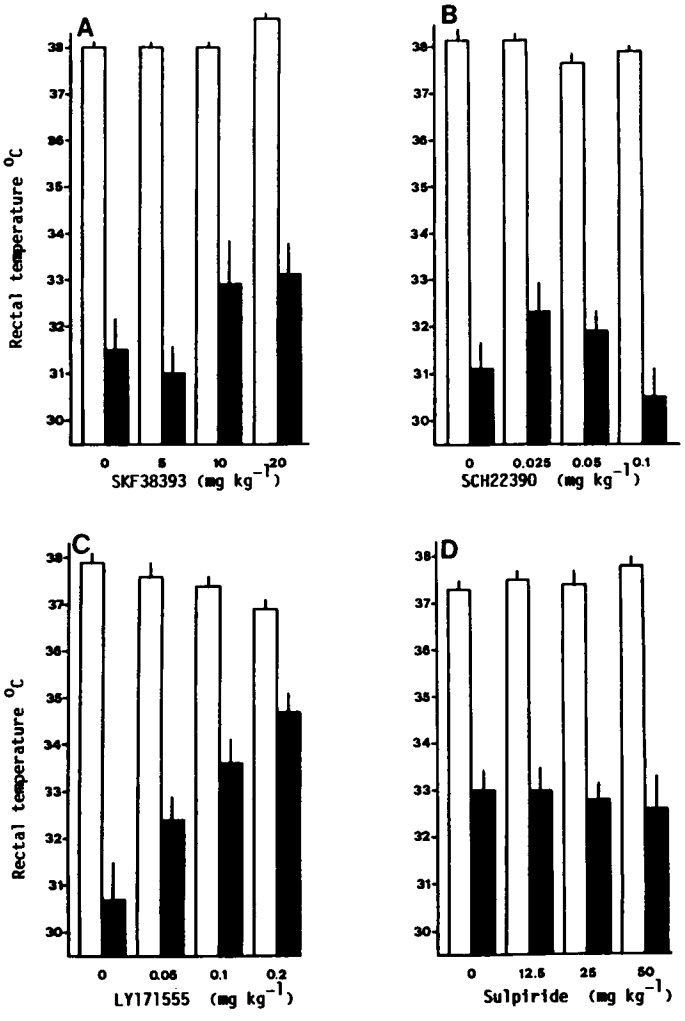

FIG. 1. Effects on rectal temperature in normal (open columns) and in reserpinized mice (closed columns) of the following D-1 and D-2 agonists and antagonists: (A) SK&F 38393, 25 min after subcutaneous administration, in the doses indicated. Anova (2 × 4) $F = 0{\cdot}927$, d.f. 3, 66 ns. (B) SCH 23390, 30 min after subcutaneous administration, in the doses indicated. Anova (2 × 4) $F = 2{\cdot}064$, d.f. 3, 75 ns., (C) LY 171555, 60 min after subcutaneous administration, in the doses indicated. Anova (2 × 4) $F = 10{\cdot}46$, d.f. 3, 70 $P < 0{\cdot}01$., (D) L-sulpiride, 90 min after endoperitoneal administration, in the doses indicated. Anova (2 × 4) $F = 0{\cdot}123$, d.f. 3, 70 ns.

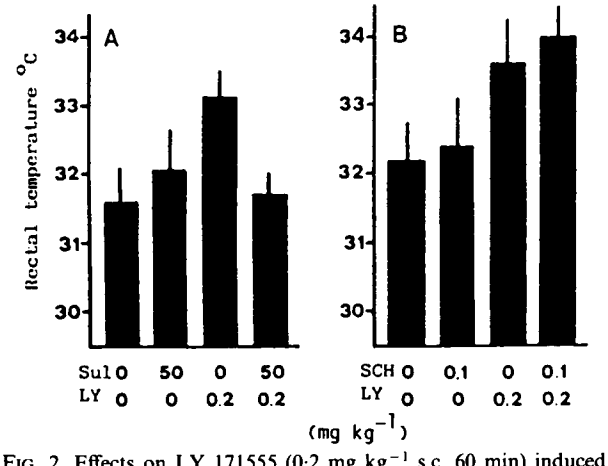

FIG. 2. Effects on LY 171555 (0·2 mg kg^{-1} s.c. 60 min) induced reduction in reserpine hypothermia in mice of: (A) L-sulpiride (50 mg kg^{-1}, i.p. 90 min) Anova (2 × 2) $F = 4{\cdot}783$, d.f. 1, 36, $P < 0{\cdot}05$., (B) SCH 23390 (0·1 mg kg^{-1}, s.c. 30 min) Anova (2 × 2) $F = 0{\cdot}09$, d.f. 1, 36 ns.

reverting sedation became effective when administered with LY 171555 (0·2 mg kg^{-1}) (Table 1).

Discussion

The present findings are consistent with the hypothesis that activation of D-2 receptors antagonizes reserpine-induced hypothermia (RIH) as previously suggested by Horowski (1978) and Krejci et al (1985). This is supported by the fact that RIH was antagonized by the selective D-2 agonist LY 171555 but not by the selective D-1 agonist, SK&F 38393, even when the latter was administered at a dose effective in reducing reserpine-induced sedation. In addition, LY 171555's effect on RIH was antagonized by the selective D-2 receptor antagonist L-sulpiride and not by the selective D-1 receptor antagonist SCH 23390.

Catecholamines have been reported to control body temperature (Jori et al 1967) and their importance in the control of locomotor activity is well established (Millan &

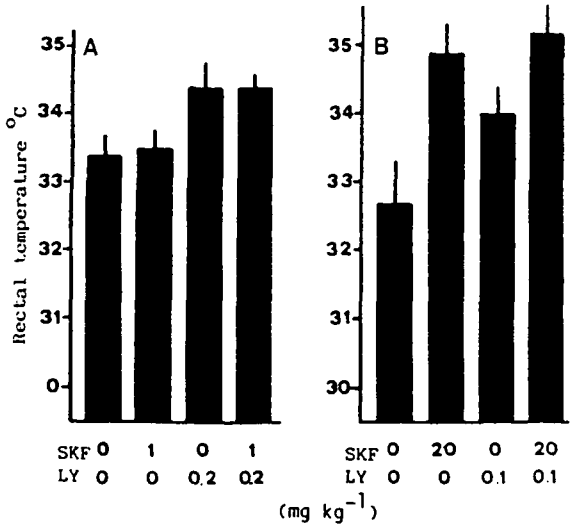

FIG. 3. Effects on LY 171555-induced reduction in reserpine hypothermia in mice of: (A) SK&F 38393 (1 mg kg^{-1}, s.c., 25 min). LY 171555 was administered at a dose of 0·2 mg kg^{-1}, 60 min. Anova (2 × 2) F = 0·127, d.f. 1, 36 ns., (B) SK&F 38393 (20 mg kg^{-1}, s.c. 25 min). LY 171 555 was administered at a dose of 0·1 mg kg^{-1}, 60 min. Anova (2 × 2) F = 1·834, d.f. 1, 37 ns.

Table 1. Effect of LY 171555 and SK&F 38393 on reserpine-induced sedation.

Treatment	Dose mg kg^{-1}	Treatment	Dose mg kg^{-1}	No. moving/ no. treated
Vehicle	—	Vehicle	—	2/10
LY 171555	0·2	Vehicle	—	3/10
Vehicle	—	SK&F 38393	1	4/10
Vehicle	—	SK&F 38393	20	9/10**
LY 171555	0·2	SK&F 38393	1	9/10*

Effects evaluated by visual observation by an observer unaware of treatment.

Statistics: Fisher's exact probability test. $^{**}P < 0.01$ vs vehicle-+vehicle; $^{*}P < 0.05$ vs respective controls.

Millan 1984). The fact that LY 171555 in a dose (0·2 mg kg^{-1}), which is effective in decreasing locomotion (Volterra unpublished results), had no effect on body temperature in the non-reserpinized mouse while antagonizing RIH, suggests that homeostatic mechanisms of temperature control are capable of normalizing effects due to D-2 receptor stimulation in non-reserpinized (normal) mice.

It is worth noting that in reserpinized mice the effects of D-1/D-2 stimulation on locomotion do not parallel those on temperature. In fact SK&F 38393 (1 mg kg^{-1}) administered to LY 171555 (0·2 mg kg^{-1})-treated mice antagonizes reserpine-induced sedation but not hypothermia in the same animals. Potentiation of locomotion with concomitant D-1/D-2 stimulation was also observed by Gershanik et al (1983) in reserpinized mice.

A difference in brain regions mediating effects on temperature and locomotion might explain this apparent discrepancy in the effects observed on temperature and sedation since cooperative D-1/D-2 effects exist in some brain regions and not in others (Stoof & Verheijden 1986; Kelly & Nahorski 1987).

In conclusion, present results indicate that D-2 but not D-1 stimulation antagonizes RIH. However, we cannot exclude that non-dopaminergic mechanisms may also be involved in LY 171555's induced reversal of RIH, since noradrenergic mechanisms have been implicated in reversal of RIH (Cox & Tha 1975) and LY 171555 has been postulated to affect noradrenaline metabolism and release (Fuller & Hemricke-Luecke 1985).

It is interesting that a D-2 involvement has also been reported in another animal model sensitive to antidepressants, the forced swimming test (Borsini et al 1988).

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