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The D2 Dopamine Receptor Agonist LY171555 Induces Catalepsy in the Mouse

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PUGLISI-ALLEGRA, S. AND S. CABIB. *The D2 dopamine receptor agonist LY171555 induces catalepsy in the mouse.* PHARMACOL BIOCHEM BEHAV 30(3) 765–768, 1988.—The dopamine agonist LY171555 (quinpirole), a specific D2 receptor agonist, induces catalepsy in mice at doses ranging from 0.3 to 10 mg/kg. The effects of an intermediate dose of this compound (1 mg/kg SC) were antagonized by 25 mg/kg of the selective D2 antagonist (−)-sulpiride (IP) injected 20 min before LY171555. SCH 23390, a selective D1 antagonist, administered (0.3 mg/kg IP) 20 min before LY171555 (1 mg/kg) enhanced the cataleptic effects of this compound. Finally, when the D1 dopamine receptor agonist SKF 38393 (20 mg/kg SC) was administered immediately beforehand, the cataleptic effects of 1 mg/kg of LY171555 were markedly reduced. These results suggest that there is a functional interaction between D1 and D2 dopamine receptors in the modulation of catalepsy.

Catalepsy Dopamine receptors LY171555 SCH 23390 (−)-Sulpiride SKF 38393 Mouse

IT has become apparent that there are two functionally distinct types of dopamine (DA) receptors: the D1 and the D2. The primary distinction seems to be that D1 receptors stimulate adenylate cyclese activity [12], whereas D2 receptors either have no effect or actually inhibit this enzyme [27]. In vivo and in vitro studies have provided evidence that stimulation of D2 receptors in the striatum inhibits DA release suggesting that at least part of these receptors are presynaptic autoreceptors [4,9].

Stimulation of presynaptic DA receptors by low doses of the mixed D1 and D2 agonist apomorphine [8] has been shown to produce inhibition of spontaneous locomotion in rodents [7, 23, 25]. This effect is antagonized by D2 DA antagonist [7, 23, 25], a result that supports the hypothesis of a selective involvement of D2 receptors in the effects of presynaptic active doses of apomorphine.

Recently, it has been shown that mice respond to low doses of apomorphine by transient catalepsy and that this effect is prevented by pretreatment with a D2 receptor antagonist [15,16]. In this study we assessed the ability of the D2 receptor agonist LY171555 [13] to induce catalepsy in mice and investigated the relative involvement of D1 and D2 receptors in this phenomenon.

METHOD

Male DBA/2 mice (Charles River Lab., Calco, Como, Italy) aged 11–12 weeks and weighing 25–28 g were used in these experiments. Animals were housed in groups of 8 in standard breeding cages (27×21×13 cm) and kept on a 12/12 hr light/dark cycle with water and food ad lib. Each experimental group for each drug dose consisted of 8 naive mice.

Cataleptic response was evaluated by placing the mouse head downward on a 45 ramp of 0.6 cm wire mesh [15, 16, 29]. Duration of immobility (4-paw criterion) was taken as the dependent measure, with an arbitrary maximum cut-off set at 120 sec. Catalepsy scores were collected every 15 min starting 5 min after the injection by a trained observer who did not know which treatment was given to the tested animal. In this test situation, all vehicle-injected mice received 0-scores since, as has been already described [15], they moved as soon as they are placed on the grid.

LY17155 [trans-(−)-4aR,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H(or 2H)-pyrazolo (3,4,-g) quinoline monohydrocloride; Eli Lilly & Company, USA], was dissolved in distilled water and injected subcutaneously in a volume of 10 ml/kg.

In an attempt to elucidate the mechanism by which the D2 receptor agonist is able to induce catalepsy in the mouse, the effects of pretreatments with selective D2 and D1 receptor antagonist and with the D1 selective agonist SKF 38393 [24] on LY171555-induced catalepsy were also evaluated. The selective D1 antagonist SCH 23390 [(R)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-olmaleate; Schering Corporation, USA] and the SKF 38393 (1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8,-diol hydrochloride; Smith, Kline & French Laboratories, USA] were dissolved in distilled water (H_2O). (−)-Sulpiride (Ravizza, Italy) was dissolved in HCl, diluted in H_2O and pH was adjusted to 7.4 with NaOH. All drugs were injected in a volume of 10 ml/kg, either subcutaneously (SC) or intraperitoneally (IP). Since each pretreatment had a different vehicle or a different route of administration, 6 groups of 8 mice each were used in this experiment: (−)-sulpiride vehicle (IP) 20 min before test dose of LY171555, 25 mg/kg of (−)-sul-

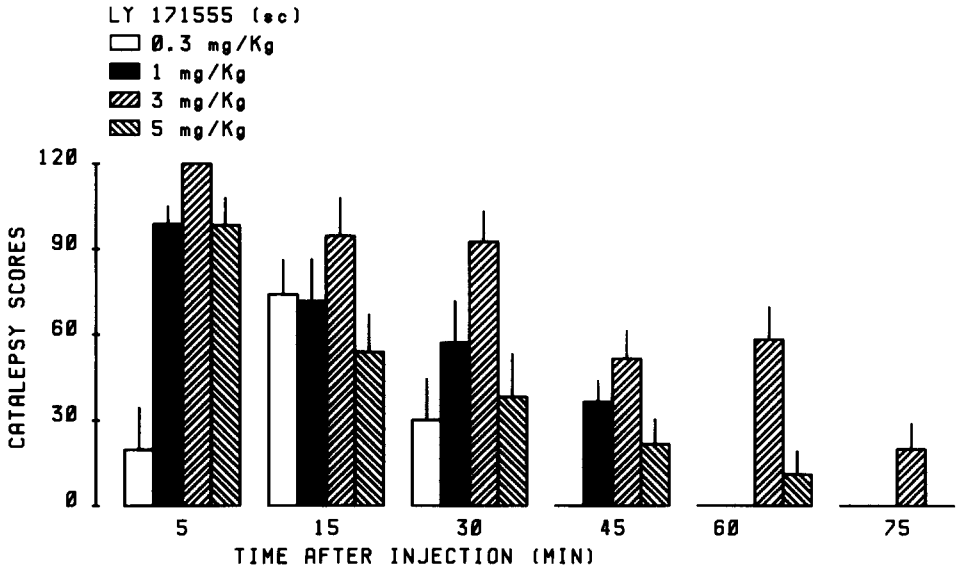

FIG. 1. Time course of cataleptic response induced by different doses of LY171555. Each point represents mean (±S.E.) catalepsy scores (sec) of 8 mice.

piride (IP) 20 min before test dose of LY171555, distilled water (IP) 20 min before test dose of LY171555, 0.3 mg/kg of SCH 23390 (IP) 20 min before test dose of LY171555, distilled water (SC) immediately before test dose of LY171555 and 20 mg/kg of SKF 38393 (SC) immediately before test dose of LY171555. The intermediate dose of 1 mg/kg of LY171555 was chosen as test dose in order to allow for both increases and decreases of the cataleptic effects of LY171555.

In additional experiments (−)-sulpiride, SKF 38393 and SCH 23390 were tested for cataleptic effects following the same experimental procedure used for LY171555.

One-way ANOVA followed by Duncan multiple range test or Student's *t*-test (two tailed criterion) were used for statistical analysis.

RESULTS

Mice injected with LY171555 (SC) clutched at the wire with limbs displaced laterally, rostrally and caudally. The onset of this effect was rapid (5 min after injection) and lasted up to 75 min after injection depending on the dose tested (Fig. 1). Thus total catalepsy scores for each animal (5–75 min) were considered for statistical analysis. The dose-response curve for total catalepsy scores is presented in Fig. 2. One-way ANOVA revealed a significant treatment effect of LY171555, $F(7,56)=7.83$, $p<0.001$. Starting from the dose of 0.3 mg/kg, LY171555 induced catalepsy dose-dependently in mice. A ceiling effect was reached at 3 mg/kg since, at 5 mg/kg, catalepsy scores were significantly reduced in comparison with 3 mg/kg ($p<0.05$ by the Duncan's test) but were no different from the catalepsy scores obtained with the higher dose of 10 mg/kg.

Both SKF 38393 (up to the dose of 20 mg/kg) and (−)-sulpiride (up to the dose of 25 mg/kg) were unable to induce cataleptic responses in our control experiment. The SCH 23390 was able to induce catalepsy dose-dependently starting from the dose of 0.5 mg/kg (Fig. 3) while the lower dose of 0.3 mg/kg had only potent akinetic effects.

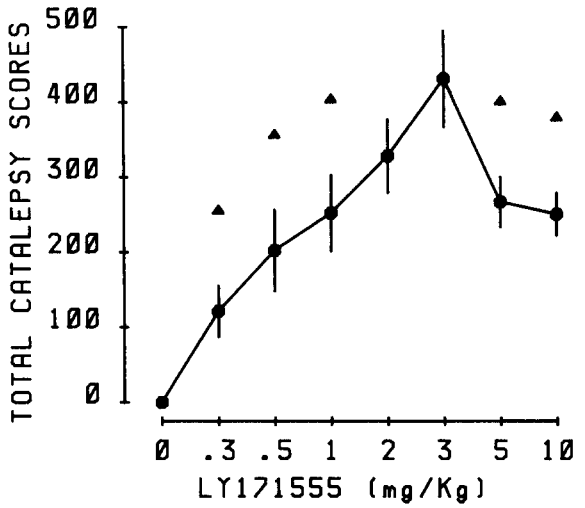

FIG. 2. Dose-response curve for cataleptic effects of LY171555. Each point represents mean (±S.E.) total catalepsy scores (5–75 min) of 8 mice. ▲=significantly different ($p<0.05$) from 3 mg/kg of LY171555 (Duncan test).

The effects of different pretreatments on LY171555-induced catalepsy are presented in Fig. 4. One-way ANOVA showed no significant differences among scores of vehicle-injected groups. The effects of LY171555 were antagonized by 25 mg/kg of the D2 selective antagonist (−)-sulpiride.

The D1 selective antagonist SCH 23390 at the dose of 0.3 mg/kg actually enhanced the cataleptic effect of LY171555. Finally, when 20 mg/kg of SKF 38393 were administered immediately before 1 mg/kg of LY171555, the cataleptic effect of this dose was significantly reduced.

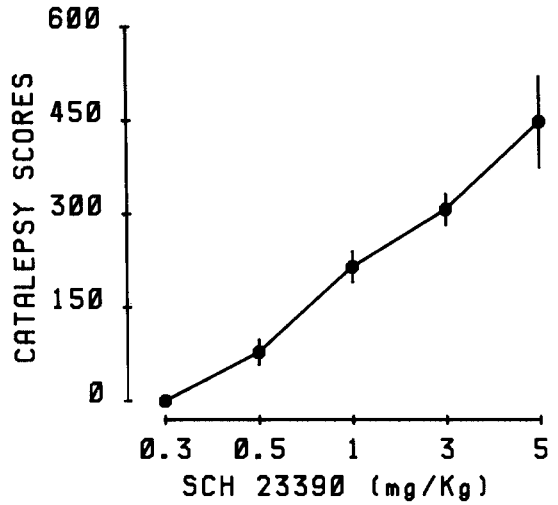

FIG. 3 Dose-response curve for cataleptic effects of SCH 23390 in mice. Each point represents mean (±S.E.) total catalepsy scores (5–75 min) of 8 mice. ANOVA revealed a significant drug treatment effect, $F(4,39)=48.579$ $p<0.001$.

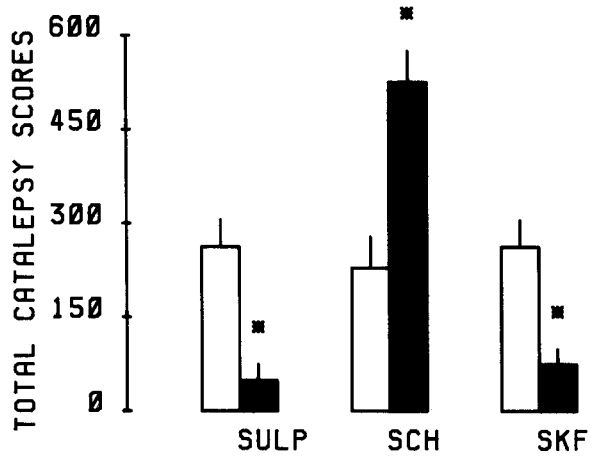

FIG 4. Effects of different pretreatments on LY171555-induced catalepsy. Open column: vehicle+1 mg/kg LY171555; dark column: [(−)-sulpiride 25 mg/kg IP (SULP), SCH 23393 0.3 mg/kg IP (SCH), SKF 38393 20 mg/kg SC (SKF)] + 1 mg/kg LY 171555. Values represent mean total catalepsy scores of 8 mice (±SE). *=significantly different from proper control group ($p<0.01$, Student's t-test).

DISCUSSION

Catalepsy is considered to be a cardinal sign of neuroleptic action in rodents, and to be associated with DA receptor blockade [16,29]. Haloperidol has nanomolar potency on D2 receptors and only micromolar potencies for D1 receptors [14]. It has therefore been suggested that D2 blockade mediates cataleptic effects of neuroleptics. However, while the selective D1 antagonist SCH 23390 has strong cataleptic effects [10, 18, 21], raclopride and sulpiride, alleged D2 selective blockers, seem to have little or no cataleptic effects [11, 17, 20]. These results can only be partly explained in terms of sulpiride's poor penetration of the blood brain barrier [11,29].

Recently, a cataleptic effect of low, supposedly presynaptic, doses of apomorphine has been described in mice [15,16] and in rats [1] adding further evidence to the hypothesis that inhibition of DA release by autoreceptors stimulation has neuroleptic like effects [17, 25, 28]. Our results, showing that the selective D2 agonist LY171555 induces catalepsy in the mouse and that this effect is prevented by the selective D2 antagonist (−)-sulpiride [19], suggest that the autoreceptors mediating catalepsy in the mouse are D2 DA receptors.

Moreover, the present results suggest that at least in the mouse catalepsy is produced when agonistic action on D1 receptors is reduced either directly, by blockade, or indirectly, by inhibition of DA release through D2 autoreceptors stimulation. In fact, only the D1 antagonist SCH 23390 and the D2 agonist LY171555 were able to induce catalepsy and a low, noncataleptic, dose of SCH 23390 brought catalepsy scores of 1 mg/kg of LY171555 to a level that could not be reached by this agonist per se indicating a synergistic effect of D1 antagonism and D2 agonism on catalepsy. This last result was not surprising since it has been found that SCH 23390 and low doses of apomorphine have additive effects on motility inhibition in rats [25] and in mice [26] and that low doses of D2 agonists potentiate SCH 23390-induced catalepsy in rats [18]. On the other hand, the D1 agonist SKF 38393 strongly reduced the cataleptic effects of 1 mg/kg of LY171555, showing that when D1 receptors are stimulated the cataleptic response is prevented. This last result would also explain the ceiling effect found at high doses of LY171555, which is probably due to partial stimulation of D1 receptors when D2 receptors are saturated.

The cataleptic effects of the D2 agonist may appear surprising to those acquainted with data obtained in the rat showing LY171555-induced stereotypic behavior and locomotion [2, 3, 10]. It should be noted, however, that mice and rats may present different behavioral responses to dopaminergic treatment in several experimental situations. For instance, apomorphine, a classic mixed D1/D2 receptor agonist, induces at high doses a wide range of stereotypic behaviors in rats while in mice it induces mainly wall climbing [6,22]. Moreover, the ED_{50} value for the locomotor inhibitory effect of SCH 23390 in mice is 75 times higher than in rats [5]. In mice, SCH 23390 has been described to partially inhibit general activity (rearing, locomotion and grooming) at the dose of 50 μkg and to stimulate grooming at lower doses [26] while 75 μg/kg has been found to be the ED_{50} value for cataleptic effects of this drug in rats [18]. In our study, 0.3 mg/kg to SCH 23390 were found to induce akinesia but not catalepsy in the mouse. However, in the case of catalepsy, differences in the testing situation used cannot be ruled out as alternative explanation since lack of cataleptic effects of 0.1 mg/kg of the D1 antagonist in rats have been recently described [21].

In conclusion, our results, showing a cataleptic effect of the selective D2 agonist LY171555 reduced by the D2 antagonist (−)-sulpiride and by the D1 agonist SKF 38393 and potentiated by the D1 antagonist SCH 23390, suggest that at least in the mouse catalepsy can be produced by stimulation of D2 receptors possibly inhibiting the release of DA and, consequently, its action of D1 receptors.

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REFERENCES

1. Balsana, J. J.; Bopat, T. R.; Gada, V. P.; Chandorkar, A. G. Small doses of apomorphine induce catalepsy and antagonize metamphetamine stereotypy in rats. Psychopharmacology (Berlin) 78:192–194; 1982.
2. Braun, R. L.; Barone, P.; Chase, T. N. Interaction of D1 and D2 dopamine receptors in the expression of dopamine agonist induced behavior. Adv. Exp. Med. Biol. 204:151–166; 1986.
3. Braun, R. L.; Chase, T. N. Obligatory D-1/D-2 receptor interaction in the generation of dopamine agonist related behaviors. Eur. J. Pharmacol. 131:301–306; 1986.
4. Chen, Y.-F.; Oparil, S. Enhanced response to the inhibitory action of LY171555, a dopamine D2-agonist, on in vivo striatal dopamine release in DOCA/NaCl-hypertensive rats. Brain Res. 400:225–231; 1987.
5. Christensen, A. V.; Arnt, J.; Hyttel, J.; Larsen, J.-J.; Svendsen, O. Pharmacological effects of a specific dopamine D-1 antagonist SCH 23390 in comparison with neuroleptics. Life Sci. 34:1529–1540; 1984.
6. Costall, B.; Naylor, R. J.; Nohria, V. Hyperactivity response to apomorphine and amphetamine in the mouse: the importance of the nucleus accumbens and caudate-putamen. J. Pharm. Pharmacol. 31:259–261; 1986.
7. Costall, B.; Lim, S. K.; Naylor, R. J. Characterization of the mechanisms by which purported dopamine agonists reduce spontaneous locomotor activity in mice. Eur. J. Pharmacol. 73:175–188; 1981.
8. Di Chiara, G.; Porceddu, M. L.; Vargiu, L.; Argiolas, A.; Gessa, G. L. Evidence for dopamine receptors mediating sedation in the mouse brain. Nature 264:564–567; 1976.
9. Dwoskin, L. P.; Zahniser, N. R. Robust modulation of (^{3}H)dopamine release from rat striatal slices by D-2 dopamine receptors. J. Pharmacol. Exp. Ther. 239:442–453; 1986.
10. Hess, E. J.; Albers, L. J.; Le, H.; Creese, I. Effects of chronic SCH 23390 treatment on the biochemical and behavioral properties of D1 and D2 dopamine receptors: Potentiated behavioral responses to a D2 dopamine agonist after selective D1 dopamine receptor upregulation. J. Pharmacol. Exp. Ther. 238:846–853; 1986.
11. Honda, F.; Satoh, Y.; Shimomura, K.; Satoh, H.; Noguchi, H.; Uchida, S.-I.; Kato, R. Dopamine receptor blocking activity of sulpiride in the central nervous system. Jpn. J. Pharmacol. 27:397–412; 1977.
12. Hyttel, J. Effects of neuroleptics on (^{3}H)haloperidol and (^{3}H)ciz(Z)-fluphentixol binding and on adenylate cyclase activity in vitro. Life Sci. 23:551–556; 1978.
13. Itoh, Y.; Goldman, M. E.; Kebabian, J. W. TL 333, a benzhydro(g)quinoline, stimulates both D-1 and D-2 dopamine receptors: implications for the selectivity of LY 141865 toward the D-2 receptors. Eur. J. Pharmacol. 108:99–101; 1985.
14. Kebabian, J. W.; Calne, D. B. Multiple receptors for dopamine. Nature 277:93–96; 1979.
15. Klemm, W. R. Experimental catalepsy is both enhanced and disrupted by apomorphine. Psychopharmacology (Berlin) 87:12–15; 1985.
16. Klemm, W. R. Neuroleptic-induced catalepsy: A D2 blockade phenomenon? Pharmacol. Biochem. Behav. 23:911–915; 1985.
17. Kohler, C.; Ogren, S. O.; Haglund, L.; Angeby, T. Regional displacement by sulpiride of (^{3}H)spiperone binding and behavioral evidence for a preferential action on limbic and nigral dopamine receptors. Neurosci. Lett. 11:51–56; 1979.
18. Meller, E.; Kuga, S.; Friedhoff, A. J.; Goldstein, M. Selective D2 dopamine receptor agonists prevent catalepsy induced by SCH 2339, a selective D1 antagonist. Life Sci. 36:1857–1864; 1985.
19. Mereu, G.; Casu, M.; Gessa, G. L. (−)-sulpiride activates the firing rate and tyrosine hydroxylase activity of dopaminergic neurons in unanesthesized rats. Brain Res. 264:105–110; 1983.
20. Ogren, S. O.; Hall, H.; Kohler, C.; Magnusson, O.; Sjostrand, S.-E. The selective dopamine D2 receptor antagonist reclopride discriminates between dopamine-mediated motor functions. Psychopharmacology (Berlin) 90:287–294; 1986.
21. Onali, P.; Mereu, G.; Olianas, M. C.; Bunse, B.; Rossetti, Z.; Gessa, G. L. SCH 23390, a selective D1 dopamine receptors blocker, enhances the firing rate of nigral dopaminergic neurons but fails to activate striatal tyrosine hydroxylase. Brain Res. 340:1–7; 1985.
22. Protais, P.; Constantin, J.; Schwartz, C. Climbing behavior induced by apomorphine in mice: A simple test for the study of dopamine receptors in the striatum. Psychopharmacology (Berlin) 50:1–6; 1976.
23. Protais, P.; Bonnet J.; Constantin, J. Pharmacological characterization of the receptors involved in apomorphine-induced polyphasic modifications of locomotor activity in mice. Psychopharmacology (Berlin) 81:126–142; 1983.
24. Setler, P.; Sarau, H. M.; Zirkle C. L.; Saunders, H. L. The central effects of a novel dopamine agonist. Eur. J. Pharmacol. 50:419–430; 1978.
25. Stahle, L.; Ungerstedt, U. Effects of neuroleptic drugs on the inhibition of exploratory behaviour induced by a low dose of apomorphine: Implications for the identity of dopamine receptors. Pharmacol. Biochem. Behav. 25:473–480; 1986.
26. Starr, B. S.; Starr, M. S. Differential effects of dopamine D1 and D2 agonists and antagonists on velocity of movement, rearing and grooming in the mouse. Neuropharmacology 25:455–463; 1986.
27. Stoof, J. C.; Kebabian, J. W. Opposing roles for D1 and D2 dopamine receptors in efflux of cyclic AMP from rat striatum. Nature 294:366–368; 1981.
28. Tamminga, C. A.; Schaffer, M. H.; Smith, R. C.; Davis, J. M. Schizophrenic symptoms improve with apomorphine. Science 200:567–568; 1978.
29. Yurek, D. M.; Randall, P. K. Simultaneous catalepsy and apomorphine-induced stereotypic behavior in mice. Life Sci. 37:1665–1673; 1985.