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LY 171555-Induced Catalepsy and Defensive Behavior in Four Strains of Mice Suggest the Involvement of Different D2 Dopamine Receptor Systems

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PUGLISI-ALLEGRA, S., P. CARLETTI AND S. CABIB. *LY 171555-induced catalepsy and defensive behavior in four strains of mice suggest the involvement of different D2 dopamine receptor systems.* PHARMACOL BIOCHEM BEHAV **36**(2) 327–331, 1990.—The D2 dopamine receptor agonist LY 171555 (0.5 to 5 mg/kg) induces dose-dependent catalepsy in C57BL/6, DBA/2 and BALB/c inbred strains of mice. This effect shows marked strain-dependent differences, since the response of C57BL/6 is significantly lower than those presented by the other two inbred strains at all doses tested. In previous studies we have shown that the D2 agonist at doses ranging from 0.5 to 5 mg/kg induces hyperdefensive responses toward nonaggressive opponents in mice of the C57BL/6 and BALB/c but not of the DBA/2 strain. Here we report that the outbred CD1 mice present both cataleptic and hyperdefensive responses when challenged with LY 171555. Forty-five percent of individuals presenting high defensive response and 11% high cataleptic scores. No correlation was found between catalepsy and hyperdefensiveness in CD1 mice following administration of 1 mg/kg of the D2 agonist. These results suggest that D2 receptor stimulation results in different behavioral responses, possibly mediated by different dopaminergic systems, depending on the genetic make up.

Catalepsy Defensive behavior D2 dopaminergic receptors Genotype LY 171555

MAJOR strain-dependent differences have been observed in the behavioral effects of the classic dopaminergic agonist apomorphine in mice, suggesting genotype-dependent modulation of central dopaminergic functioning (4, 5, 12, 20, 21, 26).

Little is known about the genotype-dependent behavioral effects of the new class of selective D1 and D2 dopamine (DA) receptor agonists, whose concomitant administration has been shown to induce the same behavioral profile as classical DA agonists (3, 8, 9, 27). Recently, we have shown that the D2 DA receptor agonist LY 171555 (23) induces a dose-dependent cataleptic response in mice of the DBA/2 strain (18). In a different set of experiments, we have also shown that LY 171555 induces hyperdefensive responses toward nonaggressive conspecifics in mice of a different strain, the C57BL/6 (19), this last effect presenting major strain differences (6). The present study aims to explore possible strain-dependent differences in the response to the cataleptic effects of LY 171555. Moreover, we have investigated the behavioral effects of LY 171555 in an outbred strain (CD1) in order to evaluate if catalepsy and hyperdefensiveness induced by D2 dopamine receptor stimulation in the mouse are related phenomena.

EXPERIMENT 1

Method

Male DBA/2 (DBA), C57BL/6 (C57) and BALB/c (BALB) mice (Charles River Lab. Calco, Como, Italy) aged 11–12 weeks and weighing 23–25 g were used in these experiments. Animals were housed in groups of 8 in standard breeding cages (27 × 24 × 13 cm) and kept on a 12/12-hr light/dark cycle with water and food ad lib. Each experimental group consisted of 8 naive mice for each drug dose.

Cataleptic response was evaluated by placing the mouse head downward on a 45° ramp of 0.6 cm wire mesh (13, 14, 18). 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 had been given to the tested animal. In this test situation, all vehicle-injected mice (H_2O, 10 ml/kg) received 0 scores since, as has already been described (13,18), they moved as soon as they were placed on the grid. Total catalepsy scores for each animal (5–75 min) were considered for statistical analysis (18).

All tests were carried out during the second half of the light period in a sound-damped cubicle where a 60-W lamp placed 2.4 m above the floor of the room was the only source of illumination.

LY 171555 [trans-(−)-4aR,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H(or 2H)-pyrazolo (3,4,-g) quinoline monohydrochloride, Eli Lilly & Company, USA], was dissolved in distilled water (H_2O) and injected subcutaneously in a volume of 10 ml/kg.

Results were statistically analyzed by two way analysis of

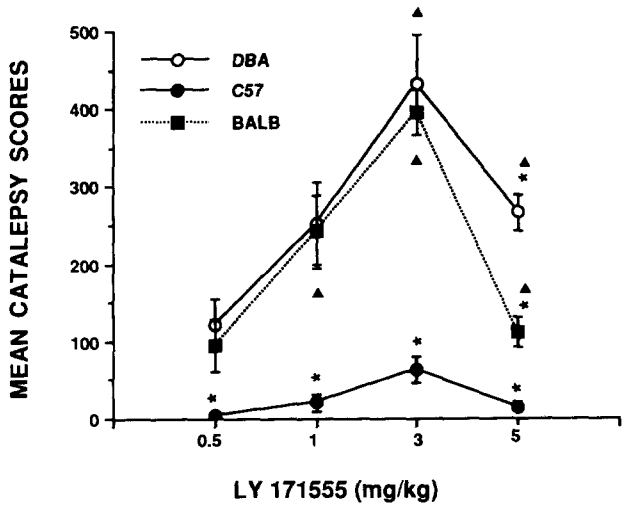

FIG. 1. Dose-response curve for cataleptic effects of LY 171555 in three strains of mice. Each point represents mean (± S.E.) total catalepsy scores (5–75 min) of 8 mice. *Significantly different ($p<0.05$) from scores of the other two strains at the same dose (Duncan test). ▲Significantly different ($p<0.01$) from scores obtained with the lower dose in the same strain (Duncan test).

variance (ANOVA), factors being: strain (3 levels: DBA, BALB, C57) and treatment (4 levels: 0.5, 1, 3, 5 mg/kg of LY 171555). Where allowed by ANOVA results, further analysis for individual between-group comparisons was carried out using post hoc tests (Duncan multiple range test).

Results

ANOVA showed a significant strain main effect, $F(2,82) = 52.23$, $p<0.001$, a significant treatment main effect, $F(3,82) = 21.87$, $p<0.001$, and a significant interaction between the two factors, $F(6,82) = 3.82$, $p<0.005$. When individual between group comparisons are considered both DBA and BALB strains are seen to exhibit a clear dose-dependent cataleptic response to the injection of the D2 DA receptor agonist, the highest effective dose being 3 mg/kg. As previously observed (18), at doses higher than 3 mg/kg, the cataleptic effect of LY 171555 tends to decline (Fig. 1).

The cataleptic response exhibited by C57 mice is significantly lower than that exhibited by the other two strains at all doses tested. Moreover, although also in this case the dose of 3 mg/kg seems the most effective, no significant difference is evident between catalepsy scores produced by the different doses of the D2 agonist in this strain (Fig. 1).

EXPERIMENT 2

In the previous set of experiments it was shown that C57 mice were the strain least sensitive to the cataleptic effects of LY 171555. We have recently shown that this strain also exhibits the strongest response to the effects of the D2 agonist as far as hyperdefensiveness is concerned, while DBA mice do not show significant changes and BALB mice are intermediate between C57 and DBA (6), both being far more sensitive than C57 mice to the cataleptic effects of the D2 agonist. On the basis of these results, it might be suggested that LY 171555-induced hyperdefensiveness and catalepsy are in negative correlation.

However, this hypothesis is consistent with the effects of LY 171555 on both C57 (high defensive response and low catalepsy) and DBA mice (no defensive response and high catalepsy) but not with those observed in BALB mice. In fact, this strain is characterized by high levels of defensive behavior (although lower than C57 mice) and by high catalepsy scores, thus pointing to a positive correlation between the two behavioral responses induced by LY 171555.

We have previously reported that, when administered to outbred CD1 mice, LY 171555 (1 mg/kg) induces a defensive response in 54% of individuals that falls within the response range of DBA mice (no effect), while the response of the other 46% falls within the range of C57 and BALB mice (6). Outbred strains represent nonhomogeneous populations characterized by both high genotypic and phenotypic variance, which present individual differences possibly related to some genetic factors characterizing inbred strains. It seems of interest to investigate whether the relationships between the two D2 receptor-mediated behaviors are an expression of the particular strains used in our study or whether they may also be envisaged in a nonhomogeneous population. In order to do this, we tested outbred CD1 mice for catalepsy and defensive behavior following administration of LY 171555.

Method

Naive male CD1 mice (Charles River Lab. Calco, Como, Italy) aged 11–12 weeks and weighing 25–28 g were housed as described in Experiment 1 and randomly assigned to experimental groups. Catalepsy was assessed as described in Experiment 1.

As far as defensive behavior is concerned, on the day of the test, naive male CD1 mice were introduced individually into the test box (transparent breeding cage with fresh hardwood sawdust on the floor) (15) 30 min after injection of either distilled water (H_2O) or LY 171555. Five min later a CD1 mouse from a different breeding cage was introduced into the box. Resident and intruder mice did not differ by more than 1 g in weight. Behavioral recordings were carried out as previously described (19) during a 5-min session. The duration (sec) of the following behavioral items (6,19) shown by the test animal was recorded: upright and sideways postures, escape and crouch, social investigation (sniff body and sniff nose), activity (horizontal and vertical), and immobility. Moreover, the behavioral items sideways and upright postures, escape and crouch were subsumed as a defense category. In an additional recording, the behavior of the opponents interacting with the test animals was also observed. No attack on the intruder of the resident was observed under these experimental conditions. Each test carried out in a sound-damped cubicle (see Experiment 1), was videotaped and later an experienced observer, unaware of the treatment condition of each animal, recorded behavioral items using a keyboard system connected to an Apple computer.

A group of 54 naive mice was used to test the correlation between catalepsy and behavioral categories and items shown during confrontation with opponents. They were assigned at random to two groups of 27 subjects, one of which was tested first for cataleptic response and the other for defensive behavior. Ten days later the first group was tested for defensive behavior and the second one for catalepsy.

Mice were injected with 1 mg/kg of LY 171555 before testing. The dose of 1 mg/kg was chosen since, on the basis of both previous (6) and preliminary experiments, it appeared to be the most suitable to detect both catalepsy and defensive behavior irrespective of the considerable individual differences expected to characterize a nonhomogeneous population. In fact, although higher doses of LY 171555 (up to 5 mg/kg) induce a further

TABLE 1

EFFECTS OF LY 171555 ON BEHAVIORAL CATEGORIES, DEFENSIVE ITEMS AND CATALEPSY IN CD1 MICE

	Vehicle	LY 171555 (1 mg/kg)
Category		
Activity	129.0 ± 16.7	49.5 ± 11.3‡
Immobility	198.2 ± 21.0	241.0 ± 10.7*
Defence	2.7 ± 1.7	42.1 ± 16.5*
Soc. investig.	14.0 ± 3.0	12.6 ± 4.0
Defensive Items		
Sideways	0.6 ± 0.5	16.8 ± 4.0*
Crouch	0.0 ± 0.0	10.2 ± 3.6†
Escape	1.7 ± 1.2	3.9 ± 1.6
Upright	0.3 ± 0.3	13.3 ± 2.9‡
Catalepsy Scores	0.0 ± 0.0	25.3 ± 9.4†

The results are expressed as mean (±S.E.) duration (sec).

*$p<0.5$, †$p<0.01$, ‡$p<0.001$, in comparison with vehicle-injected animals (Student's t-test, two-tailed). In the two testing conditions, each experimental group included 16 mice. For details see the Method section (Experiment 2).

increase in defensive items, excluding crouch, in C57 mice, they increase crouch and decrease the other defensive items in both BALB and CD1 mice, possibly as a result of a progressive motor impairment which would interfere with behavioral outcome (6).

Before ruling out a priming effect of the first injection of LY 171555, data obtained from the group injected for the first time were compared, for each behavioral test, with those obtained from the group receiving the D2 agonist 10 days later.

An additional group (n = 16) was injected with vehicle (H_2O) and tested for catalepsy and confrontation with intruders according to the aforementioned procedure. These animals were compared with a group (n = 16) of mice randomly collected from among the group of LY 171555-pretreated animals.

Student's t-test (two-tailed) was used for statistical analysis and Pearson's r coefficients on catalepsy and behavioral categories and items were calculated.

Results

No significant difference was observed between the behavioral effects of LY 171555 in naive mice and in mice that had received an injection of the D2 agonist 10 days before, either for catalepsy scores or for the behavioral categories recorded in the social test [catalepsy scores (means ± S.E.): naive = 30.8 ± 7, treated = 22 ± 7.8; $t(52) = 0.4$, n.s.; defense (mean duration ± S.E.): naive = 36.1 ± 11.7, treated = 44.7 ± 11.5; $t(52) = 0.52$, n.s.; immobility (mean duration ± S.E.):naive = 245.1 ± 9.8, treated = 220.6 ± 9.7; $t(52) = 1.74$, n.s.; activity (mean duration ± S.E.): naive = 53.2 ± 8.4, treated = 49.5 ± 8.8; $t(52) = 0.303$, n.s.; social investigation (mean duration ± S.E.): naive = 8.2 ± 1.1; treated = 11.2 ± 1.3; $t(52) = 1.774$, n.s.].

Mean (±S.E.) values for behavioral categories and items during confrontation with the opponent and for catalepsy are shown in Table 1. LY 171555 (1 mg/kg) produced a decrease of activity and an increase of immobility and defense without significantly affecting social investigation during confrontation with nonaggressive opponents. In particular, as regards defense, the D2 agonist produced a significant increase of upright and sideways postures as well as crouch, an item which is normally not affected in this test (6, 11, 19). Cataleptic effects of LY 171555 were also evident (Table 1).

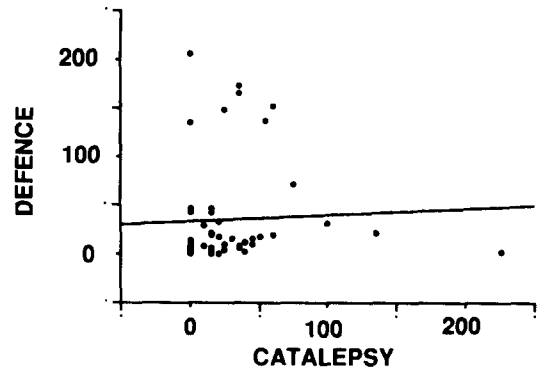

FIG. 2. Correlation between individual catalepsy scores and defensive behavior (sec) of CD1 mice (n = 54) injected with 1 mg/kg of LY 171555. For details see text.

It is worth noting that cataleptic scores are very similar to those observed in C57 mice (Experiment 1), while those related to defense are close to those previously observed in BALB mice (6).

The Pearson's r coefficient of .037 shows a lack of correlation between the two behavioral effects of LY 171555 (see also Fig. 2), indicating that catalepsy and defense are independently affected by the D2 agonist. In particular, 89% of individuals presented catalepsy scores falling in the range of C57 mice, while the remaining 11% fell in the range of BALB and DBA mice. By contrast, as we have previously (6) reported, about 55% of individuals presented defensive scores falling in the range of DBA mice, while about 45% were included in the range of C57 and BALB mice.

It must be taken into account, however, that akinetic animals have been shown to be treated by normal animals as subordinate (25). Since mice injected with LY 171555 showed decreased activity and increased immobility, the behavior of the opponent interacting with a hypokinetic mouse might, therefore, increase crouch in testing animals. If so, a positive correlation between catalepsy and crouch should be envisaged. On the other hand, since increased upright and sideways postures are also present in drug injected animals this may result in a negative correlation between such defensive items and catalepsy. Thus, when crouch, upright and sideways postures are subsumed as a unique defensive category, positive and negative correlations between catalepsy and the single defensive items may result in the absence of correlation between catalepsy and defense.

To assess this we calculated correlation between catalepsy and behavioral items recorded during interaction with nonaggressive opponents. A positive correlation between catalepsy and crouch (r = .3031, $p<0.5$), and a lack of correlation between catalepsy and upright (r = .0796), sideways posture (r = −.0075) and escape (r = .0338) were found, thus indicating that only crouch may be affected by hypokinetic effects of LY 171555 while the other defensive postures are not. This conclusion is also supported by the fact that within the defense category, no significant correlation was found between crouch and upright posture (r = −.1073), sideways posture (r = .113) and escape (r = −.14). Finally, a nonsignificant negative correlation between catalepsy and activity (r = −.2761) and no correlation between catalepsy and immobility (.0890), as well as social investigations (.010), were found, indicating that the changes in motility observed during social interactions are not related to the same factors as those involved in the D2 receptor-mediated catalepsy.

GENERAL DISCUSSION

The present results show that, when treated with the selective D2 agonist LY 171555, naive, intact mice exhibit behavioral responses, namely catalepsy and hyperdefensiveness, which are either absent or only very weakly stimulated when the mixed D_1/D_2 agonist apomorphine is used (13,14).

As regards the cataleptic effects of the D2 agonist our results confirm and extend previous results (18). Genotype appears to play a major role in the modulation of this behavioral effect since our results revealed marked strain-dependent differences in the intensity of the response.

The strain-dependent differences in the cataleptic effects of LY 171555 may depend on pharmacokinetic factors or on different D2 receptor density and distribution which could characterize the inbred strains of mice used in our study. It must be pointed out, however, that in preliminary experiments no cataleptic effects were observed at lower doses of LY 171555 (0.005–0.1 mg/kg), while a similar dose-dependent hypokinetic effect was observed in the three strains (7). These effects of LY 171555 on locomotion may represent a form of control over the role of pharmacokinetic factors.

C57 and DBA mice have been shown to be characterized by different density and distribution of DA receptors in the brain. However, higher B_{max} values for ^{3}H-spiperone binding in C57 in comparison with DBA mice have been reported in the striatum (2,16), a structure supposed to play a major role in DA-mediated catalepsy (13). Interstrain differences in spiperone binding in mesolimbic areas have also been reported; but while some authors have observed dramatically higher B_{max} values in olfactory tubercle of DBA in comparison with C57 mice (2), higher B_{max} values in limbic forebrain of the last strain compared to DBA have been shown by others (16). Both these results might be related to the different effects of LY 171555 on catalepsy and defensive behavior, nevertheless, they are not conclusive since the role of the aforementioned areas in catalepsy and defense remains to be clarified. Moreover, the limbic forebrain (16) includes a number of discrete areas receiving DA innervation (15) which may be characterized by specific DA receptor distribution patterns.

It must be pointed out that the cataleptic effects of LY 171555 may also involve presynaptic D2 receptors (13,18) localized either in target areas (striatum, nucleus accumbens) or in the substantia nigra and the ventral tegmental area. Recently, a cataleptic effect of low, supposedly presynaptic, doses of apomorphine has been described in mice (13,14) and in rats (1) adding further evidence to the hypothesis that inhibition of DA release by autoreceptors stimulation has neuroleptic-like effects (22,24). We have previously shown (18) that the selective D2 agonist LY 171555 induces catalepsy in the mouse and that this effect is prevented by the selective D2 antagonist (−)-sulpiride, suggesting that the autoreceptors mediating catalepsy in the mouse are D2 DA receptors.

The cataleptic effects of the D2 agonist may appear surprising for those acquainted with data obtained in the rat showing LY 171555-induced stereotypic behavior and locomotion in this species (8, 10, 27). It must be noted, however, that mice and rats may present different behavioral responses to dopaminergic treatment in several experimental situations [see (18) for a review].

A strain-dependent modulation of the effects of LY 171555 on defensive behavior was reported in previous studies (6,19) in which C57 mice were observed to present a clear-cut increase in defensive behavior during confrontation with nonaggressive opponents, while BALB mice were less responsive than C57 and the DBA strain did not show any significant effect of the D2 agonist on defense. These results and those relating to catalepsy seem, therefore, to indicate an inverse relationship between LY 171555-induced catalepsy and defense when C57 and DBA mice are considered and a positive or nonexistent relationship in the case of BALB mice.

To further investigate whether such a relationship between the two D2 receptor-mediated behaviors was an expression of the particular strains of mice used in our study or not we tested mice of the outbred CD1 strain for catalepsy and defensive behavior following administration of LY 171555 (1 mg/kg). No significant correlation between catalepsy and defense was observed. Furthermore, no correlation between catalepsy and defensive items, upright and sideways postures and escape was found while a positive correlation between catalepsy and crouch was evident, thus indicating that only crouch may be affected by hypokinetic effects of the D2 agonist. It is worth noting that no correlation between crouch and the other defensive items was observed in CD1 mice, thus indicating that LY 171555 affects defensive postures, upright and sideways, differently from crouch. These results are in agreement with previous results which showed no relationship between crouch and the expression of other defensive items in BALB and C57 mice treated with higher doses (up to 5 mg/kg) of LY 171555 (6,19). Moreover, it must be pointed out that mice subjected to experimental defeat experiences exhibit a clear-cut increase in upright and sideways postures but not in crouch, this increase being modulated by D2 receptors (19).

Taken together these results suggest that motor impairment neither necessarily prevents the expression of defensive behavior in the mouse nor facilitates it (25). They also indicate that hyperdefensiveness in the mouse is produced by the activation of a brain DA system, in which D2 receptors play a basic role, that differs from that involved in the mediation of cataleptic response. Such a view is consistent with a previous study indicating that DA mechanisms involved in motor behaviors are independent of those responsible for agonist behavior (17).

In conclusion, the present study shows that the D2 selective agonist LY 171555 produces different behavioral effects in the mouse, possibly activating distinct and independent DA systems. Moreover, our data indicate that the genetic make-up can independently modulate both defensive and cataleptic responses produced by stimulation of D2 DA receptors.

Further research will possibly reveal brain DA systems which play a crucial role in the expression of D2 receptor-mediated defense and catalepsy.

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