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D-1 and D-2 Receptor Blockade Have Additive Cataleptic Effects in Mice, but Receptor Effects May Interact in Opposite Ways[1]

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KLEMM, W. R. AND H. BLOCK. *D-1 and D-2 receptor blockade have additive cataleptic effects in mice, but receptor effects may interact in opposite ways.* PHARMACOL BIOCHEM BEHAV **29**(2) 223–229, 1988.—The dopaminergic role of D-1 and D-2 receptors in catalepsy was evaluated using drugs with preferential receptor affinities. The D-1 antagonist, SCH 23390, caused distinct catalepsy in mice at 1, 2, and 10 mg/kg, IP, but not at two lower doses. The selective D-1 blocker, molindone, also caused catalepsy at 5 and 10 mg/kg; and blockade of both receptor types produced additive cataleptogenic effects. Apomorphine (4 mg/kg), which is an agonist for both receptors, potentiated SCH 23390-induced catalepsy much more than it did the catalepsy induced by molindone; the potentiation was produced by higher, not lower, doses of apomorphine. To determine if the apomorphine potentiation was mediated by D-1 or D-2 receptors, we tested selective agonists in mice that were concurrently injected with selective blockers. SCH 23390-induced catalepsy was potentiated by a large dose of the D-2 agonist, bromocriptine. The catalepsy of D-2 blockade with molindone was not potentiated by the D-1 agonist, SKF 38393, which slightly disrupted the catalepsy of D-2 blockade. We conclude that catalepsy is not a simple D-2 blockade phenomenon and that preferential antagonism of either receptor type can cause catalepsy. Catalepsy is most profound when both receptor types are blocked. Dopamine agonists, in large concentrations, are known to promote movements, and thus it is not surprising that they tend to disrupt catalepsy. What is surprising is that the results suggest that the D-1 and D-2 systems interact in rather complex and seemingly opposite ways in the presence of large amounts of agonist with regard to mediation of catalepsy.

Catalepsy Dopamine Mice SCH 23390 SKF 38393 Bromocriptine Molindone Apomorphine

CATALEPSY is a state of immobility in which awkward postures are maintained; it occurs clinically in several disease states and can be produced experimentally in a variety of ways, but particularly with administration of dopamine-receptor antagonists. Most experimental catalepsy research with dopamine-antagonists has dealt with drugs that have a mixed action on the D-1 and D-2 receptor subtypes [7,15]; mixed dopamine-receptor antagonists also typically produce dose-related decrements in general locomotor activity as well as catalepsy [29]. Because most of these drugs preferentially antagonize D-2 receptors, catalepsy is commonly thought to be caused by specific D-2 antagonism [8,20]. Indeed, our recent study with a relatively preferential D-2 antagonist, molindone, indicates that antagonism of D-2 receptors does cause catalepsy [19].

What is not clear is the role of D-1 receptors in cataleptic phenomena. Primarily this lack of understanding results from the paucity of drugs that have preferential actions on the D-1 receptor. But now the role of D-1 receptors in catalepsy can be investigated because of the recent introduction of a preferential D-1 antagonist, SCH 23390 [12,13], and a preferential D-1 agonist, SKF 38393 [31,33]. Indeed, the lack of suitable pharmacological tools has caused the D-1 receptor, although it is known to mediate stimulation of adenylate cyclase, to be called "a receptor in search of a function" [15].

Both SCH 23390 and SKF 38393 have been studied in various contexts, and investigators were generally unable to ascertain any behavioral effects. In the original report on SCH 23390, for example, the authors concluded that the drug "causes no changes in gross behavior, neurological, or autonomic behavior" [13]; although catalepsy was not observed, two other reports indicate that the drug is cataleptogenic [6,25].

The experiments reported here tested several hypotheses:

(1) Haloperidol-induced catalepsy could result from its antagonism of either D-1 or D-2 receptors or both. Because our prior work showed that the preferential D-2 antagonist,

[1]A preliminary version of this research was presented at the annual meeting of the Society of Neuroscience, Nov. 12, 1986, Washington, DC.

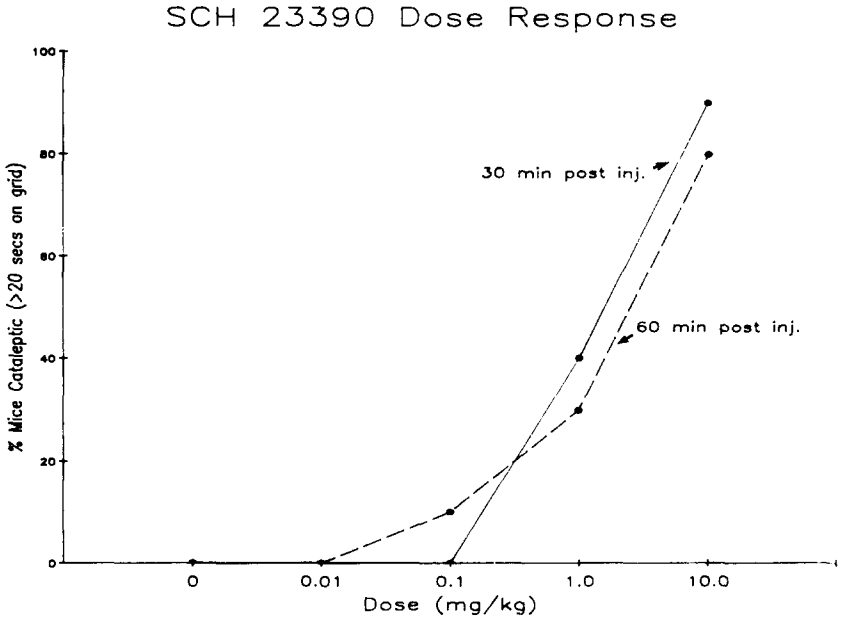

FIG. 1. Dose response data for cataleptogenic effects of the D-1 antagonist, SCH 23390. At both 30 and 60 minutes after injection, the higher doses promoted catalepsy, expressed here in terms of the percentage of mice that stayed on the inclined grid for more than 20 seconds. Data shown are medians. At 30 min post injection, the 25 percentile values for each successive dose were 2, 1, 1, 3, and 107 sec; the corresponding 75 percentile values were 5, 4, 3, 163, and >300 sec. A comparable distribution was evident for the 60-min values.

molindone, can cause catalepsy [19], we wished to test a preferential D-1 antagonist, SCH 23390.

(2) If the D-1 antagonist does not cause catalepsy, it would indicate that catalepsy is a pure D-2 phenomenon. If the D-1 antagonist does cause catalepsy, then its effect should be additive with concomitantly administered D-2 antagonist, thus explaining why haloperidol and related neuroleptics are such potent cataleptogens.

(3) A mixed agonist, such as apomorphine, markedly potentiates the catalepsy caused by haloperidol [19], but does not potentiate molindone-induced catalepsy [19]. This suggests that agonist action on D-2 receptors, when combined with D-1 antagonism, might augment catalepsy. If so, apomorphine or a preferential D-2 agonist ought to potentiate catalepsy when D-1 receptors are blocked. Opposite results might occur if a preferential D-1 agonist is given to a D-2 blocked animal.

METHOD

Subjects

Experiments were conducted on 220 male outbred Swiss white mice, weighing 20–30 g. Mice were housed in an air-conditioned vivarium, grouped 5 per standard plastic cage with bedding, which was changed three times a week. The light cycle was 12 hours light, 12 hours dark. Mice had been habituated to their room and to human contact for at least one month, and had continuous access to food and water. All testing was conducted during their light cycle, between 1300 and 1600 hours.

Induction of Catalepsy

As in previous studies [18,19], mice were tested for catalepsy by the method of placing them head down, approximately midway on a 39 cm tall × 25 cm wide sheet of hardware cloth (5 squares per cm grid) that was braced at a 45° angle. At the top of the grid, a vertical panel prevented mice from walking over the top of the grid; they could not leave the sides without falling to the floor. Access off the grid was via the bottom, which led to a plastic "home cage" containing the bedding to which they were accustomed. Mice were gently removed from their home cage by their tail and placed midway on the grid.

Under these conditions, normal undrugged mice quickly scurried down to the "home cage" at the bottom of the grid usually within 1–2 sec. Drug-induced catalepsy was scored in terms of the number of seconds mice stayed on the grid and in terms of the percentage of the mice tested which reached a criterion level of staying on for more than 20 sec. Mice were considered cataleptic rather than simply akinetic because they typically clutched at the wire with their claws and sustained abnormal postures, with limbs displaced variously in all directions.

Drugs

Drugs were prepared in sterile saline in a concentration that permitted the same small volume of drug solution (0.1 ml/10 g) to be injected as was injected with the saline control injection. Apomorphine solutions had ascorbic acid added (1 mg/ml) and sodium bisulfite (1 mg/ml) was added to the SKF 38393 to minimize decomposition. Bromocriptine was suspended in peanut oil because it is not soluble in saline. Drugs were made fresh about weekly, and stored at 42°F, with periodic analysis by HPLC to assure no change in potency. Doses, as the salt form, were: apomorphine, 0.01, 0.05, 0.1,

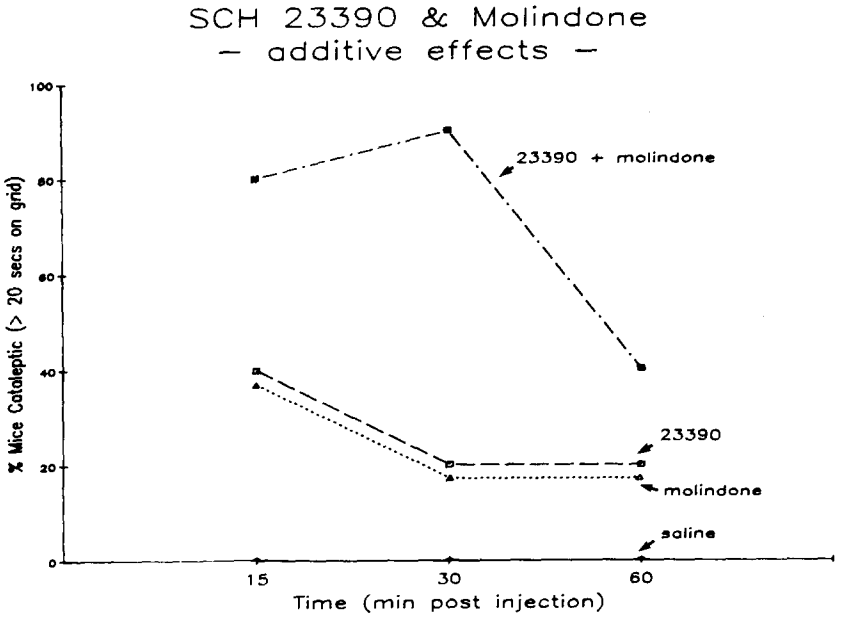

FIG. 2. Catalepsy induced by either SCH 23390 (1 mg/kg) or the D-2 antagonist, molindone (10 mg/kg), given alone, and the additive effect seen when both drugs are combined. Data shown are medians. The 25 and 75 percentile values for each treatment were: saline (2/6 sec), SCH 23390 (3/19 sec), molindone (2/24 sec), and SCH 23390 plus molindone (35/>300 sec).

1, 2, and 4 mg/kg; SCH 23390, 0.01, 0.1, 1.0, 2.0 or 10 mg/kg; SKF 38393, 10 mg/kg; molindone, 1, 5, or 10 mg/kg. All injections were intraperitoneal. When two drugs were given to the same mouse, they were given ten minutes apart. Each drug was injected via separate syringe and needle.

Experimental Design

There were five sets of experiments: (1) dose-response testing of SCH 23390 (n=50); (2) combined effects of SCH 23390 and molindone (n=30); (3) apomorphine effect on SCH 23390 or molindone catalepsy (n=60); (4) dose-response testing of apomorphine effects in mice given SCH 23390 (n=60); and (5) action of preferential agonists on catalepsy induced by antagonists that acted preferentially on the opposite receptor type (n=70). In any given experiment, each mouse received all of the treatments, with injection order randomized by Latin-square design. Ten mice were used in each dose or treatment group. In a prior study using the same methods [19], five repeated tests during 60 min of the same 10 mice after a saline injection produced essentially the same scores of time on the grid (1–3 sec). Thus, there was no indication of a "training" effect. Injections were made every 3 days. Catalepsy was assessed at 30 and 60 min after injection, except it was also evaluated at 15 min for treatments involving molindone (short half-life) and at 240 min for SCH 23390 (long half-life).

Statistical Analysis

Because the drugs caused some mice to remain cataleptic longer than the arbitrary cut-off time of 300 sec, nonparametric statistics were used (SAS software). Data were recorded in terms of the time spent immobile on the grid and the % of mice that remained immobile there for more than 20 sec. Statistical testing used the Kruskal-Wallis test on the raw data (sec elapsed before mouse left the grid). Where $p<0.05$, post-hoc Wilcoxon tests were performed on the data from selected pairs of treatment groups.

RESULTS

D-1 Blocker Induces Catalepsy

SCH 23390 caused a clear catalepsy at its two higher doses, at both 30 and 60 minutes after injection ($p<0.0001$) (Fig. 1). Median catalepsy time after the largest dose was >300 sec at 30 min post injection and 67 sec at 60 min. We tested for influence of repeated testing by the scrambled order of injections and by a separate experiment in 10 mice given repeated injections of only saline; their median scores at the 30 and 60 min times on three alternate days were 4.0/4.5 sec; 3.2/7.5 sec; and 5.0/5.5 sec.

D-1 Block Plus D-2 Block is Additive

Both SCH 23390 and molindone, given alone in doses of 1 and 10 mg/kg respectively, produced a comparable degree of catalepsy. But when these drugs were given together, the resulting catalepsy was greater than when either was given alone ($p<0.0001$) (Fig. 2). Median catalepsy times were greatest 15 min post injection, being 15.9 sec for SCH 23390 alone, 11 sec for molindone alone, and over 300 sec for both drugs combined. Post hoc tests showed that the combination results were significantly larger than either molindone alone or SCH 23390 alone.

Apomorphine Enhances Catalepsy Most with D-1 Rather Than D-2 Blockade

Over-all treatment effects in the testing of controls and apomorphine, SCH 23390, molindone, both alone and in

TABLE 1
APOMORPHINE POTENTIATION OF ANTAGONIST-INDUCED CATALEPSY

	Second Injection			
	Saline		Apomorphine (4 mg/kg)	
First Injection	30 min	60 min	30 min	60 min
Saline	3.5 (2/6)	2.5 (2/13)	—	—
Apomorphine (4 mg/kg)	13.0 (3/37)	11.0 (6/38)	—	—
SCH 23390				
0.1 mg/kg	2.0 (1/3)	3.5 (2/6)	12.5 (7/175)	57.0 (10/271)
1.0 mg/kg	30.1 (2/163)	13.5 (3/24)	91.0 (28/183)	151.0 (50/300)
Molindone				
5 mg/kg	4.9 (2/8)	2.0 (1/8)	6.5 (2/10)	2.5 (1/6)
10 mg/kg	8.6 (2/16)	3.0 (2/11)	11.0 (1/88)	2.5 (2/10)

Median catalepsy times (sec) (and 25/75 percentile values).

combination, were highly significant at both 30 and 60 min post injection ($p<0.0001$) (Table 1). These overall effects were attributable to two influences: (1) apomorphine alone caused catalepsy (compared with saline effects) ($p<0.02$ at 30 min and $p<0.05$ at 60 min); (2) apomorphine caused a distinctly greater potentiation of SCH 23390-induced catalepsy than it did for molindone-induced catalepsy at both 30 and 60 minutes and at both doses of antagonists (for the lower antagonist doses, $p<0.02$ at 30 min and <0.002 at 60 min; for the higher doses of SCH 23390, $p<0.04$ at 30 min and $p<0.0002$ at 60 min).

A follow-up dose-response analysis involved testing apomorphine given 15 min after SCH 23390 at 1 mg/kg. The apomorphine potentiation was dose-dependent, and it was the larger doses that were effective ($p<0.0001$, Table 2).

Agonist-Antagonist Interactions

D-1 agonist plus D-2 antagonist: mild interference. This combination of the agonist, SKF 38393, and the antagonist, molindone, produced no enhancement in catalepsy over that caused by molindone alone (Table 3). Indeed, there was a mild, but statistically significant reduction in catalepsy ($p<0.001$). This is consistent with the previous observation that apomorphine was not effective in enhancing molindone-induced catalepsy.

D-2 agonist plus D-1 antagonist: biphasic effect? In these experiments (see bottom half of Table 2), bromocriptine (8 mg/kg) seemed to decrease the catalepsy of lower doses of SCH 23390 (0.1 and 1.0 mg/kg), but at 2 mg/kg of SCH 23390, bromocriptine caused a two-fold increase in catalepsy time (49.5 sec vs. 21.0) at 30 min post injection ($p<0.0016$). However, none of the post-hoc tests for selected treatment pairs achieved statistical significance.

DISCUSSION

D-1 Blocker-Induced Catalepsy

Higher doses of SCH 23390 were clearly cataleptic. This has not been reported for mice, except with intracerebroventricular injection [37], although SCH 23390 reportedly causes hypomotility in rats [11,34] and mice [6]. SCH 23390-induced catalepsy has been observed in rats [33], with a potency comparable to haloperidol [6].

Full understanding of the D-1 antagonist promotion of catalepsy must consider the implications of the anatomical localization in major motor areas of the brain of D-1 receptors which appear to be concentrated in the neocortex, caudate, nucleus accumbens, and substantia nigra (pars reticulata), with diffuse distribution throughout the neocortex [1,15]. We cannot exclude the possibility that SCH 23390 results might have been mediated in part via binding with serotonin receptors. However, the affinity is 10–60 times less than the SCH 23390 affinity for the D-1 receptor [15]. The catalepsy at the lower, 1.0 mg/kg, dose is thus likely to be a pure D-1 antagonist phenomenon.

The results with molindone, given alone, replicate our earlier observation that this preferential D-2 antagonist is also cataleptogenic, but with shorter duration than SCH 23390. The shorter duration of molindone's action is attributed to its short biological half life (see [19]).

Additive Effects of D-1 Plus D-2 Blockade

The additive effects of D-1 antagonism with SCH 23390 and D-2 antagonism with molindone were quite evident; the diminished effect at 60 min is attributed to the short biological half-life of molindone [30]. The additive effect might be even more striking and prolonged with other selective D-2 antagonists that persist longer than molindone. The additive effects might explain the high cataleptogenic potency of haloperidol and other mixed antagonists.

Apomorphine Enhancement of D-1 Blocker-Induced Catalepsy

This enhancement is consistent with our earlier report [18] that apomorphine enhances the catalepsy caused by haloperidol, a drug that antagonizes both D-1 and D-2 receptors. Those studies also showed that little or no catalepsy enhancement was produced when molindone (10 mg/kg) was combined with apomorphine (8 mg/kg) [19]. In fact, our current data at 60 min (Table 1) suggest that molindone was antagonizing a tendency of this dose of apomorphine to cause catalepsy, which is consistent with the report [3] that molindone blocked the catalepsy in rats that was caused by low doses of apomorphine.

The ability of *low doses* (circa <0.1 mg/kg, IP) of apomorphine to suppress locomotion is well established (see

TABLE 2

DOSE-RESPONSE ANALYSIS OF APOMORPHINE POTENTIATION OF SCH 23390 CATALEPSY

Dose of Apomorphine (mg/kg)	Min Post Injection 15	30	60
0 (saline)	8 (4/16)	7 (3/11)	4 (3/9)
0.05	7 (3/40)	5 (3/12)	3 (2/4)
0.1	11 (7/19)	6 (3/20)	2 (2/7)
0.5	23 (4/29)	10 (4/55)	4 (2/28)
1.0	15 (6/48)	17 (6/107)	4 (3/6)
2.0	31 (17/63)	38 (26/76)	31 (7/96)

Median catalepsy times (sec) (and 25/75 percentile values).

TABLE 3

INTERACTIONS OF PREFERENTIAL AGONISTS WITH PREFERENTIAL ANTAGONISTS

	Second Injection: Saline		Preferential Agonist	
First Injection	30 min	60 min	30 min	60 min
Saline	2 (1/5)	1 (0/2)	—	—
SKF 38393 (10 mg/kg)	3 (1/9)	3 (2/4)	—	—
Bromocriptine (8 mg/kg)	3 [19]	—	—	—
			SKF 38393 (10 mg/kg)	
Molindone				
1 mg/kg	3 (1/13)	5 (2/10)	2 (1/3)	3 (2/30)
5 mg/kg	17 (7/37)	4 (1/10)	3 (1/13)	3 (1/9)
10 mg/kg	23 (9/68)	6 (2/19)	11 (2/41)	10 (1/17)
			Bromocriptine (8 mg/kg)	
SCH 23390				
0.1 mg/kg	6 (1/13)	6 (1/16)	5 (3/38)	2 (1/17)
1.0 mg/kg	18 (7/149)	6 (4/24)	10 (6/38)	3 (2/48)
2.0 mg/kg	21 (9/52)	9 (3/17)	50 (9/132)	6 (2/57)

Median catalepsy times (sec) (and 25/75 percentile values).

lit in [18]), and we have seen that it is cataleptic in mice up to 4 mg/kg [18]. Drug-induced hypomotility is not the same as catalepsy, but the two behaviors are certainly reinforcing. Our observation that it was the high doses of apomorphine that potentiated SCH 23390 catalepsy suggests that the D-1 blockade creates important conditions for demonstrating these unexpected dose effects. Our results are consistent with those recently reported [10] in which apomorphine caused behavioral depression and EEG deactivation when given in either low or high doses in rats pretreated with SCH 23390, presumably due to preferential action on a population of D-2 receptors whose action had been unmasked by the antagonism of D-1 receptors which otherwise would mediate an excitatory response [10]. Pretreatment with the D-2 antagonist, sulpiride, blocked the EEG deactivating response to apomorphine.

We are left with enigmas. Why did we see apomorphine potentiation here and in our previous study involving haloperidol [19], but failed to see such potentiation when bromocriptine was combined with haloperidol [18]? Also, why does apomorphine cause so much more enhancement of catalepsy when the antagonism is of the D-1 receptor rather than the D-2? Perhaps some insight into this issue can be derived from analysis of the results on agonist-antagonist interaction.

Agonist-Antagonist Interactions

Agonist effects on motor activity. Because D-1 antagonism caused catalepsy, it is not surprising that the D-1 agonist, SKF 38393 seemed to disrupt the catalepsy caused by molindone. The antithesis of catalepsy is compulsive movement, and some recent reports indicate that SKF 38393 may have such properties [2, 4, 23, 24].

D-1 agonistic effects have recently been reported to be expressed grossly in terms of general EEG and behavioral activation [27]. EEG activation is commonly accompanied by increased locomotor activity and/or enhanced muscle tone in rodents, suggesting that D-1 receptors enhance a state of "biological readiness" [17]. To a lesser extent, a similar effect may be produced by D-2 agonists. The D-2 agonist, bromocriptine, reportedly promotes locomotion in rats [14]. When given alone, even in low doses, bromocriptine does not have any locomotor suppression [36] or cataleptogenic properties like apomorphine [18].

Blockade of D-1 receptors with SCH 23390 reportedly antagonizes locomotor stimulation caused by apomorphine or SKF 38393 [6, 21, 25]. This parallels our observation that SCH 23390 is cataleptic ("anti-locomotor") and that SKF 38393 is antagonistic to the catalepsy.

Thus, we conclude that locomotion is promoted by both D-1 and D-2 agonists and disrupted, in the form of catalepsy, by antagonism of either D-1 and D-2 antagonists. However, we may not be justified in suggesting that both receptors independently mediate the same action on gross, whole-body movement. Our results showed that the D-2 agonist, bromocriptine, clearly enhanced the catalepsy caused by a high dose of SCH 23390. The data of Stoof and Kebabian [33] indicate that D-2 agonists inhibit D-1 mediated stimulation of adenylate cyclase, and others have confirmed that D-2 receptors mediate this inhibition [26]. Thus, we might predict that a D-1 antagonist should be potentiated by a D-2 agonist, which is what we observed in the catalepsy model. Bromocriptine is not an ideal D-2 agonist, and further studies are needed with other selective D-2 agonists.

Agonist influences on antagonist catalepsy. Dopamine agonists seem to have complex interactions with antagonists. The mixed agonist, apomorphine, clearly potentiates antagonist-induced catalepsy, especially that caused by the D-1 antagonist. This effect does not seem to be mediated by the D-1 agonist properties of apomorphine because the preferential agonist, SKF 38393, did not enhance catalepsy caused by molindone. The apomorphine effect is not entirely explained by assuming a high-affinity D-2 autoreceptor mediation of the enhancement, because both apomorphine and the D-2 agonist, bromocriptine, enhanced catalepsy at rather large doses and the bromocriptine effect appeared only with a large dose of SCH 23390.

D-2 agonists cause a direct D-2 response and may cause an indirect one that augments the functional consequences of

D-1 antagonism. Paradoxically, the D-2 agonist bromocriptine does have some motor enhancing (anti-cataleptic?) effects, such as inducing stereotypical licking and sniffing in rats and stimulation of general locomotor activity [14,22]. How can bromocriptine promote SCH 23390-induced catalepsy, rather than interfere with it? Perhaps this will not be demonstrable with other D-2 agonists. Species differences may be responsible. One simple explanation is that with the doses and conditions used bromocriptine acts preferentially on D-2 receptors [9,32] that respond to low doses of apomorphine with arrested motion and catalepsy [16]. It is also possible that motor-activating properties of bromocriptine cannot be manifest when D-1 receptors are not able to be activated by endogenous dopamine [34].

Recent studies of receptor interactions at the cellular and molecular level are provocative [5, 28, 29, 33–35], but have not yet provided a basis for explaining current findings.

We conclude that under certain conditions both D-1 and D-2 receptors can mediate motor activity. The opposite of movement is immobility, which although probably not equivalent to catalepsy, certainly would reinforce it. Thus, it is not surprising that antagonism of either receptor type promotes catalepsy. Likewise, concurrent administration of D-1 or D-2 agonist would tend to disrupt catalepsy, except perhaps in cases where high-affinity, cataleptic-promoting D-2 sites are acted upon. Important interactions of selective receptor blockade and agonist action are indicated by these data.

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