Pharmacology Biochemistry and Behavior, Vol. 46, pp. 759–768, 1993
Printed in the U.S.A.

0091-3057/93 $6.00 + .00

Selective D_1 and D_2 Dopamine Receptor Antagonists Produce Differential Effects on Reaction Time in the Rat

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Received 5 October 1992

MAYFIELD, R. D., P. K. RANDALL, W. W. SPIRDUSO AND R. E. WILCOX. *Selective D_1 and D_2 dopamine receptor antagonists produce differential effects on reaction time in the rat.* PHARMACOL BIOCHEM BEHAV **46**(4) 759–768, 1993.—The purpose of this investigation was to determine whether selectively blocking D_1 and D_2 dopamine receptors produces a differential effect on the characteristics (speed and success) of the reaction time response in rats. Animals were shaped to release a lever in response to an auditory/visual stimulus to avoid mild foot shock. The selective D_1 antagonist SCH 23390 (0, 70, and 100 μg/kg, IP) and the selective D_2 antagonists spiperone (0, 1, and 10 μg/kg, IP) and haloperidol (0, 10, and 100 μg/kg, IP) were studied for their effects on successful avoidance and response latency. SCH 23390 impaired successful avoidance and increased response latencies in a dose-dependent manner. Spiperone and haloperidol also produced dose-related decreases in successful avoidance. In contrast to the dose-related increase in response latencies produced by SCH 23990, 1 μg/kg spiperone and 10 μg/kg haloperidol significantly decreased the latencies of successful responses. Spiperone (10 μg/kg) had little effect on response latencies, while 100 μg/kg haloperidol increased them. The results of these experiments demonstrate that reaction time is differentially affected by selective dopamine receptor blockade and that the speed and success of reaction time responses can be independently modulated by D_1 vs. D_2 receptor activity.

Dopamine Reaction time Behavior Conditioned avoidance Receptor Agonist
Antagonist SCH 23390 Spiperone Haloperidol

WE have used a rodent reaction time paradigm, which is analogous to simple human reaction time, to study brain dopamine systems and their role in this discrete motor behavior. Reaction time has been demonstrated to be very sensitive to manipulations of dopaminergic systems. Deficits in reaction time can be detected when striatal dopamine stores are depleted by as little as 15–20% following 6-hydroxydopamine (6-OHDA) lesions of the nigrostriatal pathway (25). In addition, 6-OHDA lesions of the caudate nucleus, but not the nucleus accumbens, have been demonstrated to impair both the success and speed of reaction time responses (1).

A link has also been established between rodent reaction time and striatal D_2 dopamine receptor binding. In rat strains that differ in reaction time performance, the affinity of [^{3}H] spiperone to striatal D_2 receptors was higher, while D_2 receptor density (B_{max}) was lower in the more successful rat strain. Conversely, within a given strain, animals exhibiting better reaction time performance have been shown to have a lower D_2 binding affinity but greater D_2 density, as measured by [^{3}H]spiperone binding (26,32). Finally, in normal populations of animals, successful avoidance and response latency can be predicted based on the binding characteristics of striatal D_2 dopamine receptors (30).

Reaction time is also sensitive to the blockade of dopamine receptors by neuroleptic drugs, possibly analogous to their parkinson-like side effects in humans. For example, chlorpromazine, flupenthixol, and pimozide all produce deficits in both the speed and success of rodent reaction time performance (1,23,24). Since these compounds have nonselective actions at dopamine receptors, the effects of selective D_1 and D_2 receptor blockade on reaction time performance are still unknown.

Prior to the introduction of the selective D_1 antagonist SCH 23390 (9,10), most of the behavioral effects of dopamine antagonists were attributed to actions at D_2 receptors. This conclusion was based largely on the correlation between the antipsychotic potency of neuroleptics and their D_2 binding affinity (4). In addition, selective D_2 and nonselective antago-

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nists were almost equally effective in blocking agonist-induced stereotypic behavior, inhibiting conditioned avoidance and producing catalepsy (17). Thus, D_1 receptors were not thought to be active in a number of behavioral settings. Although SCH 23390 has a biochemical profile that is distinct from that of D_2 antagonists (10,12,28), its effects on a number of behavioral tests are indistinguishable from the effects of selective D_2 and mixed D_1/D_2 antagonists. For example, SCH 23390, as well as selective D_2 and nonselective dopamine antagonists, decreases spontaneous locomotion and rearing (3,7,8,27), produces catalepsy (3,16), and inhibits conditioned avoidance (6,10). However, the effect of selective dopamine antagonists on discrete motor responses such as reaction time has not been investigated.

The purpose of this investigation was to determine whether the speed and success of reaction time performance were affected differentially by selective D_1 (SCH 23390) and D_2 (spiperone, haloperidol) receptor blockade. We found that successful avoidance was impaired by both D_1 and D_2 receptor blockade. The decrease in successful avoidance produced by SCH 23390 was accompanied by an increase in response latencies. However, D_2 blockade had a biphasic effect on response latencies. Low doses (μg) of spiperone and haloperidol decreased, while higher doses increased, response latencies.

METHOD

Overview of the Behavioral Paradigm

In these experiments, reaction time was considered to be the speed with which rats released a lever from a depressed position in response to a conditioned stimulus (CS). Animals were shaped to hold a lever in a downward position. When the CS (auditory/visual) was activated, the rats released the lever within a given interval of time to avoid mild foot shock (unconditioned stimulus; UCS). The CS-UCS interval, the interval of time between the presentation of the CS and the onset of the UCS, was incrementally reduced as a function of success until the animals were successfully avoiding the UCS by releasing the lever with response latencies of 180–220 ms. The training procedure ensured that the animals were highly trained; however, some trials still occurred in which they had not released the bar within the CS-UCS interval. Thus, the primary latency-dependent variable had an artificial ceiling that was equivalent to the upper limit of the CS-UCS interval. Consequently, "response latency" as used here always refers to "successful" trials. An additional variable was recorded as "successful avoidance," which refers to the frequency of successful trials. Animals may be "unsuccessful" for two different reasons—either they do not initiate a response at all, or they initiate a response that is sufficiently slow that the CS-UCS interval is surpassed.

Reaction Time Measurement

Subjects. Three-month-old, male, Sprague-Dawley rats (N = 30) were housed in Plexiglas cages, three per cage, in a colony room maintained at 25°C on a 12L : 12D cycle. Animals had ad lib access to standard rat chow and water throughout the experiment. All behavioral testing was performed during the dark cycle.

Reaction time test chamber and shaping. The reaction time apparatus and shaping protocol have been described in detail previously (14). Briefly, the animals were conditioned in a Plexiglas operant conditioning chamber that included a floor through which current could be passed, a light, and an operant lever. The auditory stimulus was a 16-A, 600-V maximum AC relay (Cutler-Hammer), which was located outside the chamber. A standard interval timer (Lafayette) was used to control the CS-UCS interval. Response latencies were recorded to the nearest ms by a chronoscope (Standard Electric Time Corp.).

The shaping protocol consisted of two phases. After the animals had learned to hold the lever in its downward position, the CS and UCS were simultaneously initiated. The release of the lever in response to the UCS constituted an escape response. These trials, given to allow the animals to associate

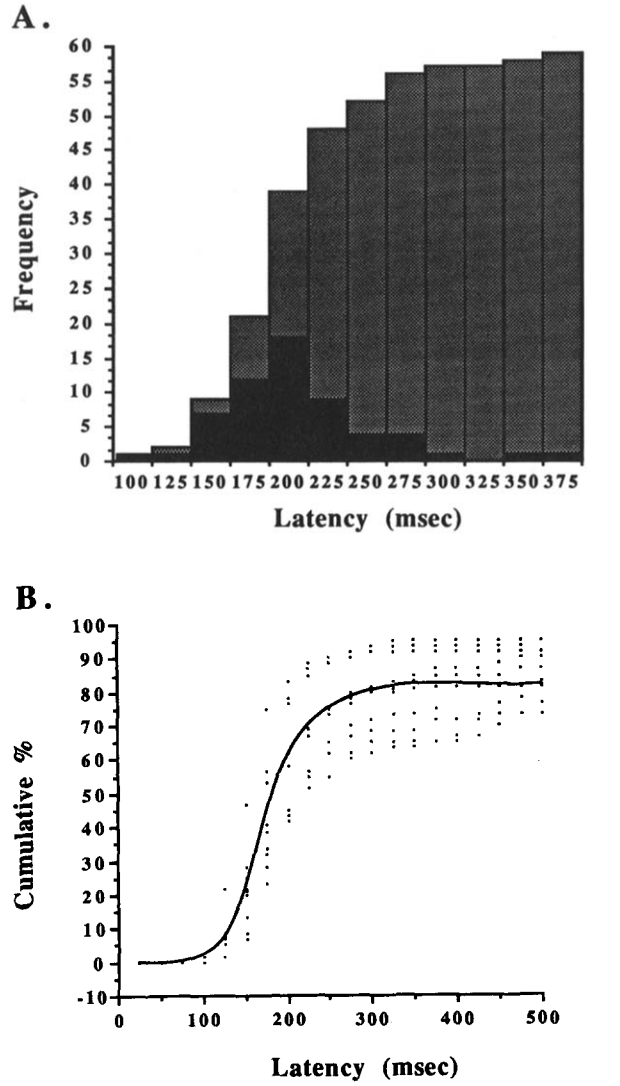

FIG. 1. (A) An example of a normal distribution of reaction time responses (in black) and the corresponding cumulative normal frequency distribution (in grey). (B) The fit of a typical reaction time data set (control conditions). The individual points represent the cumulative distributions from individual animals and the smooth line represents the best fitting nonlinear curve predicted by ALLFIT with the minimum response held constant at 0.

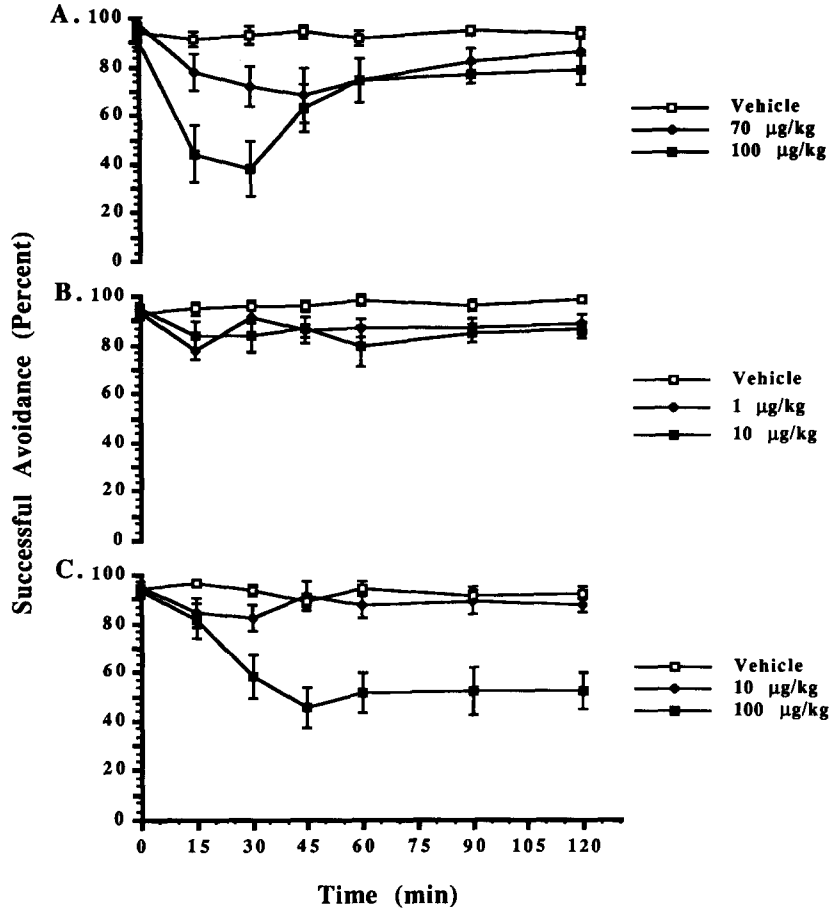

FIG. 2. (A-C) Illustrate the effects of SCH 23390 [(A) 0, 70, and 100 μg/kg, IP; $N = 8$], spiperone [(B) 0, 1, and 10 μg/kg, IP; $N = 9$], and haloperidol [(C) 0, 10, and 100 μg/kg, IP; $N = 10$] as a function of dose and time on percent avoidance. Open squares represent performance under control conditions, while filled diamonds and filled squares represent performance after the low and high drug doses, respectively. Data are expressed as mean successful avoidance ± SEM.

the CS with the UCS, were provided on the first day of conditioning only. After escaping the UCS for five consecutive trials with escape latencies of less than 180 ms, the CS was changed so that it preceded the UCS by defined intervals of time: 1000, 500, 300, or 200 ms. Each shaping session was started with a CS-UCS interval of 1000 ms. When the animals successfully avoided the UCS on five consecutive trials or on a total of 10 trials within a block of 25, the CS-UCS interval was reduced to the next shorter interval. The CS-UCS interval was returned to the next longer interval (1000 ms maximum) if the animals failed to avoid the UCS on five consecutive trials or on 10 trials within a block of 25.

Conditioning was continued until the animals were at least 80% successful at CS-UCS intervals of 1000, 500 and 300 msec, and at least 60% successful at a 200 msec CS-UCS interval. The second phase of shaping was started after these criteria were met. Each phase 2 session began with five "warm-up" trials at each of the phase 1 CS-UCS intervals (1000, 500, 300, and 200 ms), for a total of 20 consecutive trials. The animals were then returned to their home cage for 15 min before being given seven blocks of trials, 10 trials per block, at a 500-ms CS-UCS interval. The animals were returned to their home cage for 15 min between each block of trials. Conditioning was continued until the animals were at least 80% successful in avoiding the UCS for each block of trials within a given reaction time session. The total number of trials given during these sessions did not exceed 90.

Drugs and drug testing. Spiperone (RBI) and haloperidol (Janssen) were dissolved in 0.01 M tartaric acid (vehicle) and SCH 23390 (RBI) was dissolved in isotonic saline (vehicle). All drugs were administered IP in a volume of 1 ml/kg and tested against the respective vehicle during the reaction time testing sessions.

Only animals that met the behavioral testing criterion were used as subjects of the experiment. These animals received either SCH 23390 (0, 70, and 100 μg/kg; $N = 8$), spiperone (0, 1, and 10 μg/kg; $N = 9$), or haloperidol (0, 10, and 100 μg/kg; $N = 10$). The drug testing sessions were identical to the phase 2 shaping sessions except that animals received a given drug or vehicle injection after the first block of 500-ms trials. Thus, animals received 20 warm-up trials and then one block of 10 trials at the 500-ms CS-UCS interval prior to injection. Subsequently, blocks of trials were given at 15, 30, 45, 60, 90, and 120 min postinjection. Drug doses or the re-

spective vehicle were administered IP at weekly intervals in counterbalanced order.

Experimental Design and Analysis

Successful avoidance scores (percent successful trials within each block of 10 trials) and response latencies (average of successful trials within each block of trials) were analyzed independently by repeated measures ANOVA. Subsequent comparisons were made with univariate *F*-tests using the residual error term from the overall ANOVA. Bonferroni's method of controlling the overall error rate was used so that the nominal type 1 error rate was not exceeded (31).

In addition, the data were pooled across the time of peak drug effect and expressed as cumulative frequency distributions with 25-ms bin widths (see Fig. 1A). The distributions were fitted with the general logistic function (Fig. 1B), which closely approximates the cumulative normal (29), and then analyzed using the nonlinear curve fitting routine ALLFIT (5). ALLFIT has been used routinely to fit and analyze dose-response data from a variety of pharmacological and physiological systems (5,19). An advantage of ALLFIT is that the statistical analysis of constrained vs. unconstrained curve fits is more convenient than that required by the cumulative normal.

Using the terminology associated with fitting dose-response curves, the general form of the four-parameter logistic equation is given, where Y = response, a = minimum response, b = the logistic slope, c = ED_{50}, d = maximum response and x = dose.

$$Y = \frac{a - d}{1 + \left(\frac{x}{c}\right)^b} + d$$

The maximum response parameter, denoted as SA_{max} in this report, is equivalent to percent successful avoidance in most cases. Successful avoidance and SA_{max} can theoretically differ when the distributions of response latencies are truncated. That is, the estimated maximum of the cumulative distribution (SA_{max}) falls beyond the 500 ms successful response window. Under these circumstances, successful avoidance would not accurately reflect the true mean of the population of successful responses that resulted from a given drug treatment. Furthermore, a discrepancy between successful avoid-

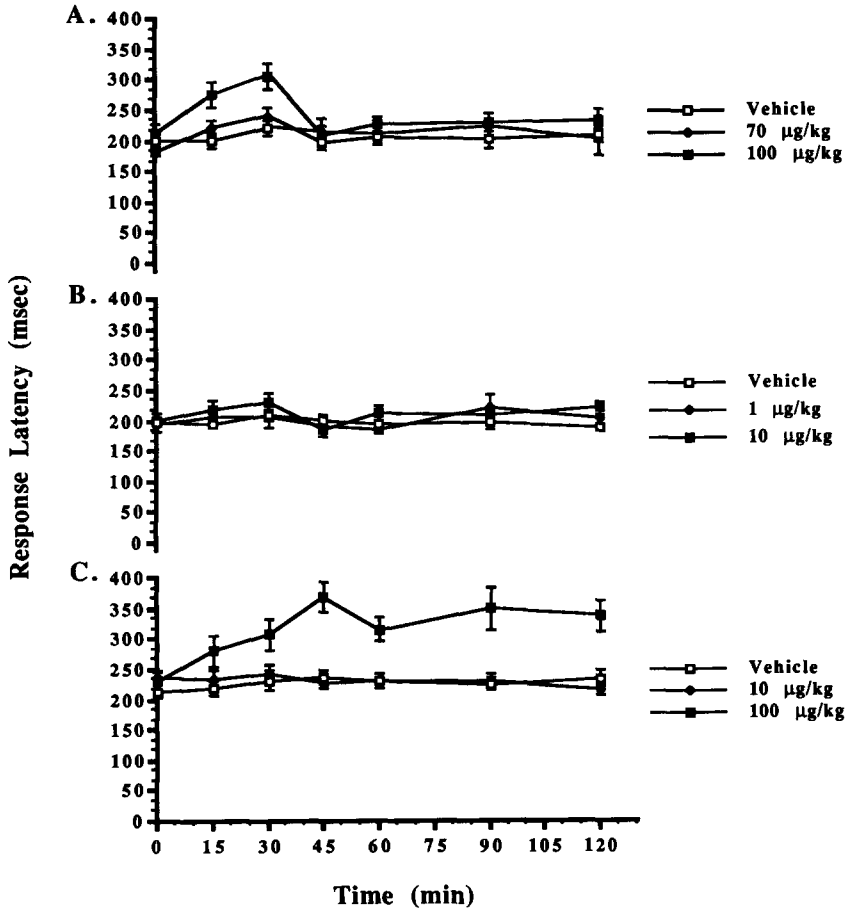

FIG. 3. (A-C) Illustrate the effects of SCH 23390 [(A) 0, 70, and 100 µg/kg, IP; N = 8], spiperone [(B) 0, 1, and 10 µg/kg, IP; N = 9], and haloperidol [(C) 0, 10, and 100 µg/kg, IP; N = 10] as a function of dose and time on response latency. Open squares represent performance under control conditions, while filled diamonds and filled squares represent performance after the low and high drug doses, respectively. Data are expressed as mean response latency ± SEM.

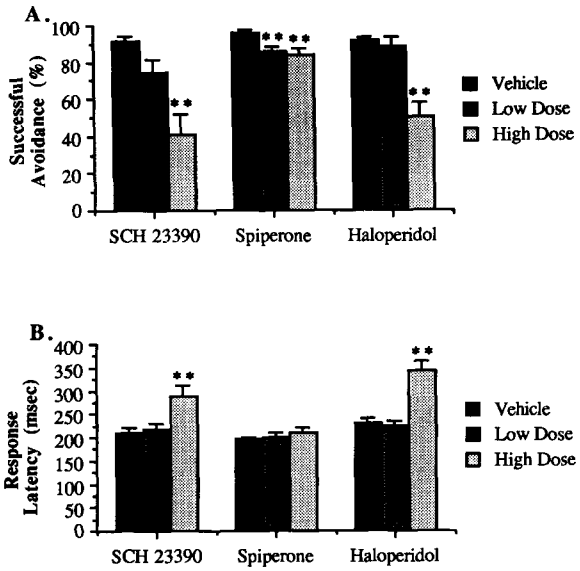

FIG. 4. (A and B) The effects of SCH 23390 (N = 8), spiperone (N = 9), and haloperidol (N = 10) on successful avoidance and response latency, respectively, as a function of dose collapsed across the time of peak drug effect. Data are expressed as the mean ± SEM (**p < 0.01).

ance and SA_{max} would indicate that drug-induced decrements in the frequency of successful responses were more related to slowed response speed rather than a simple failure to initiate responses.

The ED_{50}, when describing dose-response curves, is an estimate of the drug dose that results in a half-maximal drug response. In this report, this parameter estimate is denoted SL_{50} and approximates the median latency of the modelled population of reaction time responses. In addition, since the fitted distribution of latencies relates response success (y) as a function of response latency (x), the estimated frequency of successful responses that occur at or below any given latency can be determined from the fitted curve (see Fig. 1B). The slope (b) of the curve gives an indication of the variability in responses across the behavioral testing session. Since negative response latencies would represent anticipated trials, the minimum response parameter was constrained to 0 for all fits.

The significance of treatment effects on different parameters of the response was determined by comparing the residual variance estimates obtained from constrained vs. unconstrained fits of the data. Thus, if sharing a specific parameter or parameters degraded the fit of the data, the resulting residual sum-of-squares was significantly larger than the sum-of-squares of the residuals of the unconstrained fit and yielded a significant F-test (5). Overall drug treatment effects were tested by comparing the fit of the data when all parameters were shared vs. the unconstrained fit. Sharing all SA_{max} parameter estimates or all SL_{50} parameter estimates vs. the unconstrained fit of the data tests for overall effects on each parameter and is analogous to ANOVA main effects. Finally, sharing given pairs of parameters vs. the unconstrained fit was used to test for differences between individual parameter estimates and is analogous to individual comparisons.

RESULTS

The effects of SCH 23390, spiperone, and haloperidol on successful avoidance as a function of time are shown in Fig. 2. SCH 23390 (panel A) significantly decreased successful avoidance, $F(2, 14) = 11.37, p < 0.01$. The response to SCH 23390 peaked approximately 15–30 min after drug administration and then subsided as a function of time. This resulted in a significant dose × time interaction, $F(10, 70) = 3.13, p < 0.01$. Spiperone (panel B) produced a small but significant decrease in successful avoidance, $F(2, 16) = 9.79, p < 0.01$. The effect of spiperone was evident 15 min after drug administration and did not change as a function of time, $F(10, 80) = 0.68, p > 0.05$, indicating that the treatment effect persisted throughout the 120-min testing session. Successful avoidance was also decreased by haloperidol (panel C), $F(2, 18) = 20.54, p < 0.01$. The effect of haloperidol changed as a function of time, as indicated by a significant treatment × time interaction, $F(10, 90) = 2.27, p < 0.05$. The peak response to haloperidol occurred 45 min after drug administration and persisted throughout the remainder of the testing session.

Figure 3 shows the effects of each antagonist on response latency as a function of time. SCH 23390 resulted in a small, but significant, increase in response latency, $F(2, 14) = 4.91$, $p < 0.05$. The time of peak drug effect on response latency was roughly the same as it was for successful avoidance (15–30 min); however, the dose × time interaction was not significant, $F(10, 70) = 0.73, p > 0.05$. Spiperone treatment did not result in a significant treatment effect on response latency, $F(2, 16) = 0.25, p > 0.05$. Haloperidol significantly increased response latency, as shown in panel C, $F(2, 18) = 35.61, p < 0.01$. The time-response profile roughly mirrored that observed for successful avoidance.

In order to study the effects of each drug on the speed and success of the reaction time response in more detail, the data were collapsed across time of peak drug response based on successful avoidance. The dose × time interactions were significant for SCH 23390 and haloperidol. Thus, the data were collapsed across the 15–30- and 45–120-min trial blocks, respectively. The effects of spiperone did not change as a function of time, so the data were pooled across all blocks of trials (15–120 min).

Figure 4 (panels A and B) shows the effect of SCH 23390

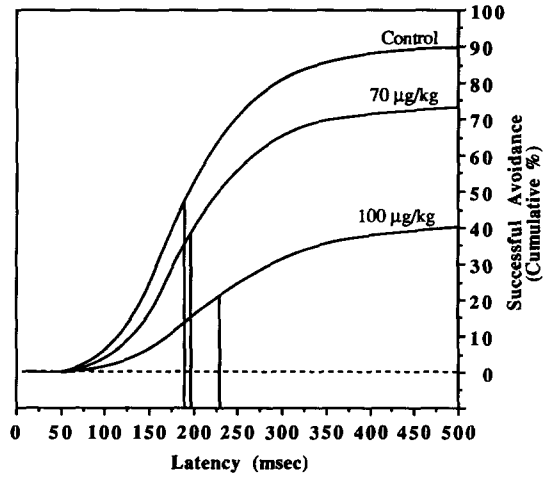

FIG. 5. Effects of SCH 23390 (0, 70, and 100 µg/kg, IP; N = 8) on the unconstrained fits of cumulative frequency distributions of raw reaction time data at the time of peak drug response (15–30 min). Minimum response parameters were held constant at 0. Drop lines illustrate SL_{50} estimates.

TABLE 1

SCH 23390: STATISTICAL ANALYSIS OF GOODNESS OF FIT FOR VARIOUS MODELS OF FIG. 5

Fit	Parameters Shared	Residual SS	*df*	*F*-Test	Confidence Level
1	None	144.5	51	–	–
2	All	8734	55	757.8	$p < 0.01$
3	All SA_{max}	677.9	53	94.1	$p < 0.01$
4	SA_{max}*, SA_{max}†	482.1	52	119.1	$p < 0.01$
5	SA_{max}†, SA_{max}‡	304.6	52	56.5	$p < 0.01$
6	All SL_{50}	277.3	53	23.4	$p < 0.01$
7	SL_{50}*, SL_{50}†	160.8	52	5.8	$p < 0.01$
8	SL_{50}†, SL_{50}‡	221.2	52	27.1	$p < 0.01$

*Vehicle (isotonic saline).
†SCH 23390 70 μg/kg.
‡SCH 23390 100 μg/kg.

on successful avoidance and response latency at the time of peak drug response. A significant decrease in successful avoidance (panel A), $F(2, 14) = 13.84$, $p < 0.01$, was accompanied by a corresponding increase in response latency (panel B), $F(2, 14) = 7.12$, $p < 0.01$. Planned comparisons failed to detect a statistical difference between control performance and the performance after 70 μg/kg SCH 23390 for either successful avoidance, $F(1, 14) = 3.12$, $p > 0.05$, or response latency, $F(1, 14) = 0.704$, $p > 0.05$. Reaction time performance was significantly worse after the 100 μg/kg dose compared to control on both successful avoidance, $F(1, 14) = 11.62$, $p < 0.01$, and response latency, $F(1, 14) = 9.36$, $p < 0.01$.

The effects of spiperone on successful avoidance and response latency at the time of peak drug effect are shown in Fig. 4 (panels A and B). In agreement with the results of the time-response analysis, successful avoidance was impaired significantly by spiperone (panel A), $F(2, 16) = 9.79$, $p < 0.01$. Individual comparisons indicated that each dose of spiperone produced a significant decrease in successful avoidance compared to control performance, $F(1, 16) = 11.6$, $p < 0.01$ (1 μg/kg), and $F(1, 16) = 17.22$, $p < 0.01$ (10 μg/kg). However, no differences in performance were detected between the 1 and 10 μg/kg doses, $F(1, 16) = 0.47$, $p > 0.05$. ANOVA failed to detect a significant treatment effect on response latency, $F(2, 16) = 1.51$, $p > 0.05$.

The effects of haloperidol on successful avoidance and response latency at the time of peak drug effect are shown in Fig. 4 (panels A and B). Haloperidol produced significant treatment effects on successful avoidance, $F(2, 18) = 24.38$, $p < 0.01$, and response latency, $F(2, 18) = 39.97$, $p < 0.01$. Planned comparisons failed to detect a statistical difference between control performance and the performance after 10 μg/kg haloperidol for either successful avoidance, $F(1, 18) = 0.20$, $p > 0.05$, or response latency, $F(1, 18) = 0.15$, $p > 0.05$. Performance after 100 μg/kg was significantly worse than control performance for both successful avoidance, $F(1, 18) = 39.19$, $p < 0.01$, and response latency, $F(1, 18) = 56.88$, $p < 0.01$.

The cumulative distributions of data that were fit with ALLFIT are shown in Figs. 5-7. The plateau of each curve represents the SA_{max} parameter estimate (analogous to successful avoidance) and the drop lines indicate the SL_{50} parameter estimate (analogous to response latency). Standard errors were taken from the dispersion matrix. For all fits, the minimum response parameter was always held constant at 0 (anticipated trials were not included in the analysis) and the slope was always allowed to diverge between curves.

For the purpose of comparison, the SCH 23390 data (see following paragraph) were also fit using the cumulative normal function rather than the logistic function. This technique resulted in SA_{max} estimates of 87.2 ± 1.3, 71.2 ± 1.1, and 39.1 ± 1.0 after 0, 70, and 100 μg/kg SCH 23390, respectively. SL_{50} estimates were 188.4 ± 3.37, 197.1 ± 4.9, and 225.5 ± 5.8 in response to the same doses of SCH 23390, respectively.

The fitted cumulative distributions of SCH 23390 data are shown in Fig. 5. Table 1 lists the results of the statistical analysis of different fits of the data. Fit 2 vs. fit 1 indicates that SCH 23390 produced an overall treatment effect. SA_{max}

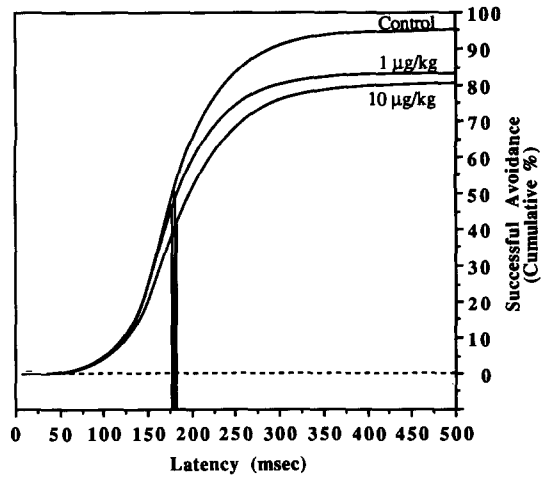

FIG. 6. Effects of spiperone (0, 1, and 10 μg/kg, IP; $N = 9$) on the unconstrained fits of cumulative frequency distributions of raw reaction time data at the time of peak drug response (15-120 min). Minimum response parameters were held constant at 0. Drop lines illustrate SL_{50} estimates.

estimates decreased significantly from 91.0 ± 0.9% under control conditions to 73.8 ± 0.9% and 41.6 ± 1.4% after 70 and 100 μg/kg SCH 23390, respectively (fit 3 vs. fit 1). The decrease in SA_{max} was accompanied by a corresponding increase in SL_{50}. SL_{50} estimates increased from 189.1 ± 1.9 ms under control conditions to 196.5 ± 2.3 and 228.4 ± 6.4 ms after 70 and 100 μg/kg SCH 23390, respectively (fit 6 vs. fit 1). Both response parameters were significantly impaired (relative to 70 μg/kg) after 100 μg/kg SCH 23390 (Table 1, fits 5 and 8 vs. fit 1). In contrast to the lack of effects detected by univariate *F*-tests, the nonlinear analysis revealed significant decrements in reaction time performance (relative to control) after 70 μg/kg SCH 23390 for both SA_{max} (Table 1, fit 4 vs. fit 1) and SL_{50} (Table 1, fit 7 vs. fit 1).

The cumulative distributions of spiperone data are shown in Fig. 6 and the results of the statistical analysis of different fits of the data are listed in Table 2. Spiperone produced an overall treatment effect, as indicated by fit 2 vs. fit 1. SA_{max} estimates were significantly decreased from 94.8 ± 0.7% under control conditions to 82.8 ± 0.7% and 80.3 ± 0.7% after 1 and 10 μg/kg spiperone, respectively (Table 2, fit 3 vs. fit 1). In contrast to the results of the univariate *F*-tests, subsequent analysis of SA_{max} indicated that spiperone produced a significant dose-dependent decrease on this parameter estimate (Table 2, fits 4 and 5 vs. fit 1). The nonlinear analysis also revealed a significant effect of spiperone on SL_{50}, indicating that spiperone did have an effect on reaction time response latencies (Table 2, fit 6 vs. fit 1). In contrast to the dose-related increase in SL_{50} estimates produced by SCH 23390, spiperone (1 μg/kg) significantly decreased this parameter estimate from 180.6 ± 1.4 ms under control conditions to 176.3 ± 1.5 ms (Table 2, fit 7 vs. fit 1). Spiperone (10 μg/kg) produced a small, nonsignificant increase in SL_{50} (182.9 ± 1.8 ms) compared to control (Table 2, fit 8 vs. fit 1).

The fitted distributions of haloperidol data are shown in Fig. 7 and the results of the statistical analysis of different fits of the data are listed in Table 3. Haloperidol produced a highly significant overall treatment effect (fit 2 vs. fit 1). Fit 3 vs. fit 1 indicates that haloperidol significantly impaired SA_{max}. SA_{max} estimates decreased from 91.5 ± 0.7% under control conditions to 86.6 ± 0.07% and 47.2 ± 2.9% after 10 and 100 μg/kg haloperidol, respectively. Subsequent analysis of SA_{max} estimates indicated that haloperidol's effect on

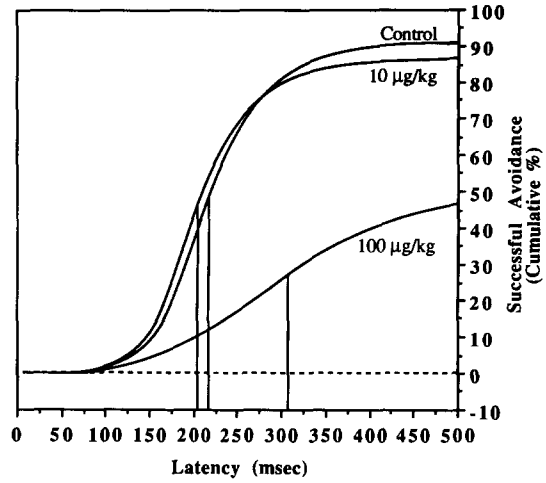

FIG. 7. Effects of haloperidol (0, 10, and 100 μg/kg, IP; $N = 10$) on the unconstrained fits of cumulative frequency distributions of raw reaction time data at the time of peak drug response (45–120 min). Minimum response parameters were held constant at 0. Drop lines illustrate SL_{50} estimates.

this parameter was dose dependent (fits 4 and 5 vs. fit 1). Figure 7 also illustrates that haloperidol produced a similar pattern of effects on SL_{50} estimates, as did spiperone (Fig. 6). The low dose of haloperidol (10 μg/kg) significantly decreased the SL_{50} parameter estimate from 217.2 ± 1.5 ms under control conditions to 204.0 ± 1.4 ms (fit 7 vs. fit 1), while 100 μg/kg significantly increased the SL_{50} parameter estimate to 306.8 ± 11.5 ms (fit 8 vs. fit 1).

DISCUSSION

The most important finding from this study was that selective D_1 and D_2 antagonists produce differential effects on reaction time performance in rats. Furthermore, it was demonstrated that different characteristics of the behavioral response (speed and success) were modulated independently by selective dopamine receptor blockade. Thus, impaired successful avoid-

TABLE 2

SPIPERONE: STATISTICAL ANALYSIS OF GOODNESS OF FIT FOR VARIOUS MODELS OF FIG. 6

Fit	Parameters Shared	Residual SS	*df*	*F*-Test	Confidence Level
1	None	151.1	51	–	–
2	All	1124	55	82.1	$p < 0.01$
3	All SA_{max}	834.2	53	115.3	$p < 0.01$
4	SA_{max}*, SA_{max}†	556.0	52	136.7	$p < 0.01$
5	SA_{max}†, SA_{max}‡	168.6	52	5.9	$p < 0.05$
6	All SL_{50}	175.8	53	4.2	$p < 0.05$
7	SL_{50}*, SL_{50}†	163.7	52	4.3	$p < 0.05$
8	SL_{50}*, SL_{50}‡	154.2	52	1.0	NS

*Vehicle (0.01 M tartaric acid).
†Spiperone 1 μg/kg.
‡Spiperone 10 μg/kg.

TABLE 3

HALOPERIDOL: STATISTICAL ANALYSIS OF GOODNESS OF FIT FOR VARIOUS MODELS OF FIG. 7

Fit	Parameters Shared	Residual SS	*df*	*F*-Test	Confidence Level
1	None	122.1	51	–	–
2	All	10640	55	663.0	$p < 0.01$
3	All SA_{max}	236.6	53	11.3	$p < 0.01$
4	SA_{max}*, SA_{max}†	178.4	52	7.7	$p < 0.01$
5	SA_{max}†, SA_{max}‡	176.6	52	7.5	$p < 0.01$
6	All SL_{50}	795.0	53	60.5	$p < 0.01$
7	SL_{50}*, SL_{50}†	214.6	52	11.7	$p < 0.01$
8	SL_{50}*, SL_{50}‡	582.1	52	52.2	$p < 0.01$

*Vehicle (0.01 M tartaric acid).
†Haloperidol 1 μg/kg.
‡Haloperidol 10 μg/kg.

ance could be accompanied by increases or decreases in response latency.

Successful avoidance was dose-dependently decreased by the D_1 antagonist SCH 23390, as well as by the D_2 antagonists spiperone and haloperidol. Successful avoidance has also been demonstrated to be impaired by nonselective dopamine antagonists (1,23,24). These similar effects of selective and nonselective dopamine antagonists on successful avoidance are consistent with a number of other reports, which demonstrate that the effects of D_1 blockade with SCH 23390 are indistinguishable from those produced by D_2 or mixed D_1/D_2 antagonists on a number of dopamine-mediated behaviors. For example, the ability of SCH 23390 to induce catalepsy (3,16), inhibit conditioned avoidance (6,10), and block spontaneous locomotion and rearing (3,7,8,27) is indistinguishable from that of D_2 or mixed D_1/D_2 antagonists.

There were, however, differences between the effects of D_1 and D_2 antagonists on the latencies of the successful responses. The dose-dependent decrease in successful avoidance that resulted from D_1 receptor blockade was accompanied by a dose-dependent *increase* in response latencies. This finding suggests that D_1 receptor blockade results in a slowing of response speed, which, in turn, results in a decrease in the number of trials initiated successfully within the 500-ms response window. In contrast, low doses (μg) of both spiperone and haloperidol significantly *decreased* the latencies of successful responses. The decreases in response latencies occurred despite deficits in successful avoidance. Thus, rather than being generally slower on all responses, animals that were treated with the D_2 antagonists simply did not respond on all trials. At higher doses, spiperone and haloperidol increased response latencies.

These results suggest that the speed of reaction time responses may be sensitive to manipulations of D_1 receptors, while D_2 receptors may be involved in modulating the probability of initiating a response. The dependence of response speed on D_1 receptor activity is supported by two findings. First, blocking D_1 receptor output with SCH 23390 lengthened response latencies. Secondly, using low doses of spiperone and haloperidol to shift the balance of D_1/D_2 receptor activity in favor of D_1 stimulation, response speed was enhanced. Similar roles for D_1 and D_2 receptors have been demonstrated in modulating other dopamine-mediated behaviors. For example, dopamine agonist-induced oral behavior is facilitated when the balance of D_1/D_2 receptor activation is shifted toward D_1 by pretreating animals with selective D_2 antagonists (13,20,21) or attenuated by selectively stimulating D_2 receptors (11). This type of D_1/D_2 interaction has also been found to modulate some components of apomorphine-induced stereotypic behavior (33).

The above hypothesis depends heavily on the ability to detect decreases in response latencies. The animals that were used in these experiments were trained extensively and were not tested until they had met a rigid performance criterion. Therefore, by design, decreases in response latencies were small and difficult to detect. However, since the animals were highly practiced, it is unlikely that the decrease in response latencies produced by D_2 blockade was due to practice effects or day-to-day variability in reaction time performance.

The decrease in response latency that was reported here is not a unique effect of D_2 receptor blockade. We have also demonstrated that response latencies decrease in response to systemically administered amphetamine, an indirect dopamine agonist (15). In addition, the local application of muscimol, a γ-aminobutyric acid-A ($GABA_A$) agonist, into the substantia nigra reticulata decreases response latency (15). Intranigral injections of $GABA_A$ agonists mimic the effects of systemically administered dopamine agonists (2,18,22). Thus, in addition to selective D_2 receptor blockade, conditions that result in or mimic dopamine receptor stimulation can also enhance response speed.

A nonlinear data analysis technique was also introduced that offers some advantages over traditional ANOVA in the analysis of reaction time data. Clearly, animals may be unsuccessful on some trials because they fail to respond at all or because they respond too slowly. The percent successful variable does not reflect this difference. Furthermore, the mean latency of successful trials may also be insensitive to this difference, or even distort the findings by systematically selecting the faster (more successful) trials for analysis. Significantly, we are unable to measure latencies greater than 500 ms because such responses are truncated. The nonlinear analysis is an attempt to more clearly describe the full distribution of response latencies in the different treatment groups. In untreated animals, there is a well-defined, bell-shaped, distribution of successful response latencies that is contained within

the 500-ms CS-UCS interval (i.e., essentially 100% success) (see Fig. 1A). If treated animals fail to respond on some trials, but respond normally on others, we would simply expect the size of the distribution (SA_{max}) to decrease. The median latency (SL_{50}) would not change. Animals receiving the low dose of both spiperone and haloperidol actually had shorter median latencies (reduced SL_{50}) than controls, while the SA_{max} was diminished. On the other hand, if responses are uniformly slower, we would expect the distribution to be truncated at the 500-ms CS-UCS interval, resulting in a greater median latency (SL_{50}), but not necessarily a change in the SA_{max}. SCH 23390, for example, increased the median latency as well as decreased the SA_{max}.

In summary, the D_1 antagonist SCH 23390 and the D_2 antagonists spiperone and haloperidol produced differential effects on the characteristics of the reaction time response. Both D_1 and D_2 blockade dose-dependently decreased successful avoidance. The decrements in success were accompanied by an increase in response latency in response to D_1 blockade and D_2 blockade with higher doses of D_2 antagonists. However, lower doses of both spiperone and haloperidol decreased response latency. It is suggested that the differential effects of D_1 and D_2 receptor blockade on reaction time were due, in part, to changes in the balance of D_1/D_2 receptor output and that D_1 and D_2 receptors may independently modulate functions that are reflected as changes in the speed and success of reaction time performance.

ACKNOWLEDGEMENTS

This work was supported in part by grants NS20827 (R.E.W. and W.W.S.), MH44799 (P.K.R. and R.E.W.), and BNS8808129 (P.K.R. and R.E.W.). R.E.W. is a Louise Pfeiffer Centennial Fellow of the College of Pharmacy and Neuropharmacology Program Head with the Institute for Neuroscience of the University of Texas.

REFERENCES

1. Amalric, M.; Koob, G. F. Depletion of dopamine in the caudate nucleus but not in nucleus accumbens impairs reaction-time performance in rats. J. Neurosci. 7:2129-2134; 1987.
2. Baumeister, A. A.; Frye, G. D. Involvement of the midbrain reticular formation in self-injurious behavior, stereotyped behavior, and analgesia induced by intranigral microinjection of muscimol. Brain Res. 369:231-242; 1986.
3. 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.
4. Creese, I.; Burt, D. R.; Snyder, D. R. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science 192:481-483; 1976.
5. De Lean, A.; Munson, P. J.; Rodbard, D. Simultaneous analysis of families of sigmoidal curves: Application to bioassay, radioligand assay, and physiological dose-response curves. Am. J. Physiol. 235:E97-E102; 1978.
6. Gerhardt, S.; Gerber, R.; Liebman, J. M. SCH 23390 dissociated from conventional neuroleptics in apomorphine climbing and primate dyskinesia models. Life Sci. 37:2355-2363; 1985.
7. Gessa, G. L.; Porceddu, M. L.; Collu, M.; Mereu, G.; Serra, M.; Ongini, E.; Biggio, G. Sedation and sleep induced by high doses of apomorphine after blockade of D-1 receptors by SCH 23390. Eur. J. Pharmacol. 109:269-274; 1985.
8. Hoffman, D. C.; Beninger, R. J. The D1 dopamine receptor antagonist, SCH 23390, reduces locomotor activity and rearing in rats. Pharmacol. Biochem. Behav. 22:341-342; 1985.
9. Hyttel, J. SCH 23390—the first selective dopamine D-1 antagonist. Eur. J. Pharmacol. 91:153-154; 1983.
10. Iorio, L. C.; Barnett, A.; Leitz, F. H.; Houser, V. P.; Korduba, C. A. SCH 23390, a potential benzazepine antipsychotic with unique interactions on dopaminergic systems. J. Pharmacol. Exp. Ther. 226:462-468; 1983.
11. Johansson, P.; Levin, E.; Gunne, L.; Ellison, G. Opposite effects of a D1 and D2 agonist on oral movements in rats. Eur. J. Pharmacol. 134:83-88; 1987.
12. Kebabian, J. W.; Calne, D. B. Multiple receptors for dopamine. Nature 277:93-96; 1979.
13. Mandel, R. J.; Yurek, D. M.; Randall, P. K. Behavioral demonstration of a reciprocal interaction between dopamine receptor subtypes in the mouse striatum: Possible involvement of the striato-nigral pathway. Brain Res. Bull. 25:285-292; 1990.
14. Mayfield, R. D.; Grant, M.; Schallert, T.; Spirduso, W. W. Tolerance to the effects of ethanol on the speed and success of reaction time responding in the rat: Effects of age and intoxicated practice. Psychopharmacology (Berlin) 107:78-82; 1992.
15. Mayfield, R. D.; Randall, P. K.; Spirduso, W. W.; Wilcox, R. E. The effects of systemically administered dopaminergic and brain regional GABA-ergic agonists and antagonists on reaction time response parameters in the rat. Soc. Neurosci. Abstr. 15: 466.7; 1989.
16. Morelli, M.; Di Chiara, G. Catalepsy induced by SCH 23390 in rats. Eur. J. Pharmacol. 117:179-185; 1985.
17. Niemegeers, C. J.; Janssen, P. A. A systematic study of the pharmalogical activities of dopamine antagonists. Life Sci. 24:2201-2216; 1979.
18. Oberlander, C.; Dumont, C.; Boissier, J. R. Rotational behaviour after unilateral intranigral injection of muscimol in rats. Eur. J. Pharmacol. 43:389-390; 1977.
19. Randall, P. K. Quantitative analysis of behavioral pharmacological data. In: Central determinants of age-related declines in motor function. New York: New York Academy of Sciences; 1988: 124-139.
20. Rosengarten, H.; Schweitzer, J. W.; Friedhoff, A. J. Induction of oral dyskinesias in naive rats by D1 stimulation. Life Sci. 33: 2479-2482; 1983.
21. Rosengarten, H.; Schweitzer, J. W.; Friedhoff, A. J. Selective dopamine D2 receptor reduction enhances a D1 mediated oral dyskinesia in rats. Life Sci. 39:29-35; 1986.
22. Scheel-Krüger, J.; Arnt, J.; Magelund, G. Behavioural stimulation induced by muscimol and other GABA agonists injected into the substantia nigra. Neurosci. Lett. 4:351-356; 1977.
23. Skjoldager, P.; Fowler, S. C. Effects of pimozide, across doses and within sessions, on discriminated lever release performance in rats. Psychopharmacology (Berlin) 96:21-28; 1988.
24. Spirduso, W. W.; Abraham, L. D.; Wolf, M. D. Effects of chlorpromazine on escape and avoidance responses: A closer look. Pharmacol. Biochem. Behav. 14:433-438; 1981.
25. Spirduso, W. W.; Gilliam, P. E.; Schallert, T.; Upchurch, M.; Vaughn, D. M.; Wilcox, R. E. Reactive capacity: A sensitive behavioral marker of movement initiation and nigrostriatal dopamine function. Brain Res. 335:45-54; 1985.
26. Spirduso, W. W.; Gilliam, P.; Wilcox, R. E. Speed of movement initiation performance predicts differences in [^{3}H]spiroperidol receptor binding in normal rats. Psychopharmacology (Berlin) 83: 205-209; 1984.
27. 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. Implications for the roles of D1 and D2 receptors. Neuropharmacology 25:455-463; 1986.
28. Stoof, J. C.; Kebabian, J. W. Opposing roles for D-1 and D-2 dopamine receptors in efflux of cyclic AMP from rat neostriam. Nature 294:366-368; 1981.
29. Waud, D. R. On biological assays involving quantal responses. J. Pharmacol. Exp. Ther. 183:577-607; 1972.

30. Wilcox, R. E.; Mudie, E.; Mayfield, D.; Young, R. K.; Spirduso, W. W. Movement initiation characteristics in young adult rats in relation to the high- and low-affinity agonist states of the striatal D2 dopamine receptor. Brain Res. 443:190–198; 1988.
31. Winer, B. J. Statistical principles. In: Experimental design. New York: McGraw-Hill; 1971.
32. Wolf, M. D.; Wilcox, R. E.; Riffee, W. H.; Abraham, L. D. Strain differences in dopamine receptor function and the initiation of movement. Pharmacol. Biochem. Behav. 13:5–7; 1980.
33. Yurek, D. M.; Randall, P. K. Simultaneous catalepsy and apomorphine-induced stereotypic behavior in mice. Life Sci. 37: 1665–1673; 1985.