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Apomorphine and Amphetamine Produce Differential Effects on the Speed and Success of Reaction Time Responding in the Rat

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MAYFIELD, R. D., P. K. RANDALL, W. W. SPIRDUSO AND R. E. WILCOX. *Apomorphine and amphetamine produce differential effects on the speed and success of reaction time responding in the rat.* PHARMACOL BIOCHEM BEHAV 46(4) 769–775, 1993.—Apomorphine, a nonselective, direct-acting dopamine agonist, and amphetamine, a nonselective indirect-acting dopamine agonist, were compared for their effects on 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 characteristics of the reaction time response of primary interest were percent successful avoidance and response latency. Apomorphine (0, 1, and 5 mg/kg, IP) significantly decreased successful avoidance, but had no effect on response latencies. Thus, the decrease in successful avoidance was not a direct result of longer latencies. Amphetamine (0, 0.5, and 1 mg/kg, IP) produced a different pattern of effects on the reaction time response. Successful avoidance was not affected by amphetamine treatment. However, response latencies were dose-dependently decreased in response to amphetamine. These results demonstrate that dopamine receptor stimulation by different dopamine agonists produces a different pattern of effects on the characteristics of the reaction time response. In addition, these results demonstrate that successful avoidance can be modulated independently of response latencies.

Dopamine Reaction time Behavior Conditioned avoidance Dopamine receptor Dopamine agonist Dopamine antagonist Amphetamine Apomorphine

REACTION time performance in the rat has been demonstrated to be sensitive to manipulations of brain dopamine systems. For example, 6-hydroxydopamine lesions (6-OHDA) of the nigrostriatal pathway that deplete striatal dopamine by as little as 15–20% result in impaired reaction time performance (23). Furthermore, 6-OHDA lesions of caudate nucleus, but not nucleus accumbens, produce deficits in reaction time performance (1). Reaction time has also been demonstrated to be sensitive to the effects of systemically administered dopamine agonists and antagonists. Apomorphine, a nonselective dopamine agonist, impairs successful avoidance in "fast-reacting" but not "slow-reacting" animals (27). However, it is not clear whether the deficits in task success were due to impaired response speed or whether the animals simply failed to initiate the response. In contrast, nonselective dopamine receptor blockade with chlorpromazine, flupenthixol, and pimozide produces clear deficits in the speed and success of reaction time performance (1,21,22).

Striatal D_2 dopamine receptors have also been linked to reaction time responding in rats. Animals that are faster and more successful at performing the reaction time task have been shown to have a lower D_2 binding affinity, but greater D_2 density, based on [^{3}H]spiperone binding (24,30). Furthermore, in normal populations of animals, the speed and success of reaction time can be predicted statistically based on the binding characteristics of [^{3}H]spiperone to striatal D_2 dopamine receptors (26). While these results do not exclude the potential importance of other brain regions in reaction time behaviors, they do suggest an important role of the striatal dopamine system in modulating reaction time performance.

Apomorphine and dextroamphetamine are two widely used dopamine agonists that increase locomotor activity at moderate stimulant doses and produce stereotypic behavior at higher doses (2,4,6,16,15). Apomorphine is a direct-acting agonist with almost an equal affinity for D_1 and D_2 receptors (20), whereas amphetamine increases the synaptic concentration of endogenous dopamine by stimulating release (8,10,29).

The purpose of the present investigation was to compare

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the effects of apomorphine and amphetamine on the speed and success of reaction time responding in rats. In addition, we were interested in determining whether the apomorphine-induced decrease in successful reaction time responding (27) was a result of slowed response speed or whether the animals simply failed to respond successfully.

METHOD

Subjects

Three-month-old, male, Sprague-Dawley rats (N = 20) 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.

Drugs

Apomorphine-HCl (RBI) was dissolved in distilled/deionized water (vehicle) and *d*-amphetamine sulfate (SKF) 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. Apomorphine solutions were made just prior to use and kept on ice away from light at all times due to the rapid oxidation of the compound in solution.

Reaction Time Measurement

Reaction time test chamber and shaping. The reaction time apparatus and shaping protocol have been described in detail previously (11). 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 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 ms, and at least 60% successful at a 200-ms 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.

Drug testing. 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 10 500-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.

Four animals did not meet the behavioral testing criterion and were not used as subjects of the experiment. The remaining 16 animals were divided into two groups. One group received apomorphine (0, 1, and 5 mg/kg; N = 8), while the other received amphetamine (0, 0.5, and 1 mg/kg; N = 8). Apomorphine was administered at 7-day intervals, while amphetamine was administered at 9-10-day intervals. Drug doses or the respective vehicle were administered IP in counterbalanced order.

Data 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 (28).

In addition to ANOVA, a nonlinear analysis was also performed on cumulative distributions of raw reaction time data. The details of this analysis technique have been reported in detail previously (Mayfield et al., submitted). Briefly, the data were collapsed across the time of peak drug effect and expressed as cumulative frequency distributions with 25-ms bin widths. The distributions were then fitted with the general logistic function, which closely approximates the cumulative normal (25), 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 (5,13). 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.

Maximum response estimates, denoted SA_{max} in this report, are equivalent to percent successful avoidance, while the ED_{50}, denoted SL_{50}, approximates the median latency of the modelled population of reaction time responses. Minimum response parameters were always held constant at 0 and the logistic slope was allowed to diverge between curves. Negative response latencies would represent anticipated trials. Thus, the minimum response parameter was constrained to 0 for all fits. Since the fitted distribution of latencies describes 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. The slope (b) of the curve gives an indication of the variability in responses across the behavioral testing session.

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(s) significantly degraded the fit of the data, the resulting residual sum-of-squares was larger than the sum-of-squares of the residuals of the unconstrained fit, yielding a significant F-test (5). Overall drug treatment effects were tested by comparing the fit of the data when all parameters are 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 apomorphine on successful avoidance and response latency as a function of time after drug administration are shown in Fig. 1 (panels A and B, respectively). Apomorphine significantly decreased successful avoidance, $F(2, 14) = 17.12, p < 0.01$. The response to apomorphine peaked within 15–30 min after drug injection, then subsided as a function of time, resulting in a significant dose × time interaction, $F(10, 70) = 8.77, p < 0.01$. No significant treatment effects on response latency were detected, $F(2, 14) = 0.156, p > 0.05$.

Figure 2 illustrates the effect of amphetamine on successful avoidance and response latency (panels A and B, respectively). In contrast to apomorphine's effect on successful avoidance, amphetamine had no effect on successful avoidance, $F(2, 14) = 0.57, p > 0.05$. A significant treatment effect was detected on response latencies, $F(2, 14) = 16.07, p < 0.01$, and Fig. 2 shows that this effect was due to a decrease in response latency. The dose × time interaction was not significant, indicating that the effects of amphetamine on response latency persisted throughout the 120-min testing session.

In order to study the effects of each drug on the reaction time response in more detail, the data were collapsed across time and sorted into cumulative frequency distributions. The apomorphine dose × time interaction was significant, so the data were pooled across the time of peak drug effect (15–30 min). The amphetamine data were collapsed across all time points. The results of the repeated measures ANOVA analysis and individual comparisons are described prior to the results of the nonlinear analysis.

Apomorphine's effects on successful avoidance and response latency at the time of peak drug response (15–30 min) are shown in Fig. 3. Apomorphine resulted in a significant decrease in successful avoidance (panel A), $F(2, 14) = 15.44, p < 0.01$. Individual comparisons failed to reveal a significant difference between control performance and the performance after 1 mg/kg apomorphine, $F(1, 14) = 2.86, p > 0.05$. Successful avoidance after 5 mg/kg apomorphine was significantly worse than control performance, $F(1, 14) = 29.49, p < 0.01$, as well as the performance after 1 mg/kg apomorphine, $F(1, 14) = 13.98, p < 0.01$. Response latencies were not affected by apomorphine treatment, $F(2, 14) = 1.19, p > 0.05$.

Figure 3 also shows the effects of amphetamine collapsed across time, as a function of drug dose, on successful avoidance and response latency, respectively. Successful avoidance

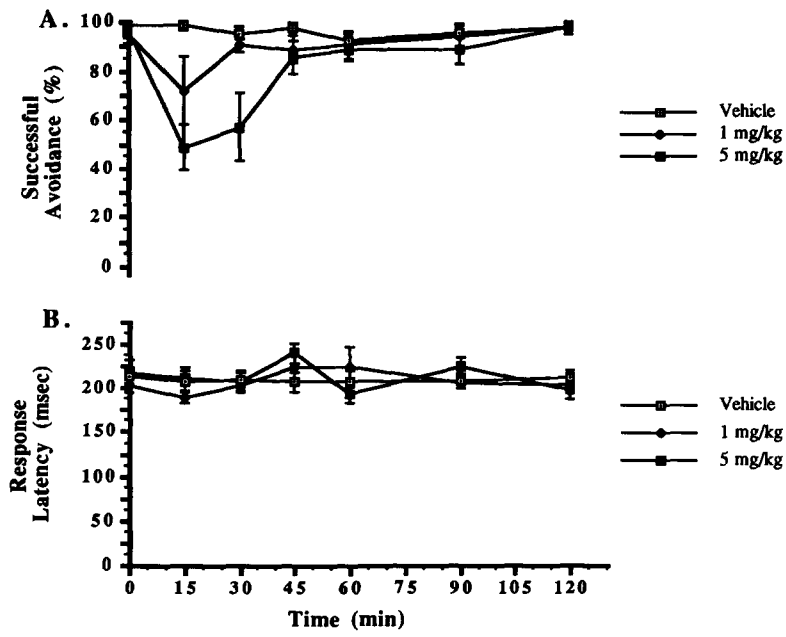

FIG. 1. (A and B) The effects of apomorphine (0, 1, and 5 mg/kg, IP), as a function of time, on percent avoidance (A) and response latency (B). Open squares represent performance under control conditions, while filled diamonds and filled squares represent performance after the 1 and 5 mg/kg doses of apomorphine, respectively. The data are expressed as mean ± SEM for each block of trials (N = 8 animals).

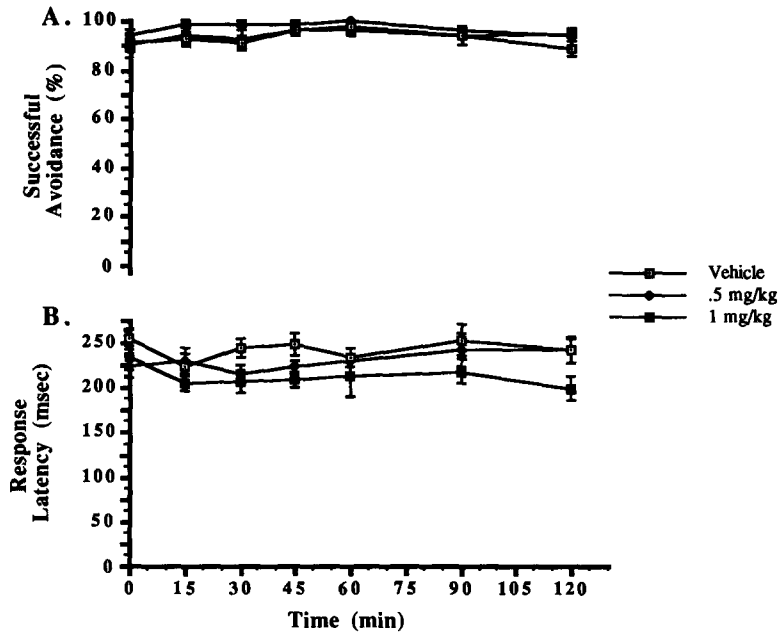

FIG. 2. (A and B) The effects of amphetamine (0, 0.5, and 1 mg/kg, IP), as a function of time, on percent avoidance (A) and response latency (B). Open squares represent performance under control conditions, while filled diamonds and filled squares represent performance after the 0.5 and 1 mg/kg doses of amphetamine, respectively. The data are expressed as mean ± SEM for each block of trials (N = 8 animals).

was unaffected by amphetamine treatment at the doses used (panel A), $F(2, 14) = 0.30, p > 0.05$. However, response latencies were significantly decreased (panel B), $F(2, 14) = 7.78, p < 0.01$. Significant effects on response latency were not detected between control and the 0.5 mg/kg dose of amphetamine, $F(1, 14) = 4.49, p > 0.05$. However, the 1 mg/kg dose of amphetamine significantly decreased response latencies from control values, $F(1, 14) = 15.51, p < 0.01$.

The unconstrained fits of data are shown in Figs. 4 and 5. 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). For all fits, the minimum response parameter was always held constant at 0 and slope was always allowed to diverge.

The fitted cumulative distributions of apomorphine data are shown in Fig. 4. Table 1 lists the results of the statistical analysis of different fits of the data. Table 1 (fit 2 vs. fit 1) indicates that apomorphine produced an overall effect on reaction time performance. SA_{max} estimates decreased from 89.9 ± 1.1% under control conditions to 79.2 ± 1.1% and 54.6 ± 1.6% after 1 and 5 mg/kg apomorphine, respectively. This decrease in SA_{max} was significant, as indicated by fit 3 vs. fit 1. Furthermore, fits 4 and 5 vs. fit 1 indicate that the decrease in the SA_{max} estimate was dose related. SL_{50} estimates were 206.7 ± 2.3 ms under control conditions and 202.5 ± 2.7 and 206.2 ± 5.6 ms after 1 and 5 mg/kg apomorphine, respectively. Fit 6 vs. fit 1 indicates that apomorphine did not have a significant effect on SL_{50} estimates.

The fitted distributions of amphetamine data are shown in

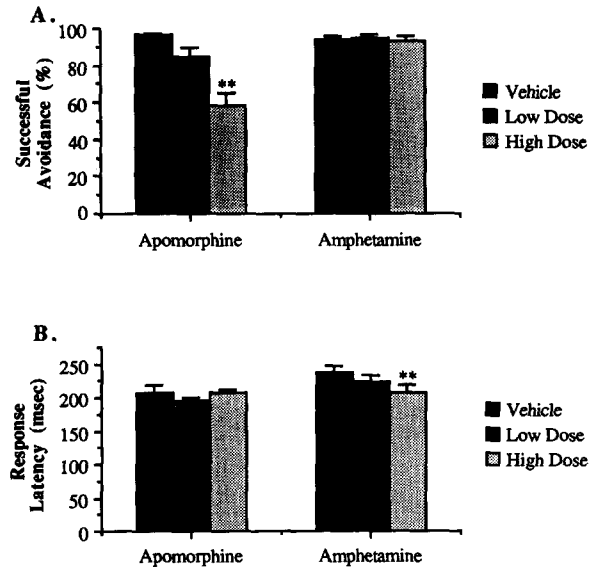

FIG. 3. Effects of apomorphine (0, 1, and 5 mg/kg, IP) and amphetamine (0, 0.5, and 1 mg/kg, IP) as a function of drug dose (N = 8 animals/condition). (A and B) The effects of apomorphine and amphetamine on successful avoidance and response latency, respectively. The data were collapsed across the time of peak drug effect for apomorphine (15–30 min) and the bars represent the mean performance ± SEM (**$p < 0.01$).

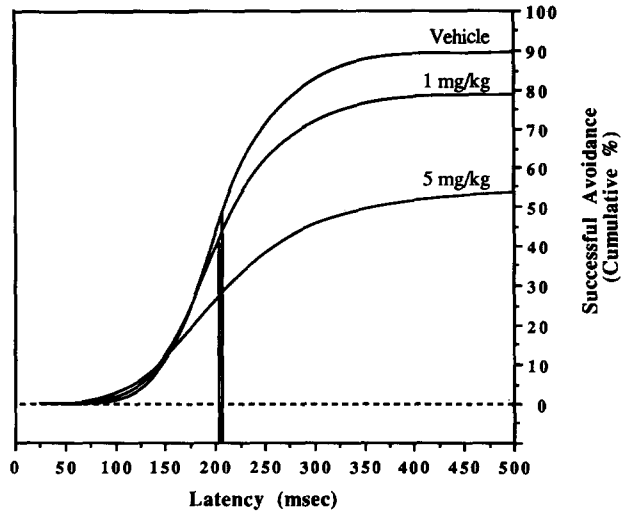

FIG. 4. Effects of apomorphine (0, 1, and 5 mg/kg, IP) on the unconstrained fits of cumulative frequency distributions of raw reaction time data at the time of peak drug response (15-30 min). Minimum response parameters were held constant at 0. Drop lines illustrate SL_{50} estimates.

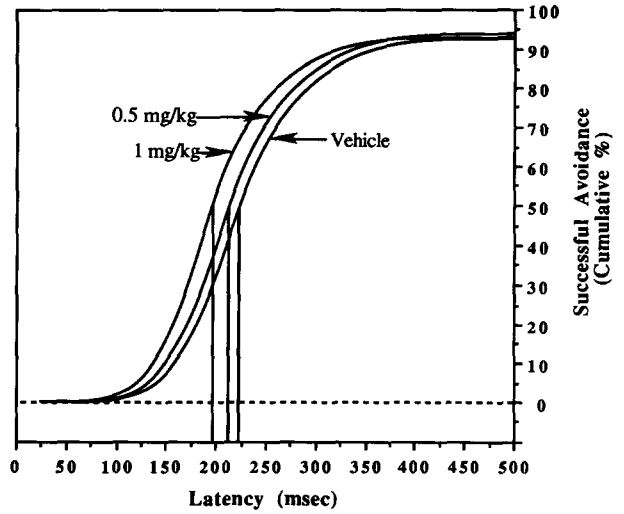

FIG. 5. Effects of amphetamine (0, 0.5, and 1 mg/kg, IP) on the unconstrained fits of cumulative frequency distributions of raw reaction time data collapsed across time (15-120 min). Minimum response parameters were held constant at 0. Drop lines illustrate SL_{50} estimates.

Fig. 5. Table 2 lists the statistical analysis of various fits of the data. Fit 2 vs.fit 1 indicates that amphetamine produced an overall treatment effect. However, this effect was not due to amphetamine's effect on SA_{max} estimates, as indicated by the lack of significance when all SA_{max} estimates were shared (fit 3 vs.fit 1). Amphetamine dose-dependently decreased SL_{50} estimates from 221.8 ± 1.5 ms under control conditions to 212.6 ± 1.4 and 195.9 ± 1.4 ms after 0.5 and 1 mg/kg amphetamine, respectively. Table 2 (fit 6 vs. fit 1) indicates that the decrease in SL_{50} was significant. Fits 7 and 8 vs. fit 1 indicate the dose-related nature of the decrease in SL_{50} estimates.

DISCUSSION

The characteristics of the reaction time response, successful avoidance and response latency, provide measures of discrete motor events that have been demonstrated to be sensitive to manipulations of the striatal dopamine system (22,23,27). In the present study, apomorphine and amphetamine produced a differential effect on the speed and success of reaction time performance in rats. While it is possible that these effects were mediated, in part, by actions on other neurotransmitter systems (e.g., serotonin or norepinephrine), the dopaminergic effects of these compounds predominate at the doses used in these experiments. Apomorphine produced a dose-dependent

TABLE 1

APOMORPHINE: STATISTICAL ANALYSIS OF GOODNESS OF FIT FOR VARIOUS MODELS OF FIG. 3

Fit	Parameters Shared	Residual SS	*df*	*F*-Test	Confidence Level
1	None	315.5	51	–	–
2	All	3542	55	130.4	$p < 0.01$
3	All SA_{max}	895.8	53	46.9	$p < 0.01$
4	SA_{max}*, SA_{max}†	543.6	52	36.9	$p < 0.01$
5	SA_{max}†, SA_{max}‡	604.1	52	46.7	$p < 0.01$
6	All SL_{50}	323.7	53	0.7	NS
7§	SL_{50}*, SL_{50}†	–	–	–	–
8§	SL_{50}†, SL_{50}‡	–	–	–	–

*Vehicle.
†Apomorphine 1 mg/kg.
‡Apomorphine 5 mg/kg.
§Not tested since sharing all SL_{50}s (Fit 6) did not significantly degrade the fit of the data compared to Fit 1.

TABLE 2

AMPHETAMINE: STATISTICAL ANALYSIS OF GOODNESS OF FIT FOR VARIOUS MODELS OF FIG. 4

Fit	Parameters Shared	Residual SS	*df*	*F*-Test	Confidence Level
1	None	127.3	51	–	–
2	All	722.7	55	59.6	$p < 0.01$
3	All SA_{max}	133.4	53	1.2	NS
4*	SA_{max}†, SA_{max}‡	–	–	–	–
5*	SA_{max}‡, SA_{max}§	–	–	–	–
6	All SL_{50}	536.0	53	81.9	$p < 0.01$
7	SL_{50}†, SL_{50}‡	175.5	52	19.3	$p < 0.01$
8	SL_{50}‡, SL_{50}§	300.9	52	69.6	$p < 0.01$

*Not tested since sharing all SA_{max}s (Fit 3) did not significantly degrade the fit of the data compared to Fit 1.

†Vehicle.

‡Amphetamine 0.5 mg/kg.

§Amphetamine 1 mg/kg.

decrease in successful avoidance. The deficits in successful avoidance were not due to slowed response speed, since response latencies were unaffected by apomorphine treatment. Amphetamine, on the other hand, had no effect on successful avoidance but decreased response latencies by as much as 25 ms.

Amphetamine, within the dose range used in this study, stimulates motor activity (3,7,19). Thus, the enhanced response speed that resulted from amphetamine treatment might have been predicted. However, the strict performance criterion that the animals were required to meet prior to drug testing insured that they were highly practiced and responding with very short latencies. From practical considerations alone, any decrease in response latency would be small and difficult to detect. On the other hand, since the animals were highly practiced, it is unlikely that decreases in response latency would be due to practice effects or systematic day to day variability in performance.

Apomorphine is also known to stimulate motor behavior within the dose range used in this study (3,14,16). However, response latencies were unaffected by apomorphine treatment. The SL_{50} of the apomorphine group was approximately 200 ms compared to 220 ms for the amphetamine group. Therefore, it is possible that apomorphine's lack of effect on response latency was due, in part, to the fact that this group was producing responses with latencies that approached an absolute minimum. Thus, drug-induced decreases in response latency would have been more difficult to detect. While this possibility cannot be discounted, it is unlikely, since all of the animals in the study were trained to the same performance criterion. In addition, we have demonstrated that response times can improve in groups of animals with control latencies of less that 190 ms (12). Furthermore, is not unusual for performance to vary slightly from group to group and it is unlikely that these differences in baseline performance contribute to the within-group variance produced by a given drug treatment.

It was previously reported that apomorphine produces differential effects on reaction time in "fast-reacting" vs. "slow-reacting" rats (27). Successful avoidance was dose-dependently impaired in animals that were considered to be "fast-reactors," while animals considered to be "slow-reactors" were unaffected by apomorphine treatment. The present results extend these findings by demonstrating that apomorphine-induced decrements in successful avoidance are not related to slowed response speed.

It was suggested that the difference in sensitivity to apomorphine in fast vs. slow rats might be due, in part, to inherent differences in the balance of D_1/D_2 dopamine receptor output in fast vs. slow animals (27). This hypothesis was also based on the results of D_2 receptor binding studies, which demonstrated that striatal D_2 receptor binding characteristics differed in fast- vs. slow-reacting animals (24,30).

We have recently provided additional support for the above hypothesis by demonstrating that selective D_1 and D_2 antagonists produce different effects on reaction time (12). Low doses of spiperone and haloperidol, both selective D_2 antagonists, decreased response latencies, while low doses of the selective D_1 antagonist SCH 23390 increased response latencies. The enhanced response speed occurred despite decreased successful avoidance and was attributed to enhanced D_1 output that resulted from blocking D_2 receptors. In addition, these effects on response latency are mimicked by local application of GABA agonists and antagonists in the substantia nigra reticulata, suggesting that the striato-nigral efferent system is important in mediating these effects (12). Together, these results suggest that reaction time response latency may be dependent on D_1 receptor activity, which is modulated by opposing D_1/D_2 receptor interactions. Opposing roles for D_1/D_2 receptors have been demonstrated to mediate dopamine agonist-induced oral behavior (9,17,18) as well as some components of agonist-induced stereotypic behavior (31). Animals that are pretreated with selective D_2 antagonists demonstrate an increased incidence of these behaviors in response to dopamine agonists. These experiments indicate that conditions that shift the balance of D_1/D_2 receptor activation toward D_1 facilitate the expression of the behavior.

The present results are also important within the frame-

work of the above hypothesis. First, the speed of reaction time responses was enhanced by dopamine receptor stimulation with amphetamine. While the effects of amphetamine are nonselective, it was important to demonstrate that dopamine receptor stimulation can produce effects on response latency that are similar to the effects of low doses of D_2 antagonists. Secondly, these results indicate that the speed and success of reaction time performance can be independently modulated by dopamine receptor stimulation. This is evident from apomorphine's effects on successful avoidance vs. response latency and amphetamine's ability to enhance response latencies without affecting successful responding.

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