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# Effects of Selective Dopamine $D_1$- and $D_2$-Agonists and Antagonists on Timing Performance in Rats

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FREDERICK, D. L. AND J. D. ALLEN. *Effects of selective dopamine $D_1$- and $D_2$-agonists and antagonists on timing performance in rats.* PHARMACOL BIOCHEM BEHAV **53**(4) 759-764, 1996. – Dopamine (DA) $D_1$- and $D_2$-agonists and antagonists were administered at fixed doses to assess putative dopaminergic involvement in timing behavior in rats performing under a peak-interval schedule. Significant shifts in response distributions to the left (consistent with the overestimation of the passage of time) were observed after treatment with the $D_1$- and $D_2$-agonists SKF 38393 and quinpirole, respectively. Both DA antagonists, eticlopride ($D_2$) and SCH 23390 ($D_1$), shifted the response distributions to the right (consistent with the underestimation of the passage of time), but neither drug produced statistically significant shifts. Based on percent shift in peak time from predrug baseline values, no significant differences were detected between agents as a function of their reported affinities for the $D_1$- or $D_2$-receptors. Results indicate the need for a systematic evaluation of each drug at various doses and a more detailed examination of the use of temporal schedules in predicting the efficacy of psychotherapeutic agents.

Time estimation Peak procedure Dopamine agonists Dopamine antagonists SKF 38393 Quinpirole SCH 23390 Eticlopride $D_1$-receptors $D_2$-receptors

HUMANS and laboratory animals are capable of performing under operant schedules in which reinforcement is dependent upon the subject's ability to respond accurately to temporal contingencies (e.g., accurately estimate event durations or discern between stimuli of varying temporal durations) (13,21,27). This ability likely reflects the simultaneous integration of several complex brain functions, such as long- and short-term memory, attention, decision making, choice responding, and internal chronometers or pacemakers. Collectively, these brain functions compose a theoretical internal timing mechanism, with components that can be conceptualized as somewhat analogous to the components of a mechanical timing mechanism, such as a stopwatch or an alarm clock [see (4,8, 34) for more detailed discussions of internal clocking models]. Like the mechanical timing mechanism, a component or components of the internal timing mechanism can be affected, either by internal or external forces, such that the mechanism's accuracy and reliability become compromised. Thus, in theory, performance of operant tasks with temporal contingencies should be differentially affected by experimental manipulations that target the complex brain functions believed to be essential for the expression of timing ability (i.e., the components of an internal clock).

The performance of both human and animal subjects responding under temporal schedules of reinforcement has been shown to be sensitive to drug and/or toxicant exposure (13,15,26,29,33). Specifically, it has been reported that agents with high affinity for cholinergic and/or monoaminergic (e.g., dopaminergic and serotonergic) systems differentially affect the performance of animals and, to some extent, humans responding under temporal schedules (9,14,17,22,27,28,30). In addition, time perception is known to be altered in humans afflicted with brain disorders (e.g., schizophrenia, major depression, Alzheimer's disease) whose symptoms can be alleviated by agents affecting cholinergic and/or monoaminergic neurotransmitter systems (24,25). It has also been shown that

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therapeutic efficacy of several antidepressants (nonspecific monoamine agonists) predicts magnitude of effect in rats performing under a temporal discrimination schedule (14). Although results from these (14,20) and other experiments (31) demonstrate a potential application of laboratory animal performance under temporal schedules in the screening of putative neuroleptic and antidepressant compounds, additional systematic examinations of the relative sensitivities and predictive validity of different time-dependent schedules are needed to establish their utility.

With respect to the dopaminergic system, a number of studies have demonstrated that rodent timing ability can be systematically affected by nonspecific dopamine (DA) agonists such as methamphetamine (18,19) and mixed $D_1/D_2$-antagonists such as haloperidol (18,20). In general, DA agonists have been shown to cause rodents to overestimate the passage of time, whereas DA antagonists cause rodents to underestimate the passage of time [see (9) for review]. It has also been demonstrated that among mixed $D_1/D_2$-antagonists, those with higher affinity for the $D_2$-receptor are more potent in terms of causing rodents to underestimate the passage of time (21); hence, the $D_2$-receptor may be more important for the expression of timing ability than the $D_1$-receptor.

In recent years, many new compounds have been developed that have much higher affinities for either the dopamine $D_1$- or $D_2$-receptor subtype than those used in previous experiments [e.g., (18-21)], making it possible to explore dopaminergic involvement in timing behavior more thoroughly. The current experiment examined the effects of the $D_1$-agonist SKF 38393, the $D_1$-antagonist SCH 23390, the $D_2$-agonist quinpirole, and the $D_2$-antagonist eticlopride on rodent time estimation ability using a peak-interval (PI) procedure (32). The PI procedure consists of both fixed-interval (FI) trials, in which a reinforcer is delivered for the first response occurring after a fixed amount of time since the presentation of a signal (e.g., light or tone), and probe trials, for which the same signal used for the FI trials is presented for two or three times as long as the FI duration, and responses have no scheduled consequences. During probe trials, the subjects' rate of response generally peaks at or about the expected time of reinforcer availability associated with the FI trials. The time from the onset of the signal that this peak in response rate (referred to as peak rate) occurs during probe trials is considered to be the peak time. It was hypothesized that both DA agonists would decrease peak time (i.e., peak response rate during probe trials would occur before the expected time of reinforcer delivery associated with the FI trials) and both DA antagonists would increase peak time (i.e., peak response rate occurs after the expected time of reinforcer availability). It was also hypothesized that changes in peak time observed after administration of $D_2$ compounds would be greater than those produced by the $D_1$ compounds.

## METHOD

### *Subjects*

Twenty 90 day old male hooded rats, derived from the Long-Evans strain and obtained from the University of Georgia Department of Psychology's breeding colony, were used in the experiment. Two rats that never achieved stability under the PI schedule and one rat that became ill after completion of testing with quinpirole but before testing with eticlopride were not included in the analyses. All subjects were housed in individual cages with free access to water, but were fed a restricted amount of food so that they remained at 85% of their free feeding weight throughout the course of the experiment as discussed by Ator (2). A 12 L : 12 D cycle, with lights on at 0600 h, was maintained throughout the course of the experiment. This experiment was approved by the University of Georgia Animal Care and Use Committee, and animal care and procedures were in accordance with the American Association for the Accreditation of Laboratory Animal Care.

### *Apparatus*

Subjects were tested in four identical Gerbrands Corp. (Model G7410; Arlington, MA) operant conditioning chambers, 28 × 28 × 24 cm. Each box was housed in its own sound-attenuated chamber. Noyes food pellets (45 mg; P. J. Noyes, Lancaster, NH) served as reinforcers. Pellets were delivered by a Davis Scientific Equipment (Model PD-190A; North Hollywood, CA) pellet dispenser into a food hopper located in the center of the front wall and 1 cm above the floor. A single response lever was located on the front wall, 3 cm from the left wall, 4 cm above the floor, and 3 cm left of the food hopper. A 5-V DC cue light, which signalled the onset of all trials, was located on the front wall, 5 cm above the lever. All trial contingencies, responses, and reinforcer deliveries for each operant box were controlled and recorded by Commodore 8032 microcomputers using software designed in-house.

### *Initial Fixed-Interval (FI) Training*

Testing occurred between the hours of 0600 and 1700, with all subjects being tested at approximately the same time of day throughout the course of the experiment. Subjects were magazine trained until they displayed reliable bar pressing on a continuous reinforcement schedule (generally after one to three daily sessions). Baseline training consisted of daily (Monday through Sunday) 120-min sessions in which all (100%) responses were reinforced according to a FI40-s schedule. Each FI40-s training trial was separated by a 60-s intertrial interval (ITI) in which the cue light was off and responding had no scheduled consequences. Subjects remained on this schedule for 20 consecutive sessions.

### *Peak-Interval (PI) Procedure Training*

During PI training, 130-s probe trials were added to the FI40-s schedule. Training consisted of daily 120-min sessions in which responses were reinforced according to a FI40-s schedule during a random 60% of the trials. The remaining 40% of the trials constituted peak trials, during which the same cue light used during FI40-s trials was illuminated for 130-s and responses had no scheduled consequences. Both FI40-s trials and 130-s peak trials were separated by 60-s ITIs. PI training continued until each subject's peak time became stable (i.e., did not vary by more than ±10% over seven consecutive sessions).

### *Drugs and Dosing Procedure*

Once stability was reached, each subject received an intraperitoneal (IP) injection of physiologic saline (also the drug vehicle) in a volume of 1.0 ml/kg, 15 min before each session, for seven consecutive sessions before drug administration. All drugs were dissolved in physiologic saline and injected IP 15 min before each drug session. SCH 23390 maleate (0.01 mg/kg) was generously donated by Schering-Plough (Kenilworth, NJ); eticlopride hydrochloride (0.01 mg/kg), SKF 38393 (1.0 mg/kg), and quinpirole hydrochloride (0.01 mg/kg) were

each purchased from Research Biochemicals International (Natick, MA). The doses were chosen based on previous literature reports (3,12,36) with the objective that the potency of each drug dose would be as similar as possible, using the rate-attenuating effects of each drug on schedule-controlled behaviors as the desired index of potency.

Subjects were randomly assigned to two groups of nine rats each after the last vehicle injection. Group A was tested using the $D_1$-specific compounds SKF 38393 and SCH 23390. Group B was tested using the $D_2$-specific compounds quinpirole and eticlopride. Within each group, subjects were randomly assigned to one of two orders of drug administration, such that in general, half were tested using an order of vehicle-agonist-vehicle-antagonist, whereas the other half was tested using the order of vehicle-antagonist-vehicle-agonist. Vehicle (saline) was administered for seven consecutive sessions, after which the first drug was administered for 10 consecutive sessions followed by three noninjection sessions, then seven vehicle injections before administration of the second (final) drug for 10 consecutive sessions.

*Data Collection and Analysis*

Responses were recorded in consecutive 1-s bins from the onset of the signal for FI40-s trials and 130-s peak trials, and during all 60-s ITIs. The responses in each bin were summed over each session and the mean bin response rate was calculated. Peak time was estimated by summing each mean bin response rate into 130 consecutive 6-s epochs. The time bin in the middle of the epoch containing the maximum number of responses was defined the peak time. The mean response rate obtained during the selected epochs was considered to be the peak rate. This method of estimating peak time and peak rate is similar to that described by Meck et al. (23).

Mean peak times and peak rates for each subject and for each group were calculated from the final seven vehicle sessions before each drug treatment. Peak time and peak rate for drug sessions was estimated from data obtained during the final seven drug sessions. Vehicle and drug peak times and peak rates were compared across groups using a repeated measures analysis of variance (ANOVA) to address the hypothesis that compounds thought to interact with dopamine receptors affect the speed of the internal clock. Percent change values were calculated for each subject by subtracting mean vehicle peak times and rates from those obtained during drug administration and then dividing by the vehicle measures and multiplying by 100. For example, if a subject had a vehicle peak time of 40 s, a drug peak time of 48 s would be calculated as a +20% change. A repeated-measures ANOVA comparing the percent shifts in peak time and peak rate of groups receiving $D_1$ compounds to the groups receiving the $D_2$ compounds was conducted to address whether effects were specific to a compound thought to have specific interactions with particular DA receptors and for possible order of administration effects. Data for the peak time end point obtained during drug sessions in which peak rate dropped below 50% of that obtained for control values were not included in the statistical analyses.

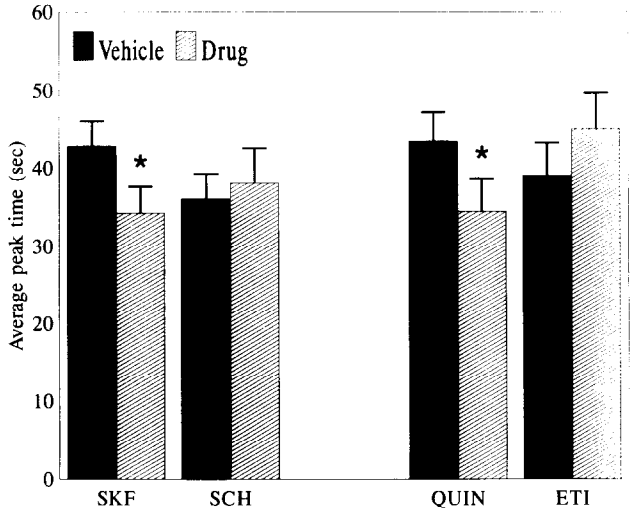


FIG. 1. Mean peak times ± SEM during vehicle and drug treatment conditions for SKF 38393 ($n$ = 9), SCH 23390 ($n$ = 8), quinpirole (QUIN) ($n$ = 9), and eticlopride (ETI) ($n$ = 8). *Significant difference from vehicle ($p < 0.05$).

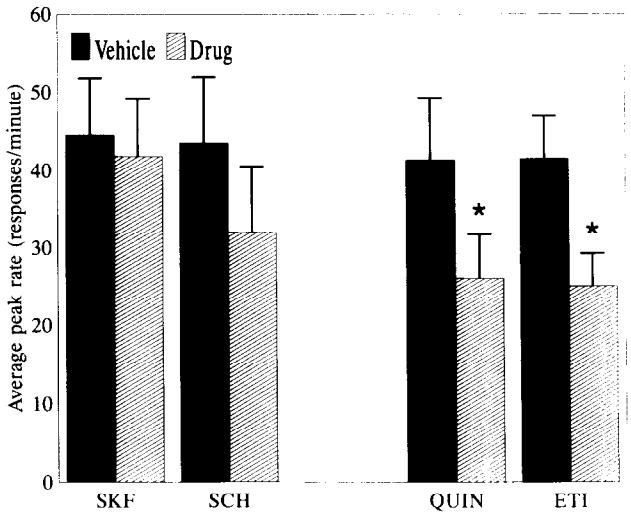


FIG. 2. Mean peak rates ± SEM during vehicle and drug treatment conditions for SKF 38393 ($n$ = 9), SCH 23390 ($n$ = 8), quinpirole (QUIN) ($n$ = 9), and eticlopride (ETI) ($n$ = 8). *Significant difference from vehicle ($p < 0.05$).

RESULTS

*Effects of $D_1$ Compounds*

The $D_1$ agonist SKF 38393 produced a significant decrease in peak time ($p < 0.01$) (Fig. 1). SKF 38393 administration did not, however, significantly affect peak rate (Fig. 2). Treatment with the $D_1$-antagonist SCH 23390 did not significantly affect peak time (Fig. 1) or peak rate (Fig. 2).

*Effects of $D_2$ Compounds*

A significant decrease in peak time was observed following treatment with the $D_2$-agonist quinpirole ($p < 0.05$) (Fig. 1). Treatment with quinpirole also resulted in a significant decrease in peak rate ($p < 0.05$) (Fig. 2). A significant decrease in peak rate ($p < 0.01$) (Fig. 2) was observed during eticlopride sessions, and although peak time was also decreased, this effects was not significant (Fig. 1).

*Comparison of $D_1$ and $D_2$ Compounds*

Magnitude of drug effect, as measured by percent change in peak time, was analyzed using a repeated-measures ANOVA comparing drug action (agonist/antagonist) and receptor affinity ($D_1/D_2$). Analysis revealed a significant effect of drug action ($p < 0.01$) but no effect of receptor affinity effect. Figure 3 shows the percent change in peak time during the 10 drug sessions for each treatment group. During the first 3 drug treatment days, the mean peak rate for each group was decreased by >50% of control values, as subjects generally responded only during the initial portion of each session (or not at all). Because of this, peak times were highly variable during the first three treatment sessions, and only those peak times that were obtained when peak rate did not drop <50% of that obtained during control sessions were included in the statistical analysis. The data from the first three sessions are presented to illustrate the tolerance that developed to each drug as exposure persisted. Treatment with the $D_1$-agonist SKF 38393 resulted in a average decrease in peak time of 19.71% across subjects. A similar 23% decrease in average peak time also resulted from treatment with the $D_2$-agonist quinpirole. A 16.71% average increase in peak time was observed in subjects treated with eticlopride, whereas treatment with SCH 23390 only resulted in an average increase in peak time of 6.5%.

*Assessment of Possible Order Effects*

A repeated-measures ANOVA comparing order of administration (first or second) for agonists (SKF 38393 and quinpirole) and antagonists (SCH 23390 and eticlopride) using magnitude of percent change in peak time was used to test for possible order of administration effects. Analysis across agonists revealed no significant agonist difference and no significant order effect. Analysis across antagonists also revealed no significant antagonist effect or significant order effect.

## DISCUSSION

The present results are consistent with previous reports in which performance of rats responding under a schedule of reinforcement with temporal contingencies was shown to be differentially sensitive to manipulations thought to affect the dopaminergic system. The DA agonists quinpirole and SKF 38393 significantly decreased peak time; the DA antagonists SCH 23390 and eticlopride both increased peak time, although not significantly. The hypothesis that peak shifts in response to $D_2$ compounds would be greater than those seen in response to $D_1$ compounds was only partially supported.

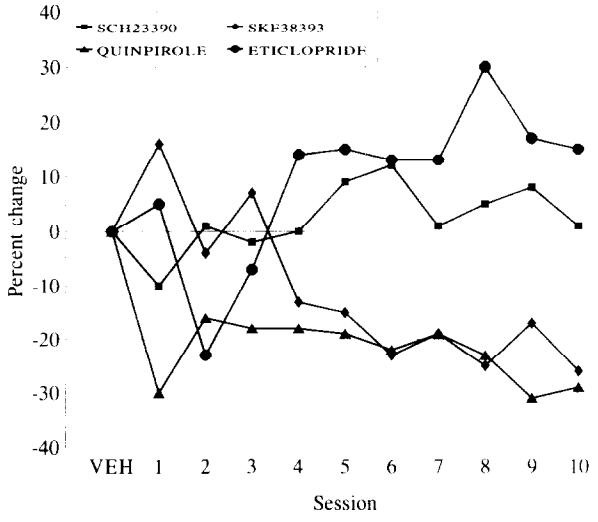


FIG. 3. Magnitude of treatment effect expressed as percent change in peak time from vehicle for $D_1$- and $D_2$-agonists and antagonists during the 10 drug treatment sessions (all $n$'s as in Fig. 1).

Previous data [e.g., (18-20)] have suggested that experimental manipulation of the DA system differentially affects rodent timing ability. These studies, however, generally involved manipulations that affected multiple neurotransmitter systems in a relatively nonspecific manner. In the present experiment, specific DA agonists (quinpirole and SKF 38393) were found to produce significant decreases in peak time. Although neither DA antagonist significantly affected peak time, both drugs did increase peak time as hypothesized. Moreover, the shifts produced by eticlopride were substantial (>16% from control values) and would likely have been significant if a larger sample size had been used. Thus, these data demonstrate that performance of rats responding under a temporal schedule can be differentially affected by agents specific for DA receptors, and therefore indirectly suggest that the DA system may also play an integral role in the expression of timing behaviors.

In the present experiment, only single doses of each drug were administered, which limits the conclusions that can be drawn regarding DA involvement in rat timing ability. Although the data do suggest that drugs believed to interact primarily with the DA transmitter system affect rat performance of a time estimation task, a more detailed exploration of the relative potencies of each drug (dose-response functions) would permit stronger conclusions regarding this issue. Although the doses of the $D_2$ compounds appeared to be about equally potent (in terms of attenuation of peak rate), the doses of the $D_1$ drugs did not appear to be comparable with respect to the peak rate measure. It is possible that the failure of SCH 23390 to affect peak time significantly reflects a difference in potency relative to the other compounds tested, rather than an inability of this drug to affect timing behavior. In addition, if the dose-response functions for each drug were known, doses with fewer rate-attenuating effects could be chosen. Because significant decreases in peak rate were noted with the $D_2$ compounds, the possibility that the effects observed were due to the drugs' effects on response rate rather than dopaminergic involvement in timing ability per se [which has been suggested (16)] cannot be discounted. The differential changes in peak time (shifts to the left and to the right, suggesting over- and underestimations of elapsed time) associated with each compound did occur, however, even though all drugs had depressive effects on peak rate.

The rate-attenuating effects of each drug must also be considered when evaluating the effects of these drugs on PI task performance. Because only one signal duration was used throughout the experiment (40 s) rather than several different FI durations (e.g., 20, 40, and 60 s), it was not possible to determine whether the changes noted in PI performance were the result of drug-induced alterations in the speed of the rats' internal clocking mechanisms (or changes in memory storage speed), or whether such changes resulted in alterations in response rates, response latencies, or both. That is, it cannot be determined whether the changes in peak time were absolute or relative effects. For example, if an 8-s shift in peak time (increase or decrease) was consistently noted regardless of the FI duration, this would suggest an alteration in response initia-

tion. On the other hand, if the shifts were consistently proportional across each FI duration (as expressed as percent shifts from baseline), this would indicate that the shifts were relative to FI duration, which suggests changes in clock or memory speed.

The present data partially support the hypothesis that affinity for the $D_2$-receptor would predict magnitude of effect on timing ability, as had been previously demonstrated by Meck (12). Both the $D_2$-antagonist eticlopride and the $D_1$-agonist quinpirole produced >15% changes in peak time, but only the $D_1$-agonist SKF 38393 produced a similar effect. Although such results suggest that the $D_2$ drugs may have been more effective at affecting the internal timing mechanism than the $D_1$ agents, it is possible that the smaller change in peak time observed in response to the $D_1$-antagonist SCH 23390 (relative to the other compounds) occurred because the dose given was too low. Because the stimulation of both DA receptor types has been shown to be necessary for the full expression of some DA-mediated behaviors and for the postsynaptic effects of DA agonists (5), it is possible that dopaminergic compounds specific to one receptor subtype may produce much different effects on timing behavior than compounds with mixed affinities for both receptor subtypes. Also, among relatively nonspecific dopaminergic compounds, those having a greater affinity for a particular receptor subtype may produce greater effects on timing ability than those having roughly equal affinities for multiple receptor types. It also cannot be discounted that the mechanisms involved with a particular receptor subtype (e.g., $D_2$) may be selective for reductions in clock speed or increases in clock speed, but not both.

In an overview of DA involvement in timing behavior, Church (9) cited several studies using temporal procedures to suggest that dopaminergic manipulations result in phasic changes in timing ability. In this instance, phasic refers to a shift (possibly indicative of under- or overestimation of time) that appears after the initial treatment, abates with subsequent exposure (tolerance), and reappears in the opposite direction of the original shift when the treatment is discontinued. Such an effect may be attributable to receptor up- or down-regulation, which has been shown to occur after repeated exposure to both nonspecific DA agonists and antagonists (1,7,35) and to those drugs specific to DA receptor subtypes (6,10,11). Because tolerance to the rate-suppressing effects of each drug was evident by the third day of administration in the present experiment, it is also likely that some degree of receptor up- or down-regulation occurred, although such an effect was not empirically explored. The changes in peak time noted after repeated exposure to the DA agonist and antagonists used in this study did not appear to decrease as drug exposure persisted, although it is possible that peak times would have begun to return closer to control values if drug treatment had continued beyond the tenth consecutive day. Shifts in the opposite direction of the treatment effect were generally evident during the three noninjection sessions following cessation of drug treatment as PI performance began to restabilize to near-predrug baseline levels. A more thorough exploration of the possible phasic nature of DA treatments on timing ability could be accomplished with longer administration periods. In addition, much stronger conclusions concerning the effects of repeated dopaminergic manipulation on timing ability could be made by quantifying the effect of such treatment using neurochemical and neurophysiological techniques.

In summary, the present data suggest that the DA system is involved in the expression of rat timing ability. The degree of specificity of such involvement (e.g., prediction of effects based on relative affinities for $D_1$- or $D_2$-receptors) that can be determined from the present experiment is, however, limited by factors such as the use of only single doses of each drug, probable differences in the potencies of each drug dose, and the possibility of receptor up- or down-regulation that may have occurred but was not quantified. These data suggest that future research into the role of the dopaminergic system in timing behavior and the potential use of temporal operant schedules in the preclinical evaluation of the therapeutic potential of pharmacologic agents is warranted.

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