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Effects of Dopaminergic Drugs on Working and Reference Memory in Rats[1]

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BUSHNELL, P. J. AND E. D. LEVIN. *Effects of dopaminergic drugs on working and reference memory in rats.* PHARMACOL BIOCHEM BEHAV 45(4) 765–776, 1993.—Changes in dopaminergic function have been associated with alterations in motor and cognitive function in man and in animals. This study was designed to assess the effects of dopaminergic drugs on these aspects of conditioned behavior in animals. Male Long-Evans rats were trained to perform an appetitive operant task that allowed daily quantification of working memory (accuracy of spatial delayed nonmatching-to-position), reference memory (accuracy of visual discrimination) and motor function [choice lever-press latency and nosepoke interresponse time (IRT) during delay]. The indirect dopamine agonist *d*-amphetamine (0.3–1.0 mg/kg) reduced nonmatching accuracy without significantly affecting discrimination accuracy, response latency, or nosepoke IRT. The D_2/D_3 agonist quinpirole (0.01–0.056 mg/kg) also decreased nonmatching accuracy without changing discrimination accuracy, but increased choice response latency and nosepoke IRT as well. The D_1 agonist SKF 38393 (1.0–3.0 mg/kg) and the D_1 antagonist SCH 23390 (0.01–0.03 mg/kg) only affected nosepoke IRT, at doses below those causing response failure. The D_2 antagonist raclopride (0.056–0.177 mg/kg) exerted no significant effects at doses that did not suppress responding completely. The selective reduction of nonmatching accuracy by *d*-amphetamine and quinpirole indicates a mnemonic impairment specific to working memory (relative to reference memory). These results suggest further 1) that stimulation of D_2/D_3, but not D_1, receptors may account for the *d*-amphetamine-induced deficit in working memory; 2) that stimulation of D_2/D_3 receptors alone by quinpirole may also impair spatial working memory, but only in conjunction with motor slowing; and 3) that antagonism of either receptor type (by SCH 23390 or raclopride) does not significantly affect memory at doses causing motor slowing and response failure.

d-Amphetamine | Dopaminergic drugs | D_1 receptors | D_2 receptors | Motor function | Quinpirole | Raclopride | Rat | Reference memory | SCH 23390 | SKF 38393 | Working memory

WHILE a great deal of experimental evidence supports important roles for dopamine (DA) in motor function and motivation, its role in mediation of memory is less well established. Many stimulant drugs enhance locomotion via activation of DA systems, and treatments that impair central DA activity interfere with motor responses (4,31). These changes in motor function frequently complicate interpretation of pharmacologic investigations of the role of DA in memory.

The potential for neuroleptic-induced motor and motivational changes to complicate studies of learning and memory is clearly indicated in a recent study of spatial navigation in the water maze (39). This study demonstrated a decay in performance of a swimming task, which developed when rats were repeatedly trained under the influence of the neuroleptic drug *cis*(*Z*)-flupentixol. This decay did not depend upon the nature of the problem used (place or cue task) nor the treatment-training interval, but appeared rather to involve conditioning of motor incapacitation (catalepsy) to the reinforcing aspects of the training environment. This conclusion is supported by a recent report (14), which showed that neither DA agonists nor antagonists affected working memory at doses that clearly decreased response speed in a delayed nonmatch-to-sample procedure in the radial maze.

Nevertheless, neuroleptic drugs have been observed to reduce accuracy of working memory in other tasks, but only in conjunction with motor slowing. Repeated dosing with haloperidol, for example, reduced accuracy of working memory in the radial-arm maze, and also slowed response speed and

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altered motor behavior (3,25). Also, two other DA antagonists, chlorprothixene and trifluoperazine, reduced response rates and response accuracy at the same doses in pigeons performing a nonspatial delayed matching-to-sample task (30).

Given that DA antagonists reduce accuracy of working memory and the rate and/or speed of responding, it is interesting that stimulation of the DA system can also impair spatial working memory in animals. For example, *d*-amphetamine reduced choice accuracy in the radial-arm maze when delays were imposed between successive arm choices (2,9,18), and also reduced choice accuracy in delayed matching-to-position tasks (16,22). Since both suppression and stimulation of the DA system have been associated with cognitive impairment, one may speculate that memory may be optimized at an intermediate level of dopaminergic activity.

Motor function was not assessed in these studies with *d*-amphetamine; thus, motoric dysfunction could have played a role in the deficits in working memory as assessed either in the radial-arm maze or with delayed matching-to-position. Furthermore, the nature of the deficit in working memory remains unresolved. That is, Kesner et al. (22) reported delay-dependent effects of *d*-amphetamine on nonmatching accuracy, indicating more rapid loss of information under the drug, while Dunnett (16) observed that *d*-amphetamine-induced changes in matching accuracy occurred independent of the delay, suggesting a drug-induced deficit of attention, rather than of memory per se. Thus, neither the source of the *d*-amphetamine-induced mnemonic deficit nor its specificity for working memory has been adequately determined.

Drugs that selectively affect subtypes of DA receptors (21,37) have also been found to affect acquisition and performance of conditioned behaviors [see (6) for review]. Apparent motivational effects have been demonstrated: the D_1 antagonist SCH 23390 caused an extinction-like decline in responding under a variable-interval schedule (32). Similarly, the D_2 antagonist metoclopramide produced extinction-like response patterns on a variable-ratio schedule (5). Other studies have reported behavioral changes that more strongly indicate cognitive differences, by accounting for potential sensory and motor effects of the compounds. For example, infusions of the D_1 antagonists SCH 23390 and SCH 39166 into the prefrontal cortex impaired monkeys' performance of an oculomotor task (35). Since the impairment was observed when the monkey was required to remember the stimulus, but not when the stimulus was present at the time of the response, these results indicated a specific effect on memory and not on sensory or motor aspects of the task.

Given that pharmacological manipulations of the DA system appear to affect cognitive and motor abilities in concert, the major goal of this study was to determine whether effects specific to memory could be demonstrated after administration of dopaminergic drugs, or whether mnemonic changes were always accompanied by alterations in motor function. It was also of interest to determine the relative sensitivities of working and reference memory to these drugs. For these purposes, the behavioral effects of *d*-amphetamine were compared to those of the D_1 agonist SKF 38393, the D_1 antagonist SCH 23390, the D_2/D_3 agonist quinpirole (36), and the D_2 antagonist raclopride.

To quantify memory, a task similar to delayed matching-to-position (DMTP) was used. DMTP has been used to assess effects of *d*-amphetamine, scopolamine, trimethyltin, aging, and lesions of the fimbria-fornix or medial septum on working memory (10,12,16,17,22). An analogous task, delayed nonmatching-to-position (DNMTP), yields results equivalent to those from DMTP, with reduced intersubject variability (13, 17). DNMTP was modified for this study to include a visual discrimination (VD) component, which does not require working memory: accuracy in this component provided a concurrent measure of reference memory (12).

Operationally, working memory was quantified as accuracy of nonmatching, and reference memory as accuracy of visual discrimination. This usage follows that of Honig (20) and Olton et al. (29), who posited working memory for processing information that changes frequently (e.g., from trial to trial) and reference memory for processing information that remains constant indefinitely (e.g., across trials and sessions). The ability of the combined DNMTP/VD task to assess both working and reference memory provided a means to determine the mnemonic specificity of any performance change observed. Changes in the shape of the retention gradients derived from performance in the nonmatching component of the task (12) were used to characterize the cognitive deficit as more rapid forgetting (steeper slope) and/or as reduced efficiency of stimulus encoding (lower intercept). Finally, measures of response rate during the delay and choice response latency permitted assessment of motor function and its possible contribution to observed changes in choice accuracy.

METHOD

Subjects

Four male, Long-Evans rats (Charles River, Raleigh, NC) were housed individually in suspended plastic cages on heat-treated pine shavings in a housing facility fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC). Lighting followed a 12L : 12D photoperiod with light onset at 6:00 a.m.; all testing occurred in the light phase of the cycle. Each animal was maintained at 350 g body weight by controlled daily posttesting feeding of standard rat chow (Ralston Purina, St. Louis, MO) in the home cage (1). Water was available ad lib in the home cage.

Apparatus

Four standard rat operant conditioning chambers were used. Each chamber was equipped with a houselight and two retractable response levers (Coulbourn Instruments, Lehigh Valley, PA), 3.4 cm in width, mounted with inside edges 13 cm apart on one wall of the chamber. A cue light was mounted directly above each lever. A food cup with a swinging plastic door (Campden Instruments, via Stoelting Co., Chicago, IL) was centered on the rear wall of the chamber. A microswitch on the door registered nosepokes into the food cup. The levers were modified to register depressions with a force of 0.15–0.20 newtons (15–20 g). Each chamber was located in a sound-attenuating shell within which white noise was provided [70 dB(A), measured at the opening of the food cup in an octave band centered at 4 kHz]. Reinforcers were 45-mg food pellets (Bio-Serv, Frenchtown, NJ). Control of experimental conditions and data collection were accomplished by minicomputer (PDP11/83, Digital Equipment, Maynard, MA) and SKED-11 interface and software (State Systems, Kalamazoo, MI).

Behavioral Training

The rats were exposed to autoshaping contingencies (11) beginning at 10 months of age and were subsequently trained to perform the DNMTP/VD task as previously described for

DMTP/VD (10,12,13) beginning at 17 months of age. Training to stable performance required a total of 62 daily test sessions across 3 calendar months.

Delayed Nonmatching-to-Position/Visual Discrimination Tests

Half the trials in each session were discrimination trials, and half were nonmatching trials. The trial types were presented with equal probability in random order; for each trial type, right and left levers were presented as samples equally often. Trials began after a 2-min dark period with no contingencies in effect. The houselight was then illuminated and, after a 10-s intertrial interval (ITI), one lever was extended into the chamber (sample). On discrimination trials, the cue light above the sample lever was lit. A response on the sample lever caused it to retract and extinguished its cue light. The delay period followed, signalled by illumination of the food cup light. The length of the delay in each trial was chosen in a pseudorandom fashion from the list of nominal sample-choice delays (1,4,8,12, and 16 s). Each value of the list was used once before the list was repeated. The first nosepoke made in the food cup after the delay ended extinguished the food cup light and extended both levers into the chamber (choice). At this point in a discrimination trial, one lever was randomly designated as correct and was illuminated by its cue light (this lever was the same as the sample lever on half the discrimination trials). A response on the illuminated lever was followed immediately by retraction of both levers, illumination of the food cup light, and delivery of a food pellet; a nosepoke in the food cup to collect the pellet then cycled back to the ITI. A response on the incorrect lever produced no pellet and a 10-s blackout period. The blackout was followed by the ITI, signalled by reillumination of the houselight. Nonmatching trials were conducted identically, except that no cue lights were used, and the correct choice response was always on the lever that had not been presented as the sample in that trial. No correction trials were given during drug testing. Each session consisted of 200 trials (20 trials at each of five delay values and two cue conditions) and required 90 to 120 min to complete.

Behavioral Variables

Nonmatching accuracy was defined as the proportion of correct choice responses on nonmatching trials averaged across delays; since the discriminative stimulus for this component of the task (i.e., the location of the sample) changed from trial to trial, nonmatching accuracy was taken to reflect accuracy of working memory. To characterize working memory in terms of component processes, nonmatching accuracy was regressed against delay to generate retention gradients, which were fit with least-squares linear functions for each animal. For these regressions, actual delay values were used, with delay defined as the time elapsed between the sample response and the last nosepoke of the delay interval. Slopes and intercepts of these gradients were then analyzed statistically to characterize the effects of treatments. In this analysis, the intercept of the gradient can be interpreted as accuracy of encoding the sample information, and its slope as retention, or the rate at which information about the sample deteriorates over time (12,19).

Discrimination accuracy was defined as the proportion of correct choice responses on visual discrimination trials, averaged across delays. The visual discrimination component did not require the animal to remember which lever was presented as the sample on each trial, but only that the lever lit by the cue light was correct. Since this information remained constant throughout the study, discrimination accuracy provided an index of reference memory.

Choice response latency was defined as the time elapsed between the last nosepoke of the delay interval (coincident with extension of the levers for choice) and the choice response. Latencies were measured separately for correct and incorrect responses, on both matching and discrimination trials. While latencies for incorrect responses were generally longer than those for correct responses, and those on discrimination trials longer than those on matching trials, these differences were not affected by the drugs used here; the latencies for the two response types and two outcomes were thus averaged and analyzed together. Nosepoke interresponse time (IRT) was calculated as the total time cumulated in delay intervals in a session divided by the total number of nosepokes emitted during all delay intervals in that session. It should be noted that feeding rats immediately prior to testing increases both IRT and choice response latency (as well as the incidence of response failure); thus, these measures reflect both motoric and motivational influences. As previously discussed (13), latency and IRT will be treated descriptively as motor effects.

Drug Administration

d-Amphetamine sulfate (Smith Kline & French Laboratories, West Point, PA), SKF 38393 (Smith Kline & French Laboratories, lot #JMH-11410-96), SCH 23390 (Schering-Plough, Bloomfield, NJ, lot #97206), quinpirole (LY 171555, Eli Lilly Co., Indianapolis, IN, lot #H10-KV4-173), and raclopride (Astra, Södertälje, Sweden, lot #880418) were all dissolved in isotonic saline at concentrations in mg/ml equal to doses in mg/kg. Doses of all drugs were calculated as the salt, and were administered in a volume of 1.0 ml/kg by intraperitoneal injection 15 min prior to behavioral testing. Doses used for each drug were: *d*-amphetamine: 0.30, 0.56, and 1.00 mg/kg; SKF 38393: 1.00, 1.77, and 3.00 mg/kg; SCH 23390: 0.010, 0.013, 0.018, 0.024, and 0.030 mg/kg; quinpirole: 0.010, 0.018, 0.030, and 0.056 mg/kg; and raclopride: 0.056, 0.100, 0.177, 0.300, and 1.00 mg/kg.

Each of the five drugs was given across a different series of tests sessions, in the following order: quinpirole, raclopride, SKF 38393, SCH 23390, *d*-amphetamine. Each dose of SKF 38393 was given once in ascending order. Each dose of the other drugs was tested twice, once in an ascending series, and once in a descending series, with each animal's performance averaged across determinations. Each dose was given in one or more 2-day blocks: in each block, half the animals were injected with drug and the other half with saline vehicle on a given test day (excluding Mondays, when all rats received saline injections); the treatments were then reversed the next day. No animal received drug more than twice per week, and at least 1 drug-free day intervened between tests with drug. Drug dosing occurred when the rats were 20–26 months of age. Baseline accuracy scores and retention gradients in these rats were equivalent to those obtained from 10–13-month-old rats performing this task (12,13).

Data Analysis

Methods for characterizing changes in working and reference memory have been described in detail (12). Nonmatching and discrimination accuracy scores, averaged across delays, were used to summarize changes in cognitive function across doses of drugs. Where inspection of the data suggested possi-

ble changes in the shape of the retention gradient, slope and intercept parameters were also analyzed. Motor function was assessed by changes in choice response latency and nosepoke IRT. High doses of the drugs used in this study tended to suppress responding altogether. A minimum of 100 completed trials (10 trials per trial type per delay) after each drug dose was deemed necessary for analysis of accuracy and latency data; sessions with fewer than 100 trials were thus excluded from analyses of accuracy data. For each dependent variable and each drug, treatment effects were tested with a one-way repeated measures analysis of variance (ANOVA) [SAS Version 6.0, General Linear Model (34)], with drug dose (including vehicle) as the repeated measure. Saline scores were averaged within each drug series and used as the vehicle control condition for that drug. The effect of asymmetrical variance-covariance matrices was minimized by using Greenhouse-Geisser degree-of- freedom (*df*) corrections; the amount of *df* correction in each analysis (ϵ) is reported after each *F*-ratio. Following each significant main effect of drug in the repeated-measures ANOVAs ($\alpha = 0.05$), single-*df* step-down *F*-tests were used to determine which doses caused significant changes from saline control. The α level for each set of these step-down tests was set by dividing the overall α (0.05) by the square root of the number of tests made (one per dose), since all the comparisons were within-subject and thus not mutually independent (38).

RESULTS

d-Amphetamine

d-Amphetamine caused a dose-related decrease in nonmatching accuracy, $F(3, 9) = 21.68$, $\epsilon = 0.54$, $P = 0.0043$, without significant effect on discrimination accuracy (Fig. 1, left). Paired comparisons of nonmatching performance after saline showed that accuracy was significantly reduced after 0.56 and 1.00 mg/kg *d*-amphetamine [$F(1, 3) = 15.40$ and 81.82, $p = 0.024$ and 0.003, respectively]. Neither choice response latency nor nosepoke IRT (Fig. 1, right) was significantly affected by *d*-amphetamine.

SKF 38393

The D_1 agonist SKF 38393, up to a dose of 3.0 mg/kg, significantly affected neither nonmatching, $F(3, 9) = 1.06$, NS, nor discrimination accuracy, $F(3, 9) = 0.97$, NS (Fig. 2, left). Response latency (Fig. 2, right) was not significantly increased by SKF 38393, $F(3, 9) = 3.19$, $\epsilon = 0.56$, NS. However, nosepoke IRT (Fig. 2, right) was significantly increased, $F(3, 9) = 14.93$, $\epsilon = 0.49$, $p = 0.012$, after 1.8 and 3.0 mg/kg [Fs(1, 3) = 58.27 and 30.80, ps = 0.005 and 0.012, respectively].

SCH 23390

After the highest dose given (0.03 mg/kg), the D_1 antagonist SCH 23390 seriously suppressed responding: no rat completed more than 35 trials on the DMTP/VD task, and all appeared lethargic upon removal from the test chambers. Data were therefore analyzed from the lower doses only. Neither nonmatching nor discrimination accuracy (Fig. 3, left) were significantly affected at these doses of SCH 23390. Nosepoke IRT (Fig. 3, right) was significantly increased, $F(4, 12) = 6.17$, $\epsilon = 0.44$, $p = 0.044$, but only after the highest dose, $F(1, 3) = 99.32$, $p = 0.002$, of SCH 23390. Response latency was not affected significantly by the drug.

Quinpirole

The D_2/D_3 agonist quinpirole impaired performance on several aspects of the DNMTP/VD task (Fig. 4). First, nonmatching accuracy (Fig. 4, left) was significantly reduced by quinpirole, $F(4, 12) = 15.49$, $\epsilon = 0.49$, $p = 0.0045$; significant reductions occurred after doses of 0.018, 0.030, and 0.056 mg/kg [Fs(1, 3) = 24.05, 216.06, and 28.47, ps = 0.016, 0.001, and 0.013, respectively]. Discrimination accuracy (Fig. 4, left) was not significantly affected by quinpirole, $F(4, 12) = 1.17$, $\epsilon = 0.31$, NS. Quinpirole also caused significant motor slowing in the task (Fig. 4, right): both response latency, $F(4, 12) = 6.22$, $\epsilon = 0.72$, $p = 0.028$, and nosepoke IRT, $F(4, 12) = 5.28$, $\epsilon = 0.56$, $p = 0.013$, were increased (Fig. 4, right). Response latency was increased by 0.018, 0.03, and 0.056 mg/kg quinpirole [Fs(1, 3) = 42.76, 52.73, and 18.12, ps = 0.007, 0.005, and 0.014, respectively], while nosepoke IRT was increased by 0.10, 0.18, and 0.03 mg/kg only [Fs(1, 3) = 223.38, 76.95, and 25.22, ps = 0.001, 0.003, and 0.015, respectively].

Raclopride

Rats given raclopride at doses above 0.10 mg/kg consistently failed to respond: no rat completed more than 25 trials after 0.177 mg/kg, or more than one trial after 0.30 mg/kg, and all were very lethargic. DNMTP/VD data were thus analyzed for 0.056 and 0.10 mg/kg raclopride doses only. Neither nonmatching nor discrimination accuracy (Fig. 5, left) nor nosepoke IRT nor response latency (Fig. 5, right) were significantly affected after these doses of raclopride.

Within-Session Effects: Retention Gradients

The effect of *d*-amphetamine on nonmatching accuracy resulted from a lowering of the intercept of the retention gradient, without a significant change in slope (Fig. 6, left). The nonmatching intercept was significantly reduced, $F(3, 9) = 8.55$, $\epsilon = 0.61$, $p = 0.022$, with a significant reduction after 1.00 mg/kg, $F(1, 3) = 20.58$, $p = 0.020$. The slopes of the gradients after *d*-amphetamine did not differ significantly from saline, $F(3, 9) = 1.80$, NS.

The reduction in nonmatching accuracy caused by quinpirole also involved a parallel downward shift in the retention gradient (Fig. 6, right). This shift reduced the intercept of the gradient , $F(4, 12) = 15.19$, $\epsilon = 0.44$, $p = 0.007$, without significantly affecting its slope, $F(4, 12) = 2.21$, $\epsilon = 0.27$, $p > 0.20$. The intercept was significantly reduced after 0.018, 0.030, and 0.056 mg/kg quinpirole [Fs(1, 3) = 23.11, 24.70, and 56.60, ps = 0.017, 0.016, and 0.005, respectively].

DISCUSSION

These studies confirm reports that *d*-amphetamine impairs working memory in rats (9,16,22). Further, the dose-effect function for *d*-amphetamine on working memory (Fig. 1, left) compares favorably with those obtained with younger rats performing this task (16,22), indicating that the age of the animals in the present study contributed little to the effects of this drug. The present findings also extend these reports by demonstrating that the mnemonic effect of *d*-amphetamine was specific to working memory, since nonmatching accuracy was significantly reduced by the drug while discrimination accuracy was not (Fig. 1, left). This specificity has not previously been reported after *d*-amphetamine treatment and suggests that, like cholinergic blockade (12,16,23,33), nonspecific

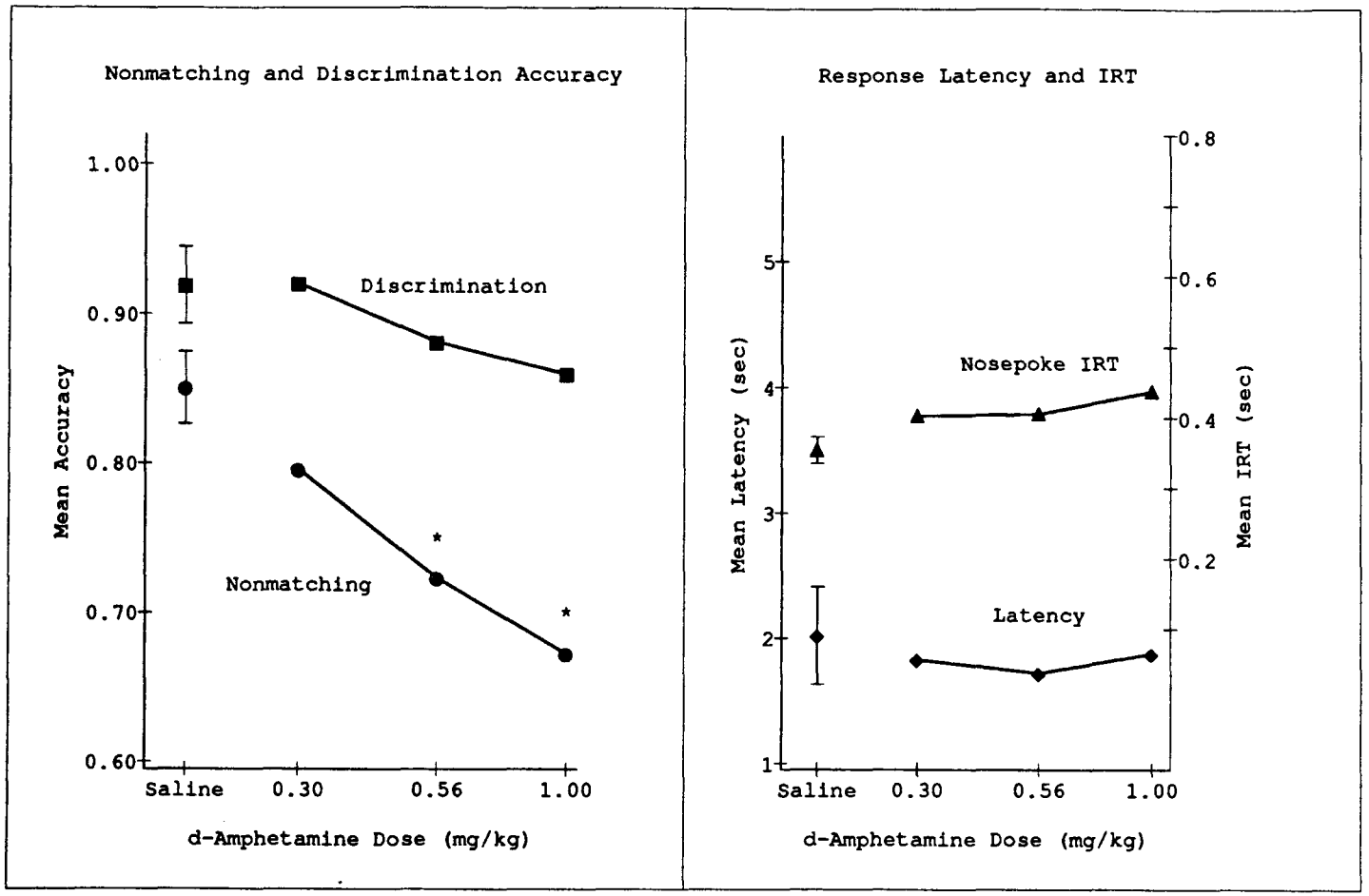

FIG. 1. Effect of *d*-amphetamine on nonmatching and discrimination accuracy (left) and nosepoke interresponse time (IRT) and response latency (right) in rats. All symbols represent group means. Error bars on the saline vehicle points indicate ±1 SEM, derived from the pooled error estimates from each analysis. *Significantly different from saline vehicle ($p < 0.05/\sqrt{3}$).

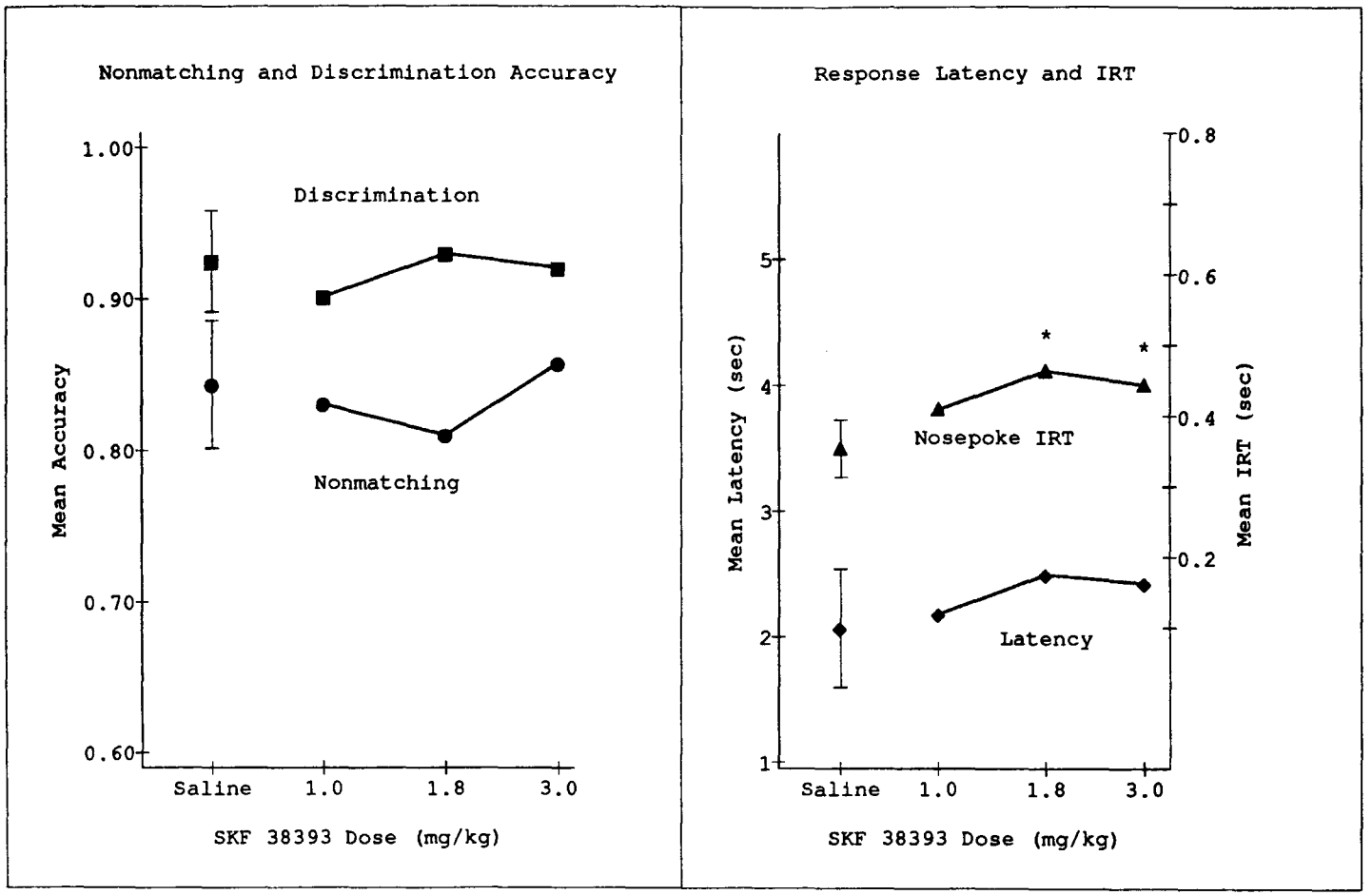

FIG. 2. Effect of SKF 38393 on nonmatching and discrimination accuracy (left) and response latency (right) in rats. Symbols as in Fig. 1. *Significantly different from saline vehicle ($p < 0.05/\sqrt{3}$).

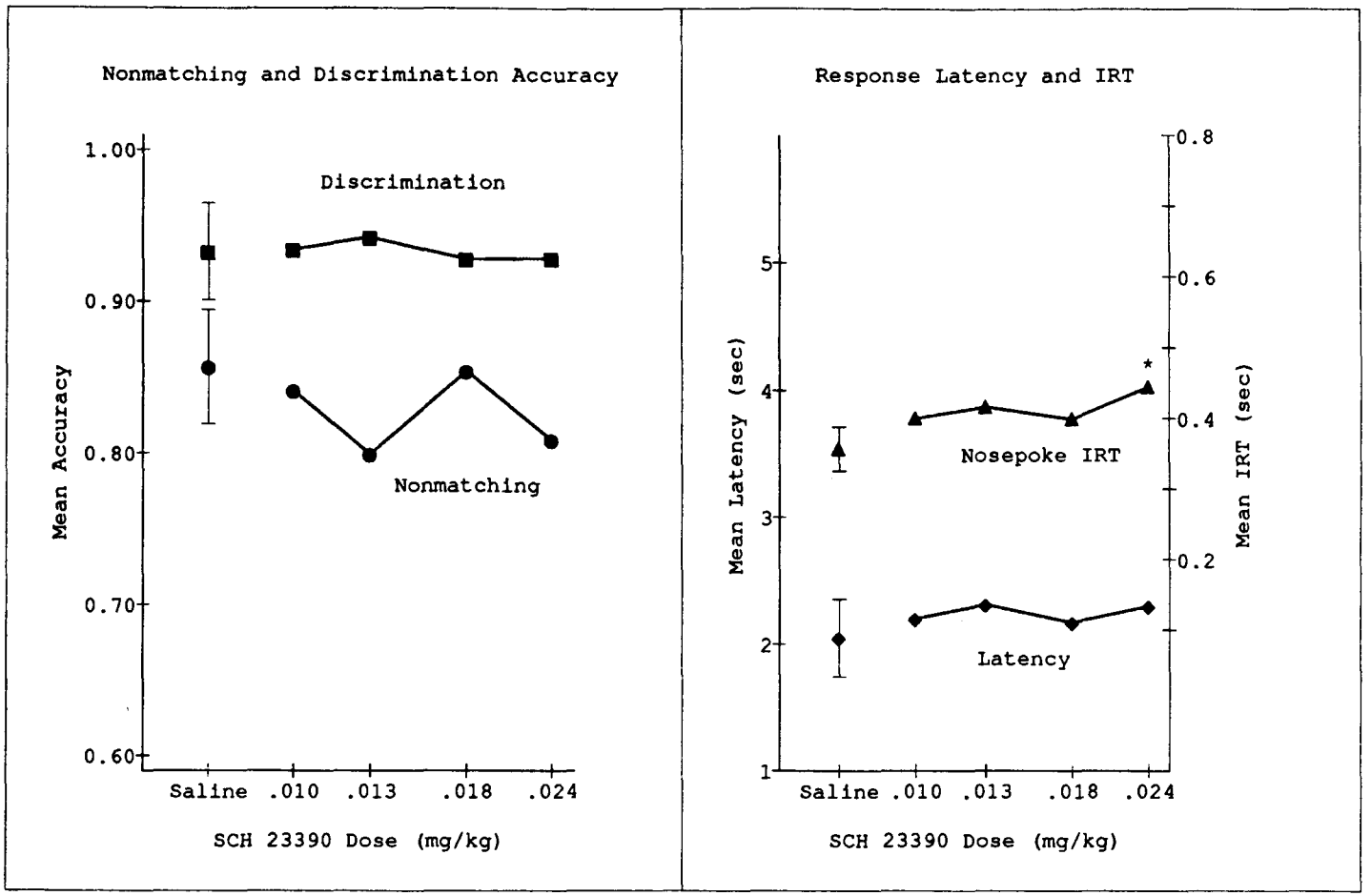

FIG. 3. Effect of SCH 23390 on nonmatching and discrimination accuracy (left) and response latency (right) in rats. Symbols as in Fig. 1. *Significantly different from saline vehicle ($p < 0.05/\sqrt{4}$).

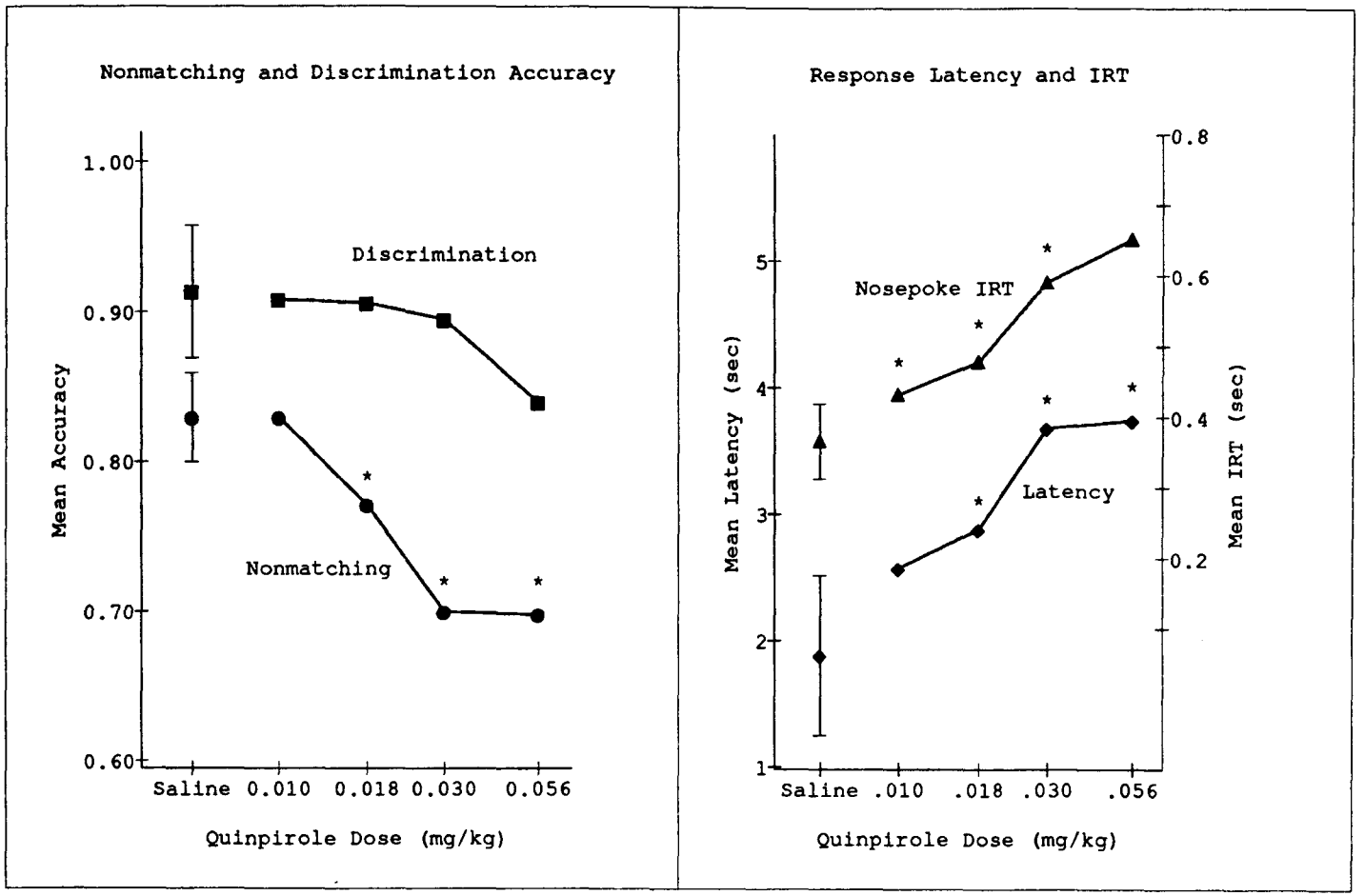

FIG. 4. Effect of quinpirole on nonmatching and discrimination accuracy (left) and response latency (right) in rats. Symbols as in Fig. 1. *Significantly different from saline vehicle ($p < 0.05/\sqrt{4}$).

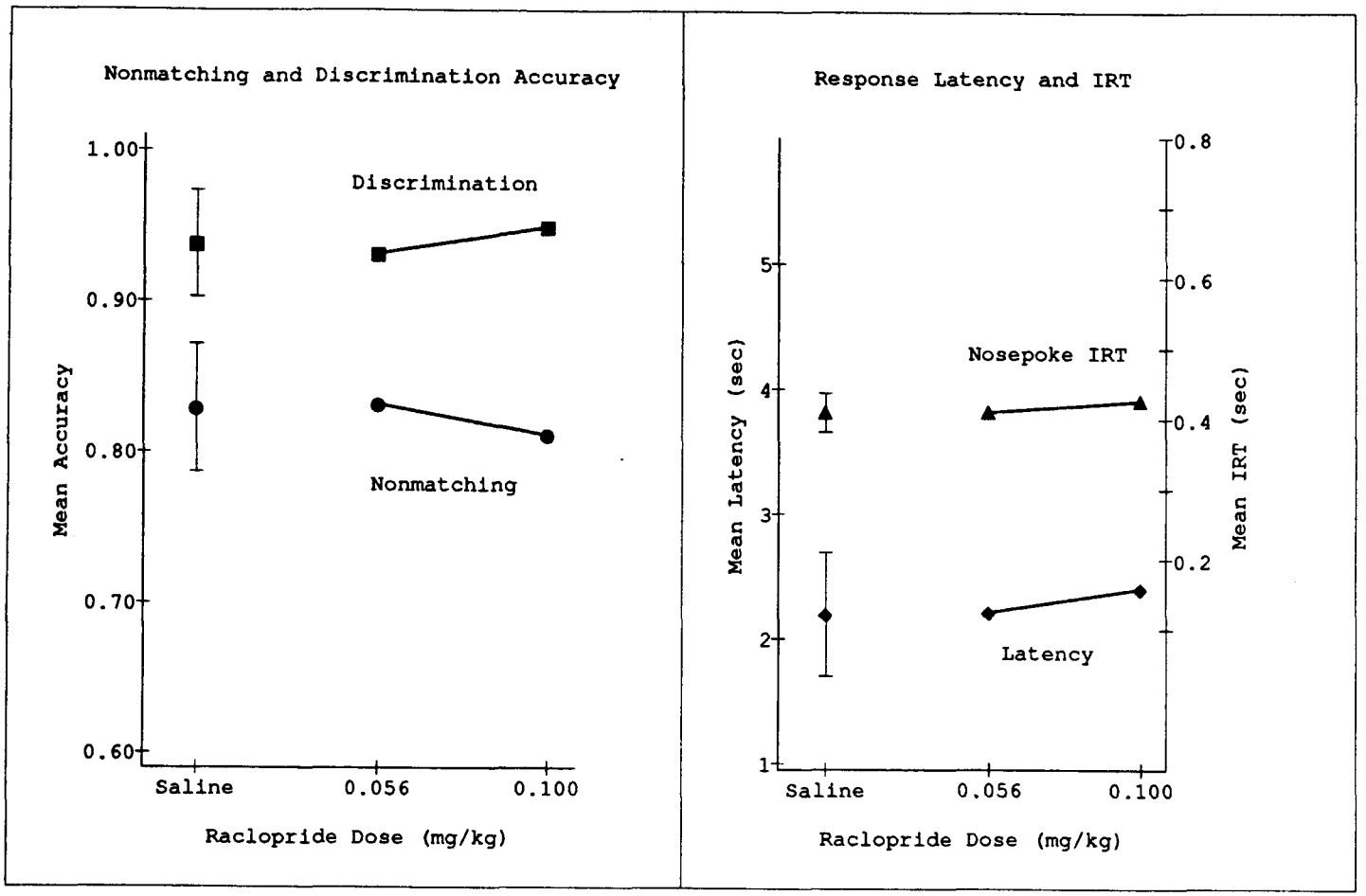

FIG. 5. Effect of raclopride on nonmatching and discrimination accuracy (left) and response latency (right) in rats. Symbols as in Fig. 1. *Significantly different from saline vehicle ($p < 0.05/\sqrt{2}$).

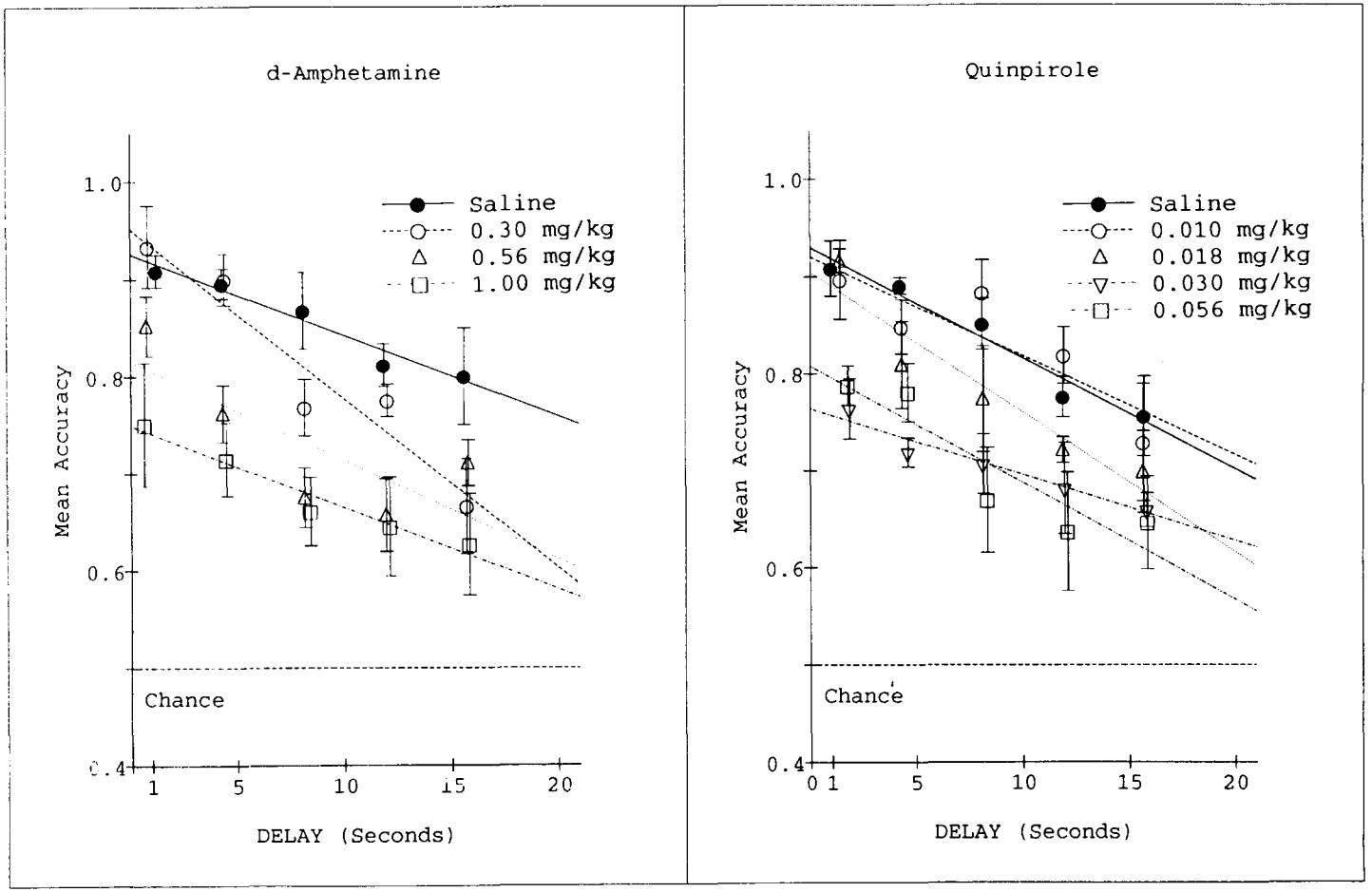

FIG. 6. Retention gradients, showing nonmatching accuracy as a function of sample-choice delay for *d*-amphetamine (left) and quinpirole (right). Points represent means (± SEM), and lines represent linear least-squares regression functions relating accuracy to delay. Accuracy decrements involved significant changes in intercept, but not in slope, of the gradients for both drugs.

dopaminergic stimulation more readily disrupts working memory than reference memory.

The fact that the *d*-amphetamine-induced change in nonmatching accuracy involved a reduction in the intercept, but not the slope, of the retention gradient supports observations of Dunnett (16), but not those of Kesner et al. (22). The delay-dependent decrease in accuracy after *d*-amphetamine seen by Kesner et al. may be due to their lack of a procedure for controlling behavior during the delay. That is, undrugged rats in their study may have been able to "bridge" the delay by positional-mediating strategies that could have been disrupted by a drug-induced increase in locomotion. If the probability of movement away from the location of the correct choice lever increased with delay, and if *d*-amphetamine increased the probability of movement, then accuracy would be expected to fall as delay increased. The present method, and that used by Dunnett (16), control such mediating strategies by requiring responding in a central location during the delay. The fact observed here and by Dunnett (16) that *d*-amphetamine did not alter the slope of the retention gradient, but only its intercept, indicates that *d*-amphetamine did not disrupt retention of the sample information as much as its encoding prior to the delay (12,19). This effect has also been seen after cholinergic challenges (12,13,23).

Quinpirole, like *d*-amphetamine, reduced nonmatching accuracy without affecting visual discrimination accuracy (Fig. 4, left). Further, the deficit induced by quinpirole on nonmatching accuracy was, like that induced by *d*-amphetamine, equivalent at all delays (Fig. 6). In contrast, we found no significant mnemonic effects of the D_1 agonist SKF 38393 in doses ranging from 1.0 to 3.0 mg/kg on nonmatching or discrimination accuracy (Fig. 2, left), while nosepoke IRT was lengthened after 1.8 and 3.0 mg/kg of the drug (Fig. 2, right). Thus, the mnemonic effect of *d*- amphetamine may be explained by the action of DA at D_2/D_3 receptors, because these effects were mirrored by the D_2/D_3 agonist quinpirole, and not by the D_1 agonist SKF 38393. (Note, however, that SKF 38393 is not a full-efficacy agonist at the D_1 receptor: see caveat below.)

Unlike *d*-amphetamine, however, quinpirole slowed responding: both nosepoke IRT and response latency increased with dose of quinpirole. This effect has been seen previously in the radial-arm maze (14,24), and may involve a presynaptic action of the drug. That is, autoreceptor-mediated inhibition of nigrostriatal DA release may slow movement. Alternatively, this slowing may represent a direct agonist effect at postsynaptic D_2/D_3 receptors, which would be masked after *d*-amphetamine by simultaneous stimulation of D_1 receptors. The latter interpretation is consistent with proposed tonic role for D_1 receptors in arousal, which, coupled with phasic stimulation of D_2/D_3 receptors, engages specific behaviors such as grooming and sniffing (8).

The significant increase in response latency observed after quinpirole was large relative to the motor effects of the other drugs. Nevertheless, this latency increase was of small magnitude relative to the delays used to generate the retention gradients. Therefore, it is unlikely motor slowing per se contributed importantly to the quinpirole-induced deficit in matching accuracy. [The magnitude of this slowing can be seen in the lengthening of delay intervals (x-values) with increasing quinpirole dose in Fig. 6 (right), particularly at short nominal delays.] Nevertheless, it is clear that changes in nonmatching accuracy did not occur in the absence of changes in motor function.

Neither SCH 23390 nor raclopride impaired nonmatching or discrimination accuracy (Figs. 3 and 5, left). SCH 23390 produced reliable response slowing after 0.024 mg/kg (Fig. 3, right) and response failure at 0.030 mg/kg. Raclopride did not significantly slow responding after 0.056 or 0.100 mg/kg; after 0.177, 0.300, or 1.00 mg/kg, responding was completely suppressed: no rat completed more than 25 trials after these doses, precluding evaluation of response accuracy or latency. Clearly, response suppression was more sensitive to these compounds than was response accuracy or speed. This pattern of motor slowing and response failure can result from decreased appetitive motivation, since response latency, nosepoke IRT, and response failure all increase when rats are fed immediately prior to testing on this task (unpublished observations). It is thus pertinent to note that both D_1 and D_2 antagonists have been reported to produce extinction-like effects on tasks involving associations of response to reward (6). This "anhedonic" action of the DA receptor antagonists may account for the response slowing and suppression induced by these drugs.

The lack of mnemonic effect of SCH 23390 in rats contrasts with reported disruption of working memory in monkeys by the D_1 antagonists SCH 23390 and SCH 39166 (35). This contrast probably reflects a difference in route of administration: mnemonic deficits were found after intracerebral infusions localized in the prefrontal cortex of monkeys, while the present study used parenteral injection. Localized infusion into an area involved in the mediation of working memory should enhance effects on that process and mitigate potential competing effects of the drug in areas mediating motivation and motor function (e.g., hypothalamus and striatum).

A caveat is in order: SKF 38393 is only a partial agonist at the D_1 receptor, exerting just 30–50% of the efficacy of DA (28). Thus, it cannot stimulate adenylate cyclase as strongly as does DA itself, which could explain its lack of effects here. Determining whether stimulation of D_1 receptors is also involved in the functional effects of *d*-amphetamine will require use of a full-efficacy D_1 agonist. Also, improvement of working memory with similar doses of SKF 38393 has been reported against a background of scopolamine-induced impairment (27). Perhaps lower levels of adenylate cyclase stimulation are necessary for remediation of drug-induced performance deficits than for improvement above a normal baseline.

It is also possible that the differential effects of the D_1 and D_2/D_3 ligands used here reflect input of other transmitter systems to working memory. For example, these drugs interact quite differently with compounds specific for muscarinic and nicotinic cholinergic receptors (26), and SCH 23390 also appears to interact with 5-HT_2 receptors in addition to D_1 receptors (7). By whatever means these drugs act on the nervous system after systemic administration, it is clear that a specific impairment of working memory can be induced by indirect stimulation of all DA receptors with *d*-amphetamine, and by direct stimulation of D_2/D_3 receptors with quinpirole, but not by stimulation of D_1 receptors with SKF 38393, or by blocking either receptor type with SCH 23390 or raclopride. It is also clear that the cognitive impairment caused by quinpirole was associated with motor slowing, a prominent feature of many dopaminergic drugs that frequently complicates the interpretation of the behavioral effects of these compounds.

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