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Titrating Matching-to-Sample Performance in Pigeons: Effects of Diazepam, Morphine, and Cholinergic Agents

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WENGER, G. R., T. J. HUDZIK AND D. W. WRIGHT. *Titrating matching-to-sample performance in pigeons: Effects of diazepam, morphine, and cholinergic agents.* PHARMACOL BIOCHEM BEHAV **46**(2) 435–443, 1993.—Five adult, male White Carneau pigeons were trained to respond under a titrating matching-to-sample schedule of reinforcement. Under this titration schedule, each trial began with the presentation of a sample stimulus (red or green light) on the center key of a three-key pigeon chamber. Completion of 15 responses on the center key resulted in the termination of the stimulus presentation and the initiation of a delay period. The length of the delay changed as a function of the pigeon's performance. During the first five trials of each session, the delay was fixed at 3 s in length. On the sixth and all subsequent trials, the length of the delay was either increased, did not change, or decreased such that accuracy was maintained at approximately 80%. Following the delay, two of the three pigeon keys were transilluminated with different colored lights (red or green). A single response upon the key transilluminated with the same stimulus color as the sample stimulus resulted in the presentation of food. A response on the key transilluminated with the stimulus color that did not match the sample stimulus resulted in a time-out period. Using this procedure, the effects of two drugs of abuse, diazepam (0.03–3 mg/kg) and morphine (0.03–10 mg/kg), a muscarinic antagonist, scopolamine (0.003–0.3 mg/kg), the quaternary derivative of scopolamine, methylscopolamine (0.003–0.3 mg/kg), a cholinesterase inhibitor, physostigmine (0.003–0.1 mg/kg), and the quaternary derivative of physostigmine, neostigmine (0.003–0.1 mg/kg), were determined. Diazepam decreased matching accuracy such that a decrease in the mean delay value for the session was observed. The decreases in the mean delay value were observed at doses that did not decrease rate of responding or increase the latency to initiate a trial. Morphine did not affect the mean delay value despite marked effects on response latency. Scopolamine, like diazepam, decreased the mean delay value but only at doses that also decreased rate of responding and increased the latency to initiate a trial. Methylscopolamine only produced effects on the mean delay and response rate at the highest dose tested (0.3 mg/kg), suggesting that the effects observed with scopolamine were centrally mediated. The only effect observed with physostigmine was a decrease in the mean delay value at the highest dose studied (0.1 mg/kg), a dose that also increased the latency to initiate a trial. When neostigmine was studied, the 0.1 mg/kg dose decreased the mean delay value and increased response latency, suggesting that the effects of physostigmine at this dose may be mediated peripherally. These results show that both diazepam and scopolamine disrupt matching accuracy. The results also suggest a greater specificity in the effect of diazepam compared to scopolamine because the separation between doses that disrupt matching accuracy and doses that suppress rate of responding is greater for diazepam than for scopolamine.

Pigeon Behavioral pharmacology Schedule-controlled behavior Matching-to-sample Titration schedule Scopolamine Methylscopolamine Physostigmine Neostigmine Diazepam Morphine

THE effect of drugs on short-term memory has been studied using a variety of techniques. One such technique, delayed matching-to-sample (5,14,36), utilizes operant conditioning to maintain a stable baseline of performance over long periods of time. Under a delayed matching-to-sample schedule of reinforcement, the subject is presented with a sample stimulus at the beginning of each trial. Following either a predetermined amount of time or completion of a specific number of responses on the key associated with the sample stimulus, the stimulus is removed and a delay initiated. Upon the completion of the delay, two or more stimuli are presented and the subject's task is to respond to the stimulus that matches the sample stimulus.

The utilization of the matching-to-sample baseline has a number of advantages for the determination of short-term memory function. For example, repeated determinations can be made in individual subjects and subjects can serve as their own controls. However, there are problems associated with

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the procedure that have decreased the utility of this baseline for studying drug effects. Typically, the subject is trained until stable performance is achieved. This stable performance is frequently associated with a high degree of accuracy that precludes the measurement of further improvement following drug administration, that is, a "ceiling effect" is frequently observed. In addition, drug-induced decrements in matching performance are subject to a "floor effect," that is, matching performance can only be decreased to "chance performance." When the subject is asked to choose between two stimuli, as is frequently the case, chance performance is equivalent to 50% accuracy.

Roberts (32) has shown that for pigeons responding under a delayed matching-to-sample baseline matching accuracy decreases with increasing length of delay. Thus, it is possible to change matching accuracy by changing the delay length. Accuracy can be increased by shortening the delay or can be decreased by lengthening the delay. If a titration schedule is used to control the length of the delay, the effect of a drug could be expressed as an effect on delay length rather than a change in percent accuracy. This change in the dependent variable makes it possible to avoid the ceiling and floor effects observed when percent accuracy is used. Previous work from this (38,39) and other laboratories (8,27,34) has shown that utilization of a titration schedule will maintain percent accuracy at a specified value, and the ceiling and floor effects are attenuated. In previous reports (38,39), the length of the delay was fixed at 3 s for the first five trials of each session. On the sixth and all subsequent trials, the length of the delay was either increased, did not change, or decreased such that accuracy was maintained at approximately 80%.

A major drawback to the use of the titrating matching-to-sample procedure for the study of drug effects on short-term memory is the limited database on the effects of drugs with known effects in other procedures. In a previous report (39), pentobarbital and phencyclidine were shown to have specific effects on performance. Pentobarbital decreased the length of the mean delay achieved during the session at doses that either increased response rate or had no significant effect on the rate of responding. Although phencyclidine produced a similar effect, the specificity of the effect on the mean delay value occurred over a narrower dose range. In contrast, cocaine and *d*-amphetamine failed to affect the mean delay value achieved during the session at doses that did not markedly affect response rate. Only when response rate was markedly decreased were decreases in the mean delay observed.

The present study extends the findings on the effects of drugs in pigeons responding under a titrating matching-to-sample baseline to four other drug classes: benzodiazepines, opioid narcotics, antimuscarinics, and cholinesterase inhibitors. The benzodiazepine, diazepam, was selected because it is known to cause memory deficits in humans (17,19,20,31). In addition, the benzodiazepines are reported to alter short-term memory in rodents using nonoperant baselines. Both active and passive avoidance have been shown to be disrupted by drugs of this class (10,18,25,26); short-term memory, as measured by procedures using mazes, has also been disrupted (16,22,30). In addition, diazepam is reported to decrease matching accuracy in pigeons responding under matching-to-sample procedures using fixed-delay values (24,35). The opioid, morphine, was included because it is reported to have little if any effect on matching accuracy of pigeons under a fixed-delay matching-to-sample baseline (23). The antimuscarinic drugs, scopolamine and methylscopolamine, and the cholinesterase inhibitors, physostigmine and neostigmine, were selected because of their effects on cholinergic transmission. The cholinergic system has been repeatedly implicated in short-term memory function in other species [for recent reviews, see (3,15,21)], and scopolamine, specifically, is reported to have adverse effects on memory in humans (11, 17,19,20). Thus, it was of interest to examine the effects of these prototype cholinergic compounds on matching performance in the pigeon.

METHOD

Subjects

Subjects were five male, White Carneau pigeons (Palmetto Pigeon Plant, Sumter, SC) weighing between 500 and 625 g when given free access to food and water. Body weights of pigeons were reduced to 80% of free-feeding weight and maintained at this weight throughout the course of the experiment by postsession feeding. Pigeons were housed individually and given free access to water, except during experimental sessions, and were maintained under a 12 L : 12 D cycle (lights were on from 7:00 a.m.–7:00 p.m.). All subjects had previous training under a titrating matching-to-sample procedure and had been previously tested after administration of other drugs of abuse.

Apparatus

Subjects were trained and tested in standard pigeon chambers (Model G7313; Ralph Gerbrands Co., Arlington, MA) that contained three response keys, each of which could be transilluminated with white, red, or green light. The chamber was housed in a sound- and light-attenuating enclosure (Model G7211; Ralph Gerbrands). Below the center key of the operant chamber a feeder trough was located. Opening of the key contacts defined the response and operated a relay mounted inside the enclosure, producing auditory feedback upon a response. A force of 0.15 N was required to open the key contacts. Responses on the keys were recorded by microprocessor equipment (TRS-80, Model III; Tandy Corp.) located in the adjacent room. Two 28-V DC light bulbs (1819) provided illumination inside the enclosure at all times except during the presentation of food and during time-out periods.

Schedule

The training of pigeons under the titrating matching-to-sample schedule has been described earlier (39). Under the final schedule, each trial began with illumination of the center key in the chamber, which was randomly assigned a green or red color. Responding on this center key under a fixed-ratio (FR) 15 schedule of reinforcement (observation phase) turned off the center key light and initiated a delay period during which all key lights were extinguished. After a delay of at least 3 s, two of the three response keys were transilluminated, one red and the other green. Which two of the three keys were illuminated on a given trial varied randomly among the left, center, and right response keys. A single response on the key that was transilluminated with the same color presented during the observation phase (matching response) was defined as a correct response and resulted in a 5-s access period to Purina pigeon checkers. A response on the key transilluminated with the color that was not presented during the observation response was defined as being incorrect and produced a 5-s time-out period during which all lights in the chamber were extinguished. Each trial was followed by a time-out period

during which no stimuli were presented and the chamber was darkened (intertrial interval). Dose-response curves for scopolamine, methylscopolamine, physostigmine, and neostigmine were determined twice: once with an intertrial interval of 10 s and once with an intertrial interval of 30 s. Dose-response curves for diazepam and morphine were determined using a 10-s intertrial interval.

Sessions continued for 50 matching trials or 1 h, whichever occurred first. The maximal 1-h session length excluded intertrial intervals and matching-to-sample delay periods. The delay value remained at 3 s for the first five trials, after which it was reset for each subsequent trial based upon the following criteria: if a correct matching response was made in five of the five previous trials, the delay value was increased by 3 s; if four of the five previous matching responses were correct, the delay value remained at its previous level; if three or less of the previous five matching responses were correct, the delay value decreased by 3 s, to a minimum of 3 s.

Data Analysis

For each session, the following values were calculated: the mean delay value across all trials, the rate of responding during the completion of the FR 15 on the observation (center) key, and the percentage of correct matching responses (accuracy). The rate of responding (running rate) was calculated by dividing the total number of observation responses on the center key by the total time required to complete the FR 15 minus the latency to the make the first FR response. Additionally, the latency to respond on the center key for each trial as well as latency to respond to the matching stimulus were totaled for the entire session. A mean latency value was then calculated by taking the total latency time to respond on the center key and dividing by the number of trials in the session. The mean latency to respond to the choice key was calculated in a similar manner.

In presenting group data for the mean delay and percent accuracy, a given subject was excluded from the group mean if it failed to complete at least 10 trials in a given session. A conservative estimate of the SEMs for control values was calculated by dividing the total standard deviation $(n-1)$ of the individual control values from all control sessions by the square root of the number of subjects. Because the data shown for scopolamine, methylscopolamine, physostigmine, and neostigmine represent duplicate determinations in each animal, the same conservative estimate of SE was calculated for this data (the total SD divided by the square root of the number of subjects). The nonparametric Mann-Whitney test was used to determine statistical significance between group means. Means were considered to be statistically different when $p < 0.05$.

Drugs

Scopolamine HBr, methylscopolamine Br, physostigmine SO_4, neostigmine Br (Sigma Chemical Co., St. Louis, MO), and morphine SO_4 (Malinckrodt, St. Louis, MO) were dissolved in 0.9% saline. All doses were calculated and are expressed as the respective salts. Diazepam was obtained from Hoffman La Roche (Nutley, NJ) in a vehicle consisting of 40% propylene glycol, 10% ethanol, and 50% water, and was diluted to the appropriate concentration with additional vehicle. Dosages of diazepam were calculated and are expressed as the free base. Drug treatments were given on Tuesdays and Fridays with Thursdays serving as saline control sessions. Injections were administered into the breast muscle in a volume of 1 ml/kg body weight. Diazepam was administered 15 min and all other drugs 5 min prior to test sessions.

RESULTS

These experiments were performed over an approximately 24-month period. Initially, the effects of scopolamine, methylscopolamine, neostigmine, and physostigmine were determined using a 10-s intertrial interval. These dose-response curves were then replicated using a 30-s intertrial interval. Under both control conditions and following drug administration, there were no significant differences between those sessions employing a 10-s intertrial interval and those employing a 30-s intertrial interval. [Analysis of the effects of all four drugs on mean delay, accuracy, rate of responding, and choice latency failed to show an effect of the intertrial interval length, multivariate analysis of variance (MANOVA), $F(1, 5)$ ranged from 0.01–1.93, with p values always greater than 0.2.] Consequently, the data from these sessions were combined and only a 10-s intertrial interval was used for the experiments with diazepam and morphine. Control rate of responding (running rate) on the center key under the FR 15 schedule ranged from a low of 1.12 ± 0.25 responses/s during the determination of the morphine dose-response curve to a high of 1.43 ± 0.33 during the determination of the physostigmine dose-response curve. The mean delay value for the session achieved under control conditions ranged from 13.1 ± 2.0 s (morphine) to 17.9 ± 3.4 s (scopolamine). Percent accuracy ranged from 82.0 ± 3.6 (neostigmine) to a high of 88.2 ± 4.6 (diazepam). The latency to initiate a trial, make the first response of the FR 15 on the center key, fluctuated considerably during the course of the experiment. Following both saline administration and drug administration, there was a tendency for pigeons to pause for considerable periods of time prior to the start of the next trial. This was most frequently observed when a high percentage of correct matching responses resulted in long delay values. This phenomena contributed to the considerable fluctuation observed in the latency to initiate a trial. In contrast, choice-key latency did not change significantly. Under control conditions, choice-key latency was brief (approximately 1–1.5 s). Following administration of all six drugs studied, the choice-key latency did not change until doses were reached that markedly decreased rate of responding. At these high doses, choice-key latency increased (data not shown).

Diazepam (Fig. 1) had no effect on performance at doses up to 0.3 mg/kg. A dose of 1 mg/kg decreased the mean delay value and percent accuracy for the session without affecting rate of responding. An apparent decrease in the mean latency to initiate a trial was observed following 1 mg/kg. Although it was observed in all five pigeons studied, the decrease was not large enough to attain statistical significance ($p = 0.12$). When the dose was increased to 3 mg/kg, diazepam suppressed responding in three of the five pigeons such that too few trials were completed to accurately calculate a mean delay value or overall percent accuracy. Thus, the data from these subjects was not included in the group means for the mean delay for the session or overall percent accuracy. However, in the two pigeons that completed a sufficient number of trials the mean delay value for the session and overall percent accuracy were decreased in the same dose-related fashion.

Morphine did not produce any significant changes in the mean delay for the session or percent accuracy (Fig. 2) over the dose range studied, 0.03–10 mg/kg. The highest dose of morphine (10 mg/kg) decreased the running rate and produced a marked increase in the latency to initiate a trial. In

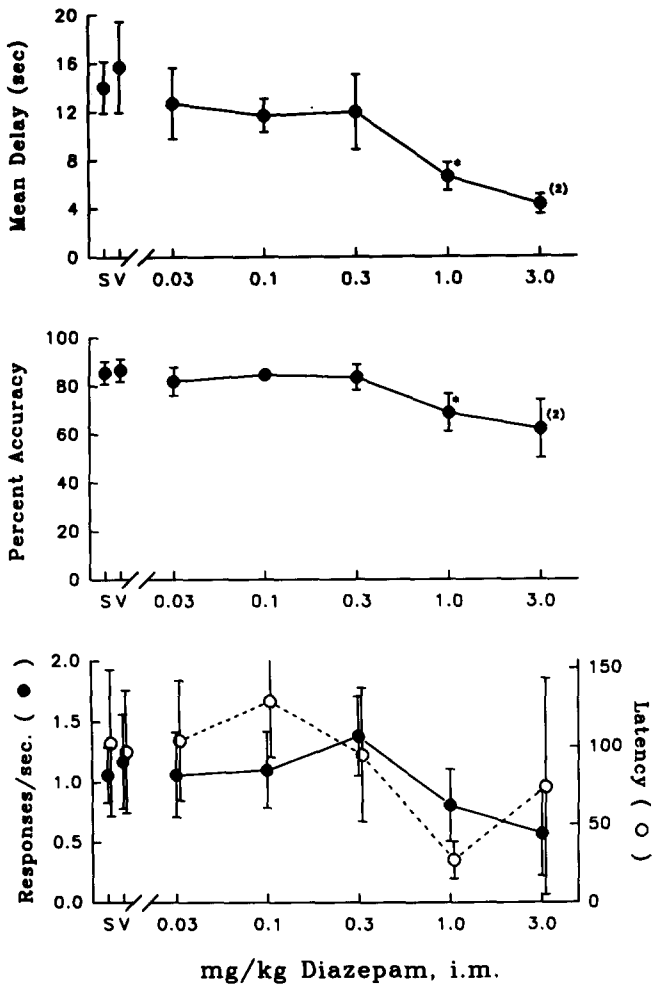

FIG. 1. Effect of diazepam on the performance of pigeons responding under the titrating matching-to-sample baseline. Abscissa, dose in mg/kg on a log scale; ordinate (top), mean delay value achieved for the session in seconds; ordinate (middle), percent accuracy for the entire session; ordinate (lower, left), rate of responding (running rate) under the FR 15 sample stimulus presentation in responses/s; ordinate (lower, right), average latency to initiate a trial in seconds. Points and brackets above S and V represent the saline and vehicle injection control mean ± SE, respectively. Data points for the effects of diazepam represent the mean ± SE of individual determinations (10-s intertrial interval) in each of five pigeons. Where subjects have not been included in the mean because of marked decreases in responding (see the Method section), the number of subjects contributing to the mean is indicated by (n). Statistical difference from saline control is indicated by an asterisk.

one of the five pigeons receiving 10 mg/kg, too few trials were completed to permit an accurate calculation of the mean delay for the session or overall percent accuracy.

The effects of scopolamine on performance maintained under the titrating matching-to-sample schedule of reinforcement are shown in Fig. 3. Scopolamine produced decreases in rate of responding at doses of 0.03 mg/kg and higher. This decrease in rate of responding was associated with a decrease in the mean delay value achieved for the session following a dose of 0.1 mg/kg. Following a dose of 0.3 mg/kg, too few pigeons completed the minimum 10 trials (see the Method section) during the session to allow statistical analysis of the effects observed. Over the entire dose range, overall percent accuracy for the session was maintained at approximately 80% due to the titrating aspect of the schedule. An increase in the mean latency was observed following the highest dose tested, 0.3 mg/kg.

To determine if the effect of scopolamine was mediated centrally or peripherally, methylscopolamine was also studied (Fig. 4). At doses below 0.3 mg/kg, this quaternary derivative had no significant effects on any measure of performance. The mean delay value and rate of responding were decreased at the highest dose studied, 0.3 mg/kg.

The effect of two cholinesterase inhibitors, physostigmine and its quaternary derivative, neostigmine, were also examined in pigeons responding under the titrating matching-to-sample baseline. Physostigmine (Fig. 5) had no significant effects below 0.1 mg/kg. The highest dose tested, 0.1 mg/kg,

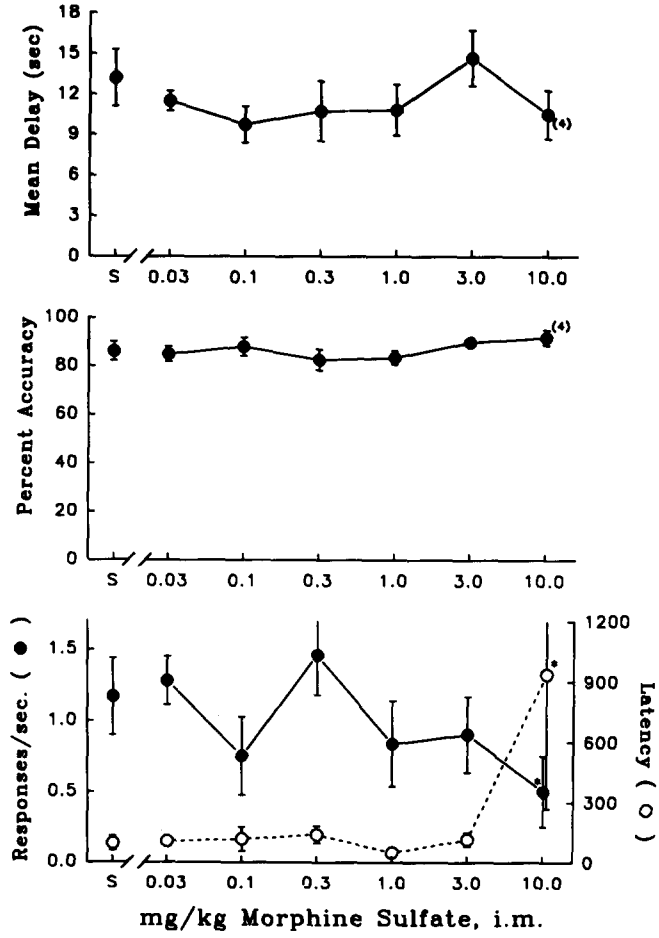

FIG. 2. Effect of morphine sulfate on the performance of pigeons responding under the titrating matching-to-sample baseline. Data presented as in Fig. 1. Points and brackets above S represent the saline injection control mean ± SE. Data points for the effects of morphine represent the mean ± SE of individual determinations (10 s intertrial interval) in each of five pigeons. Where subjects have not been included in the mean because of marked decreases in responding (see the Method section), the number of subjects contributing to the mean is indicated by (n). Statistical difference from saline control is indicated by an asterisk.

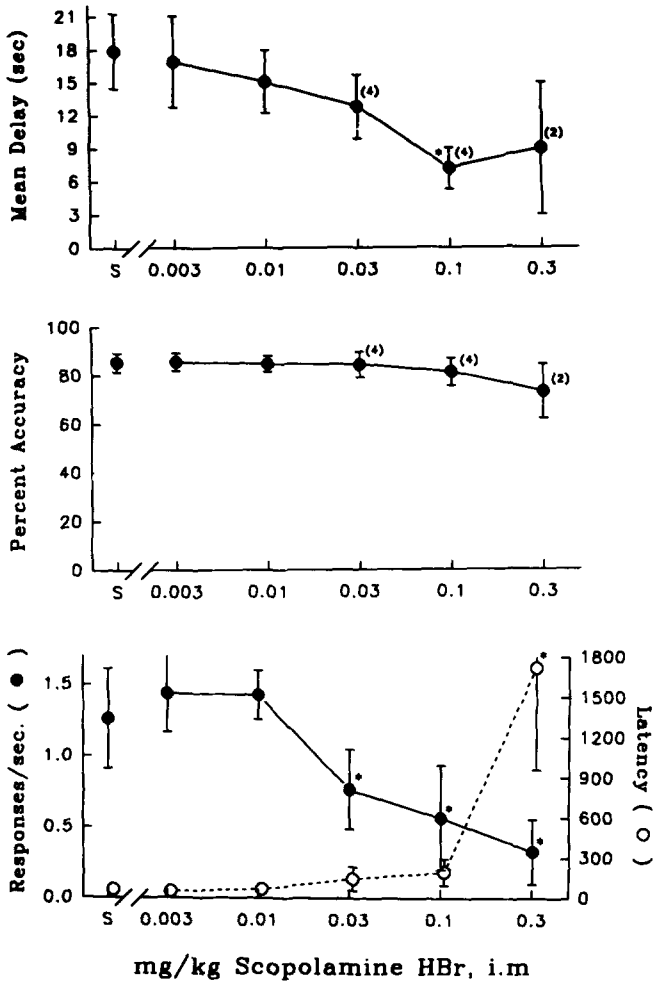

FIG. 3. Effect of scopolamine HBr on the performance of pigeons responding under the titrating matching-to-sample baseline. Data presented as in Fig. 1. Points and brackets above S represent the saline injection control mean ± SE. Data points for the effects of scopolamine represent the mean ± SE of the two determinations (one with an intertrial interval of 10 s and one with an intertrial interval of 30 s) in each of five pigeons. Where subjects have not been included in the mean because of marked decreases in responding (see the Method section), the number of subjects contributing to the mean is indicated by (n). Statistical difference from saline control is indicated by an asterisk.

produced a decrease in the mean delay for the session and an increase in the latency to initiate a trial but no changes in overall percent accuracy or rate of responding. Interestingly, neostigmine (Fig. 6) produced changes in behavior at lower doses than physostigmine. Although the group mean for the rate of responding was not different from control, 0.1 mg/kg neostigmine markedly suppressed responding in one of the five pigeons and the latency to initiate a trial was increased at doses of 0.056 and 0.1 mg/kg. At 0.1 mg/kg neostigmine, a small decrease was observed in the mean delay value for the session with no change in overall percent accuracy. In addition, the lowest dose of neostigmine, 0.003 mg/kg, produced a small but significant increase in the mean delay value (p = 0.027) and decreased the rate of responding (p = 0.02).

DISCUSSION

The present article shows that the two drugs of abuse, diazepam and morphine, have markedly different effects on matching accuracy. Diazepam caused a decrease in matching accuracy, resulting in a decrease in the mean delay value. This disruption in matching performance was relatively specific in that it occurred at doses that did not decrease response rate. In contrast to diazepam, morphine had little effect on matching accuracy and as a result no effect on the mean delay value. This lack of effect on matching accuracy was observed even at doses of morphine that decreased rate of responding and markedly increased the latency to initiate a trial.

Like diazepam, the muscarinic antagonist, scopolamine, disrupted matching performance under the titrating procedure, resulting in shorter mean delay values compared to sa-

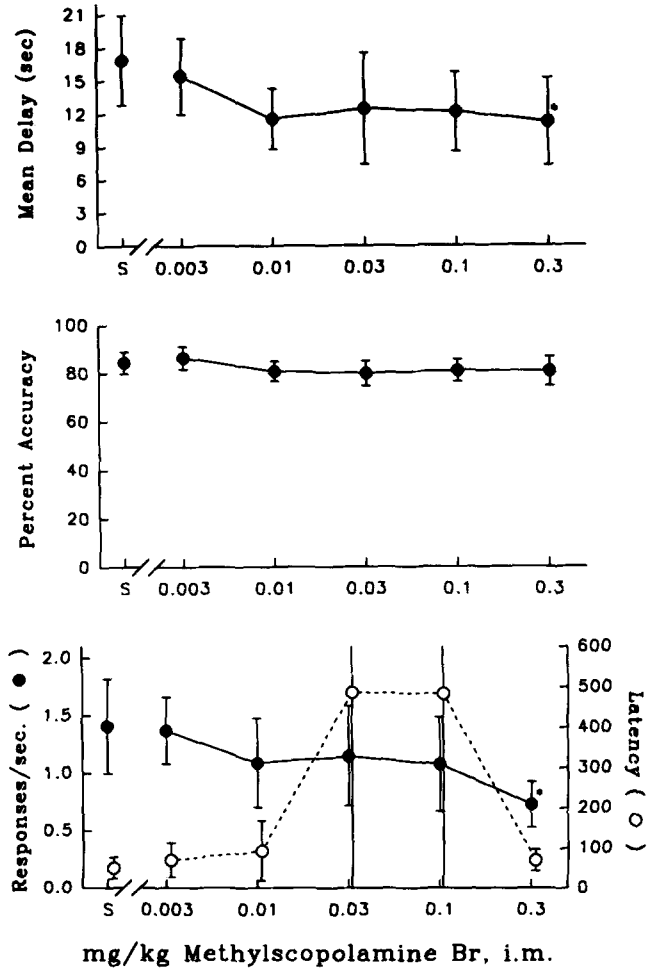

FIG. 4. Effect of methylscopolamine Br on the performance of pigeons responding under the titrating matching-to-sample baseline. Data presented as in Fig. 1. Points and brackets above S represent the saline injection control mean ± SE. Data points for the effects of methylscopolamine represent the mean ± SE of the two determinations (one with an intertrial interval of 10 s and one with an intertrial interval of 30 s) in each of four pigeons. Where subjects have not been included in the mean because of marked decreases in responding (see the Method section), the number of subjects contributing to the mean is indicated by (n). Statistical difference from saline control is indicated by an asterisk.

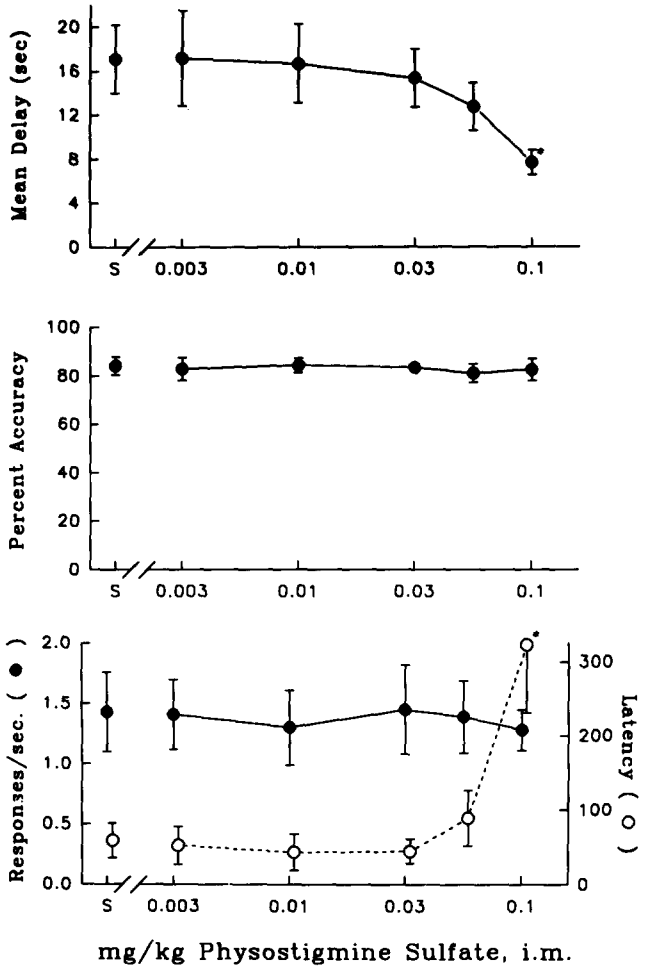

FIG. 5. Effect of physostigmine sulfate on the performance of pigeons responding under the titrating matching-to-sample baseline. Data presented as in Fig. 1. Points and brackets above S represent the saline and vehicle injection control mean ± SE. Data points for the effects of physostigmine represent the mean ± SE of the two determinations (one with an intertrial interval of 10 s and one with an intertrial interval of 30 s) in each of five pigeons. Where subjects have not been included in the mean because of marked decreases in responding (see the Method section), the number of subjects contributing to the mean is indicated by (n). Statistical difference from saline control is indicated by an asterisk.

line controls. However, unlike diazepam, this effect was observed only at doses that also decreased the rate of responding during the presentation of the sample stimulus. When the quaternary derivative, methylscopolamine, was administered prior to the start of the test session, no effects were observed until the highest dose was studied. At this high dose, methylscopolamine decreased the mean delay and decreased the rate of responding. The failure to see any effect of methylscopolamine, except at the highest dose, suggests that the effects observed following lower doses of scopolamine were centrally mediated.

The cholinesterase inhibitor, physostigmine, produced relatively little effect on matching performance under the titrating baseline. No facilitation of memory was observed at any dose, and the highest dose tested (0.1 mg/kg) decreased the mean delay value, indicating a decrease in matching accuracy. This decrease in matching accuracy observed at 0.1 mg/kg in the present study may reflect a more generalized effect of physostigmine because this dose also produced a significant increase in response latency. When the quaternary derivative of physostigmine, neostigmine, was administered, doses of 0.056 and 0.1 mg/kg increased response latency without changing the rate of responding, and, in addition, a decrease in the mean delay value was observed at 0.1 mg/kg. The similarity of effects and doses between physostigmine and neostigmine suggests that the effects observed with the high dose of physostigmine may be mediated in part by peripheral actions.

The effects observed following the lowest dose, 0.003 mg/kg, of neostigmine are difficult to explain. It is difficult to postulate a central action at this dose of neostigmine in light

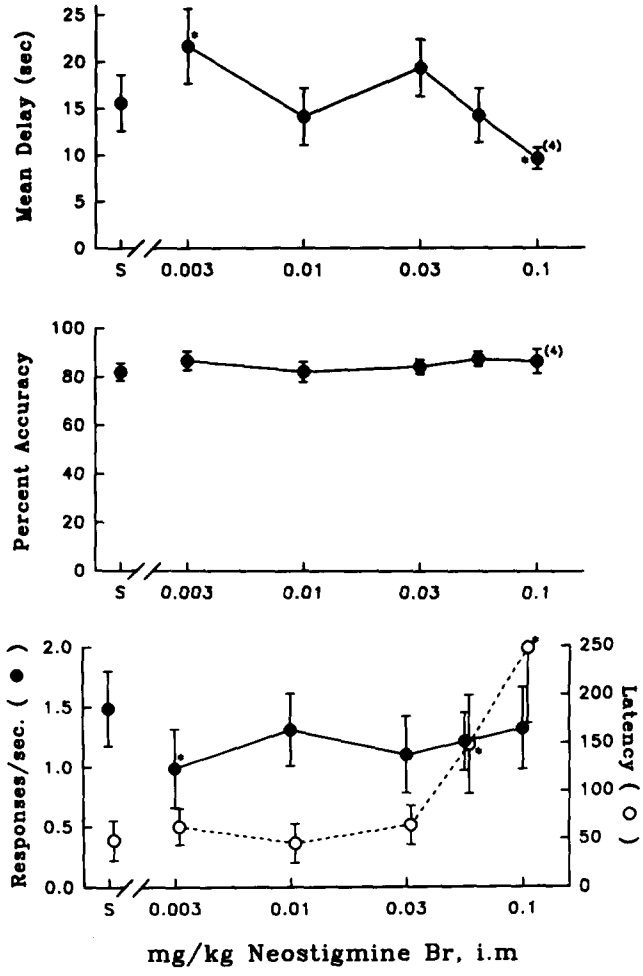

FIG. 6. Effect of neostigmine Br on the performance of pigeons responding under the titrating matching-to-sample baseline. Data presented as in Fig. 1. Points and brackets above S represent the saline injection control mean ± SE. Data points for the effects of neostigmine represent the mean ± SE of the two determinations (one with an intertrial interval of 10 s and one with an intertrial interval of 30 s) in each of five pigeons. Where subjects have not been included in the mean because of marked decreases in responding (see the Method section), the number of subjects contributing to the mean is indicated by (n). Statistical difference from saline control is indicated by an asterisk.

of the absence of effects at higher doses and in light of a lack of similar effects observed at any dose of physostigmine. There is the possibility that the small increase in the mean delay value is the result of a change in response rate and a corresponding change in the number of trials per session. However, even though the rate of responding was decreased, there was no change in the number of trials per session compared to control. Thus, this does not appear to be a valid explanation for the observation, and future experiments concentrating on the lower end of the dose-response curve will be required to answer the questions raised by this unexpected finding.

When the effects reported here are combined with previously published data using the titrating procedure (38,39), it can be seen that there is good agreement between the results obtained using the titration schedule and data obtained under fixed-delay matching-to-sample baselines. To illustrate, diazepam decreased matching accuracy in the present study and in laboratory animals responding under matching-to-sample baselines using fixed delays (24,35). There is a similar correspondence of effects with pentobarbital and phencyclidine. Both drugs have been shown to decrease the mean delay value under the titrating matching-to-sample baseline at doses that do not decrease rates of responding (38,39), and both pentobarbital (4,8,23,24) and phencyclidine (23,24) have been reported to decrease percent accuracy in pigeons responding under matching-to-sample schedules utilizing fixed delays. The similarity of effects is not limited to sedatives/hypnotics/anesthetics. The results presented here for scopolamine are consistent with previous reports showing disruption of short-term memory in laboratory animals (1,6,13), including pigeons responding under fixed-delay matching-to-sample baselines (29,33,37). Thus, drugs that have been shown to decrease the mean delay value under the titrating matching-to-sample schedule also decrease memory function under other procedures.

In the validation of any procedure, it is important to show that the procedure shows selectivity. Thus, it is interesting that not all drugs produce changes in the mean delay value under the titration procedure. Morphine failed to produce consistent effects under the titration procedure. These results are in agreement with a previous report (23) using fixed-delay values of 1, 2, 4, and 8 s in which morphine was reported to have no effect on matching accuracy in pigeons.

A review of the literature on the effects of physostigmine on memory function indicates that the effects of physostigmine on memory function are variable. Several studies using matching procedures with fixed delays have failed to show a facilitation in memory performance (12,28,33), and the results obtained with the titration procedure utilized here are in agreement with these previous studies. Other studies have shown improvement in memory following physostigmine. However, the improvements reported have been relatively small and occurred over a narrow dose range (2,9,13). Why physostigmine is reported to facilitate memory in some studies and not in others is not clear. However, it may relate to the memory task, the error rate, dose, or the species.

The overall effects of the drugs studied both in the previous reports (38,39) and here suggest that the titrating matching-to-sample schedule provides data that are comparable to other procedures while offering several important advantages. However, there is an interesting observation concerning the sensitivity of the procedure relative to matching-to-sample baselines using fixed delays. For example, when diazepam was given to pigeons responding under a matching-to-sample baseline with a 4-s fixed delay (24) doses as low as 0.3 mg/kg produced decreases in matching accuracy. In the present study, the lowest dose to produce a decrease in the delay value was 1 mg/kg. Similarly, in studies using randomly selected fixed-delay values ranging from 0–12 s (29,33,37) doses of 0.015–0.03 mg/kg scopolamine disrupted matching performance. This compares to scopolamine doses of 0.1 and 0.3 mg/kg required to decrease the mean delay value under the titration procedure reported here. This decreased sensitivity to drug effects under the titration schedule does not appear to be true for all drugs. In the previous titrating study (39), pentobarbital was shown to decrease the mean delay value at doses as low as 3 mg/kg. This compares to other studies using a fixed-delay matching-to-sample schedule that report no effect on percent accuracy at a dose of 5 mg/kg (4,8) or other studies that report a dose of 5.6 mg/kg as being the lowest dose producing decreases in matching accuracy (23,24). Similarly, in the previous study (39) phencyclidine was shown to decrease the mean delay value under the titration schedule at a dose of 1 mg/kg. This is the same dose that is reported in the literature to be the lowest dose that decreased percent accuracy using a fixed-delay matching-to-sample schedule (23,24). Thus, although there is a limited database to draw upon for comparison, there is a suggestion of a difference in sensitivity to certain drugs when results obtained under the titration procedure are compared to results obtained using fixed-delay values.

The reason for the suggested differences in sensitivity between the titration schedule and fixed-delay schedules is not clear. However, it should be noted that the control performance is different under the two procedures. Under the titration schedule, pigeons were able to maintain 80% matching accuracy at longer delay values than those reported under fixed-delay baselines (29,33,37). Thus, it is possible that the titration schedule increases the pigeon's ability to recall the original stimulus while at the same time making the performance harder to disrupt by drugs such as scopolamine and diazepam. In this regard, it is interesting that the titration schedule is less susceptible to disruption by proactive interference (38), an observation consistent with a stronger degree of stimulus control.

A second potentially important factor is that, under the baseline used in the present study, the two comparison stimuli are randomly presented on all three response keys. This attenuates the development of any position bias under control conditions or following drug administration (39). The previously cited studies using fixed-delay values presented the two comparison stimuli on the two side keys of a three-key pigeon chamber. Several studies that used two comparison stimuli and presented them only on the two side keys of a three-key pigeon chamber have shown that decreases in matching accuracy as a result of increasing delay length and/or drug administration are frequently related to the expression of position responding or bias (7,8,23). Thus, it is possible that the apparent greater sensitivity of fixed-delay schedules to scopolamine and diazepam may be more closely related to the expression of position biases and the degree of stimulus control than to whether or not a fixed-delay or a titrating-delay procedure was used. Further experiments are required to more fully understand the factors that regulate sensitivity to drug effects under the two baselines.

Finally, allowing the delay value to titrate based upon the pigeon's ability to perform at an overall accuracy rate of approximately 80% has many advantages, including eliminating the ceiling effect, minimizing the floor effect, and maintaining

an overall accuracy level that is clearly above chance performance. The length of the mean delay value for the session appears to be a valid indicator of drug performance on matching accuracy. In the present study, the delay value decreased in response to scopolamine and diazepam, it was not affected by methylscopolamine or morphine, and only the highest dose of physostigmine decreased the mean delay value for the session. This physostigmine effect was mimicked by neostigmine. Likewise, in previous studies (38,39) the delay value was decreased by pentobarbital and phencyclidine but was not decreased by cocaine or *d*-amphetamine at doses that did not markedly suppress responding. Thus, the data obtained using a titrating matching-to-sample schedule would appear to be consistent with data from other animal models of short-term memory while at the same time offering some advantages over fixed-delay schedules.

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