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Cholinergic Agents and Delay-Dependent Performance in the Rat

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BUXTON, A., O. A. CALLAN, E. J. BLATT, E. H. F. WONG AND D. J. FONTANA. *Cholinergic agents and delay-dependent performance in the rat.* PHARMACOL BIOCHEM BEHAV **49**(4) 1067–1073, 1994. – We tested cholinergic agents in delayed matching and nonmatching to position. Each task had a delay between the presentation of information and the chance to act on it later. We used a titrating procedure, new to experiments with rats, to determine the delay. Linopirdine (0.1 mg/kg), which releases acetylcholine, and physostigmine (0.1 mg/kg), a cholinesterase inhibitor, ameliorated the impairment of accuracy produced by scopolamine hydrobromide (0.1 mg/kg). In some cases, scopolamine hydrobromide decreased the number of trials, but physostigmine and linopirdine did not ameliorate that impairment. Both the muscarinic receptor antagonist, scopolamine hydrobromide (0.1 and 0.3 mg/kg), and its peripherally acting analog, scopolamine methylbromide (0.1 and 0.3 mg/kg), decreased accuracy. The impairment produced by scopolamine methylbromide suggests that the deficit produced by muscarinic receptor antagonism may have both a central and peripheral component. At the highest dose, scopolamine hydrobromide decreased the number of trials completed. Thus, some of the effects of scopolamine hydrobromide involve nonmnemonic performance factors. The performance deficits produced by scopolamine hydrobromide suggest that it may be necessary to qualify drug effects in terms of their action on both memorial and nonmemorial aspects of performance.

Delayed matching to position Delayed nonmatching to position Acetylcholine Scopolamine Physostigmine Linopirdine DuP 996 Rat

GROWING concern about the treatment of cognitive dysfunction, such as the memory impairment in Alzheimer's disease, has led to the development of animal models of cognition as a means of evaluating novel therapeutic agents. Hunter's delayed reaction tasks (11) gave rise to contemporary memory paradigms, such as delayed matching to sample and delayed nonmatching to sample, used widely with primates and pigeons. In those tasks the sample stimuli typically differed only visually. For example, the sample might consist of a single key sometimes colored red, sometimes blue, and the subject would later choose between a red key and a blue one. In the matching task the correct choice would match the color of the sample; in the nonmatching task the correct choice would not match the color of the sample. Dunnett (8) modified the tasks for use with rats, which have relatively poor vision, by using sample stimuli that differed spatially, and renamed the tasks delayed matching to position and delayed nonmatching to position. For example, in the modified paradigm a lefthand lever and a righthand lever might serve as the sample stimuli.

All of these paradigms are delayed response paradigms because each imposes a delay interval between the presentation of information and the subject's chance to act on that information. Typically, as the length of the delay increases, accuracy decreases (6,9). Such results support the supposition that performance of the tasks may involve the memorial aspect of cognition. For that reason, delayed response tasks have been used to study cognition in a variety of species. In addition, delayed response tasks have been used to study the action of psychoactive agents on cognition in both preclinical studies of nonhuman primates (3) and clinical studies of humans (14).

In the series of experiments reported here, we tested cholinergic agents for their effects on rats' performance in the positional version of a delayed response paradigm. Our use of cholinergic agents was based on substantial evidence that acetylcholine (ACh) is related to learning and memory (for a

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review, see Bartus et al. [2]). Specifically, agents that decrease (increase) cholinergic neurotransmission typically disrupt (enhance) cognition. Furthermore, many studies suggest that cholinergic dysfunction may underlie some kinds of cognitive impairment, such as the memory loss associated with Alzheimer's disease (2,16).

In two of the studies reported here, we examined the effects of scopolamine on performance in matching and nonmatching to position paradigms. In one of those studies we used the muscarinic receptor antagonist, scopolamine hydrobromide, which typically disrupts cognition; accordingly, we expected it to decrease accuracy in both paradigms. In the other study we used the peripherally acting scopolamine methylbromide, which should not affect accuracy if performance of the tasks is purely central. In three other studies we used scopolamine hydrobromide to decrease accuracy as a means of evaluating the blocking action of physostigmine and linopirdine.

In addition, we extended to rats a superior new method for determining the length of the delay interval, a titrating procedure used in studies with primates (12). By setting the delay to the duration at which the rat performed about 75% of the trials correctly, we equated performance in the delay trials, and thus controlled for individual differences before pharmacologic intervention.

METHOD

Animals

As we were not interested in acquisition, we were able to shorten the training period by using rats already experienced with matching and nonmatching tasks. We used 31 male Sprague–Dawley rats, about 12 mo old, weighing 450–750 g (Charles River, Portage, MI). They were housed individually under a normal light–dark cycle.

Apparatus

The rats performed either the matching or the nonmatching task in a standard-size operant conditioning chamber (Coulbourn Instruments, Allentown, PA). Each chamber was equipped with two retractable levers, a liquid dipper, and a house light. A Plexiglas door in the front opened to a chamber constructed mainly of stainless steel. Stainless-steel rods formed the floor. The dipper, a 0.1-ml cup on the end of the dipper arm, was located between the levers above the grid floor on one wall. A photobeam spanned the opening through which the rat gained access to the dipper. The house light was near the top of the wall above the dipper. A sound attenuating chamber, ventilated by a small fan on the back wall, enclosed each chamber. Through an interface designed and manufactured by Coulbourn Instruments, a personal computer monitored and controlled eight chambers simultaneously.

Procedure

Thirsty rats earned water in daily sessions during the week. In their home cages the rats had free access to food at all times, and free access to water on the weekends. The daily session lasted for an hour and consisted of some number, determined by the rat, of matching or nonmatching trials. Each trial had a "sample" part followed by a delay interval, then a "choice" part. In the sample part of the trial the rat made a nose-poke that interrupted the photobeam and was then faced with one lever that extended into the chamber at random. The position of the lever, left or right, served as the sample stimulus. The lever retracted from the chamber after the rat pressed it once. The rat made another nose-poke to begin the delay, at the end of which both levers extended into the chamber simultaneously for the choice part of the trial. In the matching paradigm the rat earned water each trial for choosing the lever that served as the sample, and a press on the other lever did not lead to water. In the nonmatching paradigm the rat earned water for choosing the lever that did not serve as the sample.

For each trial the computer determined at random both the position of the sample, left or right, and the type of trial by the length of the delay interval, zero or longer. Each 1-h session consisted of both zero and longer delay trials. The length of the delay was titrated to the duration at which the rat completed about 75% of the trials correctly. The titrating procedure began once the rats' accuracy in zero-delay trials stabilized and was at least 90%. We increased the delay in half of the trials each session until the rats' accuracy in those trials had stabilized and was 65–85%. The increases in delay were gradual, 1 or 2 s, and occurred between sessions, not within a session. We trained the rats for several months before we began any experiments, although some of the rats had stabilized sooner than that.

We tested the rats in five experiments once performance had stabilized with respect to two measures: accuracy in both types of trial, and the number of trials completed per session. In each experiment we tested the rats twice weekly for two consecutive weeks. We controlled for order effects by means of a Latin-square design; specifically, each rat experienced one treatment per test session and all four treatments in the 2-week experiment. No fewer than 48 h separated test sessions.

In our series of experiments we used scopolamine hydrobromide in Experiments 1–4. In Experiment 1 we tested a range of doses, 0.03 to 0.3 mg/kg, to determine the dose that would decrease accuracy and not affect the number of trials completed per session. In Experiments 2–4 we used a dose of 0.1 mg/kg of scopolamine hydrobromide to produce a deficit, and evaluated the effects of physostigmine (0.1 and 0.3 mg/kg) and linopirdine (0.1 mg/kg) on impaired and unimpaired rats. The compound in Experiment 5 was scopolamine methylbromide (0.03, 0.1, and 0.3 mg/kg). In Experiments 1 and 5 each rat experienced the three doses of scopolamine and vehicle in the Latin-square design. In Experiments 2–4, each rat had only one dose of either physostigmine or linopirdine and experienced that dose in combination with either scopolamine hydrobromide or vehicle in the Latin-square design.

The compounds were diluted in distilled water before each use. The doses refer to the base equivalents of the compounds. We delivered the compounds in a volume of 1 ml/kg by means of an intraperitoneal injection. Specifically, we injected physostigmine or linopirdine 30 min before the session and scopolamine 20 min before the session. On nontest days, the rats had either training sessions or access to water for 1 h. They had access to supplemental water for 10 min after the training and test sessions.

Drugs

Scopolamine hydrobromide, scopolamine methylbromide, and physostigmine were purchased from Sigma Chemical Company (St. Louis, MO). Linopirdine (DuP 996; 3,3-*bis*(4-pyrindinylmethyl)-1-phenylindolin-2-one) was synthesized at Syntex Discovery Research, Palo Alto, by the Institute of Organic Chemistry.

Statistical Analysis

We analyzed several measures in the form of a Latin-square design by analysis of variance (ANOVA). We applied a three-way repeated-measures ANOVA to the number of trials completed each session. To the measure, percent of trials performed correctly each session, we applied a nonparametric analogue of the three-way repeated-measures ANOVA. Pairwise comparisons using Fisher's least significant difference strategy between drug-treated groups and their vehicle-treated control groups followed ANOVA when the F ratio was significant at $p < 0.05$. We report only the results from the pairwise comparisons.

In addition, we applied log transformations to the choice latencies, the time to press the lever in the choice part of each trial. We used a two-way repeated-measures ANOVA, with main effects for delay and treatment, applied to the median choice latencies in each session.

Figures 1–4 depict group means and standard errors for accuracy, expressed in terms of percent correct and the number of trials completed per session. We assumed a binomial distribution in computing the standard errors for accuracy.

RESULTS

One of our aims was to evaluate a titrating procedure for determining the duration of the longer delay in the delayed matching and nonmatching to position paradigms. By setting the delay to the duration at which the rat performed about 75% of the trials correctly, we hoped to control individual differences before pharmacologic intervention. As evidence of such differences, the duration of the delay varied among rats from 10–18 s in the matching task, and from 10–26 s in the nonmatching task. These wide-ranging variations support the further use of the titrating procedure in similar experiments with rats.

The rats averaged about 112 trials per session in the matching task and 107 in the nonmatching task. Thus, in terms of the number of trials per session and the duration of the delay required for 75% correct performance, the matching and nonmatching tasks appeared comparable. The rats completed about 99% of the zero-delay trials correctly, but only 75–80% of the longer delay trials, and thus displayed in our two positional tasks the delay effect characteristically seen in the corresponding sample tasks.

In Experiment 1, scopolamine hydrobromide had no significant effect at the lowest dose, 0.03 mg/kg, but disrupted performance at the two highest doses, 0.1 and 0.3 mg/kg. In the delay trials, summarized in the top panel of Fig. 1, the middle dose decreased accuracy significantly in the matching task ($p < 0.01$) and the nonmatching task ($p < 0.05$). The same was true for the highest dose for both matching ($p < 0.01$) and nonmatching ($p = 0.06$). In the zero-delay trials, summarized in the middle panel of Fig. 1, scopolamine did not affect accuracy in the matching task, but impaired nonmatching accuracy at both the middle dose ($p < 0.01$) and the highest dose ($p < 0.01$). The number of trials, summarized in the bottom panel of Fig. 1, was decreased significantly by the highest dose in both the matching task ($p < 0.01$) and the nonmatching task ($p < 0.01$).

The pattern of results seen in Experiment 1 suggested that the proper dose might be close to 0.1 mg/kg, but definitely lower than 0.3 mg/kg, which seemed to produce too general an impairment, one that diminished both accuracy and the number of trials completed per session. The dose of 0.1 mg/kg seemed to produce a more selective impairment, diminishing accuracy but not the number of trials. The lowest dose, 0.03 mg/kg, seemed to produce no impairment. Accordingly, we used a dose of 0.1 mg/kg to produce the desired decrease in accuracy in Experiments 2–4.

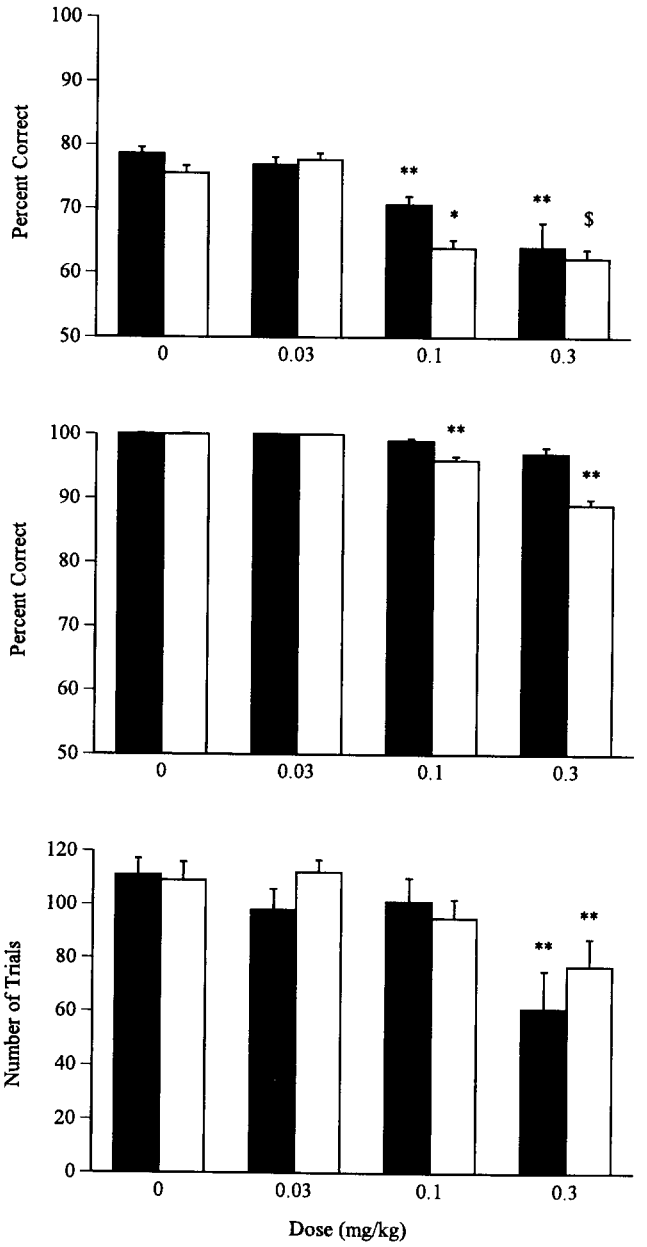

FIG. 1. Effects of scopolamine hydrobromide in the matching task (filled bars) and the nonmatching task (unfilled bars). $^{**}p < 0.01$; $^{*}p < 0.05$; and $^{\$}p = 0.06$ for comparisons with vehicle (0 mg/kg). Accuracy in delay trials (top panel) and zero-delay trials (middle panel), and number of trials (bottom panel) as functions of dose are shown as group means and standard errors.

In Experiment 2, physostigmine itself at 0.3 mg/kg decreased the number of trials per session significantly in both the matching and nonmatching tasks ($p < 0.01$ in both

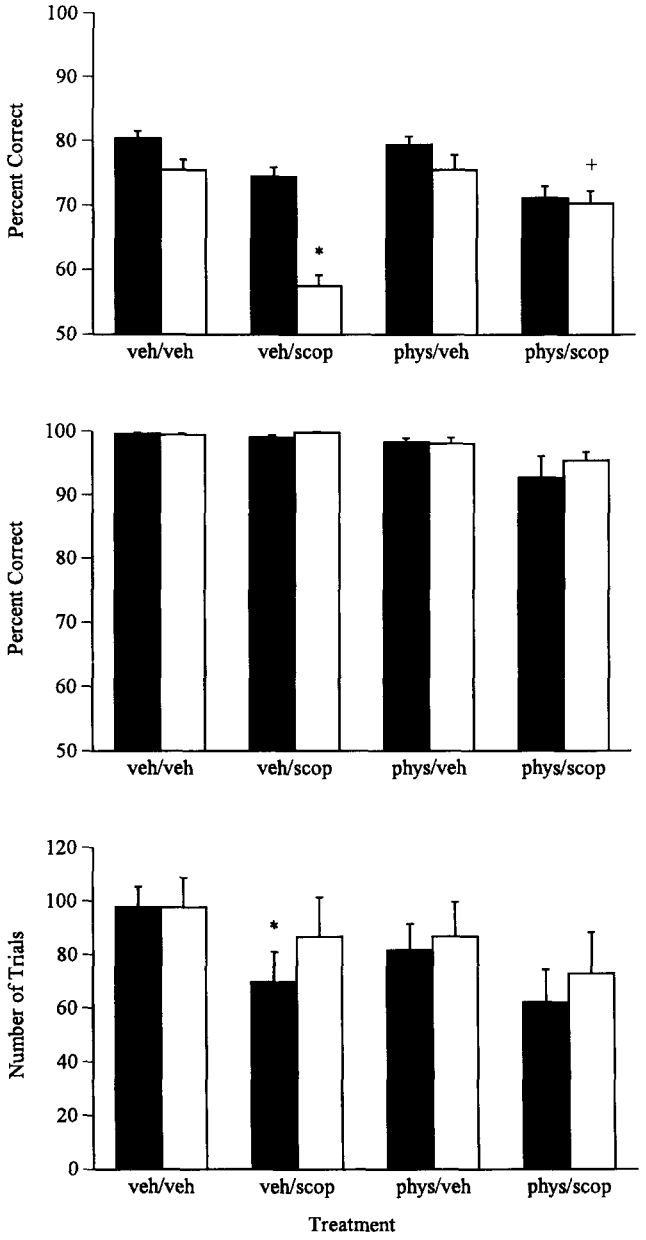

FIG. 2. Effects of physostigmine in scopolamine-induced deficit model in the matching task (filled bars) and the nonmatching task (unfilled bars). $^{*}p < 0.05$ for comparisons with vehicle-vehicle (veh/veh) and $^{+}p < 0.05$ for comparison with vehicle-scopolamine (veh/scop). Accuracy in delay trials (top panel) and zero-delay trials (middle panel), and number of trials (bottom panel) as functions of treatment are shown as group means and standard errors.

cases). These results indicated that this dose was too high, so we used a lower dose in Experiment 3.

In Experiment 3, scopolamine hydrobromide (0.1 mg/kg) produced a significant decrease in accuracy in delay trials in the nonmatching task ($p < 0.05$). As expected, physostigmine (0.1 mg/kg) produced a significant amelioration of that deficit ($p < 0.05$). Physostigmine alone did not affect accuracy or the number of trials in either task. These results are summarized in the top panel of Fig. 2. We were unable to test physostigmine for ameliorative effects in delayed matching to position because scopolamine failed to impair accuracy in that task. In zero-delay trials, summarized in the middle panel, scopolamine did not affect accuracy in either the matching or nonmatching task. The number of trials per session, summarized in the bottom panel, was decreased by scopolamine in the matching task ($p < 0.05$), but not the nonmatching task. Physostigmine did not block the action of scopolamine on number of trials in the matching task.

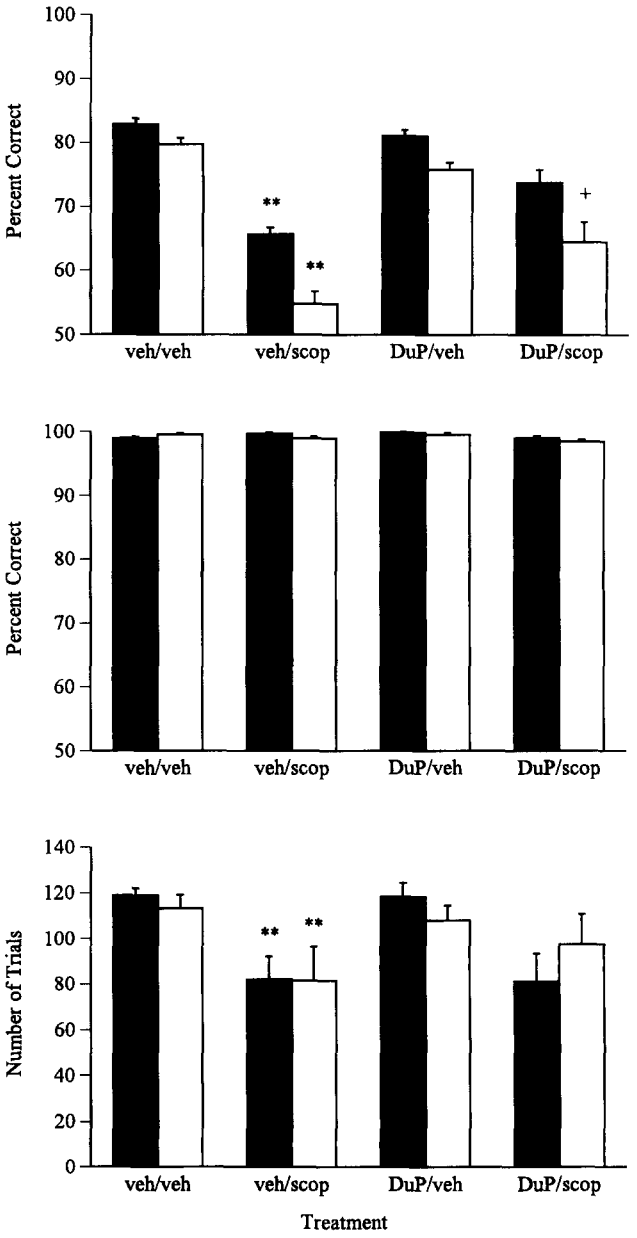

FIG. 3. Effects of linopirdine in scopolamine-induced deficit model in the matching task (filled bars) and the nonmatching task (unfilled bars). $^{**}p < 0.01$ for comparisons with vehicle-vehicle (veh/veh) and $^{+}p < 0.05$ for comparison with vehicle-scopolamine (veh/scop). Accuracy in delay trials (top panel) and zero-delay trials (middle panel), and number of trials (bottom panel) as functions of treatment are shown as group means and standard errors.

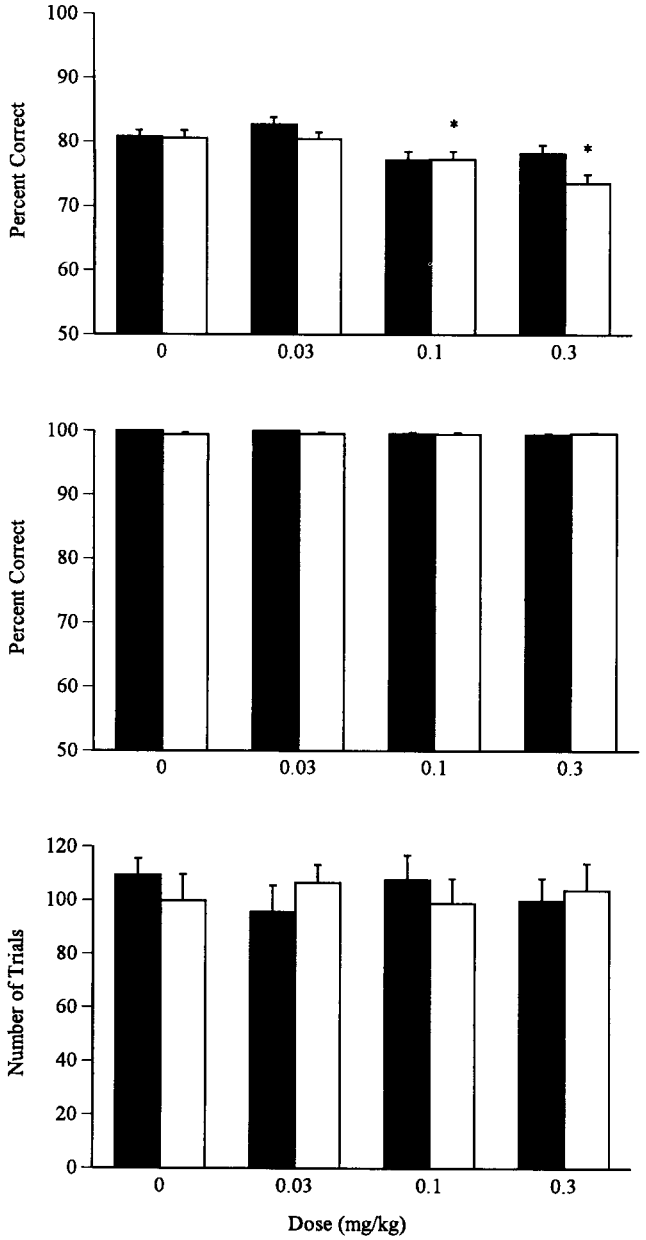

FIG. 4. Effects of scopolamine methylbromide in the matching task (filled bars) and the nonmatching task (unfilled bars). *$p < 0.05$ for comparisons with vehicle (0 mg/kg). Accuracy in delay trials (top panel) and zero-delay trials (middle panel), and number of trials (bottom panel) as functions of dose are shown as group means and standard errors.

Scopolamine hydrobromide produced the desired decrease in accuracy in Experiment 4 in the delay trials in both the matching task and the nonmatching task ($p < 0.01$ in both cases). The delay results are summarized in the top panel of Fig. 3. Linopirdine (0.1 mg/kg) produced a significant amelioration of the deficit seen in the nonmatching task ($p < 0.05$), but not the matching task. Scopolamine did not affect accuracy in the zero-delay trials summarized in the middle panel of Fig. 3, but decreased the number of trials per session in both the matching and nonmatching task ($p < 0.01$ in both cases), and did so whether linopirdine was present or absent. Thus, the blocking action of linopirdine was specific to one kind of impairment in one kind of task: the impairment of accuracy in the delayed nonmatching task. In fact, the blocking action of both linopirdine and physostigmine was specific to the impairment of accuracy. These results suggest that the ameliorative effects of cholinergic compounds on the impairment of the number of trials may be mediated by a noncholinergic mechanism.

In Experiment 5 the lowest dose of scopolamine methylbromide, 0.03 mg/kg, produced no deficit in the nonmatching task, but the two highest doses, 0.1 and 0.3 mg/kg, did produce a deficit. In the delay trials, summarized in the top panel of Fig. 4, both doses decreased accuracy in the nonmatching task ($p < 0.05$ in both cases), but had no effect in the matching task. None of the doses had a significant effect on accuracy in the zero-delay trials, summarized in the middle panel, or the number of trials per session, summarized in the bottom panel. As scopolamine methylbromide does not penetrate the brain, the results of Experiment 5 suggest that the deficits produced by scopolamine hydrobromide in Experiments 1–4 might have involved both a central component and a peripheral one.

In terms of latency to choose one lever or the other, in all of the experiments the rats chose significantly faster in delay trials than zero-delay trials ($p < 0.05$ in all cases). Typically, the rats took less than a second in delay trials, and more than a second in zero-delay trials. The interaction between delay and treatment was not significant ($p > 0.05$ in all cases). These results suggest that the rats took advantage of the delay period to approach the lever of choice more closely, and that this relatively simple kind of adaptive behavior resisted cholinergic challenge.

DISCUSSION

Our principal aim was to evaluate cognition in the rat by testing several cholinergic agents. Indeed, some aspects of the results suggested the involvement of learning and memory in matching and nonmatching tasks; for most of these the finding was that accuracy decreased as the delay interval increased. However, other aspects of the results sounded a cautionary note, suggesting that the relation between accuracy and delay might proceed from performance factors as well as cognitive ones. An advantage of the paradigms employed here is that they permit the separation of a drug's cognitive action from its action on such performance factors as motivation and arousal. Specifically, a compound that decreases the number of trials completed per session, a dependent variable sometimes overlooked in studies of this type, may be suspected of inducing a performance deficit with a motivational origin. Therefore, whereas a compound that affects accuracy but not number of trials may be related to cognition, a compound that affects both accuracy and number of trials may not be. For a salient example in the results reported here, in some cases scopolamine hydrobromide decreased the number of trials the rats completed. Our findings are consistent with those of Dawson et al. (5) and Kirk et al. (13). Such results suggest that the deficit produced by scopolamine may sometimes be a deficit of performance, and not a cognitive deficit of learning or memory.

Another focal issue is whether the scopolamine-induced deficit was mediated centrally or peripherally. To evaluate the peripheral component, we used scopolamine methylbromide, a quaternary ammonium derivative of scopolamine that "lacks

the central actions of scopolamine" (10). Van Hest suggested that even a relatively high dose of scopolamine methylbromide, 1 mg/kg, does not penetrate the brain (unpublished observation discussed in Van Hest et al. [15]). Like scopolamine hydrobromide, scopolamine methylbromide (0.1 and 0.3 mg/kg) decreased accuracy. Therefore, the deficit produced by scopolamine in the matching and nonmatching tasks might have both central and peripheral components. Our results agree with those of Dudchenko and Sarter (7), who found that both scopolamine hydrobromide and scopolamine methylbromide disrupted performance in continuous spatial delayed alternation.

Our results also suggest limits on the benefits of compounds that typically improve performance in the absence of cholinergic dysfunction. Physostigmine and linopirdine did ameliorate the scopolamine-induced deficit in the delayed nonmatching to position task. Similarly, Dawson et al. (5) showed that heptylphysostigmine ameliorated the deficit produced by scopolamine in a delayed matching to position paradigm. However, physostigmine and linopirdine did not improve performance in unimpaired rats. In contrast, physostigmine reportedly improved performance in unimpaired primates in a delayed matching to sample paradigm (3), and linopirdine improved performance in unimpaired rats and mice in an active avoidance paradigm (4). Thus, our results suggest that delayed matching and nonmatching to position paradigms may not be sensitive to compounds that typically improve performance in the absence of cholinergic dysfunction.

One explanation of that differential sensitivity is that our paradigms may place a lesser demand on the rat's cognitive capacity, despite the delay dependence of accuracy. For example, in our positional paradigm, but not the sample paradigm, the rat may profit from positional strategies to bridge the delay. Positional strategies would not exclude cognitive rehearsal, but may make it unnecessary. If accuracy derives from a positional strategy, such as proximity to the lever, it may not be improved by physostigmine or linopirdine. Thus, scopolamine may decrease accuracy by reducing the rat's use of the positional strategy. For example, recall that after the rat presses the sample lever once, the lever retracts out of the chamber. Although the end of the lever may still be visible in the opening through which it extends and retracts, the lever is inaccessible. To start the delay interval, the rat makes a nosepoke between the levers, in the area where water is delivered. Suppose that once the delay starts, the rat moves back to the sample lever and stays there until both levers extend into the chamber. When they extend into the chamber, the rat may simply choose the closer one. In that case, the positional strategy would be based on proximity to the lever. Recall, too, that the rats typically took < 1 s to choose a lever in the delay trials. As the extension of the lever takes about a second, it follows that the rat typically pressed the lever before it fully extended into the chamber. Thus, the rats might have been positioned closer to the lever in the delay trials than in the zero-delay trials. Preliminary observations and our latency data suggest that the rats may have adopted a positional strategy based on proximity to the lever. Videotape analysis that correlated positional strategy with accuracy would confirm this hypothesis. The hypothesis is consistent with results of other experiments involving delayed-response tasks with a spatial component. The results from those studies suggest that such rehearsal strategies as pressing the correct lever during the delay interval (7) may bridge the delay, and thus improve performance. Therefore, the delay dependence of accuracy in positional paradigms may derive from the delay dependence of mediational strategies.

Another possibility is that our procedure may involve greater motivation than those used by others, and tasks that differ in motivation may also differ in their sensitivity to drug effects. Food, water, and escape, rewards often used in behavioral paradigms, may differ in their elasticity of demand (1). For example, Buccafusco et al. (3) gave their monkeys only 15% of their food in the form of banana-flavored pellets during the test session. Their account suggests that the monkeys had access to other food at another time. Thus, demand for the banana pellets may have been relatively elastic because of the availability of other food that served as a substitute for the pellets. In contrast, our rats earned most of their water in the test sessions, and had only limited access to supplemental water. Although the monkey's demand for banana pellets may have been relatively elastic because other food was available, the thirsty rat's demand for water might be less elastic than the monkey's demand for banana pellets. If demand is relatively inelastic, the paradigm may also be relatively insensitive to the effects of a drug. Thus, if we were to train our rats to respond for water with another fluid available at another time, demand for water might be highly elastic, in which case the paradigm might also be more sensitive to drug effects.

In conclusion, we demonstrated the typical functional relation between delay and accuracy in experiments with rats. The results from our studies suggest that that typical functional relation may sometimes derive in part from the delay-dependence of mediational strategies or a noncognitive difference in motivation. Thus, the effects of cholinergic agents in positional versions of delayed response paradigms may be described more precisely in terms of their action on memorial and nonmemorial aspects of performance than on cognition alone. Furthermore, with respect to the role of the cholinergic system in memory, we showed that muscarinic receptor antagonism produced deficits, and that those deficits may have derived from both a peripheral and central component.

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