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Visual and Spatial Trials Paired in a New Behavioral Procedure: Effects of Benactyzine

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GRAUER, E. AND Y. KAPON. *Visual and spatial trials paired in a new behavioral procedure: Effects of benactyzine.* PHARMACOL BIOCHEM BEHAV **45**(3) 639–645, 1993.—A paired discrimination (PD) task in which visual and spatial discrimination trials were combined is offered as a method for the evaluation of drug effects on various behavioral parameters. Acquisition of the PD task is characterized by six different parameters simultaneously recorded each session. Analysis of memory requirements suggest that intact reference memory is involved in the performance of both types of trials while working memory is involved only in the performance of the spatial trial. Benactyzine (1–4 mg/kg), an anticholinergic drug, was tested for its effects on visual and spatial tasks presented either separately or in the PD combination. Benactyzine-induced mydriasis was also determined for its possible role in photophobic-induced errors. Benactyzine was found to differentially increase the number of errors performed during the spatial but not during the visual trials. The data are in accord with earlier finding of specific cholinergic involvement in working memory processes. Thus, low doses of benactyzine, and the PD task, can prove useful in the cognitive analysis of cholinergic hypofunction and its reversal by memory-enhancing drugs.

Working memory Reference memory Cholinergic antagonist Maze Mydriasis Rat

BENACTYZINE is one of the pharmacological means available for the induction of cholinergic hypofunction. The compound is a nonspecific muscarinic antagonist with some noncompetitive nicotinic antagonistic activity (1). It was first introduced as a tranquilizer (9) and as such was shown to improve learning and performance on aversively motivated and stress-related tasks (4,11–14,18,26,30). However, its anticholinergic activity received only sporadic interest in behavioral studies, and little attention was given to its effects on memory processes. Benactyzine was shown to affect rats' performance on schedules of reinforcement such as fixed ratio (FR) and variable interval (VI) (5,6,29) and monkeys' performance on DRL (15). Benactyzine effects on memory were demonstrated in simple choice behaviors in dogs, cats (25), and rats (10) but it failed to impair short-term memory in a delayed matching to sample paradigm in monkeys (21). Thus, additional investigation of the direct effect of benactyzine on memory processes and memory-related tasks might prove beneficial and establish this drug as a potential psychopharmacological model for cholinergic hypofunction.

In recent years, the most commonly used methods for the evaluation of memory processes in rats are based upon either the radial arm maze (20) or the Morris water maze (17). The advantages of these procedures are well known and are described elsewhere (7,27). However, because these procedures were originally developed to test animals with brain lesions they are efficient in detecting persistent damage but limited in the behavioral details obtained following acute drug administration, and often require repeated daily injections for a complete analysis (2,16,24,28).

A new behavioral paradigm is offered here that allows the evaluation of the effects of acute drug administration on visual as well as spatial discriminations within a single session. In this paradigm, pairs of trials are presented in which the first, visual discrimination trial, serves as a signal for the second, spatial trial. This procedure also enables the analysis of the drug effects in terms of working and reference memory processes as empirically defined (20). Thus, responses in the "visual" trials are indicative of a reference memory while responses in the "spatial" trials are indicative of working memory.

The present study consists of a number of experiments using the automated maze (3). In Experiment 1, two separate paradigms were used to evaluate the effects of benactyzine on performance of visual and spatial discriminations. Later, a new paradigm was developed in which both discrimination tasks were combined within a single session. In Experiment 2, acquisition of this new paradigm was described and the various behavioral parameters analyzed. In Experiment 3, the effects of benactyzine on performance of the combined visual/

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spatial discrimination task were evaluated. Experiment 4 was added to test for the possibility that visual impairment, associated with anticholinergic activity, may impede performance on visual cues. Thus, the extent of the mydriasis (pupil dilation) induced by benactyzine was measured.

GENERAL METHOD

ANIMALS

Male albino rats (Charles River, England), approximately 300 g at the beginning of the experiments, were used. Animals were individually housed in stainless steel cages in a 12 L : 12 D cycle in a temperature-controlled environment. Food (Altromin 1324) was available ad lib but access to water was restricted to 30 min a day only, available at about 4:00 p.m. Animals were tested daily between 8:00 a.m. and 4:00 p.m.

APPARATUS

Rats were tested in one of two identical mazes (Fig. 1), each placed in a sound-attenuated environment. The maze was a rectangular, 30 × 25 × 45-cm clear Plexiglas box with a stainless steel grid floor. Two levers, 16 cm apart, were located 5 cm above the floor on one of the narrow walls. A jewel light (28 V, 40 mA) was placed immediately above each lever and served as a cue light. Through a hole at the base of the opposite wall, a motorized liquid dispenser could introduce a small cup containing 0.2 cc liquid (10% sugar in tapwater) as reinforcement. A houselight was located above the reinforcement hole. An opaque partition extending two thirds the length of the box was placed between the two levers. Two other partitions, made of clear Plexiglas and placed perpendicularly in the end of the middle partition, divide the box into three compartments with a narrow path (the choice point) between them.

GENERAL PROCEDURE

All rats were first trained by successive approximation to press either of the two levers and receive the reinforcement.

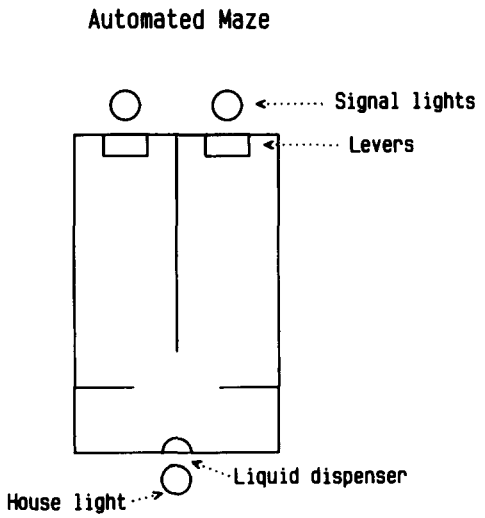

FIG. 1. Schematic representation of the automated maze (above view). The rat is required to press a lever to obtain a reinforcement. Location of the liquid dispenser ensures that the animal will be at the choice point at the beginning of the next trial.

After a stable rate of performance was established, each rat was trained in one of the following paradigms: Dark$^+$ (D^+), single alternation (SA), or paired discrimination (PD). In these, only a press on the "correct" lever (see below) was reinforced with a 6-s presentation of the reinforcement at the opposite wall. This ensured that the rat was positioned at the choice point, away from the levers, at the beginning of the next trial. A correct response also turned off the cue lights.

When relevant, cue lights were presented at a pseudorandom order in which each lever was correct 50% of the total trials and no more than three "same" cue were presented in succession.

DRUG ADMINISTRATIONS

All rats were trained to a stable performance prior to the onset of drug administration schedule. Drug injections were spaced at least 1 week apart. If performance in the two successive daily sessions prior to drug day were not stable, drug treatment was postponed. Benactyzine HCl (Aldrich Chemical Co., Milwaukee, WI) was dissolved in saline and administered SC in one of the following doses: 0, 1, 2, or 4 mg/kg. Behavioral testing began 15–30 min following injection.

STATISTICAL ANALYSIS

Data for each behavioral parameter was analyzed by analysis of variance (ANOVA). Significant main effects were further analyzed by the Dunnett's test enabling comparisons between baseline control and each of the doses of drug treatment.

EXPERIMENT 1

Two behavioral tasks (D^+, SA) were used to assess the effects of benactyzine, a cholinergic antagonists, on memory processes. The visual and spatial discrimination tasks, performed in the same behavioral apparatus, enable separate analysis of the drug effects on working and reference memory. In the visual discrimination task, visual cues remain unchanged from trial to trial and thus correct responses were indicative of intact reference memory. In the spatial discrimination task, spatial cues change from trial to trial and thus correct responses were indicative of intact working memory.

METHOD

Animals, apparatus, and general training procedures were described above. The following paradigms were used.

D^+ (Visual Discrimination Task)

Each trial begin by a random onset of one of the cue lights. The lever below the opposite (unlit) light was the correct one. This procedure was selected because mydriasis, associated with administration of anticholinergic drugs, was expected to affect behavior of animals required to approach a light while in a photophobic state.

SA (Spatial Discrimination Task)

No cue lights were presented and animals were required to alternate between the two levers. On the first trial, the correct lever was determined randomly and, if the right lever was correct in the first trial, the left lever would be correct in the second trial, the right will be again correct in the third trial, and so on.

The daily session in both tasks consisted of 50 trials with a

2-h time limit imposed. Total time to complete the daily session was recorded, as well as the number of initial errors (the first response on incorrect lever for each trial) and that of repetitive errors (repeated responses on incorrect lever for each trial).

RESULTS

The effects of benactyzine on D^+ and SA tasks are summarized in Fig. 2. Figure 2A depicts total performance time. Untreated rats completed the session in less than 20 min. Benactyzine-treated rats increased their mean performance time for up to about 75 min. ANOVA revealed a significant effect of the drug on total time in both D^+, $F(2, 28) = 7.34$, $p < 0.001$, and SA, $F(2, 38) = 19.37$, $p < 0.001$. Further analysis (Dunnett's test) showed a significant ($p < 0.05$) increase in the D^+ performance time only after 1 mg/kg benactyzine, while both 1 and 4 mg/kg of the drug were found to increase session time in the SA task.

Figures 2B and 2C depict the effects of benactyzine on the number of initial and repetitive errors, respectively. A clear increase in the number of errors is seen following benactyzine administration, specifically in rats performing the SA task. In rats performing the D^+ task, the increase is slight and is limited to the high benactyzine dose and to the initial error parameter only. ANOVA showed a significant effect of benactyzine in both initial errors, $F(2, 38) = 14.59$, $p < 0.001$, and repetitive errors, $F(2, 38) = 11.24$, $p < 0.001$, in the SA task and in initial errors, $F(2, 28) = 5.54$, $p < 0.01$, during performance of the D^+ task. Further analysis (Dunnett's test) revealed significant effects of both 1- and 4-mg/kg doses in the SA task ($p < 0.01$) and of the 4-mg/kg dose in the D^+ task ($p < 0.05$).

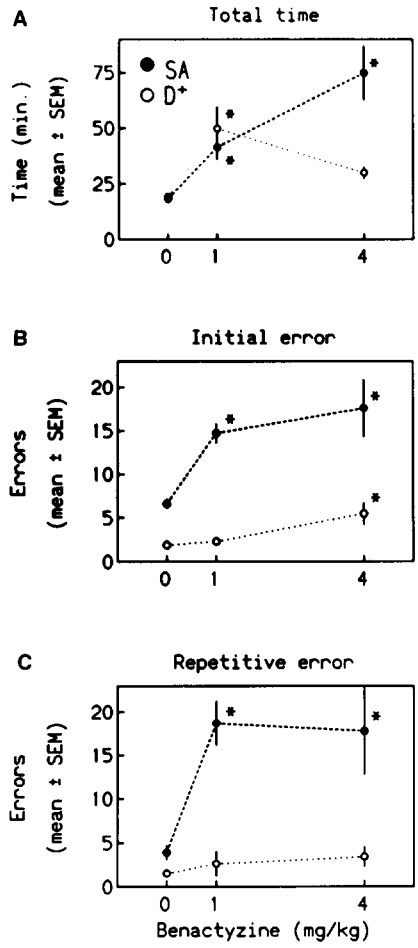

FIG. 2. Effects of benactyzine (0, 1, and 4 mg/kg) on maze performance in two discrimination tasks: Visual discrimination [Dark$^+$ (D^+)] and spatial discrimination [single alternation (SA)]. (A) Total performance time (50 trials). (B) Initial errors on incorrect lever. (C) Repeated errors on incorrect lever. *$p < 0.05$ compared to control (Dunnett's test following ANOVA).

DISCUSSION

Benactyzine was found to differentially affect performance in two discrimination tasks. At the lower dose, a significant increase in errors was seen during performance of the spatial task but not during the performance of the visual task. Thus, errors most affected were those associated with working memory process, that is, memory of events related to a given trial. One disadvantage associated with the SA performance is the almost "automated" response routine seen in untreated, overtrained animals. Because benactyzine affected rate of performance also, the results may be attributed to the disruption of motor behavior and not to any memory impairment. To minimize this pattern of responding, a new procedure was designed. It is based upon a combination of the visual and spatial tasks within the same experimental session. The procedure also enabled a more direct comparison between memory processes as well as improved the efficiency of drug testing.

EXPERIMENT 2

Acquisition of the new behavioral paradigm is described. The paradigm is based upon maze performance with visual cues relevant in some trials and spatial cues relevant in others.

METHOD

Animals, apparatus, and general training procedures were described above. The following paradigm was used.

PD (Visual/Spatial Discrimination Task)

This paradigm is a combination of both of the above procedures. The session was divided into pairs of trials. Each pair consisted of a visual discrimination trial followed by a spatial discrimination trial. In the visual discrimination trial, one of the cue lights above the levers was turned on and the correct lever was signaled by the light off cue (similar to the D^+ task). In the following, spatial trial, no cue lights were turned on and the correct lever was the one that was incorrect in the previous, visual trial (in other terms, the "sample" response was made in the first trial and a "mismatched" response was required in the second trial). Each pair of trials was followed by a 10-s time-out in which all lights, including the houselight, were extinguished.

Animals were first trained on the visual discrimination task (50 trials per daily session) for six sessions, and only after performance on this task stabilized did paired discrimination training began. The daily session included 50 pairs of trials (100 reinforcements) and the maximum time allowed was 2 h per session. Total time to complete the session, as well as responses during time-out periods, were recorded and calculated for all 100 trials of the daily session. The number of initial errors (the first response on incorrect lever for each

trial) and that of repetitive errors (repeated responses on incorrect lever for each trial) were recorded and calculated separately for the visual trials (50 trials) and for the spatial trials (50 trials). Animals were trained daily, Sunday through Thursday, until stable performance was reached.

RESULTS AND DISCUSSION

Figure 3 depicts the acquisition curves of six different parameters recorded during the performance of PD. Note that the first six sessions describe performance on visual discrimination trials alone. Spatial trials were added at session 7.

In general, about 25 training sessions were required for stable performance to take place. At that point, time to complete the session was about 40 min (Fig. 3A) and the number of responses performed during time-out periods was reduced to about 10 per session (Fig. 3B).

Acquisition is demonstrated in the reduction of both initial and repetitive errors (Fig. 3C and 3D). Errors performed during visual trials are presented separately from those performed during spatial trials. Mean number of initial errors decreased from chance level (25 errors/50 trials) to less than 10% of total trials (5 errors/50 trials). However, the rate of decrease was much higher in the acquisition of the visual task than in that of the spatial task: Animals required only 4–6 sessions to reach 90% correct responding on visual trials compared to more than 15 sessions required to reach the same criterion on the spatial trials.

The number of repetitive errors was also reduced to about five responses per session. The rapid decrease in repetitive errors during acquisition of the spatial trials suggest that animals transferred learned behavior acquired during training in the visual trials into performance of the spatial trials.

Number of errors was reduced to baseline performance after about 25 sessions. The stable performance seen afterward (sessions 25–34) ensured a reliable baseline performance during the repeated testing procedure used in the evaluation of the drug effects.

The automated behavior seen in animals during the performance of the SA task was eliminated by the pairing of the two types of trials and by the time-out period imposed between each pair of trials. Responses during time-outs were inconsequential and, for efficient performance, the animal was required to be away from the levers and at the choice point at the onset of the following, visual trial.

EXPERIMENT 3

Various doses of benactyzine were tested for their effects on performance of the PD task. The effects were analyzed in terms of performance rates, general activity scores, and errors. A special emphasis was placed on comparison between effects on performance of visual vs. spatial tasks.

METHOD

Animals, apparatus, general training procedures, and drug administration were described above, as well as the PD paradigm used.

Data Analysis

Because the same 2-h time limit was imposed on drug test sessions as on baseline sessions, some animals did not com-

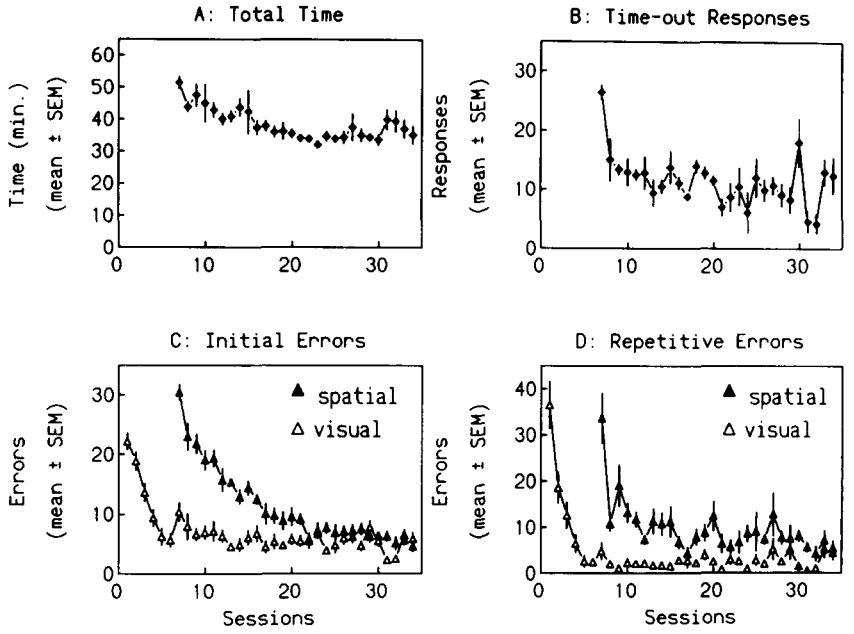

FIG. 3. Acquisition of the paired discrimination task. Training began by the presentation of visual discrimination trials alone (sessions 1–6). From session 7, spatial and visual discrimination trials were presented in pairs within the same session. (A) Total performance time. (B) Responses during time-out periods. (C) Initial errors on incorrect lever. (D) Repeated errors on incorrect levers. Point in (A) and (B) are the mean of 100 trials. Points in (C) and (D) are means of 50 trials because errors are presented separately for visual and spatial trials. $^*p < 0.05$ compared to control (Dunnett's test following ANOVA).

plete all 100 trials required. Data for these animals were adjusted under the assumption that rate of responses and errors would remain the same for the remainder of the session. Thus, for each parameter number of errors made was divided by the number of trials actually performed and multiplied by the maximum trials required.

RESULTS

Figure 4 summarizes the effects of benactyzine (0, 1, 2, and 4 mg/kg) on six parameters recorded during performance of the PD task. Following administration of 2 mg/kg benactyzine, one animal completed only 68 of the 100 trials required (mean ± SD of number of trials completed = 95.4 ± 12.1). Following administration of 4 mg/kg, 4 of the 7 animals did not complete the 100 trials required, but each completed at least 80 trials within the 2-h test (mean ± SD of number of trials completed = 90.9 ± 9.3).

The effect of benactyzine is clearly seen as a dose-dependent increase in the number of initial errors (Fig. 4C). The effect is limited only to the performance of the spatial trials and is not seen in the performance of the visual trials within the same session. One-way ANOVA indeed showed a significant effect on errors performed during spatial trials, $F(3, 24) = 13.92$, $p < 0.001$, and further Dunnett's test showed the increase to be significant ($p < 0.01$) at both 2- and 4-mg/kg doses. A tendency toward an increase in the number of repetitive errors during performance of spatial trials can also be seen (Fig. 4D), but this difference was not statistically significant.

A dose-dependent increase can also be seen in total performance time (Fig. 4A). However, this effect is significant only at the 4-mg/kg dose [one-way ANOVA main effect, $F(3, 24) = 9.77$, $p < 0.001$, with further Dunnett's test ($p < 0.01$) that showed a significant increase only at 4 mg/kg]. A nonsignificant general tendency to decrease responses performed during the time-out periods can also be seen (Fig. 4B).

DISCUSSION

Low doses of benactyzine were shown to differentially affect performance in the two trial types included in the PD task. Errors increased only during performance of the spatial trials and not during the performance of the visual trials. This finding replicates the data obtained in the two separate tasks described above in Experiment 1. However, although similar tendencies were seen in data obtained from both experiments (Figs. 2 and 4) benactyzine seemed to have an overall more potent effect on performance in the separate (D^+, SA) than in the combined (PD) tasks. This difference may be attributed to regular fluctuations seen in drug effects, or it may represent benactyzine effects on additional behavioral processes incorporated into the performance of the separate tasks but absent from the performance of the combined task (e.g., the automated behavior seen in the performance of the SA task in Experiment 1).

EXPERIMENT 4

As a potent cholinergic antagonist, benactyzine was expected to induce mydriasis. This might impair performance in the behavioral apparatus due to the onset of light stimuli, regardless of any impairment in cognitive processes. Extant of mydriasis over time was determined in animals treated with benactyzine.

METHOD

At the termination of Experiment 1, the same animals were used again in this experiment.

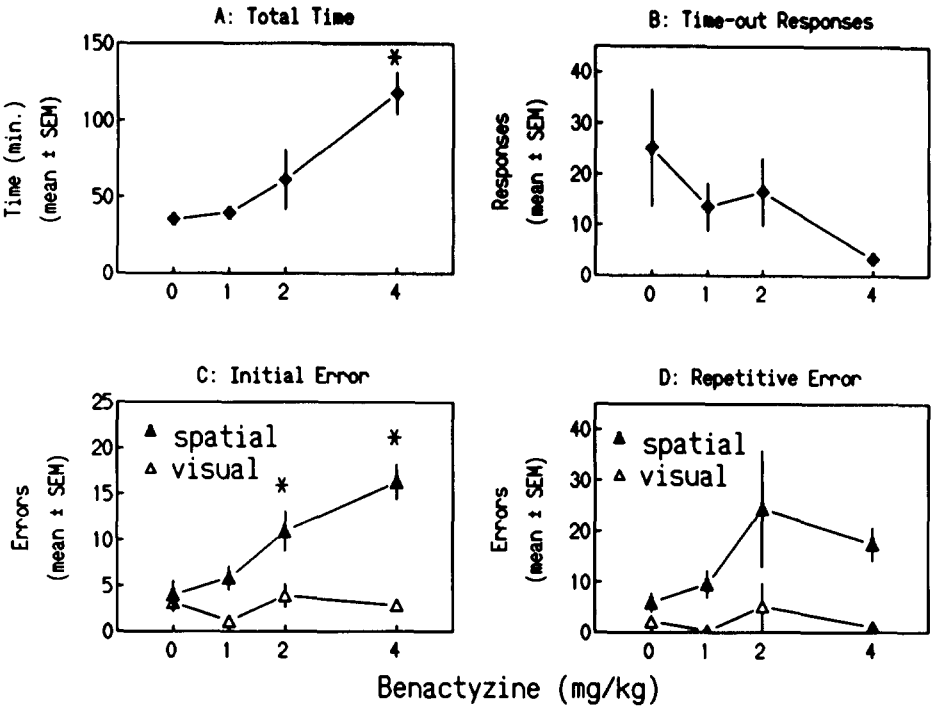

FIG. 4. Effects of benactyzine (1–4 mg/kg) on performance of the paired discrimination task. For details on (A)–(D), see Fig. 3. *$p < 0.05$ compared to control (Dunnett's test following ANOVA).

Mydriasis

Pupil dilation was measured visually through a stereomicroscope using a ×10 objective and a constant light source. A scale mounted on one of the oculars enable precise measurements of pupil dilation. Normal dilation received a score of 10–15 and maximum dilation received a score of 80.

RESULTS AND DISCUSSION

Figure 5 depicts the effects of benactyzine (1 and 4 mg/kg) on mydriasis scores obtained at different times following administration. A dose-dependent increase in the scores can be seen with peak scores reached within 15 min following injections. Only partial mydriasis was induced by 1 mg/kg and pupil size returned to normal within 2 h. At 4 mg/kg, almost full mydriasis level was seen for the first 90 min and the level remained high throughout the 2.5 h of the testing period. This may account for part of the behavioral effects seen in the performance of the visual discrimination task. The increase in errors following administration of 4 mg/kg (Fig. 2) may be explained by the photophobic state produced by the drug throughout the session.

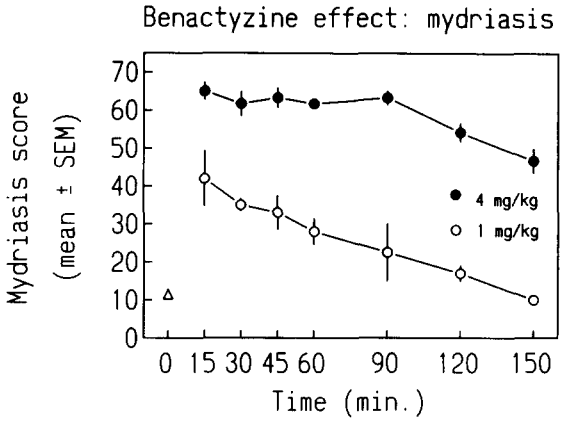

FIG. 5. Effects of benactyzine (1 and 4 mg/kg) on pupil dilation (mydriasis). Measurement were taken repeatedly at different times following administration. (Δ), mean score prior to drug administration (control).

GENERAL DISCUSSION

A combination of visual and spatial trials was designed and tested as a new behavioral paradigm for the evaluation of drug effects on behavior. Correct responding on both types of trials in the PD task requires an equal motivational level, similar proprioceptive/motor functions, and intact reference memory process. However, the performance on the spatial task requires the use of working memory as well (20). This behavioral paradigm is particularly useful in the study of behavioral drug effects, especially when memory processes may be involved.

The two types of trials in the PD task differ not only in the types of memory process they require but also in their temporal contiguity between stimulus and response (22). Contiguity exists in the visual trial, in which the visual cues are present when the response is made. However, it is absent in the spatial trial, in which the information for a correct responding must be retained from the previous, visual trial. This discontiguity involves a delay of about 6 s in which the animal runs back and consumes the liquid reinforcement. This type of delay significantly reduces the performance accuracy of hippocampal-lesioned animals as compared to control (23).

The differences between the two types of trials are also reflected in their rate of acquisition. Visual trials are acquired much faster than the spatial trials, which may suggest a quantitative difference in the level of difficulty or complexity of the trials.

Benactyzine, a cholinergic antagonist, was shown to impair performance in spatial but not in visual discrimination trials. Similar data were obtained both in the performance of the separate tasks (Fig. 2) and in the PD procedure (Fig. 4). However, the latter procedure seems more precise because it eliminates the possibility of an automated response routine. It also excludes the possible acquisition of a response pattern (e.g., left-right-left-right-left) that can be stored in reference memory (19).

The specific increase in initial errors during the performance of the spatial trials suggests that benactyzine, at a low dose, may be useful in the study of cholinergic hypofunction and cognitive impairment. The specificity of the effect suggests an impairment in working memory process alone. Other behavioral parameters, recorded simultaneously during PD performance, enable exclusion of the drug effects on other cognitive or sensorimotor functions.

The present data on benactyzine-induced working memory impairment are in accord with data available in the literature on other anticholinergic drugs (2,8,28). Indeed, the prevailing hypothesis of a correlation between cholinergic hypofunction and impaired working memory is strongly supported by the present data. However, the interpretation of benactyzine involvement in "intermediate" memory storage (22) cannot be excluded. The specific impairment seen in the performance of the PD task may thus be due to hypofunction of cholinergic neurons located in the hippocampal formation (22).

The PD task in the automated maze offers an efficient method for the simultaneous evaluation of drug effects on various behavioral parameters. Working memory process is indeed sensitive to low doses of anticholinergic drugs. Reference memory, in the same procedure, is unaffected even at much larger doses of various cholinergic blockers (unpublished data). Responses during time-out periods may serve to exclude possible nonspecific changes in responding (e.g., response perseveration), and total performance time can reliably indicate changes in activity rates. The PD task may prove useful not only in the evaluation of cholinergic hypofunction but also in the study of aging, memory enhancers, and other CNS modifications.

REFERENCES

1. Amitai, G.; Herz, J. M.; Bruckstein, R.; Luz-Chapman, S. The muscarinic antagonists aprophen and benactyzine are noncompetitive inhibitors of nicotinic acetylcholine receptor. Mol. Pharmacol. 32:678–685; 1987.
2. Beatty, W. W.; Bierley, R. A. Scopolamine degrades spatial working memory but spares spatial reference memory: Dissimilarity of anticholinergic effect and restriction of distal visual cues. Pharmacol. Biochem. Behav. 23:1–6; 1985.
3. Berger, B. D. An animal model for the measurement and manipulation of problem solving ability. In: Gershon, E. S.: Belmaker,

R. H.; Kety, S. S.; Rosenbaum, M., eds. The impact of biology on modern psychiatry. New York: Plenum Press; 1977:187–194.
4. Bignami, G. Effects of benactyzine and adiphenine on instrumental avoidance conditioning in a shuttle-box. Psychopharmacologia 5:264–279; 1964.
5. Boren, J. J. Some effects of benactyzine upon operant behavior. J. Pharmacol. Exp. Ther. 119:134–135; 1957.
6. Boren, J. J. Some effects of adiphenine, benactyzine and chlorpromazine upon several operant behaviors. Psychopharmacologia 2:416–424; 1961.
7. Brandeis, R.; Brandys, Y.; Yehuda, S. The use of the Morris water maze in the study of memory and learning. Int. J. Neurosci. 48:29–69; 1989.
8. Bushnell, P. J. Modelling working memory and reference memory in rats: Effects of scopolamine on delayed matching-to-position. Behav. Pharmacol. 1:419–427; 1990.
9. Coady, A. A clinical trial of benactyzine hydrochloride ("Suavitil") as a physical relaxant. Br. Med. J. 485–487; 1956.
10. Domer, F. R.; Schueler, E. W. Investigation of the amnestic properties of scopolamine and related compounds. Arch. Int. Pharmacodyn. 27(3–4):449–459; 1960.
11. Holton, C. H.; Sonne, E. Action of a series of benactyzine derivatives and other compounds on stress-induced behavior in the rat. Acta Pharmacol. Toxicol. 11:148–155; 1955.
12. Jacobsen, E.; Skaarup, Y. Experimental induction of conflict behavior in cats: The effects of some anticholinergic compounds. Acta Pharmacol. Toxicol. 11:125–134; 1955.
13. Jacobsen, E.; Sonne, E. The effect of benzilic acid diethylaminoethylester HCl (Benactyzine) on stress-induced behavior in the rat. Acta Pharmacol. Toxicol. 11:135–147; 1955.
14. Jacobsen, E.; Sonne, E. The effect of benactyzine on the conditioned responses in the rat. Acta Pharmacol. Toxicol. 12:310–320; 1956.
15. McDonough, J. H. Effects of anticholinergic drugs on DRL performance of rhesus monkeys. Pharmacol. Biochem. Behav. 17: 85–90; 1982.
16. McNaughton, N.; Morris, R. G. M. Chlordiazepoxide, an anxiolytic benzodiazepine, impairs place navigation in rats. Behav. Brain Res. 24:39–46; 1987.
17. Morris, R. G. M. Spatial localization does not require the presence of local cues. Learn. Motiv. 12:239–260; 1981.
18. Naess, K.; Rasmussen, E. W. Approach-withdrawal responses and other specific behaviour reactions as screening test for tranquilizers. Acta Pharmacol. Toxicol. 15:99–114; 1958.
19. Olton, D. S.; Becker, J. T.; Handelmann, G. E. Hippocampus, space and memory. Behav. Brain Sci. 2:313–365; 1979.
20. Olton, D. S.; Becker, J. T.; Handelmann, G. E. Hippocampal function: Working memory or cognitive mapping?. Physiol. Psychol. 8:239–246; 1980.
21. Penetar, D. M.; McDonough, J. H. Effects of cholinergic drugs on delayed match-to-sample performance of rhesus monkeys. Pharmacol. Biochem. Behav. 19:963–967; 1983.
22. Rawlins, J. N. P. Association across time: The hippocampus as a temporary memory store. Behav. Brain Sci. 8:479–496; 1985.
23. Rawlins, J. N. P.; Olton, D. S. The septo-hippocampal system and cognitive mapping. Behav. Brain Res. 5:331–358; 1982.
24. Richter-Levine, G.; Segal, M. Spatial performance is severely impaired in rats with combined reduction of serotonergic and cholinergic transmission. Brain Res. 477:404–407; 1989.
25. Selinvanova, A. T.; Zemliankin, A. S. Role of the central and peripheral cholinoreceptors in the processes of short-term memory. Farmakol. Toksikol. 38:647–650; 1975.
26. Stone, G. C. Effects of some centrally acting drugs upon learning of escape and avoidance habits. J. Comp. Physiol. Psychol. 53: 33–37; 1960.
27. Walker, J. A.; Olton, D. S. Fimbria-fornix lesions impair spatial working memory but not cognitive mapping. Behav. Neurosci. 98:226–242; 1984.
28. Wirsching, B. A.; Beninger, R. J.; Jhamandas, K.; Boegman, R. J.; El-Defrawy, S. R. Differential effects of scopolamine on working and reference memory of rats in the radial maze. Pharmacol. Biochem. Behav. 20:659–662; 1984.
29. Witkin, J. M.; Gordon, R. K.; Chiang, P. K. Comparison of in vitro actions with behavioral effects of antimuscarinic agents. J. Pharmacol. Exp. Ther. 242:796–803; 1987.
30. Zharkovskii, A. M.; Allikmets, L. K. Effect of cholinergic drugs on serotonin metabolism and emotional reactions in rats. Farmakol. Toksicol. 39:261–264; 1976.