Pharmacology Biochemistry & Behavior, Vol. 25, pp. 633–639, 1986. © Ankho International Inc. Printed in the U.S.A. 0091-3057/86 $3.00 + .00

Effects of Scopolamine on Components of Delayed Response Performance in the Rat

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Received 12 February 1986

VISCARDI, A. P. AND G. A. HEISE. *Effects of scopolamine on components of delayed response performance in the rat.* PHARMACOL BIOCHEM BEHAV **25**(3) 633–639, 1986.—The effects of scopolamine and methyl scopolamine on working memory processes were investigated in a paired trial, go-no go delayed response procedure in which rats initiated their own trials. Drug effects were examined concurrently on performance at three delays—no, 0, and 2.5 sec. Scopolamine disrupted no-delay (discrimination) performance in a dose-related manner. Scopolamine also progressively reduced performance at 0-delay and 2.5 sec delay more than at no-delay, but only at the highest administered dose (0.5 mg/kg). Scopolamine affected sensitivity, but not response bias. Although both scopolamine and methyl scopolamine reduced the probability of trial initiation, only scopolamine disrupted accuracy of performance on the initiated trials.

Delayed response Discrimination Working memory Scopolamine Methyl scopolamine Retention Sensitivity Bias

A growing body of evidence has implicated central cholinergic processes in memory [1,13]. A substantial portion of this evidence is based on the effects of cholinergic blockers such as atropine and scopolamine on performance in working memory experiments. However, there is at present no consensus concerning which aspects of memory are affected by these drugs—whether the drugs act on attention to or discrimination of the to-be-remembered stimuli, on a "stimulus encoding" process, on the time-dependent process of retention, or on some combination of these processes.

In a working memory experiment the appropriate response is conditional upon which particular alternative stimulus events have been presented prior to a delay between presentation of the to-be-remembered stimulus and the occasion for the response [7, 14, 16]. Drug effects on working memory processes may be operationally defined by differential effects observed at key temporal landmarks in the memory experiment. A drug effect observed at no-delay (in which the animal responds in the presence of the to-be-remembered stimulus) defines an effect on "discrimination"; a greater effect at 0-delay (in which the animal responds immediately after termination of the to-be-remembered stimulus) than at no-delay indicates an effect on a possible "encoding" process; and an effect which increases in magnitude as delay extends beyond 0-delay defines an effect on "retention."

Heise and Milar [6] have recently reviewed literature on the effects of cholinergic blockers on working memory processes. The single study that explicitly compared effects of cholinergic blockers at no-delay and 0-delay [2] found that scopolamine did not affect either no-delay or 0-delay performance in monkeys. However the effects of cholinergic blockers on retention depended on the type of memory procedure employed. Heise and Milar [6] distinguished four types of working memory procedures: continuous and paired delayed comparison and continuous and paired delayed response. (In continuous procedures each trial is both the occasion for responding with respect to the stimuli presented on the preceding trial and also the occasion for presentation of the stimulus sample to be remembered on the next trial. In paired procedures each trial consists of two events and is isolated from adjacent trials by an intertrial interval.) Heise and Milar concluded that the cholinergic blockers did not affect retention in continuous delayed response, in continuous delayed comparison, and in paired delayed comparison procedures (contrary findings with paired delayed matching to sample have recently been reported by Penetar and McDonough [10] and by Pontecorvo and Evans [11]). However, the cholinergic blockers did consistently impair retention in paired delayed response procedures.

The present research was designed to compare the effects of cholinergic blockade on the working memory processes defined by comparisons of performance at different delays. Effects of the cholinergic blocker scopolamine on go-no go paired delayed response performance of rats were measured at three different delays—no, 0, and a longer delay (2.5 sec). A paired (rather than continuous) procedure was used in order to minimize possible interference from previous trial events on present trial performance. A delayed response (rather than delayed comparison) procedure was used so that

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the discrimination required on a trial was restricted to a single stimulus. Performance at the three delays was compared directly for the same animal within a single session. The animals were required to initiate their own trials, thus increasing the likelihood that they had "paid attention" to the trial stimuli. Tendencies to respond and not respond on trials were equalized by reinforcing non-responding on no go trials as well as responding on go trials. Hence drug effects on stimulus discriminability could appropriately be separated from effects on responsivity by means of a Signal Detection Analysis.

METHOD

Subjects

Subjects were twelve naive male Sprague-Dawley derived albino rats received from Charles River Breeding Co. at approximately 60 days of age. They were pair-housed in plastic tubs with filter-paper tops in a separate room from the main animal colony. The animals were maintained on a 12-hour light/dark-cycle that began at 6:30 a.m.

Each animal was maintained on a diet of 18–22 g of Purina Lab Chow pellets per day. The rats were deprived of water for 23½ hours prior to experimental sessions, and received water for 15 min following an experimental session. The rats were tested daily, beginning at approximately 3:00 p.m., 7 days a week.

Six of the rats were arbitrarily chosen to respond to a "bright" light for reinforcement (Bright S+, Dim S−), while the remaining six rats responded to a "dim" light for reinforcement (Dim S+, Bright S−). Four rats (two from the bright group and two from the dim group) were eliminated due to excessive variability and low rates of responding, leaving four rats per group.

Apparatus

The animals were tested in two-lever operant chambers (25×24×18.5 cm) constructed at Indiana University. Two frosted glass levers, requiring 25 to 30 g of force to activate, were located 6.5 cm from the midline, and 10 cm above the grid floor. Mounted under the levers were 1.5 V lamps which could illuminate the levers from behind. Three translucent panel lights were mounted 15 cm above the floor. Two of the lights were located directly over the levers, and the third was located on the midline. Only the right panel light was used. A brass spout, protruding 2.7 cm into the chamber and 5.5 cm above the floor, was mounted on the midline and was calibrated to deliver 0.05 cc of water reinforcement. An 8 ohm, 2500 Hz Sonalert was located outside the chamber on the inside back wall of the sound attenuating boxes which enclosed the operant chambers. Bright and dim stimuli were generated respectively by either no resistor or a 4.4 kohm resistor in series with 110 VAC. A Texas Instruments 980A minicomputer, located in a room adjoining the experimental room, controlled the experiments and recorded data.

Procedure

General description. An experimental session consisted of up to 120 paired presentations (trials), each separated by a 30 sec intertrial interval during which a houselight was on. The 120 trials were comprised of three groups of 40 trials with each of the three delay conditions: no, 0, and 2.5 sec. Each group of trials was further subdivided into 20 S+ and 20 S− trials per delay.

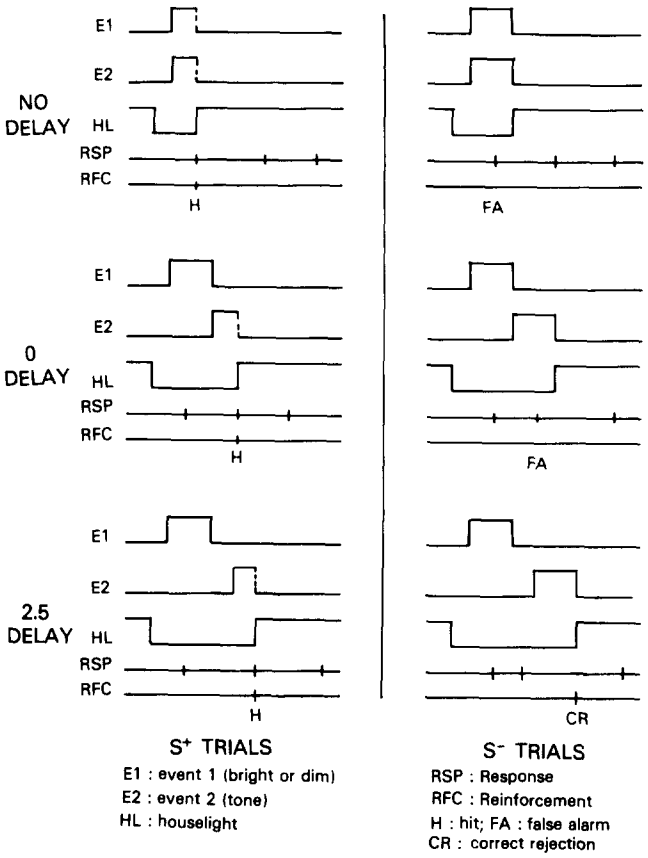

FIG. 1. Schematic representations of S+ and S− trials with no, 0, and 2.5 sec delay. Responses made during Event 2 were reinforced on S+ trials (HIT), and were not reinforced on S− trials (FALSE ALARM). A non-response during event 2 of an S− trial (CORRECT REJECTION) also produced reinforcement (shown only for 2.5 sec delay).

Each trial consisted of two *events* separated by a *delay* (see Fig. 1). During Event 1, either a bright or a dim stimulus was presented for 5 sec over the right lever. For half the subjects, the bright stimulus served as the S+; for the other half, the dim stimulus served as the S+. Following a delay a 2500 Hz tone was sounded, signalling the opportunity to respond (i.e., Event 2). A correct response [i.e., a response during Event 2 when the Event 1 stimulus was S+ (HIT), or not responding during Event 2 when the Event 1 stimulus was S− (CORRECT REJECTION)] resulted in water reinforcement, and terminated the trial. On S+ trials, reinforcement occurred immediately following the Event 2 response. Event 2 of S− trials was always 5 sec in duration. On S− trials, reinforcement occurred when Event 2 terminated, provided no response had occurred. Responses on Event 2 of S− trials (FALSE ALARM) had no programmed effect, and the trial terminated after 5 sec. In the special case of a no-delay trial, Event 1 and Event 2 coincided in time. Other than this, no-delay trials were exactly like 0 and 2.5-delay trials.

The onset of all trials was signalled by the offset of the houselight ("blackout") 2 sec prior to the illumination of the left lever. A press on the left lever (an initiating response) turned off the lever light and initiated a trial with the right lever as described above; otherwise the lever light termi-

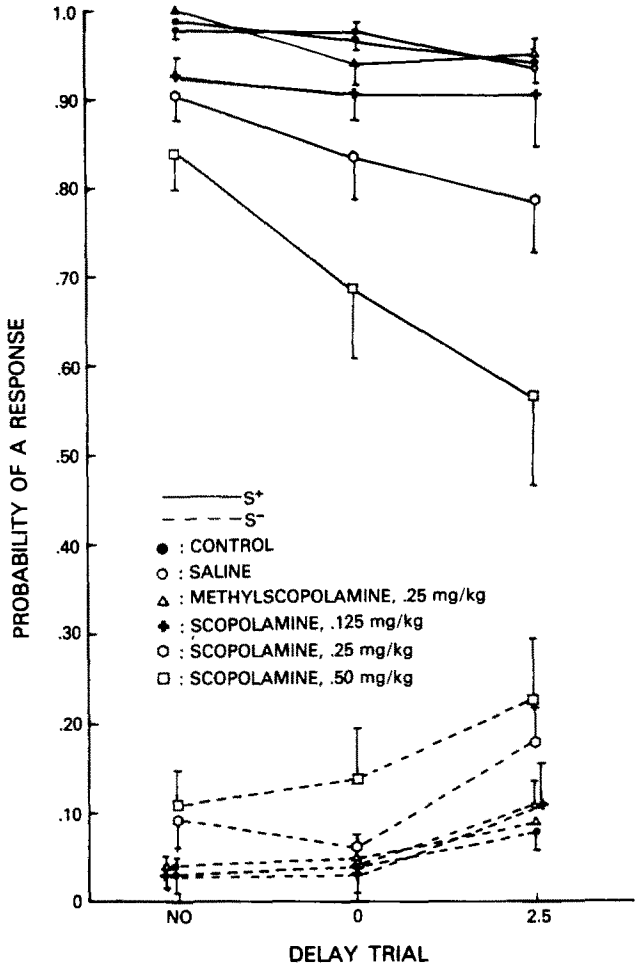

FIG. 2. Probability of a response on S+ and S− trials under various treatments as a function of delay: control (C), saline (SAL), 0.25 mg/kg methyl scopolamine (MS.25), and 0.125, 0.25, and 0.5 mg/kg scopolamine (S.125, S.25, and S.50). Standard error (SE) bars were not drawn when the SE was less than the size of the data point symbol.

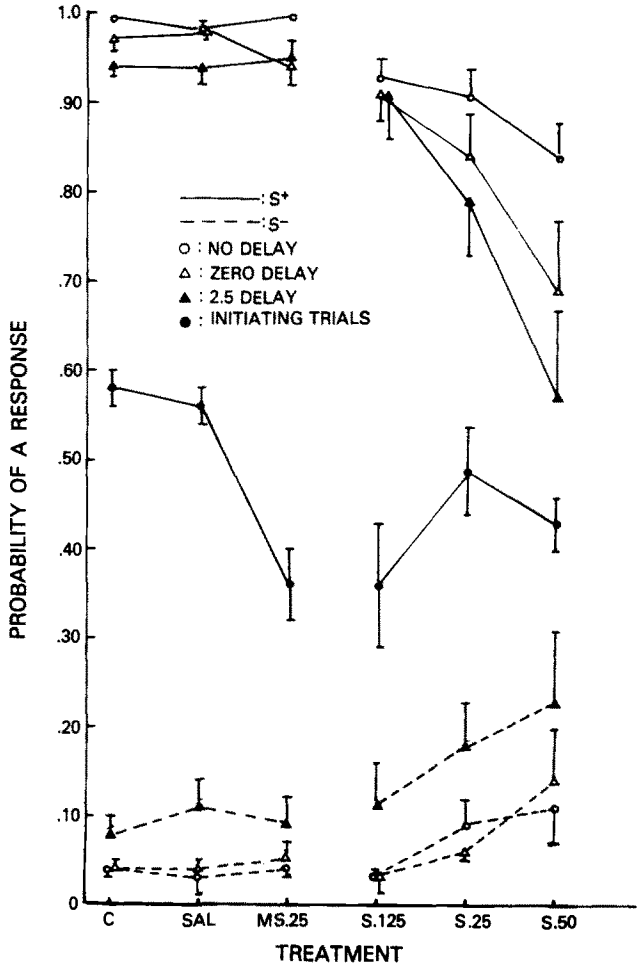

FIG. 3. Effects of the various treatments on trial initiations compared with their effects on accuracy of S+ and S− trial performance. Treatment notations are the same as Fig. 2.

nated after 5 sec, and a special 10 sec inter-initiation response interval followed (also signalled by the houselight). The houselight "blackout" period also served as a pre-trial delay: a response during this interval postponed the initiation response opportunity by 2 sec. For 2.5-delay trials only, a response in the last second of the delay between Event 1 and Event 2 postponed the onset of Event 2 by one second. With the exception of no-delay trials, a response in the last three seconds of Event 1 postponed the onset of the delay by three seconds. These pre-situation contingencies restricted responding to appropriate events, and prevented serendipitous reinforcement. They could, of course, alter delay intervals or stimulus durations. However, pilot studies indicated that once subjects were thoroughly trained, these postponements rarely occurred, and thus did not confound the analysis of data.

Training. All subjects were trained to press the right lever on a continuous reinforcement (CRF) schedule in the presence of an illuminated right panel light. When high rates of responding were attained (200 or more responses per hour), subjects were switched to a series of discrete trial schedules in which the intertrial interval was progressively increased from 5 to 10, 20, and 30 sec over sessions. A response during a 5 sec presentation of a 2500 Hz tone (i.e., the prospective Event 2) always resulted in reinforcement and termination of the trial. When a subject responded on 80–90% of the 200 trials per session (approximately 3 sessions), it was trained to initiate its own discrete trials. Following the intertrial interval, the left lever was illuminated for 5 sec. A left lever press terminated the lever light and initiated Event 1 of the discrete trial. Initiation response training continued until subjects initiated more than 75% of their 200 trials during a session (approximately 6 sessions). Subjects next began discrimination (no-delay) training. Following an initiation response, the right panel light was illuminated with either a bright or dim light concurrently with a tone. Training on no-delay trials continued until good discrimination performance was achieved (responding on 90% or more of S+ trials, and on 10% or fewer of S− trials). The animals then received zero and 2.5-delay training, which was like no-delay training

except that Event 2 (the tone) occurred either immediately or 2.5 sec (respectively) after Event 1 terminated. Finally, subjects were placed on the final delayed response procedure consisting of no, 0 and 2.5-delay trials.

Treatment. When stable performance was obtained at all three delays, intraperitoneal (IP) physiological saline (0.9% NaCl in distilled water) injections were administered until they produced no behavioral disruption (usually 2 to 3 injections). All injection days were preceded by a minimum of two consecutive sessions without injection, with the session prior to the injection day serving as the control day. Injections were given 10 min prior to placement of the animals in their experimental chambers.

Each animal then received three IP injections of each of three doses of scopolamine hydrobromide (0.125, 0.25, and 0.50 mg/kg dissolved in physiological saline) given in a semi-random (counterbalanced) order. Following preliminary data analysis, three more IP injections of 0.25 mg/kg scopolamine were given, followed by one injection of saline and two injections of methyl scopolamine bromide (0.25 mg/kg dissolved in physiological saline).

RESULTS

A systematic comparison by means of a repeated measures ANOVA showed no significant group (bright S+, dim S+) main effects and no significant interactions between group and treatment, group and delay, or group and treatment-by-delay ($p>0.05$ in each case). Consequently, results from the bright S+ and dim S+ groups were combined in all further analyses (N=8).

Figure 2 shows that S+ trial accuracy declined with increasing delay or increasing scopolamine dosage. Analysis of S+ trial performance by a repeated measures ANOVA revealed highly significant drug and delay main effects, $F(5,35)=12.0$, $p<0.001$; $F(2,14)=8.3$, $p<0.005$. In addition, there was a highly significant drug-by-delay interaction, $F(10,70)=4.5$, $p<0.001$, indicating that the effect of scopolamine increased with increasing delay.

Newman-Keuls multiple-range analyses indicated that the main effect of delay on S+ performance was due to significant ($p<0.05$) differences between no and 0-delay trials as well as between no-delay and 2.5 sec delay trials, but that there was not a significant difference between 0-delay and 2.5 sec delay trials. The drug main effects on S+ accuracy were due to significant differences between all treatments except control *vs.* saline, control *vs.* methyl scopolamine (MS), and saline *vs.* MS. These latter three treatments were therefore combined into a single treatment group for further analysis of drug-by-delay interaction [hereafter referred to as the "non-scopolamine" (NS) treatment]. The drug-by-delay interactions were compared separately for NS vs. 0.125, NS vs. 0.25, and NS vs. 0.50 mg/kg over the range from no to 0-delay trials, 0 to 2.5 sec delay trials, and from no to 2.5 sec delay trials. For each of these differences in delay, only the effects of the 0.50 mg/kg treatment were significantly different from NS, $F(1,70)=7.3$, 5.3, and 12.4, $p<0.001$, 0.05, and 0.001, respectively.

Finally, the effects of 0.125, 0.25, and 0.5 mg/kg treatment on no-delay performance were each significantly different from NS: $t(7)=3.9$, 2.8, and 4.4, $p<0.01$, 0.05, and 0.01, respectively. The effects of the 0.125 and 0.25 mg/kg treatments were not significantly different from each other, but when combined were significantly different from the 0.50 mg/kg treatment, $t(7)=3.6$, $p<0.01$.

Thus scopolamine affected S+ accuracy in a dose-related and time-related fashion. The 0.125 and 0.25 mg/kg doses significantly affected no-delay performance but did not additionally affect 0-delay and 2.5 sec delay S+ performance, while the 0.5 mg/kg dose produced progressively greater effects at no-delay, 0-delay, and 2.5 sec delay.

In contrast, scopolamine did not significantly affect S− performance. A repeated measures ANOVA of S− trial performance showed no significant effects for drug and delay, and the drug-by-delay interaction also was not significant.

Figure 3 compares S+ and S− trial accuracy, now plotted as a function of treatment with delay conditions as parameter, with probability of trial initiations. Whereas accuracy of initiated trial responding did not change under control, saline, and MS treatments and then declined systematically with increasing scopolamine dosage, trial initiations decreased under both MS and scopolamine treatment.

Trial initiations for control vs. saline treatments were not significantly different and were therefore combined and compared to the other treatments. Trial initiations for control + saline treatments were significantly different from the MS, 0.125, 0.25, and 0.5 scopolamine treatments, $t(7)=5.4$, 3.5, 2.4, and 3.2, $p<0.01$, 0.01, 0.05, and 0.02, respectively. However, the effects of MS on trial initiations were not significantly different from those of the 0.125, 0.25, and 0.5 treatments, nor were the effects of the three scopolamine treatments different from each other. Thus restriction of scopolamine action to the peripheral nervous system by means of MS decreased percentage of trial initiations but not accuracy of S+ and S− performance.

Figure 4 shows the effects on trial performance of the various treatments and delays expressed in terms of the Theory of Signal Detection non-parametric measures of sensitivity (A': [5]) and bias ((p(yes)/p(no): [12]), where p(yes) refers to the probability of a lever press and p(no) refers to the probability of no lever press on Event 2. Figure 4 indicates that sensitivity tended to decline with increasing delay and dose whereas bias did not change with either delay or dose. It is noteworthy that bias was approximately 1.0 under all conditions, indicating that, overall, the animals were equally likely to respond and not respond on trials. Evaluation of sensitivity by means of a two-factor repeated measures ANOVA revealed highly significant main drug and delay effects, $F(5,35)=18.9$, $p<0.001$; $F(2,14)=26.7$, $p<0.001$, as well as a highly significant drug-by-delay interaction, $F(10,70)=6.1$, $p<0.001$. All the post-hoc analyses which had previously been performed on the S+ and S− trial response data were also carried out with the sensitivity data, with similar results. Control, saline, and MS treatments did not differ and were again combined and labelled the NS treatment. The treatment-by-delay interaction was significantly different only for the NS *vs.* 0.50 mg/kg treatment comparison. Finally, no-delay sensitivity for the NS treatment differed from no-delay sensitivity for all doses of scopolamine; the 0.125 and 0.25 mg/kg treatments also differed significantly from the 0.50 mg/kg treatment. In contrast, similar analyses of bias revealed no significant main drug or delay effects and also no significant drug-by-delay interaction. Thus scopolamine affected only sensitivity (accuracy) of Event 2 performance: it did not affect the tendency to respond (bias).

A variety of measures of control (non-drug) performance served to establish the validity and generality of the delayed

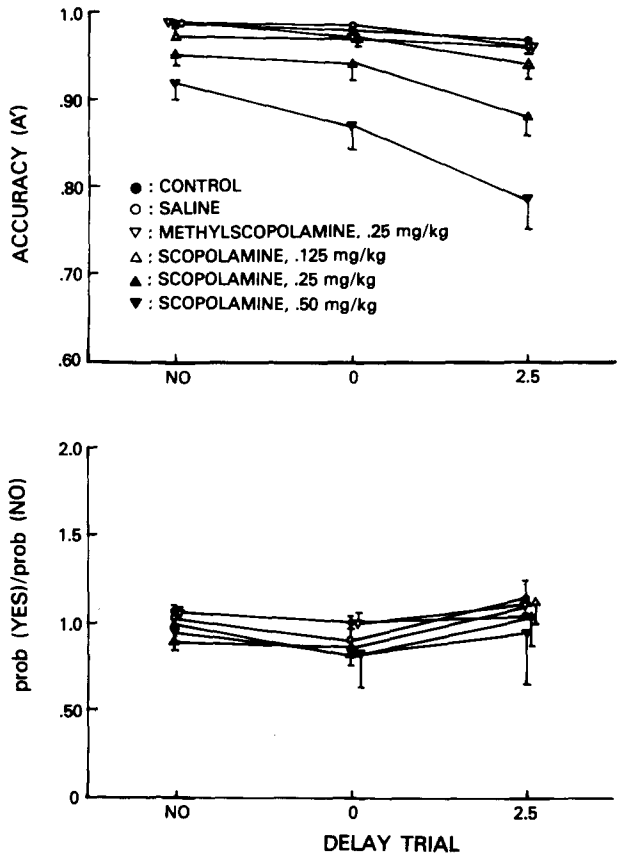

FIG. 4. Top. Accuracy (A') as a function of trial delay, at various treatment levels. An A' value of 1.0 represents perfect accuracy, and A' of 0.50 represents chance accuracy. Bottom. Bias [(p(YES)/p(NO)] as a function of trial delay for various treatment levels. A [(p(YES)/p(NO)]=1.0 represents an equal tendency to respond or not respond.

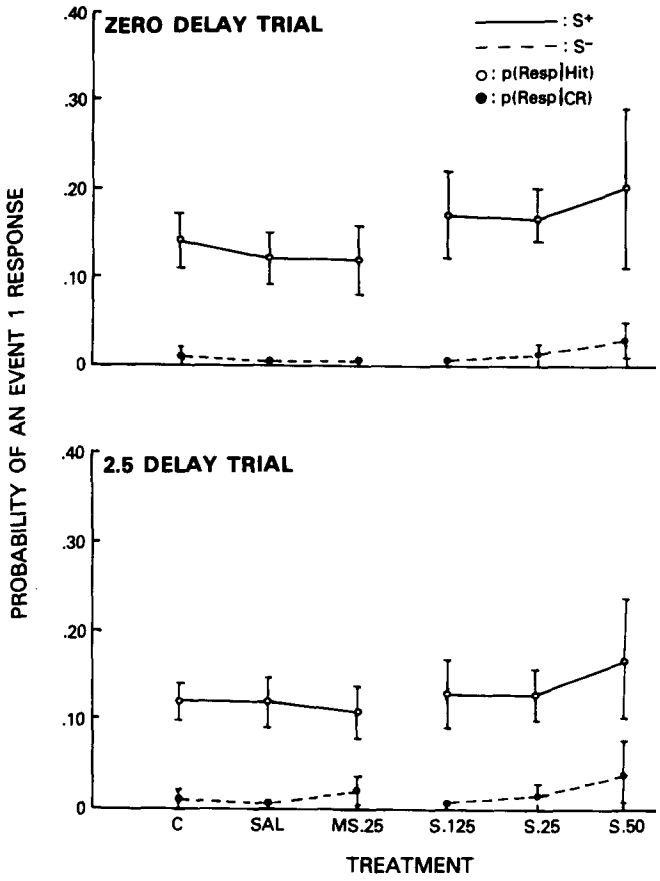

FIG. 5. The probability of an Event 1 response given a HIT (p(E1|H)), and given a correct rejection (p(E1|CR)) for 0 and 2.5-delay trials, as a function of treatment. Treatment notations are the same as Fig. 2.

response procedure. One set of observations was directed to the possibility that the animals could have "bridged the gap" between Event 1 and Event 2 by means of overt responding [4]. If they did, then the present results might not apply to other memory situations where such mediating responses cannot or do not occur. The possibility that the animals used one particular mediating response—lever pressing during Event 1—as a guide for responding on Event 2 was evaluated for the 0 and 2.5 sec conditions by determining the conditional probability of an Event 1 response *given* a Hit or a Correct Rejection (i.e., reinforcement) on Event 2. These results are presented in Fig. 5.

Figure 5 indicates that the probability of an Event 1 response prior to a Hit was always greater than the probability of an Event 1 response prior to a Correct Rejection, for both the 0 and 2.5 sec delays. Although this difference between trial types was statistically significant, $F(1,6)=6.3$, $p<0.05$, the Event 1 responding occurred on at most 20 percent of the S+ trials. Also, contrary to what would be expected if the animals used Event 1 responding as a guide to Event 2 performance, the animals almost never made more than one Event 1 response during a trial. Hence it appears most unlikely that overt responding by means of lever pressing played a significant role in the memory performance of the animals.

A second set of observations established that performance following the 30-sec intertrial interval was independent of performance on the immediately preceding trial. The p(Hit) following S+ trials under the various treatments was systematically compared with the p(Hit) following S− trials, and the p(FA) following S+ trials was systematically compared with the p(FA) following S− trials. Neither p(Hit) nor p(FA) differed significantly (t-tests) on trials preceded by S+ or S− trials, for any treatment level.

DISCUSSION

Scopolamine (0.125, 0.25, and 0.50 mg/kg) produced a dose-related disruption of no-delay (discrimination) performance in a paired delayed response procedure in which the rats initiated their own trials. In addition, the 0.5 mg/kg dose of scopolamine (but not lower doses) also significantly impaired the time-dependent process of retention: drug effects on accuracy of performance at 2.5 sec delay were significantly greater than effects at 0-delay. Thus the present

highest-dose results are in accord with the results of other delayed-response experiments (e.g., [2]) in which scopolamine impaired retention. The 0.5 mg/kg dose of scopolamine also affected 0-delay performance more than no-delay performance, suggesting that the drug may also affect a 0-delay "encoding" process distinct from the processes affected at no-delay and 2.5 sec delay.

With regard to interpretation of the present results, the possibility must be considered that the significant effects of scopolamine on longer-delay performance were not effects on memory encoding and retention, but were rather due to differential levels of stimulus control. The magnitude of drug effects typically varies inversely with level of baseline (nondrug) stimulus control (i.e., accuracy) [6]; greater drug effects could therefore have occurred at longer delays if levels of stimulus control were lower at the longer delays. However, this does not seem to be the case in the present experiment since the control accuracy-by-interval curves (Fig. 2) were nearly horizontal over the no-0-2.5 sec delay interval.

A second possibility is that the effect of scopolamine on retention was a secondary consequence of the drug's effects on no-delay accuracy. Indeed, one of the original goals of the present experiment was to determine the effects on retention of reducing the intensity difference (i.e., discriminability) between the "bright" and "dim" discriminative stimuli. This experimental manipulation was never carried out due to animal aging and attrition. However, two recent studies using delayed comparison procedures have demonstrated that reducing the discriminability of the sample stimuli does not affect retention. White [17], in a delayed matching to sample experiment with pigeons, found that reducing the difference between stimuli reduced stimulus control but did not affect retention. Spencer, Pontecorvo and Heise [14], using a continuous non-matching procedure with rats, showed that reduction of the intensity difference between bright and dim discriminative stimuli and administration of scopolamine had parallel effects on levels of stimulus control, but did not affect retention. Thus, while recognizing that these latter two experiments differed in many respects from the present one, it seems unlikely that the effect on retention observed here was a consequence of the reduction in accuracy of short-delay performance. The results of Bartus and Johnson [2], who reported that in a delayed response procedure with monkeys scopolamine affected retention at doses that did not affect no-delay or 0-delay performance, further support this conclusion.

In conclusion, the present results have specific implications for the behavioral effects of cholinergic blockade and the functioning of the central cholinergic nervous system.

(1) Methyl scopolamine, which principally affects the peripheral nervous system, affected trial initiations at a dose that did not affect accuracy of responding, whereas the same dosage of scopolamine, which has both central and peripheral activity, affected both trial initiations and accuracy. Thus, consistent with previous reports by Ksir [8], Levy, Elsmore and Hursh [9] and others, the effects of scopolamine on response accuracy are predominantly central effects whereas its effects on rate or response initiations are predominantly peripheral effects.

(2) Scopolamine affected sensitivity, and did not affect bias. Thus the signal detection analysis supports the contention that anticholinergics impair "attention" or stimulus discriminability [15] rather than "disinhibit" responding suppressed by nonreward [3].

(3) There may be no categorical answer to the question: does scopolamine affect retention as well as discrimination in memory? In the present experiment scopolamine affected both. Whether the drug will have either or both of these effects in other memory experiments depends on a variety of factors: type of memory procedure (effects on memory retention have been observed principally in paired delayed response procedures); the drug dosage (significant effects on retention were observed only with 0.5 mg/kg in the present experiment); the length of the retention interval (longer delay intervals might lead to a greater divergence of retention curves); and the level of stimulus control.

ACKNOWLEDGEMENTS

This report is based on a dissertation submitted by Anthony P. Viscardi in partial fulfillment of the requirement for the MA in Psychology from Indiana University. The research was supported in part by the office of Research and Development, Environmental Protection Agency under Grant R-809152 to George A. Heise. The Environmental Protection Agency does not necessarily endorse any commercial products used in this study; the conclusions represent the views of the authors and do not necessarily represent the opinions, policies, or recommendations of the Environmental Protection Agency.

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