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Low dose scopolamine affects discriminability but not rate of forgetting in delayed conditional discrimination

R.C. Kirk, K. Geoffrey White, and N. McNaughton
Department of Psychology, and Centre for Neuroscience, University of Otago, New Zealand

Abstract. The effect of scopolamine on remembering was examined in a delayed conditional discrimination procedure with rats. Remembering was quantified by a negative exponential function fitted to estimates of discriminability derived from a signal detection type of analysis. This function had two parameters: a measure of initial discriminability of the sample stimuli in the absence of a memory requirement (at zero delay) and a measure of rate of forgetting. Eight rats were trained on an auditory delayed conditional discrimination task until they were showing stable performance. Each rat then received doses of 0, 0.005, 0.014, 0.042, 0.125 and 0.375 mg/kg scopolamine IP in a saline vehicle. There was a highly significant, largely linear, decrease in initial discriminability. This was obvious even at the lowest dose of scopolamine. Poorer memory, as demonstrated by an increase in b, was only apparent at the highest dose. Significant changes in per cent of correct responses were also only obtained at higher doses. These results show that initial discriminability and rate of forgetting are pharmacologically as well as theoretically independent. They suggest that the measure of initial discriminability used here is a particularly sensitive measure of at least some types of cholinergic dysfunction; and they also suggest that effects of scopolamine in other working memory tasks could be more a result of changed stimulus processing than of impairment of memorial processes.

Key words: Scopolamine – Acetylcholine – Memory – Discrimination – Signal detection

Memory processes in animals can be examined particularly well in the context of delayed conditional discrimination procedures, such as delayed matching to sample or delayed detection. These procedures allow study of encoding, storage and retrieval in terms of information processing (Grant 1981) or in terms of processes of elaborative rehearsal such as prospective and retrospective encoding (Honig and Thompson 1982).

In delayed matching and delayed detection tasks, presentation of the sample stimulus to be remembered is followed by a delay or retention interval. At the completion of the retention interval the subject chooses the comparison stimulus that matches the previously presented sample (Berryman et al. 1963) or makes a choice response that is conditional on the prior sample (McCarthy and White 1987). The usual measure of discrimination in two-choice discrimination experiments is per cent correct. However, this measure does not differentiate changes in effective discriminability of alternatives from variations in response bias or perseveration. An alternative measure, Log d, gives a bias-free measure of discriminability analogous to those of signal-detection theory (e.g. d'). Log d is derived from Davison and Tustin's (1978) analysis of signal detection performance, and has an empirical basis in the matching law (Baum 1974) rather than a theoretical basis in the assumptions of signal detection theory.

White (1985, 1987) and White and McKenzie (1982) demonstrated that discriminability at time t, Log d_t, diminishes as an exponential function of the duration of the delay or retention interval. This negative exponential function (eq. 1) has two parameters, *Log* d_o which describes discriminability at zero delay (no retention interval) and b which describes rate of forgetting, or the rate at which discriminability decreases with increasing time t since presentation of the sample stimulus.

$$\text{Log } d_t = \text{Log } d_o \cdot \exp(-bt) \quad (1)$$

White (1985, 1987) showed that the parameters of the negative exponential function, Log d_o and b, afford independent higher-order measures of remembering. Log d_o is affected by factors contributing to the encoding of sample stimuli, whereas b is affected by factors that may disrupt rehearsal or interfere with retrieval, such as retroactive interference (White 1985).

The aim of the present study is to examine the differential effects of scopolamine on the two aspects of delayed matching performance identified by White. Scopolamine is a central muscarinic antagonist that blocks cholinergic receptors and has an apparently amnestic effect in memory tasks performed by humans (Caine et al. 1981) and monkeys (Aigner and Mishkin 1986). In rats, scopolamine impairs performance in the radial-arm maze (Beatty and Bierley 1986); in delayed matching to position (Dunnett 1985); and in a "continuous nonmatching-to-sample" procedure (Spencer et al. 1985).

In previous studies, the effects of scopolamine may have been due partly to impairment of attention (Heise and Milar 1984), impairments of sensory or motor processes (Milar 1981) or deficits in memorial processes (Bartus and Johnson 1976; Pontecorvo and Evans 1985). Warburton and Brown (1971) used signal detection analysis to show that scopola-

Offprint requests to: R.C. Kirk, Department of Psychology, University of Otago, P.O. Box 56, Dunedin, New Zealand

mine reduced stimulus sensitivity rather than response criterion. Spencer et al. (1985) also separated stimulus discriminability from response bias and in addition investigated the effect of delay on performance in a "continuous nonmatching-to-sample" procedure. They concluded that the drug did not affect the time-dependent process of retention in working memory. The present experiment assesses this conclusion using a different task, delayed conditional discrimination, and with the extraction of independent measures of discriminability and rate of forgetting.

Materials and methods

Subjects. Subjects were eight male Sprague-Dawley rats, 9 months of age at the beginning of the experiment. They were individually housed under a natural light-dark cycle, with all testing occurring during the light phase. The subjects were fed daily after testing with amounts of food which maintained their body weights at 85–90% of their normal free-feeding weights. Water was freely available in the living cages.

Apparatus. Eight Campden Instruments experimental chambers, 25 cm × 23 cm × 20 cm high, were used. Each chamber was fitted with two retractable levers, situated 7.5 cm on either side of a central food tray which had a hinged clear plexiglass door. When the door was opened by a nose poke a microswitch was activated, enabling nose pokes to be recorded. Chamber illumination was provided by a 2.8 W house light situated centrally on the chamber ceiling. Another light permitted back-illumination of the food tray. Each chamber was located in a separate light- and sound-attenuating enclosure. Reinforcement was provided by 45 mg Noyes food pellets dispensed individually into the food tray. Two audio-indicators mounted centrally above the food tray produced 400 Hz and 4600 Hz tones, respectively, at approximately 15 dB above the level of the noise (about 75 dB) of the ventilation fan of the sound-attenuating enclosure. Experimental events were controlled and recorded by individual Acorn Atom microcomputers programmed in ONLIBASIC.

Behavioral procedure. The conditional discrimination procedure was conducted 5 days per week, with sessions terminating after completion of 112 trials or 60 min, whichever came first. Each trial was initiated by a nose-poke response into the food tray following the completion of a 10-s intertrial interval (ITI). This nose-poke response was followed by 1-s presentation of a sample stimulus, either the 4600 Hz tone (S1 stimulus) or the 400 Hz tone (S2 stimulus). Initiation of trials by the subjects was intended to increase the likelihood of attention to sample stimulus presentation. Offset of the sample stimulus was followed by a retention interval. The retention interval lasted for 0.1, 1, 2, 4, 8, 16 or 32 s. A random order of all delay intervals was generated by the computer within each session with the following constraints. Within a block of 14 trials, seven S1 samples and seven S2 samples were presented, with one of each of the seven delay intervals arranged for both S1 and S2 trials. No more than two S1 or two S2 trials could occur consecutively. The first nose-poke response into the food tray following the completion of the programmed retention interval resulted in insertion of both levers into the chamber. This nose-poke response functioned to prevent the development of position bias or response strategies during the retention interval, such as standing in front of the appropriate lever during the retention interval and pressing the lever when it was inserted. In particular, the nose-poke response ensured that the subject was positioned centrally in the chamber at the end of the retention interval. On S1 trials, a right lever press was reinforced, and on S2 trials a left lever press was reinforced. Reinforcement was delivery of a single Noyes food pellet accompanied by a 200 ms onset of the light mounted behind the food tray.

Error responses, namely a left lever press on S1 trials or a right lever press on S2 trials, resulted in a 5-s blackout in which the houselight was turned off. Following blackout or reinforcement, the 10-s intertrial interval preceded the next trial. The total number of S1 and S2 trials, correct S1 and S2 responses at each delay and the average response latency for each delay, measured from sample-stimulus offset to lever press, were recorded.

Over 5 months of preliminary training were conducted with the conditional discrimination procedure, or slightly different versions of it in earlier sessions, in order to establish stable performance. The last ten sessions were used to determine baseline levels of performance for individual subjects.

Pharmacological procedure. Using the procedure described in the data analysis section, negative exponential functions given by equation 1 were fitted to the Log d_t measures at each delay for individual subjects. Subjects were allocated to one of two groups ($N=4$) by matching on the basis of the Log d_o and b parameters for the negative exponential functions fitted to the baseline data. At the start of drug treatment, subjects in the two groups were thus matched on baseline conditional discrimination performance. Group 1 subjects were injected with (−) scopolamine hydrochloride (Sigma) and group 2 subjects received equivalent volume injections (IP) of 0.9% NaCl, during the first 10 days of the experiment. During the second 10 days of the experiment the conditions were switched, with group 1 subjects receiving saline control injections and group 2 subjects receiving drug injections. For group 1 subjects drug administration was first in ascending order of dose, followed by descending order with one dose level administered for 1 day. The dose levels were, expressed as the weight of the salt, 0.005, 0.014, 0.042, 0.125 and 0.375 mg/kg, given in a volume of 1 ml/kg in a saline vehicle. Group 2 subjects received a descending order of scopolamine administration followed by an ascending order with doses as for group 1. Drug or saline injections were administered 10 min before the beginning of experimental sessions. Performance in the conditional discrimination procedure was maintained throughout the drug and saline conditions.

Data analysis. For each delay interval for the predrug sessions and for sessions with each drug dose, including saline, correct and error responses following each sample stimulus were summed separately for individual subjects (individual analysis) and also over all eight subjects (pooled analysis). Measures of discriminability at delay t, Log d, were derived from the ratios of correct to error responses following sample S1 (C1/E1) and following sample S2 (C2/E2) according to

$$\text{Log } d_t = 0.5 \text{ Log}\left(\frac{\text{C1}}{\text{E1}} \cdot \frac{\text{C2}}{\text{E2}}\right)$$

Table 1. Effects of scopolamine on Log d and b values for individual subjects[a]

Dose	Subject									
	5	8	9	10	12	16	18	21	Mean	Pooled
Log d_o										
0.000	1.120	0.865	1.365	(1.229)	1.288	1.411	1.245	1.465	1.249	1.188
0.005	0.858	0.720	1.059	(0.888)	0.810	0.883	0.946	1.094	0.907	0.961
0.014	1.108	0.908	1.050	0.934	0.728	0.803	1.026	1.223	0.973	0.949
0.042	(0.689)	0.828	(0.865)	0.666	0.777	0.442	0.746	1.162	0.772	0.746
0.125	0.416	0.624	(0.766)	0.758	(0.601)	(0.582)	0.666	0.965	0.672	0.512
0.375	0.210	0.151	0.356	(0.308)	0.270	(0.238)	0.493	(0.595)	0.323	0.158
b										
0.000	0.044	0.048	0.015	(0.035)	0.053	0.047	0.062	0.064	0.046	0.045
0.005	0.042	0.014	0.014	(0.024)	0.061	0.034	0.067	0.028	0.036	0.040
0.014	0.048	0.068	0.007	0.012	0.037	0.039	0.040	0.070	0.040	0.040
0.042	(0.047)	0.031	(0.031)	0.022	0.090	0.116	0.042	0.032	0.051	0.045
0.125	0.042	0.047	(0.035)	0.079	(0.081)	(0.071)	0.040	0.049	0.056	0.060
0.375	0.060	0.079	0.083	(0.068)	0.139	(0.095)	0.027	(0.082)	0.079	0.074

[a] Values in *parentheses* are estimates assigned to missing values by the GENSTAT program. The b values are untransformed. The means across subjects are also given (mean) and, for comparison, the Log d_o and b values estimated from the analysis which pooled data across subjects before estimating log d_o and b (POOLED)

Measures of response bias, Log bias (Davison and Tustin 1978), were derived according to

$$\text{Log bias} = 0.5 \text{ Log}\left(\frac{\text{C1}}{\text{E1}} \cdot \frac{\text{E2}}{\text{C2}}\right)$$

It is important to note that the delay intervals (t) used in the analysis were obtained by averaging the *actual response latencies* at the different programmed delays rather than the programmed delays themselves, because the delay was in practice terminated by a nose-poke that produced the side levers for the choice response.

Equation 1 was fitted to pooled and individual data using a nonlinear least squares algorithm in which Log d_o and b were varied until a least squares fit was obtained. In the individual data there were ten instances where fits were not possible because there were zero errors at more than four delays or in one case the subject ceased to respond in the highest dose condition.

The Log d_o and b values and the unsigned bias values (i.e. ignoring whether bias was to left or right) of the individual data were submitted to repeated measures analyses of variance that took account of missing values using the GENSTAT statistical package. Linear, quadratic and cubic orthogonal polynomials were extracted from the analysis of variance (Snedecor and Cochran 1967). The values of b and Log bias were not normally distributed, so an additional analysis of variance was conducted on each with values transformed to normality by $X' = \text{Log}_{10}[(X \times 100) + 1]$. Per cent correct data were submitted to the angular transform (arcsine of square root) as recommended by Zar (1974).

The pooled data are representative of performance but have the disadvantage of not being amenable to statistical analysis. Analyses were therefore conducted using parameter estimates of Log d_o and b for individual subjects. A problem with the individual data, however, is that more than 10% of data were missing because of zero error scores in the signal detection matrices. The ANOVAs of the individual data must, therefore, be treated with caution. The procedure used in this paper to combat this problem is a direct comparison of the pooled results with the means generated by the missing values ANOVAs. There is (see below) little discrepancy between them, and the direction of the minor discrepancies which exist would tend to reduce rather than inflate drug effects. Further, the significance levels obtained for all the important conclusions are such that an error of as much as an order of magnitude in their estimation would not change the overall conclusions. The parameter estimates for individual subjects and the missing values estimates provided by the ANOVAs are given in Table 1.

Results

Figure 1 shows the discriminability measures for each delay, based on the pooled data (summed over all subjects), for the different dose levels of scopolamine. Figure 1 also gives the values of the parameters, Log d_o and b, for the best fitting exponential functions and also the proportion of variance accounted for (VAC) and the mean squared error (MSE) for the best fitting functions. The fits of the negative exponential function to the data were excellent in all cases. For the higher drug doses the VAC proportions were smaller owing to decreased systematic variation in Log d_t values, but it is noteworthy that the MSE values remained as small as for the zero dose condition.

Values of the Log d_o parameter for the exponential functions in Fig. 1 decreased systematically with increasing dose level, whereas there was a minimal change in the corresponding values of b. Reliable changes in b in previous studies typically require b to double (e.g. Edhouse and White 1988).

The changes in overall latency to respond (nose poke plus lever press) can be seen in the divergence of the plotted delay from the programmed delay. For example, with the programmed delay of 32 s, doses of 0.0, 0.005, 0.014, and 0.042 mg/kg have nearly identical actual delays in the region of 34 s – implying a latency of 2 s. At 0.125 mg/kg

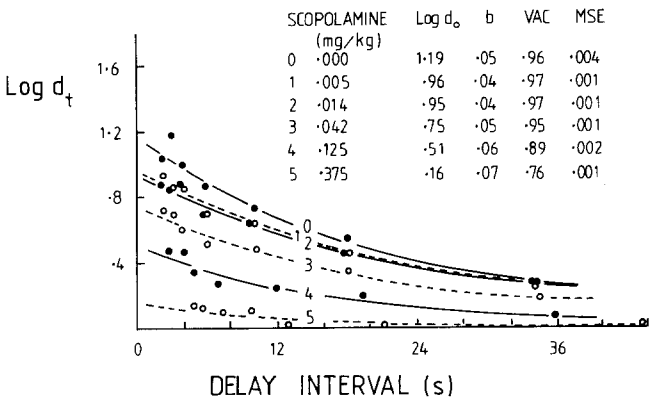

Fig. 1. Individual Log d values derived from data pooled across subjects are plotted for each delay and drug dose. The smooth curves are the result of least squares fitting of an exponential equation with two parameters: Log d_o, the value of Log d estimated for delay 0; and b the exponent of the function. VAC = proportion of variance accounted for by the fitted function; MSE = mean square error of the fitted function

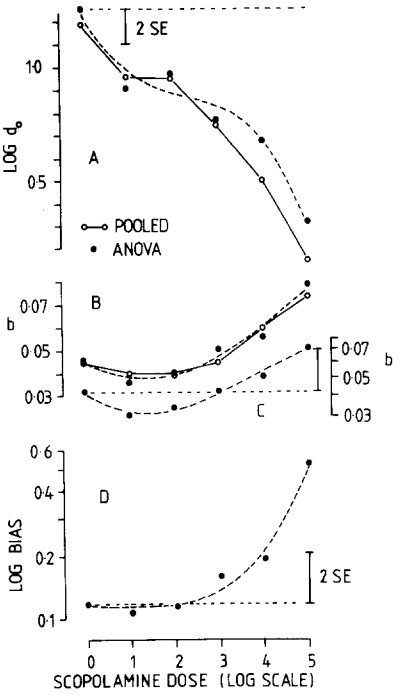

Fig. 2A–D. Dose-response curves for discriminability (Log d_o, see Fig. 1); rate of forgetting (b, see Fig. 1) and response bias (Log bias). *Solid circles* and *smooth curves* are derived from analysis of variance (ANOVA) of individual subject data. *Open circles* and *straight lines* are data from the POOLED analysis (Fig. 1) plotted for comparison. *Vertical bars* represent 2 standard errors for between point comparisons derived from the analysis of variance. Doses of scopolamine are as for Fig. 1. **A** Log d_o: there is a highly significant doses-dependent decrease in Log d_o with increasing dose of scopolamine. **B** Untransformed b: these data are plotted for comparison with the POOLED data – the smooth curve is derived from an ANOVA of the raw data but is not strictly reliable as error distribution was not normal. **C** Transformed b: the data plotted are as transformed for the ANOVA reported in the text. The qualitative conclusions are essentially the same as for *panel* **B**. There is some evidence for an increase in b at the highest dose but this result should be treated with caution. **D** Log bias: there was no evidence of changes in bias with delay at any drug dose. The data plotted are means obtained across individual subjects and delays. There is a clear effect of scopolamine on bias at higher doses, but not at the lower doses which are sufficient to change Log d_o

there may be a slight increase in latency and at 0.375 mg/kg the latency is in the region of 10 s.

The above conclusions from the group data in Fig. 1 were confirmed by analysis of individual data. Means of parameter values for individuals closely approximated the parameter values obtained in the pooled analysis (Fig. 2). There was a systematic reduction in Log d_o with increasing dose of scopolamine. The effect at the lowest dose level was more than 2 standard errors different from Log d_o for the saline condition and there was a highly significant linear decrease in Log d_o with increasing dose (linear trend: $F = 190.7$, $df = 1/25$, $P \ll 0.001$). The dose response function was also significantly nonlinear (cubic trend: $F = 11.4$, $df = 1/25$, $P < 0.0025$). The least squares dose-response function fitted by the analysis of variance is represented by the continuous curve in Fig. 2A.

Figure 2B shows that there was good agreement between the untransformed individual means for b and the values obtained in the pooled analysis. Comparison of Fig. 2B with Fig. 2C shows that the transformed data used in the analysis of variance gave very similar results. There is an apparent slightly *lower* rate of forgetting at the lower doses of scopolamine and a higher rate at higher doses. The only dose which produces a change relative to control of more than one standard error is the highest. These rather weak effects (doubling of b is not unusual in behavioural experiments) were apparently systematic (linear trend: $F = 7.9$, $df = 1/25$, $P < 0.01$; quadratic trend: $F = 4.4$, $df = 1/25$, $P < 0.05$) – but this result should be treated which caution because of the number of missing values in the ANOVA (see data analysis). Even if the reliability of these effects is accepted, it should be noted that the form of the dose-response curve is entirely different from that for Log d.

Log bias showed no variation of any kind with delay or interaction of delay with dose of scopolamine (all $F < 2.1$). Figure 2D therefore plots mean Log bias values as a function of dose, collapsed across delay condition. At increasing doses there is a systematic increase in Log bias (linear component: $F = 36.8$, $df = 1/34$, $P \ll 0.001$) but this effect does not occur at the lowest doses (quadratic component: $F = 12.8$, $df = 1/34$, $P < 0.0025$).

Figure 3 plots the variation in per cent correct with changing delay and dose for comparison with other studies. All linear and quadratic effects and interactions were significant (all $P < 0.0025$), except for the quadratic × quadratic of dose × delay. Quadratic components of dose arose as there were negligible effects on per cent correct at the three lowest doses of scopolamine and noticeable effects at the higher doses.

Discussion

The results show that scopolamine produces a simple dose related decrease in Log d_o values at surprisingly low doses (0.005 mg/kg), suggesting that this parameter is a particularly sensitive index of the drug's effects. In other tests doses as low as 0.1 mg/kg (Buresova et al. 1986) have been used, but doses in the region of 1.0 mg/kg are not uncommon

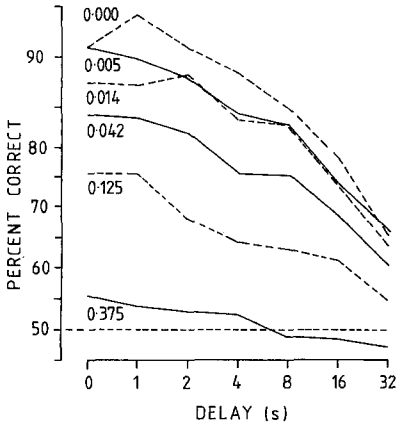

Fig. 3. Dose and delay response curves for the effect of scopolamine on percent correct responding. The nonlinear percent axis is the result of angular transform and the delay axis reflects a logarithmic transform. The numbers within the figure are the scopolamine doses in mg/kg. The delay curves differ significantly with the main effects of scopolamine being obtained, as with Log bias (Fig. 2D), at the higher doses

(Dunnett 1985; Spencer et al. 1985). It is interesting to note that Warburton and Brown (1971), using a signal detection procedure, not only demonstrated an effect on scopolamine at a low dose (0.0625 mg/kg) but also obtained an equivalent size of effect to that of the same dose in the present study (i.e. approximately a halving of their discriminability measure).

Further, this result was obtained using an auditory discrimination procedure in which the separation between the stimuli was large (100-fold). Milar (1981) reported that when the luminance separation between visual S+ and S− stimuli was large (10 fold), in a go – no go procedure, scopolamine had no effect on sensitivity (equivalent to our Log d_t measure). However, when the separation was small (1.4-fold), scopolamine decreased sensitivity. (Warburton and Brown (1971), found effects with a 3-fold luminance change.) This suggests possible qualitative differences in the functional action of scopolamine across different sensory (visual versus auditory) modalities – or could reflect the fact that the present study involved a conditional discrimination. This needs to be tested by varying discrimination difficulty across different sensory modalities within the same experimental context.

Given the reports that scopolamine interferes with memory, it is perhaps surprising that Log d_o should have been affected rather than b. Two points should be noted here. Firstly, previous experiments have not separated the equivalent of Log d_o and b and this may well have led to erroneous conclusions. In tasks such as the radial arm maze, which is very sensitive to scopolamine (Beatty and Bierley 1986), a deficit in "spatial memory" could easily result from an increase in the confusability of alternatives (equivalent to the present change in Log d) rather than any impairment in memorial processes per se. Secondly, the retention interval in the present experiment was short and does not allow us to conclude that retention would be similarly unaffected at longer intervals.

Other experiments in the literature have tended to report per cent of correct choices, or its equivalent. In comparing the present results with other experiments it is important to remember that the per cent correct measure was not obviously changed until doses were used which were orders of magnitude higher than the smallest dose producing a significant effect on Log d_o. Similarly, as noted above, when Warburton and Brown (1971) used an equivalent signal detection analysis in the context of an entirely different experimental task, they demonstrated clear effects of a very low dose of scopolamine.

A no-delay condition was not included in the present study, so there was no opportunity for the subject to respond during presentation of the sample stimuli. It is possible that scopolamine was affecting encoding processes as well as stimulus discrimination processes. If a no-delay condition was included and the scopolamine effect was as great for both no-delay and zero-delay conditions, then it could be concluded that scopolamine was affecting discrimination processes. If, however, scopolamine impaired performance more at zero-delay than at no-delay, then it could be concluded that scopolamine was affecting both discrimination and encoding processes. This possibility needs further examination.

Of particular interest is the difference in the effects of the drug on the two parameters. As was discussed in the introduction, there are good theoretical reasons for believing that Log d_o and b are essentially independent parameters. Even a cursory glance at the fitted dose-response functions shows that these two parameters are varying independently of each other. Indeed, for the first two scopolamine doses the observed effects are in opposite functional directions for Log d_o and b. It should be noted that the effect of scopolamine on b at the highest dose used cannot be a result of floor effects on the fitted function, as these would have produced the opposite results – a decrease in b rather than an increase.

One possible source of artefact in the b data (which would also operate but with a very much lesser effect on our conclusions in the case of Log d_o) is that at the higher doses the variance accounted for by the fitted function decreases. The apparent effects of scopolamine on b at high doses could, therefore, be attributed to the addition of some source of systematic or nonsystematic noise which biased the fitting function so as to produce a spurious apparent change in b. However, it should be noted that variance accounted for is dependent, in part, on b. The mean square error is probably, therefore, a better measure of fitting accuracy and this did not suggest any decrease in accuracy of the fitting functions with increase in dose. Furthermore, addition of random noise to the function, or a floor effect, would be expected to decrease b not to increase it.

It should also be noted that, at the two highest doses, which affected b, latencies of the choice responses increased. This is shown by the displacement of the data points along the delay-interval axis in Fig. 1. These changes in latency could reflect an attenuation in the control of responding by the sample stimuli at the higher scopolamine doses. Importantly, however, there is no sign of an increase in latency at the three lowest doses of scopolamine which produce large, dose-related changes in Log d_o.

The specificity of action of scopolamine, a dose-dependent decrease in Log d_o but no change in b, could be regarded as pharmacologically surprising, given that scopolamine could be expected to act on widely distributed cholinergic muscarinic receptors within the CNS. If different discrete cholinergic pathways perform qualitatively differ-

ent functions, then manipulating them simultaneously with scopolamine might produce changes in a number of cholinergic-specific psychological functions. This argument views cholinergic function as modulating a number of specific processes, such as attention, discrimination processes, and memory processes. Some support for this is seen in cholinergic lesion studies. Dunnett (1985) reported that ibotenic acid lesions of the nucleus basalis produced impairment of primarily discrimination processes, whereas fimbria-fornix transections produced impairment of memorial processes. Scopolamine in Dunnett's (1985) study produced impairments resembling the combined lesion deficits. Miyamoto et al. (1987) recently reported that lesions of the basal forebrain produced long-term memory impairment, while medial septal nucleus lesions produced short-term memory impairment. Further resolution of the roles of cholinergic function could be achieved by examining the functional effects of the cholinergic lesions described above, and of high doses of scopolamine, on the parameters Log d_o and b.

Given the exceedingly low effective doses used in the present study it seems possible that scopolamine is acting with more than its usual specificity through an action on a system of unusual sensitivity. Such a system could effectively concentrate the drug in comparison to other systems, it could have a particularly sensitive subclass of muscarinic receptor, or the observed effects could be due to peripheral rather than central actions of the drug. Further research would be needed to separate these possibilities.

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