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Scopolamine Effects on Hamilton Search Task Performance in Monkeys

EDWARD D. LEVIN*[1] AND ROBERT E. BOWMAN†

**Department of Psychology, Franz Hall, 405 Hilgard Ave. University of California, Los Angeles, CA 90024*
†Harlow Primate Lab, Department of Psychology, 22 N Charter St University of Wisconsin, Madison, WI 53715

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LEVIN, E D AND R E BOWMAN *Scopolamine effects on Hamilton search task performance in monkeys* PHARMACOL BIOCHEM BEHAV 24(4) 819–821, 1986 —The Hamilton search task, a test of spatial memory, was given to adult monkeys after administration of scopolamine Three monkeys had been exposed to lead during development and two were controls The task consisted of opening eight boxes, one per trial, for food reinforcement, with a 20 second delay between trials The monkey had to remember which boxes it had already opened and avoid them to obtain the remaining reinforcements Percent correct response, openings-to-repeat, trials per session, repetitive index and response latency were measured There were no significant lead-related effects Significant scopolamine-induced deficits were detected with four of the measures The low doses of scopolamine (1–3 μg/kg) did not affect response accuracy, but 15 and 30 μg/kg caused impairments Only 30 μg/kg substantially increased latency This is like other memory tests in monkeys and rats in that it is sensitive to anticholinergic challenge Cognitive performance deficits were detected at a dose (15 μg/kg) which did not cause increased response latency The Hamilton search task is a flexible and sensitive memory task for monkeys, analogous to the radial arm maze in the rat

Hamilton search task Scopolamine Memory Monkeys Lead

THE Hamilton search task (HST) was originally developed by G V Hamilton early in this century [5,6] This test of spatial memory was useful in assessing the abilities of a variety of species including monkeys Despite this utility, it has not been much used in research. Meyer and Settlage [10] and Harlow *et al* [7] found that frontal lobe lesions in the monkey resulted in impaired performance on the HST Levin and Bowman [8,9] found that aquisition of HST performance detected the long-term effects of postnatal lead exposure The similarity of the HST to the 8-arm maze used with the rat provides a suggestion that it may be a sensitive indicator of derangements of spatial memory function With HST not only can the length of time to remember can be altered, the number of items to be remembered can be manipulated Challenge by the anticholinergic, scopolamine, has been found to impair performance on spatial memory tests in rats [4] and monkeys [1] The effect of scopolamine on HST performance was tested in this study to determine how closely this task mirrors other spatial memory tests The long-lasting effects of neonatal lead exposure was also tested in this study Since there were no apparent effects of lead on any of the measures, this report focuses on the effects of scopolamine

METHOD

Subjects

The monkeys in this experiment were originally described by Bushnell and Bowman [3] as the lead III group There were two controls and three lead-exposed monkeys left from the original experiment They were raised in a primate nursery and given lead orally for the first year after birth, first at high acute levels and then at lower chronic levels The exposure consisted of an acute 10 mg/kg dose via nasogastric intubation on either day 8 or 9 after birth and 1.0 mg/kg/day for the next five days. This drove the blood lead values to about 80 μg/dl, where it was maintained by 0 7 mg/kg/day of lead acetate given in their daily feeding of milk formula The monkeys then received an additional intubation of 10 mg/kg lead acetate on day 29 or 30, followed by 1–3 mg/kg/day for the next ten days, with the dose depending on what was needed to reach blood lead concentrations of 250–300 μg/dl The monkeys were given chronic doses of lead acetate daily in their milk formula through week 54 after birth. The chronic dose was started at 0 7 mg/kg/day and was adjusted throughout the rest of the first year to achieve a target blood lead concentration averaging 76 μg/dl over weeks 17–52 post partum This lead administration did not produce discernable impairment in growth or weight gain. There was a transient 12–15% reduction in hematocrit during the high lead pulse which returned to normal after the 12th week

The monkeys had previously been tested for social behavior [3], locomotor activity [2], spatial reversal learning [2], and Hamilton search task acquisition [9] The lead-treated monkeys showed significant deficits in spatial reversal learning and a marginal deficit in HST acquisition At the time of

[1]Requests for reprints should be addressed to Dr Edward D Levin

TABLE 1

RESPONSE PERFORMANCE ON HAMILTON SEARCH TASK UNDER DIFFERENT DOSES OF SCOPOLAMINE. MEAN ± STANDARD ERROR OF THE MEAN

		μg/kg Scopolamine				
Measure	Saline	1	3	5	15	30
Percent Correct	† 81 6 ± 1 0	82 1 ± 2 7	83 4 ± 2 7	78 9 ± 4 3	75 9 ± 2 7	74 4 ± 2 6
Openings to Repeat	‡ 5 1 ± 0 2	5 5 ± 0 2	5 5 ± 0 3	5 0 ± 0 6	4 2 ± 0 5	4 2 ± 0 3
Trials per Session	* 12 5 ± 0 6	13 0 ± 1 1	13 9 ± 2 0	14 9 ± 1 3	15 1 ± 1 3	16 4 ± 1 2
Repetitive Index	† 11 2 ± 0 9	11 0 ± 1 4	10 0 ± 2 4	13 6 ± 2 5	14 6 ± 2 1	17 0 ± 2 3
Response Latency	‡ 2 5 ± 0 3	2 4 ± 0 3	2 4 ± 0 4	2 2 ± 0 3	2 7 ± 0 4	4 1 ± 0 5

*$p<0.07$
†$p<0.025$
‡$p<0.01$

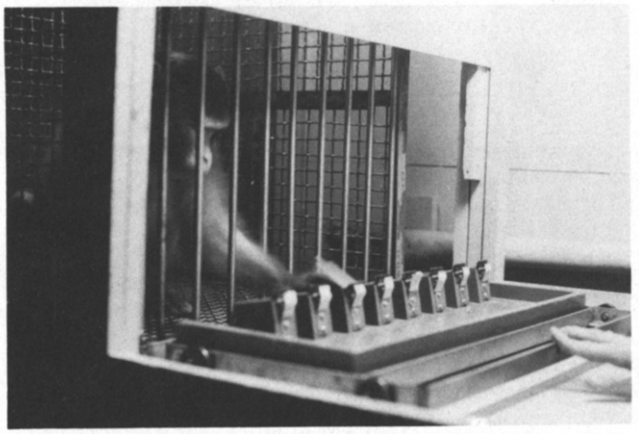

FIG 1 Monkey Z81 performs Hamilton search task in a Wisconsin general testing apparatus

the present testing the monkeys were five years old By this time the blood lead levels of the three lead-treated monkeys had returned to the control level of about 5 μg/dl

Behavioral Testing

HST was run with an apparatus (Fig 1) consisting of 8 gray boxes arranged in a row, from side to side on the stimulus tray of a Wisconsin general testing apparatus (WGTA) Each box had a lid which covered a foodwell A metal stop prevented the door from being opened more than 80 degrees, therefore the lids were self-closing Each box was baited with a chocolate bit at the beginning of the session and not rebaited thereafter Every 20 seconds the tray was pushed to within the monkey's reach and the monkey was allowed to open one box Latency to respond was measured using a hand held stopwatch After the response or 30 seconds without a response (a balk), the tray was withdrawn from the monkey's reach but remained visible for a 20 second intertrial interval Trials were repeated until all of the rewards were taken, 50 trials had elapsed or the monkey balked on three consecutive trials

The data were analyzed for response latency (seconds) and response accuracy The accuracy was assessed in four ways: percent correct, openings-to-repeat, trials/session and repetitive index Because the difficulty of obtaining rewards increased as a session progressed and more of the boxes were emptied, separate percent correct scores were calculated for opening each new box Openings-to-repeat indicated the number of boxes that were opened at the beginning of a session before a box was reopened Trials/session were counted for those sessions in which the monkeys opened all of the boxes Repetitive index was a measure of repetitions of box choices It was calculated for every box opening by taking the inverse of the number of trials that had elapsed since that box had last been opened Novel box openings were given scores of zero All the scores for a session were averaged and multiplied by 100 With this measure the less repetitive the choices, the lower the score The data were evaluated for significance by the analysis of variance For the percent correct measure the ANOVA consisted of a mixed design with lead exposure as a between factor and scopolamine dose and box opening as within measures Analysis of all of the other measures used the same design without box opening as a factor

Scopolamine Dosing

Scopolamine bromide (Sigma Co , St Louis) was injected IM in a volume of 0 1 ml/kg, 30 minutes before the beginning of the HST session Each dose (saline, 1, 3, 5, 15 and 30 μg/kg) was given four different days in a counter-balanced order Injections were given twice a week on Tuesdays and Fridays

RESULTS

None of the five response measures detected significant or marginally significant lead-related effects Four of the measures detected significant effects of scopolamine, while one detected a marginally significant effect. The means and standard errors for each measure at each scopolamine dose are presented in Table 1. With percent correct responses, scopolamine significantly impaired performance, $F(5,15)=4\ 20$, $p<0.025$. Deficits were not seen at the lower doses of 1 or 3 μg/kg, but the higher doses of 5, 15 and 30 μg/kg resulted in scores which were 3.3%, 7.0% and 8 8% lower than the saline score. A similar pattern of results was seen with the scopolamine effect on openings-to-repeat, $F(5,15)=4.64$, $p<0\ 01$ No deficits were seen at the two lowest doses The mean score for the 5 μg/kg dose was only 2 0% lower than saline, while the scores for the 15 and 30 μg/kg doses were both 17.6% lower than the saline score With trials/session each of the increasing doses resulted in a greater impairment, however the main effect of scopolamine was only marginally significant, $F(5,15)=2\ 68$, $p<0.07$ The scopolamine doses caused the following percentage increases over the saline score· 4 0% for 1 μg/kg, 11 2% for 3 μg/kg, 19 2% for 5 μg/kg, 20 8 for 15 μg/kg and 31 2 for 30 μg/kg With the repetitive index measure, the main effect of scopolamine was significant, $F(5,15)=4\ 35$, $p<0\ 025$ No impairments were seen at the 1 and 3 μg/kg doses At the 5, 15 and 30 μg/kg doses, repetitive index scores were increased by 21.4%, 30 4% and 51 8% over the saline score. With response latency, there was also a significant main effect of scopolamine, $F(5,15)=6\ 17$, $p<0\ 005$. Only the 15 and 30 μg/kg doses caused any increased latencies The latency at the 15 μg/kg dose was only slightly raised at 8 0% over saline, while the latency at the 30 μg/kg dose was greatly raised at 64 0% over saline

DISCUSSION

Lead treatment did not significantly affect performance on any of the measures, nor did it alter the scopolamine effect in any interaction On the other hand, scopolamine had an affect on all of the measures. The lower doses of 1 and 3 μg/kg did not cause any changes, except possibly with the trials/session measure. The middle dose of 5 μg/kg caused slight effects on the choice measures, while the higher doses of 15 and 30 μg/kg impaired response accuracy according to all of the measures Repetitive index was the most sensitive of the choice measures at the 5, 15 and 30 μg/kg doses, as indicated by percent decrement from saline scores This may have resulted from a more complete accounting of the data by this measure. Unlike the openings-to-repeat measure, repetitive index took into account response data from the entire session Unlike the percent correct and trials/session measures, it differentially scored incorrect trials Repetitive index was the only choice measure with which every trial contributed a piece of scalar data. With response latency only the highest dose of 30 μg/kg resulted in a substantial effect The dose of 15 mg/kg impaired response accuracy without significantly affecting response latency, demonstrating that the decline in accuracy was not merely a result of increased intertrial intervals

These data show that with a variety of response accuracy measures the HST is sensitive to the cholinergic disruption of scopolamine, as has been seen with other spatial memory tasks such as delayed response in the monkey [1] and 8-arm maze performance in the rat [4] The HST provides a good complement to the delayed response task in measuring spatial memory in monkeys With delayed response different delays can be interposed between the sample and choice portions of the task so that the decay of memory over time can be examined. With HST different numbers of boxes are left baited during different portions of the session so that decay of memory with increasing loads of information can be examined. The examination of the length of memory and the numerical capacity of memory provide assessment of the two principal components of memory function HST may provide an analog for the monkey of the rat's 8-arm maze

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