BEHAVIORAL AND NEURAL BIOLOGY 40, 1–4 (1984)

RAPID COMMUNICATION

Central vs Peripheral Anticholinergic Effects on Repeated Acquisition of Behavioral Chains

AHARON LEVY,[1] TIMOTHY F. ELSMORE, AND STEVEN R. HURSH[2]

Walter Reed Army Institute of Research, Washington, D.C. 20307

Monkeys that were required to repeatedly learn new sequences of responses to obtain food were injected with 0.2 mg/kg of atropine sulfate or methylatropine nitrate. Effects lasted 8 to 12 hr following injection. Both drugs decreased the rate at which the animals worked, but only atropine sulfate increased the number of attempts required to solve the problem and decreased overall accuracy, suggesting a peripheral mode of action for rate-decreasing effects, and a central mode of action for effects of atropine on qualitative aspects of performance.

Over the last decade many studies have established the involvement of the central cholinergic system in memory processes (see Drachman, 1977). Cholinergic blockers such as scopolamine and atropine, were found to disrupt behaviors which depend on learning and memory tasks (e.g., Bartus, Dean, Beer, & Lippa, 1982). However the exact mechanism of this performance impairment is still unknown. Recently, the cholinergic system has also been associated with pathological human conditions affecting various cognitive functions, especially Alzheimer's disease, a fact which has raised the level of interest in cholinergic memory mechanisms.

Animal behavior models have been useful in the study of cholinergic drugs. In a recent study we found that atropine sulfate impaired the performance of mice in a radial arm maze, by increasing both the running

[1] Visiting scientist from the Israel Institute for Biological Research, Ness-Ziona, Israel. Recipient of a Senior National Research Council Fellowship.

[2] The authors thank J. Morrison, P. Kluge, Y. Levy, and D. Hunter for assistance on this project. In conducting the research described in this report, the investigator(s) adhere to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council. The views of the author(s) do not purport to reflect the position of the Department of the Army or the Department of Defense (para 4–3, AR 360–5).

0163-1047/84 $3.00

time and the number of errors (Levy, Kluge, & Elsmore, 1983). In the same situation, the peripheral cholinergic blocker methylatropine nitrate did not affect the number of errors, but slightly increased the running time. The differences between the effects of these two drugs suggest that peripheral mechanisms are responsible for the rate slowing or "quantitative" effects and that central mechanisms are responsible for accuracy or "qualitative" effects.

The present study uses a different animal behavior model to test the generality of the above interpretation. Rhesus monkeys were trained to perform a task requiring them to repeatedly learn new sequences of behavior. The monkeys lived in cages equipped with a horizontal row of three translucent push panels, a food hopper for automatically dispensing 750-mg banana flavored pellets, and a light that could illuminate the hopper. The basic procedure involved a series of trials. Each trial started with all three push panels illuminated. A press on any panel would darken the three panels for 0.5 sec. Four consecutive presses constituted a trial and darkened all three panels. After 5 sec the three panels were again illuminated to signal the next trial. For each test, one specific sequence was designated as correct, e.g., left–center–right–center. Each correct response, e.g., the center key in the second position, was signalled by illuminating the food hopper for 0.5 sec. After the first correct four response sequence, a food pellet was dispensed and the hopper was illuminated for 11.5 sec. Subsequent correct sequences illuminated the hopper and provided food with a probability of .667. Typically, subjects spent the first 5 to 10 trials trying a variety of sequences. The illumination of the hopper after each correct response guided their choices until they finally emitted the entire correct sequence. Each test lasted for a maximum of 25 min or until 12 food pellets were earned. Three tests constituted a session. Six sessions were presented each day every 4 hr around the clock starting at 0600 hr. The data were analyzed in terms of the average performance per session. A number of similar procedures have been demonstrated to be sensitive to the effects of a wide variety of pharmacological agents (e.g., Thompson & Moerschbaecher 1979).

Four different trained monkeys were used in this study. Once a week, 30 min before the 1400-hr session, the monkeys were injected intramuscularly with either 0.2 mg/kg of atropine sulfate or 0.2 mg/kg of methylatropine nitrate (2 mg/ml solution in saline). Both drugs have a similar molecular weight so the molar dose was also similar (0.59 and 0.54 umole/kg, respectively). Each animal received three injections of both drugs; data were pooled across injections for analysis. Control data were taken from one saline and one noninjection day, since saline injections were found to have no effect.

Table 1 presents the data for three different measures of the monkeys' performance. Because of the repeated observations and unequal group

TABLE 1
Averages (± SEM) for Three Different Measures of the Monkeys' Performance[a]

	Hours following injection (time of day)				
	0.5 (1400)	4.5 (1800)	8.5 (2200)	12.5 (0200)	16.5 (0600)
Trials to first correct sequence					
Controls	7.5 ± 0.6	7.2 ± 0.6	7.8 ± 1.2	9.1 ± 1.2	9.2 ± 1.1
Atropine	18.6 ± 4.8**,[b]	21.7 ± 3.4**,[b]	16.9 ± 2.4**,[b]	11.3 ± 1.2[b]	11.8 ± 1.9
Methyl-atropine	9.7 ± 1.5	9.5 ± 1.4	8.0 ± 0.9	7.1 ± 0.7	8.3 ± 0.9
% correct					
Controls	72.4 ± 3.5	73.9 ± 3.7	74.6 ± 3.9	75.8 ± 4.6	71.0 ± 5.3
Atropine	42.4 ± 8.6**,[b]	30.0 ± 4.6**,[b]	51.6 ± 4.2**,[b]	58.5 ± 2.9**,[b]	63.9 ± 4.9
Methyl-atropine	43.5 ± 3.8**	66.0 ± 3.4	72.2 ± 3.4	78.5 ± 4.0	73.1 ± 5.9
Resp/min					
Controls	45.9 ± 4.5	45.8 ± 3.7	43.3 ± 3.5	43.8 ± 3.9	48.3 ± 5.4
Atropine	20.2 ± 5.6**	21.0 ± 4.4**	29.1 ± 5.5*	32.3 ± 6.1	38.6 ± 3.8
Methyl-atropine	12.2 ± 2.1**	25.9 ± 2.6**	27.3 ± 3.6*	28.1 ± 4.8*	37.9 ± 5.6

[a] Controls, $n=8$; drug $n=12$.
[b] One monkey did not perform, therefore $n=9$.
* $p < 0.05$, as compared to controls; Scheffé test.
** $p < 0.01$.

sizes, the conservative Scheffé test was used for assessment of statistical significance. The first three rows represent the average number of trials preceding the first correct sequence. On the average, with no drug treatment, the monkeys would require eight trials to make the first correct sequence. Following methylatropine this measure was not significantly different from control. However, following atropine sulfate the monkeys required many more trials until their first correct sequence, recovering gradually to control level by 12.5 hr following injection. A similar pattern was observed for percentage correct responses following the first correct sequence, shown in the second set of three rows. This atropine effect took even longer to recover (16.5 hr) than the effect on trials to first correct sequence. Methylatropine had no effect except in the first session following injection. This effect may be due to the extremely low response rate in this session. The last three rows in Table 1 show that response rate was markedly decreased by both drugs. In fact, methylatropine seemed to be somewhat more effective and it took the monkeys longer to recover following its injection (16.5 compared to 12.5 hr following atropine).

These results are similar to those of McDonough and Penetar (1983) who also showed an increase in errors and a decrease in response rate on both a repeated acquisition task and a short term memory task following 0.14 mg/kg of atropine sulfate. The fact that methylatropine nitrate did not affect qualitative aspects of performance, but did affect the rate of performance is reminiscent of our previous findings with mice (cf. Levy et al., 1983). The striking similarity of the present results with primates performing a highly complex task to those of Levy et al. using mice in a radial maze greatly strengthens the contention that the effects of atropine upon quantitative aspects of performance such as response rate are peripherally mediated, while the effects of atropine sulfate upon more qualitative aspects of performance (i.e., "cognitive processes") are centrally mediated.

REFERENCES

Bartus, R. T., Dean, R. L., Beer, B., & Lippa, A. S. (1982). The cholinergic hypothesis of geriatric memory disfunction. *Science,* **217,** 408–417.

Drachman, D. A. (1977). Memory and cognitive function in man: Does the cholinergic system have a specific role? *Neurology,* **27,** 783–790.

Levy, A., Kluge, P. B., & Elsmore, T. F. (1983). Radial arm maze performance of mice: Acquisition and atropine effects. *Behavioral and Neural Biology,* **39,** 229–240.

McDonough, J., & Penetar, D. M. (1983). The effects of cholinergic blocking agents and anticholinesterase compounds on memory, learning, and performance. *In* M. Y. Spiegelstein & A. Levy (Eds.), *Behavioral Models and the Analysis of Drug Action* (pp. 155–174). Amsterdam: Elsevier.

Thompson, D. M., & Moerschbaecher, J. M. (1979). Drug effects on repeated acquisition. *In* T. Thompson & P. B. Dews (Eds.), *Advances in Behavioral Pharmacology* (Vol. 2, pp. 229–259). New York: Academic Press.