Comparative learning impairment and amnesia by scopolamine, phencyclidine, and ketamine*

S. D. GLICK† and B. ZIMMERBERG

Albert Einstein College of Medicine, New York, N.Y. 10461

Scopolamine, phencyclidine, and ketamine were each administered to mice before or immediately after training of a passive avoidance response. Retention was measured 24 h later. All three drugs impaired retention when administered before training. Only scopolamine impaired retention when administered after training. The effect of posttraining administration of scopolamine was found to diminish as the training-injection interval increased.

Numerous studies (e.g., Deutsch, 1969) have emphasized the importance of cholinergic processes in memory. However, there has been little attempt to evaluate the relative role of cholinergic processes in the registration and storage aspects of memory. Operationally, such a distinction is contingent upon demonstrating different effects of experimental treatments administered prior to training (influencing both registration and storage) and after training (influencing only storage). Bohdanecky & Jarvik (1967) reported impairment of passive avoidance retention in mice when scopolamine (1 mg/kg) was administered prior to training; no retention deficit was found when the drug was administered immediately after training. However, Pazzagli & Pepeu (1964) reported complete impairment of avoidance retention in rats when scopolamine (10 mg/kg) was administered after training. One of the most striking differences between the two studies, aside from training procedures and rodent species, was a difference in dose. Pazzagli and Pepeu used 10 times the dose used by Bohdanecky and Jarvik. The following experiments were conducted in part to determine the relative dose sensitivity of pretraining and posttraining administrations of scopolamine. In addition, the effects of scopolamine were compared with two other drugs, phencyclidine and ketamine, recently suggested to have amnesic properties

(Corssen, Groves, Gomez, & Allen, 1969).

EXPERIMENT 1

Subjects

The Ss were naive female CF1 mice, 8-10 weeks old. They were housed 8-10 per cage and were provided with ad lib access to food and water.

Apparatus

The apparatus was similar to that described in detail by Jarvik & Kopp (1967). Briefly, the trough-shaped step-through apparatus consisted of a small and a large compartment, with a small (3.2 cm high, 2.7 cm wide) opening connecting the two compartments. The small compartment was transparent and was lighted by a Tensor light. The large compartment was opaque and was kept dark. Two parallel steel plates formed the floor of the small compartment (8 x 3.2 cm). The floor of the large compartment (18 x 3.2 cm) consisted of two pairs of plates bent up to form the sidewalls. Adjacent plates were 2-3 mm apart. Both compartments were covered with Plexiglas lids. Solid-state logic and timing circuits were connected to the three pairs of plates so that recording of latencies was automated and shock contingencies were programmed. When a mouse stood in the apparatus, it always bridged a pair of plates.

Training Procedure

A mouse was placed into the small compartment of the step-through apparatus facing away from the large compartment. After the mouse bridged the front plates of the small compartment, a timer was started. When the mouse walked into the large compartment and bridged the rear plates, the timer stopped and the mouse received a 350-microA footshock across both pairs of plates. This conditioning trial was terminated when the mouse escaped back to the small lighted compartment from which it was removed. All retest trials were

conducted with the same procedure (except without footshock) and always occurred 24 h following the conditioning trial. Mice were tested between 10:00 a.m. and 2:00 p.m. during the light phase of a 12 h-12 h light-dark cycle.

Drug Administration

Various doses of scopolamine hydrobromide (1.0-20.0 mg/kg), phencyclidine hydrochloride (1.0-20.0 mg/kg), and ketamine chloride (1.0-40.0 mg/kg) were administered intraperitoneally either 12 min prior to training or immediately after training. Different groups of mice were administered physiological saline on every occasion that corresponding groups were administered a drug. There were 20-30 mice in each drugged or saline-treated group. All groups at the same dose level were tested concurrently.

Results

The Wilcoxon rank sum test for unpaired replicates (1964) was used to compare the retest latencies of drugged and saline-treated groups. Table 1 shows the effects of pretraining administration of the three drugs on retest performance. Drug-induced impairment of passive avoidance learning increased with increasing doses of all three drugs. However, there were differences in potency. Significant impairment by scopolamine occurred with all doses ($p < .05$ for 1 mg/kg; $p < .001$ for 20 mg/kg). Significant impairment by phencyclidine occurred with all doses above 1 mg/kg ($p < .05$ for 5 mg/kg; $p < .001$ for 20 mg/kg). Significant impairment by ketamine occurred with doses equal to or greater than 10 mg/kg ($p < .05$ for 10 mg/kg; $p < .01$ for 40 mg/kg).

Table 2 shows the effects of immediate posttraining administration of the three drugs on retest performance. In contrast to the pretraining results, only scopolamine impaired retest performance when administered after training. Furthermore, the potency of posttraining scopolamine was much less than that of pretraining scopolamine.¹ Significant impairment by posttraining scopolamine occurred with doses equal to or greater than 10 mg/kg ($p < .05$ for 10 mg/kg; $p < .05$ for 20 mg/kg).

EXPERIMENT 2

Subjects, Apparatus, and Training Procedure

The identical conditions and procedures described in Experiment 1 were also employed here.

Drug Administration

Doses of 10 mg/kg of scopolamine hydrobromide were administered intraperitoneally at one of the following times after training:

*This research was supported by a USPHS grant, No. NIMH-05319, to M. E. Jarvik and by a postdoctoral fellowship from the National Institutes of Health, No. NIH5T5 GM 1674, to S. D. Glick. The authors wish to thank M. E. Jarvik for comments and discussion and Arnault Guerrier for indispensable technical assistance.

†Now at the Department of Pharmacology, Mount Sinai School of Medicine, New York, N.Y. 10029.

Table 1
Retention Medians (Seconds) as a Function of Dose of Drug Administered Prior to Training

Dose (mg/kg)	Scopolamine	Phencyclidine	Ketamine	Saline
1.0	277.7	360.5	600+	600+
5.0	202.4	132.3	520.1	589.2
10	96.7	84.3	302.8	600+
20	58.4	34.3	94.0	568.4
40			39.8	600+

Table 2
Retention Medians (Seconds) as a Function of Dose of Drug Administered Immediately After Training

Dose (mg/kg)	Scopolamine	Phencyclidine	Ketamine	Saline
1.0	600+	600+	600+	596.4
5.0	420.0	560.6	600+	600+
10	301.4	600+	540.4	586.6
20	266.6	595.0	560.2	600+
40			538.2	592.2

Immediately, 1 h, and 6 h. Different groups of mice were administered physiological saline on every occasion that corresponding groups were administered the drug. There were 15-20 mice in each druged or saline-treated group.

Table 3
Impairment of Retention Medians (Seconds) by Scopolamine as a Function of the Training-Injection Interval

Time After Training	Scopolamine	Saline
Immediate	310.3	600+
1 H	380.6	600+
6 H	597.3	600+

Results

Table 3 shows the effect of posttraining administration of scopolamine on retest performance as a function of the training-injection interval. Significant impairment ($p < .05$) by scopolamine occurred when the drug was administered immediately and 1 h after training, but not when administered 6 h after training ($p > .1$).

DISCUSSION

The results of this study strongly indicate that scopolamine influences both registration and storage aspects of memory. Since pretraining injections could influence both registration and storage, whereas posttraining injections could influence only the latter, it is not surprising that a difference in potency was observed between the two types of injections.

This difference can readily account for the discrepancy between previous studies (Pazzagli & Pepeu, 1964; Bohdanecky & Jarvik, 1967).

The time course of the posttraining injection effect is of considerable interest in that scopolamine still induced amnesia when administered as long as 1 h after training. This amnesic gradient closely resembles that produced by ECS under very similar experimental conditions (Kopp, Bohdanecky, & Jarvik, 1966). The results of recent studies have suggested that ECS effects are mediated by changes at cholinergic synapses (Adams, Hoblit, & Sutker, 1969; Thompson & Neely, 1970; Weiner, 1970). The present data are certainly consistent with this possibility.

The phencyclidine and ketamine data emphasize the specificity of the posttraining scopolamine effect. Phencyclidine and ketamine are both cataleptic agents whose effects may be mediated by adrenergic mechanisms (Chen, Ensor, & Bohner, 1966). Neither phencyclidine nor ketamine impaired retest performance when administered after training, even though both drugs produced a pretraining effect equivalent to that produced by scopolamine.

REFERENCES

- ADAMS, H. E., HOBLIT, P. R., & SUTKER, P. B. Electroconvulsive shock, brain acetylcholinesterase activity and memory. *Physiology & Behavior*, 1969, 4, 113-116.
BOHDANECKY, Z., & JARVIK, M. E.

- Impairment of one-trial passive avoidance learning in mice by scopolamine, scopolamine methylbromide and physostigmine. *International Journal of Neuropharmacology*, 1967, 6, 217-222.
CHEN, G., ENSOR, C. R., & POHNER, B. The neuropharmacology of 2-(α -chlorophenyl)-2-methylaminocyclohexanone hydrochloride. *Journal of Pharmacology & Experimental Therapeutics*, 1966, 152, 332-339.
CORSEN, G., GROVES, E. H., GOMEZ, S., & ALLEN, R. J. Ketamine: Its place in anesthesia for neurosurgical diagnostic procedures. *Anesthesia & Analgesia*, 1969, 48, 181-188.
DEUTSCH, J. A. The physiological basis of memory. In *Annual review of psychology*, Vol. 20. Palo Alto: Annual Reviews, 1969, Pp. 85-104.
JARVIK, M. E., & KOPP, R. An improved one trial passive avoidance learning situation. *Psychological Reports*, 1967, 21, 221-224.
KOPP, R., BOHDANECKY, Z., & JARVIK, M. E. Long temporal gradient of retrograde amnesia for a well-discriminated stimulus. *Science*, 1966, 153, 1547-1549.
PAZZAGLI, A., & PEPEU, G. Amnesic properties of scopolamine and brain acetylcholine in the rat. *International Journal of Neuropharmacology*, 1964, 4, 291-299.
THOMPSON, C. I., & NEELY, J. E. Dissociated learning in rats produced by electroconvulsive shock. *Physiology & Behavior*, 1970, 5, 783-786.
WEINER, N. I. Electroconvulsive shock induced impairment and enhancement of a learned escape response. *Physiology & Behavior*, 1970, 5, 971-974.
WILCOXON, R., & WILCOX, R. A. *Some rapid approximate statistical procedures*. Pearl River, N.Y.: Lederle Laboratories, 1964.

NOTE

1. Note that had 300 sec instead of 600 sec been used as the cutoff, no significant effect of posttraining scopolamine would have been found.