Pharmacology Biochemistry & Behavior, Vol. 3, pp. 1043–1050.

Influence of Central Cholinergic Pathways on Performance on Free-Operant Avoidance and DRL Schedules[1]

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(Received 24 March 1975)

KELSEY, J. E. AND S. P. GROSSMAN. *Influence of central cholinergic pathways on performance on free-operant avoidance and DRL schedules.* PHARMAC. BIOCHEM. BEHAV. 3(6) 1043–1050, 1975. – Lesions in the medial septum, as well as systemic injections of the muscarinic cholinergic blocker, scopolamine, increased responding maintained by free-operant avoidance or DRL contingencies. Systemic injections of the anticholinesterase, eserine, suppressed responding in both paradigms. The medial septal lesions eliminated the effects of these cholinergic drugs in the DRL paradigm but did not reduce the effects of these drugs on free-operant avoidance. These results indicate that cholinergic drugs may affect behavior in the DRL paradigm primarily by acting on muscarinic cholinergic neurons that pass through the septum but affect free-operant avoidance mainly by acting on different cholinergic pathways that do not pass through the medial septum.

Cholinergic pathways DRL Eserine Free-operant avoidance Scopolamine Septum

MANY experimental findings indicate that central cholinergic pathways are involved in the mediation of avoidance behavior and the inhibitory effects of nonreward. Blockade of the muscarinic components of these pathways by systemic injections of muscarinic receptor blockers such as scopolamine or atropine facilitates two-way active avoidance acquisition, retards one-way active and passive avoidance, and disinhibits or increases the rate of unrewarded responding on fixed interval (FI) and differential reinforcement of low rate (DRL) schedules as well as during habituation and extinction [2].

Remarkably similar behavioral effects are produced by damage to the septal area of the limbic system [4]. This suggests that many of the behavioral effects of systemic injections of cholinergic blockers (and of septal lesions) may be mediated by the disruption of muscarinic cholinergic pathways which originate in, terminate in, or pass through the septal area. That the effects of these treatments on active avoidance acquisition may be mediated by the disruption of a cholinergic pathway that synapses in the septum, is suggested by our earlier observation that intraseptal injections of scopolamine or atropine in both rats and cats reproduce the effects of systemic injections of scopolamine and septal lesions in several avoidance paradigms [6,9].

The present investigation was undertaken to further examine the behavioral functions of cholinergic components of the septum by observing the effects of systemic injections of scopolamine and the anticholinesterase, eserine, on responding by normal rats and rats with septal lesions in two paradigms known to be sensitive to the disinhibitory effects of septal lesions – a modified DRL schedule and a free-operant avoidance schedule [10]. The effects of intraseptal injections of these drugs were also observed in these paradigms.

GENERAL METHOD

Animals

Experimentally naive, male Sprague-Dawley rats weighing 375–425 g at the beginning of experimentation were used. They were housed in a continuously lighted, air conditioned room and had ad lib access to food and water, except where noted.

[1] This research was supported by U.S. Public Health Service Grant MH-10130 to S. P. Grossman.
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Surgical Procedure

To reduce respiratory difficulties, the rats were given intraperitoneal (IP) injections of 0.20 cc of an atropine methyl nitrate solution (50 mg/cc) 10 min before IP injections of Nembutal (50 mg/kg). Stainless-steel double-walled cannulas, consisting of a 23 ga outer guide and a 27 ga inner cannula as described by Grossman [5] were stereotaxically implanted into the septum of some rats. Stereotaxic lesions were made in the septum of other rats by passing 2 mA of anodal current for 20 sec between an indifferent electrode attached to the skin opened by the scalp incision and a stainless-steel No. 1 insect pin that was completely insulated except for the flattened cross-section of the tip. The electrodes and cannulas were inserted at an 11° lateral angle to avoid damage to the midsagittal sinus. Control operations were performed in other rats by following a similar surgical procedure except that the electrode was not lowered. All operations occurred at least 2 weeks prior to behavioral testing.

Injection Procedure

Systemic injections. A muscarinic cholinergic blocker, scopolamine hydrobromide (0.1 and 0.5 mg/kg), and an anticholinesterase, eserine sulfate (0.025 and 0.1 mg/kg) were used. Both drugs were dissolved in isotonic saline and were injected subcutaneously (SC) along the midline of the back in a volume of 1.0 ml/kg. After at least 14 sessions of acquisition training, all rats received daily SC injections of isotonic saline 30 min before each 30 min session. On the day after performance had stablized (2 consecutive saline sessions in which response and shock or reinforcement rate did not vary more than 10 percent), each rat was injected with one of the drugs and was tested 30 min later. Saline injections were given prior to each subsequent session until performance again stabilized at which time each rat received an injection of another drug or dosage. This procedure was continued until most rats received each dosage of each drug at least once. The sequence of drug administration differed for each rat.

Intraseptal injections. The drugs used were crystalline forms of the cholinergic agonist, arecoline hydrobromide (5.0–10.0 μg); the anticholinesterase, eserine sulfate (2.0–8.0 μg); and the muscarinic cholinergic blocker, scopolamine hydrobromide (5.0–10.0 μg). The procedure was the same as that used for systemic injections except for the following changes. To administer a drug, the inner cannula was removed, cleaned, tamped into a uniform layer of the crystalline drug a specified number of times and then replaced into the outer cannula 5 to 7 min prior to each 20 min session. Extensive experience with this procedure in our laboratory has shown that it permits an estimation of dosage within the range indicated above. Prior to control sessions, the inner cannula was removed and replaced empty.

Histology

Following completion of behavioral testing, the rats with lesions or cannulas were killed with an overdose of Nembutal and perfused intracardially with isotonic saline followed by a 10 percent formol-saline solution. Every fourth 50 μ thick frozen section in the area of the lesion or cannula tip was stained with cresyl violet.

Statistical Analyses

The data from the systemic injection tests were analyzed according to a group (Controls and Septals) by drug (Pre-Drug and Drug) repeated measures ANOVA design [16]. The data from the intraseptal injection tests were analyzed by means of correlated *t*-tests. The Drug : Pre-Drug comparisons for both types of injections consisted of a comparison of the data obtained during each drug session with the average of the data obtained during the two control sessions occurring immediately prior to each drug session. The raw data for rats receiving more than one injection of a given dosage were obtained by calculating the average performance of that rat for that dosage.

EXPERIMENT 1: DIFFERENTIAL REINFORCEMENT OF LOW RATES (DRL)

METHOD

Animals

Nine rats received lesions of the medial septum and 9 rats received sham operations. Cannulas were implanted into the medial septum of 14 rats. All rats were housed individually and were maintained at 85 percent of their postoperative body weight by restricted feeding throughout the experiment. Water was available ad lib.

Apparatus

An opaque white Plexiglas alley, 91.4 × 12.7 × 27.9 cm with 30.5 × 15.2 cm goal boxes at each end was used. The floor of the apparatus was made of stainless-steel rods, 0.47 cm in dia. placed 1.9 cm apart. The back panel of each goal box could be illuminated from behind. A circular Plexiglas combination of lever-food receptacle, 4.4 cm in dia. with a 0.64 cm rim was mounted on a subminiature switch in the center of the back panel of each goal box about 2.5 cm above the grid floor. A small Plexiglas tube led vertically from a feeder mounted above the back panel to the lever-food receptacle. Photocells and infrared light sources were mounted in the alley, 3.8 cm above the grid floor and 18.4 cm from the entrance of each goal box. Depressing the lever-food receptacle activated automatic recording and programming devices which scheduled reinforcements and recorded the frequency of lever presses. To prevent accidental lever presses made while the rat was removing the pellets from the food receptacle from being counted, responses occurring more frequently than 1/sec were not recorded and had no effect.

Procedure

Each day, the rat was placed into the goal box which was illuminated by lamps behind the back panel. When the rat pressed the lever-food receptacle in that goal box, 2 Noyes food pellets (45 mg each) were dropped into the receptacle and the lamps were turned off. To obtain the next reinforcement, the rat was required to press the lever-food receptacle in the goal box at the opposite end of the alley. If the rat continued to press the lever in the dark goal box in which it was just rewarded, no further reinforcements were delivered. Each such response reset the 30 sec timer which timed the delay before a response to the lever in the opposite goal box could be reinforced.

When the rat left the dark goal box in which it had just

been reinforced and crossed the first photocell in the alley, the goal box at the opposite end of the alley was illuminated. When this occurred, subsequent responses in the previously correct goal box (still dark) were not recorded and did not reset the delay timer. If the rat pressed the lever-food receptacle in the lighted goal box before 30 sec had elapsed since the last recorded response, reinforcement was not delivered, the delay-timer was reset and the light remained on. Each such response was recorded as an anticipatory error. The first lever press in the illuminated goal box which occurred 30 sec or more after the last recorded response resulted in the delivery of 2 Noyes pellets, turned off the lights and also reset the delay timer. The rat now had to run to the opposite goal box to obtain the next reinforcement, etc. The supplementary food necessary to maintain body weight at 85 percent was given in the home cage 20 to 30 min after each session.

When performance on this schedule had stabilized, the effects of systemic injections were studied on the sham-operated rats and rats with septal lesions and the effects of intraseptal injections were studied on the rats with cannulas as described in the General Method.

RESULTS

Histological

Microscopic analysis indicated that the septal lesions extended from AP = 9.0 to AP = 7.0 with the maximal damage occurring at AP = 7.9 (using coordinates from the Pellegrino and Cushman [12] atlas of the rat brain). These lesions destroyed most of the medial septal nucleus and produced slight asymmetrical damage to the lateral septal nuclei (Fig. 1).

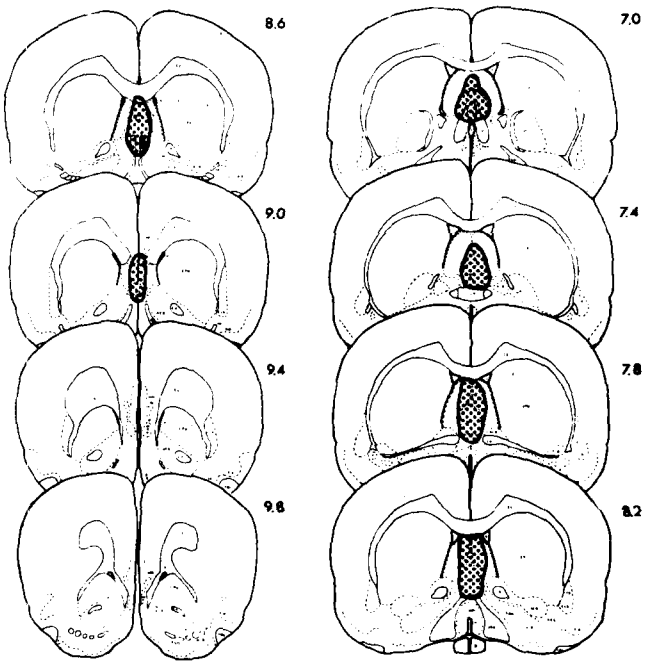

FIG. 1. Reconstruction of the septal lesions.

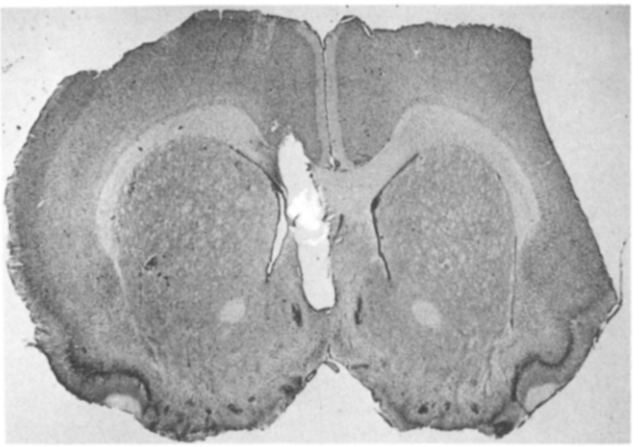

FIG. 2. Photomicrograph of a representative cannula placement in the septum.

The cannulas were placed so that their tips rested in the anterior medial septal nucleus at the dorsal aspect of the diagonal band of Broca. Most tips were located at AP = 8.6 (range: 8.3 to 9.0), H = −0.4 (range: +0.3 to −0.8) and L = 0.0 (range: 0.7 to 0.0) (Fig. 2).

Effects of Medial Septal Lesions

Rats with medial septal lesions performed very inefficiently on the DRL schedule. They emitted more responses ($p<0.05$), made more anticipatory errors/reinforcement ($p<0.01$) and received fewer reinforcements ($p<0.001$) than sham-operated controls (Table 1). This pattern of effects replicates in detail our previous observation of the effects of septal lesions in this situation [10].

Systemic Drug Effects

Injections of 0.1 mg/kg or 0.5 mg/kg of scopolamine also reliably increased the rate of responding, increased the number of anticipatory errors/reinforcement and decreased the rate of reinforcement of the sham-operated controls (Table 1). Injections of both 0.025 mg/kg or 0.1 mg/kg of eserine reliably decreased the response rate of the sham-operated control rats and the larger dose also decreased the number of reinforcements received (Table 1).

These drugs did not produce comparable effects on the behavior of rats with septal lesions. Neither dose of scopolamine nor of eserine affected rate of responding or the frequency of anticipatory errors, and only the smaller dose of scopolamine decreased their rate of reinforcement (Table 1).

Intraseptal Drug Effects

Injections of eserine (4.0–8.0 μg) into the medial septum increased the rate of reinforcement, but intraseptal injections of arecoline and scopolamine did not reliably modify responding on this schedule (Table 2).

DISCUSSION

Both medial septal lesions and systemic injections of scopolamine disinhibited responding on this modified DRL schedule, as expected, by increasing the rate of responding, and consequently, reducing the rate of reinforcement. The

TABLE 1

EFFECTS OF SYSTEMIC INJECTIONS ON DRL PERFORMANCE

	Controls				Septals			
Drug	N	Mean Responses	Mean Reinforcements	Mean Anticipatory Errors/ Reinforcement	N	Mean Responses	Mean Reinforcements	Mean Anticipatory Errors/ Reinforcement
Pre-Drug	9	91.3	37.4	0.76	7	117.1	20.8	6.70
Scopolamine (0.1 mg/kg)		111.6*	20.1‡	2.46‡		104.9	13.0*	6.85
Pre-Drug	7	91.1	34.4	0.86	6	115.0	17.8	6.19
Scopolamine (0.5 mg/kg)		133.6†	19.7‡	3.19‡		110.8	16.1	3.93
Pre-Drug	9	88.9	37.2	0.76	7	119.3	16.8	8.60
Eserine (0.025 mg/kg)		85.4*	36.6	0.73		118.9	15.6	8.76
Pre-Drug	7	87.3	38.0	0.68	6	108.8	21.8	4.31
Eserine (0.1 mg/kg)		64.1*	29.2*	0.44		104.8	18.6	4.02

*$p<0.05$ †$p<0.01$ ‡$p<0.001$

finding that the effects of systemically injected cholinergic drugs were eliminated by these lesions is consistent with the suggestion that some of the disinhibitory effects of septal lesions and of systemic scopolamine are mediated by the disruption of a muscarinic cholinergic system that originates in, synapses in, or passes through the medial septum. The observation that intraseptal injections of cholinergic drugs did not consistently modify behavior on this schedule indicates that cholinergic fibers which terminate in the medial septum may not be important in mediating this behavior.

It is unlikely that the disinhibitory effects of septal lesions and scopolamine on this schedule can be attributed to an enhancement of the reinforcing or incentive properties of the food pellets. Although similar septal lesions can enhance the consumption of sweetened milk solutions [8], knife cuts which severe the ventral connections of the septum also enhance sweet milk intake but do not disinhibit behavior in this DRL paradigm [13]. Moreover, both systemic and intraseptal injections of scopolamine significantly reduce pellet intake under conditions similar to those of this experiment ([8]; Kelsey, unpublished observations) and, in the present experiment, frequently eliminated the consumption of the pellets the rats responded so rapidly to obtain. Our results are thus consistent with the hypothesis that many of the disinhibitory effects of septal lesions and scopolamine reflect a reduced ability to withhold responses that are normally under the inhibitory control of nonreward [3].

EXPERIMENT 2: SIGNALED AND UNSIGNALED FREE-OPERANT AVOIDANCE

METHOD

Animals

Six rats with medial septal lesions and 8 sham-operated controls were housed two to a cage throughout this experiment. Twenty rats were chronically implanted in the septum with a cannula and were housed individually.

Apparatus

Two sound-isolated shuttle-boxes, 53.3 × 20.3 × 33 cm were used. They were made of clear Plexiglas except for the 2 end panels made of black Plexiglas. A black Plexiglas panel with a 10.2 × 7.6 cm hole in the center that was flush with the floor divided each box into two compartments of equal size. The floor was made of 0.64 cm dia. stainless-steel rods separated by 1.9 cm. A 6 W light bulb was mounted in each of two small enclosures 7.6 cm above a 7.6 × 12.7 cm opening in the ceiling located so that each

TABLE 2

EFFECTS OF INTRASEPTAL INJECTIONS ON DRL PERFORMANCE

Drug	N	Mean Responses	Mean Reinforcements	Mean Anticipatory Errors/ Reinforcement
Pre-Drug	9	71.0	16.3	2.86
Scopolamine (5.0–10.0 μg)		67.2	14.4	2.07
Pre-Drug	6	59.8	20.6	1.53
Eserine (2.0–6.0 μg)		61.0	21.2	1.55
Pre-Drug	12	69.4	15.6	3.16
Eserine (4.0–8.0 μg)		67.7	17.1*	2.43
Pre-Drug	5	65.7	18.2	2.03
Arecoline (5.0–10.0 μg)		64.1	17.7	1.70

*$p<0.05$

bulb illuminated only one compartment. Photocells and infrared light sources were mounted in the center of each wall and 10.2 cm to either side, 5.1 cm above the floor. Programming and recording were controlled by automated equipment. The grid shock was obtained from constant-current sources [1] and was pulsed at the rate of 1/sec with an on time of 0.5 sec.

Procedure

All rats were initially trained to avoid and escape shock in a modified, signaled free-operant avoidance paradigm in which each response postponed onset of the next shock for 28 sec (R-S interval equals 28 sec). The avoidance (and escape) response required was crossing from one compartment of the shuttle-box to the other. Seven sec prior to shock onset, a light was turned on in the compartment occupied by the rat. If the rat failed to avoid and the shock was delivered, the rat was required to make an escape response which terminated both the light and shock. The next shock was scheduled to occur in 28 sec unless the rat made a response at any time within that response-shock interval. Each such avoidance response also initiated a shock-free response-shock interval of 28 sec, and, if made during the 7 sec interval between light onset and shock onset, resulted in immediate termination of the light. When performance on this schedule had stabilized, the effects of systemic drug injections were examined on the performance of the sham-operated control rats and rats with septal lesions.

The warning light which signaled shock onset was then deactivated so that the only predictor of shock was the time elapsed since the last response. When performance on this schedule had stabilized, the effects of systemic injections of 0.025 mg/kg of eserine or 0.1 mg/kg of scopolamine were examined in both sham-operated control rats and rats with septal lesions. The effects of intraseptal injections of cholinergic compounds were also examined at this time.

RESULTS

Histological

The septal lesions and cannula implants were similar to those of Experiment 1 (Figs. 1 and 2).

Effects of Medial Septal Lesions

Rats with medial septal lesions avoided significantly more shocks ($p<0.001$) than sham-operated controls in both the signaled and the unsignaled paradigms by responding more frequently ($p<0.001$; Tables 3 and 4). In the signaled paradigm, the rats with septal lesions also avoided more reliably in response to the warning signal ($p<0.001$; Table 3). Omission of the warning signal increased the difference between the behavior of the operated and

TABLE 3

EFFECTS OF SYSTEMIC INJECTIONS ON SIGNALED FREE-OPERANT AVOIDANCE PERFORMANCE

	Controls				Septals			
Drug	N	Mean Responses	Mean CS Occurrences	Mean Shocks	N	Mean Responses	Mean CS Occurrences	Mean Shocks
Pre-Drug	7	83.8	50.9	14.6	6	101.5	40.3	0.8
Scopolamine (0.1 mg/kg)		119.0‡	31.0*	8.1		146.9‡	21.5*	0.7
Pre-Drug	7	84.3	51.2	15.7	6	118.4	25.8	2.2
Scopolamine (0.5 mg/kg)		125.5†	29.0†	13.2		161.9†	17.8	2.1
Pre-Drug	7	76.0	57.4	20.8	6	99.3	41.7	0.9
Eserine (0.025 mg/kg)		73.3	55.5	29.2‡		97.2	43.4	1.7
Pre-Drug	7	77.4	53.8	22.0	5	105.8	42.4	0.6
Eserine (0.1 mg/kg)		64.9*	56.4	43.2†		76.8*	59.4‡	22.4†

*$p<0.05$ †$p<0.01$ ‡$p<0.001$

sham-operated animals. The sham-operated rats did not compensate for the absence of the warning signal by increasing their rate of responding and consequently received about twice as many shocks as in the signaled paradigm. The rats with medial septal lesions, on the other hand, avoided as many shocks as in the signaled paradigm by greatly increasing the rate of responses emitted within 7 to 14 sec of the preceding response.

Systemic Drug Effects

Scopolamine significantly increased the rate of avoidance responding of the sham-operated control rats in both the signaled and unsignaled paradigms and decreased the number of shocks received in the unsignaled paradigm (Tables 3 and 4). The larger dose (0.1 mg/kg) of eserine reliably decreased the rate of responding of the control rats in the signaled paradigm (Table 3). Both doses of eserine reliably increased the number of shocks received in both paradigms (Tables 3 and 4).

Rats with septal lesions reacted to the systemic drug injections in much the same way as the control animals. Scopolamine increased the rate of responding in these rats, and eserine decreased the rate of responding and increased the number of shocks received in both paradigms (Tables 3 and 4).

Intraseptal Drug Effects

Intraseptal injections of cholinergic drugs tended to produce effects on responding in the unsignaled avoidance paradigm that were similar to, although smaller than, the effects seen after systemic injections (Table 5).

DISCUSSION

Both medial septal lesions and systemic injections of scopolamine improved avoidance behavior on these free-operant avoidance schedules, as expected, by greatly increasing the rate of responding. The finding that intraseptal injections of the anticholinesterase, eserine, and of the cholinomimetic, arecoline, depressed avoidance in these paradigms supports our earlier suggestion that some of the effects of septal lesions and systemically administered cholinergic drugs on avoidance performance may be mediated by their effects on a cholinergic system which appears to have muscarinic synapses in the septum [6,9]. However, our observation that medial septal lesions did not significantly reduce the effects of systemically administered cholinergic compounds on responding in both free-operant paradigms indicates that these drugs primarily affect avoidance behavior by acting on cholinergic neurons that do not pass through the medial septum.

GENERAL DISCUSSION

The principal finding of these experiments is that medial septal lesions eliminated both the rate-increasing or disinhibitory effects of systemic injections of scopolamine and

TABLE 4

EFFECTS OF SYSTEMIC INJECTIONS ON UNSIGNALED FREE-OPERANT AVOIDANCE PERFORMANCE

	Controls			Septals		
	N	Mean Responses	Mean Shocks	N	Mean Responses	Mean Shocks
Pre-Drug	7	74.5	36.3	5	135.0	1.6
Scopolamine (0.1 mg/kg)		112.7†	13.2†		174.8†	0.8
Pre-Drug	8	81.6	31.6	5	135.2	3.0
Eserine (0.025 mg/kg)		76.9	36.2*		122.4*	8.4*

*$p<0.05$ †$p<0.001$

TABLE 5

EFFECTS OF INTRASEPTAL INJECTIONS ON UNSIGNALED FREE-OPERANT AVOIDANCE PERFORMANCE

	N	Mean Responses	Mean Shocks
Pre-Drug	13	77.5	15.4
Scopolamine (5.0–10.0 μg)		79.9	12.9
Pre-Drug	6	63.9	15.4
Eserine (2.0–6.0 μg)		61.3	18.6*
Pre-Drug	10	81.8	10.0
Eserine (4.0–8.0 μg)		69.6*	16.5*
Pre-Drug	9	77.9	16.0
Arecoline (5.0–10.0 μg)		75.5	17.8*

*$p<0.05$

the rate-suppressing effects of injections of eserine on responding in the DRL paradigm but did not reduce the similar effects of these drugs on free-operant avoidance. Our finding that the effects of systemically administered scopolamine on responding in the DRL paradigm were eliminated by medial septal lesions is consistent with the hypothesis that these treatments disinhibit nonrewarded behavior by disrupting a cholinergic system that originates in the ventral tegmentum and projects to and through the medial septum to the hippocampus via the dorsal fornix and fimbria [11,15].

Our finding that the effects of systemic injections of scopolamine and eserine on free-operant avoidance were not reduced by medial septal lesions indicates that these drugs affect avoidance behavior primarily by acting on neurons located outside this septo-hippocampal projection system. Moreover, the findings that small septal lesions which presumably spare these septo-hippocampal projections also facilitate avoidance behavior [7,14] indicate that septal lesions may also affect avoidance behavior by interrupting different neural systems whose anatomy and precise function are presently unknown. That this cholinergic septo-hippocampal system nonetheless may play some role in mediating avoidance behavior is suggested by our observations that intraseptal injections of cholinergic drugs and surgical transection of the dorsal fornix [13] do affect free-operant avoidance behavior.

REFERENCES

1. Belluzzi, J. D. and S. P. Grossman. A source of "scrambled" constant current with solid state control. *Physiol. Behav.* **10:** 133–136, 1973.

2. Carlton, P. L. and B. Markiewicz. Behavioral effects of atropine and scopolamine. In: *Pharmacological and Biophysical Agents and Behavior,* edited by E. Furchtgott. New York: Academic Press, 1971, pp. 345–373.

3. Douglas, R. J. Pavlovian conditioning and the brain. In: *Inhibition and Learning*, edited by R. A. Boakes and M. S. Halliday. New York: Academic Press, 1972, pp. 529–553.
4. Fried, P. A. Septum and behavior: A review. *Psych. Bull.* **78:** 292–310, 1972.
5. Grossman, S. P. Direct adrenergic and cholinergic stimulation of hypothalamic mechanisms. *Am. J. Physiol.* **202:** 872–882, 1962.
6. Hamilton, L. W. and S. P. Grossman. Behavioral changes following disruption of central cholinergic pathways. *J. comp. physiol. Psychol.* **69:** 76–82, 1969.
7. Hamilton, L. W., J. E. Kelsey and S. P. Grossman. Variations in behavioral inhibition following different septal lesions in rats. *J. comp. physiol. Psychol.* **70:** 79–86, 1970.
8. Kelsey, J. E. The relations between septal lesions, scopolamine, the pituitary-adrenocortical system, and behavior. Unpublished Doctoral Dissertation, University of Chicago, 1971.
9. Kelsey, J. E. and S. P. Grossman. Cholinergic blockade and lesions in the ventromedial septum of the rat. *Physiol. Behav.* **4:** 837–845, 1969.
10. Kelsey, J. E. and S. P. Grossman. Nonperseverative disruption of behavioral inhibition following septal lesions in rats. *J. comp. physiol. Psychol.* **75:** 302–311, 1971.
11. Lewis, P. R. and C. C. D. Shute. The cholinergic limbic system: projections to hippocampal formation, medial cortex, nuclei of the ascending cholinergic reticular system, and the subfornical organ and supraoptic crest. *Brain* **90:** 521–540, 1967.
12. Pellegrino, L. J. and A. J. Cushman. *A Stereotaxic Atlas of the Rat Brain.* New York: Appleton-Century-Crofts, 1967.
13. Ross, J. F. and S. P. Grossman. Septal influences on operant responding in the rat. *J. comp. physiol. Psychol.*, **89:** 523–536, 1975.
14. Van Hoesen, G. W., J. N. MacDougall and J. C. Mitchell. Anatomical specificity of septal projections in active and passive avoidance behavior in rats. *J. comp. physiol. Psychol.* **68:** 80–89, 1969.
15. Warburton, D. M. The cholinergic control of internal inhibition. In: *Inhibition and Learning*, edited by R. A. Boakes and M. S. Halliday. New York: Academic Press, 1972, pp. 431–460.
16. Winer, B. J. *Statistical Principles in Experimental Design.* New York: McGraw-Hill, 1962.