Behavioral effects of intraseptal injections of adrenergic drugs in rats

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Injections of 5-10 μ g of crystalline norepinephrine into the ventromedial septum of Sprague-Dawley rats decreased the rate of responding and increased the number of shocks received on a free-operant avoidance schedule and increased the rate of anticipatory errors and decreased the number of reinforcements received on a DRL schedule. Ventromedial septal injections of the α -adrenergic receptor blocker, Dibenzyline, had opposite effects and improved performance on both schedules, whereas intraseptal injections of the β -adrenergic receptor blockers, dichloroisoproterenol and LB-46, did not modify behavior on these schedules. A different pattern of results was obtained when these drugs were injected into the dorsolateral septum. These results suggest that the septum, especially the ventromedial portion, contains α -adrenoceptive neurons that may function to modulate arousal or the effectiveness of both positive and negative reinforcement.

Recent data indicate that many of the behavioral effects of septal lesions can be attributed to the disruption of cholinergic fibers which terminate in, originate in, and/or pass through the septum. For example, many of the behavioral effects of systemic injections of the cholinergic blockers, scopolamine or atropine, are similar to those of septal lesions (Carlton & Markiewicz, 1971; Fried, 1972). Furthermore, septal lesions eliminate some of these effects of scopolamine (Kelsey & Grossman, 1975). Finally, intraseptal injections of scopolamine or atropine reproduce many of the behavioral effects of septal lesions (Hamilton & Grossman, 1969; Kelsey & Grossman, 1969).

However, the findings that neither systemic nor intraseptal injections of these cholinergic blockers reproduce all of the behavioral effects of septal lesions (Hamilton, McCleary, & Grossman, 1968; Kelsey & Grossman, 1975) indicate that these lesions disrupt noncholinergic as well as cholinergic fibers. In order to test the hypothesis that some of these noncholinergic fibers may be noradrenergic neurons which terminate in the septum, the effects of intraseptal injections of drugs which selectively affect adrenergic transmission were studied on performance on two tasks known to be affected by septal lesions (Kelsey & Grossman, 1971)—a modified free-operant avoidance schedule and a differential reinforcement of low rate (DRL) schedule. To examine the anatomical specificity of these effects, each drug was injected independently into two areas of the septum (the ventromedial and dorsolateral septum) which appear to be partially functionally (Hamilton, Kelsey, & Grossman, 1970; Poplawsky & Johnson,

1973), anatomically (Raisman, 1966), and neurochemically (Moore, Bjorklund, & Stenevi, 1971) distinct.

GENERAL METHOD

Subjects

The subjects were experimentally naive male Sprague-Dawley rats weighing about 375-425 g at the beginning of experimentation. They were housed individually in a continuously lighted room and had ad-lib access to food and water, except where noted.

Surgical Procedures

To reduce respiratory difficulties, the rats were injected IP with 0.20 cc of an atropine methyl nitrate solution (50 mg/cc) 10 min before the injection of Nembutal anesthesia (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 (1962), were stereotactically implanted either singly into the ventromedial septum or bilaterally into the dorsolateral septum at an 11° lateral angle to avoid damage to the midsagittal sinus. All operations occurred at least 2 weeks prior to behavioral testing.

Injection Procedures

The drugs used were the crystalline forms of the noradrenergic agonist, l-norepinephrine hydrochloride; the α -adrenergic receptor blocker, phenoxybenzamine hydrochloride (Dibenzyline); and the β -adrenergic receptor blockers, dichloroisoproterenol hydrochloride and [dl-4-(2 hydroxy-3-isopropylamino-propoxy)-indole] (LB-46). Drug injections were begun after behavior on the schedules had stabilized. The inner cannulas were removed, cleaned, and returned empty into the outer guide cannulas 5-7 min prior to each control session. On the day following attainment of criterion performance (two consecutive control sessions in which response and shock or reinforcement rate did not vary more than 5%), the inner cannulas were removed, cleaned, tamped into a uniform layer of the crystalline drug a specified number of times and replaced into the outer cannulas 5-7 min prior to testing. Control injections preceded subsequent sessions until performance again stabilized, at which time each rat received an injection of a different drug.

The amount of each drug injected by this procedure was determined by weighing and was found to be consistently within

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the range indicated in the tables below. All rats with bilateral cannulas in the dorsolateral septum received drugs in both cannulas prior to each drug session, and the tables reflect the combined dosages for both cannulas. All rats did not receive all drugs. The sequence of drug administration differed for each rat.

Histology

Following completion of behavioral testing, the rats were sacrificed with an overdose of Nembutal and perfused intracardially with isotonic saline followed by a 10% formol-saline solution. Every third 50- μ -thick frozen section in the area of the cannula tips was stained with cresyl violet.

Statistical Analyses

The data obtained during each drug session were compared by means of a matched-groups *t* test, with the average of the data obtained during the two criterion control sessions immediately preceding that drug session. The raw data for rats receiving more than one injection of a given drug were obtained by calculating the average control and drug performance of that rat for that drug. All *p* values are two-tailed.

Since each rat did not receive all of the drugs, the data for each drug were generated, in part, by different rats. Therefore, the variability observed in the predrug baselines reflects, not variability in the performance of individual rats (which was low), but variability in the performance between rats.

EXPERIMENT 1

Septal lesions increase the rate of responding and reduce the number of shocks received in a modified free-operant avoidance paradigm (Kelsey & Grossman, 1971). The observation that the similar effects of systemic injections of scopolamine are not reduced by septal lesions (Kelsey & Grossman, 1975) is consistent with a suggestion that these lesions increase avoidance responding, in part, by disrupting noncholinergic fibers. The present experiment was conducted to determine if some of these noncholinergic fibers are noradrenergic neurons which terminate in the septum.

Method

Subjects. Twenty-five rats were implanted in the ventromedial septum with a single cannula. Twelve rats were bilaterally implanted with cannulas in the dorsolateral septum.

Apparatus. Two sound-isolated shuttleboxes, 53.3 x 20.3 x 33 cm, were used. They were made of clear Plexiglas except for the two end panels made of black Plexiglas. A black Plexiglas panel with a 7.6 x 10.2 cm opening in the bottom that was flush with the floor divided each box into two compartments of equal size. The floor was made of 0.64-cm-diam stainless steel rods spaced 1.9 cm apart. A 6-W light bulb was mounted in each of two small enclosures 7.6 cm above a 7.6 x 12.7 cm opening in the ceiling located so that each 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 (275 μ A) was obtained from constant-current sources (Belluzzi & Grossman, 1973) and was pulsed at the rate of 1/sec with an "on" time of 0.5 sec.

Procedure. All rats were trained to escape and avoid shock in a free-operant avoidance paradigm by crossing from one compartment of the shuttlebox to the other. If shock occurred, the rat was required to make an escape response which initiated

a shock-free response-shock interval of 28 sec. Each crossing response made during that interval reset the response-shock interval, thereby postponing the onset of shock by 28 sec. The effects of intraseptal injections were examined when performance on this free-operant avoidance schedule had stabilized. All sessions lasted 20 min.

Results and Discussion

Twenty of 25 rats were successfully implanted in the anterior portion of the ventromedial septum at the dorsal tip of the diagonal band of Broca. Most of these 20 successful implants 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) (using coordinates from the atlas of Pellegrino and Cushman, 1967). A photomicrograph of a representative ventromedial septal cannula placement can be found in Kelsey and Grossman (1975). Nine of 12 rats were successfully implanted bilaterally in the dorsal portion of the lateral septal n. at AP = 8.3 (range: 8.0 to 8.6), *H* = 1.6 (range: 1.2 to 2.1), and *L* = ± 0.6 (range: -0.3 to 1.1). The data from the eight rats which had cannulas implanted outside these areas were excluded from all statistical analyses.

Application of 5-10 μ g of norepinephrine to the ventromedial septum significantly decreased the rate of responding and increased the number of shocks received (Table 1). Ventromedial septal injections of the α -adrenergic receptor blocker, Dibenzylamine, had opposite effects and significantly increased the rate of responding and decreased the number of shocks received. Bilateral injections of these α -adrenergic drugs into the dorsolateral septum had similar effects on avoidance performance, but these effects failed to reach customary levels of statistical significance (*p* > .05; Table 2). Application of the β -adrenergic blockers, dichloroisoproterenol and LB-46, did not significantly affect avoidance behavior in this paradigm when injected into either the ventromedial or dorsolateral septum (Tables 1 and 2).

These results suggest that the septum, especially the ventromedial portion, contains α -adrenoceptive neurons that are important in the mediation of behavior in this free-operant avoidance paradigm. The finding that the α -receptor blocker, Dibenzylamine, improved avoidance performance when injected into either the ventromedial or the dorsolateral septum is consistent with the conclusion that both of these areas contain neurons whose disruption facilitates two-way avoidance performance (Hamilton et al., 1970). Since intraseptal injections of the cholinergic agonist, arecoline, also decreased the rate of avoidance responding in this paradigm (Kelsey & Grossman, 1975), it seems likely that large septal lesions increase avoidance responding in this paradigm by disrupting both adrenergic and cholinergic fibers.

The observation that intraseptal injections of norepinephrine decreased avoidance behavior is at odds with the notion that enhanced noradrenergic transmission in the brain usually activates or increases the rate of many behaviors, including free-operant avoidance

Table 1
Effects of Ventromedial Septal Injections on Free-Operant Avoidance Performance

Drug	n	Mean Responses		Mean Shocks	
		Pre-drug	Change ^a ± SEM	Pre-drug	Change ± SEM
Norepinephrine (5-10 µg)	8	70.51	-3.64* ±1.41	16.92	3.31* ±1.35
Dibenzylamine (5-10 µg)	13	68.42	4.19* ±1.88	18.43	-2.76** ±.76
Dichloroisoproterenol (5-10 µg)	12	60.67	-.42 ±2.81	18.21	-1.66 ±1.60
LB-46 (5-10 µg)	10	67.23	3.32 ±4.10	17.70	.65 ±1.93

^aMean change from predrug baseline ± the standard error of the mean change following drug administration.

* $p < .05$

** $p < .01$

Table 2
Effects of Dorsolateral Septal Injections on Free-Operant Avoidance Performance

Drug	n	Mean Responses		Mean Shocks	
		Pre-drug	Change ^a ± SEM	Pre-drug	Change ± SEM
Norepinephrine (6-16 µg)	9	79.90	-4.51 ±6.65	11.67	3.88 ±3.82
Dibenzylamine (6-16 µg)	8	75.12	6.75 ±4.10	15.41	-3.41 ±2.22
Dichloroisoproterenol (6-16 µg)	9	74.78	-5.08 ±4.17	13.94	1.39 ±2.13
LB-46 (6-16 µg)	5	87.06	-1.46 ±1.62	7.75	-.35 ±.60

^aMean change from predrug baseline ± the standard error of the mean change following drug administration.

responding (Grossman & Sclafani, 1971). Recent findings, however, have indicated that the catecholaminergic neurons mediating the activation of avoidance behavior are more likely to be dopaminergic than noradrenergic (Fibiger, Phillips, & Zis, 1974). Moreover, the finding that treatments which selectively destroy noradrenergic neurons while apparently leaving most dopaminergic neurons intact frequently improve active avoidance acquisition and performance (Cooper, Breese, Grant, & Howard, 1973) supports our conclusion that the brain contains noradrenergic fibers whose activation decreases the reliability of avoidance behavior.

EXPERIMENT 2

Septal lesions increase the rate of responding in a modified DRL paradigm resulting in a decrease in the rate of reinforcement (Kelsey & Grossman, 1971). Systemic injections of scopolamine have similar effects, and these effects are eliminated by septal lesions (Kelsey & Grossman, 1975). These findings suggest that septal lesions increase the rate of responding in this paradigm,

at least in part, by disrupting cholinergic fibers. The present experiment was designed to determine if the septum also contains noradrenergic neurons that mediate responding in this paradigm.

Method

Subjects. Fourteen rats were implanted in the ventromedial septum with a single cannula. Twelve rats were bilaterally implanted with cannulas in the dorsolateral septum. The rats were maintained at 85% of their postoperative body weight by restricted feeding throughout the experiment. Water was available ad lib.

Apparatus. An opaque white Plexiglas alley, 91.4 x 12.7 x 27.9 cm, with 15.2 x 30.5 cm goalboxes at each end was used. The floor of the apparatus was made of stainless steel rods, 0.47 cm in diameter, placed 1.9 cm apart. The back panel of each goalbox could be illuminated from behind. A circular Plexiglas combination lever-food receptacle, 4.4 cm in diameter and with a 0.64-cm rim, was mounted on a subminiature switch in the center of the back panel of each goalbox 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 to each goalbox. Depressing the lever-food receptacle activated automatic recording and programming devices which scheduled reinforcements and recorded the frequency of leverpresses. To prevent accidental leverpresses 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 goalbox, which was illuminated by lamps behind the back panel. When the rat pressed the lever-food receptacle in that goalbox, two Noyes food pellets (45 mg each) were dropped into the receptacle and the lights were turned off. To obtain the next reinforcement, the rat was required to press the lever-food receptacle in the goalbox at the opposite end of the alley. Continuing to press the lever in the dark goalbox in which it was just rewarded did not result in reinforcement. Each such response was recorded as a perseverative error and reset the 30-sec timer which timed the delay before a response to the lever in the opposite goalbox could be reinforced.

When the rat left the dark goalbox in which it had just been reinforced and crossed the first photocell in the alley, the goalbox at the opposite end of the alley was illuminated. When this occurred, subsequent responses in the previously correct goalbox (still dark) were not recorded and did not reset the delay timer. If the rat pressed the lever-food receptacle in the lighted goalbox 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 leverpress that occurred in the illuminated goalbox 30 sec or more after the last recorded response resulted in the delivery of two Noyes pellets, turned off the lights, and also reset the delay timer. The rat now had to run to the opposite goalbox to obtain the next reinforcement, etc. All sessions lasted 20 min. The supplementary food necessary to maintain body weight at 85% was given in the home cage 20 min after each session. When performance on this schedule had stabilized, the effects of intraseptal injections were examined.

Results and Discussion

The successful cannula placements of both groups of rats were essentially identical to those of Experiment 1. Because of misplaced cannulas, the data of one rat of the ventromedial group and three rats of the dorso-

Table 3
Effects of Ventromedial Septal Injections on DRL Performance

Drug	n	Mean Responses		Mean Reinforcements		Errors/Reinforcement			
		Pre-drug	Change ^a ± SEM	Pre-drug	Change ± SEM	Mean Perseverative Pre-drug	Change ± SEM	Mean Anticipatory Pre-drug	Change ± SEM
Norepinephrine (5-10 µg)	13	71.36	-.52 ±2.03	15.87	-1.68** ± .62	.97	-.22* ±.10	2.83	.61** ±.22
Dibenzylamine (5-10 µg)	9	65.57	.35 ±2.03	18.48	2.18*** ± .61	.85	-.02 ±.21	2.40	-.52 ±.40
Dichloroisoproterenol (5-10 µg)	9	68.00	-.14 ±1.54	16.83	-1.24 ±1.13	.83	.04 ±.09	3.21	.27 ±.36

^aMean change from predrug baseline ± the standard error of the mean change following drug administration

**p* < .05

***p* < .02

****p* < .01

lateral group were excluded from all statistical analyses.

Injections of 5-10 µg of norepinephrine into the ventromedial septum significantly decreased the number of perseverative errors/reinforcement, but increased the number of anticipatory errors/reinforcement, resulting in a significant decrease in the rate of reinforcement (Table 3). Ventromedial septal injections of the α-adrenergic blocker, Dibenzylamine, tended to decrease the rate of anticipatory errors/reinforcement and significantly increased the rate of reinforcement. In contrast to injections into the ventromedial septum, injections of norepinephrine into the dorsolateral septum significantly decreased the number of anticipatory errors/reinforcement and significantly increased the rate of reinforcement (Table 4). Although dorsolateral septal injections of Dibenzylamine tended to have opposite effects, these effects were not statistically significant. Intraseptal injections of the β-adrenergic blockers, dichloroisoproterenol and LB-46, had only small and inconsistent effects on performance in this paradigm (Tables 3 and 4).

These data indicate that the ventromedial septum contains α-adrenoceptive, as well as cholinergic (Kelsey

& Grossman, 1975), neurons that participate in the mediation of behavior on this DRL schedule. However, since blockade of the α-adrenergic receptors of these fibers by Dibenzylamine increases the rate of reinforcement, it is clear that the opposite effects of septal lesions on this schedule (Kelsey & Grossman, 1971) cannot be attributed to destruction of these adrenoceptive fibers.

The finding that the α-adrenergic drugs had opposite effects on DRL performance when injected into the dorsolateral septum than when injected into the ventromedial septum is consistent with the hypotheses that these two areas of the septum may mediate different behavioral functions (Hamilton et al., 1970; Poplawsky & Johnson, 1973). However, because of the proximity of the dorsolateral cannulas to the lateral ventricles, it is unclear if drugs injected through these cannulas are affecting behavior by acting on neurons in the dorsolateral septum or neurons located at more distant sites. Regardless of the precise interpretation given to the effects of dorsolateral septal injections, these data indicate that the effects of ventromedial septal injections are anatomically specific and are probably not due to diffusion into the lateral ventricles.

Table 4
Effects of Dorsolateral Septal Injections on DRL Performance

Drug	n	Mean Responses		Mean Reinforcements		Errors/Reinforcement			
		Pre-drug	Change ^a ± SEM	Pre-drug	Change ± SEM	Mean Perseverative Pre-drug	Change ± SEM	Mean Anticipatory Pre-drug	Change ± SEM
Norepinephrine (6-16 µg)	6	69.12	2.21 ±1.68	14.17	2.25** ± .34	.87	.30 ±.18	3.38	-.98* ±.33
Dibenzylamine (6-16 µg)	8	75.06	4.50 ±2.38	13.59	-.41 ± .60	1.01	.12 ±.12	3.70	.46 ±.34
Dichloroisoproterenol (6-16 µg)	6	74.17	7.33* ±2.54	13.67	1.50 ± .78	1.08	.30 ±.15	3.66	-.23 ±.24
LB-46 (6-16 µg)	4	69.00	6.50 ±4.82	14.50	2.25 ±1.76	1.42	.10 ±.20	2.74	-.38 ±.55

^aMean change from predrug baseline ± the standard error of the mean change following drug administration

**p* < .05

***p* < .01

GENERAL DISCUSSION

The principal findings of this study were that injections of 5-10 μ g of norepinephrine into the ventromedial septum impaired performance in two paradigms by increasing the number of shocks received on a free-operant avoidance schedule and by decreasing the number of reinforcements received on a DRL schedule. Ventromedial septal injections of the α -adrenergic receptor blocker, Dibenzylamine, had opposite effects and improved performance in both paradigms by decreasing the number of shocks received in the avoidance paradigm and by increasing the number of reinforcements received in the DRL paradigm. Intraseptal injections of the β -adrenergic blockers, dichloroisoproterenol and LB-46, had no significant effects. These results suggest that the ventromedial septum contains α -adrenoceptive neurons that are important in mediating behavior in these two paradigms.

The major adrenergic input to these adrenoceptive neurons appears to arise from the dorsal noradrenergic bundle (Ungerstedt, 1971), although the septum probably receives some projections from the ventral noradrenergic bundle as well (Fuxe, Hokfelt, & Ungerstedt, 1970). The dorsal noradrenergic bundle has been implicated in the mediation of the effects of reward (Ritter & Stein, 1973), but our data indicate that the noradrenergic terminals in the ventromedial septum are not involved in mediating these effects. In fact, our attempts to mimic the normal discharge of these intraseptal terminals by injecting norepinephrine directly into the ventromedial septum appear to have decreased the effectiveness of both positive and negative reinforcement. Conversely, blockade of the effects of discharge of these terminals by intraseptal injections of Dibenzylamine appears to have increased the effectiveness of both positive and negative reinforcement. This interpretation that the discharge of these intraseptal adrenergic terminals may decrease the effectiveness of rewards is strengthened by our observation that similar injections of norepinephrine into the ventromedial septum of seven satiated rats decreased the 20-min intake of a preferred solution of 8% sucrose from 7.43 to 4.21 ml ($p < .05$). Our data can also be made to fit an alternative hypothesis which suggests that the dorsal and possibly ventral noradrenergic bundles are involved in mediating general behavioral alerting or arousal functions (Fuxe et al., 1970). Thus, one could argue that in low-arousal appetitive paradigms (Experiment 2) increasing arousal could increase the rate of behavior, whereas in high-arousal avoidance paradigms (Experiment 1) increasing arousal even more may result in too much arousal and the suppression of behavior. A third possibility is that there is more than one functional noradrenergic system synapsing in the septum. The finding that injections of α -adrenergic drugs into the dorsolateral septum had opposite effects on DRL performance than injections

into the ventromedial septum is consistent with this interpretation.

It is clear that any interpretation of these results depends on the efficacy of the intraseptal injection technique employed. The findings that the agonist, norepinephrine, and the α -blocker, Dibenzylamine, always had opposite behavioral effects and that intraseptal injections of adrenergic and cholinergic drugs had similar effects on free-operant avoidance but opposite effects on DRL performance (Kelsey & Grossman, 1975) suggest that these drugs are modifying behavior via their presumed action on the putative neurotransmitters rather than through some common nonspecific effects. This conclusion is further supported by the findings that while the effects of α -adrenergic drugs on free-operant avoidance did not depend on which part of the septum was injected, these drugs had opposite effects on DRL performance when injected into the ventromedial septum than when injected into the dorsolateral septum. In addition, these latter findings indicate that the effects of ventromedial septal injections are at least partially anatomically specific. In particular, since the dorsolateral cannulas are closer to the lateral ventricles, these findings indicate that the ventromedial septal injections are not affecting behavior by diffusing into these ventricles. Thus, these data indicate that the septum contains α -adrenoceptive, as well as cholinergic (Kelsey & Grossman, 1975), fibers that function to mediate behavior in these free-operant avoidance and DRL paradigms.

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