Enhancement of conditioned taste aversions by lesions of the midbrain raphe nuclei that deplete serotonin

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Electrolytic lesions of the dorsal and median raphe nuclei enhanced the avoidance of a saccharin solution that had been paired with a single injection of the toxic drug, lithium chloride. A chemically specific lesion of the same nuclei by intracerebral infusion of 5,7-dihydroxytryptamine produced the same behavioral effect. Neither lesion group differed from control animals in the consumption of an unpaired novel fluid or of an unpaired familiar fluid. Both lesions caused a significant depletion of telencephalic serotonin. The data suggest that the enhanced suppression of saccharin intake was due to damage to serotonergic neurons. Rats with electrolytic lesions in the median raphe nucleus alone showed a significant enhancement of saccharin avoidance in the taste aversion paradigm. The addition of a dorsal raphe lesion increased serotonin depletion but did not produce a significant increment in saccharin avoidance. Thus, decreased hippocampal or septal serotonin, produced by the median lesions, may be responsible for the facilitation of the learned taste aversion. Furthermore, this facilitation may be due to the development of associations between the injection procedure and non-gustatory aspects of the test situation.

Many experiments suggest that forebrain serotonin (5-HT) levels influence the sensitivity of the skin to painful stimuli. Depletion of 5-HT with p-chlorophenylalanine (PCPA) produces a marked increase in sensitivity to footshock (Harvey & Lints, 1971; Koe & Weissman, 1966; Tenen, 1967). Lesions of the midbrain raphe nuclei, which contain cells that synthesize 5-HT (Dahlström & Fuxe, 1964) also decrease the jump threshold in response to footshock (Lints & Harvey, 1969; Lorens, Sorenson, & Yungier, 1971). Similar results have been obtained with lesions in other regions that receive serotonergic input. These sites include the septal area (Lints & Harvey, 1969), the nucleus accumbens (Lorens, Sorenson, & Harvey, 1970), and the medial forebrain bundle (MFB) (Harvey & Lints, 1971; Yungier & Harvey, 1973). The effect of MFB lesions on pain sensitivity can be reversed by the administration of 5-hydroxytryptophan (5-HTP), the immediate precursor of 5-HT, which restores serotonin content to normal levels (Harvey & Lints, 1971). This supports the theory that serotonin modulates sensitivity to cutaneous pain.

The 5-HT depletion does not simply produce a

general hyperactivity, but, rather, a specific increase in sensitivity to painful stimuli. Indications of such specificity have been demonstrated in studies that deplete 5-HT either by electrolytic lesions (Yungier & Harvey, 1973) or by treatment with PCPA (Sheard & Aghajanian, 1968). Such depletions fail to alter the magnitude or habituation of the acoustic startle response. The specificity of the effects of 5-HT depletion also is supported by the report that depletion of 5-HT causes a decrease in jump, but not in flinch, thresholds (Harvey & Lints, 1971). Thus, it appears that the detection threshold for cutaneous stimuli is unchanged by 5-HT depletion, but that the response to suprathreshold painful stimuli is enhanced.

The above analysis of the role of 5-HT in behavior suggests that lesions in 5-HT pathways or in areas that receive serotonergic input would facilitate avoidance training in experiments that employ electric footshock. This has been shown to be the case whether 5-HT was depleted with PCPA administration (Brody, 1970) or by lesions in the raphe (Lorens et al., 1971), septal area (King, 1958), or nucleus accumbens (Lorens et al., 1970).

The experiments reported here examined the effects of 5-HT depletion on another type of avoidance behavior, the conditioned taste aversion. Rats

made sick following the ingestion of a novel fluid will avoid that fluid on subsequent presentations (Garcia, Hankins, & Rusiniak, 1974). Thus, the conditioned taste aversion is a passive avoidance paradigm that employs gastrointestinal distress or other drug effects rather than cutaneous pain as an unconditioned stimulus.

Brain lesions at both cortical (Braun, Slick, & Lorden, 1972; Lorden, 1976) and subcortical sites (Best & Orr, 1973; Krane, Sinnamon, & Thomas, 1976; Nachman & Ashe, 1974; Roth, Schwartz, & Teitelbaum, 1973) partially interfere with the formation of taste aversions. Several lesion studies, however, show a facilitation of this avoidance behavior. Rats with lesions of the medial septum show an enhanced aversion to saccharin stimuli previously paired with x-irradiation-induced toxicosis (McGowan, Garcia, Ervin, & Schwartz, 1969). Lesions of the lateral septum did not have this effect. Autoradiographic and degeneration studies show that the raphe nuclei project primarily to the medial rather than the lateral septum (Conrad, Leonard, & Pfaff, 1974). Thus, it is possible that the facilitation of taste aversion learning induced by medial septal lesions (McGowan et al., 1969) was due to depletion of forebrain 5-HT. The present studies examined the effects of electrolytic or chemical lesions of the mid-brain raphe nuclei on the ability of the rat to learn an aversion to a novel taste stimulus that had been paired with toxicosis, as a first step in examining the possible modulatory effects of forebrain 5-HT on taste aversion learning.

EXPERIMENT 1

The first experiment measured the effects of lesions of both the dorsal and median raphe nuclei on taste aversion learning. Since electrolytic lesions are completely nonspecific and destroy both serotonergic and nonserotonergic fibers, the effects of electrolytic lesions were compared to the effects of relatively specific chemical lesions, the infusion of the neurotoxin 5, 7-dihydroxytryptamine (5,7-DHT). Björklund, Baumgarten, and Rensch (1975) have shown that 5,7-DHT destroys 5-HT neurons, but will also cause damage to catecholamine fibers. The specificity of the 5,7-DHT lesion can be improved, however, by pretreatment with desipramine (DMI) and by injection of the toxin in a neurochemical pathway that is relatively homogeneous.

Method

Subjects. The subjects of the experiment were 23 male rats (Holtzman Co.) weighing between 350 and 400 g at the time of surgery. The rats were housed in individual cages in a colony room kept on a 12-h light-dark cycle. Purina Laboratory Chow and water were available ad lib prior to surgery and for 1 month following surgery.

Surgery. Cathodal lesions were stereotaxically placed in both the dorsal and median raphe nuclei ($N = 8$, Electrolytic group). A stainless steel insect pin, size 000 and insulated except for .5 mm at the tip, was used as an electrode. The coordinates were 1 mm anterior to lambda (AP), 1.2 mm lateral to the midline (L), and 6.7 mm ventral (V) to the surface of the skull for the dorsal lesion; they were 1.0 AP, 1.5 L, and 8.6 V for the median lesion. The electrode was inserted at a 10° angle to the sagittal plane. The incisor bar was placed 3.5 mm above the interaural line. The dorsal lesion was produced by a 2-mA current passed for 20 sec and the median lesion utilized 2 mA for 25 sec. A group of five rats served as sham-operated controls. These animals were treated the same as the Electrolytic group, except that the electrode was not lowered.

Another group of seven rats (5,7-DHT group) received infusions of 5,7-DHT creatinine sulfate (Regis Chemical Co.) at the same coordinates used for the electrolytic lesions. Animals were pretreated with DMI (25 mg/kg, IP, USV Pharmaceuticals) 30-45 min prior to infusion. A dose of $4 \mu\text{g}$ of 5,7-DHT (21 nmol, free base) at a concentration of $4 \mu\text{g}/\mu\text{l}$ was administered at both the dorsal and median coordinates. The 5,7-DHT was dissolved in a physiological saline vehicle containing .02% ascorbic acid. The infusion was made through a 30-ga stainless steel cannula attached to a microsyringe. Four additional animals received infusions of the vehicle in volumes equal to those of the 5,7-DHT infusions (Vehicle group). Ether was the anaesthesia used for all the surgical procedures.

Training. After a 1-month period of recovery from surgery, all animals were deprived of water according to the following schedule. First, water was presented for 10 min in inverted 50-ml centrifuge tubes equipped with stoppers and spouts. Next, these tubes were removed and 8-oz water bottles were placed on the cages for 45 min. This procedure was followed daily throughout the experiment. Food was available ad lib.

After 1 week of the water-deprivation schedule, all the rats were drinking a minimum of 8 ml of water during the initial 10-min test. On the drug treatment day, 50 ml of .1% sodium saccharin was presented instead of water during the 10-min drinking session. Immediately afterwards, each rat received an injection of .15 M lithium chloride (LiCl, 12 ml/kg, IP).

Testing. On the 12 days following the saccharin-toxicosis pairing, the animals were tested for conditioned taste aversions. Every other day, starting with the day after the taste-toxicosis pairing, all rats received water during the entire 55-min session. Water presentations were alternated with presentations of the taste stimuli, .1% saccharin and .9% sodium chloride. On a given taste presentation day, half the rats in each group received saccharin and the other half received saline. All rats received six presentations of water, three of saccharin, and three of saline over the course of testing. All 10-min taste tests were followed by a 45-min period of free access to water.

The main dependent variable was the amount of saccharin or saline consumed during the 10-min drinking periods. All intake data were analyzed by Kruskal-Wallis tests followed by Mann-Whitney U tests where appropriate.

The dependent measure used for the statistical analysis was the total consumption of saccharin or saline summed over the three 10-min test trials. The groups were also compared on water consumption during the 10-min trials summed for six drinking periods.

Chemical analysis. When the testing sequence was completed, all rats were sacrificed by decapitation. The brains were removed rapidly and a telencephalic dissection was made by lifting the occipital and ventral regions of the cortex to expose the corona radiata and the columns of the fornix. Bilateral cuts through the diencephalon were made using the corona radiata as guides. A coronal cut through the anterior commissure separated the telencephalon from the diencephalon. The left and right hemispheres were then separated by a sagittal cut. Left and right hemispheres were analyzed fluorometrically for 5-HT, nor-

epinephrine (NE), and dopamine (DA) (Lorden, Oltmans, & Margules, 1976). The amine data were analyzed by analysis of variance followed by Neuman-Keuls tests.

Histology. Frozen sections, 100 μ m thick, were cut through the brainstem and photographed for verification of cannula and lesion placement.

Results and Discussion

Histology. Examination of the brainstem of animals in the lesion groups showed that all but one of the electrolytic lesions were placed on the midline and destroyed a significant portion of the dorsal and median nuclei. The maximal and minimal extent of the lesions is shown in Figure 1. The rat with a lesion placed outside the raphe was excluded from the group.

The cannula placements were more difficult to assess, since little necrotic tissue was present at sacrifice. However, evidence of cannula tips placed within the dorsal and median nuclei were found in every case.

Behavioral tests. No significant differences in intake of saccharin, water, or saline were observed between the vehicle and sham-operated groups.

Figure 1. Extent of electrolytic lesions of the dorsal and median raphe nuclei. Smallest (blackened area) and largest (outlined) lesions are shown (Pellegrino & Cushman, 1967). Abbreviations: A, aqueduct; DBC, decussation of the brachium conjunctivum; FLM, medial longitudinal fasciculus; LM, medial lemniscus; rf, reticular formation.

Table 1
Mean Water and Saccharin Consumption (ml $\pm$ SD)
10-min Tests Prior to LiCl treatment

Group	n	Water	Saccharin
5,7-DHT	7	13.7 $\pm$ 1.4	11.8 $\pm$ 3.8
Electrolytic	7	15.0 $\pm$ 2.3	10.1 $\pm$ 3.6
Control	9	11.8 $\pm$ 3.8	12.2 $\pm$ 2.6

Therefore, these groups were combined to simplify data presentation. Prior to the saccharin-toxicosis pairing, there was no significant difference in saccharin intake between groups (Table 1).

After the pairing of saccharin drinking with toxicosis, all groups suppressed their intake of saccharin (Figure 2). The 5,7-DHT and Electrolytic groups did not differ significantly from each other; however, both groups drank significantly less saccharin than the control group. There were no statistically significant differences in consumption of either saline (Figure 2) or water. Water consumption ($M \pm S.E.$) during the six 10-min tests was $81.1 \text{ ml} \pm 10.6$, 80.6 ± 8.2 , and 76.6 ± 4.6 , for the 5,7-DHT, Electrolytic and control groups, respectively. Thus, the enhanced suppression of intake observed in the 5,7-DHT and Electrolytic groups was specific to the flavor paired with toxicosis and did not extend to either a familiar fluid, water, or another novel fluid, saline.

Chemical analysis. The vehicle-infusion caused a small but significant reduction (20%) in telencephalic 5-HT levels (Table 2). Both the 5,7-DHT and the electrolytic lesions caused significant depletion (75%) of telencephalic 5-HT when compared to the vehicle-infused or sham-operated groups ($p < .01$). The lesion groups did not, however, differ significantly from each other.

No significant depletion of NE or DA occurred in either the 5,7-DHT or the Electrolytic groups (Table 2) when compared to the Vehicle or Sham groups. Nor were there any significant differences between the Vehicle and the Sham groups in NE or DA levels.

Thus, depletion of 5-HT was the principal effect of the lesions on brain chemistry. The electrolytic and 5,7-DHT lesions appeared equally effective in the enhancement of taste aversion learning and the depletion of 5-HT. The effectiveness of the relatively specific 5,7-DHT lesions suggests that the enhancement of saccharin avoidance observed in both lesion groups was due to the 5-HT depletion rather than to inadvertent damage to structures within the region of the raphe nuclei.

EXPERIMENT 2

The results of the first experiment suggest that lesions of the dorsal and median raphe nuclei that

Figure 2. Saccharin (A) and saline (B) consumption in rats with electrolytic or 5,7-DHT lesions of the dorsal and median raphe nuclei and in control (Vehicle and Sham) rats following injections of LiCl.

deplete 5-HT enhance the rejection of a novel sweet-tasting solution that has been paired with toxicosis. There is growing evidence, however, that many of the behavioral changes that result from raphe lesions may be differentially attributable to either the dorsal or median nucleus. For example, median but not dorsal lesions produce hyperactivity (Geyer, Puerto, Menkes, Segal, & Mandell, 1976b; Jacobs, Wise, & Taylor, 1974). Dorsal lesions, however, increased pain-elicited aggression (Jacobs & Cohen, 1976). Median, but not dorsal, lesions also have been re-

ported to enhance reactivity to novel stimuli (Srebro & Lorens, 1975), increase the magnitude of startle responses, and cause the perseveration of unreinforced responses in y-mazes (Geyer et al., 1976b).

Recent data on the differential anatomical projections of the raphe nuclei provide a basis for functional distinctions made between the dorsal and median nuclei. Biochemical measurements following relatively discrete lesions of the dorsal or median nuclei suggest that the median nucleus provides the principle source of hippocampal and septal 5-HT (Geyer, Puerto, Dawsey, Knapp, Bullard, & Mandell, 1976a; Jacobs et al., 1974; Lorens & Guldberg, 1974). On the other hand, the dorsal nucleus contributes more heavily to striatal 5-HT than does the median nucleus.

In an attempt to distinguish between the relative contributions of the dorsal and median nuclei in the enhancement of saccharin avoidance reported in the first study, the effects of median lesions alone were compared to the effects of combined dorsal and median lesions.

Method

Unless otherwise indicated, the details of procedures followed in this experiment were the same as those used in Experiment 1.

Subjects. Twenty-three male rats (Holtzman Co.), weighing from 300-400 g at the time of surgery, received electrolytic lesions of either the median raphe nucleus alone ($N = 7$) or both the dorsal and median raphe nuclei ($N = 8$). A group of eight additional rats served as sham-operated controls.

Training and Testing. Following a 1-month recovery period, all rats were put on a water deprivation schedule and allowed water for only 55 min daily. After 1 week of the deprivation schedule, all of the rats received a 10-min presentation of water in 50-ml centrifuge tubes followed immediately by an injection of .15 M sodium chloride (NaCl, 12 ml/kg, IP). The next day, saccharin was presented for 10 min and followed by an injection of .15 M lithium chloride (12 ml/kg, IP). The injection of non-toxic sodium chloride served as a control for the injection procedure.

On the next 8 days following the saccharin-lithium pairing, water and saccharin were presented on alternate days during the 10-min test period. As in the previous experiment, water was always available for 45 min following the 10-min test period. The 10-min water and saccharin drinking data were analyzed by Kruskal-Wallis and Mann-Whitney U tests.

Chemical analysis. At the completion of the testing sequence, all of the animals were sacrificed by decapitation and telencephalic sections were analyzed as in Experiment 1, for 5-HT.

Histology. Frozen sections, 100 μ m thick, were cut through the remaining brainstem and photographed for lesion evaluation.

Results and Discussion

Histology. Examination of the brainstems of the animals in the combined Dorsal-Median group showed that all lesions were centered on the midline and were comparable to those of the Electrolytic group in Experiment 1. None of the lesions from the Median group encroached on the dorsal nucleus.

Behavioral tests. There were no significant differences between groups in the preinjection consumption of either water or saccharin (Table 3). However,

Table 2
Telencephalic 5-HT, NE, and DA Levels Following Lesions of the Dorsal and Median Raphe Nuclei

Group	n	5-HT	NE	DA
5,7-DHT	7	.25 $\pm$.21*	.33 $\pm$.04	1.34 $\pm$.11
Vehicle	4	.59 $\pm$.05**	.31 $\pm$.03	1.42 $\pm$.09
Electrolytic	7	.24 $\pm$.11*	.31 $\pm$.03	1.37 $\pm$.12
Sham	5	.74 $\pm$.03	.36 $\pm$.05	1.48 $\pm$.06

Note—Values expressed as micrograms of amine/g ($M \pm SD$) fresh weight of brains.

* $p < .01$, differs from control (vehicle or sham group).

** $p < .01$, differs from sham group.

Table 3
Mean Water and Saccharin Consumption (ml $\pm$ SD) in Rats with
Median or Dorsal and Median Raphe Lesions
Prior to LiCl Treatment

Group	n	Water	Saccharin
Dorsal-Median	8	12.4 $\pm$ 2.2	11.8 $\pm$ 3.7
Median	7	12.4 $\pm$ 1.7	11.3 $\pm$ 2.3
Control	8	13.1 $\pm$ 2.2	15.0 $\pm$ 3.3

Figure 3. Saccharin (A) and water (B) consumption in rats with electrolytic lesions of the dorsal and median raphe nuclei or the median nucleus alone after a pairing of saccharin consumption with a LiCl injection and a pairing of water consumption with an NaCl injection.

as can be seen in Figure 3, following the injections, saccharin consumption dropped from pretreatment means of 11-15 ml to means of 1.7-3.0 ml on the first saccharin test trial. Water consumption also decreased slightly in all groups compared with the pretreatment data.

A statistical analysis of the total saccharin consumption throughout all tests indicated that both the combined dorsal-median lesion group and the median lesion group drank significantly less saccharin than the control group ($p < .01$). The two lesion groups did not differ significantly from each other. A similar pattern of results was observed in total water intake. Each of the two lesion groups drank significantly less water than the control group ($p < .01$ for both) but did not differ significantly from each other.

The suppression of intake of the familiar fluid, water, usually does not occur in the conditioned aversion paradigm even if water consumption is

paired with toxicosis (Braun & Rosenthal, 1976; Braun et al., 1972; Lorden, 1976). Therefore, water intake was measured during the 45-min drinking period that followed the fourth test trial. Table 4 shows that during the 45-min drinking period, both lesion groups drank significantly ($p < .01$) more water than the control group, but did not differ from each other. When the water consumption during the 10-min test was added to water consumption during the 45-min drinking period (total water intake), the lesion and control groups did not differ from each other. Thus, the suppression of water intake does not appear to be rejection of water itself. Instead, it appears to be a response to other variables in the testing situation (e.g., the tube used for the 10-min test).

The rats in Experiment 1 that received pairings of saccharin and toxicosis showed no tendency to generalize the saccharin aversion to either water or a sodium chloride solution. Thus, it is unlikely that the enhanced suppression of water intake observed in Experiment 2 was due to generalization of the saccharin aversion. It may, however, be the result of pairing an injection of nontoxic sodium chloride with water consumption. Since rats with raphe lesions show greater sensitivity to painful cutaneous stimuli (Lints & Harvey, 1969; Lorens et al., 1971), it is possible that the enhanced depression of water intake observed in the lesion groups is due to an association between the injection procedure and some nongustatory aspect of the testing situation. This could also account for the enhanced suppression of saccharin intake in the lesion groups in both the first and second experiments.

Chemical analysis. A significant depletion of the telencephalic 5-HT was obtained in both the combined Dorsal-Median group and the Median group (Table 5). The mean depletion of telencephalic 5-HT was significantly greater ($p < .01$) in the Dorsal-Median group (-71% from control) than in the Median group (-43% from control). The greater depletion of 5-HT observed in the Dorsal-Median group, however, did not result in a greater behavioral suppression. Thus, it appears that the median lesion alone is sufficient to produce the enhanced suppression of fluid intake observed.

Table 4
Mean Water Consumption (ml $\pm$ SD) on the
4th Water Test Day

Group	n	45-min Drinking Period	Total Consumption
Dorsal-Median	8	11.6 $\pm$ 3.3*	22.9 $\pm$ 2.8
Median	7	12.4 $\pm$ 3.2*	24.3 $\pm$ 5.6
Control	8	6.6 $\pm$ 1.8	22.7 $\pm$ 2.0

* $p < .01$, differs from control.

Table 5
Telencephalic 5-HT Following Lesions of the Raphe Nuclei

Group	n	5-HT
Dorsal-Median	8	.16 ± .10*†
Median	7	.32 ± .13*
Control (Sham and Vehicle)	8	.56 ± .05

Note-Values expressed as micrograms of amine/g ($M \pm SD$) fresh weight of brain.

* $p < .01$, differs from control.

† $p < .01$, differs from median group.

GENERAL DISCUSSION

The results of both experiments indicate that lesions of the raphe nuclei that deplete forebrain 5-HT can enhance the performance of rats in a conditioned taste aversion task. Rats with lesions of the median or both dorsal and median raphe nuclei showed a greater suppression of their saccharin intake following a single pairing of taste and toxicosis than controls. Since 5,7-DHT lesions, which cause relatively little nonspecific damage, were as effective as electrolytic lesions in producing the effect, it appears likely that the enhanced suppression of intake was due to damage to serotonergic neurons.

Many experiments have shown that raphe lesions improve performance in active avoidance tasks (Hole & Lorens, 1975; Lorens, 1973; Lorens et al., 1971; Lorens & Yunger, 1974; Srebro & Lorens, 1975). The data reported here show that these lesions may also enhance passive avoidance performance. Damage to the median raphe appears to be sufficient to produce the effect. Adding a dorsal raphe lesion causes a greater depletion of forebrain 5-HT without a significant increment in the behavioral change. This suggests that the effect may be due to a loss of hippocampal or septal 5-HT. The dependence of this effect on striatal 5-HT can be ruled out (Geyer et al., 1976a).

In normal animals, increases in the magnitude of a conditioned taste aversion can be produced by increasing the concentration of the taste stimulus or increasing the dose of the toxic agent used (Garcia et al., 1974; Nowlis, 1974). The enhanced suppression of intake in the rats with raphe lesions suggests that the lesions produced a change in the subjective intensity of either the taste or the toxic effects of the drug. There is no evidence that the suppression of intake is due to a hypodipsia. In the present studies, there were no significant differences in saccharin or water intake between lesion and control animals prior to lithium injections. Nor were there significant differences in sodium chloride or water intake between lesion and control groups in Experiment 1, even after lithium injection. Furthermore, raphe lesions tend to be followed by a transient (15-20-day) hyperdipsia (Lorens et al., 1971).

The absence of any differences in sodium chloride intake or in the consumption of saccharin during the pretreatment period suggests that the enhancement of saccharin avoidance was not due to an increase in the subjective intensity of the taste stimulus. It is more likely due to an increased sensitivity to the administration of the toxic drug, lithium chloride. Since the rats in Experiment 2 suppressed their intake of water when it had been paired with an injection of nontoxic sodium chloride, it is possible that the enhanced suppression of saccharin intake was due to an increased sensitivity to the cutaneous pain caused by the injection procedure itself. The issue of whether or not raphe lesions can cause an increased sensitivity to gastrointestinal distress or whether the effects of the lesions are specific to cutaneous sensitivity needs further investigation. Since thirsty rats will drink lithium chloride readily until the toxic effects are felt (Nachman, 1963), it should be possible to compare the time it takes for lithium chloride drinking to stop in normal animals and in animals with raphe lesions. Garcia and others (1974) have argued that the neuroanatomical substrate for taste aversion learning is distinct from that associated with shock avoidance responses. Thus, it is possible that taste-toxicosis associations per se are not subject to the modulatory influences of serotonergic systems.

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