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Alteration of the Characteristics of Learned Taste Aversion by Manipulation of Serotonin Levels in the Rat

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LORDEN, J. F. AND G. A. OLTMANS. *Alteration of the characteristics of learned aversions by manipulation of serotonin levels in the rat.* PHARMAC. BIOCHEM. BEHAV. 8(1) 13–18, 1978. – Electrolytic lesions placed in the dorsal and median raphe nuclei of the rat brain deplete hypothalamic and telencephalic serotonin. These lesions also enhance the learned suppression of saccharin consumption which results from pairing the ingestion of a saccharin solution with the injection of a toxic drug. Pretreatment of rats with raphe lesions with the serotonin precursor DL-5-hydroxytryptophan (5HTP) immediately prior to the conditioning trial blocks the learning of the aversion to saccharin. In normal rats, 5HTP pretreatment also attenuates the suppressive effects of conditioning on saccharin drinking. These results differ from the findings of previous research using the flinch-jump technique. When sensitivity to shock is measured, 5HTP pretreatment in rats with forebrain serotonin depletion has been reported to restore both serotonin levels and behavior to normal. No behavioral effects are observed in normal animals. Possible explanations for the differential effects obtained in the two paradigms are discussed.

Taste aversion Serotonin Raphe lesions 5-Hydroxytryptophan

IT HAS BEEN demonstrated in a number of experimental situations that, if an animal becomes ill following the ingestion of a novel substance, the intake of that substance will be diminished upon subsequent presentations [3]. This effect is known as a learned taste aversion. It has been conceptualized as a form of classical conditioning in which some type of malaise or gastrointestinal distress serves as an unconditioned stimulus. Investigations of the central mechanism underlying taste aversion learning have shown that the phenomenon is altered by lesions at both cortical [2,9] and subcortical sites (eg., [1, 4, 7, 14, 16]).

In a recent study Lorden and Margules [10] found that both electrolytic and neurochemical (5,7–dihydroxytryptamine) lesions in the area of the dorsal and median raphe nuclei produced a significant enhancement of a learned taste aversion. Both types of lesions produced significant decreases in telencephalic serotonin (5HT) content. These results suggest that changes in central serotonergic neurons may modify the learning of a conditioned taste aversion.

Recent studies of the function of the central serotonin neurons indicate that these neurons may be involved in an animal's response to painful stimuli. Both lesions of 5HT neurons at the level of the medial forebrain bundle and inhibition of 5HT metabolism by administration of p-chlorophenylalanine produce a significant decrease in the pain threshold, as measured by the flinch-jump method [5, 18, 19, 20]. In addition lesions of 5HT neurons at the level of the raphe nuclei facilitate the acquisition of a conditioned avoidance response [13]. A role for 5HT in pain sensitivity has also been suggested by the finding that the restoration of telencephalic 5HT content to control levels in rats with medial forebrain bundle lesions returns the pain threshold to normal [5, 20, 21].

The role of central 5HT in behavior has frequently been studied using the painful cutaneous stimulus of footshock (e.g., [8, 13, 20]). The observation that raphe lesions that resulted in the depletion of central 5HT enhanced the suppressive effect of pairing a taste cue with toxicosis [10] suggests that central serotonergic neurons may mediate responsiveness to many types of noxious stimulation. The present study was designed to further explore the effects of the manipulation of serotonin levels on the development of a learned taste aversion.

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EXPERIMENT 1

METHOD

Animals

Adult male albino rats were obtained from the Holtzman Company (Madison, WI). The animals were housed individually with ad lib access to food and water prior to surgery. The lights in the colony room cycled on and off every twelve hr throughout the experiment.

Surgery

Lesions were placed using a Kopf stereotaxic instrument. The incisor bar was set 3.5 mm above the interaural line. Two lesions were made in order to destroy 5HT neurons of both the dorsal and median raphe nuclei. The electrode was inserted at an angle of 10° from the sagittal plane for both lesions. The coordinates for the dorsal lesions were: anterior- posterior (AP) = +1.0 mm from the lambdoidal suture; lateral (L) = 1.2 mm from the midline; depth (D) = −6.7 mm from the surface of the skull. For the median lesion, the coordinates were: AP = +1.0 mm from lambda; L = 1.5 mm from the midline; D = −8.6 mm from the surface of the skull. The electrode was a stainless steel insect pin (size 000) insulated except for 0.3 mm at the tip. Lesions were produced by passing a 2 mA cathodal current for 20 sec for the dorsal lesion and for 25 sec for the median lesion. Ether was used as the anesthetic for all surgery. Animals weighed 350 to 400 g at the time of surgery. Sham-operated controls were treated in an identical manner, but the electrode was not lowered into the brain.

Behavioral Training and Testing

After a 60-day recovery period during which there was ad lib access to both food and water, all animals were placed on a 23-hr water deprivation schedule. Water was available for a one-hr period and intake was measured for the first 15 min of daily access. This schedule was maintained throughout the remainder of the experiment. When intake had stabilized, all animals were weighed and a single training trial was carried out. On the training day, 50 ml of saccharin (0.1%) rather than water was provided during the initial 15-min drinking period. Immediately after the 15-min drinking period all rats were injected with 12 ml/kg of 0.15 M lithium chloride (LiCl). In addition to the pairing of the saccharin consumption with the injection of LiCl, half of the animals with lesions (Group L+5HTP, N = 7), were randomly selected to receive an injection of the serotonin precursor 5-hydroxytryptophan (5HTP) 15 min prior to saccharin presentation. The 5HTP (75 mg/kg of DL-5HTP, Sigma Chemical Company) was prepared in a 0.9% saline vehicle at a final concentration of 10 mg/ml. The remaining animals with raphe lesions (Group L+SAL, N = 7), and the sham-operated controls (Group S+SAL, N = 6), received equivolume doses of the saline vehicle 15 min prior to saccharin presentation. Thus, the sequence of events on the training day was: (1) 5HTP or saline injection 15 min prior to saccharin presentation; (2) saccharin presentation for 15 min; (3) LiCl injection immediately after saccharin; (4) water for the remaining 45 min.

Four days following the pairing of the LiCl injection with the presentation of the saccharin solution, half of the animals in each group were given 0.1% saccharin and half were given 0.9% saline to drink for 15 min. Two days later (Day 6 after training) the presentations were reversed. On the eighth day after training, all animals were again given saccharin for the first 15 min of fluid access. On all other days, water was available during the 15 min test period as well as during the remaining 45 min. Thus, all rats were tested twice following the pairing of the LiCl injection with the presentation of the saccharin solution to determine the effects of this pairing on the subsequent intake of saccharin. In addition, the presentation of the 0.9% saline solution tested for possible nonspecific effects of the treatment on the consumption of novel taste cues.

Chemical and Histological Analysis

Following completion of testing the animals were returned to ad lib food and water access. Three weeks later all animals were sacrificed by decapitation. The hypothalamus and telencephalon were dissected as previously described [11,12] and 5HT content was determined using a modification of the procedure of Maickel [6].

The brainstems were placed in 10% neutral buffered formalin and saved for histological analysis. Frozen coronal sections (100 μm) were cut through the area of the lesion and photographed to determined lesion placement.

Statistical Analysis

Differences between groups were analyzed using an analysis of variance followed by *t*-tests for specific comparisons. Within-group differences were analyzed using *t*-tests for dependent measures.

RESULTS

Histology

The lesions were comparable to the dorsal and median lesions described by Lorden and Margules [10]. In general, the lesions were centered on the midline and destroyed a major portion of both nuclei. The most anterior portion of the dorsal nucleus was spared in two cases. Three rats were dropped from the study when histology failed to confirm damage to one or both of nuclei. In addition to the raphe nuclei, the other structures that sustained damage most frequently were the periventricular grey, the medial longitudinal fasciculus, and the ventral tegmental nucleus (Fig. 1).

Behavioral Tests

There were no significant differences in body weight between groups at the time of LiCl-saccharin pairing. The mean body weight (g) for Group L+5HTP was 435.4 (SD = 30.9); for Group L+SAL, 416.8 (SD = 24.6); and for Group S+SAL, 417.4 (SD = 8.9).

Raphe lesions did not produce any significant effect on either 15 min water intake or the initial consumption of saccharin prior to LiCl administration (Fig. 2). Furthermore, sodium chloride intake did not differ significantly between groups following the pairing of the saccharin presentation with the LiCl injection. Group L+5HTP drank 13.2 ml ± 2.6 (M ± SD); Group L+SAL, 14.7 ± 3.9; and Group S+SAL, 17.1 ± 5.5. Thus, neither the raphe lesion nor treatment with 5HTP appeared to have any general effects on consumption of either familiar or novel fluids.

Significant differences in saccharin intake were found following the pairing of the saccharin presentation with the

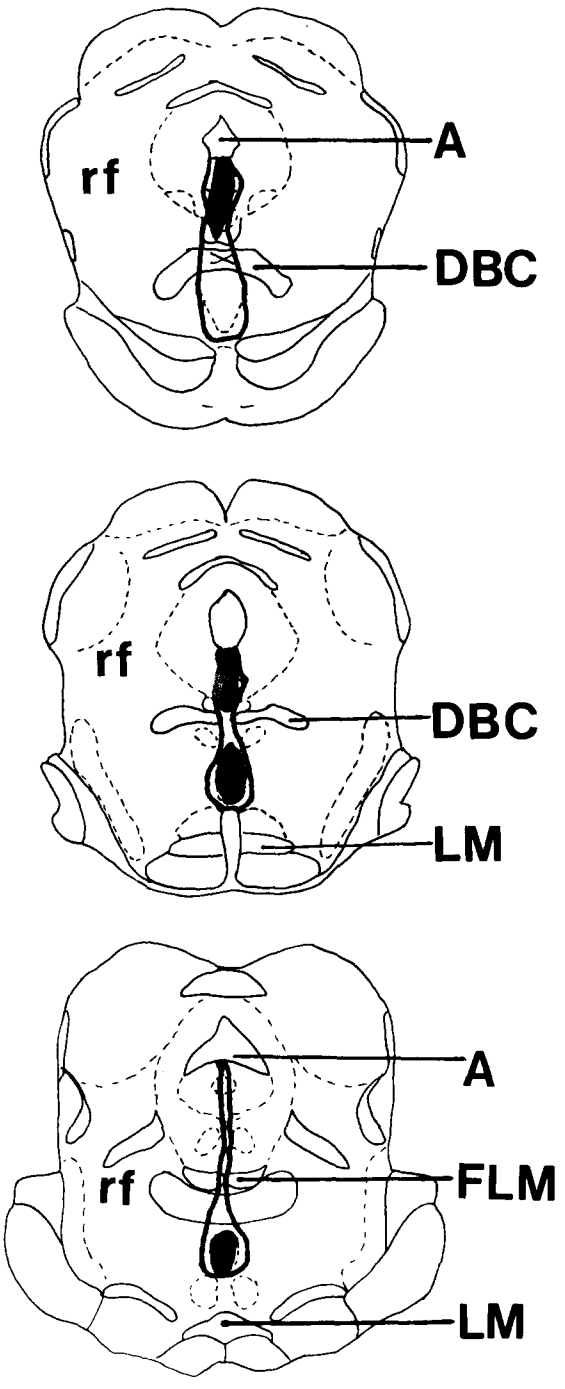

FIG. 1. Extent of electrolytic lesions of the dorsal and median raphe nuclei. Smallest (blackened area) and largest (outlined) lesions are shown [18]. Abbreviations: A, aqueduct; DBC, decussation of the brachium conjunctivum; FLM, medial longitudinal fasciculus; LM, medial lemniscus; rf, reticular formation.

LiCl injection (Fig. 2). As expected, the control group (S+SAL) showed a significant suppression of saccharin intake on the first test trial following the LiCl treatment ($p<0.01$). Group L+SAL also showed evidence of a significant saccharin aversion ($p<0.01$). Furthermore, raphe lesions alone significantly enhanced the learned aversion to

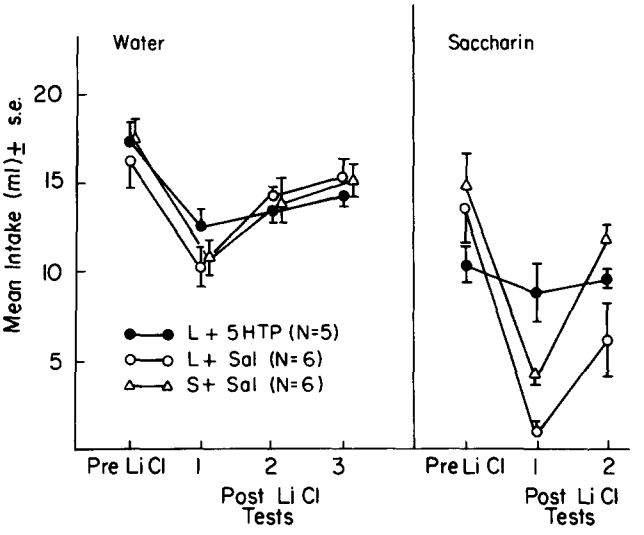

FIG. 2. Fifteen min water and saccharin consumption of Groups L+5HTP, L+SAL and S+SAL before and after a pairing of LiCl with saccharin drinking. Post LiCl water tests took place on Days 3, 5, and 7 following training. Saccharin presentations were made on Days 4, 6, and 8. (See text for a complete description of the sequence.)

saccharin ($p<0.01$, L+SAL vs. S+SAL). In contrast, Group L+5HTP drank only slightly less saccharin during the first test trial than during the training trial. This difference was not statistically significant. Group L+5HTP drank significantly more saccharin on the first test trial than either Group S+SAL or L+SAL ($p<0.01$, for both). These results indicate that pretreatment with 5HTP not only blocked the enhancement of saccharin suppression found in rats with raphe lesions but also blocked the association between saccharin and toxicosis.

On the second test presentation of saccharin neither Group L+5HTP nor Group L+SAL differed significantly from the control group, S+SAL. Furthermore, neither Group L+5HTP nor Group S+SAL differed significantly from their pre-LiCl saccharin intake. Group L+SAL, however, continued to drink significantly less saccharin than during the initial training trial ($p<0.01$). There were no significant differences in water consumption following the LiCl-saccharin pairing (Fig. 2). Thus, the difference in saccharin intake observed in the between groups comparisons cannot be attributed to differences in overall fluid consumption.

Chemical Analysis

The raphe lesions produced a significant decrease in brain 5HT content (Table 1). Both telencephalic and hypothalmic 5HT levels were significantly lower in the lesion groups than in the control group. The two lesions groups, L+5HTP and L+SAL, did not differ significantly from each other. This suggests that the difference in behavior between the two lesion groups cannot be attributed to a differential destruction of 5HT neurons.

The results indicate that in animals with lesions of the raphe nuclei, the administration of the serotonin precursor 5HTP blocks the development of a learned taste aversion. In contrast, animals with comparable raphe lesions that

TABLE 1

HYPOTHALAMIC AND TELENCEPHALIC SEROTONIN CONTENT AFTER ELECTROLYTIC LESIONS OF THE MEDIAN AND DORSAL RAPHE NUCLEI

Group	Hypothalamus (M ± SD)	Telencephalon (M ± SD)
L + 5HTP	0.812 ± 0.189(4)*	0.315 ± 0.173(4)*
L + SAL	0.738 ± 0.204(5)*	0.208 ± 0.098(6)*
S + SAL	1.372 ± 0.203(6)	0.631 ± 0.078(6)

Values expressed as μg of amine/g of fresh weight of brain. Numbers in parentheses are sample size for each determination.
*Differs significantly from Group S+SAL, $p<0.01$.

were pretreated with physiological saline showed a potentiation in the suppression of intake of the taste cue paired with toxicosis and an increase in the duration of this effect in comparison with normal rats. The latter finding is in agreement with data reported by Lorden and Margules [10] from animals with either electrolytic or 5,7-dihydroxytryptamine lesions of the dorsal and median raphe nuclei.

EXPERIMENT 2

The administration of 5HTP to rats with medial forebrain bundle lesions returns both telencephalic 5HT content and flinch-jump thresholds to normal [5]. However, no significant increases in flinch-jump thresholds have been reported in studies in which 5HTP has been administered to normal animals [5,20]. In Experiment 1, the administration of 5HTP to rats with raphe lesions appeared to have a greater effect on conditioned aversion learning than would have been anticipated on the basis of the flinch-jump data. In contrast to the flinch-jump experiments, the administration of 5HTP to animals with raphe lesions did not simply return response levels to those of normal animals, but rather appeared to completely block the development of the learned taste aversion. To further characterize the effect of 5HTP on the development of a learned taste aversion, a second experiment was conducted using normal animals as subjects.

METHOD

Sixteen normal male albino rats weighing 300–350 g were obtained from the Holtzman Company (Madison, WI). The details of this experiment, including the training procedures, were identical to those in Experiment 1, unless noted.

Ten rats (Group 5HTP) were injected with 50 mg/kg of DL-5HTP 15 min prior to the presentation of saccharin on the training day. The remaining six rats (Group SAL) received injections of 0.9% saline in a volume equivalent to the 5HTP injection. All rats received LiCl injections following saccharin presentation. The rats were tested for an aversion with presentation of saccharin on Day 4 (Test 1) and Day 5 (Test 2) after training. At the time of training the mean body weight for Group 5HTP was 368.5 g (SD = 18.2) and for Group SAL, 384.5 g (SD = 23.5).

RESULTS

Neither daily water intake nor initial saccharin intake prior to the pairing of saccharin and LiCl differed between 5HTP-pretreated and saline-pretreated groups (Table 2). When tested with saccharin four days after the LiCl treatment both groups showed a significant decrease in saccharin intake. However, the 5HTP administration appeared to attenuate this effect, since Group 5HTP drank significantly more saccharin than Group SAL. On the second saccharin test trial Groups 5HTP and SAL no longer differed significantly from each other; however, Group SAL, but not 5HTP, continued to drink less saccharin than prior to LiCl poisoning.

DISCUSSION

The results confirm the finding of Lorden and Margules [10] that lesions placed in raphe nuclei destroy 5HT neurons and enhance the learning of a conditioned taste aversion. The results further indicate that administration of the serotonin precursor 5HTP can block this effect.

Previous studies have shown that levels of forebrain 5HTP modulate sensitivity to painful cutaneous stimuli [5,20]. These results suggest that lesions of 5HT neurons might enhance the development of a learned taste aversion by increasing the subjective intensity of the LiCl administration. Studies of the parameters involved in taste aversion learning show that one means of increasing the suppression of taste-cue consumption in the conditioned aversion paradigm is to increase the dose of the toxic agent [3]. In the current study, an enhanced suppression of saccharin intake was found in animals with raphe lesions that had received an LiCl dose equal to that received by controls. Thus, this effect may have been due to an increased response in the raphe animals to the toxicity of the LiCl injection. Alternatively, animals with raphe lesions may have been more sensitive to the taste cue, and may have formed a stronger association between the taste cue and the LiCl toxicity. Such an interpretation cannot be ruled out in the current study, but seems unlikely. No

TABLE 2

THE EFFECT OF 5HTP PRETREATMENT IN NORMAL ANIMALS ON SACCHARIN INTAKE IN THE TASTE AVERSION PARADIGM

Group	N	Pre-LiCl		Post-LiCl		
		Water	Saccharin	Water	Saccharin Test 1	Saccharin Test 2
5HTP	10	15.3 ± 5.4	14.5 ± 4.0	13.3 ± 3.2	5.6 ± 4.2*†	10.5 ± 6.3
SAL	6	16.4 ± 2.3	16.9 ± 1.6	13.4 ± 1.6	1.7 ± 1.0*	8.9 ± 4.4*

*Differs significantly from pre-LiCl intake, $p<0.01$.
†Differs from Group SAL, $p<0.05$.

alterations in pre-LiCl consumption of saccharin or post-LiCl consumption of the unpaired cue sodium chloride were observed either in the present experiment or in data reported by Lorden and Margules [10] using either electrolytic lesions or more specific chemical lesions of the raphe nuclei.

The finding that pretreatment with 5HTP attenuated the acquisition of the learned aversion in rats with damage to the raphe nuclei is in keeping with the reported effects of 5HTP on shock sensitivity [5,20]. The 75 mg/kg dose of 5HTP administered to Group L+5HTP in Experiment 1 has been shown by other investigators to return both telencephalic 5HT content and shock thresholds to normal in rats depleted of serotonin by medial forebrain bundle lesions [5]. Thus, 5HTP administration may attenuate taste aversion learning by decreasing sensitivity to the toxic affects of LiCl.

There were no significant differences in saccharin intake prior to LiCl administration between rats that received 5HTP and those that did not. It cannot be argued, therefore, that failure of rats pretreated with 5HTP to avoid saccharin to the same degree as those pretreated with saline was due to the failure of 5HTP groups to drink a sufficient quantity of saccharin during training to enable them to associate its taste with the effects of the LiCl. It is possible, however, that in the taste aversion paradigm, 5HTP may produce an amnesic or perhaps, a state dependent effect [17]. This explanation of the effects of 5HTP cannot be ruled out without further testing. In addition, it cannot be conclusively stated that the effects of 5HTP on taste aversion learning are due to a central rather than peripheral action of the drug. These possibilities will have to be clarified before more definitive statements can be made about the possible mechanisms of action of 5HTP in the learned taste aversion paradigm.

The basic findings in the current study are in agreement with previous research on the effects of serotonin depletion and repletion on sensitivity to noxious stimuli [5, 8, 20, 21]; however, there are some points of disagreement. The finding that pretreatment with 5HTP attenuated the acquisition of the learned taste aversion in normal animals was unexpected. Previous work investigating sensitivity to foot-shock in normal animals indicated that pretreatment with 5HTP did not alter the flinch-jump threshold in normal animals [5,20]. The differential results in the effects of 5HTP pretreatment in these two paradigms is not the result of differences in the dose of 5HTP employed. Because of the toxicity of 5HTP in normal rats, a lower dose of 5HTP was administered in the conditioned taste aversion experiment (50 mg/kg) than that used in the shock sensitivity experiments (75 mg/kg). This suggests that the mechanism of action of 5HTP in the taste aversion paradigm differed from the mechanism of action in the shock sensitivity paradigm. Exactly what these differences are is not clear. An explanation of the effects of 5HTP in the taste aversion paradigm in terms of either a state-dependent learning effect or a peripheral action of the drug would account for this difference. It should also be noted, however, that while 5HTP administered to normal animals does not appear to reduce sensitivity to shock in normal rats, fluoxetine, a 5HT uptake blocker, does do so [15]. Thus, under some conditions an increase in 5HT at the receptor sites can decrease shock sensitivity in normal rats.

The degree to which the administration of 5HTP to rats with raphe lesions blocked the development of the learned taste aversion was also unanticipated. Normal animals administered 5HTP developed attenuated aversions; however, in rats with raphe lesions the aversion were completely blocked. The reasons for these differences are unclear. The animals with raphe lesions received a larger dose of the 5HTP; however, this dose has been shown by other investigators [5] to return telencephalic serotonin content to control levels. Thus, one might also expect the learned behavior to return to levels comparable to those seen in normal animals. Instead, the rats with raphe lesions tended to overshoot normal values and show a complete blockade of the effect. It is possible that this overshoot is a result of the development of supersensitivity in these animals. This suggests that 5HTP or its metabolites is having a supernormal effect on the postsynaptic neurons and that this effect is blocking the development of the learning. In normal animals no such supersitivity exists and the effect of the 5HTP-pretreatment is to produce an attenuation of the learning but not to block it completely. Thus, equating the doses for the supersensitivity should produce similar effect in both groups of animals. That is, the administration of a sufficient dose of 5HTP to normal rats should also block the development of a conditioned taste aversion.

Alternatively, Yunger and Harvey [21] have shown that 5HTP can be converted to serotonin in catecholamine neurons. Thus, it is possible that the synthesis and release of serotonin in animals with lesions occurs at abnormal sites. This might account for difference in effects observed when 5HTP is administered to normal rats or rats with raphe lesions. Such differences in the site of metabolism and release of the 5HTP or 5HT could alter the effects of 5HTP in the conditioned aversion paradigm. Clarification of these issues requires further experimentation.

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