Pharmacology Biochemistry & Behavior, Vol. 18, pp. 785–790, 1983.

5-Hydroxytryptophan-Induced Conditioned Taste Aversion to Ethanol in the Rat[1]

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Received 17 October 1981

ZABIK, J. E. AND J. D. ROACHE. *5-Hydroxytryptophan-induced conditioned taste aversion to ethanol in the rat.* PHARMACOL BIOCHEM BEHAV **18**(5) 785–790, 1983.—This experiment was conducted to determine the efficacy of 5-HTP in producing conditioned taste aversions (CTAs) to ethanol in rats restricted to a one-hour daily access to fluid. Administration of 100 mg/kg of DL-5-HTP immediately following novel exposure to ethanol resulted in an aversion of such magnitude that some rats refused to consume the ethanol solution. Since ethanol was the only fluid available to these rats, they eventually died, presumably of dehydration. By comparison, LiCl administration also produced a CTA to ethanol, but no such persistent rejection was observed. Both 5-HTP and LiCl also produced CTAs when saccharin and tartaric acid solutions were used as novel fluids, but these aversions were short-lived and all rats resumed drinking. The causative factor(s) in the persistent ethanol rejection until death observed in rats treated with 5-HTP remain undetermined but the results have indicated that simple CS-UCS associative learning mechanisms are probably not a primary causative factor.

Ethanol Conditioned taste aversion Serotonin Novel fluids 5-HTP LiCl

AS a recent review [16] demonstrates, numerous investigators have studied the association between central serotonergic function and voluntary ethanol consumption in experimental animals. Many pharmacological manipulations have been utilized in evaluating the role of serotonergic systems in the regulation of volitional ethanol intake in rats. Of particular relevance to the present paper are the reports describing an inhibitory effect of DL-5-hydroxytryptophan (5-HTP), the precursor to serotonin (5-HT), on ethanol consumption by rats [6, 7, 14, 27]. Since 5-HTP is the precursor to 5-HT, this inhibitory effect supports the involvement of the serotonergic system in the inhibition of volitional ethanol intake.

In a previous study from our laboratory [27], rats were adapted to a chronic fluid-deprivation drinking schedule during which they were given access to ethanol (12%, v/v) as the sole source of drinking fluid for one hour daily. Under these conditions, 5-HTP pretreatment caused a reduced intake in comparison to a predrug ethanol baseline. Following this single 5-HTP injection, approximately 25% of the rats never resumed drinking on subsequent daily exposures to the ethanol solution. After a period of persistent refusal to drink ethanol, these rats eventually died, presumably of dehydration. The persistence of the ethanol rejection, well beyond any known effects of acute drug administration, suggested the involvement of a conditioned taste aversion (CTA) to the ethanol solution.

Conditioned taste aversions are manifested as an avoidance reaction to the taste of a food or fluid which has previously been associated with illness or malaise. Presumably, CTAs are the result of a learned association [5,18] between the taste of a food or fluid (conditioned stimulus, CS) and some aversive or punishing property of a drug (unconditioned stimulus, UCS). Generally, in CTA studies, rats are injected with a drug after the ingestion of a novel-tasting fluid. A reduced intake of this fluid on the next exposure to it is taken as evidence that a CTA had developed.

In the earlier report [27] where rats died following a persistent ethanol rejection, 5-HTP was administered before drinking rather than afterward, as in a usual forward conditioning CTA paradigm. The administration of a drug (UCS) before the CS exposure, called backward conditioning, is considered only minimally effective in producing conditioned associations (CTAs) [2]. Nevertheless, the long-term rejection of ethanol to the point of death suggested the involvement of a CTA. The following experiment was performed to determine whether 5-HTP was capable of inducing a CTA using a forward conditioning paradigm and whether a CTA could possibly result in a long-term rejection until death.

To maintain comparability with the previous report [27], similar deprivation conditions, ethanol concentration, and 5-HTP dose were utilized. However, a standardized CTA

[1]This research was supported in part by Pharmacology/Toxicology Training Grant GM 07095 (to JDR) and by Biomedical Research Support Grant RR 0558613 (to JEZ).

procedure was implemented, using novel fluid exposure rather than chronic ethanol ingestion. Solutions of saccharin and tartaric acid, along with ethanol, were included as novel fluids. These other fluids were included for comparison to ethanol to determine the specificity of 5-HTP's effect. Saccharin was used because it is an example of a palatable, nonpharmacological novel fluid widely used in CTA studies. A tartaric acid solution was included because it is a less palatable, nonpharmacological fluid which results in reduced total daily fluid intake much like ethanol. For purposes of comparison, LiCl was also utilized as a UCS since this drug is commonly used for aversive conditioning in CTA studies. Under similar conditions, LiCl had previously been shown to be effective in producing a CTA to ethanol and saccharin [19].

METHOD

Subjects

The subjects were 62 adult, male Sprague-Dawley rats, weighing between 225–275 g, obtained from Murphy Breeding Laboratories, Plainfield, IN. Upon receipt, rats were housed in randomly selected pairs in stainless steel cages (26×21×20.5 cm) with free access to tap water and Wayne Lab Blox®. Environmental conditions were maintained constant with temperatures of 21–24°C and a 14/10 hour light/dark cycle.

Procedures

Following four to five days of acclimatization, the rats were restricted to one hour distilled water access daily. Food remained freely available during the 23 hours of fluid deprivation, but no food was available during the one hour fluid access. Once on the deprivation schedule, rats were weighed and placed individually in drinking cages at a specified time each day, seven days a week. Each of the experimental drinking chambers consisted of a wire-mesh cage, similar to the home cage, individually suspended in a sound-attenuated chamber with uniform fluorescent lighting. Air blowers for each quartet of chambers served to maintain constancy of air circulation, temperature, and noise level. Each chamber was fitted with a glass drinking tube connected to an external, stoppered 50 ml burette, permitting visual measurements of fluid intake to the nearest 0.1 ml during the test session. The front door of each chamber was equipped with an eyepiece to permit visual observation of the animals without disturbing their performance during the test session. After two weeks of distilled water access, daily water intake had stabliized to a baseline (less than 5% daily fluctuation). On the day chosen as the Novel Conditioning Day, one of three novel fluids was substituted for distilled water in the drinking cages as follows: 15 rats received a solution of ethanol (12%, v/v); 15 rats received a solution of saccharin (0.1%, w/v); 16 rats received a solution of tartaric acid (0.8%, w/v); and the remaining 16 rats were continued on distilled water. Immediately following the one hour Novel Day drinking session, all rats received IP injections as follows: control injections of physiological saline (0.9%, w/v) were administered to five rats from each of the four fluid groups, five additional rats of each group received LiCl (3 mEq/kg), and the remaining rats of each group received injections of DL 5-HTP (100 mg/kg) prepared as a suspension in distilled water with two drops of Tween 80 added per 5 ml of suspension. All injections were given in a volume of 2 ml/kg. Following injections, all rats were returned to their home cages as usual. On the next two consecutive days, all rats were only allowed access to distilled water in the drinking cages. On the third day (Retest Day-1) following novel conditioning, the appropriate novel fluids were again substituted for water in the drinking boxes. For the remainder of the experiment, all rats were subsequently maintained on the deprivation schedule and given access only to their respective test fluids.

The drinking data are expressed as ml/kg of body weight to minimize any differences in fluid intake between rats of different body weight. In order to determine the existence of a CTA, each rat served as its own control and the data were analyzed by comparing the Retest Day intake with Novel Day intake using the correlated, two-tailed Student's t-test. Where analyses were conducted by use of analysis of variance (ANOVA), t-tests were used for individual comparisons.

RESULTS

Figure 1 presents the volumes of the four fluids consumed on Novel Day and the first retest exposure (Retest Day-1). Treatment with 5-HTP resulted in a significantly reduced intake of ethanol, tartaric acid, and saccharin on this first retest exposure. These results indicate that 5-HTP was an effective conditioning agent, inducing a CTA to ethanol and the other novel fluids as well. LiCl administration, like 5-HTP, resulted in CTAs to all three novel fluids. The rats which were maintained on distilled water access were unaffected by either of the drug treatments.

In the NaCl-treated control groups, the Retest Day-1 intake of all three novel fluids was significantly greater than on Novel Day, while intake of distilled water remained unchanged. The increased intake of novel fluids probably reflects a reduction in neophobia [18]. This would be the predicted result since NaCl would not be expected to induce a CTA and the novel fluids were more familiar to the rats upon second exposure.

Two intervening days of distilled water access were provided to all rats between Novel Day and Retest Day. This allowed time for recovery from any drug-induced toxicosis as well as an opportunity to replenish body water in compensation for any reduced volumes consumed on Novel Day. Table 1 presents the volumes consumed on the two intervening water days for the animals exposed to ethanol on Novel Day. Each of the three groups drank significantly more on the first day in comparison to pre-novel volumes. While water intake for the NaCl and LiCl treatment groups returned toward pre-novel values on the second water day, the water intake of the 5-HTP group remained significantly elevated, suggestive of an additional component in the actions of 5-HTP in ethanol-consuming animals. Water intake (not shown) on these days was only slightly elevated in the tartaric acid groups and unchanged in the saccharin and distilled water groups.

In order to evaluate the duration of the observed CTAs, the rats were maintained on their respective fluids from the first retest day until the end of the experiment. To facilitate comparisons between the four fluid groups, Fig. 2 presents data for the first six retest days as a percentage of Novel Day ingestion. The NaCl groups were omitted because no CTA was observed and all subsequent retest values were above Novel Day. With the exception of the ethanol/5-HTP pairing, all other aversions appeared to extinguish quite rapidly. An ANOVA showed that the main effects of fluid, $F(2,25)=8.09$, $p<0.01$, drug, $F(1,25)=4.92$, $p<0.05$, and day, $F(3,25)=53.45$, $p<0.001$, were significant over the first four

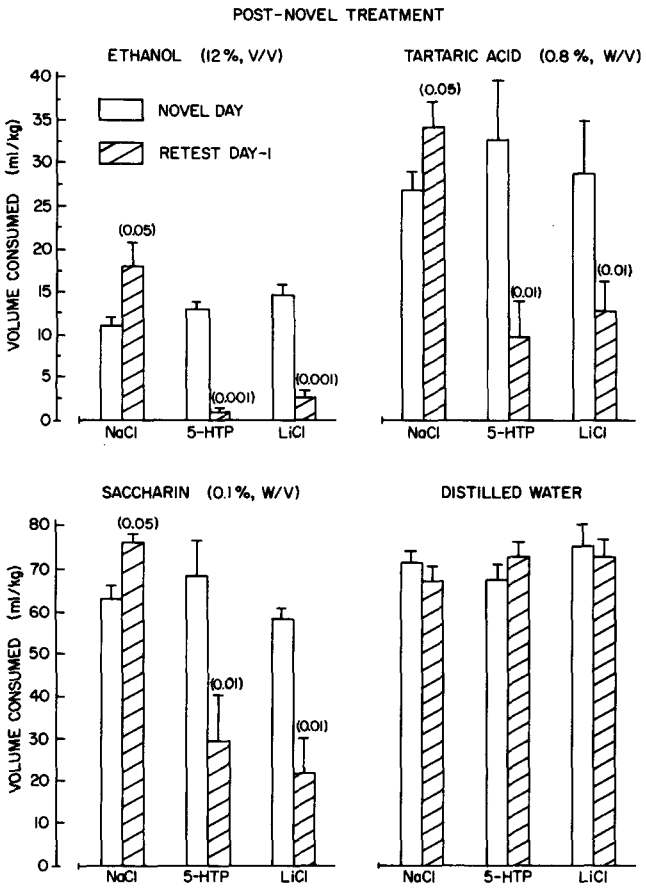

FIG. 1. Mean intake of fluids on Novel Day and Retest Day-1. Drugs were administered immediately following the drinking session on Novel Day, as described in Method section. Vertical bars indicate standard errors of the means. Probability values (shown in parentheses) indicate significant differences between Retest Day-1 and corresponding Novel Day.

TABLE 1

WATER INTAKE (ml/kg) OF RATS GIVEN ETHANOL ON NOVEL DAY

Treatment	N	Pre-Novel Day	Intervening Water Days +1	+2
NaCl	5	62.3 ± 3.2	78.7 ± 4.8*	68.3 ± 4.4
LiCl	5	59.0 ± 4.4	77.2 ± 3.4*	62.5 ± 2.9
5-HTP	4	66.0 ± 4.5	87.3 ± 5.8*	74.8 ± 4.9*

Data expressed as Mean ± S.E.M. For NaCl and LiCl groups N=5, whereas N=4 for the 5-HTP group because of mechanical problems which prevented the recording of data for one rat.

*Indicates significant difference ($p<0.001$) in comparison to Pre-Novel Day volume using correlated t-test.

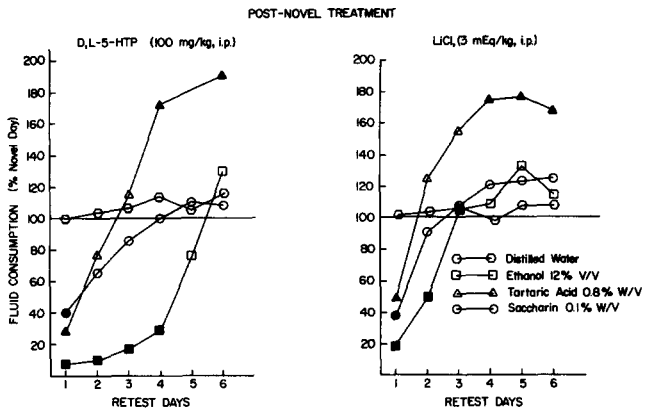

FIG. 2. Mean intake (expressed as percent of Novel Day) on six consecutive retest days. Drugs were administered immediately following the drinking session on Novel Day, as described in Method section. Filled symbols indicate significant ($p<0.05$) differences compared to Novel day.

retest days. Examination of the ethanol group alone showed that 5-HTP caused a CTA of longer duration than LiCl, drug × day, $F(3,24)=6.0$, $p<0.01$. Individual comparisons using the correlated t-test showed that the 5-HTP-induced CTA lasted four days whereas the LiCl-induced CTA lasted two days. Saccharin or tartaric acid intakes were significantly reduced by 5-HTP and LiCl on the first retest day only. Extinction of 5-HTP-induced CTAs to either of these fluids tended to be delayed in comparison to the LiCl groups, however, this effect failed significance, $F(1,16)=3.03$, $p>0.10$. Thus 5-HTP produced a CTA of longer duration than LiCl when ethanol was the novel fluid and tended to do the same with saccharin and tartaric acid. It has been suggested that the rapidity of extinction reflects the UCS strength [3], thus 5-HTP may have been a stronger UCS than LiCl in this experiment.

The group mean for the five 5-HTP-treated rats exposed to ethanol surpassed Novel Day intake by the sixth retest day, but in actuality, only three rats resumed drinking greater volumes of ethanol. The remaining two rats continued rejecting ethanol. As can be seen in Fig. 3, during the first four retest days, there were no distinguishable differences among these five rats in that all were similarly rejecting the ethanol solution. The two rats which persisted in their rejection of ethanol finally died following the drinking session on Retest Day-13. During the latter days of rejection, these rats were exhibiting signs of extreme dehydration, body weight loss, muscle weakness, tremor and ataxia.

These results clearly suggest that 5-HTP, like LiCl, is capable of inducing CTAs to novel fluids in a forward conditioning paradigm. The extended suppression of ethanol ingestion to the point of death, in 5-HTP-treated rats, while unusual in food aversion studies, replicated the similar observations [27] made using different experimental conditions.

DISCUSSION

The results of this experiment demonstrated that the administration of 100 mg/kg of DL 5-HTP in a forward-conditioning paradigm does result in conditioned taste aversions to novel solutions of ethanol, saccharin, and tartaric acid. With the ethanol solution, 5-HTP produced CTAs of

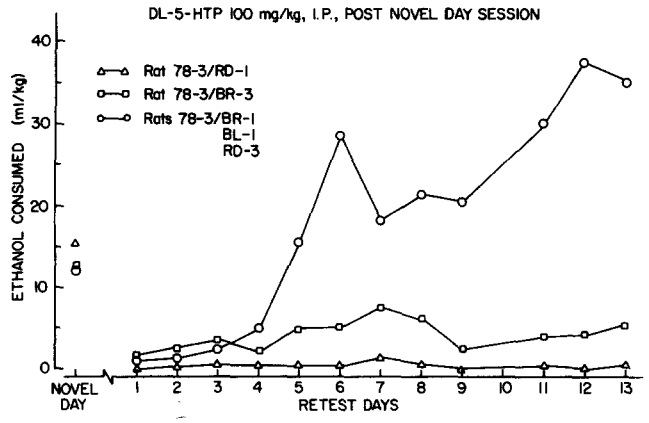

FIG. 3. Ethanol intake on 13 consecutive retest days following 5-HTP administration on Novel Day, as described in Method section. Mean values are presented for three surviving rats and individual values are presented for two rats which persisted in rejection and died following Retest Day-13.

longer duration than did a 3 mEq/kg dose of LiCl. A similar tendency of 5-HTP was also observed when solutions of saccharin or tartaric acid were utilized as Novel Fluids. Since reduced extinction rates have been considered to reflect greater CTAs [3], these results indicate that under these conditions, 5-HTP was a stronger UCS than LiCl, an agent commonly thought to be one of the most effective drugs for conditioning CTAs [17].

The persistent rejection of ethanol to death observed with two rats following the 5-HTP/ethanol pairing was of particular significance. This observation replicates an earlier result obtained from this laboratory under different experimental conditions [27]. Although a reduced intake was observed following the 5-HTP/saccharin or 5-HTP/tartaric acid pairings, no long-term rejection to death was observed, thus indicating a unique interaction between 5-HTP and ethanol. 5-HTP-induced CTAs to saccharin and tartaric acid solutions extinguished rapidly as did LiCl-induced CTAs to all three novel fluids. While conditioning mechanisms may play a role in the persistent rejection of ethanol to death, they presumably are not the only factor. Certainly the data indicate the occurrence of some drug-drug interaction between 5-HTP and ethanol, the nature of which is undetermined.

In consideration of the uniqueness of ethanol, the data have indicated that the ethanol solution was more salient than the saccharin and tartaric acid solutions. Salience has been defined as the propensity of a solution of a given taste quality (CS), to be associated with the drug UCS thereby establishing a CTA [11]. However, there is no indication in the literature that enhancing the salience of a CS could possibly produce a CTA of sufficient intensity to override the thirst drive and cause an animal to die of dehydration rather than drink the fluid. It is also possible that 5-HTP was a more severe UCS than LiCl and as such interacted with the more salient ethanol to produce the greatest aversion. Certainly, the data indicates that when injected after drinking, 5-HTP was a stronger UCS than LiCl. However, it is again difficult to suggest that these factors alone could result in the long-term rejection until death.

Another factor is that ethanol has pharmacological activity and thus a drug-drug interaction with 5-HTP could explain the phenomenon. On Novel Day, the rats consumed an average of 1.5 g/kg of ethanol and exhibited signs of intoxication, including sedation, muscle relaxation, and ataxia. Thus, not only the salience of ethanol but also its pharmacological activity could interact with both 5-HTP and LiCl. Since serotonergic involvement has been implicated in ethanol's respiratory depressant [24] and hypothermic [21] effects, 5-HTP may have enhanced these actions of ethanol. Similarly, LiCl may also have interacted with ethanol since it has been shown to enhance ethanol-induced narcosis [13]. Thus, the pharmacological activity of ethanol may have interacted with 5-HTP and LiCl to produce the greater aversions observed when ethanol was used as a novel fluid. However, some unique effect of 5-HTP is necessary to explain a specific drug-drug interaction between 5-HTP and ethanol.

An enhancement of water intake was observed for two days after the 5-HTP/ethanol pairing. All of the rats which received ethanol on Novel Day drank increased water volumes on the first intervening water day, presumably to compensate for the reduced fluid volumes consumed on Novel Day. However, only the 5-HTP/ethanol group drank increased volumes on the second intervening water day. The LiCl and saline control groups returned to normal levels of intake on this day. This 5-HTP-enhancement of water drinking was only observed in the rats which received ethanol on Novel Day and not in the rats which received either distilled water or solutions of saccharin or tartaric acid. It cannot be determined at this point whether this effect is related to the 5-HTP-induced long-term rejection of ethanol observed, but it does suggest that 5-HTP and ethanol may interact in ways which may influence fluid intake on subsequent days.

Since 5-HTP is the precursor to serotonin (5-HT) ethanol and 5-HTP may have interacted through a 5-HT-containing neuronal system to perturb some specific serotonergic function. While 5-HTP may be non-specifically taken up into catecholamine neurons at high doses, the 100 mg/kg dose utilized in this study has been reported to be relatively selective for 5-HT-containing neuronal system [4]. As the serotonin precursor, 5-HTP has been utilized in many experiments evaluating the role of 5-HT in the inhibition of ethanol ingestion [6, 7, 14, 27]. Many manipulations of the serotonergic system have been shown to influence ethanol consumption in rats. Increased ethanol intake following the central administration of serotonin neurotoxins [9,15] and reduced intake following centrally administered 5-HT [8] indicate an inhibitory effect of some central serotonin-containing neuronal system on voluntary ethanol intake. Ethanol has been shown to increase serotonin release [20], levels [1,22], and turnover [1, 23, 26] following acute treatment. Decreases in levels [26] and turnover [10,25] have also been observed. Therefore, a 5-HTP administration following acute ethanol ingestion may have resulted in a particularly potent CTA by virtue of an interaction with this inhibitory serotonergic system. However, such interactions would probably not be expected to result in the observed long-term rejection to death unless 5-HTP was profoundly enhancing the acquisition or retention of the CTA. In fact, just the opposite has been shown to occur: the administration of 5-HTP prior to the novel day drinking session was found to attenuate the formation of a LiCl-induced CTA to saccharin [12].

Another possible explanation of the death of certain ethanol rejecting rats is that 5-HTP treatment may have

caused a specific toxic effect. In our laboratory, 5-HTP treatment has only resulted in the death of fluid-deprived rats given ethanol as their sole source of fluid. In studies where an ad lib free choice between ethanol and water was allowed [6, 7, 14], 5-HTP treatment resulted in reductions in ethanol intake, but water intake usually increased in compensation. Despite the common usage of 5-HTP in such experiments, relatively few toxic effects have been reported. In one study providing a choice between water and a 4% ethanol solution, one rat was reported to die following chronic 5-HTP treatment [7]. This rat received 100 mg/kg of 5-HTP twice a day for five days and died one week after the discontinuation of drug treatment, even though it had been drinking the water which was continuously available to it. In this case, a delayed toxic effect of 5-HTP was the more likely explanation for death rather than dehydration, as postulated for our rats. While it remains possible that some toxic effect of 5-HTP could cause fluid-deprived rats to refuse to drink ethanol and thus die of dehydration, evidence presented in the previous report [27] refutes a delayed toxicity mechanism as being the direct cause of death. It was reported that when water was made available to ethanol-rejecting rats, they readily drank it and survived, while others, not given water, continued to reject this fluid and died. This observation indicates that the rejection phenomenon is specific to ethanol as a drinking fluid and that 5-HTP did not render these rats incapable of drinking or cause an irreversible and fatal toxic effect.

In conclusion, it has been shown that 100 mg/kg of DL-5-HTP is able to condition taste aversions to ethanol and other novel fluids when administered under a standard forward-conditioning paradigm. Under these conditions, certain rats were observed to exhibit a persistent rejection of ethanol and eventually die, presumably of dehydration. The death of these rats confirms an earlier observation [27] made under different experimental conditions where 100 mg/kg DL-5-HTP was given as a pretreatment to rats chronically drinking ethanol. A role for condtioned taste aversion in the persistent ethanol rejection phenomenon remains possible, however, the data have indicated that associative learning mechanisms are probably not involved as a causative factor. The persistence of the ethanol rejection is a unique result and warrants further investigation. The data have indicated that some as yet unidentified interaction between 5-HTP and ethanol may be responsible for the rejection phenomenon. Further experiments need to assess which of the potential drug-drug interactions may be responsible as well as to determine whether nonassociative interactions of 5-HTP and ethanol could account for the phenomenon independent of associative learning mechanisms.

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