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Nicotine-Induced Conditioned Taste Aversions Are Enhanced in Rats With Lesions of the Area Postrema

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OSSENKOPP, K.-P. AND L. GIUGNO. *Nicotine-induced conditioned taste aversions are enhanced in rats with lesions of the area postrema.* PHARMACOL BIOCHEM BEHAV **36**(3) 625–630, 1990.—Lesions, which destroy the area postrema and damage the adjacent nucleus of the solitary tract, attenuate or abolish conditioned taste aversions (CTA) induced by a variety of pharmacological agents. In the present experiment 2 groups of male rats received lesions of the area postrema and 2 groups were given sham lesions. One lesioned group and one sham-lesioned group were twice conditioned with 30-min access to a novel 0.15% saccharin solution followed by injection of nicotine (1 mg/kg, IP). The other 2 groups were similarly conditioned with saccharin followed by saline injections. In subequent two-bottle choice tests (saccharin vs. water), the saline-injected rats exhibited strong preferences for saccharin, the sham-lesioned rats injected with nicotine showed a weak but significant ($p<0.05$) aversion to saccharin, and the area postrema-lesioned rats injected with nicotine displayed a significantly ($p<0.05$) stronger CTA than the drug-injected sham-lesioned animals. In Phase 2 all rats were given novel chocolate metrecal (30 min) followed by injection of scopolamine HCl (1 mg/kg, IP). The area postrema-lesioned rats showed significant ($p<0.01$) preferences for the chocolate taste relative to the aversions shown by the sham-lesioned animals. Thus, area postrema lesions attenuated a scopolamine-induced CTA, but enhanced a nicotine-induced aversion. These results suggest that nicotine and scopolamine act at different neural sites in producing CTAs.

Area postrema Nicotine Scopolamine Conditioned taste aversions Brainstem lesions Rats

A number of psychoactive drugs have been found to possess both positive and aversive properties. Opiates, amphetamines, alcohol, nitrous oxide and the benzodiazepines, among others, have been found to have positive reinforcing effects, as shown by maintenance of drug self-administration behaviors, as well as aversive properties, as demonstrated by the ability of these drugs to induce conditioned taste aversions (CTAs). Nicotine is the main psychoactive component in tobacco smoke. This drug has also been found to be self-administered (12,16), yet able to induce a conditioned taste aversion (19, 21, 39) and act as an aversive stimulus in punishment and negative reinforcement paradigms (11,37).

Strong avoidance conditioning of a novel taste can be produced in rats by pairing ingestion of the novel tasting substance with exposure to a toxic agent such as lithium [e.g., (24)] or to ionizing radiation [e.g., (35)], and the suggestion has been made that it is the illness-inducing (i.e., nausea or gastrointestinal disturbance) property of these treatments which make them such effective agents in producing CTAs (9,10). It has been shown that central injections of nicotine induce vomiting in cats [e.g., (1, 2, 14, 23)] and thus studies with nicotine have been seen as possible approaches to help clarify the putative role of emetic mechanisms in the development of CTAs (21).

Nicotine has been shown to produce CTAs in rats, with dose of nicotine and number of conditioning trials directly related to the magnitude of the observed aversion (19, 21, 39). Nicotine antagonists with peripheral (hexamethonium), or peripheral and central (mecamylamine), sites of action have been used to demonstrate that the taste aversion inducing effects of nicotine are probably of central origin, since mecamylamine blocked, and hexamethonium did not alter, nicotine-induced CTAs (19,21). These findings contrast with those concerning the emetic action of nicotine. Hexamethonium has been shown to block the emetic action of nicotine along with mecamylamine [e.g., (2)], and it has been suggested that nicotine evokes vomiting by its actions on nicotine receptors within the area postrema, since ablation of this brain structure abolished the emetic action of nicotine (2, 3, 23).

The area postrema, a circumventricular organ located in the fourth ventricle, has been functionally implicated in a range of physiological and behavioral processes, and especially as a sensor for blood-borne toxins (5). This structure has a reduced blood-brain barrier and is accessible to drugs (such as hexamethonium) which do not penetrate to many other regions of the brain. Despite the fact that rats do not vomit (15), the rat area postrema has been shown to mediate the formation of a variety of CTAs in this

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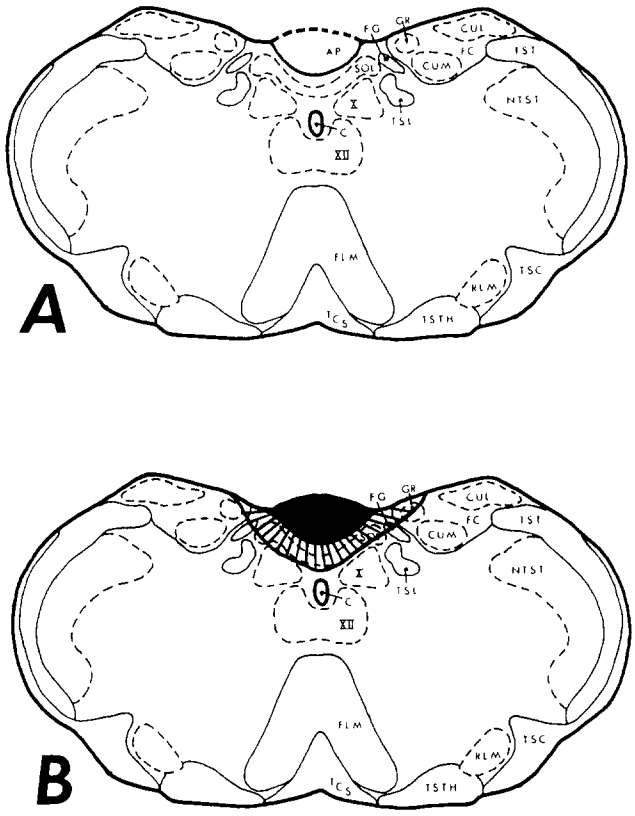

FIG. 1. Representative diagrams of coronal brainstem sections showing the degree of damage following the lesion procedure in Groups S-X and N-X. (A) Sham-lesioned groups. (B) Area postrema-lesioned groups showing the least (darkened area) and greatest (hatched area) amount of tissue damage. Diagrams adapted from Pellegrino, Pellegrino and Cushman (32).

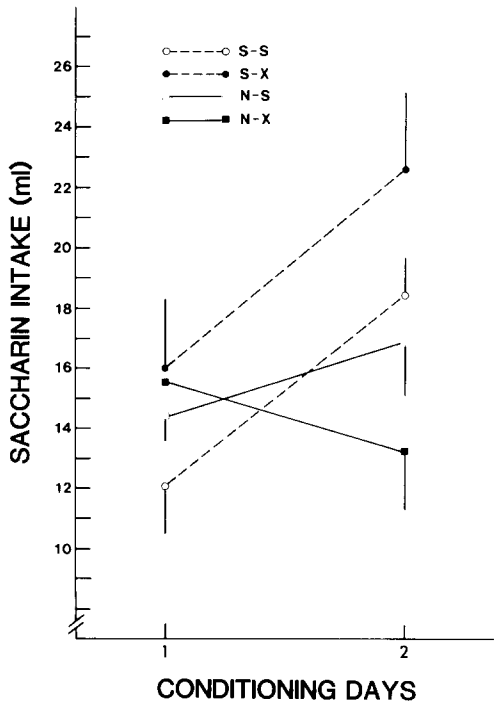

FIG. 2. Mean group saccharin solution intake levels on the two conditioning days in Phase 1. Group designations are as follows: S-S, sham-lesioned rats receiving saline injections; S-X, postremectomized rats receiving saline injections; N-S, sham-lesioned rats receiving nicotine injections; N-X, postremectomized rats receiving nicotine injections. Error bars are standard errors of the mean.

species [e.g., (4, 22, 26–29, 33, 34)]. Of special interest is the previous demonstration that postremectomized rats failed to form a CTA when scopolamine HCl was used as the unconditioned stimulus (UCS) and paired with a novel saccharin taste stimulus (29).

Within this context it was of interest to examine the role of the area postrema in the conditioning of taste aversions with nicotine. On the basis of the previous pharmacological evidence (19,21), we predicted that postremectomy in rats would result in little or no attenuation of nicotine-induced CTAs. In addition, based on previous research in our laboratory (29), we used attentuation of a scopolamine-induced CTA in postremectomized rats as a behavioral assay for integrity of the area postrema.

METHOD

Subjects

Thirty-four sexually mature Long-Evans male hooded rats (Charles River, Quebec) were individually housed in stainless steel cages. The animals were kept in a colony room maintained at approximately 20°C and a 12-hr light–12-hr dark cycle with lights on from 0600 to 1800 hr. The animals were maintained on standard laboratory chow (Purina) and tap water, which were available ad lib unless otherwise noted.

Surgical Procedure

Two groups of rats received area postrema lesions under sodium pentobarbital anesthesia (Somnotol, 65 mg/kg, IP). The animals were anesthetized and then placed in a head-holder which kept the head in a ventroflexed position. The dorsal surface of the brainstem was exposed by retracting the overlying muscles and the atlanto-occipital membrane joining the cranium and spinal column, and enlarging the foramen magnum. The floor of the fourth ventricle was viewed through an operating microscope (Zeiss, OPMI 99) and lesions of the area postrema were made by touching this structure with the tip of a small cautery. The neck muscles and scalp were then sutured and the animals were allowed to recover from the operation for at least two weeks. Two other groups of rats were treated in an identical manner except that the area postrema was not lesioned (sham-lesion procedure).

Behavioral Procedures

Phase 1. All animals were adjusted to a 23.5-hr/day water deprivation schedule over a seven-day period. On Day 8 all rats were given 30 min access to a 0.15% (w/v) sodium saccharin solution. Immediately following this drinking period some of the lesioned rats (Group N-X, n = 8) and some of the sham-lesioned rats (Group N-S, n = 9) were given IP injections of 1 mg/kg of nicotine (Sigma) dissolved in isotonic saline (1 mg/ml). This dose and route of administration were chosen on the basis of a previous study (30). The other lesioned rats (Group S-X, n = 8) and sham-lesioned rats (Group S-S, n = 9) were given IP injections of isotonic saline (1 ml/kg). On Day 9 all of the animals were treated exactly the same as on the previous day and on Days 10–12 the rats were given tap water for 30 min but not otherwise disturbed. On Days 13–15 all rats were given a two-bottle choice test; one bottle

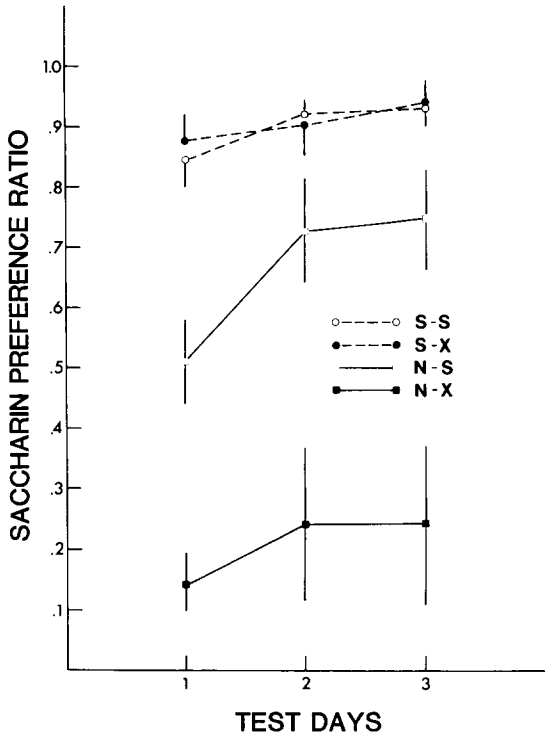

FIG. 3. Mean group saccharin preference ratios as a function of the three test trials in Phase 1. See Fig. 1 for explanation of group designations. Error bars are standard errors of the mean.

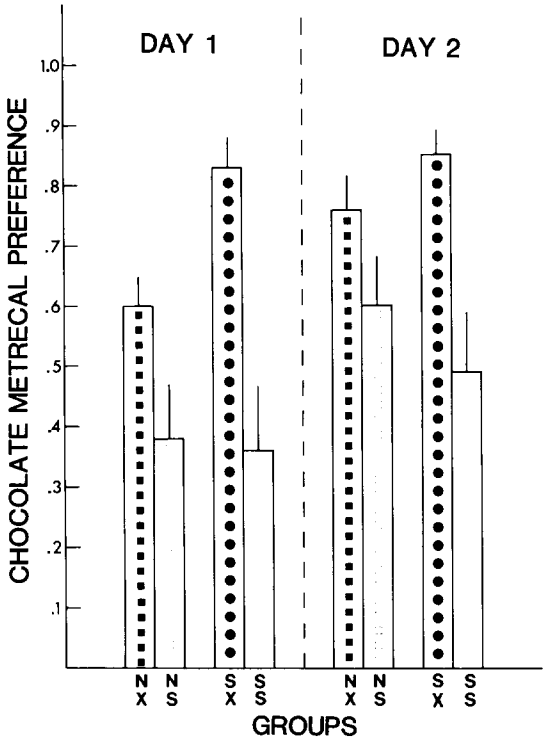

FIG. 4. Mean group chocolate metrecal preference ratios on the two test trials in Phase 2. See Fig. 1 for explanation of group designations. Error bars are standard errors of the mean.

containing tap water and the other containing saccharin solution were presented to each animal for 30 min. Positions of the bottle containing water and the bottle containing saccharin were randomly varied over test days to avoid the formation of a position habit.

Phase 2. Over the next 7 days all animals were put on an ad lib water schedule followed by a 7-day readaptation to a 23.5 hr/day water deprivation schedule. On Day 30 all rats were given 30-min access to a diluted chocolate metrecal (50% metrecal and 50% tap water) solution and immediately following the drinking period were injected IP with 1 mg/kg scopolamine HCl (Sigma, dissolved in isotonic saline, 1 mg/ml). On Days 31–33 the rats were given tap water during the daily 30-min drinking period. Then on Days 34 and 35 all animals were given a two-bottle choice test for 30 min, with one bottle containing the diluted chocolate metrecal and the other containing tap water.

TABLE 1

MEAN GROUP CHOCOLATE METRECAL SOLUTION INTAKE BY THE FOUR GROUPS ON THE CONDITIONING DAY IN PHASE 2

	Lesion Group			
	Sham Lesion		Area Postrema Lesion	
Previous Drug Exposure	Mean	SEM	Mean	SEM
Saline	14.0	1.34	19.3	2.79
Nicotine	13.3	1.40	12.4	2.30

Data Analysis

The dependent measures in this experiment consisted of a stimulus taste preference ratio obtained on two-bottle choice test days and intake volume of the taste stimulus solution on conditioning days. The preference ratio was obtained by dividing the amount of taste stimulus solution consumed by total fluid intake on that particular day. Data were analyzed with analysis of variance procedures followed by post hoc Newman-Keuls tests. The significance level used for hypothesis testing was $\alpha = 0.05$.

Histological Procedure

At the conclusion of the experiment all lesioned and sham-lesioned rats were deeply anesthetized and then perfused intracardially with isotonic saline followed by a 10% solution of formalin. The brains were removed and stored in formalin for at least two days and then coronal sections 50 μm thick were cut on a freezing microtome at the level of the brainstem containing the area postrema. These sections were mounted on slides and stained with cresyl violet.

RESULTS

Histology

Examination of the brain sections from the lesioned rats indicated complete lesions of the area postrema. In most animals there was minimal to extensive damage to the adjacent caudomedial solitary nucleus and solitary tract. A number of animals

also sustained damage to the fasciculus gracilis and the nucleus gracilis. Sham-lesioned rats did not exhibit any signs of damage to the area postrema or surrounding areas. The extent of damage for the smallest and largest area postrema lesion is shown in Fig. 1. The histological sections were very similar to those obtained in previous studies in this laboratory [see photographs of representative sections in (25, 26, 28, 29)].

Nicotine-Induced Taste Aversions

Mean group saccharin solution intake levels for all 4 groups on both conditioning days are shown in Fig. 2. An analysis of variance of saccharin intake among the 4 groups on the first conditioning day indicated no significant group differences ($p>0.30$). A comparison of mean changes in intake level from the first to the second conditioning day revealed a significant effect of the drug injection, $F(1,30)=16.87$, $p<0.001$, but not of the lesion procedure or the drug by lesion interaction ($ps>0.10$). Inspection of Fig. 2 reveals that injection of nicotine resulted in much smaller increases in saccharin intake on the second conditioning day relative to the saline-injected groups.

The data from the more sensitive two-bottle test procedure revealed a much stronger CTA (lower preference ratio) in Group N-X than in Group N-S (see Fig. 3). The 2 saline-injected comparison groups (S-X and S-S) showed comparable, high levels of saccharin preference. Statistical analyses of these data revealed a significant drug effect, $F(1,30)=55.47$, $p<0.001$, a significant lesion effect, $F(1,30)=12.60$, $p<0.001$, and a significant drug by lesion interaction, $F(1,30)=13.37$, $p<0.001$. Post hoc comparisons showed a significantly stronger aversion of the saccharin taste in Group N-X than in Group N-S ($p<0.05$), and a significantly lower preference ratio in Group N-S than in the 2 saline-treated groups ($p<0.05$), a difference most evident on the first test trial. The 2 saline-treated groups did not differ significantly ($p>0.50$). These results thus show that nicotine injections produced CTAs to the saccharin which were significantly stronger in the rats with lesions of the area postrema than in the sham-lesioned animals.

Scopolamine-Induced Taste Aversions

Group mean chocolate metrecal solution intake levels are provided in Table 1. These data were also analyzed with a two-way analysis of variance to test for any effects of the lesion procedure and previous exposure to the nicotine. Although there were no significant effects of the lesion, nor of the drug by lesion interaction ($ps>0.10$), the analysis did reveal a trend toward a significant reduction in stimulus taste solution intake in the rats previously exposed to nicotine, $F(1,30)=3.71$, $p=0.06$. This reduction in intake level probably reflects a weak generalized aversion to the sweet chocolate metrecal taste based on the previous conditioned aversion to the saccharin taste.

Figure 4 presents group mean preference ratios for chocolate metrecal as a function of test days (two-bottle choice tests). Statistical analysis revealed a significant effect of the lesion procedure on the magnitude of the scopolamine-induced CTA, $F(1,30)=19.54$, $p<0.001$, but no significant effect of the previous exposure to nicotine ($F<1$) or of the lesion by nicotine interaction ($p>0.10$). Thus, there was a significant attenuation of the scopolamine-induced taste aversions in the rats with the area postrema lesions (see Fig. 4). This finding confirms the behavioral effectiveness of the lesion procedure (behavioral assay procedure).

DISCUSSION

Depsite the fairly high dose of nicotine (1 mg/kg) used in the present experiment, there was no evidence of any severe respiratory difficulty or obvious motor ataxia. Previous studies on locomotor changes following challenge with up to 0.8 mg/kg nicotine (SC) have revealed a complex pattern of effects [e.g., (20)] but no severe impairments. Most likely the IP route of administration used in the present study resulted in less rapid vascular uptake of the drug than in the previously used SC route of administration [e.g., (19, 21, 39)]. In comparison to these previous studies, the magnitude of the obtained nicotine-induced CTA in the sham-lesioned rats in the present study was not as large, despite the large dose of nicotine employed. Very likely, this discrepancy also reflected the difference in route of administration between the studies. On the other hand, the weak CTAs displayed by the sham-lesioned rats in the present study did allow for the demonstration of relatively enhanced aversions in the area postrema-lesioned animals (i.e., the problem of a "floor effect" was avoided).

The present results are consistent with previous data suggesting that the site of action for nicotine-induced CTA is central, rather than peripheral (19, 21, 39). As predicted, the results of Phase 1 showed that integrity of the area postrema is not required in order to produce a CTA with nicotine. In contrast, the findings of Phase 2 confirmed that the conditioning of taste aversions with scopolamine HCl, a drug that also has both central and peripheral effects, is dependent on mediation by an intact area postrema [cf. (29)]. Finally, the present results also demonstrated that lesions of the area postrema not only failed to attenuate a nicotine-induced taste aversion, but in fact *increased* the magnitude of the aversion. Such enhanced aversions have been reported previously with other agents (6,25).

The experimental procedure used in the previous study, showing that a scopolamine-based CTA is dependent on an intact area postrema (29), was very similar to the one used in the present experiment. Male rats, with lesions of the area postrema or with sham lesions, experienced two conditioning trials consisting of presentation of a 0.1% sodium saccharin solution (CS) followed by IP injection of scopolamine HCl (1.0 mg/kg) as the UCS. When tested in a two-bottle choice test 4 days after the second conditioning trial, the sham-lesioned rats displayed a strong aversion to the saccharin taste. In contrast, the postremectomized rats exhibited strong preferences for the saccharin taste. These preferences were similar in magnitude to those shown by a sham-lesioned control group which had been injected with isotonic saline after drinking saccharin solution in the conditioning phase. Thus, in contrast to the present results with nicotine, centrally acting scopolamine failed to condition a taste aversion to saccharin in postremectomized rats.

Both nicotine and scopolamine HCl have peripheral and central effects. The present results showed that nicotine-induced CTAs were produced by activation of cholinergic systems not related to the area postrema. In contrast, scopolamine HCl induced CTAs by direct or indirect stimulation of the area postrema, perhaps by activation of muscarinic receptors in this structure [cf. (31)].

It has been suggested previously that perhaps all that is required to produce a CTA is that the unconditioned stimulus (UCS) drug induce a "novel" state distinguishable from the drug-naive state (8). The present findings are clearly not consistent with such a hypothesis. Scopolamine HCl produces very dramatic and clear behavioral effects dependent on central activation and not related to area postrema integrity [see (29)], yet does not induce a CTA without an intact area postrema. Thus, it is reasonable to suggest that nicotine produces CTA by activation of a specific neural pathway which results in aversive internal cues, and not as a result of induction of some general novel state.

Characterization of the aversive effects of nicotine at a behavioral level has suggested that these effects differ from those produced by such drugs as lithium or scopolamine (30,36). Parker examined the nature of the conditioned responses (CRs) elicited by

either lithium or nicotine-paired flavors to determine if they were similar (30). The procedure used was the taste reactivity test developed by Grill and Norgren (13). It was found that sucrose paired with nicotine elicited suppressed ingestion response of tongue protrusion and paw licking, but did not elicit enhanced rejection responses. In contrast, sucrose paired with lithium elicited not only suppressed ingestion responses, but also an enhanced level of rejection responses, including chin rubbing and paw treading. The authors suggested that the conditioned aversions induced with lithium were qualitatively different than those induced by nicotine. Thus, not only do these two drugs differ in their neural sites of action, with lithium-induced CTA mediated by the area postrema and nicotine-induced CTA not dependent on this neural structure, but they also differ in the types of CRs that are produced. A similar analysis has been presented for scopolamine [see (36)].

If the appearance of chin-rub CRs are related to some internal state, such as nausea or disgust, perhaps as a result of drug action on the area postrema, then it might be argued that drugs such as nicotine may not produce such internal states and, thus, may depend on a different mechanism in producing aversive effects. Such an analysis would be consistent with the observed pharmacological dissociation of the emetic properties of nicotine from its CTA effects [cf. (2,21)]. The "drug shyness" hypothesis, proposed by Hunt and Amit (17) to account for the aversive properties of self-administered drugs, would be consistent with such an analysis.

Nicotine can now be added to the list of drugs and other procedures which will induce a CTA independent of area postrema integrity. Drugs included in this list are amphetamine (4), apomorphine (6,42), morphine (41), and alcohol (18,38). It is interesting to note that all of these drugs will sustain self-administration behavior [e.g., (17)]. A nonpharmacological UCS, vestibular stimulation (motion sickness), will also induce a CTA which is independent of area postrema integrity (25,40).

In some cases postremectomies not only failed to attenuate, but actually *enhanced*, the magnitude of the induced CTA (6, 25, 40). The finding of an enhanced nicotine-induced CTA (Phase 1) in the present study, is thus compatible with these previous findings. Such enhanced aversions may reflect an influence of the area postrema on either the perception of taste stimuli or on the association of taste stimlui with the aversive consequences. Some previous research suggests that a change in the perception of taste stimuli may be involved. Edwards and Ritter (7) examined the effects of area postrema lesions on food consumption in rats. These lesions had no effect on consumption of regular laboratory food pellets, even when the rats were food deprived. However, they produced an increase in consumption of highly palatable foods, such as instant breakfast and cookies. If the area postrema-lesioned rats in the present experiment perceived the saccharin solution (a highly preferred taste in rats) as having some enhanced quality, this could account for the increased magnitude of the subsequent CTA. Enhanced quality would presumably result in a more potent taste CS and, therefore, result in stronger conditioning. This issue could be examined in future studies by testing rats with ablations of area postrema in the taste reactivity procedure (13) and comparing them to sham-lesioned animals. Postremectomized rats should exhibit enhanced ingestion responses of tongue protrusion and/or paw licking when tested with highly palatable tastes.

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