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Conditioned Taste Aversion and Latent Inhibition Following Extensive Taste Preexposure in Rats with Insular Cortex Lesions

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Conditioned taste aversion and latent inhibition following extensive taste preexposure in rats with insular cortex lesions

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Abstract

Lesions of the insular cortex (IC) attenuate acquisition of conditioned taste aversions (CTAs). We have suggested that this impairment is the expected consequence of a failure of IC-lesioned (ICX) rats to recognize unfamiliar taste stimuli as novel. That is, ICX rats treat novel taste stimuli as if they are familiar and as a result show a latent inhibition-like retardation of learning. This account anticipates that ICX rats should acquire CTAs at the same slow rate as normal rats that are familiar with the taste stimulus. The present experiment confirmed this hypothesis in a design that compared CTA acquisition in normal and ICX rats following either extensive taste familiarization or no taste familiarization prior to conditioning.

Keywords

Conditioned taste aversion; Latent inhibition; Taste neophobia; Insular cortex; Rat

1. Introduction

A conditioned taste aversion (CTA) is manifested as a reduction in consumption of a taste (conditioned stimulus, CS) that has previously been followed by gastrointestinal illness (unconditioned stimulus, US). Considerable research has been conducted to identify the neurological substrates of this learning phenomenon (e.g., Reilly, 2009), and one brain structure that has been implicated in CTA acquisition is the insular cortex (IC; e.g., Bermudez-Rattoni & McGaugh, 1991; Braun *et al.*, 1972; Cubero *et al.*, 1999; Fresquet *et al.*, 2004; Gallo *et al.*, 1992; Nerad *et al.*, 1996). However, the inconsistent experimental procedures used in these studies have made it difficult to identify the exact nature of the IC lesion (ICX) deficit. In particular, the vast majority of these studies used a single CS-US pairing to condition an aversion, which precludes the distinction between elimination and retardation of learning that would permit CTA acquisition if more conditioning trials had taken place.

When multiple CS-US pairings are utilized, ICX rats exhibit attenuated CTA learning, but are capable of fully suppressing intake (Kiefer & Braun, 1977). Recent work in our laboratory has shown that this deficit is greatest on the first conditioning trial, when ICX rats drink more of a novel CS than their nonlesioned (SHAM) counterparts (Roman *et al.*, 2006). Based upon

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these results, it is possible that the IC is involved in the evaluation of the novelty of a taste stimulus, and that lesions of this structure prevent the recognition of that novelty (e.g., Lin *et al.*, 2009). If so, then ICX rats should treat a novel taste as though it was familiar. Latent inhibition describes the delayed learning that is observed when a stimulus is familiar relative to when it is novel (e.g., Lubow, 1989, 2009), and IC lesions may cause a latent inhibition-like delay in CTA acquisition through a taste novelty deficit. It follows from this line of reasoning that ICX rats should be deficient in CTA acquisition when the CS is novel and that, irrespective of whether the CS is novel or familiar, they should acquire the aversion at the same slow rate as SHAM rats do to a familiar CS.

Using a design that prevented lesion-induced over-consumption of the CS during preexposure and conditioning, we have recently confirmed that ICX rats acquire a CTA at the same rate to a novel CS as they do to a familiar CS (Roman & Reilly, 2007). However, both sets of ICX rats showed slower acquisition relative to the SHAM rats conditioned with a familiar CS. This latter finding, inconsistent with our hypothesis, is subject to a number of interpretations. We argued that the amount of preexposure was insufficient to familiarize the SHAM rats with the CS to the level it is perceived by the ICX rats. To test this account, the present experiment quadrupled the amount of CS preexposure relative to our earlier report (300 vs. 75 ml, respectively) to determine whether this increased familiarity will result in the SHAM subjects acquiring the aversion at the same slow rate as the ICX rats.

2. Results

2.1 Anatomical

The IC is not dedicated exclusively to gustatory processing; the relevant gustatory portion of the IC is centered at approximately +0.8 mm from bregma, and extends for approximately 1 mm both anterior and posterior from that point (Kosar et al., 1986; Nakashima et al., 2000). Rats with lesions that bilaterally damaged the majority of this area were included in the statistical analyses. Rats with subtotal lesions (n = 6) were excluded from the final sample. Serial schematics of the largest and smallest lesions are displayed in Figure 1A, with accompanying photomicrographs of the IC in a neurologically intact rat (Figure 1B) and a representative IC lesion (Figure IC). These lesions were made using the same surgical parameters as, and were virtually identical in size to, those in Roman and Reilly (2007). The final sample sizes for each group of ICX and SHAM rats were: ICX-Novel (n = 7), ICX-Familiar (n = 6), SHAM-Novel (n = 9), and SHAM-Familiar (n = 8).

2.2 Behavioural

With very little variability, SHAM and ICX rats drank maximal amounts of NaCl during the 9 trials of the Preexposure 1 phase (data not shown). Unsurprisingly, then, an ANOVA found no significant main effect of lesion (SHAM vs. ICX; $F < 1$) or trials ($P > 0.30$) and no significant lesion × trials interaction ($P > 0.35$) for the volume of NaCl consumed during this phase of preexposure. On average, the rats in the Novel condition drank between 20-24 ml of water each day, with no effect of lesion and no lesion × trials interaction (both Fs < 1). The absence of any evidence of neophobia to NaCl on the first preexposure trial might be attributed to the relatively long duration of the access period (60 min versus the 15 min used in the earlier report of Roman and Reilly, 2007) which would provide sufficient time for the rats to overcome any initial hesitation to drink and still have enough time to consume the capped amount of fluid that was available. As shown on the left side of Fig. 2, SHAM-Familiar and ICX-Familiar rats drank the maximal amount (15 ml) of NaCl available during Preexposure 2. Again, no significant differences were found ($P > 0.25$). Similarly, the SHAM-Novel and ICX-Novel rats drank 15 ml of water each day during Preexposure 2.

It is evident from inspection of the Conditioning phase data displayed in Fig. 2 that the SHAM-Novel rats acquired the CTA much more rapidly than the other three groups, which themselves produced similar learning curves. These impressions of the results were confirmed with an ANOVA on the conditioning and test data that found a significant lesion × condition (Novel vs. Familiar) × trials interaction, $F_{6,156} = 4.19$, $P < 0.001$. Planned comparisons revealed that SHAM-Novel rats consumed the same amount of NaCl as the SHAM-Familiar subjects on trial 1 ($F < 1$; when intake for all rats was the maximal 10 ml), but drank less of the CS on conditioning trials 2-4 ($Ps < 0.001$). The CS intake of the two SHAM groups did not differ on trials 5 and 6 or on the test trial ($Ps > 0.05$). Additional comparisons of data from the conditioning trials showed that the CS consumption of the SHAM-Familiar subjects was not significantly different from that of either the ICX-Novel, $F_{1,26} = 3.97$, $P > 0.05$, or ICX-Familiar ($F < 1$) rats.

3. Discussion

In this experiment, we examined the ability of SHAM and ICX rats to acquire CTAs to a taste CS that was either novel or familiar. Typically, neurologically intact rats show a neophobic reaction to a novel taste stimulus and consume less of that solution during initial encounters until they learn that the taste is safe, a result of the absence of aversive postingestive consequences (e.g., Barnet, 1963; Corey, 1978; Domjan, 1977). As shown by Roman *et al.* (2006), the magnitude of this neophobic reaction is greatly attenuated if not abolished by IC lesions. As previously noted, the relatively long (60 min) duration of the Preexposure 1 trials may have precluded detection of taste neophobia. The absence of lesion-induced intake differences across the preexposure trials was an important feature of the experimental design because it ensures that the rate of CTA acquisition in the SHAM-Familiar and ICX-Familiar rats cannot be explained in terms of differential prior experience with the CS. Similarly, the use of limited intake on the first conditioning trial ensures that CTA acquisition differences between SHAM-Novel and ICX-Novel rats cannot be attributed to differential consumption that otherwise would have occurred on that trial.

The behavioural anchor of the present study is the performance of the SHAM-Novel rats that rapidly learned to suppress CS intake. As shown in Fig 2, these rats were consuming ~1 ml of the CS after two conditioning trials, a level of performance that is virtually identical to that of the SHAM-Novel rats in our previous study (Roman & Reilly, 2007). As expected, the SHAM-Familiar group exhibited latent inhibition in their delayed CTA acquisition to the familiar CS. Our hypothesis, that the SHAM-Familiar subjects given extensive CS preexposure would learn at the same slow rate as the ICX-Novel and ICX-Familiar rats, was supported by the experimental results.

The present experiment was designed to determine whether the finding of Roman and Reilly (2007), that SHAM-Familiar subjects acquired CTAs more quickly than ICX-Familiar and ICX-Novel rats, was due to the preexposure phase being too brief to fully familiarize SHAM rats with the to-be CS. The results of the present experiment confirm this analysis. It is informative that the two Familiar groups (SHAM and ICX) did not differ in CTA acquisition following extensive CS preexposure. Given that these two groups did differ in our earlier report, the relevant factor would appear to be the extent of CS preexposure and not simply that both groups consumed equivalent amounts of the CS. Furthermore, it is important to note that SHAM rats that were fully familiar with the CS learned the CTA at the same rate as ICX rats that were operationally naïve to the CS at the start of conditioning. We believe that these results support the interpretation that IC lesions disrupt CS processing. More specifically, this CS processing deficit seems to be due to an inability of ICX rats to recognize the novelty of a new tastant. In this context it is worth noting that rats with IC lesions show normal detection of,

and responsivity to, basic taste stimuli when stimulus novelty is not a factor in performance (e.g., Braun *et al.*, 1982; for a review see Braun, 1990).

To directly test the notion that the IC is involved in taste novelty detection, we recently conducted a neophobia study that examined the responses of SHAM and ICX rats to unfamiliar taste, olfactory, and trigeminal stimuli (Lin *et al.*, 2009). These experiments show that IC lesions attenuate the magnitude of the initial neophobic response to the taste (but not olfactory or trigeminal) solution while having no influence on the asymptote level of intake when the taste has become familiar. Thus, the IC appears to be specifically involved in the neophobic reactions to novel taste stimuli. It will be evident that this pattern of impaired and spared neophobic responses matches the patterns of impaired (taste) and spared (odor) aversions reported by Roman *et al.* (2006).

Our research into the neural substrates of CTA is guided by the anatomical organization of the central gustatory system in the rat (for a review see Lundy & Norgren, 2004). Briefly, taste information from the mouth is relayed to the nucleus of the solitary tract and then projects to the parabrachial nucleus (PBN) in the pons. From this brainstem nucleus, taste information ascends along two pathways to the forebrain. The first pathway involves sequential connections with the gustatory thalamus (GT; the parvicellular region of the ventral posteromedial nucleus) and the IC. The second pathway in the central gustatory system involves projections, which to varying degrees are bilateral and in most cases reciprocated, to the bed nucleus of the stria terminalis (BNST), central nucleus of the amygdala (CNA), IC, and lateral hypothalamus (LH). In addition, fibers pass between the GT and the CNA, CNA and basolateral amygdala (BLA), CNA and IC, and between BLA and IC. In a recent review of the effects of permanent brain lesions on CTA acquisition, Reilly (2009) concluded that the IC and BLA are concerned with the detection of taste novelty and that the PBN is the single most critical structure involved in the acquisition of the CS-US association that underlies taste aversion learning.

This latter conclusion is at odds with the long-standing interpretation of the finding that rats with chronic decerebrations, which disconnect the brainstem from the forebrain, are incapable of acquiring CTAs (Grill & Norgren, 1978), a result that is generally taken as definitive evidence of the importance of forebrain structures in CTA acquisition. However, the thirty-year quest to find the missing forebrain structures has proven largely unfruitful. With regard to the central gustatory system, the GT, LH, BNST, CNA, BLA and IC have all been ruled-out as contenders. Moreover, research since the late 1980s, using a wide range of procedures and stimuli, has demonstrated the importance of the PBN for CTA acquisition (e.g., Bielavska & Bures, 1994; DiLorenzo, 1988; Flynn *et al.*, 1991; Grigson *et al.*, 1998a, b; Ivanova & Bures, 1990a, b; Reilly *et al.*, 1993; Reilly & Trifunovic, 2000, 2001; Spector *et al.*, 1992; Yamamoto *et al.*, 1995). Although, of course, it remains possible that one or more forebrain structures may yet be identified as critical for CTA acquisition, we are skeptical. Rather, we believe that it is important to entertain other interpretations of the result reported by Grill and Norgren. Specifically, we favor the view that the failure of chronic decerebrate rats to acquire CTAs is the inadvertent consequence of decerebration-induced retrograde damage of the PBN that renders the PBN nonfunctional for taste aversion learning. This analysis serves to focus research attention onto two fundamental and interlocking issues: the nature of the PBN mechanisms responsible for CTA acquisition and the role of forebrain structures in the detection of taste novelty.

Returning to the present experiment, we propose that IC lesions retard CTA acquisition as a secondary consequence of an impairment of taste novelty detection/recognition that results in a latent inhibition-like retardation of learning involving taste stimuli. A number of lines of research are suggested by this analysis. First, since lesions of the BLA are known to impair CTA acquisition in much the same way as IC lesions (e.g., Morris *et al.*, 1999; St. Andre &

Reilly, 2007), it will be important to determine the nature of the interaction between these two forebrain structures. In order to encourage a systems level analysis, it will also be necessary to establish which other brain structures are implicated in the neophobic reaction to taste stimuli (for further discussion see Bernstein *et al.*, 2009). Second, it will be important to determine the neuropharmacological substrates of, and the molecular changes in, the IC and other structures that underlie the initial occurrence of, and the recovery from, taste neophobia (for a recent review of this topic see Barki-Harrington et al., 2009). Third, it will be of great interest to explore if the lesion-induced novelty detection/recognition deficit, that accounts for the attenuation of CTA acquisition, can also explain the reported deficits of CTA retention in ICX rats (e.g., Braun *et al.*, 1981; Cubero *et al.*, 1999: Gallo *et al.*, 1992). It is to be hoped that in undertaking these various lines of research a detailed and comprehensive understanding emerges of (1) how the brain detects, processes, and guides responsivity to novel taste stimuli and (2) the neural mechanisms that govern the transformation of the taste stimulus from novel to familiar.

4. Experimental procedure

4.1 Subjects

Thirty-six male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) served as subjects. They were housed individually in hanging steel mesh cages in a colony room maintained at 21°C ±2°C and kept on a 12:12-hr light cycle (lights on a 7 a.m.). All behavioral testing was conducted during the light phase of the room illumination cycle. The rats had prior experience with saccharin and sucrose but were naïve with respect to the stimuli (sodium chloride [NaCl] and lithium chloride [LiCl]) used in the present experiment. The subjects were treated in accord with local (Institutional Animal Care and Users Committee of the University of Illinois at Chicago) and national (National Institutes of Health [1986]*Guide for the Care and Use of Laboratory Animals* and the American Psychological Association's [1996] *Guidelines for Ethical Conduct in the Care and Use of Animals*) standards.

4.2 Surgery

Before surgical treatments, the 300-325 g rats were divided into two groups: SHAM (n = 17) and ICX (n = 19). Following intraperitoneal administration of sodium pentobarbital (50 mg/kg), the rats were fixed into a stereotaxic instrument (ASI; Warren, MI) with atraumatic earbars; body temperature was monitored with a rectal thermometer and maintained at 37°C with a heating pad. Prior to a midline incision that exposed the cranial sutures, a local anesthetic, Bupivacaine (0.25%; Hospira, Lake Forest, IL), was subcutaneously injected into the scalp. With the skull level between lambda and bregma, trephine holes were drilled over the IC. Using the co-ordinates of Roman and Reilly (2007), a glass micropipette (tip diameter approximately 75 μm) was lowered into two sites in each hemisphere for iontophoretic infusions of 0.15 M NMDA (*N*-methyl-D-aspartic acid; Sigma, St. Louis, MO). Site 1 (AP +1.2, ML ±5.2, DV -5.0) involved a 10 min infusion in each hemisphere whereas 6 min infusions were used at site 2 (AP +1.2, ML ±5.2, DV -4.3). The scalp incision was closed with wound clips after induction of the fourth lesion and the rats, when recovered from the temporary effects of anesthesia, were returned to their home cages. Eight non-surgical control rats were anesthetized only and 10 surgical control subjects received identical treatments as the ICX subjects except that no NMDA infusions occurred. These two sets of control subjects were combined as Group SHAM.

4.3 Apparatus

All behavioral testing occurred in the rats' home cages, with fluids presented in 100 ml inverted plastic graduated cylinders fitted with metal spouts. The volume of fluid consumed was recorded with a resolution of 0.5 ml.

4.4 Procedure

On the morning the deprivation schedule (15 min/day water access) was initiated the rats weighed 340-400 g. When fluid intake stabilized, the subjects were randomly assigned into one of two groups (Familiar or Novel) in preparation for the preexposure phases of the experiment. During the 9 days of Preexposure 1, rats in Group Familiar were allowed a maximum of 60 min to consume 25 ml of 0.9% NaCl; rats in Group Novel were given equivalent access to water. The 5 days of Preexposure 2 were identical to Preexposure 1 except the rats were given a maximum of 15 min to drink 15 ml of either NaCl (Group Familiar) or water (Group Novel). CTA conditioning began on the day after the final Preexposure 2 trial and, for all rats, involved 15 min access to 10 ml of NaCl followed, 30 min after CS bottle placement, by an intraperitoneal injection of the US (0.15 M LiCl at 1.33 ml per 100 g body weight). In total, the rats received 6 CS-US trials and 1 CS only test trial. In order to allow recuperation for the effects of US administration, each CS trial was separated by 2 days of 15 min access to water.

4.5 Histology

After the experiment, the rats were given a fatal overdose of sodium pentobarbital (100 mg/kg) and then perfused transcardially with 4% buffered formalin. The brains were removed and stored for 2 days in 4% buffered formalin, after which they were transferred to a 20% sucrose solution for an additional 2 days. The brains were cut at 50μm in a cryostat and stained with cresyl violet. Tissue was reviewed under a light microscope, and photographed using a digital camera and Q-Capture software (Quantitative Imaging, Surrey, B.C., Canada).

4.6 Data Analysis

Behavioural data from this experiment were analyzed using Statistica 6.0 software (StatSoft, Tulsa, OK). We tested the data using analysis of variance (ANOVA), with an alpha value of 0.05. Lesion and Condition results were evaluated as between-subjects variables, while Trials were tested as a within-subjects variable. In text, the behavioural data are presented as mean ± SEM.

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References

American Psychological Association. Guidelines for ethical conduct in the care and use of animals. Washington, DC: Author; 1996.

Barki-Harrington, L.; Belelovsky, K.; Doron, G.; Rosenblum, K. Molecular mechanisms of taste learning in the insular cortex and amygdala. In: Reilly, S.; Schachtman, TR., editors. Conditioned taste aversion: Behavioral and neural processes. Oxford University Press; New York: 2009. p. 341-363.

Barnett, SA. The rat: A study in behavior. Aldine; Chicago: 1963.

Bermúdez-Rattoni F, McGaugh JL. Insular cortex and amygdala lesions differentially affect acquisition on inhibitory avoidance and conditioned taste aversion. Brain Res 1991;549:165–170. [PubMed: 1654172]

Bernstein, IL.; Wilkins, EE.; Barot, SK. Mapping Conditioned Taste Aversion Associations through Patterns of cFos Expression. In: Reilly, S.; Schachtman, TR., editors. Conditioned taste aversion: Behavioral and neural processes. Oxford University Press; New York: 2009. p. 328-340.

Bielavska E, Bures J. Universality of parabrachial mediation of conditioned taste aversion. Behav Brain Res 1994;60:35–42. [PubMed: 8185850]

Braun, JJ. Gustatory cortex: Definition and function. In: Kolb, B.; Tees, RC., editors. The cerebral cortex of the rat. Cambridge, MA: MIT Press; 1990. p. 407-430.

Braun JJ, Kiefer SW, Ouellet JV. Psychic ageusia in rats lacking gustatory neocortex. Exp Neurol 1981;72:711–716. [PubMed: 7238720]

Braun JJ, Lasiter PS, Kiefer SW. The gustatory neocortex of the rat. Physiol Psychol 1982;10:13–45.

Braun JJ, Slick TB, Lorden JF. Involvement of gustatory neocortex in the learning of taste aversions. Physiol Behav 1972;9:637–641. [PubMed: 4599681]

Corey DT. The determinants of exploration and neophobia. Neurosci Biobehav Rev 1978;2:235–253.

Cubero I, Thiele TE, Bernstein IL. Insular cortex lesions and taste aversion learning: effects of conditioning method and timing of lesion. Brain Res 1999;839:323–330. [PubMed: 10519056]

DiLorenzo PM. Long-delay learning in rats with parabrachial pontine lesions. Chemical Senses 1988;13:219–229.

Domjan, M. Attenuation and enhancement of neophobia for edible substances Determinants of the enhancement of flavored-water intake by prior exposure. In: Barker, LM.; Best, MR.; Domjan, M., editors. Learning mechanisms in food selection. Baylor University Press; New York: 1977. p. 151-179.

Flynn FW, Grill HJ, Schulkin J, Norgren R. Central gustatory lesions: II. Effects on sodium appetite, taste aversion learning, and feeding behavior. Behav Neurosci 1991;105:944–954. [PubMed: 1777107]

Fresquet N, Angst MJ, Sandner G. Insular cortex lesions alter conditioned taste avoidance in rats differentially when using two methods of sucrose delivery. Behav Brain Res 2004;153:357–365. [PubMed: 15265630]

Gallo M, Roldan G, Bures J. Differential involvement of gustatory cortex and amygdala in the acquisition and retrieval of conditioned taste aversion in rats. Behav Brain Res 1992;52:91–97. [PubMed: 1335264]

Grigson PS, Reilly S, Scalera G, Norgren R. The parabrachial nucleus is essential for acquisition of a conditioned odor aversion in rats. Behav Neurosci 1998a;112:1104–1113. [PubMed: 9829788]

Grigson PS, Reilly S, Shimura T, Norgren R. Ibotenic acid lesions of the parabrachial nucleus and conditioned taste aversion: Further evidence for an associative deficit. Behav Neurosci 1998b; 112:160–171. [PubMed: 9517824]

Grill HJ, Norgren R. Chronically decerebrate rats demonstrate satiation but not bait shyness. Science 1978;201:267–269. [PubMed: 663655]

Ivanova SF, Bures J. Acquisition of conditioned taste aversion in rats is prevented by tetrodotoxin blockade of a small region centered around the parabrachial nucleus. Physiol Behav 1990a;48:543–549. [PubMed: 1963689]

Ivanova SF, Bures J. Conditioned taste aversion is disrupted by prolonged retrograde effects of intracerebral injection of tetrodotoxin in rats. Behav Neurosci 1990b;104:948–954. [PubMed: 2178348]

Kiefer SW, Braun JJ. Absence of differential associative responses to novel and familiar taste stimuli in rats lacking gustatory neocortex. J Comp Physiol Psychol 1977;91:498–507. [PubMed: 874118]

Kosar E, Grill HJ, Norgren R. Gustatory cortex in the rat. I. Physiological properties and cytoarchitecture. Brain Res 1986;379:329–341. [PubMed: 3742225]

Lin JY, Roman C, St Andre J, Reilly S. Forebrain lesions and taste, olfactory and trigeminal neophobia in the rat. Brain Res 2009;XXXX:xxx–xxx.

Lubow, RE. Latent inhibition and conditioned attention theory. Cambridge University Press; Cambridge: 1989.

Lubow, RE. Conditioned taste aversion and latent inhibition: A review. In: Reilly, S.; Schachtman, TR., editors. Conditioned taste aversion: Behavioral and neural processes. Oxford University Press; New York: 2009. p. 37-57.

Lundy, FR., Jr; Norgren, R. Gustatory system. In: Paxinos, G.; Mai, J., editors. The rat nervous system. Vol. 3rd. San Diego: Academic Press; 2004. p. 891-921.

Morris R, Frey S, Kasambira T, Petrides M. Ibotenic acid lesions of the basolateral, but not central, amygdala interfere with conditioned taste aversion: Evidence from a combined behavioral and anatomical tract-tracing investigation. Behav Neurosci 1999;113:291–302. [PubMed: 10357454]

Nakashima M, Uemura M, Yasui K, Ozaki HS, Tabata S, Taen A. An anterograde and retrograde tract-tracing study on the projections from the thalamic gustatory area in the rat: distribution of neurons projecting to the insular cortex and amygdaloid complex. Neurosci Res 2000;36:297–309. [PubMed: 10771108]

National Institutes of Health. Guide for the care and use of laboratory animals. Washington, DC: U.S. Government Printing Office; 1986. DHEW Publication No 86-23

Nerad L, Ramirez-Amaya V, Ormsby CE, Bermudez-Rattoni F. Differential effects of anterior and posterior insular cortex lesions on the acquisition of conditioned taste aversion and spatial learning. Neurobiol Learn Mem 1996;66:44–50. [PubMed: 8661250]

Paxinos, G.; Watson, C. The rat brain in stereotaxic coordinates. Vol. 5th. Academic Press; San Diego, CA: 2005.

Reilly, S. Central gustatory system lesions and conditioned taste aversion. In: Reilly, S.; Schachtman, TR., editors. Conditioned taste aversion: Behavioral and neural processes. Oxford University Press; New York: 2009. p. 309-327.

Reilly S, Grigson PS, Norgren R. Parabrachial nucleus lesions and conditioned taste aversion: Evidence supporting an associative deficit. Behav Neurosci 1993;107:1005–1017. [PubMed: 8136054]

Reilly S, Trifunovic R. Lateral parabrachial nucleus lesions in the rat: Aversive and appetitive gustatory conditioning. Brain Res Bull 2000;52:269–278. [PubMed: 10856824]

Reilly S, Trifunovic R. Lateral parabrachial nucleus lesions in the rat: Neophobia and conditioned taste aversion. Brain Res Bull 2001;55:359–366. [PubMed: 11489343]

Roman C, Nebieridze N, Sastre A, Reilly S. Effects of lesions of the bed nucleus of the stria terminalis, lateral hypothalamus, or insular cortex on conditioned taste aversion and conditioned odor aversion. Behav Neurosci 2006;120:1257–1267. [PubMed: 17201470]

Roman C, Reilly S. Effects of insular cortex lesions on conditioned taste aversion and latent inhibition in the rat. Eur J Neurosci 2007;26:2627–2632. [PubMed: 17970726]

Spector AC, Norgren R, Grill HJ. Parabrachial gustatory lesions impair taste aversion learning in rats. Behav Neurosci 1992;106:147–161. [PubMed: 1313242]

St Andre J, Reilly S. Effects of central and basolateral amygdala lesions on conditioned taste aversion and latent inhibition. Behav Neurosci 2007;121:90–99. [PubMed: 17324053]

Yamamoto T, Fujimoto Y, Shimura T, Sakai N. Conditioned taste aversion in the rat with excitotoxic brain lesions. Neurosci Res 1995;22:31–49. [PubMed: 7792081]

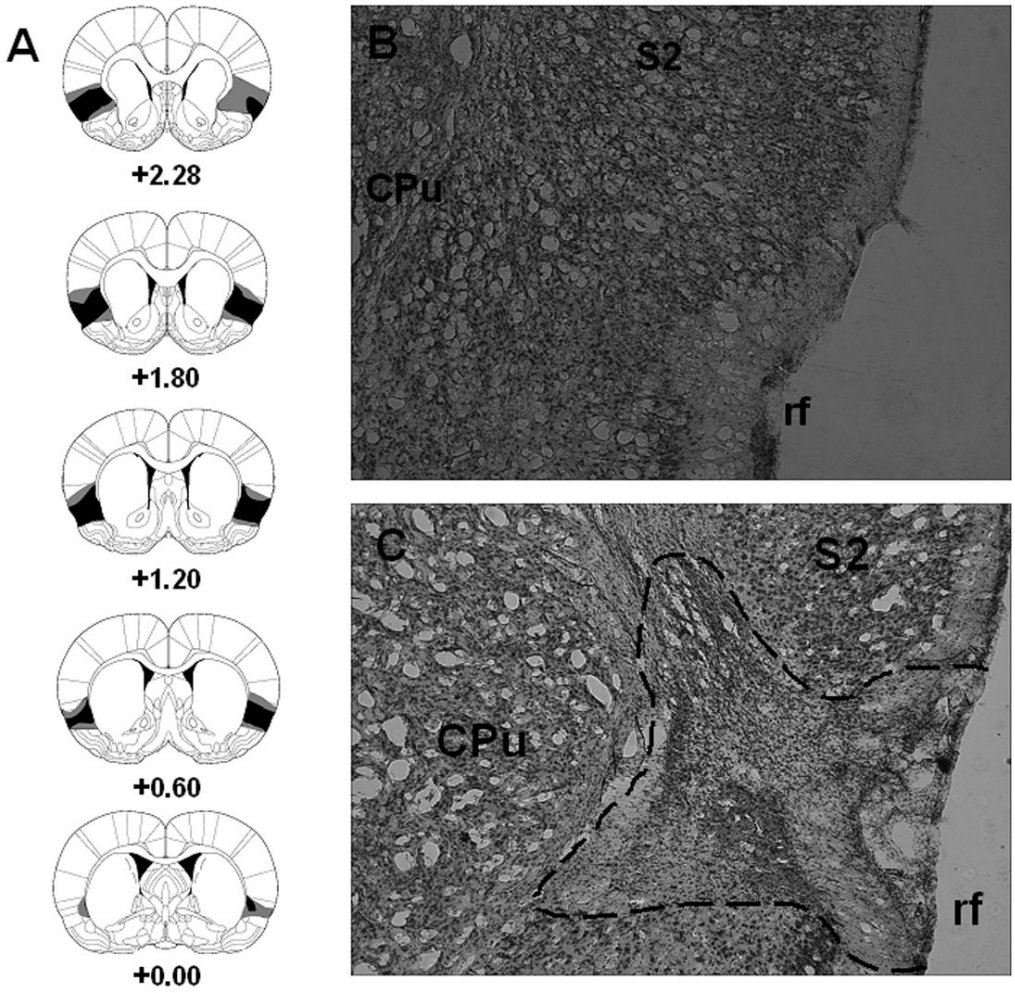

Fig. 1.

(A) Serial reconstructions of the smallest (black) and largest (gray) neurotoxic lesions of the insular cortex on diagrams adapted with permission from the Paxinos and Watson (2005) atlas. The numbers (0.00 mm, +0.60 mm, +1.20 mm, +1.80 mm, +2.28 mm) beneath each diagram refers to the anterior-posterior coordinates relative to bregma. (B) Digital photomicrograph of a cresyl violet-stained coronal section through the insular cortex of a neurologically intact subject taken at ~0.8 mm anterior to bregma. (C) Corresponding section through the insular cortex in the right hemisphere of a rat with a representative neurotoxic lesion (indicated with the dashed line). CPu, caudate putamen; rf: rhinal fissure; S2, secondary somatosensory cortex.

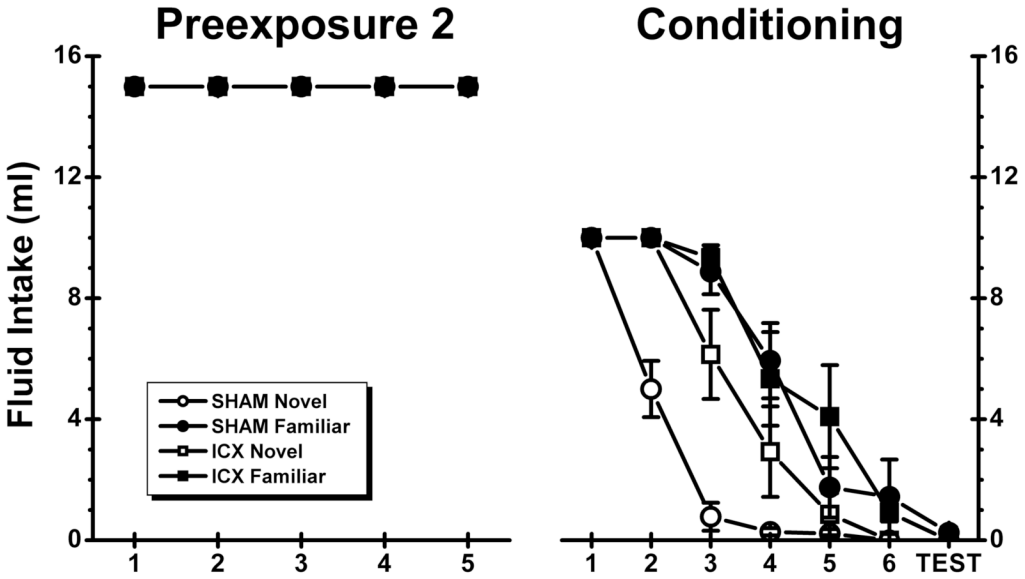

Fig. 2.
Mean (±SEM) Fluid intake for neurologically intact (SHAM) subjects and insular cortex-lesioned (ICX) rats during the Preexposure 2 and Conditioning phases of the experiment.