Role of the Gustatory Thalamus in Taste Learning

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Manuscript submitted to: *Behavioural Brain Research,* 2013.

Abstract

The present study re-examined the involvement of the gustatory thalamus (GT) in the acquisition of drug- and toxin-induced conditioned taste aversions (CTAs) using a standardized procedure involving 15-min taste trials in rats injected with morphine (Experiment 1), lithium chloride (Experiment 2) or amphetamine (Experiment 3). Contrary to previous results, GT lesions did not eliminate drug-induced CTAs. Rather, GT-lesioned rats acquired aversions of comparable magnitude to non-lesioned subjects but from an elevated intake on the first conditioning trial. A similar pattern of lesion effects was found in the acquisition of an illness-induced CTA. Thus, we conclude that GT lesions do not differentially influence CTAs conditioned with drugs or toxins. The lesion-induced elevated intake of a novel tastant confirms an unappreciated role for the GT in taste neophobia.

Keywords: aversion, drugs of abuse, palatability, neophobia, rat

1. Introduction

Taste neophobia and conditioned taste aversion (CTA) are phenomena that defend against the ingestion of toxic foods. The former refers to the reluctance, in the absence of knowledge about post-ingestive consequences, to consume a new food (e.g., [7,8,10,15]) whereas the latter refers to the reduced intake of a food that is known to have aversive post-ingestive consequences (e.g., [6,9,39,52]). In the laboratory the oral (taste) and post-ingestive (visceral malaise) features of the toxic food are usually separated and termed, respectively, the conditioned stimulus (CS) and the unconditioned stimulus (US).

Because it is a taste-guided behavior, neurobehavioral investigations of CTA learning have tended to focus on the roles of the components of the central gustatory system (e.g., [46,47,48]). In the rat, taste information is relayed from the parabrachial nucleus to the gustatory insular cortex (GC) via the gustatory thalamus (GT; for reviews see [36,65]). The present article is concerned with the role of the GT in CTA acquisition. The overwhelming majority of studies that have examined the effects of GT lesions on CTA have employed a toxin (e.g., lithium chloride; LiCl) as the US (e.g., [19,40,49, 51,59]). Moreover, these studies uniformly found that GT lesions have no influence CTA acquisition. In marked contrast, however, there are two experiments that reported that GT lesions eliminated CTA acquisition [21,53]. These latter two experiments are notably different from the former studies in that they used a rewarding dose of morphine (i.e., a dose that supports place preference learning) as the US. Together, this pattern of results encouraged the view that malaise-inducing toxins/poisons and rewarding drugs of abuse support qualitatively different types of taste learning dependent on different neural substrates (e.g., [21,22]).

The view that there are different forms of taste suppression that can be fractured apart by a neural manipulation (in this case, GT lesions) is critically dependent on all aspects of the behavioral procedures being the same, except, of course, the USs. However, the two morphine experiments involved taste trials that were 5 min in duration whereas the aforementioned LiCl studies typically employed 15 min taste trials. It is, we believe, unsafe to form strong conclusions about the existence of different processes of taste suppression on the basis of experiments that used such short access periods. In particular, 5-min trials are prone to ceiling effects on intake (which is constrained to a maximum of about 10-12 ml) that might obscure differences that otherwise would be revealed when a longer trial duration is employed. The goal of the present study was to reexamine the role of the GT in taste suppression induced with a drug of abuse (Experiments 1 and 3) and LiCl (Experiment 2). To ensure comparability, 15-min trials were used in each experiment. If the GT has a significant role in drug-induced taste suppression then lesions of this nucleus should, like those reported by Grigson et al. [21] and Reilly and Trifunovic [53], eliminate this form of learning irrespective of trial duration. On the other hand, if a different outcome is obtained with 15-min taste trials then the role of the GT in taste learning requires reevaluation.

2. Experiment 1

As noted above, only two experiments, those reported by Grigson et al. [21] and Reilly and Trifunovic [53], have investigated the influence of GT lesions on the acquisition of drug-induced taste learning. Both of these experiments employed the same design that involved 5-min CS access per trial and a 15-mg/kg morphine US. In each experiment it was found that GT-lesioned (GTX) rats injected with the morphine

US drank the same amount of the taste CS as the control GTX subjects injected with the saline vehicle. Thus, GTX rats conditioned with morphine failed to show any evidence of CS intake suppression. Experiment 1 re-examined the influence of GT lesions on drug-induced taste learning with a procedure that permitted 15-min saccharin access each trial and a 15-mg/kg morphine US.

2.1. Method

2.1.1 Subjects. Forty-one, experimentally naïve, male Sprague-Dawley rats (275 - 300 g) obtained from Charles River Laboratories (Wilmington, MA) served as subjects. They were individually housed in stainless steel hanging cages (Acme Metal Product, Chicago, IL) in a vivarium maintained at 21°C on a 12 hr light-dark cycle (lights on at 7:00 am). Animals were allowed to habituate to the facility for 3 - 5 days before surgery. All experimental treatments and procedures were conducted during the light phase of the cycle. Food and water were available at all times in the home cage except during behavioral testing as noted below. Animals were treated in accordance with guidelines from the American Psychological Association [2] and the National Institutes of Health [43]. The University of Illinois at Chicago Institutional Animal Care and Users Committee approval was obtained for all treatments.

2.1.2 Surgery. A total of 20 rats received bilateral GT lesions using the procedures of Sastre and Reilly [58]. These animals (Group GTX) were anesthetized with intraperitoneal (IP) injections of sodium pentobarbital (55 mg/kg) and secured in a Kopf Model 1900 stereotaxic instrument equipped with a digital readout (David Kopf Instruments, La Jolla, CA) using non-traumatic earbars. Cranial sutures were exposed by a midline incision; a single trephine hole (5 mm diameter) was drilled on the skull

centered over the transverse sinus at the level of the GT. Excitotoxic lesions were created with 0.15 M N-methyl-D-aspartate (Sigma-Aldrich; St Louis, MO) backfilled into a glass micropipette (tip diameter ~70 μm) and infused iontophoretically into the GT with a Midgard precision current source (Stoelting, Wood Dale, IL). There was a single 6 min -10 μA current infusion per hemisphere at -3.70 mm posterior to bregma, ±0.80 mm medial/lateral to the midline, -6.30 mm ventral to dura. Body temperature was monitored throughout the surgical procedure via a rectal thermometer and maintained at 37°C with a heating pad (Harvard Apparatus, Holliston, MA). Twenty-one rats served as control subjects (Group SHAM): 10 rats received the same surgical procedures as GTX rats except no N-methyl-D-aspartate was infused and 11 rats received only pentobarbital anesthesia.

2.1.3 Apparatus. All testing was conducted in the home cage with fluids presented in plastic graduated cylinders fitted with silicone stoppers and stainless steel sipper tubes secured to the front of the home cage by stainless steel springs. Volumes were measured to the nearest 0.5 ml.

2.1.4 Procedure. The rats were acclimated to a deprivation schedule permitting 15 min access to water each day. The experiment began when water intake stabilized (12 days) at which time the rats in each group (SHAM and GTX) were divided into subgroups according to the drug (saline or morphine) to be administered as the US on conditioning days. Each conditioning trial consisted of 15 min access to 0.15% saccharin followed, 5 min later, by an IP injection of either physiological saline (1 ml/kg body weight) or morphine sulfate (15 mg/ml/kg). A saccharin trial occurred every third day and the rats were otherwise maintained on the water deprivation schedule as described above. Conditioning trials continued until stable performance emerged in the

experimental and control groups. Thus, there were a total of four conditioning trials with US injections and a single CS only test trial; US injections were omitted on the test trial because they were superfluous. Volume consumed served as the dependent measure.

2.1.5 Data Analysis. Behavioral data was analyzed with repeated-measures analysis of variance (ANOVA) with Group as the between-subjects variable and Trial as the within-subjects variable. Significant main effects and interactions were followed-up by appropriate post hoc analyses, either planned comparisons (simple main effects) with the adjusted error term from the overall ANOVA or Tukey HSD tests. All analyses were conducted using Statistica 6.0 software (StatSoft, Inc., Tulsa, OK) with alpha level set at $p < .05$.

2.1.6 Histology. Once all experimental procedures were completed, GTX rats were injected with sodium pentobarbital (100 mg/kg; IP) and then transcardially perfused with physiological saline followed by 4% formaldehyde. Brains were extracted and stored in 4% formaldehyde and then 20% sucrose for two days each. Thereafter, the brains were frozen, sliced at 50 µm on a cryostat and stained with cresyl violet. Using a light microscope (Zeiss Axioskop 40), photomicrographs were taken with a Q-Imaging camera running Q-Capture software (Quantitative Imaging Corporation, Burnaby, B.C., Canada). Damage to the GT and surrounding regions was identified and evaluated based on the Paxinos and Watson [44] atlas.

2.2 Results and Discussion

2.2.1 Anatomical.

--- INSERT FIGURE 1 ABOUT HERE ---

Complete bilateral destruction of the GT was required for rats to be included in statistical analyses of Group GTX (see Figure 1). Of the rats that were included some minor damage extended into the centromedian, paracentral, parafasicular, and subparafasicular thalamic nuclei, as well as the VPM, but damage was unilateral and non-systematic in all animals. Misplaced lesions tended to be placed dorsolateral to the GT resulting in subtotal GT damage while increasing damage to the VPM, centromedian nucleus, and paracentral nucleus. Groups included in the behavioral analysis were: SHAM-Saline (n = 11), SHAM-Morphine (n = 10), GTX-Saline (n = 8), and GTX-Morphine (n = 8). GT Lesions in the current study were comparable in size and locus to those in our earlier work (e.g., [58,49,53,54]).

2.2.2 Behavioral.

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The water data collected over the three days preceding Trial 1 for all animals included in the final analysis are summarized in Table 1. Volume consumed was analyzed with a repeated-measures ANOVA that found no significant main effects of Group ($F < 1$) or Trial, $F(2,66) = 2.48$, $p = .09$, and no significant Group x Trial interaction ($F < 1$). Thus, GT lesions did not influence water intake, which was stable across all groups on the three days prior to the first conditioning trial.

--- INSERT FIGURE 2 ABOUT HERE ---

The behavioral data from each of the five, 15-min taste trials of Experiment 1 are summarized in Figure 2. Inspection of the figure reveals a number of notable differences relative to prior work that employed 5-min CS access. First, in SHAM rats there was a clear and substantial neophobic reaction on Trial 1 that habituated with repeated trials in the rats injected with the saline vehicle. This recovery from taste neophobia, absent in

studies employing 5-min trials [21,53], indicates that the true magnitude of drug-induced taste aversions, determined as the intake difference between saline- and morphine-injected groups, was substantially underestimated in that work. Second, GT lesions resulted in an elevated intake of saccharin on first exposure. Third, GT lesions did not eliminate drug-induced CTA. Finally, the asymptotic level of CS intake was higher in the GTX-Morphine rats than in the SHAM-Morphine subjects. These impressions of the results were confirmed with statistical analysis that found, in an initial overall ANOVA, a significant main effect of Group, $F(3,33) = 19.80$, $p < .001$, and of Trial, $F(4,132) = 2.82$, $p < .05$, and a significant Group x Trial interaction, $F(12,132) = 11.10$, $p < .001$. Follow-up planned comparisons of the interaction revealed a significant lesion effect on Trial 1 intake ($p < .0001$). That is, GTX rats consumed more of the novel saccharin tastant than SHAM subjects on the first exposure. On Trial 2, SHAM-Saline subjects significantly increased saccharin intake thereby demonstrating habituation of taste neophobia ($p < .0001$). Similarly, the GTX-Saline rats showed a significant, though numerically small, increase in saccharin intake on Trial 2 relative to Trial 1 ($p < .01$) and also maintained a significantly higher intake than the SHAM-Saline subjects on Trial 2 ($p < .05$). On Trials 3 - 5 saccharin intake was not statistically different in the two saline-injected groups ($Fs < 1$). A different pattern of performance was observed in the morphine-injected groups, each of which significantly reduced their CS consumption over the five trials of the experiment ($ps < .001$). On Trial 1, SHAM-Morphine animals consumed 11.9 (±1.22) ml of the CS compared to 17.5 (±1.80) ml in the GTX-Morphine rats, a difference of 5.6 ml. This lesion effect persisted across all trials ($ps < .01$) such that on Trial 5 the GTX-Morphine (12.14 ±2.08 ml) rats consumed 5.4 ml more of the CS than the SHAM-Morphine (6.7 ±1.70 ml) subjects. Thus, relative to intake on Trial 1, each of the groups

reduced CS intake by a similar amount across conditioning trials, suggesting that SHAM and GTX rats acquired a morphine-induced CTA at a comparable rate and of comparable magnitude.

The pattern of results in the morphine-injected rats is reminiscent of the results obtained in neurologically intact rats by Lin et al. [29]. In that study, normal rats acquired a morphine-induced CTA to a saccharin CS that was either novel or, due to prior saccharin exposure, familiar. Subjects familiarized with the CS before conditioning with a morphine US had, as expected, a much higher initial intake than their novel counterparts and, not surprisingly, showed a latent inhibition-induced delay in CTA acquisition. Of particular interest to present purposes, the final asymptotic level of morphine-induced CTA was significantly higher in rats conditioned with a familiar saccharin CS relative to those conditioned with a novel saccharin CS (~18 and ~6 ml, respectively). Thus, each group showed a similar absolute conditioned reduction in CS consumption of about 7 - 8 ml in the Lin et al. study. These data suggest that, for drug-induced CTAs, the final level of CS intake is dependent on whether the taste is novel or familiar on the first conditioning trial. Returning to the present results, the GTX-Morphine rats also displayed significantly higher CS intake at asymptote than the SHAM-Morphine subjects, which would seem to suggest that the GT lesions influenced some aspect of novelty perception or responsivity. This analysis is also supported by the lesion-induced elevation of saccharin intake on Trial 1. However, the present results also revealed that the across-trial conditioned reduction of CS intake was virtually identical in the SHAM-Morphine and GTX-Morphine rats.

3. Experiment 2

The results obtained in Experiment 1 were surprising in a number of ways, not least of which was the occurrence of a GT lesion-induced deficit in taste neophobia. Also surprising, this neophobia deficit had no subsequent influence on the rate of taste learning. We have previously reported that lesions of the GC, the cortical taste area, not only disrupt taste neophobia in a manner comparable to that reported here for GT lesions, but that the neophobia deficit consequently retarded taste learning in the GC lesioned rats [29,56,57]. Thus, the pattern of results obtained in Experiment 1 encouraged a re-examination of the effect of GT lesions on LiCl-induced CTA acquisition. Experiment 2 investigated this issue using two different designs. Using half of the rats from Experiment 1, Experiment 2A employed our standard CTA procedures with 15-min unrestricted access to the taste CS on all trials. This design provides another opportunity to determine whether GT lesions influence the magnitude of the expected neophobic reaction on Trial 1 and, if that deficit does occur, whether it has an influence on the acquisition of a CTA induced with LiCl toxicosis. Experiment 2B was similar in design to Experiment 2A, except CS intake was capped on Trial 1 to prevent lesion-induced intake differences that may otherwise occur from confounding interpretation of CTA acquisition rate in the GTX rats. Quinine (0.0001 M) was selected as the taste CS in Experiment 2 for its ability to reliably evoke a neophobic reaction. Due to the magnitude of this neophobic response 5 ml was selected as the intake cap in Experiment 2B.

3.1 Methods

3.1.1 Subjects, surgery, and apparatus. The same subjects and apparatus from Experiment 1 were used in Experiment 2. They were housed, maintained and

tested in the same manner as during Experiment 1 except for procedural differences described below.

3.1.2 Procedure. Following completion of Experiment 1, the rats were given 7 days free access to food and water, and were then divided into two groups of 20 (Experiment 2A) and 21 (Experiment 2B) animals, respectively, counterbalanced according to lesion and prior drug condition. Water intake was re-stabilized. Conditioning trials were conducted every third day with two water days intervening. Conditioning trials consisted of presentations of 0.0001 M quinine for 15-min (Experiment 2A) or 15-min to a maximum of 5 ml intake (Experiment 2B). Fifteen min after the quinine bottles were removed all rats received an IP injection of LiCl (13.3 ml/kg of 0.15 M LiCl). Because of the rate of acquisition, two conditioning trials were followed by a taste only test trial. The dependent measure was volume of quinine consumed.

3.1.3 Data analysis and histology. Histology and data analysis procedures were identical to those used for Experiment 1.

3.2 Results and Discussion

3.2.1 Anatomical. The histological analysis for this set of rats was presented in Experiment 1. Consequent to that analysis, the number of rats in each experiment were: SHAM n = 10, GTX n = 8 in Experiment 2A and SHAM n = 11, GTX = 8 in Experiment 2B.

3.2.2 Behavioral. The mean amount of water consumed over the three days preceding Trial 1 for all animals included in the behavioral analysis are summarized in Table 1. For Experiment 2A, statistical analysis found no significant main effect of

Group ($p > .20$) or Trial, ($F < 1$), and no significant Group x Trial interaction ($F < 1$). A similar analysis of Experiment 2B data revealed a significant main effect of Trial $F(2,34) = 3.38$, $p < .05$, but no Group effect ($F < 1$), and no Group x Trial interaction ($p > .20$). A Tukey test of the Trial effect indicated stable intake between days 1 and 2 ($p > .50$) with a trend ($p = .07$) toward a decrease (~1) ml on the final baseline water day. Overall, these analyses indicate that GT lesions did not influence water intake, which was stable between groups for the three days prior to the first conditioning trial of each experiment.

--- INSERT FIGURE 3 ABOUT HERE ---

The behavioral data obtained in Experiment 2 are shown in Figure 3. Analysis of the data summarized in Figure 3A for Experiment 2A revealed a significant main effect of Trial, $F(2,32) = 95.85$, $p < .0001$, as well as a Group x Trial interaction, $F(2,32) = 7.14$, $p < .01$, but no significant main effect of Group, $F(1,16) = 3.19$, $p > .05$. Post hoc planned comparisons of the interaction revealed significantly higher intake in Group GTX than in the SHAM rats on Trial 1 ($p < .05$). Each group significantly decreased intake on Trial 2 ($ps < .00001$), and there were no group differences on Trial 2 ($F < 1$). Each group further suppressed intake on Trial 3, again with no between-group differences ($F < 1$). An ANOVA of the data summarized in Figure 3B for Experiment 2B revealed a significant main effect of Trial, $F(2,32) = 68.58$, $p < .0001$. There was, however, no significant main effect of Group ($F < 1$) and no Group x Trial interaction ($F < 1$). A Tukey test showed a significant decrease from Trial 1 to Trial 2 and from Trial 2 to Trial 3 ($ps < .01$). Thus, when Trial 1 intake was equated there were no differences between SHAM and GTX animals in the rate of acquisition for a LiCl-induced CTA. Overall, the results of Experiment 2 replicated the neophobia deficits found in the GTX

rats in Experiment 1 and also replicated prior work showing that GT lesions have no influence on the acquisition of LiCl-induced CTAs.

4. Experiment 3

The two prior experiments that examined GT lesions and drug-induced taste learning employed morphine as the US [21,53]. There are, however, important differences in the mechanism of action and effect profiles of drugs of abuse (e.g., [4]). By using a different drug US, amphetamine, in a second set of experimentally naïve rats Experiment 3 was intended to extend the generality of the results obtained in Experiment 1. In addition, recent work in our laboratory, using lick pattern analysis, has revealed that palatability not only increases as taste neophobia habituates but that the palatability of a taste CS decreases following taste-drug pairings [3,27,30]. To further investigate the effects of GT lesions on taste neophobia and drug-induced CTA, Experiment 3 was conducted in drinking chambers to permit a microstructural analysis of fluid intake.

When rats voluntarily drink they do so in sustained bursts of rapid licks termed clusters, each cluster separated by pauses. The size of clusters (i.e., the mean number of licks in a cluster) has been validated as a measure of taste palatability that is independent of total intake (e.g., [11,12,13,14,23,62,63], for a review see [17]). Specifically, as the concentration of sweet solutions (e.g., sucrose and Polycose) increase so too does cluster size although, of course, there is an inverted U-shaped curve for volume consumed. On the other hand, clusters size decreases with increasing concentration of bitter solutions (e.g., quinine). Furthermore, clusters size has been

used to detect downshifts in taste palatability induced by contingent administration of illness-inducing USs [3,5,16,18,24] and, as mentioned above, by drug of abuse USs.

4.1 Method

4.1.1 Subjects and surgery. Forty experimentally naïve male Sprague-Dawley rats were acquired and housed in a manner identical to Experiment 1. Surgical procedures were also identical to those employed in Experiment 1, except 24 rats served in Group GTX.

4.1.2 Apparatus. Eight identical modular drinking chamber (Med Associates, St. Albans, VT) were used in Experiment 3. Each chamber was 30.5 cm long X 24.1 cm wide X 29.2 cm high with a clear polycarbonate door, back wall, and ceiling, the sidewalls were made of aluminum and the floor consisted of 19 parallel steel bars. In each chamber, an oval access hole (1.3 cm wide X 2.6 cm high) was centered on the right wall, 6.0 cm above the floor. Solutions were available in retractable stimulus bottles. In the extended position, the tip of the stimulus bottle spout was centered in the access hole ~0.3 cm outside the chamber to prevent constant contact. A lickometer circuit (0.3 μA) was used to monitor licking with a temporal resolution of 10 milliseconds. A shaded light bulb (100 mA, 28 V) mounted on the sidewall opposite to the sipper tube provided illumination in the chamber. Each chamber was equipped with a white noise generator (~80 dB). Chambers were connected to a computer in an adjacent room, which controlled all events and records data using programs written in the Medstate notation language.

4.1.3 Procedure. Following surgery the rats were given at least 10 days to recuperate. Thereafter, they were placed on a water deprivation schedule (15 min

access to water each day in the home cages) and habituated to the drinking boxes (15 min per day). After three such days, the 15-min daily water access periods were switched into the drinking chamber. The subjects were divided into four groups based on lesion (SHAM or GTX) and US (saline or amphetamine) yielding the following groups: SHAM-Saline, SHAM-Amphetamine, GTX-Saline, and GTX-Amphetamine. Conditioning trials commenced when water intake patterns stabilized across all groups and all dependent measures for three consecutive days. Conditioning trials occurred in a three-day cycle based on the nature of the US injection. On Day 1, experimental rats were injected with amphetamine (1 mg/kg) 5 min after 15-min access to the saccharin CS whereas unpaired control subjects were injected with an equivalent volume of physiological saline. On Day 2, 5 min after 15 min water access the rats were injected with the other US (saline or amphetamine, respectively; a balanced design that ensures all rats had equal exposure to saline and amphetamine). On Day 3, all rats were given 15-min access to water; no USs were administered. Conditioning trials continued until stable performance emerged in the experimental and control groups. Thus, there were a total of three taste-amphetamine conditioning trials and a single CS only test trial (on which the amphetamine was omitted as superfluous).

4.1.4 Dependent measures. Two dependent measures were computed: volume consumed (determined by weighing stimulus bottles before and after each session) and lick cluster size (calculated by dividing the total number of licks occurring in clusters by the total number of clusters; a cluster was defined as a run of licks separated by inter-lick intervals of less than 0.5 s).

4.1.5 Data analysis and histology. The procedures for histology and data analysis were identical to those described for Experiment 1.

4.2 Results and Discussion

4.2.1 Anatomical. Damage to the GT and surrounding areas was comparable to that reported in the GTX rats in Experiment 1, except the lesions were somewhat larger. In the rats with acceptable lesions, minor damage extended from the GT into the centromedian, paracentral, parafasicular, and subparafasicular thalamic nuclei, as well as the VPM. This damage was unilateral and non-systematic across GTX animals. A total of five animals were dropped from Group GTX due to lesions that did not completely destroy the GT bilaterally. As in the first set of rats misplaced lesions appeared to primarily damage areas dorsolateral to the GT. Thus, a majority of the GT was spared while the VPM, centromedian nucleus, paracentral nucleus, and thalamic trigeminal orosensory area sustained significant damaged. Groups included in statistical analyses were: SHAM-Saline (n = 8), SHAM-Amphetamine (n = 8), GTX-Saline (n = 9), and GTX-Amphetamine (n = 10).

4.2.2 Behavioral. Water intake data from the final three baseline trials are summarized in Table 1. Separate ANOVAs were conducted on intake and cluster size and found no significant difference of any type (all *ps* > .15). Thus, GT lesions had no influence on water consumption and the performance of all four groups was stable over the three water days prior to the first conditioning trial.

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Figure 4A shows amount consumed by SHAM and GTX rats during the four, 15-min saccharin trials of the experiment. Statistical analysis found a significant main effect of Group, $F(3,31) = 15.42$, $p < .001$, and of Trial, $F(3,93) = 8.67$, $p < .001$, as well as a significant Group x Trial interaction, $F(9,93) = 17.44$, $p < .001$. Post hoc planned comparisons of the interaction revealed a significant elevation of saccharin intake in the

GTX rats on Trial 1 compared to the SHAM subjects ($p < .001$). However, whereas the SHAM-Saline subjects demonstrated a significant recovery from neophobia on Trial 2 relative to Trial 1 ($p < .001$), saccharin intake of the GTX-Saline rats did not differ across the first two trials ($p > .25$). Groups SHAM-Saline and GTX-Saline showed stable intake across Trials 2 - 4 ($ps > .05$). Other than the Trial 1 effect noted above, there were no other intake differences between the SHAM-Amphetamine and GTX-Amphetamine groups and each acquired an amphetamine-induced CTA as indicated by a significant reduction in saccharin intake across Trials 1 - 4 ($ps < .001$). Overall, then, GTX rats showed higher levels of saccharin intake on Trial 1 relative to SHAM controls. This GT lesion-induced overconsumption completely eliminated taste neophobia, but did not appear to influence CTA acquisition. Furthermore, the Trial 1 group difference in amount of saccharin consumed did not lead to a different asymptotic level of CTA aversion as seen in Experiment 1. There are, minimally, two explanations for this difference across experiments. The SHAM-Amphetamine group failed to suppress intake on Trial 2, an anomalous pattern given our prior research [3,30], allowing the amphetamine groups to intersect. Alternatively, amphetamine, and not morphine, may produce a level of aversion capable of overcoming a Trial 1 starting difference. At present each of these two interpretations is viable and further experimentation will be needed to resolve this matter. However, irrespective of the resolution of this issue, it is clear that GT lesions did not eliminate acquisition of CTAs induced with either a morphine or amphetamine US.

An ANOVA analyzing lick cluster size (Figure 4B) found a significant main effect of Group, $F(3,31) = 7.53$, $p < .001$, and a significant interaction of Group x Trial, $F(9,93) = 4.28$, $p < .001$, but no significant main effect of Trial ($p > .25$). Post hoc analysis

revealed that on Trial 1 there were no differences between the two SHAM groups or between the two GTX groups (*Fs* < 1), but there was a significant elevation of cluster size in the GTX rats compared to SHAM subjects ($p < .001$). In the SHAM-Saline group there was a significant elevation in cluster size from Trial 1 to Trial 2 ($p < .00001$), with stable performance across Trials 2 - 4 (*Fs* < 1). The GTX-Saline group performance was constant across Trials 1 - 4 ($p > .05$). Surprisingly, although cluster size declined across Trials 1 – 4 in the SHAM-Amphetamine group, the reduction was not significant (*ps* > .05). Of course, when the cluster size of the SHAM-amphetamine group is compared to that of the SHAM-saline group a substantial difference (~130 licks) is evident on Trial 4. Finally, in the GTX-Amphetamine group there was a significant decrease in lick cluster size across Trials 1 - 3 (*ps* < .001) with stable performance on Trials 3 and 4 ($F < 1$). Increased cluster size across trials in the SHAM-Saline group is consistent with prior research showing that cluster size increases as neophobia habituates in neurologically intact rats ([27], see also [3,30]). The lack of a significant decline in lick cluster size in the SHAM-Amphetamine group was surprising given recent findings that amphetamine significantly reduced cluster size when paired, in separate experiments, with either a quinine, saccharin, sodium chloride or an aqueous odor as the CS [3,30]. Notwithstanding this anomalous performance in the SHAM-Amphetamine group, the amphetamine US caused a substantial reduction in lick cluster size in the GTX rats from ~150 on Trial 1 to ~25 on Trial 4.

As with Experiment 1 (morphine) and Experiment 2 (LiCl), the overall pattern of results in Experiment 3 demonstrates that GT lesions do not eliminate CTA, in this case to an amphetamine US. Thus, Experiment 3 adds generality to the view that GT lesions do not disrupt drug-induced CTAs. The reduction in the palatability of the taste CS in the

GTX-Amphetamine group, consistent with our previous findings in normal animals [3,30], indicates that GT lesions do not disrupt this aspect of drug-induced CTA. Intake and palatability of the saccharin solution tracked upward in the SHAM-Saline rats with the attenuation of taste neophobia, as has been previously demonstrated in normal animals [27]. Interestingly, the neophobia deficit in GTX animals was expressed as a Trial 1 elevation in both intake and palatability. Importantly, this apparent taste familiarity in the GTX-Amphetamine rats on Trial 1 did not result in a latent inhibition-like delay in CTA acquisition, as found in normal rats conditioned with a familiar taste CS (e.g., [29]; for a latent inhibition review see [35]).

5. GENERAL DISCUSSION

Examination of the literature shows that the GT has little, if any, role in CTA acquisition. The two exceptional experiments [21,53] not only employed morphine (rather than LiCl) as the US but also used a shorter CS access period (5 min versus the more standard 15 min). Before this pattern of results can confidently be interpreted as a genuine difference in the neural substrates of illness- and drug-induced CTAs, the present study examined whether the deficits found with a 5-min CS were also obtained with a 15-min CS. If GT lesions genuinely eliminate drug-induced taste learning then the duration of the CS should be irrelevant. In Experiment 1, GTX-Morphine rats suppressed intake across trials providing a clear demonstration that GT lesions do not eliminate morphine-induced CTA. In Experiment 3, the GTX-Amphetamine rats decreased intake as well as cluster size across trials. Thus, GT lesions did not have a major influence on the conditioned reductions in intake or palatability of the amphetamine-associated taste CS. Whether an initial intake difference was present

(Experiment 2A) or not (Experiment 2B), GT lesions had no influence on the acquisition of LiCl-induced CTAs. It appears that the earlier work suggesting that the GT may be a critical neural substrate for drug-induced taste learning might have employed a design that was not optimal. That is, we are inclined to the view that the 5-min trials (which limit intake to 10-12 ml) were of insufficient duration to detect the intake suppression induced by the morphine US in rats with GT lesions. Indeed, the present research suggests that the GT is not critical for the acquisition of CTAs produced by morphine, amphetamine or LiCl.

On the other hand, the GT has a role in the unconditioned reaction to a novel taste stimulus on the initial encounter. Thus far, we have termed this deficit a disruption of taste neophobia. However, given that the GT is a component nucleus in the central gustatory system, perhaps the most obvious interpretation of this finding is a lesion-induced deficit in taste perception. In particular, the present results might be taken to suggest that GT lesions are causing the rats to respond as if taste stimuli were less intense or concentrated. That said, to our knowledge, there is no evidence supportive of this account in the literature. Indeed, the evidence would seem to refute such an interpretation. For example, Reilly and Pritchard [50] used both long (24 hr, two-bottle) and short (15 min, single bottle) duration tests and found normal taste response curves for hydrochloric acid, quinine, sodium chloride and sucrose in GTX rats. Similarly, Flynn, Grill, Schwartz, and Norgren [20] found normal concentration response curves in GTX rats for hydrochloric acid, quinine, sodium chloride and sucrose during one-bottle, 15-min intake tests. Finally, Scalera et al. [59] reported normal concentration-dependent licking in GTX rats during randomly-ordered 10s presentations of six different concentrations of quinine, sodium chloride or sucrose when rats were either replete or

fluid deprived. The use of brief duration stimulus presentations increases confidence that the observed effects are attributable to taste features and minimally influenced by post-ingestive feedback. If GT lesions fundamentally influence taste perception then some indication of lesion-induced deficits should have been evident in the aforementioned studies. Thus, we can find no evidence in the literature to support the hypothesis that GT lesions disrupt the perception of taste stimuli.

The alternative interpretation of the significantly elevated intake of unfamiliar taste stimuli on the initial encounter by GTX rats concerns a disruption of taste neophobia. A single study employing discrete electrophysiological-guided ibotenic acid lesions of the GT reported a significant, but numerically small, elevation in the intake of a novel flavor CS (vinegar) on the first preexposure trial of a CTA latent inhibition experiment [49]. However, since there was no lesion-induced deficit in (i) intake across the other four flavor preexposure trials or (ii) a subsequent delay in CTA acquisition, the elevated intake on the first preexposure trial did not gain relevance in the literature[1]. The present results not only reverse this oversight but they also bring other evidence into sharper focus with regard to an involvement of the GT in taste neophobia. That it, using analysis of c-Fos activation, Lin, Roman, Arthurs, and Reilly [31] recently found that in addition to the GC, basolateral amygdala (BLA), and central nucleus of the

[1] Some prior research [34,66] is suggestive of such a deficit in GTX rats. However, as noted in a review of the role of the GT in taste-guided behavior [46], close inspection of the histological results reveals that the electrolytic lesions in the Loullis et al. study were, in fact, located dorsal to, and thus spared, the GT. The Yamamoto et al. experiment involves an opposite type of anatomical problem. That is, the ibotenic acid lesions were exceptionally large spreading so far beyond the boundaries of the GT and causing significant damage to many other structures as to defy meaningful attribution of function to structure.

amygdala, the GT was also activated by exposure to a novel, but not a familiar, taste stimulus. Furthermore, in a voluntary intake task involving 15-min trials, Lin et al. [27] reported that palatability (assessed with lick cluster size) was significantly lower when the tastant was novel relative to when the same stimulus was familiar as a consequence of repeated exposures. The finding that taste novelty/familiarity modulates palatability fits well with the result from the present Experiment 3 showing that the elevated intake expressed by GTX rats on first encounter with the saccharin tastant was accompanied by a cluster size that was more representative of a familiar than a novel taste. These lines of evidence converge to encourage the view that GT lesions disrupt a process necessary for the occurrence of taste neophobia.

The GT is reciprocally connected with the GC [26,42], which is also reciprocally connected with the BLA [37,45,61]. Of particular relevance to present purposes, bilateral lesions of either the GC or BLA disrupt taste neophobia which is characterized by an elevated intake of the novel taste stimulus on first encounter and a subsequent latent inhibition-like delay in the acquisition of CTAs [25,32,30,33,57,41,64]. A similar elevated consumption of a novel taste CS was seen in the GTX rats in the present study but this deficit appeared to have no influence on the rate of taste aversion learning. Interestingly, bilateral lesions of the medial amygdala (MeA) disrupt the initial expression of taste neophobia [33] but are reported to have no influence of CTA acquisition [1,38,55,60,66]. Finally, a recent study employing asymmetric unilateral lesions of the GC, BLA or MeA revealed that the GC and BLA form a functional unit in terms of the initial expression of taste neophobia; asymmetric unilateral lesions of the MeA and GC or MeA and BLA had no influence on taste neophobia [28]. In sum, bilateral lesions of either the GC or BLA disrupt taste neophobia and delay CTA

acquisition whereas bilateral lesions of the GT or the MeA disrupt taste neophobia but have no influence on CTA learning. Together, these results support the view that taste neophobia may involve at least two processes manifest as (i) elevated initial intake (and an increase in taste palatability) and (ii) delayed taste learning. Furthermore, the GT appears to be involved in the former but not the latter of these processes. Using the approach of Lin and Reilly [28], it will be of some theoretical importance to determine if asymmetric unilateral lesions of the GT and MeA produce deficits in taste neophobia comparable to those seen following bilateral lesions of either structure alone. Such an outcome would lead to a better understanding of the neural substrates of taste neophobia and encourage further research to determine the nature of that functional unit relative to the GC-BLA unit identified by Lin and Reilly.

The current report has in one sense succeeded in clarifying the role of the GT in taste learning. That is, we now know that lesions of the GT do not eliminate drug-induced CTA. In fact, if GT lesions have any influence on CTA acquisition induced with drugs of abuse or toxins that influence appears to be minor. In another sense, the current investigation has only begun to characterize the role of the GT in taste neophobia.

Acknowledgements

Joe Arthurs and Steve Reilly, Department of Psychology, Laboratory of Integrative Neuroscience, University of Illinois at Chicago.

This research was supported by grant DC06456 from the National Institute of Deafness and Other Communication Disorders. Portions of the data in this article were presented at the 41st annual meeting of the Society for Neuroscience in November 2011 in Washington D.C. as well as the 84th annual meeting of the Midwestern Psychological Association in Chicago, IL, in May 2012. Some of the data presented in this report was submitted in partial fulfillment of the requirements for the degree of Master of Arts for Joe Arthurs at the University of Illinois at Chicago.

Our thanks to Dr. Jian-You Lin for his technical expertise and assistance provided during all aspects of the research reported herein.

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Table 1. Water Consumption From Experiments 1, 2A, 2B and 3 Was Assessed Using one or two Dependent Measures: Intake and Cluster Size.

Experiment	Group	Intake	Lick Cluster Size
1	SHAM-Saline	19.70 (0.28) ml	-
	SHAM-Morphine	19.27 (1.08) ml	-
	GTX-Saline	20.06 (1.42) ml	-
	GTX-Morphine	20.04 (1.29) ml	-
2A	SHAM-Uncapped	17.60 (1.08) ml	-
	GTX-Uncapped	19.40 (1.51) ml	-
2B	SHAM-Capped	20.30 (1.01) ml	-
	GTX-Capped	19.38 (0.95) ml	-
3	SHAM-Saline	16.35 (1.21) g	191.23 (45.19)
	SHAM-Amphetamine	15.49 (1.25) g	139.76 (24.00)
	GTX-Saline	16.34 (1.29) g	180.38 (31.59)
	GTX-Amphetamine	16.98 (1.13) g	135.26 (17.57)

Note. Values presented are the means (±SE) from the final three water trials before the first conditioning trial of each experiment.

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Figure Captions

Figure 1: Panel A is a 10x photomicrograph from a rat with bilateral lesions representative of Group GTX. Panel B is a 100x photomicrograph of the area from Panel A indicated by the dashed rectangle (lesion border is marked by the dashed line). Abbreviations: fr = fasiculus retroflexus; GT = gustatory thalamus; ml = medial lemniscus; pf = parafasicular nucleus.

Figure 2: Experiment 1: Mean (±SE) 0.15% saccharin (ml) intake for non-lesioned (SHAM) and gustatory thalamus-lesioned (GTX) subjects.

Figure 3: Experiment 2: Mean (±SE) 0.0001 M quinine intake (ml) in SHAM and GTX rats over two conditioning trials and a CS only test trial. Panel A depicts quinine intake in subjects given unlimited access during the 15-min trials of Experiment 2A; Panel B shows consumption for subjects in Experiment 2B where intake on Trial 1 was limited to a 5 ml maximum.

Figure 4: Experiment 3: Mean (±SE) 0.15% saccharin CS directed performance for intake (g; Panel A) and lick cluster size (Panel B) in SHAM-Saline, SHAM-Amphetamine, GTX-Saline, and GTX-Amphetamine across three conditioning trials and a CS only test trial.

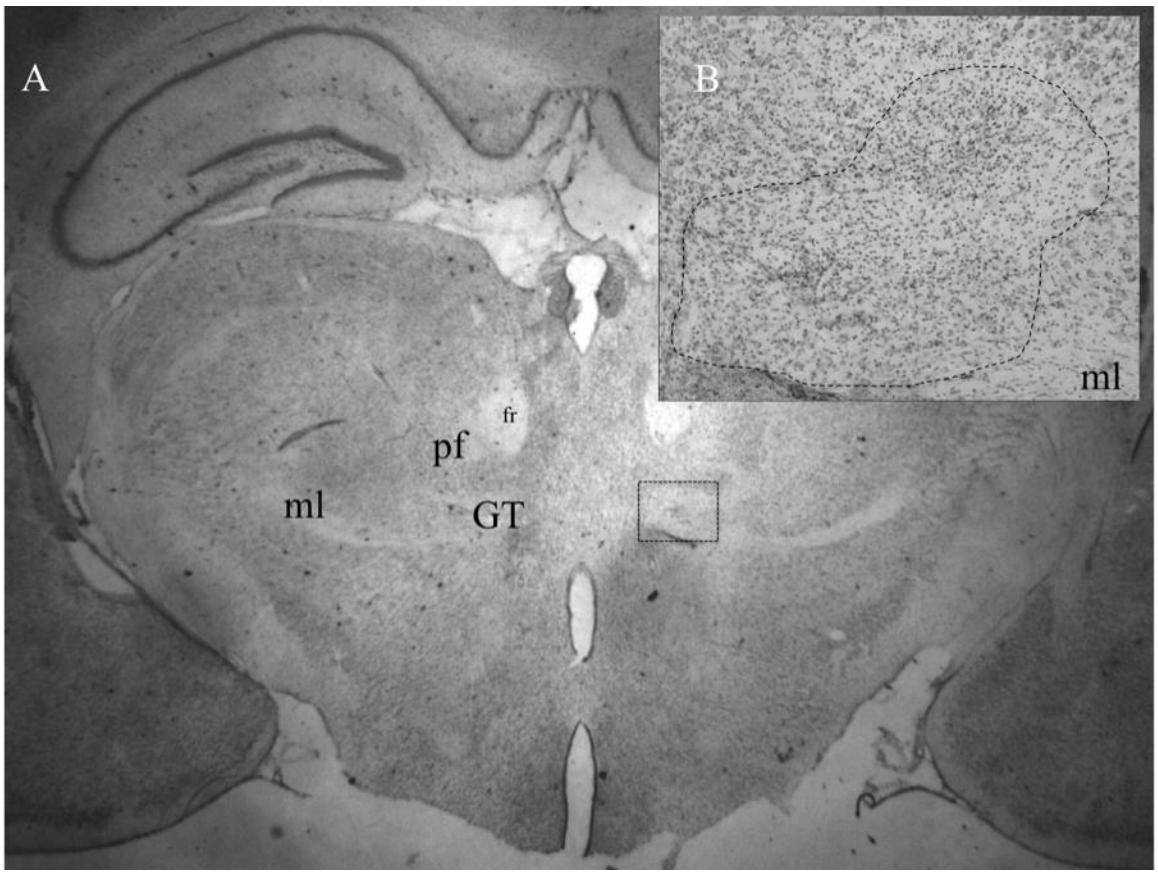

Figure 1

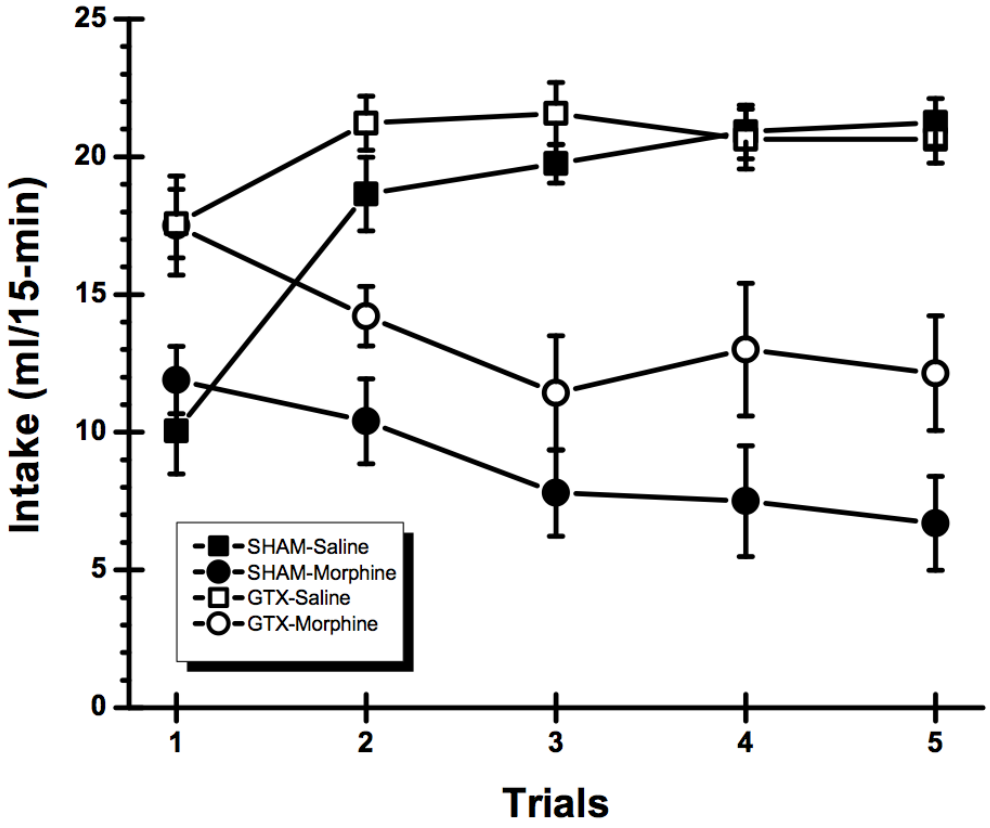
25
20
15
10
5
0
Intake (ml/15-min)
1
2
3
4
5
Trials
SHAM-Saline
SHAM-Morphine
GTX-Saline
GTX-Morphine

Figure 2

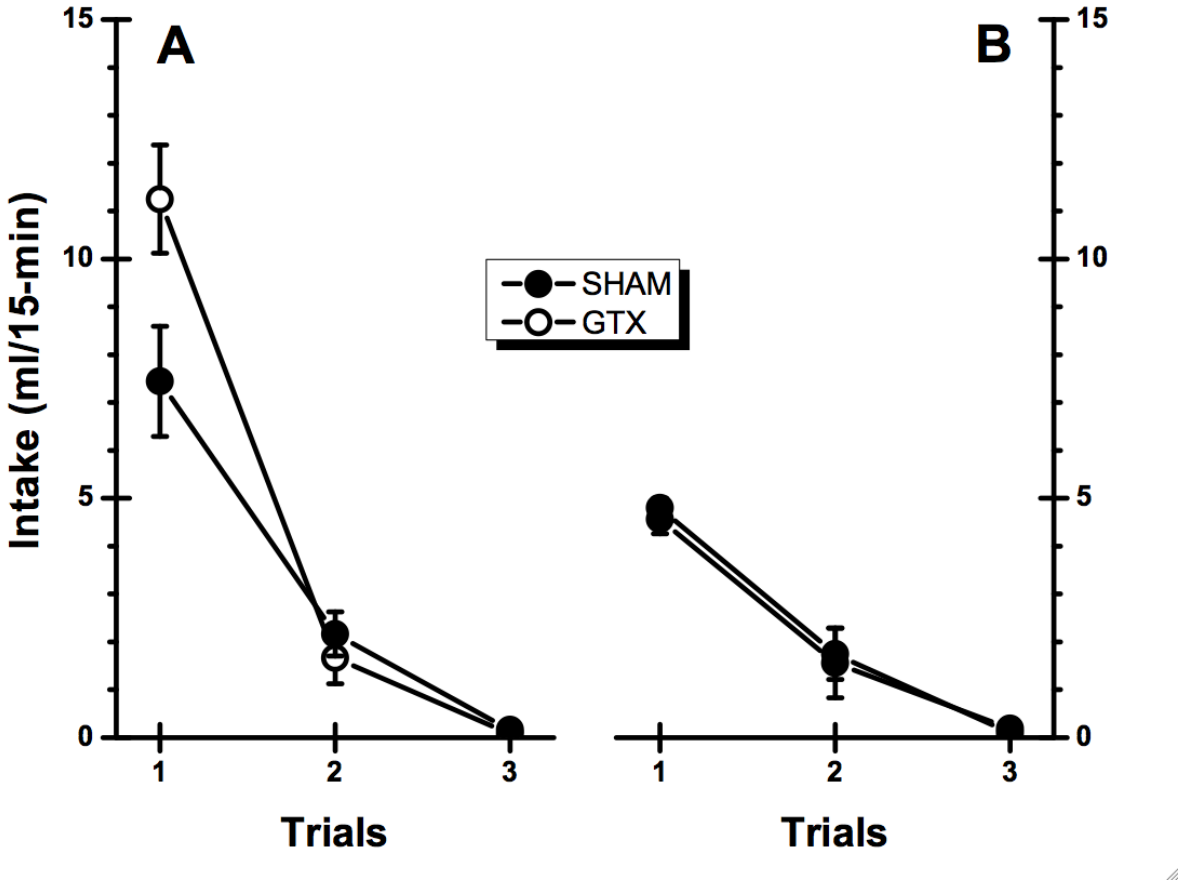

Figure 3

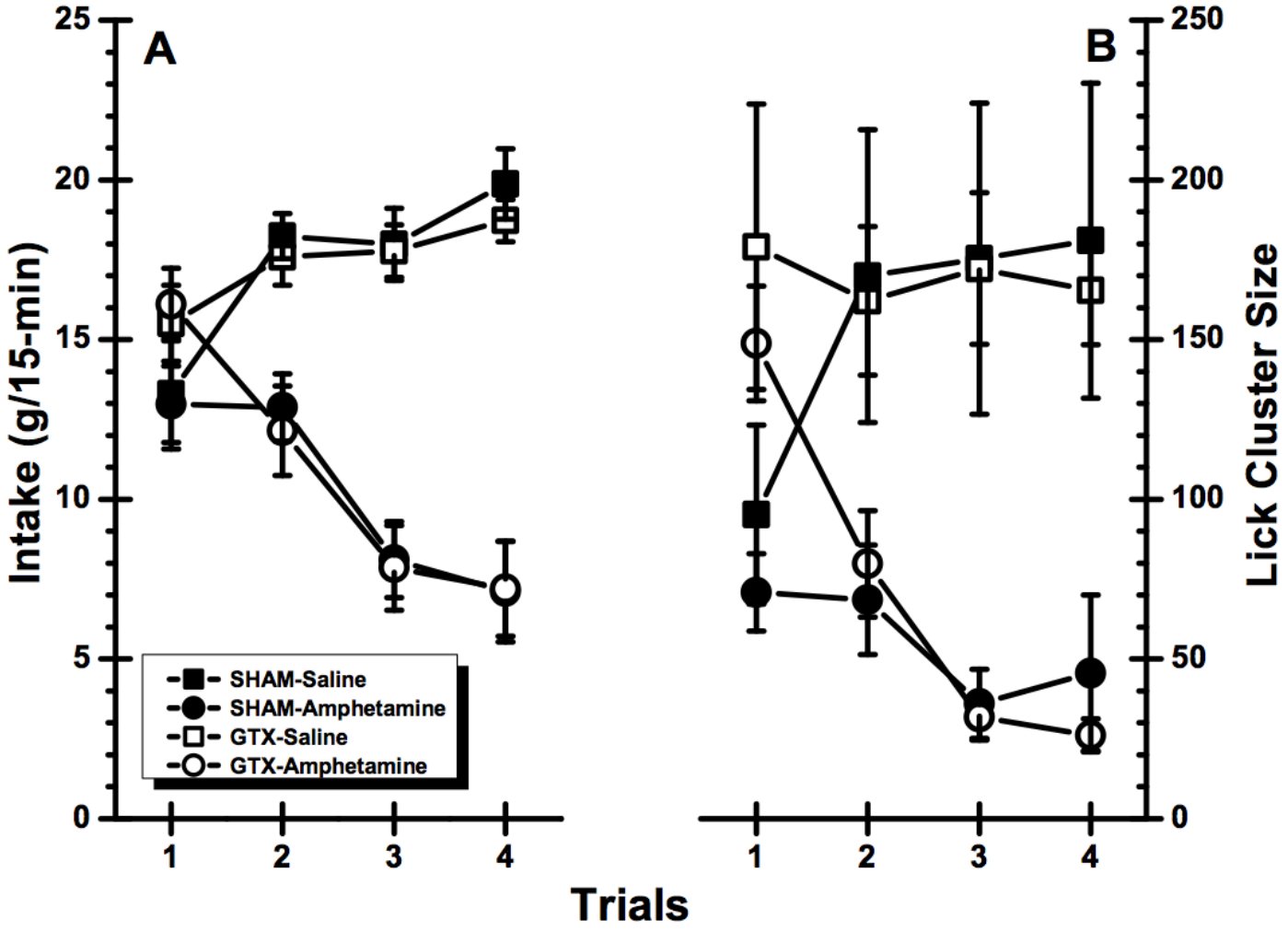
A
B
Intake (g/15-min)
Lick Cluster Size
Trials
SHAM-Saline
SHAM-Amphetamine
GTX-Saline
GTX-Amphetamine
0
5
10
15
20
25
50
100
150
200
250
1
2
3
4

Figure 4