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Gustatory insular cortex, aversive taste memory and taste neophobia

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ABSTRACT

Prior research indicates a role for the gustatory insular cortex (GC) in taste neophobia. Rats with lesions of the GC show much weaker avoidance to a novel and potentially dangerous taste than do neurologically intact animals. The current study used the retention of conditioned taste aversion (CTA) as a tool to determine whether the GC modulates neophobia by processing taste novelty or taste danger. The results show that GC lesions attenuate CTA retention (Experiment 1) and impair taste neophobia (Experiment 2). Given that normal CTA retention does not involve the processing of taste novelty, the pattern of results suggests that the GC is involved in taste neophobia via its function in processing the danger conveyed by a taste stimulus.

1. Introduction

For the hungry animal, eating a familiar, nutritious food is life sustaining and pleasurable. Eating a new food, however, is a risky undertaking because of the absence of knowledge about post-ingestive consequences – is this new food safe or is it toxic? It is assumed that fear of the life-threatening potential of a new food limits intake on the initial encounter, a phenomenon known as taste neophobia. If no harmful internal consequences follow ingestion, the initial fear reaction dissipates and consumption increases as the taste of the food becomes viewed as safe and thus more pleasurable (i.e., recovery from neophobia occurs; Barnett, 1963; Corey, 1978; Domjan, 1977; Lin, Amodeo, Arthurs, & Reilly, 2012). However, if consumption is followed by aversive consequences (e.g., gastrointestinal malaise; GIM) then the food will be avoided on later encounters, a phenomenon termed conditioned taste aversion (CTA; Barker, Best, & Domjan, 1977; Braveman & Bronstein, 1985; Milgram, Krames, & Alloway, 1977; Reilly & Schachtman, 2009). CTA is an example of Pavlovian learning in which the taste (conditioned stimulus; CS) of that food is associated with the aversive post-ingestive consequence (unconditioned stimulus; US). After as few as one taste-GIM pairing CS intake is suppressed as a consequence of a conditioned downshift in taste palatability (Garcia, Kovner, & Green, 1970; Lin, Arthurs, & Reilly, 2014). Given the critical roles of taste neophobia and CTA in survival, research has been conducted to unravel their neural substrates. Although this work has implicated the insular cortex, the nature of this involvement is not fully understood.

The insular cortex is not homogeneous and only a portion of this structure participates in taste processing. As defined by Kosar, Grill, and Norgren (1986), the gustatory insular cortex (GC) is located in the anterior region that receives taste afferents from the gustatory thalamus. With regard to taste learning, most of the studies involving the GC are concerned with its role in CTA. Thus, lesions of the GC were reported to disrupt CTA acquisition (e.g., Bermudez-Rattoni and McGaugh, 1991; Braun, Slick, & Lorden, 1972; Cubero, Thiele, & Bernstein, 1999; Fresquet, Angst, & Sandner, 2004; Gallo, Roldan, & Bureš, 1992; Nerad, Ramırez-Amaya, Ormsby, & Bermúdez-Rattoni, 1996). However, as indicated by recent findings, these deficits seem not to be related to an impairment in associating the CS with the US. For example, Roman, Nebieridze, Sastre, and Reilly (2006) found that GC-lesioned (GCX) rats were able to acquire CTAs with a comparable strength as neurologically intact animals after repeated conditioning trials, suggesting that the lesions do not prevent taste-GIM associative learning. The lesion-induced deficits were most profound on the first conditioning trial (i.e., before the US was experienced) when the GCX rats consumed nearly twice as much of the taste CS as the non-lesioned (SHAM) control subjects. This pattern of results indicates that the GC has a critical role in processing taste-related information prior to the engagement of the associative mechanism responsible for CTA acquisition. That is, it appears that GCX rats fail to recognize or react to a novel taste and, instead, they drink the taste solution as if it were known to be safe and familiar.

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Given that CTA acquisition occurs most readily when the taste is novel than when it is familiar (a general phenomenon termed latent inhibition effect; Lubow, 1989, 2009), we subsequently conducted a latent inhibition experiment to verify the taste novelty hypothesis of the GC function. Roman and Reilly (2007) found that for a preexposed (i.e., familiar and safe) taste, GCX rats acquired CTA at the same slow rate as CS preexposed SHAM animals; this normal CTA acquisition is contrary to the notion that the GC is involved in the taste-GIM associative mechanism. Furthermore, when a novel taste served as the CS, GCX rats showed impaired performance and acquired the CTA at a rate comparable to that shown by SHAM or GCX animals conditioned with a familiar taste (see also Roman, Lin, & Reilly, 2009). This latent inhibition-like effect in GCX rats indicates that this cortical region is critical for the detection and/or responsivity to taste novelty. Thus, we proposed that GC lesions delay CTA acquisition because such lesioned animals misperceive a genuinely novel taste as if it were familiar and safe. This analysis receives further support from the neophobia study of Lin, Roman, St Andre, and Reilly (2009). In that study, rats were allowed to freely consume a novel taste solution (0.5% saccharin) over four 15-min trials. GCX rats were found to consume significantly more of the neophobia-inducing taste than SHAM animals on first exposure. It is important to note that both the SHAM and GCX groups reached the same level at asymptote following repeated benign exposures (i.e., showed the same attenuation of taste neophobia), indicating that the neophobia deficits could not be attributed to either a lesion-induced increase in appetite or an insensitivity to the value of the taste stimulus.

Normal taste neophobia, as aforementioned, requires detection of taste novelty as well as a reaction to the potential danger (typically seen as a reduction in the amount consumed). How are the deficits found in rats with GC lesions to be explained? We see two possibilities. It could be that the lesioned animals fail to recognize taste novelty (i.e., they misperceive the stimulus to be a familiar taste). Or, alternatively, the GCX rats might fail to react to the potential danger (i.e., they misperceive the stimulus to be a safe taste). Experiment 1 sought to unravel the nature of this deficit by examining whether GC lesions induced after CTA acquisition influence how an animal reacts to a now familiar but unsafe taste. If the GC is involved in the process of novelty detection, we expect to find normal performance because CTA retention would appear not to involve taste novelty detection. On the other hand, if the GC mediates the reaction to a dangerous taste, GCX rats would be expected to show a retention deficit (i.e., drinking more of the devalued CS than the SHAM animals) because of an impaired ability to perceive/react to the danger conveyed by the taste.

Research into whether GC lesions influence CTA retention can be divided into two broad categories. In the early work on this issue rats with GC damage were reported to show profound deficits in the retrieval of the aversive taste memory (Braun, Kiefer, & Ouellet, 1981; Cubero et al., 1999; Kiefer, Lawrence, & Metzler, 1986; Kiefer, Leach, & Braun, 1984; Kiefer, Metzler, & Lawrence, 1985; Yamamoto, Azuma, & Kawamura, 1981; Yamamoto, Matsuo, & Kawamura, 1980). However, due to the induction technique (i.e., ablation or electrolytic lesion), the lesions in all cases damaged neural pathways passing through the GC as well as in surrounding areas. Using excitotoxic lesions, which selectively damage cell body, Stehberg and Simon (2011) found that GCX rats showed some CTA retention, albeit weaker, than the SHAM control subjects. This latter study also found that the retention intake deficits never exceeded the level of neophobia initially showed to the taste stimulus prior to the induction of GC lesions. That is, GCX rats consumed the same amount of the saccharin CS on the retention test as they drank of the novel saccharin on the first CTA trial (see also Stehberg, Moraga-Amaro, & Simon, 2011). This latter finding prompts an immediate issue concerning how to explain the CTA retention deficit. That is, is the attenuation of CTA retention a primary deficit of the GC lesions or is it a secondary consequence of lesion-induced failure to retain a taste memory (since they did not recover from neophobia in the retention test)?.[1] This issue, unfortunately, cannot be answered because a critical control group (which received GC lesions but no lithium chloride [LiCl] injections) was not included to assess the function of taste memory in the studies by Stehberg and colleagues. Furthermore, in the absence of this control group, the nature of the observed GC lesion-induced CTA deficit (attenuation or prevention) cannot be determined.

Mindful of the concerns raised from prior research, the design of the present study included several features of note. First, GC lesions were induced with a neurotoxin (NMDA) using the parameters of our previous studies (e.g., Lin et al., 2009; Roman et al., 2009), which were found to attenuate taste neophobia and to delay, but not prevent, CTA acquisition. Second, in addition to the CTA group, we also included a control group given the taste CS but not the LiCl US. As noted before, this control group allows a determination of whether GC lesions prevent the formation of taste memory. The current design also will allow us to determine the magnitude of the CTA deficit (attenuation or elimination) in GCX rats. To prevent floor effects in intake from diminishing sensitivity to the detection of group differences, the dose of LiCl (0.037 M at 5 ml/kg) was chosen from Lin, Arthurs, and Reilly (2013) to produce a moderate aversion to the taste (0.1% saccharin) used in the current study. Finally, after the completion of CTA retention tests, a taste neophobia experiment was conducted as a behavioral verification to confirm that the same lesion disrupts both phenomena.

2. Material and methods

2.1. Experiment 1: GC lesions and CTA retention

2.1.1. Animals

The experimental subjects were naïve male Sprague–Dawley rats purchased from Charles River Laboratory (Wilmington, MA). The experiment was conducted in two replications, each $n = 24$. Upon arrival, the rats were individually housed in hanging steel cages in an animal holding room with a 12-h light:dark cycle (light on at 7:00 am) and constant temperature (~22 °C). Food and water were given *ad libitum* until the experiment commenced, during which water access was limited to two daily 15-min exposures. The Animal Care and Users Committee of the University of Illinois at Chicago approved all experimental procedures. Animal care was in accord with guidelines recommended by American Psychological Association (1996) and the National Institutes of Health (1996).

2.1.2. Apparatus

Experiment 1 was conducted in the home cages. All fluids were presented in bottles equipped with silicone stoppers and stainless drinking spouts that could be attached to the front panel of the cage. The amount consumed was measured to the nearest 0.5 ml.

2.1.3. CTA Acquisition

One week after their arrival, the rats were water deprived by giving two 15-min fluid access periods, spaced 4 h apart, each day. Once morning water intake stabilized, the rats were divided

[1] We have previously demonstrated that rats with GC lesions can form a taste memory because they show normal recovery from taste neophobia (e.g., Lin et al., 2009). However, we are not sure whether this conclusion can be applied to the Stehberg and Simon (2011) results. Inspection of the two sets of histology suggests that the GC lesions in the Stehberg and Simon study extended, relative to the GC lesions in our study, into the more posterior portions of the insular cortex that may have included non-gustatory areas.