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Lactose malabsorption and taste aversion learning

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ABSTRACT

Consumption of foods can be suppressed by two feeding system defense mechanisms: conditioned taste aversion (CTA) or taste avoidance learning (TAL). There is a debate in the literature about which form of intake suppression is caused by various aversive stimuli. For instance, illness-inducing stimuli like lithium chloride are the gold standard for producing CTA and external (or peripheral) painful stimuli, such as footshock, are the traditional model of TAL. The distinction between CTA and TAL, which have identical effects on intake, is based on differential effects on palatability. That is, CTA involves a decrease in both intake and palatability, whereas TAL suppresses intake without influencing palatability. We evaluated whether lactose, which causes gastrointestinal pain in adult rats, produces CTA or TAL. Using lick pattern analysis to simultaneously measure intake and palatability (i.e., lick cluster size and initial lick rate), we found that pairing saccharin with intragastric infusions of lactose suppressed both the intake and palatability of saccharin. These results support the conclusion that gastrointestinal pain produced by lactose malabsorption produces a CTA, not TAL as had previously been suggested. Furthermore, these findings encourage the view that the CTA mechanism is broadly tuned to defend against the ingestion of foods with aversive post-ingestive effects.

1. Introduction

The present article is concerned with the nature of the learning that occurs when ingestion of a taste stimulus (conditioned stimulus; CS) is followed by the aversive internal effects (unconditioned stimulus; US) caused by lactose malabsorption. Taste learning with an aversive US can be categorized as either a conditioned taste aversion (CTA; for reviews see [1–4]) or as taste avoidance learning (TAL; [5–10]). Both types of learning cause a reduction in the amount consumed of the taste CS. However, CTA also involves a conditioned downshift in the palatability of the CS; no change in palatability occurs in TAL.

One method of assessing taste palatability in non-human animals involves detailed analysis of the patterns of licks that occur during voluntary consumption (e.g., [11–13]). A number of dependent measures can be extracted from the stream of licks, including two that are considered to accurately reflect palatability: lick cluster size ([12,14–20]; for a review see [13]), and initial lick rate [15,20–22]. Lick pattern analysis has confirmed that lithium chloride, the quintessential laboratory US used to induce CTAs, causes a reduction in both intake and palatability (e.g., [23–26]).

Using this method, we found that gallamine and hypertonic saline, each US known to cause a reduction of CS intake [27–29], also conditionally lowers the palatability of the associate taste CS [30]. Gallamine is a neuromuscular blocking agent that causes transient pain and paralysis in muscle tissues [31] and hypertonic saline is a laboratory model of visceral pain [32,33]. Thus, we interpreted our results as evidence that the different types of internal pain caused by gallamine and hypertonic saline can function as a US that supports CTA learning.

Another type of internal pain is caused by lactose malabsorption (e.g., [34,35]). Lactose, a sweet-tasting disaccharide that is found in mammalian milk, cannot be absorbed unless it is first hydrolyzed into its monosaccharide elements (galactose and glucose) by the enzyme lactase. This enzyme is present in the intestinal tract in maximal quantities at birth through weaning but thereafter levels show a steep decline in both rats and humans [36]. In adults, the hallmarks of lactose intolerance are abdominal distention and pain [37]. Unabsorbed lactose can also cause bloating, borborygmus and diarrhea. Furthermore, there is evidence that galactose also has aversive post-ingestive consequences in adult rats (e.g., [38,39]). Thus, even digested lactose can serve as an aversive US. This leads to our experimental question: Does lactose malabsorption in the adult rat induce CTA or TAL?

Only one study has investigated this issue in experimentally naïve

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rats.[1] Pelchat et al. [10] concluded that lactose-induced taste suppression should be interpreted as TAL. However, some design issues undermine confidence in this conclusion. The claim about the absence of a downshift in palatability was based on a taste reactivity analysis of responses, or absence thereof, elicited by the CS following two conditioning trials. In the standard taste reactivity procedure [40–42], the taste stimulus is infused directly into the mouth via an intraoral catheter. The evoked orofacial and somatic responses can be classified as either ingestive or aversive. Pelchat et al. used an unconventional taste reactivity procedure in which the experimental animals could voluntarily consume a solution of 40% lactose on the two conditioning trials (i.e., lactose served as the CS and the US). This design choice allows for the monitoring of voluntary intake and the recording of taste reactivity responses. However, use of the hybrid procedure has several problematic consequences. First, the experimenter relinquishes control of US dose when amount consumed by each subject is the determining factor (on the first conditioning trial of the Pelchat et al. experiment, lactose intake ranged from 0.3 ml to 15.0 ml). Second, licking and taste reactivity are competing behavioral responses, which presumably limit the opportunity for the observation of ingestive taste reactivity responses. Third, when voluntary intake is low (or zero) there are fewer (or no) opportunities for the occurrence of taste reactivity responses producing a floor effect in the detection of aversive taste reactivity responses. Finally, it is an assumption that the taste reactivity repertoire is identical in all respects during voluntary drinking and intraoral infusions.

These concerns encouraged a re-examination of the nature of the taste learning supported by lactose malabsorption. We used lick pattern analysis because intake and palatability can be assessed simultaneously with this methodology. If lactose malabsorption supports TAL there should be a decrease in total licks, but no change in lick cluster size or initial lick rate in the experimental subjects (Group Lactose) relative to the control rats (Group Control). On the other hand, if lactose malabsorption supports CTA we expect to find a reduction in total licks, lick cluster size, and initial lick rate in Group Lactose compared to Group Control. To afford comparability with our previous research (and to avoid one of the issues with the [10] design), we employed a procedure in which the CS and US were separate events. Thus, we used 0.1% saccharin as the CS and 20% lactose as the US (5.7 g/kg body weight administered at room temperature via a gastric catheter). To minimize the influence of stomach distension on performance, CS intake on the two conditioning trials was capped to a maximum of 2000 licks (~ 10 ml). Prior work reveals that clusters size is prone to increased variance when intake is capped [30]. Therefore, as in that earlier research, two CS only test trials with 15-min unlimited access were scheduled to provide a more complete picture of the palatability of the taste CS. Finally, to ensure equal exposure to the US, the rats in the control group were given an intragastric infusion of lactose 24 h after the experimental rats received each CS-US pairing.

2. Materials and method

2.1. Subjects

Twenty male Sprague-Dawley rats weighing approximately 300 g were obtained from Charles River Laboratories (Wilmington, VT). They were individually housed in polycarbonate cages (Ancare, Bellmore, NY) in a room with a 12:12 h light:dark cycle that was maintained at ~ 70 °F. The rats were given ad libitum access to food (Teklad Diet 2018; Harlan Laboratories, Madison, WI) and tap water except as noted in the Procedure section below. The University of Illinois at Chicago Animal Care and Use Committee approved all procedures. Rats were treated according to guidelines provided by the American Psychological Association [43] and the National Institutes of Health [44].

2.2. Surgery

The rats were allowed to habituate to the facility for a minimum of 5 days prior to surgery when they were anesthetized with a mixture of ketamine (100 mg/kg, ip) and xylazine (10 mg/kg, ip) and fitted with a gastric catheter (e.g., [45,46]). Briefly, sterile tubing (OD: 0.065 in; Braintree Scientific Inc., Braintree, MA) was inserted into the fundus of the stomach and secured with sutures. The tubing was routed subcutaneously to the mid-scapular region where it was attached to a dorsal port (Plastics One, Roanoke, VA) and secured with wound clips. Catheters were filled with sterile saline and closed with dust caps (Plastics One). Following surgery animals were treated with analgesics (meloxicam, 1 mg/kg, sc) and antibiotics (enrotrofloxacin, 23 mg/kg, sc) once daily for a total of 3 days. Catheters were flushed with ~ 1 ml of room temperature water daily to ensure patency.

2.3. Apparatus

Eight identical drinking chambers (Med Associates, St. Albans, VT) were used to collect lick data with a 10 ms temporal resolution. As described in detail previously (e.g., [23]), each chamber was located inside a sound-attenuating cubicle and contained a single retractable sipper tube that could be accessed via an oval-shaped hole (1.3 cm × 2.6 cm) in the middle of the right-side wall. To prevent constant contact during drinking, in the extended position the tip of the sipper tube was ~ 3 mm outside the center of the access hole. A computer in an adjoining room running Med-PC software (Med Associates) and programs written in MedState Notation controlled chamber operation and data collection.

2.4. Procedure

Subjects were adapted to a deprivation schedule that allowed 15 min access to water (capped at 2000 licks) each morning in the drinking chamber and 15 min uncapped access to water in the home cage each afternoon. When the dependent measures were stable across three consecutive morning water sessions, the rats were counterbalanced into one of two groups (n = 10/group) in terms of their performance and the experiment began the next day. Conditioning trials occurred in three-day cycles; water was always available for 15 min each afternoon in the home cage. On Day 1, 0.1% saccharin (the CS) was substituted for water in the drinking chambers and followed, 5 min after removal of the rat from the drinking chamber, by an intragastric infusion (~ 1 min; e.g., [47]), via a syringe connected to the intragastric cannula, of either lactose (5.7 g/kg; delivered via a 20% w/v lactose solution at 2.85 ml/100 g bodyweight) Group Lactose (bodyweight 451.0 ± 13.1 g) or an equivalent volume of water in Group Control (bodyweight 444.0 ± 9.4 g). Two hours after morning water access on Day 2, each rat in Group Lactose was given an intragastric infusion of water whereas the rats in Group Control were infused with lactose. Day 3 was a recovery day on which all rats were given 15-min capped access to water in the drinking chamber and no intragastric infusion. On Days 4–6, a second conditioning cycle was administered. Beginning on Day 7, two CS only test trials were administered. The test trials were identical to conditioning trials, except all rats were given 15-min unlimited access to the CS each morning and there were no intragastric infusions.

2.5. Dependent variables

The three dependent variables were: total licks, lick cluster size, and initial lick rate. Using our standard criteria (e.g., [23]), lick cluster size was defined as a run of licks separated by pauses (inter-lick intervals)

[1] Other studies have examined similar issues in non-naïve rats (i.e., [67,68]; see [69] for a discussion of the interpretational issues surrounding these results).