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Effects of gymnemic acids lozenge on reward region response to receipt and anticipated receipt of high-sugar food

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ABSTRACT

A gymnemic acids lozenge that blocks sweet taste receptors reduced the decision to consume candy in humans even before the candy was tasted after the gymnemic acids dose, suggesting that blocking sweet taste receptors reduces valuation of sweet foods. The present study used functional magnetic resonance imaging (fMRI) to test whether the gymnemic acids lozenge reduces reward region response to both intake and anticipated intake of high-sugar food, as well as ad lib candy intake relative to a placebo lozenge. Here we show for the first time that a gymnemic acids lozenge versus placebo lozenge significantly reduced activation in the striatum and orbitofrontal cortex in response to anticipated tastes of high-sugar milkshake, and significantly reduced dorsolateral prefrontal cortex response to tastes of milkshake. We also replicated evidence that a gymnemic acids lozenge versus placebo lozenge significantly reduced ad lib candy intake. Results also provide novel evidence that an initial taste of a high-sugar food increases reward region (i.e., caudate) response to anticipated intake of more of the high-sugar food. Results suggest that blocking sweet taste receptors not only reduces reward region response to intake of high-sugar foods, but also reduces anticipated reward from high-sugar foods, potentially via a feedback loop regarding the availability of sweet taste receptors to convey perceptual input regarding sweet tastes. Collectively, results imply that the gymnemic acids lozenge might prove useful in decreasing high-sugar food intake.

1. Introduction

Nearly 70% of US adults are overweight or obese, which contributes to morbidity and mortality [13]. Experiments have provided unequivocal evidence that elevated consumption of high-sugar foods contributes to excessive weight gain [35, 57], suggesting that an important public health priority is to identify interventions that reduce consumption of high-sugar foods. Indeed, numerous studies have investigated the relation of obesity to individuals differences in taste and hedonics [65].

Oral administration of gymnemic acids (GA) may represent one effective strategy for reducing consumption of high-sugar foods. GA, a triterpenoid saponin glycosides isolated from the woody vine *Gymnema sylvestre,* suppresses the sensation of sweetness from various sugars and sugar substitutes by inhibiting sweet taste receptors in experiments with humans and chimpanzees, but does not affect the perception of salty, sour, and bitter tastes [27, 33, 44, 61]. Because the structure of GA molecules is similar to glucose molecules, the former bind to sweet taste receptors on the tongue, preventing activation of these receptors by sugar molecules and firing of the chorda tympani nerve, which relays taste signalling to the brain [33, 43].

Oral administration of GA mouth rinse in humans reduced the pleasantness of sweet tastes (e.g., sucrose, aspartame) and subsequent ad lib carbohydrate intake ([7, 18, 22, 42]). A randomized double-blind experiment found that a GA lozenge versus placebo lozenge produced a 31% reduction in the number of participants who chose to eat candy immediately after GA dosing, resulting in a 44% reduction in total candy intake, and reduced pleasantness ratings of the candy when tasted after GA dosing [52]; an independent experiment replicated each of these effects [38]. Thus, these behavioral data provide evidence that a GA lozenge reduces both pleasantness (liking) of high-sugar foods and desire for (wanting of) high-sugar foods.

The first aim of this study was to extend this research by using functional magnetic resonance imaging (fMRI) to provide the first test of whether the GA lozenge reduces reward region response to tastes of high-sugar food, as well as subsequent ad lib candy intake, relative to a placebo lozenge. Tastes of high-sugar foods, whether high in fat or not, activate brain regions implicated in reward, including the striatum, midbrain, amygdala, and orbitofrontal cortex (OFC) [12, 16, 46, 47, 49, 65, 66]. Anticipated intake of high-sugar foods also activates these

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reward regions [39, 40, 50]. Critically, elevated reward region response to high-sugar food intake [20] and anticipated intake [48] predicts future weight gain, consistent with the reward surfeit model, which posits that greater reward region response to high-calorie food intake increases overeating [50] and the incentive sensitization model, which posits that greater reward region response to cues associated with hedonic pleasure from high-calorie food intake prompts overeating [4]. Findings imply that an intervention that reduces reward region responsivity to intake of and anticipated intake of high-sugar food should reduce consumption of such foods.

In the earlier experiment [52] the GA lozenge reduced desire to eat more candy, even before any candy was tasted after dosing, suggesting that blockade of sweet taste receptors reduces anticipated reward from high-sugar foods, potentially via a feedback loop regarding the availability of sweet taste receptors to convey the perception of sweet tastes. Thus, the second aim was to provide the first test of whether the GA lozenge reduces reward region response to anticipated intake of high-sugar food, a neural marker for valuation (wanting) of the high-sugar food, even before the high-sugar food is tasted after GA dosing.

This study also afforded an opportunity to test whether an initial taste of a high-sugar food increases reward region response to anticipated intake of such food, which has not been investigated previously using brain imaging. An initial taste of a high-sugar food may serve as a potent reward cue that increases desire to consume more of the food. Accordingly, the third aim was to test whether an initial taste of a high-sugar milkshake increases reward region response to anticipated taste of more of the milkshake.

2. Materials and methods

2.1. Subjects

Forty healthy men and women (mean age = 21.6 ± 4.0; BMI = 25.8, range 18.8–36.8; 72.5% female) participated in this within-subject, double-blind crossover study. Subjects were recruited in a medium-sized town in the Western US via mailings, flyers, and leaflets inviting people who like sweet foods ('Do you have a sweet tooth?') to participate in a sugar craving research trial. Inclusion criteria included age between 18 and 50, a fondness for sweet foods ('agree' or 'strongly agree' to have a sweet tooth), a desire to lose weight, and a BMI between 18 and 40. We focused on individuals with a fondness for sweet foods and a desire to lose weight because we assume that a primary motivating factor for using GA lozenges would be to lose weight by reducing sugar intake. Exclusion criteria included major psychiatric disorders as determined by screening items from the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), serious health problems (e.g., diabetes), habitual use of psychoactive drugs or medications, contraindications for MRI scanning (e.g., ferromagnetic braces), gluten or lactose intolerance, and a vegan diet. Participants provided informed written consent for the project. Oregon Research Institute's Institutional Review Board approved all methods.

2.2. Experimental design

Participants were familiarized with the fMRI paradigm before the imaging session. Order of stimuli (pictures, taste, ratings) and administration of the lozenge were discussed. Participants were instructed to anticipate receiving the chocolate milkshake when seeing the milkshake glass. They were also instructed to hold the taste in their mouth until they saw the 'swallow' cue. They practiced swallowing and placing a tic-tac in their mouth while keeping their head still in a mock fMRI scanner. All subjects attended 2 separate scan visits ≥7 days apart, completing both scans at either 8:30 AM or 12:30 PM. Participants randomly received a GA or a placebo lozenge at the first scan visit as determined by a random number table and received the opposite at the second visit. Prior to each scan, participants were fed a light healthy breakfast or lunch to standardize satiety. Breakfast consisted of one piece of toast (2 pieces if participant > 150 lbs), 1 tablespoon of peanut butter (2 tablespoons if participant > 150 lbs), 1 string cheese, and one apple. Lunch consisted of a peanut butter and jelly sandwich (2 if participant > 150 lbs), a string cheese, and an apple. At 0 min, the standard meal was provided to participants, followed by a visual analog scale (VAS) for hunger. VAS ratings were anchored by 0 (not at all), 10 (neutral), and 20 (never been more hungry). The mean (± SD) hunger rating was 5.7 ± 5.4 prior to the GA lozenge scan and 6.7 ± 4.9 prior to the placebo lozenge scan, suggesting that hunger ratings were low. At 30 min, subjects completed a 30-min MRI session, which included the high-sugar milkshake receipt and anticipated receipt paradigm and a high-resolution structural scan. We examined neural response to a high-sugar, moderate-fat milkshake because it was rated as more palatable and elicits greater reward region response than high-sugar, no fat beverages [8]. After the scan, participants received a second dose of GA lozenge or placebo and were taken to a separate room to fill out surveys. A variety of wrapped candies were present in separate bowls in the room and participants were told that this was leftover food from another study and that they were welcome to consume the candy while completing the surveys. The researcher left each participant alone and came back when the participant finished completing the surveys. The bowls were weighed before and after participant access, providing an objective measure of candy intake.

2.3. fMRI food receipt and anticipated receipt paradigm

We used a block version of our milkshake paradigm [48]. The milkshake consisted of 4 scoops of vanilla ice cream, 1.5 cups of 2% milk, and 2 tablespoons of chocolate syrup. The milkshake was prepared in house immediately prior to the scan. The GA and placebo lozenges, which were sourced by Crave Crush, were similar to a breath mint. The GA lozenge contained 3.5 mg of GA. Participants were instructed to let the lozenges slowly dissolve in their mouths. Pilot data (N = 25) indicated that the highest rated taste dimension for the GA lozenge was sweet (45.4), followed by bitter (32.8) and savory (27.6); the highest rated taste dimension for the placebo lozenge was also sweet (49.4), followed by savory (34.3), and salty (10.4).

During the fMRI paradigm (Fig. 1) participants saw a fixation cross (10 s), followed by a picture of a chocolate milkshake that predicted impending delivery of chocolate milkshake (Picture 1: 10 s). Participants were asked to anticipate tasting the milkshake while viewing this picture. After ten secs, a craving rating scale appeared below the image (5 s) and participants were asked to rate craving from 1 (weak) to 5 (strong) for the milkshake by means of a button box. After the rating, participants received the milkshake during 4 cycles of taste delivery of 10 s (total of 48 s). Participants were instructed to swallow when they saw the "swallow" cue. Taste delivery was followed by the milkshake picture (Picture 2), during which participants anticipated tasting the milkshake and rated their craving for the milkshake again. Participants then placed the GA lozenge or placebo in their mouths with their dominant hand, letting it dissolve completely (order counterbalanced; 30 s to administer) and completed the milkshake taste anticipation (Picture 3) and milkshake receipt protocols again. Given that our goal was to examine reward region response to anticipated tastes of the milkshake before the milkshake was tasted after GA dosing, we could not use an event-related design in which the event is repeated multiple times because after the first event the milkshake would have been tasted after GA dosing. Thus, we used a block design during which the cue for impending milkshake tastes was shown for a longer duration. Although we could have shown the milkshake predictive cue several times without actually delivering the milkshake tastes, this would have captured reward prediction errors (when the hedonic reward that is expected is not experienced), which was not our goal. The task was divided into 1 run with 5 blocks: 3 blocks consisting of a chocolate milkshake picture (10 s each) and 2 blocks with tastant deliveries (48 s

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