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Amygdala response to sucrose consumption is inversely related to artificial sweetener use

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Abstract

Controversy exists over whether exposure to artificial sweeteners degrades the predictive relationship between sweet taste and its post-ingestive consequences. Here we tested whether brain response to caloric sucrose is influenced by individual differences in self-reported artificial sweetener use. Twenty-six subjects participated in fMRI scanning while consuming sucrose solutions. A negative correlation between artificial sweetener use and amygdala response to sucrose ingestion was observed. This finding supports the hypothesis that artificial sweetener use may be associated with brain changes that could influence eating behavior.

Keywords

Amygdala; Insula; artificial sweetener; fMRI; sweet; flavor-nutrient conditioning

Introduction

Since 1976, obesity rates in the US have more than doubled, rising from 13% to 32% (National Center for Health Statistics, 2006). In the same timeframe, artificial sweeteners have come into wide use (Mattes & Popkin, 2009). Davidson and Swithers have proposed that experience with non-caloric sweet tastes can disrupt the predictive relationship between sweet taste and calories, which then leads to an erosion in the animal's ability to regulate intake, resulting in over-consumption and eventually weight gain (Davidson & Swithers, 2004).

In their initial experiments Davidson and Swithers (Davidson & Swithers, 2004) divided rat littermates into two groups. One group received an inconsistent combination of sweet taste and calories (sometimes the solution was caloric and sometimes it was not). The other group

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Conflict of Interest

The authors declare that they have no competing financial conflicts of interest.

received a consistent combination of sweet taste and calories. Later, when offered chow after consuming a novel sweet premeal, the rats exposed to consistent sweetness/calories compensated for the premeal calories consumed by eating less chow, while the rats exposed to the inconsistent sweeteners failed to compensate. The authors thus demonstrated that inconsistent exposure to sweetness and calories was associated with failure to regulate intake.

Subsequent studies then established that history of access to artificial sweeteners leads to increased body weight, adiposity, and caloric intake in rodents (Swithers, Baker, & Davidson, 2009; Swithers, Martin, & Davidson, 2010). Whether or not a similar effect occurs in humans is more controversial. Many studies have found correlations between artificial sweetener use and weight gain (Blum, Jacobsen, & Donnelly, 2005; Colditz et al., 1990; Fowler et al., 2008; Stellman & Garfinkel, 1988). In addition, Appleton and Blundell (2007) showed a differential effect of sweet taste on appetite as a function of artificial sweetener use. However, other studies suggest that artificial sweeteners may aid in weight loss (Rolls, 1991), or have no or inconclusive effects on BMI (reviewed in (Benton, 2005)). Moreover, several reviews have concluded that the evidence linking artificial sweetener use with increased food intake is lacking (Bellisle & Drewnowski, 2007; Mattes & Popkin, 2009).

We reasoned that if exposure to artificial sweetener erodes the relationship between sweet taste and calories, then brain response to a caloric sweet taste should vary as a function of individual differences in artificial sweetener use. We further hypothesized that such differences should occur in regions implicated in the formation of the association between oral sensory features of food and drink and their post-ingestive consequences. In this form of learning, termed flavor-nutrient conditioning (reviewed in (Sclafani, 2004)) rats consistently show a preference for a flavor previously paired with sucrose over saline infusions. Lesions to the lateral hypothalamus, brainstem, striatum and amygdala block flavor-nutrient conditioning (Bernal et al., 2008, 2009; Sclafani, Azzara, Touzani, Grigson, & Norgren, 2001; Touzani & Sclafani, 2005; Touzani, Bodnar, & Sclafani, 2009a, 2008). The neural correlates of flavor nutrient conditioning in humans are currently unknown, therefore we based our selection of regions of interest (ROI) on the animal literature. We also included insular cortex as an ROI, as this region represents primary taste cortex and has been shown to interact with hypothalamus during nutritive vs. non-nutritive tasting (Rudenga, Green, Nachtigal, & Small, 2010).

Materials and methods

Subject selection

This research protocol was approved by the Yale University Human Investigation Committee. Eighty-one subjects were recruited by advertisements posted around Yale University and the greater New Haven area. Only subjects between the age of 18 and 45 were included. Subjects were excluded if they had any non-removable metal on their body, were currently or recently taking major medications such as antidepressants, were claustrophobic, had a history of food allergies, had diabetes, or had any history of psychiatric disorder or drug abuse.

Prior to the experiment, subjects were given a description of the paradigm and provided written informed consent. All subjects completed an initial screening session. Fifty subjects were excluded after this session based on discomfort with the scanning environment, unwillingness to consume sucrose repeatedly, or ratings falling outside of the target ranges for a concurrent study, in which we sought subjects who perceived the pleasantness of strong sweet tastes to be either high or low and of weak sweet taste to be neutral. Thirty-one

subjects participated in scanning. After excluding subjects with excessive head movement or missing data, 26 subjects (16 female, age 19–38, BMI 19–28) were used for final analysis.

Stimuli

Stimuli were solutions of sucrose diluted to .045M, .09M, .13M, .18M, .32M, .56M, .7M, .85M, 1.0M, 1.25M, 1.5M, and 2.0M. Rinses and control events were dilutions of a standard artificial saliva mixture described previously (Rudenga et al., 2010).

Stimulus selection & subject screening

For screening sessions and fMRI scanning, subjects were asked to gauge their food intake so that they arrived at the experiment neither hungry nor full. Perceived internal state was then assessed using a visual analogue scale of hunger with ends labeled “I am not hungry (full) at all” and “I have never been more hungry (full)” and the midpoint labeled “neutral”. During the initial screening session, subjects completed brief training modules in using the general Labeled Magnitude Scale (gLMS) (Bartoshuk et al., 2003; Green et al., 1996) and Visual Analog Scales (VAS) and then completed two series of sucrose sampling and rating; one for rating intensity and one for rating pleasantness, in counterbalanced order. They sampled and swallowed 1 mL of each of the sucrose solutions, in randomized order and rated its intensity on the gLMS (in one series) or its pleasantness on the VAS (in a separate series). The gLMS is a linear scale with descriptors such as “weak,” “moderate,” and “strong” spaced quasi-logarithmically to reflect the magnitude of perceived intensity differences. The VAS was labeled “most unpleasant sensation ever” on the left and “most pleasant sensation ever” on the right. The goal of this procedure was to select two sucrose stimuli for each subject, one that was rated as strong and one that was rated as weak. In the current manuscript we focus on brain activation to the strong sucrose.

Questionnaires

Subjects filled out the Nutrition Questionnaire (NQ) and the Dutch Eating Behavior Questionnaire (DEBQ). The NQ assesses how frequently subjects used various artificially sweetened products, with possible answers ranging from “Never, or less than once/month” to “6+/day”. The minimum artificial sweetener use score of 0 represents no (or less than once/month) use of artificial sweeteners; while the maximum score of 24 represents consuming each class of artificially sweetened products 6 or more times a day. The NQ also assesses frequency of intake of many other foods, which are not included here.

Stimulus delivery

Subjects received the solutions through an fMRI-compatible custom-designed gustometer, described in (Rudenga et al., 2010). Each taste event consisted of delivery of one of the sucrose solutions as a 1 mL bolus over 3 sec, followed by a rest period of 13–17 s (allowing perceptual responses and blood oxygen level-dependent (BOLD) signal to peak without being contaminated by swallow-related movement), a cue to swallow the solution, a 1 mL bolus rinse of tasteless solution (delivered over 3 s), and a second rest and swallow cue. Control events consisted of delivery of 1 mL of tasteless solution over 3 s, followed by a 13–17 s rest and a swallow cue.

fMRI session

Subjects returned on a separate day for fMRI scanning. We used a 3 T Trio scanner by Siemens using standard procedures (Veldhuizen, Bender, Constable, & Small, 2007). Subjects underwent 5 functional runs of 9 min, 12 sec each as well as a structural scan after the third functional run. Each functional run consisted of 7 trials each for weak sweet (WS), strong sweet (SS), and tasteless (tls) stimuli, for a total of 35 events per stimulus. Weak

sweet taste was included for the purposes of a different experiment and brain response to weak sweet is not analyzed here.

Data analysis

Neuroimaging data were pre- and post-processed using SPM5 (Wellcome Department of Cognitive Neurology) using standard procedures (Friston et al., 1994; Veldhuizen et al., 2007). When a subject's head movement was greater than 2 mm in any direction during a single run, that run was excluded from analysis. If more than two runs needed to be discarded, the subject was excluded from data analysis. Images were normalized to the Montreal Neurological Institute template (MNI-305), smoothed with a 6-mm full-width at half-maximum isotropic Gaussian kernel, and high pass (128 s) filtered to remove noise. Normalization resulted in $3 \times 3 \times 3$ mm voxels for functional images and $1 \times 1 \times 1$ mm voxels for structural images. Condition-specific effects at each voxel were estimated using the general linear model. The response to events was modeled by a canonical HRF (Friston et al., 1994).

Analyses were based on random effects models in order to account for inter-subject variability (Strange, Portas, Dolan, Holmes, & Friston, 1999). For each subject, an SPM reflecting the smoothed response (parameter estimate) at each voxel across the whole volume was created for SS-tls. Parameter estimate images were entered into second-level analyses using a 1-sample t-test, to test for significant differences in response between strong sweet and tasteless. Artificial sweetener use scores were then entered into models as regressors to evaluate the influence of artificial sweetener use on brain response to sweet taste. Ratings of the intensity (gLMS) and pleasantness (VAS) of SS were included as covariates of no interest. All results used a cluster criterion of 5 voxels. Unpredicted peaks were considered significant at $p < 0.05$, $k \leq 5$, FDR-corrected across the entire brain at the voxel level. A region of interest approach using WFU pickatlas (Maldjian, Laurienti, Kraft, & Burdette, 2003) to select bilateral masks of amygdala, striatum, hypothalamus and insula was employed to test for predicted effects, considered significant at $p < 0.05$, $k \leq 5$, FDR-corrected across the voxels of the ROI.

Results

Group Demographics & Questionnaires

The 26 subjects included here (14 female, 23 right handed) were healthy weight or overweight (BMI Avg $\pm$ SD = 23.4 ± 2.6), aged 24.5 ± 5.8 , and represented a range of scores on the DEBQ (Emotional eating = 2.1 ± 0.8 , external eating $3.1 \pm .5$, restrained eating $2.2 \pm .8$). Artificial sweetener use scores ranged from 0 (which equates to using artificial sweetener less than once per week) to 11 (using artificial sweetener an average of 3 times per day) (5.12 ± 2.7). We found no correlation between restraint eating (measured by the DEBQ) and artificial sweetener use ($r^2 = 0.02$) in the group as a whole. When including only those who use artificial sweetener in the analysis, there was still no correlation ($r^2 = 0.09$). Subjects report the following NQ subscores, none of which were correlated with artificial sweetener use: Starches/Grains = 38.9 (14.7), $r^2 = 0.01$; Sweet foods = 32.7 (15.6), $r^2 = 0.02$, Salty Foods = 24.1 (11.8), $r^2 = 0.08$.

Stimulus Ratings

As intended, subjective ratings indicated that participants were neither hungry nor full at the time of scanning (VAS hunger ratings 11.0 ± 48.4 ; VAS fullness ratings -28.0 ± 47.1). Intensity ratings show that, as expected, SS was rated as "strong" (33.0 ± 13.3), WS was rated as "weak" (7.3 ± 15.5), and tls was rated as "weak" (5.3 ± 6.3). Ratings of the pleasantness of SS varied widely (7.5 ± 50.0), while pleasantness ratings of WS (2.3 ± 18.3) and tls (-1.5 ± 24) were near neutral.

We found no relationship between artificial sweetener use and the concentration of sucrose selected as SS ($R^2 = 0.0036$), the perceived pleasantness of SS ($R^2=0.0022$), or the intensity of SS ($R^2=0.0051$), BMI ($R^2=0.1204$) or DEBQ restraint scores ($R^2=0.0017$).

Neuroimaging

Main Effect of Consuming Sucrose—Within our taste and feeding ROI, we found two large peaks responsive to the contrast of SS-tls. These peaks span the right Rolandic operculum and insula (51,12,12; $z=5.12$; $p=0.001$; $K=418$), and the left insula and striatum (−39, −3, 15; $z=4.42$; $p=0.006$; $k=358$).

Association Between Response to Sucrose and Self-Reported Artificial Sweetener Use—To test whether brain response to sucrose is associated with artificial sweetener use, we regressed artificial sweetener use against whole brain response to SS-tls, with pleasantness and intensity ratings of SS included as covariates of no interest. We identified a significant negative correlation (15, −3, −18; $z=4.01$; $p=0.011$; Fig 1) in the amygdala. Post-hoc tests showed the strength of this correlation to be $r^2=0.43$. A trend was also identified in the insula (48, 0, 3; $z=3.44$; $p=0.135$; Fig 1) using the wfu pickatlas insula mask. However, when we refined the insula ROI to a 10mm sphere centered on a region previously shown to be responsive to taste (Rudenga et al., 2010) the effect was significant ($p=0.014$). Posthoc analyses showed the strength of this correlation to be $r^2=0.38$. No other significant effects were observed. Both of these effects remained significant when BMI and DEBQ restraint scores were included as covariates.

Discussion

We used fMRI to test whether an individual's routine use of artificial sweeteners is related to brain response to a caloric sweet taste. We reasoned that if artificial sweetener use is associated with a degradation of the association between sweet taste and the post-ingestive effects of the calories it predicts (Davidson & Swithers, 2004), then sweet taste should produce a differential response in regions that are known to signal the post-ingestive effects of flavors. Consistent with our hypothesis, we identified an inverse relationship between amygdala response to sucrose and artificial sweetener use and a trend towards a similar effect in the insula.

The amygdala and the insula have both been implicated in integrating oral sensory and homeostatic signals. The amygdala, in particular, has been shown to play a critical role in flavor nutrient conditioning in rodents (Gilbert, Campbell, & Kesner, 2003; Touzani & Sclafani, 2005; Touzani, Bodnar, & Sclafani, 2009b). Although the neural correlates of flavor nutrient conditioning in humans are unknown, amygdala response has been shown to be greater to food aromas that predict the consumption of a caloric fruit drink vs. a noncaloric tasteless solution (Small, Veldhuizen, Felsted, Mak, & McGlone, 2008) and responses to cues that predict food aromas decrease following consumption of the food represented by the odor (Gottfried, O'Doherty, & Dolan, 2003). These data confirm a role for the human amygdala in representing value of foods predicted by cues, which is in turn related to the biological utility of that food and are therefore consistent with the animal data.

The insula has also been proposed as a key region for integrating multimodal oral sensations with internal state (de Araujo & Simon, 2009). However, in contrast to the amygdala, lesions of the anterior insula do not appear to disrupt flavor nutrient conditioning (Touzani & Sclafani, 2007). However, insular lesions do produce a deficit in learning to associate flavors with nausea (conditioned taste aversion learning) (Dunn & Everitt, 1988) and Cubero and Puerto showed that rats develop preferences for flavors paired with electrical stimulation of the insula (Cubero & Puerto, 2000). In humans, response here is dependent on

hunger (Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001; Tataranni et al., 1999) and modulated by ghrelin injection (Malik, McGlone, Bedrossian, & Dagher, 2008). Moreover, the exact area where we identified a relationship between artificial sweetener use and response was previously shown to display greater interactions with the hypothalamus and striatum when subjects sampled nutritive as opposed to non-nutritive tastes (Rudenga et al., 2010), further supporting a role for this region in associating oral sensations with homeostatic and reward processing. Considered in light of these data, the current findings are consistent with the proposal by Swithers and Davidson that experiencing sweet taste without calories results in a degradation of the predictive capacity of sweet sensation, which is represented in the amygdala and insula.

Importantly, while we are able to rule out contributions of BMI, intensity perception, stimulus concentration and perceived pleasantness to the observed associations between artificial sweetener use and brain response, our design does not allow us to infer causality. Future work, in which exposure is manipulated, is clearly called for.

In summary, our results support the possibility that routine artificial sweetener use could affect amygdala and insula response to sugar and thereby influence feeding behavior.

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Figure 1. Relationship between amygdala and insula response to sweet taste and artificial sweetener use

Coronal sections showing the regions of insula and amygdala in which response to sweet taste vs. tasteless (contrast of SS -tls) correlates with artificial sweetener use. The graphs show parameter estimates at the peak voxel in the circled region for the contrast of SS-tls plotted against NQ Artificial Sweetener Use scores. The color bar represents the T-scale for the activations shown. Images are displayed at $p \leq 0.005$ and $k \geq 5$ voxels. Post-hoc tests showed the strength of this correlation in the peak voxel to be $r^2 = 0.43$ (amygdala) and $r^2 = 0.38$ (insula).

* The figure has been updated to reflect the analysis with covariates