Behavioural Brain Research 279 (2015) 139–147

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Tasting calories differentially affects brain activation during hunger and satiety

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HIGHLIGHTS

- An important function of eating is ingesting energy.
- We found no evidence for energy sensing in the oral cavity in general.
- Energy sensing was modulated by hunger state in several brain regions.
- Energy sensing is a hunger state dependent process.

ARTICLE INFO

Article history:
Received 4 September 2014
Received in revised form 5 November 2014
Accepted 9 November 2014
Available online 20 November 2014

Keywords:
Carbohydrate
Energy sensing
fMRI
Median cingulate
Oral cavity
Sweetness

ABSTRACT

An important function of eating is ingesting energy. Our objectives were to assess whether oral exposure to caloric and non-caloric stimuli elicits discriminable responses in the brain and to determine in how far these responses are modulated by hunger state and sweetness. Thirty women tasted three stimuli in two motivational states (hunger and satiety) while their brain responses were measured using functional magnetic resonance imaging in a randomized crossover design. Stimuli were solutions of sucralose (sweet, no energy), maltodextrin (non-sweet, energy) and sucralose + maltodextrin (sweet, energy). We found no main effect of energy content and no interaction between energy content and sweetness. However, there was an interaction between hunger state and energy content in the median cingulate (bilaterally), ventrolateral prefrontal cortex, anterior insula and thalamus. This indicates that the anterior insula and thalamus, areas in which hunger state and taste of a stimulus are integrated, also integrate hunger state with caloric content of a taste stimulus. Furthermore, in the median cingulate and ventrolateral prefrontal cortex, tasting energy resulted in more activation during satiety compared to hunger. This finding indicates that these areas, which are known to be involved in processes that require approach and avoidance, are also involved in guiding ingestive behavior. In conclusion, our results suggest that energy sensing is a hunger state dependent process, in which the median cingulate, ventrolateral prefrontal cortex, anterior insula and thalamus play a central role by integrating hunger state with stimulus relevance.

1. Introduction

An important function of eating is ingesting energy. From an evolutionary perspective, the ability to sense energy in the oral cavity therefore seems useful. Possibly, oral energy sensing occurs in two ways, namely (1) the sensing of energy due to a conditioned link between sensory properties of a food and the post-ingestive consequences (indirect energy sensing) and (2) the direct binding of a caloric ligand to a receptor in the oral cavity (direct energy sensing). Nowadays, there are several serious candidate receptors (such as CD36 and GPR120), that are proposed to be involved in direct fat sensing in the oral cavity [1–4].

On the contrary, although there is some indirect evidence, there is no proposed mechanism for direct oral carbohydrate (CHO) sensing. In a traditional human diet, the taste of sweet foods is usually produced by the binding of CHOs to the sweet taste receptor (a receptor to which also other compounds such as artificial sweeteners bind [5]). Therefore, there is a strong learned association between sweet taste and energy from CHO. This makes it very difficult to distinguish between direct CHO sensing and indirect

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http://dx.doi.org/10.1016/j.bbr.2014.11.019
0166-4328/

sensing through sweet taste in the oral cavity. At the same time, our diet includes many common starch-rich foods like potatoes and rice, which are high in CHO but do not taste sweet. These could be used to investigate the coupling between sweetness and energy. To our knowledge, however, no functional magnetic resonance imaging (fMRI) studies on oral CHO sensing have used this approach.

In mice, the coupling between sweetness and CHO can be bypassed by knocking out the sweet taste receptor [6–8]. Damak et al. and Zhao et al. showed that knockout mice lose their preference for artificial sweeteners, but partly retain their preference for glucose and sucrose. In line with this, both studies demonstrated that application of the taste stimuli on the tongue, resulted in near zero gustatory nerve responses for artificial sweeteners and diminished or normal responses for the CHOs. These findings point to the existence of direct CHO sensing in the absence of sweet taste transduction.

Earlier research speculated that rodents have a maltodextrin receptor in the oral cavity, based on their avid ingestive response of a maltodextrin solution compared to solutions of different mono/disaccharides [9,10]. Whereas in rodents, maltodextrin has a salient and pleasant taste, in humans it appears to be tasteless [11]. However, in humans, behavioral studies also substantiate the existence of an unidentified CHO receptor which facilitates direct oral CHO sensing [12,13]. Mouth rinsing with a sweet CHO solution, but not with a sweet non-caloric solution, improved exercise performance [13,14]. For example, mouth rinsing with a solution containing sucrose and glucose compared to a placebo solution containing aspartame, resulted in shorter time to complete a standard cycle trial [15]. Recently, a similar paradigm was tested in a neuroimaging setting and provided additional evidence for this phenomenon by showing larger CHO induced changes in the primary sensorimotor cortex compared to an equisweet non-caloric placebo when contrasted with a control solution [16]. The above results suggest that humans have an oral maltodextrin receptor similar to that of rodents.

Neuroimaging research has corroborated this hypothesis by demonstrating differences in taste activation between caloric and non-caloric solutions which were matched on sweetness [12,17–19]. For instance, Frank et al. [17] showed that primary taste areas (the anterior insula and frontal operculum) as well as frontal regions (prefrontal cortex) and regions involved in reward (striatum and anterior cingulate cortex (ACC)) responded stronger to tasting a sucrose than to tasting an equisweet sucralose solution. Similarly, Chambers et al. [12] looked at glucose and saccharin (non-caloric) and found that oral glucose, but not oral saccharin, activated the striatum and the ACC. In addition, others compared caloric and non-caloric soft drinks, sweetened with either sucrose and sucralose or a mixture of artificial sweeteners, and reported divergent activation in areas such as the amygdala, median cingulate, precentral gyrus, rolandic operculum and thalamus [18,19].

Physiological responses to oral energy, including brain activation, can be modulated by hunger state. That is, mouth rinsing with CHO in fed state did not improve exercise performance [20]. Furthermore, Smeets et al. [18] found striatal activation before, but not after consumption of 450 mL of caloric orangeade, during tasting of small sips of this same caloric orangeade. Tasting a non-caloric orangeade elicited no activation in this area, neither before nor after consumption of non-caloric orangeade. In contrast, in a study of Haase et al. [21], brain areas in which activation was greater during hunger compared to satiety in response to tasting a caloric (sucrose) and non-caloric (saccharin) stimulus partly overlapped; activation was significantly greater in the thalamus and hippocampus. Additionally, they demonstrated that during hunger, regions involved in salience (amygdala), memory (hippocampus) and maintaining energy balance (hypothalamus) were more activated than regions involved in tasting (primary and secondary taste regions such as the insula and inferior orbitofrontal cortex). During satiety, this was the other way around.

In conclusion, there is a lack of consensus about the existence of direct CHO sensing in the oral cavity in humans, the brain areas involved in this process and the modulation of energy sensing by hunger and sweetness. In the current study we intend to strengthen the evidence for direct oral CHO sensing in humans. Our main objective was to assess whether oral exposure to caloric and non-caloric stimuli elicits discriminable responses in the brain. In addition, we aimed to determine in how far these responses are modulated by hunger state and sweetness. To be able to distinguish the effect of energy from sweetness we included a stimulus containing only sweetness (sucralose solution), a stimulus containing only energy (maltodextrin solution) and a stimulus combining both (sucralose + maltodextrin solution). We hypothesize that oral exposure to caloric and non-caloric stimuli elicits differential responses in regions involved in salience (amygdala), memory (hippocampus), energy balance (hypothalamus), tasting (insula, frontal operculum and inferior orbitofrontal cortex) and reward (striatum and ACC). We expect that these differences are more pronounced during hunger compared to satiety and when sweetness and energy are combined.

2. Materials and methods

2.1. Participants

We recruited healthy, normal-weight (BMI between 18.5 and 25 kg/m^2), right handed female participants (age between 18 and 35 y), who consumed artificially sweetened beverages at least two times per month. Only women were included because structural [22] and functional [22–24] brain differences exist between both sexes. Exclusion criteria were: a restrained eating score higher than 2.80 (Dutch Eating Behavior Questionnaire [25]), an energy restricted diet during the past two months, change in body weight of more than 5 kg during the past two months, lack of appetite, stomach or bowel diseases, diabetes, thyroid disease or any other endocrine disorder, having a history of neurological disorders, use of daily medication other than oral contraceptives or paracetamol, having difficulties with swallowing and/or eating, having taste or smell disorders, being allergic and/or intolerant for products under study, smoking more than one cigarette/cigar a day, having a history of or current alcohol consumption of more than 28 units per week, exclusive consumption or avoidance of light versions of beverages, being pregnant or lactating or having any contra-indication for MRI scanning. Before enrollment, participants were screened on inclusion and exclusion criteria via a questionnaire and completed an fMRI training session in which they were familiarized with the fMRI procedure. Of the 31 enrolled participants, one dropped out during the first scan session (hunger session) because of nausea. Thirty female participants with a mean ± SD age of 22 ± 3 y and a BMI of 22.6 ± 1.4 kg/m^2 completed the study. Participants were on average at the same point in their menstrual cycle during both the hunger (mean ± SD = 9 ± 11 days) and satiety session (mean ± SD = 10 ± 9 days). This precludes biases in brain activation due to menstrual cycle phase, as sometimes seen in literature [26–28]. All participants gave written informed consent. This study was conducted according to the principles of the Declaration of Helsinki, approved by the Medical Ethical Committee of Wageningen University and registered in the Dutch Trial Register (NTR 3749).

2.2. Study design

The study had a randomized crossover design in which participants were scanned on two occasions, once during hunger and once