Satiety, taste and the cephalic phase insulin response: a crossover designed study

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Abstract

The glycemic response produced by a food depends on both the glycemic index of the food itself, and on how the body responds to the food as it is consumed and digested, also dependent on sensory cues from the food. Research suggests that taste stimulation can induce the cephalic phase insulin response, before food has reached the digestion, priming the body for an incoming glucose load. This glycemic response may consequently affect the amount of subsequent meal intake. The aim of this study was to investigate the effects on satiety of four preloads that differed in caloric content and sensory properties. Water, sucrose, sucralose, and maltodextrin were used to represent different conditions of the preload, with or without energy, and with or without sweet taste input. Individual plasma glucose concentrations were sampled at baseline, 45 minutes after consuming the preload, and after consuming an ad-libitum test meal. Hunger, desire to eat, and thoughts of food feeling were assessed every 15 minutes using a Visual Analog Scale (VAS). The results showed that consuming maltodextrin, which provided calories but not any sweet taste that may serve to trigger cephalic phase insulin release to attenuate this incoming glucose load, caused a spike in blood glucose after consuming the preload in male participants, alongside significantly greater decreases in feelings of satiety than after the other preloads. Despite the difference in postprandial blood glucose, the amount consumed across the treatments was not significantly different in either males or females. Results highlight the importance of taste in stimulating the body for the efficient and effective glucose homeostasis.

1. Introduction

As overweight and obesity are linked to multiple health problems, such as an increase in the risk of heart disease, type 2 diabetes, stroke, certain cancers, and other chronic conditions, it is important to understand the factors that control human appetite and satiety. Excessive energy intake from overconsumption is partially due to the satiating properties of foods, which in turn are associated with protein, fat, fiber content [8], sugar [36], as well as food viscosity [42], volume [35], and in some circumstances, the resting blood glucose levels of the consumer [27]. A change in blood glucose levels after eating is related to the glycemic index of the food consumed, which is a measure of the blood glucose raising potential of the food compared to a reference, usually pure glucose. The carbohydrate-content of foods can be striated into 3 groups, low GI foods such as soybean and apples, moderate GI foods such as bananas; and high GI foods such as white bread.

Consumption of high-GI foods can cause a spike in postprandial blood glucose which when declining often drops below the initial baseline. When blood glucose drops, it can promote hunger and result in overeating [30]. Conversely, the consumption of low-GI foods can lower the fluctuation of blood glucose levels [26]. Thus high GI diets are associated with overeating and hunger, which can consequently promote weight gain, where low GI diets have been proposed to affect a decrease in hunger, and food intake, promoting satiety, and are recommended for type 2 diabetes patients for weight management [3,4].

In general, high blood glucose levels trigger insulin release to uptake glucose into muscles and adipose tissues [34]. This release of insulin can occur while a person is in the process of feeding, but before food has reached the stomach, and thus before glucose from the meal has been liberated

from foods to raise blood glucose levels, termed the cephalic-phase insulin release (CPIR). The CPIR can enhance our tolerance to glucose [18], preparing the body for an upcoming increase of plasma glucose [21]. The CPIR can be triggered by several modes of stimuli, including meal expectation, visual cues, food smell or taste, and the processes of mastication and swallowing [42].

Taste signals are transmitted to the brain via the ventral forebrain gustatory pathway and stimulate ingestive motivation [38]. In humans and in rodents, when food is tasted, it induces the CPIR and increases plasma insulin levels. This mechanism occurs in rodents within the first five minutes of oral ingestion of sweet stimuli [18]. This mechanism acts through pathways including through the T1R2+T1R3 receptors, the 2 subunits that make up the sweet taste receptor [38] and a second pathway that does not require an interaction with T1R2+T1R3. The CPIR may still occur even though mice cannot perceive sweetness, as T1R3 KO mice that do not show an appetitive response to sucrose or glucose solutions still display CPIR responses [18].

A study from Just et al. (2008) in humans confirmed that sweet taste arising from nutritive and nonnutritive sweeteners (sucrose and saccharin) activated the CPIR independent of an increase in blood glucose [24]. Further, when isolating taste input through intragastric infusions of glucose in subjects tasting or not tasting during infusions, insulin was higher, and blood glucose lower if sweetness was tasted while infusions took place, indicating that taste plays a native role in glucose homeostasis [40]. Thus, our taste buds function not just to inform us of the content of our foods, but also to prepare the body for the ingestion of foods that otherwise would more negatively affect our metabolism.

In human studies, the palatable sweet taste from nutritive and nonnutritive sweeteners can elicit CPIR, resulting in a decrease in plasma glucose concentration [1]. Another study in normal-weight men found a significant increase in plasma insulin only in modified aspartame sham-feed, but not in pure forms of nutritive and nonnutritive sweeteners solutions [39]. A human study from Geiselman and Novin (1982) proposed that sugars could be rapidly absorbed and transported into the blood, causing hyperinsulinemia and consequently lowering plasma glucose concentration, so-called hypoglycemia. This drop of plasma glucose can develop into hyperphagia, an increase of hunger sensation which may lead to overeating [17].

Sucrose is a relatively high GI sweetener (although by no means the highest), which the body can digest easily, and is considered as the prototypic nutritive sweetener, providing 4 kcal of energy per gram. Even though the synthetic sweetener sucralose (branded as Splenda®) is marketed as being made from sucrose, by substituting 3 hydroxyl with 3 chlorine groups, our body cannot process it in the same manner as table sugar, and thus cannot metabolize sucralose to extract the chemical energy stored within. Therefore, sucralose provides negligible digestible calories and is considered a non-nutritive sweetener [9].

Digestible maltodextrins are short chain polymers of D-glucose units, and can be obtained by hydrolysis of different edible starches. Generally, digestible maltodextrins have dextrose equivalency (DE) less than 20. DE depends on the degree of hydrolysis; the lower degree of hydrolysis, the lower the DE. The DE of maltodextrin also correlates to the amylose/amylopectin ratio in the starch that is used to produce it, the higher amylopectin content, the higher the DE, correlating with a higher GI. Maltodextrins have a high glycemic index, and can provide

approximately 4 kcal per gram, similar to sucrose [22]. Maltodextrins, while caloric in nature, are experienced as tasteless, and thus if dosed at equivalent calories per gram to sucrose, are a good tool to separate taste from caloric intake [43].

The objective of this study was to compare the effect of 4 preloads; water, maltodextrin, sucrose, and sucralose, on satiation, hunger and blood glucose response. Water provides neither taste stimulation nor glucose. Maltodextrin has no taste but is a polymer of glucose molecules, which are readily digested. Sucrose has both glucose and taste, and sucralose, taste but no digestible glucose. Thus, our study seeks to isolate the importance of taste stimulation on the control of blood glucose, and subsequent feelings of hunger and satiety.

2. Materials and Methods

2.1. Subjects

The study was reviewed and approved by the Cornell University Institutional Review Board for Human Subject Research. Ten healthy subjects (5 men, 5 women) were recruited from the Cornell sensory listserv, and tested with over a 4 week period using RedJade sensory evaluation software (RedJade Sensory Solutions, LLC, Martinez, CA), after a pre-screening questionnaire to select those fitting demographics and availability. Demographics included no self-reported smoking behavior, no reported food allergies, liking of the test food, consumption of artificial sweeteners, acceptance of sucralose, not diabetic, and if participants were not currently actively seeking to control their weight.

2.2. Study design

The study followed a repeated measures, crossover design, where panelists underwent an identical day of testing (aside from consent and demographic questions) on 4 consecutive visits. Participants provided written consent, and were asked to complete the 4 sessions with at least 7-days washout between each test day, and were instructed to restrain from eating for 10 hours prior to each test. Each session was conducted from 10 AM to 12 PM at the Cornell Sensory Evaluation Center. On each day of testing, individuals were given a 300ml preload (see Figure 1), in a counterbalanced order. Five sets of questionnaires were given to rate hunger, fullness, desire to eat, and preoccupation with thought of food on Visual Analog Scales (VAS) throughout the course of the study. It was evident from the ratings of fullness that panelists may not have understood the

scaling completely, as net change in fullness was not positive in several panelists after the test meal, so fullness ratings were excluded from the report. Following the preload and first 2 questionnaires, an ad-libitum meal of toasted ham and cheese sandwiches was consumed, where participants were asked to eat until comfortably full. Finger stick capillary blood draws were performed 3 times on each testing day, before and after pre-load, and after test meal, to assay blood glucose level, by a licensed technician.

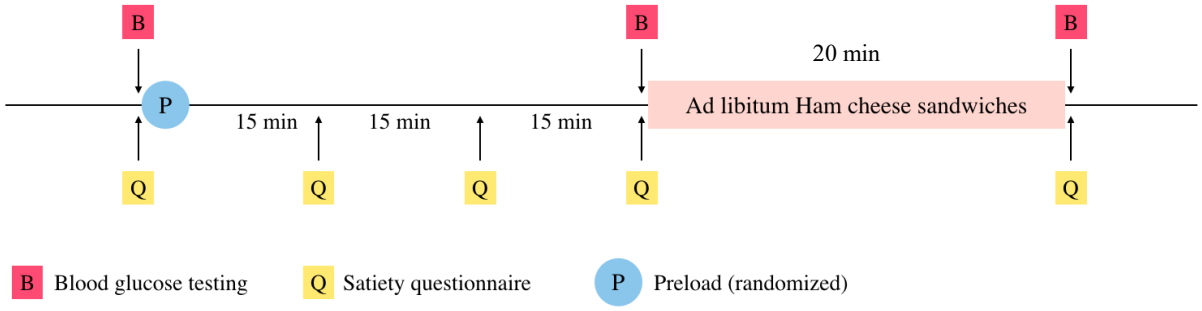

Figure 1. Study design on the test day

2.2. Pre-loads

Water: 0 kcal

Maltodextrin 4.68% w/v: 54 kcal (Eisen-Golden Laboratories, CA, USA)

Sucrose 4.5% w/v: 54 kcal (Wholesale Grocers Inc., Keene, NH, USA)

Sucralose 0.007% w/v: 0 kcal (VWR International., Radnor, PA, USA)

The four preload solutions used in the study were water, a moderately sweet sucrose solution, an equi-sweet solution of the non-caloric sweetener sucralose, and a solution of maltodextrin

containing the same number of calories as the sucrose preload. All solutions were prepared one day ahead of testing and kept overnight in the refrigerator. Sucralose at 0.007% w/v was selected based on sweetness equivalency according to a study from Wiet & Beyts (1992) [45]. Maltodextrin concentration was calculated to provide the same energy as sucrose solution [28]. Participants were also asked to rate the sweetness of each solution on the generalized Labeled Magnitude Scale (gLMS), to confirm no sweetness from maltodextrin, and equal sweetness from sucrose and sucralose.

2.3. Test Meal

Participants should be familiar with the food served in a test meal, to avoid provoking a neophobic response resulting in reluctance to eat until satiation in the manner they usually would [15]. The test meal should also ideally be easily reproducible and have a reliable measure of energy intake [19]. Moreover, the test food should be appropriate within the context of the timing of the meal, for example, breakfast food for a morning trial [6]. Therefore, toasted ham and cheese sandwiches were chosen as the test meal, as they are widely recognized for most people in the US, easily reproducible, and were appropriate for the time of the study. Serving meals ad libitum means there should always be more food that participants intend to consume, to minimize the risk of plate cleaning, that may influence when they cease eating [44]. The sandwiches were served in an excessively large portion, toasted to ensure that participants did not deconstruct the samples, and panelists were instructed to refrain from selectively eating, for example leaving crusts unconsumed.

Sandwiches were freshly made in the Sensory Evaluation kitchen during each day of the study. Each sandwich consisted of two sliced of Stroehmann® King white bread (Stroehmann Bakeries, L.C., Horsham Township, PA, USA), two Kraft® Singles American cheeses (Kraft Heinz Food Company, Chicago, IL, USA), and one slice of Great Value® water added cooked ham (Wal-Mart Stores, Inc., Bentonville, AR, USA). This provided approximately 2.37 kilocalories per gram. Approximately 500 grams of sandwiches were served to each panelist, on an 8x8x15/8 inch aluminum tray, with panelists monitored, and another tray provided if the panelist came close to finishing the first. Total food consumed to fullness was recorded by weighing the trays before and after the meal.

2.4 Statistics

Sweetness intensities of four preloads were analyzed with one-way ANOVAs and post hoc Tukey's tests, while plasma glucose concentration was measured with Friedman's tests followed by Dunn's tests corrected for multiple comparisons, and the relationship between preloads, energy consumed, and VAS ratings of satiety were analyzed using a linear mixed model, where $p < 0.05$ was considered as statistically significant. Each rating related to satiety (hunger, fullness, desire to eat, and thought of food) was subtracted from baseline ratings at the start of the testing.

3. Results

3.1 Preloads

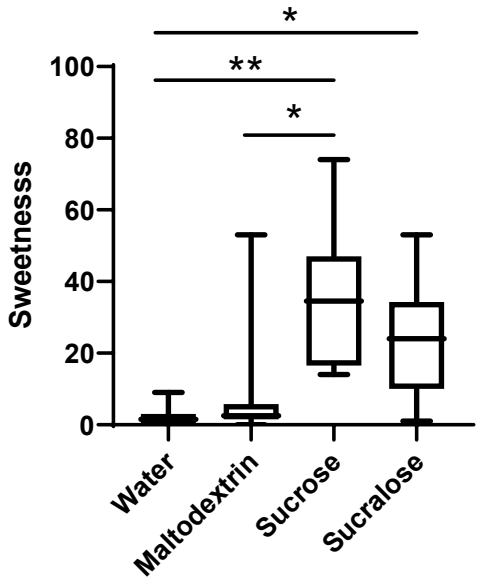

Figure 2. Sweetness intensity of water, maltodextrin, sucrose and sucralose, measured on the gLMS. Box represents median, upper and lower quartiles, whiskers show min and max.

All preload solutions were tested for sweetness, using the gLMS. The sweetness of water versus maltodextrin was not significantly different ($p=0.818$; Fig 2). For sucrose and sucralose solutions, there was also no statistically difference between these two solutions ($p=0.400$), although sucrose was sweeter than both water ($p=0.003$) and maltodextrin ($p=0.037$), and sucralose was sweeter than water ($p=0.010$). Thus we can say that sucrose and sucralose were no sweeter than one another, nor were water and maltodextrin.

3.2 Energy consumed

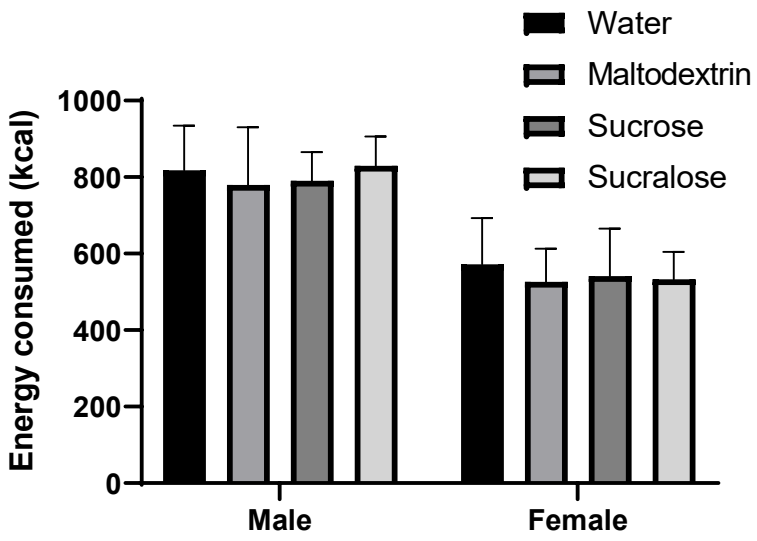

Figure 3. Energy consumed (kcal) during the test meal in male and female panelists. Bars represent mean plus SEM.

As unsurprisingly men consumed a significantly greater amount of calories than women, and male versus female responses to foods have been noted to differ [11], results were striated by sex. Within sex, no significant difference was found between how much food was consumed following any preload, in either male or female panelists (Figure 3).

3.3 Plasma Glucose Concentration

Regarding males' blood glucose concentration (Fig 4A), a significant increase in blood glucose occurred after the preload for maltodextrin ($p=0.011$). The maltodextrin preload represents the liberation of glucose into the bloodstream without the protective effects of sweet taste triggering

the CPIR. In post-hoc tests, this increase was significantly larger than sucrose ($p=0.042$), and trended larger than sucralose and water, though not significantly. No significant difference in glucose response to any of the preloads was found in females (Fig 4B).

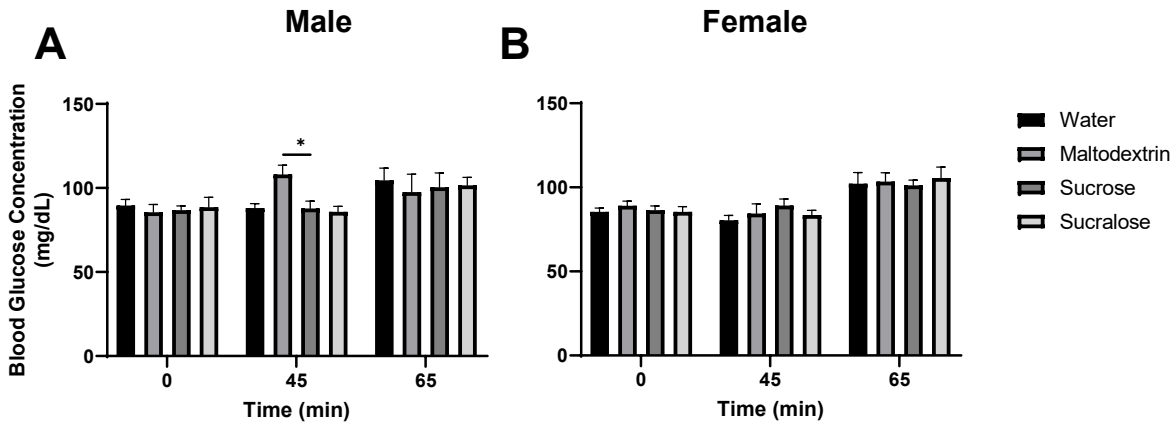

Figure 4. Blood glucose concentration (mg,dL) at baseline (0 min), after the pre load (45 min), and after the test meal (65 min) for water, maltodextrin, sucrose and sucralose preloads, in male (A) and female (B) panelists. Bars represent mean plus SEM.

3.4 *Satiety ratings*

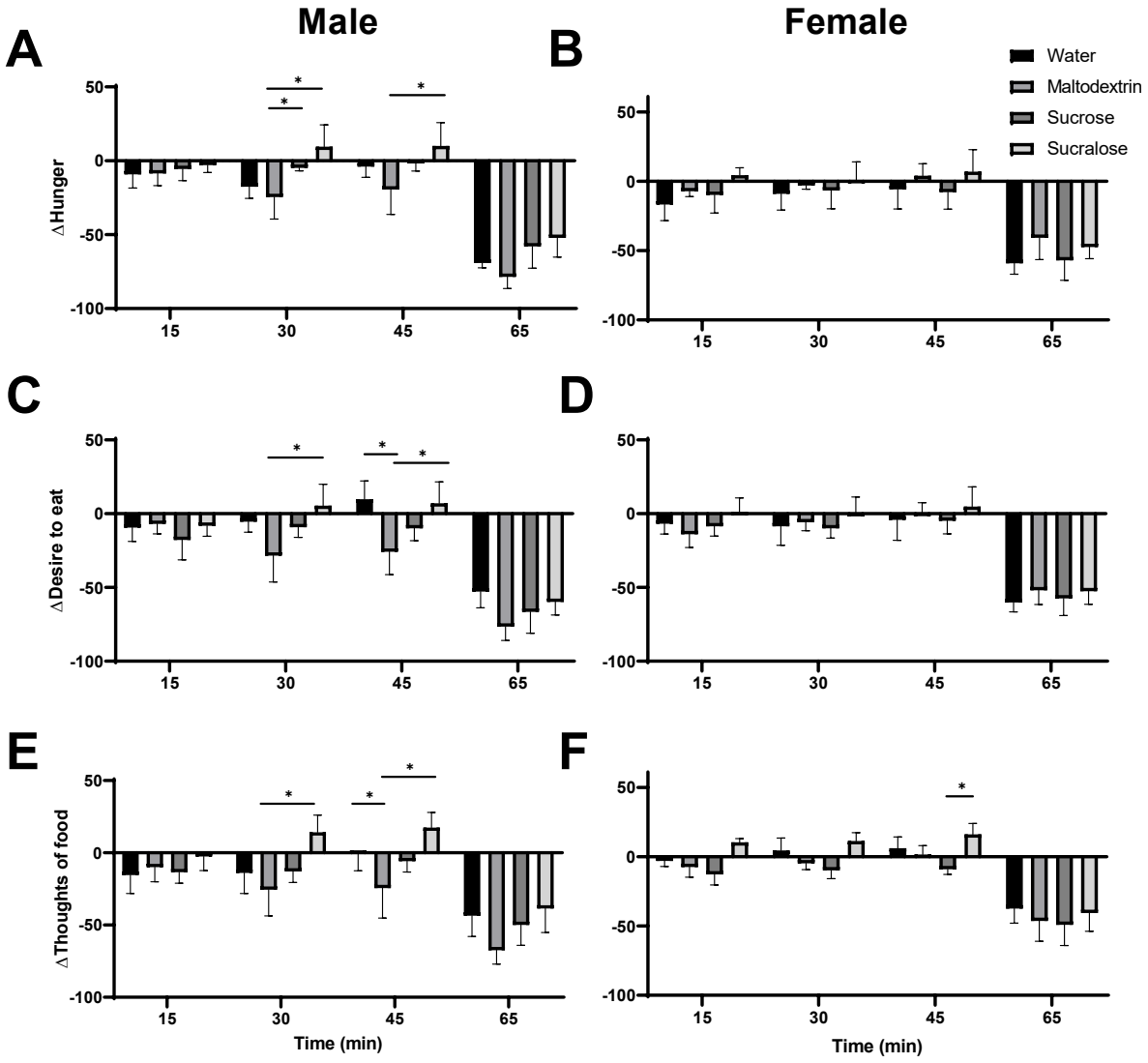

Figure 5. Difference from baseline of hunger, desire to eat, and thoughts of food in male (A, C, E) and female (B, D, F) panelists respectively. Bars represent mean plus SEM.

Significant differences between the preloads were evident again in male participants, where blood glucose also varied between preloads, with differences less apparent in females (Figure 5). After maltodextrin consumption, male subjects change in hunger, desire to eat, and preoccupation with thoughts of food significantly differed from than after other preloads, both at the 30-min and at the 45-min time point. Results were in agreement with data on blood glucose, whereby the maltodextrin preload triggered a blood glucose spike not present after other preloads. In general, results seemed to support that a change in satiety that would usually be accompanied by a blood sugar increase such as that after a meal occurred earlier with the maltodextrin preload, where no taste input acted as a prelude to the bolus of glucose the body received, although this did not affect amount of food eaten.

4. Discussion

Men and women's blood glucose concentration responded to the preloads in a different manner (Figure 4). 45 minutes after maltodextrin ingestion, plasma glucose concentration in males spiked, but this was not observed in females, which could be due to differences in body compositions in men and women. A study from Geer and Shen (2009) pointed out that men and women have different amounts of adipose tissue and sex hormones, where men had more visceral and hepatic fat and women had more of peripheral and subcutaneous fat. The higher amount of hepatic and visceral adipose tissue in men has been linked to higher insulin resistance, with women more sensitive to insulin due to estrogen [16]. When insulin resistant, the body responds less to an elevation of insulin, impairing insulin's ability to take up glucose [7]. It is possible that males in our study were more resistant than females to any insulin released through cephalic phase responses other than taste (the act of swallowing, mouthfeel, visual cues), resulting in a more prominent blood glucose spike after maltodextrin.

Water, as a control solution, did not provide calories or sweet taste, thus should not have elicited the CPIR. Within the first 45-min, after the preload but before subjects consumed the test meal, plasma glucose concentration remained stable, as seen in Figure 4. Sucrose provided both calories and sweet taste, which should elicit the CPIR, thus attenuating an increase in blood glucose arising from sucrose. Just et al. (2008) reported that an increase in plasma insulin was found within the first 5 minutes after oral stimulation from sucrose [24]. In this study, blood glucose sampling was at 45 minutes after ingestion, and thus represents a snapshot, where both glucose and insulin have affected blood glucose. However our results are reminiscent of those from a similar crossover

designed study from Smeets et al (2005), where 5 male panelists were given water, glucose, aspartame or maltodextrin [37]. In agreement with our hypothesis, an early insulin spike was observed with glucose, but not with maltodextrin. No differences in calories consumed were evident for sucrose versus water, or for any other preload. In a study by Anderson and Woodend (2003), sucrose reduced the amount consumed in a subsequent meal. Both a low (25 g sucrose/300 mL) and a high dose (135 g sucrose/300 mL) reduced subsequent meal intake and suppressed hunger [2]. In our study, we used a 4.5% w/v sucrose solution, which was around half of the lowest concentration in Anderson and Woodend's study. It is possible that any effect of sucrose on satiety was too small to measure in our study. The sucralose solution provided sweet taste but not calories. The sweet taste from sucralose may still elicit a CPIR response to cause an insulin spike [13], but without digestible glucose, sucralose should not have a significant effect on the postprandial glycemia [20]. In this study, we did not see any distinct drop in blood glucose after either sweet solution. This may also be explained by our infrequent blood sampling time, which may have missed the specific time when the glucose dropped.

Maltodextrin provided calories but no sweet taste. Maltodextrin is a starch derived product, consisting of a number of D-glucose molecules , but should not directly elicit the CPIR from taste, instead having to be digested to release glucose, by amylases and alpha-glucosidases, leading to an insulin response later in consumption [14]. In this study, we found a blood glucose spike in male panelists after subjects consumed maltodextrin, but not after water, sucrose or sucralose. Participants also reported larger drops in hunger, desire to eat, and thoughts of food after receiving maltodextrin. This indicates that the increase in blood glucose elicited by maltodextrin may have led to reduced hunger with this treatment. Blood glucose is the best known biomarker for hunger

[10]. Another explanation could lie in the natural properties of maltodextrin as a thickening agent, which forms gels and creates viscosity in solutions [14]. Maltodextrin is widely used in food industries as a bulking agent, stabilizer, or thickening agent [25]. In this study, maltodextrin may also have provided a slightly thicker mouthfeel, promoting a feeling of greater satiety than the other preloads. Evidence suggests that increasing the viscosity or texture of a solution may lead to increased feelings [31,23,5] or expectations [32,33] of satiety, or lead to lower consumption to reach the same satiety [12]. Zijlstra et al. (2008) found that subjects consumed more when receiving low viscosity liquid, and less when receiving high viscosity liquid, likely due to a slower eating rate [48]. Another study reported that consuming high viscosity food led to a slower eating rate and a delay of gastric emptying, with lower hunger and desire to eat [47]. Nonetheless, the only results we are aware of suggesting that viscosity can affect blood glucose levels concern varying viscous fiber constituents to alter thickness [41,46], thus our interpretation remains the most likely.

The mean rating of maltodextrin's sweetness was slightly higher than water, although not significantly, which may be explained by the dumping effect. Dumping is when a restricted response is offered in a questionnaire, causing people to report their feeling on another sensation on an inappropriate scale, even when the attributes are not related to one another [29]. In this case, we only asked participants to rate the sweetness of the preloads on the scale without any other attributes provided to rate on. It is possible that subjects may have detected that the preload was something other than water (for example a slight viscosity change), but since there was only sweetness to report on the ballot, subjects may have dumped their ratings into the sweetness scale. Nonetheless, the effects recorded were negligible.

Though serum glucose concentration was differentially affected by the preloads, the amount of the test meal consumed to satiate male or female panelists was not significantly different among the four solutions. This result is in agreement with a study from Kendall et al. (2018), that investigated the effects of sucrose and isomaltulose, that differently affect glycemic index, on subsequent meal intake. Results showed that subsequent energy intake and satiety did not vary significantly, compared to differing plasma glucose concentrations [27].

There were several limitations in this study that should be noted. First, we tested only ten panelists in this study, which does not represent a large sampling, and may have influenced our interpretation. Secondly, blood was not drawn as frequently as in some studies, so fine details on the temporal response were also not assessed. Future studies with higher sample size, and a greater time resolution regarding blood glucose readings may elucidate more details on this topic.

5. Conclusion

Sweet taste from nutritive and non-nutritive sweeteners activates taste receptors in the mouth, which are subsequently linked to cephalic phase insulin release. Our body uses this signal to prepare for an upcoming increase in glucose in the bloodstream; therefore, insulin is released to mediate excessive fluctuations in plasma glucose. Maltodextrin does not provide sweet taste to elicit the CPIR, while still being readily digested into glucose. Our results suggest maltdextrin produced a blood sugar spike after consuming the preload in male participants, which occurred alongside an increased change in ratings of appetite. Despite these results, the average energy consumption during the test meal was not significantly different between the four preloads. Our results imply an important role for taste input plays in controlling blood glucose, and determining satiety.

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