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The Cephalic Phase Insulin Response to Nutritive and Low-Calorie Sweeteners in Solid and Beverage Form

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Abstract

The purpose of the study was to examine the role of the cephalic phase insulin response (CPIR) following exposure to nutritive and low-calorie sweeteners in solid and beverage form in overweight and obese adults. In addition, the role of learning on the CPIR to nutritive and low-calorie sweetener exposure was tested.

Sixty-four overweight and obese adults (age: 18–50 yr, BMI: 24–37 kg/m^2, body fat percentage > 25% for men and > 32% for women) were sham-fed (at 2-minute intervals for 14 minutes) a randomly assigned test load comprised of a nutritive (sucrose) or low calorie sweetener (sucralose) in beverage or solid form in phase 1 of the study. A 2–3 ml blood sample was collected before and 2, 6, 10, 14, 61, 91 and 121 minutes after oral exposure for serum insulin and glucose analysis. During phase 2, participants underwent a 2-week training period to facilitate associative learning between the sensory properties of test loads and their post-ingestive effects. In phase 3, participants were retested for their cephalic phase responses as in phase 1.

Participants were classified as responders if they demonstrated a positive insulin response (rise of serum insulin above baseline i.e. Δ insulin) 2 minutes post-stimulus in phase 1. Among responders exposed to the same sweetener in Phases 1 and 3, the proportion of participants that displayed a rise of insulin with oral exposure to sucralose was significantly greater when the stimulus was in the solid form compared to the beverage form. Sucralose and sucrose exposure elicited similarly significant increases in serum insulin 2 minutes after exposure and significant decreases after 2 minutes in responders in both food forms. The solid food form elicited greater CPIR over 2, 6 and 10 minutes than the beverage form. There was no effect of learning on insulin responses after training. The results indicate the presence of a significant CPIR in a subset of individuals with overweight or obesity after oral exposure to sucralose, especially when present in solid food form. Future studies must confirm the reliability of this response.

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Keywords

Cephalic phase; Insulin Response; Low-calorie sweeteners; Learning; Food form; Obesity

1. Introduction

Sensory stimulation elicits a wide array of rapid physiological processes that enable the organism to mount an adaptive response to an impending challenge, such as food ingestion [1– 3]. These are termed first or cephalic phase responses and can influence digestion and metabolism by modifying vagal tone [4], gastric secretions, motility and emptying [5, 6], gut hormone release (e.g., CCK [7], GLP-1 [8] and ghrelin [9]), and post-absorptive endocrine responses (e.g., insulin [10, 11] and thermogenesis [12]). The best studied is the cephalic phase insulin response (CPIR) which modulates post-prandial glycemia. It is a neurally-mediated, small and transient spike in insulin release that precedes changes in blood glucose concentrations [13] and is correlated, possibly causally, with the magnitude of the post-prandial insulin concentration [14]. Blood glucose concentrations are higher and remain elevated longer when the CPIR is blocked than when the CPIR is present [15].

The CPIR can occur due to various stimuli that activate the parasympathetic nervous system, but is arguably most critical with ingestion of sugars. There is controversy over whether the sensation of sweetness alone is an effective stimulus for the CPIR [16–20]. It has been documented for some low-calorie sweeteners such as saccharin [21] but not sucralose [22], aspartame, stevioside, acesulfame-K or cyclamate [23]. However, there is a report of a biphasic release of insulin in isolated pancreatic islet cells following oral acesulfame-K exposure [24]. The considerable inter- and intra-individual variability in the CPIR has prompted claims that there are responders and non-responders [13, 25, 26], but very few studies make the distinction between individuals demonstrating a CPIR (responders) and those that do not in their analyses. The proportion of responders, if indeed this is a reliable distinction, to oral sweeteners is unknown.

If the insulin response to ingestion of a food or meal is excessive, post-prandial hypoglycemia may ensue and if it is insufficient, hyperglycemia may result. Thus, it is important to match the insulin response to the nature of the metabolic challenge. Through dietary experience, the sensory properties of foods become associated with the post-ingestive consequences of their ingestion so may be used by the animal to anticipate the needed response. However, there is limited data on the role of learning in cephalic phase responses. Theoretically, regular use of low calorie sweeteners could result in a diminished CPIR since sweetness would no longer predict an incoming carbohydrate load. Preliminary evidence in rodents suggests the CPIR is resistant to extinction [27]. The response in humans who are regular users of low calorie sweeteners has not been characterized. Such knowledge is critical given the high and expanding presence of low calorie sweeteners in the food supply and claims based on rodent data that their use results in higher energy intake, body weight and body adiposity [28, 29].

Low calorie sweeteners are present in foods, but are most prevalent in beverages [30]. Beverages may be especially problematic for weight management because of the energy they

provide [31] and how they may change dietary behavior [32]. Both early pancreatic exocrine and endocrine responses to oral stimulation with viscous or solid stimuli are greater than those to fluids [33]. Data from animal models indicate oral exposure to fluids reliably prompts a rapid insulin release [10, 11]. However, data from humans are mixed. It has been argued that stimulation of the CPIR requires more oral processing [16, 34]. In addition, the influence of the CPIR on appetitive indices has received limited research attention. Very preliminary data suggest it is a predictor of hunger [35, 36], but this is not observed consistently [6].

We attempt to address these gaps in the literature by examining the insulin response following exposure to nutritive and low calorie sweeteners in solid and beverage form in overweight and obese adults. In addition, the role of learning on the CPIR to nutritive and low-calorie sweetener exposure was tested. We hypothesized that 1) oral exposure to the beverage would elicit a lower CPIR compared to oral exposure to the solid food form; and 2) repeated exposure would decrease the CPIR to a low-calorie sweetener.

2. Subjects and methods

2.1 Participant eligibility

Sixty-four overweight or obese individuals (men and women) were recruited. Eligibility criteria included the following: age of 18–50 y, BMI of 24 kg/m^2 – 37 kg/m^2, body fat percentage > 25% for men and > 32% for women, not a restrained eater (dietary restraint score < 9 on the Three Factor Eating Questionnaire [37]), not a disordered eater (score < 20 on the Eating Attitudes Test-26 [38]), no purposeful use of foods or beverages that are sweetened with low calorie sweeteners > 3 times a week, no purposeful addition of low calorie sweeteners to foods and beverages >3 times a week, no Phenylketonuria, self-reported consumer of breakfast and lunch, willingness to consume test loads and food samples, palatability ratings ≥ “neither like nor dislike” for all test samples, not taking medications known to influence appetite, non-smoker >1 year, consistent diet and activity patterns, weight stable (≤ 5 kg change over the last 3 months) and have not donated blood for at least 3 months prior to participating in the study. All participants signed an informed consent form approved by the Purdue University Institutional Review Board and received monetary compensation.

2.2. Experimental design and procedures

2.2.1. Screening Visit—Potential participants meeting the eligibility criteria rated the sweetness and palatability of nutritive (sucrose) and low calorie (sucralose) sweetened beverages and solid (gelatin cubes) test loads. The energy and macronutrient composition of the beverage and gelatin cubes were matched. Participant ratings of sweetness and palatability were assessed with a General Labeled Magnitude Scale (GLMS) [39] and Labeled Affective Magnitude (LAM) scale [40], respectively. Only participants that gave a palatability rating of greater than “neither like or dislike” on the LAM scale were included in the study. After participants completed the questionnaires, a Registered Dietitian (RD) counselled participants to consume at least 100g of carbohydrate daily for 3 days prior to

their test visits to standardize carbohydrate metabolism. This amount is also the Institute of Medicine's recommended dietary reference intake (DRI) for carbohydrates [41].

2.2.2. Study Timetable—This study had 3 separate phases and a total of 20 visits (1 screening visit and 19 test visits). In Phase 1, participants reported to the laboratory once a week for 4 weeks. In Phase 2, participants reported to the laboratory daily for 14 consecutive days. In phase 3, participants reported to the laboratory once right after phase 2. The layout of the phase 1 and phase 3 visits is described in Figure 1.

2.2.3. Phase 1 Test Visit—Upon arrival on test days, participants' blood glucose concentration was measured by a glucometer (One Touch® Glucometer, LifeScan, Inc.) to confirm that participants were in a fasted state (8–10 hours fasting). Participants were then asked to answer a validated appetite questionnaire on a palm pilot [42–44]. The test session continued only if serum glucose was <110mg/dl and self-reported hunger was rated greater than "strong" on the gLMS scale. If all conditions were met, participants were placed in a semi-supine position and a catheter was placed in a vein in the antecubital space of one arm. A 9 ml blood sample was taken after catheter placement and another sample was collected 14 minutes after catheter placement. Serum insulin levels were higher by 0.9 mIU/l 14 minutes after catheter placement ($p<0.05$) possibly due to a stress response [45] experienced at the time of catheter placement and the environmental conditions. Hence, this sample was considered as the baseline sample to minimize variability in the insulin response for the remainder of the measurement session. Participants completed the appetite questionnaires right after baseline blood collection.

Immediately after participants completed their appetite questionnaire, sham feeding and serum insulin concentration measurements began. The participants were given a randomly assigned blinded test load comprised of a nutritive (sucrose) or low-calorie sweetener (sucralose) in beverage or solid form which was swished (if given liquids) or chewed (if given solids) for 15 seconds and then expectorated. The sham feeding occurred at 2-minute intervals for 14 minutes. A 2–3 ml blood sample was collected after oral exposure at 2, 6, 10 and 14 minutes for assessing insulin and glucose concentrations. At the end of the cephalic phase response measurements (16 minutes), participants completed another appetite questionnaire. Blood was collected and appetite questionnaires were completed again at 61, 91 and 121 minutes. Finally, a pre-weighed meal of macaroni and cheese (Easy Mac, Kraft Foods Inc., White Plains, NY) and 500 ml of water was presented. The meal was provided in excess of an amount likely to be consumed (2410 kcal) and the amount ingested was determined by covertly re-weighing the amount remaining. After eating, participants rated their appetite and were then allowed to leave the laboratory. This method was repeated with the remaining 3 of 4 experimental stimuli presented in a random order separated by a week.

2.2.4. Phase 2 (Training phase) Test Visit—During phase 2, participants underwent a 2-week training period to facilitate associative learning between the sensory and nutritive properties of test loads and their post-ingestive effects. The two week training period was selected based on earlier work on documented associative learning between sensory properties of food and their metabolic effects in 10 days [46]. Participants were randomly assigned to a blinded test load consisting of each food form and sweetener (nutritive solid

and beverage forms: 335 kcal; low-calorie solid and beverage forms: 33 kcal) an approximately equal number of participants trained for each food form and sweetener. Participants report to the test site daily to consume their assigned test load and could leave immediately afterwards.

2.2.5. Phase 3 Test Visit—During the week immediately after the end of Phase 2, participants were retested for their cephalic phase responses, conducted in the same manner as in Phase 1. Half of the participants received the same food form and sweetener that they were given during the training phase (learning group). The other half of the participants received the same food form, but different sweetener during the training phase (non-learning group).

2.3. Biochemical analyses

All blood samples were centrifuged and the serum was aliquotted and frozen at −80°C for analysis. Insulin was measured by an electrochemiluminescence immunoassay method using the Elecsys® 2010 Immunoassay System (Roche Diagnostic Systems, Indianapolis, IN, USA). Glucose was assessed by enzymatic colorimetry on the Cobas Integra 400 Analyzer (Roche Diagnostic Systems, Indianapolis, IN, USA).

2.4. Appetitive ratings

Hunger, fullness, desire to eat, prospective consumption were measured on visual analog scales with end anchors of “not at all” to “extremely”[42].

2.5. Study preloads

The four study preloads were comprised of:

1. Nutritive solid (NS): sucrose-sweetened (30.26% w/w) gelatin cubes (16.4 cc).
2. Low Calorie solid (LCS): sucralose-sweetened (0.066% w/w) gelatin cubes (16.4 cc).
3. Nutritive beverage (NB): sucrose-sweetened (8.8% w/w) beverage (59.2 mL).
4. Low Calorie beverage (LCB): sucralose-sweetened (0.013% w/w) beverage (59.2 mL).

2.6. Statistical analyses

1. To determine whether the proportion of responders was dependent on sweetener type and food form.

   Statistical tests: Non-parametric statistics on contingency tables i.e. Chi-square test for non-paired data and McNemar test for paired data.

2. To compare change in insulin and glucose responses and appetite ratings over time and effects of sweetener type and food form between phase 1 responders and non-responders.

Statistical test: A linear mixed model analysis on the change in insulin (Δ insulin) and glucose (Δ glucose) concentrations from baseline and appetite ratings with time, sweetener and food form as within-subject factors and responder group as a between-subject factor.

3. To determine the effects of sweetener type and food form on insulin area under the curve over the cephalic phase period in responders and non-responders.

   Statistical tests: A linear mixed model analysis on insulin positive incremental area under the curve (iAUC) over 2, 6 and 10 minutes with sweetener and food form as within-subject factors and responder group as a between-subject factor.

   3) To determine the effects of training on CPIR in participants categorized as responders in phase 1.

   Statistical test: a) RM-ANOVA conducted on the cephalic phase Δ insulin (0–10 minutes) and Δ glucose and appetite ratings with time (0, 2, 6 and 10 minutes) and training period (before and after) as within-subject factors and sweetener, food form and learning phase as between-subject factors.

   b) RM-ANOVA on positive incremental area under the curve (iAUC) for insulin with training period as a within-subject factor and sweetener, food form and training phase as between-subject factors.

Pearson statistics were used for determining associations between study outcomes. An alpha level of < 0.05 was set as the criterion for statistical significance. SAS (version 9.3, 2011, SAS Institute Inc) was used for computing insulin iAUCs. SPSS (version 22, 2013, SPSS Inc.) was used for all other statistical analyses. When significant differences were found pairwise comparisons were conducted with Bonferroni adjustments for multiple comparisons.

2.7. Participant characteristics and study flow

Sixty-four participants (23 males, 41 females; mean ± SD age: 27.2±8.6 years) with a mean (± SD) BMI of 31.2 ± 5.9 kg/m^2, body fat percentage of 35.2 ± 9.76 %, and dietary restraint score of 5.0 ± 3.9 completed the study. The flow of participant recruitment in the different phases of the study is described in Figure 2.

2.8. Assessment of responders

CPIR typically occurs between 2 and 8–10 minutes and peaks within the first 4 minutes [16, 21, 27, 47]. Hence, participants were classified as responders if they demonstrated a positive insulin response (rise of serum insulin above baseline) 2 minutes post-stimulus exposure. Responder classification was determined before training i.e. in phase 1. The characteristics of the responders to each treatment are shown in Table 1. When participants that were exposed to all sweetener and food form stimuli (*All* group) were considered, the proportion of responders did not depend on sweetener type or food form (Table 2). Among participants matched on the same food form and sweetener type during phase 1 and phase 3 i.e. *nutritive sweetener in solid and beverage form before and after training* (*N-N*) and *low-calorie sweetener in solid and beverage form before and after training (LC-LC*) group, the

proportion of responders to low calorie sweetener (sucralose) exposure was significantly greater when the stimulus was in the solid form compared to the beverage form (P<0.05) (Table 2). The proportion of responders to nutritive sweetener (sucrose) exposure did not differ significantly between the solid and beverage forms (Table 1). Among participants that were matched on the same food form but different sweeteners in phase 1 and phase 3 i.e. *nutritive sweetener (in solid and beverage form) before training and low-calorie sweetener in the same forms after training* (*N-LC*) and *low calorie sweetener in solid and beverage form before training and nutritive sweetener in the same forms after training* (*LC-N*) group, the proportion of responders did not depend on sweetener type or food form (Table 2).

3. Results

3.1. Insulin, glucose and appetitive responses

3.1.1. Participants before training—Responders in each of the nutritive solid, low-calorie solid, nutritive beverage and low-calorie beverage treatments demonstrated a statistically significant positive Δ insulin (i.e. increase in insulin concentration from baseline) 2 minutes after stimulus exposure (P<0.05) and a statistically significant decrease in the cephalic time period after (P<0.05) depicting a CPIR (Figure 3) whereas non-responders did not demonstrate a CPIR (Figure 3).

Responders had greater insulin iAUC over 2, 6 and 10 minutes after exposure to solid stimuli compared to beverage stimuli (P<0.05) (Table 3). In addition, responders also had greater insulin iAUC over 2 minutes after exposure to nutritive sweetener compared to non-nutritive sweetener (Table 3).

There was a significant time effect for Δ glucose (P<0.05) but values did not change over the cephalic phase (Figure 4). In addition, responders had higher Δ glucose after low-calorie sweetener exposure compared to non-responders (P<0.05).

Hunger, desire to eat and prospective consumption ratings increased after the cephalic phase period and decreased after lunch intake while fullness ratings decreased after the cephalic phase period, and increased after lunch intake for both responders and non-responders (Figure 5). Oral exposure to nutritive sweetener led to higher hunger, desire to eat and prospective consumption ratings than exposure to low-calorie sweetener for both responders and non-responders (P<0.05). Prospective consumption ratings were higher for responders than for non-responders (P<0.05). There was no effect of food form on appetite ratings over time. Appetite ratings after the cephalic phase period did not consistently correlate with insulin iAUC over 6, 10 and 14 minutes (data not shown). Energy intake of the lunch was higher when responders were exposed to the nutritive beverage compared to the low-calorie beverage (Mean difference: 122.2±28.5 (SE) kcal, P<0.05).

3.1.2. N-N and LC-LC participants—Responders in this group (Table 2) demonstrated a significant CPIR before training (P<0.05) (Figure 6). However, there was no CPIR after training in responders (Figure 6). In addition, there was no effect of learning on Δ insulin after training. Glucose and appetitive responses and energy intake for responders did not change after training (not shown).

3.1.3. N-LC and LC-N participants—Responders in this group (Table 2) demonstrated a trend for CPIR before training which was minimized after training (Training period, $P<0.05$ and Training Period*Time, P-value = 0.08). (Figure 7). There was no effect of learning on Δ insulin after training. Glucose and appetitive responses and energy intake for responders did not change after training (not shown).

4. Discussion

The most notable finding of the study was the identification of a possible CPIR after oral stimulation with the low-calorie sweetener, sucralose. If confirmed in further testing, it would join a limited number of other sweeteners reported to elicit a biphasic (acesulfame-K [24, 48]) or cephalic phase (saccharin [21]) insulin response. Saccharin prompts a rapid rise of insulin in rodents [49] and humans [21]. At this point, the evidence for a biphasic insulin response to acesulfame-K derives from an in vitro system with pancreatic islet cells [24]. Glucose or sucrose are nutritive sweeteners documented to promote a cephalic phase insulin response in rodents [50] and humans [23, 51].

While the ability of a number of sweeteners to elicit a CPIR has not been tested, it is intriguing that all those with a positive effect bind to the amino terminal domain of the T1R3 component of the T1R2-T1R3 heteromeric sweet taste receptor [52–56]. Whether this binding site holds special importance for the CPIR awaits further study. Aspartame is one low calorie sweetener that has not been associated with a CPIR or biphasic response in humans [51] and it binds to the amino acid terminal domain (ATD) of the T1R2 component of the sweet receptor [54, 57]. Activation of sweet receptors on pancreatic beta cells by different sweeteners elicits considerable intracellular signaling specificity [58–60] consistent with potential differential downstream effects between low-calorie sweeteners. It has also been proposed that the insulinotropic action of low calorie sweeteners for rodents is the bitter taste note associated with the effective stimuli but the mechanism in humans is not well understood [48].

We cannot characterize the sucralose effect on the CPIR as robust based on our observations in this trial. It was observed in only a subset of study participants (i.e. responders) and was not reliably reproduced. Others have failed to document a CPIR to sucralose, though they tested only 8 individuals with a 0.083% w/v liquid stimulus [22]. We noted a greater proportion of responders and greater insulin response when the sucralose was present in a solid food form. It has been suggested that beverages are not effective stimuli for a CPIR [16] and that mastication is required to elicit a CPIR [16, 18]. However, a CPIR has been noted with cognitive, visual and/or olfactory stimuli [17, 25, 61, 62] as well as to beverages [21] even in a dose response manner [63]; indicating oral mechanical processing may augment a response, but it is not necessary. The higher reliability of the CPIR to exposure to energy-yielding foods [13] raises the question of whether activation of an alternative sweetener system (e.g., homomeric T1R3 [64] receptor) tuned to nutritive carbohydrate stimuli may be sufficient to drive or augment the CPIR.

Though there are reports of a reliable CPIR [13], it is notoriously difficult to measure. The apparent fragility of the CPIR may reflect shortcomings in the methodologies used to

measure it, such as limited sample sizes, poor control of conditioned insulin secretion patterns, variable stimulus palatability, different levels of prior food deprivation and multiple food forms. In addition, selected traits of study participants including adiposity, cognitive restraint, gender and psychological responses to foods affects detection of the CPIR as reviewed previously [65]. The present study tested a larger number of individuals providing greater statistical power, standardized food forms of the test loads and controlled for many participant characteristics to minimize variability in insulin responses. However, a limitation of the present study was the lack of non-sweet and non-taste controls. Without such controls, it is not possible to definitively isolate an effect of the sweetener. The study was conducted exclusively in individuals with overweight or obesity who were neither restrained eaters nor disordered eaters, but may have been insulin resistant. Positive stimulus palatability ratings were an eligibility criterion. Participants also consumed at least 100g of carbohydrate three days prior to testing to standardize carbohydrate metabolism and fasted for 8–10 hours before the visit. Many others have failed to document a response to a variety of sweeteners [16, 19, 23, 66] as well as whole foods [67] or observed it only in subsets of individuals [25, 61, 68, 69] consistent with the present study. However, this variability should not diminish consideration of the likely implications of the CPIR. Elimination of the response leads to higher and more prolonged excursions of blood sugar post-prandially [14, 70–72] and it is notable that this signal is lost in patients with impaired glucose tolerance or pre-diabetes [73–75]. Another limitation of the present study was that participants were not screened for glucose intolerance.

Some have reported that sucralose consumption augments insulin secretion in response to an oral glucose tolerance test [76], but this has not been replicated by others [77]. Further, one trial noted an incretin response to a cola beverage containing sucralose and acesulfame-potassium, but not sucralose alone in water [78]. This suggests an action of other components in the cola or a learned association between cola consumption and carbohydrate challenge. One report noted sucralose enhanced GLP-1 release to a mashed potato meal and lowered the glycemic response in healthy adults, though insulin concentrations were unaffected [81]. Another report observed no effect of sucralose on GLP-1 or GIP concentrations nor an effect on gastric emptying [77]. In another study, exposure of healthy adults with high and low adiposity to aspartame, stevia and sucrose sweetened preloads prior to a fixed meal led to lower postprandial insulin concentrations with stevia compared to aspartame or sucrose while aspartame did not elicit a different response from sucrose [82]. Thus, evidence indicates that among the low-calorie sweeteners tested to-date, some may help to moderate post-prandial glycemia [83, 84], and none have been shown to exacerbate the response relative to nutritive preloads [85, 86]. Activation of sweet taste receptors on beta cells of the pancreas by low-calorie sweeteners (or fructose) in the presence of adequate plasma glucose concentrations may enhance insulin secretion [59, 87], but this is not relevant to the CPIR which can occur within 1–2 minutes of oral exposure to an effective sweetener [47].

Insulin, ghrelin and GLP-1 secretion are modulated by diet/lifestyle such that they rise in anticipation of regular eating events [88–91]. This suggests that, to some degree, they are conditioned responses [92], presumably to aid food digestion and the absorption and metabolism of the anticipated energy and nutrients they contain. Further, the CPIR for

insulin precedes changes of blood glucose [93] and is inhibited by cholinergic blockade [25, 47] indicating it is driven by neural rather than metabolic cues. Still it may be a primary or secondary response [47]. With respect to the latter, GLP-1 is released in small quantities directly from sweet taste receptors following activation by sweet compounds [94] and this may enhance insulin secretion via an incretin effect. A primary response may occur through parasympathetic activation [25, 47]. One recent study noted that sweet taste intensity ratings were inversely related to chronic oral sweetness exposure [95]. Interestingly, rating changes were greater for the semi-solid food than the beverage. Whether this has implications for GLP-1 release from taste receptor cells is not known. In that trial, the intervention entailed modulating sugar intake between groups. There was no treatment with a low-calorie sweetener which would have allowed isolation of sweetness versus sugar (energy) effects. This is an important question with respect to the CPIR as it has been speculated that chronic sweetness exposure in the absence of a metabolic challenge, as would be the case with low-calorie sweetener use, could lead to extinction of the CPIR. This has been tested in rodents where no evidence of extinction was noted after 10 trials with saccharin stimulation [27]. In humans, ingestion of beverages with sucralose, sucralose plus acesulfame-K or sucrose 10 times revealed no evidence that it altered their reward values [96]. The present study sought to further evaluate this question and failed to note a differential response to repeated exposure to a low calorie versus a nutritive sweetener. However, even the nutritive sweetener did not lead to a reliable response, thus precluding a clear test of the concept.

Some researchers hypothesize that the absence of cephalic phase responses may increase the risk of obesity by removing a regulatory feeding signal [97]. Others posit that exposure to food [36] or sweet items [98] can elicit cephalic phase responses, which can serve as an impetus for increased intake. However, the CPIR to both nutritive and low-calorie sweeteners did not influence subjective feelings of appetite or energy intake at the next meal in this trial despite differences in energy content. Similar findings have been reported by others [82, 99]. In addition, consumption of low calorie sweeteners for 2 weeks did not increase energy intake at an ad libitum meal, in part, supporting findings from a meta-analysis that observed no change in energy intake/day after repeated low-calorie sweetener consumption [100].

In conclusion, this study demonstrates a weak, but statistically significant CPIR following oral sucralose stimulation in a subset of individuals who were overweight or obese that was not different from the CPIR elicited by nutritive sweetener (sucrose) stimulation. In addition, the solid food form elicited a larger CPIR than the beverage form for both sweeteners. Additional studies are needed to elucidate these effects with the inclusion of non-sweet and non-taste i.e. cognitive, visual and/or olfactory stimuli.

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Highlights

- Sucralose exposure elicited cephalic phase insulin response (CPIR) in responders.
- Both sucrose and sucralose elicited the same magnitude of CPIR in responders.
- The solid food form elicited a greater CPIR compared to the beverage form.

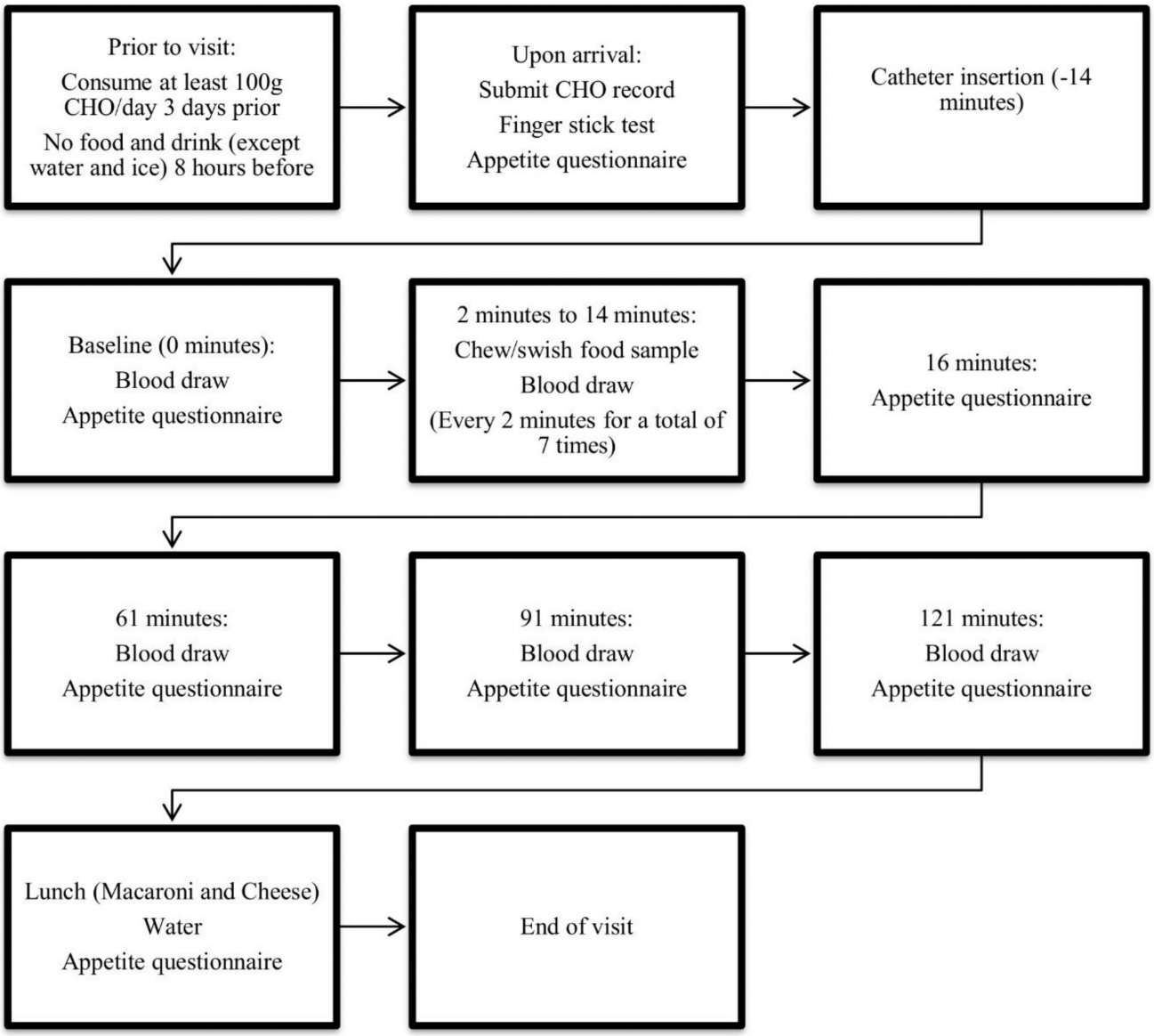

Figure 1. Layout of Phase 1 and Phase 3 visits

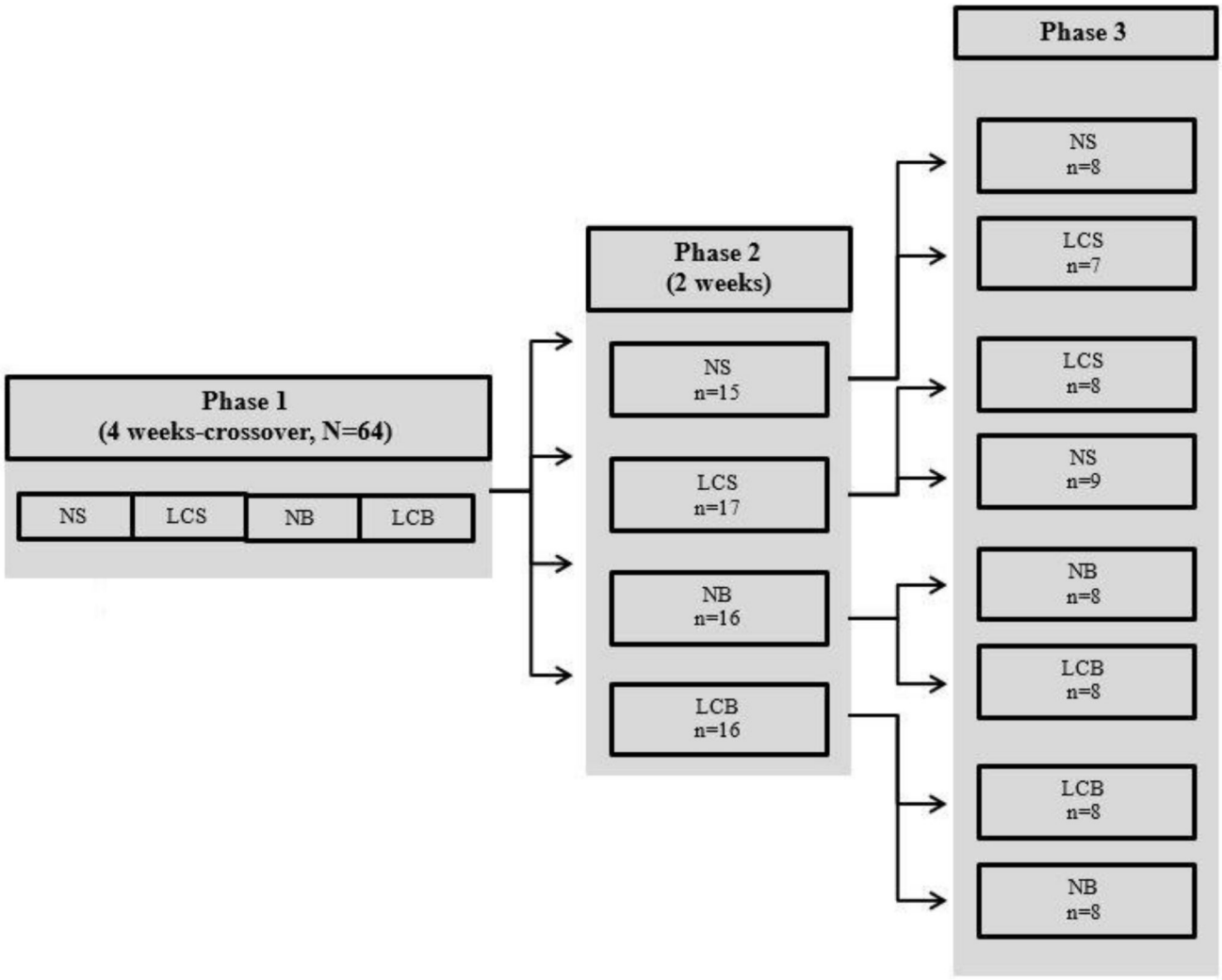

Figure 2. Flow of participants through the study phases

NS, Nutritive solid; LCS, Low-calorie solid; NB, Nutritive beverage; LCB, Low-calorie beverage

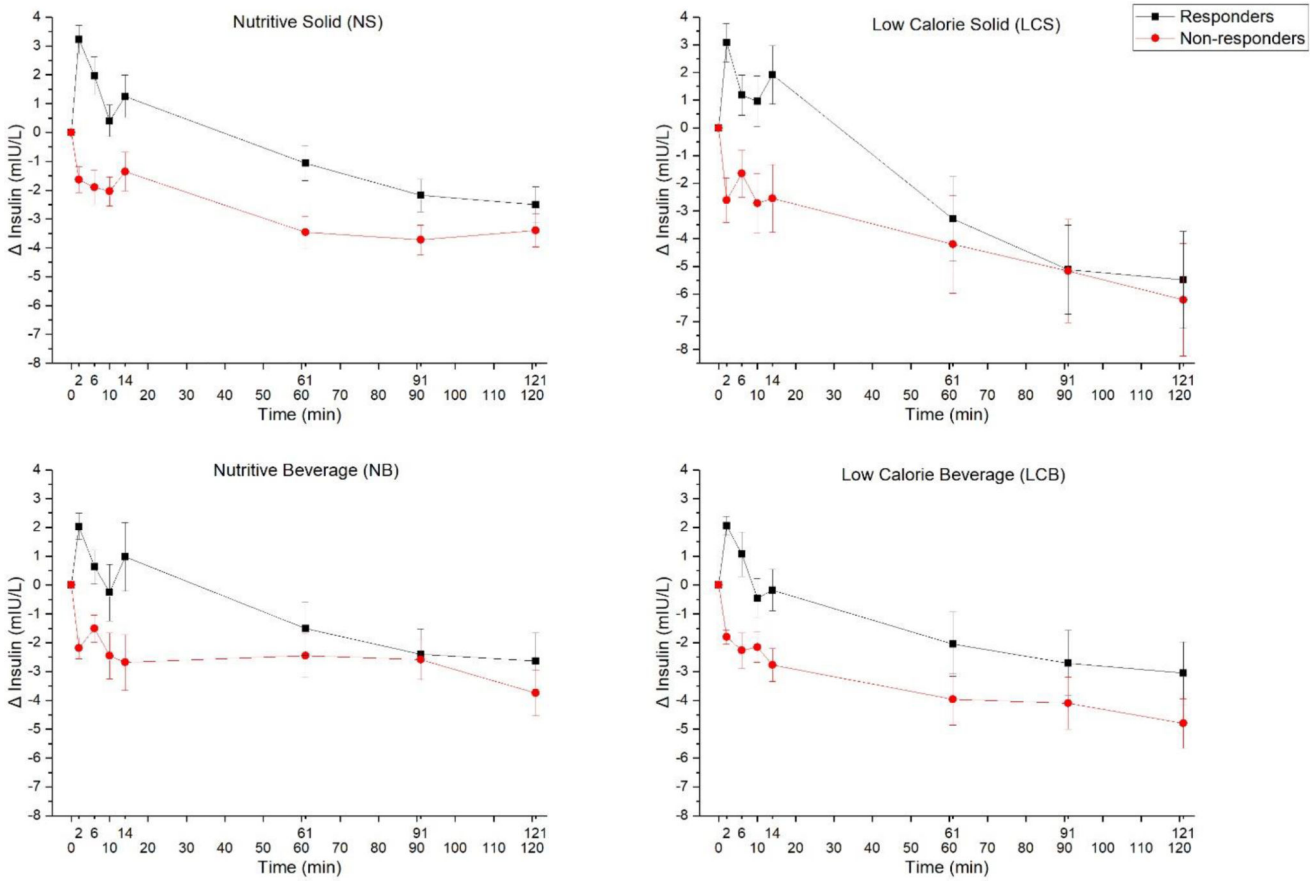

Figure 3. Insulin response over time in responders and non-res ponders in all treatments before training

Values are Mean±SE

Δ, change in insulin concentration from baseline i.e. 0 min; Responders*Time, P<0.05

Responders: 2, 61, 91, 121 min vs baseline, P<0.05; 6–121 min vs 2 min, P<0.05; 61, 91, 121 min vs 6 min, P<0.05; 61, 91, 121 min vs 10 min, P<0.05

Non-responders: 2–121 min vs baseline, P<0.05; 91, 121 min vs 2 min, P<0.05; 61, 91, 121 min vs 6 min, P<0.05; 91, 121 min vs 10 min, P<0.05

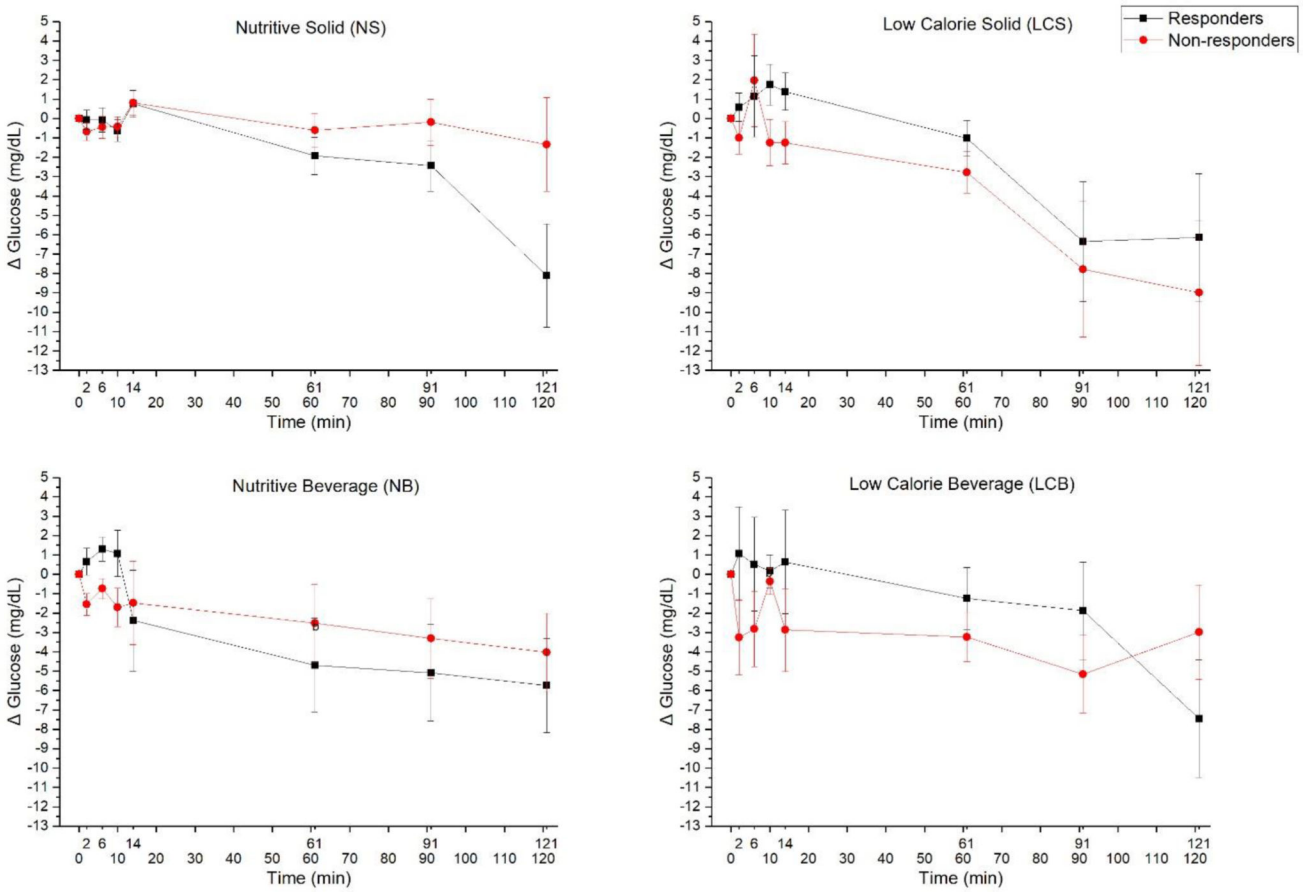

Figure 4. Glucose response over time in responders and non-responders in all treatments before training

Values are Mean±SE

Δ, change in glucose concentration from baseline i.e. 0 min; Time, P<0.05: 91 min vs baseline, 2 min, 6 min and 10 min, P<0.05 and 121 min vs baseline, 2 min, 6 min and 10 min, P<0.05; Responder*Sweetener, P<0.05

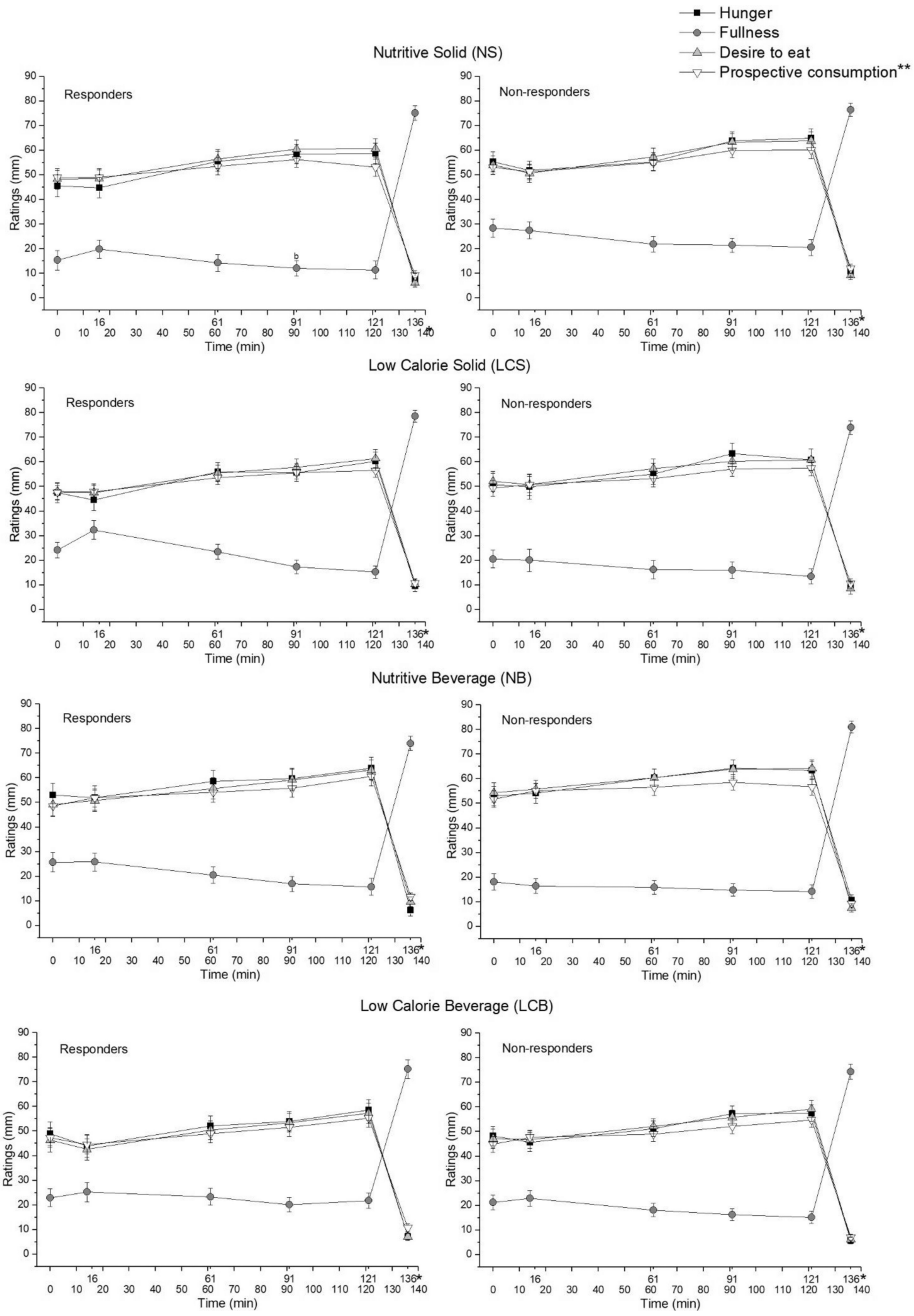

Figure 5. Mean appetite ratings for responders and non-res ponders before training in each treatment group

Values are Mean±SE

*After lunch vs. all other time points, P<0.05; **Responders vs. Non-responders

Hunger, desire to eat and prospective consumption ratings: Time, P<0.05, Sweetener, P<0.05;

Fullness: Time, P<0.05

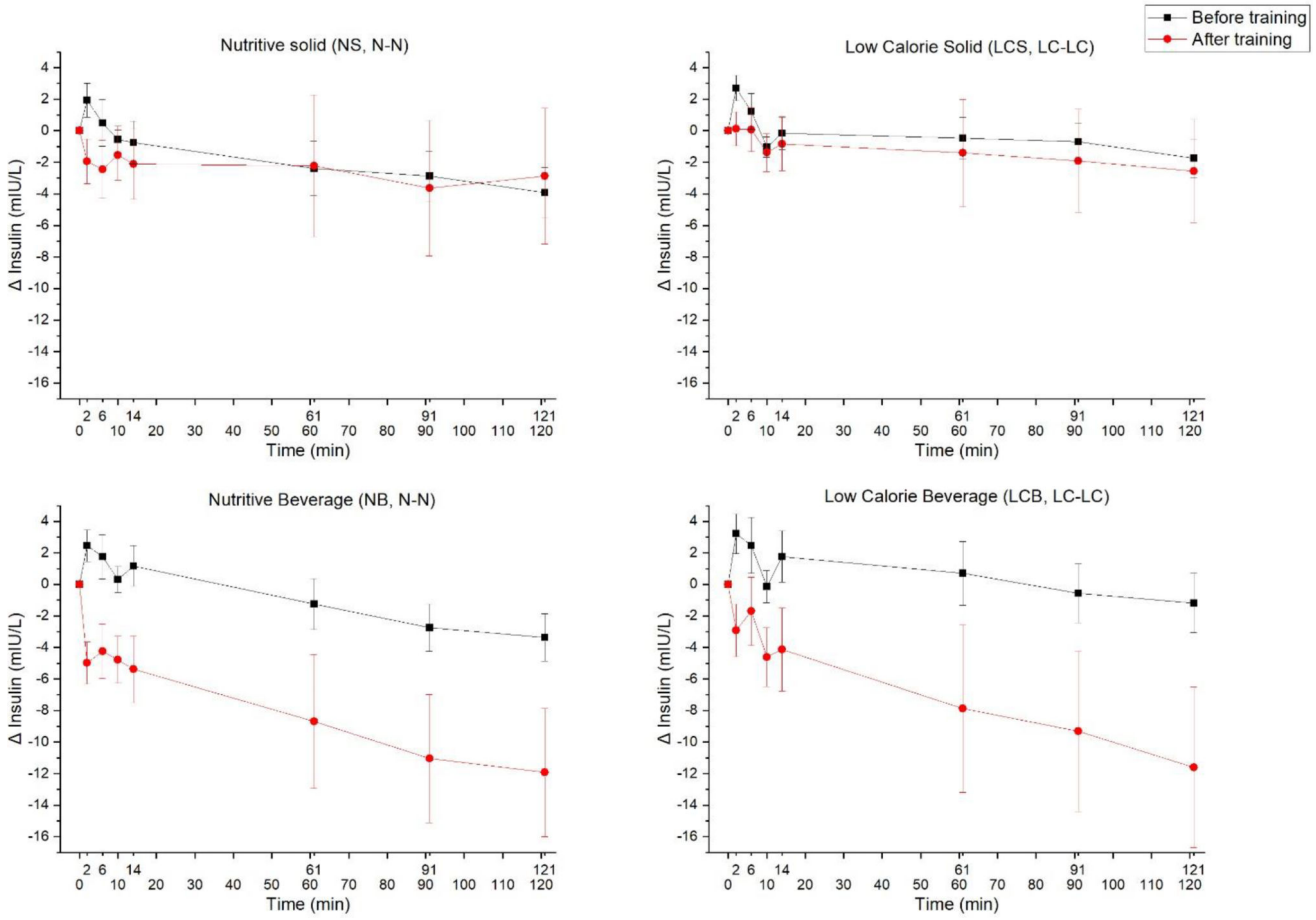

Figure 6. Insulin response over time in responders matched on same food form and sweetener before and after training

Values are Mean±SE

Δ, change in insulin concentration from baseline i.e. 0 min; Training Period*Time, P<0.05

Before training: 2 min vs baseline, P<0.05; 10 min vs 2 min, P<0.05; 10 min vs 6 min, P<0.05 After training: 2, 10 min vs baseline, P<0.05

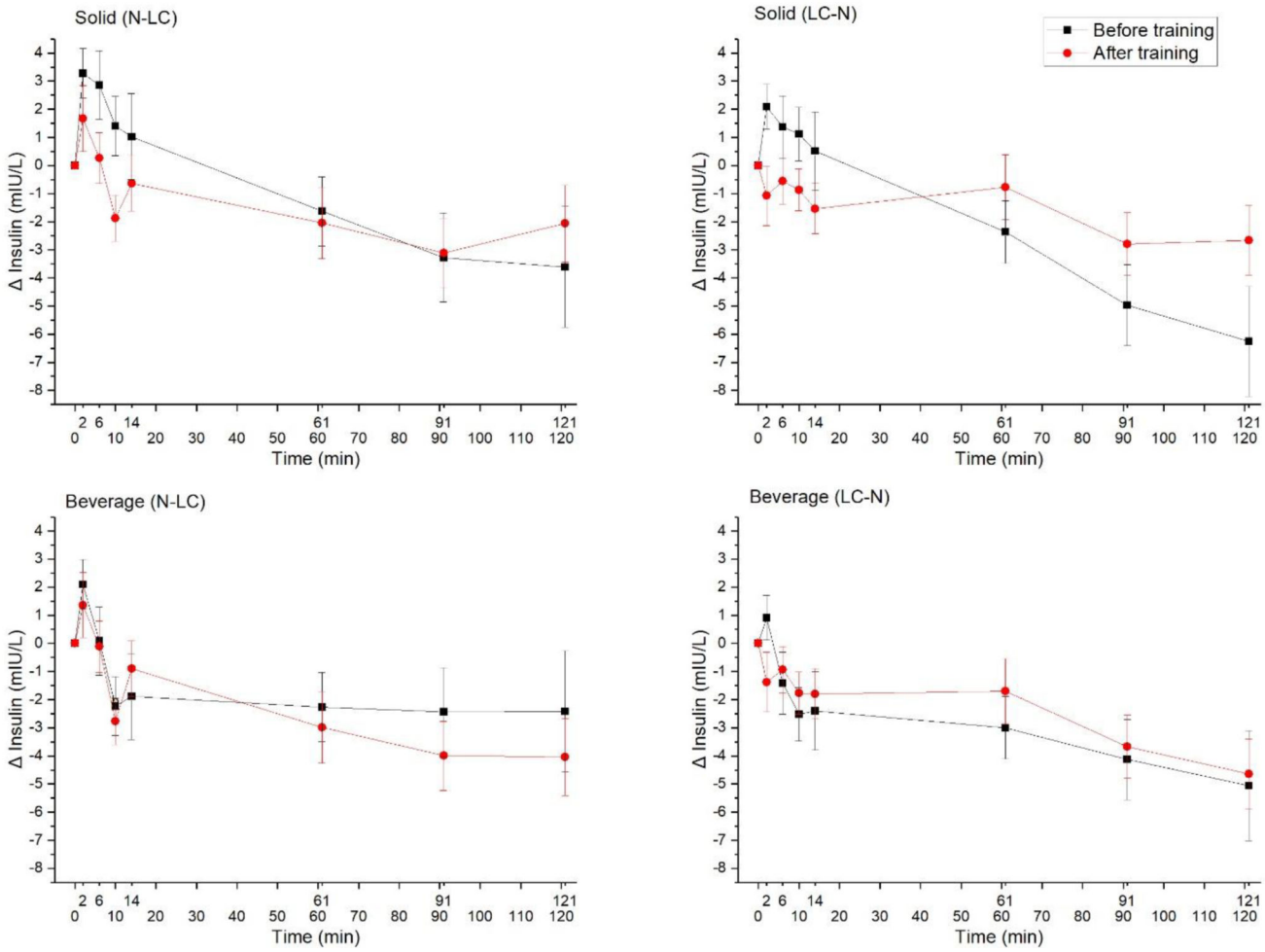

Figure 7. Insulin response over time in responders matched on same food form but different sweetener before and after training

Values are Mean±SE

Δ, change in insulin concentration from baseline i.e. 0 min; Training Period, $P<0.05$; Time, $P<0.05$, Training Period*Time, $P=0.08$

Table 1

Characteristics of responders and non-responders in each treatment group

Characteristics	Nutritive solid (n=64)		Low-calorie solid (n=64)		Nutritive beverage (n=64)		Low-calorie beverage (n=64)	
	Responders (n=29)	Non-responders (n=35)	Responders (n=36)	Non-responders (n=28)	Responders (n=26)	Non-responders (n=38)	Responders (n=25)	Non-responders (n=39)
Sex	8 M, 21 F	15 M, 20 F	12 M, 24 F	11 M, 17 F	9 M, 17 F	14 M, 24 F	8 M, 17 F	15 M, 24 F
Age (years)*	27.2±9.4	27.2±8.0	28.1±8.7	26.1±8.6	25.2±6.1	28.6±9.8	25.1±6.6	28.6±9.5
BMI (kg/m2)	31.5±6.5	31.0±5.5	32±6.5	30.2±4.9	31.2±4.9	31.3±6.6	30.2±4.3	31.8±6.7
Fat mass (%)	36.1±9.7	34.4±9.9	36.3±10.5	33.8±8.6	36.1±8.4	34.5±10.7	34.9±8.5	35.3±10.6
Fasting glucose (mg/dl)	98.4±14.1	94.2±7.0	96.1±9.8	97.5±10.8	94±8.3	96.2±8.8	94.2±12.6	96.6±10
Fasting Insulin (mIU/l)	16.8±11.1	15.3±8.1	14±7.5	17.2±8.2	15±8.1	15.9±8.6	15±8.2	16.6±10.3
HOMA-IR	4.4±3.9	3.6±1.9	4.2±5.4	4.7±3.5	3.5±2.1	3.9±2.4	3.6±2.4	4.1±2.9

*All such values are Mean±SD

Table 2

Distribution of responders according to treatment group before training.

	Treatment			
Participant groups	**Nutritive solid**	**Low-calorie solid**	**Nutritive beverage**	**Low-calorie beverage**
All	n=64 (29) *	n=64 (36)	n=64 (26)	n=64 (25)
N-N and LC-LC (Matched on same food form and sweetener in phase 1 and 3)	n=17 (7)	n=15 (12 **)	n=16 (7)	n=16 (4)
N-LC and LC-N (Matched on same food form but different sweetener in phase 1 and 3)	n=15 (6)	n=17 (9)	n=16 (7)	n=16 (8)

N-N, Nutritive sweetener before training and after training; LC-LC, Low-calorie sweetener before training and after training N-LC, Nutritive sweetener before training and low-calorie sweetener after training; LC-N, Low-calorie sweetener before training and nutritive sweetener after training

*
No. of responders in brackets

**
p-value <0.05 compared to low-calorie beverage

Table 3

Insulin positive iAUC for responders and non-responders over the cephalic time period before training.

Treatment	Insulin positive iAUC responders		
	2 minutes	6 minutes	10 minutes
Nutritive solid	3.2±0.2 *	13.9±1.0	20.6±1.9
Low-calorie solid	3.0±0.2	12.3±1.0	19.2±1.7
Nutritive beverage	2.2±0.2	7.8±1.0	9.4±1.8
Low-calorie beverage	1.8±0.2	8.5±1.1	14.1±2.0
	Insulin positive iAUC non-responders		
Nutritive solid	0±0	0.1±1.0	1.2±1.8
Low-calorie solid	0±0	1.3±1.0	3.6±1.7
Nutritive beverage	0±0	1.0±0.9	4.1±1.7
Low-calorie beverage	0±0	1.1±1.0	2.1±1.8
	Tests of fixed effects		
Responder Group	P<0.05	P<0.05	P<0.05
Responder Group*Food Form	P<0.05	P<0.05	P<0.05
Responder Group*Sweetener	P<0.05	p=0.26	p=0.36
Responder Group*Food Form*Sweetener	p=0.45	p=0.06	P<0.05

* All such values are Mean±SE. Insulin iAUC units are in mlU/l × 2, 6 or 10 minutes