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Research report

Cephalic phase insulin release in healthy humans after taste stimulation?

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ABSTRACT

In humans little is known as to whether taste solutions applied to the tongue elicit cephalic phase insulin release (CPIR). The aim of this study was to re-examine if any effect of different taste solutions on CPIR occurs. Under fasting conditions healthy human subjects sipped, and washed out their mouths with eight taste solutions (sucrose, saccharin, acetic acid, sodium chloride, quinine hydrochloride, distilled water, starch, and sodium glutamate) for 45 s and spat them out again. The taste stimuli were not swallowed; they were applied in a randomized order, each on a separate day. Blood collection for determination of plasma glucose and plasma insulin concentrations was performed 3 min before and 3, 5, 7 and 10 min after taste stimulation. Ratings of quality, intensity and hedonic characteristics were also obtained. A significant increase of plasma insulin concentration was apparent after stimulation with sucrose and saccharin. In conclusion, the current data suggest that the sweeteners sucrose and saccharin activate a CPIR even when applied to the oral cavity only.

Introduction

In human subjects, as well as in animals (Naim, Kare, & Merrie, 1978), taste stimuli can elicit insulin secretion by the beta cells of the pancreas (Bellisle, Louis-Sylvestre, Demozay, Blazy, & Le Magnen, 1983; Berthoud, Trimble, Siegel, Bereiter, & Jeanrenaud, 1980). The early increase of insulin secretion following gustatory stimulation (within 4 min) is of cephalic origin. The specific characteristic of this phenomenon (CPIR, cephalic phase insulin release) is the plasma insulin increase prior to the rise of blood glucose. Typically, plasma insulin concentrations increase within 2 min after oral stimulation, reach their maximum at 4 min and return to baseline within 10 min (Teff & Engelman, 1996; Teff, Mattes, & Engelman, 1991; Teff, Mattes, Engelman, & Mattern, 1993). It could be shown that the meal composition has no effect on the type of the early insulin response although three different types of responses have been observed: high and moderate increase or decrease of plasma insulin (Bellisle et al., 1983). Negative responses have been interpreted as the descending phase of spontaneous oscillations of insulinemia. This effect has been described in both animals and humans.

Recent experiments in animals showed that the nutritive sweetener sucrose and the non-nutritive sweetener saccharin elicited CPIR in rats, while the remaining taste modalities "sour", "salty", "bitter," and "umami" and starch failed to produce such an effect (Tonosaki, Hori, & Shimizu, 2007). It could also be shown that after chorda tympani transection CPIR was not observed after sucrose stimulation.

The question arises whether CPIR can be elicited in healthy humans by application of taste solutions, especially by sweetness. Only a few studies in humans indicate a correlation between application of taste solution and CPIR (Bruce, Storlein, Fuller, & Chisholm, 1987; Hartel, Graumbaum, & Schneider, 1993; Yamazaki & Sakaguchi, 1986). One study compared the effect of different stimuli (sucrose, saccharin, water, aspartame, and apple pie) on plasma insulin and blood glucose within the same individuals using the "sip and spit" procedure (no swallowing) without visual and olfactory stimuli (Teff, Devine, & Engelman, 1995). All stimuli except for apple pie did not provide sufficient stimulation for CPIR. Similar results were presented by Abdallah, Chabert, & Louis-Sylvestre (1997). They investigated the effect of oral sensation of nutritive and non-nutritive sweetened tablets in humans after consumption of a carbohydrate-free breakfast. The study revealed that 5-min suction of sucrose, aspartame-polydextrose or unsweetened polydextrose tablets did not induce CPIR.

The specific aim of this study was to re-examine whether sucrose, saccharin, acetic acid, sodium chloride, quinine hydrochloride, starch, and sodium glutamate can elicit CPIR in healthy humans under fasting condition.

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Materials and methods

Subjects

In a pilot study eight taste solutions were applied to five healthy subjects (3 women and 2 men, mean age 29 years ±7.6 years; age range 22–37 years). In order to differentiate plasma insulin oscillations from CPIR, blood was sampled with no oral stimulus.

For the specific investigation of the effects of administration of sucrose and saccharin a total of 20 subjects (9 women and 11 men, mean age 26 ± 5.4 years; age range 22–37 years) with mean body mass indices (BMI) of 23.3 ± 23 kg/m^2 ranging from 18 to 26.8 kg/m^2) were included. All subjects exhibited normal taste function as assessed with the "taste strips" test kit (Mueller et al., 2003).

Subjects were informed about aims of the study and provided their written consent. The study was conducted in strict compliance with the revised version of the Helsinki Declaration. The Ethics Committee of the General Medical Council of Mecklenburg Western Pomerania approved the design of the study.

Inclusion criteria for participation in the investigation were good health, age between 18 and 40 years, and normal self-rated gustatory function. *Exclusion criteria* were intake of drugs/diseases known to significantly diminish taste ability (Griffin, 1992; Schiffman & Zervakis, 2002), middle ear surgery, acute oral infections and smoking.

Taste solution

Taste solutions were sucrose (1.0 M, sweet), acetic acid (0.1 M, sour), sodium chloride (0.5 M, salty), quinine hydrochloride (0.01 M, bitter), saccharin (0.01 M), starch (5%), sodium glutamate (0.2 M), and distilled water as control. The solutions were prepared by dissolving the used substances in distilled water.

Normal gustatory (including both, tests with the "taste strips" (Mueller et al., 2003) and electrogustometry (Just, Pau, Steiner, & Hummel, 2007)) and normal intra-oral trigeminal function were ascertained at a separate occasion before the experiments proper.

Taste strips

Testing gustatory function was performed on a separate occasion in addition to the trigeminal tests. Aim was to ascertain normal taste function. The interval between the gustatory and trigeminal tests ranged from 2 to 8 days. A whole mouth approach was applied using impregnated taste strips. The area of taste strips impregnated with taste solutions was 2 cm^2, and the length of the strip was 8 cm, which compares to the capsaicin-impregnated strips (see below). Four concentrations were used for each quality (sweet: sucrose; sour: citric acid; salty: sodium chloride; bitter: quinine hydrochloride). The taste strips were presented in a randomized order starting with the lowest concentration. Before administration of each strip subjects rinsed their mouth with water. For whole mouth testing, the taste strip was placed in the midline of the tip region. With the strip still in their closed mouth, subjects had to pick one of four possible taste descriptors ("sweet," "sour," "salty," "bitter"). The total score was the sum of correctly identified tastes ranging from 0 to 16 for the whole mouth procedure.

Electrogustometry – EGM

EGM provides quantitative data related to gustatory function although this is discussed controversially (Murphy, Quinonez, & Nordin, 1995; Stillman, Morton, Hay, Ahmad, & Goldsmith, 2003). EGM is a reliable method to measure the electrical taste detection threshold.

The electric stimulus was applied with a bi-polar electrode (round surface of 0.79 cm^2) using an electrogustometer (Halle II; Haberland, Halle, Germany). The electrode was placed on two anterior regions of the tongue (tongue tip, and edge), separately for the left and right sides. Stimuli were applied in increasing strengths (2 dB steps). Stimuli of 0.5 s duration were applied unilaterally, starting at −6 dB (1.5 μA) up to 40 dB, until the subject indicated that the applied stimulus had been perceived. If the subject did not perceive the 40 dB stimulus, a 1 mA (50 dB) stimulus was applied. If no sensation was perceived, the highest possible value (50 dB) was entered into the analysis. The stimulation frequency was 2 Hz. The mean value of two consecutive measurements was used as an estimate of EGM thresholds.

Samples and measurements

Subjects fasted for 12 h overnight (no food, only water). After the fasting period, measurements started at 6 a.m. on each day. At that time an intravenous dwelling canula was inserted in a cubital vein.

For adequate baseline sampling, blood from five subjects of the pilot study was sampled for a 12 min-period (seven samples) and no oral stimulus on a separate day.

The taste-related measurement started with a first blood collection (plasma glucose and plasma insulin) prior to taste stimulation. Subjects sipped 10 mL of the taste solution. They then swished the liquid in their closed mouths for 45 s before spitting it out again. The taste solutions were given in a randomized order, each solution was presented on a separate day. Blood sampling for determination of plasma glucose and plasma insulin concentrations was done 3 min before and 3, 5, 7, and 10 min after taste stimulation, respectively.

Blood glucose levels (mmol/L) were determined by glucose oxidase method (GLUCm, Beckman Coulter Ireland Inc., Galway, Ireland). Plasma insulin concentrations (μIU/mL) were assayed using an ECLIA (Electrochemiluminescence ImmunoAssay) Kit (Roche Diagnostics GmbH, Mannheim, Germany).

Characterization of sensations

Subjects characterized the sensation of the taste solution applied by selecting one of the five "gustatory" descriptors ("sweet", "sour", "salty", "bitter", "umami", and "no taste").

Intensity ratings

Intensity ratings were assessed after 45 s of stimulation. For all investigations a numerical scale (10-item scale) ranging from 1 (very weak) to 10 (very strong) was used. Instructions for the test procedures were given prior to investigations ("please indicate when a sensation is present, assess the intensity after 10 s. and indicate the duration of the sensation").

Hedonic ratings

A one-dimensional bi-polar hedonic scale with a numeric grading from −4 (extremely unpleasant) through 0 (neither pleasant nor unpleasant) to +4 (extremely pleasant) was used to assess the hedonic tone of the presented taste stimuli.

Table 1
Blood glucose and plasma insulin concentrations (means, S.D.) in healthy humans ($n = 5$ and 20) for eight different taste substances

		before	3 min	5 min	7 min	10 min	n
Sucrose (sweet)	Glucose (mmol/L)	4.9 ± 0.3	4.9 ± 0.3	4.9 ± 0.3	4.95 ± 0.3	4.95 ± 0.3	20
	Insulin (μIU/mL)	7.9 ± 3.3	8.3 ± 2.7	9.4 ± 3.6	8.9 ± 0.3	8.1 ± 3.2	20
Starch	Glucose	4.8 ± 0.3	4.9 ± 0.4	4.9 ± 0.5	4.9 ± 0.5	4.9 ± 0.6	5
	Insulin	8.5 ± 3.3	9.3 ± 5.4	11 ± 5.9	10.6 ± 5.7	9.6 ± 5.7	5
QHCL (bitter)	Glucose	4.8 ± 0.3	4.8 ± 0.3	4.8 ± 0.3	4.8 ± 0.3	4.8 ± 0.2	5
	Insulin	8.0 ± 3.3	6.7 ± 1.8	9.6 ± 4.0	9.1 ± 3.7	9.1 ± 4.3	5
Citric acid (sour)	Glucose	5.1 ± 0.3	5.0 ± 0.2	5.0 ± 0.3	5.0 ± 0.3	5.0 ± 0.3	5
	Insulin	11.0 ± 3.9	8.4 ± 2.9	9.9 ± 4.0	10.0 ± 3.7	9.2 ± 3.0	5
Distilled water	Glucose	4.8 ± 0.2	4.8 ± 0.3	4.8 ± 0.2	4.8 ± 0.2	4.7 ± 0.2	5
	Insulin	8.8 ± 2.9	9.5 ± 4.6	10.4 ± 4.6	10.0 ± 3.3	7.5 ± 1.9	5
MSG (umami)	Glucose	4.9 ± 0.2	4.9 ± 0.3	4.9 ± 0.3	5.0 ± 0.3	5.0 ± 0.3	5
	Insulin	8.9 ± 2.7	7.2 ± 2.8	8.5 ± 3.5	9.3 ± 3.7	9.3 ± 3.0	5
NaCl (salty)	Glucose	4.9 ± 0.1	4.8 ± 0.2	4.8 ± 0.2	4.8 ± 0.2	4.9 ± 0.3	5
	Insulin	5.5 ± 3.3	5.3 ± 3.2	5.6 ± 3.6	5.8 ± 3.0	6.1 ± 2.8	5
Saccharin	Glucose	4.8 ± 0.3	4.8 ± 0.3	4.8 ± 0.3	4.85 ± 0.3	4.9 ± 0.3	20
	Insulin	8.5 ± 4.9	8.8 ± 4.4	9.4 ± 4.3	9.4 ± 5.0	9.4 ± 4.6	20

QHCL: quinine hydrochloride; MSG: sodium glutamate; NaCl: sodium chloride.

Statistical analysis

First an analysis of variance for repeated measures (rm-ANOVA) was performed among the subjects using the "stimulant" factors [sucrose, saccharin], "glucose/insulin" and the inter-subject-factor "sex" (female, $n = 9$; male, $n = 11$). In additional analyses we also investigated whether the assessment of the stimulant as more or less pleasant would influence the results (between subject factor "hedonic group" with hedonic ratings of sucrose or saccharin: "≤ -1", $n = 10$; "> -1", $n = 10$). When the analysis revealed significant main effects or significant interactions, *t*-tests were used for later testing. Pearson statistics were used for correlational analyses. The alpha level was set at 0.05. *F*-values were adjusted according to Greenhouse-Geisser. SPSS (SPSS Inc., Chicago, IL, USA) was used for statistical analyses and graphic representation of the results.

Results

In the pilot study ($n = 5$), a significant rise of plasma insulin concentration was found 5 min after simulation using sucrose, saccharin, starch and distilled water, while the blood glucose concentrations remained unchanged (Table 1). With regard to starch and distilled water, outliers caused the increase of insulin concentration, while after sucrose and saccharin stimulation in all five subjects CPIR was suggested.

EGM thresholds exhibited topographical differences being lowest at the tip of the tongue (tip vs. edge: Bonferroni tests for left and right sides: $p < 0.001$) with no significant differences between left and right side ($p > 0.05$). In comparison to normative data (Mueller et al., 2003) all individuals included in this study had scores within the normal range (whole mouth procedure; means ± standard deviation = 14.2 ± 0.8).

The baseline sampling ($n = 5$) revealed no significant changes in plasma insulin concentration within a 12 min period (Fig. 1).

Sucrose and saccharin

Plasma insulin concentrations increased significantly after stimulation with sucrose and saccharin (factor "insulin": $F[4,76] = 3.10$, $p = 0.031$). There was no significant difference between the changes of insulin concentrations induced by the two stimulants (factor "stimulant": $F[1,19] = 0.50$, $p = 0.49$; interaction between factors "insulin" and "stimulant": $F[4,76] = 0.70$, $p = 0.56$) (Fig. 2). No such changes were seen for plasma glucose which retained the same concentration during the observation period ($p > 0.12$).

Next we tested to which extent hedonic assessment of the stimulants affected the magnitude of CPIR. Nine of the 20 subjects assessed the hedonic tone of sucrose less than +2, while 11 subjects

Table 2
Hedonic and intensity ratings (means, S.D.) for the sweeteners sucrose and saccharin ($n = 20$)

	Subgroup	Sucrose	Saccharin	p
Hedonic rating		1.0 ± 2.0	−0.5 ± 1.6	0.002*
	"≤−1"	−1.8 ± 0.8	−1.8 ± 0.9	
	">−1"	1.9 ± 1.2	0.8 ± 0.9	
Sweetness intensity		7.1 ± 1.5	6.1 ± 1.5	0.008*

Mean ± S.D.
* $p < 0.05$ significant differences between measures of sucrose and saccharin.

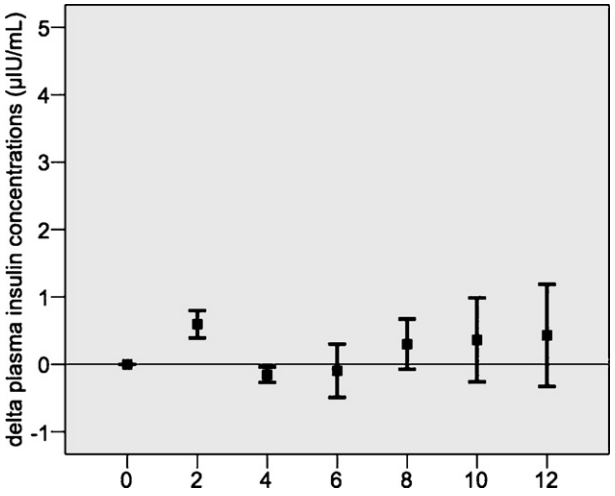

Fig. 1. Baseline curve of plasma insulin concentration (μIU/mL) of healthy humans ($n = 5$) (means, S.E.M.). No statistically significant changes in plasma insulin were found.

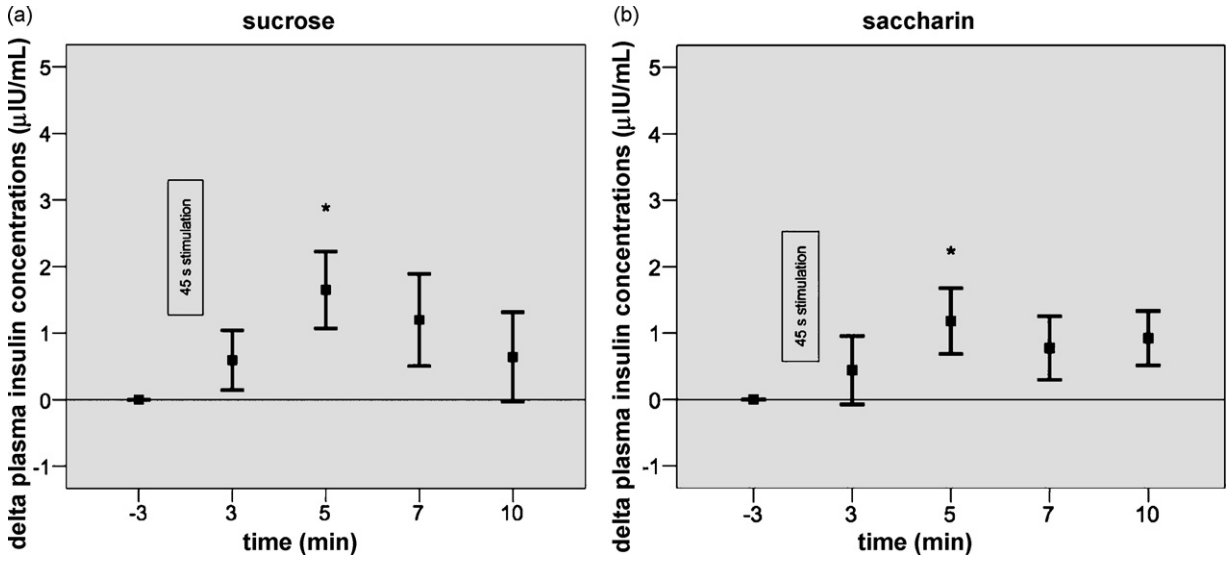

Fig. 2. (a) Effect of taste stimulation with sucrose on plasma insulin concentrations from baseline (µIU/mL) of healthy humans ($n = 20$) (means, S.E.M.) after subjects sipped and spat out the solutions after 45 s. An arrow indicates $t = 0$ min. Significant differences (*) were found between concentration before stimulation and 5 min after sucrose stimulation ($p < 0.05$). (b) Effect of taste stimulation with saccharin on plasma insulin concentrations from baseline (µIU/mL) of healthy humans ($n = 20$) (means, S.E.M.) after subjects sipped and spat out the solutions after 45 s. An arrow indicates $t = 0$ min. Significant differences (*) were found between concentration before stimulation and 5 min after sucrose stimulation ($p < 0.05$).

rated the hedonic tone of sucrose as pleasant, with grades of +2 and higher (Table 2). These two groups, however, did not differ with regard to the change of insulin plasma concentrations (also see Fig. 3a). There was no significant correlation between insulin concentrations and hedonic ratings for sucrose ($r_{20} = -0.16$, $p = 0.53$). Similar negative findings were obtained for saccharin where subjects were also divided in two groups according to their hedonic ratings (10 subjects with hedonic ratings of saccharin of −1 and less, 10 subjects with hedonic ratings of 0 and higher). In addition, there was no significant correlation between insulin concentrations and ratings of hedonics ($r_{20} = -0.15$, $p = 0.56$, Fig. 3b) or intensity.

Discussion

In the preliminary study data obtained from five healthy humans showed an increase of plasma insulin concentration for sucrose and saccharin, while blood glucose remained unchanged and very slight insulin concentration variations within a 12 min-period.

In the larger group of 20 subjects a transient and significant increase of plasma insulin concentrations was found 5 min after stimulation only for sucrose and saccharin. The magnitude of CPIR was higher than the oscillations observed in plasma insulin concentrations. In contrast to stimulation with "sweet", intra-oral stimulation with the remaining four taste qualities sour, salty, bitter and umami did not produce CPIR.

Both, animal (Berthoud, Bereiter, Trimble, Siegel, & Jeanrenaud, 1981; Berthoud et al., 1980; Louis-Sylvestre & Le Magnen, 1980) and human studies (Bellisle, 1987; Bellisle et al., 1983; Bellisle, Louis-Sylvestre, Demozay, Blazy, & Le Magnen, 1985; Louis-Sylvestre & Le Magnen, 1980; Teff et al., 1995; Teff & Engelman, 1996; Teff et al., 1991; Teff et al., 1993) showed that CPIR occurs between 2 and 8–10 min after stimulation with a peak at 4 min. The "sip and spit" procedure avoids ingestion of the taste solutions; thus, the increase of plasma insulin within 8 min after

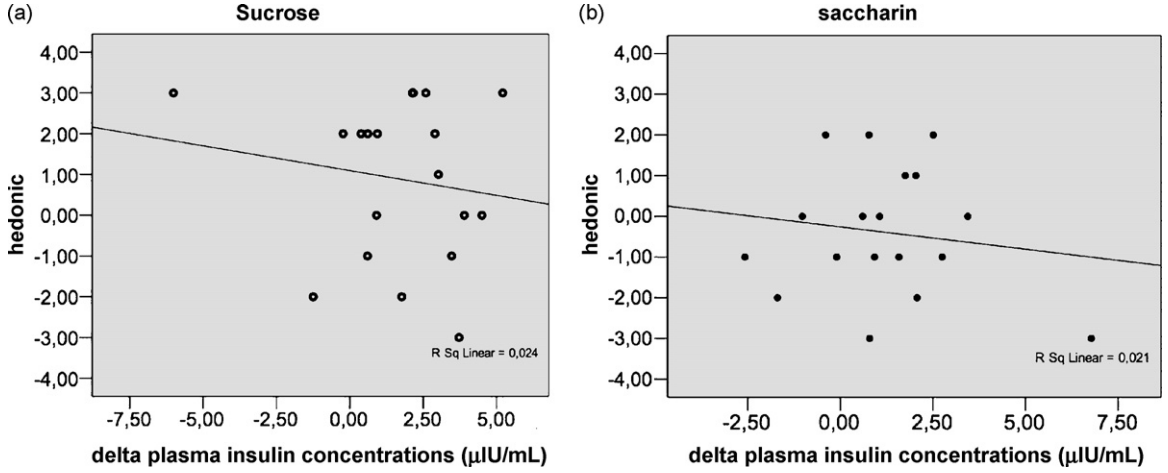

Fig. 3. (a) Scatter plot reveals that no correlation was found between insulin concentrations from baseline (µIU/mL) of healthy humans ($n = 20$) (means, S.E.M.) and hedonic ratings after sucrose stimulation ($r_{20} = -0.16$, $p = 0.53$). (b) Scatter plot reveals that no correlation was found between insulin concentrations from baseline (µIU/mL) of healthy humans ($n = 20$) (means, S.E.M.) and hedonic ratings after saccharose stimulation ($r_{20} = -0.15$, $p = 0.56$).

stimulation is related to CPIR and not to absorption of nutrients through the gastro-intestinal tract, especially when the blood glucose concentration remained unchanged during the observation period.

To our knowledge, only two studies provided blood glucose and plasma insulin concentrations of nutritive and non-nutritive sweeteners within the same individuals and other taste stimuli using an appropriate paradigm of blood sampling to measure the effect of stimulation on insulin release (Abdallah et al., 1997; Teff et al., 1995). The data presented showed no significant changes in plasma insulin and blood glucose 1 or 2 min after application of sweeteners.

In comparison to the stimulation paradigm used by Teff et al. (1995), we used a modified stimulation paradigm. The individuals had to sip and rinse continuously for 45 s before spitting out the solution, in contrast to sipping and swishing for 15 s and expectorating for a 1 or 2 min period (Teff et al., 1995). Maybe the fasting condition prior to measurements plays a significant role in terms of disclosing CPIR as a brief phenomenon with a relatively small magnitude. It has been shown, that there is an association between eating restraint and the magnitude of CPIR the latter to such an extent that subjects with greater dietary restraints exhibited greater CPIR (Simon, Schlienger, Sapin, & Imler, 1986; Teff & Engelman, 1996). With regard to CPIR regulation, palatability and hedonic rating were assumed to play a significant role in determining the magnitude of CPIR. Animal experiments exhibited evidence that CPIR occurs in response to a high palatability (Berthoud et al., 1981; Louis-Sylvestre & Le Magnen, 1980). In humans, higher insulin concentrations were found when subjects were exposed to highly palatable food (Bellisle et al., 1985; Lucas, Bellisle, & Di Maio, 1987), while in another study such correlation was not found (Teff & Engelman, 1996). In our study no significant correlation was found between the insulin concentration after 5 min stimulation and the hedonic ratings for sucrose and saccharin. One relevant explanation may be here that plain taste stimuli rather than real food were used. But the differences in hedonic ratings and sweetness intensity and the magnitude of CPIR for sucrose and saccharin suggest indirectly that pleasantness affects the magnitude of CPIR. Saccharin was less intense and less palatable and revealed a smaller CPIR than sucrose.

The current data indicated that a transient increase of plasma insulin concentration was observed for sucrose and saccharin, while the blood glucose concentration remained unchanged within this 10 min period. Based on reference data from our laboratory (3–17 μIU/mL) the increase of plasma insulin concentration was small, but could be differentiated from oscillations of plasma insulin.

Cephalic phase reflexes can be stimulated by gustatory, olfactory, structural, and thermal properties of food. The present study revealed that CPIR occurred only due to gustatory stimulation. It was not confounded by visual, olfactory and chewing stimuli which had been controlled in this study. To compare results of previous animal experiments (Tonosaki et al., 2007) with our results, the same stimuli and blood collecting paradigm were used. Using nearly the same techniques for measurement of the insulin/glucose concentrations, the results obtained in animals can also be found in humans even when venous, not arterialized blood was used. Due to sparse distal veins of the hand in 7 of 20 subjects and due to non-compliance of additional 2 subjects to insert an intravenous retrograde dwelling catheter into the vein, the catheter was inserted in all subjects in a cubital vein. Therefore venous blood instead of arterialized venous blood was used in our study. It is unlikely that blood sampling technique significantly influenced our results. Another limitation of the study is that only one baseline blood sample was taken. But the comparison of insulin variations from baseline sampling obtained on a separate day compared to those of taste stimulation-related insulin changes revealed relevant differences being higher after gustatory stimulation.

For adequate baseline sampling blood from five subjects of the pilot study was sampled for a 12 min-period (seven samples) on a separate day. During this time subjects did not receive any oral taste stimuli.

In conclusion, the present study suggests that, using an appropriate stimulation paradigm without ingestion of the stimulus, both, the non-nutritive sweetener saccharin and the nutritive sweetener sucrose have an effect on CPIR in humans under fasting conditions. The data obtained in this study will be explored further in patients with gustatory loss whose chorda-tympani nerve, which confers gustatory and general sensation from the tongue, has been transected bilaterally during middle ear surgeries. As mentioned earlier, rat experiments suggest that chorda tympani transection will dispose of CPIR.

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