# Determinants of the Cephalic-Phase Insulin Response in Obese Nondiabetic Subjects

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**Large interindividual variation is characteristic of the cephalic-phase insulin response (CPIR). Our aim was to examine the largely unknown determinants of CPIR in obese nondiabetic subjects before and after weight reduction. After a 12-hour overnight fast, 20 healthy, obese (body mass index, 31.1 to 41.4 kg/m$^2$) subjects were individually exposed to food without being allowed to eat it. Levels of insulin, glucose, C-peptide, free fatty acids, and salivation, together with assessments of feeling of hunger and desire to eat, were measured during the experiment. Subjects were divided into three groups according to CPIR before the weight reduction: positive (PR), intermediate (IR), and negative (NR) responders. CPIR measurements before and after weight reduction correlated significantly with each other ($r = .61$, $P < .01$, $n = 18$). At the beginning of the study, NR had higher fasting plasma glucose and insulin values, as well as higher postload plasma glucose values, as compared with PR and IR. These differences disappeared after weight reduction. In an intravenous glucose tolerance test (IVGTT) performed 9 to 12 months afterward, first-phase insulin secretion was significantly lower in NR. Thus, the negative CPIR during visual and olfactory exposure to food-related stimuli may be related to the attenuated first-phase insulin secretion and mildly impaired glucose metabolism, possibly related to insulin resistance.**



THE EXTERNAL food-related stimuli, ie, the sight, odor, taste, or thought of food, can stimulate autonomic and endocrine responses involved in the utilization of food, eg, salivation, insulin secretion, and exocrine pancreatic and gastric acid secretion.[1] These responses, called cephalic-phase responses, occur during the first 10 minutes between the sensory arousal and the beginning of food absorption. They can be conditioned to the environmental food-related stimuli and are modified by the palatability of the food.[2,3]

Cephalic-phase input signals are the only known physiological stimuli that produce direct neurally mediated insulin release.[4] Insulin may have an important role in the determination of food intake[5] which makes the neurally mediated cephalic-phase insulin response (CPIR) especially interesting. Both animal[6] and human[7] studies show that CPIR is of importance for normal glucose homeostasis, and an impairment of CPIR results in prandial hyperglycemia and late hyperinsulinemia.[7]

The role of the CPIR in obesity is not clear. An exaggeration of the CPIR has been documented in two animal models of obesity, the ventromedial hypothalamic syndrome[8] and bipiperidyl mustard rats.[9] In humans, blocking the CPIR decreases postprandial thermogenesis and thus could play a role in the etiology of obesity.[10] Contradictory results on the magnitude of the CPIR in obese subjects have been reported,[11,12] and negative responses may also occur among obese subjects.[11] However, reasons for this variability are not known. Therefore, our aim was to examine determinants of the CPIR in obese subjects before and after weight reduction.

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## SUBJECTS AND METHODS

### *Subjects*

Twenty subjects (four men and 16 women) were selected randomly from a group of 48 obese subjects (10 men and 38 women) participating in a long-term weight-reduction program at the Department of Clinical Nutrition, University of Kuopio. All subjects were obese (body mass index, 35.5 ± 0.71 kg/m$^2$, mean ± SE; range, 31.1 to 41.4) and nondiabetic, and had no history of bulimia according to a standardized questionnaire.[13] The mean age of the subjects was 44.2 ± 1.8 years (range, 29 to 55). The experiment was repeated for 18 subjects (four men and 14 women) after a 6-month weight-reduction period, when the mean weight loss was −11.9 ± 1.2 kg (range, −3.1 to −23.4). Two subjects dropped out of the weight-reduction program and did not take part in the follow-up study. Subjects were informed that the purpose of the study was to examine blood glucose levels in various situations, but they were not told that exposure to food was one part of the test. The study was approved by the Ethics Committee of the University of Kuopio.

### *General Procedure*

Subjects participated in the experiment individually on two different occasions within a 2-week period before and after 6 months from the beginning of the weight-reduction program. All measurements were made in the morning between 7:30 and 10:00 after a 12-hour fast.

Anthropometric, metabolic, and behavioral measurements were made during the first visit. Body composition was determined by a bioelectrical impedance method (RJL Systems, Detroit, MI). Basal metabolic rate was measured by indirect calorimetry (Deltatrac; Datex, Helsinki, Finland) and calculated according to the method reported by Ferrannini.[14]

As behavioral measures of eating, the Three-Factor Eating Questionnaire[15] and the bulimia questionnaire, BITE,[13] were used. Food intake was measured with 4-day food diaries. Calculations for nutrient intake were made using the Nutrica software package for nutrient intake analysis (Social Insurance Institution, Helsinki, Finland, 1993).

### *Cephalic-Phase Response Test*

The cephalic-phase response test was performed during the second visit (Fig 1). It consisted of two consecutive periods, baseline and food exposure, which took place in a peaceful room where a restaurant-like table was prepared for the subject. During the baseline period, the subject read a magazine including no food-related stimuli. During the food exposure period, the test food was on the table in front of the subject and the subject was asked to look at and smell the food. The subject was told that he/she could eat the food after the experiment. Energy content of the whole test meal was 905 kcal, consisting of a cup of coffee or tea (as the subject preferred), a glass of orange juice, four sandwiches with ham, cheese, and vegetables, and two kinds of chocolate cookies. The test meal was selected so that it represented a typical Finnish breakfast with generally liked items.

Blood samples for measurements of insulin, C-peptide, glucose, and free fatty acid levels were taken through an intravenous cannula that was inserted into the subject's antecubital vein. The subject rested in a recumbent position for 15 minutes after cannulation. Blood samples were taken three times (−6, −4, and −2 minutes) before the food exposure and four times (3, 6, 9, and 13 minutes) during it (Fig 1). The blood samples were placed in prechilled tubes, centrifuged, and stored without delay at −70°C until analyzed.

Salivation was measured with two preweighed dental rolls that the subject kept in his/her mouth between the cheek and lower gum in each cheek for 2 minutes. The dental rolls were reweighed after the experiment, and the amount of salivation was calculated from the difference in weight of the dental rolls. The salivation measurement was made three times: during the baseline period and at the beginning and end of the food exposure (Fig 1). One subject could not take part in the salivation measurement due to mild nausea related to the measurement. However, since analysis of other measurements indicated no effect of the nausea, this subject was not excluded from the study.

Feelings of hunger and a desire to eat the presented breakfast were determined with 10-cm visual analog scales ranging from "absent" to "extreme." Feelings of hunger were assessed at the beginning and end of the experiment, and desire to eat at the beginning and end of the food exposure (Fig 1).

### *Oral Glucose Tolerance Test*

A 2-hour oral glucose tolerance test (OGTT) with 75 g glucose dissolved in 300 mL water took place in the fasting condition immediately after the cephalic-phase response test. Blood samples for plasma insulin and glucose determinations were taken just before and 1 and 2 hours after ingestion of the solution. After the OGTT, the subject was allowed to eat the test breakfast and the amount eaten was recorded.

### *Intravenous Glucose Tolerance Test*

An insulin-modified, frequently sampled intravenous glucose tolerance test ([IVGTT] the minimal model method)[16] was performed 9 to 12 months after the beginning of the study to obtain detailed information about first-phase insulin secretion and insulin sensitivity of the subjects. All 20 subjects participated in the IVGTT, but three subjects had to be excluded due to technical problems. Insulin sensitivity ($S_I$) and glucose effectiveness ($S_G$) indexes could not be calculated for one subject. At the time of the IVGTT, the mean weight loss of subjects participating in the IVGTT was −11.1 ± 1.4 kg, ranging from −2.2 to −25.3 kg.

The IVGTT was performed in the morning after a 12-hour fast. The glucose dose of 300 mg/kg body weight was administered as a 50% solution in 1.5 minutes through an intravenous cannula in the antecubital vein and flushed with saline. An insulin dose of 0.03 U/kg body weight was administered at 20 minutes, followed by a 1.5-minute rapid flow of saline. Altogether, 25 blood samples were taken during a 180-minute period for determination of plasma glucose and insulin. The computer program MINMOD[17] was used for calculations of $S_I$ and $S_G$ indexes. The area under the insulin curve from 0 to 10 minutes during the IVGTT was calculated to reflect first-phase insulin secretion.

### *Biochemical Analyses*

Plasma glucose was analyzed by the glucose oxidase method (Glucose Auto & Stat, Model GA-110; Daiichi, Kyoto, Japan). Radioimmunoassay (RIA) was used for analyses of plasma insulin (Phadeseph Insulin RIA 100; Pharmacia Diagnostics, Uppsala, Sweden) and plasma C-peptide (RIA; Incstar, Stillwater, MN). The detection limit of insulin assays was 2.5 mU/L and the coefficient of variation was less than 5.0%. Serum free fatty acid levels were measured by a turbidometric method and analyzed with a specific analyzer (Kone, Espoo, Finland).

### *Statistical Analyses*

To classify subjects according to CPIR, the standard deviation of insulin values at baseline was calculated for each subject. Subjects whose mean insulin level during food exposure was higher than the mean baseline insulin level plus 1 SD were classified as positive responders (PR), and subjects with a mean insulin level less than the mean baseline insulin level minus 1 SD as negative responders (NR). Subjects whose mean insulin level during food exposure was within the mean baseline ± 1 SD were classified as intermediate responders (IR). CPIR was determined as the mean of insulin changes from the mean baseline to the food exposure. Changes in plasma glucose and C-peptide, serum free fatty acids, and saliva secretion were calculated similarly. Differences between the three groups were analyzed by Kruskal-Wallis one-way ANOVA. When the trend was obvious ($P < .1$), differences between the two groups were analyzed using the Mann-Whitney $U$ test. Changes within groups were analyzed by Friedman two-way ANOVA. The Spearman correlation coefficient was calculated to determine the association between CPIR and other variables. Results are expressed as the mean ± SE unless otherwise specified.

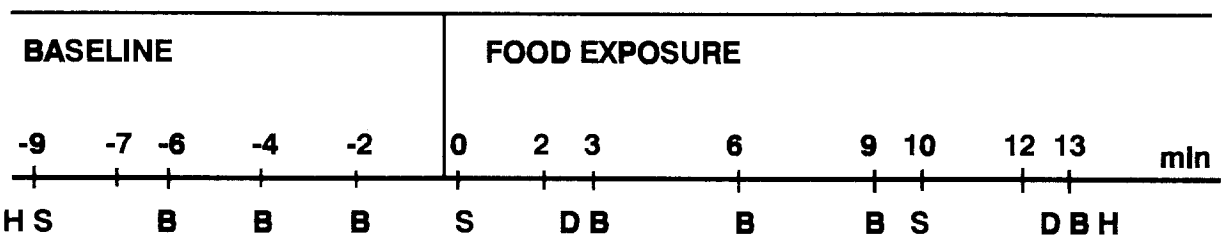
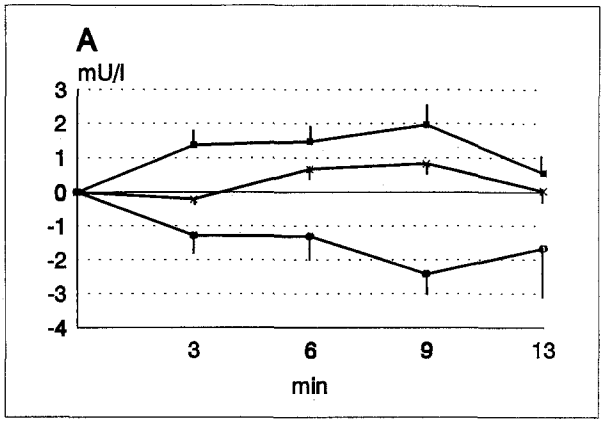



**Fig 1. CPIR test. H, feelings of hunger; S, salivation; B, blood sample; D, desire to eat.**

## RESULTS

There was large interindividual variability (−4.6 to +3.2 mU/L) in the CPIR measured before weight reduction. One man and seven women were classified as PR (CPIR, 1.3 ± 0.3 mU/L; range, 0.4 to 3.2), five women as IR (CPIR, 0.3 ± 0.1 mU/L; range, 0.03 to 0.7), and three men and four women as NR (CPIR, −1.7 ± 0.7 mU/L; range, −4.6 to −0.1) (Fig 2). Plasma insulin increased significantly from the baseline to the food exposure in PR ($P = .004$) and IR ($P = .05$), whereas the decrease was not significant in NR.

After 6 months, weight reduction was comparable in all groups (PR, −11.5 ± 0.9 kg; IR, −10.9 ± 2.7; and NR, −13.1 ± 3.0). At that time, CPIR was 0.8 ± 0.4 mU/L (range, −0.5 to 2.4) in PR, −0.2 ± 0.3 mU/L (range, −1.1 to 0.29) in IR, and −0.9 ± 0.5 mU/L (range, −2.1 to 0.4) in NR (Fig 2). The increase from the baseline to the food exposure was significant in PR only ($P = .003$). The correlation coefficient between the CPIR at baseline and after 6 months was .61 ($P = .004$, n = 18).



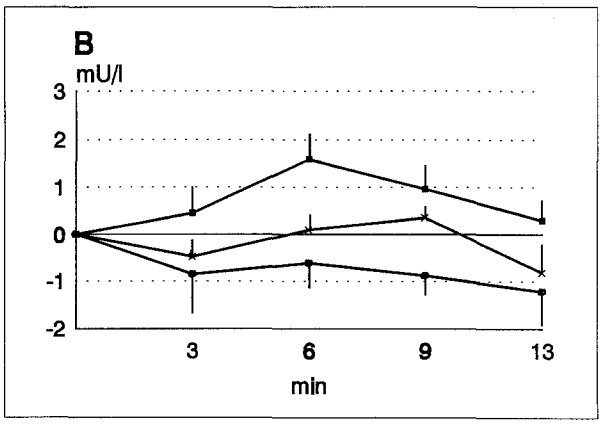




**Fig 2. (A) CPIR in PR (■), IR (X), and NR (○) before weight reduction (mean ± SE). (B) CPIR in PR, IR, and NR after 6 months of weight reduction.**

Before weight reduction, baseline plasma insulin, C-peptide, and glucose levels were significantly higher in NR as compared with PR or IR. Baseline levels of serum free fatty acids or salivation were not significantly different between groups, and neither were the mean changes of plasma C-peptide, glucose, serum free fatty acids, or salivation during food exposure. After 6 months, there were no differences between groups in any of the variables (Table 1).

Subjective responses during the CPIR test and the food intake after the experiment were not significantly different between groups either before or after weight reduction (data not shown).

Before weight reduction, fasting and 2-hour plasma glucose and fasting plasma insulin in the OGTT were significantly higher in NR than in PR or IR. After 6 months of weight reduction, there were no longer significant differences between groups (Table 2).

In the IVGTT performed 9 to 12 months after beginning the study, the insulin area under the curve (0 to 10 minutes) was significantly lower in NR than in the other groups, indicating attenuated first-phase insulin secretion in NR (Fig 3, Table 3). No significant differences were observed in $S_I$ or $S_G$ indexes between the groups (Table 3). Weight reduction was comparable in the groups at the time of the IVGTT (PR, −10.5 ± 1.6 kg; IR, −13.2 ± 3.4; and NR, −9.7 ± 2.9).

Before weight reduction, there was a significant negative correlation in the whole group between CPIR and baseline plasma glucose ($r = -.54$, $P = .007$, N = 20) and between CPIR and plasma glucose during the OGTT (0-hours, $r = -.51$, $P = .01$; 2-hours, $r = -.69$, $P < .001$; N = 20).

The correlation between CPIR at the beginning of the study and first-phase insulin secretion in the IVGTT was positive ($r = .62$, $P = .004$, n = 17). After 6 months of weight reduction, the CPIR did not correlate significantly with any of these variables.

PR, IR, and NR did not differ in age, body mass index, body composition, or basal metabolic rate at the beginning or after 6 months of weight reduction. Neither were there any significant differences between groups in the scores of the Three-Factor Eating Questionnaire or the self-rating scale for bulimia (BITE) or in food intake according to the food diaries either before or after weight reduction (data not shown).

## DISCUSSION

Our primary interest was to examine the determinants of CPIR in obese subjects before and after weight reduction when exposed to food-related stimuli without eating. The negative CPIR was associated with the higher fasting plasma glucose and insulin and postload plasma glucose before weight reduction, whereas the behavioral factors did not seem to reflect phenomena related to the CPIR. Later, subjects who had shown the negative CPIR before weight reduction had an attenuated first-phase insulin secretion in the IVGTT. This finding suggests that even after a marked weight reduction, subjects with a negative CPIR had a

**Table 1. Fasting Plasma Insulin, C-peptide, and Glucose, Serum Free Fatty Acids, and Salivation in PR, IR, and NR Before (0 months) and After a 6-Month Weight-Reduction Program (mean ± SE)**

| Variable | 0 Months | | | | 6 Months | | | |
|---|---|---|---|---|---|---|---|---|
| | PR (n = 8) | IR (n = 5) | NR (n = 7) | P* | PR (n = 7) | IR (n = 5) | NR (n = 6) | P* |
| Plasma insulin (mU/L) | | | | | | | | |
| Baseline | 12.3 ± 1.7‡ | 9.5 ± 1.9§ | 20.1 ± 2.9 | .05 | 9.6 ± 1.6 | 9.5 ± 1.5 | 10.2 ± 1.3 | NS |
| Change† | 1.3 ± 0.3 | 0.3 ± 0.1 | −1.7 ± 0.7 | — | 0.8 ± 0.4 | −0.2 ± 0.3 | −0.9 ± 0.5 | — |
| Plasma C-peptide (nmol/L) | | | | | | | | |
| Baseline | 0.76 ± 0.11 | 0.61 ± 0.08§ | 1.04 ± 0.13 | .10 | 0.58 ± 0.09 | 0.52 ± 0.06 | 0.58 ± 0.08 | NS |
| Change† | 0.02 ± 0.01 | −0.01 ± 0.01 | −0.04 ± 0.03 | NS | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.00 ± 0.01 | NS |
| Plasma glucose (mmol/L) | | | | | | | | |
| Baseline | 5.5 ± 0.1‡ | 5.2 ± 0.3§ | 6.2 ± 0.3 | .05 | 5.4 ± 0.1 | 5.3 ± 0.2 | 5.3 ± 0.2 | NS |
| Change† | 0.03 ± 0.03 | 0.06 ± 0.04 | 0.1 ± 0.05 | NS | 0.02 ± 0.04 | −0.03 ± 0.02 | 0.02 ± 0.03 | NS |
| Serum free fatty acids (mmol/L) | | | | | | | | |
| Baseline | 0.62 ± 0.03 | 0.71 ± 0.10 | 0.71 ± 0.12 | NS | 0.56 ± 0.07 | 0.44 ± 0.12 | 0.63 ± 0.06 | NS |
| Change† | 0.07 ± 0.02 | 0.12 ± 0.08 | 0.04 ± 0.03 | NS | −0.01 ± 0.05 | 0.04 ± 0.03 | 0.01 ± 0.04 | NS |
| Salivation (g) | | | | | | | | |
| Baseline | 0.48 ± 0.09 | 0.61 ± 0.12 | 0.40 ± 0.09 | NS | 0.54 ± 0.11 | 0.82 ± 0.2 | 0.64 ± 0.20 | NS |
| Change† | −0.01 ± 0.09 | 0.12 ± 0.04 | 0.11 ± 0.11 | NS | 0.09 ± 0.08 | 0.15 ± 0.16 | −0.1 ± 0.1 | NS |

*Difference between PR, IR, and NR by Kruskal-Wallis one-way ANOVA.

†Change from the mean baseline to the food exposure.

‡Difference between PR and NR: plasma insulin baseline, $P = .05$; plasma glucose baseline, $P = .04$; Mann-Whitney U test.

§Difference between IR and NR: plasma insulin baseline, $P = .04$; plasma C-peptide baseline, $P = .04$; plasma glucose baseline, $P = .04$; Mann-Whitney *U* test.

**Table 2. OGTT in PR, IR, and NR Before (0 months) and After a 6-Month Weight-Reduction Program (mean ± SE)**

| Variable | 0 Months | | | | 6 Months | | | |
|---|---|---|---|---|---|---|---|---|
| | PR (n = 8) | IR (n = 5) | NR (n = 7) | P* | PR (n = 7) | IR (n = 5) | NR (n = 6) | P* |
| Plasma glucose (mmol/L) | | | | | | | | |
| 0 h | 5.5 ± 0.1† | 5.3 ± 0.2‡ | 6.1 ± 0.2 | .05 | 5.3 ± 0.1 | 5.3 ± 0.2 | 5.3 ± 0.2 | NS |
| 1 h | 7.9 ± 0.4 | 7.8 ± 1.0 | 9.8 ± 1.1 | NS | 7.2 ± 0.6 | 6.8 ± 0.8 | 8.8 ± 0.6 | NS |
| 2 h | 6.4 ± 0.2† | 6.7 ± 0.6 | 8.8 ± 0.8 | .03 | 5.4 ± 0.3 | 6.2 ± 0.6 | 7.1 ± 0.9 | NS |
| Plasma insulin (mU/L) | | | | | | | | |
| 0 h | 14.5 ± 2.6 | 10.1 ± 2.1‡ | 20.6 ± 3.3 | .08 | 9.0 ± 1.6 | 8.9 ± 1.5 | 8.4 ± 1.4 | NS |
| 1 h | 101.0 ± 18.4 | 60.9 ± 17.6 | 94.1 ± 19.6 | NS | 64.6 ± 11.9 | 45.0 ± 10.8 | 46.6 ± 9.2 | NS |
| 2 h | 82.4 ± 11.5 | 61.5 ± 20.3 | 89.4 ± 16.6 | NS | 47.9 ± 10.7 | 37.3 ± 5.8 | 42.2 ± 7.6 | NS |

*Difference between PR, IR, and NR by Kruskal-Wallis one-way ANOVA.

†Difference between PR and NR: plasma glucose 0 h, $P = .04$; 2 h, $P = .008$; Mann-Whitney *U* test.

‡Difference between IR and NR: plasma glucose 0 h, $P = .05$; plasma insulin 0 h, $P = .04$; Mann-Whitney *U* test.

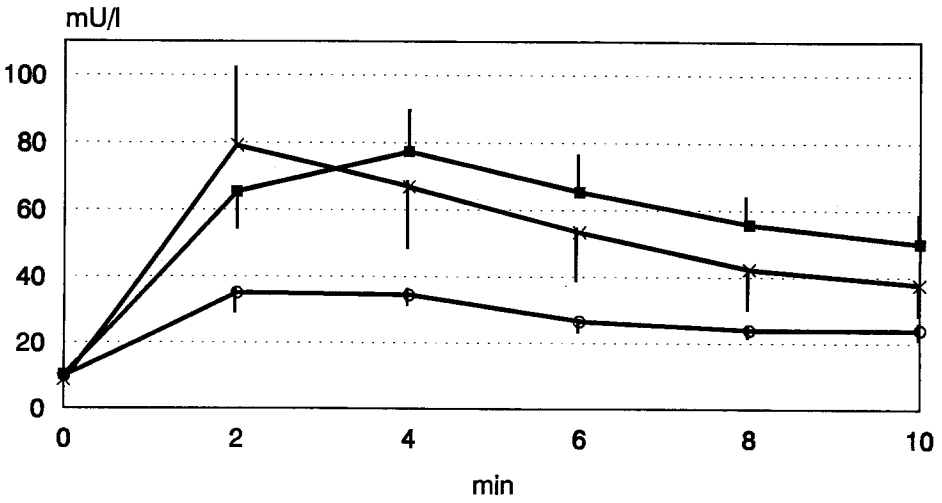



**Fig 3. First-phase insulin secretion (0 to 10 minutes) in the IVGTT in PR (■), IR (X), and NR (○) (mean ± SE). Difference between groups, $P = .07$.**

**Table 3. IVGTT in PR, IR, and NR (mean ± SE)**

| Variable | PR (n = 7) | IR (n = 5) | NR (n = 5) | P* |
|---|---|---|---|---|
| Plasma glucose (mmol/L) | 5.3 ± 0.1 | 5.3 ± 0.2 | 6.0 ± 0.4 | NS |
| Plasma insulin (mU/L) | 10.2 ± 1.3 | 8.5 ± 2.3 | 10.5 ± 2.1 | NS |
| Insulin area 0 to 10 minutes (mU × min) | 588 ± 87† | 529 ± 142‡ | 275 ± 18 | .07 |
| $S_I$ (× $10^4$ $min^{-1}/(\mu U/mL)$)§ | 2.58 ± 0.47 | 5.38 ± 1.59 | 3.70 ± 1.25 | NS |
| $S_G$ ($min^{-1}$ × $10^3$)§ | 0.018 ± 0.003 | 0.025 ± 0.003 | 0.019 ± 0.002 | NS |

*Difference between PR, IR, and NR by Kruskal-Wallis one-way ANOVA.

†Difference between PR and NR, $P = .04$; Mann-Whitney $U$ test.

‡Difference between IR and NR, $P = .05$; Mann-Whitney $U$ test.

§PR, n = 6; IR, n = 5; NR, n = 5.

defect in the secretion of insulin. Weight loss was similar in all groups and improved glucose tolerance of the subjects. However, the effect of weight loss on first-phase insulin secretion remains unknown.

It may be argued that it is not correct to divide subjects into different responder groups according to a single measurement. However, the repeatability of CPIR is high within a short period,[18] and in this study it appeared to be consistent during a 6-month period, although weight reduction may have had some impact on the CPIR. Also, although insulin responses seen in this study were weak, they were nevertheless higher than the coefficients of variation of the insulin determinations.

CPIR has been suggested to be of importance for normal glucose metabolism,[7,10] and an association between elevated fasting glucose and insulin levels and attenuated CPIR has been described in obese subjects.[12] Our results, with respect to fasting plasma glucose and insulin levels before weight reduction, are in accordance with these findings. Importantly, we noted that the connection between fasting plasma glucose and insulin levels and the CPIR can also be observed after only visual and olfactory exposure to food. Obese subjects are often characterized by elevated fasting glucose and insulin levels and impaired glucose tolerance (IGT). Thus, it can be suggested that the impaired or negative CPIR might be more common in obese than in normal-weight subjects, as Teff et al[12] have also suggested.

In this study, when glucose metabolism had improved after marked weight reduction, the association between the CPIR and the indicators of glucose metabolism markedly weakened. However, the weight loss–induced improvement in glucose metabolism did not strengthen the CPIR, which may indicate a more profound underlying defect in the insulin secretion of NR, as was the case in the present study on the basis of the IVGTT. The parameters of the IVGTT indicating $S_I$ and $S_G$ were markedly higher in our subjects as compared with subjects with diagnosed IGT ($S_I$, 3.80 ± 2.70 *v* 1.65 ± 0.95 × $10^4$ $min^{-1}/\mu U/mL$); $S_G$, 0.020 ± 0.007 *v* 0.012 ± 0.006 $min^{-1}$ × $10^3$, mean ± SD; our subjects *v* subjects with IGT[19]). Interestingly, the insulin area under the curve (calculated from 0 to 19 minutes), indicating first-phase insulin secretion, was lower in NR of this study than in subjects with IGT (503 ± 87 *v* 892 ± 543 mU × min, mean ± SD, NR *v* subjects with IGT).[19] An impairment of the pulsatile nature of insulin secretion has been observed even when glucose tolerance is only slightly impaired.[20] Thus, the diminution of the oscillatory nature of insulin secretion in NR could also explain our findings.

In summary, this study suggests that in obese subjects, a negative CPIR in the presence of visual and olfactory food-related stimuli may be associated with an impairment of first-phase insulin secretion and mildly disturbed glucose metabolism, possibly related to insulin resistance.

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