Effects of Hyperglycemia and Hyperinsulinemia on Satiety in Humans

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Hyperglycemia may influence satiety. One mechanism by which glucose could influence food intake is hyperinsulinemia. Therefore, we investigated the short-term effects of acute hyperglycemia and euglycemic hyperinsulinemia on satiety. Six healthy volunteers (aged 20 to 26 years) were studied for 240 minutes on three separate occasions in random order during (1) intravenous (IV) saline (control), (2) acute hyperglycemic hyperinsulinemia (HG) with plasma glucose at 15 mmol/L, and (3) euglycemic hyperinsulinemia (HI) with plasma insulin at 80 mU/L and glucose at 4 to 5 mmol/L. Subjective criteria for appetite like the wish to eat, prospective feeding intentions ("How much food do you think you can eat?"), and feelings of hunger and fullness were scored on a 100-mm visual analog scale (VAS) at 30-minute intervals. Appetite was also measured every 60 minutes with the use of a food selection list (FSL). Appetite (prospective feeding intentions, feelings of hunger, and the wish to eat) gradually increased over basal levels during control conditions and HI. In contrast, prospective feeding intentions and feelings of hunger gradually decreased during HG and were significantly ($P < .05$) reduced versus basal and control levels during the last hour of the experiment. The wish to eat followed the same pattern. Feelings of fullness did not significantly change in all three experiments. Total food selection was not significantly decreased during HG, but the preference for fat-rich or carbohydrate-rich items tended to be reduced. The study suggests that in humans hyperglycemia induces satiety. This effect seems not to be mediated by insulin, since HI had no effect on appetite. However, a potentiating effect of endogenous insulin on the satiating effect of high blood glucose levels cannot be excluded.

RECENT STUDIES have pointed to the influence of the blood glucose concentration on digestive functions. In healthy subjects, acute hyperglycemia induced by intravenous (IV) infusion of glucose inhibits gastric acid and pancreatic enzyme secretion, gallbladder motility, and gastric emptying.[1-4] Gastric emptying is involved in the regulation of short-term satiety and food intake.[5] The effect of hyperglycemia on satiety is poorly understood. Several studies suggest that IV infusion of glucose reduces voluntary food intake,[6,7] whereas others have demonstrated a stimulatory effect.[8] Lavin et al[9] suggest that intraduodenal but not IV infusion of glucose increases subjective feelings of satiety. One of the mechanisms by which glucose may influence food intake is hyperinsulinemia. However, the role of insulin in satiety is controversial.[8,10,11] Rodin et al[8] suggested that hyperinsulinemia increases hunger feelings and food intake in humans independently of blood glucose levels. Other studies indicate that insulin induces satiety[10,12-14] or has no effect.[11] Therefore, we investigated the short-term effect of hyperinsulinemia on satiety during hyperglycemic and euglycemic conditions in healthy subjects.

SUBJECTS AND METHODS

Subjects

Six healthy lean volunteers (one man and five women; mean age, 22 ± 1 years; body mass index, 20 to 25 kg/m^2) participated in the study. None of the subjects had a history of gastrointestinal disease or surgery, and none were taking any medication. Informed consent was obtained from each individual, and the protocol was approved by the medical ethics committee of Leiden University Medical Center.

Study Protocol

Each subject participated in three experiments performed on separate days in random order and single-blind fashion with an interval of at least 7 days: (1) control, (2) acute hyperglycemia (HG) with plasma glucose stabilized at 15 mmol/L, and (3) euglycemic hyperinsulinemia (HI) with plasma insulin targeted at 80 to 100 mU/L. Previous studies in our department have shown that after 2 hours of hyperglycemic clamping with plasma glucose stabilized at 15 mmol/L, plasma insulin levels of approximately 80 to 100 mU/L are reached.[15] The experiments were started at 8 AM after an overnight fast. Two IV cannulas—one for blood sampling and the other for infusion—were inserted into the antecubital vein of each arm. Subjects were studied in a semireclining position. The clamp procedure (description follows) was started at time 0 minutes and continued for 240 minutes. Blood samples were obtained every 20 minutes for determination of plasma insulin.

Subjective criteria for appetite like the wish to eat ("How strong is your wish to eat: very weak to very strong?"), prospective feeding intentions ("How much food do you think you can eat: nothing to very much?"), and feelings of hunger ("How hungry do you feel: not hungry at all to as hungry as I have ever felt?") and fullness ("How full do you feel: not full at all to very full?") were scored on a 100-mm visual analog scale (VAS) at 30-minute intervals.[16,17] Appetite was also measured every 60 minutes with the use of a food selection list (FSL) as described by Hill and Blundell[18] and modified to Dutch feeding customs. The subjects were presented a photograph showing six fat-rich, six protein-rich, six carbohydrate-rich (each 200 kcal), and six low-energy items. From each of these 24 items, they were asked whether they wanted to eat the amount shown (1), double the amount (2), half the amount (½), or nothing at all (0) independent of the other 23 items. At each time interval, the total amount of caloric items chosen was calculated. The subjects also indicated on a separate VAS whether they experienced feelings of nausea or abdominal discomfort.

Clamp Technique

Acute hyperglycemia at 15 mmol/L was obtained using a modified glucose clamp technique.[19,20] An acute increase in plasma glucose was induced by an IV bolus infusion of 20% glucose at time 0 minutes. The amount of glucose administered (grams) was calculated from the body weight (kilograms) using the following formula in which PGL represents the plasma glucose level (millimolars): glucose load = (target PGL − attained PGL)·body weight·0.035. After the bolus injection, the glucose infusion rate (GIR) was adjusted to maintain plasma glucose at approximately 15 mmol/L. Plasma glucose concentrations were mea-

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sured every 5 minutes using the glucose oxidase method (Beckman Glucose Analyzer; Beckman Instruments, Palo Alto, CA). The GIR was increased if the actual plasma glucose level was less than the target plasma glucose level (15 mmol/L) and vice versa. The GIR was calculated using the formula described by Ward et al[20]: $GIR_{adjusted} = (1 + \text{target PGL} - \text{present PGL/target PGL} - \text{fasting PGL}) \cdot GIR_{present}$.

HI was achieved using a modified euglycemic insulin clamp technique.[19,21] An acute increase in plasma insulin was achieved by an IV bolus infusion of insulin (Actrapid; Novo Nordisk Farma, Bagsvaerd, Denmark) at a dose of 12.5 mU/kg. After the bolus, insulin was infused continuously at a rate of 1.25 mU/kg/min to maintain a constant plasma insulin. Glucose 20% was given simultaneously to maintain plasma glucose at approximately 4 to 5 mmol/L. The GIR was adjusted depending on the actual plasma glucose level as already described. Plasma glucose concentrations were measured every 5 minutes. To prevent hypokalemia, 10 mmol potassium chloride was added to 500 mL 20% glucose during both the glucose and the insulin clamp. During the control experiment, only IV saline was given at rates comparable to the glucose infusion during clamp experiments.

Insulin Assay

The plasma insulin level was measured with a radioimmunoassay as described previously.[21]

Statistical Analysis

Results are expressed as the mean ± SEM. Satiety scores are expressed as the change over basal (time 0 minutes). Differences in plasma glucose, plasma insulin, and the satiety score were analyzed for statistical significance by multiple ANOVA. When ANOVA indicated a probability of less than .05 for the null hypothesis. Student-Newman-Keuls analyses were performed to determine which values between or within experiments differed significantly. The significance level was set at P less than .05.

RESULTS

Plasma Glucose

Basal plasma glucose concentrations were not significantly different between the three experiments (4.9 ± 0.1, 4.9 ± 0.1, and 4.6 ± 0.2 mmol/L, control, HI, and HG, respectively). During HI, plasma glucose levels stabilized within 20 to 40 minutes after starting the insulin infusion (Fig 1). During HG, plasma glucose levels of approximately 15 mmol/L were obtained.

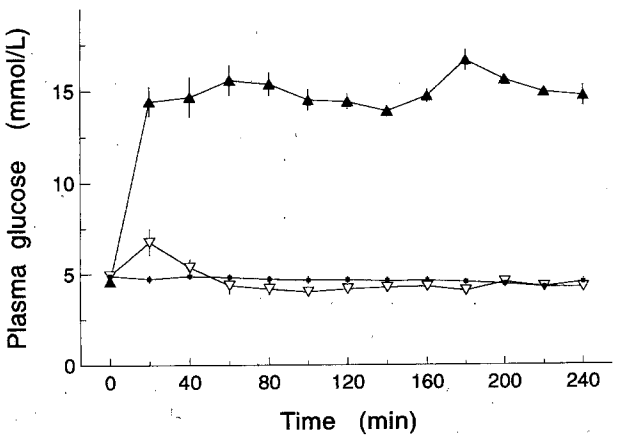

Fig 1. Plasma glucose levels (mean ± SEM) in 6 healthy subjects during 4 hours of HG (▲) or HI (▽) compared with saline infusion (■).

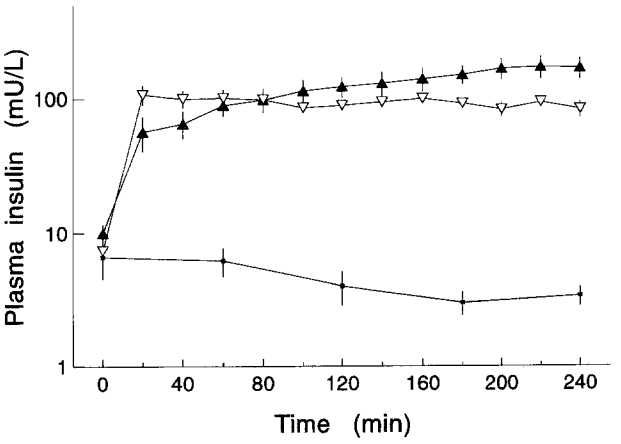

Fig 2. Plasma insulin levels (mean ± SEM) in 6 healthy subjects during 4 hours of HG (▲) or HI (▽) compared with saline infusion (■).

Plasma Insulin

Basal plasma insulin concentrations were not significantly different between the three experiments (7 ± 2, 7 ± 2, and 10 ± 2 mU/L, control, HI, and HG, respectively). No significant changes in plasma insulin were observed in the control experiment (Fig 2). During HI, insulin infusion caused a rapid increase in plasma insulin, which stabilized between 85 and 105 mU/L. During HG, a gradual increase in plasma insulin was observed. During HI and HG, plasma insulin levels were significantly ($P < .01$) increased over basal and compared with the control experiment.

Satiety Scores

The studies were well tolerated by all subjects. VAS and FSL ratings at time 0 minutes (basal values) were not significantly different between the three experiments (data not shown). Results for the changes in VAS ratings over basal are presented in Fig 3. Prospective feeding intentions, feelings of hunger, and the wish to eat followed the same pattern. These ratings of appetite gradually increased over basal during the control and HI. In contrast, prospective feeding intentions and hunger feelings were significantly ($P < .05$) reduced during HG compared with the control and HI. The reduction in the wish to eat during HG just failed to reach statistical significance ($P = .07$). Feelings of fullness did not significantly change within or between the three experiments. Results for the changes in FSL ratings over basal are presented in Fig 4. Total food selection was not significantly decreased during HG, but the preference for fat-rich or carbohydrate-rich items tended to be reduced.

DISCUSSION

The present study demonstrates that in healthy humans acute hyperglycemia induces satiety. This satiating effect during hyperglycemia seems not to be mediated by insulin, since HI (exogenous insulin) had no effect on appetite. However, an effect of concomitant endogenous hyperinsulinemia on satiety during hyperglycemia cannot be totally excluded.

The role of insulin in satiety is controversial.[8-11,13,14] Some data suggest that insulin may have an important role in inducing

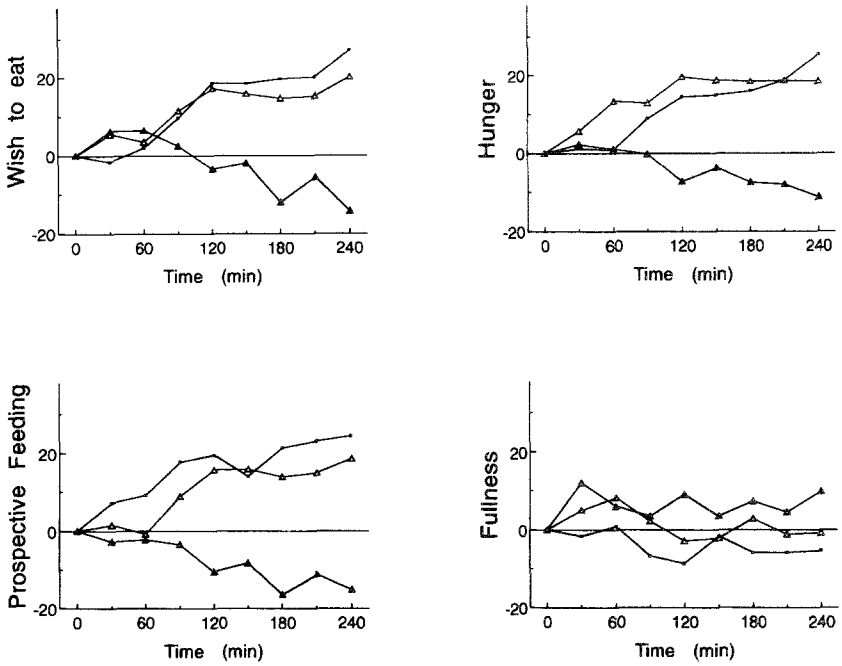

Fig 3. Mean VAS ratings (mm) for the wish to eat, prospective feeding intentions, and feelings of hunger and fullness in 6 healthy subjects during HG (▲) or HI (△) compared with saline infusion (■).

satiety.[10,13,14] Nicolaïdes and Rowland[13] showed that in rats the reduction in oral food intake by long-term IV glucose infusion is augmented when insulin is coinfused. This has also been demonstrated for short-term infusion periods.[14] These results point to a potentiating effect of insulin on hyperglycemia-induced satiety. Woods et al[10] investigated the effects of chronic (2 to 3 weeks) HG (endogenous insulin) and HI (exogenous insulin) in baboons. In their study, daily oral food intake was reduced to the same extent during both conditions. In contrast, using a nonpaired study design, Rodin et al[8] investigated the short-term satiating effects of acute hyperglycemia and insulin-induced hypoglycemia in humans. Hunger feelings and subsequent oral food intake were significantly increased during both hyperglycemia and hypoglycemia. These data suggest that insulin may increase appetite in humans. Lavin et al[9] compared the effect of IV versus intraduodenal administration of glucose on satiety ratings in humans. Intraduodenal glucose potently stimulated endogenous insulin release, increased feelings of fullness, and suppressed hunger feelings. IV glucose induced only a modest insulin release and had no effect on satiety ratings. These investigators suggest that insulin, not glucose, is involved in the regulation of satiety.[9] In another study, insulin combined with an infusion of glucose to mimic postprandial levels did not have any effect on food intake.[11]

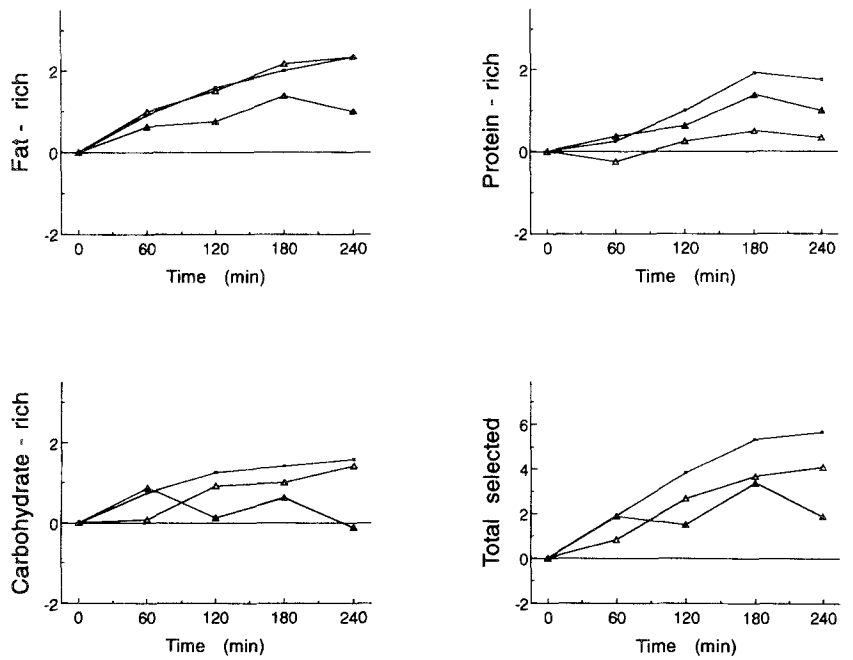

Fig 4. Mean FSL ratings (amount of items chosen) for fat-rich, protein-rich, carbohydrate-rich, and total caloric items in 6 healthy subjects during HG (▲) or HI (△) compared with saline infusion (■).

The reasons for the discrepancy between previous studies and our findings are not apparent. Differences in study design may offer an explanation. First, in the present study, satiety ratings were scored in the same group of subjects over a longer period. Second, in the aforementioned studies,[8,9] plasma glucose remained at less than 10 mmol/L, whereas acute hyperglycemia at 15 mmol/L was obtained in the present study. A dose-dependent effect of glucose on satiety cannot be excluded.

The mechanisms responsible for the inhibitory effect of hyperglycemia on short-term satiety are poorly understood. One argument is related to the effect of hyperglycemia on gastrointestinal function. Hyperglycemia impairs gastrointestinal transit, especially gastric emptying.[4] However, recent studies indicate that insulin may be involved in mediating this inhibitory effect of glucose, since gastric emptying is delayed during HI.[22] Furthermore, in the present study, satiety was scored during fasting conditions. Increased feelings of fullness were not observed during any of the three experiments. Therefore, changes in gastric emptying cannot explain the present findings. One remaining possibility is that glucose has a direct effect on certain hypothalamic satiety areas.[23,24]

In summary, the present study suggests that in humans acute hyperglycemia with endogenous hyperinsulinemia induces satiety. Since exogenous hyperinsulinemia during euglycemic conditions had no effect on appetite, this satiating effect of hyperglycemia is probably not mediated by insulin, although a potentiating effect of endogenous insulin on hyperglycemia-induced satiety cannot be excluded.

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