Modulation of Food Intake by Glucose in Patients With Type 2 Diabetes

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OBJECTIVE — A gain in body weight is a common adverse effect of glucose-lowering therapies in patients with type 2 diabetes, the mechanisms of which are not completely understood. Blood glucose is considered to play a crucial role in the regulation of food intake. On this background, we hypothesized that a short-term reduction of blood glucose concentration to normal values acutely increases food intake in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — To test this hypothesis, 12 patients with type 2 diabetes were examined twice, once during a euglycemic (5.0 mmol/l) clamp experiment and another time during a hyperglycemic (10.5 mmol/l) clamp. The experiments were performed in a single-blind fashion with the order of conditions balanced across patients. On both clamp conditions, insulin was infused at a constant rate of 2.5 mU/kg per min for 125 min. Simultaneously, a glucose solution was infused at a variable rate to achieve target glycemic levels. During the final 30 min of the clamps, the patients were allowed to eat as much as they liked from a standard breakfast buffet.

RESULTS — Compared with the hyperglycemic condition, the patients ingested on average 25 ± 10% more energy during euglycemia (645 ± 75 vs. 483 ± 37 kcal; $P = 0.029$). The increased energy intake during euglycemia was equally distributed across macronutrient components, i.e., during euglycemia the patients ate more carbohydrates (+27.1 ± 11.4%; $P = 0.037$), fat (+22.5 ± 10.0%; $P = 0.046$), and proteins (+25.2 ± 11.2%; $P = 0.046$) than during hyperglycemia. Circulating levels of insulin, amylin, leptin, ghrelin, and glucagon-like peptide-1 did not differ between the euglycemic and hyperglycemia clamp, excluding a major contribution of these hormones to the difference in food intake. Summing up the glucose administered intravenously and the food ingested yielded a remarkably similar total energy influx in both conditions (794 ± 64 vs. 790 ± 53 kcal; $P = 0.961$).

CONCLUSIONS — Together our data suggest that total energy supply to the organism is tightly regulated on a short-term basis independent of the route of influx. Alternatively, it can be hypothesized that euglycemia stimulated or that hyperglycemia suppressed food intake at the subsequent buffet meal in our type 2 diabetic patients. Regardless of these different interpretations, our data indicate an important regulatory role of glucose for food intake in type 2 diabetic patients that is of considerable clinical relevance.

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Improved glycemic control in patients with type 2 diabetes is frequently associated with body weight gain. Except for metformin, which reduces food intake (1–7), all other agents lowering blood glucose, including sulfonylurea, thiazolidinediones, and insulin, have been found to increase body weight (8,9). Lowering the pathologically elevated blood glucose levels in diabetic patients leads to a distinct reduction of glucosuria and the basal metabolic rate (2). This certainly contributes to a positive energy balance, but it is unlikely that it explains the full extent of weight gain during effective diabetes therapy. Increased food intake probably represents another factor that further adds to the treatment-associated increase in body weight, and this could well be triggered by the reduced level of blood glucose. However, given the methodical limitations to reliably assess energy intake in type 2 diabetic patients (10), this hypothesis has not yet been tested.

About 50 years ago, Mayer et al. (11) formulated the glucostatic theory, which proposed blood glucose concentration to represent a major signal in the regulation of eating behavior. Meanwhile, many other factors influencing food intake, such as leptin, insulin, and ghrelin, have been identified, and these findings yielded the insight that the regulation of hunger and satiety involves complex and redundant pathways to the central nervous system (12,13). In light of the many newly discovered signals, the potential role of glucose for the regulation of food intake became disregarded. New interest in glucose derived from the recent identification of hypothalamic glucose sensors that are tightly linked to central nervous and neuroendocrine pathways of body weight regulation (14,15). Campfield and Smith (17,20) recently formulated an innovative pattern detection and recognition theory of food intake that was largely based on their findings in rats (16,17) and in humans (18,19) indicating a prominent association of blood glucose dynamics and meal initiation (20). Also, Peters et al. (21) proposed a theoretical model in which food intake is primarily a function of the brain's glucose demand.

With regard to the gain in body weight associated with blood glucose–lowering therapies in type 2 diabetic patients, the influence of glucose on eating behavior is especially relevant. Low blood glucose levels within the hypoglycemic range are well known to be associated with profound feelings of hunger (22). There is compelling evidence that patients, even with well-controlled type 2 diabetes, feel hypoglycemic and exhibit an increase in counterregulatory hormones at blood glucose levels within the

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Abbreviations: GLP-1, glucagon-like peptide-1.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Composition of the standard breakfast buffet*

	Weight (g)	Energy (kcal)	Carbohydrates (g)	Proteins (g)	Fat (g)
3 whole-grain rolls	150	368.3	72.3	10.8	3
2 slices of whole-grain bread	120	257.6	46.3	8	3.8
Margarine	60	220.8	—	—	24
Jam	60	147.6	36	—	—
Low-fat curd	40	23.88	1.2	4.4	0.1
4 slices of poultry sausage	80	167.5	—	12.8	12.5
4 slices of cheese	80	258.6	—	20	19.2
Cheese spread	17	55.8	4.7	1.5	3.3
Fruit curd	125	118.2	11.3	6.3	5
Condensated milk	15	15.36	1.4	1	0.6
Total	747	1633.6	173.2	64.8	71.5

Note: The breakfast buffet was served with coffee or tea.

normal range, i.e., euglycemia. In combination, these data suggest a distinct elevation of the central nervous set point of glucose in these patients (23). On this background, we hypothesized that decreasing blood glucose concentration to normal levels increases hunger and, consecutively, food intake in type 2 diabetic patients.

In an attempt to test this hypothesis, we studied eating behavior in 12 type 2 diabetic patients during systematic manipulation of blood glucose concentrations by using the glucose clamp technique. Caloric intake was assessed once after acute induction of euglycemia (blood glucose: 5.0 mmol/l) and another time after induction of hyperglycemia (10.5 mmol/l). Since insulin has previously been shown in healthy subjects to affect hunger (24), identical amounts of insulin were infused in both conditions. In order to assess a potential influence of the clamp procedure on other factors regulating food intake, serum leptin, plasma amylin, ghrelin, and glucagon-like peptide-1 (GLP-1) levels were measured repeatedly during the clamps.

RESEARCH DESIGN AND METHODS

— Twelve patients with type 2 diabetes were studied (5 men and 7 women). Patients' characteristics were as follows (means ± SE [range]): age 55.3 ± 2.9 years (39–69), BMI 30.1 ± 1.8 kg/m^2 (21.5–40.7), known diabetes duration 11 ± 2 years (3–25), HbA_{1c} 9.0 ± 0.5% (7.0–14.2, upper limit of the reference range 6.7). For treatment of diabetes, 10 patients received insulin at a dose of 52 ± 14 units/day (16–168), with 6 of these patients following a multiple injection regimen. Metformin was taken by eight and sulfonylureas by two of the patients. The subjects were instructed not to take these oral hypoglycemic agents in the morning before the experiments. Each patient gave written informed consent, and the study was approved by the local ethics committee.

Each patient was tested twice, once during a euglycemic clamp and another time during a hyperglycemic clamp. The study was performed in a single-blind cross-over design with the order of conditions balanced across patients. The time interval between the experimental sessions was at least 1 week. The patients were not informed that the main outcome variable of the study was the amount of ingested food, since this information could have influenced eating behavior. Instead, they were told that the study aimed to assess the influence of blood glucose concentration on several metabolic and endocrine parameters. For the same reason, we refrained from assessing feelings of hunger and satiety by ratings to avoid subjects paying undue attention to their eating behavior.

On the days of the experiments, subjects reported to the medical research unit at 6:30 A.M. Eating as well as the ingestion of caloric drinks was allowed until 10:00 A.M. on the preceding day but not thereafter. The patients who were on insulin therapy received their regular dose of long-acting but not short-acting insulin subcutaneously immediately after reporting to the laboratory. The experiments took place in a sound-attenuated room with the patients sitting with his/her trunk in an almost upright position (~60°) and his/her legs in a horizontal position on a bed. A cannula was inserted into a vein on the back of the hand, which was placed in a heated box (50–55°C) to obtain arterialized venous blood. A second cannula was inserted into an antecubital vein of the contralateral arm. Both cannulae were connected to long thin tubes, which enabled blood sampling and adjustment of the rate of glucose infusion from an adjacent room without awareness of the patient. With this experimental setting we were able to keep the patients completely unaware of their respective blood glucose levels throughout the clamps.

After a 30-min baseline period starting at 7:30 A.M., subjects received a bolus injection of regular human insulin (Aventis, Bad Soden, Germany) at a dose of 0.02 units/kg body wt followed by a constant rate infusion of insulin (2.5 mU · kg body wt^{-1} · min^{-1}) during the next 125 min. Arterialized blood was drawn at 5-min intervals to measure glucose concentration (Glucose Analyser; Beckman Coulter, Munich, Germany). A 20% glucose solution was simultaneously infused at a variable rate to control plasma glucose levels. The target glycemic level was 5.0 mmol/l during the euglycemic clamp and 10.5 mmol/l during the hyperglycemic clamp. Blood samples for determination of serum or plasma levels of insulin, C-peptide, leptin, and ghrelin were collected every 30 min throughout the experiments.

Ninety minutes after the beginning of the clamp (9:30 A.M.), a typical German breakfast buffet of a total of 1,633.6 kcal was offered (Table 1). The patients were instructed to eat as much as they wanted during the next 30 min (i.e., until the end of the clamp) and told they did not have to worry about their blood glucose level since it would be controlled by insulin infusion for the next 3 h. After the clamp, blood glucose was monitored for at least 2.5 h until stable levels between 4.5 and 11.0 mg/dl were achieved.

Assays

Serum insulin, C-peptide, amylin, and leptin concentrations were assessed using enzyme-linked immunosorbent assays (insulin: Dako Cytomation, Cambridgeshire, U.K.; interassay coefficient of variation [CV] 7.5%, intra-assay CV 6.7%; C-peptide: Dako Cytomation; interassay CV 5.2%, intra-assay CV 4.7%; amylin: Linco Research, St. Charles, MO; interassay CV 15.4%, intra-assay CV 8.2%; leptin: Diagnostic Systems Laboratories, Sinsheim, Germany; interassay CV 4.4%, intra-assay CV 3.8%). For determination of total plasma GLP-1 as well as

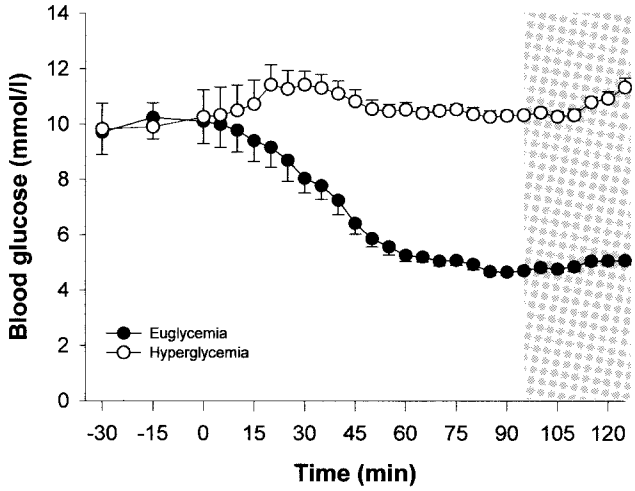

Figure 1—*Mean ± SE blood glucose concentrations during the baseline period (−30 to 0 min) and the euglycemic (●) and hyperglycemic (○) clamp (0–125 min) performed in 12 patients with type 2 diabetes. Gray area indicates the time period when the patients were allowed to eat.*

total plasma ghrelin levels, blood was collected in prefilled tubes containing EDTA (1 mg/ml) and aprotinin (500 units/ml) and than assessed using commercial radioimmunoassay (Linco Research; GLP-1: interassay CV 22%, intra-assay CV 23%; ghrelin: interassay CV 14.7%, intra-assay CV 10%).

Statistical analysis

Data are reported as means ± SE. Statistical analyses were generally based on repeated-measures ANOVA including factors for the condition (hyperglycemia versus euglycemia) and the multiple measurements during the clamps. For subsequent pairwise comparisons, Student's *t* test was used. To determine whether differences in food intake between the euglycemic and hyperglycemic condition were correlated with other patient variables, Pearson's correlation coefficients were calculated. A P value <0.05 was considered significant.

RESULTS

Blood glucose

Fasting blood glucose concentrations were nearly identical during the baseline periods before the euglycemic and hyperglycemic clamps (9.7 ± 0.8 vs. 9.8 ± 0.9 mmol/l). On both conditions, the respective target glycemic plateaus were reached about 45 min after the insulin infusion had started (Fig. 1). Steady-state blood glucose levels were on average 5.2 ± 0.1 mmol/l during the euglycemic clamp and 10.5 ± 0.1 mmol/l during the hyperglycemic clamp. As expected, the total amount of glucose infused during the hyperglycemic clamp was distinctly greater than during the euglycemic clamp (3.5 ± 0.6 vs. 1.8 ± 0.3 kcal/kg body weight; $P = 0.008$).

Food intake

During the euglycemic condition, the patients ingested on average 25 ± 10% (162 ± 65 kcal) more energy than during the hyperglycemic condition (645 ± 75 vs. 483 ± 37 kcal; $P = 0.029$). Separate analyses of ingested macronutrient components revealed that the patients ate significantly more carbohydrates (294 ± 46 vs. 215 ± 89 kcal; $P = 0.037$), proteins (109 ± 11 vs. 82 ± 8 kcal; $P = 0.046$), and fat (241 ± 27 vs. 186 ± 21 kcal; $P = 0.046$) during euglycemia than hyperglycemia. Thus, the percentage of energy ingested as carbohydrates (44 ± 3 vs. 44 ± 4% $P = 0.941$), fat (39 ± 3 vs. 39 ± 3%; $P = 0.882$), and proteins (17 ± 1 vs. 17 ± 1; $P = 0.938$) was remarkably similar for both the euglycemic and hyperglycemic conditions. Interestingly, when the total influx of energy was calculated, summing up the energy ingested by food and infused by glucose, this was almost identical for the euglycemic and hyperglycemic condition (794 ± 64 vs. 790 ± 53 kcal; $P = 0.961$).

The individual differences in total food intake between the euglycemic and hyperglycemic condition did not significantly correlate with the age ($r = -0.452$; $P = 0.168$), BMI ($r = -0.07$; $P = 0.833$), diabetes duration ($r = 0.30$; $P = 0.348$), and HbA_{1c} ($r = 0.02$; $P = 0.950$) in the patients.

Hormones

The courses of insulin, C-peptide, amylin, leptin, ghrelin, and GLP-1 concentrations during the clamps are shown in Fig. 2. In response to insulin infusion, serum insulin levels rapidly increased without any difference in concentrations between the euglycemic and hyperglycemic conditions. No further increase in systemic insulin levels was observed during the period of meal ingestion ($P = 0.388$). In contrast, serum C-peptide levels significantly decreased during the first 95 min of insulin infusion ($P < 0.001$), with this decrease being more pronounced during the euglycemic than hyperglycemic clamp ($P = 0.029$). In response to ingestion of the meal, C-peptide levels significantly increased ($P = 0.002$), and this increase was similar during the hyperglycemic and euglycemic clamp ($P = 0.191$). The courses of plasma amylin concentrations in both conditions paralleled those of C-peptide with a decrease during the first 95 min of the clamps ($P = 0.009$) followed by an increased during-meal ingestion ($P = 0.013$). However, overall there was no significant difference in amylin concentrations between the hyperglycemic and euglycemic conditions ($P = 0.265$).

Serum leptin concentrations on both conditions remained unchanged throughout the clamps. In contrast, plasma ghrelin levels significantly decreased during the first 95 min of insulin infusion ($P = 0.003$) but without any difference in this decrease between the euglycemic and hyperglycemic condition ($P = 0.819$). During ingestion of the meal, changes in plasma levels did not reach significance in the euglycemic ($P = 0.070$) or hyperglycemic ($P = 0.324$) conditions. Plasma GLP-1 concentrations also slightly decreased during the first 95 min of the clamps ($P = 0.015$), again without any difference between the euglycemic and hyperglycemic conditions ($P = 0.573$). This slight decrease of GLP-1 levels was followed by an increase during food intake ($P = 0.045$) that was similar in both conditions ($P = 0.304$).

CONCLUSIONS — The present data show that, in comparison with conditions of moderate hyperglycemia (10.5 mmol/l), during euglycemia (5.0 mmol/l) patients with type 2 diabetes increased their caloric intake from a breakfast buffet by

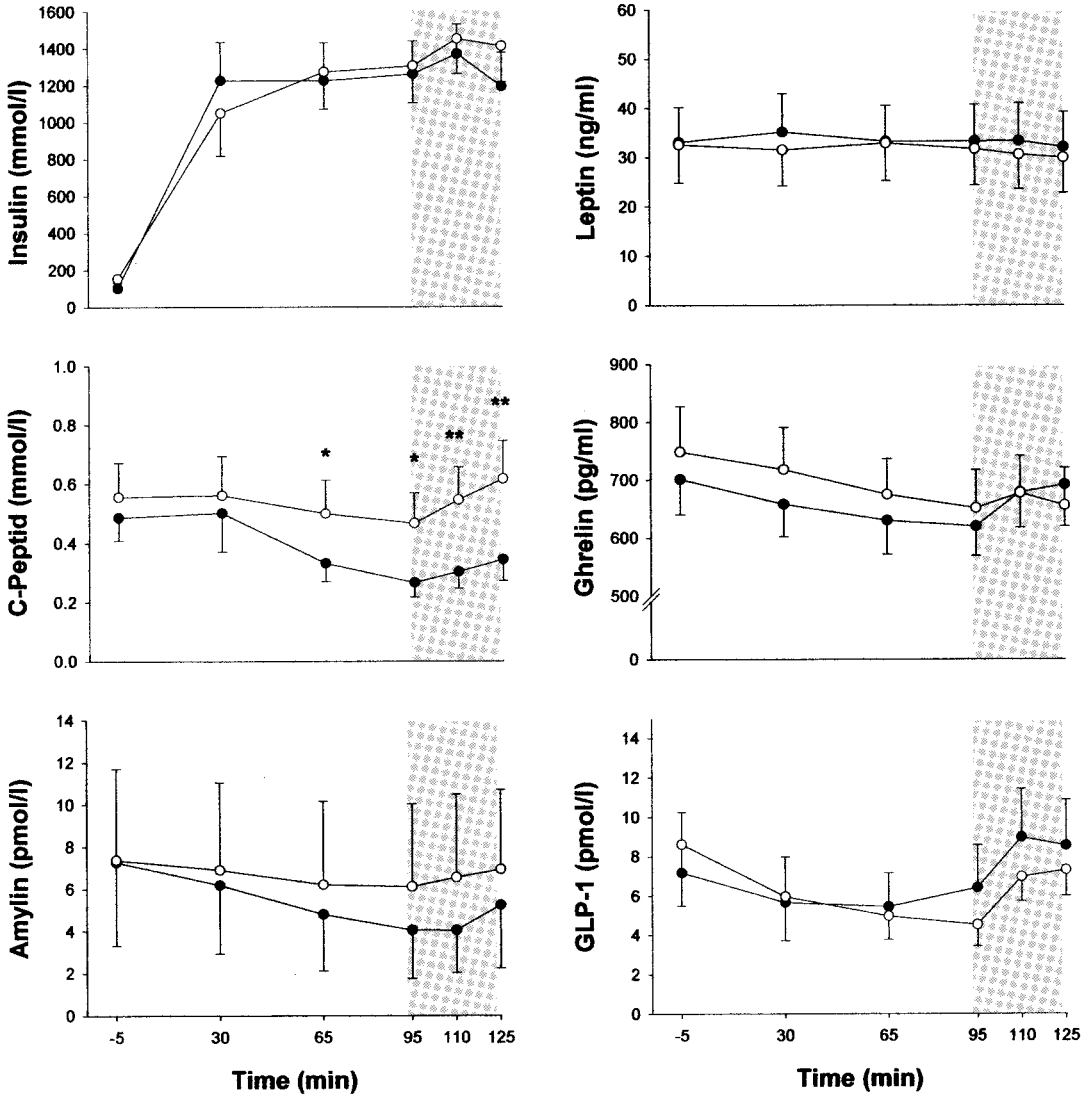

Figure 2—*Mean ± SE serum or plasma concentrations of insulin, C-peptide, amylin, leptin, ghrelin, and GLP-1 during the baseline period and the euglycemic (●) and hyperglycemic (○) clamp. Gray area indicates the time period when the patients were allowed to eat.* *P < *0.05,* **P < *0.01 for pairwise comparisons between the clamp conditions.*

~160 kcal. The increase in caloric intake involved all macronutrient components, i.e., proteins, carbohydrates, and fat, to a similar extent. On the one hand, this result supports the notion that blood glucose is a highly relevant signal to the regulation of food intake. On the other hand, since total energy influx (i.e., the sum of the energy ingested by food and infused by glucose) was virtually identical in the euglycemic and hyperglycemic condition, our data indicate a tight short-term regulation of total caloric intake that may even work independently of the currently sensed blood glucose level.

Central to the interpretation of the results is the question of whether the organism senses the influx of energy after intravenous infusion of glucose separately from sensing the signal of increased blood glucose concentrations itself. If total energy influx is the regulated variable, glucose infusion could act by generating a different satiety signal to adjust food intake. In order to explore this possibility, we assessed several candidates that are most likely involved in signaling satiety, such as insulin, amylin, leptin, ghrelin, and GLP-1. However, none of these hormones showed any changes depending on whether euglycemia or hyperglycemia was induced in our patients. This finding renders a mediation of the observed differences in food intake between conditions by these hormonal factors unlikely. However, it is still possible that other hormones and metabolic factors not measured here, such as the glucose-dependent insulinotropic polypeptide, signaled the amount of energy taken up by glucose infusion to the central nervous centers that regulate food intake.

It could be argued that a mediation of the effects of glucose infusion on food intake via energy supply and via mechanisms sensing hyperglycemia could be dissociated in the present study by including an additional saline (sham) infusion control condition. Unfortunately, such a control would introduce another confound, since circulating insulin concentrations in this condition are clearly lower than those during the hyperinsulinemic-hyperglycemic conditions of our experiments, and insulin per se is well known to suppress hunger (24), although a mediation of acute changes in food in-

take by insulin on a meal-to-meal basis has not been demonstrated in humans. Accordingly, here we refrained from such a control condition.

The alternative hypothesis is that the difference in food intake between the euglycemic and hyperglycemic condition originated directly from sensing blood glucose concentrations. Hypothalamic glucose sensors are tightly linked with central nervous networks regulating energy homeostasis (14). Additional glucose sensors are localized in the portal vein (25,26) and carotid body (27,28), which via afferent fibers to the hypothalamus and other brain areas can likewise influence eating behavior. It is worth mentioning in this context that in a stepwise hypoglycemic clamp study, we have recently shown that even slightly lowering plasma glucose levels to 4.1 mmol/l in comparison to a level of 5.2 mmol/l increased feelings of hunger in healthy subjects (29). Interestingly, this increase in hunger occurred at distinctly higher plasma glucose levels than any other symptom typical for hypoglycemia and also before the increase in counterregulatory hormones. Apart from directly influencing the central nervous centers regulating energy homeostasis, blood glucose concentration could have also modulated food intake by a peripheral action. Support for this view derives from previous findings showing that hyperglycemia slows gastric emptying (30,31). On this background, an attempt to evaluate gastrointestinal sensations in the present study would have contributed potentially useful information.

While the present study is the first assessing the influence of euglycemia in comparison to hyperglycemia on food intake in type 2 diabetic patients, one foregoing study investigated a similar issue in healthy subjects (32) while another did so in type 1 diabetic patients (33). In healthy subjects, marked hyperglycemia (12.2 mmol/l), as compared with euglycemia (5.0 mmol/l), significantly decreased feelings of hunger. In patients with type 1 diabetes, feelings of satiety were higher after 90 min of hyperglycemia (11.1 mmol/l) than after 90 min of euglycemia (5.0 mmol/l), but food intake did not differ between the hyperglycemic and euglycemic conditions. The latter result appears to contrast with the present findings. However, it should be considered that type 1 diabetic patients are commonly much more trained to control their food intake (to adjust the dose of insulin bolus injection to the meal carbohydrate content) than type 2 diabetic patients. It could well be that the type 1 diabetic patients of that foregoing study exhibited a high level of cognitive control on eating behavior that masked the influence of blood glucose on food intake.

Even more important, there are profound differences in the pathophysiology of type 2 and type 1 diabetes that may also pertain to the influence of blood glucose levels on eating behavior. Support for this view derives from the observation that the glycemic thresholds for symptomatic perceptions of hypoglycemia are frequently shifted toward lower levels in type 1 diabetic patients compared with healthy subjects (34), whereas those in type 2 diabetic patients are, on the contrary, shifted toward higher levels (23). On this background, it is tempting to speculate that changes in blood glucose concentration within the hyper- to normoglycemic range represent potent signals for hunger and food intake in type 2 diabetic patients, whereas the influence of such changes in blood glucose concentration on eating behavior in type 1 diabetes might be shifted to a lower glycemic range. In this context, it should be mentioned that none of our patients reported to feel hypoglycemic during the experiments. However, this observation does not necessarily rule out that hunger was stimulated in our patients even by apparent euglycemia since, as mentioned above, there is some evidence that hunger occurs at a lower glycemic threshold, i.e., higher glucose levels, than other symptoms of hypoglycemia.

In conclusion, our results provide evidence for an acute inhibitory influence of glucose on food intake in patients with type 2 diabetes. This inhibition is released by inducing euglycemia in these patients. It remains to be elucidated whether the influence of glucose infusion involves the generation of secondary signals reflecting total energy influx or whether changes in blood glucose concentration per se represent the relevant signal. In the latter case, blood levels of glucose by modulating eating behavior could play a critical role for the gain in body weight frequently observed during glucose-lowering therapies in type 2 diabetes.

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