

Postprandial Administration of Intranasal Insulin Intensifies Satiety and Reduces Intake of Palatable Snacks in Women

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The role of brain insulin signaling in the control of food intake in humans has not been thoroughly defined. We hypothesized that the hormone contributes to the postprandial regulation of appetite for palatable food, and assessed the effects on appetite and snack intake of postprandial versus fasted intranasal insulin administration to the brain in healthy women. Two groups of subjects were intranasally administered 160 IU insulin or vehicle after lunch. Two hours later, consumption of cookies of varying palatability was measured under the pretext of a taste test. In a control study, the effects of intranasal insulin administered to fasted female subjects were assessed. Compared with placebo, insulin administration in the postprandial but not in the fasted state decreased appetite as well as intake and rated palatability of chocolate chip cookies (the most palatable snack offered). In both experiments, intranasal insulin induced a slight decrease in plasma glucose but did not affect serum insulin concentrations. Data indicate that brain insulin acts as a relevant satiety signal during the postprandial period, in particular reducing the intake of highly palatable food, and impacts peripheral glucose homeostasis. Postprandial intranasal insulin administration might be useful in curtailing overconsumption of snacks with accentuated rewarding value. *Diabetes* 61:782–789, 2012

Observations in animals that the central nervous application of insulin decreases food intake (1,2) have led to the current concept that insulin, which reaches the brain via a receptor-mediated saturable transport (3), acts as a negative feedback signal in the homeostatic regulation of body weight (4). In humans, intranasal administration of the hormone enables the assessment of brain insulin effects in the absence of relevant systemic absorption (5). Thus, intranasal insulin has been shown to reduce food intake after acute administration (6) and to decrease body fat after long-term treatment (7). These effects were observed in men but not in women, which is in accordance with animal studies in which male but not female rats decreased food intake and lost body weight during 24 h of intracerebroventricular insulin administration (2,8). This pattern suggests that the contribution of brain insulin to the control of energy intake displays a certain degree of sex specificity. However, neuroimaging experiments have yielded evidence for food-related

central nervous effects of insulin in women (9–11). These conflicting results highlight the fact that the preconditions and mechanisms of the anorexigenic impact of brain insulin signaling in humans are poorly understood. Notably, the acute reduction in food intake elicited by intranasal insulin administration (6) but also intravenous infusion of the insulin analog detemir (12) in the fasted state was not preceded by changes in self-rated hunger, implying that central nervous insulin exerts its anorexigenic effects via signals that contribute to meal termination and satiety rather than by reducing hunger motivation in fasted subjects (13).

Recent evidence indicates that in addition to acting on homeostatic, i.e., primarily hypothalamic, networks of food intake control, insulin modulates extrahypothalamic neural pathways processing the rewarding aspects of energy intake (14). Also, recalling previous lunch decreases afternoon snack intake in women (15,16), suggesting that the reward component of insulin's satiating impact might be further promoted by the memory-improving effect of the hormone (17). Against this background, we hypothesized that intranasal insulin administration in the postprandial but not in the fasted state decreases subsequent intake of palatable snacks in women, who in this context also served as a model of moderate central nervous insulin sensitivity. We also assumed that the satiating impact of the hormone might be associated with improved recall of previous lunch intake.

RESEARCH DESIGN AND METHODS

Subjects were young healthy women who were taking oral (estrogen dominant, single-phase) contraceptives but were otherwise free of medication and were nonsmokers. All relevant illness was excluded by clinical examination. Habitual eating behavior was assessed via a lifestyle questionnaire on dietary restraint and tendency toward disinhibition (15). In brief, dietary restraint, i.e., the conscious effort to restrict calorie intake to control body weight was assessed using the restraint scale of the Dutch Eating Behavior Questionnaire (18). Only subjects with a score of 2.3, i.e., the median score for European populations (19), or less were included. Tendency toward disinhibition was assessed with the disinhibition scale of the Three Factor Eating Questionnaire (20), with an inclusion score of 8 or less. Subjects were kept unaware of hypothesized treatment effects on food intake and were informed that the experiments concerned the effect of insulin on taste preferences. Participants gave written informed consent to the studies, which conformed to the Declaration of Helsinki and were approved by the local ethics committee. All experiments were performed in a double-blind fashion.

Design and procedure of experiments I and II. For experiment I (Fig. 1A), 30 women were randomly assigned to two groups, insulin and placebo, that were closely comparable regarding age (22.27 ± 0.73 vs. 23.13 ± 0.99 years, $P = 0.49$), BMI (21.47 ± 0.37 vs. 21.13 ± 0.36 kg/m², $P = 0.51$), as well as prescreening scores of dietary restraint (1.71 ± 0.09 vs. 1.68 ± 0.08 , $P = 0.59$) and disinhibition tendency (4.47 ± 0.41 vs. 4.87 ± 0.49 , $P = 0.54$). Each woman participated in one individual experimental session (one participant per session) scheduled not to take place during her menstruation phase. Participants were instructed to abstain from caffeinated and alcoholic beverages after 2000 h on the day preceding the experiment, to have regular breakfast before 0800 h

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See accompanying commentary, p. 773.

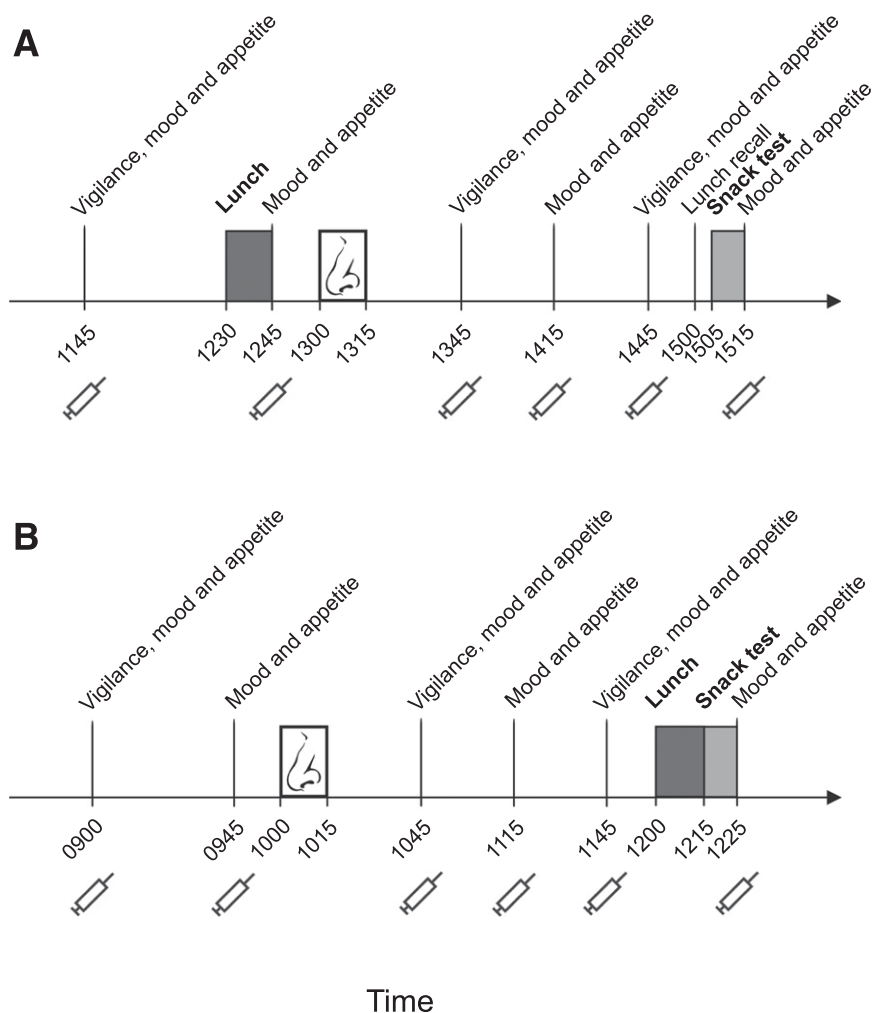


FIG. 1. Experimental procedures. A: In experiment I, healthy young women consumed lunch at 1230 h and were intranasally administered insulin (160 IU; $n = 15$) or placebo ($n = 15$) at 1300 h. At 1500 h, free lunch recall took place, and 5 min later, snack intake was assessed with the participants assuming a taste rating task. Throughout the session, vigilance, mood, appetite, and thirst were assessed, and blood samples were taken (syringe symbols). **B:** In experiment II, insulin and placebo administration, respectively, took place at 1000 h and snack intake was assessed at 1215 h immediately after lunch serving as a preload ($n = 13$). The interval between insulin administration and snack intake assessment was kept constant between both experiments.

of the experimental day and to stay fasted afterward. After arrival at the laboratory around 1100 h, a venous cannula was inserted into the subject's nondominant arm, which was positioned in a heated box (55°C) to enable drawing of arterialized venous blood.

Experimental sessions started around 1145 h with baseline blood sampling and assessments of vigilance, mood, appetite, and thirst. From 1230–1245 h lunch was served, followed at 1300 h by the intranasal administration of 16 0.1-mL puffs (8 per nostril) of insulin or placebo at 60-s intervals, amounting to a total dose of 1.6 mL insulin (160 IU; Insulin Actrapid; Novo Nordisk, Mainz, Germany) or vehicle (6,21). At 1500 h, after a further 2 h of repeated blood sampling and vigilance, mood, appetite, and thirst assessments, participants of both groups were asked to write down as precisely and completely as possible what they had had for lunch. They were left alone for 5 min to do this. Free lunch recall protocols were quantified offline by a person blinded to the respective experimental group. Immediately after lunch recall, snack intake was assessed under the pretext of a cookie taste test. The experiment ended with another assessment of vigilance, mood, appetite, and thirst.

Experiment II (Fig. 1B) was carried out to assess whether the insulin effects observed in experiment I are specific to the postprandial state. A group of 13 women (age, 22.77 ± 0.61 years; BMI, 22.89 ± 0.52 kg/m²; restraint, 2.20 ± 0.07 ; disinhibition, 3.92 ± 0.49) participated in two conditions (insulin and placebo) spaced apart 28 days, ensuring participation on identical days in the menstrual cycle (with the exception of the menstruation phase). The order of conditions was balanced across subjects. After an overnight fast, subjects arrived at the laboratory around 0815 h and, after preparation of blood sampling and baseline measurements, were intranasally administered 160 IU

insulin and placebo, respectively, at 1000 h, i.e., in the fasted state. Two hours later, snack intake was assessed following lunch, which in this instance served as a caloric preload. Substance administration, lunch procedure, snack intake assessment, repeated blood sampling, and behavioral assessments of vigilance, mood, appetite, and thirst were identical to experiment I. In both experiments, interviews at the end of the sessions confirmed that none of the participants had been aware of the purpose of the study.

Lunch and assessment of snack intake. For lunch, the participant was presented with six hot, freshly baked mini pizzas (~400 kcal; flavors "Hawaiian," bacon, cheese, and salami) each cut into quarters to conceal portion size, yielding 24 pieces of pizza. A bottle of still mineral water was also provided. The participant was asked to rate the palatability of the pizzas on a visual analog scale (VAS) anchored at 0 (not palatable) and 100 (highly palatable). Each participant was asked to consume the whole meal, being told that this was "to make the ratings fair."

The snack test at the end of experiments was based on the procedure used by Rogers and Hill (22) and by Higgs and colleagues (15,16). Three plates of cookies were placed on the table, each containing a different variety and labeled Cookie A, B, and C, respectively. The three types were premium spritz cookies, crunchy coconut cookies, and chocolate chip cookies, respectively (Coppentrath, Geeste, Germany; Table 1). Of each variety, 15 cookies broken into bite-sized pieces were provided, allowing for a considerable amount to be eaten without the plates appearing empty to ensure that participants would not restrict cookie intake based on whether the experimenter could see how much had been consumed. In addition, a glass of still mineral water was provided. The participant was instructed to taste and rate each type of cookie on a VAS

TABLE 1
Snack test cookies

	Premium spritz cookies	Crunchy coconut cookies	Chocolate chip cookies
Energy value (kcal/100 g)	537	521	523
Carbohydrate (g/100 g)	61.70	63.90	64.80
Fat (g/100 g)	29.30	27.10	26.40
Protein (g/100 g)	6.60	5.30	6.20

Nutritional values of the snacks offered to the participants during the snack intake test at the end of experiments. All values are according to the manufacturer (Coppentrath, Geeste, Germany).

assessing palatability (0–100). The importance of giving accurate ratings was emphasized and subjects were informed that during and after completion of the rating task they could eat as many cookies as they liked because any remaining cookies would be discarded, and then they were left alone for 10 min. Cookie intake was measured by weighing the cookies before and after the cookie taste test.

Measurements of vigilance, mood, appetite, and thirst. During both experiments, subjects repeatedly performed a simple 5-min PC-based vigilance task. In this task, a digital millisecond counter appeared at random intervals in the middle of the screen, starting at 0 ms to count upwards, and subjects were required to press a key as fast as possible, receiving immediate feedback in the form of the reaction time. For each 5-min task, mean reaction time was registered. Self-reported mood was assessed with 5-point scales covering the categories good/bad mood, alertness/sleepiness, and calmness/agitation (MDBF; 23), and with a checklist containing 123 adjectives assessing mood on 14 dimensions (EWL-K; 24). Appetite and thirst were rated on VASs anchored at 0 and 100. Heart rate and blood pressure were monitored throughout the experimental sessions.

Plasma glucose and hormone concentrations. In both experiments, blood glucose concentrations were monitored online using the HemoCue B-Glucose Analyzer (Ängelholm, Sweden). Blood samples for the subsequent assessment of plasma glucose, serum insulin, and C-peptide (in both experiments) as well as of plasma ACTH and ghrelin and serum cortisol and leptin (experiment I) were centrifuged immediately, and serum and plasma were stored at -20°C . Routine assays were used to determine concentrations of plasma glucose (measured in fluoride plasma according to the hexokinase method [Aeroset; Abbott Diagnostics, North Chicago, IL]); insulin, C-peptide, ACTH, cortisol (all Immulite; DPC, Los Angeles, CA); and total ghrelin and leptin (radioimmunoassay; Millipore, Billerica, MA).

Statistical analysis. Comparisons between the effects of insulin and placebo were based on ANOVA with the between-subjects factor “group” (experiment I) and the within-subjects factor “treatment” (experiment II), respectively, and the factors time or cookie type as appropriate. Significant interaction effects were specified by pairwise *t* tests. All data are presented as means \pm SE. A *P* value < 0.05 was considered significant.

RESULTS

Experiment I: postprandial intranasal insulin administration reduces appetite and intake of palatable snacks. In experiment I, lunch intake induced a sharp decline in rated appetite in both groups ($P < 0.001$ for time; Fig. 2A). Postprandial administration of insulin abrogated the subsequent rise in appetite ratings that slowly emerged in the control group before the snack test ($P = 0.04$ for group \times time). Total cookie intake at 1505 h did not differ between groups (insulin, 244.75 ± 22.94 kcal; placebo, 257.73 ± 17.09 kcal; $P = 0.65$). However, intake of chocolate chip cookies was significantly reduced in the insulin compared with the placebo group (76.11 ± 12.01 vs. 112.74 ± 13.15 kcal, $P = 0.049$; $P = 0.049$ for group \times cookie type), whereas consumption of spritz cookies and coconut cookies was not affected (both $P > 0.29$; Fig. 2B).

Accordingly, although the placebo group consumed more chocolate chip than other cookies ($P = 0.016$), this relation was absent in the insulin group ($P = 0.55$; $P = 0.021$ for the respective group effect). A corresponding pattern was revealed for snack palatability ratings, which globally did not differ between groups ($P = 0.39$; Fig. 2C) but with regard to chocolate chip cookies were distinctly reduced after insulin compared with placebo administration (56.48 ± 5.70 vs. 72.88 ± 3.92 , $P = 0.025$; $P = 0.049$ for group \times cookie type). Thus, chocolate chip cookies were rated significantly more palatable than the remaining cookie types in the placebo ($P = 0.015$) but not in the insulin group ($P = 0.22$; $P = 0.014$ for group effect).

Palatability ratings of the mini pizzas offered for lunch were comparable between the placebo (74.27 ± 5.75) and the insulin groups (75.67 ± 3.48 , $P = 0.84$). Protocols of free lunch recall yielded full data sets for the categories “number of consumed mini pizzas” and “number of pizza types.” Both scores did not differ between groups (placebo vs. insulin, 5.92 ± 0.33 vs. 5.33 ± 0.19 , $P = 0.12$; and 2.85 ± 0.22 vs. 3.00 ± 0.20 , $P = 0.61$, respectively). Throughout the experimental sessions, thirst ratings ($P = 0.50$) and mood according to MDBF (all $P > 0.33$) and EWL-K scales ($P > 0.13$) were comparable between groups, as were reaction times in the vigilance task ($P > 0.68$), heart rate ($P > 0.28$), and blood pressure ($P > 0.53$).

Experiment II: intranasal insulin administration in the fasted state does not affect appetite and snack intake. In experiment II, appetite ratings increased until they dropped after pizza and snack intake, with no differences between conditions ($P = 0.59$ for treatment \times time; Fig. 2D). Snack consumption at 1215 h did not differ regarding total intake (insulin, 355.61 ± 59.12 kcal; placebo, 314.24 ± 30.48 kcal; $P = 0.33$) and intake according to cookie type (all $P > 0.14$; Fig. 2E). Intranasal insulin did not affect palatability ratings globally ($P = 0.12$) nor according to cookie type ($P = 0.74$; Fig. 2F). Across conditions, intake ($P = 0.003$) and palatability ratings ($P = 0.039$) of chocolate chip cookies exceeded those of the remaining types. Palatability ratings of the pizza lunch were comparable between the placebo (75.62 ± 6.59) and the insulin conditions (79.69 ± 2.82 , $P = 0.59$). Insulin treatment likewise did not alter thirst ratings ($P = 0.78$), mood according to MDBF (all $P > 0.28$) and EWL-K scales ($P > 0.09$), vigilance ($P > 0.26$), heart rate ($P > 0.29$), or blood pressure ($P > 0.73$).

Exploratory comparisons between both experiments revealed that neither snack intake ($P = 0.068$) nor rated snack palatability ($P = 0.59$) generally differed between the two groups of experiment I and the subjects of experiment II (collapsed conditions). In both experiments, subjects could not correctly indicate at the end of the session whether they had received insulin or placebo (experiment I, $P = 0.12$; experiment II, $P = 0.69$; χ^2 tests).

Plasma glucose and endocrine parameters. In both experiments, blood parameters did not differ during baseline (all $P > 0.07$). In experiment I, concentrations of plasma glucose ($P = 0.016$ for group \times time) and serum C-peptide ($P = 0.021$) displayed slight reductions in the insulin compared with the placebo group that emerged after intranasal insulin administration but were no longer detectable before the snack test (Fig. 3A and B). Serum insulin ($P = 0.12$) and leptin ($P = 0.11$) were not affected by insulin administration; Fig. 3C and D). Plasma ghrelin concentrations showed the expected postprandial decrease with no significant differences between groups ($P = 0.077$;

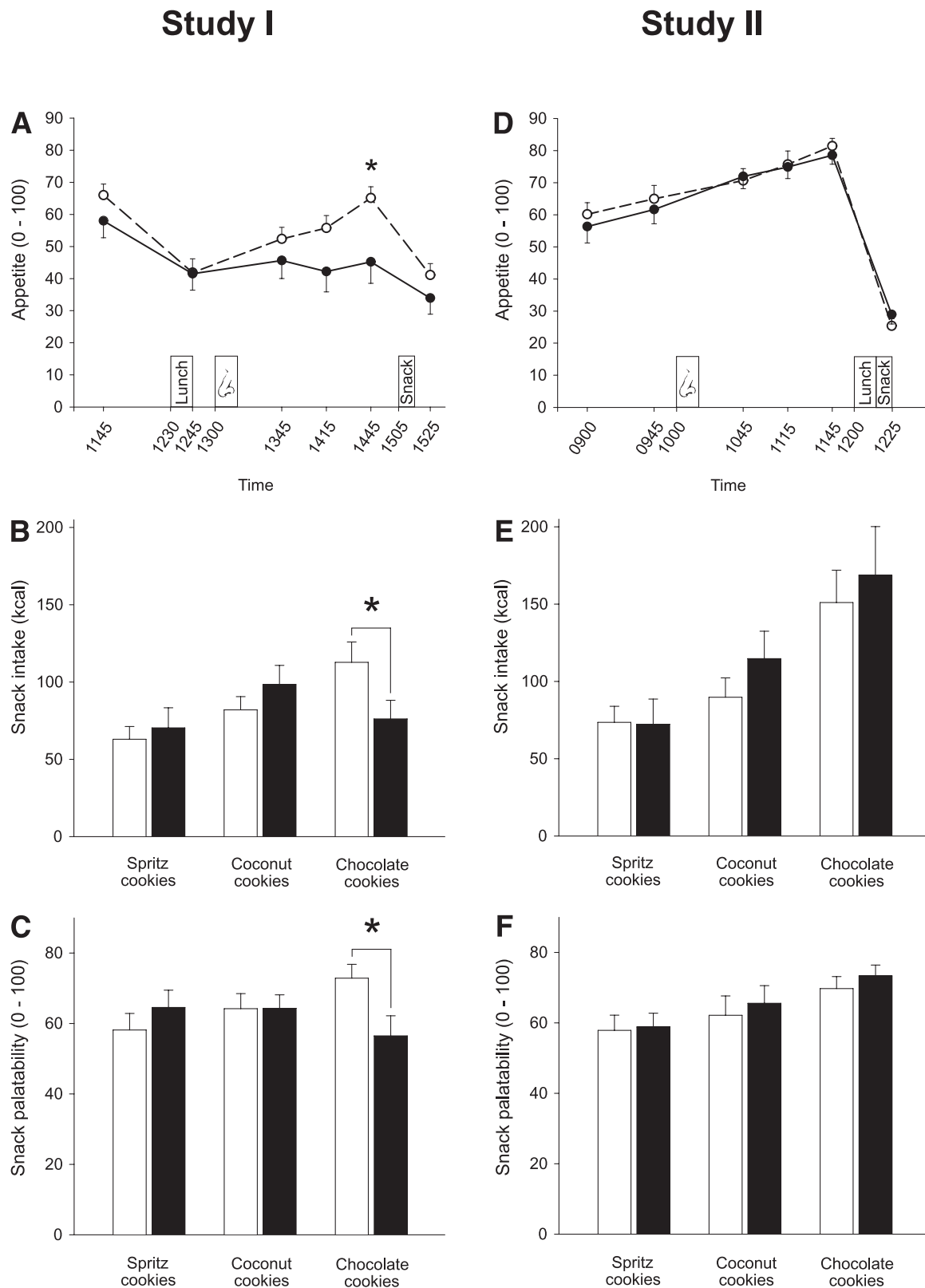


FIG. 2. Appetite and snack intake in experiments I and II. **A:** Appetite rated on visual analog scales anchored at 0 and 100 throughout experiment I in a group of subjects who were intranasally administered insulin (160 IU; black dots and solid lines; $n = 15$) at 1300 h (nose symbol) and a placebo control group (white dots and dashed lines; $n = 15$). Lunch was consumed at 1230 h and snacks were offered at 1505 h. **B:** Snack intake (kcal) assessed at 1505 h under the pretext of a taste rating session in the placebo group (white bars) and the insulin group (black bars) of experiment I. Three different types of cookies were offered. **C:** Snack palatability rated on visual analog scales anchored at 0 (not palatable) and 100 (highly palatable) during the snack test at 1505 h (experiment I). * $P < 0.05$ for comparisons between groups (t tests). **D–F:** Respective results obtained in the 13 subjects of experiment II who were intranasally administered insulin (160 IU; black dots, solid lines) (**D**; nose symbol) and placebo (white dots, dashed lines), respectively, at 1000 h. The snack test took place at 1215 h. Values are means \pm SE.

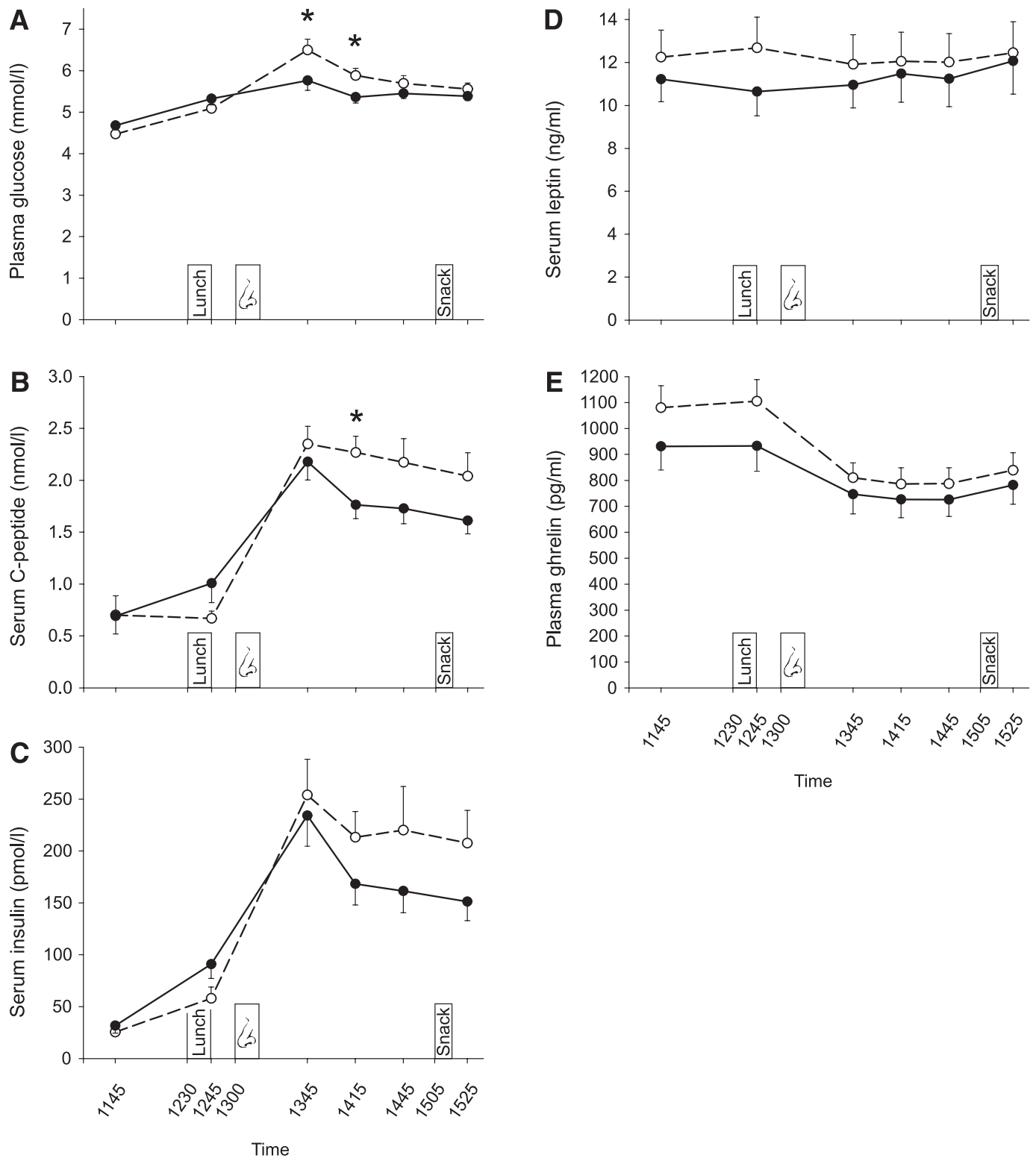


FIG. 3. Plasma glucose and hormonal parameters in experiment I. Concentrations of plasma glucose (A), serum C-peptide (B), serum insulin (C), serum leptin (D), and plasma ghrelin (E) measured throughout experiment I in a group of subjects who were intranasally administered insulin (160 IU; black dots and solid lines; $n = 15$) at 1300 h (nose symbol) and a placebo control group (white dots and dashed lines; $n = 15$). Lunch was consumed at 1230 h, and snacks were offered at 1505 h. Values are means \pm SE. * $P < 0.05$ for comparisons between groups (t tests).

Fig. 3E). Likewise, there were no treatment effects on plasma ACTH ($P = 0.42$) and serum cortisol ($P = 0.70$). In line with experiment I, in experiment II plasma glucose concentrations were slightly reduced following intranasal

($P = 0.031$ for treatment \times time), averaging 4.36 ± 0.09 mmol/L in the insulin and 4.63 ± 0.09 mmol/L in the placebo condition between 1045 h and 1145 h ($P = 0.002$). C-peptide concentrations also decreased following intranasal

insulin ($P = 0.001$ for treatment \times time; 0.30 ± 0.03 vs. 0.42 ± 0.03 nmol/L, $P = 0.001$), whereas serum insulin levels did not differ between conditions ($P = 0.57$).

DISCUSSION

Intranasal insulin administration to the brain has anorexigenic and catabolic properties in male subjects (6,7), but the precise role of the hormone in the acute regulation of food intake in humans has not yet been characterized. By demonstrating that intranasal insulin administration in the postprandial but not in the fasted state reduces appetite and snack intake in women, we provide evidence for the notion that insulin acts as a satiety signal in humans. As the insulin-induced reduction in snack intake was only found for hedonically salient but not for less palatable snacks, our findings moreover suggest that postprandial insulin in particular modulates the reward-related, non-homeostatic control of food intake.

In line with previous results (6,21,25), in both experiments plasma glucose concentrations slightly decreased immediately after intranasal insulin administration but clearly remained within the euglycemic range. It might be speculated that intranasally administered insulin accessing relevant hypothalamic structures acted on the gluco-regulatory brain-liver axis. By opening ATP-sensitive K^+ channels of glucose-responsive hypothalamic neurons (26,27), intracerebroventricularly administered insulin can decrease hepatic glucose production by more than 40% (28) and plasma glucose concentrations by more than 1 mmol/L (27) in rats. These findings are in line with related results in canines (29,30), but discordant canine data (31,32) have sparked controversy about the relevance of brain insulin for peripheral glucose homeostasis in different species. Remarkably, activation of ATP-sensitive K^+ channels by oral diazoxide has most recently been reported to suppress endogenous glucose production in healthy humans (33). Although against this background a centrally mediated effect of intranasal insulin on plasma glucose appears likely (25), more refined measures of peripheral glucose metabolism will be needed to substantiate this conclusion. Also, the decrease in C-peptide concentrations might reflect attenuated secretion of endogenous insulin due to a small ratio of intranasal insulin entering the blood stream via the nasal mucosa (10).

In experiment I, intranasal insulin administered immediately after lunch markedly enhanced the satiating effect of food intake, keeping appetite ratings at postlunch levels, whereas they slowly rose again in the control group, and reducing snack intake from chocolate chip cookies. In contrast, neither appetite nor snacking were affected by insulin administered in the fasted state in experiment II, a finding that replicates our previous results in women (6,21). Importantly, rated lunch and snack palatability as well as overall snack intake did not differ between both experiments, identifying the postprandial timing as the critical determinant of insulin's impact on chocolate chip cookie intake. Thus, although in accordance with experiments in rodents (2,8), women per se are less sensitive to the anorexigenic impact of brain insulin than men who decrease food intake in response to intranasal insulin administration in the fasted state (6), brain insulin feedback can be assumed to exert a satiating effect not only in males but also in females. Although intranasal insulin administration may have enhanced and prolonged the postprandial brain insulin signal (5,34), the sharp postlunch decline in

appetite in conjunction with meal-related insulin secretion observed in the placebo group of experiment I is in accordance with the notion of postprandial insulin acting as a physiological satiating factor. Support for this assumption comes from studies showing that the postprandial surge in circulating insulin is associated with increased satiety and reduced energy intake (35) as well as a reduction in regional cerebral blood flow in the orbitofrontal cortex (36) whose activity predicts feeding behavior, particularly in the fed state (37). Considering that remembering a preceding meal has been previously shown to decrease snack consumption (15,16) and that intranasal insulin improves declarative, hippocampus-dependent memory functions (6,17), experiment I included a free recall of lunch memory which, however, did not yield any signs of insulin-improved meal memory. Although more subtle insulin-induced cognitive changes might have eluded our attention, this finding does not support the assumption that the satiating impact of insulin depends on an improvement of food-specific memory functions.

Of note, the insulin-induced reduction in rated palatability and intake of snacks was restricted to chocolate chip cookies, which according to palatability ratings had the strongest rewarding quality but regarding nutritional values were comparable to the other snacks. This pattern suggests that in addition to promoting satiety, e.g., by enhancing the sensitivity to signals such as cholecystokinin (38), insulin administration also affected nonhomeostatic pathways that mediate reward-related "hedonic" aspects of food intake. Accordingly, in neuroimaging studies in fasted men and women who were presented pictures of food stimuli, intranasal insulin reduced activity of the fusiform gyrus (10), an area that also displays reduced activity during satiation (39) but increased activation when subjects experience food liking or food craving (40). Insulin did not affect general mood in our participants, indicating that the attenuating impact on hedonic processing is food-specific. Although the suppressive effect of central nervous insulin on food intake in general has been repeatedly demonstrated in animals (e.g., 1,2,8), recent experiments have provided a neurophysiological framework for a role of the hormone in hedonic food processing (rev. in 14). Thus, insulin receptors are expressed in dopaminergic neurons of the ventral tegmental area and substantia nigra (41), and brain administration of insulin decreases the rewarding quality of food (42–44) presumably by suppressing mesolimbic dopaminergic signaling (45). Respective experimental paradigms simulate a dessert or between-meal snack experience (46) similar to the present experiments, and it will be important to examine which types of palatable food are subject to insulin's "anhedonic" impact in humans.

In summary, we demonstrate that postprandially administered intranasal insulin enhances the satiating effect of meals and reduces palatable snack intake, suggesting that insulin acts as a relevant signal in the short-term regulation of satiety in humans. Our results were obtained in women, who in comparison with men display generally reduced sensitivity to insulin's anorexigenic brain effect (6,7,21). Thus, postprandial insulin administration might be speculated to also decrease intake of palatable snacks in obesity, which is characterized by central nervous insulin resistance (9,11,47) and a blunted association between postprandial insulin secretion and satiety (35). Considering that the rewarding effect of palatable food overriding the homeostatic control of energy intake may promote obesity (48), insulin's potential to curb the appetite

for hedonically salient, calorie-rich food deserves particular attention.

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M.H., S.H., and H.L. designed the study. M.H., S.H., M.T., and V.O. analyzed the data. M.H. enrolled students and collected data or did experiments for the study. M.H., S.H., M.T., V.O., and H.L. discussed the results and contributed to writing the manuscript. M.H. and S.H. wrote the manuscript. All authors take full responsibility for the contents of the article. M.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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