Intranasal Insulin Suppresses Food Intake via Enhancement of Brain Energy Levels in Humans

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Cerebral insulin exerts anorexic effects in humans and animals. The underlying mechanisms, however, are not clear. Because insulin physiologically facilitates glucose uptake by most tissues of the body and thereby fosters intracellular energy supply, we hypothesized that intranasal insulin reduces food consumption via enhancement of the neuroenergetic level. In a double-blind, placebo–controlled, within-subject comparison, 15 healthy men (BMI 22.2 ± 0.37 kg/m^2) aged 22–28 years were intranasally administered insulin (40 IU) or placebo after an overnight fast. Cerebral energy metabolism was assessed by ^{31}P magnetic resonance spectroscopy. At 100 min after spray administration, participants consumed ad libitum from a test buffet. Our data show that intranasal insulin increases brain energy (i.e., adenosine triphosphate and phosphocreatine levels). Cerebral energy content correlates inversely with subsequent calorie intake in the control condition. Moreover, the neuroenergetic rise upon insulin administration correlates with the consecutive reduction in free-choice calorie consumption. Brain energy levels may therefore constitute a predictive value for food intake. Given that the brain synchronizes food intake behavior in dependence of its current energetic status, a future challenge in obesity treatment may be to therapeutically influence cerebral energy homeostasis. Intranasal insulin, after optimizing its application schema, seems a promising option in this regard. ***Diabetes*** **61:2261–2268, 2012**

The central nervous system (CNS) gathers information on the body's energy availability from blood glucose and fat stores to adjust food intake behavior (1). Specifically, hypothalamic centers control downstream signaling systems, comprising several peripheral hormones, to balance energy homeostasis and body weight regulation (2–4). In this context, peripherally secreted insulin is part of a negative adiposity feedback loop (2). Experimental intracerebroventricular as well as intranasal administration of insulin into the CNS decreases food intake and body weight (5–9), whereas disruption of the physiologic hormonal feedback loop exerts reverse effects (10). The neurobiologic mechanisms underlying modulatory effects of intracerebral insulin on food consumption and body weight, however, are not entirely clear. Apart from intact brain insulin-signaling, the property of insulin as molecular energy provider facilitating glucose uptake may also be important in this regard because the cerebral energetic status per se seems to play a key role in body weight adjustment (1,11–14). Accordingly, it has been proposed that impairments in brain energy supply induce hypothalamic sensing of an imminent neuroglycopenia that results in chronically activated appetite centers and, ultimately, body weight gain (11,12). Indeed, we have recently provided experimental evidence for this assumption by demonstrating an inverse relationship between cerebral energy content, such as adenosine triphosphate (ATP) and phosphocreatine (PCr) levels, and body mass in humans (15). Compatible with a potential role of insulin in brain energy homeostasis, in vitro studies in rodents measuring the PCr and ATP content in homogenized brain slices and cultured neurons indicate that pharmacologic inhibition of insulin receptor signaling reduces neuronal ATP and PCr formation (16,17) and, vice versa, the intracerebroventricular administration of insulin enhances intracellular PCr content in these experiments (18).

Against this background, we hypothesized that the anorexigenic effects of intracerebral insulin administration are mediated through an increase in cerebral energy levels due to facilitated insulin-dependent glucose uptake and, hence, deactivation of appetite centers. To test this hypothesis, we measured brain ATP and PCr levels by ^{31}P magnetic resonance spectroscopy (^{31}P-MRS) at baseline and repeatedly after the intranasal administration of insulin (40 IU) versus placebo and assessed subsequent food intake in 15 normal-weight men.

RESEARCH DESIGN AND METHODS

Participants. Fifteen normal-weight (BMI 22.2 ± 0.37 kg/m^2) healthy men aged 24.6 ± 1.3 years (range 22–28) participated in the experiments. All subjects had a regular sleep-wake cycle 4 weeks before testing. Exclusion criteria were acute or chronic internal, neurologic, or psychiatric diseases, diabetes mellitus in first-degree family members, alcohol or drug abuse, smoking, shift work, exceptional physical or mental stress, and any kind of medication. Because sleep restriction subsequently increases food intake, participants were instructed not to go to bed later than 2300 h on the days before experimental testing and to abstain from food and caffeine for 12 h before the experiments. The study was conducted in accordance with the Declaration of Helsinki (2000) of the World Medical Association and was approved by the ethics committee of the University of Luebeck. Each participant gave written informed consent before participation.

Study protocol. The study was performed in a randomized, placebo–controlled, double-blind, cross-over design. Each subject was tested on two experimental conditions spaced at least 2 weeks apart. On the days of experimental testing, subjects reported to the Department of Neuroradiology at 0615 h after fasting for at least 8 h. One cannula was inserted into an antecubital vein for blood sampling. Baseline ^{31}P-MRS values were recorded, and insulin or placebo was administered, as described below. Immediately after the administration, a series of five continuous ^{31}P-MRS sequences was started.

At 0830 h, a standardized breakfast buffet was offered from which subjects were allowed to eat ad libitum during the subsequent 40 min (19). Table 1 details the composition of the test buffet. Volunteers were not aware of the hypothesized treatment effects on food intake or that their food intake was measured by weighing buffet components before and after food intake.

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TABLE 1
Composition of the free-choice breakfast buffet

Food	Weight (g)	Energy (kcal)	Carbohydrates (g)	Fat (g)	Protein (g)
Bread rolls	300	719	153	4	8
Whole-grain bread	165	372	71	2	12
White bread	30	75	15	0.40	2
Butter	100	773	0.60	83	0.67
Poultry sausage	40	75	0.13	4	8
Salami sausage	34	120	0.07	10	6
Semi-hard cheese	100	377	0	29	26
Spread cheese	33	87	0.63	8	3
Cream cheese	40	124	1	12	3
Jam	50	152	36	0.08	0.03
Honey	40	127	30	0	0.14
Hazelnut spread	40	142	30	0.32	3
Fruit curd	150	173	23	4	9
Vanilla pudding	125	137	21	4	4
Apple	130	72	15	0.78	0.39
Banana	150	146	32	0.30	2
Strawberry milk	200	171	18	7	7
Whole milk	750	499	36	26	25
Orange juice	400	178	36	1	4
Condensed milk	30	34	3	1	2
Sugar	24	101	24	0	0
Total		4,674	545	197	125

The breakfast buffet was served with tea and coffee.

In addition, to prevent overeating, subjects were allowed to take with them any food remaining afterward. Blood samples were obtained at baseline (0615 and 0645 h), at 5-min (glucose) and 10-min (insulin) intervals during the ^{31}P-MRS sessions, as well as at 10-min (glucose) and 20 min (insulin) intervals before and after breakfast. Feelings of hunger were assessed by a 10-point rating scale (0 = not hungry, 9 = very hungry) (7) at baseline, directly after the spectroscopy session, and after breakfast.

Intranasal spray administration. Test substances were applied by intranasal spray. Each subject was administered four puffs of insulin or placebo at 60-s intervals. Each puff consisted of 0.1 mL solution containing 10 IU of insulin (100 IU/mL; Insulin Actrapid; Novo Nordisk, Mainz, Germany) or 0.1 mL vehicle (HOE 31 dilution buffer for H-Insulin; Aventis Pharma, Bad Soden, Germany). The insulin and placebo doses were applied in a randomized order alternately into the right and left nostril. Test substances were administered by precision air pumps (Aero Pump, Hochheim, Germany) that fill the nasal cavity with aerosol, enabling the solution to effectively target the olfactory epithelium.

The dosage of intranasal insulin used here (40 IU) is the lowest dosage that has previously been shown to reduce body weight (8) and to double the insulin concentration in the cerebrospinal fluid without lowering plasma glucose values (20), whereas intranasal administration of 160 IU induces a transient increase in serum insulin levels accompanied by a slight drop in plasma glucose (7,21).

^{31}P-MRS measurements. ^{31}P-MRS measurements of the motor cortex were taken in a 3.0 Tesla MR scanner (Achieva 3T, Philips Medical Systems, Best, the Netherlands) using a double-tuned ^{1}H/^{31}P-headcoil (Advanced Imaging Research Inc., Cleveland, OH). Six ^{31}P-MRS sequences were measured as described in the study protocol. To reach a sufficient relaxation of the phosphorus metabolites, we chose a repetition time of 4,500 ms together with a three-dimensional chemical shift imaging (3D-CSI) sequence ($6 \times 5 \times 3$ voxel, 6-kHz bandwidth, 1,024 data points, 8:51-min measuring time). For better spectral resolution ^{1}H-decoupling during excitation, nuclear Overhauser effect (22) with a broadband proton decoupling during excitation (10 rectangular radio-frequency pulses at proton resonance frequency of 10-ms duration and 10-ms delay between each other to generate a 90° flip angle on the ^{1}H nuclei), and ^{1}H-decoupling during receiving (wideband alternating-phase technique for zero-residual splitting) (23) was applied using the second channel of the head coil for transmitting on the ^{1}H-resonance frequency. Magnetic Resonance User Interface (MRUI) software was used for evaluation of the spectral data. Zerofilling to 4,096 data points and apodizing by a 20-Hz Lorentzian filter was applied. Peak positions and intensities were calculated by the AMARES (advanced method for accurate, robust, and efficient spectral fitting) algorithm (23).

We examined the high-energy phosphate compounds ATP and PCr directly reflecting the overall high-energy phosphate turnover (24). PCr represents a high-energy reservoir linked to ATP in a bidirectional reaction in which ATP is formed by PCr and vice versa, catalyzed by the creatine phosphokinase, at a PCr-to-ATP molar ratio of 1:1. ATP was calculated as the sum of α-, β-, and γ-ATP. The PCr-to-inorganic phosphate (Pi) and ATP-to-Pi ratios were also evaluated as an indicator of intracellular energy status (15,25,26).

Statistical analysis. Data are presented as mean values ± SEM. Statistical analysis by SPSS software was based on ANOVA for repeated-measurements ANOVA, including the factors "treat" (insulin vs. placebo) and "time" (time points of data collection), as well as the interaction effect between these factors. For pairwise comparisons, the paired Student t test was used. Correlation analysis was performed by bivariate correlation analysis according to Pearson. A value of $P < 0.05$ was considered significant.

RESULTS

At baseline, cerebral PCr and ATP values did not differ between conditions ($P > 0.141$ for ANOVA main effects; Fig. 1*A* and *B* and Table 2). Analysis revealed an early increase in ATP values within the first 10 min after insulin administration ($P < 0.001$ for treat-by-time interaction; Fig. 1*A*), followed by distinctly higher ATP concentrations throughout subsequent ^{31}P-MRS sequences in the insulin condition compared with placebo ($P < 0.001$ for treat-by-time interaction). Similarly, intranasal insulin administration raised the PCr content ($P < 0.001$ for treat-by-time interaction; Fig. 1*B*), which persisted in the insulin condition versus placebo ($P = 0.003$ for treat-by-time interaction).

Baseline ATP-to-Pi and PCr-to-Pi ratios were comparable in both experimental conditions (all $P > 0.415$ for ANOVA main effects; Fig. 1*C* and *D* and Table 2). Results of cerebral high-energy phosphate ratios reflect the observed early rise upon insulin administration in absolute values compared with the placebo condition. In accordance, this enhancement became significant within 10 min after insulin administration ($P = 0.027$; Fig. 1*C*; $P < 0.001$ for treat-by-time interaction, respectively; Fig. 1*D*). Correspondingly, ATP-to-Pi ratios were significantly higher after intranasal insulin administration during the experiments ($P = 0.003$ for treat-by-time interaction). Similarly, PCr-to-Pi content remained significantly higher after intranasal insulin administration throughout the experiments ($P = 0.002$ for treat-by-time interaction).

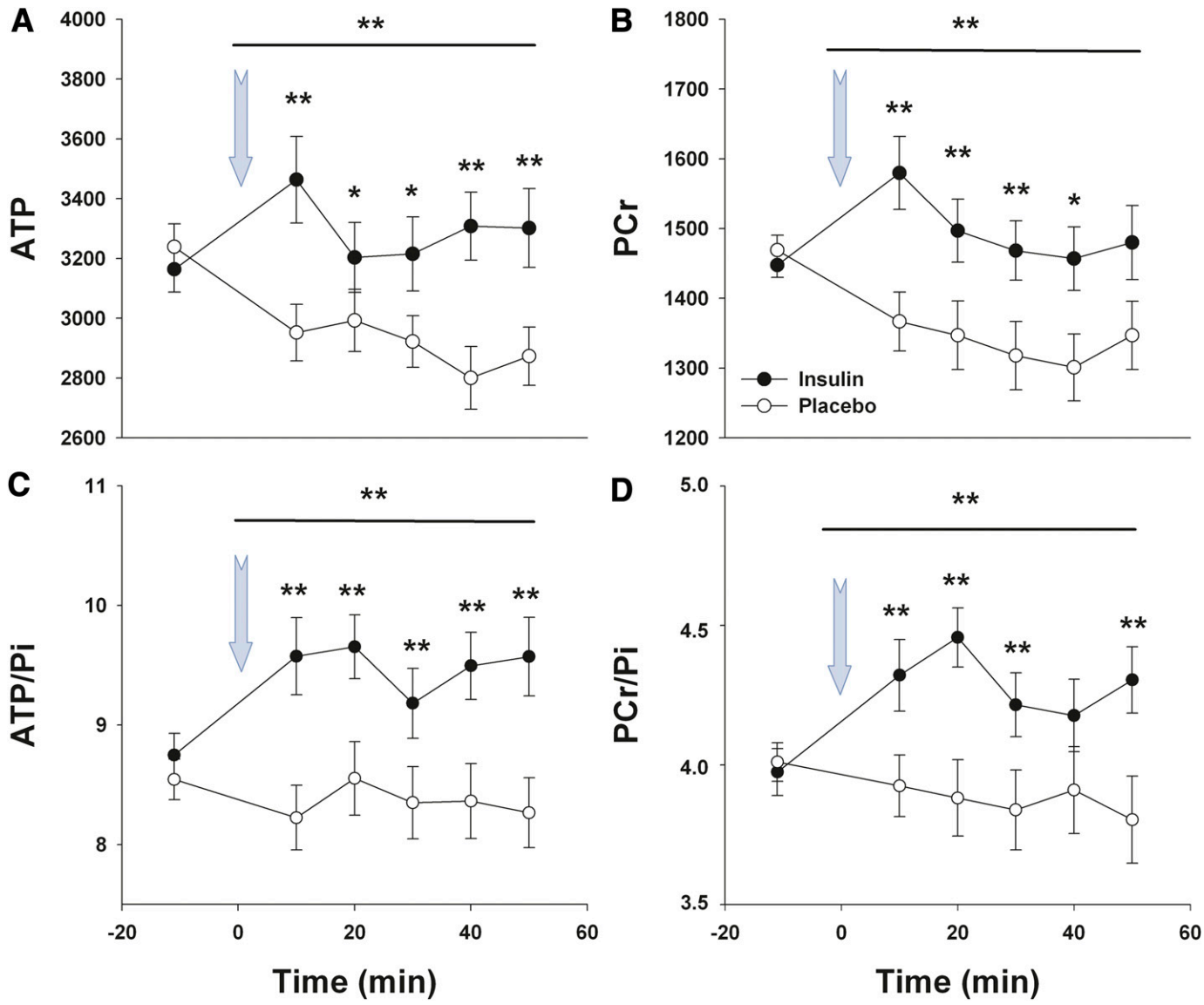

FIG. 1. Effects of intranasal insulin on cerebral energy content. Mean values ± SEM of ATP (*A*), PCr (*B*), ATP-to-Pi ratio (*C*), and PCr-to-Pi ratio (*D*) are shown after the intranasal administration of 40 IU insulin (●) or placebo (○; *n* = 15). Because phosphate values are determined by area under the spectral peak, no units are indicated for high-energy phosphate measurements. **P* ≤ 0.05; ***P* ≤ 0.01. The *arrow* indicates the time of insulin administration.

Baseline plasma glucose values were similar between the insulin (4.43 ± 0.12) and placebo (4.47 ± 0.15) experimental conditions (all $P > 0.838$; Fig. 2*A*). Correspondingly, plasma glucose concentrations were comparable throughout the entire experiments (all $P > 0.473$ for treat-by-time interaction term) and specifically during the ^{31}P-MRS session ($P = 0.865$ for treat main effect; all $P > 0.535$ for treat-by-time interaction term). Respectively, C-peptide and insulin concentrations did not differ at baseline and remained unchanged during the entire experiments (all $P > 0.174$; Fig. 2*B* and *C*).

Figure 3*A*–*D* shows the effects of intranasal insulin administration on food intake. Compared with the placebo condition, insulin significantly reduced total calorie consumption by 11.7% (168.74 ± 54.33 kcal [95% CI −258.27 to −52.20]; $P = 0.008$; Fig. 3*A*). Macronutrient comparisons indicated that this effect was particularly based on lowered carbohydrate (95% CI −151.22 to −19.17; $P = 0.015$; Fig. 3*B*) and protein intake (−53.03 to −8.50; $P = 0.010$; Fig. 3*C*) but not on reduction of fat consumption (−141.37 to 25.52; $P = 0.159$; Fig. 4*D*). Correspondingly, there was a highly significant interaction effect between the factors treatment and macronutrients ($P < 0.001$ for all). Ten-point scale hunger ratings did not differ between conditions at baseline (3.54 ± 0.41 vs. 3.83 ± 0.42; $P = 0.452$), at 60 min after insulin administration (4.86 ± 0.49 vs. 5.01 ± 0.42; $P = 0.353$), or after the end of the meal (0.23 ± 0.11 vs. 0.25 ± 0.10; $P = 0.786$).

Correlation analysis revealed that overall calorie consumption was inversely related to PCr-to-Pi ratio ($r = -0.539$; $P = 0.038$), as well as PCr ($r = -0.599$; $P = 0.018$) and ATP content ($r = -0.620$; $P = 0.014$; Fig. 4*A*–*C*), during the 20-min interval before free-choice food intake in the control condition. Moreover, the gradient of calorie intake reduction upon insulin administration versus placebo correlated with the insulin-induced increase in ATP ($r = -0.591$; $P = 0.020$) and PCr content ($r = -0.629$; $P = 0.012$; Fig. 4*D* and *E*). Such inverse correlation was also reflected by PCr-to-Pi ratios ($r = -0.748$; $P < 0.001$; Fig. 4*F*).

TABLE 2
Cerebral energy as well as Pi content assessed by ^{31}P-MRS

Brain	Baseline	10 min	20 min	30 min	40 min	50 min	*P*		
							Treat	Time	Treat × time
ATP									
Placebo	3,267 ± 80	2,952 ± 93	2,991 ± 106	2,921 ± 90	2,801 ± 112	2,873 ± 104	0.001**	0.052	<0.001**
Insulin	3,164 ± 76	3,439 ± 131	3,203 ± 117	3,208 ± 128	3,307 ± 117	3,301 ± 125			
PCr									
Placebo	1,483 ± 22	1,366 ± 45	1,346 ± 52	1,316 ± 52	1,301 ± 52	1,346 ± 52	0.007**	0.019*	0.003**
Insulin	1,448 ± 18	1,580 ± 52	1,497 ± 45	1,468 ± 43	1,457 ± 46	1,464 ± 50			
Pi									
Placebo	384 ± 10	351 ± 9	349 ± 8	352 ± 8	335 ± 8	341 ± 9	0.680	0.356	0.271
Insulin	377 ± 9	361 ± 14	332 ± 9	352 ± 10	359 ± 10	342 ± 10			
ATP-to-Pi									
Placebo	8.60 ± 0.19	8.22 ± 0.27	8.55 ± 0.33	8.35 ± 0.31	8.36 ± 0.35	8.27 ± 0.29	0.010*	0.361	0.003**
Insulin	8.67 ± 0.19	9.56 ± 0.34	9.64 ± 0.28	9.17 ± 0.31	9.47 ± 0.29	9.50 ± 0.36			
PCr-to-Pi									
Placebo	4.06 ± 0.07	3.95 ± 0.12	3.88 ± 0.15	3.83 ± 0.16	3.97 ± 0.16	3.83 ± 0.17	0.029*	0.125	0.002**
Insulin	3.97 ± 0.08	4.32 ± 0.13	4.46 ± 0.11	4.22 ± 0.11	4.18 ± 0.13	4.31 ± 0.12			

Data are mean values ± SEM. *P* values are derived from ANOVA, including a repeated-measures factor "treat" (insulin vs. placebo) and a factor "time" (including all time points after insulin spray application). Because phosphate values are determined by area under the spectral peak, no units are indicated for high-energy phosphate measurements. *$P \leq 0.05$; **$P \leq 0.01$.

FIG. 2. Concentrations (mean ± SEM) are shown of plasma glucose (*A*), serum insulin (*B*), and serum C-peptide (*C*) before and after the intranasal administration of 40 IU insulin (●) or placebo (○; *n* = 15).

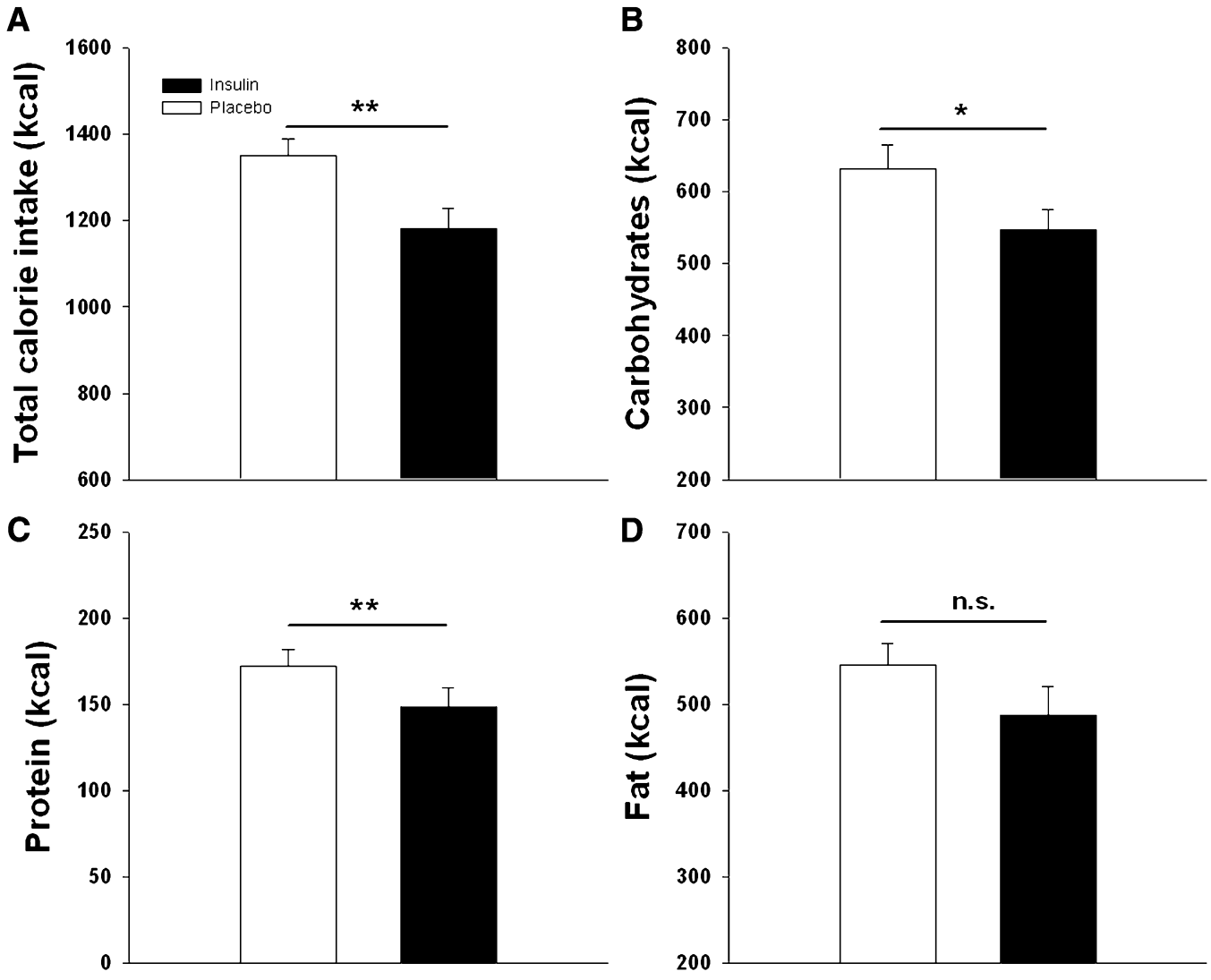

FIG. 3. *A*: **Total calorie consumption from a standardized free-choice breakfast buffet presented 100 min after the intranasal administration of 40 IU insulin (■) or placebo (□; $n = 15$). Itemized analysis is shown of ingested carbohydrates (*B*), protein (*C*), and fat (*D*). *$P \leq 0.05$; **$P \leq 0.01$. n.s., not significant.**

DISCUSSION

We here demonstrate that intranasal insulin administration considerably increases the cerebral high-energy phosphate content compared with placebo in humans. This is in line with previous data indicating that intact insulin receptor-binding increases intracellular ATP levels in vitro (27), whereas disruption of the insulin intracellular postreceptor cascade reduces ATP and PCr formation in brain tissues (16,17).

The mechanisms underlying the observed effects of intranasal insulin on the high-energy phosphate content, however, cannot be clarified by our human in vivo approach. Notwithstanding, there is evidence that brain glucose uptake partially occurs in an insulin-dependent manner (28), and it is well known that the brain uses glucose as a substrate for energy production (29,30). Therefore, one could speculate that intranasal insulin administration may facilitate the brain's energy supply, and hence increases ATP and PCr levels, which, in turn, leads to closure of the ATP-sensitive K^+ channels with subsequent food intake reduction. This reasoning is supported by the inverse relationship between brain energy levels and the amount of subsequent free-choice food consumption in the control condition. The negative relation between high-energy phosphate content and caloric intake suggests that the cerebral energy content predicts food intake in humans and is in line with data showing that ATP and PCr levels are distinctly decreased in obese and increased in low-weight subjects compared with normal-weight control subjects (15). Further support for the assumption that food intake may depend on brain energy content is provided by the correlation between the rise in cerebral high-energy phosphate content upon insulin administration and immediate calorie intake reduction in our study.

Data of insulin administration in our study confirm previous observations of an insulin-induced suppressive impact on food intake behavior (5–7,9). Compared with placebo, intranasal administration of insulin not only reduces total calorie consumption, but specified analysis also reveals that this effect is due to lowered protein and carbohydrate intake. This outcome demonstrates that increasing cerebral insulin levels even exerts an influence on the composition of ingested food. In line with previous

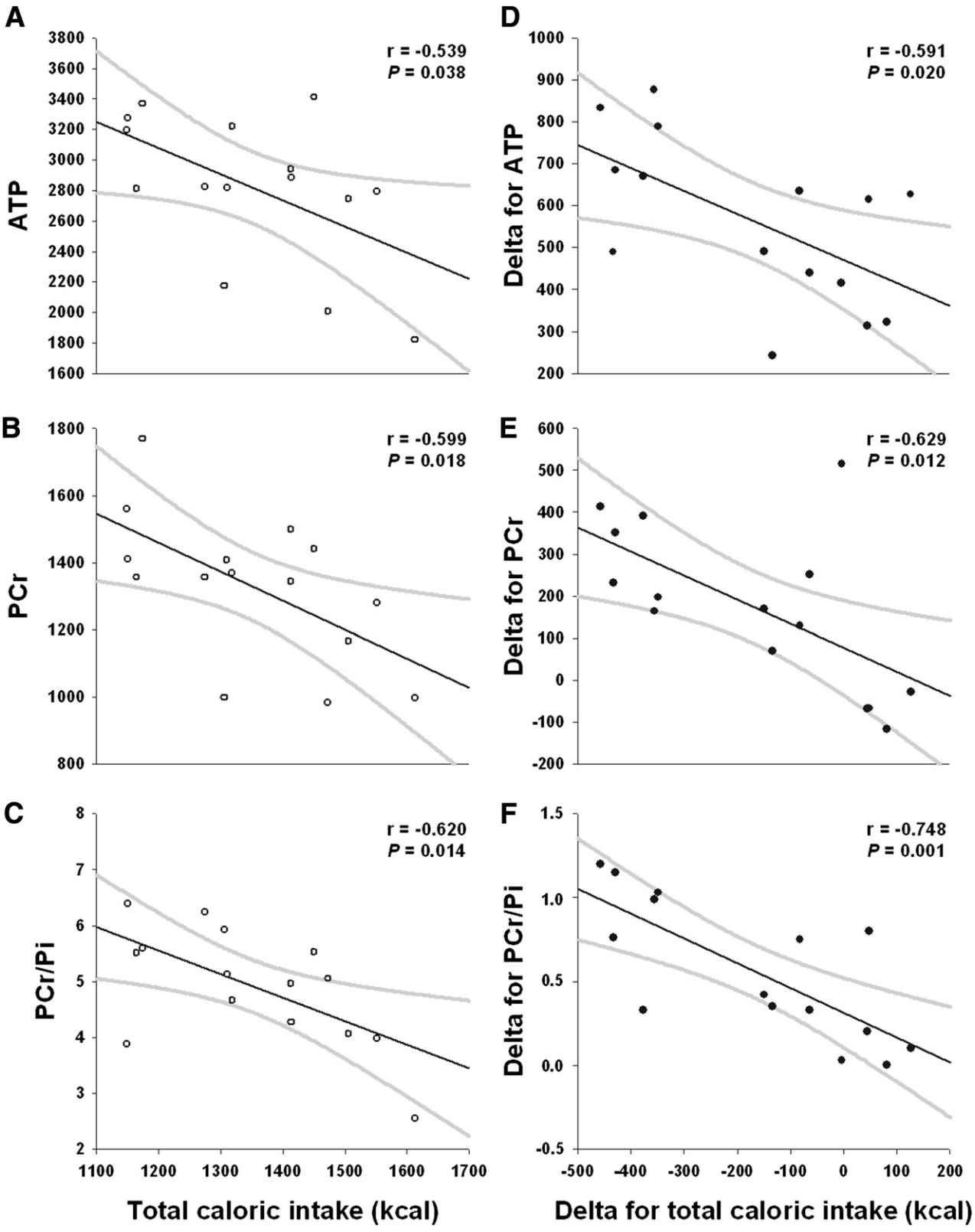

FIG. 4. Relationship between cerebral energy content and caloric consumption. Correlation between mean values of ATP (*A*) and PCr (*B*) content as well as the PCr-to-Pi ratio (*C*) during the last 20-min interval of spectroscopy measurements and subsequent overall calorie consumption in the control condition (○, *n* = 15). Correlation of the rise in ATP (*D*), PCr (*E*), and PCr-to-Pi ratio (*F*) with reduced caloric intake after intranasal insulin administration vs. placebo during the respective spectroscopy interval (●, *n* = 15; bivariate correlation analysis according to Pearson). Projected slope (*black lines*) and 95% CIs (*gray lines*) are shown.

results (7), hunger ratings remained unaffected by intranasal insulin application in this context, suggesting that the suppressive effects of insulin on food intake occur at an unconscious behavioral level.

Overall, our findings suggest that brain energy homeostasis represents one of the mechanisms that underlie the control of appetite and food consumption and are in line with previous data indicating an association between cerebral energy content and BMI (15). Hence, the assumption that the brain's own energy status is crucial for body weight adjustment is further substantiated. Our finding that the high-energy phosphate content of the brain has a predictive value for food intake may be of future relevance against a clinical background. For instance, rigorous calorie-reduced dieting may be counterproductive as a treatment of obesity because caloric reduction even worsens the pre-existing cerebral energy undersupply in obese individuals (15), resulting in the frequently observed ravenousness and therefore the undesirable yo-yo effect after diet cessation. On the basis of this assumption, one could speculate that intranasal insulin administration may be applicable to prevent this neuroenergetic decline and thereby the compensatory postinterventional body weight regain.

Although the results of our study seem to confirm the underlying hypothesis, one could argue that the distribution of intranasally applied insulin within the brain, and therefore its effects on specific brain areas such as hypothalamic appetite centers, are thus far unknown, which may cast some doubt on our reasoning. Nevertheless, the regional distribution of insulin receptors within the CNS argues for more generalized effects of insulin administration on all binding sites identified (4,31) and render obvious that the neuroenergetic rise observed here reflects a change of high-energy phosphate content in the whole brain rather than on circumscript brain areas. Also, given that intranasal insulin administration suppresses appetite and food intake, as observed here and in previous studies (5–7,9), the question arises why therapeutic insulin medication in diabetes does not cause the same effect but, right to the contrary, commonly results in body weight gain (32,33). This discrepancy may be explained by divergent characteristics in energy storage of brain and peripheral tissue targeted by insulin. Within the brain, insulin is an intracellular supplier of glucose with a negligible function for energy storage, although recent data indeed indicate that insulin promotes glycogen synthesis in human astrocytes (34). However, the synthesis and degradation of this glucose-storage molecule occur simultaneously and the net brain glycogen amount within the brain is rather small (35) compared with the liver (36) or skeletal muscles (37). Peripherally, in contrast, insulin leads to excess glucose uptake by fat tissue and therefore fosters body weight gain, which may override its anorexigenic effects within the brain. Certainly of relevance in this context is also the choice of the administered insulin dosage. To prevent intranasal insulin from entering the peripheral blood circulation, as uncovered by a transient increase in circulating insulin and drop in glucose concentrations, which occurred in previous studies applying 160 IU (7,21), we chose the significantly lower dosage of 40 IU. As expected, peripheral glucose metabolism remained unaffected by insulin administration throughout the experiments in our study.

In summary, our data provide evidence for a central role of brain energy metabolism in the regulation of food consumption and uncover an important function of cerebral insulin in humans. Our findings support the hypothesis that the brain synchronizes appetite, food-intake behavior, and body weight control in dependence of its current energetic status. Hence, alterations in CNS energy homeostasis may underlie the development of disturbances in body weight regulation such as obesity. Consequently, one future challenge will be to identify interventions that influence brain energy homeostasis and take advantage of this understanding to cure diseases characterized by body weight dysregulation. In this context, intranasally applied insulin, after optimizing its application schema, may be a potential option to combat overweight and obesity as it "refuels" an energy-deprived brain.

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No potential conflicts of interest relevant to this article were reported.

K.J.-C. conceived and designed the study, collected, analyzed, and interpreted the data, wrote and edited the manuscript, and approved the final version for submission. A.F., M.R., and U.H.M. collected the data, edited the manuscript, and approved the final version for submission. H.G.S.-E. collected and analyzed the data, edited the manuscript, and approved the final version for submission. M.H. conceived and designed the study, interpreted the data, wrote and edited the manuscript, and approved the final version for submission. K.M.O. conceived and designed the study, analyzed and interpreted the data, wrote and edited the manuscript, and approved the final version for submission. K.J.-C. is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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