Exenatide-Induced Reduction in Energy Intake Is Associated With Increase in Hypothalamic Connectivity

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OBJECTIVE—Glucagon-like peptide-1 receptor agonists such as exenatide are known to influence neural activity in the hypothalamus of animals and to reduce energy intake. In humans, however, significant weight loss has been observed in only a subgroup of patients. Why only some individuals respond with weight loss and others do not remains unclear. In this functional magnetic resonance imaging (fMRI) study, we investigated differences in hypothalamic connectivity between "responders" (reduction in energy intake after exenatide infusion) and "nonresponders."

RESEARCH DESIGN AND METHODS—We performed a randomized, double-blinded, placebo-controlled, cross-over fMRI study with intravenous administration of exenatide in obese male volunteers. During brain scanning with continuous exenatide or placebo administration, participants rated food and nonfood images. After each scanning session, energy intake was measured using an ad libitum buffet. Functional hypothalamic connectivity was assessed by eigenvector centrality mapping, a measure of connectedness throughout the brain.

RESULTS—Responders showed significantly higher connectedness of the hypothalamus, which was specific for the food pictures condition, in the exenatide condition compared with placebo. Nonresponders did not show any significant exenatide-induced changes in hypothalamic connectedness.

CONCLUSIONS—Our results demonstrate a central hypothalamic effect of peripherally administered exenatide that occurred only in the group that showed an exenatide-dependent anorexigenic effect. These findings indicate that the hypothalamic response seems to be the crucial factor for the effect of exenatide on energy intake.

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Exenatide is a long-lasting glucagon-like peptide-1 (GLP-1) receptor agonist approved for the treatment of type 2 diabetes (1,2). Single-dose applications of exenatide can increase satiety (3). In a 16-week study, about one-third of nondiabetic people lost weight, one-third remained neutral, and one-third gained weight (4). Animal and in vitro studies have suggested that central nervous mechanisms underlie the action of GLP-1 and exenatide. The GLP-1 receptor is widely expressed in the brain, with the highest concentrations in the hypothalamus (5,6), the homeostatic center of the brain (7,8). It regulates vegetative processes, including body homeostasis and metabolism, sleep, cardiovascular function, thermoregulation, and sexual behavior (9). Homeostatic information about the nutritional state is communicated directly via circulating gastrointestinal (GI) hormones, among others, and indirectly via afferent fibers of the vagal nerve (10,11). Neuroimaging experiments in mice have shown hypothalamic activation after peripheral injections of GLP-1 (12). In rodents, both peripheral and central nervous injections of GLP-1 and exendin-4 (a peptide closely resembling exenatide structurally) reduced energy intake (13), and peripherally injected exendin-4 was able to cross the blood-brain barrier (14). In rats, intraperitoneally administered exendin-4 caused the expression of *c-fos* (a marker for neural activity) in the hypothalamus and in limbic and brainstem structures. These effects were partially abolished by vagotomy, suggesting that both vagal and direct central nervous signaling pathways were involved (15).

In humans, little is known about the central nervous effects of GI peptides because of restrictions in directly investigating brain activity in vivo. In one of the few existing functional magnetic resonance imaging (fMRI) studies, infusion of the anorexigenic peptide YY caused activations in the posterior hypothalamus, the substantia nigra, the parabrachial nucleus of the brainstem, and the ventral tegmental area (16). These regions receive information from the GI tract through direct vagal afference. There are conflicting data regarding whether circulating exenatide is able to cross the blood-brain barrier in humans (10). In fMRI studies applying the orexigenic GI hormone ghrelin (17) and the anorexigenic hormones peptide YY and GLP-1 (18), other human brain areas such as the amygdala, the orbitofrontal cortex, and the insula also have been identified as being involved in the regulation of body homeostasis through GI peptides.

Drugs with different mechanisms of action than the GI peptides also seem to exert their anorexigenic effects via the hypothalamus. In one fMRI study, the serotonin-norepinephrine reuptake

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inhibitor sibutramine reduced energy intake and hunger ratings, caused weight loss, and increased hypothalamic activation in response to visualized food cues (19). Differences in hypothalamic connectedness (a measure of the influence of brain regions on each other that is measured with fMRI) were found between lean and obese people. These differences were reduced after obese people received bariatric surgery and lost weight (20).

Eating behavior can be modeled into a homeostatic part, signals from the body to the brain reflecting the need for energy, and a hedonic part, our pleasure while eating that is mostly independent of energy requirements (10). There is conflicting data as to whether GLP-1 analogs induce their effect on reduction in energy intake by influencing only the homeostatic component of hunger or by influencing the hedonic part as well (21,22).

To investigate the central nervous effects of exenatide on the hypothalamus, we performed fMRI on obese, nondiabetic men in a randomized controlled trial during continuous intravenous administration of exenatide or placebo. Our aim was to identify the potential involvement of the hypothalamus in the regulation of eating behavior by exenatide and to investigate whether previously reported differences in responsiveness to the drug's anorexigenic effects can be explained by variations in central nervous effects. An fMRI paradigm with visual stimulation (food and nonfood pictures) was used to assess brain responses during exenatide versus placebo conditions. To relate the neuroimaging findings to eating behavior, we used an ad libitum buffet to measure energy intake immediately after the fMRI session. Although we primarily tested the effect of exenatide on the homeostatic component of eating behavior, we also studied a potential hedonic effect by assessing the valence of food pictures and the tastiness of the buffet items consumed.

In addition to understanding the central nervous effects of GLP-1 agonists related to eating behavior, it is important to explore further the individual differences in responsiveness with respect to weight loss, a common secondary target of their prescription (23). It is conceivable that a better understanding of the mechanisms underlying weight loss in response to GLP-1 agonists might pave the way for clinical strategies with fewer side effects and greater efficacy.

RESEARCH DESIGN AND METHODS

Participants

We studied 24 male, obese, Caucasian, right-handed, nonsmoking, native German-speaking volunteers without any reported history of neurologic or psychiatric diseases (assessed by interview by a physician and Beck's Depression Inventory score of <18). Participants with diabetes, thyroid disease, or clinically significant abnormalities in routine blood testing were excluded. Mean (±SD) values for anthropometric data include the following: age, 29 ± 7 years (range 18–43 years); weight, 120 ± 18 kg (range 91–155 kg); BMI, 37 ± 5 kg/m^2 (range 30–46 kg/m^2); and waist-to-hip ratio, 1.00 ± 0.05 (range 0.88–1.08). All participants gave informed written consent and the study was approved by the ethics committee of the University of Leipzig and by the German Federal Institute for Drugs and Medical Devices.

Experimental design

The study was placebo-controlled, randomized, and double-blinded. Every participant had 2 study days (separated by 1 week) with infusion of either placebo or exenatide; the rest of the procedures were identical on both days. Participants arrived at the research institute at approximately 10:30 A.M. after at least 5 h of fasting (having skipped the last meal; for exact durations of fast see Supplementary Table 1). After placement of 18-gauge plastic cannulas into both cubital veins (one for drug application, one for blood draws), infusion started at t = 0, and three neuropsychological tests were performed (see ATTENTION AND MOTOR SKILLS TESTS). At t = 110 min, participants were transferred to the MRI scanner. Scanning started at t = 120 min and lasted 45 min. Inside the MRI scanner, participants viewed a screen, placed at the head end of the scanner tunnel, via a mirror attached to the head coil. The scanning session was divided into three blocks lasting 12 min each. Blocks were separated by distractors (attention task lasting 2 min) while the scanner was paused.

In the first block ("resting-state block"), a white cross on a black background was presented ("fixation cross"). Thus, brain activity was recorded in a so-called "resting" or "task-free state" to assess activity patterns of the brain when no (or as little as possible) external input was given. In a second block ("food pictures block"), pictures of food were displayed on the screen (4.5 s each) and participants rated the tastiness of food items using a keypad placed in the participant's right hand. The very left of four keys indicated "very tasty" (4 points); the very right key indicated "not at all tasty" (1 point). Pictures were separated by a 2.5-s intertrial interval. In total, 77 pictures were presented in randomized order. In a third block ("nonfood pictures block"), pictures of objects not related to food or eating were similarly presented and participants were asked, "How much do you like the depicted object?" ("very much," 4 points, to "not at all," 1 point; 77 pictures total). The order of the food pictures block and nonfood pictures block was randomized on positions two and three of all blocks. After the scan, the infusion was stopped (t = 210 min) and participants were transferred to a room with minimal distraction and asked to consume from a standardized ad libitum buffet. Participants were advised to eat "as much as you want to." At t = 240 min the kilocalories consumed were counted and at t = 290 min a final blood draw was performed. Blood draws for the assessment of blood glucose levels were made approximately every 15 min (except during neuropsychological testing, MRI scanning, and eating); blood draws for the assessment of exenatide and insulin serum levels were made at t = 0, 70, 110, 210, 240, and 290 min; visual analog scales (see below) were marked at t = 0, 110, 210, and 240 min.

Medication

Exenatide was obtained from Eli Lilly and Company. Detailed information about the preparation of the study medication is provided in the Supplementary Data. Exenatide was infused at a rate of 0.12 pmol/kg body weight/min. Targeted serum concentrations of approximately 0.1–0.2 ng/mL and infusion rates were selected based on previous studies (24–26) and our own pilot experiments.

Blood sample preparation and laboratory analyses

Blood samples were taken from the medial cubital vein. Detailed information about the preanalytical procedures is provided in the Supplementary Data. Exenatide concentrations were measured with an enzyme immunoassay kit (EK-070–94, Phoenix Pharmaceuticals, Karlsruhe, Germany) according to the manufacturer's instructions.

Visual analog scales

At four measurement intervals (beginning of the experiment, before and after the MRI scan, and after the meal) participants were asked to rate their hunger on a 100-mm visual analog scale ("How hungry do you feel right now?"). The left extreme (0 mm) indicated "not at all hungry"; the right extreme (100 mm) indicated "extremely hungry." Because the main side effect of exenatide is nausea (27), we also asked participants, "How much nausea do you feel right now?" on the same scale: 0 mm indicated "no nausea at all" and 100 mm indicated "extreme nausea." After consumption of the meal we asked, "How tasty was the buffet?" on the same scale: 0 mm indicated "not at all tasty" and 100 mm indicated "extremely tasty."

Attention and motor skills tests

To exclude that any of the obtained results were influenced by differences in attention or motor skills between placebo and exenatide, we performed three additional tests (d2 attention task, *n*-back task, finger tapping test) after 1 h of infusion. Detailed descriptions of the tests performed can be found elsewhere (28–30).

Technical fMRI parameters and data processing

fMRI data were acquired from 24 participants on a 3 Tesla MRI scanner (Siemens Tim Trio). MRI scanning was performed with a 12-channel head coil using an echo-planar imaging sequence with T2-weighted images, repetition time (TR) of 2,000 ms, echo time (TE) of 30 ms, 3×3 mm^2 in-plane resolution, 3-mm slice thickness, 1-mm interslice gap, and 28 slices per volume. T1-weighted (magnetization-prepared rapid acquisition with gradient echo) and fluid attenuated inversion recovery images were obtained to screen for morphological brain abnormalities. Before preprocessing the acquired data to exclude as much cerebrospinal fluid as possible, we manually defined a mask containing approximately 40,000 voxels covering the entire brain while excluding parts of cerebrospinal fluid. The functional data were analyzed using a standard preprocessing chain of the software system Lipsia (31); detailed information is provided in the Supplementary Data.

We then applied the so-called eigenvector centrality mapping algorithm to the preprocessed data, which generates an "eigenvector centrality value" for every brain region (32). The greater this value, the greater the connectedness of the respective brain area with the rest of the brain and thus the importance in the whole network. In more detail, eigenvector centrality mapping calculates the linear correlations of the time series of one voxel to the time series of every other voxel of the brain. The algorithm attributes a greater eigenvector centrality value to the respective voxel when the number of positive correlations with other voxels is greater and when more positive correlations are found with voxels that are attributed with high eigenvector centrality values themselves. A well-known variant of eigenvector centrality is Google's "PageRank" algorithm (32,33).

Further statistical analysis was performed with SPM 8 (34). With eigenvector centrality maps we performed paired *t* tests between the placebo and exenatide conditions for each scanning block. A small volume correction was performed based on our primary hypothesis, limiting our analysis to the hypothalamus. The small volume correction is an α-correction for a preselected region based on an a priori hypothesis (35). We created a mask using the wfu-pickatlas (36,37), which is a toolbox for SPM 8, selecting the predefined region of the hypothalamus (36). To ensure that we captured the whole of the hypothalamus, we dilated the mask for one voxel in every direction. This resulted in a mask containing 263 voxels. For analysis of the interaction exenatide/placebo and responders/nonresponders, a contrast vector was built using the mean differences in caloric intake on exenatide and placebo day (see below). We performed the interaction analysis of exenatide/placebo and the food pictures block/nonfood pictures block for each group separately. Locations of the observed differences are given in Talairach coordinates (x = right/left, y = anterior/posterior, z = superior/inferior; the origin at 0, 0, 0 is the anterior commissure; units are in millimeters), which are normalized to a standard brain (38). *P* values < 0.005, uncorrected for multiple comparisons, were considered significant. Results are mean values ± SEM unless otherwise stated.

RESULTS

Calorie intake and definition of responders and nonresponders

For the whole group ($n = 24$), mean energy intake was reduced by 10% (from

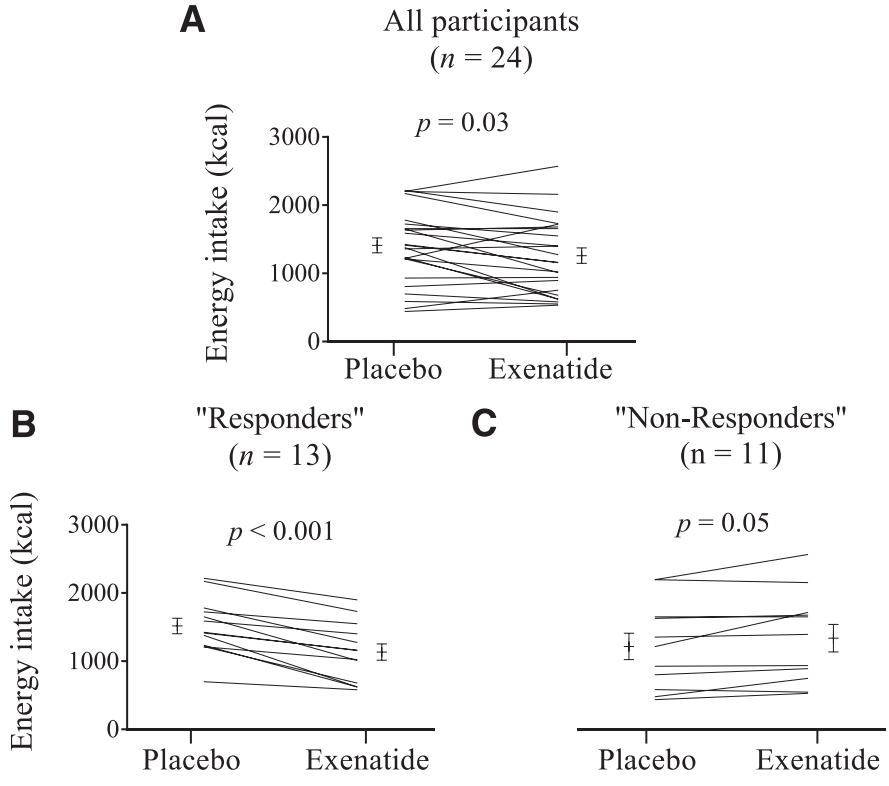


Figure 1—*Energy intake in kilocalories (kcal) from ad libitum buffet, consumed right after end of infusion and magnetic resonance imaging scan.* A*: All participants* (n = *24);* B*: responders* (n = *13);* C*: nonresponders* (n = *11).*

1,384 ± 110 kcal for placebo compared with 1,232 ± 113 kcal for exenatide; P = 0.03; median 10.9%; Fig. 1*A*). To distinguish participants in whom exenatide had a significant effect resulting in a reduction in energy intake, we defined two groups: one group of participants with a reduction of caloric intake of ≥10% after exenatide infusion (responders, n = 13; 1,516 ± 114 kcal on placebo day, 1,131 ± 121 kcal on exenatide day; $P <$ 0.001; Fig. 1*B*) and one group with <10% reduction of energy intake after exenatide infusion (nonresponders, n = 11; 1,229 ± 193 kcal on placebo day, 1,351 ± 203 kcal on exenatide day; P = 0.05; Fig. 1*C*). This cutoff is somewhat arbitrary, but a widely accepted value for day-to-day change in caloric intake with long-term clinical significance does not exist. The National Health and Nutrition Examination Survey reported a clinically relevant increase in obesity (BMI >30 kg/m^2; prevalence increased from 14.5 to 33.4%) as a result of a 13% increase in daily caloric intake (39). Our responders had a mean reduction in caloric intake of 24%, suggesting that our categorization is well within a magnitude that could translate into long-term weight changes.

There were no significant differences in age, anthropometric measures, duration of fast, and feelings of hunger at baseline between the two groups (for data see Supplementary Table 1).

Ratings for hunger, nausea, tastiness of buffet, and food pictures during MRI

Basal hunger ratings did not differ between placebo and exenatide among responders (33 ± 7 and 35 ± 7 mm, respectively; P = 0.82) and nonresponders (42 ± 7 and 37 ± 8 mm, respectively; P = 0.61). There was also no difference in basal hunger ratings between responders and nonresponders for either the placebo (P = 0.39) or exenatide experiment (P = 0.84). In responders, hunger ratings increased to 69 ± 5 mm at 210 min during placebo infusion, which was significantly greater than during exenatide (49 ± 9 mm at 210 min; P = 0.04). In nonresponders, no difference was observed (72 ± 5 vs. 68 ± 8 mm at 210 min; P = 0.72). After the meal, hunger ratings comparably fell to a minimum of 3 to 12 mm in both groups (Fig. 2*A* and *B*). Nausea ratings were not significantly different at baseline between responders and nonresponders nor during placebo nor exenatide, and they did not change significantly over time (all P values > 0.09; Fig. 2*C* and *D*). Rating of the tastiness of buffet food was comparable in responders (59 ± 6 and 56 ± 6 mm for placebo and exenatide, respectively; P = 0.57) and nonresponders (65 ± 4 and 65 ± 6 mm, respectively; P = 0.91). There were no significant differences between responders and nonresponders on the placebo (P = 0.41) or exenatide day (P = 0.28). Ratings of tastiness of food pictures during MRI scanning did not differ between placebo and exenatide. The average ratings for placebo and exenatide were 2.79 ± 0.08 and 2.79 ± 0.10, respectively (P = 0.96), for responders and 2.73 ± 0.06 and 2.73 ± 0.10, respectively (P = 0.94), for nonresponders. Ratings of valence of nonfood pictures did not differ either (data not shown).

Serum exenatide, blood glucose, and serum insulin concentrations

Average exenatide concentrations at the two measurements before and after the MRI scan for responders and nonresponders were 0.30 ± 0.04 and 0.27 ± 0.05 ng/mL, respectively (P = 0.68). Areas under the curve for the whole 290 min were 74.03 ± 14.74 and 64.08 ± 10.71 ng min/mL for responders and nonresponders, respectively (P = 0.60). Exenatide serum concentrations were not significantly different between responders and nonresponders throughout the experiment (Supplementary Fig. 1). Mean blood glucose concentrations before the start of the infusion did not differ between placebo and exenatide day (4.8 ± 0.2 and 4.8 ± 0.2 mmol/L, respectively [P = 0.44], for responders and 4.9 ± 0.2 and 4.7 ± 0.2 mmol/L, respectively [P = 0.71], for nonresponders). During exenatide infusion, blood glucose concentrations in all participants decreased to a nadir of 3.8 ± 0.1 mmol/L at 85 min, which was significantly lower than during placebo (4.5 ± 0.2 mmol/L; $P <$ 0.001). There was no significant difference between responders and nonresponders on either day (Fig. 3*A–C*). Plasma insulin concentrations were not different between placebo and exenatide, and the graphs over time for responders and nonresponders were superimposable until t = 210 min (all P values were nonsignificant). Not unexpectedly, insulin response after the buffet was less pronounced in responders on exenatide day, who ate less on that day by definition (Fig. 3*D–F*).

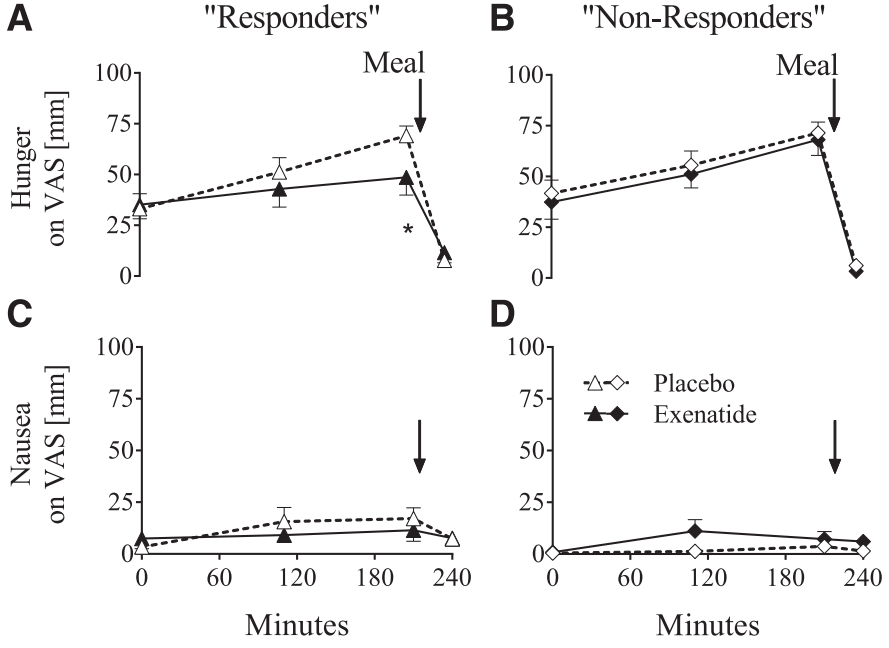


Figure 2—*Hunger ratings assessed with visual analog scale (VAS) at measurement 1 + 2 (running intravenous [IV] infusion before MRI scan), 3 (right after stop of IV infusion and right after MRI scan), and 4 (right after ad libitum buffet) for responders* (A; n = *13) and nonresponders* (B; n = *11). 0 mm = Not at all hungry, 100 mm = very hungry. Ratings for nausea among responders* (C) *and nonresponders* (D) *are referenced by 0 mm = no nausea, 100 mm = extreme nausea.* *P < *0.05.*

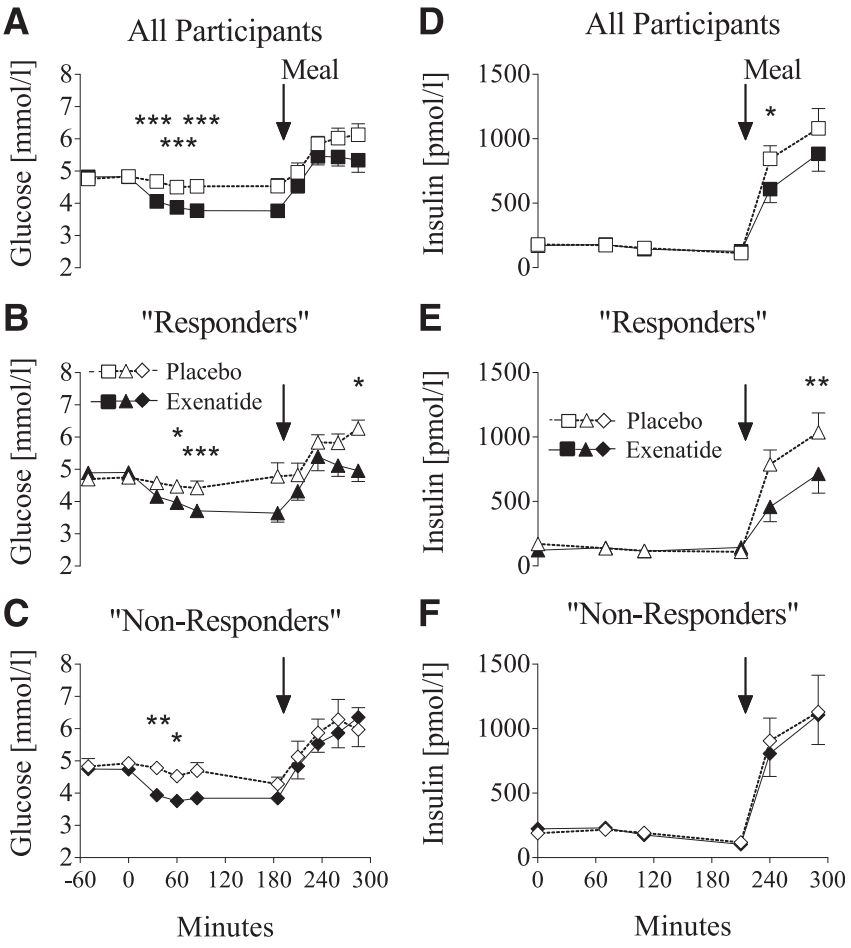


Figure 3—*Blood glucose* (left) *and insulin* (right) *concentrations for all participants* (n = *24;* top) *and for subgroups of responders* (n = *13;* middle) *and nonresponders* (n = *11;* bottom). x-*Axis values indicate time after start of infusion (placebo and exenatide). At 120 min, the MRI scan was performed, lasting approximately 75 min. Right after completion of the MRI scan, the infusion was stopped and a mixed ad libitum buffet was consumed.* *P < *0.05,* **P < *0.01,* ***P < *0.001.*

Behavioral motor skills and attention tasks (analysis of 23 participants)

The neuropsychological and motor skills tasks (d2 attention test, *n*-back task, finger tapping test) did not show any significant differences between placebo and exenatide or between responders and nonresponders (data not shown).

fMRI data

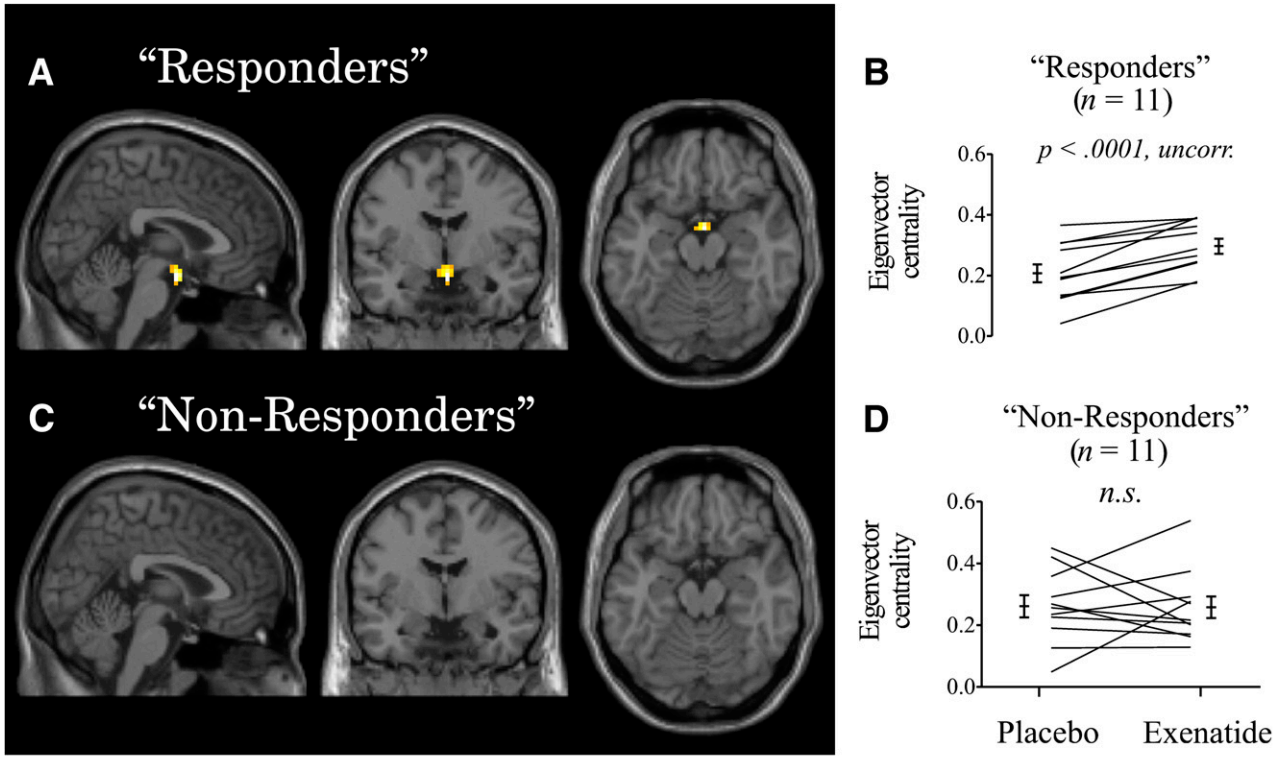
For analysis of fMRI data, we had to exclude two participants because of brain anatomical abnormalities. To exclude difficulties in normalization, one participant was excluded because of an orbitofrontal deformation after a concussion in childhood. A second participant was excluded because of a large sphenoidal sinus that resulted in artifacts, causing a complete deletion of the MRI signal in the hypothalamus. Both participants belonged to the group of responders. Neither showed any abnormal results in behavioral findings (attention and motor skills tests, questionnaires, visual analog scales, food picture ratings) and thus neither was excluded from the analyses of behavioral data.

When rating food pictures, the group of responders showed a significantly higher eigenvector centrality of the hypothalamus in the exenatide condition compared with placebo (peak at Talairach coordinates −3, −1, −17; $P < 0.0001$, uncorrected; $P = 0.01$, corrected for family wise error [FWE]; cluster size 13 voxels) (Fig. 4*A* and *E*). This effect was consistent for all 11 participants in the group of responders (Fig. 4*B*). These findings indicate a higher connectedness of this region with the rest of the brain during exenatide infusion compared with placebo. In the nonresponder group, we did not obtain significant differences in eigenvector centrality (Fig. 4*C–E*). The interaction of exenatide/placebo and responders/nonresponders with mean differences in caloric intake as a contrast vector was significant at Talairach coordinates −3, −1, −17 ($P < 0.001$, uncorrected; $P = 0.04$, FWE-corrected) (Fig. 4*E*). We did not obtain significant differences in eigenvector centrality in our region of interest in either of the two groups for rating of nonfood pictures or looking at the fixation cross. The interaction of exenatide/placebo and food pictures block/nonfood pictures block was significant for responders, with maxima at Talairach coordinates −3, −7, −14 ($P = 0.002$, uncorrected; $P = 0.046$, FWE-corrected) and 3, −7, −14 ($P = 0.003$, uncorrected; $P = 0.069$, FWE-corrected) (Fig. 4*E*).

CONCLUSIONS—In this study, 11 of the 22 obese, nondiabetic men included in the fMRI analysis decreased their energy intake during the buffet meal by at least 10%. These data are consistent with variations in weight loss observed in nondiabetic persons treated with subcutaneous exenatide over several weeks: about a third each either lost weight, remained neutral, or gained weight (4). For the purpose of our analysis, we defined a 10% reduction in energy intake as the cutoff to separate responders and nonresponders (for detailed information, see CALORIE INTAKE AND DEFINITION OF RESPONDERS AND NONRESPONDERS). Only in the group of responders were hunger ratings after 210 min significantly lower after exenatide infusion than after placebo infusion. In the 11 nonresponders, energy intake decreased <10% or increased after exenatide, and no significant effect on hunger ratings was observed.

The differences in the drug's effect on energy intake observed in our data could not be explained by differences in exenatide serum concentrations, insulin concentrations, basal hunger ratings, fasting times, anthropological measurements, or performance on attention and motor skills tasks. In addition, exenatide reduced blood glucose to the same extent in both groups, suggesting the same peripheral pancreatic effect. This strongly suggests an extrapancreatic mechanism selectively targeting eating behavior/energy intake.

Analysis of the fMRI data of responders showed an increase in eigenvector centrality, a measure for the connectedness of brain regions. Connectedness is a



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		Talairach coordinates	Peak *p*-value, uncorr.	FWE-corr.
"Responders"	Food	-3, -1, -17	< 0.0001	0.012
	Non-food		n.s.	
	"Resting state"		n.s.	
	Interaction	-3, -7, -14	0.002	0.046
	food vs. non-food	3, -7, -14	0.003	0.069
"Non-responders"	Food		n.s.	
	Non-food		n.s.	
	"Resting state"		n.s.	
Interaction "resp." vs. "non-resp."	Food	-3, -1, -17	< 0.001	0.038

Figure 4—*Differences in eigenvector centrality between exenatide and placebo while viewing food pictures inside the MRI scanner for responders* (n = *11;* A*) and nonresponders* (n = *11;* C*). Bright colors signify increasing* P *values of paired* t *test between conditions. Global maximum for responders was found as depicted at Talairach coordinates −3, −1, −17* (P < *0.0001, uncorrected); cluster size was 13 voxels. No significant results were found for nonresponders.* B *and* D *show respective eigenvector centrality values for all subjects at the global maximum. Higher values signify a higher connectedness and a greater importance of the analyzed area in brain function.* E*: Significances of differences in eigenvector centrality exenatide condition are greater than placebo condition at the location of the hypothalamus. Corr., corrected; food, food pictures block; max, maximal; nonfood, nonfood pictures block; nonresp., nonresponders; n.s., not significant; resp., responders; uncorr., uncorrected.*

proxy for the influence of a brain region on the rest of the brain. In the responders group in our study, this effect was highly significant in the hypothalamus during exenatide infusion compared with placebo. Eigenvector centrality, an algorithm similar to Google's "PageRank," gives a measure of how many important brain areas the respective area is connected to; a higher connectedness implies greater importance in the whole network of the stimulated brain function. The effect was seen only when participants rated food pictures, not when they rated nonfood pictures or were in a resting state. This clearly supports the hypothesis of a hypothalamic exenatide effect specific to states when networks of hunger/eating control are active. In the nonresponder group, among whom exenatide did not decrease energy intake, there were no differences in eigenvector centrality in the hypothalamic region between exenatide and placebo condition. The interaction

between nonresponders and responders was significant and suggests that when exenatide does not influence hypothalamic connectivity, the drug does not mediate a reduction in energy intake. Factors contributing to the different levels of responsiveness of the hypothalamus to exenatide could not be identified and will need further investigation.

The observation that the decreases in hunger and energy intake among the responders was not associated with decreased ratings of food pictures or with a decrease of the subjective tastiness of the mixed buffet strongly suggests that exenatide influences only the homeostatic—not the hedonic—component of hunger regulation (40).

The questions of whether reduced hunger and reduced energy intake after a single intravenous administration of exenatide is mediated by the same pathways as the reduction in body weight in subcutaneous long-term treatment, and whether the participants who reduced energy intake after a single dose would be those that lose weight in long-term treatment, remains open. A conclusion as to whether the influence of exenatide on the hypothalamus is mediated via peripheral receptors and afferences to the brain, or whether the circulating peptide crosses the blood-brain barrier and directly binds to central nervous GLP-1 (or other) receptors, cannot be drawn from this study design.

Our results demonstrate a central, hypothalamic effect of peripherally administered exenatide in humans, which occurred only in the group of participants who showed an exenatide-dependent reduction in caloric intake. These findings indicate that the hypothalamic response seems to be the crucial factor for the effect of exenatide on energy intake.

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H.S. conceived, designed, and performed the experiments; analyzed data; and wrote the article. S.K. and A.H. conceived, designed, and performed the experiments and analyzed data. G.L. conceived and designed the experiments, analyzed data, and contributed reagents/materials/analysis tools. K.M., J.L., and B.P. conceived and designed the study and analyzed data. F.B.-V. and A.V. conceived and designed the experiments and contributed reagents/materials/analysis tools. J.K. contributed reagents/materials/analysis tools. M.S. conceived and designed the experiments, contributed reagents/materials/analysis tools, and wrote the manuscript. All authors edited the manuscript. H.S. 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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