Liraglutide Reduces CNS Activation in Response to Visual Food Cues Only After Short-term Treatment in Patients With Type 2 Diabetes

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OBJECTIVE

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are associated with reduced appetite and body weight. We investigated whether these effects could be mediated by the central nervous system (CNS).

RESEARCH DESIGN AND METHODS

We performed a randomized crossover study in obese patients with type 2 diabetes (n = 20, mean age 59.3 ± 4.1 years, mean BMI 32 ± 4.7 kg/m²), consisting of two periods of 12-week treatment with either liraglutide 1.8 mg or insulin glargine. Using functional MRI, we determined the effects of treatment on CNS responses to viewing food pictures in the fasted condition and 30 min after meal intake.

RESULTS

After 12 weeks, the decrease in HbA1c was larger with liraglutide versus insulin glargine (Δ−0.7% vs. −0.2%, P < 0.001). Body weight decreased during liraglutide versus insulin glargine (Δ−3.3 kg vs. 0.8 kg, P < 0.001). After 10 days, patients treated with liraglutide, compared with insulin glargine, showed decreased responses to food pictures in insula and putamen (P ≤ 0.02). In addition, liraglutide enhanced the satiating effect of meal intake on responses in putamen and amygdala (P ≤ 0.05). Differences between liraglutide and insulin glargine were not observed after 12 weeks.

CONCLUSIONS

Compared with insulin, liraglutide decreased CNS activation significantly only after short-term treatment, suggesting that these effects of GLP-1RA on the CNS may contribute to the induction of weight loss, but not necessarily to its maintenance, in view of the absence of an effect of liraglutide on CNS activation in response to food pictures after longer-term treatment.

Obesity and diabetes constitute a major health burden due to their pandemic occurrence (1) and their association with adverse consequences, such as cardiovascular disease (2). Obesity is the result of a long-term excess energy intake relative to expenditure, leading to increased weight and body fat mass. The central nervous system (CNS) has a major role in the regulation of food intake and the maintenance
of body weight within narrow ranges. It has been suggested that alterations in CNS satiety and reward processing may increase food intake, comparable to the role of the CNS observed in drug addiction (3). Using functional MRI (fMRI), altered CNS activation in response to food cues was observed in obese individuals measured in specific areas involved in the regulation of food intake in humans (4,5). Activation in these areas may be influenced by several adipose tissue–derived and gut-derived hormones. These signals appear to relay information about the nutritional status of the body to the CNS (6). It is of great importance to gain more insight into the signals influencing the central regulation of food intake.

In the search for treatment of obesity, studies have been performed using adipose tissue–derived and gut-derived hormones; however, these attempts were often without success (7,8), except for glucagon-like peptide-1 [GLP-1]. GLP-1 is a gut hormone secreted after food ingestion from endoendocrine L cells located in the distal jejunum and ileum (9). GLP-1 is known mainly for its glucose-lowering effects, as it augments meal-related insulin secretion from the pancreas (10). Over the last decades, GLP-1–based therapies have been developed successfully for the treatment of diabetes. Interestingly, besides the effects on glucose regulation, the administration of GLP-1 receptor agonists (GLP-1RAs) inhibits food intake and stimulates satiety. Treatment with GLP-1RAs, such as liraglutide, is consistently associated with weight loss (11). It is suggested that these effects are at least partly mediated by effects on the CNS (12,13). Recently, we demonstrated in an experimental setting that short-term administration of a GLP-1RA, during a pancreatic-pituitary clamp, resulted in decreased CNS activation (i.e., in insula, amygdala, putamen, and orbitofrontal cortex), in obese individuals (with and without type 2 diabetes) in response to viewing food pictures (14), pointing toward a central satiating effect of GLP-1. However, the effect of treatment with GLP-1RAs in a clinical setting during the induction phase and maintenance phase of weight loss has not been investigated.

We hypothesized that the effects of GLP-1RA treatment on appetite and body weight in humans are at least partly mediated by effects on the CNS and that these effects contribute to the induction and maintenance of weight loss during GLP-1RA treatment. We performed a randomized, crossover intervention study in obese patients with type 2 diabetes and compared treatment with liraglutide with that of an active comparator, insulin glargine. We measured CNS activation in response to viewing food pictures using fMRI after 10 days (i.e., before significant changes in body weight have occurred) and after 12 weeks of treatment (i.e., after changes in body weight have occurred). We analyzed the effects of treatment in predefined areas in the CNS, which are considered to be important and involved in the regulation of feeding, as they are part of reward circuits in the CNS and are consistently associated with food cue–related activation (4,5,14,15).

**RESEARCH DESIGN AND METHODS**

**Participants**

Twenty overweight or obese patients with type 2 diabetes were included. Patients were recruited through advertisements in local newspapers and were included after written informed consent was obtained.

Patients were eligible if they were between 40 and 65 years of age, right-handed, and Caucasian and had a stable body weight (<5% reported change during the previous 3 months). Further inclusion criteria included BMI >26 kg/m² and HbA₁c level between 42 and 69 mmol/mol (6.0–8.5%). For the current treatment of diabetes, only the oral glucose-lowering agent metformin with or without sulfonylurea derivatives was allowed. Exclusion criteria were a history of neurological, cardiovascular, renal, or liver disease, malignancies, the use of any centrally acting agent or oral glucocorticoids, substance abuse, and psychiatric disorders.

All patients were treated with metformin. Twelve patients were also treated with sulfonylurea derivatives, but these were temporarily discontinued 4 weeks prior to the start of the experiments. Ten patients used antihypertensive medication, and 15 patients used cholesterol-lowering agents.

**General Experimental Protocol**

This study was a randomized, crossover, intervention study. The study consisted of two randomized treatment periods of 12 weeks, each with a 12 week washout period in between (Fig. 1A). Treatment with liraglutide was compared with treatment with an active comparator (i.e., insulin glargine) to evaluate the contribution of GLP-1 receptor activation per se, given the expected isoglycemic state in both treatment groups, thereby minimizing the possible effects of differences in glucose levels on CNS responses.

During one treatment period, patients were treated with liraglutide, which was injected in the evening, and underwent a dose escalation period, starting at 0.6 mg q.d., with weekly increments of 0.6 mg, if well tolerated, reaching a final dose of 1.8 mg q.d. by the end of the second week, which was maintained until the end of the treatment period. During the other treatment period, patients were treated with insulin glargine, started at an initial dose of 10 IU q.d. Patients were instructed to increase the daily dose based on their fasting self-monitored blood glucose levels according to a predetermined treat-to-target algorithm (16).

Six test visits with fMRI measurements were scheduled: one at the start (baseline), one after 10 days (short-term) of each treatment, and one after 12 weeks (long-term) of each treatment. On each test visit, patients arrived after an overnight fast at the research unit. Two fMRI scans were performed per test visit: one while fasted and one 30 min after the intake of a standardized liquid meal, consisting of 450 kcal (carbohydrate 56.1 g, fat 17.4 g, and protein 18.0 g; 300 mL Nutridrink [yogurt style with raspberry flavor]; Nutricia, Zoetermeer, the Netherlands). A catheter was inserted into a cubital vein for collecting blood samples for glucose measurements (at start of the test visit and every 30 min from the start of the standardized meal intake until 180 min after). A summary of the protocol is presented in Fig. 1B. At each visit, measurements of anthropometrics were performed, body composition was measured using bioelectrical impedance analysis, and a blood sample was taken.

**fMRI Protocol**

This fMRI task was used as described previously (14). In short, the fMRI task
MRI acquisition and analyses have been described in detail previously (14). In brief, MRI data were acquired on a 3.0 tesla Signa HDxt scanner (General Electric, Milwaukee, Wisconsin). Structural MRI was obtained using a T1-weighted sequence. fMRI data were acquired using an echo planar imaging T2* blood oxygenation level–dependent pulse sequence (repetition time 2,160 ms, echo time 30 ms, matrix $64 \times 64$, 211 mm² field of view, flip angle 80°) with 40 ascending slices per volume (3 mm thickness, 0 mm gap), which gave whole-brain coverage. Functional images were preprocessed and analyzed with SPM8 software (Wellcome Trust Centre for Neuroimaging, London, U.K.). T1-coregistered volumes were normalized to Montreal Neurological Institute space. Functional scans were analyzed in the context of the general linear model. At the first (single-subject) level, high-calorie food, low-calorie food, and nonfood blocks were modeled. To assess CNS activation related to viewing food pictures and, more specifically, their hedonic quality, we computed the following two contrasts: 1) activation during viewing of all food pictures versus nonfood pictures and 2) activation during viewing of high-calorie food pictures versus nonfood pictures. These first-level contrast images were entered into second-level three-way ANOVA with factors treatment (liraglutide, insulin), the time point of treatment (baseline, 10 days, 12 weeks), and meal state (fasted, postprandial). To assess the reducing effect of meal intake on CNS activation, we also analyzed the difference in activation between the fasted and postprandial conditions at each time point. A priori regions of interest (i.e., insula, striatum, amygdala, and orbitofrontal cortex) were determined based on previous studies (4, 5, 15). Differences in CNS activation are reported as significant when these survived family-wise error correction using small volume correction within the predefined regions of interest (14). To investigate whether the order of treatment affected the changes in CNS activation due to treatment, we compared analyses for groups depending on the order of treatment and performed analyses with the order of treatment as covariate.

Biochemical Analyses

The measurement of blood glucose was performed immediately after sampling using the glucose dehydrogenase method (GlucoseAnalyzer; HemoCue, Angelholm, Sweden).

Ad Libitum Lunch Buffet

At the end of each visit, 3 h and 30 min after intake of the standardized liquid meal, patients were presented an ad libitum choice lunch buffet (14) to assess energy intake, but patients were not aware that their intake was monitored and were told to eat as much as they liked.

Questionnaires

The participants were asked to score their sensation of hunger, fullness, prospective food consumption, and nausea on a 10-point Likert scale at fixed time points during the visits (1, before start of the first [fasted] MRI session; 2, before intake of the standardized meal; 3, 30 min after the meal/before the start of the postprandial MRI session; 4, after the postprandial MRI session; and 5, before the start of the ad libitum lunch buffet).

Statistical Analyses

Clinical data were analyzed with the SPSS version 20. Data are expressed as the mean ± SEM (unless otherwise stated). To analyze the longitudinal difference between treatments, a generalized estimating equation approach was used. To investigate the effect of the order of treatment on the changes in weight and HbA1c level, an interaction term was added to the model. Associations between differences in CNS activation and clinical data were calculated with the Pearson regression coefficient. Results were considered statistically significant at $P < 0.05$. 
### Study Approval
The study (clinical trial reg. no. NCT01363609, clinicaltrials.gov) was performed in accordance with the Helsinki Declaration, and all participants provided written informed consent before the start of participation. The study was approved by the Medical Ethics Committee of the VU University Medical Center.

### RESULTS

#### Clinical Characteristics Before and During Treatment Periods
Clinical characteristics before and during treatment are presented in Table 1. After 10 days of treatment with liraglutide, all patients used 1.2 mg q.d., except for one patient (using 0.6 mg). After 12 weeks, two patients used 1.2 mg, and the others 1.8 mg q.d. The mean insulin dosage after 10 days was 14.7 ± 0.8 IU, and after 12 weeks it was 29.9 ± 3.6 IU q.d.

Treatment with liraglutide resulted in significant weight loss after 12 weeks compared with insulin glargine (−3.3 and 0.8 kg, respectively; \( P < 0.001 \)). There was no significant interaction between the order of treatment and the effect on body weight (\( P = 0.1 \)). In addition, changes in waist circumference and body fat percentage differed significantly between the treatments after 12 weeks (\( P < 0.001 \) for both). Glucose levels on the different test visits are depicted in Fig. 2. Glucose levels decreased with both treatments compared with baseline (\( P < 0.001 \)), but this effect was larger after 10 days and 12 weeks of treatment with liraglutide compared with insulin glargine (\( P = 0.002 \) and \( P = 0.003 \), respectively). HbA1c levels decreased during both treatments, but this effect was also significantly larger after 12 weeks of treatment with liraglutide compared with insulin (−8 mmol/mol [−0.7%] and −3 mmol/mol [−0.2%], respectively; \( P < 0.001 \)). There was no interaction between the order of treatment and the effect on HbA1c levels (\( P = 0.3 \)). Mean energy intake at the ad libitum lunch buffet in patients treated with liraglutide was numerically lower compared with treatment with insulin glargine, but this was not statistically significant (\( P = 0.5 \) after 10 days, \( P = 0.6 \) after 12 weeks).

#### Table 1—Clinical characteristics before and during treatment

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Baseline</th>
<th>Insulin</th>
<th>Liraglutide</th>
<th>Insulin</th>
<th>Liraglutide</th>
<th>Insulin</th>
<th>Liraglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>94.6 ± 3.5</td>
<td>95.0 ± 3.4</td>
<td>94.4 ± 3.5</td>
<td>93.9 ± 3.4</td>
<td>95.4 ± 3.6</td>
<td>91.7 ± 3.5†</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.7 ± 1.1</td>
<td>31.9 ± 1.0</td>
<td>31.6 ± 1.1</td>
<td>31.5 ± 1.0</td>
<td>31.9 ± 1.0</td>
<td>30.7 ± 1.0†</td>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>108 ± 2.5</td>
<td>108 ± 2.2</td>
<td>108 ± 2.4</td>
<td>108 ± 2.2</td>
<td>108 ± 2.4</td>
<td>105 ± 2.3†</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>126 ± 1.8</td>
<td>127 ± 1.9</td>
<td>125 ± 2.4</td>
<td>125 ± 1.9</td>
<td>125 ± 2.5</td>
<td>123 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78 ± 1.9</td>
<td>79 ± 3.2</td>
<td>77 ± 1.6</td>
<td>77 ± 1.9</td>
<td>76 ± 1.8</td>
<td>76 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>67 ± 1.7</td>
<td>68 ± 2.4</td>
<td>67 ± 2.0</td>
<td>72 ± 1.8*</td>
<td>67 ± 2.4</td>
<td>71 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.1 ± 0.2</td>
<td>7.1 ± 0.2</td>
<td>7.1 ± 0.2</td>
<td>7.1 ± 0.2</td>
<td>6.9 ± 0.2</td>
<td>6.5 ± 0.1†</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>8.1 ± 0.4</td>
<td>8.3 ± 0.4</td>
<td>6.8 ± 0.3</td>
<td>6.0 ± 0.3†</td>
<td>5.2 ± 0.2</td>
<td>6.2 ± 0.3†</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.6 ± 0.3</td>
<td>4.2 ± 0.2</td>
<td>4.3 ± 0.3</td>
<td>4.0 ± 0.3</td>
<td>4.3 ± 0.3</td>
<td>4.0 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.8 ± 0.3</td>
<td>1.6 ± 0.2</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.2</td>
<td>1.4 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>37.3 ± 1.6</td>
<td>37.4 ± 1.8</td>
<td>35.9 ± 1.7</td>
<td>37.2 ± 1.7</td>
<td>37.3 ± 1.7</td>
<td>36.0 ± 1.7†</td>
<td></td>
</tr>
<tr>
<td>Intake ad libitum lunch (kcal)</td>
<td>603 ± 56.0</td>
<td>611 ± 65.4</td>
<td>600 ± 60.7</td>
<td>578 ± 62.7</td>
<td>616 ± 50.7</td>
<td>578 ± 72.2</td>
<td></td>
</tr>
</tbody>
</table>

Data are the mean ± SEM. *P < 0.05 for differences in change during liraglutide treatment compared with insulin glargine treatment. †P < 0.001 for differences in change during liraglutide treatment compared with insulin glargine treatment.

#### Figure 2
Glucose levels during test visits: at baseline test visits (A), after 10 days of treatment (B), and after 12 weeks of treatment (C). White circles, liraglutide; black circles, insulin glargine. Glucose levels decreased during both treatments, but the glucose-lowering effect of liraglutide was significantly larger (after 10 days and 12 weeks, \( P = 0.002 \) and \( P = 0.003 \), respectively).
Liraglutide Versus Insulin Lowers CNS Activation in Response to Food Pictures After Short-term Treatment

We compared the treatments at baseline, after 10 days of treatment (short term), and after 12 weeks of treatment (long term). For an overview of the effects of treatment on CNS activation in response to all food pictures and high-calorie food pictures, see also Supplementary Table 1.

At Baseline

As expected, no differences between the treatments were observed.

After 10 Days

In fasted condition, treatment with liraglutide resulted in a decreased activation in response to high-calorie food pictures compared with insulin in bilateral insula (right \( P = 0.003 \), left \( P = 0.02 \)) (Fig. 3). In the postprandial condition, decreased activation in response to food pictures and to high-calorie food pictures was observed with liraglutide treatment in comparison with insulin treatment in left putamen (\( P = 0.02 \) for food pictures, \( P = 0.01 \) for high-calorie food pictures). Furthermore, the reducing effect of the meal intake on CNS activation in response to food pictures was larger after 10 days of treatment with liraglutide in left putamen and left amygdala (\( P = 0.05 \) and \( P = 0.01 \), respectively), compared with insulin treatment. The reducing effect of meal intake in response to high-calorie food pictures in left putamen was not significantly different between liraglutide and insulin (\( P = 0.07 \)).

After 12 Weeks

No significant differences between the treatments were observed.

There was no influence of the order of treatment on differences in CNS activation after both 10 days and 12 weeks.

Appetite-Related Scores

Scores of hunger differed between treatments, with lower scores during liraglutide treatment (\( P = 0.01 \) after 10 days and 12 weeks of treatment). Other scores (including scores of nausea) did not differ between the treatments (data not shown).

Correlations Between Differences in CNS Activation and Weight Changes

We investigated whether the differences in CNS activation predicted the observed weight changes during treatment. Differences in CNS activation in response to high-calorie food pictures in the fasted condition in bilateral insula after 10 days of treatment were positively correlated with the differences in weight change after 12 weeks, but these associations were not statistically significant (right insula \( R = 0.30 \), \( P = 0.20 \); left insula \( R = 0.26 \), \( P = 0.27 \)).

Differences in CNS activation in response to food and high-calorie food pictures were not associated with food intake during the ad libitum lunch buffet or with hunger scores (\( P > 0.3 \)).

Adverse Events

During treatment with insulin glargine, three patients reported one or more mild hypoglycemic episodes. During liraglutide treatment, one patient reported one mild hypoglycemic episode. Seven patients reported mild nausea during the first days of treatment with liraglutide or during the first days after dose escalation. One of these patients vomited once. One other patient reported moderate nausea during the first week. Two patients complained about diarrhea during the first weeks of liraglutide treatment. From the patients who reported a feeling of nausea during the first days of liraglutide treatment, two also reported this at the beginning of the test visit after 10 days of treatment. After exclusion of these two patients or all of the 12 patients who reported any episode of nausea (\( n = 8 \)), the effect of liraglutide on CNS activation was similar.

CONCLUSIONS

In a crossover intervention study, we observed that liraglutide, compared with insulin, after short-term treatment (10 days), decreased CNS activation in insula and putamen in response to viewing of food and high-calorie food pictures during the fasted and postprandial states. Also, the reducing effect of a meal intake on CNS activation in putamen and amygdala was enhanced following liraglutide treatment compared with insulin treatment. However, these differences after short-term treatment did not persist during longer-term treatment (12 weeks).

Treatment with a GLP-1RA, such as liraglutide, is consistently associated with reduced appetite and weight (11,17). Results from studies in humans and rodents (12,13) have suggested that treatment with a GLP-1RA may influence the central regulation of feeding. In a previous fMRI study (14), we showed that short-term administration of a GLP-1RA, in an experimental setting, reduces CNS activation in response to food pictures in obese patients with and without diabetes. However, the effects of treatment with a GLP-1RA on CNS activation in a clinical setting had not been investigated. Despite the fact that the dosage of liraglutide after short-term treatment was lower than that after longer-term treatment, we observed the effects of liraglutide after 10 days, but could not detect any effects after 12 weeks. In general, the weight loss observed with liraglutide treatment at this dosage is more pronounced in the first 10 weeks and tends to stabilize during longer-term treatment (18). The effects of liraglutide treatment on the CNS may contribute to the induction of weight loss. In accordance, we found that patients with more pronounced decreases in CNS activation in the fasted condition during liraglutide treatment, compared with insulin, had larger decreases in weight, but these associations were not statistically significant.

The role for central effects of liraglutide in the maintenance of weight loss is, however, not clear. It is possible that treatment with liraglutide maintains weight loss through other mechanisms than those involving the CNS. It could also be suggested that the long-term effect of liraglutide treatment on the CNS may be more subtle compared with the short-term effects. Therefore, these effects may be more difficult to detect. Regardless, the difference in effect size between short- and long-term treatment could very well explain why weight loss is induced after short-term treatment, but is only maintained after longer-term treatment with liraglutide 1.8 mg.

Twelve weeks of treatment with liraglutide resulted in significant weight loss compared with insulin. It could be argued that the effects of the weight loss may have confounded the decreasing effects of liraglutide on CNS activation after 12 weeks. However, if anything, fMRI studies investigating the effect of weight loss on CNS responses to food pictures show that weight reduction may be associated with decreased CNS activation in areas involved in food motivation and reward (19,20). As a result, an effect of weight loss on the CNS would have strengthened...
Figure 3—Differences in CNS activation between liraglutide and insulin glargine after 10 days of treatment. Axial slices showing average differences in activation in brain regions where liraglutide decreases CNS activation after 10 days of treatment compared with insulin glargine in obese patients with type 2 diabetes (n = 20) in response to the viewing of high-calorie food pictures (high-calorie food > nonfood) in the fasted condition (A) and after viewing food pictures (food > nonfood) in the postprandial condition (B), including the bar charts for the effect of food pictures and high-calorie food pictures. C: A coronal slice with areas where treatment with liraglutide, compared with insulin, enhanced the reducing effect of the standardized meal intake on CNS activation in response to the viewing of food pictures (food > nonfood). The left side of the axial and coronal slices is the left side of the brain. The color scale reflects the T value of the functional activity. Results are presented at the threshold of P < 0.05, family-wise error corrected on cluster extent. In the graphs, BOLD signal intensity (effect size) is plotted (arbitrary units), mean and SEM. BOLD, blood oxygen level-dependent; ins, insulin glargine; lir, liraglutide.
the decreasing effect of liraglutide on CNS activation, and weight loss therefore cannot explain the absence of an effect of liraglutide on the CNS after 12 weeks. On the other hand, we did find a decreasing effect of liraglutide on CNS activation after 10 days, before significant weight changes occurred, suggesting that the decreased CNS activation with liraglutide may be causal in the development of weight loss. In line with this suggestion, two prospective studies (21,22) showed that altered brain responses to visual food stimuli can predict future weight changes.

It could also be argued that participants in six test visits with two fMRI sessions per visit may have induced habituation, reducing the likelihood to detect the treatment effects, especially after 12 weeks of treatment. However, the order of treatment did not affect the observed effects of treatment, so that habituation is unlikely to explain the absence of effects of liraglutide after 12 weeks of treatment.

The effects of liraglutide compared with insulin after short-term treatment were observed in insula, putamen, and amygdala. These areas have been reported to be involved in the regulation of feeding and are similar to those in which we observed acute effects of GLP-1RA administration (4,5,14). The insula is known to receive gustatory and visceral afferents and to be involved in taste memory (23). It is also engaged in the rewarding aspects of food and is connected to other reward-related areas (24). The amygdala has an important role in the association of cues with reward and emotional learning (25) and is activated by textual descriptions of desirable food (26). The putamen is also implicated in reward processing and conditioning (27).

The hypothalamus is known to be an important central area in the homeostatic control of feeding (28). In the current study, we did not observe any effects of treatment in the hypothalamus. However, it is important to realize that this area is subject to artifacts during fMRI measurements, since it is adjacent to air-filled sinuses, which can cause signal dropouts. We can therefore not exclude that liraglutide also affects activation in the hypothalamus. The effects of liraglutide in the hypothalamus have been shown in rodents (29), but further research is needed to investigate this issue in humans.

Different routes of action may be involved in the observed effects of liraglutide. Liraglutide is a GLP-1 analog with 97% amino acid sequence homology to native GLP-1 and is able to pass the blood-brain barrier (30). Therefore, it might exert its effect on the CNS by direct activation of central GLP-1 receptors (12). Indeed, it was shown that GLP-1 receptors in the CNS are required for the anorectic and weight-reducing effects of liraglutide (29). However, results from studies in rodents and humans indicate that an indirect route of action, involving intestinal vagal afferents where GLP-1 receptors are present, may also be important (31). In our current study, we were not able to distinguish between these routes of action. Investigating the central effects of a larger GLP-1RA molecule, which cannot pass the blood-brain barrier, might elucidate the contribution of the direct and indirect routes of action.

It is known that GLP-1 reduces gastric emptying, and that treatment with GLP-1RA is often associated with transient nausea (32,33). Therefore, it could be speculated that the observed CNS effects of liraglutide in our study are driven by effects on gastric emptying and/or nausea. Indeed, seven patients reported mild nausea during the beginning of treatment with liraglutide or following dose escalation. In addition, one patient reported moderate nausea. However, during the fMRI visit after 10 days of treatment with liraglutide, only two patients reported a mild sensation of nausea. After exclusion of these patients from the analyses, the effect of liraglutide on CNS activation was similar. Moreover, nausea scores did not differ between treatments. In addition, although it has been shown that liraglutide exerts a short-term reduction in gastric emptying, this effect is markedly diminished after short-term repeated dosing of liraglutide, whereas the body weight loss continues (34). Results from other studies with GLP-1RA treatment also provide arguments against nausea or delayed gastric emptying as explanations for the appetite- and body weight-reducing effects of GLP-1RA treatment. In a study in obese individuals (35), 5 weeks of treatment with 1.8 mg liraglutide, compared with placebo, did not significantly delay gastric emptying. Moreover, weight loss during GLP-1RA treatment was also observed in the absence of nausea (36), and patients in the fasted state, thus with an empty stomach, also reported reduced appetite with GLP-1 administration (37). Taken together, we conclude that the gastrointestinal effects of liraglutide after 10 days of treatment cannot explain our findings.

Although insulin and liraglutide both have glucose-lowering effects, this effect was larger with liraglutide treatment, especially after 10 days of treatment. These lower glucose levels with liraglutide are, however, unlikely to explain our results, as lower circulating levels of glucose are associated with increased activation in insula and putamen during the viewing of food pictures (38). Despite the slightly lower glucose levels with liraglutide treatment in the current study, we observed a decreased CNS activation in insula and putamen. Treatment with liraglutide has been associated with decreased glucagon levels (39). Lower glucagon levels are associated with lower satiating effects (40), which are expected to be associated with increased responses to food pictures. Therefore, lower glucagon levels during liraglutide treatment also cannot explain the observed decreases in the CNS responses to food pictures after 10 days of treatment.

In conclusion, we observed a decreasing effect on CNS activation in response to viewing food pictures after short-term treatment with liraglutide compared with treatment with insulin glargine, but no differences in CNS activation after 12 weeks. This might indicate that central GLP-1RA effects contribute to the induction phase of weight loss. The absence of an effect at 12 weeks might explain why weight loss does not proceed after the initial period of treatment with liraglutide.

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Liraglutide and Food-Related CNS Responses

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Author Contributions. J.S.t.K. designed the study, conducted the experiments, designed the fMRI paradigm, performed the data analysis, and wrote the article. D.J.V. designed the fMRI paradigm, performed the data analysis, and wrote the article. L.v.B. designed the fMRI paradigm and contributed to the writing of the article. F.B. performed the analyses of all structural MRI scans and contributed to the writing of the article. M.L.D. contributed to the writing of the article. M.D. designed the study. R.G.I.U. designed the study, performed the data analysis, and wrote the article. J.S.t.K. and R.G.I.U. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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