Selective Insulin Resistance in Homeostatic and Cognitive Control Brain Areas in Overweight and Obese Adults

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OBJECTIVE
Impaired brain insulin action has been linked to obesity, type 2 diabetes, and neurodegenerative diseases. To date, the central nervous effects of insulin in obese humans still remain ill-defined, and no study thus far has evaluated the specific brain areas affected by insulin resistance.

RESEARCH DESIGN AND METHODS
In 25 healthy lean and 23 overweight/obese participants, we performed magnetic resonance imaging to measure cerebral blood flow (CBF) before and 15 and 30 min after application of intranasal insulin or placebo. Additionally, participants explicitly rated pictures of high-caloric savory and sweet food 60 min after the spray for wanting and liking.

RESULTS
In response to insulin compared with placebo, we found a significant CBF decrease in the hypothalamus in both lean and overweight/obese participants. The magnitude of this response correlated with visceral adipose tissue independent of other fat compartments. Furthermore, we observed a differential response in the lean compared with the overweight/obese group in the prefrontal cortex, resulting in an insulin-induced CBF reduction in lean participants only. This prefrontal cortex response significantly correlated with peripheral insulin sensitivity and eating behavior measures as disinhibition and food craving. Behaviorally, we were able to observe a significant reduction for the wanting of sweet foods after insulin application in lean men only.

CONCLUSIONS
Brain insulin action was selectively impaired in the prefrontal cortex in overweight and obese adults and in the hypothalamus in participants with high visceral adipose tissue, potentially promoting an altered homeostatic set point and reduced inhibitory control contributing to overeating behavior.

Due to strong associations with numerous conditions, such as type 2 diabetes and cardiovascular disease, obesity has become a major public health concern. Obesity is associated with peripheral insulin resistance in many organs, such as muscle, liver, and adipose tissue. However, only recently was the brain identified as an insulin-sensitive organ regulating food intake (1). In humans, the central nervous effects of insulin still remain ill-defined. In search of new insights in the pathogenesis of
Brain Insulin Resistance

level aging (fMRI) studies using blood oxygen level
thalamus (6)–prefrontal brain regions and the hypo-
metabolic system of the brain were discovered before the
application of intranasal insulin in lean and
weight-obese adults. We hypothe-
ized that overweight and obese adults will show cerebral insulin resistance in
regions associated with food intake and
eating behavior.

RESEARCH DESIGN AND METHODS

Subjects
We recruited 25 healthy lean, 10 over-
weight, and 13 obese adult participants for
this study (BMI 19–46 kg/m²). Over-
weight and obese participants were
required to have a BMI >25 kg/m².
Informed written consent was obtained
from all participants, and the local ethics
committee approved the protocol. All
participants were students at the Uni-
versity of Tübingen recruited through
broadcast e-mails.

Study Design
Before the experiment, all participants
underwent a medical examination to
ensure that they did not have psychiat-
ric, neurological, or metabolic diseases.
Diabetes was ruled out by a 75-g oral
insulin tolerance test (OGTT). Any vol-
unteer treated for chronic disease or
wanting (i.e., “How much do you like the food item in general?”) was
excluded. The Patient Health Questionnaire (10) was used to address psychiatric dis-
seases, and to assess eating behavior, subjects took the German Three Factor
Eating Questionnaire (11), the eating
Disorder Examination (12), and the trait
version of the Food Craving Question-
naire (13).

To assess body fat distribution, whole-body MRI measurements were
obtained. Participant characteristics are provided in Table 1.

After the OGTT and whole-body MRI
measurement, all subjects participated in
an intranasal insulin and placebo experi-
ment (on 2 separate days with a time lag
of 7–14 days) with repetitive measure-
ment of CBF by MRI. Participants were
blinded to the order of the conditions.

Appetitive effects on memory functions and
weight loss and demonstrating bene-
cial effects on memory functions and
metabolism in healthy participants as
well as patients with diabetes and cog-
nitive impairments (5). Hence, intrana-
sal insulin is a possible therapeutic
approach for the treatment of obesity,
type 2 diabetes, and neurodegenerative
diseases.

In functional magnetic resonance im-
aging (fMRI) studies using blood oxygen
dependent contrast, insulin signif-
ically was shown to attenuate resting
activity as well as visual processing
of food images in healthy lean adults.
Thereby, regions well beyond the
homeostatic system of the brain were
modulated, especially the occipital and
prefrontal brain regions and the hypo-
thalamus (6–8). Compared with blood
oxygen level–dependent fMRI, arterial
spin labeling offers quantitative cere-
bral blood flow (CBF) measurements,
providing a well-characterized physio-
logical parameter in physiological units
(mL/100 g brain tissue/min). Hence, ar-
terial spin labeling measurements have
been proposed to be ideally suited for
pharmacological MRI studies (9).

No study has evaluated cerebral insulin
action in obese adults to our know-
edge; therefore, we aimed to identify
specific brain regions responsive to in-
tranasal insulin and regions affected
by cerebral insulin resistance. We
performed MRI using arterial spin label-
ing before and 15 and 30 min after ap-
lication of intranasal insulin in lean and
weight-obese adults. We hypothe-
ized that overweight and obese adults will show cerebral insulin resistance in
regions associated with food intake and
eating behavior.

Application of Intranasal Insulin/
Placebo
The insulin and placebo were prepared
as nasal sprays. In a randomized fashion,
participants received on one day 160
units insulin (Actrapid; Novo Nordisk,
Bagsværd, Denmark) and on the other
measurement day, vehicle as placebo.
Participants were blinded to the order
of the conditions.

Oral Glucose Tolerance Test
Before the intranasal MRI experiment
(7–14 days), participants underwent a
75-g OGTT after an overnight fast. Insulin
dositivity during OGTT was estimated
according to Matsuda and DeFronzo (14).

Measurement of Adipose Tissue by
MRI Examinations
On the same day as the OGTT, MRI ex-
aminations were performed in the early
morning on a 1.5T whole-body imager
(MAGNETOM Sonata; Siemens Health-
care, Erlangen, Germany). A whole-body
imaging protocol was used to record a
set of 90–120 parallel transverse slices.
This approach enabled quantification of
body volume, total adipose tissue (TAT),
and total mass of specific fat depots, such
as visceral adipose tissue (VAT) (15).

Whole-Brain fMRI Measurement

Data Acquisition

Scanning was performed on a 3T scan-
er (Tim Trio; Siemens Healthcare)
equipped with a 12-channel transceiver
head coil. Pulsed arterial spin labeling
images were obtained with a PICORE
Table 1—Participant characteristics

<table>
<thead>
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<th></th>
<th>Lean group</th>
<th>Overweight/obese group</th>
<th>P value</th>
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<tbody>
<tr>
<td>Sex (female/male)</td>
<td>10/15</td>
<td>11/12</td>
<td>0.594</td>
</tr>
<tr>
<td>Age (y)</td>
<td>25.88 ± 3.30</td>
<td>26.73 ± 3.55</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>22.65 ± 2.01</td>
<td>31.26 ± 4.77</td>
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<td>Waist-to-hip ratio</td>
<td>0.82 ± 0.08</td>
<td>0.86 ± 0.08</td>
<td>0.066</td>
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<tr>
<td>Lean body mass</td>
<td>54 ± 13.72</td>
<td>62.91 ± 17.01</td>
<td>0.044</td>
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<tr>
<td>Percent body fat</td>
<td>21.75 ± 6.25</td>
<td>34.96 ± 11.32</td>
<td>&lt;0.001</td>
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<td>OGTT-derived insulin sensitivity index (AU)</td>
<td>16.0 ± 7.6</td>
<td>10.24 ± 6.72</td>
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</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.2 ± 0.3</td>
<td>5.3 ± 0.3</td>
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<tr>
<td>HbA1c (mmol/mol)</td>
<td>33.15 ± 3.1</td>
<td>34.2 ± 3.04</td>
<td>—</td>
</tr>
</tbody>
</table>

Insulin and glucose values during MRI experiment

Intranasal spray*  
Fasting plasma insulin (pmol/L)  
Insulin  
Placebo  
Fasting plasma glucose (mmol/L)  
Insulin  
Placebo  
AUC insulin 0–120 min  
Insulin  
Placebo  
AUC glucose 0–120 min  
Insulin  
Placebo

Whole-body MRI (L)  
TAT  
VAT  
SAT  
Nonadipose tissue lower extremities  
Nonadipose tissue upper extremities

Data are mean ± SD. P values are comparison of unadjusted loge-transformed data by ANOVA. AU, arbitrary unit; SAT, subcutaneous adipose tissue.  
*No significant within-group differences between intranasal placebo and insulin day. P values are lean vs. obese, insulin day.

(proximal inversion with control for off-resonance effects) Q2TIPS (quantitative imaging of perfusion using a single subtraction) sequence by using a frequency offset-corrected inversion pulse and echo planar imaging readout for acquisition (16). Sixteen axial slices with a slice thickness of 5 mm (1.00-mm gap) were acquired in ascending order. Each measurement comprised 79 alternating tag and control images with the following imaging parameters: inversion time (TI) 1 = 700 ms, TI2 = 1,800 ms; repetition time = 3,000 ms; echo time = 19 ms; inplane resolution = 3 × 3 mm²; field of view = 192 mm; matrix size 64 × 64; and flip angle = 90°. The same sequence was used to estimate the equilibrium magnetization of the blood for absolute CBF quantification with the same parameters as mentioned previously, except that repetition and TI2 were chosen to be 10 and 4 s, respectively (17). In addition, a high-resolution T1-weighted anatomical image was acquired.

Image Processing

Image preprocessing was performed by using the ASLtbx (18) program with SPM8 extension (Wellcome Trust Centre for Neuroimaging). We used the general kinetic model for absolute perfusion quantification, as previously reported (19). Functional images were coregistered to the individual anatomical image and smoothed (full width at half maximum 6 mm). Perfusion images were generated by calculating the control — tag differences by using surround subtraction. For accurate CBF quantification (mL · 100 g⁻¹ · min⁻¹), we used an M0 map instead of a global value to quantify the perfusion on each voxel. The high-resolution T1-weighted image was normalized in Montreal Neurological Institute space (1 × 1 × 1 mm) using SPM8 unified segmentation normalization, and the resulting parameter file was used with the individual coregistered CBF maps in normalized space (3 × 3 × 3 mm). A brain mask was used to exclude extracranial voxels in the normalized CBF images. Baseline-corrected CBF maps were computed to quantify the CBF changes 15 and 30 min after intranasal insulin/placebo administration.

Figure 1—Study design. The order of placebo and insulin day were balanced over participants. NASAL, intranasal application of insulin or placebo; VAS, visual analog scale. (A high-quality color representation of this figure is available in the online issue.)
Statistical Analyses

Whole-brain analyses were performed using a voxelwise approach. CBF maps of each subject, corrected for basal measurement (CBF 2 – CBF 1; CBF 3 – CBF 1), were entered into a second-level analysis in SPM8 using a full factorial model to determine the effect of insulin versus placebo (factors: condition and time) 15 and 30 min after applying the spray and the effect of lean versus overweight/obese (factor: group). Additionally, a full factorial model was calculated to evaluate the effect of sex, which was entered as a separate between-subject factor. We first evaluated main effects and interactions using F-contrasts (two-tailed F tests) followed by directional T-contrasts if results of F-contrasts were statistically significant. A statistical threshold of $P < 0.05$ familywise error (FWE) corrected for multiple comparisons at a cluster level was applied to all contrasts. Furthermore, we used a region of interest (ROI) approach for the bilateral hypothalamus using a small volume correction for multiple comparisons ($P < 0.05$ FWE corrected). The hypothalamic ROI was based on the Montreal Neurological Institute coordinates of Baroncini et al. (20), including the lateral ($x: \pm 6$; $y: -10$; $z: -10 + 3$ mm sphere radius; total of 38 voxels) and medial hypothalamus ($x: \pm 4$; $y: -2$; $z: -12 + 2$ mm sphere radius; total of 16 voxels). Additionally, we extracted CBF values of significant clusters of the main effects and interactions to perform partial correlation analyses with TAT, VAT, OGTT-derived insulin sensitivity index, and eating behavior measurements adjusted for BMI ($P < 0.01$, corrected for number of tests) in SPSS version 20 software (IBM Corporation).

Behavioral and Metabolic Data

Repeated-measures ANOVAs (between-subject factor: group, lean vs. obese, and sex, men vs. women; within-subject factor: condition, insulin vs. placebo) were calculated for wanting and liking of savory and sweet foods and hunger ratings separately.

For each trait questionnaire, a MANOVA was calculated with group (lean vs. obese) and sex as between-subject factors. Results surviving a statistical threshold of $P < 0.05$ were considered statistically significant (using SPSS version 20 software) (data not shown).

For the metabolic parameters, ANOVAs were calculated to evaluate group differences for peripheral measures. Areas under the curve (AUCs) were calculated for glucose and insulin during the MRI experiment; paired t tests were used to test for significant differences between insulin and placebo spray. Results surviving a statistical threshold of $P < 0.05$ were considered statistically significant (using SPSS version 20 software).

RESULTS

MRI Data

Basal CBF

We used the basal measurement before nasal spray application to evaluate intrasubject repeatability and scanner variability. There was no significant difference in CBF on insulin versus placebo day before nasal spray application ($P = 0.96$); the mean CBF value of insulin day basal measurement (mL/100 g brain tissue/min) was 43.92 (SE 1.22); the mean CBF value of placebo day was 43.97 (SE 1.17). Furthermore, we observed a significant positive correlation between the two baseline CBF measurements ($r_{\text{spearman}} = 0.509, P < 0.0001$).

Effect of Intranasal Insulin on Regional CBF in Lean and Obese Adults

The whole-brain voxelwise analysis showed a significant main effect of group in the right lingual gyrus ($P_{\text{FWE}} = 0.047$) and a significant interaction between group and condition in the right middle frontal gyrus (MFG) ($P_{\text{FWE}} = 0.006$) (Fig. 2). Post hoc T-contrasts revealed in the right lingual gyrus increased CBF in overweight/obese compared with lean participants after insulin and placebo application and in the right MFG decreased CBF to insulin compared with placebo in lean participants and increased CBF to insulin compared with placebo in overweight/obese participants (Supplementary Table 1). More specifically, 30 min after insulin application, overweight/obese participants showed increased CBF compared with lean participants ($T = 4.59, P = 0.003$) in the right MFG, and 30 min after placebo application, lean participants showed increased CBF compared with overweight/obese participants ($T = 3.44, P = 0.01$) in the right MFG. Within-group T-contrasts showed a

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**Figure 2**—Interaction between group (lean vs. overweight/obese) and condition (insulin vs. placebo) in the prefrontal cortex (color-coded t value map; $P < 0.001$, uncorrected for display). Post hoc analyses showed a significant reduction in CBF 15 and 30 min after application of intranasal insulin compared with placebo in lean participants only. Scatter plot on the left shows significant positive correlation between the change in prefrontal CBF after insulin application and OGTT-derived insulin sensitivity index adjusted for BMI ($r = 0.608, P < 0.001$). Bar graphs on the right represent baseline-corrected changes in CBF (mean ± SE) 30 min after insulin and placebo application in the prefrontal cortex in lean and obese adults. *$P < 0.05$ for post hoc analyses. AU, arbitrary unit; R, right.
significant difference in the right MFG between insulin and placebo 30 min postspray in the lean group (T = 4.34, P = 0.012) and overweight/obese group (T = 5.42, P < 0.001) (Fig. 2, bar graph). Furthermore, the postinsulin response in the right MFG correlated negatively with the OGTT-derived insulin sensitivity index adjusted for BMI (r_{adj} = −0.608, P < 0.001) and correlated positively with the disinhibition scale of the German Three Factor Eating Questionnaire (r = 0.442, P = 0.004) and subscale for cues that may trigger food cravings of the Food Craving Questionnaire (r = 0.393, P = 0.007), also adjusting for BMI (r_{adj} = 0.339 [P = 0.03] and 0.319 [P = 0.04], respectively). Additionally, we performed an ROI analysis of the hypothalamus, revealing a significant main effect of condition (P_{FWE} = 0.028) (Fig. 3) resulting in a CBF decrease after insulin compared with placebo application (Supplementary Table 1). The hypothalamic CBF response showed no significant correlation with the OGTT-derived insulin sensitivity index, TAT, or eating behavior measurements (P > 0.05). However, we observed 15 min after insulin spray a significant positive relationship between the hypothalamic CBF response and VAT after adjusting for TAT, subcutaneous adipose tissue, and nonadipose tissue (r_{adj} = 0.371, P < 0.015, df = 42) (Fig. 3, scatter plot). Moreover, we observed a significant interaction between group and VAT for the hypothalamic CBF response (ANCOVA F = 5.56, P = 0.02). Further subgroup analyses revealed in the overweight/obese group a significant positive correlation between VAT and the hypothalamic response to insulin (r_{adj} = 0.609, P = 0.003, df = 17); no such correlation was observed in lean participants (r_{adj} = 0.245, P = 0.299, df = 19) (Supplementary Fig. 1). Hence, overweight/obese participants with lower VAT showed a stronger reduction in hypothalamic CBF 15 min after insulin application. No main effect of sex, time (15 vs. 30 min), group-by-time interaction, condition-by-time interaction, or interactions with sex were observed.

**Behavioral Data**

**Wanting/Liking Results**

Explicit rating for wanting and liking of high-caloric savory and sweet foods were evaluated 60 min after insulin and placebo application. No main effects or interactions for group (lean vs. obese), sex, or condition (insulin vs. placebo) were observed for liking. For wanting of sweet foods, we observed a significant group-by-sex-by-condition interaction (F = 8.57, P = 0.006) (Supplementary Fig. 2). Post hoc analyses showed in men only a significant difference between lean and obese participants; thereby, lean men showed a significant reduction after insulin compared with placebo for the wanting of sweet foods (P = 0.01, using Tukey-honest significant difference correction) (Fig. 4). No main effect of sex, group, or condition and interactions between condition and group or sex were observed for the wanting of sweet foods.

For wanting of savory foods, we observed a main effect of sex (F = 8.5, P = 0.006), revealing an increased wanting for savory foods in men compared with women. Furthermore, we observed a significant sex-by-condition interaction (F = 4.68, P = 0.036) and group-by-sex-by-condition interaction (F = 5.86, P = 0.02). Post hoc analyses revealed in lean participants a significant difference between men and women (P = 0.03, using Tukey-honest significant difference correction), revealing a decrease in women and an increase in men after insulin compared with placebo for the wanting of savory foods. No main effect of group or condition and no further interactions were observed for the wanting of savory foods.

**Hunger Ratings**

We observed a main effect of time, such that the subjective feeling of hunger increased with time (60 vs. 120 min post-spray) for both insulin and placebo day (F = 8.44, P = 0.006). No main effect of group, sex, or condition (insulin vs. placebo), and no interactions were found.

**Metabolic Parameters**

No significant differences were observed for AUC insulin and AUC glucose 120 min after intranasal insulin compared with placebo in either lean or obese participants (P > 0.05). However,
as expected, significant differences were found between lean and obese participants in fasting and postspray insulin and glucose concentrations ($P < 0.05$) (Table 1).

**CONCLUSIONS**

In this study, we aimed to evaluate central insulin action in lean, overweight, and obese adults to identify brain regions affected by insulin resistance. Although both lean and overweight/obese participants revealed a significant CBF decrease in the hypothalamus after insulin compared with placebo application, the prefrontal cortex responded only in the lean group with a decrease in CBF, pointing to selective insulin resistance. Of note, the magnitude of hypothalamic response correlated with the amount of VAT independent of other fat compartments in the overweight/obese group, whereas the prefrontal response to insulin was associated with peripheral insulin sensitivity and eating behavior (e.g., disinhibition, food craving). Regarding behavior, we were able to observe a significant reduction for the wanting of sweet foods after insulin application in lean men only.

The hypothalamus belongs to the brain’s homeostatic system that controls whole-body energy balance and is fundamental in the regulation of peripheral homeostasis. Both lean and overweight/obese participants notably showed a marked insulin-induced hypothalamic CBF decrease. The inhibition of the hypothalamus could lead to an increase in satiety and potentially to an attenuated response to food. Furthermore, this change in CBF probably contributes to the homeostatic control of whole-body metabolism (21). Concomitantly, we found in lean individuals that nasal insulin administration correlates with peripheral insulin sensitivity (7) and improves peripheral insulin sensitivity through hypothalamic and parasympathetic outputs in lean but not in obese men (22), providing further evidence that peripheral and central insulin sensitivity are highly linked processes. Additionally, the insulin-induced reduction in hypothalamic CBF in the current study correlates significantly with the amount of VAT independent of the individual’s other fat compartments. Thus, participants with higher visceral fat content reveal a diminished hypothalamic response to insulin, indicating a relationship between cerebral insulin resistance and metabolically unfavorable abdominal adiposity (23). Indeed, during the course of a lifestyle intervention study, individuals with high cerebral insulin sensitivity displayed more loss of visceral fat than those who were brain insulin resistant (24). According to these findings, we speculate that soluble factors like fatty acids derived from visceral fat may cause cerebral insulin resistance, which then may aggravate hypothalamic dysfunction, resulting in a vicious cycle. Furthermore, considerable evidence has been generated in rodent studies indicating the pivotal role of the hypothalamus in insulin action and regulating hepatic glucose production (25) and lipid metabolism (26,27). Alternatively, impaired hypothalamic insulin signaling could cause increased accumulation of visceral fat due to altered response of the autonomic nervous system.

The prefrontal cortex plays a crucial role in cognitive control and decision-making, including inhibitory control of feeding. Studies in successful dieters and weight loss maintainers revealed increased neural activation in the prefrontal cortex (28,29), which could be a possible mechanism in making healthy choices. Specifically, when told to resist cravings, heightened prefrontal activity was observed in successful weight loss maintainers after gastric bypass surgery (30). Furthermore, individuals’ endogenous serum insulin levels determined the reactivity of limbic regions and the prefrontal cortex to food cues after glucose ingestion (31,32). Exogenous intranasal insulin had comparable effects and reduced resting state prefrontal cortex activity in lean women (8). Concurrently, we found intranasal insulin to induce a differential pattern, reducing prefrontal cortex CBF in lean participants and increasing it in obese participants. This prefrontal response significantly correlates with peripheral insulin sensitivity. As a result, participants with higher peripheral insulin sensitivity revealed a stronger decrease, whereas those with insulin resistance showed an increase in prefrontal activity in response to intranasal insulin. Additionally, the insulin-induced activation pattern correlated positively with behavioral measurements as disinhibition and food craving. The eating disinhibition scale has also been described as the susceptibility for eating problems or disinhibited eating, which occurs when a person loses control and overeats in response to a stimulus (33). Hence, the participants more susceptible to disinhibited eating along with food craving failed to respond to insulin with a reduction in prefrontal CBF. Concomitantly, peripheral insulin resistance has been linked to food cue-induced food craving in obese individuals (34). Cerebral insulin resistance of the prefrontal cortex may promote reduced inhibitory control toward food cues after food intake and could thereby contribute to overeating behavior.

Independent of condition (insulin or placebo), overweight/obese participants showed an increase in CBF in the visual cortex after nasal spray application. This is in line with our previous neuroimaging studies showing altered food cue activity and functional connectivity in the visual cortex in obese individuals (35–37).

Additionally, we evaluated the explicit wanting and liking of high-caloric foods 60 min after insulin or placebo application. Although liking is a hedonic or affective reaction, wanting is important for the motivational aspects (incentive salience) of food reward (38). Even though we observed no sex effects on brain insulin action, we found in lean men only a significant reduction for the wanting of sweet foods after insulin application. Concomitantly, 8 weeks of intranasal insulin administration significantly reduced body fat in men but not in women, pointing to a differential sensitivity to the catabolic effects of nasal insulin based on sex (39). However, in the postprandial state, intranasal insulin reduced food intake and appetite in women 2 h after administration, indicating that insulin also affects hedonic eating in women (40). Taken together, intranasal insulin has the potential to reduce the motivational aspects for food, which can decrease food intake by intensifying satiety. However, whether these sex-specific behavioral effects are reflected by central alterations still needs to be investigated.

In summary, central insulin action was selectively impaired in the prefrontal cortex in overweight and obese adults and in the hypothalamus in adults with high VAT. The successful inhibition of the hypothalamus and prefrontal cortex could lead to an increase in satiety and potentially to an attenuated response to food, which could explain
the reduction for the wanting of sweet foods in lean men. Obesity, however, dampens this attenuation, promoting an altered homeostatic set point and potentially reducing the inhibitory control contributing to overeating behavior. The identification of hormone-brain interactions that modulate food intake can potentially aid in the development of effective obesity therapies.

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**Author Contributions.** S.K. contributed to performing the experiment, data research, and writing of the manuscript. M.H. contributed to the data research, discussion, and review and editing of the manuscript. R.V. and K.S. contributed to the review and editing of the manuscript. J.M. contributed to the discussion and review of the manuscript. H.P. contributed to the data research and review and editing of the manuscript. H.P. 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.

**References**