Marked differences in gustatory and gastrointestinal sensitivity to oleic acid between lean and obese men\(^1-4\)

Jessica E Stewart, Radhika V Seimon, Bärbel Otto, Russell SJ Keast, Peter M Clifton, and Christine Feinle-Bisset

ABSTRACT

Background: Both orosensory stimulation and feedback from the gastrointestinal tract contribute to energy intake regulation. Objective: We evaluated the hypothesis that overweight or obese subjects would be less sensitive to both oral and intraduodenal oleic acid exposure than would lean subjects. Design: Eleven overweight or obese and 8 lean men were studied on 2 occasions, during which antropyloroduodenal pressures, plasma cholecystokinin and peptide YY, and appetite were measured during 90-min intraduodenal infusions of saline or oleic acid (18:1 load: 0.78 kcal/min); energy intake (buffet lunch) was determined immediately afterward. Oral detection thresholds for 18:1 and recent dietary intake (2-d recall) were also quantified. Results: In lean subjects, the number of isolated pyloric pressure waves (IPPWs) was greater during 18:1 infusion than during saline infusion (P < 0.05); no significant differences were observed between the 18:1 and saline infusions in the overweight or obese subjects. In both groups, 18:1 stimulated plasma cholecystokinin and peptide YY and suppressed energy intake compared with saline (P < 0.05), with trends for reduced cholecystokinin and energy intake responses in the overweight or obese subjects. Detection thresholds for 18:1 were greater in overweight or obese (7.9 ± 0.1 mmol/L) than in lean (4.1 ± 0.4 mmol/L) subjects (P < 0.05). Overweight or obese subjects had greater recent energy (P < 0.05) and fat (P = 0.07) intakes than did lean subjects. There was a direct relation (r = 0.669) of body mass index with 18:1 detection thresholds and inverse relations (r < −0.51) of IPPWs with body mass index and 18:1 detection thresholds (P < 0.05). Conclusions: The ability to detect oleic acid both orally and within the gastrointestinal tract is compromised in obese men, and oral and gastrointestinal responses to oleic acid are related. This trial was registered at www.actr.org.au (Australian New Zealand Clinical Trials Registry) as 12609000557235. Am J Clin Nutr 2011; 93:703–11.

INTRODUCTION

Nutrient detection occurs at various stages of food consumption, during which the digestive products of nutrients interact with chemosensory cells within the oral epithelium (taste receptor cells) and gastrointestinal tract (enteroendocrine cells). This chemoreception initiates functional responses, including taste perception, peptide secretion, and alterations in gastrointestinal motility, which play an important role in the liking of food, appetite regulation, and satiety (1, 2). In healthy subjects, the presence of fat in the small intestine slows gastric emptying [resulting from the stimulation of pyloric, and suppression of antral and duodenal, pressure waves (PWs)] (3, 4); stimulates the release of gut hormones, including cholecystokinin (CCK) and peptide YY (PYY) (5, 6); and suppresses subsequent energy intake (5). Conversely, in obesity, evidence indicates that the gastrointestinal regulation of food intake may be abnormal. For example, studies have reported accelerated (7), normal (8), and delayed gastric emptying (9) and lower fasting and postprandial concentrations of PYY (10) in obese subjects. The mechanisms behind these abnormalities remain unclear, but may involve desensitization of gastrointestinal enteroendocrine cells, which may adapt to dietary conditions, including consumption of a high-fat diet (11).

Fundamental similarities in mechanisms involved in the detection of sweet, umami, bitter (12), and fat (13) stimuli between gastrointestinal enteroendocrine cells and taste receptor cells in the oral cavity have been shown. In the oral cavity, direct associations between sensitivity to certain (eg, bitter) tastants, dietary intake, and specific food preferences have been reported (14). In the context of obesity, both oral and gastrointestinal sensitivity to fat and the relation with regulation of fat and energy consumption.

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intake are of particular interest. We recently established in lean humans inverse associations between oral fat sensitivity with fat consumption and body mass index (BMI; in kg/m²) (15). It is currently unknown in humans whether oral sensitivity and gastrointestinal responses to fatty acids differ between lean and obese individuals and, if so, whether any differences are related to habitual energy and fat intakes and whether oral and gastrointestinal sensitivities to fatty acids are related.

The aims of this study were, therefore, to evaluate the hypotheses that gastrointestinal and oral sensitivities to oleic acid, common in the food supply, are related and that sensitivity at both locations is compromised in the obese and directly related to fat consumption. For this purpose, we investigated in lean and overweight or obese men the antropyloroduodenal motor, gut hormone, appetite, and energy intake responses to intraduodenal oleic acid infusion and quantified oral detection thresholds for oleic acid and recent dietary intakes.

SUBJECTS AND METHODS

Subjects

Eight lean (median age: 36 y; age range:19–54 y; median BMI: 23; BMI range: 21.3–25.0) and 11 overweight (n = 4)/obese (n = 7) (median age: 37 y; age range: 23–58 y; median BMI: 31; BMI range: 25.9–36.2) subjects participated in the study. Only healthy men were included, because they have been reported to be more sensitive to dietary manipulation than women (16) and to avoid any influence of the menstrual cycle on the data (17). We calculated that the inclusion of lean (n = 8) and overweight or obese (n = 11) subjects would allow us to detect differences in oral taste thresholds of 3.5 mmol/L and in the number of peak pyloric PWs of 5 between lean and overweight or obese individuals at β = 0.05 with a power of 80%. All subjects were unrestrained eaters (defined by a score of <12 on the Three Factor Eating Questionnaire) (18); were free from gastrointestinal or other disease, including diabetes (fasting glucose: overweight or obese subjects, 5.9 ± 0.1 mmol/L; lean subjects, 5.6 ± 0.1 mmol/L); were nonsmokers, consumed <20 g alcohol/d, and were not taking any medication known to affect appetite and/or gastrointestinal motility. The study was approved by the Royal Adelaide Hospital Ethics Committee and registered as a clinical trial (www.actr.org.au, registration number 12609000557235). All subjects provided written informed consent before participation.

Study outline

Each subject was studied on 3 occasions, separated by 3–14 d, in randomized order. On 2 d, the subjects received 90-min intraduodenal infusions of either oleic acid (18:1; Sigma-Aldrich, St Louis, MO) or 0.9% saline (control) to evaluate gastrointestinal hormone, motor, and energy intake responses. On the third occasion, the subjects’ oral detection thresholds for 18:1 were determined by using the 3-Alternative Forced Choice procedure (19). The subjects’ recent dietary intakes were estimated by 2-d dietary recall, weights were measured with dedicated scales (Selacs HW-200 KGY; A&D Co Ltd, Adelaide, Australia), and heights were measured while the subjects were wearing light clothing (20).

Study protocol: intraduodenal infusions

The subjects were provided with a standardized meal (beef lasagna; McCain Foods, Wendouree, Victoria, Australia) for dinner on the evening before each study at 2000 and fasted from solids and liquids thereafter until attending the laboratory at 0830. The subjects were intubated with a 16-channel manometric catheter (Dentsleeve International Ltd, Ontario, Canada) through an anesthetized nostril. The correct positioning of the catheter across the pylorus [with 6 side holes (channels 1–6) in the antrum, a 4.5-cm sleeve sensor (channel 7) and 2 channels on the back of the sleeve (channels 8 and 9), across the pylorus, and 7 side holes (channels 10–16) in the duodenum, all spaced at 1.5-cm intervals (21)], was ensured by continuous monitoring of the transmucosal potential difference (3). An additional channel, positioned ~12 cm distal to the pylorus, was used for intraduodenal infusions. After phase III of the migrating motor complex, an intravenous cannula was inserted into a forearm vein for blood sampling. Then (t = −10 min), a baseline blood sample was collected and a visual analog scale questionnaire (VAS) was used for the measurement of appetite perceptions, including fullness, hunger, desire-to-eat, and prospective food consumption (defined as “How much food do you think you could eat, if given a meal now?”), bloating and nausea (22). Each sensation was evaluated on a 100-mm horizontal line, where 0 mm represented “sensation not felt at all” and 100 mm “sensation is felt the greatest.” The subjects were asked to indicate how they were feeling at a particular time by placing a vertical stroke on the 100-mm line (22). At t = 0 min, duodenal infusion of either saline or 18:1 commenced for 90 min. The 18:1 solution was prepared by dissolving 12.9 g 18:1 with 3 mL of 1 mmol sodium hydroxide/L (Sigma-Aldrich) in distilled water to a volume of 300 mL (resulting pH: 7.9); 18:1 was kept in solution by continuous stirring throughout the study. The pH of the saline control was adjusted to 7.9 by the addition of a solution of 50 μL of 1 mmol sodium hydroxide/L. The solutions were administered at a rate of 2 mL/min (total volume: 180 mL over 90 min) by using a volumetric infusion pump (Imed Gemini PC-1; C&A Company, Royse City, TX), and 18:1 was delivered at 0.78 kcal/min (70 kcal in total) (23). During infusions, 10-mL blood samples were obtained and the VAS was completed immediately afterward, every 15 min (ie, at t = 15, 30, 45, 60, 75, and 90 min), as previously described (5, 24). At t = 90 min, the infusion was discontinued, and the subjects were extubated and offered a cold, buffet-style meal to consume until comfortably full (between t = 90 and 120 min) (25). Thereafter, the subjects were allowed to leave the laboratory.

Study protocol: oral fatty acid sensitivity

Oral sensitivity to 18:1 was determined by using the 3-Alternative Forced Choice technique—an established procedure to determine taste thresholds (19). For test meal preparation, 18:1 was mixed at various concentrations (0.02, 0.06, 1, 1.4, 2, 2.8, 3.8, 5, 6.4, 8, 9.8, and 12 mmol/L) with long-life nonfat milk (Homebrand, Woolworths, Bella Vista, New South Wales, Australia). To minimize textural cues due to the addition of fat, the samples were mixed with 5% (wt:vol) gum acacia (Deltagen, Boronia, Victoria, Australia) and liquid paraffin (Merck, Darmstadt, Germany) (26). To prevent oxidation of 18:1, the samples were mixed with 0.01% (wt:vol) EDTA (Merck). The samples were homogenized for 30 s/100 mL solution (L4RT homogenizer;
Silverson Longmeadow, MA), prepared fresh on the day of testing, and served at room temperature. To prevent confounding from nonoral sensory inputs (eg, smells), the subjects wore nose clips during the tests. The low concentrations of fatty acids used were not expected to cause irritation (26).

Taste thresholds were established on a single day of testing, and all subjects were asked to refrain from eating, drinking, or oral irritants (eg, gum, mouthwash) 1 h before testing. On arrival in the laboratory, the subjects were presented with 3 samples per set: 2 control samples and 1 “odd” sample containing 18:1 in ascending order of concentration from the lowest (0.02 mmol/L) to the highest (12 mmol/L). In each set, the subjects were asked to identify the odd sample. If they were correct, they were presented with 3 more samples at the same 18:1 concentration; if they were incorrect, they were presented with 3 samples at the next higher concentration. This testing procedure continued until the subject identified the odd sample at a given concentration 3 consecutive times, and that concentration was defined as the subject’s detection threshold for 18:1.

Two-day diet records

Recent dietary intake was estimated by using a 2-d dietary recall, during which subjects recalled all foods and beverages consumed on the previous day and on one weekend day within the previous week (20). To assist in the accurate recall of portion sizes, the subjects were provided with validated and quantified pictures of food portions for common foods, such as cereals, meats, take-away foods, spreads, vegetables, rice, pasta, and beverages (University of Otago, Department of Human Nutrition, Dunedin, New Zealand).

Data analysis

Antropyloroduodenal pressures

Antropyloroduodenal pressures were digitized and recorded on a computer-based system and were analyzed for the number and amplitude of isolated pyloric PWs (IPPWs), and the number and amplitude of duodenal PWs, as described previously (21).

Gut hormone concentrations

For the subsequent analysis of plasma concentrations of CCK and PYY, 10-mL venous blood samples were collected in ice-chilled EDTA-treated tubes containing 400 kIU aprotinin (Trasylo; Bayer Australia Ltd, Pymble, Australia) per 1 mL blood. Plasma was obtained by centrifugation of blood samples at 3200 rpm for 15 min at 4°C. The plasma samples were frozen at −70°C. Plasma CCK concentrations (pmol/L) were measured by a sensitive and specific radioimmunoassay, as described previously (27). The detection limit was 0.3 pmol/L. The intraassay CV was 5.6%, and the interassay CV was 12.3%. Immunoreactive total human plasma PYY (pg/mL) was measured with a commercially available radioimmunoassay (Linco Research, St Charles, MO) (28). The assay does not distinguish between PYY (1–36) and PYY (3–36). The intraassay CV was 2.9%, the interassay CV was 7.1%, and the detection limit was 10 pg/mL.

Energy intake and recent dietary intake

Energy intake in response to the intraduodenal infusions was quantified from the amount of food eaten at the buffet meal, the ingredients of which were weighed before and after consumption to quantify the amount (g) of food and beverages consumed. Energy intake (kJ) and macronutrient distribution (% of energy from fat, carbohydrate, and protein) were then quantified by using Foodworks (version 3.01; Xyris Software, Highgate Hill, Queensland, Australia) (25). Recent dietary intake was quantified by calculating mean energy intakes (kJ/2 d) and macronutrient distribution by using Foodworks.

Statistical analysis

All data were analyzed by using SPSS version 17 (SPSS Inc, Chicago, IL). Baseline values for VAS and hormone concentrations were calculated as the means of values at t = −10 min and t = 0 min. Baseline values for the number and amplitude of antral and duodenal PWs and IPPWs were obtained from the means of values between t = −15 and 0 min. During the 90-min infusion period, antral and duodenal PWs were expressed as total numbers and mean amplitudes, which were used to calculate the motility index (MI) (29). For IPPWs, numbers and amplitudes were expressed as means over 15-min intervals. For plasma hormone concentrations and VAS scores, mean values were calculated at each time point.

Repeated-measures analysis of variance (ANOVA) with time and treatment as within-subject factors and subject group (lean or overweight or obese) as a between-subject factor was used to analyze IPPWs, hormones, and VAS scores. Antral and duodenal pressures and energy intake from the buffet meal were analyzed by using repeated-measures ANOVA with treatment and subject group as factors. If the ANOVA indicated significant effects, pairwise comparisons (with Bonferroni corrections for multiple comparisons) were performed. Independent-samples t tests were used to compare oral 18:1 detection thresholds and recent fat and energy intakes between lean and overweight or obese subjects. Before this, oral detection thresholds were log transformed to account for the slight skewedness of the data. Pearson correlations were performed to evaluate relations between IPPWs, hormone concentrations, appetite perceptions, energy and macronutrient intakes, 18:1 detection thresholds, and BMI. For this purpose, the number of IPPWs was expressed as the area under the curve (AUC; calculated by applying the trapezoidal rule to 15-min intervals and respective data points during the 90-min infusion period), the total number between t = 0 and 90 min, and peak numbers (identified as the peak value from the 90-min profiles obtained for each subject). AUCs between t = 0 and 90 min were also calculated for plasma hormone concentrations and VAS scores and the peak concentration for plasma CCK. For all gastrointestinal and appetite variables, data obtained during saline infusion were subtracted from those obtained during the 18:1 infusion, and the resulting values were used to calculate correlations, which were exploratory and thus not corrected for multiple comparisons. Statistical significance was accepted at P < 0.05.

RESULTS

The study protocol was well tolerated by all subjects, and the treatments were not associated with any gastrointestinal symptoms or other adverse effects.
Gastrointestinal and appetite responses to intraduodenal infusions

Antral pressures

A significant effect of treatment \( F_{(1,17)} = 21.6, P < 0.001 \), but not of group, was observed on the MI of antral PWs, which was lower during 18:1 infusion than during saline infusion (Table 1).

Isolated pyloric pressure waves

No differences in baseline values were observed between subject groups or treatment days [lean subjects, saline infusion (lean-saline): 0 \( \pm \) 0; lean subjects, 18:1 infusion (lean-18:1): 0 \( \pm \) 0; overweight or obese subjects, saline infusion (overweight/obese-saline): 0 \( \pm \) 0; overweight or obese subjects, 18:1 infusion (overweight/obese-18:1): 0 \( \pm \) 0]. There was a significant treatment \( \times \) group interaction \( F_{(1,17)} = 5.3, P < 0.05 \) and a time effect \( F_{(6,102)} = 2.68, P < 0.05 \) for the number of IPPWs (Figure 1). In lean subjects, the number of IPPWs was greater during 18:1 infusion than during saline infusion \( F_{(1,17)} = 19.8, P < 0.01 \). In contrast, no difference in IPPWs was observed between 18:1 and saline in the overweight or obese subjects \( F_{(1,17)} = 2.87, P = 0.181 \). No effects of treatment, group, or time were observed on the amplitude of IPPWs (data not shown).

Duodenal pressures

A trend for a significant effect of treatment \( F_{(1,17)} = 4.3, P = 0.053 \), but not of group, was observed on the MI of duodenal PWs, which tended to be lower during 18:1 infusion than during saline infusion (Table 1).

Gut hormones

Plasma CCK concentrations

No significant differences in baseline values were observed between subject groups or treatment days (lean-saline: 0.80 \( \pm \) 0.16 pmol/L; lean-18:1: 0.98 \( \pm \) 0.23 pmol/L; overweight/obese-saline: 0.62 \( \pm \) 0.16 pmol/L; overweight/obese-18:1: 0.54 \( \pm \) 0.11 pmol/L). A significant treatment \( \times \) time interaction \( F_{(6,102)} = 3.4, P < 0.01 \) and a trend for a significant treatment \( \times \) group \( F_{(1,17)} = 3.68, P = 0.076 \) interaction for plasma CCK were observed (Figure 2A). In both lean and overweight or obese subjects, plasma CCK was greater after 18:1 infusion than after saline infusion \( F_{(1,17)} = 67.7, P = 0.001 \), and there was a trend for this effect to be greater in lean subjects \( F_{(1,17)} = 3.68, P = 0.076 \). Plasma CCK was greater during 18:1 infusion than during saline infusion between \( t = 30 \) and 90 min \( F_{(1,17)} = 4.2, P < 0.05 \).

Plasma PYY concentrations

No significant differences in baseline values were observed between subject groups or treatment days (lean-saline: 106 \( \pm \) 11 pg/mL; lean-18:1: 108 \( \pm \) 8 pg/mL; overweight/obese-saline: 138 \( \pm \) 16 pg/mL; overweight/obese-18:1: 131 \( \pm \) 12 pg/mL). A significant treatment \( \times \) time interaction \( F_{(6,102)} = 13.7, P < 0.01 \), but no group effect, was observed for plasma PYY (Figure 2B). Plasma PYY concentrations were significantly greater after 18:1 infusion than after saline infusion between \( t = 60 \) and 90 min \( F_{(1,17)} = 4.6, P < 0.05 \).

Appetite perceptions

No significant differences in baseline values were observed. A significant effect of time, but not of treatment or group, was observed on scores for hunger \( F_{(6,102)} = 6.2, P < 0.001 \), desire to eat \( F_{(6,102)} = 3.3, P < 0.01 \), and bloating \( F_{(6,102)} = 3.6, P < 0.01 \), which all increased during the infusions. No effects on fullness, prospective consumption, or nausea were observed (data not shown).

Energy and macronutrient intakes: buffet meal

Significant effects of treatment, but not of group, were observed on energy \( F_{(1,17)} = 6.7, P < 0.05 \), and protein (g) \( F_{(1,17)} = 4.6, P < 0.05 \) intakes, and a trend for a significant effect of treatment was observed on fat intake (g) \( F_{(1,17)} = 8.8, P = 0.08 \); these values were lower after 18:1 infusion than after saline infusion. A trend for a significant treatment \( \times \) group interaction \( F_{(1,17)} = 3.7, P = 0.07 \) on the amount of food consumed (g) after 18:1 infusion was observed, which was suppressed among lean \( F_{(1,17)} = 6.9, P < 0.05 \) but not obese \( F_{(1,17)} = 0.14, P = 0.908 \) subjects. In addition, the suppression by 18:1 of the

### TABLE 1

Antral and duodenal motility indexes (MIs) during 90-min intraduodenal infusions of saline or oleic acid (18:1) in lean and overweight or obese subjects

<table>
<thead>
<tr>
<th></th>
<th>Lean subjects (n = 8)</th>
<th>Overweight/obese subjects (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline 18:1</td>
<td>Saline 18:1</td>
</tr>
<tr>
<td>Antral MI (mm Hg)</td>
<td>11.4 ( \pm ) 0.8</td>
<td>9.7 ( \pm ) 1.1</td>
</tr>
<tr>
<td>Duodenal MI (mm Hg)</td>
<td>11.8 ( \pm ) 0.5</td>
<td>11.4 ( \pm ) 0.4</td>
</tr>
</tbody>
</table>

1 All values are means \( \pm \) SEMs. There were no significant treatment \( \times \) group interactions for antral and duodenal MIs (repeated-measures ANOVA).

2 Significantly different from respective saline control, \( P < 0.01 \) (repeated-measures ANOVA).

3 Trend for significant difference from respective saline control, \( P = 0.053 \) (repeated-measures ANOVA).

FIGURE 1. Mean (\( \pm \) SEM) number of isolated pyloric pressure waves (IPPWs) during 90-min intraduodenal infusions (0.78 kcal/min) of either saline or oleic acid (18:1) in lean (n = 8) and overweight or obese (n = 11) subjects. A repeated-measures ANOVA with treatment, subject group, and time as factors was used to determine statistical differences. If the ANOVA showed significant effects, pairwise comparisons were performed. Treatment \( \times \) group interaction, \( P < 0.01 \). *Overall curve significantly different between 18:1 and saline in lean subjects, \( P < 0.05 \).
amount of food eaten was lower in the obese than in the lean subjects, both in absolute (g) and in relative (%) terms (both \( P < 0.05 \)) (Table 2). No effects on the amount of food or carbohydrate (g) or the percentage of energy from fat, carbohydrate, or protein consumed at the buffet meal were observed (Table 2).

**18:1 Detection thresholds**

Detection thresholds for 18:1 were significantly greater in overweight or obese (geometric mean ± SEM: 7.9 ± 0.1 mmol/L; range: 6.4–12 mmol/L) than in lean (4.1 ± 0.4 mmol/L; range: 1–12 mmol/L) subjects (\( P < 0.05 \)).

**Recent energy and macronutrient intakes**

Overweight or obese subjects consumed significantly more energy (\( P < 0.05 \)) and tended to consume more food (g) (\( P = 0.088 \)), fat (g) (\( P = 0.076 \)), and protein (g) (\( P = 0.090 \)) than did lean subjects (Table 3). No differences in the amount of carbohydrate consumed (g) or in the percentage of energy from fat, protein, or carbohydrate consumed between groups were observed.

**Correlations between gastrointestinal and oral fat sensitivity**

**Relations between gastrointestinal functions and recent energy and fat intakes**

Inverse relations were observed between the peak number of IPPWs and recent energy (\( r = -0.532, P < 0.05 \)) and fat (g) (\( r = -0.507, P < 0.05 \)) intakes and between the AUC of IPPWs and recent energy (\( r = -0.491, P < 0.05 \)) and fat (\( r = -0.467, P = 0.053 \)) intakes. Inverse relations were also observed between the AUC of plasma CCK concentrations and recent energy (\( r = -0.580, P < 0.05 \)) and fat (\( r = -0.478, P = 0.052 \)) intakes and between peak plasma CCK concentrations and fat intake (\( r = -0.515, P < 0.05 \)).

**Relations between gastrointestinal functions and oral 18:1 detection thresholds**

An inverse relation was observed between the total number of IPPWs and oral 18:1 detection thresholds (\( r = -0.515, P < 0.05 \)) (Figure 3), and a trend for an inverse relation was observed between the AUC of IPPWs and 18:1 detection thresholds (\( r = -0.46, P = 0.055 \)). A trend for an inverse relation was also observed between the AUC of plasma CCK and oral 18:1 detection thresholds (\( r = -0.430, P = 0.075 \)), and an inverse relation was observed between the AUC of plasma PYY and oral 18:1 detection thresholds (\( r = -0.478, P < 0.05 \)).

**Relations between gastrointestinal functions and BMI**

Inverse relations were observed between both total (\( r = -0.615, P < 0.01 \)) and peak (\( r = -0.457, P < 0.05 \)) numbers of IPPWs and BMI, and a trend for an inverse relation was observed between the AUC of CCK and BMI (\( r = -0.410, P = 0.082 \)).

**Relations between oral detection threshold and recent energy and fat intakes and BMI**

A direct relation was observed between 18:1 detection thresholds and BMI (\( r = 0.669, P < 0.01 \)). Trends for relations between BMI and recent energy (\( r = 0.425, P = 0.089 \)) and fat (g) (\( r = 0.405, P = 0.088 \)) intakes were also observed.

**DISCUSSION**

The present study investigated oral and gastrointestinal sensitivities to oleic acid (18:1) in lean and overweight or obese men by determining oral detection thresholds for 18:1 and antropyloroduodenal pressure, plasma hormone, and appetite responses to the intraduodenal infusion of 18:1. The major findings were as follows: 1) both oral and gastrointestinal sensitivity to 18:1 were attenuated in the overweight or obese subjects, 2) oral and gastrointestinal sensitivity were related, and 3) oral and gastrointestinal sensitivity were related to BMI and recent fat and energy intakes.

A major finding was that overweight or obese subjects were significantly less sensitive to 18:1 in the oral cavity, requiring almost twice the concentration of 18:1 for detection when compared with lean subjects. Oral sensitivity to 18:1 was also

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**FIGURE 2.** Mean (±SEM) plasma cholecystokinin (CCK) (A) and peptide YY (PYY) (B) concentrations during 90-min intraduodenal infusions (0.78 kcal/min) of either saline or oleic acid (18:1) in lean (\( n = 8 \)) and overweight or obese (\( n = 11 \)) subjects. A repeated-measures ANOVA with treatment, subject group, and time as factors was used to determine statistical differences. If the ANOVA showed significant effects, pairwise comparisons were performed. A: Treatment \( \times \) time interaction, \( P < 0.01 \); treatment \( \times \) group interaction, \( P = 0.076 \). *Overall curve significantly different between 18:1 and saline in lean subjects, \( P < 0.05 \). #Overall curve significantly different between 18:1 and saline in overweight or obese subjects, \( P < 0.05 \). B: Treatment \( \times \) time interaction, \( P < 0.01 \); overall curve significantly different between 18:1 and saline at 60, 75, and 90 min; \( P < 0.05 \).
TABLE 2
Energy and macronutrient intakes from the buffet meal after 90-min intraduodenal infusions of saline or 18:1 in lean and overweight or obese subjects 1

<table>
<thead>
<tr>
<th></th>
<th>Lean subjects (n = 8)</th>
<th>Overweight/obese subjects (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline</td>
<td>18:1</td>
</tr>
<tr>
<td>Energy intake (kJ)</td>
<td>5241 ± 504</td>
<td>4619 ± 486 2</td>
</tr>
<tr>
<td>Energy intake (kJ) (%)</td>
<td>622 ± 514</td>
<td>—</td>
</tr>
<tr>
<td>Amount eaten (g)</td>
<td>1267 ± 146</td>
<td>964 ± 103 3</td>
</tr>
<tr>
<td>Amount eaten (g) (%)</td>
<td>303 ± 169</td>
<td>—</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>45 ± 5</td>
<td>37 ± 5  2</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>63 ± 6</td>
<td>55 ± 6  2</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>141 ± 16</td>
<td>114 ± 12</td>
</tr>
<tr>
<td>Fat (% of TEI)</td>
<td>35 ± 1</td>
<td>35 ± 2</td>
</tr>
<tr>
<td>Protein (% of TEI)</td>
<td>23 ± 2</td>
<td>24 ± 2</td>
</tr>
<tr>
<td>Carbohydrate (% of TEI)</td>
<td>42 ± 3</td>
<td>39 ± 4</td>
</tr>
</tbody>
</table>

1 All values are means ± SEMs. TEI, total energy intake. There were no significant treatment × group interactions (repeated-measures ANOVA). There were no significant interactions or main effects on the amount of carbohydrate (g) or percentage of energy from fat, carbohydrate, or protein consumed at the buffet meal (repeated-measures ANOVA).
2 Significantly different from saline control (treatment effect), P < 0.05 (repeated-measures ANOVA).
3 Trend for treatment × group interaction (repeated-measures ANOVA), P = 0.07; significantly different from saline control in lean (pairwise comparison, P < 0.05) but not in obese subjects.
4 Significantly different from lean subjects, P < 0.05 (independent-samples t test).

related to BMI, ie, individuals with higher detection thresholds for 18:1 had greater BMIs. These observations extend recent work from our laboratory, in which sensitivity to 18:1 was associated with lower BMI and dietary fat intake in lean subjects (15). Differences in oral sensitivities to certain nutrients can influence the consumption and liking of foods containing those tastants (30), and exposure effects, such as habitual nutrient consumption, can alter taste sensitivity to certain tastants (31). For example, dietary sodium restriction is associated with increased oral sodium sensitivity and a reduced preference for sodium taste in common foods (32, 33). Although, to date, no studies have evaluated changes in taste sensitivity in response to manipulations of dietary fat content, 2 studies (34, 35) have reported that limiting the amount of fat in the diet decreased preferences for, and the frequency of consumption of, previously preferred full-fat foods, and increased acceptance of lower-fat foods, which suggests a direct relation between habitual fat stimulation and the level of fat preferred in a food. The increased dietary fat consumption in the overweight or obese subjects, observed in both the current and previous (36) studies, combined with our finding that a greater concentration of 18:1 was required for its oral detection, raises the possibility that habitual fat intake modulates taste sensitivity to fats such that greater amounts are needed to elicit comparable oral taste and hedonic responses. However, our current data relate to 18:1; thus, further studies are needed to establish the application of our findings to fats in general. Nevertheless, our data are in line with recent observations of attenuated taste sensitivity to monosodium glutamate in obese women (37) and may suggest a more generalized impairment of nutrient-sensing mechanisms in obesity.

Another major finding from the present study was the marked differences in gastrointestinal responses to intraduodenal 18:1

TABLE 3
Recent energy and macronutrient intakes in lean and overweight or obese subjects 1

<table>
<thead>
<tr>
<th></th>
<th>Lean subjects (n = 8)</th>
<th>Overweight/obese subjects (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake (kJ)</td>
<td>8165 ± 601</td>
<td>10,880 ± 982 2</td>
</tr>
<tr>
<td>Amount eaten (g)</td>
<td>2098 ± 183</td>
<td>2821 ± 325 2</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>70 ± 6</td>
<td>92 ± 9 3</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>81 ± 7</td>
<td>109 ± 12 2</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>218 ± 22</td>
<td>280 ± 29</td>
</tr>
<tr>
<td>Fat (% of TEI)</td>
<td>33 ± 2</td>
<td>33 ± 2</td>
</tr>
<tr>
<td>Protein (% of TEI)</td>
<td>17 ± 1</td>
<td>18 ± 1.5</td>
</tr>
<tr>
<td>Carbohydrate (% of TEI)</td>
<td>45 ± 2</td>
<td>43 ± 3</td>
</tr>
</tbody>
</table>

1 All values are means ± SEMs. TEI, total energy intake.
2 Significantly different from lean subjects, P < 0.05 (independent-samples t test).
3 Trend for significant difference from lean subjects (independent-samples t test): P = 0.088 (amount eaten), P = 0.076 (fat, in g), P = 0.09 (protein, in g).
between lean and overweight or obese subjects. In lean individuals, it has been well established that intraduodenal infusion of triglycerides or free fatty acids stimulates pyloric pressures (28, 38), as was the case in the current study. In contrast, this stimulation was reduced in the overweight or obese subjects, which suggests that the “sensing” of 18:1 by small-intestinal receptors, at the concentration administered, was compromised. Ingestion of a high-fat diet (≈45% of energy from fat) for 2 wk attenuates the antrpyloroduodenal motor response to intraduodenal lipids (39) and accelerates gastric emptying of a high-fat meal (40), which indicates that the small-intestinal response to fat can be modified by diet and, thus, that a high habitual fat intake may be responsible for, or at least contribute to, the attenuated pyloric motor response. Our data also indicated a tendency for the plasma CCK response to 18:1 to be delayed and lower in the overweight or obese subjects than in the lean subjects, which mirrored the pattern of the pyloric response. It is possible that we were not able to obtain a more marked response, because the 18:1 load was relatively low. The infusion of 18:1 induced a small, and comparable, PYY response in both lean and overweight or obese subjects. Because PYY release is compromised in the obese (10), it is likely that, because of the small nutrient load used, 18:1 was absorbed before reaching the distal small intestine—the main site of PYY release.

Our results also indicate that the sensitivity to 18:1 within the oral cavity and the gastrointestinal tract are related, eg, oral detection thresholds for 18:1 were inversely related to pyloric pressures, and a trend for an inverse relation with plasma CCK concentrations was observed. Because of the attenuated sensitivity to 18:1 at both nutrient-sensing locations in the overweight or obese subjects, greater amounts of fat are required to elicit a taste response as well as changes in gastrointestinal function. Analogies between oral and gastrointestinal sensitivity to fat have been described in hyperphagic, obesity-prone rodents, which exhibit an enhanced preference for fat and fail to suppress food intake in response to intragastric fat infusion (41, 42). Whereas the responsiveness of the oral cavity and the upper gastrointestinal tract to nutrients has not been evaluated concurrently in humans, the functional analogies between the 2 sites are not entirely surprising. It is now known that key taste receptors found on taste cells within the oral cavity [including fatty acid–specific G-protein coupled receptors, including GPR120, GPR119, and GPR40 (43–45); K+ channels (46); and the fatty acid transporter CD36 (47)] are also located on enteroendocrine cells in the gastrointestinal tract (48, 49). The receptors responsible for fat detection are yet to be located in human lingual tissue; however, a growing body of evidence suggests that fat “taste” does exist in humans (15, 26) and is most likely involved in the oral detection of fats, analogous to other taste receptors, such as sweet or umami (50). Whether, and how, the expression and/or responsiveness of these receptors changes in response to diet (both excess and restriction) or whether inherent differences in the functionality of the receptors determines their sensitivity, which is then associated with excessive fat and energy intakes, is currently unknown. In support of the former, we recently showed that acute dietary restriction (70% of energy restriction for 4 d) significantly enhances the gastrointestinal and appetite-suppressant effects of intraduodenal lipids in obese subjects (51).

The reduced oral and gastrointestinal sensitivity to 18:1 in the overweight or obese subjects was also associated with increased energy and fat intakes, most likely through the reduced feedback on the pathways involved in intake regulation, eg, we established recently that both pyloric pressures and plasma CCK are independent determinants of acute energy intake in lean humans (2). Both measures were attenuated in the overweight or obese subjects in the current study. Thus, it appears that a greater nutrient load is required to elicit a particular response, although, because we infused duodenal 18:1 only at one load, we cannot comment on the 18:1 load required to initiate a gastrointestinal response in the overweight or obese subjects. More work is required to elucidate the mechanisms underlying nutrient sensing in humans and the pathways involved linking nutrient detection to functional and behavioral outcomes.

Some limitations of our study warrant discussion. We only included male subjects; thus, we are unable to extend our conclusions to females, although major differences seem unlikely. Although our study was adequately powered, we cannot exclude the possibility that some findings may have reached statistical significance in a larger sample size. Whereas we recognize that 2-d diet records only provide limited information on habitual energy intake, they are used for the assessment of previous dietary intake (20). Discrimination of chemosensory taste cues (from orally delivered fatty acids) from additional sensory inputs (odor, texture, irritation) may be an issue; however, we expected such influences to be negligible given our methodologic approach (26, 52).

In summary, we showed that both oral and gastrointestinal sensitivities to 18:1 are compromised in obesity and that sensitivities within the oral cavity and gastrointestinal tract are related and inversely associated with dietary fat consumption. These data suggest that decreased sensitivity to fats within both the oral cavity and the gastrointestinal tract may be a factor contributing to the pathogenesis of obesity, via an attenuated physiologic response to dietary fat ingestion, although it is important to recognize that causality cannot be inferred from association studies. Thus, future studies to determine whether decreased nutrient sensitivity is the cause, or the result, of dietary overconsumption are warranted.
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The authors’ responsibilities were as follows—JES and RVS: helped with the study design and concepts, subject recruitment, study performance, data collection, statistical analysis, data interpretation, and draft of the manuscript; BO: performed the gut hormone assays and helped with the data interpretation and revision of the manuscript; RSJK and PMC: helped with the conception and design of the study, data analysis and interpretation, and revision of the manuscript; FE: helped with the study design and concepts, data analysis and interpretation, draft and revision of the manuscript, obtained the funding, and had overall responsibility for the project. All authors approved the final draft of the manuscript. None of the authors declared a conflict of interest.

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