Obesity interferes with the orosensory detection of long-chain fatty acids in humans1–3

Michael Chevrot, Patricia Passilly-Degrace, Deborah Ancel, Arnaud Bernard, Gérardine Enderli, Marlène Gomes, Isabelle Robin, Sylvie Issanchou, Bruno Vergès, Sophie Nicklaus, and Philippe Besnard

ABSTRACT

Background: The association between the orosensory detection of lipids, preference for fatty foods, and body mass index (BMI; in kg/m²) is controversial in humans.

Objective: We explored the oral lipid-sensing system and the orosensory-induced autonomic reflex system in lean and obese subjects.

Design: Lean (BMI: 19 to <25; n = 30) and obese (BMI >30; n = 29) age-matched men were enrolled. Their oral threshold sensitivity to linoleic acid (LA) was determined by using a 3-alternative forced-choice ascending procedure, and their eating habits were established by the analysis of 4 consecutive 24-h food-consumption diaries. The effect of brief oral lipid stimulations on plasma triglyceride [(TG)pl] concentrations was analyzed in overnight-fasted lean and obese individuals subjected to a whole-mouth stimulation (sip-and-spit procedure) with a control or 1% LA emulsion for 5 min according to a within-subject randomized design.

Results: A large distribution of LA detection was shown in both groups. Mean detection thresholds were 0.053% (wt:wt) and 0.071% (wt:wt) in lean and obese subjects, respectively. No relation between the LA detection threshold and BMI was observed. The 5 subjects who detected only the higher concentration of LA (5% wt: wt) or were unable to distinguish properly between control and LA emulsions were obese. An analysis of dietary habits showed that these obese LA nontasters consumed more lipids and energy than did all other subjects. Brief whole-mouth stimulations (sip-and-spit procedure) with a control or 1% LA emulsion revealed an LA-mediated rise in (TG)pl concentrations in overnight-fasted, lean subjects. The origin of this change seemed to be hepatic. This rise in plasma triglyceride [(TG)pl] concentrations elicited a transient increase in plasma triglyceride [(TG)pl] concentrations in healthy subjects (7, 8). Presumably, this change, which was a result of the release of triglycerides stored from the previous meal (9), provides a metabolic signal that prepares the body for the lipid arrival.

It was recently reported in rats and mice that diet-induced obesity impairs the orosensory response to free LCFA s, which leads to a lower attraction for lipids (10, 11). The fact that this phenomenon was reversible and tightly linked to the size of the fat mass suggested that obesity can alter the orosensory detection of lipids in rodents. Such a phenomenon might also exist in humans. Indeed, weight loss induced by bariatric surgery alters taste sensitivity and modifies taste preferences, making high-fat and high-sugar foods less pleasant (12). Moreover, a negative association between the orosensory perception of dietary lipids

INTRODUCTION

Growing evidence supports the existence of a gustatory component in the orosensory detection of dietary lipids in humans (1). Effective stimuli are long-chain fatty acids (LCFAs)4 released by the lipase hydrolysis of triglycerides (2) and present in low concentrations in foodstuffs (3). The LCFA membrane receptor CD36, which has been identified in the apical side of human taste buds (4), seems to play a significant role in this system because subjects who carry the variant allele rs1761667-AA, which is known to reduce the CD36 gene expression (5), display a higher LCFA-detection threshold (ie, a lower sensitivity) than did G/G controls (2). An involvement of this oral LCFA-sensing system in the food selection is likely because an inverse association between CD36 gene expression and acceptance of added fat in foods was recently reported (6). Brief oral lipid stimulations (without ingestion) also elicited a transient rise in plasma triglyceride [(TG)pl] concentrations in healthy subjects (7, 8).

1 From Physiologie de la Nutrition et Toxicologie (MC, PP-D, DA, AB, MG, and PB) and Physiopathologie des Dyslipidémies (IR and BV), Unité Mixte de Recherche (UMR) U866, Institut National de la Santé et de Recherche Médicale (INSERM), Université de Bourgogne/AgroSup Dijon, Dijon, France; the Centre National de la Recherche Scientifique, UMR6265 (GE, MG, SI, and SN) and the Institut National de la Recherche Agronomique, UMR1324 Centre des Sciences du Goût et de l’Alimentation, Dijon, France (GE, MG, SI, and SN); and the Université de Bourgogne, UMR Centre des Sciences du Goût et de l’Alimentation, Dijon, France (GE, MG, SI, and SN).
2 Supported by the Burgundy Council and Centre National Interprofessionnel de l’Economie Laitière (HumanFataste program; to PB). MC is a PhD fellow of the HumanFataste program.
3 Address correspondence to P Besnard, Physiologie de la Nutrition et Toxicologie, AgroSup Dijon, 1, Esplanade Erasme, F-21000 Dijon, France. E-mail: pbesnard@u-bourgogne.fr.
4 Abbreviations used: LA, linoleic acid; LCFA, long-chain fatty acid; LNT, lean nontaster; LT, lean taster; ONT, obese nontaster; OT, obese taster; PPY, polypeptide Y; (TG)pl, plasma triglyceride.

Received October 3, 2013. Accepted for publication January 27, 2014. doi: 10.3945/ajcn.113.077198.
and BMI was reported in normal-weight volunteers (13–15). It was extrapolated that higher BMI might impair the detection of lipids in the oral cavity. Nevertheless, claims that oral LCFA detection is causally related to obesity are premature. The impact of BMI as a factor of variations in oral lipid sensitivity remains under debate because no association was shown in other trials (1, 16). None of these studies was designed to assess this issue, except one trial that showed no association between overweight or obesity and a sensitivity to LCFA (16). Likewise, whether obesity interferes with the (TG)p concentration triggered by an oral stimulation with LCFA shown in lean subjects is also unknown.

With the use of well-defined subject groups (lean BMI (in kg/m²): <25; obese BMI: >30), the current study aimed to assess the impact of obesity on the oral detection of LCFA. To do this assessment, oral detection thresholds of linoleic acid (LA), changes in (TG)p concentrations secondary to brief oral LA stimulations, and food-consumption habits were compared in lean and obese, age-matched men.

SUBJECTS AND METHODS

Subjects

A power analysis was conducted before the study to determine an appropriate sample size to achieve a power of 0.90 on the basis of a 0.5 mmol/L difference in mean threshold between lean and obese subjects, which was consistent with a previous report of LA-threshold variation with BMI in healthy subjects (13). Thirty lean (BMI: 19 to <25) and 29 obese (BMI ≥30) age-matched, adult, white men participated in the current study. For lean subjects, eligibility criteria were as follows: no regular drug intake and triglyceridemia and glycemia concentrations <1.50 g/L and <6.10 mmol/L, respectively. Because type 2 diabetic patients have blunted taste responses (17), obese, nondiabetic subjects were selected according to the following inclusion criteria: no hypoglycemic drug intake and surgical treatment of obesity, fasted glycemia concentration <6.10 mmol/L, and glycated hemoglobin <6.0%. Smokers or former smokers (<3 mo) were excluded as were subjects with severe digestive pathologies, pancreatic, renal, hepatic failures, type 1 diabetes, or treated with inhibitors of proton pumps, insulin, glucagon-like peptide 1 analogs, or dipeptid peptidase-IV inhibitors. All subjects received detailed information about the study and gave written consent at the first visit. The study was approved by a local ethics committee (volunteers protection committee Est1). Participants were subjected to 4 successive sessions. Session 1 included a medical examination (BMI determination and blood variable analyses) and a sensory screening [European Test of Olfactory Capabilities (18)]. Session 2 was devoted to the threshold determination of LA. Sessions 3 and 4 consisted of the exploration of the impact of brief oral stimulations with a control or 1% LA emulsion on blood variables. Experiments were performed in the morning in overnight-fasted subjects. The interval between sessions 3 and 4 was ≥2 wk. Dietary intakes were estimated by 2-d dietary recalls at sessions 3 and 4. Subjects were naive to psychophysical tests.

Preparation of LA emulsion

LA was chosen rather than oleic acid because the Western diet is characterized by an overconsumption of LA, which contributes to a high ω-6:ω-3 ratio that is responsible for chronic disturbances (eg, inflammation and hypertension) (19). Moreover, LA is known to bind and activate lipid receptors (ie, CD36 and GPR120) expressed in gustatory papillae (20, 21). Finally, many experiments performed in rodents that unraveled the mechanisms responsible for the orosensory detection of dietary lipids were conducted by using LA (22). LA (Sigma Aldrich) oil-in-water emulsions were prepared in a solution of 5% acacia gum (wt:wt; Fluka), 5% mineral oil (wt:wt; Cooper), and 0.01% EDTA (wt:wt; VWR international) diluted in evian mineral water (evian). Acacia gum and paraffin oil were added to limit viscosity and lubricity differences between control and experimental samples. EDTA was added to prevent the oxidation of LA (23). Samples were mixed conventionally by using a stirrer (Corning) and homogenized by using a sonicator (Misonix sonicator model S-4000; QSonica LLC). The duration of sonication was adapted to LA concentrations to obtain a similar particle size. In all cases, sonication was conducted by lapses of 30 s separated by a 1-min pause. Sonication was conducted in a hermetic chamber saturated with nitrogen, and beakers were cooled by using an ice bath to limit the formation of oxidized compounds during emulsion preparation. All samples were prepared the day before the session and stored in propylene light-protected sealed bottles under nitrogen and at 4°C. Granulometric analyses (Mastersizer 2000; Malvern Instruments Ltd) and microscopic observations (phase-contrast microscopy) of the 1% LA emulsion (1.45-min sonication) and the control emulsion (3.30-min sonication) were performed on freshly prepared emulsions and 24 h later to assess the stability of the emulsions.

LA-threshold determination

Threshold determination was conducted in sensory evaluation rooms at the Centre des Sciences du Goût et de l’Alimentation at the second session. Subjects were installed in an air-conditioned room (21 ± 1°C) in an individual sensory booth. Participants were asked to refrain from the consumption of food or beverages and the use of oral care products for ≥2 h before the session. The methodology was based on previous work described by Chalé-Rush et al (23). Thresholds were determined by using the 3-alternative forced-choice procedure, in which participants were provided with successive sets of 3 samples. Each set contained 2 control samples and one stimuli sample. Within each set, participants had to indicate which sample was different from the 2 other samples. Sets were presented in an ascending concentration from 0.00028% to 5% LA (wt:wt) spaced by 0.25 log units (18 solutions in total), which meant that participants began to evaluate the set that contained the stimuli sample with the lowest LA concentration toward the highest concentration. When the participant could not identify the stimuli sample, the LA concentration was increased for the following set. When the participant correctly identified the stimuli sample, a second set at the same LA concentration was provided. This procedure stopped when the participant identified correctly the stimuli sample at a given concentration 3 consecutive times. This concentration represented the detection-threshold value of the participant.

Samples were presented as 5-mL portions in opaque cups and were tested at room temperature. Subjects were instructed to hold
the 5-mL solution in their mouth for 7 s, spit the solution out, and wait for 20 s before tasting the next sample. The interval between 2 sets was 60–120 s, during which participants were asked to rinse their mouths with water heated to 50°C and served at ~40°C. Testing was conducted under red lighting and with participants wearing a nose clip to limit visual and olfactory inputs, respectively. To verify the ability of participants to comply with the tasting protocol, training tests were conducted before the threshold measurement. Two training sets were performed with water samples and one set with the test samples.

**Oral LA stimulation**

The impact of an oral fat stimulation on various blood variables was explored during sessions 3 and 4 at the Centre Hospitalier Universitaire de Dijon. Individuals were subjected to a whole-mouth stimulation (sip-and-spit procedure) with a control or 1% LA emulsions for 5 min, according to a within-subject randomized design. During these sessions, subjects wore a nose clip to avoid olfactory cues. Blood samples were collected from an indwelling catheter 20 and 10 min before oral stimulations (= control values) and 5, 7, 30, 10, 15, 20, 25, and 35 min after the end of the stimulation period. The patient had to sip and spit 5 times in a row the solutions that did or did not contain the LA (1%). Blood collection was performed by using an evacuated tube containing EDTA. All samples were placed on ice and centrifuged in a refrigerated centrifuge before being stored at ~20°C until assays.

**Dietary intake determination**

During sessions 3 and 4, subjects had to report their food intakes during the 2 previous days by filling out 2 consecutive 24-h food-consumption diaries. During these 4 d, participants had to maintain their eating habits and avoid food or alcohol excess. Subjects were asked by the dietitian to record all foods and drinks consumed by being as precise as possible when reporting the type of food or drink consumed (eg, skimmed milk or full-fat milk) and specifying the seasoning or additions made to food (eg, sugar, butter, oil, or sauce), the type of cooking applied (eg, baking, steaming, or frying), and the amounts of all foods, drinks, and seasoning consumed.

Dietary records were analyzed by a registered dietitian. The CIQUAL 2012 table, which is published by the Agence Nationale seasoning consumed. Butter, oil, or sauce), the type of cooking applied (eg, baking, and specifying the seasoning or additions made to food (eg, sugar, nutrition, and relevant for foods consumed in France, was used to assess the nutritional composition of foods (http://www.anses.fr/TableCIQUAL/index.htm). This database includes details about the fatty acid content in foods. When needed, this database was supplemented with new foods by calculating the nutritional composition with the use of food data from the database and standard recipes, and when this was not possible, with the use of manufacturer information. Ingested amounts were converted into grams by using reference amounts from a commonly used French reference (24). For each subject, dietary intake was calculated for each of the 4 reported days and averaged.

**Western blotting**

Plasma from subjects blood samples were ultracentrifugated (100,000 × g for 3 h with a Beckman rotor 100.2; Beckman Coulter). The supernatant fluid, which contained chylomicrons and the VLDL, was collected and stored at −20°C. After the denaturation of the collected fraction (2 µL), a separation by using SDS-PAGE (4–12%) was performed. The transfer to a polyvinylidene fluoride membrane was achieved by electroblotting. After membranes were blocked overnight with a TRis-Buffered Saline buffer that contained 5% bovine serum albumin and 0.1% Tween 20, membranes were incubated overnight at 4°C with an anti–apolipoprotein B antibody (sc 11795, 1:200 dilution; Santa Cruz Biotechnologies). After a set of washes, the appropriate peroxydase-conjugated secondary antibody was added (sc 2020, 1:12000; Santa Cruz Biotechnologies). Antibody labeling was detected by chemiluminescence (ECL-plus reagent; Perkin Elmer).

**Biochemical analysis**

Concentrations of plasma glucose and triglyceride were assayed by using standard commercial kits (Biomérieux). Plasma leptin concentrations were determined by using Enzyme-ImmunoAssay kits (Phoenix Pharmaceuticals).

**Statistics**

Results are expressed as means ± SEMs. We first checked that data for each group were normally distributed and that variances were equal. Then, we carried out a 2-tailed Student’s t test. One-factor ANOVA and the Student-Newman-Keuls test were used in dietary intake analyses to compare group data (obese taster (OT), obese nontaster (ONT), lean taster (LT), and lean nontaster (LNT) groups). Nutrient intakes were analyzed with SAS System for Windows software (version 9.3; SAS Institute Inc).

**RESULTS**

**Physicochemical and microbiological characteristics of emulsions**

The droplet size and stability of emulsions are important variables for oral lipid sensation (25). To avoid changes in these physicochemical characteristics that might interfere with the orosensory detection of LA, the duration of sonication was adapted to produce a similar particle size across the LA concentration range and with a control emulsion. As shown in Figure 1A, the droplet size varied in function of the duration of sonication. Consequently, the duration of sonication was adapted to the LA concentration used. Granulometric analyses (Mastersizer 2000 granulometer; Malvern Instrument) showed that sonications of 3.30 and 1.45 min for control and 1% LA solutions, respectively, produced emulsions with droplets of a similar size and an average diameter ~3 µm (Figure 1, A and B). Droplet profiles of these 2 emulsions were very close but not fully similar because of a subpopulation of large droplets in the control solution (Figure 1C). Control and experimental emulsions remained stable ≥24 h (Figure 1C). Moreover, to determine whether the protocol used to prepare samples did not lead to the oxidation of free LCFAs, emulsions that contained the higher LA concentration (5% wt:wt) were analyzed after sonication by using solid-phase microextraction headspace gas chromatography. A comparison of chromatograms obtained with the pure LA compound and 5% LA emulsion did not revealed...
differences in oxidation-related volatiles (data not shown). Finally, microbiological tests indicated that these samples and their processes were safe for human consumption.

Oral sensitivity to LA was decreased only in few obese subjects

To explore whether obesity affects the orosensory detection of LCFAs, the oral threshold sensitivity to LA was determined by using the 3-alternative ascending concentration procedure in selected subjects. As expected, waist circumference and fasted triglyceridemia and leptinemia were clearly higher in obese than in lean subjects (Table 1). Although fasted plasma glucose and glycated hemoglobin concentrations were slightly more elevated in obese patients, values remained in normal ranges, which provided support of an absence of glucotoxicity and, therefore, type 2 diabetes in the obese group (Table 1). As shown in Figure 2, a large distribution of LA thresholds covering 4 orders of magnitude was observed in lean and obese subjects. Distributions did not differ from each other \( (P = 0.31; \text{2-sided Wilcoxon's 2-sample test}) \), and no significant difference in oral sensitivity for LA between lean and obese subjects was observed \((0.403 \pm 0.789\% \text{ wt:wt} \text{ in lean and obese groups, respectively}; P = 0.11)\). Notably, the 5 subjects who detected only the higher concentration of LA (5% wt:wt) or were unable to distinguish properly between control and LA emulsions were obese, which suggested the existence of LA tasters and nontasters in this population.

According to the wide range of detection thresholds shown in Figure 2, it was arbitrarily postulated that subjects who displayed

![FIGURE 1. Granulometric analyses of emulsions. A: Effect of the duration of the sonication on the droplet size of control and LA emulsions. Each dot represents the median value of the droplet size. Arrows illustrate the duration of sonications used to obtain a similar emulsion between control and 1% LA solutions. B: Droplets produced by 3.30 min sonication of control emulsion and 1.45 min of 1% LA emulsion (1:10 dilution). C: Granulometric distribution of droplets in control and 1% LA emulsions at the end of sonication (t = 0) and 1 d later (t = 24 h). LA, linoleic acid.]

### TABLE 1

Main clinical variables of lean and obese subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lean ((n = 29))</th>
<th>Obese ((n = 30))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>50.69 ± 2.69</td>
<td>52.27 ± 2.13</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.76 ± 0.37</td>
<td>36.45 ± 0.99***</td>
</tr>
<tr>
<td>Waist circumference (m)</td>
<td>0.86 ± 0.02</td>
<td>1.18 ± 0.02***</td>
</tr>
<tr>
<td>Fasted plasma triglyceride (g/L)</td>
<td>0.96 ± 0.06</td>
<td>2.12 ± 0.27***</td>
</tr>
<tr>
<td>Fasted plasma glucose concentration (mmol/L)</td>
<td>4.99 ± 0.11</td>
<td>5.37 ± 0.1*</td>
</tr>
<tr>
<td>Fasted total cholesterol concentration (mmol/L)</td>
<td>5.15 ± 0.17</td>
<td>5.34 ± 0.16</td>
</tr>
<tr>
<td>Fasted Hb A₁c (%)(^{2})</td>
<td>5.33 ± 0.06</td>
<td>5.61 ± 0.08*</td>
</tr>
<tr>
<td>Fasted plasma leptin concentration (µg/L)</td>
<td>1.84 ± 0.24</td>
<td>15.66 ± 2.23***</td>
</tr>
</tbody>
</table>

\(^{1}\) All values are means ± SEMs. \(^{***}\)Student’s \(t\) test, \(*P < 0.05, ***P < 0.001.\)

\(^{2}\)Hb A₁c, glycated hemoglobin.
a sensitivity upper to 1% LA were nontasters. Therefore, the following 4 groups of subjects were distinguished: LTs (n = 25) and OTs (n = 25), for whom the LA detection threshold was <1%, and LNTs (n = 4) and ONTs (n = 5), for whom the LA detection threshold was >1%. When the 4 groups were compared, ages did not differ (P = 0.43). BMI was similar in LTs and LNTs (22.71 ± 2.00 compared with 21.99 ± 0.74, respectively; P = 0.49) and between OTs and ONTs (36.85 ± 5.66 compared with 35.26 ± 7.39, respectively; P = 0.59).

ONTs consumed more energy-dense foods

Daily dietary intake was calculated individually by averaging the reported 24-h data and was compared in groups by combining sensitivity and weight status (Figure 3). Energy intake was higher in ONTs than in OTs (P < 0.0007). ONTs also consumed more carbohydrates (P < 0.0003) and lipids (P < 0.0079), especially SFAs (P < 0.01), than did OTs (Figure 3). Protein data were similar between groups (data not shown).

Plasma triglyceride response to a brief oral stimulation by LA was lacking in obese subjects

To further explore the putative impact of obesity on the orosensory detection of free LCFAs, plasma changes after a sip-and-spit procedure by using an emulsion with or without 1% LA were explored in overnight-fasted subjects according to a randomized within-subject design. With the activation of a vagal

![FIGURE 2. Geometric means of the LA detection threshold in lean and obese subjects. A 3-alternative forced-choice ascending concentration procedure was used to determine the LA detection threshold in lean (n = 29) and obese (n = 30) subjects. This test was carried out on solutions that conained from 0.0005 to 5% LA (wt:wt). LA, linoleic acid.](image)

![FIGURE 3. Analysis of food-consumption diaries. Box-plot representations of daily consumption of energy, carbohydrates, lipids, and SFAs in LT (n = 25), LNT (n = 4), OT (n = 25), and ONT (n = 5). Box outlines represent lower and upper quartiles, outermost points correspond to smallest and largest observations, horizontal lines are median values, and diamonds in boxes are mean values. Means with the same lowercase letter were not different, P < 0.05 (Student-Newman-Keuls test). LNT, lean linoleic acid nontasters; LT, lean linoleic acid tasters; ONT, obese linoleic acid nontasters; OT, obese linoleic acid tasters.](image)
reflex loop, this physiologic investigation provided information on the functioning of the tongue-brainstem-periphery axis. For this aspect, blood samples of 23 LT, 21 OT, 4 LNT, and 4 ONT subjects present in both sessions 3 and 4 were analyzed. In LTs, the orosensory stimulation with 1% LA led to a progressive rise in (TG)pl concentrations. This phenomenon occurred rapidly after oral stimulation and was specific to LA because it was not reproduced with the control emulsion (Figure 4A). To our surprise, no change in (TG)pl concentrations was observed in OTs given an oral stimulation with 1% LA (Figure 4B). A statistical comparison between LTs and OTs highlighted that obesity impaired the (TG)pl responsiveness to 1% LA \( (P < 0.001; \text{Figure 4C}) \). By contrast, no difference was shown in LNTs compared with ONTs (Figure 4D). The LA-mediated rise in (TG)pl concentrations shown in the LT group appeared to be specific to triglycerides because plasma glucose concentrations were unchanged secondary to an oral LA stimulation (Figure 5).

(TG)pl rise triggered by an oral LA stimulation in LTs was VLDL dependent

To determine the origin of the rise in (TG)pl concentrations observed in LTs, an apolipoprotein B analysis was performed by using Western blotting in subjects who displayed the greater increase in (TG)pl concentrations in response to 1% LA oral stimulation \( (n = 7) \). As shown in Figure 6A, only one protein was detected, the molecular mass of which was similar to apolipoprotein B-100. Consistent with the rise in (TG)pl concentrations triggered by the 1% LA emulsion (Figure 4), the amount of apolipoprotein B-100 was increased 5 and 30 min after the whole-mouth stimulation (Figure 6, B and C).

DISCUSSION

The origin of differences in the orosensory detection of lipids and fat consumption remains controversial in human. The current study was designed to address the question of the impact of obesity on oral lipid detection and consumption by using psychophysical and physiologic approaches. In contrast with previously published data (13–15), a clear difference in weight status between our groups was sought to detect a possible difference in the orosensory perception of LCFAs in relation with obesity. The 3-alternative forced-choice tests revealed that the oral detection of LA was highly variable in lean and obese subjects. This large distribution, which reached 4 orders of magnitude, might have been attributable to the fact that participants were naive to psychophysical tests and were inexperienced with this unfamiliar stimulus. Despite these

![FIGURE 4. Mean (±SEM) effects of brief oral LA stimulation on plasma triglyceride concentrations in overnight-fasted lean and obese subjects. Individuals were subjected to a whole-mouth stimulation (sip-and-spit procedure) with a control or 1% LA emulsion for 5 min according to a within-subject randomized design. Blood samples were collected from an in-dwelling catheter 20 and 10 min before oral stimulation (= controls values) and at 5, 7.30, 10, 15, 20, 25, and 35 min after the end of the stimulation period. Plasma triglyceride concentrations were assayed according to procedures in Subjects and Method. A: LT \( (n = 23) \); B: OT \( (n = 21) \); C: Bar graphs of AUC of plasma TG concentrations from LT and OT subjected to a whole-mouth stimulation with a control or 1% LA emulsions. D: Bar graphs of AUC of plasma TG concentrations from LNT \( (n = 4) \) and ONT \( (n = 4) \) subjected to a whole-mouth stimulation with a control or 1% LA emulsion.* ****Student’s t test, * \( P < 0.05 \), *** \( P < 0.001 \). LA, linoleic acid; LNT, lean linoleic acid nontasters; LT, lean linoleic acid tasters; ONT, obese linoleic acid nontasters; OT, obese linoleic acid tasters; TG, triglyceride.](https://example.com/figure4.png)
In the mouse, the analysis of preference tests performed during weight-gain and -loss sequences revealed that the detection threshold for oily solutions was tightly related to the fat mass. A significant inverse correlation between a preference for fat and adiposity was shown (11). This finding was likely facilitated by the high genetic and dietary homogeneity of the murine sample, which was likely not the case in the current human sample. Nevertheless, an individual analysis of LA-threshold values revealed that obesity might have been associated with changes in the lipid perception in a few volunteers. Indeed, the 5 subjects who detected only the higher LA concentration (5% wt:wt; n = 2) or were insensitive to LA (n = 3) were obese, which suggested the existence of LA tasters and LA nontasters in obese subjects (Figure 2). The origin of this dichotomy remains elusive. It might have been attributable to genetics (eg, deleterious mutations in genes that encode for lipid-sensors expressed in the oral cavity). For example, a gene variant (rs1761667, AA allele) that decreases CD36 expression has been shown to be associated with a lower sensitivity to LCFAs in obese women (2). Alterations in the composition of saliva (29), in oral microbiota (30), and/or in the oral inflammatory status (31) that affect the chemoreception of LCFAs might be an alternative hypotheses. Future studies are required to better describe this subpopulation and explore the origin of the altered sensitivity to LCFAs.

Overconsumption of energy, especially of lipid-rich foods, was only shown in the 5 ONTs. Impairment of the orosensory detection of LCFAs might lead to a greater fat consumption, either to reach a hedonic fulfillment in individuals poorly sensitive to the presence of free LCFAs in the oral cavity or because these subjects lack the physiologic feedback that would help to limit their lipid consumption. Such a behavior might contribute to create a vicious circle that promotes obesity in these subjects who are already obese, as suggested by a previous work that showed a weakened activation in the reward circuit after the ingestion of energy-dense foods in obese subjects (32). Whether the great variability of the sensitivity to LA of naive participants has a physiologic basis or is a result of variations in their performance remains questionable and constitutes a limitation for a definitive interpretation of psychophysical testing (Figure 7).

To further study the possible association between obesity and lipid sensing in the oral cavity, individuals were subjected to a physiologic test that targeted a reflex loop by an oral lipid stimulation (Figure 7). By the activation of a vagal reflex loop (ie, the tongue-brainstem-periphery axis), this procedure normally induces physiologic changes in the (TG)pl concentration (1, 7–9), which is considered as a biomarker for oral fat sensitivity (8). Therefore, (TG)pl concentrations were assayed in overnight-fasted lean and obese subjects after brief whole-mouth stimulations with a control or 1% LA emulsion according to a within-subject, randomized crossover design. Data obtained from LA tasters (ie, with an LA detection threshold ≥1%) are shown. *P < 0.05 (Student’s t test). LA, linoleic acid; LT, lean linoleic acid tasters; OT, obese linoleic acid tasters.

limitations, we have chosen this strategy rather than to undertake experiments with trained subjects (26). A familiarization with the lipid stimulus does not seem to be systematically effective (27). Moreover, the repetition of stimulations during a short period might lead to an oral desensitization of the lipid-sensing system because a lipid-mediated downregulation of the gustatory lipid-sensor candidate CD36 has been reported in the mouse (28). Geometric means of LA-detection thresholds were not different across groups (0.053% in lean groups and 0.075% in obese groups; wt:wt). These values were of the same magnitude of those obtained in other trials that used the same protocol (13, 23). In contrast to what has been suggested in other studies (13–15), but consistent with recent experiments that used emulsions containing stearic acid (18:0) (1) or oleic acid (18:1n−9) (16), no association between the orosensory sensitivity for LA and BMI or waist circumference was shown in this study by contrasting normal weight and obese subjects.

FIGURE 5. Mean (±SEM) effects of brief oral LA stimulation on plasma glucose concentrations in overnight-fasted lean and obese subjects (LT: n = 23; OT: n = 21). Individuals were subjected to a whole-mouth stimulation (sip-and-spit procedure) with a control or 1% LA emulsion for 5 min according to a randomized crossover design. Blood samples were collected from an in-dwelling catheter 20 and 10 min before oral stimulation (= controls values) and 5, 7, 30, 10, 15, 20, 25, and 35 min after the end of the stimulation period. Plasma glucose concentrations were assayed according to procedures in Subjects and Methods. Data obtained from LA tasters (ie, with an LA detection threshold ≥1%) are shown. *P < 0.05 (Student’s t test). LA, linoleic acid; LT, lean linoleic acid tasters; OT, obese linoleic acid tasters.
secretion of TG-rich lipoparticles generated by the liver (VLDL) because it occurred after an overnight fasting. Consistent with this assumption, the VLDL marker apolipoprotein B-100 was the only one detected in plasma of lean subjects after oral LA stimulation. The involvement of a cephalic phase reflex in this effect has been supported by several observations. First, in overnight-fasted women, oral fat stimulation induced a rapid rise in plasma pancreatic polypeptide Y (PPY) concentrations, which peaked at 5 min (33). Second, the VLDL synthesis and release were enhanced by PPY in rat hepatocytes (34). Third, efferent vagal activation controlled PPY release (35). Fourth, vagal stimulation enhanced postprandial lipemia by affecting mainly the VLDL metabolism in humans (36). A dysfunction in this LA-mediated regulatory loop might exist in obese subjects because a lower PPY responsiveness has been shown during obesity in humans (37). The physiologic significance of an early peak of triglycerides remains elusive. The effect might serve as a signal for the brain to limit the size of the meal. Consistent with this assumption, a preliminary study showed that the infusion of minute quantities of a lipid emulsion into a carotid, to target the brain area preferentially, decreased food intake during the refeeding period in fasted mice (MC, PB, and S Luquet, unpublished observations, 2010). Whether an obese status interferes with this regulation remains to be explored.

In conclusion, altogether these data obtained by using 2 complementary investigations (ie, psychophysical and physiologic technics) suggest that obesity may interfere with the orosensory circuitry responsible for the detection of LCFA in humans. Although there is no systematic relation between obesity and the LA detection threshold, the data show that a lower sensitivity to LA may be associated with an overconsumption of lipid-rich foods in obese subjects only. Whether obesity is the cause or the consequence of such a phenomenon remains to be determined. Moreover, the autonomic control linking oral LCFA detection to the periphery seems to be disturbed during obesity. The current study was not designed to determine where and how this dysfunction takes place. Because inflammation is thought to

FIGURE 6. Western blotting of plasma apo B concentrations in lean LA tasters subjected to brief stimulations with a 1% LA emulsion. A: Relative apo B expressions in plasma from 3 different subjects. B: Representative data showing the evolution of plasma apo B100 concentrations 5 and 30 min after a whole-mouth stimulation with a control or 1% LA emulsion in 2 different subjects. C: Bar-graph representation of mean ± SEM changes in the relative apo B expressions in plasma 5 and 30 min after a whole-mouth stimulation with a control or 1% LA emulsions in different subjects. n = 7. Student’s t test was used for the analysis. apo, apolipoprotein; LA, linoleic acid; MM, molecular mass.

FIGURE 7. Features of psychophysical and physiologic methods used. V, VII, IX, and X denote cranial nerves. AFC, Ascending-forced choice method; CNS: central nervous system; LA, linoleic acid; NST, nucleus of solitary tract; [TG]pl, plasma triglyceride.
be an underlying cause of taste disorders (31), obesity-mediated neuroinflammation affecting, eg, the function of the vagal reflex loop is a plausible track for future investigations. Because obesity is a spreading pathology in the world, a better understanding of putative links between obesity, fatty taste, and food choices might open novel avenues for more effective dietary and/or pharmacologic interventions targeting the prevention and the treatment of obesity.

We thank Jean-Marie Perrier-Cornet, Thomas Karbowiak, and Pascale Winckler for emulsion analyses and Véronique Grivet and Philippe Loisel for their technical assistance during sessions 3 and 4.

The authors’ responsibilities were as follows—MC, PP-D, SI, BV, SN, and PB: designed the research; MC, PP-D, DA, AB, GE, MG, and IR: conducted the research; MC, GE, MG, SN, and PB: analyzed data; MC and PB: wrote the manuscript; PB: had primary responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript. None of the authors had a conflict of interest.

REFERENCES