Hedonic Eating Is Associated with Increased Peripheral Levels of Ghrelin and the Endocannabinoid 2-Arachidonoyl-Glycerol in Healthy Humans: A Pilot Study

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Background: Hedonic hunger refers to consumption of food just for pleasure and not to maintain energy homeostasis. In this condition, the subject eats also when not in a state of short-term energy depletion, and food is consumed uniquely because of its gustatory rewarding properties. The physiological mechanisms underlying this eating behavior are not deeply understood, but endogenous rewarding mediators like ghrelin and endocannabinoids are likely involved.

Objective and Design: To explore the role of these substances in hedonic eating, we measured changes in their plasma levels in eight satiated healthy subjects after *ad libitum* consumption of highly palatable food as compared with the consumption of nonpalatable food in isoenergetic amounts with the same nutrient composition of the palatable food.

Results: The consumption of food for pleasure was characterized by increased peripheral levels of both the peptide ghrelin and the endocannabinoid 2-arachidonoyl-glycerol. Levels of the other endocannabinoid anandamide and of anandamide-related mediators oleoylethanolamide and palmitoylethanolamide, instead, progressively decreased after the ingestion of both highly pleasurable and isoenergetic nonpleasurable food. A positive correlation was found between plasma 2-arachidonoyl glycerol and ghrelin during hedonic but not nonhedonic, eating.

Conclusions: The present preliminary findings suggest that when motivation to eat is generated by the availability of highly palatable food and not by food deprivation, a peripheral activation of two endogenous rewarding chemical signals is observed. Future research should confirm and extend our results to better understand the phenomenon of hedonic eating, which influences food intake and, ultimately, body mass. **(*J Clin Endocrinol Metab* 97: E917–E924, 2012)**

Historically, human beings aimed to seek food to survive, and sophisticated physiological mechanisms evolved to regulate eating behavior and energy homeostasis (1, 2). In present times, because of the availability of highly palatable food in the environment, consumption of food just for pleasure and not to maintain energy homeostasis has become more and more widespread. This phenomenon has been defined hedonic hunger (3). Thus, desiring and eating a piece of cake after a satiating meal represents a typical example of food ingestion driven by pleasure and not by energy deprivation.

As pointed out by Lowe and Butryn (3), a requisite for foods to still be desired and eaten even when there is no need for caloric ingestion is that they are extremely re-

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Abbreviations: AEA, Anandamide; 2-AG, 2-arachidonoyl-glycerol; AUC, area under the curve; CB1 and -2, cannabinoid type 1 and 2; OEA, oleoylethanolamide; PEA, palmitoylethanolamide; PPAR-α, peroxisome proliferator-activated receptors-α; VAS, visual analog scales.

warding and highly pleasurable for the subject. Therefore, although homeostatic hunger also has a hedonic component, hedonic hunger differentiates from homeostatic hunger by two main parameters concerned with the timing, quantity, and quality of the meal: first, the subject eats also when not in a state of energy depletion, and second, the food is consumed uniquely because of its gustatory rewarding properties and independently from its caloric content. It is intuitive that hedonic hunger may powerfully stimulate food intake in an environment where highly palatable foods are omnipresent and contribute to the diffusion of overweight and obesity. Therefore, understanding the physiological mechanisms underlying this eating behavior may help to contrast it.

Animal data support the view that distinguishable although overlapping neural and peripheral pathways, involving several appetite-regulating substances, drive homeostatic- and hedonic-based eating (4, 5). Schematically, in homeostatic eating, energy deficit triggers the activation of hypothalamic hunger mediators, which promote food intake; this, in turn, leads to the release of hypothalamic satiety signals that stop food consumption. In hedonic eating, instead, it has been proposed that highly palatable food activates brain reward circuits with the release of dopamine, endocannabinoids, and opiates, which induce a persistent stimulation of hypothalamic hunger signals and inhibition of satiety mediators. In this condition, the drive to eat is maintained and food is consumed also with no need for energy, and just because of its rewarding and pleasurable properties. A role for the orexigenic peptide ghrelin and the orexigenic local mediators, the endocannabinoids, in mediating reward processes has also been demonstrated (6, 7); thus, the involvement of these different chemical signals and their receptors in both homeostatic and hedonic eating seems likely. In particular, the endocannabinoid signaling system, consisting of two main local lipid mediators, the endocannabinoids anandamide [arachidonoylethanolamide (AEA)] and 2-arachidonoylglycerol (2-AG), their two G protein-coupled receptors, the cannabinoid type 1 (CB1) and -2 (CB2) receptors, and enzymes for the biosynthesis and degradation of AEA and 2-AG, has been suggested to play a fundamental role in both the homeostatic and hedonic aspects of food intake (7). We hypothesized that endocannabinoids and ghrelin responses to highly pleasurable food should differ from those to nonpalatable food to drive the motivation to eat even when there is no negative energy imbalance. Therefore, to explore the role of endocannabinoids and ghrelin in human hedonic eating, we measured peripheral changes in their levels after the hedonic consumption of food in normal-weight satiated healthy subjects.

Subjects and Methods

Eight healthy subjects, three men and five women, aged 21–33 yr (mean ± SD = 25.5 ± 3.8 yr), were enrolled into the study. They had normal eating behaviors without food restriction or dieting or bingeing, as ascertained by a semistructured clinical interview that we usually adopt in our clinical assessment of patients with eating disorders; this is a validated instrument based on the eating disorder module of the Structured Clinical Interview for Axis I DSM-IV disorders nonpatient edition (8). Their mean body mass index was 22.07 ± 2.7 kg/m^2, and subjects with a body mass index above 25 kg/m^2 and/or antecedent of obesity were excluded from the study. All subjects were drug free, had normal physical examinations, values of routine blood and urine tests, and electrocardiogram. None of them had a past history of alcohol or drug abuse. Only normal-weight healthy subjects were included in this study to explore peripheral biological responses to hedonic eating in physiological conditions.

The experimental protocol was approved by the local ethical committee, and all subjects gave their written consent after being fully informed of the nature and procedures of the study. The experiment used a within-subject repeated-measure design in which each volunteer served as his/her own control. All subjects were tested two times, 1 month apart; women were tested in the follicular phases of two consecutive menstrual cycles (d 5–10 from menses). Before the first experimental session, each participant was asked to indicate her/his more palatable food by answering the following question: "which is your most favorite food that you would eat also when satiated, just for pleasure?"

On the first test session, participants arrived at our Clinical Investigation Unit at 0830 h after a 12-h fast. At 0900 h, they were asked to rate their hunger and satiety on visual analog scales (VAS) that used a 10-cm line with labels at the extremities indicating the most negative and the most positive ratings; then they received a breakfast of 300 kcal, with 77% carbohydrates, 10% proteins, and 13% fat. Immediately after breakfast, they rated again their hunger and satiety by means of VAS. After 1 h, they were told that they would receive their favorite food, and an iv catheter was inserted into an antecubital vein to collect a first blood sample [time (T) = 0]; then the catheter was connected to a saline solution, which was slowly infused to keep it patent. Immediately afterward, each participant was exposed to the chosen palatable food for 5 min. During this time, she/he could smell and see the food but could not eat it. At the end of the exposure, each participant was asked to rate her/his hunger, satiety, urge to eat that food, pleasantness to experience a mouthful of that food, and amount of food she/he would eat by means of VAS. Then she/he was free to eat the palatable food *ad libitum* within 10 min; this time period was chosen to standardize the time of food ingestion and the times of blood sample collection among the subjects in the two experimental sessions. Additional blood samples were drawn immediately after the exposure to the palatable food (T = 5) and 15 (T = 25) and 120 (T = 130) min after eating. At the end of the session, the amount of food eaten by each participant was calculated by weighing the residual food and subtracting it from the initial amount of food provided, and then the calories eaten were calculated. On the second test session, carried out 1 month later, participants underwent the same experimental procedures of the first experimental session except for the fact that they were exposed to nonpalatable food and had to eat an amount of it with the same nutrient composition and an equal quantity of calories as the palatable food they ate in the previous session within 10 min.

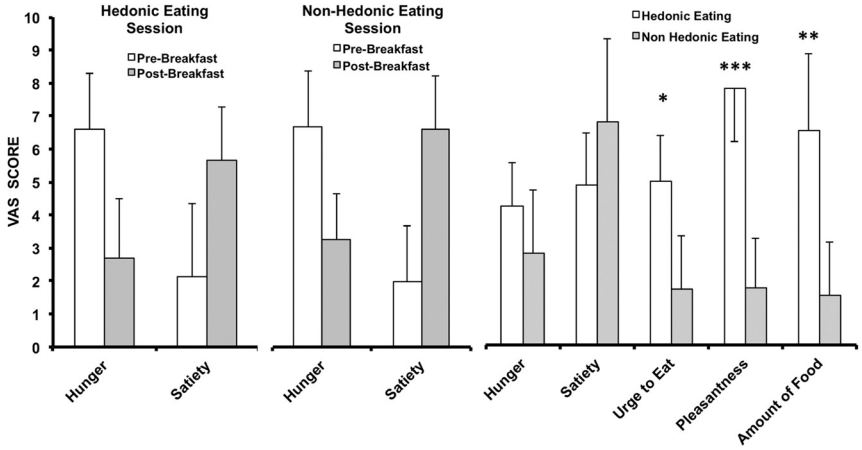

FIG. 1. VAS scores in healthy subjects before and after breakfast in both hedonic (*left panel*) and nonhedonic (*middle panel*) eating sessions and before hedonic and nonhedonic eating (*right panel*). Data are expressed as mean ± SD. *, $P < 0.007$; **$P < 0.003$; ***, $P < 0.0003$ compared with nonhedonic eating.

Palatable foods were served in dishes from which the subject was free to eat *ad libitum*; they were typical Italian cakes with chocolate or Nutella. On the basis of participants' answers to the question about their most favorite food that they would eat also when satiated, just for pleasure, bread, milk, and butter were identified as nondesirable foods and combined *ad hoc* to provide the same nutrients and calorie amounts of the pleasurable foods (see Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). Calorie and nutrient contents of palatable and nonpalatable foods were calculated by using the WINFOOD program (Medimatica, Teramo, Italy) except for subjects 2, 7, and 8, who ate packaged foods with labels. To calculate calorie and nutrient content of Italian cakes, we obtained the recipes from the confectioner who prepared them.

Blood was collected in tubes with EDTA as anticoagulant. Plasma was separated by centrifugation and stored at −20 C. Ghrelin was measured by a commercial ELISA kit (Phoenix Pharmaceuticals Inc., Burlingame, CA). Plasma glucose was determined by a commercial enzymatic UV method (Sigma Diagnostics, St. Louis, MO). Plasma levels of AEA, 2-AG, oleoylethanolamide (OEA), and palmitoylethanolamide (PEA) were determined by isotopic dilution-liquid chromatography-mass spectrometry as described previously (9, 10).

The BMDP statistical software package (11) was used for data analysis. The Shapiro-Wilk test showed that data were normally distributed. The Mauchly's sphericity test was performed to test for homogeneity of correlation among variables; because its values were nonsignificant for all the variables, differences in the hormone responses to the two isoenergetic meals were analyzed by a mixed-model ANOVA with repeated measures, followed by the *post hoc* Tukey's test. Two-way ANOVA with repeated measures was employed to analyze differences in the subjective VAS scores. The Pearson's product-moment correlation test was employed to analyze possible correlations among the variables. A level of significance of $P < 0.05$ was used for all data analyses.

Results

VAS scores

No statistically significant differences emerged in hunger and satiety scores either before or after breakfast between the test day of hedonic eating and that of nonhedonic eating. Similarly, the hunger and satiety scores before hedonic eating did not statistically differ from those before nonhedonic eating. In both test days, the hunger scores before hedonic or nonhedonic eating did not statistically differ from the hunger scores after breakfast; similarly, the satiety scores before hedonic or nonhedonic eating did not statistically differ from the satiety scores after breakfast (Fig. 1). These data demonstrate that before eating, the palatable food or the isoenergetic nonpalatable food participants were satiated and did not experience caloric restriction.

The urge to eat, the pleasantness to experience a mouthful of presented food, and the amount of food each participant would eat were significantly higher before eating the palatable food than before eating the isoenergetic nonpalatable food (Fig. 1).

Calorie ingestion and plasma glucose

The calorie amount and the nutrient composition of palatable and nonpalatable foods eaten by each subjects are shown in Table 1. No statistically significant difference emerged in the mean values of calories and nutrients of palatable and nonpalatable foods. One subject ingested a

TABLE 1. Calorie and nutrient contents (grams) of palatable and nonpalatable foods eaten by each participant

	Palatable food				Nonpalatable food			
Subject	Kcal	Lipids	Carbohydrates	Proteins	Kcal	Lipids	Carbohydrates	Proteins
S-1	425.3	6.1	71.5	21.1	389.4	4.6	74.0	13.0
S-2	316.2	18.6	33.6	3.6	319.2	20.0	31.0	3.8
S-3	1529.6	44.8	232.8	48.8	1504.0	48.6	238.0	28.5
S-4	373.0	13.0	56.0	8.0	403.0	11.0	68.0	8.0
S-5	373.0	13.0	56.0	8.0	403.0	11.0	68.0	8.0
S-6	460.0	14.4	67.0	15.6	449.9	16.2	68.0	8.0
S-7	489.0	24.6	62.1	4.8	493.8	24.3	61.2	7.5
S-8	538.2	34.6	50.3	6.4	567.1	32.4	61.3	7.5
Mean ± SD	563.0 ± 397.0	21.1 ± 12.9	78.7 ± 63.3	14.5 ± 15.0	566.2 ± 386.2	21.0 ± 14.1	83.7 ± 63.7	10.5 ± 7.7

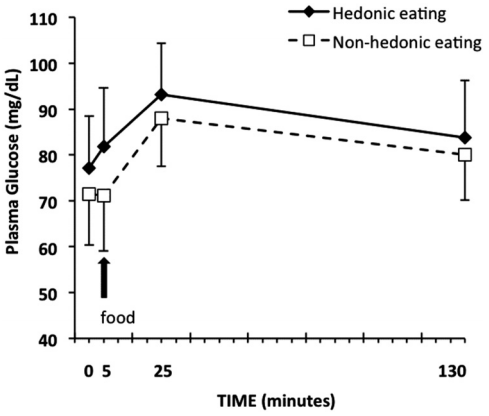

FIG. 2. Plasma glucose levels after hedonic and nonhedonic eating. Data are expressed as mean ± SD. Mixed-model ANOVA with repeated measures showed no significant effect for group [$F_{(1,56)} = 2.22$; $P = 0.14$], a significant effect for time [$F_{(3,56)} = 10.79$; $P = 0.00001$], and no significant group × time interaction [$F_{(3,56)} = 0.47$; $P = 0.7$].

large amount of calories, because his highly pleasurable food was represented by a highly caloric Italian cake. Although from this point of view, he was an outlier, his hormone responses were in the ranges of the other subjects; so we decided to retain him in our analyses.

Plasma glucose levels after hedonic eating did not significantly differ from those after nonhedonic eating (Fig. 2).

Plasma ghrelin

The timing of ghrelin changes in hedonic eating statistically differed from that in nonhedonic eating. Indeed, 5 min after the exposure to the highly pleasurable food, plasma ghrelin levels showed a more pronounced although not statistically significant increase than after the exposure to the nonpalatable food. Moreover, whereas plasma ghrelin levels progressively decreased after eating the nonpalatable food, they showed a further and statistically significant increase 120 min after eating the highly pleasurable food (Fig. 3). The total secretion of ghrelin, measured as the area under the curve (AUC), was significantly higher in hedonic than in nonhedonic eating [$F_{(1,14)} = 6.27$; $P < 0.025$] (Fig. 3).

Plasma AEA, OEA, PEA, and 2-AG

Plasma levels of AEA, OEA, and PEA significantly decreased after eating, but the timing and the magnitude of changes after hedonic eating did not differ statistically from those after nonhedonic eating (Fig. 4).

Plasma levels of 2-AG decreased after eating both the palatable and nonpalatable food; however, compared with nonhedonic eating, plasma 2-AG levels were significantly higher before the exposure to the palatable food (T = 0) and 120 min after eating it (T = 130) (Fig. 5). Plasma 2-AG AUC was significantly higher in hedonic eating than in nonhedonic eating [$F_{1,14)} = 10.59$; $P < 0.006$] (Fig. 5).

Correlations

No significant correlation emerged between the AUC or T = 0 values of 2-AG or ghrelin and VAS measures or ingested calories in both the hedonic and nonhedonic eating condition. Instead, a significant positive correlation emerged between plasma AUC of 2-AG and plasma AUC of ghrelin in hedonic eating (r = 0.907; $P = 0.002$) but not in nonhedonic eating (r = 058; $P = 0.1$).

Discussion

The endocannabinoids AEA and 2-AG are two lipid mediators that have been both described to play a major role in the stimulation of food intake. They exert this function by activating cannabinoid CB1 receptors, which are widely distributed in several brain areas, including those involved in the homeostatic and hedonic control of feeding (7). Under normal physiological conditions in rodents and men, endocannabinoids transiently increase after food deprivation and decrease after food ingestion, possibly due to stimulatory or inhibitory effects by hormones whose circulating levels are modulated by food deprivation, such as ghrelin. These changes have been described to occur in the hypothalamus or limbic forebrain in rodents and in the plasma in humans (7) (see below). However, during obesity, endocannabinoid levels appear to be permanently elevated

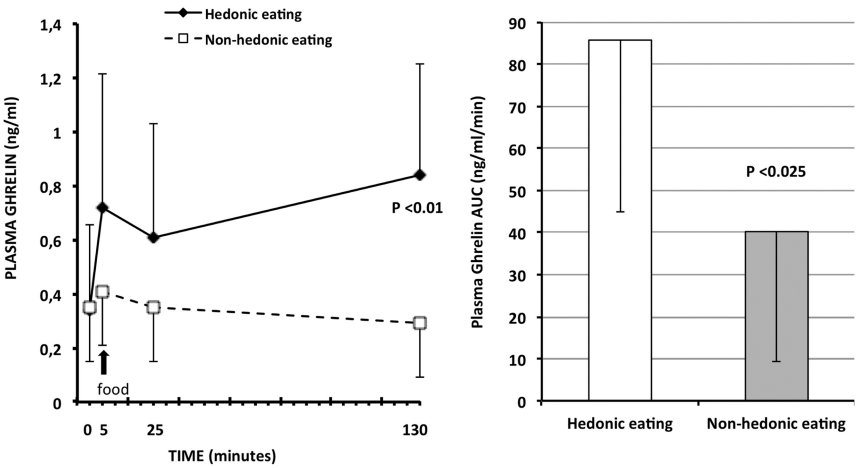

FIG. 3. Plasma ghrelin levels (*left panel*) and plasma ghrelin AUC (*right panel*) after hedonic and nonhedonic eating. Data are expressed as mean ± SD. Mixed-model ANOVA with repeated measures showed a trend toward a significant effect for group [$F_{(1,56)} = 3.84$; $P = 0.054$], a significant effect for time [$F_{(3,56)} = 4.11$; $P = 0.01$], and a significant group × time interaction [$F_{(3,56)} = 5.03$; $P = 0.003$].

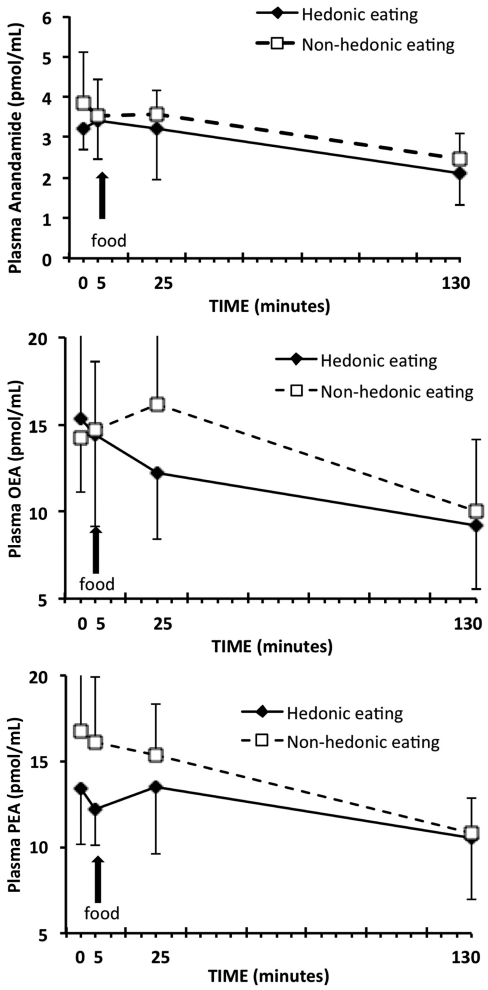

FIG. 4. Plasma levels of anandamide (*top panel*), OEA (*middle panel*), and PEA (*bottom panel*) after hedonic and nonhedonic eating. Data are expressed as mean ± SD. As for anandamide, mixed-model ANOVA with repeated measures showed no significant effect for group [$F_{(1,56)} = 0.98$; $P = 0.32$], a significant effect for time [$F_{(3,56)} = 15.97$; $P < 0.000001$], and no significant group × time interaction [$F_{(3,56)} = 0.50$; $P = 0.6$]. As for OEA, mixed-model ANOVA with repeated measures showed no significant effect for group [$F_{(1,56)} = 0.24$; $P = 0.6$], a significant effect for time [$F_{(3,56)} = 10.65$; $P = 0.00001$], and no significant group × time interaction [$F_{(3,56)} = 2.02$; $P = 0.12$]. As for PEA, mixed-model ANOVA with repeated measures showed no significant effect for group [$F_{(1,56)} = 3.40$; $P = 0.07$], a significant effect for time [$F_{(3,56)} = 11.88$; $P = 0.000001$], and no significant group × time interaction [$F_{(3,56)} = 1.95$; $P = 0.13$].

(7, 12). No study has been carried out thus far to investigate the regulation of endocannabinoid levels after hedonic eating, and in fact, to the best of our knowledge, the present one is the first study exploring peripheral biochemical changes associated with this type of eating behavior. We found that in satiated normal-weight healthy subjects, the consumption of food for pleasure was characterized by increased plasma levels of both the peripheral peptide ghrelin and the endocannabinoid 2-AG. Plasma levels of the other endocannabinoid, AEA, and of the two AEA metabolically related lipids and agonists of peroxisome proliferator-activated receptors-α (PPAR-α), OEA and PEA, instead, progressively decreased after the ingestion of both highly pleasurable and isoenergetic nonpleasurable food. In our experimental protocol, satiation was obtained by eating a breakfast of 300 kcal. Although this could seem an energy amount not enough to suppress hunger completely after 12 h fasting, eating such an amount of calories at breakfast is in line with Italian feeding habits and, therefore, best represents the natural morning feeding condition in our participants.

In our subjects, the ghrelin increase observed 5 min after the exposure to both the palatable and nonpalatable food likely represents the increased ghrelin secretion occurring in the cephalic phase of food ingestion, when subjects see and/or smell the food but do not eat it yet (13). However, after the exposure to the highly pleasurable food, such an increase was more pronounced compared with that observed in nonhedonic eating, although this difference was not statistically significant; furthermore, plasma ghrelin levels progressively decreased after eating the nonpalatable food as it occurs in homeostatic eating (14), whereas they increased after the ingestion of the palatable food. These preliminary findings show for the first time an activation of ghrelin secretion in hedonic eating and support a role for this peptide in mediating the motivation to eat even when there is no need for calories.

It has been recently shown that ghrelin not only acts as an orexigenic signal but intervenes also in the modulation of reward and motivated behaviors. A functional magnetic resonance imaging study (15) showed that iv ghrelin administration in healthy subjects increases the neural response to food pictures in brain areas implicated in reward processing and appetitive behavior such as the amygdala, ventral striatum, anterior insula, and orbitofrontal cortex. Moreover, experimental data demonstrated that injection of ghrelin into the third ventricle of mice significantly increases locomotor activity as well as extracellular dopamine levels in the nucleus accumbens (6), a neurochemical system involved in reward and motivated behavior as well as in mediating the incentive salience of food (16). Therefore, it has been suggested that ghrelin-induced activation of the mesolimbic dopaminergic reward system increases the incentive value of food and facilitates food-seeking behavior (6). Likewise, on the basis of our preliminary data, it can be tentatively proposed that an increased secretion of ghrelin activates central reward pathways, which override the physiological inhibition of food ingestion driven by the satiety condition, so that eating is maintained despite no need for calorie ingestion, and just for the rewarding properties of the highly pleasurable food.

Our findings suggest also an involvement of the endocannabinoid 2-AG in hedonic eating. In our experimental conditions, plasma levels of 2-AG were significantly higher even before the exposure to the highly pleasurable

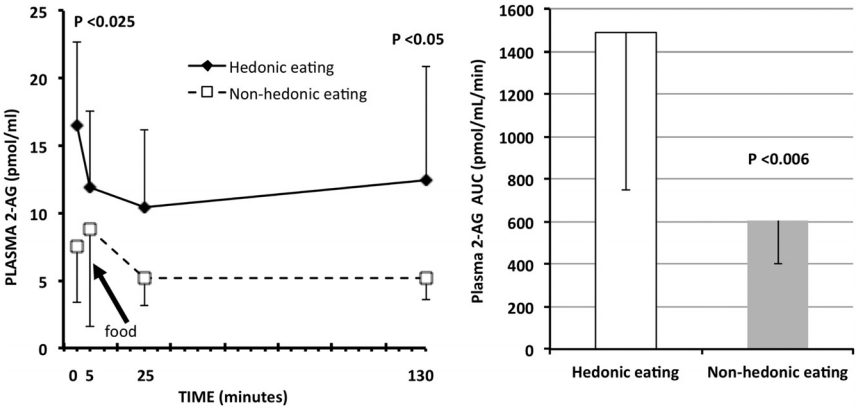

FIG. 5. Plasma levels of 2-AG (*left panel*) and plasma 2-AG AUC (*right panel*) after hedonic and nonhedonic eating. Data are expressed as mean ± SD. Mixed-model ANOVA with repeated measures showed significant effects for both group [$F_{(1,56)} = 6.77$; $P = 0.01$] and time [$F_{(3,56)} = 4.81$; $P = 0.004$] but no significant group × time interaction [$F_{(3,56)} = 2.09$; $P = 0.11$].

food, and although decreasing after eating both types of food, they were significantly higher 120 min after eating the palatable food than after eating normal food. These data suggest an activation of endogenous 2-AG production from peripheral sources before the exposure to the highly palatable food, which can be explained by the nature of our experimental protocol. Indeed, the participants in this study knew that they would eat the highly pleasurable food in the first experimental session, because, to balance the nonpalatable food to the palatable one in terms of caloric and nutrient intake, we were obliged to administer first the pleasurable food. Therefore, the premeal increase of plasma 2-AG in hedonic eating might be associated with the anticipation of the pleasure of ingesting a food with highly rewarding gustatory properties, which would promote eating in a condition of no energy deprivation. After eating the pleasurable food, the plasma levels of 2-AG, although decreasing as in nonhedonic eating, were persistently higher than after eating the nonpleasurable food, and this might be associated with the pleasure experienced during such a meal. This hypothesis is supported by several experimental data in laboratory animals. In fact, rimonabant, an antagonist of the CB1 receptor, inhibits both palatable food-induced dopamine release in the nucleus accumbens (17) and intake of palatable food in non-food-deprived animals (18), both these effects being much less strong in animals exposed to normal food. These data suggest that exposure to foods with high salience and incentive properties might stimulate an endocannabinoid tone to induce dopamine release in this limbic area (see Ref. 7 for review). This latter event might, in turn, lead to both increased motivation to consume palatable foods (also when there is no need for calorie ingestion) and heighten rewarding effects after the consumption of such foods. Therefore, the increased plasma levels of 2-AG that we observed in subjects exposed to the palatable food might be the result of spillover from the brain areas in which exposure to palatable food enhances endocannabinoid production to increase the incentive value of the pleasurable food (that is, the wanting) before food intake and to heighten its rewarding effects after consumption (and hence, its liking). A more likely possibility, however, is that plasma 2-AG levels reflect spillover from peripheral tissues, such as the small intestine or adipose tissue, which, like the brain, respond to food deprivation and refeeding with changes in local endocannabinoid levels (19). Indeed, gustatory stimulation with high-fat food was recently shown to cause elevation of endocannabinoid levels in the small intestine, which in turn was suggested, through the use of a peripherally restricted CB1 antagonist, to contribute to further consumption of fat via vagal fibers (20, 21). Spillover of endocannabinoids from peripheral organs into the plasma in humans is not unprecedented. Caraceni *et al.* (22) showed that, in patients with cirrhosis, who exhibit an overall overactive endocannabinoid system in the liver, part of circulating 2-AG comes from this organ, because its levels in the suprahepatic vein were higher than its average circulating levels.

In fact, a limitation of our study is represented by the fact that we could measure only circulating levels of endocannabinoids and ghrelin; thus, it remains to be determined whether the changes we observed in plasma reflect changes in peripheral tissues or in brain areas directly involved in reward. Indeed, during human conditions in which the brain has been suggested to produce more endocannabinoids, such as in certain neuroinflammatory diseases, this is reflected in the blood (23). Another limitation of our study is that we chose to perform only two plasma measurements after the meal, the first 10 min after finishing the ingestion of food and the second 2 h later. Therefore, we cannot exclude that more frequent measurements could have revealed different biochemical profiles. Finally, the *post hoc* power analysis showed that the present sample size had a power of 0.78 to detect a medium effect size (f = 0.30) at an α-value of 0.05 to find biochemical changes significantly different between hedonic and nonhedonic eating; therefore, our results should be regarded as preliminary.

Based on our data, an interaction between ghrelin and the endocannabinoid 2-AG can also be proposed. In fact, we found a positive correlation between ghrelin levels and those

of 2-AG, both measured as AUC, in the hedonic but not in the nonhedonic condition. In support of this interaction, it is known that administration of exogenous ghrelin to mice significantly increases 2-AG content in the hypothalamus and stimulates appetite through a CB1 receptor-mediated mechanism (24). On the other hand, indirect data also suggest that peripheral CB1 receptor activation might tonically contribute to circulating ghrelin levels in satiated rats (25). Therefore, it could be proposed that the role of peripheral ghrelin in the rewarding effects of highly pleasurable food is mediated by an activation of the endogenous production of 2-AG or vice versa. However, our data are only of correlative nature and, therefore, should be interpreted with caution. Nevertheless, it is worthwhile noting that the levels of AEA and of the anorexigenic intestinal mediator peptide YY were recently reported to decrease and increase, respectively, 1 h after a meal in normal-weight, but not obese, subjects. Yet, AEA and peptide YY levels did not negatively correlate with each other (26), in agreement with the absence of any evidence of reciprocal regulation between the intestinal peptide and the endocannabinoid.

To date, no evidence of a role for PPAR-α in the rewarding effect of food has been reported, although this nuclear receptor was recently suggested to counteract the rewarding properties of nicotine (27). Here, we also measured the plasma levels of the two PPAR-α ligands, OEA and PEA, which share metabolic pathways and enzymes with AEA. Indeed, like AEA, and in agreement with previously published studies (26, 28, 29), the levels of these two compounds decreased after food consumption. This effect occurred irrespective of the palatability of the meal and is possibly due to insulin-induced inhibition of the biosynthesis, or up-regulation of the degradation, of these compounds in our insulin-sensitive subjects (30). Indeed, it was not surprising to see that the levels of 2-AG, on the one hand, and of the *N*-acylethanolamines AEA, PEA, and OEA, on the other hand, responded to exposure to palatable food in different ways because it is now well established that 2-AG and *N*-acylethanolamines are produced and biosynthesized through different pathways and enzymes (7).

In conclusion, our preliminary findings show that when in normal-weight healthy subjects motivation to eat is generated by the availability of highly palatable food and not by food deprivation, a peripheral activation of two endogenous rewarding chemical signals is observed, although there is no biological need for caloric ingestion. Future research should confirm and extend our results to patients with obesity or with other eating disorders to better understand the phenomenon of hedonic eating, which could powerfully influence food intake and, ultimately, body mass.

Acknowledgments

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