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Unbalanced serum leptin and ghrelin dynamics prolong postprandial satiety and inhibit hunger in healthy elderly: another reason for the "anorexia of aging"[1–3]

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ABSTRACT

Background: In healthy elderly, a reduction from the appetite and food intake of younger years has been defined as the "anorexia of aging," which may cause malnutrition. Leptin and ghrelin may alter the control of hunger and satiety and thus lead to anorexia.

Objective: The aim of this study was to investigate how aging affects serum leptin and ghrelin concentrations in response to a meal and the relation of those hormones to hunger and satiety sensations.

Design: We studied 8 community-dwelling elderly ($\bar{x} \pm$ SD age: 78 ± 1 y) subjects and 8 younger (29.5 ± 1 y) control subjects. Under fasting conditions and for 4 h after an 800-kcal mixed meal, satiety and hunger were evaluated at intervals, by using a visual analogic scale. Blood samples for leptin, ghrelin, and insulin measurements were collected at the following times: 30 min before and immediately and 30, 60, 120, and 240 min after the meal.

Results: Postprandial satiety lasted significantly longer in the elderly than in the control subjects, and hunger was suppressed in the elderly throughout the observation. Fasting leptin was higher in the elderly than in the young ($\bar{x} \pm$ SE: 4.3 ± 1.9 and 1.3 ± 0.4 ng/mL, respectively; $P < 0.05$), and postprandial fluctuation was not significant. Fasting insulin also was significantly higher in the elderly than in the young (6.8 ± 1.3 and 3.5 ± 0.6 mU/L, respectively; $P < 0.05$), and the postprandial insulin rise was greater in the elderly. Fasting and postprandial ghrelin values did not differ significantly between the 2 groups. Insulin was inversely correlated with hunger and directly correlated with satiety scores.

Conclusions: In healthy elderly, anorexigenic signals prevail over orexigenic signals, and they contribute to prolonged satiety and inhibition of hunger. This condition may lead to a calorie deficit and finally to malnutrition in the elderly. *Am J Clin Nutr* 2006;83:1149–52.

KEY WORDS Aging, leptin, ghrelin, malnutrition

INTRODUCTION

Protein-energy malnutrition is a frequent condition in the elderly, in whom it is associated with a reduction in the adaptive response to physiologic and pathologic conditions (1). The causes of malnutrition are likely to be multifactorial. The so-called "anorexia of aging"—ie, an age-related decrease in calorie intake—may be one of the main risk factors for malnutrition in old age (2). Impaired control of satiety and hunger may cause anorexia at more advanced ages.

Peripheral signals influence satiety and hunger after a meal and under fasting conditions. Short-term postprandial satiety signals such as CCK and PYY have been shown to be stronger in the elderly than in younger persons (3, 4). Leptin, a hormone that functions mainly as a signal of adiposity (5), elicits long-term satiety. In the elderly, high fasting concentrations of leptin have been reported, but few data are available on leptin's relation to sensations of hunger and satiety (6–8), and no data are available on postprandial leptin concentrations in the elderly. Ghrelin, a gastric peptide, generates an orexigenic peripheral signal (9) that triggers meal initiation (10). In fact, ghrelin production has been reported to rise during fasting and to drop after a meal (11). In a small group of elderly subjects under fasting conditions, serum ghrelin was lower than in the younger controls (12), but no data are available on serum ghrelin concentrations after food consumption in the elderly.

The aim of this study was to compare the fasting and postprandial serum dynamics of leptin and ghrelin in healthy elderly subjects with those in young control subjects and to verify the role of peptides with respect to sensations of satiety and hunger in the elderly.

SUBJECTS AND METHODS

Subjects

We studied 8 elderly subjects (4 men, 4 women) with a mean (±SD) age of 77.9 ± 1 y (range: 74–82 y) and a body mass index (BMI; in kg/m^2) of 22.1–29.4 and 8 younger control subjects (4 men, 4 women) aged 29.5 ± 1 y (range: 25–38 y) with a BMI of 22.7–25.7 (BMIs were not significantly different, $P = 0.15$).

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TABLE 1
Fasting and postprandial satiety and hunger scores in 8 elderly and 8 young control subjects

	Time after the meal					*P*		
	Fasting	Immediately after	60 min	120 min	180 min	240 min	Age[2]	Time[2]	Interaction
	cm			*cm*					
Hunger									
Elderly	4.8 ± 1.1[1]	0.5 ± 0.1	0.8 ± 0.4	1.7 ± 0.6	2.9 ± 1.1	3.5 ± 1.1	0.005	< 0.001	0.279
Young	7.3 ± 0.4	0.8 ± 0.3	3.2 ± 0.7	4.6 ± 0.6	5.5 ± 0.5	6.2 ± 0.6			
Satiety									
Elderly	1.8 ± 0.7	8.4 ± 0.5	7.6 ± 0.8	6.2 ± 1.3	6.4 ± 1.4	5.1 ± 1.2	0.036	< 0.001	0.518
Young	1.1 ± 0.3	6.9 ± 0.9	5.6 ± 0.7	4.2 ± 0.6	3.2 ± 0.4	2.0 ± 0.4			

[1] $\bar{x}$ ± SE (all such values).
[2] Main effect.

We excluded subjects who had undergone any abdominal surgical procedure or who had a history of cholelithiasis, diabetes, neurologic disease, chronic gastrointestinal peptic or inflammatory disease, or malignancies or who had any acute disease. Also excluded were subjects with known cardiac, renal, or respiratory function impairment and those with a BMI < 18.5 or > 30. We also excluded subjects who were taking drugs that may interfere with gastrointestinal motility and visceral sensitivity (eg, calcium channel antagonists, nitrates, prokynetics, proton pump inhibitors, H_2 receptor antagonists, and sedatives).

Each subject provided written informed consent. The Ethics Committee of the University Hospital of Verona approved the study.

Experimental design

After an overnight fast, both groups were evaluated before eating, and they were then asked to consume the standard meal in ≈20 min. The end of the meal was considered time zero (*t*0); evaluations were then repeated every 30 min for 4 h.

The standard meal consisted of 60 g macaroni alla bolognese with 70 g meat sauce, 50 g ham, 50 g soft fatty cheese, one dinner roll, and 250 mL tap water. The total amount of energy was 800 kcal: 15% from proteins, 45% from fat, and 40% from carbohydrates.

Satiety and hunger evaluation

Visual analogue scales were used to measure subjective satiety and hunger. Satiety was defined as the sensation of fullness after eating so that a person does not feel the need to eat for some time afterward. Hunger was defined as the subjective driving force for the search for, choice of, and ingestion of food (13). Subjects were instructed to make a single vertical mark on a horizontal 10-cm bar to indicate their current feelings, ranging between "not hungry at all" and "really hungry" and between "empty" and "full." Baseline evaluations were collected 30 min before the meal, immediately after the meal, and 30, 60, 120, 180, and 240 min after the meal.

Blood samples were collected 30 min before, immediately after, and 30, 60, 120, and 240 min after the meal. After centrifugation at 3000 RPM for 15 min at 10 °C in a refrigerated centrifuge (ALC, Milan, Italy), serum and plasma samples were stocked at −80 °C for final evaluation. Commercially available enzyme-linked immunosorbent assay kits (Phoenix Pharmaceuticals, Belmont, CA) were used for leptin and ghrelin serum measurements. Both tests have an intraassay variation of <5% and an interassay variation of <14%. Plasma immunoreactive insulin underwent duplicate measurements by double-antibody radioimmunoassay with the use of a commercial kit (Diagnostics Corp, Los Angeles, CA). The detection limit of the insulin assay was 6 pmol/L, and the intraassay CV was 4.9%.

Statistical analysis

Statistical analysis was performed with SPSS for WINDOWS software (version 11.5; SPSS Inc, Chicago, IL). Results are shown as means ± SEs. Data were analyzed by using a 2-factor repeated-measures analysis of variance. $P = 0.05$ was considered to indicate significance. Leptin data were normalized by base-10 logarithm transformation. A partial correlation coefficient (after adjustment for BMI) was used to evaluate relations among the variables.

RESULTS

The mean fasting and postprandial satiety and hunger scores are shown in **Table 1**. In both, the group × time interaction was not significant ($P > 0.2$), and thus the pattern of the curves was similar in the 2 groups for both satiety and hunger sensations. Younger subjects had mean hunger scores that were significantly ($P = 0.005$) higher than those of older subjects and mean satiety scores that were significantly ($P = 0.036$) lower than those of older subjects.

The mean fasting and postprandial serum leptin concentrations are shown in **Figure 1**. Fasting serum leptin was significantly higher in the elderly than in the control subjects (4.3 ± 1.9 and 1.25 ± 0.4 ng/mL, respectively; $P < 0.05$). The group × time interaction was not significant ($P > 0.2$), and neither was the

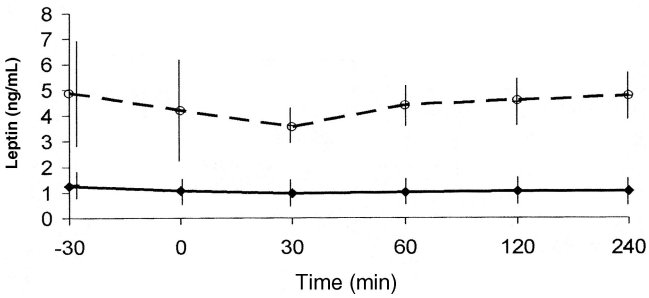

FIGURE 1. Mean (±SE) serum leptin concentrations before and after a meal in 8 elderly (- - -) and 8 young control (—) subjects. *P* values for the main effects of age and time and for the group × time interaction were 0.037, 0.236, and 0.348, respectively.

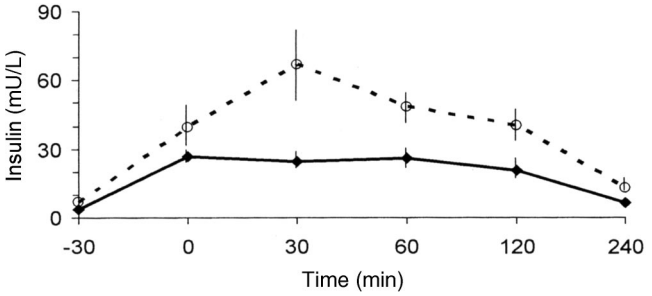

FIGURE 2. Mean (±SE) plasma insulin concentrations before and after a meal in 8 elderly (- - -) and 8 young control (—) subjects. *P* values for the main effects of age and time and for the group × time interaction were 0.014, <0.001, and 0.044, respectively.

effect of time, so that mean values of leptin showed a flat line in both the younger and older persons; younger subjects had mean values significantly ($P < 0.05$) lower than those of older subjects.

The mean fasting and postprandial plasma insulin concentrations are shown in **Figure 2**. Fasting plasma insulin was higher in the elderly than in the control subjects (6.8 ± 1.3 and 3.5 ± 0.6 mU/L, respectively; $P < 0.05$). A significant ($P = 0.044$) group × time interaction was observed, so that the pattern of the curves differed significantly between younger and older subjects. Even if an elevation of insulin concentrations was observed in both groups, this effect was significantly ($P = 0.01$) higher in the elderly group.

The mean fasting and postprandial serum ghrelin concentrations are shown in **Figure 3**. Ghrelin basal values did not differ significantly between older and younger subjects (17.8 ± 6.9 and 23.1 ± 7.1 pg/mL, respectively; $P = 0.50$). In this case, the group × time interaction, the effect of time, and age were not significant.

The hunger sensation score and the leptin, insulin, and ghrelin serum curves in the control and elderly subjects are summarized in **Figure 4**. In the presence of sustained high leptin concentrations and a greater rise in insulin, hunger in the elderly did not return to fasting concentrations with the increase in ghrelin.

The relations between satiety and hunger sensation scores and laboratory variables were evaluated by calculating partial correlations at every measurement point in each subject after control for BMI. We observed a significant positive correlation between insulin and satiety ($R = 0.374$, $P = 0.02$) and a significantly negative correlation between insulin and hunger score ($R = -0.510$, $P < 0.001$). No correlation was found between leptin or ghrelin and sensations of hunger and satiety.

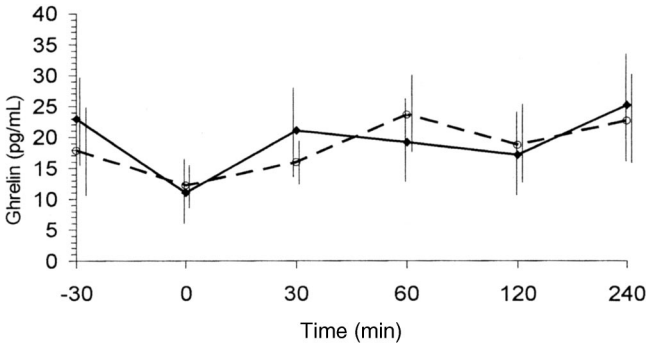

FIGURE 3. Mean (±SE) serum ghrelin concentrations before and after a meal in 8 elderly (- - -) and 8 young control (—) subjects. *P* values for the main effects of age and time and for the group × time interaction were 0.766, 0.513, and 0.901, respectively.

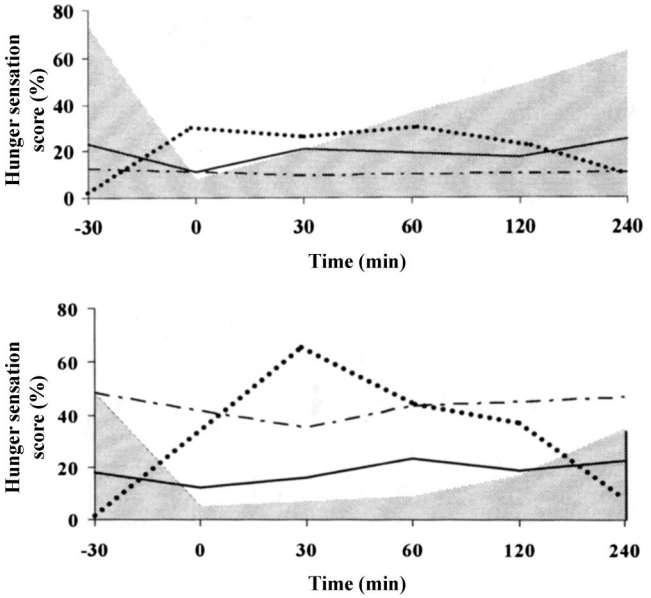

FIGURE 4. Mean hunger sensation score area (gray area) plotted against leptin (- - -), insulin (•••; mU/L), and ghrelin (—) curves in 8 younger control subjects (top) and in 8 elderly subjects (bottom). To fit the diagram scale, ghrelin values (pg/mL) were divided by 10 and leptin values (ng/mL) were multiplied by 10.

DISCUSSION

Our study showed higher serum concentrations of leptin in older than in younger control subjects and no significant change in leptin after the meal in either group. Plasma fasting and postprandial insulin concentrations were significantly higher in the elderly than in the younger subjects. The ghrelin serum profile did not differ significantly between the 2 groups. Satiety lasted significantly longer in the elderly than in the younger subjects, and hunger was suppressed throughout the postprandial period in the elderly.

Leptin was elevated in the elderly under fasting conditions, as described previously (6–8). We did not observe changes in leptin concentrations after the meal—ie, within the first 4 h of observation—in either group. These findings are in line with previous observations in adults, which suggests that leptin concentrations do not change significantly soon after a meal (14–16) and which confirms that leptin is involved in long-term food control more than in short-term modulation of food intake (17).

Our data do not show a causal link between high leptinemia and hunger inhibition in the elderly. Nevertheless, we hypothesize that elevated serum leptin may facilitate a postprandial prevalence of anorexigenic signals. High postprandial CCK concentrations characterize aging (3, 4). In this condition leptin passes more easily through the blood-brain barrier, which induces an increase in hypothalamic sensitivity to leptin (18, 19).

The higher concentrations of plasma insulin observed in the older than in the younger subjects may amplify the anorexigenic signal of leptin, because insulin stimulates central leptin action and sensitivity (20). Higher insulin concentrations in the elderly also could be responsible for inhibition of ghrelin expression and sensitivity (21).

It was been reported that fasting ghrelin is lower in the elderly than in younger persons, which suggests a role for hypoghrelinemia in the genesis of anorexia of the elderly (12). However, our data do not support these findings, and more data on larger

samples will be needed to clarify this issue. Neither basal nor postprandial ghrelin differd significantly in the 2 groups. In both groups, ghrelin dropped after the meal and returned to basal values within 4 h. Nevertheless, hunger did not follow a postprandial ghrelin rise in the elderly. Concurrent high concentrations of leptin and insulin may have been responsible for the elderly's low sensitivity to ghrelin (21–23). Furthermore, ghrelin is produced by the stomach in 2 major molecular forms: an active acylated ghrelin, which stimulates food intake, and a second type of ghrelin, desacyl ghrelin, which was thought to have no hormonal action (24). Very recently, it was shown in animal models that, in contrast with the acylated form, desacyl ghrelin decreases the intake of food (25). In the current study, we were able to measure only total serum ghrelin; it is possible that the ratio of acylated to nonacylated ghrelin may play a role in different responses to ghrelinemia in the elderly, and further studies are needed.

Some limitations of our study deserve mention. We studied a sample of healthy elderly who were free of chronic diseases and medications. It is reasonable to believe that chronic illness, medications, and malnutrition would only worsen the abnormalities shown in our subjects (2). Because of the small number of subjects, we could not evaluate the effect of sex on satiety, hunger, or peptide dynamics. In particular, it would be of interest to distinguish leptin findings according to sex. It is already well known that leptin is reduced by testosterone (26).

In the current study, we offered a meal that may be higher in calories and lipids than the average meal of many elderly. Our results should be confirmed after a more balanced meal (ie, one that is lower in energy and fat loads). Finally, visual analogue scales may be less reliable in the elderly than in younger persons (27), so satiety and hunger scores should be validated against more direct and objective markers of energy intake.

In conclusion, the current study showed higher serum concentrations of leptin in older than in younger subjects and no significant change in leptin after the meal in either group. Plasma fasting and postprandial insulin concentrations were significantly higher in the elderly than in the younger subjects. As a result, hunger was suppressed throughout the postprandial period in the elderly, despite a normal ghrelin serum profile. This condition may lead to calorie restriction and finally to malnutrition.

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VDF, MZ, GM, AD, and OB contributed to the design of the study; VDF, MZ, and EZ contributed to the design and conduct of the data analysis; VDF wrote the manuscript; MZ, EZ, GM, AD, FO, LB, FF, PR, SBS, OB, and RM contributed to the editing of the manuscript; EZ contributed laboratory evaluations; FO performed the subject screening and data collection; and RM performed the statistical analysis. None of the authors had a personal or financial conflict of interest.

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