Impaired Postprandial Response of Active Ghrelin and Prolonged Suppression of Hunger Sensation in the Elderly

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Background. The role of the orexigenic hormone ghrelin is of major interest in the altered appetite regulation of the elderly.

Methods. Basal and postprandial levels of active and total ghrelin were measured in 15 younger (mean age 35.4 years) and 19 older (80.7 years) participants following a carbohydrate-rich test meal.

Results. Our results showed that older participants felt postprandially less hungry and more full. Although basal levels were not significantly different, active and total ghrelin levels declined postprandially only in the younger study participants. Highly significant differences between the two age groups were shown for the changes of the area under the curve for active ghrelin (p = .024).

Conclusions. Our study demonstrates for the first time that differences in hunger and satiety sensations in relation to age are paralleled by a substantially different response of acylated and total ghrelin, that is, the absence of a postprandial decline in ghrelin levels.

Key Words: Ghrelin—Leptin—Elderly—Appetite regulation—Insulin.

Malnutrition has a considerably higher prevalence among older individuals compared with younger populations. This has been shown across different settings such as the community, the nursing home, and the hospital. The consequences of malnutrition in older persons are often severe, affecting quality of life, morbidity, and mortality. Although the pathophysiology of malnutrition in the elderly individuals is complex, age-related changes of food intake regulation seem to be of major relevance. It has been shown that during the interdigestive period, older people feel less hungry and experience greater and prolonged satiety postprandially. This phenomenon is not only of relevance in the acute experimental setting but it is also of considerable clinical importance. In a longitudinal study by Roberts and coworkers (1), older study participants were unable to compensate the weight loss induced by a 21-day fasting period in the following weeks when they were allowed to eat again ad libitum.

With regard to the regulation of hunger and satiety, the gastric hormone ghrelin is of great interest. Ghrelin is a 28-amino-acid protein with an n-octanoylated serine residue, discovered in 1999 by Kojima and coworkers (2) as an endogenous ligand of the growth hormone secretagogue receptor 1 (GHS-R1). The majority of ghrelin is released from neuroendocrine cells of the stomach mucosa. In small amounts, ghrelin is also synthesized in the brain, the pituitary gland, the small intestine, the adrenal gland, and the pancreas (3). At present, ghrelin is still regarded as the only orexigenic peripheral hormone. In young adults, it stimulates appetite together with food intake. Moreover, it enhances both fat-mass deposition and body-weight gain in animal experiments. Its short-term secretion is increased by fasting and inhibited by food intake. Its medium-term and long-term secretion increases in response to weight loss. Acylated ghrelin has been designated as active ghrelin. But the majority of serum ghrelin is desacyl-ghrelin, which lacks the biologically relevant acyl group and whose impact on appetite regulation is considered minor when compared with acylated ghrelin (4–11).

With regard to the association of age and ghrelin, secretion data from cross-sectional studies are contradictory. Most results in this field at present do not suggest that there is an age-associated effect on basal ghrelin when data are corrected for body composition. Until now, there have been only very few observational studies that have tested the hormonal response to a defined test meal in older persons (12–15). The aim of the present study was therefore to test whether (a) the secretion pattern of total and active ghrelin before and after a carbohydrate test meal differed between old and young study participants and (b) active ghrelin levels correlate with hunger and satiety sensations.

Participants

We studied 19 older outpatients from the Nuremberg geriatric day clinic (5 men and 14 women) with a mean age of 80.7 ± 5.6 years (range 71–89 years) and a mean body mass...
index (BMI) of 26.4 ± 5.6 kg/m². We excluded patients who suffered from diabetes, cancer, and advanced chronic disease states (chronic obstructive pulmonary disease, heart failure, chronic renal failure) and those who were taking corticosteroids. As a comparison group, we included 15 young healthy participants (10 men, 5 women) with a mean age of 35.4 ± 6.4 years (range 25-45 years) and a mean BMI of 25.3 ± 5.1 kg/m², which was similar to that of the elderly participants (t test: p > .2). All participants provided written informed consent. The Ethics Committee of the University of Erlangen-Nuremberg approved the study protocol.

**METHODS**

The experiments were performed 4 hours after a light breakfast consisting of bread, butter, and jam (39 g carbohydrates, 10 g fat, 9.5 g protein, 285 kcal). We chose lunch time for serving the test meal because we were unable to impose a strenuous regimen including transportation to our institution after a 12-hour overnight fasting period in our population of geriatric outpatients. The test meal consisted of 250 g pasta with 50 ml tomato sauce, which is equivalent to an energy content of 420 kcal. The macronutrient content amounted to 77.3 g carbohydrates, 5.4 g fat, and 12.9 g protein (75% carbohydrate, 12% fat, 13% protein).

We used visual analogue scales (VAS) to measure hunger and satiety sensations in the study participants. To characterize hunger and satiety, we adhered to the definition proposed by De Graaf and coworkers (16). Hunger was characterized by the driving sensation for the search for, choice of, and ingestion of food. Satiety was defined as the sensation of fullness after a meal with the effect that a person does not feel the need to eat for a certain interval. Participants were instructed to mark their present feelings of hunger and satiety on a horizontal 100 mm bar, ranging between “no feeling of hunger” and “very hungry” and between “empty” and “completely full.” Baseline data were collected immediately before the start of the meal at 0 minute. The participants were then asked to record their sensations of hunger and satiety again at 30, 60, 90, and 120 minutes.

Blood samples were collected into plastic tubes containing 1.2 mg EDTA and 500 KIU Trasylol. All samples were kept chilled in an ice bath until centrifugation at 3000 rpm for 15 minutes at 4°C. Plasma was acidified with 50 µl of 1 N HCL and 10 µl phenylmethylsulfonylfluoride were added per milliliter of plasma. Plasma levels of active and total ghrelin were determined using a commercial radioimmunoassay (Linco Research, St Charles, MI). The within- and between-assay coefficient of variation is 7% and 13.5%, respectively. Insulin was determined using a radioimmunoassay from DPC, Los Angeles, CA. Glucose was measured by the hexokinase method (Roche diagnostics, Mannheim, Germany). Leptin was measured by radioimmunoassay purchased from Linco Research. The intra- and interassay coefficients of variation were insulin 5.2% and 7.2% and leptin 5% and 6%, respectively.

**Statistical Analysis**

As some data—with the exception of age and BMI—did not follow the normal distribution, not even after log-transformation, descriptive statistics and statistical tests were nonparametric: The distribution of data is expressed as median ± IQR (interquartile range) or boxplot graphs. An area under the curve (AUC) was calculated for the 120-minute postprandial period individually as the mean difference between baseline and subsequent sampling points, with a 90-minute value interpolated from the 60- and 120-minute values. The U test (Wilcoxon–Mann–Whitney) was used to establish differences between the two groups. The Friedman test with post hoc pairwise Wilcoxon signed rank tests was used for statistical comparisons within groups. All p values given are two-sided and subject to a significance level of .05. In view of the exploratory character of analyses, no adjustment for multiple testing was made; pairwise post hoc tests followed the closing test procedure. Data were analyzed using the statistical software package SAS (version 9.2; SAS Institute, Cary, NC).

**RESULTS**

The score for hunger and satiety obtained by VAS are in Figures 1 and 2. A significant intra-individual difference between baseline and postprandial scoring was shown for hunger and satiety in both groups. In addition, a significant difference was observed between older and younger study participants for hunger scores at 60 minutes and for satiety scores at 60, 90, and 120 minutes, indicating that older study participants felt less hungry and fuller at the respective intervals.

Figures 3–6 show the distribution plasma levels of active ghrelin, total ghrelin, insulin, and leptin between 0 and 120 minutes. We observed no significant difference between the two groups with regard to the basal levels of all four hormones. After meal ingestion, active and total ghrelin declined significantly only in the younger study participants, whereas postprandial values for active and total ghrelin were not significantly different from baseline values in older study participants. The AUC between 0 and 120 minutes for active ghrelin, total ghrelin, and leptin are shown in Table 1. A significant difference between the younger and the older study participants was shown for active ghrelin (p = .024).

Basal leptin levels were not statistically different between both groups and, after meal ingestion, they did not change significantly over time in either of the groups. Insulin levels rose significantly from the baseline after meal ingestion in younger and older study participants. At 120 minutes, there was a significant difference (p = .013) in the mean insulin level between the younger and the older study participants, with a higher value in the second group. However, insulin concentrations over time expressed as AUC were not significantly different between the two groups.


**DISCUSSION**

It has previously been shown that hunger scores decrease and satiety scores increase with age in some (13,14,17) but not all studies (18). This phenomenon is regarded as a contributing factor to the anorexia of aging. In this respect, our data confirm most of the previous studies.

Basal ghrelin levels did not differ between our geriatric outpatients and the younger healthy controls. This was paralleled by comparable basal levels of insulin and leptin. Previous studies have shown either an inverse relationship with higher insulin and lower active ghrelin in the elderly individuals (17) or higher insulin but unchanged basal ghrelin in this age group (18). In this context, it should be noted that insulin is a potent inhibitor of ghrelin secretion (19–24).

Furthermore, Akamuzi and coworkers (25) showed acylated ghrelin to be significantly lower in older men and women in conjunction with higher BMI and higher leptin concentrations, which is another inhibitor of ghrelin (20,26). It is noteworthy that total basal ghrelin did not differ between age groups in this study. Another possible explanation for the differences between our and previous studies could be the fact that our patients were examined 4 hours after a preceding meal, whereas the participants of previous studies were examined after an overnight fasting period.

Our findings of an impaired suppression of postprandial acylated ghrelin confirm the recent data of Di Francesco and coworkers (18) who examined the postprandial response of acylated ghrelin following a much larger test meal (≈ 500 g, 800 kcal).

However, they found no difference in hunger and satiety ratings between the two groups. The reason for this lack of ghrelin suppression is as yet unknown. Although insulin is a potent inhibitor of ghrelin secretion, it is rather unlikely to be responsible in the present and previous study because the insulin response was either identical or less augmented.

A relationship between meal energy content and suppression of ghrelin has been reported in young participants (27). This, too, seems to be relevant because the energy content of

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**Table 1. Changes of Plasma Hormone Levels As “Area Under Curve” (AUC), Calculated As Mean Difference From Baseline at 30, 60, 90 (interpolated), and 120 Minutes**

<table>
<thead>
<tr>
<th></th>
<th>Range</th>
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<th>IQR</th>
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</tr>
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<tbody>
<tr>
<td>Ghrelin total (pg/ml, ₥ 120 min)</td>
<td>−871 to 264</td>
<td>−59 to 11</td>
<td>−22</td>
<td>−443 to 4452</td>
<td>−132 to −12.3</td>
<td>−46</td>
</tr>
<tr>
<td>Ghrelin active (pg/ml, ₥ 120 min)</td>
<td>−333 to 90</td>
<td>−5.4 to 6.8</td>
<td>−0.5</td>
<td>−52 to 23</td>
<td>−34 to −2.2</td>
<td>−16</td>
</tr>
<tr>
<td>Insulin (µg/ml, ₥ 120 min)</td>
<td>−37 to 40</td>
<td>3.6 to 21.4</td>
<td>11.3</td>
<td>1.9 to 59.8</td>
<td>3.3 to 12.4</td>
<td>8.6</td>
</tr>
<tr>
<td>Leptin (µg/ml, ₥ 120 min)</td>
<td>−5.1 to 1.5</td>
<td>−1.6 to 0.1</td>
<td>−0.2</td>
<td>−1.7 to 4.6</td>
<td>−0.8 to 0.5</td>
<td>−0.2</td>
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*Significant difference between groups (p value: .024).
the employed test meal in the previous report (18) was twice that of the present study.

Another possibility why ghrelin does not decrease postprandially could be an inadequate response to insulin. As another possible explanation, a different response to intestinal hormonal factors, which are also important inhibitors of ghrelin, has to be considered (19,28). The effects of glucagon-like peptide 1 on ghrelin secretion may be relevant in this regard, although its basal and postprandial levels have been shown not to differ between younger and older participants (29,30).

Although we excluded patients with serious comorbidities, our group of geriatric outpatients cannot be considered...
healthy older individuals. Therefore, interference by minor chronic diseases and the corresponding medication cannot be excluded. However, we believe that our test population was well chosen because they are at an increased risk of becoming malnourished. Hence, in our opinion, the anorexia of aging and its pathophysiological factors should also be studied in populations like ours and not only in healthy elderly individuals.

Conclusions

Our study demonstrates for the first time that differences in hunger and satiety sensations in relation to age are paralleled by a substantially different response of acylated and total ghrelin. The absence of a postprandial decline in ghrelin levels may indicate that this alteration of ghrelin secretion may be a hormonal equivalent for reduced hunger and increased satiety scores in this population, thereby contributing to the anorexia of aging in older persons with minor comorbidity.

Funding

The work of J.M.B. was supported by an unrestricted grant of the Robert Bosch Stiftung, Stuttgart, Germany.

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