Rapid Publication

Circulating Ghrelin Levels Are Decreased in Human Obesity

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Ghrelin is a novel endogenous natural ligand for the growth hormone (GH) secretagogue receptor that has recently been isolated from the rat stomach. Ghrelin administration stimulates GH secretion but also causes weight gain by increasing food intake and reducing fat utilization in rodents. To investigate the possible involvement of ghrelin in the pathogenesis of human obesity, we measured body composition (by dual X-ray absorption) as well as fasting plasma ghrelin concentrations (radioimmunoassay) in 15 Caucasians (8 men and 7 women, 31 ± 9 years of age, 92 ± 24 kg body wt, and 29±10% body fat, mean ± SD) and 15 Pima Indians (8 men and 7 women, 33 ± 5 years of age, 97 ± 29 kg body wt, and 30 ± 8% body fat). Fasting plasma ghrelin was negatively correlated with percent body fat ($r = -0.45$; $P = 0.01$), fasting insulin ($r = -0.45$; $P = 0.01$) and leptin ($r = -0.38$; $P = 0.03$) concentrations. Plasma ghrelin concentration was decreased in obese Caucasians as compared with lean Caucasians ($P < 0.01$). Also, fasting plasma ghrelin was lower in Pima Indians, a population with a very high prevalence of obesity, compared with Caucasians (87 ± 28 vs. 129 ± 34 fmol/ml; $P < 0.01$). This result did not change after adjustment for fasting plasma insulin concentration. There was no correlation between fasting plasma ghrelin and height. Prospective clinical studies are now needed to establish the role of ghrelin in the pathogenesis of human obesity.
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We recently reported (1) that the gastric hormone ghrelin (2) provides a peripheral signal to the brain that induces adiposity in rodents. To investigate a possible involvement of ghrelin in the pathogenesis of human obesity, we measured endogenous ghrelin concentrations in lean and obese Caucasian and Pima Indian individuals. We hypothesized that *1*) obese individuals would present with elevated ghrelin levels that could contribute to the pathogenesis of obesity and *2*) Pima Indians, a population with one of the highest reported prevalence rates of obesity and type 2 diabetes in the world, would present with elevated ghrelin levels when compared with Caucasians.

RESEARCH DESIGN AND METHODS

A total of 15 Caucasian and 15 Pima Indian subjects matched for age, sex, and body weight were divided into lean ($n = 7$) and obese ($n = 8$) subgroups (Table 1). Obesity was defined as BMI >30 kg/m^2, according to the criteria of both the World Health Organization and the International Obesity Task Force. All participants were between 20 and 50 years of age, nondiabetic according to an oral glucose tolerance test, and healthy according to a physical examination and routine laboratory tests. Subjects were admitted to the research ward of the Clinical Diabetes and Nutrition Section of the National Institutes of Health in Phoenix, Arizona, where they received a weight-maintaining diet (50% carbohydrate, 30% fat, and 20% protein) and abstained from exercise for at least 2 days before the study. The protocol was approved by the Tribal Council of the Gila River Indian Community and by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Disease, and all subjects provided written informed consent before participation. Body composition was measured by dual X-ray absorptiometry (DPX-L; Lunar Radiation, Madison, WI), and blood samples were collected as previously described (3). Human plasma ghrelin was measured with a commercial radioimmunoassay (Phoenix Pharmaceuticals, Belmont, CA.) that uses ^{125}I-labeled bioactive ghrelin as a tracer molecule and a polyclonal antibody raised in rabbits against full-length octanoylated human ghrelin. No cross-reactivity was found with human secretin, human vasoactive intestinal peptide, human prolactin releasing peptide-31, human galanin, human growth hormone (GH) releasing hormone, neuropeptide Y, or other relevant molecules. The interassay coefficient of variation (CV) was 9.0–13.6% ($n = 10$), and the intra-assay CV was 4.5–5.3%. Fasting plasma ghrelin concentrations were compared among the subgroups (sex, lean and obese, and Caucasian and Pima Indian) using analysis of variance. The relationships between fasting plasma ghrelin concentrations and various anthropometric and metabolic variables were examined by linear regression and Spearman's correlation coefficient analyses. Stepwise regression analysis was used to assess the relationship between fasting ghrelin concentrations and anthropometric and metabolic variables after adjusting for covariates. All of the analyses were performed using the SAS system, version 6.12 (Cary, NC).

RESULTS

No sex differences in plasma ghrelin were found ($P > 0.5$); thus, data for men and women were pooled. Fasting plasma ghrelin concentrations (Table 1) were 27% lower in obese subjects compared with lean subjects and 33% lower in Pima Indians compared with Caucasians ($P < 0.01$) (Fig. 1*A*). Fasting plasma ghrelin concentrations were 32% lower in obese Caucasians compared with lean Caucasians ($P < 0.01$) and 38% lower in lean Pima Indians compared

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CV, coefficient of variation; GH, growth hormone.

TABLE 1
Demographic and biochemical characteristics of the study population

	Lean Caucasians	Obese Caucasians	Lean Pima Indians	Obese Pima Indians
n	7	8	7	8
Sex				
Female	3	4	3	4
Male	4	4	4	4
Age (years)	32 ± 11	30 ± 7	33 ± 4	32 ± 5
Body weight (kg)	71.4 ± 9.8	109.8 ± 16.8	70.3 ± 9.6	109 ± 15.2
BMI (kg/m^2)	25.4 ± 2.3	38.2 ± 4.8	24.0 ± 1.9	37.9 ± 6.6
Body fat (%)	22 ± 9	35 ± 7	24 ± 7	35 ± 5
Plasma ghrelin (fmol/ml)	155 ± 25	106 ± 23	95 ± 13	80 ± 36
Plasma glucose (mg/dl)	87 ± 7	91 ± 4	89 ± 6	95 ± 7
Plasma insulin (μU/ml)	4 ± 3	10 ± 3	6 ± 3	18 ± 10
Plasma leptin (ng/ml)	8 ± 7	53 ± 47	10 ± 9	35 ± 27

Data are means ± SD unless otherwise indicated. Caucasians and Pima Indians in the lean and obese groups were matched for age, sex, and body weight.

with lean Caucasians ($P < 0.001$) (Fig. 1*A*). Fasting plasma ghrelin concentrations were negatively correlated with body weight ($r = -0.50$, $P < 0.01$), percent body fat ($r = -0.45$, $P < 0.05$), BMI ($r = -0.50$, $P < 0.01$) (Fig. 1*B*), and fat mass ($r = -0.55$, $P < 0.01$). Fasting plasma ghrelin concentrations were negatively correlated with leptin ($r = -0.39$, $P < 0.05$) and insulin ($r = -0.45$, $P < 0.05$). In a stepwise regression analysis, insulin and leptin were significant independent determinants of fasting ghrelin, explaining 36.5 and 14.7% of the variance (adjusted R^2), respectively.

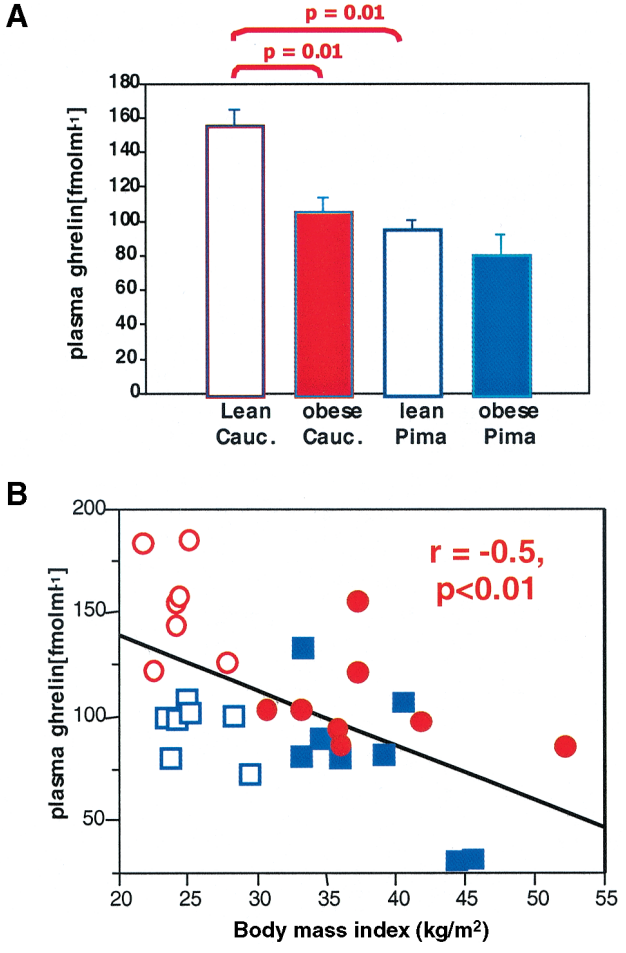

FIG. 1. ***A*: Plasma ghrelin levels in seven lean and eight obese Caucasian (Cauc.) individuals and in seven lean and eight obese Pima Indian individuals matched for age, sex, and body weight. All levels are given as the mean ± SE. □, Lean individuals; ■, obese individuals. *B*: Plasma ghrelin levels in the same 30 individuals are negatively correlated with BMI. ○, Lean Caucasians; ●, obese Caucasians; □, lean Pima Indians; ■, obese Pima Indians.**

DISCUSSION

Whereas the newly discovered gastric hormone ghrelin is undoubtedly a regulator of GH secretion (2), studies in rodents indicate that the peptide hormone also plays an important role in signaling hypothalamic centers regulating feeding and caloric state (1,4). Contrary to our hypothesis, however, obese subjects have lower plasma concentrations of the adipogenic hormone ghrelin than age-matched lean control subjects. In addition, ghrelin plasma concentrations are significantly lower in Pima Indians than in Caucasians. These data seem to indicate that ghrelin is downregulated in human obesity. This downregulation may be a consequence of elevated insulin or leptin, because fasting plasma ghrelin levels are negatively correlated with fasting plasma levels of insulin and leptin. We further speculate that decreased secretion of ghrelin, the endogenous ligand of the GH secretagogue receptor, could be responsible for decreased levels of circulating GH in obese individuals (5). We propose that the decreased plasma ghrelin concentrations observed in obesity represent a physiological adaptation to the positive energy balance associated with obesity. Careful prospective clinical studies during weight loss or weight gain are now necessary to further clarify the role of the newly discovered hormone ghrelin in the pathogenesis of human obesity.

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