

Short report

Effect of octanoic acid-rich formula on plasma ghrelin levels in cachectic patients with chronic respiratory disease

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ABSTRACT

Background: For cachectic patients with chronic respiratory disease, conventional enteral nutrition formula is an optional treatment to maintain energy balance. Molecular mechanisms by which enteral nutrition formula controls appetite and weight remain unknown. We examined whether enteral nutrition formula rich in octanoic acids would increase plasma levels of ghrelin, an appetite-stimulating hormone produced in the stomach, in cachectic patients with chronic respiratory disease.

Methods: Plasma ghrelin profiles in cachectic patients with chronic respiratory disease were assessed and compared with those in age- and sex-matched controls. Plasma levels of acyl-ghrelin, an active ghrelin modified by octanoic acids, and desacyl-ghrelin were measured separately. We examined changes in 24-h plasma ghrelin profiles before and after single administration of the formula. We also evaluated the effects of two-week administration of the formula on plasma ghrelin levels and nutritional status in the patients.

Results: The ratio of acyl-ghrelin to total ghrelin in plasma was lower in the patients than in controls. Single administration of the formula did not change plasma total ghrelin levels, but induced an increase in acyl-ghrelin levels. Two-week treatment with the formula was effective in increasing weight and acyl-ghrelin, along with improving nutritional status in patients.

Conclusion: These results show that the formula contributes to increase weight, which may be associated with an inducing of acyl-ghrelin production in cachectic patients with chronic respiratory disease.

List of abbreviations

GH: growth hormone

IGF-1: insulin-like growth factor-1

BMI: body mass index

Findings

Background

Weight loss and nutritional depletion represent independent risk factors for the incidence of pneumonia and mortality in patients with chronic respiratory diseases [1,2]. Excess energy expenditure and appetite loss are the main causes of weight loss in such patients, and are difficult to control using established treatments. Enteral nutrition formula is often used as a supplement for patients with insufficient oral calorific intake, although the effects of additional nutrition on weight gain seem to differ depending on the components of supplementation [3,4]. The contribution of formula components to weight gain and to induction of orexygenic hormones remains unclear.

Ghrelin, a novel growth hormone (GH)-releasing peptide, was isolated from the stomach [5] and induces a positive energy balance by stimulating food intake through GH-independent mechanisms. Acyl-ghrelin, an active ghrelin that induces appetite through hypothalamus, is synthesized in the stomach and inactivated as desacyl-ghrelin by deacylation. Octanoic acids are essential for acylation in the biosynthesis of acyl-ghrelin. However, opportunities for oral intake of octanoic acids are limited, with most food products showing minimal content of octanoic acids. Increased intake of octanoic acids may thus increase plasma acyl-ghrelin levels.

Based on the hypothesis that octanoic acids are necessary for acylation in biosynthesis of acyl-ghrelin, we investigated whether oral administration of an octanoic acid-rich formula would increase plasma acyl-ghrelin levels in cachectic patients with chronic respiratory

disease.

Methods

Participants

We recruited 4 in-patients (2 women, 2 men; age range, 62-72 y) and 19 out-patients (8 women, 11 men; age range, 62-78 y) with chronic respiratory disease. At enrolment, the following inclusion criteria were applied: i) stable respiratory disease for >6 months; and ii) cachexia with complaints of appetite loss. The following exclusion criteria were adopted: i) treatment with steroids, immunosuppressants or antibiotics prescribed within 3 months prior to the study, or ii) presence of pneumonia, cancer or asthma. Cachectic patients were defined as those with documented nonedematous and nonintentional weight loss >7.5% of previous normal weight over a period of ≥ 6 months and body mass index (BMI) <21 at entry. All patients provided written informed consent for participation and the Research Ethics Committee of Miyazaki University approved all study protocols in advance.

Study protocol

The present study set two protocols, as described below. First, we investigated the difference in 24-h profiles for plasma ghrelin levels with and without administration of enteral nutrition formula rich in octanoic acids using 4 in-patients with chronic respiratory disease on admission basis. The enteral nutrition formula used here provides 3.0 g of octanoic acid triglyceride and 400 kcal per 400 ml (EN Otsuka, Naruto, Japan). The formula is prepared to provide 2.8 g per day of

octanoic acid to the patients when tricaprilin hydrolyzed by lipase and free octanoic acid become 100% detached. On day 1, blood samples were taken from the patients with calorie intake limited to 1,800 kcal/day. On day 2, 400 ml of the formula was administrated between breakfast and lunch in addition to meals providing 1,800 kcal. Blood samples were drawn at 07:00, 09:00, 12:00, 14:00, 17:00, 19:00 and 21:00 to identify 24-h profiles of plasma total and acyl-ghrelin levels. As a second trial, 400 ml/day of formula was orally administered to 19 out-patients for 2 weeks. Body weight of patients were measured at baseline and after 2 weeks of formula administration. Blood samples for these patients were taken on an empty stomach before breakfast to evaluate nutrition status and plasma total and acyl-ghrelin levels at baseline and after 2 weeks of formula administration. Age- and sex-matched 10 healthy volunteers were recruited as controls to compare ghrelin levels with those in the cachectic patients at baseline. BMI in controls (20.4 ± 5.7) was higher than those in the patients.

Blood sampling and assay

Blood samplings were performed at baseline and during the week after the end of therapy to measure levels of total protein, albumin, glucose, total cholesterol, triglycerides and rapid-turnover proteins. Blood samples were taken from an antecubital vein after 30-min bed rest in the morning following an overnight fast. Plasma acyl-ghrelin and desacyl-ghrelin levels were measured by enzyme-linked immunosorbent assay (Mitsubishi Kagaku Iatron, Tokyo, Japan). Total ghrelin levels were calculated as the sum of both ghrelin levels. Immunoradiometric

assays were used to measure levels of serum GH (Ab Bead HGH Eiken; Eiken Chemical, Tokyo, Japan) and insulin-like growth factor (IGF)-1 (Somatomedin CII Bayer; Bayer Medical, Tokyo, Japan).

Statistical analysis

Data are expressed as mean \pm standard deviation (SD). Comparison of ghrelin levels between the 2 groups was analyzed using the Mann-Whitney U test. Changes in parameters between the 2 groups were analyzed using the Wilcoxon signed-rank test. Values of $p < 0.05$ were taken to indicate statistical significance.

Results

Plasma ghrelin levels in the patients with chronic pulmonary disease at study entry

Plasma acyl-ghrelin and total ghrelin levels were 11.0 ± 11.1 fmol/ml and 101.1 ± 58.8 fmol/ml, respectively, in the 19 out-patients with chronic respiratory disease (Table). Acyl-ghrelin levels trended to be lower and total ghrelin levels to be higher in the patients compared with those in controls, although there were no significant differences. The ratio of plasma acyl-ghrelin to total ghrelin in the patients (0.12 ± 0.09) was lower than that in controls (0.19 ± 0.06).

The 24-h profiles of ghrelin with and without single administration of formula

Plasma total and acyl-ghrelin levels peaked in the early morning and decreased after meals, supporting the findings of previous reports.

Figure 1 shows plasma total and acyl-ghrelin levels based on a value calculated before breakfast on the morning of day 1 as 100. Plasma total ghrelin levels with formula resembled those with no formula administration, while single administration of 400 ml of formula between breakfast and lunch induced higher acyl-ghrelin levels before dinner, remaining high until the next morning.

Effect of 2-week administration of formula on plasma ghrelin, weight, nutrition status and hormone levels

Significant increases were seen in levels of plasma acyl-ghrelin and body weight, but not total ghrelin. Levels of serum total protein, albumin and rapid turnover proteins increased after two-week administration of formula. Two-week administration of formula did not alter fasting glucose, total cholesterol, triglyceride or GH levels, but induced an increase in serum IGF-1 levels.

Discussion

This is the first paper reporting molecular analysis of plasma acyl-ghrelin and total ghrelin in cachectic patients with chronic respiratory disease. Ghrelin profiles at study entry indicated a tendency that the total plasma ghrelin levels in the patients were higher compared with those in age-and sex-matched healthy volunteers. The high plasma ghrelin levels in the cachectic patients in the present study are consistent with previously published papers reporting that there was an inverse correlation between BMI and plasma ghrelin levels [6,7]. Increased ghrelin levels are associated with maintaining energy balance

to prevent weight loss. Several clinical trials demonstrated that increased ghrelin levels due to ghrelin treatment increased appetite and weight gain in patients with cachectic disease, suggesting that a further elevation of ghrelin levels can induce appetite in cachectic patients. In cachectic patients with chronic respiratory disease, although total plasma ghrelin levels were high, acyl-ghrelin levels were low. To induce appetite, an increase in acyl-ghrelin levels is necessary, therefore, even if total ghrelin levels are high, low acyl-ghrelin levels may attenuate the orexygenic effect of ghrelin.

The present study showed that administration of formula containing high levels of octanoic acids increased plasma acyl-ghrelin levels as along with weight in patients with chronic respiratory disease. As malnutrition is a risk factor for pneumonia in patients with chronic respiratory diseases, increases in weight and serum protein levels may help to avoid pulmonary infection and exacerbation of underlying disease in patients. The study was designed for out-patients and the exact food intake including formula during the 2-week period was not measured. Weight gain may be due to the additional energy provided by the formula in addition to regular meals. In the present study, 2-week administration of the formula induced an increase in both weight and plasma acyl-ghrelin levels, suggesting the possibility that weight gain was associated with increases in acyl-ghrelin and orexygenic effect due to a decrease in plasma ghrelin levels when the patients' weight increased.

Additional induction of acyl-ghrelin induced a significant increase in IGF-1 levels. The concentration of circulating IGF-1 declines with

age [8] and this hormone is involved in physiological changes of aging such as increased cardiovascular risk, reduced muscle mass and strength, reduced exercise tolerance and impaired quality of life [9]. IGF-1 stimulates osteoblast proliferation as well as osteoclast differentiation to inhibit osteopenia [10]. Chronic respiratory disease with airflow obstruction has been shown to represent a causative risk for osteoporosis [11], so elevation of IGF-1 levels may be particularly useful for elderly individuals with chronic respiratory disease.

In conclusion, formula containing octanoic acids increased body weight and plasma acyl-ghrelin levels. This is the first trial showing a change in orexygenic hormone in patients receiving nourishment treatment. We promise that the study will contribute to nutritional management in patients with cachectic diseases.

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

JA participated in study design, data analysis and manuscript preparation. NM participated in data collection and data analysis. MN participated in manuscript preparation and editing. All authors read and approved the final manuscript.

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Figure Legend

Figure 1: 24-h profiles of plasma total (upper) and acyl-ghrelin levels (lower). Open circles show levels without administration of formula; closed circles show levels with administration of formula. Closed square indicates administration of formula. Arrows show meal-taking for in-patients with chronic respiratory disease. Data are expressed as mean \pm standard deviation.

Table

Changes in parameters before and after 2-week administration of formula

		before	after	
body weight	(kg)	39.8 ± 4.8	40.5 ± 4.7	p<0.05
acyl-ghrelin	(fmol/ml)	11.0 ± 11.1	14.8 ± 7.2	p<0.05
total ghrelin	(fmol/ml)	101.1 ± 58.8	105.7 ± 54.6	NS
total protein	(g/dl)	6.9 ± 0.6	7.3 ± 0.7	p<0.05
albumin	(g/dl)	3.8 ± 0.4	4.0 ± 0.4	p<0.05
total cholesterol	(mg/dl)	181 ± 40	184 ± 21	NS
fasting glucose	(mg/dl)	94 ± 9	91 ± 9	NS
prealbumin	(mg/dl)	15.8 ± 4.2	17.9 ± 3.9	p<0.05
transferrin	(mg/dl)	198 ± 41	231 ± 57	p<0.05
retinol binding protein	(mg/dl)	1.9 ± 0.4	2.3 ± 0.5	p<0.05
GH	(ng/ml)	1.2 ± 1.0	1.3 ± 1.1	NS
IGF-1	(ng/ml)	87 ± 36	98 ± 39	p<0.05

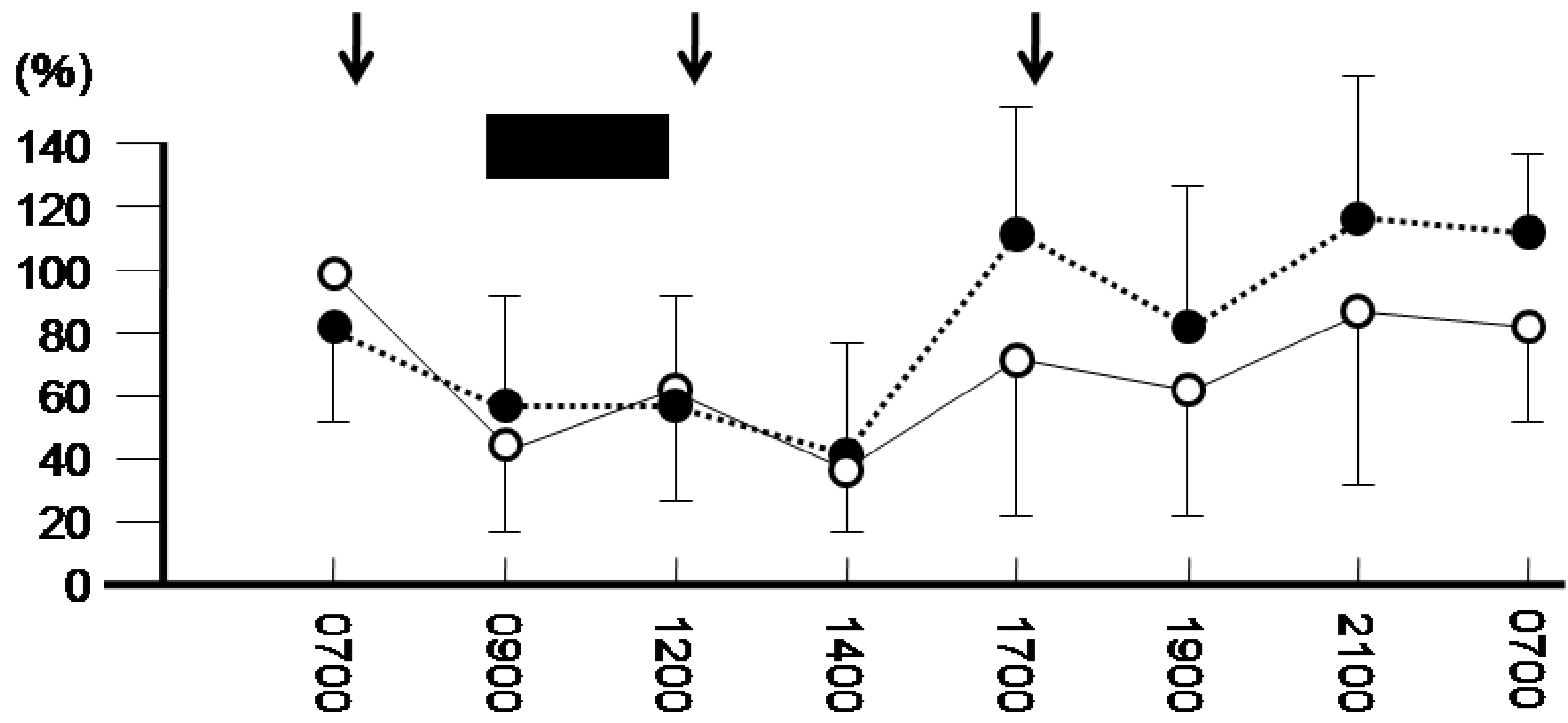
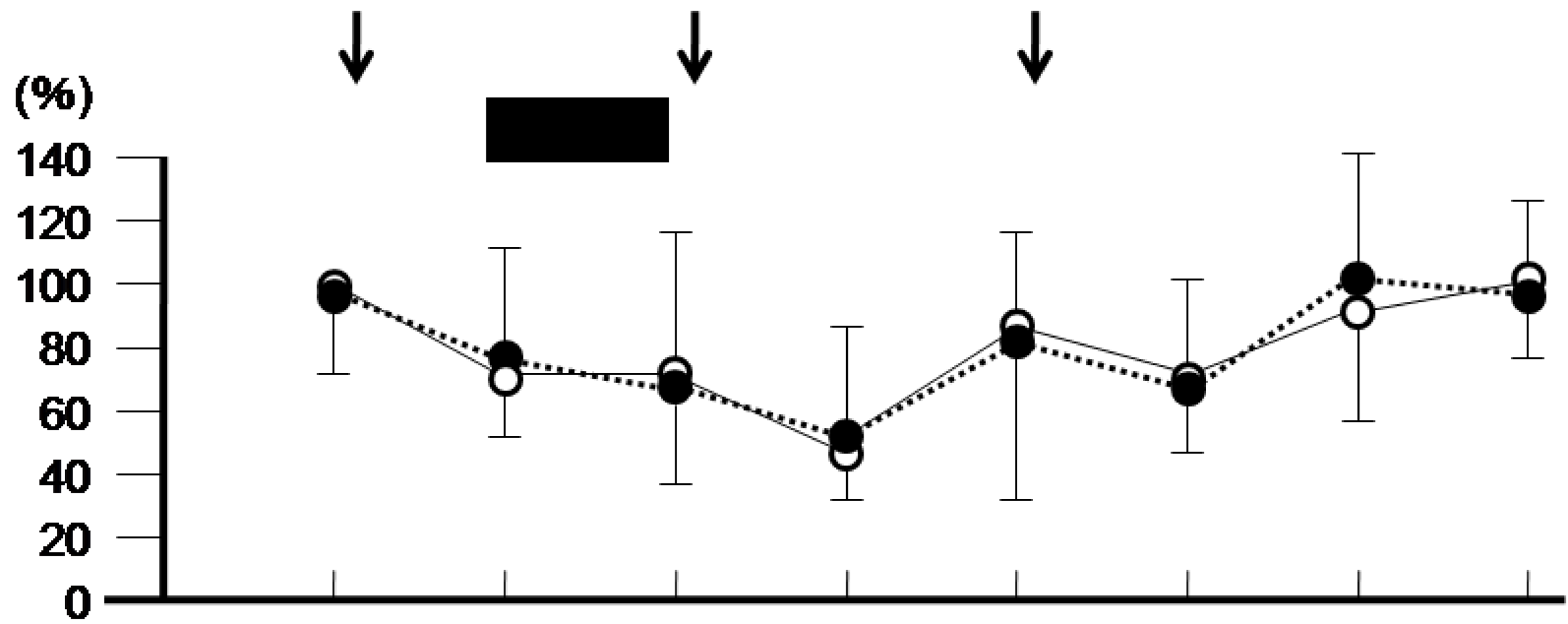


Fig. 1