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Uncoupling protein 1 gene −3826 A/G polymorphism is associated with weight loss on a short-term, controlled-energy diet in young women ☆

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Abstract

Uncoupling protein 1 (UCP1) plays an important role in thermogenesis in brown adipose tissue. Previously, we reported an association between −3826 A/G single-nucleotide polymorphism (SNP) in the promoter of *UCP1* gene and lower thermogenesis in young women, suggesting this SNP has an adverse effect on the regulation of energy balance. Based on the hypothesis that this SNP (G allele) may have resistance against diet-induced weight loss, we examined its effects on anthropometric and metabolic responses to short-term, controlled-energy diet in young women. Seventeen lean women (20.9 ± 0.2 years; body mass index, 22.1 ± 0.5 kg/m^2) were fed a controlled-energy diet (5.0 MJ/d, 62% carbohydrate, 19% protein, and 19% fat) administered by dietitians for 2 weeks. Clinical measurements were determined at baseline and after the dietary intervention. The subjects' physical activity was obtained using pedometers and self-reporting. The thermoregulatory sympathetic nervous system was evaluated using heart rate variability power spectral analysis. Upon the completion of the intervention, subjects were genotyped using an allele-specific DNA primer assay and results compared with their clinical measurements focusing on with or without the G allele. After dietary intervention, G allele subjects (A/G + G/G, n = 10) showed significantly smaller changes in body weight, body mass index, and waist circumference compared with A/A genotype subjects (n = 7). Similar changes were observed in parameters regarding glucose or lipid metabolism in both groups. These results suggest that the *UCP1* gene −3826 G allele may result in smaller weight loss after a short-term, controlled-energy diet in young, lean women.

Keywords: Genetic variation; Energy restriction; Weight loss; Waist circumference; Sympathetic nervous system; Human; Clinical study

Abbreviations: ANS, autonomic nervous system; BAT, brown adipose tissue; BMI, body mass index; ECG, electrocardiogram; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment–insulin resistance; LDL, low-density lipoprotein; REE, resting energy expenditure; SNP, single nucleotide polymorphism; SNS, sympathetic nervous system; UCP1, uncoupling protein 1.

1. Introduction

Obesity results from a prolonged energy imbalance between energy intake and expenditure. Recent studies [1-5] using ^{18}F-fluorodeoxyglucose positron emission

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tomography–computed tomography demonstrate that adult humans possess metabolically active brown adipose tissue (BAT), which can help to regulate energy expenditure through BAT-mediated thermogenesis.

Uncoupling protein 1 (UCP1) plays a key part in thermogenic function of the BAT, which allows protons to reflux over the mitochondrial inner membrane and causes dissipation of energy as heat [6]. The metabolic activities of the BAT are related to its quantity, its UCP1 content, and the extent of sympathetic nervous system (SNS) stimulation [6]. Therefore, a single-nucleotide polymorphism (SNP) in the promoter region of the *UCP1* gene, encoding mitochondrial BAT UCP1, could have an adverse effect on energy homeostasis because of reduced messenger RNA expression [7].

Although the influence of this SNP on obesity-associated trails remains controversial, we previously reported that a specific polymorphism (A/G) at position −3826 of the *UCP1* gene reduces resting energy expenditure (REE) in young women (A/G and G/G genotypes) [8], supporting the metabolic actions of BAT and its effect on resting energy balance in adult humans. Moreover, recent findings that the prevalence or the activity of BAT was positively correlated with young age and leanness [5,9,10], suggesting that this SNP have greater impact on thermogenesis in younger and leaner subjects.

Accordingly, based on the hypothesis that this SNP (G allele) of the *UCP1* gene is associated with resistance against diet-induced weight loss, we designed to examine whether this SNP influences the anthropometric and metabolic responses to short-term, controlled-energy diet in young, lean women.

2. Methods and materials

2.1. Subjects

We studied 17 female volunteers (20-22 years) recruited from our campus. A selection criteria was normal weight (body mass index [BMI] ≤25 kg/m^2) and had relatively higher body fat level (>25%; range, 25.1%-38.5%), and lack of disease or treatment known to affect weight loss. The subjects completed the standardized health questionnaire including medical history, medication, lifestyle, menstrual cycle, smoking habits, alcohol consumption, dietary habits, and physical activity. None of the subjects exercised regularly, smoked, or drank heavily. All subjects were not clinically diagnosed with hypertension, dyslipidemia, diabetes mellitus, cardiovascular disease, or other endocrine diseases; nor were they taking medications or nutritional supplements that could influence weight change, autonomic function, or glucose/lipid metabolism. The subjects were requested to maintain their usual lifestyle and body weight for at least 1 month before the intervention. All subjects gave their written informed consent for the study, which was approved by the Ethics Committee of University of Hyogo.

2.2. Dietary intervention

The hypoenergetic diet in the present study consisted of an approximately 30% reduction in energy intake during the 2-week energy-restriction period. During the dietary intervention, subjects were restricted to 5.0 MJ (1200 kcal)/d (62% carbohydrate, 19% protein, and 19% fat), consisting of 3 isoenergetic, nutritionally balanced meals. The subjects' usual diets were assessed using food records, with photographs taken using a camera-equipped cellular phone for 2 days. Nutritional values were calculated using computer-assisted procedures based on the Japanese food consumption table. During the intervention period, subjects were given test meals 3 times a day at our laboratory. Each test meal was 1.7 MJ (400 kcal) and was cooked at the food laboratory in our university. The intervention-period diet consisted of a meal plan designed by registered dietitians. Table 1 shows daily energy and nutrient intake before and during dietary intervention period. As for macronutorient balance of the test meals, percent energy as carbohydrate and protein was higher; and total energy and percent energy as fat were lower than those of subjects' usual diet. Regarding nutrient content in the test meals, fat, saturated fat, and cholesterol were lower; and calcium, iron, retinol, vitamin C, and salt were higher than in the subjects' usual diet. During the intervention period, all food, soft drinks, and alcoholic beverages besides the test meals were prohibited. To estimate subjects' daily physical activity levels, pedometers and self-reporting were used during the intervention. Dietary intervention and examinations were conducted without the subjects' menstrual period.

2.3. Experimental protocol

All subjects were examined on 2 separate occasions: before and after the 2-week dietary intervention. Subjects

Table 1
Estimates of daily nutrient intake before and during dietary intervention

	Before	Test meal	P[a]
Energy intake (MJ)	6.9 ± 0.4	5.0	<.001
Carbohydrate (% of energy)	55.7 ± 1.1	61.9	<.001
Protein (% of energy)	14.2 ± 0.6	19.3	<.001
Fat (% of energy)	30.1 ± 1.2	18.8	<.001
Carbohydrate (g)	222 ± 12	184	<.001
Protein (g)	57.9 ± 2.7	57.7	.949
Fat (g)	56.8 ± 4.9	25.0	<.001
Calcium (mg)	437 ± 46	624	.001
Iron (mg)	6.3 ± 0.4	7.4	.012
Retinol (μg)	805 ± 90	1399	<.001
Vitamin E (mg)	7.3 ± 0.5	6.6	.134
Vitamin B_1 (mg)	1.1 ± 0.3	0.9	.625
Vitamin B_2 (mg)	1.5 ± 0.6	1.2	.558
Vitamin C (mg)	84 ± 7	150	<.001
Saturated fat (g)	17.2 ± 2.0	6.3	<.001
Cholesterol (mg)	316 ± 34	169	.001
Dietary fiber (g)	12.4 ± 0.9	15.6	.001
Salt (g)	6.2 ± 0.3	7.0	.029

Data are expressed as means ± SE; n = 17. Daily nutrient intake was calculated using the Japanese food composition table.

[a] Tested by paired t test.