学 位 論 文 の 要 旨

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学　位　論　文　名　Interactions Between ACE Deletion Allele and Obesity During Intervention With Lifestyle Modification in Mild Obese Japanese

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論 文 内 容 の 要 旨

INTRODUCTION

Obesity has been recognized as one of the major risk factors for type 2 diabetes and atherosclerosis. Gene variants and modifiable environmental factors have been identified as risk factors for obesity. A several cross-sectional studies have shown the effects of the angiotensin converting enzyme (*ACE)* I/D (rs1799752), uncoupling protein 1 (*UCP1)* -3826A/G (rs1800592), α_{2B}-adrenergic receptor (α_{2B}-*ADR)* Glu^{12}/Glu^{9} (rs76700079), β_3-adrenergic receptor (β_3-*ADR)* Trp64Arg (rs4994), and paraoxonase1 (*PON1)* Glu192Arg (rs662) genotypes on obesity. A few interventional studies have also reported the relationship between these genetic polymorphisms and obesity. However, the associations between these genetic polymorphisms and obesity have been weak, and sometimes contradictory. A combination of genes, or a combination of genes with one or more environmental factors, may partially account for this missing heritability. The present study investigated the gene-gene or gene-environment interactions thought to be of key importance in the etiology of obesity by intervention.

MATERIALS AND METHODS

A total of 212 subjects, 57 men (age 54 ± 10 years) and 155 women (age 57 ± 8 years) underwent a three-month lifestyle-modified intervention using a combination of diet and exercise programs. The ethics committee of the Shimane University School of Medicine approved all study protocols, and all subjects provided written informed consent.

Information on a subject's daily diet was obtained using an established self-administered quantitative food frequency questionnaire. Average daily energy intake (kcal/day) for one month was calculated using the standard food composition tables for Japanese. Habitual physical activity was assessed before and after the intervention using the questionnaire. Daily energy expenditure (kcal/day) was calculated using metabolic equivalent units (MET) formula as follows: calories of physical activity = body weight (kg) × metabolic equivalent (MET) × time (h). Resting energy expenditure (REE) was measured by indirect calorimetric using non-dispersive infrared analysis. Body mass index (BMI) was computed as weight (kg) divided by squared height (m^2). The *UCP1* -3826A/G, β_3-*ADR* Trp64Arg, and *PON1* Glu192Arg genotypes were determined using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP); *ACE* I/D and α_{2B}-*ADR* Glu^{12}/Glu^{9} genotypes were distinguished by PCR-amplified fragment length polymorphism (PCR-AFLP). Subjects were divided into two groups based on genotype: subjects with risk allele group and subjects without risk allele group.

The genotype distribution, allele frequency, and Hardy-Weinberg equilibrium were tested by chi-square (χ^2) analysis. Comparisons between two genotypes were by Student's *t*-test to assess the differences in BMI for five gene polymorphisms at the baseline and after the intervention. To assess changes in BMI, energy intake, energy expenditure, and physical activity during intervention, we used a paired Student's *t*-test. Univariate (GLM) multivariate analysis was used to asses differences in BMI, energy intake, energy expenditure, REE, REE/kg body weight and physical activity adjusted for age and sex at the baseline, after the intervention and response to the intervention. Multiple linear regression analysis was conducted to investigate whether changes in BMI were independently related to the five gene polymorphisms and environmental factors. A nominal two-sided *P*-value of less than 0.05 was used to assess significant difference.

RESULTS AND DISCUSSION

Among 212 participants, 107 subjects (50.5 %) with 21.0 - 24.9 BMI were categorized as non-obese, 91 subjects (42.9 %) with 25.0 - 29.9 BMI were categorized as overweight and 14 subjects (6.6 %) with over 30.0 BMI were categorized as obese. The risk allele frequency was 0.39 for *ACE* I/D, 0.49 for *UCP1* -3826A/G, 0.33 for α_{2B}-*ADR* Glu^{12}/Glu^{9}, 0.24 for β_3-*ADR* Trp64Arg, and 0.35 for *PON1* Glu192Arg gene polymorphisms.

At the baseline, subjects with I/D + D/D genotypes of *ACE* had significantly higher BMI compared with the I/I genotype (25.9 ± 3.0 kg/m^2 vs. 24.6 ± 2.2 kg/m^2, $P = 0.004$), even after adjusting for age and sex. The I/D + D/D genotypes of *ACE* still had greater BMI than II genotype independently of the effects of the other gene polymorphisms, age, and sex ($\beta = 0.219$, $P = 0.001$). No association was found with BMI among the risk allele of the *UCP1*, α_{2B}-*ADR*, β_3-*ADR*, and *PON1* genes.

As a consequence of a decrease in energy balance (-500 ± 441 kcal/day) by the intervention, the mean body weight (-1.9 ± 2.1 kg) and the mean BMI (-0.8 ± 0.8 kg/m^2) were significantly reduced (P<0.001). Intervention yielded a greater decrease in BMI for subjects with I/D + D/D genotypes of *ACE* than those with I/I genotype (-0.9 ± 0.9 kg/m^2 vs. -0.6 ± 0.7 kg/m^2, P = 0.008); the significant difference remained after adjustment for age and sex. Using multiple linear regression analysis, the results showed that decrease in BMI were independently related to the change of energy intake (β = 0.461, P<0.001), BMI at the baseline (β = -0.175, P = 0.006), increases of physical activity (β = -0.120, P = 0.044), and I/D + D/D genotypes of *ACE* (β = -0.141, P = 0.020). The risk allele of the *UCP1*, α_{2B}-*ADR*, β_3-*ADR*, and *PON1* showed no significant changes in BMI by the intervention compared to those without the risk allele.

Our study demonstrated that the association between *ACE I/D* with obesity at the baseline and *ACE I/D* with weight loss through the lifestyle intervention in mild obese Japanese. Accordingly, there was sufficient experimental and clinical evidence showing that *ACE* is a major link between renin-angiotensin system (RAS) and kinin systems. It can be surmised that, at the baseline, subjects with I/D + D/D genotypes had enhanced *ACE* protein expression, which resulted in higher levels of angiotension II (Ang II), lower levels of bradykinin, and subsequent increased adipogenesis via Ang II type 1 receptor (AT_1R) on the fat cell. The effect of *ACE* genotype on BMI reduction by the intervention could be mediated by two mechanisms. First, although *ACE* I/D affects bradykinin metabolism, physical exercise overcame its effect and led to an increase of concentrations of bradykinin, which resulted in higher levels of Ang II type 2 receptor (AT_2R) and lower levels of AT_1R, and increasing insulin sensitivity, improving glucose tolerance and increasing β-oxidation of fatty acid in skeletal muscle. Second, diet restriction may have reduced *ACE* activity and increased concentrations of bradykinin and angiotensin I, which resulted in lower levels of Ang II, decreasing AT_1R expression, increasing AT_2R expression and lipolysis on the fat cell.

The polymorphic variants of the *UCP1*, α_{2B}-*ADR*, β_3-*ADR*, and *PON1* may not be great enough to change body weight in response to the lifestyle modified intervention. Environmental and behavioral factors may have overcome their effects on weight reduction.

CONCLUSION

The I/D + D/D genotypes of *ACE* had significantly higher BMI at the baseline, but lifestyle factors modified the genotypes risk of *ACE* on obesity phenotypes, as compared to the I/I genotype. The risk allele of the *UCP1*, α_{2B}-*ADR*, β_3-*ADR*, and *PON1* showed no influence on BMI at the baseline as well as response to the intervention.