Effect of β3-Adrenergic Receptor Gene Polymorphism on Aerobic Exercise-Induced Lipolytic Response

Original Research

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Abstract

Introduction: Diet and exercise interventions reduce the risk of obesity; however, fat loss varies across individuals. During moderate-intensity aerobic exercise, norepinephrine stimulates adipose lipolysis via β3-adrenergic receptors (β3AR). The β3AR Trp64Arg polymorphism has been linked to reduced lipolytic responsiveness. This study examined whether Trp64Arg influences fat breakdown during aerobic exercise in young women. We hypothesized that Trp64Arg carriers (Trp/Arg) would show a blunted rise in circulating free fatty acids (FFA) and higher respiratory quotient (RQ; VCO_2/VO_2) during exercise than that of non-carriers (Trp/Trp).

Methods: Thirty-seven healthy female university students (20–23 years) completed 40 min of cycling at 55 W after a standardized dinner and 12-h fast. Serum FFA, energy expenditure, and RQ were measured at rest and during exercise. Participants were genotyped and classified as wild-type (Trp/Trp; n = 29) or heterozygous (Trp/Arg; n = 8). Repeated-measures analyses tested group, time, and group × time effects; estimated marginal means were used for model-based summaries.

Results: Serum FFA at 40 min increased compared to that of rest in both groups, but reached significance only in the wild-type group (2.04 ± 1.25 vs 0.90 ± 0.48 mEq/L, p = 0.009). During exercise, RQ differed according to genotype (main effect of group: p = 0.003; group × time: p = 0.065), with higher RQ in heterozygous participants (0.91 ± 0.02, 95% CI 0.88–0.94) than in the wild-type group (0.86 ± 0.01, 95% CI 0.84–0.88).

Conclusions: In young women, carrying the Trp64Arg polymorphism of the β3AR gene potentially contributes to a blunted lipolytic response and relatively high reliance on carbohydrate metabolism during moderate-intensity aerobic exercise.

Key Words: Trp64Arg polymorphism, free fatty acids, respiratory quotient

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Introduction

Body fat accumulation is determined by the balance between energy intake and expenditure, with physical activity being a primary determinant of energy expenditure. Aerobic exercise activates the sympathetic nervous system and stimulates the secretion of adrenaline and norepinephrine, thereby enhancing energy metabolism via adrenergic receptors. These receptors are classified into α (α1, α2) and β (β1, β2, β3) subtypes. The β3-adrenergic receptor (β3AR) is predominantly expressed in white adipose tissue[1] and is instrumental in exercise-induced lipolysis.

During aerobic exercise, norepinephrine secretion predominates at intensities below approximately 60% of maximal oxygen consumption (VO_2max), whereas adrenaline secretion increases at higher intensities[2]. Both catecholamines can activate β3AR[3], thereby promoting the breakdown of triglycerides in white adipose tissue into free fatty acids (FFAs)

and glycerol. FFAs serve as an important fuel for contracting skeletal and cardiac muscle, whereas glycerol can be utilized for gluconeogenesis in the liver.

Carbohydrates and lipids are the primary substrates during exercise, and their relative contribution is largely determined by exercise intensity. At around 65% VO_2max, lipid oxidation can contribute approximately 50–60% of total energy expenditure, but this contribution declines as intensity approaches 85% VO_2max[4]. In addition, factors such as diet, training status, and genetic background influence lipid metabolism and the fat loss response to exercise. Polymorphisms in genes related to energy metabolism, including the β3AR gene, have been associated with inter-individual differences in body weight and adiposity and are sometimes referred to as obesity-related genes[5].

The β3AR was first identified in the 1980s[6], and the Trp64Arg polymorphism was later linked to obesity in Pima Indians[7]. In Japanese populations, approximately one-third of individuals are reported to carry this polymorphism, which has been associated with a reduction of approximately 200 kcal/day in resting energy expenditure compared with that of non-carriers[8]. In vitro studies using human visceral adipocytes have demonstrated that cells carrying the Trp64Arg variant exhibit a reduced lipolytic response to β3-adrenergic stimulation compared with wild-type cells[9].

In young Japanese men, carriers of the Trp64Arg polymorphism showed low fat oxidation at rest and during aerobic exercise compared with that of non-carriers, whereas no significant differences were observed among women[10]. One possible explanation is that measurements were obtained in the postprandial state, when elevated triglyceride levels may limit the expression of genotype-related differences in adipose tissue lipolysis. Morita et al. pooled the heterozygote and mutant homozygote groups for comparison with the wild-type group, as the Trp64Arg homozygous variant of the β3AR was infrequent[10]. Similarly, because no mutant homozygotes were identified in the present study, we compared the heterozygote group with the wild-type group. Therefore, in this study, we examined the effect of the β3AR Trp64Arg polymorphism on lipolytic responses during moderate-intensity aerobic exercise in the postabsorptive state in healthy young women.

Methods

Participants

Thirty-seven healthy female university students aged 20–23 years (body mass index [BMI] 20.0 ± 1.8 kg/m²) volunteered to participate. All participants were free of known metabolic or cardiovascular disease and were not taking medications known to affect metabolism. Written informed consent was obtained from all participants. The study was approved by the Research Ethics Committee of Nagoya Aoi University (Approval No. 2022-7) and conducted in accordance with the Declaration of Helsinki.

Pre-Exercise Standardization

On the day before testing, participants consumed a standardized evening meal providing 700 kcal with a macronutrient distribution of 15% protein, 25% fat, and 60% carbohydrate. After this meal, participants refrained from eating and consuming energy-containing beverages until the morning of the experiment (12-h overnight fast) and avoided vigorous physical activity and alcohol for 24 h prior to testing.

Anthropometrics and Body Composition

Body mass and height were measured using a calibrated scale and stadiometer, and BMI was calculated as kg/m². Body fat percentage was assessed using a multifrequency bioelectrical impedance analyzer (HBF-254C; OMRON, Kyoto, Japan) according to the manufacturer's instructions.

Exercise Protocol

On the experimental day, participants performed a 40-min bout of continuous cycling on a mechanically braked ergometer at a constant workload of 55 W. This workload corresponded to moderate-intensity exercise of approximately 4.5–4.6 metabolic equivalents (METs) in both groups. Participants were instructed to maintain a cadence that was comfortable yet sustainable for the full duration of the trial. VO_2max was not measured; therefore, exercise intensity is reported as workload (55 W) and METs rather than % VO_{2max}.

Measurement of Serum Free Fatty Acids

Venous blood samples were collected from a peripheral vein at rest (pre-exercise) and at 15, 30, and 40 min after the start of exercise. Serum FFA concentrations were determined using an acyl-CoA synthetase/acyl-CoA oxidase

enzymatic method (Free Fatty Acid Assay Kit; Cell Biolabs, San Diego, CA, USA). All samples from a given participant were analyzed in the same assay run.

Energy Metabolism and Respiratory Quotient

Energy expenditure and respiratory quotient (RQ) at rest and during exercise were assessed using open-circuit indirect calorimetry (AR-10; ARCO SYSTEM, Chiba, Japan). VO_2 and carbon dioxide production were measured, and RQ was calculated as the ratio of VCO_2 to VO_2. During exercise, data were averaged over the steady-state period to obtain mean RQ and energy expenditure.

Genotyping of β3AR Trp64Arg Polymorphism

Genomic DNA was extracted from buccal mucosa cells collected with sterile cotton swabs using the QIAamp DNA Mini Kit (QIAGEN, Hilden, Germany). The β3AR gene region containing the Trp64Arg polymorphism was amplified by PCR using KOD Plus DNA polymerase (TOYOBO, Osaka, Japan). PCR conditions were 35 cycles of denaturation at 94°C for 15 s, annealing at 60°C for 30 s, and extension at 68°C for 30 s. The primers used were: forward 5'-GCTCCGTGGCCTCACGAGAA-3' and reverse 5'-CCCAACGGCCAGTGGCCAGTCAGCG-3'. PCR products were purified using the High Pure PCR Product Purification Kit (Roche, Basel, Switzerland). The Trp64Arg polymorphism was identified by restriction fragment length polymorphism analysis using the restriction enzyme BstN1 (New England BioLabs, Ipswich, MA, USA). Participants were classified as wild-type (Trp/Trp) or carriers of the Arg allele (Trp/Arg, Arg/Arg) genotypes.

Statistical Analysis

Data are expressed as mean ± standard deviation (SD). Group characteristics and outcome variables were compared between the wild-type and heterozygous groups using Welch's t-test. Normality was assessed using the Shapiro–Wilk test. Within-group changes from rest were evaluated using the Friedman test for repeated measures; when significant, post hoc pairwise comparisons were conducted using the Wilcoxon signed-rank test with Bonferroni correction. Statistical significance was set at $p < 0.05$. Data of RQ were analyzed using a repeated-measures framework including fixed effects for group (wild-type vs heterozygous), time, and the group × time interaction, with the participant treated as a repeated factor. Estimated marginal means (EMMs) were used to summarize model-based group differences over time. Statistical significance was set at $\alpha = 0.05$ (two-sided). Model-based estimates are reported as EMM ± standard error (SE) with 95% confidence interval (95% CI). All analyses were performed using IBM SPSS Statistics Version 25.

Results

Prevalence and Baseline Characteristics of the β3AR Trp64Arg Polymorphism

Of the 37 participants, 29 (78.4%) were wild-type (Trp/Trp) and 8 (21.6%) were heterozygous (Trp/Arg). No homozygous Arg/Arg carriers were detected. Therefore, the carrier group in this study represents heterozygous individuals only and does not reflect the full allele-dose spectrum.

BMI was 19.8 ± 1.7 kg/m² in the wild-type group and 20.6 ± 1.9 kg/m² in the heterozygous group. Body fat percentage was 27.5 ± 3.6% and 29.3 ± 4.4% in the wild-type and heterozygous groups, respectively. Resting energy expenditure (EE) was 0.77 ± 0.15 kcal/min in the wild-type group and 0.77 ± 0.08 kcal/min in the heterozygous group. During exercise, EE was 3.47 ± 0.36 and 3.51 ± 0.18 kcal/min in the wild-type and heterozygous groups, respectively. Exercise intensity corresponded to 4.5 ± 0.6 METs in the wild-type group and 4.6 ± 0.5 METs in the heterozygous group. No significant differences were observed between groups for any baseline characteristic or exercise intensity (Table 1). The exercise was performed at a fixed workload (55 W) and VO_2max was not assessed; relative intensity may have varied between individuals.

Table 1. Prevalence and characteristics of the β3AR gene Trp64Arg polymorphism.

	Wild (n = 29)	**Hetero (n = 8)**	***p*-value**	***d***
BMI	19.8 ± 1.7	20.6 ± 1.9	0.321	0.438
Body Fat (%)	27.5 ± 3.6	29.3 ± 4.4	0.383	0.459
EE (kcal/min)**: Rest**	0.77 ± 0.15	0.77 ± 0.08	0.966	0.015
EE (kcal/min)**: Exercise**	3.47 ± 0.36	3.51 ± 0.18	0.705	0.157
METs	4.5 ± 0.6	4.6 ± 0.5	0.648	0.212

Data are Means ± SD; *d*: Cohen's *d* (effect size)

Serum FFA Concentrations During Exercise

In the wild-type group, serum FFA concentrations were 0.90 ± 0.48 mEq/L at rest, 0.68 ± 0.58 mEq/L at 15 min, 1.09 ± 0.58 mEq/L at 30 min, and 2.04 ± 1.25 mEq/L at 40 min after the start of exercise. Compared with resting values, FFA concentration was significantly higher at 40 min ($p < 0.001$; Table 2).

In the heterozygous group, serum FFA concentrations were 1.08 ± 0.92 mEq/L at rest, 0.65 ± 0.37 mEq/L at 15 min, 0.89 ± 0.53 mEq/L at 30 min, and 1.54 ± 1.16 mEq/L at 40 min.

Table 2. Serum FFA concentrations (mEq/L) during exercise.

	Rest	15 min	30 min	40 min
Wild-type group (n = 29)	0.90 ± 0.48	0.68 ± 0.58	1.09 ± 0.58	2.04 ± 1.25*
Heterozygous group (n = 8)	1.08 ± 0.92	0.65 ± 0.37	0.89 ± 0.53	1.54 ± 1.16

Data are Means ± SD. * Significantly different from rest ($p < 0.001$).

Changes in Serum FFA Concentrations

Changes in FFA concentration from rest are shown in Figure 1. In the wild-type group, changes from baseline were −0.22 ± 0.43 mEq/L at 15 min, 0.20 ± 0.38 mEq/L at 30 min, and 1.14 ± 1.03 mEq/L at 40 min. In the heterozygous group, corresponding changes were −0.43 ± 0.60 mEq/L, −0.19 ± 0.48 mEq/L, and 0.47 ± 0.42 mEq/L.

Compared with the wild-type group, the heterozygous group exhibited significantly smaller increases in FFA at 40 min ($p = 0.009$) after the onset of exercise (Figure 1).

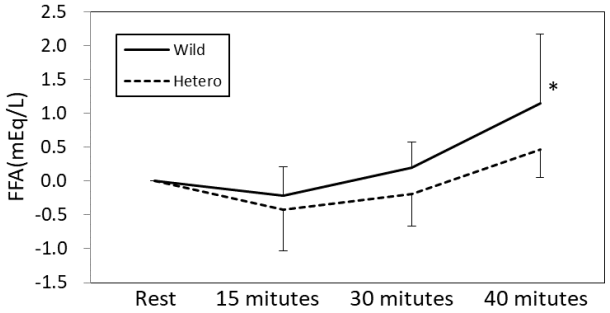

Figure 1. Changes in serum FFA concentration during exercise. *Significantly different from the heterozygous group ($p = 0.009$).

Respiratory Quotient During Exercise

Figure 2 shows the mean RQ values during exercise at 1-min intervals for each group. The group × time interaction was not significant ($F = 3.52$, $p = 0.065$); however, there was a significant main effect of group ($F = 9.81$, $p = 0.003$), with the heterozygous group showing higher RQ (mean ± SE: 0.91 ± 0.02 , 95% CI 0.88–0.94) than that of the wild-type group (0.86 ± 0.01, 95% CI 0.84–0.88) throughout the measurement period. There was also a significant main effect of time ($F = 11.44$, $p = 0.001$).

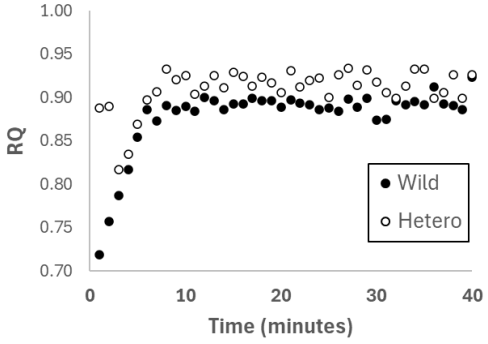

Figure 2. Respiratory quotient during exercise. Group × time interaction, $F = 3.52$, $p = 0.065$; main effect of group,

F = 9.81, p = 0.003 (Hetero > Wild); main effect of time, F = 11.44, p = 0.001. Model-based estimates (EMM ± SE) were 0.91 ± 0.02 for Hetero and 0.86 ± 0.01 for Wild, with 95% CIs of 0.88–0.94 and 0.84–0.88, respectively.

Discussion

This study investigated the influence of the β3AR Trp64Arg polymorphism on lipolytic responses during moderate-intensity aerobic exercise in the postabsorptive state in healthy young women. The main findings were: (1) carriers of the Trp64Arg polymorphism showed a slower increase in circulating FFA during exercise compared with that of non-carriers, and (2) RQ during exercise was significantly higher in carriers, suggesting greater dependence on carbohydrate metabolism.

Previous studies have linked the Trp64Arg polymorphism to obesity and type 2 diabetes[6,7]. In vitro work using human visceral adipocytes demonstrated that adipocytes carrying the Trp64Arg variant have a reduced lipolytic response to β3-adrenergic agonists compared with that of wild-type cells[9]. The present findings extend these observations to an in vivo setting by showing that young women carrying the polymorphism exhibit a blunted rise in FFA and smaller change from baseline during prolonged moderate-intensity exercise.

Earlier work in Japanese adults in their 20s indicated that men with the Trp64Arg polymorphism had lower fat oxidation at rest and during aerobic exercise than non-carriers, whereas no significant differences were observed among women[10]. However, that study evaluated responses approximately 2 h after a meal. Postprandial elevations in triglyceride-rich lipoproteins and insulin may attenuate lipolysis, potentially masking genotype-related differences. In contrast, the present study was conducted after a 12-h overnight fast, which may have facilitated the detection of differences in lipolytic capacity between genotypes even among women.

The time course of FFA responses observed in this study is broadly consistent with previous reports showing an initial decrease or plateau in serum FFA during the early phase of exercise, followed by a gradual increase as exercise continues[11,12]. In both genotype groups, FFA concentrations decreased at 15 min, likely reflecting a transient period whereby muscle FFA uptake exceeds FFA appearance in the circulation. Thereafter, FFA concentrations increased; however, the increase was slower and of smaller magnitude in the heterozygous group. This pattern supports the notion that the Trp64Arg polymorphism impairs catecholamine-stimulated lipolysis in vivo. However, because catecholamines and insulin were not measured, mechanistic interpretation were cautiously made.

The higher RQ observed in the heterozygous group during exercise further suggests a greater reliance on carbohydrate oxidation, consistent with a reduced capacity to mobilize and utilize lipids. From an applied perspective, these results may contribute to explaining inter-individual variability in substrate utilization and fat-loss responses to exercise; however, longitudinal training studies are needed before any genotype-specific exercise recommendations can be made.

In our sample, approximately 22% of healthy young women carried the Trp64Arg polymorphism, which is somewhat lower than previously reported prevalence estimates of 29–44% in Japanese women[7,10,13]. No significant genotype-related differences were observed in resting energy expenditure or energy expenditure during exercise (Table 1). This contrasts with previous reports of lower resting energy expenditure in Trp64Arg carriers[6,7]. This discrepancy may be due to the fact that our participants were non-obese, healthy women or to the relatively small sample size. The absence of Arg/Arg participants further limits inference regarding allele-dose effects.

Limitations

This study has several limitations. First, the sample size was modest, particularly for the heterozygous Trp/Arg group. Furthermore, no homozygous Arg/Arg carriers were detected, which limits result generalizability. Therefore, the carrier group in this study represents heterozygous individuals only and does not reflect the full allele-dose spectrum. This also increases the risk of Type II error, especially for detecting group × time interaction effects. Second, diet and physical activity were standardized only immediately before testing, and habitual lifestyle factors were not fully characterized. Finally, we did not assess other genetic variants involved in lipid metabolism that may also influence substrate utilization during exercise. As VO_2max was not measured and exercise was performed at a fixed workload, relative intensity may have differed between individuals. In addition, menstrual cycle phase and contraceptive status were not controlled/recorded, which may influence lipid metabolism and RQ. We also did not measure hormonal regulators of lipolysis (e.g., catecholamines, insulin), which limits mechanistic interpretation.

Conclusions

In healthy young women, carriers of the Trp64Arg polymorphism in the β3AR gene show a blunted increase in circulating FFA and higher RQ during moderate-intensity aerobic exercise in the postabsorptive state compared with that of non-carriers. Therefore, this common genetic variant may delay fat breakdown and shift substrate utilization toward carbohydrates during aerobic exercise, potentially contributing to inter-individual differences in fat loss responses to exercise-based interventions. These results should be interpreted as exploratory and require confirmation in larger cohorts, including Arg/Arg carriers, and in longitudinal intervention studies.

Conflict of Interest

The authors declare no conflicts of interest.

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