Vasopressin V1a Receptor Polymorphism and Interval Walking Training Effects in Middle-Aged and Older People

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for the Shinshu University Genetic Research Consortium

Abstract—We assessed whether single nucleotide polymorphism rs1042615 of the vasopressin V1a receptor altered the indices of lifestyle-related diseases in middle-aged and older people (mean ± SD: 64 ± 7 years), and, if so, whether it also altered the effects of interval walking training (IWT). CC, CT, and TT carriers of rs1042615 (42, 118, and 64 men, respectively; 113, 263, and 154 women, respectively) performed IWT. We included 5 sets of 3-minute fast walking at ≥70% peak aerobic capacity for walking and 3-minute slow walking at 40% peak aerobic capacity per day for ≥4 days per week for 5 months. Before IWT, the body mass index and diastolic blood pressure (DBP) for men were 25.1 ± 0.3 kg/m² (mean ± SE) and 84 ± 1 mm Hg in TT, higher than the 23.6 ± 0.4 kg/m² and 78 ± 1 mm Hg in CC, respectively (P < 0.01), differences that disappeared after IWT despite similar training achievement between groups (P > 0.6). After IWT, body mass index and DBP decreased in TT (−0.9 ± 0.1 kg/m² and −5 ± 1 mm Hg, respectively), more than in CC (−0.5 ± 0.1 kg/m² and 1 ± 1 mm Hg, respectively; P < 0.05), with a greater decrease in low-density lipoprotein cholesterol in TT than CC carriers (P < 0.01). The decreases in DBP and low-density lipoprotein cholesterol were still greater in TT carriers even after adjustment for their pretraining values. On the other hand, for women, these parameters before IWT and their changes after IWT were similar among CC, CT, and TT carriers. Thus, polymorphism rs1042615 of the V1a receptor altered body mass index and DBP in middle-aged and older men and the training-induced responses of DBP and low-density lipoprotein cholesterol, whereas women did not show any of these responses. (Hypertension. 2010;55:747-754.)

Key Words: exercise training ■ elderly ■ hypertension ■ obesity ■ cholesterol ■ receptors ■ vasopressin ■ polymorphism

Accumulated evidence suggests the importance of obesity prevention to protect against age- and lifestyle-related diseases, such as hypertension.1–4 Although exercise training has been highlighted as one of the most effective strategies,4–7 few studies have assessed how gene polymorphisms affect interindividual variation in response to exercise training in a large population of middle-aged and older people.8 This might be because there have been no uniformly and broadly available exercise training regimens calibrated to their individual physical fitness with few limitations on time and place. Without such a regimen, it might have been difficult to distinguish which caused the interindividual variation in the effects of exercise training, genetic or training regimen differences.

Recently, we have developed an exercise training regimen fitted to individual physical fitness broadly available in middle-aged and older people by combining interval walking training (IWT) and an information technology network system to track exercise intensity in individuals.9,10 Because the IWT regimen is so simple and because training achievements can be measured precisely by triaxial accelerometry,11 they have enabled us to seek polymorphisms causing interindividual variations in the lifestyle-related risk factor responses to exercise training in a large population of subjects.

Using this system, we examined the hypothesis that single nucleotide polymorphism rs1042615 of the arginine vasopressin (AVP) V1a receptor would significantly affect the interindividual variation in the body mass index (BMI), blood

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pressure, and blood lipid responses to IWT in middle-aged and older Japanese people. One reason for having the hypothesis was that we have found recently that lipid metabolism and blood pressure were markedly modulated during the active phase in mice genetically deficient in the V1a receptor, suggesting that AVP has metabolic and cardiovascular effects via the V1a receptor. Another reason was that V1a receptor distribution in the body has been suggested to vary according to animal species, individuals, and sexes. Here, we found that BMI and diastolic blood pressure (DBP) before IWT were significantly higher, but the sensitivity of DBP and low-density lipoprotein (LDL) cholesterol responses to IWT were significantly greater in men with the TT genotype rather than the CC genotype of polymorphism rs1042615 of the vasopressin V1a receptor, but we did not find any of these in women.

### Methods

#### Subjects

The study protocol was approved by the Institutional Review Board on Human Experiments, Shinshu University School of Medicine, and 799 middle-aged and older adults (mean±SD: 64±7 years; 234 men and 565 women) gave written informed consent and were enrolled in the study. Overall, 224 men and 530 women accomplished 5 months of training, returned for a posttraining assessment, and were included in the analyses. In these subjects, past incidence of hypertension, hyperlipidemia, and diabetes mellitus were 25%, 18%, and 7%, respectively, with no significant differences in the incidence between genotype groups (P=0.53 to 0.93).

#### Protocol

Physical characteristics, blood pressure, blood lipids and glucose, and peak aerobic capacity (VO\textsubscript{2peak}) were measured before and after the IWT regimen. All of the measurements except for VO\textsubscript{2peak} were performed after an overnight fast.

The detailed IWT regimen was described elsewhere. Briefly, before the start of training, subjects were invited to a community office near their homes and instructed to repeat ≥5 sets of 3-minute low-intensity walking at ~40% of the pretraining VO\textsubscript{2peak} for walking (see below for details) followed by 3-minute high intensity at ≥70% but <85% VO\textsubscript{2peak}, ≥4 days per week. The energy expenditure during daily walking at their favorite time and place was monitored with a triaxial accelerometer (Jukudai Mate, Kissei Comtec) on the right or left waist on the midclavicular line. A beeping signal alerted participants when a change of intensity was scheduled.

Every 2 weeks, the participants visited a local office to transfer their walking records from the accelerometer to a central server at the administrative center through the Internet for automatic analysis and reporting. Trainers used these reports to track daily walking intensity and other parameters in Table 1 to instruct participants on how best to achieve the target levels. Accordingly, we examined any differences in exercise intensity and energy expenditure during training between genotype groups. The study was performed from April to September in 2005, 2006, or 2007, during which time the average atmospheric temperature was 9°C to 26°C and relative humidity was 55% to 75%.

#### Measurements

**VO\textsubscript{2peak}**

We determined VO\textsubscript{2peak} by measuring energy expenditure with the accelerometer during graded walking on a flat floor: during slow, moderate, and fast walking for 3 minutes each, as reported previously, which was suggested to be in a good agreement with that by graded cycling test. Accordingly, we examined any difference in VO\textsubscript{2peak} between genotype groups (Tables 2 and 3).

**BMI and Body Fat**

BMI was calculated as body weight (in kilograms) divided by height (in meters) squared. Body fat was determined by the bioelectrical impedance method (BF-800, Tanita).

**Blood Pressure**

Systolic blood pressure (SBP) and DBP were measured by the auscultation method after the participant had been sitting for 10 minutes in a room with an ambient temperature of ~25°C and a relative humidity of ~50%. Exercise, caffeine, and smoking were avoided for >30 minutes before measurement according to American Heart Association guidelines.

**Blood Samples**

Blood samples for measuring blood lipids and glucose and for extracting DNA were collected from the antecubital vein in all of the subjects before training, whereas those for measuring blood lipids were collected in 200 men and 463 women and those for measuring blood glucose were collected in 193 men and 434 women both before and after training. Serum concentrations of cholesterol and triglycerides and the plasma concentration of glucose were determined using standard enzymatic methods.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>CT</td>
</tr>
<tr>
<td>Walking days per week</td>
<td>42</td>
<td>118</td>
</tr>
<tr>
<td>Fast walking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, minutes per day</td>
<td>28±2</td>
<td>26±1</td>
</tr>
<tr>
<td>Energy expenditure, milliliters of O₂ per kilogram per walking day</td>
<td>441±40</td>
<td>399±22</td>
</tr>
<tr>
<td>Intensity, milliliters of O₂ per kilogram per minute</td>
<td>16.1±0.6</td>
<td>15.0±0.4</td>
</tr>
<tr>
<td>Slow walking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, minutes per day</td>
<td>34±5</td>
<td>30±2</td>
</tr>
<tr>
<td>Energy expenditure, milliliters of O₂ per kilogram per walking day</td>
<td>246±24</td>
<td>233±12</td>
</tr>
<tr>
<td>Intensity, milliliters of O₂ per kilogram per minute</td>
<td>8.8±0.5</td>
<td>8.5±0.3</td>
</tr>
<tr>
<td>Total fast walking time, minutes per week</td>
<td>111±10</td>
<td>111±9</td>
</tr>
</tbody>
</table>

Values are mean±SE unless otherwise specified. CC, CT, and TT are genotypes for single nucleotide polymorphism rs1042615 of the vasopressin V1a receptor.
Table 2. Baselines of Measurements Before Training

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CC</td>
<td>CT</td>
</tr>
<tr>
<td>n</td>
<td>42</td>
<td>118</td>
</tr>
<tr>
<td>Age, y</td>
<td>68±5</td>
<td>68±8</td>
</tr>
<tr>
<td>Height, cm</td>
<td>164±6</td>
<td>164±5</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>63.4±1.2</td>
<td>65.0±0.8</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>23.0±0.6</td>
<td>23.5±0.5</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>140±3</td>
<td>136±2</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>38</td>
<td>107</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>59±2</td>
<td>60±1</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>104±8</td>
<td>115±5</td>
</tr>
<tr>
<td>n</td>
<td>38</td>
<td>102</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>102±2</td>
<td>107±2</td>
</tr>
<tr>
<td>n</td>
<td>36</td>
<td>98</td>
</tr>
<tr>
<td>VO2peak, mL/kg/min</td>
<td>21.5±0.7</td>
<td>20.6±0.4</td>
</tr>
<tr>
<td>Resting HR, bpm</td>
<td>74±3</td>
<td>77±2</td>
</tr>
<tr>
<td>Peak HR, bpm</td>
<td>125±3</td>
<td>126±2</td>
</tr>
</tbody>
</table>

Values are mean±SD for age and height and mean±SE for other variables unless otherwise specified. HDL indicates high-density lipoprotein; HR, heart rate. HR was measured with a near infrared ear pickup probe during VO2peak determination.

*Data show the significant difference from the corresponding value in CC group, P<0.001.
†Data show the significant difference from the corresponding value in CT group, P<0.05.
§Significant difference from the corresponding value in the CC group, P<0.01.

Medical Survey
Subjects were interviewed by medical staff and were asked to answer questionnaires mainly on their medications and anamnesis.

Genotype Determination
Genomic DNA was extracted from blood samples using the QIAamp DNA Blood Midi kit (Qiagen). The single nucleotide polymorphism rs1042615 of the vasopressin V1a receptor gene was analyzed with a TaqMan real-time PCR assay (Applied Biosystems) using commercially available primers and probes purchased from the Assay-on-Demand kit and TaqMan Universal Master Mix (Applied Biosystems). Fluorescence emission from amplicon formation was measured using an ABI PRISM 7900HT Sequence Detection System (Applied Biosystems).

Statistics
One-way ANOVA was used to examine any significant differences in training achievements between genotype groups (Table 1). This model was also used to examine any significant differences in physical characteristics, blood pressure, blood lipids and glucose,

Table 3. Changes in Measurements After Training

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CC</td>
<td>CT</td>
</tr>
<tr>
<td>n</td>
<td>42</td>
<td>118</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>1.4±0.2†</td>
<td>1.9±0.2†</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>2.0±0.3†</td>
<td>2.3±0.3§</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>6±2*</td>
<td>7±1‡</td>
</tr>
<tr>
<td>n</td>
<td>38</td>
<td>107</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>3±1*</td>
<td>1±1</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>2±6</td>
<td>3±6</td>
</tr>
<tr>
<td>n</td>
<td>38</td>
<td>102</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>4±2</td>
<td>4±1‡</td>
</tr>
<tr>
<td>n</td>
<td>36</td>
<td>98</td>
</tr>
<tr>
<td>VO2peak, mL/kg/min</td>
<td>3.2±0.6†</td>
<td>3.1±0.3‡</td>
</tr>
<tr>
<td>Resting HR, bpm</td>
<td>1±3</td>
<td>1±1</td>
</tr>
<tr>
<td>Peak HR, bpm</td>
<td>10±1†</td>
<td>6±2†</td>
</tr>
</tbody>
</table>

Values are mean±SE unless otherwise specified. HDL indicates high-density lipoprotein; HR, heart rate.
*P<0.05, significant differences from pretraining values.
†P<0.01, significant differences from pretraining values.
‡P<0.001, significant differences from pretraining values.
§Significant difference from the corresponding value in the CC group, P<0.05.
and VO2peak between genotype groups before and after training, respectively, and also their changes after training (Figures 1 and 2 and Tables 2 and 3). One-way ANOVA for repeated measures was used to examine any significant changes in the variables after training in each genotype group (Figure 2 and Table 3). Moreover, we examined any significant differences in their changes after training between genotype groups by ANCOVA with pretraining values, age, total fast walking time, and training period in each subject included as covariates.

χ² analysis was used to confirm Hardy-Weinberg equilibrium and also to determine any significant frequency differences in dichotomous variables using 2x3 or 2x2 contingency tables by dividing subjects into 2 groups: higher and lower BMI or DBP than the thresholds of our criteria for lifestyle-related diseases (Table 4 and Figure 3). In the analysis, because we found significant differences in genotype or allele frequency between higher and lower groups, we examined any significant differences in BMI, DBP, and LDL cholesterol before training and their changes after training between genotype groups by ANCOVA, as stated above.

Post hoc tests subsequent to ANOVA were performed to determine significant differences in the various pairwise comparisons using the Fisher least significant difference test. All of the P values <0.05 were considered significant. Values are expressed as the mean±SE unless otherwise indicated.

Results

No significant difference in the genotype frequency of rs1042615 was observed between subjects initially enrolled in the study and those who completed 5 months of training and returned for a posttraining assessment (P=0.88 to 0.99). Moreover, the genotype frequency was consistent with Hardy-Weinberg equilibrium (P=0.63 to 0.99), and no significant difference in the genotype frequency was observed between men and women (P=0.47 to 0.67).

As shown in Table 1, there were no significant differences in training achievement among CC, CT, and TT groups in either sex. As shown in Figure 1 and Table 2, BMI and DBP before IWT were significantly higher in the TT group than in other groups, whereas age, height, blood lipids and glucose, and VO2peak were similar among groups in men; however, these were all similar between groups in women.

As shown in Figure 2 and Table 3, after IWT, BMI, DBP, and LDL cholesterol for men decreased significantly in all of the groups except for DBP and LDL cholesterol in the CC group; however, the decreases in BMI, DBP, and LDL cholesterol were significantly greater in the TT group compared with the CC group, resulting in the disappearance of significant differences between groups before IWT. After adjustment for pretraining values, age, total fast walking time, and training period as covariates by ANCOVA, we confirmed that the greater reductions in DBP...
and LDL cholesterol in the TT group compared with the CC group remained ($P=0.039$ for DBP; $P=0.013$ for LDL cholesterol), whereas that in BMI disappeared ($P=0.39$). For women, there were no significant differences in the changes after IWT between groups.

Table 4 shows genotype frequencies in subjects with lower and higher BMI, blood pressure, LDL cholesterol, or glucose than the thresholds for lifestyle-related diseases determined in the present study while referring to guidelines for Japanese and US populations. As shown in Figure 3, for men, T allele frequency was significantly higher in subjects with BMI $\geq 25$ than $<25$ kg/m$^2$ before IWT. Similarly, the T allele frequency was significantly higher in subjects with DBP $\geq 85$ than $<85$ mm Hg. This finding was more prominent in subjects with both DBP $\geq 85$ mm Hg and BMI $\geq 25$ kg/m$^2$. However, these differences disappeared after IWT, except for a slightly higher T allele frequency in subjects with BMI $\geq 25$ than $<25$ kg/m$^2$. On the other hand, for women, there were no significant differences in genotype or allele frequencies between subjects with lower and higher values either before or after IWT (Table 4).

To exclude the possibility that the significantly greater reductions in DBP and LDL cholesterol for the TT group rather than the CC group (Figure 2) were caused by their higher values in the TT group before training, we compared their changes after training between genotypes in the higher group. As shown in Table 5, we confirmed that the reduction in DBP after IWT was significantly greater in the TT group rather than the CC group and, moreover, that the reduction in LDL cholesterol was significantly greater in the TT group rather than other groups, although training achievement was similar between groups ($P=0.64$ to 0.83). This significance remained after adjustment for pretraining values, age, total fast walking time, and training period by ANCOVA ($P=0.031$ for DBP; $P=0.006$ for LDL cholesterol).

Some subjects were taking medications potentially affecting autonomic function (10, 26, and 12 men; 26, 52, and 29 women) and blood lipids (3, 8, and 3 men and 15, 35, and 19 women for the CC, CT, and TT group, respectively) during the study period; however, there were no significant differences in genotypes between subjects with and without medications ($P=0.68$ to 0.96). In addition, even after excluding subjects with medication for autonomic function from the analysis, we found in men that DBP before IWT was significantly higher in the TT group compared with the other groups ($P<0.005$) and also that the reduction after IWT was significantly greater in the TT group compared with the CC group of this subset ($P=0.0022$) despite similar training achievement between groups ($P=0.91$). Similarly, after excluding subjects with medication for blood lipids from the analysis, we confirmed in men that the reduction in LDL cholesterol after IWT was significantly greater in the TT group.
group compared with the CC group (P=0.0083) despite similar training achievement between groups (P=0.56). On the other hand, for women, there were no differences in these values before IWT and there were no differences in their reductions after IWT between groups.

Discussion

There have been no studies investigating any influence of the V1a receptor polymorphism on the lifestyle-related risk factor responses to exercise training according to the previous review including the HERITAGE (Health, Risk Factors, Exercise Training, and Genetics) Family Study.8 The major findings of this study are as follows, in middle-aged and older Japanese people: (1) TT men for polymorphism rs1042615 of the V1a receptor had higher BMI and DBP than other genotype groups; (2) these differences disappeared after training; (3) TT men had significantly greater training-induced reductions in BMI, DBP, and LDL cholesterol, and the reductions in DBP and LDL cholesterol were still greater in TT men even after adjustment for their pretraining values; (4) T allele frequency was greater in the higher BMI or DBP group before training; (5) in the higher group, the reductions in DBP and LDL cholesterol after training were greater in TT than CC men, although their pretraining values were similar between genotypes; and (6) for women, these values before training and the changes after training were similar between genotype groups.

Table 5. Changes in BMI, DBP, and LDL Cholesterol After Training in Men With Higher Pretraining Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m² (≥25 kg/m²)</td>
<td>n=9  26.8±0.5</td>
<td>n=46 26.9±0.2</td>
<td>n=36 27.0±0.2</td>
</tr>
<tr>
<td></td>
<td>Before −0.8±0.1</td>
<td>Before −1.1±0.1</td>
<td>Before −1.2±0.2</td>
</tr>
<tr>
<td>DBP, mmHg (≥85 mmHg)</td>
<td>n=8  91±1</td>
<td>n=41 92±1</td>
<td>n=25 93±1</td>
</tr>
<tr>
<td></td>
<td>Before −2±3</td>
<td>Before −9±1†</td>
<td>Before −9±1†</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl (≥130 mg/dl)</td>
<td>n=16 153±4</td>
<td>n=54 151±2</td>
<td>n=27 157±4</td>
</tr>
<tr>
<td></td>
<td>Before −7±3</td>
<td>Before −7±2</td>
<td>Before −21±4‡</td>
</tr>
</tbody>
</table>

Values are mean±SE unless otherwise specified. Men who had higher pretraining values than the thresholds in parentheses were used for analysis.

*P<0.05, significant differences from corresponding values in the CC group.
†P<0.01, significant differences from corresponding values in the CC group.
‡P<0.01, significant differences from the corresponding value in CT group.

Figure 3. Allele frequencies in men with lower (gray columns) and higher (striated columns) BMI, DBP, or LDL cholesterol values than the criteria for lifestyle-related diseases in the present study. Significant differences in distribution, *P<0.05, **P<0.01, and ***P<0.001. The number of subjects in each subgroup is shown in Table 4.

**BMI and Blood Pressure Before Training and V1α Receptor Polymorphism**

Higher BMI in TT men might be caused by the metabolic effects of AVP via V1α receptor. In mice genetically deficient in V1α receptor, being fed chow containing a percentage of fat equivalent to the recommended dietary allowances for Japanese17 resulted in overt obesity compared with wild-type mice despite similar total calorie intake between groups.18 In humans, a higher prevalence of obesity was suggested in patients with AVP deficiency or in subjects with reduced AVP activity.19,20 Recently, Enhorning et al21 studied polymorphism rs1042615 of the V1α receptor in middle-aged humans in southern Sweden (n=5506; CC, CT, and TT=30.4%, 49.2%, 20.4%) and reported that CT+TT subjects had significantly higher blood glucose concentration and a tendency toward a higher prevalence of obesity than CC subjects. Similarly, in this study, TT men had slightly higher blood glucose concentration, although not significant, and significantly higher BMI (Figure 1), and, moreover, overweight men in Figure 3 show significantly higher T allele frequency. Although it remains unknown how this polymorphism was associated with these findings, disturbed circadian rhythms of physical activity might be partially involved in the mechanisms, as suggested in V1α knockout mice.22 Thus, we confirmed in the present study that TT men had higher metabolic risk factors.

In addition to the higher BMI in TT men, we found that DBP before training was higher in TT men than in other
groups (Figure 1), and, moreover, that T allele frequency was greater in the higher DBP group, as well as the higher BMI group (Figure 3). Epidemiological studies have consistently shown a higher prevalence of hypertension in the overweight population than in the normal-weight population.\(^1\) Sympathetic nerve activity is suggested to increase as body weight increases, and this is considered one of the most important mechanisms linking overweight to hypertension.\(^2\) In addition, sympathetic nerve activity positively correlates with DBP but not with SBP in middle-aged and older men.\(^3\) Thus, the higher DBP in TT men might be caused by higher BMI through sympathetic activation.

Another possible mechanism for the higher DBP in TT men might be the greater contribution of V1a receptor-mediated vasoconstriction to resting vascular tone. However, V1a receptor-mediated vasoconstriction does not occur before plasma AVP increases far above the level for maximal urine concentration in humans,\(^4\) suggesting that AVP is unlikely to be involved in resting vascular tone in the present study.

**Reductions in BMI and Blood Pressure After Training and V1a Receptor Polymorphism**

The significantly higher BMI and DBP in TT men before training disappeared after training with their greater reductions than those in CC men (Figure 2). Several studies of obese subjects of western populations demonstrated that subjects who lost weight after exercise training or other therapies reduced their blood pressure, whereas those who lost no weight did not.\(^5\) Moreover, weight loss is reported to be accompanied by reduced sympathetic nerve activity.\(^6\) In the present study, we confirmed the similar results in the subjects who were less obese than western populations, but their physical characteristics well reflected those of the age-matched Japanese population.\(^7\) These results suggest that the greater reduction in BMI in TT men evoked the greater reduction in DBP after training through attenuated sympathetic nerve activity in the subjects who were less obese than those in western populations.

In addition, the greater reduction in LDL cholesterol in TT men might also contribute to the greater reduction in DBP after training (Figure 2). Walker et al\(^8\) reported that endothelium-dependent dilation was reduced in older sedentary men when their LDL cholesterol concentration was high. Moreover, increased endothelium-dependent dilation by aerobic exercise training, leading to a reduction in DBP,\(^9\) was enhanced as LDL cholesterol decreased.\(^4\) These results suggest that the greater reduction in LDL cholesterol after training in TT men may also contribute to the greater reduction in DBP through improved endothelial function.

**Sensitivity to Training and V1a Receptor Polymorphism**

We observed greater reductions in BMI, DBP, and LDL cholesterol in TT men; however, their higher pretraining values might have affected the results. Therefore, we further examined any significant differences in the reductions between genotype groups after adjustment for pretraining values by ANCOVA and also after dividing subjects into subgroups in each genotype group according to higher or lower values than the thresholds of our criteria for lifestyle-related diseases (Table 4). As a result, we found greater sensitivity of DBP and LDL cholesterol responses to training in TT men, although the same was not found for BMI (Table 5). In addition, we confirmed that these when data were expressed as percent changes instead of absolute changes from pretraining values. These results suggest that DBP and LDL cholesterol decreased more in TT men than CC men in response to a given intensity of training and a given reduction in BMI.

Regarding the mechanisms, Hiroyama et al\(^28\) reported in V1a knockout mice that V1a receptor modulates lipid metabolism and affects cholesterol production via β-oxidation of fatty acid. Moreover, we have reported recently in mice that V1a receptor modulates lipid metabolism during the active phase more than the inactive phase.\(^12\) In addition, it is well known that aerobic exercise training increases lipid oxidative capacity.\(^7\) Thus, V1a receptors in TT men might enhance LDL cholesterol response to exercise training compared with that in CC men, which might accelerate the reduction in DBP.

Taken together, TT men had greater sensitivity to training-induced reductions in DBP and LDL cholesterol, which might be because of the combined effects of V1a receptor and exercise training on lipid metabolism. Because this occurred despite their tendency toward lower total fast walking time (Table 1), it supports our idea that even a minimal increase in physical activity would evoke rather profound effects on DBP and LDL cholesterol in the group.

**Women and V1a Receptor Polymorphism**

Different from the results in men, we observed no genotype-dependent differences in women in the present study. A possible reason might be that women had slightly lower age, BMI, and blood pressure than men. However, we confirmed the results even in the subgroup of women in which age, BMI, or blood pressure was similar to men (data not shown). Alternatively, because effects of the V1a receptor are reportedly more prominent in men than in women,\(^10\) V1a receptor polymorphism might affect phenotype in men more than in women.

**Limitations**

First, some subjects were taking medications that could affect autonomic function and blood lipids during the study period, which might have affected the results of this study. However, after excluding subjects with medications from the analysis, we confirmed the similar results in blood pressure and LDL cholesterol between genotype groups.

Second, we did not measure abdominal visceral fat, which is reportedly more associated with elevated sympathetic nerve activity.\(^29\) However, because abdominal visceral fat is more affected by exercise-induced weight loss than BMI,\(^30\) if V1a receptor is involved in this fat loss, we may have underestimated the genotype-dependent differences in body composition change after training. In addition, our method used to determine the percentage of body fat was so limited that it might not be sensitive enough to detect genotype-dependent differences.
Third, we assessed only polymorphism rs1042615, whereas this polymorphism might be linked to several other polymorphisms potentially affecting the risk factors. For example, β2-adrenergic receptor polymorphisms (Arg16Gly and Gin27Glu) were reported to be associated with obesity and hypertension in Japanese. However, we found no significant differences in frequencies of Gly16 (53.7%) or Glu27 (7.2%) alleles between genotype groups of the V1a receptor polymorphism.

**Perspectives**

The present study demonstrated that BMI and DBP before IWT and the sensitivity of DBP and LDL cholesterol responses to IWT were higher in men with the TT genotype of polymorphism rs1042615 of the V1a receptor in middle-aged and older men. Because antihypertensive treatment has proved that a 5-mm Hg decline in DBP, as in the present study, reduced the incidence of stroke by ~40% when it was maintained for 5 years, the finding strongly suggests that TT men with higher DBP and LDL cholesterol may be more encouraged to perform exercise training for clinical treatment.

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**Disclosures**

None.

**References**


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