**Abstract** There is no long-term exercise training regimen with high adherence and effectiveness for middle-aged and older people that is broadly available in the field. To solve this problem, we developed an exercise training regimen comprised of interval walking training (IWT) and an IT network system that only requires minimal staff support. We found that adherence to the 22-month IWT program was relatively higher than other previously reported long-term exercise programs requiring more personnel support and that the program was accompanied by greater improvements in lifestyle-related disease risk factors and physical fitness in middle-aged and older people. Moreover, when congenital and acquired factors affecting adherence were assessed, we found that baseline body mass index and gender for all subjects, as well as smoking and vasopressin V1a receptor polymorphisms for men, were independent determinants of adherence to the IWT program. To elucidate the mechanism underlying the effect of V1a receptor polymorphisms on adherence to an exercise program, we assessed whether voluntary locomotion was impaired in mice genetically deficient in V1a receptors (V1a KO). We found that voluntary locomotion in wild-type mice was more probable after cerebral activation, while in V1a KO mice the probability was markedly reduced with no suppression of baroreflex control of heart rate during cerebral activation. Moreover, the findings in V1a KO mice were confirmed after local infusion of a V1a receptor antagonist into the nucleus tractus solitarii of the wild-type mice. Thus, central V1a receptors play an important role in facilitating voluntary exercise and thereby contribute to adherence to the IWT program.

**Keywords**: exercise training, aging, genetics, vasopressin, baroreceptor reflex

**Introduction**

Exercise training is one of the most effective strategies for decreasing the likelihood of age- and lifestyle-related diseases (LSD), thereby promoting independence and enhancing the quality of life in the rapidly growing elderly populations of many countries. However, long-term exercise training programs for middle-aged and older people that guarantee relatively high adherence and effectiveness are not widely available.

It is well known that an exercise prescription should conform to an individual’s fitness level to achieve the desired effects; and, in most cases, individualized training is performed using machines, bicycles, and treadmills at a gymnasium or related facility where exercise intensity can be more easily monitored. These training programs are costly and limit adherence. To solve these problems, we recently developed a broadly available, remotely supervised exercise training system for middle-aged and older people. In this review, we describe the adherence to and effects of our long-term training program, as well as the factors affecting adherence. We also present genetic and pharmacological animal models to clarify the mechanism by which genetic factors affect the adherence to exercise programs in humans.

**Adherence to and effect of long-term interval walking training**

Our training program is comprised of interval walking training (IWT) programmed according to individual peak aerobic capacity for walking (VO$_{2\text{peak}}$), and an IT network system that tracks exercise intensity and energy expenditure during training and provides individual feedback. We reported previously that adherence to IWT for 5 months was very high (95%) and was accompanied by a ~15% increase in VO$_{2\text{peak}}$ and a ~20% decrease in LSD risk factors, equivalent to the outcome of facility-based training for the same period of time. However, no study has evaluated the IWT program over a longer time frame.
Therefore, we assessed the adherence and effects of IWT over 22 months, longer than our laboratory’s previous 5-month studies6,8).

Middle-aged and older men and women [n = 696, aged 65 ± 7 (SD) years] underwent IWT. The subjects were instructed to repeat ≥5 sets of fast and slow walking for 3 min each at ≥70% and 40% VO_{2peak}, respectively, per day for ≥4 days/wk over the course of 22 months. Adherence was assessed as training days accomplished relative to the target of 4 days/wk over 22 months. The effects on VO_{2peak} and the LSD score calculated according to healthcare guidelines10,11) were evaluated every 6 months.

Adherence over 22 months averaged 70% and was inversely and significantly correlated with a reduction in LSD score. As shown in Fig. 1, the subjects with the highest adherence to the exercise program exhibited the greatest reduction in LSD score. Overall, the IWT program significantly decreased the LSD score from baseline by 13% at 22 months (n = 696, P < 0.0001). Moreover, adherence was significantly positively correlated with an increase in VO_{2peak}. As shown in Fig. 2, the subjects with the highest adherence to the exercise program had the greatest increase in VO_{2peak}. Overall, the IWT program significantly increased VO_{2peak} from baseline by 12% at 22 months (n = 696, P < 0.0001).

Thus, we have developed a broadly available, remotely supervised exercise training system for middle-aged and older people with a minimal requirement for staff support12). We suggest that adherence to the 22-month IWT program was comparatively higher than adherence to other previously reported long-term exercise programs requiring greater personnel support4,13-15) and was accompanied by greater improvements in LSD risk factors and physical fitness in middle-aged and older people12).

Factors affecting adherence to the long-term IWT program

Because our results demonstrate that higher adherence to an exercise program is critical for improvements in LSD risk factors and physical fitness (Figs. 1 and 2), we attempted to identify factors affecting adherence to the 22-month IWT program. It has been suggested that gender, physical characteristics, physical activity, and other acquired factors affect adherence6,17). However, no studies have investigated genetic factors affecting adherence. This might be because there have been no uniformly and broadly available exercise training regimens, and also no systems to precisely track daily training achievements. On the other hand, the IWT program is remotely and uniformly supervised via the internet throughout the training period and requires minimal staff support, enabling us to identify factors without any bias from a varied training regimen and with less support from staff.

We recently reported that middle-aged and older Japanese men carrying the TT genotype of the rs1042615 single nucleotide polymorphism of the arginine vasopressin receptor 1a gene (AVPR1A) had a significantly higher body mass index (BMI) and diastolic blood pressure than those who did not18). However, the higher values...

Fig. 1  Adherence to prescribed walking days (APWD, A) and fast walking time (APFWT, B) over the 22-month training period vs. the change in lifestyle-related disease score from baseline to 22 months (ΔLSD score). Subjects were pooled according to their ΔLSD score: ≥1 (men = 30; women = 74), 0 (men = 93; women = 270), -1 (men = 50; women = 128), -2 (men = 19; women = 25), and ≤-3 (men = 4; women = 3). Values are means ± SE. Significant differences in adherence from those with the worst ΔLSD score (≥1), *P < 0.05 and **P < 0.01. APWD was calculated as the number of walking days completed divided by the total number of walking days prescribed for each month (4 days/wk). These monthly ratios were summed and averaged over 22 months. APFWT was calculated as the fast walking time completed divided by the total fast walking time prescribed for each month (60 min/wk). Any time in excess of 60 min/wk was regarded as “100%”. The monthly ratios were summed and averaged over 22 months. Fig. from ref12).
decreased to levels comparable to those of men with other genotypes following 5 months of IWT, suggesting that men with the TT genotype might have been physically inactive prior to IWT\(^2\). In addition, the AVPR1A microsatellite polymorphism RS3 was reported to be associated with social behavior, particularly in men\(^1\)-\(^5\), and might be linked to lower physical activity in TT men\(^1\). We therefore hypothesized that adherence to the 22-month IWT program would be affected by the RS3 and rs1042615 polymorphisms of the AVPR1A in addition to previously reported factors\(^1\)-\(^7\).

To assess our hypothesis, the independent factors affecting adherence to the 22-month IWT program were determined by multiple regression analysis after adjustments for baseline physical characteristics, physical activity, orthopedic and psychological factors, and other possible covariates, including AVPR1A polymorphisms. We found that the major determinants of higher adherence were a lower baseline BMI (\(P < 0.0001\)) and male gender (\(P < 0.0001\)). For men, in addition to BMI, smoking (\(P = 0.031\)) and AVPR1A polymorphisms (\(P = 0.033\)) were independent determinants of adherence\(^1\).

To more precisely examine the association of AVPR1A polymorphisms with adherence during the training period, we compared the monthly adherence rates over 22 months in men according to RS3 and rs1042615 polymorphisms in the AVPR1A after adjustments for baseline BMI and smoking. As shown in Fig. 3, monthly adherence rate to the exercise program (4 days/wk) gradually decreased after the first 5 months of IWT in all subjects; however, this effect was markedly enhanced in men carrying the RS3 [one or two 334 alleles] in combination with rs1042615 [TT] (group 4) compared to other carriers. We observed

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**Fig. 2** Adherence to prescribed walking days (APWD, A) and fast walking time (APFWT, B) over the 22-month training period vs. the change in peak aerobic capacity for walking from baseline to 22 months (\(\Delta VO_2\)peak). Subjects were pooled according to their \(\Delta VO_2\)peak: \(\leq -2.5\) (men = 8; women = 39), -2.4 to 0 (men = 46; women = 116), 0.1 to 2.5 (men = 52; women = 111), 2.6 to 5.0 (men = 52; women = 135), and >5.0 ml/kg/min (men = 38; women = 99). Values are means ± SE. Significant differences in adherence from those with the lowest \(\Delta VO_2\)peak (\(\leq -2.5\) ml/kg/min), **\(P < 0.01\) and ***\(P < 0.001\). APWD and APFWT determinations are made as in Fig. 1. Fig. from ref\(^1\).

**Fig. 3** Monthly adherence rate over the 22-month training period in men according to 334 allele of RS3 and C/T of rs1042615, after adjustments for possible covariates. RS3 and rs1042615 denote the microsatellite and single nucleotide polymorphism in AVPR1A, respectively. Group 1, zero 334 allele and CC/CT carriers (n = 89); group 2, one or two 334 alleles and CC/CT carriers (n = 47); group 3, zero 334 allele and TT carriers (n = 31); group 4, one or two 334 alleles and TT carriers (n = 29). Values are means ± SE. The adherence rate was calculated as the number of walking days completed divided by the total number of walking days prescribed for the month (4 days/wk) and then adjusted for baseline BMI and smoking status by multiple regression analysis. **\(P = 0.009\) and ***\(P < 0.0001\). Fig. from ref\(^1\).
a significant interactive effect of [group x time] on the adherence rate \((P < 0.0001)\), indicating a significantly greater decrease in [334 alleles–TT] carriers than other carriers. These results suggested that men carrying [334 alleles–TT] of \(AVPRI\)A polymorphisms exhibited lower adherence to the long-term IWT program\(^{12}\).

We excluded the effects of demographic, orthopedic, and psychological factors mentioned above as possible mechanisms underlying the greater reduction in adherence rate for men carrying [334 alleles–TT]\(^{4,16,17}\). However, we did not exclude the potential effects of central factors that might facilitate pressor response at the onset of voluntary exercise, which would likely affect the adherence rate via \(AVPRI\)A variations\(^{19}\).

**V1a receptors and pressor response at the onset of voluntary exercise**

Arterial blood pressure rises at the onset of voluntary exercise, which is probably advantageous for increasing blood flow to contracting muscles. Because arterial blood pressure at rest is controlled at a lower level than during exercise by the baroreflex control system, but increases rapidly at the onset of exercise, this system is thought to be important for increasing pressure to meet the subsequent intensity of exercise and to facilitate exercise. For example, we demonstrated that voluntary locomotion in mice was limited by a rapid fall in arterial pressure due to enhanced muscular vasodilation when baroreflex control was blocked by carotid sinus denervation or the administration of \(\alpha\)-adrenergic blockade (Fig. 4)\(^{26}\). From these results, we speculated that arterial pressure might not increase at the onset of exercise in men carrying [334 alleles–TT], perhaps due to impaired V1a receptor function. Therefore, we will discuss arterial pressure regulation at the onset of exercise using animal models with impaired V1a receptor function.

Arterial pressure regulation is achieved through the baroreflexes, which alters the efferent signals to the heart and peripheral vessels based on the afferent signals relayed from peripheral baroreceptors. In the cardiovascular center of the medulla, the feedback gain of the baroreflexes is further modulated by signals from higher brain regions\(^{27}\). Vasopressin V1a receptors have been reported to be richly expressed in the nucleus tractus solitarii (NTS) of the medulla\(^{28}\) and to regulate the activity of NTS neurons receiving baroreceptor input\(^{29}\); therefore, it is plausible that V1a receptors in the medulla might act as mediators that receive signals from higher brain regions and modulate baroreflex control of heart rate (HR). If this is true, V1a receptors might contribute significantly to the start of voluntary locomotion via this pathway.

Previously, we reported that increased cerebral activity suppressed the baroreflex control of HR, and this was related to the start of voluntary locomotion with a rapid increase in arterial pressure in wild-type mice\(^{30}\). Based on these results and on data from [334 alleles–TT] men, we hypothesized that suppression of baroreflex control of HR after voluntary cerebral activation would be impaired in V1a receptor knockout (V1a KO) mice, and be accompanied by a marked reduction in the probability of locomotion after cerebral activation. In addition, we hypothesized that if these responses were mediated by V1a receptors in the NTS, the findings in V1a KO mice could be confirmed after local infusion of a V1a receptor antagonist into the NTS of wild-type mice.

To assess this, we measured mean arterial pressure (MAP, arterial catheter), HR, and electroencephalogram (EEG) in freely moving male V1a KO (n = 8) and wild-type mice (WT, n = 8)\(^{11}\). Baroreflex sensitivity (\(\Delta\text{HR}/\Delta\text{MAP}\)) was determined from HR response (\(\Delta\text{HR}\)) to a

**Fig. 4** Typical examples of mean arterial pressure (MAP) and electromyogram (EMG) for a control mouse (CNT, A) and a carotid-sinus-denervated mouse (CSD, B) in free-moving state for 60 min. Arterial pressure (AP) and EMG during the time intervals indicated by the arrows in the lower figures are presented on an enlarged time scale in the upper right side of each panel. Fig. from ref\(^{26}\).
spontaneous change in MAP (ΔMAP) every 4 sec during the total resting period, which comprised ~8.7 h of the 12-h measuring period in both groups. ΔHR/ΔMAP was determined during the periods when the cross-correlation function [R(t)] between ΔHR and ΔMAP was significant. Cerebral activity was determined every 4 sec from the power density ratio of the θ to δ wave band (θ/δ) on the EEG. We found that spontaneous changes in θ/δ were synchronized with R(t) in both groups (Fig. 5); however, a significant correlation occurred during 62 ± 3% of the total resting period in WT mice, but during only 38 ± 4% of the total resting period in V1a KO mice (Fig. 6A). When R(t) and ΔHR/ΔMAP were divided into 6 bins according to the level of θ/δ, both were positively correlated with θ/δ in WT mice, while neither was correlated in V1a KO mice (Fig. 6B). Moreover, the probability that mice started to move after an increase in θ/δ was 61 ± 5% in WT mice, but only 24 ± 4% in V1a KO mice, markedly lower than in WT mice with no suppression of baroreflex control of HR (Figs. 6C and D). In addition, these findings in V1a KO mice were confirmed after local infusion of the V1a receptor antagonist into the NTS of wild-type mice (V1a BLK, n = 8).

To better understand the relationship between the suppression of baroreflex control of HR after cerebral activation and the probability of voluntary locomotion, we plotted these data for WT, V1a KO, and V1a BLK mice. As shown in Fig. 7, the probability of voluntary locomotion was highly correlated with the suppression of baroreflex control of HR after cerebral activation. Thus, central V1a receptors might play an important role in facilitating voluntary locomotion after cerebral activation by suppressing baroreflex control of HR31).

Conclusions
We have developed a broadly available, remotely supervised exercise training system for middle-aged and older

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**Fig. 5** Typical examples of measurements of a wild-type control (WT) and a V1a receptor knockout (V1a KO) mouse in the free-moving state for 60 min. Top to bottom: activity counts, ratio of θ to δ wave band in EEG (θ/δ), cerebral blood flow (CBF), cross-correlation function (R(t)) between ΔMAP and ΔHR, ΔHR/ΔMAP, HR, and MAP. *R(t) was transformed to Z_R(t). θ/δ and Z_R(t) determined every 4 sec were averaged for a period from t - 40 to t + 40 sec (21 values) while moving t by 4 sec increments. These values were used to determine the average correlation coefficient and the correlation period (Fig. 6A), as well as the probability of locomotion after voluntary cerebral activation during the resting period (Fig. 6C). Fig. from ref31).
Fig. 6  θ/δ, CBF, Z_{R(t)}, and ΔHR/ΔMAP in freely moving wild-type control (WT) and V1a receptor knockout (V1a KO) mice. Means and SE bars are presented for 8 WT and 8 V1a KO mice.

A: The average correlation coefficient between θ/δ and Z_{R(t)} determined every 8 min during the resting period (upper). The positive correlation period between θ/δ and Z_{R(t)} presented as % of the resting period (lower). Data obtained during the resting period of ~520 min in each mouse were used for the analyses. The total measuring period for each mouse was 720 min. *Values were averaged after z transformation. ***Significant difference from WT mice, P < 0.001.

B: CBF, Z_{R(t)}, and ΔHR/ΔMAP in response to graded levels of θ/δ. Data used for the analyses were the same as in Fig. 6A. CBF was expressed as % of the value at the lowest θ/δ. ΔHR/ΔMAP was determined when R(t) between ΔHR and ΔMAP was significant regardless of whether negative or positive. *Significant differences from values at the lowest θ/δ, P < 0.05.

C: The probability of locomotion within 40 sec after an increase in θ/δ. ***Significant difference from WT mice, P < 0.001.

D: CBF, Z_{R(t)}, ΔHR/ΔMAP, HR, MAP, and activity counts before and after an increase in θ/δ. Because locomotion, when it occurred, started an average of 12 sec after an increase in θ/δ, a time of 12 sec after the increase was regarded as “0 sec”, and variables were presented in the range of ±240 sec from 0 sec. Data were derived according to 2 criteria: 1) θ/δ increased to a threshold of 2 SD during the total resting period; 2) the increase was preceded by a >240 sec resting period. CBF was expressed as in Fig. 6B. *Because some ΔHR/ΔMAP were lacking when R(t) was not significant, they were interpolated from adjacent values and means and SE for the 8 mice in each group were calculated as for other variables. Red portions indicate significant differences from values at -240 to -200 sec. Fig. from ref31.
people that enables individuals to perform long-term IWT effectively without going to a gym. With this system, we demonstrated that baseline BMI and gender for all subjects, as well as smoking and \textit{AVPR1A} polymorphisms for men, were independent determinants of adherence to the long-term IWT program. Because animal models have suggested that mice with impaired V1a receptor function had a markedly lower probability of locomotion after cerebral activation, blunted sensitivity of the V1a receptor might be involved in lower adherence to a long-term IWT program in humans by attenuating the pressor responses at the onset of voluntary exercise.

Conflict of Interests
The authors declare that there is no conflict of interests regarding the publication of this article.

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