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AGT M235T and ACE ID polymorphisms and exercise blood pressure in the HERITAGE Family Study

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Rankinen, Tuomo, Jacques Gagnon, Louis Pérusse, Yvon C. Chagnon, Treva Rice, Arthur S. Leon, James S. Skinner, Jack H. Wilmore, D. C. Rao, and Claude Bouchard. AGT M235T and ACE ID polymorphisms and exercise blood pressure in the HERITAGE Family Study. *Am J Physiol Heart Circ Physiol* 279: H368–H374, 2000.—We investigated the association between angiotensinogen (AGT) and angiotensin-converting enzyme (ACE) gene polymorphisms and exercise training responses of resting and exercise blood pressure (BP). BP at rest and during submaximal (50 watts) and maximal exercise tests was measured before and after 20 wk of endurance training in 476 sedentary normotensive Caucasian subjects from 99 families. AGT M235T and ACE insertion/deletion polymorphisms were typed with PCR-based methods. Men carrying the AGT MM and MT genotypes showed 3.7 ± 0.6 and 3.2 ± 0.5 (SE) mmHg reductions, respectively, in diastolic BP at 50 watts (DBP_{50}), whereas, in the TT homozygotes, the decrease was 0.4 ± 1.0 mmHg ($P = 0.016$ for trend, adjusted for age, body mass index, and baseline DBP_{50}). Men with the ACE DD genotype showed a slightly greater decrease in DBP_{50} (4.4 ± 0.6 mmHg) than the II and ID genotypes (2.8 ± 0.7 and 2.4 ± 0.5 mmHg, respectively, $P = 0.050$). Furthermore, a significant ($P = 0.022$) interaction effect between the AGT and ACE genes was noted for DBP_{50}; the AGT TT homozygotes carrying the ACE D allele showed no response to training. Men with the AGT TT genotype had greater ($P = 0.007$) diastolic BP (DBP) response to acute maximal exercise at baseline. However, the difference disappeared after the training period. No associations were found in women. These data suggest that, in men, the genetic variation in the AGT locus modifies the responsiveness of submaximal exercise DBP to endurance training, and interactions between the AGT and ACE loci can alter this response.

genetics; exercise training; family study; intervention study; angiotensinogen; angiotensin-converting enzyme

HYPERTENSION IS A major global public health problem and results in considerable personal and financial costs both to the patients and to society in general. Blood pressure and hypertension are generally thought to be multifactorial traits influenced by several environmental and genetic factors. The association between physical activity and blood pressure has been reported repeatedly. Prospective epidemiological studies have shown a lower risk of hypertension in physically active (32) and physically fit (4) men, and several intervention studies have reported a significant reduction in systolic and diastolic blood pressure (SBP and DBP, respectively) after moderate-intensity aerobic exercise training in hypertensive subjects (17). In addition, exaggerated blood pressure response to acute maximal exercise has been suggested to predict development of hypertension in normotensive subjects (1), although not all of the data agree with this hypothesis (30).

Genetic factors play a significant role in the regulation of blood pressure, and the estimates of heritability range from 25 to 65% depending on study design (48). The regulation of blood pressure is influenced by several biological mechanisms, and most of the family studies support a polygenic model of inheritance (20), with possibly some major gene effects (14, 33). The renin-angiotensin system (RAS) plays a major role in the regulation of blood pressure. ANG II, the active end-product of RAS, is a powerful vasoconstrictor, and it increases renal sodium and fluid reabsorption by stimulating the release of aldosterone. Among the individual components of RAS, the genes encoding angiotensinogen (AGT), the precursor of ANG I and II, and angiotensin-converting enzyme (ACE), which converts ANG I to ANG II, have received the most attention with regard to blood pressure regulation and hypertension. Several linkage and association studies support the role of AGT gene in the development of essential

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hypertension (10–12, 22, 23, 25, 28, 37) and pregnancy-induced hypertension (2, 47) and in the regulation of plasma AGT levels (5, 25). The variation in the ACE gene locus is a strong determinant of the plasma ACE activity (34, 41, 44), and some studies have reported that the insertion/deletion (I/D) polymorphism in intron 16 of the ACE gene is associated with increased risk of myocardial infarction (8, 43) and left ventricular hypertrophy (38), although not all studies have confirmed these findings (29). However, the results of the studies on the ACE gene polymorphism and hypertension have been mainly negative (24, 41).

Very few studies have investigated the role of genetic factors in the regulation of blood pressure response to exercise and other stressors. A segregation analysis study of 864 subjects from 81 pedigrees showed a mixed recessive model of transmission for the DBP response to a cycle ergometer exercise test, with a gene frequency of 0.21. The phenotypic variance explained by the major gene and polygenic effects were 33.6 and 16.6%, respectively (15). In a cohort of 148 monozygotic and 111 dizygotic twin pairs with a mean age of 11.1 yr, significant genetic effects were found for SBP and DBP measured during a cycle ergometer test (46). Furthermore, the results suggested that the genetic effects found at rest also influenced the exercise phenotypes, although the effects tended to decline with higher exercise intensities. Taken together, these findings suggest that the candidate genes influencing resting blood pressure could also play a role in the regulation of exercise blood pressure. Thus the purpose of the present study was to analyze the associations between the AGT and ACE gene markers and exercise training-induced responses in resting and exercise blood pressure in 476 sedentary normotensive Caucasian subjects. In addition, possible interaction effects between the AGT and ACE gene markers on blood pressure responses were investigated.

SUBJECTS AND METHODS

Subjects. The study cohort consists of 476 Caucasian subjects (229 males and 247 females) from 99 families. The study design and inclusion criteria have been described previously (7). To be eligible, the individuals were required to be in good health, i.e., free of diabetes, cardiovascular diseases, or other chronic diseases that would prevent their participation in an exercise training program. Subjects were also required to be sedentary at baseline, defined as not having engaged in regular physical activity over the previous 6 mo. Individuals with a resting SBP >159 mmHg and/or DBP >99 mmHg were excluded. The study protocol had been approved by each of the Institutional Review Boards of the HERITAGE Family Study research consortium. Written informed consent was obtained from each participant.

Exercise training program. The exercise intensity of the 20-wk training program was customized for each participant based on the heart rate-to-oxygen consumption ($\dot{V}O_2$) relationship measured at baseline. During the first 2 wk, the subjects trained at a heart rate corresponding to 55% of the baseline maximal oxygen consumption ($\dot{V}O_{2\,max}$) for 30 min per session. Duration and intensity of the training sessions were gradually increased to 50 min and 75% of the heart rate associated with baseline $\dot{V}O_{2\,max}$, which were then sustained for the last 6 wk. The average training frequency was three times per week, and all training was performed on cycle ergometers in the laboratory. Heart rate was monitored during all training sessions by a computerized cycle ergometer system, which adjusted ergometer resistance to maintain the target heart rate. All exercise sessions were supervised by trained exercise specialists.

Blood pressure. Both resting and exercise blood pressures were measured using Colin STBP-780 automated units (San Antonio, TX), and the recordings were confirmed by technicians wearing head phones. Resting blood pressure was measured on two separate days before 11:00 AM in the postabsorptive state. Subjects were asked not to use any caffeine-containing or tobacco products within 2 h before measurements. Measurements were done in a quiet room at neutral ambient temperature (24–25°C) with the lights dimmed. Subjects rested for 5 min before the initial measurement in a reclining chair with legs slightly elevated, and their backs were supported and reclined at about 45° from the ground. After the rest period, at least four blood pressure readings were taken at 2-min intervals between measurements. The first recording was automatically discarded, and three valid measurements were kept. Resting SBP and DBP were defined as the mean of all valid readings taken on both days, i.e., a maximum of six.

Submaximal exercise blood pressure was measured during two cycle ergometer tests, both before and after training in relative steady state for 8–12 min at a constant power output at 50 watts. Blood pressure was recorded two times during each test, and the mean of four readings was used for analyses. Similarly, two exercise tests to voluntary exhaustion were performed before and after training. Maximal blood pressure was measured 15 s after the cessation of exercise, and the mean of two measurements was used for analyses. The abbreviations SBP_{50} and DBP_{50} and SBP_{max} and DBP_{max} are used for submaximal and maximal exercise blood pressure phenotypes, respectively.

Other phenotypes. $\dot{V}O_2$ was measured during the maximal exercise test using a SensorMedics 2900 metabolic measurement cart (SensorMedics, Yorba Linda, CA). $\dot{V}O_{2\,max}$ was defined as the mean of the highest $\dot{V}O_2$ values determined on each of the two maximal tests before and after training or the highest of the two values if they differed by >5%. Height was measured to the nearest 0.1 cm with the subject standing erect on a flat surface, with heels, buttocks, and back pressed against the stadiometer, and with the head positioned in the Frankfort horizontal plane. Body mass was recorded to the nearest 100 grams using a balance scale with subjects clothed only in a light-weight bathing suit. Body mass index (BMI) was calculated by dividing body mass (kg) by height squared (m^2).

Genotype determinations. Genomic DNA was isolated from lymphoblastoid cell lines following a standard protocol (36). The M235T polymorphism of the AGT gene was typed with the PCR followed by digestion with *Tth*111 I. The PCR conditions were slightly modified from those previously described (35). To lower the PCR temperatures, the upstream and downstream primers were shortened by 7 and 5 bp, respectively. The primers used were 5′-CCG-TTT-GTG-CAG-GGC-CTG-3′ (upstream) and 5′-TGC-TGT-CCA-CAC-TGG-ACC-CC-3′ (downstream). The PCR was performed in standard buffer (Perkin-Elmer, Norwalk, CT), and each 20-μl PCR reaction contained 100 ng genomic DNA, 0.3 μmol/l of each primer, 200 μM of each dNTP, and 0.5 units *Taq* polymerase (Perkin-Elmer). The reactions were incubated at 95°C for 3 min, 62°C for 15 s, and 70°C for 1.0 min, followed by 40 cycles of 95°C for 15 s, annealing at 62°C for 15 s, and

extension at 70°C for 1.0 min, and finally one cycle of 72°C for 10 min, using a model 9600 Perkin-Elmer thermal cycler. The PCR product was digested with 5 units of *Tth*111 I (New England BioLabs, Missisauga, ON, Canada) at 65°C for 5 h. The resulting fragments were separated on 8% acrylamide gel and visualized under ultraviolet (UV) light after ethidium bromide staining.

The ACE I/D polymorphism was typed with a PCR-based method using three primers as previously described (16). The final reaction mixture of 15 μl contained 100 ng of genomic DNA, 3.0 mM $MgCl_2$, 200 μM of each dNTP, 300 nM of primers flanking the insertion sequence, 140 nM of insertion-specific primer, 4.7% DMSO, and 1.0 units of *Taq* polymerase (Pharmacia Biotech, Baie d'Urfé, Québec, Canada). The PCR protocol (model 9600 Perkin-Elmer thermal cycler) consisted of one cycle of 94°C for 3 min, 55°C for 1 min, and 72°C for 1 min, followed by 35 cycles of 94°C for 30 s, 55°C for 30 s, 72°C for 45 s, and finally one cycle of 72°C for 10 min. The PCR products were separated on 3.5% agarose gel and were visualized under UV light after ethidium bromide staining.

Statistical analyses. A χ^2-test was used to confirm that the observed genotype frequencies for each marker were in a Hardy-Weinberg equilibrium. Normality of the distributions was checked with the Shapiro-Wilk statistic of the Univariate procedure of the SAS statistical software package (SAS Institute, Cary, NC). The associations between blood pressure phenotypes and the genetic markers were tested with analysis of covariance using the general linear model procedure. Baseline phenotypes were adjusted for age and BMI, and training response phenotypes were adjusted for age, BMI, and baseline value of the given phenotype. Values are given as means ± SE.

Because of sexual dimorphism of the hemodynamic phenotypes (3, 13), the analyses were performed separately in men and women. All of the family members were included in the analyses. Although it is commonly believed that the relatedness of the subjects in family study cohorts may cause problems in association analyses, a recent simulation study (Province M, Rice T, and Rao DC, unpublished data) suggests that this is not the case. In the simulation study by Province et al., based on 50 nuclear families, the data were analyzed by four methods, with the least-squares method used in the present report being one of them; the other three methods treated dependencies in different ways. The results show that failure to incorporate dependencies did not induce any bias and that for traits with even moderate familial correlations not seen often in family studies (including the current one), ignoring the dependencies by using ANOVA performed quite well. The only negative impact was a small reduction in power compared with the methods that incorporated dependencies. The SE were slightly larger, but the type I error was unaffected. Given this, we do not believe that the dependencies or relatedness of the subjects in families causes any real problem in this type of analysis.

RESULTS

The baseline characteristics of the subjects are summarized in Table 1. As a result of the intervention, $\dot{V}O_{2\,max}$ increased from 3,029 ± 39 to 3,476 ± 42 ml/min (14.8%) in men and from 1,917 ± 23 to 2,261 ± 27 ml/min (17.9%) in women ($P < 0.0001$ for both sexes). In men, SBP_{50} and DBP_{50} decreased by 6.2 ± 0.7 and 3.1 ± 0.4 mmHg, respectively, and in women, the decreases were 7.6 ± 0.8 and 3.7 ± 0.4 mmHg, respectively ($P < 0.0001$ for all). SBP_{max} increased by 10.1 ± 1.2 and 7.7 ± 1.1 mmHg, and DBP_{max} decreased by 3.1 ± 0.9 and 2.8 ± 0.8 mmHg in men and women, respectively. The training program had no effect on resting blood pressure in this normotensive sample.

Table 1. *Characteristics of the subjects of the HERITAGE Family Study at baseline*

	Men	Women
Age, yr	36.4 ± 1.0	35.0 ± 0.9
Weight, kg	84.4 ± 1.1	67.2 ± 0.9
Height, cm	177.8 ± 0.4	163.8 ± 0.4
Body mass index, kg/m^2	26.7 ± 0.3	25.1 ± 0.3
Systolic blood pressure		
Resting	119.9 ± 0.7	112.7 ± 0.6
50 W	145.8 ± 1.2	142.6 ± 1.4
Maximal	206.7 ± 1.5	178.5 ± 1.5
Diastolic blood pressure		
Resting	68.0 ± 0.6	63.9 ± 0.4
50 W	72.0 ± 0.7	69.9 ± 0.7
Maximal	83.3 ± 0.9	79.7 ± 0.8

Values are means ± SE; n = 229 and 247 subjects for anthropometric phenotypes and resting blood pressure, 225 and 243 for submaximal exercise blood pressure, and 195 and 214 for maximal exercise blood pressure in men and women, respectively.

The frequencies of the M and T alleles of the AGT M235T marker were 0.60 and 0.40, respectively, whereas those of the I and D alleles of the ACE I/D marker were 0.47 and 0.53, respectively. The allele frequencies did not differ between men and women, and the observed genotype frequencies were in Hardy-Weinberg equilibrium. Neither baseline values nor training responses of resting blood pressure were associated with the AGT or ACE genotypes.

In men, the MM homozygotes and the MT heterozygotes of the AGT M235T marker showed significantly greater decreases in DBP_{50} (3.7 ± 0.6 and 3.2 ± 0.5 mmHg, respectively) than the TT homozygotes [0.4 ± 1.0 mmHg, $P = 0.016$, adjusted for age, BMI, and baseline DBP_{50} (Table 2)]. The ACE I/D marker also showed an association with the DBP_{50} training response. However, the significance was due to the difference between the DD homozygotes and the ID heterozygotes, whereas the training response of the II homozygotes was intermediate between the two other genotypes (Table 2). The M235T and the ACE I/D markers showed a significant interaction effect on the DBP_{50} training response ($P = 0.022$). In the AGT MM and MT genotypes, the decreases in DBP_{50} were seen regardless of the ACE I/D genotype, whereas in the TT homozygotes only the men homozygous for the ACE I allele showed a decrease in DBP_{50}. The TT homozygotes carrying the ACE D allele showed no training response in DBP_{50} (Fig. 1). The SBP_{50} training response was not associated with either of the gene markers. In women, both SBP_{50} and DBP_{50} training responses were similar across the AGT and the ACE genotypes.

At baseline, SBP_{max} did not differ between the AGT genotypes in men or in women. However, the men homozygous for the T allele showed significantly ($P = 0.007$, adjusted for age and BMI) higher DBP_{max}

Table 2. *Baseline values and training responses of systolic and diastolic blood pressure measured during steady-state submaximal exercise at 50 W, according to the AGT M235T and the ACE I/D genotypes in men and women*

	AGT				ACE			
	MM	MT	TT	*P*	II	ID	DD	*P*
Men								
n	84	112	30		54	101	69	
Systolic BP								
Baseline	147.6 ± 1.7	146.3 ± 1.5	142.5 ± 2.8	0.259	148.4 ± 2.1	145.9 ± 1.5	145.2 ± 1.9	0.506
Response	−5.6 ± 1.0	−6.8 ± 0.9	−5.6 ± 1.7	0.633	−5.7 ± 1.3	−5.8 ± 0.9	−7.1 ± 1.1	0.638
Diastolic BP								
Baseline	72.1 ± 1.0	70.7 ± 0.9	72.3 ± 1.7	0.554	72.4 ± 1.3	71.7 ± 0.9	70.5 ± 1.1	0.534
Response	−3.7 ± 0.6	−3.2 ± 0.5	−0.4 ± 1.0	0.016	−2.8 ± 0.7	−2.4 ± 0.5	−4.4 ± 0.6	0.050
Women								
n	78	117	47		59	117	66	
Systolic BP								
Baseline	143.6 ± 1.7	142.5 ± 1.4	142.5 ± 2.2	0.863	144.9 ± 2.0	141.0 ± 1.4	144.5 ± 1.9	0.161
Response	−7.5 ± 1.1	−7.4 ± 0.9	−9.1 ± 1.4	0.585	−9.7 ± 1.3	−6.8 ± 0.9	−7.6 ± 1.2	0.172
Diastolic BP								
Baseline	68.5 ± 0.9	70.1 ± 0.8	68.5 ± 1.2	0.306	70.3 ± 1.1	69.3 ± 0.8	68.4 ± 1.0	0.448
Response	−3.6 ± 0.7	−4.0 ± 0.6	−2.8 ± 0.9	0.513	−3.6 ± 0.8	−3.5 ± 0.6	−4.0 ± 0.8	0.852

Values are means ± SE; *n*, no. of subjects. AGT, angiotensinogen; ACE, angiotensin-converting enzyme; BP, blood pressure; I/D, insertion/deletion.

(89.7 ± 2.3 mmHg) than the MM homozygotes (80.8 ± 1.4 mmHg) and the MT heterozygotes (83.4 ± 1.2 mmHg). The association disappeared after the training period (Fig. 2), and the training effect on DBP_{max} tended to be greater ($P = 0.045$, adjusted for age and baseline BMI) in the TT genotype (−7.8 ± 2.4 mmHg) than in the MM (−0.7 ± 1.5 mmHg) and MT (−3.3 ± 1.3 mmHg) genotypes. However, the greater training response of the TT homozygotes was explained by the higher baseline DBP_{max} values ($P = 0.623$ after adjusting for age, baseline BMI, and baseline DBP_{max}). The association between DBP_{max} and the AGT genotype did not reach statistical significance in women. The ACE genotype was not associated with maximal exercise blood pressure in men or in women.

DISCUSSION

The novel finding of the present study is that the endurance training response of submaximal exercise DBP is associated with genetic variation in the AGT locus in previously sedentary men. The homozygotes for the T allele variation in codon 235 showed a significantly smaller training response than the MM homozygotes and the MT heterozygotes. In the sedentary state, men with the AGT TT genotype also had a markedly higher (8–10%) DBP response to acute maximal exercise than the other genotypes. Previously, it

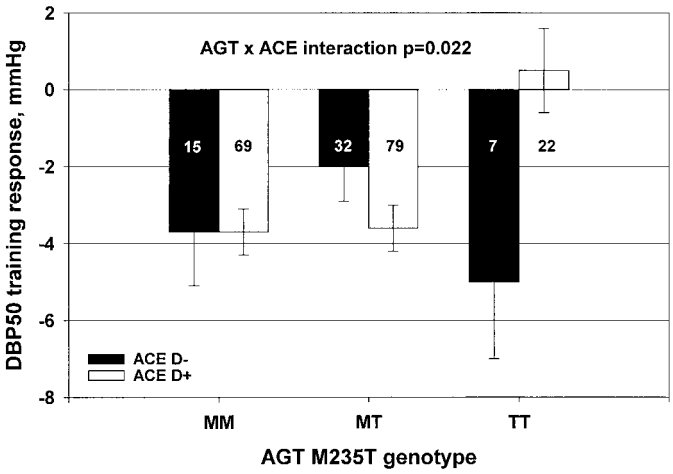

Fig. 1. Interaction between the angiotensinogen (AGT) M235T and the angiotensin-converting enzyme (ACE) insertion/deletion polymorphisms for the training response of diastolic blood pressure during submaximal exercise (DBP_{50}) in men of the HERITAGE Family Study. Values are means and SE, adjusted for age, baseline body mass index, and baseline DBP_{50}. Number of subjects in each of the genotype subgroups are shown.

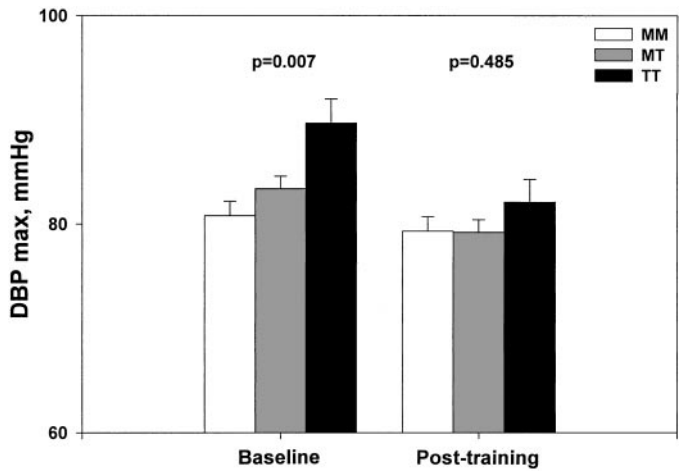

Fig. 2. Diastolic blood pressure at maximal exercise (DBP_{max}) before and after the 20-wk exercise training program according to the AGT M235T genotype in men of the HERITAGE Family Study. Values are means and SE, adjusted for age and baseline body mass index. Number of subjects as follows: MM genotype = 70; MT = 94; and TT = 26.

has been shown that the T allele was associated with elevated AGT levels (5, 25), essential hypertension (6, 10–12, 23, 25, 28) and pregnancy-induced hypertension (2, 47), and blunted renal hemodynamic response to ANG II infusion (21).

The existence of low and high responders to acute exercise and long-term exercise training has been recognized for a long time, but the mechanisms remain unknown. The identification of these mechanisms would not only help to understand the physiology of training responsiveness but would also enable the optimal utilization of endurance exercise in the primary and secondary prevention of common degenerative diseases, such as hypertension. These data from the HERITAGE Family Study suggest that DNA sequence variation in the AGT locus may explain some of the physiological interindividual variation in the responsiveness of DBP to endurance exercise training in normotensive men. Because our study cohort was normotensive but sedentary at baseline, it remains to be seen what kind of clinical relevance the AGT gene polymorphism has on blood pressure training effects in hypertensive subjects. Also, the exact mechanism behind the observed association needs further study. However, because peripheral vasodilation is one major mediator of the exercise-induced changes in blood pressure, and ANG II is a potent vasoconstrictor, it is possible that greater AGT levels in the TT homozygotes counteract exercise-induced vasodilation.

Although the DBP_{50} training response was blunted in the men carrying the TT genotype, endurance training alleviated their greater DBP response to acute maximal exercise observed in the sedentary state. This finding is potentially interesting because the risk of myocardial infarction triggered by heavy physical exertion is probably related to a sudden increase in hemodynamic load, and the risk seems to be particularly high in sedentary men (18, 31, 49). Moreover, it has been suggested that a marked blood pressure response to acute maximal exercise is associated with increased risk of developing hypertension at a later time (1), although the data are somewhat inconclusive (30). Thus it is possible that physical conditioning may be beneficial for the TT homozygotes by alleviating the abnormal hemodynamic responses to heavy physical exertion.

Despite the statistically significant association between the ACE I/D marker and the training response of the submaximal exercise DBP in men of the present study, the observation should be taken with caution. The significance was primarily due to the difference between the DD homozygotes and the DI heterozygotes, whereas the response of the II homozygotes did not differ from the other genotypes. A greater reduction in the resting DBP was recently reported in the ACE I allele carriers than in the DD homozygotes after a 9-mo exercise training program in a cohort of 18 obese hypertensive older men (19). However, the higher pretraining DBP levels in the I allele carriers was not taken into account in the statistical analyses. Moreover, the training response of resting SBP did not differ between the genotype groups. The plasma levels of ACE are strongly influenced by genetic factors, and the I/D polymorphism in intron 16 of the ACE gene seems to be a marker of a mutation responsible for most of the genetic variation in the plasma ACE levels. However, despite a strong effect on the plasma ACE level, the results from studies on the ACE polymorphism and hypertension/blood pressure have been primarily negative. This controversy could be explained by the fact that the effects of ACE on blood pressure are usually seen only when its activity is drastically reduced (9, 39). For example, in gene-targeted mice, only the animals completely lacking the ACE gene showed reduction in blood pressure levels (42). Those carrying one or more copies of the gene had no change in blood pressure despite increasing ACE levels (27, 42). On the other hand, similar experiments with the AGT gene induced a linear increase in AGT, ANG II, and blood pressure levels as a function of the number of the AGT gene copies (26, 39, 40).

Although the effect of the ACE I/D polymorphism per se on blood pressure may be marginal, the associations may be considerably stronger when the ACE substrate levels are elevated. For example, mice with only one copy of the ACE gene respond to ANG I and bradykinin infusions in a physiologically predictable manner, even though the resting blood pressure of the animals is normal (42). Moreover, the men with the ACE DD genotype show a greater pressor response to ANG I infusion than the men with the other ACE genotypes (45). Along these lines, we tested here the hypothesis that the combination of the AGT and the ACE genotypes, which have been reported to be associated with elevated gene product levels, is associated with an impaired blood pressure training response. Indeed, men carrying both the AGT TT genotype and the ACE D allele showed no change in submaximal exercise DBP, whereas a clear reduction was seen in the other genotype combinations. This observation is in line with results from the Framingham Heart Study subcohort of the National Heart, Lung, and Blood Institute Family Heart Study showing that the increased risk of hypertension associated with the AGT TT genotype is further elevated in the subjects carrying both the AGT TT and the ACE DD genotypes (6). These findings suggest that elevated ACE activity may have physiological effects when the substrate levels also are increased.

In conclusion, these HERITAGE Family Study data suggest that, in normotensive sedentary Caucasian men, the genetic variation in the AGT locus modifies the responsiveness of exercise DBP to endurance training. One can therefore speculate that men with a genetic predisposition to both high AGT and ACE levels are resistant to training-induced reductions in submaximal exercise DBP.

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