REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	2002	Editorial-Physiol. Genomics

4. TITLE AND SUBTITLE
Exercise genetics and blood pressure: focus on physical exercise and blood pressure with reference to the angiotensinogen M235T polymorphism and on angiotensinogen M235T polymorphism associates with exercise hemodynamics in postmenopausal women

5. FUNDING NUMBERS

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8. PERFORMING ORGANIZATION REPORT NUMBER
M02-46

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Same as #7 above

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Distribution is unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*
Blood pressure is a complex trait that is influenced by a number of hereditary, enviornmental, and culturally transmissible factors. Genetic factors are estimated to account for about 30% of the variance in blood pressure in adult populations, and it appears likely that this hereditary contribution is polygenic in nature. Furthermore, there is evidence that the genetic factors contributing to resting blood pressure also affect blood pressur during exercise.

14. SUBJECT TERMS
angiotensinogen, polymorphism, polygenic

15. NUMBER OF PAGES
3

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unlimited	Unlimited	Unlimited	Unlimited

tapraid4/h7-phys/h7-phys/h71102/h70235d02o | sweigarl | S=6 | 7/10/02 | 13:18 | MS: PG0081-2 | lni: 10e/mg\ejp | Input-kjp(kjp)

Physiol Genomics 10: 000–000, 2002;
10.1152/physiolgenomics.00081.2002.

editorial focus

Exercise, genetics, and blood pressure: Focus on "Physical exercise and blood pressure with reference to the angiotensinogen M235T polymorphism" and on "Angiotensinogen M235T polymorphism associates with exercise hemodynamics in postmenopausal women"

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BLOOD PRESSURE is a complex trait that is influenced by a number of hereditary, environmental, and culturally
AQ: 2 transmissible factors (3). Genetic factors are estimated to account for ~30% of the variance in blood pressure in adult populations, and it appears likely that this hereditary contribution is polygenic in nature (3, 6, 18). Furthermore, there is evidence that the genetic factors contributing to resting blood pressure also affect blood
AQ: 3 pressure during exercise (19).

Angiotensinogen (AGT) has attracted attention as a candidate gene contributing to blood pressure.
AQ: 4 AGT is a pro-hormone produced by the liver (and other tissues) that is converted to angiotensin I by renin. In turn, angiotensin I is converted to its active form, angiotensin II, by angiotensin converting enzyme (ACE). Angiotensin II raises systemic blood pressure by serving both as a vasoconstrictor and a stimulus (by way of aldosterone) for sodium retention by the kidney. Several studies have implicated angiotensinogen polymorphisms in the genetics of hypertension in adults and include reports of linkage (1, 4, 5, 10) and association (5, 10). By contrast, with the exception of the angiotensin type 1 receptor gene, for which both association with (2) and linkage to (14) blood pressure have been reported, there is little evidence to suggest an independent role for other components of the renin-angiotensin system in the genetics of human blood pressure (3, 8, 9).

Two papers in this release of *Physiological Genomics* (Refs. 12 and 17; see pages **XX** and **XX**, respectively, in this release) examine the effect of a common polymor- AQ: 5
phism in the angiotensinogen gene on blood pressure phenotypes. The polymorphism in question (M235T) involves a T-for-C substitution at nucleotide 704, which leads to a methionine-for-threonine substitution at codon 235. This polymorphism is an attractive candidate for study because of its high prevalence [with allele frequencies in the population of 0.4 and 0.6, respectively, for the T and M variants in whites (6)] and because of evidence implicating angiotensinogen in the genetics of hypertension (as noted). Furthermore, it has been reported that presence of the T allele correlates with slightly increased plasma angiotensinogen levels (reviewed in Ref. 6). However, the phenotypic effects of the M235T polymorphism may not be due to the amino acid substitution itself, but rather to a functionally significant A-6G polymorphism AQ: 6
in the AGT gene promoter that is in linkage disequilibrium with the M235T polymorphism (reviewed in Ref. 6).

The first study, by McCole and colleagues (12), examines the role of the AGT M235T polymorphism in the cardiovascular responses to exercise, in a cohort of postmenopausal women. Because of the known effect of training on blood pressure, the authors were careful to stratify their analysis by level of habitual activity in this cross-sectional study. Among their findings was a significant effect of AGT genotype on blood pressure during exercise that was dependent on level of habitual activity. In the sedentary women, but not in other subgroups, there was a statistically significant effect of AGT genotype on maximal systolic blood pressure during exercise, with subjects homozygous for the M allele

Article published online before print. See web site for date of publication (http://physiolgenomics.physiology.org).
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(who would be expected to have the lowest levels of plasma angiotensinogen at baseline) exhibiting significantly lower maximal systolic blood pressures during exercise than subjects who were homozygous for the T allele or who were heterozygous. Importantly, the genotype-specific differences in the blood pressure during exercise in the susceptible group were quite large, with the maximum systolic pressure achieved averaging between 195 and 200 mmHg in the two sedentary women homozygous for the T allele and about 150 mmHg in the six sedentary women homozygous for the M allele. In middle-aged men, cardiovascular mortality risk has been reported to increase with rising systolic blood pressure during exercise (7, 13), even after adjustment for habitual activity (7). If a similar epidemiological association exists in postmenopausal women, then differences in exercise systolic pressure of the magnitude reported by McCole et al., if confirmed, may be of clinical importance. However, the results of this study must be interpreted cautiously in light of the relatively small number of subjects (as the authors point out) and the well-known hazards of subgroup analysis. A larger, confirmatory, and longitudinal follow-up study is warranted.

The second study, by Rauramaa et al. (17), examines the effect of exercise and AGT genotype on age-related gains in resting blood pressure in a cohort of middle-aged men in Finland. Subjects were randomized to no intervention or an exercise program of moderate intensity (resulting in an estimated energy expenditure of 1,300 kcal/wk, the equivalent of a 70-kg man walking a total of 3.7 h/wk at a 15 min/mile pace). The authors achieved excellent compliance with the study program and were able to obtain follow-up data on 120 of their 140 randomized subjects over a 6-yr period. Their results revealed a significant interaction between physical activity and AGT genotype. Specifically, subjects homozygous for the M allele who engaged in exercise did not demonstrate the age-related gains in resting systolic blood pressure that occurred in individuals of other AGT genotypes (heterozygotes and individuals homozygous for the T allele) who exercised and in individuals of the same AGT genotype (homozygous for the M allele) who belonged to the control (no intervention) group. Furthermore, subjects homozygous for the M allele who exercised experienced a decrease in resting diastolic blood pressure over time, whereas subjects homozygous for this allele in the control group exhibited a gain in resting diastolic blood pressure (a difference that was statistically significant). By contrast, among heterozygous subjects and those homozygous for the T allele, there were no significant differences in the changes in resting diastolic blood pressure over time between individuals who exercised and those in the control group. The observation that AGT genotype influences the effect of aerobic training on longitudinal changes in resting blood pressure over the course of several years is novel and may potentially be of clinical value, especially if confirmed in larger cohorts and other ethnic groups.

Table 1. *Association studies of M235T AGT genotype, blood pressure, and exercise*

Subjects	Mean Age, yr	*N*	Study Design	Blood Pressure Phenotypes	Findings	Interaction with Training or Habitual Activity?	Ref.
Adult white males	22 and 45 (bimodal)	25	Cross-sectional; untrained subjects	Resting and submaximal exercise BP	Lower rise in DBP with exercise in TT males	NA	11
Adult white males and females	36	229 males, 247 females	Longitudinal (20 wk)	Resting and maximal exercise BP before and after a 20-wk training program	Lower maximal exercise DBP in MM and MT males before training but not after training	Yes	15
Adult white males and females (parents and offspring)	53 and 25 (bimodal)	257 males, 265 females	Cross-sectional; untrained subjects	Resting and submaximal exercise BP	Lower resting DBP, resting SBP, and exercise DBP in MM females with fat mass ≥24 kg but not in leaner women	NA	16
Postmenopausal females	64	61	Cross-sectional; stratified by habitual level of activity	Resting, submaximal, and maximal exercise BP	Lower submaximal and maximal SBP in sedentary MM women but not in trained women	Yes	12
Adult white males	57	120	Longitudinal (6 yr); randomized to aerobic exercise vs. habitual activity	Resting BP before and after training, over a 6-yr period	Smaller age-related gains in SBP in MM males who exercised; decreases in DBP in MM males who exercised	Yes	17

AGT, angiotensinogen; DBP, diastolic blood pressure; SBP, systolic blood pressure.

The results of these and other studies suggest that the angiotensinogen M235T polymorphism influences blood pressure but that the effect is highly sensitive to environmental context (Table 1). In four of these five studies, being homozygous for the M allele correlated with lower blood pressure (systolic, diastolic, or both) in at least one subgroup, although the specific subgroup and conditions in which the effect was observed did vary somewhat from study to study (Table 1). Importantly, the effect of AGT genotype on blood pressure appears to be affected by physical activity, but here again, the precise nature of the interaction appears to be complex. Two studies (12, 15) found that physical training or habitual activity can mask the effects of AGT genotype on blood pressure during exercise, whereas another (17) found that subjects homozygous for the M allele derive a substantial benefit in resting blood pressure from moderate training that was not seen in heterozygotes or individuals homozygous for the T allele. Such apparent discrepancies are not necessarily surprising. As shown in Table 1, there were substantial methodological differences in the studies that have examined the relationship between AGT genotype, exercise, and blood pressure. As noted, blood pressure is a complex trait that is influenced by a number of genetic and nongenetic factors. Thus the effects of unmeasured genotypes and other confounding traits (such as salt intake, alcohol use, etc.) might significantly influence the effect of AGT in any given study. For example, AGT has been found to interact significantly with the angiotensin converting enzyme insertion/deletion (ACE I/D) polymorphism (15) in the responses of exercise blood pressure to training in men and with body fat mass (in women) with respect to both resting and exercise diastolic blood pressure (16).

Much remains to be learned about the role that this and other candidate genes play in blood pressure in adults. The studies presented here illustrate how genetic polymorphisms that individually account for a small part of the variance in blood pressure in the population at large might nevertheless produce potentially important effects in select subgroups. Further understanding of these genetic effects, and how they interact with environmental factors, may some day enable physicians to use genetic information to tailor preventive and therapeutic interventions to individual characteristics.

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