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THE ASSOCIATION BETWEEN ACE GENE VARIATION AND AEROBIC CAPACITY IN WINTER ENDURANCE DISCIPLINES

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AUTHORS: Orysiak J.[1], Zmijewski P.[2], Klusiewicz A.[2], Kaliszewski P.[3], Malczewska-Lenczowska J.[1], Gajewski J.[4], Pokrywka A.[3]

[1] Department of Nutrition Physiology, Institute of Sport, Warsaw, Poland
[2] Department of Physiology, Institute of Sport, Warsaw, Poland
[3] Department of Anti-Doping Research, Institute of Sport, Warsaw, Poland
[4] Department of Biomechanics, Institute of Sport, Warsaw, Poland

Reprint request to:
Joanna Orysiak
Department of Nutrition Physiology
Institute of Sport,
Trylogii 2/16,
01-982,Warsaw, Poland
e-mail: joanna.orysiak@insp.waw.pl

ABSTRACT: The aim of the study was to examine the possible relationship between I/D polymorphism of ACE gene and selected indices of aerobic capacity among male and female athletes practising winter endurance sports. Sixty-six well-trained athletes (female n=26, male n=40), aged 18.4 ± 2.8 years, representing winter endurance sports (cross-country skiing, n=48; biathlon, n=8; Nordic combined, n=10) participated in the study. Genotyping for ACE I/D polymorphism was performed using polymerase chain reaction. Maximal oxygen consumption (VO_2max), maximal running velocity (V_{max}) and running velocity at anaerobic threshold (V_{AT4}) were determined in an incremental test to volitional exhaustion on a motorized treadmill. The ACE genotype had no significant effect on absolute VO_2max, relative VO_2max (divided by body mass or fat free body mass), V_{AT4} or V_{max}. No interaction effect of gender x ACE genotype was found for each of the examined aerobic capacity indices. ACE gene variation was not found to be a determinant of aerobic capacity in either female or male Polish, well-trained endurance athletes participating in winter sports.

KEY WORDS: genetic polymorphism, oxygen consumption, physical endurance, anaerobic threshold, athletes

INTRODUCTION

It is believed that maximal oxygen consumption (VO_2max), the load at 'lactate threshold' and mechanical efficiency are the main factors determining results in endurance sports [15]. The genetic component of VO_2max has been estimated to be about 50% [7], but the role of genetics in the attainment of world class status and elite athletic performance in those kinds of exercise is not well known yet. About 200 genes are thought to have a potential impact on physical performance and further ones are widely investigated [3,5,13]. I/D polymorphism in the angiotensin converting enzyme (ACE) gene has been the most widely studied genetic variant in terms of performance-related traits and achieving elite athlete status. In general, the I allele has been associated with endurance performance and the D allele with strength- and power-orientated events [1,18]. However, not all studies support this association between the I or D allele and physical performance [16,31].

Selected studies were focussed on determining properties of ACE I/D polymorphism, which could be related to physical performance. The ACE I/D polymorphism could be associated with athletic performance via local effects on skeletal muscle [14]. The findings of Montgomery et al. [23] suggest that significantly greater improvements in muscle endurance are related to the I allele. Moreover, Williams et al. [32] demonstrated an association between the I allele and efficiency of muscle contraction. The I allele also seems to be related to an increased proportion of type I (slow) fibres in the vastus lateralis muscle in untrained subjects [33] and muscle hypertrophic effects of increased angiotensin II [14]. Some studies have linked ACE genotype with cardiac diseases. Fairly well established is the association between ACE I/D polymorphism and left ventricular growth in response to exercise [28].

The physiological characteristics of elite cross-country skiers are a result of both genetics and adaptation to rigorous multiyear, year-round training programmes [9]. The aerobic capacity and upper body anaerobic power seem to be the most important physiological factors of success in winter endurance sports [20]. The previous studies have demonstrated associations of VO_2max and mechanical efficiency with ACE genotype in a non-athletic females [11]. It seems to be upmost of importance to determine effects of ACE genotype on aerobic capacity in competitive athletes. Thus, the aim of the study

was to examine the possible relationship between ACE gene variation and selected indices of aerobic capacity among male and female athletes practising winter endurance sports.

MATERIALS AND METHODS

Participants. Sixty-six well-trained athletes (female n=26, male n=40), who represented winter endurance sports (cross-country skiing, n=48; biathlon, n=8; Nordic combined, n=10) volunteered for the study. The subjects were medically examined and healthy. The athletes were Caucasian. They represented the highest national level of ability; most of them were medallists of national championships in their age category. Their characteristics are presented in Table 1. The programme of the study was approved by the Ethical Research Committee at the Institute of Sport in Warsaw and written informed consent obtained from individuals.

TABLE 1. AGE, TRAINING EXPERIENCE AND SOMATIC CHARACTERISTICS OF EXAMINED FEMALE AND MALE ATHLETES

Variable	Female (n=26)	Male (n=40)	Statistical significance
Age (years)	19.4 ± 3.2	17.8 ± 2.4	ns
Body mass (kg)	59.7 ± 5.8	66.2 ± 9.9	p<0.001
Body height (cm)	167.1 ± 5.0	175.6 ± 9.1	p<0.001
BMI ($kg \cdot m^{-2}$)	21.4 ± 1.7	21.3 ± 1.9	ns
Training experience (years)	7.3 ± 2.7	6.8 ± 2.8	ns
Fat mass (%)	22.4 ± 4.0	10.6 ± 1.9	p<0.001
Fat free mass (%)	77.6 ± 4.0	89.4 ± 1.9	p<0.001

ACE gene variation determination

Venous blood was taken from the volunteers and collected in EDTA tubes and stored at -20°C. DNA from blood samples was extracted using a Blood Mini kit (A&A Biotechnology, Poland) according to the manufacturer's instructions.

The genotyping was performed using two different methods for verification of results. The ACE I/D polymorphism was first determined using a primer pair described by McCauley [21]. Secondly, the results were verified using a primer pair described by Lindpaintner [17]. The PCR reaction conditions are shown in Table 2. The PCR product was analysed by electrophoresis at 80 V for 60 min using 1.5% agarose gel stained with SYBR® Safe DNA gel stain at 10,000X concentration in DMSO (Invitrogen, USA).

Anthropometric and physical performance measurement

Anthropometric measurements comprising assessment of body height, body mass and skinfold thickness at four sites (biceps, triceps, subscapular and suprailiac) were performed by an experienced anthropometrist. The percentage of body fat was calculated from these measurements using the equation of Durnin and Womersley [8]. Fat free mass was calculated from the difference between the total body mass (kg) and body fat mass (kg).

The absolute and relative VO_2max, running velocity at anaerobic threshold (V_{AT4}), and duration of exercise (T) were considered as indices of aerobic capacity. These indices were commonly used in sports diagnostics and training optimising [2,4,22]

The measurement was conducted during a preparatory period, at ambient temperature of 19-22°C, in the forenoon, 1-3 hours after a standardized breakfast. Subjects performed an incremental test to volitional exhaustion on a motorized treadmill (HP Cosmos, Germany). The test started with 8 $km \cdot h^{-1}$ for female or 10 $km \cdot h^{-1}$ for male subjects in juniors and with 10 $km \cdot h^{-1}$ or 12 $km \cdot h^{-1}$ respectively in senior athletes. For each subject the initial slope of the treadmill was 1.5%. The speed was increased every 5 min by 2 $km \cdot h^{-1}$ with 1-minute intervals (passive breaks) between stages. After five stages the speed was not increased, but inclination of the treadmill was increased by 1.5% every 1 min. Exercise test duration ranged from 12 to 15 minutes. V_{AT4} was determined by interpolation of the values at 4 $mmol \cdot L^{-1}$ blood lactate concentration [19].

Oxygen uptake was measured using an open circuit breath-by-breath automated gas analysis system (Cortex, Metalyzer, 3B-R2, Germany). The highest value of oxygen uptake registered within 60 s during the test was regarded as the VO_2max. Blood samples were

TABLE 2. THE POLYMERASE CHAIN REACTION (PCR) CONDITIONS

Method	Forward Primer (5'-3')	Reverse Primer (5'-3')	PCR reaction conditions		
McCauley et al. [21]	CTGGAGACCACT CCCATCCTTTCT	GATGTGGCCATCACAT TCGTCAGAT	Denaturation 95°C for 5 min	Annealing 30 cycles of 95°C for 1 min, 58°C for 1 min, 72°C for 2 min	Extension 72°C for 10 min
Lindpaintner et al. [17]	GCCCTGCAGGTGT CTGCAGCATGT	GGATGGCTCTCCCCG CCTTGTCTC	Denaturation 95°C for 5 min	Annealing 35 cycles of 94°C for 0.5 min, 58°C for 0.75 min, 72°C for 0.75 min	Extension 72°C for 7 min

TABLE 3. FREQUENCY OF ACE INSERTION (I) AND DELETION (D) ALLELES AND GENOTYPES IN EXAMINED FEMALE AND MALE ATHLETES

	Female (n=26)			Male (n=40)			All (n=66)			Allele (n=66)	
	II	ID	DD	II	ID	DD	II	ID	DD	I	D
Subjects	7	13	6	10	17	13	17	30*	19	64	68
	(0.27)	(0.50)	(0.23)	(0.17)	(0.50)	(0.33)	(0.21)	(0.50)	(0.29)	(0.46)	(0.54)

Note: II, ID, DD – ACE genotype; fractions in parentheses; * genotype frequency significantly different from ACE II or ACE DD; $p<0.02$

collected from the fingertip during the 4 minutes after exercise and the blood lactate concentration was determined using the LP400 photometer (Dr Lange, Germany).

Statistical analysis

Two-way analysis of variance (factors: gender and ACE I/D polymorphism) was used to assess mean differences. For variables not normally distributed, Kruskal-Wallis test and Mann-Whitney U test for post hoc analysis were used. Data are presented as mean ± standard deviation (SD). The significance of differences in allele frequencies was estimated using the χ^2 test. Statistical significance was set at $P < 0.05$. All calculations were done with SPSS version 17 (SPSS Inc.,USA).

RESULTS

No differences were found in the ACE genotype frequencies between female and male athletes (Table 3). Also, the allele frequency was statistically similar. The distribution of ACE genotype was in Hardy-Weinberg equilibrium.

The examined male and female athletes had similar age, training experience and body mass index (BMI). However, mean body mass (BM), body height and fat free body mass (FFM) (%, kg) were significantly higher ($P<0.001$) in male than in female athletes (Table 4). Age, training experience and somatic characteristics other than body composition were independent of ACE genotype. In male athletes there was no significant relation between body composition and ACE genotype. In female athletes, results of the Kruskal-Wallis test showed a significant relationship between percentage of FFM and ACE genotype, although absolute fat free body mass was independent of ACE genotype. Those females who had the DD genotype tended to have a lower percentage of FFM than those with the II genotype ($U=8.00$, $P<0.07$) (Table 4).

The ACE genotype had no significant effect either on absolute VO_2max or on relative VO_2max (divided by BM or FFM). No relationship was found between ACE genotype and V_{AT4} or V_{max} (Table 5).

The mean V_{max}, V_{AT4}, as well as absolute and relative VO_2max were significantly higher in male than in female subjects. Only VO_2max related to FFM and did not differ in relation to gender. No interaction effect of gender x ACE genotype was found for each of the examined aerobic capacity indices.

TABLE 4. MEAN FAT BODY MASS (FM) AND FAT FREE BODY MASS (FFM) IN FEMALE AND MALE ATHLETES IN RELATION TO ACE GENOTYPE VARIATION

Gender	ACE genotype	FM (%)	FFM (%)	FFM (kg)
Female	II	20.5 ± 1.6 *	79.5 ± 1.6 *	47.7 ± 5.2
	ID	22.5 ± 3.0	77.5 ± 3.0	46.4 ± 3.5
	DD	25.4 ± 5.5	74.6 ± 5.5	44.7 ± 5.4
Male	II	11.0 ± 1.6	89.0 ± 1.6	60.1 ± 10.2
	ID	10.5 ± 2.2	89.5 ± 2.2	59.4 ± 9.4
	DD	10.6 ± 2.2	89.4 ± 2.2	58.3 ± 8.4

Note: II, ID, DD – ACE genotype; * - significantly different than DD at $P<0.05$.

DISCUSSION

Taking into account the relationship between ACE genotype and effects of its expression, the II variation of the ACE gene could be desirable in endurance athletes, including cross-country skiers, biathletes, etc. It was expected that well-trained athletes practising winter endurance disciplines, with the II genotype of the ACE gene, would be

TABLE 5. AEROBIC CAPACITY INDICES OF DIFFERENT ACE GENOTYPES IN EXAMINED FEMALE AND MALE ATHLETES

Variables	Female			Male			Effects		
	II	ID	DD	II	ID	DD	Gender	Genotype	Interaction
Vmax ($Km \cdot h^{-1}$)	14.9±1.5	14.7±1.1	14.9±1.7	16.6±1.2	16.7±1.4	16.4±1.5	p<0.001	ns	ns
VO_2max ($L \cdot min^{-1}$)	3.4±0.3	3.3±0.3	3.2±0.4	4.3±1.0	4.3±1.0	4.2±1.0	p<0.001	ns	ns
VO_2max ($mL \cdot Kg^{-1} \cdot min^{-1}$)	56.3±5.3	55.3±3.4	54.0±10.1	62.9±6.8	64.3±6.7	63.6±7.9	p<0.001	ns	ns
VO_2max ($mL \cdot KgFFM^{-1} \cdot min^{-1}$)	70.5±5.5	71.0± 4.6	71.7±9.0	70.4±7.4	71.7±6.9	71.0±8.5	ns	ns	ns
V_{AT4} ($Km \cdot h^{-1}$)	11.8±1.2	12.3±1.1	11.5±2.2	12.8±1.6	13.5±1.4	13.2±1.5	p<0.001	ns	ns

Note: II, ID, DD – ACE genotype; Vmax – maximal running speed in test protocol; VO_2max – maximal oxygen uptake; VAT4 – running speed at anaerobic threshold; FFM – fat free body mass

characterized by significantly greater aerobic capacity indices, especially VO_2max, than those with ID or DD genotypes.

Many previous studies have suggested that the I allele favours endurance performance [1,24], so it was expected that in this study this relationship would be confirmed. In this study, the frequency of ACE genotypes and alleles was similar to that observed in the Polish male athletes [6]. These results are also in accordance with the results from other studies, where no association was found between ACE gene variation and endurance performance in skiers [24, 27,30]. There could be several reasons why the mentioned studies failed to find a relationship between allele I and physical performance. One of them was the mixed cohort of athletes from various sports with a small contribution of endurance athletes. Another reason could be the inclusion of elite and non-elite athletes in the analysis. Moreover, the differences in determining the character of exercise and in categorising athletes could also have introduced errors into the analysis.

The results of this analysis showed that there was no significant effect of ACE genotype on absolute or relative VO_2max. Because of the lack of somatic homogeneity in the examined group of athletes, an analysis of the relationship between ACE genotype and VO_2max divided by FFM was done. Also in this case, no association between ACE genotype and VO_2max divided by FFM was observed. Analysis of other indices (V_{AT4}, V_{max}) leads us to reject the hypothesis concerning a relationship between ACE genotype and aerobic capacity and performance in endurance exercise.

Results of this study are in accordance with previous research that has reported no association between ACE ID polymorphism and VO_2max in samples of 724 sedentary humans and 192 elite endurance athletes [27]. Goh et al., who demonstrated a relationship between ACE II genotype and VO_2max, considered inclusion in the study of athletes of different sporting disciplines as its limitation [10]. In some studies, an association between ACE II genotype and VO_2max was found in Asian athletes but not in Polish ones [12]. On the other hand, another study conducted in Asian athletes [34] demonstrated a relationship between ACE DD genotype and VO_2max. The influence of ethnic origin on the physiological mechanisms mediated by the ACE gene, which could be responsible for aerobic capacity, remains unknown.

The results presented so far may be controversial due to the sample sizes, study designs, and phenotype measurements. The effect of sample size has been observed in the studies dealing with the associations between the ACE ID polymorphism and various cardiovascular disorders [29]. The studies based on large numbers of subjects have generally failed to confirm the positive findings arising from smaller cohorts. Another reason for the lack of a relationship between ACE polymorphism and VO_2max indices could be the multifactorial influence of many genetic and environmental factors on VO_2max. The results of this study, as well as the findings of a number of current papers, demonstrated a rather minor role of ACE gene polymorphism in endurance performance. Also, this study has some limitations which should be taken into consideration. Firstly, there is an unknown range of maturity within the study group, which could mask gene-related effects on aerobic performance. Nevertheless, the results of selected studies suggest that there is a small decrease in VO_2max related to body mass during early adolescence, but remaining steady during later adolescence [25]. Much more significant changes during puberty were noted in absolute VO_2max, anaerobic power and capacity or strength [25].

Although clear gender differences in relative VO_2max and V_{AT4} were found, no interaction effect of gender x ACE genotype was found for the examined indices of aerobic capacity.

CONCLUSIONS

I/D polymorphism of ACE gene was not found to be a determinant of aerobic capacity, either in female or in male Polish, well-trained endurance athletes participating in winter sports. It is more likely that several gene loci, each with a small but significant contribution, are responsible for this genetic component. The data on the effects of ACE gene variation on various cardiovascular phenotypes in general are far from clear.

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