Role of Renin-Angiotensin System in the Formation of Emotional State in Humans

V. A. Shleptsova, N. V. Malyuchenko*, M. A. Kulikova*, M. A. Timofeeva*, J. V. Shchegolkova*, A. M. Vedjakov, O. V. Sysoeva***, and A. G. Tonevitsky****

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We studied the effect of angiotensin-converting enzyme gene polymorphism on human emotional state in humans (189 athletes and 212 volunteers not engaged in sport activity). The distribution of angiotensin-converting enzyme genotypes was estimated. The dependence of aggression on age, sex, and professional activity was evaluated. This polymorphism was associated with physical aggression in female synchronized swimmers. Physical aggression in II genotype carriers was lower than in D allele carriers. Our results indicate that individual differences in aggression depend on professional activity and are genetically determined.

Key Words: *renin-angiotensin system; genetic polymorphism; angiotensin-converting enzyme; aggression*

Components of the renin-angiotensin system (RAS) are located in the basal ganglia, cortex, hypothalamus, thalamus, forebrain, substantia nigra, brainstem, cerebellum, and pineal gland [9]. Cerebral and peripheral RAS are not interrelated, since their components cannot cross the blood-brain barrier [9,12]. The blood-brain barrier is absent in the subfornical organ. Hence, the interaction between the cerebral and peripheral RAS occurs in these brain regions [12]. Angiotensin II (AT-II) is an important and most active component of RAS. AT-II plays a regulatory role in various parts of the central nervous system and modulates function of neurotransmitters (serotonin, dopamine, norepinephrine, and epinephrine) and hypothalamic-pituitary-adrenal system (secretion of vasopressin and stimulation of the thirst center and baroreflex). AT-II exhibits antidepressant and anxiolytic properties, which manifests in a decrease in anxiety, fear, and emotional strain [7]. However, some authors report that AT-II increases fear. Previous studies showed that RAS components have a modulatory effect on human behavior and mood [2]. For example, angiotensin-converting enzyme (ACE) gene polymorphism is associated with exploratory activity. Individuals with high activity of this enzyme exhibit higher novelty seeking score [10]. RAS components have a regulatory role in memory, learning, and stress response. Published data show that AT-II inhibits memory formation via specific AT receptors [12]. ACE plays a role in degradation of substance P, which is involved in the development of mental disorders and mood disturbances [3].

AT-II concentration depends on activity of ACE, which converts AT-I into AT-II. ACE activity is associated with insertion-deletion (I/D) polymorphism of the ACE gene. This type of genetic polymorphism is characterized by the absence or presence of 287 b.p. in intron 16 in the short arm of chromosome 17. Allele I is associated with low

Department of Fundamental Medicine, M. V. Lomonosov Moscow State University; *Department of Biology, M. V. Lomonosov Moscow State University; **All-Russian Institute of Physical Training and Sport; ***Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow, Russia. ***Address for correspondence:*** varja.shlepzova@gmail.com. V. A. Shleptsova

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and allele D with high enzyme activity [6]. These data suggest that ACE polymorphism affects some personality traits. Here we studied association of ACE I/D polymorphisms with manifestations of aggression.

MATERIALS AND METHODS

We examined 189 athletes engadged in cyclic sports (skiing and boat-racing), complex coordination sports (synchronized swimming), and game sports (hockey). The observations were performed on 59 women and 130 men (mean age 14±3 and 24±5 years, respectively). All athletes were of various categories (from first category to master of sports). The control group included 212 volunteers (167 women and 45 men, mean age 17±4 years) that were not engaged in sport activity. All individuals were divided into 7 groups: group 1, female synchronized swimmers, 10-14 years old; group 2, female synchronized swimmers, ≥15 years; group 3, male athletes, ≥16 years; group 4 (control 1), girls, 10-14 years old; group 5 (control 2), female adolescents, ≥15 years; group 6 (control 3), boys, 10-14 years; and group 7 (control 4), male adolescents, ≥15 years.

Psychological traits were evaluated using the Bass—Darky questionnaire adapted by A.K. Osnitskii. This questionnaire allowed us to estimate the level of aggression by 8 scales (physical aggression, indirect aggression, anger, negativism, soreness, jealousy, verbal aggression, and feeling of guilt.

For genetic study, samples of the blood and saliva were taken. The blood was taken into 4-ml vacuum tubes (BD) with EDTA (preservative). The saliva was collected using Salivette tampons (Sarstedt). The samples were stored at -20°C. DNA was isolated from the blood and saliva by the sorption method (DNA-sorb-B).

The ACE gene I/D polymorphism was studied by PCR. The D/I-containing DNA region of the ACE gene was amplified using the following primers: 5'-ctg gag acc act ccc atc ctt tct-3' and 5'-gat gtg gcc atc aca tcc gtc aga t-3'. Amplification products consisting of 534 b.p. (I) and 243 b.p. (D) were obtained. Amplification was performed in a Biorad amplifier (37 cycles). Each cycle consisted of denaturation at 95°C for 30 sec, annealing of primers at 65°C for 30 sec, and elongation at 72°C for 30 sec. PCR products were separated by gel electrophoresis in 2% agarose gel with ethidium bromide. UV visualization was conducted on a transilluminator (maximum radiation at 254 nm).

The results were analyzed using Statistica software. The association of the ACE polymorphism with aggression was estimated by analysis of variance (ANOVA). This study was approved by the Ethics Committee of All-Russian Institute of Physical Training.

RESULTS

Studying the distribution of the ACE polymorphisms showed that the frequency of homozygotes is similar in all groups of athletes (DD 26% and II 26% for combined groups, Table 1). However, the distribution differed in control groups (Table 1). These differences can be related to natural selection of individuals that are most adapted to sport activities.

Comparison of aggression in athletes and control subjects and studying of the effect of the ACE polymorphism on manifestations of aggression showed that the ACE I/D polymorphism is associated only with physical aggression.

Physical aggression was maximum in 10-14-year-old boys not engaged in sports (Fig. 1). The level of aggression in control groups of male adolescents, girls, and female adolescents (10-14 years old; and 15 years of age or older) decreased with age. High level of physical aggression during early adolescence (10-14 years) is probably related to variations in the concentration of hormones. Various hormones, including testosterone, hydrocortisone, prolactin, and somatotropin, modulate aggressive behavior [5]. Physical aggression was low in 10-14 year old female synchronized swimmers and remained unchanged in the older age group (15 years of age or older, Fig. 2). Hence, the level of physical aggression in female synchronized swimmers of the younger age group is lower than in age-matched controls. Probably, psychological maturation of young female athletes occurs in the earlier period compared to contemporaries not engaged in sports.

TABLE 1. Distribution of ACE Gene Alleles in Athletes of Various Groups (%)

Sport activity	Genotypes		
	II	ID	DD
Synchronized swimming	24	51	25
Skiing	28	44	28
Boat-racing	29	43	28
Hockey	27.8	44.4	27.8
Combined sample			
athletes	26	48	26
control group	23	47	30

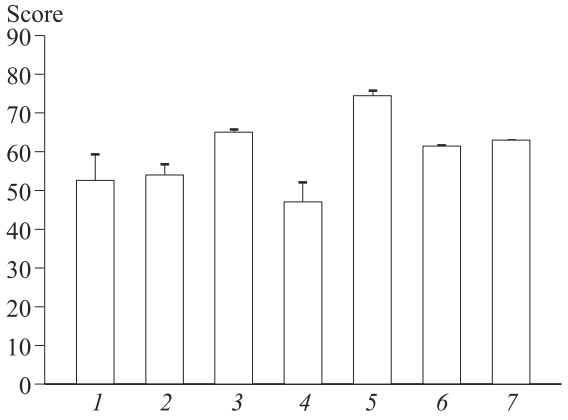

Fig. 1. Physical aggression in various groups: female synchronized swimmers, 10-14 years (*1*); female synchronized swimmers, ≥15 years (*2*); control girls, 10-14 years (*3*); control girls, ≥15 years (*4*); control boys, 10-14 years (*5*); control boys, ≥15 years (*6*); and athletes, boys ≥15 years (*7*).

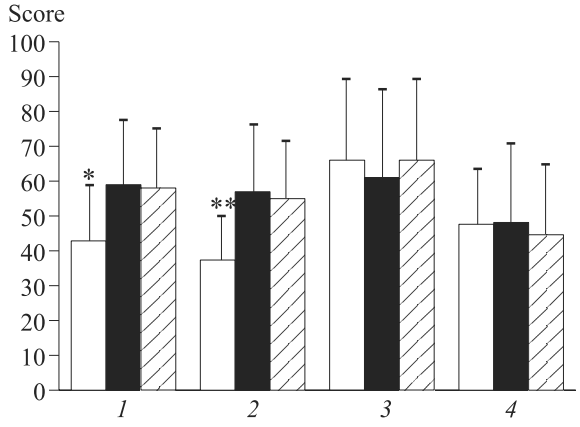

Fig. 2. Dependence of physical aggression on the ACE I/D polymorphism: female synchronized swimmers, 10-14 years old (*1*); female synchronized swimmers, ≥15 years (*2*); control girls, 10-14 years (*3*); and control girls, ≥15 years (*4*). Light bars, II genotype; dark bars, ID genotype; shaded bars, DD genotype. **p*=0.05 and ***p*=0.03 compared to carriers of the ID and DD genotypes.

The ACE I/D polymorphism was associated only with physical aggression of female synchronized swimmers (10-14 years of age or >15 years). Female athletes with the II genotype had a lower level of physical aggression than those with the ID or DD genotype (Fig. 2). Physical aggression was nearly similar in both age groups of female athletes carrying D allele (Fig. 2). No association between the ACE gene I/D polymorphism and physical aggression was revealed in control groups of male and female individuals and male athletes (>16 years). This discrepancy probably results from different hereditability of physical aggression, which depends on environmental factors (*e.g.* professional activity) [1]. The level of aggression in twins was studied using Bass—Darky questionnaire (E.F. Cocarro *et al.*) [4]. It was shown that 40% interindividual differences in the physical aggression scale are related to the additive effect of several alleles [4].

The dependence of aggression on the ACE polymorphism is related to the interaction of cerebral RAS with neurotransmitter systems (serotoninergic, dopaminergic, and other systems). AT-II decreases serotonin concentration in the subfornical organ. The observed changes are associated with a direct effect of AT-II on serotonin in this region. However, AT-II receptors were not identified on serotonin terminals. Moreover, AT-II can produce an indirect effect on serotonin terminals in the dorsal raphe nucleus [11]. High serotonin concentration is associated with reduced physical aggression. These data suggest that II genotype carriers with low activity of ACE and small amount of AT-II have a higher concentration of serotonin than D allele carriers. Hence, the level of aggression in I allele carriers is lower than in D allele carriers [8].

It seems interesting to study the causes of the association of ACE gene polymorphism with physical aggression observed only in female synchronized swimmers. The effect of AT-II on neurotransmitter systems of the brain depends not only on the concentration of AT-II, but also on the function of AT-II receptors (number and binding capacity). Published data show that estradiol decreases the binding capacity of AT-II receptors and expression of AT-II receptor mRNA in the subfornical organ [14]. Estradiol probably responds to variations in the concentration of AT-II, which abolishes the direct effect of AT-II and ACE I/D polymorphism on physical aggression. The concentration of estradiol is low in athletes [13], which contributes to the reduced effect of this hormone on AT-II receptors. Hence, it is possible to evaluate the direct effect of AT-II and ACE I/D polymorphism on physical aggression.

The adaptive response of individuals to physical load is probably related to the genotype distribution: 10-14-year old boys and girls demonstrated a higher score by the Bass—Darky scale, while in female athletes of the same age the level of physical aggression is low. Sport activity probably modulates psychological characteristics in humans.

The ACE I/D polymorphism was associated with physical aggression only in female athletes. Female athletes with the II genotype were less aggressive than those with the DD genotype.

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