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PHYSIOLOGICAL BASIS OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS) FUNCTIONS IN SPORTS EXERCISES

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Abstract

In the brief review the main elements of classic renin angiotensin aldosterone system with the new discovered components as well as essential functions of angiotensin II and aldosterone in physiological and pathological adaptation of cardiovascular system were described. The function of systemic and local RAAS was presented. An association between polymorphism of Angiotensin Converting Enzyme ACE D/I gene, and physical performance of sportsmen were discussed.

Key words: RAAS, aldosterone, angiotensin II, bradykinin, polymorphism of ACE gene, ACE2

Introduction

The effective clinical therapeutic application of ACE inhibitors and angiotensin II AT1 as well as aldosterone receptor blockers in cardiological diseases such as: hypertension, heart failure and myocardial infarctions, indicated that activation of RAAS plays a dominant role in pathogenesis of these disturbances. In last years in a lot of publications the function of RAAS in acute maximal exercise as well as in long-lasting physiological cardiovascular adaptation on physical performance were indicated (4,10,11,14,15, 24). In the recent studies the relationship between polymorphism of RAAS gene of angiotensin-converting enzyme (ACE) and physical performance were discussed (1,5,6,12,13,17,19). Therefore, in the light of the update evidence the function of the local (tissue) RAAS seems to play very important role in physical performance of sportsmen.

What does RAAS mean?

The Renin-Angiotensin-Aldosterone system (RAAS) is the hormonal cascade system which regulates and controls through main activators: angiotensin II and aldosterone, the water-electrolyte, acid-base homeostasis of the body (through regulation of kidney function) and assures the proper blood pressure (2,10). But the same components of the system are simultaneously synthesise in the different cells of the most of the tissues and organs such as: in heart, vascular cells, brain, adipose tissue, skeletal muscles and others (4,14). All the components play very important functions in the process of long-lasting physiological or pathological cardiovascular adaptation which leads to the cells proliferation and hypertrophy of heart and skeletal muscles, as well as genetically programme death of the cells described as apoptosis (4,15,28). The research studies conducted in the last years indicated that RAAS extends their function on the two independent but relative co-operated levels described as circulating and local (2,4,5,29).

Function of circulating RAAS

Classic or circulating hormonal RAAS fulfils very important control functions such as: blood pressure (especially during physical exercise), blood plasma volume and fluid and electrolyte balance regulation (especially during dehydration) (2). This system begins mainly on the activity of renin secretion in juxtaglomerular apparatus of kidney and it activates all system starting of cleaving of angiotensinogen to angiotensin I (Fig 1). Factors which stimulate of prorenin and renin secretion are: plasma hypovolemia, anaemia, low sodium diet, angiotensin II and sympathetic system stimulation. Angiotensin I in turn was converted by enzyme angiotensin-converting enzyme (ACE) to active component – angiotensin II (2,15). There was the main and as far now only one pathway (or axis) of synthesis of angiotensin II. Recently the new or the second pathway which modulate angiotensin II generation has been discovered (4,9). The beginning of the pathway is the same as before but as the result of activity of ACE2 the angiotensin I is converted to angiotensin 1-9 (ANG 1-9) and angiotensin II is changed to angiotensin 1-7 (ANG 1-7) (4) (Fig 1). The enzyme ACE2 fulfils very important role in regulation and mediation of function of RAAS, because the amplification of synthesis of angiotensin II depends on the activation of one of the two contra-

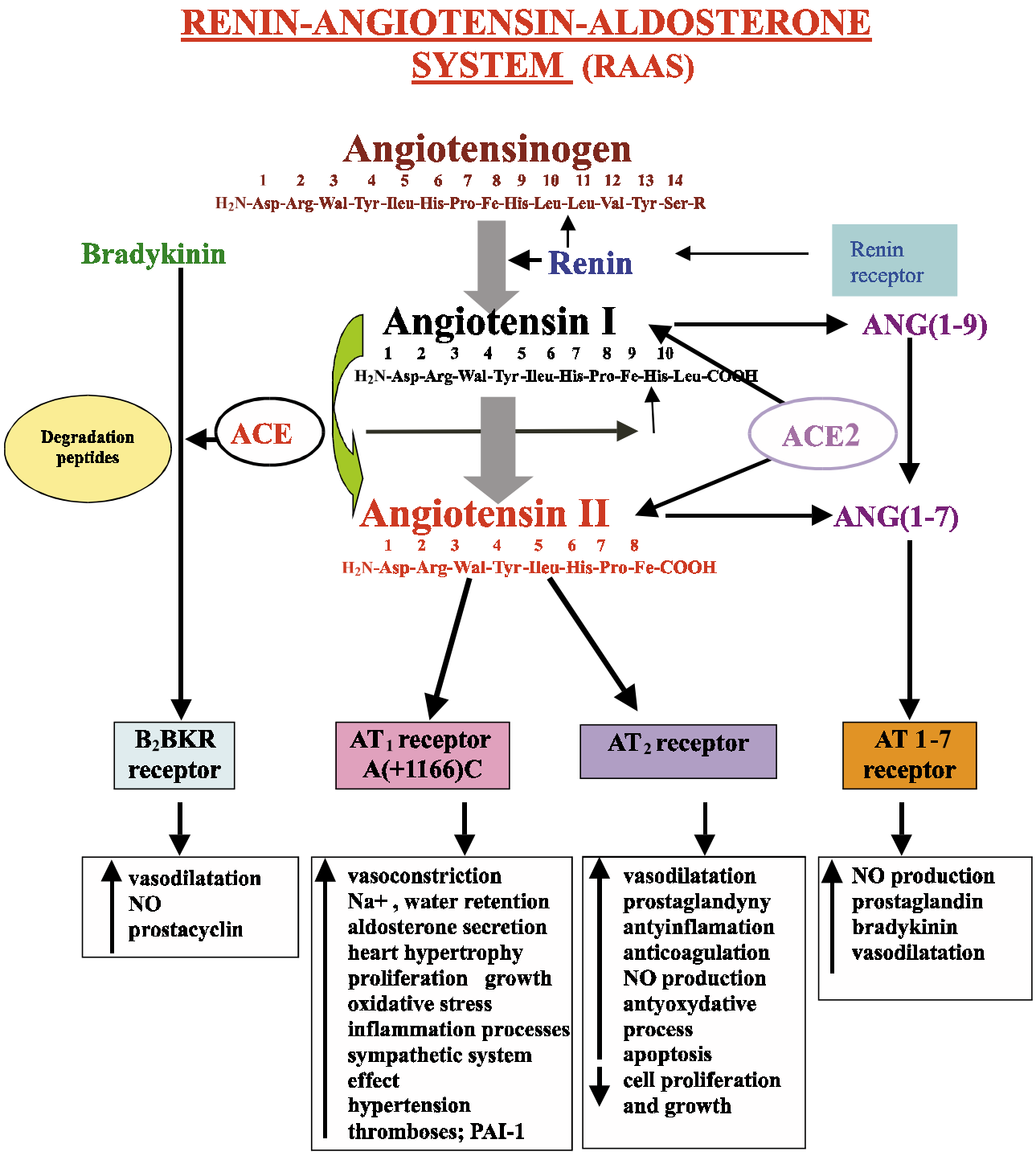

Fig.1 *Schematic presentation essential components and pathway of synthesis of angiotensin II in the classic RAAS and relevance receptors with effects of theirs actions (4,10,15). PAI-1 - Plasminogen Activator Inhibitor-1*

ry-regulating pathways which exhibit opposite effects in its generation (4,7,9). In Fig. 2 schematic presentation of circulating RAAS action on blood volume balance was depicted.

Function of local RAAS

Investigations of the last years indicated that beyond the above systemic RAAS there exists independently but partly co-operated intercellular RAAS which consists of the same components as above and exhibits autocrine*, paracrine** and intracrine*** effects of actions (4,9,10). All elements of RAAS (such as: renin, angiotensinogen, ACE, angiotensin II and aldosterone) may be synthesised within the cells of different organs or tissues or may be taken up from the circulating blood components and includes them into intracellular processes (10). Synthesised tissue angiotensin II initiates the intracellular signalling sys-

Note: The example of **autocrine*** effect may be produced of angiotensin II on the surface of endothelial cell (as a result of ACE conversion of angiotensin I) and it acts on the same cell; **paracrine**** effect it means that angiotensin II generated in the one cell acts on the other neighbour cell; **intracrine***** action indicates that active substance as angiotensin II generated within the cell and modified the function of the same cell that is generated (4,29).

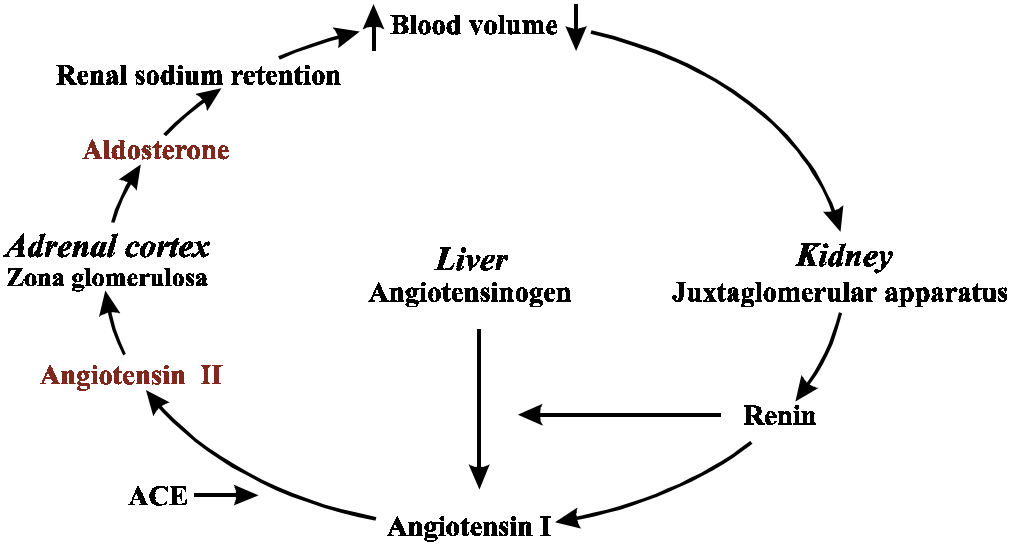

Fig. 2. *Schematic presentation of circulating RAAS action on blood volume balance (2)*
Decrease of the blood volume as well as effect of activation of sympathetic system stimulate the increase (pro-renin) renin releasing from the juxtaglomerular apparatus in kidney, that in turn changes angiotensinogen (produces in liver) present in the blood into angiotensin I (decapeptide) which in turn under the influence of ACE activity is converted to angiotensin II. Angiotensin II increases the synthesis and secretion of aldosterone in zona glomerulosa of adrenal cortex. Aldosterone in turn increases retention of renal sodium and water and increases the blood volume. Angiotensin II stimulates the release arginine vasopressin (AVP) which regulates urine concentration and antidiuresis (when the 1%-2% plasma loss). Angiotensin II stimulates increases also the thirst (when the threshold plasma loss is higher than 8%-10%).

tem which starts the cascade of changes of intracellular metabolism and expression of genes leading (apart from other effects) to the growth and hypertrophy of the cells (27). The function of local RAAS depends on the tissue where is generated. In zona glomerulosa of adrenal cortex stimulates of aldosterone secretion; in the brain it is involved with thirst and antidiuretic hormone (ADH-arginine vasopressin) secretion influences and facilitates the secretion of adrenocorticotrophic hormone (ACTH), and luteinizing hormone (LH) (15). In heart increased tissue generation of angiotensin II influences on the hypertrophy of cardiomyocytes and disturbances of its function (heart rate) (24). In coronary arteries the effect vasoconstriction or vasodilatation may be related to the stimulation of two different receptors (see latter). The local RAAS exists in almost all organs such as in: kidney, heart, brain, adrenal cortex, placenta, vasculature, male and female gonads and others (4,9,14). The studies indicated that exist alliterative pathways of generation of angiotensin II (ANG II) in the tissue RAAS (10,24).

The main of RAAS components

Renin

Renin had been the first known and key element which has started the beginning step of cascade of circulating RAAS. It is generated, stored and released in juxtaglomerular apparatus in the kidney in the form of prorenin, which protects of renin from degradation and keeps it in non active state (2). Renin releasing is controlled through the activation of baroreceptors located in macula densa (in the kidney), activation of sympathetic system, decrease of the blood pressure, and sodium depletion. Renin may be synthesised beyond the kidney too (4).

In the classic RAAS the biologic role of renin was only enzymatic cleaving of angiotensinogen to angiotensin I. But recently scientific studies indicated that renin is not only enzyme but it also fulfils the hormonal function. When the renin was coupled of renin receptor its activity was four time increased. It was postulated that renin receptor fulfils very important function in generation of tissue angiotensin II in pathological hypertrophic states (as in the heart) (4).

In the tissue RAAS the presence of renin is not necessary, there are alternative pathways of generation of angiotensin II without the first step of cascade production angiotensin I (15). Plasma Renin Activity (PRA) test indicates of activity of circulating RAAS.

Angiotensinogen (ATG)

In the classic RAAS angiotensinogen - 14 amino-acids peptide is produced in the liver together with the other α-globulins (4,9,14). Renin cleaves angiotensinogen between two leucine molecules (amino-acids 10 and 11) to form the decapeptide – angiotensin I (Fig 1). The presence of mRNA of angiotensinogen was found in (high concentration) the cells of brain structures (hypothalamus, cortex), heart muscles and endothelial cells of vasculature (4). The level of angiotensinogen in the plasma determines the amount of generation of angiotensin I and in turn angiotensin II. Polymorphism of genotype of ATG combined with the exchange of methionine with treonine

in position of 235 (M±235T) can increase the possibility of appearance of hypertension at young age (10,12).

Angiotensin-Converting Enzyme (ACE)

Angiotensin I (formed from angiotensinogen cleaved by renin) is the substrate for ACE that removes residues 9 and 10 (histidine and leucine) to form angiotensin II the octapeptide (ANG II) active component of the system (10,15). There are at least 4 main known isoforms of ACE: the somatic or the tissue ACE (cell bound ACE), soluble or circulating ACE, testicular or germinal isoform and ACE2 (see later) (4,10). Somatic ACE is an ectoenzyme (faces the lumen of vascular system) 179-kDa glycoproteine polypeptide chain consists of two homologous catalytic domains each with an independent two catalytic active centre that contain two zinc moieties (metallopeptydase). Carboksyl (COOH) portion of enzyme is hydrophobic and anchors to cell membrane. 90% of the ACE activity is connected with somatic isoform of the enzyme. Circulating of blood serum ACE cleaved from somatic ACE and forms only 10% of all activity and is excretion in bile and in urine (10). The structure of testicular or germinal ACE is different from the one that consists one of domain with one zinc active catalytic side (80-kDa glycoproteine) (13). The structure of ACE2 is similar to germinal ACE (see later) (7). ACE as a somatic form is distributing in endothelial cell (arteries and veins), epithelial cells, cardiovascular system (heart), brain, reproductive system (testis, ovary), adrenal cortex, lungs, fibroblasts and macrophages (10). Beyond the angiotensin I, bradykinin is other substrate for ACE action (3,10).

In 1990 the polymorphism insertion/deletion of ACE gene was discovered. This polymorphism is defined as either the presence (insertion, I) or absence (delation, D) of 267 base pair fragment (insert) in intron 16 of angiotensin-converting enzyme gene on chromosome 17q23 (1,5,11,15,19,20). The presence of the same two allels I (II) or D (DD) is defined as homozygote and ID as heterozygote carriers. The insertion component appears to reduce ACE expression with lower of serum as well as tissue ACE activity. In subjects with DD the activity of ACE posses about 50% and in DI intermediate (30%) values higher than in subjects with II allele (5,15). In the subject of D allele the increased incidences of myocardial infarcts, strokes, nephropathy, cardiac hypertrophy and hypertension were reported (5,15,24). Estrogens lower the activity of ACE as well as angiotensin II synthesis and stimulates increased of the bradykinin and angiotensin 1-7 which result in vasodilatation (3,16,32). Localisation in different tissues and polymorphism of ACE may indicate indirectly angiotensin II creation (13).

Note: The blood leukocytes contain exactly the same DNA materials as in all other tissue of the body, therefore the analysis of the materials extracted from sample of blood or saliva of the mouthwash gives simple way identification of the all genes (21).

Angiotensin-converting Enzyme 2 - ACE2

Recently Angiotensin-Converting Enzyme 2 - ACE2 an essential regulator of RAAS function, has been discovered (4). ACE2 hydrolyses angiotensin I to angiotensin 1-9 (ANG 1-9) and angiotensin II to angiotensin 1-7 (ANG 1-7) (7). Later ANG 1-9 is hydrolysed by ACE to angiotensin 1-7 (contrary to angiotensin II), which is a potent vasodilatator, increases the generation of NO and prostacycline, and stimulates secretion of bradykinin (4,32). The structure of ACE2 is similar to testicular or germinal isoform ACE and as monopeptidase posses only one catalytic side. The angiotensin 1-7 decreases the growth stimulation and it decreases the hypertension induced by angiotensin II. ANG1-7 forms its action through the expression of ANG1-7 receptor which nature is not yet completely recognised (4). The activity of ACE2 creates the second axis (or arm) of the cascade of changes of RAAS that is counter - regulator of effects of angiotensin II (4,7,32).

Recently study indicated that ACE2 is a functional receptor for the SARS (Sever Acute Respiratory Syndrome) virus. ACE2 inhibitors blocked the disease. Nevertheless, further studies will have to be conducted to validate the pathogenesis of SARS and ACE2 function (16).

Bradykinin

Although bradykinin is not formally a component of RAAS but there are strong functional opposite effects between angiotensin II and bradykinin.

Bradykinin results in the vasodilatation, lower the hypertension and modulates the coagulation processes through the expression of the receptor B2R. Furthermore, bradykinin stimulates the realising of NO and prostacycline (PGI2), inhibits the increased blood platelets aggregation, stimulates the production of tissue plasminogen activator and decreases insulin resistance. Bradykinin is destroyed by ACE (3,18,32). Prophylactic application angiotensin II receptor blockers (Losartan) in sportsmen did not inhibit the development of left ventricular hypertrophy (20). The results of the study indicated that the increased generation of angiotensin II, after the heavy exercises, did not directly participated in pathogenesis of the athletic performance (13,32). But application of ACE inhibitors which increase the bradykinin concentration, decreased the echocardiography left ventricular heart dimensions. Polymorphism bradykinin receptor B2BKR connected with presence or absence of the

fragment of DNA (insert) of the gene may determine high or low bradykinin levels (3). On the basis of these evidence it was hypothesised that the athlete's heart or post exercise cardiac hypertrophy can be more evidence in the curries of genotype with bradykinin receptor B2BK2 +/+ (with low activity of bradykinin) and ACE DD (with high ACE activity) (3,18,32).

Angiotensin II (ANG II) and ATR1 and ATR2 receptors

Angiotensin II is the active substance - effector - of RAAS and its action depends on the stimulation of one of two types of receptors ATR1 or ATR2 The presence of the two receptors of ANG II with exhibit opposite actions (see fig 1), beyond of ACE2 effects, creates the preventing mechanism to avoid damaging action of excess of angiotensin II and ensure the functional balance of the metabolic processes in the cells.

ATR1, as well as ATR2 receptors, belong to the same 7-transmembrane domain, G protein coupling membrane receptors family but with quite different function and signalling pathway.

The major actions of ATR1 are expressed through Gq mediated activation of phospholipase C (PLC), which, in turn, results in generation inositol 1-4-5-triphosphate (IP3) and diacylglicerol (DAG), that promote and subsequent activation of protein kinase C and increased in the intracellular level of calcium. Angiotensin II participates in many signalling responses associated with activation of tyrosine kinase receptors and tyrosine phosphorylation of intracellular proteins with activation of mitogen-activated protein kinase (MAPK) and growth factors. ANG II induces genes expression and transcription proto-oncogenes (c-fos, c-jun, c-myc), factors mediating in cells growth and differentiation (28).

The ATR1 receptor mediate most of the known actions of angiotensin II such as: vasoconstriction, activation of endothelin-1, activation of sympathetic system, secretion of aldosterone, increase structural and functional changes in the walls of (coronary) arteries, hypertrophy of the left ventricular of the heart, and smooth vassal muscles, thrombosis (by increasing of plasminogen activator inhibitor-1 (PAI-1), and platelets aggregation that inhibits fibrinolysis, intensity of arteriosclerosis development (through the rise of the vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (CAM) (4,10,14,15). Mediates also the increase of growth factors (basic fibroblast growth factor-ßFGF, platelet derived growth factor (PDGF), transforming growth factor-$ß_1$ TGF-$ß_1$). ANG II raises also the superoxide and other reactive oxygen and nitrogen species (ROS) and intensifies the oxidative stress. The amplification of inflammatory processes in different parts of the body is stimulated by the activation of TNF (Tumor Necrosing Factor) which, in turn, increases concentration of nuclear factor-κB (NFκB) and cytokin. ANG II decreases the apoptic processes (5,11,26). As an effect of the negative feedback regulation increased ANG II generation, inhibits renin secretion (10,28).

Activation of ATR2 receptors in turn, which is especially strong stimulation in period of the embryogenesis, mediate the opposite effects such as: vasodilatation, hypotension, the increase of NO production, decreased hypertrophy of the heart, smooth muscles of vascular wall, increased antyoxydative process, against thrombosis effects, and increased apoptic process (28).

ATR2 intracellular mediators through Gi coupling inhibits cell growth but increased cell differentiation, increased activation of nitric oxide and the kinin systems with acidification of the intracellular environment which is particularly relevant to vasorelaxation. ART2 increases ceramide synthesis (and caspase activity) and enhances apoptic process.

Recently studies were indicated that angiotensin receptors ATR1 and ATR2 may bind directly with each other created heterodimer with decreased angiotensin II responsiveness. The similar heterodimer may be formatted between ATR1 and bradykinin BK2R receptor that may increased signalling response to angiotensin II (4).

Aldosterone

Aldosterone (discovered 50 years ago) has been primarily known as the most important mineralocorticoid hormone, produced in zona glomerulosa of the outer layer of adrenal cortex, regulated by angiotensin II, potassium concentration and to a lesser extent adrenocorticotrophic hormone (ACTH) which promotes sodium reabsorption and retention water and excretes of potassium by the epithelial cells of renal tubules as well as regulation of blood pressure (8,15,25,29). Recent studies indicated that aldosterone may be synthesised, beyond the adrenal cortex, in other nonepithelial cells such as in: heart, brain, vasculature (endothelium), kidney and other organs. However, the production of aldosterone is potentated in pathological hypertrophic states of heart or other organs (24,25,29). The aldosterone synthase (CYP11B2) enzyme (necessary for last step of aldosterone synthesis) was detected in the normal heart cells but in pathological hypertrophic heart the expression of the gene of enzyme was up regulated (29). Animal studies and clinical trails suggested that local aldosterone plays a major pathological role in heart hypertrophy, vascular injury, independently of blood pressure and angiotensin II actions (8,15,24,25,29). Recent clinical and experimental studies indicated that aldosterone may play a major role in cardiovascular

disturbances independently to its hormonal function and hypertension effect (25,29). There are evidences that heart is the target of cardiac aldosterone actions (24). It may indicate that aldosterone (similar to angiotensin II), may exhibit autorine an paracrine action that change the function and structure of the tissues leading to hypertrophy and fibrosis of the left ventricular of the heart (24).

Aldosterone fulfils its action through the coupled mineralocortycosteroid receptors (MR) located in cytoplasm of the target cells in inactive complex with heat shock protein HSP and is transferred to the nucleus where it joins with hormonal response element of the chain of DNA which induces genomic (long-lasting up to12 hours) pathway (8,24,29).

Aldosterone and cortisone exhibit similar affinity to the same receptor but concentration of cortisone is from 100 up to 1000 - hold higher than aldosterone. Coexistence of MR and 11b-Hydroxysteroid Dehydrogenase type 2 (11b-HDS2) which converts cortisol to non active cortisone (which does not couple with receptor) enables aldosterone (which couples with receptor) exhibits its biological effects (24,25,29). In the recent studies the presence of MR, as well as the activity of 11ß-HDS2 in the cells of heart, in brain and in vascular endothelium were confirmed (8,25,29).

Aldosterone may induce the effects of non genomic or rapid response (in 2-30 minutes) pathway through activation of the membrane MR receptors and by activation of diacetylglicerol, 1,4,5 triphosphate inositol, protein Kinase C and Phospholipase C (24,25). The mineralocorticoid receptors (MR) in the heart mediate the effects by the local synthesised aldosterone or it is taken up from the blood into cells (9,24,25,30). Increased concentration of aldosterone in the tissue enhances the expression of the genes of ACE as well as angiotensin II receptor ATR1 which increases the concentration and effects of angiotensin II. (29). The tissue aldosterone and angiotensin II mutually potentiate their effects. Aldosterone increases expression of the gene of endothelin and inhibits inducible NO synthesis that may predispose to the constriction of coronary artery and myocardial infarction (8,25).

Aldosterone (as well as angiotensin II) stimulates the expression and production of plasminogen activator inhibitor type-1 (PAI-1). In men plasma PAI-1 concentrations correlate with aldosterone levels. The prolong elevation of aldosterone may potentate prothrombotic effects with massive thrombosis and pulmonary embolism and may cause myocardial and vascular fibrosis (8).

Now there are evidences that aldosterone as a risk factor may play independent and essential role in physiology and pathology of cardiovascular functions and it mediates and exacerbates damaging effects of angiotensin II (8,24,25,29).

A lot of above mentioned singes and symptoms of cardiovascular disturbances as the effects of aldosterone correspond to cardiac events observed in the subjects with supraphysiological doses of Anabolic-Androgenic Steroids (AAS) abuse. It may suggest that a lot of well known cardiac events in body builders even with sudden cardiac death are mediated with strong activation of RAAS induced by supraphysiological doses of the drugs (in press).

Aldosterone stimulates the sympathetic system (with increased nor-epinephrine) especially in heart and vascular system. Increased concentration of aldosterone and strong activation of sympathetic system may be the trigger mechanism of cardiac sudden death in same cases (24).

Polymorphism of genes of RAAS and physical performance

The special position of ACE activity in RAAS is due to a double function of this enzyme that firstly generates angiotensin II (from the angiotensin I) and secondly it hydrolysis bradykinin to the degradation products (10). Furthermore, the tissue ACE activity in subjects with DD genotype is much more higher than in II genotype curries. Recently the studies have reported that in a group of elite of sportsmen such as: rowers (1), long-distance runners (19), and high-altitude mountaineers (17), the fastest South African Ironman of triathlons (6) the variant of I allele of ACE were more frequently associated with the higher endurance performance than D allele variant. In turn, the prevalence of the subjects with DD genotype in the elite of short distance swimmers and sprinters ($\leq$200m) as well as in strength sports have been shown (30).

However, in a lot of other studies the association between athletic ability and polymorphism of ACE was not found (22,23,26). The results performed on larger groups of endurance elite of participants of Olympic Games from Australia and Great Britain did not showed the difference in distribution of ACE polymorphism in comparison with control groups (19,22,23,26).

Woods and co-workers indicated that although I/D polymorphism ACE might play a role in enhanced endurance performance it was without effects on differences in the cardiorespiratory response in the training (as results of $\dot{V}O_2$max and heart rate) (31). Zhang et al. indicated the association between the allele I of ACE gene with increased percentage of slow-twitch type I fibres in human skeletal muscle (important in long distance runners) and concluded that it might have been a mechanism for the relationship with endurance performance (33). Therefore, it is suggested that an association between polymor-

phism of ACE gene and endurance performance is probably due to a local muscle effects than cardiorespiratory adaptation of the physical exercises (31).

Our own study performed on the group of cyclists (n=31) indicated that in subjects with genotype DD of ACE the values of left ventricular masses in echocardiographic measurements had been statistically significant higher than in II carriers of the group but we did not find any effects on physical performance. This evidence might have indicated, regardless of other factors, that DD genotype of ACE might have participated with the extent of exercise induced left ventricular growth in pathogenesis of Athlete's Heart.

We examined the genotype of RAAS distribution in the groups of body builders (n=40), rowers (n=32), cyclists (n=31) and static disciplines (n=26). The study indicated that in a group of body builders with supraphysiological doses of AAS abuse, there were the statistically significant higher subjects with genotypes of ACE-DD, aldosterone synthase CYP11B2-CC, and angiotensin II receptor AT1 (±1166) – AA. This pattern of polymorphism of the genes enhances the strong activation of local RAAS and tissue aldosterone secretion and the hypertrophy of the heart as well as skeletal muscles, but may predispose also to serious cardiovascular events (in press).

Controversial results recently obtained in different studies indicated that the hypothesis of influence of polymorphism of ACE and other genes on endurance performance in sports, is much more complicated than we had thought before. Any physical exercise stimulates the expression of lots of different genes and it is impossible if only a single gene polymorphism may be exclusively associated with the endurance phenotype. It is more possible that the nature of physical performance of sportsmen is polygenic, because multiple of biochemical and hormonal systems are involved in phenotype of sports performance (2,23).

The recent evidence suggests that the athletic performance is strongly influenced by the genetic variation (23). The understanding of the gene-exercise interactions is very important to improve the ability of sportsmen performance through the appropriate training and sports specialisation. In the resent years our knowledge of the influence of local RAAS function on the physiological principle in sports has rapidly grown, therefore it should be expected that the oncoming intensive studies will elucidate all conflicting evidences between the single gene polymorphism of ACE gene (as well as other genes) and Olympic endurance achievements.

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