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MINI REVIEW ARTICLE

THE ANGIOTENSIN CONVERTING ENZYME (ACE) GENE POLYMORPHISM - INSIGHT STUDY OF THE RENAL REGULATION OF THE ARTERIAL BLOOD PRESSURE

POLOMORFIZAM GENA ZA ANGIOTENZIN KONVERTUJUĆI ENZIM – ANALIZA BUBREŽNE REGULACIJE ARTERIJSKOG KRVNOG PRITISKA

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ABSTRACT

Since the renin-angiotensin-aldosterone system (RAAS) was originally described, it has become one of the best described hormonal systems, especially regarding the fact that it plays an important role in regulating blood volume and systemic vascular resistance, and thus indirectly influencing blood pressure (BP).

On the other hand, arterial hypertension is one of the most pertinent disorders which plays an important role, not only in the progression of renal failure, but also represents a risk factor for the occurrence of end stage renal disease. Several epidemiological studies pointed out the fact that genetic predisposition accounts for about 30% of the BP variability. Up to date, there are several RAAS genes that may have effect in long-term BP control, but ACE is the most important and the most thoroughly examined.

In this review, we present available data regarding the influence of gene polymorphisms of ACE on its function, within the RAAS related BP regulation. Therefore, by specially describing all its potential physiological roles, it will likely offer a new insight in the renal regulation of the BP, along with its other, not less important, roles.

Keywords:
blood pressure regulation,
rennin-angiotensin-aldosterone system,
ACE gene polymorphisms

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SAŽETAK

Od kako je sistem renin-angiotenzin-aldosteron (RAAS) opisan, postao je jedan od najčešće proučavanih fizioloških sistema, posebno imajući u vidu da ima veoma značajnu ulogu u regulaciji volumena krvi i sistemskog vaskularnog otpora, te na indirektan način utiče i na arterijski krvni pritisak (KP).

S druge strane, arterijska hipertenzija predstavlja jednu od najznačajnijih bolesti današnjice, koja igra značajnu ulogu ne samo u progresiji bubrežne slabosti, već takođe predstavlja i faktor rizika za nastanak terminalne bubrežne insuficijencije. Nekoliko epidemioloških studija ukazuje na činjenicu da 30% varijabilnosti KP nastaje usled genetske predispozicije. Do danas, je otkriveno nekoliko RAAS gena koji mogu da imaju uticaj na dugoročnu kontrolu KP, ali je inserciono/delecioni (I/D) polimorfizam gena za angiotenzin konvertujući enzim (ACE) najznačajniji i najviše proučavan.

U ovom pregledu literature predstavićemo dostupne podatke iz literature o uticaju I/D polimorfizma ACE gena na funkciju RAAS regulacije KP. Pomoću posebnog osvrta na sve njegove potencijalne fiziološke uloge, predstavićemo i novi pogled u bubrežnu regulaciju KP, kao i u njegove ostale, ne manje značajne uloge.

Ključne reči:
regulacija krvnog pritiska, sistem renin-angiotenzin-aldosteron, polimorfizmi gena za angiotenzin konvertujući enzim

INTRODUCTION

It is well known that kidneys have an important role in the blood pressure (BP) control. Additionally, along with the heart, brain and arterial blood vessels, kidneys are prime targets of hypertensive damage, which can result in its functional and structural damage and consequent organ dysfunction (1).

Also, literature data point out the fact that hypertension represents an independent predisposing factor for heart failure, coronary artery disease, stroke and renal diseases (1, 2).

Over 70 years have passed since the renin-angiotensin-aldosterone system (RAAS) was originally described (3). By today, RAAS has become one of the best described hormonal systems, especially regarding the fact that it plays an important role in regulating blood volume and systemic vascular resistance, and thus indirectly influencing cardiac output and BP (3, 4). RAAS importance is even more notable due to the fact that arterial hypertension is a frequent condition, and represents a major cause of renal diseases (1). Angiotensin converting enzyme (ACE), as a part of RAAS, is a membrane-bound, zinc-dependent peptidase that catalyses the conversion of the Angiotensin I (Ang I) to the Angiotensin II (Ang II), a potent vasopressor. Thus, ACE is a well known part in the BP regulation system (5).

Having in mind the previously mentioned, along with the fact that ACE inhibitors are now one of the most frequently used antihypertensive drugs, the importance of ACE is even greater. They are not only used in the management of arterial hypertension, but also in the long-term management of patients with congestive heart failure and all types of nephropathies (6). Additionally, nowadays, arterial hypertension can be finely tuned by the RAS influencing drugs, especially ACE inhibitors, in the first line, with not only balanced BP control, but also with additional health benefits (6,7).

In this review we present available data regarding the influence of gene polymorphisms of ACE on its function within the RAAS related BP regulation. Therefore, by specially describing all its potential physiological roles, it will likely offer a new insight in the renal regulation of the BP, along with its other, not less important, roles.

THE RENIN ANGIOTENSIN SYSTEM PHYSIOLOGY

As the name implies, RAAS consists of three important components: renin, angiotensin and aldosterone.

Renin is a proteolytic enzyme, whose releasing from kidney juxtaglomerular cells (JG) is usually stimulated by decreased sodium delivery to the distal tubules of the kidney, renal artery hypotension or sympathetic nerve activation (acting through β1 adrenoceptors located on the JG cells) (8, 9). The physiology of the RAAS is based on the renin, which converts angiotensinogen into decapeptide Ang I. Vascular endothelium, particularly in the lungs, but also in the brain, heart and blood vessels, had an enzyme, ACE, which forms octapeptide, Ang II. Newly formatted Ang II now binds to the Ang II receptor type I (AT1) leading to systemic vascular resistance increase, sodium and water retention, aldosterone, vasopressin and norepinephrine release, which all leads to an increase in BP (**Figure 1**) (8, 9).

Previously mentioned mechanism is not the only way by which the RAAS is regulated. Namely, natriuretic peptides (ANP and BNP) released by the heart represent one more counter-regulatory system (10).

RAAS role is even more important concerning the fact that its activation is well-established pathway, contributing to arterial hypertension. This is why therapeutic manipulation of this pathway, especially via ACE inhibitors, is very important in treating hypertension and heart failure, by decreasing afterload and blood volume, and by cardiac hypertrophy inhibition (11).

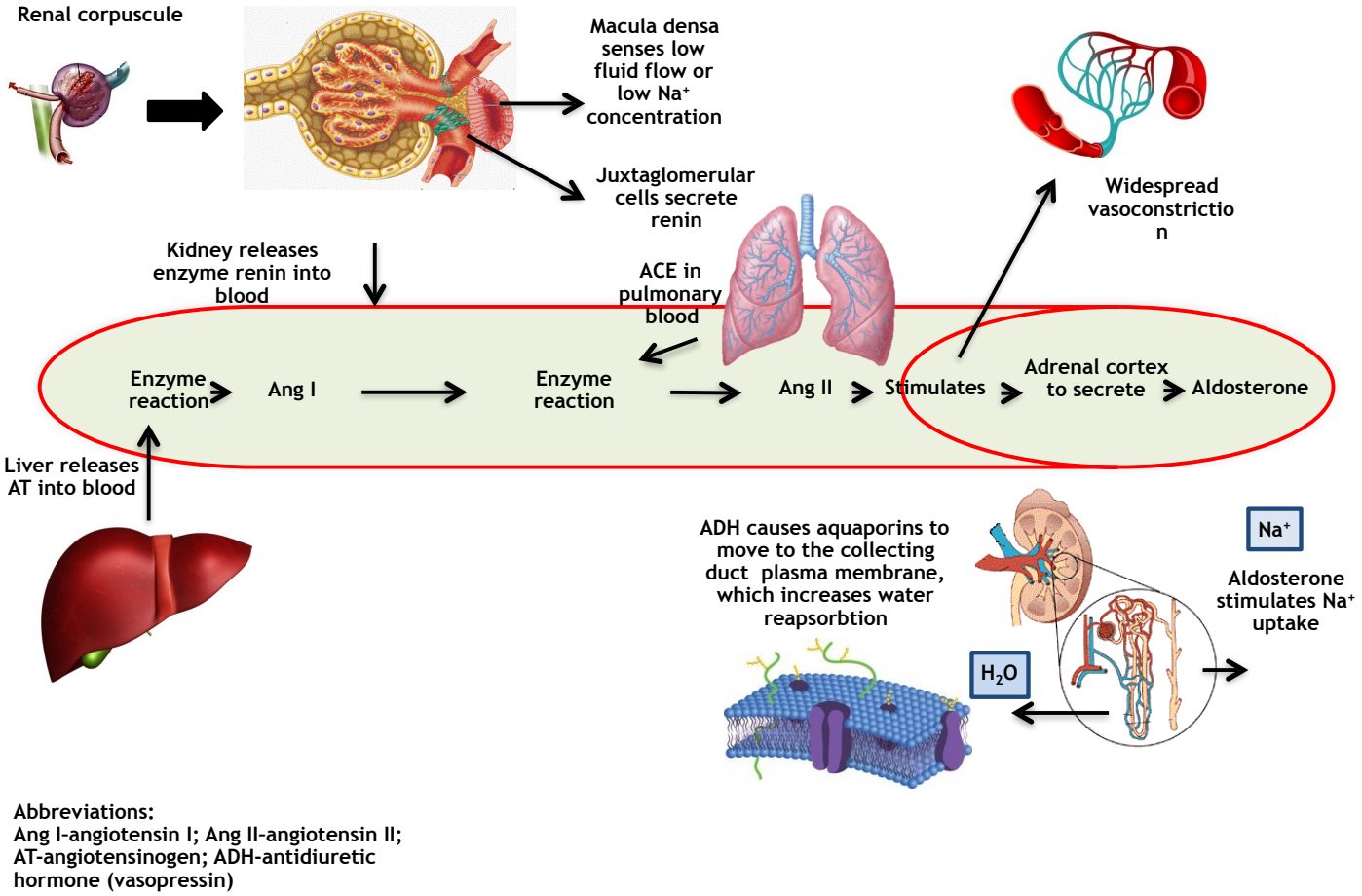

Figure 1. RAAS physiology

ACE polymorphisms - relationship with the arterial blood pressure

Arterial hypertension is one of the most pertinent disorders which plays an important role not only in the progression of renal failure, but also represents a risk factor for the occurrence of end stage renal disease (1). Several epidemiological studies pointed out the fact that genetic predisposition accounts for about 30% of the BP variability (12). Up to date, there are several RAAS genes that may have effect in long-term BP control, but ACE is the most important and the most thoroughly examined. Literature data concerning variations of the ACE gene and its impact on complications like arterial hypertension, cardiovascular diseases and nephropathy are already abundant (13).

ACE gene, which contains 26 exons and 25 introns, is located on chromosome 17q23. According to the data from the National Center for Biotechnology Information (NCBI) records, more than 160 ACE gene polymorphisms are registered. Moreover, although the majority of these polymorphisms are single nucleotide polymorphisms (SNPs), only 34 are located in coding regions and 18 of them are listed as missense mutations. ACE I/D polymorphism is one of the most commonly studied polymorphism, regardless of the fact that its location is in non-coding region, which makes it unlikely to be a functional variant. Up to date, researchers continued to use this exact polymorphism as a valid marker for the associations with cardiovascular and other complex disorders (14, 15).

The frequency of ACE I/D polymorphism in general population is presented in **Figure 2** (14). The ACE gene encodes 2 isoforms of ACE, made by initiations by 2 different promoters: the somatic form (sACE), expressed in somatic tissue, and the testicular form (tACE), expressed in germinal cells in the testes.

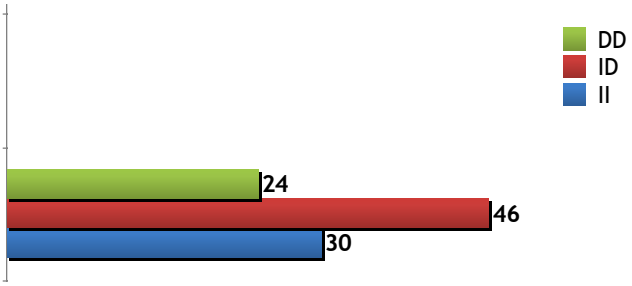

Figure 2. Frequency of ACE I/D polymorphism in general population

The plasma and tissue ACE levels are influenced by the insertion/deletion (I/D) polymorphism. Earlier studies pointed out that one of the most significant polymorphisms of ACE gene is 287-bp insertion/deletion in intron 16 (ACE I/D). Also, this polymorphism is the most often studied because of the fact that cardiovascular and other complex disorders may be connected, explained and threated by its exploring (2, 16). The DD genotype is associated with enhanced serum ACE levels and activity, while II and ID genotypes were associated with low and intermediate ACE levels (2).

Namely, several studies pointed out the role of DD genotype in the evolution of hypertension and renal dis-

eases (17, 18). Additionally, ACE DD genotype may also be associated with higher systolic BP. The explanation could be that hypertension in some patients may occur as a consequence of dysfunction of RAAS, with abnormal renin secretion, causing blood Ang I levels increment and augmentation. Previously mentioned fact is more important keeping in mind that D allele carriers have higher ACE levels, and thus more effective conversion of Ang I to Ang II. This conversion along with additive effect of arterial hypertension may result in chronic kidney disease (19).

Some studies point to the gender-dependent effect of ACE I/D polymorphism on blood ACE levels (20, 21, 22). Zhang et al. suggested that in Asian population differences in blood ACE levels between DD genotype and other genotypes were more pronounced in men than in women (21). Contrary, a study conducted by Biller and associates on Caucasian population reported the opposite results (22).

It is also worth mentioning that not only hypertension, but also androgens, may play an important role in previously mentioned additive effects, along with ACE I/D polymorphism. Namely, previous studies pointed to the fact that, although there is no significant difference in blood androgen levels, sensitivity to androgen is higher in Caucasians than in Asians (21). Also, animal studies have shown that ACE activity was higher in male mice than in females, but this gender differences cease to be notable, after gonadectomy (23).

There are numerous studies confirming a gender-dependent effect of ACE ID polymorphism on chronic kidney disease in Asian population. Namely, in hypertensive Asian males the D allele carriers showed almost 4-fold greater risk for chronic kidney disease than the I allele carriers (21).

ACE POLYMORPHISM- ATHLETIC PERFORMANCE AND/OR BLOOD PRESSURE REGULATION

Although it is well known that elite sport performance depends not only on the dedication and the quality of training, it is also a polygenic trait (24). Along with the considerable number of studies that have emphasized associations among specific genetic polymorphisms and elite athletic performance, ACE gene polymorphism is one of the most popular and the most frequently studied (25).

Namely, many studies pointed out the association between the ACE insertion/deletion polymorphism and better endurance performance. On the other hand, according to the literature data, the ACE D allele is associated with superior sprint and other anaerobic performance in elite athletes (26, 27). Additionally, there is also a connection between ACE DD genotype and some pathological conditions such as pathogenesis of atherosclerosis, thrombosis and vasoconstriction that may occur in elite athletes (28). According to the data from Montgomery et al. people with ACE DD genotype have more striking increase in left ventricular mass, in response to regular and intensive physical activity than individuals with ACE II genotype (29). Some literature data also pointed to the fact that higher ACE activity may be proarrhythmic (30).

Additionally, numerous studies also noted the role of genetic variations, particularly in ACE gene, on the interindividual BP regulation. Study conducted by He et al. on Chinese population suggested that the ACE D allele was significantly associated with hypertension (31). Also, Ahmad Ali's study confirmed these results and noted that hypertensive cases have significantly higher frequency of the ACE mutant D allele carriers than I allele carriers (32). In association to the elite sport performance, it is well known that RAAS plays an important role in the regulation of myocardial growth, by increasing of plasma Ang II concentrations, leading to left ventricular hypertrophy (33).

Therefore, a physiological role of the RAAS, along with ACE gene polymorphism, appears likely in the development of left ventricular hypertrophy and hypertension in elite athletes.

This knowledge is largely applied nowadays, not only in sports medicine, but also in the treatment of different cardiac diseases.

CONCLUSION

This review puts forward the idea that RAAS, along with the ACE in its center, is an important factor in the BP control. Also, it is a key system in preserving kidneys' structure and function. Due to these roles, ACE with its I/D gene polymorphism represents a great potential for new antihypertensive drugs therapy development. Also, the understanding of the ACE I/D polymorphism, along with other potentially significant gene polymorphisms, has important implications beyond the world of extreme elite sport performance. Based on the current growing interest not only in hypertension treatment, but also in elite sport performance enhancement, there is an increased necessity to better understand this puzzle and face the new scientific challenges and discoveries.

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