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Review

A genetic approach to essential hypertension

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Abstract. Essential hypertension (EHT) has a complex etiopathogenesis, the role of genetic polymorphisms being extensively studied. One of the systems involved in the etiopathogenesis of EHT is the renin-angiotensin-aldosterone system (RAAS). RAAS plays a role in the pathogenesis of left ventricular hypertrophy (LVH), atherosclerosis (ATS) and ischemic heart disease (IHD). RAAS genetic polymorphism plays an important role in EHT through its components. The combined effect of RAAS mutations may influence the pathophysiological process of cardiac and vascular remodeling. Patients with EHT, carriers of the RAAS polymorphism, presented dyslipidemia, obesity, carotid ATS and LVH have an increased risk for ischemic coronary and cerebrovascular events. In the future, stratification of the prognosis of hypertensive patients, as well as drug therapy will be individualized depending on the genetic profile of these patients, in order to prevent the cardiovascular and cerebral complications of EHT.

Key Words: essential hypertension, renin-angiotensin-aldosterone system genetic polymorphisms, atherosclerosis, left ventricular hypertrophy

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Introduction

EHT, often called the "silent killer", affects 20-30% of the population of the globe (Sun et al 2018). Uncontrolled EHT is a predictor of ischemic cardiovascular and cerebrovascular events, causing an 8-fold increase in the risk of stroke and a 5-fold increase in the risk of coronary accidents (Dawber et al 1980, Heidari et al 2017, Singh et al 2016, Pavlyushchik et al 2017). In 2000, the prevalence of patients with EHT was 26.4% (972 million hypertensive patients). Studies show that by 2020, 75% of the causes of death will be due to EHT. Globally, the prevalence of adult patients with controlled EHT is 35%.

Compared to Caucasians, Africans have more severe and more treatment-resistant EHT forms (Mengesha et al 2019).

One of the systems involved in the etiopathogenesis of EHT is RAAS. RAAS also plays a role in the pathogenesis of LVH and ATS (Pop et al 2015).

The physiology of the renin-angiotensin-aldosterone system (RAAS)

EHT is a complex polygenic disease (10). The components of RAAS are renin (REN), angiotensinogen (AGT), the angiotensin converting enzyme I to II (ACE), angiotensin I (AngI), angiotensin II (AngII), the AngII type 1 receptor (R1 AngII) and the AngII type 2 receptor (R2 AngII) (fig. 1) (Fountain et al 2020). REN, secreted by juxtaglomerular cells, is an aspartate protease, which activates the RAAS cascade (Wang et al 2014). It acts on AGT, secreted by the liver, which is converted to AngI. ACE is a dipeptidyl carboxypeptidase produced in the lungs, which converts AngI to AngII. Many of the pathophysiological as well as physiological roles of RAAS are mediated via AngII, which acts through the two receptors: R1 AngII and R2 AngII. Both receptors are coupled to protein G (Arumugam et al 2016). AngII plays multiple roles: it stimulates aldosterone secretion from the adrenal cortex, causes sodium (Na) reabsorption in the renal tubules and potassium (K) excretion, which leads to an increase in blood pressure (BP) (Ji et al 2017, Mohana et al 2012). On the other hand, AngII is a vasopressor that inactivates bradykinin with a vasodilatator role. AngII induces oxidative stress, causes DNA degradation, and alters the vascular endothelium. AngII increases oxidative stress and apoptosis in endothelial cells, in cells inducing myocardial fibrosis and extracellular matrix production (Žaliaduonytė et al 2017).

AngII also plays a role in stimulating RNA, mRNA and protein synthesis in cardiomyocytes (Zhou et al 2016). Not least, AngII contributes to the pathogenesis of cardiac hypertrophy by stimulating some proteins that mediate the autophagocytosis process (Mustafina et al 2014).

Increased aldosterone values influence EHT, cardiac fibrosis, diastolic dysfunction, ventricular remodeling, ATS pathogenesis. High AGT and AngII values induce advanced ATS, LVH and heart failure (HF) (Žaliaduonytė et al 2015). AngII plays an important role in the pathogenesis of ATS, EHT, LVH, HF. The only way to inhibit the effect of AngII is by suppressing

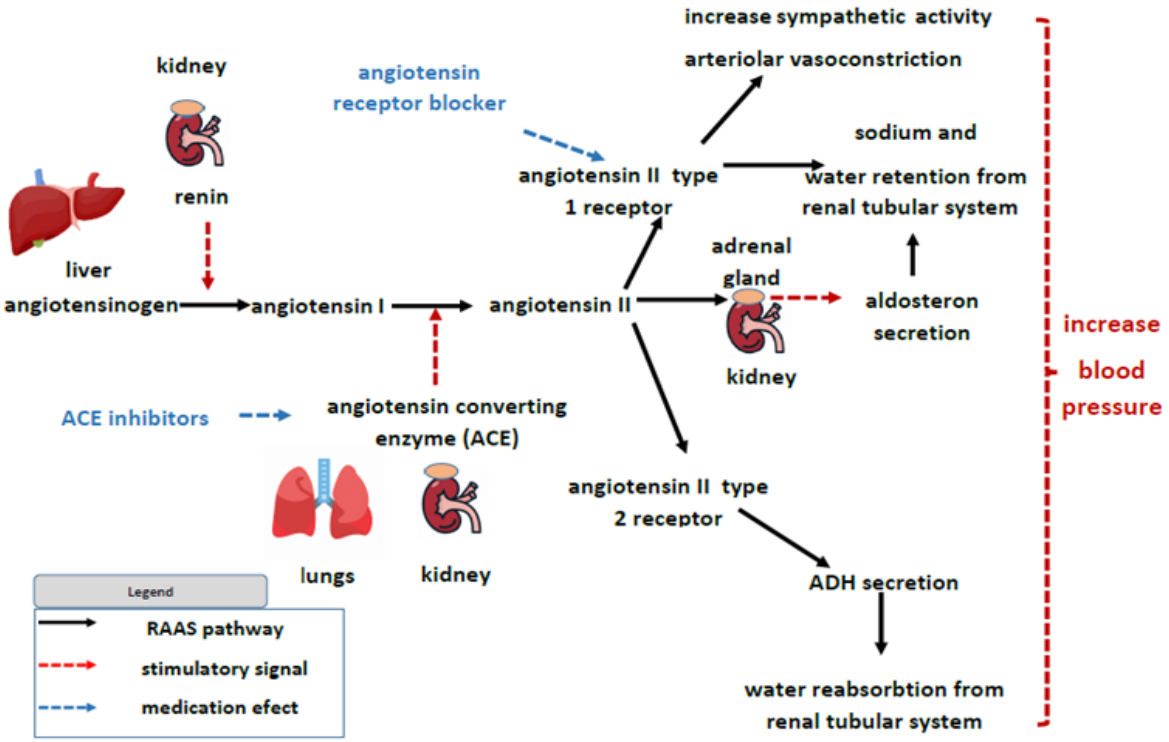

Figure 1. Renin –Angiotensin- Aldosterone System (RAAS) pathway

ACE secretion from the kidney or by antagonizing R1 AngII (Pop et al 2015).

AGT, REN, R1 AngII and R2 AngII are present in many tissues: brain, heart, vascular endothelium, vascular smooth muscles, lungs, liver, kidneys, adrenal glands, placenta, ovaries, testes (Jaźwiec et al 2018).

R1 AngII mediates the most important actions on AngII, such as stimulation of aldosterone secretion from the adrenal gland, vasoconstriction, water retention, cardiac contractility (Mustafina et al 2014). R2 AngII induces opposite effects: hypotension, vasodilatation, antihypertrophic effects, apoptosis, R1 AngII inhibition (Ji et al 2017).

RAAS has an important role in regulating BP through norepinephrine release, causes vasoconstriction, is involved in renal electrolyte and water balance homeostasis (Kolovou et al 2015, Heidari et al 2019, Pavlyushchik et al 2016). The positive role of RAAS is explained by the fact that it mediates regulation of BP values and vascular volume, response to inflammation, and vascular lesions. RAAS also has a negative role, because it is involved in the pathogenesis of EHT, induces fluid retention, mediates inflammatory processes, having a thrombotic and atherogenic effect. Changes in RAAS components are associated with chronic kidney disease (CKD) and diabetes mellitus (DM) (Jaźwiec et al 2018).

The genetic contribution of RAAS in the pathogenesis of EHT is 30-40%, the genes encoding RAAS components being involved in BP regulation.

RAAS genes and EHT

Due to the complex etiopathogenesis of EHT, the role of gene polymorphisms is being extensively studied. These genetic variants in association with dyslipidemia, insulin resistance, smoking lead to endothelial dysfunction, ATS, coronary artery involvement, ischemic heart events (Mohana et al 2012, Matsubara et al 2000).

The genetic polymorphisms located in genes encoding RAAS components that are associated with EHT include *M235T* and *T174M* (AGT gene), *I/D* and *A2350C* (ACE gene), *G83A* (REN gene), *A1166C* (R1 AngII gene), *C3123A* (R2 AngII gene) (Fig. 2) (Mohana et al 2012). The distribution of these polymorphisms is differentiated depending on sex and race.

M235T -AGT (*rs699*)

The AGT gene was the first gene encoding one of the RAAS components identified to be related to EHT. In 1992 and 1997, the *T174M* and *M235T* genetic variants were discovered. In 1992, the first study that associated the *M235T*-AGT polymorphism with EHT in Caucasians was conducted (Ji et al 2017).

M235T- AGT is a point substitution by which thymine is replaced by cytosine in nucleotide 704 (*T704C*), exon 2 of the AGT gene (Chr 1q42-q43), which determines the substitution of methionine with threonine at position 235 of AGT (*Met235Thr-M235T*) (Lynch et al 2012).

Studies suggest that the TT genotype is associated with systolic EHT in European Caucasian (French) and Japanese subjects. The risk is increased particularly in the case of women (Petkeviciene et al 2014). Individuals positive for the mutated T allele have increased AGT levels and increased BP values (Silva et al 2016). The frequency of this polymorphism is 35-40% in Caucasians, and the risk to develop high BP is 20% in homozygous carriers. The T allele is also frequent in the Chinese population.

Animal experiments have shown that AGT gene polymorphisms induce myocardial hypertrophy in mice, an effect independent of EHT (Wang et al 2003).

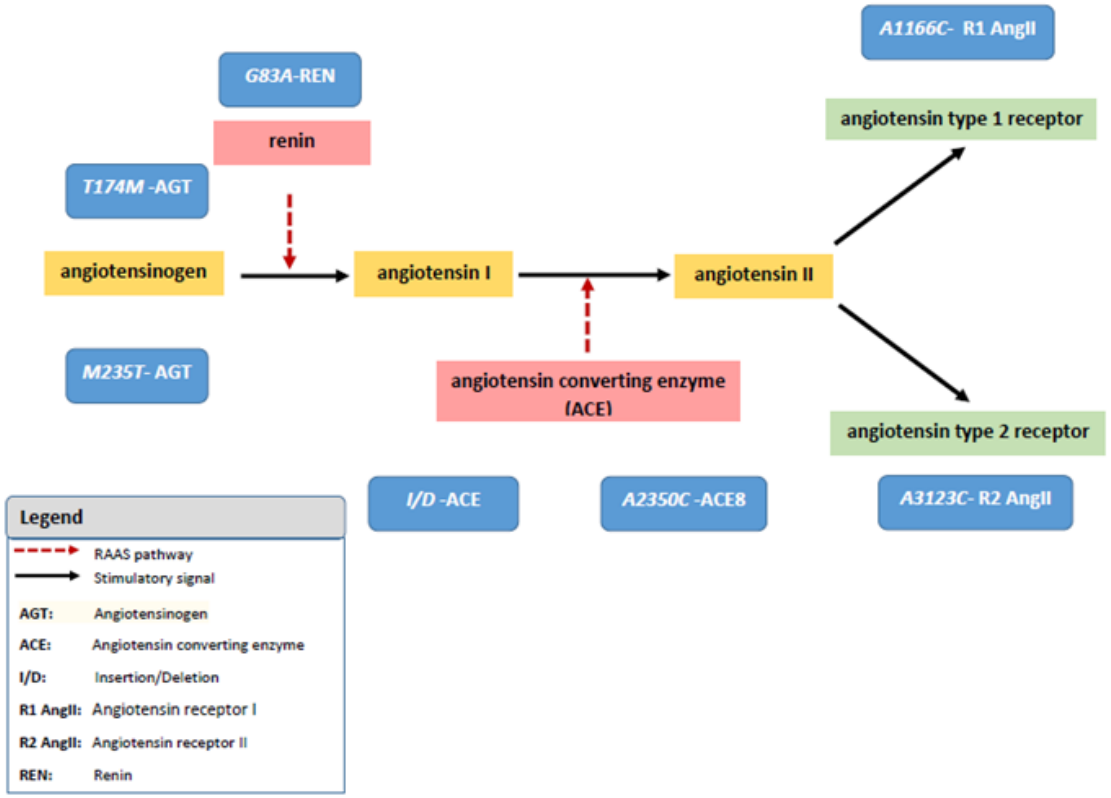

Figure 2. Renin- Angiotensin- Aldosterone System (RAAS) polymorphism

A study conducted in Brazilian patients of Caucasian origin showed that the MM genotype was not associated with EHT risk. In contrast, the TT genotype was associated with malignant EHT (Matsubara et al 2000).

In the black race, the T allele is not associated with EHT, but populations of Chinese and Japanese origin exhibited an increase in plasma AGT mRNA levels, demonstrating the association with EHT (Mohana et al 2012, Jia et al 2012).

The results regarding the association of this polymorphism with ischemic disease are controversial. Thus, in some studies, the TT genotype was identified with a high frequency in patients with ischemic disease (Borai et al 2018). On the other hand, other studies show that the M allele is frequent in patients with coronary disease and is a predictor of myocardial infarction (MI). Diabetic hypertensive patients carrying the TT genotype had an increased risk of coronary disease (Pavlyushchik et al 2016).

T174M- AGT (*rs4762*)

T174M- AGT is a point multation by which thymine is replaced by cytosine in nucleotide 521 (*T521C*), exon 2 of the AGT gene (Chr 1q42-q43), which results in the substitution of threonine by methionine at position 174 of AGT (Thr174Met-*T174M*) (Fountain et al 2020). The frequency of this genetic variation is 8-10% in the Caucasian population (Jia et al 2012). The T allele was associated with uncontrolled EHT and at the same time, patients carrying this allele had increased plasma AGT concentrations (Silva et al 2016).

A number of studies suggest the role of these polymorphisms in the pathogenesis of EHT (Say et al 2005, Glavnik et al 2007, Van Den Born et al 2007, Yuan et al 2009, Jiang et al 2009, Agachan et al 2003).

I/D -ACE (*rs1799752*)

I/D -ACE represents the insertion/deletion (I/D) of a fragment of the ACE gene of Ang I to Ang II (Chr 17q23.3), which causes an increase in both the plasma levels of ACE and its activity. Allele distribution is differentiated depending on ethnicity, so that the I allele is more common in Asian and Mongoloid populations, and the D allele is more frequent in American and European Caucasians (Singh et al 2016). In 1990, this genetic variation was associated with the risk of EHT (Ji et al 2017). This has been the most studied genetic variation associated with EHT over the past years, correlated in particular with the increase in BP in men. The D/D genotype was also associated with increased plasma and cellular ACE levels, which theoretically explains the high BP values. Previous studies showed that homozygous carriers of the D allele had increased serum ACE activity (Sun et al 2018, Singh et al 2016, Pavlyushchik et al 2016).

Studies published so far suggest the association of *I/D*-ACE with EHT (Bedi et al 2006, Eroglu et al 2006, Bautista et al 2008, Niu et al 2015, Ji et al 2010, Pan et al 2016).

The Framingham study which evaluated male subjects showed that the D/D genotype is associated with an increase in diastolic BP (Petkeviciene et al 2014).

The *I/D*- ACE genetic variation is associated with EHT in Malaysia, Bangladesh, Europe, North India (Pavlyushchik et al 2016).

In India, the I allele was associated with EHT in male patients. The D allele was associated with increases in BP in the Asian population (China, Tibet), compared to Australian carriers of the I allele (Zotova et al 2019). The D allele of the ACE gene was associated with preeclampsia and gestational EHT (Sousa et al 2018).

The *I/D*- ACE genetic variation was not associated with EHT or IHD in Brazilian Africans or Caucasians (Matsubara et al 2000). A number of studies demonstrated an association between the I/D- ACE polymorphism with ischemic cardiovascular and cerebral events (Sun et al 2018, Singh et al 2016, Pavlyushchik et al 2016). The D allele induces an increase in plasma as well as tissue ACE levels; consequently, it may indirectly cause the development of ST-segment elevation myocardial infarction (STEMI) in patients with acute coronary syndrome. Studies carried out in Saudi Arabia, Turkey and Iran demonstrate that the ACE D allele is associated with ischemic cardiac events (Silva et al 2016).

Studies conducted in Japanese patients who had ischemic cardiac events showed an association between the D allele and hypertriglyceridemia (HTG) (Singh et al 2016).

On the other hand, the *I/D*- ACE genetic variation plays an important role in the regulation of lipid metabolism. In women, the I/I genotype is associated with increased high density lipoprotein (HDL) cholesterol values. Hypertensive patients carrying the D/D genotype had hypertriglyceridemia (HTG) and high HDL cholesterol values compared to normotensive patients.

In the Caucasian population, but not in the Chinese population, the D/D genotype was associated with acute MI (AMI), coronary spasms, IHD, idiopathic dilated cardiomyopathy (IDC), hypertrophic cardiomyopathy (HCM), LVH and familial sudden cardiac death (Ko et al 1997).

Homozygous Chinese carriers of the D/D genotype as well as of the M235T- AGT genetic variation are predisposed to coronary disease and AMI (Sun et al 2011).

A2350C -ACE8 (*rs4343*)

A2350C- ACE8 is a point mutation by which adenine is replaced by guanine in nucleotide 2350 of the ACE2 gene (Chr 17q23.3). Patients carrying this genetic variation have an increased risk of EHT, IHD, diabetic nephropathy, CKD and Alzheimer's disease. The *I/D*- ACE and the *A2350C*- ACE8 genetic variations have an important role in EHT, in association with the presence of other risk factors such as smoking, alcohol consumption, obesity and DM (Lin et al 2017).

A study conducted in the Iranian population showed that there is no correlation between the *I/D*- ACE gene polymorphism, the *A2350C* genetic variation and coronary disease (Mohana et al 2012, Pavlyushchik et al 2016).

A1166C- R1 AngII (*rs5186*)

AngII exerts its roles through its receptors: R1 AngII and R2 AngII. R1 AngII is expressed in various tissues: brain (hypothalamus), adrenal gland cortex, heart, vessels, mesangial cells in the kidney (Jaźwiec et al 2018). By binding AngII to R type 1, it stimulates aldosterone release, induces vasoconstriction, water retention, vascular smooth muscle cell proliferation and hypertrophy.

The *A1166C*- R1 AngII genetic variation is a point mutation in the R1 AngII gene (Chr3q21-q25), by which adenine in nucleotide 1166 of the gene is replaced by cytosine. The *A1166C* gene polymorphism does not influence the transcription of DNA to mRNA or the translation of the R1 AngII gene, but influences the receptor function. The *A1166C*-R1 AngII genetic variation induces an increase in AngII activity and concentration, thereby influencing the increase of the carotid bulb size and activity. Muscle hypertrophy occurs as a result of increased mitoses (Jaźwiec et al 2018).

Studies conducted by a number of researchers have shown a significant association of the mutated C allele with EHT (Glavnik et al 2007, Van Den Born et al 2007, Yuan et al 2009, Jiang et al 2009, Agachan et al 2003, Bedi et al 2006).

The *A1166C*- R1 AngII genetic variation is associated with myocardial type I collagen synthesis, being involved in the pathogenesis of EHT and HF (Shamaa et al 2016, Wu et al 2013). Studies conducted in Caucasian subjects have shown an increase in arterial wall reactivity to AngII and an influence on vasomotor function in carriers of the *A1166C*- R1 AngII genetic variation (Shamaa et al 2016, Mohana et al 2012). No statistical correlation was found between the *A1166C* - R1 AngII genetic variation and the German Caucasian population or the Hispanic population (Fountain et al 2020, Mohana et al 2012).

Other studies have shown that the *C1166*- R1 AngII allele and not the A allele is one of the factors responsible for the increase in LV wall thickness (Lin et al 2007). A number of studies conducted in populations from Hungary, France (women with EHT), Japan, Tunisia have shown that the frequency of the C allele was higher in hypertensive patients (22%) compared to the frequency of the *A1166C*- R1 AngII genotype (Lin et al 2017, Fan et al 2016). The RAAS polymorphism of R1 AngII was associated with EHT in pregnancy.

The *A1166C* - R1 AngII polymorphism is involved in the development of coronary heart disease, being frequently found in the Asian population (Ko et al 1997).

Some studies analyzed the possible association between *I/D*- ACE and *A1166C*- R1 AngII and the risk of coronary disease, but did not confirm this association (Ko et al 1997).

A3123C- R2 AngII (rs *11091046*)

R2 AngII is expressed in the following tissues: brain, heart, adrenal glands, kidneys, reproductive organs (Arshad et al 2020). *A3123C* - R2 AngII is a point mutation in the AngII type 2 receptor gene (Chr xq22-q23), by which adenine is replaced by cytosine in nucleotide 3123 of the gene (Vamsi et al 2013). R2 AngII expression may influence apoptosis, also influencing the risk of EHT (Eroglu et al 2008).

Although the presence of genetic variations in R1 AngII and R2 AngII genes represented risk factors for lead poisoning, fibrosis, schizophrenia, thyroid dysfunctions, the simultaneous presence of the two genetic variations is not a predictor for cardiovascular diseases (Ji et al 2017). A number of studies have shown that in men, genetic variations located in the R1 AngII genes are predominant, while in women, those located in the R2 AngII genes prevail (Mohana et al 2012).

G83A -REN (*rs2368564*)

G83A -REN is a point mutation by which guanine is replaced by adenine in nucleotide 83 of the REN gene (Chr 1q32.1). This genetic variation is associated with an increase in REN activity. Some studies show an increased frequency of this genetic variation in patients diagnosed with EHT (Wu et al 2013, Vamsi et al 2013).

The REN gene was mentioned as being responsible for the etiology of essential EHT in various ethnic groups (Sun et al 2011).

RAAS and LVH

We wanted to highlight the relationship between RAAS polymorphism and LVH as hypertension mediated organ damage.

RAAS is involved in the pathogenesis of ischemic cerebrovascular events (MI, stroke, HF), generalized ATS, through the formation of reactive oxygen species and the induction of oxidative stress, which causes inflammation, cardiac remodeling and endothelial dysfunction (Arumugam et al 2016). The AGT gene is associated with LV remodeling after MI.

RAAS plays a role in the pathogenesis of LVH through an increase in Ang II values, via stimulation and activation of R1 AngII, which is associated with an increase in LV muscle mass (Pavlyushchik et al 2016, Sun et al 2011). This explains the effect of ACEIs and ARBs in cardiac remodeling in LVH, a beneficial effect compared to beta-blockers and diuretics (Arumugam et al 2016). The therapeutic strategy consists of preventing HF and CKD with ACEIs and AngII receptor blockers (Arumugam et al 2016).

A number of studies, which included healthy subjects (athletes) and hypertensive patients on dialysis, analyzed and demonstrated the association between RAAS components and LV remodeling in the two categories of participants (Borai et al 2018).

In Caucasian men with moderate essential EHT, the TT235 genotype was associated with LVH (Lynch et al 2012). In contradiction to the results of this study, the *MM235* genotype is associated with LV remodeling after MI (Zaliaduonyte-Peksiene et al 2014).

Literature data suggest that the trophic effects of AngII can lead to an increase in LVH. Plasma AngII was significantly correlated with LVH independently of systolic BP (Lin et al 2007). AngII has direct effects on the myocardium and may cause the development of EHT. Chronic AngII increases can lead to cardiac hypertrophy and HF (Zhou et al 2016).

The *D/D* and *I/D* genotype of ACE was significantly associated with LVH progression after MI. Furthermore, the presence of the D allele is a risk factor for HF after MI (Zotova et al 2019).

The simultaneous presence of the M235T- AGT and I/D- ACE genetic variations is associated with an increase in the risk of EHT and LVH, because the association of at least 2 genes increases the risk of cardiovascular complications (Lynch et al 2012, Wang et al 2003).

LVH severity increases significantly if at least two genetic variations are present. Comparative studies showed that the presence of the *M235T*- AGT genetic variation alone did not represent a risk factor for cardiac remodeling after MI (Žaliaduonytė-Pekšienė et al 2014). The simultaneous presence of the *M235T*- AGT and *I/D* -ACE genetic variations increases ischemic risk in hypertensive patients. Individuals homozygous for both DD -ACE and *TT235*-AGT have an increased risk of IHD, even if they do not have DM (Wang et al 2003).

The *I/D*-ACE genetic variation was frequently found in male hypertensive patients. Its association with the *M235T*- AGT genetic variation predisposes to LVH in the case of hypertensive patients (Kurbanova et al 2010).

RAAS and the risk of ATS

Atherosclerotic coronary disease is a health problem in industrialized countries, contributing to the high morbidity and mortality of patients with this diagnosis.

The physiological mechanisms of ATS are vascular inflammation, generation of reactive oxygen species and alteration of endothelial function (Žaliaduonytė-Pekšienė et al 2017, Cozma et al 2018).

RAAS plays a role in the development of oxidative stress, through an increase in NADPH activity, reactive oxygen species activation and LDL peroxidation. RAAS also induces an increase in vascular permeability, activation of pathways and production of mediators of inflammation.

In addition, RAAS is involved in the pathogenesis of endothelial dysfunction by remodeling tissues and by decreasing nitric oxide concentration, causing vasoconstriction and platelet aggregation (Ji et al 2017, Arumugam et al 2016).

RAAS components play a role in the development of EHT because they influence endothelial function and the balance between vasodilatation and vasoconstriction.

Conclusions

RAAS plays a role in the pathophysiology of cardiovascular diseases. The genetic variants involving RAAS components, mainly the *M235T*- AGT, *I/D* -ACE, *A1166C*- AngII R1 polymorphisms, influence cardiac remodeling, predispose to LVH and in the final stage of heart disease, induce HF.

In the future, stratification of the prognosis of hypertensive patients, as well as drug therapy used to prevent the cardiovascular and cerebral complications of EHT will be individualized depending on the genetic profile of these patients.

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