Adrenergic Receptors Gene Polymorphisms and Autonomic Nervous Control of Heart and Vascular Tone

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Summary
Adrenergic receptors (ARs) are the primary targets of catecholamines released from the sympathetic nerve endings during their activation. ARs play a central role in autonomic nervous system and serve as important targets of widely used drugs. Several ARs gene polymorphisms were found to be associated with cardiovascular disease in previous clinical studies. Although more precise mechanism of the polymorphisms influence on autonomic control of cardiovascular system was studied in many previous physiological studies, their results are not unequivocal. This paper reviews the results of clinical and physiological studies focused on the impact of selected common single nucleotide polymorphisms of ARs genes involved in sympathetic control on cardiovascular system and its control. In summary, many studies assessed only a very limited range of cardiovascular control related parameters providing only very limited view on the complex cardiovascular control. The overview of partially contradicting results underlines a need to examine wider range of cardiovascular measures including their reactivity under various stress conditions requiring further study. It is expected that an effect of one given polymorphism is not very prominent, but it is suggested that even subtle differences in cardiovascular control could – on a longer time scale – lead to the development of severe pathological consequences.

Key words
Adrenergic receptors • Polymorphisms • Cardiovascular control

Introduction
Adrenergic receptors (ARs) play a key role in the transmission of information within sympathetic part of autonomic nervous system (ANS). Human genome encodes 9 different types of ARs with differing pharmacological properties and localization. These receptors are located also in heart and vessels playing very important role in the cardiovascular system control and representing an important target of various medications (Ahles and Engelhardt 2014).

Cardiovascular system (CVS) disorders are among the leading cause of mortality worldwide. Genetic predisposition plays an important role in the pathogenesis of these complex diseases. Identification of the genetic factors role in the origin and development of cardiovascular disorders could bring earlier and more aimed detection of pathological processes and better prediction of future risks (Kuneš and Zicha 2009).

Thanks to the progress in pharmacology, molecular biology and genetics of adrenergic signaling pathways, several gene polymorphisms associated with altered ANS function were identified during last 20 years. The gene polymorphisms in ARs genes were most often found to be associated with cardiovascular diseases, bronchial asthma, chronic obstructive pulmonary disease and obesity (Katsarou et al. 2018). These genetic variants could modify initiation and progression of CVS disorders.
but also a response to pharmacological treatment by betablockers via their influence on sympathetic control (Kenakin 2013).

ANS assessment by evaluation of various cardiovascular and hemodynamic measures provides an important information on cardiac and vascular control state. Changes in these parameters in relation to various genotypes could indicate the potentially clinically important influence of the given genotype on ANS function. A recognition of significant relations between gene polymorphism and resulting phenotype represents a progress in the better understanding of various disorders pathogenesis. In future, genotyping of individuals can contribute to the improved cardiovascular risk estimation with the perspective of earlier and more effective therapeutic intervention. It could represent an important step forward in the personalized medicine.

The major aim of this review is to summarize information from the previous studies on the influence of selected common ARs genes polymorphisms on cardiovascular control by ANS from the physiological, pathophysiological and clinical point of view.

Polymorphisms of adrenergic receptors genes

ARs belong to the large group of receptors coupled with G protein (G protein coupled receptors – GPCR). Their activation lead to triggering of intracellular signal pathways. Structurally, these receptors are characterized as heptahelical transmembrane receptors with extracellular amino-terminal end and intracellular carboxy-terminal end (Capote et al. 2015). GPCRs are an important part of sympathetic nervous system mediating central and peripheral effects of catecholamines – most importantly norepinephrine and epinephrine. Almost every cell has in its cytoplasmic membrane one or more subtypes of ARs. These receptors are crucial for preserving cell, organ and whole body homeostasis at rest but also under physiological or pathological stress (Brunton et al. 2008).

Human genome encodes 9 ARs grouped into 3 families: α1-, α2- and β-AR. Each family is further composed of three subtypes: α1 (α1a, α1b, α1D), α2 (α2A, α2B, α2C) and β (β1, β2, β3) ARs. Binding of ligand (agonist) on ARs trigger intracellular cell signaling pathways via their binding on heterotrimeric G protein where specific type of G protein depends on the receptor family. Namely, α1-ARs are coupled with Gαq protein activating phospholipase C. Gαq protein is coupled with α2-AR causing an inhibition of adenylyl cyclase. β-ARs are coupled with Gαs proteins stimulating adenylyl cyclase (Ciccarelli et al. 2017) (Fig. 1).

In the cardiovascular system, catecholamines through ARs play a very important role in the control of heart and vessels. ARs are abundant in cardiovascular system. α1-ARs and α2-ARs are located in smooth muscle cells of vasculature and their activation leads to vasoconstriction. β1-ARs are expressed in the heart and their activation results in increased heart rate (positive chronotropic effect), increased cardiac contractility (positive inotropic effect) and increased atrio-ventricular conduction velocity (positive dromotropic effect). β2-ARs are expressed mostly in vascular smooth muscle, skeletal muscle and – to a lower extent – also in cardiomyocytes. Their activation leads to vasodilation and as a consequence to an increased perfusion of target organs (Lymperopoulos et al. 2021). Taken together, ARs play role in a wide spectrum of cardiovascular control mechanisms and also represent an important binding place of many currently used medicaments (Flordellis et al. 2004).
There are many genetic variations in the human genome characterized by the variability in DNA sequence among individuals. These variations are mostly in a form of single nucleotide substitution – single nucleotide polymorphisms (SNP). On average, they occur in almost every 100 – 300 base pairs in human genome (Hanchard 2005). SNPs can represent synonymous or nonsynonymous substitution (Fig. 2). Synonymous substitution does not lead to any change in amino acids sequence in the encoded protein (because of the degeneracy of the genetic code), they are functionally silent and evolutionarily neutral. In contrast, nonsynonymous substitution changes the corresponding amino acid in the protein potentially influencing protein function although most of them have only very small or no effect on the resulting phenotype. Polymorphisms commonly occur in different populations, with the allelic frequency corresponding to individual SNPs varying among them (Ohta 2001).

Haplotype is a combination of alleles related to various genes along the same chromosome inherited as one unit. Various combinations of alleles related to several polymorphisms – haplotypes – may occur in a certain population more frequently. Polymorphisms in coding and regulatory regions can influence protein function or expression, potentially leading to a development of various disorders or an altered drug response (Crawford and Nickerson 2005, Hanchard 2005). Therefore, SNPs are used as molecular markers in many genetic and pharmacogenomic studies focused on various diseases. In such studies, the aim is to identify SNPs that cause changes in cellular biological processes involved in the pathogenesis of various pathological conditions. Genome-wide association studies are a typical approach to identification of increased risk related alleles involving extensive genotyping of polymorphisms in a group of patients and in a healthy control population to compare differences in genotypes for all phenotypic characteristics studied. In pharmacogenetic studies, the aim is to elucidate the effects of genetic polymorphisms on drug response. The genotyping methods usually involve the production of allele-specific products for selected polymorphisms, requiring an amplification step by polymerase chain reaction (PCR), followed by their detection (Kim and Misra 2007).

Genetic factors may represent one of the causes of a large interindividual variability in ANS activity. Polymorphisms in genes for proteins involved in ANS control may alter its function, resulting in subsequently altered autonomic control of various organ systems, including cardiovascular system. Subsequent autonomic dysregulation may be associated not only with the pathogenesis of various cardiovascular diseases (hypertension, ischemic heart disease, various cardiomyopathies), but also with the development of other diseases (e.g. obesity) (Ahles and Engelhardt 2014, Kuneš and Zicha 2009).

Except for α1D, all subtypes of AR are polymorphic, with genetic variations in both coding and noncoding regions of the gene (Flordellis et al. 2004). Many polymorphisms occur in AR genes, but only some of them demonstrate also functional effect. Based on the previously published literature, we selected a set of gene polymorphisms with demonstrated significant effects on the cardiovascular autonomic control assessed through various output parameters and characteristics (Table 1).

Polymorphisms of α1A-AR genes

ADRA1A gene encodes α1A-AR localized dominantly in vascular smooth muscles but they are also present in the heart and urogenital system, gastrointestinal system and liver. α1A-AR participates in
the blood pressure control by sympathetic nerves via their vasoconstriction effects on blood vessels. α_{1A}-AR agonists as vasoconstrictors can be used to treat hypotension.

**Table 1. Focus of previous studies assessing effects of adrenergic receptors polymorphisms**

| Receptor | Polymorphism | Association | References |
|----------|--------------|-------------|------------|
| α_{1A}-AR | rs1048101 | HR | Iacoviello et al. 2006, Kelsey et al. 2012 |
| | | HR variability | Matsunaga et al. 2007a, Iacoviello et al. 2006 |
| | | PVR | Kelsey et al. 2012 |
| | | BP | Freitas et al. 2008, Nunes et al. 2014 |
| | | hypertension | Freitas et al. 2008, Gó et al. 2006 |
| | | antihypertensive treatment | Jiang et al. 2005, Zhang et al. 2009 |
| α_{2A}-AR | rs1800544 | PVR | Kelsey et al. 2012 |
| | | BP | Kelsey et al. 2012, McCaffery et al. 2002, Rana et al. 2007, Rosmond et al. 2002 |
| | | antihypertensive treatment | Kurkin et al. 2011, Yağar et al. 2011 |
| | | ADHD | Schmitz et al. 2006, Polanczyk et al. 2009 |
| | | metabolic disorders | Grudell et al. 2008, Lima et al. 2007 |
| β_{1}-AR | rs1801252 | HR | Wilk et al. 2006, Kelley et al. 2018, Mahesh Kumar et al. 2008, Ranade et al. 2002 |
| | | stroke index | Wittwer et al. 2011 |
| | rs1801253 | HR | Kindermann et al. 2011 |
| | | PVR | Kindermann et al. 2011 |
| | | inotropy | Bruck et al. 2005, Huntgeburth et al. 2011, Kindermann et al. 2011, La Rosée et al. 2004 |
| | | BP | Tikhonoff et al. 2008 |
| | | hypertension | Gjesing et al. 2007, Johnson et al. 2011, Tikhonoff et al. 2008 |
| | | antihypertensive treatment | Shahin et al. 2019, Si et al. 2014, Wu et al. 2015, Chen et al. 2018, Lee et al. 2016 |
| β_{2}-AR | rs1042713 | HR | Snyder et al. 2006, Wittwer et al. 2011, Atala et al. 2015, Eisenach et al. 2012 |
| | | HR variability | Yang et al. 2011, Atala et al. 2015 |
| | | cardiac output, stroke volume | Rokamp et al. 2013, Snyder et al. 2006, Wittwer et al. 2011 |
| | | blood pressure | Masuo et al. 2005a, Snieder et al. 2002, Snyder et al. 2006 |
| | rs1042714 | HR | Wittwer et al. 2011 |
| | | HR variability | Atala et al. 2015, Matsunaga et al. 2007b |
| | | blood pressure | Masuo et al. 2005b, Snieder et al. 2002, Komara et al. 2014 |
| | | coronary artery disease | Li et al. 2019 |
| | | overweight, obesity | Aradillas-García et al. 2017, Daghhestani et al. 2012 |
| | | insulin resistance | Mitra et al. 2019 |
| β_{3}-AR | rs4994 | coronary artery disease | Kumar et al. 2014 |
| | | hypertension | Li et al. 2018, Yang et al. 2017 |
| | | overweight, obesity | Mirrakhimov et al. 2011, Xie et al. 2020 |
| | | diabetes mellitus type 2 | Ryuk et al. 2017 |

AR, adrenergic receptor; HR, heart rate; PVR, peripheral vascular reactivity; BP, blood pressure; ADHD, Attention Deficit Hyperactive Disorder
while α1A-AR antagonists can decrease blood pressure in arterial hypertension. Activation of α1A-AR in the heart mediates increased inotropy, cardiomyocytes hypertrophy and ischemic preconditioning of the heart (Brunton et al. 2008, Docherty 2019).

Common polymorphism of ADRA1A gene rs1048101 (Arg347Cys) localized on 8th chromosome result in nonsynonymous mutation. Substitution of adenine for guanine (A>G) causes substitution of amino acid arginine (Arg) for cysteine (Cys) in amino acid position 347 – it represents a change in the translated protein potentially influencing its function. Global minor allele A frequency is 35 %, in Europe up to 57 %.

Although in vitro studies did not demonstrate any effect of polymorphic variants on receptor function (Lei et al. 2005, Shibata et al. 1996), clinical and physiological studies revealed associations between polymorphisms and several cardiovascular measures pointing towards their potential clinical significance.

Activation of vascular α1A-ARs represents major mechanism of constriction of smooth muscle cells in vasculature. However, assessment of ADRA1A gene polymorphisms effects on phenylephrine (agonist of α1A-ARs) mediated venoconstriction showed that genetic component explains only a small part of interindividual variability of the response. From 32 assessed ADRA1A gene polymorphisms (including common rs1048101 polymorphism), there was found association of altered response to phenylephrine mediated venoconstriction with only two SNPs (rs574647 and rs1079078). Therefore, an association between rs1048101 and venoconstriction mediated by agonist observed in previous studies was not confirmed on larger study (Adefurin et al. 2015, Sofowora et al. 2004).

On the other hand, during application of various stressors (cold stress test, mental arithmetics) rs1048101 polymorphism was associated with peripheral vascular resistance (PVR) reactivity indicating altered vasomotor control. The observed association was influenced by sex – Arg allele presence leads to lower increase of PVR in males while opposite effect (higher reactivity of PVR) was observed during cold stress test in females (Kelsey et al. 2012). In another study, rs1048101 polymorphism was related to the occurrence of vasovagal syncope (Arg allele) – potentially indicating altered vasomotor control in accordance with previous study (Hernández-Pacheco et al. 2014). Similarly, authors observed a significant sex-dependent association of this polymorphism with heart rate reactivity on cold stress test: females with Arg allele had more prominent heart rate increase during test, while opposite was observed in males (Kelsey et al. 2012). Resting heart rate was increased in allele Cys carriers and decreased in allele Arg carriers (Iacoviello et al. 2006).

Analysis of heart rate variability showed decreased values of low frequency power expressed as a percentage of total power (LF%), decreased LF/HF ratio and increased high frequency power (HF%). Although these indices were challenged, these results potentially point towards a shift in sympatho-vagal balance towards parasympathetic dominance in allele Cys presence (Matsunaga et al. 2007a). These findings were confirmed by decreased overall and beat to beat variability (SDNN and rMSSD measures, respectively) (Iacoviello et al. 2006). However, genome wide association study of heart rate variability identified several polymorphisms in ADRA1A gene associated with heart rate variability alterations but no effect of rs1048101 polymorphism on assessed measures was found (Newton-Cheh et al. 2007). In a small study (16 subjects), an association between Cys allele and lower dromotropic response before and during epinephrine infusion was found (Snapir et al. 2003). The results indicate that α1A-ARs could play an important role not only in vessels but also in human heart.

Considering the important role of α1A-ARs in the vascular resistance control, several studies evaluated potential influence of rs1048101 polymorphism with blood pressure values in healthy population and on arterial hypertension. Allele Cys was associated with an increased blood pressure in healthy Brazilian population (Freitas et al. 2008, Nunes et al. 2014) as well as with the hypertension (Freitas et al. 2008). In contrast, Chinese clinical study revealed association between arterial hypertension and presence of allele Arg (Gu et al. 2006). In another studies, association of this polymorphism with hypertension was not demonstrated (Iacoviello et al. 2006, Xie et al. 1999).

Pharmacogenomic studies observed interindividual variability in therapeutic response to antihypertensives. Irbesartan (angiotensin II antagonist) decreased blood pressure to a lower extent in allele Cys carriers indicating its lower effectiveness (Jiang et al. 2005). On the other hand, calcium channel blocker nifedipine decreased blood pressure in Cys allele carriers more prominently (Zhang et al. 2009).

In conclusion, despite the dominant role of α1A-ARs in vasomotor control, the results of previous studies did not provide clear conclusion about the effect of
Polymorphisms of α2A-AR genes

α2A-ARs are mostly involved in the central nervous system and cardiovascular control. ADRA2A gene encodes α2A-ARs localized in cerebral neurons, in vascular and visceral smooth muscle cells (mediating contraction) (Skinner et al. 2018). Most importantly, α2A-ARs are located in presynaptic endings on central and peripheral sympathetic nerves contributing to presynaptic inhibition of the norepinephrine release. Inhibition of sympathetic effects by presynaptic α2A-ARs results in decreased peripheral vasoconstriction followed by blood pressure decrease. On the other hand, vascular α2A-AR mediate – to a much lower extent compared to α1A-ARs – peripheral vasoconstriction (Flordellis et al. 2004).

Gene encoding α2A-ARs is polymorphic and the most commonly studied polymorphism rs1800544 (C1291G) characterized by substitution C>G is localized in the noncoding region of the ADRA2A gene. Minor allele occurs in 46 % of worldwide population, in Europe its frequency reaches 74 %.

Polymorphism rs1800544 was not analyzed in vitro – the impact of polymorphic variants on the receptor function is unclear. However, several studies revealed impact of this polymorphism on cardiovascular control indicating its effect in vivo.

Studies focused on vascular reactivity to stress demonstrated association of rs1800544 polymorphism with vascular resistance – a magnitude of PVR increase was linearly related to the number of allele G copies. Similar, but less prominent, association was observed for diastolic blood pressure. Authors suggest that increased peripheral vasoconstriction results from the decreased presynaptic function of allele G associated α2A-ARs leading to a decreased inhibition of norepinephrine release (Kelsey et al. 2012). In contradiction, several studies focused on resting blood pressure values observed an increase in allele C carriers (Kelsey et al. 2012, McCaffery et al. 2002, Rana et al. 2007, Rosmond et al. 2002). Pharmacogenomic studies observed altered response to dexmedetomidine (agonist of α2A-AR) in relation to genotype – allele C carriers had a decreased hypertensive response (Kurnik et al. 2011) while allele G was associated with a prolonged effect duration (Yağar et al. 2011) potentially indicating hypofunction effect of allele C on the receptor. In addition, association of this polymorphism with attention deficit hyperactivity disorder (ADHD) occurrence and its therapy (Schmitz et al. 2006, Polanczyk et al. 2007), as well as with obesity and metabolic disorders was found (Grudell et al. 2008, Lima et al. 2007).

In conclusion, previous studies indicate potential effect of rs1800544 on vascular control but the results are equivocal requiring further studies.

Polymorphisms of β1- and β2-ARs genes

β-adrenergic receptors play an important role in cellular signalling related mostly to cardiac sympathetic control. In human heart, the dominance of β1-ARs over β2-AR was found: ratio of β1-ARs : β2-AR number is 70 – 80 % : 30 – 20 % in ventricles and 60 – 70 % : 40 – 30 % in atria. Thus, both ARs subtypes are involved in the positive intropic and chronotropic effects of catecholamines on the heart (Leineweber et al. 2004, Svoboda et al. 2004). Many nonsynonymous polymorphisms in β-AR genes were detected with the influence on receptor function potentially affecting cardiovascular control and involved in cardiovascular disease pathogenesis (Ahles and Engelhardt 2014).

In ADRB1 gene for β1-AR two common polymorphisms (rs1801252, Ser49Gly), (rs1801253, Arg389Gly) and in ADRB2 gene for β2-AR another two common polymorphisms (rs1042713, Arg16Gly), (rs1042714, Gln27Glu) were found. These nonsynonymous substitutions with potential effects on receptor function were most frequently studied both in vitro and in vivo (Leineweber and Brodde 2004; Ahles and Engelhardt 2014).

In vitro studies focused on effect of polymorphic variants on β1-ARs function observed in rs1801252 polymorphism altered function of receptor in the presence of allele Gly (alterations in binding affinity of agonists and antagonists, in adenyl cyclase activity, receptor downregulation) (Levin et al. 2002, Rathz et al. 2002). However, another study did not confirm this polymorphism related alterations in receptor characteristics (Baker et al. 2013). Concerning rs1801253
polymorphism, several studies agree on its hyperfunction associated with Arg allele (Joseph et al. 2004, Mason et al. 1999, Warne et al. 2012), but — similarly — another in vitro studies did not find any difference in receptor function between genotypes (Baker et al. 2013, Rochais et al. 2007). Altered receptors characteristics are connected also with both β1-AR polymorphisms (rs1042713, rs1042714) (Green et al. 1995, 1994).

In vivo studies observed association of Ser49Gly (ADRB1) polymorphism with chronotropic cardiac control — a presence of Gly allele was associated with increased resting heart rate (Wilk et al. 2006) and heart rate during exercise (Kelley et al. 2018, Mahesh Kumar et al. 2008). Paradoxically, in one study this allele was related with a decrease in heart rate (Ranade et al. 2002). Evaluating cardiovascular system reactivity to orthostasis, authors observed less expressed stroke index (stroke volume standardized to body surface area) decrease in allele Gly carriers (Wittwer et al. 2011). Other hemodynamic measures (blood pressure, cardiac output, stroke volume, PVR) and heart rate variability indices were not found to be associated with this polymorphism at rest (Iacoviello et al. 2006, Kindermann et al. 2011, Sandilands et al. 2019), or during orthostasis (Matsunaga et al. 2007b).

Arg389Gly (ADRB1) polymorphism is most often associated with inotropic heart rate control changes. Several studies evaluated cardiac inotropy by dobutamine stress echocardiography. These studies agree in an increased cardiac contractility associated with allele Arg (Bruck et al. 2005, Huntgeburth et al. 2011, Kindermann et al. 2011, La Rosée et al. 2004) in accordance with hyperfunction effect of allele Arg in vitro (Joseph et al. 2004, Warne et al. 2012). In contrast, analysis of an increase in cardiac contractility evoked by dynamic exercise did not demonstrate significant effects of Arg389Gly polymorphism on cardiac inotropy (Büscher et al. 2001, Leineweber et al. 2006, Rokamp et al. 2013, Snyder et al. 2006). After application of α1-, β1-, and β2-AR agonist dobutamine allele Arg was also associated with higher increase of heart rate and higher PVR underlining the suggested hyperfunction of Arg allele (Kindermann et al. 2011). This allele was further associated with an increase of diastolic blood pressure in healthy population (Tikhonoff et al. 2008), and with an increased prevalence of hypertension (Gjesing et al. 2007, Johnson et al. 2011, Tikhonoff et al. 2008). Studies focused on antihypertensive pharmacotherapy demonstrated an association of Arg allele with more pronounced effect of beta blockers on blood pressure compared to Gly allele (Shahin et al. 2019, Si et al. 2014, Wu et al. 2015) — it confirms indirectly Arg allele hyperfunction. On the other hand, several other studies presented better response (more prominent blood pressure decrease) as a response to beta-blockers in patients with allele Gly (Chen et al. 2018, Lee et al. 2016), or no difference in therapeutical response (Baker et al. 2013).

Many of the polymorphisms of ADRB1 gene are in strong disequilibrium and some allele pairs are often inherited together in the form of haplotypes (Crawford and Nickerson 2005). In theory, separate assessment of individual polymorphisms effects could not lead to the detection of an influence of genotype on analyzed cardiovascular measures. Therefore, several studies evaluated the effects of various haplotypes — they found several significant associations or particular haplotype with alteration in blood pressure level (Mahesh Kumar et al. 2008) or in a response to pharmacotherapy of hypertension by beta-blockers (Johnson et al. 2003, Si et al. 2014).

Concluding the studies focused on two common ADRB1 gene polymorphisms, Ser49Gly polymorphism has lower influence on cardiovascular system compared to Arg389Gly polymorphism where Arg allele seems to be hyperfunctional with an increased chronotropic and inotropic cardiac control effects confirming in vitro studies.

Polymorphism Gly16Arg (ADRB2) was found to be associated with heart rate — however results of studies were not consistent. Significant associations with heart rate variability were also found — lower LF and higher HF components were found (Yang et al. 2011) in accordance with increased time domain indices (SDNN, PNN50, rMSSD) in allele Arg carriers (Atala et al. 2015). In contrast, no significant associations with heart rate variability measures were found in Matsunaga et al. (2007).

Several studies observed association of this polymorphism with basic hemodynamic measures — cardiac output and stroke volume — where Arg allele carriers had decreased values of these measures at rest (Eisenach et al. 2014), during exercise (Rokamp et al. 2013, Snyder et al. 2006). Accordingly, more prominent decrease in these measures was observed during orthostasis in Arg allele carriers (Wittwer et al. 2011). These observations indicate potential hypofunctional effect of Arg allele resulting in lower strength of cardiac contraction and subsequently in a decreased cardiac
output and stroke volume. In accordance with this concept, several studies observed decreased blood pressure in Arg allele carriers (Masuo et al. 2005a, Snieder et al. 2002, Snyder et al. 2006).

Inconsistent effects on heart rate could reflect only small influence of sympathetic activity on chronotropic cardiac control at rest. Increased heart rate in Arg carriers was observed at rest (Snyder et al. 2006, Wittwer et al. 2011), but decreased heart rate values were also found at rest (Atala et al. 2015), and during handgrip test (Eisenach et al. 2012). Arg allele was associated with a more prominent increase in heart rate during orthostasis (Wittwer et al., 2011). We assume that this effect was a consequence of a compensation of insufficient increase in cardiac contractility resulting in less prominent increase in blood pressure during orthostasis. Increased heart rate response to blood pressure change is also reflected in observed increased sensitivity of cardiac chronotropic baroreflex response (Atala et al. 2015) and following increased heart rate. These mechanisms should be confirmed by more complex study with an inclusion of a large set of hemodynamic parameters and their response to orthostatic stress.

Results of the second polymorphism Gln27Glu (ADRB2) effects analysis were less consistent. In haplotype combined with previous polymorphism – Arg16Arg/Gln27Gln – a significant association with a decreased cardiac output was found (Eisenach et al. 2014), but polymorphism Gln27Glu itself analyzed separately did not demonstrate significant association indicating weaker effect of this polymorphism (Wittwer et al. 2011). Several authors assessed heart rate during various states (Atala et al. 2015, Eisenach et al. 2012) but only one study demonstrated decreased heart rate values in Glu allele carriers (Wittwer et al. 2011). This allele was related to the increased LF component of heart rate variability (Atala et al. 2015, Matsunaga et al. 2007b), but this association was not confirmed by another study (Yang et al. 2011). Furthermore, this allele was associated with increased blood pressure values in healthy probands (Masuo et al. 2005b, Snieder et al. 2002) and in hypertensive patients (Komara et al. 2014).

In recent clinical study, increased risk of cardiovascular events was associated with Glu allele in patients suffering from coronary artery disease (Li et al. 2019). Relations of this polymorphism with obesity (Aradillas-García et al. 2017), overweight (Daghestani et al. 2012) and an increased risk of insulin resistance was also found (Mitra et al. 2019).

Concluding, from ADRB2 gene polymorphisms, Gly16Arg polymorphism has more pronounced influence on cardiovascular system (hyperfunctional Arg allele) compared to Gln27Glu polymorphism.

**Polymorphisms of β3-AR genes**

β3-ARs are localized in many human tissues including heart, vessels, brain, retina, gall bladder, kidneys and urinary tract but – most importantly – in fat tissue playing their major role in lipid metabolism (lipolysis). In contrast to β1-ARs and β2-ARs, β3-ARs are expressed in myocardial tissue only in low concentrations creating only 3% from overall number of β-ARs. β3-ARs play a role in control of cardiac ventricle function via their influence on endothelial nitric oxide synthase (eNOS), resulting in negative inotropic effect on the heart (Michel 2020, Tavernier et al. 2003).

Single nucleotide polymorphism rs4994 (Trp64Arg) with a nucleotide substitution T>C resulting to amino acid substitution (tryptophan is replaced by arginine) in intracellular end of transmembrane domain 1 (TMD1) is the most common polymorphism on ADRB3 gene. Minor allele C occurs in only 8% of population in Europe and in 12% worldwide. This polymorphism attracted increased attention because of its potential role in metabolic disorders including type 2 diabetes mellitus, obesity and related states (Yang and Tao 2019).

*In vitro* studies focused on receptor fuction demonstrated that rs4994 polymorphism influences receptor function resulting in worsening of ligand induced cAMP accumulation (Piétri-Rouxel et al. 1997).

Clinical studies demonstrated an association of rs4994 polymorphism with coronary artery disease (allele Arg) (Kumar et al. 2014) and hypertension where metaanalysis confirmed increased systolic and diastolic blood pressure values in patients with arterial hypertension carrying genotype Trp/Arg compared to Trp/Trp genotype (Li et al. 2018, Yang et al. 2017).

Since β3-ARs are primarily expressed in white and brown adipose tissues mediating lipolysis and thermogenesis, many studies focused on the metabolic effects of this polymorphism. Their conclusions agree on the significant association of this polymorphism with altered lipids concentrations, insulin and leptin levels, and blood glucose concentration (Daghestani et al. 2018, Jesus et al. 2018), as well as with the risk of overweight, obesity (Mirrakhimov et al. 2011, Xie et al. 2020) and type 2 diabetes mellitus (Ryuk et al. 2017).
Perspectives

Better understanding of the genetic influence on cardiovascular autonomic control could lead to the development of well-defined strategies aimed on clinical genetic testing and on genomic medicine. Early detection of high-risk genotypes could also motivate clinicians to focus on early detection of initial stages of cardiovascular disease enabling to apply early preventive interventions to slow down progression of these pathological states. Analysis of genetic polymorphisms could also help in personalized pharmacological intervention. I.e., some patients suffering from cardiovascular diseases could receive more effective treatment based on their genotype. Regarding multifactorial disorders, genetic analysis could be of a great importance for the selected group of people with increased risk of development of these pathological states (smokers, obese patients). The awareness of having potentially increased genetic risk could lead to their better motivation to positively influence lifestyle.

Conclusions

The results of studies focused on effects of ARs gene polymorphisms indicate functional differences between alleles related to physiological effects and influence on pathogenesis of cardiovascular disorders. However, these results are not consistent and the effects of SNPs of ARs are inconclusive. Although polymorphism rs1048101 in ADRA1A gene did not lead to altered receptor properties in vitro, studies performed in human demonstrated effects on cardiovascular measures. In fact, these effects were not consistent, similarly to the effects of polymorphism rs1800544 in ADRA2A gene. The studies were mostly focused on SNPs in ADRB1 and ADRB2 genes where in vitro studies demonstrated altered receptor properties. In accordance, in vivo studies also revealed effects on cardiovascular control related measures. Clinical studies agree on the association of rs1801253 polymorphism with hypertension and altered response to beta-blockers. Despite many studies published on these four polymorphisms their results are also not unequivocal. Polymorphism rs4994 in ADRB3 gene was less studied with a focus mostly on its metabolic effects.

Despite relatively high number of previous studies on this topic, they suffer from many limitations, including small sample size, very limited number of assessed cardiovascular control related measures, wide age range, examination protocol including only rest phase. These limitations could potentially lead to inconsistent and unclear results and conclusions. Given the small influence of given individual SNP, it is needed to perform more complex studies assessing wide variety of cardiovascular control output parameters under various physiological states to reveal subtle effects of genetic variations of adrenergic receptors on cardiac and vascular control.

Conflict of Interest

There is no conflict of interest.

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