REVIEW

This paper is dedicated to the 70th anniversary of the founding of Physiologia Bohemoslovaca (currently Physiological Research)

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

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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 beta-blockers 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: α_1-, α_2- and β-AR. Each family is further composed of three subtypes: α_1 (α_{1A}, α_{1B}, α_{1D}), α_2 (α_{2A}, α_{2B}, α_{2C}) and β (β_1, β_2, β_3) 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, α_1-ARs are coupled with $G_{\alpha q}$ protein activating phospholipase C. $G_{\alpha i}$ protein is coupled with α_2-AR causing an inhibition of adenylyl cyclase. β-ARs are coupled with $G_{\alpha s}$ proteins stimulating adenylyl cyclase (Ciccarelli *et al.* 2017) (Fig. 1).

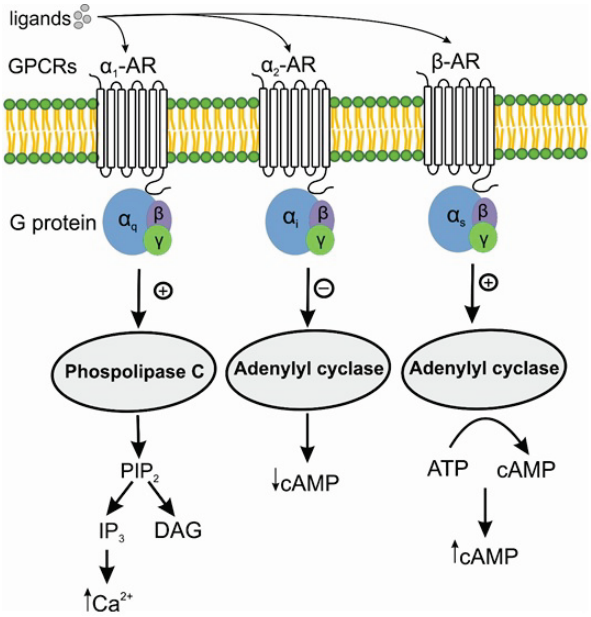

Fig. 1. Signal pathways of ARs associated with G protein activation. After activation of GPCR by ligand binding on AR, inactive heterotrimeric G protein dissociates into two separate active subunits Gα and Gβγ. Various types of G proteins lead to specific intracellular effects. While Gαq activates phospholipase C resulting in the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) releasing inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG), Gαi inhibits adenylyl cyclase activity and Gαs activates adenylyl cyclase activity influencing the intracellular level of cyclic adenosine monophosphate (cAMP) as an important second messenger.

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. α_1-ARs and α_2-ARs are located in smooth muscle cells of vasculature and their activation leads to vasoconstriction. β_1-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). β_2-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).

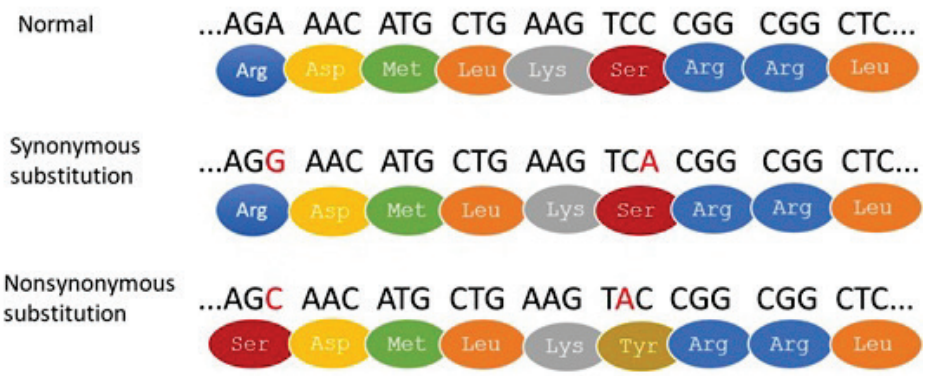

Fig. 2. Synonymous and nonsynonymous substitutions. Synonymous substitution leads to nucleotide change, but amino acid stays unchanged. Nonsynonymous substitution leads to amino acid change.

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 involves 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 α_{1D}, 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 α_{1A}-AR genes

ADRA1A gene encodes α_{1A}-AR localized dominantly in vascular smooth muscles but they are also present in the heart and urogenital system, gastrointestinal system and liver. α_{1A}-AR participates in

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, Gu *et al.* 2006
		antihypertensive treatment	Jiang *et al.* 2005, Zhang *et al.* 2009
		vasovagal syncope	Hernández-Pacheco *et al.* 2014
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	Kurnik *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, Daghestani *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

the blood pressure control by sympathetic nerves via their vasocontriction effects on blood vessels. α_{1A}-AR agonists as vasoconstrictors can be used to treat hypotension, while α_{1A}-AR antagonists can decrease blood pressure in arterial hypertension. Activation of α_{1A}-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 α_{1A}-ARs represents major mechanism of constriction of smooth muscle cells in vasculature. However, assessment of *ADRA1A* gene polymorphisms effects on phenylephrine (agonist of α_{1A}-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 occurence 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 frequenc y 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 stu dy (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 α_{1A}-ARs could play an important role not only in vessels but also in human heart.

Considering the important role of α_{1A}-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 α_{1A}-ARs in vasomotor control, the results of previous studies did not provide clear conclusion about the effect of rs1048101 polymorphism on vascular control. Assessment of PVR is relatively cumbersome resulting in only limited information on the effects of rs1048101 polymorphism on vascular control. Indirect measures like blood pressure values are influenced by many other factors potentially obscuring subtle effects. Despite these facts, the results indicate that rs1048101 polymorphism can be related to blood pressure and its control. To further elucidate this relation, more complex studies focused on vascular control and its changes during various states are needed.

Polymorphisms of α2A-AR genes

α_{2A}-ARs are mostly involved in the central nervous system and cardiovascular control. *ADRA2A* gene encodes α_{2A}-ARs localized in cerebral neurons, in vascular and visceral smooth muscle cells (mediating contraction) (Skinner *et al.* 2018). Most importantly, α_{2A}-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 α_{2A}-ARs results in decreased peripheral vasoconstriction followed by blood pressure decrease. On the other hand, vascular α_{2A}-AR mediate – to a much lower extent compared to α_{1A}-ARs – peripheral vasoconstricion (Flordellis *et al.* 2004).

Gene encoding α_{2A}-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 cardiovacular 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 α_{2A}-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 α_{2A}-AR) in relation to genotype – allele C carriers had a decreased hypotensive 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) occurence 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 β_1- and β_2-ARs genes

β-adrenergic receptors play an important role in cellular signalling related mostly to cardiac sympathetic control. In human heart, the dominance of β_1-ARs over β_2-AR was found: ratio of β_1-ARs : β_2-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 β_1-AR two common polymorphisms (rs1801252, Ser49Gly), (rs1801253, Arg389Gly) and in *ADRB2* gene for β_2-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 β_1-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 adenylyl 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 β_2-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 α_1-, β_1-, and β_2-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 alele (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 therapeutic 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 decresed 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 compenstation 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

β_3-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 β_1-ARs and β_2-ARs, β_3-ARs are expressed in myocardial tissue only in low concentrations creating only 3 % from overall number of β-ARs. β_3-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 *et al.* 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 funtion demonstrated that rs4994 polymorphism influences receptor function resulting in worsening of ligand induced cAMP accummulation (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 β_3-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 wih 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 polymophism 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 polymorphysmis 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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