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Review Article

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β_2 Adrenergic Receptor Polymorphisms and Treatment-Outcomes in Cardiovascular Diseases

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Abstract

Cardiovascular diseases (CVD) represent the major health problem in the western world and heavy social and economic burden. Under this name an eterogenous group of multifactorial conditions is included. There is appreciable inter-individual variability in the susceptibility to cardiovascular disease and in the response to the associated pharmacological treatments. Genetic polymorphism may be, at least in part, responsible for both susceptibility to disease and inter-individual variability in response to pharmacological treatments. The sympathetic system plays a central role in the CVD, and its effects are mediated by means of both α- and β-adrenergic receptors (ARs). In CVD, chronic activation of the cardiac sympathetic nervous system leads to abnormalities at several levels of the βAR signal transduction pathway. Given the pivotal role of β_2ARs in the regulation of cardiac output and peripheral vascular resistance, it has been proposed that adrenergic receptors are an appropriate target for investigating possible links between receptor polymorphisms, drug responses and susceptibility to CVD. Pharmacogenetics can be used as a tool for stratified pharmacological therapy in cardiovascular medicine. β_2AR gene is highly polymorphic with multiple single-nucleotide polymorphisms (SNPs). Among β_2AR variants there are 3 polymorphisms that cause changes in the amino acid sequence and alteration in regulation of signal transduction. In particular, Arg16Gly is associated with increased agonist-induced down-regulation, Gln27Glu leads to resistance to down-regulation, and Thr164Ile causes receptor uncoupling from the G protein. These polymorphisms have been implicated in various cardiovascular and metabolic phenotypes. In this review, we will discuss the role of β_2AR genetic polymorphisms from the molecular level to the clinical findings and the impact of β_2ARs genetic variability on drug response in the management of CVD.

Keywords

β_2 Adrenergic receptor; Polymorphism; Cardiovascular diseases

Introduction

Cardiovascular diseases (CVD) represent the major health problem in the western world and heavy social and economic burden [1]. Under this name, a heterogenous group of multifactorial conditions is included. There is appreciable inter-individual variability in the susceptibility to CVD and in the response to the associated pharmacological treatments [2]. The genomic era and the mapping of the human genome deeply changed medicine, introducing new, genetically determined factors to define the clinical "picture". Understand the genetics of CVD is of importance for primary and secondary prevention and might foster individualized treatment strategies for optimal drug response. Genetic polymorphism may be, at least in part, responsible for both susceptibility to disease and inter-individual variability in response to pharmacological treatments [3,4].

The sympathetic system plays a central role in the CVD [5,6] and its effects are mediated by means of both α- and β-adrenergic receptors (ARs). Under experimental conditions, transgenic overexpression of α_{1B}AR and β_1A and high levels of β_2AR in the heart, as well as long-term stimulation of β_1AR or β_2AR by means of selective drugs, cause enlargement of cardiac size [6-10]. In CVD, chronic activation of the cardiac sympathetic nervous system leads to abnormalities at several levels of the βAR signal transduction pathway [11]. Reduction in the number of receptors (down regulation) and responsiveness (uncoupling) cause blunted adrenergic-mediated responses that contribute to the progression of congestive heart failure. Given the pivotal role of β_2ARs in the regulation of cardiac output and peripheral vascular resistance, it has been proposed that ARs are an appropriate target for investigating possible links between receptor polymorphisms, drug responses and susceptibility to CVD [12]. Pharmacogenetics can be used as a tool for stratified pharmacological therapy in cardiovascular medicine. Identify responders and non-responders to CVD therapies could lead to improved quality of care and better allocation of medical resources. β_2AR gene is also polymorphic, with 3 variants that cause changes in the amino acid sequence and alteration in regulation of signal transduction [13]. In particular, Arg16Gly is associated with increased agonist-induced down-regulation [14], Gln27Glu leads to resistance to down-regulation, and Thr164Ile causes receptor uncoupling from the G protein [15]. These polymorphisms have been implicated in various cardiovascular and metabolic phenotypes [16,17].

In this review, we will discuss the role of β_2AR genetic polymorphisms from the molecular level to the clinical findings and the impact of β_2AR genetic variability on drug response in the management of CVD.

Beta Adrenergic Receptors

The sympathetic nervous system plays an important role in the pathogenesis of hypertension, and its effects are mediated by means of both α- and β-ARs [18]. βARs are the targets for the endogenous catecholamine noradrenaline and adrenaline. They are expressed in many cell types throughout the body and play a pivotal role in regulation of cardiac, pulmonary, vascular, endocrine and central nervous system [19].

There are three different βARs subtypes identified pharmacologically. These receptors are encoded by three separate genes: β1-, β2- and β_3-ARs [20]. β_1ARs are the predominant subtype expressed in the heart and the kidney. In the heart β_1ARs

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activation mediate the increase in chronotropy, inotropy and AV-node conduction [21]. In Kidney, β_1ARs are present mainly on iuxtaglomerular cells, where cause renin release [13].

β_2ARs are abundantly expressed in many cell types; promoting vasodilation in vascular smooth muscle cells, inotropism in cardiac myocytes, and bronchodilation in bronchial smooth muscle [13]. Moreover β_2ARs activate glucose metabolism potentiating the gluconeogenesis and glycogenolysis [19].

β_3ARs are located mainly in adipose tissue and are linked to the regulation of body weight and metabolism [19]. β_3ARs are not consistently expressed in the human heart and the importance of its role on cardiovascular disease is not clearly understood.

The βARs are members of G-protein-coupled receptor family [21]. βARs share a common structure with seven transmembrane-spanning segments, an extracellular amino terminus and a cytoplasmic carboxy terminus [22].

The binding of agonist to the receptor leads to the interaction with the stimulatory guanine nucleotide–binding protein, Gs. Gs is a heterotrimer protein, consisting of an α, β and γ subunits [23]. Each subunit exists in multiple isotypes with differential specificity for effector signaling. The Gαs subunits activate adenylatecyclase that causes the conversion of adenosine 5'triphosphate to cyclicadenosine 3', 5' monophosphate (cAMP). Consequently βARs typically elevate the level of cAMP an important mediator of cell signaling [24]. cAMP binds to the regulatory unit of protein kinase A, promoting the release of its catalytic unit, which phosphorylates a number of downstream target proteins [25].

βARs like other G-protein-coupled receptors, have developed elaborate autoregulatory processes of receptor desensitization [26]. The heterologous desensitization or 'non-agonist-specific' desensitization is a rapid process in which Protein Kinase A phosphorylates agonist activated βARs at serine in the third intracellular loop and the proximal cytoplasmic tail, leading to the uncoupling of the receptor from its signal-transducing G protein Gαs. On the other hand, the 'agonist-specific' or homologous desensitization of βARs is mediated by members of the family of serine/threonine kinases termed G protein–coupled receptor kinases (GRKs) [27]. GRK phosphorylates the β2AR at multiple serines and threonines in the cytoplasmic tail, and enhances the affinity of the receptor for interaction with cytosolic proteins known as the β-arrestins [27]. The binding between β-arrestin and βAR serves to uncouple the receptor from Gs [26,27] promote receptor internalization [28], and by virtue of the scaffolding action of β-arrestins [29], bring other proteins into the receptor's microdomain. β-arrestin binding subsequently directs the internalization of desensitized βARs that can lead to one of several outcomes, including receptor degradation or receptor recycling back to the sarcolemmal membrane [26,30]. Prolonged agonist exposure cause a net loss of cellular receptors (down-regulation) with the activation of degradation mechanisms (Ubiquitination) that are independent of receptor phosphorylation [22]. To restore the membrane complement of βAR is now required the transcription at the βAR gene level and post-translation conversion of mRNA to protein [26,30]. Recent evidence suggests that also PI3Kγ partecipates to the regulation of βAR signaling, interacting with GRK2 at the membrane level, and phosphorylating the adaptative protein AP1 [31]. Activation of PI3K results in βAR upregulation [32].

β_2AR Polymorphisms

The β_2ARs gene is located on chromosome 5q31-33 and contains only one exon that encodes for 413-amino acid [33]. This gene is highly polymorphic with multiple single-nucleotide polymorphisms (SNPs) [34]. In 2000, Drysdale et al. have been reported 13 single base substitutions in the β_2AR coding region [35]. Actually, a total of 49 single nucleotide SNPs have been identified [36]. However, the relevance, both *in vitro* and *in vivo*, of some of these additional variants and their haplotypes has not been studied in detail [36].

Five of β2AR non-synonymous SNPs code for amino acid changes [36,37]. In NH_2 terminus region there is the substitution of an arginine with a glycine at position 16 (Arg16Gly), while at position 27 glutamine replaces glutamic acid (Gln27Glu); in first transmembrane spanning region at position 34 with Valine become Methionine (Val34Met); in the fourth transmembrane spanning region at position 164 there is the substitution of a Threonine with Isoleucine (Thr164Ile) and in fifth transmembrane spanning region the serine in position 220 changes in cysteine (Ser220Cys) [38]. The analysis of βARs gene also showed that the 3'-UTR contained a poly-C repeat of variable length (11, 12, 13 or very rarely 14C), which is interrupted by polymorphisms at two different positions, giving rise to additional genetic variation.

Many studies have demonstrated the presence of eight additional SNPs within the 1.5 kb 5'-untranslated region (UTR) upstream from the ATG start codon [36,39]. This region contains a short open reading frame for a 19 amino acid leader peptide, called the Beta Upstream Peptide (BUP) or the 5'-leader cistron (LC), that control the β2AR gene expression at translational level [39]. The SNP at position -47 from the start codon within the BUP region which substitutes an Arginine for a Cysteine (Cys-19Arg) seems to reduce β2AR expression level [40]. Moreover, two of the eight 5'-UTR SNPs create and ablate restriction enzyme sites (Mspa 1 and BSu36 I, respectively [39] and were therefore intensively investigated. Another 5'-UTR SNP, which appears potentially to be important, results from a base change (T/C) at –367bp from the start codon [39,40]. It interrupts a consensus AP-2 site 7bp downstream of an overlapping Sp-1/AP-2 site, a region also containing strong positive promoter activity that can alter gene expression through differences in transcription factor transactivation [40].

Gly16Arg and Gln27Glu are two common β2AR SNPs in the general population and their allele frequencies vary with ethnicity [41]. The allele frequency for Arg16 among Caucasians was 0.39, 0.5 in African Americans and 0.40 in Asians; while the allele frequency for Gln27 was 0.40, 0.23 and 0.14, respectively for Caucasian, in African American and Asian population [41]. The allele frequency for Cys-19Arg in the Caucasian was 0.35, in African American 0.21 and Asian 0.1037. The Thr164Ile SNP is rare and exists only in the heterozygous state; the frequency of heterozygosity was 3–5% in all populations studied [42]. Also the Val34Met polymorphism is exceedingly rare and its allele frequency is <0.001% [42]. The Val34Met polymorphism seems not to alter receptor function, and its functional consequence has not been studied [16,43].

There is tight-linkage disequilibrium within the β_2AR gene [35]. As a result we have common haplotypes: Arg-19 is always associated with Gly16, while Cys19 is associated with either Arg16 or Gly16 [35,37]. Glu27 is almost always associated with Gly16, whereas Gln27 is associated with either Arg16 or Gly16. Finally, Ile164 is closely

associated with Gly16 and Gln27. Accordingly, the WT-β2-AR consists of Cys-19Cys–Arg16Arg–Gln27Gln–Thr164Thr [38,44-46].

Functional Effects of β_2AR Gene Polymorphisms

To characterize the functional role of β_2AR polymorphisms on agonist induced responses, β_2AR constructs expressing the SNP at position 16,27 and 164 were assessed in specialized cell lines [43,47,48]. *In vitro* studies have demonstrated that the Gly16 and Gln27 variants do not alter basal or agonist-induced ligand binding and adenyl cyclase activity [48]. However, the Arg16Gly and Gln27Glu variants affect agonist-stimulated receptor down-regulation [16,48]. Gly16 genotype enhanced agonist induced down-regulation of the β2AR compared with the wild type16; moreover, the Arg16Gly genotype has similar patterns of agonist-induced down-regulation, implying that Arg16 seems to be a recessive allele [11]. On the other hand, the Gln27 genotype showed attenuation of β2AR agonist-promoted desensitization in comparison with those with the Gln27 genotype [11].

The Gly16 variant has a dominant effect on Glu27 allele since theGly16/Glu27receptors underwent even greater agonist-promoted down-regulation than did the wild type Gln27 β2AR [48]. Conversely, the Arg16/Glu27 double mutant β2AR variant was found to be completely resistant to down-regulation [48].

In HLM cells both Gly16 and Glu27 polymorphism were resistant to isoprenaline-induced desensitization compared to the wild type (Arg16 and Gln27) [49], however, in the same cells β2AR homozygous or heterozygous for Glu27 showed greater short- and long-term desensitization than those homozygous for Gln27, whereby in this population sample the presence of Glu27 was always associated with the presence of Gly1648.

The Glu27 β2AR has been reported to mediate cardiac hypertrophy [16,50]. To test the ability of the Gln27Glu variant to interfere with hypertrophic responses, Iaccarino et al. [51] used HEK293 lines overexpressing Glu27 and Gln27 variants of the human β2AR and assessed their ability to mitogen activated protein kinases (extracellular signal-regulated kinase (ERK) and p38) [52,53]. In this study was found that the Glu27 β2AR variant magnifies the catecholamine induced activation of ERK and p38, compared with wild type. Indeed, a measure of cardiac cell hypertrophy indicator, the activity of the ANF promoter, showed that β2AR causes hypertrophy responses in a fashion that is dependent on not only the density of the β2AR, but also the presence of the Glu27 mutation [51]. In COS-7 cells transfected with Arg19Cys genotypes McGraw et al. showed that Cys19 (BUP) allele leads to a consistently greater β2AR expression as compared with the Arg19 variant [47]. Interestingly, levels of the mRNA transcripts between genotypes were similar indicating that Arg19Cys regulates receptor translation, but not the transcription [41]. Since one function of the β2AR leader peptide is to modulate β2AR expression, the Arg19Cys polymorphism could represent a genetic basis for variable β2AR expression, responsiveness or by this a predictive for phenotype variations [34,38].

The Gln27Glu polymorphism's association with β2AR agonist-induced receptor desensitization may be explained, at least in part, by its association through linkage disequilibrium with Arg19 (BUP) Cys since Gln27 is co-inherited with Arg19 (BUP) and Glu27 is co-inherited with Cys19 (BUP) [34,35].

Also 3'-UTR poly-C repeats polymorphisms alter β2AR expression levels. Caucasians with the Arg16 genotype present three different haplotypes defined by the length of the poly-C repeats, with haplotype frequencies ranging from 14% to 43% [36]. An *in vitro* study showed that cells transfected with the Arg16-11C haplotype presented lower mRNA and receptor expression, more extensive mRNA degradation and a greater tendency for β2AR down-regulation as compared with the other two haplotypes [54]. Such differences in Arg16 genotype may result in important phenotypic variation in the in vivo responses to β2AR agonists, and may in part, explain the discrepancies in clinical studies investigating the relationship between treatment responses and Arg16-Gly polymorphism alone [37]. To date, variations of the poly-C repeat have yet to be investigated in clinical studies, and it is highly likely that assessment of the effects of poly-C polymorphism in conjunction with other β2AR polymorphisms or haplotypes would better predict therapeutic responses to β2AR agonists. Further studies, preferably clinical trials, are required to determine the functional significance of poly-C polymorphism and its interactions with other known SNPs [37].

The effect of the Thr164Ile polymorphism on β2AR binding affinity and coupling to Gs has been studied in CHW-1102 cells. In these cells, Thr164Ile polymorphism exhibited decreased receptor binding affinity with epinephrine, isoproterenol, and norepinephrine [55]. Furthermore, Ile164-β2AR showed diminished reduced basal and agonist-induced activation of the adenylyl cyclase, implying a diminished β2AR-G protein interaction [48].

The impact of the β2AR 16Gly and Glu27 variants on agonist-induced desensitization, have been investigated in studies *in vivo*, and data were quite controversial [42]. In healthy subjects, some studies have found that the increase of heart rate, contractility and blood pressure are not significantly affected by the Arg16 and Gln27 variants genotypes [38,56-58]. On the other hand, in normotensive Austrian Caucasians was found that basal mean blood pressure was higher in volunteers homozygous for Gly16Gly than in volunteers homozygous for Arg16Arg [14].

Various studies have investigated the impact of the Arg16Gly and/or Gln27Glu polymorphisms of the β2AR on vascular responsiveness. Some studies showed that beta agonist-infusion-induced the decrease in total peripheral resistance is larger in volunteers homozygous for Arg16 than in homozygous Gly16 [14,38,56]. Conversely, other investigations have demonstrated that Isoprenaline induced increases in forearm blood flow or dilation of hand vein and found that volunteers homozygous Gly16 exhibited larger vasodilatory responses than did volunteers homozygous Arg16 [57,59].

Because the Glu27 variant of β2AR causes resistance to down-regulation and therefore attenuation of agonist promoted functional desensitization [50,60] it can be considered a gain-of-function mutation because of the longer duration of stimulation. Indeed, subjects who are homozygous for Glu27 have a significantly higher maximal forearm vasodilation to intra-arterial Isoproterenol than those who are homozygous for Gln27, regardless of the amino acid present at position 16 [57]. It is therefore conceivable to speculate that cardiac Glu27 β2AR drives an exaggerated hypertrophic response to catecholamines [57]. Some other reports in the literature contradict these findings, showing that other β2AR-dependent physiologic responses are depressed in the presence of the Glu27 polymorphism *in vivo*. Interestingly, Bruck et al. found that volunteers homozygous for Glu27 β2AR exhibited a slowed onset in desensitization of cardiac responses or in down-regulation of lymphocyte β2AR density, and this

occurred although volunteers carried two or one allele Gly16 [58,60]. There is not a consensus on the reasons for the discrepancies between *in vitro* and *in vivo*. One possible explanation is the antagonizing effect on desensitization of the Gly16 polymorphism, which is in linkage disequilibrium with Glu27; although this viewpoint is also challenged by recent evidence showing that the Gly16 allele may lead to enhanced physiologic responses *in vivo* [15].

The Thr164Ile variant of the β2AR occurs only rarely and is found only in the heterozygous form [11] , the majority of subjects carrying the Thr164Ile polymorphisms are also carriers of Gly16 variant in combination with the Gln27 variant [35,60].

Thr164Ile variant does alter ligand binding and G protein coupling. In cells transfected with cDNA that mimics this SNP, the Ile164 receptor displays a lower binding affinity for β2AR agonists, a 50% reduction in agonist-induced adenylyl cyclase activity, and uncoupling of the receptor from the G protein compared with the wild-type receptor [43,55]. The impact of the Thr164Ile mutation on β2AR function *in vivo* was first studied in transgenic mice, expressing the Ile164 receptor specifically only in cardiomyocytes. This study confirmed in the myocardium a lower basal and isoprenaline stimulated adenylyl cyclase activity, resulting in lower resting heart rates and inotropic and lusitropic indices [61]. The Ile164 variant of the β2AR gene in endothelial cells loses the ability to mediate cell specific responses to catecholamine [62,63]. To gain better insight on the role of Ile164 on atherosclerosis, Piscione et al. explored the effect of this polymorphism on VSMC proliferation in culture [64]. VSMCs were infected with either adenoviral (Ad) β2AR Thr164 or the Ad β2AR -Ile164 and then stimulated with isoproterenol to evaluate β2AR induced cell proliferation [64]. This reduced responsiveness is not explained by altered expression levels but rather is due to an intrinsically impaired signaling capacity of the receptor variant. In humans, the 164 polymorphism associated with blunted increases in heart rate and contractility evoked by cardiac β2AR agonist stimulation compared with volunteers carrying the wild-type isoforme [44,65,66]. Similarly, vascular responses and vasodilation in humans carrying the Ile164 variant of the β2AR gene is also impaired [63]. The presence of Ile164 allele has been shown to be associated with blunted β2AR-mediated venodilatation in phenylephrine preconstricted hand veins [63,67]. Another study found decreased heart rate and inotropic response to systemic terbutaline in healthy Thr164/Ile heterozygotes [44].

The analysis of effects of β2AR polymorphisms is therefore inevitably complicated by the strong LD among SNPs which results in the occurrence of several common haplotypes resulting in multilocus effects [35]. The different distribution of some haplotypes in different ethnic groups may produce inconsistent claims for an association [44]. These limitations make most unlikely that genetic-epidemiological data alone give details in relevant functional alterations of polymorphic β2AR [42,44,45]. Taken together, the available data demonstrate that the β2AR polymorphism might affect functional responsiveness in vitro, *ex vivo* and *in vivo* and appear to be associated with cardiovascular disease states in which β2AR are considered to be important.

β_2AR Gene Polymorphisms in Coronary Artery Disease and Heart Failure

Chronic exposure of the heart to elevated levels of catecholamines lead to pathologic changes in the heart, resulting in continued elevation of sympathetic tone and a progressive deterioration in cardiac function [68]. In particular, dysfunctional myocardium is characterized by a down-regulation of β1AR, whereas the number of β2AR remains relatively stable [68]. β2ARs play a pivotal role in the control of myocardial contractility of the failing heart [69]. The central role played by sympathetic nervous system and its receptors in cardiovascular conditions makes polymorphisms in receptors genes attractive candidates for risk factor and/or predictors of response to treatment [4,38,44].

For instance, the impact of β2AR polymorphisms on coronary atherosclerosis and cardiovascular clinical events is highly controversial. In the study of Yamada et al., none of the β2AR polymorphisms was associated with increased risk form of myocardial infarction in a Japanese population [70]. On the other hand, a large series of studies support the association with atherosclerosis. In an observational cohort study in the elderly the Glu27 allele of the β2AR was associated with a lower risk of incident coronary events in this elderly population [71]. Analysis of the patient cohort from the Physicians' Health Study demonstrated that only specific haplotype combinations ([non-Gly16-Gln27]-Thr164 and Gly16-Gln27-Ile164) increased the risk for myocardial infarction but this association disappeared after adjustment for other polymorphisms [72]. Furthermore, Barbato et al. demonstrated that that prevalence of Glu27 variant is higher among CAD patients in central European population and the presence of this allele should be considered an independent disease risk factor for coronary artery disease [73]. Zak et al. observed a significantly higher prevalence of the Arg allele of Arg16Gly polymorphism in coronary artery disease (CAD) patients than healthy controls [74]. A significant correlation between 27Glu allele carrier state and CAD was noted in patient population in Saudi Arabia [75]. Although the rare incidence, individuals with the Ile164 allele and normal left ventricular (LV) function show blunted haemodynamic responses to adrenergic stimulation [42]. Barbato et al. showed that Thr164Ile polymorphism negatively modulates β2-agonist-mediated myocardial contractile performance in patients with normal and failing myocardium and this β2AR variant is associated with adverse long-term prognosis of patients with congestive heart failure (HF) due to idiopathic cardiomyopathy [65]. Moreover, Piscione et al. found a relationship between β2AR Ile164 polymorphism and coronary and peripheral artery disease in a prospective study in which were enrolled 330 patients undergoing elective or urgent percutaneous coronary intervention (PCI) for CAD documented [64]. Interestingly, this study evidenced that Ile164 polymorphism frequency was higher in CAD (12.1% vs. 3%, $p > 0.008$) than the control population; β2AR Ile164 mutant is associated with an earlier and more aggressive CAD, and it adversely affects prognosis in patients with severe CAD undergoing PCI. This evidence also showed that a group of patients with peripheral artery disease exhibited a higher prevalence of the Ile164 genotype (7%) with a more severe clinical phenotype than those with Thr164 [64]. These data support the concept that β2AR polymorphism may predict prognosis in CAD.

Nevertheless studies that address the association of β2AR polymorphisms and outcomes in patients with ischemic heart disease present conflicting results. First of all, McLean showed that specific genetic variations present in the β2AR genes would predict left ventricular (LV) remodeling in patients chronically treated with a β1 selective antagonist following a first ST elevation myocardial infarction (STEMI) [76]. Specifically, the Glu27Glu variant was associated with an approximately seven-fold increased risk of LV

end systolic dilatation and a four-fold risk of end diastolic volume enlargement and LV ejection fraction decline at 6 months when compared to the full cohort [76].

One complication of myocardial infarction is the development of adverse LV remodeling and progression to HF. Increased cardiac adrenergic activity is one of the major determinants of the progression of LV dysfunction and the poor outcomes of the patients with HF. Acute and long-term therapy with βAR antagonists (β-blockers) has become a standard following acute myocardial infarction and heart failure [77]. Therapy with β-blockers reduce infarct size and mortality among myocardial infarction and HF patients, most likely by decreasing cardiac energy requirements and modifying arrhythmic risk. Some studies suggested that genetic polymorphisms may mediate differential therapeutic end points of β-blocker treatment, including left ventricular ejection fraction improvement, survival, and hospitalization due to HF exacerbation. However, the association of genetic β2AR polymorphisms and therapeutic end points of β-blocker treatment is objected of controvery. Pacanowski et al. investigated the influence of β1AR and β2AR haplotype variation on the incidence of death, non-fatal myocardial infarction, and nonfatal stroke as well as the pharmacogenetics of β-blocker (atenolol) and calcium channel blocker (verapamil) based antihypertensive therapy in the INternational VErapamil SR/Trandolapril STudy— GENEtic Substudy (INVEST-GENES) [78]. Authors showed that patients with the β2AR haplotype containing the Arg16 and Gln27 alleles would be at relatively higher risk for cardiovascular events and that atenolol would be beneficial as compared with sustained-release verapamil (verapamil SR). Pharmacogenetic analysis revealed that the risk for the primary outcome was significantly higher in Gly16-Glu27-haplotype in verapamil SR–treated patients but not in atenolol-treated patients. The analysis revealed that patients with at least one copy of the Ser49-Arg389 β1AR haplotype and zero copies of the Gly16-Glu27 β2AR haplotype (representing 42% of the study population) had better outcomes when treated with atenolol than with verapamil SR (HR 0.42, 95% CI 0.21–0.82, P = 0.01). Comparing this result to the HR of 0.64 when considering the β1AR gene alone suggests that a consideration of both genes may be even more informative for identifying those most likely to benefit from β-blocker therapy [78]. In another study performed on 80 heart failure patients treated with the non-selective β-blocker carvedilol, Kaye et al. demonstrated that subjects carriers of the Glu27 allele were more likely to have an increase in ejection fraction or fractional shortening than those who were homozygous for the allele encoding the Gln27 variant (63vs. 26%, P = 0.003) thus suggesting that determination of β2AR status may be of value for tailoring individual therapy in patients with HF [79]. In contrast, De Groote observed that β2AR polymorphisms did not explain inter individual variability in the response to β-blocker therapy [80]. In a recently published study, a β2AR haplotype (Arg16Arg26/Gln27Gln) was associated with increased risk for death or heart transplantation in 220 patients, 95 and 80% of whom were on an ACE inhibitor/angiotensin receptor blocker and a β-blocker at baseline [81]. When considered relative to β-blocker use, this association was most strongly driven by those not on a β-blocker (HR of 3.52 vs. HR of 1.55). These results suggest that certain genotypes/haplotypes may be at increased risk of adverse outcomes and that β-blockers may attenuate the risk associated with that genotype/haplotype. Interestingly, these findings are consistent with those from an acute coronary syndrome population, in which the Arg16Gln27 haplotype was also associated with adverse outcomes, even among those treated with a β-blocker [82]. Collectively, these data may suggest that the Arg16Gln27 haplotype of the β2AR may be a high-risk haplotype group deserving of more aggressive therapy. Confirm to this view derives from Troncoso et al. who have evaluated the influence of Gln27Glu β2AR polymorphism on the variable response to treatment with carvedilol in patients with chronic HF [83]. The results of this study showed that chronic HF patients with the Glu27β2AR allele have a better response to carvedilol [83].

For the more clinically relevant outcome of survival in HF patients, the results are mixed. Brodde et al. observed that HF patients with the Arg16Arg–Gln27Gln-β2AR seem to have a more pronounced adverse outcome (heart transplantation) and increased risk for sudden cardiac death [42]. In a prospective study on large cohort of clinically treated HF patients who had been prescribed metoprolol or carvedilol Sehnert et al. failed to found significant effect of β2AR genotypes on incidence of critical end point of survival in β-blocker–treated HF patients [84]. Similar results were obtained by de Groote et al. that found no association between functional βAR polymorphisms and survival in patients with stable HF [85]. However, the authors demonstrated, with a univariate analysis, a possible association between the combined β2ARGly16Gly/β2ARGln27Gln genotype and survival [85]. Recently, Petersen et al. showed that β1AR Arg389-homozygous and β2AR Gln27-carrier HF patients treated with carvedilol present a two-fold major risk of mortality relative to all other genotype combinations [86]. There was no difference in survival in metoprolol-treated HF patients between genotype groups [86]. The data indicate that patients with β1AR and β2AR genotypes may benefit more from metoprolol than carvedilol treatment.

In HF, the Thr164Ile polymorphism is characterized by reduced exercise tolerance and higher mortality [57]. However, pathophysiological mechanisms contributing to the poor outcome of these patients are not clear and it is unclear whether the poor outcome is related to direct effects of the Ile164 polymorphism on the myocardial contractile performance or to systemic haemodynamics. Preliminary study showed that in chronic HF-patients, terbutaline-induced increases in heart rate, but not in contractility, were not different in patients with the Thr164Thr or the Thr164Ile variant of the β2AR [65,66,73]. On the other hand, Wagoner et al. assessed in chronic HF-patients either heterozygous Thr164Ile or homozygous Thr164Thr exercise capacity and found that patients with the Thr164Ile variant of the β2AR 8 had a lower peak $V\dot{}O2$ than patients homozygous Thr164Thr [87]. Moreover, Liggett et al. [11] genotyped 259 patients with HF due to ischemic or dilated cardiomyopathy and found that the allele frequencies for the Arg16Gly, Gln27Glu and Thr164Ile polymorphisms of the β2AR did not differ with those assessed in 212 healthy controls. However, those patients carrying the Thr164Ile polymorphism had much more rapid progression to transplantation or death [11]. This data is challenged by the observation from Leineweber, showing that the frequency of the Ile164 allele is almost identical in healthy controls, chronic HF-patients and heart transplantation-patients [88].

β_2AR Gene Polymorphisms in Hypertension

Hypertension is the most important risk factor for cerebral ictus, myocardial infarction and heart failure, as well as the one with the highest incidence in the population, peaking at 60-70% at advanced age. It is well known that LV hypertrophy is a multifactorial condition, influenced by a complex interplay of hemodynamic, neurohumoral, and genetic determinants [38,89], and blood pressure

can usually explain no more than 25% of the overall variance of LV mass index (LVMi) [90]. Thus BP normalization can explain only part of the change in LVMi. In particular, the activity of the sympathetic nervous system appears to play a major role, since it is possible to induce in normotensive off springs of hypertensive patients a 10% increase or decrease in LV mass (LVM), in absence of any change in blood pressure and in accord to maneuvers of chronic activation or deactivation of the sympathetic nervous system [91]. The increase in LVM induced by these maneuvers is prevented by β–blockade [91].

Moreover, several studies have identified genetic factors that influence blood pressure and metabolic responses to β-blockers, thiazide diuretics, and renin–angiotensin system antagonists. Whether such pharmacogenetic differences translate to differences in the clinical outcome of antihypertensive therapy is less clear, particularly when patients receive multiple drugs that are titrated to a target blood pressure [5]. A pharmacogenetic approach to treating hypertension could not only reduce the number and cost of medications but also reduce morbidity and mortality if the outcome of drug treatment differs by genotype. Given functional relevance of β2AR polymorphisms on expression and properties of the β2AR, in recent years their possible association with hypertension has been extensively studied, but altogether, the results fell short of unequivocally demonstrating a causal association of these polymorphisms and hypertension [14,92,93]. The association between hypertension and Gly16 variant was found in Africans [12], but no association either for Arg16 or Gly16 with hypertension was confirmed in a Japanese population [94]or black and white Americans [95]. Another study on German twins showed that Arg16 variant seems to be associated with increased blood pressure values and a higher risk to develop hypertension in white subjects [96]. Another study investigated sib-pairs from 55 pedigrees and about 2500 additional subjects from 589 families, found that the risk for hypertension was greater for those subjects carrying the Gly16 and Glu27 alleles [97].

Association studies relating polymorphisms of different genes to hypertension often result in controversial findings [98-100]. It has been suggested that the use of relaxed selection criteria may increase background noise and mask possible genotype-phenotype relationships [101]. For this reason, restrictive inclusion criteria, such as those requiring similar race, age, body dimension, duration, and severity of hypertension, as well as no previous pharmacologic treatment, may strengthen the conclusion of our study [51].

The sympathetic activation increases LVM in normotensive offspring of both hypertensive parents, in absence of any change in blood pressure [91] and this response is prevented by β–blockade. Furthermore, in hypertensive patients, β-blockade induces a vascular remodeling that correlates with changes in left ventricular wall thickness [102]. Based on these observations Iaccarino et al. [50] assessed the impact of the β2AR polymorphisms on cardiac and vascular target organ damage in a population of untreated essential hypertensive patients after evaluation of clinical, anamnesis and biochemical data. This study showed Arg16Gly, Glu27Gln, and Thr164Ile polymorphisms had no effect of on systolic, diastolic, mean arterial blood pressure and heart rate, although Arg16 affected the age of the onset of hypertension [50]. The main result of this study is that for the first time it is shown that β2AR gene polymorphism affects cardiac remodeling in response to hypertension. In particular, the presence of Glu27 variant is associated to a significantly higher risk of cardiac hypertrophy and all other measured cardiac indexes were significantly higher than those in patients with the Gln27 allele. This observation holds true even after correction for all factors that influence cardiac remodeling (body mass index, blood pressure levels, age and sex). The effects of Glu27 polymorphism are more predominant in younger patients while it seems to fade with age. The effect of the presence of Glu27 polymorphism on the cardiac remodeling might be related to the gain-of-function in signal transduction induced by the mutation on β2AR gene [11]. Consequently, it could be hypothesized that the reduction of sympathetic activation should be particularly effective to induce LV hypertrophy reduction in Glu27 β2AR patients [50].

Therefore, in another study Iaccarino et al. [51] investigated the effects of β2AR variants on the LVMi regression when BP is reduced with β1-blockers (Atenolol), which are unable to completely block β2AR [103,104] rather than with angiotensin-converting enzyme (ACE) inhibitors (Enalapril), which in hypertension reduce the whole sympathetic discharge [105-107]. In this prospective follow up study were selected untreated hypertensive patients descent for the Gly16Arg, Gln27Glu, and Thr164Ile β2AR polymorphisms and left ventricular echocardiographic hypertrophy and assigned selected patients to enalapril or atenolol to assess LV hypertrophy regression. After 2 years, antihypertensive therapy reduced BP similarly in both groups. Interestingly, when was considered the whole population, Glu27 patients showed a higher reduction in LVMi than Gln27 patients independently from treatment [51]. Moreover, the patients harboring Glu27 β2AR showed a larger regression of LVMi when treated with enalapril rather than atenolol. These results have suggested that in Glu27 patients an important effect of antihypertensive therapy on regression of LV hypertrophy is mediated through a non–BP-dependent mechanism, but depend on enhanced hypertrophic effect of the sympathetic system [51]. ACE inhibitors, which reduce the sympathetic discharge overall 107, are also able to reverse LV hypertrophy through the reduction of the hypertrophic effect of catecholamines [91]. This property may be particularly relevant in Glu27 patients, because by reducing sympathetic activation, it may prevent the more marked catecholamine-mediated hypertrophy stimulus induced by the Glu27 β2AR variant.

Thr164Ile has been shown to cause impaired vasodilator function *in vivo*, suggesting that this variation has the most profound consequences on receptor function and may increase peripheral vascular resistance [44,58]. There have been few previous studies to investigate the effect of Thr164Ile on hypertension. Pereira et al. reported increased systolic blood pressure in Thr164Ile heterozygotes compared to non carriers in a ethnically mixed Brazilian population108. Furthermore, no significant association between Thr164Ile genotype and hypertension w as found in a linkage study with 638 participants from 212 Polish pedigrees with clustering of hypertension [74]. The lack of consistency amongst these studies may be attributable to ethnic differences in study subjects. Another explanation could be that analyses were not stratified by gender in any of these previous studies, probably due to the loss of power resulting from the reduction in sample size. Thr164Ile heterozygosity was associated with increased diastolic blood pressure in women, but not in men in the population of Copenhagen City Heart Study [109].

β_2AR Gene Polymorphisms and Metabolic Phenotype

Adrenergic receptors regulate lipid mobilization, energy expenditure and glycogen breakdown through endogenous catecholamines which are involved in the regulation of adipose tissue lipolysis, nonesterified fatty acid distribution, lipoprotein

metabolism, glucose homeostasis, vascular tone and blood pressure. Thus, the β2AR gene constitutes a potential candidate gene to explain part of the genetic predisposition to metabolic disorders.

Current studies allow the speculation that the Glu27 variant might be associated with higher indices of obesity, higher body fat, larger fat cell volume and higher fasting insulin levels when compared with the Gln27 allele110 [38]. However, although the Glu27variant has been associated with obesity and Type II diabetes [110], the findings have not been replicated in all studies [111-114].

Iaccarino et al. tested the hypothesis that in hypertensive patients a given polymorphism of β2ARs might predict the occurrence of metabolic adverse events during βAR blocking treatment [17]. In particular, in this study were evaluated the effects of β2AR polymorphism in hypertensive population, which are involved in glucose and lipid metabolism, on the occurrence of diabetes and dyslipidemia observed after long-term treatment with β-blockers. The β2AR Glu27 variant resulted associated with a larger occurrence of dyslipidemia due to increased serum triglycerides, independently from treatment [17].

Treatment with β-blockers in these patients associates with a further significant increase of elevated serum triglycerides and combined dyslipidemia. On the contrary, β-blockade in patients harboring this polymorphism did not change the occurrence of diabetes or low HDL. This result is particularly noteworthy, because it allows identifying a subpopulation where the occurrence of dyslipidemia after β-blockade is very likely, with an incidence that is above 60%. The identification of this subpopulation makes safer the long-term treatment with β–blockers in patients who do not carry the polymorphism and who represent the majority of hypertensive patients [17]. These data are in line with those of Iwamoto et al. [115] and Ehrenborg et al. [116] who described the same association between the β2AR Glu27 variant and hypertriglyceridemia in unselected populations. The mechanism by which the β2AR Glu27 variant is associated with a larger incidence of dyslipidemia is presently unknown. However, the key role of β2AR in the regulation of lypolysis is acquired. Indeed, it has been demonstrated that in skeletal muscle, β2AR subtype is the only receptor involved in this function, whereas in adipose tissue β1- and β3AR are also involved [117-119]. The Glu27 is a gain-of-function variant that causes an increase in the β2AR signaling, and therefore, it is possible to speculate that the resulting physiology is an increased lypolysis, leading to hypertriglyceridemia. Regarding the reasons why β-blocker treatment is associated with an increased incidence of dyslipidemia in patients with the β2AR Glu27 variant, it can be hypothesized that the β1AR β–lockade induced by atenolol or metoprolol, two rather selective β1 antagonists [119], may result in the preferential activation of β2ARs. The consequence of this phenomenon would be even larger in patients with the β2AR genetic variant resulting in dyslipidemia. The relevance of this finding includes the possibility to predict those patients that are highly likely to develop this side effect and consequently to extend to the majority of the patients the benefits of chronic β-blockade.

Conclusions

β2AR gene polymorphism represents a unique example of investigation in the genetics of CVD. The amount of data accumulating should be summed up in systematic meta-analysis. This would be necessary to finally pose the final word on whether this polymorphism is a viable predictor for many feature of CVD. The jury has been in consultation for long enough and the time has come for a final verdict.

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