Pharmacogenomics of Adrenergic Receptors; from Hypertension to Heart Failure

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Abstract: Cardiovascular medicine is a leading area of pharmacogenomics (PGx). A number of PGx studies have linked genetic polymorphisms to patients’ response to the drugs in the pharmacotherapy against cardiovascular diseases. Among them, PGx of adrenoceptors is one of the most important fields, because adrenergic networks play important roles in cardiovascular systems. The excess of adrenergic stimuli result in cardiovascular disorders, such as hypertension and heart failure (HF). One of the aims of PGx studies of adrenoceptors is the personalization of β-blocker therapy. In this review, we have described biological and clinical impacts on genetic variants of adrenoceptors, some of which have showed clear association with the reduction in heart rate and blood pressure in response to β-blockers. Beyond anti-hypertension therapy, PGx of adrenoceptors would contribute to the individualization of pharmacotherapy against HF.

Keywords: Hypertension, heart failure, pharmacogenomics, polymorphism, β-blocker.

One of the most important goals of pharmacogenomics (PGx) is to achieve the appropriate use of drugs for each individual, called individualized or personalized medicine. So far, PGx studies of adrenergic receptor (AR) genes have been focusing mainly on β-blocker therapy [1-3], because β-blockers have been widely used in cardiovascular diseases, including ischemic heart disease, hypertension and chronic heart failure (CHF).

The blood pressure is the product of the cardiac output (CO) and the peripheral vascular resistance (PVR). Since the activation of adrenergic system increases both CO and PVR, adrenergic system plays an important role in hypertension [4]. Nowadays, blockade of β adrenergic system is no longer the first-line therapy against uncomplicated hypertension in the United States, because of their relative ineffectiveness for primary prevention [5]. β-blocker therapy causes a wide range of adverse effects, especially, impairment of glucose and lipid metabolism [6], resulting in less effective protection against cardiovascular diseases than other classes of anti-hypertensive drugs. Therefore, it is uncertain whether or not pharmacogenic information of ARs will be clinically applied to anti-hypertension therapy as a definitive predictor of blood pressure control; however, in spite of decline of clinical importance of β-blockers as anti-hypertensive drugs, PGx studies of ARs in hypertension therapy have clearly proved that the effectiveness of β-blockers in lowering blood pressure and heart rate is influenced by genetic polymorphisms of ARs.

In contrast to clinical use against uncomplicated hypertension, β-blockers are now recognized as the first-line drugs in anti-heart failure (HF) therapy. Despite negative inotropic effects, β-blockade not only increases CO [7] but also improves the prognosis of HF [8-12], though the molecular mechanisms remain to be fully elucidated. Since myocardium is exposed to excess of adrenergic stimuli in failing hearts [13], the pharmacological relevance of β-blockers in anti-HF therapy is explained by the concept that β-blockade antagonizes the neurohumoral factors and rests the feeble myocardium [2]. Importantly, decrease in heart rate and systolic blood pressure are closely associated with clinical outcome of this therapy [14]. Therefore, it could be accepted that genetic polymorphisms of ARs are predictive biomarkers for clinical outcome in β-blockade therapy against HF.

Among various ARs, a2ARs and β1,3ARs are major players at sympathetic nervous terminus in anti-HF therapy. a2ARs are localized at pre-synaptic region of sympathetic nerve terminus, while βARs are at post-synaptic membrane (Fig. 1). Presynaptic a2ARs regulate the release of norepinephrine (NE) into synaptic cleft, while βARs transduce NE signals into cardiac myocytes. It is important that expression level of each βAR is altered in failing hearts, compared with physiologically normal hearts; β1AR is downregulated in failing hearts [15]. In contrast, β2AR and, possibly, β3AR are upregulated in myocardium in the process of cardiac remodeling [15]. So far, intensive efforts have been made to identify the AR gene polymorphisms, some of which have been revealed to result in functional alteration by molecular biological analyses.

In this article, we have reviewed the biological functions and clinical impacts of genetic polymorphisms of ARs, especially β1, β2, a2c polymorphisms, which have been well studied. Pharmacogenomic understanding of ARs may explain the inter-individual variation in the response to β-blockers, contributing to the personalization of β-blocker therapy.
1. FUNCTIONAL PROPERTIES OF ADRENERGIC RECEPTORS

$\beta_1$AR There are two common polymorphisms in $\beta_1$ adrenergic receptor, Ser49Gly and Arg389Gly [16]. The Ser49Gly polymorphism is located in the extracellular N-terminal region of the receptor. Gly49 receptor is rapidly downregulated by long-term agonist stimulation, compared with Ser49 receptor in vitro [17, 18]. Arg389Gly polymorphism occurs in the region between the seventh transmembrane domain and the intracellular tail of the receptor. In vitro study revealed that Gly389 variant exhibited slightly lower basal adenyl cyclase activity than Arg389 variant [19]. In addition, isoprenaline-induced adenyl cyclase activation was about three to four times smaller in cells expressing Gly389 variant than in that expressing Arg389 [20]. Cardiac-targeted transgenesis in a mouse model showed that hearts from young mice with the overexpression of Gly389 variant exhibited decreased basal cardiac contractility and reduced contractile response to dobutamine compared with Arg389 hearts. Older mice expressing Gly389 displayed a phenotypic switch, with increased $\beta$-agonist signaling to adenyl cyclase and increased cardiac contractility, compared with Arg389-expressing hearts. In addition, hemodynamic response to $\beta$-receptor blockade was greater in the Arg389 mice [2, 21].

$\beta_2$AR Various polymorphisms were reported in the coding and promoter regions of $\beta_2$AR gene [22]. Among them, biological functions of Arg16Gly and Gln27Glu polymorphisms have been well documented. Both polymorphisms are located in the extracellular amino terminus of $\beta_2$AR.

Arg16Gly and Gln27Glu polymorphisms do not influence ligand binding or adenyl cyclase activation in vitro in Chinese hamster fibroblasts expressing $\beta_2$AR variants but alter the extent to which the receptors undergo downregulation [23]. Gly16 allele is more susceptible to downregulation via agonist stimulation than is Arg16 allele. Gln27 allele is more resistant to receptor downregulation than is Gln27 allele [23].

$\alpha_2C$AR $\alpha_2C$AR is the presynaptic inhibitory autoreceptor that is known to have a critical role in regulating neurotransmitter release from sympathetic nerves and from adrenergic neurons. Small et al. identified a polymorphic $\alpha_2C$AR that consists of an in-frame 12-nucleic-acid deletion that encodes a receptor lacking the Gly-Ala-Gly-Pro sequence in the third intracellular loop (denoted Del322–325). The deletion type $\alpha_2C$AR has a significant impact on agonist-promoted formation of the active receptor-G protein ternary complex. Impaired $\alpha_2C$ AR-G protein coupling results in altered functions in three downstream signaling pathways; the adenyl cyclase, inositol phosphate, and mitogen-activated protein (MAP) kinase [24]. The loss of normal synaptic autoinhibitory feedback caused by this genetic variation leads to enhanced presynaptic release of NE [25, 26].

2. POLYMORPHISMS OF ADRENERGIC RECEPTOR AND RISK FOR HYPERTENSION

$\beta_1$AR The previous study that investigated the difference in blood pressure among genotype-discordant siblings revealed that siblings with Gly389 allele had significantly lower resting diastolic blood pressure than those homozygous for Arg389 [27]. In the CAREGENE study in patients with coronary artery disease, resting diastolic blood pressure was significantly lower in patients homozygous for Gly389 than in those with Arg389 allele [28]. However, in the patients with essential hypertension, there are no differences in resting blood pressure among Arg389Gly genotypes [29–32]. In case-control study of normotensive versus hypertensive subject, results are controversial; Bengtsson et al. and Shioji et al. showed that the prevalence of Gly389 variant was significantly lower in hypertensive than in normotensive subjects [27, 33]. On the other hand, Filigheddu et al. and Radnade et al. found that the prevalence of Arg389Gly polymorphism was not significantly different between hypertensive and normotensive subjects [34, 35]. For Ser49Gly, there are no associations between resting blood pressure and genotypes in the patients with essential hypertension, as is the case with Arg389Gly [29–32].
Many studies have examined whether βAR Arg16Gly or Gln27Glu polymorphism influences the susceptibility to hypertension or the risk for elevated blood pressure, but have yielded conflicting results [1, 36]. Most of studies didn’t detect significant genotype associations. A few studies observed significant genotype effects; however, there is no consistency and it could not be elucidated which of the two variants is more strongly associated with hypertension.

3. POLYMORPHISMS OF ADRENOCEPTORS AND RISK FOR HF

To the best of our knowledge, there is no report that described genotyping-dependent differences in prevalence of Ser49Gly genotype or Arg389Gly genotype, itself, in CHF patients versus controls [37-43]. This suggests that Ser49Gly and Arg389Gly polymorphism are not risk factor for CHF. However, it was reported that Arg389Gly genotype contributed to onset of CHF, synergistically with α2C AR genetic polymorphism, as described below.

β1 AR

No case-control study has reported the difference in the distribution of Arg16Gly and Gln27Glu polymorphisms between the CHF patients and the controls [39, 44].

α2C AR

α2C AR insertion (Ins)/deletion (Del) and β1 AR Arg389Gly polymorphisms have been suggested to act synergistically in the development of CHF in African Americans [40]. Individuals homozygous for β1 AR Arg389 and α2C AR Del had an adjusted odds ratio of 10.11 for CHF in a case–control analysis. However, we failed to detect an effect of α2C AR Del allele on HF risk in Japanese people [41]. Metra et al. observed in a study of 260 CHF patients and 230 normal subjects from an Italian Caucasian population that β1 AR and α2C AR polymorphisms are not associated with an increased risk of CHF [42].

4. POLYMORPHISMS OF ADRENOCEPTOR AND THE RESPONSE FOR B-BLOCKER TREATMENT IN ANTI-HYPERTENSION AND ANTI-HF THERAPIES

4.1. Anti-Hypertension Therapy

Several studies have investigated in possible effects of β1 AR Arg389Gly polymorphism on blood pressure responses to β-blocker treatment in hypertensive patients (Table 1). Concerning metoprolol, patients homozygous for Arg389 had a significant greater reduction in 24-hr and day-time diastolic blood pressure [29]. This result was reproducible; Liu et al. found that the decrease in systolic, diastolic and mean arterial blood pressure was significantly larger in patients homozygous for Arg389 variant [32]. On the other hand, this polymorphism did not show the genotype-dependent differences in antihypertensive response to atenolol [30, 31, 34]. Thus, the genotype effect on response to β-blocker antihypertensive medication may be dependent on the drugs used in the clinical trial and the contribution of β1 AR Arg389Gly polymorphism to the drug response is observed among patients with metoprolol treatment but not those with atenolol. There are few reports on the association between β2 AR or α2C AR polymorphisms and antihypertensive drug efficacy.

4.2. Anti-HF Therapy

PGx studies of ARs in CHF, reported so far, have been summarized in Table 2. In this section, we introduce some representative studies in detail.

β1 AR

Intensive effort has been made for a long time to investigate the importance of β1 AR genetic polymorphisms in response to β-blocker in CHF since Borjesson M et al. suggested their pharmacogenomic association in 2000. In 92 CHF patients treated with β-blockers at different points during their follow-up, the patients with Gly49 allele had a significantly lower risk of death or cardiac transplantation within 5 years than patients homozygous for the Ser49 β1 AR [45]. Magnusson et al. suggested that this genetic effect is shown only in CHF patients with a low dose of β-blocker; there is no association between β1 AR Ser49Gly and β-blocker responsiveness in the patients treated with high dose of β-blocker [43].

β1 AR Arg389Gly polymorphism is another interest of PGx of ARs in CHF. Arg389 homozygotes treated with bucindolol had an age-, gender-, and race-adjusted 38% reduction in mortality (P=0.03) and a 34% reduction in mortality or hospitalization (P=0.004) vs. placebo, while Gly389 carriers had no clinical response to bucindolol compared with the placebo group [46]. On the other hand, in MERIT-HF trial, this polymorphism did not show the effect

Table 1. β1 AR Arg389Gly Polymorphism and Response to Beta-Blocker

<table>
<thead>
<tr>
<th>β-Blocker</th>
<th>N</th>
<th>Outcomes</th>
<th>β-Blocker Response</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy volunteers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>34</td>
<td>BP response to a single dose</td>
<td>Arg &gt; Gly</td>
<td>[54]</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>16</td>
<td>Reduction in exercise-induced HR and BP increase</td>
<td>Arg &gt; Gly</td>
<td>[55]</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>18</td>
<td>Reduction in dobutamine-induced HR</td>
<td>Arg &gt; Gly</td>
<td>[56]</td>
</tr>
<tr>
<td>Hypertensive patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>40</td>
<td>24-hr and day-time diastolic blood pressure</td>
<td>Arg &gt; Gly</td>
<td>[29]</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>61</td>
<td>BP response</td>
<td>Arg &gt; Gly</td>
<td>[32]</td>
</tr>
<tr>
<td>Atenolol</td>
<td>147</td>
<td>BP and HR response</td>
<td>Arg = Gly</td>
<td>[30]</td>
</tr>
<tr>
<td>Atenolol</td>
<td>101</td>
<td>BP and HR response</td>
<td>Arg = Gly</td>
<td>[31]</td>
</tr>
<tr>
<td>Atenolol</td>
<td>270</td>
<td>BP response</td>
<td>Arg = Gly</td>
<td>[34]</td>
</tr>
</tbody>
</table>

BP: blood pressure, HR: heart rate.
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Table 2. Pharmacogenetic Studies of the Responsiveness to β-Blockers in CHF Patients

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Study Population</th>
<th>β-Blocker</th>
<th>N</th>
<th>Outcomes</th>
<th>β-Blocker Response</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>β1-AR Ser49Gly</td>
<td>DCM</td>
<td>Metoprolol CR/XL</td>
<td>61</td>
<td>LVEDD</td>
<td>Gly carriers &gt; Ser</td>
<td>[60]</td>
</tr>
<tr>
<td></td>
<td>DCM</td>
<td>Metoprolol CR/XL</td>
<td>139</td>
<td>Death or heart transplantation</td>
<td></td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>Carvedilol and bisoprolol</td>
<td>199</td>
<td>LVEF</td>
<td>No associations</td>
<td>[51]</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>Carvedilol and metoprolol</td>
<td>637</td>
<td>Death or heart transplantation</td>
<td>No associations</td>
<td>[48]</td>
</tr>
<tr>
<td>β1-AR Arg389Gly</td>
<td>CHF</td>
<td>Carvedilol</td>
<td>224</td>
<td>LVEF</td>
<td>Arg &gt; Gly carriers</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td>DCM</td>
<td>Carvedilol</td>
<td>135</td>
<td>LVEF</td>
<td>Arg/Arg &gt; Arg/Gly</td>
<td>[50]</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>Metoprolol CR/XL</td>
<td>61</td>
<td>LVEF</td>
<td>Arg &gt; Gly carriers</td>
<td>[60]</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>Bucindolol</td>
<td>1040</td>
<td>(515 treated)</td>
<td>Death</td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>Carvedilol and bisoprolol</td>
<td>199</td>
<td>LVEF</td>
<td>No associations</td>
<td>[51]</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>Metoprolol CR/XL</td>
<td>600</td>
<td>(307 treated)</td>
<td>Death or hospitalization</td>
<td>No associations</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>Carvedilol and metoprolol</td>
<td>637</td>
<td>Death or heart transplantation</td>
<td>No associations</td>
<td>[48]</td>
</tr>
<tr>
<td>β1-AR Arg16Gly</td>
<td>CHF</td>
<td>Carvedilol and bisoprolol</td>
<td>199</td>
<td>LVEF</td>
<td>No associations</td>
<td>[51]</td>
</tr>
<tr>
<td></td>
<td>DCM</td>
<td>Carvedilol</td>
<td>135</td>
<td>LVEF</td>
<td>No associations</td>
<td>[50]</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>Carvedilol and metoprolol</td>
<td>637</td>
<td>Death or heart transplantation</td>
<td>No associations</td>
<td>[48]</td>
</tr>
<tr>
<td>β2-AR Gln27Glu</td>
<td>CHF</td>
<td>Carvedilol</td>
<td>80</td>
<td>LVEF or LVFS</td>
<td>Glu carriers &gt; Gln</td>
<td>[49]</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>Carvedilol and bisoprolol</td>
<td>199</td>
<td>LVEF</td>
<td>No associations</td>
<td>[51]</td>
</tr>
<tr>
<td></td>
<td>DCM</td>
<td>Carvedilol</td>
<td>135</td>
<td>LVEF</td>
<td>No associations</td>
<td>[50]</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>Carvedilol and metoprolol</td>
<td>637</td>
<td>Death or heart transplantation</td>
<td>No associations</td>
<td>[48]</td>
</tr>
<tr>
<td>α2C-AR Ins/Del</td>
<td>CHF</td>
<td>Metoprolol CR/XL</td>
<td>54</td>
<td>LVEF</td>
<td>Del carrier &gt; Ins</td>
<td>[53]</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>Carvedilol and metoprolol</td>
<td>637</td>
<td>Death or heart transplantation</td>
<td>No associations*</td>
<td>[48]</td>
</tr>
</tbody>
</table>

AR adrenergic receptor, DCM dilated cardiomyopathy, CHF chronic heart failure, LVEDD left-ventricular end-diastolic diameter, LVEF left-ventricular ejection fraction, LVFS left-ventricular fractional shortening.

* A weak univariable trend toward better survival in black patients was observed, as an additive function of the number of alleles in the ADRA2C deletion polymorphism (hazard ratio: 0.55, 95% confidence interval: 0.28 to 1.11, p = 0.094, n = 156).

on the inter-individual variability in the risk of all-cause mortality or hospitalization [47]. Sehnert et al. also revealed that Arg389Gly did not significantly influence survival in metoprolol-treated or carvedilol-treated HF patients [48]. These results may be attributable to a drug-specific interaction between genotype and responsiveness to β-blocker treatment.

β2-AR In contrast to β1-selective β-blockers, such as bisoprolol and metoprolol, carvedilol inhibits β2-AR. Therefore, several studies focused on the polymorphisms of β2-AR gene, especially in PGx of carvedilol treatment. Kaye et al. showed that subjects with the Gln27 allele were more likely to have significantly increased left ventricular ejection fraction (LVEF) or left ventricular fractional shortening (LVFS) in 62% of cases in response to carvedilol, compared with only 26% of individuals homozygous for the Gln27 [49]. However, other studies failed to detect positive associations between β2-AR polymorphisms and improvement of cardiac function [50, 51]. Furthermore, there was no β2AR genotype-dependent difference in risk of death or cardiac transplantation during β-blocker treatment [48].

α2C-AR Regitz-Zagrosek et al. showed that genetic variation in α2C-AR Del allele is independently associated with survival and the absence of cardiac events in patients with severe HF due to idiopathic dilated cardiomyopathy [52]. In this clinical study, the number of patients treated with β-blockers increased continuously from 25% at presentation to 76% during the study period. Considering this report, patients with the α2C-AR Del allele may have a better prognosis than other patients receiving β-blocker treatment. Despite the small sample size, Lobmeyer et al. examined the relation between Ins/Del and LVEF improvement and reported that patients with both β1-AR Arg389/Arg389 and α2C-AR Del-carrier status benefited substantially more from metoprolol CR/XL treatment in terms of cardiac function [53].
DISCUSSION

We have reviewed the biological and clinical impacts of genetic polymorphisms of ARs. In some of these variants, clinical pharmacological studies have demonstrated their association with the alteration in heart rate or blood pressure in response to β-blockers, as shown in Table 1. It should be noted that the association of genetic variants with these parameters are consistently observed in healthy volunteers [54-56] but not in the patients with hypertension. The response to β-blockers may be determined not simply by the genetic polymorphisms but by concomitant conditions in hypertension. Therefore, to achieve the personalization of β-blocker therapy in hypertension, other clinical profiles should be taken into account. And it should be also emphasized that clinical impacts of genetic polymorphisms on long-term outcomes, not on blood pressure/lowering effects, should be highly considered in anti-hypertension therapy by β-blockers, because β-blockers are no longer first-line therapy because of their ineffectiveness in primary prevention against cardiovascular diseases.

With the decline in β-blockade therapy as first choice in uncomplicated hypertension, the interest in PGx of ARs may shift to anti-HF therapy; however, PGx of HF will be more complicated than that of hypertension. Several concerns should be considered in PGx study of HF as described below;

1. Cause of HF: The response to β-blockers is better in HF with idiopathic dilated cardiomyopathy than that with ischemic cardiomyopathy.

2. Choice of the agent: β₁ selectivity and inverse agonistic effects influence the drug response.

3. End point: Primary end points should be cardiac death or cardiac events; however, in the case of genetic polymorphisms with low allelic frequency, statistic errors are likely to occur, because of limited number of cardiac death or cardiac events.

4. Racial differences: There are large racial differences in the drug response, frequency of genetic polymorphisms, and the prognosis of HF.

5. Possible involvement of other adrenergic signal-related genes: Adrenergic signals are regulated not simply by ARs. For example, the concentrations of NE in synaptic cleft are likely to be altered by its reuptake through NE transporter (NET). Indeed, we have reported the association between the NET gene polymorphism and β-blocker response [57]. Moreover, the involvement of the genes responsible for post-synaptic signaling pathway, such as G protein-coupled receptor kinase 5 [58], remains to be fully addressed.

Despite the difficulties described above, PGx studies of ARs should be encouraged. Based on the recent clinical trial [59], β-blockers are now the first-line drugs comparable to angiotensin-converting enzyme inhibitors (ACEIs), in early HF. Given the intrinsic negative inotropic property of β-blockers, PGx of ARs might give the answer to the question, “β-blockers or ACEIs?” to each individual patient in early HF.

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