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 adrenoreceptors is the personalization of β-blocker therapy. In this review, we have described biological and clinical impacts on genetic variants of adrenoreceptors, 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 adrenoreceptors 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 pharmocogenomic 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, α_2ARs and $\beta_{1\text{-}3}$ARs are major players at sympathetic nervous terminus in anti-HF therapy. α_2ARs are localized at pre-synaptic region of sympathetic nerve terminus, while βARs are at post-synaptic membrane (Fig. **1**). Presynaptic α_2ARs 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; β_1AR is downregulated in failing hearts [15]. In contrast, β_2AR and, possibly, β_3AR 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 β_1, β_2, α_{2C} 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.

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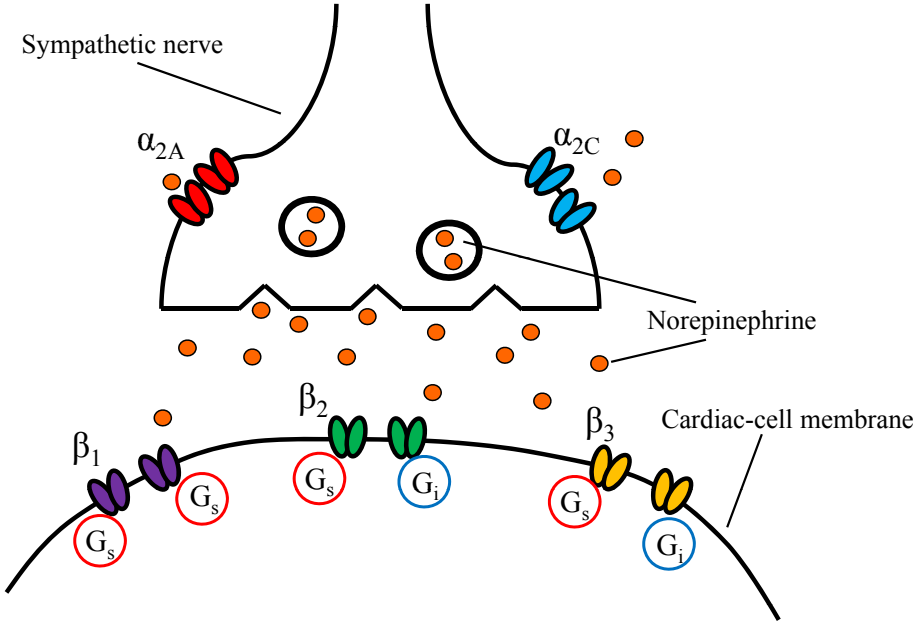

Fig. (1). Adrenergic receptors in the human heart.

1. FUNCTIONAL PROPERTIES OF ADRENORECEPTORS

β1AR There are two common polymorphisms in β_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 adenylyl cyclase activity than Arg389 variant [19]. In addition, isoprenaline-induced adenylyl 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 β-agonist signaling to adenylyl cyclase and increased cardiac contractility, compared with Arg389-expressing hearts. In addition, hemodynamic response to β-receptor blockade was greater in the Arg389 mice [2, 21].

β2AR Various polymorphisms were reported in the coding and promoter regions of *β2AR* 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 β_2AR.

Arg16Gly and Gln27Glu polymorphisms do not influence ligand binding or adenylyl cyclase activation *in vitro* in Chinese hamster fibroblasts expressing β_2AR variants but alter the extent to which the receptors undergo downregulation [23]. Gly16 allele is more susceptible to dowregulation *via* agonist stimulation than is Arg16 allele. Glu27 allele is more resistant to receptor downregulation than is Gln27 allele [23].

α2CAR α_{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 α_{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 α_{2C}AR has a significant impact on agonist-promoted formation of the active receptor-G protein ternary complex. Impaired α_{2C} AR-G protein coupling results in altered functions in three downstream signaling pathways; the adenylyl 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 ADRENORECEPTOR AND RISK FOR HYPERTENSION

β1AR 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 Ranade *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].

β_2AR Many studies have examined whether β_2AR 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 ADRENORECEPTORS AND RISK FOR HF

β_1AR To the best of our knowledge, there is no report that described genotyping-dependent differences in prevalence of Ser49Gly genotype or Arg389Gly genotype, by 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 α_{2C}AR genetic polymorphism, as described below.

β_2AR 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].

α_{2C}AR α_{2C}AR insertion (Ins)/deletion (Del) and β_1AR Arg389Gly polymorphisms have been suggested to act synergistically in the development of CHF in African Americans [40]. Individuals homozygous for β_1AR Arg389 and α_{2C}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 α_{2C}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 β_1AR and α_{2C}AR polymorphisms are not associated with an increased risk of CHF [42].

4. POLYMORPHISMS OF ADRENORECEPTOR 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 β_1AR 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 β_1AR 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 β_2AR or α_{2C}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.

β_1AR Intensive effort has been made for a long time to investigate the importance of β_1AR 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 β_1AR [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 β_1AR Ser49Gly and β-blocker responsiveness in the patients treated with high dose of β-blocker [43].

β_1AR 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. β_1 AR Arg389Gly Polymorphism and Response to Beta-Blocker

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

BP: blood pressure, HR: heart rate.

Table 2. Pharmacogenetic Studies of the Responsiveness to β-Blockers in CHF Patients

Polymorphism	Study Population	β-Blocker	N	Outcomes	β-Blocker Response	Ref.
β_1-AR Ser49Gly	DCM	various	92	Death or heart transplantation	Gly carriers > Ser	[45]
		Metoprolol CR/XL	61	LVEDD	Gly carriers > Ser	[60]
	DCM	Metoprolol CR/XL	139	Death or heart transplantation	Gly carriers > Ser in treated with low dose	[43]
	CHF	Carvedilol and bisoprolol	199	LVEF	No associations	[51]
	CHF	Carvedilol and metoprolol	637	Death or heart transplantation	No associations	[48]
β_1-AR Arg389Gly	CHF	Carvedilol	224	LVEF	Arg > Gly carriers	[21]
	DCM	Carvedilol	135	LVEF	Arg/Arg > Arg/Gly > Gly/Gly	[50]
	CHF	Metoprolol CR/XL	61	LVEF	Arg > Gly carriers	[60]
	CHF	Bucindolol	1040 (515 treated)	Death	Arg > Gly carriers	[46]
	CHF	Carvedilol and bisoprolol	199	LVEF	No associations	[51]
	CHF	Metoprolol CR/XL	600 (307 treated)	Death or hospitalization	No associations	[47]
	CHF	Carvedilol and metoprolol	637	Death or heart transplantation	No associations	[48]
β_2-AR Arg16Gly	CHF	Carvedilol and bisoprolol	199	LVEF	No associations	[51]
	DCM	Carvedilol	135	LVEF	No associations	[50]
	CHF	Carvedilol and metoprolol	637	Death or heart transplantation	No associations	[48]
β_2-AR Gln27Glu	CHF	Carvedilol	80	LVEF or LVFS	Glu carriers > Gln	[49]
	CHF	Carvedilol and bisoprolol	199	LVEF	No associations	[51]
	DCM	Carvedilol	135	LVEF	No associations	[50]
	CHF	Carvedilol and metoprolol	637	Death or heart transplantation	No associations	[48]
α_{2C}-AR Ins/Del	CHF	Metoprolol CR/XL	54	LVEF	Del carrier > Ins	[53]
	CHF	Carvedilol and metoprolol	637	Death or heart transplantation	No associations*	[48]

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.

β 2AR In contrast to β_1-selective β-blockers, such as bisoprolol and metoprolol, carvedilol inhibits β_2AR. Therefore, several studies focused on the polymorphisms of *β_2AR* gene, especially in PGx of carvedilol treatment. Kaye *et al.* showed that subjects with the Glu27 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 β_2AR polymorphisms and improvement of cardiac function [50, 51]. Furthermore, there was no β_2AR genotype-dependent difference in risk of death or cardiac transplantation during β-blocker treatment [48].

α_{2C}AR Regitz-Zagrosek *et al.* showed that genetic variation in α_{2C}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 α_{2C}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 β_1AR Arg389/Arg389 and α_{2C}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: β_1 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.

ACKNOWLEDGEMENTS

This study is partially supported by Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science (to S. N) and by Grants-in-Aid for Scientific Research from Ministry of Health, Labour and Welfare (to Y. F.).

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Received: February 02, 2010 Revised: July 15, 2010 Accepted: August 07, 2010