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### β₁- and β₂-Adrenoceptor polymorphisms and cardiovascular diseases

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β₁- and β₂-Adrenoceptors (AR) play a pivotal role in the regulation of cardiovascular function. Both β-AR subtypes are polymorphic: two single nucleotide polymorphisms (SNPs) have been described for the β₁- (Ser49Gly, Arg389Gly) and four for the β₂-AR (Arg-19Cys, Arg16Gly, Gln27Glu, Thr164Ile), and they are possibly of functional relevance. In recombinant cell systems, Gly49-β₁-AR are more susceptible to agonist-promoted down-regulation than Ser49-β₁-AR, whereas Arg389-β₁-AR are three to four times more responsive to agonist-evoked stimulation than Gly389-β₁-AR. With respect to β₂-AR, the Cys-19 variant is associated with greater β₂-AR expression than the Arg-19 variant; Gly16-β₂-AR are more susceptible, whereas Glu27-β₂-AR are almost resistant to agonist-promoted down-regulation; Thr164-β₂-AR are three to four times more responsive to agonist-evoked stimulation than Ile164-β₂-AR. Several studies addressed potential phenotypic consequences of these SNPs in vivo by influencing and/or contributing to the pathophysiology of cardiovascular/pulmonary diseases such as hypertension, congestive heart failure, arrhythmias or asthma. At present, it appears that these β-AR SNPs are very likely not disease-causing genes but possibly predictive for the responsiveness to agonists and antagonists. Patients carrying one or two alleles of the Gly389-β₁-AR are poor or non-responders to agonists and antagonists, whereas patients homozygous for the Arg389-β₁-AR are good responders. Subjects carrying the Ile164-β₂-AR exhibit blunted responses to β₂-AR stimulation. Asthma patients carrying the Arg16-Gln27-Thr164-β₂-AR haplotype who receive regularly short- or long-acting β₂-AR agonists are rather susceptible to agonist-induced desensitization and in consequence exhibit reduced bronchodilating and -protective effects and/or increased asthma exacerbations. The clinical relevance of these findings is still under debate.


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Keywords: β₁-Adrenoceptor; β₂-Adrenoceptor; cardiovascular diseases; genotype; haplotype; phenotype; single nucleotide polymorphism

Abbreviations: AC, adenylyl cyclase; ADR, adrenaline; AR, adrenoceptor; DOBU, dobutamine; GRK, G protein-coupled receptor kinase; ISO, isoprenaline; HF, heart failure; NA, noradrenaline; SALB, salbutamol; SNP, single nucleotide polymorphism; TER, terbutaline; TMD, transmembrane spanning domain; ZIN, zinterol

**β-Adrenoceptors (AR) in the cardiovascular system**

β-AR are characterized by a seven transmembrane spanning domain (TMD) structure, an extracellular amino terminus, and three intra- and extracellular loops, and an intracellular carboxyl terminus. Agonist binding to β-AR induces the activation of an associated heterotrimeric G protein (containing the three subunits Gₐ, Gᵢ, and Gₑ). The activated Gₐ-subunit dissociates from the G protein complex and stimulates (Gₐₛ) or inhibits (Gₐᵢ) adenylyl cyclase (AC), and therefore modulates the intracellular amount of cyclic AMP (for review, see Brodde et al., 2006; Leineweber et al., 2006a).

At present, three β-AR subtypes have been identified in mammals, β₁-, β₂- and β₃-AR. In the human heart, both β₁- and β₂-AR coexist, and the β₁-AR subtype predominates in atrial (60–70%; 40–30%) as well as in ventricular tissue.
(70–80%:30–20%)” (for review, see Brodde and Michel, 1999). β₁-AR exclusively couple to the stimulatory Gαs. In rat and mouse heart, however, β₂-AR couple to not only Gβγ, but also Gαs probably in an agonist-specific manner: fenoterol stimulates predominantly Gαs while terbutaline (TER), salbutamol (SALB) and zinterol (ZIN) stimulate both, Gαs and Gβγ (Xiao et al., 2003). Whether or not β₂-AR also couple to Gαs in human hearts, is still a matter of debate. However, in isolated human right atrial membranes pertussis toxin pretreatment (irreversible inhibition of Gαs) enhances AC activation in response to ZIN (for review, see Steinberg, 1999).

Despite the fact that β₁-AR predominate in the human heart, β₂-AR are more effectively coupled to AC than β₁-AR and the extent of functional responsiveness of β₁- and β₂-AR is tissue- and/or agonist-specific (for review, see Brodde and Michel, 1999). In isolated human right atria, isoprenaline (ISO) and adrenaline (ADR) cause nearly identical increases in force of contraction via β₁- and β₂-AR, however, in isolated ventricular preparations increases in force of contraction are maximal via β₁-AR stimulation and only submaximal via β₂-AR stimulation. In vivo, ISO and ADR infusion-induced increases in heart rate are mediated by β₁- and β₂-AR stimulation to about the same degree. On the other hand, noradrenaline (NA) increases contractility almost exclusively via β₁-AR in isolated human right atria and ventricular preparations, and it exerts its positive inotropic and chronotropic effects in vivo also almost exclusively via β₁-AR.

In addition to their cardiac effects, β₂-AR also mediate lipolysis and regulate the release of renin (and by this activation of the renin-angiotensin-aldosterone system), while β₁-AR mediate vasodilation, bronchodilation, relaxation of uterine muscles and glycogenolysis (for review, see Brodde and Michel, 1999).

Physiologically, in white and brown adipocytes, β₂-AR are coupled to stimulatory Gαs and modulate energy metabolism and thermogenesis. Several reports have also discussed a potential role of β₂-AR in vasodilation and relaxation of airway smooth muscles (for review, see Leineweber et al., 2004). Whether or not β₂-AR exist in the human heart, is still unclear. Several groups found neither on the transcriptional nor on the functional level any evidence for β₂-AR mRNA or β₂-AR mediated effects (for review, see Brodde and Michel, 1999). On the other hand, in endomyocardial biopsy samples from the right intraventricular septum of cardiac transplant patients, Gauthier et al., (1996; 1998) found β₂-AR coupled to the Gαs/nitric oxide (NO) pathway mediating negative inotropic effects.

β₁-AR in heart failure (HF)

In human HF, the β₁-AR density is decreased (down-regulation). β₂-AR are uncoupled from the Gαs–AC-pathway (desensitization), amount and activity of the inhibitory Gβγ are increased (while Gαs is unchanged) as is the expression and enzymatic activity of G protein-coupled receptor kinases (GRKs), which phosphorylate the agonist-occupied β₁-AR receptors and thus facilitate their endocytosis (predominately β₁-AR) or uncoupling from Gαs (predominately β₂-AR) (for review, see Brodde, 1991; Brodde and Leineweber, 2004). In ventricular cardiomyocytes from patients with HF (increased inhibitory Gαs activity, see above), but not in cardiomyocytes from non-failing human hearts (normal Gαs activity), β₂-AR couple to Gαs, thereby directly mediating negative inotropic effects (Gong et al., 2002).

The consequence of these changes is a reduction in cardiac β₁-AR functional responsiveness; the extent of β₂-AR down-regulation and β₁-AR desensitization is directly related to the severity of HF and an attribute to the compensatory and chronically elevated activity of the sympathetic nervous system, as reflected by increased plasma NA levels (for review, see Brodde and Leineweber, 2004). Consequently, antagonism of the deleterious effects of catecholamines on the heart in HF by β₁-AR blockers (predominantly β₁-AR blockade) has beneficial effects, reflected by the up-regulation of the down-regulated β₁-AR, the re-sensitization of the uncoupled β₂-AR to the Gαs–AC pathway, normalization of Gαs activity, and the decrease in GRK amount and enzymatic activity (for review, see Brodde, 2007).

Thus, β₁-AR blockers improve left ventricular function, relieve HF symptoms and increase survival in patients with HF (Bouzamondo et al., 2001). However, despite their success as therapeutic agents, clinical studies have also shown that the responses among patients with HF to β₁-AR blocker are variable (Shin and Johnson, 2007). Genetic variations may account – at least in part – not only for the development and progression of HF but also for the variable responses to β₁-AR blockers in patients with HF.

β₁-AR single nucleotide polymorphisms (SNPs)

β₁-AR

For the β₁-AR, 12 nucleotide polymorphisms (SNPs) exist, but only two have functional relevance (see Figure 1): in the amino terminus of the receptor at position 145 (Ser49Gly, allele frequency, see Table 1) and in the proximal part of the carboxyl terminus (within the Gαs-binding domain of the β₁-AR) at position 1165 (Arg389Gly, allele frequency, see Table 1). A strong linkage disequilibrium (LD; a measurement how often alleles are inherited together) exists between both SNPs, thus creating common haplotypes (defined as a set of closely associated alleles inherited together on one chromosome). Gly49 is always associated with Arg389, while Gly389 is always associated with Ser499, so that the haplotype Gly49Gly–Gly389Gly occurs very rarely, if at all. Accordingly, the wild-type (WT)-β₁-AR consists of Ser49Ser–Arg389Arg (for review, see Leineweber et al., 2004).

Consequently, because of such strong LD, conclusions from a single locus investigated in vitro (site-directed mutagenesis of the WT-β₁-AR) are difficult to relate to ex vivo or in vivo findings. Investigations of single loci in vitro revealed that Gly49-β₁-AR had no effect on agonist binding and on basal and maximal ISO-stimulated AC-activity but enhanced agonist-induced down-regulation. Gly389-β₁-AR, on the other hand, exhibited slightly lower basal and three- to four-fold lower maximal ISO-stimulated AC-activity, probably due to reduced coupling to the Gαs–AC-pathway. In addition, Gly389-β₁-AR had less short-term agonist-promoted desensitization than Arg389 β₁-AR (for review, see Leineweber et al., 2004).

Although there is good in vitro evidence for such functional differences ex vivo (in human tissue natively expressing the different β1-AR SNPs) and in vivo. In isolated right atria obtained from patients undergoing coronary artery bypass grafting and chronically treated with atenolol, the inotropic potency but not the maximal effects of NA and ISO were lower when homozygous for the Gly389-β1-AR than when carrying the Arg389-β1-AR (Sandilands et al., 2003). In isolated atria from patients chronically treated with metoprolol or atenolol or not treated with β1-AR selective blockers at all, the inotropic potency or maximal effects of NA were not different when carrying the various Arg389Gly β1-AR polymorphisms (Molenaar et al., 2002). On the other hand, in isolated right ventricular trabeculae from non-failing and failing human...
hearts, inotropic potency and maximal effects of ISO were lower when from patients homozygous for the Gly389-β1-AR than from those carrying the Arg389-β1-AR (Liggett et al., 2006). In isolated human fat cells, however, the lipolytic response to dobutamine (DOBU, β1-AR selective agonist) was not different with regard to the various Arg389Gly β1-AR polymorphisms (Rydén et al., 2001).

Whether or not these discrepancies are caused by genotype-dependent differences between the various β1-AR SNPs in concert with a tissue and/or agonist-specific β1-AR responsiveness (see above) is not known at present. Of note, in HF patients treated with β1-AR selective blockers β1-AR are up-regulated while β2-AR are re-sensitized, and by using ISO (a non-selective β1- and β2-AR agonist) additional β2-AR responses probably modulate putative β1-AR genotype-dependent differences.

In young and middle-aged healthy subjects dynamic exercise (associated with increases in endogenous NA) revealed no genotype-dependent differences between subjects carrying the Gly389- or the Arg389-β1-AR variant with regard to increases in heart rate, contractility, blood pressure and plasma renin activity (extracardiac β1-AR mediated effect) (for review, see Leineweber et al., 2004). On the other hand, exercise-evoked maximal aerobic power (peak VO2) was least in subjects carrying the Gly389-β1-AR (Defoor et al., 2006). In contrast to the endogenously increased NA during exercise, increasing doses of exogenous DOBU caused significantly smaller increases in heart rate, contractility, blood pressure and plasma renin activity in healthy young subjects carrying one or two alleles of the Gly389-β1-AR than in subjects carrying the Arg389-β1-AR (La Rosee et al., 2004; Bruck et al., 2005a). Consistently, patients undergoing coronary artery bypass grafting under cardiopulmonary bypass and carrying one or two alleles of the Gly389-β1-AR required more and longer inotropic support by ADR than those homozygous for the Arg389-β1-AR (Leineweber et al., 2007).

Thus, in vivo position 389 does not determine functional responsiveness to a physiologic stimulus (exercise-induced increase in endogenous NA), but modulates the β1-AR response in a genotype-dependent manner to a pharmacological stimulus (exogenous infusion of DOBU and ADR). Vice versa, subjects carrying one or two alleles of the Gly389-β1-AR exhibit less responsiveness to β1-AR selective blockers (i.e. reduction in heart rate, contractility, blood pressure and plasma renin activity), however, independent of the underlying β1-AR stimulus: none (Sofowora et al., 2003), exercise (Liu et al., 2003) or DOBU infusion (Bruck et al., 2005a).

Thus, genetic variation in the β1-AR – predominately at position 389 – not only modulates functional responsiveness to agonists but also affects the impact of β-AR blockers in vivo.

For the β2-AR, 19 SNPs have been identified, and at least four are of functional consequence (see Figure 2 and Table 2): (i) at position –47 (Cys-19Arg) within the short open reading frame of the Beta Upstream Peptide (BUP; a 1.5 kb region upstream to the start codon containing the main transcriptional regulatory activity for β2-AR gene expression); (ii) and (iii) within the coding region within the extracellular amino terminus at
position 46 (Arg16Gly) and position 79 (Gln27Glu); and (iv) within the fourth TMD at position 491 (Thr164Ile) of the \( \beta_2 \)-AR (for review, see Leineweber and Brodde, 2004; Leineweber et al., 2004; Brodde and Leineweber, 2005). Strong LDs exist between these SNPs, resulting in common haplotypes: Arg-19 is always associated with Gly16, while Cys-19 is associated with either Arg16 or Gly16. 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-\( \beta_2 \)-AR consists of Cys-19Cys-Arg16Arg–Gln27Gln–Thr164Thr (for review, see Leineweber and Brodde, 2004; Leineweber et al., 2004; Brodde and Leineweber, 2005).

Investigations of single loci in vitro revealed: Cys-19Arg affects receptor expression on the transcriptional level (Arg-19 decreases \( \beta_2 \)-AR expression); Gly16-\( \beta_2 \)-AR enhance agonist-induced down-regulation but Glu27-\( \beta_2 \)-AR reduce it (both without affecting agonist binding affinities and/or basal/maximal agonist-stimulated AC-activity); Ile164-\( \beta_2 \)-AR lower agonist binding affinities, reduced basal/maximal agonist-stimulated AC-activity and exhibit less maximal agonist-stimulated internalization. Studies investigating different combinations at position 16 and 27 in vitro revealed: Arg-19Arg-Gly16Gly–Gln27Gln–Thr164Thr-\( \beta_2 \)-AR and Arg-19Gly-Gly16Gly–Glu27Glu–Thr164Thr-\( \beta_2 \)-AR have a similar down-regulation profile in comparison with the WT-\( \beta_2 \)-AR (suggesting that Gly16 dominates the phenotype), while Cys-19Cys–Arg16Arg–Glu27Glu–Thr164Thr-\( \beta_2 \)-AR have no such agonist-promoted down-regulation (for review, see Leineweber and Brodde, 2004; Brodde and Leineweber, 2005).

With regard to the strong LD between position 16 and 27, the Cys-19Cys-Arg16Arg–Glu27Glu–Thr164Thr-\( \beta_2 \)-AR does almost not exist in nature (<1% of the population). Also, the Ile164-\( \beta_2 \)-AR is not only rare in nature, but exists only in the heterozygous state; that is, the chance of forming a gamete homozygous for Ile164-\( \beta_2 \)-AR is therefore very low and possibly lethal due to a total loss of \( \beta_2 \)-AR responsiveness.

As mentioned above, \( \beta_2 \)-AR play a pivotal role in the regulation of heart rate and contractility, vasodilation and bronchodilation. In vivo, independent whether single loci or haplotypes were investigated, several studies found \( \beta_2 \)-AR-mediated increases in heart rate and contractility to be genotype-independent for the \( \beta_2 \)-AR variants Arg16Gly and Gln27Glu, but blunted in subjects carrying one allele of the Ile164-\( \beta_2 \)-AR (for review, see Leineweber et al., 2004; Brodde and Leineweber, 2005).

### Table 2 Position, frequency and phenotype consequences of the functional \( \beta_2 \)-Adrenoceptor single nucleotide polymorphisms

<table>
<thead>
<tr>
<th>SNP</th>
<th>Amino acid position</th>
<th>Common→minor allele</th>
<th>Caucasians</th>
<th>African-Americans</th>
<th>Asians</th>
<th>Latino-Hispanics</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-47T</td>
<td>–19</td>
<td>Cys→Arg</td>
<td>0.35</td>
<td>0.21</td>
<td>0.08–0.12</td>
<td>n.d.</td>
</tr>
<tr>
<td>A46G</td>
<td>16</td>
<td>Gly→Arg</td>
<td>0.38–0.46</td>
<td>0.49–0.51</td>
<td>0.54–0.59</td>
<td>n.d.</td>
</tr>
<tr>
<td>C79G</td>
<td>27</td>
<td>Gln→Glu</td>
<td>0.35–0.46</td>
<td>0.20–0.27</td>
<td>0.07–0.20</td>
<td>n.d.</td>
</tr>
<tr>
<td>C491T</td>
<td>164</td>
<td>Thr→Ile</td>
<td>0.02–0.04</td>
<td>0.02–0.04</td>
<td>0–0.01</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Only in the heterozygous state.

| AC, adenylyl cyclase; ADR, adrenaline; n.d., not determined; ISO, isoprenaline; SALB, salbutamol; SNP, single nucleotide polymorphism; TER, terbutaline.
Similar to cardiac responses, vasodilator responses to β2-AR stimulation are blunted in subjects carrying one allele of the Ile164-β2-AR when compared with subjects homozygous for the Thr164-β2-AR (Dishy et al., 2004; Bruck et al., 2005b).

β2-AR agonists are widely used to treat acute bronchospasm (short-acting agonists) and as an adjunct to anti-inflammatory therapy (long-acting agonists) in asthma. Similar to β-AR blockers in the treatment of HF, responses to β2-AR agonists are variable with regard to loss in bronchodilating and bronchoprotective effects and/or increased frequency of exacerbations due to β2-AR desensitization (for review, see Taylor, 2007). Such adverse effects are less pronounced in asthma patients carrying the Gly16Gly–Gln27Gln- or Gly16Gly–Glu27Glu-β2-AR than in patients carrying the Arg16Arg–Gln27Gln-β2-AR when treated with regular short-acting β2-AR agonists (for review, see Hawkins et al., 2008). Consistent with these findings, also the venous vasodilator response in healthy subjects is desensitized upon 2 h continuous ISO-infusion or 2 weeks oral treatment with TER with the haplotype order Arg16Arg–Gln27Gln-β2-AR (Dishy et al., 2001; Bruck et al., 2005b).

Thus, while position 16 and 27 have no functional impact on heart rate and contractility, the Arg16Arg–Gln27Gln-β2-AR in vascular and bronchial smooth muscle is rather susceptible to agonist-induced desensitization. With regard to the agonist- and tissue-dependent responsiveness of cardiac β2-AR (see above), an impact of the different β2-AR variants Arg16Gly and Gln27Glu can not be excluded. The functional responsiveness of the Ile164-β2-AR appears generally blunted, in an agonist- and tissue-independent manner.

**Clinical implications of β-AR polymorphisms**

In HF, both β1- and β2-AR and the accompanying signalling cascade (Gαs, Gαi, cyclic adenosine monophosphate (cAMP), GRKs) are altered, probably modulated also by the genetic variants of the β1- and β2-AR. Assuming that β1- and β2-AR SNPs are involved in the pathogenesis of HF, differences in the allele frequencies of these SNPs between cohorts with and without HF and in their prognosis are expected. However, neither for the Ser49- or Gly49- nor for the Arg389- or Gly389-β2-AR differences in allele frequencies were found. Furthermore, studies investigating the outcome of HF (worsening of clinical conditions, hospitalization, transplantation or death, mortality) are rather inconsistent (for review, see Brodde, 2008). While in three studies the outcome was better in HF patients carrying one or two alleles of the Gly49-β2-AR, two studies did not find an association between the different Ser49Gly β2-AR variants and the outcome of HF (for review, see Brodde, 2008). However, with regard to the strong LD between position 49 and 389, that is, Gly49 is always associated with Arg389, inconsistent results are actually expected. Consistently, however, the Arg389Gly β2-AR polymorphism seems not to affect the outcome of HF at all (for review, see Muthumala et al., 2008).

β2-AR mediate vasodilation; in hypertension vascular responses to β2-AR stimulation are impaired (for review, see Brodde and Michel, 1999). Since β2-AR SNPs modulate the desensitization of β2-AR and by this vasodilator responsiveness (see above) the different β2-AR variants might play a role in the development and or maintenance of hypertension. However, in many studies the β2-AR variants Arg16Gly or Gln27Glu had no influence on the development of hypertension (for review, see Brodde, 2008). However, a potential association between the Ile164–β2-AR variant and hypertension was found in women (Sethi et al., 2005) but not in men (Iaccarino et al., 2004; Sethi et al., 2005). No differences in the allele frequencies of the Arg16- or Gly16- and Gln27- or Gln27- and Thr164- or Ile164-β2-AR were observed between cohorts with and without HF (for review, see Leineweber and Brodde, 2004; Brodde and Leineweber, 2005). While HF patients with the Arg16Arg–Gln27Gln-β2-AR seem to have a more pronounced adverse outcome (heart transplantation) and increased risk for sudden cardiac death (for review, see Brodde, 2008) data on the role of the Ile164-β2-AR in HF are rather conflicting. Chronic HF patients carrying the Thr164Ile-β2-AR exhibit lower exercise capacity (peak VO2) than Thr164Thr-β2-AR patients (Wagoner et al., 2000) and a rapid progression to either death or heart transplantation during a 3 year follow-up (Liggett et al., 1998). However, because of the low prevalence of the Thr164Ile-β2-AR variant in the general population (see Table 2), the latter finding was obtained in only 10 out of 239 chronic HF patients (Liggett et al., 1998). On the other hand, several recent studies could not confirm this finding of a rapid progression of HF in patients heterozygous for the Thr164Ile-β2-AR. Forleo et al. (2004) in 171 consecutive patients with dilated cardiomyopathy did not find an association between the Thr164Ile-β2-AR polymorphism and the risk of HF, and De Grootte et al. (2005) in 444 consecutive patients with chronic HF and Barbato et al. (2007) in 31 chronic HF-patients and 24 controls did not find an association between the Thr164Ile-β2-AR polymorphism and 3.5 or 2 year, respectively, survival. We (Leineweber et al., 2006b) genotyped 309 heart-transplanted patients, 520 patients with stable chronic HF and 328 controls for the Thr164Ile-β2-AR polymorphism under the assumption that – if Thr164Ile-β2-AR patients indeed undergo rapid progression to death or heart transplantation, as suggested by Liggett et al. (1998) – the prevalence of the Thr164Ile-β2-AR variant and the frequency of the Ile164 allele should be much higher in heart-transplanted patients than in patients with stable chronic HF or healthy controls. In contrast to this assumption, we found the prevalence of the Thr164Ile-β2-AR variant in the heart-transplanted patients not different from that in the patients with stable chronic HF or the controls (Leineweber et al., 2006b).

As mentioned, β2-AR blockers up-regulate the down-regulated β2-AR, re-sensitize the uncoupled β2-AR, and improve left ventricular function, HF symptoms and survival in patient with HF, probably in a β1- and/or β2-AR genotype-dependent manner. However, investigations on the impact of the different β1- and β2-AR SNPs on left ventricular remodelling and the improvement in left ventricular function and survival in HF patients are limited and have to be interpreted carefully with regard to the study design [i.e. cohort registries vs. placebo-controlled or -uncontrolled clinical trials and β-AR blocker treatment: β1-AR selective vs. β2-AR non-selective blockers as well as time of intake].

**β-Adrenoceptor polymorphisms and CVD**

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and does (for review, see Muthumala et al., 2008)]. Studies investigating the effect of β-AR blockers on left ventricular remodelling and function found that the beneficial effects were more pronounced in HF patients homozygous for the Arg389-β-AR (Mialet-Perrez et al., 2003; Terre et al., 2005) or Gln27-β-AR (Kaye et al., 2003). Studies investigating the effect of β-AR blockers on survival are inconclusive: a sub-study of the MERIT HF (Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure) found no association between the β-AR variants Ser49Gly and Arg389Gly and all-cause death and/or hospitalization (White et al., 2003); in another study, five-year survival was significantly better in HF patients carrying one or two alleles of the Gly49-β-AR (and, due to the strong LD between position 49 and 389, carrying one or two alleles of the Arg389-β-AR) than in HF patients homozygous for the Ser49 β-AR (Magnusson et al., 2005). On the contrary, in the BEST trial (Beta-blocker Evaluation of Survival Trial) survival and reduction in hospitalization were reduced more in HF patients homozygous for the Arg389-β-AR and treated with bucindolol (β₁- and β₂-AR non-selective β-AR blocker with sympatholytic effects) than in HF patients homozygous for the Arg389-β-AR on placebo, whereas there was no such difference in outcome between HF patients receiving bucindolol or placebo when homozygous for the Gly389-β-AR (Liggett et al., 2006). Finally, a placebo-uncontrolled study investigating a cohort of clinically treated HF patients receiving metoprolol or carvedilol found no association between transplant-free survival and the different β₁- and β₂-AR SNPs (Sehnert et al., 2008); unfortunately, information regarding duration and dose of the respective β-AR blocker before registration in this study is missing.

Recently, Rochais et al. (2007) investigated in HEK-293 cells expressing either the Gly389- or the Arg389-β-AR dynamic conformational changes of both receptor variants during activation (by ISO and NA) or inhibition (by bisoprolol, metoprolol and carvedilol) via fluorescence resonance energy transfer microscopy. In this setting position 389 did neither affect the kinetics of agonist-induced receptor activation nor did it influence basal or maximal cAMP levels or even reveal differences in Gₛ activation. On the other hand, while position 389 again did not affect the response to bisoprolol and metoprolol (decrease in basal cAMP levels), the Gly389-β-AR variant exhibited a more than two-fold lesser basal cAMP reduction in response to carvedilol than the Arg389-β-AR variant. Consistently, in neonatal rat cardiomyocytes expressing either the Gly389- or the Arg389-β-AR, the Gly389-β-AR did not respond to carvedilol while the Arg389-β-AR responded with a 25% reduction of the beating frequency. Of note, while Rochais et al. (2007) did not find genotype-dependent differences in basal and maximal CAMP formation or activation of Gₛ in HEK-293 cells, the expression of the Arg389-β-AR variant in neonatal rat cardiomyocytes led already under basal conditions to a higher beating frequency than the Gly389-β-AR variant. In a clinical setting, Chen et al. (2007) investigated Caucasian patients with nonischemic cardiomyopathy treated ≥1 year with maximal tolerable carvedilol doses. They found that only 45% of patients carrying the Gly389-β-AR variant responded at all to carvedilol (left ventricular ejection fraction: basal 24 ± 7% vs. follow-up 30 ± 14%) whereas 81% of patients carrying the Arg389-β-AR variant responded with a significant increase in left ventricular ejection fraction (basal 22 ± 7% vs. follow-up 41 ± 12%). Thus, at present, β-AR SNPs are very likely not disease-causing genes but possibly predictive for the responsiveness to agonists and antagonists. Patients carrying one or two alleles of the Gly389-β-AR are poor or non-responders whereas patients homozygous for the Arg389 β-AR are good responders to antagonists. Such SNP differences are not of consequence for survival in HF patients.

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Conflict of interest

None.

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