Beta-3 Receptor Agonists

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Abstract

Beta-3 adrenergic receptors (β3-AR) have a more widespread tissue distribution in the human body as compared to beta1- and beta2 (β1/2)-adrenergic receptors, including in the bladder, brain, adipose tissue and cardiovascular system. Thus, β3-AR are potential drug targets for a wide range of therapeutic areas, both cardiovascular and non-cardiovascular including overactive bladder (OAB), depression, metabolic syndrome, obesity and heart failure (HF). β3-AR agonists that are selective to the β3-AR include CL 316,243, amibegron (SR58611A), mirabegron (YM-178) and vibegron (RVT-901). However, in HF, study results regarding a possible inotropic effect of β3-AR agonists remain equivocal and some authors report a negative inotropic effect in HF and β3-AR antagonists are also under study.

Keywords: heart failure, beta-3 adrenergic receptors, mirabegron

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Introduction

Beta-3 adrenergic receptors (β3-AR) belong to the superfamily of G protein-coupled receptors and show a more widespread tissue distribution in the human body as compared to beta1- and beta2 (β1/2)-adrenergic receptors. For example β3-AR have been described to be present in the bladder, brain, adipose tissue and cardiovascular system, among other tissues. Thus, β3-AR are potential drug targets for a wide range of therapeutic areas, both cardiovascular and non-cardiovascular including overactive bladder (OAB), depression, metabolic syndrome, obesity and heart failure (HF).[1]

Selective beta-3 adrenergic agonists

β3-AR agonists that are selective to the β3-AR include CL 316,243, amibegron (SR58611A), mirabegron (YM-178) and vibegron (RVT-901). These β3-AR agonists have different profiles. For example, CL 316,243 has anti-obesity and anti-diabetic properties and amibegron has antidepressant effects in animal models. Mirabegron is approved for the treatment of OAB syndrome, and vibegron is currently under development in human clinical trials also for the treatment of that condition. Newer β3-selective compounds showing interesting profiles as potential drugs for the treatment of obesity and non-insulin-dependent diabetes have recently been reported.[1]

Cardiovascular/metabolic properties and therapeutic concepts

Adipose tissue and diabetes. β3-AR mediate lipolysis in white adipose tissue and thermogenesis in brown adipose tissue.[2-4] The presence of the Arg64 allele in the first intracellular loop of the β3-AR gene may predispose subjects to abdominal obesity, which may in turn predispose them to insulin resistance and the earlier onset of type 2 diabetes mellitus.[5] β3-AR agonists appear to be of significance not only for the treatment of obesity, but also in terms of the risks of cardiovascular disorders related to visceral obesity, the form of obesity, which is more directly linked to augmented β3-AR activity.[6,7]

Vascular smooth muscles. β3-AR produce the sustained peripheral vasodilation, which is predominant in skin and fat.[8,9] Studies have shown that the relaxation of rat thoracic aorta was caused by selective β3-AR agonists.[10-13] A β3-AR-mediated vasorelaxation was also observed in the canine pulmonary artery.

[14] The presence of β3-AR has also been reported in veins of rats.[15] Also in rats, it was demonstrated that β3-AR stimulation causes a vasodilation of microvessels in the islets of Langerhans.

[7,16]

Endothelium. In human vessels, β3-AR vasorelaxation was found to be mediated partly through the production of nitric oxide (NO) [17], which may be caused by the functional coupling of β3-AR agonists to NO production.[7,18,19]
Cardiac effects. β3-AR stimulation of the human heart results in a negative inotropic effect, which is confirmed in several animal models. These findings suggest that β3-AR may participate in the pathophysiology of HFrEF. Functional β3-AR stimulation occurs in the normal left ventricle, causing a direct inhibition on sodium (Na+) channels and producing negative inotropy.[22] It has been found that β3-AR activation inhibits the L-type Ca2+-channel in both normal and HF rat myocytes. In HF, β3-AR stimulation-induced inhibition of Ca2+-channels was enhanced, which was responsible for the reduced inotropic response.[7,22], and an increased activity of the sympathetic nervous system led to the downregulation of cardiac β1- and β2-AR in HF.[20] Reduced β1- and β2-AR expression leads to a decrease in the contractile response to β-AR agonists.[23] Contrary to β1- and β2-AR, the abundance of the negatively inotropic β3-AR increases in the failing myocardium.[18] β3-AR lack the phosphorylation sites for cAMP-dependent protein kinase or β-AR kinase[23], and thus may not be downregulated in HF. Accordingly, the high adrenoceptor tone during HF may alter the cardiac contractile activity as a result of unmasked β3-AR stimulation in the presence of reduced β1- and β2-AR.[24] Overstimulation of the relatively desensitization-resistant β3-AR[25] after increased sympathetic tone and norepinephrine release in the setting of HF in humans may further decrease cardiac inotropy.[18] The levels of β3-AR mRNA and proteins show an increase in the failing heart compared with the nonfailing heart. If the β3-AR are too high, they might contribute to the loss of cardiac function and be the functional loss of the β3-AR in HF.[26] These study results may suggest the treatment options with specific antagonists of the human cardiac β3-AR for correcting the disordered adrenergic regulation of the failing heart.

Contrary to the aforementioned evidence, it has been reported that increased intracellular myocyte sodium (Na+) levels represent a key adverse pathophysiological feature of HF, and that the β3-AR mediates the stimulation of the only export route for Na+, the sodium-potassium (Na+-K+)-pump. The upregulation of the β3-AR may thereby represent a useful compensatory mechanism. Thus β3-AR agonists may be a potential therapeutic option for the treatment of HF.[27]

However, study results regarding the inotropic effect of β3-AR agonists remain equivocal. As mentioned above, some authors conclude that there is a negative inotropic effect (mainly in HF models)[21,28], whereas others do not agree.[29,30] The reasons for this discrepancy probably include the type and dose of the agonist used (with high doses of non-specific agonists producing opposing positive inotropic effects) and the control systems mediating for reflex orthosympathetic reactions leading to intense peripheral vasodilatation.[29]

Data from experimental models (summarised in table 1; but by no means exhaustive) have shown promising effects on cardiac function in HF and relevant co-morbidities.[30] These include beneficial effects on oxidative stress[31], augmentation in left ventricular contractility[32], diabetes-induced cardiac dysfunction[33], cardiac arrhythmia control after myocardial infarction[34], pulmonary hypertension[35-37] and erectile function (ED).[38]

Many of these direct and indirect mechanisms combine to modulate chronic myocardial remodelling. One important aspect is cardiac myocyte hypertrophy. It has been shown that β3-AR attenuate cardiac myocyte hypertrophy in response to a continuous or repetitive infusion of isoprotenerol or angiotensin II and a reduction of hypertrophy in response to different β3-AR agonists. This anti-hypertrophic effect of β3-AR was NO-dependent. β3-AR expression also greatly reduced myocardial interstitial fibrosis due to isoproterenol and angiotensin II infusions.[40] Similar protective effects of β3-AR were reported with preferential β3-AR agonists in mice exposed to trans-aortic constriction, with the subsequent decreased hypertrophy and preserved LV function.[41]

Protective effects of β3-AR agonists at the myocardial level are probably reinforced from indirect effects in peripheral cells/tissues, i.e. through the coronary vasodilatation via β3-AR-induced endothelial dependent relaxation, as well as the paracrine release of NO and its effects to improve LV relaxation. Moreover, the antioxidative effects of β3-AR signalling may preserve the endothelium of microvasculature from oxidative activation and the ensuing recruitment of monocytes initiating subendothelial inflammation at the core of sustained endothelial dysfunction. Whether this might prevent from chronic development of vascular atherosclerosis or chronic development of diastolic dysfunction initiating HFrEF[42] has yet to be tested in trials with interventions and long follow-up.[40]

Table 1. Involvement of β3-AR signalling in the pathophysiology of listed pathologies and involved tissues in different animal models.

<table>
<thead>
<tr>
<th>Effect/medical condition</th>
<th>Organ/tissue</th>
<th>Species</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Heart</td>
<td>Sheep</td>
<td>Bundgaard et al. 2010 [30]</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>Heart</td>
<td>Rat</td>
<td>Kong et al. 2010 [31]</td>
</tr>
<tr>
<td>Cardiac contractility</td>
<td>Heart</td>
<td>Mice/human (transgenic)</td>
<td>Kohout et al. 2001 [32]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Heart</td>
<td>Rat</td>
<td>Dinčer et al. 2001 [33]</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>Heart</td>
<td>Dog</td>
<td>Zhou et al. 2008 [34]</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Pulmonary artery</td>
<td>Dog</td>
<td>Tagaya et al. 1999 [35]</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Lung</td>
<td>Rat</td>
<td>Dumas et al. 1998 [36]</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Pulmonary artery</td>
<td>Pig</td>
<td>García-Álvarez et al. 2016 [37]</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Corpus cavernosum/ penile artery</td>
<td>Human</td>
<td>Mitidieri et al. 2017 [38]</td>
</tr>
<tr>
<td>Cardiac remodelling</td>
<td>Cardiac myocyte</td>
<td>Mice/human (transgenic)</td>
<td>Belge et al. 2014 [39]</td>
</tr>
<tr>
<td>Heart failure/ cardiac remodelling</td>
<td>Heart</td>
<td>Mice/knockout mice</td>
<td>Niu et al. 2012 [41]</td>
</tr>
</tbody>
</table>
with hypertensive structural heart disease, being at high risk of developing HFpEF. Beta3-LVH is a randomized, placebo-controlled, double-blind, two-armed, multicentre, European, parallel group study. A total of 296 patients will be randomly assigned to receive either mirabegron or placebo over 12 months. Beta3-LVH is the first large-scale clinical trial to evaluate the effects of mirabegron on LVMi and diastolic function in patients with LVH.

Moreover, there are ongoing clinical trials in the fields of pulmonary hypertension, erectile dysfunction and obesity β3AR agonists. The Beta3 Agonist Treatment in Chronic Pulmonary Hypertension Secondary to Heart Failure (SPHERE-HF) study will evaluate the efficacy and safety of mirabegron in patients with pulmonary hypertension secondary to HF. The Mirabegron For Erectile Dysfunction pilot will evaluate the effect of mirabegron on men with both OAB symptoms and mild to moderate ED. The Efficacy of Pharmacological Stimulation of BAT and WAT in Lean and Obese Young Adults (MiraBAT) is conducted to determine whether the pharmacological stimulation of supraclavicular Brown Adipose Tissue (BAT or “Brown Fat”) and subcutaneous White Adipose Tissue (WAT) using mirabegron is as effective in increasing oxidative metabolism in BAT and WAT as is the exposure to cold. The Effects of β3-Adrenergic Receptor Agonists on Brown Adipose Tissue study will test the hypothesis that human BAT can be activated using mirabegron. The efficacy of mirabegron will be compared with cold exposure, as well as a placebo.

Conclusions

In conclusion, the pleiotropic protective properties of selective β3-AR agonists make these interesting therapeutic agents, especially in the complex syndrome of HF with all its predisposing cardiometabolic conditions and comorbidities.

Declarations of interest

The authors declare no conflict of interest.

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