Circulation: Heart Failure

EDITORIAL

Not All β-Receptors Appear the Same in Heart Failure: Emergence of β3-Agonists as a Therapeutic Option

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Heart failure (HF) remains a leading global cause of mortality and is an economic burden on healthcare systems. Despite recent advances in clinical therapy, the prognosis remains poor.

See Article by Bundgaard et al

β-ARs (β-adrenergic receptors) belong to the family of GPCRs (G-protein–coupled receptors) and play a central role in HF progression. The ability of β-ARs to influence critical cellular signaling in cardiac myocytes makes them an effective target for HF therapies. β3-ARs were discovered in 1989 and were first found in human cardiac biopsies in 1996.[1] A critical difference from β1- and β2-ARs, the predominant β-ARs present in the heart, is the lack of GRK (GPCR kinase) phosphorylation sites and a PKA (protein kinase A) consensus sequence at the cytosolic C-terminal domain of the β3-AR.[2] Because of this, the β3 receptor does not undergo GRK-mediated desensitization and downregulation seen in other β-receptors following myocardial injury. Thus, in failing myocardium, β3-AR levels remain unchanged or even increased[3] compared with β1-AR and β2-AR levels. Contrary to the earlier belief that β3-AR stimulation exacerbates HF, results indicating its cardioprotective role have prompted a reevaluation of this receptor signaling in HF, making it a constantly evolving area of research.

Potential beneficial effects of β3-AR stimulation in cardiomyocytes in mostly mediated by the nitric oxide (NO)/cGMP/PKG (protein kinase G) signaling axis (Figure). This results in (1) decreased cytosolic Ca^{2+} transients leading to a decrease in contractility,[2] (2) deglutathionylation of β1 subunit of Na^+-K^+ ATPase increasing its pump function,[4] (3) inhibition of β1/β2-AR generated cAMP by β3-AR generated cGMP, thus acting as a brake to prevent β1/β2-AR-PKA mediated adverse downstream signaling events,[2] and (4) mitochondrial biogenesis and inhibition of opening of mitochondrial permeability transition pore preventing cardiomyocyte apoptosis.[1,2] In endothelial cells, stimulation of β3-ARs results in vasorelaxation by diffusion of endothelium generated NO into the adjoining vascular smooth muscle cells and downstream sGC (soluble guanylate cyclase)/PKG signaling.[2]

From the various above stated beneficial mechanisms, Bundgaard et al in the past have outlined a β3-AR–mediated cardioprotective role of Na^+-K^+ ATPase in animal models of HF[4] and this potential benefit in clinical trials.[5] In a sheep model of HF, agonist-driven β3-AR stimulation appears to improve systolic function mediated by this Na^+-K^+ ATPase mechanism.[4] In the BEAT-HF trial (Beta3 Adrenoreceptor Agonist in Chronic Heart Failure), chronic use of a β3-AR agonist mirabegron, an Food and Drug Administration– approved agent for overactive bladder, was evaluated in patients with stable HF in NYHA class II and III with left ventricular ejection fraction (LVEF) <40% and on stable pharmacotherapy. No improvement in LVEF was observed after 6 months of mirabegron treatment. However, in a subset of patients who had baseline LVEF<40% but milder symptoms,

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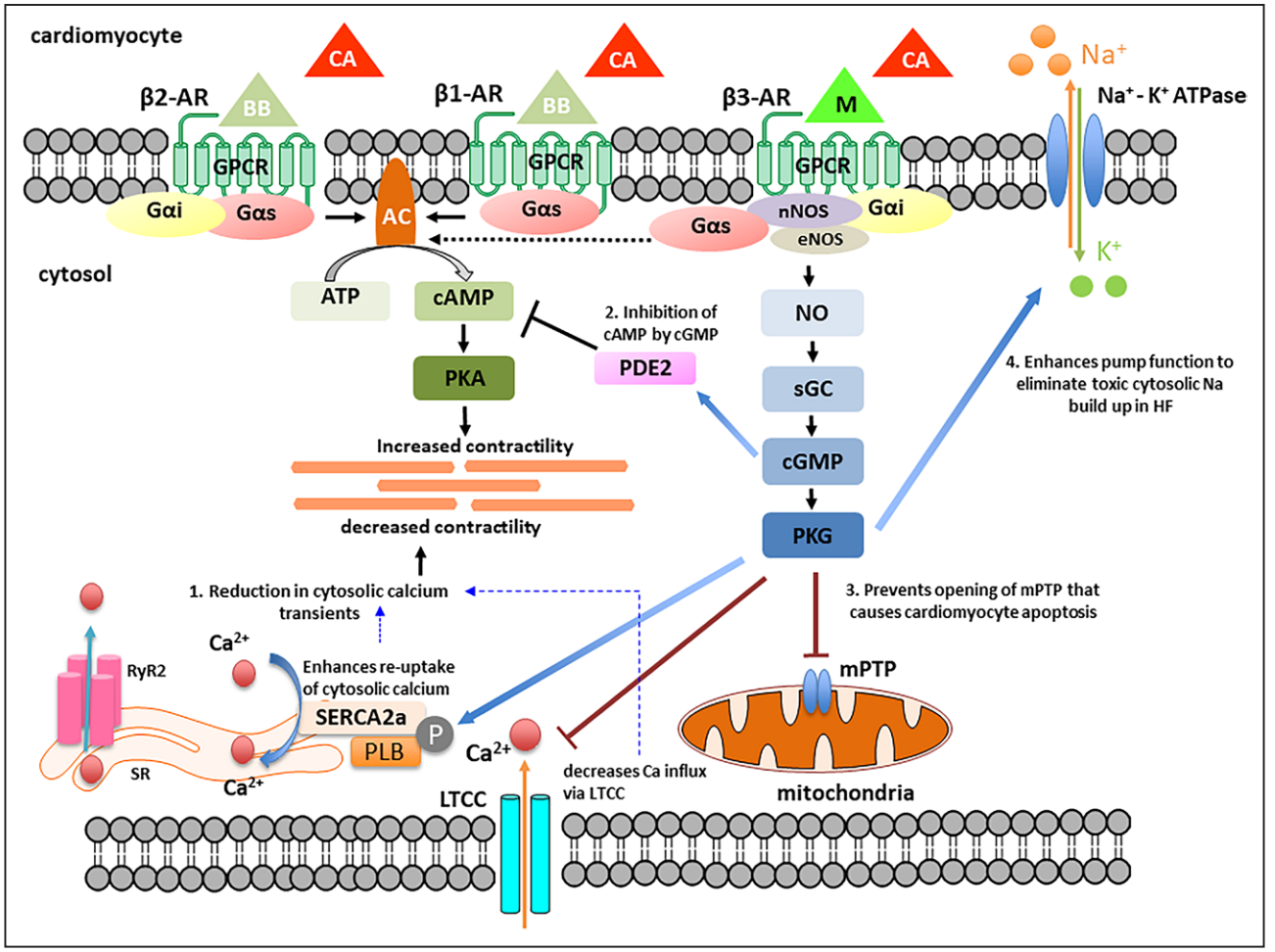

Figure. Cardioprotective cellular mechanisms mediated by β3-AR (β3-adrenergic receptor) stimulation.
β3-ARs are transmembrane receptors that are a type of GPCR (G-protein–coupled receptor). In the heart, their ligands are primarily catecholamines: epinephrine and norepinephrine. As the name suggests, GPCRs relay intracellular signals by binding to G-proteins in the cytosol. Various classes of GPCRs signal by binding to either of the 3 different subunits of G-proteins: Gα, Gβ, and Gγ. Based on their ability to regulate adenylyl cyclase (an enzyme that synthesizes cAMP from ATP) activity, Gα is further subdivided into Gαs (Gα stimulatory) and Gαi (Gα inhibitory) subunits. While downstream signaling via Gαs increases contractility, signaling via Gαi decreases contractility in cardiomyocytes. Under pathological conditions, β1-ARs bind to Gαs, and β2-ARs bind to both Gαs and Gαi. In the current study by Bundgaard et al[6], since β-blockers (blocks β1/β2-AR activity) were administered, β1/β2-AR downstream signaling would have been inhibited. Although previous studies have demonstrated that in human ventricular myocardium β3-AR signals by binding to Gαi, we speculate that there is a possibility that β3-ARs might mediate downstream signaling via Gαs as well. β3-AR signaling via the NOS (NO synthase)/NO/cGMP/PKG (protein kinase G) axis results in multiple cardioprotective mechanisms (numbered 1–4). Although in the current and past studies and clinical trials involving β3 stimulation, only the increase in Na^+-K^+ ATPase activity has been investigated, the overall cardioprotection might involve these other mechanisms as well. AC indicates adenylyl cyclase; BB, β-blocker; Ca^+, calcium; CA, catecholamines; eNOS, endothelial nitric oxide synthase; HF, heart failure; K^+, potassium; LTCC, L-type calcium channel; M, β3 agonist mirabegron; mPTP, mitochondrial permeability transition pore; Na^+, sodium; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; P, phosphorylation; PDE2, phosphodiesterase 2; PKA, protein kinase A; PKG, protein kinase G; PLB, phospholamban; RyR2, ryanodine receptor; sGC, soluble guanylate cyclase; and SR, sarcoplasmic reticulum.

mirabegron significantly improved LVEF.[5] Drawing parallels with the sheep HF model, the authors attributed this to mirabegron's effect on Na^+-K^+ ATPase.

Bundgaard et al[6] have conducted a separate study to assess short-term hemodynamic effects of mirabegron in patients in NYHA class III or IV with baseline LVEF ≤35% and on stable pharmacotherapy. In this issue of *Circulation: Heart Failure*, they report that oral administration of mirabegron did not have an effect after 3 hours but after 7 days lead to a significant increase in cardiac index, stroke volume index, and decreased pulmonary vascular resistance (PVR) compared to the placebo-treated group. All measurements were made at rest as well as during submaximal exercise (after 3 hours and after 7 days). Improvements in cardiac index, stroke volume index, and decrease in PVR were observed only at rest and not during exercise.[6] Importantly, the positive effects of mirabegron on cardiac hemodynamics were not associated with reductions in blood pressure, an increase in heart rate, or altered renal function. Like the previous BEAT-HF trial, Bundgaard et al[6] attribute this also to mirabegron's effect on Na^+-K^+ ATPase. Although an important protective

mechanism, the overall beneficial effects of mirabegron administration are most likely a collective effect of multiple mechanisms (stated above) as opposed to a single mechanism. Although the effect of β3-AR stimulation on cardiomyocyte cytosolic Na^+ export has been extensively studied in the context of HF, the effects of β3-AR stimulation on Na^+ influx in HF remain unexplored including whether β3-AR stimulation in HF influences voltage-gated Na^+ channels or the NCX (sodium-calcium exchanger). In the current study (mirabegron n=11) as well as the previous BEAT-HF trial (mirabegron n=8), the authors report that patients with low EF and mild symptoms seem to benefit from mirabegron use. However, the sample size of both exploratory studies is small and underpowered to draw specific conclusions.

Seven days after mirabegron treatment, the decrease in PVR was not associated with a statistically significant increase in pulmonary capillary wedge pressure.[6] Although there was a trend toward the mirabegron group having a slightly higher pulmonary capillary wedge pressure compared to the placebo group. This will be an important parameter to evaluate with chronic use of mirabegron as an increase in pulmonary capillary wedge pressure will be indicative of worsening LV failure. As mere speculation, the effect of mirabegron on significantly decreasing PVR, without significantly increasing pulmonary capillary wedge pressure could be attributed to the dual action of β3-ARs expressed in pulmonary arteries and the heart. In cardiomyocytes, β3-AR stimulation improves LV function by counteracting the effect of β1/β2-ARs and all the beneficial signaling events outlined in paragraph 3. In pulmonary arteries, β3-AR stimulation decreases PVR by inhibiting pulmonary artery SMC proliferation, vasodilation, and attenuation of vascular proliferation in the lungs.[7] Because mirabegron-mediated effects were assessed 7 days after administration, the beneficial effects of the above-mentioned processes would have occurred only in part and not in entirety. Therefore, the long-term effects of mirabegron on cardiopulmonary circulation should be evaluated.

cAMP-mediated positive inotropic effects of β1-AR agonists are only helpful in the short term. Their chronic use results in declining cardiac reserve over time. In contrast, cGMP-mediated effects of β3-AR stimulation can dampen the sustained positive inotropy caused by the catecholaminergic stress-driven response of β1/β2-AR. This makes β3-AR agonists potentially better for long-term treatment of HF compared to these positive inotropes. Besides mirabegron, other β3 agonists and downstream signaling targets have also been explored for their cardioprotective effects. In animal models of HF, nebivolol, a β-blocker, and a β3-AR agonist reduced infarct size and cardiomyocyte apoptosis. Nebivolol also has a vasodilatory effect that is mediated by eNOS (endothelial NO synthase)/NO generation in endothelial cells and reduces PVR,[2] similar to mirabegron. Interestingly, metoprolol, a β1 antagonist, prevented downregulation of the β3-AR after myocardial infarction in mice. This resulted in enhanced activity of S1PR1 (sphingosine-1 phosphate receptor kinase) leading to increased S1P (sphingosine-1 phosphate) secretion which confers cardioprotection.[8] This indicates that crosstalk between β1 antagonism and β3-ARs plays a role in β3-AR–mediated cardioprotection. In the current study,[6] since all patients were administered β-blockers, besides the cardioprotective effects mediated by Na^+-K^+ ATPase, the crosstalk between β-blockers and acute β3-AR stimulation might also play a role. Like mirabegron, 2 other β3 agonists vibegron, and solabegron have been evaluated in clinical trials and found to be effective in treating overactive bladder.[9] Going forward, it remains to be seen if these β3 agonists will have similar or better cardioprotective effects than mirabegron.

In the current study,[6] 300 mg of mirabegron was administered. This is more than the highest dose (200 mg) used in trials to treat overactive bladder.[10] A higher dose may be justified since the cellular energy requirements of smooth muscle cells of the detrusor muscle, whose primary function is storage, is distinct from cardiomyocytes with a primary pump function. It may well be that the degree of β3-AR stimulation required in the 2 different tissue types will be different to achieve clinically relevant physiological effects, although this is not explored in the Bundgaard et al's article. Also, β3-AR is the predominant β-AR in the detrusor muscle[11] but is the least expressed β receptor in the myocardium, potentially requiring higher doses of the drug. Nevertheless, administration of higher doses doesn't always correlate with better clinical outcomes and increases the potential risk of off-target effects. Side effects of antimuscarinic agents, often used to treat overactive bladder, are increases in heart rate, QT interval, and a decline in cognitive function in elderly patients. Mirabegron did not increase heart rate[6] or QT interval.[5] Although up to 50 mg/day, it did not affect cognitive function[12]; this will need to be evaluated for 300 mg/day. In animal studies, mirabegron exacerbated atherosclerosis by activating brown fat-mediated lipolysis.[13] Another off-target effect that needs careful assessment.

β3-AR's opposing mode of action to β1/β2-ARs combined with its vasodilatory effects makes it an interesting target for HF therapies. Nevertheless, because of its regulatory role in multiple processes involving the heart, pulmonary circulation, urinary bladder, and adipose tissue metabolism, agonist targeting needs to proceed with caution to ensure the least off-target effects. Taken together, the current study results, past trials, and data from animal models highlight the importance of the β3-AR signaling axis in HF. The emergence of β3-AR pharmacological targeting for HF therapy is exciting and shows that β1- and β2-ARs are not the only β-ARs in the failing myocyte that can be therapeutically targeted.

ARTICLE INFORMATION

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Disclosures

None.

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