Phosphodiesterase 2 as a Therapeutic Target for Heart Failure
Is Upregulation an Option?

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Heart failure (HF) is a chronic progressive cardiac disease with high morbidity and mortality. A key pathophysiological feature of HF is chronic overexertation of the sympathetic nervous system and release of catecholamines. The subsequent activation of cardiac β-adrenoceptors (β-ARs) results in molecular and structural changes that lead to cardiac hypertrophy, myocardial fibrosis, or electromechanical dysfunction. This cascade of cellular events creates a setting for lethal cardiac arrhythmias and increases the prognostic risks for mortality and detrimental cardiovascular outcome. Accordingly, pharmacological intervention with β-blockers remains a mainstay practice in clinical management of HF.

Nevertheless, chronic β-blocker therapy is known to be accompanied by adverse side effects that include bradycardia, heart block, bronchospasm, fatigue, muscle cramps, and sleep disturbances. Furthermore, not all patients experiencing HF benefit from β-blocker treatments or tolerate the doses necessary to achieve disease improvement. These disadvantages prompted the quest for alternative medication against HF with therapeutic targets other than β-ARs.

Article, see p 120

There are 3 subtypes of β-ARs: β1-, β2-, and β3-AR. Both β1-AR and β2-AR can be found in healthy cardiac cells, and the expression of β1-AR is considerably low in the unstressed heart. In the failing heart, β1-AR and β2-AR expression are, respectively, decreased and increased. However, changes in β1-AR levels are somewhat controversial, varying from increase to decrease. After catecholamine stimulation, both β1-AR and β2-AR couple to adenylyl cyclase stimulatory G protein, Gs, leading to cAMP accumulation within the myocyte and activation of protein kinase A (PKA). In contrast, β3-AR activation increases the activity of protein kinase G via cGMP-dependent signaling. The cAMP/PKA signaling is in principle responsible for the positive inotropic, lusitropic, and chronotropic effects mediated by stimulation of β-ARs. By contrast, cGMP/PKG signaling is considered a form of myocardial brake that reduces maladaptive hypertrophy, enhances cell survival signaling and mitochondrial function, protects against ischemia–reperfusion injury, and blunts the stimulatory effects of catecholamines. These actions of cGMP are believed to be beneficial in HF partly because they may act against cAMP-induced cardiac remodeling. Moreover, enhancement of β2-AR–coupled cGMP signaling may explain, in part, the therapeutic benefit on the preservation of cardiac function when β1-blockers are used in HF.

The level and subcellular distribution (compartmentalization) of cAMP and cGMP are regulated by cyclic nucleotide–hydrolyzing phosphodiesterases (PDEs). At present, 11 different PDE family members (PDE1–11) have been described, of which PDE4, 7, and 8 are selective for the hydrolysis of cAMP and PDE5, 6, and 9 for cGMP. PDE1, 2, 3, 10, and 11 can hydrolyze both cAMP and cGMP. As the sole means of terminating a cyclic nucleotide–dependent signal, PDEs provide a mechanism for controlling intracellular concentrations of cyclic nucleotides. Among the PDE members expressed in the heart, PDE2 exhibits the unique property, after being activated by cGMP, of producing conformational changes of cAMP to increase its hydrolysis by 10- to 30-fold. This unique property of cGMP-activated cAMP eraser stages PDE2 in the center of a negative cGMP/cAMP cross talk. More notably, the observation that myocardial PDE2 is upregulated in human HF implicates its upregulation or activation as a highly attractive new therapeutic option in the management of HF.

In the current issue of Circulation Research, Vettel et al provided evidence to argue for a cardioprotective effect of PDE2 under chronic β-AR stress conditions, most likely via a predominant role in heart rate (HR) regulation. The authors found that specific pharmacological inhibition of PDE2 in healthy experimental animals leads to an exclusive increase in HR, whereas overexpression of the phosphodiesterase in heart-specific PDE2 transgenic mice results in HR decrease. Under pathological conditions of chronic β-AR stimulation, PDE2 contributes to myocardial β-AR desensitization and protects the damaged heart from excessive sympathetic stress on inotropy and chronotropy. The initiation of heart beat is known to be based on a mutual interplay between ion channels of the cell membrane clock (membrane clock) and cellular calcium cycling clock (Ca2+ clock). In this study, the authors showed that the accumulation of cAMP in response to β-AR stimulation is markedly blunted in PDE2-overexpressed myocytes, and the induced cAMP-dependent Ca2+ signaling, including ion channels of both membrane and Ca2+ clock, is...
attenuated (Figure). Under the condition of HF, chronic over-excitation of the sympathetic nervous system significantly increases arrhythmia susceptibility and dampens cardiac contractile performance after cardiac ischemia–reperfusion injury. Vettel et al further found that elevated abundance of myocardial PDE2 protects against ventricular arrhythmia induced by acute β-AR stimulation and improves ventricular function in experimental myocardial infarction induced by left anterior descending artery ligation. In short, PDE2 overexpression may offer a potential dual protection to the failing heart by limiting HR without the depression of contractile performance. As a consequence, an increase in expression or activity of PDE2 may be beneficial because it lowers arrhythmia susceptibility and preserves cardiac contractile function during ischemic injury in the failing heart.

The concept of targeting PDEs for therapeutic management of HF is not new, although the theoretical basis is inhibition of PDE. For example, milrinone, a PDE3-selective inhibitor, is reported to be effective in increasing cardiac contractility in patients with HF. However, its clinical indication has been curtailed because it increases cardiac mortality. Other studies evaluated the efficacy of PDE5-selective inhibitors, sildenafil and tadalafil, in chronic HF. It is evident from those clinical investigations that depending on morpho-functional impairments and staging of HF, as well as dosing and duration of treatments, the outcome may vary from no significant changes in HR and systolic or diastolic blood pressure to significant improvement of hemodynamics and clinical parameters, even to reversal of maladaptive chamber remodeling. Treatment with rolipram, a PDE4-selective inhibitor, however, has no effect on positive inotropic and lusitropic effects of catecholamines in ventricular myocardium of patients with HF treated with the β-blocker, carvedilol.

In light that none of the currently available PDE inhibitors has yet been shown convincingly to improve the clinical symptoms of patients with HF, the findings by Vettel et al may offer an alternative therapeutic approach to the treatment of HF. However, several issues require further clarification before this approach can be put into practice. The first issue concerns the compartmentalization of cyclic nucleotide signaling. In addition to structural segregations of a cell based on visible membrane-delimited organelles, cellular compartmentalization can be described as functional domains that are temporally and spatially regulated. To this end, the β-agonist isoproterenol induces cAMP accumulation and PKA activation in both soluble and particulate subcellular fractions of rabbit heart. However, prostaglandin E1 increases only the soluble fraction of cAMP/PKA signaling. Moreover, adenylyl or guanylyl cyclase is unevenly distributed within the cell such that cAMP and cGMP concentrations are at their highest

Figure. The role of phosphodiesterase 2 (PDE2) in the regulation of heart rate in healthy and failing heart. In healthy heart, the initiation of heart beat is based on a mutual interplay between ion channels of the cell membrane clock (M clock) and cellular calcium cycling clock (Ca2+ clock) mediated by a dynamic balance between the stimulatory cAMP/protein kinase A (PKA) system activated by β1/β2-ARs and the inhibitory cGMP/PKG cascade activated by β3-AR. In the failing heart where PDE2 expression is upregulated, heart rate response to chronic β-AR stimulation is restrained. This is attributed to the unique property of PDE2 as a cGMP-activated cAMP eraser that attenuates β-AR–induced accumulation of intracellular cAMP, along with the induced increase in L-type Ca2+ channel (Ica,L) current and fractional release of Ca2+ from the sarcoplasmic reticulum (SR), key components of the respective M clock and Ca2+ clock machineries for the initiation of heart rate. Under the scenario in which the expression of β3-AR is increased, the Ica,L current is further suppressed via activation of cGMP/PKG signaling. AG indicates adenylyl cyclase; β-AR, β-adrenoceptors; GC, guanylyl cyclase; Gi, adenylyl cyclase inhibitory G protein; Gs, adenylyl cyclase stimulatory G protein; M clock, membrane calcium clock; NOS3, endothelial nitric oxide synthase; PKA, protein kinase A; PKG, protein kinase G; PLB, phospholamban; PyR, ryanodine receptor; SERCA, sarcoendoplasmic reticulum calcium transport ATPase; and SR, sarcoplasmic reticulum.
close to the cyclase enzymes and at their lowest in the areas containing the PDEs. It is, therefore, conceivable that the specific subcellular localization of PDE2 may dictate the local magnitude and duration of cAMP/PKA signaling. A general limitation of transgenic overexpression is the potential spill-over of the protein of interest within the subcellular compartments. Although Vettel et al.9 used an elegant heart-specific PDE2 transgenic mouse model, the possibility still exists that PDE2 may not be physiologically located. As a consequence, the subcellular signaling specificity may have been lost, and every PKA subset present in the cell would be affected (in this scenario, it is suppressed). This issue becomes even more critical when PDEs could be redistributed within the cells under pathological conditions.28 Further insights at the subcellular level on the role of PDE2 in local regulation of cAMP/cGMP signals in cardiac myocytes under HF are, therefore, crucial for the development of novel therapeutic interventions that target PDE2.

The second issue concerns cross talk between cGMP and cAMP signaling pathways, which has been appreciated for some time and again demonstrated in cardiomyocytes by Vettel et al.9 Whereas this study posits PDE2 as a central component of the negative cGMP/cAMP cross talk, whether monotherapy targeting this PDE is clinically effective in HF remains to be seen. Moreover, because the cAMP-hydrorylizing activity of PDE2 is increased in the presence of cGMP, strategies to maintain high intracellular cGMP levels would in theory provide additional benefits. In this regard, a randomized double-blind PARADIGM-HF trial (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] With ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure)29 in patients with HF who exhibit reduced ejection fraction reported that combined use of valsartan, an angiotensin receptor blocker, with sacubitril, a compound that increases cellular cGMP because of inhibition of the natriuretic peptide–degrading enzyme neprilysin, reduces cardiovascular mortality, duration of hospitalization, and all-cause mortality when compared with monotherapy by the use of a proven dose of angiotensin-converting enzyme inhibitor. It is, therefore, likely that combined use of conventional HF therapy with compounds that target PDE2 will generate enthusiasm as our understanding of the role of PDE2 in the crosstalk between cGMP and cAMP signals advances.

The third issue concerns the long-term value of targeting PDE2 for HF therapy. It is well recognized that on prolonged treatment, many beneficial effects against HF of currently available PDE inhibitors are offset by cardiac mortality, most commonly in the form of fatal arrhythmia or sudden cardiac death. Vettel et al.9 reported that cardiac phenotypes in elderly heart-specific PDE2 transgenic mice are well sustained without out cardiac pathology and premature death. Given that the roles played by PDE2 and other PDE isoforms vary among mammalian species, a cautionary note is that results from animal study may not recapitulate in humans. In particular, results from tissue-specific manipulation of protein of interest in animal studies should be viewed solely as proof of principle. In theory, clinical application of PDE2 to the myocardium could be accomplished by gene therapy. Nevertheless, this approach is fraught with technical and ethical problems of its own.

The pathophysiological mechanisms that underlie HF are complex, making the development of effective, rational therapeutic management of its clinical symptoms an arduous task. Although the concept of targeting PED2 for the treatment of HF is still immature, the findings of Vettel et al.9 do point to a new direction for therapeutic strategy to protect ventricular arrhythmia during excessive sympathetic stress and improve ventricular function after severe cardiac insults via cGMP-activated cAMP inhibition by PDE2. Because the hitherto available therapies against HF and prevention of sudden cardiac death are only moderately efficient, an augmentation of expression or enzyme activity of PDE2 may offer a potentially promising option in the development of new HF therapy.

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References


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