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Targeting Cyclic Nucleotide Phosphodiesterase in the Heart: Therapeutic Implications

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Abstract

The second messengers, cAMP and cGMP, regulate a number of physiological processes in the myocardium, from acute contraction/relaxation to chronic gene expression and cardiac structural remodeling. Emerging evidence suggests that multiple spatiotemporally distinct pools of cyclic nucleotides can discriminate specific cellular functions from a given cyclic nucleotide-mediated signal. Cyclic nucleotide phosphodiesterases (PDEs), by hydrolyzing intracellular cyclic AMP and/or cyclic GMP, control the amplitude, duration, and compartmentation of cyclic nucleotide signaling. To date, more than 60 different isoforms have been described and grouped into 11 broad families (PDE1–PDE11) based on differences in their structure, kinetic and regulatory properties, as well as sensitivity to chemical inhibitors. In the heart, PDE isozymes from at least six families have been investigated. Studies using selective PDE inhibitors and/or genetically manipulated animals have demonstrated that individual PDE isozymes play distinct roles in the heart by regulating unique cyclic nucleotide signaling microdomains. Alterations of PDE activity and/or expression have also been observed in various cardiac disease models, which may contribute to disease progression. Several family-selective PDE inhibitors have been used clinically or pre-clinically for the treatment of cardiac or vascular-related diseases. In this review, we will highlight both recent advances and discrepancies relevant to cardiovascular PDE expression, pathophysiological function, and regulation. In particular, we will emphasize how these properties influence current and future development of PDE inhibitors for the treatment of pathological cardiac remodeling and dysfunction.

Keywords

Cyclic Nucleotide; Phosphodiesterase; Heart

Introduction

Cyclic adenosine 3′,5′-monophosphate (cAMP) and cyclic guanosine 3′,5′-monophosphate (cGMP) are two critical intracellular second messengers regulating fundamental cellular processes in the cardiovascular system, from acute effects on muscle contraction/relaxation to chronic effects on gene expression and cell growth/survival. Phosphodiesterases (PDEs), by catalyzing the hydrolysis of cAMP and cGMP to 5′AMP and 5′GMP, limit the diffusion of cyclic nucleotide and thus regulate the amplitude, duration, and compartmentation of cyclic nucleotide signaling. Recent data suggest that specific cyclic nucleotide-mediated functions depend on the assembly of multiple divergent macromolecular complexes containing unique cyclases, PDEs, kinases, and anchoring proteins [1]. PDEs constitute a superfamily with

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multiple isoforms that differ in tissue distribution, biochemical properties, and sensitivity to chemical inhibitors. At least 22 genes encoding more than 60 different PDE isoforms have been identified and grouped into 11 broad families (PDE1–PDE11). Alternate splicing and transcription start sites also contribute multiple different isoforms, many of which possess species-specific tissue and/or cellular distribution. In the myocardium, at least six different PDE families have been described, including PDE1, 2, 3, 4, 5, and 8. PDE1, 2, and 3 are dual-specific PDEs that can hydrolyze either cAMP or cGMP, whereas PDE4 and 8 specifically hydrolyze cAMP and PDE5 specifically hydrolyzes cGMP. The relative contribution of each PDE family may vary depending upon the species, developmental stage, cell type, and degree of stress on the heart. Given that PDEs are associated with many physiological functions that may become impaired during disease, it is feasible to target particular pathological conditions by modulating individual PDEs.

Several family-selective PDE inhibitors have been used clinically or are currently being investigated in clinical trials for the treatment of various cardiovascular diseases. For example, PDE3 inhibitors such as amrinone, enoximone, and milrinone have been used to treat congestive heart failure (CHF) [2]. Short-term therapy has improved hemodynamics in more severe CHF patients via positive inotropic effects on the heart and vasodilatory effects on peripheral vasculature [3]. However, chronic treatment with PDE3 inhibitors resulted in increased mortality, primarily as a result of arrhythmias and sudden death [2]. While PDE5 inhibitors have recently been used in treating pulmonary hypertension by reducing pulmonary vascular resistance [4,5], their direct effects on the myocardium have been debated. Growing evidence suggests that PDE5 inhibitors such as sildenafil have beneficial effects in various experimental models of ischemia–reperfusion, left and right ventricular hypertrophy, and congestive heart failure [6,7]. Currently, a multicenter, NIH-funded clinical trial NCT00763867 (RELAX) is aimed at evaluating the effects of chronic sildenafil treatment on improving health outcomes and exercise capacity in patients with diastolic heart failure (http://clinicaltrials.gov/ct2/show/NCT00763867). To date, small-molecule inhibitors are only available for PDE5 as therapeutics, and clearly more in vivo studies using selective compounds against other family members are needed. The in vivo studies for PDE1, 2, and 8 have been limited due to a lack of selective inhibitors. This review will discuss the regulation and function of several myocardial PDE isozymes and their therapeutic implications in chronic heart failure.

Myocardial PDE Expression, Regulation, and Function

PDE1

Ca^{2+}/calmodulin-stimulated PDEs (PDE1) constitute a large family of enzymes, encoded by three genes, PDE1A, PDE1B, and PDE1C, which include multiple splice variants. In vitro, the activity of PDE1 family members can be stimulated up to tenfold by Ca^{2+}/calmodulin [8]. Thus, PDE1 isozymes are believed to be important in the crosstalk of second messenger Ca^{2+} and cyclic nucleotide signaling [9]. However, they differ in their regulatory properties, substrate affinities, specific activities, Ca^{2+} sensitivities, and tissue/cell distribution. PDE1 family members are considered dual-substrate enzymes. In vitro, PDE1A and PDE1B isozymes hydrolyze cGMP with much higher affinity than cAMP, and PDE1C isozymes hydrolyze both cAMP and cGMP with equally high affinity. In vivo, several studies demonstrated that PDE1A and PDE1B primarily regulate cGMP [10–12]. PDE1C has been shown to regulate intracellular cAMP levels in various cell types [13–15]; however, a role in cGMP regulation has not been described in vivo.

It has been reported that Ca^{2+}/CaM-stimulated PDE1 represents the majority of cGMP-hydrolyzing activity in the human myocardium, although the identity of PDE1 isoform and cell type(s) responsible for this PDE activity was not characterized in these studies [16,17]. PDE1A mRNA expression and/or activity has been described in cardiac tissue from several

species including human [18], bovine [8], canine [19], and rat [20]. Early studies suggested that Ca^{2+}/CaM-stimulated PDE1 activity was absent from cardiomyocytes and restricted to non-myocytes in the adult rat heart [21]. However, we recently reported that PDE1A mRNA and protein were detected not only in human, rat, and mouse hearts but also in isolated neonatal and adult rat ventricular myocytes [12]. Furthermore, PDE1A protein expression was significantly upregulated in hearts and cardiomyocytes from various pathological hypertrophy animal models and in isolated neonatal and adult rat ventricular myocytes treated with neurohumoral stimuli angiotensin II (Ang II) and isoproterenol [12]. Using various loss-of-function strategies in isolated neonatal and adult rat ventricular myocytes, we demonstrated that PDE1A regulates cardiomyocyte hypertrophy [12]. In contrast, it was also previously reported that PDE1A protein was not detected in the human heart [17], whereas PDE1C protein was highly expressed in human cardiomyocytes and localized along the Z-lines and M-lines of cardiomyocytes [17]. PDE1C expression was also found in mouse hearts and/or cardiomyocytes [12,22,23]. However, there were no significant changes in PDE1C protein levels observed in a pressure overload mouse model of cardiac remodeling [22]. In the rat heart, PDE1C expression level was much lower, and it appears that PDE1C expression levels are varied with species (human>mouse>rat) [12]. The expression level of PDE1B in normal hearts appeared very low or not detectable [12]. The discrepancy of PDE1 protein expression in the heart and cardiomyocytes may be rationalized by differences in antibody species cross-reactivity, tissue/cell preparation, or the degree of stress/stimulation.

Interestingly, IC86340, a selective PDE1 inhibitor, was able to reduce myocyte hypertrophy in an isoproterenol-induced hypertrophy mouse model [12]. Because IC86340 inhibits all PDE1 isozymes and both PDE1A and PDE1C are expressed in the mouse heart, it is uncertain which PDE1 isozyme(s) confers the anti-hypertrophic effects of IC86340. Nevertheless, these findings demonstrate that PDE1 isozymes play a critical role in regulating cardiac myocye hypertrophy and myocardial remodeling. PDE1 isozymes are also present in vascular smooth muscle cells, and PDE1C and PDE1A were upregulated in idiopathic pulmonary arterial hypertension (PAH) and experimental models of PAH [24]. Chronic infusion of the PDE1 inhibitor 8MM-IBMX reversed hypoxia and monocrotaline-induced pathological lung remodeling and normalized pulmonary arterial pressure [24]. Further investigation using genetically manipulated models targeting specific PDE1 isozymes in the heart are needed to address the potential contribution of PDE1 family in heart failure (Table 1).

PDE2

PDE2 is able to hydrolyze both cAMP and cGMP with high affinities, and cGMP by binding to its N-terminal GAF domains greatly stimulates its catalytic activity. For this reason, PDE2 family members are also referred to as cGMP-stimulated PDEs. PDE2 has been found in both atrial and ventricular myocytes in various different species, from frog to human. The biological function of PDE2 mainly involves a cGMP-mediated activation of PDE2 and subsequent decrease in cAMP. For example, in frog ventricular myocytes [25,26] and human atrial myocytes [27], NO depressed the isoproterenol-mediated stimulation of L-type Ca^{2+} channel [$I(Ca^{2+})$] via cGMP activation of PDE2 and inhibition of cAMP-stimulated I(Ca) current [25]. However, the NO inhibitory effect appears to be mediated by PKG but not PDE2 in other mammalian ventricular myocytes such as rat, rabbit, and human [28,29], implying species specificity. Real-time cyclic nucleotide monitoring in cardiomyocytes determined that PDE2 is tightly coupled to β-AR stimulated pool of adenylyl cyclase. Thus, PDE2 shapes the cAMP response (via β1/β2) to catecholamines via β3-AR activation and subsequent NO/cGMP production to suppress myocyte inotropy [30]. PDE2 also primarily modulates the particulate guanylyl cyclase (pGC) pool of cGMP at the sarcolemmal membrane in adult rat ventricular myocytes [31]. While most studies of PDE2 function have relied on the PDE2 inhibitor, erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA), this weakly potent compound also inhibits

adenosine deamidase. Novel selective PDE2 inhibitors such as 9-(6-phenyl-2-oxohex-3-yl)-2-(3,4-dimethoxybenzyl)-purin-6one (PDP), with nanomolar potency, have recently been employed in functional studies in other tissues [32]. Given the dual role of PDE2 in myocyte cGMP and cAMP compartmentation, the potential therapeutic effects of targeting myocardial PDE2 remain to be determined.

PDE3

The PDE3 gene family contains two subfamilies, PDE3A and PDE3B. PDE3A is relatively abundant in cardiomyocytes, VSMCs, and platelets, whereas PDE3B is predominantly expressed in adipocytes, hepatocytes, and pancreatic cells [33,34]. It has long been considered that PDE3A represents the major PDE3 activity in myocardium [35]; however, a recent study demonstrated that PDE3B accounts for ≈30% of the total PDE3 cAMP-hydrolyzing activity in mouse hearts [36]. PDE3B associates with PI3Kγ in a macromolecular complex, which is critical for regulating local cAMP homeostasis and may play an important role in regulating cardiac function [36,37]. Studies of PDE3A$^{-/-}$ and PDE3B$^{-/-}$ mice demonstrated that PDE3A is the major PDE3 subtype responsible for the functional cardiac effects of PDE3 inhibition [38].

PDE3 inhibitors, via increasing cAMP in cardiac muscle, enhance the rate and magnitude of developed contraction and relaxation. Concurrently, in vascular smooth muscle, elevated cAMP via PDE3 inhibition reduces total vascular resistance and enhances coronary blood flow. These inotropic and vasodilatory actions justified the development and clinical use of PDE3 inhibitors for the acute treatment of CHF [3,39,40]. However, increased mortality due to arrhythmias and sudden death has been found in many clinical trials [2,41]. Thus, PDE3 inhibitors are currently used mainly as adjunct therapy to treat patients in cardiogenic shock. The observations from chronic PDE3 inhibitor clinical trials closely resemble chronic β-AR agonist therapy that also increased mortality in heart failure patients [42,43].

Studies in isolated cardiomyocytes showed that chronic inhibition or downregulation of PDE3 significantly increased cardiomyocyte apoptosis similar to that observed with chronic β-AR and angiotensin II stimulation [44,45]. The proapoptotic effect of PDE3 inhibition on cardiomyocyte is likely mediated by localized cAMP involved in the sustained induction of transcription repressor ICER (inducible cAMP early repressor). ICER-mediated apoptosis occurs in part through the inhibition of CREB-mediated transcription and downregulation of Bcl-2 [44,46]. Under physiological conditions, ICER expression is transiently induced [47, 48]; however, sustained elevation of ICER has been shown to induce cell death in neurons [48] and cardiomyocytes [44,46]. Chronic induction of ICER is controlled by an autoregulatory positive feedback loop (called PDE3A-ICER feedback loop) where PDE3A appears to be a key mediator [49]. Catecholamine stimulation and/or PDE3 inhibition may trigger the PDE3A-ICER feedback loop, which is essential in maintaining ICER induction and subsequent cardiomyocyte apoptosis. These findings suggest that strategies that block the PDE3A-ICER feedback loop will reduce cardiomyocyte apoptosis and also provide insights on the adverse effects observed with chronic PDE3 inhibition in CHF patients [41,50].

It is not surprising that PDE3A protein and activity was significantly reduced in human failing hearts with both dilated and ischemic cardiomyopathy [44]. Similarly, dowregulation of PDE3A protein expression was also seen in mouse hearts with cardiac dysfunction induced by chronic pressure overload and doxorubicin [51], as well as in hypertrophied rat hearts [52]. Concomitantly, a reciprocal upregulation of ICER was observed in these failing human and animal hearts [44]. In contrast, PDE3A-ICER feedback loop triggered via pressure overload or doxorubicin was prevented in transgenic mice expressing myocyte-specific constitutively active form of MEK5a (CA-MEK5a) [51]. Similarly, in a rat model of myocardial infarction, PDE3A-ICER-associated increase in myocyte apoptosis and cardiac dysfunction was

prevented with valsartan treatment [53]. These results suggest that the PDE3A-ICER feedback regulation may represent a common mechanism of cAMP signaling in the pathologic progression of heart failure of various etiologies.

PDE4

PDE4 belongs to a large family of enzymes that specifically hydrolyze cAMP with high affinity. Four PDE4 genes (*PDE4A*, *B*, *C*, and *D*) encoding more than 20 variants have been identified. Recent reports suggest that senescent PDE4D$^{-/-}$ mice develop progressive cardiomyopathy and accelerated heart failure after myocardial infarction (MI) [54]. These effects in PDE4D$^{-/-}$ mice were attributed to the loss of PDE4D3 from the macromolecular complex of sarcolemmal ryanodine receptor (RyR2). Loss of PDE4D3 in the RyR2 complex leads to PKA hyperphosphorylation of RyR2, causing a "leaky" receptor [54]. Decreased association of PDE4D3 with RyR2 macrocomplex and PKA hyperphosphorylation was also observed in human failing hearts [54]. This suggests that reduced PDE4D3 in heart failure may contribute to RyR2 PKA hyperphosphorylation and diastolic SR Ca^{2+} leak observed in failing hearts, which are also correlated to exercise-induced arrhythmia and sudden death [55]. Exercise-induced sustained and non-sustained ventricular arrhythmias were observed in PDE4D knockout mice and upon PDE4 inhibition with rolipram, which were prevented in RyR2-S2808A knock-in mice lacking RyR2 hyperphosphorylation [55]. These findings shed light on the potential adverse cardiac effects that PDE4 inhibitors may have on chronic treatment of asthma and stroke. Other cardiac functions of PDE4 isoforms include tethering of PDE4D3 and PDE4D5 to mAKAP and β-arrestin, respectively, to control local cAMP involved in myocyte hypertrophy and β_2-AR desensitization [56].

PDE5

PDE5 is a cGMP-specific hydrolyzing PDE and consists of a single gene (*PDE5A*). Recently, there has been renewed interest in investigating the role of PDE5 inhibition in the heart. Many of the functional studies using PDE5 inhibitors such as sildenafil have elicited beneficial effects, i.e., preventing acute ischemia–reperfusion injury and chronic pressure overload induced remodeling and systolic dysfunction in animal models [6,57,58]. The acute and/or chronic protective effects of sildenafil are linked to various known regulators of cardiovascular function, such as endothelial nitric oxide synthase and inducible NOS [59–61], mitochondrial ATP-sensitive potassium channels (mitoK_{ATP}) [62], and more recently the regulator of G protein signaling 2 (RGS2) [63], which often involve PKG activation. However, it has been debated whether PDE5 inhibitors mediate cardioprotective effects directly though PDE5 expressed in the myocardium. Early studies reported that PDE5 expression is nearly undetectable in human myocardium under basal conditions [16,64]. Several studies have since demonstrated increased PDE5A activity and protein expression in failing human and mouse myocardium [60,65] and to a greater extent in mouse hearts [65]. PDE5A expression was also confirmed in isolated cardiomyocytes by combining immunoblotting/immunostaining with PDE5A gene silencing [66]. Despite this, a recent study failed to detect PDE5A expression and activity in isolated cardiomyocytes from hypertrophied mouse hearts [22]. The discrepancy of PDE5A expression in the heart may be attributed to differences in the magnitude of injury, antibody cross reactivity, and/or interspecies variation.

A few reports have suggested that the PDE5 inhibitor sildenafil may elicit non-selective PDE1 inhibition in the heart [65] or lung [67]. While the plasma concentration of sildenafil is rarely measured in vivo, there is evidence in normal and PAH patients that peak plasma levels reached ~1 μM from a 100-mg oral dose of sildenafil [68] (www.pfizer.com/files/products/uspi_viagra.pdf). In vitro, sildenafil inhibits PDE1/5/6 with IC_{50} values of 280, 3.5, and 37 nM, respectively [16], and 1 μM sildenafil significantly inhibited PDE1 cGMP-hydrolytic activity in mouse hearts in vitro [65]. Whether this concentration

inhibits PDE1 in intact cells remains speculative. In contrast, sildenafil modulates acute β-AR-induced contractile responses in human hearts with measured plasma levels ~50 nM [69], which is below the IC_{50} for PDE1. Chronic anti-hypertrophic effects of sildenafil have also been observed in which free plasma levels of ~10 nM were reported [70]. Tadalafil, the more selective PDE5 inhibitor with less potency for PDE1, also protects hearts from ischemia–reperfusion injury [71]. Recently, myocyte-specific PDE5A overexpression exacerbated MI-induced cardiac dysfunction in mice [72]. Taken together, with the observations that sildenafil efficacy depends on PDE5 translocation to z-disks [58] and that PDE1 and PDE5 inhibitors have additive anti-hypertrophic effects in myocytes [12], there is growing evidence of myocyte-specific PDE5A regulation of acute and chronic cardiac function.

The cardiac protective effects of sildenafil obtained in rodent models await confirmation in human patients. The National Heart Lung and Blood Institute sponsored clinical trial RELAX (http://clinicaltrials.gov/ct2/show/NCT00763867) is currently evaluating the effects of chronic sildenafil treatment on cardiopulmonary performance and left ventricular function in elderly patients with normal LV ejection fraction or diastolic heart failure [8]. It should be noted that the potential cardioprotective effects of PDE5 inhibition via sildenafil, tadalafil, or vardenafil in CHF may involve indirect beneficial effects on the pulmonary and systemic vasculature. There is convincing evidence that sildenafil lowers pulmonary vascular resistance, thus preventing pulmonary remodeling and dysfunction by directly targeting PDE5A in the pulmonary microvasculature [5]. However, one study reported that sildenafil had positive inotropic effects in hypertrophied rat RV via indirect PDE3A inhibition and cAMP elevation [73]. This may warrant consideration with the development of PDE5 inhibitor therapy in heart failure, given the potential risks of chronic inotropic stimulation in CHF, as with PDE3 inhibition [41]. However, most reports implicate that the sildenafil effects on LV remodeling are mediated by cGMP/PKG signaling [58]. The cause for such discrepancy on the right and left heart remains unknown.

PDE5 inhibitors may have limited effects on vascular tone in humans, which indirectly contribute to the cardioprotective effects. For instance, sildenafil improved hemodynamics in preventing ischemia–reperfusion injury [62] and increased coronary vasodilation and coronary blood flow in canine coronary stenosis [74] and in humans [75]. Moreover, sildenafil improved hemodynamics in patients with ischemic and dilated cardiomyopathies [76]. However, the vascular hemodynamic effects may not contribute to the potent cardiac protective effects of PDE5 inhibitors in the experimental animal models in which ventricular loading is not altered due to proximal fixed obstruction. Finally, PDE5 inhibitors, sildenafil and vardenafil, have also been implicated in stimulating ischemia-induced angiogenesis in mice [77,78]. Nonetheless, PDE5 inhibition may elicit protective signaling in the vasculature and promote changes in vascular tone and angiogenesis, which may indirectly affect cardiac performance during heart failure of various etiologies.

PDE8

PDE8 specifically hydrolyzes cAMP with high affinity. Two PDE8 genes (*PDE8A* and *8B*) have been identified. A unique property of PDE8 is the insensitivity to general PDE inhibitor IBMX. PDE8A is highly abundant in testis, but is also present in human and mouse hearts [79]. A recent study with PDE8A knockout mice demonstrated that PDE8A is expressed in ventricular myocytes of mouse hearts [23]. Myocytes from PDE8 KO hearts elicited greater ISO-induced increases in $[Ca^{2+}]$ transients, L-type Ca^{2+} channel currents (I_{Ca}), and Ca^{2+} spark activity, suggesting that PDE8A controls cAMP involved in Ca^{2+} handling in cardiomyocytes [23]. Interestingly, PDE8A deletion resulted in leaky RyR channels observed by a compensatory increase in SR Ca^{2+} refilling [23]. The mechanism for these effects is currently

being studied. The effect of PDE8A deficiency on chronic pathological cardiac remodeling and cardiac dysfunction also deserve further investigation.

Conclusion and Perspective

Cardiomyocytes express multiple structurally and functionally distinct PDE isozymes. Most of our knowledge regarding PDE regulation and function in cardiomyocytes is limited to five PDE family members (PDE1, 2, 3, 4, and 5). The development of more selective pharmacological tools and cell-specific genetic models will undoubtedly accelerate the discovery of novel isoforms in regulating cardiac function applicable to therapeutic intervention. It is now evident that cyclic nucleotide signaling is regulated in discrete compartments to maintain homeostasis and simultaneously control diverse cellular functions. Alterations of PDE expression or activity may disrupt the fine balance of cAMP and cGMP, contributing to the progression of cardiovascular diseases. For instance, PDE1A and PDE5A are upregulated in various models of cardiac disease [12,72,73], and PDE1 and PDE5 inhibitors show beneficial effects in experimental animals [12,70,80]. Conversely, downregulation of PDE3A and PDE4D expression may be responsible for the deleterious cardiac effects of chronic PDE3 or PDE4 inhibitors in the heart [44,54]. Therefore, understanding the regulation and function of individual PDE isoforms in normal and diseased hearts will be important not only for the development of novel therapeutics but also to predict the potential cardiovascular toxicity of PDE inhibitors used for the treatment of other diseases.

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Table 1

Myocardial PDE families, substrate specificity, changes in expression/activity, and effects of selective inhibitors or downregulation

Family	Isoforms	Substrate/regulation	Changes in expression/activity	Inhibitors	Effects of inhibited activity or downregulated expression
PDE1	*PDE1A*	Ca^{2+}/CaM-stimulated, cAMP, cGMP	↑PDE1A in hypertrophy heart [12,20]	IC86340	↓Myocyte hypertrophy via PKG activation [12]
	PDE1C			8-MM-IBMX	
				Vinpocetine	
PDE2	*PDE2A*	cGMP-stimulated, cAMP, cGMP	↑PDE2A in hypertrophy heart [20]	EHNA, BAY 60-7550, PDP	↑ßAR-mediated cAMP signaling, myocyte inotropy and Ca^{2+} transients [30]
					Modulates subsarcolemmal pGC cGMP pool [31]
PDE3	*PDE3A*	cGMP-inhibited, cAMP-selective	↓PDE3A in hypertrophy or failing heart [44,45, 52]	Milrinone, cilostamide, enoxamone	↑Myocyte contraction and relaxation via L-type Ca^{2+} channels [81–83] and SERCA2 [84, 85], respectively
	PDE3B				↑ICER expression and myocyte apoptosis [44, 45]
PDE4	*PDE4A-D*	cAMP-specific	↓PDE4A, PDE4B in hypertrophied myocytes [52]	Rolipram, roflumilast, cilomilast	↑RyR2 PKA hyperphosphorylation and diastolic SR Ca^{2+} leak [54]
			↓PDE4D in RyR2 complex in failing heart [54]		Regulates local cAMP signaling via macromolecular complex with mAKAP or β-arrestin [56,86]
PDE5	*PDE5A*	cGMP-specific	↑PDE5A in hypertrophy or failing heart [72,73]	Sildenafil, tadalafil, vardenafil	↓Ischemia–reperfusion injury via PKG, NOS, mitoK_{ATP}, and PKC [71,80,87]
			↓PDE5A in failing canine heart [88]		↓Cardiac hypertrophy, remodeling and dysfunction via PKG, RGS2, $G_q\alpha$ signaling [63,70]
PDE8	*PDE8A*	cAMP-specific	Unknown	None	↑βAR signaling L-type I_{Ca} and $[Ca^{2+}]_i$ transients [23]

PDE phosphodiesterase, *Ang II* angiotensin II, *ISO* isoproterenol, *CaM* calmodulin, *PKG* cGMP-dependent protein kinase, *βAR* beta-adrenergic receptor, *pGC* particulate guanylyl cyclase, *SERCA2* sarcoplasmic reticulum Ca^{2+} -ATPase, *ICER* inducible cAMP early repressor, *RyR2* ryanodine receptor, *PKA* protein kinase A, *SR* sarcoplasmic reticulum, *mAKAP* muscle-specific A-kinase anchoring protein, *NOS* nitric oxide synthase, *mitoK_{ATP}* mitochondrial ATP-sensitive potassium channel, *PKC* protein kinase C, *RGS2* regulator of G-protein signaling 2