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An update of cyclic nucleotide phosphodiesterase as a target for cardiac diseases

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Abstract

Introduction-----—Cyclic nucleotides, cAMP and cGMP, are important second messengers of intracellular signaling and play crucial roles in cardiovascular biology and diseases. Cyclic nucleotide phosphodiesterases (PDEs) control the duration, magnitude, and compartmentalization of cyclic nucleotide signaling by catalyzing the hydrolysis of cyclic nucleotides. Individual PDEs modulate distinct signaling pathways and biological functions in the cell, making it a potential therapeutic target for the treatment of different cardiovascular disorders. The clinical success of several PDE inhibitors has ignited continued interest in PDE inhibitors and in PDE-target therapeutic strategies.

Areas covered-----—This review concentrates on recent research advances of different PDE isoforms with regard to their expression patterns and biological functions in the heart. The limitations of current research and future directions are then discussed. The current and future development of PDE inhibitors is also covered.

Expert opinion-----—Despite the therapeutic success of several marketed PDE inhibitors, the use of PDE inhibitors can be limited by their side effects, lack of efficacy, and lack of isoform selectivity. Advances in our understanding of the mechanisms by which cellular functions are changed through PDEs may enable the development of new approaches to achieve effective and specific PDE inhibition for various cardiac therapies.

Keywords

Cyclic nucleotide; phosphodiesterase (PDE); cardiac diseases; PDE inhibitor

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1. Introduction

Canonical cyclic nucleotides, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), regulate numerous biological processes in the heart, including inotropic/chronotropic functions, metabolism and structural remodeling. cAMP can be generated through membrane adenylyl cyclases (mACs) upon the stimulation of various G-protein coupled receptors (GPCRs). cAMP can also be generated by soluble AC (sAC) in response to cellular HCO^{-}_{3}/CO^{-}_{2}/pH in the cytoplasm, nucleus, or mitochondria. cGMP can be produced by activating soluble guanylyl cyclases (sGCs) by nitric oxide (NO)/carbon monoxide (CO) or particulate guanylyl cyclases (pGCs) by natriuretic peptides (NPs). cAMP/cGMP degradation is catalyzed by a large family of PDEs with more than 100 different PDE variants derived from 21 genes and grouped into 11 broad families (PDE1-PDE11) [1]. Common cAMP and cGMP effector molecules in the heart include cAMP-dependent protein kinase (PKA), exchange protein activated by cAMP (Epac), and cGMP-dependent protein kinase (PKG). Under normal conditions, PKA-mediated phosphorylation of ion channels and contractile proteins are essential for increasing heart rate and contractility in response to fight-or-flight. For example, PKA phosphorylates L-type Ca^{2+} channels (LTCC) and ryanodine receptor (RYR) to induce intracellular Ca^{2+} elevation, thus enhancing myocyte contractility [2]. In addition, PKA phosphorylates phospholamban (PLB) and induces Ca^{2+} re-uptake in the sarcoplasmic reticulum (SR), leading to faster myofilament relaxation [2]. Abnormal cyclic nucleotide synthesis, degradation, and signaling have been implicated in a number of cardiac diseases including atrial fibrillation, maladaptive cardiac remodeling, and cardiac dysfunction [3].

Increasing evidence has indicated the existence of multiple functionally distinct “pools” of cyclic nucleotides. For example, catecholamines, prostaglandin 2 (PGE2), and adenosine are all able to elevate cAMP elevation in cardiomyocytes (CMs). cAMP generation through β-adrenergic receptor (β-AR) activation by catecholamine stimulates profound CM contraction, while cAMP elevation by PGE2 has a limited role in CM contractility [4]. Chronic activation of β1-AR-derived cAMP signaling elicits detrimental effects such as promoting CM hypertrophy and apoptosis [5,6], while cAMP signaling through activation of adenosine receptors is protective [7,8]. In addition, cAMP produced by adenylyl cyclase 5 (AC5) and AC6 have different cardiac effects: AC5-derived cAMP is detrimental [9,10], whereas AC6-derived cAMP is protective in pathological cardiac remodeling [11,12]. Moreover, modulation of distinct cyclic nucleotide signaling pathways via inhibition of different PDEs elicit distinct effects on CM viability: PDE1 inhibition promotes CM survival [13,14]; PDE3 inhibition promotes CM death [15]; and PDE4 inhibition has no significant effect on CM viability [15]. These differences might be due to different PDEs coupling to distinct cyclic nucleotide-dependent signalosomes. Although most studies have shown negative inotropic [16–20] and cardioprotective effects [21,22] of cGMP in the heart, cGMP from two different sources may have different mechanisms of action [23]. These lines of evidence indicate that cyclic nucleotide signaling events arising from different origins have distinct/unique or even opposing biological functions.

There has been increasing interest and effort to understand how the versatility/specificity of diverse cyclic nucleotide-mediated functions are achieved in individual cell types. In the past

decade, approaches using subcellular-targeted Fluorescence Resonance Energy Transfer (FRET)-based cAMP/cGMP sensors have significantly advanced this field by demonstrating that cAMP/cGMP are not freely diffusible and multiple compartmentalized cAMP/cGMP "pools" exist in the cell [24–28] (for detailed reviews, see references [29–31]). It is believed that the versatility/specificity of cAMP/cGMP signaling is achieved through compartmentalization of diverse, discrete cAMP/cGMP pools that are associated with different multi-protein complexes each containing unique cyclases, PDEs, kinases, and other signaling molecules, leading to different biological functions (Figure 1).

2. Cardiac PDEs

2.1 Overview of cardiac PDEs

Among 11 PDE families, PDE1-5, and PDE8-10 have been reported in the heart [32–40]. PDE1, 2, 3, and 10 hydrolyze both cAMP and cGMP with different affinities and rates. PDE4 and 8 are cAMP-specific PDEs. PDE5 and 9 are cGMP specific PDEs. The relative expression of PDE and the contribution of PDE activity in the myocardium may be varied with species. Dysregulation in PDE expression, activation and subcellular localization affect cardiac function and have been implicated in a number of cardiac diseases. An overview of the isoforms, substrates, kinetic properties, regulatory properties and expression levels among different species of these PDEs is summarized in Table 1.

2.1.1 Cardiac dual-substrate PDEs—Cardiac dual-substrate PDEs include PDE1, PDE2, PDE3 and PDE10. These PDEs hydrolyze both cAMP and cGMP through a catalytic domain, but some of them can be regulated through a GAF domain by either cAMP or cGMP. The PDE1 family members are encoded by three different genes (*PDE1A*, *PDE1B* and *PDE1C)*, and activated by Ca^{2+}/calmodulin (CaM). The PDE2 family members are encoded by one gene, *PDE2A,* with 3 different splice variants (PDE2A1-3). By binding to the N-terminal GAF domain, cGMP is able to stimulate PDE2 activity, thus is referred to as cGMP-stimulated PDEs. The PDE3 family members are encoded by two different genes (*PDE3A* and *PDE3B)*. Three different PDE3A variants (PDE3A1-3) are defined. PDE3 binds to both cAMP and cGMP with high affinities, but the Vmax for hydrolyzing cGMP is at least 10-fold lower than that of cAMP, which allows cGMP to act as a potent competitive inhibitor of cAMP hydrolysis by PDE3. However, this inhibitory effect of cGMP is mainly for PDE3A [41,42], as PDE3B is only ≈10% as sensitive to cGMP inhibition as PDE3A [43]. Both PKA and protein kinase B (PKB) can induce a phosphorylation of PDE3 to stimulate PDE3 activity [1]. The PDE10 family members are encoded by one gene (*PDE10A*) with three splice variants identified (PDE10A1-3) [44–46]. It has been shown that PKA phosphorylates PDE10A and induces its translocation from membrane to cytosol [47,48]. It has also been reported that cAMP binds to the N-terminal GAF domains and increases PDE10A activity [49].

2.1.2 Cardiac cAMP-specific PDEs—PDE4 is encoded by 4 different genes (*PDE4A*, *PDE4B*, *PDE4C* and *PDE4D*), with a number of different variants [50]. PDE4 family members are subdivided into 4 groups depending on the length of the N-terminal upstream conserved regions (UCRs): long isoform; short isoform; super-short isoform and dead-short

isoform [50]. UCRs mediate the homo- and hetero-dimerization of long isoform PDE4 [51]. UCRs also play a functional role in modulating the activity of PDE4 catalytic unit [50]. The long forms can be phosphorylated by PKA [1]. The catalytic domains of PDE4B, 4C, and 4D isozymes contain ERK phosphorylation motifs, and ERK phosphorylation leads to an inhibition of their activities [1]. PDE8 family members are encoded by two different genes (*PDE8A* and *PDE8B*) [52]. PDE8 includes N-terminal REC (receiver) and PAS (Per, Arnt and Sim) domains and C-terminal catalytic domain, even though REC and PAS domains are not completed in some variants [53,54]. The regulatory functions of PDE8 REC and PAS domains are not well understood. PDE8 has the highest cAMP affinity among all PDEs, and is the only PDE family insensitive to pan PDE inhibitor IBMX [1].

2.1.3 Cardiac cGMP-specific PDEs—PDE5 is encoded by a single gene *PDE5A*, which gives rise to 3 variants (PDE5A1-3) [55]. PDE5A variants are different in their N-terminus, which contains two GAF domains: GAF-A and GAF-B [55,56]. PDE5A is activated by cGMP binding to the GAF-A domain and cGMP-dependent kinase (PKG) phosphorylation of a serine near the GAF-A domain, which is critical for PDE5A in negative feedback regulation of cGMP signaling [55]. PDE9 is encoded by a single gene *PDE9A*, with more than 20 variants reported [57,58].

2.2 Regulation and function of PDEs in heart

2.2.1 PDE1—PDE1 activity is one of the major PDE activities in the human myocardium [59,60]. PDE1 inhibitor IC86340 or vinpocetine attenuates cardiac hypertrophy and fibrosis in mouse hearts induced by chronic neurohormonal stimulation with isoproterenol (ISO) or angiotensin II (Ang II), respectively [61,62]. These findings suggest a critical role of PDE1 in pathological cardiac remodeling and the therapeutic potential of targeting PDE1 in cardiac diseases associated with cardiac remodeling. Among the three PDE1 genes, the expression of PDE1A and PDE1C, but not PDE1B, has been detected in hearts from various species (Table 1) [32]. PDE1A expression appears to be consistent among human, rat and mouse hearts [32]. PDE1A expression is upregulated in hearts with hypertrophy or heart failure (HF) in various species, predominantly in CMs and activated cardiac fibroblasts (CFs) [32,61]. Differently, PDE1C expression in the heart varies with species: highest in human, modest in mouse, and very low in rat hearts [32]. PDE1C expression is further increased in failing human and mouse hearts, primarily restricted in CMs [33]. There is no PDE1C expression detected in mouse CFs under both basal and stimulated states [33]. These findings suggest different PDE1 isozymes are differentially expressed in cardiac cells.

In cultured rat neonatal or adult CMs, PDE1A expression is upregulated by hypertrophic stimuli such as Ang II or ISO [32]. CM hypertrophy stimulated by phenylephrine (PE) or Ang II is significantly alleviated by specifically knocking down Pde1a with shRNAs or PDE1 inhibitor IC86340 [32]. Although PDE1A is able to hydrolyze cAMP and cGMP in the cell-free system, PDE1A was found to primarily hydrolyze cGMP in rat CMs [32]. Consistently, PDE1A inhibition stimulates PKG activation and PKG is a critical mediator for the anti-hypertrophic effects of PDE1A inactivation [32]. These results indicate that PDE1A activation plays a critical role in CM hypertrophy by antagonizing the cGMP/PKG signaling. Interestingly, PDE1A does not regulate CM viability [33]. In addition to CMs, PDE1A

upregulation was found in activated CFs within fibrotic regions of diseased hearts *in vivo* as well as in cultured CFs stimulated by Ang II or TGF-β *in vitro* [61]. Pde1a shRNA or PDE1 inhibitor IC86340 blocks Ang II or TGF-β-induced CF activation, extracellular matrix (ECM) synthesis, and pro-fibrotic gene expression in rat CFs [61]. PDE1A hydrolyzes both cAMP and cGMP in CFs. The effect of PDE1A inhibition against CF activation is dependent on cAMP/Epac1/Rap1 and cGMP/PKG signaling [61]. Despite these studies demonstrating critical roles of PDE1A in rat CMs and CFs *in vitro*, the role of PDE1A in cardiac disease development *in vivo* remains unknown. Future studies using Pde1a knockout (KO) or conditional KO mice are required to address the functional role of PDE1A *in vivo*. In addition, the sources of cyclic nucleotides that are regulated by PDE1A in CMs and CFs also remain to be determined. Moreover, the molecular mechanisms underlying PDE1A-mediated regulation of CM hypertrophy and CF activation remain to be characterized.

With the availability of global Pde1c KO mice [33], the roles of PDE1C in the heart have been studied in mouse cardiac disease models. For example, it has been shown that Pde1c KO alleviates cardiac hypertrophy, interstitial fibrosis, and dysfunction induced by chronic pressure overload via transverse aortic constriction (TAC) in mice [33]. *In vitro*, Pde1c KO and inhibition abolishes mouse adult CM hypertrophy and apoptosis [33], which appears to be dependent on cAMP/PKA signaling [33]. PDE1C does not directly regulate CF function in isolated CFs, which is consistent with the fact that PDE1C is not expressed in CFs [33]. Interestingly, the conditioned medium from Pde1c-KO CMs, but not Pde1c-WT CMs, attenuates CF activation [33], suggesting that PDE1C regulates CM-derived secreted factors that mediate CF activation and cardiac fibrosis. Recently, the mechanistic action of PDE1C in regulating CM viability has been further studied *in vitro* and *in vivo* [14]. It has been shown that in CMs, PDE1C but not PDE1A regulates CM viability [14]. PDE1C promotes CM death/apoptosis through antagonizing the adenosine type 2A receptor ($A_{2A}R$)/cAMP signaling [14]. In particular, a novel multiprotein complex comprised of $A_{2A}R$, PDE1C, and transient receptor potential subfamily C3 (TRPC3) has been characterized in the plasma membrane and perhaps T tubules of CMs (Figure 1) [14]. It is believed that PDE1C is activated by TRPC3-derived Ca^{2+} and subsequently antagonizes $A_{2A}R$/cAMP signaling, thereby promoting CM death/apoptosis. Indeed, Pde1c KO or PDE1C inhibition attenuates doxorubicin-induced cardiac toxicity and dysfunction in mice, which is significantly diminished by $A_{2A}R$ antagonism [14]. Another study has reported the acute positive inotropic and lusitropic effects of a pan PDE1 inhibitor ITI-214 in dogs and rabbits with HF [63]. The effects of ITI-214 appear related to the cAMP signaling that is different from β-AR but related to $A_{2B}R$ [63]. It is believed that acute cardiac effects are mediated by inhibiting PDE1C. Taken together, these findings provide novel evidence for microdomain regulation of A_2R-derived cAMP signaling by PDE1C in CMs.

2.2.2 PDE2—The expression of PDE2 has been found in different species including human, rat and mouse heart (Table 1) [64–66]. PDE2A has been detected in both CMs and CFs in the heart, with higher expression in CFs than CMs [64,67]. PDE2 expression is altered under pathological situations. For example, PDE2A protein levels are significantly increased in the left ventricular myocardium from patients with end-stage dilated

cardiomyopathy or ischemic cardiomyopathy as well as in rat hearts after chronic β-AR stimulation [65].

PDE2A is important in acute cardiac contractility, CM death, and chronic cardiac remodeling. It has been reported that PDE2A modulates L-type Ca^{2+} current in frog ventricular CMs and human atrial CMs *in vitro* [68,69]. PDE2 inhibition increases the inotropic effects of β2-AR stimulation in rat left ventricular myocardium *ex vivo*, likely by potentiating the β2-AR/cAMP signaling [70]. NO/cGMP by activating PDE2A blunts the β-AR mediated cardiac inotropic effect [71]. Consistently, PDE2A upregulation in failing hearts desensitizes against acute β-AR responsiveness [65]. These results suggest that PDE2A regulates CM contractility by primarily regulating β-AR/cAMP signaling. Chronic inhibition of PDE2 with BAY 60-7550 has been shown to attenuate CM hypertrophic growth *in vitro* and TAC-induced cardiac hypertrophy *in vivo*, which appears to be mediated by cAMP/PKA dependent phosphorylation of nuclear factor of activated T cells (NFAT) [34]. This anti-hypertrophic effect of PDE2A inhibition appears not to take place through regulating β-AR signaling because increasing β-AR induces cardiac hypertrophy [2]. Another study showed that PDE2 inhibition reverses the cardiac remodeling and HF induced by chronic pressure overload or sympathetic hyperactivation, through promoting sGC/cGMP signaling [66]. Interestingly, a recent study reported a PDE2A2 variant in mitochondrial outer membranes of CM, where PDE2A2 regulates cAMP generated at the plasma membrane by plasma membrane AC (Figure 1) [72]. Specifically inhibiting mitochondrial PDE2A2 with genetic tools promotes PKA-dependent phosphorylation of dynamin-related protein 1 (Drp1), alters mitochondrial morphology, and thus triggers mitochondria-dependent cell death in rat neonatal CM [72]. This finding suggests that different PDE2A variants may localize and function differently in CMs.

However, using transgenic mice with CM-specific overexpression of PDE2A3 (Tg-Pde2a3) has shown inconsistent results [73]. It was found that the Tg-Pde2a3 mice have a decreased heart rate without altering the cardiac inotropic effects, thus protecting against catecholamine-induced ventricular arrhythmia [73]. CMs isolated from Tg-Pde2a3 mice reveal a remarkable reduction of Ca^{2+} leakage and of basal phosphorylation levels of ryanodine receptor type 2 (RyR2), which may contribute to the anti-arrhythmic effects of PDE2A expression [73]. In addition, Tg-Pde2a3 mice exhibit improved ventricular function and increased animal survival rate after myocardial infarction (MI) for 14 days without significant change of infarct sizes [73]. There are a number of possibilities for the discrepancy between PDE2A inhibition and PDE2A overexpression. One possibility could be due to the undesired effects resulted from mistargeting of overexpressed PDE2A. The second possibility could be due to multiple existing PDE2A variants that have different subcellular localizations and distinct functions. PDE2 inhibitors target all PDE2A variants while only one variant was altered in the transgenic mice. The third possibility could be that the cardiac protective effects seen in global Pde2a-KO mice are also contributed by PDE2A in non-CM of the heart such as CF, endothelial cells (ECs) and macrophages. For example, it was reported that CFs express higher levels of PDE2A compared to CMs [67]. PDE2 accelerates CF to myofibroblast phenotype conversion [67]. It was also reported that the induction of PDE2A expression by tumor necrosis factor-α contributes to increased EC permeability [74]. These non-CM effects are important in cardiac remodeling and

dysfunction. Nevertheless, cardiac cell-specific Pde2a KO mice and/or genetically engineered Pde2a variant-specific mutant mice are required to further characterize the roles and cellular/molecular mechanisms of PDE2A in cardiac biology and diseases.

2.2.3 PDE3—Both PDE3A and PDE3B have been reported in heart tissue and CMs (Table 1) [35,75,76]. PDE3A is highly expressed in the myocardium of normal hearts [35]. But the changes of PDE3A expression in diseased hearts appear to be varied in different studies. For example, decreased PDE3A expression and/or activity has been reported in failing mouse and human hearts [35,77], pacing-induced failing dog hearts [78,79], and CMs isolated from rat hypertrophic hearts [35,80]. However, increased PDE3A expression and/or activity has also been described in failing rat hearts [81], failing mouse hearts [82], and ISO-induced hypertrophic mouse hearts [83]. The discrepancies may be related to the differential regulation of PDE3A expression in different cell types in the heart. PDE3A is expressed in CMs, CFs, ECs, smooth muscle cells (SMCs), immune cells, and platelets, all of which can be changed in diseased hearts.

PDE3 activity has been first known to regulate cardiac contractile function, which is the basis for using PDE3 inhibitors to treat congestive heart failure. Although PDE3 inhibitors improve cardiac function, they increase mortality in HF patients [84]. The development of Pde3a and Pde3b KO mice have helped to define PDE3A, but not PDE3B, as primarily responsible for regulating the contractile function in the heart [85,86]. Global Pde3a KO increases cardiac contractility and relaxation through cAMP-dependent elevations of Ca^{2+} transient amplitudes and SR Ca^{2+} contents [86]. This is consistent with increased PLB phosphorylation, sarcoplasmic reticulum Ca^{2+} ATPase 2 (SERCA2) activity, and SR Ca^{2+} uptake rate by Pde3a KO [86]. The role of PDE3A in regulating SERCA2 function is further supported with the finding of a multiprotein complex in the sarcoplasmic reticulum (SR) containing PDE3A, A-kinase anchor protein 18 (AKAP18), PLB, and SERCA2 (Figure 1) [87]. In contrast to Pde3a KO, transgenic mice with myocardium-specific overexpression of PDE3A1 (Tg-Pde3a1) reveal a significant reduction of heart rate and cardiac contractile function [88].

Chronic inhibition of PDE3 activity or reduction of PDE3A expression induces CM apoptosis, which is associated with a persistent induction of inducible cAMP early repressor (ICER) [35]. ICER is a transcriptional repressor of cAMP response element-binding protein (CREB)-dependent genes including the anti-apoptotic molecule B-cell lymphoma 2 (Bcl2), thus promoting CM apoptosis. A following study further demonstrated the existence of a positive feedback loop between PDE3A and ICER, in which PDE3A reduction/inhibition activates cAMP/PKA signaling that increases ICER protein stability through PKA-dependent ICER phosphorylation [76]; ICER serves as the transcriptional repressor for PDE3A, thus down-regulating PDE3A expression. The reciprocal regulation of PDE3A and ICER levels is also confirmed in human and mouse diseased hearts [35]. Preventing PDE3A reduction, or ICER induction, is found to be able to disrupt the PDE3A-ICER feedback loop and protect CMs from apoptosis [35]. For example, overexpressing PDE3A1 in Tg-Pde3a1 mice increases CM survival and protects hearts from acute ischemia/reperfusion (I/R) injury *in vivo* [88]. Alternatively, activation of extracellular signal-regulated kinase 5 (ERK5) increases C-terminus of Hsc70-interacting protein (CHIP) ubiquitin ligase activity, which

promotes ICER ubiquitination and degradation, thus protecting CMs from apoptosis [89]. In addition to CM apoptosis, PDE3 inhibition by Cilostamide exerts pro-hypertrophic effect in rat neonatal CMs [34]. Consistently, Ang II-induced cardiac remodeling and dysfunction are attenuated in Tg-Pde3a1 mice [90]. These results support the conclusion that PDE3A down-regulation seen in failing hearts may play a detrimental role to the myocardium.

However, this conclusion is challenged by the results from two recent studies. For example, it has been shown that global Pde3a KO, but not Pde3b KO, reduces pathological cardiac remodeling and dysfunction in a non-ischemic heart disease mouse model by chronic pressure overload with TAC [91]. PDE3B is detected in the T-tubules in close proximity to mitochondria in CMs (Figure 1), and global Pde3b KO but not Pde3a KO protects mouse hearts from acute I/R-induced injury [75]. The discrepancies among these studies remain unknown. PDE3A and PDE3B are expressed in a large amount of different cell types that could influence cardiac remodeling and functions directly or indirectly. Therefore, tissue-specific Pde3a or Pde3b KO mice are necessary in future studies.

2.2.4 PDE4—PDE4-devoted cAMP-hydrolyzing activity in human hearts is much lower than that in rodent hearts [92]. This is primarily due to other non-PDE4 activities that are much higher in human hearts than those in rodent hearts [92]. PDE4 expression levels have been found to be consistent between human and rodent hearts (Table 1) [92]. Among four different PDE4 genes, PDE4A, PDE4B and PDE4D were reported in human and rodent hearts [36,92,93]. The expression/activity of PDE4A, PDE4B and PDE4D were found to be decreased in failing and hypertrophic hearts as well as in diseased CMs [36,80,92,94].

PDE4 activity appears to be important in the excitation-contraction coupling in rodent hearts. It has been shown that PDE4 inhibition promotes the inotropic effects in response to β-AR stimulation as well as enhanced spontaneous diastolic Ca^{2+} waves [95]. In CMs, different PDE4 variants appear to be localized within discrete subcellular compartments, and associated with distinct signaling complexes (Figure 1), thus yielding different biological functions [96]. For example, PDE4B was found to be associated with the $Ca_V1.2$ subunit of LTCC in response to β-AR stimulation (Figure 1) [97]. Functional studies using CM from Pde4b KO mice further showed increased contraction and Ca^{2+} transient, which promotes ventricular tachycardia [97]. At least four PDE4D variants were detected in human and/or rodent hearts, including PDE4D3, 4D5, 4D8 and 4D9 [87]. PDE4D3 was found in the complex with RyR2 channels (Figure 1) [36]. Pde4d KO mice exert hyperphosphorylated “leaky” RyR2 channels, which is associated with age-related cardiomyopathy, exercise-induced arrhythmia and accelerated myocardial infarction [36]. However, another study showed that in murine and failing human hearts, PDE4D associates with SERCA2 but not with RyR2, based on the co-immunoprecipitation study (Figure 1) [98]. PDE4D thus regulates baseline SR Ca^{2+} release and contractility [98]. Actually, PDE4 inhibition potentiates the phosphorylation of both RyR2 and PLB and increases both SR Ca^{2+} leak and SR Ca^{2+} load [95], suggesting both RyR2 and SERCA2 may be regulated by PDE4. Different from PDE4B, PDE4D does not regulate L-type Ca^{2+} current [98]. These results indicate the important roles of PDE4 in regulating cardiac functions via association of distinct multiprotein complexes.

PDE4 is also important in chronic regulation of cardiac remodeling. For example, PDE4D has been shown to directly interact with heat shock protein 20 (Hsp20) in CMs, which is important for maintaining Hsp20 in a hypo-phosphorylated state [99]. It is known that Hsp20 is cardioprotective during cardiac stress and the protective ability of Hsp20 depends on Hsp20 phosphorylation at Ser16 by PKA [100]. Therefore, PDE4 inhibition or expressing the peptide disrupting PDE4D and Hsp20 interaction results in Hsp20 phosphorylation, and protects against chronic β-AR-induced CM hypertrophy *in vitro* and TAC-induced cardiac hypertrophy and fibrosis *in vivo* [99,101]. In addition, it has been shown that PDE4D3 is targeted by the muscle-selective AKAP (mAKAP) to a signaling complex containing PKA, Epac1 and ERK5 signaling molecules at perinuclear regions (Figure 1) [102,103]. This signaling complex is important in regulating CM hypertrophy [102,103]. Since the overall PDE4 expression is decreased in failing hearts and PDE4 isoform inactivation often exerts unfavorable cardiac outcomes, it is reasonable to speculate that increasing PDE4 expression may be beneficial in heart failure. A recent study using transgenic mice with myocardium-specific overexpression of the main PDE4B isoform expressed in mouse myocardium, PDE4B3, unveils a protective role of PDE4B in ISO-induced pathological cardiac remodeling [94]. Interestingly, the moderate levels of PDE4B3 overexpression in CMs via the AAV9 vector is sufficient to protect against cardiac dysfunction induced by chronic β-AR stimulation and TAC without modifying cardiac function in healthy mice [94]. This finding suggests that cardiac gene therapy with PDE4B3 may be a new approach to treat heart failure [94]. Similarly, the cardiac protective effect has been reported for a small allosteric modulator UCR1C that activates PDE4 long isoforms [104]. PDE4 activation by the small allosteric modulator reduces nuclear PKA activity and CREB phosphorylation, hence inhibiting β-AR-stimulated cardiac myocyte hypertrophy [104]. This result suggests that PDE4 activating compound could also be useful in combatting heart failure.

2.2.5 PDE5—PDE5A is expressed in human and mouse hearts [105–108] and increases under pathological conditions (Table 1) [37,106,107,109]. PDE5A expression is detected in isolated CMs [108,110]. However, it has also been reported that PDE5A is expressed only in CFs but not CMs in mouse hypertrophied hearts [111]. The inconsistence might be due to differences in PDE5A antibodies or the variability in the severity of cardiac diseases.

In normal hearts, PDE5A appears to negatively regulate catecholamine-induced contractile function through cGMP-PKG signaling. For example, PDE5 inhibitor, sildenafil, attenuates isoproterenol-stimulated cardiac contractility [112–115]. PDE5 is detected in the Z-band of mouse CM and the localization of PDE5 to Z-bands is critical for PDE5-mediated regulation of contractility, which is dependent on endothelial nitric oxide synthase (eNOS) and PKG (Figure 1) [110]. The effect of PDE5 inhibitor on cardiac contractility is largely diminished in failing hearts, which is associated with reduced Z-band localization of PDE5A [114]. These findings implicate that PDE5 regulates highly localized cGMP pools in normal hearts.

The studies of PDE5 inhibitors in I/R injury and doxorubicin-induced cardiotoxicity have revealed important beneficial effects of PDE5 inhibition on myocardium protection. For example, PDE5 inhibition by sildenafil has been shown to protect hearts against experimental I/R injury in rabbits, when sildenafil was given prior to the ischemia [116], or sildenafil was applied at the time of reperfusion [117]. Chronic sildenafil treatment 3 days

post-MI also alleviates the progression of cardiac dysfunction [118]. In addition, PDE5 inhibition has been shown to attenuate CM apoptosis and left ventricular dysfunction in a chronic doxorubicin-induced cardiomyopathy model [119]. In isolated CMs, sildenafil protects CMs from ischemia-stimulated necrosis and apoptosis [120], suggesting a critical role of PDE5 in regulating CM viability.

Because PDE5A is upregulated in failing or hypertrophic hearts, the role of PDE5A induction in disease development has been extensively investigated in different cardiac remodeling models. For example, chronic inhibition of PDE5 by sildenafil enhances cGMP level and PKG activity, thus alleviating cardiac hypertrophy and improves cardiac function induced by TAC [115,121], as well as by chronic β-AR stimulation [122]. More importantly, sildenafil is able to reverse pre-established hypertrophic heart disease [115], which supports the therapeutic significance with PDE5 inhibitors. Furthermore, the role of PDE5A elevation has been investigated in genetically modified PDE5A with inducible CM-specific overexpression of PDE5A. It was found that overexpression of PDE5A in transgenic mice suppresses PKG activation and worsens TAC-induced cardiac hypertrophy, fibrosis, and dysfunction in a dose-dependent manner [123]. The adverse effects of PDE5A overexpression are blocked by sildenafil [123]. However, the role of PKG is challenged by other studies. For example, genetic deletion of PKG in mice (except SMCs) does not worsen cardiac hypertrophy induced by TAC [124], ISO infusion [124], Ang II infusion [125], or CM-specific overexpression of Ang II type 1 receptor (AT1R) [126]. These findings do not support the role of PKG in PDE5-mediated regulation of cardiac remodeling. Additionally, PDE5 inhibition with sildenafil has moderate or no effect on Ang II-induced CM hypertrophy, but suppresses profibrotic gene expression [125]. This study suggests a potential cardioprotective effect of PDE5 derived from non-CMs. Therefore, tissue-specific Pde5a KO mice are required to precisely understand the cellular and molecular mechanisms of PDE5A in pathological cardiac remodeling and dysfunction. Another possibility is that cGMP/PKG signaling may not be the only downstream signaling that contributes to the cardiac protective effect of PDE5 inhibition. Elevation of cGMP through PDE5 inhibition may regulate the activity of other PDEs, such as inhibiting PDE3 or activating PDE2, which would lead to changes in PKA activity.

2.2.6 PDE8—Both PDE8A and PDE8B have been reported in human and mouse hearts, as well as mouse CM (Table 1) [38,53,127]. To date, cardiac-related study of PDE8 is limited to PDE8A. A study using Pde8a KO mice showed that PDE8A deficiency potentiates ISO-induced intracellular Ca^{2+} transient and LTCC currents [38]. However, the underlying molecular mechanism remains unknown.

2.2.7 PDE9—PDE9A has been detected in the heart and isolated CMs (Table 1) [57]. PDE9A expression is significantly increased in failing human hearts [39]. Recent evidence has indicated a pathophysiological role for PDE9 in heart diseases. PDE9A inhibition or knockdown blocks pro-hypertrophic stimulation in CMs [39]. Pde9a KO mice have less severe cardiac remodeling under pressure overload [39]. Importantly, PDE9A inhibition has been found to reverse pre-existing cardiac dysfunction, providing the clinical significance of using PED9A inhibition as potential therapeutic approach for cardiac diseases [39]. PDE9A

inhibition has been shown to reverse cardiac hypertrophy or dysfunction in a natriuretic peptide receptor (NPR)/cGMP-dependent manner (Figure 1) [39], which is different from the PDE5A inhibition that is linked to the NO/cGMP pathway. The mechanistic difference between PDE5A and PDE9A is further supported by a study that shows distinct microRNA expression profiles under PDE5 and PDE9 inhibition in TAC-induced cardiac dysfunction [128]. For example, PDE5 inhibition reduces most of microRNAs associated with the disease state, whereas PDE9 inhibition has no impact [128]. MicroRNAs play important roles in regulating gene expression [129]. The different microRNA profiles elicited by PDE5 and PDE9 inhibition suggest that PDE5 or PDE9 inhibition protects against cardiac remodeling via modulating the expression of different sets of genes.

2.2.8 PDE10—PDE10A2 is the major PDE10A isoform expressed in the heart [40]. Recent study by our lab has shown that PDE10A expression is significantly increased in failing mouse and human hearts, while is decreased in mouse exercised hearts (Table 1) [40]. PDE10A directly regulates CM hypertrophy and CF activation, proliferation and ECM accumulation [40]. We have found that PDE10A inhibition or deficiency alleviates cardiac hypertrophy, cardiac fibrosis and cardiac dysfunction in both Ang II-induced and TAC-induced cardiac disease model, indicating an important role of PDE10A in pathological remodeling [40]. Moreover, inhibiting PDE10A by specific and selective PDE10A inhibitor TP-10 effectively ameliorated pre-established cardiac remodeling, suggesting a potential therapeutic effect of targeting PDE10A on pathological cardiac remodeling [40]. In addition to the cardiac role of PDE10A, it appears that PDE10A is connected to the regulation of energy homeostasis and insulin sensitivity [130–132]. PDE10A is also known to express and have a role in the brown and white adipose tissue where it is involved in the control of thermogenic expression [131,132]. Impaired thermogenesis and insulin response are associated with the development of HF [133]. Therefore, it would be intriguing to identify the metabolic contribution of adipose PDE10A in cardiac remodeling and dysfunction in the future.

3. Therapeutic application and development of PDE inhibitors in combatting cardiac diseases

There are increasing lines of evidence that support the critical roles of PDEs in regulating cardiac functions and remodeling in preclinical animal models. Therefore, increasing clinical trials on extending new indications such as cardiac disorders have been conducted with some existing marketed PDE inhibitors. Drug repurposing has apparent benefits including less safety concerns, saving time and reduced cost. In this section, we focus on the current status of marketed PDE inhibitors and PDE inhibitors under clinical trials, as well as their effects in clinical studies on cardiac diseases.

3.1 PDE3 inhibitors

PDE3 inhibition elevates cAMP in cardiac muscle and subsequently increases the rate and magnitude of cardiac contractility, which is the basis for using PDE3 inhibitors to treat congestive heart failure. Also, PDE3 inhibition stimulates vascular relaxation, thus reducing peripheral and pulmonary vascular resistance and enhances coronary blood flow. Thus,

PDE3 inhibitors such as milrinone have become powerful drugs for the short-term treatment of life-threatening heart failure due to their inotropic and vasodilatory actions. Several PDE3 inhibitors are currently FDA approved and marketed inside or outside the USA. Milrinone is FDA-approved in 1987 for the treatment of acute HF or chronic HF [134,135]. Milrinone markedly improves cardiac performances including increasing cardiac contractility, cardiac relaxation, and vasodilation [135]. Concerns about its adverse effects, such as an increased risk of supraventricular and ventricular arrhythmias, and hypotension, make Milrinone to be used with special cautions [134,136]. There are continued interests and efforts in optimizing the therapeutic regiment for using PDE3 inhibitors in treating heart failure. For example, a phase II clinical trial is ongoing to test a hypothesis that carefully monitoring and optimizing Milrinone levels in children following cardiac surgery may improve clinical outcomes and reduce the duration of Milrinone infusion (ClinicalTrials.gov Identifier: NCT01841177).

3.2 PDE5 inhibitors

There are at least four PDE5 inhibitors, sildenafil, vardenafil, tadalafil, and avanafil, approved by FDA and marketed in the US, and originally recommended as the first-line treatment of erectile dysfunction [137]. The presence of abundant PDE5 in lung vascular smooth muscle makes PDE5 inhibitors an important modality for treatment of pulmonary hypertension [138]. Because of promising animal study results, there have been substantial studies attempting to test the effects of PDE5 inhibitors as therapeutics for cardiac diseases. For example, a meta-analysis in 928 patients with reduced left ventricular ejection fraction reveal the beneficial effect of PDE5 inhibitors Sildenafil or Udenafil, including improved clinical outcomes, exercise capacity and pulmonary hemodynamics [139]. Sildenafil has been tested in patients with chronic HF. A clinical study in 45 HF patients randomized to placebo or Sildenafil treatment for 1 year, shows that Sildenafil treatment improves left ventricle and diastolic function, and cardiac geometry in HF patients [140]. Moreover, Sildenafil has also been evaluated in clinical trials for its effect on diabetic cardiomyopathy. It has been found that chronic Sildenafil treatment results in improved cardiac geometry and cardiac kinetics, and reduced circulating proinflammatory chemokines in 59 diabetic men with non-ischemic and non-failing diabetic cardiomyopathy [141]. However, there are also some clinical studies that reveal disappointing results. For example, a clinical study was carried out in 52 patients with HFpEF and pulmonary hypertension and randomized to Sildenafil or placebo treatment for 12 weeks. The observation is that Sildenafil does not alter cardiac structure nor function on echocardiography compared with placebo [142]. In addition, a large scale clinical trial (the RELAX study) was conducted to test the effects of sildenafil on cardiac and pulmonary function in approximately 200 elderly patients with HFpEF. Sildenafil showed no effect on maximal or submaximal exercise capacity, clinical status, quality of life, LV remodeling, diastolic function parameters in these patients [143]. The inconsistent clinical results might be due to the variations in patient subjects with regard to the differences in etiologies of disease development, associated health problems, as well as other medications taken. Thus, clinical trial studies with more rigorous protocols are required in the future.

3.3. Other PDE inhibitors with therapeutic potential or perspective

Preclinical studies in animal models have suggested the potential therapeutic effects by targeting several other PDEs. For example, the pan PDE1 inhibitor IC86340 exerts protective effect against pathological cardiac remodeling and dysfunction in various pre-clinical mouse heart failure models, such as pressure overload-induced heart failure [33], ISO-induced cardiac hypertrophy [32], as well as doxorubicin-induced cardiac toxicity [14]. A different pan PDE1 inhibitor, ITI-214, has been shown to improve cardiac function in dog and rabbit models of heart failure [63]. Another PDE1 inhibitor, vinpocetine, attenuates pathological cardiac remodeling induced by chronic Ang II-infusion in mice [62]. Vinpocetine has been used to prevent and treat cerebrovascular disorders such as stoke and dementia, and remains widely available in dietary supplements [144]. Based on the excellent safety profile of vinpocetine in humans, targeting PDE1 might be a promising therapeutic strategy in treating cardiac diseases. Similarly, studies have found that the inhibition of PDE2 by Bay-607550 and inhibition of PDE9 by PF-04447943 all elicit improved cardiac function and reverse cardiac remodeling in pressure overload-induced heart failure in mice [34,39,66]. A recent study also showed that PDE10A inhibition by TP-10 ameliorates pre-existing pathological cardiac remodeling and dysfunction induced by chronic pressure overload in mice [40]. Importantly, several PDE10A inhibitors have been tested in humans and successfully passed phase I clinical trials (ClinicalTrials.org), suggesting PDE10A is a drug-able target. Thus, inhibiting PDE10A may represent a novel therapeutic strategy for cardiac diseases with pathological cardiac remodeling.

4. Conclusions

PDEs, as negative cAMP and/or cGMP modulators, play important roles in regulating the amplitude, duration, and compartmentalization of cyclic nucleotide signaling. PDEs exist in a superfamily with more than 20 different genes and a large number of variants (isozymes). The diversities of PDEs including substrate specificities, enzymatic properties, subcellular localizations, and expression profiles, enable individual PDEs to regulate unique cyclic nucleotide signaling pathways and specialized cellular functions. Thus, targeting a specific PDE allows selectivity, altering only one or few cyclic nucleotide signaling pathways without a global change of cellular cyclic nucleotides. Dysregulation of PDE expression/activation have been implicated in a number of cardiac diseases, and most of them appear to play causative roles in the disease development. Thus, inhibiting or activating altered PDEs may be attractive therapeutic strategies to treat cardiac diseases. Up to date, most of our knowledge of individual PDEs in cardiac biology and diseases come from studies with global KO mice or systemic PDE inhibitions in rodents. Because many PDEs are also expressed in non-cardiac organ/tissues that may have an indirect impact on the heart, the cardiac functions of individual PDEs should be evaluated carefully with considerations of non-cardiac tissue contributions. In addition, different PDE variants encoded by the same gene could have distinct cellular/subcellular localizations and play differential roles in the heart. Developing more specific genetic tools capable of targeting individual variants is needed. Moreover, differences in PDE expression and function in rodents and humans should be carefully evaluated.

5. Expert Opinion

5.1 Limitations of currently available PDE activity modulators

Currently, the major PDE activity modulators are PDE inhibitors. All PDE inhibitors developed up to date are family-specific and they do not have sufficient specificities to distinguish the isozymes within the same family. Using genetic approaches, it has been shown that different PDE isozymes in the same family could exert distinct functions in individual cells. For example, PDE1C, but not PDE1A, regulates CM viability [14,33]. PDE3A, but not PDE3B, regulates CM contractile function [85,86]. PDE4B, but not PDE4D, regulates the L-type Ca^{2+} current [98], while PDE4D, but not PDE4B, regulates Ca^{2+} release from the RyR2 [97]. Therefore, there is an urgent need to develop isozyme-selective PDE inhibitors.

In contrast, PDE activation appears to be beneficial in certain cases. For example, PDE3A1 overexpression in CMs protects CMs and mouse hearts against I/R induced cell death and cardiac injury [88]. Similarly, CM-specific overexpression of PDE4B3 in transgenic mice protects against pathological cardiac remodeling induced by chronic β-AR stimulation [94]. Interestingly, AAV9-mediated gene transfer has been used to achieve a moderate level of PDE4B3 expression in CMs, which promisingly elicits protective effects against cardiac dysfunction induced by chronic β-AR stimulation and TAC without affecting cardiac function in healthy mice [94].

5.2 Targeting multiple PDEs

Several studies have reported that administering two or more PDE inhibitors with submaximal dose could yield additive or synergistic effects, with the possibility to generate less toxicity [145–148]. For example, synergism between PDE3 and PDE4 has been found in various cell types [145–149]. Inhibition of PDE3 and PDE4 synergistically stimulate lipolysis in mouse and rat adipocytes [145], activate brown adipose tissue [147], inhibit vascular SMC migration [146], suppress effect on VCAM-1 expression and eosinophil adhesion to activated human lung microvascular ECs [149], as well as increase spontaneous firing of sinoatrial node cells [148]. Interestingly, a recent clinical trial testing dual PDE3 and PDE4 inhibitor Ensifentrine (RPL554) revealed a promising improvement and well-tolerated effect for the treatment of COPD [150].

In CMs, *in vitro* and *in vivo*, the inhibitors of PDE1, 5, and 10 are all able to suppress CM hypertrophy [33,40,121]. An additive effect was reported for PDE1 inhibition by IC86340 together with PDE5 inhibition by Sildenafil in neonatal rat CM hypertrophy [32], suggesting that targeting different PDEs concurrently have additive or synergistic effects. In CMs, PDE5 regulates the sGC/cGMP/PKG signaling [56,66], whereas PDE9A regulates pGC/cGMP/PKG signaling [39]. It would be interesting to determine the effects of inhibiting PDE5 and PDE9 together in the future. In addition, PDE2 activity is stimulated upon increasing cGMP. It would also be of value to determine the effects of inhibiting PDE2 together with PDE5 or with PDE9.

5.4 Targeting specialized signalosomes

Numerous studies have supported the notion that individual PDEs are tethered to a precise signalosome via binding partners in an isoform-specific manner, each containing unique cyclase, PDE, kinases, and/or other signaling molecules (Figure 1). The signalosomes control cyclic nucleotide signaling locally and specifically, which lead to different biological functions [27,28,34]. Promoting or disrupting isoform-specific protein-protein interactions within specific signalosome may yield a greater specificity compared to current PDE inhibitors. The disruption of protein-protein interaction is often achieved by small molecule compounds or peptides. For example, a peptide that induces the disruption of the Hsp20-PDE4D complex has been shown to promote PKA phosphorylation of Hsp20 and alleviate cardiac myocyte hypertrophy [28]. A small molecule or a peptide that disrupts the AKAP18-PKA complexes has been shown to increase cardiac myocyte contractility [28]. It remains to be examined whether targeting specialized signalosomes by disruption of protein-protein interaction might be efficacious in clinical settings.

In addition, defining the sources of cyclic nucleotides regulated by PDEs in the signalosomes could be important. For example, it has been shown that PDE1C exists in a multi-protein complex with $A_{2A}R$ and TRPC3 in CMs, which is critical in regulating CM viability [14]. TRPC3-derived Ca^{2+} activates PDE1C, which antagonizes $A_{2A}R$-derived cAMP through PDE1C hydrolysis of cAMP [145]. This finding results in the hypothesis that promoting cAMP synthesis and inhibiting cAMP degradation together produce additive or synergistic effects. Indeed, it has been shown that low doses of A_2R agonist combined with PDE1 inhibitor or TRPC inhibitor provide synergistic effects on CM survival [1]. PDE9A has been shown to complex with NPR in CMs [39]. It would be of great interest to examine the additive/synergistic effects from the PDE9 inhibitor in combination with NPR agonists.

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Article highlights

- PDEs play an important role in regulating the amplitude, duration, and compartmentalization of cyclic nucleotide signaling.
- Dysregulation of PDE expression and activation have been implicated in a number of cardiac diseases.
- Increasing pre-clinical and clinical evidences support that inhibiting PDEs may be attractive therapeutic strategies to treat cardiac diseases.
- It would be of value to determine the effect of targeting multiple PDEs or targeting specialized signalosomes on combating cardiac disorders in the future.
- Understanding the cellular and molecular mechanisms of PDEs enable the development of new approaches to achieve effective and specific PDE inhibition for various cardiac therapies.

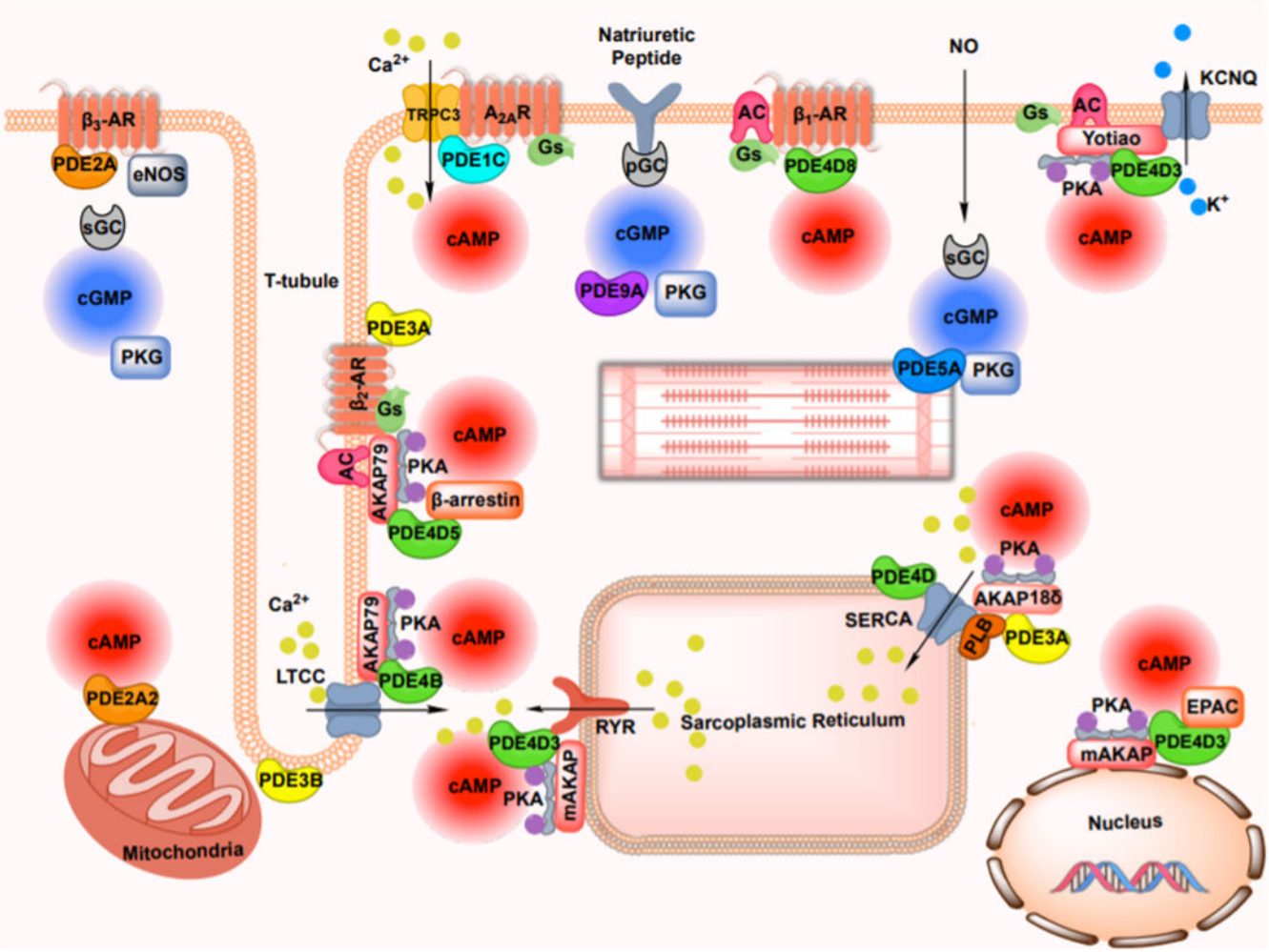

Figure 1: Schematic representation of cyclic nucleotide and PDE compartmentalization in cardiac myocyte.

Compartmentalized cyclic nucleotide signaling is generated by individual G-protein coupled receptors, and established via the formation of multiple spatially segregated signalosomes, in which combination of cyclic nucleotide effectors, phosphodiesterase and scaffolding proteins form specific complexes via protein-protein interaction. PDE, phosphodiesterase; AR, adrenergic receptor; AC, adenylyl cyclase; sGC, soluble guanylyl cyclase; pGC, particulate guanylyl cyclase; PKA, protein kinase A; PKG, protein kinase G; cAMP, cyclic adenosine 3′,5′-monophosphate; cGMP, cyclic guanosine 3′,5′-monophosphate; LTCC, L-type calcium current; PLB, phospholamban; RYR, ryanodine receptor; SERCA, sarcoplasmic reticulum Ca^{2+} ATPase; AKAP, A-kinase anchor protein; TRPC, transient receptor potential subfamily C; $A_{2A}R$, adenosine type 2A receptor; KCNQ, voltage-gated potassium channels of the KCNQ subfamily; NO, nitric oxide; EPAC, exchange protein activated by cAMP; eNOS, endothelial nitric oxide synthase.

Table 1.

Biochemical Characteristics of Cardiac PDEs

Family	Gene	Substrate	$K_m(\mu M)$		Regulators	Species-dependent expression in the heart
			cAMP	cGMP		
PDE1	1A	cAMP,cGMP	115	5	+Ca^{2+}/CaM	• equally expressed in human, rat and mouse hearts, and both CMs an CFs • upregulated in mouse, rat and human failing hearts • upregulated in rat CMs by hypertrophic stimuli • upregulated in rat CFs by fibrotic stimuli
	1B	cAMP,cGMP	24	2.4		• not detected in normal human, rat and mouse hearts
	1C	cAMP,cGMP	1	1		• expressed highest in human, modest in mouse, very low in rat hearts, and in mouse CMs • increased in failing human and mouse hearts, primarily restricted in CMs
PDE2	2A	cAMP,cGMP	30	20	+CGMP	• detected in human, rat and mouse hearts, and both CMs and CFs, with higher expression in CFs than CMs • upregulated in human and mouse failing hearts
PDE3	3A	cAMP,cGMP	0.15	0.15	−cGMP	• expressed in human, rat, dog and mouse hearts and CMs• increase or decrease in diseased hearts, varied by studies
	3B					• expressed in mouse hearts and CMs
PDE4	4A	cAMP	5	N/A	+PKA, −ERK	• expressed in human, rat and mouse hearts and CMs • decreased expression in human failing hearts and rat hypertrophic CMs
	4B					• expressed in human, rat and mouse hearts and CMs • decreased expression in human failing hearts and rat hypertrophic CMs
	4C					• not detected in normal rat heart
	4D					• expressed in human, rat and mouse hearts and CMs • decreased expression in human and rat failing hearts and rat hypertrophic CMs
PDE5	5A	cGMP	N/A	5	+PKG	• expressed in human, rat and mouse hearts, and both CMs and CFs • upregulated in human, rat and mouse failing hearts, and diseased CMs
PDE8	8A	cAMP	0.05	N/A		• expressed in human and mouse hearts, and mouse CMs
	8B					• expressed in human and mouse hearts, and mouse CMs
PDE9	9A	cGMP		0.1		• expressed in human and mouse hearts, and CMs • upregulated in human and mouse failing hearts
PDE10	10A	cAMP,cGMP	0.3	13	+CAMP	• expressed in human and mouse hearts, and both CMs and CFs • upregulated in human and mouse failing hearts • upregulated in mouse CMs by hypertrophic stimuli • upregulated in mouse CFs by fibrotic stimuli