HHS Public Access

Author manuscript

Handb Exp Pharmacol. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Handb Exp Pharmacol. 2017 ; 243: 249–269. doi:10.1007/164_2016_82.

Cardiac Phosphodiesterases and their Modulation for Treating Heart Disease

Grace E. Kim, PhD[a] and **David A. Kass, MD**[a,b]

[a]Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland [b]Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland

Abstract

An important hallmark of cardiac failure is abnormal second messenger signaling due to impaired synthesis and catabolism of adenosine 3',5'-cyclic monophosphate (cAMP) and cyclic guanosine 3',5'-cyclic monophosphate (cGMP). Their dysregulation, altered intracellular targeting, and blunted responsiveness to stimulating pathways all contribute to pathological remodeling, muscle dysfunction, reduced cell survival and metabolism, and other abnormalities. Therapeutic enhancement of either cyclic nucleotide can be achieved by stimulating their synthesis and/or by suppressing members of the family of cyclic nucleotide phosphodiesterases (PDEs). The heart expresses seven of the eleven major PDE sub-types - PDE1, 2, 3, 4, 5, 8, and 9. Their differential control over cAMP and cGMP signaling in various cell types, including cardiomyocytes, provides intriguing therapeutic opportunities to counter heart disease. This review examines the roles of these PDEs in the failing and hypertrophied heart, and summarizes experimental and clinical data that has explored the utility of targeted PDE inhibition.

Keywords

myocardium; heart failure; phosphodiesterases; protein kinase A; protein kinase G; cyclic nucleotides

Introduction

Phosphodiesterases (PDEs) are a superfamily of enzymes that hydrolyze the cyclic nucleotides adenosine 3',5'-cyclic monophosphate (cAMP) and cyclic guanosine 3',5'-cyclic monophosphate (cGMP). Both cyclic nucleotides are synthesized in specific intracellular compartments by corresponding cyclases, and are selectively catabolized by members of the PDE superfamily. The resulting localized activation elicits targeted cellular responses to multiple stimuli. Levels of both myocardial cyclic nucleotide synthesis and hydrolysis are altered by physiological and pathological stress, and play an important role in diseases such as cardiac failure. Therapies to restore their signaling to improve cardiac

Address Correspondence: David A. Kass, M.D., Division of Cardiology, Ross Research Building, Room 858, 720 Rutland Avenue, Baltimore, MD, 21205, TEL: (410) - 955-7153, FAX: (410) - 502-2558.

function and suppress maladaptive organ and molecular remodeling have been and continue to be pursued. Targeting PDEs is particularly attractive as highly specific and potent small molecule inhibitors have been developed for many of the enzymes, and their expression in particular cell types and intracellular nanodomain regulation affords targeted influences over cyclic nucleotide signaling. Inhibitors of PDE3 are in clinical use for acute heart failure, PDE4 for psoriasis and chronic obstructive lung disease, and PDE5 for erectile dysfunction and pulmonary hypertension). None are presently approved for chronic heart failure, but several are being studied for such indications. This review describes the role and potential utility of pharmacological targeting of PDEs in the diseased heart, focusing first on those for which clinical data has been generated, followed by those where only pre-clinical data has been obtained thus far.

Cyclic Nucleotides: Cardiac Second Messengers with Pleiotropic Effects

Both cAMP and cGMP modulate a wide range of myocardial properties including contraction and relaxation, diastolic stiffness, heart rate, cell growth and survival, interstitial fibrosis, vascular tone, and endothelial permeability and proliferation. Cyclic AMP is generated by adenylate cyclase (AC type 5 and type 6 in the heart) and it activates one of two cognate proteins: protein kinase A (PKA) or exchange protein directly activated by cAMP (Epac). In the cardiomyocyte, PKA phosphorylates multiple proteins controlling excitation-contraction coupling and sarcomere function. These include troponin I (Kentish et al., 2001), titin (Yamasaki et al., 2002), myosin binding protein C (Nagayama et al., 2007; Stelzer et al., 2006), phospholamban (MacLennan and Kranias, 2003), the ryanodine receptor (RyR2) (Reiken et al., 2002), and the L-type calcium channel (Verde et al., 1999). Epac is a guanine nucleotide exchange factor (GEF) protein that can activate calcium-calmodulin activated kinase II (CamKII) signaling to alter calcium cycling and gene transcription (Gloerich and Bos, 2010). In the cardiomyocyte, both PKA and Epac are engaged by cAMP synthesis coupled to β-adrenergic G-protein coupled receptor stimulation.

Cyclic GMP is generated by either a soluble guanylate cyclase (sGC) activated by nitric oxide, or a receptor-bound cyclase (GC-A or GC-B) in the intracellular domain of the natriuretic peptide receptor. The targeted kinase is cGMP-stimulated kinase (cGK1 in the heart, also called PKG-1) that phosphorylates many of the same calcium homeostasis and sarcomere proteins targeted by PKA (e.g. phospholamban, TnI, titin, myosin binding protein C). However, other cGK1 targets oppose neurohormonal stimulation pathways, such as regulator of G-protein signaling 2 and 4 (RGS2, RGS4) that counter Gq- and Gi-receptor coupled agonism (Takimoto et al., 2009; Tokudome et al., 2008), ion channels like transient potential receptor canonical type 6 (TRPC6) that stimulate calcineurin/NFAT signaling (Kinoshita et al., 2010; Koitabashi et al., 2010; Nishida et al., 2010), and RhoA which regulates Rho-kinase signaling (Sawada et al., 2001), and myosin light chain phosphatase (Surks et al., 1999). In the myocyte, cGK1 does not stimulate L-type calcium current. Thus, cGK1 generally acts as a myocardial brake, that can counter cAMP/PKA stimuli acutely and chronically suppress stress-mediated signaling.

Upon synthesis, local regulation of cyclic nucleotides is exquisitely controlled by members of the PDE superfamily. The 11 family members of PDEs are expressed by nearly 100 isoform variants (Maurice et al., 2014) that differ mainly in their N-terminus regulatory domains. By contrast, their catalytic domains are broadly conserved, with each species having subtle differences to provide cAMP- and/or cGMP-substrate specificity (Bender and Beavo, 2006; Francis et al., 2011). PDEs pose unique opportunities for pharmacological modification of cyclic nucleotide signaling because they are selectively expressed in various cell types. PDEs 1–5, 8 and 9 are expressed in myocardium, with some species-dependent differences in isoform expression, notably in PDE1 (Table 1). PDE1, 2, 3 are all dual substrate esterases, PDE5 and PDE9 are selective for cGMP, and PDE4 and PDE8 are selective for cAMP. Preclinical studies have established a role in cardiac regulation for all of these species, while clinical data related to heart disease only exists for PDE3 and PDE5. Importantly, all of these PDEs are dysregulated in conditions of cardiac failure, infarction, and hypertrophy, often but not always displaying increased expression. This applies to disease in multiple experimental models as well as in humans (Table 2). Furthermore, studies using either selective pharmacological or genetic modulators of these PDEs have revealed their potent impact on disease pathophysiology, supporting therapeutic potential (Table 3).

PDE3 and Dilated Cardiomyopathy

The first exploration for a therapeutic role of PDE modulation to treat heart disease evolved with the discovery that PDE3 modulated cAMP, and that its inhibition could potentially enhance PKA- (and Epac-) dependent signaling in the diseased heart. PDE3 is expressed in two primary isoforms, PDE3A and PDE3B, and both are found in cardiomyocytes. PDE3A is the predominant form (Meacci et al., 1992; Sun et al., 2007), and its three splice variants differ in intracellular compartmentation (Wechsler et al., 2002) as well as regulation by PKA and PKC (Vandeput et al., 2013). These isoforms operate in microdomains, for example PDE3A localizes to the sarcolemmal membrane), and this allows for regulation of compartmentalized PKA signaling (Leroy et al., 2008; Zaccolo, 2009; Zaccolo and Pozzan, 2002). While PDE3 can hydrolyze both cAMP and cGMP, it favors cAMP due to a much higher V_{max} for this substrate.

PDE3 inhibition results in increased L-type calcium current (Verde et al., 1999) which stimulates contractility (Weishaar et al., 1987), an effect principally mediated by PDE3A (Sun et al., 2007). PDE3A co-immuno-precipitates with a protein complex containing SERCA2a, phospholamban and A-kinase anchoring protein 18 (AKAP18) in a PKA-phosphorylation dependent manner (Ahmad et al., 2015). This specifically targets a pool of cAMP to regulate calcium cycling via the sarcoplasmic reticulum (Beca et al., 2013). Broad PDE3 inhibition can also stimulate arrhythmia by excessive calcium entry and internal release from the SR coupled to both PKA and Epac2-CamKII activation (Bobin et al., 2016). PDE3 also influences cellular apoptosis as revealed in studies of myocardial infarction. In this condition, PDE3A inhibition can damage the heart by increasing activity of ICER (inducible cAMP early repressor) to suppress Bcl2 expression and promote apoptosis (Ding et al., 2005; Yan et al., 2007). Enhancing PDE3A expression is cardioprotective against ischemia-reperfusion (Oikawa et al., 2013). However, the opposite holds for PDE3B, whose

gene deletion is protective against cardiac ischemia/reperfusion injury (Chung et al., 2015). Summary signaling is shown in Figure 1.

Given the potential for PDE3 inhibition to improve myocardial hemodynamics by enhancing contractility while also dilating veins and arteries to reduce cardiac load, it became the first PDE targeted for inhibition to treat heart failure. While acute responses appeared promising, trials with sustained PDE3 inhibition increased adverse events and mortality in HF patients (Cuffe et al., 2002; DiBianco et al., 1989; Metra et al., 2009; Packer et al., 1991). Di Bianco et al. compared milrinone (10 mg/qid) to the cardiac glycoside digoxin (DiBianco et al., 1989), but found no added benefit over digoxin. In the pivotal 6-month PROMISE study (The Effects of Oral Milrinone on Mortality in Severe Chronic Heart Failure), Packer et al. found no improvement in heart function over placebo (Packer et al., 1991), but rather increased arrhythmia, hypotension, and greater mortality. The subsequent OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart failure) study also reported no clinical benefit over placebo (Cuffe et al., 2002). Despite this, short-term PDE3 inhibition remains in use for acute decompensated HF.

Several conclusions evolved from these studies. One was that doses yielding substantive acute inodilator responses were probably too high to avoid chronic toxicity. Another was that interventions substantively increasing intracellular calcium transients may pose arrhythmogenic risks. As these trials predated the era of broad β-adrenergic blockade use, some hypothesized that PDE3 inhibition might be safe if combined with such therapy. This was tested in the ESSENTIAL trials (Studies of Oral Enoximone Therapy in Advanced HF), examining enoximone combined with background β-blockade (Metra et al., 2009). Unlike the earlier studies, enoximone did not worsen mortality; however, it also did not improve symptoms or exercise capacity.

Despite this history, there interest remains in modulating PDE3 (Movsesian et al., 2011). This has evolved in part from recent data that isoform-specific targeting might enhance beneficial effects while avoiding toxicity. For example, PDE3A rather than PDE3B is required to enhance myocyte contractility and calcium cycling (Beca et al., 2013; Sun et al., 2007). However, mice lacking PDE3B also show protection against ischemic reperfusion, so selective targeting only of the PDE3A isoform would seem undesirable (Chung et al., 2015). However, splice variants PDE3A1 and A2 also differ, with unique phosphorylation responses to PKA and PKC (Vandeput et al., 2013) due to specific protein-protein interactions. Thus, one approach being explored is to express a disrupting peptide to interfere with a specific isoform protein complex to dislocate the PDE from its normal effectors without impacting the other isoform. If successful, this approach might avoid unwanted effects from non-selective inhibitors.

PDE5 and Dilated Cardiomyopathy

PDE5A was the first cGMP-selective isotype discovered. Its esterase activity is stimulated both by cGMP binding to regulatory GAF-domains in the N-terminus, and by cGK1 phosphorylation at S92 (Corbin et al., 2000; Francis et al., 2002; Rybalkin et al., 2003), creating a negative feedback loop. Immunocytochemical evidence has shown that PDE5A

localizes to the Z-disk in the cardiomyocyte, but this can become diffuse in mammalian models of hypertrophy and heart failure (Takimoto et al., 2005a; Zhang et al., 2008) and in the absence or suppression of nitric oxide synthase synthase III (Nagayama et al., 2008; Takimoto et al., 2005b). At the Z-disk, it predominately targets cGMP generated by the nitric oxide-soluble guanylyl cyclase (NO-sGC) pathway, having only minimal impact on natriuretic peptide (NP)-stimulated cGMP pools (Fischmeister et al., 2006; Lee et al., 2015; Takimoto et al., 2005a).

PDE5A is expressed at very low levels in the normal myocardium, but is upregulated in DCM (Andersen et al., 2012; Shan et al., 2012) and in RV hypertrophy associated with pulmonary hypertension (Nagendran et al., 2007). There remains some controversy regarding PDE5A expression in the human heart, based primarily on differences in immunoblot data (Degen et al., 2015). As gene deletion models – even conditional ones - have not been successful, absolute proof of the role of normal PDE5A in the heart *in vivo* remains indirect. However, myocyte specific overexpression models have shown PDE5A upregulation worsens the consequences of pressure overload (Zhang et al., 2010) and myocardial infarction (Pokreisz et al., 2009), and that subsequent genetic suppression of the same gene is sufficient to reverse pathological hypertrophy/fibrosis induced by pressure-overload (Zhang et al., 2010).

In experimental models, PDE5A inhibition stimulates cGK1 activity to suppress multiple cardiac signaling pathways engaged in pathological hypertrophy and HF. This includes blockade of calcineurin/NFAT signaling (Takimoto et al., 2005c), its activation of regulators of G-protein signaling (RGS2/4) to block Gq-activated cascades (e.g. from angiotensin or endothelin-1) (Takimoto et al., 2009), inhibition of transient receptor potential canonical ion channel - type 6 (Trpc6) (Seo et al., 2014), improvement of proteasome degradation of misfolded proteins (Ranek et al., 2013), enhanced mitochondrial and consequent cytoprotection against ischemic injury linked to glycogen synthesis kinase 3-β and mitogen activated kinase ERK1/2 (Das et al., 2008), and other mechanisms. cGK1 activation can also improve diastolic function by phosphorylating titin to increase distensibility (Bishu et al., 2011). Figure 2 summarizes these PDE5A effects on cGMP/cGK1 signaling.

The clinical effects of PDE5A inhibition on dilated HF have been principally studied in patients who also had pulmonary hypertension, as the latter is an approved therapeutic target for PDE5A inhibitors. Lewis et al. (Lewis et al., 2007) tested 12 weeks of sildenafil therapy and found peak oxygen consumption and cardiac output was enhanced and coupled to improved exercise capacity and quality of life. Similar results were observed by others (Behling et al., 2008; Kim et al., 2015), including data showing PDE5A inhibition improves LV function and exercise oscillatory ventilation, the latter a clinical index of DCM outcome (Murphy et al., 2011). The extent to which direct myocardial effects underlie benefit from PDE5A inhibition in DCM remains speculative. Systemic arterial vasodilation is minimal, so LV unloading is unlikely, but PDE5A inhibition can dilate small arteries that may enhance skeletal muscle oxygenation (Ghofrani et al., 2004). As of now, no definitive multicenter trial of PDE5A inhibition in DCM has been conducted. A pivotal >2000 patient NIH-sponsored trial (PITCH-HF) was initiated in November 2013, but then terminated 4 months later due principally to budget constraints.

Another form of DCM for which PDE5A inhibition has been studied is associated with Duchenne muscular dystrophy. This disease is caused by missense mutations in the dystrophin gene that results in full disruption of the dystro-sarcoglycan complex essential to normal skeletal and cardiac muscle function and survival. Duchenne patients develop near total loss of skeletal motor function by their early teens, and heart failure generally follows. The dystro-sarcoglycan complex also anchors neuronal NOS at the plasma membrane of skeletal muscle (Brenman et al., 1995), and its absence leads to disrupted NO signaling that is thought to depress microvascular flow leading to ischemia (Kobayashi et al., 2007; Loufrani et al., 2002). The impact on NOS dyslocalization in cardiomyocytes is less clear, though cGMP signaling appears to be depressed and its activation maybe therapeutic. Seo et al (Seo et al., 2014), reported hyper-active mechano-stimulated force, intracellular calcium, and associated arrhythmia in myocytes from a DMD mouse model that were all potently suppressed by cGMP activation. This effect was also achieved by chronic PDE5A inhibition, that further improved both in vivo cardiac function and reduced hypertrophy. The latter data support studies reported from mouse and canine models of DMD (Adamo et al., 2010; Albert et al., 2012).

Human trials have shown that acute PDE5A inhibition improves microvascular flow in skeletal muscle to match contractile stress in Duchenne patients (Nelson et al., 2014). However, when tested in non-ambulatory adults with advanced Duchenne skeletal and cardiac disease, 6 months of sildenafil therapy did not improve heart function (Leung et al., 2014). Furthermore, a recently completed international multicenter trial of tadalafil in ambulatory boys with Duchenne and no cardiac disease also failed to improve motor capacity. This could indicate that PDE5A is not the right target for improving cGMP signaling, but that modulating cGMP synthesis or using other PDE inhibitors might be successful. It may also require some gene correction in addition to any modulation of cGMP signaling to achieve benefits.

PDE5A and Non-dilated Heart Disease

About half of all patients with heart failure symptoms have ventricles that do not dilate but rather present with an ejection fraction in the normal range. This is often termed heart failure with a preserved EF (HFpEF), a multifactor syndrome that has proven difficult to treat, with no current specific evidence-based therapy (Shah et al., 2016). While HFpEF implies a central role for heart disease, the reality is more complex as many other organ pathophysiologies contribute, including from the lung, kidney, skeletal muscle, neuroregulatory systems, and adipose tissue. Common co-morbidities are type-2 diabetes, obesity, hypertension, cardiac hypertrophy, pulmonary hypertension, inflammatory disease, and renal insufficiency (Shah et al., 2016).

Since cGK1 activation can reduce hypertrophy, fibrosis, PH, while improving metabolism and potentially renal function, it has been an attractive strategy for treating HFpEF. In patients with LV diastolic dysfunction and PH, chronic sildenafil treatment lowered mean pulmonary artery pressure and improved RV function and LV relaxation (Guazzi et al., 2011). A subsequent study, however, found no benefit on either invasive hemodynamics or exercise performance (Hoendermis et al., 2015). More convincingly, a larger 6-month

multicenter trial of the same drug in HFpEF patients also reportedno benefits over placebo (Redfield et al., 2013). However, the patient cohort for this study included few subjects with PH, and a majority lacked LV hypertrophy and many did not have diastolic dysfunction. Prior animal data has shown that the influence of PDE5A inhibition to counter pressure-overload induced cardiac disease requires the presence of sufficient maladaptive remodeling so that cGK1 has something useful to suppress (Nagayama et al., 2009). Perhaps more importantly, other studies have found human HFpEF myocardium contains very little cGMP and has low cGK1 activity, neither being attributable to elevated PDE5A activation (van Heerebeek et al., 2012). This makes it less likely that PDE5A inhibition could have much impact.

HFpEF particularly affects older women and reduced NO-signaling consequent to menopause maybe provide another reason for little impact from PDE5A inhibition. In women, the estrogen receptor couples to NOS-dependent cGMP synthesis via a non-transcriptional signaling pathway (Haynes et al., 2000; Leung et al., 2007). As this NO-derived cGMP is the primary target of PDE5A, its decline post menopause may limit the efficacy of PDE5A inhibition. Consistent with this hypothesis, Sasaki et al. (Sasaki et al., 2014) found that female mice with Gαq-over expression or pressure-overload induced heart disease responded favorably to PDE5A inhibition, but this benefit was lost if the mice underwent ovariectomy. The efficacy of PDE5A inhibition was restored if exogenous estrogen was subsequently provided. This may have contributed to differences in results from the two hemodynamic studies, with negative data coming from mostly female patients (>75%) (Hoendermis et al., 2015) and positive results from mostly males (Guazzi et al., 2011).

Lastly, PDE5A inhibition has been studied in patients with type 2 diabetes and evidence of ventricular dysfunction but no heart failure symptoms. Chronic sildenafil treatment improved some indexes of LV contraction and morphology (Giannetta et al., 2012). Additional studies in this disease have not yet been reported. Further, whether this relates to myocardial, vascular, or potentially metabolic effects such as improved insulin sensitivity (Ho et al., 2014; Ramirez et al., 2015) from PDE5A inhibition, remains unclear.

Potential roles for PDE1, PDE2 and PDE9 in Heart Failure

PDE1

The PDE1 family is encoded by three genes *PDE1A, PDE1B* and *PDE1C*. PDE1A is selective for cGMP, whereas PDE1B and PDE1C display balanced substrate selectivity. All three isoforms are expressed in human myocardium (Table 1), with PDE1C the predominant ventricular isoform (Loughney et al., 1996; Lukowski et al., 2010; Miller et al., 2009; Vandeput et al., 2007). By contrast, PDE1A is the predominant isoform in rat and mouse heart (Miller et al., 2009). All three require activation by calcium/calmodulin making them of interest in cardiac stress conditions. In rodents, PDE1A expression is pathologically upregulated in myocytes and fibroblasts in response to Gq-coupled agonists (e.g. angiotensin II), and by myocardial stress such as infarction (Miller et al., 2011), pressure overload, and chronic isoproterenol infarction (Miller et al., 2009). Broad PDE1 inhibition was effective in vitro in suppressing myocyte hypertrophy and fibroblast activation, and in vivo against

isoproterenol infusion. (Figure 1) While it is likely PDE1A is engaged in these behaviors, PDE1A knockout mice remain yet to be reported. PDE1C global knockout mice have been generated and studied for their role in the olfactory system (Cygnar and Zhao, 2009). Preliminary data from these mice has revealed protection against pressure overload hypertrophy and apoptosis (Knight et al., 2014). The mechanism for the former remains unclear, while the latter appears related to cAMP rather than cGMP signaling. Broad PDE1 inhibitors have already been developed for human use and tested in patients with schizophrenia (Heckman et al., 2015). Cardiovascular studies of the hemodynamic and direct myocardial effects of non-selective PDE1 inhibitors in larger mammals are also ongoing, and clinical studies may follow.

PDE2A

PDE2A is a dual-substrate enzyme which provides important cyclic nucleotide cross-talk as it is activated by cGMP, binding to regulatory GAF domains, to enhance hydrolysis of cAMP (Martins et al., 1982). PDE2A is encoded by a single gene giving rise to three N-terminal variants (Rosman et al., 1997). PDE2A3 is expressed in human, and found in cardiomyocytes and vascular endothelial cells (Sadhu et al., 1999). Zaccolo et al reported PDE2A modifies myocyte responses to β-adrenergic co-stimulation (Mongillo et al., 2006; Vandecasteele et al., 2001), controlling localized PKA-II at the plasma membrane in a cGMP-regulated manner (Zoccarato et al., 2015). Both NP- and NO-stimulated cGMP pathways are linked to PDE2A activation in quiescent adult and neonatal cardiac myocytes (Fischmeister et al., 2006); however, the physiological role cGMP hydrolysis in vivo remains unclear.

As with most of the other PDEs, PDE2A expression rises in the failing heart. Hypoxia increases PDE2A expression and activity through HIF1α and TNF-α signaling in cultured human umbilical vein endothelial cells (Chen et al., 2016). Myocardial expression is increased in rat hypertrophy (Mehel et al., 2013; Yanaka et al., 2003) and in canine pacing-induced HF models (Mehel et al., 2013). Similar increases are reported in human ischemic or non-ischemic dilated HF, but not in hypertrophy (Mehel et al., 2013). PDE2A overexpression in isolated rat myocytes reduces L-type calcium current and corresponding calcium transients and sarcomere shortening following β-adrenergic stimulation. Chronic upregulation depresses hypertrophy induced by sustained β-adrenergic stimulation (Mehel et al., 2013), suggesting its activation is beneficial.

An alternative view was reported by Zoccarato et al. (Zoccarato et al., 2015), who found PDE2A *inhibition* suppresses norepinephrine-stimulated hypertrophy in the rat. Here, the mechanism was linked to an increase in cAMP-PKA signaling pathway that in turn increased NFAT phosphorylation. This curtailed the nuclear translocation of NFAT and downstream pro-hypertrophic signaling. Both studies reported regulation of cAMP by PDE2A amplified by cGMP, but their differences may relate to the precise conditions and local signaling linked to the stress trigger and cyclic nucleotide cross-talk. For instance, computer modeling (Zhao et al., 2016) predicts PDE2A hydrolyzes increasing amounts of cAMP as β-AR stimulation is enhanced, and hydrolyzes more cGMP at low levels of NO stimulation. Differences in cyclic nucleotide regulation, such as relocalization of PDE4 and

targeted stimulation of PKA isoform subtypes, are also induced by sustained adrenergic stimuli, and could alter net PDE2A responses (Fields et al., 2016). Figure 2 summarizes this signaling.

Therapeutic targeting of PDE2A in the intact myocardium poses further challenges in that its expression in myocytes and vascular endothelial cells may present opposing effects. For example, Chen et al. (Chen et al., 2016) revealed that NPs released after myocardial infarction increase endothelial permeability to amplify the post-injury inflammatory response. This was related to endothelial-specific NP receptor-guanylyl cyclase activation, though not to cGMP-activated cGK1 regulation. Rather, the newly generated cGMP stimulated PDE2A activity, further potentiating the esterase's hypoxia-induced expression; this in turn lowered cAMP to promote endothelial leakiness. Thus, blockers of PDE2A might concomitantly reduce post-ischemic inflammation via endothelial-targeted activity, while increasing adrenergic-stimulated contractility but also suppressing hypertrophic signaling in the myocyte.

PDE9A

PDE9A is the most selective for cGMP from all the 11 species (Fisher et al., 1998; Soderling et al., 1998), and has been clinically developed and tested for its potential to treat cognitive disorders such as Alzheimer's and schizophrenia (Duinen et al., 2015). It is expressed most prominently in brain (though still at low levels), but also in gut, kidney, and heart. Unlike PDE1, PDE2, or PDE5, there are presently no known mechanisms regulating its hydrolytic activity. The wide range of N-terminal splice variants are instead likely to impact subcellular targeting (Wang et al., 2003). Lee et al reported PDE9A is also upregulated in diseased myocardium, showing protein expression increases in human both dilated HF and HFpEF (Lee et al., 2015). In mice subjected to pressure overload, PDE9A deletion or its pharmacological inhibition led to improved LV function, and reduced fibrosis and hypertrophy. Importantly, PDE9A regulation of cGMP is distinct from PDE5A, in that the former selectively hydrolyzes cGMP derived from NP stimulation. This was confirmed in neonatal and adult cardiomyocytes and the intact heart (Figure 2). While inhibition of each selective PDE was linked to cGK1 activation, the protein targeting of the kinase as well as impact on transcriptional regulators as deduced by non-biased phospho-proteomics was distinct (Lee et al., 2015). These results have potentially significant therapeutic implications as NOS declines in many HF patients (Umar and van der Laarse, 2010), and as mentioned, is compromised in women by the decline in estrogen post menopause. Targeting PDE9A inhibition may circumvent obstacles posed by depressed NO-dependent signaling.

Beyond single small molecule PDE suppression

Advances in biochemical and cloning techniques helped unveil the structural similarities as well as differences among PDE species, and facilitated small molecule design for highly potent and selective inhibitors. Still, our capacity to influence isoform subtypes remains poor, while data increasingly shows how this is central to their intracellular regulation. The concept of protein complex disruption for the cAMP signalosome may be easier to achieve given the existence of A-kinase anchoring proteins (AKAPs) (Esseltine and Scott, 2013;

Nygren and Scott, 2015). These proteins act as coordinators of a cAMP-cyclase, targeted effector kinase, and regulatory PDEs to provide microdomain control. Equivalent proteins for cGMP-kinase signaling have not been found and this may make it more difficult to target a specific cGK1 pool.

Another issue is whether targeting a single PDE is the optimal approach, or whether strategic combinations may prove more effective. For example, both PDE5A and PDE9A regulate cGMP, but the results showing different proximal triggers and shared as well as different downstream effectors might raise the potential for combined efficacy. Synergy between PDE3 and PDE4 inhibition has been reported in myocytes (Mika et al., 2013). A particularly striking example was reported in a study of steroid production (Shimizu-Albergine et al., 2012) in testicular Leydig cells, where inhibition of PDE4 or PDE8 alone resulted in modestly elevated testosterone production, but their combination increased this 100-fold.

Conclusion

Since their discovery over 50 years ago, the importance of PDEs for fine tuning localized second messenger signaling has been increasingly recognized. While much structural chemistry and pharmacology is already established, our understanding of sub-cellular physiology and full therapeutic potential has lagged. Novel approaches beyond single-target small molecule inhibitors, combining stimulation with hydrolytic suppression, using dual PDE suppression, or disrupting protein complexes to target specific isoforms, may all ultimately change the therapy landscape. New work with several PDEs not been previously known for relevance to heart disease has already opened up new territory and opportunities. Thus, while the PDE field has in many ways matured, its impact on human disease remains to be fully leveraged, and exciting times lie ahead.

References

Tadalafil and Sildenafil for Duchenne Muscular Dystrophy Clinicaltrials.gov: NCT01359670.

Adamo CM, et al. Sildenafil reverses cardiac dysfunction in the mdx mouse model of Duchenne muscular dystrophy. Proc Natl Acad Sci U S A. 2010; 107:19079–83. [PubMed: 20956307]

Ahmad F, et al. Regulation of sarcoplasmic reticulum Ca2+ ATPase 2 (SERCA2) activity by phosphodiesterase 3A (PDE3A) in human myocardium: phosphorylation-dependent interaction of PDE3A1 with SERCA2. J Biol Chem. 2015; 290:6763–76. [PubMed: 25593322]

Albert CL, Sleeper M, Sweeney HL. Abstract 9504: Phosphodiesterase Modulation of Cardiomyopathy in Murine and Canine Models of Muscular Dystrophy Treated With Sildenafil and Tadalafil. Circulation. 2012; 126:A9504–A9504.

Andersen RO, et al. Sgt1 acts via an LKB1/AMPK pathway to establish cortical polarity in larval neuroblasts. Dev Biol. 2012; 363:258–65. [PubMed: 22248825]

Beca S, et al. Phosphodiesterase type 3A regulates basal myocardial contractility through interacting with sarcoplasmic reticulum calcium ATPase type 2a signaling complexes in mouse heart. Circ Res. 2013; 112:289–97. [PubMed: 23168336]

Behling A, et al. Effects of 5'-phosphodiesterase four-week long inhibition with sildenafil in patients with chronic heart failure: a double-blind, placebo-controlled clinical trial. J Card Fail. 2008; 14:189–97. [PubMed: 18381181]

Bender AT, Beavo JA. Cyclic nucleotide phosphodiesterases: molecular regulation to clinical use. Pharmacol Rev. 2006; 58:488–520. [PubMed: 16968949]

Bishu K, et al. Sildenafil and B-type natriuretic peptide acutely phosphorylate titin and improve diastolic distensibility in vivo. Circulation. 2011; 124:2882–91. [PubMed: 22144574]

Bobin P, et al. Calmodulin kinase II inhibition limits the pro-arrhythmic Ca2+ waves induced by cAMP-phosphodiesterase inhibitors. Cardiovasc Res. 2016; 110:151–61. [PubMed: 26851245]

Brenman JE, et al. Nitric oxide synthase complexed with dystrophin and absent from skeletal muscle sarcolemma in Duchenne muscular dystrophy. Cell. 1995; 82:743–52. [PubMed: 7545544]

Chen W, et al. Endothelial Actions of ANP Enhance Myocardial Inflammatory Infiltration in the Early Phase After Acute Infarction. Circ Res. 2016; 119:237–48. [PubMed: 27142162]

Chung YW, et al. Targeted disruption of PDE3B, but not PDE3A, protects murine heart from ischemia/reperfusion injury. Proc Natl Acad Sci U S A. 2015; 112:E2253–62. [PubMed: 25877153]

Corbin JD, et al. Phosphorylation of phosphodiesterase-5 by cyclic nucleotide-dependent protein kinase alters its catalytic and allosteric cGMP-binding activities. Eur J Biochem. 2000; 267:2760–7. [PubMed: 10785399]

Cuffe MS, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA. 2002; 287:1541–7. [PubMed: 11911756]

Cygnar KD, Zhao H. Phosphodiesterase 1C is dispensable for rapid response termination of olfactory sensory neurons. Nat Neurosci. 2009; 12:454–62. [PubMed: 19305400]

Das A, Xi L, Kukreja RC. Protein kinase G-dependent cardioprotective mechanism of phosphodiesterase-5 inhibition involves phosphorylation of ERK and GSK3beta. J Biol Chem. 2008; 283:29572–85. [PubMed: 18723505]

Degen CV, et al. The emperor's new clothes: PDE5 and the heart. PLoS One. 2015; 10:e0118664. [PubMed: 25747598]

DiBianco R, et al. A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. N Engl J Med. 1989; 320:677–83. [PubMed: 2646536]

Ding B, et al. Functional role of phosphodiesterase 3 in cardiomyocyte apoptosis: implication in heart failure. Circulation. 2005; 111:2469–2476. [PubMed: 15867171]

Duinen MV, et al. Treatment of Cognitive Impairment in Schizophrenia: Potential Value of Phosphodiesterase Inhibitors in Prefrontal Dysfunction. Curr Pharm Des. 2015; 21:3813–28. [PubMed: 26044976]

Esseltine JL, Scott JD. AKAP signaling complexes: pointing towards the next generation of therapeutic targets? Trends Pharmacol Sci. 2013; 34:648–55. [PubMed: 24239028]

Fields LA, Koschinski A, Zaccolo M. Sustained exposure to catecholamines affects cAMP/PKA compartmentalised signalling in adult rat ventricular myocytes. Cell Signal. 2016; 28:725–32. [PubMed: 26475678]

Fischmeister R, et al. Compartmentation of cyclic nucleotide signaling in the heart: the role of cyclic nucleotide phosphodiesterases. Circ Res. 2006; 99:816–828. [PubMed: 17038651]

Fisher DA, et al. Isolation and characterization of PDE9A, a novel human cGMP-specific phosphodiesterase. J Biol Chem. 1998; 273:15559–64. [PubMed: 9624146]

Francis SH, et al. Phosphorylation of isolated human phosphodiesterase-5 regulatory domain induces an apparent conformational change and increases cGMP binding affinity. J Biol Chem. 2002; 277:47581–7. [PubMed: 12359732]

Francis SH, Blount MA, Corbin JD. Mammalian cyclic nucleotide phosphodiesterases: Molecular mechanisms and physiological functions. Physiological Reviews. 2011; 91:651–690. [PubMed: 21527734]

Ghofrani HA, et al. Differences in hemodynamic and oxygenation responses to three different phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension: a randomized prospective study. J Am Coll Cardiol. 2004; 44:1488–96. [PubMed: 15464333]

Giannetta E, et al. Chronic Inhibition of cGMP phosphodiesterase 5A improves diabetic cardiomyopathy: a randomized, controlled clinical trial using magnetic resonance imaging with myocardial tagging. Circulation. 2012; 125:2323–33. [PubMed: 22496161]

Gloerich M, Bos JL. Epac: defining a new mechanism for cAMP action. Annu Rev Pharmacol Toxicol. 2010; 50:355–75. [PubMed: 20055708]

Guazzi M, et al. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. Circulation. 2011; 124:164–74. [PubMed: 21709061]

Haynes MP, et al. Membrane estrogen receptor engagement activates endothelial nitric oxide synthase via the PI3-kinase-Akt pathway in human endothelial cells. Circ Res. 2000; 87:677–682. [PubMed: 11029403]

Heckman PR, Wouters C, Prickaerts J. Phosphodiesterase inhibitors as a target for cognition enhancement in aging and Alzheimer's disease: a translational overview. Curr Pharm Des. 2015; 21:317–31. [PubMed: 25159073]

Ho JE, et al. Effect of phosphodiesterase inhibition on insulin resistance in obese individuals. J Am Heart Assoc. 2014; 3:e001001. [PubMed: 25213566]

Hoendermis ES, et al. Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial. Eur Heart J. 2015; 36:2565–73. [PubMed: 26188003]

Kentish JC, et al. Phosphorylation of troponin I by protein kinase A accelerates relaxation and crossbridge cycle kinetics in mouse ventricular muscle. Circ Res. 2001; 88:1059–1065. [PubMed: 11375276]

Kim KH, et al. PDE 5 inhibition with udenafil improves left ventricular systolic/diastolic functions and exercise capacity in patients with chronic heart failure with reduced ejection fraction; A 12-week, randomized, double-blind, placebo-controlled trial. Am Heart J. 2015; 169:813–822. e3. [PubMed: 26027619]

Kinoshita H, et al. Inhibition of TRPC6 channel activity contributes to the antihypertrophic effects of natriuretic peptides-guanylyl cyclase-A signaling in the heart. Circ Res. 2010; 106:1849–60. [PubMed: 20448219]

Knight WE, et al. Abstract 25: The Role of cAMP-Phosphodiesterase 1C Signaling in Pathological Cardiac Remodeling and Dysfunction. Circulation Research. 2014; 115:A25.

Kobayashi K, et al. Relation of spasms and myoclonus to suppression-burst on EEG in epileptic encephalopathy in early infancy. Neuropediatrics. 2007; 38:244–50. [PubMed: 18330839]

Koitabashi N, et al. Cyclic GMP/PKG-dependent inhibition of TRPC6 channel activity and expression negatively regulates cardiomyocyte NFAT activation Novel mechanism of cardiac stress modulation by PDE5 inhibition. J Mol Cell Cardiol. 2010; 48:713–24. [PubMed: 19961855]

Lee DI, et al. Phosphodiesterase 9A controls nitric-oxide-independent cGMP and hypertrophic heart disease. Nature. 2015; 519:472–6. [PubMed: 25799991]

Leroy J, et al. Spatiotemporal dynamics of beta-adrenergic cAMP signals and L-type Ca2+ channel regulation in adult rat ventricular myocytes: role of phosphodiesterases. Circ Res. 2008; 102:1091–100. [PubMed: 18369156]

Leung DG, et al. Sildenafil does not improve cardiomyopathy in Duchenne/Becker muscular dystrophy. Ann Neurol. 2014; 76:541–9. [PubMed: 25042693]

Leung SW, et al. Non-genomic vascular actions of female sex hormones: physiological implications and signalling pathways. Clin Exp Pharmacol Physiol. 2007; 34:822–6. [PubMed: 17600565]

Lewis GD, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation. 2007; 116:1555–62. [PubMed: 17785618]

Loufrani L, Levy BI, Henrion D. Defect in microvascular adaptation to chronic changes in blood flow in mice lacking the gene encoding for dystrophin. Circ Res. 2002; 91:1183–9. [PubMed: 12480820]

Loughney K, et al. Isolation and characterization of cDNAs corresponding to two human calcium, calmodulin-regulated, 3',5'-cyclic nucleotide phosphodiesterases. J Biol Chem. 1996; 271:796–806. [PubMed: 8557689]

Lukowski R, et al. Cardiac hypertrophy is not amplified by deletion of cGMP-dependent protein kinase I in cardiomyocytes. Proc Natl Acad Sci U S A. 2010; 107:5646–51. [PubMed: 20212138]

MacLennan DH, Kranias EG. Phospholamban: a crucial regulator of cardiac contractility. Nat.Rev.Mol.Cell Biol. 2003; 4:566–577. [PubMed: 12838339]

Martins TJ, Mumby MC, Beavo JA. Purification and characterization of a cyclic GMP-stimulated cyclic nucleotide phosphodiesterase from bovine tissues. J Biol Chem. 1982; 257:1973–9. [PubMed: 6276403]

Maurice DH, et al. Advances in targeting cyclic nucleotide phosphodiesterases. Nat Rev Drug Discov. 2014; 13:290–314. [PubMed: 24687066]

Meacci E, et al. Molecular cloning and expression of human myocardial cGMP-inhibited cAMP phosphodiesterase. Proc Natl Acad Sci U S A. 1992; 89:3721–5. [PubMed: 1315035]

Mehel H, et al. Phosphodiesterase-2 is up-regulated in human failing hearts and blunts beta-adrenergic responses in cardiomyocytes. J Am Coll Cardiol. 2013; 62:1596–606. [PubMed: 23810893]

Metra M, et al. Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trials. Eur Heart J. 2009; 30:3015–26. [PubMed: 19700774]

Mika D, et al. Differential regulation of cardiac excitation-contraction coupling by cAMP phosphodiesterase subtypes. Cardiovasc Res. 2013; 100:336–46. [PubMed: 23933582]

Miller CL, et al. Role of Ca2+/calmodulin-stimulated cyclic nucleotide phosphodiesterase 1 in mediating cardiomyocyte hypertrophy. Circ Res. 2009; 105:956–64. [PubMed: 19797176]

Miller CL, et al. Cyclic nucleotide phosphodiesterase 1A: a key regulator of cardiac fibroblast activation and extracellular matrix remodeling in the heart. Basic Res Cardiol. 2011; 106:1023–39. [PubMed: 22012077]

Mongillo M, et al. Compartmentalized phosphodiesterase-2 activity blunts beta-adrenergic cardiac inotropy via an NO/cGMP-dependent pathway. Circ Res. 2006; 98:226–234. [PubMed: 16357307]

Movsesian M, Wever-Pinzon O, Vandeput F. PDE3 inhibition in dilated cardiomyopathy. Curr Opin Pharmacol. 2011; 11:707–13. [PubMed: 21962613]

Murphy RM, et al. Exercise oscillatory ventilation in systolic heart failure: an indicator of impaired hemodynamic response to exercise. Circulation. 2011; 124:1442–51. [PubMed: 21875912]

Nagayama T, et al. Control of in vivo left ventricular [correction] contraction/relaxation kinetics by myosin binding protein C: protein kinase A phosphorylation dependent and independent regulation. Circulation. 2007; 116:2399–2408. [PubMed: 17984378]

Nagayama T, et al. Sustained soluble guanylate cyclase stimulation offsets nitric-oxide synthase inhibition to restore acute cardiac modulation by sildenafil. J Pharmacol Exp Ther. 2008; 326:380–7. [PubMed: 18456872]

Nagayama T, et al. Pressure-overload magnitude-dependence of the anti-hypertrophic efficacy of PDE5A inhibition. J Mol Cell Cardiol. 2009; 46:560–7. [PubMed: 19159628]

Nagendran J, et al. Phosphodiesterase type 5 is highly expressed in the hypertrophied human right ventricle, and acute inhibition of phosphodiesterase type 5 improves contractility. Circulation. 2007; 116:238–248. [PubMed: 17606845]

Nelson MD, et al. PDE5 inhibition alleviates functional muscle ischemia in boys with Duchenne muscular dystrophy. Neurology. 2014; 82:2085–91. [PubMed: 24808022]

Nishida M, et al. Phosphorylation of TRPC6 channels at Thr69 is required for anti-hypertrophic effects of phosphodiesterase 5 inhibition. J Biol Chem. 2010; 285:13244–53. [PubMed: 20177073]

Nygren PJ, Scott JD. Therapeutic strategies for anchored kinases and phosphatases: exploiting short linear motifs and intrinsic disorder. Front Pharmacol. 2015; 6:158. [PubMed: 26283967]

Oikawa M, et al. Cyclic nucleotide phosphodiesterase 3A1 protects the heart against ischemia-reperfusion injury. J Mol Cell Cardiol. 2013; 64:11–9. [PubMed: 23988739]

Packer M, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. N Engl J Med. 1991; 325:1468–75. [PubMed: 1944425]

Pokreisz P, et al. Ventricular phosphodiesterase-5 expression is increased in patients with advanced heart failure and contributes to adverse ventricular remodeling after myocardial infarction in mice. Circulation. 2009; 119:408–16. [PubMed: 19139381]

Ramirez CE, et al. Treatment with Sildenafil Improves Insulin Sensitivity in Prediabetes: A Randomized, Controlled Trial. J Clin Endocrinol Metab. 2015; 100:4533–40. [PubMed: 26580240]

Ranek MJ, et al. Protein kinase g positively regulates proteasome-mediated degradation of misfolded proteins. Circulation. 2013; 128:365–76. [PubMed: 23770744]

Redfield MM, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA. 2013; 309:1268–77. [PubMed: 23478662]

Reiken SR, et al. PKA phosphorylation of the cardiac calcium release channel (ryanodine receptor) in normal and failing hearts: role of phosphatases and response to isoproterenol. J.Biol Chem. 2002

Rosman GJ, et al. Isolation and characterization of human cDNAs encoding a cGMP-stimulated 3',5'-cyclic nucleotide phosphodiesterase. Gene. 1997; 191:89–95. [PubMed: 9210593]

Rybalkin SD, et al. PDE5 is converted to an activated state upon cGMP binding to the GAF A domain. EMBO J. 2003; 22:469–78. [PubMed: 12554648]

Sadhu K, et al. Differential expression of the cyclic GMP-stimulated phosphodiesterase PDE2A in human venous and capillary endothelial cells. J Histochem Cytochem. 1999; 47:895–906. [PubMed: 10375378]

Sasaki H, et al. PDE5 inhibitor efficacy is estrogen dependent in female heart disease. J Clin Invest. 2014; 124:2464–71. [PubMed: 24837433]

Sawada N, et al. cGMP-dependent protein kinase phosphorylates and inactivates RhoA. Biochem Biophys Res Commun. 2001; 280:798–805. [PubMed: 11162591]

Seo K, et al. Hyperactive Adverse Mechanical Stress Responses in Dystrophic Heart Are Coupled to Transient Receptor Potential Canonical 6 and Blocked by cGMP-Protein Kinase G Modulation. Circ Res. 2014; 114:823–32. [PubMed: 24449818]

Shah SJ, et al. Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap. Circulation. 2016; 134:73–90. [PubMed: 27358439]

Shan X, et al. Differential expression of PDE5 in failing and nonfailing human myocardium. Circ Heart Fail. 2012; 5:79–86. [PubMed: 22135403]

Shimizu-Albergine M, et al. cAMP-specific phosphodiesterases 8A and 8B, essential regulators of Leydig cell steroidogenesis. Mol Pharmacol. 2012; 81:556–66. [PubMed: 22232524]

Soderling SH, Bayuga SJ, Beavo JA. Identification and characterization of a novel family of cyclic nucleotide phosphodiesterases. J Biol Chem. 1998; 273:15553–8. [PubMed: 9624145]

Stelzer JE, Patel JR, Moss RL. Protein kinase A-mediated acceleration of the stretch activation response in murine skinned myocardium is eliminated by ablation of cMyBP-C. Circ.Res. 2006; 99:884–890. [PubMed: 16973906]

Sun B, et al. Role of phosphodiesterase type 3A and 3B in regulating platelet and cardiac function using subtype-selective knockout mice. Cell Signal. 2007; 19:1765–71. [PubMed: 17482796]

Surks HK, et al. Regulation of myosin phosphatase by a specific interaction with cGMP- dependent protein kinase Ialpha. Science. 1999; 286:1583–1587. [PubMed: 10567269]

Takimoto E, et al. cGMP catabolism by phosphodiesterase 5A regulates cardiac adrenergic stimulation by NOS3-dependent mechanism. Circ Res. 2005a; 96:100–109. [PubMed: 15576651]

Takimoto E, et al. cGMP catabolism by phosphodiesterase 5A regulates cardiac adrenergic stimulation by NOS3-dependent mechanism. Circ Res. 2005b; 96:100–9. [PubMed: 15576651]

Takimoto E, et al. Chronic inhibition of cyclic GMP phosphodiesterase 5A prevents and reverses cardiac hypertrophy. Nat Med. 2005c; 11:214–22. [PubMed: 15665834]

Takimoto E, et al. Regulator of G protein signaling 2 mediates cardiac compensation to pressure overload and antihypertrophic effects of PDE5 inhibition in mice. J Clin Invest. 2009; 119:408–20. [PubMed: 19127022]

Tokudome T, et al. Regulator of G-protein signaling subtype 4 mediates antihypertrophic effect of locally secreted natriuretic peptides in the heart. Circulation. 2008; 117:2329–39. [PubMed: 18443239]

Umar S, van der Laarse A. Nitric oxide and nitric oxide synthase isoforms in the normal, hypertrophic, and failing heart. Mol Cell Biochem. 2010; 333:191–201. [PubMed: 19618122]

van Heerebeek L, et al. Low myocardial protein kinase G activity in heart failure with preserved ejection fraction. Circulation. 2012; 126:830–9. [PubMed: 22806632]

Vandecasteele G, et al. Cyclic GMP regulation of the L-type Ca(2+) channel current in human atrial myocytes. J Physiol. 2001; 533:329–40. [PubMed: 11389195]

Vandeput F, et al. Cyclic nucleotide phosphodiesterase PDE1C1 in human cardiac myocytes. J Biol Chem. 2007; 282:32749–57. [PubMed: 17726023]

Vandeput F, et al. Selective regulation of cyclic nucleotide phosphodiesterase PDE3A isoforms. Proc Natl Acad Sci U S A. 2013; 110:19778–83. [PubMed: 24248367]

Verde I, et al. Characterization of the cyclic nucleotide phosphodiesterase subtypes involved in the regulation of the L-type Ca2+ current in rat ventricular myocytes. Br J Pharmacol. 1999; 127:65–74. [PubMed: 10369457]

Wang P, et al. Identification and characterization of a new human type 9 cGMP-specific phosphodiesterase splice variant (PDE9A5). Differential tissue distribution and subcellular localization of PDE9A variants. Gene. 2003; 314:15–27. [PubMed: 14527714]

Wechsler J, et al. Isoforms of cyclic nucleotide phosphodiesterase PDE3A in cardiac myocytes. J Biol Chem. 2002; 277:38072–8. [PubMed: 12154085]

Weishaar RE, et al. Subclasses of cyclic AMP-specific phosphodiesterase in left ventricular muscle and their involvement in regulating myocardial contractility. Circ Res. 1987; 61:539–47. [PubMed: 2820608]

Yamasaki R, et al. Protein kinase A phosphorylates titin's cardiac-specific N2B domain and reduces passive tension in rat cardiac myocytes. Circ.Res. 2002; 90:1181–1188. [PubMed: 12065321]

Yan C, et al. Activation of extracellular signal-regulated kinase 5 reduces cardiac apoptosis and dysfunction via inhibition of a phosphodiesterase 3A/inducible cAMP early repressor feedback loop. Circ Res. 2007; 100:510–519. [PubMed: 17272811]

Yanaka N, et al. cGMP-phosphodiesterase activity is up-regulated in response to pressure overload of rat ventricles. Biosci Biotechnol Biochem. 2003; 67:973–9. [PubMed: 12834273]

Zaccolo M, Pozzan T. Discrete microdomains with high concentration of cAMP in stimulated rat neonatal cardiac myocytes. Science. 2002; 295:1711–1715. [PubMed: 11872839]

Zaccolo M. cAMP signal transduction in the heart: understanding spatial control for the development of novel therapeutic strategies. Br J Pharmacol. 2009; 158:50–60. [PubMed: 19371331]

Zhang M, et al. Expression, activity, and pro-hypertrophic effects of PDE5A in cardiac myocytes. Cell Signal. 2008; 20:2231–6. [PubMed: 18790048]

Zhang M, et al. Myocardial remodeling is controlled by myocyte-targeted gene regulation of phosphodiesterase type 5. J Am Coll Cardiol. 2010; 56:2021–30. [PubMed: 20970280]

Zhao CY, Greenstein JL, Winslow RL. Roles of phosphodiesterases in the regulation of the cardiac cyclic nucleotide cross-talk signaling network. J Mol Cell Cardiol. 2016; 91:215–27. [PubMed: 26773602]

Zoccarato A, et al. Cardiac Hypertrophy Is Inhibited by a Local Pool of cAMP Regulated by Phosphodiesterase 2. Circ Res. 2015; 117:707–19. [PubMed: 26243800]

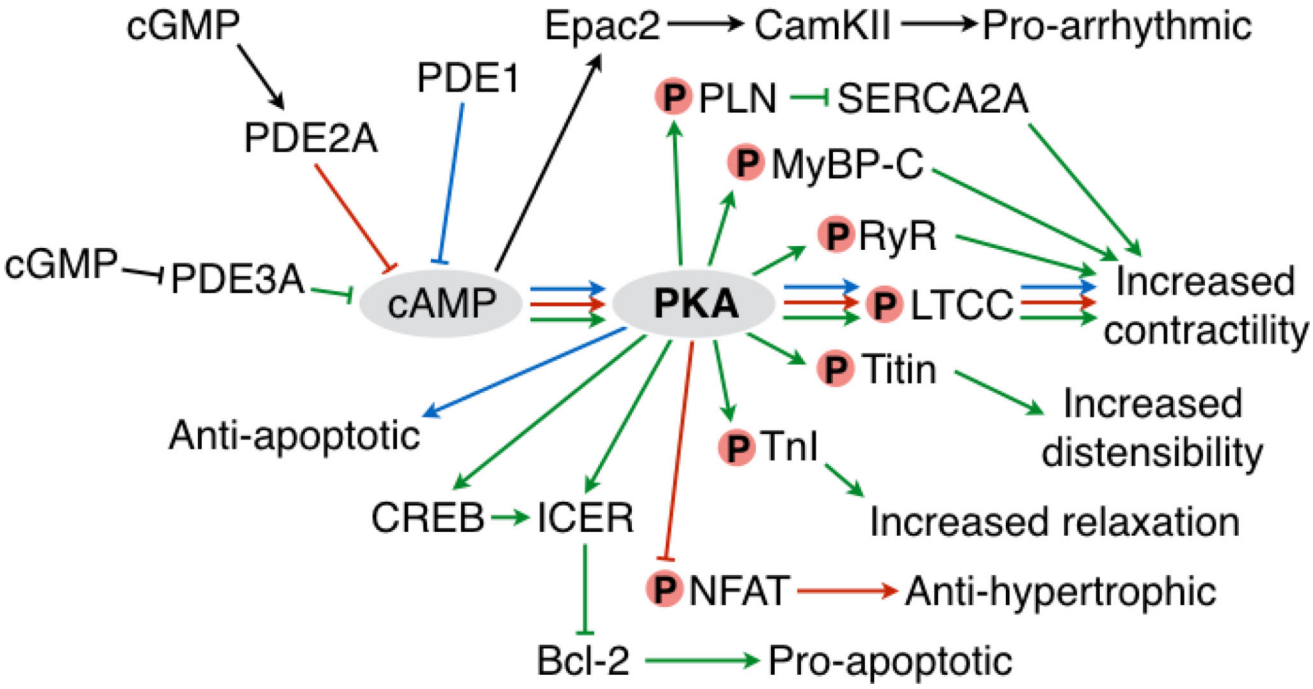

Figure 1.

Signaling pathways and their myocardial effects coupling PDE-cAMP modulation with the activation of protein kinase A, epac, and their downstream effectors. Pathways for which published data has defined a link between a given PDE and specific downstream effects have been color coded: PDE1 in blue, PDE2A in red, and PDE3A in green.

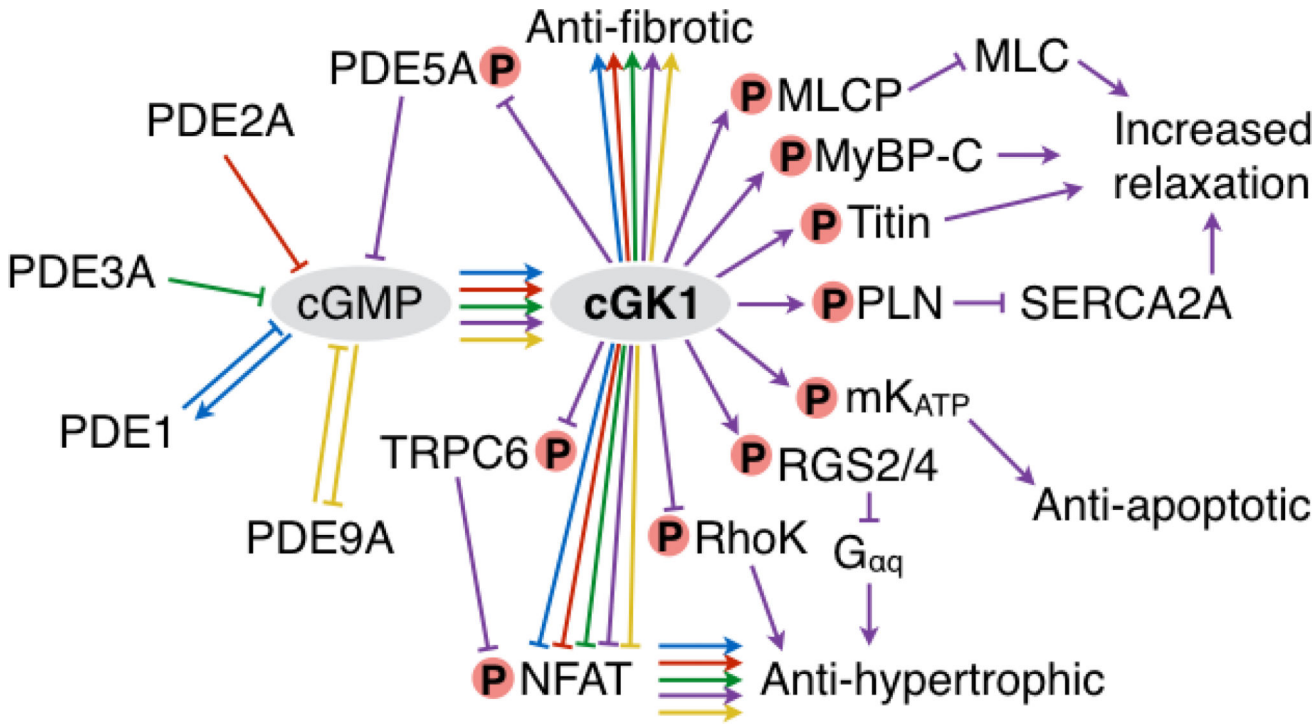

Figure 2.

Signaling pathways and their myocardial effects coupling PDE-cGMP modulation with cyclic GMP activated protein kinase (cGK1) and their downstream effects. Pathways that regulate cardiac cGMP signaling. Pathways for which published data has defined a link between a given PDE and specific downstream effects have been color coded: PDE1 in blue, PDE2A in red, and PDE5A in purple, and PDE9A in yellow.

Table 1

Specificity and Regulation of PDEs Expressed in Myocardium

PDE	Substrate	Regulator
1A*	cAMP/cGMP	Calcium/calmodulin activated
1B		
1C†		
2A	cAMP/cGMP	cGMP activated cAMP hydrolysis
3A‡	cAMP/cGMP	cGMP inhibited
3B		
5A	cGMP	cGMP activated
9A	cGMP	None known

* prominent isoform expressed in mouse and rat;

† prominent isoform in human, dog, rabbit;

‡ predominantly expressed myocardial isoform

Table 2

Pathologic Alterations in Myocardial PDE Expression (*In Vivo* Studies)

PDE Family	Change	Species	Cardiomyopathy	References
1A	Increased	Rat	Hypertrophy (aortic constriction)	Yanaka et al., 2003
		Human	Post-myocardial infarction	Miller et al., 2011
		Mouse	Hypertrophy (ISO, AII, , TAC)	Miller et al., 2009; Miller et al., 2011
		Rat	Isoproterenol-induced HCM	
2A	Increased	Rat	Hypertrophy (aortic constriction)	Yanaka et al., 2003
		Human	DCM, ICM, but not in AS	Mehel et al., 2013
		Dog	Pacing-induced HF	
		Rat	Isoproterenol-induced HCM	
3A	Decreased	Human	DCM	Ding et al, 2005
		Dog	Pacing-induced HF	Smith et al, 1997
5A	Increased	Human	DCM, ICM	Pokreisz et al., 2009; Lu et al., 2010; Shan et al., 2012; Nakano et al., 2016
		Human	RV hypertrophy, DCM, AS	Nagendran et al., 2007; Vandenwijngaert et al., 2013 Shan X et al, 2012
		Mouse	TAC-induced HCM	Lu et al., 2010; Vandenwijngaert et al., 2013
9A	Increased	Human	DCM, HF and AS	Lee et al., 2015
		Mouse	TAC-induced HCM	

ISO (isoproterenol); AII (angiotensin II); TAC (transaortic constriction); HCM (hypertrophic cardiomyopathy); DCM (dilated cardiomyopathy); ICM (ischemic cardiomyopathy); RV (right ventricle); AS (aortic stenosis); HF (heart failure)

Table 3

In Vivo Myocardial Effects Of Pharmacologic or Genetic PDE Interventions

PDE Family	Intervention	Model/Patient/ Clinical Trial	Outcome	References
1A	*Pre-clinical*			
	IC86340	Pressure-Overload (TAC) in mouse	Inhibition attenuated TAC_induced hypertrophy	Miller et al., 2009
	IC86340	Myocardial infarction in mouse	Inhibition reduced collagen deposition and myofibroblast formation	Miller et al., 2011
2A	*Pre-clinical*			
	--	Hypertrophy (stressor: isoprenaline) in rat	PDE2A upregulation; β-AR desensitization	Mehel et al., 2013
	BAY 60-7550	Pressure-Overload (TAC) in mouse	Inhibition attenuated hypertrophy and fibrosis	Zoccarato et al., 2015
3A	*Pre-clinical*			
	Genetic deletion	PDE3A$^{-/-}$ and 3B$^{-/-}$ mouse	Greater baseline heart rate in 3A$^{-/-}$ with normal contractility	Sun et al., 2007
	Genetic deletion	Ischemia in PDE3B$^{-/-}$ mouse	Protection against infarction	Chung et al., 2015
	Milrinone	PDE3A and PDE3B KO mice	PDE3A, but not 3B, associate with SERCA2A and phospholamban at the SR to mediate inotropic effects	Beca et al., 2013
	Milrinone	Myocardial infarction in PDE3A1 overexpressing mouse	Hypertrophic hearts with β-AR desensitization in transgenic hearts; inhibition attenuated the beneficial protection against infarction and apoptosis in overexpressing mouse	Oikawa et al., 2013
	Clinical			
	Milrinone	mild-to-moderate HF patients in sinus rhythm	Slight improvements in exercise tolerance; increased supraventricular arrhythmias and sinus tachycardia	di Bianco et al., 1989
	Milrinone	PROMISE trial	Long-term treatment did not improve cardiac function; instead increased mortality, hypotension, palpitations and syncope	Packer et al., 1991
	Milrinone	OPTIME-CHF	Short-term treatment did not shorten hospitalization or abate symptoms; new arrhythmias and significant hypotension	Cuffe et al., 2002
	Enoximone	ESSENTIAL trial	Long-term treatment with lowered dose did not improve cardiac function; no increased adverse effects	Metra et al., 2009
5A	*Pre-clinical*			
	Over-expression	Myocyte targeted PDE5A overexpressing mouse	Worsened cardiac hypertrophy and/or chamber dysfunction and dilation from pressure overload or myocardial infarction	Pokreisz et al., 2009; Zhang et al., 2010
	Sildenafil	TAC-induced HCM in WT, RGS2 KO, GFPdgn TG mouse	Treatment blunted hypertrophy and protected cardiac function in each respective mouse model	Takimoto et al., 2005a; Takimoto et al, 2009; Ranek et al., 2013
	Sildenafil	DMD mouse model	Treatment ameliorated and reversed depressed cardiac function	Adamo et al., 2010
	Sildenafil	Hypertensive mongrel dogs	Increase in LV diastolic capacitance; natriuretic peptide B (BNP) stimulation amplified this effect	Bishu et al., 2011

PDE Family	Intervention	Model/Patient/ Clinical Trial	Outcome	References
	Tadalafil	DMD dog model	One-month treatment slowed cardiac remodeling and dysfunction	Sweeney et al., 2013
	Sildenafil	DMD mouse model	Chronic treatment prevented DMD-associated hypertrophy and cardiac dysfunction	Seo et al., 2014
	Clinical			
	Sildenafil	DCM patients with PH	Three-months treatment enhanced cardiac output and V_{O2}, improving exercise capacity and quality of life	Lewis et al., 2007b
	Sildenafil	DCM patients	Three-months treatment improved LV function and exercise oscillatory ventilation	Murphy et al, 2008
	Sildenafil	Patients with LV diastolic dysfunction and PH	Mean pulmonary artery pressure lowered; RV function and LV relaxation improved	Guazzi et al., 2011
	Sildenafil	T2DM patients with diabetic CM	Mild improvements in cardiac strain and torsion	Giannetta et al., 2012
	Sildenafil	RELAX trial	Long-term treatment yielded no improvements	Redfield et al, 2013
	Udenafil	ULTIMATE trial	Exercise capacity and subjective functional capacity improved	Kim et al., 2015
	Sildenafil	DMD/BMD patients with cardiomyopathy	Six-months treatment worsened cardiac dilation	Leung et al., 2014
9A	*Pre-clinical*			
	Genetic deletion	Hypertrophy (stressor: TAC) in PDE9A$^{-/-}$ mouse	Protection against hypertrophy and fibrosis	Lee et al., 2015
	PF-04449613	TAC-induced HCM in mouse	Inhibition attenuated cardiac hypertrophy, remodeling and function	

TAC (transaortic constriction); KO (knock out) HCM (hypertrophic cardiomyopathy); RGS2 (regulator of G protein substrate 2); GFPdgn (green fluorescent protein degron CL1; a ubiquitin proteasome substrate); TG (transgenic); DMD (Duchenne muscular dystrophy) V_{O2} (maximal oxygen uptake); LV (left ventricle); RV (right ventricle); T2DM (type 2 diabetic mellitus);

Handb Exp Pharmacol. Author manuscript; available in PMC 2017 November 01.