Phosphodiesterases and Cyclic GMP Regulation in Heart Muscle

The cyclic nucleotide cGMP and its corresponding activated kinase cGK-1 serve as a counterbalance to acute and chronic myocardial stress. cGMP hydrolysis by several members of the phosphodiesterase (PDE) superfamily, PDE1, PDE2, and PDE5, regulate this signaling in the heart. This review details new insights regarding how these PDEs modulate cGMP and cGK-1 to influence heart function and chronic stress responses, and how their inhibition may provide potential therapeutic benefits.

Cyclic guanosine monophosphate (cGMP) is a critical second messenger molecule central to a broad array of intracellular functions. In the heart, cGMP regulates vascular tone, platelet function, cardiomyocyte contraction, mitochondrial function, and stress-response signaling (86). Cyclic GMP is synthesized by two distinct pathways; one involves soluble guanylyl cyclase (sGC) activated by nitric oxide (NO) and the other particulate guanylyl cyclase (pGC) coupled to natriuretic peptide (NP) receptors. Upon generation, cGMP has two primary targets. One is cGMP-dependent protein kinase (cGK-1), which signals both by phosphorylation of target substrates, and by protein-protein interactions (20). Alternatively, cGMP binds to and influences members of the phosphodiesterase (PDE) superfamily that regulate cyclic nucleotide hydrolysis to 5’ monophosphate forms (21). In the heart, the net effect of cGMP/cGK-1 stimulation is to blunt activation pathways, diminishing hypertrophy, fibrosis, cellular toxicity, and maladaptive remodeling (86).

Most of the research regarding the cardiac role of cGMP/cGK-1 signaling initially focused on the impact of stimulating cGMP synthesis. Clinical therapies were developed using NO donors (or organonitrates) or natriuretic peptides and became established as heart disease treatments. However, over the past decade, interest has turned to the PDEs that control cGMP degradation. Of the 11 members of the PDE superfamily, cardiac mRNA expression has been reported for 7, PDE1–5, PDE8a, and PDE9a (51, 96), with functional roles reported thus far for all but PDE9a. PDE5 is selective for cGMP, whereas PDE1 and PDE2 hydrolyze cAMP as well. PDE3 principally hydrolyzes cAMP but can be competitively inhibited by cGMP. PDE4 and PDE8 are selective for cAMP, whereas PDE9a is the most highly specific for cGMP.

Although discovered 30 years ago, the identities and relative role of cGMP-PDEs in the normal and diseased heart are only recently being revealed. PDE5 has garnered the most attention following the development of selective, orally bioavailable inhibitors, but PDE1 and PDE2 are also under study. This work has revealed cGMP-PDE-suppression of β-adrenergic stimulated contractility (6, 57, 73, 82) and amelioration of maladaptive cardiac remodeling induced by sustained pressure-overload (56, 83), ischemia/reperfusion or infarction (14, 38), doxorubicin toxicity (19, 34), and volume overload heart failure (31). In this review, we discuss myocardial regulatory effects of cGMP-PDEs and current efforts to translate these findings into new therapies for the treatment of heart failure.

PDE1: The Ca2+ Calmodulin-Dependent PDE

PDE1 was the first dual-substrate esterase identified, and its activity is potently stimulated by calcium (Ca2+)/calmodulin (CaM) (76). The PDE is encoded by three genes (PDE1a, 1b, and 1c) that exhibit species-dependent expression, and it has multiple splice variants varying in size from 50 to 90 kDa (21, 44). Myocyte PDE1c expression (the predominant human isoform) appears in a striated banding pattern co-localizing with desmin (z-disk) (89). PDE1 isoforms have a similar structure yet different regulatory properties, Ca2+ sensitivities, specific activities, and substrate affinities. The NH2 terminus contains Ca2+/CaM binding domains and phosphorylation regulatory sites (confirmed in some isoforms), and a conserved catalytic domain resides at the COOH terminus. Phosphorylation of PDE1A by protein kinase A or of PDE1B by CaM-dependent kinase II (CaMKII) decreases its sensitivity to Ca2+/CaM, inhibiting activation (75, 77).

Each of the three PDE1 isoforms have been linked to different biological processes and varying expression levels among mammalian species. Enhanced expression of PDE1A in vascular smooth muscle was shown as a mechanism for chronic tolerance to organonitrates (30), and this isoform also regulates cGMP hydrolysis in controlling...
smooth muscle tone (58). PDE1B is more important to neural/CNS function, such as memory and learning, and to immune modulation (64), whereas PDE1C regulates smooth muscle proliferation (68, 70). PDE1A and PDE1B both hydrolyze cGMP with higher affinity than cAMP (50, 58), whereas PDE1C hydrolyzes both cyclic nucleotides with similar affinity (17, 70). PDE1 expression and activity have been detected in normal heart and isolated myocytes from multiple species including human, mouse, rat, bovine, and canine (10, 42, 50, 89), with PDE1A expression predominating in mice and PDE1C dominant in humans (29, 89).

Due to the lack of selective inhibitors suitable for in vivo studies as well as the absence of PDE1A genetic loss-of-function models or any reported data from an existing PDE1C knockout mouse, little is known about the role of PDE1 in the intact heart. As a result, most existing data derives from in vitro studies (FIGURE 1). In 2009, Miller et al. (50) provided the first demonstration of a cardiac impact, showing PDE1A was upregulated in hypertrophied rat hearts and isolated cardiomyocytes (adult and neonatal cells). Inhibition of PDE1 with IC86340 (a proprietary compound) or by gene silencing of PDE1A blunted hypertrophy stimulation, an effect coupled to cGK1 activation. PDE1C expression was unaltered and PDE1B was nearly undetectable in these rodent cells. PDE1A was also shown to play a major role in cardiac myofibroblast function and extracellular matrix synthesis. Upregulation of PDE1A in rodent fibroblasts induces pathological fibrotic remodeling, linked to the regulation of unique pools of cAMP and cGMP in perinuclear and nuclear regions. Both cAMP-Epac1-Rap1 and cGMP-PKG signaling appear to be involved in PDE1A-mediated collagen regulation (49).

Human heart studies have identified PDE1C as the dominant species responsible for cGMP hydrolysis (54, 88, 89). However, these data derive from cell-free conditions that lack the normal

**FIGURE 1. Regulation of myocardial remodeling by PDE1A**
Calcium entry coupled to G-protein-coupled receptors (GPCR) activate a calmodulin (CaM) that in turn stimulates PDE1A to hydrolyze either cAMP or cGMP, the former coupled to β-adrenergic receptor-coupled signaling (β1/2-AR), the latter generated by either NO- or NP-activated guanylate cyclase. Hydrolysis of cAMP by PDE1A can impact myofibroblast formation and matrix synthesis by preventing its stimulation of Epac1 and Rap1. Hydrolysis of cGMP blunts the activation of PKG that in turn augments hypertrophic signaling [shown here coupled to Cm-activated kinase (CaMKII) and calcineurin (Cn)].
stoichiometry of cAMP/cGMP as well as localized cell compartmentation. Both factors could be very important since PDE1C has equal affinity for both cyclic nucleotides. Translation of these in vitro experiments to the intact heart remains to be performed.

PDE2: The cGMP Stimulated to Reduce cAMP

PDE2 is also a dual-substrate esterase, and although some studies have shown it can hydrolyze NP-stimulated cGMP in cardiac myocytes (8), most have described catalytic activity on cAMP that is enhanced by low levels of cGMP (3, 53, 79). This positions PDE2 as a regulator of cyclic nucleotide cross talk. PDE2 is encoded by a single gene, PDE2A, and expressed as three splice variants (PDE2A1–3). These differ in their NH2 terminus, which impacts subcellular localization [PDE2A1 is cytosolic, whereas PDE2A2 and PDE2A3 are membrane-associated (66)]. Crystal structure data identified two tandem cGMP-binding domains (GAF-A and GAF-B) in the NH2 terminus (26, 47). GAF-B is mainly involved with cGMP binding to allosterically and positively stimulate PDE2 cAMP hydrolysis via conformational changes (48, 93, 95). The full GAF-A/B domain appears to be involved with homodimerization (26, 62). PDE2 is expressed in cardiac tissue of various species, including human, rat, and bovine (80), and has been detected in rodent neonatal myocytes (53). Functional evidence using selective inhibitors has been reported in adult myocytes as well (8, 79). PDE2 is detected in the cytosol, plasma membrane, sarcoplasmic reticulum, Golgi, and nuclear membrane (4), and its substrate preference depends in part on this localization.

PDE2 can hydrolyze both cGMP and cAMP in cardiac myocytes, and this selectivity depends on the extent of co-activation. In adult cells without concomitant cAMP stimulation, inhibiting PDE2 raises cGMP at the plasma membrane as detected by a cGMP-sensitive ion channel. This regulation is observed when cGMP is generated by NP-rGC- but not NO-sGC-dependent signaling (8). However, PDE2 switches to cAMP hydrolysis in cells stimulated by β-adrenergic agonists (18, 53, 87). In this setting, cGMP co-generated by β3-AR-coupled NO-NOS activation binds to the GAF domain to enhance PDE2 hydrolysis of cAMP and thereby reduce the net contractile response to a β-agonist (53, 79) (FIGURE 2). Intriguingly, this same regulation is not observed in adult cells when cGMP is generated via NP stimulation (81), whereas it is detected with both cGMP-synthetic pathways in neonatal myocytes (79). This highlights compartmentation that develops with cell maturation.

Compartmentalized regulation of β-AR stimuli by PDE2 extends to protein kinase A (PKA) activation (79) (FIGURE 2). Myocytes have two PKA isoforms, with PKA-RII residing mainly in the particulate fraction and PKA-RI in the soluble fraction, and each have different distal targets and thus signaling impact. Isoproterenol preferentially activates PKA-RI over RI. If NO-sGC-cGMP is co-stimulated, cAMP-PKA-RII is blunted due to PDE2 activation, whereas PKA-RI increases as the cGMP competes for cAMP at the catalytic site of PDE3 in this same microdomain. However, if cGMP is generated via NP stimulation, only PKA-RI is influenced via the PDE2 mechanism. Whether this same compartmentalized regulation exists in adult myocytes and/or is altered by heart disease remains unknown.

As with PDE1, there is some evidence that PDE2 activity increases in heart disease. This has been demonstrated in rat ventricle subjected to pressure overload (94) or to angiotensin II-induced hypertrophy (52). However, PDE2 gene expression was unaltered in both conditions, suggesting posttranslational changes occurred. Although potent selective PDE2 inhibitors have been generated (e.g., BAY 60-7550), agents active in vivo or genetic gain and loss of function models remain lacking. Thus the role of PDE2 in cardiac physiology and disease is still largely unknown.

PDE5A: The cGMP-Activated, cGMP-Specific PDE

PDE5A was the first cGMP-selective PDE discovered and was initially detected in platelets, lung (11, 22), and vascular smooth muscle (45). This constellation and corresponding physiological effects led investigators to pursue a drug development program with the goal of treating hypertension and coronary artery disease. Sildenafil was the first selective inhibitor developed and clinically tested, and although the initial trials for these disorders revealed little efficacy, a now famous “side effect” was uncovered, and erectile dysfunction became the drug’s first therapeutic target. Nearly a decade later, PDE5A inhibition was approved for treating pulmonary hypertension. However, its role in the heart remained less certain, as early studies showed minimal PDE5A expression and/or effects in cardiac muscle or cells (12, 90). However, subsequent research in multiple models of heart disease revealed prominent effects from PDE5A inhibition, and this growing evidence has led to clinical trials in patients with heart failure.

PDE5A is encoded by a single gene expressed as three splice variants (PDE5A1–A3). These vary in their NH2 termini, although functional differences have not been identified. Expression in vascular smooth muscle is particularly robust in lung and corpus cavernosum, lower in systemic arteries, and...
much lower in the heart. Expression in cardiomyocytes in animals and humans has now been reported by multiple laboratories (19, 29, 43, 59, 63, 74, 82), and although levels are low in normal hearts, they can rise substantially with hypertrophy or cardiac failure (43, 59, 63, 74, 83). Importantly, the specificity of both immune-reactive PDE5A used for histological and protein assays, and the selectivity of enzyme targeting by inhibitors such as sildenafil are supported by gene-silencing studies (97). Enhanced expression of PDE5A in hypertrophic disease has been linked to oxidative stress (43), although the mechanism for this interaction has not been defined.

As was true for PDE2, PDE5A is posttranslationally activated by cGMP binding to GAF regulatory domains, but in this instance catalytic activity against cGMP is increased (7, 69). Cyclic GMP binds to GAF-A, and this further influences GAF-B, resulting in a confirmation change at the NH2 terminus stimulating catalytic activity (78, 92, 99). PDE5A is also phosphorylated by cGK-1 at serine 102 (human) (13), increasing the affinity of both the enzyme’s catalytic site and allosteric site for cGMP (13). Intriguingly, NO-coupled cGK-1 activation enhances PDE5A activity in adult cardiac myocytes, whereas NP-pGC-cGMP has no impact (7), indicating localized regulation. The negative feedback loop can turn into a positive loop in the presence of a competitive inhibitor such as sildenafil. This occurs since the binding affinity at the catalytic site is stimulated by rising cGMP and cGK-1 activity induced by PDE5 inhibition, but this now further enhances competitive binding for the false substrate rather than cGMP.

As is broadly true of cyclic nucleotide regulation, cardiomyocyte modulation by PDE5A is highly compartmentalized. Immunohistology has shown PDE5A normally localizes to the sarcomere z-disk (57, 82). In this location, it modifies a cGMP pool generated by sGC but not by pGC, and this pool can negatively regulate β-AR contractile stimulation (57, 73, 82). The mechanism for this involves sympathetic activation of cAMP and concomitant cGMP via a β3-AR-NOS3-sGC pathway. The latter results in cGK-1 phosphorylation of troponin I at S23 and S24 (and likely other sites), desensitizing the myofilaments to Ca2+ (40) (FIGURE 3). A slight

**FIGURE 2. Cross-talk regulation by myocyte PDE2**

PDE2 is a dual esterase, although most data have identified its hydrolysis of cAMP activated by cGMP. Without concomitant adrenergic stimulation, PDE2 can hydrolyze a cGMP pool coupled to natriuretic peptide receptor/particulare guanylate cyclase (NPR, pGC). However, in the presence of β-AR stimulation, cGMP activates PDE2 to reduce cAMP levels. The source of cGMP can be both via NPR- or NO/β3-AR-coupled pathways. When coupled to the latter, the regulated cAMP pool activates both PKARI and RII isoforms. When coupled to the former, the regulated pool only interacts with the PKARI isoform.
reduction of L-type calcium channel current may also occur (91). This capacity of sildenafil to acutely suppress β-AR stimulation was the first PDE5A-inhibitor behavior translated from rodent to human (6). However, PDE5A does not always maintain its sarcomeric localization but can take on a more diffuse distribution in the cytosol. This was first revealed in myocytes from dilated cardiomyopathic hearts (73) and also has been demonstrated in models in which NOS3 is either genetically deleted or pharmacologically inhibited (57, 82). When PDE5A migrates away from a sarcomeric localization, it no longer modulates acute β-AR stimulation. However, the change in localization is reversible, as revealed by studies in which NOS3 activity was reestablished (82) or bypassed by chronic direct sGC stimulation (57). The molecular mechanisms for PDE5A intracellular localization shifts, and the full extent of their functional consequences remains unknown.

**PDE5a as a Contributor to and Therapeutic Target for Heart Disease**

Evidence that PDE5A modulation plays an important role in myocardial disease has largely come from studies using selective small molecule inhibitors. Initial reports identified subacute effects on cardiac ischemic protection and a capacity to induce preconditioning (14, 38). A chronic impact was first demonstrated in a model of pressure-overload hypertrophy, where PDE5A inhibition both suppressed evolving disease and reversed preexisting hypertrophy, interstitial fibrosis, and chamber and myocyte dysfunction (43, 56, 83, 98). PDE5A inhibition has also been effective in treating

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**FIGURE 3. Regulation of myocyte stress-stimulation pathways by PDE5A**

LTCC, L-type calcium channel; TRPC, transient receptor potential canonical channel; Mito, mitochondria; K\textsubscript{ATP}, ATP-sensitive potassium channel; TnC, TnT, TnI, troponin C, T, and I, respectively; SR, sarcoplasmic reticulum; NFAT, nuclear factor of activated T-cells; MEF-2, myocyte enhancer factor 2; MAPK, mitogen activated kinase; RGS, regulator of G-protein signaling. See text for details.
dilated cardiomyopathy due to doxorubicin toxicity (19, 35) and sustained volume overload due to mitral regurgitation (31). Studies have also suggested a benefit in hearts of dystrophin-deficient mice (1), identifying a potential value for the treatment of patients with muscular dystrophy.

As noted, PDE5A expression and activity increase in experimental and human heart disease, and this could itself contribute to the disease by suppressing cGMP-dependent signaling. Several studies have tested this hypothesis. In one experiment, hearts with myocyte-targeted PDE5A overexpression were subjected to infarction, and the resulting pathological remodeling worsened (63). In a second report, Zhang et al. (98) investigated mice with cardiomyocyte-specific PDE5A expression controlled by a tetracycline-sensitive promoter. Animals with ~5× normal cardiac PDE5A activity had normal rest function; however, their response to pressure overload greatly worsened, displaying increased mortality, hypertrophy, fibrosis, and more failure. This was reversible by adding doxycycline to the drinking water to lower myocyte PDE5A expression and enhance cGK-1 activity. Intriguingly, manipulation of solely myocyte PDE5A (and thus cGK-1 activity) impacted interstitial fibrosis and TGF-β-related signaling, both rising as myocyte PDE5A activity increased and declining when it was suppressed. This highlights important cross talk between myocyte cGMP/cGK-1 signaling and matrix remodeling.

The mechanisms for PDE5A cardiac modulation are largely attributed to cGMP activation of cGK-1 (FIGURE 3). For example, stimulation of Gq-coupled signaling and of the calcineurin/NFAT pathway play an important role in pressure-overload disease, and cGK-1 can suppress both cascades. Binding and activation of regulator of G-coupled protein 2 and 4 (RGS2, RGS4) by cGK-1 (84, 85) inhibits Gq-coupled signaling by enhancing GTP dissociation from the activated subunit. Mice lacking RGS2 develop rapid and exacerbated heart failure and this response is insensitive to PDE5A inhibition despite induction of enhanced cGK-1 activity (84). Expression of a dominant negative RGS4 also blocks ANP-mediated anti-hypertrophic effects (85).

Cn/NFAT is another potent inducer of pathological remodeling. This pathway is activated in hearts subjected to pressure-overload and, in particular, those in which PDE5A expression increased (98), and blocked by small-molecule inhibitors of PDE5A (56). Recent studies identified cGK-1-mediated phosphorylation and consequent suppression of members of the transient receptor potential canonical (TRPC) channels as key regulators of this behavior (67). TRPC3 and TRPC6 are upregulated by pressure-overload hearts and traffic Ca²⁺ entry linked to CaM-Cn stimulation and subsequent NFAT activation (39). cGK-1 phosphorylation of TRPC6 (T70, S322) markedly suppresses channel conductance and its coupled activation of the NFAT pathway (33, 60). Last, studies suggest PDE5A inhibition also suppresses activation of CaMKII, PKCα, and Akt kinases (28, 56, 98), although the exact mechanisms remain unclear.

Another important group of cGK-1 targeted proteins regulates mitochondrial function and cell survival signaling, and these appear to underlie PDE5A inhibitor effects in ischemic myocardium (FIGURE 4). A major downstream cGK-1 target is extracellular-regulated kinase ERK1/2, which in turn inactivates GSK-3β to upregulate Bcl-2/Bax and counter apoptosis. Activated cGK-1 also stimulates mitochondrial K<sub>ATP</sub> channel opening and PKCε, which together lower oxidative stress (14–16). The latter is also linked to phosphorylation of phospholemman, a regulator of the Na⁺/K⁺-ATPase (46), and this may lower intracellular Na⁺ during reperfusion, thereby blunting mitochondrial damage. cGK-1 also phosphorylates RhoA to reduce activation of Rho-kinase and may also provide protection (9). Similar mechanisms are thought to underlie the beneficial effects of PDE5A inhibition against doxorubicin toxicity (19). Anti-apoptotic and anti-inflammatory effects from PDE5 inhibition were reported in rats with heart failure due to mitral regurgitation (31). In a novel application of this signaling, Hoke et al. used sildenafil or PDE5A gene silencing to precondition adipose-derived stem cells and showed their survival once transplanted into infarcted ventricular tissue was enhanced, as was recipient heart function and vascular density, while fibrosis declined (27).

In addition to troponin I, PDE5A-modulated cGK-1 can also modify the sarcomeric protein titin. Titin serves as a molecular spring and provides a major component of diastolic stiffness in the heart. Changes in its physical characteristics are thought to contribute to diastolic dysfunction in heart disease (37). cGK-1 phosphorylates titin and reduces its stiffness (36). Sildenafil and B-type NP enhance titin phosphorylation and LV compliance in canine heart failure (5). These data reflect acute modulation, and the chronic impact of such changes (as well as the previously described effect on TnI) remain to be determined.

Some Caveats Regarding PDE5A Regulation in the Stressed Heart

For changes in PDE5A expression/activity to impact the heart (or indeed any organ), there must be...
sufficient cGMP synthesis and relevant molecular targeting by cGK-1. This explains why there is minimal influence in the normal heart, where neither condition is met, but effects are observed in stress conditions. In this regard, the magnitude of stress plays an important role. Hearts subjected to mild pressure overload that do not trigger Cn or ERK1/2 pathways display negligible effects from PDE5A inhibition, whereas those with more severe stress and concomitant increases in these molecular pathways are favorably impacted (55).

Another intriguing feature of PDE5A myocardial effects is that current evidence indicates signaling for the LV may differ from the RV. Nagendran et al. (59) reported benefits on RV function from PDE5A inhibition, but surprisingly this was coupled to a rise in cAMP and PKA activity rather than cGMP or cGK-1. They proposed that PKA activation oc-

![Diagram](image)

**FIGURE 4.** Myocardial response cascades coupling PDE5A inhibition to cytoprotection and survival signaling in ischemia/reperfusion and doxorubicin toxicity

Inhibition of PDE5A triggers PKG activation, which in turn is linked to ERK1/2 activation, phosphorylation, and inactivation of GSK3β, which increased $K_{ATP}$ channel opening and suppressed opening of the MPTP. Anti-apoptotic effects are linked to co-activation of NOS isoforms and the protein Bcl-2. See text for details. ERK, extracellular response kinase; GSK-3β, glycogen synthase kinase 3β; Bcl-2, b-cell lymphoma 2; MPTP, mitochondrial permeability transition pore; PKC, protein kinase C; PLM, phospholemman.
curred from the rise in cGMP, which competitively inhibited PDE3. Two other studies tested chronic PDE5A inhibition in models of pulmonary artery constriction, and neither found a decline in hypertrophy, fibrosis, or other RV maladaptions (2, 72). Just why the RV may be so different from the LV remains a puzzle. However, to the extent to which similar signaling is activated, including cGK-1 stimulation, the kinases/phosphatases that cGK-1 modifies, and the compartmentation of this signaling, all remain to be determined. These questions are important, since PDE5A inhibitors are widely used to treat pulmonary hypertension, and direct effects on the RV could play an important role.

**Clinical Translation**

Unlike PDE1 and PDE2, chronic in vivo inhibitors against PDE5A exist, and this greatly facilitated rapid translation of experimental findings to clinical studies in patients with heart disease. Several single-center (n = ~50 patients), placebo-controlled studies have been reported, which tested the acute and chronic effects of sildenafil treatment in patients with dilated heart failure. These revealed benefits on peripheral blood flow, pulmonary ventilation, exercise capacity, and clinical symptoms (24, 25, 41). Recently, two trials reported benefits on both cardiac function and morphology due to chronic PDE5A inhibition. Guazzi et al. (25) found modest but significant improvement in systolic and diastolic function without evidence of systemic vasodilation in dilated cardiomyopathy patients treated with sildenafil for 1 year. In a second study, patients with chronic diabetes and mild hypertrophy showed improvement in LV mass-to-volume ratio, ventricular torsion, and reduced TGF-β activation (23). Multi-center studies of PDE5 inhibitors for heart disease have been initiated. The NIH RELAX trial is a randomized, placebo-controlled study of 225 patients with heart failure and a preserved ejection fraction testing the efficacy of sildenafil. Results should be available in late 2012. A second NIH trial, PITCH-HF, will start in 2012 and study 2,000 patients with dilated cardiomyopathy, testing the efficacy of tadalafil.

A second disease for which PDE5 inhibitors are currently being tested is muscular dystrophy from dystrophin mutations. In skeletal muscle, this disorder results in dislocalization of neuronal NOS from the plasma membrane, which is thought to limit vascular perfusion when motor demand increases (71). Preclinical studies showed potential benefit from PDE5A inhibition (1, 32), and several clinical trials are now testing this hypothesis. The REVERSE-DMD trial focuses on the heart and is testing sildenafil therapy in patients with Duchenne or Becker dystrophy (Clinicaltrials.gov: NCT01168908). Two other studies are testing tadalafil in both syndromes (NCT01070511, NCT01359670) and are focusing more on skeletal muscle function.

**What’s Next?**

A little over 10 years ago, a literature review of cGMP catabolism and the heart would have yielded remarkably few studies. In the brief period since, substantial interest has developed in this field; studies now support at least three PDEs, and potential repurposing of existing PDE5A inhibitors for heart failure is being clinically tested. Many questions remain. In particular, the in vivo role of PDE1 and PDE2 and whether these could be targeted safely to favorably impact heart disease remain to be determined. The regulators of cGMP-PDE compartmentation, the relative role played by different species, and how each are impacted by disease and treatments all require further study. Last, the list of relevant PDEs may not yet be complete. PDE9A is also highly selective for cGMP, and although it is expressed more in the brain and bladder (65), it is expressed in heart (61), and this increases in the preconditioned heart (65). Ongoing research should determine whether this PDE also plays a role in myocyte physiology and disease.

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