Old dog, new tricks: novel cardiac targets and stress regulation by protein kinase G

Peter P. Rainer1* and David A. Kass2

1Division of Cardiology, Medical University of Graz, Auenbruggerplatz 15, A-8036 Graz, Austria; and 2Division of Cardiology, Johns Hopkins Medical Institutions, Baltimore, MD, USA

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Abstract

The second messenger cyclic guanosine 3’5’ monophosphate (cGMP) and its downstream effector protein kinase G (PKG) have been discovered more than 40 years ago. In vessels, PKG1 induces smooth muscle relaxation in response to nitric oxide signalling and thus lowers systemic and pulmonary blood pressure. In platelets, PKG1 stimulation by cGMP inhibits activation and aggregation, and in experimental models of heart failure (HF), PKG1 activation by inhibiting cGMP degradation is protective. The net effect of the above-mentioned signalling is cardiovascular protection. Yet, while modulation of cGMP-PKG has entered clinical practice for treating pulmonary hypertension or erectile dysfunction, translation of promising studies in experimental HF to clinical success has failed thus far. With the advent of new technologies, novel mechanisms of PKG regulation, including mechanosensing, redox regulation, protein quality control, and cGMP degradation, have been discovered. These novel, non-canonical roles of PKG1 may help understand why clinical translation has disappointed thus far. Addressing them appears to be a requisite for future, successful translation of experimental studies to the clinical arena.

Keywords

Protein kinase G • cGMP-dependent protein kinase type 1 • Cardiac mechanosensing • Proteasome • Redox regulation • Phosphodiesterase

1. Introduction

Protein kinase G (PKG) is a major downstream effector of the nitric oxide (NO) and natriuretic peptide (NP) signalling pathways, each being linked to a respective guanylate cyclase (soluble—sGC, particulate—pGC) to generate cyclic guanosine 3’5’ monophosphate (cGMP), thereby activating the kinase (Figure 1). Levels of cGMP and thus PKG activation are also regulated by a select group of phosphodiesterases (PDEs) that control cGMP hydrolysis. This signalling system is highly compartmentalized, generating local pools of cGMP and indeed differential PKG activation which both shares and displays distinct signalling effects depending on how it was generated. In arterial smooth muscle, PKG1 activation induces relaxation and plays an important role in blood pressure regulation. In the heart, many studies have established its action as a brake on stress-response signalling. Much of this action relates to the capacity of PKG to suppress selective G-protein-coupled receptor agonism,1,2 phosphorylate proteins in the sarcomere,7,8,15 suppress transforming growth factor beta (TGFβ) cascades,13 and antagonize members of transient receptor potential cation channels.10,16,17 Recent work has expanded this list to include mechanosensing11 and protein quality control,3 and has revealed novel PDE regulators that illuminate the compartmental nature of this signalling.6 In addition, post-translational oxidation of the PKG1α isoform impairs its brake-like function, revealing a new mechanism whereby oxidative stress adversely impacts stress-response signalling.12 For this review, we have focused particularly on these recent findings. In addition, we discuss some of the continuing controversies that offer alternative perspectives on the role of cardiac PKG1α and its regulation by PDE5.

2. PKG regulation of transient receptor potential canonical channel 6: a new role in mechanosensing

In 2006, several studies established that members of the transient receptor potential canonical channel (TRPC) family of non-selective cation channels are involved in myocardial hypertrophy.18–21 TRPCs consist of six transmembrane domains with intracytoplasmic N- and C-termini, forming homo- or heterotetramers.22 TRPC subtypes can respond to intracellular calcium depletion (termed store-operated) and/or be coupled to G-protein-coupled receptor agonism through stimulation by diacylglycerol (DAG). Two family members in particular, TRPC3 and TRPC6, appear involved. Both are up-regulated in cardiac disease such as hypertrophy from pressure overload,10,23 and calcium entering through either channel has been linked to the activation of calcineurin-nuclear factor of activated T cells (NFAT) signalling.
Expression of dominant negative TRPC forms (3, 6, or 4) was protective against pathological cardiac stress. In 2012, Davis et al. further revealed that TRPC6 is pivotal to myofibroblast activation and thus scar formation in the heart and elsewhere. Expressing dominant negative channels may differ, however, from embryonic gene deletion, and indeed, slightly different results were reported in mice in which TRPC3 or TRPC6 was knocked out. In our work, we found that deletion of either channel alone did not suppress maladaptive hypertrophy from chronic pressure overload, whereas combined deletion was effective. Domes et al. found that deletion of TRPC3 but not TRPC6 blocked hypertrophy and fibrosis stimulated by angiotensin II (All), though this effect was lost in TRPC3/6 double-knockout (KO) animals. The cause for the differences between studies, or why co-deleting TRPC6 eliminated the protection observed by knocking out TRPC3 in the latter study, remains unclear. Both channels may form heterotetramers with each other and other TRP channels, so interaction may be one factor.

The reason we focus on these channels here is that both are phosphorylated by PKG in their N-terminus, which reduces channel conductance, and in the case of TRPC6, associated hypertrophy. Expression of dominant negative TRPC forms (3, 6, or 4) was protective against pathological cardiac stress. In 2012, Davis et al. further revealed that TRPC6 is pivotal to myofibroblast activation and thus scar formation in the heart and elsewhere. Expressing dominant negative channels may differ, however, from embryonic gene deletion, and indeed, slightly different results were reported in mice in which TRPC3 or TRPC6 was knocked out. In our work, we found that deletion of either channel alone did not suppress maladaptive hypertrophy from chronic pressure overload, whereas combined deletion was effective. Domes et al. found that deletion of TRPC3 but not TRPC6 blocked hypertrophy and fibrosis stimulated by angiotensin II (All), though this effect was lost in TRPC3/6 double-knockout (KO) animals. The cause for the differences between studies, or why co-deleting TRPC6 eliminated the protection observed by knocking out TRPC3 in the latter study, remains unclear. Both channels may form heterotetramers with each other and other TRP channels, so interaction may be one factor.

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myocyte hypertrophy was greater if TRPC6 was mutated so that it could not be phosphorylated at these sites, whereas phosphomimetic forms were protected.10  

More recently, this same signalling interaction between PKG and TRPC6 was discovered to play an important role in myocyte mechanosensing. Upon an acute rise in systolic myocardial load (for example increasing muscle or cell length, while allowing for systolic shortening against a fixed afterload—auxotonic contraction), cardiac muscle augments its developed force. The initial response, known as the Frank-Starling mechanism, is calcium independent and related to myofilament calcium sensitivity.30 PKG impacts this dependence by phosphorylation of troponin I (TnI) that desensitizes myofilaments to calcium,7,31,32 an effect that is most notable when beta-adrenergic co-stimulation is present. This is achieved primarily via the NO-sGC pathway, and by inhibiting PDE5A which targets cGMP generated by sGC.8 Models in which hearts express the skeletal isoform of TnI that lacks the S23, S24 PKG phosphorylation sites have confirmed their importance.7,8,31 PKG1α also modifies myocardial passive stiffness by phosphorylating titin in its spring region (N2B, N2BA).15 This may also impact contractile force. Lastly, recent evidence supports PKG modulation of myosin-binding protein C, and this likely influences the kinetics of myocardial contraction.34 PKG also impacts a calcium-dependent contractility response that occurs in myocardium subjected to a sustained afterload increase. This is historically known as the Anrep effect35 and has been linked to stretch-activated G-protein-coupled receptors such as the All type 1 receptor36 and subsequent mitogen-activated protein (MAP) kinase stimulation of the sodium—hydrogen exchanger (NHE-1).37 The latter then triggers reverse-mode sodium—calcium exchange (NCX)38 to increase cytosolic calcium.39–41 Other studies found that stretch-activated cation channels (SACs) are crucial and that this response is inhibited by blocking SACs using compounds such as gadolinium or the spider toxin GsMTx.42–44 In support of this, we found that PKG stimulation virtually eliminated loading stress-induced contractile responses, an effect that required expression of TRPC6.41 Myocytes and cardiac muscle lacking TRPC6 display a 30% decline in stress-stimulated contractility, whereas PKG stimulation alone reduced stress-stimulated contractility by ~90%. Intriguingly, genetic deletion of TRPC6 eliminated PKG modulation.41 In a mouse model of Duchenne muscular dystrophy, this mecano-stimulated response including force, calcium, and arrhythmia was largely increased. Selective TRPC3/6 antagonism or TRPC6 gene deletion restored this mecano-response to normal levels, and PKG activation fully blocked it.41

Few studies have yet examined the interplay between PKG modulation and TRPC3 or TRPC6 in vivo. Domes et al. used a rescue model, where PKG1 is deleted from all tissues except from smooth muscle, and found that this greatly amplified hypertrophy and fibrosis induced by All in mice that also lacked TRPC3/6. This was worse than with PKG1 deletion alone, so some interaction seems present.25,45 In contrast, Klaiber et al. found that mice lacking the NP-coupled guanylate cyclase (GC-A) in myocytes exhibited worse hypertrophy from All infusion, and this was ameliorated if TRPC3/6 genes were also deleted.46 From our work,11 the interaction of PKG on TRPC6 showed more potent mecano-modulatory effects than gene deletion of TRPC6 alone, so coupling to other channel subtypes with phosphorylated TRPC6 acting like a dominant negative seems likely.

TRPC1, another mechanosensitive channel, is also modified by PKG phosphorylation,47 resulting in inhibition of smooth muscle hyperpolarization. Whether this impacts cardiac mecano-sensing remains to be explored.

### 3. PKG and proteasomal function

Protein synthesis and degradation represent a finely tuned equilibrium. The removal of dysfunctional proteins prevents their accumulation and aggregation and concurrent cell damage.48 There are two main pathways for clearance of misfolded or aggregated proteins, the ubiquitin proteasome system (UPS) and autophagy. 

Ranek et al. found that overexpressing constitutively active PKG1α or activating PKG by PDE5 inhibition stimulates proteasome peptide activities and reduces misfolded and ubiquitinated protein accumulation. This was demonstrated in cultured neonatal rat ventricular myocytes (NRVMs) and a transgenic mouse model of desmin-related cardiomyopathy that exhibits intracellular protein aggregates (αB-crystalline812G05 overexpressors). Interestingly, the increase in proteolytic activity did not affect all known targets of the UPS but demonstrated substrate specificity. Evidence for PKG phosphorylation of proteasome subunits remains indirect, with data showing an acidic shift of the isoelectric points of 20S (β5) and 19S (Rpt6) proteasome subunits.3

In smooth muscle, stimulation with 8-bromo-cGMP decreases PKG1α (but not PKG1β) expression by inducing ubiquitination and degradation. PKG1 inhibition with the specific inhibitor DT-2 or mutation of the PKG1α autophosphorylation site serine 64 abolished this response, suggesting that PKG1 catalytic activity is required for this feedback loop.49

PKG also partakes in the endoplasmic reticulum stress response (ERSR). PDE5 inhibition with sildenafil reduced ER stress in isoproteenol-treated rats and pressure-overloaded (transverse aortic constriction—TAC) mice in a PKG-dependent manner.50 The mechanism remains uncertain. A similar effect was observed with vasonatrin, a synthetic chimera of atrial (ANP) and C-type natriuretic peptides (CNPs) in diabetic rats exposed to ischaemia/reperfusion. This was linked to a fall in the expression of the chaperone 78 kDa glucose-regulated protein (GRP78) and the transcription factor CCAAT/enhancer binding protein (CHOP). The protection was mimicked by cGMP stimulation and prevented by PKG inhibition. Silencing PKG1α in cardiomyoblast H9c2 cells exposed to hypoxia blunted protection from vasonatrin on ER stress, whereas overexpressing PKG1α did the opposite.51

### 4. Redox regulation of PKG localization and activity

Oxidant stress modifies many upstream components of the cGMP-PKG signalling pathway. NO synthase (NOS) oxidation induces enzyme uncoupling where less NO and more superoxide are generated,52 and oxidation of sGC reduces NO responsiveness.53 First described in vascular tissue, these oxidant targets play a role in myocyte pathophysiology as well.54,55

In 2007, Eaton et al. revealed that PKG1α itself is targeted by oxidation,54 proposing this as a cGMP-independent activation mechanism relevant to vascular smooth muscle hyperpolarization and vasorelaxation.57 Oxidation was shown to occur at cysteine 42 residues between the two homodimers in the N-terminus, just above the leucine zipper motif that mediates PKG1α dimerization, localization, and interaction with substrates.56,58–61 PKG1α responsiveness to H2O2, the direct transnitrosylating NO donor nitrocteyne,62 or H2S63 renders it a redox sensor. Oxidative activation through disulfide bond formation may
occur in the absence of cGMP; indeed, low levels of cGMP favour this modification. Increasing cGMP levels reduces H$_2$O$_2$-induced activation likely related to its impact on PKG N-terminus configuration that separates the C42 residues.

As mentioned, PKG1$\alpha$ oxidation facilitates microvascular dilation, regulating blood pressure in intact mice as revealed in animals harbouring a C42 serine substitution (redox-dead PKG1$\alpha$-C42S). These animals display blunted blood pressure reduction to nitroglycerine administration and are resistant to hypotension induced by septic shock. H$_2$O$_2$ promotes the translocation of PKG1$\alpha$ from the cytoplasm to the cell membrane where it phosphorylates membrane proteins. In smooth muscle (Figure 2A), this impacts large-conductance Ca$^{2+}$-activated potassium (BK$_{Ca}$) channels, resulting in PKG-dependent activation of hyperpolarizing K$^{+}$ currents and coronary vasodilation by H$_2$O$_2$.

In the normal heart, PKG1$\alpha$ oxidation is less present, but it increases in ischaemic heart disease in humans, and in canine and mouse models of heart failure (HF). However, whereas PKG1$\alpha$ oxidation is a gain of function in vessels, in the heart, it is a loss of function with respect to its capacity to counter pathological stress remodelling. C42S PKG1$\alpha$ knockin mice exposed to sustained pressure overload developed less hypertrophy and fibrosis. Membrane translocation of PKG1$\alpha$ upon G$\alpha_q$-protein or pressure-load stimulation is also observed in cardiomyocytes and has been proposed to enhance suppression of G$\alpha_q$-coupled signalling. When oxidized, however, PKG1$\alpha$ returns to the cytosol, reducing its effective targeting of membrane-localized contributors to the hypertrophic response. One example was its suppression of TRPC6-related signalling, which is reduced when PKG$\alpha$ oxidation is present (Figure 2B). In contrast, the permanently reduced form remained at the membrane where it displayed TRPC6 antagonism.

Another redox-dependent effect on PKG1$\alpha$ is S-guanylation (covalent adduction of cGMP) at cysteine 195. This occurs in the presence of 8-nitro-cGMP, a nitrated derivative of cGMP that is endogenously generated under conditions associated with excess reactive oxygen species (ROS) and NO production. The result is also activation of the kinase. Of note, ROS may also directly impact PKG effector molecules, such as TRPC6.

**Figure 2** Oxidative regulation of PKG in smooth and cardiac muscle cells. In smooth muscle cells, oxidant activation of PKG (cysteine 42 disulfide formation) induces PKG translocation to the cell membrane where it phosphorylates Ca$^{2+}$-activated potassium channels (BK$_{Ca}$) and induces hyperpolarization and vasorelaxation. Preventing oxidant PKG activation by substituting cysteine 42 with serine (C42S, redox-dead PKG) impairs this process. cGMP activation of PKG is still present; however, it appears that oxidant and cGMP activation impede each other (NTG: nitroglycerine). In contrast, in cardiomyocytes, oxidant activation of PKG is still present; however, it appears that oxidant and cGMP activation impede each other (NTG: nitroglycerine). In contrast, in cardiomyocytes, oxidant activation of PKG, such as happens with neurohumoral activation (G$\alpha_q$) or pressure overload (TAC) retains oxidized PKG (PKG$\alpha$ox) in the cytosol. Redox-dead PKG$\alpha$C42S, which may still be activated by cGMP, localizes to the cell membrane where it attenuates TRPC6-related calcium entry and associated maladaptive signalling.
5. Enhancing the myocardial stress response by inhibiting PDE9 vs. PDE5: new approaches for treating heart disease

Cyclic AMP- and GMP-degrading PDEs consist of 21 genes and are grouped into 11 gene families according to their substrate affinity, selectivity, and regulation. They degrade cyclic nucleotides by hydrolysing them to their 5’-monophosphate form. PDEs either hydrolyse cAMP (PDEs 4, 7, 8), cGMP (PDEs 5, 6, 9), cAMP cGMP-sensitively (PDEs 3, 10), or both cAMP and cGMP (PDEs 1, 2, 11).71,72 These major species are further modified by alternative splicing to yield over 100 different isoforms and reside in specific microdomains to confer fine-tuned cyclic nucleotide signalling and target specificity.72

Of the three cGMP-selective PDEs, PDE5, PDE6, and PDE9, only the first and last are thought to be expressed in the heart. PDE5 was the first cGMP-selective enzyme discovered, and its inhibition has provided successful clinical therapy for erectile dysfunction and pulmonary hypertension.73,74 Although many investigations find PDE5 expressed in the myocardium with amplified expression in forms of cardiac disease such as hypertrophy and dilated HF,75,76 not all studies have observed this. Indeed, controversies with respect to the amount and functional impact of PDE5 in the myocardium endure.45,77–79 The growing body of data in adult myocytes and hearts, using genetic PDE5 deletion as well as small molecule inhibitors, however, clearly supports its role.

In the effort to explore cardiac PDE5 regulation, some studies have questioned the role of PKG1a, too.5,80 These reports used a rescue mouse model, in which PKG1α is re-expressed in vascular smooth muscle, while otherwise globally deleted. The model improves the severe early mortality of the global KO81 but still has 50% mortality at 1 year.82 This may be important as two alternative models that do not display such a severe underlying phenotype have confirmed PKG1α’s role in the heart. In one study, PDE5A was overexpressed solely in myocytes to block PKG activation, revealing exacerbated disease after pressure overload or infarction.83 In another study, PDE5A gene expression was reversible (tetracycline-sensitive promoter), and this led to enhanced PKG activity and improvement of pre-established disease.84 Frantz et al. used another approach with sGC1 (PKG1α and 1β) selectively knocked out in cardiac myocytes only.85 This resulted in worsened maladaptive responses to AII and pressure-overload stimulation.

Animal models of heart disease ranging from muscular dystrophies,11,86–88 pressure-overload hypertrophy,84,89 ischaemia/infarction,90–92 and doxorubicin cardiotoxicity,93,94 have reported amelioration of myocardial disease from PDE5 inhibition and cardioprotection by PKG94,95 (for review96). Efforts at human translation continue, and single-centre trials support chronic treatment that improves clinical status, cardiac morphology and function, and exercise capacity in HF patients with depressed systolic function and concomitant pulmonary hypertension.97–99 PDE5 inhibition was not useful, however, in the only reported multicentre trial to test PDE5 inhibition in human HF. This trial focused on HF with preserved ejection fraction (HFpEF), the form of disease where the ejection fraction (EF) is in a normal range.100 In HFpEF, both myocardial cGMP and corresponding PKG activity appear to be very low.101 So, unless PDE5 up-regulation was responsible for low cGMP levels, an inhibitor is unlikely to help. To date, there are no data showing that PDE5 is up-regulated in patients studied in this trial, many of which had normal blood pressure, no ventricular hypertrophy, and even mild diastolic disease. In a follow-up subgroup analysis, Borlaug et al. reported that PDE5 inhibition might have depressed left ventricular function and limited exercise reserve.102 This study, however, was too small to make definitive conclusions, and there was no significant difference in exercise capacity between groups. It is possible that anti-adrenergic effects of sildenafil as observed in normal healthy subjects103 or prior animal models104,105 play a role.

Two additional under-powered single-centre studies in Duchenne and Becker muscular dystrophies did not show benefits from PDE5 inhibition despite prior encouraging animal data.106,107 Overly advanced cardiomyopathy in the former and absence of heart disease in the latter may explain these findings.

While there are many potential reasons for the difficulty in translating PDE5 inhibition benefit, one that has become a prominent focus is the requirement for NO-sGC-derived cGMP for PDE5 regulation to be effective.108,109 The same diseases studied have abnormal NO signalling and might impact the efficacy of this approach. Earlier studies established the requirement for NOS3 and consequent cGMP synthesis for PDE5 inhibition to blunt beta-adrenergic inotropy.103–105 NOS3 knockout mice or mice with NOs inhibited (L-NAME) do not display anti-adrenergic effects with sildenafil.105 In myocytes, in which cGMP signals at the membrane or cytosol were detected, PDE5 inhibition did not augment cGMP content generated by NP stimulation at the plasma membrane but did increase cGMP stimulated by an NO donor.109

Another example where NO-dependent signalling is compromised and in turn limits the efficacy of PDE5 inhibition as a counter-stress brake is females that lack sex hormones. Female mice with either a Goxv-over-expression genotype or subjected to sustained pressure overload developed cardiac dysfunction and hypertrophy. This was ameliorated by co-administration of a PDE5 inhibitor. However, if they underwent ovariectomy, the benefit from PDE5 inhibition was completely lost and recovered by treatment with exogenous oestrogen. This signalling couples oestrogen to NO-cGMP stimulation and again reveals the tight link between NO-cGMP and PDE5 modulation.110

All these data led to an important question: Is there a way to modulate cGMP signalling by a PDE that does not depend on its synthesis by the NO-sGC pathway? The alternative synthetic path is coupled to NP receptors. Prior work had highlighted PDE2 as a potential NP-targeting PDE.109,111 However, in vivo, the data on PDE2 have shown that it primarily modulates cAMP levels, being stimulated by cGMP to do so.112–114 Another possibility is PDE1, a Ca2+-calmodulin (CaM)-activated PDE that hydrolyses both cAMP and cGMP.115,116 Data for its role in the heart remain limited; however,115 and a selective impact on cGMP is uncertain.

There is another PDE that was known to be highly selective for cGMP—namely PDE9A. PDE9 was discovered in the late 1990s, and its expression is found not only in the brain, gut, and kidneys but also in the heart.118 It has the highest selectivity for cGMP over cAMP.118,119 PDE9A protein expression is found in both human and mouse myocardium with extremely low levels of expression in the normal state, but with elevated expression in disease conditions. Notably, in human HFpEF and HF with reduced ejection fraction (HFrEF), expression is increased.6 Both genetic and pharmacologic inhibition of PDE9A suppressed experimental hypertrophic heart disease, fibrosis, and dysfunction induced by sustained pressure overload. It also blunted hypertrophic signalling cascades in isolated myocytes subjected to endothelin or phenylephrine stimulation.
The particularly intriguing aspect of PDE9A is that it targets cGMP generated by the NP pathway but is largely insensitive to cGMP produced by sGC. This meant that intact mice with NOS inhibited by L-NAME provided in the drinking water were still susceptible to improvement of pressure-overload stress by PDE9A inhibition, whereas PDE5A inhibition did not provide benefit under these conditions. In addition, phospho-kinome analysis by mass spectrometry and transcription factor analysis revealed that suppression of PDE9A or PDE5A yields distinctive molecular footprints, indicating that these are not redundant pathways, but individualistic—sharing some but also exhibiting different downstream targets (Figure 1). They are localized to different regions of the muscle cell—PDE5A at the z-disc, and PDE9A at the T-tubular membrane, and this likely contributes to these compartmentalized signalling effects.

6. Concluding remarks

Knowledge about cGMP-PKG signalling has vastly expanded since the discovery of cGMP and PKG in the late 1960s. Despite the exponential increase in knowledge and the unravelling of detailed signalling properties, translation of successful experimental studies into efficacious clinical HF therapies has failed thus far. With discovering new layers of complexity and PKG regulation, such as signalling in intra-cellular microdomains, redox regulation, and cGMP degradation, we gain some insight into why these studies may have failed. The NO/sGC, NP/pGC – cGMP – PDE5/9 molecules are all druggable and potentially excellent candidates for therapeutic interventions. Many pharmacologic compounds targeting this signalling are already in clinical development, so we can reasonably expect that new therapeutic compounds will be available in the next decade.

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References


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