The Role of cGMP-Dependent Protein Kinase in Controlling Cardiomyocyte cGMP

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The role of cGMP as a second messenger in physiological and pathophysiological processes is widely appreciated.\(^1\)\(^–\)\(^3\) The successes of drugs that target the cGMP-signaling pathway (nitrovasodilators and PDE5 inhibitors [sildenafil, tadalafl, vardenafil]) have inspired interest in other cardiovascular benefits that might derive from a better understanding of this pathway.\(^2\)\(^–\)\(^4\)\(^–\)\(^7\) Elevation of cGMP in cardiomyocytes or intact heart is associated with a negative inotropic effect,\(^8\) blunting and/or reversal of cardiac hypertrophy,\(^9\) protection against ischemia/reperfusion injury,\(^4\)\(^–\)\(^7\) and changes in apoptosis.\(^9\)\(^,\)\(^10\) Activation of the cGMP-dependent protein kinase (PKG)I and phosphorylation of target proteins is involved in each of these processes, although the precise mechanisms that bring about these effects are not fully understood.\(^1\)\(^,\)\(^2\) cGMP activation of PKG in cardiomyocytes lowers cellular calcium, which can reduce contractility and counter calcium- and/or mediated dephosphorylation/activation/nuclear translocation of NFAT (nuclear factor of activated T cells), which promotes expression of a cadre of prohypertrophic genes.\(^2\)\(^–\)\(^5\)\(^,\)\(^6\) PKG-mediated phosphorylation of an unknown protein increases opening of mitochondrial \(K^+\)/ATP channels, thereby diminishing damages resulting from ischemia/reperfusion or myocardial infarction.\(^11\)\(^,\)\(^12\) Moreover, cGMP elevation suppresses \(\beta\)-adrenergic signaling in the heart and is associated with activation of PKG phosphorylation of troponin (TnI).\(^8\)\(^,\)\(^13\)\(^,\)\(^14\) PKG activation increases the GTPase activity of RGS2 (regulator of G protein–coupled signaling proteins), which rapidly hydrolyzes cGMP and phosphorylates/activates PDE5 (PDE)5, whereas PDE5 action limits the cytosolic cGMP pool near the plasma membrane and activated by ANP, and the cytosolic NO-stimulated GC (NO-GC).\(^16\)\(^,\)\(^17\)\(^,\)\(^19\) Fischmeister and colleagues have previously shown that the members of PKG target of PKG that elicits this effect is unknown. Notably, this is the first feed-forward effect to be defined for cGMP synthesis and breakdown in cardiomyocytes. cGMP pools are indicated by the oval and hexagon containing cGMP-signaling proteins. Dotted boundaries indicate that these pools are restricted but not impermeable; surrounding question marks indicate that spatial dimensions of the pools are poorly understood. ANP activation of pGC increases cGMP production in the subsarcolemmal region, resulting in PKG activation. The activated PKG acts on ANP-activated pGC to increase cGMP synthesis (++) and generate feed-forward regulation. Diamond with a question mark indicates that the target of PKG could be a protein that influences pGC activity and/or ANP sensitivity. Interactions that localize PDE2 to this region are unknown and indicated by the approximated black octagon. NO activation of the NO-GC increases cGMP synthesis in the cytosolic pool; PKG activated by the increase in cGMP phosphorylates/activates PDE5 (+ + +), which rapidly hydrolyzes cGMP, resulting in negative-feedback regulation of cGMP in this pool.

Several groups have provided evidence for spatially and functionally distinct cellular pools of cGMP.\(^16\)\(^,\)\(^17\) In this issue of Circulation Research, Castro et al document surprising new complexities involved in modulating cGMP level in cardiomyocytes in response to atrial natriuretic peptide (ANP) or nitric oxide (NO).\(^18\) Distinct cGMP pools are generated by action of the particulate guanylyl cyclase (pGC), which is located on the plasma membrane and activated by ANP, and the cytosolic NO-stimulated GC (NO-GC).\(^16\)\(^,\)\(^17\)\(^,\)\(^19\) The report by Castro et al demonstrates that PKG activation in response to ANP activation of pGC elicits a strong feed-forward mechanism that further enhances cGMP production in the subsarcolemmal pool (Figure).\(^16\)\(^,\)\(^20\) The biological effects of both pools are apparently mediated by activation of PKGI.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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Figure. Diagram depicting effect of activation of PKG on cGMP synthesis and breakdown in cardiomyocytes. cGMP pools are indicated by the oval and hexagon containing cGMP-signaling proteins. Dotted boundaries indicate that these pools are restricted but not impermeable; surrounding question marks indicate that spatial dimensions of the pools are poorly understood. ANP activation of pGC increases cGMP production in the subsarcolemmal region, resulting in PKG activation. The activated PKG acts on ANP-activated pGC to increase cGMP synthesis (++) and generate feed-forward regulation. Diamond with a question mark indicates that the target of PKG could be a protein that influences pGC activity and/or ANP sensitivity. Interactions that localize PDE2 to this region are unknown and indicated by the approximated black octagon. NO activation of the NO-GC increases cGMP synthesis in the cytosolic pool; PKG activated by the increase in cGMP phosphorlates/activates PDE5 (+ + +), which rapidly hydrolyzes cGMP, resulting in negative-feedback regulation of cGMP in this pool.
feedback regulation of cytosolic cGMP; this is mediated by activation of PKG, which phosphorylates and activates PDE5. The resulting increased cGMP breakdown blunts further elevation of cGMP and lowers cytosolic cGMP. In the absence of PDE inhibitors, there is modest increase in cGMP in response to NO. Allosteric cGMP binding in PDE5 and phosphorylation by PKG increase catalytic activity and are important in negative-feedback regulation of cGMP in several tissues.1,21,22 Surprisingly, in the present report, only a role for PDE5 phosphorylation is indicated.18 Allosteric cGMP binding in PDE5 increases the rate of phosphorylation by PKG but is not required for phosphorylation or PDE5 activation.18 However, the allosteric site has higher affinity for cGMP than does the catalytic site; presumably, both sites on a PDE5 molecule would bind nearby cGMP based on their respective affinities for cGMP. However, there may be unknown influences that impact PDE5 regulatory mechanisms in intact cells. By all accounts, PDE5 in cardiomyocytes is very low and localized to z-bands;2,5 this localization is sensitive to PKGI action and sustained NO-GC activity, which would be predicted to foster allosteric cGMP binding by PDE5, as well as phosphorylation by PKGI. Curiously, it appears that the cytosolic cGMP pool in cardiomyocytes is confined by PDE5, which is low in abundance and not free to diffuse in that pool. The results reported by Castro et al18 provide exciting insights into the contrasting mechanisms controlling cGMP signaling in the heart, but there is still controversy in the field regarding the effects of PKGI and PDE5 in cardiomyocytes.23–25 The conflicting results could have several explanations. However, compelling results from numerous studies (including the present study) support a role for cGMP and PKG action in cardiac function.

These new findings18 raise many questions regarding cGMP signaling in the heart and use of therapies that target this pathway. Although the GCs and PDEs that define cellular cGMP pools are confined to particular regions, the localization of PKG is unclear. Are PKGs that mediate the effects in these regions persistently localized therein or recruited following cGMP elevation? What mechanism provides for PKG localization/recruitment? Is the same PKGI isoenzyme involved in each pool? PKGα and PKGIβ differ in affinity for cGMP, as well as in substrates in some instances, which could influence signaling.1,26 What is the role of the relatively abundant PDE1, which participates in controlling cGMP levels in some region of the cardiomyocyte and effects biologically meaningful changes? How is pGC activated by PKG, and what mechanism provides for termination of this feed-forward process? What is the role of PKGI, PDE5, and cGMP signaling in normal cardiomyocytes because there are minimal effects on cardiac function when PKGI is absent or when PDE5 is blocked in individuals taking PDE5-selective inhibitors.26,29 Acute effects of PDE5 inhibition in cardiomyocytes and in studies using mice and humans are modest.11 Will chronic use of PDE5 inhibitors alter regulation of the cGMP pools and/or roles of PDEs 1, 2, and 5 in cardiac functions? If cGMP signaling is primarily cardioprotective against stressors, eg, ischemia/reperfusion or pressure overload, how is this regulated? Lastly, species differences in proteins involved in signaling pathways and changes that occur when cells are cultured present a challenge to extrapolating findings to functions in human tissues. However, this elegant piece of work by Castro et al provides a significant advance in understanding cGMP signaling and opens new avenues for investigation of this complex pathway.

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References


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