Regression of Cardiac Hypertrophy by Cyclic Guanosine Monophosphate-Dependent Protein Kinase Signaling

Are Myocytes Active Sources or Mere Beneficiaries?*

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Left ventricular hypertrophy (LVH) in response to elevated systemic pressure forms an adaptive mechanism that allows the heart to maintain cardiac output in the face of external stress. However, because hypertrophy is associated with complex electrophysiological, structural, molecular, mechanical, and metabolic remodeling (1,2), it ultimately becomes a leading risk factor for heart failure, arrhythmias, and sudden cardiac death.

Current treatment options for patients with hypertension or pressure overload LVH center upon load reduction by using various pharmacological agents, including diuretics, angiotensin-converting enzyme inhibitors, and angiotensin II receptor antagonists, as well as beta-adrenergic receptor and calcium-channel blockers. Despite the widespread availability and clinical use of these agents, the incidence of LVH remains unacceptably high. The clear unmet need to suppress or even reverse the pathological remodeling associated with LVH has prompted researchers to develop and test alternative approaches that target mechanistic effectors of the disease within cardiomyocytes instead of focusing on modulating pre-load and afterload. In recent years, a wealth of information has been generated regarding the complex molecular signaling cascades and feedback mechanisms that underlie LVH progression and regression. Importantly, various endogenous negative regulators of hypertrophy have been identified, raising the possibility for more mechanistic approaches for the treatment of LVH by selectively targeting native molecules in a tissue-specific manner. In this issue of the Journal, Zhang et al. (3) provide highly compelling evidence of the potential to target myocyte-specific phosphodiesterase type 5 (PDE5) expression in order to modulate the cardiac hypertrophic response to pressure overload.

PDE5-mediated signaling as a therapeutic target for LVH. Several endogenous molecules have been shown to mediate the progression or regression of cardiac hypertrophy by either activating or repressing complex signaling cascades within cardiac myocytes (4–6). Of interest is the cyclic guanosine monophosphate (cGMP) signaling pathway, which has emerged as a promising target for anti-hypertrophic interventions. cGMP is the second messenger for membrane-bound guanylate cyclase receptors, which play a central role in cardiovascular regulation and function. cGMP production in multiple cell types can be readily stimulated by inhibiting PDE levels. Notably, PDE5 inhibitors, such as sildenafil, which promote nitric oxide production and smooth muscle relaxation, are highly effective in treating erectile dysfunction. A major downstream effector of cGMP signaling in cardiomyocytes is cGMP-dependent protein kinase G (PKG), which phosphorylates several downstream targets that profoundly affect cellular function. In recent years, various investigators have shown that PDE5 is expressed in cardiomyocytes and can indeed regulate PKG activity, raising the possibility that sildenafil may have important cardiac benefits as well. Indeed, the effectiveness of sildenafil for treating cardiovascular disorders including ischemia-reperfusion injury, doxorubicin toxicity, and LVH was later demonstrated in a series of studies by multiple groups (7–11). These rodent and pre-clinical studies provided the impetus for initiating a multicenter National Institutes of Health–sponsored clinical trial designed to test the effectiveness of PDE5 inhibition in patients with heart failure and a preserved ejection fraction. Despite this impressive progress, the basic biology and mechanisms underlying the PDE5/cGMP/PKG signaling cascade that promotes or suppresses hypertrophic remodeling remains somewhat unclear, mainly because of the fairly nonspecific nature of the pharmacological tools used in these studies. For example, concentration levels of sildenafil that effectively reverse LVH inhibit multiple PDE isotypes, including PDE1, which is also highly expressed in the myocardium. More importantly, a recent report by Lukowski et al. (12) raised important doubts regarding the molecular basis of sildenafil-mediated LVH regression by suggesting nonmyocyte targets that are independent of PKG signaling and that may affect mitochondrial function.

Are myocyte sources or targets of PDE5 mediated anti-LVH signaling? As mentioned, the controversy regarding the mechanistic basis of LVH regression by sildenafil was...
recently fueled by the elegant findings of Lukowski et al. (12) who used transgenic mouse models to test the effects of global PKG deletion as well as myocyte-specific PKG expression in the context of global gene silencing on the cardiac response to stress. Their findings that myocyte PKG levels (or lack thereof) did not affect stress-induced disease progression prompted them to conclude that the anti-hypertrophic response afforded by sildenafil was mediated by other, as-yet-undefined targets, which require further investigation (12). Zhang et al. (3) present a highly compelling counterargument in favor of myocyte-specific PKG as an active source of LVH remodeling and regression by taking a direct approach for the investigation of the molecular basis of sildenafil treatment. Specifically, these authors created transgenic murine models that closely mimicked the bidirectional changes in myocardial PDE5 activity levels observed in patients before and after chronic treatment with sildenafil. This genetic approach allowed them to directly investigate the role of physiologically relevant PDE5 expression levels in myocytes while avoiding the confounding limitations associated with global gene deletion strategies. Indeed, these authors found that enhancement of myocyte PDE5 expression levels suppressed PKG activation and worsened the cardiac response to pressure overload at the organ, cellular, and molecular levels. Subsequent gene-targeted down-regulation of myocyte PDE5 levels after the development of pressure overload LVH effectively reversed cardiac dysfunction and associated remodeling.

**Therapeutic implications: what does the future hold?**

The report by Zhang et al. (3) offers several important insights into the mechanisms underlying LVH progression and regression by focusing on a key cell signaling pathway. In doing so, these authors elegantly demonstrate how pre-clinical and clinical studies not only benefit from but also inform basic studies, which can then be designed to explore novel strategies for treating multiorgan disorders, such as LVH and heart failure. In this case, Zhang et al. (3) targeted the PDE5/cGMP/PKG signaling cascade in order to reverse cardiovascular dysfunction. In a “tour-de-force” study, the authors confirmed the importance of intrinsic myocyte-specific PKG levels in modulating the cardiac response to stress. Their study further illustrates the importance of understanding the limitations and advantages of using transgenic mouse models that artificially alter the expression levels of a target gene, often with “toxic” consequences. Indeed, the present report highlights the need for achieving a comprehensive understanding of the complex signaling cascades that mediate disease progression/regression within the context of physiologically relevant alterations in the expression levels of target molecules. In a sense, we have come full circle, as the “side effects” of an initial, disappointing attempt to treat angina pectoris using PDE5 inhibitors served as the basis for the now standard treatment of erectile dysfunction. And in turn, the side effects of the erectile dysfunction treatment, coupled with a growing mechanistic understanding of the protective signaling cascade associated with PKG activation, foreshadow new and exciting treatments for a range of cardiovascular disorders. In light of the present findings (3), we can look forward to new cardiomyocyte-specific and isotype-selective strategies for therapeutic modulation of the cGMP-PKG pathway, potentially using targeted gene transfer approaches.

**REFERENCES**


**Key Words:** cGMP ■ hypertrophy ■ phosphodiesterase type 5 ■ protein kinase G ■ sildenafil.

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