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Cyclic GMP signaling in cardiovascular pathophysiology and therapeutics

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ABSTRACT

Cyclic guanosine 3',5'-monophosphate (cGMP) mediates a wide spectrum of physiologic processes in multiple cell types within the cardiovascular system. Dysfunctional signaling at any step of the cascade — cGMP synthesis, effector activation, or catabolism — have been implicated in numerous cardiovascular diseases, ranging from hypertension to atherosclerosis to cardiac hypertrophy and heart failure. In this review, we outline each step of the cGMP signaling cascade and discuss its regulation and physiologic effects within the cardiovascular system. In addition, we illustrate how cGMP signaling becomes dysregulated in specific cardiovascular disease states. The ubiquitous role cGMP plays in cardiac physiology and pathophysiology presents great opportunities for pharmacologic modulation of the cGMP signal in the treatment of cardiovascular diseases. We detail the various therapeutic interventional strategies that have been developed or are in development, summarizing relevant preclinical and clinical studies.

Contents

1. Introduction

Cyclic guanosine 3',5'-monophosphate (cGMP) is a ubiquitous intracellular second-messenger that mediates a vast array of physiologic processes, from ion channel conductance to cell growth and apoptosis to cellular mobility and contractility. In the cardiovascular system, cGMP signaling is vital to endothelial, vascular smooth muscle, and cardiac myocyte function. Generated by guanylyl cyclase isoforms in response to natriuretic peptides (NPs) and nitric oxide (NO), cGMP exerts its actions through cGMP-gated cation channels, cGMP-dependent protein kinases (PKGs), and cGMP-regulated phosphodiesterases (PDEs) that in turn hydrolyze cyclic nucleotides. Since the discovery of cGMP in rat urine nearly 50 years ago (Ashman et. al, 1963), the field of cGMP signaling research has grown exponentially. Abnormalities at each step of the cGMP signaling cascade, from cGMP synthesis to its degradation, have been implicated in cardiovascular disease and thus represent potential targets for pharmacologic therapies.

cGMP has two distinct pathways that regulate its synthesis, one coupled to natriuretic peptide hormone, and the other a simple gas (nitric oxide) (Fig. 1). No other second messenger, not even cyclic adenosine monophosphate (cAMP), is activated by a gas. The significance of NO-cGMP signaling was recognized by the 1998 Nobel Prize in Physiology and Medicine that was awarded for the major discoveries surrounding nitric oxide (Arnold et al., 1977; Katsuki et al., 1977; Schultz et al., 1977; Ignarro et al., 1987a, 1987b). Natriuretic peptide-mediated cGMP signaling was discovered in the early 1980s, when a polypeptide hormone was isolated from heart atrial muscle tissue and found to have potent diuretic (natriuretic) and hypotensive properties

Abbreviations: BH4, tetrahydrobiopterin; cGMP, cyclic guanosine 3',5'-monophosphate; cAMP, cyclic adenosine 3',5'-monophosphate; DEA/NO, diethylamine NONOate; DGC, dystrophin glycoprotein complex; NO, nitric oxide; NOS, nitric oxide synthase; NP, natriuretic peptide; NPR, natriuretic peptide receptor; PDE, phosphodiesterase; pGC, particulate guanylyl cyclase; PKG, protein kinase G (cGMP-dependent protein kinase); sGC, soluble guanylyl cyclase; VSMC, vascular smooth muscle cell; cGMP, signaling in cardiovascular pathophysiology and therapeutics.

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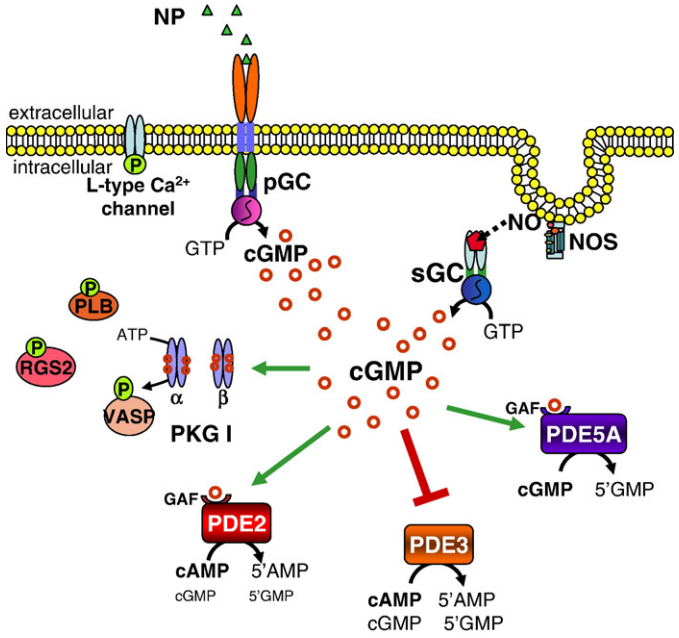

Fig. 1. cGMP signaling cascade. cGMP is produced by particulate (pGC) and soluble (sGC) guanylyl cyclases, upon natriuretic peptide and nitric oxide activation, respectively. cGMP can then activate cGMP-dependent protein kinase (PKG) and either activate (green arrow) or inhibit (red arrow bar) various phophodiesterase isoforms. PKG-I phosphorylates several protein targets, including phospholamban (PLB), vasodilatory-stimulated phosphoprotein (VASP), regulator of G protein signaling 2 (RGS2), and the L-type calcium channel. PDE2 and PDE3 catabolize both cAMP and cGMP, whereas PDE5 specifically catabolizes cGMP. Upon cGMP binding to its regulatory GAF domain, PDE2 undergoes a conformational change and increases its enzymatic activity for cAMP. PDE5 similarly increases its catalytic activity for cGMP by an order of magnitude upon cGMP binding to its regulatory GAF domain. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(de Bold, 1982; Ackermann et al., 1984; Atarashi et al., 1984; Atlas et al., 1984; Bloch et al., 1985; de Bold, 1985). The discovery of atrial natriuretic peptide was momentous in its implication of the heart as more than a circulatory pump or electrically conductive tissue but also an endocrine organ; a finding which ultimately helped shift the conceptual paradigm of heart failure to the current neurohormonal model.

Each of these pathways couples to a distinct guanylyl cyclase isoform — soluble (sGC) and particulate (pGC) guanylyl cyclase respectively. These cyclases differ in their intracellular distribution, with sGC historically described as a cytosolic protein and pGC being a membrane bound protein. However, their intracellular localization is more nuanced, and recent studies support distinct pools of cGMP generation with different downstream effects (Castro et al., 2006; Takimoto et al., 2007; Nausch et al., 2008). Cyclic GMP activates three types of effector molecules, with cGMP-dependent protein kinases (PKGs) and phosphodiesterases (PDEs) predominating in the cardiovascular system. A third type of effector molecule, cGMP-gated cation channels, exists in retinal and olfactory neuroepithelium and nephrons, but neither protein expression nor physiological function of these channels have been established in the cardiovascular system. Cyclic GMP-PKG signaling within the vascular endothelium stimulates cell proliferation and increases permeability (Draijer et al., 1995a, 1995b; Vaandrager & de Jonge, 1996; Holschermann et al., 1997; Hood & Granger, 1998; Smolenski et al., 2000; Kook et al., 2003); it inhibits cell proliferation and mediates vasorelaxation in vascular smooth muscle (Archer et al., 1994; Bolotina et al., 1994; Cornwell et al., 1994; Murad et al., 1985); while in cardiac myocardium, it inhibits hypertrophy and modulates contractility (Lohmann et al., 1991; Shah et al., 1994; Takimoto et al., 2005b; Kinugawa et al., 1997; Vila-Petroff et al., 1999; Tatsumi et al., 2000). In all three tissues, cGMP-PKG signaling also mediates cellular apoptosis (Fukuo et al., 1996; Wu et al., 1997; DeMeester et al., 1998; Arstall et al., 1999; Suenobu et al., 1999; Taimor et al., 2000).

Lastly, cGMP catabolism is regulated by a subgroup of the 11 member phospho-diesterase superfamily. PDEs play a role in not only spatiotemporal regulation of cGMP signal but also cross-regulation of the cAMP signal. The strategy of inhibiting PDEs to enhance cGMP and related signaling has already been harnessed with the PDE5A inhibitor sildenafil, a common treatment for erectile dysfunction (Boolell et al., 1996). PDE inhibition has been further examined for the treatment of a variety of cardiovascular diseases, including pulmonary hypertension and now chronic heart failure, and this continues to be a highly active and promising field of research (Bethke et al., 1992a, 1992b; Eddahibi et al., 1998; Gillies et al., 2002; Reffelmann & Kloner, 2003; Guazzi & Samaja, 2007; Lewis et al., 2007a; Attina et al., 2008; Baliga et al., 2008; Park, 2008).

This review summarizes our current understanding of cGMP signaling within the cardiovascular system, specifically in vascular endothelial and smooth muscle cells and cardiac myocytes. Several others have reviewed specific aspects of nitric oxide and natriuretic peptide, PKG, and PDE5 signaling (Kass et al 2007a; Hofmann et al, 2009; Saraiva & Hare, 2006; Rastaldo et al., 2007; Schulz et al., 2008; Woodard & Rosado, 2008). After discussing the major elements of the cGMP signaling pathway, we focus on the role of dysfunctional cGMP signaling in cardiovascular disease and the potential targets that this poses for the pharmacological treatment of cardiovascular diseases.

2. cGMP Signaling

2.1. Generation by guanylyl cyclases

The biosynthesis of cyclic GMP from guanosine triphosphate (GTP) is catalyzed by two different isoforms of guanylyl cyclase, one which functions as the biosensor for nitric oxide and the other, as the plasma membrane receptor for natriuretic peptides.

2.1.1. Nitric oxide-mediated biosynthesis of cGMP

Nitric oxide was long considered to be merely a toxic air pollutant until its identification as a labile factor released from endothelial cells, initially termed “endothelial derived relaxant factor” (EDRF) (Furchgott & Zawadzki, 1980; Cherry et al., 1982). After seminal work demonstrating that EDRF, as induced by stimulating cells with acetylcholine, increased cGMP levels, activated PKG, and phosphorylated the same vascular smooth muscle proteins as did nitrovasodilators (Rapoport et al., 1983; Rapoport & Murad, 1983), EDRF and nitric oxide were proposed to be one and the same (Furchgott et al., 1987; Ignarro et al., 1987a, 1987b).

Nitric oxide is produced by nitric oxide synthase (NOS) which exists as three isoforms — neuronal nitric oxide synthase (NOS-1 or nNOS), inducible nitric oxide synthase (NOS-2 or iNOS), and endothelial nitric oxide synthase (NOS-3 or eNOS) (Alderton et al., 2001). The NOS isoforms were named by order of their discovery and initially reported expression pattern. However, all three isoforms have been detected in cardiac myocytes, vascular smooth muscle cells, and vascular endothelial cells (Koide et al., 1993; Balligand et al., 1995; Kurihara et al., 1998; Gyurko et al., 2000; MacNaul & Hutchinson, 1993). Inducible NOS expression is, as its name implies, inducible, whereas eNOS and nNOS expression are constitutive and also inducible. Capable of associating with soluble, membrane, or cytoskeletal proteins, the NOS isoforms can be mobile within the cell and vary in their subcellular localization. They are active as homodimers with a central heme prosthetic group and require a complex array of cofactors and co-substrates to effectively generate