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cGMP-Dependent Protein Kinase in the Regulation of Cardiovascular Functions

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1. Introduction

Cyclic GMP-dependent protein kinase (PKG) was discovered in 1970 in lobster muscle (Kuo & Greengard, 1970). It is a serine/threonine protein kinase specifically activated by cyclic guanosine monophosphate (cGMP). PKG is a ubiquitous intracellular second messenger mediating the biological effects of cGMP elevating agents including nitric oxide (NO), natriuretic peptides, and guanylin (an intestinal peptide involved in intestinal fluid regulation). It is now well recognized that PKG plays a central role in a broad range of physiological processes, such as contractility and proliferation of smooth muscle and cardiac myocytes, platelet aggregation, synaptic plasticity and learning, behavior, intestinal chloride reabsorption, renin secretion, and endochondral ossification (Francis et al., 2010; Hofmann et al., 2009; Lincoln et al., 2001; Lohmann & Walter, 2005). This chapter will focus on the role of PKG in the regulation of cardiovascular functions under physiological and pathophysiological conditions.

2. PKG structure and tissue distribution

In mammalian cells PKG exists as two types, PKG-I and PKG-II, respectively. They are encoded by two separated genes *prkg1* and *prkg2*. The human *prkg1* gene is located on chromosome 10 at p11.2 - q11.2 and has 15 exons. The NH_2 terminus (the first 100 residues) of PKG I is encoded by two alternative exons that produce the isoforms PKG Iα and PKG Iβ. The human *prkg2* gene is located on chromosome 4 at q13.1 - q21.1 and has 19 exons. PKG-I and PKG-II is composed of two identical subunits of the homodimer about 75-80 kDa and 84-86 kDa, respectively and shares common structural features. Each subunit of the enzyme consists of a regulatory domain and a catalytic domain. The regulatory domain is composed of an N-terminal domain and a cGMP binding domain. The N-terminal domain mediates homodimerization, suppression of the kinase activity in the absence of cGMP, and interactions with other proteins including protein substrates. The cGMP binding domain contains a high and a low cGMP affinity binding sites. The two cGMP-binding sites interact allosterically. Binding of cGMP releases the inhibition of the catalytic center by the N-terminal autoinhibitory/pseudosubstrate domain and allows the phosphorylation of target

proteins. The catalytic domain contains a MgATP and a target protein-binding site, which catalyze the phosphate transfer from ATP to the hydroxyl group of a serine/threonine side chain of the target protein. When stimulated with cGMP, the phosphotransferase activity increases by 3- to 10-fold (Francis et al., 2010; Hofmann et al., 2009).

PKG-I is predominantly localized in the cytoplasm (except in the platelets where it is with the membrane). PKG-II is anchored to the plasma membrane by N-terminal myristoylation. In general, PKG-I and PKG-II are expressed in different cell types. PKG-I exists at high concentrations in all types of smooth muscle cells (~0.1μM) including vascular smooth muscle cells and at lower levels in vascular endothelium and cardiomyocytes. The enzyme has also been detected in other cell types such as fibroblasts, certain types of renal cells and leukocytes, and in specific regions of the nervous system. Platelets express predominantly PKG Iβ while both PKG Iα and PKG Iβ isoforms are present in smooth muscle, including uterus, blood vessels, intestines, and trachea. PKG-II is expressed in several brain nuclei, intestinal mucosa, kidney, chondrocytes and the lung but not in cardiac and vascular myocytes (Francis et al., 2010; Hofmann et al., 2009).

Existing research results show that PKG-I is the major type of the enzymes in the cardiovascular system involved in the regulation of vascular tone, regulation of vascular smooth muscle cells and myocardial cells proliferation and phenotypic modulation, and inhibiting platelet aggregation. Both PKG-Iα and PKG-Iβ can be specially activated by cGMP, with the former is about 10 times more sensitive to cGMP than the latter. PKG can also be activated by cAMP, although more than 100 times less potent than cGMP. The main role of PKG-II is phosphorylation in the intestinal mucosa of cystic fibrosis transmembrane conductance regulator, regulation of intestinal chloride ion/fluid secretion, inhibition of renin secretion in the kidney, and the regulation of bone tissue and bone endochondral bone growth (Francis et al., 2010; Hofmann et al., 2009; Lincoln et al., 2001; Lohmann & Walter, 2005).

3. PKG function in the cardiovascular system

3.1 Blood vessels

3.1.1 Vasodilatation

PKG is involved in vasodilatation caused by cGMP elevating agents including endothelium-derived NO, ANP, CNP, and exogenous nitrovasodilators (Gao, 2010; Hofmann et al., 2009). In certain vessel types such as ovine perinatal pulmonary artery and vein (Dhanakoti et al., 2000; Gao et al., 1999) as well as porcine coronary artery and vein (Qin et al., 2007; Qi et al., 2007) relaxation caused by nitrovasodilators is primarily mediated by PKG. Studies show that the expression and activity of PKG can be modulated by physiological variables such as oxygenation (Gao et al., 2003).

Activation of calcium activated potassium (BK) channels has been implicated as a mechanism for PKG-mediated relaxation of vascular smooth muscle in a number of vessel types including cerebral artery (Robertson et al., 1993), coronary artery (White et al., 2000), and pulmonary artery (Barman et al., 2003), which leads to increased membrane polarization and thus decreased Ca^{2+} influx and vasodilatation. PKG may stimulate BK channels by direct phosphorylation of the α-subunit at serine 1072 (Fukao et al., 1999) or through

activation of protein phosphatase 2A (Zhou et al., 1996). In ovine basilar arterial smooth muscle cells PKG has been shown to play a larger role in the regulation of BK activity in fetal than in adult myocytes, indicating a developmental changes in the role of PKG (Lin et al., 2005).

PKG may also modulate Ca^{2+} release from the inositol-trisphosphate receptor (IP_3R) of the sarcoplasmic/endoplasmic reticulum (SERCA) through phosphorylation of IP_3R-associated cGMP kinase substrate (IRAG), a 125-kDa protein that resides in the SERCA membrane in a trimeric complex with PKG Iβ and IP_3R. In aortic smooth muscle cells of mice expressing a mutated IRAG protein that does not interact with the IP_3R the inhibition of cGMP on hormone-induced increases in $[Ca^{2+}]_i$ and contractility are blunted (Geiselhöringer et al., 2004). NO-, ANP-, and cGMP-dependent relaxation of aortic vessels is also attenuated in IRAG-knockout mice (Desch et al., 2010).

Increasing evidence has pointed to Ca^{2+} desensitization through interference with RhoA and Rho kinase (ROK) signaling as a key mechanism for PKG-mediated vasodilatation (A.P. Somlyo & A.V. Somlyo, 2003). PKG may phosphorylate RhoA at Ser188, resulting in increased extraction of Rho A from cell membranes and thus reduced activation of this small GTPase protein and attenuated vasocontractility (Loirand et al., 2006). PKG may suppress the inhibitory effect of ROK on myosin light chain phosphatase (MLCP) by phosphorylation of the regulatory subunit of MLCP, myosin phosphatase targeting subunit (MYPT1), at Ser695 and Ser852, which leads to decreased phosphorylation of MYPT1 at Thr696 and Thr853 by ROK, increased activity of MLCP, decreased phosphorylation of myosin light chain (MLC), and diminished vasoreactivity (Wooldridge et al., 2004; Gao et al., 2007 &2008). The effect of PKG on MLCP requires its binding to the leucine zipper domain in the C-terminal of MYPT1. The expression of the leucine zipper domain in MYPT1 is modulated by various physiological and pathophyiological conditions (Chen et al., 2006; Dou et al., 2010; Payne et al., 2006), which may alter the action of PKG on MLCP. Studies also show that PKG/MYPT1 signaling plays a greater role in mediating relaxation of proximal arteries induced by NO than that of distal arteries in coronary vasculature (Ying et al., 2011).

A number of PKG substrates not mentioned above may also be targeted by PKG and involved in PKG-mediated vasodilatation, such as phosphodiesterase 5 (PDE5), phospholamban, and RGS (regulator of G-protein signaling) proteins (Schlossmann & Desch, 2009). It is worth noting that cGMP may affect vasodilatation by PKG-dependent and independent mechanism. Global PKG-knockout causes only a slight hypertension in young mice whereas in the adult the basal blood pressure of the PKG-knockout mice is not different from the control (Pfeifer et al. 1998), indicating other mechanisms may take place to compensate the lose of PKG in maintaining a normal blood pressure.

3.1.2 Phenotype modulation and antiproliferation action

Vascular smooth muscle cells (VSMCs) exist in either a differentiated, contractile or a dedifferentiated, synthetic phenotype. A normal PKG activity appears critical to maintain vascular smooth muscle cells in a contractile and differentiated state. Repetitively passaged VSMCs of the rat aorta do not express PKG and exist in the synthetic phenotype. Transfection of PKG Iα cDNA induces a morphologic change of VSMCs consistent with the contractile phenotype, which is prevented by the inhibition of PKG (Dey et al., 2005).

Myocardin is a smooth muscle and cardiac muscle-specific transcriptional coactivator of serum response factor (SRF) while E26-like protein-1 (Elk-1) is a SRF/myocardin transcription antagonist. PKG-I has been shown to decrease Elk-1 activity by sumo modification of Elk-1, thereby increasing myocardin-SRF activity on SMC-specific gene expression and keeping the cells in a contractile phenotype (Choi et al., 2010). In VSMCs of ovine fetal pulmonary veins hypoxia-induced reduction in PKG protein expression is closely correlated with the repressed expression of VSMC phenotype markers, along with a reduced expression of myocardin and increased expression of Elk-1. It is postulated that the increased expression of Elk-1 resulting from the downregulation of PKG under hypoxia displaces myocardin from SRF and thereby leads to suppression of SMC marker genes and activation of expressions of genes related with the synthetic phenotype (Zhou et al., 2007 & 2009). The PKG-dependent modulation of phenotypes of VSMCs appears to need the cysteine-rich LIM-only protein CRP4 to act as a scaffolding protein that promotes cooperation between SRF and other transcription factors and cofactors since PKG stimulation of the SM-α-actin promoter is suppressed when CRP4 is deficient in PKG binding (Zhang et al., 2007).

PKG has been reported to exert anti- and pro-atherogenic effects in vascular smooth muscle. In coronary and cerebral arterial smooth muscle cells (El-Mowafy et al., 2008; Luo et al., 2011) the proliferation induced by vascular mitogens was inhibited by the cGMP elevating agent or PKG I transfection. However, 8-Br-cGMP stimulated proliferation of aortic SMCs from the wide-type mice but not from PKG I-deficient mice (Wolfsgruber et al., 2003). The contradictory effects may have in part resulted from differences in PKG activation levels (i.e., basal activation vs. hyperactivation). For instance, PKG at low activation levels prevents apoptosis whereas high-level activation causes apoptosis of aortic SMCs of the mice (Wong & Fiscus, 2010).

3.2 Heart

3.2.1 Cardiac contractility

A critical role for PKG in the negative inotropic effect caused by NO and cGMP has been demonstrated in myocardial preparations from PKG I-deficient juvenile mice, from the cardiomyocyte-specific knockout adult mice (Wegener et al., 2002), and in rat ventricular myocytes with the PKG inhibitor (Layland et al., 2002). The Ca^{2+} current of rat ventricular cells is inhibited by cGMP and a catalytically active fragment of PKG (Mery et al., 1991). In murine cardiac myocytes overexpressing PKG I the basal and stimulated activities of L-type Ca^{2+} channels are inhibited by NO and the cGMP analog (Schroder et al. 2003). Hence, PKG may exert its negative inotropic effect action by reducing $[Ca^{2+}]_i$ through inhibiting the activity of Ca^{2+} channels. Recent studies suggest that PKG I-mediated inhibition of L-type Ca^{2+} channels of cardiac myocytes may result from the phosphorylation of Ca_v 1.2 α_{1c} and β_2 subunits (Yang et al., 2007).

PKG may also reduce $[Ca^{2+}]_i$ of cardiomyocytes through phosphorylation of phospholamban, which leads to an increased activity of the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) and thereby an increased Ca^{2+} uptake from the cytosol. Indeed, phospholamban of the rabbit cardiac myocytes is phosphorylated by cGMP in a manner sensitive to the inhibition of PKG. Moreover, the inhibitory effect of contractility of the cardiac myocytes caused by cGMP is prevented by the inhibition of PKG or SERCA (Zhang et al., 2005). C-type natriuretic

peptide and the cGMP analog have been found to cause positive inotropic and lusitropic responses of murine hearts, which are associated with an increased phosphorylation of phospholamban (Wollert et al., 2003). These observations are in vary with those obtained in studies by Zhang et al. discussed above. The underlying reasons for the different inotropic effects remain to be determined (Wollert et al., 2003).

In intact cardiomyocytes of the rat, the negative inotropic and relaxant effects of DEA/NO, an NO donor, occur without significant changes in the amplitude or kinetics of the intracellular Ca^{2+} transient. The effect is diminished in the presence of the inhibitor of soluble guanylyl cyclase (sGC) or PKG, indicating a PKG-dependent Ca^{2+} desensitization of the myofilaments. Meanwhile, hearts treated with DEA/NO showed a significant increase in troponin I phosphorylation (Layland et al., 2002). The PKG may reduce the Ca^{2+} sensitivity of cardiac myofilaments through phosphorylation of cardiac troponin I (cTnI) at the same sites (Ser23/24) as those phosphorylated by PKA (Layland et al., 2005). Studies suggest that cardiac Troponin T may serve as an anchoring protein for PKG to facilitate preferential and rapid cTnI phosphorylation (Yuasa et al., 1999).

3.2.2 Antihypertrophy

An increased left ventricular mass has been recognized as an independent risk factor that correlates closely with cardiovascular risk and has strong prognostic implications. In the mice administration of sildenafil, which elevates cGMP level by inhibiting PDE5, suppresses the development of cardiac hypertrophy caused by chronic pressure overload and can even reverse pre-established cardiac enlargement. These effects are associated with an increased activity of PKG I (Takimoto et al. 2005). Mice with myocyte-specific PDE5 gene overexpression develop more severe cardiac hypertrophy and PKG activation is inhibited as compared to controls in response to pressure overload. Under such a cardiomyopathic state, the suppression of PDE5 expression/activity in myocytes enhanced PKG activity and reversed all previously amplified maladaptive responses (Zhang et al., 2010). In contrast to many studies which indicate an antihypertrophic role for PKG, Lukowski et al. have found that total PKG I-knockout and myocyte-specific rescue of PKG expression (in the context of global gene silencing) did not affect isoproterenol and stress-induced development of cardiac hypertrophy in mice (Lukowski et al., 2010). It is suspected that the lack of differences between controls and PKG I-deficient mice may be in part due to that PKG I-targeted cascades have not been activated under the experimental conditions (Kass & Takimoto, 2010).

RGSs are GTPase-accelerating proteins that promote GTP hydrolysis by the alpha subunit of heterotrimeric G proteins, thereby accelerating signal termination in response to GPCR stimulation (Schlossmann & Desch, 2009). Among more than 30 RGS proteins, RGS4 is richly expressed in murine coronary myocytes. In cultured cardiac myocytes, atrial natriuretic peptide stimulated PKG-dependent phosphorylation of RGS4 and association of RGS4 with the alpha subunit of Gq protein. Mice lacking guanylyl cyclase-A (GC-A), a natriuretic peptide receptor, have pressure-independent cardiac hypertrophy, reduced expression and phosphorylation of RGS4 in the hearts compared with wild-type mice. The RGS4 overexpression in GC-A-KO mice reduced cardiac hypertrophy and suppressed the augmented cardiac expressions of hypertrophy-related genes. These results suggest that GC-A activation may counteract cardiac hypertrophy via RGS4 in a PKG-dependent mechanism (Tokudome et al., 2008). It appears that ANP-cGMP-PKG-RGS signaling is

involved in β-adrenergic but not angiotensin II (Ang II)–induced (Gs vs. Gaq mediated) cardiomyocyte hypertrophy. ANP attenuated Ang II-stimulated Ca^{2+} currents of cardiomycytes but had no effect on isoproterenol stimulation. The effect of ANP on Ang II stimulation was eliminated in cardiomyocytes of mice deficient in GC-A, in PKG I, or in RGS2. Furthermore, cardiac hypertrophy induced by Ang II but not by β- adrenoreceptor was exacerbated in mice with cardiomyocyte-restricted GC-A deletion (Klaiber et al., 2010).

Multiple subclasses of transient receptor potential (TRP) channels are expressed in the heart. These channels, especially the TRPC subclass, have been implicated being involved in the regulation of the cardiac hypertrophic response, most likely coordinating signaling within local domains or through direct interaction with Ca^{2+}-dependent regulatory proteins. Overexpression of TRPC6 in mice lacking GC-A exacerbated cardiac hypertrophy while the blockade of TRPC channels attenuated the cardiac hypertrophy. ANP inhibited agonist-evoked Ca^{2+} influx of murine cardiomyocytes. The inhibitory effects of ANP were abolished by PKG inhibitors or by substituting an alanine for threonine 69 in TRPC6, suggesting that PKG-dependent phosphorylation of TRPC6 at threonine 69 is a critical target of antihypertrophic effects elicited by ANP (Kinoshita et al., 2010)

3.2.3 Cardioprotective action against ischemia-reperfusion injury

In isolated murine heart and cardiomyocytes elevation of cGMP by the activators of soluble or particulate guanylyl cyclase, by the inhibitor of PDE5, or by the cGMP analog elicits potent protection against myocardial ischemia-reperfusion injury and reduces cardiomyocyte necrosis and apoptosis. These effects are accompanied by an increased PKG activity and attenuated by PKG inhibitors or by selective knockdown of PKG in cardiomyocytes (Das, 2008 et al.; Gorbe et al., 2010). It is generally recognized that ischemia/reperfusion injury arises primarily from the opening of the mitochondrial permeability transition pore (mPTP) in the first minutes of reperfusion. cGMP-PKG signaling may prevent opening of mPTP via activation of the mitochondrial K_{ATP} channels, direct phosphorylation of an unknown protein on the mitochondrial outer membrane, and upregulation of the antiapoptotic protein Bcl-2 (Costa et al.,2008; Deschepper, 2010). Glycogen synthase kinase 3β (GSK-3β) plays a central role in transferring cardio protective signals downstream to target(s) that act at or in proximity to the mPTP. Phosphorylation and inhibition of GSK-3β has also been demonstrated being involved in PKG-mediated cardioprotective action (Das et al., 2008; Juhaszova et al., 2009; Xi et al., 2010).

3.3 eNOS activity and endothelial permeability

PKG I has been detected within a range of 0.15 to 0.5 μg/mg cellular protein in adult artery and vein endothelial cells (ECs) and in microvascular ECs (Diwan et al., 1994; Draijer et al., 1995; MacMillan-Crow et al., 1994). There are only limited studies on the role of PKG in the regulation of endothelial function, which is related to eNOS activity and endothelial permeability (Butt et al., 2000; Draijer et al., 1995; Moldobaeva et al., 2006; Rentsendorj et al., 2008). Studies using recombinant human eNOS suggest that the enzyme can be phosphorylated at Ser^{1177}, Ser^{633}, Thr^{495} and activated by PKG II in a manner independent of Ca^{2+} and calmodulin (Butt et al., 2000). Cyclic GMP analog inhibits an increase in $[Ca^{2+}]_i$ and endothelial permeability caused by thrombin in cultured ECs expressing PKG I but not those lacking PKG expressing (Draijer et al., 1995). In human pulmonary artery endothelial cells infected with adenovirus encoding PKG Iβ the cGMP analog prevents the increase in

endothelial permeability caused by H_2O_2. The barrier protection effect was not affected by inhibition of the expression of VASP, a PKG substrate (Moldobaeva et al., 2006; Rentsendorj et al., 2008).

3.4 Anti-platelet aggregation action

Substantial evidence supports a critical role for PKG in mediating the anti-platelet aggregation action caused by cGMP elevating agents such as endothelium-derived NO (EDNO) and exogenous nitrovasodilators (Walter & Gambaryan, 2009; Dangel et al., 2010). PKG Iβ is the predominate isoform of the enzyme in platelets. The concentration of PKG Iβ in human platelets is 3.65μM, which is higher than that of any other cell type examined (Antl et al., 2007; Eigenthaler et al., 1992). In PKG-deficient murine platelets the inhibition of the cGMP analog on granule secretion, aggregation and adhesion is severely affected (Massberg et al. 1999; Schinner et al., 2011). The effect of PKG may be in part mediated by IRAG. IRAG is abundantly expressed in platelets and constitutively formed in a macrocomplex with PKGIβ and the $InsP_3R$. PKGIβ phosphorylates IRAG at Ser664 and Ser677 in intact platelets, resulting in attenuated release of Ca^{2+} from the sarcoplasmic reticulum evoked by IP_3. Targeted deletion of the IRAG-$InsP_3RI$ interaction in $IRAG^{\Delta12/\Delta12}$ mutant mice causes a loss of NO/cGMP-dependent inhibition of $[Ca^{2+}]_i$ increase and platelet aggregation. The preventive effect of NO on arterial thrombosis in the injured carotid artery was observed in wide-type platelets but not in $IRAG^{\Delta12/\Delta12}$ mutants (Antl et al. 2007).

Vasodilator-stimulated phosphoprotein (VASP) belongs to the Ena-VASP protein family. It is associated with filamentous actin formation and may play a widespread role in cell adhesion and motility. In VASP-deficient mice, the inhibitory effect of NO on platelet adhesion is impaired. Under physiologic conditions, platelet adhesion to endothelial cells was enhanced in VASP null mutants. Under pathophyiological conditions, the loss of VASP augments platelet adhesion to the postischemic intestinal microvasculature, to the atherosclerotic endothelium of ApoE-deficient mice, and to the subendothelial matrix of blood vessels (Massberg et al. 2004). In VASP-deficient mice, although cGMP-mediated inhibition of platelet aggregation is impaired, cGMP-dependent inhibition of agonist-induced increases in cytosolic calcium concentrations and granule secretion is preserved (Aszódi et al., 1999).

Although it is a currently prevailing concept that PKG signaling inhibits platelet function, some studies show that activation of NO-cGMP-PKG pathway promotes platelet aggregation (Blackmore, 2011; Li et al., 2003; Zhang et al., 2011). In PKG knockout mice platelet responses to von Willebrand factor (vWF) or low doses of thrombin are impaired and bleeding time is prolonged. Human platelet aggregation induced by these agents is also diminished by PKG inhibitors but enhanced by cGMP (Li et al., 2003). A defect in platelet aggregation in response to low doses of collagen or thrombin also occurs in platelet-specific sGC-deficient mice (Zhang et al., 2011). It appears that cGMP at low concentrations promotes while at higher concentrations inhibits platelet aggregation (Blackmore et al., 2011; Li et al., 2003).

4. PKG and cardiovascular diseases

4.1 Hypertension

Global deletion of eNOS (Huang et al., 1995), sGC (Friebe et al., 2007), or PKG I (Pfeifer et al. 1998) results in hypertension in mice. About 80% of the mice that are deficient in PKG I died

at age of 8-week. Those lived to adulthood showed no significant difference in blood pressure from the wild type animals, indicating compensatory mechanisms are functioning (Pfeifer et al. 1998). Loss of PKG I abolishes NO- and cGMP-dependent relaxations of smooth muscle (Pfeifer et al. 1998). In mice with a selective mutation in the N-terminal protein interaction domain of PKG Iα also results in reduced vasodilator response to EDNO and cGMP and increased systemic blood pressure, suggesting that the hypertension results from a diminished response of blood vessels to cGMP (Michael et al., 2008). Vascular reconstitution of PKG Iα or PKG Iβ in PKG I-deficient mice restores the diminished vasodilatation to NO and cGMP and normalizes the elevated blood pressure, (Weber et al., 2007). In spontaneously hypertensive rats (SHR) cardiomyocytes PKG-I expression is decreased, making the NO/cGMP-dependent regulation on calcium transient in cardiomyocytes weakened, and promoting cardiac hypertrophy (Mazzetti et al., 2001).

Abnormality in the renin-angiotensin-aldosterone system is an important etiologic event in the development of hypertension. Renal renin mRNA levels under stimulatory (low-salt diet plus ramipril) and inhibitory (high-salt diet) conditions were elevated in PKG II deficient mice. The deletion of PKG II abolishes the attenuation of forskolin-stimulated renin secretion caused by 8-Br-cGMP in cultured renal juxtaglomerular cells. Activation of PKG by 8-Br-cGMP decreased renin secretion from the isolated perfused rat kidney of the wild-type mice but not that of PKG II-/- mice. These findings suggest that PKG II exerts an inhibitory effect on renin secretion (Wagner et al., 1998). Mice deficient in PKG II display no elevated blood pressure, suggesting that PKG II is not critically involved in the regulation of overall systemic blood pressure (Hofmann et al., 2009).

4.2 Atherosclerosis

In an animal model of late-stage atherosclerosis obtained by feeding 8-week-old rabbits with hypercholesterol diet for 50 weeks the protein levels of sGC and PKG I of the aorta were reduced. These changes were most prominent in the neointimal layer. Phosphorylation of VASP at Ser239, a specific indicator of PKG activity, was also reduced. The preferential down-regulation of cGMP/PKG signaling in neointima suggests a direct connection of these changes to neointimal proliferation and vascular dysfunction occurred in atherosclerosis (Melichar et al., 2004). It seems that the decreased PKG expression occurred only at late-stage atherosclerosis, as the protein level of PKG was unaltered in Watanabe heritable hyperlipidemic rabbits of three month old (Warnholtz et al., 2002). Thrombospondin-1 and osteopontin are extracellular matrix (ECM) proteins involved in the development of atherosclerosis. PKG may exert its anti- atherosclerotic effect in part through these two ECM proteins, since their expression could be marked reduced by PKG I (Dey et al., 1998). Interestingly, postnatal ablation of PKG I selectively in the VSMCs of mice reduced atherosclerotic lesion area, which would suggest that smooth muscle PKG I promotes atherogenesis (Wolfsgruber et al., 2003).

4.3 Diabetic vascular disease

High glucose exposure has been found to reduce the protein and mRNA levels of PKG I as well as PKG I activity in cultured rat VSMCs. PKG I protein levels were decreased in femoral arteries from diabetic mice. Glucose-mediated decrease in PKG I levels was inhibited by the superoxide scavenger or NAD(P)H oxidase inhibitors. High glucose

exposure increased the protein levels and phosphorylated levels of p47phox (an NADPH oxidase subunit) in VSMCs, associated with increased superoxide production. The suppressed PKG expression and increased superoxide production were prevented by transfection of cells with siRNA-p47phox, suggesting that NADPH oxidase-derived superoxide may mediate the high glucose-induced downregulation of PKG occurred in diabetic blood vessels (Liu et al., 2007). Studies also show that activation of PKG by expression of constitutively active PKG suppressed high glucose-induced VSMC proliferation and inhibited first gap phase (G1) to synthesis phase (S) phase progression of the cell cycle. These changes were accompanied with reduced glucose-induced cyclin E expression and cyclin E-cyclin-dependent kinase 2 activity as well as inhibition of glucose-induced phosphorylation of retinoblastoma protein (Rb) and p27 degradation. It suggests that PKG may inhibit VSMC proliferation through attenuation of cyclin E expression and increase in p27 protein stability, which leads to decreased CDK 2 activity and reduced Rb phosphorylation, thereby resulting in cell cycle arrest and cell growth inhibition (Wang & Li, 2009). Increased activity of transforming growth factor-β (TGF-β) is implicated in the development of diabetic macrovascular fibroproliferative remodeling. High glucose was found to stimulate the expression of thrombospondin1 (TSP1), a major activator of transforming growth factor-β (TGF-β), and to stimulate TGF-β activation in primary murine aortic SMCs. These effects were inhibited by overexpression of constitutively active PKG. Since PKG is downregulated in diabetic vasculature, it is likely that the downregulation of PKG action may relieve its suppression on TSP1 expression and TGF-β activity, thereby leading to augmented vascular remodeling in diabetes (Wang et al., 2010).

4.4 Pulmonary arterial hypertension

PKG expression and/or activity are/is reduced in animal models of pulmonary arterial hypertension (PAH) induced by ligation of the ductus arteriosus of fetal lambs (Resnik et al., 2006) and in caveolin-1 (Cav-1) knockout mice (Zhao et al., 2009). Cav-1, a 21-kDa integral membrane protein, is an intracellular physiological inhibitor of eNOS activity. Mice deficient in Cav-1 led to chronic eNOS activation and PAH. Activation of eNOS in Cav-1$^{-/-}$ lungs resulted in an impaired PKG activity through tyrosine nitration, probably at Tyr345 or Tyr549 of the catalytic domain of human PKG Iα. The PAH phenotype in Cav-1$^{-/-}$ lungs could be rescued by overexpression of PKG 1α. The treatment of these mice with either a superoxide scavenger or an eNOS inhibitor reverses their pulmonary vascular pathology and PAH phenotype, suggesting that an increased peroxynitrite formed from chronic overproduction of NO and superoxide may result in tyrosine nitration and loss of activity of PKG. Clinically, lung tissues from patients with idiopathic PAH have been found to display reduced Cav-1 expression, increased eNOS activation, and PKG nitration (Zhao et al., 2009). In ovine fetal pulmonary veins hypoxic exposure also causes peroxynitrite-mediated PKG nitration, reduced PKG activity, and suppressed dilator response to 8-Br-cGMP (Negash et al., 2007).

An upregulated ROK activity is implicated in a number of cardiovascular diseases including PAH (Satoh et al., 2011). ROK augments vasoconstriction primarily by inhibiting MLCP activity through phosphorylation of the regulatory subunit MYPT1 at Thr696 and Thr853, which leads to increased Ca^{2+}-sensitization of smooth muscle. The effect of ROK can be counteracted by the stimulatory action of PKG through phosphorylation of MYPT1 at Ser695

and Ser852. Pulmonary arteries from fetuses exposed to chronic intrauterine hypoxia (CH) displayed thickening vessel walls and diminished relaxant response to 8-Br-cGMP, two important characteristics of newborn PAH (Bixby et al., 2007; Gao et al., 2007). Rp-8-Br-PET-cGMPS, a specific PKG inhibitor, attenuated relaxation to 8-Br-cGMP in control vessels to a greater extent than in CH vessels while Y-27632, a ROCK inhibitor, potentiated 8-Br-cGMP-induced relaxation of CH vessels and had only a minor effect in control vessels. The specific activity of PKG was decreased while ROK activity was increased in CH vessels as compared with the controls. The phosphorylation of MYPT1 at Thr696 and Thr853 was inhibited by 8-Br-cGMP to a lesser extent in CH vessels than in controls. The difference was eliminated by Y-27632. These data indicate that the attenuated PKG-mediated relaxation in pulmonary arteries exposed to chronic hypoxia in utero is due to inhibition of PKG activity and due to enhanced ROCK activity. Increased ROCK activity may inhibit PKG action through increased phosphorylation of MYPT1 at Thr696 and Thr853 (Gao et al., 2007). In contrast to pulmonary arteries, relaxation of pulmonary veins of fetuses exposed to (CH) displayed no changes in the thickness of vessel walls and relaxant response to 8-Br-cGMP. In these veins phosphorylation of MYPT1 at Thr696 by ROK and at Ser695 by PKG was diminished as compared with control veins, suggesting that CH attenuates both PKG action and ROK action on MYPT1, resulting in an unaltered response to cGMP (Gao et al., 2008).

Bone morphogenetic proteins (BMPs) are members of the TGF-β superfamily. Mutations in the BMP type II receptor (BMPR-II) are responsible for the majority of cases of heritable PAH. Dysfunction in BMP signaling is implicated in idiopathic PAH and in a number of experimental models of PAH (Toshner et al., 2010). Studies found that PKG I may regulate the activation of BMP receptor and receptor-regulated Smad, a key mediator for BMP signaling, at the plasma membrane and regulate the expression of BMP target genes in the nucleus. These mechanisms may enable PKG I to compensate for the aberrant cellular responses to BMP caused by mutations in BMPRII found in PAH patients. Indeed, the overexpression of PKG I restores normal BMP responsiveness in cells expressing signaling deficient PAH mutant receptors such as the mutant BMPRII-Q657ins16 (Schwappacher et al., 2009; Thomson et al., 2000).

4.5 Nitrate tolerance

Nitroglycerine (NTG) is a widely used vasodilator in the treatment of angina pectoris and acute heart failure. It is converted inside the cell to NO or an NO-related intermediate and causes vasodilatation in a cGMP-dependent fashion. The effectiveness of NTG is often diminished when it is continuously used for a period of time, termed nitrate tolerance. The underlying mechanisms include an increased production of reactive oxygen species (ROS), impairment of biotransformation of NTG by aldehyde dehydrogenase, desensitization of sGC, upregulation of phosphodiesterases, and downregulation PKG activity (Münzel et al., 2005). In human arteries and veins, nitrate tolerance is associated with decreased PKG activity (Schulz et al., 2002). In the arteries of rats and rabbits, nitrate tolerance induced by low-dose NTG is associated with decreased PKG activity, while the tolerance induced by high-dose NTG is associated with decreased PKG protein level and activity (Mülsch *et al.*, 2001). In porcine coronary arteries nitrate tolerance induced by NTG at low concentrations is prevented by the scavenger of ROS. However the tolerance induced by NTG at higher concentrations is not affected by the scavenger of ROS and shows cross-tolerance to the NO

donor and 8-Br-cGMP. Meanwhile, the protein and mRNA levels of PKG are reduced. It seems that the tolerance induced by NTG at higher concentrations may be due to suppression of PKG expression resulting from sustained activation of the enzyme (Dou et al., 2008). A diminished expression and activity of PKG was also observed in pulmonary veins of newborn lambs after prolonged exposure to the NO donor (Gao et al., 2004).

Activation of MLCP is a key mechanism for vasodilatation induced by nitrovasodilators such as NTG and NO. MLCP is a heterotrimer, composed of a catalytic subunit PP1cδ, a regulatory subunit MYPT1, and a subunit with unknown function. The regulatory subunit MYPT1 exists as isoform either with or without leucine zipper domain in its C-terminal [MYPT1 (LZ+) and MYPT1 (LZ−), respectively]. The presence of leucine zipper is necessary for PKG binding to MYPT1 and for PKG-mediated stimulatory effect on MLCP. Studies consistently demonstrate that the expression of MYPT1 (LZ+) determines the sensitivity to cGMP-mediated vasodilatation (Lee et al., 2007; A.P. Somlyo & A.V. Somlyo, 2003). Nitrate tolerance induced under *in vitro* conditions in porcine coronary arteries and induced under *in vivo* preparations in murine aorta show a decreased protein levels of MYPT1 (LZ+) but not of PP1cδ. The decrease in the MYPT1 (LZ+) protein level of coronary artery can also be induced by the NO donor and 8-Br-cGMP in a manner sensitive to the inhibitors of sGC and PKG, respectively. The tolerance to NTG in porcine coronary artery and mouse aorta is ameliorated by proteasome inhibitors. Therefore a downregulation of MYPT1 (LZ+) caused by increased proteasome-dependent degradation may contribute to development of nitrate tolerance (Dou et al., 2010).

5. Conclusion

Overwhelming evidence, obtained by genetic manipulation and pharmacological tools, under both *in vivo* and *in vitro* conditions, suggests that PKG is the primary enzyme in mediating vasodilatation, antiproliferation of vascular smooth muscle, and anti-platelet aggregation action induced by endogenous and exogenous nitrovasodilators via cGMP elevation (Francis et al., 2010; Gao, 2010; Hofmann et al., 2009; Walter & Gambaryan, 2009). Studies also support a barrier protection effect in the vascular endothelium (Moldobaeva et al., 2006; Rentsendorj et al., 2008). Increasing evidence also suggests that PKG exerts negative inotropic and antihypertrophic actions in the heart (Takimoto et al. 2005; Yang et al., 2007; Zhang et al., 2010) as well as a cardioprotective action against ischemia-reperfusion injury (Das et al., 2008; Juhaszova et al., 2009; Xi et al., 2010). Despite substantial progress has been made in elucidating the role of PKG in the regulation of cardiovascular functions there are many aspects remain to be explored. For instance, the developing and ageing aspects for the role of PKG, the gender difference, and the heterogeneity in the role of PKG in different vasculatures. Also, the roles of many PKG substrates in the regulation of cardiovascular activities remain to be defined (Schlossmann & Desch, 2009).

Dysfunction in NO-cGMP signaling is a common initiator and independent predictor of cardiovascular events (Vanhoutte et al., 2009). An impaired PKG action has been implicated in various cardiovascular disorders such as hypertension, atherosclerosis, diabetic vascular disease, pulmonary arterial hypertension, and nitrate tolerance (Francis et al., 2010; Gao, 2010; Hofmann et al., 2009). Cardiovascular alterations are a long-term process comprising functional and structural changes with remarkable complexities, which undoubtedly make

the dissection of the role of PKG rather challenging. However, a better understanding of its role and the underlying mechanism will be of great therapeutic significance.

6. References

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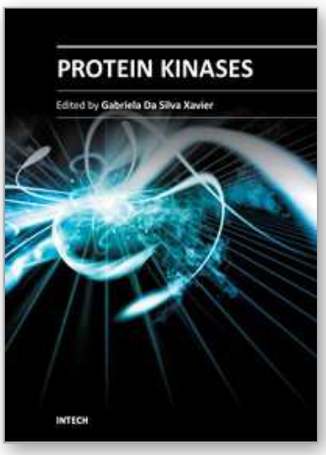

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Proteins are the work horses of the cell. As regulators of protein function, protein kinases are involved in the control of cellular functions via intricate signalling pathways, allowing for fine tuning of physiological functions. This book is a collaborative effort, with contribution from experts in their respective fields, reflecting the spirit of collaboration - across disciplines and borders - that exists in modern science. Here, we review the existing literature and, on occasions, provide novel data on the function of protein kinases in various systems. We also discuss the implications of these findings in the context of disease, treatment, and drug development.

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