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Species- and tissue-dependent effects of NO and cyclic GMP on cardiac ion channels

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ABSTRACT

Biochemical studies have established the presence of a NO pathway in the heart, including sources of NO and various effectors. Several cardiac ion channels have been shown to be modified by NO, such as L-type Ca^{2+} , ATP-sensitive K^{+} , and pacemaker *f*-channels. Some of these effects are mediated by cGMP, through the activity of three main proteins: the cGMP-dependent protein kinase (PKG), the cGMP-stimulated phosphodiesterase (PDE2) and the cGMP-inhibited PDE (PDE3). Other effects appear independent of cGMP, as for instance the NO modulation of the ryanodine receptor- Ca^{2+} channel. In the case of the cardiac L-type Ca^{2+} channel current ($\text{I}_{\text{Ca,L}}$), both cGMP-dependent and cGMP-independent effects have been reported, with important tissue and species specificity. For instance, in rabbit sinoatrial myocytes, NO inhibits the β -adrenergic stimulation of $\text{I}_{\text{Ca,L}}$ through activation of PDE2. In cat and human atrial myocytes, NO potentiates the cAMP-dependent stimulation of $\text{I}_{\text{Ca,L}}$ through inhibition of PDE3. In rabbit atrial myocytes, NO enhances $\text{I}_{\text{Ca,L}}$ in a cAMP-independent manner through the activation of PKG. In ventricular myocytes, NO exerts opposite effects on $\text{I}_{\text{Ca,L}}$: an inhibition mediated by PKG in mammalian myocytes but by PDE2 in frog myocytes; a stimulation attributed to PDE3 inhibition in frog ventricular myocytes but to a direct effect of NO in ferret ventricular myocytes. Finally, NO can also regulate cardiac ion channels by a direct action on G-proteins and adenylyl cyclase.

Key words: cGMP – nitric oxide - cardiac tissue – ion channels – cAMP – cyclic nucleotide phosphodiesterases – cGMP-dependent protein kinase – L-type calcium current

INTRODUCTION

The cyclic nucleotides cAMP and cGMP participate in the main regulations of cardiac function. They act as second messengers for sympathetic and parasympathetic systems, nitric oxide (NO) and natriuretic peptides. Noradrenaline released from sympathetic nerve terminals binds to β -adrenergic receptors (β -ARs) coupled to Gs which activate cAMP synthesis by adenylyl cyclases. Classically, cardiac effects of cAMP are attributed to phosphorylation by cAMP-dependent protein kinase (PKA) of several proteins critically involved in excitation-contraction coupling, including the L-type Ca^{2+} channels (which underlies the L-type Ca^{2+} current, $I_{\text{Ca,L}}$), phospholamban, ryanodine receptor and several contractile proteins (Rapundalo 1998; Bers 2002). PKA also activates the cAMP response element-binding protein (CREB) family of transcription factors (Muller *et al.* 2001). Other cAMP targets in the heart include the exchange protein directly activated by cAMP (Epac) and *f*-channels (Abi-Gerges *et al.* 2000; Sartiani *et al.* 2002; Robinson and Siegelbaum 2003). Acute increase in cAMP has chronotropic, inotropic and lusitropic effects, which are counteracted by acetylcholine (ACh) released from sympathetic nerves. ACh binds to muscarinic M2 receptors which inhibit cAMP synthesis through pertussis toxin sensitive Gi proteins (Méry *et al.* 1997; Harvey and Belevych 2003). While an acute stimulation of the cAMP pathway is beneficial for the heart, a sustained activation, as occurs for instance in transgenic mice with cardiac overexpression of β 1-ARs (Engelhardt *et al.* 1999) or Gs (Iwase *et al.* 1996) leads to hypertrophic growth, ventricular dysfunction and, ultimately, to heart failure (Port and Bristow 2001). A similar situation is found in different forms of human chronic heart failure, which are all associated with elevated catecholamines (Swynghedauw 2004).

cGMP is often represented as the mirror of cAMP. In the short term, cGMP opposes the positive effects of cAMP on cardiac function (Fischmeister and Méry 1996), and is sometimes considered as the second messenger involved in parasympathetic regulation of the heart (Massion *et al.* 2003). Intracardiac cGMP production is due to two different forms of guanylyl cyclases (GC): the soluble GC (sGC), which is activated by NO, and the particulate GC (pGC), which is activated by natriuretic peptides (NPs) ANP, BNP and CNP. NO is produced by cardiac myocytes and endothelial cells nearby, and two NO-synthases (NOS), endothelial (eNOS) and neuronal (nNOS), coexist in cardiac myocytes (Massion *et al.* 2003; Damy *et al.* 2004). A third, inducible form (iNOS) is expressed in pathological conditions such as septic shock (Abi-Gerges *et al.* 1999) or heart failure (Massion *et al.* 2003; Paulus and Bronzwaer 2004). Upon NO or NP action, cGMP accumulates and interacts with several targets, such as cGMP-dependent protein kinase (PKG) and phosphodiesterases (PDEs), which attenuate the β -adrenergic response (Lohmann *et al.* 1991; Fischmeister and Méry 1996). In transgenic mice with cardiac overexpression of eNOS or iNOS there is no cardiac abnormality except for the loss of β -adrenergic responsiveness (Massion *et al.* 2003; Paulus and Bronzwaer 2004; Champion *et al.* 2003; Ziolo *et al.* 2001). As seen with β -blockers, such a mechanism may prove to be protective in heart failure, and could account for the anti-hypertrophic effect of chronic cGMP pathway stimulation by NO (Kempf and Wollert 2004) or NPs (Tokudome *et al.* 2004).

During the last decade, we have studied cyclic nucleotide signalling in healthy and diseased adult cardiac myocytes. With a physiologist approach, we favoured functional rather than biochemical approaches. This is why we generally chose to work on intact, differentiated cardiac myocytes, isolated from small adult animals (frog, rat, mice) or from human atrial appendage. On these myocytes, we apply the patch clamp technique to record ionic currents, and in particular $I_{Ca,L}$ which serves as a marker of cAMP and cGMP changes, as well as

associated PKA and PKG activities in response to diverse stimuli. We developed original methods to study the spatio-temporal organisation (compartmentation) of cyclic nucleotide signalling pathways, and showed that cyclic nucleotide PDEs play a key role in defining this compartmentation.

cAMP and β -adrenergic regulation of cardiac function

Two types of β -AR (β_1 -AR and β_2 -AR) participate in the sympathetic stimulation of cardiac function (Xiao *et al.* 2004). We showed that both β_1 -AR (Hartzell *et al.* 1991; Hartzell and Fischmeister 1992) and β_2 -AR (Skeberdis *et al.* 1997a; 1997b) activated $I_{Ca,L}$ through cAMP elevation and PKA phosphorylation. We currently study $I_{Ca,L}$ regulation by β_3 -AR, which are expressed in the human heart (Moniotte *et al.* 2001), and have a negative inotropic effect in the ventricle (Gauthier *et al.* 1996) involving activation of eNOS (Gauthier *et al.* 1998). We found that β_3 -AR activate $I_{Ca,L}$ in human atrial tissue (Skeberdis *et al.* 1999; Gendviliene *et al.* 2002), indicating tissue specificity in the downstream signalling of this receptor. Other types of receptors also activate $I_{Ca,L}$ through an elevation in cAMP, for instance 5-HT₄ (Blondel *et al.* 1997; Vandecasteele *et al.* 1998) and glucagon (Méry *et al.* 1990) receptors.

Opposite effects of cAMP and cGMP on cardiac ionic channels

In 1986, we showed for the first time that intracellular cGMP counteracted the effects of cAMP on $I_{Ca,L}$, and suggested that cGMP action involved PDE2 (Hartzell and Fischmeister 1986). This early hypothesis was confirmed much later, owing to the characterisation of EHNA as a selective PDE2 inhibitor (Méry *et al.* 1995). However, differences exist among species. In guinea pig (Levi *et al.* 1989) and rat (Méry *et al.* 1991), PKG accounts for the inhibitory effect of cGMP on $I_{Ca,L}$, while PDE2 dominates in frog. In human, low concentrations of cGMP stimulate $I_{Ca,L}$ through PDE3 inhibition, and high concentrations

inhibit this current by stimulation of PDE2 (Vandecasteele *et al.* 2001). This versatility of cGMP actions on cardiac function was largely confirmed in subsequent studies, in particular in those using KO or transgenic mice for genes of the cGMP pathway (Wegener *et al.* 2002). $I_{Ca,L}$ inhibition by cGMP participates to the anti-hypertrophic action of cGMP (Fiedler *et al.* 2002). However, in one animal species (rabbit), the results clearly differ. Indeed, PKG exerts stimulatory effects on rabbit cardiac $I_{Ca,L}$, both in atrial (Wang *et al.* 2000) and ventricular myocytes (Han *et al.* 1993; 1998; Kumar *et al.* 1997), although the latter may be restricted to the newborn stage (Kumar *et al.* 1997; 1999).

Does cGMP mediate the effects of NO in cardiac myocytes?

In 1993, we showed for the first time that β -AR stimulation of $I_{Ca,L}$ is antagonized by a NO-donor (Méry *et al.* 1993). We established that this effect is mediated by an elevation of cGMP (Abi-Gerges *et al.* 1997), which stimulates PDE2 in frog (Méry *et al.* 1995; Dittrich *et al.* 2001) and PKG in rat (Abi-Gerges *et al.* 2001). Surprisingly, while PKG stimulation by cGMP can inhibit $I_{Ca,L}$ directly by phosphorylation of the channel main subunit (Méry *et al.* 1991; Jiang *et al.* 2000), PKG activation triggered by NO is mediated by a pertussis-sensitive G_i proteins, thus inhibiting adenylyl cyclase activity (Abi-Gerges *et al.* 2001). The functional consequence of the inhibitory effect of cGMP on $I_{Ca,L}$ is the negative inotropic effect of NO (Chesnais *et al.* 1999a). In human atrial tissue, NO, like cGMP (Vandecasteele *et al.* 2001), exerts a dual action on $I_{Ca,L}$, due to the opposite action of cGMP on PDE2 and PDE3 (Kirstein *et al.* 1995). But NO has also cGMP-independent effects (Fischmeister and Méry 1996). For instance we found that very low doses of NO activate G_s , stimulating adenylyl cyclase and $I_{Ca,L}$, and G_i , hence stimulating the muscarinic K^+ channels (Abi-Gerges *et al.* 2002). NO may also bind superoxide anions to form peroxynitrite, which exerts specific effects on cardiac

$I_{Ca,L}$ (Campbell *et al.* 1996; Malan *et al.* 2003) and contraction (Ronson *et al.* 1999; Chesnais *et al.* 1999b).

NO and cGMP effects on other cardiac channels

Although much effort has been devoted to examine the effect of NO and cGMP on cardiac Ca^{2+} channels, other cardiac ion channels have also been shown to be regulated by this pathway. For instance, in rabbit ventricular myocytes, the ATP-sensitive K^+ channel current $I_{K(ATP)}$ is activated by NO donors, and this involves both activation of PKG (Han *et al.* 2002) and cGMP-independent effects (Sasaki *et al.* 2000). The hyperpolarization-activated pacemaker current I_f is also activated by NO and cGMP in guinea pig sinoatrial myocytes due to cGMP-inhibition of PDE3, but this effect is transient due to a subsequent cGMP-activation of PDE2 (Herring *et al.* 2001). In human atrial myocytes, I_f is enhanced by the atrial natriuretic peptide ANP, and this effect likely involves cGMP-inhibition of PDE3 (Lonardo *et al.* 2004). Finally, Ahmmed *et al.* (2001) found that NO reduces the voltage-dependent fast Na^+ current in guinea pig and mouse ventricular myocytes, through a mechanism involving activation of both PKG and PKA.

Does cGMP mediate the effects of acetylcholine in cardiac myocytes?

In the early 70's, the observation that cGMP increases upon parasympathetic stimulation, together with its negative inotropic properties led many scientists to hypothesise that cGMP was responsible for the cardiac effects of ACh (Goldberg *et al.* 1975). However in the mid-80's, the study of the muscarinic regulation on isolated cells showed that ACh blocks β -AR stimulation of $I_{Ca,L}$ but not a direct stimulation by cAMP (Fischmeister and Hartzell 1986; Hescheler *et al.* 1986), demonstrating that the effect of ACh was due exclusively to adenylyl cyclase inhibition (Harvey and Belevych 2003). The discovery of NO in the beginning of the

90's and of the multiple sources of NO in the heart has renewed interest for the participation of NO/cGMP in the parasympathetic regulation of the heart. This brought contradictory results however (Méry *et al.* 1997; Harvey and Belevych 2003; Massion *et al.* 2003; Herring *et al.* 2002). Our contribution to this debate has been to test the effects of NOS inhibitors on ACh regulation of $I_{Ca,L}$ (Méry *et al.* 1996; Vandecasteele *et al.* 1998), and to examine muscarinic regulation of $I_{Ca,L}$ and cardiac force in a eNOS-deficient mouse strain (Vandecasteele *et al.* 1999). We found that without eNOS, muscarinic regulation is not modified, in frog, mouse or man.

Cyclic nucleotide phosphodiesterases

Our interest for PDE comes from the fact that cGMP can abolish all cardiac effect of cAMP by activating its hydrolysis (Hartzell and Fischmeister 1986). Since the beginning of the 90's, more than ten PDE families are known (Rybalkin *et al.* 2003; Maurice *et al.* 2003), often with several genes in the family and several splice variants for each gene. In the cardiac myocyte, 4 PDE families have been identified (Maurice *et al.* 2003): PDE1 (Ca^{2+} /calmodulin-activated); PDE2 (cGMP-activated); PDE3 (cGMP-inhibited); and PDE4. PDE1, 2 and 3 hydrolyse both cAMP and cGMP; PDE4 hydrolyses exclusively cAMP. PDE1 and 2 display a low affinity for both substrates, while PDE3 and 4 have a high affinity. Some evidence exists suggesting that the cGMP-specific PDE5, which is the target of sildenafil (Viagra™) might be also present in cardiac myocytes (Maurice *et al.* 2003; Reffelmann and Kloner 2003; Takimoto *et al.* 2005a; 2005b). Using family-specific PDE inhibitors, we showed that PDE3 and PDE4 modulate β -AR stimulation of $I_{Ca,L}$ in frog cardiomyocytes (Fischmeister and Hartzell 1990; 1991) as well as in rats (Verde *et al.* 1999). In frog, PDE2 is recruited only upon cGMP elevation (Méry *et al.* 1995), but in human atrial cells, PDE2 regulates $I_{Ca,L}$ even in basal conditions (Rivet-Bastide *et al.* 1997), as does PDE3 (Kirstein *et al.* 1995). Some

heterogeneous expression or distribution of the different PDE isoforms may account for their variable contribution to cardiac function between species and tissues (Hove-Madsen *et al.* 1996).

Subcellular compartmentation of cAMP and cGMP

The first evidences for a compartmentation of the cAMP pathway were obtained in the 70's, in studies showing important differences between β -AR and PGE1 stimulations on cardiac cAMP level in subcellular fractions, and phosphorylation and/or activation of various PKA targets (Keely 1977; Brunton *et al.* 1979). But it was only recently that cyclic nucleotide compartmentation in the heart was recognised, owing to the discovery of PKA anchoring proteins (AKAP) (Michel and Scott 2002) and macro-molecular complexes (Marx *et al.* 2002), and to the development of fluorescent probes allowing to visualize the changes in cAMP (Adams *et al.* 1991; Zaccolo *et al.* 2000; Nikolaev *et al.* 2004) and cGMP (Honda *et al.* 2001) concentrations in intact cells.

In 1996, we developed a double-barrelled micro-perfusion technique that allowed to apply an activator of the cAMP pathway on one side of the cell, and monitor its effect on the other side (Jurevičius and Fischmeister 1996). Using the Ca^{2+} current as a marker of cAMP/PKA inside the cell, we demonstrated that in frog ventricular myocytes cAMP generated by a β -AR stimulation did not diffuse freely inside the cell, but remained confined on the side of the cell where it was produced. This cAMP compartmentation involves PDE activity, mainly type 3 and 4 isoforms (Jurevičius *et al.* 2003), since when these PDEs are inhibited, cAMP freely diffuses in the cytoplasm. A compartmentation would also participate in cGMP effects. Indeed, we showed that application of a NO-donor on one side of a cardiac cell very efficiently blocks β -AR stimulation of $\text{I}_{\text{Ca,L}}$ on the exposed part, but has very little effect on the other part, indicating that diffusion of cGMP signals is also limited (Dittrich *et al.* 2001).

In order to visualise changes in cAMP concentration, we developed two types of strategies: i) the fluorescent probe FICRhR developed by Adams *et al.* (1991) was introduced inside a myocyte while measuring $I_{Ca,L}$ simultaneously (Goaillard *et al.* 2001); and ii) a channel that is directly opened by cAMP beneath the membrane (Rich *et al.* 2000) was expressed in cardiac myocytes by adenoviral transfer. This channel is formed by the α subunit of the rat olfactory (CNGA2), that belongs to the CNG channel family (Cyclic Nucleotide Gated Channels. Since the wild type CNGA2 has a higher affinity for cGMP than for cAMP, we used mutant forms, more sensitive to cAMP. With this approach we showed that cAMP generated by β -AR is compartmented in rat ventricular myocytes, due to strong PDE3 and PDE4 activities (Rochais *et al.* 2004). The role of PDE4 in this compartmentation was just confirmed by an independent study (Mongillo *et al.* 2004). We show in addition that PDE activation is under the control of PKA since PKA inhibition reveals global cAMP signals upon β -AR stimulation (Rochais *et al.* 2004).

cAMP pathway in hypertrophy and heart failure

The molecular components of the cAMP pathway are critically modified in all forms of heart failure (Port and Bristow 2001; Lohse *et al.* 2003; Movsesian 2004). Increased levels of catecholamines in hypertrophy and heart failure lead to a loss of β -AR is observed, principally of β_1 -AR, an increased expression of β ARK responsible for β -AR desensitisation, an increase in G_i proteins (El-Armouche *et al.* 2003), a decreased adenylyl cyclase activity, and a globally decreased cAMP level. One of the consequence is a diminished phosphorylation of PKA targets, in particular phospholamban (PLB), phosphatase 1 inhibitor (I-1) (El-Armouche *et al.* 2004) and contractile proteins (Van der Velden *et al.* 2003), leading to a diminished efficiency in Ca^{2+} cycling (Hasenfuss and Pieske 2002) and to the collapse of the contractile response to a β -AR stimulation. Other alterations concern cAMP control of gene expression,

with a desensitisation of CRE (cAMP Responsive Element) transcriptional activity (Muller *et al.* 2001). In contrast, the ryanodine receptor (RyR2) is hyperphosphorylated by PKA in heart failure (Marx *et al.* 2000), indicating a profound perturbation of cAMP targeting in the diseased cell.

In a similar manner, chronic exposure to β_1 -AR agonists in cellular or animal models, the cardiac overexpression of β_1 -AR (Engelhardt *et al.* 1999), Gs proteins (Iwase *et al.* 1996), or PKA (Antos *et al.* 2001), all lead to hypertrophy, apoptosis, and heart failure, through intracellular Ca^{2+} elevation and activation of calcineurin/NFAT (Saito *et al.* 2002). But, while chronic activation of the cAMP pathway participates to its own collapse, any elevation of cAMP does not automatically cause deleterious effects. For instance, transgenic mice overexpressing β_2 -AR in the heart (Milano *et al.* 1994), AC6 (Roth *et al.* 1999) or AC8 (Lipskaia *et al.* 2000; Georget *et al.* 2002; 2003) do not show early signs of hypertrophy or heart failure. As stated by a recent editorial (Bers and Ziolo 2001) “When is cAMP not cAMP?” We believe that cAMP compartmentation is a key actor and determines the quality of the response.

NO/cGMP pathway in hypertrophy and heart failure

In hypertrophy and heart failure, the heart produces and secretes important quantities of ANP, BNP and CNP (Abassi *et al.* 2004), and BNP is being used as a diagnosis marker of heart failure (Tabbibizar and Maisel 2002). NO production is also increases in the failing heart, in part due to iNOS (Massion *et al.* 2003; Paulus and Bronzwaer 2004) and nNOS expression (Damy *et al.* 2004). A large body of evidence indicates that NP (Tokudome *et al.* 2004; Rosenkranz *et al.* 2003) and NO (Kempf and Wollert 2004) exert a direct anti-hypertrophic effect in cardiac myocytes. Increased NP and NO production is likely to represent a protective mechanism, independently of their peripheral actions. These effects of NP and NO are

mediated by cGMP, which would inhibit the calcineurin/NFAT pathway via a PKG-mediated inhibition of $I_{Ca,L}$ (Méry *et al.* 1991; Fiedler *et al.* 2002). But PKG could also act at the transcriptional level independently of NFAT, on other transcription factors such as SRF, ATF-1, CREB, etc. (Pilz and Casteel 2003), as well as on mitochondrial biogenesis (Nisoli *et al.* 2003).

Conclusion

In 1975, Goldberg and colleagues introduced the Yin-Yang hypothesis based on their observations that cAMP and cGMP exerted opposite actions on cardiac function. Thirty years later, our understanding of how these two cyclic nucleotides mediate their cardiac actions has greatly progressed, but the Yin-Yang hypothesis remains essentially valid. Today, we know that the NO/cGMP pathway not only antagonizes the cAMP pathway under acute conditions, but most importantly also in the chronic setting, with cAMP activating and cGMP inhibiting the hypertrophic program. Both cyclic nucleotides appear to be compartmentalized and it is likely that their relative concentrations in different subcellular compartments will determine the overall response of the heart to hormones, neurotransmitters and NO. Since cAMP signalling is altered in hypertrophy and heart failure, it is likely that cGMP signalling will be too. A major challenge will be to understand the remodelling of cAMP/cGMP signalling and its subcellular compartmentation during hypertrophy, and how this contributes to the development of heart failure.

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