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Electrophysiological effects of natriuretic peptides in the heart are mediated by multiple receptor subtypes

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ABSTRACT

Natriuretic peptides (NPs) are a family of cardioprotective hormones with numerous beneficial effects in cardiovascular system. The NP family includes several peptides including atrial NP (ANP), B-type NP (BNP), C-type NP (CNP) and *Dendroaspis* NP (DNP). These peptides elicit their effects by binding to three distinct cell surface receptors called natriuretic peptide receptors A, B and C (NPR-A, NPR-B and NPR-C). NPR-A (which binds ANP, BNP and DNP) and NPR-B (which is selective for CNP) are particulate guanylyl cyclase (GC)-linked receptors that mediate increases in cGMP upon activation. cGMP can then target several downstream signaling molecules including protein kinase G (PKG), phosphodiesterase 2 (PDE2) and phosphodiesterase 3 (PDE3). NPR-C, which is able to bind all NPs with comparable affinity, is coupled to the activation of inhibitory G-proteins (G_i) that inhibit adenylyl cyclase (AC) activity and reduce cAMP levels. NPs are best known for their ability to regulate blood volume and fluid homeostasis. More recently, however, it has become apparent that NPs are essential regulators of cardiac electrophysiology and arrhythmogenesis. Evidence for this comes from numerous studies of the effects of NPs on cardiac electrophysiology and ion channel function in different regions and cell types within the heart, as well as the identification of mutations in the NP system that cause atrial fibrillation in humans. Despite the strong evidence that NPs regulate cardiac electrophysiology different studies have reported varying effects of NPs. The reasons for disparate observations are not fully understood, but likely occur as a result of several factors, including the fact that NP signaling can be highly complex and involve multiple receptors and/or downstream signaling molecules which may be differentially activated in different conditions. The goal of this review is to provide a comprehensive summary of the different effects of NPs on cardiac electrophysiology that have been described and to provide rationale and explanation for why different results may be obtained in different studies.

1. Introduction

Natriuretic peptides (NPs) are a well-recognized family of peptide hormones that play essential roles in regulating cardiovascular function in normal physiology and in disease states (Levin et al., 1998; Potter et al., 2006). The first member of the NP family to be discovered was atrial NP (ANP), which is also referred to as atrial natriuretic factor (ANF) (de Bold et al., 1981; Flynn et al., 1983). Subsequently, two additional members of the NP family were identified and denoted brain (or B-type) NP (BNP) (Sudoh et al., 1988) and C-type NP (CNP) (Sudoh et al., 1990). A fourth NP, called *Dendroaspis* NP (DNP), was initially discovered in the venom of snakes (Schweitz et al., 1992). There is evidence that DNP may also be present in mammals (Lisy et al., 2001; Schirger et al., 1999).

NPs are best known for their capacity to regulate blood pressure and cardiovascular homeostasis as a result of their ability to induce natriuresis, diuresis, and vasodilation and to modulate endothelial permeability (Kuhn, 2004; Potter et al., 2006). What is not as well appreciated is that NPs have emerged as potent regulators of cardiac electrophysiology (Perrin and Gollob, 2012). Consistent with this, a number of studies have demonstrated effects of NPs on ion channels in the heart and the occurrence of arrhythmias in mice lacking specific components of the NP system. Furthermore, mutations in the ANP gene have now been clearly linked to inherited

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cardiac arrhythmias in humans (Abraham et al., 2010; Hodgson-Zingman et al., 2008). Nevertheless, despite clear evidence for electrophysiological effects of NPs in the heart, there is inconsistency in the literature such that different studies have reported a number of different effects for reasons that are often unknown. This is likely due to a number of factors including the complexity of NP signaling in the heart, different patterns of expression of NPRs and/or downstream signaling molecules in different cell types in the heart and studies being performed in different species or experimental conditions. Accordingly, the goal of this review is to provide a comprehensive summary of the different effects of NPs on cardiac electrophysiology that have been described and to provide some rationale and explanation for why different results may be obtained in different studies.

2. Natriuretic peptides and their receptors

All NPs (ANP, BNP, CNP, DNP) are expressed in the myocardium of the heart and all are present in the circulation at different concentrations (Potter et al., 2006; Schirger et al., 1999; Vollmar et al., 1993; Wei et al., 1993). In normal physiological conditions ANP circulates at the highest levels. CNP, on the other hand, is present at very low concentrations in the circulation suggesting it may act primarily as a paracrine hormone (Chen and Burnett, 1998; Potter et al., 2006). ANP and BNP are produced and stored in atrial granules and their release is increased upon atrial stretching (Edwards et al., 1988; Friedewald et al., 2008). NPs are also produced in, and released from cardiac fibroblasts (Harada et al., 1999; Horio et al., 2003; Tsuruda et al., 2002). It is important to note that the local concentrations of NPs in the heart are likely much greater than circulating levels because these peptides are produced locally within the heart and have the opportunity to act in autocrine or paracrine fashions.

NPs are synthesized as pre-pro-hormones that undergo processing to produce biologically active peptides (Potter et al., 2006). NPs are characterized by their distinctive ring structure due to the presence of disulfide bonds between specific cysteine residues in the peptides (Fig. 1). Mature ANP (a 29 amino acid peptide), BNP (a 32 amino acid peptide) and DNP (a 38 amino acid peptide) have N- and C-terminal extensions of variable length. Mature CNP comes in two forms (a 53 amino acid form that does not circulate and a 22 amino acid form that is present in the circulation). Unlike the other NPs, CNP lacks any C-terminal extension. The presence or absence of these C-terminal extensions, as well as their length, importantly affects proteolytic degradation of NPs so that CNP (with no C-terminal tail) has the shortest half-life and DNP (with the longest C-terminal tail) has the longest half-life (Dickey and Potter, 2011; Potter et al., 2006).

NPs exert their biological effects by binding to three distinct cell surface receptors denoted NP receptors A, B and C (NPR-A, NPR-B and NPR-C; Fig. 2) (Nakao et al., 1992), which are all highly expressed in the hearts of mammals, including humans (Anand-Srivastava and Trachte, 1993; Dickey et al., 2007; Nunez et al., 1992; Potter et al., 2006).

Under normal conditions NPR-A binds ANP, BNP and DNP while NPR-B is selective for CNP (Fig. 2) (Dickey and Potter, 2011; Potter et al., 2006). NPR-A and NPR-B are particulate guanylyl cyclase (GC) receptors that have an extracellular binding domain for interaction with NPs and a GC enzyme domain located on the intracellular side of the plasma membrane. Binding of NPs to NPR-A or NPR-B results in activation of these GC enzymes and an increase in intracellular cGMP levels (Fig. 3). cGMP activates protein kinase G as well as phosphodiesterase 2 (PDE2) and inhibits phosphodiesterase 3 (PDE3) (Bender and Beavo, 2006; Lohmann et al., 1991, 1997; Maurice et al., 2003; Omori and Kotera, 2007; Zaccolo and

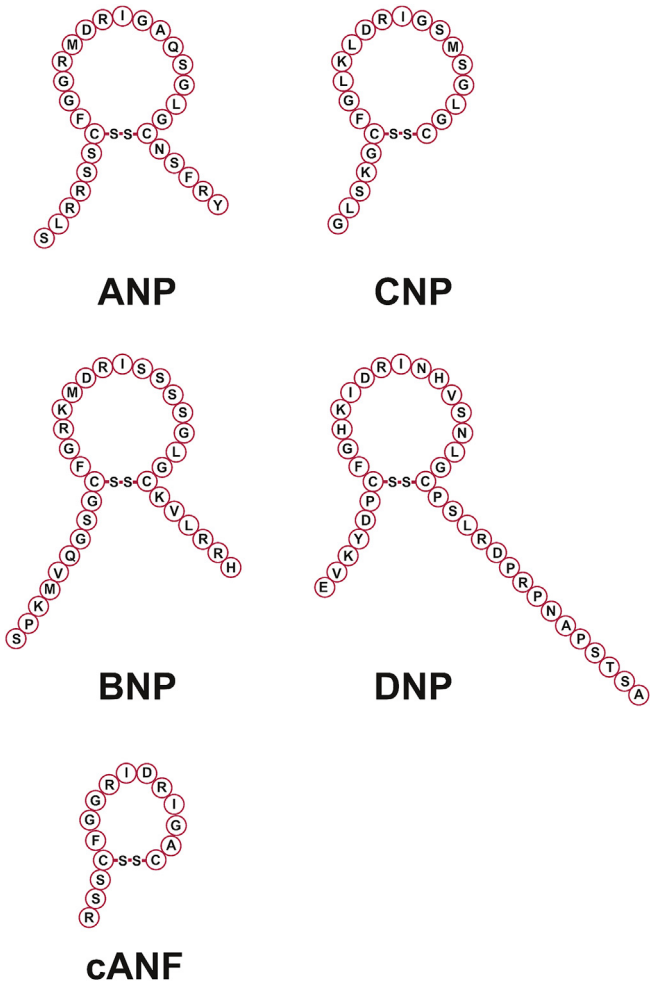

Fig. 1. Amino acid sequence and structure of natriuretic peptides. ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CNP, C-type natriuretic peptide; DNP, *Dendroaspis* natriuretic peptide; cANF, synthetic agonist of natriuretic peptide receptor C (NPR-C). Figure originally published in Jansen and Rose (2015).

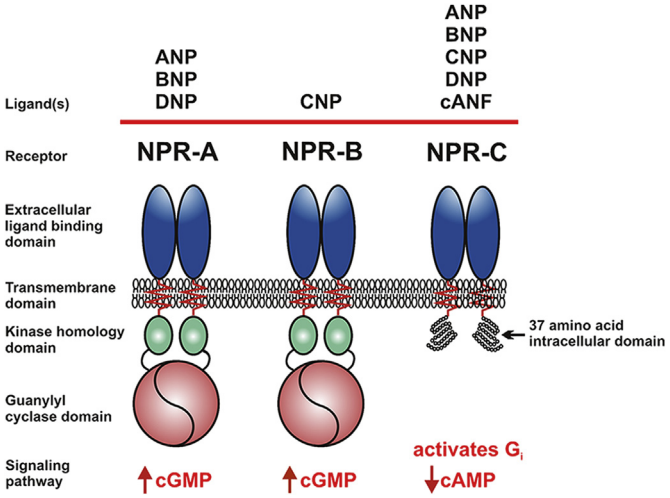

Fig. 2. Structure and function of natriuretic peptide receptors. NPR-A, natriuretic peptide receptor A; NPR-B, natriuretic peptide receptor B; NPR-C, natriuretic peptide receptor C. NPR-A and NPR-B are particulate guanylyl cyclase-linked receptors that mediate the production of cGMP upon ligand binding. NPR-C is coupled to the activation of inhibitory G-proteins (G_i) that cause a reduction in cAMP production.

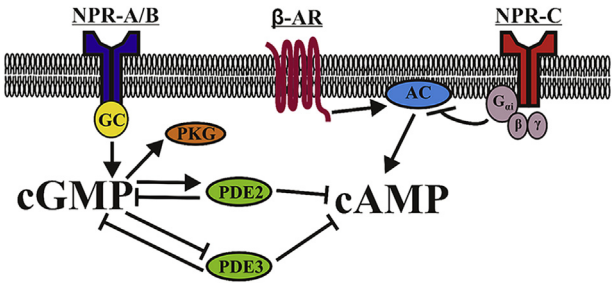

Fig. 3. Intracellular signaling pathways activated downstream of natriuretic peptide receptors. β-AR, β adrenergic receptor; GC, guanylyl cyclase; AC, adenylyl cyclase; PKG, protein kinase G, PDE2, phosphodiesterase 2; PDE3, phosphodiesterase 3. Note that cAMP concentrations can be regulated by NPR-A and NPR-B via effects on PDEs as well as by NPR-C via effects on AC activity. Figure originally published in Jansen and Rose (2015).

Movsesian, 2007). PKG can phosphorylate numerous targets, including ion channels, in the heart while PDEs hydrolyze cAMP and cGMP and thus are critically involved in the regulation of cyclic nucleotide levels in the heart. Both PKG and PDEs are known to play important roles in regulating cardiac electrophysiology.

Elevation of intracellular cGMP following activation of NPR-A and NPR-B can lead to the modulation of intracellular signaling pathways in a highly complex manner. For example cGMP can activate PDE2 and inhibit PDE3. While PDE2 and PDE3 both hydrolyze cAMP (and cGMP) they are oppositely regulated by cGMP. Specifically, cGMP activates PDE2, which promotes cyclic nucleotide hydrolysis whereas cGMP inhibits PDE3, which causes an increase in cyclic nucleotides (Maurice et al., 2003). Whether PDE2 or PDE3 dominates the response to cGMP likely depends on a number of factors including the basal and stimulated levels of GC and adenylyl cyclase (AC) activities as well as the abundance and subcellular localization of each PDE subtype. Recent studies have shown that cGMP signaling is compartmentalized in cardiomyocytes and that the cGMP produced by NPs and particulate GC enzymes is tightly controlled by PDE2 localized near the plasma membrane (Castro et al., 2006). The concentration of cGMP that accumulates in the myocytes is also a critical determinant of how PDE2 and PDE3 contribute to an overall response because it takes more cGMP to activate PDE2 than it does to inhibit PDE3 (Bender and Beavo, 2006; Rivet-Bastide et al., 1997; Vandecasteele et al., 2001). Thus, low levels of cGMP would only inhibit PDE3 while higher concentrations of cGMP can simultaneously inhibit PDE3 and activate PDE2. In addition to these effects on PDEs, cGMP also activates PKG, which can phosphorylate numerous targets in the heart including ion channels (Feil et al., 2003; Lohmann et al., 1997; Mery et al., 1991; Ono and Trautwein, 1991; Wang et al., 2000). Thus, once NPs activate NPR-A or NPR-B and increase cGMP there is a range of potential signaling pathways that could contribute to the overall effects of NPs on cardiac electrophysiology. How NPs utilize these different pathways is still incompletely understood.

The third NP receptor, NPR-C, is able to bind all NPs with comparable affinity (Anand-Srivastava, 2005; Rose and Giles, 2008). Unlike the other NPRs, NPR-C does not contain a GC domain and has no ability to directly modulate cGMP levels (Anand-Srivastava, 2005). It may be partly due to this observation that NPR-C was originally classified as a 'clearance receptor' with no signaling function (Maack et al., 1987). Rather, it was hypothesized that NPR-C functioned to remove NPs from the circulation for degradation, thereby modulating the available concentration of NPs in the circulation that can bind to NPR-A and NPR-B.

While some studies of NPR-C have been interpreted in the context of this clearance hypothesis (Matsukawa et al., 1999) it is now well known that NPR-C is coupled to a pertussis toxin sensitive inhibitory heterotrimeric G protein (G_i) (Fig. 3) (Anand-Srivastava, 2005; Rose and Giles, 2008). The evidence for this is overwhelming and clearly demonstrates that NPR-C is involved in the activation of G_i-dependent signaling pathways in the heart. Interestingly, NPR-C is not a traditional 7 transmembrane domain G-protein coupled receptor. Instead, NPR-C contains a specific G_i-activator domain within the 37 amino acid intracellular portion of the receptor that is activated when NPs are bound to NPR-C (Anand-Srivastava et al., 1996; Pagano and Anand-Srivastava, 2001; Zhou and Murthy, 2003). In this way, activation of NPR-C leads to the inhibition of AC activity and a reduction in intracellular cAMP levels via the $G_{\alpha i}$ subunit. Activation of NPR-C also modulates phospholipase C (PLC_β) signaling via the $\beta\gamma$ subunit of the G_i protein (Anand-Srivastava, 2005). The reader is referred to several excellent reviews that address the basic structure and biology of NPs and their receptors in greater detail (Anand-Srivastava, 2005; Lucas et al., 2000; Potter et al., 2006; Rose and Giles, 2008).

A number of studies have examined NPR expression patterns in the heart and these studies reveal important regional differences in expression that have implications for understanding the effects of NPs in different regions of the myocardium. Specifically, while mRNAs for all three NPRs are present throughout the heart, NPR-C is the most highly expressed and is present at higher levels than NPR-A and NPR-B (Anand-Srivastava and Trachte, 1993). Furthermore, expression of all NPRs is higher in the atria (right and left) than in the ventricular myocardium under normal conditions (Egom et al., 2015). Expression of NPRs has also been studied in the sinoatrial node (SAN; the pacemaker of the heart). These studies demonstrate that all three NPRs are more highly expressed in the SAN than the ventricular myocardium (Egom et al., 2015). Expression of NPR-C is higher in the right atrium than the SAN while expression of NPR-A and NPR-B is similar in the SAN and working atria (Egom et al., 2015; Springer et al., 2012).

3. Effects of NPs on heart rate and cardiac electrophysiology *in vivo*

A number of studies have measured the effects of different NPs on heart rate (HR) and electrophysiological properties *in vivo* using several model organisms as well as in humans (Table 1) (Clemo et al., 1996; Gollob et al., 2006). For example, in anesthetized and vagotomised dogs, ANP was found to have no effect on HR while CNP elicited a significant increase in HR (Beaulieu et al., 1996, 1997). This increase in HR elicited by CNP was associated with an increase in the frequency of spontaneous action potentials (APs) in the sinoatrial node (SAN) as measured with microelectrode recordings in atrial preparations. Infusion of BNP in anesthetized dogs and mice also failed to change HR (Bielmann et al., 2015; Bishu et al., 2011). Other studies, however, have reported reductions in HR in dogs following ANP administration (Goetz et al., 1986; Kleinert et al., 1986; Koyama et al., 1986; Lambert et al., 1994). Reductions in HR following ANP infusion have also been reported in rats (Ackermann, 1986; Ackermann et al., 1984; Allen and Gellai, 1987; Hirata et al., 1985). In humans ANP has been shown to have no effect on HR in some studies (Crozier et al., 1993; Volpe et al., 1990, 1987), while others suggest that ANP can either increase or decrease HR depending on the dose of ANP being delivered (Biollaz et al., 1986; Bussien et al., 1986; Franco-Saenz et al., 1987; Nicholls and Richards, 1987; Weidmann et al., 1986). The cellular and molecular mechanisms for these changes in HR were not investigated in detail in these studies.

The effects of ANP on other electrophysiological parameters have also been assessed. In dogs, ANP has been reported to decrease atrial effective refractory period (AERP) or monophasic AP duration

Table 1
Summary of the effects of natriuretic peptides in the heart *in vivo* and in multicellular cardiac preparations.

Parameter	Species	Cell-type	Peptide	Effect	References
HR, beating rate	Mouse		BNP/CNP	↑	(Azer et al., 2014; Azer et al., 2012; Springer et al., 2012)
			BNP	No effect	(Bielmann et al., 2015)
	Dog		ANP	No effect	(Beaulieu et al., 1996; Stambler and Guo, 2005)
				↓	(Goetz et al., 1986; Kleinert et al., 1986; Koyama et al., 1986; Lambert et al., 1994)
			BNP	No effect	(Bishu et al., 2011)
			CNP	↑	(Beaulieu et al., 1996; Beaulieu et al., 1997)
	Rat		ANP	↓	(Ackermann, 1986; Ackermann et al., 1984; Allen and Gellai, 1987; Hirata et al., 1985)
	Human		ANP	No effect	(Crozier et al., 1993; Volpe et al., 1990; Volpe et al., 1987)
			ANP	↑	(Biollaz et al., 1986; Bussien et al., 1986; Weidmann et al., 1986)
				↓	(Franco-Saenz et al., 1987)
ERP	Human	Atrial	ANP	↓	(Crozier et al., 1993)
		Ventricular	ANP	No effect	
	Dog	Atrial	ANP	↓/No effect	(Clemo et al., 1996; Stambler and Guo, 2005)
		Ventricular	ANP	↑	(Murakawa et al., 1998)
				No effect	(Stambler and Guo, 2005)
	Rat, Goat	Atrial	ANP	No effect	(Hodgson-Zingman et al., 2008; Wijffels et al., 1997)
APD	Human, Rabbit	Atrial	ANP	↓	(Kecskemeti et al., 1996)
	Mouse	SAN	BNP/CNP	↑	(Azer et al., 2014; Springer et al., 2012)
		Atrial	BNP/CNP	No effect	(Azer et al., 2014; Springer et al., 2012)
	Dog	Atrial	ANP	↓/No effect	(Stambler and Guo, 2005)
		Ventricular	ANP	No effect	
	Guinea pig	Ventricular	ANP	↓	(Kecskemeti et al., 1996)
				No effect	(Yang et al., 1989)
CV	Mouse	SAN, Atrial	BNP/CNP	↑	(Azer et al., 2014)

ERP, effective refractory period; APD, action potential duration; CV, conduction velocity.

in control conditions, but to have no effect on AERP and AP duration after vagal blockade (Stambler and Guo, 2005). At higher doses of ANP there was no effect on AERP in dogs (Clemo et al., 1996). ANP also had no effect on AERP in rats or goats (Hodgson-Zingman et al., 2008; Wijffels et al., 1997). In humans, ANP infusion sped conduction in the atria (as evidenced by a reduction in PR interval) and shortened AERP (Crozier et al., 1993). ANP was shown to have no effect on ventricular effective refractory period in one study (Stambler and Guo, 2005) while a separate investigation found that ventricular effective refractory period was increased following ANP administration (Murakawa et al., 1998).

The effects of ANP on AP duration, which is a determinant of refractory period, have also been studied in isolated papillary muscles, again with conflicting results. For example, ANP decreased AP duration in human and rabbit atrial papillary muscles (Kecskemeti et al., 1996), but had no effect on AP duration in guinea pig ventricular papillary muscles (Kecskemeti et al., 1996; Yang et al., 1989).

Clearly, the reported effects of NPs on HR and electrophysiological parameters have been conflicting. Differences in species, region of the heart under investigation (sinoatrial node, atria, ventricles) and experimental conditions could all contribute to the differences that have been observed in different studies. For example, as discussed in further detail below, different NPRs can be activated in different experimental conditions. Furthermore, signaling downstream of these receptors is complex, involving multiple interacting pathways. Experimental conditions that favor the activation of one signaling pathway over others can result in the same peptide eliciting different effects on cardiac electrophysiology as distinct pathways are targeted. These factors have likely contributed importantly to the conflicting observations among different studies. It is also important to note that NPs can affect cardiac electrophysiology *in vivo* through direct effects in the heart as well as via effects in the autonomic nervous system (Clemo et al., 1996; Gollob et al., 2006). NPs are present in the circulation, but are also produced locally in the heart, including in myocytes and fibroblasts (Huntley et al., 2006; Jansen and Rose, 2015; Potter et al., 2006; Rose and Giles, 2008). Thus, the local concentrations of NPs within the heart are likely much higher than those present in the circulation and this needs to be considered when interpreting the effects of NPs on cardiac electrophysiology. Most recently (as mentioned above) it is becoming evident that the expression and/or regulation of NPRs and downstream signaling molecules can be unique in different regions of the myocardium and this may also impact the effects of NPs on cardiac electrophysiology.

4. Electrophysiological effects of NPs and NPRs in cardiomyocytes

To better understand the electrophysiological effects of NPs in the heart a number of studies have been performed using isolated cardiomyocytes and/or isolated hearts (Table 2). The majority of these studies have focused on the L-type Ca^{2+} current ($I_{Ca,L}$), which has emerged as a key target of regulation by NPs. However, several other ion channels have also been found to be affected by NPs including the Na^+ current (I_{Na}), the hyperpolarization activated current carried by HCN channels (I_f), and several K^+ currents including the transient outward K^+ current (I_{to}), delayed rectifier K^+ currents (I_{Ks}) and ATP-sensitive K^+ currents. These findings are discussed in detail below.

As was the case for effects of NPs *in vivo*, the data describing NP effects on $I_{Ca,L}$ in the heart are inconsistent. In ventricular myocytes (rat, rabbit) NPs, including ANP, BNP and DNP, can decrease $I_{Ca,L}$ via cGMP-PKG signaling (Park et al., 2012; Sodi et al., 2008; Tohse et al., 1995) suggesting these effects are mediated by NPR-A and NPR-B. ANP has also been shown to reduce $I_{Ca,L}$ in mouse embryonic stem cells (Miao et al., 2010), chick embryonic myocytes (Bkaily et al., 1993) and frog ventricular myocytes (Gisbert and Fischmeister, 1988) via the activation of cGMP signaling implying a role for NPR-A. We have shown that the NPR-C selective agonist, cANF (Fig. 1), can inhibit isoproterenol (ISO) stimulated $I_{Ca,L}$ in mouse ventricular myocytes and frog atrial myocytes indicating that NPR-C can also contribute to the inhibition of $I_{Ca,L}$ in the heart (Rose and Giles, 2008; Rose et al., 2003).

In human atrial myocytes ANP has been shown to increase $I_{Ca,L}$ in some conditions (e.g. when GTP is absent from the pipette

Table 2
Summary of the effects of natriuretic peptides on ionic currents in the heart.

Parameter	Species	Cell type	Peptide	Experimental condition	Effect	References
I_{Na}	Mouse, Rat, Guinea pig, Chick	Atrial, ventricular, embryonic cardiomyocytes	ANP (1–100 nM)	Basal	↓	(Sorbera and Morad, 1990)
				Basal; ISO (10 nM)	No effect	(Bkaily et al., 1993; Hua et al., 2015; Sorbera and Morad, 1990)
I_{to}	Human	Atrial myocytes	ANP (10 nM)	Basal; ISO (100 nM)	↓	(Le Grand et al., 1992)
$I_{Ca,L}$	Human	Atrial myocytes	ANP (10 nM/100 nM)	Basal; ISO (10 nM/100 nM)	↑ or ↓	(Boixel et al., 2001a; Le Grand et al., 1992)
	Mouse	SAN myocytes	BNP/CNP (100 nM)	Basal	↑	(Springer et al., 2012)
			CNP (100 nM)	ISO (100 nM)	↓	(Rose et al., 2004)
		Atrial myocytes	ANP/BNP (100 nM)	Basal	No effect	(Hua et al., 2015; Springer et al., 2012)
				ISO (10 nM)	↑	
	Rat	Ventricular myocytes	BNP (500–1000 nM)	Basal	↓	(Sodi et al., 2008)
	Rabbit, Chick, Mouse	Ventricular, embryonic cardiomyocytes	ANP(1–100 nM)/DNP (10–1000 nM)	Basal	↓	(Bkaily et al., 1993; Miao et al., 2010; Park et al., 2012; Tohse et al., 1995)
				Basal; ISO (100 nM)		
	Frog	Atrial myocytes Ventricular myocytes	ANP/CNP (1–100 nM)	Basal	↓	(Gisbert and Fischmeister, 1988; Rose et al., 2003)
				ISO (≥100 nM)		
sK_{ATP}	Rat	Ventricular myocytes	BNP CNP ≤1 nM	Basal	No effect	(Burley et al., 2014)
			≥10 nM		↓	
I_f	Human	Atrial myocytes	ANP (0.1 nM)	Basal	↑	(Lonardo et al., 2004)
	Mouse	SAN myocytes	BNP/CNP (100 nM)	Basal	↑	(Springer et al., 2012)
				ISO (100 nM)	No effect	(Rose et al., 2004)
		Embryonic cardiomyocytes	ANP (20 nM)	Basal	No effect	(Miao et al., 2010)
I_K	Chick	Embryonic cardiomyocytes	ANP (0.1–10 nM)	Basal	↑	(Bkaily et al., 1993)
I_{Ks}	Guinea pig, Mouse	SAN, embryonic cardiomyocytes	ANP (20–100 nM)	Basal	↑	(Shimizu et al., 2002)
					No effect	(Miao et al., 2010)

I_{Na}, sodium current; I_{to}, transient outward K^+ current; $I_{Ca,L}$, L-type Ca^{2+} current; sK_{ATP}, ATP activated K^+ current; I_f, hyperpolarization activated current, I_K, delayed rectifier K^+ current; I_{Ks}, slowly activating delayed rectifier K^+ current.

solution) and decrease it in others (e.g. when GTP is included in the pipette solution) (Boixel et al., 2001a; Le Grand et al., 1992). These inhibitory effects of ANP have been attributed to changes in cGMP signaling (i.e. NPR-A). A role for cAMP signaling via PDEs has also been suggested based on the finding that the inhibitory effects of ANP on $I_{Ca,L}$ were blocked by IBMX (Boixel et al., 2001a) although a separate study showed that ANP could still inhibit $I_{Ca,L}$ in the presence of the global PDE inhibitor IBMX (Le Grand et al., 1992). We have shown that ANP can stimulate $I_{Ca,L}$ in human atrial myocytes in basal conditions and in the presence of ISO (Hua et al., 2015). As discussed in detail below, we have shown that stimulatory effects of NPs on $I_{Ca,L}$ involve a cGMP-mediated inhibition of PDE3 (Springer et al., 2012).

These variable results are likely related to an incomplete understanding of how NPs signal through their different receptor subtypes in different conditions. Based on this hypothesis, we have undertaken several comprehensive studies to determine the electrophysiological effects of NPs on ion channel function in the SAN and atria in mice and humans. Given the complexity of NP signaling in the heart, our goal has been to determine how different NPRs and signaling molecules contribute in different cell types and experimental conditions.

Our studies demonstrate that NPs can potently regulate HR through effects on the specialized pacemaker myocytes in the SAN (Azer et al., 2012; Rose et al., 2007; Springer et al., 2012). Critical for pacemaker activity, SAN myocytes display spontaneous action potentials (APs) during which the myocytes gradually depolarize during the diastolic period until the threshold for the next AP is reached. This diastolic depolarization (DD) is the fundamental feature that enables spontaneous activity in SAN myocytes (DiFrancesco, 1993; Irisawa et al., 1993). Several ionic mechanisms contribute to the generation of the DD including the hyperpolarization activated current I_f, a T-type Ca^{2+} current ($I_{Ca,T}$), two forms of L-type Ca^{2+} current ($Ca_V1.3$ and $Ca_V1.2$), a delayed rectifier K^+ current (I_{Kr}), sodium current (I_{Na}) and an inward Na^+-Ca^{2+} exchange current (I_{NCX}) driven by sarcoplasmic reticulum (SR) Ca^{2+} release (Lakatta et al., 2010; Lei et al., 2004; Mangoni and Nargeot, 2008). Modulation of these currents alters the DD slope, which is a major mechanism for eliciting changes in HR.

We found that, in basal conditions, BNP and CNP both dose-dependently increase HR in isolated Langendorff-perfused mouse hearts with very similar EC_{50} values in the nanomolar range (Springer et al., 2012). Furthermore, in isolated SAN myocytes, BNP and CNP each increased spontaneous AP firing frequency in association with increases in the DD slope and AP duration, but without differences in maximum diastolic potential (MDP). Voltage clamp studies revealed that these changes in AP firing properties were the result of increases in I_f and total $I_{Ca,L}$ (i.e. carried by $Ca_V1.2$ and $Ca_V1.3$) in the presence of BNP or CNP. I_f and $I_{Ca,L}$ were increased in association with shifts in the voltage dependence of channel activation ($V_{1/2(act)}$). To determine the mechanism for these electrophysiological effects we used NPR-C knockout (NPR-$C^{-/-}$) mice and a pharmacological approach. These studies demonstrate that the stimulatory effects of BNP and CNP on spontaneous AP firing, I_f and $I_{Ca,L}$ in NPR-$C^{-/-}$ mice are indistinguishable from wildtype mice, indicating that NPR-C does not contribute to changes in SAN function in basal conditions. However, the effects of BNP were completely antagonized by the NPR-A blocker A71915. Also, the effects of BNP and CNP on SAN myocyte electrophysiology were occluded by the PDE3 inhibitor milrinone. Collectively, these experiments illustrate that BNP and CNP can potently increase HR and spontaneous AP firing in SAN myocytes by activating the GC-linked NPR-A and NPR-B receptors and inhibiting PDE3 activity (Springer et al., 2012). Consistent with these findings, ANP has also been shown to elicit a cGMP-dependent increase in I_f in human atrial myocytes (Lonardo et al., 2004).

Importantly, although NPR-C did not affect SAN function in basal conditions, it does contribute importantly in the presence of β-adrenergic receptor (β-AR) activation (Azer et al., 2012; Springer et al., 2012). Specifically, in addition to the experiments described

above, we demonstrated that cANF (NPR-C agonist) has no effect on HR (measured by ECG in Langendorff-perfused hearts) or SAN myocyte AP firing in basal conditions in mice. In contrast, in the presence of ISO, cANF dose-dependently decreases HR and slows spontaneous AP firing by decreasing the DD slope in SAN myocytes (Azer et al., 2012). These effects of cANF are completely absent in NPR-$C^{-/-}$ mice confirming they are mediated by the NPR-C receptor. To explore the contributions of different NPRs to these responses we compared the effects of BNP and CNP (which can activate NPR-A/B as well as NPR-C) to cANF (which only activates NPR-C). These measurements show that BNP and CNP increase HR and AP firing in submaximal (10 nM) doses of ISO, but these effects are smaller than those observed in basal conditions because, in the presence of ISO, BNP and CNP activate NPR-A/B (which mediate an increase in HR and AP firing) as well as NPR-C (which mediates a decrease in HR and AP firing). Most strikingly, in the presence of maximum doses of ISO (1 μM) BNP and CNP switched to eliciting reductions in HR and slowing spontaneous AP firing in SAN myocytes. Once again, we proved that this response occurred in association with the simultaneous activation of multiple NPRs. Specifically, we showed that selectively activating NPR-C in the presence of 1 μM doses of ISO with cANF resulted in a larger reduction in HR and AP firing than those seen with BNP or CNP. However, blocking NPR-A enabled BNP to reduce HR to a similar extent as cANF because in these condition BNP can only target NPR-C. Finally, when BNP was applied in the presence of 1 μM ISO in NPR-$C^{-/-}$ mice it elicited an increase in HR rather than a decrease because only the NPR-A receptor (which is stimulatory) could be activated. Collectively, these studies demonstrate that NPs can modulate SAN function via the NPR-A/B receptors (stimulatory) and NPR-C (inhibitory) and that these receptors elicit opposing effects. Because of this, NPs can increase HR and SAN function in some conditions, but decrease HR in others and this is dependent on the extent of β-AR activation (i.e. AC activity) (Azer et al., 2012).

We have also studied the effects of CNP and cANF on $I_{Ca,L}$ and I_f in the presence of maximum doses of ISO (1 μM) in mouse SAN myocytes (Rose et al., 2004). Consistent with the effects described above, we found that CNP can decrease $I_{Ca,L}$ via the NPR-C receptor. This was confirmed with the use of a synthetic G_i-activator peptide corresponding to the portion of the NPR-C receptor responsible for activating G_i. Interestingly, neither CNP nor cANF had any significant effect on I_f in SAN myocytes treated with ISO. The reasons why I_f was not modulated when $I_{Ca,L}$ was are not known, but may indicate a compartmentation of cAMP signaling downstream of NPR-C in the SAN.

In addition to modulating HR, we have also found that NPs can affect P wave duration and PR interval indicating changes in conduction across the atria and through the atrioventricular node (Azer et al., 2012; Springer et al., 2012). To explore this further we have studied the effects of ANP, BNP and CNP on atrial myocyte electrophysiology in mice and humans (Hua et al., 2015; Springer et al., 2012). These studies reveal important similarities, as well as differences, from the effects observed in SAN myocytes.

In contrast to SAN myocytes, neither ANP nor BNP have any effect on atrial myocyte AP morphology in basal conditions in mice (Hua et al., 2015; Springer et al., 2012). In the presence of low doses of ISO (10 nM); however, both NPs increased atrial myocyte AP duration in association with increases in atrial $I_{Ca,L}$. Similarly to the SAN, these increases in atrial $I_{Ca,L}$ occurred following activation of NPR-A and the inhibition of PDE3. We have also shown that ANP stimulated $I_{Ca,L}$ in human right atrial myocytes (Hua et al., 2015). Interestingly, we showed that, in the human, this stimulatory effect is seen in basal conditions and in the presence of ISO (10 nM) whereas in mice ANP only stimulated atrial $I_{Ca,L}$ in the presence of ISO. We (Hua et al., 2012, 2015; Springer et al., 2012) and others (Rozmaritsa et al., 2014; Vandecasteele et al., 2001; Vinogradova et al., 2008) have shown that SAN (mice, rabbits) and human atria have constitutive PDE3 activity while mouse atria do not. Since PDE3 is a key mediator of the stimulatory effects of NPs this explains why effects are observed in basal conditions in mouse SAN and human atrial myocytes, but not in mouse atrial myocytes. Thus, differences in PDE activity among different cell types or species are a critical determinant of how NPs affect cardiac electrophysiology.

These studies highlight another critical point, which is that in some conditions a single NPR can dominate the response to NPs while in other conditions NPs can activate multiple NPRs simultaneously. This leads to the activation of multiple interacting signaling pathways and can result in distinct electrophysiological effects of NPs in different conditions. This likely explains some of the inconsistent findings in the literature and illustrates the importance of considering how multiple NPRs may be contributing the overall effects of NPs.

Collectively, our studies demonstrate that the GC-linked NPRs and NPR-C can contribute to the electrophysiological effects of NPs in the heart and that cAMP is a central target for regulation (via GMP mediated effects on PDEs and via effects on AC activity). Furthermore, $I_{Ca,L}$ and I_f are key ionic currents that are targeted by NPs. Nevertheless, it is possible that other ion channels, such as Na^+ or K^+ channels, may also be modulated by NPs. For example, one study has reported that ANP could inhibit I_{Na} in rat and guinea pig ventricular myocytes (Sorbera and Morad, 1990), although it must be noted that this study measured I_{Na} without the use of Ca^{2+} channel blockers, which may affect the validity of this finding. Indeed ANP had no effect on I_{Na} in fetal chick ventricular myocytes (Bkaily et al., 1993) or mouse atrial myocytes (Hua et al., 2015). The absence of effects of ANP on atrial I_{Na} was somewhat surprising because studies in isolated rat and rabbit ventricular myocytes demonstrate that cardiac Na^+ channels are sensitive to cAMP (Lu et al., 1999; Matsuda et al., 1992; Yarbrough et al., 2002) and it is clear that NPs can modulate cAMP, which affects other ion currents such as $I_{Ca,L}$. Thus, additional studies will be required to determine whether NPs can modulate I_{Na} in atrial or ventricular myocytes in some experimental conditions, but not others.

NP effects on K^+ channels have not been extensively studied; however there is evidence that ANP can increase I_{to} in human atrial myocytes (Le Grand et al., 1992) and I_{Ks} in guinea pig SAN myocytes (Shimizu et al., 2002). ANP also increased K^+ current in chick embryonic cardiomyocytes (Bkaily et al., 1993). Finally, there is evidence that BNP and CNP can modulate an ATP sensitive K^+ current in rat ventricular myocytes (Burley et al., 2014). Several K^+ currents, including I_{Kur} (carried by $K_V1.5$), I_{Kr} (carried by K_V11 family) and I_{Ks} (carried by K_V7 family) are importantly regulated by cAMP (Aflaki et al., 2014; Cui et al., 2000; Ding et al., 2002; Kiehn et al., 1998; Li et al., 1996). Given that cAMP is central to the electrophysiological effects of NPs in the heart it will be important to study the effects of NPs on these K^+ channels in more detail.

5. Effects of NPs on electrical conduction

Changes in HR and P wave duration in the presence of NPs are suggestive of changes in patterns of electrical conduction within the SAN and the atria. This has been studied using high resolution optical mapping in isolated atrial preparations that enable the assessment of activation patterns and conduction properties in the SAN and the atria (Azer et al., 2014; Hua et al., 2015). Similar to the studies in isolated myocytes, mapping studies in atrial preparations show that NPs have complex effects on conduction that can be mediated by multiple NPRs and which are dependent on experimental conditions. In basal conditions BNP and CNP increased local conduction velocity (CV) in the SAN and atria and also increased DD

slope and AP duration in the SAN. Interestingly, this occurred in conjunction with a superior shift in the leading pacemaker site within the SAN. Changes in location of the leading pacemaker site are thought to be an important mechanism for changing SAN function and HR *in vivo* (Bouman et al., 1968; Fedorov et al., 2006; Glukhov et al., 2010). These stimulatory effects were mediated by the NPR-A and NPR-B receptors. ANP has also been shown to increase CV in the right and left atria in the presence of low (10 nM) doses of ISO via activation of NPR-A (Hua et al., 2015) (discussed further below).

In the presence of maximum doses of ISO (1 μM) NPR-C made a critical contribution to the effects of BNP and CNP on electrical conduction (Azer et al., 2014). Specifically, BNP, CNP and the NPR-C agonist cANF each decreased SAN and atrial CV and also decreased AP duration in these regions of the myocardium. In the presence of ISO these NPs now shifted the leading pacemaker site inferiorly within the SAN. The effects of cANF were larger than BNP and CNP and were blocked by the NPR-C antagonist AP-811. Furthermore, the inhibitory effects of BNP were absent in NPR-$C^{-/-}$ hearts where BNP instead produced a further increased in CV. Thus, in these experimental conditions, BNP and CNP elicit their effects via the NPR-A/B receptors as well as NPR-C, which have opposing effects on electrical conduction.

6. Electrophysiological effects of NPs and NPRs in cardiac fibroblasts

Although cardiac myocytes account for the majority of myocardial volume fibroblasts are, in fact, the most numerous cell type in the heart (Souders et al., 2009). Fibroblasts are generally regarded as non-excitable cells that play essential roles in the production and secretion of collagens and other extracellular matrix proteins (Brilla and Maisch, 1994; Brilla et al., 1995). Inappropriate deposition of extracellular matrix can result in pro-arrhythmic structural remodeling due to the disruption of electrical conduction in regions of enhanced fibrosis within the myocardium (Burstein and Nattel, 2008; Rohr, 2009). More recently it has also become clear that cardiac fibroblasts express a number of ion channels and display oscillations in membrane potential (Baudino et al., 2006). Some ion channels that have been functionally characterized in cardiac fibroblasts include K^+ channels (Chilton et al., 2005; Shibukawa et al., 2005), transient receptor potential (TRP) channels (Du et al., 2010; Harada et al., 2012; Rose et al., 2007) and, most recently, voltage-gated Na^+ channels (Chatelier et al., 2012). Although still poorly understood, it is hypothesized that cardiac fibroblasts may couple to cardiomyocytes via gap junctions, thereby affecting electrophysiological properties of the heart (Chilton et al., 2007; Kohl, 2003; Kohl et al., 2005).

Cardiac fibroblasts produce and secrete ANP, BNP and CNP (Harada et al., 1999; Horio et al., 2003; Tsuruda et al., 2002) which all have potent antifibrotic and antiproliferative effects on fibroblasts in the heart (Rose and Giles, 2008). Assessment of NPR expression specifically in cardiac fibroblasts demonstrates that all NPRs are present and that NPR-C is the most abundant NPR in rodent and human cardiac fibroblasts (Cao and Gardner, 1995; Huntley et al., 2010, 2006; Redondo et al., 1998). It has also been demonstrated that NPR-B may be more highly expressed in fibroblasts (ventricular) than cardiomyocytes (Doyle et al., 2002).

The electrophysiological effects of CNP, which is the most potent antifibrotic NP in the heart (Horio et al., 2003), have been measured in rat ventricular fibroblasts (Rose and Giles, 2008; Rose et al., 2007). Both CNP and the selective NPR-C agonist cANF potently activated a non-selective cation current that appears to be carried by the TRPC family of ion channels. Evidence for this includes blockade of the CNP/NPR-C activated current by Gd^{3+}, SKF 96365 and 2 aminoethoxydiphenyl borate (2-APB) which are all known to block a number of TRP channels (Clapham, 2003; Clapham et al., 2001; Rose et al., 2007). Furthermore, the effects of CNP and cANF on this non-selective cation current were blocked by the phospholipase C antagonist U73122 and mimicked by intracellular application of the diacylglycerol (DAG) analogue 2-oleyl-2-acetyl-*sn*-glycerol (OAG). The latter finding is a defining characteristic of members of the TRPC family, including TRPC3, 6, and 7, which are activated by DAG independently of protein kinase C (PKC) (Hofmann et al., 1999). Consistent with this hypothesis, cardiac fibroblasts were shown to express TRPC3 at relatively high levels, as well as TRPC6 and 7 at lower levels. Finally, the effects of CNP and cANF on TRPC-like currents in cardiac fibroblasts were antagonized by pertussis toxin supporting the hypothesis that CNP acts via NPR-C and G_i in cardiac fibroblasts. PLCβ signaling has been shown to be activated via the βγ subunits of these G_i proteins (Anand-Srivastava, 2005; Murthy et al., 2000; Zhou and Murthy, 2003). Interestingly, TRPC3 channels have been directly implicated in the pathogenesis of atrial fibrillation (AF) (Harada et al., 2012; Rose et al., 2012), although it is presently unknown if NP effects on TRPC channels affect arrhythmogenesis.

Further evidence for a role for NPs in regulating arrhythmogenesis via effects on cardiac fibroblasts comes from our studies of NPR-C ablation in mice (Egom et al., 2015). Specifically, NPR-C knockout (NPR-$C^{-/-}$) mice were found to display impaired SAN function (as evidenced by a prolongation of sinoatrial node recovery times) and increased susceptibility to AF in association with a slowing of conduction throughout the atrial myocardium including in the SAN itself. Interestingly, AP morphology in isolated SAN and atrial myocytes was not altered in NPR-$C^{-/-}$ mice. Rather, NPR-$C^{-/-}$ mice were found to display increased fibrosis and increased expression of collagens I and III in the SAN and atrial myocardium indicating that atrial arrhythmogenesis and conduction slowing occurred due to structural remodeling of the extracellular matrix. This is consistent with data demonstrating that enhanced fibrosis can be an important contributor to conduction disturbances leading to AF and SAN dysfunction (Burstein and Nattel, 2008; Wolf et al., 2013). Also noteworthy was the observation that ventricular structure, function and arrhythmogenesis were all normal in NPR-$C^{-/-}$ mice indicating that the phenotype in these mice is restricted to the atrial myocardium. This is consistent with the finding that NPRs, including NPR-C, are more highly expressed in the atrial myocardium compared to the ventricular myocardium (Egom et al., 2015).

Collectively, these studies demonstrate that NPs have acute effects on ion channels in cardiac fibroblasts and that loss of NPR-C results in SAN dysfunction and AF due to a slowing of atrial conduction in association with enhanced fibrosis. Several questions remain to be answered, which should provide further crucial insight into how NPs affect cardiac electrophysiology and arrhythmogenesis via their effects on cardiac fibroblasts. For example, the precise identity of the TRPC channels that are modulated by CNP remain to be identified. Also, whether these channels are also modulated by other NPs or downstream of NPR-A/B has not been investigated. NPs have potent antifibrotic effects which can be mediated by the GC-linked NPRs as well as NPR-C (Horio et al., 2003; Huntley et al., 2010, 2006); however, whether these effects involve changes in fibroblast electrophysiology, possibly via calcium influx through non-selective cation channels, remains unknown. Ongoing experiments are also needed to determine how the loss of NPR-C leads to atrial fibrosis. NPs are known to elicit their antifibrotic effects, at least in part, by opposing the actions of profibrotic compounds including angiotensin II and transforming growth factor β in cardiac fibroblasts (Jansen and

Rose, 2015). Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) are also involved in the antifibrotic effects of NPs (Jansen and Rose, 2015). Accordingly, it is possible that loss of NPR-C affects one or more of these signaling molecules in atrial fibroblasts.

7. Mutations in the NP system and atrial fibrillation

Recently, mutations in genes encoding NPs have been identified, which result in the occurrence of AF in humans. For example, an adenine to cytosine substitution at nucleotide 190 in exon 2 of the *NPPA* gene (the gene that encodes ANP) results in the production of a proANP peptide fragment that augments the slow delayed rectifier K^+ current (I_{Ks}) when this channel is expressed heterologously (Abraham et al., 2010). Computational modeling predicts that this mutation would also lead to alterations in $I_{Ca,L}$ and atrial AP shortening, which would create a substrate for AF by reducing refractoriness and shortening the wavelength of re-entry.

Another study (Hodgson-Zingman et al., 2008) identified a family with a frameshift mutation in the *NPPA* gene that results in the production of a 40 amino acid mutant ANP (mANP) that consists of the normal 28 amino acid ANP with an abnormal 12 amino acid C-terminal extension (Fig. 4). This mANP was found to circulate at concentrations 5 to 10 times greater than wildtype ANP in patients affected by this mutation due to an increased resistance to proteolytic degradation (Dickey et al., 2009; Hodgson-Zingman et al., 2008). Initially, this led to the hypothesis that mANP may simply enhance the effects of wildtype ANP and that this could create a substrate for AF. More recently, the cellular and molecular mechanisms by which mANP could create a substrate for AF were investigated in mice and humans (Hua et al., 2015). Surprisingly, these studies demonstrate that ANP and mANP have opposing effects on atrial electrophysiology independent of doses. Specifically, ANP was shown to increase AP upstroke velocity (V_{max}), AP duration and $I_{Ca,L}$ in isolated atrial myocytes via the NPR-A receptor in mice. Optical mapping studies in intact mouse atrial preparations further demonstrated that ANP speeds electrical conduction throughout the atria and increases atrial effective refractory period in association with increased AP duration. In contrast, mANP (delivered at the same doses as ANP) was found to decrease atrial AP V_{max}, shorten atrial AP duration, decrease atrial $I_{Ca,L}$, slow atrial CV, and shorten the atrial refractory period. These effects were mediated by the NPR-C receptor as the effects of mANP were completely absent in NPR-$C^{-/-}$ mice. Importantly, ANP and mANP also had opposing effects on $I_{Ca,L}$ in human right atrial myocytes isolated from atrial biopsies obtained from cardiac surgery patients. Finally, mANP was shown to be highly pro-arrhythmic in atrial programmed stimulation studies which showed that delivery of premature stimuli in the presence of mANP resulted in re-entrant conduction patterns, ectopic foci of activation and disorganized conduction in the atria in mice. In contrast, no arrhythmias were observed during atrial programmed stimulation in the presence of wildtype ANP indicating that ANP is protective in the heart. Collectively, these studies demonstrate that ANP and mANP have opposing effects on atrial electrophysiology and arrhythmogenesis via distinct receptor signaling pathways.

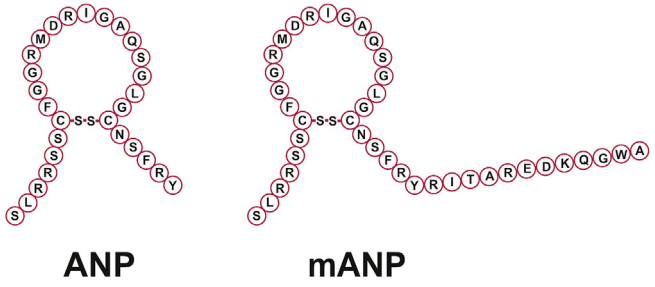

Fig. 4. Structure and amino acid sequence of wildtype ANP and mutant ANP (mANP). Note that mANP consists of the wildtype ANP (28 amino acids) with an abnormal 12 amino acid C-terminal extension.

The discovery of mutations in the *NPPA* gene that lead to AF clearly strengthens the conclusion that NPs are essential regulators of cardiac electrophysiology and arrhythmogenesis. These studies also strongly suggest that wildtype ANP is protective against the development of a substrate for the initiation and maintenance of AF by increasing AP duration and speeding atrial conduction, both of which would increase the wavelength of re-entry. The ability of ANP to protect against arrhythmias has not been well studied; however, there is evidence that ANP can reduce the incidence of post-operative AF during cardiothoracic surgeries (Nojiri et al., 2012; Sezai et al., 2007, 2015). Further studies are needed to determine the mechanism(s) for these observations. It must also be noted that, as discussed above, some studies have shown that wildtype ANP can decrease $I_{Ca,L}$ in human atrial myocytes in some conditions (Boixel et al., 2001a; Le Grand et al., 1992), which could decrease AP duration and favor a substrate for AF. Once again, the different patterns of results may be due to differences in experimental conditions which could result in the activation of distinct intracellular signaling pathways. Clarification of these issues should help in the future design of synthetic NPs that could be modified in ways that would favor one signaling pathway over another in order to optimize the protective effects of NPs.

8. Effects of NPs in heart disease and therapeutic considerations

Numerous studies have demonstrated that NPs have protective effects in the heart in the setting of cardiovascular disease. For example, preventing the secretion of ANP or BNP or genetically ablating NPs and their receptors enhances the development of heart failure (HF) in animal models (Lopez et al., 1995; Oliver et al., 1997; Tamura et al., 2000; Wada et al., 1994; Yasuno et al., 2009). It was initially thought that during the progression of cardiac diseases such as hypertension and HF, the heart increases its production and release of NPs in order to compensate for cardiac stress (Burnett et al., 1986; Richards, 2004; Wei et al., 1993). Indeed, circulating levels of ANP and BNP are used diagnostically and prognostically in human heart disease and elevations in these peptides has been associated with worsening of HF (Boerrigter et al., 2009; Richards, 2004; Wright and Struthers, 2006). More recently; however, it has become clear that human cardiovascular disease is actually associated with dysregulation of the NP system. For example, recent studies using more sophisticated and sensitive assay techniques have reported that patients with HF and hypertension actually lack mature functional BNP, suggesting alterations in the biological processing and degradation of proBNP or mature BNP itself (Belluardo et al., 2006; Hawkridge et al., 2005; Macheret et al., 2012; Mangiafico et al., 2013; Miller et al., 2011; Niederkofler et al., 2008; Nishikimi et al., 2013). Hypertension and heart failure should therefore be viewed as NP deficient pathological states.

This deficiency and hyporesponsiveness of the NP system forms the basis for the therapeutic use of NPs. Accordingly, several synthetic NPs are currently in use or in development for the treatment of heart failure including nesiritide (recombinant BNP), carperitide (recombinant ANP) and CD-NP, which is a chimeric NP that combines CNP with the C-terminal tail of DNP (Fig. 5) (Potter et al., 2006; Rose, 2010). Given the overwhelming evidence that NPs

elicit electrophysiological effects in the heart, it is possible that NPs could also be used as novel antiarrhythmic compounds in HF. NPs may protect against arrhythmias in a number of ways including via their effects on ion channel function in cardiomyocytes as well as through their antifibrotic effects in cardiac fibroblasts (because fibrosis is a major cause of electrical disturbances in the heart).

Although numerous studies demonstrate protective effects of NPs on cardiovascular function in HF, very few studies have evaluated the effects of NPs specifically on cardiac electrophysiology and arrhythmogenesis in the setting of heart disease. In one study performed in rats with HF, ANP was found to inhibit atrial $I_{Ca,L}$ less effectively than in sham controls (Boixel et al., 2001b). It has also been reported that BNP and CNP can decrease $I_{Ca,L}$ in ventricular myocytes from HF rats, although it is unclear how these responses compared to normal or sham rats (Moltzau et al., 2014a). There is also evidence that BNP and CNP can elicit distinct effects on sarcoplasmic reticulum Ca^{2+} handling and Ca^{2+} transient morphology in rats with HF, and that these effects involve changes in cGMP and PDEs (Moltzau et al., 2014a, 2014b; Qvigstad et al., 2010); however, the implications of these effects on cardiac electrophysiology and arrhythmogenesis are not known.

Clearly, there is a need to thoroughly and systematically evaluate the effects of NPs, and the role of the different NPRs, on cardiac electrophysiology and arrhythmogenesis in HF. Within such studies it will be essential to consider how changes in expression of NPRs and/or specific signaling molecules that are known to mediate the electrophysiological effects of NPs change in the setting of heart disease. For example, there is evidence that cGMP may be primarily produced by NPR-B activation rather than NPR-A activation in the failing heart due to a reduction in NPR-A activity (Dickey et al., 2007), which would suggest that CNP may more effectively enhance cGMP-dependent NP effects than ANP or BNP in this disease state. Cardiac hypertrophy and HF are also associated with a number of changes in PDE activity that could have implications for how NPs affect cardiac electrophysiology in heart disease. For example, hypertrophy and HF have been associated with increases in expression or activity of PDE2 and PDE5 as well as down-regulation of PDE3 (Guellich et al., 2014). Interestingly, recent evidence suggests that PDE5 may be retargeted within the left ventricle in the setting of pathological cardiac hypertrophy such that NP signaling, which is not modulated by PDE5 in the normal heart, may be importantly affected by PDE5 in heart disease (Zhang et al., 2012). Also, it has been recently shown that PDE9 expression is upregulated in the left ventricle in heart failure and that it plays an important role in regulating cGMP production downstream of NPRs in hypertrophic heart disease (Lee et al., 2015). The implications of these changes in PDE activity on the electrophysiological effects of NPs in HF are yet to be determined.

It will also be important to consider how novel chimeric NPs that are being developed for the treatment HF may affect cardiac electrophysiology in patients receiving these compounds. The electrophysiological effects of CD-NP, for example, are largely unexplored although CD-NP has been shown to decrease HR in anesthetized dogs (Lisy et al., 2008) suggesting it may have direct effects on ion channels in the SAN, as is the case for native NPs. CD-NP is unique because can bind all three NPRs (Dickey and Potter, 2011; Rose, 2010), which will likely result in this peptide having distinct effects on cardiac electrophysiology that will depend on how these NPRs (and their downstream signaling molecules) are activated in specific disease states or patients.

Collectively, the studies described above indicate that there are important changes in expression and function of NPRs and PDEs in the heart in pathological conditions. These changes likely have important implications for how NPs elicit effects on cardiac electrophysiology in heart disease; however, this has not been thoroughly studied.

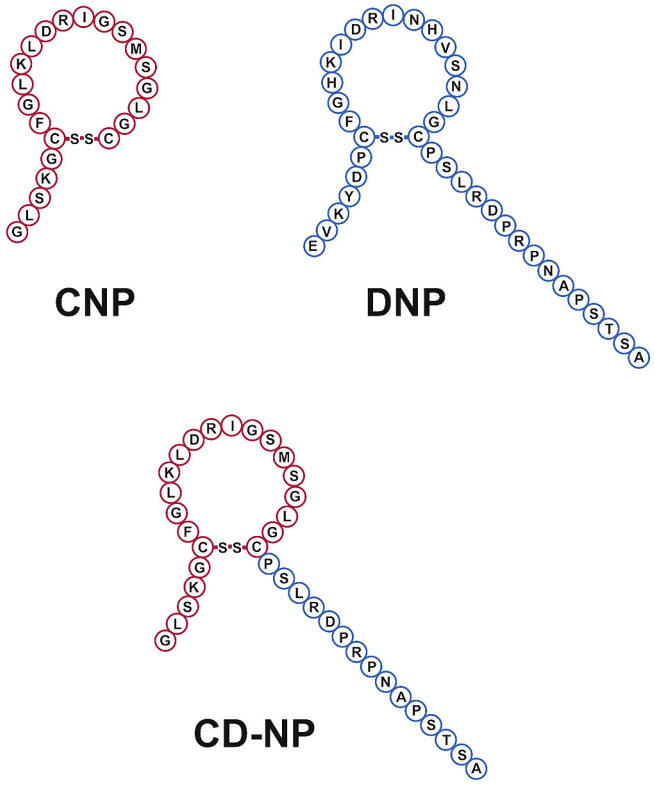

Fig. 5. Structure and amino acid sequence of CD-NP. CD-NP is a chimeric natriuretic peptide that is formed by combining wildtype CNP with the C-terminal tail of DNP.

9. Conclusion

NPs are critical regulators of cardiac function that are best known for their effects on blood pressure, natriuresis and diuresis. In addition to these well-known effects NPs are also potent and critical regulators of HR and electrophysiological properties in the heart though effects on ion channels in cardiomyocytes and cardiac fibroblasts. These findings, in combination with the identification of mutations in the NP system that lead to cardiac arrhythmias such as AF, firmly establish an essential role for NPs as regulators of cardiac electrophysiology and arrhythmogenesis.

Despite this significant progress in our understanding of the electrophysiological effects of NPs in the heart there is still much to be learned. NP signaling is highly complex and is distinct within different regions and cell types in the heart. Furthermore, NP signaling is likely altered in the setting of cardiovascular disease. Accordingly, further studies are needed to better understand how NPs elicit their electrophysiological effects in the heart in different conditions. It is essential to consider how different NPRs and signaling pathways, which can be activated simultaneously by NPs, contribute to the overall effects of NPs in normal hearts and in cardiovascular disease. Doing so should help in the future development of customized NPs for the treatment of cardiac arrhythmias.

Editors' note

Please see also related communications in this issue by Ripplinger et al. (2016) and Schindler and Brand (2016).

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