CONTEMPORARY REVIEW

The role of atrial natriuretic peptide in modulating cardiac electrophysiology

Mark J. Perrin, MBBS, PhD, Michael H. Gollob, MD

From the University of Ottawa Heart Institute, Ottawa, Ontario, Canada.

Since the discovery of atrial natriuretic peptide (ANP) in 1981, significant progress has been made in understanding the mechanism of its release and its role in salt and water balance in the body. It has also become clear that ANP plays a key role in cardiac electrophysiology, modulating the autonomic nervous system and regulating the function of cardiac ion channels. The clinical importance of this role was established when mutations in *NPPA*, the gene encoding ANP, were identified as a cause of familial atrial fibrillation. This review examines our current understanding of the electrophysiological effects of ANP, and their physiological relationship to clinical studies linking ANP and atrial fibrillation.

KEYWORDS Atrial natriuretic peptide; Electrophysiology; Ion channels; Atrial fibrillation; Action potential duration; Autonomics; Genetics

ABBREVIATIONS **AERP** = atrial effective refractory period; **AF** = atrial fibrillation; **ANP** = atrial natriuretic peptide; **ANS** = autonomic nervous system; **APD** = action potential duration; **cAMP** = cyclic adenosine monophosphate; **cGMP** = guanosine monophosphate; **Cx43** = connexin 43; $\mathbf{I_{CaL}}$ = L-type calcium current; $\mathbf{I_f}$ = nonselective cation (funny) current; $\mathbf{I_{Ks}}$ = slow delayed rectifier current; **NPR** = natriuretic peptide receptor; **PKG** = protein kinase G

(Heart Rhythm 2012;9:610–615)

Introduction

Shadowed by the large body of scientific work examining the humoral physiology of atrial natriuretic peptide (ANP)—its synthesis, secretion, and end-organ effects (diuretic, natriuretic, and hypotensive; see Saito[1] for recent review)—studies performed to elucidate the electrophysiological consequences of ANP have received little attention.

However, the recent identification of mutations in the gene encoding ANP in patients with atrial fibrillation (AF) has firmly established a role for ANP in normal cardiac electrophysiological function.[2,3] ANP modulates cardiac electrophysiology in 2 ways: first, by acting upon the autonomic nervous system (ANS) to inhibit sympathetic and excite parasympathetic activity—predicting specific *indirect* effects on cardiac electrophysiology (Figure 1)[5]; second, through *direct* regulation of specific cardiac ion channels, such as attenuation of the inward calcium current (I_{CaL})[6,7] and, as suggested by increasing evidence, through interaction with a wide range of other cardiac ion channels.[8,9]

Most studies investigating the downstream protein targets of ANP have been performed in animals or cell-expression systems. Unfortunately, the divergent effects of ANP in different animal species have made it difficult to extrapolate these results to humans under normal and disease conditions. Therefore, the limited number of human studies and experimental models utilizing human tissue are of special importance for understanding the final combinatory effect of ANP in cardiovascular physiology.

This article examines the known actions of ANP on the ANS, the evidence for a direct effect of ANP to regulate cardiac ion channel function, and the clinical relevance of this information in light of recent discoveries connecting ANP and vulnerability to AF.

Electrophysiological effects

The effect of ANP on the autonomic nervous system

Inhibition of sympathetic efferent activity

ANP acts on the ANS to inhibit sympathetic activity. The spectral analysis of heart rate variability[10] and microneurographic recordings of the right peroneal nerve[11,12] during ANP infusion provide strong evidence for ANP-induced sympathoinhibition in normal human subjects. This *neural* effect of ANP is balanced by its *humoral* action, whereby salt and water excretion unloads arterial baroreceptors and increases sympathetic outflow. This balance may explain why a measurable degree of ANP sympathoinhibition is absent when arterial blood pressure is significantly reduced in patients with congestive heart failure.[13]

The mechanism of ANP-induced sympathoinhibition is not clear. ANP has been postulated to activate cardiac mechanoreceptors directly and thus enhance the reflex bra-

Dr Perrin was supported by a postgraduate scholarship from the University of Ottawa, and Dr Gollob was supported by the Canadian Institutes of Health Research and the Heart and Stroke Foundation of Ontario. **Address reprint requests and correspondence:** Dr Michael Gollob, Ottawa Heart Institute, University of Ottawa, Rm 3228,40 Ruskin St, Ottawa, ON, Canada K1Y4W7. E-mail address: mgollob@ottawaheart.ca.

1547-5271/$ -see front matter doi:10.1016/j.hrthm.2011.11.019

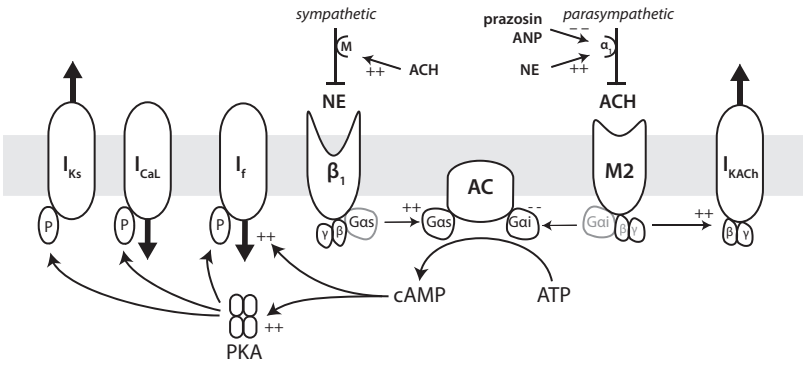

Figure 1 Schematic of autonomic modulation of cardiac ion channels by atrial natriuretic peptide (ANP). Norepinephrine (NE) binding to presynaptic α_1 receptors on parasympathetic fibers is antagonized by ANP, resulting in the augmentation of acetylcholine (ACH) release and the activation of M2 receptors.[4] M2 receptors activate I_{KACh} (acetylcholine-activated potassium current) by G-protein β and γ subunits and inhibit adenylate cyclase (AC) through inhibitory G protein ($G_{\alpha i}$), resulting in the reduced activity of sympathetically activated ion channels (I_f = funny current; I_{CaL} = L-type calcium current; I_{Ks} = slow delayed rectifier current). The magnitude of ANP effect is therefore dependent on basal AC activity, which, at rest, is moderate in the atria and low in the ventricles. ACH may also activate muscarinic receptors (M) on sympathetic nerve endings, thus inhibiting NE release. ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; PKA = protein kinase A.

dycardia associated with increases in cardiac volume.[14,15] Alternatively, ANP may directly inhibit sympathetic outflow at a central or ganglionic location. Floras examined these possibilities in 26 human subjects by applying nonhypotensive lower body negative pressure to unload cardiac mechanoreceptors during ANP infusion. If ANP activated cardiac mechanoreceptors, a reflex sympathetic surge was expected in response to a release of lower body negative pressure. Instead, he recorded an attenuation of sympathetic activity. This result was then confirmed by a blunted postganglionic sympathoneural response to the cold pressor test (nonbaroreflex sympathetic activation). It was concluded that ANP must act at an alternative site, that is, central or ganglionic, and that the mechanism of action of ANP is different in humans as compared to previous results obtained from small animal studies.[12]

Which of the 2 alternative sites—central or ganglion—represents the predominant target for ANP is uncertain. In addition to high ANP expression from atrial myocardium, ANP is expressed in the central nervous system—most strongly in the hypothalamus.[16] And while there is minimal passage of ANP across the blood–brain barrier (≤0.4% of injected quantities),[17] there is extensive and specific binding of peripheral ANP in circumventricular regions (eg, pituitary plexus and choroid plexus).[17] This raises the possibility that cardiac ANP may act centrally, although indirectly via these structures, to modulate the ANS.

ANP may also act on the sympathetic ganglia directly. Although neuronal cell bodies do not express ANP receptors, glial and fibroblast cells possess specific binding sites.[18] ANP induces guanosine monophosphate (cGMP) production and inhibits stimulated catecholamine synthesis in rat sympathetic ganglia.[19] Thus, although the precise mechanism of action is unknown, ANP appears to be one of the many complex influences on ganglionic transmission.[5]

Excitation of vagal efferent activity

ANP stimulates vagal efferent activity. Stambler and Guo demonstrated that ANP infusion in anesthetized dogs shortened atrial effective refractory period (AERP) and monophasic action potential duration recorded from the right atrium. The magnitude of the reduction in AERP and monophasic action potential duration was equivalent to that found in prior studies examining the effect of direct stimulation of vagal efferent fibers. Both combined vagal and β-adrenergic blockade (vagotomy, atropine, and propranolol) and selective vagal blockade (vagotomy and atropine) abolished these effects entirely.[20,21]

In a comprehensive investigation of the effect and mechanism of ANP-induced vagoexcitation, Atchison and Ackermann[22] first demonstrated that ANP enhanced reductions in heart rate owing to parasympathetic simulation in a denervated rat model. Then, with experimentally manipulated autonomic modulation, the administration of prazosin alone, or in combination with ANP, was found to produce the same degree of reduction in the heart rate as that found with ANP alone, suggesting a common mode of action.[4] Prazosin is a selective blocker of the α_1-adrenergic receptor (preganglionic location); the authors hypothesized that ANP may similarly interfere with norepinephrine activation of this receptor. To complete their studies, it was shown that ANP did not attenuate heart rate increases owing to norepinephrine in isolated rat atrial tissue specimens, arguing against a postsynaptic mechanism.[23] The hypothesized mode of action of ANP gleaned from this work is shown in Figure 1.

Direct cardiac effects of ANP

The literature examining the direct action of ANP on cardiac ion channels is confused by a marked interspecies variation of the effect (Table 1). This variation probably relates to varied expression of ANP-interacting receptors and differing protein expression levels of downstream targets.

This problem may be illustrated by considering the many possible results of ANP-receptor binding (Figure 2). ANP bound to natriuretic peptide receptor A (NPR-A) stimulates the production of cGMP by guanylate cyclase. cGMP at a lower concentration *inhibits* phosphodiesterase III, while cGMP at a higher concentration *activates* phosphodiesterase II, thus subsequently increasing or reducing cyclic adenosine monophosphate (cAMP) concentration, respectively.[35] ANP binding to natriuretic peptide receptor C (NPR-C), however, activates an inhibitory G protein that reduces cAMP.[36] Furthermore, phosphorylation of the L-type calcium channel by cGMP-dependent protein kinase G (PKG) may reduce its function directly.[37] The final combinatory effect of ANP in a cell will relate both to the basal level of