The role of natriuretic peptides in cardioprotection

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Abstract

Atrial natriuretic peptide (ANP) and brain (B-type) natriuretic peptide (BNP) are circulating hormones of cardiac origin that play an important role in the regulation of intravascular blood volume and vascular tone. The plasma concentrations of ANP and BNP are elevated in heart failure, and they are considered to compensate for heart failure because of their diuretic, natriuretic, and vasodilating actions and inhibitory effects on renin and aldosterone secretion. Evidence is also accumulating from recent work that ANP and BNP exert their cardioprotective functions not only as circulating hormones but also as local autocrine and/or paracrine factors. In studies using cultured

neonatal myocytes and fibroblasts, exogenous administration of both ANP and ANP antagonists demonstrated that ANP has antihypertrophic and antifibrotic functions. Corroborating these in vitro results, mice lacking natriuretic receptor-A (NPR-A), the receptor for ANP and BNP, develop cardiac hypertrophy and fibrosis independent of their blood pressure. Recent studies also suggest that the intracardiac natriuretic peptides/cGMP system plays a counter-regulatory role against the intracardiac renin – angiotensin – aldosterone system and TGF-beta mediated pathway. In a clinical setting, human recombinant ANP and BNP may be used for a therapy of heart failure; however, further evaluation is required in the future.

The hormones known as natriuretic peptides (NPs) are important in maintaining cardiovascular, endocrine, renal, and vascular homeostasis (Brenner et al., 1990; Drewett and Garbers, 1994; de Bold et al., 2001; McGrath et al., 2005; Pandey, 2005a; Rubattu et al., 2006; Kishimoto et al., 2011). The NPs hormone family includes atrial and brain natriuretic peptides (ANP, BNP). C-type natriuretic peptide (CNP), a third member of the NPs family, was also isolated and identified, however each NP was revealed to be derived from a different gene (Rosenzweig and Seidman, 1991; LaPointe, 2005; Schulz, 2005). ANP and BNP have diuretic, natriuretic, vasorelaxant, antiproliferative, antiinflammatory, and antihypertrophic properties that help to modulate body fluid volume, blood pressure (BP), and cardiovascular diseases (CVDs) (McGrath et al., 2005; Ellmers et al., 2007; Wang T.J. et al., 2007; Pandey, 2011; Volpe et al., 2014; Cannone et al., 2019). Although the role of NPs in metabolic regulation has received little attention, they have a powerful effect on lipid and glucose metabolism and may contribute to the pathophysiological relationship between metabolic and CVD diseases (Schlueter et al., 2014; Jordan et al., 2018). ANP has been proven to improve insulin resistance by inducing lipolysis and lipid oxidation (Birkenfeld et al., 2008; Coue and Moro, 2016). The sequence structures of all three NPs (ANP, BNP, and CNP) are extremely similar, they bind to cognate cell surface receptors, and they trigger distinct biological and physiological functions (Brenner et al., 1990; Koller and Goddel, 1992; Anand-Srivastava and Trachte, 1993; Khurana and Pandey, 1993; Pandey, 2008). ANP, BNP, CNP, and urodilatin are all members of the endogenous NP family, and they all play a role in blood pressure, renal failure, and cardiovascular disease (de Bold, 1985; Levin et al., 1998; Pandey, 2011; Rubattu and Volpe, 2014).

There are three types of NP receptors: NP receptor-A (NPRA), NP receptor-B (NPRB), and NP receptor-C (NPRC) (NPRC). GC receptor-A (GC-A/NPRA) and GC receptor-B (GC-B/NPRB) are two proteins that have an intrinsic intracellular guanylyl cyclase (GC) catalytic domain. Levin et al., 1998; Pandey, 2005a) (Drewett and Garbers, 1994; Levin et al., 1998; Pandey, 2005a). Both ANP and BNP bind to and activate NPRA, which, in response to hormone binding, creates the intracellular second messenger cGMP. CNP both activates NPRB and generates cGMP. All three NPs (ANP, BNP, and CNP) bind to NPRC, which does not have a GC catalytic domain and hence does not enhance intracellular cGMP levels (Fuller et al., 1988; Garbers, 1992; Koller and Goddel, 1992; Khurana and Pandey, 1993; Matsukawa et al., 1999). The regulatory effect of ANP and BNP is mediated through NPRA, which is a key locus (Lucas et al., 2000; Tremblay et al., 2002; Pandey, 2005a). If we want to grasp both receptor biology and CVDs originating from cell- and tissue-specific aberrant hormone-receptor interplay, we must first gain insight into the complexities of ANP-BNP/NPRA/cGMP signalling. Binding of ANP and BNP to the extracellular domain of NPRA appears to cause a conformational change, allowing the signal to be relayed to the intracellular GC catalytic region of NPRA, which triggers the synthesis of the second messenger cGMP in target cells and tissues (Pandey and Singh, 1990; Garbers, 1992; Koller and Goddel, 1992).

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