Is Natriuretic Peptide Receptor C a New Target for Hypertension Therapeutics?

YanFei Qi, Mohan K. Raizada

See related article, pp 846–855

Natriuretic peptides (NPs) include atrial NP (ANP), B-type NP, and C-type NP. NPs exert cardiovascular protective effects through interaction with their receptors. There are 2 major classes of NP receptors (NPRs): guanylyl cyclase–coupled receptors A and B (NPR-A and NPR-B) and inhibitory guanine nucleotide regulatory protein (inhibitory G protein)–coupled receptor C (NPR-C; Figure). The cardiovascular protective effects of NPs have been primarily attributed to the elevation of intracellular cGMP via NPR-A and NPR-B.\(^1\) NPR-C, initially identified as a clearance receptor,\(^2\) has been shown to inhibit adenylyl cyclase via the \(\alpha\) subunit of the inhibitory G protein and to stimulate phospholipase C signaling via the \(\beta\gamma\) subunits of the same inhibitory G protein.\(^3\) NPR-C is widely distributed in many tissues and cell types and has higher density than NPR-A and NPR-B in most tissues.\(^4\) Ligands for NPR-C include ANP, B-type NP, C-type NP, and C-type ANP (C-ANP\(_{4–23}\) [des(Gln18,Ser19,Glu20,Leu21,Gly22)ANP\(_{4–23}\)-NH\(_2\)]). C-ANP\(_{4–23}\), a ring-deleted analog of ANP, is a specific and selective NPR-C agonist (Figure). Multitudes of studies have underscored the importance of NPs and NPR-C in regulating cardiovascular homeostasis and have proposed NPs and NPRs as potential targets for therapy of cardiovascular diseases.

Both genetic and pharmacological evidence have implicated the involvement of NPs and NPR-C in hypertension. For example, polymorphisms in NPR-C gene seem to be associated with hypertension.\(^5\) In addition, administration of B-type NP decreases blood pressure in both animal hypertension models and humans.\(^6,7\) It is in this context that the study of Li et al\(^8\) in this issue of Hypertension is relevant. Li et al\(^8\) have demonstrated that intraperitoneal injection of C-ANP\(_{4–23}\) decreases levels of inhibitory G protein \(\alpha\) and oxidative stress and also prevents the increase in blood pressure in prehypertensive spontaneously hypertensive rats (Figure). In addition, it attenuates high blood pressure in adult spontaneously hypertensive rat and restores vasorelaxation toward control levels. This is the first indication that NPR-C agonist could be considered as a therapeutic target for hypertension and related pathophysiology. However, significant issues must be addressed to move this concept forward such as given below.

First, prevention studies are relevant but have limited clinical significance in view of the lack of reliable markers for hypertension/cardiovascular diseases. Thus, long-term reversal studies and their validation, with the use of multiple animal models of hypertension, would be extremely valuable. Second, NPR-C also acts as a clearance receptor for NPs. Thus, it is relevant to determine the chronic effects of C-ANP\(_{4–23}\) treatment on overall health and physiology of the animal, given the observation that genetic changes in NPR-C result in abnormalities. In addition, C-ANP\(_{4–23}\) could increase ANP levels, which may lead to unwanted pathophysiological consequences. Third, development of proteins/peptides as therapeutic agents is challenging as a result of tremendous technical and financial restrictions, not to mention significant compliance issues. Innovative nanoparticles\(^9\) and plant-based technologies \(^10\) are now available to encapsulate therapeutic peptides for oral delivery (Figure). Adapting any of these techniques to deliver C-ANP\(_{4–23}\) orally would be the logical next step in providing conceptual support for the therapeutic potential of this peptide.

In summary, activation of the NPR-C signaling pathway represents a new therapeutic opportunity to refine and improve existing therapies to achieve target-organ protection, blood pressure control, and optimal volume homeostasis.
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