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TRANSLATIONAL PERSPECTIVE

C-Type Natriuretic Peptide in Essential Hypertension

Old Ways for a New Time

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SUMMARY

Multiple mechanisms are involved in essential hypertension. Antihypertensive drugs mainly target increased activity of the sympathetic nervous system, altered production of vasoactive mediators, vascular inflammation, fibrosis, and increased peripheral resistance. C-type natriuretic peptide (CNP) is an endothelium-derived peptide that exerts vascular signaling through two receptors: natriuretic peptide receptor-B (NPR-B) and natriuretic peptide receptor-C (NPR-C). This perspective recapitulates the effects of CNP on the vasculature in relation to essential hypertension. Notably, the risk of hypotension when used as therapy is minimal for the CNP system as compared to its related natriuretic peptides, atrial natriuretic peptide, and B-type natriuretic peptide. As modified CNP is currently being introduced as therapy in congenital growth disorders, we propose that targeting the CNP system either by administering exogenous CNP or altering the endogenous concentrations via inhibition of its degradation may represent an important tool in the pharmacological armory for managing long-term essential hypertension. (J Am Coll Cardiol Basic Trans Science 2023;8:568-571) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In essential hypertension, the vascular endothelium is characterized by decreased production of vasodilatory mediators and increased production of vasoconstrictive mediators, proinflammatory and profibrotic cytokines, and reactive oxygen species. Over time, increased peripheral vascular resistance and stiffening of the arterial walls become important pathophysiological changes. Accordingly, the complexity of this common condition makes it difficult to develop therapeutic agents without adverse side effects. Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are expressed in cardiomyocytes and released to circulation. ANP and BNP as therapeutic agents are approved for treatment of decompensated heart failure in Japan and the United States, respectively. However, their side effect in the form of hypotension severely hampers their clinical utility. The concept of using cardiac natriuretic peptides has also been considered in relation to hypertension, but the risk for adverse effects still overshadows the potential benefit. C-type natriuretic peptide (CNP), however, is expressed mainly in vascular endothelial cells and is released in small concentrations in response to cytokines and shear stress acting locally on the blood vessels. Although CNP is categorized as a natriuretic peptide, as defined by its primary peptide structure, the natriuretic effect of this peptide is much lower compared with ANP or

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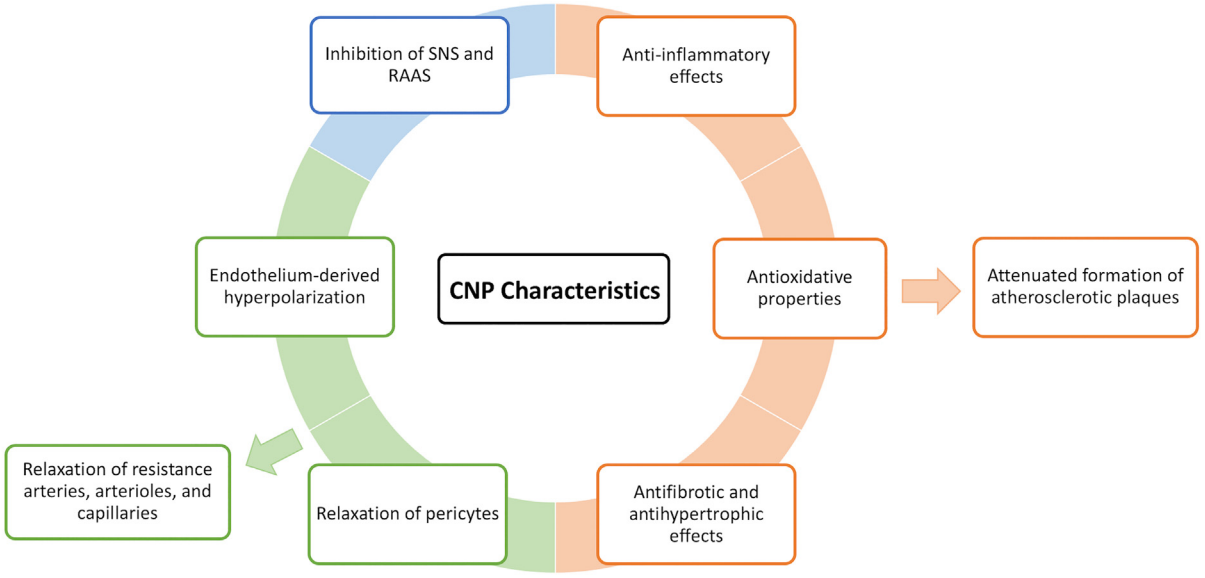
FIGURE 1 **CNP Characteristics**



The various effects of C-type natriuretic peptide (CNP) aiming toward vascular homeostasis and resulting in decreased blood pressure. RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system.

BNP. Collectively for all natriuretic peptides, recent years have revealed that they may in fact be directly involved in some forms of essential hypertension (Figure 1), as low concentrations are strongly associated with the early diagnosis of essential hypertension.[1]

CNP REDUCES PERIPHERAL VASCULAR RESISTANCE

Endothelium-derived hyperpolarization is an important mechanism involved in CNP-induced relaxation of resistance arteries. In endothelium-derived hyperpolarization, vascular smooth muscle cell membrane potentials are kept hyperpolarized, which reduces contraction and vascular tone. The role of CNP as an endothelium-derived hyperpolarizing factor is not fully understood, although 2 main pathways have been suggested (Figure 2). First, CNP binding to natriuretic peptide receptor (NPR)-B receptors on the vasculature leads to protein kinase G activation, resulting in K^+ efflux and membrane hyperpolarization. More recent studies also describe CNP binding to NPR-C receptors on vascular smooth muscle cells, leading to opening of inwardly rectifying potassium channels through activation of an inhibitory G protein. The vasodilatory effect of CNP increases toward the distal vasculature and is most pronounced in precapillary arterioles and capillaries. CNP acts via NPR-B receptors on so-called pericytes to regulate blood flow and pressure.[2] Mice with pericyte-specific NPR-B receptor knockout display elevated peripheral resistance and chronic arterial hypertension, while renal function is preserved. CNP/NPR-B signaling in pericytes prevents endothelin-1-induced pericyte contraction through activation of cyclic guanosine monophosphate-dependent protein kinase I and inhibition of phosphodiesterase 3A. Also, the results suggest that long-term administration of CNP has potential in long-term treatment of hypertension, whereas short-term CNP administration may be less relevant. A possible explanation is that the acute vasodilatory response, especially in larger vessels, greatly relies on the nitric oxide system, which seems impaired in spontaneously hypertensive rats (SHRs),[3,4] and interaction between CNP and the nitric oxide system remains controversial. Furthermore, CNP administration in mice does not affect renal function,[2] whereas ANP or BNP can induce worsening of renal failure because of excessive vasodilation and hypotension. To date, we are not aware of studies reporting life-threatening CNP-induced hypotension, which may be explained partly by the short half-life of CNP in plasma (minutes). In contrast, if CNP is to be introduced as a treatment modality in essential hypertension, CNP forms with extended half-lives

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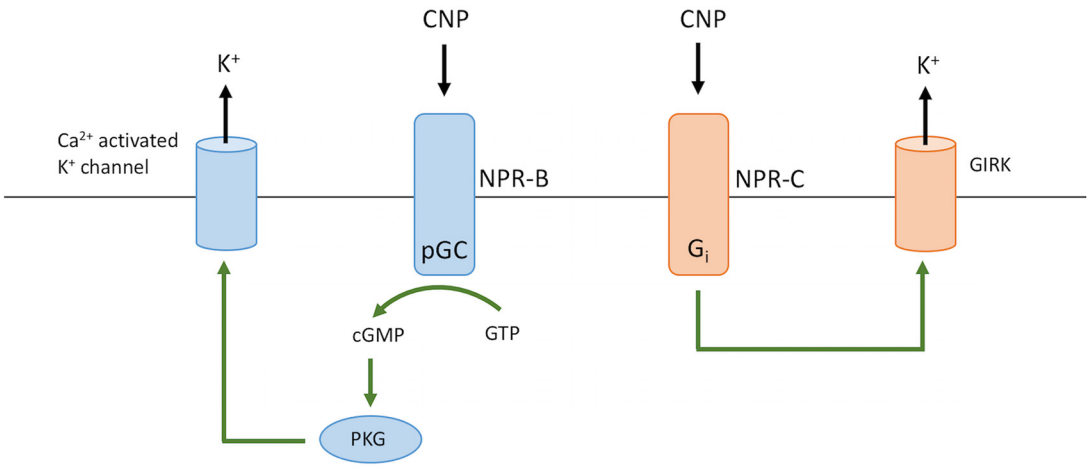
FIGURE 2 Endothelium-Derived Hyperpolarization



The 2 main pathways identified in C-type natriuretic peptide (CNP)–induced endothelium-derived hyperpolarization in vascular smooth muscle cells of resistance arteries. First, binding of CNP to natriuretic peptide receptor (NPR)-B results in activation of a particulate guanylyl cyclase (pGC), which converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). In turn, cGMP activates protein kinase G (PKG), which phosphorylates and consequently stimulates opening of Ca^{2+}-activated potassium channels, resulting in potassium (K^+) efflux from the vascular smooth muscle cells. Second, CNP binding to NPR-C results in activation of an inhibitory G protein (Gi) with subsequent potassium efflux from G protein–coupled inwardly rectifying potassium channels (GIRK).

may be needed, as is the case for CNP treatment in growth disorders.[5]

CNP IS ANTI-INFLAMMATORY AND REVERSES OXIDATIVE STRESS

CNP release from endothelial cells is stimulated by proinflammatory cytokines and lipopolysaccharide. Corresponding to individuals with essential hypertension, SHRs display increased expression of proinflammatory cytokines in both the heart and the vasculature.[3,4] Chronic treatment with CNP in SHRs has been shown to decrease left ventricular expression of interleukin-1β, interleukin-6, and TNF-α3, supporting previous findings in aortas of SHRs.[4] In an earlier study, Moyes et al[6] compared wild-type mice with endothelial cell-specific CNP-knockout mice, in which increased levels of leukocyte rolling on vascular beds together with neutrophils and macrophage accumulation in extravascular tissues following TNF-α administration were observed. After long-term treatment with CNP, recruitment of immune cells to the vascular walls and extravascular tissues significantly decreased, most likely because of down-regulation of adhesion molecules and selectins.

CNP HAS ANTIFIBROTIC AND ANTIHYPERTROPHIC EFFECTS

In essential hypertension, stiffening of arterial walls because of hypertrophy and fibrosis reduces elasticity and maintains high blood pressure. It is well known that natriuretic peptides act as antifibrotic and antihypertrophic peptides on cardiac and vascular tissues, although the precise mechanisms of this action remain to be fully understood. Profibrotic and prohypertrophic mediators, especially TGF-β1, stimulate release of CNP from fibroblasts. TGF-β1 induces collagen synthesis and fibrosis in vascular smooth muscle cells and cardiomyocytes through activation of Smad proteins.[4] Studies conducted by Caniffi et al[3,4] have demonstrated that CNP down-regulates the expression of TGF-b1 and Smad proteins in cardiac tissue and aortas of SHRs. CNP administration also decreases interstitial and perivascular collagen deposits in the cardiac tissue[3] and reduces aortic collagen content and medial wall thickness.[4] Possibly, the antihypertrophic and antifibrotic effects are coupled to the CNP/NPR-B pathway. However, these effects of CNP could depend on the type of vessel and/or the nature of injury responsible for inducing hypertension.

CNP INHIBITS THE SYMPATHETIC NERVOUS SYSTEM AND THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Drugs that target the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) are a key strategy in lowering blood pressure. Multiple studies and reviews have described the inhibitory effects of ANP and BNP on the SNS and RAAS, but whether CNP attenuates the activity of these systems is less understood. In some studies, CNP displays an inhibitory effect on the RAAS and SNS through activation of neuronal NPR-B receptors. These findings are still derived from animal studies in transgenic rats (TGRs) with neuron-specific overexpression of a dominant-negative NPR-B receptor to mimic NPR-B homozygous knockout mice without the unwanted NPR-B-knockout phenotype. Compared with wild-type rats, mean arterial pressure, systolic and diastolic blood pressure, and heart rate were all increased in TGRs, indicating a state of increased sympathetic activity. It was also reported that CNP acts on NPR-B receptors to reduce intraneuronal calcium currents and thereby inhibits norepinephrine release from sympathetic neurons. Additionally, TGRs displayed increased concentrations and activities of potent peptide vasoconstrictors (eg, renin, angiotensin II).

FUTURE PERSPECTIVES

Currently available small-molecule drugs in the field of hypertension include diuretic agents and drugs that target the RAAS. Even though these therapeutic agents have proved effective in reducing systemic blood pressure, they affect various physiological pathways and hormones, causing pronounced side effects and therapeutic resistance, often leading to polypharmacy. CNP administration, in contrast, represents specifically targeted therapy and would proposedly result in a much lesser spectrum of side effects, targeting hypertension with increased efficacy and tolerability. So far, most clinical CNP studies are based on animal models, and the next challenge we face is translating this from bench to bedside. One of the potential challenges we may meet in this translation is the subcutaneous administration of peptides that could interfere with patient compliance. Meanwhile, in addition to decreasing peripheral blood pressure, animal studies have shown that CNP has various beneficial effects on vascular homeostasis, such as reducing inflammation and fibrosis. These effects can proposedly be translated to human systems and could benefit patients with essential hypertension. In perspective, we suggest that clinical attention may now be given to the CNP system in relation to human hypertension.

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