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Review

Roles of atrial natriuretic peptide and its therapeutic use

Yoshihiko Saito (MD, FJCC)*

First Department of Internal Medicine, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan

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Summary Since the discovery of atrial natriuretic peptide (ANP), there has been tremendous progress in our understanding of the physiologic and pathophysiologic, diagnostic, and therapeutic roles of ANP. The diagnostic application of ANP and brain natriuretic peptide (BNP) has been reviewed by many investigators, and meta-analyses of therapeutic use of BNP were reported from the USA. However, there are few reviews concerning the therapeutic use of ANP in patients with various conditions. Therefore, this review focuses on the recent clinical evidence of ANP in therapeutic use and experimental data that rationally support the therapeutic use of ANP.

Contents

* Tel.: +81 744 29 8850; fax: +81 744 22 9726.
E-mail address: yssaito@naramed-u.ac.jp.

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Introduction

Since the discovery of atrial natriuretic peptide (ANP) at the end of 1983 [1] and the beginning of 1984 [2], major advances have taken place in our understanding of the physiology and pathophysiology of the heart. Before the discovery of ANP, the heart was believed to function solely for the delivery of blood to all organs in the body; after ANP was elucidated, it became evident that the heart also regulates blood pressure, fluid volume, and electrolyte balance [3,4]. Therefore, the heart plays at least two major biological roles: a pumping function and an endocrine function.

During the past three decades, evidence accumulated that a number of hormones, paracrine factors, and intracellular signaling molecules are involved in heart development, cardiac contraction, cardiac hypertrophy, and heart failure (HF). Among these biologically active substances, ANP and B-type natriuretic peptide (BNP) are the best-investigated molecules, and are now clinically used as diagnostic tools and therapeutic drugs in HF.

In 1995, the Ministry of Health and Welfare of Japan approved recombinant ANP (carperitide) for intravenous administration in patients with acute heart failure (AHF) and acutely decompensated heart failure (ADHF). However, the recombinant form of BNP (nesiritide) was not approved for therapeutic use in Japan. In contrast, in the USA, the Food and Drug Administration (FDA) approved nesiritide in 2001. Therefore, the clinical evidence for ANP has been compiled mainly in Japan, whereas the evidence for BNP is mainly from the USA. Several reviews and meta-analyses concerning BNP use were generated using data obtained in the USA [5—7]. In this context, this review focuses on recent clinical data regarding ANP as a therapeutic agent in several diseases, as well as experimental data from genetically engineered mice which may rationalize the clinical usefulness of ANP.

Discovery of natriuretic peptide (NP) family

The discovery of atrial-specific granules, which resemble the electron-dense granules observed in endocrine organs, by Kirsh [8] in 1956 marks one of the first milestones on the road of ANP research. In 1979, deBold [9] found that the number of atrial-specific granules is decreased by water deprivation and increased by salt loading, suggesting that atrial-specific granules contain a biologically active substance involved in volume regulation. At the end of 1983 and the beginning of 1984, a new peptide with 28 amino acid residues was isolated by deBold from rat atrial tissues [1], and by Matsuo and Kangawa from human atrial tissues [2]. The peptide was designated as ANP, and exhibits diuretic, natriuretic, and vasodilating activities. Following the discovery of ANP, Matsuo and Kangawa also isolated brain natriuretic peptide, or B-type natriuretic peptide (BNP) from the porcine brain in 1988 [10], and C-type natriuretic peptide (CNP) from the porcine brain in 1990 [11]. ANP is mainly synthesized in the atria and BNP in the ventricles; thus, ANP and BNP are cardiac hormones [12—14]. The expression of ANP and BNP is increased in cardiac hypertrophy in response to atrial or ventricular wall stress, respectively, as well as in HF. CNP is synthesized in endothelial cells, macrophages, neurons, and osteoblasts, although cardiac expression of CNP is low [3,4].

Biological actions of ANP and BNP

ANP and BNP bind their common receptor, guanylyl cyclase-A (GC-A), which is a membrane-type guanylyl cyclase, and leads to biological actions through a cGMP-dependent pathway (Table 1). Classically ANP and BNP possess diuretic, natriuretic, and hypotensive activity. ANP induces dilation of arteries and veins in an endothelium-independent manner. In vascular smooth muscle cells (SMCs), GC-A is expressed abundantly; binding of ANP or BNP produces cGMP and activates cGMP-regulated protein kinase I (cGKI) [15]. SMCs express both cGKIα and cGKIβ· Earlier reports showed that cGKI inhibits vascular smooth muscle contraction by multiple mechanisms, including the cGKIβ/inositol 1,4,5-triphosphate-associated cGMP kinase substrate (IRAG), the cGKIα/regulator of G protein signaling subtype 2 (RGS2), and the cGKIα/myosin light chain phosphatase (MLCP) signaling pathway. cGKIβ/IRAG signaling inhibits release of Ca^{++} from sarcoplasmic reticulum (SR) cGKIα binds, phosphorylates, and activates RGS2, which terminates signaling by Gq-coupled receptors for contractile agonists [16]. There-

Table 1 Biological actions of atrial and brain natriuretic peptides.

Diuresis
Natriureis
Hypotensive action
Inhibition of aldosterone secretion
Anti-hypertrophic action
Anti-fibrotic action
Inhibition of cell proliferation
Smooth muscle cell
Mesangial cell
Fibroblasts
Enhancement of permeability of macromolecules through endothelium
Angiogenic action