Brain Natriuretic Peptide in Hypertension

Tadanao Takeda, and Masakazu Kohno

Brain natriuretic peptide (BNP) was first identified in the porcine brain and later isolated from porcine, rat, and human hearts. In humans, plasma BNP concentrations are progressively elevated with increasing severity of hypertension, particularly when left ventricular hypertrophy (LVH) is present. This presumably reflects increases in ventricular mass associated with increased synthesis and constitutive secretion of BNP from ventricular tissue. In this respect, plasma BNP may be a marker for hypertensive LVH. Acute administration of BNP induces significant natriuresis and suppresses plasma aldosterone in hypertensive subjects. However, further studies are necessary to clarify the pathophysiological significance of BNP in essential hypertension. (*Hypertens Res* 1995; 18: 259-266)

Key Words: brain natriuretic peptide, hypertension

The role of the heart as an endocrine organ was conclusively demonstrated by de Bold *et al.* in 1981 (1), and the identification of atrial natriuretic peptide (ANP), the first member of the natriuretic peptide family, was demonstrated by Kangawa and Matsuo in 1984 (2). The second member of this family, brain natriuretic peptide (BNP), was first identified in the porcine brain and later isolated from the porcine heart (3). Porcine BNP consists of 26 amino acid residues that share considerable homology with the sequence of ANP. BNP elicits a spectrum of diuretic, natriuretic, and hypotensive effects, similar to those induced by ANP. Subsequently, a low-molecular-weight form of human BNP, human BNP-32, which corresponds to the C-terminal sequence (77-108) of the human BNP precursor deduced from the cDNA sequence, was found in human atrium (4, 5) and human plasma (6).

This paper summarizes available data concerning the structure of BNP and the release mechanism of this peptide. Secondly, studies documenting the biological effects of BNP under physiological and pathophysiological conditions are reviewed. Thirdly, studies documenting plasma concentrations of this peptide and its physiological role in hypertension are reviewed. Finally, the possibility of BNP as a novel form of therapy for hypertension is discussed.

Structure

In normal man the major circulating form of BNP consists of 32 amino acids (human BNP-32) with a characteristic ring structure, formed by an intramolecular disulfide bridge, and amino- and carboxyl-terminal tails (5) (Fig. 1). The central

structure is similar to both ANP and the recently described C-type natriuretic peptide (CNP), but the terminals vary considerably in length and amino acid composition (7). Human BNP-32 is also the major circulating form of BNP in hypertensive patients (8) (Fig. 2).

A single copy gene encodes human BNP and, similarly to the ANP gene, it consists of three exons and two introns. A characteristic feature that distinguishes between the messenger RNA of the peptides is a highly conserved sequence in the 3' untranslated region of the BNP form consisting of four sets of AUUUA (9, 10), which is considered to produce messenger RNA instability (11). This finding suggests that at the transcriptional level the BNP gene expression is regulated in a different manner from that of ANP.

Secretion

ANP and BNP are cosecreted through the coronary sinus from human heart (4, 8) (Fig. 3), but ANP is secreted mainly from the atria and BNP from the cardiac ventricles. For instance, plasma levels of both BNP and ANP increase during dynamic exercise and are correlated with each other in hypertensive subjects (12). The increase of both peptides is inhibited by the administration of angiotensin-converting enzyme inhibitor (ACEI) (Fig. 4). Supraventricular tachycardias provoke transient elevations of both plasma BNP and ANP (13). Like ANP, several studies have demonstrated positive correlations between BNP release and the left ventricular end-diastolic pressure (14), pulmonary artery wedge pressure, and pulmonary artery pressure (15) in normal subjects, hypertensive subjects,

From the First Department of Internal Medicine, Osaka City University Medical School, 1-5-7 Asahi-machi, Abeno-ku, Osaka 545, Japan.

Address for Reprints: Tadanao Takeda, M.D., First Department of Internal Medicine, Osaka City University Medical School, 1-5-7 Asahi-machi, Abeno-ku, Osaka 545, Japan.

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Fig. 1. Structure of atrial natriuretic peptide, brain natriuretic peptide, and C-type natriuretic peptide.

Fig. 2. Profiles by reverse-phase high performance liquid chromatography of immunoreactive BNP in extracts of pooled plasma from hypertensive subjects and normotensive subjects. The elution positions of standard human BNP-32 and human ANP (1-28) are shown by the arrows.

Fig. 3. Intracardiac sites of ANP and BNP concentrations in patients undergoing cardiac catheterization.

Fig. 4. Plasma ANP and BNP increase during dynamic exercise and are correlated with each other in hypertensive subjects. Plasma ANP (a) and plasma BNP (b) levels at rest and at a 75W workload before (○) and during (●) treatment. Statistical analysis was done by three-way analysis of variance. F, the effect of treatment; Fi, the interaction between treatment and the level of activity. ** $p < 0.01$; *** $p < 0.001$; † Statistically not significant.

Table 1. Biological Actions of Brain Natriuretic Peptide

Endocrine	Inhibition of plasma renin activity Inhibition of aldosterone secretion Inhibition of endothelin secretion
Renal	Increase in urinary sodium excretion Increase in glomerular filtration rate Inhibition of glomerular mesangial cell proliferation
Cardiovascular	Reduction in systemic vascular resistance Reduction in right atrial pressure and PAWP Inhibition of VSMC proliferation and migration
CNS	Central regulation of cardiovascular system

VSMC, vascular smooth muscle cell; PAWP, pulmonary artery wedge pressure; CNS, central nervous system.

and patients with congestive heart failure. Actually, an immunocytochemical study using antisera highly specific for ANP and BNP indicates the coexistence of ANP and BNP in the secretory granules of human cardiac myocytes (16).

However, there is some evidence that the response of BNP release to various stimuli differs from that of ANP. Richards *et al.* (17) have demonstrated that the change from upright to supine posture stimulates ANP release, but has no effect on the plasma BNP concentration. They have also demonstrated that pressor infusions of angiotensin II increase plasma levels of both peptides, but the increment in BNP is much less than that in ANP. Horio *et al.* (18) have examined the serial changes in ANP and BNP in patients with acute myocardial infarction treated with early coronary angioplasty. Plasma levels of both peptides are increased on the first day of the infarction. During the clinical course of the infarction, ANP levels soon decrease, while BNP levels remain elevated 2 weeks after the infarction and also exhibit a high level at 4 weeks. Therefore, it is likely that the regulation of plasma BNP and its response to various stimuli is different from that of ANP. Actually, there is evidence to suggest that the secretion of BNP is augmented by the activation of protein kinase C, but that, unlike ANP, it does not depend on the free intracellular calcium concentration (19).

Biological Effects of BNP

The natriuretic effects of BNP have been clearly demonstrated in animal and human studies using pharmacological doses (20–22). Although the exact cellular mechanism is not clear, BNP increases urinary sodium excretion. BNP binds to receptors in cultured inner medullary collecting duct cells and inhibits sodium uptake by these cells (23). There is also indirect evidence for the inhibition of sodium transport in the proximal tubule (24). BNP also may increase urinary sodium excretion by alteration of the glomerular filtration rate. However, this process may not be necessary for the increase in urinary sodium excretion, because infusions of BNP sufficient to cause natriuresis do not alter the glomerular filtration rate (25).

Biological actions of BNP under physiological and pathophysiological conditions are summarized in Table 1. Various kinds of endocrine effects have been demonstrated. It is a potent inhibitor of aldosterone secretion like ANP (26, 27). BNP also inhibits plasma renin activity in dogs (28). In humans, a decline (21) or no significant change (29, 30) in plasma renin activity during the infusion of BNP has been reported.

Interaction between BNP and endothelin has been shown. In cultured vascular endothelial cells, endothelin-1 is stimulated by angiotensin II and thrombin, and this can be potently inhibited by BNP as well as ANP (31, 32). Taken together with endothelin stimulation of BNP and ANP secreted from the heart (33–36), these findings suggest the existence of a cardiac-endothelium feedback mechanism (Fig. 5). In glomerular mesangial cells, BNP also inhibits endothelin-1 production induced by angiotensin II (37), arginine vasopressin (38), and platelet-derived growth factor (39).

The hemodynamic effects of BNP have been demonstrated in various species. Pharmacological doses of BNP cause a profound and sustained fall in blood pressure in hypertensive rats (22). However, in hypertensive subjects blood pressure was not significantly changed during infusions of BNP (25). In patients with congestive heart failure, a significant fall in pulmonary artery wedge pressure, right atrial pressure, and systemic vascular resistance associated with a rise in the cardiac index was observed (30).

Central regulation of the cardiovascular system may be also affected by BNP. In rats the injection of BNP into sites in the ventrolateral medulla causes a reduction in heart rate and blood pressure (40). In addition, the intracerebroventricular injection of BNP attenuates the stimulatory effect of endothelin-1 on arginine vasopressin release (41).

Plasma BNP in Hypertension

The plasma BNP concentration is modestly elevated in many patients with untreated essential hypertension as compared with normotensive controls, although the values in normotensive and hypertensive subjects overlap (8, 42). BNP concentration is also modestly elevated in patients with secondary

Fig. 5. Possible existence of a cardiac-endothelium feedback loop.

hypertension associated with diseases such as primary aldosteronism and Cushing syndrome (42). Hypertensive patients with left ventricular hypertrophy (LVH) have higher plasma BNP concentrations than those without LVH and much higher BNP concentrations than normotensive controls. Interestingly, there is a close, positive correlation between BNP levels and echocardiographic left ventricular mass index (8) (Fig. 6).

A heart perfusion experiment performed by Langendorff's method before and after atrial removal in normotensive rats indicates that about 55% of all BNP is secreted from the ventricle. In contrast, about 95% of ANP is secreted from the atria (43). On the other hand, a heart perfusion study before and after atrial removal in experimental hypertension with severe LVH in rats suggests that most BNP (70%) is secreted from the hypertrophied ventricles (43) (Table 2). These findings suggest the hypothesis that in hypertensive subjects with LVH, a considerable amount of BNP is secreted from the hypertrophied left ventricle and, therefore, the major origin of circulating BNP in these patients may be the hypertrophied ventricles. Hence, plasma BNP concentrations are increased in hypertension, and this is most pronounced when LVH is present. Previously, Mukoyama *et al.* have demonstrated that plasma BNP concentration is high in congestive heart failure and often surpasses the concentration of ANP (42). Plasma BNP concentrations in patients with severe heart failure (NYHA class III or IV) are much higher than those in patients with less severe failure (NYHA class I or II). It is therefore likely that plasma BNP concentrations better reflect left ventricular mass and load.

Fig. 6. Relationship of plasma BNP concentration to left ventricular mass index in the hypertensive subjects.

Recently, we (44) have demonstrated that long-term therapy with ACEI can reduce elevated concentrations of ANP and BNP in hypertensive patients (Fig. 7), and that the reduction in BNP is closely related to diminishing LV mass (Fig. 8). In contrast, there is no significant relationship between reductions in BNP and mean blood pressure. Thus, changes in plasma BNP appear to reflect the magnitude of regression of LVH rather than changes in blood pressure level during antihypertensive treatment.

In hypertensive rats with severe LVH, we (45) have shown that the reduction in ventricular mass by chronic ACEI therapy and angiotensin-II receptor antagonism reduces the BNP secretory rate from

Table 2. Concentrations of Atrial and Brain Natriuretic Peptides in the Perfusate from Isolated Hearts before and after Atrial Removal in Wistar-Kyoto Rats and Spontaneously Hypertensive Rats with Deoxycorticosterone-Acetate and Salt

Measurements	WKY	DOCA-salt SHR
Systolic BP (mmHg)	133±6	268±10*
Ventricular/ body weight (mg/g)	2.80±0.12	4.81±0.59*
ANP		
Before atrial removal (pg/min)	1,914±205	4,260±420*
After atrial removal (pg/min)	109±15	352±60*
Secretory rate from atria (%)	94±1	92±1*
BNP		
Before atrial removal (pg/min)	207±16	603±51*
After atrial removal (pg/min)	118±15	422±30*
Secretory rate from ventricles (%)	57±4	70±5*

WKY, Wistar Kyoto rats; SHR, spontaneously hypertensive rats; DOCA, deoxycorticosterone acetate; BP, blood pressure; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide.

* $p < 0.05$ vs. WKY.

Fig. 7. A. Changes in plasma brain natriuretic peptide (BNP) concentration (upper panel) and plasma atrial natriuretic peptide (ANP) concentration (lower panel) by enalapril-based treatment. * $p < 0.05$ versus values at entry. B. Changes in plasma BNP concentration (upper panel) and plasma ANP concentration (lower panel) by lisinopril-based treatment. $p < 0.05$ versus values at entry.

the cardiac ventricles, but not from the atria. In this study, there was a close, positive correlation between BNP secretory rate from ventricles and ventricular weight in this LVH model before and after antihypertensive therapy.

Although we have no direct evidence, this animal study (45) and our clinical study (44) of BNP and LVH suggest that the regression of LVH by ACEI therapy may cause reduced secretion of BNP from cardiac ventricles. Several explanations have been advanced for the close relation between reductions

in plasma BNP concentration and those in LV mass. First, LV mass and LV synthesis of BNP may have been reduced concomitantly by long-term blockade of angiotensin II in the heart. In fact, angiotensin II is related to BNP secretion from cardiomyocytes as well as the growth of cardiomyocytes (46). An alternative explanation attributes the observed relationship between BNP reduction and LVH regression to reduced BNP secretion from the cardiac ventricles. This explanation seems at odds with findings that LV systolic func-

Fig. 8. The relation between changes in plasma brain natriuretic peptide concentration (dBNP) and in left ventricular mass index (dLVMI) in the enalapril group, and both groups during antihypertensive treatment. ○ = enalapril-based treatment group; ● = lisinopril-based treatment group.

tion was not changed by the regression of LVH and that there was no significant relation between changes in plasma BNP concentration and those in LV systolic function. Therefore, it is likely that changes in the plasma concentration of BNP reflect the magnitude of regression of LVH in essential hypertension. Thus, plasma BNP concentration may be a useful marker for LVH during antihypertensive therapy in essential hypertensive patients.

LVH increases the hypertensive patient's risk of cardiovascular events, cardiovascular death, and all-cause mortality (47, 48). The risks are maximized when the patient has concentric hypertrophy, with increases in both relative wall thickness and mass (49). In our recent study (44) concerning BNP and LVH, BNP levels were positively correlated with LV mass index and relative wall thickness, and the reduction in BNP levels by ACEI was closely related to a reduction in LV mass. In these respects, plasma BNP may be valuable as a prognostic predictor in hypertension. Indeed, plasma BNP levels have an independent significant relationship to mortality in patients with chronic congestive heart failure (50).

BNP As a Novel Form of Therapy for Hypertension

There are two published reports of the effects of exogenous BNP infused in patients with hypertension. Richards *et al.* (51) infused human BNP over a period of 2 h in six male patients with untreated, uncomplicated, mild to moderate essential hypertension. Achieved intravenous plasma BNP immunoreactivity was similar to levels previously

observed in heart failure or severely complicated hypertension. Plasma cyclic GMP increased, sodium excretion rose 2.5-fold, and plasma aldosterone fell to 50% of placebo values. Blood pressure and heart rate were unchanged. Their data suggest that in essential hypertension, pathophysiological plasma concentrations of human BNP have significant, acute effects that promote natriuresis and suppress plasma aldosterone. These effects are similar to those of comparable doses of ANP, but the plasma half-life of BNP is considerably longer than that of ANP. Therefore, these two peptides may play separate, complementary roles in fluid volume and blood pressure homeostasis in hypertension.

La Villa *et al.* (52) infused human BNP in increasing amounts, to raise its plasma concentrations to the pathophysiological range, and evaluated whether and at what plasma level this hormone influences cardiovascular function. BNP induced progressive reductions in left ventricular end-diastolic volume and end-systolic volume, whereas stroke volume did not show any significant change. Cardiac output, arterial pressure, and peripheral vascular resistance did not change significantly. Their data suggest that BNP, at pathophysiological plasma concentrations, influences cardiovascular homeostasis mainly by reducing cardiac preload.

However, more clinical trials studying the effects of BNP treatment in patients with hypertension are necessary to fully evaluate the therapeutic potential of this peptide.

Conclusion

Plasma BNP concentrations are progressively elevated with increasing severity of hypertension, particularly when LVH is present. This presumably reflects increases in ventricular mass associated with increased synthesis and constitutive secretion of BNP from ventricular tissue. In this respect, plasma BNP may be a marker for hypertensive LVH. Acute administration of BNP induces significant natriuresis and suppresses plasma aldosterone in hypertensive subjects. However, this peptide fails to lower systemic blood pressure significantly in these subjects. Therefore, this possible new form of therapy for hypertension needs further testing in animal and human hypertension.

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