Brain Natriuretic Peptide: Its Relevance to the Cardiologist

B.M.Y. CHEUNG

From the Department of Medicine, University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong

CHEUNG, B.M.Y., ET AL.: Brain Natriuretic Peptide : Its Relevance to the Cardiologist. *Brain natriuretic peptide, or B-type natriuretic peptide (BNP), is a cardiac hormone secreted mainly from the ventricles. It is natriuretic, diuretic, vasodilatory, lowers blood pressure and suppresses the renin-angiotensin-aldosterone system. Its concentration in plasma is normally very low but is markedly raised in congestive heart failure, suggesting that it may have a pathophysiological function. Short-term intravenous infusion of BNP is beneficial in heart failure but an effective oral agent is not yet available. Plasma BNP concentration may be measured to assess cardiac function, as it correlates directly with pulmonary capillary wedge pressure and inversely with ejection fraction.*

Brain natriuretic peptide, atrial natriuretic peptide, natriuresis, heart failure

Introduction

Brain natriuretic peptide (BNP), was discovered in 1988 and belongs to a family of natriuretic peptides which also includes atrial natriuretic peptide (ANP) and C-type natriuretic peptide (CNP) (Fig. 1).[1] Brain natriuretic peptide is a misnomer, because although it was first discovered in porcine brain, it is produced largely by cardiac ventricular muscle and is a circulating hormone.[2] BNP is hardly detectable in the rat or human brain. Some authors therefore prefer to use the term "B-type natriuretic peptide".

Structure

In man, the major circulating form of BNP is a peptide consisting of 32 amino acid residues. The 10th and the 26th amino acid residues are cysteine. These two residues link up via a disulphide bond to form a 17-amino acid loop. This 17-amino acid loop is a structural motif which is common to the three natriuretic peptides (Fig. 1). The primary structures (amino acid sequences) of ANP and CNP are highly conserved amongst mammalian species. In contrast, the amino acid sequences of BNP in different mammalian species diverge considerably.[3] Therefore, the homologous peptide for each species should be studied, and extrapolation across species should be avoided.

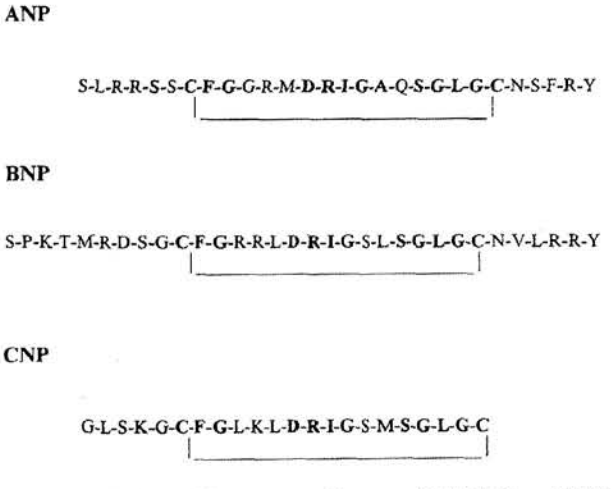

Figure 1. *Amino acid sequences of human ANP, BNP and CNP. Residues common to all three peptides are indicated by bold type. Disulphide linkages between two cysteine residues are shown.*

Receptors

BNP binds to the same receptors on the cell surface membrane as ANP.[4] Surprisingly, a receptor which binds BNP only has not been found. Three subtypes of ANP

Address for reprint: Dr. B.M.Y. Cheung, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong. Tel: (852) 2855 4768 Fax: (852) 2872 5828

Received June 16, 1995; accepted with revision July 3, 1995.

receptors have been identified: ANPR-A, ANPR-B and ANPR-C (Fig. 2). BNP binds to ANPR-A and ANPR-C. ANPR-B binds CNP with high affinity, but not ANP or BNP.

The ANPR-A receptor has intrinsic guanylate cyclase activity and catalyses the formation of cyclic GMP (cGMP) when ANP or BNP binds to the receptor. Cyclic GMP is believed to be the second messenger mediating the biological actions of the natriuretic peptides.

The ANPR-C receptor is a smaller protein without the intracellular domain which generates cGMP. Moreover, it binds not only ANP, BNP and CNP, but also truncated forms of ANP. It has been suggested that this receptor has no biological function but serves as a clearance receptor instead.[5]

RECEPTOR	LIGAND
ANPR-A	ANP, BNP
ANPR-B	CNP
ANPR-C	ANP, BNP, CNP, C-ANP, ANP (5-25), etc.

Figure 2. *Known subtypes of ANP receptors and the ligands which are known to bind to each subtype with high affinity. C-ANP and ANP(5-25) are synthetic truncated forms of ANP.*

Synthesis and Release

The main source of BNP in the circulation is the heart. BNP messenger RNA (mRNA) is readily detectable in rat ventricles as well as atria, in contrast to ANP which is predominantly synthesized and stored in the atria.[6] As the ventricles are larger in mass compared to the atria, the majority of BNP in the circulation comes from the ventricles. This has been confirmed in cardiac catheterisation studies in man which showed that there was a significant step-up in the plasma BNP level between the aorta and atrioventricular vein which drains the ventricles.[7]

What controls the secretion of BNP is not fully understood. It is probable that, like ANP, BNP is released upon stretch of the myocardium. Volume expansion is associated with increased BNP levels, while haemodialysis reduces plasma BNP levels.[8,9] Although dietary salt loading increases plasma levels of BNP, acute intravenous saline loading which would increase plasma ANP does not increase plasma BNP.[10] Similarly, changing the pacemaker mode from atrial to ventricular pacing increases ANP much more so than BNP.[11] My view is that ANP is pre-formed and is released acutely in response to stimulus, whereas BNP is not stored to the same extent but is synthesised upon stimulation. This may account for the delay in the BNP response, and is supported by experiments using isolated perfused rat hearts, in which BNP mRNA but not ANP mRNA increased following a rise in atrial pressure, although there was increased secretion of both peptides.[12]

Elimination

BNP is eliminated in the circulation by at least two mechanisms. Firstly, it binds to ANPR-C, the clearance receptor and is then internalised.[5] These clearance receptors have a widespread distribution and are present on vascular endothelium. Secondly, BNP is metabolised by neutral endopeptidase, which cleaves BNP *in vitro*.[13] Inhibiting this enzyme increases plasma BNP levels in man.[14] BNP has a longer half-life in the circulation compared to ANP.[2,15] This may be due to either the lower affinity of BNP for the clearance receptor,[2] or the lower affinity of BNP as a substrate of neutral endopeptidase.[13]

Physiological Function

When BNP was originally discovered, it was shown to have natriuretic, diuretic and hypotensive effects in the rat.[1] *In vitro*, BNP enhances the production of cGMP and inhibits aldosterone production in adrenal cells.[16] In laboratory animals, BNP lowers blood pressure, increases urinary flow rate and sodium excretion.[17] There have been several studies on the effect of intravenous BNP infusion in man.[15,18-21] The earliest study used porcine BNP and showed suppression of the renin-angiotensin-aldosterone system and increased urinary cGMP excretion.[18] There was a trend towards increased urinary sodium excretion, but it should be noted that porcine BNP differs in sequence from human BNP. When human BNP was available, several groups infused BNP in man at different doses using different protocols.[15,19-21] They all showed that BNP has a significant natriuretic effect. Studies employing BNP at supraphysiological doses also showed some hypotensive effect and suppression of the renin-angiotensin-aldosterone system.[19-21] At a low dose which increases plasma BNP concentration within the physiological range, BNP has a significant natriuretic effect without altering blood pressure and heart rate.[15] Moreover, the effects of ANP and BNP seem to be additive.

Heart Failure

It was discovered quite early on that plasma BNP levels are increased markedly in heart failure.[22] The circulating concentration of BNP in normal subjects is in the low picomolar range, but this is increased by one to two orders of magnitude in heart failure. The increase is related to the degree of heart failure. As the effects of BNP include vasodilation, natriuresis and suppression of the renin-angiotensin-aldosterone system, BNP has been postulated to be an endogenous hormone counteracting the development of heart failure.[2] The administration of ANP to heart failure patients has been disappointing as the natriuretic effect of ANP seems to be blunted in such patients. In contrast, BNP, when infused intravenously in heart failure patients, led to a marked natriuretic response, accompanied by a decrease in pulmonary capillary wedge pressure and an increase in cardiac output.[23] BNP, unlike ANP, may therefore be a useful therapeutic agent in heart failure, but additional studies are needed to confirm the initial findings of Yoshimura et al.[23] BNP is now available commercially for intravenous use, but being a peptide, it is both expensive, unstable and cannot be given orally. A more rational approach might be the use of oral neutral endopeptidase inhibitors, such as candoxatril, which can be used to augment endogenous BNP levels.[14] These agents lower pulmonary capillary wedge pressure, but it remains to be shown if they are useful clinically in the long-term treatment of heart failure.[24] Heart failure has a mortality similar to many malignant cancers and therefore exploring new ways of treating heart failure is worthwhile. However, several new drugs, e.g. milrinone, flosequinan, developed for the treatment of heart failure have been withdrawn because of increased mortality with treatment. Of concern was the observation that a drug might improve cardiac function, symptoms and exercise tolerance of patients but at the same time worsen survival. Thus therapeutic application of BNP in heart failure should remain cautious.

Besides heart failure, BNP levels are increased also in cor pulmonale and renal failure. There is considerable research interest in the role of BNP in these conditions.[25,26]

Hypertension

Until recently, there were no humoral abnormalities consistently associated with essential hypertension. Several groups have now described a significant correlation between blood pressure and plasma concentrations of natriuretic peptides, including BNP.[27-29] The reason for the increase in plasma BNP in hypertension is as yet uncertain, but it may be related to ventricular hypertrophy or dysfunction commonly found in hypertension.

Neutral endopeptidase inhibitors, which augment endogenous levels of natriuretic peptides, have been studied in hypertensive patients. There are discrepant reports on their efficiency in hypertension,[30,31] so further information on the effects of long-term treatment with these agents is required to fully assess their therapeutic potential.

Myocardial Infarction

Plasma level of BNP rises in myocardial infarction within the first 24 hours, peaking at 21 hours.[32] The rise in BNP is more marked than the rise in ANP,[33] and correlates with peak creatinine kinase and infarct size.[32] As BNP is synthesised in the ventricular myocardium, it is tempting to speculate that BNP is released as a consequence of myocardial damage. Interestingly, the BNP level in the acute phase correlates with the ejection fraction in the convalescent phase, raising the possibility that measuring the plasma BNP level after acute myocardial infarction may be of prognostic value. Furthermore, Motwani and colleagues have followed the changes in plasma BNP levels and ejection fraction for 6 months after acute myocardial infarction and found a significant correlation between BNP and ejection fraction throughout this period.[34]

Comparison of BNP with the other Natriuretic Peptides

BNP is different from ANP in a number of ways. Firstly, analysis of the cDNA of BNP revealed that it contains the destabilising sequence: "TATTTAT" which suggests that the turnover of BNP mRNA may be high, and that it may be synthesised in bursts. Secondly, the primary structure of BNP in different species is less well-conserved than those of ANP.[3] Thirdly, the storage and release of the two peptides are different. ANP is synthesised mainly in the atria and stored as granules. BNP is synthesised mainly in the ventricles and is not stored to the same extent. Under stimulation, BNP mRNA increases acutely, followed by a rise in BNP secretion. In contrast, stored ANP is released from atrial granules immediately in response to stimuli. Lastly, BNP has a longer half-life in plasma which may be due to a lesser infinity for the clearance receptor.[2,15]

C-type natriuretic peptide (CNP) is the most recently recognised member of the family of natriuretic

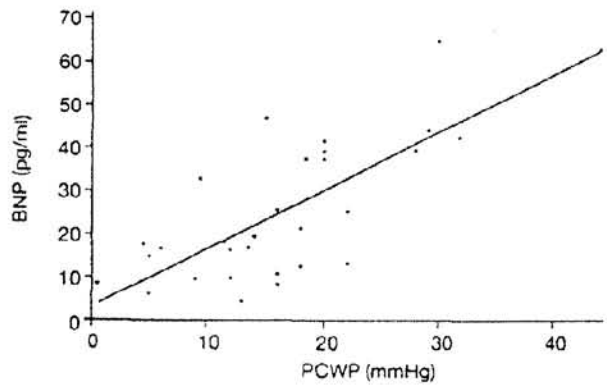

Figure 3. *Correlation between pulmonary arterial BNP concentrations and pulmonary capillary wedge pressure ($r = 0.73$, $p < 0.001$, $n = 30$). Reproduced from Haug et al.[39] with permission of Clinical Cardiology Publishing Company Inc, and/or the Foundation for Advances in Medicine and Science Inc, Mahwah, NJ 07430, USA.*

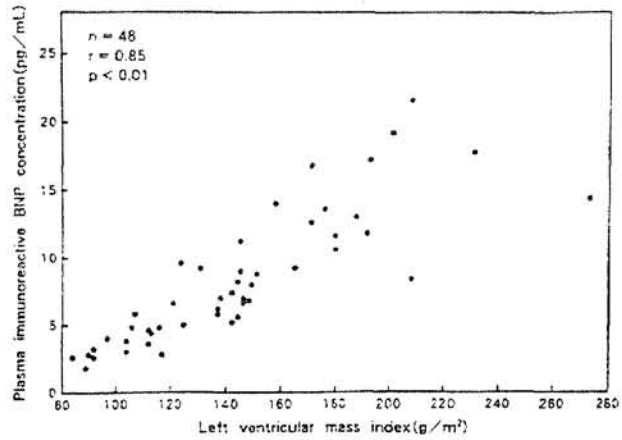

Figure 4. *Correlation between plasma BNP concentration and left ventricular mass index in hypertensive patients. Reproduced from Kohno et al.[27] with permission.*

peptides and is distinct from ANP and BNP.[35] CNP is found mainly in the central nervous system, but is also synthesized and released from endothelial cells and circulates in plasma.[28,36] Vascular smooth muscle cells express ANPR-B, a guanylate-cyclase coupled receptor specific for CNP.[4] The binding of CNP to this receptor activates guanylate-cyclase generating cGMP which mediates vasodilation.[37] CNP is also anti-mitogenic and inhibits the proliferation of vascular smooth muscle cells.[38] Thus, CNP may be an important paracrine factor in controlling vascular tone and vascular remodelling, but does not appear to possess the same systemic effects characteristic of ANP and BNP.

Clinical Importance of BNP

BNP acts in conjunction with ANP and other factors to control sodium excretion. Thus, in hypertension, heart failure, renal failure and pre-eclampsia, BNP may play an important pathophysiological role. The therapeutic use of BNP in some of these conditions remains experimental.

As plasma BNP concentration can be measured readily by radioimmunoassay, there is much recent interest in the measurement of BNP as an index of cardiac function. Plasma BNP levels correlate with pulmonary capillary wedge pressure (Fig. 3)[39] and inversely with ejection fraction.[34,40] The plasma level of BNP may therefore be used as an index of cardiac dysfunction. In fact, plasma BNP level is as sensitive as echocardiography in detecting asymptomatic left ventricular dysfunction.[40] Hence, measurement of BNP may be useful after myocardial infarction, in deciding whether or not to introduce an angiotensin converting enzyme inhibitor,[34] or in optimising treatment of heart failure, especially outside specialised centres where echocardiography is not readily available. Plasma BNP levels also correlate strongly with left ventricular mass in hypertensive patients (Fig. 4).[27] This raises the possibility that plasma BNP might be useful for the detection of left ventricular hypertrophy, which is associated with increased cardiovascular morbidity and mortality in the hypertensive population. Indeed, in hypertrophic obstructive cardiomyopathy, the plasma level of BNP is markedly raised, so plasma BNP might be used, in conjunction with echocardiography, to screen for this condition.[41]

Conclusion

BNP is a circulating cardiac hormone which may be measured to assess cardiac function. A raised BNP level is a sensitive measure of cardiac dysfunction although not specific for any disease state. Therapeutic agents which augment the endogenous levels of ANP and BNP are now being evaluated for use as therapeutic agents in hypertension and heart failure.

References

1. Sudoh T, Kangawa K, Minamino N, et al. A new natriuretic peptide in porcine brain. Nature (London) 1988; 332:78-81.
2. Mukoyama M. Nakao K, Hosoda K, et al. Brain natriuretic peptide as a novel cardiac hormone in humans. J Clin Invest 1991; 87:1402-12.
3. Suga S, Nakao K, Hosoda K, et al. Receptor selectivity of natriuretic peptide family, atrial natriuretic peptide, brain natriuretic peptide and C-type natriuretic peptide. Endocrinology 1992; 130:229-39.
4. Koller KJ, Lowe DG, Bennett GL, et al. Selective activation of the B natriuretic peptide receptor by C-type natriuretic peptide (CNP). Science (Washington, DC) 1991; 252:120-3.
5. Maack T, Suzuki M, Almeida FA, et al. Physiological role of silent receptors of atrial natriuretic factor. Science 1987; 238:675-8.
6. Ogawa Y, Nakao K, Mukoyama M, et al. Natriuretic peptide as cardiac hormones in normotensive and spontaneously hypertensive rats. Circ Res 1991; (69):491-500.
7. Yasue H, Yoshimura M, Sumida H, et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation 1994; 90:195-203.
8. Lang CC, Coutie WJ, Khong TK, et al. Dietary salt loading increases plasma brain natriuretic peptide levels in man. J Hypertens 1991; 9:779-882.
9. Lang CC, Choy AJ, Henderson IS et al. Effect of haemodialysis on plasma levels of brain natriuretic peptide in patients with chronic renal failure. Clin Sci 1992; 82:127-31.
10. Lang CC, Choy AM, Turner K, et al. The effect of intravenous saline loading on plasma levels of brain natriuretic peptide in man. J Hypertens 1993; 11:737-41.
11. La Villa G, Padeletti L, Lazzeri C, et al. Plasma levels of natriuretic peptides during ventricular pacing in patients with a dual chamber pacemaker. Pacing Clin Electrophysiol 1994; 17:953-8.
12. Mantymaa P, Vuolteenaho O, Marttila M, et al. Atrial stretch induces rapid increase in brain natriuretic peptide but not in atrial natriuretic peptide gene expression in vitro. Endocrinology 1993; 133:1470-3.
13. Kenny AJ, Bourne A, Ingram J, et al. Hydrolysis of human and pig brain natriuretic peptides, urodilatin, C-type natriuretic peptide and some C-receptor ligands by endopeptidase-24.11. Biochem J 1993; 291:83-8.
14. Lang CC, Motwani JG, Coutie W, et al. Influence of candoxatril on plasma brain natriuretic peptide in heart failure [letter] Lancet 1991; ii:255.
15. Cheung BMY, Dickson JEC, Ashby MJ, et al. Effects of physiological increments in human α-atrial natriuretic peptide and human brain natriuretic peptide in normal male subjects. Clin Sci 1994; 86: 723-30.
16. Hashiguchi T, Higuchi K, Ohashi M, et al. Effects of porcine brain natriuretic peptide (pBNP) on human adrenocortical steroidogenesis. Clin Endocrinol 1989; 31:623-30.
17. Kita T, Kida O, Kato J, et al. Natriuretic and hypotensive effects of brain natriuretic peptide (BNP) in spontaneously hypertensive rats. Life Sci 1989; 44:1541-5.
18. McGregor A, Richards M, Espiner E, et al. Brain natriuretic peptide administered to man: actions and metabolism. J Clin Endocrinol Metab 1990; 70:1103-7.
19. Holmes SJ, Espiner EA, Richards AM et al. Renal, endocrine and haemodynamic effects of human brain natriuretic peptide in normal man. J Clin Endocrinol Metab 1993; 76:91-6.
20. Flurkowski CM, Richards AM, Espiner EA, et al. Renal endocrine and haemodynamic interactions of atrial and brain natriuretic peptides in normal men. Am J Physiol 1994; 266 (4 pts 2):R 1244-50.
21. La Villa G, Fronzaroli C, Lazzeri C, et al. Cardiovascular and renal effects of low dose brain natriuretic peptide infusion in man. J Clin Endocrinol Metab 1994; 78(5): 1166-71.
22. Mukoyama M, Nakao K, Saito Y, et al. Increased human brain natriuretic peptide in congestive cardiac failure. N Engl J Med 1990; 323: 757-8.
23. Yoshimura M, Yasue H, Morita E, et al. Haemodynamic, renal and hormonal responses to brain natriuretic peptide infusion in patients with congestive cardiac failure. Circulation 1991; 84: 1581-1588.17.
24. Northridge DB, Jackson NC, Metcalf NJ, et al. Effects of candoxatril, a novel endopeptidase inhibitor compared to frusemide in mild chronic heart failure. Br J Clin Pharmacol 1991; 32: 645.
25. Lang CC, Coutie WJ, Struthers AD, et al. Elevated levels of brain natriuretic peptide in acute hypoxaemic chronic obstructive pulmonary disease. Clin Sci 1992; 83:529-33.
26. Ishizaka Y, Yamamoto Y, Fukunaga T, et al. Plasma concentration of human brain natriuretic peptide in patients on haemodialysis. Am J Kidney Dis 1994; 24(3):461-72.
27. Kohno M, Horio T, Yokokawa K, et al. Brain natriuretic peptide as a cardiac hormone in essential hypertension. Am J Med 1992; 92:29-34.
28. Cheung BM, Brown MJ. Plasma brain natriuretic peptide and C-type natriuretic peptide in essential hypertension. J Hypertens 1994; 12:449-54.
29. Buckley MG, Markandu ND, Miller MA, et al. Plasma concentrations and comparisons of brain and atrial natriuretic peptide in normal subjects and in patients with essential hypertension. J Hum Hypertens 1993; 7(3):245-50.
30. Bevan EG, Connell JMC, Doyle J, et al. Candoxatril, a neutral endopeptidase inhibitor: efficacy and tolerability in essential hypertension. J Hypertens 1992; 10:607-13.
31. Tunny TJ, Ziesak, Armstrong R, et al. Inhibition of endopeptidase EC 3.4.24.11 by candoxatril lowered blood pressure and increased urinary but not plasma atrial natriuretic peptide in essential hypertension. J Hypertens 1993; 11 Suppl 5:S222-3.
32. Arakawa N, Nakamura M, Aoki H, et al. Relationship between plasma level of brain natriuretic peptide and myocardial infarct size. Cardiology 1994; 85:334-40.
33. Mukoyama M, Nakao K, Obata K, et al. Augmented secretion of brain natriuretic peptide in acute myocardial infarction. Biochem Biophys Res Commun 1991; 180:431-6.
34. Motwani JG, McAlpine H, Kennedy N, et al. Plasma brain natriuretic peptide as an indicator for angiotensin-converting-enzyme inhibition after myocardial infarction. Lancet 1993; 341:1109-13.
35. Sudoh T, Minamino N, Kangawa K, et al. C-type natriuretic peptide (CNP): A new member of natriuretic peptide family identified in porcine brain. Biochem Biophys Res Commun 1990; 168:863-870.
36. Stingo AJ, Clavell AL, Heublein DM, et al. Presence of C-type natriuretic peptide in cultured human endothelial cells and plasma. Am J Physiol 1992; 263:H1318-21.

37. Furuya M, Takehisa M, Minamitaki Y, et al. Novel natriuretic peptide, CNP, potently stimulates cyclic GMP production in rat cultured vascular smooth muscle cells. Biochem Biophys Res Commun 1990; 170:201-8.
38. Furuya M, Yoshida M, Hayashi Y, et al. C-type natriuretic peptide is a growth inhibitor of rat vascular smooth muscle cells. Biochem Biophys Res Commun 1991; 177:927-31.
39. Haug C, Metzele A, Kochs M, et al. Plasma brain natriuretic peptide and atrial natriuretic peptide concentrations correlate with left ventricular end-diastolic pressure. Clin Cardiol 1993; 16(7):553-7.
40. Choy AJ, Darbar D, Lang C et al. Detection of left ventricular dysfunction after acute myocardial infarction: comparison of clinical, echocardiographic and neurohormonal methods. Br Heart J 1994; 72:16-22.
41. Yoshibayashi M, Kamiya T, Saito Y et al. Increased plasma levels of brain natriuretic peptide in hypertrophic cardiomyopathy. N Eng J Med 1993; 329:433-4.