Molecular and physiological effects of nesiritide

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BACKGROUND: Nesiritide (Natreco, Janssen-Ortho Inc, Canada), or recombinant human B-type natriuretic peptide (BNP), is a molecule identical in structure to endogenous BNP-32. This peptide is secreted from cardiac myocytes in response to volume and pressure overload. While high levels of circulating BNP are measured by commercially available assays during acute decompensated heart failure (ADHF), the detection of alternate, potentially more active, but undermeasured forms of BNP needs to be considered.

AIM: The present review summarizes the molecular and physiological effects of nesiritide in the setting of hospitalized patients with ADHF. In particular, an overview of the molecular structure and circulating isoforms of BNP is given, followed by a discussion of the vasodilatory, renal, antag-onistic neurohormonal, pulmonary, anti-inflammatory and cardiac remodeling effects of recombinant human BNP.

SUMMARY: Nesiritide has beneficial effects in the treatment of ADHF that go beyond the traditional goals of reducing pulmonary capillary wedge pressure, preload and afterload, and relieving symptoms of dyspnea. Therefore, the unique pharmacological profile of this medication provides an additional treatment option for Canadian patients with ADHF.

Key Words: *Acute decompensated heart failure; BNP; Nesiritide*

Nesiritide (Natreco, Janssen-Ortho Inc, Canada) has recently been approved in Canada for the treatment of hospitalized patients with acute decompensated heart failure (ADHF). The molecular structure is identical to the 32 amino acid isoform of endogenously secreted B-type natriuretic peptide (BNP), giving it a unique pharmacological profile that allows for rapid relief of ADHF symptoms (dyspnea), reducing preload, afterload and pulmonary capillary wedge pressure (PCWP) without increasing heart rate. In addition, it reduces neurohormonal activation and has a beneficial effect on cardiac remodeling. The present review not only summarizes the molecular and physiological effects of this therapeutic agent, but gives insight into the rationale of giving more BNP in the form of recombinant human BNP (rhBNP) to the already overloaded BNP condition of ADHF.

BASIC MOLECULAR SCIENCE

In response to increased atrial and ventricular pressure and volume stimuli that occurs during ADHF, cardiac myocytes synthesize natriuretic peptides (NPs). While there are several types of NPs that all share a common amino acid ring structure, eg, atrial NP, BNP, C-type, D-type, V-type and the renal peptide urodilatin (1), the present review will primarily focus on BNP.

Secreted primarily from the ventricles at the transcriptional level, BNP serves the neurohormonal function of counteracting the detrimental effects of heart failure (HF). Before BNP circulates in its active form (BNP-32), the prohormone (proBNP-108) is cleaved by an

Les effets moléculaires et physiologiques du nésiritide

HISTORIQUE : Le nésiritide (Natreco, Janssen-Ortho Inc., Canada), un peptide natriurétique de type B recombinant (PNB), est une molécule à la structure identique à celle du PNB-32 endogène. Cet peptide est sécrété par les myocytes cardiaques en réponse à une surcharge de volume et de pression. Bien que des taux élevés de PNB circulants soient mesurés au moyen de titrages commerciaux pendant une insuffisance cardiaque aiguë décompensée (ICAD), le dépistage d'autres formes de besoins de PNB, peut-être plus actifs, mais trop peu mesurés, doit être envisagé.

OBJECTIF : La présente analyse résume les effets moléculaires et physiologiques du nésiritide chez des patients hospitalisés atteints d'ICAD. Notamment, les auteurs présentent un aperçu de la structure moléculaire et des isoformes circulants des PNB et exposent les effets de remodelage vasodilatateur, rénal, neuro-hormonal antagoniste, pulmonaire, anti-inflammatoire et cardiaque des PNB humains recombinants.

RÉSUMÉ : Le nésiritide a des effets bénéfiques dans le traitement de l'ICAD, lesquels dépassent les objectifs classiques de réduction de la pression capillaire bloquée, de la précharge et de la postcharge et du soulagement des symptômes de dyspnée. Ainsi, le profil pharmacologique unique de ce médicament en fait une nouvelle possibilité de traitement pour les patients canadiens atteints d'ICAD.

endoprotease within the myocyte into BNP-32 and NT-proBNP-76 (2). Beyond having different molecular weights – BNP-32: low molecular weight; proBNP-108: high molecular weight – they also behave in different biochemical ways. BNP-32 has a half-life of only 22 min, while NT-proBNP-76 circulates for 1 h to 2 h (3). Despite initially being secreted in equal amounts by the heart, proBNP-108, rather than the more active BNP-32, appears to be the peptide that is measured in greater quantities by commercial assays (4).

Herein lies the debate as to the significance of assays being more sensitive to high molecular weight than low molecular weight peptides. While discussion still continues as to what represents a clinically relevant BNP cutoff value for the diagnosis of ADHF (5), and while it seems intuitive that higher levels of assay-measured BNP would correlate with greater burden of HF, one must probe deeper. Recall that what is measured may in fact actually be the less active peptide, or in other words, the NP that perhaps offers less physiological benefit to patients. By comparing levels of BNP-32 in New York Heart Association class IV patient plasma measured by the chemically non-specific, but routinely used Triage point-of-care test (Biosite, USA) with levels measured by sophisticated mass spectral analysis, Hawkrigde et al (6) were able to confirm that point-of-care tests may skew results by overpresenting high molecular weight BNP values.

NPs exert their effects when in contact with NP receptors that then activate the production of second messenger cyclic GMP (cGMP)-dependent signalling cascades (7). For BNP, the specific receptor NP receptor type-A, highly stimulated during states of HF,

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Figure 1) Summary diagram of the physiological effects of nesiritide. BNP B-type natriuretic peptide

appears to become resistant to persistently high levels of BNP, as evidence gathered from animal studies suggests. Finally, the upregulation of phosphodiesterase during severe HF may impair cGMP activity, and increased clearance of BNP by the ectoenzyme neutral endopeptidase may result in even further BNP reduction (8).

Therefore, while produced in response to HF overload states, and ideally designed to offer the cardiorenal and vascular system protection from failure, the reality may be that there is a relative deficiency of active BNP, and matters are further complicated by potential receptor resistance (9). In recognition of these issues, the hypothesis that offering patients rhBNP such as nesiritide (Natreacor, Janssen-Ortho Inc, Canada) during ADHF has been proposed. Experimental studies suggest clinical benefit to hospitalized patients, the mechanisms of which will be discussed in the following section.

PHYSIOLOGICAL SUMMARY

In the presence of HF, BNP acts at various locations within the body (Figure 1). BNP targets the vasculature, influences which hormones are secreted and recognized, and influences the functioning of the kidneys, lungs and even the heart, all with the aim of minimizing the effects and, ultimately, the symptoms of ADHF.

Vasodilation

While the exact mechanisms are not yet fully understood, NPs appear to promote nitric oxide release (10). Additionally, as described in detail in the previous section, activation of NP receptors signals cGMP, thereby activating calcium/potassium channels, resulting in vasorelaxation in both endothelial and vascular smooth muscle cells.

One of the first studies to examine BNP effects on human arteries and veins was completed by Protter et al (11), in which isolated internal mammary artery and saphenous vein samples were exposed to BNP. This study concluded that BNP was a more potent dilator of constricted arteries than veins. Studying several different NPs, Schmitt and colleagues (12) examined forearm blood flow and vascular volume in control subjects and in patients with HF. The results challenged Protter's findings by proposing that in HF, venous, but not necessarily arterial relaxation is conserved. Attenuation of NPs on the arterial system, but not venous system was further reviewed by Houben et al (10).

Clinically, these theories were explored when 127 patients hospitalized for ADHF requiring the placement of Swan-Ganz catheters were given either an intravenous infusion of nesiritide or standard medical therapy. Subjects receiving nesiritide significantly decreased their PCWP, right atrial pressures and systemic vascular resistance. Slight increases ($+0.4 \pm 0.69$ L/min/m²) in cardiac index were also reported in patients receiving an infusion of 0.030 µg/kg/min compared with controls ($P < 0.001$) (13). The Vasodilation in the Management of Acute CHF (VMAC) study was a randomized, double-blind trial that assigned patients to receive either intravenous nesiritide ($n=204$) or nitroglycerin ($n=142$) for 3 h in addition to standard care (14). Main outcome measures included PCWP and self-evaluated dyspnea. At 3 h, patients receiving nesiritide had lower PCWP values and decreased dyspnea when compared with controls (14). Finally, both animal (15) and human trials (16) have demonstrated the direct effect of nesiritide infusion on increasing coronary artery blood flow and reducing coronary resistance, ultimately lowering wall stress and myocardial oxygen demands. Additional research will be required to elucidate whether nesiritide is truly a balanced systemic vasodilator.

Antagonization of neurohormones

It is accepted practice to prescribe angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and even spironolactone to patients in HF with the goal of decreasing the effects of the renin-angiotensin-aldosterone system (17). Neurohormonal activation initially serves to augment low cardiac output by increasing contractility and low blood pressure by increasing systemic vascular resistance. Furthermore, the kidneys retain sodium with the goal of increasing free water. However, if the renin-angiotensin-aldosterone system remains activated and left unchecked, it results in a state of tachycardia, increased afterload and excessive fluid, eventually leading to increased myocardial wall stress, cardiac remodelling, hypertrophy and debilitating symptoms such as decreased exercise tolerance and dyspnea (18).

BNP is intended to endogenously antagonize, in a multifactorial manner, the harmful effects of long-term neurohormonal activation. Specifically, BNP appears to overcome the vasoconstrictive effects of endothelin-1 (19), leading to both venous and arterial dilation as described above. Furthermore, BNP suppresses the activity of the renin, aldosterone, noradrenaline system (20), and possibly even the levels of the remodelling cytokines tumour necrosis factor- α and interleukin-6 (21). Clinical trials have supported these ideas, including a randomized study in which patients received either placebo or a short (4 h) nesiritide infusion (0.025 µg/kg/min to 0.05 µg/kg/min). While only a small sample size was recruited to receive nesiritide ($n=12$), reductions in preload, systemic vascular resistance, noradrenaline and aldosterone levels with an accompanying slight increase in cardiac output (but without tachycardia) were reported (19). Furthermore, Colluci et al (13) also described significant reductions in plasma aldosterone levels with nesiritide treatment compared with patients in ADHF receiving placebo infusion.

Significant renal dysfunction is common in patients hospitalized for HF (22). Acutely, HF decreases renal blood flow with resultant decreases in glomerular filtration rates. If allowed to persist, clinical evidence of renal failure in the form of proteinuria, glomerulosclerosis and tubulointerstitial fibrosis and increased creatinine eventually appear (21). While rhBNP promotes natriuresis (23), conflicting study results have questioned the degree of nesiritide's action on the renal system during HF. In a more recent study in patients receiving perioperative nesiritide infusion versus placebo, Metzner et al (24) observed that nesiritide might play a role in the maintenance of glomerular filtration rates by enhancing renal vasodilation. Knowing that BNP reduces angiotensin II and aldosterone levels, it is quite plausible that BNP can also cause a direct augmentation of diuresis. Indeed, this was described clinically in the VMAC trial. While urinary output did not increase in this trial, patients receiving nesiritide required fewer diuretics than standard-of-care patients (14). Similarly, two other trials (19,25), also studying

patients in HF, were able to show that nesiritide increased urinary sodium excretion and urine output. Again, further study is required to clarify these issues.

Effects of BNP on the pulmonary and cardiac systems

In both the earlier, nonrandomized trial conducted by Colucci et al (13) and the subsequent randomized VMAC trial (14), measures of improved global clinical status and dyspnea were described following the use of nesiritide. While VMAC subjects receiving nesiritide infusion reported reductions in dyspnea at 3 h compared with patients receiving placebo ($P=0.03$), this effect was not sustained at 24 h. To further explore this topic, the action of BNP on bronchodilation was studied in eight subjects with asthma, but not HF. Protocol involved intravenous nesiritide bolus (2 µg/kg) followed by continuous infusion over 3 h with increasing doses of 0.01 µg/kg/min, 0.02 µg/kg/min and 0.03 µg/kg/min every hour. Both forced expiratory volume in 1 s and forced vital capacity statistically increased ($P=0.012$ and $P=0.017$, respectively) (26). From the above data, it would seem that BNP also acts directly on bronchioles; however, further confirmatory studies are required to better elucidate exact mechanisms before definitive conclusions may be offered.

Thus far, our discussion has focused on BNP's ability to vasodilate, suppress endocrine function and promote renal homeostasis, but the role of the NPs on suppressing excessive collagen production and fibrosis during cardiac remodelling must also be mentioned. If allowed to continue unimpeded, remodelling may eventually lead to impaired cardiac lusitropy and diastolic dysfunction (23). Tamura et al (27) created genetically modified mice to exhibit BNP deficit. Not

only did these mice have increased numbers of fibrotic lesions, but when exposed to ventricular pressure overload these lesions were further increased in both number and size. Furthermore, mice created to lack NP receptor type-A also demonstrated increased fibrotic burden (28). Fibrosis not only requires fibroblast proliferation, which secretes transforming growth factor-beta, but also increased deposition of extracellular matrix proteins. Using cardiac fibroblasts obtained from two human male subjects, and analysed using Western blot analysis, Kapoun et al (28) demonstrated that BNP indeed reduced transforming growth factor-beta-induced cell proliferation, as well as collagen and fibronectin proteins.

CONCLUSIONS

HF is a complex syndrome affecting multiple organs, and no longer is considered just a state of hemodynamic compromise. Although BNP and nesiritide effectively reduce both preload and afterload, therefore reducing symptoms of ADHF, they also have demonstrated additional benefits such as decreasing neurohormonal activation, decreasing inflammation and ultimately reducing cardiac remodelling. The suppression of these mechanisms is import to protect the myocardium from further HF insult, and ultimately to improve long-term patient survival.

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REFERENCES

- Martinez-Rumayor A, Richards AM, Burnett JC, Januzzi Jr JL. Biology of the natriuretic peptides. *Am J Cardiol* 2008;101(Suppl A):3A-8A.
- Liang F, O'Rear J, Schellenberger U, et al. Evidence for functional heterogeneity of circulating B-type natriuretic peptide. *J Am Coll Cardiol* 2007;49:1071-8.
- Agency for Healthcare Research and Quality. Testing for BNP and NT-proBNP in the Diagnosis and Prognosis of Heart Failure. Evidence report #142, September 2006. <<http://www.ahrq.gov/clinic/tp/bnptp.htm>> (Version current at May 20, 2008).
- Lam CS, Burnett Jr JCB, Costello-Boerrigter L, Rodeheffer RJ, Redfield MM. Alternate circulating pro-B-type natriuretic peptide and B-type natriuretic peptide forms in the general population. *J Am Coll Cardiol* 2007;49:1193-202.
- Worster A, Balion CM, Hill SA, et al. Diagnostic accuracy of BNP and NT-proBNP in patients presenting to acute care settings with dyspnea: A systematic review. *Clin Biochem* 2008;41:250-9.
- Hawkrige AM, Heublein DM, Bergen HR 3rd, Cataliotti A, Burnett JC Jr, Muddiman DC. Quantitative mass spectral evidence for the absence of circulating brain natriuretic peptide (BNP-32) in severe human heart failure. *Proc Natl Acad Sci USA* 2005;102:17442-47.
- Pandey KN. Biology of natriuretic peptides and their receptors. *Peptides* 2005;26:901-32.
- Chen HH. Heart failure: A state of brain natriuretic peptide deficiency or resistance or both! *J Am Coll Cardiol* 2007;49(10):1089-91.
- Daniels LB, Maisel AS. Natriuretic peptides. *J Am Coll Cardiol* 2007;50:2357-68.
- Houben AJHM, van der Zander K, de Leeuw PW. Vascular and renal actions of brain natriuretic peptide in man: Physiology and pharmacology. *Fundam Clin Pharmacol* 2005;19:411-19.
- Protter AA, Wallace AM, Ferraris VA, Weishaar RE. Relaxant effect of human brain natriuretic peptide on human artery and vein tissue. *Am J Hypertens* 1996;9:432-36.
- Schmitt M, Gunaruwan P, Payne N, et al. Effects of exogenous and endogenous natriuretic peptides on forearm vascular function in chronic heart failure. *Arterioscler Thromb Vasc Biol* 2004;24:911-17.
- Colucci WS, Elkayam U, Horton DP, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. *N Engl J Med* 2000;343:246-53.
- Publication Committee for the VMAC Investigators (Vasodilation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: A randomized controlled trial. *JAMA* 2002;287:1531-40. (Erratum in *JAMA* 2002;288:577).
- Zellner C, Protter AA, Ko E, et al. Coronary vasodilator effects of BNP: Mechanisms of action in coronary conductance and resistance arteries. *Am J Physiol* 1999;276(3 Pt 2):H1049-57.
- Michaels AD, Klein A, Madden JA, Chatterjee K. Effects of intravenous nesiritide on human coronary vasomotor regulation and myocardial oxygen uptake. *Circulation* 2003;107:2697-701.
- Arnold JM, Liu P, Demers C, et al. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: Diagnosis and management. *Can J Cardiol* 2006;22:22-45. (Erratum in 2006;22:271).
- Libby P, Bonow RO, Mann DL. *Braunwald's Heart Disease*. Toronto: Elsevier Health Sciences, 2007.
- Abraham WT, Lowes BD, Ferguson DA, et al. Systemic hemodynamic, neurohormonal, and renal effects of a steady-state infusion of human brain natriuretic peptide in patients with hemodynamically decompensated heart failure. *J Card Fail* 1998;4:37-44.
- Fonarow GC. Pharmacologic therapies for acutely decompensated heart failure. *Rev Cardiovasc Med* 2002;3(Suppl 4):S18-27.
- Burger AJ. A review of the renal and neurohormonal effects of B-type natriuretic peptide. *Congest Heart Fail* 2005;11:30-8.
- Heywood JT. The cardiorenal syndrome: Lessons from the ADHERE database and treatment options. *Heart Fail Rev* 2004;9:195-201.
- Boerrigter G, Burnett JC Jr. Recent advances in natriuretic peptides in congestive heart failure. *Expert Opin Investig Drugs* 2004;13:643-52.
- Mentzer RM, Oz MC, Sladen RN, et al; NAPA Investigators. Effects of perioperative nesiritide in patients with left ventricular dysfunction undergoing cardiac surgery: The NAPA trial. *J Am Coll Cardiol* 2007;49:716-26.

25. Marcus LS, Hart D, Packer M, et al. Myocardial disease: Hemodynamic and renal excretory effects of human brain natriuretic peptide infusion in patients with congestive heart failure. A double-blind, placebo-controlled, randomized crossover trial. *Circulation* 1996;94:3184-9.
 26. Akerman MJ, Yaegashi M, Khiangte Z, Murugan AT, Abe O, Marmur JD. Bronchodilator effect of infused B-type natriuretic peptide in asthma. *Chest* 2006;130:66-72.
 27. Tamura N, Ogawa Y, Chusho H, et al. Cardiac fibrosis in mice lacking brain natriuretic peptide. *Proc Natl Acad Sci USA* 2000;97:4239-44.
 28. Kapoun AM, Liang F, O'Young G, et al. B-type natriuretic peptide exerts broad functional opposition to transforming growth factor-beta in primary human cardiac fibroblasts: fibrosis, myofibroblast conversion, proliferation, and inflammation. *Circ Res* 2004;94:453-61.
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