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Review

Brain natriuretic peptide: Much more than a biomarker

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ABSTRACT

Brain natriuretic peptide (BNP) modulates several biological processes by activating the natriuretic peptide receptor A (NPR-A). Atria and ventricles secrete BNP. BNP increases natriuresis, diuresis and vasodilatation, thus resulting in a decreased cardiac workload.

BNP and NT-proBNP, which is the biologically inactive N-terminal portion of its pro-hormone, are fast and sensitive biomarkers for diagnosing heart failure. The plasma concentrations of both BNP and NT-proBNP also correlate with left ventricular function in patients with acute exacerbation of COPD, even without history of heart failure. Several studies have been conducted *in vitro* and *in vivo*, both in animals and in humans, in order to assess the potential role of the NPR-A activation as a novel therapeutic approach for treating obstructive pulmonary disorders. Unfortunately, these studies have yielded conflicting results.

Nevertheless, further recent specific studies, performed in *ex vivo* models of asthma and COPD, have confirmed the bronchorelaxant effect of BNP and its protective role against bronchial hyperresponsiveness in human airways. These studies have also clarified the intimate mechanism of action of BNP, represented by an autocrine loop elicited by the activation of NPR-A, localized on bronchial epithelium, and the relaxant response of the surrounding ASM, which does not expresses NPR-A.

This review explores the teleological activities and paradoxical effects of BNP with regard to chronic obstructive respiratory disorders, and provides an excursus on the main scientific findings that explain why BNP should be considered much more than a biomarker.

1. Background

Natriuretic peptide (NP) hormones are small cardiovascular-derived peptides characterized by a 17 amino acid ring and include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) [1]. NPs are encoded by different genes, synthesized as prepropeptides and stored as high molecular mass propeptides (proANP, proBNP and proCNP). The cleavage of propeptide results in the formation of the daughter ANP, BNP and CNP, which are characterized by lower molecular mass [1].

NPs modulate several biological effects by interacting with specific natriuretic peptide receptors (NPRs) including NPR-A, NPR-B and NPR-C, a family of homologous single-transmembrane, glycosylated receptors [2,3]. The stimulation of NPR-A and NPR-B activates an intracellular particulate domain with guanylate cyclase (GC) activity that promotes the synthesis of cyclic guanosine monophosphate (cGMP) [4]. NPR-C does not modulate cGMP levels but inhibits adenylyl cyclase (AC), activates phospholipase C (PLC), and removes NPs from the circulation. In fact NPR-C serves as a "clearance" receptor leading to internalization and lysosomal degradation of NPs [5,6].

ANP and BNP are the biological ligands of NPR-A, whereas CNP preferentially binds to NPR-B. ANP and BNP both have a relatively high affinity for their respective receptor sub-types, although ANP is about 10 fold more potent than BNP [1,7]. NPR-A is expressed in the cardiovascular system (cardiac atria and ventricles, aorta and peripheral vasculature), kidney, skin, platelets, and sympathetic fibers [1]. In both animals and man NPR-A has also been widely identified on a variety of pulmonary cells such as endothelial and smooth muscle cells of pulmonary blood vessels, type II alveolar cells, and epithelial and airway smooth muscle cells in bronchi and bronchioles [8–12], whereas NPR-B is mainly expressed in veins as compared with arteries [7].

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2. Cardiovascular and renal actions of NPs

Under physiological conditions ANP is secreted from cardiac atria, BNP from both atria and ventricles, whereas CNP is released primarily from nervous tissue and vascular endothelium [1]. However, in a number of cardiovascular disorders and conditions associated with elevated blood pressure or volume overload, increased gene expression of ANP may be detected in the left ventricle [13] in association with rapid and constant enhancement of BNP transcripts [14,15].

ANP and BNP have similar pharmacological profiles since they act on the same NP receptor and can induce natriuresis, vasodilatation and inhibition of aldosterone synthesis. Furthermore, these NPs have antimitogenic effects on endothelial and vascular smooth muscle cells [16]. In the central nervous system both ANP and BNP induce thirst suppression, inhibition of the release of antidiuretic and adrenocorticotropic hormones, as well as a reduction of sympathetic tone. Altogether, these effects contribute to the hypotensive properties of NPs [16].

The action of CNP is different compared with that of ANP and BNP since it acts as an autocrine/paracrine mediator in blood vessels, through the modulation of vascular tone and cell growth [1,16]. Thus, CNP is less effective at inducing diuresis and natriuresis compared with the other NPs but is more effective at modulating the autonomic control of vascular tone [17,18].

These pharmacological properties of NPs underpin why they have been implicated in the pathogenesis of congestive heart failure, as proposed by Woodard and Rosado [19]. In fact, ANP and BNP increase both natriuresis and diuresis and induce local vasodilatation in response to cardiac failure, whereas CNP modulates the cardiac remodeling and inhibits the proliferation of vascular smooth muscle cells (VSMCs) [19]. Taken together, these actions of NPs lead to a reduction in blood pressure and circulatory volume, resulting in a decreased cardiac workload [19].

3. BNP as a biomarker

There is a large body of evidence that the levels of BNP and the biologically inactive N-terminal portion of its pro-hormone, NT-proBNP, correlate well with the severity of heart failure [20]. Since they function as an indicator of increased ventricular mass and a surrogate marker for heart failure, NT-proBNP and BNP are regarded as biomarkers, namely biological parameters that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention[21].

NT-proBNP has a longer plasma half-life and exists at considerably higher concentrations compared with BNP[22]. It is significantly more stable at room temperate and current laboratory assays are highly sensitive and specific. Furthermore, all commercially available NT-proBNP assays utilize the same set of antibodies, which greatly simplifies interlaboratory comparisons.

When used in conjunction with other clinical information, BNP and NT-proBNP levels are useful in establishing or ruling out the diagnosis of heart failure in patients with acute dyspnea [23]. For both BNP and NT-proBNP to exclude acute heart failure in symptomatic patients, very low values are necessary [24]. For BNP, the value is approximately 20 to 30 pg/mL, while for NT-proBNP, a cut point that has a negative predictive value of 98% to 99% is 300 pg/mL. Values above these levels, whether or not they are below the rule in cut point, may be associated with heart failure. However, the International Collaborative Of NT-proBNP (ICON) study [25] suggested that, for the exclusion of acute heart failure, a general age-independent cut-point of 300 pg/mL should be used, whereas for diagnosis of heart failure, age-dependent cut-points are more useful: namely NT-proBNP >450 pg/mL for patients <50 years; >900 pg/mL for patients in between 50 and 75 years; and NT-proBNP >1800 for patients >75 years.

Since the use of BNP and NT-proBNP for the diagnosis of heart failure has dramatically impacted the standard of care in this pathological condition, all major societies recommend the use of these biomarkers for the diagnosis of heart failure in their clinical practice guidelines [20,26,27]. BNP and NT-proBNP concentrations typically fall with therapies proven to improve mortality in heart failure with decreased left ventricular ejection fraction [28–30]. BNP-guided therapies decrease mortality and reduce cardiovascular events, although they do not decrease overall hospitalizations.

Adding routine BNP testing in patients with a history of asthma or chronic obstructive pulmonary disease (COPD) increases the detection of newly diagnosed or previously unrecognized chronic heart failure by approximately 20% [31]. In any case, BNP levels are elevated in patients with pulmonary diseases, at least in those with concomitant right ventricular (RV) dysfunction and pulmonary arterial hypertension [32], although BNP levels are significantly lower in right heart failure due to COPD compared with right heart failure due to left ventricular systolic heart failure [33].

Elevated BNP concentrations identify significant pulmonary hypertension with a sensitivity of 0.85 and specificity of 0.88 and predicted mortality [34]. It has been shown that plasma BNP levels may be elevated in patients with COPD and correlate not only with pulmonary arterial pressure but also with forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and partial arterial oxygen pressure [35]. However, there is contrasting documentation indicating that plasma BNP levels are also elevated in patients with stable COPD without pulmonary hypertension or cor pulmonale [36]. In these patients, there is no significant correlation between plasma BNP level and pulmonary function or hypoxia, but there is a significant correlation between plasma BNP level and % ejection fraction and pulmonary artery systolic pressure. Intriguingly, they are also increased in patients with COPD with normal right ventricular function after exercise [37].

Several studies have highlighted the importance of the BNP dosage in detecting left ventricular dysfunction in patients with acute exacerbation of COPD (AECOPD), even without history of heart failure [38–40], although echocardiographic examinations are able to document cardiac systolic and diastolic dysfunction in only a small number of patients during the AECOPD [41]. Whatever the case may be, the period until the onset of an AECOPD in subjects with high plasma BNP level seems to be significantly shorter [36]. Furthermore, in patients with AECOPD, BNP levels independently predict the need for intensive care [42], and elevated levels of NT-proBNP are strong predictors of early mortality among patients admitted to hospital with an AECOPD independently of other known prognostic indicators [43]. There may be a link between an elevated level of BNP or NT-proBNP and increased cardiovascular mortality in AECOPD, although the data currently available are not conclusive [44].

4. NPs and airway smooth muscle cell

Several studies documented that airway smooth muscle (ASM) cells obtained from subjects with asthma display mechanical and phenotypical differences from that of ASM obtained from non-asthmatic subjects. ASM cells obtained from subjects with asthma showed a marked increase in force generation, capacity of shortening, degree of shortening and sensitivity to agonists [45,46]. Moreover, hypertrophy of ASM in patients with severe asthma has been associated with a 5-fold greater positivity for markers of proliferating than ASM obtained from healthy subjects [47]. However, other studies failed to document mechanical differences between ASM derived from asthmatic and non-asthmatic donors [48,49]. An increased amount of expression of contractile cytoskeletal proteins that characterizes the contractile phenotype has also been described [50], as well as phenotypic differences in the sensitivity to proliferative and apoptotic stimuli for ASM [51]. Studies on the expression of components of the contractile cytoskeletal have also been observed in ASM obtained by endobronchial biopsy from subjects with asthma, demonstrated as an increased mRNA expression of myocytic markers, including myosin light chain kinase (MLCK) and total smooth muscle myosin heavy chain, when compared to ASM obtained from