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POTENTIALS OF BRAIN NATRIURETIC PEPTIDE (BNP) IN PHYSIOLOGY

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Abstract- The brain natriuretic peptide (BNP) has been claimed to be potential biomarker of cardiovascular disease since 2005, but its action on cardiovascular - renal hemodynamic in human is still not established like ANP. It reported effects such as lowering of blood pressure and after load, induction of natriuresis/diuresis without changes in renal blood flow and filtration still awaiting the experimental evidence. The present paper has been compiled after thorough search of available literatures in pubmed to review information pertaining to the source, synthesis, release, mechanism of action and physiological role of BNP in cardio-renal physiology & related disorders.

Keywords- Confusion matrix, Data Mining, Decision tree, Neural Network, stacking ensemble, voted perceptron

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Introduction

Discovery of the natriuretic peptides triggered a new arena of mechanism in cardiovascular-renal physiology, leading a new approach for advanced diagnostic and therapeutic monitoring in the management of heart failure. Numerous studies including clinical trials have been published in the last two decade measuring BNP or NT-pro-BNP suggesting actions in cardiovascular, renal, and endocrine homeostasis [1]. However, the available published reports have focused selected & limited view point, missing of comprehensive understanding & knowledge regarding mechanism of action & significance of its variable laboratory values in different pathologic conditions.

Natriuretic peptides in general terms are polypeptide hormones comprising the cardiac-derived peptide system [2,3]. In humans, three main natriuretic peptides have been studied having 17 amino acid disulphide ring structure, but genetically distinct & diverse source of origin and actions in cardiovascular, renal, and endocrine homeostasis [4]. The natriuretic peptides family consists of (1) Atrial natriuretic peptide (ANP) of atrial origin (2) B-Type (Brain) natriuretic peptide (BNP) of ventricular origin (3) C- type natriuretic peptide (CNP) of endothelial origin. All of these peptides have demonstrated role in homeostasis of cardiovascular renal physiology such as inhibition of the renin-angiotensin-aldosterone system, modulation of many other actions of hormones, paracrine/ autocrines, cytokines and growth factors. It is also reported that some of natriuretic peptides are stimuli to counteract fibrotic and inflammatory stimuli causing hypertrophic and remodeling responses in the heart and possibly in the vasculature [5,6]. The two peptides [ANP & BNP] have been reported as markers of cardiac differentiation, while third natriuretic CNP in particular has been shown to play a role in the development of the reproductive and central nervous systems by promoting vertebral and longitudinal bone growth [7].

Recent evidence indicates that ANP and BNP also act as paracrine factors, exerting antihypertrophic and antifibrotic effects in the heart. They exert both their hormonal and paracrine effects through activation of their common receptor, guanylyl cyclase-A (GC-A; also known as natriuretic peptide receptor-A). These receptor said to be expressed in a variety of tissues, including kidney, blood vessel, adrenal gland and heart, and coupled to an increase in the intracellular concentration of cGMP. The significance of ANP/BNP-GC-A signaling in various physiological and pathophysiological settings has been examined in a number of studies using mice lacking genes encoding components of this signaling pathway and physiological and pathophysiological relevance of ANP and BNP as cardiac hormones in health and disease[8,9].

Brain-type natriuretic peptide (BNP) is a 32-amino acid peptide was first identified from brain but also synthesized within the ventricles. The 108-amino acid BNP is not stored as a prohormone. It is first synthesized as pre-pro-BNP, and undergo proteolysis, cleaved in

BNP (32 amino acids) and the N-terminal piece of pro-BNP (NT-pro -BNP; 76 amino acids). Both BNP and NT-pro-BNP have been reported as sensitive diagnostic markers for heart failure in patients [10].

Source, Synthesis and Release

The BNP molecule consists of 32 amino acids attached by a cystine bridge with an N-terminal and a C-terminal. There is a common 17-amino acid ring structure that shares a high degree of homology with other family members of natriuretic peptides. The differences between members of the family are within the N- and C-terminal portions, and account for difference in role of the function of the particular peptide [10,11].

BNP has been named because of its presence in the brain but it is present at the highest concentration in the heart, and within the heart in ventricular myocytes (12). Contrary to ANP and CNP, there is considerable species specificity for BNP. BNP shares the same receptors and have the same effects as ANP when administered to experimental animals (13). In normal conditions the concentration of BNP in plasma and cardiac atrial tissue is far lower than that of ANP, making it difficult to envision a significant role of this hormone in blood pressure-volume homeostasis in physiological conditions. However, in pathological conditions, such as in ventricular hypertrophy, the synthesis of BNP in myocytes increases markedly leading to increase in plasma levels even higher than those of ANP (12, 14). In cardiac ventricles, BNP is not stored in granules but released is essentially by myocytes suggesting that it has an important paracrine effect in the regulation of ventricular mass and indicate that plasma levels of BNP may serve as an important biochemical marker to detect ventricular hypertrophy and heart failure in humans (14). The release of these peptides by the heart is stimulated by atrial and ventricular distension, as well as by neurohormonal stimuli, usually in response to homeostatic changes in normal cardiovascular-renal physiology.

Mechanism of Action

The human BNP gene is located on Chromosome 1 and encodes the 108 amino acid prohormone - pro BNP. In circulation, BNP hormone is split into n-terminal part of the prohormone termed NT-pro BNP under the action of proteolytic enzyme furin [15].

BNP mediates its action of natriuresis, vasodilatation, renin-inhibition, anti-mitogenesis, and positive lusitropism via natriuretic peptide-A receptor (NPR-A) activated by 30, 50-cyclic guanosine monophosphate (cGMP) [16]. Yamamoto et al, proved that BNP is superior to both N-terminal or C-terminal ANP as a marker for ventricular systolic or diastolic dysfunction and ventricular hypertrophy in patients with, or at risk for, cardiac disease [17]. Specifically, BNP demonstrated greater sensitivity and specificity than N-terminal or C-terminal ANP for reductions in ejection fraction or increases in left ventricular (LV) mass. Richards et al. reported that NT-Pro-BNP measured 2-4 days after myocardial infarction independently predicted LV function and 2-year survival [18]. One hundred and twenty-two patients with suspected CHF underwent an extensive evaluation by an independent panel of cardiologists blinded to the BNP data. BNP, ANP, and N-ANP were evaluated. Although all peptides correlated with the diagnosis, BNP had the highest sensitivity (97%) and specificity (84%) for the diagnosis of CHF [19].

The half life of BNP is around 20 minutes while half life of NT-pro BNP is around 120 minutes. The BNP is degraded by circulating neutral endopeptidase (NEP) enzyme, which are widely expressed in the kidney, lung, and vascular wall. Inhibition of this enzyme increases circulating levels of natriuretic peptide and potentiates their effects. Little is known on the exact clearance mechanism of NT-pro BNP, although it has been suggested that the kidneys play a major role in this clearance [20].

Methods of BNP Estimation

BNP and NT-pro BNP assays are available on either fully automated analyzers or as a point-of-care whole blood assay. All available BNP assays detect BNP fragments without significant cross-reactivity to related peptides (ANP, CNP, urodilantin, NT-pro ANP, NT-pro CNP, and fragments) or other peptide hormones. Commercially available assays to measure either BNP or NT-pro BNP are immunometric sandwich assays, incorporating two monoclonal antibodies that bind to different epitopes of the antigen to be detected (i.e. either BNP or NT-pro BNP). Currently, there are three different diagnostic tests for the measurement of BNP approved by the FDA for aiding in the diagnosis of congestive cardiac failure [21]. The most accepted method is rapid point-of-care test-fluorescence immunoassay for determination of BNP concentrations in human plasma was introduced in 2000 (Triage BNP; Biosite Diagnostics, San Diego, CA, USA) which takes 15-20 minutes to perform. The Shionogi BNP test is one-step immunoradiometric assay that uses two different monoclonal antibodies that recognize the C-terminal structure and the disulphide bond mediated ring structure. The FDA has also approved a fully automated blood test for quantification of N-terminal pro-BNP (NT-Pro-BNP) in 2002 (Roche Diagnostics) which is by electro-chemilluminescence with a processing time of only 18 mins.

Factors Affecting BNP

The reference ranges for BNP and NT-pro BNP vary depending on the assay method employed. A suggested 'normal' range for BNP is 0.5-30 pg/ml (0.15-8.7 pmol/l). The suggested decision cut-point for the detection of heart failure for the BNP point-of-care assay is 100 pg/ml [22]. The plasma levels of these peptides have been shown to fluctuate on a day-to-day basis and are correlated with a variety of characteristics including the individual's age, sex [23,24], BMI [25], and renal function [26]. Common genetic polymorphisms in the promoter region of the BNP gene have also been shown to be associated with increased levels of circulating BNP [27]. The variability in natriuretic peptide levels in patients in turn provide clinical relevance for the interpretation of assay results and the utility of natriuretic peptide levels for guiding HF therapy[28]. While using BNP and NT-proBNP as predictive values in screening of patients with symptoms suggestive of heart failure (HF), the reference value in representative group of subjects living in the specific region of world has been also been found to different, thus suggesting that geographical variation is also one the factor needs consideration[29] . Akhtar et al have suggested that a trend of leucocytosis with elevated BNP level necessitates further studies to explore the relationship between increased leucocytes count and BNP level prior to use BNP as biomarkers in any disease condition [30]. Body mass index has been associated with lower BNP level in

one of the community based cross sectional study of blacks suggesting that racial variation and obesity contribute its significance in clinical relevance for interpretation of assay results [31].

Potential Role of BNP in Cardiovascular-Renal Homeostasis

Circulating BNP acts as an antagonist of the renin angiotensin aldosterone system, and protects the body from plasma overload by inducing diuresis, natriuresis, vascular dilatation and inhibition of the sympathetic nerves system [32]. It actions are mediated by two major pathways, one acting on veins and arteries causing vasodilatation and second due to its action on renal tissue modulating the renin angiotensin system. Both these action collectively alters the response of vascular system to salt and water handling such as increased venous compliance leading to decrease central venous pressure, decrease in cardiac output by decreasing ventricular preload, decreased systemic vascular resistance and systemic arterial pressure, increased glomerular filtration rate (GFR) and filtration fraction, potassium sparing and thus result in natriuresis (increased sodium excretion) and diuresis (increased fluid excretion). In summary, it seem obvious that BNP via its systemic vasodilation mechanism and natriuretic action results in decreased blood volume, arterial pressure, central venous pressure, pulmonary capillary wedge pressure, and cardiac output and responsible for cardiovascular-renal homeostasis by regulating attenuation of sympathetic vascular tone & counter regulatory system for the renin-angiotensin-aldosterone system.

Genetically altered knockout mice with either disruption of ANP production or deletion of the NPR-A receptor, which binds ANP and BNP, have elicited the role of endogenous natriuretic peptides in cardiorenal homeostasis. Tamura et al. demonstrated in a BNP gene knockout model that these mice have significant ventricular fibrosis, despite normal hemodynamic [33]. Stevens et al. established that the transition from experimental mild CHF to severe CHF could be accelerated utilizing a natriuretic peptide receptor antagonist which resulted in premature sodium retention, impaired renal natriuretic response to volume expansion, activation of the renin-angiotensin-aldosterone system (RAAS), and further increases in cardiac filling pressures [34]. A meta-analysis of 19 studies, in which plasma BNP was used to estimate the relative risk of death or cardiovascular events in patients with CHF reported that for every 100 pg/mL increase in plasma BNP there was an associated 35% increase in the relative risk of death[30]. Val-HeFT trial suggested that patients with a reduction in plasma BNP at 24 months when compared with baseline had the best prognosis [35]. On the basis of the fact that BNP is an important prognostic indicator in CHF, the utility of serial BNP measurements to monitor the response therapies is currently being investigated in the treatment of disorders of cardiorenal function such as CHF. Human recombinant ANP (Carperitide) has been approved for the clinical management of acute decompensated CHF in Japan since 1995. Human recombinant BNP (Nesiritide) has been approved for the same clinical indication in the USA since 2000. Human recombinant Uro (Ularitide) is currently undergoing phase III clinical trails in Europe [36]. Though these trials led to the approval of human recombinant BNP for the management of acute decompensated CHF, but recent studies have cast doubt on their safety and effectiveness.

There is increasing evidence from vascular studies that BNP preferentially acts on the venous system resulting in preload reduction, in contrast to atrial natriuretic peptide which acts preferentially on the arterial system to reduce after load. BNP and CNP are unlikely to modulate sodium excretion under physiological conditions. Lastly, decreased natriuretic peptides plasma level following medical therapy of HF, suggesting the role of their measurement in monitoring inpatient disease progression and outpatient medical programs. The future of natriuretic peptides lies in risk stratification in other cardiac diseases, such as acute coronary syndrome, and possibly determining severity of valvular disease. Although there is substantial work done in elucidating the power of natriuretic peptides in clinical practice, more research is necessary to reach a consensus regarding how to appropriately utilize and interpretate the BNP level in prediction and screening of cardiac disease and its treatment regimens [37].

Anti-Hypertrophyc, Anti-Fibrotic and Anti-Inflamatory Effects of Natriuretic Peptides in the Heart

It has been shown that BNP affects the gene expression and antagonize the cell growth, production of collagen and fibronectin, as well as inhibition of the expression of several pro-inflammatory, profibrotic and pro-trans-formation genes in cultured cardiac myofibroblasts [38]. Evidence of strong correlation between plasma BNP level with level of cardiac hypertrophy and cardiac failure further strengthened the anti-hypertrophic, anti-fibrotic and anti-inflammatory action on BNP on heart. Hypotensive effect on heart is seen after specific deletion of GC-A in the heart rather than systemic deletion of this receptor in the entire organism [28]. These findings hypothesized a negative role of BNP on cardiac growth and remodeling by eliciting hypertrophic stimuli, suggesting its potential role in end-organ damage of cardiovascular renal system.

Effect of Natriuretic Peptides on Lipid Metabolism in Adipocytes

Infusion of BNP into human have been shown to cause increased hydrolysis of triacylglycerol leading to production of non-esterified free fatty acids (NEFA) and glycerol. These effects were found to be same as produced by β receptor agonists (9). It is proposed that the lipolytic action of BNP may be mediated by increased cGMP and activation of PKG through GC-A receptors binding with BNP as an independent pathway of insulin. It is seen that the potency of ANP -induced lipolysis is the greatest as compared to BNP, indicate that sensitivity of natriuretic peptides receptors is seat determine potency of lipolytic action of natriuretic peptides on lipid metabolism [39]. Further research in experimental models may help to understand the precise mechanism of lipolytic action of BNP and will add one more physiological potentials of BNP in cardiovascular renal physiology.

BNP Level and Migraine

Migraine has been related with an increased risk for ischemic stroke and cardiovascular events. In a recent published report, it is reported that migraine patients have been found to be associated with increased pro-BNP levels with higher serum IL-1beta and IL-6 levels, and lower IL-10 levels. These findings support that association of BNP level may indicate cardiac involvement in patients with migraine [40]. Increased cytokines levels may be related to neurogenic inflammation in the pathogenesis of migraine. However,

there is insufficient data describing role of pro-brain natriuretic peptide (pro-BNP) in migraine and more structured based clinical experimental data are required to determine the role of cytokines and pro-BNP in migraine.

BNP Level and Exercise

Increased BNP levels in healthy individuals have been demonstrated immediately after exercise with ill-defined relevance to mild, moderate and severe exercise suggesting that transient rise in BNP level following exercise may be attributed to sympathetic activation leading to increased blood pressure, heart rate and left ventricular filling pressures during the exercise (41). This study provides strength to the earlier reports advocating relationship between elevated plasma concentrations of natriuretic peptides and cardiovascular diseases, especially heart failure. Thus knowledge of BNP behavior under physiological conditions needs to explore as a screening tool for proper assessment of load in health and cardiac disease.

Conclusion

The published data on BNP reveals that its role in pathophysiology of different disease conditions is still in infancy stage and need further research on human and experimental models to advance our understanding of the cellular and molecular mechanisms, the physiological control processes, and possible avenues of therapeutic intervention. Continued efforts are warranted to identify molecular targets of natriuretic peptide system to further enhance our knowledge of natriuretic peptides application in cardiovascular system and molecular basis of the development and progression of cardiovascular diseases.

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