NATRIURETIC PEPTIDES ARE CARDIOVASCULAR MARKERS FOR HEART FAILURE

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Abstract

The natriuretic peptides are structurally related hormones that regulate blood volume blood pressure ventricular hypertrophy. Three distinct natriuretic peptides have been isolated in humans, they are : atrial natriuretic peptide (ANP); brain natriuretic peptide (BNP) and C type natriuretic peptide (CNP). Their action is on the tissue of the heart, kidney and central nervous system Brain natriuretic peptide (BNP) and atrium natriuretic peptide (ANP) have antischemic properties and because of their natriuretic, diuretic and vasodilatators effects they can be used in the future as therapeutic agents in heart failure. They are markers of heart failure and can be a predictor of long term cardiovascular mortality independent of left ventricular ejection fraction.

Keywords: ANP= atrial natriuretic peptide; BNP= brain natriuretic peptide; CNP= C type natriuretic peptide.

Natriuretic polypeptides are peptides which exert actions on heart, kidney and central nervous system. They are a family of structurally related but genetically distinct hormones that regulate ventricular hypertrophy blood pressure blood volume, fat metabolism, pulmonary hypertension, long bone growth[4]. De Bold[1] et al. reported the first, direct evidence that the iv injection of atrial but not ventricular homogenates into rats elicited a decrease in blood pression and an increase in renal sodium and water excretion. After that, several groups purified peptides of varying sizes from atrial tissue that possess both natriuretic and smooth muscle relaxing activity They are three: the atrial natriuretic peptide (ANP), the brain natriuretic peptide (BNP) and C type natriuretic peptide (CNP).

The atrial natriuretic peptide (ANP)

The atrial natriuretic peptide was the first discovered in 1984.

It has natriuretic effects[9], diuretic and vasodilatators effects. It is synthesized as prehormon, like all natriuretic peptides Human pre proANP has in length 151 aminoacids. The 126 aminoacids proANP is the predominant form stored in atrial granules[4].

It is released from storage granules in the myocardium because it is secreted from the cardiac atria[26]. The primary stimulant for ANP release is atrial wall stretch resulting from increased intravascular volume ANP is perfused in to coronary sinus and is distributed in a endocrine manner to various target organs. Hormones like endothelin, angiotensin, and arginine vasopressin,

stimulate the release of ANP [10]. The release of atrial natriuretic peptide (ANP) and of brain natriuretic peptide(BNP) is influenced by the tension of the left ventricular wall. In normal people his concentration in venous blood is at f mol level. approximately 10fmol/ml (1 fmol = 3,5 pmol/ml). The concentration of atrial natriuretic peptide (ANP) is markedly elevated 10 to30 fold in heart failure with low ventricular ejection fraction and low cardiac output. Also the concentration of ANP is elevated in hypertrophyc cardiomiopathy and hypertensive left ventricular hypertrophy[26]. During infarction of the myocardium and post infarction the concentration of the atrial natriuretic peptide and brain natriuretic peptide rise due to release from myocardium [25].

Atrial natriuretic peptide antagonizes the renin angiotensin aldosterone system.

He inhibits the release of endhothelins (secreted by vascular endothelium) with vasoconstrictor action[11].

Atrial natriuretic peptide inhibit baroceptor mediated tachycardia and reduce the levels of cathecolamines from blood.

Atrial natriuretic peptide is a coronary vasodilatator and reduces the symptoms of angina.

In 1993, Lerman and all[24] published their findings that N terminal proatrial natriuretic peptide is an indicator of asymptomatic ventricular dysfunction. The plasma concentration of Atrial natriuretic peptide would be a powerful predictor of long term mortality independent of left ventricular ejection fraction.

Brain natriuretic peptide (BNP)

Brain natriuretic peptide was initially purified from porcine brain extracts. In humans is secreted exclusively from the heart (ventricles). His name is also B type natriuretic peptide [20]. It was found in much higher concentrations in ventricles of patients undergoing congestive heart failure or myocardial infarction. His actions are similar with those of atrial natriuretic peptide[19]. Brain natriuretic peptide is synthesized as a preprohormon of 134 residues and the prohormon has 108 residues of aminoacids released from storage granules from the myocardium. His concentration in normal people, in the venous blood is 1 fmol/ml (3,5 pg/ml) BNP is stored with ANP in atrial granules but BNP is not stored in granules in the ventricles[23].

The concentration of brain natriuretic peptide is markedly elevated in heart failure and is associate with low ventricular ejection fraction and low cardiac output, in hypertrophic cardiomiopathy and ventricular hypertrophy during arterial hypertension[18]. In congestive heart failure the concentration of BNP plasmatic is 200-300 fold greater than normal for this reason is an ideal indicator of cardiac stress and correlate with poor prognoses [17].

Also like atrial natriuretic peptide it is very high post infarction of the miocard.

All natriuretic peptides can interact with other neurohormones mechanisms.

An elevated plasma level of brain natriuretic peptide post myocardium infarct is a marker for those with impaired ventricular function who would benefit from ACE inhibition [20].

Plasma natriuretic peptides might help to identify heart failure patients as a screening test to select which patient require further investigation such as echocardiography.

A way to identify mild to moderate heart failure is by measuring the plasma natriuretic peptide levels. The brain natriuretic peptide is superior to atrium natriuretic peptide to identify left ventricular systolic dysfunction [21].

Natriuretic peptide levels may be even more useful as prognostic than diagnostic markers. The elevated plasma level of brain natriuretic peptide is an independent predictor of mortality in patients with chronic heart failure [20].

C type natriuretic peptide (CNP)

Is not present in the myocardium, is present in the central nervous system [2] and in chondrocytes and in cytokine exposed endothelial cells[8]. Human pro CNP contains 103 aminoacids residues. Normal plasma CNP concentration are in low femtomole per milliliter range [27].

His vasodilators and natriuretic effects are weaker than those of the other natriuretic peptides [3].

Until now we don't know the physiological factors that control his release.

In the normal subject is detectable in the venous blood at a concentration of picomoli. C type natriuretic peptide concentration is not elevated in heart failure.

C type natriuretic peptide is mainly a neurotransmitter, involved in the control of cardiovascular mechanism and is possible to reduce vascular smooth muscle cell proliferation [27].

Clearance of natriuretic peptides

The clearance of natriuretic peptides from the circulation occurs by: first via C receptors mediated endocytosis [6] and second by degradation with the aid of an enzyme which contains Zn a neutralendopeptidase [7]. The half life of atrial natriuretic peptide is 3 minutes. The half life of brain natriuretic peptide is 22 minutes and the half life of C type natriuretic peptide is 2,6 minutes.

The C receptor is a clearance receptor with the function of removal of natriuretic peptides from the blood. These receptors are present in kidney, heart endothelium adrenals and central nervous system.

Brain natriuretic peptide and atrial natriuretic peptide have antiischemic properties in humans and their natriuretic, diuretic and vasodilatory properties make them very attractive as therapeutic agents in heart failure in the future.

Therapeutic applications of natriuretic peptides

They can potentially be used as therapeutic agents for the therapy of congestive heart failure, hypertension and renal failure. The infusion of synthetic ANP (anaritide or carperitide)[13] in hypertensive patients or in patients with chronic heart failure [13] have resulted in decreased blood pressure and elevated water and sodium excretion[13]. In patients with acute renal failure the data from trials using anaritide was contradictory. Nesiritide is a human recombinant BNP with its trade name Natrecor has been shown to cause potent vasorelaxation accompanied with increase in

natriuresis, in diuresis and decrease in plasma aldosterone and endothelin in patients with acute heart failure. The US Food and Drug Administration approved the use of BNP (nesiritide) [14] in heart failure in 2001.Additional clinical trials are necessary to evaluate to define the benefits, risks and parameters required for optimal treatment in humans.

One clinical benefit of natriuretic peptides comes from their diagnostic use, because ANP and BNP are increased in patients with heart failure, with hypertension and chronic renal failure.BNP values heave been successfully used to predict poststroke mortality, post cardiac surgery atrial fibrillation [16] and the risk of death in patients with heart failure. BNP has been suggested to be a better guide for optimal treatment of heart failure than classical clinical measurements BNP levels more than 500 pg/ml are more likely to be confirmative of a primary diagnosis of heart failure and predictor for long term adverse prognosis: the value between 100-500 pg/ml suggests o reasonable likelihood for the diagnosis of heart failure but require exclusion of other potential factors like pulmonary disease resulting in right heart failure and under 100 pg/ml indicate that heart failure doesn't exist[17]. Thus BNP has emerged as a new tool to manage heart failure.

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