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RESEARCH ARTICLE

Hypoxia-Inducible Factor mediates the Release of Natriuretic Peptides

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ABSTRACT

Background: The physiology of natriuretic peptides is insufficiently known. The function of mechanical heart alone, mediated by large and rapid volume overloads, has been suggested to be the key operator in the synthesis and release of natriuretic peptides from the endocrine heart. Researchers have concluded that terrestrial mammals, including humans, have a powerful endocrine system that responds to the mechanical stress of the heart by causing instantaneous diuresis and natriuresis. Although one of the most important and valid paradigms in cardiology is that mechanical load increases the oxygen consumption of heart, the investigation of the relationship between mechanical load and oxygen metabolism has been neglected in the studies on circulating natriuretic peptides.

Purpose: To develop a comprehensive conceptual model explaining how the oxygen metabolism plays a central role in the biology of natriuretic peptides.

Conclusions: All cells including cardiac myocytes, share an oxygen sensing pathway which is regulated through a nuclear transcription factor, the Hypoxia-Inducible Factor. When the oxygen concentration is normal Hypoxia-Inducible Factor is rapidly oxidized, whereas in hypoxic conditions, Hypoxia-Inducible Factor starts to accumulate and trigger downhill the expression of hundreds of genes such as the genes for A-type and B-type natriuretic peptide. As a result of diuresis, natriuresis, and plasma shift from intravascular space to extravascular space, circulating natriuretic peptides cause volume contraction and hemoconcentration contributing to the transport of oxygen into tissues and organs.

Implications: Understanding the biology of natriuretic peptides in cardiac diseases would increase the usefulness of plasma measurement of natriuretic peptides.

Keywords: Natriuretic peptide, hypoxia-inducible factor, hypoxia, oxygen

Introduction

In 1964, an extensive electron microscopy study was published, showing that mammalian heart atria had numerous small granules near the nuclei resembling those previously found in pancreatic insulin-secreting cells.[1] The authors concluded that the granules, which could not be found in heart ventricles, were 'presumably secretory in nature'. When extracts of atrial tissue were infused twenty years later into a rat's circulation, it caused a strong natriuretic and diuretic response.[2] Mammalian heart atria had an atrial natriuretic factor that caused these effects, which rapidly led to the isolation and characterization of circulating cardiac peptides: first atrial natriuretic peptide (ANP) or A-type natriuretic peptide, and then brain natriuretic peptide (BNP) or B-type natriuretic peptide[3] and they were localized with a double immunogold technique in the granules.[4,5]

Later a third member of the natriuretic peptide family, namely the C-type natriuretic peptide was found in cardiovascular system, mainly with paracrine actions.[6] These findings profoundly changed our view on the heart that originated from the times of William Harvey; it was not exclusively a mechanical pump but also an endocrine organ which had effects on the cardiovascular system. Despite the enormous scientific activity that proliferated from the discovery (the key phrase "natriuretic peptide" returned 47,000 papers from PubMed as of January 2024), the role of circulating natriuretic peptides and additional sequences derived from these remains confusing in cardiac diseases, and the standardization of natriuretic peptides inclusion criteria across cardiac diseases varies. These problems stem from the fact that the question what is the physiological function of natriuretic peptides in healthy humans has not been properly answered.

However, in the mid-1980's, a seminal letter was published in Nature[7] which showed that a large and rapid intravascular volume load in rats caused high plasma levels of ANP. This finding was confirmed with isolated perfused hearts, showing that ANP originated from the atria as a consequence of stretching; the authors more than doubled the intravascular volume of a rat (8ml during 1 min) but they did not relate their findings to any metabolic parameters. Since then, the mechanical stress alone, likely to result from varying volume excesses without any relation to oxygen metabolism, has constituted a frozen paradigm in the cardiology of natriuretic peptides, as evidenced by several influential consensus and position papers.

The mechanical stress paradigm has remained as a cornerstone in the vast majority of executed clinical studies on natriuretic peptides. Because of the strong emergence of molecular biology during the 1980-90's, during which departments of physiology were transformed into departments of molecular biology, the research on the physiology of natriuretic peptides came to an end soon after its start; a bridge between basic science and cardiology was disrupted. Although one of the most important and valid paradigms in cardiology is that mechanical load increases oxygen consumption,[8] the investigation of the relationship between mechanical load and oxygen metabolism has been neglected in the clinical studies on natriuretic peptides and the mechanical stress paradigm has persisted. From the standpoint of physiology, it is

difficult to understand why the mechanical stress were the physiological stimulus for the function of natriuretic peptides. In that case, the release mechanism should be able to detect the error signal for the peripheral need of natriuretic peptides among laminar and turbulent flows within atrial lumen which are further disturbed by physical activity. Therefore, we should perhaps explore for a circulating factor or a condition in human body that are independent of mechanical load and regulate the synthesis and release of natriuretic peptides. When the physiology of natriuretic peptides in healthy human adults is known then the measurement of circulating natriuretic peptides could be better capitalized in the diagnosis and follow-up of cardiac diseases.

An oxygen sensing pathway, existing in all cells, has been found to be activated also in cardiac myocytes during low oxygen tension.[9] Could this pathway operate as a link between the mechanical and the endocrine heart and better explain the pathophysiology of natriuretic peptides in cardiac diseases? Based on published papers, the scope of the review is to show how the oxygen metabolism plays a crucial role in the synthesis and release of natriuretic peptides.

Hypoxia-Inducible Factor

During biological evolution, oxygen homeostasis has been a critical constraint in all cellular functions. Due to the importance of maintaining cellular oxygen concentrations within a narrow range, metazoans have developed a Hypoxia-Inducible Factor (HIF) pathway through which all cells respond to a reduced oxygen tension. The function and structural components of HIF are phylogenetically conserved across the animal kingdom and HIF can be regarded as a master operator in oxygen regulation. Oxygen-dependent functions of cardiac myocytes are also mediated by this mechanism. The discoverers of the HIF pathway were awarded a Nobel Prize in 2019.

Hypoxia-Inducible Factor is a nuclear heterodimeric transcription factor, a protein, functioning as a principal regulator of adaptive responses to reduced oxygen concentrations.[10] HIF comprises a labile α subunit (α 1-3), which is regulated, and a stable β subunit, which is constitutively expressed. Both are helix-loop-helix factors belonging to the PAS-domain family of transcription factors. When oxygen tension is normal, HIF-1α is rapidly oxidized by hydroxylase enzymes, whereas in hypoxic conditions, HIF-1α starts to accumulate, triggering the downhill expression of a large number of genes.

Hypoxia was a direct and sufficient stimulus for the expression of both A-type[11] and B-type[12]natriuretic peptides from cardiac myocyte cultures via the HIF pathway. In pigs, the surgical reduction of blood flow to an area of the ventricular wall, causing hypoxia, increased the BNP gene expression distally to the lesion.[13] When the HIF pathway was specifically prevented in hypoxic conditions in the cell lines derived from human cardiac myocytes, the release of BNP was inhibited, providing evidence that hypoxic conditions, HIF and BNP were directly interrelated.[14] Similar results were obtained, without any mechanical stress, in a retinal pigment epithelium cell culture of human origin.[15] In isolated beating rabbit atria, acute hypoxia significantly increased ANP secretion, HIF-1α mRNA and protein levels in the circumstances during which the atrial mechanical activity was clearly decreased.[16]

However, these findings have been unable to challenge the prevailing mechanical stress paradigm.

Physiology of Natriuretic Peptides

To better understand the regulatory systems behind the plasma levels of natriuretic peptides in cardiac diseases, it is worth revisiting what is assumed to be the physiology of natriuretic peptides. Researchers concluded indirectly from volume load experiments with extensive atrial stretch that terrestrial mammals, including humans, have a powerful endocrine system that responds to the mechanical stress of the heart and rapidly counteracts volume excesses by causing instantaneous diuresis and natriuresis. However, large volume overloads rarely occur in circulation under physiological conditions; on the contrary, we are in constant danger of becoming dehydrated. In addition, it was the laboratory rat that was used in the volume overload experiments[7] and this species originates from warm and arid conditions. Furthermore, the endocrine volume control is mainly achieved by thirst and urine concentration, regulated by antidiuretic hormone (ADH), during a time scale of hours. The large reservoir and the short half-lives of natriuretic peptides in heart atria suggest that they are responding to a momentary and urgent condition such as the low oxygen concentration in circulation.

Additionally, an important feature that has been disregarded when interpreting the results of studies on natriuretic peptides is hemoconcentration. Circulating natriuretic peptides can cause both an extrarenal shift of plasma water through the vessel wall and a transcapillary shift of albumin, contributing significantly to a subsequent reduction of the plasma volume amplified by glomerular natriuresis and diuresis.

Experimentally, an ANP infusion increased hematocrit and decreased plasma volume in nephrectomized rats and the authors concluded that the changes were due to the efflux of fluid from vascular capillaries.[17] In line with these findings, a similar infusion of ANP into human subjects caused a shift of plasma water from intravascular to extravascular space and was further followed by an albumin escape.[18] Due to its additional effects on the secretion of other hormones (renin, aldosterone, and erythropoietin), and the lymphatics and spleen, ANP has a pivotal role in the regulation of intravascular-interstitial fluid shifts.[19]

The hemoconcentration that follows a rapid intravascular volume contraction, leads to a higher oxygen-carrying capacity of blood and contributes significantly to oxygen transport to tissues and organs, whereas a decrease in blood pressure is secondary in importance.

Natriuretic Peptides in diseases

During an acute stress the frequency of heartbeats increases because of the sympathetic activity, and the oxygen consumption of the heart also increases. The human body becomes prepared for action to perform better under stressful conditions. Although clearly a pathophysiological state, with a frequency of heartbeats well above the normal range, paroxysmal atrial tachycardia functions like a physiological rhythm, during which polyuria is a common but less studied finding that cannot be explained by the activity of antidiuretic hormone.[20] In experimental animals, pacing directly stimulated the release of ANP from

isolated rat atria[21] and also in conscious dogs having a complete atrioventricular block without elevations in atrial pressure.[22] In patients during paroxysms of atrial fibrillation, there was a distinct increase of hematocrit that returned to the normal level during sinus rhythm.[23] Again, the oxygen metabolism operated as a direct and sufficient factor regulating the release of natriuretic peptides during atrial tachycardia with natriuresis, diuresis, and water shift into extravascular space. Most likely, although not proven so far, the HIF pathway is functioning during atrial fibrillation.

The obstructive sleep apnea (OSA) disease is interesting from the angle of natriuretic peptide physiology as it is associated with intermittent hypoxemia due to repeated ventilatory obstruction during sleep. Several studies have found an increased hematocrit during OSA[24] and elevated plasma levels of natriuretic peptides.[25] However, the source of natriuretic peptides (atria or ventricles) remains to be shown in this clinical condition.

In both heart failure and acute coronary syndrome, the oxygen metabolism of the heart becomes stressfully disturbed, and elevated plasma levels of natriuretic peptides can be measured, determining the diagnosis and prognosis of cardiac diseases. Due to the remodeling in these pathological conditions with variable oxygen gradients across the myocardium the ventricles shift to a fetal state and start to express and release natriuretic peptides. In this case, the biology of natriuretic peptides differs from that seen during atrial fibrillation as no diuresis or natriuresis are found. According to fragmentary findings, when ventricular-biopsy specimens were collected from the patients undergoing coronary bypass surgery, HIF-1α was detected in myocardial samples with pathological evidence of acute ischemia or early infarction.[26]

Oxygen metabolism plays a central role in the cardiac biology of natriuretic peptides in mammals, and mechanical load affects the endocrine heart.[27-31] The synthesis and release of natriuretic peptides respond in myocytes to a reduced concentration of oxygen through the HIF pathway which mediates the hypoxia responses of all cells. Although the atrial fibrillation is a heart disease it follows the physiological pathway of natriuretic peptide secretion by causing natriuresis, diuresis and plasma shift from intravascular to extravascular space. In heart failure and infarction, the gene expression of ventricles shifts toward fetal direction (remodeling) and ventricles start to express natriuretic peptides. It is not known why high plasma levels of natriuretic peptides do not cause natriuresis, diuresis, or plasma shift in these diseases; the biology of fetal gene expression of heart should be explored further. The biology of natriuretic peptides is summarized in Figure 1.

Prolonged and repetitive breath-hold periods of seals while they are sleeping, a possible model for OSA studies, were associated with high plasma levels of ANP which were normalized when they started breathing again.[32]

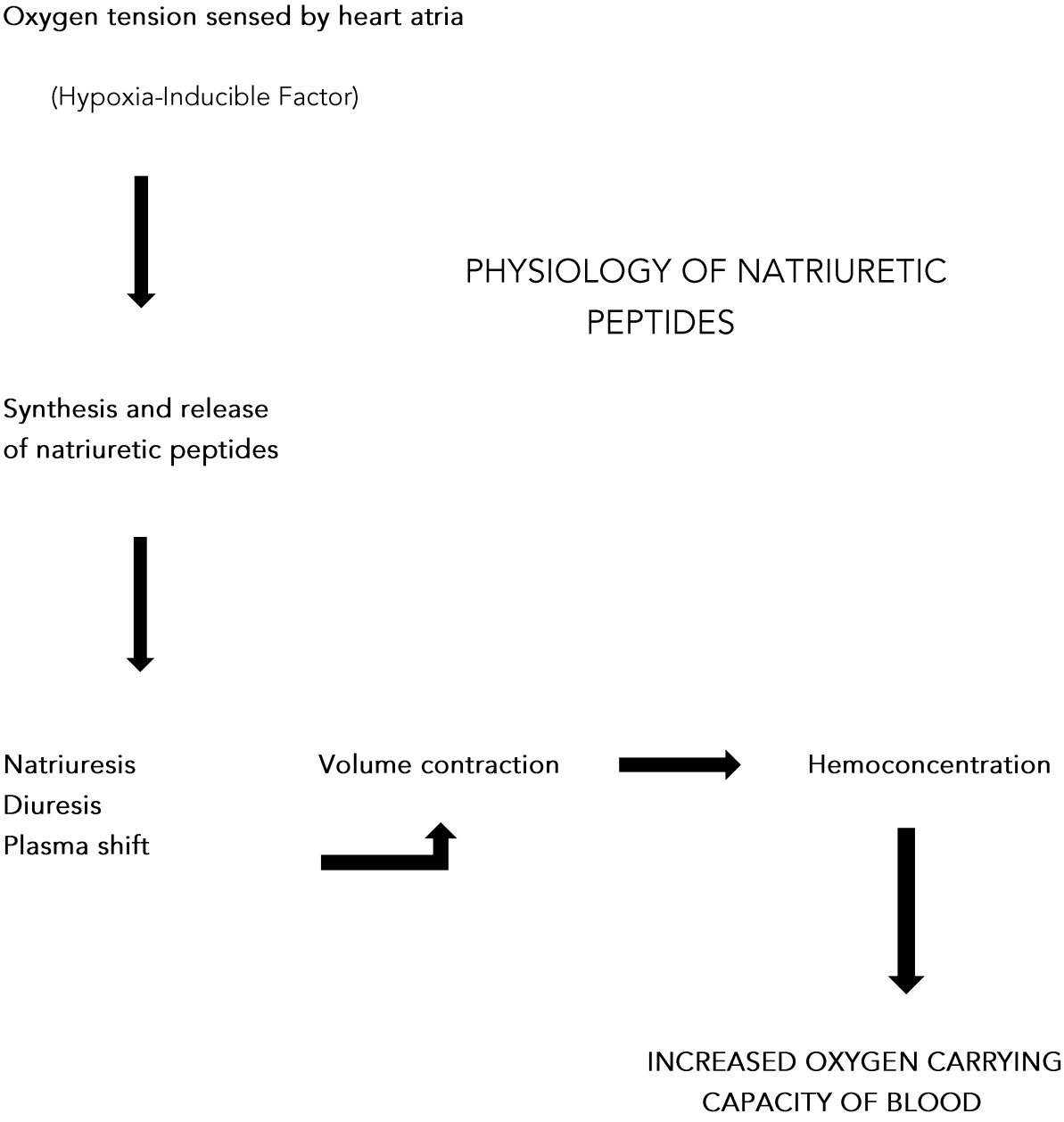

Figure 1. Biology of natriuretic peptides. The natriuretic peptide system is hypoxia sensitive and contributes to the regulation of oxygen transport. Hypoxia-Inducible Factor (HIF) mediates the hypoxic responses of all cells including cardiac myocytes. Atrial fibrillation stimulates the physiological atrial pathway of natriuretic peptide secretion. In heart failure and infarction, ventricles shift to fetal gene expression (remodeling) and start to express natriuretic peptides without natriuresis, diuresis, or plasma shift.

Conclusions and future directions

Measured natriuretic peptides, used in the diagnosis and follow-up of the cardiac diseases[33] in which hypoxic conditions predominate and where HIF has a central role, could be better explained by the oxygen metabolism of heart. The release of natriuretic peptides could be explored by means of the *in vitro* heart perfusion system that has been previously used in the studies of oxygen delivery into heart.[34] New tracers currently in development show significant promise for the direct imaging of oxygen and hypoxia directly from the heart.[35,36] The function of Hypoxia-Inducible Factor is a potential therapeutic target in cardiac diseases.

Mechanical stress and oxygen metabolism are strongly interrelated with each other in the heart. What if the circulating NT-proBNP concentration correlates directly with the oxygenation status of myocardium in ventricular heart diseases?

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