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Production and Release of Natriuretic Peptides to the Blood and Their Action in Blood Pressure Control (Review Article)

Stephanie de Godoy Ricca[1], Lorena Coimbra Rocha de Souza[1], Maico Elisvan da Silva[1], Tallyta Malumayer da Silva[1], Romeu Rodrigues de Souza[1]

[1]Department of Human Anatomy, Faculty of Medicin, Uninove University, São Paulo, SP, Brazil

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ABSTRACT

Introduction: the atrium cardiomyocytes have a group of structures collectively called the secretory apparatus, consisting of the pores of the nuclear membrane, the mitochondria, the endoplasmic reticulum and the Golgi apparatus. These device produces and secretes into the bloodstream, peptides called natriuretic peptides. They are called ANP (atrial natriuretic peptide) and BNP (brain natriuretic peptide), and they work by lowering blood pressure, due to its diuretic action on the kidney. In this work, a literature review was carried out on the ultrastructure and action of the constituent elements of the cardiomyocyte secretory apparatus. ANP and BNP are stored in the cytoplasm of cardiomyocytes in the form of granules of varying sizes. In the presence of arterial hypertension (AH), there is an increase in pressure on the walls of the atria, inducing the secretion of natriuretic peptides (NPs) into the bloodstream, which promote natriuresis, reducing systemic blood pressure. The present work was carried out using the databases of Lilacs, Bireme, Medline via Pubmed and Scielo without distinction of language, in the period between October 2021 and October 2022, using the descriptors "atrial cardiomyocytes, natriuretic peptides and blood pressure". Basic and applied studies performed with healthy human beings and laboratory animals were selected, thus excluding studies with patients and animals presenting any type of comorbidity.

Keywords: Atrial muscle cells; Ultrastructure; Rodents; Aging; Natriuretic peptides; ANP; BNP; Blood pressure.

Introduction

Atrial cardiomyocytes produce and secrete into the bloodstream, peptides called natriuretic peptides. They are the Atrial Natriuretic Peptide (ANP) and the Brain Natriuretic Peptide (BNP)[1]. Due to their diuretic action in the kidneys the natriuretic peptides act by lowering blood pressure. ANP also has other important actions, such as decreasing the risk of cardiac hypertrophy and arrhythmias[2-4]. Structural components of atrial cardiomyocytes, collectively called the secretory apparatus are responsible to produce and secrete ANP and BNP. These structures are the pores of the nuclear membrane, the mitochondria, the endoplasmic reticulum and the Golgi apparatus[5]. In the present work, a bibliographic review will be carried out on to explain the structure and function of the components of the cardiomyocyte secretory apparatus.

The physiological role of ANP hormone in chronic blood pressure homeostasis is well understood. The chronic hypotensive action of ANP is determined by vasodilation of the vasculature, which is probably mediated by attenuation of vascular sympathetic tone at one or several prejunctional sites[6]. Cardiac natriuretic peptides [atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP)] and the renin-angiotensin-aldosterone system are opposing control mechanisms for arterial blood pressure. Natriuretic peptides buffer renal vascular hypertension via renin-independent effects, such as vasorelaxation. The latter possibility is supported by experiments in isolated perfused mouse kidneys, in which physiological concentrations of ANP and BNP elicited renal vasodilatation and attenuated renal vasoconstriction in response to angiotensin II[7].

BNP levels can be used to differentiate between breathless patients with a respiratory disease and those with pulmonar arterial hipertension. BNP has been shown to correlate with mean pulmonary arterial pressure and pulmonary vascular resistance in patients with pulmonar arterial hypertension, whether primary or secondary. BNP is also a predictor of mortality in patients with primary pulmonary hypertension[8]. On the other hand, as ANP and BNP, may also be involved in the mechanisms acting against a further increase in blood pressure, they may be useful biomarkers for the diagnosis and treatment of hypertensive patients.

What Are Natriuretic Peptides?

Natriuretic peptides ANP and BNP are hormones produced in atrial cardiomyocytes and secreted into the bloodstream[9,10]. The peptides are stored in the form

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of spherical granules of varying sizes from 150 to 250 nm in diameter in the cytoplasm of cardiomyocytes of the atria[11–13] (Fig.1A). The granules containing ANP are also called type A. They are spherical and well delimited. Those containing BNP are smaller, with surface spikes, being also called type B (Fig. 1B).

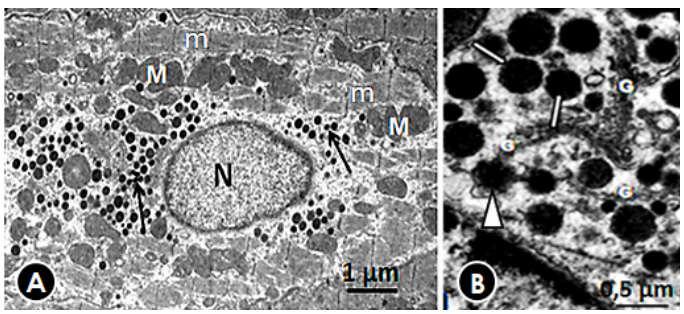

Figure 1. Electron photomicrographs of sections of atrial cardiomyocytes. A- At low magnification, shows NP granules of various sizes (arrows), dispersed in the cardiomyocyte cytoplasm. Figure B, shows ANP (white arrows) and BNP (arrowhead) granules with greater magnification. M-myofibrils. N-Nucleus. M-mitochondria. G-Golgi apparatus.

Production and secretion of natriuretic peptides

Natriuretic peptides are chemical substances that are produced and stored in the cytoplasm of cardiomyocytes in the form of granules of varying sizes[9]. In the presence of arterial hypertension (AH), there is an increase in pressure on the walls of the atria and consequent distension of its walls, inducing the secretion of natriuretic peptides into the bloodstream, that promotes natriuresis and diuresis and reducing systemic blood pressure[1,14,15].

The production and secretion of natriuretic peptides depend on structural components of the atrial cardiomyocytes. Among these components, the most important are the pores of the nuclear membrane, the euchromatin, the Golgi complex, and the mitochondria[5]. Several studies have shown that different factors interfere in the production of natriuretic peptides by cardiomyocytes. For example, estrogen hormones and aerobic training. They act by stimulating cardiomyocytes for the production and secretion of natriuretic peptides[2,16,17,18,19,20]. Resistance training is another factor that triggers the release of peptides into the bloodstream[21].

Other studies have shown that there is also variation in the number of ANP granules in cardiomyocytes in different species[22,23,24,25,26].

Natriuretic Peptides and Blood Pressure Control

When blood pressure rises, atrial cardiomyocytes secrete peptide hormones into the bloodstream. Thus, they act on the kidneys by increasing diuresis and blood pressure lower. For this reason, the peptides are called natriuretic peptides. There are several natriuretic peptides. However, in this work we will particularly highlight the natriuretic peptides ANP and BNP, which are also generically called NPs (natriuretic peptides). ANP and BNP are stored in the cytoplasm of atrial cardiomyocytes as granules of varying numbers and sizes. Both hormones are involved in controlling blood pressure.

In the presence of arterial hypertension (AH), there is an increase in pressure in the walls of the atria, promoting the secretion of NPs into the bloodstream, inducing natriuresis and reducing systemic arterial pressure[1].

ANP also has other important actions, such as decreasing the risk of cardiac hypertrophy and arrhythmias[2,4,27,28].

It is known that the prevalence of arterial hypertension (AH), especially systolic hypertension, is higher in middle-aged women[29,30]. The mechanisms by which AH occurs in this age group are still the object of discussion[31]. As NPs act to control BP, the authors have sought to assess the relationship between NPs and several other factors including aging and hypertension.

Another peptide, BNP, is also produced in the atria in humans, but its initial discovery was made in the brain of monkeys[32]. It is also stored in atrial cardiomyocytes in the form of granules.

BNP granules are smaller than ANP granules[33]. Although ANP like BNP are produced by cardiomyocytes in the right and left atriums, NPs have been most studied in the right atrium.

In the present work, we carried out a literature review study on the ANP and BNP secretory apparatus of atrial cardiomyocytes and their relationship with blood pressure.

Other Functions of Natriuretic Peptides

As we know, natriuretic peptides are stored in the cytoplasm of atrial cardiomyocytes, inside granules. When needed, they are secreted into the bloodstream. The factor that triggers its secretion into the bloodstream is the increase in blood pressure against the atrial walls, due to the increase in systemic blood pressure. Once released into the bloodstream, natriuretic peptides act on blood vessels, inhibiting vasoconstrictor mechanisms and on renal tubules, increasing diuresis, and lowering blood pressure[7,34,35,36,37].

The cardiac natriuretic peptides [(atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP)] are opposing mechanisms of renin-angiotensin-aldosterone system for arterial blood pressure control[7]. Accumulating behavioral evidence suggests that ANP and BNP hormones also modulate anxiety symptoms and panic attacks[38]. Recent studies suggest that manipulations of the ANP system could be a potential target for pharmacotherapeutic intervention to treat alcohol use disorder[39]. Finally, less recognized is the fact that natriuretic peptides potently affect lipid and glucose metabolism. Once released, natriuretic peptides raise renal sodium excretion, elicit vasodilation, and are the physiological antagonists of the renin-angiotensin system[40].

Discovery of ANP and BNP peptides

In the 1950s, it was observed that atrial cardiomyocytes had, in their cytoplasm, a substance capable of reducing systemic arterial pressure by inducing natriuresis and decreasing blood volume. Subsequently, the electron microscope showed that this substance was present in granules in the cytoplasm of atrial cardiomyocytes. Biochemical analysis of the granules showed that the substance was composed by the natriuretic peptides. Bruno Kisch described that ANP was present in granules, in atrial cardiomyocytes of guinea pigs, for the first time, in 1956[41]), Later, it was found that the chemical substance contained in the granules acted as a natriuretic factor. Thus, the substance was called Atrial Natriuretic Factor and later, Atrial Natriuretic Peptide[42]. This was followed by a period of active research, and to date about 11 000 papers have been published with regard to the cardiac natriuretic peptides[43].

To confirm the function of ANP, De Bold[1] prepared extract from atria and it was injected into the peritoneum of rats. It was observed an increase in diuresis, renal sodium excretion and a decrease in blood pressure in the animals that received the atrial extract. After this, numerous studies have been carried out on atrial cardiomyocytes and on ANP granules in various situations, both from a morphological and functional point of view, confirming the initial findings.

BNP granules have been described more recently. They are also known as granules that contain Brain Natriuretic Peptide (recognized as BNP) (figure 2). BNP (Brain Natriuretic Peptide) is so named because it was initially identified in the brain of monkeys. Subsequently, it was found that, in humans, BNP is also released by the cardiac atria and ventricles into the circulatory system in response to an overload of pressure or volume. Like ANP, BNP also promotes increased diuresis and vasodilation[44,45,46], and is therefore a hormone with a hypotensive effect, like ANP.

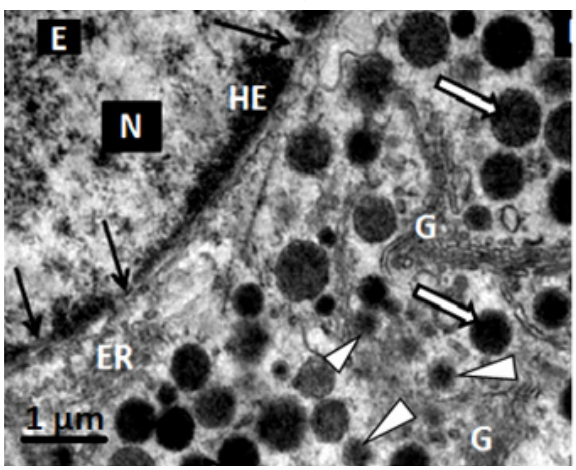

Figure 2. Electron micrograph of the right atrium of an LDLR-Knockout mouse, showing ANP (white arrows) and BNP (arrowheads) granules in the cardiomyocyte cytoplasm. Also shown are the endoplasmic reticulum (ER) and the Golgi complex (G). The cardiomyocyte nucleus (N) shows dispersed euchromatin (E) and heterochromatin (HE) as a band close to the nuclear membrane. This appears as two thin membranes showing nuclear pores (black arrows).

Ultrastructure of atrial cardiomyocytes

Atrial cardiomyocytes have a central nucleus (Fig. 1A), evident cytoplasmic organelles, such as the Golgi apparatus, mitochondria and endoplasmic reticulum, in addition to the presence of natriuretic peptides under the shape of granules of varying numbers and sizes (Figure 2).

Most NP granules are found dispersed among the cytoplasmic components of cardiomyocytes[23,48,55], (Figure 2) and also close to the nucleus, with a few being spread throughout the cytoplasm, in positions more distant from the nucleus[49].

The quantitative distribution of these granules is different in the right and left atria. There are more granules in right atrium cardiomyocytes than in left atrium cardiomyocytes[25].

The nuclear and cytoplasmic components of cardiomyocytes involved in the production and release of ANP and BNP are nuclear chromatin, the pores of the nuclear membrane, the Golgi apparatus, mitochondria and the endoplasmic reticulum. For this reason, the set of these components was called by some authors the cardiomyocyte secretory apparatus[5]. These components will also be evaluated in this work.

The production of NPs in each cardiomyocyte depends on intracellular mechanisms that control the transcription and continuous formation of new molecules [50]. The transcription process depends on the nuclear membrane to carry out the mRNA output from the nucleus to the cytoplasm, as well as the transport of proteins, factors that depend on the pores of the nuclear membrane[51].

The transport of proteins occurs through another protein called Ran guanosine triphosphate (Ran GTPase), responsible for the regulation of several processes, among which the transport of substances from the nucleus to the cytoplasm, mitosis, formation of nuclear membrane and mainly the biogenesis of pores of the nuclear membranes themselves[52].

According to others[53], the participation of Ran GTPase in protein transport between the nucleus and the cytoplasm is crucial for protein synthesis and, therefore, for the production of NPs.

Ultrastructural aspect of ANP and BNP granules

On the ultrastructure, the ANP granules appear as spherical, regular bodies and appear in the sections as circles containing sharp boundaries, enveloping a halo around a darker area containing the ANP (Figure 3).

Skepper *et al*[54] analyzed the dimensions of atrial granules in rat cardiomyocytes and found that they measure from 100 to 250 micrometers in diameter, with variations in other species.

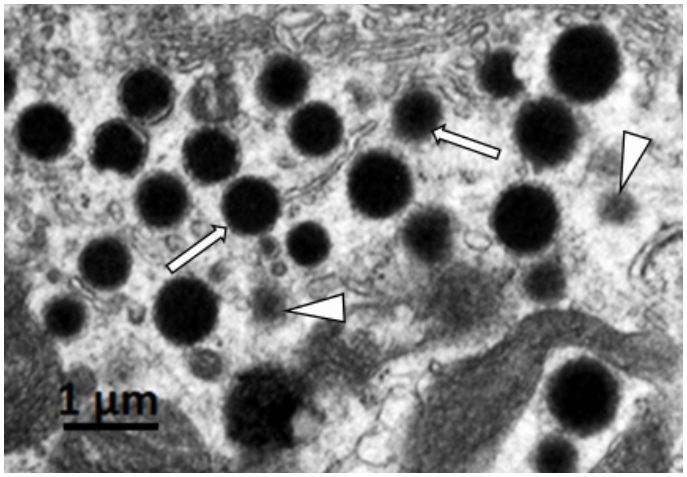

Figure 3. Electron micrograph of LDLR-Knockout mouse right atrium cardiomyocyte, showing ANP granules (white arrows and BNP (arrowheads) with greater magnification, dispersed in the cardiomyocyte cytoplasm.

When Bruno Kisch in 1956[41] first described ANP granules in guinea pigs, it was still unknown what kind of substance the granules contained. Later, it was found that they contained a chemical substance that acted as a natriuretic factor, and, thus, the substance was called Atrial Natriuretic Peptide[42].

To verify the function of the peptides contained in the granules it was prepared an extract from atria and injected it into the peritoneum of rats[1]. It was observed an increase in diuresis, renal sodium excretion, a decrease in blood pressure and an increase in hematocrit in the animals that received the atrial extract. Since this discovery, numerous studies have been carried out on atrial cardiomyocytes and on ANP granules in various situations and conditions.

Regarding BNP, although it is also present in atrial cardiomyocytes, it is mainly produced in the brain and has a short lifespan, only 22 min[46]. BNP is considered as an emergency hormone of the heart, reflecting the moment of ventricular overload[56]. For this reason, dosages of BNP have been used for diagnosis and prognosis of heart disease[4,9].

BNP granules were discovered more recently. When viewed under a transmission electron microscope, these granules are also spherical, do not have a halo, and are generally smaller than those of ANP, often showing spikes on their surface[44] (Fig. 3). In humans it is produced, mainly by the atria and cardiac ventricles, in response to an overload of pressure or volume. Like ANP, BNP promotes diuresis and vasodilation[44,45,46,47]. For this reason, it also acts in blood pressure control.

Mechanism of action of Natriuretic Peptides (ANP and BNP) in controlling blood pressure and other actions of these peptides

Studies have confirmed that both peptides, ANP and BNP, have a decisive action in blood pressure control mechanisms[48]. When released into the bloodstream, ANP and BNP act on the renal tubules and produce a reduction in blood pressure, by increasing the secretion of sodium and water, and a consequent drop in blood volume[26,49,50,] These combined actions of NPs, promote a decrease in excess blood volume[51], resulting in a drop-in blood pressure.

To clarify the actions of the ANP, it was showed[52] that the bilateral removal of the atria, in experimental animals, eliminated the release of these peptides and blocked the excretion of water and sodium with fluid retention in the tissues. due to increased plasma volume.

To confirm the importance of these hormones, it was demonstrated[53] that ANP also acts in monitoring the treatment of patients with heart failure, suggesting that the peptide could serve as a therapeutic parameter, proposing the return of the peptide to baseline serum levels as an objective treatment, and no longer just the improvement of symptoms.

Some authors[54] report that ANP promotes beneficial effects, not only on the cardiovascular system, but also has antioxidant activities. Others[47] reported that ANP has other important actions in addition to increasing diuresis, including vasodilation, suppression of the renin-angiotensin-aldosterone system and inhibition of cardiomyocyte hypertrophy.

To better elucidate the function of ANP, some authors[55] mention that fish adapted to swimming in both salt and fresh water, such as salmon, had significantly higher concentrations of ANP to maintain homeostasis and regulation of sodium when these fish migrate from fresh water to salt water.

NPs also participate in other physiological activities, in addition to those previously mentioned, such as participation in the glomerular filtration rate and renal excretion of water and other electrolytes[56]. In addition to these actions of NPs, these peptides also have a function of inhibiting sympathetic flow and endothelial cell proliferation and smooth muscle of the vessel wall[55].

The stimuli for release of natriuretic peptides by cardiomyocytes

It is considered that the stimuli for the release of NPs is the hyper stretch of the walls of the atria, which, physiologically, results from the increase in pressure within the cardiovascular system[51]. Increased intra-atrial pressure can occur due to volume expansion, constricting agents, water immersion, atrial tachycardia and a salt-rich diet. The increase in intra-atrial pressure could promote the stretching of the atria and the release of NPs into the bloodstream.

Among other factors that promote the release of NPs into the bloodstream, the following are mentioned: training, hypoxia, ischemia and increased stress[55].

Finally, it is important to mention that the release of NPs from cardiomyocytes occurs through an exocytosis mechanism[25]. NPs are expelled from atrial heart cells by this mechanism and enter the bloodstream. So, they can promote their actions.

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Corresponding author
Romeu Rodrigues de Souza
Email: souzarrd@uol.com.br