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ORIGINAL RESEARCH ARTICLE

Heart as an endocrine-metabolic organ

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ABSTRACT

Historically, the heart has been considered a vital organ due to its function as an impeller and aspirating blood pump, allowing the fi siological perfusion to every corner of the human body. However, behind this pump role lies a little-discussed function, that is, the endocrine-metabolic role of the heart, as a hormone synthesizing organ and, because of its pump function, a distributor of hormones foreign to it. Understanding the incidence of peptides synthesized in the heart offers a new perspective on the relevance of the heart in homeostasis and how cardiovascular disease can alter metabolism. The present work aims to review the most current information on the role of natriuretic peptides produced in the heart and their endocrine-metabolic function. These are atrial, brain and C-type natriuretic peptides. It is concluded that the conception of the heart as an organ of endocrine-metabolic regulation, whose hormones are essential for the homeostasis of the organism, is fundamental for the medicine of this century and for future advances in new therapeutic strategies to improve the quality of life of patients.

Keywords: heart; metabolism; atrial natriuretic peptide; encephalic natriuretic peptide; c-type natriuretic peptide

1. Introduction

The heart is a vitally important organ, its main function is to pump blood throughout the body carrying nutrients to all tissues[1]. It is located in the thoracic cage, in the space called the middle mediastinum. It is closely related to the lungs at its edges, to the sternum in its anterior face and to the esophagus in its posterior part[2]. Its base is directed upwards, to the right and slightly backwards, the great blood vessels are born from it, its apex rests on the diaphragm[3]. Its internal configuration is given by four chambers, two upper ones called atria or atria, and two lower ones, the ventricles[4]. It is enveloped by a fibro-serous layer called the pericardium, which provides a means of fixation and protection by preventing excessive stretching. Its wall is structured by three layers, the epicardium, the outermost and in relation to the pericardium; the myocardium, which contains cells called myocardiocytes, which allow contractile function; and the endocardium, the inner layer, formed by connective tissue and through which the conduction system runs[5]. Its tissue is characterized by a layer of cardiac striated muscle and a fibrous skeleton that forms the valvular orifices[6].

The rate at which the heart beats per minute is regulated by the cardiovascular center of the medulla

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oblongata, sending chemical signals through the sympathetic and parasympathetic nerves. In addition, there is a humoral control mediated by vasoconstrictor hormones: adrenaline, noradrenaline, angiotensin, vasopressin, serotonin; and vasodilator hormones: bradykinin, histamine, prostaglandins[7]. To perform its pump function effectively and efficiently, it is related to other organs and systems, kidney, central nervous system and endocrine system[8]. However, the heart fulfills another function in addition to maintaining a constant blood flow, namely the control of different metabolic processes through the secretion of natriuretic peptides (NP).

2. Natriuretic peptides

In 1981, the biochemist Alfredo de Bold discovered the presence of a hormone that allowed blood pressure regulation by means of diuresis and natriuresis in trials with knockout (KO) rats through the injection of atrial muscle extracts. In later years, a polypeptide synthesized from cardiac cells was isolated and named natriuretic peptide (NP)[9].

After its discovery, different types of this hormone were identified, which are classified into: Atrial or atrial natriuretic peptide (ANP), Brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). **Table 1** summarizes some characteristics of the NPs.

ANP consists of a long chain of 28 amino acids that in turn forms a ring of 17 amino acids linked by a disulfide bond. It is synthesized, stored and secreted by atrial myocardiocytes, released as a prohormone (pro-ANP) and then converted to its active form ANP[10,11]. Atrial myocyte granulocytes play the role of storing this peptide, but it can be located in other organs in smaller proportions. The synthesis of this peptide occurs from a 151 amino acid precursor gene (pre-proANP), which is degraded to form proANP, a 126 amino acid peptide that is stored as granules in atrial cardiomyocytes[12]. After a stimulus, this prohormone is released and is located in the periphery of the cardiac cells. By means of a prohormone convertase, corin, this compound is cleaved into a 1-98 N-terminal ANP and the 28-amino acid ANP in its active form. The half-life from ANP secretion is 2–5 min, while the N-terminal atrial natriuretic pro-peptide (NT-ANP) can continue to circulate in blood vessels for 60 min[13,14]. The secretion of pro-ANP is regulated by atrial myocyte stretch in situations of increased atrial wall tension reflecting increased volume and pressure loads[15].

Table 1. Hormones secreted by the heart—types of natriuretic peptides.

Type	Atrial natriuretic peptide-ANP	Brain natriuretic peptide-BNP	C-type natriuretic peptide-CNP
Origin	Atrial myocytes	Cardiac ventricle	Vascular Endothelium Heart Nerve Tissue
	Peptide of 28	Peptide of 32	Peptide of 22
Structure	amino acids	amino acids	amino acids
	Corina	Corina	Furina
Peptide activator		Furina	
	Heart	Heart	
	Brain	Brain	Blood vessels
Receiving organs	Kidneys	Kidneys	Heart
	Blood vessels	Blood vessels	Connective tissue
	Skeletal muscle	Adipose tissue	Kidneys
	Stomach	Stomach	
	Adipose tissue	Adipose tissue	
Binding receptors	NPR-A	NPR-A	NPR-C
	NPR-B	NPR-B	NPR-B

The name BNP refers to the fact that it was discovered in porcine brains and subsequently isolated in human ventricles. This hormone has a structure of 32 amino acids with a similarity in the ring found in ANP. It is synthesized by ventricular myocardiocytes and to a lesser extent by atrial myocardiocytes. To give rise to this hormone, a pre-proBNP precursor is formed and then becomes proBNP[16,17]. This compound is cleaved in the presence of a serine protease, corin, or by an endoprotease, furin, which produce the 32 amino acid BNP, which is the active form of this peptide, and an N-terminal peptide chain pro-brain natriuretic peptide (NT-proBNP) of 76 amino acids. Once secreted, these two compounds remain in the blood circulation for 20 to 90 minutes. BNP differs in its storage relative to ANP, since it is synthesized exclusively by necessity, stimulated by increased ventricular myocyte pressure[18–20].

Finally, CNP differs in its origin with the previous peptides, since it is not synthesized directly by the heart but in the nervous tissue of the heart and in greater proportion by the vascular endothelium[21]. It is produced from the prohormone proCNP, which terminates its encircling form with a 22 amino acid structure and the ring characteristic of all NPs[22]. It is synthesized from the NPPC gene which forms a pre-proCNP precursor of 126 amino acids and thereafter a proCNP of 103 amino acids, to be finally secreted as CNP-53 bound to the intracellular serine endoprotease furin[23]. The presence of furin allows this compound to be cleaved into CNP-53 and CNP-22. These two compounds have similar functions, but are differentiated by the site of their predominance, CNP-53 being found in greater proportion in the heart, endothelium and brain; whereas CNP-22 is found in cerebrospinal fluid and plasma[24].

In general, NPs are synthesized, stored and released physiologically; however, there are certain conditions that increase their expression, the most important of which is cardiac wall stress induced by hypertrophy or volume overload[25–27].

The NPs present receptors in the different organs in which they act, and are classified into three: NPR-A and NPR-B, which are receptors of ANP and BNP mainly and CNP in a smaller proportion, which form part of the family of particulate guanylyl cyclases, and NPR-C, which is a receptor of CNP26. NPR-A and NPR-B receptors are distributed in the body in organs such as the heart, brain, kidneys, blood vessels, skeletal muscle, stomach and adipose tissue. In addition to being similar in location, they are also similar in structure. They contain three domains, a 450 amino acid segment where NPs are bound, a 570 amino acid transmembrane segment (kinase homology domain), and a guanylyl cyclase domain where cGMP, which is a second messenger of NPs, is synthesized[28]. The process of NP reception is given by three steps: 1) The NP is in its basal form, guanylyl cyclase activity is repressed through kinase homology domain, 2) The NP binds to the receptor, taking its active form, making the guanylyl cyclase domains bind, 3) There is a dephosphorylation of the hormone binding sites, allowing the receptor to become inactive and repeat the process of activation and hormone reception[29].

NPR-C has a single domain of 440 amino acids and a tail of 37 amino acids and is found in endocrine glands, lungs, kidneys and, to a greater extent, in endothelial cells[30]. The binding of the receptor to a PN allows a series of reactions to take place that removes the peptides from the blood. This gives it the function of control and clearance of NPs[31]. If there is any dysfunction of this receptor it would be reflected in the alteration of NPs in the blood plasma. In the organs in which this receptor is found, it has been discovered that its structure consists of 37 amino acids, contains two disulfide bonds and is glycosylated; being a shorter chain than that of other receptors, it does not have catalytic activity, but it does have signaling activity. There is another mechanism of neprilysin-mediated degradation of PNs; currently the degradation of this type 2 integral membrane metalloproteinase is an important pharmacological target for the treatment of heart failure with reduced ejection fraction (HF-REF)[32].

3. Heart more than just a pump

NPs play an important physiological role, intervening in different cellular processes that regulate the homeostasis of the human organism[33]. The cardinal effects are diuresis, natriuresis and vasodilatation; however, it is important to recognize that their mechanisms of action are not limited to these, since they actually exert effects on the heart itself, vasculature, at the renal level, are closely related to lipid metabolism, adipose tissue and oxidative stress, i.e., they constitute a group of hormones whose functions are autocrine and paracrine[34–36]. The main functions of NPs are illustrated in **Figure 1**.

3.1. Natriuretic peptides and heart

NPRs are expressed in cardiac myocytes and fibroblasts, which demonstrates an evident relationship of NPs with their main organ of synthesis. ANP exerts the most important functions, consisting of antihypertrophic and antifibrotic effects[37,38]. It has been shown in studies with KO mice that blocking the genetic coding of ANP is related to the development of cardiac hypertrophy and hypertension in response to chronic hypoxia and high salt diets[39,40]. Furthermore, in the context of volume overload, similar results independent of salt intake were found to be associated with the development of cardiac hypertrophy and ANP genetic disruption[41,42].

The mechanism by which ANP exerts an antihypertrophic effect is the inhibition of the canonical transient receptor potential 6 (TRPC-6), a process mediated by protein kinase G (PKG). TRPC-6 is responsible for inducing cardiac hypertrophy through the activation of nuclear factor of activated T cells (NFAT), calcineurin and the activation of proteins such as MKP-1, p38MAPK and ERK[43,44].

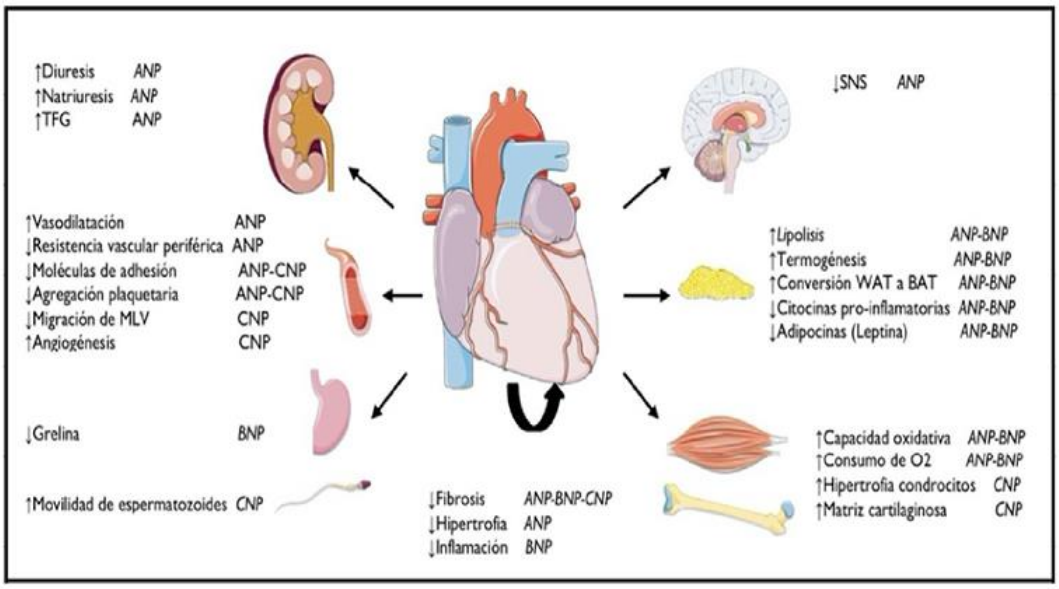

Figure 1. Functions of NPs: heart, kidney, blood vessels, digestive system, neurological system, muscle and connective tissue.

BNP and CNP exert functions in the heart, although to a lesser extent compared to ANP. Among the most striking features is the inhibition of fibrosis, the antihypertrophic effect is less compared to ANP. The mechanisms proposed to explain its antifibrotic role are the inhibition of transforming growth factor beta (TGF-B) by BNP and the reduction of collagen synthesis by CNP, the latter increasing its production in the face of pro-fibrotic stimuli[45]. BNP has the capacity to modulate the inflammatory reaction in the context of cardiac injury, reducing monocytes, B lymphocytes and NK cells in peripheral blood, as well as regulating monocyte chemotaxis and production of inflammatory molecules by macrophages in cardiac tissue[46].

In addition, in clinical practice, ANP and BNP/Pro-BNP are used as the best established biomarkers for the diagnosis and prognosis of heart failure (HF), where increased plasma levels of these NPs would indicate the presence of HF even with preserved ejection fraction, while a negative result would rule out the pathology. Despite this, there are no standardized limits regarding plasma concentrations[47,48].

3.2. Natriuretic peptides and blood vessels

ANP and CNP are the main NPs acting at this level, however, it is essential to bear in mind that both are synthesized in the heart and vascular endothelium[49]. That is, their effects could be mediated by both. The available evidence is based on in vitro studies and ex vitro studies in KO mice[50]. ANP contributes to PKG activation through its binding to NPR-A and NPR-B, a process mediated by cGMP, stimulating the Ca2/calmodulin-dependent nitric oxide synthase enzyme complex, thus resulting in increased production of nitric oxide (NO), promoting relaxation of vascular smooth muscle cells, which lowers systemic blood pressure through vasodilatation[46,51]. An indirect effect related to vascular function is the inhibitory action exerted by NPs on the RAAS, decreasing vascular resistance. In vitro studies in human umbilical vein endothelial cells demonstrate that the ANP genetic variant, C2238, is related to oxidative stress-dependent endothelial dysfunction[52–55].

ANP and CNP demonstrated a reduction in the expression of adhesion molecules such as MCP-1 and P-selectin, which are important in the atherosclerotic process by stimulating leukocyte infiltration through endothelial cells in the context of a lesion and stimulating platelet adhesion and aggregation[56,57]. Migration of vascular smooth muscle cells from the medial layer to the intimal layer of the endothelium contributes to the formation of atheromatous plaques. ANP, BNP and CNP inhibit this migration, with CNP exerting a greater effect compared to the other NPs[58]. In addition, CNP plays an important role in angiogenesis and vascular remodeling after ischemic events by activating NPR-C, which is coupled to inhibitory G protein (Gi), extracellular signal-regulated kinases 1/2 (ERK1/2) and protein kinase B (Akt) to promote endothelial proliferation and migration[59]. Sangaralingham et al. demonstrated in a 12-year follow-up epidemiological study that elevated plasma CNP concentrations were associated with a higher incidence of fatal and non-fatal cardiovascular events[60].

3.3. Natriuretic peptides and kidneys

All NPs provide cardiorenal protection; however, it is CNP that has the least capacity to produce renal effects and ANP that exerts the most important functions. The main actions exerted by NPs are natriuresis and diuresis[61,62]. Na reabsorption through the collecting tubule is dependent on the amiloride-sensitive sodium channel (ENaC), and at the level of the thick ascending limb of the loop of Henle by the Na-K-2Cl cotransporter with the help of sodium and potassium adenosine triphosphatase (Na-K-ATPase), which allows the passive entry of this ion from the tubular lumen into the bloodstream. ANP inhibits the function of ENaC and Na-K-ATPase, causing the effect of natriuresis[63,64]. ANP interacts with the RAAS, inhibiting renin secretion and aldosterone production, decreasing among others its antidiuretic effect[65,66]. It favors diuresis by inhibiting angiotensin II-induced vasopressin secretion by the neurohypophysis[67,68]. Vasopressin acts at the level of the distal tubule and collecting tubules, through its V2 receptor, which can also be inhibited by ANP. In addition, it induces an increase in glomerular filtration rate (GFR) by causing vasodilatation of the afferent arteriole and vasoconstriction of the efferent arteriole. It may interfere with the vasoconstriction of the afferent arteriole mediated by the sympathetic nervous system through noradrenaline[69].

Studies suggest that ANP increases GFR through relaxation of intraglomerular mesangial cells in the space between the capillary endothelium and podocytes, increasing the filtration area[70]. There are data on patients with chronic kidney disease (CKD) who have low levels of corin, crucial in the activation of ANP, i.e.,

in this group the development of arterial hypertension is favored; however, the mechanisms are not fully elucidated[71,72].

3.4. Natriuretic peptides and neurohormonal system

The NPs act by modulating the activity of the autonomic nervous system, ANP decreases heart rate by inhibiting the sympathetic system, causing vagal function to predominate. Sympathetic inhibition at the renal level causes a decrease in renin secretion, mentioned above, as well as effects on vasopressin[73].

3.5. Natriuretic peptides and metabolism

Lipid metabolism is regulated especially by two lipases, lipoprotein lipase and hormone-sensitive lipase. They mediate the processes of entry, storage and exit of free fatty acids (FFA) and glycerol through the hydrolysis of triglycerides[74]. Hormone-sensitive lipase is especially important as it contributes to the above process, and from this, glycerol is transported to the liver, and utilized for gluconeogenesis, while FFA are transported via serum albumin to tissues where they are catabolized for energy[75,76]. The stimulation of lipolysis is regulated by adrenergic stimuli and insulin, which contribute to the conversion of the inactive to the active form of hormone-sensitive lipase[77].

Adipose tissue is closely related to NPs, where NPR-A that binds ANP and BNP and NPR-C that promotes their elimination are expressed[78,79]. NPs induce free fatty acid and glycerol synthesis by stimulating lipolysis in adipose tissue through the activation of hormone-sensitive lipase, an action mediated by the ANP/cGMP/PKG complex[80–82]. Moro et al. demonstrated that ANP infusion in young patients was associated with increased plasma concentrations of free fatty acids and glycerol, through effects independent of the adrenergic system[83]. Aerobic and endurance exercise enhance the process of ANP-induced lipolysis in human adipose tissue[84,85].

The fat deposits that form the adipose tissue are divided according to their coloration and have individual characteristics, these are: brown adipose tissue (BAT), white adipose tissue (WAT) and beige or brite adipose tissue (bAT)[86]. WAT is involved in the storage and mobilization of energy substrates and expresses a wide variety of hormones such as leptin, adiponectin, angiotensin, visfatin, glucocorticoids, sex steroids and even inflammatory modulators such as interleukin-6 (IL-6), as well as being involved in the process of hormone-sensitive lipase-mediated free fatty acid expression[87,88]. In contrast, BAT has abundant mitochondria which have uncoupling protein 1 (UCP1), which uncouples oxidative phosphorylation from ATP synthesis, replacing it with heat generation, the activation of peroxisome proliferator- activated receptor γ co-activator 1 α (PGC1a) stimulates mitochondrial genesis and the production of vascular endothelial growth factor (VEGFB), which promotes the entry of free fatty acids for heat production, that is, they contribute to the thermogenesis process; the activation of mitochondrial uncoupling and thermogenesis in the BAT depends on the joint action of the adrenergic system and thyroid hormones[89–91].

NPs promote the conversion of adipose tissue WAT into BAT, in addition they promote the expression of thermogenic genes encoding PGC1a and UCP1, a process mediated by the PNA/cGMP/PKG⁄p38 MAPK complex[92–95]. These data demonstrate the influence of NPs on metabolism by increasing energy expenditure through the regulation of lipolysis increasing FFA availability and contributing to the thermogenesis process favoring mitochondrial biogenesis.

NPs play an important role in skeletal muscle by increasing mitochondrial biogenesis and enhancing oxidative capacity[96,97]. Moro et al. demonstrated that physical training positively regulates the expression of genes encoding RPN-A in skeletal muscle, in addition to the positive association, after 8 weeks of aerobic training, between the levels of this receptor, its signaling and genes encoding proteins involved in the oxidative

phosphorylation process, in addition to genes encoding peroxisome proliferator-activated receptor γ co-activator 1 α (PGC1a). There were changes in plasma concentrations of ANP and BNP after physical training, suggesting a physiological link between the signaling of these NPs by their receptor with the capacity for oxidative regulation and oxygen consumption in skeletal muscle[98].

ANP inhibits the secretion of adipokines by adipocytes, proinflammatory cytokines and chemokines by macrophages in adipose tissue, many of these related to insulin resistance in the context of obesity, such as leptin, IL-6, TNF-α tissue inhibitor of metalloproteinase (TIMP)-1, RBP-4, as well as chemokines (MCP-1, MIP-1β, MCP-2 and GRO-α)[99,100]. BNP exerts effects by inhibiting ghrelin, an appetite-regulating hormone[101]. CNP is related to functions such as stimulation of chondrocyte proliferation and hypertrophy, production of cartilaginous matrix, modulation of sperm motility, testicular germ cell development[102,103].

4. Impact of cardiovascular disease on metabolism

In pathological conditions, such as arterial hypertension, there is hyperactivation of the RAAS and the sympathetic nervous system (SNS) with increased sodium and water retention; in heart failure, in addition to these 2 previously mentioned characteristics, there is volume overload and cardiac stress induced by stretching of the chambers, which causes an increase in the secretion of PNs, particularly ANP, a process that does not occur in arterial hypertension since studies have not demonstrated a compensatory role of PNs in response to an increase in BP; however, a failure of this peptide system is related to the pathogenesis of the disease[104–106].

Hyperactivation of the RAAS and SNS in the initial stages of heart failure provides a compensatory mechanism to increase cardiac output and peripheral vasoconstriction in order to maintain cardiovascular homeostasis; over time, prolonged activation of these systems becomes detrimental and contributes to disease progression, from here on the action of regulatory mechanisms is crucial, including increased secretion of PNs, especially ANP and BNP which offer protective effects by inducing diuresis, natriuresis, vasodilatation, protecting the patient from volume overload. However, during the evolution of the disease, these NPs gradually lose their natriuretic effect, suggesting the appearance of renal resistance to them. There are several hypotheses that explain this mechanism, including a local increase in NP degradation or a decrease in the renal concentration of NPR-A1.

Currently, sacubitril/valsartan therapy has innovated the treatment of heart failure by combining an angiotensin II receptor antagonist with an inhibitor of neurolysin, a molecule related to the degradation of NPs, having BP-lowering effects and increasing diuresis and natriuresis[107]; whose metabolic effects in this context are equally remarkable. In a post-hoc analysis of the PARADIGM trial, patients with heart failure and diabetes with HbA1c $\geq$ 6.5% who were randomized to sacubitril/valsartan therapy had better glycemic control than subjects receiving enalapril. During follow-up monitoring of HbA1c concentrations and new use of insulin or oral hypoglycemic agents, the results were significantly lower in the sacubitril/valsartan group compared with the control group. In a cohort of subjects with hypertension and obesity, eight weeks after initiation of sacubitril/valsartan treatment, insulin sensitivity and lipolysis in abdominal subcutaneous adipose tissue increased. These data suggest the importance of the role of the cardiovascular system, and specifically of NPs in the context of cardiovascular disease on metabolism.

5. Conclusions

Beyond its function as an aspirating and impelling pump, the conception of the heart as an organ of endocrine-metabolic regulation, whose hormones are elementary for the homeostasis of the organism, is fundamental for the medicine of this century and for the advances to come.

Understanding the different natriuretic peptides and their clinical usefulness, as well as the different degrees of cardiac dysfunction and their impact on different metabolic/hormonal axes, is very important and should not be underestimated in order to provide a comprehensive approach to patients with cardiometabolic diseases. It should be noted that the discovery and study of atrial natriuretic peptides has not only been beneficial for the diagnosis and prognosis of heart failure, but also contributes to the development of new therapeutic strategies to improve the quality of life of patients.

Conflict of interest

The authors declare no conflict of interest.

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