Antagonistic Atrial Natriuretic Peptide with the Renin-Angiotensin-Aldosterone System and Effects on Systemic Blood Pressure Regulation

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Abstract: The atrial natriuretic peptide (ANP) presents, from the point of view of systemic blood pressure regulation, a relevant antagonistic association when compared to the renin-angiotensin-aldosterone system (RAAS). Through a careful review, the aim of the study was to evidence the process and the link between systems and hormones, from prohormone secretion, conversion, interaction with receptors, ANP action, correlating its antagonistic effects to RAAS, and the association between the mechanisms of action and SBP. The method adopted was a systematic review through electronic scientific articles in the database of the Virtual Health Library, PubMed and Cochrane. The process of searching and selecting the articles followed the rule of systematic review – PRISMA. The study demonstrates that the effects of ANP release due to cardiac atrial expansion are effectively counterregulators to the effects of RAAS malfunction, acting in a way to preserve the back, cardiac and vascular issues from blood pressure control. This mechanism acts via hydroelectrolytic regulation, especially through processes of resorption and excretion of sodium and water by the removal tubules, where the RAAS acts to increase blood volume and ANP acting to potentiate diuretic mechanisms. It is concluded that the degrading effects of the malfunction of RAAS, to some extent, be counter-regulated by the effects of ANP release, acting in the control of systemic blood pressure, alone or concomitantly with pharmacological treatment.

Keywords: Atrial natriuretic peptide, Heart failure, Angiotensin-so-language-suppressing enzyme inhibitors, Angiotensin II, Angiotensin antagonist.

1. INTRODUTION

The atrial natriuretic peptide (ANP) hormone has particular functions in relation to renal and cardiac physiology. The secretion of this hormone adds endocrine characteristics to the heart and is obtained through cardiomyocytes, especially when there is distension of the atrial volume, this means that the increase in blood volume generates expansion of the atrial cavities, the same effect on cardiomyocytes and the release of ANP in the systemic circulation [1,2].

When circulating through the system, the ANP presents important physiological effects, such as the elevation of natriuresis and diuresis levels, acting at specific points of the recurrent tubules, exposing relevant antagonistic characteristics when compared to the renin-angiotensin-aldosterone system (RAAS). Every physiological mechanism generated from the release of renin by the kidneys triggers a series of reactions, the conversion of the angiotensinogen peptide into angiotensin I (ANG I), which is widely metabolized in the lungs by the angiotensin-converting enzyme (ACE), turning into angiotensin II (ANG II), unlike the previous sister molecule, exerts a strong influence on the increase in systemic blood pressure (SBP), through vasoconstriction and increased resorption of salt and water by renal tubular cells. Acting as a potent stimulator, ANG II acts as the main initiator of aldosterone release by the adrenal glands, whose effects show some similarity, increasing sodium resorption in the renal tubules and consequently increasing blood volume and SBP. In this case, there is an overlap of similar effects between ANG II and aldosterone [2].

Another relevant factor is cardiac natriuretics with potential vasodilator and diuretic effects, contributing to blood pressure (BP) homeostasis. The fine mechanism of action of ANP stands out, implying a series of reactions, involving its membrane receptors, among them, the natriuretic peptide receptor A (NPR-A) and the action of corine protein, responsible for the conversion of the pro-atrial natriuretic peptide N-terminal (NT-proANP) into ANP, possessing this strong affinity for its receptors [3,4]. It is also necessary to consider the action on the vascular system, causing dilation of the vessels and, decreasing sodium reabsorption at the renal level, it also acts on the cardiac system through anti-hypertrophic and

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antifibrotic properties, playing a role as a protective hormone for the muscle, inhibiting the responses of the sympathetic nervous system, which is responsible for sending antagonistic nervous signals to the ANP [5,6].

In this review, the different hormonal processes in the cardiovascular and renal systems are carefully presented, especially the antagonistic effects of ANP on RAAS. To understand these actions, the aim of the study was to evidence the process and the link between systems and hormones, from prohormone secretion, its conversion, interaction with receptors, ANP action, correlating its antagonistic effects to RAAS, and the association between the mechanisms of action and SBP.

2. METHODOLOGY

The work is a systematic review study with a critical analysis of the antagonistic atrial natriuretic peptide with the renin-angiotensin-aldosterone system. The systematic search was performed through electronic scientific articles in databases of PubMed, Cochrane Library and Virtual Health Library (VHL), in addition to these databases, books were used to complement the investigated data. The investigation of the articles was researched using the keywords: Atrial Natriuretic Peptide; Heart Failure; Angiotensin-Suppressing Enzyme Inhibitors; Angiotensin II; and Angiotensin antagonist, with interposition of the Boolean operator "AND" (natriuretic peptide atrial AND heart failure AND renal system AND angiotensin-converter enzyme inhibitors AND angiotensin II AND angiotensin antagonist).

The inclusion criteria were articles in English, fully available. After research criteria, the titles and abstracts describing the physiology and antagonistic effects of angiotensin, in addition to prohormone secretion, its conversion, interaction with the receptors and ANP action were examined in all conditions according to the proposed theme, thus, a series of articles for the review were found, following the rules of systematic review – PRISMA [7].

3. RESULTS

A total of 109 studies were identified. After excluding duplicates, 92 studies were selected for careful evaluation, and 41 studies were ruled out since they did not satisfy the eligibility criteria. Finally, 51 papers were included in this literature review (Figure **1**).

Aphorisms linked to results renin-angiotensin-aldosterone system; angiotensinogen, angiotensin I and angiotensin II; pharmacology, renin-angiotensin-aldosterone system and its inhibitors; angiotensin-converting enzyme inhibitors; ANG II receptor antagonists – ANG II receptor blockers; atrial natriuretic peptide and its RAAS antagonist effects; physical exercise – stimulus for endogenous release of ANP; degrading effect of neprilysin on ANP were compiled in the discussion.

4. DISCUSSION

4.1. Renin-Angiotensin-Aldosterone System

It is through the enzymatic protein "Renin" released into the circulation by the juxtaglomerular cells (JG), that the entire cascade of action of RAAS begins. Afferent arterioles are extremely sensitive to BP due to the presence of baroreceptors, variations in pressure are quickly perceived by these vessels, which act as a gateway to the blood of glomerular capillaries, forming a capillary tangle in Bowman's corpuscle. The reduction of SBP, perceived by baroreceptors at the afferent arteriolar level, stimulates the release of renin by JG cells in the peripheral circulation, initiating the entire system. Another region of interest that participates in the release of renin when stimulated is the dense macula (DM), an extra region that arises from the distal tubule and comprises part of the juxtaglomerular apparatus. These cells are sensitive to changes in sodium chloride (NaCl) concentration, i.e., a decrease in NaCl concentration causes DM cells to become sensitized and stimulates in a paracrine way JG cells to release renin. The reninre acts as the main mediator in the regulation of RAAS [8-10].

4.1.1. Angiotensinogen, Angiotensin I and Angiotensin II

Angiotensinogen is a peptide produced by liver cells which is found with circulating renin, an inciting encounter that causes the conversion of angiotensinogen into ANG I. ANG I is preponderantly metabolized in the lungs, is converted into ANG II through ACE, concentrated not only in the endothelium coating the pulmonary capillaries, but also in other systems, with greater influence on pressure balance.

ANG II acts directly on the kidneys, performing its vasoconstrictive functions at the eferent arteriolar level, through angiotensinergic I (AT I) receptors expressed in various organs, such as the heart, liver, lung and kidneys, contributing to increased vascular resistance

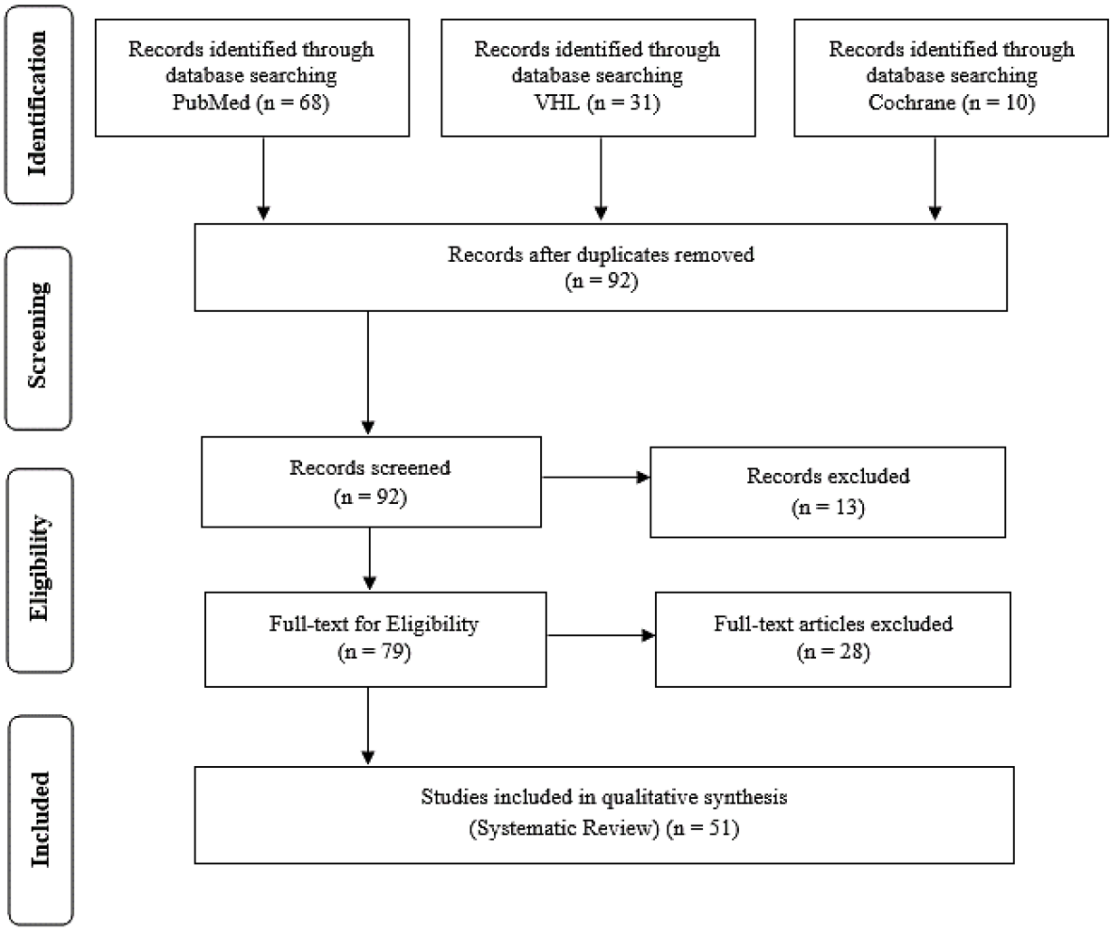

Figure 1: Flowchart.

and decreased renal perfusion, generating increased SBP. Another highlight is the resulting natriuretic effects, increasing the reabsorption of sodium and water in the renal tubules, an effect mediated by the decreased renal perfusion, which invariably decreases the pressure in the peritubular capillaries, promoting the absorption of large amounts of sodium and water, triggering a progressive increase in the volume and constituents of the peripheral circulation. Most of the deleterious effects on the renal system generated by the increase in BP come from the ANG II molecule, which directly preserves and increases at a high cost the glomerular filtration rate through high pressure and, conversely, decreases renal perfusion, contributing to hypoxia, especially in the functional units of the kidneys, nephrons. It is possible to note that all the effects produced by ANG II contribute significantly to the increase in SBP [11,12].

Concomitantly with this system, and analyzing another molecule with a close association, aldosterone, which is directly influenced by ANG II, stimulates its secretion by the adrenal glands, specifically in the glomerulosal zone of the cortex (GZC). Aldosterone, unlike the other molecules mentioned, which are classified as peptides, is a hormone synthesized from cholesterol in the GZC region [13,14].

Studies showed a behavioral and evolutionary association of humans in relation to aldosterone. This behavior contributes strongly to epidemiological data on systemic arterial hypertension (SAH), so that the dietary intake in the past, in terms of the amount of sodium present in the diet was about five times lower than the usual intake, it is assumed that, the RAAS, especially the effects mediated by aldosterone on circulating sodium levels, worked in such a way as to preserve sodium, not excrete it. Physiologically, aldosterone contributes only to the absorption of a maximum of 5% sodium, such process occurs in the distal tubules of the kidneys, however, it is worth noting that the mechanism of renal filtration, due to its very high perfusion, reaches an average of 180 liters of blood plasma per day. It is possible to understand how significant is the influence of aldosterone on the regulation of SBP [14].

The mechanisms presented so far allow us to reason about the strong bond between the molecules present in the RAAS. It is important to note and observe that each of the components, whether peptides, renin, ANG I, ANG II or the hormone aldosterone, have their characteristic independent effects, however, the whole system acts through a cascade of reactions with overlapping effects, analogous effects, that is, the renin acts on angiotensinogen, which in its final phase potentiates vasoconstrictor and natriuretic issues directly influencing the release of aldosterone, with effects similar to ANG II, overlapping and potentiating results in SBP, tending hypertensive conditions [9].

The effects resulting from the imbalance of RAAS cause a series of deleterious consequences to several systems, among the main ones are the cardiovascular and renal systems. Thus, it is observed the activation of the release of renal renin, in which it promotes the conversion of angiotensinogen enzymes into ANG I, converted into ANG II by the action of ACE. The latter, in addition to contributing to BP elevation, activates the adrenal glands to release aldosterone, a hormone that also has functions similar to ANG II, increasing BP simultaneously (Figure **2**) [15,16].

The consequences of hypertension in the cardiovascular system, specifically in the heart, when not adequately controlled, can contribute to the development of heart failure (HF), which, among other factors, contribute to the reduction of the systolic ejection fraction. HF is a pathology characterized by decreased blood pumping capacity through the heart, with extensive signs and symptoms. The deleterious repercussions, the progressive increase in HF and the decrease in the systolic ejection fraction by left ventricle involvement are closely related to circulating and excessive levels of the RAAS constituents. In the long term, elevated SBP levels require greater contractile force of the left ventricle to expel the blood component of the ventricular cavity through the aorta, generating a harmful cardiac remodeling in this context [16-18].

Another system, the renal, plays central functions when addressing concepts about RAAS. The pathogenesis developed by the kidneys as a function of SAH is characterized by remodeling at the cellular level of the renal tubules, affecting the functional units of the renal system, the nephrons. These cells, very much due to ANG II, end up developing properties very similar to that of fibroblasts, producing type I collagen, collagen that has higher resistance characteristics, attributing fibrotic aspect to the tubules [8,9,11].

In continuity with this reasoning, chronic arterial hypertension jointly promotes a certain vascular remodeling. The pressure too exerted on the vascular walls causes chemical reactions called oxidative stress, aggressions that release substances titrated from damage-associated molecular patterns (DAMPs), these, especially in arterial areas promote in the subendothelial region a certain dysfunction, which over

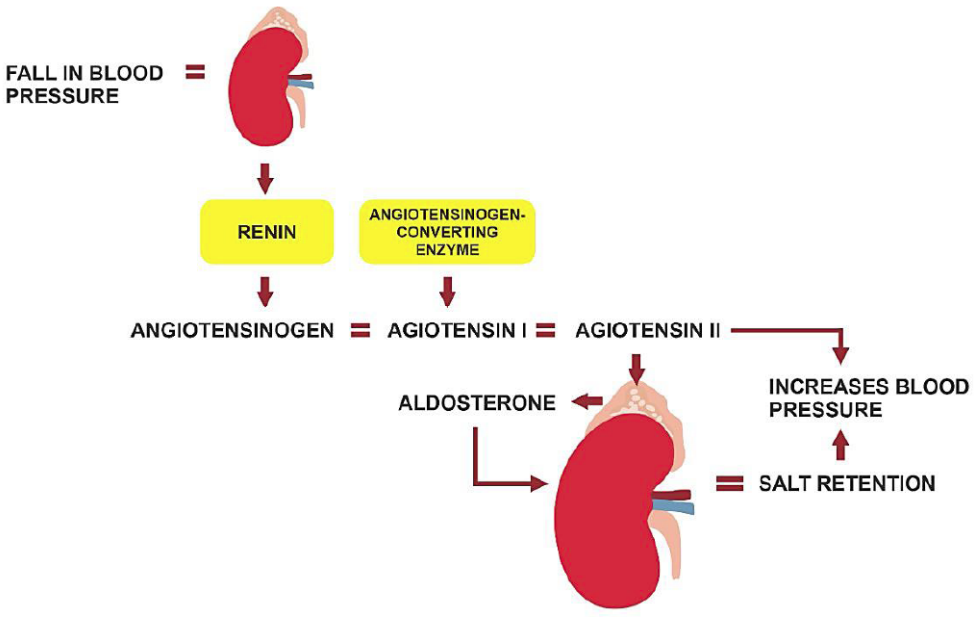

Figure 2: Mechanism of action of the renin-angiotensin-aldosrerone system.

time leads to a continuous stiffening, loss of flexibility, characterizing arteriosclerosis. These factors together contribute to the imminent increase in the risk of arterial wall disruptions, such as the development of potentially lethal aneurysms [19-21].

4.2. Pharmacology, Renin-Angiotensin-Aldosterone System and its Inhibitors

They are classified in different ways, whose functions also differ, especially in terms of the mechanism of action. In this context, it is possible to find drugs that inhibit the angiotensinogen-converting enzyme and ANG II receptor antagonist (ARA-II) medications, as there is a broad approach to the proposed theme, only two classes of medicines have been mentioned in this work, but it is important to make it clear that there are several others. Thus, the pharmacodynamic behavioral concepts of these two different classes of antihypertensive available in the market were addressed.

4.2.1. Angiotensin Converting Enzyme Inhibitors (ACEI)

Used for antihypertensive treatment, classified as inhibitor of the ANG I-converting enzyme inhibitor. These drugs act by inhibiting ACE at the capillary endothelial level, preventing the conversion of ANG I into ANG II, jointly inhibiting the potential hypertensive effects exerted by ANG II. In this sense, the natriuretic implications stand out, with greater excretion of sodium and water [22,23].

Another fact inherent in the effects of ACE-inhibiting drugs concerns their action on bradykinin molecules. ANG II acts concomitantly in the degradation of bradykinin, a polypeptide that exerts a potent vasodilator effect, offsetting the vasoconstrictive characteristics of RAAS. Therefore, the administration of ACE inhibitors as an antihypertensive measure acts, in addition to the direct route, inhibiting the conversion of ANG I into ANG II, also preserving vasoactive polypeptide molecules of bradykinin [22-25]. The main exponents when it comes to ACE inhibitors are the chemical compounds, captopril, enalapril and ramipril, prescribed according to the individuality and response of each patient [26].

4.2.2. ANG II Receptor Antagonists – ANG II Receptor Blockers

Another drug class, ANG II receptor antagonists, act at the level of cellular receptors. Thus, the conversion of ANG I into ANG II is not altered, its circulation and metabolization are not modified. The systemic sites where the highest concentration of AT I receptors occurs are located in the vascular smooth musculature, lung, liver, kidneys, heart, aorta and adrenal, which allows the induction of ANG II to its various stimuli.

Another class of receptors occurs in the system, angiotensinergic-II (AT II) receptors. These receptors trigger antagonistic effects when compared to AT I receptors, in a certain way, the binding of ANG II to AT II receptors measures counterregulatory responses in view of the same molecule binding to AT I receptors. ANG II receptor antagonists act exclusively on AT I receptors, inhibiting the binding between ANG II and its AT I receptors [27,28].

In this sense, the biochemical relationship that occurs due to the interactions of antagonist drugs with The AT I receptors, the conformational alterations resulting from the binding between the drug and its receptor, are the result of changes in the AT I receptors, so that such alterations present great difficulty in the process of disconnection even with high concentrations of circulating ANG II [27,28]. Examples of the most commonly used chemical compounds belonging to the class of angiotensin receptor antagonists are losartan, valsartan and olmesartan [29]. Such drug classes presented belong to first-line drugs used in clinical medicine for antihypertensive treatment [30].

Associating the harmful secondary factors induced by the maintenance of arterial hypertension, it is observed that the development of HF is closely related to SAH, and drug action is predominant in the treatment for the non-progression of cardiac dysfunction. Another condition directly related to SAH is acute myocardial infarction (AMI), a clinically relevant finding, as it represents greater weight in the number of deaths in hypertensive patients [31,32].

In this sense, there are factors that contribute to the ACEI being relatively more efficient when compared to ANG II receptor blockers. Thus, ACEI medications bring with them the ability to preserve bradykinin molecules, whose mechanism mentioned earlier acts through vasoactive responses [33,34]. On the other hand, patients tend to have greater intolerance with the ACEI class, making or not associated ARA-II dosages with ACEI or other drugs of other classes a first-line alternative for antihypertensive treatment, following individual drug adaptation criteria for each patient [35].

4.2.3. Atrial Natriuretic Peptide and its RAAS Antagonist Effects

The ANP discovered by Adolfo J de Bold and presented in his study in 1981, added endocrine characteristics to the heart muscle. The author observed that the atrial myocytes presented secretory granules representatively similar to the granules of the hormone-producing cells, whose main effects were translated at the renal level, by increasing the natriuresis in the distal tubules and collectors, allowing to correlate it antagonistically with the effects generated by RAAS [1].

The atrial peptide is synthesized in the form of a pre-prohormone. In its inactive state, this polypeptide contains 151 amino acids, suffers a certain cleavage before being stored in cardiomyocytes, turning into pro-ANP containing 126 amino acids, then are stored. These, in turn, when stimulated, as a function of the cell stretch, release the peptide that, in contact with the enzymatic protein corine, is cleaved in its active conformation, containing 28 amino acids [36]. One point to be highlighted about the corine enzyme are the possible mutations that the enzyme undergoes in hypertensive patients, significantly impairing BP control, largely due to the final effects of cleavage that the protein exerts on pro-ANP [37].

HF is closely related to inappropriate and joint action of both the sympathetic nervous system and RAAS, mainly due to the prolonged act of the systems together. In this sense, strategies that combine ACEI or ARA-II plus ANP promoters tend to act together in the treatment of HF, including ANP as a clinical marker for the diagnosis of HF [5].

When in circulation, the ANP acts on the kidneys favoring the increase in the glomerular filtration rate, by increasing the pressure in the glomerular capillaries, the process occurs by afferent arteriolar vasodilation and efferent arteriolar contrition, in this case, very similar to the effects of ANG II, however, they promote reduction of sodium and water reabsorption at tubular level, and limitation of the secretion of renin, precursor of ANG II, collaborating with mechanisms of decreased peripheral vascular resistance, volume, cardiac output, consequently decreased blood pressure (Figure **3**) [38].

Another study believed the interpretation of the protective effects that ANP exerts on the kidneys, when infused during cardiovascular surgeries with extracorporeal circulation, for example in myocardial revascularization. This surgical intervention usually presents a high probability of acute kidney injury, and the excessively controlled administration of intraoperative ANP has demonstrated a protective effect at the renal level, against the degrading effects of circulating RAAS on the kidneys [39,40]. Not only does the renal system benefit, but also does the heart benefit on a large scale from the protective effects generated by the ANP, observing that rats with low levels of ANP presented cardiac hypertrophy, confirming its anti-hypertrophic effects [41]. Also in another study, the antagonistic effect exerted by the

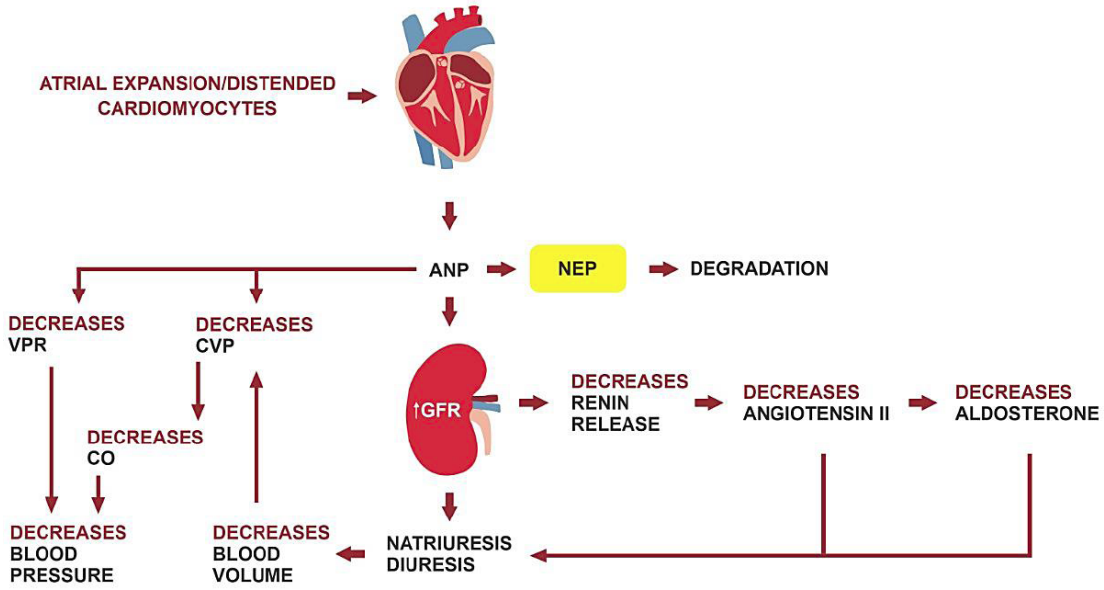

Figure 3: Renal and extra renal events of atrial natriuretic peptide production. **Legend:** (ANP) atrial natriuretic peptide; (NEP) neprilysin; (GFR) gromerular filtration rate; (CVP) central venous pressure; (CO) cardiac output; (VPR) vascular peripheral resistance.

ANP on RAAS, and in the control exercised over BP, some protection against hypertrophy and cardiac fibrosis was evidenced. It was observed that the increase in the expression of NPR-A transmembrane receptors of mice reduced the size of cardiomyocytes, without altering other primordial cardiac functions. When looking specifically at ANP, mice with low levels of this hormone called cardiac hypertrophy [42].

The attributions of the ANP, natriuresis and diuresis, are mediated by NPR-A receptors. It is through the link between ANP and NPR-A that much of the effects of the atrial natriuretic peptide hormone occur. ANP also promotes the increase of CGM-c (cyclic guanosine monophosphate) [43]. CGM-c promotes changes in intracellular calcium levels, a fact that contributes even more to its physiological effects, in order to keep mesangial cells relaxed [44]. It is possible to notice that the ANP due to the stimulation of the CGM-c potentiates vasodilation, diuresis, and these effects are against regulatory to RAAS [45].

4.2.4. Physical Exercise – Stimulus for Endogenous Release of ANP

Knowing the natriuretic, diuretic and hypotensive effects that ANP exerts on the body, measures that stimulate its release tend to be potent aids in controlling the effects generated by the imbalance of RAAS. In this sense, the practice of physical exercises becomes an ally when one thinks of provoking an increase in atrial expansion in the cardiovascular system for consequent release of ANP [46].

ANP levels increase substantially after physical activity. The release of ANP is directly proportional to the intensity of the exercise, emphasizing in this case the individuality and predisposition of each patient regarding the practice and intensity of the exercise itself. It was observed that patients who developed HF had high levels of ANP and that, when predisposed to physical activity, they benefited from additional plasma peptide levels, increasing the survival of these patients [47]. In another study, conducted with 28 cycling athletes, through urine collection before and after training, there was a high urinary rate of pro-ANP, and an increase in the glomerular filtration rate, largely due to vasodilator effects, generating a reduction in renal overload [48].

Pharmacological interactions in conjunction with physical activity, which promotes the release of ANP, act in association to mitigate the effects of uncontrolled RAAS, tending to BP regulation [24,47,48].

4.2.5. Degrading Effect of Neprilysin on ANP

ANP molecule suffers intense degradation by the activity of neprilisin, an enzyme that makes up RAAS and is responsible for reducing the effects of ANP on the system (Figure **3**). This mechanism is often observed in cases of HF, a pathology that is attenuated by the vasoactive effects of peptides. Medications called LCZ696 (neprilisin inhibitors) have positive effects, preserving ANP levels in the systemic circulation [49]. The association occurs due to the benefits presented by natriuretic peptides in HF patients, thus, LCZ696 acts predominantly benefiting patients with the pathology, especially when it comes to reducing the formation of edema [50]. Inhibition of enzyme activity, through the pharmacological use of LCZ696, promotes increased ANP levels resulting in increased Levels of GMP-c, optimizing the vasodilator effects of peptides [51].

5. CONCLUSION

The effects generated by the RAAS are, when physiologically established for the maintenance of homeostasis, fundamental for the regulation and maintenance of SBP, however, abnormalities not yet fully clarified, cause this system to present dysfunctions, which lead to homeostatic lack of control, peripheral vasoconstriction, increased sodium resorption and water in the recurrent tubules, among other repercussions responsible for the elevation of BP. On the other hand, the discovery of the hormone ANP revealed endocrine characteristics to the heart, and had effects contrary to the effects of RAAS, causing peripheral vasodilation, increased natriuresis and consequent increase in the elimination of sodium and water, contributing to decreased volume and BP. Therefore, the atrial natriuretic peptide hormone has physiological characteristics evidently antagonistic to RAAS.

AUTHOR CONTRIBUTIONS

One of the reviewers (FGA) made the selection of articles according to the exclusion criteria of duplicate articles and titles. After this process, the abstracts were evaluated and a new exclusion was decided by the same reviewer. A second reviewer (RRR) decided on the conflicting points and made the decision to choose the articles and the final review of the work. Data extractions were reviewed by reviewers (FGA and RRR).

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DECLARATION OF POTENTIAL CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ABBREVIATIONS

ACE = Angiotensin-converting enzyme

ACEI = Angiotensin converting enzyme inhibitors

ANG I = Angiotensin I

ANG II = Angiotensin II

ANP = Atrial natriuretic peptide

AT I = Angiotensinergic I

AT II = Angiotensinergic II

BP = Blood pressure

CGM-c = Cyclic guanosine monophosphate

DM = Dense macula

GZC = Glomerulosal zone of the cortex

HF = Heart failure

JG = Juxtaglomerular cells

MDAP = Molecular damage-associated patterns

NaCl = Sodium chloride

NPR-A = Natriuretic peptide receptor A

NT-proANP = pro-atrial natriuretic peptide N-terminal

RAAS = Renin-angiotensin-aldosterone system

SAH = Systemic arterial hypertension

SBP = Systemic blood pressure

VHL = Virtual Health Library

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