CorSalud 2016 Jul-Sep;8(3):177-182

CorSalud

Cuban Society of Cardiology

Review Article

Cardiocentro Ernesto Che Guevara Santa Clara Cuba

Aldosterone: its implications for heart disease

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Este artículo también está disponible en español

ARTICLE INFORMATION

Received: March 22, 2016
Accepted: April 28, 2016

Competing interests
The authors declare no competing interests

Acronyms
CAD: coronary artery disease
ACE: angiotensin-converting enzyme
HT: hypertension
MR: mineralocorticoid receptors
RAAS: renin-angiotensin-aldosterone system

On-Line Versions:
Spanish - English

ABSTRACT
Aldosterone is one of the components of the renin-angiotensin system. There are theoretical elements and clinical evidence of its relationship with heart diseases. Numerous bibliographic references were reviewed with the objective of describing the main characteristics of aldosterone and its relationship with these diseases. It has traditionally been thought that the action of aldosterone was restricted both, to the reabsorption of sodium and water, and to the excretion of potassium at the renal level. In recent years it has been shown to play a major role in many processes of the pathogenesis of coronary artery disease and cardiac and vascular remodeling.
Key words: Renin-angiotensin system, Aldosterone, Coronary artery disease, Ventricular remodeling, Vascular remodeling, Heart Failure

Aldosterona: sus implicaciones en las enfermedades del corazón

RESUMEN
La aldosterona constituye uno de los componentes del sistema renina-angiotensina-aldosterona. Existen elementos teóricos y evidencia clínica de su relación con las enfermedades del corazón. Se revisaron numerosas referencias bibliográficas con el objetivo de describir las principales características de la aldosterona y su relación con estas enfermedades. Tradicionalmente se ha pensado que la acción de la aldosterona se restringía tanto a la reabsorción de sodio y agua, como a la excreción de potasio a nivel renal. En años recientes se ha demostrado que desempeña una función primordial en muchos procesos de la patogenia de la enfermedad arterial coronaria y los remodelados cardíaco y vascular.
Palabras clave: Sistema renina-angiotensina, Aldosterona, Enfermedad arterial coronaria, Remodelación Ventricular, Remodelación vascular, Insuficiencia cardíaca

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INTRODUCTION

The basic scheme of the renin-angiotensin-aldosterone system (RAAS) was established more than 50 years ago. Its activation starts with the release of the synthesized renin in the juxtaglomerular apparatus of the kidney. This enzyme acts on the angiotensinogen, one globulin of hepatic origin, consist-

ing of 14 amino acids, and transforms it into a decapeptide, the angiotensin I, which becomes the octapeptide angiotensin II, by the action of the angiotensin-converting enzyme (ACE), which is also responsible for the degradation of bradykinin, a potent vasodilator. When activating AT1 receptors, the angiotensin II stimulates the aldosterone synthesis as one of the final products of this enzymatic chain[1].

Although the origin of renin is always renal, its precursor, prorenin, can also be synthesized in the liver, suprarenals, the aorta, heart and testicles. The angiotensinogen can be produced in other tissues different from the liver. The evidence that the fundamental components of RAAS are found in various territories in which angiotensin II is synthesized demonstrates the existence of local systems. They have been located in the heart, vessels, kidney, suprarenals, pancreas, central nervous system, reproductive system and the lymphatic and adipose tissues. Local systems appear to be independently regulated but can interact with the circulating system and they are involved in processes such as cell growth, extracellular matrix formation, vascular proliferation, endothelial function and apoptosis. Therefore, they play an important function in the pathophysiology of cardiovascular disease and probably in the mechanism of action of RAAS inhibitors drugs. Recently, the existence of this fully functional system within some cells (myocytes, fibroblasts and cells of the smooth vascular muscle) has been proved, which has been called intracrine or intracellular RAAS. In the synthesis of angiotensin I, in these intracellular systems, cathepsin could participate and its step to angiotensin I is, at times, mediated by the kinase. Its physiological role is poorly understood, but may be important to understand cardiovascular diseases and suggest new therapeutic strategies[1]. It has been described that in the cardiac fibroblasts, the intracellular RAAS is activated by high concentrations of glucose and it is involved in the extracellular matrix formation; thus, the originated angiotensin II also stimulates the formation of aldosterone[2].

For many years, aldosterone was considered a hormone dedicated to renal control in its function of minerals excretion, which explains the term "mineralocorticoid" used to describe this hormone. The discovery of numerous mineralocorticoid receptors (MR) in extrarenal places and research on fibrinogenic and proinflammatory effects of this hormone have expanded the knowledge of the capabilities of aldosterone in its direct involvement in the pathogenesis of hypertension (HT), heart failure, chronic kidney disease and metabolic syndrome[3,4].

ALDOSTERONE

Synthesis

In the aldosterone synthesis intervenes the aldosterone synthetase. This enzyme is stimulated by the adrenocorticotropic hormone, endothelin-1, vasopressin, potassium, magnesium, atrial natriuretic peptide, dopamine and serotonin (**Figure**). Once activated, it acts on secondary metabolites of cholesterol, as it is the case of 11-deoxycorticosterone, corticosterone and 18-OH corticosterone, from which aldosterone is synthesized.

Effects

The aldosterone, final product of RAAS, is a hormone (mineralocorticoid) secreted by the glomerular area of the adrenal gland cortex, which was synthesized and characterized in 1953.

Halfway of the 1990s, it was demonstrated the fact that aldosterone acted mainly in epithelial cells of the distal convoluted tubule, the collecting tubule, the distal colon and the salivary and sweat glands, where it produces stimulation of sodium (Na) and water reabsorption, as well as potassium (K) excretion. The reabsorption of water and sodium causes an increase in blood pressure, by expanding the extracellular volume. These effects are mediated by aldosterone joining MR, encoded in the NR3C25 gene. However, after cloning the molecule of MR, in 1987, it was shown that these were also found in other tissues such as the vascular endothelium, the cells of the smooth muscle tissue of the middle layer of the blood vessels, cardiac tissue (miocardiocytes, fibroblasts and macrophages), kidney (podocytes and mesangial cells), adipocytes, monocytes and brain[6-8].

Genomic and non-genomic effects

The activation of MR (mediates genomic effects) by aldosterone promotes multiple deleterious effects at renal, cardiac and vascular levels, including endothelial dysfunction, hypertension, neurohormonal activation, cardiovascular and renal remodeling (hypertrophy, fibrosis and apoptosis), decreased of arterial adaptability and stimulates the expression of cell adhesion molecules; also, it promotes platelet activation, of the activator's inhibitor of plasminogen type I (prothrombotic effect), oxidative and pro-

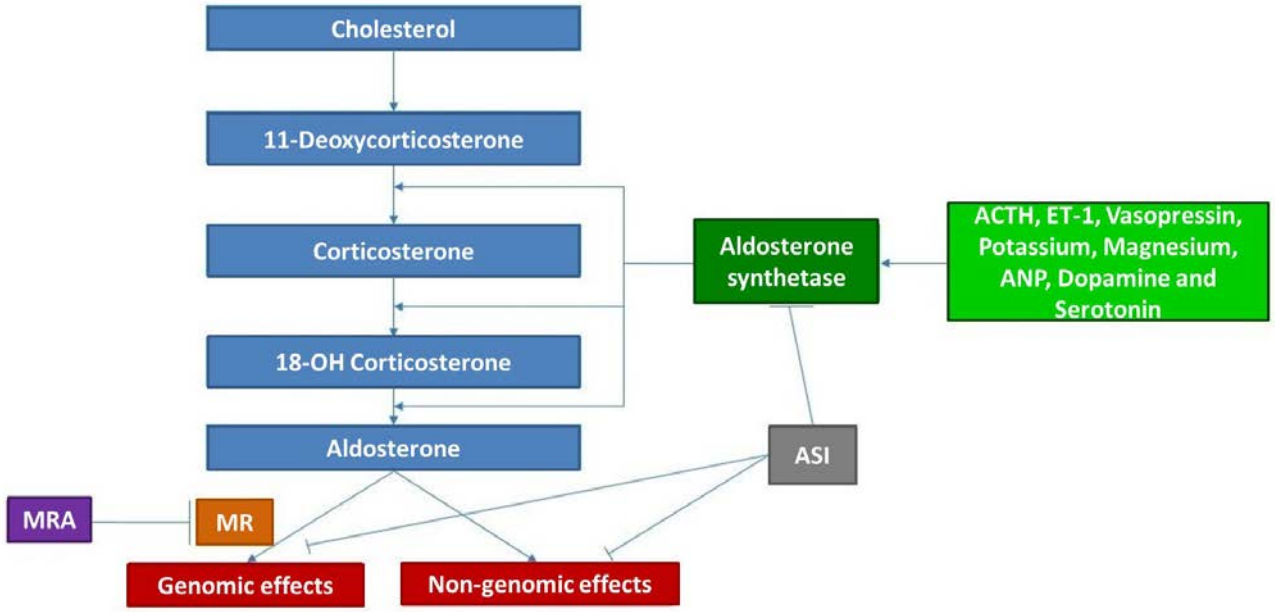

Figure. Synthesis and effects of aldosterone. ACTH: adrenocorticotropic hormone, ANP: atrial natriuretic peptide, ASI: aldosterone synthase inhibitors, ET-1: endothelin-1, MR: mineralocorticoid receptor, MRA: mineralocorticoid receptors antagonist

arrythmic stress and proinflammatory effects[9-13].

Moreover, the activation of the central MR produces an increase of the sympathetic tone in the kidneys, the heart, the smooth muscular cells of the vascular layer, and the vasopressin release and decreased sensitivity of the baroreceptors. In addition, when activating the MR, the aldosterone regulates the expression of the angiotensin-converting enzyme in the miocardiocyte, which suggests the existence of a positive feedback mechanism that activates the RAAS[14].

All these effects are called genomic because they depend on the transcription and translation of the MR. On the other hand, aldosterone produces rapid, independent effects of transcription and translation of MR (non-genomic effects), which may be mediated by the G-protein coupled to the 30 receptor and the activation of the epithelial growth factor receptor[7].

These effects have been described in the cells of the smooth vascular muscle and other tissues in which aldosterone induces a rapid increase of Na influx and intracellular calcium concentration; the first, by incrementing the cotransporter activity of Na-K-Cl_2, the Na-H exchange and inhibiting the Na/K pump-dependent on adenosine triphosphate (ATP-[ATPase]), and the second through voltage dependent channels, and the activity of the complex adenosine monophosphate to the cyclic monophosphate (cAMP)-protein kinase A, phospholipase C, phosphatidylinositol 3-kinase, and diacylglycerol. Likewise, aldosterone induces rapid phosphorylation of extracellular signals into cells of the smooth vascular muscle, endothelial, renal, where it promotes mitogenic and profibrotic phenotype and stimulates the transcription of the epithelial growth receptor[7,15,16].

Non-genomic effects also occur independent of the hemodynamic factors and play an important role in the mechanisms by which aldosterone contributes to endothelial dysfunction, vasoconstriction, and resistant hypertension, cardiovascular and renal remodeling, inflammation, heart failure, insulin resistance and chronic kidney disease[3,7,9,10,15-19].

Uniquely, aldosterone, in the cells of the smooth vascular muscle, exerts its effect by two mechanisms: either by activating the G-protein coupled to the 30 receptor as well as by joining the MR and producing vasodilation, apoptosis and activation of the phosphoinositide 3-kinase enzyme; also it emits regulatory extracellular signals of kinases and phosphorylation of myosin light chains[16].

In contrast, the activation of endothelial cells by aldosterone from joining the MR reinforces vasoconstriction and vasodilator response deteriorates.

All of this confirms that aldosterone plays a fundamental function as cell regulator in the functioning of several organs, regardless of its effects on the kidneys, and it is directly involved in the genesis of several cardiovascular and renal diseases[7,12].

ALDOSTERONE AND CORONARY ARTERY DISEASE

While a large number of experimental studies indicate that aldosterone is an important stimulus for cardiovascular diseases in animal models, some data from clinical studies support its deleterious effects on the cardiovascular system through the activation of the MR. Likewise, the positive effects of spironolactone in patients with coronary artery disease (CAD) has been proved; however, there are insufficient randomized clinical tests.

Two tests have evaluated the relationship between aldosterone levels and the risk of death or occurrence of acute ischemic episode in patients with CAD. For seven years Tomaschitz *et al.*[20] observed 3156 patients with demonstrated CAD by coronary angiography and they found that high aldosterone levels were independently associated with cardiovascular mortality. Ivanes *et al.*[21] studied 799 patients with CAD without heart failure, and they found that elevated aldosterone levels were strongly associated, and independently, with mortality, as well as the occurrence of acute ischemic events.

Amano *et al.*[22] conducted a prospective study on 156 patients with CAD, to which was performed angioplasty with implantation of bare metal stent and there was found that elevated levels of aldosterone at the time of the procedure are an independent predictor of intrastent restenosis.

In addition, Rita *et al.*[23] studied the progression of the carotid atherosclerotic plaque in 848 patients with no symptoms of cardiovascular disease, family history of this disease and absence of risk factors. They evaluated variables as: levels of plasma aldosterone, age, sex, total cholesterol, systolic pressure, diabetes and smoking, and concluded that only aldosterone levels behaved as an independent predictor of plaque progression.

However, future clinical studies are needed to prove that spironolactone produces beneficial effects in patients with CAD, in absence of myocardial infarction and heart failure, or preventing intrastent restenosis.

ALDOSTERONE, CARDIAC REMODELING AND HEART FAILURE

Cardiac remodeling is characterized by changes in the size, structure and function of the heart. It represents an early and progressive response of this organ to ischemia, volume/pressure overload or mechanical damage caused by a progressive decrease in the cardiac function[24].

Preclinical studies have shown that the activation of the MR has a key role in the pathogenesis of the cardiac remodeling in patients with heart failure or after an acute myocardial infarction[25,26].

In patients with heart failure, the elevated plasma levels of aldosterone and its cardiac biosynthesis are increased due to the activation of the aldosterone synthetase enzyme. It has been shown that the high plasma levels are related to the mortality, in patients with heart failure; also, between the cardiac levels and left ventricular remodeling in patients with acute myocardial infarction. Although this increase may be an adaptive response to maintain blood pressure in the short term, the persistence of these elevated levels in patients with heart failure produces deleterious consequences on cardiovascular structures[27].

Aldosterone causes endothelial dysfunction, significant HT, fibrosis, and cardiac and perivascular remodeling; as well as glomerulosclerosis and interstitial fibrosis in the kidney. Before the development of fibrosis, aldosterone causes cardiac inflammatory and intracoronary lesions characterized by infiltration of monocytes/macrophages, focal ischemia, and necrotic changes, in addition to increased expression of proinflammatory molecules (cyclooxygenase-2, osteoporine, protein 1, growth factor β1 and connective tissue), collagen, metalloproteases and NADPH oxidase. These changes facilitate progression to heart failure independently of blood pressure and levels of angiotensin II; however, they are attenuated significantly by the antagonists of MR. The expression of these receptors causes severe coronary endothelial dysfunction and dilated cardiomyopathy, and it accentuates the MR error in the pathological hypertrophy[28,29].

The overexpression of aldosterone synthetase or MR in the cardiomyocytes alone does not induce fibrosis, suggesting that the presence of aldosterone is necessary but not sufficient, and other trigger factors (sodium, oxidative stress, angiotensin II, endothelin-1) are required to induce cardiac remodeling[30].

CONCLUSIONS

Aldosterone is one of the main regulatory factors of the cardiovascular diseases' progression. The MR's activation by aldosterone intervenes and aggravates pathophysiological processes, which are the target of therapeutic interventions in patients with coronary artery disease and heart failure.

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