American Journal of Biomedical Science & Research

www.biomedgrid.com

ISSN: 2642-1747

Mini Review

The Role of Hyperaldosteronism in the Pathogenesis of Neuroleptic Cardiomyopathy

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To Cite This Article: *Volkov V P. The Role of Hyperaldosteronism in the Pathogenesis of Neuroleptic Cardiomyopathy. Am J Biomed Sci & Res. 2019 - 5(3). AJBSR.MS.ID.000916. DOI:* 10.34297/AJBSR.2019.05.000916.

Received: September 13, 2019; **Published:** September 26, 2019

Abstract

A brief review of the literature deals with the role of aldosterone in the pathogenesis of neuroleptic cardiomyopathy due to the side effects of cardiotoxic antipsychotic drugs. Various physiological and pathophysiological effects of aldosterone, its effect on myocardium and participation in cardiac remodeling during morphogenesis of neuroleptic cardiomyopathy are considered.

Keywords: Neuroleptic cardiomyopathy; Pathogenesis; Aldosterone

Introduction

Neuroleptic cardiomyopathy (NCMP) is a little-studied iatrogenic pathology of the heart due to the side cardiotoxic effects of antipsychotic (neuroleptic) drugs [1-4]. Along with the fact that the etiology of the disease is quite clearly defined, its pathogenesis remains not fully studied. Analysis of the literature data on the development of different types of cardiomyopathies allows us to make some assumptions about the pathogenesis of NCMP. One of the possibilities of heart damage with long-term use of antipsychotics is their indirect effect through the influence of these drugs on the overall metabolism in the body. So, it is well known that one of the most serious side effects of neuroleptic therapy is metabolic syndrome [5-9]. One of the links of neuroendocrine dysfunction in metabolic syndrome is hypercorticism, that is, an increase in the formation and excretion of all steroid hormones of the adrenal cortex [10], including aldosterone, which plays a certain and, presumably, a significant role in the pathogenesis of NCMP [11]. This brief review of the literature is devoted to this issue.

First, it is necessary to highlight several pathophysiological aspects related to this hormone. Thus, aldosterone is a mineralocorticoid produced mainly in the glomerular zone of the adrenal cortex and in smaller quantities - in the brain, myocardium, vascular endothelium [12-14]. The main activator of the synthesis of aldosterone is the renin - angiotensin system. Inhibit the formation and secretion of the hormone primarily atrial and brain natriuretic peptides [13]. The main effects of aldosterone are an increase in sodium reabsorption in the distal tubules of the kidneys and the associated fluid retention; the consequence of reducing natriuresis is an increase in potassium excretion in the urine [11-16]. Aldosterone also increases the severity of local intravascular inflammation, causes damage to the endothelium of peripheral vessels, increases the number of receptors for angiotensin II in vessels, accelerates apoptosis of cardiomyocytes and potentiates the effects of renin-angiotensin system [11,13,17,18]. In this regard, it is important to note that, in addition to the distal renal tubules, aldosterone receptors are present in endothelial cells, cardiomyocytes and fibroblasts of the heart muscle [11,13,19]. It was found that the interaction of aldosterone with these receptors directly affects the state of the extracellular matrix of the myocardium, causes an acceleration of fibroblast proliferation, as well as an increase in the synthesis and accumulation of collagen types I and III, resulting in myocardial fibrosis [19,20-27], which plays a leading role in the appearance of diastolic dysfunction induced by the action of this hormone [21]. It should be emphasized that the development of fibrosis of the heart muscle under the action of aldosterone is not mediated by sodium and fluid retention but is a consequence of direct stimulation of myocardial receptors [28]. This effect is realized primarily by increasing the synthesis of aldosterone not in the adrenal glands, but in the myocardium [29,30], in the aorta and in the coronary sinus [30]. It is also believed that aldosterone which is namely locally synthesized and fixed to the membrane receptors of the heart plays an important role in the processes of ventricular remodeling [31,32]. The triggering effect of aldosterone in relation to fibrosis of the heart muscle is likely determined by the influence of this hormone on the activity of collagenase.

According to CG Brilla et al. [33], aldosterone enhances the expression of type III collagen gene in cardiac fibroblasts by inhibiting the activity of this enzyme. In addition, many authors have revealed the direct influence of hyperaldosteronism on the processes of cardiac remodeling and hypertrophy [34-37] and demonstrated a direct correlation of aldosterone level with myocardial mass [38,39]. One of the mechanisms of aldosterone participation in cardiac remodeling is its induction of generalized inflammation and oxidative stress [24,25,40], as well as increased activity of matrix metalloproteinases [22&40]. All this is accompanied by an increase in the ultrasonic density of the myocardium, an increase in the stiffness of the walls of the left ventricle, violations of its filling and the appearance of diastolic dysfunction due to the development of extensive fibrosis [22,41,42]. These phenomena accelerate the progression of heart failure, increase the electrical heterogeneity of the myocardium, which underlies the mechanisms of re-entry and reduce the threshold for the occurrence of life-threatening ventricular arrhythmias [22]. The elongation of the QT interval is observed on the electrocardiogram [41,42]. It is appropriate to recall that this electrophysiological phenomenon is a very characteristic feature of the cardiotoxic action of neuroleptics and developing NCMP [43-48].

Diastolic dysfunction induced by the action of aldosterone has been found by many researchers [35,37,42,49,50]. Myocardial fibrosis plays a leading role in its development [50,51]. Hyperaldosteronism entails a decrease in the number of contractile elements per unit volume of the myocardium, the development of tissue hypoxia and disruption of the synchronous operation of cardiomyocytes [22]. At the same time, one of the mechanisms of the negative effect of aldosterone on the structure of the heart muscle is its ability to activate cardiomyocyte apoptosis [22,52]. This process is known to be of importance in the pathogenesis of cardiac remodeling [53-58]. Aldosterone can influence on the development of cardiovascular diseases, including NCMP, through the formation of endothelial dysfunction [22,59]. The development of aldosterone-induced endothelial dysfunction is associated with decreased bioavailability of NO and activity of NO-synthase [60]. At the cellular level, aldosterone alters signals from the transcriptional nuclear factor NF-kB, induces oxidative stress and enhances the penetration of reactive oxygen species into the vascular wall, which is a serious importance in the genesis of endothelial dysfunction [25,61].

Thus, in addition to the direct cardiotoxic side effect of neuroleptic drugs, their indirect effect on the overall metabolism of the body, the development of neuroendocrine dysfunction and metabolic syndrome, an important component of which is hyperaldosteronism, is essential in the pathogenesis of NCMP. The diverse damaging effect of aldosterone on the heart plays an important role in the development of NCMP [11].

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