European Journal of Pharmacology 786 (2016) 186–193

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

Roles of aldosterone in vascular calcification: An update

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ARTICLE INFO

Article history:
Received 24 December 2015
Received in revised form
20 May 2016
Accepted 25 May 2016
Available online 26 May 2016

Keywords:
Aldosterone
Vascular calcification
Genomic mechanisms
Non-genomic mechanisms
Vascular smooth muscle cells

ABSTRACT

Both clinical and experimental studies have demonstrated that vascular calcification (VC) is a common pathology shared in many chronic diseases such as chronic kidney disease (CKD) and diabetes. It's an independent risk factor for cardiovascular events. Since the pathogenesis of VC is complicated, current therapies have limited effects on the regression of VC. Therefore, it is urgent to investigate the potential mechanisms and find new targets for the treatment of VC. Aldosterone (Aldo), a mineralocorticoid hormone, is the metabolite of renin-angiotensin-aldosterone system (RAAS) activation, which can exert genomic and non-genomic effects on the cardiovascular system. Recent data suggests that Aldo can promote VC. Here, we summarized the roles of Aldo in the process of VC and a series of findings indicated that Aldo could act as a potentially therapeutic target for treating VC.

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1. Introduction

Vascular calcification (VC) is a pathological process that extra-skeletal calcium-phosphate crystals deposit in the vascular system. And it has several forms, including intimal and medial calcification, and can also be found in the valves of heart. VC frequently occurs in atherosclerosis, hypertension, diabetes, chronic kidney disease (CKD) and aging (Wu et al., 2013). In the past, VC was considered to be passive and degenerative. However, recent studies have revealed that it is an active, dynamic cell-mediated process within the vessel wall of complex pathology, involving the trans-differentiation of vascular smooth muscle cells (VSMCs) into osteoblast-like cells, VSMCs apoptosis and matrix vesicle release

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http://dx.doi.org/10.1016/j.ejphar.2016.05.030
0014-2999/

(Karwowski et al., 2012). A recent meta-analysis of 30 prospective cohort studies demonstrated that the presence of VC was associated with a 3–4 fold higher risk for cardiovascular events and mortality (Rennenberg et al., 2009). Moreover, VC may induce a range of severe clinical complications, including increased aortic stiffness, valvular sclerosis and stenosis, and chronic heart failure (Sage et al., 2010). Over several decades, multiple studies have indentified the unfavorable results of VC. However, owing to the complicated mechanisms of VC, no effective drugs and non-drug therapies have been found yet (Leonard et al., 2013).

There are multiple factors involved in VC, among which aldosterone (Aldo) is a new and pivotal one. As an important metabolite of renin-angiotensin-aldosterone system (RAAS) activation, Aldo, a mineralocorticoid hormone, regulates a series of biological processes in vivo via a paracrine/autocrine manner (Catena et al., 2014). Under physical condition, Aldo plays an important role in regulating blood pressure, fluid volume, and sodium and potassium balance. However, once Aldo is over activated, it can promote the progression of cardiovascular diseases and events (Pacurari et al., 2014). McCurley and Jaffe reviewed several detrimental effects of Aldo in the vasculature (enhance vascular oxidative stress, promote vessel inflammation and apoptosis) (McCurley et al., 2012). Recently, a series of studies have demonstrated that Aldo can promote VC, which implicates a newly potential target for treating VC (Lang et al., 2013; Wu et al., 2012). However, the studies about the roles of Aldo in promoting VC were limited and the underlying mechanisms are still unclear.

In this review, we summarized the roles of Aldo in VC and explored the potential mechanisms for it influencing VC. We attempted to give clinicians in-depth insights into Aldo on VC. In the light of the complexity of VC, we mainly focused on two aspects: genomic and non-genomic actions of Aldo in VC.

2. The basic ways of Aldo actions

There are two ways for Aldo to mediate biological functions in vivo and in vitro (Fig. 1). Firstly, Aldo causes the classical effects by binding to the cytosolic mineralocorticoid receptor (MR) in genomic responses. Since the response time required to fully activate this pathway is quite long, the effects of genomic responses can be ameliorated by MR antagonists like spironolactone (Dorrance, 2014; Losel et al., 2003). Once Aldo and MR form the Aldo-MR complex, it enters the nucleus and binds to the MR response elements (MRE), regulating the transcription of target genes. Then, these genes are translated into multiple Aldo-induced proteins including VC associated markers such as alkaline phosphatase (ALP) and bone morphogenetic protein 2 (BMP2) (Jaffe et al., 2005, 2007). Secondly, Aldo can also exert non-genomic responses, which don't require gene transcription and translation. It is found that the non-genomic responses are mediated through membrane receptors which are largely unknown, and then enhanced by the subsequent activation of second messengers and protein kinases (Falkenstein et al., 2000; Losel et al., 2003). It is important to notice that non-genomic effects are generally rapid and insensitive to MR antagonists (Dorrance, 2014).

3. Possible mechanisms for Aldo to promote VC

The MR is expressed on vascular cells, including VSMCs and endothelial cells (ECs), and it has much higher affinity to Aldo than cortisol. However, in active circulation, the concentration of cortisol (1 μM) is much higher than that of Aldo (1 nM). To prevent excess activation of MR by the abundant cortisol, microsomal 11-beta-hydroxysteroid dehydrogenase type 2 (11βHSD), which

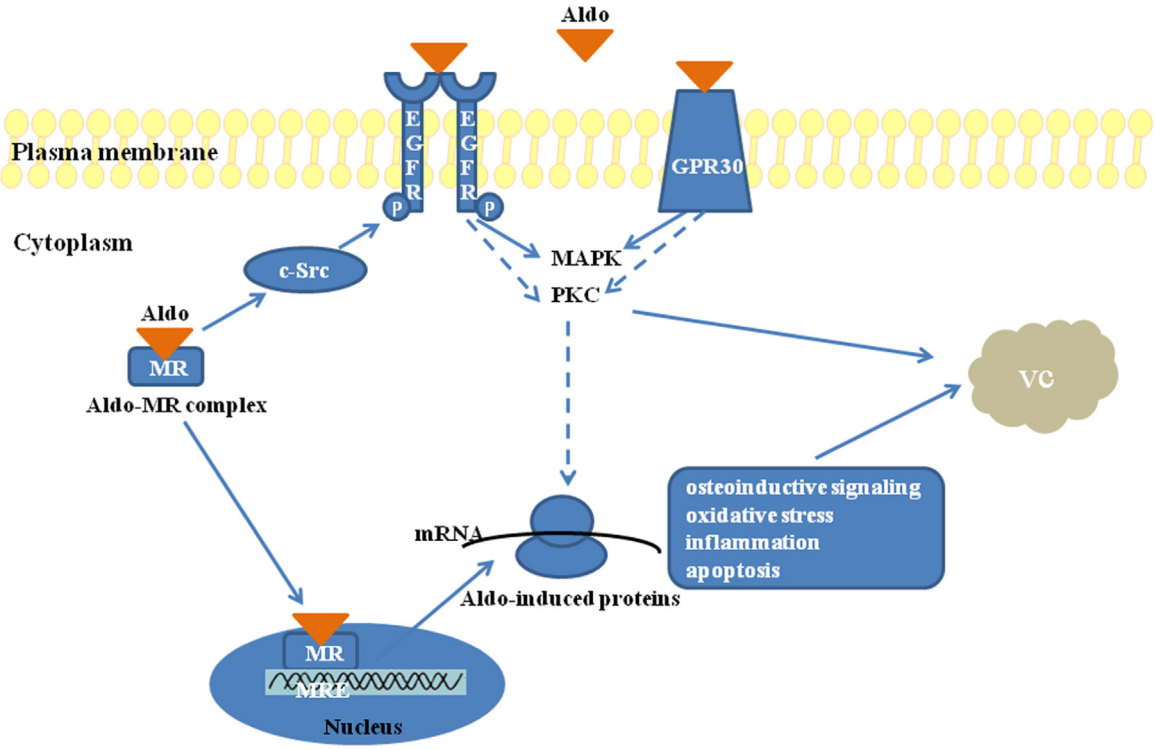

Fig. 1. Aldo promotes VC via genomic and non-genomic actions. **Genomic action:** Aldo diffuses across the plasma membrane, binds to the MR, and forms the Aldo-MR complex. Then it translocates to the nucleus and binds to the MRE, thereby enhances multiple Aldo-induced proteins synthesis. They regulate vascular osteoinductive signaling, oxidative stress, inflammation and apoptosis. **Non-genomic actions:** Aldo activates PKC and MAPK through EGFR and GPR30. And these effects are MR-dependent or -independent to work in a unifying effort for promoting VC. Aldo, aldosterone; *c*-Src, the cytosolic tyrosine kinase; EGFR, epidermal growth factor receptor; GPR30, G protein-coupled receptor; MAPK, mitogen-activated protein kinase; MR, mineralocorticoid receptor; MRE, MR response elements; PKC, protein kinase C; VC, vascular calcification.