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THE VASCULAR EFFECTS OF ALDOSTERONE.

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Introduction.

Aldosterone in addition to its synthesis in the zona glomerulosa of the adrenal gland is produced at the vascular level in both endothelial and smooth muscle cells[1,2]. This mineralocorticoid exerts actions in the vascular wall through genomic and non-genomic effects. Genomic actions imply the binding of aldosterone to cytoplasmatic mineralocorticoid receptors, which have been found in both endothelial and smooth muscle cells[3-5] and involve transcription and protein synthesis[3]. The non-genomic effects of aldosterone are observed in a few minutes and are insensitive to transcription inhibitors, they seem to involve both mineralocorticoid and an unidentified membrane receptor[2] and the activation of different signaling pathways.

Numerous studies at both clinical and experimental levels have shown that this mineralocorticoid acting on endothelial cells or smooth muscle cells induces vascular alterations through endocrine and/or paracrine mechanisms which can affect vascular wall. The interaction of aldosterone to its receptors in endothelial cells produces swelling and stiffness. This increase in cell volume is associated with cell rigidity and produced numerous gaps between cell-to cell contacts[6,7] which alters blood flow as well as vascular permeability and, consequently, can have an impact on vascular function and structure and can induce an inflammatory process.

The effect of aldosterone on the endothelial dysfunction: mechanism involved.

An increasing number of studies have suggested that aldosterone contributes to endothelial dysfunction associated with different pathological situations, which is mainly characterized by impaired endothelium-dependent relaxations[8]. Treatment with the mineralocorticoid receptor antagonist, spironalactone, ameliorated the relaxing response to acetylcholine in rats infused with angiotensin II, suggesting that aldosterone mediates vascular reactivity changes induced by angiotensin II[9]. Similarly, the administration of a new selective mineralocorticoid receptor blocker, eplerenone, improved endothelial function in spontaneous hypertensive rats (SHR), a genetic model of hypertension. The improvement in endothelial function was observed with two different doses of eplerenone that each have a different impact on blood pressure, one of them inducing an important blood pressure reduction, although not being able to normalize it, and the other one having a minor impact on blood pressure levels[10]. This supports that aldosterone can exert deleterious effects on endothelium through hemodynamic- and non hemodynamic mechanisms. The idea that aldosterone alters endothelial function through mechanisms that do not involve an increase in hemodynamic stress is also supported by the observation that chronic administration of this mineralocorticoid reduced to a similar extent

the relaxing response to acetylcholine in aorta of both normotensive and hypertensive rats without changes in blood pressure[11].

Aldosterone also seems to participate in endothelial dysfunction associated with atherosclerosis, since in two different models of atherosclerosis in nonhuman primates and rabbits placed on 1% cholesterol diet, the blockade of mineralocorticoid receptors with eplerenone ameliorates endothelial function without any change in either plasma cholesterol or blood pressure levels[12,13]. Similarly, the administration of spironolactone for 1 month in addition to standard diuretic/ACE inhibitor therapy ameliorate forearm vasculature endothelial function in patients with NYHA class II to III heart failure, supporting the role of aldosterone in the endothelial dysfunction associated with heart failure[14].

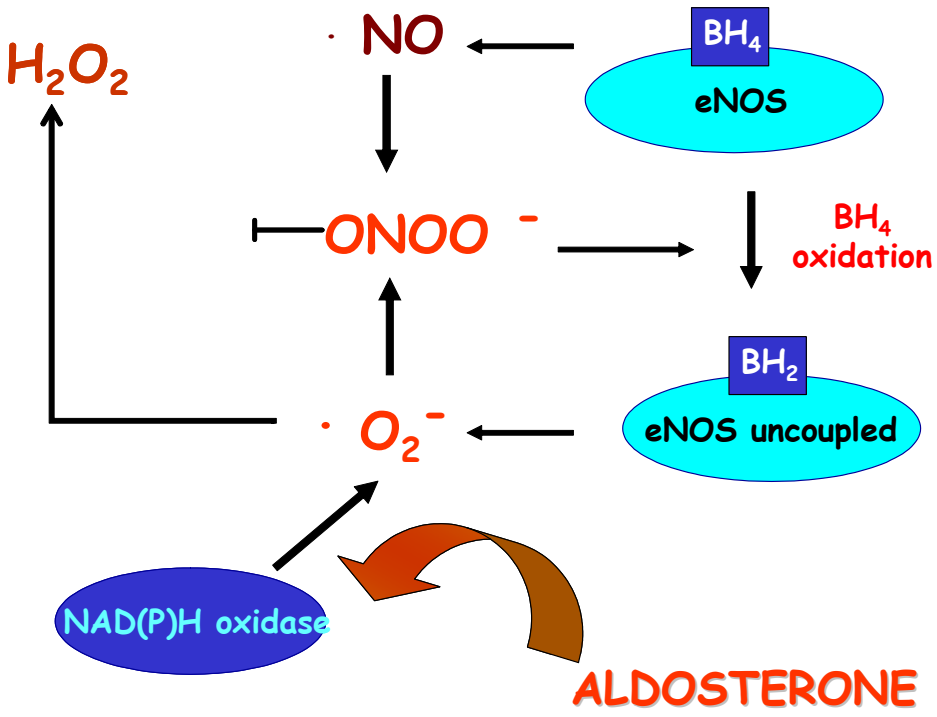

***Figure 1**. Inactivation of nitric oxide (NO) by superoxide anions ($.O_2^-$) and the consequent production of peroxynitrites ($ONOO^-$). Effect of aldosterone.*

Numerous studies have shown that the main mechanism underlying the endothelial dysfunction associated with different cardiovascular risks is a reduction in nitric oxide (NO) availability. This decrease can involve not only a reduction in NO production but also an increase in NO inactivation by reactive oxygen species (ROS)[15] **(Fig. 1)**. Blockade of mineralocorticoid receptors prevented the decrease in endothelial NO synthase (eNOS) associated with hypertension and heart failure in rats[10,16,17] supporting a negative control of aldosterone in the expression of the enzyme involved in NO synthesis in these pathological situations **(Fig. 2)**. These actions of aldosterone on NO production involved direct effects of this factor on endothelial cells because they were observed not only in rats with heart failure but also in cultured cells[16,18]. In addition, aldosterone can negatively regulate the activation of this enzyme through at least two different mechanisms. Firstly, this factor induces an uncoupling of eNOS consequence of a deficiency in its cofactor 4-tetrahydrobiopterin (BH_4)[18]. In absence or presence of low levels of BH_4, eNOS produces ROS instead of NO[19] **(Fig. 1)**. Another mechanism through which aldosterone can

modulate eNOS activation, and consequently NO production is by reducing the dephosphorylation of the N-terminal 1179 serine residue of eNOs[16]. It has been shown that serine residue is an important target for activation of the PI3 kinase-PKB/Akt pathway involved in eNOS activation[20].

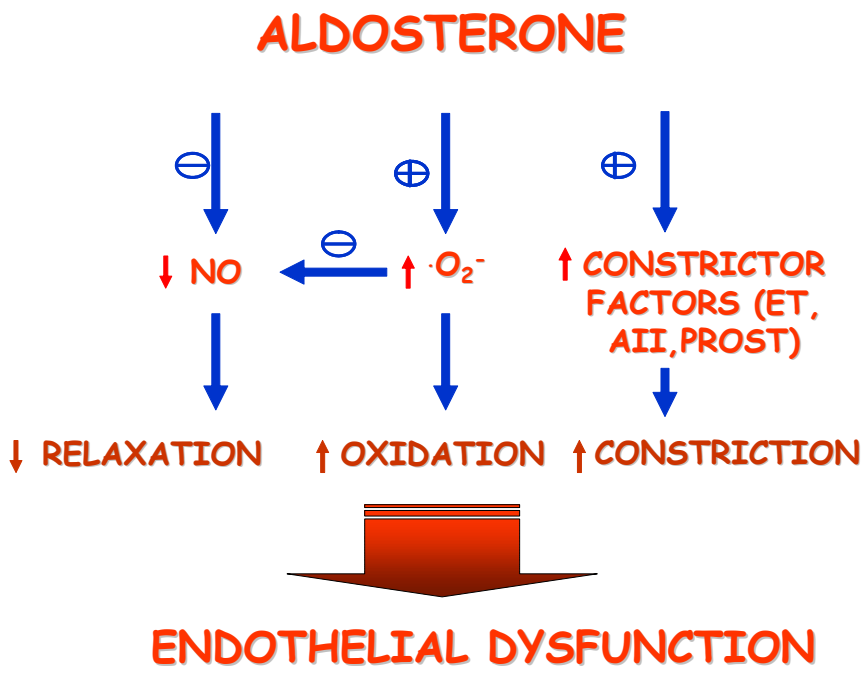

***Figure 2**. Mechanisms involved in aldosterone participation in endothelial dysfunction. NO: nitric oxide; $.O_2^-$: superoxide anions; ET: endothelin; AII: angiotensin II; PROST: prostamoids.*

Different studies have shown that the administration of aldosterone is associated with an increase in oxidative stress. The chronic administration of this mineralocorticoid to uninephrectomized rats with dietary 1% NaCl increased H_2O_2 production by monocytes and lymphocytes[21]**.** Similarly, aldosterone administration increased vascular superoxide production in normal rats[22]. This seems to be a direct effect of aldosterone because it is able to increase ROS generation in rat mesangial cells through the membranous translocation of subunits p47phox and p67phox of NAPDH oxidase, an important enzyme involved in superoxide anion production[23]. The prooxidant action of aldosterone is further supported by the fact that the administration of eplerenone is able to block the expression of NAD(P)H oxidase in different pathological situations including hypertension and atherosclerosis[10,12,24]. In addition to its ability to enhance ROS generation, aldosterone can contribute to an increase in oxidative stress by inhibiting the antioxidant systems involved in ROS removal since we have observed that eplerenone is able to reverse the reduced glutathione levels observed in hypertensive rats, the most important systemic antioxidant agent[10].

An exaggerated production of vasoconstrictor factors that can modulate the vasodilatory effect of NO might be an additional mechanism through which aldosterone leads to endothelial dysfunction **(Fig. 2)**. Among these factors it is possible to include endothelin, prostanoids and angiotensin II. It has been shown that endothelin receptor antagonism improved relaxations to acetylcholine in rats infused with aldosterone[25]. Moreover, the infusion of this mineralocorticoid was accompanied by an increase in endothelin production in both large and small arteries[26]. Prostanoids participation can be

proposed since we have found that aldosterone induced endothelial dysfunction in both normotensive and hypertensive rats that was reversed by the administration of a COX-2 inhibitor[11]. Finally, a possible role of angiotensin II could be also proposed because aldosterone can increase local production of angiotensin II by upregulating angiotensin converting enzyme[12,27]. In addition, aldosterone upregulates angiotensin II receptors[28].

The effect of aldosterone on vascular structure.

Aldosterone not only affects vascular function but also vascular structure. This affirmation is supported by the fact that its administration in rats is associated with vascular remodeling in both large and small vessels characterized by media thickness[25,29,30]. In addition, patients with primary aldosteronism showed an increased media-to-lumen ratio consequence of both media thickness and narrowed lumen in resistance arteries from gluteal subcutaneous tissue[31]. Moreover, different studies have shown that the administration of mineralocorticoid receptor antagonists in different models of hypertension is associated with amelioration of vascular remodeling[9.10.29.32]. Likewise, eplerenone has been shown to attenuate constrictive remodeling and collagen accumulation in pig coronary arteries after angioplasty[33]. An increase in extracellular matrix can account for these vascular structural changes since aldosterone is a well known profibrotic factor. In addition, a role of changes in smooth muscle cell size cannot be ruled out since it has been shown that aldosterone induces hypertrophy in these cells[34] **(Fig. 3)**. Components of extracellular matrix are major determinants of mechanical properties in large arteries. Therefore, aldosterone could modulate mechanical properties of the vascular wall through alterations in vascular structure. Supporting this idea is the observation that eplerenone decreased aortic arterial stiffness[30], which is a significant and independent marker of cardiovascular risk[35].

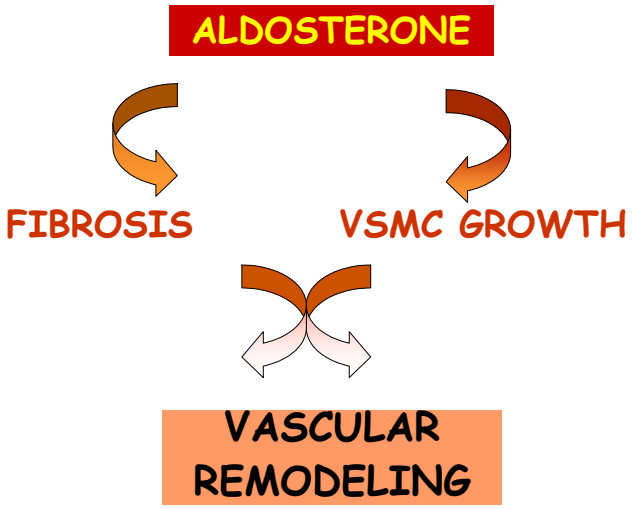

***Figure 3**. Mechanisms involved in aldosterone participation in vascular remodeling.*

Several potential mediators could particiapate in the vascular profribotic effect of aldosterone including endothelin, angiotensin II, plasminogen activator inhibitor (PAI-1), growth factors, and oxidative stress[36,37]. Supporting the participation of endothelin in these processes is the observation that blockade of the endothelin system normalized vascular

remodeling in both large and small vessels as well as extracellular matrix in aldosterone-induced hypertension[9,29]. In addition, endothelin A receptor antagonism was also able to reduce oxidative stress in these animals, supporting the participation of an increase in ROS in the vascular structure alterations which can trigger extracellular matrix accumulation[9]. Similarly, we have observed that treatment with eplerenone normalized aortic media-to-lumen ratio in SHR. This effect was accompanied by a reduction in the vascular expression of the main enzyme involved in ROS production (NADP(H) oxidase)[10].

Salt content of the diet appears to be crucial for the profibrotic effect of aldosterone. In fact, infusion of aldosterone produces a dose-dependent increase in cardiac fibrosis in the presence of a high-salt diet, but not in the presence of a low-salt diet, suggesting that aldosterone-induced organ damage develops as a result of inappropriate plasma aldosterone levels for salt status[37]. Finally, it is necessary to mention that hemodynamic stress, an important stimulus for structural changes, can also mediate the deleterious effects of aldosterone on vascular structure since changes in blood pressure are a common observation after either aldosterone administration or mineralocorticoid receptor antagonism[9,10,25,29,38-42].

The effect of aldosterone on vascular inflammation.

Vascular inflammation plays a central role in the initiation, progression and complications of atherosclerosis, which is considered a chronic low-grade inflammatory process[43]. Several studies have suggested that aldosterone is a proinflammatory factor since its administration is accompanied by an inflammatory process. In rats fed a high salt-diet, aldosterone produced an inflammatory cell infiltration in coronary arteries. This inflammation process was associated with ischemic and necrotic lesions of the adjacent myocardium. This cell infiltration was preceded by an increase in proinflammatory mediators such as ICAM-1,MCP-1, cytokines and COX-2[38,44,45]. Similarly, we have observed that chronic administration of aldosterone to rats was associated with an increase in aortic COX-2 expression. This stimulation was observed in both normotensive and hypertensive animals and with no changes in blood pressure, suggesting that this effect appears to be independent of previous blood pressure levels and acting through non-hemodynamic mechanisms[39]. In addition, aldosterone can participate in the vascular inflammation associated with hypertension since the blockade of mineralocorticoid receptors ameliorated the vascular inflammatory process in different models of hypertension.

All these data support that aldosterone plays an important role in the vascular inflammation response upregulating adhesion molecules, chemokines and cytokines, as well as growth factors that in turn promote the recruitment and adhesion of inflammatory cells, thus contributing to the initiation and progression of atherosclerotic lesion. This role is confirmed by the fact that the administration of mineralocorticoid receptor antagonist reduced atherosclerotic lesion in different models of atherosclerosis[12,13,24]. This reduction in atherosclerotic process was accompanied by a reduction in inflammatory markers[13,24]. The pro-inflammatory role of aldosterone seems to involve the system NF-κB/I-κB since the reduction in vascular inflammatory markers observed in genetic hypertensive rats was accompanied by both a decrease in the expression of NF-κB as well as an increase in the aortic expression of its inhibitor I-κB. This supports that a reduction in the activity of the system is involved in the reduction in the inflammatory process produced by antagonims of

the mineralocorticoid receptors[39]. This participation is also supported by previous studies in which the cardiac inflammatory process induced by the administration of aldosterone in rats feeding with high sodium was associated with an increase in NF-κB activity. The administration of a mineralocorticoid receptor antagonist reduced not only this activation but also the presence of inflammatory markers[40,44].

The NF-κB activation initiates the transcription of various inflammation-relevant genes coding for surface adhesion molecules, chemokines, cytokines, coagulation factors, and matrix proteins though the stimulation of different intracellular pathways[46]. Kobayshi et al[47] have showed recently that NF-κB-mediated adhesion molecules induced by aldosterone involved the expression of lectin-like Ox-LDL (LOX-1)receptors because eplerenone reduced the increase in the renal expression of LOX-1 and ICAM-1 and VCAM-1 in Dahl-sensitive rats. In addition, other pathways have been implicated in the actions of aldosterone through NF-κB-mediated activation such the isoform ε of Protein kinase C, extracellular signal-regulated kinase (ERK) as well as Rho-kinase[48].

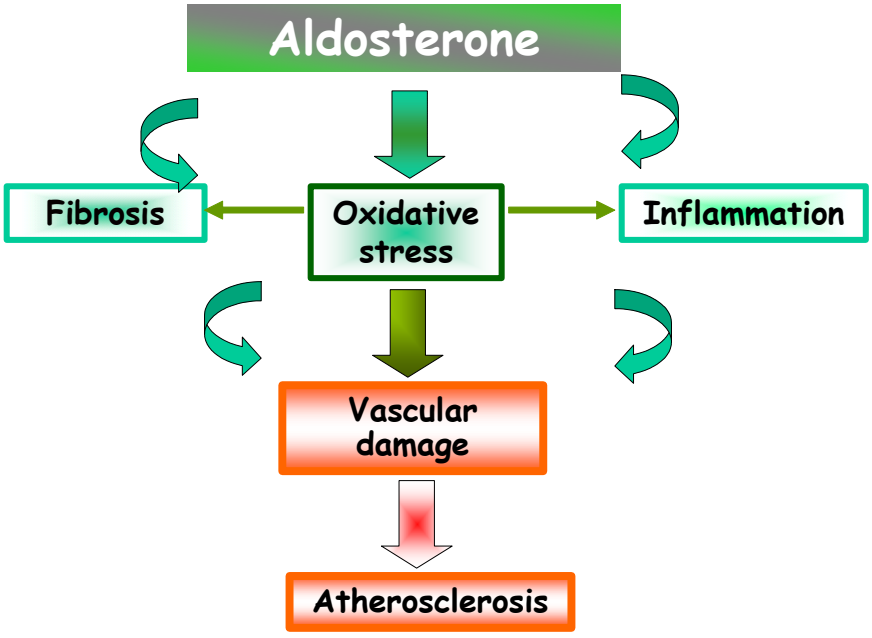

***Figure 4**. Role of aldosterone in the development of vascular damage and atherosclerosis.*

In summary, aldosterone by binding its receptors in endothelial and smooth muscle cells can trigger changes in the vascular wall that can involve both functional and structural alterations through its prooxidant, proinflammatory and profibrotic effect **(Fig. 4)**. These changes can participate in the vascular damage associated with different cardiovascular risk factors and facilitate the development of atherosclerosis. Consequently, blockade of the mineralocorticoid receptors may exert beneficial effects by abrogating pathophysiological aldosterone role in the development of cardiovascular disease.

REFERENCES

1. **Schiffrin EL**. Effects of aldosterone on the vasculature, *Hypertension,* 2006; 47: 312-318.
2. **Skøtt O, Uhrenholt TR, Schjerniog J, Hansen PBL, Rasmussen LE, Jensen BL.** Rapid actions of aldosterone in vascular health and disease-friend or foe?, *Pharmacol Ther*, 2006; 2: 495-507.
3. **Fuller PJ, Young MJ**. Mechanisms of Mineralocorticoid Action, *Hypertension,* 2005, 46: 1227-1235.
4. **Jaffe IZ, Mendelshon ME.** Angiotensin II and aldosterone regulate gene transcripcion via functional mineralocorticoid receptors in human coronary artery smooth muscle cells, *Cir Res,* 2005, 95: 643-650.
5. **Takeda Y, Miyamori I, Inaba S, Furukawa K, Hatakeyama H, Yoneda T, Mabuchi H, Takeda R.** Vascular aldosterone in genetically hypertensive rats. *Hypertension*, 1997, 29:45-48.
6. **Oberleithner H, Riethmuller C, Ludwig T, Hausberg M, Schillers H.** Aldosterone remodels human endothelium, *Acta Physiol (Oxf),* 2006; 187: 305-312.
7. **Oberleithner H, Luwig T, Shahin V, Stock C, Schwab A, Hausberg M, Kusche K, Schillers H.** Differential action of steroid hormones on human endothelium. *J Cell Sci*, 2006, 119: 1926-1932.
8. **Haller H.** Endothelial function: general considerations, *Drugs*, 1997, 53;1-10.
9. **Virdis A, Neves MF, Amir F, Viel E, Touyz RM, Schiffrin EL.** Spironolactone improves angiotensin-induced vascular changes and oxidative stress, *Hypertension*, 2002,40:504-510.
10. **Sanz-Rosa D, Oubiña MP, Cediel E, De las Heras N, Aragoncillo P, Balfagon G, Cachofeiro V, Lahera V.** Eplerenone reduces oxidative stress and enhances eNOS in SHR: vascular functional and structural consequences. *Antioxid. Redox. Signal*. 20057 () 1294–1301.
11. **Blanco-Rivero J, Cachofeiro V, Lahera V, Aras-López R, Márquez-Rodas I, Salaices M, Xavier FE, Ferrer M, Balfagón G**. Participation of prostacyclin in endothelial dysfunction induced by aldosterone in normotensive and hypertensive rats. *Hypertension,* 2005,46: 107–112.
12. **Rajagopalan S, Duquaine D, King S, Pitt B.** Mineralocorticoid receptor antagonism in experimental atherosclerosis. *Circulation.*, 2002, 105: 2212-2216.
13. **Takai S, Jin D, Muramatsu M, Kirimura K, Sakonjo H, Miyazaki M.** Eplerenone inhibits atherosclerosis in nonhuman primates. *Hypertension,* 2005,46: 1135-1139.
14. **Farquharson CAJ, Struthers AD.** Spironolactone increases nitric oxide bioactivity, improves endothelial vasodilator dysfunction, and suppresses vascular angiotensin I/angiotensin II conversion in patients with chronic heart failure. *Circulation*. 2000, 101:594–597.
15. **Münzel T, Just H, Harrison DG.** The physiology and pathophysiology of the nitric oxide/superoxide system. *In Vascular Endothelium: Physiology, Pathology and*

Therapeutic Options. Born, G.V.R. and Schwartz, C.J.,Eds. Schattauer, Stuttgart. (1997) pp. 205–220.

16. **Kobayashi N, Yoshid K, Nakano S, Ohno T, Honda T, Tsubokou Y, Matsuoka H.** Cardioprotective mechanisms of eplerenone on cardiac performance and remodeling in failing rat hearts. *Hypertension.* 2006, 47:671-679.
17. **Thai HM, Do BQ, Tran TD, Gaballa MA, Goldman S.** Aldosterone antagonism improves endothelial-dependent vasorelaxation in heart failure via upregulation of endothelial nitric oxide synthase production. *J Card Fail.* 2006,3:240-245.
18. **Nagata D, Takahashi M, Sawai K, Tagami T, Usui T, Shimatsu A, Hirata Y, Naruse M.** Molecular mechanism of the inhibitory effect of aldosterone on endothelial NO synthase activity. *Hypertension ,* 2006, 476:1-7
19. **Vasquez-Vivar J, Kalyanaraman B, Martasek P, Hogg N, Masters BS, Karoui H, Tordo P, Pritchard KA Jr.** Superoxide generation by endothelial nitric oxide synthase: the influence of cofactors. *Proc Natl Acad Sci U S A*. 1998, 95:9220–9225.
20. **Michell BJ, Chen Z, Tiganis T, Stapleton D, Katsis F, Power DA, Sim AT, Kemp BE.** Coordinated control of endothelial nitric-oxide synthase phosphorylation by protein kinase C and the cAMP-dependent protein kinase. *J Biol Chem.* 2001, 276: 17625–17628.
21. **Ahokas RA, Warrington KJ, Gerling IC, Sun Y, Wodi LA, Herring PA, Lu L, Bhattacharya SK, Postlethwaite AE, Weber KT.** Aldosteronism and peripheral blood mononuclear cell activation: a neuroendocrine-immune interface. *Circulation Res* 2003, 93: e124-e135.
22. **Iglarz M, Touyz RM, Viel EC, Amiri F, Schiffrin EL.** Involvement of oxidative stress in the profibrotic action of aldosterone - Interaction with the renin-angiotensin system. *Am J Hypert*. 2004, 17:597–603.
23. **Miyata K, Rahman M, Shokoji T, Nagai Y, Zhang GX, Sun GP, Kimura S, Yukimura T, Kiyomoto H, Kohno M, Abe Y, Nishiyama A**. Aldosterone stimulates reactive oxygen species production through activation of NADPH oxidase in rat mesangial cells. *J Am Soc Nephrol.* 2005,16:2906-2912.
24. **Suzuki J, Iwai M, Mogi M, Oshita A, Yoshii T, Higaki J, Horiuchi M.** Superoxide production and these increases were inhibited by eplerenone eplerenone with valsartan effectively reduces atherosclerotic lesion by attenuation of oxidative stress and inflammation. *Arterioscler Thromb Vasc Biol.* 2006, 26:917-921.
25. **Park JB, Schiffrin EL.** ET_A receptor antagonist prevents blood pressure elevation and vascular remodeling in aldosterone-infused rats. *Hypertension.* 2001, 37: 1444–1449.
26. **Larivière R, Thibault G, Schiffrin EL**. Increased endothelin-1 content in blood vessels of deoxycorticosterone acetate-salt hypertensive but not in spontaneously hypertensive rats. *Hypertension.* 1993, 21: 294–300.
27. **Sugiyama T, Yoshimoto T, Tsuchiya K, Gochou N, Hirono Y, Tateno T, Fukai N, Shichiri M, Hirata Y.** Aldosterone induces angiotensin converting enzyme gene expression via a JAK2-dependent pathway in rat endothelial cells. *Endocrinology*., 2005, 146: 3900-39006.

28. Ullian ME, Schelling JR, Linas SL. Aldosterone enhances angiotensin II receptor binding and inositol phosphate responses. *Hypertension*., 1992, 20: 67–73.

29. Lacolley P, Labat C, Pujol A, Delcayre C, Benetos A, Safar M. Increased carotid wall elastic modulus and fibronectin in aldosterone-salt-treated rats: effects of eplerenone. *Circulation.* 2002, 106: 2848-2853.

30. Pu Q, Neves MF, Virdis A, Touyz RM, Schiffrin EL. Endothelin Antagonism on aldosterone-induced oxidative stress and vascular remodeling. *Hypertension*, 2003, 42: 49-55.

31. Rizzoni D, Porteri E, Castellano M, Bettoni G, Muiesan ML, Muiesan P, Giulini SM, Agabiti-Rosei E. Vascular hypertrophy and remodeling in secondary hypertension. *Hypertension.* 1996; 28: 785–790.

32. Nagata K, Obata K, Xu J, Ichihara S, Noda A, Kimata H, Kato T, Izawa H, Murohara T, Yokota M. Mineralocorticoid receptor antagonism attenuates cardiac hypertrophy and failure in low-aldosterone hypertensive rats. *Hypertension.* , 2006, 47: 656-664.

33. Ward MR, Kanellakis P, Ramsey D, Funder J, Bobik A. Eplerenone suppresses constrictive remodeling and collagen accumulation after angioplasty in porcine coronary arteries. *Circulation.* 2001, 104: 467–472.

34. Hatakeyama H, Miyamori I, Fujita T, Takeda Y, Takeda R, Yamamoto H. Vascular aldosterone. Biosynthesis and a link to angiotensin II-induced hypertrophy of vascular smooth muscle cells. *J. Biol. Chem*., 1994, 269; 24316–24320.

35. Safar ME. Systolic blood pressure, pulse pressure and arterial stiffness as cardiovascular risk factors. *Curr Opin Nephrol Hypertens*., 2001, 10: 257–261.

36. Epstein M. Aldosterone and the hypertensive kidney: its emerging role as a mediator of progressive renal dysfunction: a paradigm shift. *J Hypertens*., 2001, 19: 829–842.

37. Stowasser M. New perspectives on the role of aldosterone excess in cardiovascular disease. *Clin Exp Pharmacol Physiol*. 2001, 28: 783–791.

38. Rocha R, Martin-Berger CL, Yang PC, Scherrer R, Delyani J, McMahon E. Selective aldosterone blockade prevents angiotensin II/salt-induced vascular inflammation in the rat heart. *Endocrinology*, 2002, 143: 4828–4836.

39. Sanz-Rosa D, Cediel E, de las Heras N, Miana M, Balfagon G, Lahera V, Cachofeiro V. Participation of aldosterone in the vascular inflammatory response of spontaneously hypertensive rats: role of the NFkappaB/IkappaB system. *J Hypertens*. , 2005, 23; 1167-1172.

40. Rocha R, Rudolph AE, Frierdich GE, Nachowiak DA, Kekec BK, Blomme EA, McMahon EG, Delyani JA. Aldosterone induces a vascular inflammatory phenotype in the rat heart. *Am J Physiol Heart Circ Physiol*. , 2002, 283: H1802-1810.

41. Rizzoni D, Castellano M, Porteri E, Bettoni G, Muiesan ML, Agabiti-Rosei E. Vascular structural and functional alterations before and after the development of hypertension in SHR. *Am J Hypertens*., 1994, 7:193–200.

42. Lahera V, Cachofeiro V, Balfagon G, Rodicio JL, Aldosterone and its blockade: a cardiovascular and renal perspective. *ScientificWorldJournal*., 2006, 6: 413-424.

43. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*, 2002, 105:1135–1143.

44. Sun Y, Zhang J, Lu L, Chen SS, Quinn MT, Weber KT. Aldosterone-induced inflammation in the rat heart : role of oxidative stress. *Am J Pathol*., 2002, 161:1773-1181.

45. Joffe HV, Adler GK. Effect of aldosterone and mineralocorticoid receptor blockade on vascular inflammation. *Heart Fail Rev*., 2005, 10:31-37.

46. de Winther MP, Kanters E, Kraal G, Hofker MH. Nuclear factor kappaB signaling in atherogenesis. *Arterioscler Thromb Vasc Biol*., 2005, 25: 904-914.

47. Kobayashi N, Hara K, Tojo A, Onozato ML, Honda T, Yoshida K, Mita S, Nakano S, Tsubokou Y, Matsuoka H. Eplerenone shows renoprotective effect by reducing LOX-1-mediated adhesion molecule, PKCε-MAPK-p90RSK, and Rho-kinase pathway. *Hypertension. ,* 2005, 45:538–544.

48. Mihailidou AS, Mardini M, Funder JW. Rapid, nongenomic effects of aldosterone in the heart mediated by epsilon protein kinase C. *Endocrinology*, 2005, 145:773–780.