REVIEW

Aldosterone as a Cardiovascular Risk Hormone

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Abstract. The pathophysiological role of aldosterone in the development of cardiovascular disease has long been considered to be due its potent volume expansion/hypertensive effect mainly via mineralocorticoid receptor (MR) expressed in renal tubular epithelial cells. However, recent accumulating lines of evidence from clinical and experimental studies have suggested that direct cardiovascular effect of aldosterone contributes to the development of cardiovascular injury via MRs in non-epithelial tissue. A series of recent clinical studies have revealed that patients with primary aldosteronism have higher incidence of cardiovascular and renal complications than those with essential hypertension, and that aldosterone antagonism has cardiovascular protective effect in patients with heart failure independent from blood pressure. Numerous experimental studies have shown that both inflammation and oxidative stress play an initial and key role in the development of aldosterone-induced cardiovascular injury via non-epithelial MR activation. In this review, we discuss recent research progress in aldosterone and MR effects, with special emphasis on the pathophysiological role of aldosterone in cardiovascular diseases and the possible molecular mechanism(s) of cardiovascular injury by non-epithelial MR activation.

Key words: Aldosterone, Mineralocorticoid receptor, Vascular, Oxidative stress, Angiotensin

(*Endocrine Journal* 54: 359–370, 2007)

IT was the early 1950s that Simpson, Tait, and others isolated for the first time aldosterone, initially termed ‘electrocortin’, as a salt-retaining substance from the adrenal extracts [1]. Since then, it has been appreciated for a long time that aldosterone is a key hormone that regulates extracellular fluid volume and sodium/potassium homeostasis. From the classical endocrinological point of view, aldosterone produced by and secreted from adrenal glomerulosa in response to angiotensin (Ang) II, ACTH, and potassium, binds to mineralocorticoid receptor (MR) in epithelial cells, including distal nephron of the kidney, colon, and salivary and sweat glands, thereby leading to increases in sodium and water absorption and potassium excretion [2–4].

Under physiological and pathological conditions, renin-angiotensin-aldosterone system (RAAS) plays a

key role in cardiovascular homeostasis, whose inappropriate activation is responsible for the development of cardiovascular disease [5–7]. Indeed, an accumulating body of evidence from numerous clinical and experimental studies using angiotensin-converting enzyme (ACE) inhibitors and Ang II type 1 receptor (ATI) blockers (ARB) has underscored the pathophysiological significance of Ang II-induced cardiovascular injury and its underlying molecular and cellular mechanism(s) [5–12]. On the other hand, the pathophysiological role of aldosterone in the development of cardiovascular disease has been less appreciated.

However, two recent clinical studies, Randomized Aldactone Evaluation Study (RALES) [13] and Eplerenone Neurohormonal Efficacy and Survival Study (EPHESUS) [14], in which MR antagonists were used for heart failure patients, have uncovered the importance of aldosterone and clinical benefit of MR antagonism in cardiovascular disease. Numerous experimental studies have also shown that the pathophysiological role of aldosterone in cardiovascular disease is mediated not merely by its volume expansion/

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hypertensive effect, but also by its pro-inflammatory action through MR activation in non-epithelial cells of cardiovascular tissue [15, 16]. This review focuses specifically on the current concept of aldosterone-induced cardiovascular injury and its possible underlying cellular and molecular mechanisms.

Pathophysiological role of aldosterone in cardiovascular disease

Evidence from clinical studies

For many years, primary aldosteronism (PA) has been considered as a rare cause of secondary hypertension. However, recent development of the diagnostic screening test for measurement of aldosterone/renin ratio (ARR) and its accurate localization by adrenal venous sampling highlighted higher incidence of PA (5–15% among unselected hypertensive patients) than previously thought [17–20]. Furthermore, it has been shown that PA patients have increased incidence of left ventricular hypertrophy (LVH), proteinuria, and stroke, arguing against the classical paradigm that PA has less cardiovascular events than other forms of hypertension [21–24]. Moreover, several clinical studies have shown that PA patients have shown a higher incidence of proteinuria, cerebral hemorrhage, and LVH than did matched age- and sex- essential hypertension (EHT) patients despite higher blood pressure and longer duration in EHT group [22–24]. These results suggest that aldosterone is directly involved in the development of cardiovascular injury by the mechanism(s) other than its sodium-water retention and hypertensive effect.

The possible relationship between aldosterone and cardiac disease has been well recognized until early 1990's. Duprez *et al.* reported a significant correlation between plasma aldosterone concentrations (PAC) and left ventricular mass in mild to moderate, untreated EHT patients [25]. In addition, Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) revealed a significant positive correlation between PAC and the mortality rate in congestive heart failure patients [26]. However, recent reports from the Framingham Offspring Study have shown that the relationship between PAC and cardiovascular disease appears to be more complex than originally thought [27, 28]. In normotensive population, increased PAC

even within the physiological ranges was predisposed to the development of hypertension [28]. In population free of myocardial infarction and heart failure, PAC was positively correlated with concentric left ventricular remodeling and inversely with left ventricular diastolic dimension in women, but not in men [27].

The most convincing lines of evidence to support the importance of aldosterone on cardiovascular disease have been drawn from the recent clinical trials using MR antagonists in cardiovascular disease [13, 14, 29]. In RALES trial, low-dose (12.5 mg) of spironolactone, a non-selective MR antagonist, combined with the best tailored conventional therapy (ACE inhibitor, diuretics, *etc.*), led to a striking improvement in both the morbidity and the mortality by 30% and 35%, respectively, in moderate to severe heart failure patients [13]. In EPHEsus trial, eplerenone (EPL), a new selective MR antagonist, has been shown to decrease the rate of death from any cause and cardiovascular causes by 15% and 17%, respectively, in patients with heart failure after myocardial infarction (MI) [14]. In the 4E (Eplerenone, Enalapril, and Eplerenone/Enalapril)-LVH Study, EPL has been shown to be as effective as ACE inhibitor, enalapril, in regression of LVH and blood pressure control in EHT patients with LVH [29]. This study also confirmed that the combination of EPL and enalapril was more effective in reducing LVH and blood pressure than enalapril alone [29]. Thus, aldosterone antagonism could cause cardiovascular protection in cardiovascular disease even under normal PACs.

Evidence from experimental animal models

The pathophysiological role of aldosterone in cardiovascular injury has long been considered mainly by its volume expansion and blood pressure-elevating effects. However, numerous lines of evidence have emerged to support the direct role of aldosterone in cardiovascular injury through the mechanism independent of its salt-water retention and hypertensive effects [15, 16, 30].

Brilla *et al.* have shown for the first time that administration of aldosterone with high-salt intake causes hypertension, cardiac hypertrophy with ventricular fibrosis [31, 32]. In addition, administration of low doses of spironolactone reversed the aldosterone-induced cardiac hypertrophy with minimal changes in blood

pressure [31, 32]. Since then, several studies have provided and confirmed the similar results that aldosterone (or mineralocorticoids) under high-salt intake induces cardiovascular injury independent of blood pressure or hypokalemia, suggesting its direct cardiovascular effect rather than its hemodynamic effect [33, 34].

The cardiovascular protective effects by MR antagonism through blood pressure-independent mechanism have been also observed in other hypertensive animal models with activated RAAS, such as Ang II/salt hypertensive rats or stroke-prone spontaneously hypertensive rats (SHR-SP) [35–38]. For example, Rocha *et al.* reported that myocardial and vascular injury induced by Ang II/salt treatment was almost prevented by EPL treatment or adrenalectomy without affecting blood pressure, and that such cardioprotective effect by adrenalectomy was completely abolished by aldosterone administration [36]. The same protective effect of aldosterone antagonism on renovascular and/or cerebrovascular injury, independent of hemodynamic effect, has been demonstrated in Ang II/salt hypertensive, Ang II/L-NAME, and SHR-SP rats [35, 37, 38]. These findings suggest that aldosterone, independent of RAAS, plays a pivotal role in pathophysiology of cardiovascular injury.

Moreover, recent studies have shown that the cardiovascular protective effect of aldosterone antagonism is also applicable to atherosclerotic animal models. Rajagopalan *et al.* have reported for the first time that EPL improved endothelium-dependent vasorelaxation and reduced vascular superoxide generation and NAD(P)H oxidase activities in diet-induced hypercholesterolemic rabbits [39]. A similar cardiovascular protective effect of aldosterone antagonism was confirmed in atherosclerotic animal models, such as apoE-deficient mice and high cholesterol-fed monkey; EPL reduced intimal thickness, vascular inflammation, oxidative stress, and restored endothelium-dependent vasorelaxation [40, 41]. It should be noted

that EPL did not affect blood pressure or serum cholesterol levels in each atherosclerotic animal model. It is thus apparent that the anti-atherosclerotic effect of aldosterone antagonism is mediated by its direct vascular effect.

The beneficial role of aldosterone antagonism has also been demonstrated in experimental animal models of myocardial ischemia and heart failure [16, 42, 43]. Cardiac remodeling after MI causes initially adaptive, but later deleterious effect on myocardial function, resulting in expansion of infarct size, ventricular dilation, and excessive cardiac fibrosis. The effect of EPL treatment on these maladaptive cardiac remodeling has been extensively studied using post-MI rats [42]. Administration of EPL improved cardiac function, such as positive developed pressure over time (dp/dt), ejection fraction (EF), left ventricular end diastolic pressure (LVEDP), possibly due to the protection against reactive fibrosis in the viable myocardium rather than affecting infarct healing. In canine heart failure model caused by intracoronary microembolization, EPL treatment also improved cardiac function (left ventricular end-diastolic volume, LVEDP, and EF) with concomitant reduction in cardiomyocyte cross-sectional area and reactive cardiac fibrosis [43]. Taken together, all these findings support the contention that aldosterone has direct action on cardiovascular tissue via nonepithelial MR as a risk hormone.

MR activation in epithelial and non-epithelial cells

Structure of MR

MR, a member of the steroid hormone receptor (SHR) superfamily, functions as a ligand-dependent transcriptional factor [3, 4]. The MR comprises three major domains: N-terminal domain, DNA-binding domain, and ligand binding domain (LBD) [44] (Fig. 1).

Fig. 1. Structure of mineralocorticoid receptor (MR)

Schematic representation of functional domain of MR is depicted. Amino acid numbering is based on the human MR sequence.

The DNA binding domain contains binding site to the consensus sequence on the promoter/enhancer region of target genes, so-called "hormone-responsive element", with a high sequence homology (90%) among other SHRs [45]. The LBD with a moderate sequence homology (~60%) possesses a strong structural conservation with glucocorticoid receptor (GR); aldosterone, cortisol, and corticosterone exhibit similar binding affinity for MR [44, 46]. In the absence of ligand, MR associates with heat-shock proteins (HSP), which tether MR predominantly in the cytoplasm. When ligand binds to MR, its conformational change leads to dissociation of HSPs and translocation of the MR-ligand complex to the nucleus, where it binds to the promoter region of target genes to regulate transcription [47, 48]. The N-terminal domain with a low sequence homology (~15%) contains several lysine residues modified by a small ubiquitin-related modifier (SUMO) [3], which plays a potential role in transcriptional repression [49]. It has also been shown that the N-terminal domain contains a trans-activation function [50]. Therefore, the N-terminal domain is involved in the transcriptional regulation of MR.

MR activation in epithelial tissue

Although MR is the principal effector of the cellular response to aldosterone, both cortisol and aldosterone bind to MR with almost equal binding affinity. Moreover, given that plasma concentration of cortisol (corticosterone in rodents) is at least two orders of magnitude greater than that of aldosterone, MR could be exclusively occupied by cortisol unless there exists a regulatory mechanism that determines the specificity for aldosterone-MR interaction. It is now established that the specificity of MR occupancy by aldosterone in epithelial cells is determined at a pre-receptor level by 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) [4, 51]. 11 β -HSD2 metabolizes biological active cortisol to inactive cortisone (corticosterone to 11-deoxycorticosterone in rodents); 11 β -HSD2 co-expressed with MR in epithelial cells protects MR from cortisol access [51] (Fig. 2a). The importance of this mechanism is exemplified by the syndrome of apparent mineralocorticoid excess (AME), a condition characterized by severe juvenile hypertension and hypokalemia due to inactivating mutation of 11 β -HSD2 in the presence of suppressed PRA and PAC [51]. Other AME syndrome includes pseudoaldosteronism

due to licorice ingestion and glycyrrhizic acid both of which inhibit 11 β -HSD2 in renal tubular cells.

MR activation in non-epithelial tissue

After the molecular cloning of MR in the late 1980's [44], MR has been shown to be expressed not only in epithelial cells of the kidney, colon, and salivary and sweat glands, but also in non-epithelial cells in the brain, heart, and vascular tissues [52]. On the other hand, it has been also shown that amount of 11 β -HSD2 in non-epithelial cells of the cardiovascular tissue is much less than that in epithelial cells; very low levels in vascular smooth muscle cells (VSMC) and endothelial cells (EC) and negligible levels in cardiomyocytes [2, 15]. Since MR in non-epithelial cells should be exclusively occupied by glucocorticoids with very limited accessible aldosterone, non-epithelial cells in the cardiovascular tissue have not been considered as a target for aldosterone. However, recent clinical and experimental evidence on cardiovascular effect by aldosterone has shed the light on the significance of MR activation in such non-epithelial cells.

Differential roles of aldosterone and cortisol in the non-epithelial MR had been already reported in the early 1990's [53, 54]. Gomez-Sanchez reported that intracerebroventricular infusion of aldosterone caused hypertension, whose effect was antagonized by the concomitant infusion of corticosterone, but not by a selective GR agonist, RU26988 [53], suggesting that aldosterone action is prevented by glucocorticoid by its competitive binding to MR in the brain. The same antagonizing effect of glucocorticoids on cardiac MR was also shown by Funder's group [54]; in cardiac hypertrophy induced by aldosterone/salt hypertension, the concomitant administration of corticosterone blunted blood pressure elevation and cardiac fibrosis. In addition, cardiomyocytes hypertrophy induced by aldosterone was suppressed by co-treatment with corticosterone *in vitro* [55]. These findings from pharmacological experiments were confirmed by the experiment using transgenic (TG) mice selectively overexpressing 11 β -HSD2 in cardiomyocytes [56]; TG mice developed severe cardiac hypertrophy with rapid progression to decompensated heart failure in the absence of hypertension, whose structural and functional sequels were ameliorated by treatment with EPL. Collectively, these results suggest that, unlike MRs in epithelial tissue, glucocorticoids block rather

Fig. 2. Mechanism of MR activation in epithelial and non-epithelial cells.

a) In epithelial cells, 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) which metabolizes active cortisol to inactive cortisone (or corticosterone to 11-deoxycorticosterone in rodents) determines ligand specificity for MR by protecting MR from cortisol access.

b) In the steady state of non-epithelial cells, "the MRs preoccupied by glucocorticoids in physiological concentrations" prevent themselves from activation by aldosterone under low 11 β -HSD2 activity. The increased aldosterone accessible to non-epithelial MRs somehow induces MR activation, thereby leading to functional and structural changes in cardiovascular tissue.

than activate MRs in non-epithelial tissue. Therefore, quite distinct from the classical concept of epithelial MR regulation, a novel concept of non-epithelial MR regulation has been postulated. That is, "the pre-occupied MRs by glucocorticoids in physiological concentrations" prevent themselves from activation by aldosterone in cardiovascular non-epithelial tissue with negligible levels of 11 β -HSD2. Thus, the increased aldosterone accessible to MRs through yet unknown mechanism(s) could induce MR activation, thereby leading to functional and structural sequels in cardiovascular tissue (Fig. 2b).

The molecular mechanism(s) underlying MR activation in non-epithelial tissue remains unknown. One possible explanation is that extra-adrenal synthesis of aldosterone may function as a potential autocrine/paracrine factor in cardiovascular tissue, whose concentrations should be higher than those in plasma. Indeed, there have been several lines of evidence supporting this possibility; expression of aldosterone synthase (CYP11B2) mRNA and aldosterone production in rodent vascular tissue [57, 58]; expression of CYP11B2 mRNA regulated by Ang II and low-salt/high-potassium in rat cardiac tissue [59]; expression of

CYP11B2 mRNA in human cardiovascular tissue [60, 61]. Moreover, the possible production of aldosterone by the human failing left ventricle has been reported, deduced from the sampling data of higher aldosterone levels from coronary-sinus than those from aorta obtained during cardiac catheterization [62]. These results argue for the extra-adrenal synthesis of aldosterone, such as in cardiovascular tissue. On the contrary, a number of contradictory results have been also reported. For example, Gomez-Sanchez *et al.* have recently reported that ventricular CYP11B2 mRNA levels are far less than those in the adrenal glands, and that cardiac aldosterone levels are comparable to plasma levels in rats under the different salt-intake conditions [63]. Furthermore, Ang II stimulation of CYP11B2 mRNA and protein expression as well as aldosterone synthesis in rat cardiac tissue has not been confirmed [64]. It remains to be determined whether the extra-adrenal synthesis of aldosterone and its paracrine action could indeed cause the activation of non-epithelial MRs in cardiovascular tissue in physiological or even suppressed PAC.

A novel and intriguing hypothesis for MR activation in non-epithelial tissue has recently been proposed by

Funder's group [15]. That is, glucocorticoid-MR complex, which is inactive under the steady-state condition, can be activated by lowering NADH levels and/or generation of reactive oxygen species (ROS) during local inflammatory response [15]. This postulated mechanism could well explain the paradox of aldosterone-induced cardiovascular injury even in the physiological PAC. The possible positive feedback system may exist, whereby inflammation and oxidative stress activate glucocorticoid-MR complex to exacerbate further inflammation. Should such a vicious cycle operate, cardiovascular MR might function as a 'death receptor'. This intriguing hypothesis is based on the fact that 11 β -HSD2 does not only convert cortisol to cortisone, but also co-substrate NAD to NADH, an important determinant of cellular redox states [65]. The differential redox-dependent modifications of MR and GR activity [66, 67], and the importance of NADH in transcriptional repression through its co-repressor activation have been suggested [68, 69]. Alternatively, this phenomenon can also be explained by mechanisms that certain conformational changes of MR protein occurs by specific changes of cellular context induced by inflammation or oxidative stress. However, further studies are necessary to prove whether redox-sensitive transcriptional co-factor(s) and/or conformational changes of MR are involved in the regulation of MR activation in non-epithelial tissue.

MR activation and cardiovascular injury

The mechanism(s) by which non-epithelial MR activation contributes to the development of cardiovascular injury is currently one of the interesting subjects

under intensive investigations. It has been shown that the hallmark of aldosterone-induced cardiovascular injury is vascular inflammation and perivascular fibrosis preceded by monocytes/macrophages infiltration in coronary, renal, or cerebral arteries [35, 37] (Fig. 3). A series of recent studies further revealed that increased expression of pro-inflammatory genes, such as VCAM-1, COX-2, and osteopontin, are preceded by 'aldosterone-induced vasculitis' [30, 36, 70]. We have also demonstrated that physiological concentrations of aldosterone (as low as 10^{-10} M) directly acts on endothelial cells to induce osteopontin gene expression through the non-epithelial MR activation [71]. Since these inflammatory responses have been shown to be substantially abolished by treatment with MR antagonist independent of lowering blood pressure, it is assumable that MR activation in cardiovascular tissue plays a critical role in the initiation and the development of vascular inflammatory response. If that is the case, what causes inflammatory response after MR activation in cardiovascular tissue? The overall mechanism has not been fully understood yet, but two possible mechanisms could be postulated as discussed below.

Oxidative stress

It has been well established that Ang II-mediated oxidative stress is responsible for the development of cardiovascular injury through the inflammatory response [5, 7, 11, 12]. In other words, oxidative stress mainly generated by NAD(P)H oxidase induces redox-sensitive pro-inflammatory gene expression in vascu-

Fig. 3. Aldosterone induces vascular inflammatory changes in coronary artery via MR activation. Representative photomicrographs of control (a) control rats, (b) rats treated with aldosterone and high-salt (Aldo-rats), and (c) Aldo-rats co-treated with a MR antagonist, eplerenone. Vascular inflammatory response, including cellular infiltration and fibrotic change in perivascular space were observed in the coronary artery in Aldo-rats (b), whose effect was ameliorated by co-treatment with eplerenone (c). (unpublished data by Yoshimoto *et al.*; Masson-trichrome stain, magnification: $\times 200$)

lar cells. It has already been shown that aldosterone is partly responsible for the Ang II-induced oxidative stress and cardiovascular injury based on the amelioration of the Ang II-induced vascular inflammation and oxidative stress by spironolactone [72]. Enhanced NAD(P)H oxidase gene expression and activity and superoxide formation in cardiovascular tissue have been shown in aldosterone- (or other mineralocorticoid)-induced hypertensive rats, whose effects were substantially abolished by MR antagonists with only a minimal change in blood pressure [73–78]. Furthermore, cardiovascular inflammatory phenotype induced by aldosterone has been substantially ameliorated by co-treatment with anti-oxidants and/or NAD(P)H oxidase inhibitors [74, 78, 79]. These experimental results suggest that oxidative stress induced by NAD(P)H oxidase plays a major role in the aldosterone-induced cardiovascular injury through the non-epithelial MR activation. It is therefore assumable that aldosterone-induced oxidative stress stimulates a series of pro-inflammatory genes expression, such as adhesion molecules and chemokine, via a redox-sensitive mechanism, thereby leading to initiation of cardiovascular inflammatory phenotype. The increased oxidative stress may also lead the further activation of MRs preoccupied by glucocorticoids, thus accounting for the vicious cycle of the aldosterone-induced cardiovascular injury [15]. However, the molecular mechanism underlying NAD(P)H oxidase expression and activation after MR activation remains to be determined.

Ang II

The involvement of Ang II in the development of aldosterone-induced cardiovascular injury has been shown by several *in vitro* and *in vivo* studies; aldosterone up-regulates the expression of AT1 receptors in VSMC and cardiomyocytes [80, 81]; the intracellular Ang II signaling is enhanced by the co-treatment with aldosterone in VSMC [82, 83]. Furthermore, it has been recently reported that aldosterone upregulates angiotensin-converting enzyme (ACE) gene expression in neonatal rat cardiomyocytes [84] and EC [85]; aldosterone in physiological concentrations (as low as 3×10^{-9} M) induces ACE gene expression and its enzyme activity mainly via MR-mediated pathway in rat EC (Fig. 4). However, we have also shown that a glucocorticoid receptor (GR) antagonist, RU486, partially but significantly inhibits the aldosterone-induced ACE gene expression [85], suggesting a possible involvement of GR as well as MR in the aldosterone-induced endothelial ACE expression.

ACE is currently recognized as an important risk factor for the development of cardiovascular injury [86–88]. While renin is a rate-limiting enzyme for Ang II generation in systemic RAS, ACE is a key enzyme for Ang II generation in local RAS. It is thus assumable that cardiovascular ACE upregulation by aldosterone increases local Ang II generation. Taken together with the upregulation of T1 receptor and enhancement of its intracellular signaling by aldosterone, it is strongly suggested that local RAS is responsible for the development of aldosterone-induced cardiovascular injury. In agreement with this assumption,

Fig. 4. Aldosterone induces ACE gene expression via MR-mediated pathway in rat aortic endothelial cells. Aldosterone dose-dependently increased ACE mRNA levels in rat aortic endothelial cells, whose effect was blocked by a MR antagonist, spironolactone. ACE mRNA levels were measured by real-time RT-PCR.

Fig. 5. “Vicious cycle” by aldosterone in local renin-angiotensin system (RAS).

Aldosterone up-regulates ACE and AT1 receptor and potentiates the AT1 post-receptor signaling, thereby increasing local action of Ang II, which may partly contribute to aldosterone-induced cardiovascular injury in a “vicious cycle”. ARB: Ang II type 1 receptor (AT1) antagonist.

it has recently been reported that AT1 receptor antagonist, Losartan, partly but significantly, prevented aldosterone-induced hypertension, cardiac fibrosis, and ROS generations in cardiovascular tissue [74]. As systemic RAS is completely suppressed under the aldosterone-excess state, it is suggested that Ang II locally generated via MR activation partly contributes to the development of aldosterone-induced cardiovascular injury in the “vicious cycle” (Fig. 5). However, since these findings are largely obtained from experimental animal models *in vivo* and cell experiments *in vitro*, the pathophysiological significance of

augmented Ang II action by aldosterone remains elusive in human cardiovascular disease.

Conclusion

In contrast to the classical concept that aldosterone is only involved in body electrolyte and water homeostasis mainly mediated by the kidney, a growing body of recent evidence suggests that aldosterone exerts its pathophysiological effects on non-epithelial MRs in cardiovascular system. However, the current understanding of the mechanism(s) of non-epithelial MR activation and its intracellular signaling cascade remains unknown. Elucidation of the molecular mechanism(s) of ligand-dependent transcriptional regulation by MR and GR in non-epithelial tissue will help to understand the pathophysiological role of aldosterone as a cardiovascular risk hormone as well as the therapeutic benefit of MR antagonists in patients with cardiovascular disease.

Acknowledgement

We are grateful to Drs. Toru Sugiyama, Yuki Hirono, Maya Skurada, and Ms. Noriko Suzuki for their research and technical contribution. The work cited was supported in part by Grants-in-aid from the Ministry of Education, Science, Sports and Culture, and the Ministry of Health, Welfare and Labor, of Japan.

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