Endocrine
https://doi.org/10.1007/s12020-018-1610-8

REVIEW

The emerging role of aldosterone/mineralocorticoid receptors in the pathogenesis of erectile dysfunction

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Received: 4 January 2018 / Accepted: 17 April 2018

Abstract

Purpose Aldosterone is an old hormone that has been discovered for more than fifty years. The clinical application of its receptors' inhibitors, especially spirolactone, has benifited patients for decades worldwide. In this review, we briefly summarized the molecular mechanism of aldosterone/mineralocorticoid receptors (Ald-MRs) signaling in cardiovascular diseases and its emerging role in erectile dysfunction.

Methods We searched PubMed, Web of Science, and Scopus for manuscripts published prior to December 2017 using key words " aldosterone " AND " erectile dysfunction " OR " cardiovascular disease " OR " mineralocorticoid receptors ". Related literature and clinical perspectives were collated, summarized and discussed in this review.

Results The increase of reactive oxygen species production, inhibition of endothelial nitric oxide synthase system, and induction of inflammation are ubiquitous in vascular endothelial cells or vascular smooth muscle cells after the activation of Ald-MRs pathway. In addition, in cardiovascular diseases with over-active Ald-MRs signaling, MRs blockade could reverse the injury and improve the prognosis. Notably, multiple studies have correlated aldosterone and MRs to the pathogenesis of erectile function, while the mechanism is largely unperfectly identified.

Conclusion In conclusion, we summarize the current evidence to highlight the potential role of aldosterone in erectile dysfunction and provide critical insights into the treatment of the disease.

Keywords Aldosterone · Erectile dysfunction · Cardiovascular disease · Receptors

Introduction

Aldosterone (Ald) is the primary mineralocorticoid hormone, which was mainly synthesized by the glomerular zone of the adrenal cortex in response to hyperkalemia or sodium depletion [1]. In addition, a number of peripheral tissues can produce local Ald as well and perform different functions apart from the effects in distal neprhone [2]. Ald binds to mineralocorticoid receptors (MRs) forming a Ald-MRs complex, which subsequently binds to the glucocorticoid response elements of Ald target genes [3]. The activation of aldosterone/mineralocorticoid receptors (Ald-MRs) signaling has been demonstated to play a pivotal role in cardiovascular disease, psychological stress, as well as stroke [4]. More recently, increasing evidence indicated that Ald-MRs activation also participate in the pathogenesis of erectile dysfunction (ED).

As the life expectancy of human beings is approaching 80 years in many countries, ED become a serious problem that impacting 50% men over 60 and 75% men over 70 [5–7]. Worldwide, it is estimated that the number of ED patients would be approximately 322 million in 2025 [8]. In addition, ED becomes more challenging for managing when it occurs in young men [9]. ED shares multiple risk factors with cardiovascular diseases and frequently occurs in patients with hypertension, heart failure or metabolic diseases. Cardiovascular comorbidities, including hypertension and coronary heart disease, diabetes, metabolic syndrome, and depression have been demonstrated to be independent risk factors for the pathogenesis of

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Published online: 02 May 2018

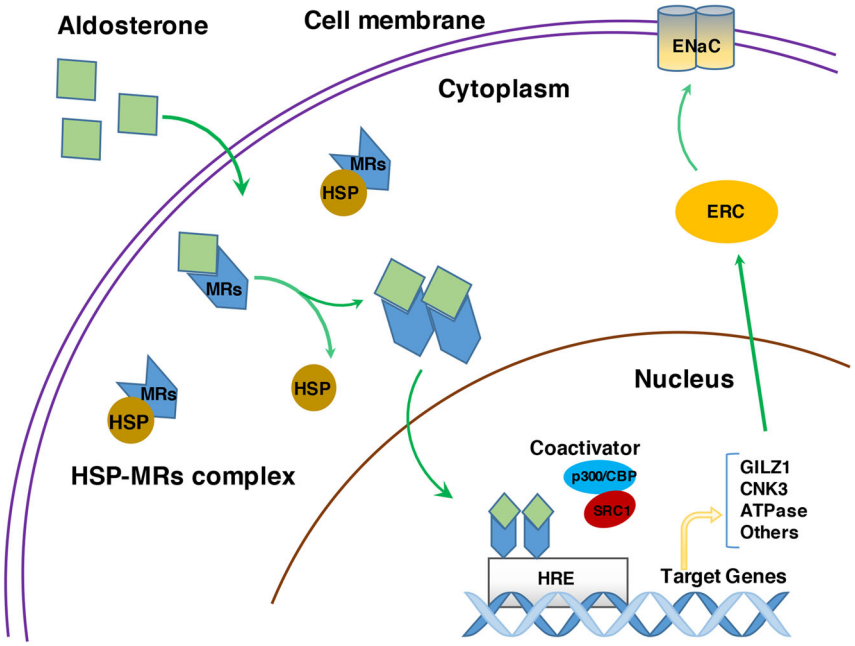

Fig. 1 The canonical aldosterone-mineralocorticoid receptors (Ald-MRs) signaling on sodium transport. The classical Ald-MRs signaling on sodium transport in the kidney involves activation of the MRs, resulting in its dissociation from chaperone molecules, its translocation into the cell nucleus, and the binding to hormone response elements (HRE) in the target gene to enhance the expression of downstream regulators

ED [10, 11]. In addition, lifestyle factors, such as exercise, smoking, and body mass index have all been linked to ED [12–14].

ED is characterized by the consistent inability to attain or maintain a penis erection that are sufficient to complete a satisfactory sexual intercourse. A satisfactory erection is controlled and completed by the orchestration of central and peripheral neural system, cardiovascular and hormonal system. Impairment of any of the above systems could lead to the occurrence of ED. Of all the reasons causing ED, hormonal factors have been the least studied. Although the molecular mechanism of the hormone on sexual function is largely unclear, hormone levels altered significantly with age in men, with the testosterone and growth hormone (GH) decreased [15]. Some hormone disorders, such as hyperprolactinemia, has been investigated and demonstrated for its cause and effect with ED [16]. However, the role of most hormones, including testosterone, thyroxine, dehydroepiandrosterone (DHEA/S) or Ald in ED remains unclear [15, 17–21]. It has been reported that MRs exists in human penile corpus cavernosum, and its physiological effect in vitro might be enhancing the noradrenaline-induced contraction [22, 23]. More recently, elevated plasma Ald concentration has been demonstrated to be an independent risk factor for ED [24]. To date, the role of Ald-MRs signaling in ED has not been summarized. Here, we review literature of the Ald-MRs signaling pathway as well as its emerging roles in ED and shed light on the research of this virgin field.

The canonical and non-canonical Ald-MRs signaling

The canonical ALD-MRs signaling on sodium transport

The classical Ald-MRs signaling on sodium transport in the kidney involves activation of the MRs, resulting in its dissociation from chaperone molecules, its translocation into the cell nucleus, and the binding to hormone response elements (HRE) in the target gene to enhance the expression of downstream regulators [25] (Fig. 1). Moreover, peripheral tissues, such as brain and vascular wall, could also produce Ald, which playing critical roles in multiple biological functions [26, 27]. The renin-angiotensin-aldosterone system (RAAS) is one of the most important systems in controlling the cardiovascular system, as well as participating in the pathogenesis of cardiovascular diseases. With RAAS activation, the physiological role of Ald is stimulating the reabsorption of sodium and the secretion of potassium, one of the most critical step maintaining blood pressure and extracellular fluid volume in most vertebrates [28]. In Ald-sensitive distal nephrons, sodium, potassium and water are highly regulated by a wide variety of stimuli, especially endocrine hormones. The epithelial sodium channel (ENaC) and the aquaporin 2 (AQP2) water channel of principle cells are the two most important members, of which ENaC is regulated by Ald and AQP2 by arginine vasopressin (AVP). In principal cells of the Ald-sensitive distal nephron, ENaC regulates the apical entry of sodium and play a role in the

rate-determining step for transepithelial sodium transportation. The Ald signaling has been demonstrated to regulate the formation and stability of the functional ENaC regulatory complex (ERC) through inducing chaperone (GILZ1) and a scaffold protein (CNK3) [29, 30]. As a result, the density of ENaC at apical membrane could elevate for two to five fold [31]. This effect of Ald in principal cells is mediated by the MRs, which can trigger the expression of a number of genes [32]. In addition, Ald signaling can activate the sodium pump through inducing the transcription of both the α and β subunits of the Na-K-ATPase [33] (Fig. 1). It is worth noting that glucocorticoid hormones bind to MRs with the similar affinity with Ald. And the abundance of circulating glucocorticoid hormones is 10^2 to 10^3 fold higher than Ald. However, the binding between MRs and Ald is highly selective in vivo due to the coexpression of the enzyme 11 beta-hydroxysteroid dehydrogenase type 2 (11βHSD2) [34]. Moreover, 11HSD2 metabolizes circulating glucocorticoid hormones (cortisol) into inactive 11-dehydro-derivatives (cortisone), which have low affinity for MRs [35, 36].

The non-canonical Ald-MRs signaling

The MRs exists in a variety of tissues, such brain, heart, muscle, and vasculature, in addition to the Ald-sensitive distal nephron, which means the Ald-MRs signaling is widely spread in the human body [37–41].

In the central nervous system, MRs is highly expressed in a number of brain regions, such as cerebral arteries, immune cells, striatal neurons, and hippocampal neurons [42]. In addition, the rat brain has the enzymatic machinery for the synthesis of adrenal corticosteroids as well as Ald [43]. Ald could cause inflammation in the brain through MR-dependent way, reflected by increased gene expression of CCL7, CCL8, and IL-1β [44]. Increased reactive oxygen species (ROS) production caused by Ald can be inhibited by spironolactone, which is endothelial cell MRs-mediated [44].

Basal expressions of MRs and 11βHSD2, but not 11-beta-hydroxylase (CYP11B1) or Ald synthase (CYP11B2) were found in human atria and HL-1 myocytes [45]. In atrial fibrillation (AF) the expression of MRs increased, augmenting the effects of Ald with or without the increasing of plasma or local Ald [45]. In mice with myocardial infarction, Ald has a direct toxic effect on myocardium by oxidative activation of CaMKII, inducing cardiac rupture and increased mortality [46]. In addition, Ald regulates the expression of cardiac voltage-operated Ca^{2+} channels and enhances beating in cultured neonatal rat ventricular myocytes, which contribute to the deleterious effect of an excess of this steroid in vivo on cardiac function [47]. In male Wistar rats, injections of Ald can induce significant cardiomyocyte apoptosis over the range of 100 μg to 10 mg kg^{-1} [48]. Burniston et al. [48] proposed that high circulating levels of Ald are clearly capable of damaging all types of striated muscle.

In addition to striated muscle, the Ald-MR signaling also plays a role in the skeletal muscles. The RAAS is activated in skeletal muscle wasting with accompanying cachexia, which activates the PKD1/HDAC5/TFEB/MuRF1 pathway to induce skeletal muscle atrophy [49]. Interestingly, local renin-angiotensin systems (RASs) in skeletal muscle may be a critical regulator of myoblasts during proliferation [50].

MRs are expressed in inflammatory cells such as mononuclear leukocytes [39, 51]. In angiotensin II-induced hypertension, activated T-cell contributes to the inflammatory response, and inhibition of this process could have therapeutic benefit in the treatment of this disease [52, 53]. In dendritic cells, Ald promotes the activation of MAPK pathway and the secretion of IL-6 and TGF-β1 [54]. Moreover, T-regulatory lymphocytes suppress Ald-mediated vascular injury, in part through the effect of innate and adaptive immunity [55].

In addition to the tissues mentioned above, MRs and 11βHSD2 are also expressed in vascular endothelial cells and vascular smooth muscle cells (VSMCs) [37, 56]. In rat models of Ald-induced hypertension, Ald-stimulated endothelial cells and facilitated the macrophage adhesion and infiltration, increase oxidative stress, and upregulate inflammatory genes through an MR-dependent mechanism [57–59]. With the stimulation of Ald, MRs in VSMCs promotes vascular calcification in vitro, as well as modulates endogenous gene expression [60, 61].

Last but not the least, 11βHSD2, an NAD^+-dependent enzyme expressed in Ald-selective epithelial tissues, was found to be expressed in the penile corpus cavernosum of both rats and human beings. Furthermore, MRs was presented in human penile corpus cavernosum (hPCC) [22, 62]. In addition, Muguruma et al. [23] reported that Ald had a direct effect on human penile cavernous tissue, but acts to significantly enhance the noradrenaline-induced contraction. As a result, these evidence collective indicated that Ald-MRs signaling functions actively in the penile corpus cavernosum in an unknown manner. Strinkingly, our previous data indicated that Ald has an inflammatory effect in the corpus cavernosum penis, inducing NF-κB activation via an MRs-dependent pathway, which may be prevented by selective MRs antagonists [63]. However, further investigations are needed to confirm the Ald-MRs activation in ED patients and illustrate the underlying molecular etiology of this disease.

The biological function of Ald-MRs activation

Increasing the generation of ROS

Ald not only favors renal sodium reabsorption in the distal convoluted tubule, but also has direct effects of increasing

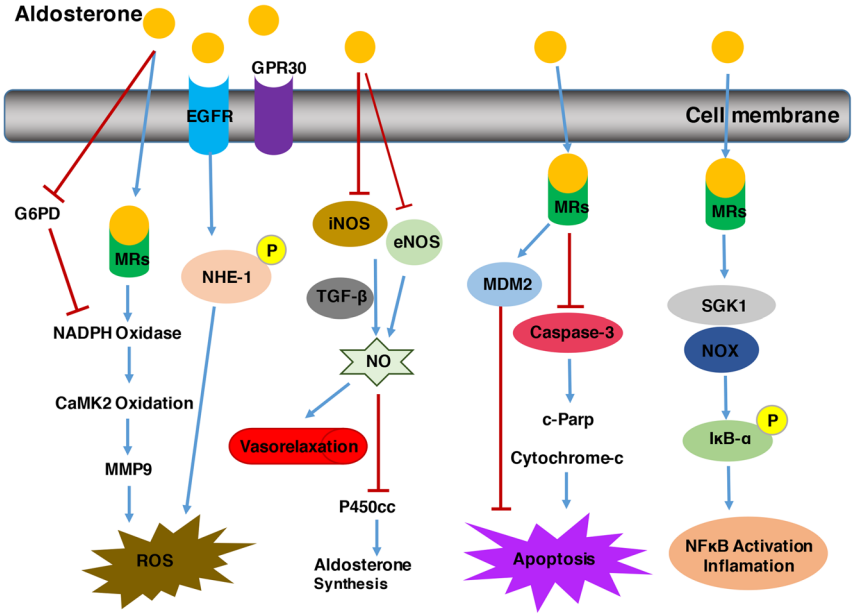

Fig. 2 A schematic figure of the biological function of aldosterone-mineralocorticoid receptors (Ald-MRs) activation. The activation of Ald-MRs pathway could cause the increase of reactive oxygen species production, inhibition of endothelial nitric oxide synthase system, and induction of inflammation

the amount of ROS [64–66]. Ald induces the generation of ROS through several mechanisms. A well-studied pathway is the direct activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and then oxidative stress by Ald in endothelial cells, heart or macrophage [59, 67, 68]. And Ald induces the decrease of glucose-6-phosphate dehydrogenase (G6PD), which is a critical determinant of the intracellular redox state, to enhance the oxidation of NADPH and impair endothelial function [69]. Ald can as well induce CaMKII oxidation by recruiting NADPH oxidase, which promotes matrix metalloproteinase 9 (MMP9) expression in cardiomyocytes [46]. This effect was confirmed and reversed by myocardial CaMKII inhibition, overexpression of methionine sulfoxide reductase A and NADPH oxidase deficiency, which could prevent the induced cardiac rupture after myocardial infarction [46]. In renal cells, it has been reported that Ald stimulates the mitochondria to generate ROS [70–72]. Exposure of podocytes to Ald reduces increased production of ROS and reversed by the mitochondrial respiratory chain complex I inhibitor [72]. Ald enhanced the cardiac Na^+/H^+ exchanger (NHE-1) activity via transactivation of the epidermal growth factor receptor (EGFR), the formation of ROS, and phosphorylation of the exchanger [73]. It is important to note that Ald could stimulate ROS production by directly activating of the G protein-coupled receptor GPR30, which means the bypass of the MRs activation [74] (Fig. 2).

Inhibition of nitric oxide synthase (NOS)

Multiple animal models have indicated that Ald induces unfavorable action in the vasculature, the effect of Ald on endothelial cells, especially on the function of endothelial NOS (eNOS), are imperfectly defined. Ald inhibited IL-1-induced iNOS expression posttranscriptionally and decrease the NO synthesis in a TGF-beta-dependent manner [75]. In human umbilical vein endothelial cells, Ald inhibits eNOS function through bimodal mechanisms of 5, 6, 7, 8-tetrahydrobiopterin deficiency and protein phosphatase 2A activation [76]. Moreover, Ald escape is causally related with upregulation of nNOS [77]. In addition, administration of a MRs inhibitor, i.e., spironolactone, prevents the decrease in eNOS in the left ventricular and aorta, and improves NO-dependent vasorelaxation [78]. There is a negative feedback regulation that NO production by adrenal zona glomerulosa cells decreases Ald synthesis [79, 80]. NO inhibits Ald production by acting on P450scc and other P450-dependent steroidogenic enzymes, and the process might be modulated by oxygen [81, 82] (Fig. 2).

Apoptosis signaling

Ald induces apoptosis through enhancing the ubiquitination and degradation of the apoptosis repressor [83]. MRs antagonism could reverse the effect and protect cardiac cells from apoptosis by preventing the degradation of apoptosis repressors [83]. In vascular endothelial cells, MR antagonism, i.e., spironolactone, also prevent apoptosis by inhibiting the activity of caspase-3, releasing of cytochrome c and cleavaged PARP in an NO-independent manner [84]. MDM2, which participates in anti-apoptosis response, can be induced by Ald in MRs-positive vascular smooth muscle cell [85]. In vivo assay shows that Ald has a myotoxic effect and triggers apoptosis in both myocyte and skeletal muscle cells [48]. On the contrary, MRs shows its survival-promoting actions in hippocamp. Antagonism of MRs

with spironolactone (SPIRO) causes a dose-dependent increase in hippocampal neuronal apoptosis in the absence of the glucocorticoid receptors (GR) agonist dexamethasone (DEX) [86] (Fig. 2).

Inflammation pathway

Ald induces inflammation and fibrosis in the heart through oxidation of NADPH and cardiac RAS [87]. This can be proved by the effect of MRs antagonism which substantially reduced NADPH oxidation and lipid peroxidation, and protects the vasculature from apoptosis [88]. Inflammation factors and oxidative stress induced by Ald and MR trigger the activation of NF-κB [89]. Ald also activates NF-κB in kidney epithelial cells lines through calcium-mediated NOX and NOS activation, or by inducing SGK1 [63, 90, 91]. In addition, the activation of NF-κB and the phosphorylation of IκB-alpha can be blocked by MRs antagonism [63, 92]. Moreover, Ald-stimulated activation of NFκB in the heart is prevented in NOX2-deficient mice [66]. However, in neutrophils, MRs has an anti-inflammatory effects when neutrophils interacting with vascular endothelial cells [51] (Fig. 2).

Remodeling pathway

Ald causes a substrate for atrial arrhythmias characterized by myocyte hypertrophy, atrial fibrosis, and disturbances of conduction [93]. MRs play a critical role in mediating the transition from left ventricular hypertrophy to failure with chronic pressure overload. The effects of MR stimulation are associated with alterations in the interstitial matrix and myocyte apoptosis and may be mediated, at least in part, by oxidative stress and inflammation [94]. In addition, the effects of Ang-II and MR activation in the heart remodeling are additive [95]. Long-term treatment with eplerenone, a MR antagonist, inhibits the progression of left ventricular dysfunction and relieves cardiac remodeling, partially by a reduction in collagen accumulation, in animal models of chronic heart failure [96, 97]. Similarly, spironolactone blocks the development of gap junction remodeling (GJR), a key remodeling process in hypertrophied hearts, and also potently reversed established GJR [98]. Comparing with MR antagonists, FAD286, an Ald synthase inhibitor, can reduce the ROS and normalize redox status, in addition to improving remodeling in experimental chronic heart failure [99].

Clinical association of Ald-MRs activation

Ald-MRs activation and diseases

As Ald maintains the electrolyte balance and plays a key role in the long-term regulation of Na^+ and K^+ in the distal tubules and collecting ducts of the kidney, the characteristic manifestation of Ald dysregulation is hypertension and hypokalemia. The classic association between Ald and hypertension has been extensively studied and reviewed, and will not be discussed in this review. Here, we focus on the non-canonical role of Ald in multiple diseases, especially sexual dysfunction, and discuss their potential connections.

As described above, Ald-MRs activation is involved in dysfunctions of central nervous system [44]. It has been proved that elevated Ald increase the risk of stroke independent of blood pressure and other risk factors [100]. MRs activation by RAAS contributes to brain infarction and post-stroke vascular death in white patients [101]. In the case of psychological disorders, low-affinity membrane version of the MRs contributes to the initial phase of psychological stress reaction, which is complemented by the GR which terminates the stress response [102]. Moreover, patients with major depression have a high functional activity of the MRs signaling [103]. The homeostasis between MRs and GRs is known to affect brain serotonin systems and may play an etiologic role in serotonin receptor changes observed in patients with major depression [103]. In both depression and aging, MRs expression in the brain, especially in the hippocampus and in the prefrontal cortex, is reduced [104].

Among all the Ald-MRs related diseases, cardiovascular diseases are of the most extensively studied. In congestive heart failure elevated Ald accounts for oxidative stress, nitrosative stress, a proinflammatory phenotype, and wasting [105]. In keeping with that, the increase of Ald in the failing ventricles is in proportion to severity, and is an independent risk factor of mortality [106, 107]. During the myocardial infarction, plasma Ald concentrations increase, and the subsequently excessive activation of Ald signaling pathways increases mortality of individuals with myocardial infarction [108, 109]. Although the underlying mechanism for this protection remains unclear, MRs antagonists, both eplerenone and spironolactone, can reduce mortality after myocardial infarction [110, 111]. Moreover, MRs antagonists also significantly decrease morbidity and mortality in heart failure patients for whom oxidative stress frequently exists [112]. In the case of prognosis, levels of plasma Ald of patients after myocardial infarction are independent predictors of survival and hospitalization for heart failure over a 5-year-follow-up period [113]. In addition, in AF, the expression of MRs and the subsequent genomic effects of Ald-MRs signaling are increased [45]. MRs expression increases in patients with chronic renal diseases, which has been reviewed elsewhere [114, 115]. Several clinical trials show that MRs antagonist slow down the progression of chronic kidney disease in diabetes patients [116, 117]. It is important to noted that in eNOS deficient mice, Ald-MRs

blockade presents more beneficial effect than RAS inhibition, which means an impaired endothelial NO response could lessen the benefit of RAS inhibition in specific diseases [118]. Moreover, it is Ald rather than Ang II plays a direct role in the pathogenesis of renal injury by L-NAME through inflammation [119].

ED has a strong association with cardiovascular diseases, and the link between them has been recently reviewed [120]. In spontaneously hypertensive rats (SHR), which displayed fewer erections, circulating levels of Ald, and relative weights of pituitary, adrenal glands, and accessory organs were equivalent with control strains [121]. As mentioned above, MRs signaling could be active in corpora cavernosa of the penis [22, 62]. And our previous study proposed the concept that increased levels of plasma Ald contribute to ED [122]. The role Ald-MRs activation in ED is supposed to share the pathogenic mechanism in cardiovascular. Therefore, whether it is active in vascular endothelial cells or VSMCs, considering that MRs activation causes various organ damages including cardiovascular injury, MRs antagonists might have therapeutic benefits and reverse the pathogenic effects of Ald-MRs signaling, such as ROS increasing, eNOS inhibition, or inflammation. However, the mechanism of Ald-MRs signaling in ED remains unclear. Investigations of the penile effects of MRs activation have the potential to provide new treatment approaches for ED. Moreover, the expression of MRs in arteries is increased with the diameter of the blood vessels [41]. In other words, MRs also expresses in capillaries and arterioles [123, 124]. Thus, the active Ald-MRs signaling is also hypothesized to chronically impact the microcirculation of hPCC and cause the pathogenesis of ED, especially in patients with elevated Ald levels.

Evidence for Ald-MRs antagonist in ED treatment

Spironolactone is the first MRs antagonist and has been used for over fifty years [125]. However, one of adverse events during spironolactone treatment was ED, in addition to gynecomastia or breast pain [111, 126, 127]. This notably estrogenic effect are caused by the progestational and antiandrogenic function of spironolactone, which competitively binds to androgen receptors [128, 129]. Eplerenone, a more selective MRs antagonists, does not show the adverse event of impotence in men during the treatment of left ventricular dysfunction and heart failure [110]. ED is even not listed as an adverse event in the Eplerenone in Mild Patients Hospitalization and SurvIval Study in Heart Failure trial (EMPHASIS-HF) [130]. In addition, a newly developed MRs antagonist BAY 94-8862, which benefited patients with heart failure and chronic kidney disease, could also be an alternative for ED therapy [131]. However, the therapeutic role of eplerenone or BAY 94-8862 for ED have not been studied and remains unknown.

As we discussed before, Ald functions can partially bypass MRs and mediated by EGFR or GPR30, which cannot be blocked by MRs antagonist. Therefore, Ald synthase inhibitors, a new class of drugs, are likely to be a promising choice to fully block the deleterious effects of Ald [132]. However, the Ald synthase in 11-β-hydroxylase step is homologous to the enzyme during the generation of cortisol. Therefore, the selectivity of Ald synthase inhibitors is the primary limitation of the currently reported inhibitors, such as LCI699 and FAD286 [133, 134]. Interestingly, insufficient production of glucocorticoids and mineralocorticoids of patients with autoimmune Addison's disease causes sexual dysfunction including ED [135]. Furthermore, the symptoms could be resolved after hormone replacement therapy [135]. Although the mechanism remains unclear, cortisol and Ald might play an essential role in the physiological erectile function. Therefore, completely blockade of might hampers the erectile function as well.

Conclusion and perspective

In conclusion, we briefly reviewed the current knowledge of Ald-MRs signaling from bench to clinics. The original aim of the review was to elucidate the role of Ald-MRs signaling in the pathogenesis of ED. However, studies about Ald or MRs in ED were insufficient to fully elucidate the mechanism. ED shared a number of risk factors with cardiovascular disease. Therefore, in this review, we discussed as well the molecular mechanism Ald-MRs signaling, and the effect of MRs antagonist in cardiovascular disease. The increase of ROS production, inhibition of eNOS system, and induction of inflammation were supposed to be ubiquitous in vascular endothelial cells or VSMCs after the stimulation of Ald-MRs. In addition, in most diseases with over-active Ald-MRs signaling, MRs blockade could reverse the injury and improve the prognosis. We suggest that further research into the signaling mechanisms underlying the effects of Ald and MRs activation in the reproductive organs, especially with erectile function, will provide important insights into causes and therapies for ED.

Acknowledgements We thanked Dr. Yang Sun for proof reading of our manuscript, and sincerely thanked the generous help from all the members of the Department of Urology, Shandong Provincial Qianfoshan Hospital, Shandong University.

Funding This work was supported by the National Natural Science Foundation of China.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. B.C. Rossier, M.E. Baker, R.A. Studerr, Epithelial sodium transport and its control by aldosterone: the story of our internal environment revisited. Physiol. Rev. **95**, 297–340 (2015)
2. P.J. Fuller, Y. Yao, J. Yang, M.J. Young, Mechanisms of ligand specificity of the mineralocorticoid receptor. J. Endocrinol. **213**, 15–24 (2012)
3. F. Jaisser, N. Farman, Emerging roles of the mineralocorticoid receptor in pathology: toward new paradigms in clinical pharmacology. Pharmacol. Rev. **68**, 49–75 (2016)
4. J.W. Funder, The role of aldosterone and mineralocorticoid receptors in cardiovascular disease. Am. J. Cardiovasc. Drugs **7**, 151–157 (2007)
5. M. Heinrich, J.M. Prieto, Diet and healthy ageing 2100: will we globalise local knowledge systems? Ageing Res. Rev. **7**, 249–274 (2008)
6. J.R. Mola, Erectile dysfunction in the older adult male. Urol. Nurs. **35**, 87–93 (2015)
7. NIH Consensus Conference. Impotence. NIH consensus development panel on impotence. JAMA **270**, 83–90 (1993)
8. I.A. Ayta, J.B. McKinlay, R.J. Krane, The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. BJU Int. **84**, 50–56 (1999)
9. S.D. Cohen, The challenge of erectile dysfunction management in the young man. Curr. Urol. Rep. **16**, 84 (2015)
10. A.D. Seftel, P. Sun, R. Swindle, The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. J. Urol. **171**, 2341–2345 (2004)
11. R.W. Lewis, K.S. Fugl-Meyer, G. Corona, R.D. Hayes, E.O. Laumann, E.D. Moreira Jr., A.H. Rellini, T. Segraves, Definitions/epidemiology/risk factors for sexual dysfunction. J. Sex. Med. **7**, 1598–1607 (2010)
12. C.G. Bacon, M.A. Mittleman, I. Kawachi, E. Giovannucci, D.B. Glasser, E.B. Rimm, Sexual function in men older than 50 years of age: results from the health professionals follow-up study. Ann. Intern. Med. **139**, 161–168 (2003)
13. Y.C. Huang, C.C. Chin, C.S. Chen, A.W. Shindel, D.R. Ho, C.S. Lin, C.S. Shi, Chronic cigarette smoking impairs erectile function through increased oxidative stress and apoptosis, decreased nNOS, endothelial and smooth muscle contents in a rat model. PLoS ONE **10**, e0140728 (2015)
14. M.J. Pagano, A. De Fazio, A. Levy, A. RoyChoudhury, P.J. Stahl, Age, body mass index, and frequency of sexual activity are independent predictors of testosterone deficiency in men with erectile dysfunction. Urology **90**, 112–118 (2016)
15. J. Buvat, M. Maggi, L. Gooren, A.T. Guay, J. Kaufman, A. Morgentaler, C. Schulman, H.M. Tan, L.O. Torres, A. Yassin, M. Zitzmann, Endocrine aspects of male sexual dysfunctions. J. Sex. Med. **7**, 1627–1656 (2010)
16. M. De Rosa, S. Zarrilli, G. Vitale, C. Di Somma, F. Orio, L. Tauchmanova, G. Lombardi, A. Colao, Six months of treatment with cabergoline restores sexual potency in hyperprolactinemic males: an open longitudinal study monitoring nocturnal penile tumescence. J. Clin. Endocrinol. Metab. **89**, 621–625 (2004)
17. W.J. Reiter, A. Pycha, G. Schatzl, A. Pokorny, D.M. Gruber, J. C. Huber, M. Marberger, Dehydroepiandrosterone in the treatment of erectile dysfunction: a prospective, double-blind, randomized, placebo-controlled study. Urology 53, 590–594; discussion 594–595 (1999).
18. A. Morales, A. Black, L. Emerson, J. Barkin, I. Kuzmarov, A. Day, Androgens and sexual function: a placebo-controlled, randomized, double-blind study of testosterone vs. dehydroepiandrosterone in men with sexual dysfunction and androgen deficiency. Aging Male. **12**, 104–112 (2009)
19. G.E. Krassas, K. Tziomalos, F. Papadopoulou, N. Pontikides, P. Perros, Erectile dysfunction in patients with hyper- and hypothyroidism: how common and should we treat? J. Clin. Endocrinol. Metab. **93**, 1815–1819 (2008)
20. A. Veronelli, A. Masu, R. Ranieri, C. Rognoni, M. Laneri, A.E. Pontiroli, Prevalence of erectile dysfunction in thyroid disorders: comparison with control subjects and with obese and diabetic patients. Int. J. Impot. Res. **18**, 111–114 (2006)
21. M. Caprio, C. Mammi, I.Z. Jaffe, M.C. Zennaro, A. Aversa, M. E. Mendelsohn, A. Fabbri, G.M. Rosano, The mineralocorticoid receptor in endothelial physiology and disease: novel concepts in the understanding of erectile dysfunction. Curr. Pharm. Des. **14**, 3749–3757 (2008)
22. T. Kishimoto, T. Fukawa, K. Yamaguchi, Y. Yamamoto, H. Nakatsuji, H. Izaki, M. Takahashi, T. Fukumori, H.O. Kanayama, Mineralocorticoid receptor expression in human penile corpus cavernosum. J. Med. Invest. **60**, 21–26 (2013)
23. H. Muguruma, Y. Kawanishi, H. Sugiyama, J. Kagawa, S. Tanimoto, M. Yamanaka, K. Kojima, H. Anzai, A. Numata, T. Kishimoto, H.O. Kanayama, Effect of aldosterone on isolated human penile corpus cavernosum tissue. BJU Int. **102**, 500–503 (2008)
24. F. Wu, S. Mao, T. Yu, H. Jiang, Q. Ding, G. Xu, Elevated plasma aldosterone is an independent risk factor for erectile dysfunction in men. World J. Urol. **34**, 999–1007 (2016).
25. C. Hellal-Levy, J. Fagart, A. Souque, M.E. Rafestin-Oblin, Mechanistic aspects of mineralocorticoid receptor activation. Kidney Int. **57**, 1250–1255 (2000)
26. M. Bader, Tissue renin-angiotensin-aldosterone systems: targets for pharmacological therapy. Annu. Rev. Pharmacol. Toxicol. **50**, 439–465 (2010)
27. M.D. Taves, C.E. Gomez-Sanchez, K.K. Soma, Extra-adrenal glucocorticoids and mineralocorticoids: evidence for local synthesis, regulation, and function. Am. J. Physiol. Endocrinol. Metab. **301**, E11–E24 (2011)
28. L.G. Palmer, G. Frindt, Na+and K+transport by the renal connecting tubule. Curr. Opin. Nephrol. Hypertens. **16**, 477–483 (2007)
29. R. Soundararajan, D. Melters, I.C. Shih, J. Wang, D. Pearce, Epithelial sodium channel regulated by differential composition of a signaling complex. Proc. Natl Acad. Sci. USA **106**, 7804–7809 (2009)
30. R. Soundararajan, T. Ziera, E. Koo, K. Ling, J. Wang, S.A. Borden, D. Pearce, Scaffold protein connector enhancer of kinase suppressor of Ras isoform 3 (CNK3) coordinates assembly of a multiprotein epithelial sodium channel (ENaC)-regulatory complex. J. Biol. Chem. **287**, 33014–33025 (2012)
31. G. Frindt, Z. Ergonul, L.G. Palmer, Surface expression of epithelial Na channel protein in rat kidney. J. Gen. Physiol. **131**, 617–627 (2008)
32. D. Pearce, R. Soundararajan, C. Trimpert, O.B. Kashlan, P.M. Deen, D.E. Kohan, Collecting duct principal cell transport processes and their regulation. Clin. J. Am. Soc. Nephrol. **10**, 135–146 (2015)
33. F. Verrey, E. Schaerer, P. Zoerkler, M.P. Paccolat, K. Geering, J. P. Kraehenbuhl, B.C. Rossier, Regulation by aldosterone of Na

+,K+-ATPase mRNAs, protein synthesis, and sodium transport in cultured kidney cells. J. Cell Biol. **104**, 1231–1237 (1987)
34. A. Odermatt, D.V. Kratschmar, Tissue-specific modulation of mineralocorticoid receptor function by 11beta-hydroxysteroid dehydrogenases: an overview. Mol. Cell. Endocrinol. **350**, 168–186 (2012)
35. N. Farman, M.E. Rafestin-Oblin, Multiple aspects of mineralocorticoid selectivity. Am. J. Physiol. Ren. Physiol. **280**, F181–F192 (2001)
36. J. Huyet, G.M. Pinon, M.R. Fay, M.E. Rafestin-Oblin, J. Fagart, Structural determinants of ligand binding to the mineralocorticoid receptor. Mol. Cell. Endocrinol. **350**, 187–195 (2012)
37. M. Caprio, B.G. Newfell, A. la Sala, W. Baur, A. Fabbri, G. Rosano, M.E. Mendelsohn, I.Z. Jaffe, Functional mineralocorticoid receptors in human vascular endothelial cells regulate intercellular adhesion molecule-1 expression and promote leukocyte adhesion. Circ. Res. **102**, 1359–1367 (2008)
38. J.W. Funder, P.T. Pearce, R. Smith, A.I. Smith, Mineralocorticoid action: target tissue specificity is enzyme, not receptor, mediated. Science **242**, 583–585 (1988)
39. L.A. Calo, F. Zaghetto, E. Pagnin, P.A. Davis, P. De Mozzi, P. Sartorato, G. Martire, C. Fiore, D. Armanini, Effect of aldosterone and glycyrrhetinic acid on the protein expression of PAI-1 andp22(phox) in human mononuclear leukocytes. J. Clin. Endocrinol. Metab. **89**, 1973–1976 (2004)
40. A. Sato, J.W. Funder, High glucose stimulates aldosterone-induced hypertrophy via type I mineralocorticoid receptors in neonatal rat cardiomyocytes. Endocrinology **137**, 4145–4153 (1996)
41. M. Lombes, M.E. Oblin, J.M. Gasc, E.E. Baulieu, N. Farman, J. P. Bonvalet, Immunohistochemical and biochemical evidence for a cardiovascular mineralocorticoid receptor. Circ. Res. **71**, 503–510 (1992)
42. Q.N. Dinh, T.V. Arumugam, M.J. Young, G.R. Drummond, C. G. Sobey, S. Chrissobolis, Aldosterone and the mineralocorticoid receptor in the cerebral circulation and stroke. Exp. Transl. Stroke Med. **4**, 21 (2012)
43. C.E. Gomez-Sanchez, M.Y. Zhou, E.N. Cozza, H. Morita, M.F. Foecking, E.P. Gomez-Sanchez, Aldosterone biosynthesis in the rat brain. Endocrinology **138**, 3369–3373 (1997)
44. Q.N. Dinh, M.J. Young, M.A. Evans, G.R. Drummond, C.G. Sobey, S. Chrissobolis, Aldosterone-induced oxidative stress and inflammation in the brain are mediated by the endothelial cell mineralocorticoid receptor. Brain Res. **1637**, 146–153 (2016)
45. C.T. Tsai, F.T. Chiang, C.D. Tseng, J.J. Hwang, K.T. Kuo, C.K. Wu, C.C. Yu, Y.C. Wang, L.P. Lai, J.L. Lin, Increased expression of mineralocorticoid receptor in human atrial fibrillation and a cellular model of atrial fibrillation. J. Am. Coll. Cardiol. **55**, 758–770 (2010)
46. B.J. He, M.L. Joiner, M.V. Singh, E.D. Luczak, P.D. Swaminathan, O.M. Koval, W. Kutschke, C. Allamargot, J. Yang, X. Guan, K. Zimmerman, I.M. Grumbach, R.M. Weiss, D.R. Spitz, C.D. Sigmund, W.M. Blankesteijn, S. Heymans, P.J. Mohler, M. E. Anderson, Oxidation of CaMKII determines the cardiotoxic effects of aldosterone. Nat. Med. **17**, 1610–1618 (2011)
47. N. Lalevee, M.C. Rebsamen, S. Barrere-Lemaire, E. Perrier, J. Nargeot, J.P. Benitah, M.F. Rossier, Aldosterone increases T-type calcium channel expression and in vitro beating frequency in neonatal rat cardiomyocytes. Cardiovasc. Res. **67**, 216–224 (2005)
48. J.G. Burniston, A. Saini, L.B. Tan, D.F. Goldspink, Aldosterone induces myocyte apoptosis in the heart and skeletal muscles of rats in vivo. J. Mol. Cell. Cardiol. **39**, 395–399 (2005)
49. P. Du Bois, C. Pablo Tortola, D. Lodka, M. Kny, F. Schmidt, K. Song, S. Schmidt, R. Bassel-Duby, E.N. Olson, J. Fielitz, Angiotensin II induces skeletal muscle atrophy by activating TFEB-mediated MuRF1 expression. Circ. Res. **117**, 424–436 (2015)
50. A.P. Johnston, J. Baker, M. De Lisio, G. Parise, Skeletal muscle myoblasts possess a stretch-responsive local angiotensin signalling system. J. Renin. Angiotensin. Aldosterone. Syst. **12**, 75–84 (2011)
51. A. Bergmann, C. Eulenberg, M. Wellner, S. Rolle, F. Luft, R. Kettritz, Aldosterone abrogates nuclear factor kappaB-mediated tumor necrosis factor alpha production in human neutrophils via the mineralocorticoid receptor. Hypertension **55**, 370–379 (2010)
52. A. Vinh, W. Chen, Y. Blinder, D. Weiss, W.R. Taylor, J.J. Goronzy, C.M. Weyand, D.G. Harrison, T.J. Guzik, Inhibition and genetic ablation of the B7/CD28 T-cell costimulation axis prevents experimental hypertension. Circulation **122**, 2529–2537 (2010)
53. T.J. Guzik, N.E. Hoch, K.A. Brown, L.A. McCann, A. Rahman, S. Dikalov, J. Goronzy, C. Weyand, D.G. Harrison, Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. J. Exp. Med. **204**, 2449–2460 (2007)
54. A.A. Herrada, F.J. Contreras, N.P. Marini, C.A. Amador, P.A. Gonzalez, C.M. Cortes, C.A. Riedel, C.A. Carvajal, F. Figueroa, L.F. Michea, C.E. Fardella, A.M. Kalergis, Aldosterone promotes autoimmune damage by enhancing Th17-mediated immunity. J. Immunol. **184**, 191–202 (2010)
55. D.A. Kasal, T. Barhoumi, M.W. Li, N. Yamamoto, E. Zdanovich, A. Rehman, M.F. Neves, P. Laurant, P. Paradis, E.L. Schiffrin, T regulatory lymphocytes prevent aldosterone-induced vascular injury. Hypertension **59**, 324–330 (2012)
56. M. Lombes, N. Farman, J.P. Bonvalet, M.C. Zennaro, Identification and role of aldosterone receptors in the cardiovascular system. Ann. Endocrinol. **61**, 41–46 (2000)
57. Q. Pu, M.F. Neves, A. Virdis, R.M. Touyz, E.L. Schiffrin, Endothelin antagonism on aldosterone-induced oxidative stress and vascular remodeling. Hypertension **42**, 49–55 (2003)
58. R. Rocha, A.E. Rudolph, G.E. Frierdich, D.A. Nachowiak, B.K. Kekec, E.A. Blomme, E.G. McMahon, J.A. Delyani, Aldosterone induces a vascular inflammatory phenotype in the rat heart. Am. J. Physiol. Heart Circ. Physiol. **283**, H1802–H1810 (2002)
59. Y. Sun, J. Zhang, L. Lu, S.S. Chen, M.T. Quinn, K.T. Weber, Aldosterone-induced inflammation in the rat heart: role of oxidative stress. Am. J. Pathol. **161**, 1773–1781 (2002)
60. I.Z. Jaffe, M.E. Mendelsohn, Angiotensin II and aldosterone regulate gene transcription via functional mineralocortocoid receptors in human coronary artery smooth muscle cells. Circ. Res. **96**, 643–650 (2005)
61. I.Z. Jaffe, Y. Tintut, B.G. Newfell, L.L. Demer, M.E. Mendelsohn, Mineralocorticoid receptor activation promotes vascular cell calcification. Arterioscler. Thromb. Vasc. Biol. **27**, 799–805 (2007)
62. B.J. Waddell, S. Hisheh, Z.S. Krozowski, P.J. Burton, Localization of 11beta-hydroxysteroid dehydrogenase types 1 and 2 in the male reproductive tract. Endocrinology **144**, 3101–3106 (2003)
63. F. Wu, Z.Q. Xiong, S.H. Mao, J.M. Hu, J.Q. Wang, H.W. Jiang, Q. Ding, Aldosterone induces inflammatory cytokines in penile corpus cavernosum by activating the NF-kappaB pathway. Asian J. Androl. **20**, 24–29 (2018)
64. R.F. Reilly, D.H. Ellison, Mammalian distal tubule: physiology, pathophysiology, and molecular anatomy. Physiol. Rev. **80**, 277–313 (2000)
65. M.K. Rude, T.A. Duhaney, G.M. Kuster, S. Judge, J. Heo, W.S. Colucci, D.A. Siwik, F. Sam, Aldosterone stimulates matrix metalloproteinases and reactive oxygen species in adult rat ventricular cardiomyocytes. Hypertension **46**, 555–561 (2005)

66. S. Johar, A.C. Cave, A. Narayanapanicker, D.J. Grieve, A.M. Shah, Aldosterone mediates angiotensin II-induced interstitial cardiac fibrosis via a Nox2-containing NADPH oxidase. Faseb. J. **20**, 1546–1548 (2006)
67. S. Keidar, M. Kaplan, E. Pavlotzky, R. Coleman, T. Hayek, S. Hamoud, M. Aviram, Aldosterone administration to mice stimulates macrophage NADPH oxidase and increases atherosclerosis development: a possible role for angiotensin-converting enzyme and the receptors for angiotensin II and aldosterone. Circulation **109**, 2213–2220 (2004)
68. F. Iwashima, T. Yoshimoto, I. Minami, M. Sakurada, Y. Hirono, Y. Hirata, Aldosterone induces superoxide generation via Rac1 activation in endothelial cells. Endocrinology **149**, 1009–1014 (2008)
69. J.A. Leopold, A. Dam, B.A. Maron, A.W. Scribner, R. Liao, D. E. Handy, R.C. Stanton, B. Pitt, J. Loscalzo, Aldosterone impairs vascular reactivity by decreasing glucose-6-phosphate dehydrogenase activity. Nat. Med. **13**, 189–197 (2007)
70. Y. Yuan, Y. Chen, P. Zhang, S. Huang, C. Zhu, G. Ding, B. Liu, T. Yang, A. Zhang, Mitochondrial dysfunction accounts for aldosterone-induced epithelial-to-mesenchymal transition of renal proximal tubular epithelial cells. Free Radic. Biol. Med. **53**, 30–43 (2012)
71. A. Zhang, Z. Jia, X. Guo, T. Yang, Aldosterone induces epithelial-mesenchymal transition via ROS of mitochondrial origin. Am. J. Physiol. Ren. Physiol. **293**, F723–F731 (2007)
72. C. Zhu, S. Huang, Y. Yuan, G. Ding, R. Chen, B. Liu, T. Yang, A. Zhang, Mitochondrial dysfunction mediates aldosterone-induced podocyte damage: a therapeutic target of PPAR-gamma. Am. J. Pathol. **178**, 2020–2031 (2011)
73. V.C. De Giusti, M.B. Nolly, A.M. Yeves, C.I. Caldiz, M.C. Villa-Abrille, G.E. Chiappe de Cingolani, I.L. Ennis, H.E. Cingolani, E.A. Aiello, Aldosterone stimulates the cardiac Na(+)/H(+) exchanger via transactivation of the epidermal growth factor receptor. Hypertension **58**, 912–919 (2011)
74. V.C. De Giusti, A. Orlowski, M.C. Ciancio, M.S. Espejo, L.A. Gonano, C.I. Caldiz, M.G. Vila Petroff, M.C. Villa-Abrille, E.A. Aiello, Aldosterone stimulates the cardiac sodium/bicarbonate cotransporter via activation of the g protein-coupled receptor gpr30. J. Mol. Cell. Cardiol. **89**, 260–267 (2015)
75. T.Y. Chun, L.J. Bloem, J.H. Pratt, Aldosterone inhibits inducible nitric oxide synthase in neonatal rat cardiomyocytes. Endocrinology **144**, 1712–1717 (2003)
76. D. Nagata, M. Takahashi, K. Sawai, T. Tagami, T. Usui, A. Shimatsu, Y. Hirata, M. Naruse, Molecular mechanism of the inhibitory effect of aldosterone on endothelial NO synthase activity. Hypertension **48**, 165–171 (2006)
77. E.H. Bae, H.J. Cho, I.J. Kim, S.Y. Joo, J.H. Shin, S.K. Ma, J. Lee, S.W. Kim, Altered regulation of renal nitric oxide, atrial natriuretic peptide and cyclooxygenase systems in aldosterone escape in rats. Regul. Pept. **159**, 117–122 (2010)
78. H.M. Thai, B.Q. Do, T.D. Tran, M.A. Gaballa, S. Goldman, Aldosterone antagonism improves endothelial-dependent vasorelaxation in heart failure via upregulation of endothelial nitric oxide synthase production. J. Card. Fail. **12**, 240–245 (2006)
79. C.J. Hanke, T. O'Brien, K.A. Pritchard Jr., W.B. Campbell, Inhibition of adrenal cell aldosterone synthesis by endogenous nitric oxide release. Hypertension **35**, 324–328 (2000)
80. J.A. Muldowney 3rd, S.N. Davis, D.E. Vaughan, N.J. Brown, NO synthase inhibition increases aldosterone in humans. Hypertension **44**, 739–745 (2004)
81. J.M. Sainz, C. Reche, M.A. Rabano, C. Mondillo, Z.J. Patrignani, J.M. Macarulla, O.P. Pignataro, M. Trueba, Effects of nitric oxide on aldosterone synthesis and nitric oxide synthase activity in glomerulosa cells from bovine adrenal gland. Endocrine **24**, 61–71 (2004)
82. C.J. Hanke, W.B. Campbell, Endothelial cell nitric oxide inhibits aldosterone synthesis in zona glomerulosa cells: modulation by oxygen. Am. J. Physiol. Endocrinol. Metab. **279**, E846–E854 (2000)
83. Le.T.Y. Loan, M. Mardini, V.M. Howell, J.W. Funder, A.W. Ashton, A.S. Mihailidou, Low-dose spironolactone prevents apoptosis repressor with caspase recruitment domain degradation during myocardial infarction. Hypertension **59**, 1164–1169 (2012)
84. T.A. Williams, A. Verhovez, A. Milan, F. Veglio, P. Mulatero, Protective effect of spironolactone on endothelial cell apoptosis. Endocrinology **147**, 2496–2505 (2006)
85. Y. Nakamura, S. Suzuki, T. Suzuki, K. Ono, I. Miura, F. Satoh, T. Moriya, H. Saito, S. Yamada, S. Ito, H. Sasano, MDM2: a novel mineralocorticoid-responsive gene involved in aldosterone-induced human vascular structural remodeling. Am. J. Pathol. **169**, 362–371 (2006)
86. C. Crochemore, J. Lu, Y. Wu, Z. Liposits, N. Sousa, F. Holsboer, O.F. Almeida, Direct targeting of hippocampal neurons for apoptosis by glucocorticoids is reversible by mineralocorticoid receptor activation. Mol. Psychiatry **10**, 790–798 (2005)
87. T. Nakamura, K. Kataoka, M. Fukuda, H. Nako, Y. Tokutomi, Y.F. Dong, H. Ichijo, H. Ogawa, S. Kim-Mitsuyama, Critical role of apoptosis signal-regulating kinase 1 in aldosterone/salt-induced cardiac inflammation and fibrosis. Hypertension **54**, 544–551 (2009)
88. Y. Wei, A.T. Whaley-Connell, J. Habibi, J. Rehmer, N. Rehmer, K. Patel, M. Hayden, V. DeMarco, C.M. Ferrario, J.A. Ibdah, J. R. Sowers, Mineralocorticoid receptor antagonism attenuates vascular apoptosis and injury via rescuing protein kinase B activation. Hypertension **53**, 158–165 (2009)
89. N. Queisser, N. Schupp, Aldosterone, oxidative stress, and NF-kappaB activation in hypertension-related cardiovascular and renal diseases. Free Radic. Biol. Med. **53**, 314–327 (2012)
90. N. Queisser, N. Schupp, H. Stopper, R. Schinzel, P.I. Oteiza, Aldosterone increases kidney tubule cell oxidants through calcium-mediated activation of NADPH oxidase and nitric oxide synthase. Free Radic. Biol. Med. **51**, 1996–2006 (2011)
91. V. Leroy, S. De Seigneux, V. Agassiz, U. Hasler, M.E. Rafestin-Oblin, M. Vinciguerra, P.Y. Martin, E. Feraille, Aldosterone activates NF-kappaB in the collecting duct. J. Am. Soc. Nephrol. **20**, 131–144 (2009)
92. S.U. Sonder, A. Woetmann, N. Odum, K. Bendtzen, Spironolactone induces apoptosis and inhibits NF-kappaB independent of the mineralocorticoid receptor. Apoptosis **11**, 2159–2165 (2006)
93. J.C. Reil, M. Hohl, S. Selejan, P. Lipp, F. Drautz, A. Kazakow, B.M. Munz, P. Muller, P. Steendijk, G.H. Reil, M.A. Allessie, M. Bohm, H.R. Neuberger, Aldosterone promotes atrial fibrillation. Eur. Heart J. **33**, 2098–2108 (2012)
94. G.M. Kuster, E. Kotlyar, M.K. Rude, D.A. Siwik, R. Liao, W.S. Colucci, F. Sam, Mineralocorticoid receptor inhibition ameliorates the transition to myocardial failure and decreases oxidative stress and inflammation in mice with chronic pressure overload. Circulation **111**, 420–427 (2005)
95. A. Di Zhang, A. Nguyen Dinh Cat, C. Soukaseum, B. Escoubet, A. Cherfa, S. Messaoudi, C. Delcayre, J.L. Samuel, F. Jaisser, Cross-talk between mineralocorticoid and angiotensin II signaling for cardiac remodeling. Hypertension **52**, 1060–1067 (2008)
96. G. Suzuki, H. Morita, T. Mishima, V.G. Sharov, A. Todor, E.J. Tanhehco, A.E. Rudolph, E.G. McMahon, S. Goldstein, H.N. Sabbah, Effects of long-term monotherapy with eplerenone, a novel aldosterone blocker, on progression of left ventricular dysfunction and remodeling in dogs with heart failure. Circulation **106**, 2967–2972 (2002)

97. M.R. Ward, P. Kanellakis, D. Ramsey, J. Funder, A. Bobik, Eplerenone suppresses constrictive remodeling and collagen accumulation after angioplasty in porcine coronary arteries. Circulation **104**, 467–472 (2001)
98. J. Qu, F.M. Volpicelli, L.I. Garcia, N. Sandeep, J. Zhang, L. Marquez-Rosado, P.D. Lampe, G.I. Fishman, Gap junction remodeling and spironolactone-dependent reverse remodeling in the hypertrophied heart. Circ. Res. **104**, 365–371 (2009)
99. P. Mulder, V. Mellin, J. Favre, M. Vercauteren, I. Remy-Jouet, C. Monteil, V. Richard, S. Renet, J.P. Henry, A.Y. Jeng, R.L. Webb, C. Thuillez, Aldosterone synthase inhibition improves cardiovascular function and structure in rats with heart failure: a comparison with spironolactone. Eur. Heart J. **29**, 2171–2179 (2008)
100. G.P. Vyssoulis, E.A. Karpanou, V.E. Tzamou, S.M. Kyvelou, A. P. Michaelidis, T.P. Gialernios, D.V. Cokkinos, C.I. Stefanadis, Aldosterone levels and stroke incidence in essential hypertensive patients. Int. J. Cardiol. **144**, 171–172 (2010)
101. B.S. Huang, F.H. Leenen, The brain renin-angiotensin-aldosterone system: a major mechanism for sympathetic hyperactivity and left ventricular remodeling and dysfunction after myocardial infarction. Curr. Heart Fail. Rep. **6**, 81–88 (2009)
102. M. Joels, H. Karst, R. DeRijk, E.R. de Kloet, The coming out of the brain mineralocorticoid receptor. Trends Neurosci. **31**, 1–7 (2008)
103. E.A. Young, J.F. Lopez, V. Murphy-Weinberg, S.J. Watson, H. Akil, Mineralocorticoid receptor function in major depression. Arch. Gen. Psychiatry **60**, 24–28 (2003)
104. C. Otte, K. Wingenfeld, L.K. Kuehl, S. Richter, F. Regen, D. Piber, K. Hinkelmann, Cognitive function in older adults with major depression: Effects of mineralocorticoid receptor stimulation. J. Psychiatr. Res. **69**, 120–125 (2015)
105. V.S. Chhokar, Y. Sun, S.K. Bhattacharya, R.A. Ahokas, L.K. Myers, Z. Xing, R.A. Smith, I.C. Gerling, K.T. Weber, Hyperparathyroidism and the calcium paradox of aldosteronism. Circulation **111**, 871–878 (2005)
106. Y. Mizuno, M. Yoshimura, H. Yasue, T. Sakamoto, H. Ogawa, K. Kugiyama, E. Harada, M. Nakayama, S. Nakamura, T. Ito, Y. Shimasaki, Y. Saito, K. Nakao, Aldosterone production is activated in failing ventricle in humans. Circulation **103**, 72–77 (2001)
107. G. Guder, J. Bauersachs, S. Frantz, D. Weismann, B. Allolio, G. Ertl, C.E. Angermann, S. Stork, Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. Circulation **115**, 1754–1761 (2007)
108. F.M. Gutierrez-Marcos, A. Fernandez-Cruz, J. Gutkowska, C. Herrero, A. Blesa, V. Estrada, C. Loscos, J.M. Lopez-Novoa, Atrial natriuretic peptide in patients with acute myocardial infarction without functional heart failure. Eur. Heart J. **12**, 503–507 (1991)
109. F. Beygui, J.P. Collet, J.J. Benoliel, N. Vignolles, R. Dumaine, O. Barthelemy, G. Montalescot, High plasma aldosterone levels on admission are associated with death in patients presenting with acute ST-elevation myocardial infarction. Circulation **114**, 2604–2610 (2006)
110. B. Pitt, W. Remme, F. Zannad, J. Neaton, F. Martinez, B. Roniker, R. Bittman, S. Hurley, J. Kleiman, M. Gatlin, Eplerenone Post-Acute Myocardial Infarction Heart Failure E, Survival Study I, Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N. Engl. J. Med. **348**, 1309–1321 (2003).
111. B. Pitt, F. Zannad, W.J. Remme, R. Cody, A. Castaigne, A. Perez, J. Palensky, J. Wittes, The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N. Engl. J. Med. **341**, 709–717 (1999)
112. M.B. Nolly, C.I. Caldiz, A.M. Yeves, M.C. Villa-Abrille, P.E. Morgan, N. Amado Mondaca, E.L. Portiansky, G.E. Chiappe de Cingolani, H.E. Cingolani, I.L. Ennis, The signaling pathway for aldosterone-induced mitochondrial production of superoxide anion in the myocardium. J. Mol. Cell. Cardiol. **67**, 60–68 (2014)
113. B.R. Palmer, A.P. Pilbrow, C.M. Frampton, T.G. Yandle, L. Skelton, M.G. Nicholls, A.M. Richards, Plasma aldosterone levels during hospitalization are predictive of survival post-myocardial infarction. Eur. Heart J. **29**, 2489–2496 (2008)
114. M. Quinkler, D. Zehnder, K.S. Eardley, J. Lepenies, A.J. Howie, S.V. Hughes, P. Cockwell, M. Hewison, P.M. Stewart, Increased expression of mineralocorticoid effector mechanisms in kidney biopsies of patients with heavy proteinuria. Circulation **112**, 1435–1443 (2005)
115. J.P. Bertocchio, D.G. Warnock, F. Jaisser, Mineralocorticoid receptor activation and blockade: an emerging paradigm in chronic kidney disease. Kidney Int. **79**, 1051–1060 (2011)
116. K. Ando, H. Ohtsu, S. Uchida, S. Kaname, Y. Arakawa, T. Fujita, E.S. Group, Anti-albuminuric effect of the aldosterone blocker eplerenone in non-diabetic hypertensive patients with albuminuria: a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. **2**, 944–953 (2014)
117. G.L. Bakris, R. Agarwal, J.C. Chan, M.E. Cooper, R.T. Gansevoort, H. Haller, G. Remuzzi, P. Rossing, R.E. Schmieder, C. Nowack, P. Kolkhof, A. Joseph, A. Pieper, N. Kimmeskamp-Kirschbaum, L.M. Ruilope; Mineralocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy Study G., Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. JAMA **314**, 884–894 (2015)
118. T. Kosugi, M. Heinig, T. Nakayama, S. Matsuo, T. Nakagawa, eNOS knockout mice with advanced diabetic nephropathy have less benefit from renin-angiotensin blockade than from aldosterone receptor antagonists. Am. J. Pathol. **176**, 619–629 (2010)
119. T. Suehiro, K. Tsuruya, H. Ikeda, J. Toyonaga, S. Yamada, H. Noguchi, M. Tokumoto, T. Kitazono, Systemic aldosterone, but not angiotensin II, plays a pivotal role in the pathogenesis of renal injury in chronic nitric oxide-deficient male rats. Endocrinology **156**, 2657–2666 (2015).
120. B. Musicki, A.J. Bella, T.J. Bivalacqua, K.P. Davies, M.E. DiSanto, N.F. Gonzalez-Cadavid, J.L. Hannan, N.N. Kim, C.A. Podlasek, C.J. Wingard, A.L. Burnett, Basic science evidence for the link between erectile dysfunction and cardiometabolic dysfunction. J. Sex. Med. **12**, 2233–2255 (2015)
121. J.T. Clark, A. Sahu, J.J. Mrotek, S.P. Kalra, Sexual function and neuropeptide Y levels in selected brain regions in male spontaneously hypertensive rats. Am. J. Physiol. **261**, R1234–R1241 (1991)
122. F. Wu, S. Mao, T. Yu, H. Jiang, Q. Ding, G. Xu, Elevated plasma aldosterone is an independent risk factor for erectile dysfunction in men. World J. Urol. **34**, 999–1007 (2016)
123. F.A. DeLano, G.W. Schmid-Schonbein, Enhancement of glucocorticoid and mineralocorticoid receptor density in the microcirculation of the spontaneously hypertensive rat. Microcirculation **11**, 69–78 (2004)
124. M. Zhao, I. Celerier, E. Bousquet, J.C. Jeanny, L. Jonet, M. Savoldelli, O. Offret, A. Curan, N. Farman, F. Jaisser, F. Behar-Cohen, Mineralocorticoid receptor is involved in rat and human ocular chorioretinopathy. J. Clin. Invest. **122**, 2672–2679 (2012)
125. M. Lainscak, F. Pelliccia, G. Rosano, C. Vitale, M. Schiariti, C. Greco, G. Speziale, C. Gaudio, Safety profile of mineralocorticoid receptor antagonists: Spironolactone and eplerenone. Int. J. Cardiol. **200**, 25–29 (2015)
126. H.S. Zarren, P.M. Black, Unilateral gynecomastia and impotence during low-dose spironolactone administration in men. Mil. Med. **140**, 417–419 (1975)

127. D.J. Greenblatt, J. Koch-Weser, Gynecomastia and impotence: complications of spironolactone therapy. JAMA **223**, 82 (1973)
128. M. Epstein, D.A. Calhoun, Aldosterone blockers (mineralocorticoid receptor antagonism) and potassium-sparing diuretics. J. Clin. Hypertens. **13**, 644–648 (2011)
129. C. Bonne, J.P. Raynaud, Mode of spironolactone anti-androgenic action: inhibition of androstanolone binding to rat prostate androgen receptor. Mol. Cell. Endocrinol. **2**, 59–67 (1974)
130. F. Zannad, J.J. McMurray, H. Krum, D.J. van Veldhuisen, K. Swedberg, H. Shi, J. Vincent, S.J. Pocock, B. Pitt, E.-H.S. Group, Eplerenone in patients with systolic heart failure and mild symptoms. N. Engl. J. Med. **364**, 11–21 (2011)
131. B. Pitt, L. Kober, P. Ponikowski, M. Gheorghiade, G. Filippatos, H. Krum, C. Nowack, P. Kolkhof, S.Y. Kim, F. Zannad, Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. Eur. Heart J. **34**, 2453–2463 (2013)
132. M. Hargovan, A. Ferro, Aldosterone synthase inhibitors in hypertension: current status and future possibilities. JRSM Cardiovasc. Dis. **3**, 2048004014522440 (2014)
133. A. Fiebeler, J. Nussberger, E. Shagdarsuren, S. Rong, G. Hilfenhaus, N. Al-Saadi, R. Dechend, M. Wellner, S. Meiners, C. Maser-Gluth, A.Y. Jeng, R.L. Webb, F.C. Luft, D.N. Muller, Aldosterone synthase inhibitor ameliorates angiotensin II-induced organ damage. Circulation **111**, 3087–3094 (2005)
134. X. Bertagna, R. Pivonello, M. Fleseriu, Y. Zhang, P. Robinson, A. Taylor, C.E. Watson, M. Maldonado, A.H. Hamrahian, M. Boscaro, B.M. Biller, LCI699, a potent 11beta-hydroxylase inhibitor, normalizes urinary cortisol in patients with Cushing's disease: results from a multicenter, proof-of-concept study. J. Clin. Endocrinol. Metab. **99**, 1375–1383 (2014)
135. A. Granata, G. Tirabassi, V. Pugni, G. Arnaldi, M. Boscaro, C. Carani, G. Balercia, Sexual dysfunctions in men affected by autoimmune Addison's disease before and after short-term gluco- and mineralocorticoid replacement therapy. J. Sex. Med. **10**, 2036–2043 (2013)