**IN TRODUCTION**

In human beings aldosterone is a principal steroid hormone with mineralocorticoid activity. Aldosterone is produced by aldosterone synthase (CYP11B2), which belongs to the cytochrome P450 (CYP) family and shares 93% homology with its isoenzyme 11-β-hydroxylase (CYP11B1), the enzyme catalysing synthesis of glucocorticoids (1). The main site of aldosterone synthesis is located in the glomerular zone of the adrenal cortex (2). There is also evidence for non-adrenal synthesis of aldosterone, specifically in the brain (3, 4), the heart and the adipose tissue (4-9), although the synthesis of aldosterone in the heart still remains a matter of dispute (10-12).

In the adrenal cortex synthesis and secretion of aldosterone are stimulated by potassium ions, angiotensin II (Ang II), angiotensin III (Ang III), vasopressin (AVP), ACTH, β-endorphin, endothelins, adrenomedullin, cholecystokinin and pentagastrin, whereas aldosterone synthesis and secretion may be inhibited by atrial natriuretic peptide, dopamine, somatostatin and nitric oxide (NO) (13-20).

Classical actions of aldosterone are attributed to the kidney and include promotion of transepithelial sodium transport, chloride reabsorption, and potassium and magnesium secretion (21, 22). Thanks to the renal effects, aldosterone plays a fundamental role in maintenance of sodium-potassium balance, and in the regulation of blood volume and blood pressure (22, 23). Dietary salt intake constitutes a key factor determining secretion of aldosterone and potency of its sodium retaining effect (23-25). In rats maintained on normal or high-salt diet plasma aldosterone concentration is low, whereas low-salt diet increases plasma aldosterone concentration and abundance of aldosterone-sensitive sodium channels in the renal tubules (23-25). Moreover, a stimulatory effect of mineralocorticoids on sodium appetite was also demonstrated (26, 27).

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**Review article**

D. SZTECHMAN, K. CZARZASTA, A. CUDNOCH-JEDRZEJEWSKA, E. SZCZEPANSKA-SADOWSKA, T. ZERA

**ALDOSTERONE AND MINERALOCORTICOID RECEPTORS IN REGULATION OF THE CARDIOVASCULAR SYSTEM AND PATHOLOGICAL REMODELLING OF THE HEART AND ARTERIES**

In the review we discuss the role of mineralocorticoid receptors (MRs) in regulation and pathological remodelling of the cardiovascular system and the therapeutic potential of pharmacological targeting of MRs in cardiovascular diseases. MRs are expressed in organs involved in cardiovascular homeostasis: brain, heart, kidneys and vessels. The excessive activation of MRs has deleterious effects on the cardiovascular system through sympatho-excitation, elevated salt appetite, and renal retention of salt with consequent positive sodium balance, fibrosis and remodelling of the heart and arteries, and with propensity for atrial and ventricular arrhythmias. Hence, it provides basis for a common pathophysiological milieu of hypertension and heart failure. Furthermore, MR-mediated changes in the cardiovascular system are potentiated by renin-angiotensin system and activation of angiotensin type 1 receptors. Due to low selectivity, MRs bind both aldosterone and GCs – cortisol in humans and corticosterone in laboratory rodents. The binding of GCs to MRs is determined by availability of tissue specific 11β-hydroxysteroid dehydrogenase of type 1 (11β-HSD1) or type 2 (11β-HSD2). 11β-HSD1 metabolizes GCs to either active or inactive metabolites depending on the presence of special cofactors, whereas 11β-HSD2 transforms GCs only into inactive metabolites allowing for selective stimulation of MRs by aldosterone. 11β-HSD2 is expressed in the vascular wall, renal epithelium and some groups of cardiovascular neurons in the brain. In contrast, cardiac expression of 11β-HSD2 is low, thus, both aldosterone and GCs interact with cardiac MRs. The importance of MRs in the cardiovascular pathology is reflected in clinical guidelines that recommend use of MR blockers, spironolactone and eplerenone, in the treatment of heart failure, myocardial infarction and hypertension. Furthermore, new MR blockers and selective inhibitors of 11β-HSD1 have been developed and are currently tested in clinical trials.

**Key words:** aldosterone, mineralocorticoid receptor, glucocorticoid receptor, cortisol, corticosterone, 11β-hydroxysteroid dehydrogenase, heart, heart failure, hypertension, cardiovascular system
Currently, there are solid grounds to believe that aldosterone regulates cardiovascular parameters via its effects exerted in the central nervous system (CNS). Firstly, aldosterone is a steroid that enters the brain in direct proportion to its plasma level (28). Secondly, there is evidence for synthesis of aldosterone within the brain of the rat (4, 29), although it is not yet clear whether it can be synthesized in the normal human brain (30). Finally, mineralocorticoid receptors (MRs) were detected in the regions of the brain that are involved in the cardiovascular regulation (31, 32) and they play an essential role in the central blood pressure regulation (31, 33-37).

In addition, significant number of studies indicate that activation of MRs by aldosterone and glucocorticoids (GCs) directly influences morphology and biochemical composition of vascular and cardiac tissues (38). A large body of evidence shows that disturbances in synthesis and secretion of aldosterone and/or overactivation of MRs play a key role in pathophysiology of cardiovascular diseases (39, 40). Furthermore, recent findings disclosed that aldosterone may also affect the cardiovascular system via MR-independent pathways, which appear to be mediated by G-protein coupled estrogen receptor 30 (GPER, GPR 30) (41-43).

The main purpose of the present review is to summarise current knowledge concerning mechanisms of action of aldosterone in the heart, vessels, and in the brain cardiovascular regions, and to discuss consequences of excessive stimulation of the cardiovascular system by mineralocorticoids. We also discuss positive and negative consequences of application of the treatment interfering with the synthesis or action of aldosterone in the cardiovascular pathology. The detailed analysis of the cellular mechanisms of action of mineralocorticoids has been provided elsewhere in several excellent review articles (31, 39, 41, 44-48).

MINERALOCORTICOID RECEPTORS

Distribution of mineralocorticoid receptors

In the kidney, aldosterone plays its major physiological role via MRs located in the distal portion of the nephron, namely in the distal convoluted tubule, connecting tubule and the cortical and medullary portions of the collecting duct (49). Renal MRs have been detected in the principal cells, intercalated cells, mesangial cells, podocytes, fibroblasts, renal endothelium and vasculature (49-52). Apart from the kidney, MRs are expressed in the vascular endothelium and vascular smooth muscle cells (VSMCs) of several vascular beds including the aorta, coronary vessels, mesenteric and renal interlobar arteries (38, 44, 53-55).

In the heart, MRs are also expressed in cardiomyocytes, fibroblasts, and inflammatory cells, such as macrophages and T-lymphocytes (38, 44, 55-59). Furthermore, MRs are also expressed in neurons, microglia and astrocytes of the cerebral cortex, limbic system and cardiovascular regions of the brain – specifically in the brainstem, the hypothalamus and circumventricular organs (60-63).

Genomic actions of aldosterone

The classical genomic MRs belong to transcription factors activated by steroids and are involved in the regulation of gene expression (64). They share structural homology with other intracellular steroid hormone receptors for GCs, progestrone, androgens and estrogens (64-66). Genomic MRs are principal receptors for aldosterone; however, they have low selectivity and except for aldosterone, they bind other mineralocorticoids, such as deoxycorticosterone (DOC) and GCs (38).

The genomic MRs, which are engaged in induction or suppression of the transcription processes, are composed of three domains: the N-terminal transactivation domain (NTD), DNA-binding domain (DBD) located in the central part of the receptor, and the ligand binding domain (LBD) located at the C-terminal part of the receptor (64). Under resting conditions complexes formed with heat shock proteins (HSP 70, HSP 90) keep MRs inactive in the cytoplasm. Binding of the ligand with LBD causes dissociation of HSP to the cytoplasm, and this results in activation of MRs due to a change in conformation of their structure. Next, MRs shift into the nucleus and associate with hormone response element (HRE) or negative steroid response element (nSRE) DNA sequences in the promoter region of the target genes (64, 67). Initiation of transcription and translation processes by aldosterone results in synthesis of so-called aldosterone induced proteins. The process of activation is regulated by a specific combination of coregulatory proteins, such as: coactivators (SRC, PBP/TRAP220, CBP) and corepressors (NCOR, SMRT) (64).

As the mechanism of action of the ligands via MR activation has a multistage character, the effects of genomic action of aldosterone can be noted not earlier than after one hour, and they may last for several hours (64, 68).

Non-genomic actions of aldosterone

The non-genomic actions of aldosterone induce rapid cellular responses that are caused by activation of MR-dependent and MR-independent pathways (42, 69). The biological effects of non-genomic actions of aldosterone develop rapidly within seconds to minutes. They appear to play particularly significant role in the brain, especially in the hippocampus and the brainstem, as well as in the cardiomyocytes, endothelial cells and VSMCs (43, 46, 48, 64, 70-73). The MR-dependent non-genomic actions of aldosterone are mediated by MRs associated with the cellular membrane by scaffolding proteins, such as striatin and caveolins, and transactivation of several G-protein coupled receptors and receptor tyrosine kinases (48), such as insulin-like growth factor 1 receptor (IGF1R), platelet derived growth factor receptor (PDGFR), epidermal growth factor receptor (EGFGR), and angiotensin type 1 receptor (AT1R) (48). It is noteworthy that both MRs and AT1Rs are upregulated in the left ventricle of the infarcted heart (40, 74) and in the CNS of hypertensive and chronically stressed rats (32, 75) as previously reported by us, and that MR-dependent transactivation of AT1Rs was shown to participate in cardiac remodelling and fibrosis (76, 77) as well as in sympathoexcitation (78).

Inhibition of MRs with spironolactone or eplerenone limit the MR-dependent non-genomic effects of aldosterone; however, inhibitors of transcription and translation do not affect the response (42). Stimulation of these receptors accounts for rapid effects engaging numerous cell signalling pathways; however, the molecular mechanism of their activation has not been fully elucidated yet (48, 64). Thus far, it has been shown that rapid effects of aldosterone are associated with activation of protein kinase C (PKC), cyclic adenosine 3’5’-monophosphate (cAMP) and phosphoinositide 3-kinases (PI3K) with further downstream activation of numerous cell-specific kinases, ion channels and pumps (41, 42). Specifically, evidence has been provided for the involvement of inositol triphosphate (IP3), mitogen activated protein kinase (MAPK) phosphatases (MKP-1), cSrc kinase, extracellular signal-regulated kinase (ERK), NADPH oxidase and induction of ROS, sodium hydrogen antiporter (NHE-1), and Na+/K+-ATPase (79-85). The biological effects of non-genomic effects induced by aldosterone...
Aldosterone and cortisol bind with MRs with similar affinity (95-99), whereas concentration of GCs in plasma is 100 (free) to 1000 (total) times higher than that of mineralocorticoids (64). Thus, in most of the tissues, probability of binding of GCs to MRs and GC receptors (GRs) is significantly greater than the chance of binding of aldosterone. Cortisol in humans and corticosterone in rodents contain a hydroxyl group at carbon C-11 and are active steroid hormones. Conversion of this group into a keto group results in the transformation of active steroids into inactive cortisone and 11-dehydrocorticosterone, respectively (100). The conversion can be catalysed by two microsomal isozymes, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) and 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) (99). The former compound is a bidirectional enzyme with dehydrogenase activity that catalyses conversion of GCs into the inactive ketoanalogues as well as reductase activity that converts the inactive metabolites to active GCs (101-104). In contrast, 11β-HSD2 manifests exclusively unidirectional dehydrogenase activity and catalyses oxidation of cortisol into inactive cortisone. At low concentrations or in the absence of 11β-HSD2, MRs interact with cortisol, which is present in significantly higher concentration in plasma and tissues than aldosterone. Thus, a tissue-specific expression of these two isoforms of 11β-HSD determines the pre-receptor regulation of GR and MR activation and tissue-specific actions of aldosterone (102, 103, 105). The direction of enzymatic activity of 11β-HSD1 also depends on availability of cofactors, in particular oxidised/reduced forms of NADP+/NADPH. 11β-HSD1 has reductase activity in the presence of NADPH as a cofactor, whereas it shows dehydrogenase activity when NADP" is available (106). The production of NADPH occurs in the endoplasmic reticulum lumen and depends on the activity of other enzymes. For instance, it was shown that its production requires presence of hexose-6-phosphate dehydrogenase (H6PDH), which causes fivefold increase in stimulation of oxidoreductase activity and sixfold decrease in dehydrogenase activity of 11β-HSD1 (107). When H6PDH is absent, 11β-HSD1 acts mainly as a dehydrogenase. Nonetheless, in vivo 11β-HSD1 has mostly reductase activity, thus it facilitates activation GRs (108-110).

Importance of tissue-specific expression of 11β-HSD2 for activation of mineralocorticoid receptors

The affinity of 11β-HSD2 to substrates is approximately 100-times greater than the one of 11β-HSD1 (99, 111). Consequently, relatively small amount of 11β-HSD2 is sufficient for protection of MRs from binding with GCs (99, 109). Thus, when both isoforms of 11β-HSD are expressed, the higher binding affinity of 11β-HSD2 to the substrates and its specific intracellular localisation cause that 11β-HSD2 plays a dominant role in metabolism of corticosteroids (105, 109). Thanks to availability of 11β-HSD2 in epithelial cells of the distal portion of the nephron and in the VSMCs, these cells respond specifically to mineralocorticoids in spite of the presence of GCs (38, 112-115). On the other hand, the lack or low expression of 11β-HSD2 and presence of 11β-HSD1 in the inflammatory cells and adipocytes make MRs in these cells chief targets for highly abundant cortisol in humans and corticosterone in rodents (38, 45).

In the heart the expression of 11β-HSD2 is relatively low and MRs in the cardiomyocytes are occupied mainly by endogenous GCs (112, 116, 117). Available data suggests that
GCs may act as antagonists for cardiomyocyte MRs, thus they may confer some protective effects under condition of high aldosterone levels (118-121). This notion is further substantiated by preclinical studies indicating that there is an association between 11β-HSD2 activity and the cardiovascular pathology. Specifically, selective overexpression of 11β-HSD2 in cardiomyocytes, which leads to selective activation of MRs by aldosterone, resulted in cardiac hypertrophy, fibrosis, heart failure and early death suggesting that endogenous GCs occupying MRs provide protective effects against aldosterone-mediated activation of MRs in the cardiac muscle (122). Nonetheless, under conditions of increased oxidative stress, such as in the heart failure or hypertension, GC-MR complexes may become activated by reactive oxygen species (ROS) (39). In line with this, it was shown that activation of MRs by GCs results in coronary vessels and heart muscle injury in a low-aldosterone model of hypertension and heart failure, which in turn is in contradiction with protective action of GCs in the cardiac muscle (123).

Moreover, there is a relationship between the decreased activity of 11β-HSD2 and hypertension in humans (124, 125). DNA methylation as well as epigenetic suppression of 11β-HSD2 cause the increase in the ratio of active 11β-HSD1 to 11β-HSD2, thereby escalating action of GCs on the MRs and GRs and promoting development of the cardiometabolic syndrome. Therefore, it is suggested that 11β-HSD1 constitutes the pharmacological target for the development of selective antagonists that presumably should alleviate pathological consequences of diseases associated with overstimulation of GRs, such as obesity, diabetes type 2 and cardiometabolic syndrome (39, 64, 126).

In the brain, a relatively high expression of 11β-HSD2 was found in the nucleus of the solitary tract (NTS) (36, 64). Some reports show that 11β-HSD2 mRNA is also expressed in the hypothalamic paraventricular nucleus (PVN), the supraoptic nucleus (SON) and the subfornical organ (SFO) (127, 128). Thus, MRs in the key structures of the CNS involved in the cardiovascular regulation may be selectively targeted by aldosterone. However, expression of 11β-HSD1 dominates in other regions of the brain (36, 64), where GCs seem to play the dominant role in MR activation.

**ALDOSTERONE AND THE HEART**

**Effects of cardiac mineralocorticoid receptors overstimulation**

Expression of MRs was detected in human cardiac tissues obtained from the atria and ventricles, and it is reasonable to assume that these receptors are stimulated by aldosterone circulating in the blood (40, 64, 129). Besides, *de novo* synthesis of aldosterone by CYP11B2, aldosterone synthase, was detected in the atria and in ventricular cardiomyocytes, thus it is suggested that locally synthesised aldosterone may play a role in the pathogenesis of cardiac hypertrophy and fibrosis (5, 64, 67). Nonetheless, expression of the aldosterone synthase in the cardiac muscle is several orders of magnitude lower than in the adrenals, suggesting that it is mainly the blood-borne aldosterone that binds to MRs in the heart (67).

Based on results from experiments in mice with cardiomyocyte specific overexpression of 11β-HSD2, it was postulated that under pathological conditions excessive binding of mineralocorticoids with MRs leads to cardiac injury (122). Moreover, in a study by Silvestre et al. (130) investigating interactions between aldosterone, MRs and AT1Rs, it was shown that in rats with myocardial infarction (MI) the expression of mRNA for aldosterone synthase increases two-folds and aldosterone level almost quadruples in the residual intact myocardium. In addition, the upregulation of aldosterone synthase was dependent on activation of AT1Rs, whereas blockade of MRs significantly limited the post-infarct deposition of collagen in the heart (130). The results from animal studies were confirmed by findings in patients with congestive heart failure, which proved that increased expression of MR mRNA and protein was present in cardiomyocytes obtained from the left ventricle of the failing heart (131). Increased expression of MRs was also reported in the atrial tissue obtained from patients with atrial fibrillation (AF) (129). Furthermore, both in AF patients and in a mouse model of AF increased expression of 11β-HSD2 and aldosterone-dependent increase in connective tissue growth factor (CTGF) were observed (132).

A growing body of evidence indicates that under pathological conditions proinflammatory and fibrogenic phenotypes develop in the heart and coronary vessels (41, 133-135). In a hypertensive model of uninephrectomized rats exposed to chronic treatment with aldosterone and salt, aldosterone-dependent remodelling and fibrosis of the heart and coronary arteries was mediated by activation of NADPH oxidase, production of ROS and induction of the proinflammatory response manifested by cardiac expression of proinflammatory mediators and recruitment and accumulation of macrophages in the vessels and cardiac tissue (133, 134). In addition, it was shown in a genetic mouse model of cardiac-specific hyperaldosteronism and systemic hypertension that fibrotic changes in the heart involve increased expression of chemotactrant proteins (galectin 3, monocyte chemoattractant protein 1, osteopontin), leading to infiltration of the cardiac tissue with macrophages (136). Furthermore, cardiac fibrosis at least partially depends on aldosterone-induced decrease in antifibrotic factors, such as brain natriuretic peptide (BNP) and bone morphogenic peptide (133, 134, 136). Additionally, aldosterone contributes to progression of cardiac fibrosis by increase in expression of PAI-1 and tissue inhibitor of metalloproteinase 1 (TIMP-1), which are dependent on aldosterone-mediated suppression of natriuretic peptides (67, 136).

Together with inflammatory dependent fibrogenic response, aldosterone promotes fibroblasts proliferation and hypertrophy as well as collagen and fibronectin synthesis due to activation of several essential enzymatic pathways. Among these actions are: phosphorylation of ERK and activation of ERK/MAPK and RAS-Raf-MEK-ERK signalling cascades, activation of p38 mitogen-activated protein kinase (p38MAPK), enhancement of expression of transforming growth factor-β (TGF-β) and suppression of expression of inducible nitric oxide synthase (iNOS) (67, 137, 138). Experiments in a mouse model of cardiomyocyte-specific overexpression of human MRs revealed that prolonged overstimulation of cardiac MRs leads to endothelial dysfunction of coronary vessels manifested by decreased sensitivity to NO-mediated vasodilatory responses to acetylcholine. This desensitization was associated with increased cardiac levels of ROS, cardiac NADPH oxidase (NOX) activity, and increased expression of the NOX subunit gp91phox (139). The negative effects of MR overstimulation could be prevented by treatment with MR antagonist, antioxidant vitamins E and C, or NADPH oxidase inhibitor. Together, these findings suggest that overstimulation of MRs in cardiomyocytes may activate a paracrine mechanisms, which lead to NOX-dependent increase in ROS in the coronary vessels (139).

Increase in fibronectin and cardiac fibroblast-mediated collagen synthesis as well as decrease in matrix metalloproteinase (MMP) activity are further enhanced by local
intracardiac interactions between aldosterone and Ang II, as aldosterone upregulates AT1R expression resulting in activation of NADPH oxidase and ROS generation (138, 140-142). This aldosterone-mediated progression of cardiac pathological remodelling leads to decreased cardiac compliance, diastolic and systolic dysfunction, propensity for arrhythmias and may result in sudden cardiac death (138, 143).

Furthermore, conditional overexpression of MRs in cardiomyocytes in mice results in cardiac infiltration of inflammatory cells, cardiac fibrosis, and prolongation of action potential duration due to downregulation of the transient outward potassium current (Ito) with simultaneous elevation of L-type calcium channel activity. These changes lead to prolongation of PQ interval and QRS complex, ventricular arrhythmias and greater mortality rate (144). In this line, experiments on isolated cardiomyocytes revealed that aldosterone exerts positive chronotropic effect (145). It was also shown that overexpression of MRs in the cardiomyocytes leads to increased beating frequency (146), which may contribute to proarrhythmic phenotype.

Effects of selective suppression of cardiac mineralocorticoid receptors

Experiments with cardiomyocyte-specific down-regulation or deletion of MRs highlight the importance of excessive stimulation of MRs in the cardiac pathophysiology. It has been shown that deletion or inactivation of the MR gene lessened progression of left ventricular dilatation, as well as reduced the development of myocardial hypertrophy and heart failure in animal models of MI and pressure overload-induced cardiac hypertrophy (57, 144, 147-149). Furthermore, Fraccarollo et al. (57) showed that genetic ablation of MRs in the cardiomyocytes prevented post-infarct generation of myocardial and mitochondrial superoxide and abolished upregulation of the NADPH oxidase subunits (Nox2 and Nox4), improved healing of the MI, increased capillary density of the non-infarcted myocardium and thickness of the infarction zone scar. Thus, the cardiomyocyte-specific MRs ablation prevented adverse cardiac remodelling associated with cardiac hypertrophy and fibrosis (57). These changes were accompanied by improvement in hemodynamic parameters, such as left ventricular filling pressure, left ventricular ejection fraction, end systolic and end diastolic left ventricular volumes as well as by reduction in pulmonary oedema (57).

The crucial role of MRs in cardiac remodelling and fibrosis was also shown in 11-deoxycorticosterone (DOC)/salt induced hypertension in a model of MR-null mice, not expressing MRs in the myocardium. In comparison to wild type mice, eight-week exposure of mice lacking cardiac MRs to DOC/salt treatment resulted in lower expression of profibrotic factors (PAI-1, VEGFα, TGF-β, and integrin β1), inflammatory markers (MCP-1, CCR5, CD14, and CD81), and oxidative stress markers (p22phox) with eventual reduction of cardiac fibrosis (38, 150).

Role of mineralocorticoid receptors in cardiac remodelling in hypertension

Experimental studies strongly support involvement of MRs in cardiac remodelling in aldosterone and Ang II dependent hypertension, and in essential hypertension. Specifically, rats on high salt intake treated with aldosterone infusion show increased expression of c-fos, c-jun, proinflammatory-related genes, such as NFXB, p38MAPK, and TGF-β1, as well as elevated ROS generation in cardiomyocytes and peripheral blood mononuclear cells (PBMCs) that eventually lead to reparative cardiac fibrosis and coronary vasculopathy (151, 152). Accordingly, it was suggested that analysis of biochemical profile of PBMCs may have a predictive value for evaluation of cardiovascular risk prior to evident clinical symptoms (151). Furthermore, blockade of MRs with eplerenone significantly reduced oxidative stress in the heart and kidney of mice rendered hypertensive by chronic infusion of Ang II (153).

The study of Konishi et al. (154) showed significantly higher expression of 11β-HSD2, MRs and collagen 1 and collagen 3 in the left ventricle of stroke-prone spontaneously hypertensive rats (SHR-SP) with malignant hypertension, suggesting that aldosterone and MRs may play a role in remodelling of the heart in essential hypertension.

ALDOSTERONE AND VESSELS

Effects of mineralocorticoid receptors' stimulation in vascular wall

Vascular MRs are effectively and selectively stimulated by aldosterone. In vessels aldosterone exerts both rapid non-genomic, and delayed genomic effects, and participates in the regulation of the vascular tone and remodelling of the vascular wall, as manifested by VSMCs' proliferation and hypertrophy and vascular fibrosis (155, 156).

Binding of aldosterone to MRs in the arterial wall leads to increased expression of MMPs, TGF-β1, CTGF and galectin-3 with eventual remodelling of the extracellular matrix (ECM), manifested by increase in collagen to elastin ratio as well as increase in content of fibronectin and proteoglycans. These aldosterone-induced changes translate into impaired elasticity and compliance resulting in the arterial stiffness (157). Evidence from experiments in mice with conditional inactivation of MRs in VSMCs indicates that the remodelling of the arteries and development of hypertension is mostly dependent on activation of MRs in the VSMCs (158). In contrast to MRs expressed in the VSMCs, it seems that endothelial MRs are not significantly involved in the regulation of the arterial blood pressure and development of hypertension (38, 52, 159).

Numerous studies indicate that aldosterone promotes proliferation of VSMCs through activation of kinases – the classical MAPK-ERK1/2 and Big MAP kinase 1 (BMK1) pathways (160, 161). Furthermore, in human VSMCs and in the aorta of rats aldosterone significantly increases expression of MDM2, one of the oncoproteins with anti-apoptotic properties that is involved in the hypertrophy and hyperplasia of VSMCs (162-164). Similarly, aldosterone-dependent increase in galectin-3 expression leads to cell proliferation, adhesion, and fibrosis with subsequent pathological remodelling of the arterial wall. Recent studies showed that overexpression of galectin-3 promotes aldosterone-induced collagen 1 synthesis, whereas galectin-3 inhibition attenuates this process (157). Thus, galectin-3 is required for inflammatory and fibrotic responses to aldosterone in VSMCs and constitutes an important biomarker of cardiovascular fibrosis (157, 165). Furthermore, chronic blockade of MRs with eplerenone, selective MR antagonist, protects vascular wall from aldosterone-induced pathological remodelling, as it was shown in the rat model of adrenal aldosterone-producing adenoma (163). In addition, emerging evidence indicates that aldosterone-induced remodelling of the arterial wall is in part dependent on activation of placent growth factor (PGF) – FMS-like tyrosine kinase 1 (Ftn1) pathway (166).

Under physiological conditions, VSMC MRs contribute to the regulation of vascular tone in large arteries and participate in maintenance of normal blood pressure. A recent study in mice...
with conditional inactivation of MRs in the VSMCs showed that MRs expressed in VSMCs play essential role in determining magnitude of contractions and relaxations of aorta induced by extracellular calcium and NO, respectively. Their presence is also necessary for efficient expression of VSMC contractile proteins and their regulators (53). Furthermore, aldosterone-dependent activation of Nox1 subunit of NADPH oxidase and formation of ROS is responsible for hypercontractility of the resistance arteries obtained from stroke-prone spontaneously hypertensive rats (167). By activating MR-dependent ROS formation, aldosterone participates in the development of inflammatory response in the vascular wall, eventually leading to vascular injury (167). Furthermore, aldosterone may stimulate thrombogenesis via activation of platelets and by reducing fibrinolysis, whereas the treatment with MR antagonists hinders these effects (168-173).

**Interaction of mineralocorticoid receptors and AT1Rs in the vascular wall**

Ang II is the most significant effector of the RAS (174). It exerts its physiological actions through angiotensin type 1 (AT1R) and type 2 (AT2R) receptors which belong to membrane-bound G-protein coupled receptor family (GPCR) (175). Numerous studies revealed that Ang II is critically involved in remodelling of the cardiovascular system. In *vivo* studies showed that Ang II stimulates the production of ECM components and promotes proliferation of VSMCs (175, 176). Furthermore, evidence from *in vivo* experiments showed that Ang II-induced vascular fibrosis and remodelling are mediated by AT1R and involve AT1R-dependent increase in expression of collagen, fibronectin, osteopontin and proteoglycans. In addition, activation of AT1Rs in the coronary arteries promotes development and progression of atherosclerosis, eventually leading to MI, heart failure and stroke (175, 177, 178). A large body of evidence also indicates that chronic overactivation of vascular AT1R results in hypertension (175, 179, 180).

There is a close relationship between Ang II signalling pathways and activation of MRs in the vascular wall. Thus, hypertension occurring in response to administration of Ang II at least partially depends on activation of MRs in the VSMCs (38).

Moreover, it has been shown that in hypertensive transgenic Ren-2 rats overexpressing the mouse renin gene and high concentration of plasma Ang II, mitochondrial abnormalities, enhanced apoptosis, increased intracellular lipid accumulation and vascular injury are largely mediated by increased activation of MRs (160). This is manifested by significant attenuation of elevated NADPH oxidase activity, lipid peroxidation, and apoptosis as well as by reduced expression of AT1R and renin in vascular wall after inhibition of MRs with spironolactone in this model of hypertension (160).

Emerging evidence indicates that MR upregulation may also cause pathological alterations in venous vessels. For instance, remodelling of venous grafts after implantation into the arterial circulation is dependent on RAS and MRs. Specifically, elevated expressions of mRNAs encoding the MRs, 11β-HSD2, AT1R, and the angiotensin-converting enzyme (ACE) were demonstrated in human venous VSMCs obtained from the saphenous veins used for coronary artery by-pass surgery (181). Furthermore, in a mouse model of the inferior vena cava implants into the abdominal aorta, it was shown that expression of MRs is upregulated after vein grafting. Moreover, blockade of MRs significantly decreased remodelling of the venous wall, which was manifested by decrease in graft intima-media thickness, reduced fibrosis, and lower infiltration of inflammatory cells in the wall of the venous graft (181), suggesting a critical role of MRs in the vascular remodelling of the venous grafts.

**CENTRLY MEDIATED CARDIOVASCULAR EFFECTS OF ALDOSTERONE**

Aldosterone and mineralocorticoid receptors in the central nervous system

Multiple studies argue for significant role of aldosterone in the central regulation of the cardiovascular system, however thus far there is no full consensus about the origin of aldosterone acting on the central cardiovascular neurons. Available evidence indicates that aldosterone may be locally synthesised in the brain. Specifically, expression of the mRNA for the aldosterone synthase was demonstrated in the hypothalamus, hippocampus, amygdala, cerebrum, and cerebellum (3, 28, 182). Nevertheless, the hormone may also have an access to the brain via the circumventricular organs, and to some extent it can penetrate the blood-brain barrier (36, 183).

Findings of a recent study by Wang *et al* (127) indicate that blood-derived aldosterone may influence local production of aldosterone in the hypothalamic cardiovascular nuclei, namely PVN and SON, via MR- and AT1R-dependent mechanisms operating in the subfornical organ (SFO), and that aldosterone upregulates AT1R signalling in the PVN through activation of MRs. Furthermore, stimulation of the SFO and its downstream connections to the hypothalamic PVN neurons by circulating aldosterone appears to be necessary for development of hypertension in rats maintained on increased salt intake and chronically infused with aldosterone (127).

Expression of MRs is high in several regions of the brain participating in the regulation of blood pressure (31, 36, 64). Especially noteworthy is presence of MRs in the sympathetic preautonomic neurons of the PVN (62) as these neurons send projections to several autonomic motor nuclei in the brainstem and the spinal cord (184, 185). In addition, MRs are expressed in the SFO, one of the circumventricular organs lacking the blood-brain barrier with extensive connections with the PVN. Activation of MRs in the SFO by aldosterone present in the bloodstream leads to excitation of preautonomic neurons present in the hypothalamus (127). Furthermore, there is a large body of evidence indicating that MRs expressed in the NTS participate in the elevation of salt appetite induced by aldosterone (186, 187). In addition, MR expressing neurons in the NTS project to the limbic-forebrain circuits and affect arousal and motivational behaviour (187). MRs expressed in the limbic system and the forebrain affect memory processes, appraisal and coping strategies under stress conditions; however, it seems that these MRs are mainly targeted by GCs (187).

**Cardiovascular effects of stimulation of mineralocorticoid receptors and AT1Rs in the brain**

Functional studies show that stimulation of the central MRs play a significant role in endocrine responses to stress and in regulation of mood and cognition (31, 64, 187). Stimulation of MRs in the brain also activates sympathetic nervous system and increases arterial blood pressure, and these effects are associated with stimulation of the brain RAS and the induction of oxidative stress as well as activation of aldosterone-MR-ENaC-ouabain cascade in the CNS (78, 183, 188-191).

Furthermore, it was shown that blood-borne aldosterone increases sympathetic activity via MR-dependent activation of p44/42 MAPK signalling pathway in the PVN neurons, which are crucial for aldosterone-induced sympathetic response. These aldosterone-induced MAPK activation and sympathetic excitation partially depend on AT1R stimulation in the brain (78).

Taken together, aldosterone, locally synthesised or blood-borne, and brain MRs contribute to sympatho-excitation. This
chronically increased sympathetic activity promotes development and progression of hypertension and is associated with the end-organ damage as well as cardiovascular complications such as MI, stroke and heart failure (192, 193). Similarly to aldosterone, *i.e.* via MAPK induction, Ang II increases AT1R expression in the PVN, contributing thereby to sympathetic excitation in heart failure (78).

In the brain, the pre-receptor control of GCs binding to MRs by 11β-HSD2 cannot be efficient due to relatively poor expression of this enzyme in the CNS. It is suggested that in most instances brain MRs are occupied by GCs. However, higher expression of 11β-HSD2 in the NTS, PVN, SON and SFO suggests that these cardiovascular centres may be selectively targeted by aldosterone (36, 64, 127, 128). In addition, aldosterone may become a dominant ligand interacting with MRs in pathological conditions, in which its concentration increases excessively or its action is facilitated by concomitant factors, such as sodium overload, Ang II, oxidative stress or cytokines (39, 64). Main steps of synthesis and metabolism of aldosterone and its interaction with angiotensins and other cardiovascular factors are illustrated in Figs. 1 and 2.

**Fig. 1.** Major steps of aldosterone synthesis and its interactions with cortisol and renin-angiotensin system. Aldosterone is synthesized from cholesterol in a chain of reactions catalyzed by cytochrome p450 and hydroxysteroid 3-beta dehydrogenase 2. Depending on a cell type, at each step of aldosterone synthesis precursors of cortisol can be synthesized. The availability of cortisol for mineralocorticoid receptors (MRs) is determined by presence of active 11β-HSD1 and 11β-HSD2, that are converting cortisone to cortisol, and cortisol to inactive cortisone, respectively. Aldosterone binds either to cytosolic or to cell membrane-associated MRs. In absence of 11β-HSD2 cortisol binds to both glucocorticoid receptors (GRs) and MRs. The activation of cytosolic MRs leads to transcription and synthesis of proteins and enzymes. Binding of aldosterone to MRs associated with the cell membrane causes activation of several intracellular pathways and MR-dependent rapid non-genomic effects as well as delayed changes in the gene expression. The MR-independent non-genomic effects of aldosterone are associated with activation of GPR30 (GPER) and EGF receptors. Ang II is cleaved from angiotensinogen by actions of renin and ACE. Ang II binds to AT1Rs and AT2Rs. Other key components of RAS include Ang III, Ang 1-7, receptor Mas, and ACE-2. Activation of AT1Rs in the adrenal cortex stimulates synthesis and release of aldosterone. Aldosterone upregulates expression of AT1Rs, AT2Rs and ACE, and enhances binding of Ang II to AT1Rs increasing thereby activity of the renin-angiotensin system. Some non-genomic effects of aldosterone are independent of MRs and overlap with AT1R signaling pathways. The cross-talk between aldosterone and Ang II reciprocally potentiates effects of both hormones on remodelling of the cardiovascular system.

The arrows indicate the direction of interactions and their stimulating character. **Abbreviations:** CYP11A1, cytochrome P450 family 11 subfamily A member 1; CYP17A1, cytochrome P450 family 17 subfamily A member 1; CYP21A2, cytochrome P450 family 21 subfamily A member 2; CYP11B1, cytochrome P450 family 11 subfamily B member 1; CYP11B2, cytochrome P450 family 11 subfamily B member 2; HSD11B1, hydroxysteroid 11-beta dehydrogenase 1; HSD11B2, hydroxysteroid 11-beta dehydrogenase 2; HSD3B2, hydroxysteroid 3-beta dehydrogenase 2; ACE, angiotensin converting enzyme; GR, glucocorticoid receptor; AT1R, angiotensin type 1 receptor; AT2R, angiotensin type 2 receptor; MAS, proto-oncogene G protein-coupled receptor; ENaC, epithelial sodium channel; SGK1, serum and glucocorticoid regulated kinase; PKC, protein kinase C; cAMP, cyclic adenosine 3'5'-monophosphate; PI3K, phosphoinositide 3-kinases; EGFR, epidermal growth factor receptor; NHE-1, N+/H+ exchanger; GPER, G protein-coupled estrogen receptor; GRPR30, G protein-coupled receptor 30; IP3, inositol 1,4,5-trisphosphate; MAPK, mitogen-activated protein kinase; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; JNK, c-Jun N-terminal kinase; p38MAPK, p38 mitogen-activated protein kinase; cSrc, cytoplasmic tyrosine-protein kinase; MKP-1, mitogen-activated protein kinase phosphatase 1.
Numerous studies, performed on experimental animals and on patients suffering from cardiovascular pathology, argue for multifarious involvement of aldosterone-MR axis in pathogenesis of cardiovascular diseases. In patients with heart failure concentration of aldosterone in plasma correlates positively with hypertrophy of the left ventricle, and with mortality (194, 195). Furthermore, in hypertensive patients plasma aldosterone level is correlated with vascular stiffness (196). In addition, several studies in rat models and human subjects reveal that in congestive heart failure, and in hypertensive patients plasma aldosterone is associated with vascular stiffness (196). In hypertension without systolic dysfunction of the left ventricle, elevated levels of plasma aldosterone are associated with local production of aldosterone in the heart muscle (7, 130, 197). Both in hypertension and in heart failure, elevated concentration of aldosterone is associated with increased activation of RAS, and several studies have shown that Ang II and stimulation of AT1Rs play essential role in negative effects of aldosterone on the cardiovascular system (28, 120, 130, 182, 198, 199). However, there is also indirect evidence showing that aldosterone may promote hypertrophic remodelling of the heart independently of RAS. Such a possibility is strongly supported by the study performed on hypertensive patients with primary aldosteronism, whose blood pressure was matched with blood pressure of patients with primary hypertension. The patients with primary aldosteronism manifested significantly higher left ventricular wall thickness and left ventricular mass index, as well as longer PQ interval and greater left ventricular concentric remodelling than the patients with essential hypertension despite of significantly lower plasma renin activity (182). Currently, the role of inflammatory processes as a key factor in aldosterone-induced cardiovascular pathology is intensely explored (38, 45, 130, 151, 181, 200).

Experimental studies provide evidence that overstimulation of the brain MRs plays a significant role in development of hypertension and heart failure (183, 201). It has been shown that circulating Ang II increases expression of MRs and AT1Rs in the heart.
SFO and that this leads to increased production of aldosterone in the hypothalamus, as well as to an enhanced stimulation of AT1Rs in the PVN. Finally, activation of the PVN neurons results in overstimulation of the preautonomic neurons of the sympathetic system innervating the cardiovascular system and in progression of hypertension. In support of this assumption is the finding that elimination of MR or AT1R gene expression in the PVN prevents development of hypertension induced by subcutaneous infusion of Ang II (127, 202). Similar effects were obtained in rats treated with intrabrain infusion of Ang II (203), which suggests a critical MR-dependent central component of Ang II-induced hypertension. In line with these findings in hypertensive animal, there is also evidence that centrally acting aldosterone increases activity of the hypothalamic RAS and participates in generation of increased sympathetic activity in the heart failure (28, 201, 204).

THERAPEUTIC PERSPECTIVES OF INHIBITION OF MINERALOCORTICOID RECEPTORS

The above survey clearly indicates that excessive stimulation of mineralocorticoid receptors plays a critical role in the development of hypertension and cardiac failure. In humans, the pathogenic role of aldosterone was particularly well documented in salt-dependent hypertension, heart failure, and cardiometabolic syndrome (9, 205-208). Several clinical trials were carried out in order to evaluate the effectiveness of inhibition of MRs in cardiovascular patients. In majority of them, classical steroidal MR antagonists spironolactone and eplerenone were used, though there were also attempts to evaluate effectiveness of non-steroidal MR antagonist (49, 172, 205, 209-211).

Several large clinical trials provided a robust evidence for the efficacy of MR antagonists in chronic heart failure patients in NYHA functional class III or IV. Specifically, in the RALES study, blockade of MRs by spironolactone reduced the risk of sudden death from cardiac incidents and from progressive heart failure by 30% (205, 212). Similar results were obtained for eplerenone in the EPHEUS study in patients with chronic heart failure (213). Moreover, in the EMPHASIS-HF study, the benefit of eplerenone treatment in addition to optimal pharmacotherapy with ACE inhibitors, angiotensin-receptor blockers (ARBs), and β-blockers was also confirmed in patients with moderate systolic heart failure and NYHA functional class II symptoms (214).

The efficacy of MR antagonists in patients with primary hypertension is less evident. The recent systemic review of placebo-controlled clinical trials by Tam et al. (215) showed that application of eplerenone as the antihypertensive treatment in patients with primary hypertension results in a modest reduction of systolic and diastolic blood pressure, and the effects of eplerenone on mortality and morbidity are not well supported (215). However, addition of low-dose eplerenone to RAS inhibitors resulted in renoprotective effects in hypertensive patients with non-diabetic chronic kidney disease (CKD) in the EVALUATE Study Group (216). Furthermore, a growing body of evidence indicates that MR antagonists, especially low-dose spironolactone, improve blood pressure control in patients with resistant hypertension (217).

A growing body of evidence indicates that MR antagonists have antiarrhythmic properties in patients with atrial fibrillation (AF) (218). Namely, in the SPIR-AF study, addition of spironolactone to the pharmacotherapy decreased incidence of AF (219). Furthermore, a recent meta-analysis by Neefs et al. suggests that MR antagonists decrease the incidence of new-onset AF and recurrent AF (220).

It should be emphasized that MR antagonists exert also several side-effects, which may hamper their efficacy in cardiovascular patients. The side-effects inherent to administration of spironolactone or eplerenone result mainly from suppression of the renal tubule MRs and secondary hyperkalaemia and renal insufficiency. Usually, the side effects of MR antagonists related to hyperkalaemia do not exceed 10 – 12% of patients (44, 221). Nevertheless, they constitute an important factor limiting the dosage of both these antagonists and impose necessity of frequent laboratory monitoring of potassium and creatinine levels. The risk of hyperkalaemia can be reduced by avoidance of potassium-retaining drugs or potassium-containing foods. Recently, positive effects of administration of potassium-binding substances, such as RLY5016, sodium zirconium cyclosilicate or Patiromer, on plasma potassium level were reported in patients with chronic heart failure and in those with CKD treated with RAAS inhibitors (222, 223). In addition, structural similarity of spironolactone to progesterone and its relatively high affinity for androgen receptors result in progestational and anti-androgenic effects, which are manifested by gynecomastia, breast tenderness, impotence, loss of libido, and irregular menstrual bleedings (224).

Since there are currently only two registered substances, which block MRs, spironolactone and eplerenone, there is a great interest in novel drugs that decrease activation of MRs in patients with cardiovascular diseases. Thus, safety and tolerability of new non-steroidal MR antagonists, in particular aparenrenone, esaxerone and finerenone, have been tested in healthy volunteers and patients with heart failure, CKD, diabetes and hypertension. Of these three compounds, finerenone appears to be the most promising non-steroidal MR antagonist (49, 225, 226).

Effectiveness of finerenone in lowering oxidative stress biomarkers in blood was equal to that of spironolactone, whereas a risk of hyperkalaemia and renal dysfunction was lower in patients receiving finerenone. It is believed that finerenone has higher affinity for cardiovascular tissue than for renal tissue (cardiac-to-renal activity ratio) in comparison to spironolactone, however, the hypotensive effectiveness of finerenone is lower in comparison to spironolactone (227, 228). Furthermore, finerenone, was evaluated in the ARTS-HF study in a group of patients with heart failure and reduced LVEF, and with mild or moderate CKD or T2DM (229). Currently, this non-steroidal MR antagonist is tested for safety, efficacy and reduction of renal and cardiovascular morbidity and mortality in the ongoing phase 3 clinical trials: FINESSE-HF (EUCTR2015-002168-17), FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049), studies that will include over 14,000 participants (230-232).

Selective antagonists of 11β-HSD1 were also synthesized and tested in preclinical studies and in healthy human subjects. They show good safety profiles in clinical trials and seem to be particularly useful for treatment of Cushing syndrome, and metabolic syndrome characterized by obesity, dyslipidaemia, insulin resistance and hypertension. In addition to their metabolic effects, these inhibitors also show a modest blood pressure-lowering effect in T2DM patients and patients with obesity (233-236). Moreover, preclinical studies in mouse and rat models indicate that pharmacological inhibition of 11β-HSD1 confers protective effects against adverse cardiovascular remodelling (117, 237, 238). Nonetheless, efficacy of 11β-HSD1 inhibitors in preventing vascular and cardiac remodelling or reducing adverse cardiovascular outcomes has not been established yet in clinical trials (117, 239, 240).

Recently, inhibitors of aldosterone synthase (CYP11B2) have been developed and are currently screened for their
therapeutic potential in cardiovascular diseases (239, 241). Some of these compounds have been tested in the clinical studies in healthy volunteers and in patients with primary aldosteronism (51, 242-245). Highly homologous structure of aldosterone (CYP11B2) and cortisol (CYP11B1) synthases render selective inhibition of aldosterone synthase difficult. Thus, the initial human trials showed that even though aldosterone synthase inhibitors, such as LC1699, are well tolerated and exert blood pressure-lowering effect, their low selectivity for aldosterone synthase leads to suppression of both aldosterone and glucocorticoids (243). However, recently published trials in healthy humans indicate that new highly selective inhibitors of aldosterone synthase – LY3045697 and RO683619 – potently blunt aldosterone release with insignificant effects on plasma concentrations of cortisol and ACTH, offering a potential advantage over less selective aldosterone synthase inhibitors previously evaluated in human trials. These new compounds exhibit significantly more potent and selective inhibition of CYP11B2 over CYP11B1. They are well tolerated by healthy subjects and their administration is not associated with significant side-effects, however multiple application of high doses can result in hyperkalaemia (244). Furthermore, new highly selective aldosterone synthase inhibitors with low affinity for CYP11B1 have been recently developed and successfully tested in monkeys (246).

SUMMARY

Mineralocorticoid receptors play a critical role in regulation and pathological remodelling of the cardiovascular system. MRs are expressed in organs involved in cardiovascular homeostasis: brain, heart, kidneys and vessels. Due to low selectivity, MRs bind both aldosterone and GCs and binding of GCs to MRs is largely determined by availability of tissue specific expression of 11β-HSD2, which converts GCs to inactive metabolites and allows for selective stimulation of MRs by aldosterone. 11β-HSD2 is expressed in the vascular wall, renal epithelium and some diencephalic and brain-stem nuclei involved in the regulation of water-electrolyte balance and blood pressure. In contrast, cardiac expression of 11β-HSD2 is low, thus, both aldosterone and GCs interact with cardiac MRs. As it is shown in Fig. 2, the excessive activation of MRs exerts several deleterious effects on the cardiovascular system, chiefly through sympato-excitation, elevated salt appetite, renal retention of salt with consequent positive sodium balance, fibrosis and remodelling of the heart and arteries, as well as with propensity for atrial and ventricular arrhythmias. Furthermore, MR-mediated changes in the cardiovascular system are potentiated by RAS and activation of AT1Rs. The importance of MRs in the cardiovascular pathology is reflected in clinical guidelines that recommend use of MR blockers, spironolactone and eplerenone, in the treatment of heart failure, myocardial infarction and hypertension. Furthermore, new MR blockers, selective inhibitors of 11β-HSD1 and selective aldosterone synthase inhibitors have been developed and are currently tested in clinical trials.

Abbreviations: 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; ACE, angiotensin converting enzyme; ACTH, adrenocorticotropic hormone; AF, atrial fibrillation; Ang II, angiotensin II; Ang III, angiotensin III; ARB, angiotensin receptor blocker; ARTS-HF study, The Mineralocorticoid Receptor antagonist Tolerability Study-Heart Failure; AT1R, angiotensin type 1 receptor; AT2R, angiotensin type 2 receptor; AVP, vasopressin; BMK1, Big MAP kinase1; BNP, brain natriuretic peptide; CBP, CREB-binding protein; CCR5, C-C chemokine receptor type 5; CKD, chronic kidney disease; CNS, central nervous system; cSrc, cytoplasmic tyrosine-protein kinase; CTGF, connective tissue growth factor; CYP11B2, aldosterone synthase (cytochrome P450 family 11 subfamily B member 2); DBD, DNA-binding domain; DOC, 11-deoxycorticosterone; ECM, extracellular matrix; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; ENaC, epithelial sodium channel; EPHESUS, Eplerenone Post Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; ER, endoplasmic reticulum; ERK, extracellular signal-regulated protein kinase; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; Flt1, FMS-like tyrosine kinase 1; GCs, glucocorticoids; GPCR, G-protein coupled receptor family; GRs, glucocorticoid receptors; HRE, hormone response element; HSP, heat shock protein; H6PDH, hexose-6-phosphate dehydrogenase; iNOS, inducible nitric oxide synthase; IP3, inositol triphosphate; Ito, transient outward potassium current; LBD, ligand binding domain; LVEF, left ventricular ejection fraction; MAPK, mitogen activated protein kinase; MCP, membrane cofactor protein-1; MEK, mitogen-activated protein kinase/ERK kinase; MI, myocardial infarction; MKP-1, MAPK phosphatase-1; MMP, matrix metalloproteinase; MRA, mineralocorticoid receptor antagonist; MRs, mineralocorticoid receptors; NoC0R, nuclear receptor corepressor; NFκB - nuclear factor kappa B (nuclear factor κ-light-chain-enhancer of activated B cells); NHE-1, sodium hydrogen antiporter; NO, nitric oxide; NOK, NADPH oxidase; nSRE, negative steroid response element; NTD, N-terminal transactivation domain; NTS, nucleus of the solitary tract; NYHA, New York Heart Association; PAI-1, plasminogen activator inhibitor 1; PBMCs, peripheral blood mononuclear cells; PBP, peroxisome proliferator-activated receptor (PPAR)-binding protein; PGF, placental growth factor; PI3K, phosphoinositide 3-kinases; PKC, protein kinase C; PVN, hypothalamic paraventricular nucleus; p38MAPK, p38 mitogen-activated protein kinase; RAAS, renin-angiotensin-aldosterone system; Raf, family of serine/threonine protein kinases (acyron for rapidly accelerated fibrosarcoma); RALES, Randomized Aldactone Evaluation Study; Ras, family of GTP-binding proteins; RAS, renin-angiotensin system; ROS, reactive oxygen species; SFO, subfornical organ; SHR-SP, stroke-prone spontaneously hypertensive rat; SMRT, silencing mediator of retinoic acid and thyroid hormone receptor; SON, supraoptic nucleus; SIRP-AF study, spironolactone-atrial fibrillation study; SRC, steroid receptor coactivator; TGFB, transforming growth factor β; TIMP-1, tissue inhibitor of metalloproteinase 1; TRAP220, thyroid hormone receptor-associated protein (subunit 220); T2DM, type 2 diabetes mellitus; VEGFA, vascular endothelial growth factor A; VSMCs, vascular smooth muscle cells.

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Author’s address: Dr. Tymoteusz Zera, Department of Experimental and Clinical Physiology, Laboratory of Centre for Preclinical Research, Medical University of Warsaw, 1B Banacha Street, 02-097 Warsaw, Poland.
E-mail: tzera@wum.edu.pl