On the Pleiotropic Actions of Mineralocorticoids

Florian Lang

Department of Physiology, Eberhard Karls University of Tübingen, Tübingen, Germany

Key Words

Mineralocorticoids · Electrolyte transport · Salt appetite · Blood pressure · Glucose · Fibrosis · Calcification · Blood platelets

Abstract

Classical effects of mineralocorticoids include stimulation of Na^+ reabsorption and K^+ secretion in the kidney and other epithelia including colon and several glands. Moreover, mineralocorticoids enhance the excretion of Mg^{2+} and renal tubular H^+ secretion. The renal salt retention following mineralocorticoid excess leads to extracellular volume expansion and hypertension. The increase of blood pressure following mineralocorticoid excess is, however, not only the result of volume expansion but may result from stiff endothelial cell syndrome impairing the release of vasodilating nitric oxide. Beyond that, mineralocorticoids are involved in the regulation of a wide variety of further functions, including cardiac fibrosis, platelet activation, neuronal function and survival, inflammation as well as vascular and tissue fibrosis and calcification. Those functions are briefly discussed in this short introduction to the special issue. Beyond that, further contributions of this special issue amplify on mineralocorticoid-induced sodium appetite and renal salt retention, the role of

mineralocorticoids in the regulation of acid-base balance, the involvement of aldosterone and its receptors in major depression, the mineralocorticoid stimulation of inflammation and tissue fibrosis and the effect of aldosterone on osteoinductive signaling and vascular calcification. Clearly, still much is to be learned about the various ramifications of mineralocorticoid-sensitive physiology and pathophysiology.

© 2014 S. Karger AG, Basel

Introduction

Mineralocorticoids are key hormones regulating extracellular volume homeostasis [1, 2]. Their release is up-regulated in extracellular volume depletion, they enhance salt intake by upregulating salt appetite [3, 4] and they decrease renal salt loss by stimulating salt reabsorption in the aldosterone-sensitive nephron segments [1, 2]. Moreover, mineralocorticoids curtail salt loss by stimulating salt (re)absorption in colon [5, 6], sweat glands and salivary glands [6]. At least in part due to extracellular volume expansion, mineralocorticoids enhance cardiac output and blood pressure [7, 8]. However, the mineralocorticoid receptor [9–11] is expressed in a wide variety of tissues [10]. The mineralocorticoid receptor binds aldo-

sterone, cortisol and corticosterone with similar affinity [10, 12] but the inactivation of glucocorticoids by 11 β -hydroxysteroid dehydrogenase 2 (HSD2) in aldosterone-target cells confers some aldosterone specificity in those cells [10, 12, 13]. More recent research revealed further functions of mineralocorticoids, which are seemingly unrelated to extracellular volume regulation. This brief overview will address some of those functions. Moreover, several of those functions are amplified in separate short reviews of this special issue.

Effects of Mineralocorticoids

Mineralocorticoids are powerful regulators of renal tubular salt transport [1, 2]. They upregulate the epithelial Na⁺ channels, the apical K⁺ channels and the Na⁺/K⁺ ATPase and thus stimulate renal tubular Na⁺ reabsorption and K⁺ secretion in the aldosterone-sensitive nephron segments [1, 2]. The aldosterone-induced renal Na⁺ retention in the distal nephron leads to extracellular volume expansion, which inhibits Na⁺ reabsorption in the proximal tubule and thick ascending limb resulting in reduced Ca²⁺ and Mg²⁺ reabsorption in those nephron segments [14, 15]. As a result, aldosterone leads to magnesuria and calciuria [14, 15]. Mineralocorticoids further stimulate renal tubular H⁺ secretion and thus generate alkalosis [16–18]. Aldosterone modifies renal acid excretion in part by upregulating both H⁺ pumps and Cl[−]/HCO₃[−] exchanger pendrin [18]. Mineralocorticoids upregulate pendrin in a variety of further tissues [19]. The functional significance of mineralocorticoid-sensitive pendrin regulation in those tissues remained elusive.

Mineralocorticoids further enhance salt appetite [2, 4] and thus foster salt intake, as amplified in separate reviews of this special issue [20, 21]. Enhanced salt intake and renal salt retention lead to extracellular volume expansion with increase of blood pressure [7, 8, 22]. The effect of mineralocorticoids on blood pressure does, however, not depend on the effect of mineralocorticoids on the distal nephron [23] but is attributed in part to vascular inflammation [24, 25], to enhanced endothelial stiffness, which compromises the release of nitric oxide [26–30] and direct effects of the mineralocorticoid receptor in vascular smooth muscle [31]. Besides leading to systemic hypertension, mineralocorticoids could foster pulmonary hypertension [32].

Moreover, mineralocorticoids increase vascular stiffness [33, 34] and vascular as well as soft tissue calcifica-

tion [25, 35, 36], as amplified in a separate contribution to this special issue [37]. Mineralocorticoids influence tissue calcification in part by downregulation of klotho [38, 39].

Mineralocorticoids further stimulate cardiac and renal fibrosis [33, 40–56], as discussed in a further contribution to this special issue [57].

The increase of blood pressure following aldosterone action affects the heart, which is further affected by direct effects of mineralocorticoid receptors on cardiac function, electrical conduction, oxidative stress, inflammation and fibrosis [43, 58, 59].

Mineralocorticoid receptors are further involved in the regulation of adipogenesis as well as adipose tissue expansion and may contribute to insulin resistance and obesity [60–63]. Mineralocorticoids affect neuronal function and survival [3, 64–67] as amplified in a separate review of this special issue [21].

Mineralocorticoids upregulate the pore-forming Ca²⁺ channel protein Orai1 [68] and thus increase the Ca²⁺ concentration [69] in blood platelets. Activation of Orai1 contributes to store-operated calcium entry (SOCE) [70, 71], thus leading to platelet activation [72–74], cytoskeletal reorganization with respective shape changes [75] and cell membrane scrambling with phosphatidylserine translocation to the outer platelet membrane surface [76–80]. Phosphatidylserine at the platelet surface enhances in turn thrombin formation and platelet procoagulant activity [77–79, 81]. Moreover, increased Ca²⁺ concentration triggers platelet degranulation, integrin $\alpha_{IIb}\beta_3$ activation and adhesion of platelets [72]. Orai1 protein abundance and thus Ca²⁺ entry are upregulated by the serum- and glucocorticoid-inducible kinase isoform SGK1 [82, 83], a kinase strongly upregulated by mineralocorticoids [84]. Orai1 is further upregulated by the isoform SGK3 [85]. SGK1 upregulates in megakaryocytes the transcription factor NF- κ B, which in turn stimulates Orai1 expression [82]. Mineralocorticoids thus enhance the sensitivity of platelets to activators and mineralocorticoid excess is thus expected to foster thrombosis and vascular occlusive disease [82]. On the other hand, specific activation of the endothelial mineralocorticoid receptor may counteract thrombosis [86].

Mechanisms Involved in Mineralocorticoid Effects

Mineralocorticoids are, at least partially, effective by binding to the mineralocorticoid receptor, which acts as a ligand-dependent transcription factor regulating gene

expression [9, 34, 36, 46, 48, 87–89]. The receptor is similar to the glucocorticoid receptor and may be activated by glucocorticoids [90]. Activation of the mineralocorticoid receptor upregulates a wide variety of genes involved in transport such as channels, carriers and transport-regulating signaling molecules including the serum- and glucocorticoid-inducible kinase SGK1 [91, 92].

Mineralocorticoid receptor activation further triggers inflammation in part due to stimulation of reactive oxygen species generation by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and mitochondria [43]. In the heart, activation of mineralocorticoid receptors leads to activation of the Na^+/H^+ exchanger NHE-1 with subsequent increase of cytosolic Na^+ and Ca^{2+} entry through reversal of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger [93]. Notably NHE1 is upregulated by oxidative stress [93] and SGK1 [94, 95].

The effects of mineralocorticoids are augmented by Ras-related C3 botulinum toxin substrate 1 (Rac1), a Rho-family small GTPase [96].

Besides their effect on gene expression, mineralocorticoids could exert nongenomic effects [3, 33, 56, 66, 67, 97–104], which are, at least partially, mediated by angiotensin-II receptor and G protein-coupled receptor 30 [43]. Signaling involved in nongenomic mineralocorticoid action includes stimulation of phosphatidylinositol-3-kinase (PI3K) [105, 106].

As apparent from blood platelets [68], mineralocorticoids may further influence protein translation, which is regulated by the translation initiation factors eIF-4E and eIF-2 α eIF-4E [107, 108] as well as the inhibitory 4E-binding protein 4E-BP1 [107]. 4E-BP1 is phosphorylated by PI3K [109] and subsequently binds eIF-4E, thus inhibiting translation [109]. Mineralocorticoids activate PI3K leading to redistribution of the initiation factors to the proximity of mRNA [107]. Initiation of

translation requires both actin polymerization and PI3K activation [110].

Pathophysiology of Mineralocorticoid Excess

Excessive mineralocorticoid action is associated with enhanced risk of vascular disease, such as hypertension, heart failure, cardiac electrical remodeling, atrial fibrillation, atherosclerosis and fibrosis [33, 58, 111–116]. The cardiovascular disease in mineralocorticoid excess is the result of extracellular volume expansion with hypertension [7, 8, 41], endothelial stiffness with compromised NO release [26–30], cardiovascular inflammation and fibrosis [43, 57, 117, 118] as well as calcification with enhanced vascular stiffness [35–37]. Moreover, vascular events may result from enhanced Ca^{2+} entry into blood platelets [69] with enhanced degranulation, aggregation and adhesion [68] and eventually acute thrombotic occlusion following atherosclerotic plaque rupture [82, 119] and ischemic cardiovascular events such as myocardial infarction or ischemic stroke [120]. In the kidney, excessive mineralocorticoid action leads to renal inflammation, fibrosis, podocyte injury, and mesangial cell proliferation [121]. The pathophysiological consequences of mineralocorticoid action could be reversed by mineralocorticoid receptor antagonists [58, 63, 116, 122–140]. The therapeutic potential of mineralocorticoid receptor antagonists is thus not only confined to their diuretic action, but involves prevention of tissue fibrosis, vascular calcification and vascular occlusive disease.

Disclosure Statement

The author has no conflicts of interest to disclose.

References

- 1 Briet M, Schiffrin EL: Aldosterone: effects on the kidney and cardiovascular system. *Nat Rev Nephrol* 2010;6:261–273.
- 2 Pearce D, Bhargava A, Cole TJ: Aldosterone: its receptor, target genes, and actions. *Vitam Horm* 2003;66:29–76.
- 3 Sakai RR, McEwen BS, Fluharty SJ, Ma LY: The amygdala: site of genomic and nongenomic arousal of aldosterone-induced sodium intake. *Kidney Int* 2000;57:1337–1345.
- 4 Vallon V, Huang DY, Grahmmer F, Wyatt AW, Osswald H, Wulff P, Kuhl D, Lang F: SGK1 as a determinant of kidney function and salt intake in response to mineralocorticoid excess. *Am J Physiol Regul Integr Comp Physiol* 2005;289:R395–R401.
- 5 Harvey BJ, Alzamora R, Stubbs AK, Irnaten M, McEneaney V, Thomas W: Rapid responses to aldosterone in the kidney and colon. *J Steroid Biochem Mol Biol* 2008;108:310–317.
- 6 Weber KT: Aldosteronism revisited: perspectives on less well-recognized actions of aldosterone. *J Lab Clin Med* 2003;142:71–82.
- 7 Funder JW: Aldosterone, hypertension and heart failure: insights from clinical trials. *Hypertens Res* 2010;33:872–875.
- 8 Xanthakis V, Vasan RS: Aldosterone and the risk of hypertension. *Curr Hypertens Rep* 2013;15:102–107.
- 9 Gekle M, Bretschneider M, Meinel S, Ruhs S, Grossmann C: Rapid mineralocorticoid receptor trafficking. *Steroids* 2014;81C:103–108.

- 10 Hawkins UA, Gomez-Sanchez EP, Gomez-Sanchez CM, Gomez-Sanchez CE: The ubiquitous mineralocorticoid receptor: clinical implications. *Curr Hypertens Rep* 2012;14: 573–580.
- 11 Martinierie L, Munier M, Le Menuet D, Meduri G, Viengchareun S, Lommes M: The mineralocorticoid signaling pathway throughout development: expression, regulation and pathophysiological implications. *Biochimie* 2013;95:148–157.
- 12 Fuller PJ, Yao Y, Yang J, Young MJ: Mechanisms of ligand specificity of the mineralocorticoid receptor. *J Endocrinol* 2012;213:15–24.
- 13 Odermatt A, Kratschmar DV: Tissue-specific modulation of mineralocorticoid receptor function by 11 β -hydroxysteroid dehydrogenases: an overview. *Mol Cell Endocrinol* 2012; 350:168–186.
- 14 Dai LJ, Ritchie G, Kerstan D, Kang HS, Cole DE, Quamme GA: Magnesium transport in the renal distal convoluted tubule. *Physiol Rev* 2001;81:51–84.
- 15 Tomaschitz A, Ritz E, Pieske B, Rus-Machan J, Kienreich K, Verheyen N, Gaksch M, Grubler M, Fahrleitner-Pammer A, Mrak P, Toplak H, Kraigher-Krainer E, Marz W, Pilz S: Aldosterone and parathyroid hormone interactions as mediators of metabolic and cardiovascular disease. *Metabolism* 2014;63:20–31.
- 16 Laski ME, Sabatini S: Metabolic alkalosis, bedside and bench. *Semin Nephrol* 2006;26: 404–421.
- 17 Levine DZ, Jacobson HR: The regulation of renal acid secretion: new observations from studies of distal nephron segments. *Kidney Int* 1986;29:1099–1109.
- 18 Wagner CA: Effect of mineralocorticoids on acid-base balance. *Nephron Physiol* 2014;128: 26–34.
- 19 Pelzl L, Pakladok T, Pathare G, Fakhri H, Michael D, Wagner CA, Paulmichl M, Lang F: DOCA sensitive pendrin expression in kidney, heart, lung and thyroid tissues. *Cell Physiol Biochem* 2012;30:1491–1501.
- 20 Fu Y, Vallon V: Mineralocorticoid-induced sodium appetite and renal salt retention: evidence for common signaling and effector mechanisms. *Nephron Physiol* 2014;128: 8–16.
- 21 Murck H, Buettner M, Kircher T, Konrad C: Genetic, molecular and clinical determinants for the involvement of aldosterone and its receptors in major depression. *Nephron Physiol* 2014;128:17–25.
- 22 Shibata H, Itoh H: Mineralocorticoid receptor-associated hypertension and its organ damage: clinical relevance for resistant hypertension. *Am J Hypertens* 2012;25:514–523.
- 23 Wu J, Luft FC: Mineralocorticoid-receptor signalling in vascular smooth muscle. *Nephrol Dial Transplant* 2013;28:1360–1362.
- 24 Barrett KV, McCurley AT, Jaffe IZ: Direct contribution of vascular mineralocorticoid receptors to blood pressure regulation. *Clin Exp Pharmacol Physiol* 2013;40:902–909.
- 25 Koenig JB, Jaffe IZ: Direct role for smooth muscle cell mineralocorticoid receptors in vascular remodeling: novel mechanisms and clinical implications. *Curr Hypertens Rep* 2014;16:427.
- 26 Lang F: Stiff endothelial cell syndrome in vascular inflammation and mineralocorticoid excess. *Hypertension* 2011;57:146–147.
- 27 Oberleithner H, Ludwig T, Riethmüller C, Hillebrand U, Albersmann L, Schafer C, Shahin V, Schillers H: Human endothelium: target for aldosterone. *Hypertension* 2004;43: 952–956.
- 28 Oberleithner H: Is the vascular endothelium under the control of aldosterone? Facts and hypothesis. *Pflügers Arch* 2007;454:187–193.
- 29 Oberleithner H, Kusche-Vihrog K, Schillers H: Endothelial cells as vascular salt sensors. *Kidney Int* 2010;77:490–494.
- 30 Sugiyama T, Yoshimoto T, Tsuchiya K, Gochou N, Hirono Y, Tateno T, Fukai N, Shichiri M, Hirata Y: Aldosterone induces angiotensin converting enzyme gene expression via a JAK2-dependent pathway in rat endothelial cells. *Endocrinology* 2005;146:3900–3906.
- 31 McCurley A, Pires PW, Bender SB, Aronovitz M, Zhao MJ, Metzger D, Chambon P, Hill MA, Dorrance AM, Mendelsohn ME, Jaffe IZ: Direct regulation of blood pressure by smooth muscle cell mineralocorticoid receptors. *Nat Med* 2012;18:1429–1433.
- 32 McGraw AP, McCurley A, Preston IR, Jaffe IZ: Mineralocorticoid receptors in vascular disease: connecting molecular pathways to clinical implications. *Curr Atheroscler Rep* 2013;15:340.
- 33 Briet M, Schiffrin EL: Vascular actions of aldosterone. *J Vasc Res* 2013;50:89–99.
- 34 Lacolley P, Challande P, Osborne-Pellegrin M, Regnault V: Genetics and pathophysiology of arterial stiffness. *Cardiovasc Res* 2009;81: 637–648.
- 35 Jaffe IZ, Tintut Y, Newell BG, Demer LL, Mendelsohn ME: Mineralocorticoid receptor activation promotes vascular cell calcification. *Arterioscler Thromb Vasc Biol* 2007;27: 799–805.
- 36 Voelkl J, Alesutan I, Leibrock CB, Quintanilla-Martinez L, Kuhn V, Feger M, Mia S, Ahmed MS, Rosenblatt KP, Kuro OM, Lang F: Spironolactone ameliorates PIT1-dependent vascular osteoinduction in klotho-hypomorphic mice. *J Clin Invest* 2013;123:812–822.
- 37 Lang F, Ritz E, Alesutan I, Voelkl J: Impact of aldosterone on osteoinductive signaling and vascular calcification. *Nephron Physiol* 2014; 128:40–45.
- 38 Alesutan I, Feger M, Pakladok T, Mia S, Ahmed MS, Voelkl J, Lang F: 25-Hydroxyvitamin D₃ 1 α -hydroxylase-dependent stimulation of renal klotho expression by spironolactone. *Kidney Blood Press Res* 2013;37:475–487.
- 39 Tang C, Pathare G, Michael D, Fajol A, Eichenmüller M, Lang F: Downregulation of Klotho expression by dehydration. *Am J Physiol Renal Physiol* 2011;301:F745–750.
- 40 Artunc F, Amann K, Nasir O, Friedrich B, Sandulache D, Jahovic N, Risler T, Vallon V, Wulff P, Kuhl D, Lang F: Blunted DOCA/high salt induced albuminuria and renal tubulointerstitial damage in gene-targeted mice lacking SGK1. *J Mol Med (Berl)* 2006; 84:737–746.
- 41 Azibani F, Fazal L, Chatziantoniou C, Samuel JL, Delcayre C: Aldosterone mediates cardiac fibrosis in the setting of hypertension. *Curr Hypertens Rep* 2013;15:395–400.
- 42 Bae EH, Kim IJ, Joo SY, Kim EY, Kim CS, Choi JS, Ma SK, Kim SH, Lee JU, Kim SW: Renoprotective effects of sildenafil in DOCA-salt hypertensive rats. *Kidney Blood Press Res* 2012;36:248–257.
- 43 Brown NJ: Contribution of aldosterone to cardiovascular and renal inflammation and fibrosis. *Nat Rev Nephrol* 2013;9:459–469.
- 44 Chen H, Sun F, Zhong X, Shao Y, Yoshimura A, Liu Y: Eplerenone-mediated aldosterone blockade prevents renal fibrosis by reducing renal inflammation, interstitial cell proliferation and oxidative stress. *Kidney Blood Press Res* 2013;37:557–566.
- 45 Fagart J, Huyet J, Pinon GM, Rochel M, Mayer C, Rafestin-Oblin ME: Crystal structure of a mutant mineralocorticoid receptor responsible for hypertension. *Nat Struct Mol Biol* 2005;12:554–555.
- 46 Fejes-Toth G, Naray-Fejes-Toth A: Early aldosterone-regulated genes in cardiomyocytes: clues to cardiac remodeling? *Endocrinology* 2007;148:1502–1510.
- 47 Lahmer T, Hermans R, Schmaderer C, Chang J, Stock K, Lutz J, Heemann U, Baumann M: Mineralocorticoid receptor antagonism and aldosterone synthesis inhibition do not improve glomerulosclerosis and renal interstitial fibrosis in a model of chronic kidney allograft injury. *Kidney Blood Press Res* 2012; 35:561–567.
- 48 Latouche C, Sainte-Marie Y, Steenman M, Castro Chaves P, Naray-Fejes-Toth A, Fejes-Toth G, Farman N, Jaisser F: Molecular signature of mineralocorticoid receptor signaling in cardiomyocytes: from cultured cells to mouse heart. *Endocrinology* 2010;151:4467–4476.
- 49 Lucisano S, Buemi M, Passantino A, Aloisi C, Cernaro V, Santoro D: New insights on the role of vitamin D in the progression of renal damage. *Kidney Blood Press Res* 2013;37: 667–678.
- 50 Makowka A, Olejniczak-Fortak M, Nowicki M: A comparison of the antihypertensive and anti-inflammatory effects of aliskiren and ramipril add-on therapy in peritoneal dialysis patients – a pilot open label study. *Kidney Blood Press Res* 2012;36:18–25.

- 51 Okazaki A, Mori Y, Nakata M, Kimura T, Sonomura K, Sakoda C, Matsuoka E, Ishida M, Yamahara H, Kishimoto N, Nakagawa H, Matsubara H: Peritoneal mesothelial cells as a target of local aldosterone action: upregulation of connective tissue growth factor expression via serum- and glucocorticoid-inducible protein kinase 1. *Kidney Blood Press Res* 2009;32:151–160.
- 52 Tylicki L, Lizakowski S, Rutkowski P, Renke M, Sulikowska B, Heleniak Z, Donderski R, Bednarski R, Przybylska M, Manitus J, Rutkowski B: The enhanced renin-angiotensin-aldosterone system pharmacological blockade – which is the best? *Kidney Blood Press Res* 2012;36:335–343.
- 53 Vallon V, Wyatt AW, Klingel K, Huang DY, Hussain A, Berchtold S, Friedrich B, Grahmmer F, Belaiba RS, Gorlach A, Wulff P, Daut J, Dalton ND, Ross J Jr, Fogel U, Schrader J, Osswald H, Kandolf R, Kuhl D, Lang F: SGK1-dependent cardiac CTGF formation and fibrosis following DOCA treatment. *J Mol Med (Berl)* 2006;84:396–404.
- 54 Yamahara H, Kishimoto N, Nakata M, Okazaki A, Kimura T, Sonomura K, Matsuoka E, Shiotsu Y, Adachi T, Matsubara H, Iwasaka T, Mori Y: Direct aldosterone action as a profibrotic factor via ROS-mediated SGK1 in peritoneal fibroblasts. *Kidney Blood Press Res* 2009;32:185–193.
- 55 Young M, Funder JW: Aldosterone and the heart. *Trends Endocrinol Metab* 2000;11:224–226.
- 56 Young M, Funder J: Mineralocorticoid action and sodium-hydrogen exchange: studies in experimental cardiac fibrosis. *Endocrinology* 2003;144:3848–3851.
- 57 Artunc F, Lang F: Mineralocorticoid stimulation of tissue fibrosis. *Nephron Physiol* 2014.
- 58 Bienvenu LA, Reichelt ME, Delbridge LM, Young MJ: Mineralocorticoid receptors and the heart, multiple cell types and multiple mechanisms: a focus on the cardiomyocyte. *Clin Sci (Lond)* 2013;125:409–421.
- 59 Galuppo P, Bauersachs J: Mineralocorticoid receptor activation in myocardial infarction and failure: recent advances. *Eur J Clin Invest* 2012;42:1112–1120.
- 60 Bender SB, McGraw AP, Jaffe IZ, Sowers JR: Mineralocorticoid receptor-mediated vascular insulin resistance: an early contributor to diabetes-related vascular disease? *Diabetes* 2013;62:313–319.
- 61 Feraco A, Armani A, Mammi C, Fabbri A, Rosano GM, Caprio M: Role of mineralocorticoid receptor and renin-angiotensin-aldosterone system in adipocyte dysfunction and obesity. *J Steroid Biochem Mol Biol* 2013;137:99–106.
- 62 Garg R, Adler GK: Role of mineralocorticoid receptor in insulin resistance. *Curr Opin Endocrinol Diabetes Obes* 2012;19:168–175.
- 63 Ronconi V, Turchi F, Appolloni G, di Tizio V, Boscaro M, Giacchetti G: Aldosterone, mineralocorticoid receptor and the metabolic syndrome: role of the mineralocorticoid receptor antagonists. *Curr Vasc Pharmacol* 2012;10:238–246.
- 64 Berardelli R, Karamouzis I, D'Angelo V, Zichi C, Fussotto B, Giordano R, Ghigo E, Arvat E: Role of mineralocorticoid receptors on the hypothalamus-pituitary-adrenal axis in humans. *Endocrine* 2013;43:51–58.
- 65 De Kloet ER, Joels M, Holsboer F: Stress and the brain: from adaptation to disease. *Nat Rev Neurosci* 2005;6:463–475.
- 66 Deutsch SI, Mastropaolo J: Discriminative stimulus properties of midazolam are shared by a GABA-receptor positive steroid. *Pharmacol Biochem Behav* 1993;46:963–965.
- 67 Rupprecht R, Holsboer F: Neuroactive steroids: mechanisms of action and neuropsychopharmacological perspectives. *Trends Neurosci* 1999;22:410–416.
- 68 Liu G, Liu G, Alzoubi K, Umbach AT, Pelzl L, Borst O, Gawaz M, Lang F: Upregulation of store operated Ca channel Orai1, stimulation of Ca²⁺ entry and triggering of cell membrane scrambling in platelets by mineralocorticoid DOCA. *Kidney Blood Press Res* 2014;38:21–30.
- 69 Oh-hashii S, Takata M, Ueno H, Tomoda F, Yasumoto K, Iida H, Sasayama S: Cytosolic free calcium concentration in platelets in patients with renovascular hypertension and primary aldosteronism. *J Hum Hypertens* 1992;6:71–74.
- 70 Braun A, Vogtle T, Varga-Szabo D, Nieswandt B: STIM and Orai in hemostasis and thrombosis. *Front Biosci (Landmark Ed)* 2011;16:2144–2160.
- 71 Parekh AB: Store-operated CRAC channels: function in health and disease. *Nat Rev Drug Discov* 2010;9:399–410.
- 72 Bergmeier W, Stefanini L: Novel molecules in calcium signaling in platelets. *J Thromb Haemost* 2009;7(suppl 1):187–190.
- 73 Braun A, Varga-Szabo D, Kleinschnitz C, Pleines I, Bender M, Austinat M, Bosl M, Stoll G, Nieswandt B: Orai1 (CRACM1) is the platelet SOC channel and essential for pathological thrombus formation. *Blood* 2009;113:2056–2063.
- 74 Varga-Szabo D, Braun A, Nieswandt B: Calcium signaling in platelets. *J Thromb Haemost* 2009;7:1057–1066.
- 75 Bearer EL, Prakash JM, Li Z: Actin dynamics in platelets. *Int Rev Cytol* 2002;217:137–182.
- 76 Borst O, Munzer P, Gatidis S, Schmidt EM, Schonberger T, Schmid E, Towhid ST, Stellos K, Seizer P, May AE, Lang F, Gawaz M: The inflammatory chemokine CXC motif ligand 16 triggers platelet activation and adhesion via CXC motif receptor 6-dependent phosphatidylinositol 3-kinase/Akt signaling. *Circ Res* 2012;111:1297–1307.
- 77 Harper MT, Poole AW: Store-operated calcium entry and non-capacitative calcium entry have distinct roles in thrombin-induced calcium signalling in human platelets. *Cell Calcium* 2011;50:351–358.
- 78 Mahaut-Smith MP: A role for platelet TRPC channels in the Ca²⁺ response that induces procoagulant activity. *Sci Signal* 2013;6:pe23.
- 79 Mushtaq M, Nam TS, Kim UH: Critical role for CD38-mediated Ca²⁺ signaling in thrombin-induced procoagulant activity of mouse platelets and hemostasis. *J Biol Chem* 2011;286:12952–12958.
- 80 Varga-Szabo D, Braun A, Nieswandt B: STIM and Orai in platelet function. *Cell Calcium* 2011;50:270–278.
- 81 Wolfs JL, Comfurius P, Rasmussen JT, Keuren JF, Lindhout T, Zwaal RF, Bevers EM: Activated scramblase and inhibited aminophospholipid translocase cause phosphatidylserine exposure in a distinct platelet fraction. *Cell Mol Life Sci* 2005;62:1514–1525.
- 82 Borst O, Schmidt EM, Munzer P, Schonberger T, Towhid ST, Elvers M, Leibrock C, Schmid E, Eysenstein A, Kuhl D, May AE, Gawaz M, Lang F: The serum- and glucocorticoid-inducible kinase 1 (SGK1) influences platelet calcium signaling and function by regulation of Orai1 expression in megakaryocytes. *Blood* 2012;119:251–261.
- 83 Schmidt EM, Kraemer BF, Borst O, Munzer P, Schonberger T, Schmidt C, Leibrock C, Towhid ST, Seizer P, Kuhl D, Stournaras C, Lindemann S, Gawaz M, Lang F: SGK1 sensitivity of platelet migration. *Cell Physiol Biochem* 2012;30:259–268.
- 84 Lang F, Bohmer C, Palmada M, Seeböhm G, Strutz-Seeböhm N, Vallon V: (Patho)physiological significance of the serum- and glucocorticoid-inducible kinase isoforms. *Physiol Rev* 2006;86:1151–1178.
- 85 Schmid E, Bhandaru M, Nurbaeva MK, Yang W, Sztajn K, Russo A, Leibrock C, Tyan L, Pearce D, Shumilina E, Lang F: SGK3 regulates Ca²⁺ entry and migration of dendritic cells. *Cell Physiol Biochem* 2012;30:1423–1435.
- 86 Lagrange J, Li Z, Fassot C, Bourhim M, Louis H, Nguyen Dinh Cat A, Parlakian A, Wahl D, Lacolley P, Jaissner F, Regnault V: Endothelial mineralocorticoid receptor activation enhances endothelial protein C receptor and decreases vascular thrombosis in mice. *FASEB J* 2014;10.1096/fj.13-238188.
- 87 Firsov D: Revisiting sodium and water reabsorption with functional genomics tools. *Curr Opin Nephrol Hypertens* 2004;13:59–65.
- 88 Kellner M, Peiter A, Hafner M, Feuring M, Christ M, Wehling M, Falkenstein E, Losel R: Early aldosterone up-regulated genes: new pathways for renal disease? *Kidney Int* 2003;64:1199–1207.

- 89 Sekizawa N, Yoshimoto T, Hayakawa E, Suzuki N, Sugiyama T, Hirata Y: Transcriptome analysis of aldosterone-regulated genes in human vascular endothelial cell lines stably expressing mineralocorticoid receptor. *Mol Cell Endocrinol* 2011;341:78–88.
- 90 Baker ME, Funder JW, Kattoula SR: Evolution of hormone selectivity in glucocorticoid and mineralocorticoid receptors. *J Steroid Biochem Mol Biol* 2013;137:57–70.
- 91 Lang F, Stournaras C: Serum and glucocorticoid inducible kinase, metabolic syndrome, inflammation, and tumor growth. *Hormones (Athens)* 2013;12:160–171.
- 92 Lang F, Voelkl J: Therapeutic potential of serum and glucocorticoid inducible kinase inhibition. *Expert Opin Investig Drugs* 2013;22:701–714.
- 93 Ennis IL, Aiello EA, Cingolani HE, Perez NG: The autocrine/paracrine loop after myocardial stretch: mineralocorticoid receptor activation. *Curr Cardiol Rev* 2013;9:230–240.
- 94 Voelkl J, Lin Y, Alesutan I, Ahmed MS, Pasham V, Mia S, Gu S, Feger M, Saxena A, Metzler B, Kuhl D, Pichler BJ, Lang F: Sgk1 sensitivity of Na⁺/H⁺ exchanger activity and cardiac remodeling following pressure overload. *Basic Res Cardiol* 2012;107:236.
- 95 Voelkl J, Pasham V, Ahmed MS, Walker B, Sztajn K, Kuhl D, Metzler B, Alesutan I, Lang F: Sgk1-dependent stimulation of cardiac Na⁺/H⁺ exchanger Nhe1 by dexamethasone. *Cell Physiol Biochem* 2013;32:25–38.
- 96 Nagase M, Fujita T: Role of Rac1-mineralocorticoid-receptor signalling in renal and cardiac disease. *Nat Rev Nephrol* 2013;9:86–98.
- 97 Christ M, Sippel K, Eisen C, Wehling M: Non-classical receptors for aldosterone in plasma membranes from pig kidneys. *Mol Cell Endocrinol* 1994;99:R31–R34.
- 98 Mohammed SF, Ohtani T, Korinek J, Lam CS, Larsen K, Simari RD, Valencik ML, Burnett JC Jr, Redfield MM: Mineralocorticoid accelerates transition to heart failure with preserved ejection fraction via 'nongenomic effects'. *Circulation* 2010;122:370–378.
- 99 Pietranera L, Saravia FE, McEwen BS, Lucas LL, Johnson AK, De Nicola AF: Changes in Fos expression in various brain regions during deoxycorticosterone acetate treatment: relation to salt appetite, vasopressin mRNA and the mineralocorticoid receptor. *Neuroendocrinology* 2001;74:396–406.
- 100 Quinn S, Harvey BJ, Thomas W: Rapid aldosterone actions on epithelial sodium channel trafficking and cell proliferation. *Steroids* 2014;81C:43–48.
- 101 Roy JW, Hill E, Ruan YC, Vedovelli L, Pausescu TG, Brown D, Breton S: Circulating aldosterone induces the apical accumulation of the proton pumping V-ATPase and increases proton secretion in clear cells in the caput epididymis. *Am J Physiol Cell Physiol* 2013;305:C436–C446.
- 102 Wehling M, Christ M, Theisen K: Membrane receptors for aldosterone: a novel pathway for mineralocorticoid action. *Am J Physiol* 1992;263:E974–E979.
- 103 Wendler A, Albrecht C, Wehling M: Nongenomic actions of aldosterone and progesterone revisited. *Steroids* 2012;77:1002–1006.
- 104 Williams JS: Evolving research in nongenomic actions of aldosterone. *Curr Opin Endocrinol Diabetes Obes* 2013;20:198–203.
- 105 Liu SL, Schmuck S, Chorzyczewski JZ, Gros R, Feldman RD: Aldosterone regulates vascular reactivity: short-term effects mediated by phosphatidylinositol 3-kinase-dependent nitric oxide synthase activation. *Circulation* 2003;108:2400–2406.
- 106 Mutoh A, Isshiki M, Fujita T: Aldosterone enhances ligand-stimulated nitric oxide production in endothelial cells. *Hypertens Res* 2008;31:1811–1820.
- 107 Lindemann S, Tolley ND, Eyre JR, Kraiss LW, Mahoney TM, Weyrich AS: Integrins regulate the intracellular distribution of eukaryotic initiation factor 4E in platelets. A checkpoint for translational control. *J Biol Chem* 2001;276:33947–33951.
- 108 Rosenwald IB, Pechet L, Han A, Lu L, Pihan G, Woda B, Chen JJ, Szymanski I: Expression of translation initiation factors eIF-4E and eIF-2α and a potential physiologic role of continuous protein synthesis in human platelets. *Thromb Haemost* 2001;85:142–151.
- 109 Weyrich AS, Dixon DA, Pabla R, Elstad MR, McIntyre TM, Prescott SM, Zimmerman GA: Signal-dependent translation of a regulatory protein, Bcl-3, in activated human platelets. *Proc Natl Acad Sci USA* 1998;95:5556–5561.
- 110 Munzer P, Tolios A, Pelzl L, Schmid E, Schmidt EM, Walker B, Frohlich H, Borst O, Gawaz M, Lang F: Thrombin-sensitive expression of the store operated Ca²⁺ channel Orail in platelets. *Biochem Biophys Res Commun* 2013;436:25–30.
- 111 Dabrowski R, Szwed H: Antiarrhythmic potential of aldosterone antagonists in atrial fibrillation. *Cardiol J* 2012;19:223–229.
- 112 Lee TM, Chung TH, Lin SZ, Chang NC: Endothelin receptor blockade ameliorates renal injury by inhibition of RhoA/Rho-kinase signalling in deoxycorticosterone acetate-salt hypertensive rats. *J Hypertens* 2014;32:795–805.
- 113 Ma TK, Szeto CC: Mineralocorticoid receptor antagonist for renal protection. *Ren Fail* 2012;34:810–817.
- 114 Namsolleck P, Unger T: Aldosterone synthase inhibitors in cardiovascular and renal diseases. *Nephrol Dial Transplant* 2014;29(suppl 1):i62–i68.
- 115 Nguyen Dinh Cat A, Jaisser F: Extrarenal effects of aldosterone. *Curr Opin Nephrol Hypertens* 2012;21:147–156.
- 116 Zannad F, Gattis Stough W, Rossignol P, Bauersachs J, McMurray JJ, Swedberg K, Struthers AD, Voors AA, Ruilope LM, Bakris GL, O'Connor CM, Gheorghiade M, Mentz RJ, Cohen-Solal A, Maggioni AP, Beygui F, Filippatos GS, Massy ZA, Pathak A, Pina IL, Sabbah HN, Sica DA, Tavazzi L, Pitt B: Mineralocorticoid receptor antagonists for heart failure with reduced ejection fraction: integrating evidence into clinical practice. *Eur Heart J* 2012;33:2782–2795.
- 117 McCurley A, McGraw A, Pruthi D, Jaffe IZ: Smooth muscle cell mineralocorticoid receptors: role in vascular function and contribution to cardiovascular disease. *Pflugers Arch* 2013;465:1661–1670.
- 118 Ueda K, Nagase M: Mineralocorticoid receptor activation as an etiological factor in kidney diseases. *Clin Exp Nephrol* 2014;18:16–23.
- 119 Gawaz M: Role of platelets in coronary thrombosis and reperfusion of ischemic myocardium. *Cardiovasc Res* 2004;61:498–511.
- 120 Bigalke B, Stellos K, Geisler T, Kremmer E, Seizer P, May AE, Lindemann S, Melms A, Luft A, Gawaz M: Expression of platelet glycoprotein VI is associated with transient ischemic attack and stroke. *Eur J Neurol* 2010;17:111–117.
- 121 Fourkios VG, Hanslik G, Hanusch F, Lepenies J, Quinkler M: Aldosterone and the kidney. *Horm Metab Res* 2012;44:194–201.
- 122 Allen LA, Shetterly SM, Peterson PN, Gurtwitz JH, Smith DH, Brand DW, Fairclough DL, Rumsfeld JS, Masoudi FA, Magid DJ: Guideline concordance of testing for hyperkalemia and kidney dysfunction during initiation of mineralocorticoid receptor antagonist therapy in patients with heart failure. *Circ Heart Fail* 2014;7:43–50.
- 123 Baker WL, White WB: Safety of mineralocorticoid receptor antagonists in patients receiving hemodialysis. *Ann Pharmacother* 2012;46:889–894.
- 124 Bombardier AS, Klemmer PJ: Mineralocorticoid receptor blockade in chronic kidney disease. *Blood Purif* 2012;33:119–124.
- 125 Collin M, Niemann F, Jaisser F: Mineralocorticoid receptor modulators: a patent review (2007–2012). *Expert Opin Ther Pat* 2014;24:177–183.
- 126 Funder JW: Mineralocorticoid receptor antagonists: emerging roles in cardiovascular medicine. *Integr Blood Press Control* 2013;6:129–138.
- 127 Hammer F, Krane V, Stork S, Roser C, Hofmann K, Pollak N, Allolio B, Wanner C: Rationale and design of the Mineralocorticoid Receptor Antagonists in End-Stage Renal Disease Study (MiRenDa). *Nephrol Dial Transplant* 2014;29:400–405.
- 128 Markowitz M, Messineo F, Coplan NL: Aldosterone receptor antagonists in cardiovascular disease: a review of the recent literature and insight into potential future indications. *Clin Cardiol* 2012;35:605–609.

- 129 Mavrakanas TA, Gariani K, Martin PY: Mineralocorticoid receptor blockade in addition to angiotensin converting enzyme inhibitor or angiotensin II receptor blocker treatment. An emerging paradigm in diabetic nephropathy: a systematic review. *Eur J Intern Med* 2014;25:173–176.
- 130 Piotrowski DW: Mineralocorticoid receptor antagonists for the treatment of hypertension and diabetic nephropathy. *J Med Chem* 2012;55:7957–7966.
- 131 Pitt B: The role of mineralocorticoid receptor antagonists in patients with American College of Cardiology/American Heart Association stage B heart failure. *Heart Fail Clin* 2012;8:247–253.
- 132 Richards AM: Mineralocorticoid receptor antagonists for heart failure. *Expert Opin Pharmacother* 2011;12:2801–2815.
- 133 Roscioni SS, de Zeeuw D, Bakker SJ, Lambers Heerspink HJ: Management of hyperkalaemia consequent to mineralocorticoid-receptor antagonist therapy. *Nat Rev Nephrol* 2012;8:691–699.
- 134 Sato A: Mineralocorticoid receptor antagonists: their use and differentiation in Japan. *Hypertens Res* 2013;36:185–190.
- 135 Seawell MR, Al Darazi F, Farah V, Ramathan KB, Newman KP, Bhattacharya SK, Weber KT: Mineralocorticoid receptor antagonism confers cardioprotection in heart failure. *Curr Heart Fail Rep* 2013;10:36–45.
- 136 Shavit L, Lifschitz MD, Epstein M: Aldosterone blockade and the mineralocorticoid receptor in the management of chronic kidney disease: current concepts and emerging treatment paradigms. *Kidney Int* 2012;81:955–968.
- 137 Talatinian A, Chow SL, Heywood JT: Expanding role of mineralocorticoid receptor antagonists in the treatment of heart failure. *Pharmacotherapy* 2012;32:827–837.
- 138 Van den Berg TN, Rongen GA, Frohlich GM, Deinum J, Hausenloy DJ, Riksen NP: The cardioprotective effects of mineralocorticoid receptor antagonists. *Pharmacol Ther* 2014;142:72–87.
- 139 Young MJ: Targeting the mineralocorticoid receptor in cardiovascular disease. *Expert Opin Ther Targets* 2013;17:321–331.
- 140 Zwadlo C, Bauersachs J: Mineralocorticoid receptor antagonists for therapy of coronary artery disease and related complications. *Curr Opin Pharmacol* 2013;13:280–286.