30 YEARS OF THE MINERALOCORTICOID RECEPTOR

Nongenomic effects via the mineralocorticoid receptor

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Abstract

The mineralocorticoid receptor (MR) belongs to the steroid hormone receptor family and classically functions as a ligand-dependent transcription factor. It is involved in water-electrolyte homeostasis and blood pressure regulation but independent from these effects also furthers inflammation, fibrosis, hypertrophy and remodeling in cardiovascular tissues. Next to genomic effects, aldosterone elicits very rapid actions within minutes that do not require transcription or translation and that occur not only in classical MR epithelial target organs like kidney and colon but also in nonepithelial tissues like heart, vasculature and adipose tissue. Most of these effects can be mediated by classical MR and its crosstalk with different signaling cascades. Near the plasma membrane, the MR seems to be associated with caveolin and striatin as well as with receptor tyrosine kinases like EGFR, PDGFR and IGF1R and G protein-coupled receptors like AT1 and GPER1, which then mediate nongenomic aldosterone effects. GPER1 has also been named a putative novel MR. There is a close interaction and functional synergism between the genomic and the nongenomic signaling so that nongenomic signaling can lead to long-term effects and support genomic actions. Therefore, understanding nongenomic aldosterone/MR effects is of potential relevance for modulating genomic aldosterone effects and may provide additional targets for intervention.

Key Words
- cardiovascular
- corticosteroids
- growth factor receptors
- aging
- renin–angiotensin system

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Early milestones in aldosterone research

In 1953 aldosterone was isolated and characterized by Simpson and Tait and subsequently in 1960 genomic steroid actions were described (Clever & Karlson 1960). Already very early on, aldosterone effects that were very rapid and therefore could not be reconciled with a genomic mechanism were described (Ganong & Mulrow 1958, Klein & Henk 1964, Spach & Streeten 1964, Fujii *et al.* 1990). These effects of aldosterone included rapid flux of ions in erythrocytes and the kidney, stimulation of Na^+-K^+ pump activity and changes in cardiovascular parameters including a decrease in cardiac output and an increase in peripheral resistance. However, neither their nongenomic nor their nonepithelial origin was fully appreciated and it took until 1984 for a nongenomic mechanism to be demonstrated (Moura & Worcel 1984). Shortly after in 1987 the classical MR was cloned and characterized (Arriza *et al.* 1987).

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Beginning in the 1990s, nongenomic signaling effects were investigated on a cellular level and a membrane receptor for aldosterone was postulated. Based on the findings that actinomycin D and cycloheximide were not able to block the influence of aldosterone on the activity of the sodium–proton exchanger and on cell volume in HML cells, a nongenomic signaling mechanism was deduced by Wehling and coworkers (Wehling *et al.* 1991, 1992, Christ *et al.* 1994, Wildling *et al.* 2008). Because glucocorticoids were less effective to induce these effects and MR antagonists could not block them, the existence of a new membrane aldosterone receptor was postulated. Although exhibiting some inconsistencies, data on rapid calcium and cAMP signaling in skin cells of global MR knockout mice seemed to support this hypothesis (Haseroth *et al.* 1999). Several attempts were made to isolate and characterize such an aldosterone specific membrane receptor from HML and porcine kidney membranes but never completely convincingly succeeded (Wehling *et al.* 1991, 1992, Eisen *et al.* 1994, Wildling *et al.* 2008). Thereafter, it was shown that many of the nongenomic aldosterone effects seem to depend on classical MR (Liu *et al.* 2003, Callera *et al.* 2005*b*, McEneaney *et al.* 2010*a*). In cells without endogenous MR, many of the rapid signaling effects like activation of MAP kinases could only be detected after transfection of an MR expression plasmid. Expressing exclusively the E/F domain of the MR was sufficient for the induction of rapid aldosterone effects (Grossmann *et al.* 2005, 2008). Additionally, it was shown that some aldosterone effects cannot be blocked by spironolactone but by other MR antagonists like K^+ canrenoate or RU28313 so that ineffectiveness of spironolactone does not necessarily mean that the classical MR is not involved in an effect (Alzamora *et al.* 2000, Mihailidou & Funder 2005). Nevertheless, aldosterone was still able to induce rapid signaling if aldosterone was conjugated to BSA or PEG and in cells devoid of classical MR so that both MR-dependent and -independent mechanisms seem to lead to nongenomic aldosterone effects (Le Moellic *et al.* 2004, Grossmann *et al.* 2005, Wildling *et al.* 2008, Ashton *et al.* 2015). While early works focused on characterizing transporters and intracellular signaling molecules like calcium ions and kinases (Funder 2005, Grossmann & Gekle 2009), more recent studies have identified additional interaction partners of the MR at the plasma membrane.

Interaction partners at the plasma membrane

For the rapid MR-dependent aldosterone effects, a localization of the classical MR near the plasma membrane has been indicated in several studies (Grossmann *et al.* 2010, Callera *et al.* 2011, Coutinho *et al.* 2014, Ashton *et al.* 2015). Since the MR lacks a palmitoylation site that has been identified as transmembrane domain in other steroid receptors, it does not seem to be directly inserted into the plasma membrane. Most likely this is achieved by an association of MR to the cytosolic side of the plasma membrane by scaffolding proteins that are associated to or inserted in the cell membrane (Grossmann *et al.* 2010).

Scaffolding proteins

Recently, striatin and caveolin-1 (CAV1) were identified as candidates for such scaffolding proteins (Coutinho *et al.* 2014, Ashton *et al.* 2015). For both proteins evidence for

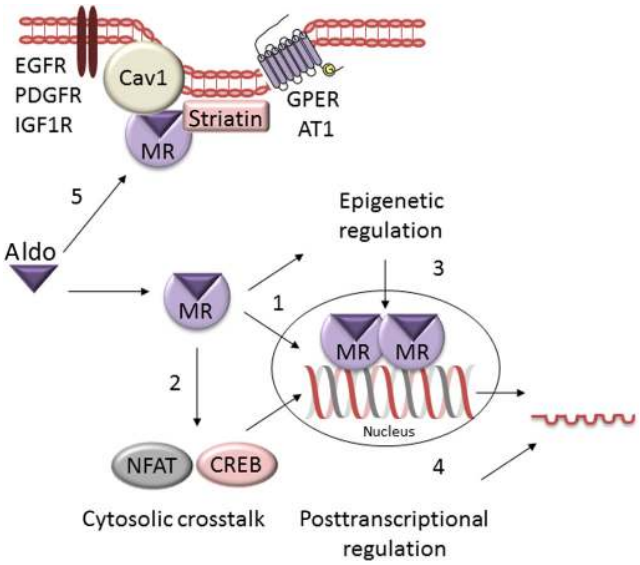

Figure 1
Aldosterone/MR signaling. Aldosterone (aldo) has several mechanisms of action. (1) It can bind to cytosolic MR and initiate translocation of MR into the nucleus, where the MR homodimerizes and acts as a transcription factor. (2) Additionally, aldosterone and MR can initiate a crosstalk with other cytosolic signaling pathways, like for example NFAT and CREB signaling, which ultimately may affect genomic signaling. (3) Genomic MR signaling may be influenced by epigenetic regulation by histone modification or promoter methylation and also by (4) posttranscriptional regulation for example by microRNAs. (5) Aldosterone can also bind to MR attached to the plasma membrane by scaffolding proteins like Cav1 and striatin. There it may elicit nongenomic effects by interacting with receptors, i.e. receptor tyrosine kinases like EGFR, PDGFR and IGF1R or GPCR like AT1 or GPER1.

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an involvement in nongenomic signaling as part of a larger membrane complex exists (Fig. 1).

Striatin Striatin is a scaffolding protein that contains several protein-binding domains, which enable it to interact with and activate different signal transduction molecules. These domains include a caveolin binding motif that attaches it to the plasma membrane, a coiled-coil-domain, a Ca^{++}-calmodulin-binding site and WD-repeat domains for interactions with Gαi proteins and PP2A phosphatase (Hwang & Pallas 2014). In endothelial cells and murine heart tissue, complexes between striatin and MR have been described that can be disrupted by aldosterone but cannot be restored by spironolactone (Pojoga *et al.* 2012, Ashton *et al.* 2015). Activation of MR by high levels of aldosterone increases striatin levels in vascular cells and in tissues of mouse models with elevated aldosterone concentrations (Ricchiuti *et al.* 2011, Pojoga *et al.* 2012). Lowering striatin levels in endothelial cells reduces nongenomic aldosterone/MR-dependent ERK phosphorylation without affecting EGF-induced ERK phosphorylation or genomic MR signaling (Coutinho *et al.* 2014). The relevance of striatin for MR signaling is further suggested by the analysis of heterozygous striatin KO mice with low striatin levels and salt sensitive blood pressure. In this model, pAKT/AKT ratio, another potential nongenomic MR signaling pathway, is reduced while MR expression and genomic signaling are increased (Garza *et al.* 2014). Consequently, striatin seems to play a role in nongenomic MR signaling. A similar role in nongenomic steroid receptor signaling has been described for striatin in estrogen receptor alpha signaling, where striatin is involved in the activation of AKT and eNOS and estrogen-mediated protection of arteries after injury (Lu *et al.* 2004, Bernelot Moens *et al.* 2012).

Caveolin Caveolins are membrane-bound scaffolding proteins enriched in caveolae that help to form microdomains for signal transduction, i.e. for PI3K/AKT signaling, ERK1/2, NO, eNOS, G protein-coupled receptors (GPCRs), tyrosine kinases and PKC (Yang *et al.* 2016). For other steroid receptors, caveolin acts as a control point for crosstalk with other signaling pathways (Igarashi *et al.* 2013). Both AT1 and MR coimmunoprecipitate with CAV1 in rat, mouse and human tissues and the MR contains a caveolin binding motif in the middle of n-terminal domain (between aa 450 and 460 (FPFMDGSYFSF) (Ushio-Fukai & Alexander 2006, Pojoga *et al.* 2010*b*, Coutinho *et al.* 2014). Aldosterone induces caveolin-1 expression in endothelial cells (BAEC), an effect that can be inhibited by spironolactone (Igarashi *et al.* 2013). In *Cav1* KO mice an interaction between MR and striatin is no longer detectable and MR expression is reduced (Pojoga *et al.* 2010*a*, Coutinho *et al.* 2014). Conversely, during sodium load, CAV1 and MR expression are increased and more complexes between the two can be detected (Ricchiuti *et al.* 2011). There are several indications that Cav1 is associated with MR signaling although the exact mechanisms remain to be investigated. In *Cav1* KO mice on a high salt diet, MR blockade increases blood pressure and vascular contraction but reduces eNOS expression and vasorelaxation so that MR seems to play a beneficial role (Pojoga *et al.* 2010*a*). Additionally, *Cav1* KO mice and carriers of *Cav1* gene variants are prone to insulin resistance, dyslipidemia and other metabolic abnormalities probably due to impaired aldosterone/MR signaling (Pojoga *et al.* 2011, Baudrand *et al.* 2016). After challenge with L-NAME and angiotensin II (angII), *Cav1* KO mice showed disturbed MR signaling with reduced MR and PAI-1 expression and were protected from myocardial damage despite higher increases in systolic blood pressure than WT mice (Pojoga *et al.* 2010*b*).

Overall, there are indications that both striatin and caveolin are involved in nongenomic MR signaling by associating classical MR to the plasma membrane. Additionally, CAV1 is an excellent candidate for linking the MR to membrane receptors like receptor tyrosine kinases and also GPCRs, for which transactivation or a crosstalk with classical MR has been demonstrated. Furthermore, CAV1 is also associated with many other molecules like eNOS and c-SRC, which are activated as a result of rapid aldosterone/MR signaling, suggesting that a larger membrane signaling complex exists for mediating various nongenomic aldosterone effects and that the classical MR is an integral part of this complex.

Membrane receptors

As part of rapid MR signaling, transactivation of receptor tyrosine kinases including EGFR, PDGFR and IGF1R has been described. For GPCRs even more complex synergistic activities have been reported especially for AT1 and GPER1. GPER1 has even been declared an aldosterone receptor although direct binding of aldosterone has not been shown. All of these receptors are located in close proximity to the putative MR scaffolding proteins described previously and they have been mostly studied as modulators of pathological MR effects.

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EGFR Of the membrane receptor tyrosine kinases involved in aldosterone signaling, the epidermal growth factor receptor (EGFR) seems to be of special importance as a signal integrator for both physiological and pathophysiological aldosterone effects. The EGFR is associated to CAV1 and can be transactivated by aldosterone/MR either through a C-SRC- or ROS-dependent mechanism, which then leads to downstream MAP kinase and/or PI3 kinase signaling (Mazak *et al.* 2004, Grossmann *et al.* 2005, 2008, McEneaney *et al.* 2007, Huang *et al.* 2009). Importantly, the EGFR cascade is also linked to other important signaling components of aldosterone like G protein-coupled AT1 and GPER signaling and PDGFR activation. Physiological MR effects mediated via EGFR include processes that enhance surface expression of different transporters like ENaC (McEneaney *et al.* 2007), NHE1 (Gekle *et al.* 2002) or NHE3 (Drumm *et al.* 2006) in epithelial tissues. Pathophysiological MR actions mediated by EGFR include proinflammatory effects in vessels, where aldosterone can increase lipoxygenase expression via MAPK activation (Limor *et al.* 2009) and where enhanced TGFbeta, ICAM1 and collagen I expression in VSMCs of aged rats can be attenuated by MR or MAP kinase inhibitors (Krug *et al.* 2010). In conjunction with AT1 signaling, aldosterone via EGFR can also induce a mitogenic response and enhanced cell migration (Min *et al.* 2005, Montezano *et al.* 2008). Transactivation of EGFR by aldosterone/MR can furthermore aggravate fibrosis through induction of fibroblast proliferation via PDGFR, PI3K and MAP kinase signaling shown in kidney and by augmenting collagen synthesis in vascular and HEK cells in a favorable micromilieu (Gekle *et al.* 2007, Huang *et al.* 2012). A truncated MR variant without DNA-binding domain is sufficient to enhance extracellular matrix production, which supports a nongenomic nature of the effect (Grossmann *et al.* 2008). In the kidney, aldosterone via MR additionally induces mesangial cell proliferation via ROS-dependent activation of EGFR, leading to combined ERK1/2 and PI3K/mTOR signaling (Huang *et al.* 2009). There is a close interaction between genomic and nongenomic aldosterone signaling because aldosterone/MR can both transactivate the EGFR and enhance its expression (Dorrance *et al.* 2001, Nakano *et al.* 2005, Meinel *et al.* 2013). Furthermore, nongenomic aldosterone-mediated ERK1/2 phosphorylation seems to enhance MR nuclear shuttling and thereby transactivation activity (Grossmann *et al.* 2005).

PDGFR Another receptor tyrosine kinase located in caveolae and involved in aldosterone signaling is the platelet-derived growth factor receptor (PDGFR). It can also be transactivated by MR and AT1, which then lead to C-SRC activation, increased NADPH oxidase activity and cell migration (Montezano *et al.* 2008). Additionally, PDGFR-C-SRC signaling is involved in aldosterone-dependent proinflammatory responses, namely increased ICAM and VCAM expression and stimulation of monocyte adhesion to VSMCs. Together with the EGFR, PDGFR induces fibroblast proliferation in the kidney (Huang *et al.* 2012). Interestingly, PDGF was shown to stimulate nuclear MR translocation in pulmonary artery smooth muscle cells as well as cell proliferation (Preston *et al.* 2013) indicating that nongenomic aldosterone effects support genomic ones.

IGF1R A third receptor tyrosine kinase, interacting with aldosterone signaling is the insulin-like-growth factor 1 receptor (IGF1R), which has been investigated in renal epithelial cells and in fibroblasts of different origin (Holzman *et al.* 2007, Mitts *et al.* 2010). Its transactivation by aldosterone in cardiac fibroblasts cannot be inhibited by spironolactone, involves activation of Gα13 and c-src and leads to enhanced elastogenesis (Bunda *et al.* 2007, 2009). Likewise in renal fibroblasts, a rapid MR-independent fibronectin synthesis that requires C-SRC mediated IGF1R transactivation with subsequent ERK1/2 phosphorylation has been described (Chen *et al.* 2013). Besides transactivating IGF1R, aldosterone again can genomically increase its expression (and that of hybrid receptor), leading to VSMC growth, migration, protein synthesis and insulin resistance (Cascella *et al.* 2010, Sherajee *et al.* 2012). In a diabetes mouse model with over-expression of aldosterone synthase, an increase in IGF1R expression was associated with protection against diabetes-associated cardiac changes (Fazal *et al.* 2014), suggesting that in this scenario nongenomic signaling may even exert some beneficial effects.

AT1 Besides receptor tyrosine kinases, GPCRs are also important interaction partners of nongenomic aldosterone/MR signaling. For angII receptor I (AT1), a complex interaction with aldosterone/MR signaling on different levels is reported in literature and spironolactone, for example, can inhibit angII-mediated pathological effects by improving cardiac and vascular changes, including fibrosis, hypertrophy and oxidative stress in rats (Ullian *et al.* 1992, 1996, Fiebeler *et al.* 2001, Virdis *et al.* 2002, Neves *et al.* 2003, 2005). Besides a genomic component whereby aldosterone regulates ACE

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(and thereby angII synthesis), MR and AT1 expression in the cardiovascular system, MR and AT1 signaling cascades also interact on a nongenomic level (Zennaro *et al.* 1996, Sugiyama *et al.* 2005, Hirono *et al.* 2007, Tsai *et al.* 2013). In VSMCs this was shown by demonstrating a synergistic effect of angII and aldosterone on ERK1/2 phosphorylation that results in cell proliferation, migration and cell senescence (Mazak *et al.* 2004, Min *et al.* 2005, 2007). In the brain the crosstalk between MR and AT1 and MAP kinase signaling is involved in increased sympathetic drive and hypertension (Xue *et al.* 2011, Zhang *et al.* 2012). As a second common signaling mechanism, IGF1R and redox-dependent activation of kinases like RHOA kinase was described, which support VSMC migration (Montezano *et al.* 2008). Furthermore, aldosterone-induced rapid vasoconstriction in coronary arterioles was dependent on AT1 and possibly AT1 dimer formation but in this case, spironolactone was not able to block the effect of aldosterone (Kushibiki *et al.* 2007, Yamada *et al.* 2008). While aldosterone-dependent phosphorylation of ERK1/2, JNK and NFκB requires AT1, angII-dependent activation of NFκB requires MR (Lemarie *et al.* 2008). Additionally, transactivation of the MR by angII (and AT1) with subsequent regulation of MR-dependent genes has been demonstrated (Xiao *et al.* 2004, Jaffe & Mendelsohn 2005). Relevance of G protein-coupled receptor signaling for pathological aldosterone effects is demonstrated by the attenuation of cardiac damage including ROS production, myocyte cell death and hypertrophy by either MR or AT1 blockade and the involvement of GRK2 and GRK5 (Cannavo *et al.* 2016).

GPER1 Another G protein-coupled receptor with special relevance for nongenomic aldosterone signaling is G protein-coupled estrogen receptor 1 (GPER1), alias GPR30, which is best known for conveying nongenomic estrogen effects in different model systems but has also been proposed to be a novel aldosterone receptor. As estrogen receptor in the cardiovascular system, it influences vascular tone through modulation of p-eNOS/eNOS and pERK/ERK ratios as well as apoptosis via PI3K, c-SRC and EGFR and also influences PKA (Filardo *et al.* 2000, 2002, Meyer *et al.* 2016). A protective role in pulmonary hypertension, atherosclerosis and diabetes has been postulated (Barton & Prossnitz 2015, Prossnitz & Hathaway 2015).

An interaction between aldosterone, MR and GPER1 signaling was first described in VSMCs by Gros and coworkers who later showed that ERK1/2 phosphorylation was stimulated by aldosterone via GPER1 and MR and could be inhibited by eplerenone or the GPER1 antagonist G15 (Gros *et al.* 2007, 2011). Likewise, apoptosis induction via PI3K, ERK1/2 as well as MLC phosphorylation was enhanced by aldosterone via both receptors. Interestingly, GPER1 had no effect on corticosterone- or angII-mediated ERK1/2 phosphorylation (Gros *et al.* 2011). In endothelial cells aldosterone and the GPER1 agonist G1 both induced ERK phosphorylation and also apoptosis. These experiments suggest a crosstalk between aldosterone and GPER1 signaling but do not prove a direct binding or interaction between aldosterone and GPER1.

Further support for a crosstalk comes from experiments showing that nanomolar concentration of aldosterone are able to enhance angII-mediated vasoconstriction in human coronary microarteries in a GPER1- and EGFR-dependent manner (Batenburg *et al.* 2012). In mesenteric resistance arteries, aldosterone led to enhanced maximal phenylephrine-induced vasocontraction that could be reversed by GPER1 inhibitor and to reduced acetylcholine-induced vasorelaxation depending on MR and GPER1 (Ferreira *et al.* 2015). Likewise, vasocontraction in diabetic db/db mice in response to phenylephrine could be reduced by MR or GPER1 inhibitors, however, aldosterone-induced vasorelaxation was only dependent on MR (Ferreira *et al.* 2015). Furthermore, aldosterone could endothelium-dependently inhibit phenylephrine-mediated vasoconstriction of aortic rings via GPER1 (Gros *et al.* 2013). This suggests that the effects of aldosterone on vascular tone and function are complex and dependent on both receptors MR and GPER1 and the dominant cell type, i.e. endothelial and vascular smooth muscle cells. Interestingly, striatin does not only serve as a scaffolding protein for MR but also for GPER1; and MR-striatin complexes can be disrupted by G1 and restored by the GPER antagonist G36 but not by spironolactone (Ashton *et al.* 2015).

Experiments in other organs suggest that GPER1 also plays a role in nongenomic aldosterone signaling in heart, kidney and in tumors. However, although pegylated aldosterone could induce ERK1/2 phosphorylation and superoxide production in H9c2 cells, it was not able to aggravate the infarct size in an *ex vivo* rat model of myocardial infarction like unmodified aldosterone. This indicates that GPER1 activation at the membrane is not sufficient to trigger pathophysiological aldosterone effects in myocardial reperfusion injury (Ashton *et al.* 2015). Furthermore, in rat cardiomyocytes, aldosterone and G1 could enhance sodium bicarbonate cotransporter (NBC) activity depending on GPER1, EGFR, ROS production and

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AKT stimulation (De Giusti *et al.* 2015). In cardiac vagal neurons vagal tone and thereby bradycardia was increased via GPER1 and calcium signaling (Brailoiu *et al.* 2013, De Giusti *et al.* 2015) while in the kidney, a sensitization of renal connecting tubule glomerular feedback by aldosterone involved nongenomic effects via GPER1, classical MR and sodium–proton exchanger 1 (NHE1) (Ren *et al.* 2014). In addition, aldosterone induced cell proliferation and migration of tumor cells via GPER1, and it also induced pulmonary tumor spread that could be inhibited by spironolactone and GPER1 inhibition (Feldman *et al.* 2016). Functionally, MR and GPER1 contribute to proliferation and migration of breast and endothelial cancer cells by mediating an upregulation of NHE1 (Rigiracciolo *et al.* 2016). Consequently, there are many indications for functional involvement of GPER1 in rapid aldosterone/MR signaling (Ashton *et al.* 2015) (Fig. 2). However, although estradiol was shown to bind to the plasma membrane fraction in GPER1 over-expressing HEK cells or SKBr3 cells with endogenous GPER1 expression, no binding of aldosterone was found and displacement of 3H-estradiol was also not possible. In these cellular systems, aldosterone elicited no recruitment of GTPyS to the plasma membrane, which would have supported a direct GPER1 activation by aldosterone as a ligand (Cheng *et al.* 2014). It has also not been fully elucidated why specific MR antagonists sometimes are able to block G1 and GPER1 effects so that further work is required to establish the exact role of GPER1 for nongenomic aldosterone signaling.

In summary, nongenomic aldosterone signaling often seems to rely on classical MR and a crosstalk with membrane-associated signaling cascades, including receptor tyrosine kinase and GPCR pathways. Although many participating signaling components have been identified, the precise spatial and temporal sequence of events has not been elucidated. Also the existence and identity of a possible additional aldosterone receptor is still not clear.

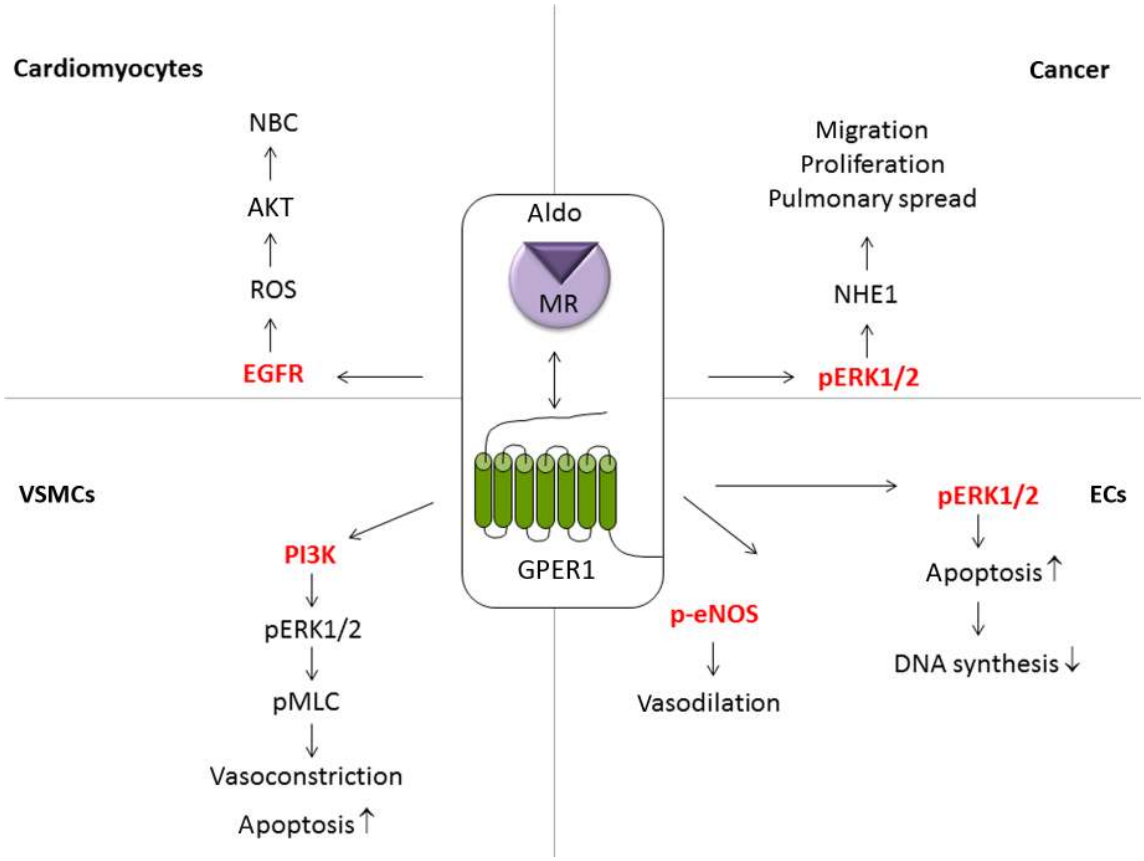

Figure 2
Functional interaction between aldosterone and GPER1. There are many indications for a functional interaction between aldosterone/MR and GPER1 signaling, especially in cardiovascular cells (endothelial cells (ECs), vascular smooth muscle cells (VSMCs) and cardiomyocytes) as well as in tumor cells. NBC, sodium bicarbonate cotransporter; pMLC, phosphorylated myosin light chain.

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Target tissues of nongenomic MR effects

Nongenomic MR signaling has been mostly studied as modulator of physiological and pathological genomic MR effects. Consequently, they have been especially well characterized not only in classical epithelial MR target organs like the kidney but also in cardiovascular tissues. They are often involved in ion transport but can also facilitate pathological MR effects that lead to inflammation, fibrosis and impaired tissue and organ function.

Nongenomic aldosterone effects in the kidney

The MR is best known for its effects in classical epithelial tissues like kidney, where it increases sodium reabsorption and potassium secretion through genomic changes in ion transporters like epithelial sodium channel (ENaC), Na^+-K^+-ATPase and sodium–proton exchanger (NHE). The abundance of transporters at the plasma membrane is stabilized through aldosterone-dependent expression of proteins like SKG1, GILZ, CNKSR3 and ubiquitin-specific protease 2–45 (Oberfeld *et al.* 2011). In addition, a rapid increase in transport activity within minutes that cannot be explained by transcriptional regulation was detected for many of the transporters, suggesting that nongenomic effects enhance genomic effects by ensuring their early start or by perhaps functioning as feedback loops.

ENaC ENaC consists of three subunits and sodium reabsorption depends on the surface abundance of the subunits and their open probability. Genomically, aldosterone directly regulates ENaCα expression, which facilitates sodium reabsorption. Via a genomic regulation of SGK1 expression and activity, aldosterone leads to phosphorylation of the ubiquitin ligase, NEDD4-2, which abolishes ubiquitination and degradation of ENaC subunits beta and gamma. Furthermore SGK is involved in phosphorylation of regulatory proteins that facilitate trafficking of ENaC subunits to the cell surface (Liang *et al.* 2010). Besides genomically controlling the expression and degradation of ENaC subunits, aldosterone also influences subcellular trafficking of ENaC subunits to the cell membrane and influences ENaC open probability by nongenomic mechanisms. Through activation of EGFR, PKC and PKD, rapid trafficking of ENaC subunits to the apical membrane followed by prolonged increased apical membrane expression and activity was reported (Loffing *et al.* 2001, McEneaney *et al.* 2008, 2010*b*, Kusche-Vihrog *et al.* 2008, Dooley *et al.* 2013). Subcellular trafficking seems to be modulated by members of the RAS GTPase superfamily and associated kinases that are known to modulate cytoplasmic cytoskeleton structure (Karpushev *et al.* 2010). For example, for RHOA, an increase in ENaC subunit insertion into the plasma membrane through effects on microtubule was reported (Pochynyuk *et al.* 2006, 2007). For RAC-1, which also enhances ENaC activity, an upregulation of MR nuclear translocation and transcriptional activity was demonstrated and even a ligand independent activation of the MR was shown (Staruschenko *et al.* 2004, Shibata *et al.* 2008, Pavlov *et al.* 2004). Activation and enhanced expression of KRasA in renal cells by aldosterone furthermore led to an increased open probability of ENaC via the PI3K signaling cascade (Staruschenko *et al.* 2004). Furthermore, Blazer-Yost and coworkers and Yu and coworkers (Blazer-Yost *et al.* 1997, Yu *et al.* 2013) show that aldosterone also influences epigenetic regulation by promoter methylation and by histone modification, which may both be important for ENaC expression (Zhang *et al.* 2006, 2007). Enhanced nongenomic aldosterone-induced ENaC activity was also reported to rely on channel methylation (Stockand *et al.* 2000, Zhou & Bubien 2001). In summary, aldosterone-induced sodium reabsorption by ENaC has genomic and nongenomic elements. Besides facilitating genomic effects, nongenomic effects can also be involved in regulatory feedback loops, as can be seen for ENaC activity which can be decreased by enhanced nongenomic MR-MAP kinase activation (Booth & Stockand 2003, Grossmann *et al.* 2004).

Na^+-K^+-ATPase In the collecting tubule early effects of aldosterone on Na^+-K^+-ATPase activity have been described in adrenalectomized animals but are controversial (Doucet & Katz 1981, El Mernissi & Doucet 1984, Fujii *et al.* 1990). Discrepancies in reports may result from indirect effects of other transporters on Na^+-K^+-ATPase pump activity or from different isoforms expressed in different models and tissues (Summa *et al.* 2004). Again just like for ENaC, Na^+-K^+-ATPase response to aldosterone seems to involve trafficking of preexisting subunits to the membrane as well as *de novo* synthesis (El Mernissi & Doucet 1984, Blot-Chabaud *et al.* 1990, Kolla & Litwack 2000, Summa *et al.* 2001, Musch *et al.* 2008). *SGK*, an MR target gene, and aldosterone were shown to stimulate long-term effects synergistically but independently (Alvarez de la Rosa *et al.* 2006).

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Aldosterone-induced trafficking of the Na^+-K^+-ATPase α and β subunits to the basolateral membrane was dependent on PKD, suggesting a nongenomic mechanism (Dooley *et al.* 2013). Furthermore, activation of PKC was shown to be required for aldosterone-induced genomic increase in α1-Na^+-K^+-ATPase mRNA, thus functionally linking nongenomic to genomic effects (Le Moellic *et al.* 2004). Therefore, overall, Na^+-K^+-ATPase activity seems to facilitate chronic sodium reabsorption in the collecting duct mediated by genomic and modulated by nongenomic aldosterone signaling events. However, a rapid inhibitory component on Na^+-K^+-ATPase activity mediated by PKC in cardiomyocytes and vascular tissue was also described for aldosterone (Alzamora *et al.* 2003, Mihailidou *et al.* 2004).

NHE For both NHE1 and NHE3 rapid aldosterone-dependent changes in signaling and ion transport activity have been reported. While NHE1 is expressed ubiquitously at the basal membrane of polarized tissues and also in unpolarized cells, NHE3 is expressed in apical membranes in the renal and intestinal tissues that are responsible for Na^+ absorption and proton secretion or rather HCO_3^- absorption. A rapid stimulation of NHE1 has been one of the earliest and best investigated nongenomic effects described for aldosterone in different renal cell lines and was mediated for example by intracellular calcium and ERK1/2 phosphorylation in MTAL and MDCK-C11 cells (Gekle *et al.* 1996, 1998, 2001, Watts *et al.* 2006, Pinto *et al.* 2008). NHE1 is not only known for its effects on electrolyte and acid–base regulation but also for its function as a regulator of cytoskeletal function which affects various transport processes, cell motion and cell volume and perhaps also fibronectin synthesis (Markos *et al.* 2005, Leite-Dellova *et al.* 2008, Zhang *et al.* 2010, Braga-Sobrinho *et al.* 2012). Furthermore, NHE1 is also important for other organs like vasculature and heart (Ebata *et al.* 1999, Michea *et al.* 2005, Miyata *et al.* 2005, Matsui *et al.* 2007, De Giusti *et al.* 2011) and a genomic increased NHE1 expression induced by aldosterone has been additionally described in various tissues (Karmazyn *et al.* 2001). In strips of human arteries, aldosterone-induced changes in intracellular pH mediated by NHE1 could be blocked by the MR antagonist RU28318 and could be mimicked by cortisol but only in the presence of an 11beta-hydroxysteroid dehydrogenase 2 inhibitor (Alzamora *et al.* 2000).

In the proximal tubule NHE3 activity and expression at the apical brush border, but not total NHE3 expression, were aldosterone sensitive, suggesting an increase in trafficking to the plasma membrane. Although the effect is persistent and lasting over several days, the involvement of the EGFR signaling pathways indicates a possible nongenomic mechanism (Krug *et al.* 2003, Drumm *et al.* 2006). Furthermore, it has been demonstrated that NHE3 expression is increased via SGK1 and genomic effects on the long-term (Musch *et al.* 2008). Conversely, aldosterone inhibited maximal velocity of NHE3 via ERK1/2 in MTAL, thus reducing bicarbonate reabsorption (Good *et al.* 2006, Watts *et al.* 2006). It was postulated that by counteracting the overall proton excreting effect of aldosterone, the kidney is enabled to regulate Na^+ balance and volume while maintaining acid–base balance (Good *et al.* 2002).

H^+-ATPase Aldosterone is involved in acid–base homeostasis not only through NHE but also through nongenomic regulation of electrogenic vacuolar type H^+-ATPase. Enhanced proton secretion is achieved rapidly within 15 min and most probably by influencing microtubule and PKC-dependent rapid trafficking of the pumps to the cell membrane (Gekle *et al.* 1997, Winter *et al.* 2004, Dos Santos *et al.* 2009). These effects not only occur in kidney but also in other organs (Ehrenfeld *et al.* 1985, Harvey 1992, Roy *et al.* 2013). Again the effects of aldosterone on H^+-ATPase seem to combine rapid nongenomic and genomic effects as it has been shown in proximal renal tubule (Leite-Dellova *et al.* 2011).

Overall, nongenomic aldosterone signaling in the kidney seems to facilitate genomic signaling by rapidly activating transporters either by inhibiting their degradation or by enhancing their surface expression through facilitating intracellular trafficking.

Nongenomic effects in the cardiovascular system

After exploring physiological MR function in kidney and other epithelial target tissues, the cardiovascular system was identified as a main target for pathological MR actions (Brilla & Weber 1992, Brilla *et al.* 1994, Young *et al.* 1994). The importance of the MR for eliciting pathological effects was impressively shown by several clinical trials including RALES, EPHESUS, EMPHASIS-HF, TOPCAT and the 4E study, in which MR antagonists were used in patients with cardiovascular diseases (Pitt *et al.* 1999, 2003*a*,*b*, 2014, Zannad *et al.* 2010). New genomic target genes were identified that support pathological effects, including *PAI-1, CTGF, PGF* and *EGFR*. In animal models, activated MR was shown to increase endothelial dysfunction,

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oxidative stress, inflammation and tissue remodeling. Consequently, nongenomic aldosterone effects were extensively studied as modulators of pathological effects in cardiovascular tissues and cells.

Vascular smooth muscle cells In VSMCs nongenomic aldosterone signaling has been demonstrated to lead to vasoconstriction, although the underlying signaling pathways are complex and they include ERK phosphorylation, intracellular calcium, cAMP and NHE, PLC, IGF1 and c-SRC, PI3K and PDGFR (Wehling *et al.* 1994, Christ *et al.* 1995, Ebata *et al.* 1999, Manegold *et al.* 1999, Michea et al. 2005, Yamada *et al.* 2008, Gros *et al.* 2011) (Fig. 3). Enhanced vasoconstriction may also include PKC and L- or T-type calcium channels in the glomerular microcirculation (Arima *et al.* 2003) and can be mediated by enhanced ROS production via c-SRC and p38 (Callera *et al.* 2005*a*,*b*). As described above, a crosstalk with receptor tyrosine kinases like EGFR, IGF1R and PDGFR and their transactivation seem to be a common theme as well as a crosstalk with GPCRs, especially AT1 and GPER1 (Mazak *et al.* 2004, Gros *et al.* 2011). Aldosterone also impairs guanylyl cyclase activity by cysteinyl thiol oxidation in VSMCs, which enhances vascular contractility (Maron *et al.* 2009).

Endothelial cells In endothelial cells NO production can be rapidly stimulated by aldosterone through enhanced NO synthase activity and phosphorylation mediated by PI3K (Liu *et al.* 2003, Uhrenholt *et al.* 2003, Mutoh *et al.* 2008). This can somewhat counteract the overall vasoconstrictor effect of aldosterone in vessels via PLC and IP3 which usually prevails (Arima *et al.* 2004). On the other hand aldosterone can enhance ROS availability in endothelial cells, for example, by activating NADPH oxidase via c-SRC and RAC-1 (Iwashima *et al.* 2008) or by reducing G6PD activity and GSH levels (Leopold *et al.* 2007). This can decrease overall NO bioavailability by peroxynitrite formation or uncoupling of eNOS by eNOS cofactor depletion, which will lead to preferential ROS and not NO production (Landmesser *et al.* 2003, Thomas *et al.* 2006). Furthermore, enhanced ROS production can also inhibit eNOS itself (Sanz-Rosa *et al.* 2005, Nagata *et al.* 2006). By increasing ENaC insertion into the plasma membrane aldosterone via MR can also increase cellular volume and stiffness, a state associated with decreased formation of NO. This observation provides a comprehensive link between high salt and hypertension but also between inflammation and vascular injury, because C-reactive protein, an acute phase protein of inflammation, has been shown to enhance this process (Kusche-Vihrog *et al.* 2008, 2011, Fels *et al.* 2010). Also regulation of local vasoconstrictors like endothelin-1 and angII are mediated by aldosterone and may be of relevance for endothelial function (Lariviere *et al.* 1993, Sugiyama *et al.* 2005).

Vessels Not surprisingly, in clinical studies with healthy individuals, rapid aldosterone actions on the vasculature seem to depend on the adrenergic and health status of the individuals. Infusion of aldosterone usually leads to a rapid increase in vascular resistance and a decrease in

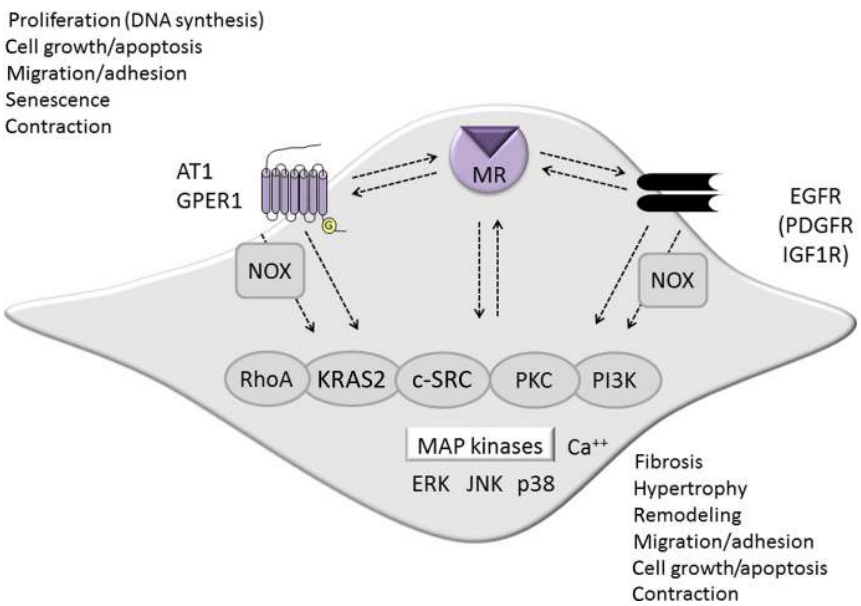

Figure 3
Components of rapid aldosterone signaling in VSMCs. Vascular smooth muscle cells (VSMCs) are one of the best studied models for nongenomic MR signaling pathways. As common interaction partners of the MR, GPCR like AT1 and GPER1 as well as receptor tyrosine kinases like EGFR, PDGFR and IGF1R have been identified at the membrane. In the cytosol, rapid MR signaling influences not only ROS homeostasis and the activity of different signaling molecules like small GTPases like RhoA and KRas but also kinases like c-src, PKC, PI3K, MAP kinases (including ERK, JNK and p38) and Ca^{++} signaling.

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forearm blood flow within the first 10 min after infusion (Wehling *et al.* 1998, Schmidt *et al.* 1999, 2001, 2003, Romagni *et al.* 2003, Gunaruwan *et al.* 2005). After inhibiting NO synthase, enhanced vasoconstriction was reported (Schmidt *et al.* 2006, Nietlispach *et al.* 2007), suggesting that a rapid vasodilation occurs via NO synthesis in the endothelium while vasoconstriction is mediated by vascular smooth muscle cells. Also renal plasma flow was reduced after aldosterone infusion if the effect of the endothelium is excluded by simultaneous application of L-NMMA to inhibit NO synthase (Schmidt *et al.* 2006). Likewise, Hwang and coworkers show that in healthy older people, acute MR antagonism impairs endothelial function by inhibiting NO formation and endothelium-dependent vasorelaxation (Hwang *et al.* 2016). This fits well to observations made by Liu and coworkers and confirmed by Heylen and coworkers who showed that acute aldosterone application can lead to a vasodilation dependent on NO generation from the endothelium and to vasoconstriction via ROS in endothelium-denuded vessels (Liu *et al.* 2003, Heylen *et al.* 2009). Consequently, in mouse mesenteric vessels and endothelium-denuded rings, aldosterone rapidly leads to enhanced vasoconstriction (Yamada *et al.* 2008, Gros *et al.* 2011).

In conclusion, nongenomic aldosterone signaling in VSMCs seems to lead to increased ROS formation, tyrosine kinase receptor activation, GPCR activation and supports overall vasoconstriction which aggravates pathological MR effects in vessels and supports genomic effects. In endothelial cells, aldosterone can rapidly activate or inactivate eNOS and NO depending on cell context, which again mainly seems to facilitate pathological MR effects but may also be part of a regulatory feedback loop. In addition, orthostasis is known to induce rapid aldosterone secretion, which may play a role in rapid hemodynamic adaptation to changes in posture by inducing vasoconstriction as a physiological response.

Heart The detrimental effects of aldosterone/MR in the heart mimic those of the vasculature and include inflammation, fibrosis, cardiac hypertrophy and electrical remodeling. In ischemia-reperfusion experiments of the heart, aldosterone and low concentrations of cortisol both led to comparable exacerbation of damage via the MR (Mihailidou *et al.* 2009). Genomically, proinflammatory genes like *ICAM-1, VCAM-1, PAI-1* and *SPP-1* and osteopontin are upregulated by aldosterone/MR in addition to profibrotic genes for collagen I and III, CTGF and PGF (Nguyen Dinh Cat & Jaisser 2012). These genomic effects again seem to be supported and enhanced by nongenomic effects. One important mediator in this seems to be the generation of ROS through enhanced NOX activation and possible G6PD decrease. A rapid aldosterone-dependent increase in nongenomically generated ROS by NOX activation followed by myocyte apoptosis and ASK1 activation was demonstrated by Hayashi and coworkers in neonatal cardiomyocytes, and in adult ventricular cardiomyocytes, enhanced ROS production led to ERK1/2 activation and increased MMP-2 and MMP-9 activity (Rude *et al.* 2005, Hayashi *et al.* 2008).

A rapid increase in contractility was detected by some groups after aldosterone treatment in rat isolated working heart (Moreau *et al.* 1996, Barbato *et al.* 2002) while other groups found no effect on contractility or a reduced contractility in human trabeculae (Chai *et al.* 2005, Matsui *et al.* 2007). During ischemia, nongenomic aldosterone effects reduce coronary blood flow and thereby impair cardiac metabolic and contractile function (Fujita *et al.* 2005). Aldosterone/MR can also directly stimulate hypertrophy in neonatal rat ventricular myocytes through the activation of ERK, JNK and PKCα (Okoshi *et al.* 2004). Additionally, aldosterone via PKCε leads to a rapid but prolonged activation of $Na^+K^+2Cl^-$ cotransporter and a decrease in Na^+-K^+-ATPase activity, which supports myocyte hypertrophy (Mihailidou *et al.* 1998, 2000, 2002, 2004). Increased intracellular sodium may then affect calcium content and thereby contractile status of cardiomyocytes. Sodium influx is also enhanced by NHE1 activation via EGFR and ROS (Matsui *et al.* 2007, De Giusti *et al.* 2011) and may lead to cell swelling. Changes in intracellular pH mediated by changes in NHE1 or sodium bicarbonate cotransporter activity may also account for increased myofilament responsiveness to calcium and thereby modulated contractility (Barbato *et al.* 2004, De Giusti *et al.* 2015). Furthermore, cardiac injury, i.e. perivascular and interstitial fibrosis and hypertrophy, induced by DOCA can be reduced by NHE1 blockade (Fujisawa *et al.* 2003, Young & Funder 2003). Aldosterone also increases monophasic action potential duration within minutes after intravenous application which may support the development of arrhythmias (Tillmann *et al.* 2002). In HL-1 cells, aldosterone activates p38 to induce cardiotropin-1 expression, a cytokine with hypertrophic effects on cardiomyocytes (Lopez-Andres *et al.* 2008). Similarly, p38 activation is required for aldosterone-induced *Ctgf* gene expression in ventricular

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cardiomyocytes (Lee *et al.* 2004). In both cases nongenomic pathways regulate genomic effects.

In cardiac fibroblasts, aldosterone can stimulate collagen-I-deposition and elastogenesis via Galpha13, C-SRC and IGF1R signaling (Bunda *et al.* 2007, 2009). In neonatal cardiac fibroblasts aldosterone favors cell cycle progression and cell proliferation mediated by AT1 via ERK1/2 activation which enhances the expression of cyclins D1 and E2 (Wang *et al.* 2013). Again nongenomic and genomic pathways are closely intertwined and seem to be of pathophysiological relevance.

Taken together, the role of nongenomic MR effects has been best characterized in classical epithelial MR target organs like kidney and colon and in the cardiovascular system for modulating physiological and pathological processes. However, nongenomic MR effects have been also well studied in the brain (Joels *et al.* 2012) and are becoming increasingly important in other tissues of pathological relevance like adipose tissue and immune cells (Vecchiola *et al.* 2016).

Conclusions

In summary, the existence of nongenomic aldosterone signaling has been well established and many of the signaling components have been identified. The involvement of the classical MR in many of the nongenomic signaling effects has been proven, although an additional membrane receptor may exist. A possible candidate for such a receptor is GPER1 but further investigations for this are required. Crosstalk between nongenomic aldosterone signaling and other signaling pathways has been demonstrated including signaling of receptor tyrosine kinases like EGFR, PDGFR and IGF1R and also GPCRs like AT1 and GPER1. Nongenomic aldosterone signaling occurs in various tissues including epithelial tissues like kidney and colon and nonepithelial tissues like heart, vasculature and brain. Most data are available for kidney and cardiovascular tissue, where the rapid effects seem to support physiological and pathophysiological genomic effects of aldosterone and MR or may be involved in regulatory loops. Because of the close interaction between genomic and nongenomic effects, nongenomic aldosterone signaling can also lead to long lasting and persistent effects. They also may provide new targets for modulation of pathophysiological aldosterone/MR actions.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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