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Mineralocorticoid receptor signaling: Crosstalk with membrane receptors and other modulators

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ABSTRACT

The mineralocorticoid receptor (MR) belongs to the steroid receptor superfamily. Classically, it acts as a ligand-bound transcription factor in epithelial tissues, where it regulates water and electrolyte homeostasis and controls blood pressure. Additionally, the MR has been shown to elicit pathophysiological effects including inflammation, fibrosis and remodeling processes in the cardiovascular system and the kidneys and MR antagonists have proven beneficial for patients with certain cardiovascular and renal disease. The underlying molecular mechanisms that mediate MR effects have not been fully elucidated but very likely rely on interactions with other signaling pathways in addition to genomic actions at hormone response elements. In this review we will focus on interactions of MR signaling with different membrane receptors, namely receptor tyrosine kinases and the angiotensin II receptor because of their potential relevance for disease. In addition, GPR30 is discussed as a new aldosterone receptor. To gain insights into the problem why the MR only seems to mediate pathophysiological effects in the presence of additional permissive factors we will also briefly discuss factors that lead to modulation of MR activity as well. Overall, MR signaling is part of an intricate network that still needs to be investigated further.

1. Introduction

The mineralocorticoid receptor (MR) belongs to the steroid receptor superfamily together with receptors for progesterone, estrogens, androgens and glucocorticoids. In classical target tissues like epithelia of the kidney, colon, sweat and salivary glands, the MR is activated by aldosterone and subsequently increases sodium and water reabsorption, enhanced potassium secretion and thereby contributes to the maintenance of blood pressure. Meanwhile it has been shown that the MR is expressed in cells of non-epithelial tissue like heart and vasculature, where it can lead to pathophysiological changes initiated by inflammation or an altered micromilieu followed by fibrosis, hypertrophy and remodeling.

Regarding the mechanisms of MR activation and MR action, there are still several unsolved questions. (i) What are the different mechanisms of activation considering the high glucocorticoid concentrations and the fact that the MR seems to be activated in the absence of altered hormone concentrations? Glucocorticoids like cortisol can bind to the MR with an affinity that is comparable to that of aldosterone. In classical MR target epithelial tissues an enzyme called 11-beta hydroxysteroid dehydrogenase 2 is responsible for inactivating cortisol to cortisone that no longer binds to the MR. Especially in cells that do not express this enzyme, like cardiomyocytes, MR-specific signaling is not well understood. (ii) How is differential control of gene expression by MR and GR achieved despite the fact that only common response elements have been described? In its inactive state, the MR is primarily located in the cytosol associated to a multicomponent complex. Binding of aldosterone then leads to nuclear translocation, where it binds as a homodimer to glucocorticoid response elements (GRE) and regulates gene expression and ultimately protein expression. Given that MR and GR share a common hormone response element (HRE) makes it difficult to explain MR-specific effects and therefore the existence of additional MR binding sites has been postulated [1]. (iii) What determines whether MR activation elicits physiological or pathophysiological effects?

From these questions the hypothesis of further non-canonical signaling pathways can be derived. Strong indications for the existence of complementary MR signaling pathways came from reports of MR effects that occur independently of transcription. For example, as early as 1984 a rapid, actinomycin D-independent effect of aldosterone on sodium flux in arterial smooth muscle cells has been described [2] and later rapid effects on MAP kinase phosphorylation, cAMP/CREB and PKC signaling have been demonstrated

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and termed non-genomic effects [3]. Of course these non-genomic effects may also affect gene transcription indirectly because for example CREB acts as transcription factor [4,5]. Taken together these findings suggest that there is an intense cross-talk between MR outside the nucleus and other signaling components that is crucial for its non-canonical actions. These interactions include different membrane receptors, namely receptor tyrosine kinases and the angiotensin 1 receptor that are especially thoroughly investigated and will be the focus of this review. Furthermore, interaction of the MR with micromilieu factors like reactive nitrosative species have been described to lead to pathophysiological relevant activation of the MR and therefore contribute to disturbed tissue homeostasis (see Figs. 1 and 2).

2. MR interaction with receptor tyrosine kinases

Receptor tyrosine kinases are cell surface receptors mainly for growth factors. They are not only responsible for cell growth, differentiation and death but are also involved in pathological changes like tumor growth or vascular remodeling [6]. Activation of these receptors occurs not only by binding of ligands but also by a mechanism called transactivation (see below). Recently it has been shown that functional receptor tyrosine kinases are also located in the nucleus, where they potentially interact with transcription factors, for example the activated nuclear MR. However, little is known about the functional impact of nuclear receptor tyrosine kinases as well as about the interaction with the MR [7]. The receptor tyrosine kinases considered are epidermal growth factor receptor (EGFR), insulin receptor (IR)/insulin-like growth factor receptor (IGF-1 receptor), platelet-derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR).

2.1. EGFR

The EGFR is an important protagonist in a variety of physiological and pathophysiological settings including fetal development, proliferation, differentiation, migration, vasoconstriction and cancer. The EGFR (ErbB1) belongs to a family of membrane tyrosine kinases additionally including ErbB2, ErbB3 and ErbB4. In the presence of their ligands, the members of this family act as homo- or heterodimers resulting in activation of different signaling pathways including Ras/Raf-1/MAPK, c-Src, PI3/Akt and phospholipase Cγ. Furthermore, the EGFR can act as a mediator of angiotensin II, endothelin-1 and aldosterone-induced effects [8–11]. With respect to the MR, it has been shown to interact with the EGFR either via transactivation in a non-genomic [4,12] or in a genomic way via altered expression. In the renocardiovascular system it has been demonstrated that this transactivation can promote fibrosis [10,11,13].

2.1.1. Modes of Interaction between MR and EGFR

An MR-dependent increase in EGFR expression was found in the heart, aorta and the kidney [14–18]. As underlying mechanism an MR-specific SP1-dependent responsive element was identified, which differs from classical GRE elements and shows no responsiveness to the glucocorticoid receptor (GR) [15]. MR-induced enhancement of EGFR expression increases the amount of the EGFR molecules available for transactivation by MR and other receptors of vasoactive substances [14–16,18]. Downstream signaling molecules affected by the non-genomic MR–EGFR crosstalk or mediating it are versatile and include NADPH oxidase, c-Src, PKC (protein kinase C), PKD (protein kinase D), Ca^{2+}, reactive oxygen species, Rho/Rhokinase and ki-Ras-2a (Kirsten rat sarcoma viral oncogene homolog) [4,12,19–22].

Conversely, EGFR/ERK signaling can also influence genomic activity of MR by affecting its nuclear translocation [4].

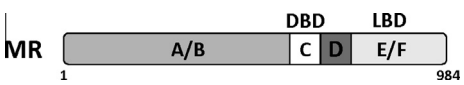

Fig. 1. Scheme of MR domains. The N-terminal region A/B is responsible for cofactor binding and is the most variable among steroid receptors. The C domain consists of the DNA binding domain (DBD) and is followed by the hinge region D. The C-terminal E/F region possesses a ligand binding domain (LBD) and is involved in the dimerization of steroid receptors.

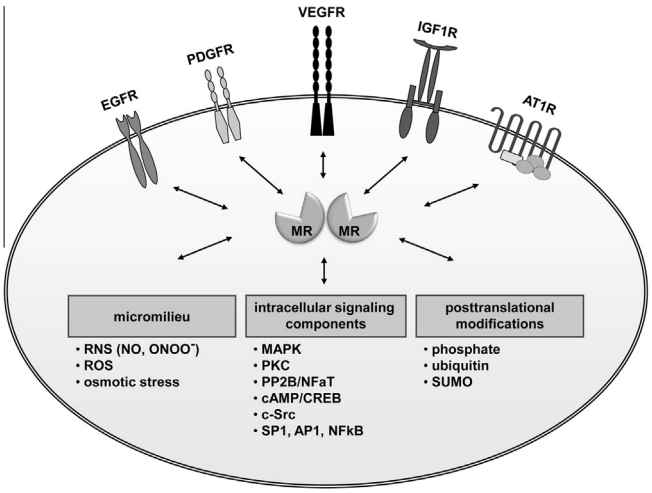

Fig. 2. Scheme of MR crosstalk with other signaling pathways. Interactions between MR signaling and different membrane receptors like angiotensin II receptor I (AT1R) and different receptor tyrosine kinases exist. These include the epidermal growth factor receptor (EGFR), the insulin-like growth factor receptor (IGF-1R), the platelet-derived growth factor receptor (PDGFR) and the vascular endothelial growth factor receptor (VEGFR). Furthermore, MR signaling may be modulated by micromilieu factors, possibly through posttranslational modification and by crosstalk with other signaling components.

2.1.2. Physiological effects

Crosstalk between the MR and the EGFR is of particular importance because of its contribution to physiological effects on the one hand and also pathophysiological effects on the other hand. An important physiological implication is the MR–EGFR-induced reabsorption of sodium. Previous studies of McEneaney et al. established the EGFR as a mediator of the signaling between aldosterone-induced MR and PKD leading to an increased trafficking and activity of the epithelial sodium channel (ENaC) in renal collecting duct M1 cells [12,23]. In human RPTEC cells (primary renal proximal tubule epithelial cells) the activity and surface expression of NHE3 (sodium-proton-exchanger 3) is stimulated via MR–EGFR crosstalk, which also activates NHE1 in MDCK cells, where it regulates cellular pH and volume [19,24,25]. The MR-induced NHE1 stimulation in rat ventricular myocytes is known to be abolished by spironolactone, eplerenone and the EGFR kinase inhibitor AG1478, suggesting that it is mediated by EGFR transactivation. This enhanced NHE1 stimulation was shown to be accompanied by formation of ROS and phosphorylation of the exchanger [26].

2.1.3. Pathophysiological effects

2.1.3.1. Remodeling. Besides the physiological relevance of the interaction between aldosterone-induced MR and the EGFR, the pathophysiological actions gain more and more importance. Studies in different tissues associate the MR–EGFR interaction with vascular dysfunction, proliferation, inflammation, aging and fibrosis.