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Rapid mineralocorticoid receptor trafficking

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ABSTRACT

The mineralocorticoid receptor (MR) is a ligand-dependent transcription factor that physiologically regulates water-electrolyte homeostasis and controls blood pressure. The MR can also elicit inflammatory and remodeling processes in the cardiovascular system and the kidneys, which require the presence of additional pathological factors like for example nitrosative stress. However, the underlying molecular mechanism(s) for pathophysiological MR effects remain(s) elusive. The inactive MR is located in the cytosol associated with chaperone molecules including HSP90. After ligand binding, the MR monomer rapidly translocates into the nucleus while still being associated to HSP90 and after dissociation from HSP90 binds to hormone-response-elements called glucocorticoid response elements (GREs) as a dimer. There are indications that rapid MR trafficking is modulated in the presence of high salt, oxidative or nitrosative stress, hypothetically by induction or posttranslational modifications. Additionally, glucocorticoids and the enzyme 11beta hydroxysteroid dehydrogenase may also influence MR activation. Because MR trafficking and its modulation by micro-milieu factors influence MR cellular localization, it is not only relevant for genomic but also for nongenomic MR effects.

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Contents

1. MR enigma

The mineralocorticoid receptor (MR) with its endogenous ligand aldosterone is one of the main effectors in the renin-angiotensin-aldosterone-system (RAAS) and has a pivotal role in water-electrolyte homeostasis and regulation of blood pressure. It belongs to the steroid receptor superfamily that consists of the progesterone, the estrogen, the androgen and the glucocorticoid receptor. Steroid receptors possess a common structure comprising the domains A–F. The N-terminal A/B domain is the most variable among the receptors and is responsible for cofactor binding. The C domain of the MR is the DNA binding domain and possesses a 94% amino acid identity to the DNA binding domain of its closest relative, the glucocorticoid receptor (GR). After a short hinge region comes the C-terminal ligand binding domain that is also involved

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in dimerization. Of the steroid receptors, the mineralocorticoid receptor has been the least appreciated for a long time because of the more obvious clinical implications in for example cancer and immunological disease of its relatives. Consequently, many of the basic molecular observations concerning signaling and trafficking of the MR have been deduced from other steroid receptors, regardless of possible differences between them. The lack of interest changed after the importance of the MR for pathological changes in the cardiovascular system and the kidneys became apparent. In two pivotal clinical studies that were followed by many others, the beneficial effect of MR antagonists like spironolactone and eplerenone for patients with cardiovascular disease was proven; however, without understanding the underlying mechanisms [1–3]. Since then, MR activation has been shown to be involved in different pathophysiological effects in the reno-cardiovascular system including endothelial dysfunction, inflammation, hypertrophy and fibrosis in both clinical studies and animal experiments [4–7]. It is well known, that the MR functions as a ligand-dependent transcription factor at hormone response elements called glucocorticoid response elements (GRE) that it shares with the GR. However, the GR acts in an anti-inflammatory and immunosuppressive way on the cardiovascular system, suggesting additional signaling mechanisms. The trigger that causes the MR to turn from a receptor regulating water-electrolyte homeostasis and not causing any harm into a receptor mediating pathological effects in the cardiovascular system is also an enigma. Of note, the MR needs to be inadequately activated to confer pathological effects as can be judged by the positive effects of MR antagonists. One way to achieve this is by having inappropriately high aldosterone levels in relation to salt status in an individual. Although such a scenario is likely in case of hyperaldosteronism caused by adrenal adenoma or hyperplasia, this does not seem to apply for the majority of patients benefitting from MR antagonists as in the above mentioned clinical studies, where aldosterone levels and salt status of participants were unremarkable. In animal studies, it is striking that aldosterone application only leads to pathological changes in the presence of additional permissive factors like salt, aging or oxidative stress, in other words a parainflammatory micro-milieu. Several mechanisms for differential action of MR and GR have been investigated. New MR specific DNA-binding elements have been postulated, protein–protein interactions in the cytosol explored and posttranscriptional regulatory mechanisms investigated without completely explaining MR actions. An additional regulatory option are ligand-dependent or independent mechanisms that affect MR trafficking and therefore subcellular localization and thereby MR interaction partners and activity. It has been already shown for other molecules like the EGFR that alternative subcellular distribution of the receptors can influence signaling and possibly progression of diseases. Consequently, studying rapid trafficking and its modulation seems relevant for understanding MR actions.

2. MR trafficking

Although classical genomic signaling is the most investigated pathway of MR signaling, the steps leading up to transcriptional gene regulation are still not completely understood. With some cell-type specific exceptions, the MR seems to predominantly reside in the cytosol in its unliganded state [8–11]. There it is associated with a large heterocomplex of chaperone molecules including HSP90, HSP70, p23 and proteins with tetratricopeptide repeat sequences such as FKBP52, 52, HOP/p60, Cyp40, PP5 [10,12]. This complex enables the MR to stay in its high affinity state for ligands. Nevertheless, the localization of the MR is dynamic, meaning that there is an equilibrium between cytosolic and nuclear localization which can shift in either way, depending on the presence of ligands or other stimulating factors [13]. After binding of ligand, nucleocytoplasmic shuttling of the MR occurs and the equilibrium of MR localization is shifted to the nucleus. Previously, it was thought that dissociation of the chaperone molecules from the MR is a prerequisite for MR shuttling. Current studies suggest that there are two modes of nuclear MR trafficking. Besides a rapid mode with $t_{1/2}$ = 4–10 min [8,14,15], a slower transport to the nucleus with $t_{1/2}$ around 40–60 min has been described [8]. The rapid shifting seems to be a highly regulated process dependent on the presence of HSP90 because it can be inhibited by the HSP90 inhibitor geldanamycin. Geldanamycin leads to dissociation of MR from HSP90 and in some cases has also been found to be involved in MG132-inhibited degradation of MR, suggesting that HSP90 may protect MR from proteasomal degradation [8,15]. Importantly, HSP90 is located both in the cytoplasm and the nucleus and the HSP90-MR complex does not dissociate immediately upon steroid binding as postulated in the classical model [8,9,15,16]. Data point to the fact that HSP90 stays associated to MR for the first 10 min in the nucleus and then dissociates after facilitating MR binding to the insoluble chromatin fraction. Accumulation of MR in the nucleus is still possible in the presence of geldanamycin mediated by the slower transport mechanism within $t_{1/2}$ 40–60 min supposedly reflecting diffusion. Consequently, translocation per see does not seem to be impaired without HSP90 but rapid trafficking.

Recent evidence suggests that more of the associated proteins of the cytosol are involved in MR transport and nuclear pore transition [15,17]. Coimmunoprecipitation experiments suggest that a sophisticated machinery of proteins is involved in MR trafficking to nuclear DNA, which besides HSP90 include the dynein/dynactin motor complex and FKBP52 [8,18]. The interaction between MR and HSP90 seems to influence the composition of the rest of the heterocomplex, with an inverse relationship between HSP90 and HSP70 content and an enrichment of dynein, FKBP52 and p23 in HSP90 containing complexes. Consequently, loss of HSP90 implies loss of the interacting acidic protein p23 and FKBP52 which leads to dissociation from dynein/dynactin and impaired trafficking. Especially, the exchange between FKBP51 and FKBP52 seems to be of primary importance as they compete for the binding of HSP90 and dynein/dynactin can only bind to FKBP52 and not to FKBP51 [19]. The switch leading to the exchange of FKBP51 to FKBP52 in vivo seems to be binding of ligand, i.e. aldosterone. Accordingly, FKBP51 was shown to inhibit MR action [12]. The importance of the FKBP51/52 ratio for the nuclear cytoplasmic equilibrium of the MR was further emphasized by studies in FKBP52 knockout MEF cells, in which nuclear localization of MR is lower and trafficking is impaired. In line with these observations, the cardiomyocytes cell line HL-1 with predominantly nuclear localization of the MR possesses a low expression of HSP90. In agreement with GR trafficking, MR was found to be associated with tubulin via the HSP90, FKBP52 and dynein/dynactin interaction [8]. When the cytoskeleton was disrupted, rapid geldanamycin-sensitive MR transport was no longer possible, although the slower transport persists [8]. To facilitate the rapid transport, the MR possesses three nuclear localization sites (NLS). NLO is a serine/threonine-rich NLS that is located in the N-terminus and which mediates nuclear localization of unliganded as well as agonist-induced MR signaling. NLS1 is a bipartite basic motif localized at the border between the DNA-binding domain and the hinge region, which acts in concert with NLO and NL2 and stimulates nuclear uptake of agonist-treated receptor. NLS2 resides within the ligand binding domain and also depends on agonist or antagonist actions [20]. In unliganded cytoplasmic MR the NLS are supposedly masked by chaperones such as HSP90. Nuclear trafficking takes place via active transport through nuclear pore complexes and involves binding of MR to importin alpha, which translocates into the

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