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Genomic and Non-genomic Aldosterone Signaling

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Abstract

Mineralocorticoids exhibit two modes of signaling. The classical mode found mainly in target epithelial tissue is dependent upon binding and activation of a cytosolic MR. Binding results in translocation to the nucleus where the MR homodimerizes and activates GRE regulated genes. A more rapid signaling pattern occurs in epithelial tissue and non-epithelial issues. Some of these effects are mediated by the classical MR trafficking to the plasma membrane where it can directly or indirectly interact with other signaling pathways. Mineralocorticoids also appear to activate other as of yet unknown receptors that contribute to the rapid signaling seen in some cells.

Keywords: Aldosterone; mineralocorticoid; mineralocorticoid receptor; transcription; hormone response element; HRE; receptor; steroid hormone

Abbreviations: GRE: Glucocorticoid Response Element; HRE: Hormone Response Element; MR: Mineralocorticoid Receptor

Introduction

Steroid hormones are lipophilic hormones based on the cholesterol molecule. Steroid hormones include the sex hormones - estrogen, progesterone, and testosterone; glucocorticoids mainly cortisol in human; and mineralocorticoids. The main mammalian mineralocorticoid is aldosterone. Steroid and steroid-like hormones such as vitamin D and thyroid hormone are lipophilic and exert their predominant actions by binding cytosolic receptors. Although aldosterone functional studies have dated back to the 1950s studies examining receptor signaling had largely lacked compared to the other steroid receptors. There has been a renewed interest in aldosterone signaling with the recent discoveries that much pathology are associated with alterations in aldosterone [1-7]. This renewed interest has resulted in several excellent review articles documenting genomic and non-genomic effects of aldosterone [3,4,8-16] to name a few. The purpose of this short-review is to highlight major advances in the understanding of mineralocorticoid receptor (MR) signaling through the classical genomic pathway and the rapid non-genomic signaling of the MR.

Aldosterone has two modes of activation - a rapid mode that works in minutes and the classical, slow mode (see [17-22] for earlier topical reviews). The classical mode of activation involves binding of aldosterone to a cy-tosolic MR which translocates to the nucleus and induces gene transcription. The classical MR pathway often takes hours for effect and is inhibited by the MR antagonists, spironolactone and eplerenone, as well as the transcriptional and translational inhibitors, actinomycin D and cyclohexamide. In contrast, the rapid mode of activation is not affected by these com¬pounds.

Classical MR signaling

The classical MR is encoded by the NR3C2 gene located in locus 4q31.1. It codes for a 984 amino acid protein [8]. The cytoplasmic MR, like all steroid receptors, can be divided into several domains [3,7,23,24]. Typically it is divided into 6 major regions although some authors restrict this to three or four domains [3,8,23,24]. The N-terminal portion consists of 602 amino acids and is sub- divided into two domains [8]. The A and B domains in the N-terminal are the most variable between the steroid receptors and bind to coregulators [3,8,23,24]. The central domain (C domain) is highly conserved region consisting of 66 amino acids [7,8] and possesses a DNA-binding domain with two zinc fingers. It is 94% homologous to the glucocorticoid receptor [3]. This domain is followed by a hinge region, D, and then thecarboxal-terminal consisting of 251 amino acids [7,8].

The C-terminal is the ligand binding domain [7,8] and also contributes to the binding of co-regulators [24]. Several studies have examined the requirements of the C-terminal domain for ligand binding as recently reviewed [7,24]. For example, deletion mutations have shown that the last four residues are required for aldosterone binding [25]. The naturally occurring mutation (L979P) totally abolishes aldosterone binding and leads to pseudohypoaldosteronism [26].

The cytoplasmic MR is seen in high concentrations in specific tissues known to be mineralocorticoid sensitive such as the kidney and colon. MR immunostaining is present in all parts of the distal nephron, but is most prominent in the distal tubule and along the collecting ducts [27]. It has an equally high affinity for both aldosterone and glucocorticoids [18,28]. This is owing to the high homology of the ligand binding domains between the two receptors [18,28]. Glucocorticoids are present in the blood 100-1000 x greater than aldosterone [8]. Specificity of the cytosolic MR receptor for aldosterone over glucocorticoids such as cortisol and corticosterone is due to the presence of the enzyme,11beta-hydroxysteroid dehydrogenase [17,18,28]. This enzyme rapidly converts glucocorticoids to an inactive form.

The cytosolic MR has also been reported in other tissues at low levels and has been implicated for several pathologies [4]. These may be activated by either aldosterone or glucocorticoids [29-33]. Of note, aldosterone can also bind glucocorticoid receptors. Thus, there may be some redundancy and partial overlap between the mineralocorticoid and glucocorticoid systemsalthough clearly separate biological actions are associated with each one [34]. Thiscould explain some of the pathophysiological affects aldosterone has in alternative target tissues outside the kidney and colon [29-33]. Progesterone is also able to bind to the cytosolic MR with the same affinity as aldosterone and cortisol but acts as an antagonist or when acting alone as a partial agonist [24,35,36]. This is due to the rapid dissociation of progesterone from the MR complex [24].

Translocation of the activated cytoplasmic MR to the nucleus binds to specific DNA sequences to activate gene transcription. A sequence specific for MR binding has not been discovered. Instead, the activated MR binds to the hormone response element (HRE) of a gene that is also used by glucocorticoids - the glucocorticoid response element (GRE) [3]. MR binding may also occur at progesterone activated transcription sites [37,38]. The HRE is composed of an inverted repeat separated by three nucleotides, which generally appears as the sequence AGAACAnnnTGTTCT [38]. This HRE binding sequence is similar for the GRE as well as progesterone and androgen binding, but different for estrogen and thyroid hormone [38].

The cytosolic MR when unbound to ligand is a large heterocomplex bound to heat shock proteins, chaperone molecules and other proteins such as HSP90, HSP70, p23, FKB51, FKBP52, 52, HOP/p60, Cyp40, and protein phosphatase 5 (PP5) [3,24,39,40]. Binding of these adjunct proteins keeps the receptor in a high affinity ligand binding state and prevents protein degradation by the proteasome [24,25]. HSP90 is critical for binding of ligand to the MR. FKBP51, FKBP52, and pp5, on the other hand, are not required to maintain the steroid receptors in their ligand-binding competent conformation, but are involved in the affinity of the receptors for their ligands. Association of FKBP52 has no affect on the ligand binding affinity for the MR but increases the affinity for the androgen, progesterone and glucocorticoid receptors. Association of FKB51 to the MR receptor, on the other hand reduces the ligand binding affinity [24].

Binding of ligand to the MR causes translocation to the nucleus. As previously stated, in epithelial cells the main ligand is aldosterone, while in non-epithelial cells it is cortisol. Upon binding of ligand, the cytoplasmic MR HSP90 dissociates from the receptor [18,25]. The MR is then transported to the nucleus [41,42] where it binds the GRE as a homodimer [43-45]. Hetrodimers between the MR and glucocorticoid receptor can also translocate to the nucleus [46]. It has been recently shown that there is a biphasic translocation. A rapid mode occurs with half time of 4–10 minutes [3,23,47,48] and a second slower translocation to the nucleus occurs with a half time of 40–60 minutes [3,48]. The role of HSP90 binding and translocation of the MR is confusing. While previous studies indicated that binding of ligand resulted in the dissociation of HSP90 [18,43-45], newer studies indicate that binding of HSP90 is essential for translocation to the nucleus [23,48].

Loss of HSP90 results in loss of interaction of proteins p23 and FKBP52 and ultimately dissociation from the dynein molecular motor [48]. This prevents the rapid phase of translocation although the slower phase is unaffected. In a recent study by Grossman et al. [23], binding of HSP90 to the activated MR remained intact for 6 minutes during the time that rapid translocation to the nucleus occurred and that inhibition of HSP90 prevented translocation [23]. In that same study, they demonstrated that binding of HSP90 to the MR homodimer increased binding to the GRE. They propose that binding of HSP90 helps stabilize the protein from degradation and assists in translocation to the nucleus. HSP90 also assists in MR binding to the GRE. Once bound to the GRE the HSP is removed which allows formation of the MR homodimer and gene transcription [23]. HSP90 binding is not required for DNA binding of the glucocorticoid receptor and thus HSP90 may act as a coregulator for differentiating different effects between the MR and glucocorticoid receptor that recognize the same HRE.

Post-translational modifications of the cytosolic MR receptor

The kidney MR isphosphorylated in the resting state which is critical for aldosterone binding [49,50]. However, removal of phosphate from serine/threonine residues is required for binding of the activated MR dimer to DNA [50]. Unconfirmed reports indicated that T735 and S737 phosphorylation may be responsible for this [41]. A gain of function mutation was described in the brown Norway rat at (Y73C) which accounts

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for differences in mineralocorticoid function between those and Fischer 344 rats. The mutation resulted in a greater MR transactivation induced by either aldosterone or progesterone [51]. The MR is phosphorylated within minutes of aldosterone stimulation on serine/threonine residues by PKCalpha [52]. Inhibition of PKC alpha prevented the late aldosterone response [52]. This demonstrates cross talk between the genomic and non-genomic actions of aldosterone signaling. Low concentrations of aldosterone (1 nM) increased phosphorylation only on serine residues. Whereas higher concentrations (10 nM) also induced phosphorylation on threonine residues.

Interaction of p53 with the cytosolic MR after stimulation with high doses of aldosterone resulted in CDK5 phosphorylation of the MR at S128 and S250 in the N-terminal domain. This resulted in decreased transcriptional activity without altering translocation to the nucleus [53]. This could be due to interference with binding of coactivators or due to differences in dimerization. MR dimerization in the cytosol prior to translocation of the nucleus fails to activate DNA transcription [23].

As mentioned above, the native unstimulated MR is a heterocomplex of several proteins. Association of HSP90 stabilizes the complex and reduces its degradation. It is also mono-ubiquitinated [54]. Phosphorylation of the MR by Erk 1/2 results in removal of the mono-ubiquitination an subsequent degradation of the MR. Aldosterone stimulation results in downregulation of the MR complex by targeting the complex to the proteosome [55]. Several studies have confirmed ligand induced poly-ubiquitination (reviewed in [8]) these have however resulted in contradictoryconclusions. Substitution of two potential targets for poly-ubiquitination, K367 and K715, failed to alter aldosterone stimulated proteosome degradation.

Five highly conserved sumoylation sites were predicted andcharacterized by mutations in MR. There are three in the N- terminal domain and one in theligand binding domain (K89, K399, (K428), K494, K953) (reviewed in [8]). PIAS1 is a SUMO ligase. Overexpression of PIAS1 resulted in reduced activity of a recorder gene using either the MMTV promotor or GRE. Mutationof these putative MR sumoylation sites had no effect on the transcription of the MMTV promoter, suggesting that PIAS1-mediated sumoylation occurred on MR transcriptional co-factors. In contrast, when the GRE2 promoter was used, substitution of the lysine sumoylation sites resulted in increased transcriptional activity after PIAS1 treatment compared to the native MR. This suggests that sumoylationrepression is promotor dependent. It has also recently been shown that the MR can be acetylated at K677. This results in reduced recruitment of RNA polymerase II while not affecting MR nuclear translocation [8,56,57].

Rapid non-genomic effects of aldosterone

Aldosterone has been shown to exhibit several rapid non-genomic effects (see [3,8-11,14,16,58-60] for reviews). While once seemed obscure and controversial the phenomenon has now received wide-spread acceptance. In 2015 over 7000 Medline entries relate to this topic [61]. Some rapid effects of aldosterone are clearly linked to activation of the cytoplasmic MR [9,10,14,16,62]. Most effects, however, are not affected by spironolactone or eplerenone suggesting that they are mediated by another yet unknown receptor(s). These have been designated type IIb steroid receptors [61]. The rapid mode of activation may involve several different components acting immediately or within 15 minutes. These include activation of Na^+/H^+ exchange, cAMP metabolism, mobilization of Ca^{2+}, PKC activation, protein phosphorylation via other kinases such as sgk, protein translocation, and protease activation (prostatin) and mitogen-activated protein kinases, especially the extracellular signal–regulated kinases [13,16,61,63-69].

The nature of a membrane bound receptor has yet to be elucidated. There is reasonable evidence that a small portion of the classic cytoplasmic MR resides in the plasma membrane [14]. Rapid activation of ERK 1/2, p38 and c-Jun only occurs in cells transfected with the classic MR [62]. Moreover the water soluble MR receptor RU21318 inhibit rapid effects of aldosterone [13,70]. It has been proposed that the membrane bound estrogen receptor GPR1 (formally known as GPR30) is a target receptor for aldosterone [71]. The possibility is attractive in that pM concentrations of aldosterone activated ERK 1/2 phosphorylation which was partially attenuated by GPER1 antagonists [71]. These initial studies in vascular smooth muscle have been confirmed in other studies (see [14,58] for review)This finding while attractive is not without controversy [61]. Direct binding of aldosterone to GPER1 has not been demonstrated [61]. Moreover, aldosterone was not shown to replace estrogen from the receptor in a competitive assay [72]. So, for now, this still remains just an attractive possibility for “the” membrane bound MR.

Direct activation of signaling molecules can also not be ruled out. For example, aldosterone directly binds to the PKC alpha c domain with a binding affinity within its normal physiological range. Association of aldosterone to the subunit results in PKC alpha autophosphorylation [73,74]. The MR has been shown to interact with the EGRF receptor and that disruption of cholesterol rich regions of the membrane perturbed this interaction [75]. Aldosterone also causes the rapid phosphorylation of the IGF-1 receptor, IRS-1 and Akt via the action of PI3 kinase [76].

Aldosterone has been shown to cause a rapid activation in ERK 1/2 phosphorylation. Furthermore, inhibition of non-genomic ERK1/2 phosphorylation was found to impair cytoplasmic-nuclear shuttling of MR and thereby transactivation of GRE. This effect depended on the N-terminal domain which was later shown to be directly phosphorylated by MR [54,62]. Because aldosterone/MR can rapidly activate ERK phosphorylation, this would suggest activation of genomic signaling by non-genomic MR effects. However, mutating the six predicted ERK1/2 sites in the A/B domain of the MR had no

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effect on trafficking but regulated the ubiquitination state of MR and therefore degradation [54].

Conclusion

Mineralocorticoids exhibit two modes of signaling. The classical mode found mainly in target epithelial tissue is dependent upon binding and activation of a cytosolic MR. Binding results in translocation to the nucleus where the MR homodimerizes and activates GRE transcriptionally regulated genes. A more rapid signaling pattern occurs in epithelial tissue and other tissues that are not typically depicted as target tissues for these hormones. Some of these effects appear to be mediated by the classical MR trafficking to the plasma membrane where it can directly or indirectly interact with other signaling pathways. Mineralocorticoids also appear to activate other as of yet unknown receptors that contribute to the rapid signaling seen in some cells.

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