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Research Article

Evolution of the Mineralocorticoid Receptor and Gender Difference in Cardiovascular Pathology

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Abstract

Retracing the evolution of Mineralocorticoid Receptors (MR) obliges us to take an instructive as well as fascinating leap back in time. This journey teaches us that the relationship between MRs and what we consider their natural ligand, aldosterone, has not always been an exclusive one. MRs operated for a very long time in the oceans and, in any case, in an aquatic environment, stimulated by ligands other than aldosterone, and exercising functions that we still do not know well but which were certainly different from those they currently perform in terrestrial vertebrates, where they maintain normal sodium and body fluids. The history of MRs was initially intertwined with that of female sexual hormones, in particular with progesterone, which was one of the first agonists for MRs, before becoming, with the transition to the terrestrial environment, an important antagonist. This initial intertwining could be the cause of the sexual dimorphism that can be glimpsed when these receptors are overstimulated, as emerges from many experimental studies and some clinical data and/or when antagonistic drugs for these receptors are studied. This must be taken into account in the planning of clinical studies, especially randomized controlled trials, in which the presence of the two sexes must always be well balanced and in the interpretation of the results which must always be performed being well aware of the gender of participants. This does not always happen, however.

More Information

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Introduction

The Mineralocorticoid Receptor (MR) is part of the Nuclear Receptor (NR) family which also includes the Glucorticoid Receptor (GR), the Progesterone Receptor (PR), the Estrogen Receptor (ER) and the Androgen Receptor (AR), [1].

In the classical vision the principal, if not exclusive, task of the Mineralocorticoid Receptor (MR) is to regulate the body's water and electrolyte balance, being stimulated to do so by its natural ligand: aldosterone, in the Aldosterone-Sensitive-Distal-Nephron (ASDN) [1]. A major turning point in our knowledge on this topic came with the cloning of the specific aldosterone receptor in the Evans laboratory at the Salk Institute [2]. This result was an impressive achievement as it allowed, on the one hand, to reconstruct the evolutionary history of this receptor and, on the other, to demonstrate that this receptor is present in many non-epithelial tissues where it performs tasks that have little or nothing to do with sodium reabsorption.

The evolution of mineralocorticoid receptors

The presence of MRs in a wide variety of vertebrates permitted an analysis of the evolutionary path of this receptor and led to an unexpected and surprising conclusion: as Funder [3] wittily pointed out a few years ago, "in all ligand-receptor systems, an obvious question is: which came first, signal or receptor—chicken or egg. For aldosterone and MRs, the answer is unequivocal: the MRs preceded aldosterone by millions of years".

According to an updated phylogeny [4] an ancestral (mineralo) Corticoid Receptor (CR) has been found in lampreys and hagfish, which are cyclostomes (jawless fish), a taxon that evolved at the base of the vertebrate line and MR and GR evolved from this ancestral CR. A distinct MR first appears in cartilaginous fish [5] but no trace of aldosterone has been found in the serum of these fish.

The first creature in which aldosterone appears is the lungfish [1,3]: This animal, as the name indicates, has both gills and lungs, marking the transition from an obligated aquatic to a terrestrial milieu: thus the MR which we consider the "natural" receptor for aldosterone, appears in evolution well before the appearance of its current ligand.

The evolution of ligands

Another important element to consider is the evolutionary path of the ligands. As Baker and Katsu [4] point out, the evolution of MR'-ligands follows approximately the same path that leads to the synthesis of aldosterone and cortisol starting from progesterone (Figure 1). The position of each steroid in this sequence coincides with its appearance, in the evolutionary scenario, as a ligand of MR. For example, Aldo,

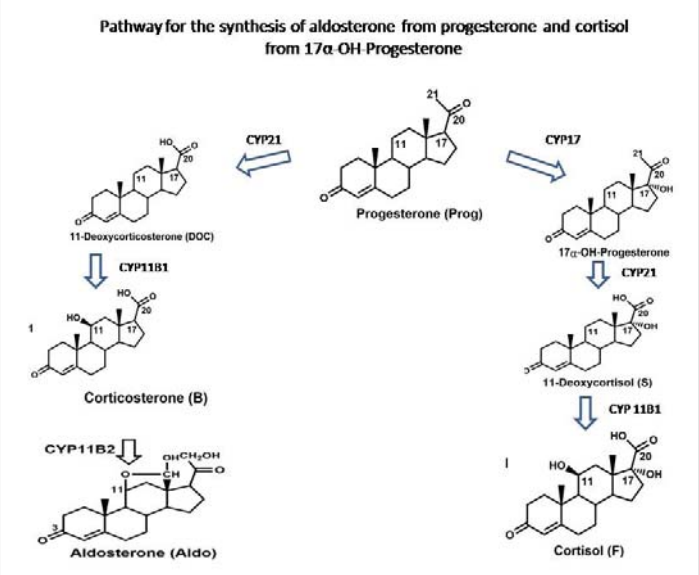

Figure 1: Pathway for the synthesis of aldosterone from progesterone. It is interesting to note that aldosterone which is the terminal of the cycle appears late in vertebrates, at the moment of the transition to land, while progesterone which is at the beginning of the cycle was present in ancestral fish.

which is at the end of the synthetic pathway, is not present in the serum of ancestral fish [5], while progesterone and 11-deoxycortisol, which are at the beginning of the pathway, have been found in the serum of ancestral Atlantic sea lamprey [6,7], Corticosterone (B) is present in the serum of cartilaginous fish, and Cortisol (F) and Corticosterone (B), but not Aldo, are found in ray-finned fish [8]. As above cited, Aldo first appears in lungfish [1] the closest extant forerunners of tetrapods (Table 1).

The role of progesterone

Of particular interest, from this perspective, is the role of progesterone. Characterization of MR in various fish has demonstrated that, in contrast to terrestrial animals, fish MRs were activated by progesterone and its derivative, spironolactone [9,10]. These findings suggest that progesterone was a physiological agonist for MR in fish, whereas in most terrestrial tetrapods (rodents, alligators, xenopuses), progesterone is an antagonist of MR [3] and, interestingly, Prog is an antagonist also for human MR [10]. According to Fuller [11], the switch in the MR response to progesterone and related compounds is a striking evolutionary event that was perhaps mandatory if the appearance of aldosterone, as a specific mediator of the homeostatic salt retention required for terrestrial life, was to be tolerated.

Geller syndrome: A journey back in time

Geller, et al. [12] described a mutation in the MR that causes markedly exacerbated hypertension in pregnancy. This mutation: a substitution of leucine for serine at residue 810 which lies in the ligand binding domain of the MR, alters the receptor's specificity, allowing mineralocorticoid antagonists such as progesterone and other steroids lacking 21-hydroxyl groups, normally MR antagonists, to function as agonists [13].

The discovery of this syndrome makes us understand that the possibility of living in the terrestrial environment, adequately managing the balance of the internal fluids and electrolytes is linked to the spatial position of a couple of amino acids. In other words, the MR of people affected by this mutation returns to the ancestral functioning it had in fish living in the oceans, "forgetting" the functioning learned when these ancestral vertebrates transitioned to the terrestrial environment.

Geller syndrome and monogenic forms of hypertension: Rare but dangerous

Geller Syndrome is due to hyperstimulation of the MR by progesterone in the presence of very low circulating aldosterone values. It is characterized by high blood pressure, associated with hypokalemia that occurs during pregnancy; it is important to remember that the MR antagonist, spironolactone, is absolutely contraindicated because it is an agonist for mutant MR. For pregnant women with exacerbated hypertension, termination of pregnancy is advised to improve symptoms efficiently [14].

Other clinical situations in which the MRs are stimulated in the absence of elevated aldosterone are:

a) Liddle's Syndrome (LS), due to the germline mutation in the *SCNN1G* gene which leads to an amplified activity of the epithelial sodium channel (ENaC) in the ASDN, independent of aldosterone activity [15]. Definitive diagnosis mainly depends on genetic screening; however, the prevalence of LS in the hypertensive population is still unclear. A relatively high frequency of young patients with Liddle syndrome has been reported in China and the discovery of new pathogenic genes and variable penetrance indicates that the prevalence of LS could well be much higher than currently estimated [16].

LS patients have a very elevated blood pressure associated with hypokalemia and show remarkable response to the ENaC blocker, amiloride, and the potassium-sparing diuretic, triamterene. A salt-limited diet is also recommended [17]

Table 1: The presence of nuclear receptors in various types of fish and the evolutionary path of mineralocorticoid ligands. Note that aldosterone is absent in ancestral fish and only appears with the advent of the Lungfish.

Ancestral fish	Active nuclear receptors	Mineralocorticoid ligands
Amphioxus	3-Ketosteroid receptor (R) Progesteron R	unknown
Cyclostomes (lamprey, Hagfish)	Estrogen R, progesteron R,corticosteroid R	11-deoxycortisol
Cartilaginous fish (skates, shark)	Estrogen R, androgen R, progesteron R, glucocorticoid R, mineralocorticoid R	1-alfa-hydrossycorticosterone, propgesteron
Teleost Fish (Zebrafish, Sturgeon, Salmon)	Estrogen R, androgen R, progesteron R, glucocorticoid R, mineralocorticoid R	cortisol, progesterone
Lobe finned Fish (Lungfish)	Estrogen R, androgen R, progesteron R, glucocorticoid R, mineralocorticoid R	aldosterone
References: [1,4-6,9,10]		

b) Apparent Mineralocorticoid Excess (AME) which is inherited as an autosomal recessive trait caused by inactivating HSD11B2 variants. Physiologically, the enzyme 11β-HSD2 catalyzes the metabolic conversion of cortisol to cortisone and thereby prevents the MRs from cortisol oversaturation. However, because of the mutated gene, cortisol-mediated overstimulation of the MRs ensues.

AME can be divided into two types: a severe phenotype (AME-I) and a mild phenotype (AMEII), [18].

Taken together, these syndromes demonstrate the importance that sodium retention plays in the genesis of hypertension and vascular damage even in the presence of extremely reduced circulating aldosterone.

The role of progesterone in pregnancy

Geller Syndrome is fascinating from an evolutionary point of view but has a rather modest clinical relevance given that this mutation is not particularly frequent (only a handful of cases have been described in the literature). Nevertheless, the syndrome is important for pointing out the protective role that progesterone has in the female gender, particularly in pregnancy, when the MR has all the amino acids in the right places.

In pregnancy, aldosterone levels increase disproportionally to renin activity and play a significant role in the sodium retention required for the late stages of fetal growth [19]. The evolutionary purpose of sex-specific increased aldosterone levels in women is most likely due to the physiological needs of pregnancy. In a healthy pregnancy, plasma volume expansion and the increasing demands of a growing feto-placental unit require an increase in renal blood flow (~50% increase), increased sodium retention as well as increased RAAS activation, as reviewed elsewhere [20].

However, the pathophysiological effects of increased aldosterone on mineralocorticoid receptors are mitigated during pregnancy by progesterone, which increases by over 100 fold leading to heightened sodium excretion, a phenomenon observed in pregnant women [21,22]. However, the antialdosterone effect of female hormones is not limited to the pregnancy period, but in all likelihood extends to the entire pre-menopausal period.

The protective actions of sexual hormones

Epidemiological studies have revealed that premenopausal women are protected against the development of CVD when compared to age-matched men. In addition, women present with CVD a decade later than men, a timeframe that coincides with the postmenopausal loss of female hormones [23]. In particular, Salt Sensitivity of Blood Pressure (SSBP) appears to depend on female sex hormones. Multiple clinical studies indicate that cessation of sex hormone production, associated with menopause, increases the risk of SSBP [24,25]. Shulman, et al. reported that surgical induction of menopause with elective hysterectomy and oophorectomy increases SSBP in middle-aged women [26]. Olivieri, et al. [27] demonstrated that kanrenoate, an MR Antagonist (MRA), was twice as effective in reducing SBP in women in menopause than in men, suggesting that postmenopausal hypertension is largely dependent on mineralocorticoid receptor activation and selectively sensitive to MRAs.

Estrogen also plays an important role in counteracting the harmful effects of aldosterone. The cessation of estrogen production in postmenopausal women leads to an increase in BP, and early estrogen replacement therapy could prevent this increase and atherosclerotic progression [28,29]. Furthermore, experimental studies have shown that circulating aldosterone levels increase after menopause [30] and estrogen therapy reduces this increase [25,31], lastly, it has been demonstrated that the administration of 17-beta-oestradiol reduces salt sensitivity of blood pressure in postmenopausal women.

The role of estrogens and progesterone in clinical practice

Menopausal Hormone Therapy (MHT) is commonly recommended in appropriate patients for the management of menopausal symptoms.

Particularly interesting, considering the topic we are dealing with, are the effects of Drospirenone (DRSP) on the cardiovascular system. DRSP derived from 17-alpha-spirolactone, combines the therapeutic effects of progestogens and anti-mineralocorticoids [32]. The anti-mineralocorticoid effects of 3 mg of DRSP are comparable to those of 25 mg of spironolactone [33]. Compared to traditional estrogen-progestin therapies, DRSP can counteract the water and sodium retention triggered by estrogen-induced RAAS activation. This may potentially mitigate estrogen-related weight gain and lower BP, especially in hypertensive postmenopausal women [34]. A retrospective analysis revealed that continuous, long-term treatment with DRSP notably reduced 24-hour systolic BP and diastolic BP, consequently lowering the risk of CVD in early menopausal women with stage 1 hypertension [35].

Exogenous estrogen effects: Before menopause, the cardiovascular protective effects of estrogens have been well described [36]. After menopause, estrogen levels in women drop significantly and the risk of hypertension significantly increases [37]. Consequently, the administration of exogenous estrogen might reasonably be expected to have a similar BP-lowering effect. However, the impact of exogenous estrogen treatment on BP in humans has yielded inconsistent findings [38].

In postmenopausal women receiving estrogen therapy, the lowest risk of hypertension was observed with the use of non-oral estradiol at the lowest effective dose and for the shortest duration. This suggests that a minimized risk of hypertension

may be achieved by using non-oral estradiol, at the lowest effective dose, and for a shorter duration.

Apart from its cardiovascular effects, MHT also showed favorable effects on multiple systems. An umbrella review revealed that MHT was associated with reduced risks of bone fracture and diabetes mellitus [39]. However, it was linked to increased risks of stroke, venous thromboembolism, gallbladder disease, as well as breast, ovarian, esophageal, gastric, and colorectal cancer [39].

In conclusion, the cardiovascular protective role of hormone therapy has not been conclusively validated in clinical trials, while some important adverse effects have been observed.

This heterogeneity appears to be closely associated with the initial time, administration route, dosage, formulation, and duration. Future studies are needed to evaluate the actual usefulness of these drugs in menopausal women.

The role of salt excess in men and women

Primary hyperaldosteronism, but also other pathologies such as chronic kidney disease or diabetes, may cause excessive sodium retention. In the classical view, a salt excess within the body causes damage by leading to an increase in plasma volume and subsequent increase in blood pressure [40]. However, our understanding of body sodium homeostasis has been reshaped after the discovery that Na^+ can accumulate in the interstitium of tissue without commensurate water retention [41,42]. Studies of 23Na-magnetic resonance imaging revealed that Na^+ is stored in the interstitium of the skin and skeletal muscle in humans and the concentration of this stored Na+ has been correlated with higher BP [43] The discovery of this nonosmotic Na^+ storage is of paramount importance because recent animal studies suggest that Antigen-Presenting Cells (APCs) can be activated by high concentrations of extracellular Na+ via an Epithelial Na+ Channel (ENaC)-dependent pathway [44] and 23Na human studies using magnetic resonance imaging have shown that tissue Na^+ concentrations in individuals with hypertension are comparable to the levels that can activate APC [43]. Under conditions of high extracellular sodium, the assembly of ENaC subunits is promoted by the salt-sensing kinase SGK1 in MR of APCs [45,46]. This assembly facilitates sodium entry into APCs through ENaC and initiates a series of reactions that generate highly reactive oxidative products called Isolevuglandins (IsoLGs), which react with endogenous proteins to form IsoLG-protein adducts. These adducts are presented to T cells as neoantigens, triggering the synthesis of IL-6, IL-1b, and IL-23, which stimulate the differentiation of naive T cells into pro-inflammatory T cells [47]. Moreover, the release of inflammatory cytokines (IL-17, INF-gamma) acts on the vasculature to decrease NO bioavailability and promote salt-sensitive BP [48]. Overall, this activation cascade results in kidney inflammation [49], vascular dysfunction, and eventual fibrosis and hypertension [50]. Furthermore salt can act directly on T-cells and macrophages to polarize them towards a pro-inflammatory phenotype [51], interestingly, CD8+ T-cells also express MR, and selective deletion of MR in T-cells prevents hypertension [52].

Gender differences in immune system activation

While the mechanisms described above may play an important role in the development of hypertension and organ damage in males, studies conducted in females support an anti-inflammatory role of the female immune system limiting the damage of excess salt in the interstice. For instance, a dysregulation of ENaC with ensuing salt-sensitive BP has been reported in male but not in female diabetic mice by Veiras, et al. [53]. Adoptive transfer experiments of CD4+ and CD8+ T-cells induce hypertension in males [54] and similar experiments with female CD4+ and CD8+ T-cells support anti-hypertensive properties in the female T-cell population [55]. In parallel, a large body of literature established that females have more T regulatory cells (Tregs), and more anti-inflammatory and anti-hypertensive subset of T-cells that suppresses immune function and attenuates the increases in BP [56,57]. These dimorphisms are partially lost with menopause [57].

Progesterone (PROG) could be at the root of these differences between males and females regarding immune system behavior.

PROG is an immunomodulatory molecule [58] that can inhibit mature dendritic cells and the dendritic cell-mediated proliferation of T cells, favoring immune tolerance [59]. Furthermore, PROG suppresses the activity of potent type I interferon-producing dendritic cells [60] and in addition to the tissue-specific effects, PROG has a range of immunosuppressive effects on innate leukocytes reducing inflammatory cell infiltration [60]. Lastly, in vitro studies have also demonstrated the PROG inhibition of human neutrophil degranulation and the generation of free radicals [61].

How to align gender-specific therapeutic approaches with evolutionary data

From what has been described so far, it is clear that the two sexes have different sensitivity to salt, both as regards the cardiovascular system and the immune system. This diversity could be due to the different functioning of MRs, particularly those located in non-epithelial tissues, and this could imply a different use, in the two sexes, of drugs that block the activity of these receptors.

An epidemiological survey conducted in Southwestern Europe has revealed that the incidence of Heart Failure with preserved Ejection Fraction (HFpEF) is notably higher in women across all age groups, with a particularly pronounced difference observed among elderly patients [62]. Data from China have confirmed that females with HFpEF tend to be older and have a poorer prognosis compared to males [63].

An example of gender-specific treatment with MR Aantagonist (MRA) drugs comes from a post hoc analysis of the Top Cat study. In an exploratory, post hoc, non-pre-specified analysis of the TOPCAT trial [64] subjects with symptomatic HF and a left ventricular ejection fraction ≥45% were randomized to spironolactone or placebo therapy.

There were no sex differences in outcomes in the placebo arm, but spironolactone therapy was associated with reduced all-cause mortality in women but not in men, with a significant interaction between sex and treatment arm. This finding is hypothesis-generating only and will require substantial validation prior to clinical application. However, given the paucity of effective therapies in patients with HFpEF, a prospective study of the effect of MRA in women with HFpEF is warranted.

Various clinical studies indicate that MR antagonists decrease BP to a greater extent in women as compared with men [27,65] and experimental data also indicate that MR blockade protects female rodents from salt-sensitive hypertension [66].

Emerging evidence implicates the MR, specifically within the endothelial cells (EC-MR) lining the blood vessels, in mediating some of the sex differences observed in cardiovascular pathology. Recent research has attributed an important role to this EC-MR which reacts to the sodium load and also to the high-fat diet differently in the two sexes. This could depend on the interaction between progesterone and estrogen receptors with EC-MRs [66].

Faulkner, et al. [67] have demonstrated that premenopausal women have a heightened expression of EC-MR compared to men, and this increase is secondary to progesterone receptor activation.

There is also clinical data supporting the sexual dimorphic role of EC-MR in obesity-induced endothelial dysfunction. For instance, in a prospective cohort study of African American patients with hypertension and obesity, women taking spironolactone had improved BP control, which was not seen in spironolactone-treated men [68].

Another randomized trial showed that MR inhibition did improve coronary endothelial function in patients with obesity and diabetes [69]. Obese women with diabetes had a worse coronary microvascular function than males and this was associated with enhanced aldosterone production in women ŧ70].

Lastly, preclinical investigations have demonstrated that endothelial EC-MR contributes to vascular disease in a sexually dimorphic manner since EC-MR contributes to vascular disease in males by inducing the inflammation of large vessels, whereas in females, EC-MR drives endothelial dysfunction in microvessels [71].

Clearly, it is essential to confirm these sex differences in sufficiently powered randomized control trials to evaluate the sex-specific efficacy of MR antagonists in different disease states to determine precision medicine treatment paradigms.

Conclusion

In conclusion, one of the mechanisms by which excess body sodium can increase blood pressure and induce damage in various organs is the stimulation of MR and ENaC present in various cells of the vascular and immune systems. Many experimental data and some clinical data suggest that this mechanism acts differently in men and women. Therefore, consideration of Sex as a Biological Variable (SABV) in the design, analysis, and reporting of clinical and preclinical studies should be a critical factor. Nevertheless, even after the National Institutes of Health (NIH) implemented its policy requiring the assessment of SABV in experimental designs in 2015, we are still far from the goal of equitable female inclusion [72] and the female sex remains underrepresented in hypertension trials, where women account for 38% of enrolled participants [73]. Further experimental studies on both male and female animals, but also an enrollment that includes an adequate number of women in MR antagonist drug trials, and a separate evaluation of the data between the two sexes, could add further important knowledge to this field.

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