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Salt Sensitivity of Blood Pressure in Women

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Abstract

Purpose of Review-—Several clinical and large population studies indicate that women are more salt-sensitive than men, yet the precise mechanisms by which the sexually dimorphic onset manifests remains incompletely understood. Herein, we evaluate recent epidemiological data and highlight current knowledge from studies investigating sex-specific mechanisms of salt sensitive blood pressure (SSBP).

Recent Findings-—Emerging evidence indicates that women of all ethnicities are more salt-sensitive than men, at all ages both pre- and post-menopausal. However, menopause exacerbates severity and prevalence of SSBP, suggesting that female sex chromosomes predispose to and female sex hormones mitigate SSBP. Results from both human and rodent studies support the contribution of an enhanced and inappropriate activation of the aldosterone-endothelial cell mineralocorticoid receptor (ECMR) axis promoting vascular dysfunction in females. Increases in adrenal response to angiotensin II, in association with higher ECMR expression and activation of endothelial ENaC (epithelial sodium channel) in females compared to males are emerging as central players in the development of endothelial dysfunction and SSBP in females.

Summary-

Female sex increases the prevalence and susceptibility of SSBP and sex hormones and sex chromosome complement may exert antagonistic effects in the development of the female heightened SSBP.

Keywords

Aldosterone; Mineralocorticoid receptor; Endothelium; Immune activation; Inflammation; Sex Differences

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Conflicts of Interest

The authors declare no conflicts of interest

Introduction

Sex differences in cardiovascular diseases (CVD) is a field of ongoing study. Until recently, the general dogma is that premenopausal women garner a favorable, sex-specific protection against CVD due in large part to the beneficial effects of female sex hormones. Years of research, predominantly in men and male animal models, feed the misconception that women are less salt-sensitive. Salt sensitivity of blood pressure (SSBP), where BP increases or decreases more than 10% in response to changes in dietary salt consumption[1], is a heritable pathophysiological trait that accounts for 50–80% of essential hypertension diagnoses[2–6]. SSBP is present in approximately half of those with essential hypertension and contributes to resistant hypertension in most cases[7]. Biological sex and sex hormones, in combination with genetic predisposition, influence the mechanisms that regulate the onset and development of SSBP. Further confounding this sex-specificity is the demonstrated increases in SSBP in women following menopause. The purpose of this review is to summarize the most recent epidemiological and experimental data demonstrating that SSBP in women changes throughout the reproductive lifespan. We will summarize emerging evidence that mechanisms underlying SSBP involve sex-specific activation of the renin-angiotensin-aldosterone system (RAAS) and increased propensity for vascular dysfunction in women, whereas renal sodium retention and immune activation, which were first identified in male patients and animal models, may play lesser roles in SSBP in women than in their male counterparts.

Women Demonstrate Greater Salt Sensitivity of Blood Pressure than Men

Epidemiological data

Despite a relatively robust rodent literature indicating that male rodents are more salt-sensitive than females, a large body of evidence indicates that women are more salt-sensitive than men. SSBP is common in both men and women, however, many large population studies around the globe have revealed that SSBP is more prevalent in women. The GenSalt study, in Chinese adults, revealed higher drops (−8.07 vs. −7.05 mmHg, P=0.0004) and increases (+6.35 vs. 5.25 mmHg, P<0.0001) in systolic BP in women compared to men in response to low and high-salt dietary interventions respectively[8, 9]. The Dietary Approaches to Stop Hypertension (DASH) study of Black, White, and Asian Americans also indicated that a low sodium diet reduces BP in women to a greater extent than in men. The combination of the DASH diet and a low level of sodium lowered systolic BP by 6.8 mmHg in men vs. 10.5 mmHg in women (P< 0.001)[10, 11]. Further, analysis of the Hypertensive Pathotype (HyperPath) and the Hypertension Insulin–Resistance Study (HTN-IR) cohorts composed of individuals from the USA, France, Spain and Mexico uncovered a 30% greater salt-sensitive prevalence in women compared to men[3, 12]. Most notably, the results of the INTERSALT study, composed of >10,000 patients from 32 countries, revealed a significant higher association of BP and sodium excretion in women than in men[2, 13]. Altogether, these studies indicate that women are more salt-sensitive than men and are thereby at higher risk for developing SSBP, posing a sex-specific cardiovascular health dilemma.

Racial differences and genetic predisposition

Considering the aforementioned large population studies were conducted in multiple countries, the sex-specificity for SSBP persists across ethnicities. Studies in which race was assessed do note, however, that individuals of African descent display a higher incidence overall for SSBP regardless of sex, with ~70% prevalence compared to ~50% in White populations[14, 15]. Remarkably, in a population of relatively high socioeconomic status, greater increases in systolic BP with salt loading were seen in hypertensive African American versus hypertensive White women (23.0 vs 14.8 mmHg, $P<0.01$), while no difference in SSBP was observed between the normotensive women[16]. Recently, genetic studies investigated whether genetic variations in both estrogen receptor (ER) and Lysine-specific demethylase 1 (LSD1), a salt-sensitive epigenetic regulator, could contribute to this racial and sex predominance[12, 17]. Multivariate analyses of both the HyperPATH and Hypertension Insulin–Resistance cohorts documented that ESR2 (gene coding for ER-β) rs10144225 minor risk allele carriers had a significantly positive association with SSBP, in premenopausal women only ($\beta = +4.4$ mm Hg per risk allele, $P = 0.004$). The association persists after adjustment for age, body mass index, underlying disease and race, but interestingly, in individuals of African descent, the prevalence of risk allele carriers was significantly higher than that of the nonrisk allele carriers, whereas a greater number of nonrisk allele carriers was observed in individuals of European descent ($P < 0.0005$)[12]. Further analysis of the HyperPATH cohort also revealed greater SSBP in the *LSD1* risk allele carriers (rs587168) than the nonrisk homozygotes African Americans and demonstrated that this difference was driven by females, especially postmenopausal women. No difference in SSBP was observed between LSD1 genotypes in individuals of European descent[17]. In addition to this apparent genetic predisposition, women of African descent have higher prevalence for obesity and diabetes, two major risk factors for SSBP, which may underlie some of the racial propensity for that population. While further studies are needed to elucidate the respective contribution of genetic and environmental factors for racial disparities in SSBP among women, a recent report demonstrates that a potassium intake higher than the US dietary goal (87 mmol/day) abrogates the racial difference in SBBP[15], indicating that differences in diets in addition to genetic predisposition could contribute to racial differences.

Sex differences in taste for salt

Interestingly, differences in diet may also contribute to the sexual dimorphic onset of SSBP[18]. Remarkably, a higher proclivity for dietary salt consumption is reported in Japanese women compared to men, which likely adds and participates to the adverse effects of SSBP[19]. While it remains to be demonstrated whether these data are translatable to other populations, compelling evidence from experimental studies support the female higher proclivity for salt[9, 20, 21] which likely originates phylogenetically in the need to preserve sodium losses during pregnancy. Salt preference may be driven by sex hormone levels, as some studies indicate that during the luteal phase of the menstrual cycle women exhibit an increased preference for salt, however, other studies posit that sodium preference is not correlated with any particular menstrual phase[22–25]. This is in congruence with animal studies reporting that salt preference develops with sexual maturity but also that ovariectomy does not abolish the higher female taste for salt[21]. A deduction from these data is that either

testosterone represses salt appetite or that both female sex hormones and chromosomes influence dietary salt intake. Reports indicate that testosterone suppresses salt taste in adulthood[26, 27], but also rule out, using the FCG mouse model described previously, the contribution of sex chromosome completement to the regulation of salt taste[27]. Nevertheless, further studies are needed to delineate not only the contribution of sex steroid hormones and sex chromosomes but also the influence of genetic predisposition[28] in the regulation of salt intake in humans.

Effects of menopause, sex hormones and chromosomes

Importantly, results from the HyperPath and HTN-IR studies indicate that salt-sensitivity is more prevalent in women at all ages and reproductive stages[3, 12]. However, multiple clinical studies indicate that cessation of sex hormone production, particularly estradiol, associated with menopause increases the risk of SSBP[29, 30]. The WHO-CARDIAC study, spanning 25 countries, revealed that in 21 centers in 17 countries worldwide, menopause increased SSBP prevalence in the 2,212 women (48–56 years old) studied as assessed by a correlation of systolic BP and 24-hour sodium excretion[14, 31]. These data suggest that SSBP in postmenopausal women increases by two potential contributing factors: loss of female sex hormones production in combination or not with the natural process of aging. Using an unusual protocol to assess SSBP[32], Shulman et al., reported that surgical induction of menopause with elective hysterectomy and oophorectomy increased SSBP in middle age women[33]. Concomitantly, others report that transdermal estrogen replacement therapy decreases salt-sensitivity in postmenopausal women[34] suggesting that estrogens exert protective effects against SSBP despite the counterintuitive female heightened salt-sensitivity. In rat models of SSBP, notably the Dahl Salt-Sensitive (DSS) and the Spontaneously hypertensive (SHR) rat, multiple groups have investigated the mitigating role of estradiol on SSBP. Ovary-intact and actively cycling female DSS rats demonstrate only a mild SSBP phenotype compared to the males of these models whom depict greater increases in SSBP[35–37], which contrasts to clinical data suggesting that reproductive-aged women are more prone to SSBP. However, these models have been utilized to demonstrate the crucial role of female sex hormones in the development of SSBP. Ovariectomy (OVX) ablates the sex difference in SSBP between male and female DSS rats[36, 37]. A caveat to this observation is that OVX increases BP in the absence of high salt diet in rat models[35, 37, 38]. In addition, high salt diet has no additive effect on OVX-mediated elevations in BP in DSS rats and reduction in salt intake is unable to restore BP in OVX DSS female rats[38], which muddles conclusions of sex hormone contribution specifically in salt sensitive increases in BP in female DSS. Moreover, OVX appears to have no effects on salt sensitivity in previously hypertensive female rats (SHR)[35, 37]. Therefore, while female sex hormones incontestably exert protective effects on BP, the study of the contribution of female sex steroids to SSBP is confounded either by pre-existing hypertension or salt-independent effects of OVX on BP.

While menopause is associated with reduced estrogen and progesterone levels, it also involves an increase in the testosterone to estrogen ratio. Testosterone supplementation increases BP in young OVX female SHR on high salt diet[39] and, seemingly congruently, suppression of endogenous androgen production by orchidectomy reduces BP in male

rat models, including DSS, Sabra and Sprague-Dawley, which is restored to normal levels following testosterone supplementation[40–42]. However, as observed with OVX in the absence of high salt diet, testosterone supplementation in OVX female rats and orchidectomy in male rats respectively elevate and decrease BP in the absence of high salt diet as well[43]. This may suggest that androgens exert negative BP effects in males and females independently of salt.

Although sex steroid hormones play a key role in the control of the cardiovascular system, emerging evidence supports a role for sex chromosomes as well. The four-core genotype (FCG) mouse, in which gonadal sex is separated from the sex chromosome complement, enables comparisons of XX and XY mice with ovaries or testes. With this model, Ji et al. showed that in mice with intact ovaries/testes, angiotensin II (ANGII) induces higher elevation in BP in male compared to female mice. However, in gonadectomized FCG mice, mice with XX chromosome complement demonstrate greater BP response to ANGII irrespective of their previous priming with ovaries or testes, indicating that XX chromosome complement alone promotes increases in BP in the absence of intact sex hormone complement[44]. These data are in concordance with others that report similar “ying-yang” biological functions of chromosomes vs. hormones in other biological systems[45]. These data suggest that female sex chromosomes predispose females to a pro-hypertensive state that is rigorously regulated by sex hormones, indicating that deficits or mechanisms that negate these sex hormone effects are sex-specifically detrimental to BP control in females.

Contribution of Aldosterone to Salt Sensitivity in Women

Salt consumption directs the kidneys to balance dietary sodium by decreasing reabsorption of sodium and increasing natriuresis thereby maintaining sodium and volume homeostasis[5, 46, 47]. In salt-sensitive women, emerging clinical and experimental evidence indicates that females do not suppress the renin-angiotensin-aldosterone system (RAAS) as efficiently as males, thereby resulting in a sex-specific balance favoring higher RAAS activation despite high sodium intake[3, 12, 17]. The key RAAS pathway components involved in SSBP are ANGII and aldosterone, though by sex- and reproductive stage-specific mechanisms. Previously established sexually dimorphic RAAS activation in males involves enhanced angiotensin-converting enzyme (ACE), ANGII, and angiotensin II receptor type 1 (AT1R) axis activation which promotes vasoconstriction and increases sympathetic activation. In contrast, premenopausal women have greater activation of the angiotensin-converting enzyme 2 (ACE2), angiotensin (Ang) (1–7), mitochondrial assembly receptor (MasR), and angiotensin II receptor type 2 (AT2R) axis which usually counter ACE-ANGII-AT1R axis activation by increased vasodilation, increased nitric oxide (NO) production and inhibition of sympathetic activation[48–50]. Following menopause and the concomitant loss of ovarian estrogen production, women have decreased circulating Ang (1–7) and thereby lose the counter regulatory protection leading to an increased activation of the ACE-ANGII-AT1R axis[35, 48]. Therefore, together, these data raise the question of why females have an inadequate response to salt if they exhibit lower ANGII activation. A potential answer may be found in the fact that women produce more aldosterone than men, as reported in the Framingham Offspring Study[3, 51]. Consistent with this observation,

Shukri et al., demonstrated that higher salt sensitivity in pre and postmenopausal women is associated with enhanced aldosterone production in response to ANGII in liberal and salt-restricted diet[3, 51]. Similar dysregulation of the RAAS in favor of an increased aldosterone sensitivity was also reported in salt sensitive women of African descent carriers of *LSD1* (rs587168) and ESR2 (rs10144225) risk alleles[12, 17]. In both Balb/C and C57BL6 mice, female mice demonstrate higher sensitivity of aldosterone production in response to increases and decreases in sodium intake, respectively, overall demonstrating higher aldosterone and adrenal aldosterone synthase expression than males[52, 53]. Experiments in rat adrenocortical cells confirmed that females display higher adrenal response to ANGII and extend these findings by demonstrating that this involves increased adrenal aldosterone synthase (CYP11B2) expression[3]. Higher AT1R expression in female adrenals compared to that of males is a potential explanation for heightened aldosterone production in females[53, 54]. While potentially compensating for the reduced activation of the conventional RAS signaling pathway, the heightened adrenal ANGII sensitivity and ANGII-mediated aldosterone production provide a source of SSBP.

The evolutionary purpose of sex-specific increased aldosterone levels in women, independent of sodium intake, 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[55]. However, while ANGII levels increase in pregnancy, aldosterone levels increase disproportionally to renin activity and plays a significant role in the sodium retention required for the late stages of fetal growth[56, 57]. Although pregnant women have significantly higher aldosterone levels, concurrent high elevations in progesterone levels antagonize excess activation of the mineralocorticoid receptor (MR), and in fact, mutations that excessively activate MR significantly increase BP specifically in pregnancy[58]. High salt intake is not a significant predictor of hypertension in pregnancy, however, aldosterone levels above that which would be normal for pregnancy are associated with gestational hypertension[59]. Therefore, the regulation of aldosterone by female sex is a mechanism wired to protect plasma volume expansion in pregnancy in an environment in which salt intake may be scarce. However, in women consuming westernized levels of dietary sodium and with many population risk factors (i.e. obesity, diabetes), these pro-aldosterone mechanisms predispose women to an increased risk for vascular disease and hypertension.

Endothelial Mineralocorticoid Receptor (MR) Expression and Activation are Elevated in Salt-Sensitive Women

The specificity of female sex to increase aldosterone production in the presence of elevated dietary salt consumption indicates that aldosterone-targeted therapeutics are more efficacious in women. Indeed, clinical studies indicate that MR antagonists decrease BP to a greater extent in women compared to men[60–62]. Experimental data also indicates that MR blockade protects female rodents from SSBP[52]. Our group has demonstrated that sex-specific receptor expression is responsible for the sex-specific efficacy of MR blockade. We showed that premenopausal women and cycling female mice have heightened expression of

endothelial MR compared to men, which is increased in female mice and human endothelial cells via increased endothelial progesterone receptor activation[63]. Concomitantly, we showed in Balb/c mice, a mouse model recapitulating the sex-specific salt sensitivity developed by humans, that MR blockade restored endothelium-dependent relaxation, a measure of endothelial function, and BP in female mice[52, 54]. Sex-specific endothelial dysfunction developed in females in response to sodium restriction and ablated by either MR blockade or selective deletion in MR in endothelial cells further supports a heightened aldosterone-endothelial MR axis activation in female mice[53, 54]. Combined, these data show that salt-sensitive premenopausal females have higher aldosterone sensitivity than males and are therefore more likely to have higher activation of endothelial MR leading to vascular dysfunction and giving rise to SSBP[2, 3, 52].

Salt sensitivity is associated with increased vascular resistance consecutive to endothelial dysfunction[64], which may play a more significant role in females than in males. Recently, vasodysfunction was proposed as a central regulator of SSBP in that salt-sensitive individuals increased BP following excess intake of sodium not from increased renal sodium retention or increased cardiac output, but instead from the failure to adequately decrease vascular resistance[65, 66]. This theory is also supported by numerous experimental studies in Dahl SS rats and salt-sensitive dogs reporting an impaired ability of these animals to decrease systemic vascular resistance to offset the initial increase in pressure associated with salt intake[67–69]. Furthermore, comparative studies between male, intact female and OVX female DSS rats report no differences between groups in fluid and sodium balance on high salt diet (8%), indicating that sodium retention is not the contributor to the sex difference in SSBP[38] in these models. Therefore, the vasculature may play a more significant role in SSBP in females, potentially due to a disruption of NO-mediated signaling. Indeed, increases in asymmetrical dimethylarginine (ADMA), a potent endogenous nitric oxide (NO) synthase inhibitor, which decreases NO bioavailability and causes abnormal or inhibited vasodilatory mechanisms is a key contributor to reduced vasomotion in salt sensitive individuals[65] notably in women of African descent[70]. In female experimental mouse models, our recent work reports a decrease in NO bioavailability in response to endothelial MR activation in vessels from female mice exclusively[52–54]. Although female sex hormones, notably estrogens, enhanced NO bioavailability and vascular health[30], salt sensitive females demonstrate heightened sensitivity to salt-induced decreases in vascular compliance, potentially predisposing them to SSBP.

Salt sensitive renal pressure natriuresis is blunted in females

Disruption of healthy pressure natriuresis, or the shifting of sodium retention and renal function to increase BP in response to dietary salt, was established by Guyton and colleagues predominantly in male subjects. Recent findings suggest that these mechanisms may play a lesser role in BP control in salt sensitive women. In the Balb/C mouse model of salt-sensitive hypertension, both chronic sodium intake over seven days as well as acute sodium load did not result in increased sodium retention in female mice in association with increased BP induced by high salt diet. In fact, females excreted sodium load more readily than males[52]. These sex differences in renal mechanisms controlling BP in response to salt may be related to differences in renal endothelin (ET-1) and NO

signaling but also in renal sodium channel expressions. Within the collecting duct, ET-1 promotes sodium excretion through the activation of its endothelin B (ET_B) receptor which leads to a decrease in epithelial sodium channel (ENaC) open probability[71, 72]. While this mechanism is common in both sexes, in females, ET-1 also activates ET_A receptor which increases sodium excretion via a neuronal NO synthase (NOS1)-dependent mechanism[73]. Remarkably, OVX ablates this female-specific mechanism, reduces inducible and endothelial (NOS2, NOS3) NOS expression and increases ET_A and ET_B receptor expression in the inner medulla, while estrogen supplementation restores NOS levels. Together, these data indicate that estrogen is protective against disruptions in pressure-natriuresis in times of sodium loading, however, rendering that SSBP in estrogen-intact women likely involves extra-renal mechanisms[71–75]. Based on the key role of the ET-1 system in renal sodium handling, its contribution to SSBP is not surprising and highlighted by the observation that deletion in collecting duct ET-1 or its receptors results in marked salt-sensitive hypertension in male mice. However, counterintuitively, lack in functional ET_B receptor alone induces SSBP in females only, suggesting that the sex-specific contribution of ET_A and ET_B might be altered in response to high salt consumption[72, 76]. While additional studies are required to investigate the contribution of the ET-1 system in salt sensitive women, these data provide additional mechanistic explanations for the female heightened ability to excrete sodium. Further supporting this point, Veiras et al. demonstrated that Sprague Dawley female rats excrete acute sodium loading more readily than males and that proximal tubule sodium reabsorption is downregulated in females compared to males[77]. This study also highlighted significant sex differences in proximal and distal tubule sodium transporter expression, favoring low proximal tubule reabsorption and increased distal tubule reabsorption which reduces sodium load encountering the distal collecting duct reducing ENaC reabsorption of sodium. ENaC expression and activity increases with MR activation in the distal collecting duct, which enhances sodium and water reabsorption in exchange for urinary potassium excretion[78]. ENaC protein expression and activity are increased by estrogen in several tissues including the kidneys[79], however, counterintuitively, women and female rodents present with similar or heightened efficiency at excreting salt load compared to males[52, 77, 80] even in the absence of estrogen[38] which likely minimizes renal ENaC contribution to SSBP in females[81]. On the other hand, endothelial cell ENaC (EnNaC) membrane abundance increases in response to endothelial cell MR activation[82] resulting in reduction of eNOS activity (endothelium NO synthase) and NO production and thus excessive arterial stiffness[83]. While this mechanism has not been described in the context of SSBP, compelling evidence indicates that aldosterone-induced endothelial MR activation increases EnNaC and promotes EnNaC-mediated endothelial and vascular stiffness in female mice[84–86]. Therefore, one could speculate that the aldosterone-MR-EnNAC axis activation in female vasculature predisposes to SSBP predominantly rather than shifting in the pressure natriuresis curve.

Sex-specific Contribution of the Immune System to Salt-Sensitive Hypertension

Another organ system known to express ENaC and involved in the development of hypertension is the immune system. T-cells infiltrating the kidney and the vasculature

are major contributors to hypertension by inducing vascular and renal inflammation and cytokine release promoting sodium retention and vasoconstriction thereby increasing BP[87–92]. While salt can act directly on T-cells and macrophages to polarize them towards a pro-inflammatory phenotype[14], recent evidence introduces monocyte-derived dendritic cell (DC) activation as a potential initial step in the cascade of activation. DCs express ENaC in response to increases in extracellular Na^+, which triggers a cascade of events leading to the formation of reactive oxygen species and the production of isolevuglandins (isoLGs). IsoLGs are highly reactive products from lipid oxidation whose accumulation activates T-cells, notably $CD8^+$ T-cells. IsoLGs induce the release of inflammatory cytokines (IL-17, INF-γ) which act on the vasculature to decrease NO bioavailability and promote SSBP[93–96]. Interestingly, $CD8^+$ T-cells also express MR and selective deletion of MR in T-cells prevents hypertension[97] providing another source of T-cell activation and potentially another avenue for the aldosterone-MR axis to promote SSBP. While these latter mechanisms may play a crucial role in the development of hypertension in males, whether they contribute to the heightened SSBP in females remains to be demonstrated. Indeed, studies conducted in females mostly support an anti-inflammatory role of the female immune system and potentially a limited contribution to SSBP[98]. For instance, while adoptive transfer experiments identified male $CD4^+$ and $CD8^+$ T-cells as major effectors of hypertension in males[99], similar experiments with female $CD4^+$ and $CD8^+$ T-cells support anti-hypertensive properties in this latter T-cell population[100, 101]. In parallel, a large body of literature established that females have more T regulatory cells (Tregs), an anti-inflammatory and anti-hypertensive subset of T-cells that suppresses immune effector function and attenuates increases in BP[102–104]. Lastly, further arguments in support of a protective role of the female immune system against SSBP are provided by a recent study in which deficiency of CD14, a cell surface LPS receptor for monocytes and macrophages associated with CVD, in female Dahl Salt Sensitive rats caused greater renal injury and more significant response to SSBP with increased renal infiltration of macrophages compared to males. Rescue experiments via bone marrow transplant from $CD14^{+/+}$ females abrogated the effect. In addition, ovariectomy abolished the sex difference supporting the contribution of female sex steroid hormones[4]. Previous research has shown that estrogen upregulates and promotes increased CD14 expression *in vivo* in female mice and *in vitro* in cultured monocytes[105]. These findings suggest that CD14 cells protect females from SSBP via sex steroids, notably estrogen-dependent mechanisms and would likely further minimize the contribution of the immune system to the female heightened SSBP.

Microdomains of Interstitial Sodium Retention: Skin & Skeletal Muscle

Recently, studies have postulated that sub-compartments of interstitial sodium retention contribute to SSBP. The skin and skeletal muscle are microdomains for sodium retention, and contribute to immune activation in salt-sensitive populations[106] where high dietary salt consumption induces increased sodium storage in skin and muscle microdomains[107]. Measurement of sodium disposition in the skeletal muscle and skin of animal and human tissue, with ^{23}-sodium magnetic resonance imaging (^{23}Na-MRI), indicates skin and muscle sodium correlates with BP in salt-sensitive patients[106, 108] with increased retention in these microdomains[102]. In a cohort of 70 prehypertensive adults, ^{23}Na-MRI revealed increased

sodium retention in skin is associated with increased accumulation of isoLGs and responses manifested in SSBP[96]. Routinely, results from studies using this technique demonstrate that the specific microdomain, skin or skeletal muscle, for interstitial sodium retention following salt loading is sex-dependent. Several studies suggest that men have higher sodium storage in skin whereas women have higher storage in skeletal muscle[109–111] but Braconnier et al. revealed increased muscle sodium accumulation following salt loading, regardless of sex[112]. Looking to recapitulate this phenotype in a rodent model, Gohar et. al. investigated how salt loading influenced skin and muscle sodium depots in Sprague Dawley rats but found no difference between sexes[113]. With several human studies demonstrating sex-specific compartmentalization of interstitial sodium storage, yet limited studies overall conducted using ^{23}Na-MRI, it is difficult to fully elucidate how interstitial sodium compartments contribute to the sex-specific mechanisms of SSBP. Women are more salt-sensitive than men, and also display sex-dependent deposition of interstitial sodium, therefore, more studies are necessary to demystify how microdomain sodium accumulation contributes to SSBP in women. Additionally, it is unknown whether skeletal muscle sodium uptake is influenced by presence or absence of sex hormones or phases of menstrual/estrous cycle. Since pregnancy normally induces increased blood volume and water retention to meet the physiological demands of pregnancy, it is likely that there is an increase in interstitial sodium retention in either skin or skeletal muscle or both as an evolutionary adaptation to ensure species survival. In potential contradiction with the aforementioned findings, novel recent evidence by Rossitto et al. supports that tissue sodium excess in high salt diet conditions is systemic rather than skin-specific and similar in both sexes. Moreover, while the authors show that hypertensive patients exhibit isotonic skin sodium excess, they also demonstrate that skin sodium accumulation is unlikely to be the cause of experimental hypertension if water-independent[114]. Therefore, more studies are required over the full lifespan of women to elucidate if and how interstitial sodium microdomains could contribute to SSBP.

Conclusion

The most recent scientific findings illustrate that women, regardless of their ethnicity, menopausal status or age, are more salt-sensitive than men, and that, counterintuitively, female sex steroid hormones mitigate SSBP. While additional studies are still required to fully identify the underlying mechanisms of the heightened female salt sensitivity, notably to decipher the respective role of sex chromosome versus sex hormones, strong evidence from both the human and rodent literature support a role for inadequate RAAS suppression and inappropriately high aldosterone production. This, in conjunction with sex-specific increases in endothelial MR expression and EnNaC activity, likely leads to diminished NO bioavailability and vascular dysfunction promoting BP elevation, as depicted in Figure 1. While activation of both the innate and adaptative immune systems have been identified as main contributors to SSBP in males, experimental evidence would support a protective role for both $CD14^+$ and Tregs in females. A potential new player to the sexually dimorphic onset of SSBP is the contribution of interstitial sodium microdomains, though further studies are required to fully elucidate its role.

Perspectives

Despite few contradictory reports[29], we estimate it reasonable, based on the strong epidemiological data presented, to state that women are more salt-sensitive than men throughout lifespan and regardless of ethnicity. However, despite numerous studies, mostly in rat models and also in menopausal women, the origin of heightened female predisposition to SSBP and the respective contribution of sex steroid hormones and chromosome complement remain rather elusive. The discrepancy in the protocol used to assess salt sensitivity[32], the lack of good animal models recapitulating the human phenotype, the inconsistencies in the phenotype of the DSS female rats[115] but also the recently identified alternative BP trajectories through the menopause transition[116] complexify the study of the etiopathology of SSBP in humans. Moving forward, the use of standardized and validated protocol both in human[117] and animal studies appears crucial. The Balb/C and FVBN mice, recently identified as spontaneously developing SSBP and recapitulating the human sex difference[52, 118], may represent new tools for mechanistic studies as well as excellent background for new transgenic models. In addition, the four-core genotype mouse model[36], as well as the growing transgender population, may offer new opportunities to further investigate the role of sex chromosome complement as well as both male and female sex steroids in the development of salt sensitive hypertension.

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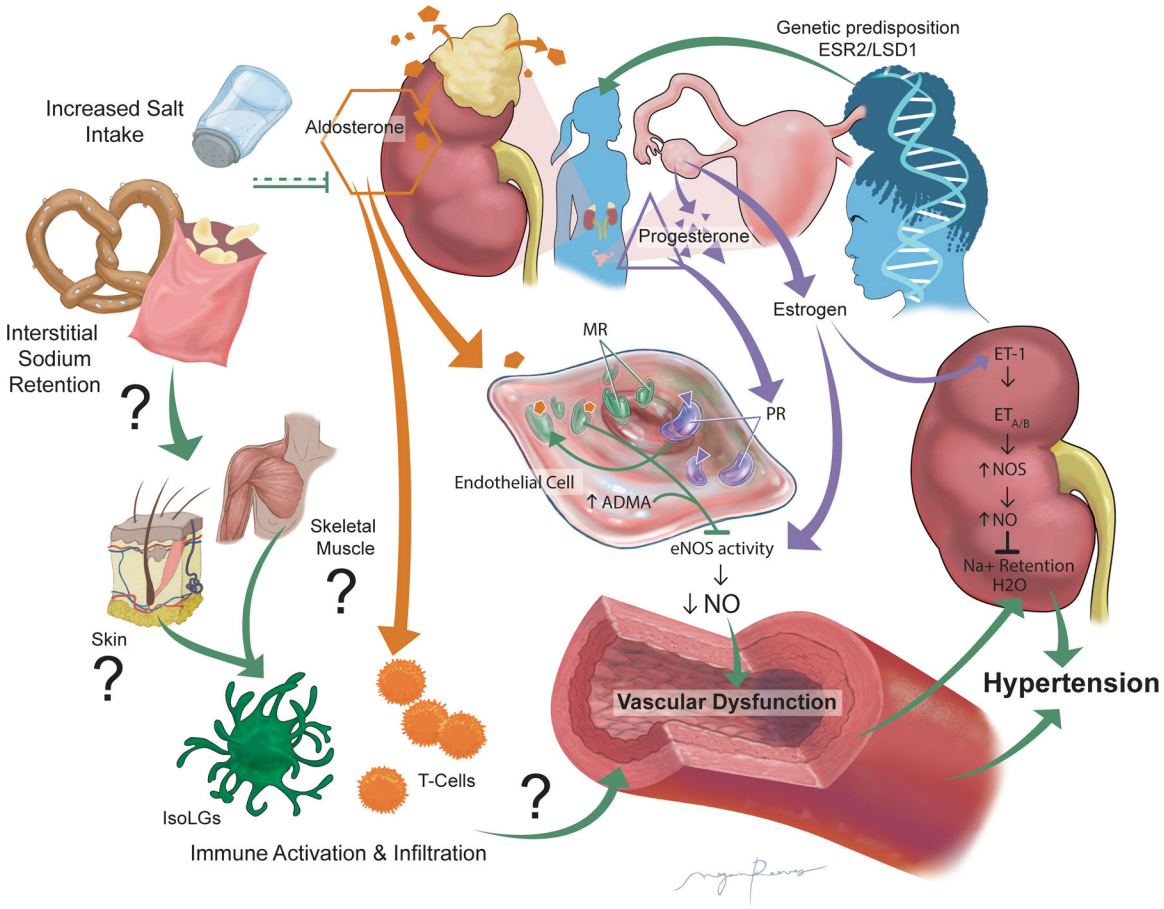

Figure:

Schematic illustrating the potential mechanisms involved in the female heightened salt sensitivity of blood pressure and proposing an overactivation of the "aldosterone-endothelial cell mineralocorticoid receptor axis" leading to reduced nitric oxide production, vascular dysfunction and ultimately hypertension. Abbreviations: ADMA: asymmetrical dimethylarginine; ESR2: gene coding for estrogen receptor β; eNOS: endothelial nitric oxide synthase; ET-1: Endothelin 1; ET_A: Endothelin receptor A; ET_B: Endothelin receptor B; IsoLGs: isolevuglandins; LSD1: Lysine-specific demethylase 1; MR: mineralocorticoid receptor; Na^+: sodium; NO: Nitric oxide; NOS: Nitric oxide synthase; PR: Progesterone receptor.