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INFLAMMATION AND CARDIOVASCULAR DISEASES (A KIRABO, SECTION EDITOR)

Female Sex, a Major Risk Factor for Salt-Sensitive Hypertension

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Abstract

Purpose of Review High dietary salt is a significant contributor to essential hypertension in clinical populations. However, although clinical studies indicate a higher prevalence of salt sensitivity in women over men, knowledge of salt-sensitive mechanisms is largely restricted to males, and female-specific mechanisms are presently being elucidated.

Recent Findings Male-specific mechanisms of salt-sensitive hypertension are well published and predominantly appear to involve dysfunctional renal physiology. However, emerging novel evidence indicates that aldosterone production is sex-specifically heightened in salt-sensitive hypertensive women and female rodent models, which may be regulated by intra-adrenal renin-angiotensin system activation and sex hormone receptors. In addition, new evidence that young females endogenously express higher levels of endothelial mineralocorticoid receptors (MRs) and that endothelial MR is a crucial mediator of endothelial dysfunction in females indicates that the aldosterone-endothelial MR activation pathway is a novel mediator of salt-sensitive hypertension.

Summary Heightened aldosterone levels and endothelial MR expression provide a 2-fold sex-specific mechanism that may underlie the pathology of salt-sensitive hypertension in women. This hypothesis indicates that MR antagonists may be a preferential treatment for premenopausal women diagnosed with salt-sensitive hypertension.

Keywords Salt · Hypertension · Salt-sensitive hypertension · Aldosterone · Mineralocorticoid receptors

Introduction

Hypertension is a significant threat to cardiovascular health and a diagnosis of hypertension is the most accurate predictive risk factor for cardiovascular events and mortality [1, 2, 3••]. The vast majority of hypertensive patients are essential hypertensives, in which there is no known underlying cause, and of these patients, dietary salt consumption is a causative factor in roughly 50–80% of cases [4–6]. The overarching present clinical notion is that there are subsets of "salt-sensitive," as opposed to "salt-resistant," patients whose blood pressure increases or decreases with high or low salt consumption, respectively. The concept of salt-sensitive hypertension is not a new phenomenon; however, emerging data on the mechanisms begins to shed light on the clinical presentation of salt sensitivity, notably its regulation by biological sex. The focus of this review is to summarize recent literature suggesting that sex discrepancies in salt-sensitive mechanisms may be attributable to aldosterone-mediated endothelial dysfunction in women.

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Salt Sensitivity Is Clinically Higher in Women than in Men

Large population studies indicate that salt-sensitive changes in blood pressure (BP) are increased in women both in amplitude of salt-induced changes in BP and in overall prevalence of a change in BP in response to dietary salt. The Dietary Approaches to Stop Hypertension (DASH) diet intervention study (multi-center, 456 patients), which is characterized by low sodium content, revealed higher decreases in BP in response to the diet in women than in men, albeit other dietary factors are altered by the DASH diet (potassium intake, macronutrients, etc.) [7]. In addition, in the GenSalt study (China,

1904 patients), BP response to both low- and high-salt diet interventions resulted in significantly greater reductions and increases in BP in women than men, respectively [8]. With regard to salt sensitivity prevalence, the HyperPATH study (multi-center, 1592 patients) demonstrated that salt sensitivity was significantly more common in women in a diagnosed hypertensive population [3••]. Most notably, the INTERSALT study (52 centers, 32 countries, > 10,000 patients) revealed a significantly higher association of blood pressure and sodium excretion in the women of the large and diverse cohort [9]. Collectively, these large-scale clinical trials indicate that risk of salt-sensitive hypertension is a significant health concern in women and strongly advocate for the identification of female-specific mechanisms of salt-induced hypertension.

Compounding the higher risk of salt-sensitive hypertension, women may be more likely to excessively consume sodium than men. The importance of a sex-specific preference for dietary salt is illustrated in results from a Japanese study which showed that increased taste for salt correlated with salt-sensitive BP only in the women in their cohort [10]. This sex difference may emerge early on, even prior to puberty, as a Korean study demonstrated a higher salt intake among obese girls aged 8–9 compared to boys [11]. Another study in a Korean population demonstrated that obesity increases sodium intake only in women [12]. However, this may be population-specific as a 2015 Brazilian study found that sodium intake in the hypertensive men of their study exceeded that of the women [13], albeit this study did not normalize to body weight. In animal models, several studies spanning five decades show that female rats exhibit a higher preference for NaCl drinking water compared to age-matched males [14–16], which is attributable to suppression effects of testosterone [17]. Increased taste for sodium is in itself likely to increase the prevalence of salt-sensitive hypertension in women; however, Kojima et al. also demonstrated that a history of familial hypertension is more predictive of salt sensitivity in a cohort of Japanese women than in men [18]. Therefore, a sex-conferred preference for salt, increased likelihood of genetic predisposition, and a higher BP response to dietary salt alterations likely collectively contribute to a higher risk of salt sensitivity in women.

Salt-Sensitive Hypertension Is Associated with Inappropriate Aldosterone Production in Women

Numerous clinical and experimental studies demonstrate that renal salt-mediated hypertension mechanisms predominate in men and male animals. Studies from our lab and others show that male mice [19••, 20], rats [21], and humans [22] excrete acute sodium loads less efficiently than females, feeding the notion that male sex reduces natriuresis under high sodium intake. Recent reviews expand on the potential mechanisms and present the hypotheses that male sex promotes renal endothelin-1 and impaired redox homeostasis [23•] and pro-inflammatory T cell infiltration [24•].

The classical physiological adaptation to an increase in dietary sodium intake is suppression of the salt-retentive hormones angiotensin II (AngII) and aldosterone. Several studies over the last few decades support the hypothesis that aldosterone suppression is a key mechanism yielding protection from salt-sensitive hypertension [25, 26]. However, emerging clinical and experimental data indicate that dietary salt intake governs aldosterone production in a sex-specific manner favoring higher production in women, which may be a token mechanism contributing to the higher prevalence of salt-sensitive hypertension in women.

Shukri et al. recently presented measurements of aldosterone levels in men and women in response to AngII infusion, importantly in a patient population in which women demonstrated higher prevalence of salt sensitivity [3••]. They showed that AngII increases aldosterone production more so in women than in men on both low and liberal salt diets, however only in women that are younger than 51 years of age (i.e., likely premenopausal). These data indicate that an adrenal-centric mechanism predisposes women, particularly younger women, to maintain higher aldosterone levels in response to stimuli, such as AngII, and that sodium intake has a reduced effect to decrease aldosterone levels in women than in men. This notion is supported by experimental evidence from our laboratory in which we demonstrated that 7 days of high-salt diet did not suppress adrenal CYP11B2 expression nor aldosterone levels, in contrast to males in which we showed high-salt diet–induced decreases in both [19••]. Further investigation indicated that high salt increased adrenal angiotensinogen levels only in female mice, indicating that the intra-adrenal renin-angiotensin system is activated by high dietary salt in female mice.

Importantly, these studies collectively indicate that salt sensitivity is closely tied with high aldosterone production in premenopausal females only. In the study by Shukri et al., the effect of AngII to increase aldosterone sex-specifically was lost in women over 51 years of age and, in addition, our salt-sensitive female mice were actively cycling young females [3••, 19••]. In accordance, studies indicate that adrenal physiology is potentially regulated by sex hormones. In human adrenocortical cells, Caroccia et al. showed that estradiol regulates aldosterone synthesis in a receptor-dependent manner, with G protein–coupled receptor-1 (GPER1) and estrogen receptor-β (ERβ) activations promoting and reducing, respectively, aldosterone secretion [27]. In accordance, a recent report showed that adrenal cell proliferation and turnover is more active in females than males, which is dependent on the inhibitory effects of testosterone [28]. These two studies indicate that high estrogen/low testosterone levels, characteristic of premenopausal women, potentiate adrenal cell

proliferation and aldosterone secretion. The continued exploration of the effects of sex hormones to promote aldosterone production in salt-sensitive models is certainly warranted given the current evidence.

MR Activation Is a Key Player in Salt-Sensitive Females

Several clinical trials, including EPHESUS and ASCOT, as well as multiple experimental reports suggest that MR blockade is more effective at reducing blood pressure and cardiovascular risk in women and female animals than in males [8–10, 29–31]. Although these studies did not separate by salt sensitivity, a recent study by our laboratory demonstrated that MR blockade protected female salt-sensitive mice from hypertension, indicating that MR activation plays a mediatory role [19••]. Although MR antagonists act as a mild diuretic and promote sodium excretion, the sex-specific efficacy of MR antagonists on blood pressure in women is unlikely due to increased natriuresis. Our laboratory demonstrated that high-salt diet promoted increased diuresis and natriuresis in female mice compared to males, despite that only females developed salt-sensitive hypertension [19••]. In addition, a recent study demonstrated that glomerular filtration rate, urine flow rate, and sodium excretion in response to an acute volume expansion on high-salt diet were significantly greater in female mice than in males [20]. A second recent study also indicates no sex difference in renal blood flow in male and female salt-sensitive hypertensive mice [32]. Therefore, renal hemodynamic alterations and sodium retention are unlikely the MR-mediated mechanisms predisposing females to salt sensitivity.

Salt-Sensitive Activation of Endothelial Mineralocorticoid Receptors Is Heightened in Women

The role of aldosterone-MR activation to promote salt-sensitive hypertension may involve a crucial mediator in the vascular endothelium. A recent report by our laboratory demonstrates that endothelial-specific MR expression is endogenously heightened in premenopausal women and female mice compared to that in males [33••]. We also showed that endothelial progesterone receptor activation leads to increases in endothelial MR expression in female mice. Given that circulating progesterone levels are increased in premenopausal females compared to both males and postmenopausal women, these novel data demonstrate a role for progesterone-induced predomination of endothelial MR in premenopausal women. We have also recently demonstrated that female mice placed on a sodium-restricted diet significantly increase adrenal CYP11B2 expression and plasma aldosterone levels more so than males [34•, 35•]. These data, combined with those indicating that sex hormones upregulate adrenal aldosterone production, provide a 2-sided milieu indicating that endothelial MR activation is significantly heightened in premenopausal females compared to that in both males and postmenopausal females. Therefore, the clinical [3••] and experimental [19••] data that suggest that aldosterone levels are higher in salt-sensitive premenopausal females indicate a susceptibility to endothelial MR activation.

Endothelial Dysfunction Is a Crucial Mediator of Hypertension in Salt-Sensitive Women

An emerging hypothesis, most notably touted by Kurtz et al., indicates that vascular dysfunction, i.e., a failure to reduce total peripheral resistance, may be an overlooked key mechanism of salt-sensitive hypertension [36]. More specifically, studies indicate that renal arteriole dysfunction, but not sodium retention, is a causative factor in salt sensitivity in a Japanese population, as summarized elsewhere [37•]. This notion is supported by other older reports indicating that salt sensitivity is associated with an increased systemic vascular resistance [38] and decreased forearm flow-mediated dilation [39, 40]. In addition, two recent studies have demonstrated that short-term (7 days) salt loading, even in non-hypertensive individuals, impairs flow-mediated dilation in the forearm skin microvasculature in a Croatian patient population [41]. Unfortunately, however, these studies did not separate their results by sex.

Despite a lack of direct sex-specific study of dietary salt-induced vascular dysfunction, emerging evidence indicates that vascular endothelial dysfunction is a key mechanism for hypertension in women. Although premenopausal females characteristically demonstrate higher endothelial-dependent vasorelaxation responses, studies indicate that vascular endothelial damage occurs earlier in women in various hypertensive pathologies [42–45]. Given this notion, the higher prevalence of endothelial MR expression in females may be a key mediator predisposing them to salt-sensitive hypertension. Studies by our laboratory as well as Jaffe et al. confirm that mice with endothelial-specific MR deletion are protected from obesity-associated endothelial dysfunction [33••, 46•]. We have additionally shown that MR antagonism ablates salt-sensitive endothelial dysfunction and hypertension in female mice, in association with high aldosterone levels and with no associated impairment in renal sodium handling [19••]. Furthermore, in female sodium-restricted mice, we demonstrated that reduced NO bioavailability mediated high aldosterone-associated endothelial dysfunction, and both MR antagonism and endothelial MR deletion restored endothelial relaxation responses and NO bioavailability [34•, 35•]. These data indicate a role for endothelial MR activation in the salt-sensitive pathology in female mice.

The Effects of Aldosterone-MR Activation on Blood Pressure May Shift Following Menopause

Menopause is an important consideration for the study of salt-sensitive mechanisms in women. Premenopausal women characteristically exhibit lower prevalence of hypertension than age-matched men; however, this sex difference begins to neutralize in the years immediately following menopause, and in older age groups (70+), hypertension rates are higher in women. Although hypertension prevalence in premenopausal women is less than in men, 2017 NHANEs data show that 19% of women ages 20–44 and 44% of women ages 45–54 (age groups generally considered premenopausal or peri-menopausal) are hypertensive [47]. Therefore, roughly 1 out of 3 premenopausal women is at a higher risk of cardiovascular events due to hypertension. This is of significant clinical impact as earlier onset of hypertension predisposes women to cardiovascular events later in life, and also, hypertension in women of reproductive ages increases the risk of pregnancy complications such as preeclampsia, which has a chain reaction to increase cardiovascular risk of both mother and fetus throughout the remainder of their lifetimes. Therefore, it is crucial that mechanisms of salt-sensitive hypertension in both pre- and postmenopausal women continue to be investigated.

Impaired natriuresis may play a more important role in salt-sensitive hypertension in postmenopausal women. The Tromso study revealed that sodium excretion significantly decreased in a population of women aged 55–69 compared to women aged 40–54 [48]. The US National Health and Nutrition Examination Survey (NHANES) reports a similar decrease in sodium excretion in women aged 45–69 compared to 20–44 years of age [49]. Therefore, renal, rather than endothelial, MR activation may play a larger role in aldosterone-mediated hypertension in salt-sensitive postmenopausal women. In addition, however, the overall contribution of aldosterone to salt sensitivity in postmenopausal women may be diminished. The Shukri et al. study demonstrated that a female sex–conferred increase in both AngII-induced aldosterone production and renal plasma flow is eliminated in women over the age of 51 on both low and liberal salt diets [3••]. Therefore, reduced aldosterone production coupled with a reduction in renal plasma flow and overall increased salt retention presents in salt-sensitive postmenopausal women, indicating other mechanisms play a larger role in salt sensitivity in these women, as reviewed elsewhere [50]. This notion is in line with our reported data that progesterone, whose levels decrease notably following menopause, potentiates endothelial MR sensitivity.

Conclusion

Recent emerging data provides evidence for a 2-pronged novel hypothesis that may explain the higher prevalence of salt sensitivity in women: females are more likely to maintain, or increase, aldosterone production in response to increased dietary sodium which leads to endothelial dysfunction, and consequently hypertension, via activation of endothelial MR expression. Given the evidence that AngII-induced aldosterone decreases with aging in women and that progesterone increases endothelial MR expression, this hypothesis pertains specifically to premenopausal women. Therefore, MR antagonists, which are currently not a first-line treatment for essential hypertension, may be a preferential targeted treatment for salt-sensitive hypertensive young women.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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- •• Of major importance

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