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Sex-specific immune modulation of primary hypertension ☆

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ABSTRACT

It is well known that the onset of essential hypertension occurs earlier in men than women. Numerous studies have shown sex differences in the vasculature, kidney and sympathetic nervous system contribute to this sex difference in the development of hypertension. The immune system also contributes to the development of hypertension; however, sex differences in immune system modulation of blood pressure (BP) and the development of hypertension has only recently begun to be explored. Here we review findings on the effect of one's sex on the immune system and specifically how these effects impact BP and the development of primary hypertension. We also propose a hypothesis for why mechanisms underlying inflammation-induced hypertension are sex-specific. These studies underscore the value of and need for studying both sexes in the basic science exploration of the pathophysiology of hypertension as well as other diseases.

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1. Introduction

The onset of essential hypertension occurs earlier in men than women [1]. This BP sex difference in humans is also observed in experimental animal studies. Females have lower BP than males in numerous animal models of hypertension [2]. There has been an exponential growth over the last 10 years in our understanding of how multiple end organs including the kidney, peripheral vasculature and key brain regions involved in central regulation of sympathetic outflow contribute to sex differences in the development of hypertension and within the past couple of years, several excellent reviews have been written on this topic [3–11].

We and others have shown that the gonadal hormones play a key role in sex differences in the development of hypertension. Ovarian hormone deficiency due to premature ovarian failure [12] or menopause [13] is associated with an increased frequency of hypertension in women and numerous animal models of hypertension have shown that 17β-estradiol replacement prevents the rise in BP due to ovarian hormone depletion [2]. For example, we have shown that the increase in BP induced by ovariectomy in the angiotensin II (Ang II) [14]- and aldosterone [15]-infusion models of hypertension can be prevented by 17β-estradiol replacement. As in other models of hypertension, the young female spontaneously hypertensive rat (SHR) has lower BP than the male SHR. Once the female SHR reaches the age at which the estrous cycle ceases, the sex difference in BP disappears [5]. In contrast to many experimental models of hypertension, ovariectomy in the young SHR has no effect on BP, rather studies suggest testosterone plays a key role in the sex differences in BP in SHR. Reducing the levels of testosterone in the male SHR lowered BP [16]. Furthermore, congenic studies in which the SHR Y chromosome was replaced with a Y chromosome from the normotensive Wystar Kyoto (WKY) rat lowered BP as well as testosterone levels [17,18]. The sex chromosomes can also contribute to sex differences in hypertension independently of the gonadal hormones. Using the four core genotype mouse model, which enables separation of sex chromosome effects from gonadal sex effects, we showed that BP was higher in gonadectomized XX mice compared to gonadectomized XY mice regardless of whether they were male (born with testes) or female (born with ovaries) [19]. Thus, the ovarian and testicular hormone status along with the sex chromosome complement and age of the animal all contribute to sex differences in the development of hypertension.

Recently, studies have demonstrated the immune system is activated in hypertension [20]. Inflammation and adaptive immunity in particular have emerged from both clinical and experimental data as important contributors to the development of hypertension [21,22]. Inflammatory mechanisms in the kidney, peripheral vasculature, and central nervous system (CNS) all have been shown to be involved [23–27]; however, these studies were

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conducted primarily in males. Recent studies in females demonstrate sex-specific modulation of the immune system in hypertension. The focus of this review is to examine our current knowledge of the impact of one's sex on immune modulation of BP and the development of the primary cause of hypertension, namely, essential hypertension. Immune modulation of other causes of hypertension such as pulmonary hypertension and preeclampsia are beyond the scope of this review. We also propose a new hypothesis regarding the mechanisms by which the sex chromosomes and gonadal hormones regulate inflammation-induced hypertension. Identification of the cellular mechanisms underlying these robust sex differences in BP may lead to sex-specific preventive strategies and therapeutics that ultimately result in reductions in the incidence of hypertension, delays in the onset of this disease and improved treatments for high blood pressure in both men and women.

2. Materials and methods

2.1. Animals

Rag-1$^{-/-}$ and wild type (WT) mice on the C57BL/6 background were purchased from Jackson Labs. All methods were approved by the Georgetown University and the University of Arizona Animal Care and Use Committees.

2.2. T-cell isolations

Mature CD3$^+$ T-cells were isolated from the spleens of male or female WT mice using Pan T-cell isolation kits (Miltenyi) and negative magnetic sorting for CD3$^+$ isolation. The CD4$^+$ and CD8$^+$ T-cell subpopulations were then isolated by flow cytometry, as described previously [28].

2.3. Adoptive transfer

Both male and female Rag-1$^{-/-}$ mice (10–11 weeks old) were injected via the jugular vein with CD4$^+$ or CD8$^+$ T-cells (2×10^7/mouse), as described previously [28].

2.4. Telemetry

Four weeks after adoptive transfer, radiotransmitters (Data Sciences Int.) were implanted into Rag-1$^{-/-}$ mice. One week later and after a stable baseline was established, osmotic minipumps containing Ang II (490 ng/kg/min) were inserted subcutaneously, then mean arterial pressure (MAP), heart rate (HR), and body weight were recorded for 2 weeks, as described previously [28].

2.5. Immunohistochemistry assessment of infiltrating T-cells in the subfornical organ

2.5.1. Immunoperoxidase staining

Primary antibodies against CD3$^+$ T-cells were obtained from AbCam. Sections were incubated overnight at 4 °C with primary antibody, 1:200, diluted in Tris buffer, pH 7.4, containing 2% normal goat serum and 0.2% Triton X-100. The presence of IgGs in the sections was probed by skipping the primary antibody incubation and directly incubating the tissue samples with biotinylated anti-mouse IgGs. Sections were washed and incubated for 120 min in biotinylated secondary antibodies (1:300; Jackson ImmunoResearch), followed by Avidin/Biotinylated enzyme Complex (ABC) complex for 30 min (Vectastain Elite kit; Vector Laboratories) and reaction with diaminobenzidine tetrahydrochloride (Sigma–Aldrich) for 5–15 min in Tris, pH 7.7. Finally, sections were washed thoroughly, mounted onto gelatin-coated slides, air-dried overnight, dehydrated, and coverslipped. Using an Olympus XI microscope fitted with a digital camera, photomicrographs of the SFO from the different groups following immunohistochemical processing were obtained.

3. The role of immune system in sex differences in the development of hypertension

One of the earliest studies implicating a role for the immune system in hypertension was performed by Grollman and colleagues in 1967. They demonstrated that hypertension could be induced in a normal male rat by transplanting this animal with lymph cells from the renal infarction rat model of hypertension [29]. Blood pressure was also shown to be increased in a normal rat by adoptive transfer of splenocytes isolated from a male rat made hypertensive by deoxycorticosterone acetate and sodium chloride treatment [30]. The converse to these gain of function studies was shown in the male SHR. Blood pressure was attenuated in the SHR by transplanting the thymus from a normotensive WKY male rat into the male SHR [31]. While these early studies demonstrated the immune system plays an important role in the development of hypertension, the cellular and molecular mechanisms of specific immune cell types responsible for driving the inflammation-induced hypertension was not defined.

A seminal study published by Guzik et al. [23] in 2007 showed that mice which lack both B- and T-cells due to a deficiency in the recombinant activating gene-1 (Rag-1$^{-/-}$) had lower BP following two weeks of Ang II infusion compared to WT mice. When mature T-cells (CD3$^+$) isolated from WT mouse spleen were replaced in these Rag-1$^{-/-}$ mice through adoptive transfer (CD3 → Rag-1$^{-/-}$), the magnitude of the Ang II-induced hypertension was restored to WT levels. T-cells were also shown to contribute to hypertension in the male Dahl salt-sensitive (DSS) rat. The T-cell surface glycoprotein CD3 zeta chain (CD247) and the Rag-1 gene were recently deleted in DSS rats resulting in the elimination of mature CD3$^+$ T-cells [32,33]. This new DSS strain exhibited lower BP than their DSS littermates.

In the Guzik et al. paper, the sex of the animals used was not reported. When this experiment was repeated in both male and female mice, we discovered that both the sex of the T-cell and the sex of the Rag-1$^{-/-}$ host were critical biological determinants of susceptibility and resistance to T-cell-induced hypertension. The female Rag-1$^{-/-}$ mouse (Rag-1$^{-/-}$-F) was resistant to T-cell induced hypertension compared to the male Rag-1$^{-/-}$ mouse (Rag-1$^{-/-}$-M) independently of the sex of the transferred T-cells, i.e., CD3^F → Rag-1$^{-/-}$-F and CD3^M-Rag-1$^{-/-}$-F both had lower BP than CD3^M-Rag-1$^{-/-}$-M mice after Ang II infusion [34]. We also found that the sex of the T-cells was critical since CD3^F → Rag-1$^{-/-}$-M had lower BP than CD3^M → Rag-1$^{-/-}$-M after Ang II infusion, i.e., the only difference between these hypertensive and normotensive male mice was the sex of the T-cell [28].

To further investigate which T-cell populations were contributing to the sex-specific T-cell effects on BP, we isolated CD4$^+$ and CD8$^+$ T-cell populations from the spleen of WT male and female mice and transferred these cells into the male Rag-1$^{-/-}$ host. Four weeks after adoptive transfer, there was little difference in basal MAP or basal HR between CD4^M → Rag-1$^{-/-}$-M and CD4^F → Rag-1$^{-/-}$-M or between CD8^M → Rag-1$^{-/-}$-M and CD8^F → Rag-1$^{-/-}$-M. Fig. 1 shows that adoptive transfer of both CD4^M and CD8^M → Rag-1$^{-/-}$-M resulted in a greater MAP response to Ang II compared to either CD4^F or CD8^F T-cells. In fact, no differences in MAP were observed in the Ang II time course between the CD4^F → Rag-1$^{-/-}$-M and the

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