Sex Differences in Regulation of Blood Pressure

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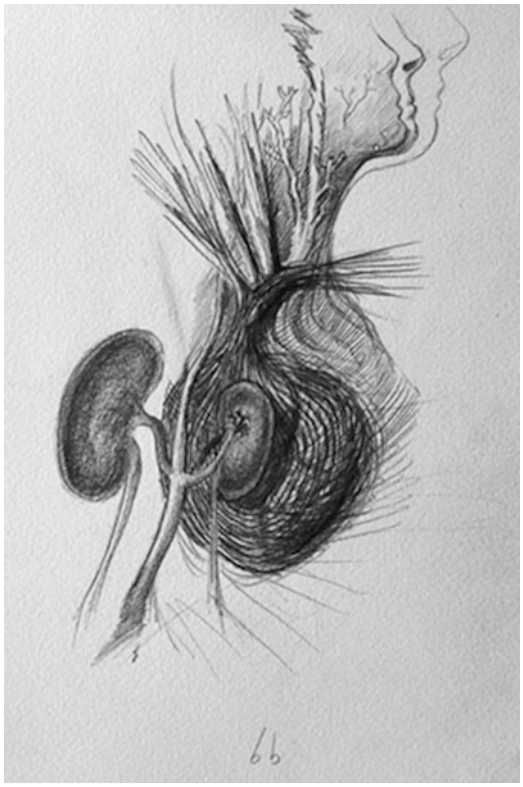

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Abstract

Hypertension is one of the leading risk factors for cardiovascular disease, myocardial infarction, and stroke. There are gender differences in the prevalence of hypertension and in the mechanisms responsible for hypertension in

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humans. This review will discuss the mechanisms for regulation of blood pressure, sex differences that have been identified in animal studies, and the gender differences that have been identified in humans.

Keywords
Hypertension · Obesity · Metabolic syndrome · Postmenopausal women · Hypogonadism · Immune system-mediated hypertension · Androgens · Estrogens · Endothelin

Introduction

Hypertension affects approximately 72 million US adults, with an overall prevalence of 29.3% [6, 24]. Hypertension is also a major public health problem worldwide both because of its high prevalence and also its role as a major risk factor for cardiovascular and kidney disease. The Global Burden of Disease Study identified hypertension as the leading global risk factor for mortality and the third leading global risk factor for disease burden in both men and women [16, 41]. Hypertension is not only a key risk factor for cardiovascular disease but the leading cause of death in both women and men. Moreover, more than half of all deaths in the United States (USA) are related to diseases which are aggravated by hypertension: heart disease, stroke, and renal failure [16]. Despite increasing awareness of cardiovascular disease and treatment of cardiovascular disease risk factors, the incidence of cardiovascular disease has increased over the last decade, especially in women. Thus, the control of blood pressure (BP) is paramount to protect the quality of life in men and women.

Prevalence of hypertension is significantly and independently associated with increasing age, increasing body mass index (BMI, kg/m^2), being African-American, and having less education [43]. Younger women have a lower prevalence of hypertension than men. In fact, the prevalence of hypertension is higher in men than women at young and middle ages and lower at elderly ages [24]. As such, women older than 60 years tend to have a higher prevalence of hypertension compared to men of similar ages. The highest prevalence of hypertension occurs among black women, older than 75 years, in whom prevalence rates exceed 70% [43].

Around the world, women with hypertension are more likely to be treated than men ([34, 54]; US). However, there are society differences as to whether men or women are better controlled for their hypertension. In the US National Health and Nutrition Examination Survey (1999–2004), 61.4% of women with hypertension were treated compared to 56.8% of hypertensive men. However, only 44.8% of treated women achieved BP control compared to 51.1% of treated men [21, 43]. Studies from the German Health Examination Surveys (GHES) showed that men are less aware of their hypertension, received less treatment for their hypertension, and had lower control of their BP than did women, which was a new finding in the 2008–2011 compared with 1998 studies in which there were no gender differences observed among those treated for hypertension [54]. In data from the US National Health and Nutrition Examination Survey (NHANES) IV (1999–2004), 50.8% of men and 55.9% of women had uncontrolled BP, despite the fact that women more frequently had their BP measured in the previous 6 months [30]. Furthermore, in a comparison of the NHANES III cohort (ending in 1999) with the NHANES IV cohort (ending in 2004), hypertension was less well-controlled in women than men, although the drugs used to treat hypertension were similar between men and women. BP normally falls during the night, and non-dipping BP at night is associated with increased target organ damage in both men and women [53, 61, 68]. Non-dipping BP in women appears associated with greater target organ damage than in men [4, 61], and postmenopausal women are more likely than premenopausal women to exhibit nocturnal non-dipping of BP [68].

Drug treatment regimens are also different in men and women often depending on the culture. In the GHES, younger women were more often prescribed β-adrenergic receptor blockers [54] and less angiotensin-converting enzyme

inhibitors (ACEIs) than men. The Swedish Primary Care Cardiovascular Database (SPCCD) studies recently reported that women were also more often treated than men, more often treated with diuretics, and men were treated with ACEIs or angiotensin receptor blockers (ARBs) [34]. Men also interrupted their treatment more often than women. There are no gender specific guidelines for treatment of hypertension. In addition, whether certain classes of antihypertensive medications are more efficacious in men or women is virtually unstudied or has been studied but not evaluated for gender differences. The fact that animal studies have shown that there are sex differences in the mechanisms responsible for hypertension suggest that there may also be different mechanisms responsible for the hypertension in men and women, and further human studies are warranted.

Increased BP is independently and continuously associated with cardiovascular disease (5). Hypertension is defined as a systolic BP of 140 mmHg and higher or a diastolic BP of 90 mmHg and higher; prehypertension is defined as a BP between 120 and 39 systolic or 80–89 mmHg diastolic [47]. The higher the BP, the greater the risk for target organ injury, including myocardial infarction, heart failure, renal injury, and stroke [26], and an increase in cardiovascular disease risk begins with blood pressures as low as 115/75 mmHg [32]. Previously, hypertension was considered controlled if BP was less than 140/90 mmHg or, for those with diabetes or chronic kidney disease, less than 130/80 mmHg. However, the recent multicenter Systolic Blood Pressure Intervention Trial (SPRINT) showed that intensive reduction of BP with medications to 120 mmHg in individuals with hypertension and elevated cardiovascular disease (CVD) risk caused such a significant reduction in event rates, including myocardial infarction, acute coronary syndrome, stroke, decompensated heart failure, and cardiovascular disease-related death, that the trail was halted early [66].

SPRINT was performed in men and women average age 70 years > 50 years old [59], and the results were consistent across pre-specified clinical subgroups including age, sex, race, tertiles of SBP, history of cardiovascular disease, and any history of chronic kidney disease. Interestingly, only 2.8 medications were needed to reduce BP to 120 mmHg in subjects versus 1.8 medications in the standard treatment group [66]. Only 35–36% of the subjects in the SPRINT were women, and since the trial was stopped early, the data were not statistically significant that treating lower levels of BP was actually successful in reducing events in women [70]. The new American College of Cardiology/American Heart Association guidelines recommended stricter blood pressure control, and treatment in women was relegated to "Other Groups", despite that >50% of women over the age of 70 years are hypertensive.

Mechanisms Responsible for Hypertension

BP control is mediated via the kidney since studies have shown that the way the body manages salt and water is central to the level of BP [22, 23]. A normal kidney, when given a salt load, will cause an increase in BP such that there is a shift in the pressure-natriuresis relationship, whereby at higher salt content, the BP increases. As the salt is excreted with water by the kidney, the BP will return to normal levels in a few hours. In abnormal kidneys, when a salt load is taken, the BP increases, but this time the kidney is unable to excrete the salt and water, and the BP remains elevated causing a permanent shift in the pressure-natriuresis relationship to higher blood pressures. Thus during the steady state, elevated BP becomes necessary for salt excretion to be maintained at "normal" levels. This is why sodium excretion levels are similar for animals with similar salt intake regardless of one that is hypertensive and one that is normotensive.

Many homeostatic and hormonal systems contribute to BP regulation, including the renin-angiotensin system, the sympathetic nervous system via the renal nerves, the eicosanoid system,

the oxidative stress/nitric oxide system, obesity and metabolic syndrome, the endothelin system, and sex steroids. In this review, the mechanisms and the sex differences in them will be discussed in terms of studies done in common animal models.

The Spontaneously Hypertensive Rat (SHR) as a Model of Hypertension

The SHR is a model that develops elevated BP as they progress through puberty [48]. When young, the BP is similar between males and females, but after puberty, the BP is significantly higher in males than females. Castration of male SHR reduces BP to levels found in females. Ovariectomy of the females has no effect on the BP, but testosterone treatment after puberty increases BP as in males. Thus the hypertension in the males is androgen-mediated, but the hypertension in the females is independent of estrogens. With aging, the BP remains static after approximately 9 months of age in the males, but in females, BP increases after cessation of estrous cycling, between 10 and 12 months of age, such that by 16 months of age, BP is similar to or higher in females than males [46]. This model has been used as a model of postmenopausal hypertension.

The mechanisms regulating BP are not only different between male and female SHR but are also different between aging and young animals. For example, in young SHR, the hypertension is mediated via the renin-angiotensin system (RAS) [49] and the sympathetic nervous system (SNS) [28]. This is not the case in aging animals as will be described below.

Role of the Renin-Angiotensin System (RAS)

Angiotensin II is an important regulator of BP [5]. Angiotensin (Ang) II is produced by the conversion of angiotensinogen to Ang I by renin and subsequent conversion of Ang I to Ang II by Ang I-converting enzyme (ACE). Ang II has its biological activity to increase BP through the Ang II AT1 receptor (AT1R). This makes up the vasoconstrictor arm of the RAS. Androgens have been shown to increase angiotensinogen synthesis in SHR [49], whereas estrogens have been shown to reduce expression of AT1Rs [5]. In addition to it's vascular effects, in the kidney, Ang II causes sodium reabsorption via the proximal tubule, also leading to increase in BP. Ang II can also be converted by ACE2 to Ang(1–7) [5], a vasodilator that has biological activity via the Mas receptor. Estrogens have activity to increase ACE2 activity and promote the vasodilatory effects of Ang(1–7). Thus there are sex differences in the RAS that can affect BP.

Essential hypertension in humans is associated with activation of the RAS in many cases. Even salt-sensitive hypertension, which is considered a low-renin hypertension and is prevalent in African-American individuals [63], is associated with abnormally elevated plasma renin activity compared to levels that should be accomplished when salt levels are elevated. Both men and women are prescribed ACEI and AT1R antagonists, although in some societies as mentioned above, men receive RAS blockers more frequently than women [34]. Both ACEIs and ARBs reduce BP to similar normotensive levels in young male and female SHR [49, 80], showing the RAS plays a greater role in the hypertension in male SHR than females since BP at baseline is higher in males. Furthermore, in the presence of male-level androgens in females, enalapril also lowers the BP [49], suggesting that androgens are working through the RAS to increase BP in male SHR.

The hypertension developed with Ang II infusion in rodents is also sex dependent. If the endogenous production of Ang II is blocked by enalapril, female rats exhibit a greater pressor response than males, but the hypertension is not salt sensitive, whereas it is in males [55]. Male mice, regardless of whether the endogenous RAS is blocked or not, have a greater pressor response to Ang II than females [67, 71]. Zimmerman and colleagues also reported that candesartan, an ARB, does not prevent the pressor response to Ang II infusion in

males, but does prevent the response in female SHR. In addition they showed that depressor response to candesartan in the females is mediated via production of Ang(1–7) [80].

The contribution of the RAS of the hypertension in aging SHR is different, however. Enalapril reduces the BP to 100 mmHg in male SHR, aged 16–18 months, but to only 130 mmHg in age-matched females [74]. Thus the RAS is a major mediator of the hypertension in aging males, but in aging females, there are other mediators of the hypertension.

The Sympathetic Nervous System

As noted above, β-adrenergic receptor antagonists are common antihypertensive medications given to men and women. As noted above, in some studies women are prescribed them more frequently than men [54], although there is little evidence that they are better at controlling BP in women.

Studies in young SHR show that renal denervation reduces BP by 8–10% in both males and females. β-blockers, such as terazosin and propranolol, reduce BP in both male and female SHR [28, 37, 38]. β-Blockers had a greater effect in reducing BP in old females than in young females [38], suggesting that aging may be associated with increased sympathetic activation in female SHR. The RAS is thought to be stimulated by activation of the sympathetic nervous system. In aging female SHR, renal denervation reduced BP, but concomitant renal denervation followed by chronic losartan (ARB) treatment caused a further reduction in BP, but the rats still remained significantly hypertensive (approximately 140 mmHg) [37]. These data suggest that the hypertension in aging female SHR is mediated by both the sympathetic nervous system and the RAS independently and that other mechanisms contribute to the hypertension in aging females. These data have significant implications for hypertension in postmenopausal women and suggest that inappropriate, inefficacious medications may contribute to their resistant hypertension.

The mechanisms responsible for sympathetic activation in SHR are not clear. Activation of the melanocortin-4 receptor (MC4R) in the hypothalamus has been shown to increase sympathetic activation, and leptin is one of the mediators of MC4R activation. This is one of the mechanisms thought to play a role mediating obesity-induced sympathetic activation and hypertension since leptin is produced in adipose tissue. Da Silva and colleagues reported that intracerebroventricular (ICV) blockade of the MC4R reduces BP in young male SHR [8]. However, similar ICV infusion of MC4R antagonist in young and old female SHR failed to reduce BP, whereas the antagonist reduced BP in aging male SHR [39]. Thus the data suggest that different mechanisms may be responsible for activation of the sympathetic nervous system in males and females. The mechanism(s) that mediate sympathetic activation and hypertension in humans is not clear. In morbidly obese humans with MC4R deficiency, BP, heart rate, and urinary catecholamine excretion, all indicators of sympathetic activity, are reduced [14]. Thus whether the MC4R plays a role in mediating hypertension by causing activation of the sympathetic nervous system in men and women remains to be determined.

The Role of 20-HETE

Arachidonic acid can be converted by cytochrome P450 (CYP) ω-hydroxylases to 20-hydroxyeicosatetraenoic acids (20-HETE), respectively [51]. 20-HETE is a vasoconstrictor produced in endothelial cells. In the kidney, 20-HETE is also produced in renal tubules and reduces sodium reabsorption. Thus the location of 20-HETE production in the kidney (vascular vs tubular) determines whether it is prohypertensive or antihypertensive, respectively. An increase in plasma 20-HETE has been shown to occur in humans with acute ischemic stroke [77, 78] and acute coronary syndrome [81]. Thus 20-HETE could contribute to BP control in humans.

With regard to SHR, Zhang et al. [79] reported that adenoviral vector delivery of a CYP4A1

cDNA caused a decrease in BP in young male SHR, whereas the antisense CYP4A1 cDNA caused an increase in BP in control Sprague-Dawley rats. The investigators interpreted the data to mean that 20-HETE is important in both maintaining normotension and in contributing to hypertension. In old female SHR, blockade of 20-HETE reduces BP, but there is no effect of the inhibitor on BP in young females [75, 76]. To our knowledge, there have been no studies in which inhibitors of 20-HETE synthesis have been given to old male SHR.

Interestingly, the combination of enalapril and the eicosanoid synthesis inhibitor, 1-aminobenzotriazole (1-ABT), has different effects on BP in old female SHR depending on which drug is given first [33]. Treatment of old female SHR with either 1-ABT or enalapril reduces BP to similar levels. Addition of enalapril to the 1-ABT causes a significantly greater reduction in BP than does the addition of 1-ABT to enalapril. However, the BP remained approximately 125–130 mmHg. The data suggest that both the RAS and 20-HETE contribute independently to a part of the hypertension in old female SHR but that 20-HETE may also have activity via the RAS mechanism.

Whether 20-HETE plays a role in mediating the BP in men and women or whether 20-HETE blockade would cause a reduction in BP, and thus could be a novel antihypertensive agent in individuals with resistant hypertension, is unknown and is a topic for further discovery.

Role of Oxidative Stress/Nitric Oxide System

Oxidative stress is defined as the production of superoxide or other reactive oxygen and/or nitrogen species (ROS/RNS) [52]. The NADPH oxidase pathway, the xanthine oxidase pathway, and mitochondria are thought to contribute to the production of ROS. ROS are naturally produced as a consequence of mitochondrial energy production and play important roles in mediating intracellular signaling mechanisms. Superoxide that is produced in the vasculature can bind nitric oxide (NO), thus binding NO and causing vasoconstriction. The combination of superoxide and NO also produces peroxynitrite, a strong oxidant that is a vasodilator that with time causes tachyphylaxis resulting in vasoconstriction. Peroxynitrite can also oxidize other factors, such as the vasodilator, prostacyclin, which causes vasoconstriction.

Oxidative stress has been implicated as playing a role in mediating hypertension, since treatment of adult male SHR with tempol, the superoxide dismutase mimetic, causes a reduction in their BP [56]. Adult female SHR do not respond with a reduction in their BP when tempol is given [19]. However, if SHR are given tempol from weaning, there is an attenuation of their BP in both males and females, suggesting that oxidative stress may be playing a role in development of hypertension in males and females but that maintenance of hypertension in male, but not female SHR, is mediated by oxidative stress. Male SHR also have a depressor response to an NADPH oxidase inhibitor, apocynin, whereas females do not. Sullivan et al. [62] reported that male SHR exhibit greater excretion of hydrogen peroxide than females. Interestingly, the levels of F2-isoprostanes, an indicator of oxidative stress, is similar in plasma of male and female SHR, are higher in kidney tissue of males than females, but excretion rate of F2-isoprostanes is tenfold higher in females than males. Plasma total antioxidant capacity measured in serum is similar in males and females, whereas basal and NADPH-stimulated lucigenin chemiluminescence, an indicator of NADPH oxidase activity, is not different in kidneys of males and females, but higher in aortae of male SHR. Thus the lack of a depressor response to tempol is not due to lack of oxidative stress in female SHR. Female mREN2 rats are hypertensive and also do not respond to tempol [42].

In order to evaluate the mechanisms responsible for the pressor response to oxidative stress, we gave molsidomine, a drug that causes an increase in both superoxide and nitric oxide. Molsidomine caused an increase in BP in male SHR but not females or male WKY controls [18]. The increase in BP in males was accompanied by an increase in lucigenin chemiluminescence, an indicator of

increased oxidative stress, an increase in nitrate/nitrite excretion, an index of NO production, and an increase in renal expression of catalase and glutathione peroxidase in WKY males, but not SHR males [18, 19]. Because it was hypothesized that the lack of a response in females was mediated by the increased endogenous NO levels, rats were given nitro-L-arginine methyl ester (L-NAME), the nonselective NOS inhibitor, after molsidomine treatment [35]. While L-NAME increased the BP in females, there was no protective effect with molsidomine.

Endothelial NOS requires cofactors, such as calcium and tetrahydrobiopterin, for activity. In oxidative stress situations, tetrahydrobiopterin is converted to dihydrobiopterin causing the "uncoupling" of eNOS, such that the enzyme produces superoxide rather than NO. In male SHR we tested the hypothesis that infusion of tetrahydrobiopterin would circumvent the increased production of superoxide thus causing a reduction in BP. Studies in male SHR showed that, indeed, tetrahydrobiopterin infusion did reduce BP in male SHR; however, the mechanism was independent of NO and was due instead to a reduction in the synthesis of androgens [17]. Since the BP in male SHR is androgen dependent, a reduction in androgens mediated the reduction in BP.

Unfortunately, there are no studies in humans that suggest that oxidative stress contributes to hypertension. Clinical trials using various antioxidants, such as vitamin E or C, either have shown no benefit to BP, or actually increased BP. Although most studies said the data were "factored for sex," the data were evaluated separately for men and women. Since in our studies and others hypertension in female animals is independent of oxidative stress, it is possible that the antioxidants were effective in men, but not women. In addition, the studies were performed in individuals who had been hypertensive for years. In our studies we found that if the NO system is blocked, tempol and apocynin are incapable of reducing BP in male SHR [73]. These data suggest that an active NO system is necessary for antioxidants to reduce the BP. If the individuals in the clinical trials had significant endothelial dysfunction and thus reductions in synthesis of NO, then the antioxidant therapy would not be expected to be effective. Perhaps antioxidant therapy would be more beneficial in younger men who have little endothelial dysfunction.

Role of the Immune System

Although there have been numerous animal studies showing that T cells contribute to hypertension, the data in humans is less striking (see review [50]). ACEI does reduce the number of circulating CD4+ T cells. Data from the Multicenter AIDS Cohort Study indicate that untreated HIV-positive patients with chronically low numbers of CD4+ T cells have a lower prevalence of systolic hypertension than treated HIV patients and uninfected control subjects [57]. In addition, Herrera et al. [25] showed in a small cohort of essential hypertensive individuals receiving mycophenolate mofetil (MMF), an inhibitor of T cell production, for rheumatoid arthritis or psoriasis, that their BP fell. When MMF was discontinued, BP returned to previously high levels, suggesting that amelioration of hypertension was the result of immune suppression. Whether there are sex differences in the immune system-mediated increase in BP in humans is unknown, however.

Sex differences have been shown to be present in the hypertension in SHR. Tipton et al. [65] reported that there are sex differences in the type of T cells that infiltrate the kidney in SHR. They found that the circulating levels of anti-inflammatory CD3+ and CD4+ and pro-inflammatory CD3 + CD4 + RORγTh17 cells were higher in female SHR than males and that males had more immune-suppressive circulating CD3 + CD4 + Foxp3+ T regulatory cells. The kidneys of females also had higher levels of CD8+ and T regulatory cells than males, whereas kidneys of male SHR had higher levels of CD4+ and Th17 cells. MMF decreased BP in both male and female SHR, but the reduction was greater in the females, suggesting an immune component in the hypertension in both males and females.

Interestingly, unlike discussed above, experimental hypertension in females that has an immune component is responsive to antioxidants, such as tempol or apocynin. For example, tempol/apocynin [40] and MMF [64] reduce BP in a mouse model of lupus erythematosus. In addition, the reduced uterine perfusion pressure (RUPP) model of preeclampsia, which mimics conditions in women, is associated with increases in T(H)17 cells that secrete IL-17, autoantibodies activating the AT1R (AT1-AA), and placental oxidative stress [12]. Tempol not only reduced the BP in the model [58] but also reduced urinary excretion of F2-isoprostanes and AT1-AAs [12]. Why immune system-mediated hypertension in females is susceptible to antioxidants but not SHR hypertension when the immune system is activated in SHR females is not clear and requires further study. Studies into the role played by the immune system in hypertension in aging men and women or animals, and whether or not there are sex differences, are limited and will also require additional research.

Role of Obesity and Metabolic Syndrome

Obesity is a common risk factor for hypertension in both men and women of all ages. Over 70% of adults in the United States with hypertension are currently overweight or obese [47]. Epidemiological and longitudinal studies clearly demonstrate an association between increasing body weight and increasing BP, and the increase in prevalence of hypertension increases with increasing BMI. Whether there are gender differences in the increase in BP with increasing body weight in humans has not been studied to our knowledge.

Sex differences in BP have not been well studied in animal models of obesity. BP measurements in males and females exist but in most cases, have not been done at the same time or by the same groups. For example, telemetry studies in the obese, male MC4R knockout rat show that their BP is not different than control Wistar rats [60], whereas telemetry BP is significantly higher in obese female MC4R knockout rats than WT controls [39]. In addition, no studies have been done in which the increase in body weight has been correlated with BP level. Future studies will need to be done to address this question.

Role of Sex Steroids

Numerous studies have shown that sex steroids affect BP. Acutely, both androgens and estrogens cause vasodilation. In experimental animals, chronic estrogens cause an increase in eNOS expression [69] and thus cause vasodilation which should reduce BP. Androgens have different effects on BP whether they are given to males or females. Postmenopausal women often have elevated androgen levels. Women with polycystic ovary syndrome (PCOS), the most common endocrine abnormality in young reproductive-aged women, develop elevated BP with chronic androgen excess [2, 13].

BP increases in men and women as they age and endogenous sex hormone levels drop [47]. As mentioned previously, the prevalence of hypertension increases more in women after menopause when estrogen levels drop than in age-matched men. However, the role that lack of estrogens play in hypertension in postmenopausal women is controversial. There have been no studies to our knowledge in which ambulatory BP has been serially measured over the perimenopausal transition. Hormone replacement therapy (HRT), even with estradiol rather than conjugated equine estrogens (CEE), has not been shown to consistently lower BP in postmenopausal women. The method of drug delivery, whether oral or transdermal, whether estradiol or CEE, likely contributes to the variable BP effect. In addition, many studies have been short term (e.g., < 1 year). Ichikawa et al. [27] reported lower diastolic and mean BP with transdermal HRT for 12 and 24 months in normotensive postmenopausal women. In another study by Prelevic et al. [45], healthy postmenopausal women who had been taking HRT for at least 5 years had blood pressures similar to untreated age-matched controls or the BP was even higher than controls.

A recent meta-analysis supports these previous findings, that oral HRT had a neutral effect on BP in both normotensive and hypertensive postmenopausal women [29]. Transdermal estrogen and micronized progesterone had a beneficial effect on normotensive women, but had only a neutral effect on hypertensive women. These data do not support estrogens as being the major modulator of BP control in postmenopausal women.

Obesity is associated with reductions in androgen synthesis in men and male animals. For example, in the male obese Zucker rat, androgen levels by 22 weeks of age are reduced by almost 70% compared to their lean littermates [10]. By the time these rats are 32 weeks of age, the obese rats have elevated BP, whereas the lean rats do not. Testosterone supplements in the obese Zucker rats cause a further increase in BP despite the fact that the supplements reverse the inflammation, insulin resistance, and hyperlipidemia. BP does not increase with testosterone supplements in lean Zucker rats. These data suggest that androgen supplements in obese men may reduce some of the cardiovascular risk factors, but care should be taken to monitor their BP carefully.

Alternatively, as shown in Table 9.1, the effects of androgens in women and female rats are very different than in men or male rats. Androgen supplements in normotensive female Sprague-Dawley rats have the opposite effect as in males and cause an increase in food intake, an increase in body weight, increased inflammation and hyperlipidemia, and an increase in BP [76]. This is a model of polycystic ovary syndrome (PCOS) in women [36]. Women with PCOS have elevated BP and many of them are overweight or obese [15]. Because women with PCOS are young when diagnosed, their elevated BP often does not meet the current guidelines for treatment. It remains to be seen how the SPRINT may change those guidelines.

Table 9.1 Sex differences in response to androgens

Parameter	Obese Zucker males	Female Sprague Dawley rats
Body weight	Decrease	Increase
Inflammation	Decrease	Increase
Insulin resistance	Decrease	Increase
Cholesterol	Decrease	Increase
Blood pressure	Increase	Increase

Female-to-male transsexual individuals who take high doses of androgens for virilization also develop PCOS-type symptoms [3], elevated BP, and elevated endothelin levels [20]. In contrast, men with various forms of hypogonadism display significantly higher endothelin levels in comparison with age-matched healthy males, and testosterone therapy decreased ET-1 levels in these individuals [7].

The mechanisms by which androgens can increase BP in females are not clear. Androgen supplements do not increase BP in female rats that are null for CYP4A2 [9], one of the ω-hydroxylases that produce 20-HETE, suggesting that activation of the 20-HETE pathway may contribute. Also, if the MC4R is blocked or if the rats are MC4R null, androgens fail to increase their BP [9], suggesting that an active MC4R system is necessary to increase BP in females with androgens.

Role of Endothelin

Endothelin is known to be one of the most potent vasoconstrictors. A thorough review of sex differences in endothelin (ET1), the receptors, ET_A and ET_B, and the mechanisms responsible is available elsewhere [20]. In postmenopausal women, plasma endothelin levels are increased [31], suggesting that endothelin may contribute to the increased BP following menopause.

The mechanism by which endothelin increases in postmenopausal women is not clear. However, Ang II increases preproendothelin synthesis [1], and thus activation of the RAS after menopause could contribute to the elevated ET-1. While untreated postmenopausal women have been shown to have elevated levels of endothelin, hormone replacement therapy (HRT) with either micronized 17β-estradiol and dydrogesterone or CEE and medroxyprogesterone results in further increases in endothelin levels [11, 44]. Thus the

role that the endothelin system plays in mediating gender differences in BP in humans remains to be elucidated.

In young and old male and female SHR, endothelin likely plays little role in their BP. In aging females ET_A receptor antagonism reduces the BP by approximately 10 mmHg [72, 73, 75], but the rats remain very hypertensive. If the three systems, the RAS (with enalapril), 20-HETE (with aminobenzotriazole (1-ABT)), and the ET_A receptor (with ABT-627 – Abbott Labs), are all blocked together, the BP in old female SHR is reduced to approximately 120 mmHg [33]. These data suggest that in aging women, especially those who have essential hypertension that is hard to control, several drugs from different categories of antihypertensives may be beneficial in managing their BP.

Summary

Sex differences in BP control employ a myriad of mechanisms and the mechanisms are different whether the subjects are young or aging. As shown in Fig. 9.1, in young male SHR, the hypertension is mediated via androgens to activate the MC4R and subsequently activate the sympathetic nervous system. Androgens also activate the RAS by increasing expression of angiotensinogen and thus increasing renin activity leading to increases in Ang II. In addition, androgens activate the oxidative stress pathway and could in turn increase RAS acitvity. In young female SHR, sex steroids and the MC4R do not contribute to the hypertension, and thus only activation of sympathetic nervous system and the RAS control their BP.

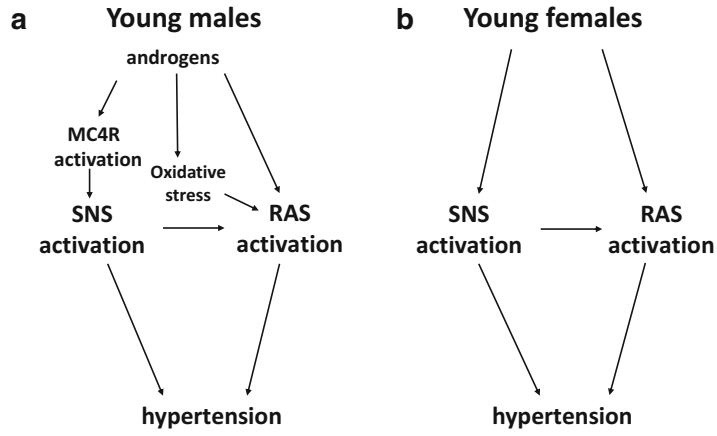

Fig. 9.1 Mechanisms responsible for hypertension in young male (**a**) and female (**b**) SHR. Abbreviations: *MC4R* melanocortin-4 receptor, *SNS* sympathetic nervous system, *RAS* renin-angiotensin system

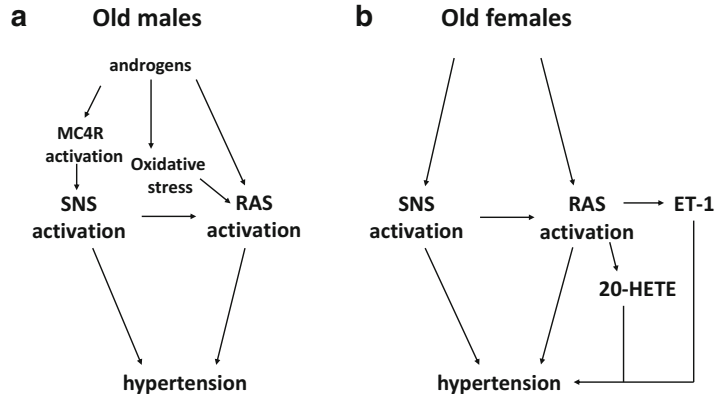

Fig. 9.2 Mechanisms responsible for hypertension in old male (**a**) and female (**b**) SHR. Abbreviations: *MC4R* melanocortin-4 receptor, *SNS* sympathetic nervous system, *RAS* renin-angiotensin system, *ET-1* endothelin

As shown in Fig. 9.2, the aging males do not change their mechanisms responsible for the hypertension. In aging females, however, there is a role for RAS activation of both endothelin (ET-1) and 20-HETE, both of which are vasoconstrictors and increase the BP.

Future studies are needed to clarify the mechanisms responsible for their hypertension, whether they are similar or different than in SHR, and then how these mechanisms can impact the way hypertension in men and women is addressed therapeutically, especially in this age of "precision medicine." The problem of non-compliance with antihypertensive medications needs to be addressed to determine why it is that the medications are not taken or are dropped. To improve compliance, more education is needed to convince individuals that despite their current lack of symptoms without antihypertensive medication, treatment of hypertension reduces the probability of them developing major debilitating cardiovascular diseases, such as myocardial infarction and stroke, later. Finally, future studies are needed to develop new pharmacological tools to specifically address the various mechanisms responsible for hypertension in men and women individually in order to develop more "precision medicine" approach.

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