Androgens and Hypertension
Role in Both Males and Females?

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It is now well accepted that blood pressure (BP) in normotensive men and prevalence of hypertension in men is greater than in women.1 After menopause, the prevalence of hypertension increases in women until it exceeds that in men.1 Because cardiovascular disease (CVD) is the leading cause of morbidity and mortality in both men and women, and hypertension is a leading risk factor for CVD, determining the mechanisms responsible for the sex differences in BP and prevalence of hypertension is important in protecting against CVD. Evidence suggests that androgens can contribute to BP control in women just as in men, because androgens are elevated in young women with conditions such as polycystic ovary syndrome,2 and there is evidence that androgens tend to increase in women after menopause.3 The mechanisms by which androgens control BP in both men and women remain to be elucidated.

In the current issue of Hypertension, Wu et al4 extend their previous observations on the mechanisms responsible for androgen-mediated hypertension. They reported previously that treatment of male rats with 5α-dihydrotestosterone (DHT; 40 to 120 mg/kg body weight) caused an increase in BP and intrarenal expression of CYP4A and 20-hydroxy-5,8,11,14-eicosatetraenoic acid (20-HETE),5 that was prevented by CYP4A ω-hydroxylation inhibition (with HET-0016).6 In addition, DHT increased, and HET-0016 decreased, renal microvascular markers of oxidative stress. These data were the first to suggest that 20-HETE contributes to androgen-induced increases in oxidative stress. Subsequently, Ishizuka et al7 reported that adenoviral vector-mediated overexpression of CYP4A in endothelial cells increased 20-HETE, activated nuclear factor κB (NF-κB), and increased expression of inflammatory mediators.

In the current issue of Hypertension and based on these previous studies, Wu et al8 addressed whether 20-HETE–mediated activation of NF-κB contributes to androgen-mediated hypertension. In fact, they found that DHT in male rats activated NF-κB (p65 nuclear translocation), and blockade of 20-HETE abolished the activation of NF-κB. Furthermore, the inhibitor of κB kinase inhibitor, parthenolide, reduced androgen-dependent, 20-HETE–mediated increases in BP without affecting basal or DHT-mediated increases in 20-HETE in renal interlobular arteries. As shown in the Figure, the data suggest the following schema: androgens upregulate CYP4A ω-hydroxylases and increase vascular 20-HETE. 20-HETE activates NF-κB, which activates NADPH oxidase and production of reactive oxygen species, that would decrease bioavailability of NO for vasodilatation, and, thus, renal vasoconstriction would occur to increase BP.

One reason that BP is higher in normotensive men compared with women may be because of androgen-mediated upregulation of 20-HETE and increased renal microvascular reactivity in men. 20-HETE then could activate NF-κB leading to increases in oxidative stress and, together, increasing BP. The androgen receptor gene contains NF-κB enhancer sequences,8 and NF-κB can upregulate expression of tumor necrosis factor-α and interleukin-6, both of which increase the expression of the androgen receptor,9 thus setting a positive feedback to promote further an androgen-stimulated increase in BP, 20-HETE, and inflammation.

One problem with this scenario is that, in men, androgens are thought to be anti-inflammatory.10 In fact, a reduction in androgens is associated with increases in CVD and endothelial dysfunction in men.11 One difference between studies in men and studies in rats may be the level of androgens. Doses used to cause a rapid increase in BP in rats, as in the present study, are significantly higher than those in men. It is possible that androgens promote CVD and hypertension in men, but, by the time of diagnosis, a compensatory downregulation of androgen synthesis has occurred that attempts to protect against CVD. No studies have determined whether normotensive men with elevated levels of androgens are predisposed to CVD and hypertension and then develop hyperandrogenemia.

In contrast, women who have hyperandrogenemia, such as those with polycystic ovary syndrome, exhibit increases in inflammation and inflammatory cytokines, hypertension, oxidative stress, and NF-κB activation and are at increased risk for CVD both during their reproductive years and after menopause.2 Thus, these observations strongly fit the data found in the current article and in previous studies by these investigators. Whether 20-HETE levels are increased in women with polycystic ovary syndrome has not been determined, however.

The other condition in which androgens may be increased in women is after menopause, although this remains controversial. Laughlin et al12 reported that, whereas plasma testosterone and estradiol levels fall shortly after menopause, testosterone then begins to increase, and by age 70 years, testosterone levels were similar to those found in premenopausal women without decreasing estradiol levels. Again, to our knowledge,
Figure. Potential mechanisms by which androgens could increase BP. Androgens could upregulate cytochrome P450 4A \( \omega \)-hydroxylases, which would increase 20-HETE levels. 20-HETE would activate NF-\( \kappa \)B, which would activate NADPH oxidase to increase production of reactive oxygen species (ROS) and decrease NO bioavailability. The reduction in NO would increase renal vasoconstriction, leading to hypertension.

there are no studies in which changes in 20-HETE have been measured in postmenopausal women, nor are there studies as yet to address the role of 20-HETE or epoxyeicosatrienoic acids (EETs) in the development of postmenopausal hypertension.

In the present study by Wu et al., the studies were performed in male rats. However, in 2008, Singh and Schwartzman reported that intrarenal microvascular 20-HETE and EET levels were higher in females than males but that the ratio of 20-HETE to EETs was lower in females than males. Chronic DHT increased systolic BP and 20-HETE and reduced EETs in both females and males, but the 20-HETE:EET ratios were similar in the 2 sexes. These data showed that the increase in BP in females was likely attributed to DHT-mediated increases in vasoconstrictor 20-HETE, as well as reductions in vasodilator EETs. One caveat to this study is that the doses of DHT were significantly higher than those used in studies involving sex steroids and sex differences in CVD.

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