Testosterone and Blood Pressure Regulation

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Key Words

Testosterone • Androgens • Blood pressure • Hypertension • Sex difference

Abstract

Background: There is substantial evidence that androgens may play a role in determining sex-specific blood pressure. Men are at higher risk for developing coronary heart disease or hypertension compared to premenopausal women. However, effects of androgens on the renal and cardiovascular system are complex. This review provides a critical overview of testosterone actions. **Methods:** We searched Pubmed library for experimental, animal and clinical studies, using the keywords 'blood pressure', 'hypertension', 'testosterone' and 'androgens'. **Results:** While acute administration of testosterone seems to decrease vascular tone, the long-term net effect of androgens appears to be vasoconstriction via upregulation of thromboxane A₂ expression, norepinephrine synthesis, angiotensin II expression, and endothelin-1 action. Furthermore, androgens cause cardiac hypertrophy, promote atherosclerosis, vascular remodelling and stimulate renal prohypertensive processes involving the renin-angiotensin-aldosterone system. Androgens seem to promote oxidative stress in the kidney and may also play a role in the differentiation of brain areas involved in blood pressure regulation. **Conclusion:** The effects of sex steroids on different parts of the renal-vascular system are complex and often contradictory. In sum, net effects of androgen action seem to be vasoconstriction, atherosclerosis and stimulation of

the renin-angiotensin-aldosterone system. Therefore, androgens may determine blood pressure and the prevalence of cardiovascular disease.

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Introduction

Sex-Dependent Blood Pressure Regulation

Various epidemiological, clinical and experimental studies have indicated that androgens may be important determinants of sex-specific differences in arterial blood pressure. Sexual dimorphism in blood pressure develops in puberty and persists during adulthood [1–4]. Systolic blood pressure in men younger than 60 years is about 6–7 mm Hg higher than in women, diastolic blood pressure is elevated by about 3–5 mm Hg [5]. In women older than 60 years, particularly systolic blood pressure increases. This transition takes about 5–20 years [6] until finally, hypertension becomes as prevalent in women as in men. Although the fall in estrogens after menopause may in part be responsible for this phenomenon, studies in animals suggest that the shift in the androgen/estrogen ratio after menopause and the resulting 'imbalance' might explain the transition in cardiovascular and renal function more precisely [7]. Following menopause also responsiveness to androgens might increase. Hormone replacement therapy after menopause has not been shown to significantly decrease blood pressure [8–10].

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A number of clinical studies have indicated that androgens may affect the cardiovascular and renal system in human beings. Men have a higher risk for developing coronary artery disease and hypertension than premenopausal women [11–13]. Men with hypotestosteronemia and hyperestrogenemia have a lower incidence of coronary artery disease [14]. After orchiectomy mortality from heart disease in men decreases slightly [15]. In support, chronic anovulation and hypertestosteronemia in women, as it occurs in the polycystic ovary syndrome, is associated with hypertension [16] and an increased risk for myocardial infarction and coronary disease [15, 17–19]. Anabolic steroids (synthetic derivatives of testosterone) are known to be associated with hypertension, ventricular remodelling, myocardial ischemia and sudden cardiac death [20]. However, studies on the effects of anabolic steroids have to be interpreted carefully since their use is often clandestine and few controlled studies have been performed.

In some studies, an association between lower testosterone levels in men and hypertension [21, 22], coronary artery disease [14, 23, 24] or myocardial infarction [15] has been shown. Since circulating testosterone may decrease during stress, such as myocardial infarction, surgery, hypoxia, head trauma or psychological pressure [15], the results of these studies may reflect the response of testosterone following cardiovascular damage. A direct correlation between androgens and the renal-vascular system still needs to be shown in large clinical studies. Contradictory results in past clinical trials may be due to heterogeneous study groups regarding age and prevalence of cardiovascular disease, differences in duration of androgen treatment and the type of androgenic preparation being used.

Animal Models of Sex-Dependent Blood Pressure Regulation

Sex-specific differences in blood pressure can be observed in animals as well. Male spontaneously hypertensive rats (SHR) [25–27], Dahl salt-sensitive rats [28, 29], deoxycorticosterone acetate-salt hypertensive rats [30], and New Zealand genetically hypertensive rats [31] have higher blood pressure than females. Castration in these models decreases blood pressure [25–27, 32, 33], whereas administration of testosterone to castrated males or ovariectomized females reverses this effect [25, 26]. Ovariectomy itself has no effect on the development of hypertension in females [26]. Also conversion from testosterone to the more potent androgen dihydrotestosterone was not found to be relevant in promoting hypertension. Administration of finasteride, which blocks this conversion, did not attenuate hypertension [27].

Androgen-Modulated Cardiovascular Mechanisms

Vascular Tone

The androgen receptor is expressed in vascular cells of rats [34] and testosterone relaxes coronary arteries in rabbits in vitro [35, 36] and in vivo. Short-term intracoronary testosterone administration in men with coronary artery disease causes coronary artery vasodilation and increases coronary blood flow within minutes that cannot be antagonized with androgen receptor blockers [37]. Blockers of transcription (actinomycin D) and translation (cycloheximide) do not inhibit vasodilation induced by physiological concentrations of testosterone in porcine coronary arteries [38]. Thus, the acute effects of testosterone appear to be androgen receptor independent and nongenomic. Testosterone-induced vasodilation cannot be abolished by inhibition of aromatase activity as shown in rats [39] and rabbits [36]. Administration of dihydrotestosterone, which cannot be aromatized, caused similar vasodilation in porcine coronary arteries as testosterone [40] indicating that estrogen does not contribute to testosterone-induced vasodilation.

Interestingly, testosterone-induced vasodilation is preserved in endothelial denuded vessels of various species [36, 40–42]. Testosterone, like progesterone and estradiol, mediates vasodilation of porcine coronary arteries precontracted with prostaglandin $F_{2\alpha}$ and potassium [43]. However, the mechanism behind this phenomenon is not yet fully elucidated. Testosterone and progesterone do not only seem to inhibit calcium entry via receptor-operated calcium channels and voltage-operated calcium channels [44, 45] like estradiol, but may regulate additional pathways such as potassium channel conductance [36, 40] that lead to vasorelaxation. Interestingly, testosterone does not activate nitric oxide synthesis in bovine [46] and rat endothelium [47] and inhibitors of nitric oxide synthase or guanylate cyclase did not abolish testosterone-mediated vasodilation in rat studies [36, 47, 48].

Beneficial effects of testosterone on vascular tone have been shown in clinical case-control studies or randomized, double-blind crossover trials. Testosterone ameliorates ST segment depression in patients with angina pectoris after exercising [15, 37, 49, 50] and myocardial ischemia in patients with coronary artery disease [50, 51].

Testosterone also stimulates various vasoconstricting pathways, both directly and indirectly. By increasing tyrosine hydroxylase activity in SHR, testosterone promotes norepinephrine synthesis and may hence contribute to the development of hypertension in SHR [52, 53]. Testosterone stimulates release of the vasoconstrictor

Fig. 1. Androgen effects on the vasculature. vCAM-1 = Vascular cell adhesion molecule-1.

neuropeptide Y in rats [54], and promotes endothelin-1 action in porcine coronary artery rings [38]. Also in patients undergoing a sex change testosterone increases endothelin-1 [55]. Testosterone is pro-vasoconstricting by inhibiting action of some vasodilating effectors such as adenosine as shown in isolated rat heart [56]. Both testosterone [57, 58] and its precursor androstenedione [59] increase thromboxane A₂ receptor expression via an androgen receptor-dependent mechanism. This may explain the higher responsiveness of male rat aortas to thromboxane A₂ compared to castrated males [58]. Testosterone increases thromboxane A₂ mimetic-mediated coronary artery constriction in guinea pigs in vivo and in vitro [60]. In rats inhibition of cytochrome P450 4A, which is expressed in vascular tissues and is stimulated by androgens, reduces production of 20-hydroxyeicosatetraenoic acid (20-HETE) [61]. 20-HETE regulates vascular tone by sensitizing smooth muscle cells to vasoconstrictors and promotes myogenic, mitogenic and angiogenic actions. This suggests that 20-HETE may be involved in androgen-induced hypertension.

In sum, testosterone seems to be able to trigger both vasodilating and vasoconstricting processes, partly de-

pending on pretreatment and initial condition of the vascular cells. It may be the net effect of testosterone-mediated vasodilation and vasoconstriction that determines vascular tone and by these means regulates blood pressure. Figure 1 provides an overview of androgen effects on the vasculature.

Vascular Growth and Atherogenesis

Studies trying to elucidate testosterone's role in promoting vascular growth and atherosclerosis have revealed conflicting mechanisms: testosterone increases homocysteine levels in transsexuals [55], release of neuropeptide Y as shown in porcine coronary arteries [38] and synthesis of angiotensin II (Ang II) in SHR [27], known to cause vasoconstriction and induce atherosclerotic mechanisms. Testosterone also promotes mitogenic effects on rat vascular smooth muscle cells [62]. It increases expression of vascular cell adhesion molecule-1 and thus enhances adhesion of monocytes to vascular endothelium in humans [63]. In addition, it induces plaque formation in chicks [64]. Testosterone itself lowers high-density lipoprotein and increases low-density lipoprotein levels as shown in female transsexuals [65], triggers diet-

Fig. 2. Androgen effects on the heart and kidney. PRA = Plasma renin activity.

induced atherosclerosis in female monkeys and exacerbates arterial remodelling in these animals [66].

However, there are studies suggesting anti-atherosclerotic effects of testosterone. In rabbits, it inhibits post-injury-induced vascular plaque formation [35]. In cholesterol-fed rabbits, testosterone protects against development of atherosclerosis independent of lipid profiles [67]. However, it does not inhibit vascular smooth cell proliferation in rabbits in vivo [68] or migration of vascular smooth cells as shown in rats in vitro [69].

After all, it is not clear whether the anti-atherosclerotic effect is truly androgen dependent or whether it is based on a conversion of testosterone to estradiol and estradiol metabolites. Inhibition of atherosclerosis after treatment with dehydroepiandrosterone, which is a precursor of androstenedione, is reversed by the aromatase inhibitor fadrozole in rabbits [70]. However, the final mediator of the anti-atherosclerotic effect has not been identified so far.

Cardiac Mechanisms

The androgen receptor is expressed in cardiac myocytes of multiple species including humans [71]. Both tes-

tosterone and dihydrotestosterone cause cardiac hypertrophy. In baroreceptor-denervated rats, testosterone induces, whereas estradiol inhibits cardiac hypertrophy [72]. Androgens stimulate growth of cardiac myocytes in vitro, suggesting that this effect is direct [71]. In contrast to testosterone, action of dihydrotestosterone in these cells is associated with an increase in atrial natriuretic peptide. Figure 2 summarizes androgen action on the heart.

Androgen-Modulated Renal Mechanisms

As discussed above testosterone may contribute to the development of atherosclerosis and damage of glomerular endothelial cells may influence renal function [55]. Men are at higher risk for developing renal injury than women [73]. The incidence of end-stage renal failure caused by glomerulonephritis and hypertensive glomerular sclerosis is higher in men than in women. Compared with females, ageing males have a decreased glomerular filtration rate and develop glomerular injury, glomerulosclerosis and proteinuria earlier than females [7, 74, 75]. Castration of rats at an early age prevents renal injury and hypertension. Transplantation of prehypertensive kidneys from SHR to Wistar-Kyoto rats results in the development of hypertension [76]. In contrast, hypertension is ameliorated in patients receiving kidney transplants from normotensive human donors [77]. Whereas transplantation of kidneys from male SHR to female SHR does not significantly increase blood pressure, transplantation of female kidneys to male SHR does not attenuate hypertension [78]. This observation suggests that hypertension in SHR does not result from an intrinsic effect of the kidney itself, but seems to be due to an extrinsic factor influencing renal function.

The androgen receptor is expressed in kidneys [27, 75] and seems to mediate the effects of testosterone on blood pressure as summarized in figure 2. Administration of the androgen receptor antagonist flutamide lowers blood pressure in male rats to the level of females or castrated males [27]. In addition, flutamide is able to attenuate salt-induced hypertension [79].

Disruption of the CYP4A14 gene (arachidonic acid ω-1 hydroxylase) in mice results in an increase in renal vascular resistance and blood pressure that is severer in males than in females [80]. Castration in these animals is able to lower blood pressure, while administration of exogenous testosterone reverses this effect.

Fig. 3. Testosterone-dependent regulation of the ENaC in the aldosterone-sensitive distal nephron. Sodium reabsorption via the ENaC is classically mediated by aldosterone (A) that binds to the mineralocorticoid receptor (MR) and activates mineralocorticoid receptor target genes, such as serum- and glucocorticoid-regulated kinase 1 (SGK1). Serum- and glucocorticoid-regulated kinase 1 inactivates Nedd4-2 by phosphorylation and prevents Nedd4-2-mediated endocytosis of the ENaC. In addition, testosterone (T) binds to the androgen receptor (AR) and is able to upregulate expression of the ENaC α -subunit.

Pressure-Natriuresis Relationship and the Renin-Angiotensin-Aldosterone System

Interestingly, the pressure-natriuresis relationship in men is shifted to the right compared to women [7, 76, 81]. At comparable renal perfusion pressures male SHR and ovariectomized SHR receiving testosterone excrete significantly less sodium and water than females, ovariectomized females or castrated males [26, 75].

Males have higher plasma renin activity than females [7, 26, 75, 82] independent of age and ethnic origin. Also plasma renin activity in postmenopausal women is higher than in premenopausal women [83]. Interestingly, plasma renin activity is lowered after castration of male SHR and increased by administration of testosterone to ovariectomized females. The increase in plasma renin activity correlates positively with the dose of testosterone given [7].

Furthermore, male rats have higher angiotensinogen mRNA levels than females. This phenomenon is regulated by androgens [84, 85] and stimulates the renin-angiotensin-aldosterone system (RAAS), resulting in an increased retention of sodium and water in males.

Administration of enalapril, an angiotensin-converting enzyme inhibitor, was able to reduce blood pressure in male and ovariectomized SHR receiving testosterone by 60%, whereas blood pressure could be lowered only by about 40% in intact female, castrated male and ovariectomized female SHR [27]. This supports the hypothesis that androgens might in part cause hypertension via

stimulation of the RAAS. An increase in Ang II has been suggested to cause oxidative stress, such as stimulation of superoxide production, quenching of nitric oxide, increase in peroxynitrite and enhanced release of vasoconstrictor F_2 -isoprostanes. This would decrease the renal vascular response to vasodilators, increase the response to vasoconstrictors such as Ang II and might stimulate endothelin production [7]. In addition, F_2 -isoprostanes have been shown to activate thromboxane receptors [86] whose expression is regulated by androgens in aortic vascular smooth muscle cells.

In how far aldosterone release is influenced by androgens has not been fully clarified yet. Some clinical studies in humans suggest sex differences in aldosterone levels that correlate with differences in blood pressure [87, 88]. However, corticotropin-stimulated aldosterone release decreased in response to testosterone replacement in castrated male rats [89].

Androgen Regulation of Proximal and Distal Renal Tubule

In vivo microperfusion in rats revealed that androgens might directly stimulate the RAAS of the proximal tubule [90]. The exact mechanism of testosterone-induced renal injury is still unknown, but increased renal sodium reabsorption in the proximal tubule might lower pressure natriuresis and decrease sodium delivery to the macula densa [75]. This again might stimulate renin release, decrease preglomerular resistance and in combination with

the increase in arterial pressure lead to renal injury and hypertension.

The aldosterone-sensitive distal tubule is an important control point in the regulation of renal sodium, potassium and water excretion. Interestingly, the epithelial sodium channel (ENaC) is not only a target for aldosterone action, but seems to be regulated by testosterone as well (fig. 3). Testosterone stimulates expression of the ENaC α -subunit in human renal HKC-8 cells in vitro and in male Wistar rats in vivo [91]. By these means, androgens promote sodium and water reabsorption in the distal tubule. This mechanism might contribute in part to the sexual dimorphism in blood pressure.

Influence of Androgens on Central Blood Pressure Regulation

Female SHR that were treated with testosterone shortly after birth show a higher increase in blood pressure when exposed to testosterone in adulthood than control females [92]. Neonatal differentiation of brain areas that regulate blood pressure might therefore determine responsiveness of blood pressure to androgens in adulthood. Androgen binding sites can be found in the area postrema and in the preoptic region [93], suggested to regulate in part blood pressure and heart rate [94]. Therefore, sex-dependent differences in blood pressure might in part result from a sexually dimorphic pattern of the brain which determines central blood pressure regulation.

Counterplayers: Estrogens and Progestins

Estrogens are known to have a merely protective role regarding the cardiovascular and renal system. For example, estradiol causes acute and long-term vasodilation in human and ovine endothelium [95, 96], attenuates the vascular remodelling process by inhibiting vascular inflammation, neointima formation and recruitment of macrophages [97, 98], prevents mitogen-induced proliferation of cardiac fibroblasts [99] and vascular smooth muscle cells [97], and reduces glomerulosclerosis and tubular damage [100] in rats. However, studies relating estrogens with hypertension have contradictory results. Different types of estrogenic preparations seem to have specific effects as seen in multiple clinical studies [101]: while contraceptive estrogenic preparations seem to increase blood pressure, conjugated equine estrogens do

not affect blood pressure. However, estradiol has a pressure-lowering effect. In hypertensive animal models, administration of estradiol resulted in a decrease in blood pressure [28, 92, 102, 103]. In contrast, ovariectomy does not prevent hypertension in SHR [27]. This suggests that the pressure-lowering effect of estradiol might not reflect a physiological process, but has to be contributed to the high doses given.

Conclusions

Androgens have diverse, even contradictory effects on the cardiovascular and renal system. In this review, we have tried to examine testosterone actions critically and outline mechanisms that may explain sex differences in blood pressure. However, findings of experimental trials are often species specific and cannot simply be applied to the human organism.

Whereas acute effects of testosterone administration may be beneficial as far as they cause vasodilation in men with coronary artery disease, long-term exposure to androgens may trigger multiple vasoconstricting mechanisms. Experimental studies have shown that androgens cause upregulation of thromboxane A_2 expression, nor-epinephrine synthesis, Ang II expression, endothelin-1 action, release of neuropeptide Y and attenuation of adenosine action. Therefore, vasoconstricting pathways may outweigh vasodilating effects in the long term. There is substantial evidence that androgens promote vascular remodeling and atherosclerosis and finally increase blood pressure. Anti-atherosclerotic effects as shown in some studies might not be truly androgen dependent.

Androgens also stimulate pro-hypertensive processes through various pathways involving the RAAS and promote oxidative stress in the kidney.

Taking into account that localized enzyme systems exist in various tissues such as the kidney, heart and vasculature, autocrine or paracrine mechanisms might be involved in inhibitory or stimulating actions of androgens as well. Age-dependent metabolism of estrogens and androgens certainly influences the net effects of sex hormones on the cardiovascular and renal system. Whether androgen-induced hypertension causes renal injury or whether androgen-induced renal injury determines the development of hypertension remains to be investigated.

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