Testosterone and Secondary Hypertension
New Pieces to the Puzzle
Matthias Barton, Eric R. Prossnitz, Matthias R. Meyer

See related article, pp 1263–1271

The absence of estrogen, in males or after menopause in women, is independently associated with increased cardiovascular risk.1 A number of factors have been implicated as the underlying cause, including effects at the cell-organ level (eg, inflammatory activation, increased oxidative stress, and increased vasconstriction),1 as well as changes in cardiovascular physiology (eg, sympathetic activation, increased blood pressure, and insulin resistance). All of these parameters are sensitive to modulation by sex steroid hormones,1 particularly 17β-estradiol, testosterone, and its more active metabolite, 5α-dihydrotestosterone, which is produced from testosterone by 5α-reductase.1,2

Testosterone is the main male sex steroid hormone but is also produced by women.2 Testosterone is converted to 17β-estradiol by aromatase in numerous tissues, including the vasculature and adipose tissue, representing an important local source of estrogen.3 In obesity, aromatase-derived 17β-estradiol formation may represent an important cause of feminization in males and the increased risk of estrogen-sensitive cancers in obese females.3

Androgenic Steroids and Cardiovascular Risk
In many countries, including the United Kingdom, the United States, Canada, and Australia, anabolic androgenic steroids, such as testosterone, are controlled substances, and their nonmedical use is considered drug abuse.4,5 Testosterone has been used since the 1930s for nonmedical, athletic purposes, especially in male and female body builders and swimmers.6 Because testosterone abuse may increase arterial blood pressure,7 leading to left ventricular hypertrophy,8 it should be included among the differential diagnoses of secondary arterial hypertension. Moreover, testosterone abuse has been associated with myocardial infarction because of coronary vasospasm9 or thrombosis.10–12 Among the mechanisms of how exogenous, as opposed to endogenous, testosterone contributes to increased in cardiovascular risk, coagulatory activation, as well as accelerated progression of coronary artery disease, have been described.10 Sex steroids dilate human coronary arteries,13 and diminished vasodilator activity in response to testosterone under hypertensive conditions has been reported,14 yet research into the mechanisms of testosterone’s contribution to or aggravation of hypertension, particularly in the presence of genetic risk, remains scarce.

Novel Links Between Testosterone and Arterial Hypertension
Genomic, as well as rapid, nongenomic effects of sex steroids contribute to cardiovascular homeostasis and likely to cardiovascular protection in premenopausal women and possibly also in men.15 Nongenomic effects of testosterone were described >40 years ago16 and include rapid changes in calcium signaling. Sex steroid-induced vasodilation (reviewed in Reference 17) is mediated via both membrane subpopulations of nuclear steroid receptors, such as the androgen receptor (AR),18 as well as novel G protein–coupled receptors.19,20 AR-mediated rapid effects of testosterone (or its more active metabolite 5α-dihydrotestosterone) have been described; however, other receptors also appear to be involved.18

In the present issue of Hypertension, Chignalia et al21 now present new evidence on genomic and nongenomic mechanisms of testosterone action on vascular smooth muscle cells in arterial hypertension through modulating associated cellular events, thus setting the stage for further aggravation of hypertension. Using animal models of normotension and polygenic hypertension, the investigators found that, in vascular smooth muscle cells from male animals, testosterone regulates cellular processes, such as phosphorylation of the nonreceptor tyrosine kinase, c-src, which mediates vascular contraction and hypertrophy,22 key events contributing to the increased vascular resistance in hypertension.23 Importantly, c-src is upregulated in experimental polygenic hypertension24 and has been implicated in rapid, nongenomic sex steroid signaling.

Chignalia et al21 also observed greater production of reactive oxygen species in response to testosterone in vascular smooth muscle cells from hypertensive as compared with normotensive animals. These effects were not attributed to conversion of testosterone to 17β-estradiol, because the aromatase inhibitor anastrazole had no effect on reactive oxygen species formation. Although testosterone effects on steady-state mRNA levels did not differ much with regard to NADPH oxidase subunits Nox1 and p22phox, the investigators report a striking difference with regard to the expression of Nox4, which was upregulated in response to testosterone only in vascular smooth muscle cells from normotensive but not from hypertensive animals. Although one might consider this
testosterone stimulates cell migration as early as 2 hours after testosterone treatment reported by Chignalia et al. The findings reported by Chignalia et al are novel and important because they provide some of the first molecular information on how genetic background might determine the prohypertensive effects of testosterone. In fact, such a genetic vascular predisposition could also underlie the development or aggravation of secondary arterial hypertension associated with testosterone abuse in humans. From these findings, one could hypothesize that cells derived from animals (or humans) with a genetic predisposition to arterial hypertension will respond to a greater degree to testosterone, showing greater increases in reactive oxygen species production and insufficient induction of "protective" NADPH oxidase subunit Nox4, resulting in an overall greater oxidative stress burden.

Several questions remain that provide opportunities for further research in this area. Because Chignalia et al used only cells from male animals, one obvious question would be to what extent the effects of testosterone would be present in cells from females, which also produce testosterone and 5α-dihydrotestosterone. Recently, the role of sex chromosomes as determinants of cellular responses has received increasing attention, and often the sex of the cells used is not even determined in studies investigating the effects of sex steroids. Such information would be of interest, because females are known to be largely protected from hypertension until menopause. Furthermore, this information might be clinically relevant because sex differences in clinical responsiveness to antihypertensive therapy have been described. As indicated previously, information from in vivo studies using exogenous testosterone at doses known to cause hypertension in humans is required to assess effects on vascular hypertrophy in vivo.

Finally, identification and characterization of new receptors mediating nongenomic testosterone signaling, for which GPRC6A represents a potential candidate, as well as cellular targets such as the "protective" Nox4, should be studied further with regard to their role in the effects of testosterone on vascular homeostasis. This might ultimately allow us to understand the mechanisms underlying the testosterone-induced increases in blood pressure in normotensive individuals and those genetically at risk. Finally, the work of Chignalia et al reminds us once again that testosterone abuse should be included in the differential diagnoses of secondary hypertension, particularly in young patients, and that fighting testosterone abuse represents an important opportunity in the primary prevention of hypertension.
Sources of Funding
This work was supported by the Swiss National Science Foundation grants 108258, 122504 (to M.B.), 135874, and 141501 (to M.R.M.) and the National Institutes of Health grants CA116662, CA118743, and CA127731 (to E.R.P.).

Disclosures
None.

References
32. Afar B. Testosterone and blood pressure: is the decreased sodium excretion the missing link? Hypertension. 2012;59:e41.
Testosterone and Secondary Hypertension: New Pieces to the Puzzle
Matthias Barton, Eric R. Prossnitz and Matthias R. Meyer

_Hypertension_. 2012;59:1101-1103; originally published online May 7, 2012;
doi: 10.1161/HYPERTENSIONAHA.112.195149

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/59/6/1101

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in_Hypertension_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to_Hypertension_is online at:
http://hyper.ahajournals.org/subscriptions/