COMMENT

Testosterone and vascular reactivity

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ABSTRACT

The mechanisms by which male sex hormones modulate cardiovascular function are a subject of contemporary interest. Several lines of evidence indicate that androgens can exert acute vasorelaxing effects. On the other hand, chronic exposure to androgens has been shown to promote increases in blood pressure and compromise renal function. In the present issue of Clinical Science, Malkin and co-workers show that testosterone replacement impairs vascular reactivity in men with androgen deficiency. These studies may shed light on the functional and therapeutic significance of the diverging acute and chronic cardiovascular effects of androgens.

Accumulating evidence indicates that androgens can affect the function of the cardiovascular system in humans and animals. Men have higher blood pressure than premenopausal women and are more prone to developing hypertension and coronary artery disease. Several clinical and experimental studies suggest that the cardiovascular actions of androgens mediate this sex disparity. This contention is challenged by the apparent lack of correlation between testosterone levels and cardiovascular disease in men. In addition, androgens have been shown to also exert direct vasodilator effects in arteries from both humans and experimental animals, which might actually prove beneficial in the setting of cardiovascular disease. These opposing findings appear difficult to reconcile unless the underlying mechanisms are considered.

Early studies in the 1940s indicated that testosterone administration alleviates symptoms and ECG abnormalities in men with angina [1]. It was only much later that Yue et al. [2] demonstrated that testosterone has a direct and rapid vasodilator effect in coronary arteries and aortas of rabbits. Subsequent studies showed that this effect is independent of a functional androgen receptor and does not require gene transcription. Testosterone appears to induce vasodilation by blocking a membrane-associated calcium channel [3] and/or opening of a potassium channel [4]. Peripheral and coronary artery vasodilation might therefore explain the haemodynamic benefit observed in response to acute administration of testosterone in men with heart failure or stable angina. However, the effect of long-term exposure to elevated levels of testosterone on vascular reactivity remains a subject of debate.

The study by Malkin et al. [5] in the present issue of Clinical Science investigated the acute effect of testosterone in isolated peripheral resistance arteries from humans. They confirmed an acute vasodilator effect of testosterone in arteries from healthy men and men suffering from heart failure. Since the experimental design allowed for direct comparison of the reactivity of resistance vasculature to various pharmacological agents in a longitudinal setting, the authors went a step further and addressed the question of whether prolonged exposure to testosterone might have a different chronic effect on vascular reactivity. This question is particularly important in the light of previous studies showing an impaired vascular reactivity following administration of high doses of androgens [6]. Malkin et al. [5] tested the vasoconstritor and vasodilator response of subcutaneous resistance arteries from hypogonadal men before and after 3 months of testosterone replacement therapy. They found that vessels from men with androgen deficiency had an augmented vasodilator response to testosterone. After chronic administration of androgens, however, not only was this augmented effect attenuated, but constriction in response to adrenergic agonists was enhanced while endothelium-mediated relaxation to acetylcholine was diminished. Furthermore,
endothelium-independent vasodilation in response to a nitric oxide donor was reduced. These findings might be interpreted to mean that the acute vasodilator effects of testosterone could be offset by a chronic impairment of vascular reactivity following long-term exposure to testosterone. Indeed, another recent human study [7] supports the assertion that testosterone supplementation can alter endothelium-mediated dilation as assessed by forearm blood flow response to acetylcholine.

A large body of evidence now indicates that androgens may affect cardiovascular function through mechanisms that involve gene expression in target organs, as would occur when chronic exposure to naturally occurring androgens is considered. The presence of endogenous androgens allows blood pressure to rise to higher levels in experimental models of hypertension [8]. Removal of androgens or blockade of their receptor in male hypertensive animals reverts the blood pressure levels to those found in females. Mechanistic studies revealed that androgens stimulate synthesis and activity of several vasoconstrictor factors, such as the renin–angiotensin system and endothelin, and may promote oxidative stress [8]. Also, androgens can increase renal tubular sodium and water re-absorption, which in turn may increase blood pressure [9]. These experimental data point to a permissive role of endogenous androgens in the development of hypertension, but the importance of this effect has not been thoroughly investigated in men suffering from cardiovascular diseases. It is nevertheless evident that a discrepancy exists between a potentially beneficial role of testosterone-induced vasodilation, which occurs acutely, and its pro-hypertensive actions, which develop over time. In this framework, the data presented by Malkin et al. [5] deserve special consideration.

As was the case in numerous previous studies, high concentrations of testosterone (in the micromolar range) were required to elicit vasodilation in the study by Malkin et al. [5]. Although attributable to the specific conditions of an in vitro setting, this requirement calls into question the functional relevance of testosterone-induced vasodilation and calls for attention when considered in the clinical setting. Indeed, the use of testosterone supplements in aging men and women has significantly increased in recent years, with the potential benefit of enhancing muscle mass and bone strength and improving libido. This occurred despite the lack of clinical trials to address the safety of such therapy with regard to cardiovascular and renal function [10].

The finding that total and bioavailable testosterone levels decline in men with chronic cardiovascular disease, such as hypertension [11], suggested to some investigators that restoring testosterone levels by exogenous supplementation might be curative or beneficial in this setting. Experimental and clinical data, such as presented in the study by Malkin et al. [5], however, should call for caution. Androgens may have contrasting cardiovascular effects depending on the pre-existing endogenous levels, dose and mode of administration. Thorough exploration of the mechanisms involved in the actions of androgens upon the cardiovascular system, especially of non-genomic versus genomic pathways, is required for bridging the gap between their observed acute and chronic effects.

REFERENCES

4 Ding, A. Q. and Stallone, J. N. (2001) Testosterone-induced relaxation of rat aorta is androgen structure specific and involves K+ channel activation. J. Appl. Physiol. 91, 2742–2750