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Perspectives

Do androgens play a beneficial role in the regulation of vascular tone? Nongenomic vascular effects of testosterone metabolites

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The marked sexual dimorphism that exists in human cardiovascular diseases has led to the dogmatic concept that testosterone (Tes) has deleterious effects and exacerbates the development of cardiovascular disease in males. While some animal studies suggest that Tes does exert deleterious effects by enhancing vascular tone through acute or chronic mechanisms, accumulating evidence suggests that Tes and other androgens exert beneficial effects by inducing rapid vasorelaxation of vascular smooth muscle through nongenomic mechanisms. While this effect frequently has been observed in large arteries at micromolar concentrations, more recent studies have reported vasorelaxation of smaller resistance arteries at nanomolar (physiological) concentrations. The key mechanism underlying Tes-induced vasorelaxation appears to be the modulation of vascular smooth muscle ion channel function, particularly the inactivation of L-type voltage-operated Ca^{2+} channels and/or the activation of voltage-operated and Ca^{2+}-activated K^+ channels. Studies employing Tes analogs and metabolites reveal that androgen-induced vasodilation is a structurally specific nongenomic effect that is fundamentally different than the genomic effects on reproductive targets. For example, 5α-dihydrotestosterone exhibits potent genomic-androgenic effects but only moderate vasorelaxing activity, whereas its isomer 5β-dihydrotestosterone is devoid of androgenic effects but is a highly efficacious vasodilator. These findings suggest that the dihydro-metabolites of Tes or other androgen analogs devoid of androgenic or estrogenic effects could have useful therapeutic roles in hypertension, erectile dysfunction, prostatic ischemia, or other vascular dysfunctions.

5α-dihydrotestosterone; 5β-dihydrotestosterone; hypertension; vascular relaxation; vasodilation

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