Pharmacological Reports
2008, 60, 29–37
ISSN 1734-1140

Renal vascular cytochrome P450-derived eicosanoids in androgen-induced hypertension

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Abstract:
Androgen has been linked to higher incidence of cardiovascular disease based on the simple observation that men have more cardiovascular and renal events than women at similar ages. The Cytochrome P450 (CYP)-derived eicosanoids, 20-hydroxyeicosatetraenoic acid (20-HETE) and epoxyeicosatrienoic acids (EETs) have been implicated in the regulation of blood pressure *via* their vasoactive properties as vasoconstrictors and vasodilators, respectively, as well as *via* inhibition and activation of endothelial nitric oxide synthase. Since, 20-HETE and EETs have opposing vascular effects, their relative levels may determine vascular resistance and tone. We characterized the renal vascular production of 20-HETE and EETs in male and female rats before and after treatment with 5α-dihydrotestosterone (DHT). In renal interlobar arteries from male rats, the ratio between 20-HETE and EETs levels was 2-fold higher than that observed in arteries from female rats (1.86 ± 0.22 *vs.* 0.85 ± 0.13). Importantly, treatment with DHT significantly increased this ratio by 85 and 230% in arteries from male and female rats, respectively. Moreover, DHT treatment eliminated the difference in the ratio of 20-HETE to EETs between males and females. DHT treatment increased blood pressure in both male and female rats by 21.3 ± 4.0 and 15.3 ± 5.1 mmHg, respectively. The primary enzyme responsible for 20-HETE synthesis in the renal vasculature, CYP4A8, was significantly induced by treatment with DHT while the major epoxygenase in the kidney, CYP2C23, was down regulated by DHT. We conclude that increased vascular tone brought about by downregulation of CYP2C23 and decreased levels of vasodilatory EETs and by induction of CYP4A8 and enhanced production of 20-HETE may constitute important factors in androgen-induced hypertension.

Key words:
gender differences, arachidonic acid, blood pressure, kidney, 20-HETE, EET