Abstract

Introduction: Two major product groups originate from the arachidonic acid metabolic pathway of cytochromes P450: epoxyeicosatrienoic acid (EETs) and 19 and 20-hydroxyeicosatetraenoic acid (19- and 20-HETE). These metabolites play an important role in the regulation of blood pressure, inflammatory responses, regulation of sodium excretion and other crucial physiological processes.

Hypothesis: Our studies were based on the hypothesis that abnormalities in the production and function of these cytochrome P450 metabolites significantly contribute to the pathophysiology of hypertension development, in particular in the angiotensin II-dependent models.

Objective: To investigate if the increased bioavailability of the above-mentioned metabolites in the kidney tissue will result in blood pressure reduction in the ANG II - dependent rat model of hypertension.

Methods: The two methods to increase the concentration of EETs was chosen. In the first part of the study, we administered a soluble epoxide hydrolase inhibitor cAUCB [cis-4- [4- (3-adamantan-1-yl-ureido) cyclohexyloxy] benzoic acid, at a dose of 26 $mg.l^{-1}$ administered in drinking water], an enzyme responsible for inactivation of biologically active forms of EETs. In the second series of the experiments we applied a synthetic EET analogue, called EET-A [(sodium 2- (Z- (13- (3-pentyl) ureido) –tridec-8-enamido) malonate), at a dose of 10 mg.kg-1 administered in drinking water]. To increase the renal concentration of 20-HETE, we used fenofibrate (Lipanthyl 265M) at a dose of 3.2 $g.kg^{-1}$ of food.

Results: Both treatments (with cAUCB and EET-A analogue) mitigated the development of malignant hypertension in our rat models, probably due to the suppression of the vasoconstrictive axis and activation of the vasodilatory axis of RAAS. Treatment with fenofibrate also significantly attenuated the development of malignant hypertension, however, we did not observe an increased concentration of 20-HETE in these animals, although we observed the activation of the CYP4A enzyme (responsible for the formation of 20-HETE in rats). We suspect that the main mechanism underlying the blood pressure reduction in this case might be primarily associated with the direct interaction of fenofibrate with the renin Ren2 gene, which resulted in the attenuation of the prohypertensive axis of RAAS.

Conclusion: We confirmed that EETs intrarenal deficiency might significantly contribute to the pathophysiology of angiotensin II-dependent form of hypertension in our rat models.