Abstract

Introduction: Epoxyeicosatrienoic acids (EETs) are converted by the enzyme soluble epoxid hydrolase (sEH) to the biologically inactive dihydroxyeicosatrienoic acids (DHETs). EETs are significantly involved in the control of blood pressure, they influence vascular tone and renal transport mechanism. sEH inhibitor reduce blood pressure by increasing the bioavailability of EETs in many models of hypertension.

Aim of the study: To determine that sEH inhibitor decreases blood pressure and improves the renal function during the development of malignant hypertension in transgenic rats after the induction of the mouse renin gene.

Methods: Hypertension in Cyp1a1-Ren-2 transgenic rats was induced through a dietary administration of the natural xenobiotic indole-3-carbinol (I3C, 0.3 %) for 3 and 11 days. I3C activates the renin gene. At the same time, during a three-day induction of hypertension, the inhibitor of nitric oxide synthase L-NAME (600 mg/l) was administered in drinking water. The sEH inhibitor c-AUCB was given in drinking water at a dose of 13 or 26 mg/l, starting 48 hours before the initiation of I3C and L-NAME administration. Radiotelemetric measurement of blood pressure was performed and renal excretory parameters were monitored in the conscious animals. The effects on renal hemodynamics and excretory function were determined by acute renal studies in the anesthetized animals.

Results: I3C administration in Cyp1a1-Ren-2 transgenic rats resulted in malignant hypertension with the rise in systolic blood pressure, the loss of body weight (BW), the rise in proteinuria, markedly lowered renal blood flow (RBF) and glomerular filtration rate (GFR) and substantially impaired renal autoregulatory efficiency. *c*-AUCB treatment significantly attenuated the development of hypertension, the loss of BW and the degree of proteinuria. Moreover, *c*-AUCB treatment prevented the reduction in RBF and GFR, significantly increased sodium excretion, improved autoregulatory efficiency of RBF and GFR and significantly improved the suppressed slope of pressure–natriuresis relationship in I3C-induced rats. The treatment with c-AUCB increased the renal EETs/DHETs ratio and prevented the development of renal damage in I3C-induced Cyp1a1-Ren-2 rats. Antihypertensive and renoprotective actions of the treatment with the sEH inhibitor c-AUCB were completely abolished by concomitant administration of L-NAME.

Conclusion: Treatment with the sEH inhibitor c-AUCB substantially attenuates the development of malignant hypertension and improves the impaired renal function in I3C-induced Cyp1a1-Ren-2 transgenic rats. Beneficial effects of this treatment were completely abolished by administration of L-NAME. . The improvement of renal mechanisms is likely responsible for the antihypertensive effect of c-AUCB treatment. Antihypertensive actions of sEH inhibitor in this ANG II dependent form of malignant hypertension are dependent on the interactions of endogenous bioavailability of EETs and NO.