The role of renal dysfunction in pathophysiology of congestive heart failure progression: preclinical animal studies.

Abstract

The thesis describes effects and pharmacological targets of eicosanoids, especially epoxyeicosatrienoic acids (EETs) that are epoxygenase metabolites of arachidonic acid (AA), in animal model of congestive heart failure (CHF) induced by volume overload via aorto-caval fistula (ACF) in hypertensive transgenic rats (TGR). Our data show that ACF TGR exhibits tissue deficiency of EETs in the left ventricle and kidney, probably mainly caused by increased EETs degradation by soluble epoxide hydrolase (sEH). Treatment by orally active EETs analogue (EET-A) improved the survival rate in ACF TGR compared to placebo. However, after adding EET-A to angiotensin-convertase enzyme inhibitor (ACEi) treatment, the survival of ACF TGR only tended to improve compared with the effects of EET-A or ACEi given alone. The protective effects of EET-A treatment were mediated by improving cardiac parameters and reducing lung congestion, not dominantly by renal mechanisms. We also found that among male (not in female) the combination of sEH inhibitor (sEHi) and ACEi treatment worsened the mortality of ACF TGR compared to ACEi monotherapy. Our data support the notion that targeting the CYP-dependent epoxygenase pathway of AA should be considered in attempts to develop new pharmacological strategies for HF treatment and enhance the importance of testing the gender differences in pre- and clinical studies.

Keywords

chronic kidney disease, congestive heart failure, cytochrome P450, EET-A, epoxyeicosatrienoic acid, pressure-volume analysis, renin-angiotensin-aldosterone system, soluble epoxide hydrolase