SP073
IN OBESE ZSF1 RATS, FEMALES SHOW INCREASED SALT-SENSITIVITY COMPARED TO MALES

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INTRODUCTION AND AIMS: We have shown recently that increasing kidney tissue epoxygenase-15-epoxygenase (15-LOX) by blocking soluble epoxide hydrolase (sEH) and thereby blocking EETs degradation to inactive dihydroxyeicosatetraenoic acids (DHETEs) substantially attenuated the progression of chronic kidney disease (CKD) in Ren-2 transgenic hypertensive rats (TGR) subjected to 5/6 renal mass reduction (5/6 NX). In this study we examined if, in this model, addition of sEH inhibition to the complex (dual) renin-angiotensin system (RAS) blockade would bring additional renoprotective effects in already established CKD.

METHODS: TGR aged 9 weeks underwent 5/6 NX and then were left untreated for 6 weeks to develop CKD. Then dual RAS blockade: ACE inhibition (trandolapril) + angiotensin AT1 receptor blockade (losartan) in drinking water was instituted, alone or combined with sEH inhibition (<AUC50, 3 mg/l in drinking water). During the 60 weeks follow-up period, albuminuria and urinary creatinine excretion was repeatedly determined. The following experimental groups were investigated: 1) sham-operated TGR, 2) untreated 5/6 NX TGR, 3) 5/6 NX TGR + RAS blockade, 4) 5/6 NX TGR + RAS + sEH blockade. Sham-operated transgene-negative normotensive Hannover-Sprague Dawley (HanSD) rats served as basic controls. In separate groups renal glomerular and tubulointerstitial injury was assessed, and effects of two weeks treatment on systolic blood pressure (SBP, measured by telemetry) and on kidney ANG II, ANG 1-7, EETs and DHETEs levels were determined.

RESULTS: All untreated TGR died by week 14 after 5/6 NX. RAS blockade increased the final survival rate to 23%, normalized SBP (116 ± 3 vs. 198 ± 3 mmHg, p<0.0015), reduced albuminuria (46 ± 5 vs. 102 ± 12 mg/24 h, p<0.001) and intrarenal ANG II (27 ± 8 vs. 109 ± 14 fmoI/g, p<0.0015) and did not alter kidney EETs/DHETEs ratio. After addition of sEH blockade kidney EETs/DHETEs ratio increased to 2.89 ± 0.42 (p<0.001 vs. 5/6 NX TGR treated with RAS blockade) and the final survival rate increased to 42%. Albuminuria, glomerular filtration rate, glomerulosclerosis index and index of tubulointerstitial injury were also improved comparing with RAS blockade only.

CONCLUSIONS: Addition of sEH blockade to the RAS blockade brings about additional renoprotective effects on the CKD progression in 5/6 NX TGR, even when applied in the advanced phase of the disease.