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Effect of Carnosine and SGLT2i on non-diabetic kidney disease in TGRNeph-hAT1 rats

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Chronic Kidney disease (CKD) is related to a group of heterogeneous disorders affecting kidney structure and function. Previous studies in our lab have disclosed a beneficial effect of carnosine feeding on renal parameters in diabetic mice. Other pre-clinical studies and clinical trials in diabetic models and patients with diabetes have demonstrated a beneficial effect of sodium glucose co-transporter 2 inhibition (SGLT2i) on renal end-points. It is currently not known if carnosine or SLT2i are reno-protective irrespective of the underlying aetiology of CKD. To address this question, we made use of TGRNeph-hAT1 rats (TGR) in which the AT1R is exclusively overexpressed in podocytes. Phenotypic changes in this model are reminiscent of focal segmental glomerulosclerosis (FSGS) and the animals present with progressive proteinuria and increased plasma lipid levels. The following questions were addressed: 1.) Does carnosine supplementation in TGRNeph-hAT1 rats ameliorates albuminuria and improves renal pathology?
2.) Does carnosine influence tubuloglomerular feedback? 3.) Does empagliflozin treatment improves renal end-points in TGRNeph-hAT1 rats and is this related to activation of the tubuloglomerular feedback (TGF)? 4.) Does treatment with empagliflozin or carnosine changes the expression in kidney RAAS components?
The major findings are the following: 1. Carnosine treatment didn't change urinary albumin or protein levels nor podocyte damage in TGRNeph-hAT1 rats. However, it alleviated glomerular hypertrophy, which might be due to the activation of TGF. 2. Empagliflozin treatment of TGRNeph-hAT1 is dependent on the timing of treatment. While it slightly, but not significantly, decreased albuminuria when treatment was installed at the on set of albuminuria, pre-emptive treatment increased albuminuria. 3. Both carnosine and SLT2i treatment changed renal RAAS expression. Further studies are required to address if carnosine really affects TGF and if so how this is mediated in mechanistic terms. Also, the finding that pre-emptive SGLT2i treatment worsens albuminuria warrant further studies in this model.