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# Implications of the carnosine-carnosinase system in diabetic nephropathy

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In humans, both carnosine-degrading and synthesizing enzymes, i.e. carnosinase (CN1) and Carnosine synthase (CARNS) are expressed in the kidney. While polymorphisms that are associated with the susceptibility to develop diabetic nephropathy (DN) have been described for CN1, no such polymorphisms for CARNS have been reported. Therefore, the studies described herein particularly focus on the role of CN1 in the progression of DN and try to elucidate if carnosine has vasoprotective properties and if this is possibly mediated via improvement of the intracellular redox milieu in methylglyoxal (MGO)-challenged cultured endothelial cells.

This thesis partly makes use of clinical cohorts to understand the role of urinary CN1 in the progression of DN and describes in vitro studies to assess the relation between MGO, redox homeostasis and carnosine in the context of vascular damage. Two main hypotheses were put forward: 1) in patients with DN the extent of urinary CN1 is increased due to impairment of the glomerular filtration barrier and leakage from the serum. Because high renal CN1 concentrations may lead to depletion of renal carnosine stores, an association between the extent of urinary CN1 and renal function deterioration is expected. 2) MGO affects the redox status in cultured endothelial cells thereby causing cellular structural damage. Carnosine can ameliorate this damage by virtue of its anti-oxidant properties.

The main findings of this study are as follows: 1) CN1 can be reliably detected in spot and in 24-hr urine samples by ELISA. 2) In T2DM patients the prevalence and extent of urinary CN1 increased in parallel with albuminuria (median urinary CN1 0.1 vs 0.2 vs 1.5 mg/24-hr, $p<0.0001$; prevalence: 61 vs. 81 vs. 97% $p<0.05$ in normo-, micro- and macroalbuminuria, respectively). Patients with poor eGFR displayed higher median urinary CN1 concentration rates in comparison to patients with preserved eGFR. Multivariate linear regression analysis revealed that albuminuria and eGFR are the main independent predictors of urinary CN1 ($R^2=0.37$, $p<0.0001$). 3) The correlations between urinary CN1 and albuminuria were also found in spot urine samples of chronic kidney disease patients irrespective of the baseline disease (non-diabetic vs diabetic). 4) MGO affects cell viability in a dose and cell density dependent manner. Based on the low cell number of TUNEL positive cells, MGO-induced cell death is unlikely mediated through apoptosis mechanisms, albeit that apoptosis might contribute to the overall cell death. Carnosine counteracts MGO-mediated toxicity in short and long term MGO exposure conditions. Carnosine but not MGO affects the intracellular redox milieu confirming the anti-oxidant properties of carnosine.