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Attenuation of Renovascular Damage in Zucker Diabetic Fatty Rat by NWT-03, an Egg Protein Hydrolysate with ACE- and DPP4-inhibitory activity.

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Background: As positioned by the American Diabetes Society [2008], medical nutrition therapy is important in preventing diabetes, managing existing diabetes, and preventing, or at least slowing, the rate of development of diabetes complications. This includes secondary and tertiary prevention interventions by healthy nutrition and functional foods for individuals with diabetes and seek to prevent (secondary) or control (tertiary) complications of diabetes. Dipeptidyl peptidase 4 (DPP4) and angiotensin-converting enzyme (ACE) are regarded important target-enzymes in glycemic control and renovascular protection. Here we studied the effect of NWT-03, an egg protein hydrolysate with DPP4- and ACE-inhibitory activity, on renovascular damage in Zucker diabetic fatty rats (ZDF). Comparisons were made to rats treated with vildagliptin, intended as a positive control for the effect of DPP4-inhibition.

Methods: ZDF received 1 g/kg per day NWT-03 (n=9) or 3 mg/kg per day vildagliptin (n=7) from age 10 to 25 weeks via the drinking water, or remained untreated (n=7). Metabolic and renal function parameters were assessed (i.e. blood glucose, insulin, cholesterol, and 24h albumin excretion, amongst others), the kidney removed for histological analysis of glomerulosclerosis and expression of pro-inflammatory/fibrotic markers (RT-PCR and western blot), and the aorta removed for isotonic recordings of endothelium-dependent relaxation (EDR) to acetylcholine (0.01 - 100 µmol/L) in ring preparations pre-constricted with phenylephrine (1 µmol/L) during organ bath studies.

Findings: Hyperinsulinemic and-glycemic ZDF typically developed signs of diabetes type-2 and renovascular damage associated herewith (albuminuria, glomerulosclerosis, and impaired EDR). NWT-03 did not improve metabolic parameters, but neither did vildagliptin despite a 5-fold increase in GLP-1 levels. NWT-03 and vildaglipliptin both reduced renal Il-1β / Il-13 mRNA expression and glomerulosclerosis, but only NWT-03 additionally reduced renal TNFα mRNA / $P22^{phox}$ protein expression and albuminuria, and restored aorta EDR. Indomethacin (dissolved in NaHCO3) added to the organ bath (20 min pre-incubation, 10 µmol/L final concentration) improved EDR, indicating a role of cyclooxygenase (COX-)derived contractile prostanoids opposing relaxation in ZDF. This indomethacin effect was reduced in NWT-03, but not vildagliptin aorta, and coincided with decreased renal COX-1/2 protein expression.

Conclusion and Interpretation: Long-term supplementation with egg protein hydrolysate NWT-03 attenuated renovascular damage in this preclinical rat model of diabetes type 2. Comparative to the DPP4-inhibitor vildagliptin, the results suggest that the effects of NWT-03 in the present study were related to its ACE-inhibitory activity additional to its DPP4-inhibitory properties. Development of protein hydrolysates following a multiple target strategy may be of profit to functional food formulations.

References

American Diabetes Association, Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, *et al*. (2008) Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care 31 Suppl 1: S61-78.