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THE CARDIOVASCULAR & METABOLIC DISEASES EXPERTS

Antidiabetic drugs exendin-4 and metformin prevent renal damages independently of blood glucose reduction in insulin resistant hypersensitive Dahl rats fed a high salt/sucrose diet.

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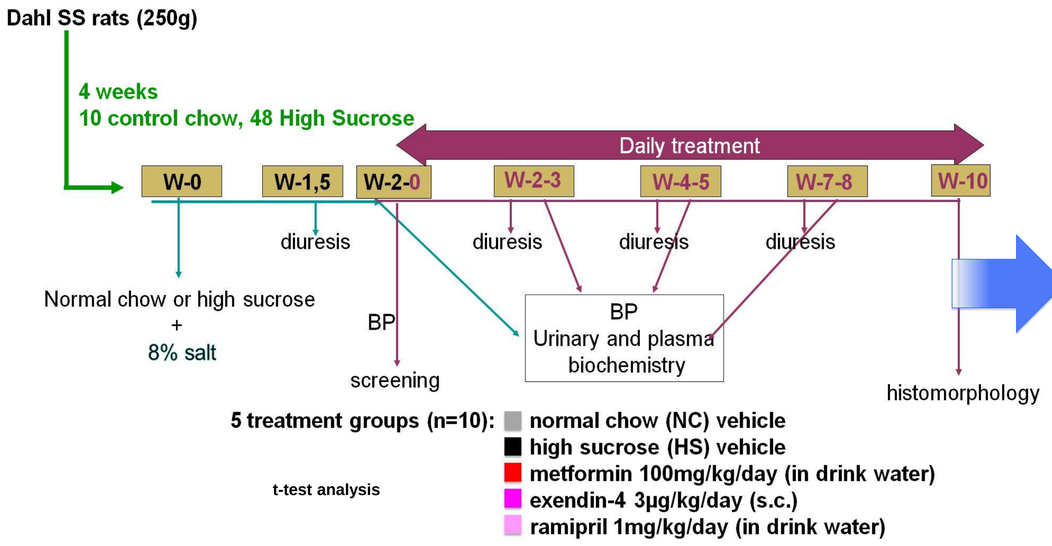
Objectives

Disregarding glucose control, antidiabetic compounds should be tested on micro/macrovascular complications during insulin resistance associated to high blood pressure. The aim of this study was to evaluate the effects of the GLP-1 analog exendin-4 and metformin in high sucrose / 8% salt fed Dahl rats, a model of insulin resistance associated with hypertension leading to renal injury.

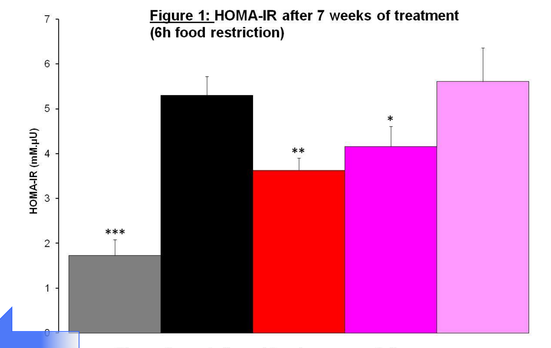


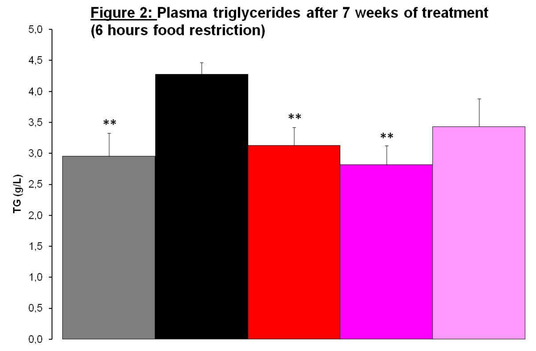
Methods

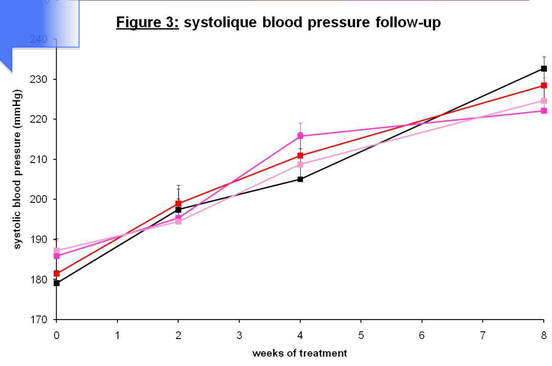
Dahl rats were fed with a normal chow (NC) or a 60% sucrose diet (HS) for 4 weeks. Salt (8%) was then added to both diets for 2 additional weeks. After this diet period, five groups (n=10) were treated for 9 weeks: NC+salt, HS+salt, HS+salt+metformin (100mg/kg/day), HS+salt+exendin-4 (3µg/kg/day) and HS+salt+ramipril (1mg/kg/day, a low dose known to have no anti-hypertensive effect). Plasma metabolites, renal function parameters and arterial blood pressure (tail cuff method) were followed. Histomorphology analysis was performed (PAS for structure analysis and Trichrome Masson for fibrosis analysis).

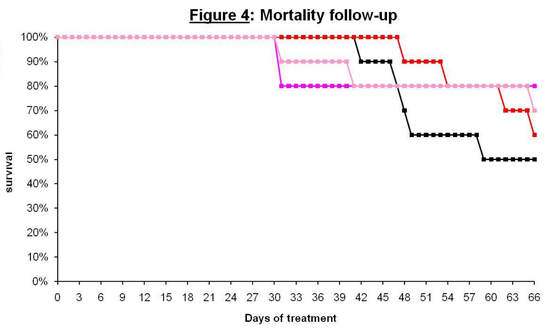
Metabolic syndrome: results

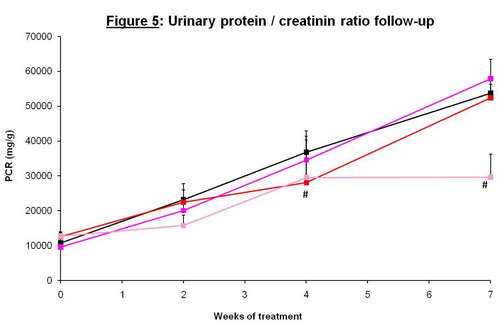
After 13 weeks of HS diet, blood glucose remained normal (105.3±0.9 *vs* 103±3.7mg/dL in NC rats). Metformin and exendin decreased blood glucose respectively by 11% ($p<0.05$) and 8%. HOMA-IR was 3 fold increased in HS rats *vs* NC rats. Metformin and exendin significantly decreased it respectively by 32% and 21% (cf fig.1). Plasma triglycerides were increased in HS rats by 45%. Metformin and exendin decreased it respectively by 27% and 34% (cf fig.2). In conclusion the model displayed insulin resitance associated to hypertriglyceridemia and the main features of this dysmetabolic state are improved by metformin and exendin. Furthermore, the strong hypertension (reaching 230mmHg) was not improved by the treatments (cf fig.3) even if they delayed the mortality (cf fig.4).

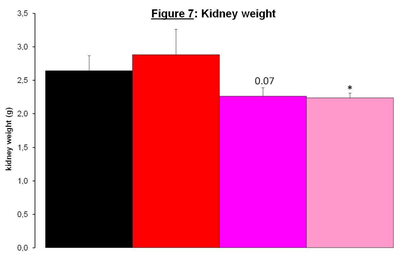


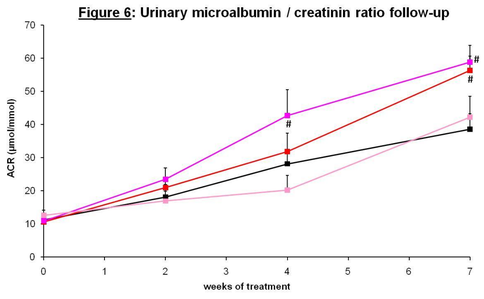


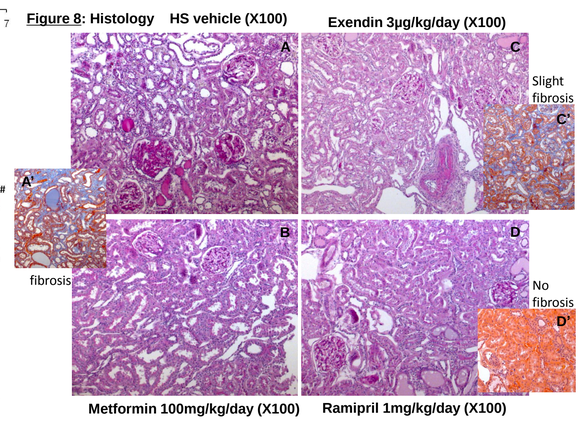












Renal complication: results

After 7 weeks of treatment, ramipril significantly prevented the increase in urinary protein/creatinin ratio (cf fig.5) without affecting urinary microalbumin/creatinin ratio (cf. fig.6). By contrast neither exendin nor metformin prevented the rise in proteinuria. After 10 weeks of treatment, both exendin and ramipril prevented the increase in kidney wet weight by 12% and 15% respectively (cf fig.7). Renal histology (cf fig.8) in HS vehicle rat showed a marked thickening of mesangium with diffuse glomerular sclerosis (A) but also tubular atrophy associated with a patchy interstitial infiltration of mononuclear cells and fibrosis (A'). Metformin only moderately attenuated interstitial infiltration but did not prevented glomerular sclerosis (B). By contrast, exendin (C) clearly decreased the extent of glomerular damages (i.e. glomerular sclerosis), interstitial infiltration, tubular atrophy and fibrosis (C'). Ramipril largely prevented glomerular sclerosis and tubulo-interstitial infiltration, atrophy and fibrosis (D, D').

Conclusion and perspectives

Dahl –salt sensitive rats fed a high sucrose/ high salt diet is of interest to study pre-diabetic nephropathy in association with insulin resistance, hypertension and renal structural damages. Without affecting blood pressure as the main risk factor of nephropathy our data point out the effects of exendin-4 in the prevention of interstitial inflammation leading to progressive glomerular sclerosis and fibrosis. It is concluded that independently of any blood glucose lowering properties an early treatment with exendin-4 during the time course of insulin resistance could prevent renal damages *via* anti-inflammatory/anti fibrosis mechanisms.

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