CHRONIC ADMINISTRATION OF A NEW DUAL NEP/ECE INHIBITOR OR LOSARTAN IMPROVES RENAL FUNCTION IN MICE WITH DIABETIC NEPHROPATHY

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INTRODUCTION

Diabetic nephropathy is the most common cause of end stage renal disease in the USA. It is estimated that approximately 30% of patients with Type 1 or Type 2 diabetes will develop diabetic nephropathy. Endothelins (ET) are potent vasoconstrictors, growth factors and proinflammatory agents and have been implicated in the pathogenesis of diabetic nephropathy whereas atrial natriuretic peptide (ANP) is vasorelaxant, antifibrotic and antiinflammatory. The novel Abbott compound has a dual action to inhibit both endothelin converting enzymes (ECE) and neutral endopeptidase (NEP), an enzyme which degrades natriuretic peptides, like ANP. The dual action of the Abbott compound would therefore reduce ET production and increase ANP, and accordingly may have efficacy in the treatment of diabetic nephropathy.

The novel Abbott NEP/ECE inhibitor was evaluated in streptozotocin (STZ) induced diabetic mice maintained on a high-fat diet in which markers of diabetic nephropathy were observed. The angiotensin receptor antagonist losartan was used as a positive control.

METHODS

C57BL/6J male mice (4-6 weeks of age; Harlan UK) were placed on a high-fat diet (D12492 60% of kcal derived from fat: Research diets, New Jersey, USA) for 3 weeks prior to the administration of STZ 50 mg/kg ip once daily for 5 days. Two weeks later drug treatment was initiated in the diabetic mice and the Abbott compound (30 & 100 mg/kg po) and losartan (10 & 50 mg/kg po) dosed once daily for 120 days. At regular intervals during the study blood pressure was measured (via an indireckt tail cuff method). C0/day food samples collected (after a 4 hour fast) for analysis of HbA1c, plasma glucose, insulin, creatine, urea and animals placed in metabolic cages for 24h with free access to food and water for the collection of urine to determine urine volume, glucose excretion, microalbuminuria and creatinine content. At the study termination, blood was taken for the additional plasma analyses of total cholesterol, TAG, NEFA, glycerol, ketone bodies, ALT and serum cystatin C and tissues were taken for histopathological analysis.

Statistical Analysis: Data adjusted means + SEM (calculated from the residuals of the statistical model). Data were analysed by analysis of covariance (Body weight and BP), or robust regression using baseline values as the covariate followed by Williams’ test for difference from STZ + vehicle.

RESULTS

Fig. 1 Effect of STZ treatment on blood pressure, plasma glucose, insulin and urinary glucose excretion, microalbuminuria and microalbuminuria to creatinine ratio in STZ-induced diabetic C57BL/6J mice

Fig. 2 Effect of Losartan and the Abbott compound on body weight, mean blood pressure and microalbuminuria to creatinine ratio in STZ-induced diabetic C57BL/6J mice

Fig. 3 Effect of Losartan and the Abbott compound on kidney weight, serum cystatin C, plasma ketone bodies and triacylglycerol in STZ-induced diabetic C57BL/6J mice at study termination (Day 120)

SUMMARY AND CONCLUSIONS

- Treatment of high-fat fed C57BL/6J mice with STZ produced the expected phenotype of weight loss, hyperglycaemia, insulinopenia, hyperphagia, polydipsia and glycosuria. A modest but significant microalbuminuria developed and urinary urea, creatinine and protein were all elevated (data not shown).
- Losartan significantly reduced blood pressure, but had no effect on body weight or food intake and did not alter the indices of glycaemic control in plasma or urine. Indicative of an amelioration of diabetic nephropathy, losartan significantly reduced urinary microalbuminuria, kidney weight and increased cystatin C levels.
- The dual NEP/ECE inhibitor produced very similar improvements in diabetic nephropathy to those seen with Losartan. The dual NEP/ECE inhibitor had no sustained effect on body weight and little or no effect on food intake or on the indices of glycaemic control in plasma or urine. However, unlike losartan the dual NEP/ECE inhibitor had no effect on blood pressure.
- Significant improvements in plasma ketone bodies and triacylglycerol were observed with both losartan and the dual NEP/ECE inhibitor and plasma NEFA and cholesterol were also significantly reduced (data not shown).
- The dual NEP/ECE inhibitor significantly reduced the development of diabetic nephropathy and this effect was independent of any action on blood pressure.

REFERENCES