Effect of exercise and rosiglitazone on neprilysin protein expression in db/db diabetic mice
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Background and aim: Diabetic nephropathy (DN) is one among the main microvascular complications of uncontrolled diabetes, which eventually lead to end stage renal disease. Alteration in renin-angiotensin system (RAS) is considered to be the primary cause underlying the disease process. Hyperglycemia activates RAS and causes an increase in the level of Angiotensin II (Ang II). Emerging evidence suggests that the deleterious effects of Ang II could be opposed by the formation of Ang (1-7), partly generated by the actions of Angiotensin converting enzyme 2 (ACE2) and neprilysin (NEP). NEP is a neutral endopeptidase, a member of zinc-containing metallopeptidase group, which plays a crucial role in the formation of Ang (1-7) from Ang I. Our previous studies reported that renal NEP is decreased in diabetic animal models. We tested the hypothesis that exercise training or rosiglitazone treatment improve glucose homeostasis, up regulate renal NEP protein expression and improve albuminuria in diabetic db/db mice. We also hypothesized that changes in renal NEP could be detected in the urine and be used as an index for intrarenal status and progression of chronic kidney disease.

Materials and methods: Seven weeks old lean and db/db male mice were subjected either to exercise training or rosiglitazone treatment (20 mg/kg/day) for 10 weeks. Exercise groups were run on a mouse forced exercise walking wheel system at a speed of 8 m/min for 1 hour a day, 7 days a week. Weekly monitoring included 24-hr urinary volume, albumin, creatinine and blood glucose.

Results: db/db mice demonstrated hyperglycemia (p<0.0001 Vs lean controls), albuminuria (p<0.0001 Vs lean controls) and decreased NEP levels in the kidney. Exercise training or rosiglitazone treatment significantly attenuated hyperglycemia (p<0.0001 Vs untreated db/db mice) and reduced urinary albumin excretion (p<0.001 Vs untreated db/db mice). Improvements were seen as early as 2 weeks after the initiation of treatment. In addition, db/db mice subjected to exercise or rosiglitazone treatment demonstrated a significant increase in renal and urinary NEP protein expression compared to untreated db/db mice.

Conclusion: Exercise training and rosiglitazone treatment normalized hyperglycemia and up regulated neprilysin levels in the kidney of db/db mice. Augmentation of renal neprilysin could have a pivotal role in the pathogenesis of diabetic nephropathy. The data suggest that urinary NEP reflects intrarenal RAS status in chronic kidney disease and may be used as an early marker of diabetic nephropathy.

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