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AdipoRon Ameliorates Diabetic Nephropathy through Activation of Intracellular Ca++-AMPKa-PPARa in Podocytes and Type 2 db/db Mice

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Objectives : Adiponectin is produced by adipose tissue and low levels of adiponecin correlate with albuminuria in diabetic nephropathy. Its' protective effects on diabetic nephropathy are exhibited through the activation of AMPK-PPARα pathway by binding to adiponectin receptors, AdipoR1 and AdipoR2. We investigated the possible role of orally active synthetic small-molecule adiponectin agonist, adipoRon in the view of prevention and development against lipotoxicity in diabetic nephropathy in type 2 diabetic mice model and murine podocytes.

Methods : Male db/db mice and db/m controls were fed either a regular diet chow or a diet containing AdipoRon (30 mg/kg/day p.o. for 4 weeks from 17 to 20 weeks of age). Serum, urine and renal tissue specimen were obtained to analyze for changes in metabolic parameters, relevant molecular levels and their association with regard to structural influence

Results : Diabetes-induced albuminuria, GBM thickening, foot process widening, nephrin loss, glomerular matrix expansions, and intrarenal inflammation were relieved by adipoRon treatment. The protective role of adipoRon seems to occur through a direct activation of both intrarenal AdipoR1 and -R2 which in turn increases the expression of CaMKK -phospho-Ser431LKB1-phospho-Thr172AMPK-PPARα independently of systemic levels of adiponectin. Subsequent increment in the expression of PGC-1α, phospho-Ser75ACC, phospho-Ser1177eNOS-NO and decreased level of SREBP-1c promoted reduction in lipid-induced oxidative stress. In murine podocytes cultured in high-glucose media, adipoRon remarkably increased AdipoR1 and -R2 expression and intracellular Ca++, which subsequently activated phospho-Ser431LKB1-phospho-Thr172AMPK-PPARα and their downstream signals, including phospho-Ser75ACC, phospho-Ser1177eNOS-NO, resulting in decreased oxidative stress-induced apoptosis.

Conclusions : Our study suggests adipoRon as a promising therapeutic agent of diabetic nephropathy via ameliorating podocyte damage by means of reduced lipotoxicity-induced oxidative stress.

Keywords : Diabetic nephropathy, AdipoRon, AMPK, Lipotoxicity