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The effect of PGC1a activators on diabetic tubulopathy

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Background: While there is emerging evidence for defective mitochondrial function in diabetic nephropathy, the role of mitochondria in renal disease is unclear. PGC1a is the master mitochondrial regulator gene and was reported to be expressed lower in diabetic kidneys compared to normal kidneys in human and mice. Proximal tubules exclusively use ATP as their energy source to filtrate or reabsorb substances continuously, and tubular fibrosis seems to be a common pathway in which all chronic kidney diseases culminate including diabetic nephropathy. Therefore it is important to understand the mechanism underlying mitochondrial dysfunction in renal tubule cells in diabetes.
Methods: We evaluated the change of mitochondrial biogenesis in diabetic nephropathy using HKC-8 cells (human proximal tubular cells) and primary cultured mice tubular cells (mice RTECs). Metformin and AICAR were used to activate PGC1a under high glucose (HG) ambience or a diabetic state. Streptozotocin induced diabetic mice were analyzed to elucidate the effect of PGC1a activation on diabetic tubulopathy.
Results: HKC-8 or mice RTECs subjected to HG exhibited a downregulation of PGC1a accompanied by mitochondrial fragmentation and depolarization, low mitochondrial DNA copy, and inhibition of mitophagy. Futhermore, increased reactive oxygen species which were generated from mitochondria coincide with elevated TGF beta expression and EMT (epithelial-mesenchymal transition) markers in renal tubular cells under HG ambience. PGC1a activation using metformin or AICAR restored the effects of HG in HKC-8 and mice RTECs. Treatment with metformin or AICAR increased PGC1a expression, attenuated tubular damage in diabetic mice.
Conclusion: We demonstrate PGC1a activation in cell and mouse model of diabetic nephropathy which exerts a renoprotective phenotype by attenuating tubular injury.

Keywords: diabetes, fibrosis, mitochondria, tubule