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DIABETIC NEPHROPATHY

HIF activation in prevention of diabetic nephropathy

Diabetic nephropathy is a major cause of end-stage renal disease; however, approaches to effectively prevent or slow the progression of this disease are lacking. New findings demonstrate that activation of hypoxia-inducible transcription factors (HIFs) prevents diabetes-induced alterations in renal oxygen metabolism and might prevent or ameliorate the progression of diabetic nephropathy.

Tissue hypoxia is thought to have an essential role in the pathogenesis of diabetic nephropathy. Kidneys of diabetic rats develop pronounced hypoxia, attributed at least in part to uncoupling of oxidative phosphorylation and increased oxygen consumption. According to researcher Fredrik Palm, these changes would be expected to activate HIF, which would act to mount an antioxidant defense by inducing the transcription of hypoxia-responsive genes. "We were puzzled as to why HIF was not activated, and decided to collaborate with Masaomi Nangaku to study what would happen if HIF was activated early during disease development," explains Palm.

Palm and colleagues induced chronic HIF activation in nondiabetic and streptozotocin-induced diabetic rats by adding cobalt chloride to their drinking water. "This experimental model of type 1 diabetes mellitus presents all the clinical hallmarks of early diabetic nephropathy, such as glomerular hyperfiltration, kidney hypertrophy, albuminuria and tubulointerstitial fibrosis," says Palm. "Cobalt chloride activates HIF by preventing degradation of the HIF α-subunit, resulting in pronounced and sustained HIF activation."

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The researchers found that administration of cobalt chloride prevented intrarenal hypoxia in diabetic rats by attenuating the diabetes-induced increase in oxygen consumption. This effect was accompanied by normalization of tubular sodium transport and mitochondrial respiration. Activation of HIF also reduced glomerular filtration rate, proteinuria and tubulointerstitial injury compared with untreated diabetic rats.

Palm and colleagues then investigated the potential involvement of oxidative stress by administering the superoxide dismutase mimetic tempol to cobalt-chloride-treated and untreated diabetic rats. They found that tempol normalized the diabetes-induced renal hypoxia in untreated diabetic rats, but had no effect in cobalt-chloride-treated diabetic rats, suggesting that HIF activation improved oxidative stress status.

The researchers are planning further studies to assess whether HIF activation can reverse established alterations in kidney function. "Pharmacologic interventions are currently only initiated once a patient presents with signs of diabetic nephropathy," explains Palm. "We need to know if HIF activation is as successful in reversing disease progression as it seems to be in preventing disease onset."

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