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DIABETES

Urea inhibits insulin secretion in CKD

Insulin resistance is common in patients with chronic kidney disease (CKD) but the contribution of β-cell dysfunction in this setting is unclear. Researchers now show that the uraemic metabolite, urea, acts directly on pancreatic β cells to impair insulin secretion.

Accumulating evidence suggests that urea can induce toxicity through several mechanisms including oxidative stress and the induction of post-translational modifications, such as *O*-GlcNAcylation. These findings, together with the understanding that persistent oxidative stress causes β-cell dysfunction and that *O*-GlcNAcylation can impair insulin secretion, led Vincent Poitout and colleagues to assess the effects of urea on pancreatic β-cell function. "We tested our hypothesis in three preclinical models: a mouse model of CKD induced by 5/6 nephrectomy; a mouse model of elevated circulating urea levels induced by urea feeding; and isolated islets exposed to elevated levels of urea," says Poitout.

> "Urea at concentrations observed in moderate CKD directly impairs pancreatic β-cell function"

In all three models the researchers observed a defect in insulin secretion induced by urea. Mice with CKD had elevated levels of circulating urea and exhibited defective insulin secretion in response to glucose. Normal mice fed urea and isolated islets treated with urea displayed similar defects in insulin secretion, suggesting a direct effect. To investigate the underlying mechanisms, the researchers evaluated oxidative stress and protein *O*-GlcNAcylation. Oxidative stress was increased in islets from mice with CKD and treatment of these mice with an antioxidant restored insulin secretion.

Assessment of pancreatic sections from 5/6 nephrectomized mice showed increased *O*-GlcNAcylation of proteins in islets, with similar findings observed in pancreatic sections from nondiabetic patients with CKD. Treatment of these mice with the antioxidant prevented the increase in islet protein *O*-GlcNAcylation. In addition, inhibition of *O*-GlcNAcylation restored insulin secretion in 5/6 nephrectomized mice and in isolated islets. "We identified that the defect induced by urea resulted from reduced glycolytic flux, specifically resulting from *O*-GlcNAcylation of the glycolytic enzyme, phosphofructokinase-1," notes Poitout. Blocking *O*-GlcNAcylation prevented the inhibitory effect of urea on phosphofructokinase-1 activity and restored glucose utilization in islets exposed to urea.

"Our findings suggest that in addition to diabetes causing CKD, that conversely CKD might cause diabetes," says Poitout. "Clearly this link remains to be established but if confirmed, our mechanistic studies suggest that therapeutic interventions aimed at mitigating oxidative stress might be beneficial in preserving insulin secretion in these patients."

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