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PERSPECTIVES

Strategies in diabetic nephropathy: apelin is making its way

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Diabetic nephropathy, one of the major microvascular complications of diabetes, is a leading cause of end-stage renal disease. This pathological entity is morphologically characterized by glomerular hypertrophy and thickening of tubular basal membranes, in association with progressive mesangial expansion. As the disease progresses, clinical manifestations include albuminuria, hypertension and declining glomerular filtration rate. Experimental and clinical studies have demonstrated the significant role of various inflammatory molecules in the setting of diabetic nephropathy, including acute phase reactants, inflammatory cytokines, adhesion molecules and chemokines (for review see Navarro-González & Mora-Fernández, 2008). Current treatment approaches include renin–angiotensin–aldosterone system inhibition, dietary sodium restriction and diuretic therapy. Nevertheless, new strategies are needed to slow down progression of diabetic nephropathy. In this issue of *The Journal of Physiology*, Chen and colleagues (2014) examined a possible mechanism involved in the beneficial effects of apelin-13 on experimental diabetic nephropathy.

The adipokine apelin is a peptide known as the endogenous ligand of the G-protein-coupled receptor APJ. Apelin-13, the most active member of the apelin group, has emerged as a beneficial peptide with anti-obesity and antidiabetic properties, and thus, as a promising therapeutic target in metabolic disorders (for review see Castan-Laurell *et al.* 2011). Recently, Day *et al.* (2013) showed, for the first time, that apelin-13 exerts renoprotective effects in diabetic FVB/Ove26 mice. These authors observed that the whole-kidney and glomerular hypertrophy, as well as renal inflammation, was inhibited after treatment with apelin-13. These effects correlated with upregulation of the antioxidant catalase (Day *et al.* 2013).

Chen *et al.* (2014) have added an important contribution by investigating the role of histone acetylation in apelin-induced effects on the diabetic kidney. Experiments carried out by these investigators demonstrated that apelin-13 inhibits histone hyperacetylation induced by either diabetes in the Akita mouse or high glucose concentration in cultured mesangial cells. This effect is mediated by selective upregulation of the expression of histone deacetylase HDAC1 (Chen *et al.* 2014). It is known that histone acetylation levels are regulated through the opposing activities of histone acetyltransferases and deacetylases, and that histone acetylation–deacetylation equilibrium plays a critical role in the control of gene expression. The participation of histone acetylation in the pathophysiology of diabetic nephropathy is still not well understood. As Chen *et al.* (2014) explain in their article (see their *Discussion*), previous studies demonstrated that histone hyperacetylation induces overexpression of inflammation-associated genes; and on the contrary, evidence has been accumulating that HDAC inhibitors exert renoprotective effects on the diabetic kidney. These controversies remain to be resolved. Probably, the identification of the individual transacetylase/deacetylase enzyme isoform involved in each case could contribute to elucidation of this issue.

In the studies performed by Chen *et al.* (2014), the levels of two HDACs (HDAC1 and HDAC2) and two histone acetyltransferases (PCAF and GCN5) were determined. The expression level of only HDAC1 was affected by apelin-13 treatment in Akita mouse kidneys. In parallel with the diminution in histone acetylation levels, apelin-13 significantly reduced the diabetes-induced increase in renal monocyte chemotactic protein 1, intercellular adhesion molecule 1, inducible nitric oxide synthase and p65 [the active form of the transcriptional subunit of nuclear factor-κB (NF-κB)] phosphorylation levels of Akita mice (Chen *et al.* 2014). Interestingly, Ashburner *et al.* (2001) demonstrated that HDAC1 expression represses tumour necrosis factor-induced NF-κB-dependent gene expression. Consistent with this, the authors showed a direct association of HDAC1 with the Rel homology domain of p65. In diabetic nephropathy, an increase in the NF-κB p65 subunit and NF-κB–DNA binding depends on Toll-like receptor protein 2 (TLR2) upregulation (Mudaliar *et al.* 2013). In this connection, trichostatin A, a histone deacetylase inhibitor, upregulates the expression of both TLR2 mRNA and protein in the human THP-1 cell line (Li *et al.* 2013). Taking this information into account, it could be interesting to investigate whether the apelin-induced anti-inflammatory effects in diabetic nephropathy are mediated by direct association of the increased HDAC with p65 and/or TLR2 downregulation.

In summary, the recently described effects of apelin on whole-body metabolism (for review see Castan-Laurell *et al.* 2011) and, especially, on the diabetic kidney (Day *et al.* 2013; Chen *et al.* 2014) lead to the proposal that apelin may be a novel therapeutic tool for treatment of diabetic nephropathy. The investigation by Chen *et al.* (2014) showed that apelin-13 alters the histone acetylation–deacetylation balance, exposing a wide spectrum of potential targets for the beneficial effects of this adipokine on diabetes-induced renal injury. Further investigations focused on elucidation of these mechanisms could contribute to evaluation of the risk–benefit ratio of apelin-13 treatment.

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