DIABETIC NEPHROPATHY

Renoprotective effects of angiotensin 1–7

In new research, Gavin Oudit and colleagues report that angiotensin (Ang) 1–7 ameliorates diabetic nephropathy by reducing renal fibrosis, oxidative stress, inflammation and lipotoxicity.

Activation of the renin–angiotensin system and generation of Ang II has a key role in the pathogenesis of diabetic nephropathy. Although Ang 1–7 is known to counteract the effects of Ang II and is renoprotective in this disease, the mechanisms are not fully elucidated.

To investigate how Ang 1–7 exerts its beneficial effects on the diabetic kidney, the researchers used *db/db* mice—a well-accepted genetic model of type 2 diabetes mellitus. “We studied these animals at 6 months of age, at which stage the nephropathy is well established,” explains Oudit.

The researchers found that *db/db* mice had increased kidney and body weight, mesangial size and urinary albumin excretion compared with wild-type controls. Ang 1–7 treatment (administered for 28 days using subcutaneous micro-osmotic pumps) increased renal Ang 1–7 levels, significantly decreased kidney (but not body) weight, ameliorated mesangial expansion and normalized urinary albumin excretion.

Renal fibrosis—a hallmark of diabetic nephropathy—and levels of phosphorylated STAT3, which has a role in the development of fibrosis, were also increased in *db/db* mice compared with wild-type controls. Both features were significantly reduced after Ang 1–7 treatment.

As oxidative stress, lipotoxicity and inflammation are involved

in the progression of diabetic nephropathy, the researchers also investigated the effects of Ang 1–7 on levels of reactive oxygen species (ROS), lipids and inflammation in *db/db* mice. They showed that Ang 1–7 treatment reduced ROS production, NADPH oxidase activity and lipid accumulation in the kidneys and decreased adipocyte size, macrophage infiltration and fibrosis in the perirenal adipose tissue of these mice.

“The dramatic renoprotective effects of Ang 1–7 in our murine model were the result of reduced inflammation and lipotoxicity,” concludes Oudit. Consistent with these findings, his research group recently showed that Ang 1–7 protects against diabetic cardiomyopathy in *db/db* mice via similar mechanisms.

Oudit and colleagues believe that Ang 1–7 therapy could be a promising new treatment for diabetic nephropathy. “We need to enhance Ang 1–7 levels in diabetic kidneys,” says Oudit. “The use of stable analogues of Ang 1–7 will be particularly attractive in this setting, certainly enhancing the action of angiotensin-converting enzyme 2, which cleaves Ang II into Ang 1–7, is also a worthwhile consideration.”

Ellen F. Carney

Original article Mori, J. *et al.* Angiotensin 1–7 mediates renoprotection against diabetic nephropathy by reducing oxidative stress, inflammation and lipotoxicity. *Am. J. Physiol. Renal Physiol.* doi:10.1152/ajprenal.00655.2013

Further reading Mori, J. *et al.* Angiotensin 1–7 ameliorates diabetic cardiomyopathy and diastolic dysfunction in *db/db* mice by reducing lipotoxicity and inflammation. *Circ. Heart Fail.* doi:10.1161/CIRCHEARTFAILURE.113.000672