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Mechanisms of Adiponectin Action: Implication of Adiponectin Receptor Agonism in Diabetic Kidney Disease

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Adiponectin, an adipokine secreted by adipocytes, exerts favorable effects in the milieu of diabetes and metabolic syndrome through its anti-inflammatory, antifibrotic, and antioxidant effects. It mediates fatty acid metabolism by inducing AMP-activated protein kinase (AMPK) phosphorylation and increasing peroxisome proliferative-activated receptor (PPAR)-α expression through adiponectin receptor (AdipoR)1 and AdipoR2, respectively, which in turn activate PPAR gamma coactivator 1 alpha (PGC-1α), increase the phosphorylation of acyl CoA oxidase, and upregulate the uncoupling proteins involved in energy consumption. Moreover, adiponectin potently stimulates ceramidase activity associated with its two receptors and enhances ceramide catabolism and the formation of its anti-apoptotic metabolite, sphingosine 1 phosphate (S1P), independently of AMPK. Low circulating adiponectin levels in obese patients with a risk of insulin resistance, type 2 diabetes, and cardiovascular diseases, and increased adiponectin expression in the state of albuminuria suggest a protective and compensatory role for adiponectin in mitigating further renal injury during the development of overt diabetic kidney disease (DKD). Mechanism of action for AdipoRon, an orally active synthetic adiponectin receptor agonist as a promising drug for restoration of DKD without inducing systemic adverse effects, is explored. Its renoprotective role against lipotoxicity and oxidative stress by enhancing the AMPK/PPARα pathway and ceramidase activity through AdipoRs is revealed herein.