Reno-protective effect of NECA in diabetic nephropathy: implication of IL-18 and ICAM-1

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Abstract
Diabetic nephropathy (DN) remains the most common cause of end-stage renal disease. Although, adenosine acts as a local modulator with a cytoprotective function, extracellular adenosine usually disappears quickly due to a rapid uptake into adjacent cells. Therefore, we investigated the effect of 5′-(N-ethylcarboxamido)-adenosine (NECA), a stable, nonselective adenosine receptor agonist, on diabetes-induced increases in inflammatory cytokines and adhesion molecules. The enhancement of adenosine receptor action by NECA was examined in the renal tissues of rats with streptozotocin-induced diabetes. Daily i.p. injections of NECA at 0.3 mg/kg/day were given to rats, over a two-week period, six weeks after the induction of diabetes. Morphological changes were assessed in kidney sections. Oxidative stress was examined by measuring tissue malondialdehyde. Gene expression of interleukin (IL)-18, tumor necrosis factor (TNF)-α and intercellular adhesion molecule (ICAM)-1 was measured by real-time PCR. Activation of cellular, proapoptotic pathways was demonstrated by measuring the activation of c-Jun NH(2)-terminal kinases (JNK)-mitogen-activated-protein kinase (MAPK). We found that diabetes-induced malondialdehyde formation activated the production of IL-18, TNF-α and ICAM-1, which, in turn, activated pro-apoptotic pathways in diabetic rats. Treatment with NECA protected diabetic rats by exerting hypoglycemic and antioxidant effects as well as reducing gene expression of proinflammatory cytokines. These effects were associated with deactivation of JNK-MAPK. In addition, diabetic rats treated with NECA showed mild glomerular effects and vacuolation of tubular epithelium. We can conclude that activation of adenosine receptors is a potential therapeutic target in DN. NECA acts via multiple mechanisms including: reducing diabetes-induced oxidative stress, inhibiting gene expression of IL-18, TNF-α and ICAM-1, and blocking activation of the JNK-MAPK pathway.