

Role of The Lallikrein-Kinin System in Diabetic Retinopathy

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In diabetic patients bearing retinopathy, advanced-glycation end-products, cytokines, chemokines and oxidative stress trigger an inflammatory response within retinal vasculature featured by increased vascular permeability, loss of capillaries and ultimately angiogenesis. Since it has been shown that KKS activation played a key role in the development of inflammation, vascular dysfunction, leukostasis and edema following brain injury, we and others thought to investigate the role of KKS in the development of diabetic retinopathy. KKS includes tissue and plasma kallikrein (PK) and their respective substrate low- and high-molecular weight kininogen, which upon activation produce bradykinin (BK) and kallidin (KD), two potent and selective B₂ receptor agonists. Endogenous cleavage of BK and KD by carboxypeptidase-N generates the B₁ receptor agonists, des-Arg⁹-BK and des-Arg¹⁰-KD, respectively. Components of the KKS have been found in the vitreous of patients with an exudative diabetic retinopathy and carbonic anhydrase-I-induced retinal edema in rats was found to be mediated by activation of KKS. In streptozotocin (STZ)-induced diabetic rats, intravitreal injection of PK induced retinal edema and hemorrhage and treatment of STZ-rats with a small molecule PK inhibitor significantly inhibited the development of retinal edema. On another hand, kinin B₁ receptors which are maintained at low level or absent under normal physiological conditions are markedly expressed in the retinal vasculature of STZ-diabetic rats. Since B₁ receptor peptide antagonists, des-Arg⁹-[Leu⁸]-BK and R-715, reduced or abolished retinal edema in diabetic rats but were not suitable as drug candidates, we developed a potent and selective non-peptide B₁ receptor antagonist, FV-60135-02. We showed that topical instillation of FV-60135-02, started 7 days after initiation of diabetes abolished retinal vascular leakage. In addition, diabetes-associated increase of retinal mRNA levels of B₁R, B₂R, iNOS, eNOS, COX-2, ICAM-1, VEGF α , VEGF receptor type 2, IL-1 β and HIF-1 α was reversed by FV-60135-02. Leukostasis and leukocyte infiltration were significantly increased in the retina of diabetic rats and again this was fully inhibited by FV-60135-02. Taken together, these data point towards a major role of KKS activation in the development of diabetic retinal edema and leukostasis. Thus, inhibition of kinin production pathways or blockade of kinin B₁ receptors should be regarded as innovative and promising therapeutic approaches of diabetic retinopathy.