

ENDOGENOUS ANGIOGENIC INHIBITORS IN DIABETIC MACULAR EDEMA IN DIABETIC RETINOPATHY

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Increased retina vascular permeability is associated with diabetic retinopathy and other ocular diseases. Previous studies have demonstrated that a number of peptide angiogenic inhibitors, such as pigment epithelium-derived factor (PEDF), kallistatin and angiostatin, are present at high levels in ocular tissues, including the retina and vitreous. Decreased levels of PEDF, angiostatin and kallistatin in the retina and vitreous are associated with diabetic retinopathy. Recently, we have found that these endogenous angiogenic inhibitors also contribute to the regulation of retinal vascular permeability. As shown by the Evans blue-albumin leakage method, both the streptozotocin (STZ)-induced diabetes and oxygen-induced retinopathy (OIR) Brown Norway rat models developed significant vascular hyper-permeability in the retina. The hyper-permeability in these rat models were confirmed by measuring the leakage of fluorescein-labeled albumin into the retina. PEDF, angiostatin and kallistatin significantly reduced vascular permeability in the retina of STZ-diabetic rats and in OIR rats. These effects appeared to be dependent on the dose and time of the administration of these peptides. The effects on vascular permeability required only less than one-tenth of the doses needed for their anti-angiogenic activities, suggesting that the effects on vascular permeability are independent on their anti-angiogenic activities. In contrast, these angiogenic inhibitors did not affect vascular permeability in normal retina. These results suggest that these endogenous angiogenic inhibitors contribute to the maintenance of the integrity of the blood-retina barrier, and reduced levels of these peptides in diabetic retina may contribute to the development of vascular hyper-permeability and diabetic macular edema. These results also suggest that PEDF, kallistatin and angiostatin may have therapeutic potential in the treatment of ocular diseases associated with retinal vascular hyper-permeability.