

Inhibitors of Advanced Glycation Endproducts (AGEs) in the Treatment of Diabetic Retinopathy

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The formation of advanced glycation endproducts (AGEs) is a natural function of ageing but accumulation of these adducts is accelerated in diabetes and this may represent a key pathophysiological event in retinal disease. Often in association with the receptor for AGEs (RAGE), AGEs are linked to neurodegeneration and irreversible changes in the extracellular matrix. They also induce vascular dysfunction and illicit chronic pro-inflammatory signalling events. Since many cells and tissues of the eye are profoundly influenced by such processes, it is fitting that advanced glycation and RAGE are now receiving considerable attention as a possible modulator in visual disorders.

This lecture reviews ongoing research into novel therapeutic approaches that prevent accumulation of AGEs or block RAGE and thereby prevent diabetic retinopathy. Particular emphasis will be placed on the progressive retinal vascular and neuroglial dysfunction occurring in diabetes and how this is linked to aberrant pathways that evoke AGE formation. Using data obtained from a range of complementary in vitro and in vivo approaches, it will be demonstrated that a range of pathogenic responses within the retina are linked to AGE adduct formation and pro-inflammatory signalling via RAGE. We have established robust and clinically-relevant microvascular and neuroglial lesions that signal progression of retinopathy in diabetic animal models. Using new, specific AGE-inhibitors we demonstrate that these key parameters such as acellular capillary formation, infiltration and activation of CD11b positive microglia and various pro-inflammatory pathways can be prevented. Furthermore, RAGE signalling can be linked to many of these responses and blockade of this receptor may be a new and exciting target to prevent progression of diabetic retinopathy.

The lecture will introduce novel data in the context of the AGE hypothesis but will also highlight important new pathogenic pathways that contribute to diabetic retinopathy. Possibilities for therapeutic intervention will also be discussed.