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Advanced glycation end products, their receptors and diabetic angiopathy.

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The role of chronic hyperglycemia in the development of diabetic microvascular complications and in neuropathy has been clearly established by intervention studies. However, the biochemical or cellular links between elevated blood glucose levels, and the vascular lesions remain incompletely understood. This review focuses on the consequences of hyperglycemia on the formation of advanced glycation end-products (AGEs), and on the role of AGEs and of their specific receptors (RAGE) in the functional and anatomical alterations of the vascular wall. AGEs are formed during the Maillard reaction by the binding of aldoses on free NH(2) groups of proteins, which, after a cascade of molecular rearrangements, result in molecules of brown color and specific fluorescence. Experimental studies have indicated that the binding of AGEs to RAGE activates cells, particularly monocytes and endothelial cells. Activated endothelial cells produce cytokines, and express adhesion molecules and tissue factor. The role of AGEs in increased oxidative stress, and in the functional alterations in vascular tone control observed in diabetes, in part related to a reduction in nitric oxide, is also discussed. The microvascular retinal, glomerular and nerve lesions induced by experimental diabetes in animals are prevented by an inhibitor of AGEs formation, aminoguanidine. The administration in diabetic animals of recombinant RAGE, which hinders AGEs-RAGE interaction, prevents hyperpermeability and vascular lesions. These data suggest a central role of AGEs and RAGE in the development of chronic complications of diabetes.

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