

Glycation, Inflammation, and RAGE

A Scaffold for the Macrovascular Complications of Diabetes and Beyond

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Abstract—The cardiovascular complications of diabetes represent the leading cause of morbidity and mortality in affected subjects. The impact of hyperglycemia may be both direct and indirect: indirect consequences of elevated blood glucose lead to generation of advanced glycation endproducts, the products of nonenzymatic glycation/oxidation of proteins/ lipids that accumulate in the vessel wall, and are signal transduction ligands for Receptor for AGE (RAGE). Although enhanced in diabetes, AGE accumulation also occurs in euglycemia and aging, albeit to lower degrees, driven by oxidant stress and inflammation. In hyperglycemia, production of 3-deoxyglucosone, at least in part via the polyol pathway, provides an amplification loop to sustain AGE generation, oxidant stress, and vascular activation. Furthermore, recruitment of inflammatory cells bearing S100/calgranulins, also ligands for RAGE, augments vascular dysfunction. We hypothesize that activation of RAGE is a final common pathway that transduces signals from these diverse biochemical and molecular species, leading to cardiovascular perturbation. Ultimately, these pathways synergize to construct a scaffold on which the complications of diabetes in the vasculature and heart may be built. We propose that antagonism of RAGE will provide a unique means to dismantle this scaffold and, thereby, suppress initiation/ progression of vascular disease and cardiac dysfunction that accompany diabetes and aging. (*Circ Res.* 2003;93:1159- 1169.)

Key Words: receptors _ glycooxidation _ hyperglycemia _ polyol pathway _ vascular disease