

Protein Glycation, Diabetes, and Aging

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ABSTRACT

Biological amines react with reducing sugars to form a complex family of rearranged and dehydrated covalent adducts that are often yellow-brown and/or fluorescent and include many crosslinked structures. Food chemists have long studied this process as a source of flavor, color, and texture changes in cooked, processed, and stored foods. During the 1970s and 1980s, it was realized that this process, called the Maillard reaction or advanced glycation, also occurs slowly in vivo. Advanced glycation endproducts (AGES) that form are implicated, causing the complications of diabetes and aging, primarily via adventitious and crosslinking of proteins. Long-lived proteins such as structural collagen and lens crystallins particularly are implicated as pathogenic targets of AGE processes, AGE formation in vascular wall collagen appears to be an especially deleterious event, causing crosslinking of collagen molecules to each other and to circulating proteins. This leads to plaque formation, basement membrane thickening, and loss of vascular elasticity. The chemistry of these later-stage, glycation-derived crosslinks is still incompletely understood but, based on the hypothesis that AGE formation involves reactive carbonyl groups, the authors introduced the carbonyl reagent aminoguanidine hydrochloride as an inhibitor of AGE formation in vivo in the mid 1980s. Subsequent studies by many researchers have shown the effectiveness of aminoguanidine in slowing or preventing a wide range of complications of diabetes and aging in animals and, recently, in humans. Since, the authors have developed a new class of agents, exemplified by 4,5-dimethyl-3-phenacylthiazolium chloride (DPTC), which can chemically break already-formed AGE protein-protein crosslinks. These agents are based on a new theory of AGE crosslinking that postulates that α -dicarbonyl structures are present in AGE protein-protein crosslinks. In studies in aged animals, DPTC has been shown to be capable of reverting indices of vascular compliance to levels seen in younger animals. Human clinical trials are underway.