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Editorial

Relationship Between Advanced Glycation End-Products and Cardiovascular Disease

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Advanced glycation end-products (AGEs) are produced by a non-enzymatic reaction between sugar and amino groups of proteins, lipids and nucleic acids in both diabetic and non-diabetic conditions (1). AGEs can be classified based on chemical structure (fluorescent or non-fluorescent) or molecular weight (low or high molecular weight) (2).

Extracellular and intracellular accumulation of AGEs trigger their pathological effects via two pathways: disruption of protein function and activation of receptor for AGE (RAGE) (3). It has been established that AGE accumulation contributes to a wide range of diseases including metabolic, reproductive, neurodegenerative and cardiovascular (4).

Recent reports have revealed a relationship between high levels of AGEs and cardiovascular disorders. It has also been found that there are a significant correlation between diabetes and increased risk of developing cardiovascular disease (5, 6). This evidence suggests the important role of AGEs in the cardiovascular complications, so it is necessary to detect molecular mechanisms of AGEs that contribute to the pathogenesis of cardiovascular diseases.

AGE-induced crosslinking and glycation of extracellular and intracellular proteins such as collagen, elastin, laminin and Ca^{2+} homeostasis proteins (sarco/endoplasmic reticulum Ca^{2+}-ATPase) lead to diastolic dysfunction and cardiomyocyte contraction (7).

By using its receptor, i.e., RAGE, AGE activates signaling pathways that produce pro-inflammatory cytokines (IL-6, TNF-α, TGF-β), vascular adhesion molecules (VCAM-1, ICAM-1, endothelin-1), lysyl oxidase and the vasoconstrictor protein, and lead to oxidative stress, which in turn results in endothelial damage (4). AGEs also upregulate profilin-1 expression that leads to endothelial hyperpermeability (8).

AGE-RAGE signaling in vascular smooth muscle cells is involved in the proliferation and apoptosis of these cells via the ERK/MAPK and Akt/mTOR pathways, and contributes to atherosclerosis (9). AGE-induced RAGE activation results in MMP2/9 activation, decreased activity of myocardin (a protein responsible for smooth muscle cell differentiation) and vascular calcification (10).

AGEs increase both the activation and the aggregation of platelets by upregulating adhesion molecules such as P-selectin and platelet endothelial cell adhesion molecule 1 (PECAM1), and platelet glycoproteins as well as increasing the activities of cyclooxygenase and thromboxane A2 (11).

Conclusion

Taken together, AGEs should be considered important risk factors for cardiovascular disease because of direct effects on the atherosclerosis process or indirect effects, via RAGE signaling, on platelet activity, endothelial cell behavior and vascular smooth muscle cell function. Future research should focus on finding new AGE adducts serving as markers of vascular tissue damage and new drugs targeting the AGE/RAGE pathway.

Conflict of Interest Disclosures

None.

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