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Department of Synthesis and Technology of Drugs, Medical University of Lublin
Department of General Chemistry, Medical University of Lublin

KRZYSZTOF SZTANKE, KAZIMIERZ PASTERNAK

The Maillard reaction and its consequences for a living body

The Maillard reaction called nonenzymatic browning starts in a living body with an attack by nucleophilic reaction with a free amino group present in a protein on an aldehyde group of reducing sugars (for instance glucose) to form early stage product such as Schiff base, which is called aldimine. Then, aldimine successively causes an intramolecular redox rearrangement to form a more stable Amadori compound. The Amadori compound further causes a series of reactions with other proteinous amino groups to form a brown fluorescent material and to cause a crosslinking between proteins. These final products are called advanced glycation end products (AGEs) and form nonenzymatically. Historically, Maillard reported in 1912 that a heated solution of amino acid and reducing sugar is coloured into brown and since then this reaction is called the Maillard reaction. At that time Maillard already suggested that the reaction could take place under physiological conditions in a living body (2, 9).

These changes, known collectively as the Maillard reaction, have been suggested as factors in diabetic complications and the ageing process (1).

Recently, evidence has accumulated that those advanced glycation end products (AGEs) could play an important role in the aetiology of the Alzheimer disease. AGEs are generated by an irreversible reaction through the nonenzymatic, long term glycosylation of proteins and are strongly resistant to proteolytic processes. They induce protein crosslinking and they could thus inhibit the physiological functions of many proteins. Moreover, it is suggested that they contribute to the transformation of the soluble form of beta amyloid into its unsoluble version. AGEs are also demonstrable in neurofibrillary tanglers. A further mechanism by which AGEs might be pathogenic is via their induction of oxidative stress. Advanced glycation end products probably exert their pathological effects directly because of their chemical properties and by indirect receptor-mediated mechanism (15).

AGEs could also play an important role in a decrease of elasticity of the cardiovascular system, which is one of the normal ageing process of mammals. The potential explanation for this decreased elasticity is that glucose can react nonenzymatically with long-lived proteins such as collagen an lens crystallin, and link them together, producing advanced glycation end products (2). It has been observed that nonenzymatic glycosylation and insolubility increases in colagen with age and diabetes. The collagen adducts from aged and diabetic individuals had absorption and fluorescence spectra identical to those of collagen samples that underwent nonenzymatic browning with glucose in vitro. Their likely occurrence throughout the body could explain the correlation between arterial stiffening, decreased joint mobility, and the severity of microvascular complications in the type I diabetics (11). An eye ball crystallin is a specific protein causing no metabolic turnover after being biosynthesized, and it was found that, when the crystallin undergoes the Maillard reaction, increase in fluorescence and colouring in

brown occurs, closely similar to the changes of the eye ball lens with ageing and the development of senile and diabetic cataracts. Nonenzymatic glycosylation of protein does not increase with age in normal human lenses (3,12).

It was that beta$_2$-microglobulin modified with advanced glycation end products is a major constituent of amyloid fibrils in hemodialysis-associated amyloidosis. Acidic beta$_2$-microglobulin, but not normal beta$_2$-microglobulin, was brown in colour and fluoresced, both of which are characteristic of advanced glycation end products of the Maillard reaction (10).

It was shown that over time vascular matrix accumulates proteins nonenzymatically modified by advanced glycosylation end products (AGEs). In view of the fact that macrophages/monocytes have AGE-specific receptors associated with the expression of several growth factors, AGEs can mediate initial monocyte-vessel wall interactions that occur over formation of vascular lesions. AGEs formed in vivo and in vitro are chemotactic for human blood monocytes, sub-endothelial AGEs can selectively induce monocyte migration across an intact endothelial cell monolayer and subsequent monocyte interaction with AGE-containing matrix results in the expression of platelet-derived growth factor. Forming in vivo glucose-derived protein adducts can act as signals for the normal turnover of senescent tissue protein by means of AGE-specific receptor system. Time dependent glucose-induced deposition of AGEs on matrix proteins may promote monocyte infiltration into the subendothelium. Subsequent AGE-triggered macrophage activation and elaboration of proliferate factors may normally co-ordinate remodelling but may also lead to the diverse pathogenic changes typical of arterio- and atherosclerosis in diabetic and ageing populations (4).

Coronary artery disease and cerebrovascular disease, due to the rapid progression of atherosclerosis, is the principal cause of death in diabetes mellitus. The modification of low-density lipoproteins (LDL) by advanced glycosylation end products (AGEs) may play a central role in the development of atherosclerosis, especially in diabetic patients. An AGE-modified form of LDL (AGE-LDL) has been found to circulate in human plasma and AGE modifications have been identified as present on both the apoprotein (ApoB) and the phospholipid components of LDL. AGE-ApoB, AGE-lipid and oxidized LDL (Ox-LDL) in diabetic patients were significantly higher than those in patients without diabetes. An especially marked elevation of AGE-LDL was found in diabetic patients with end-stage renal disease (ESRD). The correlation between the serum total cholesterol and the AGE-LDL (AGE-ApoB and AGE-lipid) was significant. An AGE-modified LDLs may represent a particularly atherogenic form of LDL, and AGE–LDLs as well as AGE-peptides are likely to contribute to the development of atherosclerosis in diabetic patients (7,17).

The accumulation of advanced glycosylation end products (AGEs) is believed to contribute to the chronic complications of diabetes mellitus. Advanced glycosylation end products of the Maillard reaction accumulate at a faster than normal rate in arteries and the circulation of patients with diabetes. The increase in circulating AGEs peptides parallels the severity of renal functional impairment in diabetic nephropathy (8). Pseudodiabetic renal glomerulal changes were observed in mice after repeated injections of glycosylated proteins. Mice given glycosylated proteins had glomerular-basement-membrane thickening on electron microscopical examination. This feature is characteristic of human experimental diabetic renal disease. These results suggest that there may be a link between plasma-protein glucosylation and diabetic nephropathy (8,14).

An AGE-modified form of human hemoglobin (Hb-AGE) has been identified. Termed haemoglobin-AGE accounts for 0.42 percent of circulating hemoglobin in normal individuals but increases to 0.75 percent in patients with diabetes-induced hyperglycaemia (6).

Structure elucidation of a specific fluorophore from the ageing extracellular matrix revealed the presence of protein crosslink, the product of the Maillard reaction formed through nonenzymatic glycosylation of lysine and arginine residues. The unexpected finding that a pentose instead of a hexose is involved in the crosslinking process suggested that the crosslink

named pentosidin might provide insight into abnormalities of pentose metabolism in ageing and disease (13).

The products of advanced glycation of the Maillard reaction are formed in vivo on a variety of blood constituents, including haemoglobin, the lipid and apolipoprotein components of low-density lipoproteins (LDLs),beta$_2$-microglobulin and immunoglobulins. The formation of AGEs on long-lived connective tissue and matrix components largely accounts for the increase in collagen crosslinking that accompanies normal ageing and which occurs at an accelerated rate in diabetes. AGEs can activate cellular receptors and initiate a variety of pathophysiological responses. They modify an appreciable fraction of circulating low-density lipoproteins preventing uptake of these particles by their high-affinity tissue receptor (16). AGE proteins are chemotactic for human monocytes and stimulate macrophages in situ via AGE receptors to secrete inflammatory cytokines such as TNF-alpha and IL-1. AGE proteins are also known to stimulate mesangial cells to produce fibronectin (10).

Incubating proteins with glucose leads, through early products such as Schiff base and Amadori adduct, to advanced glycation end products (AGEs); this is referred to as the Maillard reaction. Several lines of evidence have emphasized a potential role for advanced glycation end products in the pathogenesis of diabetic complications and an ageing process (10).

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SUMMARY

The Maillard reaction (nonenzymatic browning) leads through early stage products such as Schiff base and Amadori adduct to advanced glycation end products (AGEs). AGE crosslinks of the Maillard reaction are formed under physiological conditions in a living organism on a variety of blood constituents, on long-lived connective tissues and matrix components. Recently evidence has accumulated that AGE crosslinks as the final products of the Maillard reaction have been suggested as factors in diabetic complications and the ageing process.

Reakcja Maillarda i jej konsekwencje dla żywego organizmu

Reakcja Maillarda (nieenzymatyczne brązowienie) prowadzi do powstania zaawansowanych końcowych produktów glikacji poprzez wczesne produkty glikacji, takie jak zasada Schiffa i addukt Amadoriego. Powiązane krzyżowo białkowe polimery AGE, będące wynikiem reakcji Maillarda, tworzą się w warunkach fizjologicznych w żywym organizmie w składnikach krwi, tkance łącznej i składnikach substancji międzykomórkowej. Obecnie zebrane dowody sugerują, że powiązane krzyżowo białkowe polimery AGE, będące końcowymi produktami reakcji Maillarda, należą do czynników powodujących powstawanie powikłań cukrzycowych i sprzyjających procesowi starzenia.