Role of methylglyoxal adducts in the development of vascular complications in diabetes mellitus

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Abstract

Various theories have been proposed to explain the hyperglycaemia-induced pathogenesis of vascular complications of diabetes, including detrimental effects of AGEs (advanced glycation end products) on vascular tissues. Increased formation of the very reactive dicarbonyl compound MGO (methylglyoxal), one of the side-products of glycolysis, and MGO-derived AGEs seem to be implicated in the development of diabetic vascular complications. Although the exact role of MGO and MGO adducts in the development of vascular complications is unknown, receptor-mediated activation of vascular cells by the MGO-arginine adduct hydroimidazolone, as well as intracellular modifications of protein by MGO, seem to be involved. The aim of this mini-review is to assess to what extent MGO is related to vascular complications in diabetes.

Introduction

Prolonged exposure to hyperglycaemia has detrimental effects on endothelial cell function and is the primary causal factor in the majority of diabetic complications. One of the hypotheses about how hyperglycaemia causes diabetic complications is the increased intracellular formation of AGEs (advanced glycation end products) [1]. The accumulation of the triose phosphates glyceraldehyde 3-phosphate and dihydroxyacetone phosphate in endothelial cells, as a consequence of intracellular hyperglycaemia, leads to the formation of the highly reactive dicarbonyl compound MGO (methylglyoxal). In cultured endothelial cells, MGO accumulates rapidly under hyperglycaemic conditions, and it has been demonstrated that MGO is the most important precursor in the formation of AGEs [2]. MGO is converted and detoxified by the glyoxalase system. MGO reacts with arginine residues in proteins to form the non-fluorescent products 5-hydro-5-methylimidazolone and tetrahydropyrimidine, and the major fluorescent product argpyrimidine (Figure 1) [3,4]. Although MGO reacts primarily with arginine, the MGO-lysine adducts Nε-(carboxymethyl)lysine and MOLD (MGO–lysine dimer) have been identified, which accumulate with age [5,6]. Plasma concentrations of MGO [3] as well as those of hydroimidazolone [4] and argpyrimidine [7] are increased in diabetic patients. The presence of argpyrimidine has been demonstrated in arterial walls of the kidneys of diabetic patients, in atherosclerotic lesions and in human lenses. In addition, argpyrimidine formation is induced by ischaemia/reperfusion [3]. The only presented data on the tissue localization of hydroimidazolone are those of Professor P. Thornalley and co-workers, presented at the American Diabetes Association 2003, demonstrating that hydroimidazolone increased markedly and selectively in diabetic retinas of streptozotocin-treated rats, while other AGEs, including CML [Nε-(carboxymethyl)lysine], CEL [Nε-(1-carboxyethyl)lysine], argpyrimidine and pentosidine, were not significantly increased.

Inhibitors of the formation of AGEs, i.e. aminoguanidine, pyridoxamine and benfotiamine, which directly or indirectly decrease AGE formation, have been shown to retard or prevent the development of nephropathy, retinopathy and neuropathy in diabetic rats [8,9]. The fact that these inhibitors are all able to lower the concentration of MGO may underscore the significance of MGO in microvascular complications. Although MGO has been linked directly to microvascular complications [10], the mechanisms and the particular MGO adducts involved are unknown.

MGO-derived hydroimidazolone: a ligand for AGE receptors

A mechanism by which MGO-modified proteins may exert their effects on cellular function is via interaction with specific AGE receptors, including RAGE (receptor for AGEs) [11]. RAGE is a multiligand member of the immunoglobulin superfamily and is expressed on the surface of a variety of cell types, including endothelial cells, smooth muscle cells and monocytes. Increased RAGE expression has been shown on both endothelium and vascular smooth muscle cells of diabetic patients [12]. The interaction of circulating...
AGEs with RAGE has been shown to generate oxidative stress that results in activation of NF-κB (nuclear factor-κB) and, in endothelial cells, the expression of cell adhesion molecules, thus causing a general vasculopathy [12]. CML is a major AGE that has been recognized as a ligand for RAGE. Binding of CML-modified albumin to RAGE on monocytes leads to phosphorylation of p38 MAPK (mitogen-activated protein kinase) and ERK1/2 (extracellular-signal-regulated kinase 1/2), activation of NF-κB and secretion of pro-inflammatory cytokines. In addition to CML, the MGO adduct hydroimidazolone appears to be the most likely candidate for receptor recognition, as demonstrated in monocytes and macrophages [11]. The binding and degradation of minimally MGO-modified proteins by human monocytes and macrophages was accompanied by the induction and secretion of the cytokines interleukin 1β and tumour necrosis factor-α [11,13,14], which may have physiological importance in the development of diabetic vascular complications, since recent data have suggested that underlying chronic pro-inflammatory processes play a central role in microvascular and large artery disease in diabetes mellitus. When the accumulation of hydroimidazolone-modified proteins is indeed an aetiological factor in vascular complications via the induction of a state of low-grade inflammation, the inhibition of this receptor-mediated cell activation with specific antagonists may provide a basis for therapeutic intervention. Whether MGO-modified proteins are also ligands for AGE receptors on other cell types, such as endothelial cells, needs to be determined. In this regard, the induction of apoptosis [15] suggest the involvement of a cellular receptor. The hydroimidazolone receptor may be a good candidate, because hydroimidazolone can be rapidly formed under these experimental conditions [16].

**Intracellular targets of MGO and biological consequences thereof**

MGO-modified proteins may have different biological functions: some are protein cross-links, such as MOLD, and some are recognition factors for specific AGE-binding receptors, such as hydroimidazolone. In addition to the extracellular accumulation of MGO adducts, the intracellular accumulation of MGO and formation of AGES may alter cell function and may also be an important contributor to diabetic angiopathy. In endothelial cells exposed to high glucose, basic fibroblast growth factor is one of the main AGE-modified proteins in endothelial cells; AGE-modified basic fibroblast growth factor has markedly decreased mitogenic activity [17]. Overexpression of glyoxalase I in endothelial cells completely prevented both hyperglycaemia-induced AGE formation and increased macromolecular endocytosis, demonstrating the importance of MGO in the formation of AGES and in cell function [2].

An oxidative stress-dependent process plays a central role in the generation of MGO-derived AGES [18]. Other important proteins modified by MGO are certain mitochondrial membrane proteins [19] and antioxidant enzymes [20]. These protein modifications result in increased oxidative stress. Although the hyperglycaemia-induced production of reactive oxygen species by the mitochondrial electron-transport chain inside cultured endothelial cells has been
demonstrated to be a common element linking the different mechanisms of hyperglycaemia-induced vascular damage, the exact mechanism of the formation of reactive oxygen species is not completely clear. Because MGO-modified proteins lead to an increase in oxidative stress, the hyperglycaemia-induced increase in the levels of MGO may contribute to the hyperglycaemia-induced increased production of oxidative stress and, as a consequence, vascular complications.

Recently, Hsp27 (heat-shock protein 27) has been identified as a major MGO-modified protein in tumour cells [21] and endothelial cells [22], in which argpyrimidine was identified as the MGO adduct. In tumour cells, argpyrimidine–Hsp27 seems to be essential to its repressing activity for cytochrome c-mediated caspase activation. So far, the function of the argpyrimidine–Hsp27 modification in endothelial cells is unknown.

**Conclusion**

In summary, recent data have demonstrated that MGO is very important in the glycation reaction, and that MGO adducts are major AGEs involved in the vascular complications of diabetes.

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**References**


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