Effect of methylglyoxal on intestinal cells: possible molecular mechanisms

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Methylglyoxal (MG) is endogenously produced under physiological conditions as a by-product of glycolysis and by auto-oxidation of glucose and lipid peroxidation. The digestive system can take up MG from exogenous sources, which include dietary MG and MG formed by the gut microbiome. MG is a highly reactive molecule, able to react with macromolecules forming covalent adducts resulting in advanced glycation end-products formation. MG can also enter the cell nucleus and reacts with nucleic acids resulting in MG-nucleic acid adducts formation. The MG-adducts show changes in molecular stability and function. Several studies have demonstrated a key role of MG in diabetes and other diseases (such as cancer, and cardiovascular diseases). Aim of the study was to investigate the effects of MG in intestinal cells; in fact, the intestinal epithelium is highly exposed to dietary and endogenous harmful stimuli, including MG. Using Caco-2 cells, we demonstrated that MG treatment induced an increase in cytosolic and mitochondrial reactive oxygen species. MG-induced oxidative stress was associated with activation of NF-KB pathway, with consequent increased expression of pro-inflammatory molecules such TNFα. Moreover, a higher phosphorylation of Ser-139 residue of the histone variant H2AX, forming g-H2AX, was observed in MG-treated cells, suggesting that MG induced DNA damage. Our results demonstrated a decrease in histone deacetylases (HDAC1/2/8) levels, consistent with the increase in acetylated histone H4 levels, in MG-treated cells. These results suggest an additional mechanism for MG-induced cellular damage through epigenetic perturbation. These molecular alterations reflected in impairment of intestinal barrier functions, evaluated by trans-epithelial electrical resistance (TEER). The study of MG-induced alterations in intestinal cells deserves of further investigation to better understand its potential role in the onset of inflammatory intestinal diseases.