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Endothelial cell and macrophage responses induced by methylglyoxal: potential role of mTORC1

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The role of methylglyoxal (MGO), mainly formed as byproduct of glycolysis, in the development of diabetic complications has been widely recognized. Indeed, plasma and tissue levels of MGO are increased in diabetic patients. As such, it is believed that MGO contributes to endothelial dysfunction, low-grade chronic inflammation and insulin resistance. In keeping with its reactive nature, MGO is capable of reacting with amino acids and nucleic acids, which may lead to wrongly folded protein with possibly functional loss, damage of genetic material and dysregulation in transcriptional regulation of genes. Previous studies performed in our laboratory have indicated that endothelial cells treated with MGO display a gene signature that is compatible with activation of the p53 pathway. Formal evidence that MGO indeed activates p53 is however lacking. The current thesis underlies the hypothesis that MGO causes DNA damage, which in turn activates a DNA repair response that includes activation of p53. Consequently, p53 activation will affect the activity of the mTORC1 pathway leading to a decreased phosphorylation of down-stream kinases and activation of autophagy. The hypothesis was tested by addressing the following questions: 1) does MGO indeed cause DNA damage, 2) is this associated with p53 activation, 3) what are the consequences for the mTORC1 pathway. Since mTORC1 also is of pivotal importance in M1 and M2 macrophages polarization, we further addressed: 4) if MGO influences macrophage polarization, 5) what is the role of mTORC1 herein and 6) does MGO prime macrophage to produce pro-inflammatory mediators. Because carnosine has been reported to alleviate many of MGO induced effects we finally addressed the influence of carnosine on processes referred above. The main findings are that MGO causes DNA damage, activation of p53 and inhibition of mTORC1 in endothelial cells. There was a tendency that mTORC1 was more activated in M2 as compared to M1 macrophages, yet MGO did not affect polarization in either M1 or M2 macrophages. MGO was able to increase the production of pro-inflammatory mediators, which might be associated with increased oxidative stress. The findings that MGO induces HO-1 expression and phosphorylation of ERK1/2 indeed corroborate the involvement of oxidative stress. While carnosine was not able to counteract the effects on p53 activation and mTORC1 inhibition it significantly reduced the induction of HO-1, which is in line with its proposed anti-oxidative character.

As the MGO concentrations used in this doctoral thesis by far exceed the concentrations reported in physiological conditions, it would be prudent to take some caution in generalizing or extrapolating the findings reported herein. Nonetheless, the concentrations we used are well in the range previously reported for many in vitro models and as such contribute to the discussion on the in vitro effects of MGO. Inasmuch as MGO concentrations in serum of diabetic patients may not suffice to activate p53 directly, in conjunction with other noxious signals it may potentially contribute to DNA damage. The role of p53 activation for diabetic complications has been illuminated in various diabetic models, e.g. in db/db and STZ-induced diabetic nephrology (DN) mice, whether this is a direct consequence of MGO remains to be addressed.