

Interplay of methylglyoxal and immune cells

Citation for published version (APA):

Zhang, X. (2023). Interplay of methylglyoxal and immune cells: implications for type 2 diabetes? [Doctoral Thesis, Maastricht University]. Maastricht University. https://doi.org/10.26481/dis.20231213xz

Document status and date: Published: 01/01/2023

DOI: 10.26481/dis.20231213xz

Document Version: Publisher's PDF, also known as Version of record

Please check the document version of this publication:

 A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.

• The final author version and the galley proof are versions of the publication after peer review.

 The final published version features the final layout of the paper including the volume, issue and page numbers.

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Summary

Chapter 8

Summary

People with type 2 diabetes (T2D) are at high risk of developing cardiovascular diseases and low-grade inflammation is thought to be an important contributor. Inflammatory response involves innate immune cell recruitment and activation. Alterations in immunometabolism and induction of trained immunity in innate immune cells are linked to hyperglycaemia and dysregulation of these cells are implicated in diabetes-related pathological conditions. In addition, elevated methylglyoxal (MGO) levels are observed under hyperglycaemia conditions. **Chapter 1** introduced the alterations of immune cells and MGO in low-grade inflammation, as well as their potential role in T2D and its complications. Abnormal metabolism of MGO is linked with inflammation and epigenetic changes, which may contribute to cardiovascular disease. This thesis mainly aims to investigate the interactions between MGO and innate immune cells in relation to T2D.

Chapter 2 reviewed the formation and metabolism of MGO, the direct bactericidal effects of MGO, and the link between MGO and immune cell activation as potential mediator during host defence. Our current knowledge regarding the effects of MGO on immune cells mainly involve the induction of inflammation, apoptosis, and suppression of phagocytosis in neutrophils, monocytes and macrophages, and inhibition of lymphocyte activity. However, these effects of MGO remain debatable due to several reasons: 1) differences between endogenously produced MGO (i.e., within cells) and exogenously administrated MGO, 2) the use of unpurified MGO in most published studies and 3) the use of different concentrations of MGO and different incubation times in the different experimental studies.

In **Chapter 3**, we investigated whether postprandial levels of MGO in plasma and tissues originates from exogenous glucose and whether this increased plasma MGO concentration leads to a fast formation of MGO-derived advanced glycation endproducts (AGEs). A glucose tolerance test (GTT) with universally labelled D(+)¹³C glucose was performed in healthy humans (oral (O)GTT) and in C57BL/6J mice (intraperitoneal (IP)GTT). We demonstrated that the newly formed MGO in human plasma during the OGTT is completely derived from exogenous glucose. Moreover, a fast formation of protein-bound MGO-derived AGEs during the OGTT was observed. In mice, we confirmed that the formation of postprandial MGO is derived from exogenous glucose in plasma, and we also showed that the increased MGO in pancreas, spleen, kidney, subcutaneous and visceral adipose tissue (SAT and VAT), liver, and skeletal muscle during the IPGTT originates from exogenous glucose.

In **Chapter 4**, we evaluated MGO levels in circulating cells and investigated whether MGO formation in these cells during a glucose tolerance test originates from exogenous glucose, and whether obesity affects glucose-derived MGO formation. OGTT was performed in 19 abdominally obese individuals and IPGTT was performed in both C57BL/6J and db/db mice, with universally labelled D(+)¹³C glucose. We found that MGO is present in extremely high concentrations in circulating immune cells compared to plasma, and increases during a GTT. Obesity increases exogenous glucose-derived MGO formation during the GTT in plasma, circulating immune cells, as well as in pancreas, liver, spleen, kidney, VAT, and SAT, but decreases MGO formation in erythrocytes. The lower levels of postprandial MGO in RBCs of db/db mice are most likely due to their low expression of glucose transporter GLUT1 compared to lean mice. The MGO stress in the postprandial phase may contribute to the detrimental effects and long-term complications due to postprandial glucose spikes.

In **Chapter 5**, we assessed the contribution of glycolysis in the exogenous glucose-derived MGO formation in mice during an IPGTT. 2 Deoxyglucose (2DG), which blocks glycolysis, was used in combination with universally labelled D(+)¹³C glucose during the IPGTT in C57BL/6J mice. We found that glycolysis contributes to exogenous glucose-derived MGO formation in liver, skeletal muscle, SAT, and bone marrow, but not in blood cells, or in pancreas, spleen, kidney, and VAT. The postprandial MGO formation in plasma, blood cells, or in pancreas, spleen, kidney, and VAT is possibly formed spontaneously from glucose or is due to a direct uptake. Although a further validation is required, the findings in this chapter provide new insights into potential pathways for postprandial MGO formation.

Chapter 6 studied the effects of MGO on immune cell counts and activation, as well as on trained immunity. To investigate this, C57BL/6J mice received either a single intravenous injection of MGO, or a long-term exposure of MGO as supplemented in drinking water. Neither treatment showed robust effects on immune cell count or activation. Interestingly, a single high-dose MGO injection, but not long-term MGO intake via drinking water, enhanced LPS-induced nitric oxide production and proinflammatory gene expression in BMDMs from these

mice, suggesting the induction of trained immunity. We confirmed this innate training effect of MGO in primary human monocytes, where trained immunity was induced by β -glucan, and MGO formation was enhanced during training. This β -glucan-induced trained immunity was blunted by the MGO scavenger aminoguanidine during the training, while it was enhanced by adding additional MGO. These findings indicate that MGO does not directly affect immune cell counts or activation, but play a potential role in trained immunity.

To connect the experimental findings with clinical data, in **Chapter 7**, we investigated whether fasting or post-glucose-load plasma MGO concentrations are associated with circulating immune cell counts and activation in a large human cohort study. We included 696 participants (54% normal glucose tolerance, 13% prediabetes, and 33% T2D) from The Maastricht Study. Associations were analysed with multiple linear regression adjusted for age, sex, body mass index, education, smoking, systolic blood pressure, medication use, and glucose metabolism status. We found that higher fasting plasma MGO concentrations were significantly associated with higher numbers of intermediate and non-classical monocytes, while with lower activation for intermediate monocytes. No consistent associations were shown for post-OGTT plasma MGO levels with either immune cell counts or activation. These findings support a potential interaction between plasma MGO and circulating intermediate monocytes, as a possible contributor to the increased risk of cardiovascular disease in individuals with T2D.