Unraveling the role of dicarbonyl stress in the progression of type 2 diabetes and vascular dysfunction

Dicarbonyl stress occurs when hyperglycaemia metabolites, including methylglyoxal, accumulate as a consequence of their increased production and/or decreased detoxification by scavenging systems. This toxic condition has been associated with metabolic and age-related diseases, such as type 2 diabetes (T2D), both of which are characterized by a pro-inflammatory and pro-oxidant state (1).

Methylglyoxal is mainly produced as a side-product of glycolysis and is the major precursor of the Advanced Glycated End products (AGEs), responsible for cellular damage and tissue dysfunction. Methylglyoxal is mainly detoxified by the glyoxalase system, which contributes to prevent or counteract the dicarbonyl stress. Studies have been centered on understanding the molecular basis of endothelial dysfunction in diabetes, unveiling a central role of methylglyoxal-glyoxalase 1 imbalance in the onset of vascular complications (2).

By the use of murine and cellular models, genetically manipulated or exposed to environmental hits, we aim at clarifying whether and how methylglyoxal plays a role in: i. the endothelial dysfunction, which represent the first step in the initiation, progression and clinical outcome of vascular complications, such as retinopathy, nephropathy, impaired wound healing and macroangiopathy; ii. the alteration of glucose homeostasis, that is crucial in the onset of T2D.

We have explored the effect of high methylglyoxal levels on the hemodynamic action played by insulin on endothelium. We used two different approaches to increase methylglyoxal levels: the administration of methylglyoxal \textit{in vivo} in mice and \textit{in vitro} to endothelial cells, or the inhibition of the glyoxalase 1 by a chemical inhibitor. These studies have demonstrated that MGO prevents the insulin signaling activation thereby blunting the endothelial release of the vasodilator nitric oxide (NO), while sustaining the MAPK pathway activation and the downstream endothelin-1 release. This resistance to insulin response is mediated by ERK kinase activation (3). By a micro-array approach, we then identified the miR-190a and miR-214 downregulation that, through their respective targets KRAS and PHLLP2, acts as contributing factor to the methylglyoxal-induced endothelial insulin-resistance (4, 5).

We are taking advantage by the use of a transgenic mouse model knock-down for glyoxalase 1 (Glo1KD) to test the effect of the endogenous increase of methylglyoxal levels, which better resemble the pathophysiological condition. Methylglyoxal derived AGEs accumulation in endothelial cells from Glo1KD mice impairs the angiogenic process ex vivo. Impaired angiogenesis leads to the long-term complications and is a major contributor of the high morbidity in patients with Diabetes Mellitus. We provided data demonstrating that methylglyoxal-induced increase of NF-kB is responsible for the de-regulation of the anti-angiogenic HoxA5 gene in Glo1KD endothelial cells (6).

We are currently testing the potential role of dicarbonyl stress in the pathogenesis of T2D, and the advantage of using the Glo1KD mouse is the opportunity to evaluate whether and which alterations result from the methylglyoxal increase by itself, excluding the presence of confounding factors deriving from hyperglycemia and obesity. Data obtained so far demonstrate that methylglyoxal accumulation in Glo1KD mice induce an age-related impairment of glucose tolerance. This defect is related to a diabetes-like senescence-associated proinflammatory phenotype of islets resulting in the impairment of glucose stimulated insulin secretion.

These data provide new evidence for an active role of MGO in the etiology of T2D, paving the way for novel prevention approaches to T2D progression.

The general aim of this research activity is to elucidate the molecular basis useful for the identification of novel markers and therapeutic strategies to prevent or counteract the dicarbonyl stress, responsible for the tissue dysfunction typical of T2D and other age-related disease.
References:

Keywords:
Diabetes Mellitus; Endothelial dysfunction; Glucotoxicity.

Contacts:
e-mail: c.miele@ieos.cnr.it; c.nigro@ieos.cnr.it; tel: 081 7463248

Website(s):
www.ieos.cnr.it