

Alpha-dicarbonyl stress

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VALORISATION ADDENDUM

V

A vertical strip on the right side of the page features a grayscale microscopic image of several overlapping, rounded cells. The cells have a textured, slightly granular appearance. A large, bold, white letter 'V' is superimposed on the bottom right of this strip, extending from the bottom edge of the page.

Valorisation

The burden of obesity is one of the largest health problems in modern-time society and affects over 600 million adults worldwide. An elevated BMI increases the risk of developing insulin resistance, type 2 diabetes and related complications. This poses an enormous emotional and social economic burden on obese individuals and health care systems. The ever-increasing prevalence of obesity and, as a result, type 2 diabetes shows the growing need to better understand their link and the need for new therapeutics. The work presented in this thesis aimed to unravel the intermediate step linking central obesity to type 2 diabetes and related complications. Our main findings were that α -dicarbonyl stress is 1) implicated in the development of obesity and insulin resistance and 2) increased in individuals with type 2 diabetes and 3) that this is reversible by weight loss interventions. This chapter describes how these current findings may be applied in order to prevent or reverse the obesity-induced development of insulin resistance and type 2 diabetes and provides a perspective on potential future research steps to translate current findings into clinical practice.

Identification of new treatment targets

This thesis extensively investigated the role of α -dicarbonyl stress in obesity, insulin resistance and type 2 diabetes and underlines the potential of α -dicarbonyls as potential treatment targets.

Two independent studies in a mouse model of obesity, as described in chapter 5 and 6, demonstrated that α -dicarbonyls are implicated in the development of obesity and obesity-related complications including adipose tissue inflammation and insulin resistance. Predominantly body weight gain and insulin resistance were improved upon α -dicarbonyl inhibition, but also adipocyte hypertrophy and adipose tissue inflammation were significantly improved when α -dicarbonyl stress was reduced. These findings highlight α -dicarbonyl stress as an exciting potential treatment target for the burden of obesity and the related development of insulin resistance.

In the field of insulin resistance, this thesis also provided new insights into modifications of the insulin protein. *In vitro* studies demonstrated that MGO can form adducts on insulin, which consequently leads to an impairment of the normal insulin signalling cascade. Although future studies are needed to identify such modifications on insulin *in vivo*, these findings provide possible new therapeutic windows for insulin resistance.

Another major finding of this thesis was that postprandial α -dicarbonyl stress in plasma is increased in patients with type 2 diabetes. Previous studies have revealed the importance of postprandial glucose excursions in the development of (cardio)vascular diabetic complications. Based on literature, from which it is known that increased fasting α -dicarbonyl stress is associated with the development of diabetic complications, and our current findings on postprandial α -dicarbonyl stress, we hypothesize that these compounds could make the link between glucose excursions after a meal and (cardio)vascular disease in patients with type 2 diabetes. Our finding that these postprandial α -dicarbonyl excursions are reversible by weight loss interventions underline α -dicarbonyl compounds even more as potential treatment targets in the reduction or prevention of severe diabetic complications.

Options for new treatment strategies

In this thesis, several treatment strategies, all aimed to reduce α -dicarbonyl stress, were explored and showed promising effects: 1) Quenching of α -dicarbonyls by pyridoxamine, 2) Increased metabolism of MGO and GO by glyoxalase-1 (GLO1) overexpression and 3) Reduction of α -dicarbonyls by weight loss interventions.

Pyridoxamine

Pyridoxamine is a vitamin B6 analogue with anti-glycating properties through quenching of α -dicarbonyls. Several clinical trials have already demonstrated the efficacy of pyridoxamine as a treatment of diabetic nephropathy. As described in this thesis, extensive research in an animal model of obesity demonstrated that pyridoxamine is a very successful compound in the reduction of obesity itself and obesity-induced complications. Characteristic features of obesity, including body weight gain, adipocyte hypertrophy, adipose tissue inflammation and severe insulin resistance were improved by pyridoxamine. These findings created high expectations for clinical use of pyridoxamine and make it thus worth testing pyridoxamine as an effective treatment candidate in human obesity. A randomized controlled clinical trial with pyridoxamine in obese individuals would provide insight into the applicability of this compound in the treatment of obesity and obesity-associated complications, including micro- and macrovascular complications, insulin resistance and inflammation.

Induction of GLO1

In addition to pyridoxamine, this thesis has also demonstrated the efficacy of GLO1 overexpression in an obese mouse model. This genetic modification not only reduced high-fat diet (HFD)-induced body weight gain, but also reduced glucose intolerance,

adipocyte hypertrophy and adipose tissue inflammation. Previous studies described multiple ways to induce GLO1 gene expression. Synthetic drugs like candesartan, but also more naturally available compounds have been demonstrated to possess GLO1-stimulating properties. Polyphenols such as resveratrol and flavonoids are known to upregulate GLO1 expression. A very recent study revealed a successful combination of two polyphenols, trans-resveratrol and hesperetin, resulting in improved glycemic control and vascular function in obese subjects through induction of the GLO1 enzyme. In addition, isothiocyanates, like phenethyl isothiocyanate and sulforaphane, which can be found in cruciferous vegetables, are known to stimulate GLO-1 by activating the cell-defense master switch nuclear factor-erythroid 2 (Nrf2). Previous research showed that GLO1 has an Nrf2-responsive element in its promoter, and that exposure to sulforaphane induced expression and activity of GLO1, with consequently a decrease in MGO.

Weight loss interventions

A third intervention strategy to reduce α -dicarbonyl stress that has been documented in this thesis is based on weight loss interventions. We demonstrated that patients with type 2 diabetes are characterized by postprandial increases of plasma α -dicarbonyls. In obese women, these excursions were reversible within three weeks of weight loss, either by energy restriction or Roux-en-Y gastric bypass. We hypothesize that other lifestyle interventions, such as increasing the level of physical activity, would also decrease (postprandial) α -dicarbonyl stress.

α -Dicarbonyls as biomarkers

Biomarkers are of large clinical value in the prevention, diagnosis and treatment of diseases. Based on findings of this thesis, indicating the involvement of α -dicarbonyls in obesity, insulin resistance and type 2 diabetes, we hypothesize that plasma measurement of α -dicarbonyl stress may therefore serve as an excellent marker of deranged glucose metabolism, and may thus serve as a marker of increased risk of type 2 diabetes and possibly also for diabetic complications. Nowadays, UPLC-MS/MS is used for valid and precise measurements of α -dicarbonyls. However, this technique is expensive, time-consuming and it requires too much plasma to use it as a tool for biomarker measurement. Therefore, development of a new, quick diagnostic tool to measure α -dicarbonyls in small blood samples would be of significant value for the social and economic burden of type 2 diabetes. The use of α -dicarbonyls as biomarkers and risk predictors of type 2 diabetes and related complications would enable clinical doctors to make a diagnosis at an early stage of the disease and to set up an adequate treatment strategy, amongst other things aimed to reduce plasma α -dicarbonyl stress.