P041 Dicarbonyl stress and beta-cell dysfunction

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Methylglyoxal may be involved in the early stages of decline in glucose tolerance and decline in pancreatic beta-cell function leading to type 2 diabetes. Methylglyoxal and methylglyoxal-modified proteins increase during short-term increases in glucose concentration, infusion of exogenous methylglyoxal in rats and mice impaired glucose tolerance and glyoxalase 1 (Glo1) prevented beta-cell toxicity. We investigated the role of methylglyoxal and protein glycation on beta-cell function and the development of diabetes, with focus on the interactions of cells with the extracellular matrix. Impairments in adhesion of MIN6 insulinoma cells to methylglyoxal-glycated collagen IV were assessed *in vitro* using atomic force microscopy force spectroscopy and methylglyoxal glycation adducts within the pancreas visualised by immunostaining. Minimal glycation of collagen IV at integrin binding sites impaired binding of MIN6 cells *in vitro* and resulted in a 91% decrease in the energy necessary to detach the cells from collagen. Evidence from high fat diet fed mice showed that the methylglyoxal concentration of the pancreas was increased in the insulin resistant, pre-diabetic state with methylglyoxal-derived glycation adducts within the pancreas predominantly localised to the extracellular matrix *in vivo*. We conclude that glycation of extracellular matrix collagen IV likely impairs adhesion of beta-cells to the extracellular matrix in pre-diabetes *in vivo* and may thereby contribute to beta-cell glucotoxicity and dysfunction with progression to type 2 diabetes mellitus.