Role of the extracellular matrix protease ADAMTS5 in diet induced insulin resistance

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The regulation of insulin action in response to nutrient excess is complex, and how this contributes to insulin resistance in diseases such as obesity and type 2 diabetes is equivocal. The extracellular matrix (ECM) is critical for tissue development and cellular homeostasis. Emerging research suggests that ECM remodelling is associated with the development of insulin resistance, obesity and type 2 diabetes. The ADAMTS5 (adamalysin-like metalloproteinases with thrombospondin motifs-5) enzyme is a key protease involved in ECM remodelling during both development and disease. The role that ADAMTS5 plays in insulin mediated glucose metabolism is unknown, although ADAMTS5 levels are elevated in insulin resistant animal and cell models where insulin mediated glucose uptake is impaired (Deshmuhk *et al.*, 2015; Voros, *et al.*, 2006). Based on these findings, our aim was to elucidate the role of ADAMTS5 in the development of diet induced insulin resistance.

At 8 weeks of age, male and female C57BL6:ADAMTS5$^{+/+}$ (Wildtype, WT) and C57BL6:ADAMTS5$^{-/-}$ (Knockout, KO) mice were placed on a control chow (CHOW) or high fat diet (HFD) for 13 weeks. In response to HFD, both male and female mice had significantly (P<0.05) greater body weight and fat mass compared to mice on CHOW diet. However, no differences between WT and KO mice were observed for body weight, fat and lean mass, food intake, physical activity, energy expenditure, and carbohydrate and fat oxidation. To determine the effect of genetic deletion of ADAMTS5 on whole body glucose metabolism an oral glucose tolerance test and insulin tolerance test were performed, and homeostatic model assessment (HOMA) was determined. Taken together the results suggest that genetic deletion of ADAMTS5 does not influence glucose metabolism in male and female CHOW fed mice. However in response to HFD, male KO mice showed a significantly greater level of insulin resistance compared with WT mice that appeared to be compensated for by elevated pancreatic beta cell function. In contrast, female KO mice when compared to WT appear to be protected against insulin resistance in response to HFD. The underlying mechanisms that account for the sexual dimorphism in glucose metabolism in ADAMTS5 KO mice in response to HFD remains to be determined. These results further add to the body of research that highlight the important role that ECM remodelling may play in the development of insulin resistance.

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