

P027 Multiple Roles of Calpain-10 in Insulin Secretion

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Calpain-10 (CAPN10) is the first type 2 diabetes susceptibility gene to be identified through a genome scan. We examined both chronic and acute exposure of INS-1 β -cells to high glucose environments and found that this leads to increased CAPN10 expression. Specific manipulation of CAPN10 expression through use of a CAPN10-containing vector demonstrated that regulated insulin secretion correlates with calpain-10 protein content. First phase secretion is mediated by soluble N-ethyl maleimide sensitive fusion protein attachment receptor (SNARE) proteins. The t-SNAREs syntaxin-1 and SNAP-25 both co-immunoprecipitate with the 54kDa isoform of calpain-10. Furthermore SNAP-25 undergoes a Ca^{2+} -dependent partial proteolysis during exocytosis, with calpain protease inhibitor similarly suppressing both insulin secretion and SNAP-25 proteolysis alike. Second phase secretion is in part characterised by rearrangement of the actin cytoskeleton. We find that there is co-localisation of the 54kDa isoform of calpain-10 with the cytoskeleton, and that actin cytoskeletal rearrangement is also sensitive to calpain inhibition. Based on our results we hypothesise that calpain-10 is a Ca^{2+} sensor functioning at multiple points along the insulin secretory pathway.