

P020 Role of carboxypeptidase E in palmitate-induced beta-cell ER-stress and apoptosis

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Obesity is a principal risk factor for type 2 diabetes and elevated fatty acids reduce β -cell function and survival. An unbiased proteomic screen identified targets of palmitate in β -cell death. The most significantly altered protein in both human islets and MIN6 β -cells treated with palmitate was carboxypeptidase E (CPE). Palmitate reduced CPE protein levels within 2 hours, preceding ER-stress and cell death, by a post-translational mechanism involving translocation to Golgi and lysosomal degradation. Palmitate metabolism and Ca^{2+} flux were required for CPE loss and β -cell death. Chronic palmitate exposure, but not acute stimulation, increased the proinsulin to insulin ratio. CPE null islets had increased apoptosis *in vivo* and *in vitro*. Palmitate did not induce additive ER-stress and apoptosis in CPE deficient islets. Reducing CPE ~50% with shRNA also resulted in increased apoptosis. Conversely, over-expression of CPE partially rescued β -cells from palmitate-induced ER-stress and apoptosis. Thus, carboxypeptidase E is degraded prior to palmitate-induced β -cell death and the loss of CPE contributes to β -cell apoptosis. CPE is a novel link between hyperlipidemia, β -cell death pathways and a critical enzyme in the insulin secretory pathway. These findings help explain some of the phenotype of type 2 diabetes.