

P013 Acute and chronic insulin signaling in beta-cells
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Despite considerable study, the roles and mechanisms of insulin signaling in the beta-cell remain unclear. Previous studies have established a role for calcium mobilization from intracellular stores in acute insulin signaling. Using human islet cells, we found that insulin-induced calcium signaling requires the sequential activation of calcium stores sensitive to NAADP and IP₃. Islet cells from mice lacking CD38, an enzyme capable of generating NAADP, demonstrated reduced responsiveness to insulin. Using a number of approaches, we determined that insulin did not induce a robust feed-forward stimulation of insulin exocytosis. However, a transient increase in accessible c-peptide contents was observed at 90 minutes in dispersed human islet cells exposed to 0.2-200 nM insulin. The increase in c-peptide levels was calcium-dependent and required new protein synthesis. In long-term studies, exposure to 0.2 nM exogenous insulin resulted in significant protection from serum withdrawal-induced apoptosis. This effect was associated with pdx-1 translocation to the nucleus in primary mouse beta-cells. The ability of insulin to prevent apoptosis was impaired in islets from pdx-1^{+/-} mice. These results indicate that the pro-survival effects of insulin in beta-cells require both alleles of pdx-1 and suggest that insulin may be an important endogenous regulator of pdx-1.