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Acute and chronic effects of fatty acids on insulin secretion, oxygen consumption, intracellular calcium signaling and gene expression profile in mouse and human pancreatic islets

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Abstract

In contrast to acute stimulation of insulin secretion (IS) by free fatty acids, chronic hyperlipidemia and hyperglycemia are characteristics of type 2 diabetes and they are known to cause β-cell dysfunction termed "glucolipotoxicity". It has also been shown that the expression of PGC-1α is elevated in islets from different animal models of diabetes but its mechanistic role in □-cell glucolipotoxicity remains unclear. The goal of this study was to evaluate the interconnection between expressions of PGC-1α, mitochondrial energy metabolism, calcium signaling and insulin secretion (IS) in mouse and human islets. To duplicate glucolipotoxicity in vitro, islets were cultured for 3 days with 0.5 mM palmitic acid (PA) at 1% albumin and different concentrations of glucose: 10, 16 and 25 mM. The inhibitory effect of PA on IS was evident at 16 mM in mouse and human islets. Despite inhibition of IS by PA, the oxygen consumption rate (OCR) in response to step-wise increases of glucose or due to FCCP were similar in control and PA treated mouse islets, suggesting that inhibition of IS by PA occurred at steps downstream of ATP production. Gene expression of PGC-1α, PPAR-□, CPT-1A, Cyt c and Cox5b were increased and expression of GCK was decreased after mouse and human islets exposure to 16 mM glucose and 0.5 mM PA. Increasing the glucose to 25 mM in the presence of PA led to even greater inhibition of IS and the gene expression profile exhibited the following characteristic changes: decreased expression of PGC-1α, slightly increased expression of CPT-1A with no changes in expression of PPAR-□, Cyt c, Cox5b or GCK. These changes were associated with increased basal OCR and decreased stimulation of respiration by glucose but normal response to FCCP (demonstrating intact coupling of Ox/Phos). The inhibition of IS was correlated with impaired glucose-stimulated calcium influx. We conclude that the phenotypic manifestation of glucolipotoxicity depends characteristically on the glucose concentration: at 16 mM glucose islets exhibit an adaptive response as evidenced by increased expression of PGC-1α, PPAR-□, CPT-1A and Cox5b with lowered GCK but this adaptation collapses at 25 mM glucose.

Biography

Dr. Nicolai M. Doliba is a Research Assistant Professor of Biochemistry and Biophysics at Translational Research Center, Perelman school of medicine, University of Pennsylvania. His research focuses on the role of bioenergetics, ion transport and metabolic coupling factors in nutrient- and drug-stimulated insulin release by pancreatic beta-cells at normal conditions and during diabetes mellitus.