

P014 Nutrient sensing in pancreatic β -cells suppresses mitochondrial superoxide generation and its contribution to apoptosis
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Prolonged exposure of cultured pancreatic islets to high glucose has been proposed to cause superoxide generation that results in beta cell dysfunction; this process is attributed to high rates of Krebs cycle-flux and mitochondrial electron transport. We have examined in freshly isolated and FACS-purified rat beta cells whether their glucose-induced metabolic changes are associated with higher H_2O_2 and superoxide production. Glucose (0 to 20 mM) concentration-dependently increased cellular NAD(P)H and $FADH_2$ levels with EC_{50} around 8 mM but did not stimulate H_2O_2 or superoxide production. Between 0 and 5 mM, glucose exhibited a concentration-dependent suppression in the production of these radicals, more markedly so in the beta cell subpopulation with higher than in that with lower metabolic responsiveness to glucose. Superoxide levels were also lower after addition of 1) rotenone, thenoyl-trifluoroacetone or antimycin A; 2) the mitochondrial fuels leucine and succinate; 3) the SOD mimetic MnTBAP. In low glucose-cultured beta cells, superoxide scavenging prevented apoptosis and induction of catalase and glutathione peroxidase mRNA. These data demonstrate that superoxide generation is elevated in beta cells with lower mitochondrial metabolic activity and contributes to apoptosis that occurs after a prolonged state of reduced glucose signalling.