Signal – Transduction in Pancreatic β-cell Function and Survival

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The insulin secretory process is regulated by a sophisticated interplay between glucose and a plethora of additional factors. Besides the actions of other nutrients, incretin factors such as GIP and GLP-1, innervation and systemic growth factors, also autocrine and paracrine regulatory loops within the islet of Langerhans modulate function of the insulin-producing β-cell. Although this modulation of function is well appreciated, the underlying molecular mechanisms involved remain poorly understood. The actions of the actual factors are mediated by β-cell membrane receptors coupled primarily to either G-proteins or tyrosine kinases, which subsequently activate respective second messenger cascades. Due to differences in cytoarchitecture between rodent and human islets, the human β-cell may be subjected to a unique extracellular milieu, which may have implications for signal-transduction and thereby β-cell function and survival. Exposure of the pancreatic β-cell to stimulatory glucose concentrations leads to the activation of a cascade of reactions, which ends in the release of stored insulin. This complex of processes starts with the uptake of glucose by the β-cell high capacity but low affinity glucose transporters and proceeds with the conversion of glucose into glucose-6-phosphate by the β-cell isoform of glucokinase. Metabolism of glucose in glycolysis and the Krebs cycle results in the generation of ATP. The coupling of glucose metabolism to electrical activity remains central in all models of β-cell stimulus-secretion coupling. The resting membrane potential of the pancreatic β-cell is set by the ATP-sensitive potassium (K_{ATP}) channel. Elevation in the ATP/ADP ratio leads to closure of K_{ATP} channels, which in turn results in depolarization of the plasma membrane. The
subsequent opening of voltage-gated L-type Ca\textsuperscript{2+} channels leads to an increase in cytoplasmic free Ca\textsuperscript{2+} concentration, [Ca\textsuperscript{2+}], which promotes insulin secretion. It is of interest to note, that [Ca\textsuperscript{2+}] is not only increasing but is increasing and decreasing in an oscillatory manner, which may be crucial for both β-cell function and survival. Dysregulation of [Ca\textsuperscript{2+}] results in β-cell apoptosis. Signal-transduction will be discussed in light of pancreatic β-cell function and survival.

References