Cellular mechanisms of insulin secretion

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Glucose stimulates insulin secretion by generating triggering and amplifying signals in β-cells. The triggering pathway involves metabolism of glucose, closure of K⁺-ATP channels, membrane depolarization, Ca²⁺ influx and rise of cytosolic [Ca²⁺], which serves as the triggering signal for exocytosis of insulin granules. The amplifying pathway also depends on glucose metabolism but does not involve any change in membrane K⁺-ATP channel activity. It requires that [Ca²⁺] is high in β-cells but does not imply any further rise. The effect consists in an increase of [Ca²⁺] efficacy on exocytosis. The triggering pathway thus predominates over the amplifying pathway that remains functionally silent as long as [Ca²⁺] has not been raised. It will be shown how the hierarchy and interaction of the two pathways permit control of insulin secretion in time and amplitude, contribute to the biphasic time-course of secretion, and may account for the permissive (or potentiating) action that glucose exerts on insulin secretion evoked by non-metabolized agents. Emphasis will be put on the importance of β-cell synchronization within islets for the generation of [Ca²⁺] oscillations and pulsatility of insulin secretion. Possible mechanisms of the amplifying pathway will be discussed, and the role of amplifying signals for the control of insulin secretion in situations of β-cell K⁺-ATP channel dysfunction will be envisaged. Nutrients whose metabolism in β-cells leads to an increase in the ATP/ADP ratio mimic the effects of glucose on the two pathways, whereas drugs and certain non-metabolized nutrients (e.g. arginine) only produce a triggering signal. In contrast, most hormones and neurotransmitters do not produce a triggering signal (hence do not induce insulin secretion), but activate an amplifying pathway that involves mechanisms (mainly protein kinases A and C) distinct from those mediating the amplification by glucose.