

cAMP effectors in glucose-stimulated insulin secretion

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Glucose-stimulated insulin secretion is pulsatile and involves coordinated oscillations of the cytoplasmic Ca^{2+} and cAMP concentrations beneath the beta-cell plasma membrane. Glucose-induced cAMP oscillations are enhanced by elevations of the cytoplasmic Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) but conditions raising cytoplasmic ATP trigger cAMP elevations without accompanying $[\text{Ca}^{2+}]_i$ rise. The cAMP oscillations correlate with pulsatile insulin release from single beta-cells and inhibition of adenylyl cyclases suppresses both cAMP oscillations and pulsatile insulin release. The cAMP-activated guanine nucleotide exchange factor Epac2 is an important mediator of the cAMP action in glucose-stimulated insulin secretion. Accordingly, specific activation of Epac restores pulsatile insulin release in cells treated with adenylyl cyclase inhibitors and siRNA-mediated knock-down of Epac2 reduces the secretory response. Protein kinase A (PKA) inhibitors diminish the secretory response to subsequent glucose stimulation, but do not affect already manifested glucose-induced insulin oscillations. The reduced secretory response is due to a dissociation of the initial $[\text{Ca}^{2+}]_i$ and [cAMP] elevations such that Ca^{2+} triggers exocytosis before the amplifying cAMP signal is manifested, and can be restored by activation of Epac. These results demonstrate that temporal coordination of Ca^{2+} and cAMP signals are important for appropriate induction of glucose-induced pulsatile insulin release. Both PKA and Epac2 partake in initiating insulin secretion, but the cAMP-dependence of established pulsatility is mediated by Epac2.