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Coordinated activation of mitochondrial respiration and exocytosis mediated by PKC signaling in pancreatic β cells

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Abstract

Mitochondria play a central role in pancreatic β-cell nutrient sensing by coupling their metabolism to plasma membrane excitability and insulin granule exocytosis. Whether non-nutrient secretagogues stimulate mitochondria as part of the molecular mechanism to promote insulin secretion is not known. Here, we show that PKC signaling, which is employed by many non-nutrient secretagogues, augments mitochondrial respiration in INS-1E (rat insulinoma cell line clone 1E) and human pancreatic β cells. The phorbol ester, phorbol 12-myristate 13-acetate, accelerates mitochondrial respiration at both resting and stimulatory glucose concentrations. A range of inhibitors of novel PKC isoforms prevent phorbol ester-induced respiration. Respiratory response was blocked by oligomycin that demonstrated PKC-dependent acceleration of mitochondrial ATP synthesis. Enhanced respiration was observed even when glycolysis was bypassed or fatty acid transport was blocked, which suggested that PKC regulates mitochondrial processes rather than upstream catabolic fluxes. A phosphoproteome study of phorbol ester-stimulated INS-1E cells maintained under resting (2.5 mM) glucose revealed a large number of phosphorylation sites that were altered during short-term activation of PKC signaling. The data set was enriched for proteins that are involved in gene expression, cytoskeleton remodeling, secretory vesicle transport, and exocytosis. Interactome analysis identified PKC, C-Raf, and ERK1/2 as the central phosphointeraction cluster. Prevention of ERK1/2 signaling by using a MEK1 inhibitor caused a marked decreased in phorbol 12-myristate 13-acetate-induced mitochondrial respiration. ERK1/2 signaling module therefore links PKC activation to downstream mitochondrial activation. We conclude that non-nutrient secretagogues act, in part, *via* PKC and downstream ERK1/2 signaling to stimulate mitochondrial energy production to compensate for energy expenditure that is linked to β-cell activation.-Santo-Domingo, J., Chareyron, I., Dayon, L., Galindo, A. N., Cominetti, O., Giménez, M. P. G., De Marchi, U., Canto, C., Kussmann, M., Wiederkehr, A. Coordinated activation of mitochondrial respiration and exocytosis mediated by PKC signaling in pancreatic β cells.

Keywords: ERK signaling; energy metabolism; human islets; phosphoproteome.