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Review

Mitochondrial signals drive insulin secretion in the pancreatic β-cell

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This article is dedicated to Prof. Andras Spät at the occasion of his 70th birthday.

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ABSTRACT

β-Cell nutrient sensing depends on mitochondrial function. Oxidation of nutrient-derived metabolites in the mitochondria leads to plasma membrane depolarization, Ca^{2+} influx and insulin granule exocytosis. Subsequent mitochondrial Ca^{2+} uptake further accelerates metabolism and oxidative phosphorylation. Nutrient activation also increases the mitochondrial matrix pH. This alkalinization is required to maintain elevated insulin secretion during prolonged nutrient stimulation. Together the mitochondrial Ca^{2+} rise and matrix alkalinization assure optimal ATP synthesis necessary for efficient activation of the triggering pathway of insulin secretion. The sustained, amplifying pathway of insulin release also depends on mitochondrial Ca^{2+} signals, which likely influence the generation of glucose-derived metabolites serving as coupling factors. Therefore, mitochondria are both recipients and generators of signals essential for metabolism-secretion coupling. Activation of these signaling pathways would be an attractive target for the improvement of β-cell function and the treatment of type 2 diabetes.

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Abbreviations: AGC, aspartate–glutamate carrier; BCATm, branched chain amino transferase; cICD, cytosolic isocitrate dehydrogenase; GDH, glutamate dehydrogenase; GLP-1, glucagon-like peptide-1; LDH, lactate dehydrogenase; mtDNA, mitochondrial DNA; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase; PEP, phosphoenolpyruvate; SCS, succinyl-CoA synthetase; Tfam, mitochondrial transcription factor A; TFB1M, mitochondrial transcription factor B1.

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1. Introduction

The pancreatic β-cells secrete insulin into the blood stream. The hormone binds to receptors in target tissues such as liver muscle and fat to lower blood glucose and to store energy in the form of glycogen, lipids and proteins (Biddinger and Kahn, 2006; Defronzo, 2009).

Insulin secretion in turn is controlled by circulating nutrients, gastrointestinal hormones and the autonomic nervous system that acutely stimulate the release of the hormone into the blood stream. A step increase in glucose concentration elicits biphasic insulin secretion, composed of a transient first phase and a long lasting second phase best seen in the portal vein (Blackard and Nelson, 1970; Wollheim and Sharp, 1981; Wollheim, 2000; Henquin,

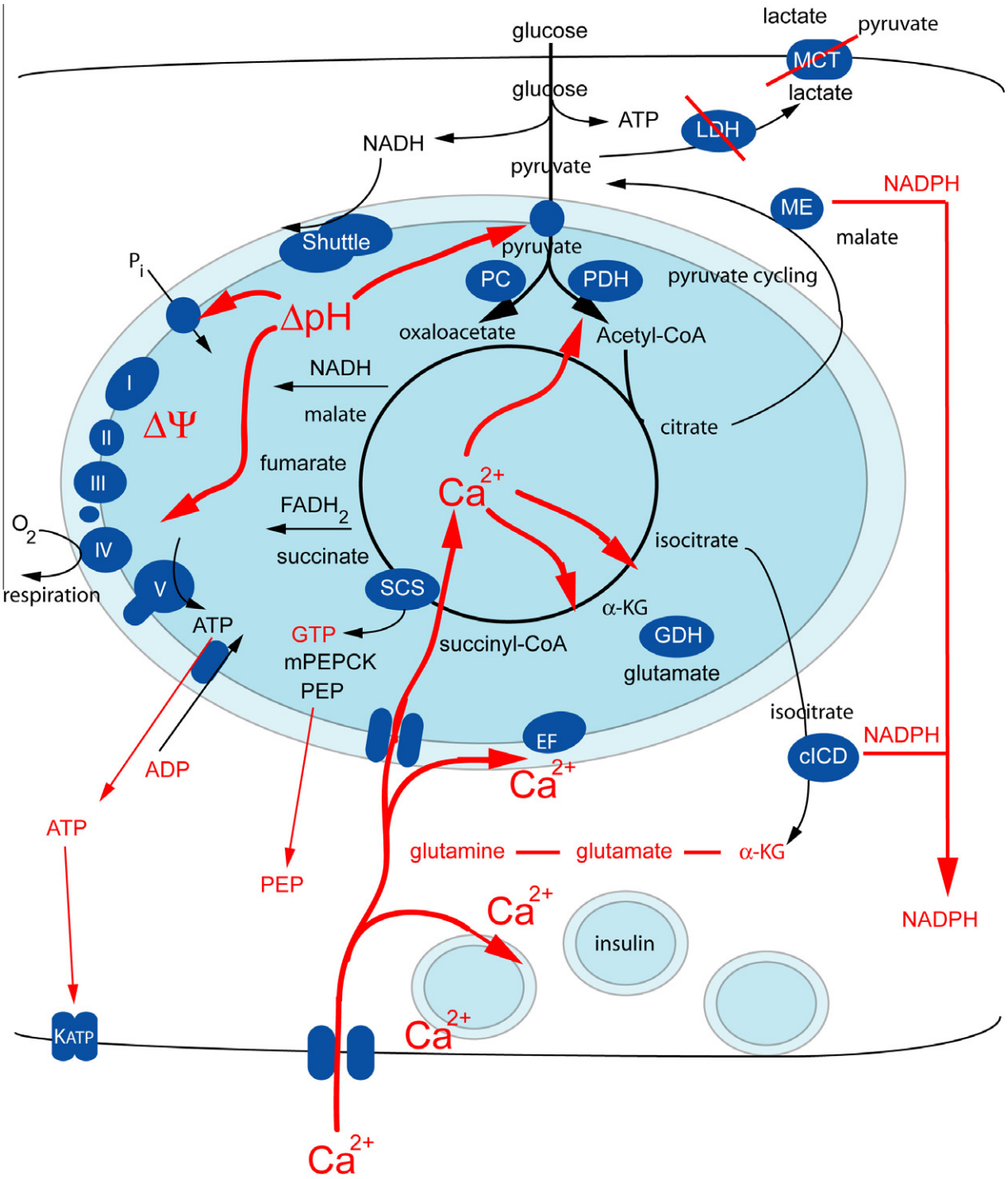

Fig. 1. Central role of mitochondria in metabolism-secretion coupling in the insulin-releasing β-cell. Proteins (dark blue): I–V, complexes of the respiratory chain and the ATP-synthase; cICD, cytosolic isocitrate dehydrogenase; EF, protein with EF-hand domain in the intermembrane space; GDH, glutamate dehydrogenase; LDH, lactate dehydrogenase; ME, malic enzyme; MCT, monocarboxylate transporter; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase; mPEPCK, mitochondrial phosphoenol-pyruvate carboxykinase; SCS, succinyl-CoA synthase; Shuttle, glycerolphosphate and malate-aspartate shuttle. Metabolic pathways and most metabolites (black). Metabolites with potential signaling function (red). Activating functions of Ca^{2+} and matrix pH signals in metabolism-secretion coupling (bold red arrows).