Tight regulation of the mitochondrial Ca^{2+} signal during glucose stimulation in pancreatic β-cells.

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Increases in the cytosolic Ca^{2+} concentration ($[Ca^{2+}]c$) in pancreatic β-cells mediate glucose-stimulated insulin secretion. It has been suggested that increases in the mitochondrial Ca^{2+} concentration ($[Ca^{2+}]m$) are also involved in insulin secretion promoting mitochondrial ATP production. However, $[Ca^{2+}]m$ dynamics during glucose stimulation require further clarification. Using mitochondrial Ca^{2+} indicator CEPIA2*mt*, we here analyzed glucose-stimulated $[Ca^{2+}]m$ dynamics in a pancreatic β-cell line MIN6. During glucose stimulation, $[Ca^{2+}]c$ showed oscillatory changes with intervals of 2–3 min. $[Ca^{2+}]m$, on the other hand, showed very subtle and unexpected changes: it decreased with an increase in $[Ca^{2+}]c$ and increased with a decrease in $[Ca^{2+}]c$. However, upon shRNA-mediated knockdown of MICU1, a gatekeeper protein of mitochondrial calcium uniporter (MCU), $[Ca^{2+}]m$ increased in phase with $[Ca^{2+}]c$ oscillations having much greater amplitudes than those in control cells. Despite the remarkable increase in $[Ca^{2+}]m$ dynamics, glucose-stimulated $[Ca^{2+}]c$ dynamics remained almost the same. These results indicate that $[Ca^{2+}]m$ is tightly regulated by MICU1 during glucose stimulation, and that increases in $[Ca^{2+}]m$ above the baseline level seem not to be necessary for the generation of glucose-stimulated $[Ca^{2+}]c$ oscillations.