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Physiological Role of Kv Channels in the Insulin Secretion from Islet β-Cells

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Summary

Background and Aims: In pancreatic β-cells, activation of delayed rectifier K^+ (Kv) channels might repolarize cells and attenuate glucose-stimulated action potentials to suppress insulin secretion. Among Kv channel families, Kv2.1 is reportedly expressed in islet β-cells as the major component of Kv currents in rodents. In this study, we aimed to elucidate the physiological role of Kv2.1 channels for insulin secretion and the possible involvement of Kv2.1 channels in the ghrelin-operated β-cell signaling pathway.

Materials and Methods: Islets of Langerhans were isolated from age-matched male Wistar and diabetic GK rats by collagenase digestion. In rat single β-cells, cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) was measured by fura-2 microfluorometry, while membrane potentials and whole cell currents were measured in the presence of tolbutamide by nystatin-perforated patch-clamp technique. Insulin release from rat isolated islets was determined by ELISA.

Results: Kv2.1 channel blockers strongly attenuated Kv channel currents and potentiated the glucose-induced insulin release in β-cells. Exposure of cells to ghrelin attenuated the glucose-induced action potential firing by rapidly repolarizing the membrane and shortening the duration of bursting in a reversible manner. Voltage-dependent outward Kv channel currents evoked by depolarizing pulses were significantly increased by ghrelin in a cAMP signaling-dependent manner. In the presence of the channel blocker, ghrelin did not affect the Kv channel currents and insulin release. The Kv2.1 immunofluorescence intensity in the islets of diabetic GK rats was stronger than that in normal Wistar rats. Kv2.1 channel blocker-sensitive Kv channel current density in β-cells was larger in GK rats. Blockade of Kv2.1 channels potentiated the glucose-induced $[Ca^{2+}]_i$ increases and insulin release in β-cells of diabetic GK rats.

Conclusion: Kv2.1 channels may physiologically limit glucose-induced Ca^{2+} entry to suppress insulin secretion in β-cells. Ghrelin may attenuate membrane excitability via activation of Kv2.1 channels. Enhanced expression and excessive activity of Kv2.1 channel may be causally related to impaired insulin secretion in diabetic rats. Blockade of this channel can promote insulin release, providing a potential therapeutic tool to treat type 2 diabetes.