Paracrine control of glucagon secretion in the pancreatic α-cell: Studies involving optogenetic cell activation

Akademisk avhandling

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av Caroline Miranda

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ABSTRACT
The mechanisms controlling glucagon secretion by α-cells in islets of Langerhans were studied. We generated mice with the light-activated ion channel ChR2 specifically expressed in β-, α-, and δ-cells, and explored the spatio-temporal relationship between cell activation and glucagon release. In paper I, ChR2 was expressed in β-cells and photoactivation of these cells rapidly depolarized neighbouring δ-cells but produced a more delayed effect on α-cells. We showed that these effects were mediated via electrical signalling from the β- to δ-cells via gap-junction. Once activated, the δ-cells released somatostatin which repolarized the α-cells following its intercellular diffusion from the δ- to the α-cells. In paper II we used a novel antibody for detection of somatostatin, which showed great efficiency compared with commercially available antibodies. Immunostaining of intact islets showed an islet-wide network involving α- and δ-cells. Furthermore, we used immunostaining to compare the islet architecture as pertaining to δ-cell number, and morphology between islets from healthy human donors and type 2 diabetic donors and found that the number of δ-cells in type 2 diabetic islets is reduced. In paper III we expressed ChR2 in α- and δ-cells in two novel mouse models. We showed that photoactivation of α-cells depolarized the α-cells and evoked action potential firing, effects that were associated with stimulation of glucagon secretion regardless of the glucose concentration. In islets exposed to 1 mM glucose, photoactivation of δ-cells transiently hyperpolarized α-cells, produced a long-lasting inhibition of glucagon exocytosis and inhibited glucagon secretion at 1 mM glucose but had no additional inhibitory effect at 6 or 20 mM glucose. The effect of somatostatin was so strong that it was possible to suppress glucagon secretion by photoactivation of δ-cells even when measurements were performed using the perfused mouse pancreas.

Keywords: Glucagon, α-cell, somatostatin, δ-cell, optogenetics, secretion, type 2 diabetes