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

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Academicum, Medicinaregatan 3, den 3 september, klockan 13:00

av **Caroline Miranda**

Fakultetsopponent:

Prof. Marjan Rupnik

Medical University of Vienna, Austria

Avhandlingen baseras på följande delarbeten

I. Briant, L. Reinbothe, T. Spiliotis, J. **Miranda, C**. Rodriguez, B. Rorsman, P. δ-cells and β-cells are electrically coupled and regulate α-cell activity via somatostatin. J. Physiol. 2018, Jan 15: 596(2): 197-215

II. **Miranda, C**. Kothegala, L. Lundequist, A. Garcia, G. Belekar, P. Krieger, J-P. Presto, J. Rorsman, P. Gandasi, N.R. Structural correlations influencing regulation of somatostatin-releasing δ-cells *(Manuscript)*

III. **Miranda, C**. Tolö, J. Santos, C. Kothegala, L. Mellander, L. Hill, T. Briant, L. Tarasov, A.I. Zhang, Q. Gandasi, N.R. Rorsman, P. Dou, H. Intraislet paracrine crosstalk between islet cells unveiled by optogentic activation of α- and δ-cells. *(Manuscript)*

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

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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-cell 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

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