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Physiology and Pathophysiology of Hormone Secretion from Islets of Langerhans

Akademisk avhandling

Som för avläggande av medicinsk vetenskap doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hall 2119, House 2, Hälsovetarbacken, Arvid Wallgrens backe 5, den 17 november 2023, klockan 13:00

av **Samuel Acreman**

Fakultetsopponent:

Dr Caroline Bonner

L'Institut Pasteur de Lille, France

Avhandlingen baseras på följande delarbeten

I. Acreman, S., Ma, J., Denwood, G., Gao, R., Rorsman, P., Zhang, Q. The endoplasmic reticulum plays a key role in α-cell intracellular Ca^{2+} dynamics and glucose-regulated glucagon secretion.

II. Gandasi, N.R., Gao, R., Kothegala, K., Pearce, A., Santos, C., Acreman, S., Basco, D., Benrick, A., Chibalina, M.V., Clark, A., Guida, C., Harris, M., Johnson, P.R.V., Knudsen, J.G., Ma, J., Miranda, C., Shigeto, M., Tarasov, A.I., Yeung, H.Y., Thorens, B., Wernstedt Asterholm, I., Zhang, Q., Ramracheya, R., Ladds, G., Rorsman, P. GLP-1 metabolite $GLP\text{-}1^{(9\text{-}36)}$ is a systemic inhibitor of mouse and human pancreatic islet glucagon secretion.

III. McLaughlin, K., Acreman, S., Nawaz, S., Cutteridge, J., Clark, A., Knudsen, J.G., Denwood, G., Spigelman, A.F., Manning Fox, J.E., Singh, S.P., MacDonald, P.E., Hastoy, B., Zhang, Q. Loss of tetraspanin-7 expression reduces pancreatic β-cell exocytosis Ca^{2+} sensitivity but has limited effect on systemic metabolism. *Diabetic Medicine* 2022; 39(12):e14984. doi: 10.1111/dme.14984.

IV. Gao, R., Acreman, S., Ma, J., Miranda, C., Dou, H., Zhao, R., Maghera, J., Ellis, C., Dickerson, M., Tarasov, A., Clark, A., Yang, T., Gilon, P., Macdonald, P.E., Jacobson, D.A., Rorsman, P., Zhang, Q. A mechanism for rapid cross-talk between pancreatic α- and δ-cells and its role in hypoglycaemia-induced glucagon secretory failure.

SAHLGRENSKA AKADEMIN

INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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Physiology and Pathophysiology of Hormone Secretion from Islets of Langerhans

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Abstract

Diabetes is a metabolic disorder stemming from the improper regulation of blood glucose levels by hormones secreted by pancreatic islets of Langerhans. **Paper I** describes the mechanism by which glucose can regulate glucagon secretion, independent of membrane potential, from pancreatic α-cells, via modulation of endoplasmic reticulum Ca^{2+} handling. **Paper II** shows that the GLP-1 metabolite GLP-$1^{(9\text{-}36)}$ acts directly on α-cells to inhibit glucagon secretion, via activation of G_i-coupled glucagon receptors. **Paper III**, shows that the islet autoantigen tetraspanin-7 regulates β-cell transmembrane Ca^{2+} influx and the Ca^{2+} sensitivity of exocytosis. **Paper IV** demonstrates that α-cells and their neighbouring δ-cells exhibit a novel paracrine signalling loop. δ-cells react to the activity of adjacent α-cells, secreting somatostatin, to prevent glucagon hypersecretion. This mechanism becomes sensitised following exposure to hypoglycaemia, leading to excessive intra-islet somatostatin secretion, impairing glucose counter-regulation. Together, these papers reveal novel mechanisms governing the regulation of islet hormone secretion, which may lead to improvements in therapies for diabetes.

Keywords: Islet; diabetes; glucagon; insulin; somatostatin; incretin; pancreas; hypoglycaemia; tetraspanin-7; GLP-1; endoplasmic reticulum.

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