

**P068** GLP-1 secreted from alpha cells, is upregulated in islets of mice deficient in PC2

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GLP-1 is synthesised in the intestinal L-cells through the cleavage of proglucagon by proprotein convertase 1 (PC1). Pancreatic alpha cells also express proglucagon cleaved by PC2, to yield glucagon. Evidence suggests that alpha cells can adapt to produce GLP-1. It is unclear how GLP-1 is released from alpha cells.

Glucagon secretion was stimulated from alphaTC1-6 cells in response to low glucose. GLP-1 release by these cells was inhibited by low glucose. GLP-1 and glucagon release was stimulated in response to 40mM KCl. PC2<sup>-/-</sup> mice were studied to determine whether this changes proglucagon processing from glucagon to GLP-1. Glucagon was virtually absent in PC2<sup>-/-</sup> islets. Conversely GLP-1 levels were increased in PC2<sup>-/-</sup> islets. PC2<sup>-/-</sup> mice displayed improved glucose tolerance.

This suggests that GLP-1, produced in alpha cells, may exist in a separate sub-section of secretory granules that are responsive to membrane depolarisation, but not glucose. Loss of PC2 from the pancreatic alpha cell causes loss of glucagon secretion, but interestingly, an increase in GLP-1. This switch from glucagon to GLP-1 may improve glucose tolerance. The importance of GLP-1 production in the islet remains unknown, however it may have a role in augmenting beta cell mass.