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cGMP kinase I regulates glucagon release

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Blood glucose levels are tightly controlled by the two peptide hormones glucagon and insulin. At hyperglycaemia, B-cells in the islets of Langerhans secrete insulin, whereas islet A-cells release glucagon at hypoglycaemia to stimulate e.g. glucose production in the liver. Previously, an important role for nitric oxide (NO) in the development of type-1 diabetes mellitus (insulin dependent diabetes mellitus) was reported [1]. The mechanisms are unknown whereby NO modulates islet (mal-)function. We hypothesized that NO signals via the cGMP/cGMP kinase I (cGKI) pathway to modulate the endocrine control of blood glucose levels. Glucose homeostasis was studied in the conventional cGKI knockouts (KOs) and in cGKI rescue mice (RM) [2] in comparison to age- and littermate controls. The cGKI mutant mice were significantly hyperglycemic at fasting. Further *in vivo* analysis of RM revealed no changes of the serum insulin levels, but the serum glucagon was significantly increased in comparison to controls. We anticipated that endogenous cGKI could directly affect the release of glucagon, because immunofluorescence of Langerhans islets demonstrated that the cGKI protein localized mainly to the glucagon-secreting A-cells in control mice, but was absent from B-cells and not detectable in the islets of gene-targeted cGKI mice. The essential beta subunit of the soluble guanylyl cyclase ($sGC\beta_1$) [3] and the cGMP-degrading phosphodiesterase-5 (PDE-5), both important cGMP signaling components in many cells, were also detectable in A-cells of all genotypes analyzed. To identify a specific function for the pathway in A-cells, we measured the hormone output of isolated islets at physiologically low (6 mM) and high (20 mM) concentrations of glucose. Interestingly, the glucose-induced suppression of glucagon release was abolished in islets that lacked cGKI, whereas the total glucagon content of the islets was not changed.

Taken together, our approach identifies a new function of the cGMP-cGKI signaling pathway in pancreatic A-cells. The genetic disruption of islet cGKI results in an abnormal release of glucagon, which leads to a hyperglycaemic fasting phenotype indicative for a pre-diabetic syndrome.

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References

1. Burkart V, Kolb H: **Nitric oxide in the Immunopathogenesis of Type I Diabetis.** *Handb Exp Pharmacol* 2000:525-544.
2. Weber S, Bernhard D, Lukowski R, Weinmeister P, Wörner R, Wegener JW, Valtcheva N, Feil S, Schlossmann J, Hofmann F, Feil R: **Rescue of cGMP Kinase I Knockout Mice by Smooth Muscle-Specific Expression of Either Isozyme.** *Circ Res* 2007, **101:**1096-1103.
3. Friebe A, Mergia E, Dangel O, Lange A, Koesling D: **Fatal gastrointestinal obstruction and hypertension in mice lacking nitric oxide-sensitive guanylyl cyclase.** *Proc Natl Acad Sci USA* 2007, **104:**7699-7704.