Insulin is secreted upon glucose stimulation by both gastrointestinal enteroendocrine K-cells and L-cells engineered with the preproinsulin gene

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Resumen

Transgenic mice carrying the human insulin gene driven by the K-cell glucose-dependent insulinotropic peptide (GIP) promoter secrete insulin and display normal glucose tolerance tests after their pancreatic beta-cells have been destroyed. Establishing the existence of other types of cells that can process and secrete transgenic insulin would help the development of new gene therapy strategies to treat patients with diabetes mellitus. It is noted that in addition to GIP secreting K-cells, the glucagon-like peptide 1 (GLP-1) generating L-cells share/many similarities to pancreatic p-cells, including the peptidases required for proinsulin processing, hormone storage and a glucose-stimulated hormone secretion mechanism.

In the present study, we demonstrate that not only K-cells, but also L-cells engineered with the human preproinsulin gene are able to synthesize, store and, upon glucose stimulation, release mature insulin. When the mouse enteroendocrine STC-1 cell line was transfected with the human preproinsulin gene, driven either by the K-cell specific GIP promoter or by the constitutive cytomegalovirus (CMV) promoter, human insulin co-localizes in vesicles that contain GIP (GIP or CMV promoter) or GLP-1 (CMV promoter). Exposure to glucose of engineered STC-1 cells led to a marked insulin secretion, which was 7-fold greater when the insulin gene was driven by the CMV promoter (expressed both in K-cells and L-cells) than when it was driven by the GIP promoter (expressed only in K-cells). Thus, besides pancreatic beta-cells, both gastrointestinal enteroendocrine K-cells and L-cells can be selected as the target cell in a gene therapy strategy to treat patients with type 1 diabetes mellitus.

Palabras clave

Palabras clave de autor: Type 1 diabetes mellitus; preproinsulin gene; gastrointestinal enteroendocrine cells; K-cells; L-cells

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