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GUT HORMONES FOR β-CELL SURVIVAL AND REGENERATION IN TYPE 1 DIABETES

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Abstract:

Transplantation of islets from human cadaver pancreases can replace insulin therapy in patients with type 1 diabetes, but is limited by shortage of donor organs; also, the insulin-dependent state returns in 90% of patients at 5 years after islet transplantation (1). As an alternative to islet transplantation, recent studies have revealed the feasibility of β-cell regeneration in the pancreases of diabetic animal models (2). Therefore, β-cell regeneration has become an area of intensive research, with the potential to expand and restore the pancreatic β-cell mass and restore normoglycemia in human subjects with either type 1 or type 2 diabetes. The potential for β-cell regeneration may be realized by stimulating this process using one or more β-cell putative growth factors, such as the gastrointestinal peptides, gastrin (3), glucagon-like peptide-1 (GLP-1) (4), and long-acting GLP-1 receptor agonists (GLP-1 analogs) such as exendin-4 (4,5), exenatide (6), and liraglutide (7).

Studies in our laboratory have demonstrated that it is possible to regenerate β-cells and correct hyperglycemia in nonobese diabetic (NOD) mice, an animal model for human type 1 diabetes, using combinations of peptides such as epidermal growth factor (EGF) and gastrin, or GLP-1 and gastrin. In these studies, we found that treatment of acutely-diabetic NOD mice with a short course (2-3 weeks) of EGF + gastrin (8) or GLP-1 + gastrin (9) reduced or corrected hyperglycemia in most mice, and the effect persisted long-term (6-10 weeks) after treatments were stopped. Correction of hyperglycemia correlated with increases in pancreatic β-cell mass and insulin content, indicating that the peptide therapies had induced β-cell regeneration as the mechanism of diabetes reversal. Interestingly, β-cell regeneration did not incite an autoimmune

β-cell destructive response and immunotherapy was not required. We obtained preliminary data to suggest that the peptide therapies had dampened the autoimmune response, possibly by acting on immune cells directly and/or indirectly via effects on regenerating β-cells.

Long-acting GLP-1 receptor agonists (exenatide, liraglutide) are approved or are soon to be approved for clinical use in type 2 diabetes (6,7). Recently we obtained evidence that these GLP-1 receptor agonists can regenerate β-cells and reduce/correct hyperglycemia in NOD mice with type 1 diabetes. We found that liraglutide could restore pancreatic β-cell mass and correct hyperglycemia after diabetes onset in NOD mice, and gastrin potentiated the effects of liraglutide (10). Similarly, exenatide restored pancreatic β-cell mass and reversed diabetes in NOD mice (11).

In other studies, we found that peptides that induced pancreatic β-cell regeneration in NOD mice also had this effect on adult human pancreatic tissue. The combination of EGF and gastrin induced neogenesis of human islet β-cells from pancreatic exocrine duct epithelial cells, both in vitro and after the cells were implanted in immunodeficient mice, and this resulted in an increase in functional (insulin-secreting) β-cells (12). Also, combination therapy with GLP-1 and gastrin reduced hyperglycemia in streptozotocin-diabetic immunodeficient mice implanted with human pancreatic cells by inducing β-cell neogenesis from exocrine duct epithelial cells in the pancreatic cell preparations (13).

Clinical trials of these peptide therapies for β-cell regeneration in type 1 diabetes are in the planning stages and a few are in early phase 1 and 2 studies. EGF + gastrin, exenatide + gastrin, and exenatide ± different immunotherapeutic drugs are some of the combination therapies being tested for β-cell regeneration in patients with type 1 diabetes, either without or in conjunction with islet transplantation in order to expand the donor β-cell mass before and/or after transplantation.

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