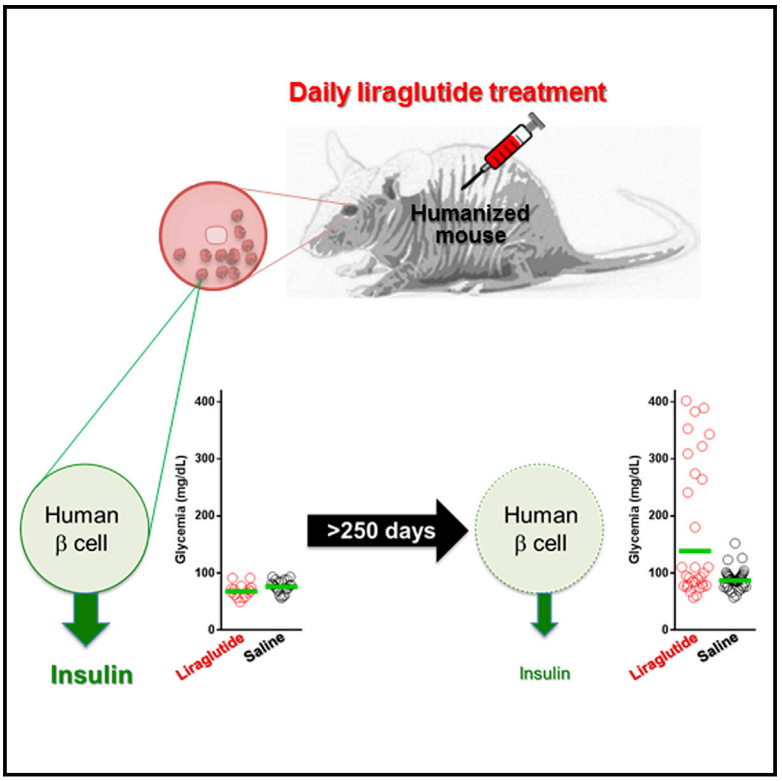
Short Article

Cell Metabolism

Liraglutide Compromises Pancreatic β Cell Function in a Humanized Mouse Model

Graphical Abstract



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In Brief

Using a humanized mouse model, Abdulreda et al. show that, following initial improvement in human pancreatic function, prolonged daily liraglutide treatment for over 200 days is associated with compromised insulin release and dysregulated glucose homeostasis, indicating islet cell metabolic exhaustion.

Highlights

- A humanized mouse model generated by intraocular islet transplantation
- Liraglutide promoted initial function of human islets transplanted into mice
- Liraglutide has beneficial short-term effects on human islet function
- Long-term, daily liraglutide treatment compromised human islet function

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Liraglutide Compromises Pancreatic β Cell Function in a Humanized Mouse Model

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SUMMARY

Incretin mimetics are frequently used in the treatment of type 2 diabetes because they potentiate β cell response to glucose. Clinical evidence showing short-term benefits of such therapeutics (e.g., liraglutide) is abundant; however, there have been several recent reports of unexpected complications in association with incretin mimetic therapy. Importantly, clinical evidence on the potential effects of such agents on the β cell and islet function during long-term, multiyear use remains lacking. We now show that prolonged daily liraglutide treatment of >200 days in humanized mice, transplanted with human pancreatic islets in the anterior chamber of the eye, is associated with compromised release of human insulin and deranged overall glucose homeostasis. These findings raise concern about the chronic potentiation of β cell function through incretin mimetic therapy in diabetes.

INTRODUCTION

Incretin mimetics, or glucagon-like peptide-1 (GLP-1) analogs, are a relatively new family of antidiabetic agents. Several GLP-1 analogs are currently used, and more are being developed for the treatment of type 2 diabetes (T2D) (Saulsberry et al., 2015; Tella and Rendell, 2015). GLP-1 is an incretin, a polypeptide secreted by intestinal L cells in response to food ingestion. Incretins contribute to glucose homeostasis by stimulating insulin secretion from pancreatic β cells, suppressing prandial glucagon secretion from α cells, reducing gastric emptying and intestinal absorption, and promoting satiety. GLP-1 is also rapidly inactivated by dipeptidyl peptidase-4 (DPP-4). While the GLP-1 analog liraglutide shares 97% homology to human GLP-1, it is, however, less susceptible to degradation by DPP-4, and hence, its effects last longer. This has led to the use of GLP-1 analogs, such as liraglutide, as long-acting incretin mimetics to improve glycemic control in T2D patients. Although liraglutide has longer activity compared to GLP-1, its half-life is still limited, thus requiring daily injections (Buse et al., 2009, 2010). While extended-release formulations of GLP-1 analogs (e.g., dulaglutide) have been developed to allow once-weekly administration, these and other antidiabetic agents (e.g., sitagliptin and metformin) have demonstrated less-impressive reductions in glycated hemoglobin (A1C) and BMI for T2D patients than liraglutide (Chitnis et al., 2014; Dungan et al., 2014; Lee et al., 2014; Trujillo and Nuffer, 2014).

Available clinical data show the short-term benefits of therapy with incretin mimetics (e.g., liraglutide) in diabetes and other conditions typically during the first few years of use (Davies et al., 2015; Inoue et al., 2014; Katout et al., 2014; Mateos and Wajchenberg, 2012). However, preclinical and clinical data on the potential impact of such therapeutics on the human β cell after continuous, multiyear use are currently lacking (Consoli and Di Biagio, 2011; Devaraj and Maitra, 2014; Inoue et al., 2014; Wajchenberg, 2007). Notably, reports on undesired side effects and potentially life-threatening complications in association with the use of GLP-1 analogs have been emerging, and concerns about these effects after long-term use of such agents are increasingly being expressed (Prescrire Int., 2015). Gastrointestinal adverse effects are frequently reported with incretin mimetic therapy, and there have been several reports on increased risk of pancreatitis and pancreatic or neuroendocrine tumors with these therapies (Butler et al., 2013; Chalmer et al., 2015; Consoli and Formoso, 2015; Devaraj and Maitra, 2014).

Although incretin mimetics have been used in the clinic for more than a decade, a conclusive review of their potential effects on the human islet during long-term, continuous use has been difficult due to inconsistencies in treatment duration and reporting biases in clinical trials (Butler et al., 2013; Consoli and Formoso, 2015; Devaraj and Maitra, 2014). Additionally, it is neither feasible to exert varied yet well-controlled experimental conditions nor ethical to manipulate treatment conditions in human subjects to investigate this outstanding question in the meantime. Liraglutide's beneficial effects on pancreatic β cells were initially demonstrated by pioneering studies using mice (Bock et al., 2003; Larsen et al., 2001; Sturis et al., 2003). Liraglutide was reported to reduce hyperglycemia in T2D mouse models by increasing pancreatic β cell mass through enhanced proliferation (Rolin et al., 2002). While rodent islets have been and are likely to remain the workhorses of research in islet biology, increasing evidence showing distinct structural and functional features of the rodent and human islets underscores the need for conducting studies with primary human islets (Cabrera