GLP-1–Based Therapies and the Exocrine Pancreas: More Light, or Just More Heat?

Edwin A.M. Gale

GLP-1–based therapies are the most promising new treatment for type 2 diabetes to have been introduced in recent years. Long-term outcome studies are not yet available, but in the interim they have cleared many—although not all—of the hurdles for acceptability, efficacy, and safety. GLP-1 is a proglucagon-derived peptide secreted from the L cells of the gut in response to food. It is rapidly inactivated by dipeptidyl peptidase-4 (DPP-4) enzymes following secretion. The fraction of intact GLP-1 that survives enzymatic degradation boosts the insulin response to oral glucose, accounting for much of the incretin effect. Inhibition of DPP-4 enhances the physiological GLP-1 response to food and lowers circulating glucose without inducing hypoglycemia. The long-term consequences of inhibition of DPP-4—a widely distributed protease whose substrates include neuropeptides and chemokines—are unknown, but the safety profile of this class of agent currently appears favorable (1).

Native GLP-1 has a short half-life in the circulation and is therefore unsuitable for clinical use. This has prompted development of analogs that are both resistant to degradation and appropriate for use at pharmacological doses. These have proved remarkably effective in reducing body weight as well as plasma glucose and have been particularly useful in obese individuals who might otherwise have been candidates for bariatric surgery. The main side effects that have been reported are nausea and vomiting, and in some cases they are so severe as to lead to circulatory collapse and cardiovascular or renal problems (2). Animal safety studies with liraglutide have identified a higher than expected number of cases of a rare C-cell carcinoma of the thyroid (3), and acute pancreatitis has been reported in humans treated with liraglutide or exenatide (4).

GLP-1 receptors are abundant on pancreatic β-cells, an observation that gave rise to the hope that GLP-1–based therapies would induce pancreatic β-cell regeneration, the Holy Grail of diabetes therapy. These hopes have been dashed because β-cell proliferation has been observed only in immature, as opposed to adult, rodent islets (5), and fully differentiated adult human β-cells appear unable to proliferate (6). However, GLP-1 receptors are present on other cells that retain proliferative capacity, thereby raising the possibility that stimulation of these receptors might promote unwanted proliferation of healthy or abnormal cells in tissues such as the thyroid and exocrine pancreas.

A "worst-case" scenario has been described in alarming terms. According to this hypothesis, stimulation of GLP-1 receptors in the exocrine pancreas could lead to overgrowth of the cells lining the smaller ducts, resulting in partial obstruction, increased back pressure within the pancreatic acini, and low-grade inflammation. Although typically subclinical, this process might (according to the hypothesis) develop into acute pancreatitis in rare or predisposed cases. More typically, low-grade chronic inflammation would occur, predisposing to metaplasia and generation of premalignant pancreatic intraepithelial (PanIN) lesions, which have the potential to progress to pancreatic adenocarcinoma over the course of time (7). PanIN lesions express the GLP-1 receptor, and the prevalence of these lesions in the aging population increases in parallel with the risk of pancreatic cancer (8).

Although this hypothesis relies on several conceptual leaps, Butler et al. (7) have steadily joined the dots together in such a way as to indicate plausibility in some experimental situations. Central to their argument is the existence and role of GLP-1 receptors on healthy and premalignant pancreatic exocrine cells, described further by Gier et al. (9) in this issue of *Diabetes*. Pancreatic ductal adenocarcinoma accounts for most cases of carcinoma of the pancreas, but the cell of origin remains in some dispute.

Pancreatic duct glands (PDGs), tiny outpouchings from the wall of pancreatic ducts, have recently been proposed as the stem cell compartment responsible for new duct and acinar cells, and as a potential source for the progenitor cells of pancreatic cancer (10,11). Butler and colleagues found GLP-1 receptors in the PDGs of several species, including man. In the rat, 12 weeks of high-dose exenatide therapy caused pancreatic weight to increase in treated animals relative to body weight (which fell with exenatide). This was associated with marked expansion of PDG number and volume, mucinous metaplasia, and changes in columnar cells resembling low-grade PanIN lesions. A second experiment was performed in mice with a knock-in *Kras* mutation which renders them susceptible to dysplasia and pancreatic cancer formation. Exenatide induced more extensive changes against this background, including mucinous metaplasia and formation of PanIN lesions. PDGs and PanIN cells expressed the GLP-1 receptor in both of these studies, as did human PanIN lesions from nonneoplastic lesions adjacent to pancreatic carcinoma. Finally, a human pancreatic duct cell line was exposed to exenatide, and preproliferative changes with increased cyclin D1 expression were observed. The authors concluded that exenatide has the potential to induce focal proliferative changes in pancreatic duct cells, particularly when exhibited against a susceptible genetic background, and that these changes might potentially lead to metaplasia and premalignant lesions.

From the Department of Diabetic Medicine, University of Bristol, Bristol, U.K.
Corresponding author: Edwin A.M. Gale, edwin.gale@bristol.ac.uk.
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How then are we to understand the results of Nyborg et al. (12), which also appear in this issue of *Diabetes*? The report describes extensive preclinical safety studies performed in mice, rats, and nonhuman primates, and finds no evidence that long-term exposure to high doses of liraglutide produced any structural change in the exocrine pancreas. The authors, who work for the manufacturers of liraglutide, found no excess of pancreatitis in mice, and no pancreatitis at all, whether macroscopic or microscopic, in rats or monkeys, even when the latter were treated for up to 2 years at exposures up to 60-fold greater than those obtained in humans (12). Similarly negative toxicology results have been published for the DPP-4 inhibitor sitagliptin (1).

Although undoubtedly reassuring, these findings are somewhat less conclusive than might appear at first glance. The analysis describes routine preclinical screening that was performed unblinded by trained toxicological pathologists at a time when no question had been raised as to possible effects of GLP-1 agonists on the exocrine pancreas. A single slice appears to have been taken through the middle of the pancreatic body and subjected to routine staining. This rapid screening procedure should be contrasted with the detailed search reported by Gier et al., in which a minimum of 40 longitudinal sections through the rat pancreas were examined with Alcian blue and PAS stains in addition to hematoxylin and eosin. Furthermore, and in contrast to some or all of the humans treated with this agent, the animals in the study by Nyborg et al. were lean, nondiabetic, and had no genetic or environmental predisposition to pancreatic disease. We may accept the conclusion of the authors, which is that high-dose liraglutide did not produce pancreatitis or systematic structural disruption of the exocrine pancreas in these animals, but a systematic search of the whole organ by experts in pancreatic pathology would be needed before we could conclude that exposure to liraglutide was totally benign.

Where then does this leave us? In one sense, not much further forward. Those who already believe in the safety of the GLP-1–based therapies will conclude that they are safe, and those who do not will draw the opposite conclusion. It helps no one that the debate has become highly adversarial. How then can we move things forward?

The launch of a new drug represents a large scale experiment whose long-term outcome is notoriously difficult to monitor. These difficulties are multiplied when the new agent has pleiotropic effects and potentially unpredictable outcomes. Nor does recent experience breed confidence in the current system of postmarketing safety monitoring, based as it is on a dialogue between the mirror bureaucracies of pharmaceutical companies and regulatory authorities. Safety concerns arising within this system are slow to surface. The process leading to the removal of troglitazone and of rosiglitazone was, for example, jumpstarted by individuals who were prepared to step outside regulatory channels in order to achieve results—and who encountered considerable hostility in the process (13). The situation becomes even more highly charged when, as in the present instance, clinicians raise safety concerns which have yet to register on the regulatory radar. Such concerns tend to be vigorously discouraged by manufacturers, at least until a threshold is reached at which the potential threat has to be acknowledged.

When it comes to the GLP-1 therapies, it would seem that this threshold has now been reached. A possibility has been raised that has some biological plausibility, and that is backed by a signal for pancreatic carcinoma in safety reports from two regulatory authorities (14,15). Although we may sympathize with the manufacturers, whose market position is vulnerable to safety concerns, warranted or unwarranted, and who find themselves in the invidious position of trying to prove a negative (2), safety is nonetheless their responsibility. It is equally understandable that clinicians might feel outraged at a threat to a popular and effective form of therapy, but safety is also their responsibility. Drug safety is everyone's business, and risk denial is not an acceptable substitute for risk assessment.

A salient feature of the debate has been the lack of common ground between proponents, who all too frequently appear to be talking past each other. The Butler group has tended to focus upon histopathological changes and the cellular mechanisms that might potentially underlie these, whereas other groups have concentrated upon different types of animal studies—for example, chemically induced pancreatitis—or have argued the lack of a human safety signal for pancreatitis in administrative databases (16). Science is based upon mechanism and reproducible experiments. There is, therefore, a clear need for other groups, preferably independent, to repeat, refute, replicate, or reinterpret what has already been done. The potential effects of GLP-1 on the endocrine pancreas have been examined in considerable detail, and the exocrine pancreas requires the same detailed attention. The human pancreas holds the final answer, and autopsy material from those exposed to GLP-1 therapies should be examined whenever possible. Furthermore, since primates are the nearest nonhuman equivalents to humans, it is to be hoped that the companies involved will permit full independent expert review of the primate material they have available. Time alone will show whether there will, or will not, be a long-term increase in exocrine pancreatic disease in those already exposed to these therapies; but the stakes are high, and we must be vigilant to any possibility of harm.

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