Incretin Effects on $\beta$-Cell Function, Replication, and Mass

The human perspective

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There is a progressive deterioration in $\beta$-cell function in patients with type 2 diabetes. At diagnosis, islet function may be reduced by up to 50% compared with healthy control subjects, and there is also likely to be a reduction in $\beta$-cell mass of up to 60%. The reduction in $\beta$-cell mass is due to accelerated apoptosis. Currently, few pharmacological therapies address this reduction in $\beta$-cell mass and function. This means that patients are generally subjected to an increasing polypharmacy to control their diabetes, with most eventually being treated by insulin. Incretin hormones, which are released from the gastrointestinal tract after a meal, enhance glucose-dependent insulin secretion from the pancreas, aiding the overall regulation of glucose homeostasis in healthy subjects. In addition, these hormones, especially glucagon-like peptide (GLP)-1, have a number of protective effects on the $\beta$-cells, including a reduction in apoptosis and enhancement of $\beta$-cell proliferation and neogenesis. These benefits are lost to a significant extent in patients with diabetes. The recently developed diabetes therapies, GLP-1 receptor agonists, such as exenatide and liraglutide, appear to have beneficial effects on $\beta$-cell function and hence offer promise for durable glycemic control as well as potentially reducing the micro- and macrovascular complications associated with type 2 diabetes.

**The Clinical Course of Type 2 Diabetes**—The clinical course of type 2 diabetes is characterized by a progressive decline in $\beta$-cell mass and function. Although the elevated levels of fasting glucose and impairment of insulin action in peripheral tissues may predate the diagnosis of type 2 diabetes, chronic hyperglycemia only results after a prolonged period of $\beta$-cell degeneration, a process that may begin as much as 12 years before diagnosis, involving a progressive reduction in functionality and mass (1,2). In the UK Prospective Diabetes Study, it was estimated that, at diagnosis, type 2 diabetic patients may have already lost up to 50% of their $\beta$-cell function. Because most current therapeutic options address the impaired glucose action or stimulate insulin secretion rather than the declining $\beta$-cell function, the ongoing decline in $\beta$-cell function leads to eventual failure of most antidiabetic therapies (3,4). Indeed, some secretagogues may accelerate $\beta$-cell failure. In the UK Prospective Diabetes Study, which involved >5,000 patients newly diagnosed with type 2 diabetes treated with either intensive therapy involving insulin or conventional therapy (diet alone), progressively worsening glycemic control and decline in $\beta$-cell function was reported regardless of the therapy used (3). In the cohort who received the conventional therapy regimen, $\beta$-cell function declined from 53% of normal at year 1 to 28% at year 6 (3). Glycemic control mirrored the decline in $\beta$-cell function. In many patients, addressing declining glycemic control due to secondary treatment failure by progression to multiple classes of agents will eventually lead to the use of insulin. Moreover, several classes of antidiabetic therapy are associated with weight gain (4,5), which will worsen insulin resistance, thereby undermining treatment efficacy. The possibility of the increase of cardiovascular risk, both due to increased weight and as a consequence of treatment-related cardiovascular events, also raises concerns of the safety of polypharmacy in these patients. If $\beta$-cell deterioration is able to be modified, this would raise the possibility of altering the clinical course of the disease by targeting the primary defect.

**The $\beta$-Cell in Type 2 Diabetes**—Physiologically, $\beta$-cells secrete insulin at low levels between meals to control hepatic glucose output and at higher levels after meals to facilitate the uptake of glucose (6). Insulin secretion with meals occurs in two distinct phases: a first phase that reduces basal glucagon secretion, thereby decreasing hepatic glucose production, and a second phase, commencing 10 min or so after glucose exposure, that is sustained until normoglycemia (blood glucose levels of 71–99 mg/dL) is restored (6). The first-phase insulin response is almost abolished or at least severely blunted in patients with type 2 diabetes (7), although levels of fasting insulin may be higher than normal (8). The loss in $\beta$-cell function appears to be accompanied by a reduction in $\beta$-cell mass (9).

Maintenance of $\beta$-cell mass involves a dynamic balance between cell replication, neogenesis, and apoptosis. For patients with type 2 diabetes, there appears to be a shift toward an increase in apoptosis that outweighs cell renewal. $\beta$-Cell apoptosis is multifactorial; chronic exposure of the $\beta$-cells to elevated levels of glucose leads to “glucotoxicity,” a process where hyperglycemia causes cellular dysfunction and mortality (10). Lipotoxicity, associated with high concentrations of free fatty acids, commonly observed in people who are obese, are insulin-resistant, or have type 2 diabetes, has also been linked to increased metabolic stress of the $\beta$-cells (11).

The reduction in $\beta$-cell mass in type 2 diabetes was demonstrated convincingly...
in a series of studies that compared β-cell mass in patients with type 2 diabetes with that in healthy control subjects (9). Using pancreatic autopsy tissue, Butler et al. (9) showed that obese patients with impaired fasting glucose or type 2 diabetes had a 40% (P < 0.05) and 63% (P < 0.01) reduction in β-cell mass compared with obese individuals without diabetes (9). Compared with lean nondiabetic subjects, lean patients with type 2 diabetes had a 41% deficit in relative β-cell mass (P < 0.05). Evidence suggests that a decrease in β-cell mass of ≥50% leads to the development of diabetes in primates (12). Butler et al. also demonstrated a significantly increased frequency of apoptotic events in patients with type 2 diabetes compared with nondiabetic case subjects. The implication for prevention of type 2 diabetes is that strategies that avoid the increased frequency of β-cell apoptosis may potentially be of clinical benefit.

**INCRETIN HORMONES, NOTABLY GLP-1**—The decline in β-cell function in type 2 diabetes has been linked with impaired action of the incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. These hormones are secreted from the intestine in response to energy intake and glucose and may potentiate as much as 70% of the meal-induced insulin response in healthy individuals (13). In patients with type 2 diabetes, the incretin response and subsequent insulin secretory response after oral glucose is typically reduced by 50% compared with healthy control subjects (14). These observations suggest that deficient incretin secretion may play a critical role in the pathogenesis of type 2 diabetes.

Although in normal subjects both GIP and GLP-1 act as incretin hormones, diabetes is often associated with a blunted or absent response to GIP (15). Even when infused at pharmacological levels, GIP only marginally stimulates insulin secretion in type 2 diabetes; hence, GLP-1 has been investigated as a potential pharmacological agent to treat type 2 diabetes. In healthy subjects, infusion of physiological levels of GLP-1 resulted in an increase in insulin secretion. By contrast, in patients with type 2 diabetes, the insulin response to physiological levels of GLP-1 was substantially reduced, thought to be because physiological levels of GLP-1 can no longer compensate for the loss of the GIP response (16) (Fig. 1). Infusion of GLP-1 at pharmacological levels (1 pmol/kg/min), however, augmented the “late phase” (20–120 min) insulin response to levels similar to those observed in healthy subjects (17) (Fig. 1).

**ANIMAL DATA**—As discussed above, the acute effect of GLP-1 on the β-cells is potentiation of glucose-dependent insulin secretion (18). Other effects include enhancement of insulin biosynthesis, stimulation of insulin gene transcription, increased expression of mRNA for glucose transporter 2 and glucokinase, stimulation of β-cell proliferation, and induction of islet neogenesis from precursor ductal cells, leading to an increase in β-cell mass as well as an inhibitory effect on β-cell apoptosis (19–21).

In vivo studies, GLP-1 improved glucose tolerance in animal diabetic models (20), suggesting that GLP-1 has a functional effect on β-cell activity. These beneficial effects appear to be due, at least in part, to changes in β-cell mass (22).

The above data from animal studies (20,22) support that activation of the GLP-1 receptor may increase β-cell mass. These findings are largely supported by data from in vitro human-cell studies. For example, in a study of isolated human islet cells, Farilla et al. (19) reported a reduction in the number of apoptotic β-cells after treatment for 5 days with GLP-1. Furthermore, the GLP-1–treated cells contained more insulin and were capable of more glucose-dependent insulin secretion. Likewise, Buteau et al. (23) noted that β-cell apoptosis induced by gluco- and lipotoxicity was prevented by GLP-1.

However, there are important differences between rates and capacity for islet cell turnover and growth between rodents and humans (24), such that it is not a reliable assumption to extend the findings from animal studies to human studies. Because it is not possible to evaluate β-cell mass noninvasively in humans, the question regarding the effects of GLP-1 on β-cell proliferation and apoptosis cannot be reliably determined in longitudinal or interventional studies. Data from long-term studies demonstrating durability of the response will offer the most reliable indication of a therapeutic effect on β-cell function.

Currently, most prescribed therapies fail to address the progressive decline in β-cell function and impaired action of the incretin hormones that underlie type 2 diabetes (25). Restoration of the activity of the incretin hormones, especially GLP-1, would not only improve insulin secretion, thereby restoring glycemic control, but may also help both to preserve and to protect β-cell mass and function (26).

**EFFECT OF GLP-1 AGONISTS ON β-CELL MASS AND FUNCTION**—Although native GLP-1 is rapidly degraded by the enzyme DPP-4 in the plasma, limiting its therapeutic potential because of its short half-life (<2 min), the beneficial properties of GLP-1 have been harnessed with the development of the longer-acting GLP-1 receptor agonists, liraglutide and exenatide (27). Exendin-4 is a naturally occurring GLP-1 receptor agonist, found in the lizard Heloderma suspectum, that has a 53% overlap of the natural amino acid sequence with mammalian GLP-1 but is more stable and less rapidly degraded than native human GLP-1 (28). Exenatide (synthetic exendin-4) has a relatively short half-life (2.4 h) (28) and hence must be administered twice daily. Liraglutide is an

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**Figure 1**—Pharmacological, but not physiological, levels of GLP-1 enhance insulin secretion in patients with type 2 diabetes. Reproduced with permission from Springer, from Højberg et al. (16) (A), and Vilsbøll et al. (17) (B).
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acylated derivative of human GLP-1, sharing 97% sequence identity with the native peptide, modified only by the addition of a glutamic acid residue at position 26, allowing attachment of a C16 palmitoyl group and substitution of arginine for lysine at position 34 (29). The longer half-life of ~12-15 h after subcutaneous injection (30) makes it suitable for once-daily administration (31). In addition to lowering A1C and improving other markers of glycemia, these GLP-1 receptor agonists are associated with direct and indirect effects on β-cell function, volume, and morphology. Liraglutide and exenatide are associated with a significant increase in β-cell mass and differentiation in rodents (32), and a reduction in β-cell apoptosis is observed in vitro (33–35). Exposure to liraglutide in mice with diabetes resulted in a significant increase in β-cell mass (P < 0.05) and β-cell proliferation rate (P < 0.001) when compared with control subjects (32). Inhibition of β-cell apoptosis in isolated human pancreatic cells was also reported after liraglutide administration, with β-cell proliferation increasing by up to threefold after incubation for 24 h (36). In animal and human studies, exenatide was shown to increase β-cell mass while at the same time causing a significant reduction in plasma glucose levels (20,37). These studies support the hypothesis that liraglutide and exenatide may have a protective effect on β-cell mass in type 2 diabetes.

EARLY CLINICAL STUDIES
Although the direct effects of liraglutide and exenatide on β-cell mass have not yet been demonstrated in clinical studies because of the lack of a suitable noninvasive technology, beneficial effects on islet cell function have been consistently reported.

Thus, in patients with type 2 diabetes, a single subcutaneous injection of liraglutide (7.5 μg/kg) was associated with improved β-cell responsiveness to elevated plasma glucose (31). In this randomized double-blind placebo-controlled crossover study involving 10 patients with type 2 diabetes, the insulin secretion rate area under the curve increased by ~70% (1,130 vs. 668 pmol/kg, P < 0.001) after liraglutide administration and approached levels similar to those observed in healthy subjects (1,206 pmol/kg). Improved β-cell function, as assessed by glucose-induced insulin secretion, maximal insulin secretion after arginine infusion, and the proinsulin/insulin ratio (Fig. 2), was also reported by Degn et al. (38) after 1 week of treatment (38). The latter is an important finding given that a raised proinsulin-to-insulin ratio denotes decreased insulin release in response to glucose and is a central feature of prediabetes and type 2 diabetes (39). Insulin secretion and β-cell function (measured using the homeostasis model assessment [HOMA]) was also reported in a study by Degn et al. (38). In that study, the first-phase insulin response and the insulin response to an arginine stimulation test with the presence of hyperglycemia were markedly increased (P < 0.001), whereas the proinsulin-to-insulin ratio fell (P = 0.001). The disposition index (peak insulin concentration after intravenous bolus of glucose multiplied by insulin sensitivity as assessed by HOMA) almost doubled during liraglutide treatment (P < 0.01), consistent with an improvement in β-cell function. These beneficial effects of liraglutide on β-cell function were also observed (40) in a double-blind randomized parallel-group placebo-controlled 12-week study involving 190 patients with type 2 diabetes randomized to liraglutide (0.045–0.75 mg). Mean β-cell function, assessed by the HOMA model, was significantly higher in patients receiving 0.75 mg liraglutide (P = 0.0002) after 12 weeks than in the placebo group. HOMA measures the ability of the β-cells to release insulin during fasting conditions. Furthermore, there was also a significant decrease in the proinsulin-to-insulin ratio after 12 weeks compared with placebo (P = 0.02).

First-phase insulin secretion, which is decreased in patients with type 2 diabetes, is partially restored with liraglutide (41). In a 14-week randomized dose-ranging (0.65, 1.25, or 1.9 mg/day) placebo-controlled study, first-phase insulin release was partially restored at liraglutide doses of 1.25 mg (118% increase) and 1.9 mg (103% increase). Second-phase insulin release was also shown to be increased in the 1.25 mg/day group (79%) (Fig. 2). Arginine-stimulated insulin secretion also increased significantly at the two highest dose levels versus placebo by 114 and 94%, respectively (P < 0.05). The findings from this study imply an improvement in the biphasic insulin response to hyperglycemia after administration of liraglutide. To assess the effect of liraglutide on β-cell function under normal living conditions, Mari et al. (42) used a β-cell model to analyze 24-h triple meal experiments conducted in a randomized double-blind placebo-controlled crossover study in 13 patients with type 2 diabetes. A clear enhancement of β-cell function was observed that was related to an improvement of glucose levels. Liraglutide was also shown to restore, in part, the potentiation peak (potentiation of insulin secretion by repeated glucose stimulation), which is blunted in diabetes. This phenomenon has also been observed with exenatide (43,44) and suggests a potentiating effect, possibly mediated by direct stimulation of the GLP-1 receptor.

Several studies investigating possible direct effects of exenatide on islet cell function have been conducted. In placebo-controlled studies, significant improvements in indices of β-cell function such as HOMA-B (45) and proinsulin-to-insulin ratio have been observed (46,47). Mari et al. (43) assessed postprandial β-cell function in patients with type 2 diabetes receiving exenatide (5 or 10 μg) or placebo whose diabetes was inadequately controlled by metformin with or without
a sulfonylurea. After the treatment period, patients (n = 73) who underwent a meal tolerance test showed a 72 and 40% (5 and 10 µg, respectively) increase in insulin secretion with exenatide compared with a 21% reduction in the placebo-treated patients. A significant (P < 0.05) improvement in first- and second-phase insulin secretion with exenatide or exenatide with rosiglitazone was observed in a 20-week open-label multicenter study involving 137 patients with type 2 diabetes on metformin (48). In the same study, insulin sensitivity was observed to be significantly higher in exenatide- and rosiglitazone-treated patients than in those on exenatide alone (P = 0.014). Overall, therapy with exenatide with rosiglitazone was found to offset the weight gain observed with rosiglitazone and elicited an additive effect on glycemic control with significant improvements in β-cell function and insulin sensitivity. Exenatide is also demonstrated to improve β-cell sensitivity to glucose (49). Finally, in comparison with glimepiride, exenatide was associated with a significant improvement in the HOMA-B index (48).

PHASE 3 CLINICAL DATA—Clinical data from the phase 3 liraglutide trial program add convincing support to the hypothesis that GLP-1 receptor agonists have a beneficial effect on β-cell function. The Liraglutide Effect and Action in Diabetes (LEAD) program was a phase 3 trial program that compared the efficacy and safety of once-daily liraglutide at doses of 0.6, 1.2, and 1.8 mg with those of standard treatments as monotherapy or in combination with other commonly used oral agents for type 2 diabetes (50–55). The program comprised six individual randomized controlled studies that included 4,456 patients from 40 countries.

Data from the LEAD program support that liraglutide has a rapid and sustained glycemic effect and is associated with weight reduction. Liraglutide’s glucose-lowering action is strictly glucose dependent with low hypoglycemic risk. In clinical trials, 1.2 and 1.8 mg liraglutide decreased A1C from baseline by −0.84 and 1.14%, respectively, over 52 weeks, achieving a significantly greater reduction than sulfonylureas, which showed a decrease from baseline of −0.51% (52). Liraglutide was also associated with a significantly greater reduction in fasting plasma glucose and postprandial glucose in this trial. When used in combination with oral therapies, liraglutide yielded reductions in A1C of −1.0 to −1.5% at a dose of 1.2 and 1.8 mg (all reductions were significant vs. placebo) (50,51,53–55). Across five trials, liraglutide produced weight reductions of up to −3.2 kg (50–55). In the LEAD studies, 1.2 and 1.8 mg liraglutide demonstrated significant improvement versus placebo on multiple indices of β-cell function including HOMA-B (50,53), proinsulin-to-insulin ratio (50,51,53), and proinsulin-to-C-peptide ratio (54). Across all six studies, an improvement of between 20 and 44% from baseline in HOMA-B was observed (55) (Fig. 3). In combination with glimepiride and metformin, liraglutide therapy was associated with a 25% improvement in HOMA-B (51). Changes in the proinsulin-to-insulin ratio ranged between −0.11 and 0.01 across the LEAD trials (55). In a head-to-head comparison of liraglutide, HOMA-B was reduced from baseline to a significantly greater extent with 1.8 mg/day liraglutide (32%) than with 10 µg/day exenatide (3%) after the addition of each agent to metformin and/or a sulfonylurea (56). No differences in the proinsulin-to-insulin ratio or fasting C-peptide were observed. In comparison with glimepiride, both doses of liraglutide significantly improved insulin resistance (as assessed by HOMA-1R) relative to sulfonylurea monotherapy (52).

Three similarly designed 6-month placebo-controlled trials involving patients with type 2 diabetes inadequately controlled on metformin or a sulfonylurea evaluated the effects of the addition of exenatide to metformin alone, or metformin and a sulfonylurea together (46,47,57). Relative to placebo, there was a reduction of A1C with exenatide of ∼1.5% across all trials from baseline levels of 8.2–8.6%. All patients started treatment with 5 µg injected twice daily for the first month, followed by 10 µg thereafter. A reduction in the proinsulin-to-insulin ratio toward more physiological proportions was observed with both doses of exenatide in the study reported by Buse et al. (46), whereas a significant reduction in this ratio was only observed with the 10-µg exenatide dose in the trial reported by DeFronzo et al. (47).

Long-term durability of the response to liraglutide was demonstrated in the LEAD-3 trial, which compared liraglutide (1.2 or 1.8 mg) with 8 mg glimepiride daily during 52 weeks of treatment. Both doses of liraglutide reduced A1C to a significantly greater extent than glimepiride (P = 0.0014 and P < 0.0001 for the 1.2- and 1.8-mg doses, respectively). Liraglutide was also associated with increased insulin secretion and better β-cell function as well as significant weight loss and reduced systolic blood pressure (52).

CONCLUSIONS—The pivotal role of the deterioration in β-cell mass and function that occurs in patients with type 2 diabetes underscores the importance of addressing this defect. It is likely that protecting the β-cells from further decline in function and their eventual failure might alter the natural history of type 2 diabetes and, if addressed early enough, could potentially prevent progression from impaired glucose tolerance to diabetes. The incretin therapies offer considerable promise as a means of targeting the primary defect in type 2 diabetes: β-cell dysfunction. Evidence supports that the GLP-1 receptor agonists exert positive beneficial effects on the β-cells and suggests that they are capable of preserving β-cell function, thereby limiting disease progression and the development of its micro- and macrovascular complications.
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