

**MARZIEH SALEHI, MD**Division of Endocrinology and Metabolism,  
University of Cincinnati Medical Center,  
Cincinnati, OH**DAVID A. D'ALESSIO, MD**Division of Endocrinology and Metabolism,  
University of Cincinnati Medical Center,  
Cincinnati, OH

# New therapies for type 2 diabetes based on glucagon-like peptide 1

## ABSTRACT

Cells in the gastrointestinal tract secrete several hormones that stimulate insulin secretion, one of which is glucagon-like peptide (GLP-1). Several new drugs act through the GLP-1 signaling system to stimulate insulin release and regulate blood glucose levels in patients with diabetes. One such compound, exenatide (Byetta), has recently become available, and others are in clinical development.

## KEY POINTS

Incretins are gastrointestinal hormones that are released after eating and stimulate insulin secretion. They are necessary for normal glucose tolerance.

One of the major incretins, GLP-1, lowers blood glucose in patients with diabetes by enhancing insulin secretion, reducing glucagon levels, and delaying gastric emptying.

Because GLP-1 is rapidly metabolized in the circulation by dipeptidyl peptidase IV (DPP-IV), its use in therapy is limited. Therefore, researchers are creating GLP-1 mimetics that are resistant to DPP-IV, as well as compounds that block DPP-IV activity.

These drugs have trophic effects on pancreatic islet cells in rodents, but this promising effect has not yet been demonstrated in humans.

A NEW CLASS of antidiabetes drugs consists of agents that supplement, mimic, or slow the metabolism of the endogenous hormone glucagon-like peptide (GLP-1). Several such agents are under development, and one has been approved by the US Food and Drug Administration.

These drugs will be attractive, for a variety of reasons. They promote glucose tolerance via several mechanisms. In short-term clinical studies, they have shown promising glucose-lowering effects. Also, they may have a better safety profile than the insulin secretagogues, since they stimulate insulin secretion only if blood glucose levels are above fasting levels, lessening the risk of hypoglycemia. Furthermore, preclinical data suggest that these agents may be able to delay or even halt the progression of diabetes, raising the possibility that they could be used in the early stage of diabetes to alter its course.

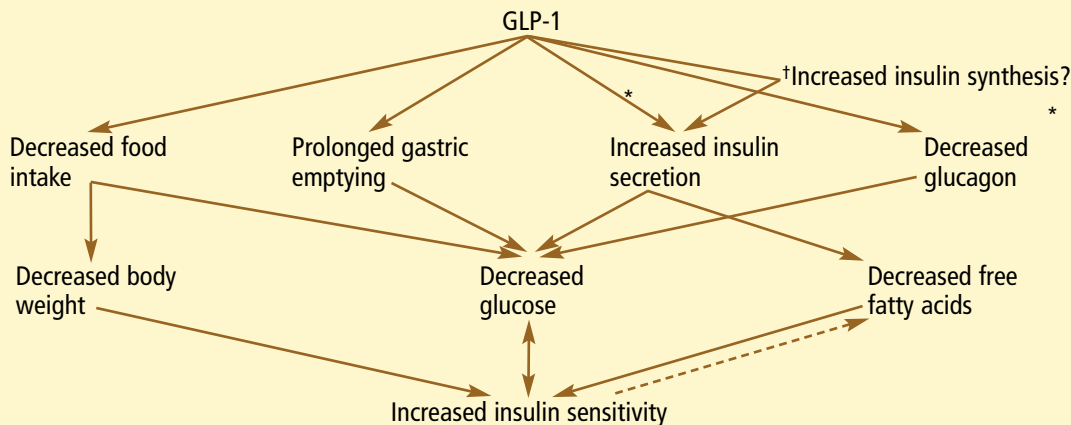
This paper reviews the mechanism and promise of these new drugs.

## TOO MUCH GLUCAGON, NOT ENOUGH INSULIN

From 1997 to 2000, the incidence of diagnosed type 2 diabetes mellitus increased across all age groups in the United States by about 40%.<sup>1</sup> Much of this alarming rise can be attributed to a higher frequency of obesity and its metabolic consequences. The problem is not unique to the United States: by 2030, the worldwide prevalence of diabetes is estimated to be 1.5 times that in 2000.<sup>2</sup>

Insulin resistance, related in part to obesity and elevated circulating fatty acids, is very common in patients with diabetes. However,

## How glucagon-like protein 1 (GLP-1) counteracts diabetes



**FIGURE 1.** Antidiabetogenic effects of GLP-1. The glucose-lowering effect of GLP-1 is caused by improvement in multiple pathogenetic pathways associated with type 2 diabetes.

abnormal secretion of both of the pancreatic islet hormones (glucagon, secreted by the alpha cells; and insulin, secreted by the beta cells) also plays a central role in the pathogenesis of type 2 diabetes.

Insulin secretory defects, due to either functional abnormalities of the pancreatic beta cells or an overall reduction in beta-cell mass, are present at the time diabetes is diagnosed and worsen over time.<sup>3</sup> As beta-cell function progressively declines, treatment must be gradually intensified to maintain target glucose levels, so that eventually many patients with type 2 diabetes need insulin therapy.

Diabetic patients have abnormally high levels of glucagon both while fasting and during hyperglycemia. Elevated glucagon in combination with insulin deficiency contributes to increased hepatic glucose production, leading to hyperglycemia both during fasting and after meals.

Considerable evidence supports the maintenance of tight glucose control to mitigate the complications of diabetes. Fortunately, advances in pharmacology over the last 2 decades have expanded the number of drugs

and drug classes available for patients with type 2 diabetes. Researchers have been developing drugs that act at the key pathogenic steps in the diabetes process (FIGURE 1). One of these new drug classes is the GLP-1 agents.

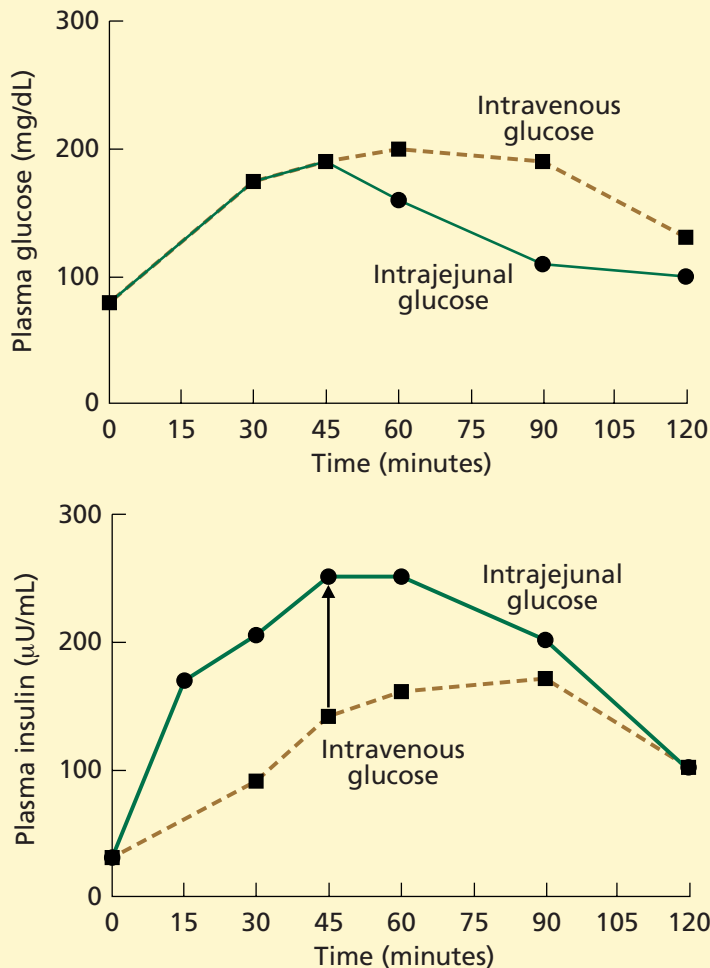
### ■ GLP-1 AND THE INCRETIN EFFECT

The concept that gut factors stimulate pancreatic endocrine secretion was hypothesized soon after secretin was discovered in 1902.<sup>4</sup> In 1906, Moore and his colleagues<sup>5</sup> tested this notion by giving gut extracts to patients with diabetes, which reduced their glycosuria. In the 1920s, Zunz and Labarre<sup>6</sup> introduced the term *incretins*, gastrointestinal hormones released in response to food ingestion that stimulate internal secretions of the pancreas, based on studies in which intestinal extracts free of secretin lowered glucose levels in dogs.

Incretins enhance pancreatic endocrine secretion at physiologic concentrations.<sup>4</sup> The magnitude of the incretin effect can be seen by comparing how much insulin levels rise after an oral glucose load vs during an isoglycemic intravenous glucose infusion (FIGURE 2). In non-diabetic people, insulin secretion rates are typ-

**Incretins may account for 30% to 60% of postprandial insulin secretion**

### Insulin secretion is greater after jejunal vs intravenous glucose loading



**FIGURE 2.** The incretin effect: a larger insulin response (shown with arrow) was generated in response to intrajejunal glucose administration compared with that to intravenous glucose administration, despite a similar plasma glucose level in both experiments.

FROM MCINTYRE N, HOLDSWORTH CD, TURNER DS. NEW INTERPRETATION OF ORAL GLUCOSE TOLERANCE. LANCET 1964; 41:20-21. REPRODUCED WITH PERMISSION FROM ELSEVIER.

ically twice as high after an oral glucose load as after a matched intravenous glucose infusion.<sup>7</sup> In fact, the incretin effect is thought to account for 30% to 60% of postprandial insulin secretion.<sup>8</sup>

There are two major incretins: glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1).

### PHYSIOLOGY OF GLP-1

#### Secretion and degradation of GLP-1

GLP-1 is actually a product of the glucagon gene, which is expressed both in pancreatic alpha cells and in a population of specialized intestinal endocrine cells called L cells, located mostly in the lower small intestine and colon. Proglucagon is cleaved primarily to glucagon in alpha cells and to GLP-1 in L cells.

GLP-1 secretion is stimulated by nutrients in the lumen of the gut,<sup>9</sup> and plasma levels parallel those of insulin.<sup>10</sup> Although the mechanism by which nutrients stimulate the L cells to secrete GLP is not known, neural pathways may be involved, since serum GLP-1 concentrations increase as early as 5 to 10 minutes following ingestion of carbohydrates and lipids,<sup>10</sup> well before the nutrients pass into the lower gut where most L cells are located.<sup>11</sup>

Once released from L cells, GLP-1 is rapidly metabolized by a widely distributed serine protease, dipeptidyl peptidase IV (DPP-IV),<sup>12</sup> resulting in a half-life of 1 to 2 minutes in the circulation. DPP-IV, which is located on endothelial cells as well as in soluble form in plasma, cleaves the two N-terminal amino acids from GLP-1, causing a substantial loss of insulintropic activity.<sup>13</sup>

#### Biologic action of GLP-1

To date, only one receptor specific for GLP-1 has been identified. The GLP-1 receptor (GLP-1-R) is a G protein-coupled receptor linked to the activation of the adenylate cyclase pathway.<sup>14</sup> GLP-1-R is expressed in a variety of tissues, including pancreatic alpha and beta cells, specific brain areas (hypothalamus, hindbrain, and midbrain), vagal afferent nerves, stomach, lungs, heart, and kidneys. It does not seem to be expressed in the liver, skeletal muscles, or adipose tissue,<sup>15</sup> although this is still a point of debate.

The major effects of GLP-1 on target tissues are summarized below:

**In beta cells,** GLP-1 strongly enhances glucose-stimulated insulin secretion both in vivo<sup>16</sup> and in vitro.<sup>17</sup> It also increases insulin biosynthesis by up-regulating insulin gene expression.<sup>17,18</sup> The higher the plasma glucose level, the greater the effect of GLP-1 on



insulin secretion, with the greatest effect in hyperglycemic conditions<sup>19</sup> and little to no effect when the blood glucose concentration is less than 65 mg/dL.<sup>20</sup> The glucose dependency of GLP-1 and other incretins in stimulating insulin secretion provides an internal safeguard against hypoglycemia.

Studies in rodents showed that GLP-1 increases beta-cell mass by enhancing beta-cell proliferation,<sup>21</sup> increasing the differentiation of new beta cells from progenitor cells in the pancreatic duct epithelium,<sup>22</sup> and reducing beta-cell apoptosis.<sup>23,24</sup> Therefore, in addition to mediating acute insulin secretion, GLP-1 drugs hold the promise of long-term benefits by maintaining or enhancing beta-cell mass in patients with type 2 diabetes. However, studies are needed to confirm this effect in humans.

**In the stomach,** intravenous infusion of GLP-1 slows gastric emptying in a dose-dependent manner,<sup>25</sup> which can significantly attenuate postprandial glycemic excursions.<sup>26</sup> This effect occurs at periphsyologic concentrations of GLP-1 and appears to be independent of the plasma glucose concentration.<sup>25</sup>

The mechanisms by which GLP-1 influences pancreatic secretion and gastric motility may be mediated by vagal pathways.<sup>27</sup> In clinical studies, administration of subcutaneous doses of GLP-1 in patients with type 2 diabetes improves postprandial glucose levels, primarily due to delayed gastric emptying.<sup>28</sup>

**In alpha cells,** GLP-1 lowers basal glucagon secretion in healthy subjects<sup>29</sup> and in patients with type 2 diabetes.<sup>19</sup> It may act directly via its receptor on alpha cells<sup>30</sup> or indirectly by increasing insulin or somatostatin secretion, which in turn inhibits glucagon secretion.<sup>31</sup> Here again, the higher the glucose level, the greater the effect of GLP-1; thus, GLP-1 does not affect the normal glucagon secretion that occurs as part of the counterregulatory response to hypoglycemia.<sup>20</sup>

**In the liver,** GLP-1 has potent indirect effects on glucose metabolism by regulating insulin and glucagon secretion.<sup>29,32</sup> However, in addition, intestinal L cells secrete GLP-1 directly into the portal circulation, raising the possibility that glucose production or uptake

by the liver could be directly regulated.

In experiments in which plasma insulin and glucagon levels were clamped, GLP-1 increased hepatic glucose uptake in dogs,<sup>33</sup> and decreased hepatic glucose production in humans.<sup>34</sup> Therefore, GLP-1 may have an islet-independent influence on hepatic glucose metabolism, although the physiologic and clinical significance of this effect is unproven.

**Effect on food intake and obesity.** Intracerebroventricular administration of GLP-1 acutely reduces food intake in fasted rats,<sup>35</sup> suggesting that central GLP-1 receptors mediate anorexia. Intravenous infusion of GLP-1 reduces appetite and enhances satiety in humans, leading to a lower caloric intake regardless of the subject's body weight<sup>36</sup> or diabetes status.<sup>37</sup> Long-term use of GLP-1<sup>38</sup> or a GLP-1 receptor agonist<sup>39</sup> causes weight loss in patients with type 2 diabetes. Similarly, giving subcutaneous GLP-1 for 5 days just before meals in nondiabetic obese people resulted in a significant 15% reduction of their caloric intake and a weight loss of 0.5 kg.<sup>40</sup>

**Effect on insulin sensitivity.** Extended administration of GLP-1 improves insulin sensitivity in diabetic patients,<sup>38</sup> while short-term infusion has no effect. These results argue against a direct effect of GLP-1 on insulin sensitivity. Rather, since GLP-1 lowers circulating levels of glucose and free fatty acids,<sup>19,38</sup> the enhancement of insulin sensitivity seen with long-term use of GLP-1 may be the indirect result of its metabolic effects.

**GLP-1 reduces appetite and enhances satiety**

## ■ THERAPEUTIC POTENTIAL OF GLP-1 AGENTS IN DIABETES

### Natural GLP-1

Due to its very short half-life, GLP-1 has to be administered via a continuous infusion or frequent injections, limiting its clinical usefulness. However, it could be useful in situations that otherwise require intravenous infusion of insulin, such as in acute coronary syndromes,<sup>41</sup> or during management of hyperglycemia in intensive care units.<sup>42</sup>

Acute intravenous infusion of GLP-1 has been shown to normalize fasting glucose levels in various subgroups of patients with type 2 diabetes, even those who have poor glycemic

control.<sup>19</sup> Continuous subcutaneous infusion of GLP-1 also lowered glucose levels whether it was given by itself<sup>38</sup> or in combination with metformin<sup>43</sup> or pioglitazone.<sup>44</sup>

Besides these insulinomimetic, glucagonostatic, and appetite effects,<sup>38</sup> biphasic insulin secretion was recovered following overnight GLP-1 infusion.<sup>45</sup>

### GLP-1 mimetics

Strategies designed to circumvent degradation of GLP-1 by DPP-IV have resulted in GLP-1 mimetics (GLP-1-R agonists) with longer half-lives than natural GLP-1.

**Albumin-bound GLP-1 mimetics.** One approach to longer-acting forms has been to modify the GLP-1 molecule to promote albumin binding, which results in slow absorption from subcutaneous injection sites and a longer plasma half-life with persistent activity. Preclinical and clinical studies of this class of drug have shown effects similar to those of GLP-1 infusions.

Liraglutide (NN2211, Novo Nordisk, Copenhagen, Denmark), the most studied compound in this group, includes a C-16 fatty acyl derivative, that binds to albumin. It has an elimination half-life of 12 hours following a subcutaneous dose.<sup>46</sup>

In patients with type 2 diabetes, a single dose of liraglutide at bedtime reduced fasting and postprandial glucose values as a result of enhanced insulin secretion, suppressed glucagon release, and delayed gastric emptying.<sup>47</sup> Similar results were reported when liraglutide was given for 1 week to a group of patients with type 2 diabetes, although gastric emptying was not affected and gastrointestinal side effects were minimal.<sup>48</sup>

In the longest trial yet reported,<sup>49</sup> 190 patients with type 2 diabetes were randomized to receive liraglutide in one of five doses, placebo, or glimepiride for 12 weeks. The glucose-lowering effect was comparable in the highest-dose liraglutide group (0.75 mg) and the glimepiride group, with an absolute reduction in hemoglobin A<sub>1c</sub> of about 0.8 percentage points. More than 95% of the patients in the liraglutide groups completed the study. Adverse effects were minimal, mainly gastrointestinal.

**Exendin-4.** This 39-amino-acid peptide is

naturally produced in the saliva of the Gila monster lizard (*Heloderma suspectum*). It has 53% homology with the amino acid sequence of GLP-1 and is a potent GLP-1 receptor agonist.

Exendin-4 is naturally resistant to DPP-IV, with a half-life of 4 hours in humans following subcutaneous injection,<sup>50</sup> but otherwise displaying effects similar to those of native GLP-1 on islet function, gastric emptying, and food intake.<sup>51</sup> Acute infusion of exenatide in diabetic patients diminished postprandial glycemia, possibly by prolonging gastric emptying. Some experiments in nondiabetic individuals demonstrated a persistent increased insulin secretion, which was glucose-dependent and lasted for up to 3 hours after discontinuing the infusion.<sup>50</sup>

Exenatide (Amylin Pharmaceuticals, San Diego, CA) is a synthetic form of exendin.

In phase 1 clinical trials, exenatide was well tolerated in subcutaneous doses of 0.1 µg/kg or less, whereas doses greater than 0.3 µg/kg resulted in nausea and vomiting.<sup>52</sup>

Dose-titrating studies (phase 2) identified an optimal glucose-lowering dose of 0.05 to 0.2 µg/kg given subcutaneously twice daily.<sup>53</sup> Nausea and vomiting were dose-limiting adverse effects, but were minimized by starting therapy with 5 µg twice daily for 1 month followed by a maintenance dose of 10 µg twice daily.<sup>53</sup>

In phase 3 studies,<sup>54-56</sup> exenatide in two dosage schedules or placebo was given to three groups of patients with type 2 diabetes not achieving target blood glucose concentrations with metformin or sulfonylurea alone or in combination, as reflected in group average hemoglobin A<sub>1c</sub> levels of 8.2% to 8.7%. Exenatide was given as twice-daily subcutaneous injections of 5 µg for 1 month followed by 5 or 10 µg twice daily for 30 weeks; there were 110 to 245 patients in each treatment group. Hemoglobin A<sub>1c</sub> values declined in a dose-dependent fashion in the exenatide group, by about 1 percentage point in those completing the study receiving 10 µg twice a day. Furthermore, treated patients lost 1.6 to 2.8 kg, which was statistically significant (FIGURE 3).

Overall, exenatide was well tolerated.

**Exenatide must be given by subcutaneous injection**





The most common adverse effect was mild to moderate transient nausea, reported by 30% to 50% of treated patients compared with 7% to 23% of controls. Fewer than 3% of patients who received exenatide discontinued the study because of nausea. Among those who were taking sulfonylurea and exenatide, about 35% had mild hypoglycemia,<sup>39</sup> whereas those who were taking metformin and exenatide did not show any increased rate of hypoglycemia compared with the placebo group.

Exenatide was approved for marketing (as Byetta) in the United States in April 2005.

### DPP-IV inhibitors

The rationale behind using DPP-IV inhibitors as antidiabetic agents is to enhance plasma concentrations of intact, biologically active, endogenous GLP-1. Since DPP-IV also inactivates GIP and a host of other peptides, DPP-IV inhibitors might also improve glycemic control by increasing the levels of these other hormones.

Inactivation of DPP-IV in animal models increased intact GLP-1 levels and improved insulin secretion and glucose tolerance.<sup>57,58</sup> Consistent with these results, rats with DPP-IV deficiency have better glucose tolerance than control animals.<sup>59,60</sup>

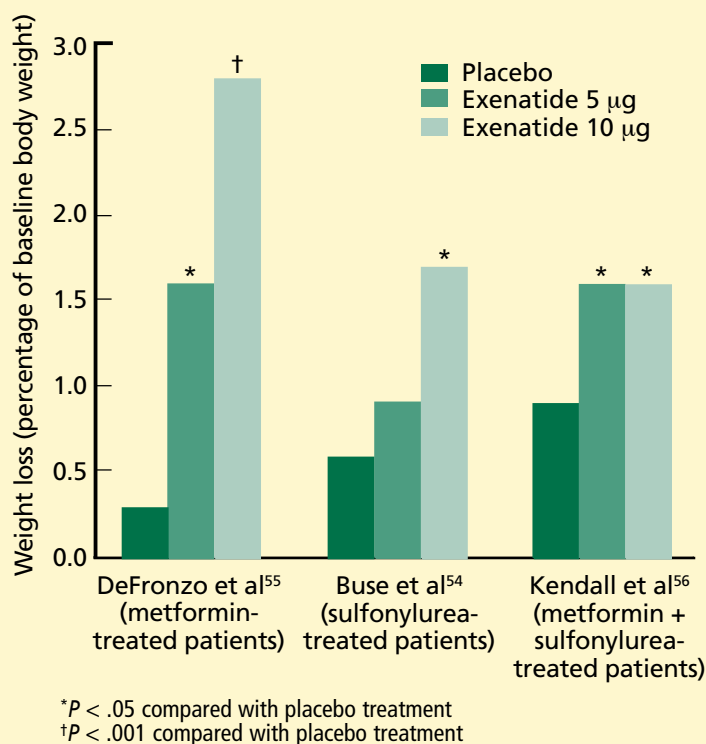
Based on these and other animal studies in which DPP-IV inhibitors improved metabolic outcomes and showed limited toxicity, these agents have advanced into human trials. Two of these agents have undergone 1-month studies in humans, performed by the same group of investigators.

**NVP-PP728** (Novartis AG, Basel, Switzerland), given for 4 weeks to patients with diet-controlled type 2 diabetes, resulted in a significant reduction in hemoglobin A1c (0.5%).

**LAF237** (Novartis AG, Basel, Switzerland), also given for 4 weeks to patients with diet-controlled diabetes, lowered postprandial glucose levels by suppressing glucagon and by increasing beta-cell function. This effect was associated with a doubling of plasma GLP-1 concentrations.

The experience so far with DPP-IV inhibitors is that they are well tolerated with few adverse effects. They do not seem to have a major effect on gastric function or body

### Patients lose weight on exenatide



**FIGURE 3.** Change in body weight from baseline at 30 weeks in clinical trials with exenatide. The mean body weight at baseline was 95 to 101 kg.

DATA FROM BUSE JB, HENRY RR, HAN J, KIM DD, FINEMAN MS, BARON AD; EXENATIDE-113 CLINICAL STUDY GROUP. EFFECTS OF EXENATIDE (EXENDIN-4) ON GLYCEMIC CONTROL OVER 30 WEEKS IN SULFONYLUREA-TREATED PATIENTS WITH TYPE 2 DIABETES. DIABETES CARE 2004; 27:2628–2635; DEFONZO RA, RATNER RE, HAN J, KIM DD, FINEMAN MS, BARON AD. EFFECTS OF EXENATIDE (EXENDIN-4) ON GLYCEMIC CONTROL AND WEIGHT OVER 30 WEEKS IN METFORMIN-TREATED PATIENTS WITH TYPE 2 DIABETES. DIABETES CARE 2005; 28:1092–1100; AND KENDALL DM, RIDDLE MC, ROSENSTOCK J, ET AL. EFFECTS OF EXENATIDE (EXENDIN-4) ON GLYCEMIC CONTROL OVER 30 WEEKS IN PATIENTS WITH TYPE 2 DIABETES TREATED WITH METFORMIN AND A SULFONYLUREA. DIABETES CARE 2005; 28:1083–1091.

weight. Thus far, coadministration of DPP-IV inhibitors and exogenous GLP-1 has not been studied.

**Comment.** Although there is not yet enough experimental or clinical information available to make firm comparisons between GLP-1 mimetics and DPP-IV inhibitors, several major differences are apparent. DPP-IV inhibitors can be given by mouth and seem to have minimal side effects. However, they depend on endogenous GLP-1, and possibly other peptides, whose levels are increased only into the upper physiologic range. GLP-1 mimetics such as exendin-4, on the other

hand, must be given by injection. The plasma levels of these drugs can be boosted to higher levels than those of natural GLP-1 are during therapy with DPP-IV inhibitors, with potentially greater potency—but also more adverse responses, particularly nausea.

It will be important to determine the relative potency of these general classes of drugs and also the degree to which they activate the range of GLP-1 actions that are beneficial for glucose regulation.

### SUMMARY

- The endogenous GLP-1 signaling system is an attractive target for antidiabetic therapy, as GLP-1 has a range of actions that promote glucose tolerance.
- Given that GLP-1 is inactivated quickly, multiple strategies have been used to improve

the stability of this compound against its metabolism by DPP-IV, leading to GLP-1-based drugs.

- Based on short-term clinical studies, GLP-1 agonists and DPP-IV inhibitors have shown promising glucose-lowering effects due to improvement of several pathophysiologic components of type 2 diabetes. Also, they may be safer than the existing insulin secretagogues, since their effect on insulin secretion depends on glucose levels above fasting, lowering the potential for hypoglycemia. Furthermore, preclinical data suggest that these agents may be able to delay or even halt the progression of diabetes; therefore, they can perhaps be utilized as treatment at early stage of diabetes.

- Longer studies are required to further determine the clinical use of GLP-1-based drugs in metabolic syndrome and obesity. ■

### REFERENCES

1. US Centers for Disease Control and Prevention. <http://www.cdc.gov/diabetes/statistics/incidence>.
2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27:1047–1053.
3. Turner RC, Holman RR. The UK Prospective Diabetes Study. UK Prospective Diabetes Study Group. *Ann Med* 1996; 28:439–444.
4. Kieffer TJ, Habener JF. The glucagon-like peptides. *Endocr Rev* 1999; 20:876–913.
5. Moore B, Edie E, Abram J. On the treatment of diabetes mellitus by acid extract of duodenal mucous membrane. *Biochem J* 1906; 1:28–38.
6. Zunz E, La Barre J. Contributions a l'étude des variations physiologiques de la sécrétion interne du pancréas: relations entre les sécrétions externe et interne du pancréas. *Arch Int Physiol Biochim* 1929; 31:20–44.
7. McIntyre N, Holdsworth CD, Turner DS. New interpretation of oral glucose tolerance. *Lancet* 1964; 41:20–21.
8. Nauck MA, Homberger E, Siegel EG, et al. Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab* 1986; 63:492–498.
9. Layer P, Holst JJ, Grandt D, Goebell H. Ileal release of glucagon-like peptide-1 (GLP-1). Association with inhibition of gastric acid secretion in humans. *Dig Dis Sci* 1995; 40:1074–1082.
10. Elliott RM, Morgan LM, Tredger JA, Deacon S, Wright J, Marks V. Glucagon-like peptide-1 (7-36) amide and glucose-dependent insulinotropic polypeptide secretion in response to nutrient ingestion in man: acute post-prandial and 24-h secretion patterns. *J Endocrinol* 1993; 138:159–166.
11. Eissele R, Goke R, Willemer S, et al. Glucagon-like peptide-1 cells in the gastrointestinal tract and pancreas of rat, pig and man. *Eur J Clin Invest* 1992; 22:283–291.
12. Deacon CF, Johnsen AH, Holst JJ. Degradation of glucagon-like peptide-1 by human plasma in vitro yields an N-terminally truncated peptide that is a major endogenous metabolite in vivo. *J Clin Endocrinol Metab* 1995; 80:952–957.
13. Vahl TP, Paty BW, Fuller BD, Pigeon RL, D'Alessio DA. Effects of GLP-1-(7-36)NH<sub>2</sub>, GLP-1-(7-37), and GLP-1-(9-36)NH<sub>2</sub> on intra-venous glucose tolerance and glucose-induced insulin secretion in healthy humans. *J Clin Endocrinol Metab* 2003; 88:1772–1779.
14. Thorens B. Expression cloning of the pancreatic beta cell receptor for the gluco-incretin hormone glucagon-like peptide 1. *Proc Natl Acad Sci U S A* 1992; 89:8641–8645.
15. Bullock BP, Heller RS, Habener JF. Tissue distribution of messenger ribonucleic acid encoding the rat glucagon-like peptide-1 receptor. *Endocrinology* 1996; 137:2968–2978.
16. Kreymann B, Williams G, Ghatei MA, Bloom SR. Glucagon-like peptide-1 7-36: a physiological incretin in man. *Lancet* 1987; 2:1300–1304.
17. Drucker DJ, Philippe J, Mojsov S, Chick WL, Habener JF. Glucagon-like peptide I stimulates insulin gene expression and increases cyclic AMP levels in a rat islet cell line. *Proc Natl Acad Sci U S A* 1987; 84:3434–3438.
18. Fehmman HC, Habener JF. Insulinotropic hormone glucagon-like peptide-I(7-37) stimulation of proinsulin gene expression and proinsulin biosynthesis in insulinoma beta TC-1 cells. *Endocrinology* 1992; 130:159–166.
19. Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 1993; 36:741–744.
20. Nauck MA, Heimesaat MM, Behle K, et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. *J Clin Endocrinol Metab* 2002; 87:1239–1246.
21. Xu G, Stoffers DA, Habener JF, Bonner-Weir S. Exendin-4 stimulates both beta-cell replication and neogenesis, resulting in increased beta-cell mass and improved glucose tolerance in diabetic rats. *Diabetes* 1999; 48:2270–2276.
22. Abraham EJ, Leech CA, Lin JC, Zulewski H, Habener JF. Insulinotropic hormone glucagon-like peptide-1 differentiation of human pancreatic islet-derived progenitor cells into insulin-producing cells. *Endocrinology* 2002; 143:3152–3161.
23. Farilla L, Bulotta A, Hirshberg B, et al. Glucagon-like peptide 1 inhibits cell apoptosis and improves glucose responsiveness of freshly isolated human islets. *Endocrinology* 2003; 144:5149–5158.



24. Li Y, Hansotia T, Yusta B, Ris F, Halban PA, Drucker DJ. Glucagon-like peptide-1 receptor signaling modulates beta cell apoptosis. *J Biol Chem* 2003; 278:471–478.
25. Meier JJ, Gallwitz B, Salmen S, et al. Normalization of glucose concentrations and deceleration of gastric emptying after solid meals during intravenous glucagon-like peptide 1 in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2003; 88:2719–2725.
26. Nauck MA, Niedereichholz U, Ettler R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am J Physiol* 1997; 273:E981–E988.
27. Imeryuz N, Yegen BC, Bozkurt A, Coskun T, Villanueva-Penacarrillo ML, Ulusoy NB. Glucagon-like peptide-1 inhibits gastric emptying via vagal afferent-mediated central mechanisms. *Am J Physiol* 1997; 273:G920–G927.
28. Dupre J, Behme MT, Hramiak IM, McDonald TJ. Subcutaneous glucagon-like peptide 1 combined with insulin normalizes post-cibal glycemic excursions in IDDM. *Diabetes Care* 1997; 20:381–384.
29. Hvidberg A, Nielsen MT, Hilsted J, Orskov C, Holst JJ. Effect of glucagon-like peptide-1 (proglucagon 78-107amide) on hepatic glucose production in healthy man. *Metabolism* 1994; 43:104–108.
30. Heller RS, Kieffer TJ, Habener JF. Insulinotropic glucagon-like peptide 1 receptor expression in glucagon-producing alpha-cells of the rat endocrine pancreas. *Diabetes* 1997; 46:785–791.
31. Fehmann HC, Goke R, Goke B. Cell and molecular biology of the incretin hormones glucagon-like peptide-I and glucose-dependent insulin releasing polypeptide. *Endocr Rev* 1995; 16:390–410.
32. Van Dijk G, Lindskog S, Holst JJ, Steffens AB, Ahren B. Effects of glucagon-like peptide-I on glucose turnover in rats. *Am J Physiol* 1996; 270:E1015–E1021.
33. Dardevet D, Moore MC, Neal D, DiCostanzo CA, Snead W, Cherrington AD. Insulin-independent effects of GLP-1 on canine liver glucose metabolism: duration of infusion and involvement of hepatportal region. *Am J Physiol Endocrinol Metab* 2004; 287:E75–E81.
34. Prigeon RL, Quddusi S, Paty B, D'Alessio DA. Suppression of glucose production by GLP-1 independent of islet hormones: a novel extrapancreatic effect. *Am J Physiol Endocrinol Metab* 2003; 285:E701–E707.
35. Turton MD, O'Shea D, Gunn I, et al. A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature* 1996; 379:69–72.
36. Verdich C, Flint A, Gutzwiller JP, et al. A meta-analysis of the effect of glucagon-like peptide-1 (7-36) amide on ad libitum energy intake in humans. *J Clin Endocrinol Metab* 2001; 86:4382–4389.
37. Gutzwiller JP, Drewe J, Goke B, et al. Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. *Am J Physiol* 1999; 276:R1541–R1544.
38. Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. *Lancet* 2002; 359:824–830.
39. [www.amylin.com](http://www.amylin.com).
40. Naslund E, King N, Mansten S, et al. Prandial subcutaneous injections of glucagon-like peptide-1 cause weight loss in obese human subjects. *Br J Nutr* 2004; 91:439–446.
41. Nikolaidis LA, Mankad S, Sokos GG, et al. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. *Circulation* 2004; 109:962–965.
42. Meier JJ, Weyhe D, Michaely M, et al. Intravenous glucagon-like peptide 1 normalizes blood glucose after major surgery in patients with type 2 diabetes. *Crit Care Med* 2004; 32:848–851.
43. Zander M, Taskiran M, Toft-Nielsen MB, Madsbad S, Holst JJ. Additive glucose-lowering effects of glucagon-like peptide-1 and metformin in type 2 diabetes. *Diabetes Care* 2001; 24:720–725.
44. Zander M, Christiansen A, Madsbad S, Holst JJ. Additive effects of glucagon-like peptide 1 and pioglitazone in patients with type 2 diabetes. *Diabetes Care* 2004; 27:1910–1914.
45. Rachman J, Gribble FM, Barrow BA, Levy JC, Buchanan KD, Turner RC. Normalization of insulin responses to glucose by overnight infusion of glucagon-like peptide 1 (7-36) amide in patients with NIDDM. *Diabetes* 1996; 45:1524–1530.
46. Agerso H, Jensen LB, Elbrond B, Rolan P, Zdravkovic M. The pharmacokinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative, in healthy men. *Diabetologia* 2002; 45:195–202.
47. Juhl CB, Hollingdal M, Sturis J, et al. Bedtime administration of NN2211, a long-acting GLP-1 derivative, substantially reduces fasting and postprandial glycemia in type 2 diabetes. *Diabetes* 2002; 51:424–429.
48. Degen KB, Juhl CB, Sturis J, et al. One week's treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and alpha- and beta-cell function and reduces endogenous glucose release in patients with type 2 diabetes. *Diabetes* 2004; 53:1187–1194.
49. Madsbad S, Schmitz O, Ranstam J, Jakobsen G, Matthews DR. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. *Diabetes Care* 2004; 27:1335–1342.
50. Egan JM, Clocquet AR, Elahi D. The insulinotropic effect of acute exendin-4 administered to humans: comparison of nondiabetic state to type 2 diabetes. *J Clin Endocrinol Metab* 2002; 87:1282–1290.
51. Edwards CM, Stanley SA, Davis R, et al. Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. *Am J Physiol Endocrinol Metab* 2001; 281:E155–E161.
52. Kolterman O, Young G, Parker J, Amin D, Prickett K. Stimulation of endogenous insulin secretion by subcutaneous AC-2993 (synthetic exendin-4) in healthy overnight fasted volunteers [abstract]. *Diabetes* 1999; 48:A199.
53. Nielsen LL, Baron AD. Pharmacology of exenatide (synthetic exendin-4) for the treatment of type 2 diabetes. *Curr Opin Investig Drugs* 2003; 4:401–405.
54. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 2004; 27:2628–2635.
55. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005; 28:1092–1100.
56. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 2005; 28:1083–1091.
57. Pospisilik JA, Stafford SG, Demuth HU, et al. Long-term treatment with the dipeptidyl peptidase IV inhibitor P32/98 causes sustained improvements in glucose tolerance, insulin sensitivity, hyperinsulinemia, and beta-cell glucose responsiveness in VDF (fa/fa) Zucker rats. *Diabetes* 2002; 51:943–950.
58. Ahren B, Holst JJ, Martensson H, Balkan B. Improved glucose tolerance and insulin secretion by inhibition of dipeptidyl peptidase IV in mice. *Eur J Pharmacol* 2000; 404:239–245.
59. Marguet D, Baggio L, Kobayashi T, et al. Enhanced insulin secretion and improved glucose tolerance in mice lacking CD26. *Proc Natl Acad Sci U S A* 2000; 97:6874–6879.
60. Conarello SL, Li Z, Ronan J, et al. Mice lacking dipeptidyl peptidase IV are protected against obesity and insulin resistance. *Proc Natl Acad Sci USA* 2003; 100:6825–6830.

ADDRESS: Marzieh Salehi, MD, Division of Endocrinology and Metabolism, University of Cincinnati Medical Center, PO Box 670547, Cincinnati, OH 45267-0547; e-mail [salehim@email.uc.edu](mailto:salehim@email.uc.edu).