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Essay for the 2011 CIHR/*CMAJ* award: glucagon-like peptides for metabolic and gastrointestinal disorders

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The two highest-ranking winners of the 2011 CIHR/*CMAJ* competition for Top Achievements in Health Research are Daniel Drucker, and Gideon Koren and colleagues for the Motherisk team. Dr. Drucker describes his work on translational biology of glucagon-like peptides for metabolic and gastrointestinal disorders in the following essay. The essay by Dr. Koren and colleagues and synopses of the other four winning achievements are available at www.cmaj.ca.

Type 2 diabetes arises as a result of insufficient insulin production, commonly in the setting of impaired insulin action. Type 2 diabetes and obesity are major health problems that often affect the same patient. These conditions are increasing in prevalence and are associated with substantial health care costs, impaired quality of life, and considerable morbidity and mortality. The available treatments for these metabolic disorders have traditionally been complicated by incomplete efficacy, the need for frequent and expensive self-monitoring of blood glucose levels and associated adverse effects such as weight gain and hypoglycemia. Because the successful treatment of diabetes is directly associated with a decrease in its related complications, improvements in controlling blood glucose levels lead directly to enhanced quality of life for patients with diabetes.

I have studied how gastrointestinal hormones control the ingestion, absorption and disposal of nutrients for more than 25 years. In 1987, as a research fellow funded by the Medical Research Council, I described the action of a novel peptide hormone, glucagon-like peptide-1 (GLP-1), on insulin-producing islet cells.[1] Glucagon-like peptide-1 directly stimulates the synthesis and secretion of insulin from islet cells. These findings yielded a new area for biologic investigation, namely the physiologic relevance and biologic activity of GLP-1 and related peptides. Since that discovery, my research has delineated how GLP-1 acts in the body to control the growth and survival of islet β cells, the regulation of food intake and body weight, and the function and survival of cardiovascular tissues.[2–4] My work has shown how this hormone works in the immune system and in the control of postprandial lipid metabolism.[5,6] The Drucker laboratory has generated novel mouse models lacking GLP-1 activity, permitting the delineation of the endogenous physiologic importance of the GLP-1 system in multiple tissues.[7–9] My work also described the importance of the enzyme that degrades GLP-1, dipeptidyl peptidase-4 (DPP-4), showing that genetic elimination of DPP-4 produces healthy mice with improved insulin secretion and better glucose control.[10]

As a result of these studies and related investigations by other leading scientists, the pharmaceutical industry has developed two new classes of drugs to treat type 2 diabetes, which are based on the potentiation of GLP-1 activity.[11] The first approved GLP-1 receptor agonist, exendin-4, was discovered by John Eng, and my team and I cloned the gene encoding the protein.[12] The Drucker laboratory has published numerous papers showing the glucoregulatory and meta-

Competing interests: Daniel Drucker is a consultant for Arisaph Pharmaceuticals, Diartis Pharmaceuticals, Eli Lilly, GlaxoSmithKline, Merck Research Laboratories, Novo Nordisk, NPS Pharmaceuticals, Takeda and Transition Pharmaceuticals; he has received grants from GlaxoSmithKline, Merck and Novo Nordisk; he has received payment for lectures from Eli Lilly, Merck and Novo Nordisk; and he has patents pending and receives royalties for his work on dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-2 analogues. No other competing interests were declared.

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Key points

- Therapies for type 2 diabetes have traditionally been characterized by incomplete efficacy, the need to self-monitor blood glucose levels, and associated adverse effects such as weight gain and hypoglycemia.
- Dr. Drucker's work on glucagon-like peptide-1 and dipeptidyl peptidase-4 has led to the development of several new classes of therapy for type 2 diabetes.
- These new therapies have improved the lives of patients with diabetes by reducing the need for self-monitoring blood glucose levels and lowering the risk of hypoglycemia and weight gain.
- The success of these agents has led to scientific investigations into how gut hormones exert their actions in various tissues, thereby exemplifying the translational importance of basic science.

bolic actions of GLP-1 in experimental models of diabetes. Because exendin-4 must be injected twice daily, and because a more recently approved agent, liraglutide, requires injection only once daily, I led the first Phase III trial of a once-weekly version of exendin-4. This drug, exenatide, has been approved for use in Europe, with approval in North America expected soon.[13]

A second class of drugs based on GLP-1 activity, the DPP-4 inhibitors, was approved in 2007. These drugs lower blood glucose levels by inhibiting the enzymatic breakdown of GLP-1, thereby prolonging its action. Multiple DPP-4 inhibitors, which can be taken once daily in tablet form, have been approved for the treatment of diabetes.

Improving the lives of people with diabetes

These two new classes of incretin-based therapy have improved the lives of people with diabetes for two principal reasons. First, as GLP-1 stimulates insulin and lowers blood glucose levels only when they are elevated, the risk of unpleasant hypoglycemic reactions associated with the use of these drugs is much lower than with most other antidiabetes agents. As a result, there is less need for self-monitoring blood glucose levels. Second, many classes of antidiabetes drugs (insulin, sulfonylureas and thiazolidinediones) cause weight gain. The DPP-4 inhibitors do not cause weight gain; in fact, taking GLP-1 receptor agonists, such as exenatide and liraglutide, often results in meaningful weight loss. The ability to lower blood glucose and simultaneously reduce body weight is a marked improvement in the options for treatment available to patients with type 2 diabetes.

The success and increasing popularity of these drugs have led to investigations into how these hormones, exemplified by GLP-1, exert their actions in various tissues. Multiple long-acting forms of GLP-1 are now being developed to treat diabetes and obesity, including several new preparations than can be administered once weekly, once monthly or semiannually. In addition, the first analogue of glucagon-like peptide-2, teduglutide,[14] is expected to be approved for the treatment of short bowel syndrome in 2012.

The elucidation of the biology of these two peptides has exemplified the translational importance of basic science, and the GLP-1 receptor agonists and DPP-4 inhibitors have improved the health of millions of people with type 2 diabetes worldwide.

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