



## Experimental and clinical pharmacology

# Incretin mimetics and enhancers: mechanisms of action

Johannes B Prins, University of Queensland Diamantina Institute for Cancer, Immunology and Metabolic Medicine, and the Centres for Health Research, Princess Alexandra Hospital, Brisbane

## Summary

**The incretins are peptide hormones secreted from the gut in response to food. They increase the secretion of insulin. The incretin response is reduced in patients with type 2 diabetes, so drugs acting on incretins may improve glycaemic control. Incretins are metabolised by dipeptidyl peptidase, so selectively inhibiting this enzyme increases the concentration of circulating incretins. A similar effect results from giving an incretin analogue that cannot be cleaved by dipeptidyl peptidase.**

Key words: diabetes, dipeptidyl peptidase, glucagon-like peptide, glucose-dependent insulintropic polypeptide.

(*Aust Prescr* 2008;31:102–4)

## Introduction

It has been known for many decades that an oral glucose load causes a greater release of insulin than a similar glucose load given intravenously. This difference (40–60% in the area-under-the-curve of the insulin time-concentration graph) is due to the 'incretin effect'. By increasing insulin secretion, the incretins lower blood glucose.

## Physiology

The incretins are peptide hormones. They are released into the circulation, in response to luminal nutrients, within minutes of eating. In humans, the major incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). GLP-1 is secreted by the L cells in the ileum and colon, while GIP is secreted by the K cells in the duodenum.

Both incretins have hormonal effects on multiple organs, notably the endocrine pancreas, the gut and the brain (Table 1). Their predominant role is regulation of energy homeostasis. They stimulate insulin secretion in a glucose-dependent manner, delay gastric emptying and suppress appetite. This combination of effects makes a significant contribution to glucose homeostasis, particularly the control of postprandial glucose. Subsequent studies have identified other actions including improvement in pancreatic  $\beta$  cell glucose sensitivity and, in animal studies, promotion of pancreatic  $\beta$  cell proliferation and reduction in  $\beta$  cell apoptosis.

The circulating incretins act via specific G-protein-coupled receptors. There are clinically important differences in the tissue distribution of these receptors. The GLP-1 receptor is expressed in pancreatic islet  $\alpha$  and  $\beta$  cells, heart, central nervous system, kidney, lung and gastrointestinal tract. The GIP receptor is expressed predominantly in the pancreatic islet  $\beta$  cells and less so in the central nervous system and adipose tissue.

Table 1

### Incretins and their actions

Glucagon-like peptide-1 (GLP-1)	Glucose-dependent insulintropic polypeptide (GIP)
Secreted by L cells in the distal gut (ileum and colon)	Secreted by K cells in the proximal gut (duodenum)
Stimulates glucose-dependent insulin release	Stimulates glucose-dependent insulin release
Suppresses hepatic glucose output by inhibiting glucagon secretion in a glucose-dependent manner	
Enhances $\beta$ cell proliferation and survival in animal models and isolated human islets	Enhances $\beta$ cell proliferation and survival in islet cell lines
Delays gastric emptying	Delays gastric emptying
Cleared by dipeptidyl peptidase 4 inactivation and renal elimination	Cleared by dipeptidyl peptidase 4 inactivation and renal elimination
Anorexic	
Controls fasting glycaemia	

The incretin response to a meal lasts approximately 2–3 hours because, despite rapid metabolism and the short half-life (1–2 minutes) of each incretin molecule, the stimulus of nutrients in the gut persists and so there is ongoing production of incretins. The major mechanism of metabolism of the incretins is cleavage by dipeptidyl peptidase 4 (DPP4), an enzyme that is ubiquitously expressed, including in endothelial cells.

## Incretins in diabetes

The clinical relevance of the incretin system came to light when it was recognised that the incretin response is markedly attenuated in people with type 2 diabetes. The lack of nutrient-induced release of GLP-1 contributes significantly to hyperglycaemia in these patients through a relative reduction in postprandial insulin response, the subsequent failure of glucagon suppression and a lack of appetite suppression. The concentration of GIP is near normal, but its effect on insulin secretion is diminished. These observations uncovered a new therapeutic strategy for type 2 diabetes – that of promoting the activity of the incretin system.

Two pharmacological approaches have been taken to enhance the incretin effect in type 2 diabetes. One approach is to administer GLP-1 'analogues' (GLP-1 receptor agonists) that are resistant to cleavage by DPP4. The other approach is to inhibit DPP4 activity. This effectively increases the half-life and therefore the circulating concentrations of the incretins. The effectiveness of both approaches suggests that there is no significant reduction in GLP-1 sensitivity in subjects with diabetes.

## GLP-1 receptor agonists

The administration of an incretin analogue resistant to cleavage by DPP4 has been successfully pursued by a number of pharmaceutical companies. Two drugs are now in clinical use or late stage clinical trial. As they are peptides they need to be given by subcutaneous injection, but long-acting formulations are being developed to see if once-weekly injections are possible.

Exenadin is a peptide with approximately 50% homology to GLP-1. It is found in the saliva of a lizard known as the Gila monster. The molecule is a potent activator of the GLP-1 receptor and is resistant to cleavage by DPP4 and other peptidases so it has a long circulating half-life. The clinical formulation (exenatide) is in use in many parts of the world.

Another analogue of human GLP-1 has been made by adding a C-16 fatty acid. The resultant compound (liraglutide) is resistant to DPP4 cleavage and has a long circulating half-life. It maintains normal activity at the GLP-1 receptor.

The incretin effect on insulin secretion is glucose-dependent; insulin production is only enhanced by GLP-1 in the presence of hyperglycaemia. This is therapeutically highly advantageous because hypoglycaemia is not an effect of treatment.

A therapeutically beneficial additional effect of the GLP-1 analogues is significant weight loss (of up to 3 kg in clinical trials). This results from the combined effect of delayed gastric emptying and central effects to induce anorexia and (possibly) nausea. Additionally, the delayed gastric emptying causes nausea and vomiting in some patients.

The incretin analogues show direct effects which preserve  $\beta$  cell mass in animal models. They also have *in vitro* and *in vivo* effects which promote  $\beta$  cell proliferation and reduce  $\beta$  cell apoptosis.

The 'downsides' of the analogue approach are that there is no alteration or restoration in GIP concentrations or activity, administration is via injection, and the long-term consequence (if any) of prolonged GLP-1 receptor activation is unknown.

## Inhibition of dipeptidyl peptidase 4

DPP4 is a member of a large family of peptidases which have a wide range of actions. As GLP-1 and GIP are the only known substrates of DPP4, it is important for drugs to selectively inhibit this enzyme and not the other peptidases to limit adverse effects on other systems. Of particular relevance is the need to avoid inhibiting DPP8 and 9 as this can cause renal and skin toxicity, and immunosuppression.

Sitagliptin and vildagliptin are two DPP4 inhibitors that are highly specific for DPP4. They have long half-lives, allowing once-daily oral therapy. Two hours after a single dose there is almost complete inhibition of DPP4 and at 24 hours there is approximately 85% inhibition. In patients with type 2 diabetes, the drugs effectively restore GLP-1 circulating concentrations and the postprandial response of GLP-1 to that of a non-diabetic person. Fasting incretin levels remain low, but detectable, and the drugs also reduce fasting blood glucose in patients with type 2 diabetes, predominantly by reducing glucagon secretion. They also return the impaired  $\beta$  cell glucose sensitivity towards normal, an action that contributes to postprandial glucose control.

In animal models of type 2 diabetes, sitagliptin and vildagliptin preserve  $\beta$  cell mass (and function). If this effect also occurs in patients, then the drugs may delay or prevent the characteristic  $\beta$  cell deterioration seen in type 2 diabetes.

## Future directions

The development of drugs to manipulate the incretin system is fascinating. It teaches us much about the pathophysiology of glucose homeostasis and type 2 diabetes. Based on currently available evidence, these drugs will provide additional therapies for type 2 diabetes.

A key set of data that will become available over the next few years will highlight the effect of these drugs on the pancreatic islet, with particular emphasis on their ability to prevent or delay secondary  $\beta$  cell failure. Should this be apparent in patients with type 2 diabetes, a strong case could be made for starting these

drugs very early in the disease, perhaps even in the pre-diabetic phase. This therapy would depend on favourable outcomes in long-term studies.

### Further reading

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*Professor Prins has received research funding and/or honoraria for lectures or Advisory Board membership from Merck Sharp & Dohme, NovoNordisk and Novartis.*

### Self-test questions

*The following statements are either true or false (answers on page 111)*

7. Stimulating the receptor for glucagon-like peptide causes weight gain.
8. Incretin analogues cause hypoglycaemia in patients with type 2 diabetes.



## Experimental and clinical pharmacology

# Incretin mimetics and enhancers: clinical applications

*Anne T Reutens, Endocrinologist and Clinical researcher, and Jonathan E Shaw, Deputy Director, International Diabetes Institute, Melbourne*

### Summary

**Mimicking or enhancing the actions of incretin can help to control type 2 diabetes. Exenatide and liraglutide are injectable glucagon-like peptide-1 receptor agonists, while vildagliptin and sitagliptin are oral dipeptidyl peptidase 4 inhibitors. These drugs have their main effects on postprandial glucose, but also lower fasting glucose concentrations. Glucagon-like peptide-1 agonists lower glycated haemoglobin by about 1–1.7% and induce weight loss, but frequently cause transient nausea. Dipeptidyl peptidase 4 inhibitors reduce glycated haemoglobin by 0.5–1%. They have infrequent adverse effects, but no effect on weight. Longer-term data are required to establish their full adverse event profile and their efficacy in reducing the macro- and microvascular complications of diabetes.**

Key words: dipeptidyl peptidase, glucagon-like peptide, exenatide, liraglutide, sitagliptin, vildagliptin.

*(Aust Prescr 2008;31:104–8)*

### Introduction

The incretin effect is a normal physiological response involving gut hormones. These incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), stimulate pancreatic  $\beta$  cells to increase insulin secretion in response to oral carbohydrates. In type 2 diabetes, the secretion of GIP remains normal but the insulin response to it is impaired. GLP-1 concentrations are reduced in type 2 diabetes but the pancreatic response is relatively preserved. Using agonists to mimic the action of incretin, or inhibiting incretin metabolism to enhance the effect, are new strategies to treat type 2 diabetes.<sup>1</sup> The main effect of the drugs is to lower postprandial glucose. This is particularly attractive, as postprandial glucose concentrations are more strongly linked to cardiovascular disease than is fasting glucose.<sup>2</sup>

### GLP-1 receptor agonists (mimetics)

GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase 4 (DPP4), so its potential as a drug is very limited. However, drugs which are synthetic agonists at the GLP-1 receptor resist cleavage by DPP4.

### Exenatide

Exenatide is an agonist which is administered twice daily before meals by subcutaneous injections from a pre-filled pen. The