

# New therapies for diabetes: Incretin mimetics and gliptins

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## Article points

1. Incretin mimetics possess the potential to achieve glucose homeostasis with minimal risk of iatrogenic hypoglycaemia.
2. Enhancing the incretin effect by blocking the breakdown of GLP-1 is the mechanism of action of DPP-IV inhibitors.
3. Any future strategy to manage diabetes in a clinical setting and meet the needs of individual patients should include new classes of drugs.

## Key words

- DPP-IV inhibitors
- GLP-1
- Gliptins
- Incretin mimetics

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**Incretin hormones are peptides that are released from the intestinal tract in response to mixed meals and contribute to glucose homeostasis by promoting glucose-dependent insulin secretion. The incretin effect is observed experimentally when insulin responses to oral and intravenous glucose loads are compared. An enhanced response is seen with oral, as opposed to parenteral, glucose (Elrick et al, 1964; Perley and Kipnis, 1967). In this article the authors review the mechanisms and pathways by which these therapies work.**

Two hormones secreted from the gastrointestinal tract – glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) – account for more than 50% of the incretin effect of a mixed meal. They rapidly stimulate insulin release in the presence of hyperglycaemia. GLP-1 has 30 amino acids and GIP has 42 amino acids (McIntyre et al, 1964; Nauck et al, 1986). GIP is derived from K cells located in the jejunum and responds more to dietary fat than glucose. GLP-1 is secreted by L cells in the ileum, predominantly in the presence of glucose. This occurs in association with neural signalling arising from a food stimulus. These mechanisms induce insulin secretion through direct activation of G-protein coupled receptors expressed on pancreatic  $\beta$ -cells (Vilsboll and Holst, 2004). In type 2 diabetes the  $\beta$ -cell response to GIP is largely lost, but GLP-1 receptor sensitivity remains. The reasons for reduced GIP responsiveness remain unclear, but may be associated with reduced GIP receptor expression in people with significant insulin resistance (Rudovich

et al, 2005). Current developments have therefore focused on the role of GLP-1 in glucose homeostasis.

## Signalling mechanisms of incretin hormones

Insulin secretion in response to glucose is triggered by  $\beta$ -cell depolarisation: an influx of calcium, in conjunction with calmodulin, causes insulin granules to fuse with the cell membrane, releasing their contents. When GLP-1 binds to receptors on the  $\beta$ -cell membrane, signalling pathways are activated, this results in 3',5'-cyclic adenosine monophosphate-dependant protein kinase A activation. GLP-1 cannot trigger insulin release by itself as its insulinotropic effect is dependent on ambient glucose. At glucose levels close to the threshold for triggering insulin secretion, GLP-1 has very little effect (Triplitt et al, 2006).

## Therapeutic potential

From the therapeutic point of view, this means that incretin mimetics possess the potential to achieve glucose homeostasis

with minimal risk of iatrogenic hypoglycaemia. In contrast, sulphonylureas and meglitinides trigger insulin release irrespective of ambient glucose and can produce hypoglycaemia. As the site of action of the incretins is separate from those activated by secretagogues, they have the further advantage of providing an additive, rather than competitive, effect (Zander et al, 2002).

In addition to its glucose-dependent action on insulin secretion, GLP-1 has been shown to suppress glucagon secretion, delay gastric emptying and induce satiety, with a resultant reduction in food intake (Levy, 2006) which offers the potential for weight reduction. Elevated glucagon levels are found in people with type 2 diabetes and contribute to background and postprandial hyperglycaemia. By its direct action on islet  $\alpha$ -cells, GLP-1 reduces excess glucagon secretion without having an impact on its protective effect in hypoglycaemia. In rodents, suppression of apoptosis and proliferation of  $\beta$ -cells have been demonstrated. Should this preserving effect be demonstrated in humans it would represent a very significant milestone in treatments aimed at reversing the inexorable decline of  $\beta$ -cells seen in type 2 diabetes.

The key properties of GLP-1 are summarised in *Box 1*.

**Long-acting GLP-1 agonists/ analogues and DPP-IV inhibition**

The potential for incretin action to be applied in a clinical setting has been recognised for many years. However, in its native form there are a number of drawbacks. In vivo GLP-1 only remains active for 1–2 minutes owing to proteolytic inactivation by the enzyme dipeptidyl peptidase IV (DPP-IV), therefore, as it will be destroyed in the intestine it needs to be given parenterally.

Long-acting GLP-1 analogues that are resistant to DPP-IV inactivation and mimic the action of the native hormone have been under development. The peptides exendin-3

and exendin-4, were isolated from the saliva of the lizard species *Heloderma*; *H. horridum* – the Mexican beaded lizard, and *H. suspectum* – the Gila monster (Eng et al, 1990; Eng et al, 1992; respectively). Exendin-4 has a 50% homology with human GLP-1, binds to pancreatic GLP-1 receptors in vitro and resists deactivation by DPP-IV. This GLP-1 agonist has a therapeutic action of about 6 hours, reaching a peak plasma concentration after 2 hours.

**Incretin mimetics**

**Exenatide**

The first incretin mimetic to become commercially available is exenatide (Byetta; Amylin Pharmaceuticals, San Diego and Eli Lilly & Company, Basingstoke). Exenatide is synthetically produced exendin-4. It was granted approval for clinical use by the US Food and Drug Administration in April 2005 and gained a European licence in 2006.

Exenatide is administered by subcutaneous injections of 5  $\mu$ g or 10  $\mu$ g BD.

**Key trials**

Phase III trials involving 1600 people with type 2 diabetes treated over a minimum of 6 months evaluated exenatide as additional therapy in individuals who had not achieved satisfactory glycaemic control with maximally tolerated doses of metformin, sulphonylureas or a combination of the

**Page points**

1. Incretin mimetics possess the potential to achieve glucose homeostasis with minimal risk of iatrogenic hypoglycaemia.
2. By its direct action on islet  $\alpha$ -cells, GLP-1 reduces excess glucagon secretion without having an impact on its protective effect in hypoglycaemia.
3. The first ‘incretin mimetic’ to become commercially available is exenatide.

**Box 1. Summary of the key properties of GLP-1 (Drucker, 2001; 2003).**

- Stimulates glucose-dependent insulin secretion
- Suppresses glucagon secretion
- Slows gastric emptying
- Reduces food intake
- Improves insulin sensitivity
- *This in turn*
- Increases  $\beta$ -cell mass and maintains  $\beta$ -cell efficiency
- Long-term effects have been demonstrated in animals

### Page points

1. The most common side-effect of exenatide was mild to moderate nausea.
2. Other preparations requiring once-daily or once-weekly administration are being studied.
3. Liraglutide is a human GLP-1 analogue linked to a fatty acid.
4. DPP-IV inhibitors block DPP-IV-mediated inactivation of GLP-1.
5. In addition to the impact on GLP-1 action, these agents may potentially affect other peptides.

two agents (Buse et al, 2004; DeFronzo et al, 2005; Kendall et al, 2005). In all studies, exenatide reduced HbA<sub>1c</sub> by about 1% when compared with placebo over 30 weeks. When exenatide 10 µg was added to metformin there was an average 2.8 kg weight loss. This did not appear to plateau at the end of the study period (DeFronzo et al, 2005).

The most common side-effect of exenatide was mild to moderate nausea; with a prevalence of 36–39% with 5 µg BD and 45–50% with 10 µg BD. However, this generally dissipated in the early weeks of therapy (Riddle et al, 2006). Only 4% of patients withdrew from the studies because of nausea. There were reports of hypoglycaemia when exenatide was added to sulphonylurea, but not when added to metformin. Adverse affects were related to rapid dose-escalation: their incidence was reduced by slowing titration (Fineman et al, 2004).

To assess the likely position of exenatide in people failing to achieve adequate control on other oral therapies, treatment algorithms have been explored in an intention-to-treat analysis (Heine et al, 2005). In a 26-week study, 551 people with type 2 diabetes on metformin and sulphonylurea with an HbA<sub>1c</sub> of 7–10% were randomised to exenatide (5 µg BD for a month followed by 10 µg BD) or insulin glargine (using a forced-titration protocol aiming for a morning blood glucose of 100 mg/dl [5.4 mmol/l]). The percentages of participants achieving HbA<sub>1c</sub> ≤ 7% (48% for insulin glargine versus 46% for exenatide) were not significantly different. Weight loss in the exenatide arm was 2.3 kg (± 0.2 kg) while weight gain in the insulin glargine group was 1.8 kg (± 0.2 kg). Criticism of the study focused on the failure of investigators to match the larger insulin glargine doses (average of only 15 units) used in the Treat-to-Target Trial (Riddle et al, 2003). If dose titration had achieved better fasting plasma glucose levels, a difference in outcome HbA<sub>1c</sub>

might have been observed.

### Liraglutide

Liraglutide, (known as NN2211; being developed by Novo Nordisk, Crawley), is a human GLP-1 analogue linked to a fatty acid (Juhl et al, 2002). Liraglutide binds to interstitial albumin at the injection site and is slowly absorbed. The albumin complex delays absorption and is resistant to DPP-IV degradation with a half-life of 12 hours (Agero et al, 2002). In studies using 0.6 mg daily and 0.75 mg daily, liraglutide has been shown to significantly reduce fasting plasma glucose and HbA<sub>1c</sub> (placebo-corrected difference of -0.75% for the highest dose) with no effect on weight gain and little effect on fasting insulin levels (Madsbad et al, 2004). In a 5-week study involving titration to higher doses (2 mg daily) of liraglutide, an average weight loss of 2.9 kg (2.1–3.6 kg) was observed when used as add-on therapy to metformin and compared with glimepiride (Nauck et al, 2006). Nausea was the most common reported side-effect but few trial participants withdrew as a consequence.

### Longer-acting agents

Currently there are studies examining the impact of prolonged action of GLP-1 receptor agonists. In addition, research is focusing on modifying human GLP-1 sequencing in order to increase resistance to enzymatic degradation of by DPP-IV. Other preparations requiring once-daily or once-weekly administration are being studied in an attempt to improve concordance and acceptability.

### DPP-IV inhibitors (gliptins)

#### Mechanism of action

DPP-IV inhibitors block DPP-IV-mediated inactivation of GLP-1. This in turn results in prolongation of endogenous GLP-1 activity, with higher plasma levels being achieved in vivo (Idris and Donnelly, 2007).

In addition to the impact on GLP-1 action, these agents may potentially affect other peptides, including peptide

**Page points**

1. Vildagliptin is a competitive and reversible inhibitor of DPP-IV that is administered orally.
2. In elucidating the underlying actions on  $\beta$ -cell function, vildagliptin was shown to significantly increase acute insulin response to glucose.
3. Sitagliptin is primarily cleared via the kidneys whereas vildagliptin is hepatically metabolised.
4. Sitagliptin has been shown to improve HbA<sub>1c</sub>, fasting glucose and  $\beta$ -cell function.

YY, neuropeptide Y, growth hormone-releasing hormone and vasoactive intestinal polypeptide, involved in regulatory systems (Deacon, 2004). It is further recognised that DPP-IV is important in T-cell activation. Long-term data on the use of DPP-IV inhibitors remain limited.

The properties of DPP-IV inhibitors are summarised in *Box 2*.

**Vildagliptin**

Vildagliptin (Galvus; Novartis, Frimley) is a competitive and reversible inhibitor of DPP-IV that is administered orally. It is metabolised by hydrolysis in the liver. In a 1-year study (Dejager et al, 2006) comparing vildagliptin 50 mg BD and metformin 1 g BD in drug-naïve people with type 2 diabetes and an average baseline HbA<sub>1c</sub> of 8.7% the mean change from baseline to endpoint HbA<sub>1c</sub> was -1% and -1.4% respectively. While non-inferiority of vildagliptin compared with metformin was not confirmed, gliptin monotherapy did result in early and sustained reduction in HbA<sub>1c</sub>. Gastrointestinal side-effects were less common than with metformin and there was no change in weight or significant hypoglycaemia with vildagliptin (Dejager et al, 2006).

In a further study comparing vildagliptin

50 mg BD with rosiglitazone 8 mg daily in drug-naïve people with type 2 diabetes, the mean change in HbA<sub>1c</sub> for those on vildagliptin from baseline to endpoint was -1.1%, which satisfied the non-inferiority criterion of <0.4% difference between treatments. Lipid profile was improved in the vildagliptin-treated arm, with greater reduction in triglycerides, total cholesterol and low-density lipoprotein. Mean weight gain of 1.6 kg was observed over the 24-week study period in those treated with rosiglitazone, whereas vildagliptin did not affect body weight (Rosenstock et al, 2007).

When vildagliptin was added to insulin in people with poor glycaemic control (HbA<sub>1c</sub> 7.5%–11%) a significant reduction in HbA<sub>1c</sub> was observed (-0.5% vildagliptin versus -0.2% placebo). In addition, no difference in insulin dosages were noted and fewer and less severe hypoglycaemic episodes were recorded in the vildagliptin-treated group (Fonseca et al, 2006).

In elucidating the underlying actions on  $\beta$ -cell function, vildagliptin was shown to significantly increase acute insulin response to glucose – an effect that continued for 2–4 weeks after ceasing therapy (D'Alessio et al, 2006). In addition, a 6-week insulin clamp study comparing vildagliptin with placebo showed a 15% improvement in insulin sensitivity (Azuma et al, 2006).

**Box 2. Summary of the properties of dipeptidyl peptidase-IV (DPP-IV) inhibition (adapted from Ahren, 2007).**

- Increases fasting and postprandial GLP-1 levels
- Reduces fasting and postprandial glycaemia
- Improves  $\beta$ -cell function
  - Increases insulin secretion, reduces proinsulin: insulin ratio
  - Increases  $\beta$ -cell mass
- Inhibits glucagon secretion
  - Reduces hepatic glucose production
- Increases insulin sensitivity
- Reduces postprandial lipaemia
- No effect on gastric emptying or body weight
- Reduces HbA<sub>1c</sub> by approximately 1%
- is safe and tolerable

**Sitagliptin**

Sitagliptin (Januvia; Merck, Sharpe & Dohme, Hoddesdon) is primarily cleared via the kidneys. In three studies, sitagliptin was shown to improve HbA<sub>1c</sub>, fasting glucose and  $\beta$ -cell function compared with placebo. HbA<sub>1c</sub> was reduced by 1.05% with no hypoglycaemia and no change in body weight during a 12-week study (Nonaka et al, 2006). In another study, 741 people were randomised to placebo, sitagliptin 100 mg or 200 mg daily over 24 weeks. HbA<sub>1c</sub> reductions of 0.61% and 0.76% were recorded respectively for the 100 mg and 200 mg groups. Additionally, fasting plasma glucose levels were reduced compared with

**Page points**

1. When sitagliptin was used as add-on therapy in metformin-treated patients, reductions in HbA<sub>1c</sub> were similar to those achieved in patients who had glipizide added – but with significantly less hypoglycaemia.
2. Early studies with incretin mimetics show promising improvements in glycaemic control with significant and continuing weight loss being achieved.
3. Enhancing the incretin effect by blocking the breakdown of GLP-1 is the mechanism of action of the DPP-IV inhibitors.

placebo.

A homeostasis model assessment of β-cell function (HOMA-B) showed an increase of 13% and a reduction in proinsulin:insulin ratio with sitagliptin, suggesting an improvement in β-cell function (Aschner et al, 2006). This was corroborated in another monotherapy study comparing sitagliptin with placebo. Sitagliptin 100 mg was associated with a 0.6% reduction in HbA<sub>1c</sub> as well as improvements in fasting proinsulin:insulin ratio and HOMA-B (Raz et al, 2006).

Sitagliptin has been used in combination therapy. When sitagliptin was used as add-on therapy in metformin-treated patients, reductions in HbA<sub>1c</sub> were similar to those achieved in patients who had glipizide added – but with significantly less hypoglycaemia (Ruddy et al, 2006). In patients on pioglitazone, the addition of sitagliptin 100 mg produced a 0.70% reduction in HbA<sub>1c</sub> with no change in body weight between the placebo and sitagliptin arms (Rosenstock et al, 2006).

Table 1 summarises the chemical characteristics of the incretin mimetics and gliptins currently undergoing trials.

**Conclusions**

New therapies that enhance the incretin effect will increasingly become available to patients and clinicians in everyday practice.

Early studies with incretin mimetics show promising improvements in glycaemic control with significant and continuing weight loss being achieved. Although nausea is common after starting treatment, this tends to be less when treatment is commenced on a lower dose and infrequently leads to cessation of therapy. Because these agents are administered as a once- or twice-daily injection, there will inevitably be some patients who will reject this form of therapy, but with the possibility of a once-weekly preparation in the future this may change.

Enhancing the incretin effect by blocking the breakdown of GLP-1 is the mechanism of action of a new therapeutic class – the

**Table 1. GLP-1 agents and DPP-IV inhibitors. Adapted from Levy (2006) and Green (2006).**

Agent	Chemical characteristics	Manufacturer
<b>GLP-1 receptor agonists</b>		
Exenatide (Byetta)	DPP-IV resistant peptide (naturally occurring but bioengineered)	Amylin Pharmaceuticals (San Diego) and Eli Lilly & Company (Basingstoke)
Liraglutide (NN2211)	GLP-1 analogue with fatty acyl adduct to promote albumin binding	Novo Nordisk (Crawley)
CJC-1131	GLP-1 analogue which covalently binds to albumin after subcutaneous injection (Drug Affinity Complex technology)	ConjuChem Inc (Montreal)
Albugon	GLP-1 analogue covalently bound to albumin prior ex vivo	Human Genome Sciences (Rockville) and GlaxoSmithKline (Uxbridge)
<b>DPP-IV inhibitors (phase III/IV)</b>		
Vildagliptin (Galvus)	Reversible inhibitor	Novartis (Frimley)
Sitagliptin (Januvia)	Reversible inhibitor	Merck Sharp & Dohme (Hoddesdon)
Alogliptin (SYR-322)	Reversible inhibitor	Takeda (Wooburn Green)
Saxagliptin (BMS-477118)	Covalently bound inhibitor	Bristol-Myers Squibb (Uxbridge)

DPP-IV inhibitors. These agents are generally well tolerated and effective in lowering blood glucose in people with type 2 diabetes. As oral preparations they have clear advantages over the parenterally administered GLP-1 analogues/agonists in terms of acceptability. By contrast, however, they are generally weight neutral.

With time it is likely that both classes will be used earlier in the natural history of diabetes than their initial licenses in Europe are likely to or do permit. The potential for these agents to improve  $\beta$ -cell durability is an exciting prospect for a metabolic condition that inexorably progresses even with optimum treatment.

Any future strategy to manage diabetes in a clinical setting and meet the needs of individual patients should include new classes of drugs. Incretin mimetics and gliptins offer novel mechanisms of action in the diabetes therapeutic portfolio. ■

Agero H, Jensen LB, Elbrond B et al (2002) The pharmacokinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative, in healthy men. *Diabetologia* **45**:195–202

Ahren B (2007) DPP-4 Inhibitors – Clinical Data and Clinical Implications. *Diabetes Care* [Epub ahead of print]

Aschner P, Kipnes MS, Lunceford JK et al (2006) Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* **29**: 2632–7

Azuma K, Radikova Z, Mancino JM et al (2006) DPP-4 inhibition improves insulin resistance (IR) in type 2 diabetes mellitus. *Program and abstracts of the American Diabetes Association 66th Scientific Sessions*, 9–13 June 2006, Washington, DC. Abstract 5-LB

Buse JB, Henry RR, Han J et al (2004) Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulphonylurea treated patients with type 2 diabetes. *Diabetes Care* **27**: 2628–35

D'Alessio DA, Watson CE, He Y-L et al (2006) Restoration of an acute insulin response to glucose (AIRg) in drug-naïve patients with type 2 diabetes by 3-month treatment with vildagliptin. *Program and abstracts of the American Diabetes Association 66th Scientific Sessions*, 9–13 June 2006, Washington, DC. Abstract 454-P

*Association 66th Scientific Sessions*, 9–13 June 2006, Washington, DC. Abstract 454-P

Deacon CF (2004) Therapeutic strategies based on glucagon-like peptide 1. *Diabetes* **3**: 2181–9

DeFronzo RA, Ratner RE, Han J (2005) Effects of exenatide (exendin-4) on glycemic control over 30 weeks in metformin-treated patients. *Diabetes Care* **28**:1092–100

Dejager S, Lebault A, Couturier A, Schweizer A (2006) Sustained reduction in HbA<sub>1c</sub> during one-year treatment with vildagliptin in patients with type 2 diabetes. *Program and abstracts of the American Diabetes Association 66th Scientific Sessions*, 9–13 June 2006, Washington, DC. Abstract 120-OR

Drucker DJ (2001) Development of glucagon-like peptide-1-based pharmaceuticals as therapeutic agents for the treatment of diabetes. *Current Pharmaceutical Design* **7**:1399–412

Drucker DJ (2003) Glucagon-like peptides: regulators of cell proliferation, differentiation, and apoptosis. *Molecular Endocrinology* **17**:161–71

Elrick H, Stimmler L, Hlad CJ Jr et al (1964) Plasma insulin response to oral and intravenous glucose administration. *Journal of Clinical Endocrinology and Metabolism* **24**:1076–82

Eng J, Andrews PC, Kleinman WA et al (1990) Purification and structure of exendin-3, a new pancreatic secretagogue isolated from *Heloderma horridum* venom. *Journal of Biological Chemistry* **265**: 20259–62

Eng J, Kleiman WA, Singh L et al (1992) Isolation and characterization of exendin-4, an exendin-3 analogue, from *Heloderma suspectum* venom. Further evidence for an exendin receptor on dispersed acini from guinea pig pancreas. *Journal of Biological Chemistry* **267**: 7402–5

Fineman MS, Shen LZ, Taylor K et al (2004) Effectiveness of progressive dose-escalation of exenatide (exendin-4) in reducing dose-limiting side effects in subjects with type 2 diabetes. *Diabetes/Metabolism Research and Reviews* **20**:411–17

Fonseca V, Dejager S, Albrecht D, Shirt L, Schweizer A (2006) Vildagliptin as an add-on to insulin in patients with type 2 diabetes. *Program and abstracts of the American Diabetes Association 66th Scientific Sessions*, 9–13 June 2006, Washington, DC. Abstract 467-P

Green BD, Flatt PR, Bailey CJ (2006) Dipeptidyl peptidase (DPP-IV) inhibitors: a newly emerging drug class for the treatment of type 2 diabetes. *Diabetes and Vascular Disease Research* **3**: 159-65

Heine RJ, Van Gaal LF, Johns D et al (2005) Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Annals of Internal Medicine* **143**: 559–69

Page points

1. As oral preparations the DPP-IV inhibitors have clear advantages over the parenterally administered GLP-1 analogues/agonists in terms of acceptability.
2. Any future strategy to manage diabetes in a clinical setting and meet the needs of individual patients should include new classes of drugs.

## New therapies for diabetes: Incretin mimetics and gliptins

- Idris I, Donnelly R (2007) Dipeptidyl peptidase-IV inhibitors: a major new class of oral antidiabetic drug. *Diabetes, Obesity and Metabolism* **9**: 153–65
- Juhl CB, Hollingdal M, Sturis J et al (2002) Bedtime administration of NN2211, a long-acting GLP-1 derivative, substantially reduces fasting and postprandial glycemia in type 2 diabetes. *Diabetes* **51**: 424–9
- Kendall DM, Riddle MC, Rosenstock J et al (2005) Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients treated with metformin and a sulfonylurea. *Diabetes Care* **28**: 1083–91
- Levy JC (2006) Therapeutic intervention in the GLP-1 pathway in type 2 diabetes. *Diabetic Medicine* **23**(Suppl 1): 14–19
- Madsbad S, Schmitz O, Ranstam J (2004) 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* **27**: 1335–42
- McIntyre N, Holdsworth CD, Turner DS (1964) New interpretation of oral glucose tolerance. *Lancet* **41**: 20–1
- Nauck M, Stockmann F, Ebert R, Creutzfeldt W (1986) Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia* **29**: 46–52
- Nauck MA, Hompesch M, Filipczak R et al (2006) Five weeks of treatment with the GLP-1 analogue liraglutide improves glycaemic control and lowers body weight in subjects with type 2 diabetes. *Experimental and Clinical Endocrinology and Diabetes* **114**: 417–23
- Nonaka K, Kakikawa T, Sato A et al (2006) Twelve-week efficacy and tolerability of sitagliptin, a dipeptidyl peptidase-IV (DPP-4) inhibitor in Japanese patients with T2DM. *Program and abstracts of the American Diabetes Association 66th Scientific Sessions*; 9–13 June, Washington, DC. Abstract 537-P
- Perley MJ, Kipnis DM (1967) Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic subjects. *Journal of Clinical Investigation* **46**: 1954–62
- Raz I, Hanefeld M, Xu L et al (2006) Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. *Diabetologia* **49**: 2564–71
- Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators (2003) The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* **26**: 3080–6
- Riddle MC, Henry RR, Poon TH et al (2006) Exenatide elicits sustained glycaemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulphonylureas with or without metformin. *Diabetes Metabolism Research and Reviews* **22**: 483–91
- Rosenstock J, Brazg R, Andryuk PJ et al (2006) Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Clinical Therapeutics* **28**: 1556–68
- Rosenstock J, Baron MA, Dejager S et al (2007) Comparison of vildagliptin and rosiglitazone monotherapy in patients with type 2 diabetes: a 24-week, double-blind, randomized trial. *Diabetes Care* **30**: 217–23
- Ruddy MK, Bergman AJ, Zheng W et al (2006) Sitagliptin, a DPP-4 inhibitor, does not inhibit the pharmacokinetics of the sulfonylurea glyburide. *Program and abstracts of the American Diabetes Association 66th Scientific Sessions*, 9–13 June 2006, Washington, DC. Abstract 558-P
- Rudovich A, Kaiser S, Engeli S, Pfeiffer AFH (2005) Gastric inhibitory polypeptide receptors are present in human subcutaneous adipose tissue: effects of central obesity and weight loss. *Program and abstracts of the European Association for the Study of Diabetes 41st Annual Meeting*; 12–15 September 2005; Athens, Greece. Abstract 549
- Triplitt C, Wright A, Chiquette E (2006) Incretin mimetics and dipeptidyl peptidase-IV inhibitors: potential new therapies for type 2 diabetes mellitus. *Pharmacotherapy* **26**: 360–74
- Viltsboll T, Holst JJ (2004) Incretins, insulin secretion and type 2 diabetes mellitus. *Diabetologia* **47**: 357–66
- Zander M, Madsbad S, Madsen JL, Holst JJ (2002) 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* **359**: 824–30