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Dipeptidyl peptidase IV (DPP IV) inhibitors: a newly emerging drug class for the treatment of type 2 diabetes

BRIAN D GREEN, PETER R FLATT, CLIFFORD J BAILEY

Abstract

Inhibitors of the enzyme dipeptidyl peptidase IV (DPP IV) provide a strategy for the treatment of type 2 diabetes. DPP IV rapidly inactivates the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). Inhibition of DPP IV prolongs and enhances the activity of endogenous GLP-1 and GIP, which serve as important prandial stimulators of insulin secretion and regulators of blood glucose control. In clinical trials DPP IV inhibitors (or 'gliptins') have shown efficacy and tolerability in the management of hyperglycaemia in type 2 diabetes, without causing weight gain or hypoglycaemia.

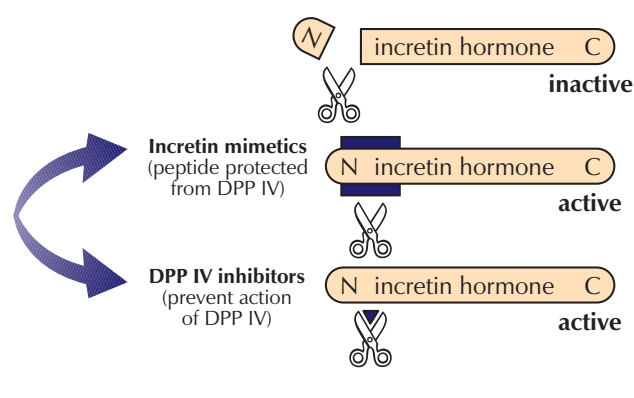
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Key words: dipeptidyl peptidase IV, DPP IV, gliptin, incretin hormones, DPP IV inhibition.

Introduction

Dipeptidyl peptidase IV (DPP IV or DPP-4; EC 3.4.14.5) is a prolyl peptidase which preferentially cleaves proteins and peptides after a proline amino acid residue. DPP IV is commonly characterised by an ability to cleave Xaa-Pro or Xaa-Ala dipeptides preferentially from the N-terminus of polypeptides (where Xaa is any amino acid except Pro). DPP IV is also the CD26 T-cell activating antigen found in almost all human organs and tissues.¹ Tissues which strongly express DPP IV include the exocrine pancreas, kidney, gastrointestinal tract, biliary tract, thymus, lymph nodes, uterus, placenta, prostate, adrenal, sweat glands, salivary and mammary glands. DPP IV is anchored to the plasma membrane of endothelia of almost all organs examined, and is also found solubilised in body fluids such as blood plasma and cerebrospinal fluid.² The broad distribution of DPP IV gives it ready access to endocrine peptides, neuropeptides and a

Figure 1. The two-pronged strategy for unlocking the therapeutic potential of the incretin hormones
Physiologically, N-terminal dipeptides are cleaved from the incretin hormones by DPP IV activity, rendering them non-insulinotropic. To circumvent this, two main strategies have been developed: incretin analogues resistant to DPP IV, and DPP IV inhibitors to minimise degradation of endogenous incretin hormones



wide range of paracrine and autocrine peptides and polypeptides.^{1,3}

Although DPP IV is a pleiotropic enzyme that cleaves and generally inactivates a wide variety of peptide hormones,¹ it has become renowned for its inactivation of two intestinal hormones known as the incretins. These include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). Initial interest in the incretin hormones as potential antidiabetic hormones was aroused by their potent insulin-secreting activity, and consequent lowering of prandial plasma glucose. However, degradation of GLP-1 and GIP by DPP IV is rapid (half-life less than two minutes) and leads to formation of metabolites that are devoid of insulin-releasing activity. Thus, preventing the degradation of the incretin hormones, by DPP IV inhibition, became an attractive therapeutic strategy (figure 1).³⁻⁹ Generation and screening of numerous synthetic incretin analogues has spawned a range of DPP IV-resistant analogues of GLP-1 and GIP (recently reviewed).^{4,7} Several of these analogues are currently undergoing preclinical and clinical trials, and the GLP-1 mimetic, Byetta (exendin/exenatide), was introduced in the US in 2005.⁷ The present review evaluates the concept, therapeutic potential and limitations of DPP IV inhibitors as potential antidiabetic agents.

School of Biological Sciences, Queens University Belfast, Belfast, BT9 5AG, UK.
Brian D Green, Lecturer in Nutritional Biochemistry

School of Biomedical Sciences, University of Ulster, Coleraine, UK.
Peter R Flatt, Professor of Biological and Biomedical Sciences

School of Life and Health Sciences, Aston University, Birmingham, UK.
Clifford J Bailey, Professor of Clinical Science

Correspondence to: Dr Brian D Green

School of Biological Sciences, Queens University Belfast, David Keir Building, Stranmillis Road, Belfast, BT9 5AG, UK.
Tel: +44 2890 976541; Fax: +44 2890 976541
E-mail: b.green@qub.ac.uk

Table 1. Key actions of the incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide)

GLP-1 and GIP	GLP-1 only
↓ plasma glucose	↑ feeling of satiety
↑ glucose-dependent insulin secretion	↓ food intake
↑ biosynthesis of insulin	↓ body weight
↑ expansion of beta-cell mass*	↓ glucagon secretion
↑ beta cell survival*	↓ gastric acid secretion
↑ peripheral glucose uptake and disposal*	↓ hepatic insulin extraction
↓ gastric emptying rate	

Key: ↑ increase; ↓ decrease; * noted in preclinical studies but yet to be confirmed in clinical studies

Antidiabetic actions of the incretin hormones

Although GLP-1 and GIP were discovered as, and gained prominence as, insulin-releasing peptide hormones,⁵ later research ascribed to them a number of other potentially important pancreatic and extrapancreatic actions (table 1). In the pancreatic islets, GLP-1 and GIP have beneficial actions on the beta cells, such as expansion of beta-cell mass and increased beta-cell survival.¹⁰ Extrapancreatic actions include the reduction of hepatic insulin clearance¹¹ and apparently 'insulin-like' effects on skeletal muscle,¹²⁻¹⁴ liver¹⁵ and adipose tissue,¹⁶⁻¹⁹ which serve to promote glucose uptake and metabolism. Other antidiabetic actions of the incretin hormones are summarised in table 1 and detailed elsewhere.^{4,7} Most noteworthy are the inhibition of glucagon secretion, induction of satiety, tendency for weight loss and the reduced rate of gastric emptying²⁰ associated with GLP-1.

Other members of the DPP IV enzyme family

Improvements in our knowledge of DPP IV, and in particular the discovery of a family of enzymes with DPP IV-like activity, have reopened the issue of inhibitor selectivity. Examples of enzymes which possess DPP IV-like activity are: fibroblast activation protein (FAP), dipeptidyl peptidase II (DPP II, also known as DPP 7 or quiescent cell proline dipeptidase [QPP]), dipeptidyl peptidase 8 (DPP 8) and dipeptidyl peptidase 9 (DPP 9).

FAP is a membrane-bound protease capable of dipeptidyl peptidase activity to cleave N-terminal dipeptides from polypeptides. FAP also possesses collagenolytic activity that can degrade gelatin and type I collagen.²¹ Although FAP does not appear to be expressed ubiquitously like other members of the DPP IV enzyme family, it has been found in the alpha cells of the pancreas and in serum.²² DPP II is expressed

across a range of human tissues.²³ Similarity between the activities of DPP II and DPP IV is most neatly demonstrated by the fact that many of the established inhibitors of DPP II activity were originally described as DPP IV inhibitors. DPP 8 and DPP 9 are widely distributed post-proline cleaving dipeptidases. Their DPP IV-like activity is demonstrated by their ability to hydrolyse substrates derived from H-Ala-Pro and H-Gly-Pro.²² Although DPP 8 and DPP 9 have not yet been associated with any particular biological process, it remains a distinct possibility that many of the functions ascribed to DPP IV may actually be derived from the activity of DPP 8 and/or DPP 9. Selective inhibition of DPP 8/9-attenuated T-cell activation suggests that these enzymes are involved in the immune system.²⁴ Earlier observations that the plasma of DPP IV-deficient mice is capable of cleaving the substrate Gly-Pro-pNA25 indicates that, in hindsight, the existence of other DPP IV-like enzymes could have been foreseen.

Preclinical data on DPP IV inhibition

The concept of DPP IV inhibition as a strategy for the treatment of diabetes has been supported and strengthened by studies employing rodents with selective 'knockout' or mutation of DPP IV.²⁵⁻²⁷ Mice lacking DPP IV are viable and healthy, with no significant N-terminal degradation of the incretin hormone GLP-1 detected in plasma.²⁵ Consistent with higher levels of active GLP-1, and potentially more active GIP, mice lacking DPP IV have enhanced glucose tolerance and increased levels of plasma insulin. Furthermore, DPP IV-deficient mice have improved insulin sensitivity and appear to resist hepatic lipid accumulation when fed a high-fat diet.²⁸ There are indications of a role for DPP IV in obesity since DPP IV-deficient mice resist weight gain on a high-fat diet, have lower food intake and show increased energy expenditure.²⁸

Preclinical testing of several DPP IV inhibitors in diabetic rodents has revealed the potential of these compounds to preserve incretin action and lower plasma glucose. Concomitant administration of the DPP IV inhibitor valine-pyrrolidide with intravenous GIP improved the insulinotropic effect of GIP, enhanced glucose clearance and reduced glucose excursions.²⁹ Another DPP IV inhibitor, P32/98 (isoleucine thiazolidide), substantially decreased circulating DPP IV activity and improved glucose tolerance in Zucker fatty rats.³⁰ Long-term, twice-daily administration of P32/98 to Zucker rats for three months decreased body weight gain without affecting food intake.³¹ Similarly, high-fat fed mice treated for eight weeks with the DPP IV inhibitor NVP DPP728 showed increased levels of intact GLP-1, improved glucose tolerance and increased glucose-stimulated insulin secretion.³² In Zucker rats, NVP-DPP728 amplified the early phase insulin response and reduced glucose excursions to normal.³³

Chronic (12 weeks') administration of P32/98 to Zucker fatty rats improved glucose tolerance and increased insulin levels without significantly altering beta-cell mass or islet morphology.³¹ However, studies in streptozotocin diabetic rodents suggest that P32/98 and LAF237 can enhance islet neogenesis, beta-cell survival and insulin biosynthesis.^{32,34} Also, the des-fluoro analogue of sitagliptin improved both

Table 2. Clinical development of DPP IV inhibitors

Inhibitor	Name	Company	Clinical phase	Specificity data	Type of action	Status
R1438	Aminomethylpyridine	Roche	2	$K_i = 0.1$ nM	Reversible inhibitor	
NVP DPP728		Novartis	2	$IC_{50} = 22$ nM	Covalently bound inhibitor	Discontinued
PSN9301		Prosidion	2	Not available	Reversible inhibitor	
P32/98	Isoleucine thiazolidide	Probiobdrug	2	$K_i = 80$ nM	Reversible inhibitor	?
GSK823093C	Denagliptin	Glaxo Smithkline	3	Not available	-	On hold
MK-0431	Sitagliptin (Januvia)	Merck	3	$IC_{50} = 18$ nM	Reversible inhibitor	NDA submitted to FDA and EMEA 2006 ^a
LAF237	Vildagliptin (Galvus)	Novartis	3	$IC_{50} = 3.5$ nM	Reversible inhibitor	NDA submitted to FDA and EMEA 2006
BMS-477118	Saxagliptin	Bristol-Myers Squibb	3	$K_i = 0.45$ nM	Covalently bound inhibitor	
SYR-322	Alogliptin	Takeda	3	Not available	-	
NN-7201	-	NovoNordisk	-	Not available	Reversible inhibitor	
ALS 2-0426	-	Alantos	1	Not available	-	

Key: NDA = New drug application; FDA = American Food and Drug Administration; EMEA = European Medicines Evaluation Agency; '-' = not known.

^aReceived regulatory approval in Mexico, August 2006.

the function and the morphology of the islet beta cells in high-fat fed streptozotocin diabetic mice.³⁵

The improved glucose control and increased insulin secretion noted during administration of DPP IV inhibitors has been tentatively attributed mainly to increased circulating concentrations of active GLP-1(7-36)amide. Acute and longer-term (three weeks') administration of LAF237 (vildagliptin) to Zucker fatty rats exerted a dose-dependent suppression of DPP IV activity and increased glucose-stimulated circulating levels of intact biologically active GLP-1. This was accompanied by improved glucose tolerance and beta-cell function.³⁶ Despite increased active GLP-1 and the known effects of GLP-1 to reduce weight gain, three weeks' administration of LAF237 did not significantly affect body weight in this study.³⁶

There is evidence to suggest that DPP IV inhibition as a strategy for improving glycaemic status is more effective in mild and moderate hyperglycaemic type 2 diabetes than in severe diabetes. This may reflect greater beta-cell reserve in earlier stages of disease development. Thus, administration of valine-pyrrolidide during the early stages of diabetes (from six weeks of age) in *db/db* mice improved glucose tolerance, whereas this was not seen with treatment at a late stage (at 23 weeks of age).³⁷ Although this is an area in need of fur-

ther research, current indications are that DPP IV inhibitors may be more useful as an early intervention strategy to address impaired glucose tolerance and the early stages of type 2 diabetes.³⁷

Clinical progress of DPP IV inhibitors

Several DPP IV inhibitors have progressed in clinical development, and their characteristics have recently been reviewed.^{3,38} These agents have consistently reduced blood glucose, predominantly postprandially, and this appears to be associated with increases in active circulating GLP-1 (and possibly other incretins) as well as reductions in glucagon. Acutely, DPP IV inhibitors seem to increase the insulin response to glucose. When glycaemic control improves the improved insulin response may be less apparent, possibly due to the reduced glycaemic stimulus. Table 2 lists the specificity ($[K_i]$ or median inhibitory concentration $[IC_{50}]$), type of action and stage of clinical development of DPP IV inhibitors. Tablet formulations of vildagliptin (Galvus) and sitagliptin (Januvia) are most advanced in clinical development. Apart from preliminary accounts of P32/98 and NVP-DPP728 (now superseded by the longer-acting LAF237),^{39,40} most published studies in type 2 diabetic patients relate to vildagliptin and sitagliptin.

Table 3. Medium- and long-term clinical studies with the DPP IV inhibitors LAF237 (vildagliptin, Galvus) and MK-0431 (sitagliptin, Januvia) in type 2 diabetes

Study	Inhibitor	Dose	Duration (weeks)	Other intervention	n	Study design	Effect on glycaemic control
Ahren <i>et al.</i> (2004) ^{40,41}	LAF237	100 mg/day	4	Diet only	37	RDBPC	↓ FPG 0.7 mmol/L ↓ PPG 1.4 mmol/L
Ahren <i>et al.</i> (2004), ⁴⁸ (2005) ⁴⁹	LAF237	50 mg/day	52	Metformin	107	RDBPC*	↓ FPG 1.1 mmol/L ↓ PPG 2.4 mmol/L ↓ HbA _{1C} 1.1%
Ristic <i>et al.</i> (2005) ⁴²	LAF237	25–100mg/day	12	Diet only	279	PC	↓ FPG 0.54 mmol/L** ↓ PPG 0.89 mmol/L** ↓ HbA _{1C} 0.53%**
Mari <i>et al.</i> (2005) ⁴³	LAF237	200 mg/day	4	Diet only	20	RDBPC	↓ FPG 1.2 mmol/L
Dejagers <i>et al.</i> (2006) ^{46†}	LAF237	100 mg/day	52	Diet only	526	RDBC	↓ HbA _{1C} 1.0%
Rosenstock <i>et al.</i> (2006) ^{47†}	LAF237	100 mg/day	24	Diet only	459	RDBPC	↓ HbA _{1C} 1.1%
Herman <i>et al.</i> (2005) ^{51†}	MK-0431	25–100 mg/day	12	Diet only	552	RDBPC	↓ FPG 0.95 mmol/L** ↓ HbA _{1C} 0.7%**
Brazg <i>et al.</i> (2005) ^{56†}	MK-0431	100 mg/day	4	Metformin	28	RDBPC	↓ FPG 1.1 mmol/L
Rosenstock <i>et al.</i> (2006) ^{55†}	MK-0431	100 mg/day	24	Pioglitazone	353	RDBC	↓ HbA _{1C} 0.7%
Ascher <i>et al.</i> (2006) ^{53†}	MK-0431	100 mg/day	24	Diet only	741	RDBPC	↓ FPG 0.9 mmol/L ↓ PPG 2.6 mmol/L ↓ HbA _{1C} 0.79%
Karasik <i>et al.</i> (2006) ^{54†}	MK-0431	100 mg/day	24	Metformin	701	RDBPC	↓ HbA _{1C} 0.65%

* For first 12 weeks, ** for the 100 mg/day dose, ↓ = decrease, † = conference abstract

Key: PC = placebo-controlled; RDBPC = randomised double-blind placebo-controlled; RDBC = randomised double-blind comparator; FBG = fasting blood glucose; FPG = fasting plasma glucose; PBG = post-prandial blood glucose; PPG = post-prandial plasma glucose.

Vildagliptin

When vildagliptin (100 mg/day for four weeks) was administered to patients with type 2 diabetes that was inadequately controlled by lifestyle (diet and exercise), there were reductions in fasting (by 0.7 mmol/L) and postprandial (by 1.4 mmol/L) plasma glucose without a significant change of insulin.⁴⁰ However, postprandial glucagon concentrations were reduced and concentrations of active GLP-1 were doubled.⁴¹ In a 12-week dose-ranging study, vildagliptin (25–100 mg/day) reduced HbA_{1C} by about 0.4% at the higher doses (50 and 100 mg/day) and increased postprandial insulin concentrations at the 100 mg/day dose.⁴² A higher dose of vildagliptin (100 mg twice daily) for four weeks improved the day glucose profile while lowering concentrations of insulin and glucagon.⁴³ Intact GLP-1 and GIP concentrations were increased by the vildagliptin therapy. The acute insulin response to an intravenous glucose challenge was increased after 12 weeks' treatment with vildagliptin at 100 mg/day.⁴⁴ There is preliminary evidence that vildagliptin (100 mg/day) can reduce the post-prandial triglyceride excursion after a fat-rich meal.⁴⁵

During longer-term studies vildagliptin has shown greater and sustained reductions of HbA_{1C}. A 52-week comparator study between vildagliptin (100 mg/day) and metformin (2,000 mg/day) in diet-treated patients with type 2 diabetes found a 1.0% reduction in HbA_{1C} with vildagliptin. However, this was less than the 1.4% reduction in HbA_{1C} observed with metformin.⁴⁶ In a 24-week comparator study vildagliptin (100 mg/day) produced a similar reduction in HbA_{1C} (by 1.1%) to rosiglitazone (8 mg/day).⁴⁷ During the longer-term monotherapy studies, vildagliptin had little effect on body weight and was generally well tolerated.

When given as an add-on therapy to metformin, vildagliptin (50 mg/day) for 12 weeks reduced HbA_{1C} by an additional 0.7% and reduced basal and postprandial glycaemia, with a slight increase in postprandial insulin concentrations.⁴⁸ The study was extended to one year, during which the vildagliptin was associated with a sustained 1.0–1.1% reduction of HbA_{1C} and provided evidence of improved insulin sensitivity.⁴⁹

Sitagliptin

Although there are few full published accounts of the effects of sitagliptin on glycaemic control in patients with type 2 diabetes, the preliminary reports and conference abstracts suggest similar efficacy to vildagliptin. Sitagliptin has been shown to increase plasma concentrations of active GLP-1 in normal subjects.⁵⁰ In patients with type 2 diabetes inadequately controlled by lifestyle, a 12-week dose-ranging study (25–100 mg/day) found a 0.7% reduction in HbA_{1C} at the 100 mg/day dose of sitagliptin without any change in body weight.⁵¹ Trials using sitagliptin as monotherapy (100 mg/day) for 18 weeks and 24 weeks showed that it reduced HbA_{1C} by 0.6% and 0.79%, respectively, and was associated with reductions in basal and postprandial glucose.^{52,53} When sitagliptin (100 mg/day) was given for 24 weeks as an add-on therapy to metformin there was an additional 0.65% reduction in HbA_{1C},⁵⁴ and as an add-on to pioglitazone there was an additional 0.7% reduction in HbA_{1C}.⁵⁵

General clinical considerations

Clinical studies with DPP IV inhibitors have substantiated the antihyperglycaemic effects seen in preclinical studies (table 3). Several clinical studies have confirmed that concentrations of active GLP-1 and GIP are increased by DPP IV inhibitors, but it remains to be established whether increased levels of incretin hormones represent the only antidiabetic mechanism of action of these inhibitors. The DPP IV inhibitors are likely to influence a multitude of biological peptides,^{1,3,38} with metabolic sequelae. The profile of effects seen with DPP IV inhibitors does not exactly mimic the administration of incretin hormones. For example, DPP IV inhibitors have not consistently raised postprandial insulin concentrations, they do not appear to cause significant weight loss and they do not incur the same amount of reported nausea. On the other hand, they retain considerable glucagon-lowering effects and are not associated with serious hypoglycaemic episodes when given as monotherapy. Whether DPP IV inhibitors can preserve pancreatic beta-cell function during the progressive natural history of human type 2 diabetes and whether they can improve insulin action are also equivocal, from present evidence. It is encouraging that, despite the diversity of targets for DPP IV inhibition, reports to date indicate good tolerability without evidence of threatening adverse events.

Quite where DPP IV inhibitors would fit into the typical algorithms for treatment of type 2 diabetes remains a matter for debate. If preservation of human pancreatic beta-cell function is established then these agents would become firm candidates for early therapy. Initial evidence from the studies described above⁴⁰⁻⁵⁶ suggests that the blood glucose-lowering efficacy of DPP IV inhibitors as monotherapy may not be as substantial as that of metformin or sulphonylureas, at least during the first 3–6 months of therapy. However, efficacy was sustained to one year. Since efficacy was retained when used as add-on therapy to metformin or a thiazolidinedione, combination therapy is an attractive option.

While the foregoing deliberations have been directed towards type 2 diabetes, possible benefits have been sug-

gested in combining DPP IV inhibitors with insulin therapy in type 1 diabetes. This is based on the observations that secretion of incretin hormones is normal in type 1 diabetes⁵⁷ and that administration of GLP-1 can improve glycaemic control in type 1 diabetes.⁵⁸ Long-term treatment of streptozotocin-diabetic rats with P32/98 increased weight gain, increased nutrient intake, increased insulin secretion by remaining beta-cells and markedly improved glucose tolerance.³⁴ If there are no beta-cells remaining, the potential value of a DPP IV inhibitor in type 1 diabetes would be to decrease glucagon, hopefully without compromising the counter-regulatory capability. Whether DPP IV inhibitors, acting presumably via incretins, could assist beta-cell neogenesis after near complete beta-cell loss in human diabetic states remains unknown. Also, possible effects of DPP IV inhibitors on T-cells and chemotaxis and their impact on autoimmune beta-cell destruction have yet to be explored.

Potential limitations of DPP IV inhibitors

Selectivity

The elucidation of several new members of the DPP IV family will have consequences for the development of DPP IV inhibitors. Compounds previously thought to be specific for DPP IV could in fact be inhibitors of other members of the DPP IV enzyme family. For example, the DPP IV inhibitor Val-boro-Pro appears to be relatively unselective for DPP IV as it may also inhibit FAP.⁵⁹ Val-boro-Pro may also inhibit DPP 8, DPP 9 and DPP II (also known as QPP or DPP 7).⁶⁰ A number of DPP IV inhibitors have recently been tested for selectivity to DPP IV, FAP, DPP 8, DPP 9 and DPP II enzymes.⁶⁰ In this study, compounds which were individually selective for either DPP IV, DPP 8/9 or DPP II were identified, allowing an evaluation of the potential toxicity and tolerability of each type of inhibition. The DPP 8/9-selective inhibitor produced alopecia, thrombocytopenia, reticulocytopenia, multiorgan histopathological changes, enlarged spleen and mortality in rats. This inhibitor also produced gastrointestinal toxicity in dogs. Furthermore, the DPP II-selective inhibitor produced reticulocytopenia in rats. However, investigation of the DPP IV-selective inhibitor demonstrated no apparent toxicity.⁶⁰ Off-target inhibition has been cited as a possible reason for the observed toxicities of P32/98, which include thrombocytopenia, ataxia, seizures, convulsions, tremor, diarrhoea and adverse effects on the lungs after four weeks' treatment.⁶⁰ Thus, antidiabetic DPP IV inhibitors should be highly selective for DPP IV and unselective for DPP 8/9.

Specificity

As mentioned earlier, DPP IV is a pleiotropic enzyme which cleaves and generally inactivates a wide range of peptides that contain proline, alanine or serine that are penultimate to the N-terminus.^{1,3} Many of these are regulatory peptides that are involved in metabolic, vascular, neural, immunological and other physiological control processes. Thus, the action of DPP IV inhibitors is fundamentally different to that of incretin hormones, acting on diverse substrates rather than through specific receptors on target tissues.³ This has prompted concerns relating to possible adverse effects of

DPP IV inhibitors. However, it must be noted that theoretical concerns have not, to date, been borne out by preclinical and clinical testing.

Other sources of DPP IV inhibition

There are reports that commonly used antidiabetic drugs can affect circulating DPP IV activity. Metformin has been reported to reduce DPP IV activity in patients with type 2 diabetes and in diabetic animal models.⁶¹⁻⁶⁴ Whilst this has not been a universal finding,^{65,66} metformin treatment increased active levels of GLP-1 in obese, non-diabetic human males⁶¹ and reduced inactivation of exogenously administered GLP-1 in obese-diabetic (*ob/ob*) mice.⁶⁴ Also, the degradation of GLP-1(7-36)amide to GLP-1(9-36)amide by pooled human plasma was inhibited by metformin, offering an explanation for the higher levels of active GLP-1.⁶¹ There are reports of reduced serum DPP IV activity brought about by the peroxisome proliferator-activated receptor-gamma (PPAR γ) agonist, pioglitazone and by the meglitinide, nateglinide.^{62,67} The possible effects of these and other commonly used antidiabetic drugs on DPP IV activity warrant further investigation.

Neutral endopeptidase 24.11 (NEP-24.11)

It is evident that the body possesses other enzymes which degrade incretin hormones, in particular neutral endopeptidase 24.11 (NEP-24.11; EC 3.4.24.11). This is a widespread membrane-bound zinc metalloproteinase with a broad substrate specificity.⁶⁸ NEP-24.11 is involved in the inactivation and renal clearance of peptide hormones and is found in high concentrations in the kidney. Incubation of GLP-1 or GIP with human NEP-24.11 generates multiple peptide fragments,^{68,69} and up to 50% of *in vivo* degradation of GLP-1 may be due to NEP-24.11. A recent study demonstrated that whilst DPP IV inhibition improves the insulinotropic and antihyperglycaemic activity of GLP-1, the effect could be further enhanced by concomitant NEP-24.11 inhibition.⁷⁰ It remains to be seen whether the antihyperglycaemic effect of DPP IV inhibition could be chronically augmented by combining this with an inhibitor of NEP-24.11.

Conclusions

Since DPP IV has been a major impediment to the therapeutic application of incretin hormones, two strategies have been adopted to exploit antidiabetic incretin activity. The first involves generation of DPP IV-resistant incretin analogues and mimetics such as exenatide (Byetta), which was launched in the US in 2005.⁷ Other incretin mimetics are expected to follow.¹ The second strategy has been the development of DPP IV inhibitor compounds, several of which have completed phase III clinical trials. Although some questions remain about the mechanisms of action of DPP IV inhibitors, clinical trials so far indicate that these compounds can increase active incretin hormones, reduce circulating glucagon and benefit beta-cell function. DPP IV inhibitors have produced sustained improvements in glycaemic control in type 2 diabetes with apparent tolerability, lack of weight gain or serious hypoglycaemia, and with few adverse effects.

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