Dipeptidyl Peptidase-4 Inhibition—Advances in our Understanding of Diabetes Management

a report by

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Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are the two major incretin hormones in humans. These peptides are released from endocrine cells in the intestinal mucosa in response to food ingestion, and play a pivotal role in blood glucose regulation. Among other actions, they act on pancreatic islet cells to enhance glucose-induced insulin secretion. This so-called 'incretin effect' explains why a greater amount of insulin is released in response to an oral glucose load compared with that elicited by an isoglycemic intravenous glucose challenge,[1] and in healthy subjects it accounts for up to 70% of glucose-induced insulin secretion.[1]

The two incretin hormones have effects on the β cell in addition to their ability to stimulate insulin secretion. They induce insulin gene expression and stimulate all steps of insulin biosynthesis, thereby ensuring that continued supplies of insulin are available for secretion. They also upregulate the expression of other genes involved in β-cell function (e.g. GLUT 2 and glucokinase).[2] Additionally, *in vitro* and pre-clinical *in vivo* studies have demonstrated that they both stimulate β-cell proliferation and neogenesis and exert anti-apoptotic effects, leading to expansion of the β-cell mass. However, while both incretins share effects on the β-cell, GLP-1 also exhibits activity at sites other than the β-cell. Glucagon secretion is inhibited, thereby suppressing endogenous glucose production; gastric emptying is delayed, minimizing post-prandial glucose excursions; and there is a marked effect to reduce appetite and promote satiety, leading to reduced food intake and, in the longer-term, to bodyweight loss.[3] More recent studies have indicated that GLP-1 may also have some beneficial cardiovascular effects.[3]

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The Incretin Hormones and Type 2 Diabetes

The incretin effect is reduced in patients with type 2 diabetes, possibly explaining why the insulin response to an oral glucose challenge is blunted and delayed compared with healthy non-diabetic subjects.[4] Subsequent studies revealed that the subjects with type 2 diabetes have impairments in incretin action. Thus, although GLP-1 retains its insulinotropic activity, its potency in this respect is reduced.[5] In contrast, the insulinotropic effect of GIP is severely impaired, with the ability of GIP to stimulate second-phase insulin secretion being absent, although a first-phase response is present.[6] Furthermore, additional studies indicated there were also disturbances in secretion of the incretin hormones. While levels of GIP are relatively normal in individuals with type 2 diabetes,[7] these subjects may exhibit modest but significant deficits in meal-stimulated GLP-1 secretion compared with non-diabetic controls.[7]

These observations suggested that dysregulation of incretin activity may be involved in the impaired glucose regulation in type 2 diabetes. However, it appears that the incretin defect is a consequence rather than a cause of the diabetic state,[8] although it may contribute to impairments in insulin secretion once glucose homeostasis begins to deteriorate. Such findings suggested that interventions to enhance incretin activity might correct underlying incretin deficits in individuals with impaired glucose regulation and lead to improvements in glucose control. Accordingly, a continuous infusion of GLP-1 resulted in a blood glucose profile in subjects with diabetes that was very similar to that in non-diabetic controls, not only in the overnight (fasting) period, but also during the following day in response to meals.[9] The proof-of-concept that it was possible to improve glucose homeostasis by augmenting GLP-1 activity on a chronic basis was shown in a study in which patients with type 2 diabetes received continuous subcutaneous infusions of GLP-1 over a six-week period. This was associated with a marked reduction in blood glucose levels at one week, with the reduction persisting for the duration of the study,[10] demonstrating that tachyphylaxis to the continued presence of GLP-1 does not occur. In this study, GLP-1 was well tolerated and led to a significant reduction in glycated hemoglobin (HbA_{1c}) levels, which was accompanied by a small but significant weight loss.[10]

Further advantages of exploiting the actions of GLP-1 come from the glucose-dependent nature of its insulinotropic and glucagonostatic activity. Thus, in subjects with type 2 diabetes and fasting hyperglycemia, an intravenous infusion of GLP-1 stimulated insulin and suppressed glucagon secretion to reduce blood glucose levels. However, these effects became less evident as blood glucose levels declined, and once normoglycemia had been reached both insulin and glucagon levels had returned to basal values, despite the ongoing GLP-1 infusion.[11] The consequence of this is that there is a minimal risk for hypoglycemia associated with elevated GLP-1 levels, which

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distinguishes the incretin hormones from insulin and other insulin secretagogs used to treat hyperglycemia (e.g. sulphonylureas and glinides), where the effects on β cells are not glucose-dependent.

Therapeutic Application of Glucagon-like Peptide-1

The native incretins cannot be used therapeutically because they are rapidly degraded *in vivo* by the enzyme dipeptidyl peptidase-4 (DPP-4).[12] This enzyme is a serine peptidase, which is identical to the T-cell antigen CD26. It has a widespread distribution, being found as a membrane-expressed protein in renal and intestinal brush-border membranes, on hepatocytes and vascular endothelium, and in a soluble form in plasma.[13] Cleavage of the incretin hormones by DPP-4 appears to be a primary step in their metabolism, and results in the formation of metabolites that have lost their insulinotropic activity. This degradation is extensive, occurring in both normal subjects and in patients with type 2 diabetes, and means that only a small proportion of GLP-1 (both endogenous and exogenously administered peptide) survives in the intact form.[12] This understanding of the pivotal role of DPP-4 in the degradation of GLP-1 led directly to the proposal that preventing the action of DPP-4, thereby increasing levels of intact GLP-1, may be a novel approach to allow the beneficial effects of the incretins to be harnessed for the treatment of type 2 diabetes.[12] Subsequently, both DPP-4-resistant analogs of GLP-1 and inhibitors of DPP-4 have been developed, and compounds from both classes are now approved and in clinical use as antidiabetic agents.

Dipeptidyl Peptidase-4 Inhibitors

The first DPP-4 inhibitor to be approved for use in treating type 2 diabetes was sitagliptin. Vildagliptin has now also received regulatory approval, and a number of other inhibitors (e.g. alogliptin, saxagliptin, BI 1356, and others) are either under regulatory review or in late-stage clinical development. These agents are all low-molecular-weight compounds, although they differ widely in terms of their chemical structure. Some (e.g. vildagliptin and saxagliptin) are peptide-like and based on a dipeptide structure, whereas others are non-peptidomimetic; this latter group encompasses significant chemical diversity, including β-amino-acid-based compounds (e.g. sitagliptin), modified pyrimidinediones (e.g. alogliptin), and xanthines (e.g. BI 1356). These compounds show selectivity for DPP-4 versus other members of the DPP-4-like family of proteases, including DPP-8 and DPP-9. This may be important since inhibition of DPP-8 and/or DPP-9 has been shown to be associated with toxicity and mortality in some,[14] but not all,[15] pre-clinical studies. However, it should be emphasized that the inhibitors in clinical development have been well tolerated and do not appear to be causally associated with adverse side effects in humans. The compounds have good oral bioavailabilty and are generally suitable for once-daily dosing. This inhibits plasma DPP-4 activity by 60–90% over a 24-hour period, which is sufficient to elevate the intact forms of both incretin hormones by two- to three-fold.

Clinical proof-of-concept for using DPP-4 inhibitors was obtained by Ahren et al.[16] using NVP-728, a predecessor of vildagliptin, and showed the effects of the drug to be consistent with the actions of GLP-1. Thus, DPP-4 inhibition is associated with improved insulin secretion relative to prevailing glycemia (although absolute levels do not increase) and suppressed glucagon levels,[17] which results in lowering of both fasting and post-prandial glucose concentrations.[18] In clinical trials lasting up to two years, treatment with DPP-4 inhibitors (vildagliptin or sitagliptin) has been shown to have sustained antihyperglycemic effects and result in significant lowering of HbA_{1c} concentrations, both when used in monotherapy[19–22] and especially when used in combination with metformin.[23–25] Although non-inferiority to metformin was narrowly missed in one study,[19] the antihyperglyemic effects of DPP-4 inhibitors appear to be similar to those of sulphonylureas[24] and glitazones.[26–28] They also provide additional reductions in HbA_{1c} levels when added to therapy of patients with inadequate glycemic control on metformin,[23,29] sulphonylurea,[30,31] glitazones,[32,33] and insulin.[34] In particular, the combination with metformin is interesting, as there appear to be complementary mechanisms of action. Thus, metformin administration to healthy subjects is associated with increased plasma GLP-1 concentrations,[35] with pre-clinical evidence suggesting that this is due to increased secretion and the upregulation of pre-proglucagon gene expression.[36] In addition, DPP-4 inhibition prevents the degradation of this GLP-1, leading to additive increases in intact GLP-1 levels,[35] and in patients with type 2 diabetes this is accompanied by additive reductions in HbA_{1c} levels when the two agents are administered together.[37]

Throughout the clinical trials, treatment with DPP-4 inhibitors has been associated with improvements in β-cell function (proinsulin/insulin ratio, HOMA-beta), but these agents do not produce the weight loss that is obtained with GLP-1 receptor agonists. This is most probably because the more modest increments in intact GLP-1 that are achieved with DPP-4 inhibition are insufficient to affect appetite and food intake. However, their weight neutrality is in itself advantageous in patients with type 2 diabetes since many are already overweight or obese, and several other oral antihyperglycemic agents (e.g. sulphonylureas, glinides, glitazones) are associated with marked weight gain; importantly, clinical trial data indicate that the DPP-4 inhibitors do not prevent any weight loss induced by metformin and they do not exacerbate the weight gain associated with glitazones. So far, the DPP-4 inhibitors seem to be well-tolerated and not to be associated with significant adverse events; in the clinical trials, their side effect profile resembles that of placebo. Consistent with the glucose-dependent effects of GLP-1, these agents also appear to pose no undue risk for hypoglycemia.

Conclusion

The antihyperglycemic efficacy of treatment with DPP-4 inhibitors in type 2 diabetes has now been established in clinical trials of up to two years' duration. This approach takes advantage of the body's own physiological mechanisms for maintaining glucose homeostasis, including the glucose-dependent stimulation of insulin secretion and suppression of glucagon suppression, and results in improvements of the β-cell dysfunction that is characteristic of the disease. Together, these mechanisms improve glucose uptake and reduce endogenous glucose production without posing any meaningful risk for hypoglycemia. The results so far are encouraging, showing that DPP-4 inhibitors give clinically relevant and sustained reductions in HbA_{1c} levels, although it remains to be seen whether they will be able to have an impact on the progressive deterioration of β-cell function that is seen in type 2 diabetes or whether, in clinical use, they will share the beneficial effects on β-cell mass which have been demonstrated in pre-clinical studies.

Currently, the published efficacy data relate primarily to sitagliptin and vildagliptin, but given that all of the compounds in development appear to result in sufficient DPP-4 inhibition to provide near-maximal protection of the incretins, it seems unlikely that glycemic efficacy will be further improved. Therefore, any differentiation between compounds will most likely be based on differences in their metabolism and elimination and compound-specific characteristics, which may affect their side-effect profile. To date, clinical trials have indicated that DPP-4 inhibition with all the inhibitors in development is

associated with a good safety profile, and these compounds have been well tolerated, although, as with any new drug class, this must be confirmed after clinical experience with drug exposure over several years. Due to DPP-4 being identical to CD26, and given the role of CD26 in the immune system, there were early concerns that long-term DPP-4 inhibition might have adverse effects on immune function. However, this has not been borne out by data from clinical trials. A recent meta-analysis based predominately on trials 30 weeks or less in duration did suggest there may be a slightly increased risk for infection (nasopharyngitis and urinary tract infection) associated with DPP-4 inhibitors,[38] although as additional, longer-term data in greater numbers of subjects are becoming available, there does not seem to be any difference in the incidence, severity, or type of infection in subjects exposed to DPP-4 inhibition compared with non-exposed individuals.[39] This apparently benign side effect profile, together with their oral availability, may also favor the eventual use of DPP-4 inhibitor monotherapy in subjects with pre-diabetes, where DPP-4 inhibition has been shown to improve β-cell function and prandial glycemia (e.g. impaired fasting glucose[40] or impaired glucose tolerance[41]).

Finally, the recently emerging data demonstrating some beneficial cardiovascular effects of exogenous GLP-1 raises the possibility that DPP-4 inhibitors may share this property. Therefore, it is encouraging that data from some of the clinical studies show that DPP-4 inhibition results in small but statistically significant reductions in blood pressure, and may have a favorable cardiovascular safety profile.[25,42,43] We now await the results of long-term trials to see whether these new agents are able to prevent the progressive deterioration of glycemic control that currently occurs in type 2 diabetes, and whether they will be able to ameliorate the macrovascular complications on the disease. ■

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