Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes Therapy

a report by
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The prevalence of type 2 diabetes is rising dramatically, and some predictions state that the worldwide number of subjects with diabetes by 2030 will be 370 million, along with a concomitant rise in pre-diabetic conditions. Since type 2 diabetes is increasing and most patients do not reach their therapeutic goals, novel treatment options are needed.

While insulin resistance is constant in the course of type 2 diabetes, islet function declines continuously over time, and disease progression of type 2 diabetes is characterised by a loss of islet function. Hyperglycaemia, free fatty acids, cytokines, adipokines and toxic metabolic products may lead to a loss of β-cell function and β-cell mass in the islets. The α cells in the islet additionally develop a disturbance of glucagon secretion. In healthy subjects, glucagon secretion is suppressed under hyperglycaemic conditions, whereas in type 2 diabetes glucagon secretion is elevated, leading to excessive glucose production by the liver.

The therapeutic options currently available do not address the problem of islet-cell dysfunction. Both sulfonylureas and glinides stimulate insulin secretion from the β cells, metformin and glitazones act on insulin resistance and α-glucosidase inhibitors delay the digestion of sucrose and the breakdown of complex carbohydrates. Exogenous insulin replaces the endogenous secretory insulin deficit, although it potentially causes weight gain and hypoglycaemia. The progressive loss of islet function observed in type 2 diabetes is not ameliorated by any of the current therapeutic options.

Incretin Hormones and Incretin-based Therapies

The incretin hormones glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) stimulate insulin secretion after a meal. The incretin effect – which leads to an enhanced insulin response after oral glucose compared with intravenous glucose – is reduced or even absent in patients with type 2 diabetes, but can be restored by raising concentrations of the incretin hormones.

The promising therapeutic potential of GLP-1 as a pharmacological tool for treating type 2 diabetes was discovered in the 1990s. In contrast to other insulinotropic agents, e.g. the sulfonylureas, the insulinotropic effect of GLP-1 depends even more closely on the actual glucose concentration, which allows the possibility of glucose normalisation without the risk of hypoglycaemia. In patients with type 2 diabetes, exogenous GLP-1 increases insulin secretion and normalises both fasting and post-prandial blood glucose. Furthermore, it has the ability to restore the blunted first phase of insulin secretion in type 2 diabetes.

Besides the glucose-lowering effects, GLP-1 has a variety of additional ‘non-insulinotropic’ physiological actions that may be advantageous in type 2 diabetes therapy, i.e. it suppresses glucagon secretion from the α cells and slows gastric emptying. Therefore, it contributes to satiety and to a slower passage and resorption of carbohydrates. Additionally, GLP-1 acts as a mediator of satiety in the hypothalamus, where it is also found as a neurotransmitter. Patients with type 2 diabetes having received GLP-1 as a continuous infusion have lost bodyweight. Furthermore, GLP-1 stimulates β-cell formation from precursor cells and also inhibits their apoptosis, leading to an increase in β-cell mass and to an improvement in β-cell function.

Dipeptidyl Peptidase-4 Inhibitors Utilise Incretin Action in Type 2 Diabetes

Due to the action of dipeptidyl peptide-4 (DPP-4), the biological half-life of exogenous GLP-1 is only one to two minutes, therefore treatment with native GLP-1 is not feasible. DPP-4 is a ubiquitous enzyme that can be detected in the endothelium of different organs and is measurable as circulating enzymatic activity in plasma. Besides GLP-1 and GIP, additional peptides, such as pituitary adenylate cyclase-activating polypeptide (PACAP) and gastrin-releasing peptide (GRP), are substrates of DPP-4 (see Table 1). However, DPP-4 has a greater affinity to GLP-1 than other peptides, including GIP. DPP-4 cleaves and inactivates GLP-1 within a few minutes. DPP-4 preferentially cleaves peptides with the amino acid alanine or proline in position 2 of the N-terminus of the peptide chain. The degradation products of GLP-1 are a dipeptide (His-Ala) and GLP-1(9-36)amide, which has GLP-1-antagonistic properties under various conditions.

In order to utilise the GLP-1 effects, long-acting GLP-1 receptor agonists have been developed as an injectable therapy and DPP-4 inhibitors as oral treatment option.

DPP-4 is also expressed as CD26 on the cell membrane of activated T lymphocytes. Here, the enzymatic properties of the DPP-4/CD-26

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molecule do not seem to be important. Therefore, the influence of DPP-4 inhibitors on immunological CD26-mediated functions is not expected. In clinical studies with DPP-4 inhibitors, no serious side effects or adverse effects on immunological regulatory mechanisms were observed.

DPP-4 belongs to a whole enzyme family of endopeptidases; therefore, DPP-4 inhibitors need to be highly selective in order to inhibit DPP-4 only and not other DPPs. The DPP-4 inhibitors sitagliptin (Merck Pharmaceuticals) and vildagliptin (Novartis Pharmaceuticals) are two compounds of the DPP-4 inhibitor class that have been approved in various countries. Currently undergoing clinical studies are alogliptin (Takeda Pharmaceuticals) and saxagliptin (AstraZeneca and Bristol-Myer-Squibb Pharmaceuticals). The structures of the molecules are shown in Figure 1, and more DPP-4 inhibitors are in development.

Sitagliptin and vildagliptin are more highly selective compared with other proline-selective peptidases. In humans, the pharmacokinetic and pharmacodynamic properties and tolerability have been assessed in numerous clinical studies. Post-prandially active endogenous GLP-1 concentrations are increased two- to three-fold by DPP-4 inhibitors. They also have a low propensity to be involved in drug–drug interactions as either a perpetrator or a substrate for metabolism, especially with other antihyperglycaemic oral agents. In clinical studies and broad clinical application to date they have been safe, with an intrinsic hypoglycaemia risk near the level of metformin or placebo. Hypoglycaemia occurs only when combined with sulfonylureas. Nasopharyngitis, urinary tract infections, gastrointestinal symptoms and skin reactions are adverse events that are reported infrequently.

It is debatable whether DPP-4 inhibitors are able to positively influence the disease progression of type 2 diabetes by slowing the loss of β-cell mass and function. The effect of sitagliptin and vildagliptin was investigated extensively in animal models. DPP-4 inhibitors increased the number of insulin-positive β cells in islets and the β- to α-cell ratio in different diabetic animals was normalised. Additionally, the islet insulin content was higher and glucose-stimulated insulin secretion in isolated islets was improved compared with glipizide-treated mice.

According to the results from animal studies, DPP-4 inhibitors may have the potential to delay or prevent disease progression in type 2 diabetes and to improve β-cell mass and function.

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### Table 1: Important Substrates of Dipeptidyl Peptidase-4

<table>
<thead>
<tr>
<th>With Influence on Activity and Elimination</th>
<th>Without Influence on Activity or Elimination</th>
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<tbody>
<tr>
<td>GLP-1</td>
<td>GHY</td>
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<tr>
<td>GIP</td>
<td>Interleukin-1p</td>
</tr>
<tr>
<td>GEP-2</td>
<td>Interleukin-2</td>
</tr>
<tr>
<td>PACAP</td>
<td>IGF-1</td>
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<tr>
<td>Peptide Y</td>
<td>Prolactin</td>
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<tr>
<td>Substance P</td>
<td>hCG</td>
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GLP = glucagon-like peptide; GRH = growth-hormone-releasing hormone; GIP = glucose-dependent insulinotropic peptide; PACAP = pituitary adenylate cyclase-activating polypeptide; IGF = insulin-like growth factor; hCG = human chorionic gonadotropin; RANTES = regulated on activation normal T cell expressed and secreted.

### Figure 1: Chemical Structure of Dipeptidyl Peptidase-4 Inhibitors

In a 12-week dose-finding study with saxagliptin in monotherapy in drug-naïve patients, the saxagliptin dose improved the glycaemic parameters of HbA1c and fasting and post-prandial glucose.

### Clinical Studies with Dipeptidyl Peptidase-4 Inhibitors

All clinical studies with either sitagliptin or vildagliptin in monotherapy or in combination with other antidiabetic treatment options are summarised in Table 2. In monotherapy, sitagliptin and vildagliptin improved glycaemic control in both the fasting and post-prandial states, as well as β-cell function in patients with type 2 diabetes. Both led to a significant reduction in glycated haemoglobin (HbA1c) compared with placebo and with fasting plasma glucose reductions in clinical studies of up to 104 weeks. In meal tolerance tests, two-hour post-prandial plasma glucose concentrations were also significantly reduced. Parameters for β-cell function (post-prandial insulin and C-peptide responses, homeostasis model assessment [HOMA]-B and proinsulin–insulin ratio) were improved. Treatment with DPP-4 inhibitors was weight-neutral. In head-to-head comparisons of DPP-4 monotherapy with either metformin or rosiglitazone monotherapy in drug-naïve patients, the efficacy in improving glycaemic parameters was comparable. In a 12-week dose-finding study with saxagliptin in monotherapy in drug-naïve patients, the saxagliptin dose improved the glycaemic parameters of HbA1c and fasting and post-prandial glucose.
As an add-on combination to ongoing metformin therapy in patients with type 2 diabetes not reaching therapeutic goals, both DPP-4 inhibitors reduced HbA1c and fasting and post-prandial plasma glucose. The reduction in HbA1c after adding sitagliptin was identical to the reduction after adding the sulfonylurea glipizide to ongoing therapy with metformin.22,23 The β-cell function parameters mentioned above were also improved. The combination of sitagliptin and metformin led to significantly higher GLP-1 concentrations than either therapy alone; however, the mechanism behind this phenomenon is not completely understood. The additional DPP-4 inhibitor therapy was generally well tolerated, and no increased incidence of hypoglycaemia or adverse events were observed.15,24–26

In combination studies, DPP-4 inhibitors as an add-on therapy to pioglitazone monotherapy were investigated in patients. Similarly, as observed in the above-mentioned studies, the glycaemic parameters were reduced and more patients reached a target HbA1c <7% with the combination therapy. β-cell function parameters also improved with the add-on therapy. Sitagliptin and vildagliptin were well tolerated in relation to adverse events, including hypoglycaemia. The additional DPP-4 inhibitor therapy was weight-neutral.13–15

A direct comparison of sitagliptin added to an ongoing treatment with metformin showed similar efficacy to the addition of glipizide.
to metformin. Sitagliptin was non-inferior in this 52-week study compared with glipizide. HbA1c, and fasting glucose decreased equally in both groups. As expected, the occurrence of hypoglycaemic episodes was much greater in the glipizide group than in the sitagliptin group. Bodyweight showed an increase of 1.1 kg in the glipizide-treated patients, whereas the patients on sitagliptin experienced weight loss of 1.5 kg.22

Conclusions

The therapeutic principle of GLP-1 with multiple modes of action, in addition to its glucose-normalising effect, adds a completely novel and attractive perspective to diabetes therapy. The inhibition of glucagon secretion and the improvement of β-cell function address unmet and important needs in type 2 diabetes therapy. DPP-4 inhibitors are oral agents that do not exclusively act via pharmacological concentrations of GLP-1-like activity, but raise endogenous levels of GIP and other peptide hormones possibly involved in metabolic control within the physiological range.27 The DPP-4 inhibitors sitagliptin and vildagliptin have been shown to be effective, well tolerated and safe over a two-year time period in clinical studies. Long-term safety based on CD26 effects remain unknown, but to date no significant alterations of immune function have been observed. Both of the DPP-4 inhibitors have been effective in mono- and combination therapies with metformin or thiazolidinediones. They did not show an increased incidence of hypoglycaemic events in mono- or combination therapies, and the incidence of adverse events was comparable to the incidence observed in the control groups.

Whether therapy with DPP-4 inhibitors is capable of influencing the natural progressive course of type 2 diabetes with β-cell failure is not yet known. If the effects of DPP-4 inhibitors observed on β-cell mass and function in pre-clinical studies are also applied to human studies, DPP-4 inhibitors could eventually be used in pre-diabetic stages and the early stages of diabetes to slow or prevent the progression of type 2 diabetes.