DRUG WATCH

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Dipeptidyl peptidase inhibitors as new drugs for the treatment of type 2 diabetes

Abstract Inhibitors of the regulatory protease dipeptidyl peptidase-IV (DPP-IV) are currently under development in preclinical and clinical studies (several pharmaceutical companies, now in Phase III) as potential drugs for the treatment of type 2 diabetes. Their development is based on the observation that DPP-IV rapidly inactivates the incretin hormone glucagon-like peptide-1 (GLP-1), which is released postprandially from the gut and increases insulin secretion. DPP-IV inhibitors stabilise endogenous GLP-1 at physiological concentrations, and induce insulin secretion in a glucose-dependent manner; therefore, they do not demonstrate any hypoglycaemic effects. Furthermore, they are orally bioavailable. In addition to their ability to protect GLP-1 against degradation, DPP-IV inhibitors also stabilise other incretins, including gastric inhibitory peptide and pituitary adenylate cyclase-activating peptide. They also reduce the antagonistic and desensitising effects of the fragments formed by truncation of the incretins. In clinical studies, when used for the treatment of diabetes over a 1-year period, DPP-IV inhibitors show improved efficacy over time. This finding can be explained by a GLP-1-induced increase in the number of beta cells. Potential risks associated with DPP-IV inhibitors include the prolongation of the action of other peptide hormones, neuropeptides and chemokines cleaved by the protease, and their interaction with DPP-IV-related proteases. Based on their mode of action, DPP-IV inhibitors seem to be of particular value in early forms of type 2 diabetes, either alone or in combination with other types of oral agents.

Introduction

Dipeptidyl peptidase-IV (DPP-IV) inhibitors are novel types of potential drugs for the treatment of type 2 diabetes. The original concept that inhibition of DPP-IV would improve glucose tolerance was based on the observation that glucagon-like peptide-1 (GLP-1) is rapidly cleaved and inactivated by the protease DPP-IV (see [1] for detailed references). Inhibition of this proteolytic inactivation should prolong the action of GLP-1, which is released postprandially from the L-cells in the gut and increases insulin secretion (the 'incretin' concept), resulting in improved glucose tolerance. The possibility that other mediators may contribute to these effects should not be excluded. Initial preclinical and clinical studies (performed by several companies, now in Phase III) on DPP-IV inhibitors have shown promising results [2, 3], and the first inhibitors may reach the market within 3–4 years.

General pharmacological value of DPP-IV inhibitors

Prior to the discovery of DPP-IV inhibitors, it was known that patients with type 2 diabetes have reduced levels of active GLP-1. This may be at least partly responsible for impaired insulin secretion, one of the major pathophysiological factors in the development of type 2 diabetes. In fact, some therapies for type 2 diabetes are based on the enhancement of insulin secretion through the action of sulphonylureas. Unfortunately, due to their mode of action, which leads to insulin secretion in a glucose-independent manner, treatment with this class of insulinotropic

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agents can lead to hypoglycaemia and favour obesity. It was initially postulated that inhibition of DPP-IV would extend the half-life of endogenous GLP-1 and other incretins known to induce insulin secretion from the beta cell in a glucose-dependent manner. It was further proposed that the glucose dependence of insulin secretion via this mechanism would greatly decrease the risk of hypoglycaemia. In type 2 diabetic patients, the amount of incretin released is not adequate for the regulation of glucose homeostasis. Stabilisation of active GLP-1 via inhibition of DPP-IV might be sufficient to achieve a physiological insulinotropic effect. The impaired insulin secretion observed in type 2 diabetes is restored to the normal level by the administration of exogenous GLP-1, as demonstrated by the normalisation of the first phase of insulin secretion [4]. This differentiates the mechanism of action of DPP-IV/GLP-1 from that of the sulphonylureas. In addition, DPP-IV inhibitors should enhance the physiological role of other incretins, including gastric inhibitory peptide (GIP) and pituitary adenylate cyclase-activating peptide (PACAP) (Fig. 1). The relative contributions of these two proteins to insulin secretion are not yet fully understood. However, a recent study by Ahrén and Hughes [5] demonstrated the importance of the stabilisation of other incretins by inhibitor treatment. When exogenous GLP-1 or PACAP-38 is administered to mice in conjunction with a DPP-IV inhibitor, the insulin response is increased by 75–80% relative to that observed during treatment in the absence of inhibitor. Similarly, in mice, the co-administration of a DPP-IV inhibitor with GIP or gastrin-releasing peptide results in a 25–40% increase in the insulin response as compared with that observed during treatment with the incretins alone. Therefore, the treatment of type 2 diabetes patients with DPP-IV inhibitors should help to restore impaired glucose homeostasis. Furthermore, the glucose dependence of the insulin-releasing effect of DPP-IV inhibitors should offer a significant advantage over currently used insulin secretagogues.

The time course of the pathophysiological processes associated with type 2 diabetes is not yet completely understood. It is generally agreed that these impairments are already present during an early phase of the disease. Consequently, the treatment of early phases of type 2 diabetes with DPP-IV inhibitors should be indicated. In addition to their use as a monotherapy during early phases of type 2 diabetes, combining DPP-IV inhibitors with existing medications could significantly improve current therapy. DPP-IV inhibitors could replace sulphonylureas, or at least strongly reduce the doses of sulphonylureas, thereby increasing the therapeutic window for these agents and decreasing the risk of hypoglycaemic events. Furthermore, DPP-IV inhibitors are not known to increase body weight; in fact, they may protect against obesity, as observed in DPP-IV knockout mice fed a high-fat diet [6].

Fig. 1 Schematic drawing of the role of DPP-IV in the inactivation of incretins (GLP-1, GIP, PACAP) (see text). DPP-IV-truncated GLP-1 and GIP act as weak receptor antagonists
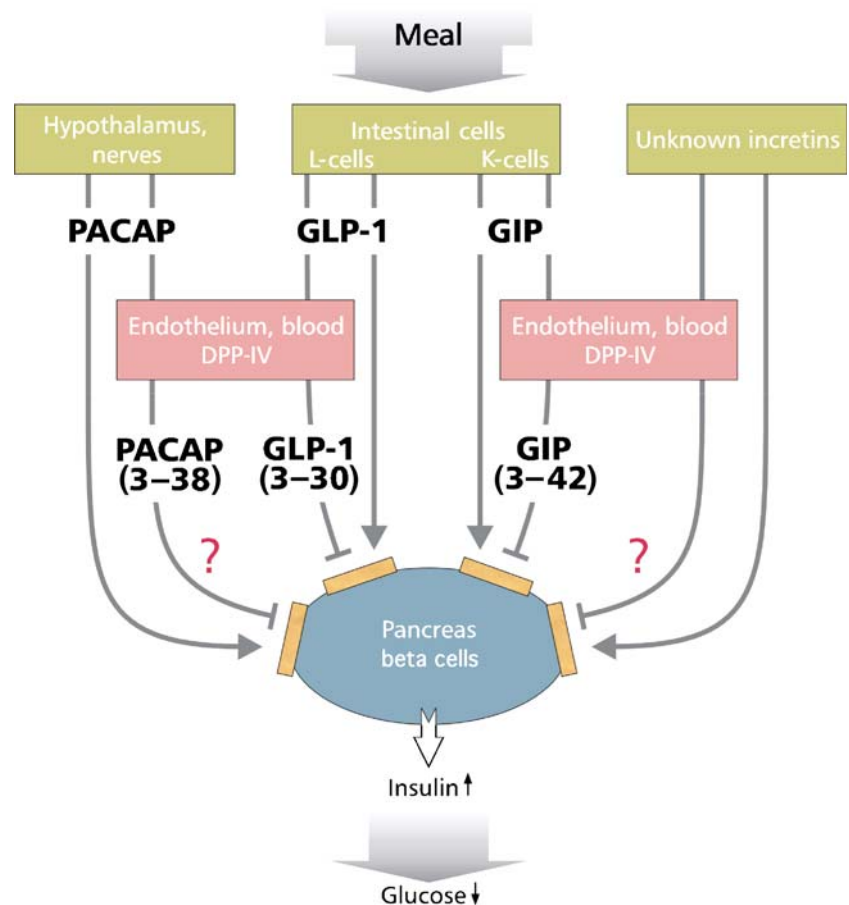
The effect of treatment with DPP-IV inhibitors on GLP-1 concentrations

Delayed gastric emptying, nausea and vomiting are GLP-1-related side-effects. These are seen with high, non-physiological concentrations (above about 60 pmol/l in human plasma), which are only achieved after exogenous admintration of the incretin. DPP-IV inhibition raises the proportion of active GLP-1 rather than the total GLP-1 concentration (up to 30 pmol/l after a meal [7]). In this way, inhibition supports the physiological role of GLP-1 without producing the GLP-1 concentrations that induce the GLP-1-related side-effects.

Complex mechanisms of DPP-IV inhibitor action

In order to explain the insulinotropic effects of DPP-IV inhibitors, mechanisms other than those that prevent GLP-1 degradation in the circulation have to be taken into account. The stabilisation of GLP-1 as a result of DPP-IV inhibition in the gastrointestinal tract, and the effects of GLP-1 on sensory nerves (described by Holst and Deacon in the present issue [8]) are plausible explanations. Furthermore, DPP-IV inhibitors stabilise not only GLP-1, but also other insulinotropic hormones and neuropeptides, as mentioned above (Fig. 1). However, the presence of additional potential mediators of DPP-IV inhibition does not necessarily diminish the role played by GLP-1.

Indeed, some experimental studies have demonstrated reduced total GLP-1 secretion during treatment with a DPP-IV inhibitor. However, more important than the total concentration of GLP-1 are the proportions of active and inactive GLP-1. Only one-third to one-half of the postprandial GLP-1 in the plasma of healthy subjects and type 2 diabetic patients consists of active GLP-1, the rest being the inactive fragment formed by truncation [7]. During treatment with a DPP-IV inhibitor, the relative proportion of the active form is clearly increased [9].

DPP-IV-truncated GLP-1 and GIP act as receptor antagonists [10, 11], thereby decreasing the direct effects of native peptides and possibly desensitising the receptors (as observed after the DPP-IV truncation of chemokines [12, 13]). In other physiological systems, increased receptor stimulation/internalisation results in the compensatory up-regulation of peptide synthesis/secretion. Such a feedback mechanism might occur in intestinal L-cells, but other more complex interactions between the different incretins are also possible (Fig. 1). Again, these feedback mechanisms might be influenced by the ratio of active/intact GLP-1, which is increased when DPP-IV is inhibited.

Slow onset of insulinotropic effects of DPP-IV inhibitors

Both short- and long-term (probably adaptive) insulinotropic effects are observed during DPP-IV inhibition. In OGTTs following a single administration, DPP-IV inhibitors show clear and immediate effects in normal and diabetic animals [14]. Long-term diabetes treatment with these inhibitors results in further improvement. For example, glucose tolerance in diabetic patients was higher after the administration of inhibitors for 4 weeks than it was initially (see [2]). In fact, HbA_1c levels have been observed to be reduced for at least 12 weeks with treatment (in a mixed application with metformin [3]). At present, the extent to which these long-term glucose-lowering effects observed in humans can be explained by the prolonged stabilisation of GLP-1 or other incretins is not clear. Treatment with GLP-1 is well known to inhibit beta cell apoptosis and induce beta cell proliferation in animals. The stabilisation of other incretins or peptide factors via DPP-IV inhibition may have a similar protective effect on beta cells [15].

Potential risks associated with DPP-IV inhibitors

DPP-IV is a pleiotropic enzyme that cleaves, and thereby generally inactivates, a variety of peptide hormones, neuropeptides and chemokines (reviewed in [16, 17]). Furthermore, it acts as a binding protein for fibronectin and adenosine deaminase, and is a co-stimulator of T-cell activation. Whereas the latter physiological functions of DPP-IV are not dependent upon its enzymatic activity, and therefore should not be affected by inhibitors, they may well affect the regulatory functions of DPP-IV.

In addition to stabilising the incretins GLP-1, GIP and PACAP, DPP-IV inhibitors also prolong the action of the hormones peptide YY and growth hormone-releasing hormone, the neuropeptides neuropeptide Y and substance P, and chemokines such as stromal cell-derived factor-1 (CXCL12) and macrophage-derived chemokine (CCL22). Potential side-effects resulting from the prolongation of action of these messengers include neurogenic inflammation (substance P, neuropeptide Y), increases in blood pressure (neuropeptide Y), enhanced general inflammation, and allergic reactions (chemokines). However, to date, such side-effects have not been observed in preclinical animal or clinical human studies [17].

Other potential side-effects associated with DPP-IV inhibitors may result from the inadvertent inhibition of related enzymes. DPP-IV belongs to a group of serine proteases, of which the physiological importance is largely unknown [18]. The enzymes most closely related to DPP-IV are fibroblast activation protein-α (FAP, also termed seprase), DPP-II (also termed DPP 7 or quiescent proline peptidase), DPP 8, and DPP 9. Prolyl endopeptidase (also known as prolyl oligopeptidase) and prolyl carboxypeptidase are less closely related. With the exception of FAP, all are intracellular (cytosolic or lysosomal) enzymes that are not involved in peptide inactivation. Like DPP-IV, FAP is a cell-surface enzyme; however, unlike DPP-IV, its expression is very restricted during development. It is expressed in adults on activated fibroblasts, and on a few types of cancer (melanomas, sarcoma cell lines, reactive tumour stromal fibroblasts), although the precise physiological functions of the enzyme are not known. DPP 8 and DPP 9 are widely distributed cytosolic enzymes, and their inhibition has been sug-

gested to be responsible for at least some of the toxic effects of DPP-IV inhibitors identified to date, including alopecia, thrombocytopenia, anaemia, enlarged spleen, multiple histological pathologies, and animal mortality [19]. Consequently a DPP-IV inhibitor should demonstrate high specificity with respect to other peptidases mentioned above.

Concluding remarks

DPP-IV inhibitors support the physiological role of GLP-1 by increasing the proportion of the endogenous active form of the incretin. Their effects are only needed postprandially, when GLP-1 is released from L-cells in the gut. The resulting active GLP-1 levels are within the physiological range and do not reach the pharmacological concentrations achieved by the exogenous administration of GLP-1. Consequently, the side-effects associated with the exogenous application of GLP-1/agonists have not been observed and should not be expected. The reduction of the antagonistic effects of GLP-1 fragments formed by truncation of the incretin by DPP-IV also contributes to the insulinotropic effects of these agents. Furthermore, DPP-IV inhibitors are orally bioavailable and therefore offer greater benefits compared with injectable agents in terms of patient compliance. Conversely, the doses of GLP-1 injectable agents used induce immediate pharmacological effects without risk of hypoglycaemia [20]. Given their related, but distinct, modes of action, GLP-1 agonists and DPP-IV inhibitors appear to complement one another, suggesting that a combination of the two agents may be of benefit.

In addition to GLP-1, DPP-IV cleaves other insulinotropic peptides, including GIP and PACAP; the influence of DPP-IV inhibitors on their physiological functions and interactions is not well understood. Nevertheless, the presence of other mediators of DPP-IV inhibition would not necessarily diminish the role of GLP-1. The long-term effects of DPP-IV inhibitors, especially in humans, await investigation. The potential risks associated with the stabilisation of other peptide hormones, neuropeptides and chemokines should also be considered, e.g. enhancement of inflammatory or allergic reactions. Increasing the specificity of the inhibitor for DPP-IV may reduce the side-effects caused by the inhibition of related enzymes.

Because DPP-IV inhibition primarily supports the physiological functions of endogenous GLP-1 and other insulinotropic hormones, it can be anticipated that such inhibitors will be of particular relevance in early forms of type 2 diabetes. Protective effects on beta cells would be of great value in these patients and might partly restore their impaired insulin secretion. Combination therapies with other types of oral agents, especially those enhancing the action of insulin on target cells (i.e. insulin sensitisers) should provide additional benefits and increased potencies.

Due to the fact that levels of GLP-1 secretion are lower than normal in obese individuals and type 2 diabetic patients, treatment with DPP-IV inhibitors may restore endogenous active GLP-1 to normal levels, thereby affording excellent therapeutic effects. In addition, if elevated GLP-1 levels result in increased beta cell mass in the long-term, treatment with DPP-IV inhibitors would offer great potential in the prevention, or even cure, of type 2 diabetes.

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