DPP-4 inhibition and islet function

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ABSTRACT

During recent years, dipeptidyl peptidase-4 (DPP-4) inhibition has been included in the clinical management of type 2 diabetes, both as monotherapy and as add-on to several other therapies. DPP-4 inhibition prevents the inactivation of the incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). This results in stimulation of insulin secretion and inhibition of glucagon secretion, and there is also a potential β-cell preservation effect, as judged from rodent studies; that is, it might target the key islet dysfunction in the disease. In type 2 diabetes. This reduces 24-h glucose levels and reduces HbA_{1c} by ≈ 0.8–1.1% from baseline levels of 7.7–8.5%. DPP-4 inhibition is safe, with a very low risk for adverse events including hypoglycemia, and it prevents weight gain. The present review summarizes the studies on the influence of DPP-4 inhibition on islet function.
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KEY WORDS: Dipeptidyl peptidase-4 inhibition, Glucagon secretion, Insulin secretion

INTRODUCTION

In the early 1990s, intravenous infusion of the gut incretin hormone, glucagon-like peptide-1 (GLP-1), was found to reduce the insulin requirement of meal ingestion in patients with type 2 diabetes[1]. This discovery was followed by developments that led to the present day incretin-based therapy. A challenge in the early development was that GLP-1 is rapidly inactivated by the enzyme, dipeptidyl peptidase-4 (DPP-4)[2,3], making native GLP-1 unsuitable as a therapeutic regimen. This challenge resulted in two successful therapeutic strategies: the use of DPP-4 resistant GLP-1 receptor agonists and the use of DPP-4 inhibitors[3,4]. Both these approaches are now, after many years of development, established in the clinical management of type 2 diabetes worldwide.

DPP-4 INHIBITION AND CLINICAL EFFECTS

DPP-4 inhibition as treatment of type 2 diabetes is a strategy that is based on the prevention of the inactivation of GLP-1 by specifically blocking the catalytic site of the enzyme. This is achieved by small molecules binding to the active site in the DPP-4 enzyme. This results in increased circulating concentrations of the active form of the hormone[4,5]. This in turn augments the GLP-1-induced effects on islet function, which is achieved through stimulation of G ($G_{\alpha s}$) protein coupled GLP-1 receptors, which are expressed in several organs, including the pancreatic β-cells[6]. Activation of β-cell GLP-1 receptors stimulates insulin secretion in a glucose-dependent manner[6]. GLP-1 has also been shown to trophically increase β-cell mass in rodents by promoting β-cell replication and differentiation of β-cell precursors in the pancreatic duct epithelium, and by exerting antiapoptotic effects[7,8]. In addition, it is well documented that GLP-1 inhibits glucagon secretion[9].

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The success of clinical treatment with strategies that improve islet function, such as incretin therapy, is based on the targeting of pathophysiological processes. The key defect underlying type 2 diabetes is islet dysfunction, which involves impaired β-cell function with insufficient release of insulin, reduced β-cell mass and augmented glucagon secretion[10]. Therefore, DPP-4 inhibition, through the increase in GLP-1 levels, is a therapeutic approach targeting the key pathophysiological defect in the disease.

A proof-of-concept study of DPP-4 inhibition as a therapy for type 2 diabetes was published in 2002 and showed that 4 weeks of treatment with the DPP-4 inhibitor, NVP-DPP728, improved metabolic control with reduced fasting and prandial glucose levels, and reduction of HbA_{1c}[11]. Several small molecule DPP-4 inhibitors have subsequently been identified and developed, and are now approved for use in the treatment of type 2 diabetes or are in different stages in clinical development. Sitagliptin was the first DPP-4 inhibitor to be approved, and now also vildagliptin, saxagliptin and linagliptin have been approved in several countries. Furthermore, alogliptin has been approved in Japan. They are all orally active compounds that efficiently inhibit DPP-4 activity after oral administration[12–16]. In clinical use or in late clinical development, DPP-4 inhibitors reduce HbA_{1c} by approximately 0.5–0.8% when used in monotherapy and by 0.8–1.1% when used in combination with metformin, sulfonylureas or thiazolidinediones, although these values depend on the baseline values of the studied patients[3]. Furthermore, the DPP-4 inhibitors are associated with a very low risk for hypoglycaemia and do not induce weight gain. DPP-4 inhibition is therefore a therapeutic strategy that meets several of the unmet needs in type 2 diabetes. The different DPP-4 inhibitors have several similarities, and they all efficiently inhibit DPP-4 activity in patients with type 2 diabetes, although they differ in chemical structure and pharmacokinetic characteristics[17].

INSULIN SECRETION IN ANIMAL STUDIES

Acute Effects

In 1998, Pederson *et al.*[18] studied the oral administration of the DPP-4 inhibitor iso-thiazolidide (20 μmol/300 g bodyweight) together with glucose (1 g/kg) in obese and lean Zucker rats. They found that the insulin response to oral glucose was augmented with the DPP-4 inhibitor along with improved glucose tolerance and that the effects were more pronounced in the obese versus the lean rats. Also Balkan *et al.*[19] explored the potential of DPP-4 inhibition to stimulate insulin secretion after oral glucose in obese and lean Zucker rats, as shown in a study published in 1999. They administered the DPP-4 inhibitor NVP-DPP728 at 10 μmol/kg through an oral tube 30 min before administration of glucose (1 g/kg). They found that in obese Zucker rats, NVP-DPP728 augmented the insulin response to oral glucose in association with improved glucose tolerance. These effects were also observed in the lean Zucker rats, although to a lesser degree. Results from a paracetamol test showed that gastric emptying was not affected by NVP-DPP728, suggesting that the primary reason for the improved glucose tolerance was the increased insulin response. The authors also showed that the active GLP-1 concentrations were augmented by DPP-4 inhibition; therefore, the authors concluded that NVP-DPP728, through increasing GLP-1 levels, stimulates insulin secretion in rats[19]. The following year, it was also shown that the DPP-4 inhibitor, valine pyrrolidide (100 μmol/kg), when given through oral gavage, augmented the insulin response and improved glucose tolerance after oral glucose (150 mg) in both control mice and in mice rendered insulin resistant by a high-fat diet[20]. Also in that study, the GLP-1 response to oral glucose was increased by DPP-4 inhibition, again suggesting that DPP-4 inhibition augments insulin secretion after oral glucose by increasing the active concentrations of GLP-1[20]. Similar augmentation of the insulin response to glucose gavage has been shown for LAF 237 (vildagliptin) in control and high-fat fed mice[21]. Furthermore, sitagliptin has been shown to stimulate insulin secretion from isolated islets and in the perfused pancreas after 10 weeks of treatment in a diabetes model in mice consisting of a combination of streptozotocin with high-fat feeding[22]. Also, BI1356 (linagliptin; 3 mg/kg) increased the insulin response to oral glucose in Zucker fatty rats along with improved glucose tolerance[23]. Hence, it is now well documented in animal studies that DPP-4 inhibition stimulates insulin secretion, and that the effect is pronounced in insulin-resistant animals. The latter finding is corroborated by the demonstration that the insulin secretory response to GLP-1 is augmented in insulin-resistant mice compared with normal mice[24]. The hypothesis explaining these findings is that the islet adaptation to insulin resistance that involves upregulated insulin secretion also involves an increased sensitivity to GLP-1.

Several animal studies have explored the mechanisms of improved β-cell function after DPP-4 inhibition in animal studies. A most likely explanation is that GLP-1 contributes. However, there are also other potential substrates for DPP-4 that might contribute. One such substrate is GIP, the concentration of which is also increased after DPP-4 inhibition[25], and another potential substrate for DPP-4 is the neuropeptide, pituitary adenylate cylcase activating polypeptide (PACAP)[26]. Interestingly, the insulin secretory responses to all these three bioactive peptides (GLP-1, GIP and PACAP) have been shown to be augmented by the DPP-4 inhibitor, valine-pyrrolidide, in model experiments in mice[27]. However, a study in mice with genetic deletion of GIP and GLP-1 receptors (DIRKO; double incretin receptor knockout mice) showed that after oral glucose (1.5 mg/g bodyweight), neither valine pyrrolidide nor the DPP-4 inhibitor, SYR106124, augmented the insulin response, and neither of these two DPP-4 inhibitors nor the DPP-4 inhibitors TP8211 or LAF237 (vildagliptin) had an effect on glucose tolerance[28]. This would suggest that the acute influences on insulin secretion by DPP-4 inhibition are mediated only by the incretin hormones. Nevertheless, a contribution by other bioactive peptides can at present not be excluded, especially on a long-term basis, and needs to be explored further.

Although incretin hormone receptors, such as GLP-1 receptors, are expressed in the β-cells, a recent study suggested that a direct β-cell action of the incretin hormones might not entirely explain the improved islet function after DPP-4 inhibition[29]. The alternate mechanism might be an indirect action through stimulation of afferent nerves in the gut. The evidence for this is that oral administration of a low dose of the DPP-4 inhibitor, sitagliptin, inhibited DPP-4 activity in the gut, but not in the circulation, and this low-dose sitagliptin was sufficient to augment the insulin response to oral glucose; furthermore, the effect was associated with increased nerve activity and absent in mice with deletion of the GIP or GLP-1 receptors. The results are compatible with the view that incretin hormones released after oral glucose are stabilized locally in the gut by DPP-4 inhibition and that this local DPP-4 inhibition, through prevented local incretin hormone inactivation, is sufficient to activate local afferent nerves that mediate the signal to stimulated insulin secretion[29]. Such an indirect effect seems consistent with previous data after GLP-1 administration in rodents. Thus, it has been shown first that in rats a ganglionic blockade impairs the insulinotropic action of GLP-1[30], and in mice a sensory deafferentation by capsaicin has been shown to prevent a low-dose GLP-1 administration from stimulating insulin secretion[31]. These results together suggest that GLP-1 already within the gut after its release activates afferent nerves, which after central relaying activates efferent nerves that stimulate insulin secretion[32]. DPP-4 inhibition might, through prevention of the local inactivation by GLP-1 in the gut, activate this neural circuit. Whether this is a mechanism that also improves glucose metabolism in humans remains to be established.

It was recently also shown that insulin secretion in response to DPP-4 inhibition requires normal β-cell glucose signaling. The evidence for this was obtained in a study in mice with dominant negative overexpression of the hepatic nuclear factor 1α (HNF-1α) in β-cells, which disrupts glucose signaling.

Table 1 | Potential mechanistic explanation for stimulated insulin secretion by dipeptidyl peptidase-4 inhibition

1	Stimulation of GLP-1 receptors on β-cells through prevented inactivation of GLP-1
2	Stimulation of GIP receptors on β-cells through prevented inactivation of GIP
3	Stimulation of PACAP receptors on β-cells through prevented inactivation of PACAP
4	Augmentation of β-cell glucose signaling through β-cell receptor activation
5	Activation of GLP-1 receptors on enteric afferent autonomic nerves eliciting neurally-induced insulin secretion

GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; PACAP, pituitary adenylate cylcase activating polypeptide.

In these mice, DPP-4 inhibition only marginally increased insulin secretion after oral glucose compared with wild-type mice[33]. Hence, there are several potential mechanistic explanations for the augmented insulin secretion by DPP-4 inhibition (Table 1).

Long-term Effects

In 2002, an 8-week long-term study was reported in which control and insulin-resistant high-fat fed mice were given the DPP-4 inhibitor, NVP-DPP728 (daily dose 0.12 mμmol/g bodyweight), in the drinking water for the 8-week period. It was found that glucose tolerance after gastric glucose gavage was still increased after 8-week DPP-4 inhibition in both groups of mice, and this was accompanied by increased plasma levels of insulin and intact GLP-1. Also, glucose-stimulated insulin secretion from islets isolated from NVP-DPP728-treated animals was increased as compared with islets from control animals[34]. Similar results were evident after 8 weeks of treatment with vildagliptin of mice overexpressing human islet amyloid polypeptide in β-cells: DPP-4 inhibition after 8 weeks still augmented the insulin response to oral glucose, and it was also shown that islets isolated from vildagliptin-treated animals had a marked improvement of glucose-stimulated insulin secretion[35]. Furthermore, sitagliptin increased insulin secretion from isolated islets and in the perfused pancreas after 10 weeks of treatment in a diabetes model in mice consisting of a combination of streptozotocin with high-fat feeding[22]. Thus, these studies show that increased insulin secretion persists during long-term DPP-4 inhibition in mice.

β-CELL MASS IN ANIMAL STUDIES

GLP-1 is known to exert trophic effects on β-cell mass[8]. In long-term studies in normal or diabetic rodents, GLP-1 (or the GLP-1 receptor agonist, exendin 4) increases β-cell mass, promotes β-cell replication and differentiation of β-precursor cells in the pancreatic duct epithelium. GLP-1 has also anti-apoptotic effects in rodent cells. Studies have been undertaken to explore whether DPP-4 inhibition might also exert such an effect. One study examined the influence of the DPP-4 inhibitor P32/98 on β-cell survival and islet neogenesis in streptozotocin-diabetic rats[36]. A clear increase in both β-cell mass and replication rate was found, suggesting that DPP-4 inhibition, like GLP-1, increases β-cell mass by stimulating neogenesis. Another study explored this by studying mice pretreated with a high-fat diet and a low dose of streptozotocin, which is a rodent model of type 2 diabetes[22]. These mice and healthy control mice were treated for 10 weeks with either the DPP-4 inhibitor, sitagliptin, or the sulfonylurea, glipizide, and it was found that sitagliptin clearly increased β-cell mass compared with diabetic controls, whereas no such effect was observed by glipizide. That study also found, however, that sitagliptin did not affect the number of Ki67-positive nuclei compared with diabetic controls, suggesting that the improved β-cell mass is not a result of increased proliferation rate and might be explained by the prevention of apoptosis. Furthermore, another study in the model of neonatal streptozocin administration in rats showed that 19 days of treatment with vildagliptin (60 mg/kg daily) stimulates β-cell mass both by increasing replication and regeneration, and by inhibiting apoptosis[37]. Hence, islet studies in rodents have clearly shown an ability of DPP-4 inhibition to increase β-cell mass, although there are some controversial findings in regard to the mechanisms, which might depend on the different models studied. In any case, the improvement of β-cell mass by DPP-4 inhibition is similar to the direct action of GLP-1, and might add to the beneficial effect of this treatment. In fact, an 8-week study in the model of hIAPP-overexpressing β-cells showed that the distorted islet topography seen in this model was normalized by vildagliptin[35]. Whether DPP-4 inhibition, or any GLP-1 based therapy, also increases islet cell mass in humans with type 2 diabetics has, however, not yet been established.

INSULIN SECRETION IN HUMAN STUDIES

Several studies have shown that DPP-4 inhibition in patients with type 2 diabetes improves surrogate measures of β-cell function, such as the homeostasis model assessment of β-cell function index[38–41] and the proinsulin to insulin ratio[38,39,42,43]. The first study exploring the influence of DPP-4 inhibition on insulin secretion in humans by analysing insulin levels after a challenge showed that the insulin levels after meal ingestion were the same after treatment with NVP-DPP728 for 4 weeks as after placebo[11]. Because at the same time glucose levels were lower after DPP-4 inhibition than after placebo, an analysis of the insulin response in relation to glucose (insulinogenic index) was found to be increased by NVP-DPP728 by approximately 25%. Therefore, the conclusion from that study was that total insulin secretion was sustained and not altered by DPP-4 inhibition, and that therefore in the face of lowered glycemia, β-cell function was increased. A similar conclusion was reached in a 4-week study on vildagliptin (Figure 1) and a 6-week study on vildagliptin, which both showed sustained insulin secretion after meal despite reduced glycemia compared with placebo as evidenced by the increased insulin secretory rate[44,45].

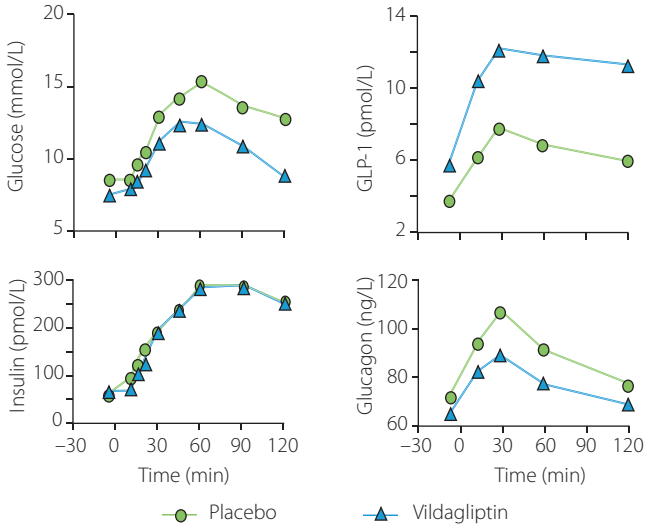

Figure 1 | Glucose, glucagon-like peptide-1 (GLP-1), insulin and glucagon levels in patients with type 2 diabetes after meal ingestion after 4 weeks of treatment with vildagliptin or placebo. Means ± SEM are shown. Adapted from reference 44 with permission from The Endocrine Society.

The stimulation of meal-induced insulin secretion by DPP-4 inhibition has been shown to be a sustained effect, which persists also after long-term treatment. This was clearly shown in a 52-week study in metformin-treated patients with type 2 diabetes to whom vildagliptin was added[46]. A meal test was undertaken after 12, 24 and 52 weeks, and it was shown that insulin secretion, as judged by insulin levels after meal ingestion, increased after 12 weeks and remained elevated after both 24 and 52 weeks. By modeling the C-peptide data after meal ingestion in subjects treated for 28 days with vildagliptin, it was also shown that the DPP-4 inhibitor clearly increased insulin secretory rate and also increased the glucose sensitivity in the β-cells; that is, the β-cell response to glucose[25]. Furthermore, for quantification of the effect, a compartmental analysis showed that after vildagliptin treatment for 6 weeks, the insulin secretory response to meal ingestion at the ambient glucose level was potentiated by 50%[45].

Insulin secretion is also increased by DPP-4 inhibitors when analyzed as the insulin response to oral glucose in subjects with type 2 diabetes, both when examining vildagliptin[39,47] and sitagliptin[48]. Although not quantified in direct comparisons, it seems that the insulinotropic action of DPP-4 inhibition is more pronounced after oral glucose than after meal ingestion. Interestingly, the insulin response to oral glucose was not increased by vildagliptin in healthy subjects[49], which shows the glucose-dependency of the effect; the healthy subjects had a fasting glucose of 4.5 mmol/L, whereas the subjects with type 2 diabetes had a fasting glucose of 8.3 mmol/L.

A few studies have used more advanced techniques of measuring insulin secretion after treatment with DPP-4 inhibition than measuring insulin or C-peptide after meal or oral glucose ingestion in humans. One study examined the insulin secretory response to intravenous glucose, to a glucose ramp and to an intravenous arginine in addition to a high glucose infusion after 3 months of treatment with vildagliptin in patients with type 2 diabetes[50]. The technique enables evaluation both of the insulin response to glucose and the maximal insulin secretory capacity. It was found that, when compared with placebo treatment, vildagliptin increased by approximately 20% the insulin secretory response to intravenous glucose, and the slope relating insulin secretion to glucose; the maximal insulin secretory response to high glucose and intravenous arginine showed a clear trend to being stimulated as well[50]. Furthermore, another study used a hyperglycemic clamp in association with a 75-g oral glucose enabling glucose clamping at 15.5 mmol/L together with enteral stimulation and showed that the DPP-4 inhibitor saxagliptin increased insulin secretion by 18.5% after 12 weeks of treatment in patients with type 2 diabetes[51]. Furthermore, the insulin secretory response to high glucose (15 mmol/L) plus intravenous arginine was increased by approximately 15% after 1 year of treatment with vildagliptin[52]. Therefore, more advanced methods enabling quantification of the insulin secretory responses show stimulation of insulin secretion by DPP-4 inhibition, and the results show that this effect persists with a durability of at least 1 year.

An important question is whether insulin secretion is sustainly increased after discontinuation of therapy; that is, whether a disease-modifying effect might be evident for DPP-4 inhibition. If so, this would fit the hypothesis that an increased β-cell mass has evolved. One study examining vildagliptin has indeed shown that after 2 years of treatment, but not 1 year of treatment, sustained increase in insulin secretion is seen after 4 weeks of discontinuation of therapy[53]. However, a study using the arginine-stimulated hyperglycemic clamp technique showed that although a clear stimulation of insulin secretion was seen after 1 year of treatment with vildagliptin, after a 12-week washout after the 1-year treatment this stimulated insulin secretion was not maintained[52]. Therefore, no clear evidence exists so far for a disease-modifying effect of DPP-4 inhibition and more studies are required on long-term influences on islet function of DPP-4 inhibition in patients with type 2 diabetes.

Glucagon Secretion

GLP-1 is known to inhibit glucagon secretion, as has been shown both in experimental studies in animals and humans[9,54,55]. A recent study in humans showed that approximately 50% of the glucose-reducing effect of GLP-1 is mediated by the inhibition of glucagon secretion[56].

In animals, the influence of DPP-4 inhibition on glucagon secretion has not been studied in great detail. One study has shown that DPP-4 inhibition by sitagliptin reduces non-fasting glucagon levels in mice, showing inhibition of glucagon secretion[22]. In humans, it was shown in 2004 that DPP-4 inhibition (by vildagliptin) lowers glucagon levels after meal ingestion[44]. That study served a mixed meal to subjects with type 2 diabetes

after 4 weeks of treatment with vildagliptin and found that the increase in glucagon levels by the meal ingestion was reduced by approximately 50% versus the placebo group (Figure 1). It has also been shown that this inhibition of glucagon correlates with the reduced glycemia after a meal, suggesting that the reduction of glucagon is of significant importance for improved glycemia[44,45].

It has also been documented that glucagon levels were reduced after oral glucose by both sitagliptin[47] and vildagliptin[46]. A reduction in glucagon levels after a combined intravenous and oral glucose clamp has also been documented after treatment with saxagliptin; the reduction was estimated to be 21% versus placebo[51]. Furthermore, a study combining the measurement of glucagon levels with hepatic glucose output after meal ingestion showed that DPP-4 inhibition by vildagliptin reduced both glucagon levels and hepatic glucose production[57]. Hence, it is clear that glucagon levels are reduced by DPP-4 inhibition in humans.

A recent study evaluated the long-term effect of vildagliptin on glucagon secretion[58]. The study was carried out in metformin-treated patients with type 2 diabetes in whom vildagliptin was added. Before adding vildagliptin and after 2 years of vildagliptin treatment, meal tests were undertaken. It was found that the glucagon response to a meal was reduced by vildagliptin after the 2-year study period, showing that the inhibition of glucagon secretion by vildagliptin is long standing. This was in contrast to the sulfonylurea glimepiride, which in the same study was shown to increase glucagon secretion after 2 years of treatment.

To examine whether the inhibitory action of DPP-4 inhibition of glucagon secretion is glucose dependent, as the stimulation of insulin secretion, we recently carried out a study on glucagon secretion in hyper- and hypoglycaemia after 4 weeks of treatment with vildagliptin in subjects with type 2 diabetes[59]. The study protocol involved an initial meal ingestion, followed, after 120 min, by a sequential clamp of glucose at 7.5, 5.0 and 2.5 mmol/L. The results showed that although vildagliptin clearly suppressed glucagon after meal ingestion and at clamps at 7.5 and 5.0 mmol/L glucose, the glucagon counterregulation to the hypoglycemic clamp at 2.5 mmol/L was sustained and the same as in a placebo group (Figure 2)[59]. This shows that vildagliptin inhibits glucagon secretion in hyperglycemia, but sustains glucagon secretion in hypoglycaemia, which shows the increased glucose sensitivity of the DPP-4 inhibitor. The mechanism behind the sustained glucagon response to hypoglycaemia could involve reduced insulin secretion with low intra-islet insulin concentrations (as a result of the hypoglycaemia), increased autonomic nerve activity and/or increased concentrations of GIP, the other incretin hormone, the concentration of which is also increased by vildagliptin[25]. Evidence exists for all these three mechanisms: vildagliptin reduces insulin secretion during hypoglycemia and has a tendency to increase autonomic nerve activity during hypoglycemia[59], and GIP has been shown to stimulate glucagon secretion, at least during euglycemia[60]. Regardless of the mechanisms, the results suggest that vildagliptin might protect from hypoglycemia through this sustainment of glucagon secretion, which might explain the low risk for hypoglycaemia when vildagliptin is also combined with insulin treatment[61].

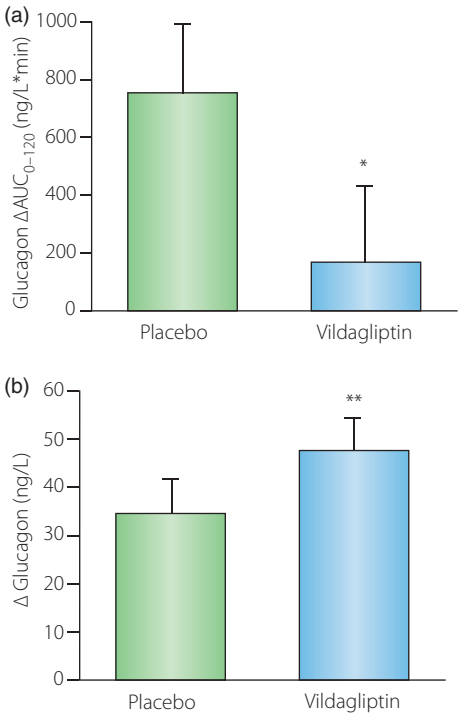

Figure 2 | Glucagon response to (a) meal ingestion or (b) hypoglycemia induced by lowering glucose levels to 2.6 mmol/L in patients with type 2 diabetes after 4 weeks of treatment of with vildagliptin or placebo. Means ± SEM are shown. Asterisks show the probability level of random difference between the groups; *$P < 0.05$, **$P < 0.01$. Adapted from reference 58 with permission from The Endocrine Society.

CONCLUSION

DPP-4 inhibition as therapy for type 2 diabetes has been rationally developed based on knowledge of the physiology and metabolism of GLP-1 in association with the knowledge that islet dysfunction is the key defect in type 2 diabetes. The successful development of DPP-4 inhibition was made possible by researchers with a deep knowledge of the pathophysiology of diabetes and the key involvement of islet dysfunction together with knowledge on integrated metabolism and a close cooperation between academic units and the research-oriented pharmaceutical industry. DPP-4 inhibition has thus been shown to stimulate insulin secretion and inhibit glucagon secretion. Furthermore, the effects of DPP-4 inhibition on islet hormone secretion are glucose-dependent, which explains the low risk for hypoglycemia during this treatment. Finally, rodent studies have also shown that DPP-4 inhibition increases β-cell mass. Therefore, DPP-4 inhibition targets the key islet dysfunction in type 2 diabetes, which might explain the successful experience gained by this novel therapy after its first 5 years of clinical use.

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