The Function and Role of Dipeptidyl Peptidase-4 Inhibitors in the Management of Type 2 Diabetes

a report by
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Glucagon-like Peptide-1-based Therapy for Type 2 Diabetes

Post-prandial hyperglycaemia in people with type 2 diabetes mellitus (T2DM) may be due to defects in insulin secretion, suppression of glucagon secretion, impaired glucose effectiveness (defined as the ability of glucose *per se* to stimulate its own uptake and suppress its own release) and impaired insulin action (the ability of insulin to stimulate glucose uptake and suppress glucose release). Changes to the rate of gastric emptying can also alter post-prandial glucose concentrations.[1]

Glucagon-like peptide-1 (GLP-1) is produced by the enteroendocrine L cells of the intestinal mucosa and is released in response to meal ingestion. It arises from the post-translational processing of proglucagon by prohormone-convertase-1 (PC-1) in the enteroendocrine L cells of the intestinal mucosa.[2] GLP-1 enhances insulin secretion and inhibits glucagon release in a glucose-dependent manner.[3] In addition, it delays gastric emptying[4] and, when infused in pharmacological concentrations, enhances satiation and facilitates weight loss in people with T2DM.[5] However, its utility as a therapeutic agent in T2DM has been limited by its extremely short half-life.

The major form of secreted GLP-1, GLP-1-(7,36)-amide, requires the presence of the two N-terminal amino acids for biological activity. The widely distributed enzyme dipeptidyl peptidase-4 (DPP-4) rapidly converts the active peptide to the inactive GLP-1-(9,36)-amide. Therefore, GLP-1-based therapy for T2DM has required the development of GLP-1 receptor agonists resistant to the action of DPP-4.[6] These compounds have similar effects to GLP-1, inducing satiety and weight loss in clinical practice.[7]

An alternative therapeutic strategy to enhance glycaemic control has been to inhibit DPP-4, and thereby raise endogenous concentrations of active GLP-1.[8] These lower fasting and post-prandial glucose concentrations.[9]

Glucagon-like Peptide-1 Physiology

Glucose tolerance is dependent on the quantity and pattern of post-prandial pancreatic insulin and glucagon secretion as well as on the action of insulin on the various tissues (liver, muscle and fat depots) to alter glucose utilisation. Hepatic- and peripheral-insulin action has been shown to be significantly impaired in T2DM. In addition, glucose effectiveness is defined as the function of glucose *per se*, in the absence of dynamic changes in insulin concentrations, to influence its own uptake and suppress its own release, which plays a significant role in post-prandial, glucose homeostasis – especially in people with T2DM. This process is impaired in T2DM.[10] In experiments where insulin and glucagon concentrations are kept constant in the presence or absence of GLP-1, there is no evidence of a direct effect of this hormone on glucose metabolism in T2DM.[11,12]

Impaired or delayed stomach emptying or carbohydrate absorption reduces post-prandial glycaemic excursions. GLP-1 infusion has been shown to delay gastric emptying and, together with enhancing insulin secretion, improve post-prandial hyperglycaemia in individuals with T2DM.[13] In detailed studies of the effect of GLP-1 on gastric motility, this hormone has been shown to relax the proximal stomach and increase gastric volume and accommodation, possibly through inhibition of vagal cholinergic pathways.[14] Interestingly, despite increasing stomach volume, this alone does not alter satiety, implying a possible effect of GLP-1 on stomach compliance or the central perception of satiety. Such effects require intact vagal pathways and no effects are seen in patients with cardiovagal neuropathy.

An alternative therapeutic strategy to enhance glycaemic control has been to inhibit DPP-4, and thereby raise endogenous concentrations of active GLP-1.

In addition to the gut, GLP-1 is also produced in the brain and is secreted predominantly in a set of hindbrain neurons (area postrema and tractus solitarius) that project to specific cells in the hypothalamus, brainstem, and midbrain that express the GLP-1 receptor.[15] These circuits are implicated in appetite regulation and food intake. On the other hand, knockout of the GLP-1 receptor does not affect weight,[16] consistent with the presence of multiple neuropeptides involved in weight maintenance and regulation.[15]

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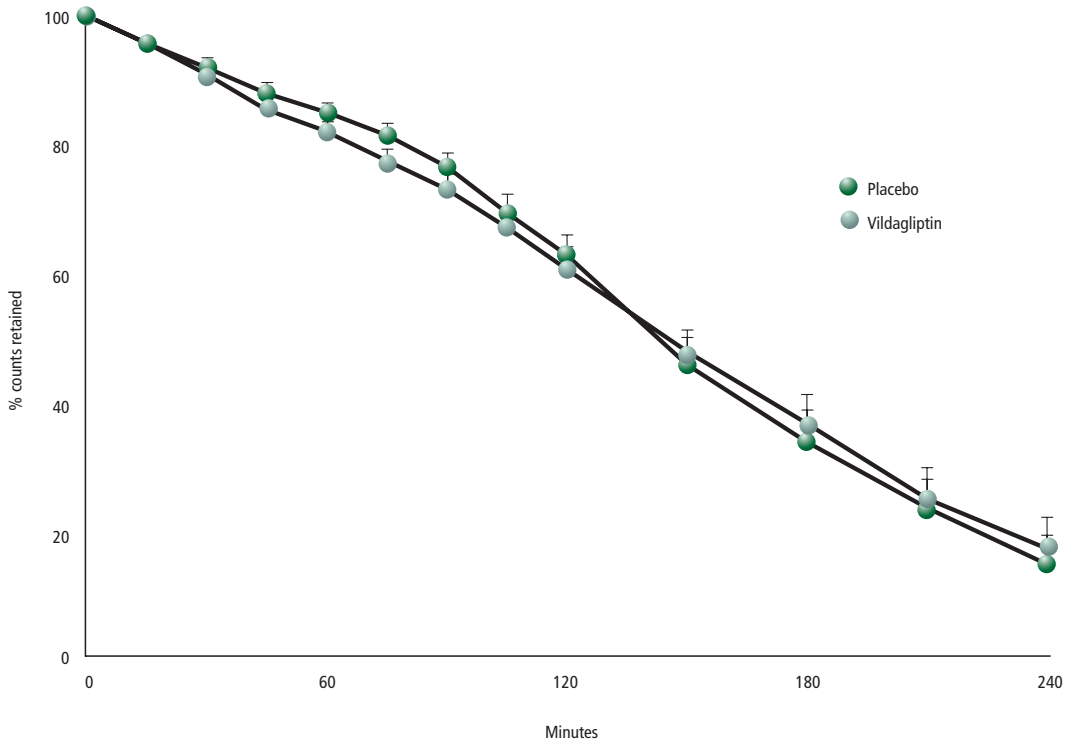
Figure 1: Gastric Emptying of Solids – Vildagliptin versus Placebo



The advent of GLP-1-based therapy for the treatment of T2DM has prompted increased interest in its role in regulating caloric intake given the effect of the native hormone, as well as GLP-1 receptor agonists, on caloric intake and body weight[5,17] and gastrointestinal function.[4,11]

Dipeptidyl Peptidase-4 Inhibitors and their Metabolic Effects

GLP-1 and DPP-4 inhibitors both lower post-prandial glucose concentrations in people with T2DM, at least in part due to their ability to enhance insulin secretion and to inhibit glucagon release.[8,18] In pharmacological doses, GLP-1 is also a potent inhibitor of gastric emptying.[13] In contrast, DPP-4 inhibition does not alter gastric emptying.[19] Moreover, the rate, pattern or amount of glucose that enters the systemic circulation following ingestion of a mixed meal is unaltered by vildagliptin. Given the relatively small elevations in active GLP-1 concentrations produced by DPP-4 inhibitors, some authors have suggested that the actions of DPP-4 inhibitors are not mediated through GLP-1.[20] Indeed, inhibition of DPP-4 raises concentrations of other hormones such as glucose-dependent insulinotropic peptide (GIP), neuropeptide Y (NPY) and peptide YY (PYY).[21] However, DPP-4 inhibition in mice lacking the GLP-1 and GIP receptors did not alter glucose concentrations, implying that GLP-1 and GIP action are necessary for DPP-4 inhibitors to lower glucose.[22]

DPP-4 inhibitors lower post-prandial glucagon concentrations. However, post-prandial C-peptide concentrations are unchanged, despite lower glucose concentrations in the presence of these compounds. This pattern has been consistently demonstrated.[23] At a given glucose concentration, DPP-4 inhibition increases insulin and decreases glucagon release, resulting in higher portal insulin and lower glucagon concentrations.[24] The net effect is to lower fasting and post-prandial concentrations.

Clinical Role of Dipeptidyl Peptidase-4 Inhibitors

Most clinical trial data regarding the efficacy of DPP-4 inhibition in the treatment of T2DM pertain to vildagliptin and sitagliptin; only the latter is currently available for clinical use. As they have the ability to produce glucose-dependent improvements in beta- and alpha-cell function (with little risk of hypoglycaemia), and in the absence of significant side effects, such compounds have been considered to be first-line agents for the treatment of diabetes. Against this must be balanced their cost, especially compared with more established therapy, and the relative paucity of data pertaining to their long-term safety.[25]

GLP-1 and DPP-4 inhibitors both lower post-prandial glucose concentrations in people with T2DM, at least in part due to their ability to enhance insulin secretion and to inhibit glucagon release.

The addition of vildagliptin to patients already given metformin reduced glycated hemoglobin (HbA_{1c}) by 0.8% after 12 weeks compared with placebo, and this difference was maintained during an open-label extension for 52 weeks.[23] Similarly, in a 24-week double-blind,

randomised, multicentre, placebo-controlled parallel-group study performed in 354 drug-naïve patients with T2DM, the adjusted-mean change in HbA_{1c} was -0.5+0.2%.[26] Vildagliptin was comparable to rosiglitazone in efficacy and was not associated with weight gain in another 24-week study.[27] Combination therapy with thiazolidendiones[28] and metformin[29] is also effective.

> In summary, DPP-4 inhibitors are a useful adjunct to the treatment of T2DM given that they are well tolerated, do not cause hypoglycaemia and, especially in combination with metformin, are effective in improving glycaemic control.

Similar clinical studies have also been reported for sitagliptin[30] with significant HbA_{1c} lowering in combination with metformin[31] or a thiazolidendione.[32,33] Sitagliptin was approved for the treatment of T2DM in the US in October 2006.

Conclusions

In summary, DPP-4 inhibitors are a useful adjunct to the treatment of T2DM given that they are well tolerated, do not cause hypoglycaemia and, especially in combination with metformin, are effective in improving glycaemic control. Unlike GLP-1 receptor agonists they do not cause weight loss, although this may be due to a far lower incidence and severity of gastrointestinal side effects.

On a more cautious note, DPP-4 is a ubiquitous enzyme that seems to play an important part in immune regulation as well as in the process of invasion and metastasis of multiple tumors *in vitro*.[34–36] The consequences of DPP-4 inhibition on these processes by agents used to treat diabetes are unknown. It has also been suggested that DPP-4 may also be important in the process by which the blastocyst implants in the endometrium.[37] GLP-2, like GLP-1 a product of post-translational processing of proglucagon by PC-1, is a growth factor for intestinal mucosa.[2,38,39] The consequences of long-term elevation of GLP-2 on the intestine are unknown. Therefore, caution should be exercised when prescribing a DPP-4 inhibitor to patients with a prior history of malignancy or to women of reproductive age given these as yet unresolved concerns. ■

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