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Glucagon-like peptide-1 mediates the therapeutic actions of DPP-IV inhibitors

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Abbreviations DPP-IV: Dipeptidyl peptidase-IV · GIP: gastric inhibitory peptide · GLP-1: Glucagon-like peptide-1

Introduction

Our opponents in this debate, Nauck and El-Ouaghli, have challenged the standard view that the therapeutic actions of the dipeptidyl peptidase-IV (DPP-IV) inhibitors are mediated by glucagon-like peptide-1 (GLP-1) [1]. Based on the findings that exogenously administered GLP-1 is rapidly and extensively degraded by DPP-IV [2], and that this degradation appears to be mediated by DPP-IV [3], it was proposed that DPP-IV inhibitors could enhance the survival of intact, biologically active GLP-1 and thus be of use in the treatment of type 2 diabetes mellitus [2, 4]. Although the kinetic studies performed by Mentlein et al. clearly demonstrated that DPP-IV may have substrates in addition to GLP-1 [5, 6], the effect of this enzyme on GLP-1 was considered to be of particular importance because: (1) GLP-1 is extremely susceptible to rapid degradation by DPP-IV, as compared with the majority of other substrates; (2) DPP-IV degradation is the primary route of GLP-1 inactivation; (3) GLP-1 is perhaps the most potent and efficacious insu-

linotropic hormone in the body [7], whereas gastric inhibitory peptide (GIP), the other major incretin hormone, has no insulinotropic effects in patients with type 2 diabetes [8]; and (4) DPP-IV inhibitors have no metabolic effect in mice with a targeted deletion of the GLP-1 and GIP receptor genes [9].

The authors of the previous article have listed five arguments that have caused them to doubt that GLP-1 is the only, or at least the major, mediator of the remarkable hypoglycaemic effects of DPP-IV inhibitors observed in clinical studies [10–12]. We would certainly agree that there are other potential substrates for DPP-IV whose extended survival might contribute to the therapeutic effects of these inhibitors; nonetheless, we believe that the protection of GLP-1 against degradation is the major mechanism involved. In the remainder of this paper, we shall respond to each of the five arguments in turn.

DPP-IV inhibition causes little increase in endogenous GLP-1

The question at issue is whether the observed increases in plasma concentrations of active GLP-1 are sufficient to explain the effects of DPP-IV inhibition on insulin secretion. We would argue that it is impossible to compare the effects of DPP-IV inhibitors on peripheral venous concentrations of active GLP-1 with those of infusions of exogenous GLP-1, even if both interventions result in similar systemic elevations in active GLP-1. GLP-1 is degraded so extensively that an increase in peripheral concentrations of the intact peptide is frequently not detectable after intake of smaller meals [13]. Moreover, it has been shown that, while virtually all of the GLP-1 stored in the granules of the L-cells is intact [14], a very large proportion—probably as much as 75%—of the GLP-1 that leaves the gut has already been degraded into the inactive metabolite [14, 15] (Fig. 1). Further degradation amounting to about 40–50% takes place in the liver [16]; thus, only about 10–15% of newly secreted GLP-1 reaches the systemic circulation in the active form (Fig. 1). Endothelial DPP-IV in the capillaries of

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10–15% of secreted amount leaves liver

Fig. 1 Schematic diagram of the endocrine pathway for the actions of GLP-1. GLP-1 secretion is stimulated by nutrients in the gut lumen (a magnified intestinal villus with an open-type L-cell is shown in the lower left-hand corner). GLP-1 diffuses across the basal lamina into the lamina propria and is taken up by a capillary and broken down by DPP-IV, which is located on the luminal surface of the endothelial cells (white cells lining the capillary). Consequently, only 25% of the GLP-1 secreted reaches the portal circulation. In the liver, a further 40–50% is destroyed, which means that only 10–15% enters the systemic circulation where it gets carried to the pancreas and the brain via the endocrine pathway (perhaps even less will reach these regions because of the continued proteolytic activity of soluble DPP-IV present in plasma)

the lamina propria is responsible for this degradation, which can be completely prevented by DPP-IV inhibition [14]. Furthermore, if DPP-IV inhibitors are observed to raise systemic venous concentrations of active GLP-1, it follows that they must also have increased portal venous plasma concentrations by a factor of 2–3, since portal blood is diluted as it enters the systemic circulation. In line with this, the local concentration of GLP-1 in the lamina propria of the gastrointestinal mucosa will also be increased (due to the fraction of the portal plasma flow that is derived from perfusion of the lamina propria). These increases in active GLP-1 concentrations are sufficient to explain the effect of the DPP-IV inhibitors. The extensive degradation of GLP-1 that occurs before it enters the systemic circulation has led to the suggestion that GLP-1 exerts numerous actions either locally in the gut or in the hepatic portal bed [17]. Once released, but before it enters the capillaries and comes into contact with endothelial DPP-IV, GLP-1 may interact with afferent sensory nerve fibres arising from the nodose ganglion, which send impulses to the nucleus of the solitary tract and onwards to the hypothalamus (Fig. 2). The recent observation that the GLP-1 receptor is expressed in nodose

Fig. 2 Schematic diagram of the neural pathway for the actions of GLP-1. GLP-1 secretion is stimulated by nutrients in the gut lumen (a magnified intestinal villus with an open-type L-cell is shown at the lower left-hand corner), and newly released GLP-1 diffuses across the basal lamina into the lamina propria. On its way to the capillary, it may bind to and activate sensory afferent neurons (f) originating in the nodose ganglion (c), which may, in turn, activate neurons of the solitary tract nucleus (a). The same neuronal pathway may be activated by sensory neurons in the hepatportal region (e) [33] or in the liver tissue (d) [34]. Ascending fibres from the solitary tract neurons may generate reflexes in the hypothalamus, and descending impulses (perhaps from neurons in the paraventricular nucleus) may activate vagal motor neurons (b) that send stimulatory (h) or inhibitory (g) impulses to the pancreas and the gastrointestinal tract

ganglion cells supports this view [18]. It has also been demonstrated that the intraportal administration of GLP-1 increases impulse activity in the vagal trunks [19], which may be reflexly transmitted to the pancreas [20]. Studies in rats have shown that ganglionic blockade reduces the insulin response to the intraportal administration of GLP-1 and glucose compared with that elicited by glucose alone [21]. Thus, under physiological conditions, the neural pathway may be more important than the endocrine route for GLP-1-stimulated insulin secretion.

It should be noted that insulin levels are not elevated during inhibitor treatment [10, 11]; consequently, this situation should not be compared with infusion studies resulting in elevated insulin levels. The insulinotropic actions

of GLP-1 appear to be due to an increase in the insulinogenic index, such that the same degree of insulin secretion is produced at lower glucose levels. The doses of exogenous GLP-1 required to elicit this effect have yet to be established.

DPP-IV inhibitors have little effect on gastric emptying

It is argued that, at doses that affect blood glucose, GLP-1 invariably inhibits gastric emptying [22], whereas a similar deceleration has not been observed in studies employing DPP-IV inhibitors—a conclusion that is difficult to deduce from the reference given for the latter statement [23]. The impression given by the statement that gastric deceleration accompanies the hypoglycaemic effects of GLP-1 is opposite to what was actually reported in the supporting reference, as similar glucose lowering was obtained with all doses of GLP-1 tested, whereas gastric emptying was inhibited in a dose-dependent manner [22]. In other words, the dose–response relationship was shifted to the right. Despite this, we agree that the evidence to date suggests that the effect of the inhibitors on gastric emptying is either weak or absent. This may be related to the observation that there was no change in body weight over 1 year’s inhibition of DPP-IV [12]. Based on the fact that inhibitor treatment merely doubles peripheral concentrations of intact GLP-1, and given the dose–response relationship for gastric emptying defined by Meier et al. [22], DPP inhibitors would not be expected to have a major effect on gastric emptying, despite a rather pronounced effect on glucose levels. The most important difference between DPP inhibitors and exogenous GLP-1 may be related to the fact that infusions of GLP-1 affect the islets via the endocrine pathway, whereas endogenously produced GLP-1 is likely to influence gastric motility by interacting with afferent sensory neurons in the gastrointestinal tract (Figs. 1, 2). This interaction may take place at a stage at which newly secreted GLP-1 is not yet, or is only partially, degraded by DPP-IV (i.e. before its entry into the capillaries of the gastrointestinal tract or prior to its passage through the liver). It follows that DPP-IV inhibition may not greatly influence this activation, since there is little or no change in local concentrations of intact GLP-1, whereas higher concentrations of exogenous GLP-1 may access and activate the same sensory neurons as endogenous GLP-1 does [17].

GLP-1 and incretin mimetics cause nausea/vomiting while DPP-IV inhibitors do not

It has been established that nausea will be elicited when circulating concentrations of active GLP-1 exceed 60 pmol/l. Such concentrations may be reached initially after subcutaneous injection of GLP-1 or GLP-1 mimetics, but are never seen when DPP-IV inhibitors are used. It is possible that interaction with receptors in the area postrema—an area of the blood–brain barrier with leaky fenestrated capillaries—is the pathway for this side-effect [24, 25], which

would therefore be affected by circulating concentrations of GLP-1.

Meal-stimulated levels of GLP-1 fall in response to DPP-IV inhibition

It is argued that feedback inhibition of L-cell secretion during inhibitor treatment, as demonstrated by Deacon et al. [26], leaves “little potential for plasma concentrations of endogenously secreted GLP-1 to rise into the therapeutically relevant range.” There are several comments to be made here. First, all studies have shown that the peripheral concentration of intact GLP-1 does increase (by a factor of 2) during inhibitor treatment, in spite of decreased L-cell secretion. Second—given that the hepatportal receptors may be of importance—concentrations of active GLP-1 in the portal plasma will be increased due to the inhibition of endothelial DPP-IV in the capillaries of the intestines and to the dilution factor discussed above. Third, we should bear in mind that, for both GLP-1 and GIP secretion, the measurements of feedback inhibition reported to date are based on acute studies. In contrast, the effects of DPP-IV inhibitors develop slowly, and early effects on glucose levels may be inconspicuous compared with those that only become apparent after 4–12 weeks. Concentrations of active GLP-1 and GIP may change over this period, in agreement with the hypothesis that the secretion of GLP-1 is decreased in type 2 diabetes, presumably as a consequence of the diabetic state [27, 28]. Incretin secretion or sensitivity to their effects might improve with gradual improvements in metabolism. For example, it has been reported that high glucose levels downregulate the GIP receptor [29], while the response to GIP has been seen to improve following antihyperglycaemic therapy with glyburide to reduce fasting glucose levels in diabetic patients [30].

DPP-IV inhibition has delayed effects on glucose homeostasis

As mentioned above and by our opponents, the effects of the inhibitors develop slowly, whereas the effects of GLP-1 are immediate. It is currently unknown why this is so, but it seems probable that this is related to increased secretion over time, and possibly to an enhanced effect of the incretin hormones, sensitivity to which is greatly reduced in untreated diabetes [8, 31].

We conclude that all the arguments put forward by our opponents can, in fact, be turned around to support the hypothesis that the main effects of DPP-IV inhibitors are mediated by GLP-1. We would like to add that this discussion has, perhaps, focused too much on insulin secretion, and that one of the more important therapeutic effects of GLP-1 may be the inhibition of glucagon secretion, as also seems to be the case for the DPP-IV inhibitors—once again, a striking similarity [11, 32]. Our opponents suggest that pancreatic neuropeptides may be alternative mediators, and this certainly remains a possibility. However, the im-

portance of pancreatic innervation for postprandial insulin secretion in humans remains unclear. We conclude that the evidence available to date is consistent with the hypothesis that the protection of GLP-1 is a major contributor to the effects of DPP-IV inhibition.

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