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RESEARCH LETTER

Dipeptidyl peptidase-4 inhibition increases portal concentrations of intact glucagon-like peptide-1 (GLP-1) to a greater extent than peripheral concentrations in anaesthetised pigs

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Abbreviations

DPP-4	Dipeptidyl peptidase
GLP-1	Glucagon-like peptide-1
NC	Neuromedin C

To the Editor: The dipeptidyl peptidase (DPP-4) inhibitors widely used for diabetes treatment may be viewed as being surprisingly effective, particularly when compared with the other class of incretin-based therapy, the glucagon-like peptide-1 (GLP-1) analogues (mimetics), because the inhibitors are associated with only modest increases in peripheral intact GLP-1, whereas much higher agonist concentrations can be achieved using the analogues. It has been calculated that only 10–15% of newly secreted GLP-1 reaches the pancreas as the intact hormone via the circulation [1, 2] because of local and hepatic DPP-4-mediated degradation, leading to the suggestion that GLP-1 may act more locally by interacting with afferent neurons within the intestine or portal vein before it is degraded by DPP-4. Thus it could be speculated that local concentrations of intact GLP-1, particularly after administration of DPP-4 inhibitor, may be much higher than peripheral venous concentrations, which could, at least partially, explain the effectiveness of the inhibitors [3]. However, it is at present unknown what the actual concentrations of endogenous GLP-1 are in the various vascular beds and how much intact GLP-1 concentrations in sites such as the portal vein rise following DPP-4 inhibition.

We therefore measured the concentrations of GLP-1 in different vascular compartments before and after DPP-4 inhibition with vildagliptin (1 mg/kg) in anaesthetised (α-chloralose) pigs (n=6) given intravenous neuromedin C (NC, 120 nmol), a known stimulus for GLP-1. Blood samples were obtained simultaneously from a carotid artery and the femoral, hepatic and portal veins and analysed for total GLP-1 using the 'side-viewing' antiserum 2135, reacting with a mid-sequence of GLP-1, and intact GLP-1 concentrations by sandwich ELISA. DPP-4 activity was assayed by a fluorescence assay (see electronic supplementary material [ESM] Methods).

NC augmented concentrations of total GLP-1 six- to eightfold, both before and after vildagliptin administration (see Fig. 1). Both total and intact GLP-1 concentrations were highest in the portal vein and decreased progressively as the distance from the site of release increased, with lowest concentrations being found in the peripheral venous plasma. Before vildagliptin administration, GLP-1 was extensively degraded by DPP-4 at all sites (incremental AUC for intact arterial GLP-1 before being 79.2±14.8 pmol/l×min, while intact portal GLP-1 after was 460.0±65.5 pmol/l×min), indicating that the peripheral (and therefore pancreatic islet) exposure to intact GLP-1 amounts to only 20% of the splanchnic/portal exposure (see

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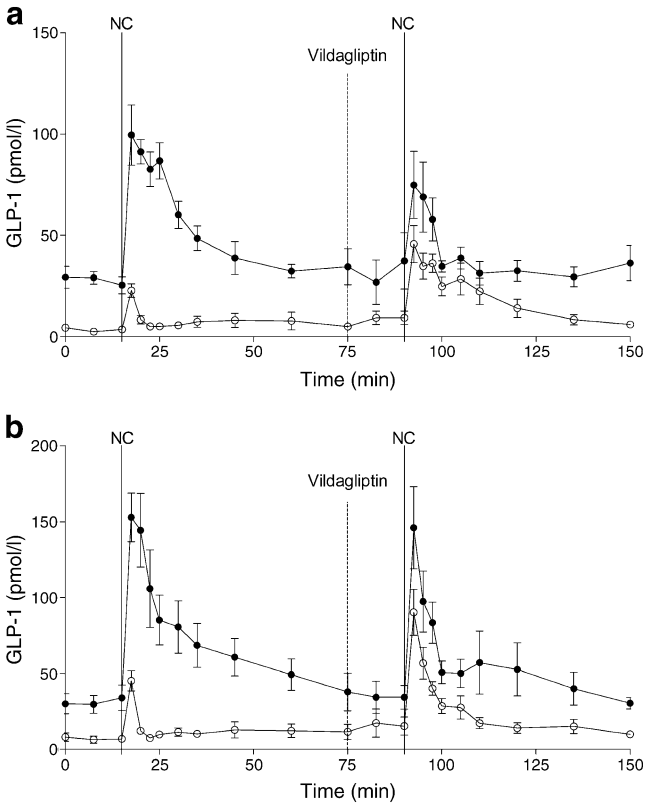

Fig. 1 Intact and total GLP-1 profiles in the carotid artery (**a**) and the portal vein (**b**). Data are means±SEM, n=6. NC significantly increased the secretion of intact GLP-1 both before and after vildagliptin. After the first NC bolus, peak concentrations of intact GLP-1 in all the vascular compartments were lower than total GLP-1 before vildagliptin administration. Black circles, total GLP-1; white circles, intact GLP-1

ESM Fig. 1). Similarly, the increase in GLP-1 concentration in peripheral venous plasma during stimulation amounted to only 8% of the increase in the portal concentration.

In contrast, total GLP-1 concentrations were reduced after vildagliptin administration. Total and intact incremental AUCs were similar after vildagliptin, indicating full protection of GLP-1 with this inhibitor dose.

Relative to the basal period, administration of vildagliptin resulted in 86.0±4.0% inhibition of plasma DPP-4 activity in the portal vein, but, taking the dilution of the sample in the assay incubation mixture into account, this is probably equivalent to close to 100% inhibition in vivo [4]. This assumption is supported by the finding that, after DPP-4 inhibition, the concentrations of intact GLP-1 equalled the concentrations measured with the assay for total GLP-1, indicating complete protection of GLP-1 from DPP-4-mediated degradation.

Our observations confirm the predictions made on the basis of observed rates of degradation in studies of secretion from isolated perfused porcine intestine and after GLP-1 infusion in anaesthetised catheterised pigs [1, 5]. After vildagliptin, the concentrations of intact GLP-1 increased in all vascular beds. It is of particular interest that the portal concentrations of intact GLP-1 rose to as much as 90 pmol/l during NC stimulations. Although it could be argued that NC is not a physiologically relevant stimulus for GLP-1 secretion, it should be noted that the peripheral concentrations of total GLP-1 after NC were raised to levels that are similar to those observed after large meals in humans [3], suggesting that the stimulus strength is physiologically relevant. In studies with peripheral administration of GLP-1, full glucose-lowering activity is usually observed at an infusion rate of 1.2 pmol kg^{-1} min^{-1}, which results in systemic concentrations of intact GLP-1 of about 20 pmol/l [6]. In fact, if peripheral concentrations of intact GLP-1 increase above 60 pmol/l, gastrointestinal side effects and nausea are usually observed [7]. It is therefore clear that the concentrations of endogenous intact GLP-1 at the sites where it is thought to act, namely in the plasma draining the gut and in the portal region, are very high after DPP-4 inhibition, and even comparable to concentrations achieved after administration of clinically relevant doses of GLP-1 agonists.

The total GLP-1 response was attenuated by about 50%. This is in agreement with both experimental and clinical results obtained with DPP-4 inhibitors [8], and supports the hypothesis that GLP-1 may negatively feedback on L cell secretion, possibly by way of a paracrine effect of somatostatin-28 from neighbouring D cells. Thus the increase in intact GLP-1 resulting from DPP-4 inhibition may limit the secretion of the L cell, and this may explain why DPP-4 inhibitors typically increase intact GLP-1 concentrations by only two- to threefold rather than the expected fivefold. Together, these observations may offer some explanation of why the DPP-4 inhibitors have surprisingly similar antihyperglycaemic efficacy to the GLP-1 agonists, but without the gastrointestinal side effects.

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