Perspectives in Diabetes

Inhibition of the Activity of Dipeptidyl-Peptidase IV as a Treatment for Type 2 Diabetes

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The insulinotropic hormone, glucagon-like peptide 1 (GLP-1), which has been proposed as a new treatment for type 2 diabetes, is metabolized extremely rapidly by the ubiquitous enzyme, dipeptidyl peptidase IV (DPP-IV), resulting in the formation of a metabolite, which may act as an antagonist at the GLP-1 receptor. Because of this, the effects of single injections of GLP-1 are short-lasting, and for full demonstration of its antidiabetogenic effects, continuous intravenous infusion is required. To exploit the therapeutic potential of GLP-1 clinically, we here propose the use of specific inhibitors of DPP-IV. We have demonstrated that the administration of such inhibitors may completely protect exogenous GLP-1 from DPP-IV–mediated degradation, thereby greatly enhancing its insulinotropic effect, and provided evidence that endogenous GLP-1 may be equally protected. Preliminary studies by others in glucose-intolerant experimental animals have shown that DPP-IV inhibition greatly ameliorates the condition. GLP-1 has multifaceted actions, which include stimulation of insulin gene expression, trophic effects on the β-cells, inhibition of glucagon secretion, promotion of satiety, inhibition of food intake, and slowing of gastric emptying, all of which contribute to normalizing elevated glucose levels. Because of this, we predict that inhibition of DPP-IV, which will elevate the levels of active GLP-1 and reduce the levels of the antagonistic metabolite, may be useful to treat impaired glucose tolerance and perhaps prevent transition to type 2 diabetes. The actions of DPP-IV, other than degradation of GLP-1, particularly in the immune system are discussed, but it is concluded that side effects of inhibition therapy are likely to be mild. Thus, DPP-IV inhibition may be an effective supplement to diet and exercise treatment in attempts to prevent the deterioration of glucose metabolism associated with the Western lifestyle. *Diabetes* **47:1663–1670, 1998**

In a study of the susceptibility of a number of regulatory peptides to the amino-dipeptidase activity of the enzyme, dipeptidyl peptidase-IV (DPP-IV), Mentlein et al. (1) in 1993 found the two incretin hormones, glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP), to be substrates for this enzyme. At about the same time, in a published abstract, Buckley and Lundquist described degradation of GLP-1 by plasma and the resulting formation of an inactive metabolite truncated by the two NH_2-terminal residues (2). The latter authors also mentioned the use of bacitracin to prevent the degradation and the finding that analogs substituted with D-amino acids in positions 7 and 8 were resistant to the degradation. In our laboratory, the importance of these findings was quickly realized, and a thorough investigation of DPP-IV–mediated metabolism of GLP-1 in humans was initiated. We found that endogenous as well as exogenous GLP-1 was extensively degraded to the metabolite GLP-1(9-36) amide (3). An abstract by Grandt et al. (4) and subsequent studies by Bjerre-Knudsen and Pridal (5) and our own group (6) suggested that GLP-1(9-36) amide might, in fact, act as a GLP-1 receptor antagonist, acting not only on the pancreatic GLP-1 receptor, but also antagonizing the gastrointestinal effects of GLP-1 (6). In further studies (7), we demonstrated the extensive degradation of exogenous GLP-1 given intravenously or subcutaneously to patients with type 2 diabetes as well as control subjects. The degradation was particularly dramatic for subcutaneously administered GLP-1 (up to 90%; Fig. 1). Not only did this observation explain the ineffectiveness (short duration of action) of subcutaneously injected GLP-1 to normalize blood glucose in patients with type 2 diabetes (8), but it also formed the basis for the proposition (7) that "inhibition (of DPP-IV) may prove useful…in the management of type 2 diabetes, as has been the case for the development of angiotensin-converting enzyme inhibitors to treat hypertension and the suggested use of neutral endopeptidase inhibitors to enhance endogenous atrial natriuretic peptide activity in the treatment of heart failure. Inhibition of GLP-1(7-36) amide degradation would not only increase the availability of the biologically active peptide but would also reduce the effect of feedback antagonism at the level of the receptor." The use of GLP-1 analogs resistant to NH_2-terminal degradation was also suggested (7).

In further studies, we investigated the metabolism of GLP-1 in vivo in pigs and found that the half-life of the conversion
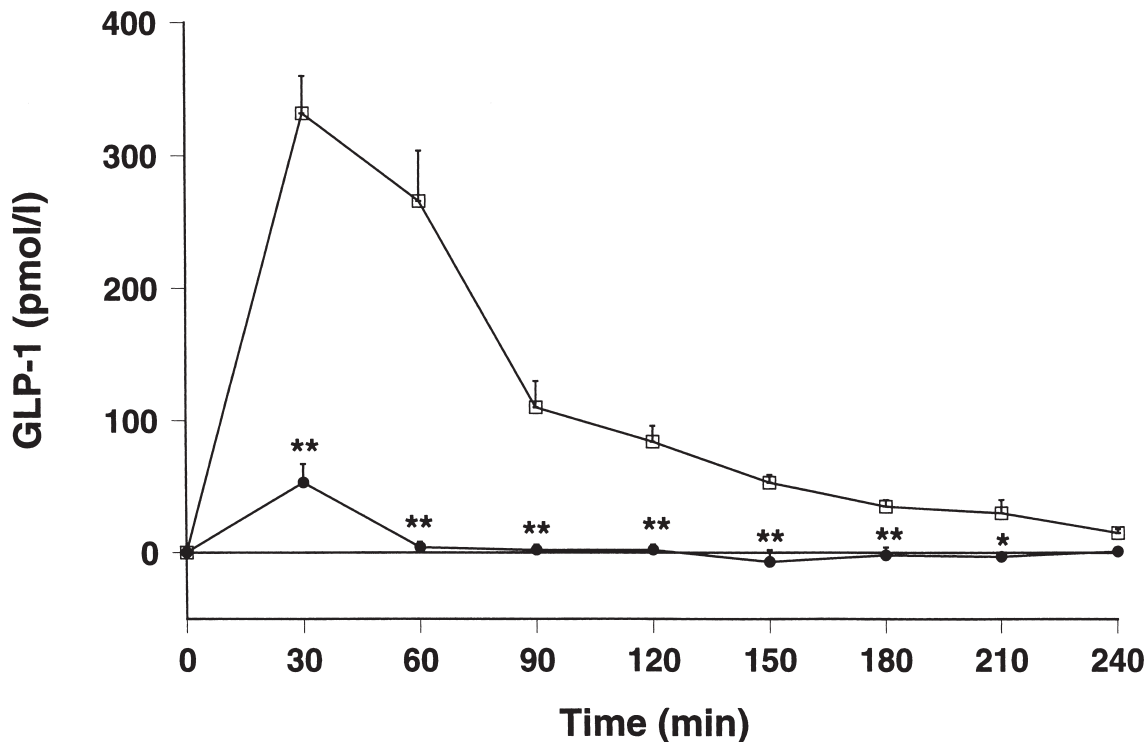
FIG. 1. Increase in plasma concentrations of total (□) and intact (●) GLP-1 after subtraction of endogenous levels and after subcutaneous administration of GLP-1(7-36) amide (1.5 nmol/kg) in type 2 diabetic subjects ($n = 8$). *$P < 0.05$; **$P < 0.001$.

of intact GLP-1 to its NH_2-terminally truncated metabolite was between 1 and 1.5 min (9) (whereas the half-life on incubation with plasma was 20–30 min). In fact, the clearance of GLP-1 exceeded cardiac output by a factor of 2. Thus, the peptide may be degraded before it reaches its presumed target organs. The metabolite, in turn, was eliminated from the circulation with a half-life of 4–5 min, mainly as a result of renal extraction. This value corresponds closely to the half-lives determined in previous investigations of GLP-1 metabolism, in which the NH_2-terminal metabolism was disregarded (10). We next demonstrated that analogs substituted at position 8 of GLP-1(7-36) amide (corresponding to position 2 of the actual peptide) could be designed to be largely resistant to the actions of DPP-IV, but retained a high affinity for the GLP-1 receptor; such analogs may therefore be useful clinically (11). We, finally, investigated in anesthetized pigs, the effects of inhibition of DPP-IV on the effects of infused GLP-1 using the specific inhibitor, val-pyrrolidide (12). With this inhibitor, it was possible to completely inhibit the NH_2-terminal degradation of GLP-1 (Fig. 2); simultaneously, the insulin response to glucose was greatly augmented. It was concluded that DPP-IV inhibition may "be a viable approach to the management of diabetes" (12). A number of recently published preliminary reports support this conclusion: Pauly et al. (13) reported that inhibition of DPP-IV by Ile-thiazolidide in rats augmented insulin responses to glucose and enhanced glucose clearance; Balkan and colleagues (14,15) made similar findings using a Sandoz inhibitor, SDZ 272-070, and also showed improved glucose tolerance in obese Zucker rats and in rats rendered insulin resistant by fat-enriched diets.

The purpose of this review is to discuss the potential clinical use of DPP-IV inhibition in view of the evidence available at present. In the following 11 points, the pros and cons of this approach will be discussed.

1. Side effects of DPP-IV inhibition. The side effects of DPP-IV inhibition are of paramount importance. DPP-IV is reported to act not only to degrade regulatory peptides with Pro or Ala in position 2 (1), but also to play an important role in the immune system. Thus in addition to its enzymatic actions, DPP-IV, as a membrane-associated molecule on the surface of T-cells (where it is also known as CD26), has a function in the immune system by contributing to T-cell activation and proliferation (16). Here, its role in transduction of activation signals is dependent on its interaction with other membrane-expressed antigens such as CD45 (17). Whether this function of DPP-IV/CD26 is dependent on its enzymatic activity has not yet been conclusively demonstrated. In studies using specific competitive and irreversible inhibitors, which block up to 95% of the enzymatic activity (18) or mutant CD26 molecules devoid of enzymatic activity (19), T-cell activation was unimpaired, suggesting that the enzymatic activity of the molecule was not required. However, another study using DPP-IV inhibitors indicated that the enzymatic activity was involved in the signal transduction cascade (20). Studies using mutant DPP-IV/CD26 molecules have indicated a role for the enzymatic activity in modulating the responsiveness of T-cells (21), while others have indicated that it is important but not essential for its co-stimulatory activity (22), and suggested that DPP-IV/CD26 functions to augment the cellular responses. It therefore appears that the immune functions of DPP-IV are largely
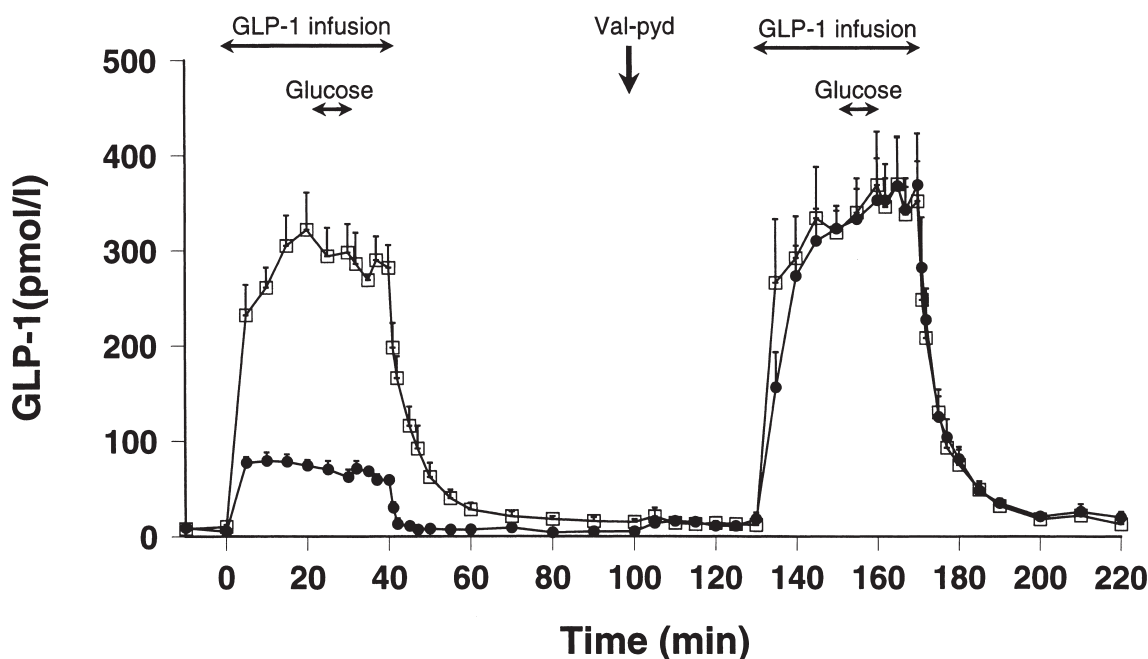
FIG. 2. Plasma concentrations of total (□) and intact (●) GLP-1 in blood sampled from the carotid artery of anesthetized pigs during intravenous infusions of GLP-1(7-36) amide (5 pmol · kg^{-1} · min^{-1}). Intravenous glucose (0.2 g/kg) was given during 21 min and 30 min of each GLP-1 infusion; a DPP-IV inhibitor (val-pyrrolidide; 300 μmol/kg) was given at 100 min.

independent of the catalytic site of its dipeptidase activity (23), so that blockade of this site with small molecule inhibitors should not compromise its immune functions. In agreement with this view, the already known DPP-IV inhibitors differ greatly with respect to their potencies as DPP-IV inhibitors and their effects on lymphocytes. Thus val-pyrrolidide, the inhibitor employed in some of the studies mentioned above, was reported to inhibit DPP-IV with an IC_{50} (the concentration causing 50% inhibition) of 6 μmol/l, whereas it caused <50% inhibition of mitogen-induced DNA synthesis in lymphocytes at the highest tested dose (5×10^{-4} mol/l) (24). To further support that DPP-IV does not have vital or irreplaceable functions, Fischer rats devoid of DPP-IV have been found to be completely viable and have a normal phenotype (also with respect to glucose tolerance [25]), and from studies of their T-cell activation (26), it was concluded that the presence of DPP-IV/CD26 was unnecessary. Upregulation of compensatory mechanisms caused by the inherent lack of DPP-IV in these animals cannot, however, be excluded. Thus, it will be necessary to conduct studies of prolonged DPP-IV inhibition, e.g., with already available compounds (several are reported in the literature) to investigate this. Notably, a compound with a half-life of 8 days (presumably the half-life of the enzyme) has been described (27). This compound may be particularly suitable for the study of long-term "side" effects.

As mentioned, a number of other regulatory peptides, including the duodenal incretin hormone, GIP, and two members of the pancreatic polypeptide (PP) family, peptide YY (PYY) and neuropeptide Y (NPY), are also substrates for DPP-IV (but not PP itself) (1,29). No studies have been conducted so far in which the protection of these hormones was determined. In DPP-IV–deficient Fischer rats, GIP levels

were reported to be reduced and pancreatic sensitivity to GIP decreased, perhaps as compensatory measures (25). Most likely, levels of intact GIP will increase on DPP-IV inhibition. Elevated levels of GIP may contribute to enhanced glucose tolerance (although presumably not in human type 2 diabetes, see below), and this "side effect" therefore, must be considered expedient.

On digestion with DPP-IV, the 36 amino acid peptides PYY and NPY generate NH_2-terminally truncated 3-36 metabolites (29). NPY is a neuropeptide and probably plays a limited role as a circulating peptide (see below). PYY, however, is a gut hormone, produced in the L-cells, the same cells that produce GLP-1. While GLP-1 stored in the L-cell almost exclusively consists of intact GLP-1 (28), about 40% of stored PYY is accounted for by PYY 3-36 (30), indicating that part of the truncated form found in plasma (30) is not generated by DPP-IV digestion in the circulation. And in contrast to the metabolite of GLP-1, PYY 3-36 is highly active, retaining full activity toward the Y2 receptors, but losing its effects on Y1 receptors (31). Some of the peripheral actions of PYY, which are mainly related to its functions as one of the hormones of the "ileal brake mechanism" (inhibition of upper gastrointestinal functions elicited by the presence of food in the distal small intestine [32–34]) seem to be mediated via Y2 receptors (35) but Y1 receptors may also be involved (36). Thus, the extent to which inhibition of DPP-IV increases the ratio of intact-to-truncated PYY in the circulation is difficult to predict, but will, if it occurs, cause a change toward activation of more Y1 and fewer Y2 receptors. However, the consequences of this change are also difficult to predict. Presumably, PYY-mediated regulation of gastrointestinal functions will be marginally affected, but perhaps other, mainly Y1 receptor-regulated

functions such as blood flow regulation, could be affected (34). In initial human studies of DPP-IV inhibition, careful blood pressure control will be required.

The hypothalamic peptide, growth hormone-releasing hormone (GRH), which is structurally related to GLP-1, is also a substrate for DPP-IV and is inactivated by digestion (37). However, DPP-IV–resistant analogs of GRH are rapidly degraded by enzymes other than DPP-IV (38), and it is uncertain whether inhibition of DPP-IV will affect the actions of GRH released to the pituitary portal circulation.

2. Long-term efficacy of the compound. Indeed, the very fact that the DPP-IV–deficient Fischer rats (25) seem completely unaffected might suggest that compensatory mechanisms may take over in DPP-IV–deficient animals. Similarly, other routes of GLP-1 degradation might be uncovered or induced during continuing DPP-IV inhibition. Thus, first, will GLP-1 degradation remain inhibited on long-term inhibitor administration? Second, will the effects of DPP-IV inhibition themselves show tachyphylaxis (i.e., will there be tachyphylaxis to the effects of an increased level of intact GLP-1)?

These questions cannot be answered presently, but must be investigated in long-term studies of DPP-IV inhibition. Again, such studies could be conducted in experimental animals using the available inhibitors such as val-pyrrolidide. With respect to tachyphylaxis to GLP-1, this important question has been addressed in a few studies of GLP-1 administration. In two studies in which GLP-1 was infused continuously for 7 days to patients with type 2 diabetes, there was no sign of tachyphylaxis with respect to its effects on glucose metabolism (39,40), and in a recent study the antidiabetic effect of a GLP-1 analog delivered by engineered cells transplanted into glucose-intolerant mice was preserved for the duration of the experiment (1 month) (41). However, no studies have addressed the question directly. In addition, there is evidence that the gastrointestinal effects of GLP-1 (see below) may show tachyphylaxis (42). It must be borne in mind, however, that development of tachyphylaxis may depend on the dosage scheme. The continued presence of elevated levels of (active) GLP-1 might promote tachyphylaxis as opposed to discontinuous therapy, although the relatively small increases in GLP-1 levels that may be obtained by DPP-IV inhibition may be less prone to cause tachyphylaxis.

3. Is it possible to protect endogenous GLP-1 from degradation? This essential question has not been addressed so far. DPP-IV–mediated degradation of GLP-1 is extensive, reflecting the widespread distribution of the enzyme, and occurs not only in plasma but also in numerous tissues, with, for example, the liver being one of the major sites for inactivation of the circulating peptide (9). In a recent study, we showed that, although GLP-1 in the gut is stored entirely in the intact form, 50% of the newly secreted peptide released from isolated perfused preparations of pig ileum was already degraded by the time it reached the local venous drainage (28). This degradation could be completely prevented by intraluminal or intravascular val-pyrrolidide (28). In our study of administration of the same compound to pigs in vivo (12), we found that degradation of GLP-1, secreted in the basal state, was greatly reduced (determined by comparison of levels of intact and total [intact + metabolite] GLP-1 with and without inhibitor; Fig. 2). However, the consequences for GLP-1 secretion in relation to meals have not been

investigated. Our prediction is that it will be possible to protect endogenous GLP-1 extensively from degradation.

4. Is full protection of endogenous GLP-1 enough to have a significant effect in type 2 diabetes? In our original study (3), levels of total GLP-1 increased from ~12.6 to 22.3 pmol/l postprandially. The levels of intact GLP-1 increased from 3.3 to 9.9 pmol/l; the difference was reasonably accounted for by the concentration of the metabolite. With a DPP-IV inhibitor, it could be predicted that all of the 12.6 and 22.3 pmol/l would occur as intact, biologically active peptide, a two- to fourfold increase. In addition, there would be no antagonist (9-36 amide) to antagonize the actions of GLP-1. In our experiments conducted in patients with type 2 diabetes, full normalization of blood glucose levels was obtained during intravenous infusion of GLP-1 at a rate of 1.2 pmol · kg^{-1} · min^{-1} (43). This infusion rate increases levels of intact GLP-1 to 15–20 pmol/l (7), and on top of this, there is a concentration of 80–100 pmol/l of the antagonistic metabolite. Thus, one would predict that DPP-IV inhibition might produce plasma levels of intact GLP-1 that would be large enough to significantly and unopposedly affect the target organs for GLP-1. The effect would be largest postprandially, but inspection of the 24-h profile for plasma GLP-1 (44) reveals that although there are clear meal-related increases, GLP levels remain elevated throughout the day, once the digestive processes are initiated by breakfast ingestion. In addition, there is evidence that even fasting subjects may have a small but significant secretion of GLP-1 ([3] and studies by Toft-Nielsen et al. [45], in which it was shown that the basal levels could actually be significantly suppressed by somatostatin infusion). The preliminary studies (13–15) cited earlier reveal that administration of DPP-IV inhibitors to glucose-intolerant rodents does in fact improve glucose tolerance (but, clearly, in these studies the responsible mechanism could not be deduced). Our prediction is that DPP-IV inhibition will have a significant effect.

5. What is the rationale for treating type 2 diabetes with increased availability of GLP-1? Or, in other words, why is it that the GLP-1 these patients produce cannot help their β-cells keep up insulin production? The answer to this question is twofold. First, there is now evidence that the secretion of GLP-1 is impaired in type 2 diabetes (M.-B. Toft-Nielsen, S. Madsbad, J.J.H., unpublished studies of meal-induced GLP-1 secretion in 55 patients with type 2 diabetes). The initial meal-induced increase seems to be the same, but the duration of the increase is markedly shorter. However, the deficient response does not seem to be responsible for diabetes, but rather to be a consequence of diabetes. This is because GLP-1 secretion is only slightly impaired in patients with impaired glucose tolerance and with a high probability for transition to overt diabetes (J. Lindqvist, J. Pigon, J.J.H., S. Efendic, unpublished observations) (if the GLP-1 deficiency had been a primary cause, one would have expected a similar impairment of secretion in prediabetes); indeed, in identical twins discordant for type 2 diabetes (at the time of investigation), GLP-1 secretion was impaired in the diabetic but less so in the glucose-tolerant twin (47). Thus, the decreased postprandial GLP-1 response in type 2 diabetes may aggravate the disease but does not cause the disease. More importantly, however, it seems that an important and perhaps primary defect in type 2 diabetes may be an impaired incretin function (i.e., little augmentation of insulin secretion after oral as compared with

intravenous glucose administration [48,49]). Furthermore, in the (rather few) patients with type 2 diabetes so far investigated for this, all had a greatly decreased or absent insulin response to the "other" incretin hormone, namely, GIP from the upper gut (49,50). The impaired incretin function is not due to impaired secretion of GIP. If anything, GIP levels are elevated in these patients (47,48), but it has been proposed that there may be defective expression of the GIP receptor (49). This is important because GIP is the "first-in-line" incretin; because GIP signaling is defective, meal-induced insulin secretion is also defective. This cannot be overcome with endogenous or exogenous GIP because the patients are insensitive to GIP, but it may be compensated for with GLP-1 (50). Thus GLP-1 treatment may be considered a substitution therapy that restores the defective incretin effect. This is probably the reason why GLP-1 treatment in itself is effective and shows little or no tachyphylaxis; a mere overdosing with one of the compounds that take part in the regulation of blood glucose presumably would have activated downregulatory mechanisms. At any rate, the defective GIP signaling in type 2 diabetes provides the rationale for a "substitution therapy" with GLP-1.

6. Will the antidiabetogenic effect of DPP-IV inhibition be similar to that of GLP-1 infused intravenously? As discussed above, the maximum levels of intact GLP-1 achieved by DPP-IV inhibition will correspond to those normally observed for "total GLP-1" (i.e., 20–30 pmol/l). On top of this comes absence of the antagonistic metabolite. However, it cannot be excluded that the higher levels of biologically active GLP-1 may negatively feed back on the GLP-1 cells to inhibit endogenous secretion (there is evidence that this may occur [51]). In patients with long-standing type 2 diabetes, intravenous GLP-1 is remarkably effective, in the sense that it is possible to completely normalize blood glucose even in patients with high fasting blood glucose values and little residual insulin secretory capacity, but in such patients the predominant mechanism of action is likely to be inhibition of hepatic glucose production, secondary to inhibition of glucagon secretion (43,52,53), and a similar glucose-lowering effect may be observed in C-peptide negative patients with type 1 diabetes (54). In such type 2 patients, the glucose-lowering effect of GLP-1 is a slow process, proceeding with a rate constant of ~0.27% per minute (as compared to 0.44% per minute in patients with greater insulin secretion) (53). These figures presumably reflect the fact that GLP-1 in itself has little effect on peripheral glucose disposal (45). Possibly, with low doses of GLP-1, this mechanism, although capable of lowering blood glucose in the fasting patients, may not be sufficient to also effectively dispose of dietary carbohydrates, resulting in inadequate blood glucose control on an average. With larger doses of GLP-1, it is likely that glucagon inhibition will be more extensive, and that gastrointestinal and satiety effects are more pronounced (see below). At any rate, with an infusion rate of 2.4 pmol · kg^{-1} · min^{-1}, a remarkable improvement of glycemic control may be achieved for up to 7 days in poorly controlled patients (40). With DPP-IV inhibition, the levels of intact GLP-1 that result from this infusion rate may not be attainable. Possibly, therefore, this therapeutic principle may be best applied to patients with some insulin secretory reserve, in whom the glucose-lowering effect results from a combination of reduced hepatic glucose production plus increased insulin-mediated glucose disposal. As noted above, in acute, preliminary studies, DPP-IV inhibition effectively

improved (oral) glucose tolerance in glucose-intolerant animals (with considerable insulin capacity [13–15]). This raises the question of whether all of the effect is, in fact, due to protection of endogenous GLP-1 (because oral glucose is a rather weak stimulus for GLP-1 secretion). As noted above, the other incretin hormone, GIP, may also be protected, and its effects are therefore enhanced; in addition, elevated levels of the "ileal-brake" hormone, PYY, may dampen postprandial glucose excursions. However, in this context, this lack of specificity of DPP-IV inhibition must be considered expedient.

7. Is the compound intrinsically safe? With this, we think of the toxicology of the compound (i.e., side effects apart from those due to DPP-IV inhibition). We will have to consider that the patients likely to benefit from a DPP-IV inhibitor will have to take the drug every day for several decades of their lifetime. Any side effect will probably seriously limit the usefulness of the compound. On the other hand, if a nontoxic compound can be developed, it is likely to have a vast applicability. In view of the fact that efficient and apparently nontoxic inhibitors already exist, such compounds would seem fairly easy to develop. In fact, a nontoxic, orally active compound with reasonable pharmacokinetics (see below) might actually make one of the greatest dreams of the diabetologist to come true: it might prevent the transition from impaired glucose tolerance to overt type 2 diabetes. This is because elevated levels of active GLP-1 would be expected to restore the (mild) incretin deficiency (discussed above) and normalize completely glucose levels (as shown in the first animal studies). The lowered glucose levels would then remove the demand on the β-cell thereby reducing insulin secretion, which together would lead to normalization of insulin sensitivity. All of these plus perhaps specific direct effects of GLP-1 might result in promoted growth and survival of the β-cells (55–57). It could be envisaged that the drug could be given to patients discovered by population screening in the 40–70 age-group, having borderline elevations of fasting blood glucose (perhaps as low as 5.9 mmol/l). Oral glucose tolerance tests may also be carried out on a screening basis, leading to the identification of individuals with impaired glucose tolerance and perhaps a family history of type 2 diabetes. Since the treatment can be predicted to have little effect unless blood glucose is truly elevated (GLP-1 has very little effect in subjects with normal glucose levels regardless of dose because its actions are glucose dependent [58]) and because it should be nontoxic, over-treatment would be expected to have inconspicuous negative effects (except perhaps for hypothetically causing an increased tendency to postprandial reactive hypoglycemia, see below). On the contrary, treatment might still have beneficial effects on body weight (see below).

This new principle of diabetes treatment should be viewed under the perspective that ~50% of patients with type 2 diabetes have irreparable complications at the time of diagnosis. It is generally assumed that the complications are due to long-standing disturbances of glucose metabolism. If it were possible to improve glucose metabolism at an earlier stage, it might be possible to reduce the prevalence of complications. In addition, the existence of an efficient treatment of early impaired glucose metabolism with few or no side effects would be an incentive for general practitioners to try to identify such cases among their patients at a much earlier stage. Thus with DPP-IV inhibitor, it may be possible to prevent or delay type 2 diabetes and its complications.

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