2. DPPIV Inhibition: Promising Therapy for the Treatment of Type 2 Diabetes

PAUL E. WIEDEMAN

Abbott Laboratories, Department R4CP, Building AP9B, 100 Abbott Park Road, Abbott Park, IL 60064-6113, USA

Progress in Medicinal Chemistry – Vol. 45 63
Edited by F.D. King and G. Lawton
DOI: 10.1016/S0079-6468(06)45502-8

INTRODUCTION

TYPE 2 DIABETES PANDEMIC

Diabetes is a major health problem encountered across the globe. Nearly 200 million individuals worldwide suffer from diabetes of which 90–95% are type 2 diabetics [1]. Some staggering figures include India, home to 35.5 million diabetics, China with 23.8 million, the United States with 16 million, Russia with 9.7 million and Japan with 6.7 million. The incidence of diabetes has not peaked. By 2025, the diabetic population of Africa, the Eastern Mediterranean, the Middle East and Southeast Asia is expected to increase by 100%. Rises are anticipated in other regions as well, including Central and South America (85%), the Western Pacific (75%), North America (50%) and Europe (20%). Already diabetes is the fourth main cause of mortality in the majority of developed countries. Healthcare systems will certainly be strained to meet the growing demand of this pandemic, as even now 50% of patients are undiagnosed. The growing diabetic population requires additional therapies with alternative mechanisms of action and improved tolerability. There are currently five main classes of oral antidiabetics, each limited in one way or other by the degree of efficacy and side effects [2]. Concerns with sulfonylureas centre on hypoglycemia and weight gain. Non-sulfonylurea secretagogues have the same issues along with a more complex dosing schedule. Patients on thiazolidinediones are prone to weight gain and oedema. Biguanides and α-glucosidase inhibitors often produce significant gastrointestinal distress. Inhibition of dipeptidyl peptidase IV (DPPIV) cleavage of glucagon-like peptide-1 (GLP-1) is a highly validated target for the treatment of type 2 diabetes. Several DPPIV inhibitors are in clinical development, and the first requests for regulatory review have been filed. The reported clinical data have established proof of concept in man, confirming the possibility that DPPIV inhibitors will be the next major new class of oral antidiabetic drug.

INHIBITION OF DPPIV AS A STRATEGY TO ENHANCE THE INCRETIN EFFECT

The phenomenon of increased insulin secretion following oral administration of glucose compared to intravenous administration is known as the incretin effect. An agent responsible for this effect is the incretin hormone, GLP-1. In response to the oral ingestion of nutrients, proglucagon is processed and GLP-1 is released from enteroendocrine L-cells in the distal small intestine and colon. Binding of GLP-1 to its G-protein-coupled receptor on pancreatic β-cells increases glucose-stimulated insulin secretion [3, 4]. Additional desirable effects of GLP-1 include increased insulin gene

expression [5], and increased pancreatic β-cell proliferation and islet neogenesis [6]. By contrast and also of benefit are the inhibition of glucagon secretion [7, 8] and decreased gastric emptying that results in the slowed rate of nutrient absorption [9,10]. GLP-1 receptors are also expressed in hypothalamic nuclei responsible for modulating feeding behaviour, and peripheral administration of GLP-1 promotes satiety and inhibits food intake in man [11, 12]. In total these effects demonstrate that GLP-1 (7–36) amide has multiple biological effects that contribute to glucose homeostasis and promotes normalization of post-meal glucose levels. It is important to recognize that GLP-1 augments insulin secretion in a glucose-dependent manner. Unlike sulfonylurea drugs or insulin, enhancing endogenous GLP-1 levels does not increase the risk of hypoglycemia.

Infusion of active GLP-1 and GLP-1 (7–36) amide reduces post-meal and fasting glycemia in patients with non-insulin-dependent diabetes mellitus; thus establishing the potential of GLP-1-based therapy for the treatment of type 2 diabetes [13–15]. This effect occurs despite a blunting of the incretin effect in type 2 diabetics [16]. The key problem, however, is that active GLP-1 (7–36) amide is rapidly converted to inactive GLP-1 (9–36) amide by the action of DPPIV via the cleavage of the N-terminal dipeptide (His-Ala) of GLP-1 (7–36) amide [17, 18]. The short half-life of GLP-1 (7–36) amide in the circulation (<2 min) makes it impractical as a therapeutic agent and has led to the development of alternative strategies to enhance the anti-diabetogenic activity of GLP-1. One successful approach that will not be covered in this chapter is the development of GLP-1 receptor agonists that are resistant to DPPIV cleavage [19]. This approach remains an active area of research and development [20]. Exenatide (Byetta) is the first marketed GLP-1 receptor agonist. It is effective in reducing glycosylated haemoglobin, HbA_{1c} (biomarker for glycemic control) levels in type 2 diabetics but is a twice-a-day injectable peptide with nausea as a prominent side effect [21]. Another strategy that is the focus of this chapter is to increase the circulating half-life of endogenous GLP-1 by inhibiting its enzymatic degradation by DPPIV [17] (Fig. 2.1).

Another incretin hormone, glucose-dependent insulinotropic polypeptide (GIP), is also degraded by DPPIV [18]. Similar to GLP-1, GIP is a 42-amino acid peptide secreted by endocrine K cells of the duodenum in response to ingestion of nutrients [22]. The physiological actions of GIP include glucose-dependent potentiation of insulin secretion and regulation of insulin gene transcription. In contrast to GLP-1, glucose tolerance is not improved in type 2 diabetics treated with exogenous GIP [23]. However, it has been reported that the response to GIP improves in diabetic patients treated with glyburide to reduce fasting glucose levels [22]. Studies with hyperglycemic diabetic rats or normal rats made hyperglycemic by glucose clamp have

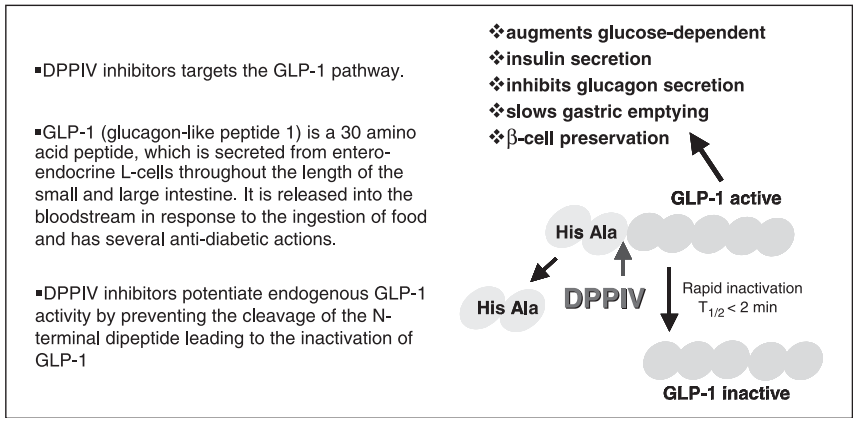

Fig. 2.1 Inhibition of DPPIV sustains endogenous GLP-1 and modulates the incretin effect.

decreased expression of pancreatic GIP receptor, which in turn causes a loss of insulinotropic response to GIP [24]. Taken together, these data support the notion that the initial effect of DPPIV inhibition in human diabetes is primarily by GLP-1, but raises the possibility that in the long run, when glucose levels fall, treatment with DPPIV inhibitors could also improve the insulinotropic action of GIP.

DIPEPTIDYL PEPTIDASE IV

DPPIV (EC 3.4.14.5; also known as lymphocyte cell surface protein CD26) was first described in 1967 [25]. DPPIV is a post-proline cleaving serine protease with a catalytic triad of Ser-Asp-His oriented inversely to classical serine proteases and with significant homology to other α,β-hydroxylases. DPPIV is expressed as a 110 kDa glycoprotein on the surface of cells of most tissues including kidney, liver, intestine, placenta, prostate, skin, lymphocytes and endothelial cells. DPPIV is catalytically active as a dimer. Proteolytic cleavage of DPPIV from cell surfaces results in a soluble circulating form with a monomeric mass of approximately 100 kDa. In addition to cleaving GLP-1, DPPIV may play a role in the cleavage of other substrates with accessible amino-terminal Xaa-Pro- or Xaa-Ala-dipeptide sequences, resulting in their inactivation or alteration in their biological activities. Potential DPPIV substrates include growth hormone releasing hormone, GIP, pituitary adenylate cyclase-activating polypeptide 38 (PACAP38), substance P, bradykinin, gastrin releasing peptide, neuropeptide Y, peptide YY,

certain chemokines such as RANTES (regulated on activation normal T cell expressed and secreted), stromal cell-derived factor, eotaxin and macrophage-derived chemokines [26]. Long-term safety concerns have arisen because these possible DPPIV substrates include chemokines, vasoactive peptides, neuropeptides and gastrointestinal peptides. Despite *in vitro* cleavage of these peptides by DPPIV, many of the activities associated with these peptides appear not to be physiologically regulated *in vivo* by DPPIV action. Those that appear to be regulated by DPPIV peptidase activity are described below.

GLP-1 and GIP have been validated as *in vivo* substrates of DPPIV in DPPIV knockout (DPPIV KO) mice and DPPIV-deficient Fisher rats [27, 28]. The importance of GLP-1 and GIP in the gluco-regulatory action of DPPIV inhibitors has been shown in double incretin receptor (i.e., GLP-1R and GIPR) knockout mice where the glucose-lowering effect of DPPIV inhibitors is abolished [29]. DPPIV-deficient mice are healthy, have normal blood glucose levels in the fasted state but reduced glucose excursion after a glucose challenge [27]. The active, insulinotropic form of GLP-1 and glucose-dependent insulin levels are both increased in DPPIV KO mice compared to wild-type littermates. Similarly, DPPIV-deficient Fisher rats have a phenotype of improved glucose tolerance and enhanced glucose-dependent insulin secretion [28].

Similarly, PACAP38 has been validated as an additional target of *in vivo* DPPIV peptidase activity. PACAP38 is a neuropeptide that is involved with signalling to pancreatic nerves and is therefore associated with neural regulation of islet function. Preservation of endogenous levels of PACAP38 with a DPPIV inhibitor may be an additional way that the inhibitors enhance antidiabetic effects. PACAP38 was administered exogenously to both wild-type and DPPIV-deficient mice [30]. In the DPPIV-deficient mice, the rate of PACAP38 clearance was reduced and little of the DPPIV metabolite, PACAP(3–38) was observed. In another study in mice, PACAP38 was administered intravenously with glucose following previous administration of a DPPIV inhibitor [31]. As was observed in the same study with GLP-1, the PACAP38-treated animals showed increased insulin levels and a greater rate of glucose elimination.

Although DPPIV clearly regulates GLP-1 (and probably GIP and PACAP38) action *in vivo*, the DPPIV enzyme may have a broader role in metabolic control. In this regard, DPPIV KO mice show resistance to diet-induced obesity with a concomitant reduction in adiposity compared to wild-type mice [32]. Consequently, long-term inhibition of DPPIV may have the potential to decrease the body weight. However, DPPIV inhibitors currently in clinical development have not demonstrated weight reduction, but several trials have shown weight neutrality.

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