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Inhibition of dipeptidyl peptidase IV activity as a therapy of Type 2 diabetes

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Dipeptidyl peptidase IV (DPP IV) is a ubiquitous, multifunctional, serine protease enzyme and receptor with roles in the control of endocrine and immune function, cell metabolism, growth and adhesion. As an enzyme, DPP IV cleaves the N-terminal dipeptide from the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. This inactivates the hormones, thereby cancelling their prandial insulinotropic effect. One approach to restore incretin activity as a therapy for Type 2 diabetes has been the development of DPP IV inhibitors. Inhibitors of DPP IV have shown efficacy and tolerability when used to control the hyperglycaemia of non-insulin-dependent animal models and human Type 2 diabetes. These DPP IV inhibitors prolong active incretin hormone concentrations and may exert additional antidiabetic effects. If long-term clinical trials confirm sustained and safe control of blood glucose, DPP IV inhibitors (known as 'gliptins') may be expected to provide a new treatment modality for Type 2 diabetes.

Keywords: diabetes, dipeptidyl peptidase IV, incretin hormones

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1. Introduction

The concept of dipeptidyl peptidase IV (DPP IV) inhibitors arose through improvements in our understanding of the physiological inactivation of incretin hormones. The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are sister hormones that potentiate postprandial insulin secretion and glucose clearance [1]. These peptides have pleiotropic effects on a range of tissues. Key actions, shown in Table 1, include the stimulation of insulin release from the pancreas [2], reduction of hepatic insulin clearance [3] and insulin-like effects on skeletal muscle [4-6], liver [7] and adipose tissue [8-11], which serve to promote glucose uptake and metabolism. GLP-1 and GIP have beneficial actions on the pancreatic β-cell, such as expansion of cell mass and increased cell survival [12].

The primary amino acid sequence of GLP-1 and GIP reveals a highly conserved alanine penultimate to the N-terminus, thus making these peptides ideal putative substrates for DPP IV (Figure 1). The major metabolites generated by DPP IV processing of GLP-1 and GIP, namely GLP-1(9-36)amide and GIP(3-42), respectively, retain the ability to bind to their specific receptors, but are rendered non-insulinotropic (Figure 2) [13-16]. The action of ubiquitous DPP IV reduces the half-life *in vivo* of GLP-1 and GIP to < 2 min [13,17,18]. The timing of these findings coincided with other observations that demonstrated the therapeutic potential of incretin hormones in relation to Type 2 diabetes [2]. Therefore, two strategies were conceived to harness the antidiabetic potential of incretin hormones. Initially came the development of analogues of GLP-1 and GIP resistant to DPP IV (see recent reviews [1,19]), and thereafter came the development of inhibitors of DPP IV. It is the

Table 1. Overview of functional characteristics of GLP-1 and GIP.

	GLP-1	GIP
Released in response to a mixed meal	√	√
Lower blood glucose	√	√
Glucose-dependent stimulation of insulin secretion	√	√
Suppress glucagon secretion	√	-
Enhance β-cell survival	√	√
Stimulate β-cell expansion	√	√
Extrapancreatic glucose-lowering actions	√	√
Suppress gastric acid secretion	-	√
Inhibition of gastric emptying	√	-
Inhibition of hepatic insulin extraction	√	√
Enhance satiety	√	-
Reduce body weight	√	-

√: Yes; -: Effect uncertain; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1.

aim of this review to summarise the most recent and important advances in the development of DPP IV inhibitors as a new drug class for the treatment of Type 2 diabetes [20,21]. In particular, how the recent discovery of several DPP IV-related proline specific peptidases has prompted a re-evaluation of DPP IV inhibitors and their degree of selectivity is discussed.

2. Background

2.1 Type 2 diabetes

Type 2 diabetes represents ~ 90% of all cases of diabetes and is characterised by two main defects: i) impairment of pancreatic β-cell function, and ii) impairment of insulin sensitivity of muscle, adipose tissue and liver. Ideally, future treatment strategies should seek to address both of these defects, as well as the resultant hyperglycaemia [22,23]. Type 2 diabetes is a major debilitating illness throughout the world and resulting complications place a growing burden on healthcare budgets.

2.2 DPP IV and related enzymes

Despite the vast array of different proteases found physiologically, few can cleave the peptide bond following a proline amino acid residue. Fewer still can cleave this bond when it is located just two positions from the N-terminus. Serine proteases that carry out this specific cleavage function are termed the 'postproline dipeptidyl aminopeptidases'. Many of these proteases belong to the DPP IV gene family. The family of enzymes related to DPP IV comprise: i) DPP IV, ii) fibroblast activation protein (FAP), iii) DPP 8, iv) DPP 9 and v) DPP II, also known as DPP 7 or quiescent cell proline dipeptidase (QPP) [24]. DPP IV is usually identified by its postproline aminopeptidase activity, that is, its ability to preferentially cleave Xaa-Pro or Xaa-Ala dipeptides from the N-terminus of polypeptides (where Xaa is any amino acid except Pro).

2.2.1 *DPP IV (EC 3.4.14.5)*

DPP IV doubles as the cell-surface CD26 T-cell-activating antigen and is expressed in almost all organs and tissues [25]. In humans it is strongly expressed in the exocrine pancreas, kidney, gastrointestinal tract, biliary tract, thymus, lymph nodes, uterus, placenta, prostate, adrenal, sweat glands, salivary and mammary glands. It is also found on endothelia of all organs examined, including spleen, lungs, brain and vessels supplying the liver [26]. In addition to being a cell-surface ectoenzyme anchored to the plasma membrane, DPP IV is found solubilised in body fluids such as blood plasma and cerebrospinal fluid. The distribution of DPP IV activity gives it ready access to endocrine peptides, neuropeptides and a wide range of paracrine and autocrine peptides and polypeptides.

2.2.2 *FAP*

FAP is a type II membrane-bound serine protease with 52% similarity to DPP IV. There has been speculation that FAP could be involved in wound healing as well as tumour growth and proliferation. It has also been linked with liver injury and chronic liver disease [27,28]. FAP is capable of dipeptidyl peptidase activity to cleave N-terminal dipeptides from polypeptides, and collagenolytic activity that can degrade gelatin and type I collagen [29]. A common active site in FAP is used for both functions [29]. Immunopurified recombinant FAP possesses DPP IV-like activity, as demonstrated by its ability to cleave an Ala-Pro-NH F_3 Mec substrate [27]. FAP does not appear to be as ubiquitously expressed as other members of the DPP IV enzyme family, but has been found in serum and the α-cells of the pancreas [28].

2.2.3 *DPP 8 and 9*

DPP 8 and 9 are soluble postproline cleaving dipeptidases localised in the cytoplasm. Although DPP 8 and 9 share ~ 50% amino acid similarity to human DPP IV, they appear

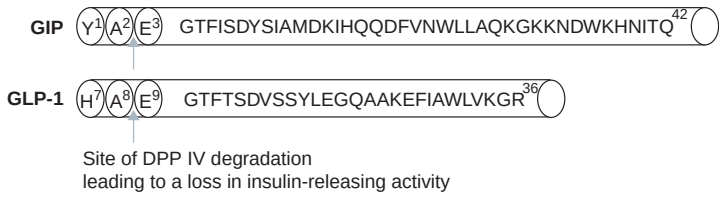

Figure 1. Degradation of incretin hormones by DPP IV. Incretins GLP-1 and GIP possess a highly conserved alanine amino acid residue penultimate to the N-terminus, making them ideal putative substrates for DPP IV. His^7-Ala^8 and Tyr^1-Ala^2 dipeptides are removed from GLP-1 and GIP, respectively, leading to noninsulinotropic metabolites GLP-1(9-36)amide and GIP(3-42).
DPP IV: Dipeptidyl peptidase IV; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1.

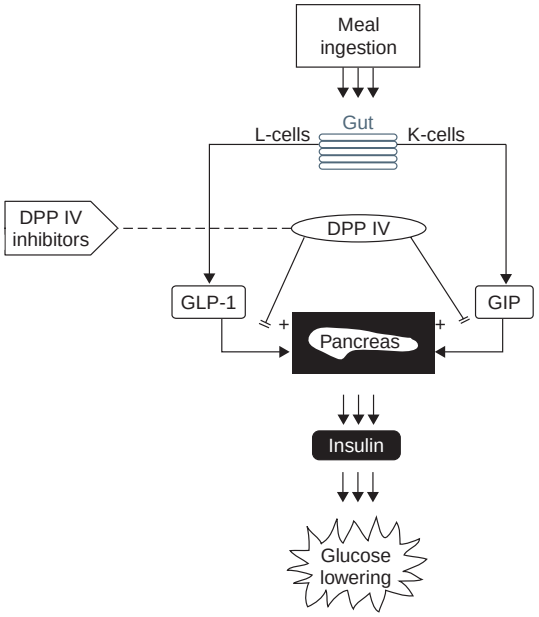

Figure 2. DPP IV inhibitor mode of action. The incretin hormones GLP-1 and GIP, released from the L- and K-cells of the intestine, stimulate insulin release from the pancreas, leading to lower plasma glucose concentrations. However, enzymatic cleavage by ubiquitous DPP IV renders them noninsulinotropic. DPP IV inhibitors prevent processing by DPP IV and, therefore, improve incretin-stimulated insulin release and glucose lowering.
DPP IV: Dipeptidyl peptidase IV;
GIP: Glucose-dependent insulinotropic polypeptide;
GLP-1: Glucagon-like peptide-1.

to be more closely related to each other (~ 76% similarity) [30]. They are widely distributed in human tissues, but have not yet been associated with any particular biological process. DPP 8 and 9 are active as monomers and hydrolyse H-Ala-Pro- and H-Gly-Pro-derived substrates [28]. It remains a distinct possibility that many of the functions ascribed to DPP IV may actually be derived from the activity of DPP 8 and/or 9. The recent discovery of DPP 8 and 9 has had major implications for the specificity of DPP IV inhibitors, to avoid inhibition of DPP 8 and 9.

2.2.4 *DPP II (DPP 7 or QPP) (E.C. 3.4.14.2)*

DPP II was originally referred to as dipeptidyl aminopeptidase II [31] and its activity was detected by the hydrolysis of Lys-Ala-derived chromogenic or fluorogenic substrates at acidic pH. DPP II activity has been detected in a range of mammalian tissues [32]. Recent evidence has strongly indicated that DPP II, DPP 7 and QPP are not different enzymes, but in fact the same enzyme with three different names in the literature [32,33]. Although only a few compounds have been discovered with an inhibitory effect on DPP II activity, they were all originally described as DPP IV inhibitors. Compounds such as Val-boro-Pro and Ala-Pyrr-2-CN, as well as aminoacyl pyrrolidines and thiazolidine derivatives actually have a higher potency towards DPP IV [34-36]. There are two compounds, Ala-ψ[CS-N]-Pyrr and Ala-ψ[CS-N]-Thia, with more selectivity towards DPP II than DPP IV [37].

2.3 Natural substrates of DPP IV enzyme activity

Table 2 lists examples of the extensive range of physiological regulatory peptides identified as substrates or potential substrates of DPP IV. All of these peptides have either Ala, Pro or Ser penultimate to the N-terminus. It is evident that DPP IV acts on several chemokines that affect the immune system. Chemokine substrates of DPP IV include RANTES, eotaxin, interferon-γ-inducible protein-10, monocyte chemotactic protein (MCP)-1, -2 and -3, stromal cell-derived factor-1α and -β, granulocyte chemotactic protein-2 and macrophage-derived chemokine (see Table 2) [25]. By altering chemokine activity, DPP IV can modify specificity for, and ability to activate, immune receptors. For example, the peptide RANTES(1-68), which is chemotactic for lymphocytes, monocytes, dendritic cells, eosinophils, basophils and NK cells, is truncated to RANTES(3-68) by DPP IV. RANTES(3-68) is unable to increase cytosolic calcium levels and induce chemotaxis in human monocytes [38]. Furthermore, RANTES(3-68) antagonises the chemotactic effects of RANTES(1-68) and other chemotactic proteins

Table 2. Physiological regulatory peptides identified as substrates of DPP IV

Peptide	N-terminus	Reference
GLP-1 (7-36)amide	His-Ala-Glu-	[101]
GLP-1 (7-37)	His-Ala-Glu-	[101]
GLP-2 (1-33)	His-Ala-Asp-	[102]
GIP (1-42)	Tyr-Ala-Asp-	[101]
GHRH	Tyr-Ala-Glu-	[101]
GHRH (1-29)	Tyr-Ala-Asp-	[103]
GHRH (1-44)	Tyr-Ala-Asp-	[101]
Peptide histidine methionine	His-Ala-Asp-	[101]
PACAP (1-27)	His-Ser-Asp-	[44-46]
PACAP (1-38)	His-Ser-Asp-	[44-46]
Gastrin-releasing peptide	Val-Pro-Leu-	[104]
Substance P	Arg-Pro-Lys-	[104]
Insulin-like growth factor-1	Gly-Pro-Glu-	[25]
Bradykinin	Arg-Pro-Pro-	[105]
Neuropeptide Y	Tyr-Pro-Ser-	[106]
Peptide YY (1-36)	Tyr-Pro-Ile-	[106]
Prolactin	Thr-Pro-Val-	[104]
Human chorionic gonadotropin-α	Ala-Pro-Asp-	[104]
Luteinising hormone α-chain	Phe-Pro-Asn-	[25]
Thyrotropin-α	Phe-Pro-Asp-	[25]
Enkephalins	Tyr-Pro-Val-	[107]
Vasostatin-1	Leu-Pro-Val-	[108]
Trypsinogen	Phe-Pro-Thr-	[104]
Trypsinogen propeptide	Phe-Pro-Thr-	[104]
Procolipase	Val-Pro-Asp-	[104]
IL-2	Ala-Pro-Thr-	[104]
IL-1β	Ala-Pro-Val-	[109]
α_1-Microglobulin	Gly-Pro-Val-	[104]
Tyr-melanostatin	Tyr-Pro-Leu-	[104]
Endomorphin-2	Tyr-Pro-Phe-	[110]
Enterostatin	Val-Pro-Asp-	[111]
β-Casomorphin	Tyr-Pro-Phe-	[104]
Corticotropin-like intermediate lobe peptide	Arg-Pro-Val-	[104]
Aprotinin	Arg-Pro-Asp-	[104]
RANTES	Ser-Pro-Tyr-	[112]
Granulocyte chemotactic protein-2	Gly-Pro-Val-	[38]
SDF-1α	Lys-Pro-Val-	[113]
SDF-1β	Lys-Pro-Val-	[113]
Macrophage-derived chemokine	Gly-Pro-Tyr-	[114]
MCP-1	Glu-Pro-Asp-	[38]
MCP-2	Glu-Pro-Asp-	[112]

DPP IV: Dipeptidyl peptidase IV; GHRH: Growth hormone-releasing hormone; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1; MCP: Monocyte chemotactic protein; PACAP: Pituitary adenylyl cyclase-activating peptide; SDF: Stromal cell-derived factor.

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