Can J Diabetes 38 (2014) 473–479

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Review

Emerging Roles of Dipeptidyl Peptidase 4 Inhibitors: Anti-Inflammatory and Immunomodulatory Effect and Its Application in Diabetes Mellitus

Lin Yang MD, Jiao Yuan BD, Zhiguang Zhou MD, PhD *

Diabetes Centre, Institute of Metabolism and Endocrinology, The Second Xiangya Hospital and Key Laboratory of Diabetes Immunology, Ministry of Education, Central South University, Changsha, China

ARTICLE INFO

Article history:
Received 14 October 2013
Received in revised form
5 January 2014
Accepted 19 January 2014

Keywords:
anti-inflammatory
DPP4 inhibitors
immunomodulatory
type 1 diabetes
type 2 diabetes

Mots clés :
anti-inflammatoire
inhibiteurs de la DPP-4
immunomodulatoire
diabète de type 1
diabète de type 2

ABSTRACT

Dipeptidyl peptidase 4 (DPP4) inhibitors have been widely used in the treatment of type 2 diabetes mellitus. It is well known that DPP4 inhibitors exert their antidiabetes effects mainly by inhibiting the enzymatic degradation of glucagon-like peptide-1 and glucose-dependent insulinotropic peptide. The anti-inflammatory effect of DPP4 inhibitors was proved by preclinical and clinical studies of type 2 diabetes and coronary artery disease. Preclinical data using DPP4 inhibitors-based therapies in studies of nonobese diabetic mice demonstrated additional effects, including immunomodulation, preserving beta-cell mass, promoting beta-cell regeneration and reversing newly diagnosed diabetes. Thus, these data show that DPP4 inhibitors may be effective for type 1 diabetes mellitus. However, their potential clinical benefits for type 1 diabetes remain to be evaluated. This paper will provide an overview of the progress of the anti-inflammatory and immunomodulatory effects of DPP4 inhibitors in treating both type 1 and type 2 diabetes.

RÉSUMÉ

Les inhibiteurs de la dipeptidyl-peptidase-4 (DPP-4) ont été grandement utilisés dans le traitement du diabète sucré de type 2. On sait que les inhibiteurs de la DPP-4 exercent principalement leurs effets antidiabétiques en inhibant la dégradation enzymatique du GLP-1 (*glucagon-like peptide -1*) et du GIP (*glucose-dependent insulinotropic peptide*). L'effet anti-inflammatoire des inhibiteurs de la DPP-4 a été prouvé par des études précliniques et cliniques sur le diabète de type 2 et la coronaropathie. Les données précliniques sur les traitements par inhibiteurs de la DPP-4 qui ont été obtenues au cours d'études sur des souris diabétiques non obèses ont démontré des effets supplémentaires, dont l'immunomodulation, la préservation de la masse des cellules bêta, la stimulation de la régénération des cellules bêta et l'inversion du diabète nouvellement diagnostiqué. Par conséquent, ces données montrent que les inhibiteurs de la DPP-4 peuvent être efficaces contre le diabète sucré de type 1. Cependant, leurs bienfaits cliniques potentiels sur le diabète de type 1 restent à évaluer. Cet article donne un aperçu des progrès réalisés en ce qui a trait aux effets anti-inflammatoires et immunomodulatoires des inhibiteurs de la DPP-4 dans le traitement du diabète de type 1 et du diabète de type 2.

Introduction

Dipeptidyl peptidase 4 (DPP4) also known as CD26, is a 110-kD cell surface type II transmembrane protein. It possesses serine protease activity and co-stimulatory function for the immune system (1,2). DPP4 was initially identified as a therapeutic target for type 2 diabetes owing to its degradation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). After a meal, these incretins could regulate blood glucose levels by stimulating insulin release, delaying gastrointestinal emptying, inducing satiety, decreasing glucagon release and preserving beta-cell mass (3,4). Sitagliptin was first granted approval for the treatment of type 2 diabetes as a selective DPP4 inhibitor in 2006 (5). Since then, a series of selective DPP4 inhibitors have been developed and granted approval (Table 1). In addition to their anti-diabetes action, DPP4 inhibitors have also shown many other

Lin Yang and Jiao Yuan contributed equally to the paper.

* Address for correspondence: Zhiguang Zhou, MD, PhD, Middle Ren-Min Road, No. 139, Changsha 410011, China.
E-mail address: zhouzg@hotmail.com

1499-2671/$ – see front matter © 2014 Canadian Diabetes Association
http://dx.doi.org/10.1016/j.jcjd.2014.01.008

Table 1
Dipeptidyl peptidase 4 inhibitors as therapy for type 2 diabetes mellitus

Generic name (trade name)	Company	Active compound code	Recommended dosage	Current status
Sitagliptin phosphate (Januvia)	Merck	MK-0431	100 mg qd	Approved in >40 countries, including USA, Europe and China
Vildagliptin (Galvus)	Novartis	LAF-237(NVP-LAF-237)	50 mg bid	Approved in Europe and China
Saxagliptin (Onglyza)	Bristol-Myers Squibb and Astra Zeneca	BMS-477118	5 mg qd	Approved in Europe, USA and China
Alogliptin (Nesina)	Takeda Pharmaceuticals	SYR-322	25 mg qd	Approved in USA and Japan
Linagliptin (Trajenta)	Boehringer Ingelheim	BI-1356	5 mg qd	Approved in USA
Gemigliptin (Zemiglo)	LG Life Sciences	LC15-0444	50 mg qd	Approved in Korea
Teneligliptin (Tenelia)	Mitsubishi Tanabe	MP-513	20 mg qd	Approved in Japan
Anagliptin (Suiny)	Sanwa kagaku kenkyusho	SK-0403	100 mg bid	Approved in Japan
Dutogliptin tartrate (Newlystar)	Phenom ix Corp	PHX-1149	200 mg bid	Phase III clinical trial
Denagliptin (stopping development)	Glaxo Smith Kline	GSK-823093		Phase III clinical trial
	Novartis	NVP-DPP728		Phase II clinical trial
	Dong-A	DA-1229		

bid, twice a day; *qd*, Every day.

benefits, such as anti-inflammation (1,5) and cardiovascular protective effect (1,6). More excitingly, evidence also suggests their potential immunomodulatory effect in animal experiments and that would seem to have therapeutic benefits for patients with type 1 diabetes (7–10).

Physiological function of DPP4

DPP4 is a 766-amino-acid membrane protein that belongs to a family of homologous enzymes that cleave N-terminal dipeptides from proteins containing proline (Pro) or alanine (Ala) in the penultimate position (11). It exerts noncatalytic functions by binding to contiguous proteins on the cell membrane or in the extracellular matrix (2). DPP4 is widely expressed (lung, brain, pancreas, kidney, vessels, prostate, uterus, thymus, lymph nodes and spleen) on the surface of cells, including epithelial, endothelial cells and immune cells, such as natural killer cells, lymphocytes and monocytes (1).

Enzymatic function of DPP4

DPP4 can play an important role in the inactivation of incretins (1,5,11), such as GLP-1 and GIP. Aside from the enzymatic inactivation of incretins, DPP4 also plays an important role in the post-translational cleavage/maturation of chemokines that are secreted upon T-cell activation. RANTES, also known as chemokine (C-C motif) ligand (CCL) 5, stromal cell-derived factors-1 (SDF-1, also known as CXCL12), eotaxin (CCL11), interferon-inducible T-cell chemoattractant (ITAC, also known as CXCL11), neuropeptide Y (NPY), peptide YY, inflammatory protein-10 (IP10, also known as CXCL10) and the macrophage-derived chemokine (MDC, also known as CCL22) are some of the chemokines currently thought to be processed by DPP4 through protein cleavage (1,5,11). Inhibition of DPP4 not only increases the half-life of incretin peptides, contributes to better glucose control during the postprandial state through suppressive effects of GLP-1/GIP on glucagon release, gastric motility and appetite suppression (3,4), but also prevents cleavage/maturation of chemokines such as CXCL11 (12), SDF-1 (13) and MDC (14) by DPP4. Further details about the substrates of DPP4 can be found in the reviews on this topic (1,5,11).

CD26 expression and T-cell function

As a cell surface antigen, CD26 is considered to have a co-stimulatory function in T-cell activation and proliferation (1,2). It has been suggested that adenosine deaminase (ADA) co-localizing with adenosine receptors on dendritic cells interacts with CD26 expressed on lymphocytes, and this co-stimulatory signal potentiates T-cell activation and induces the production of the T helper (Th) 1 proinflammatory cytokines (15). Meanwhile, ADA directly binding to CD26 appears to be involved in the costimulation of T-cell activation events in vitro, as exogenously added ADA was found to result in enzyme-independent synergism with the T-cell receptor (TCR)-CD3 complex augmenting T-cell proliferation (16). Aside from synergistic interaction with the TCR-CD3 complex, clustering of CD26 dimers on T cells by caveolin-1 on antigen presenting cells may also lead to T-cell activation (17). It is currently unknown whether the serine protease activity of CD26 plays any role in T-cell activation or function (2). In addition to its role as a T-cell activation marker, the level of cell surface CD26 expression on different T cell subsets may play supporting roles. It was reported that $CD4^+CD25^-$ or $CD4^+$ $FoxP3^{-/low}$ effector T lymphocytes expressed high levels of CD26, but T regulatory cells (defined as $CD4^+CD25^{high}$ or $CD4^+FoxP3^{high}$) were negative or low on CD26 expression (18). Recently, $CD26^{high}CD8^+$ T cells were shown to belong to the early effector memory T cell subset, and CD26-mediated co-stimulation of $CD8^+$ T cells elicited cytotoxic effects preferentially through granzyme B, tumour necrosis factor (TNF)-alpha, interferon-gamma and Fas ligand (19). Moreover, Bengsch et al (20) found that human Th17 cells were phenotypically characterized by high CD26 expression in both viral and autoinflammatory diseases, such as Crohn's disease, ulcerative colitis, primary biliary cirrhosis, autoimmune hepatitis and viral hepatitis (20). They also reported that CD26 expressed by Th17 cells is enzymatically active and can regulate T-cell migration by chemokine cleavage (20). Based on this evidence, CD26 may have important roles in T-cell biology and T-cell–mediated immune response.

Soluble CD26

A soluble form of CD26 (sCD26), which lacks the short intracellular tail and the transmembrane domain, exists in serum and possesses DPP4 enzyme activity (21). It was demonstrated in 1 study that stimulation of THP-1 cells and purified human monocytes with a combination of sCD26 and lipopolysaccharide (LPS) enhanced the expression of TNF-alpha, interleukin (IL)-6, c-Fos, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) p65, NF-kappaB p50 and cut-like homeobox (CUX)1 compared with stimulation by LPS alone, and addition of the DPP4 inhibitor sitagliptin abolished the sCD26-mediated enhancement of protein expression, except IL-6 (22). In contrast, another study