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Review

Inhibition of multifunctional dipeptidyl peptidase-IV: Is there a risk of oncological and immunological adverse effects?☆

Tomas Stulc[a,*], *Aleksi Sedo*[b]

[a] *3rd Department of Internal Medicine, 1st Faculty of Medicine, Charles University, Prague, Czech Republic*
[b] *Institute of Biochemistry and Experimental Oncology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic*

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ABSTRACT

Inhibitors of dipeptidyl peptidase-IV (DPP-IV) are a novel class of anti-diabetes drugs; inhibiting the breakdown of incretins, they increase their biological availability and decrease thus blood glucose levels. However, in addition to regulating glucose homeostasis, DPP-IV has many diverse functions, such as modulating cell growth, differentiation and transformation and immune function. Within the immune system, DPP-IV exerts mainly stimulating effects, while its relation to malignancies is highly variable. Therefore, long-term inhibition of this enzyme could have serious side effects including immune dysregulation or increased risk of cancer. Although the data on the effects of DPP-IV inhibitors in humans are scarce, the increased risk of infections and the tendency towards a higher incidence of some tumours fall in line with experimental evidence suggesting the possibility of their adverse immunological and oncological effects. Further research is obviously needed to clarify the effector mechanisms of DPP-IV inhibitors on immune function and tumour biology. Most important, however, is obtaining reassuring safety data from adequately powered, long-term trials of DPP-IV inhibitors in humans. In the meantime, all the potential risks of DPP-IV inhibitors should be kept in mind, and this class of drugs needs to be regarded with some degree of caution.

Contents

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* *Corresponding author at*: 3rd Department of Internal Medicine, U Nemocnice 1, Praha 2, CZ 128 21, Czech Republic. Tel.: +420 22496 2918; fax: +420 22491 9780.
E-mail address: tstulc@lf1.cuni.cz (T. Stulc).
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1. Introduction

Inhibitors of dipeptidyl peptidase-IV (DPP-IV) are a novel class of glucose-lowering drugs, which are based on augmenting the incretin-signalling pathway. Incretins are peptide hormones released by intestine during nutrient absorption to reduce post-prandial hyperglycaemia. They are rapidly inactivated by the enzymatic activity of DPP-IV, resulting in a very short half-life of a few minutes. The two most important incretins are glucagon-like peptide 1 (GLP-1) and the glucose-dependent insulinotropic peptide (GIP). The immediate effect of incretins is to stimulate insulin secretion in a glucose-dependent manner. In addition, GLP-1 inhibits glucagon secretion, delays gastric emptying, decreases appetite and – in experimental setting – increases beta cell mass and survival [1–3].

Recent advances in the understanding of incretins' biology have resulted in the development of DPP-IV inhibitors (commonly referred to as gliptins) for the treatment of type 2 diabetes mellitus. Currently, sitagliptin, vildagliptin and saxagliptin are approved for use in Europe, and several other molecules are in the late stages of clinical development [4]. Inhibiting the enzymatic activity of DPP-IV, gliptins decrease the breakdown of incretins and increase their biological availability and glucose-lowering effect. Gliptins are weight neutral, have very low risk of hypoglycaemia, and are generally well tolerated, which makes them promising treatment of type 2 diabetes mellitus.

However, the use of DPP-IV inhibitors may have other effects in addition to regulating glucose homeostasis, inherent to their mode of action. DPP-IV is widely expressed throughout the body and has many diverse functions, including modulation of immune function, and of cell growth, differentiation, apoptosis and transformation [5–7]. Long-term inhibition of this enzyme could therefore have serious side effects such as immune dysregulation or increased risk of cancer. In this review, we summarize the available data in this field and discuss the relevance of the experimental results to the clinical use of DPP-IV inhibitors in humans.

2. Dipeptidyl peptidase-IV at a glance

Dipeptidyl peptidase-IV (EC 3.4.14.5) – identical to leukocyte differentiation antigen CD26 – is a ubiquitous plasma membrane peptidase with multiple, organ specific biological functions; it was originally described by Hopsu-Havu in early sixties [8]. In addition, soluble form of DPP-IV, lacking the transmembrane and cytoplasmic domain, is present in the serum and other body fluids [5,6]. Both membrane-bound and soluble forms of DPP-IV appear in a homodimeric form. Multiple physiological functions of DPP-IV are executed by three mechanisms, including (1) proteolytic degradation of biologically active molecules, (2) adhesion to extracellular matrix proteins, and (3) co-stimulatory role in T-cell activation (Fig. 1). In addition, DPP-IV participates in multimolecular complexes (e.g. with ADA, chemokine receptor CXCR4, or plasminogen receptor) involved in signalling, and it also serves as a co-receptor for HIV internalization in some immune cells [7,9,17]. DPP-IV selectively cleaves N-terminal dipeptides from substrates with proline aminoacyl residue on the penultimate position, regulating their functional half-time, but in same cases also shifts their receptor preference and thus modifies their functional potential qualitatively [10]. Interestingly, proline residue in such position is conserved in many biologically active peptides, and thus seems to represent a proteolytic checkpoint enabling their fine regulation by DPP-IV. In addition to GLP-1 and GIP, known substrates of DPP-IV include GLP-2 and a number of neuropeptides and cytokines with important roles mainly in immune system and in cell

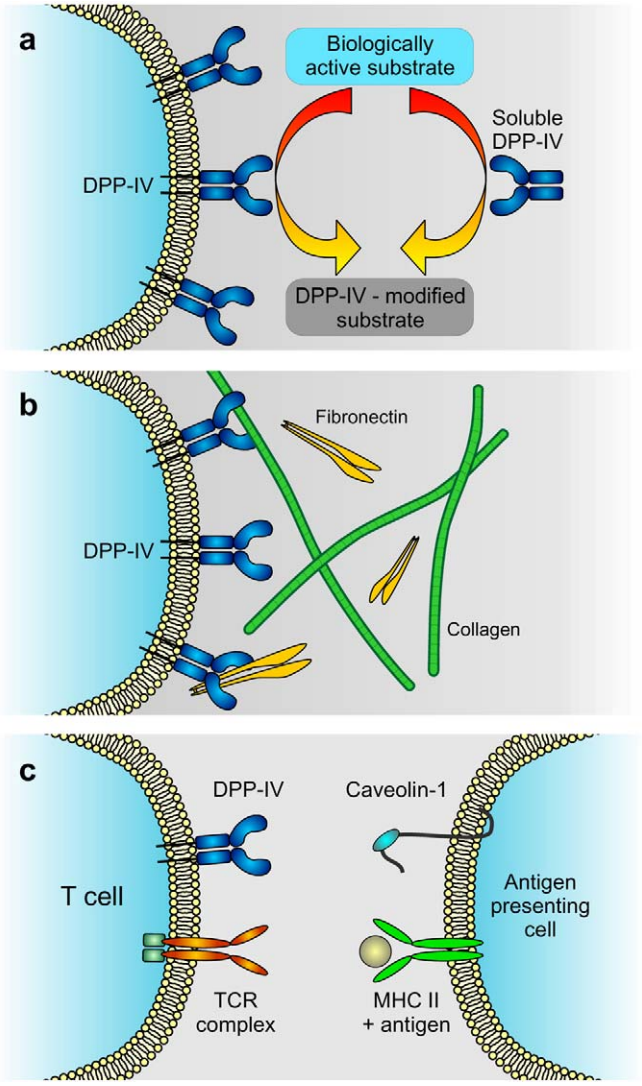

Fig. 1 – Multiple physiological functions of DPP-IV are mediated through several mechanisms [7]: (a) By cleaving N-terminal dipeptides from biologically active molecules, it regulates (usually inhibits) their activity (for details, see Table 1). (b) Adhesion function mediates interaction of cells with extracellular matrix components such as collagen and fibronectin. (c) Co-stimulatory role in T-cell activation: T-cells are stimulated via interaction of T-cell receptor (TCR) with class II major histocompatibility complex (MHC-II) of antigen-presenting cells (APCs). T-cell response to antigen is enhanced through binding of DPP-IV with caveolin-1 on the surface of APCs [17].