

■ R E V I E W

A guardian angel: the involvement of dipeptidyl peptidase IV in psychoneuroendocrine function, nutrition and immune defence

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A B S T R A C T

Dipeptidyl peptidase IV (DPP IV, also known as CD26; EC 3.4.14.5) is a non-integrin receptor glycoprotein with multiple functions, including cell adhesion, cellular trafficking through the extracellular matrix and co-stimulatory potential during T cell activation. By virtue of its exopeptidase activity, DPP IV plays a key regulatory role in the metabolism of peptide hormones. Based on data emerging from different biomedical specialties, it appears worthwhile to highlight the different facets of DPP IV in nutrition, immune responses and peptide hormone metabolism. The presentation of the complex regulatory circuits in which DPP IV appears to be involved may also serve as a note of caution, in view of attempts to apply selective inhibitors of DPP IV enzymic activity for the treatment of disease, e.g. Type II diabetes.

INTRODUCTION

Dipeptidyl peptidase IV (DPP IV; EC 3.4.14.5) has a unique enzymic activity, cleaving dipeptides from peptides and proteins carrying proline in their penultimate position, a feature which protects peptides from being digested by non-specific proteases [1]. DPP IV is associated with the plasma membrane of a variety of cells, including the venous portion of capillary endothelial cells [2], hepatocytes [3,4], enterocytes [5,6] and cells of the renal glomeruli and proximal tubules [7,8]. Expression of DPP IV defines a higher degree of cell maturation and differentiation [9,10]. The functional specificity of DPP IV is defined by the site of DPP IV expression and the substrates available [11]. Organ-specific functions and regulatory circuits appear to have an impact on DPP IV expression, such as a proline-rich diet in the intestinal epithelium [12], interferon- γ in kidney [13] and

antigenic [14,15] or mitogenic [16] stimulation of T lymphocytes.

Since its first description in 1966 [17], DPP IV served primarily as a target for studies in membrane protein biochemistry. DPP IV was shown to be an example for mechanisms of membrane protein turnover [4,18], glycosylation events [19,20], membrane polarization [21] and organ-specific differences in the regulation of protein expression [22]. Reports on an involvement of DPP IV in cell adhesion [23] and immune function [24] allowed a first glimpse of the many biological processes in which DPP IV appears to be involved.

SUBSTRATES

Many neuropeptides, immunopeptides and peptide hormones share the feature of having proline residues at specific positions in their sequence, which fulfill two

Key words: dipeptidyl peptidase IV, nutrition, peptide hormone metabolism, psychiatric disorders.

Abbreviations: ADA, adenosine deaminase; DPP IV, dipeptidyl peptidase IV; NPY, neuropeptide Y; PEP, prolyl endopeptidase.

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Table 1 Known substrates for DPP IV

Substrate	Effect of modulation by DPP IV	Consequences	Psychoneuroendocrine implications
Growth hormone releasing factor [25,31]	Degradation	Decreased induction of growth hormone release	Inhibition of energy consumption; catabolic effect
Glucagon-like peptide 1 [32], glucagon-like peptide 2 [33] and gastric inhibitory peptide [26]	Degradation	Loss of potent insulinotropic and blood glucose-normalizing effect	Catabolic (and diabetogenic) effect
Procolipase [34]	Partial activation	Breakdown of lipids in the digestive tract; release of enterostatin	Modulation of satiety
Fibrinogen α chain [35]	Hydrolysis	Inhibition of fibrinogen polymerization	Relevance unknown
Kentsin [36]	Degradation	Loss of (a) anovulatory effect, (b) inhibitory effect on intestinal transit, and (c) potent analgetic effect (opiate-receptor independent, naloxone-sensitive)	Enhanced nociception
Enterostatin [37,38]	Degradation and inactivation	Loss of inhibitory effect on caloric intake	Inhibition of satiety
Human chorionic gonadotropin [39]	Degradation	Unknown	Modulation of satiety
N-Procalcitonin [40]	Potent bone-cell mitogen	Unknown; presumably inactivation	Unknown
Trypsinogen [34]	Degradation	Unknown	Unknown

Table 2 Substrates for DPP IV in inflammatory responses

Abbreviations: SDF-1 α , stromal-cell-derived factor 1 α ; CXCR, C-X-C chemokine receptor type 4; IL, interleukin; TNF- α , tumour necrosis factor- α ; IP-10, interferon-inducible protein 10; RANTES, regulated on activation, normal T cell expressed and secreted; CCR, C-C chemokine receptor.

Substrate	Effect of modulation by DPP IV	Consequences	Immunological implications
SDF-1 α [60]	Degradation to SDF-1 α -(3–68)	Loss of lymphocyte chemotactic activity; SDF-1 α -(3–68) blocks effect of intact SDF-1 α by occupying CXCR-4	Modulation of lymphocyte chemotaxis; inhibition of HIV entry via CXCR-4
Lymphotoxin (aa 1–5), IL-2 fragments, murine IL-6 (aa 1–12), IL-1 (aa 1–6) [61]	Degradation	Abolished competition with full-length peptide for receptor binding (not proven)	Reversed inhibitory effect on inflammatory response (not proven)
Eotaxin [62]	Inactivation	Th2-chemokine; loss of ability to attract eosinophils	Inhibition of inflammatory Th2 responses
TNF- α [56]	Degradation	Monocytes; main source of TNF- α ; main target for interferon- γ secretion by CD26-positive cells	Inhibition of monocyte participation in inflammatory responses
IP-10 [63]	Inactivation	Loss of chemotactic ability for CD4-positive T cells	Inhibition of chemotactic attraction of CD4-positive cells to inflammatory sites of the skin
Monocyte chemotactic protein [64]	Degradation, inactivation	Loss of monocyte chemotactic function	Inhibition of monocyte participation in inflammatory responses
RANTES [63,65]	Altered receptor specificity: RANTES-(3–68) does not bind to CCR1, but still binds to CCR5; no increase in cytosolic Ca ²⁺ in monocytes	Inhibition of monocyte chemotaxis with simultaneous enhancement of T cell migration	RANTES-(3–68) is a chemotaxis inhibitor, but protects monocytes from cytopathic effects of HIV-1 infection

major tasks. First, they determine the properties of the secondary structure of the peptides, necessary for their biological activity, e.g. membrane passage, receptor

binding. Secondly, these residues serve as cleavage points for proline-specific peptidases such as DPP IV [1]. In consequence, modification of peptide substrates [25] and

the use of inhibitors of DPP IV [26] have both been shown to prolong the biological half-lives of substrates, with potential clinical and pharmaceutical implications [27]. The number of substrates for DPP IV is even larger when a joint effect of DPP IV and other peptidases, such as aminopeptidase N (CD13), is taken into account, leading to the hydrolysis of peptides carrying proline at the third or a later position from the N-terminus. For instance, sequential N-terminal degradation of bradykinin has been proven to involve DPP IV [28,29]. In Table 1, potent bioactive peptides that are metabolized primarily by DPP IV are listed. An overview of immunologically relevant substrates for DPP IV (Table 2) further expands the presumptive role of DPP IV in immune responses to a complex immunomodulatory function.

INVOLVEMENT IN IMMUNE FUNCTION

The role of DPP IV in immune function has been reviewed in detail [41–43]; only some aspects shall be addressed here. The T lymphocyte antigen, CD26, has been shown to have DPP IV activity. High expression of the antigen defines a distinct subset of T lymphocytes with memory cell capacity [43,44]. In a human umbilical cord endothelial cell monolayer model, CD26^{bright} lymphocytes predominantly transigrate monolayers without a chemokine gradient, in contrast to CD26-negative cells [45,46]. Given the memory cell phenotype of these cells, early tissue invasion may be important for the initiation of inflammatory processes wherever appropriate.

Like other ectopeptidases involved in immunologically relevant functions, such as CD10 and CD13 (aminopeptidase N), the expression of CD26/DPP IV is strictly developmentally regulated [47]. During thymocyte maturation, CD26-associated enzymic activity is ontogenically controlled and may be involved in thymic deletion of emerging T cell clones [9]. Surface CD26 antigen expression is important for T cell activation and co-stimulation. Since CD26 has only a six-amino-acid membrane-anchoring domain, signal transduction must be mediated by other cell membrane components. In fact, CD26 has been shown to co-precipitate the tyrosine kinase CD45 [43]. Other authors suggest that CD26-mediated signal transduction occurs via the CD3 (T cell receptor-associated complex) ζ chain [48]. These data suggest a complex interaction between CD26, CD45 and the CD3 ζ chain, as discussed [49,50]. Only CD26-positive T lymphocytes appear to be capable of producing interferon- γ [51]. DPP IV enzymic activity is capable of augmenting the cellular responses of CD26-transfected Jurkat cells to external stimuli mediated by CD26 and/or the CD3–T-cell-receptor complex, leading

to enhanced interleukin-2 production [52]. However, the enzymic activity is not mandatory for T cell activation via CD26 [53]. CD26 serves as the membrane-anchoring protein for ecto-adenosine deaminase (ADA) [54] which, in addition to its cell-protective effect of detoxifying extracellular adenosine or 2'-deoxyadenosine, interacts with different cell surface proteins [55]. The capacity of CD26 to bind to ADA further adds to the importance of this membrane antigen in T cell protection, adhesion and activation.

Monocytes have been reported to have a surface peptidase with a substrate specificity and sensitivity to inhibitors of enzymic activity identical with those of DPP IV [56]. However, monocytes and cells from the monocytic cell line U937 known to carry the enzyme were not detected by two antibodies known to recognize DPP IV. The nature of this 'DPP IV-like enzyme' [56] remains to be elucidated. The presence of DPP IV-like enzymic activity on the surface of monocytes involves DPP IV in the degradation of components of the extracellular matrix, implying a role for DPP IV in tissue invasion. In addition, Bauvois and colleagues [56] also showed degradation of tumour necrosis factor- α by a DPP IV-like enzyme and tripeptidyl endopeptidase on monocytes, which are the main source of this cytokine [57,58]. Interestingly, surface expression of DPP IV on lymphoblastic HL-60 cells is enhanced upon cytokine-induced differentiation into macrophages, but lost upon differentiation into neutrophils [59], suggesting selective expression of DPP IV on macrophages, with potential relevance for tissue invasion as pointed out above.

CLINICAL ASPECTS OF DPP IV

Inflammatory/autoimmune diseases and AIDS

In cases of allograft rejection, the number of CD26-positive lymphocytes and DPP IV activity in serum showed sharp increases that were reversible by immunosuppression. Inhibition of DPP IV enzymic activity led to a delay in allograft rejection [66]. In patients with systemic lupus erythematosus, DPP IV activity in serum was shown to be markedly decreased, with DPP IV activity on lymphocytes only being decreased in patients with active disease [67]. Similar observations were made in animal models of systemic lupus erythematosus [68]. In synovial fluid from patients with rheumatoid arthritis, DPP IV activity showed a decrease, while the activities of other peptidases, namely proline endopeptidase and lysosomal dipeptidyl peptidase II, were increased [69]. Specific inhibition of DPP IV activity suppressed alkylamine- and adjuvant-induced arthritis [70,71], pointing to a role for DPP IV enzymic activity in the pathogenesis of experimentally induced arthritis. Plas-

Table 3 DPP IV in disease

Disease/condition	DPP IV activity	DPP IV/CD26 expression
Allograft rejection [79]	↑ in serum	↑ on lymphocytes
Systemic lupus erythematosus [67]	↓ in serum in all patients ↓ in lymphocytes of patients with active disease	No data available
Rheumatoid arthritis [69]	↓ in synovial fluid	No data available
Pregnancy [80]	↓ in serum	No data available
AIDS [78]	Normal	↓ no. of DPP IV-positive lymphocytes
Major depression [81]	↓ in serum	No data available
Schizophrenia [82]	↓ in serum	No data available
Fibromyalgia [83]	Normal	No data available
Anorexia nervosa [84]	↑ in serum	↓ no. of DPP IV-positive lymphocytes

minogen and streptokinase have both been shown to bind to DPP IV expressed on rheumatoid synovial fibroblasts [72]. Interestingly, fibronectin, a ligand for DPP IV [73,74], competes with streptokinase, since both proteins bind to DPP IV via the amino acid sequence Lys-Thr-Ser-Arg-Pro-Ala, common to both ligands [72]. Binding of streptokinase to DPP IV resulted in a rise in intracellular calcium in fibroblasts and in concomitant plasminogen activation. Thus the role of DPP IV in the pathogenesis of arthritis is not only confined to its enzymic activity.

In the course of HIV infection, the surface expression of the HIV envelope protein gp120/gp41 complex is not only responsible for the initiation of cell-to-cell membrane fusion leading to the formation of syncytia, but also initiates apoptosis in CD4-positive cells. Jacotot et al. [75] showed that increased expression of CD26 on CD4-positive T cells led to an enhanced induction of apoptosis by the gp120/gp41 complex. Apparently, signalling via CD26, usually leading to T cell activation [76], is modified following HIV infection, involving CD26 in the mechanism of triggering apoptosis. In contrast, transfection studies using wild-type CD26 and mutant CD26 devoid of DPP IV activity [77] suggested that the presence of DPP IV activity reduces the efficiency of HIV infection, whereas the absence of DPP IV activity correlates with a higher susceptibility to apoptosis, apparently due to an enhanced expression of CD95 (Apo-1/Fas). The overall number of CD26-positive memory T cells has been shown to be significantly lower in HIV-infected subjects [78], which may be the result of apoptotic death induced by the gp120/gp41 complex. Interestingly, DPP IV activity in the serum of these patients was normal, allowing for the hydrolysis of RANTES (regulated on activation, normal T cell expressed and secreted) and SDF-1 α (stromal-cell-derived factor 1 α) mentioned above and, consequently,

resulting in a protective effect against HIV entry. This, however, remains speculative and awaits further results.

Table 3 gives an overview of the changes in DPP IV activity and expression observed in various diseases, including psychiatric disorders.

PSYCHOMODULATORY ASPECTS

Substrates for DPP IV

Many of the peptide hormones and proteins that have been shown (or are assumed) to be substrates for DPP IV have, in fact, been at the centre of psychoneuroendocrine research in past years (for a review, see [85]). Taking the potency of peptide hormones such as neuropeptide Y (NPY) or Substance P into account, the impact of DPP IV on their biological activity and, similarly, changes in DPP IV activity in some psychiatric or psychosomatic diseases may have been underestimated in recent years. In addition to the substrates described in Tables 1 and 2, those with primarily neuroendocrine and/or psychomodulatory function are listed in Table 4.

Changes in DPP IV serum activity in psychiatric disorders

The analysis of DPP IV activity in sera from patients with psychiatric or psychosomatic disorders has revealed distinct changes in a variety of diseases. However, these changes are, in some cases, difficult to appreciate and may be subject to misinterpretation.

Diseases in which a decreased serum activity of DPP IV has been shown

Maes et al. [81] have performed extensive studies on DPP IV activity in sera from patients with major depression and schizophrenia. These patients showed a decrease in

Table 4 Substrates for DPP IV with neuroendocrine and psychomodulatory function

Substrate	Effect of modulation by DPP IV	Consequences
Endomorphin-I [86]	Degradation and inactivation	Loss of potent μ -agonistic effect
β -Casomorphin [87,88]	Degradation and inactivation	Loss of analgesic (naloxone-sensitive) and stimulatory effect on dietary intake
Kentsin [36]	Degradation	Loss of (a) anovulatory effect, (b) inhibitory effect on intestinal transit, and (c) potent analgesic effect (opiate-receptor independent, naloxone-sensitive)
Peptide YY [89], NPY (analogue of peptide Y)	Modulation of receptor specificity/loss of Y1-receptor-mediated functions	Phase-shift in the endogenous circadian rhythm of thalamic neurons; blood pressure recovery during endotoxic and haemorrhagic shock [90]
Substrate P [91]	Degradation to a more potent heptapeptide	More profound effect on transmission of nociception, depression of blood pressure and relaxation of smooth muscle

serum DPP IV activity as compared with healthy controls, a change that was apparently independent of anti-depressants and anti-psychotic drugs [82]. The assumption that these changes may reflect a certain degree of immunosuppression was not correlated with changes in lymphocyte subsets or altered lymphocyte transformation tests.

Diseases with increased activity of DPP IV in serum

Patients with hyporectic eating disorders show an increase in DPP IV serum activity and a decrease in the proportion of peripheral blood lymphocytes expressing CD26 [84]. This finding sheds new light on the changes of immune function in patients with eating disorders, with regard to the notion that patients with eating disorders, especially anorexia nervosa, often remain immunocompetent [92].

Diseases without alterations in DPP IV activity in serum

In fibromyalgia, changes in DPP IV serum activity, presumed to exist because of (a) the presence of depressive symptoms and (b) the role of DPP IV in the degradation of collagen and other components of the extracellular matrix, could not be observed [83]. Rather, the serum activity of another peptidase, prolyl endopeptidase (PEP), was shown to be decreased in patients with fibromyalgia. Since PEP is known to be involved in post-proline cleavage, with Substance P as a substrate, the authors concluded that a decreased serum activity of PEP may be related to aberrant pain perception and depressive symptoms. The same authors showed a higher PEP serum activity related to stress-induced anxiety, whereas DPP IV activity in serum was not altered [93]. In contrast with DPP IV, PEP in serum has been reported not to share its membrane-bound counterpart's substrate specificity [94]. Thus changes in DPP IV activity may be clinically more relevant for the metabolism of Substance P than changes in PEP activity in serum.

NUTRITIONAL ASPECTS

DPP IV degrades peptides and proteins to small peptides and amino acids that are suitable for transport and reutilization. Degradation by DPP IV represents a rate-limiting step for the intestinal and renal transport of proline-containing peptides. Enzymes such as trypsinogen and procolipase are among the many substrates described. The insulinotropic hormone, glucagon-like peptide 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 normalization of elevated glucose levels. By deactivation of glucose-dependent insulinotropic polypeptide [26,95] and glucagon-like peptide 1 [96], DPP IV abolishes their potent insulinotropic effects, so that their activity in serum lasts only a few minutes. For this reason, the use of inhibitors specific for DPP IV enzymic activity has been proposed as a novel strategy to treat Type II diabetes [96]. The participation of DPP IV in the reabsorption of proline-containing di- and tri-peptides from the renal proximal tubuli [97] may be regarded as a safeguard mechanism to recover proline.

NPY is one of the most potent orexigenic peptide hormones [98–100] and a known substrate for DPP IV. The modulation of receptor specificity for NPY after degradation by DPP IV [89] deserves special attention with regard to nutritional control. The orexigenic effect of NPY appears to be mediated by hypothalamic receptors of subtypes Y1 and Y5 [101,102]. Consequently, the altered receptor specificity of NPY after degradation by DPP IV may alter the influence of NPY on appetite and satiety. Similarly, the enhanced gastric motility induced by binding of NPY to NPY1 receptors [103] would be abrogated after peptide degradation by DPP IV.

SOLUBLE DPP IV

Origin and function

DPP IV activity is detectable in serum [104], urine, seminal plasma [105] and amniotic fluid. The origin of soluble DPP IV is not completely understood, although inflammatory and malignant processes in tissues expressing high amounts of DPP IV have been shown along with increased DPP IV activity in serum, probably due to tissue disruption. A release or cleavage of membrane-bound DPP IV from outer membranes by an active and regulated mechanism, although unproven, has been suggested [106,107]. Comparison of DPP IV purified from human serum showed that, apart from the N-terminal membrane-anchoring domain that was missing from DPP IV from serum, DPP IV from serum and kidney were indistinguishable immunologically, enzymologically and with regard to the capacity to bind ADA [104]. Studies of cultured peripheral blood T lymphocytes from patients with oral cancer [108] have led to the assumption that DPP IV from activated T lymphocytes is shed into the bloodstream. In hepatoma-bearing rats, a loss of DPP IV from the hepatoma plasma membrane paralleled an increase in DPP IV serum activity, suggesting a transfer of DPP IV into the serum [109]. On the other hand, decreased surface expression and altered protein processing, resulting in premature degradation, may account for the loss of membrane-bound DPP IV as well. Studies on lymphoblastic HL-60 cells suggested that a decrease in DPP IV expression is

not associated with increased cleavage of DPP IV into the culture medium [59]. To date, there is no report that definitely proves the origin of DPP IV in serum from the membrane-bound form of any tissue.

An analysis of biological variations in serum activity of DPP IV has revealed a low intra- and inter-individual variability of DPP IV serum activity, a slightly higher activity of DPP IV in serum in summer, and an overall low amplitude of changes in DPP IV activity in the course of 1 year [110]. However, significant changes may develop rapidly, for example a decrease in DPP IV serum activity within the first weeks of pregnancy (M. Hildebrandt, unpublished work).

Function of DPP IV in serum

Due to the presence of a soluble form of DPP IV in serum, any peptide circulating in the blood carrying proline in the penultimate N-terminal position is a candidate substrate for DPP IV and will be metabolized within minutes, resulting in activation, inactivation or modulation of its biological effect. Although serum DPP IV, like membrane-bound DPP IV, has been shown to bind ADA [104], we assume that the main function of soluble DPP IV is probably exerted via its enzymic activity. Table 5 lists potential substrates for DPP IV; in addition to the substrates listed in Tables 1, 2 and 4, these may help to elucidate the complex functions of DPP IV enzymic activity and, consequently, the broad implications that changes in DPP IV activity may have.

Table 5 Potential substrates for DPP IV among bioactive peptides

Abbreviations: ACTH, adrenocorticotrophic hormone (corticotropin); CLIP, corticotropin-like intermediary peptide; MIF, melanocyte-stimulating hormone release-inhibiting factor I.

Substrate	Function	Effect of metabolism by DPP IV
ACTH-(18–39) (CLIP) [111]	Expression in raphe nuclei: stimulates paradoxical sleep and enhances excitability in the hippocampal CA1 region; inhibits β -endorphin-triggered prolactin release	Unknown; equal effects of N-terminal CLIP fragments 18–24 and 20–24 (result of metabolism by DPP IV) on paradoxical sleep
Gastrin-releasing peptide [39]	Gastrin release; insulin release; involved in pituitary hormone secretion; increased secretion of ACTH via corticotropin releasing hormone; suppression of glucose intake	Inactivation
Pancreatic polypeptide [112]	Pancreatic polypeptide is able to raise glucocorticoid secretion acting directly on the inner adrenocortical cells	Inactivation
Tyr-[Trp ²]MIF-I, Tyr-MIF-I, Tyr-[Lys ²]MIF-I [113]	Bioactive peptides isolated from brain tissue; Tyr-MIF-I and Tyr-[Trp ²]MIF-I bind to μ opiate receptors: potent analgetic effect	Inactivation
Morphiceptin [114]	μ Opioid receptor agonist	Inactivation
Substance P-(3–11) [115]	More potent than Substance P	Unknown
Brain natriuretic peptide-32 [116]	Diuretic/natriuretic and vasorelaxant peptide	Unknown
Gly-Pro-Arg-Pro [117]	Inhibitor of fibrin polymerization	Unknown; presumably inactivation
His-Pro-Phe-His-Leu-D-Leu-Val-Tyr [118]	Renin inhibitor	Unknown; presumably inactivation

DPP IV-LIKE PEPTIDASES

Other peptidases have been described that have DPP IV-like substrate specificity, T cell activation capacity and sensitivity towards DPP IV-specific inhibitors. Duke Cohan and colleagues [119] isolated a monomeric form of serum DPP IV of molecular mass 175 kDa, in contrast with the size of 105–110 kDa reported previously. This large serum DPP IV-like peptidase was shown to express functional DPP IV activity, with substrate and inhibitor specificities and a pH-activity profile similar to those of CD26. Analysis of peptides after limiting proteolysis and N-terminal sequencing revealed no identity with CD26, but some identity with other peptidases. Unlike CD26, the serum form did not bind ADA-1. The conservation of DPP IV activity and five epitopes specific to recombinant soluble CD26 suggest, however, significant structural similarity. Of note, a 60 kDa DPP IV protein fragment has been described by several groups [120], which has been shown conclusively to represent a part of DPP IV protein and which may associate with DPP IV to form a 175 kDa protein complex.

More recently, two enzymes with post-proline cleaving activity and a catalytic triad similar to that of DPP IV have been described. Quiescent cell proline dipeptidase is expressed intracellularly in CD26-negative lymphocytic cell lines and non-lymphocytic cell lines also, and acts over a broad pH range [121]. A 100 kDa protein with DPP IV-like activity, termed N-acetylated α -linked acidic dipeptidase-like protein, has been isolated from rat and human ileum [122,123]. Another member of the same gene family that also possesses DPP IV-like activity, N-acetylated α -linked acidic dipeptidase II, is expressed in testis, ovary and distinct areas of the brain [123]. DPP IV- β , an 82 kDa protein with CD26-like DPP activity, has been described [124,125]. DPP IV- β and CD26 differ in their sensitivity towards inhibitors of DPP IV, allowing their distinction. Taken together, it appears that, in addition to the evolutionary conservation of DPP IV structure, some redundancy of DPP IV function has been provided.

OUTLOOK: TOWARDS A MORE GENERALIZED VIEW OF DPP IV ENZYMIC ACTIVITY

'...if we break up a living organism by isolating its different parts it is only for the sake of ease in analysis and by no means in order to consider them separately. Indeed when we wish to ascribe to a physiological quality its value and true significance we must always refer it to its whole and draw our final conclusions only in relation to the effects in the whole' (Claude Bernard).

How are we to understand the physiological role of DPP IV enzymic activity? In fact, some aspects of DPP

IV appear contradictory: some substrates of DPP IV exert an effect that directly opposes the effects of other substrates of DPP IV. Examples of this include the regulation of fat intake, natriuresis and the chemotactic ability of immunocompetent cells. However, this view does not take into account the fact that these antagonizing substrates may differ in (a) speed of metabolism by DPP IV, (b) biological importance, and (c) tissue- or organ-specific role.

Some aspects of DPP IV function and substrates, however, appear to be clearly defined. Based on the effects and substrates described, we assume that DPP IV activity enhances nociception by inactivation of potent analgesic μ -opiate receptor agonists and by processing Substance P to a more potent derivative, a process which may best be described as an 'arousal reaction' and which may involve additional circuits via other substrates for DPP IV. Furthermore, an elevation of DPP IV activity would exert an immunoprotective effect, mainly via expansion of T cell activation, but also by an inhibitory effect on corticosteroid release. Based on the experimental and clinical data available, the apparently contradictory effects of T cell proliferation and immunoprotection on the one hand, but chemokine inactivation on the other, may be explained by a bimodal action of DPP IV in immune function: immune reactions that have been initiated by other mechanisms are supported by DPP IV enzymic activity, while other immune reactions are rather reduced, thus focusing the immunosurveillance on processes that are already under way. In fact, *in vitro* studies that deliberately address the effect of inhibition of DPP IV on T cell proliferation, thus studying secondary responses upon stimulation, may imitate an already active inflammatory process rather than a baseline immune response. Furthermore, cleavage of chemokines such as eotaxin [62] suggests an inhibition of Th2-like cytokine responses by DPP IV activity. This adds to the observation that high expression of DPP IV/CD26 defines a Th1/Th0 phenotype among T cells and correlates with enhanced production of Th1-like cytokines, namely interferon- γ [51]. The net effect of DPP IV activity would be a shift towards a Th1 cytokine response, in part attributable to a degradation of cytokines involved in Th2-like responses.

The inactivation of potent insulinotropic peptides by DPP IV, together with an increase in glucose intake due to inactivation of gastrin-releasing peptide, would result in an enhanced availability of glucose in blood. We assume that an increase in DPP IV activity would result in an overall decreased digestive activity, which, together with the enhanced availability of blood glucose, may be a nutritional status required for an organism's 'state of alert'. These rather catabolic effects of DPP IV match well with the assumption that anabolic effects of insulinotropic peptides, but also of growth hormone releasing factor and other mitogens, are abolished by DPP IV.

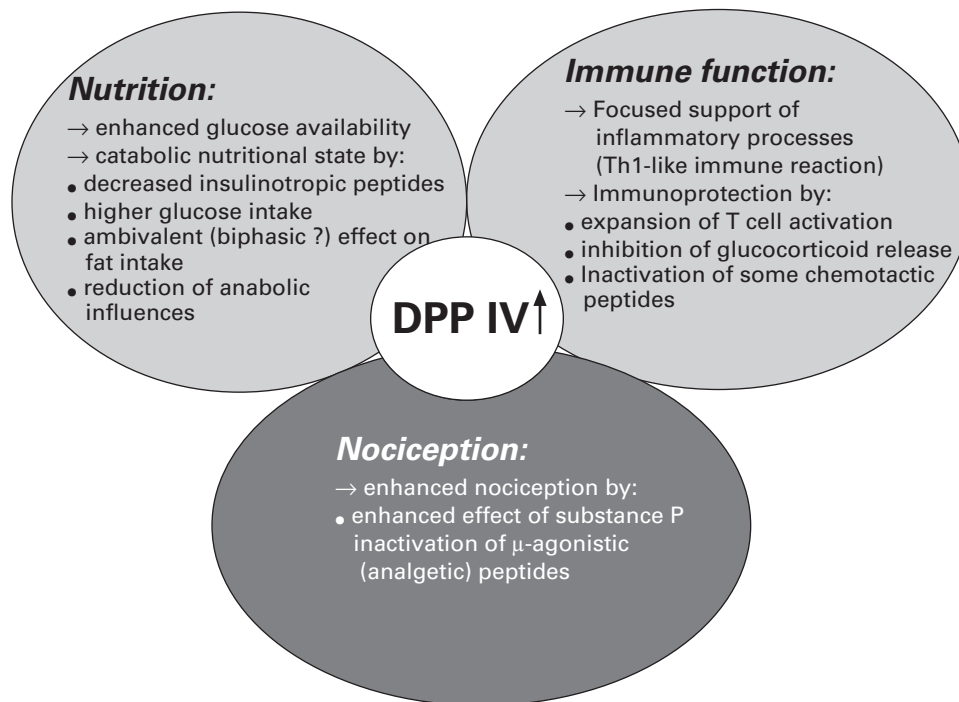


Figure 1 Functions of DPP IV in various regulatory circuits

These observations represent a shielding and supportive role of DPP IV in a state of alert. Figure 1 represents an attempt to summarize the involvement of DPP IV in regulatory circuits.

In clinical terms, the observation that patients with hyporectic eating disorders show elevated levels of DPP IV activity in serum underscores the putative shielding effect of DPP IV: in spite of severe malnutrition, immune defence is enhanced, or DPP IV elevation represents at least an attempt to compensate for the immunocompromised state caused by malnutrition. In line with this view, enhanced nociception and an increased availability of blood glucose would add to the defence mechanism. Finally, the severe malnutrition makes a more catabolic predisposition mandatory, which includes the inactivation of anabolic bioactive proteins.

Inversely, potential consequences of decreased DPP IV activity, as observed in patients with major depression, would be compromised immunosurveillance, a rather anabolic nutritional status, decreased nociception and a reduced inhibitory effect on corticosteroid synthesis. In fact, this more generalized view of DPP IV function matches well with observations of a decreased mitogenic response of lymphocytes [126] and decreased pain perception [127] in patients with major depression. With regard to nutritional aspects, however, caloric intake has been reported to be normal or rather reduced in these patients [128].

The presentation of the multifaceted function of DPP IV, with potential involvement in regulatory circuits of

immune function, nutrition, cell adhesion and peptide hormone metabolism, as a 'guardian angel' is, given the actual state of knowledge, to be understood only as a working hypothesis. Although not validated, it is intended as a cautious comment on attempts to use specific inhibitors of DPP IV enzymic activity for therapeutic purposes, e.g. Type II diabetes [32,96], in view of the broad implications that this may have for circuits that are only partly understood. To date, no human disease has been reported to be specifically associated with a loss of DPP IV expression. Given the highly conserved structure of DPP IV in evolution and, perhaps, redundancy of the specific post-proline cleavage activity provided by very few other enzymes, DPP IV activity may be too important as a 'guardian angel' to be lost or abrogated by the use of selective inhibitors.

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