REVIEW

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

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ABSTRACT

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-1α, stromal-cell-derived factor 1α; 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-1α [60]	Degradation to SDF-1α-(3–68)	Loss of lymphocyte chemotactic activity; SDF-1α-(3–68) blocks effect of intact SDF-1α 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 fuction	Inhibition of monocyte participation in inflammatory responses
RANTES [63,65]	Altered receptor specifity: 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 transmigrate 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-1α (stromal-cell-derived factor 1α) 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-1 [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 analgetic 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 re-utilization. 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.

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