Ectopeptidases

CD13/Aminopeptidase N and CD26/Dipeptidylpeptidase IV in Medicine and Biology

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Chapter 10

Therapeutic Strategies Exploiting DP IV inhibition

Target disease: Type 2 Diabetes.

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1. INTRODUCTION

Peptides containing proline residues have been shown to be resistant to proteolytic cleavage at their linkages. Many regulatory, neuronal and immune peptides contain proline residues determining their peptide chain conformation and biological activity. Consequently, during evolution an exclusive set of proline-specific peptidases emerged capable of regulating the activity of such peptides. They are believed to be involved in peptide hormone processing and regulation. To this enzyme group belongs the exopeptidase dipeptidyl peptidase IV (DP IV, CD26, EC 3.4.14.5) and structurally similar DP IV-like enzymes (such as DP II) as well as other mechanistically but not structurally related enzymes (such as attractin) (chp. 7 this book by Abbott and Gorrell) Some of the natural substrates of DP IV-like enzymes turn out to be important regulators of vital mammalian functions.

DP IV is involved in a number of different physiological regulation processes. On the one hand, the enzyme is a peptidase which can change the activity of a number of peptide hormones, neuropeptides and chemokines in a very specific manner (Mentlein 1999; Lambeir *et al* 2001; Zhang *et al* 1999 and chp. 9 this book by De Meester *et al*), while on the other hand the DP IV protein molecule exerts protein-protein interactions, so mediating the regulation of intracellular signaling cascades independent of its peptidase activity (Hegen *et al* 1993; De Meester *et al* 1999).

Frequently, the low endogenous concentration of the bioactive forms of such hormones may be the cause of disorders. Hence, the pharmacological approach to inhibit the degradation of such endogenous peptides rather than

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Table 1. Target diseases for DP IV inhibition

Target disease	Effect of DP IV inhibitors	Development stage	Comments	Reference
AIDS	suppression of chemokine cleavage, suppression of HIV-interaction	cell culture	mechanism not fully understood	(Shioda *et al* 1998; Schols *et al* 1998; Jiang *et al* 1997; Ohtsuki *et al* 2000; Callebaut and Hovanessian, 1996)
Autoimmune diseases	general immuno-suppressive effects	cell culture and animal models	high doses necessary	(Reinhold *et al* 2000; Kubota *et al* 1992).
Rheumatoid Arthritis	suppression of disease	animal models		(Tanaka *et al* 1997; Tanaka. *et al* 1998)
Multiple sclerosis	suppression of EAE	animal experiments		(Steinbrecher *et al* 2000)
Psoriasis	reduction of keratinocyte hyperproliferation	cell culture and animal experiments		(Novelli *et al* 1996; Reinhold *et al* 1998)
Graft rejection	suppression of graft rejection	animal experiments		(Korom *et al* 1999a; Korom *et al* 1997; Korom *et al* 1999b)
Wound healing	promotion of wound healing			(Prager *et al* 1994; Kohl *et al* 1989; Ghersi *et al* 2001)
Anxiety	suppression of NPY cleavage, decrease of anxiety	effective in animal models		unpublished results
Type 2 diabetes	inhibition of incretin cleavage, improvement of metabolic regulation	phase II studies		(Hoffmann *et al* 2001; Ahr *et al* 2001)
Cancer	inhibition of spread of metastases inhibition of angiogenesis	cell culture, animal models	DP IV and fibroblast activation protein (FAP) are involved	(AbdelGhany *et al* 1998; PinciroSanchez *et al* 1997)

(GLP-1) were identified and described in the eighties (Bell *et al* 1983; Schmidt *et al* 1985).

GIP and GLP-1, currently known as incretins, make up the endocrine component of the entero-insular (gut-pancreas) axis – a concept describing the neural, endocrine and substrate signaling pathways between the small intestine and the islets of Langerhans (Unger and Eisentraut, 1969). Together, the incretins are responsible for over 50 % of nutrient-stimulated insulin release, and thus represent the most important meal-related impetus for insulin secretion. In addition to stimulating insulin secretion, the incretins share a number of non-insulin mediated effects that contribute synergistically towards effective glucose homeostasis. Both peptides have been shown to inhibit gastric motility and secretion (Schirra *et al* 1996; Pederson and Brown, 1972) to promote β-cell glucose competence (Huypens *et al* 2000), and to stimulate insulin transcription and biosynthesis (Fehmann and Habener 1992; Drucker *et al* 1987). In addition, GIP has been shown to play a significant role in the regulation of fat metabolism (Pederson, 1994) while GLP-1 has been shown to stimulate β-cell differentiation and growth (Hui *et al* 2001) as well as to restore islet-cell glucose responsiveness (Zawalich *et al* 1993).

The incretins were tested for treatment of T2D and it was found that the main advantage over the existing antidiabetic drugs is the strong glucose dependence of their insulinotropic action, thus preventing hypoglycemia. However, there are at least two disadvantages: as polypeptides they are not orally available; furthermore, it was found that the natural polypeptides have a very short half-life. Subsequently, it was shown by Mentlein that the bioactive form of GLP-1, GLP-$1_{7\text{-}36}$, as well as GIP both containing an alanine in penultimate position are *in vitro* substrates of purified human placenta DP IV (Mentlein *et al* 1993). Thus, the fast biodegradation *in vivo* could be at least in part due to DP IV activity (Kieffer *et al* 1995; Pauly *et al* 1996b; Deacon et.al, 1995).

It was Pauly and colleagues who first postulated the link between the possible benefits of DP IV inhibition and glycemic control due to enhancement of the incretin effect (Figure 2) (Pauly *et al* 1996a and b). The hypothesis that DP IV inhibition could improve glucose tolerance was later shown to be correct in both Wistar rats and diabetic fatty Zucker rats (Pauly *et al* 1999; Pederson *et al* 1998) These findings have been corroborated by similar studies in mouse, rat and pig (Deacon *et al* 1998; Balkan *et al* 1999; Ahren. *et al* 2000).

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