DPP IV

New and Emerging Clinical Applications Part I

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Dipeptidyl peptidase IV (DPP IV) is present on the brush border of the intestine, kidney, liver, surface of T cells and other cells of haematopoietic origin, where it is known as CD26. The blood soluble form of DPP IV is identified as sCD26. In the pancreatic and common bile duct, DPP IV is referred to as GP110.

DPP IV participates in the process of T cell activation and is identical to the lymphocyte activation marker CD26. Reduced DPP IV expression is directly associated with carcinogenesis. Decreased expression of DPP IV has also been linked to increased invasion and metastasis (Duke-Cohan 1995).

The lack or absence of DPP IV in the enterocyte of the small intestine prevents the digestion of peptide fragments that may in their undigested form elicit a host of immune/inflammatory responses (Duke-Cohan 1995).

In the brush border, DPP IV plays a crucial role in the breakdown of small peptides to form di- and tri-peptides that can then be transported across the intestine. Partial digestion of gluten proteins and milk proteins has been linked to exacerbation of gastrointestinal symptoms and other systemic parameters in a number of conditions.

DPP IV – Gluten sensitivity

Celiac sprue can manifest in infancy and childhood after introduction of cereals into the diet. A child may present with failure to thrive, apathy, anorexia, pallor, generalized hypotonia, abdominal distention, and muscle wasting. Those with 'Gluten sensitivity' may have similar findings, but may not express the degree of villous atrophy as those with Celiac sprue (Duke-Cohan 1995). What is common between those with Celiac sprue and those with 'gluten sensitivity' is reduced expression of DPP IV (Hadjivassiliou 1999).

The syndrome of gluten sensitivity is contingent upon intolerance to dietary gluten and is immunologically mediated with strong association with certain human leukocyte (HLA) class II alleles. The vast majority of patients with gluten sensitivity have the HLA DQ2 allele (Hadjivassiliou 1998). Of those with gluten sensitivity, approximately 6% of those may have neurological complications (Hadjivassiliou 1999). Histological abnormalities range from normal to subtotal or total villous atrophy of the small intestinal mucosa (Hadjivassiliou 1999).

"Therefore, the alteration in DPP IV peptidase enzymatic activities in the brush border of the small intestinal epithelial cells may be responsible for an incomplete degradation of gluten, resulting in the production of toxic peptides.**"**

Those with gluten sensitivities often report improvements on the "Elimination diet" but clinicians may find compliance and total abstinence of gluten and dairy rich foods to vary.

In children with Celiac sprue the treatment thus far has been a lifetime removal of gluten rich foods. The genetic basis for DPP IV supplementation is based on the assertion that there is a defective gene that codes for DPP IV in those with celiac disease (Clot 2000). Biopsies of the proximal small intestine of children with Celiac disease have shown to cytochemically have significantly decreased DPP IV enterocyte activity.

It has also been suggested that there are two polymorphisms of DPP IV and this may increase the susceptibility in acquiring celiac disease (Clot 2000). Therefore, the alteration in DPP IV peptidase enzymatic activities in the brush border of the small intestinal epithelial cells may be responsible for an incomplete degradation of gluten, resulting in the production of toxic peptides. Clinical trials utilizing oral supplementation of DPP IV in humans is currently not available. This is alarming as the in vitro data and evidence to support lower levels of enterocyte DPP IV concentration in humans has been verified (Meester 2003, Shan 2002). Abeit, enzymes are not a substitute for exclusionary diet, the addition of DPP IV may lessen or remove excess dietary exorphins that aggravate biochemical and immunologic problems associated with celiac disease or those with gluten sensitivity.

DPP IV – Atopic Dermatitis

In newborns, the opiod active Casomorphins may be enzymatically released from milk (β –casein). The newborns gastrointestinal wall may be permeable to β-casomorphins and the permeation of exogenous β-casomorphins may be partly responsible for atopic dermatitis in children (Koch 1988).

The permeability of the infant gut to undigested macromolecules is higher than in the adults (Bjarnason 1995). This has also been shown in children with autism (D'Eufemia 1996).

A wide range of reactions to β –casomorphin has been described in the literature. Pseudoallergic reactions by inducing histamine release from immune cells and a possible link to Sudden infant death syndrome (SIDS) has been suggested (Kurek 1996, Kurek 1999).

The bioactive peptide β –casomorphin from bovine source may be related to multiple neurological manifestations, ranging from postpartum psychosis to Type I diabetes in children (Meisel 2000, Drash 1994). Before clinicians jump to conclusions and blame cow's milk for all non-breast fed infant's health concerns, it is important to realize that that β –casomorphins are also present in mother's milk. It has been demonstrated that the presence of β-casomorphin-5 and 7 (BCM-5, BCM-7) in human milk during different phases of lactation may be linked to atopic dermatitis. It seems counter intuitive that human breast milk could possibly be responsible for causing atopic dermatitis, as it's vital to properly nourish the infants. However, in the last century the number of breast-fed children exhibiting atopic dermatitis symptoms has rapidly increased (Arvola 2004). Atopic dermatitis (AD) commonly affects infants and children and more than two thirds demonstrate the beginning of disease within the first year of life (Christophers 2001). Interestingly, there may be a role for DPP IV in this disease process.

"Furthermore, DPP IV activity in the infant's with atopic dermatitis were significantly lower in comparison with the control group (91% of the results in the dermatitis group were lower than the mean in the control group)."

To illustrate this connection between DPP IV and atopic dermatitis in infants, researchers collected blood samples from twenty-three children with atopic dermatitis and from a control group, which included 13 breastfed healthy infants, without allergy symptoms (Jarmołowska 2007). Samples of breast milk from mothers of infant's with atopic dermatitis and from the mothers with infants in the control group were evaluated.

The results of the trial displayed a negative correlation between DPP IV activity in infant's serum and casomorphin contents of mother's milk in only the infants with atopic dermatitis. This means that in the allergic group, high level of casomorphins in mother's milk corresponded with low DPP IV activity in infant's sera. This was exclusively observed in the group of mothers and infants with atopic dermatitis, with no such relationship in the control group. Furthermore, DPP IV activity in the infant's with atopic dermatitis were significantly lower in comparison with the control group (91% of the results in the dermatitis group were lower than the mean in the control group).

Intervention of DPP IV in infants has never been evaluated, however, treatment with probiotics has been described in the literature (Kalliomaki 2001, Ouwenhand 2001, Viljanen 2006). A unique method of increasing DPP IV activity may be with supplementation of specific bacteria. Specifically, Lactobacillus helveticus and Lactobacillus rhamnosus are two unique strains that contain analogs of DPP IV that are recognized for their ability to digest exorphins (gluteomorphins/casomorphins) (Varmanen 2000).

The presence of the DPP IV analogs produced by these bacteria (L. rhamnosus and L. helveticus) may have an important role in treatment of atopic dermatitis until oral DPP IV clinical trials are conducted.

DPP IV inhibitors – Is there a risk with long term use?

DPP IV has many other roles beyond aiding in the breakdown of bioactive peptides in the gut. CD26/DPP IV may serve as a useful marker in oncology (Wesley 2004) and conversely, it may serve diverse biological processes; including cell differentiation, adhesion, immunomodulation, and apoptosis, functions critical to control neoplastic transformation.

DPP IV evidence - highlights:

• Intestinal hydrolysis and assimilation of prolyl peptides in gliadin and casomorphins may decrease autoantibody production and decrease the risk of neuroimmune dysregulation and autoimmunity.

• DPP IV plays a key role in modification, processing and/or inactivation of peptides (e.g. peptide hormones, various cytokines, chemokines and neuropeptides).

• DPP IV has tumor suppressor function and regulates the activities of mitogenic peptides implied in cancer development.

• Analogs of DPP IV produced by Lactobacillus helveticus and Lactobacillus rhamnosus are recognized for their ability to digest exorphins.

DPP IV has also been shown to induce arrest and cell death in prostate cancer cells (Wesley 2004). The ability of DPP IV to regulate the cell proliferation, differentiation and apoptosis has also been observed in other forms of cancer including: ovarian, colon, lung, and melanocytic cancers (Wesley 1999, Wesley 2004, Morrison 2004, Sedo 1994, Morimoto 1998). Based on this it is alarming that new drugs have been developed that specifically inhibits DPP IV.

Recently, DPP IV inhibitors have hit the market as treatment for Type II diabetes. DPP IV rapidly inactivates two hormones, Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).These hormones play an important role in glucose homeostasis, particularly in the postprandial period. In response to nutrient intake, GIP (secreted from K cells located in the

duodenum and proximal jejunum) and GLP-1 (secreted from L cells located mainly in the ileum) stimulate insulin secretion (Drucker 2006, Mikhail 2006). GLP-1 inhibits postprandial glucagon release, delays gastric emptying, and may promote early satiety; actions that attenuate the increase in blood glucose after meals (Mikail 2006). Therefore, GLP-1 has received a great deal of interest as a potential antidiabetic drug. However, as stated above, DPP IV rapidly inactivates GLP-1 and GIP (Barnett 2006). Therefore, drugs that are "incretin enhancers" inhibit the action of DPP IV and prolong the effect of GLP-1 and GIP, thus lowering post-prandial glucose and reducing fasting glucose concentrations.

Given the diverse actions of DPP IV and its involvement in processes related to cancer metastasis, long-term inhibition may increase the metastatic potential of colon (Masur 2006) and prostate cancer cell lines (Wesley 2005). ■

References

Arvola T, Moilanen E, Vuento R, Isolauri E. Weaning to hypoallergenic formula improves gut barrier function in breast-fed infants with atopic eczema. J Pediatric Gastroenterol. Nutr. 2004;38(1):92–6.

Barnett A. DPP-4 inhibitors and their potential role in the management of type 2 diabetes. Int J Clin Pract. 2006;60(11):1454-1470.

Bjarnason I, MacPherson A, Hollander D. Intestinal permeability: an overview. Gastroenterology. 1995; 108(5):1566-8.

Christophers E, Fo¨lster-Holst R. Atopic dermatitis versus infantile eczema. J Am Acad Dermatol. 2001;45:2–3.

Clot F, Babron MC, Percopo S, Giordano M, Bouguerra F, Clerget-Darpoux F, Greco L, Serre JL, Fulchignoni-Lataud MC. Study of two ectopeptidases in the susceptibility to celiac disease: two newly identified polymorphisms of dipeptidylpeptidase IV. Journal of Pediatric Gastroenterology Nutrition. 2000; 30(4):464-6.

Drash AL, Kramer MS, Swanson J, Udall JN. Infant feeding practices and their possible relationship to the etiology of diabetes mellitus: work group on cow's milk protein and diabetes mellitus. Pediatrics. 1994;94: 752–754.

Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368(9548):1696-1705.

Duke-Cohan JS, Morimoto C, Rocker JA, Schlossman SF:Anovel form of dipeptidylpeptidase IV found in human serum. J Biol Chem.1995; 270: 141 07-1 41 14.

Hadjivassilou M, Grunewald RA, Davies-Jones GA. Gluten sensitivity: a many headed hydra [editorial]. Br Med J. 1999; 318: 1710-1.

Jarmołowska B, Bielikowicz K, Małgorzata I, Sidor K. Serum activity of dipeptidyl peptidase IV (DPPIV; EC 3.4.14.5) in breast-fed infants with symptoms of allergy. Peptide. 2007; 678-682.

Kalliomaki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants developing or not developing atopy. J Allergy Clin Immunol. 2001;107:129–34.

Koch G, Wiedemann K, Drebes E, Zimmermann W, Link G, Teschemacher H. Human b-casomorphin-8 immunoreactive material in the plasma of women during pregnancy and after delivery. Regul Pept. 1988;20:107–17.

Kurek M, Malaczynska T. Nutritive casein formula elicits pseudoallergic skin reactions by trick testing. Int Arch Allergy Immunol. 1999;118:228–9.

Kurek M, Rue M, Czerwionka-Szaflarska M, Doroszewska G, Przybiela B. Exorphins derived from cow's milk casein elicit pseudo-allergic wheal-and-flare reactions in healthy children. Rev fr Allergol. 1996;36(2):191–6.

Meester I, Lambeir AM, Proost P, Scharpe S .Dipeptidyl peptidase IV substrates. An update on in vitro peptide hydrolysis by human DPPIV.Adv. Exp. Med. Biol. 2003; 524: 3–17.

Meisel, H. & FitzGerald, R. J. Opioid peptides encrypted in intact milk protein sequences. Br. J. Nutr. 2000;84(suppl. 1):S27-S31.

Mikhail N. Exenatide: a novel approach for treatment of type 2 diabetes. South Med J. 2006;99(11):1271-1279.

Morimoto, C., and S.F. Schlossman. The structure and function of CD26 in the T-cell immune response. Immunol.Rev. 1998;161:55–70.

Morrison, M.E., S. Vijayasaradhi, D. Engelstein, A.P. Albino, and A.N. Houghton. A marker for neoplastic progression of human melanocytes is a cell surface ectopeptidase. J. Exp. Med. 1993;177:1135–1143.

Ouwehand AC, Isolauri E, He F, Hashimoto H, Benno Y, Salminen S. Differences in Bifidobacterium flora composition in allergic and healthy infants. J Allergy Clin Immunol. 2001;108:144–5.

Sedo A, Kraml J. Dipeptidyl peptidase IV in cell proliferation and differentiation. Sb Lek 1994;95:285–8.

Shan L, Molberg O, Parrot I, Hausch F, Filiz F, Gray GM, Sollid LM, Khosla C. Structural basis for gluten intolerance in celiac sprue. Science 2002;297(5590):2275-9.

Varmanen, P., Savijoki, K., Avail, S., Palva, A., Tynkkynen S-54X-prolyl Dipeptidyl aminopeptidase gene (pepX) is part of the ginRA operon in Lactobacillus rhamnosus, Journal of Bacteriology 2000;182(1): 146-154

Viljanen M, Savilahti E, Haahtela T Probiotics in the treatment of atopic eczema/ dermatitis syndrome in infants: a double-blind placebo-controlled trial. Arch Dermatol. 2006;142 (9):1201-3.

Wesley UV, Albino AP, Tiwari S, Houghton AN. A role for dipeptidyl peptidase IV in suppressing the malignant phenotype of melanocytic cells. J Exp Med 1999; 190:311–22.

Wesley UV, McGroarty M, Homoyouni A. Dipeptidyl peptidase inhibits maligant phenotype of prostate cancer cells by blocking basic fibroblast growth factor signaling pathway. Cancer Res. 2005;65:1325-1334.

Wesley UV, Tiwari S, Houghton AN. Role for dipeptidyl peptidase IV in tumor suppression of human non small cell lung carcinoma cells. Int J Cancer 2004; 109:855–66.