DPP IV

New and Emerging Clinical Applications, Part II

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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 CD26. 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. Foremost is the association between a deficiency of DPP IV and children with regressive autism.

Autism and the Basis for Enzyme Therapy

Regressive autism describes a child that appears to develop typically, but subsequently starts to lose social skills, speech and at approximately 18 months, is diagnosed with autism.

For the past decade, *Defeat Autism Now!* or "DAN" doctors have been using DPP IV clinically to treat the symptoms of autism. Dozens of video and audio lectures from DAN doctors are available online, www.danwebcast.com free of charge, and outline hundreds, perhaps thousands, of cases that focus on children with autism.

Treatments include a vast array of prescription medications to natural molecules ranging from Diflucan, Methylcobalamin and notably the enzyme DPP IV (DAN! 2008). The basis for DPP IV therapy is largely due to the research or Dr. Andrew Wakefield. Nearly a decade ago, Wakefield, a Canadian trained surgeon, authored a highly controversial paper reporting endoscopic findings of gastrointestinal inflammation in a prospective case series of 12 children with autism (Wakefield 1998). Two years later, Wakefield published a second paper describing endoscopic, laboratory and histopathological features in a series of children with regressive autism (Wakefield 2000).

The cohort was comprised of 60 children with autism including the 12 children in the 1998 study. The results indicated that endoscopically and histologically there were consistent patterns of ileocolonic pathology in the children with regressive autism (Wakefield 2000). Wakefield further suggested that the pathology may be a new variant of inflammatory bowel disease (IBD), as it lacks the features of either Crohn's disease or Ulcerative Colitis. Interestingly, each of the 60 children save one had abdominal pain, constipation, diarrhea or an alternating variation. Intraepithelial Lymphocyte Ileal Lymphonodular Hyperplasia (ILNH) was graded as moderate to severe in 54 of the 58 children where the ileum was visualized (Wakefield 2000). Adversaries to the Wakefield theory of "Enterocolitis" have suggested that there were methodological flaws in Wakefield's research and that definitive conclusions cannot be drawn from his work (Macdonald 2007). Despite criticism in the scientific literature of the theory of 'Enterocolitis,' others have published data supporting the original Wakefield findings.

A study of 21 children with regressive autism (Furlano 2001) also illustrated immunohistochemical changes in the children with autism. Furlano described a distinct lymphocytic colitis in participants with autism in which the epithelium appears particularly affected. Eoosinophilic infiltration of the Lamina propria was found to be a statistically significant abnormality when compared with normal controls (Furlano 2001). In the years to follow, many other papers were published, all with one universal message — gastrointestinal inflammation is present in children with regressive autism (Afzal 2003, Ashwood 2003, 2004, Horvath 1999, Torrente 2002, Wakefield 2005).

DPP IV – Gluteomorphins/Casomorphins and Autism

Opiod peptides from gluten (gluteomorphins) and casein (casomorphins) can stimulate T-cells, induce peptide-specific T-cell responses and abnormal levels of cytokine production, which may result in inflammation, autoimmune reactions and disruption of neuroimmune communications (Jyonouchi 2001). The opiod peptides from inadequate digestion of casein and gluten have been shown to be absorbed in excess by autistic children, as reflected by very high levels of urinary peptides (Hattock 1991, Horvath 1999, Nelson 2001, Reichelt 1990, 1994, 1997, 2003, Whiteley 1999). Excessive peptides from undigested casein and gluten are suspected to exert significant toxicity (Schuppan 2000).

One potential cause of the abnormal peptide content in the urine of children with regressive autism is a defect in DPP IV expression on enterocytes (Reichelt 1990). Breakdown of these exogenous peptides by DPP IV results in inactivation of their opioid activity (Jyonouchi 2001). Therefore, a genetic defect in DPP IV enzyme expression could result in biological active peptides circulating in the bloodstream with neurological consequences (Hattock 1991). In animal models it has been shown that epitopes from gliadin are highly resistant to cleavage at the intestinal surface membrane and are often unaffected by even pancreatic endoproteases (Tiruppathi 1993). Most proteases and peptidases are unable to hydrolyze the substituted and conformationally constrained amide bond of proline residues in gliadins and casomorphins. This constitutes a major digestive obstacle for those with compromised DPP IV activity in the intestinal brush border as the increased concentration of gluten derived-oligopeptides and casomorphins from milk protein can cross the intestinal barrier and gain access to subepithelial lymphocytes.

DPP IV and dipeptidylcarboxypeptidase I (DCP I) also known as angiotensin converting enzyme or peptidyl dipeptidase A, are rate limiting in the breakdown of the amide bond of proline residues in gliadins and can cleave peptide sequences in casomorphins. These conclusions have been verified in human adult biopsies (Schuppan 2000), where supplementation of DPP IV leads to rapid cleavage of these gliadin peptides to much smaller units; too small to bind to the major histocompatibility complex Human Leukocyte antigens (HLA) molecule.

The above serves as the basis for supplementation of DPP IV as enzyme therapy for celiac sprue and gluten/casomorphin sensitive children with regressive autism. Currently the main option is strict exclusion of gliadin and dairy rich foods.

DPP IV - Enzyme therapy and Autism

Beyond the case reports by DAN! doctors, the clinical data available in the literature is scarce for intervention of DPP IV for the treatment of regressive autism. However, in an uncontrolled pilot study, enzyme therapy was evaluated in those with autism between the ages of two and 21 (Brudnak 2002). This small, uncontrolled trial appears to be the only clinical trial implementing oral supplemental enzymes to address the theory that foods are not just nutrients, but bioactive substances that may impact those with autism.

The following enzymes and activities were utilized in the study: Caso-Glutenase (DPP IV) 10,000 AU; Bromelain 230 BTU; acid fast protease 100 SAPU; lactase 330 LacU; phytase 125 U; galactose 100 mg (One-half to one capsule with each meal).

Galactose was included in the enzyme formula to function as a "genomeceutical" to potentially increase the expression of DPP IV/CD26. This has been shown in murine enterocytes where galactose can increase the expression of DPP IV (Smith 1991). The participants in the study were evaluated on 13 parameters; eye contact, socialization, attention, mood, anxiety/compulsion, stimming, comprehension, speech, sound sensitivity, digestion and sleep.

The results of the study displayed an overwhelmingly positive trend for each of the 13 parameters. The authors reported, "An overwhelmingly positive trend is seen for each of the parameters. The two greatest improvements were seen in socialization and hyperactivity with 90% and 80% improvements, respectively." "The lowest improvements were for stimming, speech and sound sensitivity, each scoring 50%" (Brudnak 2002).

It should be noted that of the original 46 participants that started the trial, only 22 remained for the entire 12-week period. The authors suggested that families were instructed not to start any new therapies while in the study, however, several families had an unexpectedly strong desire to implement other treatment approaches during the 12 weeks. These participants were therefore not eligible to continue in the trial, leaving 22 participants completing the 12 weeks.

Conclusion

Clinical evidence pertaining to the use of DPP IV enzyme therapy is scarce. However, an impressive body of preclinical evidence suggests significant clinical utility from oral administration of this enzyme. Reproducible findings consistent with inflammatory bowel disease, as well as recognition of a trend for gross under expression of DPP IV among autistic patients provides a sound rationale for proposing oral therapy with the enzyme. Preclinical evidence demonstrating neurological consequences of circulating partial digestion products of gliadin and casein lend further support for attempting oral DPP IV therapy. Positive outcomes produced in the one available pilot trial, as well as the case reports presented through DAN! webcasts, strengthen the basis for implementing oral DPP IV therapy in autistic patients.

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