Scientific References from,

"Living Life to the Fullest...Dietary Effects on Neurotransmitters, Depression and Anxiety"

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1. **Addolorato G, et al. "Rapid regression of psoriasis in a coeliac patient after gluten-free diet. A case report and review of the literature." Digestion. 2003;68(1):9-12.**
http://www.ncbi.nlm.nih.gov/pubmed/12949434

ABSTRACT

BACKGROUND:
Several skin disorders are present in patients affected by coeliac disease (CD) - among them, psoriasis has been described. However, at present the relationship between CD and psoriasis remains controversial since there are few and contrasting data on this topic.
METHOD:
Here we describe a case of psoriasis in a CD patient not responding to specific therapies for psoriasis.
RESULT:
The regression of skin lesions after gluten-free diet (GFD) was evident in a short time.
CONCLUSION:
The present case supports the association between CD and psoriasis and the concept that psoriasis in CD patients can be improved by GFD. Future studies are needed to clarify the possible mechanisms involved in this association.

2. **Rao AV, et al. "A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome." Gut Pathogens, 2009 Mar 19;1(1):6.**
http://www.ncbi.nlm.nih.gov/pubmed/19338686

ABSTRACT

Chronic fatigue syndrome (CFS) is complex illness of unknown etiology. Among the broad range of symptoms, many patients report disturbances in the emotional realm, the most frequent of which is anxiety. Research shows that patients with CFS and other so-called functional somatic disorders have alterations in the intestinal microbial flora. Emerging studies have suggested that pathogenic and non-pathogenic gut bacteria might influence mood-related symptoms and even behavior in animals and humans. In this pilot study, 39 CFS patients were randomized to receive either 24 billion colony forming units of Lactobacillus casei strain Shirota (LcS) or a placebo daily for two months. Patients provided stool samples and completed the Beck Depression and Beck Anxiety Inventories before and after the intervention. We found a significant rise in both Lactobacillus and Bifidobacteria in those taking the LcS, and there was also a significant decrease in anxiety symptoms among those taking the probiotic vs controls ($p = 0.01$). These results lend further support to the presence of a gut-brain interface, one that may be mediated by microbes that reside or pass through the intestinal tract.

3. **Severance EG, et al. "Gastrointestinal inflammation and associated immune activation in schizophrenia." Schizophr Res. 2012 Jun;138(1):48-53.**
http://www.ncbi.nlm.nih.gov/pubmed/22446142

ABSTRACT

Immune factors are implicated in normal brain development and in brain disorder pathogenesis. Pathogen infection and food antigen penetration across gastrointestinal barriers are means by which environmental factors might affect immune-related neurodevelopment. Here, we test if gastrointestinal inflammation is associated with schizophrenia and therefore, might contribute to bloodstream entry of potentially neurotropic milk and gluten exorphins and/or immune activation by food antigens. IgG antibodies to Saccharomyces cerevisiae (ASCA, a marker of intestinal inflammation), bovine milk casein, wheat-derived gluten, and 6 infectious agents were assayed. Cohort 1 included 193 with non-recent onset schizophrenia, 67 with recent onset schizophrenia and 207 non-psychiatric controls. Cohort 2 included 103 with first episode schizophrenia, 40 of whom were antipsychotic-naïve. ASCA markers were significantly elevated and correlated with food antigen antibodies in recent onset and non-recent onset schizophrenia compared to controls ($p \leq 0.00001$-0.004) and in unmedicated individuals with first episode schizophrenia compared to those receiving antipsychotics ($p \leq 0.05$-0.01). Elevated ASCA levels were especially evident in non-recent onset females ($p \leq 0.009$), recent onset males ($p \leq 0.01$) and in antipsychotic-naïve males ($p \leq 0.03$). Anti-food antigen antibodies were correlated to antibodies against Toxoplasma gondii, an intestinally-infectious pathogen, particularly in males with recent onset schizophrenia ($p \leq 0.002$). In conclusion, gastrointestinal inflammation is a relevant pathology in schizophrenia, appears to occur in the absence of but may be modified by antipsychotics, and may link food antigen sensitivity and microbial infection as sources of immune activation in mental illness.

4. **Douglas-Escobar M, et al. "Effect of intestinal microbial ecology on the developing brain." JAMA Pediatr. 2013 Apr;167(4):374-9.**
http://www.ncbi.nlm.nih.gov/pubmed/23400224

ABSTRACT

The mammalian gastrointestinal tract harbors a highly diverse microbial population that plays a major role in nutrition, metabolism, protection against pathogens, and development of the immune system. It is estimated that at least 1000 different bacterial species cohabit the human intestinal tract. Most recently, the Human Microbiome Project, using new genomic technologies, has started a catalog of specific microbiome composition and its correlation with health and specific diseases. Herein we provide a brief review of the intestinal microbiome, with a focus on new studies showing that there is an important link between the microbes that inhabit the intestinal tract and the developing brain. With future research, an understanding of this link may help us to treat various neurobehavioral problems such as autism, schizophrenia, and anxiety.

5. **Karlsson H, et al. "Maternal antibodies to dietary antigens and risk for nonaffective psychosis in offspring." Am J Psychiatry. 2012 Jun;169(6):625-32.**
http://www.ncbi.nlm.nih.gov/pubmed/22535227

ABSTRACT

OBJECTIVE:
The authors analyzed archival dried blood spots obtained from newborns to assess whether levels of immunoglobulin G (IgG) directed at dietary antigens were associated with a later diagnosis of a non-affective psychotic disorder.
METHOD:
The study population consisted of individuals born in Sweden between 1975 and 1985 with verified register-based diagnoses of nonaffective psychoses made between 1987 and 2003 and comparison subjects matched on sex, date of birth, birth hospital, and municipality. A total of 211 case subjects and 553 comparison subjects consented to participate in the study. Data on factors associated with maternal status, pregnancy, and delivery were extracted from the Swedish Medical Birth Register. Levels of IgG directed at gliadin (a component of gluten) and casein (a milk protein) were analyzed in eluates from dried blood spots by enzyme-linked immunosorbent assay. Odds ratios were calculated for levels of IgG directed at gliadin or casein for nonaffective psychosis.
RESULTS:
Levels of anti-gliadin IgG (but not anti-casein IgG) above the 90th percentile of levels observed among comparison subjects were associated with nonaffective psychosis (odds ratio=1.7, 95% CI=1.1-2.8). This association was not confounded by differences in maternal age, immigrant status, or mode of delivery. Similarly, gestational age at birth, ponderal index, and birth weight were not related to maternal levels of anti-gliadin IgG.
CONCLUSIONS:
High levels of anti-gliadin IgG in the maternal circulation are associated with an elevated risk for the development of a nonaffective psychosis in offspring. Research is needed to identify the mechanisms underlying this association in order to develop preventive strategies.

6. **Braunschweig D, et al. "Autism: maternally derived antibodies specific for fetal brain proteins." Neurotoxicology. 2008 Mar;29(2):226-31.**
http://www.ncbi.nlm.nih.gov/pubmed/18078998

ABSTRACT

Autism is a profound disorder of neurodevelopment with poorly understood biological origins. A potential role for maternal autoantibodies in the etiology of some cases of autism has been proposed in previous studies. To investigate this hypothesis, maternal plasma antibodies against human fetal and adult brain proteins were analyzed by western blot in 61 mothers of children with autistic disorder and 102 controls matched for maternal age and birth year (62 mothers of typically developing children (TD) and 40 mothers of children with non-ASD developmental delays (DD)). We observed reactivity to two protein bands at approximately 73 and 37kDa in plasma from 7 of 61 (11.5%) mothers of children with autism (AU) against fetal but not adult brain, which was not noted in either control group (TD; 0/62 p=0.0061 and DD; 0/40 p=0.0401). Further, the presence of reactivity to these two bands was associated with parent report of behavioral regression in AU children when compared to the TD (p=0.0019) and DD (0.0089) groups. Individual reactivity to the

37kDa band was observed significantly more often in the AU population compared with TD (p=0.0086) and DD (p=0.002) mothers, yielding a 5.69-fold odds ratio (95% confidence interval 2.09-15.51) associated with this band. The presence of these antibodies in the plasma of some mothers of children with autism, as well as the differential findings between mothers of children with early onset and regressive autism may suggest an association between the transfer of IgG autoantibodies during early neurodevelopment and the risk of developing of autism in some children.

7. **Lau NM, et al. "Markers of Celiac Disease and Gluten Sensitivity in Children with Autism." PLoS One. 2013 Jun 18;8(6):e66155.**
http://www.ncbi.nlm.nih.gov/pubmed/23823064

ABSTRACT

OBJECTIVE:
Gastrointestinal symptoms are a common feature in children with autism, drawing attention to a potential association with celiac disease or gluten sensitivity. However, studies to date regarding the immune response to gluten in autism and its association with celiac disease have been inconsistent. The aim of this study was to assess immune reactivity to gluten in pediatric patients diagnosed with autism according to strict criteria and to evaluate the potential link between autism and celiac disease.
METHODS:
Study participants included children (with or without gastrointestinal symptoms) diagnosed with autism according to both the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview, Revised (ADI-R) (n = 37), their unaffected siblings (n = 27), and age-matched healthy controls (n = 76). Serum specimens were tested for antibodies to native gliadin, deamidated gliadin, and transglutaminase 2 (TG2). Affected children were genotyped for celiac disease associated HLA-DQ2 and -DQ8 alleles.
RESULTS:
Children with autism had significantly higher levels of IgG antibody to gliadin compared with unrelated healthy controls ($p<0.01$). The IgG levels were also higher compared to the unaffected siblings, but did not reach statistical significance. The IgG anti-gliadin antibody response was significantly greater in the autistic children with gastrointestinal symptoms in comparison to those without them ($p<0.01$). There was no difference in IgA response to gliadin across groups. The levels of celiac disease-specific serologic markers, i.e., antibodies to deamidated gliadin and TG2, did not differ between patients and controls. An association between increased anti-gliadin antibody and presence of HLA-DQ2 and/or -DQ8 was not observed.
CONCLUSIONS:
A subset of children with autism displays increased immune reactivity to gluten, the mechanism of which appears to be distinct from that in celiac disease. The increased anti-gliadin antibody response and its association with GI symptoms points to a potential mechanism involving immunologic and/or intestinal permeability abnormalities in affected children.

8. **Ventura MT, et al. "Intestinal permeability in patients with adverse reactions to food." Dig Liver Dis. 2006 Oct;38(10):732-6.**
http://www.ncbi.nlm.nih.gov/pubmed/16880015

ABSTRACT

BACKGROUND:
An abnormal intestinal permeability could contribute to establish an altered sensitivity to food-allergen**.**
AIM:
To evaluate the intestinal permeability in subjects with adverse reactions to food on allergen-free diet.
SUBJECTS:
Twenty-one patients with food allergy and 20 with food hypersensitivity on allergen-free diet were enrolled and divided in four groups according to the seriousness of their referred clinical symptoms when they were on a free diet.
METHODS:
Intestinal permeability was evaluated by Lactulose/Mannitol ratio urinary detection determined by anion-exchange chromatography.
RESULTS:
Statistically significant different Lactulose/Mannitol ratio was evidenced in subjects with food allergy ($p=0.003$) or hypersensitivity ($p=0.0008$) compared to control patients. The correlation between Lactulose/Mannitol ratio and the seriousness of clinical symptoms, by using Spearman test, was statistically significant for food allergy ($p=0.0195$) and hypersensitivity ($p=0.005$) patients.
CONCLUSIONS:
The present data demonstrate that impaired intestinal permeability, measured in our conditions, is present in all subjects with adverse reactions to food. In addition, for the first time, we report a statistically significant association between the severity of referred clinical symptoms and the increasing of Intestinal Permeability Index. These data reveal that intestinal permeability is not strictly dependent on IgE-mediated processes but could better be related to other mechanisms involved in early food sensitisation, as breast-feeding, or microbial environment that influence the development of oral tolerance in early infancy.

9. **Bischoff SC, et al. "Intestinal permeability--a new target for disease prevention and therapy." BMC Gastroenterol. 2014 Nov 18;14:189.**
http://www.ncbi.nlm.nih.gov/pubmed/25407511

ABSTRACT

Data are accumulating that emphasize the important role of the intestinal barrier and intestinal permeability for health and disease. However, these terms are poorly defined, their assessment is a matter of debate, and their clinical significance is not clearly established. In the present review, current knowledge on mucosal barrier and its role in disease prevention and therapy is summarized. First, the relevant terms 'intestinal barrier' and 'intestinal permeability' are defined. Secondly, the key element of the intestinal barrier affecting permeability are described. This barrier represents a huge mucosal surface, where billions of bacteria face the largest immune system of our body. On the one hand, an intact intestinal barrier protects the human organism

against invasion of microorganisms and toxins, on the other hand, this barrier must be open to absorb essential fluids and nutrients. Such opposing goals are achieved by a complex anatomical and functional structure the intestinal barrier consists of, the functional status of which is described by 'intestinal permeability'. Third, the regulation of intestinal permeability by diet and bacteria is depicted. In particular, potential barrier disruptors such as hypoperfusion of the gut, infections and toxins, but also selected over-dosed nutrients, drugs, and other lifestyle factors have to be considered. In the fourth part, the means to assess intestinal permeability are presented and critically discussed. The means vary enormously and probably assess different functional components of the barrier. The barrier assessments are further hindered by the natural variability of this functional entity depending on species and genes as well as on diet and other environmental factors. In the final part, we discuss selected diseases associated with increased intestinal permeability such as critically illness, inflammatory bowel diseases, celiac disease, food allergy, irritable bowel syndrome, and--more recently recognized--obesity and metabolic diseases. All these diseases are characterized by inflammation that might be triggered by the translocation of luminal components into the host. In summary, intestinal permeability, which is a feature of intestinal barrier function, is increasingly recognized as being of relevance for health and disease, and therefore, this topic warrants more attention.

10. **Thomas KR, et al. "Gliadin stimulation of murine macrophage inflammatory gene expression and intestinal permeability are MyD88-dependent: role of the innate immune response in Celiac disease." J Immunol. 2006 Feb 15;176(4):2512-21.**
http://www.ncbi.nlm.nih.gov/pubmed/16456012

ABSTRACT

Recent studies have demonstrated the importance of TLR signaling in intestinal homeostasis. Celiac disease (CD) is an autoimmune enteropathy triggered in susceptible individuals by the ingestion of gliadin-containing grains. In this study, we sought to test the hypothesis that gliadin initiates this response by stimulating the innate immune response to increase intestinal permeability and by up-regulating macrophage proinflammatory gene expression and cytokine production. To this end, intestinal permeability and the release of zonulin (an endogenous mediator of gut permeability) in vitro, as well as proinflammatory gene expression and cytokine release by primary murine macrophage cultures, were measured. Gliadin and its peptide derivatives, 33-mer and p31-43, were found to be potent inducers of both a zonulin-dependent increase in intestinal permeability and macrophage proinflammatory gene expression and cytokine secretion. Gliadin-induced zonulin release, increased intestinal permeability, and cytokine production were dependent on myeloid differentiation factor 88 (MyD88), a key adapter molecule in the TLR/IL-1R signaling pathways, but were neither TLR2- nor TLR4-dependent. Our data support the following model for the innate immune response to gliadin in the initiation of CD. Gliadin interaction with the intestinal epithelium increases intestinal permeability through the MyD88-dependent release of zonulin that, in turn, enables paracellular translocation of gliadin and its subsequent interaction with macrophages within the intestinal submucosa. There, the interaction of gliadin with macrophages elicits a MyD88-dependent proinflammatory cytokine milieu that facilitates the interaction of T cells with APCs, leading ultimately to the Ag-specific adaptive immune response seen in patients with CD.

11. **Volta U, et al. "Serological tests in gluten sensitivity (nonceliac gluten intolerance)." J Clin Gastroenterol. 2012 Sep;46(8):680-5.**
http://www.ncbi.nlm.nih.gov/pubmed/22138844

ABSTRACT

GOALS:
To characterize the serological pattern of gluten sensitivity (GS) and to compare it with that found in celiac disease.
BACKGROUND:
GS has recently been identified as a new clinical entity included in the spectrum of gluten-related disorders, but it is still lacking of diagnostic markers.
STUDY:
Sera from 78 patients with GS and 80 patients with celiac disease were retrospectively assessed for immunoglobulin (Ig)G/IgA antigliadin antibodies (AGA), IgG deamidated gliadin peptide antibodies (DGP-AGA), IgA tissue transglutaminase antibodies (tTGA), and IgA endomysial antibodies (EmA).
RESULTS:
IgG AGA were positive in 56.4% of GS patients and in 81.2% of celiac patients, with high antibody titers in both groups. IgA AGA were detected in 7.7% of GS patients and in 75% of celiac patients, showing lower enzyme-linked immunosorbent assay activities in GS than those found in celiac disease. Only 1 of the 78 patients with GS was positive for IgG DGP-AGA (detected in 88.7% of patients with celiac disease). IgA tTGA and IgA EmA were negative in all GS patients, whereas their positivity in celiac patients was 98.7% and 95%, respectively. Patients with GS displayed a variegated clinical picture with intestinal and extraintestinal symptoms (abdominal pain, bloating, diarrhea, constipation, foggy mind, tiredness, eczema/skin rash, headache, joint/muscle pain, numbness of legs/arms, depression, and anemia) together with normal or mildly abnormal small intestinal mucosa.
CONCLUSIONS:
The serological pattern of GS is characterized by IgG AGA positivity in more than half of cases associated to IgA AGA in a few patients, but without EmA, tTGA, and DGP-AGA, which are the specific markers of celiac disease.

12. **Hollon J, et al. "Effect of gliadin on permeability of intestinal biopsy explants from celiac disease patients and patients with non-celiac gluten sensitivity." Nutrients. 2015 Feb 27;7(3):1565-76.**
http://www.ncbi.nlm.nih.gov/pubmed/25734566

ABSTRACT

BACKGROUND:
Intestinal exposure to gliadin leads to zonulin upregulation and consequent disassembly of intercellular tight junctions and increased intestinal permeability. We aimed to study response to gliadin exposure, in terms of barrier function and cytokine secretion, using intestinal biopsies obtained from four groups: celiac patients with active disease (ACD), celiac patients in remission (RCD), non-celiac patients with gluten sensitivity (GS) and non-celiac controls (NC).

METHODS:
Ex-vivo human duodenal biopsies were mounted in microsnapwells and luminally incubated with either gliadin or media alone. Changes in transepithelial electrical resistance were monitored over 120 min. Media was subsequently collected and cytokines quantified.
RESULTS:
Intestinal explants from all groups (ACD (n = 6), RCD (n = 6), GS (n = 6), and NC (n = 5)) demonstrated a greater increase in permeability when exposed to gliadin vs. media alone. The increase in permeability in the ACD group was greater than in the RCD and NC groups. There was a greater increase in permeability in the GS group compared to the RCD group. There was no difference in permeability between the ACD and GS groups, between the RCD and NC groups, or between the NC and GS groups. IL-10 was significantly greater in the media of the NC group compared to the RCD and GS groups.
CONCLUSIONS:
Increased intestinal permeability after gliadin exposure occurs in all individuals. Following gliadin exposure, both patients with gluten sensitivity and those with active celiac disease demonstrate a greater increase in intestinal permeability than celiacs in disease remission. A higher concentration of IL-10 was measured in the media exposed to control explants compared to celiac disease in remission or gluten sensitivity.

13. **Tuncer S, et al. "Regression of conjunctival tumor during dietary treatment of celiac disease." Indian J Ophthalmol. 2010 Sep-Oct;58(5):433-4.**
http://www.ncbi.nlm.nih.gov/pubmed/20689203

ABSTRACT

A 3-year-old girl presented with a hemorrhagic conjunctival lesion in the right eye. The medical history revealed premature cessation of breast feeding, intolerance to the ingestion of baby foods, anorexia, and abdominal distention. Prior to her referral, endoscopic small intestinal biopsy had been carried out under general anesthesia with a possible diagnosis of Celiac Disease (CD). Her parents did not want their child to undergo general anesthesia for the second time for the excisional biopsy. We decided to follow the patient until all systemic investigations were concluded. In evaluation, the case was diagnosed with CD and the conjunctival tumor showed complete regression during gluten-free dietary treatment. The clinical fleshy appearance of the lesion with spider-like vascular extensions and subconjunctival hemorrhagic spots, possible association with an acquired immune system dysfunction due to CD, and spontaneous regression by a gluten-free diet led us to make a presumed diagnosis of conjunctival Kaposi sarcoma.

14. **Addolorato G, et al. "Affective and psychiatric disorders in celiac disease." Dig Dis. 2008;26(2):140-8.**
http://www.ncbi.nlm.nih.gov/pubmed/18431064

ABSTRACT

Several extraintestinal clinical manifestations have been reported in celiac disease (CD). Among them, growing evidence suggests the association between CD and affective and psychiatric disorders. In this review the most frequent affective and psychiatric disorders associated with CD and the possible mechanisms involved in these associations were analyzed. The available data suggest that screening for CD in patients with affective and/or psychiatric symptoms may be useful since these disorders could be the expression of an organic disease rather than primary psychiatric illnesses.

15. **Pynnönen PA, et al. "Gluten-free diet may alleviate depressive and behavioural symptoms in adolescents with coeliac disease: a prospective follow-up case-series study." BMC Psychiatry. 2005 Mar 17;5:14.**
http://www.ncbi.nlm.nih.gov/pubmed/15774013

ABSTRACT

BACKGROUND
Coeliac disease in adolescents has been associated with an increased prevalence of depressive and disruptive behavioural disorders, particularly in the phase before diet treatment. We studied the possible effects of a gluten-free diet on psychiatric symptoms, on hormonal status (prolactin, thyroidal function) and on large neutral amino acid serum concentrations in adolescents with coeliac disease commencing a gluten-free diet.
METHODS
Nine adolescents with celiac disease, aged 12 to 16 years, were assessed using the semi-structured K-SADS-Present and Lifetime Diagnostic interview and several symptom scales. Seven of them were followed at 1 to 2, 3, and 6 months on a gluten-free diet.
RESULTS
Adolescent coeliac disease patients with depression had significantly lower pre-diet tryptophan/competing amino-acid (CAA) ratios and free tryptophan concentrations, and significantly higher biopsy morning prolactin levels compared to those without depression. A significant decrease in psychiatric symptoms was found at 3 months on a gluten-free diet compared to patients' baseline condition, coinciding with significantly decreased coeliac disease activity and prolactin levels and with a significant increase in serum concentrations of CAAs.
CONCLUSION
Although our results of the amino acid analysis and prolactin levels in adolescents are only preliminary, they give support to previous findings on patients with coeliac disease, suggesting that serotonergic dysfunction due to impaired availability of tryptophan may play a role in vulnerability to depressive and behavioural disorders also among adolescents with untreated coeliac disease.

16. **Gabrielli M, et al. "Association between migraine and Celiac disease: results from a preliminary case-control and therapeutic study." Am J Gastroenterol. 2003 Mar;98(3):625-9.**
http://www.ncbi.nlm.nih.gov/pubmed/12650798

ABSTRACT

OBJECTIVES:
Subclinical celiac disease (CD) has been associated with various neurological disorders, the most common being neuropathy and cerebellar ataxia. The aims of the present study were to assess the following: 1) the prevalence of CD in patients affected by migraine; 2) whether there are regional cerebral blood flow abnormalities in migraine patients with CD compared to migraine patients without CD; and 3) the effects of a gluten free diet in migraine patients with CD.
METHODS:
A total of 90 patients affected by idiopathic migraine were enrolled, and 236 blood donors were used as controls. Serum IgG antitransglutaminase (TgA) and IgA antiendomysial (EmA) were measured. In positive cases, diagnosis was confirmed endoscopically. A gluten free diet was started in the patients diagnosed with CD, who were followed for 6 months. A single photon emission CT brain study was performed before and after a gluten free diet.
RESULTS:
Four of 90 (4.4%; 95% CI = 1.2-11.0) migraine patients were found to have CD compared with 0.4% (95% CI = 0.01-2.3) blood donor controls ($p < 0.05$). During the 6 months of gluten free diet, one of the four patients had no migraine attacks, and the remaining three patients experienced an improvement in frequency, duration, and intensity of migraine. Single photon emission CT studies showed a regional baseline reduction in brain tracer uptake in all four patients. Such reduction in uptake completely resolved at follow-up.
CONCLUSIONS:
Our results suggest that a significant proportion of patients with migraine may have CD, and that a gluten free diet may lead to a improvement in the migraine in these patients.

17. **Delgado M. "Inhibition of interferon (IFN) gamma-induced Jak-STAT1 activation in microglia by vasoactive intestinal peptide: inhibitory effect on CD40, IFN-induced protein-10, and inducible nitric-oxide synthase expression." J Biol Chem. 2003 Jul 25;278(30):27620-9. Epub 2003 May 15.**
http://www.ncbi.nlm.nih.gov/pubmed/12754213

ABSTRACT

Interferon (IFN)-gamma is one of the most important microglia stimulators in vivo participating in inflammation and Th1 activation/differentiation. IFN-gamma-mediated signaling involves the activation of the Jak/STAT1 pathway. The neuropeptides vasoactive intestinal peptide (VIP) and the pituitary adenylate cyclase activating polypeptide (PACAP) are two potent microglia-deactivating factors that inhibit the production of proinflammatory mediators in vitro and in vivo. The present study investigated the molecular mechanisms involved in the VIP/PACAP regulation of several IFN-gamma-induced microglia-derived factors, including IFN-gamma-inducible protein-10 (IP-10), inducible nitric-oxide synthase (iNOS), and CD40. The results indicate that VIP/PACAP inhibit Jak1-2 and STAT1 phosphorylation, and the binding of activated STAT1 to the IFN-gamma activated site motif in the IFN regulatory factor-1 and CD40 promoter and to the IFN-stimulated response

element motif of the IP-10 promoter. Through its effect in the IFN-gamma-induced Jak/STAT1 pathway, VIP and PACAP are able to control the gene expression of IP-10, CD40, and iNOS, three microglia-derived mediators that play an essential role in several pathologies, i.e. inflammation and autoimmune disorders. The effects of VIP/PACAP are mediated through the specific receptor VPAC1 and the cAMP/protein kinase A transduction pathway. Because IFN-gamma is a major stimulator of innate and adaptive immune responses in vivo, the down-regulation of IFN-gamma-induced gene expression by VIP and PACAP could represent a significant element in the regulation of the inflammatory response in the central nervous system by endogenous neuropeptides.

18. **Dejda A, et al. "Neuroprotective potential of three neuropeptides PACAP, VIP and PHI." Pharmacol Rep. 2005 May-Jun;57(3):307-20.**
http://www.ncbi.nlm.nih.gov/pubmed/15985713

ABSTRACT

Pituitary adenylate cyclase activating polypeptide (PACAP), vasoactive intestinal peptide (VIP) and peptide histidine-isoleucine (PHI), are structurally related endogenous peptides widely expressed in the central and peripheral nervous system and showing rich profile of biological activities. They act as neurotransmitters, neuromodulators and neurotrophic factors. Recently, their neuroprotective potential has been revealed in numerous in vitro and in vivo models. Thus, PACAP and VIP protected the cells from neurotoxic effects of ethanol, hydrogen peroxide (H2O2, beta-amyloid and glycoprotein 120 (gp120). Moreover, PACAP showed neuroprotection against glutamate, human prion protein fragment 106-126 [PrP(106-126)] and C2-ceramide. Both peptides reduced brain damage after ischemia and ameliorated neurological deficits in a model of Parkinson's disease. Neuroprotective potential of PHI has not been thoroughly investigated yet, but several results obtained in the last years do not exclude it. The mechanism underlying neuroprotective properties of PACAP seems to involve activation of adenylyl cyclase (AC) --> cyclic adenosine 3',5'-mono-phosphate (cAMP) --> protein kinase A (PKA) and mitogen-activated protein (MAP) kinase pathways, and inhibition of caspase-3. PACAP can also, yet indirectly, stimulate astrocytes to release neuroprotective factors, such as regulated upon activation normal T cell expressed and secreted (RANTES) and macrophage inflammatory protein 1 (MIP-1) chemokines. Neuroprotective activity of VIP seems to involve an indirect mechanism requiring astrocytes. VIP-stimulated astrocytes secrete neuroprotective proteins, including activity-dependent neurotrophic factor (ADNF) and activity-dependent neuroprotective protein (ADNP), as well as a number of cytokines. However, in the activated microglia, VIP and PACAP are capable of inhibiting the production of inflammatory mediators which can lead to neurodegenerative processes within the brain. In conclusion, studies carried out on the central nervous system have shown that PACAP, VIP, and likely PHI, are endowed with a neuroprotective potential, which renders them (or their derivatives) promising therapeutic agents in several psychoneurological disorders linked to neurodegeneration.

19. **Hernanz A, et al. "Gastrointestinal peptide profile in children with celiac disease." J Pediatr Gastroenterol Nutr. 1987 May-Jun;6(3):341-5.**
http://www.ncbi.nlm.nih.gov/pubmed/2892903

ABSTRACT

In order to investigate if a plasma profile of gastrointestinal peptides reflects changes in jejunal mucosa in celiac disease, we studied basal and postprandial plasma levels of gastrin, secretin, somatostatin, vasoactive intestinal polypeptide (VIP), and neurotensin in children with untreated and treated celiac disease and in a control group of children. Basal and 30-min postprandial secretin concentrations were statistically significantly lower in untreated celiac children compared to both treated celiac (p less than 0.01 and p less than 0.05, respectively) and control children (p less than 0.001). Plasma secretin levels 30 min after a breakfast meal were also statistically significantly lower (p less than 0.001) in treated celiac children with respect to the control group. In both untreated and treated celiac groups, basal and postprandial plasma levels of somatostatin and VIP were statistically significantly decreased (p less than 0.001) compared to control children. Moreover, there was a significant rise in postprandial levels of neurotensin after a breakfast meal in untreated celiac children. On the contrary, there was no rise of neurotensin in healthy children. These findings seem to indicate that determination of plasma profile of gastrointestinal peptides in children with celiac disease may be useful in monitoring the development of this disease and, thus, the number of jejunal biopsies could be decreased.

20. **Rossignol DA, et al. "Hyperbaric treatment for children with autism: a multicenter, randomized, double-blind, controlled trial." BMC Pediatrics 2009, 9:21.**
http://www.biomedcentral.com/1471-2431/9/21/abstract

ABSTRACT

BACKGROUND
Several uncontrolled studies of hyperbaric treatment in children with autism have reported clinical improvements; however, this treatment has not been evaluated to date with a controlled study. We performed a multicenter, randomized, double-blind, controlled trial to assess the efficacy of hyperbaric treatment in children with autism.
METHODS
62 children with autism recruited from 6 centers, ages 2–7 years (mean 4.92 ± 1.21), were randomly assigned to 40 hourly treatments of either hyperbaric treatment at 1.3 atmosphere (atm) and 24% oxygen ("treatment group", n = 33) or slightly pressurized room air at 1.03 atm and 21% oxygen ("control group", n = 29). Outcome measures included Clinical Global Impression (CGI) scale, Aberrant Behavior Checklist (ABC), and Autism Treatment Evaluation Checklist (ATEC).

RESULTS

After 40 sessions, mean physician CGI scores significantly improved in the treatment group compared to controls in overall functioning ($p = 0.0008$), receptive language ($p < 0.0001$), social interaction ($p = 0.0473$), and eye contact ($p = 0.0102$); 9/30 children (30%) in the treatment group were rated as "very much improved" or "much improved" compared to 2/26 (8%) of controls ($p = 0.0471$); 24/30 (80%) in the treatment group improved compared to 10/26 (38%) of controls ($p = 0.0024$). Mean parental CGI scores significantly improved in the treatment group compared to controls in overall functioning ($p = 0.0336$), receptive language ($p = 0.0168$), and eye contact ($p = 0.0322$). On the ABC, significant improvements were observed in the treatment group in total score, irritability, stereotypy, hyperactivity, and speech ($p < 0.03$ for each), but not in the control group. In the treatment group compared to the control group, mean changes on the ABC total score and subscales were similar except a greater number of children improved in irritability ($p = 0.0311$). On the ATEC, sensory/cognitive awareness significantly improved ($p = 0.0367$) in the treatment group compared to the control group. Post-hoc analysis indicated that children over age 5 and children with lower initial autism severity had the most robust improvements. Hyperbaric treatment was safe and well-tolerated.

CONCLUSION

Children with autism who received hyperbaric treatment at 1.3 atm and 24% oxygen for 40 hourly sessions had significant improvements in overall functioning, receptive language, social interaction, eye contact, and sensory/cognitive awareness compared to children who received slightly pressurized room air.

21. **Addolorato G, et al. "Regional cerebral hypoperfusion in patients with celiac disease." Am J Med. 2004 Mar 1;116(5):312-7.**
http://www.ncbi.nlm.nih.gov/pubmed/14984816

ABSTRACT

BACKGROUND:

Neurological and psychiatric disorders occur in approximately 10% of patients with celiac disease. Although some of these alterations respond to a gluten-free diet, the etiology of these abnormalities is uncertain. Because of a case report that cerebral hypoperfusion in a celiac patient resolved after a gluten-free diet, we studied brain perfusion changes in untreated celiac patients, treated celiac patients, and healthy controls.

METHODS:

A total of 15 untreated celiac patients without conditions affecting brain perfusion were enrolled; none had neurological or psychiatric disorders other than anxiety or depression. We also studied 15 celiac patients who were on a gluten-free diet for almost 1 year, and 24 healthy volunteers of similar sex and age. All subjects underwent cerebral single photon emission computed tomography examination.

RESULTS:

Of the 15 untreated celiac patients, 11 (73%) had at least one hypoperfused brain region, compared with only 1 (7%) of the 15 celiac patients on a gluten-free diet and none of the controls ($P = 0.01$). Cerebral perfusion was significantly lower ($P < 0.05$) in untreated celiac patients, compared with healthy controls, in 7 of 26 brain regions. No significant differences in cerebral perfusion were found between celiac patients on a gluten-free diet and healthy controls.

CONCLUSION:
There is evidence of regional cerebral blood flow alteration in untreated celiac patients.

22. **Hadjivassiliou M, et al. "Transglutaminase 6 antibodies in the diagnosis of gluten ataxia." Neurology. 2013 May 7;80(19):1740-5.**
http://www.ncbi.nlm.nih.gov/pubmed/23576621

ABSTRACT

OBJECTIVES:
The previous finding of an immunologic response primarily directed against transglutaminase (TG)6 in patients with gluten ataxia (GA) led us to investigate the role of TG6 antibodies in diagnosing GA.
METHODS:
This was a prospective cohort study. We recruited patients from the ataxia, gluten/neurology, celiac disease (CD), and movement disorder clinics based at Royal Hallamshire Hospital (Sheffield, UK) and the CD clinic, Tampere University Hospital (Tampere, Finland). The groups included patients with idiopathic sporadic ataxia, GA, and CD, and neurology and healthy controls. All were tested for TG6 antibodies. Duodenal biopsies were performed in patients with positive serology. In addition, biopsies from 15 consecutive patients with idiopathic sporadic ataxia and negative serology for gluten-related disorders were analyzed for immunoglobulin A deposits against TG.
RESULTS:
The prevalence of TG6 antibodies was 21 of 65 (32%) in idiopathic sporadic ataxia, 35 of 48 (73%) in GA, 16 of 50 (32%) in CD, 4 of 82 (5%) in neurology controls, and 2 of 57 (4%) in healthy controls. Forty-two percent of patients with GA had enteropathy as did 51% of patients with ataxia and TG6 antibodies. Five of 15 consecutive patients with idiopathic sporadic ataxia had immunoglobulin A deposits against TG2, 4 of which subsequently tested positive for TG6 antibodies. After 1 year of gluten-free diet, TG6 antibody titers were significantly reduced or undetectable.
CONCLUSIONS:
Antibodies against TG6 are gluten-dependent and appear to be a sensitive and specific marker of GA.

23. **Hadivassiliou M. et al. "Gluten Sensitivity from Gut to Brain." Lanct Neurol 2010;9:318-30.**
http://www.ncbi.nlm.nih.gov/pubmed/20170845

ABSTRACT

Gluten sensitivity is a systemic autoimmune disease with diverse manifestations. This disorder is characterised by abnormal immunological responsiveness to ingested gluten in genetically susceptible individuals. Coeliac disease, or gluten-sensitive enteropathy, is only one aspect of a range of possible manifestations of gluten sensitivity. Although neurological manifestations in patients with established coeliac disease have been reported since 1966, it was not until 30 years later that, in some individuals, gluten sensitivity was shown to manifest solely with neurological dysfunction. Furthermore, the concept of extraintestinal presentations without enteropathy has only recently become accepted. In this Personal View, we review the range of neurological manifestations of gluten sensitivity and discuss recent advances in the diagnosis and understanding of the pathophysiological mechanisms underlying neurological dysfunction related to gluten sensitivity.

24. **Hallman M, et al. "Toll-like receptors as sensors of pathogens." Pediatr Res. 2001 Sep;50(3):315-21.**
http://www.ncbi.nlm.nih.gov/pubmed/11518816

ABSTRACT

Initial recognition of microbes, as they enter the body, is based on germ line-encoded pattern recognition receptors that selectively bind to essential components of pathogens. This allows the body to respond immediately to the microbial invasion before the development of active immunity. The signal-transducing receptors that trigger the acute inflammatory cascade have been elusive until very recently. On the basis of their genetic similarity to the Toll signaling pathway in Drosophila, mammalian Toll-like receptors (TLRs) have been identified. By now, nine transmembrane proteins in the TLR family have been described. Mammalian TLR4 is the signal-transducing receptor activated by the bacterial lipopolysaccharide. The activation of TLR4 leads to DNA binding of the transcription factor NF-kappaB, resulting in activation of the inflammatory cascade. Activation of other TLRs is likely to have similar consequences. TLR2 mediates the host response to Gram-positive bacteria and yeast. TLR1 and TLR6 may participate in the activation of macrophages by Gram-positive bacteria, whereas TLR9 appears to respond to a specific sequence of bacterial DNA. The TLRs that control the onset of an acute inflammatory response are critical antecedents for the development of adaptive acquired immunity. Genetic and developmental variation in the expression of microbial pattern recognition receptors may affect the individual's predisposition to infections in childhood and may contribute to susceptibility to severe neonatal inflammatory diseases, allergies, and autoimmune diseases.

25. **Clett E, et al. "The capacity of foodstuffs to induce innate immune activation of human monocytes in vitro is dependent on food content of stimulants of Toll-like receptors 2 and 4." British Journal of Nutrition (2011), 105, 15–23.**
http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=7948379&fileId=S0007114510003004

ABSTRACT

The ingestion of fatty meals is associated with a transient, low-grade systemic inflammatory response in human subjects, involving the activation of circulating monocytes and the secretion of pro-inflammatory cytokines. However, it is not yet clear how different foodstuffs may promote inflammatory signalling. In a screen of forty filter-sterilised soluble extracts from common foodstuffs, seven were found to induce the secretion of TNF-α and IL-6 from human monocytes in vitro. To investigate what may differentiate inflammatory from non-inflammatory food extracts, stimulants of Toll-like receptor (TLR) 2 and TLR4 were quantified using human embryonic kidney-293 cells transfected with each TLR, and calibrated with defined bacterial lipopeptide (BLP) and lipopolysaccharide (LPS) standards. These assays revealed that while most foods contained undetectable levels of TLR2 or TLR4 stimulants, all TNF-α-inducing foods contained stimulants of either TLR2 (up to 1100 ng BLP-equivalent/g) or TLR4 (up to 2700 ng LPS-equivalent/g) in both the soluble and insoluble fractions. TLR stimulants were present mainly in meat products and processed foods, but were minimal or undetectable in fresh fruit and vegetables. The capacity of food extracts to induce TNF-α secretion in monocytes correlated with the content of both TLR2 (r 0·837) and TLR4 stimulants (r 0·748), and was completely abolished by specific inhibition of TLR2 and TLR4. LPS and BLP were found to be highly resistant to typical cooking times and temperatures, low pH and protease treatment. In conclusion, apparently unspoiled foodstuffs can contain large quantities of stimulants of TLR2 and TLR4, both of which may regulate their capacity to stimulate inflammatory signaling.

26. **Erridge S. "Stimulants of Toll-like receptor (TLR)-2 and TLR-4 are abundant in certain minimally-processed vegetables." Food Chem Toxicol. 2011 Jun;49(6):1464-7.**
http://www.ncbi.nlm.nih.gov/pubmed/21376773

ABSTRACT

Stimulants of the innate immune receptors Toll-like receptor (TLR)-2 and TLR4 have been shown to promote insulin resistance and atherosclerosis in animal models of these diseases. As minimally processed vegetables (MPV) can contain a relatively large bacterial load compared to other foodstuffs, we aimed to quantify the abundance of stimulants of TLR2 and TLR4 in MPV using a transfection-based bioassay calibrated with Escherichia coli LPS and the synthetic lipopeptide Pam(3)CSK(4). Of 5 classes of MPV and 3 classes of related vegetable products considered to be likely to contain a high microbial load, diced onion and bean sprouts contained the highest levels of stimulants of TLR2 (up to 18.5 μg Pam(3)CSK(4)-equivalents per g) and TLR4 (up to 11.4 μg LPS-equivalents per g). By contrast, the majority of fresh whole vegetables examined reproducibly contained minimal or undetectable levels of TLR2- or TLR4-stimulants. The accumulation of TLR-stimulants in MPVs correlated well with growth of enterobacterial spoilage organisms. In

conclusion, the modern trend towards eating minimally processed vegetables rather than whole foods is likely to be associated with increased oral exposure to stimulants of TLR2 and TLR4.

27. **Feighery C. "Fortnightly review: coeliac disease." BMJ. 1999 Jul 24;319(7204):236-9.**
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1116331/

No Abstract Available
"Coeliac disease is an inflammatory disease of the upper small intestine and results from gluten ingestion in genetically susceptible individuals.1,2 Inflammation may lead to the malabsorption of several important nutrients. Clinical and mucosal recovery after institution of a gluten free diet is objective evidence that the enteropathy is gluten induced. In 1950, Dicke observed the central role of gluten in the pathogenesis of coeliac disease.3 Coeliac disease is closely related to dermatitis herpetiformis.4 In dermatitis herpetiformis, skin rash and a similar small intestinal enteropathy to that of coeliac disease are typically present, and both respond to withdrawal of gluten."

Summary points

- In coeliac disease, dietary gluten causes inflammation of thesmall intestine, which may affect absorption of important nutrients including iron, folic acid, calcium, and fat soluble vitamins.
- Studies show coeliac disease to be a common disorder, possibly affecting 1 in 200 of the general population, the majority of patients being diagnosed in adulthood
- Many patients have minimal symptoms, and gastrointestinal symptoms are frequently absent.
- Coeliac disease should be considered in a wide range of clinical situations including anaemia or osteoporosis and in patients with a range of associated disorders such as type 1 diabetes.
- The diagnosis and screening for coeliac disease has been facilitated by testing for endomysial autoantibodies.
- Treatment consists of permanent withdrawal of gluten from the diet, which results in complete remission.

28. **Fera T, et al. "Affective disorders and quality of life in adult coeliac disease patients on a gluten-free diet." Eur J Gastroenterol Hepatol. 2003 Dec;15(12):1287-92.**
http://www.ncbi.nlm.nih.gov/pubmed/14624151

ABSTRACT

BACKGROUND:
Psychiatric symptoms, common in untreated coeliac disease patients, may improve after gluten withdrawal.

AIMS:
To estimate the incidence of psychiatric disorders in coeliac disease patients on gluten withdrawal and to evaluate: (1) the psychological weight of a chronic disease that involves a restrictive diet and a limited life style; (2) the acceptance of the disease; (3) the effects of both disease and diet on behaviour and quality of life.
PATIENTS AND METHODS:
Three groups of 100 patients (coeliac disease patients, diabetic patients and healthy controls, respectively) were assessed by means of a professional semi-structured diagnostic interview based on DSM-IV criteria. This interview, together with specific psychiatric questionnaires, ruled out axis or II psychopathological disturbances.
RESULTS:
The modified Self-rating Depression Scale and State and Trait Anxiety Inventory Y2 scores were significantly higher in both coeliac and diabetic patients than in healthy controls. The duration of gluten restriction was related to significantly higher modified Self-rating Depression Scale scores in patients with a more recent diagnosis. Quality of life was poorer in both coeliac and diabetic patients than in healthy controls and significantly correlated with anxiety. The Illness Behaviour Questionnaire showed a high psychological and somatic perception of illness in both coeliac and diabetic patients. Its subscale scores correlated significantly with anxiety and depression symptoms.
CONCLUSIONS:
In coeliac disease, affective disorders should be ascribed to difficulties in adjusting to the chronic nature of the disease rather than directly to the disease itself, thus giving an indication for preventive liaison psychiatric interventions.

29. **Rao AV., et al. "A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome." Gut Pathogens, 2009 Mar 19;1(1):6.**
http://www.ncbi.nlm.nih.gov/pubmed/19338686

ABSTRACT

Chronic fatigue syndrome (CFS) is complex illness of unknown etiology. Among the broad range of symptoms, many patients report disturbances in the emotional realm, the most frequent of which is anxiety. Research shows that patients with CFS and other so-called functional somatic disorders have alterations in the intestinal microbial flora. Emerging studies have suggested that pathogenic and non-pathogenic gut bacteria might influence mood-related symptoms and even behavior in animals and humans. In this pilot study, 39 CFS patients were randomized to receive either 24 billion colony forming units of *Lactobacillus casei* strain Shirota (LcS) or a placebo daily for two months. Patients provided stool samples and completed the Beck Depression and Beck Anxiety Inventories before and after the intervention. We found a significant rise in both *Lactobacillus* and *Bifidobacteria* in those taking the LcS, and there was also a significant decrease in anxiety symptoms among those taking the probiotic vs controls ($p = 0.01$). These results lend further support to the presence of a gut-brain interface, one that may be mediated by microbes that reside or pass through the intestinal tract.

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ABOUTDR. TOM O'BRYAN

Dr. Tom O'Bryan is an internationally recognized speaker and workshop leader specializing in the complications of Non-Celiac Gluten Sensitivity and Celiac Disease as they occur inside and outside of the intestines. He is the founder of www.theDr.com. He recently hosted the paradigm-shifting "The Gluten Summit: A Grain of Truth," bringing together 29 of the world's experts on Celiac Disease and Non-Celiac Gluten Sensitivity at www.theglutensummit.com.