Veterinary Quarterly

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/tveq20

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Available online: 01 Nov 2011

To cite this article: AS. Peña & J.B.A. Crusius (1998): Food allergy, coeliac disease and chronic inflammatory bowel disease in man, Veterinary Quarterly, 20:sup3, 49-52

To link to this article: http://dx.doi.org/10.1080/01652176.1998.9694969

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FOOD ALLERGY, COELIAC DISEASE AND CHRONIC INFLAMMATORY BOWEL DISEASE IN MAN

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ABSTRACT
It is often stated that the gastrointestinal tract has a limited number of responses to pathogens. Entirely different agents can produce a similar histopathological reaction. However, the expression of the disease in man is very heterogeneous, it varies with the age of the subject and is to a certain extent genetically determined. For example, food allergy is frequent in childhood and not common in adulthood. The intestinal mucosa in the child with cows milk allergy shows a 'flat' mucosa, which may be indistinguishable of that observed in gluten sensitive enteropathy or coeliac disease. Subjects with other forms of food allergy may have a morphologically normal small intestinal mucosa, occasionally with increased IgE plasma cells and often only characterised by an increased...
intestinal permeability. An abnormal intestinal permeability is one of the hallmarks of an inflamed gut, however, subjects with a latent form of coeliac disease have an abnormal permeability only without overt signs of inflammation.

Recently, it has become clear that what determines the characteristics of the intestinal inflammatory response is dependent on the cytokines involved during the response and this seems to be the same in the stomach, the small intestine and the colon. A so-called Th1 response, with an increased production of IFN-γ, TNF-α and other pro-inflammatory cytokines, occurs in the stomach when infected by *Helicobacter pylori*, in the small intestine when the subject with coeliac disease consumes normal bread and during the active phases of Crohn’s disease. A Th2 response is characteristic of the allergic subject and there is some evidence that it is the predominant response in subjects with ulcerative colitis. We still do not know the fine-tuning of the cytokine response but IL-12 appears to be a key cytokine in polarising the response to a Th1 type. More recently it has become clear that the intestinal mucosa has a unique subset of CD4+ T cells that secrete TGF-β (Th3 cells) that provide help for IgA. These cells have downregulatory properties for Th1 cells and therefore play an important role in the active suppression of oral tolerance and IgE response. What determines that an individual develops one of these diseases? It is now clear that these different pathological entities are multifactorial. Different environmental factors and a complex genetic predisposition where more that one gene and more than one chromosome are involved. The extent and severity of the inflammatory response depends on the genetic diversity of the bacteria or the amount of the antigen on the one hand and on the genetic constitution of the host on the other. The abnormal immune response in the human gut is predominantly a Th1-like inflammatory response. This can be elicited by bacteria, peptides, possibly the bacterial flora and some viruses. The recent findings in the pathogenesis of the intestinal inflammatory response will probably alter the therapy of the future.

**INTRODUCTION**

The immune system of the gastrointestinal tract is constantly being stimulated by a variety of peptides and bacteria. The majority of the proteins that are ingested and digested are important nutrients for the organism and the bacterial flora contributes to the homeostatic milieu of the intestine participating also in the nutrition of the host, for example with the production of folic acid and other vitamins. It is therefore not surprising that the immune system of the gut is mainly directed to avoid inflammation. The lining of the tube together with the inter-epithelial lymphocytes and macrophages are programmed to down-regulate the immune response, a phenomenon known as oral tolerance.

**ORAL TOLERANCE**

The mechanisms by which orally administered antigens induce a lack of systemic response involve a chain of complicated immunological events. Low doses of antigen induce an active cellular suppression where unique T cell subsets play an important role. CD4+ T cells that secrete TGF-β (Th3 cells), provide help for IgA, one of the hallmarks of the intestinal immune response. These cells have downregulatory properties for Th1 cells and therefore play an important place in the active suppression of oral tolerance and IgE response. The gut-associated lymphoid tissue (GALT) also contributes to protect the host from reacting to ingested antigens. T cells in these organs secrete IL-4 as a primary T-cell growth factor whereas those T cells in lymph nodes of the rest of the organism secrete IL-2 (4). When large doses of antigen enter the intestinal mucosa, Th2 responses are induced but anergy and/or deletion of CD8+ T cells takes place suppressing these cells (16). The importance of this phenomenon resides in the fact that oral tolerance has been used to treat autoimmune diseases in animal models and are present induction of oral tolerance to fed proteins is being tested in several human diseases, such as multiple sclerosis, rheumatoid arthritis, type I diabetes and uveitis (27).

**FOOD ALLERGY**

Hypersensitivity to food or food components produces a mixture of digestive and extra-digestive clinical symptoms. A genetic predisposition is important and genes involved in IgE production and mast cell degranulation appears to be involved. Unfortunately it is a relatively common condition and approximately 6% of asthmatics and 6% of atopic dermatitis patients have a documented single or multiple food allergy (20). Recent studies have found that children with atopic eczema with food allergy have intestinal inflammation. When children with cow’s milk allergy are challenged with cow’s milk, eosinophil cationic protein, TNFa and α-1 antitrypsin are significantly increased in the faeces (15). Up till now the only treatment was by careful elimination of the offending food. More recently, probiotics, such as lactobacillus GG have shown to promote a local IgA response and improve permeability defects and by these mechanisms be useful in the treatment of atopic dermatitis and food allergy (14).

**HELICOBACTER PYLORI GASTRITIS**

The extent and severity of the inflammatory response depends on the genetic diversity of the bacteria on the one hand and on the genetic constitution of the host on the other. For example, some strains of *H. pylori* have a 40 kb segment that includes the cytotoxin-associated gene (cagA), a virulence marker associated with duodenal ulcer and gastric cancer. Other strains have a homologue of the Bordetella pertussis toxin, a protein that is secreted and induces IL-8 in gastric epithelial cells (26). This cytokine is one of the most important factors in determining the neutrophil infiltration a hallmark of the gastritis induced by *H. pylori*. Only few studies have been directed to understand the host response in the regulation of the inflammatory response in the stomach, in spite that it is known that interleukin-1β (IL-1β) and its natural specific inhibitor, the interleukin-1 receptor antagonist (IL-1ra) are involved in maintaining the gastric mucosal integrity. Recent reports have indicated that allele 2 of the biallelic TaqI polymorphism of the IL-1β gene and allele 2 of the pentaallelic IL-1ra gene are associated with an increased production of their gene products in healthy individuals. Since the relative balance between the production of these two cytokines are important in modulating the inflammatory response on gastrointestinal mucosa we have recently studied whether these polymorphic genes are involved in the susceptibility to peptic ulcer disease. We studied 159 unrelated Spanish patients attending the University Hospital of Zaragoza, Spain with acute gastroduodenal bleeding due to
this disease. Patients with duodenal ulcer and repeated bleedings were more often found to be non-carriers of the IL-1ra allele 2 than controls (p=0.045, OR=2.71). Furthermore, bleeding duodenal ulcer patients non-carriers of IL-1β allele 2 were often found to be carriers of allele 2 of the IL-1ra gene (p=0.0001), whereas this was not the case in both bleeding gastric ulcer patients, and in controls (9).

CELIAC DISEASE
Occasionally, peptides of a wheat-containing diet produce inflammation in the small intestine of certain individuals, such as the case of celiac disease or gluten-sensitive enteropathy. A working hypothesis to understand the pathogenesis of celiac disease is that peptides produced by the ingestion of gluten (gliadin and related prolamines) are bound to HLA-class II molecules in the late endosomal or lysosomal compartment of enterocytes during uptake across the small intestinal epithelium (29). This is an early event characterized by HLA-DR overexpression in the villus enterocytes (13). Trimmed peptides are, possibly mediated by dendritic cells or monocytes/macrophages in the lamina propria, presented to antigen specific CD4+ T cells (5). This elicits a predominantly Th1 pattern of cytokine production by the celiac disease associated HLA-DQ restricted T cell clones. Both HLA-DQ2 and DQ8 restricted gliadin-specific T cells have been shown to produce IFN-γ which is involved in the damage to the epithelial cells of the small intestine since the histological changes can be blocked by anti-IFN-γ antibodies in vitro (18). TNFα, also produced by several clones may in conjunction with IFN-γ have a toxic effect or like IFN-γ increase class II expression on the surface of epithelial cells. In the lamina propria this leads to increased expression of adhesion molecules such as ICAM-1 on T lymphocytes and macrophages (22, 24, 25). During this process autoreactive T cells prolifereate, creating a situation which is very similar to the process that takes place in other autoimmune diseases. Occasionally, this inflammatory destruction of the small intestinal integrity initiated by gluten-peptides goes further and develops into a proper autoimmune disease requiring the use of immunosuppressive drugs in addition to a gluten-free diet (17). The genetic basis of the inflammatory response in celiac disease resides in several chromosomes. A primary association exists with the combination of alleles DQA1*0501-DQB1*02 at the HLA-DQ locus. These alleles are arranged either in cis or trans configuration, whereas a minority of patients carries the HLA-DR4 associated DQB1*0302 (DQ8 determined serologically) (23). It is possible that the variants of the much less polymorphic MHC class III genes play a modulatory role in the control of inflammation. For example, although very strong linkage disequilibrium has been demonstrated between genes of the disease-associated HLA-B8-DR2-DQ2 extended haplotype, varying degrees of recombination on less well-conserved haplotypes exist. It may thus be the combination of alleles at the primary disease associated DQ loci and at other non-HLA genes that determine the clinical outcome of the disease (7).

INFLAMMATORY BOWEL DISEASE
Other mechanisms exist in the small and large intestine that initiate and maintain a chronic inflammatory state such as is the case in chronic inflammatory bowel diseases (ulcerative colitis and Crohn’s disease). One recent and interesting possibility is that these patients have lost the tolerance against their own bacterial flora. Recent studies have shown that faecal extracts of both homologous and heterologous persons stimulate lamina propria lymphocytes of patients with inflammatory bowel disease to produce pro-inflammatory cytokines whereas lymphocytes from control persons only react against heterologous faecal extracts (8). These studies need confirmation, however, whatever the cause, it is clear that these patients have an abnormal regulation of the inflammatory response. A mucosal imbalance exists between interleukin-1α and its receptor antagonist in favour of IL-1β (6). Data has also shown a significant production of pro-inflammatory cytokines (IL-1β, IL-6 and TNFα), both at the mRNA in the intestinal mucosa, detected by the polymerase chain reaction (10) and by the ELISA-spot technique (TNFα) (12). Lamina propria mononuclear cells of patients with inflammatory bowel disease that produce increased amount of IL-1β and TNFα have an early acute relapse (18). Functionally active NFκB has been found in nuclear extracts of neutrophils of patients with inflammatory bowel disease (19). On the other hand, it is possible that some of these patients have a defect in the inhibition of the pro-inflammatory response. Preliminary evidence suggests that in some patients IL-4 cannot down regulate monocytes of active IBD patients (11, 19, 21, 28).

In summary, the abnormal immune response in the human gut is predominantly a Th1-like inflammatory response. Bacteria, peptides, and possibly the bacterial flora and some viruses can elicit this. We have documented in this review in a concise manner some of these mechanisms. The recent findings in the pathogenesis of the intestinal inflammatory response will probably alter the therapy of the future. The most recent therapeutic modalities are pointed towards the control of different cytokines involved in the inflammatory process, the inhibition of adhesion molecules of macrophages and neutrophils, or the development of cytokines that regulate inflammation (1). Also under review is the possible application of the interleukin-1 receptor antagonist, although its short half-life and the need to use very high doses to reach therapeutic levels undermine its efficacy (2).

REFERENCES
ROLE OF SHORT-CHAIN FATTY ACIDS IN THE HIND GUT

W. von Engelhardt1,2, J. Bartels1, S. Kirschberger1, H.D. Meyer zu Düttingdorf1, and R. Busche1

ABSTRACT

Short-chain fatty acids (SCFA) are produced by microbial fermentation in the hindgut in considerable amounts. Most of the anions in hindgut contents are SCFA, mainly acetate, propionate, and butyrate. SCFA are rapidly absorbed. Mechanisms involved in the transepithelial transport are discussed. Besides the contribution to the overall energy metabolism of animals or men, SCFA have a number of further important effects on the colonic mucosa. Factors affecting the pH of compartments in the mucosa, cell swelling, stimulation of mucus release, and mucosal blood flow are mentioned. Controversial reports are known on the role of SCFA in the metabolism of colonocytes. In spite of the conflicting opinions on the interaction between SCFA metabolism and the development of colitis ulcerosa, diverticulosis and colorectal cancer seems to exist. The obscure differences between the effects of SCFA on cell proliferation, differentiation and apoptosis of colonocytes in vivo and in vitro indicate that besides direct effects of SCFA systemic effects such as neural and humoral factors are of crucial importance. The opposing effects of SCFA on proliferation and apoptosis in normal colonocytes and in colon cancer cells may open possibilities for prevention and/or therapy of patients with colonic diseases.

INTRODUCTION

The major end-products from anaerobic breakdown of polysaccharides by intestinal microorganisms are short-chain fatty acids (SCFA), mainly acetate, propionate, and butyrate. The major fermentation substrates include cellulose, hemicellulose and pectin, substrates that are not digested by host enzymes. Considerable amounts of SCFA can be produced in the large intestine. Calculations of SCFA production in dog and in man with a small rather simple hind gut accounts for about 7% of energy maintenance requirement of these species (19, 100). In animals with a voluminous fermentation chamber in the hindgut, maintenance energy derived from SCFA comes up to 80% (5, 11, 100). This may illustrate that SCFA are of major significance for a number of further processes, especially in the hind gut mucosa. Excellent reviews on physiological and clinical aspects of SCFA in the large intestine has been published recently (6, 20, 48, 63, 73, 75, 79, 199).

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