The Role of Probiotics in Irritable Bowel Syndrome, Food Allergies, and Detoxification of the Bowel

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Abstract

Irritable bowel syndrome and inflammatory bowel disease are two diseases of the intestinal tract. They share some common symptoms such as pain and discomfort among other issues. While IBS has usually been characterized as a functional disease or syndrome with a diagnosis made on a cluster of symptoms in the absence of notable structural abnormalities, IBD is a very similar disorder, at least with a cursory review of symptoms. However, IBD does differ in that it is a collection of disorders characterized by chronic mucosal and/or inflammation of the intestines. I will touch on how they are similar and how they are different. Treatment options are discussed, including the role of the gastrointestinal (GI) flora. Further, we will discuss how the gastrointestinal flora relate to food allergies (FA) and how the same FA can have a relationship with IBS. Discussion is given to detoxification of the gut and how it can play a role in IBS and FA. Concluding, an explanation of how probiotics may be used to help turn off inflammation and detoxify the gastrointestinal tract is presented.

Introduction

Irritable bowel disease (IBS) and inflammatory bowel diseases (IBD) are two diseases of the gastrointestinal (GI) tract that share many common symptoms and appear to be very similar. Of the things that they share, we know that altered mucosal permeability is characteristic. Additionally, there is an altered interaction of the mucosal flora with immune cell activation. That is to say, something goes wrong with the gut's immune system. There is a concomitant change in gut motility. There seems also to be a role in symptom modulation with life stressors. Such stressors can be physical (viral or parasitic infection), psychosocial or some combination of those.

Irritable Bowel Disease

IBD is typically separated into two different diseases; Crohn's disease (CD) and ulcerative colitis (UC). In CD, the proinflammatory cytokine tumor necrosis factor (TNF-α) seems to play a major role in the pathogenesis of the disease. It has a key part in the altered mucosa of the GI tract.[1,2] The expression of TNF-α in the intestinal mucosa is increased in patients with CD.[3]

A number of clinical studies using TNF-α monoclonal antibodies have clearly shown a beneficial response. This has been at the clinical level as well as upon histological examination.[4]

When this therapy fails, it has been associated with an early reactivation of TNF-α secretory capacity by immune cells. It is thought that perhaps enhanced function of T-helper 1 (Th1) cells that secrete TNF-α factor is in the pathogenesis of CD, therefore any decrease would be of benefit. I will discuss below how manipulating the gut microflora can accomplish this.

The similarity between IBD and IBS is strong. They have the same chronically recurring symptoms (or very similar ones) including abdominal pain and discomfort, urgency and bloating, and alteration of bowel habits. IBD is further characterized by inflammation or ulceration ("organic" changes) in the small and or large intestines which are not associated with IBS.

Irritable Bowel Syndrome

IBS is typically classified as a functional disorder as opposed to being organic and is diagnosed in the absence of structural abnormalities. In fact, once such structural abnormalities are found, the diagnosis is no longer applicable.

There has been a veritable explosion of literature on the subject of bowel disease and IBS specifically in recent years. This is especially true for the elusive triggers of the syndrome. It has been suggested that enhanced response to psychosocial and physical stressors is a plausible mechanism to explain many of the clinical findings with IBS. That is also true for the majority of the reported physiological alterations.[5]

It has been demonstrated that alterations in the gut immune system are present in IBS. Quantitative measurements have shown that there is an increase in mast cells in the Ileum and colonic mucosa.[6]

There is evidence of overall cellular activity in the colon, higher number of mast cells and tryptase, which is known to have inflammatory properties, in the colonic lamina propria in patients with IBS.[7]

Also of great interest is that there is considerable increase in inducible nitric oxide synthetase (iNOS) in colonic mucosa. This has been shown in unselected patients with IBS.[8] This means that they're having an effect at the molecular level. Previously, I have discussed this in a paper on genomeceuticals and their applications to autism. I mentioned that there are natural compounds which might be able to reverse what I had theorized to be a genetic switch.

Molecular Changes

Changes at the molecular level seem to be driving both IBS and IBD. There is preliminary evidence that there is reduced frequency of a high producer allele for the anti-inflammatory cytokines IL-10 and TGF-ß suggesting a reduced production of cytokines in patients compared with controls.[9] In order for that to happen, something has to be changing the transcription pattern of the genes responsible for those cytokines.

A similar problem seems to be occurring with IBD. Recent studies have been looking at the NOD gene. NOD proteins are thought to be cytosolic receptors for bacterial signals and have a role in the activation of NF-κB. The mechanism may be that different concentrations of bacteria in the colon vs. the ileum contribute to the association of NOD2 mutations and the disease. IBS probably has similar molecular changes, though perhaps with different genes. There is also a genetic background associated with UC and the HLA gene on chromosomes 3, 7, and 12.[10]

In Crohn's Disease (CD) we see an increased expression of Th1 cells whereas an atypical Th2 response is

associated with Ulcerative Colitis (UC). It is not just a matter of T helper cell phenotypes. The idea that there is a balance of cytokine production in the GI tract in response to various stressors seems more likely. Cytokine gene regulated differences between diseases are clearly more complex than just the production of more or less Th1 vs Th2 cells.

Again, it may be that different concentrations of bacteria in the colon and ileum may contribute to the association of NOD2 mutations and diseases of the ileum. Altering the flora should have a positive or negative effect on the diseases depending on what strains are used.

Current Therapies

Current therapies that target IBD go after things such as TNF-α and other inflammatory cytokines. Also, inhibitors of mitogen activated protein kinase (MAP k) is another agent in the therapeutic strategy. Clearly, anything that can help decrease inflammation is being looked at as a potential target. What remains clear is that the triggering factor initiating the inflammatory response remains unclear.

In IBS an immune response to infection – a dis-inhibition of the immune system during chronic sustained stress or some combination of both are plausible mechanisms. There seems to be, given the evidence above, a low-grade inflammation after pathogen clearing or resolution of the stress event in a subset of individuals which may be related to inability to downregulate the inflammatory response. This could be due to genetic factors, or early programming of anti-inflammatory systems.

For both syndromes, histological and functional alterations of the mucosal barrier have been reported. Increased permeability and luminal flora, for instance.[11-13]

A brief comment on UC is warranted. UC is characterized by chronic inflammation of the colon and does not involve the small intestine. Typically, the inflammatory process begins at the rectum and spreads proximally in a pattern in continuous and confluent inflammation. Common sites of involvement include the rectum, recto sigmoid area. The rectum is almost always involved and continuous biopsies reveal superficial inflammation.

Crohn's disease is characterized by transmural (involving all layers of the bowel wall) in any part of the gastrointestinal tract. The most common sites include small intestine, colon, and stomach. Abdominal pain is common and may be mistaken for acute appendicitis. Stools are often non-bloody. The distal colon is not involved. Weight loss and fever are common. Occasionally, an inflamed tender loop of small bowel is palpable upon a physical examination. A differential diagnosis of the disease is also quite extensive. One of the most life threatening complications of IBD is the development of toxic megacolon, which appears in about 1 to 3% of patients.[14]

Despite the name, you don't have to have a dilated colon to accompany toxic megacolon. It's associated with fulminate course characterized by a septic-like picture that includes fever, tachycardia, hypertension, leukocytosis, and changes in mental status. A physical examination may reveal absent bowel sounds, abdominal and/or rebound tenderness. Urgent surgical consultation is essential in patients with suspected toxic megacolon. Most patients will require colostomy, if symptoms do not respond to medical management.

Of interest is the psychological and alternative medicine therapies in IBS. Drosman and Colleges recorded the result of a large and successful multi-center, randomized trial comparing cognitive therapy with education and moderate to severe functional bowel disorder. Investigators randomized 215 patients, to either Cognitive Behavior therapy or education. The Cognitive Behavior therapy was significantly more effective than education, with a response rate of 70% compared to 37% respectively. This gives an application for children with diseases such as autism or other disease where children are known to have gastrointestinal disturbances. These results were significant and were confirmed through protocol analysis. The authors concluded that 12 week Cognitive Behavioral therapy was more effective than education, regardless of symptoms or severity. The caveat: the patients with severe depression did not feel better.[15]

Food Allergies

Probiotics are increasingly being used to manage patients with Food Allergies (FA). Allergic reactions to food are gaining interest. The small intestine is where most reactions to food manifest in the GI tract. Most allergic reactions to food are not IgE mediated, although in children they probably are. Primary allergic reactions to food include infantile formula protein intolerance.

Both hyper-IgE syndrome and FA can result in the early onset of skin rash, eosinophilia. FA can be a life threatening disorder that can result in anaphylactic reactions. Food induced anaphylactic reactions are being recognized with increasing frequency. This explains the extraordinary efforts manufacturers are going to to warn customers about the possible inclusion of common allergens such as peanuts, corn, wheat, dairy, etc. We also know that anti-IgE monoclonal antibodies are being used to reduce the frequency and severity of such reactions. The use of probiotics for such a reduction would be advantageous.[16]

Mucosal inflammation is characteristic of most allergic disorders in the intestinal tract. FA are able to alter gut motility and are accompanied by diarrhea, maldigestion, malabsorption, and abdominal pain. Most experts believe that the increase in allergic disease may be associated with the improved hygiene of our society. By minimizing our exposure to antigens, we fail to stimulate the gut immune system. As a result, leukocytes that would normally differentiate into T-helper cells of one subset become T-helper cells of another subset capable of producing inflammatory cytokines.

However, by challenging the microflora of the gut, it is possible to alter the microflora and boost the immune system. That is to say, probiotics appear to be able to exert a genomeceutical effect on T cells and shift their expression profile and cytokine production patterns. This may not occur with differentiated T cells but it may be possible with the naive ones

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at the very least. The former remains to be seen but should prove an interesting area for further study.

Cow's milk allergy is not uncommon in infants and children and creates a barrier to providing complete nutrition during this important developmental phase. Intact milk proteins are known to stimulate the secretion of proinflammatory cytokines in susceptible people. Specific strains of bacteria can protect the host from allergic sensitization. *Lactobacillus rhamnosus* has been shown to downregulate hypersensitivity reaction and inflammation in patients with food allergy through improved antigen specific immune responses.[17]

The ability of probiotics to confer enhanced humoral and cell mediated resistance against pathogens has been documented.[18] For example, it was demonstrated that a significant increase in leukocyte proliferative responses, phagocytic capacities and localized antibody production occurs in response to oral administration of lactic acid bacteria in mice infected with salmonella.

Lactobacillus casei has been associated with increases in specific mucosal and serum antibodies in children with acute rotavirus diarrhea.[19]

Our group that has been working with others looking at cyclooxygenase (COX) 1 and 2 and their role in GI health. It is known that over expression of COX2 is indicative of inflammation and cancer. COX 1 is associated with GI integrity and is a housekeeping enzyme. Acidophilus and Bifidobacterium were assayed for their ability to exert an effect on these genes. The latter showed a three-fold increase of COX1/COX2 ratios signifying a shift in the ratio towards a healthy expression profile. In other words, COX2 was down regulated and COX1 was up regulated. Previous work by our group has suggested a genomeceutical effect supporting the ability of the probiotics to regulate gene expression in a beneficial manner.

Detoxification

It is well established that a build-up of toxic material in the GI tract can be potentially life-threatening. It seems reasonable that high doses of a toxic substance during development can have potentially disastrous results. Such effects could range from neurological impairment to altered immune and gene function. Additionally, as we have seen here, there may be a cross-over role with gut-related adult diseases.

Current popular treatment protocols designed to void the body of toxic substances are being established. Such protocols may employ chelating agents such as ethylenediaminetetra-acetic acid (EDTA) or dimercaptosuccinic acid (DMSA) to effectively clear substances such as heavy metals from the body.

The prophylactic administration of probiotics *a priori* would prevent any recycling of the toxic substances or at least minimize it. As the probiotics contact and process the various substances, undoubtedly some mutations will be suffered by the probiotic genomes. For this reason, a constant replenishment of the supply is important to avoid a genetic drift, which might otherwise knock out endogenous detoxifying enzymes in the bacteria.

It is well established that the intestines are a major source of immune competence.[20] Probiotics may beneficially affect IBS in the following ways:

- Assist in decreasing aberrant inflammatory process
- Reestablish correct gut motility
- Correct altered gut motility
- Decrease gaseous bloating due to infections
- Increase immune response to parasites (infections)
- Exclude parasites and pathogens

IBS, FA, infections, and detoxification are uniquely connected via the GI microflora. Alterations in this flora may either positively or negatively affect health. We have seen for instance that the addition of *Lactobacillus* and *Bifidobacterium* can lower inflammation in the gut. There is every reason to expect that they can assist with IBS and FA related inflammation as well. Further, probiotics provide a unique mode of detoxification of the gut both during and after healing. Not only can the probiotics assist with clearance of foreign matter, but they also aid in a number of other important processes such as reestablishing a correct bacterial population ratio between the various parts of the GI tract. Taken together, it is easy to see how probiotics therapy is at the advent of natural approaches to irritable bowel syndrome, food allergies, and detoxification.

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