The Influence of Commensal Bacteria on the Gut-Brain Axis: Implications for Understanding and Treating Functional GI Disorders

Stephen COLLINS*, Premsyl BERCIK, Emmanuel DENOU and Elena VERDU

McMaster University Medical Centre, 1200 Main Street West, Hamilton, L8N3Z5, Ontario, Canada

Received for Publication, May 20, 2009

The gut-brain axis has been described as a bi-directional neuro-humeral communication system and is implicated in the pathogenesis of functional gastrointestinal disorders such as irritable bowel syndrome (IBS). Recent work has shown that a subset of patients with IBS show evidence of low grade immune activation and inflammation in the colonic mucosa. This review focuses on the role of the intestinal microbiota and discusses the interrelationship between the intestinal microbiota and maintaining of low grade inflammation, gut dysfunction or behavioral changes using murine models and clinical studies. The findings in murine models show that perturbation of gut flora is a putative mechanism for gut dysfunction in IBS and together with clinical studies they indicate that dysbiosis in patients with IBS psychiatric co-morbidity.

Key words: Microbiota; flora; nervous system; behaviour; irritable bowel syndrome.

The notion that the commensal bacteria of the gastrointestinal tract influence behaviour through the gut-brain axis has long been suspected. The pharaohs of Egypt, kings of France and many others have used frequent colonic cleansing as a way of maintaining wellness. However, the scientific basis for this is poorly understood.

There has been a recent revitalization of our interest, as well as our capacity to investigate, the intestinal microbiota \(^{(29, 35)}\). There are approximately \(10^{14}\) bacteria in the human gastrointestinal tract and their combined metabolic activity exceeds that of the liver. The number of bacteria exceeds the number of cells in the human body by a factor of 10 and the number of genes exceeds that of the human genome by a factor of 10–100. This remarkable ecosystem is separated from the human body by a single layer of epithelium. Beneath this is the body’s most sophisticated immune system—the mucosal immune system which is also the largest component of the body’s immune apparatus \(^{(23, 35)}\). It is indeed the largest lymphoid organ in the body and accounts for 80% of the immunocytes in the body. The total number of interepithelial lymphocytes is equivalent in size to the total cellularity of the spleen. The IGA production by the gut exceeds 3 grams a day.

The intestinal microbiota plays an important role in maintaining wellness in the host and has been previously reviewed \(^{(2, 16)}\). For example, the intestinal microbiota generate energy from components of the diet that are indigestible by the human body. In addition, the commensal bacteria influence the handling and storage of fat by the human body \(^{(1, 16)}\). These bacteria imprint and maintain normal gut physiology and tightly regulate intestinal epithelial function, including its barrier role. In addition, the microbiota synthesize vitamins from dietary precursors, metabolize certain drugs for therapeutic advantage, and metabolize dietary carcinogens. Recent work has shown that the microbiota also influence intestinal angiogenesis \(^{(37)}\).

By far the most important role of the gut microbiota is the instruction and lifelong education of the mucosal immune system \(^{(22)}\). Commensal bacteria are responsible for the presence of inflammatory cells in the normal gut. In germ-free mice, the mucosal immune system is rudimentary, secondary lymphoid structures are barely formed, and inflammatory cells are infrequent. The normal complement of inflammatory and immune cells in the gut has been referred to as “physiological inflammation” or controlled inflammation and represents mutual recognition between the microbiota and host. Perturbation of the mutualistic relationship between the host and gut bacteria, known as dysbiosis \(^{(15)}\), results in changes to this degree of controlled inflammation resulting, at one extreme, in inflammatory bowel disease and, possibly, at the other extreme in the small increment in controlled inflammation seen in certain sub-types of patients with functional bowel disorders \(^{(5)}\). Other
examples of this imbalance or dysbiosis are helicobacter pylori induced ulceration and gastric cancer in certain predisposed individuals and the development of clostridium difficile colitis in some patients after antibiotic treatment (15).

Functional gastrointestinal disorders such as the irritable bowel syndrome are chronic abdominal symptom complexes for which there are no discernible underlying structural abnormalities. These are chronic conditions which are influenced by emotion. In addition, up to 60% of these patients have significant psychiatric co-morbidity including anxiety and depression (7). Inflammatory bowel disease is also impacted by stress and behavioural changes such as depression and these may influence the natural history of the disease (26).

Animal research has indicated the role of the gut-brain axis in the context of inflammation. McHugh et al. showed that the induction of experimental colitis in rats resulted in suppression of food intake and that this was mediated by both peripheral and central IL1 (27). Qiu et al. (31) showed that quiescent colitis induced by the hapten, DNBS, could be reactivated by a sub-threshold dose of the hapten together with a combination of restraint and acoustic stress and this was mediated via T-lymphocytes; the susceptibility to stress-induced colitis could be adoptively transferred via CD4 cells into naive mice.

More recently, Ghia et al. (12) have shown that the inflammatory reflex, first described by Tracey (40), in response to LPS administration also applies to chronic colitis. Furthermore, Ghia et al. (11) showed that induction of depression in mice results in an increased susceptibility to inflammatory stimuli such as DSS colitis and that this was due to impaired vagal inhibitory modulation of intestinal macrophages. The activity was mediated via the α7 sub-unit of nicotinic acetylcholine receptor. These findings illustrate the functional presence of a brain-gut axis that modulates intestinal inflammation. The question arises as to whether microbiota are involved.

Several studies have shown that experimental stress alters the intestinal microbiota. The study by Tannock and Savage in 1974 (39) showed that environmental stress reduced lactobacilli and increased cloform in the rat intestine. Bailey and Coe (3) described alterations in gut flora in infant monkeys subjected to maternal deprivation. In addition, Bailey and Coe have shown that pre-natal stress alters bacterial colonization in infant monkeys (4). The mechanisms underlying stress-induced changes in the gut microbiota are unclear but may result from a combination of stress-induced changes in gut motility (34), epithelial function (24) and immune function (22). In addition, stress may alter neurotransmitter release in the gut and Freestone et al. (8) showed that norepinephrine, for example, could enhance the growth of E. coli. Stress also increases macromolecular uptake in the gut as was shown by Killian (17) and an increased susceptibility in maternally deprived mice was shown by Varghese et al. (41) to be accompanied by an increase in intestinal permeability. Taken together, these results support the notion that stress and depression influence the composition of gut bacteria, and may also influence their growth and access to the intestinal wall, resulting in an increase in inflammation.

The brain-gut axis is a bidirectional communication system involving nerves, hormones, cytokines and other substances. The question therefore arises as to whether gut bacteria communicate with the central nervous system. Green et al. used an in vitro preparation to show that certain bacteria such as salmonella and E. coli are recognized by the enteric nervous system and facilitate their uptake in presentation to Peyer’s patches via norepinephrine-containing nerves (13). In another study, colonization of the cecum of rats with Campylobacter jejuni resulted in an increase in c-fos staining in the nucleus of the tractus solitarius, the lateral parabrachial nucleus and the paraventricular nucleus in the brain stem (10). These suggest the existence of a vagal pathway mediating the presence of these non-invasive pathogenic bacteria and brain activity. The latter was accompanied by the development of anxiety-like behavior on formal psychological testing. Similar results were obtained by Lyte et al. using the genetically modified E. Coli, Citrobacter rodentium (21). The unusual finding was that these changes in brain stem activity and in behaviour occurred very quickly, within hours, of the inoculation of these bacteria and in the absence of a discernible inflammatory response of the host. These results were obtained with pathogenic non-invasive bacteria but the role of the intestinal flora in these responses is unclear.

Several clinical observations suggest that qualitative or quantitative changes in the activity of commensal bacteria may result in alteration in behaviour. The classic example is that of hepatic encephalopathy in which patients even in deep coma respond to the administration of oral antibiotics with or without laxatives (29). Studies have also demonstrated the abnormal breath excretion of hydrogen and other fermentation products in the breath of females with depression (18, 20). The authors then showed that dietary modification ameliorated this profile as well as improved depression (19). There has been longstanding speculation that there may be a relationship...
between the gut microbiota and autism. Some studies have demonstrated abnormal commensal bacterial profiles in autistic patients and others have shown at least temporary improvement in symptoms of autism following the administration of antibiotics (6, 33, 43). These results provide a basis for considering experimental evidence of interactions between commensal bacteria and the brain.

Sudo et al. (48) was the first to demonstrate that the brain-gut axis is abnormal in germ-free mice. Using mild restraint stress in young mice, he showed that the ACTH response was abnormal and that this could be normalized by Bifidobacterium infantis, and reduced following colonization with feces from SPF mice. The reversibility was transient, indicating that in young mice, there is a window in which bacteria influence the imprinting of the hypothalamic pituitary stress response.

Another strategy has been to perturb the intestinal microbiota using antibiotics. In a recent study, Verdu et al. (42) showed that the administration of neomycin bacitracin and primaricin altered gut flora and that this resulted in a small increment in “physiological” or “controlled” inflammation in the gut. This increment in inflammation was not accompanied by mucosal damage. The perturbation of bacteria was also accompanied by an increase in substance P in the gut wall and via an increased responsiveness to colorectal distension, indicating a degree of visceral hyperalgesia. As a reduction in lactobacillus was the main perturbation found in this study following antibiotic therapy, administration of lactobacillus paracasei was attempted. This normalized the above-described changes in physiological inflammation, substance P content of the gut wall, and the response to colorectal distension. These findings indicate that gut flora regulate intestinal physiological inflammation, sensory neurotransmitter content, and sensory perception in the gut.

Using the same approach, we next examined the effect of this perturbation of commensal bacteria on behaviour and our results showed significant changes in reduced latency to step down, and in light box/dark box studies, showed an increase in the total time spent in the light box and the number of crossovers. When the antibiotics were given by intraperitoneal injection at 10% of the orally administered dose, no changes in behaviour were seen. These results indicate that perturbation of the intestinal microbiota results in changes in behaviour. The mechanisms underlying this remain to be elucidated.

The clinical implications of these findings with respect to functional disorders are clear. As already mentioned, functional GI disorders are accompanied by psychiatric co-morbidity in 60% of patients (7). In addition, those patients with primary affective disorders have more GI symptoms than control subjects (9). Furthermore, in patients with inflammatory bowel disease there is a relationship between relapses and depression and/or stress (26). Our current conceptualization of functional GI disorders such as irritable bowel syndrome is fragmented. There are those who believe that this is a primary “psychosomatic disorder” in which behavioural changes such as anxiety and depression, and a tendency towards symptom reporting and seeking of healthcare are the dominant features. The role of gut dysfunction as a basis for GI symptom generation in this model is unclear.

The last 10 years has seen the emergence of a peripheral model in which acute bacterial infection or antibiotic use triggers chronic gastrointestinal dysfunction and symptom generation. Whether these 2 models are mutually exclusive is debatable. Factors such as bacterial infection (36), antibiotic use (28, 32), and stress are each known to perturb the intestinal microbiota and lead to low-grade inflammation. Low grade inflammation is now increasingly recognized as being present in a subset of IBS patients including those with psychiatric co-morbidity (14, 30). Thus, it is possible that in these patients, dysbiosis induced by stress, bacterial infection or antibiotic usage could also result in changes in behaviour, and thus account not only gut for dysfunction, but also as a contributing factor to the psychiatric co-morbidity.

This scenario is plausible given the evidence showing dysbiosis in patients with irritable bowel syndrome. Increased colonic fermentation has been observed in IBS patients compared to controls by King et al. (1998) and by Treem et al. (1996). More recently, Pimentel et al. have shown bacterial overgrowth is associated with symptoms in some IBS patients, although the findings do remain controversial. More direct evidence was found using 16S rRNA sequences by Kassinen et al. Lactobacilli were extinct in the libraries derived from IBS patients. Other smaller changes were detected in symptomatic subgroups. In other studies using molecular approaches, clostridium difficile was the dominant group in some IBS patients. Temporal instability was also seen in another group of IBS patients over 6 months, compared to controls, but unfortunately no correlation was made between the microbiotal profiles and symptom relapse or remission.

CONCLUSION

Thus, in conclusion, there is evidence of bacterial involvement in the bidirectional brain-gut axis. Primary
changes in behaviour may result in changes in intestinal bacteria which in turn perturb gut function and may lead to an increase in inflammation. In addition, primary changes in the intestinal microbiota, induced by antibiotics, infection or other factors can result not only in changes in low grade inflammation, such as is seen in IBS, and gut pathophysiology (visceral hyperalgesia), but also in changes in behaviour. Taken together, these observations support the use of probiotics in the treatment not only of gastrointestinal changes, but also of the behavioural changes that occur in this common category of gastrointestinal diseases.

REFERENCES


