THE SECOND BRAIN

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ABSTRACT
The ability of the microbiota of the gut to communicate with the brain and influence behaviour is an emerging topic of research.The enteric microbiota interacts with the host to form a relationship that governs homeostasis. Despite the unique enteric bacterial fingerprintof each individual there appears to be a certain balance that confers health benefits. A decrease in desirable bacteria therefore leads to a disturbed gastrointestinal, neuroendocrinal and immune relationship leading to a diseased condition. Studies are focussing on the impact of the microbiota on the host specially its effect on the brain.There are many studies which have demonstrated germ free mice displaying altered stress response, neurochemistry and anxiety in comparison to normal mice. Data obtained from such experiments show that modulation of enteric microbiota may be a useful strategy in stress related disorders, gastrointestinal disorders such as Irritable Bowel Syndrome (IBS) and Inflammatory bowel disease.

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Key words: Germ free mice, anxiety, microbiota, probiotics.

INTRODUCTION
There is a lot of current research which is looking for a link between the gut and brain. Scientists are of the opinion that the microbiota in our intestines may have a major impact on our minds. There is a complex bidirectional communication between the gut and the brain thereby leading to the formation of gut brain (GBA)(1). The gut brain axis includes the CNS (central nervous system), ANS (autonomic nervous system), ENS(enteric nervous system) and the hypothalamic pituitary axis (HPA).

The autonomic system with the sympathetic and parasympathetic parts sends afferent signals arising from the lumen of the attendance and transmitted through enteric spinal and vagal pathways to CNS . The hypothalamic pituitary axis is considered as an efferent pathway for stress of any kind(2).

Environmental stress and cytokines activate the secretion of corticotrophin from the hypothalamus thus

stimulating adrenocorticotrophic hormone secretion from the pituitary gland which causes a release of cortisol. Cortisol is a stress hormone that affects many organs including the brain.

The bidirectional communication of GBA allows the brain to influence the activities of the intestinal cells such as immune cells, epithelial cells, enteric neurons andsmooth muscle cells. The same cells are under the influence of the gut microbiota(3).

GUT BRAIN
The gut brain lies within the walls of the digestive system. The brain and the gut are connected by an extensive network of neurons, many chemicals and hormones. It provides a constant feedback about how hungry we are, whether or not we are experiencing stress or we have ingested a disease causing microbe(4)

The enteric nervous system is often referred to as our "second brain". There are a hundred million neurons connecting the brain to the enteric nervous system. The enteric nervous system is so extensive that it can act as an independent entity without any input from our central nervous system, although they are in regular communication. The central nervous system is in communication with the gut via the sympathetic and parasympathetic partsof the autonomic nervous system (Fig.1).

MICROFLORAAND GUT BRAIN AXIS
Both clinical and experimental research suggests an important influence of microbiota on the GBA. Almost twenty years ago hepatic encephalopathy was treated

by using oral antibiotic therapy thus suggesting a gut micro brain interaction (5). A number of researchers suggest the role of microbiota influencing depression and anxiety disorders (6-7). More recently their role in autism has also been suggested (8-9). Functional gastro-intestinal disorders (FGID) are also linked to a disturbed GBA (10-12). An irritable bowel syndrome was linked with an alteration in the GBA (13-14). Evidence suggests that post infectious IBS was effectively treated with certain pro-biotics and non-systemic anti-biotics (15-17). Certain researches have shown that visceral hyper-sensitivity and symptoms of IBS can be transferred from IBS patients to germ free mic (18). Thus a disruption of GBA and gut micro-biota led to FGID (19). (Fig.1)

BEHAVIOURAL AND NEUROCHEMICAL CHANGES ASSOCIATED WITH GROWTH IN GERM FREE MICE

Neufeld and colleagues used germ free mice to demonstrate that when there is an absence of the normal micro-biota, it resulted in a reduction in anxiety behaviour. These authors show an up-regulation in the Brain Derived Neurotrophic factor(BDNF) in the Dentategyrus of the Hippocampus in germ free animals. BDNF is crucial for regulation of multiple aspects of cognitive and emotional behaviours (20). There is a clear relationship between chronic stress states, major depression and BDNF (21). The association between anxiety and BDNF appears to be more complex with the authors finding positive, negative and no correlation between hippocampal levels and anxiety (22-23) Interestingly a down regulation of 5-HT autoreceptors was also present in the Dentate gyrus of germ free mice (24).Sudo et aldemonstrated that male germ free mice have an increased stress response (although no basal changes) in the hypothalamic adrenal pituitary axis function coupled with decreased hippocampal and cortical BDNF (25). Thus gender may play a crucial role in the molecular studies conducted by Neufeld and colleagues. Recent data suggests that neurochemical and endocrine but not immune effects is seen in germ free mice (26). However,inspite of these limitations the work of Neufeld et al did show a direct link between anxiety related behaviour and microbiota(27).

USE OF PROBIOTICS AND THEIR RELATION WITH BEHAVIOUR OF CENTRAL NEUROTRANSMITTERS.

Probiotics are beneficial in the treatment of the gastrointestinal symptoms of disorders such as Irritable Bowel Syndrome (IBS)(28) Clinical evidence supports the role of probiotic intervention in reducing the anxiety and stress response (29-30). A recent study assessed the effect of a combination of Lactobacillus helveticusand Bifidobacteriumlongum on both human subjects and rats showed that these probiotics reduced anxiety in animals and had beneficial effects in the psychological behaviour of rats with a decrease in the level of cortisol (31).Some probiotics have the potential to lower inflammatory cytokines (32-33).Lactobacillus reuteri, a potential probiotic is known to modulate the immune system and reduce the rise of corticosterone in mice(34).

ANTIBIOTICS AND BEHAVIOUR

Frequent administration of antibiotics in children and adults have shown to reduce the diverse fecalmicrobiota and delay in the colonization of probiotic strains like Lactobacillus (35).Thus antibiotic disruption of gut flora has also been linked to functional gastrointestinal symptoms(36).

INFECTION AND BEHAVIOUR

Infections due to enteric bacterial pathogens causes acute mucosal inflammation(37)and is noted as a risk factor for the development of post infectious IBS (38-39).In recent studies Bercik et al sought to examine how chronic gut inflammation alters behaviour and Hippocampal BDNF (40). There have been many studies using Citrobacterrodentium as an infectious agent to investigate gut brain axis function. When mice were infected and behaviour tested at 7-8hrs following infection, there was an increase in anxiety (41) and psychological stress which affects the intestinal function and host microbe interaction(42).Enteric microbiota affecting the brain function was demonstrated when Campylobacter jejuni, a food borne pathogen led to an activation of regions of the brain involved in the processing of gastrointestinal sensory information in mice (43).The vagus nerve is involved in transmission of signals from the GI tract to the central nervous system during a Salmonella typhimurium infection (44).To establish this fact, rats were infected with bacteria and vagotomy performed in half the animals 28 days prior to infection. Salmonella increased inflammation in the ileum and the mesenteric lymph node while it decreased the systemic immune response. Vagotomy prevented these infection associated changes

IRRITABLE BOWEL SYNDROME AND GUT MICROBIOTA

Alterations in the Gut Microbiota in IBS

Alteration of the gut microbiota has been suggested as a pathologic etiology in IBS. Change in gut flora may contribute to low-grade inflammatory responses. From

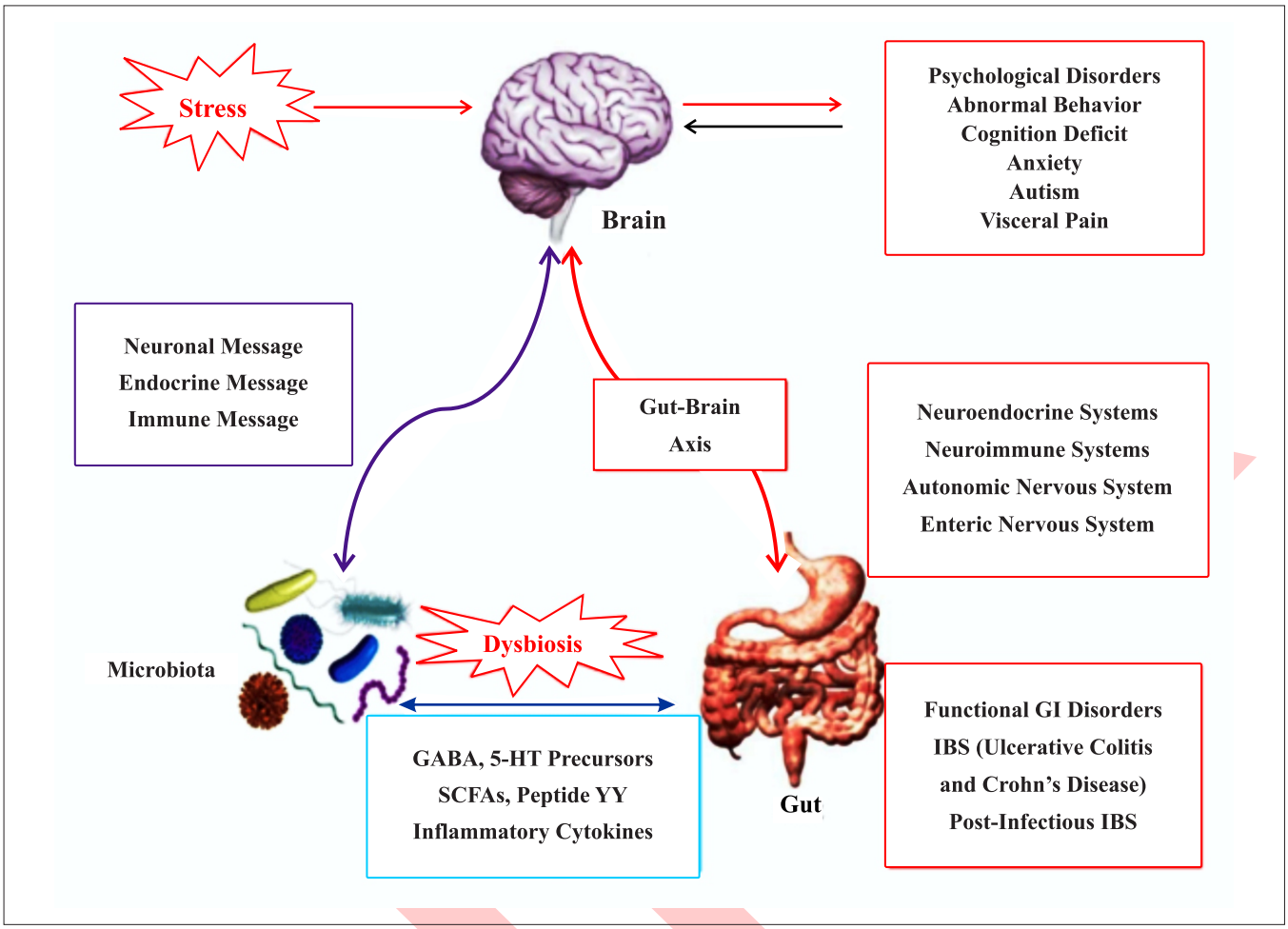

Fig.1 The Gut Brain Axis

clinical and epidemiologic studies, presence of small bowel bacterial overgrowth (SIBO) has been demonstrated in IBS patients (45-46). GI infection or antibiotics can perturb the composition of gut microbiota and this alteration has been associated with symptoms in IBS (47). The increased quantity of gut microbiota is a suggested evidence of the association of gut microbiota with IBS; however, its prevalence in IBS is not consistent. Studies on the relationships between the alterations in gut microbiota and GI disorders have limitations. The diversity of bacteria and the clinical symptoms of IBS are great and there are no exact molecular or organic markers to diagnose IBS. The assessment of the composition of gut microbiota is difficult and is confounded by large individual variations in microbiota. In addition, according to regions and countries, diverse eating culture (such as consumption of yogurts and fermented foods) and medicinal administration can change the composition of gut microbiota in individuals (48). Molecular techniques are widely used because of difficulties in culturing the gut microbiota, but these methods also have limitations. For example, dead organisms. The exact role of this alteration is still controversial in the pathophysiology of IBS. This is due to the limited knowledge of gut microbiota due to the complexity, variability and instability of the indigenous gut microbiota of human subjects(49-51).

Post-infectious Irritable Bowel Syndrome

It has been reported that the majority of patients recovered from acute infectious colitis due to Salmonella species, Campylobacter jejuni or Shigella species suffer from symptoms of IBS (52-55). Post-infectious IBS is known to develop in 6%-31% of acute infectious colitis and the risk factors include younger age, female gender, bloody stool and duration of diarrhea (55-57). There is a great deal of evidences for increased inflammation in patients with post-infectious IBS. Mild inflammation is seen in the colonic mucosa in patients with post-acute enteritis IBS. The number of chronic inflammatory cells in the colonic mucosa is

increased in patients with IBS compared to those who do not develop IBS, with increases in the activation of T cells and inflammatory cytokine expression after 3 months of infection (58). IL-1β mRNA levels and the number of enterochromaffin cells are increased in the colorectal mucosa of patients with IBS compared to those without IBS (59-60). These studies support the role of low-grade inflammation in the mechanism of IBS.

Alterations in Quantity of the Gut Microbiota

Alteration of the indigenous gut microbiota in the pathogenesis of IBS is not only related to the types of microorganisms comprising the microbiota but also to their numbers. SIBO has been suggested to play a role in the generation of IBS symptoms including abdominal distention, bloating and flatulence. This is additional indirect evidence that alterations in the gut microbiota are pathogenic factors in IBS. SIBO might lead to increased gas fermentation, gas production and altered gut movement(61-62). However, the prevalence of SIBO in IBS is not consistent between clinical studies varying from 4% to 84%. This inconsistency is due to the problems of hydrogen breath test that is commonly used as a diagnostic tool. A recent study using the jejunal culture method showed that SIBO was observed in only 4% of patients with IBS and that the prevalence of SIBO was not significantly different in IBS patients compared to healthy control groups (45). This result did not show a strong relationship between IBS and SIBO, but slightly increased counts of small bowel bacteria were observed in IBS patients. Although the degree of bacterial overgrowth did not meet the criteria of SIBO, this result suggested that quantitative change of gut microbiota might be associated with pathogenesis of IBS.

Studies using antibiotics to target the intestinal microbiota to treat IBS have been of non-absorbable antibiotics including neomycin or rifaximin led to a significant improvement in IBS symptoms (63-64). A recent paper showed that a large double-blind, placebo-controlled trial in which subjects were administered 550 mg dose of rifaximin 3 times daily for 3 weeks significantly relieved IBS symptoms of bloating and abdominal pain and improved stool consistency in patients with IBS without constipation (46). A possible explanation for this effect was suggested that the antibiotics reduced bacterial products such as short-chain fatty acids that cause IBS symptoms(65). Total concentration of short-chain fatty acids in jejunal secretions of SIBO patients is significantly higher than in healthy control. These organic acids may affect the bowel movement and clinical symptoms as a recent study showed that the concentrations of fecal acetic acid/propionic acid are correlated with GI symptoms, quality of life and negative emotion. In addition, antibiotic treatment may reduce the local mucosal engagement of bacteria to reduce the immune reaction between the host and the microbiota(66) performed. In some studies, short-term useof non-absorbable antibiotics including neomycin or rifaximin led to a significant improvement in IBS symptoms (42-43). A recent paper showed that a large double-blind, placebo-controlled trial in which subjects were administered 550 mg dose of rifaximin 3 times daily for 3 weeks significantly relieved IBS symptoms of bloating and abdominal pain and improved stool consistency in patients with IBS without constipation (46). A possible explanation for this effect was suggested that the antibiotics reduced bacterial products such as short-chain fatty acids that cause IBS symptoms (65). Total concentration of short-chain fatty acids in jejunal secretions of SIBO patients is significantly higher than in healthy control. These organic acids may affect the bowel movement and clinical symptoms as a recent study showed that the concentrations of fecal acetic acid/propionic acid are correlated with GI symptoms, quality of life and negative emotion. In addition, antibiotic treatment may reduce the local mucosal engagement of bacteria to reduce the immune reaction between the host and the microbiota(66).

CONCLUSION

Strong evidence suggests that gut microbiota has an important role in bidirectional interactions between gut and the nervous system.There is an interaction with CNS via regulation of brain chemistry and influence on the neuroendocrinal system thereby associated with stress response anxiety and memory function. Many of these effects are strain specific suggesting a role of probiotic therapy as an adjunct for neurologic disorders. In addition the gut flora can be restored using probiotics and possibly by diet. FGID and IBS are thus, now considered asmicrobiome GBA disorders.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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