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Review Article

Gut Dysbiosis and the Gut-Brain Axis

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Abstract

The bidirectional communication pathway known as the gut-brain axis is discussed with regard to both gut-to-brain and brain-to-gut communications. In particular, the influence of the gut microbiota on the development of emotional behavior, stress- and pain-modulation systems, as well as brain neurotransmitter systems is reviewed. The literature on the potential role of the gut microbiota on central nervous disorders such as autism and anxiety-depressive behaviors as well as its role in Parkinson's and Alzheimer's disease is reviewed. The potential contribution of intestinal dysbiosis to psychiatric disorders in patients with bowel disorders is also considered.

The literature on the influence of the brain on gut bacteria, notably disruption of the microbial balance within the gut and promoting inflammatory bowel disease, is discussed. Disturbance of homeostasis within the body and particularly the GI system apparently increases susceptibility to infectious disease and also can trigger a cascade of molecular reactions. These reactions can feed back to the central nervous system and the brain via the gut-brain axis, adversely affect the brain and behavior.

Finally, gut dysbiosis and its health sequalae are reassessed together with the potential benefits derived from ingesting prebiotics and probiotics on gut, brain and systemic health.

Keywords: *Gut-Brain Axis; Gut Microbiota; Prebiotics; Probiotics*

Introduction

There are many aphorisms related to food, including "you are what you eat", "an army marches on its stomach", "the way to a man's heart is through his stomach", "people who love to eat are always the best people" and so forth. Implicit in these sage comments is that not only is food good for you, as in a healthy and balanced diet, but that there is a connection between the gut, digestion and both physical and mental health. This possible relationship has been studied in some detail over the past 20+ years and identified as the emerging concept of a gut microbiota-brain axis or, simply, the gut-brain axis (GBA).

The gut-brain axis

Gut-to-brain Communication

The gut-brain axis is the term for the bidirectional interactions and communication between the central nervous system (CNS), the enteric nervous system[1], and the gastrointestinal tract [1-4]. Research studies indicate that brain function and behavior is influenced through neural, endocrine and humoral pathways by changes in the gut microbiota. These various pathways or connections between the CNS and the gastrointestinal (GI) tract likely involve but are not wholly dependent on the vagus nerve, the immune system and bacterial metabolites and products [5]. In support of this is the concept that the gut microbiota serves as a virtual endocrine organ[2] because of its capability of metabolically producing and regulating multiple compounds that enter the circulation and influence the function of various organs and systems [4-6].

[1]The enteric nervous system or intrinsic nervous system is one of the main divisions of the autonomic nervous system. It includes a number of neural circuits controlling motor functions, local blood flow, mucosal transport and secretions as well as modulating immune and endocrine functions.

[2]The endocrine system is a messenger system, principally through the hypothalamus, comprising feedback loops of hormones released by internal glands into the circulatory system and regulation of various target organs.

An interesting pre-clinical study on mice clearly demonstrated the importance and potency of the gut-brain axis [7]. A strain of mice that typically are timid and shy were fed a cocktail of antibiotics that changed the composition of their gut bacteria which, in turn, completely changed their behavior such that they became bold and adventurous. It was noted that the antibiotic treatment also boosted levels of brain-derived neurotrophic factor in the hippocampus, an effect that promoted neural connections, an important factor in memory and mood. Following cessation of the antibiotic regimen, the mice soon reverted to their usual, cautious behavior and their brain biochemistry also returned to normal [7]. This pre-clinical research study demonstrated that intestinal microbiota influence brain chemistry and behavior independently of the autonomic nervous system, gastrointestinal-specific neurotransmitters, or inflammation.

The studies cited here clearly indicate that through the GBA, gut microbiota can influence normal physiology and may contribute to diseases ranging from inflammation to obesity [1].

It has also been suggested that the gut microbiota may influence the development of emotional behavior, stress- and pain-modulation systems, as well as brain neurotransmitter systems [2]. There are also suggestions that the gut microbiota affect or influence central nervous disorders such as autism and anxiety-depressive behaviors [3]. It is also possible that intestinal dysbiosis might contribute to psychiatric disorders in patients with bowel disorders.

Moreover, the gut microbiota may affect host susceptibility to many immune-mediated diseases and disorders [8] as well as inflammasome[3] activation in the brain and various inflammatory disorders [5]. Interestingly, recent studies on the communication between the gut microbiota and the brain have attracted considerable attention because of the GBA's suspected involvement in diverse diseases. In particular, chronic kidney disease is commonly associated with hypertension and characterized by immune dysregulation, metabolic disorder and sympathetic activation, all of which are linked to gut dysbiosis and altered brain-microbiota "crosstalk" [9]. It has also been suggested that various metabolites secreted by the gut microbiota can affect the cognitive ability of patients diagnosed with neurodegenerative diseases [10]. In particular, these metabolites from the gut microbiota impact communication pathways between the brain and gut, causing signal dysfunction and neuroinflammatory effects.

It follows, therefore, that through communications with the endocrine, nervous and immune systems, the gut microbiota regulates host homeostasis, including blood pressure and kidney functions. Further, through the gut-brain axis, the gut microbiota has crucial roles in a variety of diseases, including hypertension and chronic kidney disease. It has to be stressed, however, that the mechanisms involved in these interactions are not understood.

Brain-to-gut communication

In addition to the gut-to-brain communication, there is very strong evidence that the brain can directly influence the GI tract through the GBA, and visa-versa. This connection or crosstalk between brain and gastrointestinal (GI) system is clear from the familiar release of digestive juices at the thought of eating even before any food is ingested. This principle of a conditioned response was enunciated in Pavlov's research with salivating dogs early in the 20th Century [11]. Commonly referred to as the "Second brain", it has been suggested that the human gut is the only organ to possess its own and independent nervous system, an intricate network of 100 million neurons embedded in the gut wall [12]. It appears that this neural network is so sophisticated that the gut continues to function even when the primary neural conduit between it and the brain, namely the vagus nerve, is severed [12].

[3]Inflammasomes are multiprotein complexes that mediate the activation of caspase-1, which promotes secretion of the proinflammatory cytokines interleukin 1β (IL-1β) and IL-18, inducing inflammation in response to infectious microbes and molecules derived from host proteins.

For decades, starting back in the 1920s and probably before that, stomach ulcers were a common and accepted facet of modern life, notably from financial worries, job insecurity and occupation-related stress in corporate and professional life. In recent years, the literature has reported that the brain can exert a powerful influence on gut bacteria. Many studies have shown that even mild stress can disrupt the microbial balance in the gut [13,14]. Changes in the gut microbiota caused by chronic stress are reported to promote inflammatory bowel disease [15] as well as impair the antidepressant and neurogenic effects of fluoxetine, a standard selective serotonin reuptake inhibitor [16].

Disturbance of homeostasis within the body and particularly the GI system apparently causes the host to become more vulnerable to infectious disease and also trigger a cascade of molecular reactions. It is then possible for the latter to feed back to the central nervous system and the brain via the gut-brain axis. Certainly, there is evidence that stress-induced changes in the gut microbiome conversely may affect the brain and behavior. Inflammatory cytokines produced within the gut during infection disrupt brain neurochemistry, increasing susceptibility to anxiety and depression. This process could be a causative factor in the observation that over half of people with chronic GI disorders such as Crohn's disease, ulcerative colitis and irritable bowel syndrome are also plagued by anxiety and depression [7,12,13].

Gut dysbiosis

The condition commonly known as intestinal dyspepsia[4] is caused by several factors, including poor diet, natural aging, stress and antibiotic therapy. The term primarily refers to the bacterial imbalance arising from an overgrowth or preponderance of bad bacteria and yeast. Three bacterial pathogens commonly cause gastric issues, namely *Helicobacter pylori* (*H. pylori*), *Escherichia coli (E. coli)* and *Clostridium difficile* (*C. difficile*). Infections by these pathogens cause diarrhea, stomachache and fever. It is also known from preclinical studies on rodents that chronic stress disturbs gut microbiota, triggering an immune system response and facilitating colitis [16].

It should be noted, however, that whereas the large intestine contains most of the gut microbiome, and the small intestine does not contain many bacteria, there is a condition known as small intestinal bacterial overgrowth (SIBO) that can arise. This is a condition that occurs when an excessive number of bacteria colonize the small intestine and can cause bloating, diarrhea or constipation.

Gut dysbiosis is the term for this imbalance in the numbers and types of intestinal bacteria although, in fact, there are in fact three types of dysbiosis [17] with all three often being present at the same time:

- **Type 1:** Loss of beneficial ("good") bacteria from the gut
- **Type 2:** Overgrowth or preponderance of bad bacteria and yeast
- **Type 3:** Loss of overall gut microbiome diversity, i.e. of both good and bad bacteria.

The perturbations to the structure of complex commensal communities found with dysbiosis can negatively impact the host immune system and lead to subsequent development of immune-mediated diseases [18]. As a result, gut dysbiosis commonly may manifest as dyspepsia and such digestive problems as acid reflux, heartburn, food intolerance, flatulence and bloating.

However, dysbiosis can cause dysregulation of signaling pathways in the gut-brain axis, affecting the vagus nerve and the immune system, and lead to altered permeability of the blood-brain barrier and neuroinflammation [5]. This can lead to a variety of chronic illnesses and conditions, i.e. immune-mediated diseases and inflammatory conditions [10,11,15,16,18], which may include but are not limited to:

[4]Dyspepsia, also known as indigestion, is the discomfort or pain occurring in the upper abdomen, often after eating or drinking. It is not a disease but a symptom and affects up to 30% of the population. Common symptoms include bloating, discomfort, feeling too full, nausea and gas.

- Acne, skin rashes and psoriasis
- Allergies
- ADHD or attention deficit disorders
- Anxiety or depression
- Autism
- Colorectal cancer
- Chronic fatigue
- Crohn's disease
- Inflammation and aching joints
- Irritable bowel syndrome
- Obesity
- Type 1 diabetes mellitus
- Ulcerative colitis.

Causes of gut dysbiosis

Gut dysbiosis can have many causes, including natural aging but diet [19] and, as previously noted, stress [14-16] can contribute to the condition. In fact, a recent preclinical study with mice [20] indicated that stress-induced changes in gut microbiota are involved in the pathogenesis of depressive disorders and impairs the antidepressant and neurogenic effects of a standard selective serotonin (5-HT) reuptake inhibitor, fluoxetine. The reduction in fluoxetine efficacy apparently results from alterations in the serotonergic pathway of tryptophan metabolization and decreased neurogenesis in the hippocampus.

There is increasing evidence that various medications (prescription and non-prescription) and notably antibiotics also cause changes of the gut microbiota [21-26]. It is well-known that a course of antibiotic therapy severely impacts the gut microbiota, inducing type 3 dysbiosis. However, after therapy is terminated, this condition can be ameliorated by a healthy and balanced diet combined with fermented foods, e.g. yoghurt, sauerkraut and prebiotic and probiotic supplements.

Of greater concern is the increasing evidence of cognitive impairment by antibiotic-induced gut dysbiosis [27,28], especially with chronic use. Interestingly, cognitive dysfunction is highly prevalent in ICU patients [29] whereas incident new and persistent cognitive impairment is a less common but potentially preventable problem after critical illness. Chronic comorbidities and the number of ICU stays increase the risk of post-ICU cognitive dysfunction irrespective of age.

The literature also indicates that the Western (American) diet[5] and common bacterial infections may be associated with brain and systemic inflammation and an increased risk of subsequent dementia [30,31].

[5]The typical Western (American) diet is low in fruits and vegetables, and high in fat and sodium. Further, this diet consists of large portions, high calories and excess sugar, the latter accounting for over 13% of the daily caloric intake with beverages constituting some 47% of these added sugars.

The inflammasome pathway[6], apparently activated by gut dysbiosis, has been linked to neuroinflammatory conditions such as multiple sclerosis, Alzheimer's and Parkinson's diseases but also anxiety and depressive-like disorders [5,10]. The potential role of gut dysbiosis in neurodegenerative disorders like Parkinson's and Alzheimer's diseases also has been commented upon by other researchers [13,32].

There is likely to be a reciprocal influence of microbiota and inflammasome activation in the brain but the precise mechanism whereby gut dysbiosis causes inflammasome activation in the brain is unclear. However, it presumably involves the production of pro-inflammatory cytokines (interleukin-1β and interleukin-18) that communicate with the brain via the gut-brain axis.

It follows from current research efforts that gut dysbiosis not only induces dyspepsia and other gastric conditions such as irritable bowel disease but also, through the gut-brain axis, may have a significant impact on the immune system and in neurodegenerative disorders.

Remediation

When the balance of the gut microbiota is disturbed and gut dysbiosis has developed, restoring the right balance in the GI tract can be challenging. If gut dysbiosis is the result of serious bacterial infection, then pharmacological intervention may be mandatory. but the GI tract then may require replenishment of beneficial bacteria by means of prebiotic and probiotic supplementation.

As previously noted, chronic kidney disease (CKD) is commonly associated with hypertension and is characterized by immune dysregulation, metabolic disorder and sympathetic activation, all conditions that are linked to gut dysbiosis and altered host-microbiota crosstalk [9]. There are indications that therapeutic strategies for CKD and hypertension that target the gut microbiota now include dietary intervention, probiotics, prebiotics and synbiotics [9]. Likewise, a potential causal link between SIBO and motor function in Parkinson's disease may encourage studies directed at a therapeutic approach based on the manipulation of the gut microbiota with probiotics and prebiotics [32].

It should also be noted that because probiotics are reported to prevent changes in hippocampal neurogenesis and expression in hypothalamic genes involved in synaptic plasticity [3], they may profoundly affect the brain-gut interactions via the gut-brain axis [14]. This effect would attenuate the development of stress-induced disorders in both the upper and lower gastrointestinal tract and suggests new therapeutic approaches.

It is interesting that the Ukrainian immunologist Élie Metchnikoff in the early years of the 20th Century ascribed the extraordinary longevity and outstanding health of Bulgarian people, compared to that of the rest of the world, to dietary differences, notably the consumption of large amounts of natural yoghurt [33]. His findings were supported by the long-held tradition of physicians in the Near- and Middle-East of treating digestive (gastrointestinal) disorders, liver problems and poor appetite with soured milk. Metchnikoff believed that absorption of toxins generated and released by bacteria within the biosystem shortened the human life span and he contended that the microorganisms in yoghurt slowed or reversed the adverse health effects of pathogens in the intestinal tract. In other words, Metchnikoff's contentions over 100 years ago that probiotics are essential to intestinal, systemic and mental health are not only valid in the 21st Century but are supported by modern scientific studies.

In the past ten years, fecal microbiota transplantation (FMT) has gained increased attention for the treatment of gut infections, particularly those caused by *Clostridium difficile* (*C. diff)*. FMT, however, is not a new treatment in that the first fecal transplantation in modern

[6]As previously noted, inflammasomes are a group of intracellular multimeric protein complexes that activate inflammatory caspase-1, and the inflammasome pathway is a major inflammatory pathway.

times was performed in 1958 [34]. Centuries ago, the practice of treating gut aliments with microbiota appears to have originated with Chinese healers treating patients with "yellow soup", which was a mixture of fecal matter and water [35]. Folktales from the 17th Century include treatment of indigestion in livestock with ruminal microorganisms from healthy animals [36]. Nowadays, FMT treatment of animals is studied for therapeutic, prophylactic and immunogenic uses [37]. With regard to human patients, clinical trials studying FMT have generally shown positive outcomes for the treatment of *C. diff* [38].

Conclusion

Research studies indicate that the gut microbiota influences the development of emotional behavior, stress- and pain-modulation systems, and brain neurotransmitter systems [2]. Further, perturbations of the gut microbiota by probiotics and antibiotics can modulate some of these effects. Research studies suggest that several mechanisms, including endocrine and neurocrine pathways, are involved in gut microbiota-to-brain signaling [2]. Conversely, the brain can alter microbial composition and behavior of the gut via the autonomic nervous system. It follows that the gut microbiota and the gut-brain axis have a far great influence on gastric, systemic and neuronal health than previously recognized. Further, maintaining good GI health and a balanced gut microbiota through dietary means and employing prebiotic and probiotic supplementation are essential to human health.

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