Nutritional Effects on the Gut Microbiome & the Brain-Gut Axis: Unlocking the Therapeutic and Preventative Potential of Nutrition for Gut Dysbiosis Associated Diseases

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Abstract

Diet plays a pivotal role in the overall health of an individual. Not only does it help carry out and regulate certain physiological functions, but it also can determine the composition of the gut microbiome. While the relative number of microorganisms that make up the gut microbiome vary between individuals and can be dependent on different environmental factors, there is evidence to suggest that composition of the microbiome can correlate with overall health or disease. When the GI microbiome is disturbed or suddenly changes it results in microbiome dysbiosis, a condition that correlates with the presence of certain diseases. Diseases linked to microbiome dysbiosis range from metabolic disorders, inflammatory bowel diseases to disorders of the brain. Many of these diseases are linked to the connection between the brain and the gut, known as the brain-gut axis. This bidirectional communication is important to maintain normal intestinal function, but is also responsible for the GI response to emotions as well as the emotional response to GI disturbances. By exploiting the interaction between microbiome health and nutrition, diet can be used to alleviate disease symptoms, protect against the development of certain conditions, and better maintain overall health. This review will examine the effects of nutrition on the microbiome, diseases linked to disruption of the normal microbiome, and the way that altering the diet can mitigate symptoms or prevent disease.

Keywords: Gut-Brain Axis; Nutrition; Microbiome; SCFA; Gut dysbiosis

Introduction

Colonizing the human gastrointestinal (GI) tract are a myriad of different bacterial species that are important in carrying out everyday functions and survival. There is a complex ecosystem of bacteria, viruses, fungi and protozoa, known collectively as the gut microbiome, and has been shown to be extremely important for human health (Cani, 2018) Consisting of ten more times bacterial cells than human cells, the gut microbiome is "essentially an organ" and in recent years, has become widely studied to determine its composition, and its impact on overall health (Eckburg et al., 2005;Thursby & Juge, 2017)

The composition of the microbiome, much like a fingerprint, varies between individuals. The types of bacteria that colonize an individual's GI tract have been shown to impact physiological function, such as; the body mass index (BMI), digestion, immune response, allergies, and incidence of metabolic, neurologic and gastrointestinal diseases (Thursby & Juge, 2017) A "healthy" gut microbiome is important for carrying out a multitude of different functions, including: metabolic and endocrine pathway regulation, modulating immune responses, production of necessary vitamins, metabolites and neurotransmitters and maintaining overall heath (Marilyn Hair & Jon Sharpe, 2014)

Within the last decade, there have been extensive studies performed to determine the mechanism, and implications of a cross-talk between the gut microbiome and the central nervous system (CNS). This communication between the intestinal cells and the brain is known as, the gut-brain axis (GBA). Being a relatively new field of study, there is still much to research and learn about the gut-brain axis, but some studies have already found evidence to suggest this system is crucial for the maintenance of homeostasis and that dysfunction within the system and its players can increase the incidence of certain diseases and severity of clinical signs (Rutsch et al., 2020)

Throughout an individual's lifetime, the bacteria colonizing the GI tract can fluctuate mildly or can be wildly altered by different environmental and emotional stressors. The use of antibiotics, addition of dietary supplements, change of environment, aging, and diet can alter the composition of the microbiome (Hasan & Yang, 2019). While these changes can be normal and not cause any issues, an abrupt microbial shift can lead to a loss of homeostasis within the gut, known as microbiome dysbiosis. This condition has been shown to correlate with higher risk for intestinal diseases such as inflammatory and irritable bowel disorders and extra-intestinal diseases, including asthma, allergies and metabolic syndrome (Carding et al., 2015).

This review aims to present information about the gut microbiome, and the ways in which it can be altered. It will also look at the implications that gut dysbiosis plays on overall health and how disruption of the gut correlates to certain disease states. While there is a myriad of different diseases linked with microbiome health, this review will emphasize a select few diseases including; inflammatory bowel diseases, colorectal cancer, and Parkinson's disease. Lastly, this review will discuss the potential of using nutrition as a way to prevent or alleviate conditions associated with gut health.

Gut Microbiome

Living inside the human gut is a complex and diverse ecosystem consisting of trillions of microorganisms that assist the body in carrying out important physiological functions and maintaining homeostasis (Sender et al., 2016) (Thursby & Juge, 2017). Composed mainly of symbiotic bacteria, the gut microbiome is generally beneficial to the host and is responsible for breakdown of food to important metabolites, protection against harmful opportunistic pathogens, influencing immunologic responses and interacting with endocrine and metabolic pathways (Valdes et al., 2018)The types of bacteria that make up the microbiome can be important in maintaining and determining the overall health of an individual.

The microbiome is shaped in part by host genetics and environmental factors. Gender, age, environment, body mass index (BMI), diet, etc. have all been shown to alter gut microbiome (Haro et al., 2016), (Goodrich et al., 2014). When these alterations occur, it can be reflected in the health and physiology of the host. Studies done in germ free (GF) mice have shown that the gut microbiome composition is a potential factor involved in the development of obesity, type 2 diabetes and maturation of the immune system (Ge et al., 2017; Magne et al., 2020) Some studies have even started to implicate certain microbiome compositions and densities within the gut with personality traits and the development of psychiatric disorders (Johnson, 2020)

The predominant bacterial phyla present within the average human microbiome are *Firmicutes* and *Bacteroidetes*, which make up about 75% of the microbiome, followed by *Proteobacteria* and *Actinobacteria.* (Riaz Rajoka et al., 2017)(Matsuoka & Kanai, 2015). The ratio within the gut of *Firmicutes* to *Bacteroides* seems to be important and has been studied in depth. It has been hypothesized that an imbalance in this ratio can be a factor in the development of obesity and other diseases, but there is still no clear connection between an unbalanced ratio and disease (Riaz Rajoka et al., 2017). There is, however, a correlation between a reduction of *Firmicutes* and the onset of inflammatory bowel diseases, like Crohn's disease (CD). Conversely, patients diagnosed with ulcerative colitis (UC) and with higher levels of *Firmicutes* have been shown to respond better to treatment (Matsuoka & Kanai, 2015).

It is inevitable that there will be changes in the microbiome over time, the majority of which will not result in any noticeable effects, however, abrupt shifts in diet, stress, environment or physical trauma can lead to detrimental changes within the gut. Such changes can be so severe that they disrupt the normal microbiome, making room for opportunistic, potentially harmful pathogens to dominate, and causing what is known as gut dysbiosis (Carding et al., 2015)

Gut-Brain Axis

In recent years, there has been an increase in studies done about the once controversial idea of a connection between the enteric nervous system (ENS) and central nervous system (CNS) known as the gut-brain axis (GBA). This complex network is a bidirectional communication between the gut and the brain with side involvement from the autonomic nervous system (ANS), hypothalamic-pituitary-adrenal axis and pro-inflammatory cytokines (Rutsch et al., 2020) The ENS consists of over 100 million nerve cells spanning from the esophagus through the GI tract. The connection between the ENS and CNS is responsible for controlling

digestion, development of the immune system, ensuring intestinal barrier integrity, and links cognition and digestion. Over the last decade, studies in GF mice have shown the importance of the microbiome in proper brain development and signaling (Luczynski et al., 2016)

For example, the role of the microbiome in the gut-brain axis has been studied in GF mice and normally reared mice undergoing prolonged antibiotic treatment. GF and antibiotic treated mice had stunted and decreased neurogenesis of the hippocampus, that could be reversed when treated with probiotics and physical activity (Möhle et al., 2016) The impact of the microbiome on the GBA can also be illustrated by the high incidence of depression in individuals with inflammatory bowel diseases, hypothesized to be caused by a prolonged exposure to high levels of inflammatory cytokines commonly associated with IBD (Breit et al., 2018) The bidirectionality of the gut-brain axis can be observed when studying post stroke behavior in individuals. One study performed in mice, found that the presence and severity of brain lesions can cause gut dysfunction and microbial dysbiosis. Conversely, they also found the state of the gut can influence the outcome of a stroke by modulating the systemic immune response and inflammation (Singh et al., 2016).

The gut microbiome is able to carry out its communication with the CNS through signaling pathways including the vagus nerve, immune system, and metabolites produced by the microbes within the microbiome (Rutsch et al., 2020).

The vagus nerve provides a connection between the GI tract and the brain. Information from the ENS can influence the vagal nerve to modulate the gut immune system, digestion, and enteric reflexes. It can also be implicated in neurologic diseases when pathogens from the gut ascend to the brain and cause inflammation that influences brain function (Breit et al., 2018). For instance, *Lactobacilli*, and *Bifidobacteria* within the microbiome can produce neurotransmitters, including acetylcholine, gamma-aminobutyric acid (GABA), and serotonin, which are important in brain signaling (Pokusaeva et al., 2017) Normally, over 90% of serotonin is generated in the gut. In germ free mice, serum levels of serotonin are significantly reduced, highlighting the role that the microbiome plays in regulating production of this neurotransmitter (Yano et al., 2015)

Short Chain Fatty Acids (SCFA) are carboxylic acids with a 2-6 carbon tail. These metabolites are generated within the gut during the fermentation of starch and fibers by bacteria (J. Tan et al., 2014) The main SCFA within the gut include acetate, butyrate and propionate which are produced by anaerobic bacteria within the gut when they ferment fiber. (Venegas et al., 2019) SCFAs are beneficial metabolites important for signaling, regulating immune response and maintaining homeostasis. When there are higher levels of SCFAs there is reduced inflammation, increased intestinal mucus and less barrier permeability (Hendler & Zhang, 2018).

Implication of Gut Dysbiosis in Disease

A healthy gut is colonized by diverse and primarily beneficial bacteria. By occupying space in the gut, the healthy microbiome creates a barrier that protects against the overgrowth of harmful bacteria and discourages opportunistic pathogenic bacteria from getting outside the gut and causing disease. This barrier and diversity can be lost due to physical trauma to the gut, antibiotic use, abrupt changes in diet, resulting in disruption of gut homeostasis, otherwise known as gut dysbiosis (Degruttola et al., 2016).

When the normal microbiome is replaced by mostly gram-negative bacteria, this can lead to immune dysfunction and inflammation due to an increase in nuclear factor kappa B (NF-kB) translocation to the nucleus in enterocytes, leading to upregulation of pro-inflammatory cytokines (*Dysbiosis and Leaky Gut - Illinois Chiropractic Society*, n.d.).

Increased cytokine production in response to gut dysbiosis can lead to the so-called “leaky gut” syndrome. Leaky gut occurs when gut dysbiosis leads to the disruption of the mucosal barrier, resulting in increased epithelial barrier permeability and allows for PAMPs from pathogenic bacteria, primarily LPS, to reach the lamina propria. When this occurs, it can lead to low-grade chronic inflammation systemically, including in some instances the brain (Mu et al., 2017)

Gut Dysbiosis in GI Disease

Inflammatory bowel disease including Crohn’s Disease, and Ulcerative Colitis are associated with dysbiosis of the gut microbiome. Studies have shown a marked difference in the composition of the microbiome in healthy individuals versus those diagnosed with inflammatory bowel disease disorders (Schäffler et al., 2016). Using 16S rRNA sequencing to characterize the mucosal-adherent intestinal microbiome of colonic tissues from individuals with Crohn’s Disease, researchers found that there was a correlation of the numbers of mucosa-attached bacterial communities with disease activity (Schäffler et al., 2016)

Colorectal cancer is the second leading cause of cancer in the U.S and is a major concern due to its high incidence and mortality rate in Westernized societies. Research has shown that there is a correlation between the risk of colon cancer and the homeostasis of the gut microbiome, implicating lifestyle choices in the risk for cancer. The low fiber content of the Western Diet leads to changes in the microbiome including increase of *E. coli*, leading to more pro-inflammatory patterns and for a reduction in the conversion of fiber to butyrate. Decreased butyrate leads to dysfunction of colonocytes and potentially cancer. Current research implicates an increase of mucosal-adherent *Fusobacterium nucleatum* in the over-activation of TLR4-mediated signaling through MYD88, leading to nuclear translocation of NFkB, leading to colonocyte dysfunction and increased risk for developing cancer (Yang et al., 2017). The abundance of *F. nucleatum* and its ability to colonize the human gut is influenced by gut dysbiosis caused by diet that induces inflammation (Liu et al., 2018). A further study in germ-free mice found transferability of the dysbiotic microbiome leading to CRC. The GF mice were inoculated with stool samples from individuals with CRC and stool samples of healthy individuals, finding that those given CRC-associated stool samples developed inflammation, dysplasia, and polyps in the colon (Wong et al., 2017)

Neurologic Disorders Associated with Gut Dysbiosis

There has been evidence to suggest that some neurological disorders and diseases such as, Parkinson’s, and Alzheimer’s, can be linked to dysbiosis of the microbiome in the gut. The ability of the microbiome composition to have an effect on neurological disorders implicates a role for the gut-brain axis in the pathogenesis of these diseases. Links between the gut microbiome and Parkinson’s Disease (PD) were first suspected when a high percentage of patients presented with constipation or GI upset (Baldini et al., 2020)Parkinson's Disease (PD) is a neurodegenerative disorder of the CNS that typically presents with motor deficits. It

is one of the leading causes of dementia and affects nearly 10 million people worldwide (Marras et al., 2018)Hallmarks of the diseases include cerebellar inflammation and the presence of inclusions bodies in Purkinje cells called Lewy bodies, which are made up mostly of misfolded neuronal protein aggregates called alpha synuclein (Dutta et al., 2019)Studies have shown that the microbiome differs between PD patients and healthy individuals – leading researchers to believe that the composition of the microbiome could play a role in disease pathology (Chiang & Lin, 2019)The mechanisms by which microbial dysbiosis can affect the progression of PD is thought to occur through a decrease in production of SCFA levels, in addition to gut barrier dysfunction and increased expression of pro-inflammatory cytokines in the small intestinal mucosa. Microbiome dysbiosis can impair the integrity of the epithelial barrier, making the gut wall more permeable to pro-inflammatory molecules. This increase in intestinal permeability potentially allows for pathogenic bacteria and LPS to escape the gut and pass into the systemic vasculature causing a systemic increase of proinflammatory cytokines leading to systemic inflammation (Dutta et al., 2019)

One recent study in Parkinson's shows the role of the gut microbiome in PD progression by using GF transgenic mice that overexpress alpha synuclein. In the GF mice there was a reduction in microglia activation and symptoms associated with PD, but when the intestines of the mice were treated with microbially produced SCFAs, the clinical symptoms of the diseases were restored. These results lead to the hypothesis that some SCFA play a role in maturation of microglia sensing the alpha synuclein. Furthermore, the study also reported that when the microbiome of PD patients was transplanted into the mice, the disease conditions worsened, providing some evidence that the microbiome is implicated in the development and worsening of clinical signs of PD (Sampson et al., 2016)

Effect of Nutrition on Gut Microbiome Composition to influence health

As stated previously, one of the factors known to modulate the composition of the gut microbiome is diet. Over the years, there have been a number of studies that have sought out to determine how different diets (Mediterranean, high protein, low carb, etc.) and consumption of different dietary supplements and additives can alter the microbiome composition within the gut. The current understanding is that diet has a strong effect on the microbiome that inhabit the gut and can correlate with risk of developing chronic inflammatory diseases (Tilg et al., 2018).

Food additives, emulsifiers, and diets high in fats have been shown to lead to a shift in microbiota composition and subsequently an increased risk for development of Inflammatory Bowel Disease (Chassaing et al., 2017)(Laudisi et al., 2019). Some food additives have also been shown to potentially affect the gut-brain axis by being linked to an increased incidence in behavioral disorders, like anxiety (Holder et al., 2019). To reduce inflammation and inhibit opportunistic pathobionts from colonizing the gut, diets that increase SCFAs have shown to be beneficial. In studies done in animal models of Inflammatory Bowel Diseases, addition of fructooligosaccharides, soluble fiber, or resistant starches were shown to increase SCFA production by microbiome, thereby reducing inflammation within the intestine (Lewis & Abreu, 2017). Consuming fermented products and probiotics has also been shown to increase the amount of SCFA and can help reduce the risk for gut dysbiosis (Markowiak-Kopeć & Śliżewska, 2020)

In an effort to discern the risk associated with different diets and specific *F. nucleatum*-associated colorectal cancer, it was found that a diet high in fiber and whole grains correlated

with a lower risk for development of colorectal cancer, if it was associated with *F. nucleatum*. However, if the CRC was not associated with *F. nucleatum* overgrowth, the dietary changes including higher fiber content did not rescue the risk of CRC (Mehta et al., 2017).

New Directions to Study the Interplay of the gut microbiome, intestinal epithelium and central nervous system

Currently, the majority of microbiome studies are carried out in germ free (GF) mice models. However, as research continues to be done in this field, different animal models are being discovered that may be more appropriate and accurate for microbiome research that is more directly translatable to humans. They also have an anatomically much more similar GI tract and diet to humans than mice, because while mice tend to eat solely grains and cereals, humans have a much more varied diet. Mice also produce different enzymes than humans, have differing metabolic pathways, and have different neurological and intestinal anatomy (Ambrosini et al., 2019). These similarities point to dogs being a valuable model for human microbiome and disease research, because their responses to stressors and treatments will more accurately align with and represent human microbiome responses.

Studies done in dogs have shown that canines to spontaneously develop many analogous diseases to humans, including cancer, inflammatory bowel diseases (IBD), diabetes, and heart failure, adding to the argument that dogs would be a useful model for studying human diseases (Schneider et al., 2018). A study done in canines with naturally occurring type 2 diabetes mellites (T2DM), found similarities in disease states between humans and dogs with T2DM, including the presence of increased LPS in serum, bile acid impairment and increased Gammaproteobacteria in the gut of both species (Jergens et al., 2019).

Furthermore, dogs have also been shown to harbor microbiomes that are much more similar to humans than the microbiome of the murine models. Dogs also exhibit clinical signs associated with gut dysbiosis that parallel those of humans. Much like in humans with IBD, dogs with IBD have been shown to have altered gut microbiota and dysbiosis when compared to healthy controls. In these dogs, treatment via therapy with glucocorticoids and dietary alterations showed potentially beneficial shifts in bacterial populations and improved barrier functions (Atherly et al., 2019).

There is still much to be discovered and understood about the interaction between the gut microbiome and the CNS. Some of the limitations in the knowledge about the GBA are due to the fact that the majority of studies are performed in murine models. While these models have offered some insight into the gut-brain communication, they are limited in their ability accurately represent humans because they differ in neurological and GI anatomy and physiology. These models also differ from humans in terms of life-span and spontaneous development of clinically similar diseases. Dogs could be a valuable model when studying the GBA, because their gut microbiome taxonomically and functionally overlaps up to 60% with that of humans (Coelho et al., 2018). In addition, brain to body ratio in dogs and the process of aging, specifically with regards to memory function in the brain, has been described as very similar. Moreover, dogs spontaneously develop neurological dysfunction analogous to human Alzheimer's Diseases (AD) when they age (Ambrosini et al., 2019). Further studies carried out in dogs with canine cognitive dysfunction could be useful to determine possible treatment options in people with AD.

As previously stated, there is a growing concern that murine models are limiting the discovery of therapeutic drugs and treatments intended for human market, because they are predominantly grain-fed, and ferment these grains in a large cecum which is missing in dogs and humans. This results in a largely different composition of the microbiome, with less than 10% taxonomic and functional overlap with that of humans (Beresford-Jones et al., 2021). Furthermore, spontaneously occurring diseases, and the pathogenesis of such diseases, is vastly different in mice compared to humans (Schneider et al., 2018). An alternative to in vivo models could be cellular 3D-organoid systems, which are in vitro models containing cells obtained from primary tissues or stem cells in a host that can be propagated and made into complex models of systems containing different types of cells that mimic organ systems and tissues (Mochel et al., 2018). These models allow for a deeper understanding of disease pathology through the ability to isolate specific cells from organs, investigate drug safety and efficacy on those cells and allow for development of personalized medicine treatment options, because of the ability perform ex vivo trials on organoid to evaluate drug efficacy (Clevers, 2016).

Organoids developed from intestinal epithelial cells from dogs can provide more insight on the GI diseases like CRC and IBD that spontaneously occur in both humans and canines (Chandra et al., 2019) Recent work using 3D organoids successfully established a culture system of canine primary intestinal stem cells that have shown to be similar in both physiology and function of intestines in vivo (Ambrosini et al., 2019). This system can be used to compare the function and pathology of intestinal epithelial cells when challenged with inflammatory bowel diseases in comparison to healthy intestinal cells (Kingsbury et al., 2018).

Another in vitro model, known as microfluidic systems, can work in tandem with organoid systems to create essentially “organs-on-chips”, which can provide better understanding of the interactions and composition of the gut microbiota, as they enable co-culture of epithelial cells with the microbiome (Tauzin et al., 2020) . This technique is potentially more beneficial than current models because it can be designed to better mimic the interaction of epithelial cells with the microbiome in detail (H. Y. Tan & Toh, 2020).

Conclusion

Within the human gut there are a plethora of microorganism whose distribution is constantly shifting and is shaped by environment and lifestyle choices. This system of microorganisms aides the body in a multitude of physiological functions and is important for maintaining overall health. If there is a severe disruption to the normal gut microbiome, known as gut dysbiosis, then host homeostasis is lost and there is potential for metabolic, GI, and neurological disease.

Consumption of certain diets and probiotics can modulate the gut composition, either beneficially or negatively. There is evidence that suggests that diet could be manipulated to help prevent disease or mitigate diseases symptoms. Reduction of inflammation is key to maintain health and preventing disease. This can be accomplished through diet by avoiding long-term consumption of the so-called Westernized diet and instead opting for diets high in fiber and cooked whole grains that promote SCFA production and reduction in inflammation.

Moving forward, there is a lot of research still left to be done. It would be beneficial for more research to be done in different animal models, specifically companion animals, because they share our environments, and their GI system, anatomy and physiology is more closely replicated in humans. Further research could also be done examining different diets on specific diseases states. Lastly, it would be beneficial to have more research performed on the gut-brain axis and getting a better understanding of how this system is able to carry out its functions and communicate.

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