Commentary

Are there any correlations between gut microbes and neuropathology?

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ABSTRACT

The brain and other organs require a wide range of chemicals, which the gut bacteria create like a virtual organ. The link between humans and microorganisms is symbiotic; we feed the microbes, and they in turn provide us necessary chemicals. Around 1000 species of bacteria have been found in the human gut, and the Bacteroidetes and Firmicutes phyla make up around 80% of the entire microbiota in the human gut. Diet, exercise, stress, illness, and medicine are the primary factors determining microbiota structure in adults.

Given the high prevalence of these diseases, we investigate the role of the gut microbiota in multiple sclerosis, autism, Parkinson's disease, and Alzheimer's disease in this narrative review. We concentrate on preclinical research that advances knowledge of disease pathogenesis.

INTRODUCTION

The adult human brain weighs about 1.5 kg, which is comparable to the weight of the microbiota in the stomach. The number of cells in the human body and the number of bacteria in the microbiota are comparable. The microbiota, as opposed to human cells, has a higher DNA content and gene content. In a symbiotic connection, microorganisms and humans have co-evolved, and while we feed the germs, they in turn generate compounds that are essential for the survival of our brains and other organs. Our cells wouldn't have enough room for all the microbial DNA we need if it were to be directly incorporated there. Therefore, the symbiotic relationship is crucial for our bodies to function properly.

Microbiota structure

The architecture and function of the gut microbiota are now better understood because to developments in DNA sequencing and bioinformatics. Within the microbiota architecture, bacteria predominate over other organisms like viruses, fungi, and archaea. There are 25 recognised phyla of bacteria at the moment, including the *Firmicutes, Bacteroidetes, Actinobacteria, Cyanobacteria, Fusobacteria, Proteobacteria, and Verrucomic. The Bacteroidetes and Firmicutes groups are thought to make up about 80% of the entire human gut microbiota.*

The genera *Clostridium*, *Lactobacillus*, *Bacillus*, *Clostridium*, *Enterococcus*, and *Ruminicoccus* are all members of the *Firmicutes phylum*. The *Bacteroides* and *Prevotella* genera make up the majority of the *Bacteroidetes phylum*. The *Bifidobacterium* genus controls the *Actinobacterium phylum*. This lack of agreement is brought on by the notable inter-individual variations in microbiota structure. The prevailing consensus is that a healthy condition is linked to higher levels of microbial diversity in adulthood as well as high levels of resistance and resilience. Additionally, while certain genera have been labelled as possible pathogens, others have been categorised as advantageous symbionts. A change in the symbiont to pathogen ratio may make people more susceptible to disease. Generally considered to be helpful bacteria, *Bifidobacteria* and *Lactobacilli* are routinely offered as probiotic supplements (live *Biotherapeutics*). Disease states have been linked to strains of the Clostridium genus or Lipopolysaccharide (LPS) producing taxa such *Enterobacteriaceae*. The *Firmicutes/Bacteroidetes* ratio, which examines the connection between the two main phyla, has been linked to a number of disorders despite being somewhat debatable. The basic gut microbiota is largely constant in adults. Diet, exercise, stress, illness, and medication are the key determinants of structure. A Mediterranean diet high in fruit, vegetables, nuts, fermented foods,

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and fish is widely acknowledged to produce the best microbiome. Up to 80% of clinically recommended drugs have an impact on the gut flora, many of them negatively. Although broad-spectrum antibiotics have a significant effect, the microbiota does progressively return to its pre-antibiotic state after such treatment. It could take up to 12 weeks.

Microbe to brain communication

Microbes can make every significant neurotransmitter. GABA, norepinephrine, dopamine, serotonin, and histamine are some of these neurotransmitters. For instance, all lactobacilli generate GABA to variable degrees. However, it is extremely unlikely that these neurotransmitters will reach the brain and have an effect there, even when created by gut microbes. They might, however, have an impact on the vagus nerve and other brain communication networks, such as the enteric nervous system. It has been demonstrated that Bifidobacteria raise plasma tryptophan levels in the case of serotonin. The human brain has a certain amount of storage space for the latter, which is the substance that serotonin is made of. It appears likely that food and Bifidobacterial production are significant contributors to the preservation of healthy central serotonergic function. If diet were the only source of tryptophan, going without food for a few days would probably have a significant impact on how you felt. In these situations, the synthesis of microbials offers a significant improvement over dietary tryptophan. Although not entirely eliminated, the channels for communication between gut microorganisms and the brain do involve neurological, endocrine, immunological, and metabolic systems. A significant pathway for bidirectional information signaling between the gut and the brain is the lengthy, meandering vagus nerve.
The bloodstream carries a number of crucial substances from the gut to the brain. Many of them are produced by gut microorganisms or have their production controlled by them. These include tryptophan, leptin, short-chain fatty acids, and ghrelin. Butyrate, propionate, and acetate are some of the short-chain fatty acids. Because it inhibits Histone Deacetylases (HDACs), butyrate regulates epigenetic processes. Although free fatty acid receptors are sparsely distributed in the mammalian brain, it also has the capacity to impact these receptors. The gut microbiota has been studied by a number of groups over the past ten years in relation to a number of neurological disorders, viewing such conditions as abnormalities of the brain-gut microbiota axis. Several reviews of these studies have been published. However, a drawback in the majority of these clinical investigations is the absence of adequate control for pertinent factors such diet, exercise levels, and medication use. If not properly controlled, the effect of nutrition on the gut flora can be a significant confounder. This was amply demonstrated in a recent study on autism by Yap et al. We'll look at some of the major neurological diseases' reported findings here.

Parkinson's disease

James Parkinson, an East London surgeon who published the first comprehensive account of the ailment in 1817 under the title "An Essay on the Shaking Palsy," is the term given to Parkinson's Disease (PD), sometimes known as the "shaking palsy." The neurologist Jean-Martin Charcot is credited with creating the phrase "Parkinson's illness." The disorder can have a significant negative impact on quality of life and is characterised by sluggish movements (bradykinesia), resting tremor, rigidity, and postural instability. Dopamine neuron degeneration in the substantia nigra's zona compact area is the underlying pathophysiology of the condition. The majority of current treatments concentrate on improving dopamine transmission in the nigrostriatal pathways. Although initially beneficial in treating symptoms, such medicines typically lose their effectiveness with time. Alternative treatments are obviously needed, and many people believe that the gut microbiota makes a good therapeutic target.

The pathogenesis of parkinson's disease has been linked to the protein alpha-synuclein. The aetiology of the disorder is thought to be mostly based on alpha-synuclein aggregation, and since dopaminergic neurones in the substantia nigra are highly susceptible, they are thought to degenerate with such buildup. Alpha-synuclein is thought to originate in the gut and spread like a prion to the brain, most likely by the vagus nerve, according to mounting evidence. The molecule can collect to produce what are known as disease biomarkers, and it may be the means through which sickness travels from the periphery to the brain. Additionally, it is thought that alpha-synuclein contributes to the autonomic dysfunction that many PD patients experience. Before the development of H2 antagonists and proton pump inhibitors, vagotomy was a widely used surgical procedure to treat peptic ulcers. It was used for decades as a medication, and although it wasn't completely without side effects, for many people, it did relieve symptoms. The majority of people who have undergone such surgery and are still living are now in their later years. A Swedish register research that looked at patients who had undergone vagotomies to determine their likelihood of developing Parkinson's disease (PD) proposed that truncal vagotomies may have a preventive effect. They discovered that patients who underwent a full truncal vagotomy did indeed have a lower likelihood of developing Parkinson's disease, while those who underwent a superselective vagotomy did not.

Multiple sclerosis

The demyelination of nerve cells in the brain and spinal cord is a symptom of MS, an inflammatory disease. Although relapsing/ remitting is the most typical pattern of presentation, some people have a more severe form of primary progressive disease. Although there are many different symptoms, movement, sensation, or equilibrium are typically involved. The illness can have a severe detrimental impact on quality of life, despite breakthroughs in treatment. Increases in myelination patterns in the prefrontal cortex in germ-free mice support the idea that the gut microbiome regulates myelination. In a pilot trial of MS patients, FMT was evaluated. Nine MS patients were enlisted, and they had FMTs once a month for a maximum of six months. The change in blood cytokines served as the main outcome indicator. Intestinal permeability and gut microbiota composition were the secondary outcomes. Microbiota enrichment was noticed, and the FMT reduced intestinal permeability in two individuals who had it at baseline. The study was in its early stages and was undoubtedly constrained by the tiny sample size. Overall, it can be said that FMT is safe for MS patients.

Autism

Early onset autism is a disease marked by underdeveloped social skills, challenges with receptive and expressive communication, and the occurrence of repetitive behaviours. Epidemiological data point to an increase in the disorder's prevalence, while this could just be a result of shifting diagnostic trends. Co-morbidity with digestive disorders is common. The most frequent symptom is constipation, which is followed by stomach pain, diarrhoea, and occasionally vomiting. Overall, males are more likely to have the illness than girls are, and autistic children often grow into autistic adults, however early behavioural interventions can lessen symptoms. Studies conducted in germ-free environments corroborate the association between gut microbiota and autism. These animals exhibit behavioural alterations resembling those seen in autism. Germ-free mice are equally likely to interact with an inanimate object as another mouse when given the choice. For socially active animals, such behaviour is abnormal. It is possible to stop the formation of behavioural alterations in germ-free animals by undergoing conventional colonisation at an early stage. In fact, many of the behavioural abnormalities in these animals can be undone by giving them a single bacterial strain like Bacteroides fragilis or Lactobacillus reuteri.

Numerous dietary therapies, including as the Mediterranean diet, gluten-free diets, and ketogenic diets, have been used to treat autism. Here, we will concentrate on directly affecting microbial therapies like probiotics, sometimes known as psychobiotics when used to treat diseases like this one that have a behavioural component. A psychobiotic is a type of bacterium that, when consumed in sufficient quantities, benefits mental wellness.

DISCUSSION

The study of the relationship between neurological disorders, the microbiota in the stomach, and the brain is new and, for the most part, in its infancy. The literature is biassed in favour of preclinical investigations because of this and the difficulty in conducting well-controlled clinical studies. As a result, speculative reviews rather than papers that specifically address carefully phenotyped patient populations are now more frequently published.

Here, we have identified the specific clinical research needed to advance the field. The likelihood of nutritional therapies increases as we gain a better knowledge of the role of gut microorganisms in disease development. For instance, it was. investigate the potential contribution of dietary gluten to neurodegeneration. After a prolonged gluten-free diet, cortical excitability to TMS regulated the electrocortical alterations in celiac disease. The utility of gluten-free diets to treat cognitive impairment, however, is still up for debate. However, a wide range of other nutritional therapies could be used to treat the aforementioned disorders. Such large-scale research will be expensive and require numerous research facilities. The research must be powered similarly to that for pharmaceutical therapies, and the studies must be double-blind, random-allocation studies with a parallel-group design in order to produce relevant results. Ample powering is required, but obtaining such large-scale non-pharmaceutical business funding will be difficult.