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The Brain-Gut Axis in Alzheimer's Disease

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Abstract

There is a vast colony of microbes in the human gut that not only maintains intestinal function but also has intricate links to the brain via the "microbiota-gut-brain" (MGB) axis. The axis now has been demonstrated to have implications for the treatment of several neuro-psychological illnesses, including Alzheimer's Disease (AD), a condition that affects a person's ability to connect socially and communicate effectively. Previously thought to be a rare disorder, it is now thought to affect 1 in 9 individuals in the United States. Unfortunately, there is not FDA-approved drug for the primary symptoms of AD, and the current cognitive-behavioral therapy procedures for the condition are time-consuming and expensive. Scientists are currently investigating the MGB axis to identify potential treatment targets to reduce AD symptoms. This review aims to highlight the functioning of the MGB axis; research into this dysfunction may effectively demonstrate the need of innovative AD treatment approaches, ranging from probiotics and dietary changes to more contemporary techniques like fecal transplants, vagal nerve stimulation, and gene therapy. Not simply behavioral intervention therapy, but also microbes, may hold the key to curing AD.

Keywords

Alzheimer's Disease, Neurodegenerative Pathways, Gut-Brain Axis, Microbiota, Brain

1. Introduction

The human GI tract is home to a vast colony of microbes collectively referred to as the gut "microbiota". The GI houses an enormous variety of viruses, bacteria, protozoa, fungus, and archaea, and the number of bacteria in this microbial colony along is estimated to be $3.8*10^{13}$, which is more than the total number of human cells [1]. In the past decade, research on the "gut-brain axis"—a bidirec-

tional interaction between the gut and the brain—has garnered greater interest [2]. There is increasing evidence that the gut microbiota influences a complex interplay between the humoral, neural, immune, and endocrine systems, all of which link the intestinal system to the cognitive and emotional centers of the brain [3].

Reports of various GI tract symptoms occurring in patients with neurodegenerative diseases underline the microbiota-gut-brain axes important in mental and psychological health. Major neurodegenerative diseases, such as Alzheimer's and Parkinson's, are associated with memory loss and confusion and commonly report GI tract symptoms like nausea and diarrhea [4]. Nausea and diarrhea and other GI tract symptoms affect 80% of patients suffering from Alzheimer's disease (AD) and 90% of patients suffering from Parkinson's Disease (PD) [3]. This increased prevalence has been reported to occur due to the imbalance of gut microorganisms, which can lead to bacterial viruses, thus expediting the pathogenesis of AD and PD [5]. If this trend continues, more than 6 million patients could be suffering from severe AD and PD. Additionally, mood disturbances, anxiety, and stress play a role in GI tract disorders such as irritable bowel syndrome, inflammatory bowel disease, and peptic ulceration. Recent studies suggest that the gut microbiota of AD patients is altered compared to healthy individuals and that alterations to the gut microbiota can modify pathology and neuro inflammation. However, the exact mechanisms through which the gut microbiota influences AD remain unknown. Thus, the goal of this literature review is to evaluate the different neurological pathways associated with the microbiota-gut brain axis that influence the progression of AD, as well as understand future gut-related treatment options for AD, a neurodegenerative condition characterized by impairments in behavior, social, and communication skills [5].

2. Enteric Nervous System

The enteric nervous system (ENS) consists of an intricate network of more than 100 million neurons in the gut and is one of the three divisions of the autonomic nervous system, the others being the sympathetic and parasympathetic systems [6]. The ENS forms a large division of the peripheral nervous system (PNS) that is uniquely able to orchestrate GI behavior independent of the central nervous system (CNS) [5].

Unlike the PNS, the ENS neural control mechanism of the gut is highly complex. The ENS's role in neurological diseases, as a portal or participant for pathogenesis of neurodegenerative diseases, has become increasingly evident. The ENS, also referred to as the "second brain" of the human body, shares the CNS's morphology and neurochemistry. As a result, ENS dysfunction is frequently linked to the pathogenic pathways that result in CNS illnesses, which corresponds to neurological diseases like AD [7]. Therefore, enteric neuronal degeneration may be to blame for the GI symptoms seen in neurological diseases; however, this has yet to be elucidated.

3. Microbiota-Gut Brain Axis

Although the ENS can operate independently of the CNS, the microbiota-gut-brain (MGB) axis constantly mediates interactions between the two systems. Broadly defined, the MGB-axis is a complex interplay between the gut microbiota, ENS, neuroendocrine, parasympathetic, and sympathetic systems, and the CNS [7]. This complex communication and interaction system results in the CNS's ability to influence enteric behavior and, subsequently, the gut's ability to communicate with the brain [8]. The CNS functions more as a receiver of impulses than a transmitter, proven by the fact that approximately 90 percent of vagus nerve fibers carry impulses from the gut toward the brain [9]. These CNS impulses, in turn, disable reflexes that control motility of the GI tract [4]. However, the effects of the CNS on microbiota composition are likely mediated by a disruption of the normal luminal/mucosal habitat that can also be restored using probiotics and possibly diet [9].

Clinical, epidemiological, and immunological evidence support the substantiation of the two-way interaction between the gut and the cognitive and emotional centers of the CNS. One study continues to elucidate mechanisms of action to explain the effects of microbiota, both directly and indirectly, on emotional and cognitive centers of the brain and has demonstrated that fluctuations of the microbiota are linked to changes within these systems [4]. For example, several mood disorders, such as anxiety and depression now have well-established links to functional GI disruptions, whereas GI disease (e.g. irritable bowel syndrome, irritable bowel disease) often involve psychological comorbidities associated with alteration of the gut microbiome [5]. These reports of mood changes arising from the transmission of impulses from the bowel to the CNS, an association between various psychological disorders and GI tract symptoms referred to earlier [4], and improvement of learning, memory, and depression by stimulating the vagus nerve ("Vagal nerve stimulation", VNS). The vagus nerve is one of the main components of the parasympathetic nervous system that controls the body's "rest and digest" and "feed and breed" responses, as opposed to the sympathetic nervous system generating a "fight or flight" response to impending danger. VNS modulates the transmission of impulses from the gut to the brain through vagus afferent fibers [3] which improves the functioning of specific cognitive and mood centers of the brain.

Additionally, fecal microbiota transplants (FMT), commonly known as "bacteriotherapy", have been reported to improve symptoms in neurological illnesses with a malfunctioning MGB axis [10]. Studies involving FMT, a procedure that delivers healthy humor donor stool to an adult's intestinal tract, have revealed promising effects of FMT in conditions such as AD. Furthermore, FMT's underlying mechanism in AD is that it increases Firmicutes phylum bacteria in patients with AD, since patients with AD have decreased Firmicutes phylum bacteria in their MGB [2]. Firmicutes phylum bacteria play a significant role in the homeostatic balance between the gut bacteria and human health, thus making

FMT and the increase in Firmicutes phylum bacteria important to improving symptoms of AD [6]. In a clinical investigation, significant long-term improvement in the behavioral symptoms of AD was seen in 18 persons with GI symptoms and AD 7 to 8 weeks after daily doses of FMT were administered as a drink [3]. Correspondingly, in a pathological study, 0.2 mL of FMT was intragastrically, through the stomach, given from a healthy wild-type mouse model to AD pathology-like transgenic mice and effectively reactivated the glial cells and reduced amyloid-beta, Aβ, pathology, neurofibrillary tangles, and cognitive impairment, all factors that have been stated to increase in patients with AD, thus improving AD-related symptoms [6]. While FMT showed promising effects in alleviating Aβ pathology, another study demonstrates FMT's ability to shift the gut-microbiome closer to the control patients. After 4 weeks of FMT treatment, the gut microbiota diversity in AD patients remained unaltered, suggesting that FMT did not affect the overall structure of the gut microbial communities, however when measuring the UniFrac distance, a distance metric used for comparing biological communities, of the recipient patient samples were significantly decreased compared with those of the control patients, suggesting that FMT would promote colonization of donor microbes and shift the bacterial community of patients with AD toward that of the control patients [8].

4. Alzheimer's Disease

Alzheimer's Disease is a gamut of neurodevelopment disorders affecting 5.8 million Americans. AD is characterized by impairments in social interaction and communication and repetitive and stereotyped interests and behaviors, resulting in cognitive decline, pervasive developmental disorders, and reduced alertness [5]. Though the American Psychiatric Association (APA) has laid down specific criteria for diagnosing AD [10] there is an overlap between the symptoms of AD and non-AD diseases. Interestingly, GI tract disturbances also factor into the broad scheme of these diseases.

Since the characterization of the disease, AD diagnosis has been based on behavioral observations and criteria established by the APA rather than any concrete biomarkers [3]. Recently, genetic markers of AD were identified by "reverse phenotyping", a technique that characterizes phenotypes based on a particular genetic sequence [11]. The genetic marker data obtained has helped establish the role of genes such as the Apolipoprotein E (APOE) gene and the "neurogenerative risk gene" APOR transcription factor 4 in the pathogenesis of AD.

Interestingly, research has revealed that variations in specific "Alzheimer's genes" also cause alterations in the MGB axis, indicating an underlying link between Alzheimer's and the gut. This is corroborated by studies reporting the development of Alzheimer-like symptoms in germ-free mice and reports of adults with AD having a distinct set of gut microbes and experiencing more GI tract symptoms than their non-AD counterparts. A meta-analysis of 15 studies with

2215 adults demonstrated that adults with AD were 2 to 4 times more likely than non-AD counterparts to experience abdominal pain, constipation, and diarrhea [9]. Evidence from such studies has spurred scientists to decode the MGB axis in AD and explore the possibility of genetic biomarkers as a therapeutic target for a condition without approved medication.

5. Microbiota-Gut-Brain Axis in AD

5.1. Intestinal Barrier Pathway: The 'Leaky Gut' Hypothesis

The metabolites of the gut microbiota preserve the epithelial integrity of the intestinal wall, commonly referred to as the "intestinal barrier". Affected gut microbiota, the entrance of pathogenic bacteria, environmental chemicals, and dietary macromolecules are a few examples of factors that have been associated to defects in this barrier. These result in "leaky gut", a functionally compromised intestinal barrier with increased permeability. This leakiness; enables bacteria to enter the bloodstream from the intestines and activate the release of cytokines by the brain, inducing an immunological response that ultimately changes some cytokine activities in the brain [6].

Studies have demonstrated that adults with AD exhibit higher levels of immune-mediated inflammatory cytokines, such as interleukins, tumor necrosis factor-α (TNF-α), and transforming growth factor beta-1, compared to their non-AD counterparts. This has led to the postulation that their guts may be "leakier" than normal [10]. Given that actions of these cytokines alter normal neural development in adults, it stands to reason that a stronger intestinal barrier would protect and positively impact brain functions. This explains why probiotics are being thoroughly investigated, both in the antenatal period and in adults with AD, for their possible role in mitigating some of the symptoms of AD. There is also a potential underlying genetic basis for the cytokine variations seen in AD [5]; this opens up prospects for exploring prenatal testing and targeted gene therapy for AD in the future.

5.2. The Neuronal Pathway

Myelin is an insulating sheath that envelops nerve cells and facilitates efficient transmission of electrical nerve impulses [11]. Any change in the amount of myelin, and consequently the nerve sheath's thickness, can impact the way in which the nerve impulses are sent and cause a variety of neurological symptoms. Recent research has revealed the importance of a health gut microbial colony in controlling myelin-related genes in prefrontal cortex, a region of the brain thought to be impaired in AD. Increased myelination in this area of the brain was seen in experiments using germ-free mouse axons; this result was only reversed when the brain was colonized with traditional gut bacteria [4]. The results of this study support the association between healthy gut microbiota and a normally functioning prefrontal cortex. The clinical implication of this finding is that MGB axis dysfunction possibly correlates with the cognitive and social dysfunction

seen in AD [10].

Another important neural pathway in the MGB axis is formed by the vagus nerve. The vagus nerve senses the metabolites and transfers this information into the CNS to generate a specific response. Stress suppresses the vagus nerve and has a deleterious impact on the GI tract and gut bacteria. Targeting this nerve through procedures like VNS would be of interest to restore the balance in the MGB-axis, since VNS oversees a vast array of crucial bodily functions, including control of mood, immune response, digestion, and heart rate. It establishes one of the connections between the brain and the intestinal tract and sends information about the state of inner organs to the brain via vagal afferent fibers [6]. Conventional VNS entails inserting a device under the skin in the chest wall and attaching a wire to the left vagus never. When turned on, the device "stimulated" vagus nerve by sending electrical signals through the aforementioned vagal afferent fibers. Vagal afferent fibers, which are distributed to all the layers of the digestive wall but do not cross the epithelial layer. Consequently, these fibers can only sense indirect microbiota signals, through the diffusion of bacterial compounds or metabolites. Interactions between gut endocrine cells (EEC) and vagal afferents are at the interface of gut chemo sensing, which is when EEC's interact with the vagal afferent fibers to produce a change. When the EEC's release hormones, the brain pathways are activated because the EEC's are able to communicate through toll-like receptors (TLR) [9]. Such stimulation demonstrates promising results in AD as VNS in AD patients with cognitive decline improved social skills, attentiveness, and mood in addition slowed the rate of cognitive decline [11].

5.3. The Serotonin Pathway

For effective functioning, the ENS relies on more than 30 neurotransmitters (chemical messengers). Amongst these, serotonin, an important regulator of mood and cognition [3], is postulated to be significant in the MGB axis in AD. Serotonin influences adult neurodevelopment, particularly in domains related to social behavior, repetitive behavior, and sensory development. Elevated serotonin levels have been reported in adults with AD, suggesting the importance of serotonergic systems, systems related to serotonin molecules, in the pathogenesis of AD [6]. In addition, individuals with AD have considerably reduced serotonin availability in their CNS when compared to controls [7]. The results of this study and numerous others endorse a strong link between serotonin and AD. Targeting the MGB-axis to alter central serotonin levels and maybe relieve AD symptoms seems reasonable given that the majority of the body's serotonin levels are produced by gut bacteria rather than the CNS. Serotonin remains a promising heritable biomarker that may be used to locate individuals who may benefit from future treatment regimens.

5.4. The Immune System Pathway

Numerous immunological problems, including autoimmunity, activation of

"immune-like" microglia and astroglia cells, important CNS cells that support the function of neurons in the brain and elevated T-cell activation have been linked to AD [11]. A key risk factor for AD, according to research conducted over the past 20 years, is pre- and post-natal immunological dysregulation. Prenatal insults such as maternal infections can cause immunological activation and raise a child's risk of developing AD in the future. Postnatally, the affected children show unique profiles of immunological dysregulation, inflammation, and endogenous autoantibodies, such as Aβ aggregates [4].

In addition to the aforementioned systemic and CNS immunological imbalances, AD patients have also been found to have immune-related problems with their GI tracts and makeup of their gut microbiota. Certain amino acids may be able to improve the intestinal barrier, alter the mucosal immune system, and block abnormal gut-CNS signaling pathways, according to prior research. As a result, these immunomodulation methods, such as probiotics and FMT, are anticipated to affect CNS neuronal activity and treat the behavioral issues related to AD [11].

5.5. Metabolite Pathway

Epithelial cells obtain their energy from metabolites such as short-chain fatty acids (SCFAs), which are synthesized by gut bacteria. Such metabolites contribute to the preservation of the intestinal epithelial barrier and the critical immunological and anti-inflammatory protection it offers [12]. Additionally acknowledged as important mediators of the gut-brain axis, bacteria-derived SCFAs undergo changes in production in a variety of neuropsychological disorders, such as AD and Autism Spectrum Disorder.

Animal and epidemiological studies have shown evidence that SCFAs may be one of the environmental triggers of AD in patients [13]. Adults with AD have been found with elevated amounts of SCFAs in their stool samples [14]. In particular, it has been demonstrated that rats can develop reversible behavioral abnormalities similar to AD when exposed to propionic acid, a significant SCFA generated by gut bacteria associated with AD [15]. The considerable effects of SCFAs may be mediated by manipulation of particular AD genes or by modification of mitochondrial activity, both of which may serve as useful biomarkers and therapeutic targets in AD [16].

6. Conclusion

The gut microbiota is a master regulator of inflammation in the body and therefore is very important for developing and progressing diseases involving peripheral and central inflammation. Understanding how gut microbiota can influence AD progression may reveal an important therapeutic target that could control several pathogenic mechanisms in the ENS. Since initial studies revealed profound effects of gut-microbiota alteration in AD-related pathology and patients have a significantly altered gut-microbiota composition compared to healthy

controls, interest in the field has increased. The current review attempts to explain the impact of the MGB on the development of AD and elucidate how the gut microbiota-brain axis could affect various pathways implicated in the disease. The "leaky gut" hypothesis suggests that the intestinal barrier in adults with AD is compromised, making them prone to the deleterious effects of cytokines. This indicates a promising therapeutic role of probiotics, both in the antenatal and postnatal periods, to alleviate the symptoms of AD. The existence of neuronal pathways in the gut-brain axis implicates vagal nerve stimulation as a promising treatment modality for the disorder. The elucidation of serotonergic, immune-mediated, and metabolite pathways opens avenues for targeted therapies for AD. Although several studies have given rise to a general hypothesis of how the gut microbiota could modulate AD-related pathology, few specific details about each targeted pathway are present, such as specific biological substrates and connotations. Thus, genetic aberrations and other under-explored biomarkers may provide a more wholesome understanding of AD. In summary, although research elucidating the connection between the gut-microbiota brain axis and AD has come far over a short period of time, using new tools and approaches will accelerate investigations to understand and therapeutically target this connection entirely.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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