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Microbiota Gut-Brain Axis and Neurodegenerative Disease. A systematic review on Alzheimer's disease, Amyotrophic lateral sclerosis and Parkinson Disease

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Keywords
gut dysbiosis, central nervous system, gastrointestinal tract, enteric nervous system, neuroimmune system, neuroendocrine system, autonomic nervous system (ANS)

ABSTRACT

This review highlights the microbiota gut-brain axis and neurodegenerative diseases excluding studies on animal models. Gut microbiota is capable of modulating some brain activities via the microbiota gut-brain axis. A bidirectional communication exists between the gastrointestinal (GI) tract and the central nervous system (CNS) in the microbiota gut-brain axis. Gut dysbiosis has been linked to neurodegenerative diseases as a result of the imbalance in the composition of its microbiota, which has a damaging effect on the host's health. The association between the role and mechanism of CNS disease and gut microbial is yet to be fully explored. Although some studies have shown a positive relationship between a rich diverse microbial community and the brain of the host, and a negative relationship between microbial dysbiosis, intestinal infection and human brain health, our knowledge, however, is limited due to the inability to identify the major players in this heterogeneous microbial community.

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INTRODUCTION

Clinicians and biomedical researchers have shown great interest in the role of gut microbe function and the central nervous system (CNS), mainly in the modulation of cholecystokinin. However, this has been extended to a generalized description; the microbiota gut –brain axis especially in its link to neurodegenerative disease.[1] The human body and its microbial community such as the skin, vaginal mucosa, oral mucosa and most importantly the gut, co-exist in a symbiotic relation-

ship. This relationship plays a vital role in health and neurodegenerative diseases.[2] Microbiome is inherited maternally during vaginal delivery through the vaginal fluid enriched with microbiota. This becomes a major player of immune defense and eventually becomes modified to suit the individual's unique composition.[3,4]

Microbiota concentration is highest in the gut of the human body.[5] This can be a source of energy for cells as they provide essential micro nutrients such as thiamine, vitamins A, B, D and K. They also provide nutrients in form of short chain fatty acids (SCFAs) like acetate, propionate, and butyrate; as the ultimate energy source for colonocytes. When SCFAs like butyrate, acetate, and propionate are stimulated, it could result in an increased production of immunoglobulin (IgG).[6] Gut microbiota also serves as a barricade between humans and their environment especially in the protection of environmental hazards[3] and when it is disease-free, can prolong the lifespan of humans.[6]

Disruptions of gut microbiota barrier can lead to many diseases.[7] It was previously considered stable and unique for each individual but has now been reported to have long lasting changes.[1] This could be secondary to pathophysiological disruption of short intraluminal regulatory loop that leads to major dysfunction of various cells and microflora, thus, affecting the enteric nervous system(ENS) within the submucosal and muscularis layers of the colon.[8]

Gut dysbiosis has been linked to neurodegenerative diseases as a result of the imbalance in its composition which alters and causes damaging effect on the host's health.[9]

The aim of this review is to highlight the microbiota gut-brain axis and functional linkages to neurodegenerative diseases such as Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS) and Parkinson Disease (PD), excluding animal models.

Discussion

Communication between gut microbiota and the development of the central nervous system (CNS)

Microbiota which consists of bacteria, viruses, fungi and other microorganisms can alter adult hippocampus neurogenesis (AHN), thus affecting the pathogenesis of symptoms of diseases of CNS.[7,10] It helps in the permeability and maintenance of the blood brain barrier (BBB) and is important in the maturation of glia cells of the CNS. The absence of a complex host microbiota could result in an altered glial cells number, a decrease in permeability and could halt the development of the blood brain barrier, thus, causing an impaired immune response resulting in CNS disease.[11]

Although, invasive pathogen by microbes is not the only route to the aetiology of neurodegenerative diseases, it has a systemic impact on the microbiota community via the enteric nervous system, immune system, blood stream, intercellular signaling and the vagus nerve.[5]

The Microbiome Gut-Brain Axis

The association between the role and mechanism of CNS disease and gut microbial have yet to be fully explored.[11] A bidirectional communication exists between the gastrointestinal (GI) tract and the central nervous system (CNS) in the microbiota gut-brain axis. This is effective under physiological conditions in immune defense, digestive system modulation, perception and sensory response to visceral stimuli, secondary to its incorporation to the CNS, neuroendocrine and neuroimmune systems, autonomic nervous system (ANS) and enteric nervous system (ENS).[3] Studies have reported four key section to the gut-brain axis, these include: activation of the immune defense, neuroendocrine pathways regulation, autonomic sensorimotor connections and lastly, the interaction between the blood brain barrier and gut microbiota metabolites.[2] Microbially derived molecules such as short-chain fatty acids (SCFAs), secondary bile acids, and tryptophan metabolites mediate the communication of microbes and the CNS, although CNS modulation via neuroimmune and neuroendocrine mechanisms interacts with enterochromaffin cells, mucosal immune system and enteroendocrine cell and sometimes enters the systemic circulation and penetrates the blood-brain barrier, it still remains difficult to ascertain if they induce responses only or get to the brain directly via long-distance neural signaling with vagal and/or afferents from the spinal cord.[12] SCFA are the main microbial mediators in the gut–brain axis.[2] SCFA are released from action of microbiota in the gut which are further metabolized by intestinal absorption and finally removed through urination.[11]

The gut microbiome harbours 150 times more genes than the human genome.[2] They are

heterogeneous group of bacterial species, fungi and viruses found in the gastrointestinal tract having a symbiotic relationship with the human host. The microbiome plays an important function in metabolism, blood-brain barrier integrity, immune defense, secretion, maintaining homeostatic balance of barrier integrity and coordinating the transfers of signals through primary afferent pathway of the vagus nerve to the CNS via the gut-brain axis. The vagus nerves serves as the primary afferent pathway for various factors influencing the formation of microbiota, these include: medications, lactation, ingested meal and parturition.[11]

The use of functional imaging, for example, functional magnetic resonance imaging (fMRI) and Positron emission tomography (PET) revealed resting brain function alteration in patients with functional gastrointestinal disorders, via the possibility of gut-brain axis dysfunction.[13]

Intriguingly, the concept that microbiome influences the gut-brain axis may seem debatable but it is used routinely by clinician to treat patients. For instance, the use of oral antibiotics medication and laxatives for treatment of patients with altered mental state secondary to hepatic encephalopathy.[1]

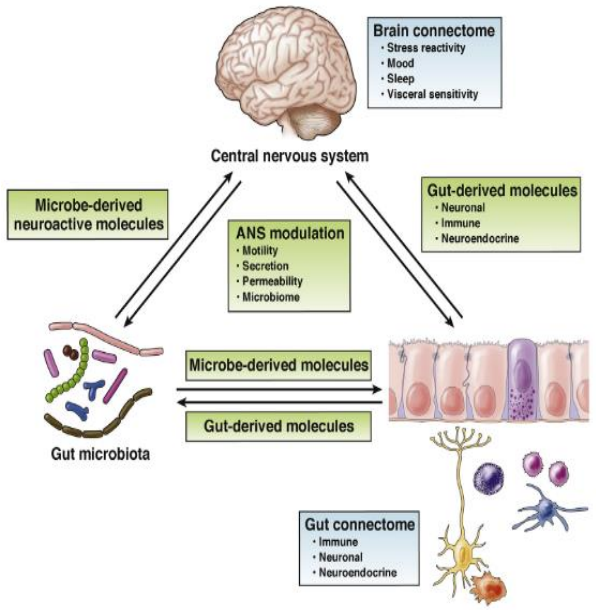

Figure 1. Bidirectional interactions of four key sections in the gut-brain axis[12].

The Gut Microbiota in Neurodegenerative disorders

The aetiology of most neurodegenerative diseases are multifactorial and speculative, there is possibility that the apotheosis of these mechanism of gut microbiome-host symbiotic relationship contribute to a large extent to the disease pathogenesis in the genetically-predisposed.[14] Microbiota research on neurodegenerative diseases is still in the infancy stage, interestingly, recent studies have linked the potential role of the gut-microbiota axis on central nervous system (CNS) related conditions and its influence on the gut brain axis. [5,7,11] Chronic neuroinflammation is a unique feature associated with the pathology of most neurodegenerative diseases (ALS, PD, AD).[6] Although, bacterial toxin has been linked to the aetiology of neurodegenerative disease, systemic inflammation and its infectious burden is suggested to be the prime factor that predisposes to neurodegeneration or immune response of the host to gut dysbiosis rather than an isolated single infectious agent. This inflammation is the initial stimulus to the neuropathological cascade seen in neurodegenerative disease that drifts gradually along the sacral autonomic nerves and dorsal motor nucleus of the vagus nerves, to the midbrain cortex through trans-synaptic spread and hence degeneration of the CNS.[5,14] Gut mucosa lymphocytes secrete pro-inflammatory mediators which causes protein misfolding in neighbouring enteric neurons. This is the main cause of pathogenesis seen in neurodegenerative disease such as AD and PD.[14]

Although, bacteria causes misfold of amyloid protein as seen in Alzheimer's disease (AD) and Parkinson disease (PD), aggravating oxidative stress, neuroinflammation and progressive neurodegeneration, neurodegeneration could also provide a favourable atmosphere for the growth of microbes via the micro-environmental change [5,6] Spirochetes, herpes simplex virus type 1 and *chlamydophila pneumoniae* infections have been associated with the brain of AD patients and fungal infection in both AD and Amyotrophic lateral sclerosis (ALS).[5] Prion-like transmission through molecular mimicry pathway suggests that microbiota is vital in prion-like transmission seen in neurodegenerative disease.[10] Minuit quantities of cyanobacteria which produce β-N-methyl amino-L-alanine (BMAA) are reported to be increased in the brain of patients with AD, PD and amyotrophic lateral sclerosis (ALS). This has been linked to the misfolding of proteins and aggregation seen in neurodegenerative disease.[3]

Constipation is a common symptom in PD, this is likely due to neurodegeneration of autonomic centers of the enteric nervous system (ENS).[9] Urinary tract infection is also a common symptom seen in neurodegenerative disease especially in AD and PD. A variety of microbes have been identified in healthy urinary tracts using novel laboratory culture methods, this could be linked to the immune system modulation**.** Interestingly, microbiome found in the skin have been suggested to be linked to microbiological and amyloid axis between the skin and the brain, but no detailed evidence has been reported.[14]

While research has focused on neural and inflammatory signaling, the future role of circulating metabolites of gut microbe-has been under-explored.[2]

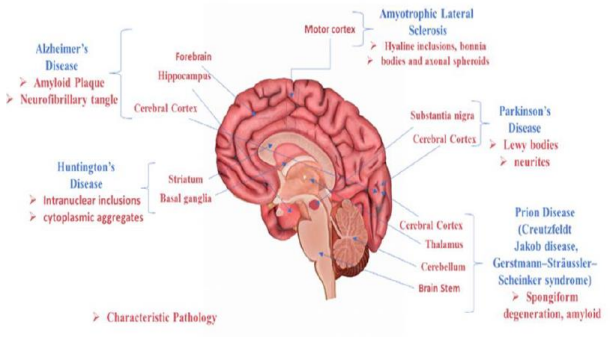

Figure 2. Interaction between gut microbiota and neurodegenerative disorders[15].

Gut Microbiota and Alzheimer's disease (AD)

AD is a progressive degenerative neurological disease with intracellular neurofibrillary tangles, extracellular β-amyloid (Aβ) and senile plaques.[7] No detailed study on the interaction of gut microbiota and alzheimer's disease has been reported[5], however a study reported the gut microbiota imbalance and the development of AD as a result of inflammation and increasing the permeability of the intestine and endothelium.[6,7] High levels of inflammatory markers, total and phosphorylated tau protein have been reported in AD patient with *Helicobacter pylori (H. Pylori)* infection.[6] Studies have also linked the association of serum antibodies and AD and a reduction in brain-derived neutrophilic factor (BDNF).[5,7] High levels of inflammatory markers (as shown in figure 3), total and phosphorylated tau protein have been reported in AD patient with *Helicobacter pylori (H. Pylori)* infection.[6]

Gut microbial diversity is reduced in patient with Alzheimer's disease (AD). Patients with AD show an increase in intestinal bacteria such as *Bacteroides, Bacteroidetes* resulting in an exaggerated translocation of Lipopolysaccharide (LPS) to the CNS from the gut. This would in turn cause neuroinflammation and exacerbate AD, while a decrease in *Bifidobacterium, Firmicutes* seen in AD patients is associated with a decrease in permeability of the intestine.[11] Excessive high fat diet, for example corn oil causes an alteration in the composition of gut microbiota thereby increasing intestinal permeability. This is associated with an increased risk of AD, however diet containing n-3 polyunsaturated fatty acids have not been linked to AD. Intestinal microbial metabolites of dietary fats for example Trimethylamine N-oxide(TMAO) can serve as a biomarker for AD, which supports the association of excessive high fat diet meal seen in western diet with AD.[6]

Intriguingly, although gut microbiota such as *E. coli*, *Bacillus subtilis*, *Mycobacterium tuberculosis, Staphylococcus aureus*, *Salmonella typhimurium*, and *Salmonella enterica*, and fungi are capable of secreting amyloid (resulting in a rise of CNS amyloid levels distorting the dynamic amyloid protein causing aggregation in the brain and a high risk in AD), they are also able to reduce amyloid of patients with AD via an indirect diet-mediated mechanism. For example *Bacillus spp* and *Lactobacillus spp* produces acetylcholine, a deficient neurotransmitter in AD.[6, 7]

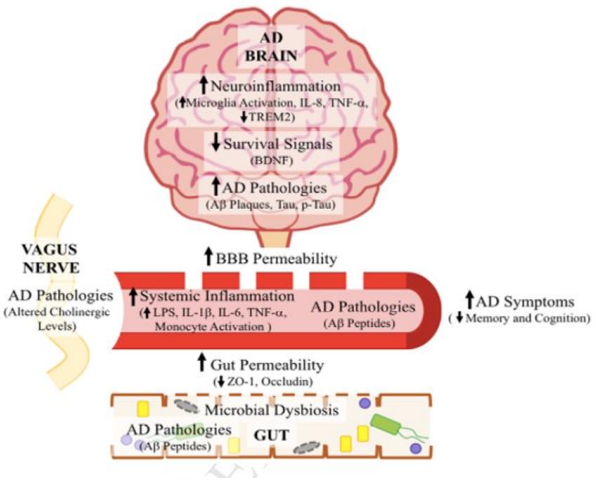

Figure 3. Interaction between gut microbiota and inflammatory markers in the pathogenesis of AD[6]. Tumour necrosis factor (TNF), triggering receptor expressed on myeloid cells-2 (TREM2,), zonula occludens (ZO), interleukins (IL), lipopolysaccharide (LPS).

Gut Microbiota and Amyotrophic Lateral sclerosis (ALS)

ALS is a progressive degenerative disorder that affects the brain and spinal cord neurons, it is a multi-system disorder that affects the gastrointestinal tract which could be as a result of the increased permeability of the intestine that would increase circulating lipopolysaccharide (LPS).[6, 10] Chronic neuroinflammation and microglial activation are features of ALS.[6] The pathogenesis of ALS involves increase circulating LPS (derived from gram-negative bacteria cell walls) and innate immune response, suggesting a concept of gut-derived neurotoxins. Tight junction proteins (occludin, VE-cadherin/CD144) and the junction adhesion molecule (JAM)) in the lumber spine are reduced leading to the disruption of the blood-spine cord barrier (BSCB) and blood brain barrier (BBB) in patients with ALS thus, facilitating permeability and increased exposed of motor neurons to the toxic substance released from the gut (Figure 4).Dysfunction of intestinal barrier can lead to the passage of toxins to the blood from the lumen of the intestine.[10] Constipation is a common symptom in ALS, however details about the effect of changes in the gut microflora on gastrointestinal motility in ALS patients seem skeptical.[6,10]

In a nutshell, research on the dynamics and relationship of gut microbiota and the stages of ALS is limited.[10]

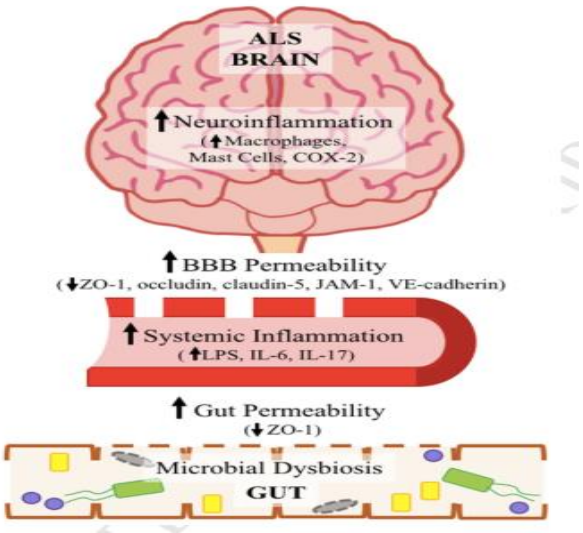

Figure 4. Interaction between gut microbiota and the pathogenesis of ALS[6]. Tumour necrosis factor (TNF), cyclooxygenase (COX), interleukin (IL), vascular endothelial (VE), zonula occludens (ZO).

Gut Microbiota and Parkinson Disease (PD)

The loss of dopamine neurons in the substantia nigra, aggregation of misfolded protein (α-synuclein), calcium overload, mitochondrial dysfunction and oxidative stress account for most of the pathogenesis seen in PD.[11]

Although, there is inadequate information on the microbiota-host relationship in PD[5], recent studies have shown the role of gut microbiota bi-directional communications between gut and brain in the pathogenesis of PD. Studies have reported over expression of protein inclusions (α-synuclein) causing misfolding and aggregation in PD,[3] which reaches the brain via the glossopharyngeal and vagus nerves.[11] Interestingly, misfold and aggregation of α-synuclein is not specific to PD, there is a descending gradient in the frequency of amount of lewy bodies seen in the GI tract. This ranges from submandibular gland with the highest frequency, to lower oesophagus, stomach, small intestine, large intestine and rectum with the lowest frequency. The vagal innervation from the dorsal motor nucleus of the vagus nerve (DMNV) and the enteric nervous system (ENS) dopaminergic neurons distribution coincide with the descending gradient of the amount of lewy body's pathology.[9]

A clinical staging system of PD (Braak stages) proposes that the genesis of neurodegenerative disease is via a dual-hit mechanism in which the neurodegenerative process starts in the olfactory bulb following inhalation and in the ENS of the gut secondary to neurotropic pathogen ingestion. This later advances forward to the temporal lobe from the olfactory bulb and backward to the intermediolateral nucleus (IML) cord or dorsal motor nucleus of the vagus (DMNV) and then to the brain stem from the gut through the sympathetic and parasympathetic nerves respectively as illustrated in Figure 5.

Gut microbiota dysbiosis have been linked to patients with PD and increased incidence of small intestinal bacteria overgrowth (SIBO) compared to control.[3,11]Over-proliferation of gut microbiota alters intestinal motility.[16] Constipation is a common and early symptom of PD, and can be as a result of prolong intestinal transit time secondary to impaired colonic motility.[9] It is 2 times more prevalent in patients with PD compared to control, and a 2 times probability of individuals with constipation having PD within 10 years.[3] Intriguingly, a high prevalence of

Helicobacter pylori (H. Pylori) infection has been reported in patient with PD.[9] Studies have linked changes in intrinsic ratios of gut microbiota fecal specimens with PD.[8] The faecal samples of patients with PD shows an increase in bacteria such as Lactobacillus and a decrease in *Prevotella, Clostridium coccoides* and *Bacteroides fragilis faecal samples*. The decrease *Prevotella* counts is associated with an increase in permeability of the gut and a decrease in synthesis of mucin. Although *Prevotella* counts is not unique to the diagnosis of PD alone, the hydrogen sulfide they secrete is reported to have a protective effect on dopaminergic neurons.[11] Studies have also reported an abundance of *Enterobacteriaceae* count isolated from faecal sample in patients with gait anomaly and postural instability, suggesting a link of microbiota to the PD. Further research on the early communication between gut microbiota and PD would give new useful insights in the intervention for diagnosing and treating patients with PD.[11]

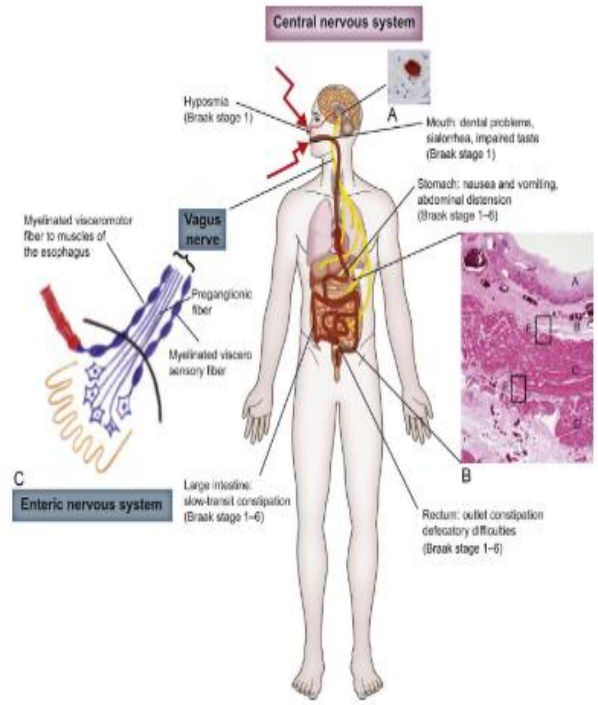

Figure 5. Genesis of neurodegenerative disease via dual-hit mechanism involving the olfactory bulb and ENS[9].

Conclusion

Gut microbiota is capable of modulating some brain activities via the microbiota gut-brain axis. Although, studies have shown a positive relationship between rich diverse microbial community and the brain of the host, and a negative relationship between microbial dysbiosis, intestinal infection and human brain health, our knowledge however, is limited due to the inability to identity the major players in this heterogeneous microbial community. These findings are particularly promising in finding out if microbiota changes precede or succeed the pathogenesis seen in neurodegenerative disease.[6] This review excluded literatures on evidence from animal and pharmacological models which some other previous studies focused. Although animal models can be controlled experimentally, this microbial community can be easily misrepresented or missed when scanning for total composition of the microbiota composition**.** Besides**,** reduced diversity in microbiota population is seen more in animal models compared to humans.

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Abbreviations

AD: Alzhemier's disease
AHN: Adult hippocampus neurogenesis
ALS: Amyotrophic lateral sclerosis
ANS: Autonomic nervous system
BBB: Blood brain barrier
BDNF: Brain derived neurotrophic factor
BMAA: β-N-methyl amino-L-alanine
BSCB: Blood-spinal cord barrier
CNS: Central nervous system
COX: Cyclooxygenase
ENS: Enteric nervous system
fMRI: Functional magnetic resonance imaging
GI: Gastrointestinal
IL: Interleukin
JAM:Junction adhesion molecule
LPS: Lipopolysaccharide
PD: Parkinson disease
PET: Positron emission tomography
SCFAs: Short chain fatty acids
SIBO: Small intestinal bacteria overgrowth
TMAO: Trimethylamine N-oxide
TNF: Tissue necrosis factor
TREM2: Triggering receptor expressed on myeloid cells-2
ZO: Zonula occludens

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