The influence of gut microbiota alteration on age-related neuroinflammation and cognitive decline

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Abstract
Recent emerging research on intestinal microbiota and its contribution to the central nervous system during health and disease has attracted significant attention. Age-related intestinal microbiota changes initiate brain aging and age-related neurodegenerative disorders. Aging is one of the critical predisposing risk factors for the development of neurodegenerative diseases. Maintaining a healthy gut microbiota is essential for a healthy body and aging, but dysbiosis could initiate many chronic diseases. Understanding the underlying mechanisms of gut microbiota alterations/dysbiosis will help identify biomarkers for aging-related chronic conditions. This review summarizes recent advances in microbiota-neurodegenerative disease research and will enhance our understanding of gut microbiota dysbiosis and its effects on brain aging.

Key Words: brain aging; cognitive decline; dysbiosis; fecal microbiota transplantation; gut-microbiota; neuroinflammation; prebiotics; probiotics

Introduction
"All Diseases Begin in the Gut," proclaimed by the father of modern medicine, Hippocrates, more than 2000 years ago (Lyon, 2018), still holds its relevance in maintaining optimal health situation and microbiota dysbiosis. Over the past several years, a healthy digestive system's power and potential in modulating whole body functions have received tremendous attention. Recent studies identified a biochemical link between the brain and the bacteria in the gut known as the “gut microbiota-brain axis,” the mutualistic and bidirectional communication between the digestive tract and the central nervous system (CNS). The connection between gut and brain works by “bottom-up signaling” (from the digestive system to the brain), also known as the “gut-brain axis”) or “top-down signaling” (from the brain to the gut, also referred to as the “brain-gut axis”). Increasing evidence in the recent few years has highlighted the “bottom-up” and the “top-down” interplay between the gut microbiota and the brain in many neurological and neurodegenerative diseases (Wang and Wang, 2016).

The gut microbiota has both positive and negative effects on the brain. Under normal body conditions, gut microbiota plays a critical role in many brains' biological and physiological processes, such as myelination, glial cell activation, and neurogenesis. Additionally, the microbiota can effectively modulate behavior and influence psychological processes such as mood and cognition (Hsiao et al., 2013). The current scientific literature vehemently suggests that the gut microbiome can influence the brain aging process and the initiation and progression of neurodegenerative disorders, making the gut-brain crosstalk a promising and exciting research area in the neuroscience field. Studies have demonstrated that alterations in the gut microbiota composition, also known as dysbiosis, can negatively influence brain functions by causing neuroinflammation (Fransen et al., 2017). Aging is a complicated process usually accompanied by chronic low-grade neuroinflammation known as inflammaging (Franceschi et al., 2000) along with a decline in cognition and memory (Peters, 2006). Dysbiosis is a disturbance of the commensal homeostasis between the host and the gut microbiota, and the outcome is chronic inflammation and a decreased production of some essential microbiota metabolites such as short-chain fatty acids (SCFAs).

Many studies have underscored the importance of gut microbiota alteration being the root cause of many diseases resulting in severe health implications and co-morbid conditions, such as inflammatory bowel disease, obesity, diabetes, cancer, cardiovascular disease, anxiety, and autism (Blumberg and Powrie, 2012; Cenit et al., 2017). Furthermore, intestinal dysbiosis plays a fundamental role in aging and many age-related neurodegenerative disorders, including Parkinson’s disease (PD) (Gorecki et al., 2019) and Alzheimer’s disease (AD) (Winek et al., 2016). The crucial information related to microbiota and its role in brain aging has emerged only in recent years. However, the evidence on the mechanisms is still unclear, and more studies are needed to determine its role in brain aging and age-related neurodegenerative disorders. Therefore, this review will summarize recent advancements in gut-brain axis dysregulation and related-neurodegenerative diseases. Future therapeutic implications for gut microbiota modulation are also summarized.

The search strategy and selection criteria were limited to articles published in peer-reviewed journals. A literature review of the past two decades (from 2000 to 2021) was conducted by searching the PubMed and Web of Science databases to identify articles reporting the relation between gut microbiota alteration, healthy brain aging, and age-related neuroinflammation and cognitive decline.

Gut Microbiota and Homeostasis
An enormous number of different microbes colonize in the mammalian intestine, and the concentration of these microorganisms increases gradually from the ileum to the colon (Sender et al., 2016). The gut microbiota has both positive and negative effects on the body and the brain, in particular. The host gut microbiota contributes to several biological and physiological processes, including regulating gut motility, preventing foreign pathogen colonization in the gut, releasing neurotransmitters, and producing various antioxidants (Bercik et al., 2012; Haseeb Anwar et al., 2019). In normal physiological conditions, the density of the human microbiome is highest in the colon. Four phyla that constitute the bulk of the gut microbiota, namely Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria, are the most abundant organisms, approximately 64%, 23%, 8%, and 3% of the population, respectively (Barengo et al., 2016). The Firmicutes: Bacteroidetes ratio, the prevalent phyla of the bacterium in the intestine, is an indicator of the...
standard of metabolic health, and alteration in this ratio represents an index of abnormal conditions (Mariot et al., 2009). Notably, the gut microbiota changes at different developmental stages and aging (Mariot et al., 2009). For example, Proteobacteria predominates in neonate’s guts and considerably reduces from 16% in childhood to 4.6% during adulthood (Shin et al., 2015).

Microbiota populations can be influenced by various stress factors, such as diet, infections, drugs, illness, and aging (O’Mahony et al., 2009; Claesson et al., 2012; Davey et al., 2012). In these abnormal conditions, fecal microbiome biodiversity is decreased and represents underlying features of dysbiosis (Claesson et al., 2013). Gut microbiota dysbiosis occurs when the composition of resident commensal communities changes compared to the normal condition (Petersen and Round, 2014). Studies have shown that gut dysbiosis plays a role in developing and progressing diseases, including: infectious diseases, GI diseases, respiratory diseases, psychological diseases, and autoimmune diseases (Shreiner et al., 2015). Microbiota dysbiosis is also observed in subjects with metabolic and neurological disorders (Blumberg and Powrie, 2012). In addition, current evidence indicates that the impairment in the quantity and composition of gut microbiota affects cognitive functions and synaptic plasticity (Salami, 2021).

Healthy gut microbiota keeps the brain healthy and protects against different types of neurological disorders. Many recent studies investigated the idea that the host microbiota and their microbiome are essential in a healthy brain’s fundamental biological processes. For instance, intestinal bacteria maintain microbial cells in a healthy mature steady-state condition during development, which is necessary to prevent neuroinflammatory and neurodegenerative disorders at the later phase of life (Rothhammer et al., 2016; Erny et al., 2017). Microbiota dysbiosis, resident immune cells in CNS, play an essential role in modulating neurogenesis, maintaining homeostasis and cognition in healthy brains (Graeber and Streit 2010; Williamson et al., 2011). However, microbial overactivation augments neuronal damage, neuroinflammation, and dysfunction in aging and neurodegenerative diseases. Furthermore, the absence of host-microbiota led to deficits in microglia maturation, differentiation, morphology, function, and gene expression profiles in mice harboring no intestinal microbiota and immune activity called germ-free (GF) mice compared with normal mice (Erny et al., 2015). These findings suggest that maternal microbiota contributes to microglia’s early development and has important brain development implications.

### Gut Microbiota-Brain Axis

A plethora of evidence has provided insights into the possible mechanisms and pathways that connect the intestinal microbiota and its metabolites with the brain and their involvement in regulating brain development and function (Hisao et al., 2013; Erny et al., 2015). Based on the available literature, there are five major possible communication pathways of gut microbiota to influence the brain. These include neural networks, neuroendocrine system, gut microbiota metabolic system, gut immune system, and barriers system pathways (Wang and Wang, 2016), as shown in Figure 1.

Figure 1 | Gut-brain axis.

Five major possible communication pathways of gut microbiota and the brain: the neural network, neuroendocrine system, gut immune system, gut microbiota metabolic system, and barriers system. Created with BioRender.com. HPA: Hypothalamic-pituitary-adrenal.

The gut bacteria can interact with the brain through neuronal networks via two neuroanatomical pathways. The first neuroanatomical pathway directly connects the gut and brain by the autonomic nervous system and vagus nerve in the spinal cord (Bonaz et al., 2017). The second neuroanatomical route is bidirectional communication through the enteric nervous system in the gut and autonomic nervous system and vagus nerve within the spinal cord (Furness, 2012). Another route of communication between gut bacteria and the brain is through the neuroendocrine system by the hypothalamic-pituitary-adrenal (HPA) axis, which regulates the body’s response to stress (Umesaki et al., 1999; Sudo et al., 2004). Gut microbiota can produce neuroactive hormones by secreting protein peptides and hormones that stimulate the release of corticotropin-releasing hormone, a primary polypeptide hormone regulating the HPA axis. Studies have shown that the lack of gut microbiota or dysregulation of the HPA axis is characterized by abnormal glucocorticoid levels which lead to depression-like behaviors (Holboer 2000; Gosselin and Rivest, 2008). These studies suggest that gut microbiota maintains CNS homeostasis by modulating the activity of the HPA axis.

Gut bacteria also synthesize some neurotransmitters and neural regulators such as serotonin or dopamine that directly or indirectly influence brain functions (Brenchley and Powrie, 2012), such as brain-derived neurotrophic factor (BDNF), tryptophan, and dopamine. Gut microbiota also releases metabolites such as SCFAs and tryptophan, which control brain inflammation. A recent study highlighted the relationship of gut microbiota and neuroinflammation in mice treated with antibiotics by gut microbiota and released under a specific tryptophan diet-control gut microbiota and astrocyte activation by acting through the microbial aryl hydrocarbon receptor (Rothhammer et al., 2018). Tryptophan is one of the essential amino acids supplied by dietary protein and can be catabolized by gut microbiota, producing various indole-derivatives (Roager and Licht, 2018). It has been shown that these tryptophan catabolites have a positive or protective impact on neurological and neuroinflammatory diseases (Roager and Licht 2018; Rothhammer et al., 2018). Another study reported that treatment with SCFAs as a dietary supplement rescues microbial function otherwise impaired in GF animals and can reverse microglia’s immature phenotype (Erny et al., 2015). SCFAs are metabolites produced by the microbiome and mainly from the fermentation of non-digestible carbohydrates and the digestion of proteins and peptides (Rios-Covian et al., 2016). It is considered one of the most studied microbiota metabolic products such as acetate, butyrate, propionate, valeric, isovaleric, and isobutyric acid (Erny et al., 2009). Under physiological conditions, SCFAs perform a wide range of physiologic functions, ranging from regulating and activating the immune system to microbial cell homeostasis (Canfora et al., 2015; Levy et al., 2017). These findings further explain the understanding of microbiota dysbiosis (Ingham et al., 2019) that impacts microglia in the brain. The gut immune system is another system that influences the brain through innate immune receptors (toll-like receptors [TLRs]) in the digestive system and activates adaptive immune cells (McKernan et al., 2011; Furusawa et al., 2013). TLRs are the first step in the entry of metabolites, byproducts, and cytokines into the blood circulation through the mucosal barrier dysfunction. The mucosal barrier dysfunction facilitates the entry of metabolites, byproducts, and cytokines into the blood circulation and stimulation and regulation of the HPA axis (Brenchley and Douek 2012; Konig et al., 2016), and the outcome is a profound increase in the permeability of BBB for unwanted substances (Nezari-Zadeh et al., 2009).

### Animal Models of Aging-Induced Gut Microbiota Modulation

Using rodents as a model system in microbiota-related research is considered a powerful tool that can be utilized under controlled conditions to further understand the gut microbiota brain axis. There are two main animal models that have been used to study the microbiota in normal and pathogenic conditions with aging. In one model, the rodents are treated with antibiotics for 6 weeks to induce gut microbiota dysbiosis (Brenchley et al., 2016). Antibiotic administration substantially reduces bacterial bioavailability and decreases microbiota diversity (Dudek-Wicher et al., 2018). In addition, antibiotic administration negatively impacts cognition by reducing the expression of cognition-related proteins (brain-derived neurotrophic factor [BDNF] and synaptophysin) in different brain regions (Frohlich et al., 2016). The second model includes raising the rodents in a germ-free environment, called GF rodents (Al-Asmakh and Zadjali 2015; Fransen et al., 2016). The germ-free animals model is an excellent model that stimulates the abnormal brain structure, development, and behavioral dysfunctions (Salami, 2021). Furthermore, other methods have been used to produce a positive...
or negative intervention in aging research, such as dietary manipulations, treating with probiotics/prebiotics, and fecal microbiota transplantation (FMT) (Drastich et al., 2018). FMT technique is used by transplanting the gut microbiota from aged to young subjects to study whether the gut microbiota in aged subjects can affect the brain structure and functions in the young subjects (Borody et al., 2013).

Initial animal and human studies used fecal analysis to assess the gut microbiota composition and its metabolic products. Numerous advanced techniques, such as meta-omics analysis and next-generation high-throughput sequencings (16S ribosomal RNA (rRNA) microbial profiling), DNA microarrays, mass spectrometry, metabolomics, and shotgun metagenomics, were utilized to understand the gut microbiota-brain axis and identify microbial communities, composition, and functions (Mariat et al., 2009; Zwielysner et al., 2009; Fraher et al., 2012, Ticnesi et al., 2018; Li et al., 2020). These techniques enable one to determine the microbial diversity, quantity, and qualitative information of specific bacterial types, and gut microbiota changes during the initiation and progression of the disease states (Fraher et al., 2012).

Gut Microbiota Alterations and the Normal Aging Process

An imbalance of the intestinal homeostasis is linked with the normal aging process and many infectious and neurodegenerative diseases in the elderly (Wong et al., 2019). In human studies, the gut microbiota tends to have a different composition, stability, and diversity of gut microbiota than young adults (Woodmansey et al., 2004; Mueller et al., 2006; Jeffery et al., 2016). In one clinical study, the microbiota dysbiosis change between the aged (60–90 years) and young (18–40 years) was analyzed using 16S rRNA sequencing sampling (Claesson et al., 2011). The study observed that in the elderly, the phylum Bacteroidetes is dominant at 57%, and phylum Firmicutes is dominant at 40%. However, in young subjects, the phylum Bacteroidetes dominated by 41%, and the phylum Firmicutes dominated by 51%. A similar result was observed in other studies showing a decrease in Firmicutes/Bacteroidetes ratio (from 0.5 to 0.6) of the human microbiota between adults (25 to 45 years old) and the elderly (70–90 years old) (Mariat et al., 2009). Another clinical study that recruited 371 people from newborn to centenarians reported a significant difference in 35 genera in aged human gut microbiota by performing 16S rRNA sequencing (Xu et al., 2019). Interestingly, beneficial genera (Oxalobacter, Butyrivibrio, and Lactobacillus) were lost, whereas genera (Parsimonomas, Butycincomonas, and Anaerotruncus) related to inflammation and disease increased.

Human and rodent gut microbiota share Firmicutes and Bacteroidetes, major microbial phyla (Nguyen et al., 2015; Gopalakrishnan et al., 2021). There were significant differences observed in these phyla ratio levels, communities, and composition. In contrast to humans, the ratio of two main phyla, Firmicutes and Bacteroidetes, was increased in mice and rats with advanced age (18–20 months) to almost nine-fold compared to young (2–6 months) and was associated with increased anxiety-like behaviors (Hoffman et al., 2017; Spychala et al., 2018; Li et al., 2020). Similarly, microbiota changes were also investigated by decreasing the bacteria in Tenericutes levels and increasing Firmicutes and Actinobacteria levels, resulting in an increase in the Firmicutes to Bacteroidetes ratio (Kim et al., 2016, 2017).

During aging, microbiota alteration occurs mainly by decreasing microbiota diversity and increasing in pathologiical bacteria, Proteobacterium, and relatively low proportions of beneficial bacteria, Bifidobacterium. Besides alterations in microbial biodiversity, the production of beneficial microbiota metabolites such as SCFAs is also drastically reduced, which may be linked to the aging-related process (Erny et al., 2015; Chen et al., 2019). The administration of antibiotics in adult mice resulted in decreased SCFAs concentrations and cognitive impairments compared to the control group (Frohlich et al., 2016). These findings indicate that SCFAs change with aging and could play an essential role in the pathophysiology of disease and cognitive decline. Compared to young, aged mice showed a reduction of SCFAs metabolites by 68% acetate and propionate and 80% of the butyrate levels. These reduced levels were in parallel with the cognitive impairments (Spychala et al., 2018). In all these studies, significant changes were observed between the intestine flora and host with aging in both humans and animals, and these changes gradually reach a stage of microbiota dysbiosis. Therefore, understanding the changes in the microbiome with aging may provide potential biomarkers of the initiation of the aging process.

Gut Microbiota Alteration and Age-Related Neuroinflammation

Since chronic low-grade systemic inflammation contributes to age-related diseases, many studies have shown that gut microbiota modulates the inflammmaging and could be a key determinant for age-related neuroinflammation and neurodegeneration. The fecal microbiota transplantation was also used to examine the effects of microbiota dysbiosis on the chronic and inflamed immune system with aging (Fransen et al., 2017; Li et al., 2020). It was found that the microbiota triggers innate immunity and produces inflammatory responses mimicking inflamming with heightened intestinal inflammation and increased circulation of inflammatory cytokines in both serum and brains. Bacteria populating the gut can secrete large amounts of metabolites and byproducts such as double-stranded RNA, lipopolysaccharides, and lipopolysaccharidases (LPS). These bacterial components contribute to the signaling pathways involved in the excessive production of pro-inflammatory cytokines such as interleukin (IL)-8 and IL-6 (Biagi et al., 2013) which could lead to an increase in LPS production level in plasma and brains, a cell membrane byproduct of gram-negative bacteria. At the molecular level, the increase in LPS level is correlated with the increased expression of TL4R, myeloid differentiation protein-88, and the nuclear translocation of nuclear factor kappa beta (NF-kB) in both intestinal and brain tissues (Wu et al., 2021). Another study also showed that bowel inflammation triggers neuroinflammation in rats (Villaran et al., 2010). It was observed that LPS induced ulcerative colitis mediates systemic inflammation leading to exacerbated BBB permeability, induced inflammation in the substantia nigra region of the brain, and dopaminergic loss. They also investigated that non-selective macrophage depletion by an intravenous administration of liposome-encapsulated docetaxol reduced the peripheral and neuroinflammatory response. These studies explain that the mucosal translocation of bacterial LPS and LPS-binding proteins into the systemic circulation could promote the chronic low-grade systemic inflammation mainly found in the older subjects and can initiate CNS inflammation by activation LPS/TL4R pathway in brain glial cells (Stehele et al., 2012; Ghosh et al., 2015; Kim et al., 2016). In addition, LPS increases the BBB permeability by activating TL4R/IRF-3 signaling pathway in the endothelial cell in the blood vessel and disrupted the intestinal epithelium barrier (Choi et al., 2012). Higher levels of LPS were also found in the hippocampal and superior temporal lobe of the postmortem brain lysates of AD patients (Zhao et al., 2017). In another study, increased bacterial populations in AD patients’ brain tissue were investigated using 16S rRNA sequencing (Emery et al., 2017). Related to these studies, LPS challenged GF mice showed microglial morphological and functional dysregulation and impairments in the release of the pro-inflammatory cytokine interleukin-6 (IL-6). This leads to necrosis factor-a (Eny et al., 2015; Kim et al., 2016; Matovitch-Natan et al., 2016). Accordingly, a significant increase in the pro-inflammatory cytokines and impairments in oxidative stress protein expression was also investigated in young rat serum and brains after transplanting aged human microbiota (Li et al., 2020). Based on all these studies, the gut microbiota represented a pro-inflammatory phenotype in aged subjects promoting the idea that age-related neuroinflammation are modulated by chronic peripheral inflammation.

Moreover, the substances synthesized by gut microbiota, either as metabolic byproducts or constituents of bacterial structures, can promote protein aggeration in brain tissue in some neurodegenerative disorders. For example, many gut microbiota species are associated with the production of amyloid fibers, such as Escherichia coli (E.coli) and Bacillus subtilis. These amyloid fibers can cross the intestinal and BBB layer, promote amyloid-B protein formation and accumulation in the brain, and enhance AD pathogenesis in the elderly (Kowalski and Mulak, 2019; Li et al., 2019). The findings are supported by studies reporting a reduction in amyloid protein concentration in the serum and brain in the AD transgenic mouse model treated with antibiotics (Minter et al., 2016; Harach et al., 2017). It was hypothesized that the increased levels of stress-related proteins in aging brains could be the possible reason for neuroinflammation and subsequent neurodegenerative diseases (Biagi and Shaper, 2011). Many studies indicate that gut microbiota alteration and dysbiosis could alter the expression of various genes and associated synaptic proteins and promote the accumulation of inflammatory proteins in the brain, inducing neuroinflammation, astrocyte activation, neuronal apoptosis, and cognitive decline (Biagi and Shaper, 2011). In addition, several years before the onset of age-related neurodegenerative disorders, as shown in Figure 2. It is proved that microbiota alteration activity gradually increases with aging, and this imbalance causes glial cells to turn into a reactive state and subsequently induce inflammation in the brain.
Gut Microbiota Alteration and Age-Related Cognitive Decline

Many recent studies found that age-related neuroinflammation and cognitive decline are associated with the integrity of microbiota-gut-brain axis function. The gut microbiota alteration with aging amounts to leakiness of the gut epithelial barrier and BBB, loss of the enteric nervous system, altered neurotransmitters, metabolites, and mucosal immune function resulting in successive pro-inflammatory cytokine release (Biagi et al., 2010; Fransen et al., 2017). So far, there are limited studies available underlining the mechanisms associating gut-brain axis and age-related microbiota alteration with cognitive decline in humans. However, few studies report a low microbiota diversity between healthy older adults and those with cognitive impairments (Claesson et al., 2011, 2012). A recent preclinical study reported a significant decrease in the anti-inflammatory genus Faecalibacterium in people with subjective cognitive decline compared to the normal healthy group (Sheng et al., 2021). Subjective cognitive decline is the first symptomatic manifestation of preclinical AD (Rabin et al., 2017). It was suggested that the gut microbiota has emerged as an essential player in the development of vascular cognitive impairment in elderly patients with cerebral vascular disease (Li et al., 2018). Vascular cognitive impairment is a cognitive impairment that is attributed to cerebrovascular disease in the elderly such as atherosclerosis, ischemic and hemorrhagic stroke (Li et al., 2018; Iadecola et al., 2019). A summary of human studies comparing the changes in the gut microbiome composition between living subjects suffering from cognitive symptoms and healthy older subjects is presented in Table 1.

| Reference          | Number and characteristics of subjects | Mean age (yr) | Gut microbiota alteration in cognitive decline patients compared to healthy older adults |
|--------------------|----------------------------------------|---------------|-------------------------------------------------------------------------------------|
| Cattaneo et al., 2017 | 73 patients with dementia 71 ± 7 (cases) |               | The microbiota of patients with dementia had higher pro-inflammatory gut microbiota (Escherichia/Shigella) and reduced anti-inflammatory taxon (Eubacterium rectale). |
| 10 controls        | 68 ± 6 (controls)                      |               |                                                                                     |
| Vogt et al., 2017  | 25 patients with dementia 71 ± 7 (cases) |               | Subjects with cognitive impairments had decreased Firmicutes and increased Bacteroidetes |
| 25 controls        | 69 ± 8 (controls)                      |               | Reduced the abundance of 13 anti-inflammatory taxa, including Bifidobacterium, Alastipes, Bilophila, and Clostridium. |
| 18 with mild cognitive decline | 68 ± 6 (cases) |               | A strong correlation with cognitive decline was observed in Verrucomicrobia abundance. |
| Zhuang et al., 2018 | 43 patients with dementia 70 ± 9 (cases) |               | Subjects with dementia had fecal microbiota composition alteration characterized by an abundance of several species including Bacteroides, Actinobacteria, Ruminococcus, Lachnospiraceae, and Selenomonasalatale. |
| 43 controls        |                                       |               |                                                                                     |
| Saji et al., 2019  | 34 patients with dementia 75 ± 9 (cases) |               | Subjects with dementia had a low abundance of Bacteroides and high Firmicutes/Bacteroidetes ratio and other bacteria. |
| 94 controls        |                                       |               |                                                                                     |
| Sheng et al., 2021 | 67 patients with cognitive decline 67 ± 6 (cases) |               | Subjects with dementia had a low abundance of Firmicutes, class Clostridia, Clostridiales, Ruminococcaceae, and Faecalibacterium. |
| 38 controls        | 73 ± 8 (controls)                      |               | A significant decrease in the abundance of the anti-inflammatory genus Faecalibacterium |

Table 1 | Overview of the main human studies comparing the fecal gut microbiota composition between subjects suffering from cognitive symptoms and healthy older subjects

Evidence from animal studies suggests that the alterations in gut microbiota may drive cognitive impairments and behavioral dysregulation in aged mice due to the prolonged exposure of the brain to microbiota metabolites and pro-inflammatory cytokine (Caraciolo et al., 2014; Enry et al., 2015; Leung and Thurer 2015; Manderino et al., 2017). Several studies state that the FMT technique to investigate the effects of transferring gut microbiota from old to young rodents, focusing on age-related signs of cognitive decline and neuroinflammation. The results suggest that mice receiving an aged microbiota began to behave like older mice by exhibiting impaired motor strength and cognitive behaviors (D’Amato et al., 2020; Li et al., 2020; Wu et al., 2021). Besides cognition impairments, another study observed alteration of one hundred forty proteins involved in synaptic plasticity and neurotransmission in the hippocampus, in addition to downregulation of proteins involved in glucose transport at the BBB by using Label-free quantitative proteomics (D’Amato et al., 2020). All these detected alterations in protein expression in the hippocampus region in young recipients contributed to the dysfunction of the normal aging brain process. In addition, a substantial reduction of SCFA-producing bacteria was also reported in young mice receiving fecal transplantation from aged mice.

Moreover, fecal microbiota transplants from aged donor rats significantly decreased the regional homogeneity and the density of dendritic spines. Furthermore, it changed the synaptic structures by reducing the expression of cognition proteins such as BDNF, N-methyl-D-aspartate receptor NR1 subunit, and synaptophysin in the hippocampus and prefrontal cortex regions in the young feral recipient rats (Li et al., 2020). These studies provide a shred of direct evidence for the contribution of gut microbiota to age-related cognitive decline and in the brain’s physiological function and structure. In contrast to these studies, another study confirmed the increased hippocampal neurogenesis, intestinal growth, and pro-longevity signaling in young recipients after receiving fecal microbiota from aged mice (Kundu et al., 2019). These findings suggest that gut microbiota transplants from aged subjects could have beneficial protection from neurological and neurodegenerative disorders in young subjects.

Potential Therapeutic Possibilities Targeting Gut Microbiota Dysbiosis to Reduce Age-Related Disorders

As life expectancy began increasing with the turn of this century, the risk of having a neurogenerative disease increased with aging. Having a healthy aging brain and delaying the onset of neurodegenerative disorders is a big challenge. So far, the effective pharmacological therapies developed for neurological conditions mainly were based on targeting proteins or genes within the brain. The intestinal microbiome emerged as a promising target for anti-aging interventions based on the emerging appreciation of a gut-microbiota brain axis. Therefore, microbiota alteration could become a promising therapeutic target for neuroinflammation and cognitive decline related to aging and other neurodegenerative diseases.

Fecal microbiota transplantation

Research on the gut-brain axis has identified several promising targets for the gut microbiota. One possible therapy is the method involving restoring gut microbiota’s composition and function by introducing fecal contents from healthy young subjects into the aged subject’s gastrointestinal (GI) tract, known as fecal microbiota transplantation (FMT). The FMT method has been used in more than 300 clinical trials for many GI target diseases, including constipation, irritable bowel syndrome, and autoimmune diseases (Choi and Cho 2016; Hollingsworth et al., 2021). A recent study reported that the beneficial effects of FMT from 3-months aged mice to 24-month-old mice improved the inflammatory and cognitive function, in particular spatial learning and memory (D’Amato et al., 2020). However, the use of FMT is limited due to the unknown long-term efficacy of this method and the reported unexpected side effects. For example, a recently published case study identified a 56-year-old female patient with chronic radiation colitis who developed adhesion ileus after 2 days of the FMT (Harsch and Konturek, 2019). Researchers speculate the adverse side effect because the transplantation of colonic bacterial flora and the colon could have led to the trapping of a gut segment in a preexisting adhesion. In addition, the possibility of transferring the endotoxins or infectious agents to the recipient subjects could worsen GI complications (De Leonibus et al., 2013; Schwartz et al., 2015). Besides these factors, sex differences in the microbiota might also play an essential factor since many studies showed that the gut microbiome varies between males and females in human and rodent studies (Dominiani et al., 2015; Borgho et al., 2018). Therefore, further investigation is needed to prove the use of the FMT technique to improve the cognitive decline in aged humans. However, isolation of a defined group of bacteria from the fecal sample then transported into the recipient’s intestine would be a safer alternative to the FMT method (Buflle et al., 2015; Wymore et al., 2015).

Probiotics and prebiotics

Supplementation with probiotics and prebiotics is a promising alternative therapeutic option for treating gut alteration in aging. Prebiotics are nondigestible and fermented food components that selectively promote beneficial commensal microbiota growth and activity (Franco-Robles and Franco, 2011). Probiotics and prebiotics from the fecal sample then transported into the recipient’s intestine would be a safer alternative to the FMT method (Buflle et al., 2015; Wymore et al., 2015).
metabolism in the intestine are SCFAs. In contrast, probiotics are supplements that supply beneficial bacteria to GI to modulate gut microbiota composition and function, such as Bifidobacterium lactis (Franco-Robles and Lopez, 2015). In addition, the beneficial effect of probiotics in healthy cognitive function has been considered in many human and animal studies.

Studies have shown that the utilization of probiotics and prebiotics increases the production of SCFAs, improves age-related memory alteration, reduces immune responses, and decreases inflammation and oxidative stress in the brain (Brussow, 2013). Another study suggested that probiotics and prebiotics improve learning and memory in rats by increasing butyrate production in the intestine and simultaneously increasing the BDNF expression and decreasing the pro-inflammatory cytokine concentrations in the hippocampus (Romo-Araiza et al., 2018). Furthermore, it has been found that probiotics can improve CNS dysfunction by increasing both the diversity and intestinal bacterial populations (Kaur et al., 2016). A recent study found that aged (26 years) administering a multi-strain probiotic for 12 weeks showed significant improvement in brain function, mental flexibility, alleviation stress, and increased serum BDNF levels (Kim et al., 2021). In addition, a probiotic mixture has also shown an improvement in aged mice memory and reduction in glial activation, and modified microbiota composition in the feces and the brain (Ho et al., 2019; Yang et al., 2020). Also, the single mono-strain probiotic administration improved memory function in young and older adults suffering from mild cognitive impairments (Sanborn et al., 2020; Xiao et al., 2020) and aged mice (Wang et al., 2020). Besides the beneficial effects of probiotics on cognitive improvement, several issues are necessary to be addressed. The pharmacological effects of the probiotics are strain-specific, which means each strain is specific for a unique host type (Mus et al., 2009; Stenman et al., 2020). Therefore, understanding the role of aging in probiotic research is needed to elucidate the more efficient probiotic strains that can offer health benefits in different individuals. Defining the mechanisms of the probiotics is also needed to improve the probiotic effects in preventing diseases and modulating the immune system. However, using probiotics in healthy individuals to modulate the gut microbiota remains highly debated and controversial. In addition, the long-term efficacy of probiotics in the intestine and fecal microbiota is still unknown.

Conclusion and Future Perspective

Even though gut microbiota dysbiosis has been considerably studied in recent years, the underlying causes remain unclear. This review discussed and focused on gut microbial in brain aging neuroinflammation, cognitive decline, and intestine aging. Thus, the potential therapeutic options to reduce gut dysbiosis and cognitive decline in aging. The discussed studies could pave the way for reinforcing microbiota dysbiosis as a potential biomarker in aging and provide strong evidence for manipulating gut microbiota with probiotic and prebiotic therapy as an essential option to prevent and treat different neurodegenerative diseases. The most critical unmet need in the gut brain axis is to find the relationship between specific pathological biomarkers and microbiota changes. This has sprouted a plethora of studies aimed at modifying the gut microbiota composition in the elderly that potentially could reduce inflammation and improve cognitive decline. However, the critical questions to be answered are: does brain aging start from the brain or digestive system? is microbiota responsible for the incidence of brain aging and age-related diseases? Does peripheral systemic inflammation emerge from gut bacteria? Understanding the role of dysbiosis in aging and altering the gut microbiota may prove helpful in attenuating inflammation and the associated diseases. Furthermore, identifying the biochemical and mechanical signaling that mediates dysbiosis could help early detection of neuroinflammation and neurodegenerative diseases.

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