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Mini Review

Effect of Microbiota on Neurodegenerative Diseases

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Abstract

There is growing awareness that the gut- brain axis and its regulation by microbiota may play an important role in the biological and physiological basis of age-related and neurodegenerative diseases. Microbiota-induced neural, immune and endocrine signals are associated with obesity, inflammatory diseases, and various neurological and psychiatric disorders.

Understanding the contribution of intestinal microbiota to the development and functioning of the nervous system has the potential to intervene using novel microbial-based approaches to the treatment of neurological disorders. In the future, it is likely that such disorders will be treated with microbiota transplantation, antibiotics or probiotics. It is known that diet is the major factor affecting microbiota composition; dietary regulation and probiotic supplementation may contribute to the prevention of microbiota-based neurodegenerative diseases. In this review, the role of microbiota and diet in neurodegenerative disorders was investigated.

Keywords: *Microbiota; Parkinson's Disease; Alzheimer's Disease; Diet; Probiotics*

Microbiota and aging

Intestinal microbiom develops throughout life, but the diversity and stability of the microbiota decreases with aging [1,2]. It has been shown that microbial composition is influenced by the diet and health status of the individual [3]. In addition to many drugs used by the elderly, digestive and motility dysfunction, malabsorption of nutrients and a weakened immune system all contribute to the formation and balance of intestinal microbiota composition [4,5]. Decrease in intestinal stability and diversity in the elderly is accompanied by a decrease in brain volume and cognitive functions. Age-related changes in brain morphology correlate with impaired immune system, increased oxidative stress, and amyloid plaque accumulation in the brain. All of these reflect impaired cognitive and behavioral functions and indicate various age-related memory disorders such as Alzheimer's disease. Recent studies have strengthened the importance of microbial diversity in maintaining health as we age [5]. Therefore, it is understood that maintaining a healthy microbiome is very important for having a healthy brain for a lifetime from cradle to grave.

It is now well known that the intestinal microbiota undergoes a dynamic change during aging [1]. It is interesting that the number of bifidobacteria decreases with age and the number of clostridia increases [6]. A decrease in *Bifidobacteria* spp., a decrease in butyrate-producing species (*Ruminococcus* spp., *Faecalibacterium* spp., etc.) and an increase in species known to increase the inflammatory response (*Escherichia* spp., *Enterobacteriaceae* spp., *Bacteroid* spp., *Clostridium difficile*, etc.) may be seen.There may be an increase in pathogenic bacteria (pathobiotics) due to an increase in *Proteobacteria* spp. [1,7].

Increasing evidence suggests that intestinal microbiota is essential for human health and is a key player in bi-directional communication between gut-brain axis. The early life disturbance of the developing intestinal microbiota has the potential to have a significant impact on neurodevelopment and can potentially lead to negative mental health consequences in later life. Similarly, the microbiota can contribute to the aging process and the trajectory of neurodegenerative diseases.

Reference search method and selection criteria

References for this review were defined by searching PubMed journals published between January 1, 2010 and July 1, 2019 using the following terms: "neurodegenerative disease", "Alzheimer", "Parkinson", "nutrition", "diet", "microbiota". The number of articles found with the words "neurodegenerative disease and microbiota was 335 and 164 of them were reviews. The number of articles found with the words "neurodegenerative disease, microbiota and diet" is 52. In this review, it was aimed to examine the literature on the relationship between microbiota and diet with Alzheimer's disease (AD) and Parkinson's disease (PD). So that search criteria were narrowed with the words "Neurodegenerative disease, AD, PD and diet". Articles found with the words "neurodegenerative disease, AD, microbiota and diet" were 14 and 12 of them were reviews. Thirteen of the 18 articles found with the words "neurodegenerative disease, PD, microbiota and diet were reviews. When the word "diet" is replaced with " nutrition" the number of articles found for Alzheimer's Disease (AD) is 9, of which 3 are reviews. When the word "diet" is substituted with "nutrition" for Parkinson's Disease (PD), the number of articles found is 21, of which 12 are reviews. The focus is primarily on peer-reviewed journal articles in humans (including original observational case control, cohort or intervention studies, or other investigations of the original work) and involving the relationship between at least one of the above neurological conditions with gut and diet. However, as selection criteria were narrowed, the number of human studies decreased. Therefore, the most relevant articles from the selected ones are included in this review. Studies involving other microbiomes (eg, lung, nose, mouth), case reports and case series were excluded.

Microbiota and neurodegenarative diseases

Neurodegenerative diseases are usually caused by various factors affecting the composition of the intestinal microbiota at an older age. Malnutrition is associated with decreased microbial diversity and contributes to increased local and systemic inflammation in the elderly. This condition is called "inflammaging" a condition due to chronic inflammation. Multiple comorbidity affects the microbiota composition directly or with drugs used, such as antibiotics, metformin or proton pump inhibitors.

Alzheimer's Disease (AD), Parkinson Disease (PD), Multiple Sclerosis (MS) and Amyloid Lateral Sclerosis (ALS) are classified as neurodegenerative diseases. Although each of these diseases has different physiological symptoms, most of them have common aetiology associated with pathologies occurring during normal aging. Oxidative damage and inflammation are two major systemic conditions that aggravate neurodegeneration, and both are exacerbated by normal physiological regression with age. Indeed, oxidative damage in PD and AD is an important factor in their progression, particularly in areas affected by degeneration, particularly in AD, which are selectively susceptible to oxidative stress. The slow accumulation of ROS in neurons stimulates cytokine release and consequently microglial activation and neuroinflammation. The pathology of oxidative damage and inflammation forms a vicious cycle called "inflammation", a chronic low-grade systemic pro-inflammatory condition characterized by high cytokines and inflammatory mediators [8]. Inflamm-aging describes a common basis for a wide range of age-related pathologies, including neurodegeneration.

In recent years, there has been an increase in the incidence of neurodegenerative diseases including obesity, diabetes, cardiometabolic diseases, cancer and even depression, anxiety disorders, and schizophrenia. Increased consumption of animal protein, saturated fat and refined carbohydrates are responsible for nutritional factors that play a role in this increase [9].

While the consumption of refined carbohydrates (sugary foods/drinks) increased in the diet as a result of the western type diet, consumption of fiber foods decreased in parallel. As a result, the intake of prebiotic nutrients is reduced, so the likelihood of proliferation of probiotics in the intestine is reduced. Probiotics are defined as living organisms that have a positive effect on the health of the host when taken in sufficient amounts and these beneficial effects are considered to extend from inflammatory diseases to neurodegenerative disorders.

Especially the nutritional habits of the individual is one of the major factors affecting the gastrointestinal system microbiota [10]. In various studies, intestinal microbiota has been shown to be effective in the pathogenesis of many diseases outside the gastrointestinal tract due to its close relationship with nutrition, inflammation, immune system, neural and endocrine system [9,11].

Microbiota is affected by various factors such as diet, physical activity, age, stress, medications. It is known that inflammatory diseases are as common as obesity in western societies whose diet is typically rich in refined carbohydrate and saturated fat from high amounts of animal origin. The high animal fat/high sugar and refined carbohydrate diet is associated with postprandial inflammation and neurodegeneration [12]. The dominant bacterial species that make up about 90% of total microflora are *Bacteroidetes* (B) and *Firmicutes* (F). Western-type, high-energy diets change the intestinal microbiota profile and increase the population of *Firmicutes*. A complex carbohydrate-rich diet is associated with an increase in B/F ratio [13].

In one study [14], changes in intestinal microbiota and high fructose-induced hippocampal neuroinflammation were investigated in high fructose-fed mice. High fructose diet was found to cause hippocampal neuroinflammatory response, reactive gliosis (gliosis) and neuronal losses in C57BL/6N mice. Fructose-fed mice showed changes in gut microbiota composition, short chain fatty acid (SCFA) reduction, intestinal epithelial barrier disorder, inflammatory dysfunction, elevated serum endotoxin levels and FITC-dextran. The findings of this study suggest that intestinal dysbiosis is a critical factor for hippocampal neuroinflammation due to the high fructose diet in possibly mediated C57BL/6N mice, which weakens the intestinal epithelial barrier. This study emphasizes a novel intervention strategy to reduce the neuronal deterioration caused by western-style diet and the risk of neurodegenerative disease through SCFA supplementation or dietary fiber consumption.

Parkinson disease

Parkinson's Disease (PD) is a neurodegenerative disease with an increasing health problem in the elderly. PD is characterized by neuroinflammation and loss of midbrain dopaminergic neurons and also abnormal movements that show some non-motor symptoms [15]. In addition, changes in intestinal function, particularly constipation, have often been found to precede the onset of prototypic motor symptoms associated with PD. Genetics plays an important role in the risk of disease development, while environmental factors and gene-environment interactions contribute to the risk of developing the disorder [16]. In fact, evidence suggests that intestinal microbiota is an important environmental factor related to the risk of PD [17,18]. One study confirmed a significant decrease in *Prevotellaceae* levels in PD patients compared to controls [19]. They also found a positive correlation between *Enterobacteriaceae* levels and the severity of postural instability and gait difficulty, suggesting the role of intestinal microbiota in the PD phenotype. Another study showed that "anti-inflammatory" butyrate-producing bacteria were significantly higher in control feces than PD patients. However, the *Ralstonia* genus *Proteobacteria*, which are supposed to be "pro-inflammatory" were significantly higher in the mucosa of PD patients than in controls [20]. In one study, it was reported that intestinal microbiota was involved in motor deficits and neuroinflammation in a PD model [16]. This finding reveals that changes in the intestinal microbiota are a risk factor for PD.

In Parkinson's disease, it has been reported that the disease can begin in the intestine and spread to the brain through the gut-brain axis. Indeed, microbiota analyzes in Parkinson's patients showed a decrease in *Prevotella* strains and an increase in *Enterobacteria* [21]. However, the relationship between intestinal microbiota and brain diseases suggests that a healthy microbiota may be one of the keys to longevity.

Parkinson's disease (PD) is usually characterized by cardinal motor disorders. However, a number of non-motor symptoms precede the motor phase and are the main determinants of quality of life. To date, there is no disease-modifying treatment for PD patients. The gold standard levodopa therapy relies on the restoration of dopaminergic neurotransmission, thereby alleviating motor symptoms, while non-motor symptoms remain untreated. One of the most common non-motor symptoms is gastrointestinal dysfunction, usually associated with low-grade mucosal inflammation and alpha-synuclein accumulations in the enteric nervous system. Accumulating evidence suggests that the enteric nervous system plays a role in the pathological progression of PD towards the central nervous system. Furthermore,

different components of the intestine may provide a central role in the gut-brain axis, a bi-directional communication system between the digestive system and the central nervous system. Dietary components may affect the gut-brain-axis by altering the composition of the microbiota or by creating a neuronal functionality in both the ENS and the CNS. Today, the most widely used probiotic bacteria are *Lactobacilli, Enterococci, Biobacteria, Yeasts* and mixtures of different beneficial bacteria [22]. Several studies have reported the benefits of probiotics by increasing intestinal epithelial integrity, protecting against barrier disruption, stimulating a healthy homeostasis of the mucosal immune system, and suppressing pathogenic bacterial growth [23,24]. In addition, different strains of probiotic bacteria have been shown to be effective in stimulating intestinal motility and reducing GI dysfunction. Studies on the use of probiotics in the treatment of PD are very limited. One study showed that PD patients suffering from chronic constipation receiving fermented milk containing *Lactobacillus casei Shirota* for five weeks increased stool consistency and decreased bloating and abdominal pain [25].

Probiotics can be a powerful tool to alter the PD-associated microbiota composition and improve GI function and therefore reduce intestinal leakage, bacterial translocation, and related neuro-inflammation in ENS. Improving GI function by supplementing with probiotics may not only lead to better functioning and/or protection of the intestines, but may also improve levodopa absorption and reduce behavioral and cognitive disorders such as anxiety, depression and memory problems seen in PD patients [24].

Two well known nondigestible carbohydrates are fructo-oligosaccharides (FOS) synthesized from fructose and galacto-oligosaccharides (GOS) from lactose. GOS and FOS reach the colon, where most of them are metabolized by *Bifidobacteria*, more or less unchanged. SCFA, lactose, hydrogen, methane and carbon dioxide are metabolic products that cause an acidic environment in the colon, which prevents survival and proliferation of pathogenic bacteria. SCFA is important for the maintenance of intestinal epithelial integrity and homeostasis and regulation of mucosal immunological responses. Prebiotics have been shown to have an impact on intestinal motility and constipation and immune function, which may be highly related to inflammation and GI-related symptoms in PD [26]. In addition, GOS and FOS have been shown to increase brain-induced neurotrophic factor (BDNF) levels in the dentate gyrus of the hippocampus in rats [27]. Since the BDNF signal is critical for neuronal protection, survival, and plasticity, GOS and FOS supplementation may have effects on brain neuroprotection. It has been shown that the PD fecal microbial population is lower in SCFA butyrate-producing bacteria, which can be corrected by the use of prebiotic fibers [28].

Although the mechanisms that cause neurodegeneration are different in each neurodegenerative disease, chronic inflammation modulated by the intestinal microbiota is typically maintained as a prominent feature in the progressive nature of neurodegeneration. This may mean that inflammation actually begins in the intestine and its effect is sometimes in the intestine (such as inflammatory bowel disease), sometimes in a distant organ; endocrine system (such as diabetes or thyroiditis) or neural system (such as Alzheimer's or Parkinson's disease).

Alzheimer's disease

Alzheimer's disease (AD) and vascular dementia are the most common causes of decreased cognitive functions in the aging population in Western countries. Aging and age-related disorders, such as Alzheimer's disease, are the result of progressive leakage of the blood-brain barrier (BBB). It is clear that stress can have significant effects on the microbiota [29] and the effect of stress on the aging brain can be particularly detrimental [30]. Both aging and stress can impair gastrointestinal barrier function and produce a proinflammatory phenotype through microbiota [31]. In addition, both aging and stress may adversely affect the permeability of BBB [32]. Together, they all have the potential to accelerate inflammation-related aging "inflamm-aging" processes in the brain.

Changes in the composition of the intestinal microbiota may increase the permeability of the intestinal barrier and the blood-brain barrier. As a result, inflammation increases at systemic and CNS levels. The results of animal studies using germ-free mice indicate the key role of intestinal microbiota in early brain development and adult neurogenesis. In the elderly, overstimulation of the immune system causes "inflammaging" to a chronic, low-grade inflammation. This leads to disruption of intestinal barriers, increased proinflammatory cytokines and circulating bacterial derivative products, disruption of the blood brain barrier and neuroinflammation. The results of stu-

dies in germ-free mice confirm the effect of microbiota on microglia maturation. This may be mediated by short-chain fatty acids (SCFAs), products of bacterial metabolism. Similarly, specific products of microbial tryptophan metabolism modulate astrocyte activity through aryl hydrocarbon receptors [33].

Intestinal microbiota may affect CNS function by direct synthesis of various neurotransmitters and neuromodulators such as serotonin, dopamine or SCFAs. The intestinal microbiota signals may alter the function of intestinal enterochromaffin cells that produce different hormones and neurotransmitters, including serotonin. Disorders along the brain-gut-microbiota axis can significantly contribute to the pathogenesis of neurodegenerative diseases such as Alzheimer's disease (AD).

AD is the most common cause of dementia characterized by a progressive decline in cognitive functions. The main feature of the disease is the accumulation of amyloid beta (Aβ), followed by the formation of plaques and neurofibrillary tangles of hyperphosphorylated tau protein [34]. These deposits trigger neuroinflammation leading to synapse loss and neuronal death. It is still unclear what triggers the formation of amyloid plaque, but intestinal microbiota is certainly considered to play an important role in this process. Tau is a highly soluble protein that modulates the stability of axonal microtubules. According to the Tau hypothesis, altered and aggregated forms of this protein appear to be toxic stimulants that contribute to neurodegeneration [33].

According to the age of onset; AD is classified as early onset (EOAD) that begins before the age of 65 and late onset (LOAD) that begins above this age. EOAD constituting 1 - 5% of all cases is associated with mutations in APP, PSEN1 and PSEN2 genes, which are mostly autosomal dominant inheritance. Most cases of AD are of the LOAD type, where different genes contribute to disease susceptibility. These genes encode proteins involved in amyloid precursor protein (APP) metabolism, immune response, inflammation, intracellular exchange, or lipid metabolism, indicating potential pathogenetic factors. Other, non-genetic, risk factors for LOAD include cerebrovascular diseases, brain injury, hypertension, type 2 diabetes and obesity [35]. There is a change in the intestinal microbiota in metabolic syndrome, type 2 diabetes (T2DM) and obesity [36], which are risk factors for AD [37,38]. There is accumulating evidence that intestinal microbiota may be directly associated with the pathogenesis of dementia by triggering metabolic diseases and low-grade inflammation. Different mechanisms may explain the link between intestinal microbiota changes in obesity and T2DM and development of AD. For example, different studies have shown that an intestinal microbiota that changes due to obesity increases intestinal permeability and contributes to insulin resistance and systemic inflammation leading to T2DM [39]. In contrast, insulin resistance and T2DM are risk factors for the development of AD. In addition, the vascular effects of obesity and T2DM related to changes in the intestinal microbiota appear to play an important role in the development of AD [40]. The designation of Alzheimer's disease as type 3 diabetes [41,42] confirms this relationship between AD and Type 2 DM, obesity and metabolic syndrome.

Although it has been suggested that changes in the intestinal microbiota observed in diabetes and obesity may be associated with the risk of developing AD, further studies are needed to explain the mechanisms involved in the link between specific intestinal microbes and obesity, T2DM and AD.

In one study, *Helicobacter pylori* infection was associated with AD. Mini-Mental State Test scores corresponding to more severe cognitive impairment were lower in AD patients with *H. pylori* infection; In addition, *H. pylori* infection was associated with disease severity and progression in PD patients. Significantly higher levels of *H. pylori*-specific IgG antibodies were found in the cerebrospinal fluid and in the serum of patients with AD [43].

Another possibility is that the entry point of pathogens may be the olfactory nerves, because the plasma membrane is the only barrier between the nasal cavity and the brain. Poor dental hygiene has also been associated with AD. Although data are limited, some studies have shown an increase in serum antibodies to bacteria due to periodontitis in AD patients [44,45].

A study of Alzheimer's disease patients revealed that the variety of intestinal microbiota decreased compared to healthy controls. Especially in Alzheimer's group, decrease in *Firmicutes* and A*ctinobacteria* and increase in *Bacteroidetes* have been described [46].

Alzheimer's disease (AD) is the most common form of dementia. The etiopathogenesis of this destructive disease, however, is not fully understood. Recent research in rodents has shown that changes in the intestinal microbiome may contribute to amyloid deposition, but that AD-related microbial populations are not characterized in humans. For this purpose, bacterial taxonomic composition of fecal samples from participants with and without dementia due to AD was defined in one study [47]. Analyzes revealed that AD participants exhibited reduced microbial diversity of intestinal microbiomes and differed from individuals matched with control age and sex in composition. There was a wide variation in the bacterial diversity of AD participants including decreased *Firmicutes*, increased *Bacteroidetes* and decreased *Bifidobacterium*. Moreover, a correlation between different abundant strains of AD and cerebrospinal fluid (CSF) biomarkers was observed. These findings suggest that as well as adding AD to the growing list of diseases associated with intestinal microbial changes, intestinal bacterial populations can be a target for therapeutic intervention.

The results of numerous studies confirm that probiotics have a beneficial effect by increasing intestinal epithelial integrity, protecting against barrier disruptions, reducing proinflammatory response, and inhibiting the initiation or progression of neuroinflammation and neurodegeneration. In addition, supplementation with *Lactobacilli* and *Bifidobacteria*-based probiotics in a clinical study significantly improved the Mini-Mental State Examination scores in AD patients [33].

Dietary fibers are metabolized by gastrointestinal (GI) bacteria to short-chain fatty acids (SCFAs). In one study, the potential role of SCFAs in β-amyloid (Aβ) mediated pathological processes, which play a key role in the pathogenesis of Alzheimer's disease (AD), was investigated. In this study, it was found that some selected SCFAs could potentially inhibit Aβ aggregation *in vitro* [47].

One of the most effective approaches to change the intestinal microbiota is dietary intervention. Food-based therapies may affect the intestinal microbiota composition, as well as directly affect neuron function in both ESS and CNS. It has been shown that the intake of plant-based foods, probiotics, antioxidants, soybeans, nuts, and omega-3 polyunsaturated fatty acids, as well as low saturated fat, animal proteins, and refined sugar, a healthy diet inhibits the inflammatory response, reduces insulin resistance and ultimately reduces the risk of neurocognitive impairment and AD.

Prebiotic fructooligosaccharides (FOS) play a major role in the regulation of intestinal microbiota. In one study [48], it was aimed to investigate the protective effect and mechanism of FOS against AD by regulating the intestinal microbiota. In this study, male Abscess/PSEN 1dE9 (APP/PS1) transgenic (Tg) mice were administered FOS for 6 weeks. Cognitive deficits and amyloid deposition were evaluated. Phosphorylation of C-Jun N-terminal kinase (JNK) as well as levels of synaptic plasticity markers including postsynaptic density protein 95 (PSD-95) and synapsin I were determined. The intestinal microbial component was detected by 16S rRNA sequencing. In addition, levels of glucagon-like peptide-1 (GLP-1) in the intestine and GLP-1 receptor (GLP-1R) in the brain were measured. The results showed that FOS treatment improves cognitive deficits and pathological changes in Tg mice. FOS significantly changed the expression levels of synapsin I and PSD-95, as well as the decrease in the phosphorylated level of JNK. The sequencing results showed that FOS reversed the modified microbial composition. In addition, FOS increased GLP-1 and decreased GLP-1R in Tg mice. These findings show that FOS has beneficial effects against AD by regulating the intestinal microbiota-GLP-1/GLP-1R pathway.

Sesamol, an antioxidant lignan from sesame oil, has lipid-lowering and neuroprotective bioactivities. In one study, it was aimed to elucidate the systemic protective effects of sesamol on dietary cognitive deficits and to determine possible connection between intestine and brain [49]. Sesamol prevented body weight gain, insulin resistance and hyperlipidemia caused by high fat diet (HFD). This study demonstrated that the possible mechanism of neuroprotective effects of sesamol may be due to ApoE and that the beneficial effects of sesamol on intestinal microbiology/metabolites can be translated into the treatment of metabolic and neurodegenerative diseases.

Several studies have also shown that the activity of the intestinal microbiota can alter the host epigenome that acts on gene expression [50]. In addition, epigenetic mechanisms are involved in neurogenesis, neuronal plasticity, learning and memory, as well as disorders such as depression, dependence, schizophrenia, and cognitive dysfunction [51]. In conclusion, it has been suggested that intestinal microbiota may play a role in the pathogenesis and risk of neurodegenerative disorders through highly dynamic and reversible epigenetic modifica-

tions [51]. Therefore, it is predicted that modulating the microbiota and its metabolic products will allow the epigenome to be modulated and thus prevent or treat mental illnesses. In addition, metabolites produced by fiber fermentation by microbiota are known to inhibit histone deacetylases (HDACs) and reduce inflammation through epigenetic modifications [52].

Microbiota, diet and neurodegenerative diseases

Evidence shows that changes in the microbiota composition may contribute to the onset of neurodegenerative diseases that increase with age. Adults undergo dramatic changes in microbiota composition following dietary modifications. In addition, aging is related to specific changes in microbiota diversity that results in health outcomes in the elderly. Since microbiota can interfere significantly with the human cognitive system, understanding the composition of microbiota in healthy humans is essential to maintaining brain and mental health throughout life.

Dietary patterns

Dietary patterns can regulate the intestinal microbiome by changing the nutrient content of the intestine. Recent advances have shown that dietary intervention may affect intestinal microbial gene richness. Low microbiome richness is known to be less healthy and is associated with metabolic dysfunction and low-grade inflammation. Diet style with high fiber content can increase the richness of microbiome. Unhealthy diets that contain high levels of saturated fat or salt can accelerate neuroinflammation. In addition, saturated fat is considered to be a risk factor for both neuro-immune and neuro-psychiatric disorders [53].

The Mediterranean diet (MD) is considered one of the healthiest diet models. Adherence to the Mediterranean diet is associated with less cognitive decline, dementia or AD [54]. Many of the characteristic components of MD have functional properties that have a positive impact on health. Eating habits are the main determinants of the microbial majority in the intestine, and dietary components affect both microbial populations and their metabolic activities from the early stages of life. Mediterranean diet patterns (MDPs) are used to consume cereals (preferably whole grains), legumes, nuts, vegetables and fruits in high amounts and frequency; MDPs also include small amounts of fish and seafood, low ethanol intake usually in the form of wine, moderate to small amounts of poultry and dairy products, white meat and eggs. The main source of dietary fat for MDPs is olive oil and adequate daily water intake should be guaranteed. MD is noted for its role in the prevention of cognitive decline and the risk of dementia and Alzheimer's disease (AD). In fact, many dietary components, such as vegetables, fruits, legumes, and cereals, prevent oxidative stress and have positive effects on AD. Thus, antioxidant compounds found in some MDPs (eg, polyphenols, vitamins C, E, B12, folate and carotenoids) can prevent the harmful effects of oxidative stress in brain aging and thus reduce the risk of AD [55]. Therefore, MD is inversely related to oxidative stress and lipid peroxidation markers.

Higher adherence to a Mediterranean-style diet is associated with higher intake of polyphenols and other food bioactive substances found in fruits, vegetables, cereals and beverages such as wine, coffee and tea, as well as many antioxidant nutrients [56].

Several studies have pointed to the neuroprotective effect of coffee or caffeine consumption against cognitive impairment and neurodegenerative diseases, which is stronger among women than men [57].

A systematic review and meta-analysis of 74 studies in older individuals found that moderate alcohol intake reduced the risk of cognitive impairment or dementia, whereas heavy drinking was associated with a higher trend for cognitive impairment and dementia risk [59]. In total, these studies show that mild to moderate alcohol consumption can protect against AD and dementia. However, the importance of drinking patterns and specific beverages is not known.

Pre-Probiotics and synbiotics

Probiotics are bacterial species that have a beneficial effect recognized for health when taken in sufficient amounts by individuals. They also successfully compete with potential pathogens and stimulate host immune responses. As these bacteria affect many aspects of human physiology, it is not surprising that recent research has demonstrated significant effects on brain function. In fact, these bacteria produce serotonin (5-hydroxytryptamine) precursor tryptophan, L-3,4-dihydroxyphenylalanine (DOPA) and dopamine precursor

tyrosine and other amino acids such as γ-amino butyric acid (GABA) and glycine that act as neurotransmitters. Research has shown that microbiota strongly influences brain activity and thus behavior [60].

Probiotics can alleviate neuro-psychiatric disorders through hormonal and neuro-chemical mechanisms. For example, *B. longum* NCC3001 can normalize murine hippocampal BDNF expression and *L. rhamnosus* (JB-1) can make different arrangements of GABA transcription at different CNS sites. Specific probiotics may have anxiolytic effects in many types of neurobehavioral disorders that show the common neural and endocrine etiology of these disorders. For example, *L. helveticus* R0052 and *B. longum* R0175 may ameliorate both anxiety and depression in rats [53].

Prebiotics are indigestible oligosaccharides that affect the host by selectively stimulating a limited number of bacterial growth and/or activity in the intestine. Prebiotics can be used to improve the growth of specific species with probiotic properties, alter the intestinal microbiota composition in the process, and consequently improve health. In fact, the fermentation products of prebiotics are usually SCFA, and their main health benefits include anti-inflammatory and anti-apoptotic activities and prevention of colorectal cancer and colitis.

The classic prebiotics for adults, FOS, inulin, GOS and lactulose, are found in vegetables such as artichoke, onion, chicory, garlic and leek, all naturally present. Dietary supplementation with these prebiotics increased *Latobacilli, Bacteroides, Lachnospiraceae* and *F. prausnitzii* [61].

Probiotics have a strong therapeutic effect in stress-related gastrointestinal disorders. It has been suggested that probiotics can alleviate neuropsychiatric disorders through hormonal and neurochemical mechanisms. Because of the positive effects of probiotics on neuropsychiatric disorders, a new term "psychobiotics" has been proposed to describe this effect. A psychobiotic is defined as a "living organism that, when taken in sufficient amounts, produces health benefits in patients suffering from a psychiatric illness" [62].

The combination of probiotics and prebiotics is called a synbiotics. Probiotics, prebiotics and/or synbiotics may affect the composition of the intestinal microbiota and possibly increase intestinal epithelial integrity and reduce the pro-inflammatory response, affecting the initiation or progression of the neurodegenerative process.

Polyphenols

Polyphenols have prebiotic-like effects by increasing the growth of beneficial bacteria and preventing the growth of pathogens [63]. The uptake of polyphenols is associated with consumption of fruits such as grapes, apples, pears, cherries and various berries, and contains 200 to 300 mg of polyphenols per 100g of fresh weight [64]. Also, a cup of tea or a large cup of coffee contains about 100 mg of polyphenol. Red wine, chocolate, legumes and nuts also contribute to polyphenol intake.

Flavonoids, a subclass of polyphenols, have been recognized as promising agents that can identify different aspects of synaptic plasticity, resulting in improved memory and learning in both animals and humans [65,66].

Recent research into the pharmacological effects of dietary polyphenols includes neuroprotection, free radical scavenging, antioxidation, apoB and LDL-cholesterol reduction, antiinflammation, carcinogenesis suppression, DNA damage prevention, and the like. features. These properties offer strong potential for the treatment of AD, PD, CVD and cancers.

Regulation of the microbiota composition using polyphenols or other probiotics and prebiotics can help restore bowel balance and establish new therapeutic intervention in neuropathologies. Since brain dysfunctions are associated with dysbiosis of the intestinal microbiota, a stabilization of the microbiota composition may help to partially or completely reverse these diseases.

Micronutrients and vitamins

Essential antioxidant trace elements such as Zinc (Zn), Selenium (Se) and/or insulin sensitizers (Chromium (Cr), Zn) have been deeply involved in the protection of the brain, as reported in numerous studies in animals and humans. Selenoproteins, namely Selenoprotein P

and Glutathione peroxidase, protect brain cells against oxidative stress. A low Se state increases the risk of cognitive decline [56]. Therefore, it can be argued that an optimal Se condition to protect a healthy brain is a potential protector. However, no consistent clinical evidence has been found as to whether Se supplementation is beneficial for the treatment of AD. Zn also has a positive effect on brain health by increasing insulin sensitivity, reducing inflammation and oxidative stress. Cr deficiency increased insulin resistance and oxidative stress [67]. Indeed, in insulin-resistant conditions (T2DM and MetS), increased Cr uptake is associated with improved cognitive functions [68].

Among vitamins, high dietary tocopherol intake is associated with decreased AD or dementia incidence. Mechanisms supporting the relationship between vitamin B and brain are mostly related to homocysteine (Hcy) metabolism, a marker of vitamin B deficiency. Hcy is catabolized by a remethylation cycle mediated by folate and vitamin B12, which provides the methyl group for various metabolic steps. Clinical evidence has shown an association between high plasma (Hcy) and the occurrence of AD and hyperhomocysteinemia has therefore been proposed as an important risk factor for AD [56,69].

Another commonly investigated vitamin is vitamin D. Vitamin D is still insufficient in most populations and especially in the elderly. Some vitamin D receptors are found in the brain and many mechanisms have been identified to support its role in the brain [70]. Balion., *et al.* [71] identified 37 studies that could be included in the meta-analysis. Results based on 8 studies using MMSE showed that participants with 25-hydroxyvitamin D (25 (OH) D) concentrations > 50 nmol/L had a higher MMSE score than < 50 nmol/L concentrations.

W-3 PUFAs

Long chain omega-3 (w-3) PUFAs, EPA and DHA, have been associated with the maintenance of the integrity and function of neuronal membranes and the reduction of brain inflammation [72]. For example, DHA, an important component of phospholipid cell membranes, can alter the amyloid precursor protein (APP), thereby reducing amyloid formation and increased clearance, the main component of AD plaques.

Observational evidence focused on the relationship between long-chain w-3 PUFA uptake or w-3 PUFA status and cognitive functioning, cognitive decline, or dementia. More than 30 studies have been conducted and the majority of studies have shown beneficial relationships [73].

Conclusion

Understanding the effect of intestinal microbes on gut-brain axis communication has recently been the subject of important research. In this respect, it has become increasingly clear that brain development and function depend on the variety and structure of the intestinal microbiota and therefore may affect mental health. Evidence is accumulated for the role of intestinal microbiota in age-related diseases such as Parkinson's, Alzheimer's diseases. Large amounts of amyloid, lipopolysaccharides (LPS) and other toxins as a source of intestinal microbiota may contribute to systemic inflammation and disruption of physiological barriers. Bacteria or their products, especially in the elderly, may pass from the gastrointestinal tract and oronasal cavity to the CNS. Bacterial amyloids may be involved in misfolding the prion protein and increasing amyloid deposition. Moreover, intestinal microbiota products may pave the way for microglia that cause an inflammatory response in the CNS; this results in pathological microglial function, ultimately increased neurotoxicity and impaired amyloid clearance.

There is a clear link between the intestinal microbiota and most of the most common chronic diseases, from obesity and diabetes to depression and Parkinson's disease and different types of cancer. Therefore, changing the lifestyle to a healthier one which includes exercise and a healthy diet can reduce the risk for both cardiometabolic diseases and neurodegenerative diseases.

Dietary factors can affect multiple brain processes by regulating neurotransmitter pathways, synaptic transmission, membrane fluidity and signal-transduction pathways.

So that, a better understanding the health effects of nutrition on CNS and the effect of a diet rich in polyphenols, antioxidants, omega 3 faty acids will provide precise information to maintain health and this will provide new opportunities for the development of microbiota-based treatments for neuronal diseases.

As a result, recovery of the intestinal microbiota by dietary intervention and probiotic treatment or fecal microbiota transplantation may be a new therapeutic target for neurodegenerative diseases, and healthy intestinal microbiota maintains brain homeostasis by reducing the level of CNS inflammation, vascular pathology and the aggregations of misfolded proteins.

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Volume 11 Issue 9 September 2019