Opinion Letter

Use of Peptide-Related Substances in Treatments of Neurodegenerative Diseases

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Foreword

Microbial settlement of mammals is an evolution-driven process that modulates host physiology, many of which are related to immunity and nutrient intake. Bacteria - the primary macrophages in the brain - are involved in a myriad of processes as the first line of defense against inflammation and infections, including brain development, brain function, and immune response in the central nervous system. According to these roles, the microbial function is involved in the initiation or developing of multiple CNS diseases, Alzheimer's disease (AD), Parkinson's disease (PD), and even autism spectrum disorder (ASD) and depression. L6Chi Monocytes provide a link between antibiotic-induced changes in microbiota and adult neurogenesis and hippocampus.
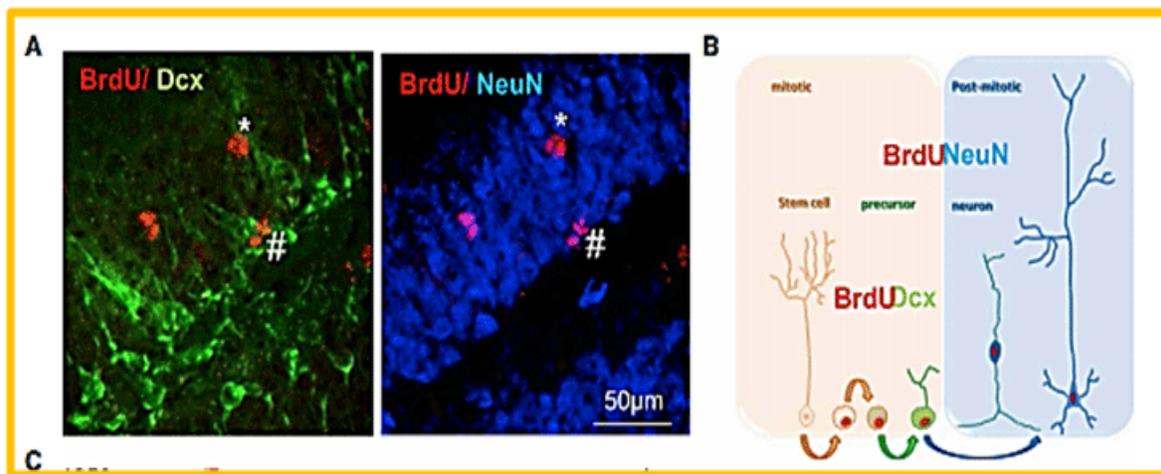
Finding bacteria in the brain is usually terrible news. The brain is protected from the body's pet by the blood-brain barrier and is considered a sterile organ. When its borders are breached, things like meningitis and meningitis can cause. If this is confirmed - the infection has not been completely abolished - the work opens up new avenues of research into microbial and disease.If bacteria actually enter the brain from the intestines while a person is alive, it is a real paradigm shift that the brain had, among other organs, considered sterile. To find bacteria where samples are non-traumatic, non-infectious merely is unpredictable.

The Bacteria may enter the Brain through the Blood-Blood Barrier

There are places where it is not so strong. Brain damage and subsequent neuronal apoptosis are the main courses of dementia and finally death due to the current situation of palliative treatments of the neurodegenerative diseases, Alzheimer's, Parkinson's and many

more. The amyloid hypothesis is currently losing its dominant leading position in the efforts seeking a remedy.

The Ratio of Vaccines / Electrons of Human Microbiota Varies with Age

In humans, the microbiota of the intestines plays a vital role in maintaining host health by providing energy, nutrients and immune protection. Applying current molecular methods is necessary to overcome the limitations of classical culturing techniques in order to obtain an accurate description of the microbiota composition. The report on a comparative assessment of human microbiota from three age groups: infants, adults, and elderly We show that the microbiota of the human intestine passes from puberty to adulthood and is altered as aging: the counts of major bacterial groups Clostridium leptum, Clostridium coccoides, activates, Bifidobacterium, Lactobacillus, Escherichia coli were evaluated by quantitative PCR (qPCR) PCR and is short for "polymerase chain reaction". PCR is a DNA enhancement

method, so if you have one molecule of DNA you can increase it to thousands of molecules within how much it is achieved by using an enzyme called DNA polymerase raw material or "building blocks" of DNA.By comparing profiles to a variety of species, We have seen age-related changes in the human fecal microbe. The microbiota of babies was usually diagnosed at low levels of bacteria. Coccoidea species were highly represented in the microbiota of infants, while elderly subjects exhibited high levels of E. coli and Bacteroidetes. We have seen that the relationship between firms and Bacteroidetes develops during different stages of life. For infants, adults, and elderly, we measured a ratio of 0.4, 10.9, and 0.6, respectively.

Conclusion

It is confirmed that qPCR is a powerful technique in studying diverse and complex stool microbiota. Our work proves that the fecal microbial composition develops throughout life, from a young age to old age [1].

Table : Composition of the human microbiota compared in three age groups

| | n | All-bacteria (a) | TaqMan detection | | | | SYBR-Green detection | |
| | | | Firmicutes | Firmicutes | | | | Firmicutes |
			C. leptum group (b)	C. coccoides group (b)	Bacteroides/ Prevotella group (b)	Bifidobacterium genus (b)	E. coli (b)	Lactobacillus/ Leuconostoc/ Pediococcus group (b)
Infant	21	10.7 ± 0.1 (A)	-3.2 ± 0.4 (A)	-3.2 ± 0.4 (A)	-1.5 ± 0.3 (A)	-0.6 ± 0.2 (A)	-1.5 ± 0.3 (A)	-3 ± 0.2 (A)
Adult	21	11.5 ± 0.1 (B)	-0.7 ± 0.1 (B)	-1.2 ± 0.1 (B)	-1.5 ± 0.1 (AB)	-2.3 ± 0.3 (B)	-3.8 ± 0.1 (B)	-3.9 ± 0.3 (AB)
Elder	20	11.4 ± 0.1 (B)	-1.1 ± 0.1 (C)	-1.8 ± 0.1 (A)	-1 ± 0.1 (A)	-2.3 ± 0.3 (B)	-2.4 ± 0.2 (C)	-4.2 ± 0.2 (B)

n represents the number of samples in each group.
(a) All-bacteria results obtained by qPCR were expressed as the mean of the log_{10} value ± SEM.
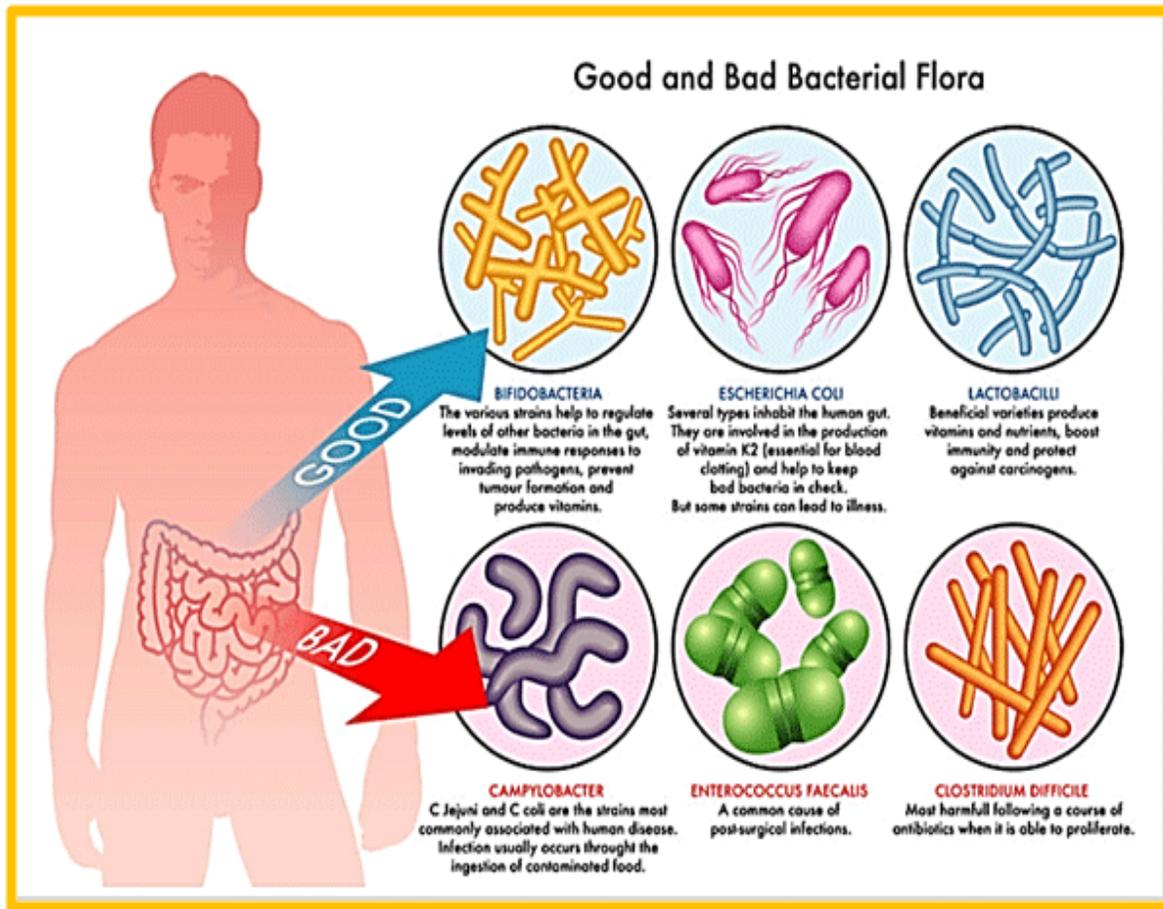(b) Results were expressed as the mean of the log_{10} value ± SEM of normalized data calculated as the log of targeted bacteria minus the log of All-bacteria number.
The non parametric Wilcoxon test was performed.
Data not sharing the same letter within a column are significantly diferrent at $p < 0.05$.

The results illustrate measurable progress of bacterial species and colonize the human digestive system at various stages of life. This progression is observed and easily quantified using qPCR to assess the number of bacteria belonging to the essential dominant subdominant groups of human microbiota and stool. The ratio of firms/electrons increases from birth to adulthood, and changes with advanced age. This ratio appears to be relevant in highlighting differences between

infants, adults, and the elderly. This can be related to changes that include bacterial profiles at different stages of life. Results also indicate some patterns and transition points in the compositional changes in gut microbiota with age. In addition, the transporter property prediction results suggest that nutrients in the gut might play an essential role in changing the gut microbiota composition with age [2].

Good and Bad Bacterial Flora

BIFIDOBACTERIA
The various strains help to regulate levels of other bacteria in the gut, modulate immune responses to invading pathogens, prevent tumour formation and produce vitamins.

ESCHERICHIA COLI
Several types inhabit the human gut. They are involved in the production of vitamin K2 (essential for blood clotting) and help to keep bad bacteria in check. But some strains can lead to illness.

LACTOBACILLI
Beneficial varieties produce vitamins and nutrients, boost immunity and protect against carcinogens.

CAMPYLOBACTER
C Jejuni and C coli are the strains most commonly associated with human disease. Infection usually occurs throught the ingestion of contaminated food.

ENTEROCOCCUS FAECALIS
A common cause of post-surgical infections.

CLOSTRIDIUM DIFFICILE
Most harmfull following a course of antibiotics when it is able to proliferate.

Research in mice and humans suggests that intestinal bacteria can affect the structure of blood vessels in the brain and can be responsible for producing defects that can lead to stroke or epilepsy. The study, reported in Nature, adds to the emerging picture that connects bacteria and digestive disorders. Cerebral anomalies (CCM) are clusters of dilated, thin blood vessels that can lead to seizures or strokes when blood leaks into the surrounding brain tissue. A team of scientists from the University of Pennsylvania has studied the mechanisms that cause CCM vulnerability to form in genetically modified mice and have shown an unexpected link to intestinal bacteria. When bacteria were eliminated several lesions were greatly diminished.

Study Regarding Microbiome and Dementia

From this study, he hopes to learn if and how the abdominal microbiome composition, intestinal permeability and inflammation in patients with dementia are interrelated. Dysbiosis can lead to increased intestinal permeability, translocation and bacterial inflammation that may affect pathogenesis and progression of dementia. The new aspect of the study will be to understand the relationship between the composition of intestinal microbial, intestinal invasion and the occurrence of dementia. This will help to better understand the pathogenesis of dementia and lead to the development of novel therapeutic strategies. If the hypothesis is correct, the study will be the basis for the development of new treatment options for dementia. During aging, the microbial composition of the intestines undergoes changes. There was a decrease in diversity, loss of taxis and increased phthalate batteries. Diet and place of residence play a vital role in microbiome design. Aging is also associated with inflammation which is often referred to as "inflammation" associated with increased intestinal permeability, bacteria lining and bacterial translocation. Because the risk factor for developing dementia, especially AD, is getting older, it is very likely that the intestinal axis-brain is critically involved in the development of dementia. Animal studies so far show that AD is associated with changes in the intestinal bacterial composition with a decrease in beneficial, anti-inflammatory genres. Moreover, genetic changes in amyloid genes can affect microbial composition in mice, indicating a vicious circle in AD development. In humans, studies on the composition of microbial intestines in patients with dementia have not been published. However, there is evidence that microbial composition in surgical plates varies in dementia associated with cognitive function. Integration of the microbiome based approach

with the Amyloid beta work. The more updated approach is based on the Gut-Brain axis where gut microbiota enter the brain via leaky gut and damaged BBB, causing inflammation [3], over activity of Galia cells, infection and mechanical or other cellular damages leading to neuronal cell death and finally distracting brain operation until the stage of Interception which is contemporarily defined as thesenseof the internal state of the body [4]. Depression is another disease that affects many millions of people. Although its etiology remains poorly understood, it is generally accepted that depression is a multi factorial disorder with numerous interacting systems underlying its pathogenesis. Several clinical observations suggest that dysregulation

of the immune system might also play a role in the development of depression, at least in a subset of susceptible individuals. For example, depression frequently occurs as a comorbidity of medical conditions characterized by a chronic inflammatory component including rheumatoid arthritis, cancer, type 2 diabetes, stroke, obesity, and coronary artery disease. Itencompasses the brain process of combining signals transmitted from the body to specific sub-regions, such as the brain stem, thalamus, sensory insula, and the frontal cortex, which allows for a nuanced show of the physiological state of the body. It is essential to maintain the homeostatic conditions in the body, and perhaps, assistance, self-awareness, is reached.
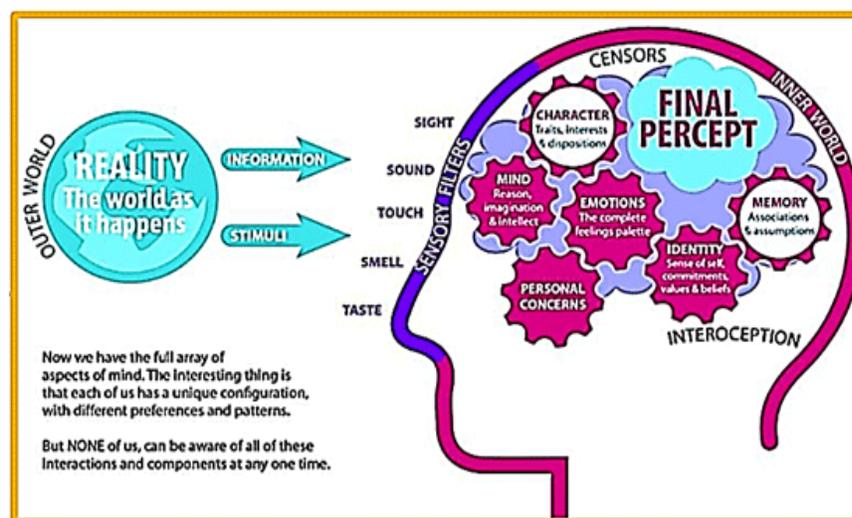

The currently applied attitude opens new avenues for the possible way of combat regarding these malfunctions of our protecting system: treating the brain entering microbiota in the emotional brain, aiming at the prevention of inflammation and subsequent infections of the brain. The penetration of the microbiota into the brain evokes the protective and defense systems. Antimicrobial peptides like the amyloids are presented by the digestive system to combat and eradicate the microbes and prevent inflammation and infection, but such polypeptides can also aggregate and present the damaging and killings of neuronal cells, like synapse damages. The combat strategy must take these effects into consideration [ ].Mainly among these diseases are conditions associated with neurodegenerative disorders associated with dementia, such as Alzheimer's disease (AD), Parkinson's (PD) and stroke. While in the early stages, these circumstances are related to the function of cells in entirely different brain regions, thus affecting different types of neuronal cells; It is likely that the final stages share similar cellular and molecular developments leading to neuronal death and ultimately show clinical symptoms. In this context, various environmental and genetic factors, ranging

from trauma at the top to protein mutations and toxic exposure, may trigger a cascade of cellular events that eventually lead to neuronal death. One active candidate trigger protein, and thus a potential target for therapeutic manipulation is the potent pro-inflammatory / pro-apoptotic cytokine, tumor necrosis factor-α (TNF-α). TNF-α is secreted by the brain resident macrophages (the microglial cell) in response to various stimuli. It has been demonstrated to play a significant role in central nervous system (CNS) neuroinflammation-mediated cell death in AD, PD and amyotrophic lateral sclerosis (ALS) as well as several other CNS complications [ ]. Recently, agents that regulate peripheral TNF-α levels have been shown to be therapeutic agents worthy of use with ethanol and Remicade (Infliximab), both of which show beneficial properties against rheumatoid arthritis and other peripheral inflammatory diseases. Unfortunately, these agents are primarily unable to penetrate the brain-blood barrier, which significantly limits their use of the state of neuroinflammation in CNS. However, thalidomide, a small molecule drug, can inhibit TNF-α protein synthesis, and unlike larger molecules, it is able to cross the blood-brain barrier. Thus thalidomide and its analogs are candidates

for excellent candidates for use in determining the potential value of anti-TNF-α therapies in a variety of diseases termed by inflammation within the nervous system. As a result, we chose to discuss the relevance of untreated TNF-α expression in diseases of CNS, to some extent, the peripheral nervous system. In addition, we consider the utilization of thalidomide derivative agents as anti-TNF-α therapeutic in the definition of neuroinflammation. For many years, most drugs reaching late-stage trials had a single target: misfolded beta-amyloid proteins that comprise plaques. But the pipeline is becoming diversified with drugs that target the biology of aging. We know that aging is the most significant risk factor for Alzheimer's. It can result in a cascade of dysfunction in our brains involving inflammation, mitochondria,

proteostasis, oxidation, cellular stress, and vascular and epigenetic changes. Our 2017 Clinical Trials Report found that 30 of the 126 drugs in trials for Alzheimer's are still targeting beta-amyloid3, but novel targets are gaining ground. Twelve drugs focused on inflammation are in trials. Another 14 targeting aspects of mitochondrial dysfunction and 11 focused on vascular targets have also made it to the clinic. It is therefore a two-way avenue:

1) Combat brain microbiota invasion.

2) Prevent formation of by digestion of natural antimicrobial peptides, Amyloid beta (A).
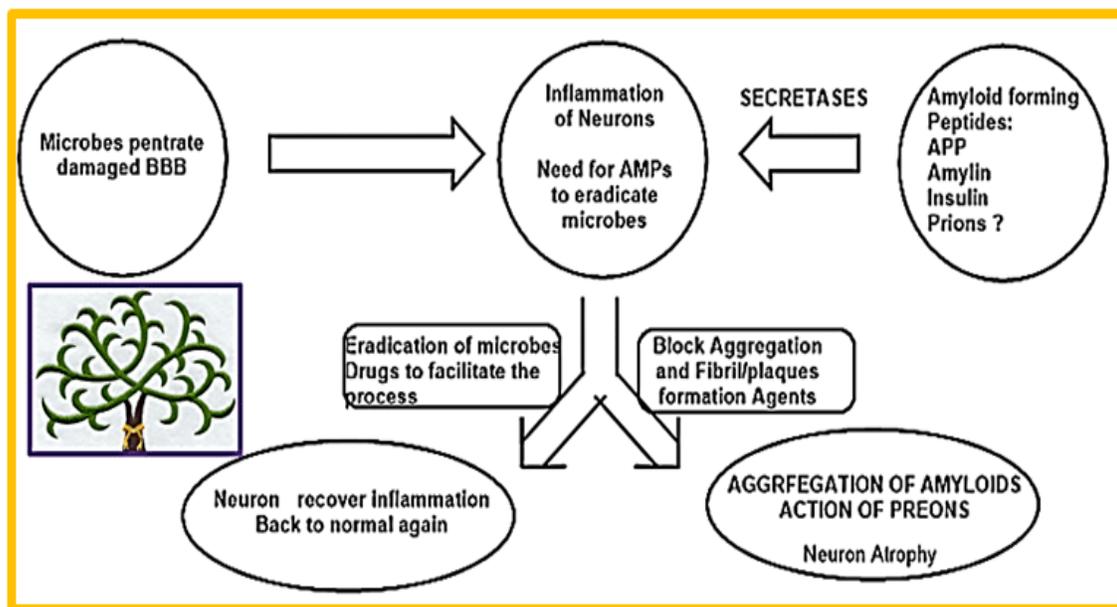
The neurodegeneration is in most cases age dependent, so is the composition of the gut microbiome. Neonatal and young humans pose a different blend of microbes than the elderly. Some researchers estimate that such changes may affect the cerebralmicrobiota and trigger inflammation and infection leading to morbidity. Inflammation causing microbiota, like the Bacteria. Helicobacter pylori might be a proper target to control in the intestine system, preventing it from moving into the brain and causing the damage there. Experiments [9] with mice indicate that such an attitude might be beneficial. However, the antibacterial agent is to become tuned and more selective as compared to the current situation. Some structural modification, like N-methylation might provide tools for such quest [ ]. Infectious microorganisms and their products can, with the invasion of the host, quickly activate the innate immune system, which in turn modifies many brain-mediated functions, involved in thermoregulation, neuroendocrine control. The accumulation of evidence suggests that

changes in intestinal contents can affect the central nervous system (CNS). The My New Gut project, which is currently underway, focuses on the role of microbiology in the development of diet and brain disorders, among others. The purpose of the new microbiota is to understand what the composition of bacteria defines healthy intestines, and how this knowledge can be translated into effective and targeted therapies for diseases in which it appears to play a central role [ ]. At this point in time, it is possible to seek remedy the best way available, although knowledge regarding the microbiota in the brain is limited, effort proceed in the optimal manner possible. In drawing 1, the approach considers the combat with the gut microbiota aside the very well-established research aimed at the amyloid b problem. However, Alzheimer's disease and gut microbiota modifications, the long way between preclinical studies and clinical evidence are still before us [ ]. Recently, agents that regulate peripheral TNF-α levels have been shown to be therapeutic agents suitable for use with ethanol

and Remicade (Infliximab), both of which show beneficial properties against rheumatoid arthritis and other peripheral inflammatory diseases. Unfortunately, these agents are primarily unable to penetrate the blood-brain barrier, which significantly limits their use of the state of neurulation in CNS. However, thalidomide, a small molecule drug, can inhibit TNF-α protein synthesis, and in contrast to larger molecules, it can cross the blood-blood barrier. Thus thalidomide and its analogs are candidates for excellent candidates for use in determining the potential value of anti-TNF-α treatments in a variety of diseases that are eliminated by inflammation within the nervous system. As a result, we chose to discuss the relevance of TNF-α expression treated in diseases of CNS, to some extent, the peripheral nervous system. In addition, we consider the utilization of thalidomide derivative agents as anti-TNF-α therapeutic in the definition of neuroinflammation [ ]. The perceived connections between the microbial of our intestines and the central nervous system (CNS) are thought to be a paradigm shift in neuroscience with possible implications not only for understanding the pathophysiology of stress-related psychiatric disorders but also for their treatment [ ]. Thus, the intestinal microbium and its effect on the host barrier function is located as a critical junction within the brain

axis. The synthesis of preclinical evidence indicates that microbiota of the intestines can alter the development of the brain, it's functioning, and its behavior by the pathological, endocrine and nerve pathways of the intestinal-brain-bowel axis. Detailed mechanistic insights explaining these specific interactions are not currently developed. However, the idea that "leaking leakage" may facilitate communication between the microbiota and these signaling keys and trajectory trajectories has been won. Deficiencies in intestinal permeability can inhibit low-grade chronic inflammation observed in disorders such as depression and intestinal microbial play a critical role in regulating intestinal permeability. In this review we will discuss a possible role played by gut microbiota in maintaining intestinal barrier function and CNS results when it becomes disruptive. We will review both clinical and pre-clinical evidence to support this concept, as well as the key features of the gut microbiota necessary for proper intestinal barrier function. Based on the assumption that there is a connection, an axis between the gut and the brain, Canadian researchers investigated the influence of the eradication of inflammatory-causing bacteria, namely an Helicobacter pylori infection in the intestinal system on the CNS.
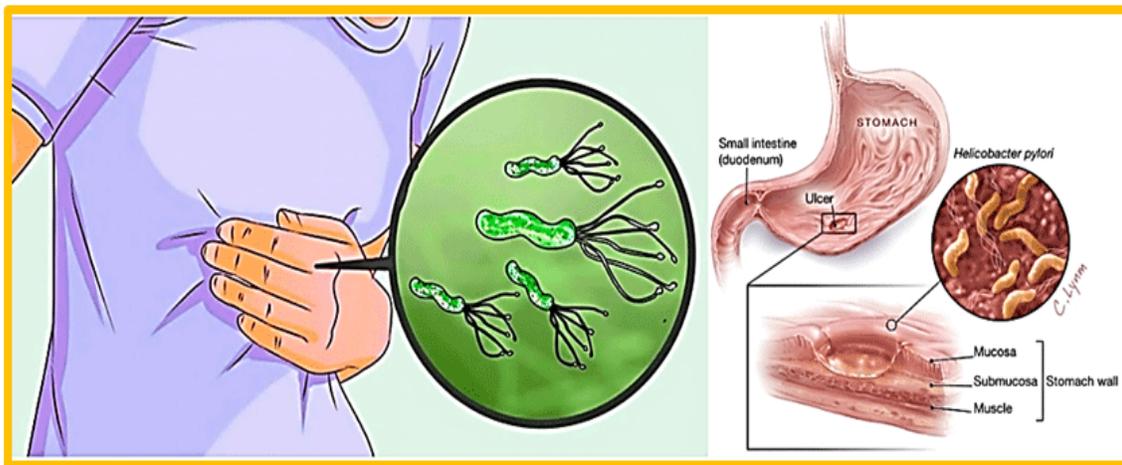
Helicobacter pylori (H pylori) is a common bacterium that exists in millions of people around the world. In the United States, more than 50% of people over the age of 60 are affected. Helicobacter pylori are found in the lining of the stomach. It is known to be responsible for 60% to 80% of gastric ulcers (those occurring in the stomach) and 70% to 90% of duodenal ulcers (those occurring in the first part of the small intestine). The recognition of a link between this bacterium and peptic ulcer disease (occurring in the stomach or duodenum) by Dr. Barry J. Marshall and Dr. John R. Warren, both from Australia, was made in 1983, and they won the Nobel Prize in Physiology Works internally) and medicine in 2005. Now understand that peptic ulcer disease is not caused by stress or by eating foods rich in acid. This is often caused by H. pylori bacteria. The accumulation of evidence suggests that changes in bacterial gut content can affect the central

nervous system (CNS) because there is a continuous flow in and out of the brain during sleep and awakening .Most of these studies concerned the effects of acute inflammation and early CNS changes that occurred prior to the onset of the inflammatory response to infection. The effect of chronic GI inflammation and CNS inflammation has not yet been studied. Previous studies have shown that vaginal sensory exposure is responsible for rapid changes occurring in the brain within a few hours of GI infection [14b]. However, multiple pathways may be involved in communication between the intestines and CNS, in particular during chronic inflammation when pro-inflammatory cytokines may Transferring peripheral immune signals to the central nervous system through sensory nerves, sequential organs, and blood-brain barrier cells [ ].

Alzheimer's Patients Have a Unique Microbiome

Researchers have found that people living with Alzheimer's disease have a unique [13], less diverse, community of intestinal microorganisms than their healthy counterparts. Specifically, the microbiology of people with Alzheimer's disease showed specific increases and decreases in the common intestinal bacteria, especially Bifidobacterium, an essential resident of the human gut. They also tied the abnormal levels of these bacterium families to the number of Alzheimer's proteins in the spinal fluid of the participants.

Gut Microbiome Alterations in Alzheimer's disease
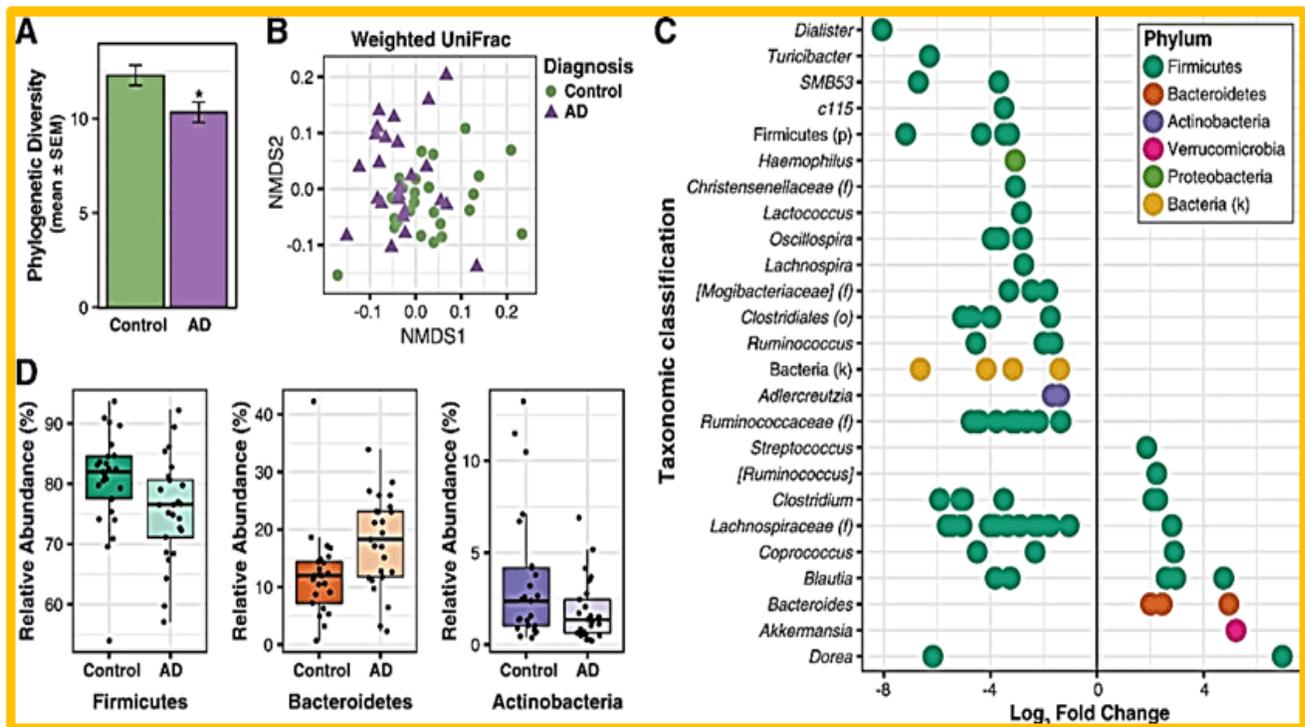
It is suggested that a unique microbiome of people with Alzheimer's disease can contribute to the progression of their disease, through the intestinal axis and brain. These findings in human and mouse models point to the stimulating prospect that restoring a healthy bacterial system can prevent or slow the development of Alzheimer's in populations at risk. Bacteroides, Bifidobacterium, Faecalibacterium, Ruminococcus-These are the names of some 100 trillion bacteria that live and work in your stomach. These microscopic creatures, collectively known as the microbiome, help our body digest food, nutrients, prepare vitamins B and K, and produce immune molecules that fight wound healing. The most impressive role of this busy work force may be, surprisingly, in the brain. While the digestive system and brain feel distant from one another in the body, they are actually connected by a direct 24/7 line of biochemical communication, created by individual neuronal cells and immune pathways. This is called the abdominal-brain axis. In the gut, the bacteria form neuroactive compounds, including 90% of our neurotransmitter serotonin, which regulates our emotions. In turn, the brain can send signals to the digestive system, for example,

to stimulate or suppress digestion. With regard to Alzheimer's disease, the activity of intestinal bacteria may play a significant role. Intestinal plants can produce amyloid that enters the bloodstream and crosses the blood barrier in the blood to reach the brain. One of the symptoms of Alzheimer's disease is the accumulation of amyloid plaque between nerve cells (neurons) in the brain. Lipopolysaccharide, a component of the bacterial cell membrane, can enter the blood of the body and trigger inflammatory processes that contribute to the pathology of Alzheimer's disease. A low antioxidant diet or high in pro-inflammatory fatty acids can facilitate these microbiota results. However recently reported observations lead to the hypothesis that superoxide dismutase [Cu-Zn] also known as superoxide dismutase 1 or (SOD1) antioxidation reflects tau but not amyloid accumulation, which may lead to prooxidant-based neurodegeneration and cognitive dysfunction [ ]. Toward the end of this, scientists are characterized by the bacterial tectonic consistency of fecal samples from participants with and without a diagnosis of dementia due to AD. The analysis revealed that the microbial colon of the AD participants has decreased and the

microbial diversity is different in composition from age control and gender - individuals. There were differences between the prevalence of bacteriological abundance, including a decrease in the number of vaccinations, increased bacteriostasis, decreased bifidobacterium in the microbial of AD participants. Furthermore, people have found a correlation between the levels of general and differentially abundant cerebral fluid (CSF) biomarkers of AD. These findings add AD to the growing list of diseases related to microbial changes in the intestines, and suggest that bacterial communities in the gut may be the target of therapeutic intervention.

Final Remarks

The gut microbiome has been shown to influence various aspects of CNS biology through multiple mechanisms, including the alteration of both neurotransmitter levels (17) and BBB permeability (18). Furthermore, the gut microbiome is closely associated with CNS diseases such as AD, depression, PD, and even autismspectrum disorder (ASD) [15]. However, most of the research so far has shown only that different proportions of genera bacteria are associated with several CNS diseases; Our understanding of specific signaling pathways through which microbial modulation of CNS diseases remains poor. Importantly, microglia may be crucial mediators linking intestinal microbial and CNS diseases, considering that microglia are essential immune cells in the central nervous system, and their dysfunction has been shown to be associated with most CNS-related diseases. Moreover, new studies have discovered that intestinal microbial controls the maturation and function of microglia [16] although the precise mechanisms are yet to be elucidated. Indeed, as summarized by this study, multiple CNS diseases, such as AD, PD, and ASD, that are closely associated with microglia are also related to the gut flora.
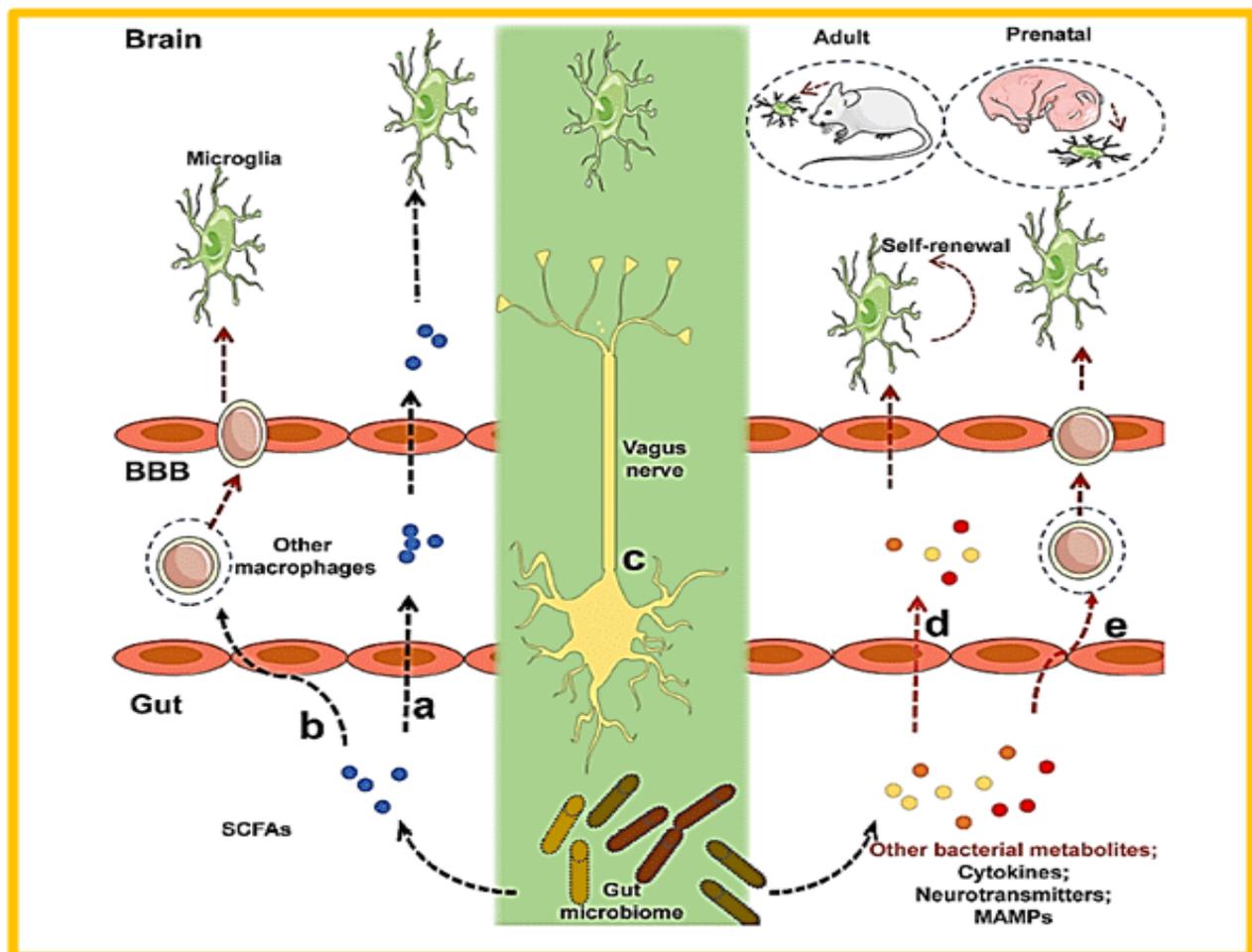
Figure Potential mechanisms by which microbiota in the intestines regulate the maturation and function of microglia. (A) Short-chain fatty acids (SCFA) generated by microbiota in the intestines cross the blood-blood barrier (BBB) through the host's circulatory system, and focus the microglia on regulating their functioning or maturation. (B) Immune cells expressing receptors that identify SCFA can be transferred to the brain via the BBB after signaling using SCFA from bowel plants. (C) The gut microbiota can communicate directly with the resident microglia of the brain through wag nerve. (D) Prior to recognition receptors SCFAs are expressed, microbial or other microbial metabolites associated with molecular patterns (MAMPs) generated by gut microbiota can cross the BBB and target microglia to modulate their function or maturation. (E) Peripheral macrophages that can detect the relevant metabolites or MAMPs can be transferred to the brain using BBB after receiving signals from bacterial or MAMP metabolites released by the intestinal flora. Black lines indicated that the parallel paths were recognized in previous research, and red lines represented an unclear path. Black lines represent known paths and red lines indicate indistinct paths. (Credit ref. [17])

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