A REVIEW ON HEPATITIS IN GUT BRAIN AXIS AND ITS NEURODEGENERATIVE DISEASE

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Abstract
The human gut is home to a complex community of microorganisms, known as the gut microbiome, which plays a crucial role in various aspects of our health, including development, aging, and disease. Recent advances in sequencing technologies and methods that don't require culturing bacteria have allowed scientists to study how these microbes interact with our bodies in greater detail, moving beyond simple correlations.
One significant area of interest is the communication between the gut microbiome and the brain, often referred to as the "microbiota-gut-brain axis." This connection is important because it can influence brain functions and has the potential to affect the onset and progression of neurodegenerative diseases.
In this review, we explore how the microbiota-gut-brain axis operates and its implications for neurodegenerative conditions. Understanding these mechanisms could lead to new ways to address these diseases.
The human gut is home to a diverse group of microorganisms called the gut microbiome, which plays a vital role in our overall health, influencing everything from development to aging and disease. Thanks to advances in sequencing technologies, scientists can now study these microbes more thoroughly, looking at how they interact with our bodies rather than just observing correlations. One fascinating area of research is the link between the gut microbiome and the brain, known as the "microbiota-gut-brain axis." This connection is significant because it can impact brain function and may play a role in the development and progression of neurodegenerative diseases.
In this review, we discuss how the microbiota-gut-brain axis works and what it means for conditions like Alzheimer's and Parkinson's disease. Gaining a better understanding of these interactions could open up new avenues for treatment and prevention.
Key Words: *Gut microbes, gut -liver -brain-axis, antibiotic, hepatic encephalopathy, neurotramitter*

INTRODUCTION
Hepatitis is an inflammation of the liver, and there are five types of viruses that can cause hepatitis. The most common ones are hepatitis A, B, C, and E. Hepatitis D, or hepatitis delta virus (HDV), is unique because it can only exist if hepatitis B is present.
All these viruses can cause acute illness, with symptoms that last several weeks. These symptoms include yellowing of the skin and eyes (jaundice), dark urine, extreme fatigue, nausea, vomiting, and abdominal pain. Recovery can take from several months to a year.
Hepatitis can be contracted in various ways, including contaminated water, casual

contact, or sexual intercourse, making it a risk for everyone.

In the **1960s, Baruch Blumberg** discovered that one type of blood-borne hepatitis was caused by a virus, which was later named hepatitis B virus. His work led to important diagnostic tests and an effective vaccine. Blumberg received the Nobel Prize in Physiology or Medicine in 1976 for this significant discovery.

Different hepatitis viruses?

Scientists have identified five distinct hepatitis viruses, labelled A, B, C, D, and E. While all of these can cause liver disease, they have some important differences.

Hepatitis A (HAV) is primarily found in the faeces of infected individuals and is mostly spread through contaminated food or water. Certain sexual practices can also transmit HAV. Most infections are mild, and most people recover fully and gain immunity against future infections. However, some cases can be severe and even life-threatening. Many people in areas with poor sanitation have been exposed to this virus. A safe and effective vaccine for HAV was developed, with the virus being isolated **by Purcell in 1973**.

Hepatitis B (HBV) is transmitted through contact with infectious blood, semen, and other body fluids. It can spread from infected mothers to their babies during childbirth, as well as from family members to infants in early childhood. Transmission can also occur through contaminated blood transfusions, medical procedures, and injection drug use. Healthcare workers are at risk if they experience accidental needle stick injuries while treating infected patients. A safe and effective vaccine is available for HBV, which was initially referred to as the **"Australia antigen**" after it was discovered in the blood of an Australian Aborigine.

Hepatitis C (HCV) is mainly spread through contact with infected blood, such as through blood transfusions, contaminated medical injections, and injection drug use. Sexual transmission is possible but less common. There is currently no vaccine for HCV. The discovery of this virus was made by scientists **Harvey J. Alter, Michael Houghton, and Charles M. Rice.**

Hepatitis D (HDV) can only infect individuals who are already infected with HBV. Co-infection with HDV and HBV can lead to more severe disease and worse outcomes. Vaccines for hepatitis B also protect against HDV. The hepatitis D virus was discovered in 1977 **by Mario Rizzetto and his colleagues in Turin, Italy.**

Hepatitis E (HEV) is primarily transmitted through contaminated food or water. It is a common cause of hepatitis outbreaks in developing countries and is increasingly recognized as a significant health issue in developed nations. While safe and effective vaccines have been developed for HEV, they are not widely available. Hepatitis E was discovered by **Dr. Mohammad Sultan Khuroo** in Kashmir and is also known as enteric hepatitis.

Hepatic encephalopathy (HE)

Hepatic encephalopathy (HE) is a neurological disorder that occurs in people with liver insufficiency. Although the exact causes of HE are not fully understood, it is primarily treated with medications aimed at reducing ammonia levels, improving neurotransmitter signaling, and modulating the gut microbiota. Patients with liver disease have significantly different gut microbiota compared to healthy individuals, and these changes are linked to the development of HE. The gut microbiota plays a crucial role in several aspects of HE's pathogenesis, including ammonia toxicity, bile acid circulation, the GABA-ergic tone hypothesis, and neuroinflammation. These factors can lead to cognitive and motor issues in patients. Restoring a balanced gut microbiota or using specific probiotics may have positive effects on neurological symptoms in HE.

HE can present a wide range of neurological or psychiatric symptoms, from mild cognitive dysfunction to severe conditions like lethargy, altered consciousness, and even coma, particularly in patients with liver failure or portosystemic shunting.

HE is generally categorized into three types:

- **Type A** occurs due to acute liver failure,
- **Type B** results from portosystemic bypass or shunting, and **Type C** is linked to cirrhosis.

In this condition, liver dysfunction disrupts the body's metabolic processes, allowing substances like ammonia and bile acids to accumulate in the brain due to increased permeability of the blood-brain barrier. This accumulation leads to neurological disorders, while an impaired lymphatic system struggles to remove these harmful substances, potentially worsening the situation.

Symptoms

- **Tiredness**
- **Decreased appetite**
- **Stomach pain**
- **Loose stools**
- **Nausea and vomiting**
- **Pain in the joints**
- **Yellowing of the skin and eyes (jaundice)**
- **Dark-colored urine**

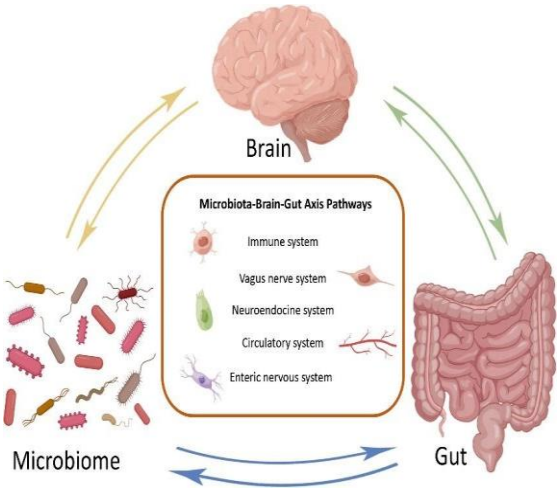
The Gut-Brain Axis

The gut-brain axis refers to the two-way communication between the central nervous system (CNS) and the enteric nervous system (ENS). This connection links the brain's emotional and cognitive centers with the functioning of the intestines. The gut microbiota plays a crucial role in this axis.

The human body is an incredibly complex ecosystem, home to trillions of bacteria and other microorganisms that live in various places, including the skin, mouth, reproductive organs, and intestines. These beneficial microbes are essential for maintaining the body's balance and may also

play a role in the development of several metabolic and mental health disorders.

The interaction between the microbiota and the brain is facilitated through a complex network involving neural, endocrine, immune, and humoral pathways. In clinical practice, there is growing evidence of interactions between the gut microbiota and the brain, especially in relation to central nervous system disorders like autism and anxiety-depressive behaviours, as well as functional gastrointestinal disorders such as irritable bowel syndrome (IBS).



The concept was first highlighted by Fredric Sheikh, who cultured *Escherichia coli* from healthy individuals, while Joshua Lederberg suggested the term **"microbiota**."

There is a symbiotic relationship between our bodies and these microorganisms, meaning they depend on each other for survival. The total weight of these microbes is about 1-2 kg, which is similar to the weight of the human brain. The gut alone hosts around 100 trillion microbes, including bacteria, yeasts, parasites, viruses, and protozoa.
The composition of the microbiota varies throughout different parts of the gut, as illustrated in the diagram below**.**

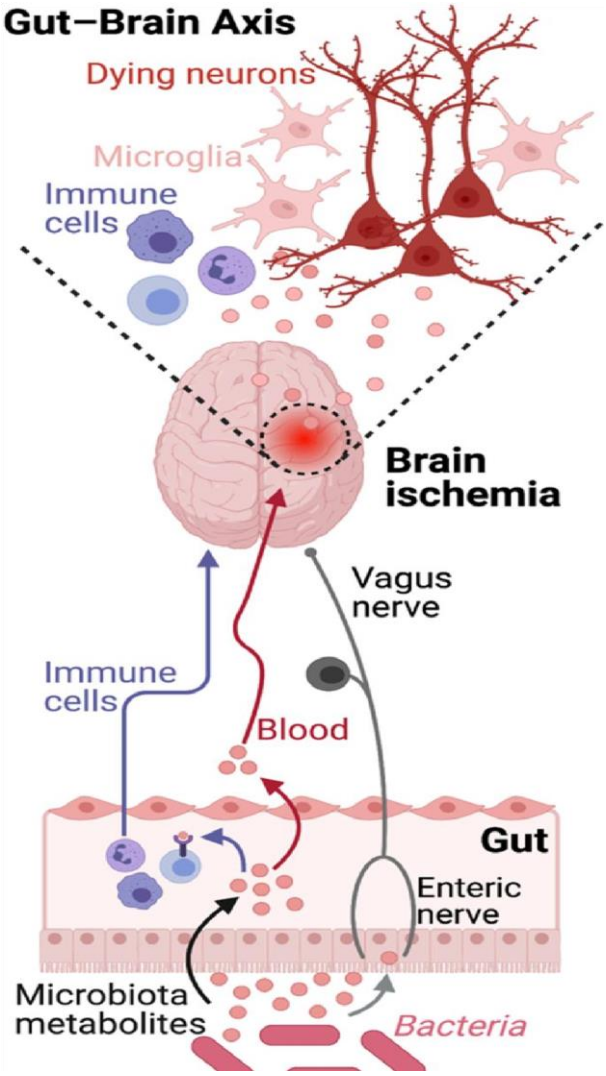
Microbiota and hepatic encephalopathy

Compared to cirrhotic patients without cognitive dysfunction, those with minimal hepatic encephalopathy (MHE) and overt hepatic encephalopathy (OHE) show distinct changes in their gut microbiota profiles. Research by Bajaj and colleagues first highlighted that the differences in stool microbiome composition between healthy individuals and those with cirrhosis were more pronounced when analyzed by hepatic impairment. Specifically, the abundance of *Lachnospiraceae* and *Ruminococcaceae* was significantly higher in the healthy control group. In contrast, *Enterobacteriaceae*, *Fusobacteriaceae*, *Alcaligenaceae*, *Lactobacillaceae*, and *Leuconostocaceae* were significantly lower in healthy individuals compared to cirrhotic patients, regardless of their level of impairment.
Disorders in the intestinal microbiota are characterized by low diversity, an overgrowth of harmful microbes, and a reduction of beneficial ones in patients with hepatic encephalopathy (HE). Compared to

healthy individuals, the intestinal microbiota of cirrhotic patients has an abundance of approximately 75,245 genes based on quantitative metagenomics.

Cognitive and motor disorders in these patients arise from various areas of the impaired central nervous system (CNS). Psychometric tests and diffusion kurtosis imaging (DKI) have been used to evaluate cognitive function and changes in brain structure in patients with liver cirrhosis.

This suggests a potential connection between changes in the microbiota and structural brain impairments in cirrhotic patients. Studies by Ahluwalia and others utilized magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) to explore the relationship between changes in the CNS and gut microbiota in HE. They found that *Enterobacteriaceae* was positively correlated with astrocyte swelling, while certain native taxa were negatively correlated, providing further insight into the understanding of HE.



MICROBIOTA-GUT-BRAIN-AXIS

Microglia are crucial immune cells in the brain and make up about 10% of all brain cells. Once thought to be passive, we now know that they play active roles in brain health, development, and disease.

In a healthy brain, microglia help with:

-Neurogenesis: They support the growth of new neurons.

- Synaptic Pruning: They refine and remove unnecessary connections between neurons.
- Blood-Brain Barrier Integrity: They help keep the barrier that protects the brain intact.
- Myelin Maintenance: They support the health of the protective layers around nerve fibers.
- Cleaning Up: They remove dead cells and debris, keeping the brain tidy.

When the brain faces challenges, like in neurodegenerative diseases, microglia respond quickly. In Alzheimer's disease, for example, they are the first to react to harmful beta-amyloid plaques, gathering around them. Research has shown that microglia are key players in Alzheimer's, with many genes linked to the disease being expressed in these cells.

In Parkinson's disease, studies have found increased numbers of activated microglia, suggesting they are involved in inflammation that may worsen the disease. However, some research shows mixed results, indicating the need for more studies to fully understand their role in Parkinson's.

Microglia are also linked to other neurodegenerative diseases like amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Huntington's disease, where they can contribute to harmful inflammation.

In summary, microglia are essential for a healthy brain but can also become problematic in various diseases, highlighting the importance of ongoing research into their complex roles.

Mechanisms of microglial activation

Microglia are important immune cells in the brain, making up about 10% of all brain cells. They used to be seen as passive, but we now understand that they actively support brain health, development, and play a role in diseases.

In a healthy brain, microglia help with:

- Growing New Neurons: They assist in creating new brain cells.
- Refining Connections: They help strengthen important connections between neurons and remove the ones that aren't needed.
- Protecting the Brain Barrier: They help maintain the protective barrier that keeps harmful substances out of the brain.
- Maintaining Myelin: They support the protective layers around nerve fibers, which are crucial for proper communication between neurons.
- Cleaning Up: They remove dead cells and other debris, keeping the brain clean and functioning well.

When the brain encounters problems, like in neurodegenerative diseases, microglia quickly respond. For instance, in Alzheimer's disease, they are among the first to react to toxic betaamyloid plaques, gathering around them. Research shows that

microglia are crucial in Alzheimer's, as many genes related to the disease are found in these cells.

In Parkinson's disease, studies have shown that there are more activated microglia, indicating they might contribute to inflammation that can worsen the disease. However, some studies have produced mixed findings, highlighting the need for more research to fully understand their role in Parkinson's.

Microglia are also linked to other neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Huntington's disease, where they can cause harmful inflammation.

In short, while microglia are essential for keeping the brain healthy, they can also become problematic in various diseases, which is why ongoing research into their complex roles is so important.

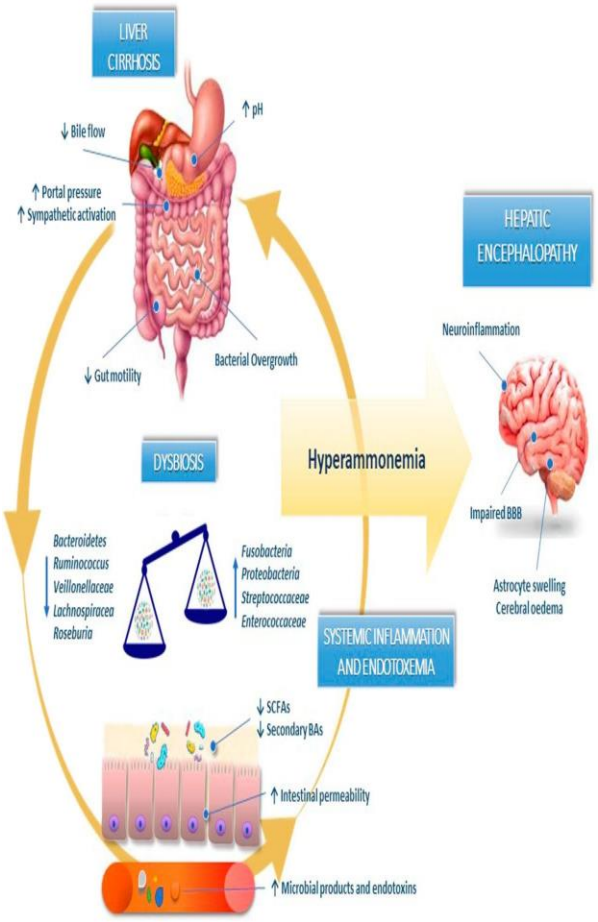
From the Ammonia Hypothesis to the Gut-Liver-Brain Axis

Neurological issues and cognitive decline related to liver problems are often caused by substances in the blood that disrupt the blood-brain barrier. Since the late 1800s, ammonia has been identified as a major factor in the development of hepatic encephalopathy (HE), particularly after observations in dogs with certain liver conditions.

Ammonia mainly comes from the gut as a byproduct of breaking down proteins, amino acids, and bacterial activity. Other organs, like the brain and kidneys, also contribute to ammonia production by processing glutamine. Under normal conditions, the liver effectively removes about 85% of ammonia from the blood coming from the gut, converting it into urea, which is then excreted through the kidneys and intestines. Only a small amount (about 15%) makes it into the rest of the bloodstream.

When liver function is impaired or if there are problems with blood flow or urea cycle enzymes, ammonia can build up in the blood, leading to hyperammonemia. Additionally, excessive ammonia production in the gut can enter the brain, where brain cells called astrocytes help remove it by turning it into glutamine.

Furthermore, a lack of certain beneficial bacteria that produce short-chain fatty acids and convert primary bile acids into secondary ones can worsen gut imbalances and compromise the intestinal barrier. This complex interaction between liver health, ammonia levels, and gut health is crucial for understanding the impact on brain function in liver disease.



GUT MICROBIOTA IN LIVER CIRRHOSIS

Culture-independent Studies on Gut Microbiome in Human Cirrhosis

first characterstic fecal microbial communities in patients with liver cirrhosis using pyrosequencing of the 16s rRNA V3 region ' compared to healthy individual ,cirrhotic patients had lower microbial diversity, as estimated by the Shannon diversity index ,and changes in the intestinal microbial community composition both in terms of phyla (with a marked decrease in the relative abundance of bacteroidetes and enrichment in proteobacteria and fusobacteria) and families (enrichment in enterobacteriacease, pasteurellaceae,streptococceae, veillonellaceae and depletion in lachnopiraceae.

INTESTINAL BACTERIA METABOLITES IN THE GUT–BRAIN AXIS

Ammonia

Hyperammonemia patients with or without cirrhosis have a motor and cognitive dysfunction, suggesting that ammonia affects the brain function through underlying mechanisms . Ammonia-induced central nervous system toxicity is the main mechanism of HE. Excessive production of ammonia by gut bacteria such as S. salivarius contributes to increased ammonia levels in the blood and astrocyte edema .

The primary therapeutic approaches of hyperammonemia include reducing ammonia production and promoting ammonia metabolism . Some studies have reported that hyperammonemia can be reduced by modifying intestinal microbiota. Bacillus Lactis consumes intestinal ammonia and increases overall survival in chronic and ALF mice. Fecal microbiota transplantation (FMT) was shown to attenuate hyperammonemia in HE animal models, which is an accessible and useful treatment option for patient Shen et al. modified intestinal microbes to reduce urease activity, and transplanted them into the intestines of mice with liver injury. There

was a significant reduction in mice morbidity and mortality. Moreover, Kurtz et al. modified the oral probiotic Escherichia coli nissle 1917 in order to create a strain (SYNB1020) that produces l-arginine and consumes NH3 in the vitro system.

Bile Acids

Bile acids promote lipid digestion as well as absorption andmodulate cellular metabolic activities by binding nuclear receptor, including Farnesoid X Receptor (FXR), Pregnane X Receptor (PXR), Vitamin D Receptor (VDR), and the Glucocorticoid Recptor (GR) .

Serum bile acids are elevated during cirrhosis. In an HE animal model, activated apical sodiumdependent BA transporter (ASBT) was shown to promote intestinal bile acid reabsorption, which contributed to increased serum bile acid levels . However, the homeostasis of the bile acid pool has an intricate connection with intestinal bacteria. Fecal bile acid profile is modulated by gut microbiota in cirrhosis.

Chenodeoxycholic (CDCA) and Enterobacteriaceae show a strong positive correlation. Meanwhile, Ruminococcaceae and Deoxycholic acid (DCA) had a positive correlation. After treatment with rifaximin, Veillonellaceae, the ratio of primary and secondary BA levels decreased in six early cirrhotics.

Short-Chain Fatty Acids

Short chain fatty acids produced by intestinal microorganisms, including butyrate, propionate and acetate, protect the integrity of the intestines and reduce intestinal inflammation.

Butyrate, as the main component of SCFAs modulates protein tight junctions to enhance gut barrier function. Its abnormal levels are associated with liver disease severity SCFAs can cross the BBB; therefore, they play a regulatory role in the gut–brain axis . In healthy individuals, Ruminococcaceae and Faecalicatena fissicatena are positively correlated with SCFAs, which are both, however, decreased in cirrhosis patients. SCFAs provide energy for colonic epithelial cell metabolism. However, the ability to convert carbohydrates into SCFAs is diminished in cirrhosis patients. There is a further reduction of SCFAs in cirrhosis with HE. Butyrate has a negative correlation with inflammatory markers and serum endotoxin. SCFAs bind the G-protein-coupled receptor 43 (GPR43) to promote the regression of inflammation. Furthermore, SCFAs down regulate system inflammation and regulate neutrophils, macrophages, and other immune cells . They also have a strong anti-inflammatory effect on microglial and astrocyte models in vitro; therefore, SCFAs may have some potential for regulating neuroinflammatory processes.

Neurotransmitter

Gamma-Aminobutyric Acid

GABA is an important bioactive compound and a crucial inhibitory neurotransmitter in the nervous system. It is mainly produced in the gut by Bifidobacterium and Lactobacillus, although the GABAergic

neurons also produce a small amount of GABA . Lactobacillus can regulate GABA concentrations and the expression of GABA receptors in the CNS through the gut– brain axis. In feces, the increased abundance of Bifidobacterium longum enhances the risk of HE . Elevated GABA levels are associated with physiological and psychological processes in HE. Gut ammonia is considered as an essential factor in elevated GABAergic tone. A study by Cauli et al. found out that hyperammonemia selectively increased the GABAergic tone of the cerebellum, ventral thalamus, and the ventro medial thalamus in hyper ammonemic rats.

The underlying mechanism by which ammonia increases GABA concentration is associated with GABA transaminase activity or neuronal tricarboxylic acid cycle. Moreover, Fried et al. reported that ammonia enhances the release of GABA from enteric glia, subsequently altering intestinal neurotransmission, resulting in intestinal motility disorders and an increase in gut ammonia levels . Studies have also established that changes in GABAA receptor density are up-regulated in hyperammonemia models. In hyperammonemia, elevated GABA concentration and GABAA receptor density correlate to promote CNS disorders, although the expression of the GABAA receptor subunit is not consistent. For instance, GABAA receptor subunit a1 was found to be increased while the alpha-5 subunit was reduced in the hyperammonemia rat model.

Glutamate

Glutamate is an excitatory neurotransmitter that regulates nervous system development through NMDA and AMPA receptors . When ammonia levels increase in the brain, glutamate binds ammonia, forming glutamine under the catalytic activity of glutamine synthetase. Accumulation of glutamine and ammonia is associated with brain edema. Studies have found that the extracellular concentration of glutamate increases due to abnormal uptake, transport and release of glutamate. Learning and memory impairment is associated with the abnormal glutamate-NO-cGMP metabolic pathway in the brain.

5-Hydroxytryptamine

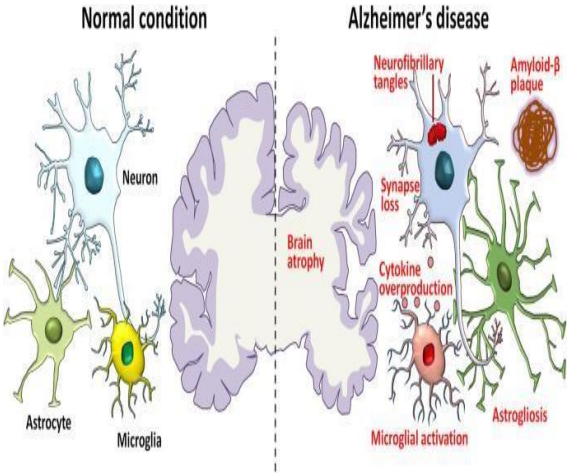
Gut tract is the leading site for 5-HT synthesis. High colonic and blood 5-HT levels are associated with specific gut microbiota metabolites, although the mechanism of 5-HT synthesis that is regulated by microbiota has not been established. Indigenous spore-forming bacteria (Sp) from mouse and human microbiota act on colonic entero chromaffin cells (ECs) to produce 5-HT. Moreover, probiotics can stimulate the gut–brain axis and increase 5-HT and serotonin transporter (5-HTT) expression, which may promote brain development and function. Dysfunction of 5-HT receptor and excess serotonergic brain activity is involved in HE development.

MICROBIOTA–GUT–BRAIN AXIS IN NEURODEGENERATIVE DISEASES

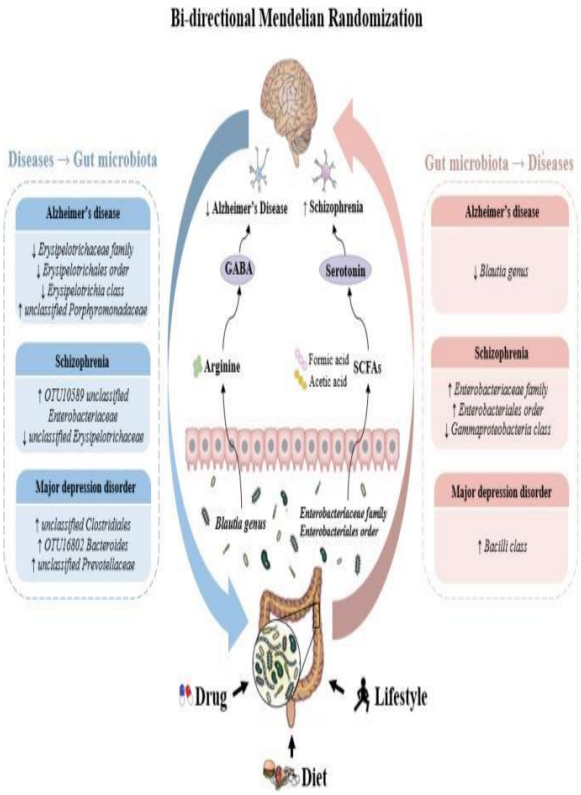
Interaction

between gut microbiota and microglia The interaction between microglia and gut microbiota begins early in life. A recent study demonstrated that early-life admin istration of a broadspectrum antibiotic cocktail led to altered microglial morphology and myelin-related gene expression in adolescent mice, accompanied by anxiety-like and compulsive-like behaviors. Throughout the host lifespan, the gut microbiome provides essential signals to microglia during health and disease. Notably, among the neuronal and glial cells, microglia are the most vulnerable to alterations in the gut microbiome.

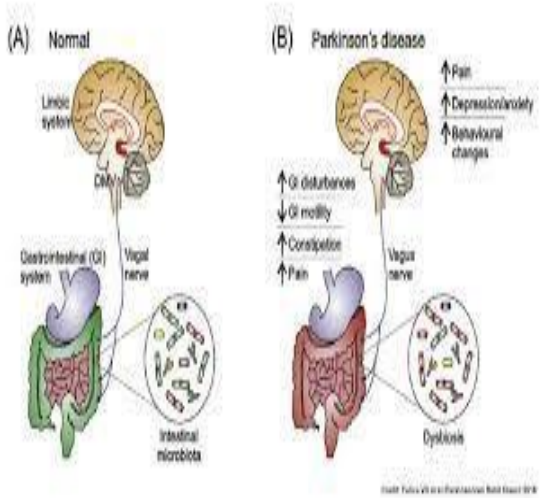
Alzheimer's disease.



Accumulating evidence has demonstrated the interaction between gut microbiota and microglia in AD. In the triple transgenic AD (3xTg-AD) mouse model, the development of AD pathologies, including Aβ plaque, hyperphosphorylated tau, synaptic dysfunction, and microglial activation appears to be influenced by the gut microbiome. This is evident as SPF 3xTg-AD mice exhibit greater AD pathologies compared to GF 3xTg-AD mice. Importantly, FMT from AD patients to GF 3xTg-AD mice restored the main AD pathologies and microglial activation.196 Similar findings have been reported in GF and antibiotic-treated amyloidogenic APP/PS1 mice.54,197–199 It was reported that GF condition confers protection against Aβ pathology and microglial activation in APPSWE/PS1L166P (APP/PS1-21) mice. However, this protection was diminished following FMT from 12-month-old conventionally raised APP/PS1-21 mice to 4-month-old GF APP/ PS1-21 mice.198 Similar trends were also observed in APP/PS1-21 following gut microbiota depletion using long-term (5-week) and short-term (7-day) antibiotic treatment.54,197 Long-term perturba tion of gut microbiome using antibiotic cocktail resulted in reduced Aβ deposition, reduced plaque-localized microglia and altered transcriptional profile of microglia (increased homeostatic microglial genes and decreased MGnD genes) in 7-weekold male APP/PS1-21 mice. Interestingly, these effects were absent in female mice, suggesting potential sexual dimorphism in their responses to gut microbiome manipulation.



Parkinson's disease



Although GI symptoms and gut microbiota alterations are common in PD patients during the disease course, the underlying mechanisms linking the gut microbiome and PD have only been unveiled recently. The first corroboration arises from the study by Sampson et al., which demonstrated that the development of α-synuclein pathology, microglial activation, and motor deficits in α-synuclein-overexpressing (ASO) mice appear to be influenced by the gut microbiome. This is evident as SPF ASO mice exhibit greater PD pathologies compared to their GF and antibiotic treated counterparts. Importantly, FMT from PD patients to GF ASO mice restored the main disease features, including α-synuclein mediated motor dysfunction.s In another study, transgenic rats overexpressing α-synuclein displayed progressive gut dysbiosis with aging, whereas a short-term antibiotic treatment mitigated α synuclein expression in the forebrain. Furthermore, FMT from 1 methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)treated mice induced motor impairments and neurotransmitter loss in healthy mice. Conversely, FMT from healthy mice ameliorated gut dysbiosis and PD pathologies in MPTPinduced mice, including gut inflammation , glial activation, neurotransmitter abnormalities, and motor dysfunction. In addition, the development of GI dysfunction and motor symptoms following chronic rotenone administration occurs only in conventionally raised mice, but not in GF mice. These studies substantiated the significance of the

microbiota–gut–brain axis in the pathogenesis of PD.

Huntington's disease.

HD is an autosomal dominant neurode generative disease caused by a CAG repeat expansion in the huntingtin (HTT) gene. This results in misfolding and accumulation of mutant huntingtin protein in brain cells, including neurons, microglia, and astrocytes. In addition to motor, cognitive, and psychiatric abnormalities, HD patients experience a range of GI disturbances, including nutrient deficiency, diarrhea, and unin tended weight loss. However, it was only recently that gut dysbiosis has been revealed in preclinical HD models and HD patients, and studies examining the interaction between gut microbiota and microglia remain absent. The initial evidence of gut dysbiosis emerged from the R6/1 transgenic mouse model of HD. A notable difference in gut microbiota composition was observed between R6/1 mice and wildtype (WT) mice at 12 weeks of age (early disease stage), which coincided with the manifestation of motor deficits and weight loss. Gut dysbiosis and intestinal barrier impairment were also detected in R6/2 mice.

EFFECTS OF CLINICAL TREATMENT ON THE INTESTINAL METABOLOME IN HEPATIC ENCEPHALOPATHY

Treatments for HE target disease causing agents, control infections, reduce absorption of intestinal ammonia, and correct the metabolic dysfunction caused by liver diseases. Several drugs, including antibiotics and laxatives, are used to treat HE. Probiotics and

other drugs are also used in clinical practice. Clinical therapeutic drugs may or may not alter the intestinal metabolome to achieve therapeutic effect. We discuss the effects of several commonly used drugs on the intestinal microbiota of HE patients.

THERAPY

Given the fundamental role of gut microbiota alteration in HE development, it is not surprising that most therapeutic strategies recommended by current guidelines primarily target gut microbiota or their bioproducts.

Lactulose

Lactulose, a synthetic non-absorbable disaccharide, is part of the therapeutic armamentarium to treat HE since its first trials in the 1960s . Behind the cathartic effect that reduces the contact time between luminal contents and the intestinal mucosa, lactulose lowers colonic pH creating a hostile environment for urease-producing gut flora and stimulating growth-acid-resistant, non-urease producing species. Furthermore, it reduces the absorption of ammonia by non-ionic diffusion. In 2014, the European and American. Associations for the Study of the Liver (EASL/AASLD) published a joint practice guideline in which they recommended lactulose as the treatment of choice for OHE and secondary prevention after an index event .

Interestingly, patients who responded to lactulose treatment had a favorable modification of bacterial taxa. A recent

randomised controlled trial conducted in patients with HE found significant differences between lactulose responders and non-responders in Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria .

The apparent disconnection between reduction in blood ammonia and microbial changes, found in some studies, could be related to microbial changes below the detectable threshold or the relatively low sample size of the studies.

Probiotics

The World Health Organization defines probiotics as "live microorganisms that confer a health benefit on the host" . Probiotics, with their pleiotropic effects, may be helpful to treat HE for their ability to suppress bacterial urease activity, lower ammonia absorption through pH reduction, modulate the immune response, and reduce intestinal permeability and uptake other toxins (indoles, oxindoles, phenols, and mercaptans).

Furthermore, probiotics enhance the hepatic clearance of ammonia and other toxins by lowering gut-derived inflammatory signalling and oxidative stress in the liver (Solga, 2003).

The most utilised probiotics include strains of lactic acid-producing bacilli (i.e., Lactobacillus and Bifidobacterium), non-pathogenic strains of E. coli (i.e., E. coli Nissle 1917), Streptococcus salivarius, a non-pathogenic strain of yeast (i.e., Saccharomyces boulardii), and a mixture of strains like VSL#3, which consists of eight different probiotic strains: Streptococcus salivarius subp. thermophilus, Bifidobacterium breve, B. longum, B. infants, Lactobacillus acidophilus, L. plantarum, L. paracasei, and L. bulgaricus.

Antibiotics

Rifaximin is a common antibiotic used to treat patients with HE. It improves hyperammonemia, endotoxemia, and cognitive dysfunction. Other antibiotics such as neomycin are not recommended because of their side effects . Although rifaximin has bactericidal and bacteriostatic effects, it does not change the abundance of dominant intestinal bacteria in HE patients. In addition, it does not control the abundance of Gram negative bacteria. It decreases blood endotoxin levels through unknown mechanisms. It is postulated that it can regulate the metabolism of intestinal bacteria or stabilize intestinal barrier functions .Other studies have shown that it has immunomodulatory effects as it reduces inflammation by regulating bacteria. Rifaximin was shown to improve the immune system in 59% of MHE patients .

Fecal Microbiota Transplant:

FMT is an emerging treatment approach that is aimed at rebuilding intestinal microbiota to treat diseases, and is gradually being generalized for the treatment of various intestinal dysfunction diseases, such as inflammatory bowel disease (IBD)
. A few animal experiments have shown that FMT has obvious protective effects on

CCL4-induced ALF rats . This beneficial effect is not only observed in the improvement of cognitive function, but can also improve the markers of disease activity associated with the gut-liver-brain axis disorder. FMT was shown to significantly reduce neuroinflammatory responses in CCL4-induced cirrhotic mice.

It also provided effective protection in HE by restoring normal intestinal permeability and improving liver damage indicators. TOLL-like receptors are important mediators of inflammatory responses. Hepatic TLRs and serum ammonia levels were found to be significantly down-regulated in cirrhosis rats after FMT . Although clinical trials of FMT are ongoing, we discussed its effectiveness and safety in clinical treatment based on the published results.

In patients with HE, FMT may reduce ammonia synthesis by shifting the gut microbiota composition to bacterial taxa low in urease, diminishing ammonia uptake by re-establishing intestinal barrier integrity, and increasing ammonia clearance by improving liver function. Earlier studies on animal models correlated FMT with lower ammonia production in the gut, reduced risk of encephalopathy, and protective effect against carbon tetrachloride-induced acute hepatic dysfunction . Interestingly, if the donor was a patient with HE, FMT results in neuroinflammation and microbial ecological disorders (Liu et al., 2020). In a paradigmatic case report, Kao et al. first demonstrated that serial FMT in a patient with mild HE improved the cognitive function, assessed with Stroop test and inhibitory control test.

Conclusion:

The gut-brain axis plays a crucial role in the interplay between the gut microbiome and brain health, particularly in conditions like hepatitis. Emerging research suggests that liver diseases, including hepatitis, can influence gut microbiota composition and function, which in turn may affect neurological outcomes. This bidirectional communication highlights the importance of maintaining gut health as a potential strategy for mitigating neurological complications associated with liver disease. Future studies are essential to unravel the specific mechanisms involved, ultimately guiding the development of targeted therapies that address both gut and brain health in individuals affected by hepatitis and other liver-related conditions.

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