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Gut Microbiota and Gut-Brain Axis in Health and Disease: A Narrative Review

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Abstract
Microbiota, a composition of trillions of microorganisms, plays essential roles in metabolism, immunity, and gut-brain axis connection. It helps in the digestion and production of valuable metabolites and keeps intestinal integrity intact. A balanced microbiota or eubiosis supports health; dysbiosis causes leaky gut syndrome, systemic inflammation, and chronic diseases.
Therefore, the purpose of this review is to provide an analysis of the microbiota-gut-brain axis (GBA), as well as important microbial metabolites like trimethylamine N-oxide (TMAO), short chain fatty acids (SCFAs), and their implications concerning health and disease states. A comprehensive search of references related to microbiota was conducted on PubMed using

the following search terms: “microbiota, gut-brain axis, dysbiosis, eubiosis, microbiota composition, microbial metabolites”.
Major metabolites such as SCFAs help with the regulation of immune functions, act as protectors of the blood-brain barrier, and are known to support neuroprotection, while deleterious substances such as TMAO find association with cardiovascular diseases.
Dysbiosis in the gut finds association with various chronic diseases such as type 2 diabetes, hypertension, and neurodegenerative disorders. Changes in microbial composition disrupt metabolic processes and provoke systemic inflammation. A better understanding of these mechanisms would facilitate the early detection of diseases based on the recognition of specific bacterial shifts and/or metabolite imbalances. Microbiota-health-improving relationships are still being explored, demonstrating the need for additional studies aimed at developments of specific treatments for disease prevention and treatment.
Keywords: microbiota, gut-brain axis, SCFAs, dysbiosis

1. Introduction

The topic of microbiota and its connection to the human body is widely researched and new connections are still being discovered that can affect the functioning of our body. The microbiota consists of microorganisms, including commensal bacteria, that inhabit the human gastrointestinal tract. An individual's gut microbiome is estimated to contain over 100 trillion bacteria, with their concentration increasing from the stomach to the intestines and colon, reaching approximately 10^{12}–10^{14} bacteria per gram of tissue (Rinninella et al., 2019a). These microbes collectively have a genetic makeup that is 100 times larger than the human genome, and their total mass in the body is estimated to be between 1 and 3 kg (Ley et al., 2006; Turnbaugh et al., 2007).

The gut microbiota plays a crucial role in metabolism by assisting in the digestion of dietary fibers and producing short-chain fatty acids (SCFAs), which serve as an energy source and have anti-inflammatory effects. An estimated 5–10% of our daily energy comes from the fermentation processes carried out by gut bacteria (N I, 1984) . It also provides protective functions by reinforcing the gut barrier through the secretion of mucus, antimicrobial peptides, and immunoglobulin A (IgA). Structurally, it helps maintain intestinal epithelial integrity and supports cell regeneration. The relationship between the human host and gut microbiota is symbiotic, meaning both benefit from each other. The balanced coexistence of beneficial

microbes is known as eubiosis (Barrientos-Durán et al., 2020) This balance is essential for overall health due to the microbiota–gut–brain axis (GBA), a bidirectional communication system linking the gut microbiota and the brain through the enteric nervous system (ENS), vagus nerve, immune system, neurotransmitters, SCFAs, and other pathways (Dinan & Cryan, 2015; Margolis et al., 2021).The opposite condition is dysbiosis, which refers to a disruption in the composition and function of the intestinal microbiota and has a negative impact on the functioning of the body (Weiss & Hennet, 2017) . Dysbiosis can result in a pathological condition known as "leaky gut" syndrome (LGS), characterized by increased intestinal permeability due to a compromised intestinal barrier (Bischoff et al., 2014; Wasiak & Gawlik-Kotelnicka, 2023) . This allows bacterial components, toxic metabolites, and inflammatory factors to enter the bloodstream, with the effects becoming more severe in the presence of dysbiosis (Kinashi & Hase, 2021a). One such component, bacterial lipopolysaccharide (LPS), is detected by Toll-like receptors (TLRs), particularly TLR4 (Vaure & Liu, 2014) . This activation stimulates the release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), IL-6, IL-8, and IL-12, leading to both localized and systemic inflammation (Berkes, 2003; Mu et al., 2017).

In the following article, we will discuss the topic of microbiota, GBA and their selected mechanisms such as Trimethylamine N-oxide (TMAO) and SCFAs and their impact on the functioning of the human body in health and disease.

2. Microbiota development and composition

The development of the microbiota begins in the fetal stage and is significantly shaped by the mode of delivery, whether vaginal or cesarean. Furthermore, its composition is influenced by an infant's diet, especially whether they are breastfed or formula-fed (Pantazi et al., 2023). Any disturbances in microbiota balance during the first 2–3 years of life can adversely affect development and elevate the risk of future health issues (Quigley, 2017)

The composition of the microbiota is highly individualized, yet in healthy individuals, the proportions remain relatively consistent. Around 60% to 80% consists of Firmicutes, 20% to 40% is made up of Bacteroidetes, while Proteobacteria and Actinobacteria account for approximately 5% (Beam et al., 2021; McCallum & Tropini, 2024; Rinninella et al., 2019b). Short-term dietary changes can influence about 20% of microbiota variability, whereas long-term dietary habits have a more significant impact (Leeming et al., 2019). The types of food

consumed shape the growth of specific bacterial species, leading to three primary microbiota enterotypes. The first, dominated by Bacteroides, is commonly associated with the Western diet, which is prevalent in highly industrialized countries and characterized by low fiber and high fat intake. The second, where Prevotella is dominant, is typical of less industrialized regions where diets are richer in fiber and less processed. The third enterotype, with higher levels of Ruminococcus, resembles the first and is found in individuals consuming large amounts of protein and fat (Campaniello et al., 2022; G. D. Wu et al., 2011).

While the microbiota composition is unique to each person, it is influenced by various factors, as presented in Figure 1.

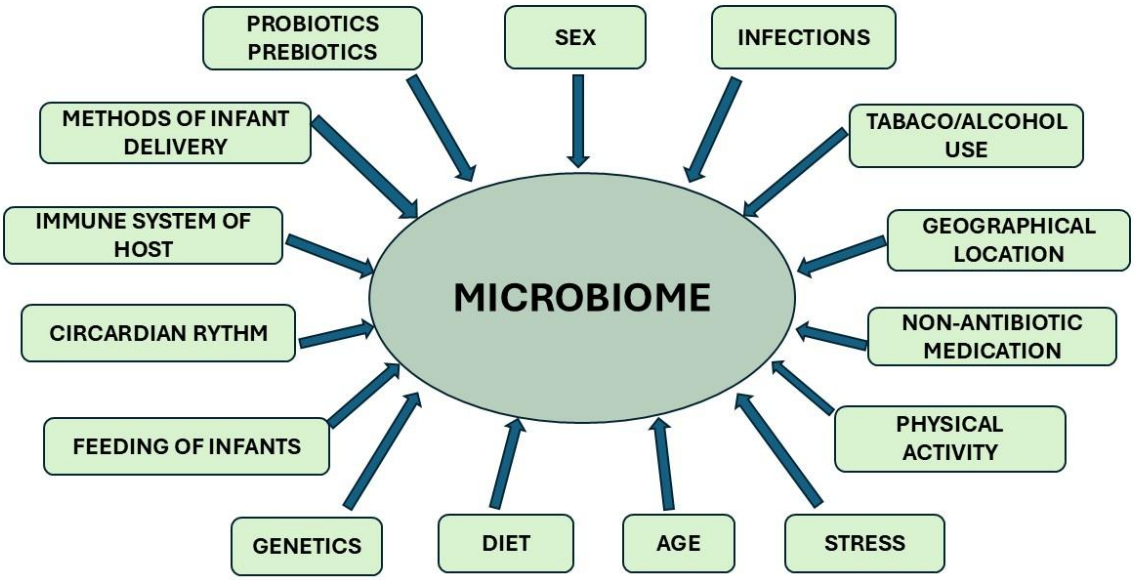

Figure 1. Factors influencing microbiome (Chou et al., 2015; Dominguez-Bello et al., 2016; Dwiyanto et al., 2021; Fitzstevens et al., 2017; Forslund et al., 2015a; Goodrich et al., 2014; Gubert et al., 2020; Hemarajata & Versalovic, 2013a, 2013b; Prakash et al., 2021; N. Qin et al., 2015; Salazar et al., 2023; Voigt et al., 2016; P. Zhang, 2022; Zheng et al., 2020).

3. Gut-brain axis and bacterial metabolites

As previously mentioned, the GBA facilitates bidirectional communication between the human gut microbiota and itself.

Gut secretion, motility, and immune regulation are influenced by both the autonomic nervous system, via the vagus nerve, and the enteric nervous system (ENS), which consists of enteric

neurons and glial cells. This allows the body to independently regulate the composition of the microbiota (Cavin et al., 2020; Furness, 2012). In turn, gut microbes can communicate with the central nervous system (CNS) through neuronal, hormonal, and immune signaling pathways, impacting various bodily functions. Additionally, short-chain fatty acids (SCFAs) such as acetate and propionate, produced by intestinal bacteria, can regulate human gene expression through histone hyperacetylation (Dalile et al., 2019; Martin-Gallausiaux et al., 2021a) . The microbiota influences CNS function by producing neurotransmitters such as acetylcholine, catecholamines, and gamma-aminobutyric acid (GABA), as well as biogenic amines like histamine. Norepinephrine slows gut transit and reduces the frequency of migratory motor complexes. Additionally, it has anti-inflammatory effects and plays a role in behavior and cognition, influencing learning, memory, and attention (Dicks, 2022a; Mittal et al., 2017). Similarly, adenosine exerts local anti-inflammatory and immunomodulatory effects (B. Estrela & Abraham, 2011).

Microbiota also plays a role in modifying tryptophan metabolism (Dicks, 2022b; Rudzki & Maes, 2020a) . Most tryptophan is broken down through the kynurenine pathway, a process regulated by bacterial lipopolysaccharide (LPS) and pro-inflammatory cytokines, which activate the key enzymes indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase. As a result, serotonin production from tryptophan decreases. During inflammation, tryptophan metabolism shifts towards increased kynurenine levels, disrupting its downstream metabolites (TRYCATs), such as quinolinic acid (QUIN) and kynurenic acid (KYNA). This imbalance can harm the central nervous system, as QUIN overstimulates NMDA receptors, leading to excessive excitation, while excessive KYNA, despite its neuroprotective properties, contributes to neurodegeneration and cognitive decline (Kennedy et al., 2017; D. Li et al., 2022; Rudzki & Maes, 2020b).

3.1 SCFAs

Short-chain fatty acids (SCFAs), which are produced through the bacterial breakdown of fibers, have gained significant attention for their beneficial effects on host health. These include acetate, propionate, and butyrate, among others. SCFAs play a key role in modulating immune system activity, regulating appetite, improving calcium absorption, and supporting glucose balance (Martin-Gallausiaux et al., 2021b; Tan et al., 2023). They also help maintain the integrity of the blood-brain barrier (BBB), preventing neurotoxic substances from entering

the brain (Huang et al., 2024). SCFAs are able to cross the BBB and impact early brain development by influencing the production of neurotransmitters like serotonin and dopamine (Srikantha & Mohajeri, 2019). The free fatty acid receptors FFA2 and FFA3, found in different regions of the brain, are activated by SCFAs (Dinan et al., 2015).

Propionic acid (PA) has been shown to support neuroregeneration through mechanisms involving these receptors and the inhibition of class I/II histone deacetylase (HDAC) activity (Hao et al., 2020). Furthermore, SCFAs have neuroprotective effects and, through epigenetic modifications, enhance memory formation and neural plasticity (Mohajeri et al., 2018). In individuals with multiple sclerosis (MS), long-term PA supplementation has been associated with beneficial outcomes, such as reduced relapse rates and slower disease progression. PA also modulates the immune system by increasing the number of functional Treg cells and decreasing Th1 and Th17 cell populations (Duscha et al., 2020). Acetate, on the other hand, is crucial for lipid metabolism and glucose regulation (González Hernández et al., 2019; Hu et al., 2020). In mice, gut microbes convert dietary fructose into acetate, which serves as a source of acetyl-CoA for lipid synthesis (Zhao et al., 2020). Acetate also has anti-inflammatory effects, inhibiting NF-κB activation and reducing the production of pro-inflammatory mediators such as TNF-α (Tedelind et al., 2007). Butyrate is vital for regulating anti-inflammatory responses by modulating the expression of forkhead box protein P3 (Foxp3), which is crucial for inhibiting excessive inflammation (Furusawa et al., 2013). Butyrate has also been shown to stimulate the release of glucagon-like peptide-1 (GLP-1) and peptide YY (PPY) from L cells in the colon. These hormones play a key role in slowing gastric emptying, reducing appetite, enhancing insulin secretion, and inhibiting glucagon release (L. Zhang et al., 2021). Additionally, butyrate helps regulate glucose homeostasis by promoting intestinal gluconeogenesis (De Vadder et al., 2014a). Through a cAMP-dependent mechanism, butyrate boosts the expression of intestinal genes involved in gluconeogenesis (De Vadder et al., 2014b). Furthermore, butyrate supports the integrity of the intestinal barrier by increasing the transcription of Claudin-1. This process is facilitated by the interaction between the transcription factor SP1 and the Claudin-1 promoter, leading to a reorganization of ZO-1 and Occludin on the cell membrane (Wang et al., 2012).

3.2 TMAO

TMAO is mainly generated by the small intestinal microbiota from dietary compounds such as choline, betaine, carnitine, and deoxycarnitine, which are found in abundance in meat, eggs,

and dairy products. Several factors influence plasma TMAO levels, including diet, gut microbiota composition, medication use, and liver flavin monooxygenase activity (Janeiro et al., 2018) TMAO has been linked to cardiovascular diseases (CVC) by enhancing platelet reactivity, elevating the risk of thrombosis, and impairing endothelial function (Boini et al., 2017; Ge et al., 2023a; Zhu et al., 2016) . TMAO is considered a potential biomarker for predicting the likelihood of CVD and the risk of major adverse cardiovascular events (MACE), such as heart attack, stroke, and mortality (Lever et al., 2014; Mente et al., 2015; Trøseid et al., 2015) . Additionally, elevated levels of TMAO precursors like choline and betaine are independently linked to the presence of CVD and poorer outcomes, even after accounting for other cardiovascular risk factors (Tang et al., 2015). Moreover, it stimulates the activation of the NLRP3 microglial inflammasome, worsening neurological damage in ischemic stroke (Ge et al., 2023b).

4. Impact on immunity and neuroinflammation

Chronic systemic inflammation from LGS can disrupt the hypothalamus–pituitary–adrenal (HPA) axis, which is vital for supplying energy sources such as glucose, amino acids, and free fatty acids to support immune function. This disruption leads to an overproduction of glucocorticoids and catecholamines, causing hypercortisolemia and HPA axis overactivity, which is associated with impaired glucocorticoid receptor function (Misiak et al., 2020; Q. Wu et al., 2020). Moreover, increased intestinal permeability can activate T-cells, which may trigger autoimmune disorders in the gut or other organs if these activated lymphocytes spread (Kinashi & Hase, 2021b).

Systemic inflammation also affects BBB, compromising its ability to regulate the movement of substances, ions, and cells into the brain (Kealy et al., 2020). This BBB disruption has been observed in several psychiatric conditions, including those related to cognitive decline, such as Alzheimer's disease (Daneman & Prat, 2015). Impaired BBB and inflammation contribute to a reduction in the number and function of astrocytes, a type of glial cell (Rudzki & Maes, 2020c) . Astrocytes have TLR4 receptors on their surface, which, when activated by LPS, initiate a heightened proinflammatory response (Sofroniew, 2015) . Additionally, astrocytes are essential for regulating levels of gamma-aminobutyric acid (GABA) and glutamate by reabsorbing these neurotransmitters (Dienel et al., 2020).

An important factor in the role of bacteria in neuroinflammation is the release of outer membrane vesicles (OMVs) by Gram-negative bacteria. These small, spherical structures

carry various cargo molecules, such as LPS, outer membrane proteins (OMPs), lipooligosaccharides (LOS), phospholipids, peptidoglycan (PGN), periplasmic components, and virulence factors like enzymes and toxins (Toyofuku et al., 2019). OMVs from bacteria like Porphyromonas gingivalis or Treponema denticola have been shown to induce pro-inflammatory responses by increasing the production of TNF-α and IL-8 and triggering the secretion of IL-1β. This results in the activation of monocytes and macrophages, causing inflammatory cell death and tissue damage both in vitro and in vivo (Cecil et al., 2017). Another study found that OMVs from H. pylori can cross the blood-brain barrier (BBB) and enter the brain, where they are taken up by astrocytes. This interaction activates glial cells, disrupts neuronal function, and promotes amyloid-β pathology, contributing to cognitive decline (Xie et al., 2023). Furthermore, PGN, a component of bacterial cell walls, can cross the BBB and is recognized by PGN-sensing molecules (PGLYRP2 and NOD1), which are highly expressed in neurons of areas like the prefrontal cortex, hippocampus, and cerebellum. These findings suggest that PGN may directly affect neuronal function (Arentsen et al., 2017; Gonzalez-Santana & Diaz Heijtz, 2020).

5. Changes in microbiota in disease

Disorders in the composition of the microbiota are observed in many disease states such as type 2 diabetes (T2DM), gastroenterological diseases (irritable bowel syndrome, chronic constipation, and gastroesophageal reflux disease), hypertension, cardiovascular diseases, chronic kidney disease, and psychiatric disorders (Denman et al., 2023; Z. Li et al., 2024; Liu et al., 2024; Napolitano et al., 2023; Ohkusa et al., 2019; Rahman et al., 2022; Riedl et al., 2017; Yang et al., 2018). As previously mentioned, this is a condition called dysbiosis, which causes GBA disruption, leading to further dysfunction of the human body. Dysbiosis can be assessed by testing the composition of the microbiota or the levels of specific metabolites such as SCFAs or LPS.

For example, one of the more frequently studied diseases in which dysbiosis has been demonstrated is T2DM, what has been confirmed by a metagenome-wide association study (MGWAS). The microbiota in T2DM showed an increase in opportunistic pathogens like Bacteroides caccae and Escherichia coli, alongside a reduction in butyrate-producing bacteria such as Faecalibacterium prausnitzii and Roseburia species. T2DM patients also exhibited higher levels of mucin-degrading Akkermansia muciniphila and sulfate-reducing Desulfovibrio (J. Qin et al., 2012). Notably, Lactobacillus correlated positively with fasting

glucose and HbA1c, while Clostridium showed negative associations with key metabolic markers. Some researchers suggest that gut microbiome alterations in T2DM may be partially influenced by metformin, which increases Escherichia species while reducing butyrate-producing bacteria (Forslund et al., 2015b).

Similary, dysbiosis has also been noted in hypertension, another civilization disease. A study analyzing the metabolome and metagenome in a cohort of hypertensive, pre-hypertensive, and healthy individuals found that hypertensive patients had reduced microbial richness and diversity, along with a distinct metagenomic profile marked by an overgrowth of Prevotella and Klebsiella. Interestingly, the gut microbiome of pre-hypertensive individuals closely resembled that of hypertensive patients. Moreover, fecal transplants from hypertensive donors to germ-free mice led to increased blood pressure in the recipients, indicating a potential role of gut microbiota in blood pressure regulation (J. Li et al., 2017) . A cohort study of 6,953 Finnish participants by Palmu et al. identified 45 microbial genera linked to elevated blood pressure (BP), with 27 belonging to the Firmicutes phylum (Palmu et al., 2020)Another study found associations between hypertension and 18 genera, including Anaerovorax, Clostridium IV, Oscillibacter, and Sporobacter, with Veillonella notably prevalent in hypertensive patients (Sun et al., 2019).

Dysbiosis also applies to psychiatric diseases such as autism spectrum disorder (ASD). Research has shown a link between specific gut bacteria and ASD. Studies report a higher prevalence of Clostridium in ASD patients compared to the general population, along with a possible increase in Lactobacillus in their fecal samples. Additionally, individuals with ASD exhibit elevated levels of bacterial families such as Ruminococcaceae, Enterobacteriaceae, Pasteurellaceae, and Lachnospiraceae in their digestive tract (De Angelis et al., 2015; Finegold et al., 2012) . Moreover, Research suggests that children with autism have lower overall SCFAs levels, with a notably significant decrease in butyrate (De Angelis et al., 2013).

6. Conclusions and future directions

Gut microbiota is important to our health and is particularly important for metabolism, the immune system, and the gut-brain axis. This intricate network of microorganisms helps with digestion, immune defense, and intestinal barrier integrity, but dysbiosis could result in systemic inflammation, metabolic disorders, and neuroinflammatory conditions. There are multiple factors, such as birth, diet, and environment, that can determine microbiota composition, with dietary habits having a major effect on microbial equilibrium. Helpful

metabolites such as short chain fatty acids (SCFAs) do immune modulation and neuroprotection, and harmful ones do the opposite, such as trimethylamine N-oxide (TMAO) that increases the risk of cardiovascular diseases. Chronic diseases such as diabetes, cardiovascular diseases, and neurodegeneration are associated with dysbiosis.

Over the years, the topic of microbiota has been gaining popularity. This is due to the large amount of research conducted on the composition of the microbiota and its metabolites versus the state of the human body's proper functioning in health and pathological mechanisms that can lead to disease. By learning about the various mechanisms, we gain knowledge of how they affect us and how we can modify this.

First of all, by studying the composition of the microbiota, we can recognize given diseases earlier and start treatment in earlier stages of the disease, often asymptomatic. This will be possible by recognizing individual characteristics such as an increase in the number of a particular bacterial species, or disturbed proportions. This will enable faster treatment and prevention of the consequences of a given disease. Secondly, thanks to the knowledge of factors affecting the composition of the microbiota, we can influence its composition, thereby preventing the occurrence of dysbiosis. In addition, through the use of probiotics, prebiotics and fecal microbiota transplants, we can more directly influence the bacterial species present in our digestive system. Using beneficial species, we can prevent the development of a particular disease, as well as reduce its severity and symptoms. These ways can also be used for treatment.

However, the state of our knowledge is still not complete. Further research on the microbiota and GBA is needed to fully understand the mechanisms and connections linking them. In the future, this will enable us to better understand the functioning of the human body.

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The authors declare no conflicts of interest.

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