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The Impact of Gut Bacterial Metabolites on Brain Disorder

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Abstract:

Recent technological advancement and expanded efforts have led to a tremendous growth in the collective knowledge of the human microbiome. The gut microbiome has been connected with human health and disease including all those affecting the brain. Abnormalities in this microbiota gut brain axis have emerged as a significant component in the pathophysiology of depression, prompting exploratory research into the neuroactive potential of gut microbial metabolic products. Over the last decade, research has revealed a plethora of complicated interactions between the microbiota and the immunological and metabolic systems, many of which have important consequences for human health. In present study, we emphasize accumulating evidence suggesting the microbiome exerts effect on the brain via multiple routes linking the stomach to the central nervous system. While knowledge of the influence of gut bacteria on neurological function is still developing, understanding the gut-microbiome brain links has the potential to transform neuroscience by discovering possibly new etiologies for mental and neurodegenerative diseases. Overall, our results show that patients with diverse brain disorders have changed bacterial metabolites, as well as the possible neuroactive effects of gut-derived SCFAs, *p*-cresol, serotonin derivatives, and bacterial amyloids on disease onset and progression. The results of this study might lead to more understanding of the gut–brain axis and, as a response, to possible diagnostic, therapeutic, or preventative measures for brain disorders.

Keywords: Probiotic, SCFAs, Brain diseases, Lipopolysaccharides, Gut metabolites

1. Introduction

The study of the human microbiome has evolved technological advances in culture-independent research. Most studies use the 16S rRNA gene (hence, 16S) to sequence the bacteria that make up a microbial community. The sequences are then compared to databases of previously studied bacteria. The metagenomic study, which entails sequencing all of the microbial DNA in a complex community, has the extra benefit of assessing the genetic potential of the microbial population. Additional techniques for analyzing the microbial transcriptome, proteome, and metabolome provide more information at ever higher levels of microbial physiology. We won't get into particular technical details in this section; nevertheless, readers who are interested are referred to recent review articles (Morita et al., 2019).

Characterizing the microbiome in healthy individuals is an essential first step in understanding how the microbiome affects health and disease. The two most prevalent bacterial phyla are Bacteroidetes and Firmicutes, and healthy adult humans typically harbor more than 1000 different types of bacteria from these phyla. The gut has a more diverse microbiota than other parts of the body, and even among those who appear to be in good health, there is a considerable variation in the microbiota's makeup. To explain the microbial variability in the populations of healthy individuals, researchers have sought certain stable patterns of microbial communities in the human population (Zaiss et al., 2019). The gut microbiome has a variety of effects on brain health: Lipopolysaccharides, for example, are structural bacterial components that provide low-grade immune system activation. CNS inflammation can be caused by overstimulation or bacterial dysbiosis or intestine bacterial overgrowth (for example, Staphylococcus aureus bacteria can grow out of control and cause staph infection) (Tran & Mohajeri, 2021).

Bacterial enzymes can synthesize neurotoxic compounds such as D-lactic acid, which lactobacillus bacteria produced, and bacteria of the species Bifidobacterium (phylum Actinobacteria). Most living forms do not use D-lactic acid in their core metabolic activities (Mika & Fleshner, 2016). While ammonia, another neurotoxic metabolite produced by bacterial enzymes, has a variety of neurotoxic effects, such as altering the transport of water, electrolytes, and amino acids between astrocytes (a kind of glial cell in the central nervous system) and neurons. Acute and chronic

neurological signs and symptoms are caused due to high amounts of ammonia in the blood (Waclawiková & El Aidy, 2018). In the vitro intoxication of chronic ammonia leads to an increase in the extracellular level of glutamate in the brain, resulting in the activation of N-methyl-D-aspartate receptors, which decreases phosphorylation of protein kinase C, resulting in the activation of NA/K-ATPase, according to animal studies (Mika & Fleshner, 2016). Ammonia poisoning occurs as a result of ATP depletion. Emotion, learning, and stress responses are all influenced by certain short-chain fatty acids (Waclawiková & El Aidy, 2018). Different type of bacteria associated with Gut microbiome produced from the Honey bee mentioned in the table 01. It has the potential to affect the nonspecific nerve that links the brain and the stomach. These metabolites also covered a wide variety of illnesses, such as IBD and IBS, while adjusting the gut microbiota by changing our nutritional tools, such as food, prebiotics, and probiotics (Needham et al., 2020).

Short-chain fatty acids (SCFA) are a significant source of energy for the intestinal mucosa and are crucial for affecting carcinogenesis and immune responses in the gut. SCFA is released by microbes from inedible dietary fibers. According to two recent preclinical studies, butyrate, a plentiful bioactive SCFA in the gut, has a complex and possibly context- and concentrationdependent role in colon cancer. In transgenic mice with a combination mutation in the tumor suppressor gene (APC) and a deficit in the mismatch repair gene (MSH2), butyrate has been reported to accelerate tumor growth (Lagkouvardos et al., 2015).

Table 01*: Gut microbiome produced from the Honey Bee with its biological functions (Waclawiková & El Aidy, 2018).*

Inferred or Demonstrated function of Bacteria	Bacteria	Host Niche
Host adhesion/biofilm formation	*Snodgrassella alvi*	Gut/ileum
Protection from opportunists	*S.alvi*	Gut/ileum
Immune cascade and melanization	*Frischella perrara*	Ileum/pylorus
Stimulation of adult immune response	*Gut community ,S.alvi*	Hindgut
Differential adult immune response	*F. perrara, S.alvi*	Ileum/pylorus
Enriched carbohydrate metabolism	Gut community	Hindgut
Digestion of complex carbohydrates	*Gilliamella apicola*	Gut/ileum
Metabolism of toxic sugars	*G.apicola*	Gut/ileum
Increased larval survival	*Parasaccharibacter apium*	Hive/larvae/queen/gut
Pioneer species early colonization	*Lactobacillus firm*	Hive/larvae/all castes
Insulin signaling	Gut community	Hindgut
Growth and development	Gut community	Hindgut

This is because lowering butyrate levels through antibiotic therapy or a low-carb diet both reduce tumor growth, yet giving butyrate to animals receiving antibiotics also reduces tumor growth. Grp109a is a receptor for butyrate; however, animals lacking it showed increased carcinogenesis brought on by inflammatory stimuli or APC mutation and signaling through Grp109a reduced tumorigenesis brought on by both stimuli (Ghazalpour et al., 2016). As a result, it was discovered that butyrate inhibits carcinogenesis. We anticipate further investigation on how butyrate produced by bacteria affects colitis and colorectal cancer. The research in this section demonstrates how crucial it is to assess the microbiota's functionality in order to fully understand how it influences both health and disease a list of the bacterial species was mentioned in the table 02 (Haase et al., 2018). Several metabolites produced by gut bacteria have the potential to induce encephalotoxicity. The name "encephalotoxicity" refers to brain malfunctions in general, and "toxic" implies that the malfunction that caused of toxins in the brain. D-lactic acid and ammonia are the most investigated (Mika & Fleshner, 2016). We briefly discussed their common involvement in clinical syndromes, followed by a discussion of the contradictory roles of short-chain fatty acids, which may help to reduce inflammation but also contribute to the etiology of autism spectrum diseases (ASD) (Waclawiková & El Aidy, 2018).

Table 02: A list of the human Gut bacterial species with its strains (Needham et al., 2020).

Eubacterium	Bacteria	Strain
Most Dominant Species of the bacterium present in the GUT	*Bacteroides caccae*	JCM9498
	Bacteroides dorei	JCMI347I
	Bacteroides finegoldi	JCMI3345
	Bacteroides fragilis	JCMIIOI9
	Bacteroides intestinalis	JCMI3265
	Bacteroides ovatus	JCM5824
	Bacteroides stercoris	JCM9496
	Bacteroides thetaiotaomicron	JCM5827
	Bacteroides uniformis	JCM5828
	Bacteroides vulgatus	JCM5826
	Bacteroides xylanisolvens	JCMI5633
	Blautia hansenii	JCMI4655
	Clostridium asparagiforme	DSMI598I
	Clostridium nexile	ATCC27757
	Collinsella aerofaciens	JCM7790
	Coprococcous comes	ATCC27758
	Dorea formicigenerans	ATCC27755
	Dorea longicatena	DSMI38I4
	Eubacterium cylindroides	JCMI026I
	Eubacterium siraeum	ATCC29066
	Parabacteroides distasonis	JCM5825
	Parabacteroides johnsonii	JCMI3406
	Parabacteroides merdae	JCM9497
	Roseburia intestnalis	DSMI46I0
	Ruminococcus gnavus	ATCC29I49
	Ruminococcus lactaris	ATCC29I76
	Ruminococcus productus	JCMI47I
	Ruminococcus torques	ATCC27756
Lactic Acid Bacteria	*Enterococcus faecalis*	ATCC700802 JCMII34
	Lactobacillus casei subsp.casei	ATCC7469
	Lactobacillus casei subsp.rhamnosus	JCMII30
	Lactobacillus gasseri	JCM8794
	Lactobacillus johnsonii	
	Lactobacillus plantarum	JCMII58
	Lactobacillus reuteri	JCMII49
	Lactobacillus lactis	JCMIII2
	Leuconostoc mesenteroides	JCM6I24
	subsp.mesenteroides	
Bifidobacteria	*Bifidobacterium adolescientis*	JCMI275
	Bifidobacterium animalis subsp lactis	JCMI0602
	Bifidobacterium bifidum	JCMI254
	Bifidobacterium breve	JCMII92
	Bifidobacterium catenulatum	JCMII94
	Bifidobacterium infantis	ATCCI5697
	Bifodobacterium longum	JCMI2I7
	Bifidobacterium pseudocatenulation	JCMI200
	Bifidobacterium pseudolomgum	JCMI205
Butyrate-producing Bacteria	*Clostridium bolteae*	JCMI2243
	Clostridium indolis	JCMI380
	Clostridium ramosum	JCMI298

	Clostridium difficile	JCMI296
Pathogen	*Clostridium perfringens*	JCMI290
	Fusobacterium nucleatum subsp.nuclwatum	JCM8532

Chemicals produced from the Gut microbiota

There is different types of chemicals are produced from the different types of microorganism present in the Gut, these play an important role in the human body and also caused different types of diseased (Gray et al., 2017).

i. D-lactic acid

D-lactic acid is a toxic enantiomer produced by the bacterial gut or some types of microbes. It may also be found in contaminated food, beverages, and the microbiota during pathological conditions such as bowel syndrome (Mika & Fleshner, 2016). It is essentially a product of microbial carbohydrate fermentation. When bowel resection allows for the transport of a high carbohydrate load to the colon, a high amount of D-lactate is generated. In the event of different types of abdominal surgery, D-lactate levels in the blood rise, leading to increased intestinal permeability and bacterial translocation across the intestinal mucosal barrier (Needham et al., 2020). Nonsurgical causes of intestinal hyperpermeability increased D-Lactate absorption from the lumen. D-lactate toxicity is most common when serum D-lactate levels are above 3mmol|L, and it can also cause acidosis and encephalopathy (damage or disease that affects the brain) (Needham et al., 2020). A patient with D-lactate poisoning who has both encephalopathy and acidosis may also have symptoms such as memory loss, personality changes, weariness, and cerebellar symptoms such as ataxia or dysarthria, which are the results of brain degeneration. Syncope, coma, and respiratory failure are among the symptoms that might be severe. Several studies have linked psychological disorders including anxiety and depression to syncope (Waclawiková & El Aidy, 2018). A temporary loss of awareness and postural tone induced by global cerebral hypoperfusion is referred to as "syncope." D-lactate encephalopathy has been linked to thiamine deficiency in certain instances (Sarkar et al., 2016). In a study of individuals with CFS and neurocognitive impairment, a high quantity of D-lactate generating bacteria was discovered in the feces, raising the possibility that microbial D-lactate contributes to the symptoms of people with CFS. Patients with CFS have been discovered to have high intestinal permeability, which improves in response to glutamine, N-acetylcysteine, and zinc processing, as well as the adoption of a "leaky gut," also known as increased intestinal permeability (Sarkar et al., 2016). Leaky gut symptoms are commonly associated with mood disorders such as sadness and anxiety. Because the inflammatory reaction, the body produces as a result of the leaking might result in several neurocognitive issues (Tran & Mohajeri 2021).

ii. Tryptophan

Tryptophan, a building block for serotonin synthesis, can be transformed into kynurenic acid during times of stress or inflammation. Tryptophan may also have a direct effect on the amount of tryptophan in the brain, which can influence brain processes. Microbes in the gut can metabolize tryptophan, an important amino acid that is used to make indole, serotonin, and melatonin (Waclawiková & El Aidy, 2018). Furthermore, bacteria such as pseudomonas have been demonstrated to synthesize serotonin from accessible tryptophan and use it for virulence and intercellular communication (Sarkar et al., 2016). The gut microbiota reduces the amount of circulating tryptophan, which affects serotonergic neurotransmission and hence the functioning of the central and enteric nervous systems. Low serotonin levels have been linked to sadness, weariness, and a decline in cognitive abilities (Sarkar et al., 2016).

Other metabolites of tryptophan metabolism by gut bacteria that have been linked to brain and behavior include kynurenine, quinoline, indole, and indole derivatives (Filosa et al., 2018). Which act as neurotransmitters, and metabolic regulators, and may also act as a ligand for AHR, a basic helix-loop-helix transcription factor. EIF5a, IR76B, and PXR are all metabolites that control host cells. Indole derivatives can be produced by some microbial species, such as Pepto *streptococcus* Russell and *Lactobacillus* species. Kynurenine and quinoline are thought to disrupt brain functioning, resulting in depression-like symptoms. In addition, indole and indole derivatives like indole acetic acid and indole propionic acid affect CNS metabolism in both animals and humans (Filosa et al., 2018). Tryptophan catabolism mediated by the gut microbiota is one of the most critical regulating mechanisms for the GBA (Sarkar et al., 2016).

Bacteria are caused to produce tryptophan shikimic acid or anthranilate in both animals and humans. While the saprophytic microflora in humans is unable to provide significant quantities of tryptophan, other strains, such as Escherichia coli, can manufacture this amino acid (Filosa et al., 2018). Furthermore, the amino acids phenylalanine and tyrosine are precursors of dopamine, a critical neurotransmitter produced by the host, and certain commensal bacteria secrete amines linked to these amino acids that activate GPR56 (Tran & Mohajeri 2021). Polyamines, such as putrescine and spermidine, are produced via intestinal bacteria and may be detected in the human colon at quantities of 0.5 to 1Mm. It may increase polypeptide translation and cell proliferation by supporting the hypocone modification of the eukaryotic translation initiation factor (Waclawiková & El Aidy, 2018).

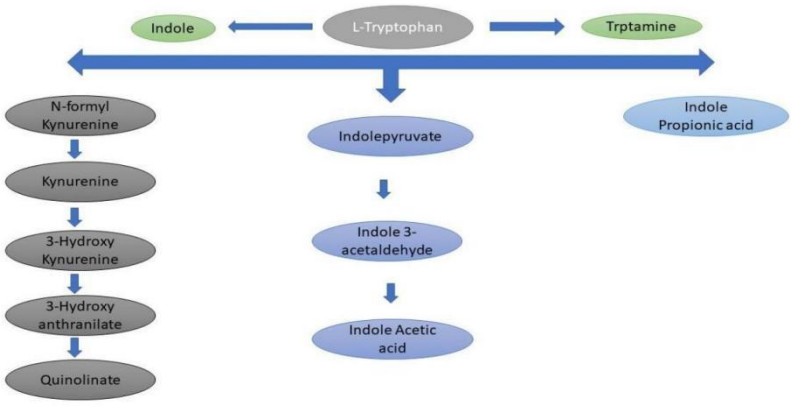

Figure 01: *The empirically documented routes for each of the examined neuro-active tryptophan metabolites of microbial origin. The enzymes that are involved in these pathways are listed below. The approaches used to forecast the "TRYP-6" production routes are also explained in the following sections (Tran &Mohajeri 2021).*

iii. Short-chain fatty acids

Short-chain fatty acids (SCFAs) are the most common metabolites in the human colon, with a combined luminal concentration of higher than 0.1 M. Gut microbes creates enormous amounts of short-chain fatty acids like butyrate, propionate, and acetate (Filosa et al., 2018). Furthermore, because SCFs are natural HDAC inhibitors, they may promote the acetylation and phosphorylation of host proteins including histones, resulting in enhanced gene expression and cell signaling. SCFs can directly inhibit type I and II HDACs, as well as type III HDACs like Sirtuin 1. They produce SCFA by digesting fiber, which may have a variety of effects on the brain, including hunger reduction. SCFA causes physiological stress in several organs, including the brain. Short-chain fatty acid absorption in the brain has been reported in rats after the injection of C-14 SCFAs into the carotid artery. All of these metabolites are detectable in human CSF in concentrations of 0-171 M for acetate, 0-6 M for propionate, and 0-28 M for butyrate, but the average concentration of butyrate in human brain tissues was found to be 17.0 p mol/mg, while propionate was 18.8 p mol/mg (Filosa et al., 2018). However, the concentration of butyrate in the brains of mice supplied with live *Clostridium butyricum* ranges from 0.4 to 0.7 mol/g, which is likely to be higher than the concentration seen in peripheral blood. SCFAs play a vital role in brain development by maintaining the integrity of the blood-brain barrier (Tran & Mohajeri 2021). This is primarily related to the regulated transit of chemicals and nutrients from the circulation to the brain. We may deduce from this observation that SCFAs may influence BBB function and that GF mice may diminish the expression of tight junction proteins such as claudin and occluding permeability to enhance BBB permeability. The anaerobic fermentation of indigestible polysaccharides is caused the production of SCFAs (Dodd et al., 2017). In the large intestine, gut microbiota produced the major metabolites are SCFAs may impact brain functions directly or indirectly (Filosa et al., 2018). SCFAs are absorbed primarily through the H+-dependent monocarboxylate transporter, which binds to (GPCRs) such as (FFAR2 and EFAR3) in colonocytes. SCFAs have an impact on intestinal mucosal immunology, barrier integrity, and function. They may interact with these receptors, promoting systemic circulation signals to the brain (Sarkar et al., 2016).

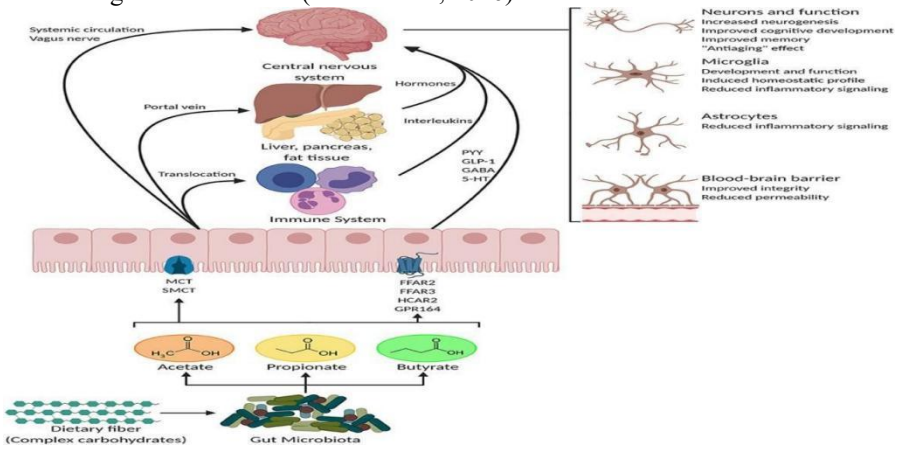

Figure 02: *Illustrations figure of small chain fatty acids, in addition, the interaction of SCFAs with the brain has the potential to influence emotion, cognition, and the pathophysiology of brain illnesses (Tran & Mohajeri 2021).*

These microbial metabolites have a negative and beneficial impact on the development of the CNS and the inflammatory response (Filosa et al., 2018). Useful metabolites are produced in association with a balanced population of various microorganisms in the gut in the best-case scenario (Sarkar et al., 2016). Furthermore, these microorganisms create a variety of compounds that benefit the host (Needham et al., 2020). In dysbiosis, on the other hand, the synthesis of toxic metabolites increases while the production of good metabolites decreases. Beneficial metabolites like SCFs and Trp metabolites assist the functional maturation of CNS cells including microglia, oligodendrocytes, and astrocytes, as well as the integrity of the BBB and gut barrier (Sarkar et al., 2016).

As a result, these metabolites help to sustain neurological function, CNS formation, and the production of regulatory immune cells that help to maintain immunological tolerance (Filosa et al., 2018). Negative immunological responses, such as the formation of pathogenic Th17 cells, may be triggered. Only a few of the host receptors implicated are GPCRs, transcription factors, nuclear ligand receptors, and TLRs. Harmful metabolites get across the BBB and gut barrier, triggering systemic inflammatory responses, neuronal cell death, and tissue damage (e.g. demyelination), all of which aggravate CNS disorders (Needham et al., 2020). Not only poisonous microbial metabolites, but also pathogenic bacteria cells and T lymphocytes migrate from the stomach to the CNS during pathological conditions, causing inflammation. Dopaminergic neurons in the *Substantia Nigra* create Parkinson's disease (PD), which results in dopamine insufficiency in the midbrain (Filosa et al., 2018). Dopamine is necessary for control of the bodily movement. Many genes and their polymorphisms have been linked to the development of Parkinson's disease (Filosa et al., 2018). The presence of neurotoxic protein termed Lewy bodies in the midbrain, which is made up of -synuclein oligomer, is a pathogenic hallmark of PD. Dysbiosis of the gut has also been reported in Parkinson's disease patients. The gut microbiome can influence PD development in animal models. Mice colonized with feces from Parkinson's patients exhibited PD-like clinical characteristics, such as -synuclein and brain aggregation (Needham et al., 2020). Patients with Parkinson's disease had lower levels of unsaturated fatty acid metabolism and higher levels of secondary bile acid metabolites such as deoxycholic acid (DCA) and lithocholic acid, as according to metabolite profiling (LCA). In a group of PD patients with impaired mobility, SCFproducing bacteria and microbial carbohydrate processing activities were considerably reduced. In furthermore, Alzheimer's disease is a degenerative neurological ailment marked by the build-up of harmful misfolded amyloid-protein plaques in the brain. In this case, extracellular-amyloid plaques develop in the basal, temporal, and orbitofrontal neocortex. SCF levels in Alzheimer's disease patients are lower than in Parkinson's disease patients (Sarkar et al., 2016). C4 levels in the blood have been found to be lower in Alzheimer's patients who had amyloid accumulation in their brains and endothelial dysfunction. Increased blood LPS and inflammatory cytokines are linked to AD pathogenesis. What function do SCFs play in the etiology of Alzheimer's disease. The gut microbial ecology can be altered by aging and oxidative stress, resulting in lower amounts of SCFs. The polymerization of A1-40 or A1-42 peptides into neurotoxic multimeric a forms is prevented by SCF treatment. In a humanized AD mouse model, probiotic therapy increased the hippocampus concentration of SCFs and reduced anxiety-like behavior (Filosa et al., 2018).

A. Short chain fatty acids and Autism spectrum disorder

Communication deficiencies, repetitive habits, and sensitivity to environmental changes are among the behavioral signs of ASD, which is classified as a group of neurodevelopment disorders (Sun et al., 2018). In addition, the relevance of SCFAs in ASD is still debatable. According to a new article published in the New England Journal of Medicine, structural brain anomalies in autistic children that occurred during parental brain development suggest that the origins of autism may be detected in utero (Sun et al., 2018). Furthermore, immunological stimulation (maternal immune activation) in pregnant mice can cause behavioral alterations in their offspring that are comparable to ASD. Bacteroides fragilis corrects gut permeability, changes microbial composition, and improves communicative, stereotypic, anxiety-like, and sensorimotor behaviors in the MIA model with a single probiotic (Needham et al., 2020). Furthermore, pyrosequencing the gut microbiome from fecal samples revealed low levels of the phylum firmicutes with a substantially larger abundance of Bacteroidetes (Gao et al., 2020).

Bacteroidetes are SCFA-producing bacteria, and their metabolites, such as propionic acid, may modulate the gut-brain axis, influencing the CNS and autistic behavior. Children have greater amounts of propionic acid and acetic acid but low levels of butyric acid, according to De Angelis and colleagues. SCDAs, such as AA, PPA, and BA, are non-digested carbohydrates that have a role in the pathophysiology of ASD (Gao et al., 2020). PPA produced by ASD-associated species (such as Clostridia, Bacteroides, and Desulfovibrio), has anti-inflammatory and antibacterial properties, as well as the ability to elicit autistic-like behavior in mice. It is mostly concerned with CNS development (Dai et al., 2015). Some ASD patients have experienced GI difficulties such as stomach pain, diarrhea, and food

sensitivity. Firmicutes, Fusobacteria, and Verrucomicrobia were found to be reduced in ASD patients, whereas Bacteroidetes were shown to be greater (Flint et al.., 2015). Researchers discovered that increased levels of Th17-inducing gut microbial species such as segmented filamentous bacteria (SFB) Bifidobacterium adolescents and specific *E. coli* isolate boost ASD development in children during pregnancy. Intestinal CD11c+ DCs can trigger pathogenic Th17 responses by recognizing microbial TLR3 ligands and producing IL-1, IL-23, and IL-6. The role of the microbial community at the start of ASD was demonstrated using an FMT model. The progeny of GF mice humanized with microorganisms from ASD patients' feces displayed behavioral abnormalities (Dai et al., 2015). Butyric acid is another SCFA produced by the gut microbiome; the phylum Firmicutes is home to the majority of butyrate-producing bacteria in the human gut (Ghasemian et al., 2016).

In comparison to conventional mice, germ-free mice had greater amounts of monoamines (dopamine, serotonin, and adrenaline) and lower levels of BDNF, as well as anxiety-like behavior. The involvement of serotonin (5-HT, hydroxy tryptamine) as a connection for the gut-brain axis in ASD was recently discovered in this research. It may have a role in CNS and ENS development (Duda et al., 2015).

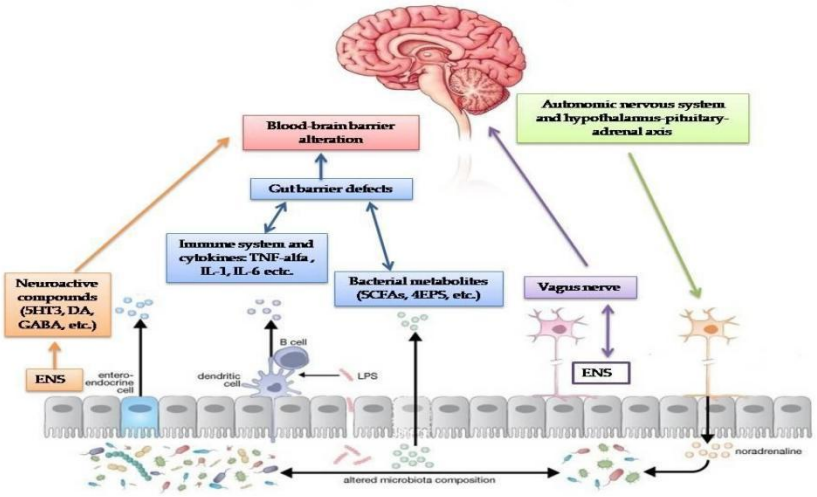

Figure 03: *SCFAs and Autism spectrum disorder, It stimulates oxidative phosphorylation and fatty acid oxidation, which is critical for mitochondrial function. Because it upregulates physiological stress pathways, it may be beneficial in a variety of neurological functions such as depression and dementia (Sarkar et al., 2016).*

iv. Ammonia

Ammonia has a poisoning impact on the central nervous system of humans, as well as causing psychological and behavioral problems. Gut bacteria like *S. salivarius* produce a lot of ammonia, which can lead to a rise in blood ammonia levels and astrocyte edema (Saito et al., 2018). Recent research has also revealed that patients suffering from shock and hypoxia have a high quantity of ammonia in their blood. Hypoxia, or a lack of oxygen, impairs thinking, affects consciousness, causes sadness, and causes extreme anxiety. Hepatic encephalopathy, a neurological system illness caused by severe liver disease, is also linked to NH3. When the liver is not working correctly, "ammonia levels in the blood rise", which can go to the brain and impair brain function (Saito et al., 2018). An individual suffering from hepatic encephalopathy appears befuddled. Its toxicity is caused by glutamine, which is metabolized in the brain via NH3 and can result in anxiety, irritability, mood swings, and personality changes. NH3 widens BBB connections, enabling pathogens, tiny molecules like glutamate, neutrophils, and water to pass through. Hyperammonemia has the potential to cause irreparable brain damage (Sarkar et al., 2016).

v. Gamma-aminobutyricric acid

In the human brain, GABA functions as a neurotransmitter (a chemical messenger). It is an amino acid that may be found in nature. Because it inhibits specific brain signals and reduces nervous system activity, GABA works as an inhibitory neurotransmitter (Molinero et al., 2019). *Lactobacillus* and *Bifidobacterium* species produce the majority of GABA. GABA has a soothing impact when it binds to the proteins known as GABA receptors, which can aid with anxiety, tension, and terror. It might potentially be used to prevent seizures. It can also change the host's behavioral pattern and affect glucose homeostasis. We've also shown that giving healthy rats GABA-producing Lactobacillus Brevis DPC6108 can raise insulin levels in the bloodstream (Molinero et al., 2019). As a result, the goal of this research was to see if endogenous microbial GABA synthesis may help improve metabolic and behavioral outcomes

in a mouse model of metabolic dysfunction. For 12 weeks, obese and metabolically dysfunctional mice were given one of two GABA-producing strains, L. Brevis DPC6108 or L. Brevis DSM32386, daily. The mice's behavioral and metabolic profiles were examined after 8 and 10 weeks of intervention, respectively (Sarkar et al., 2016).

Interference with both *L. Brevis* strains reduced various metabolic disorders during the force swim test, including decreased mesenteric adipose tissue accumulation, increased insulin secretion in response to a glucose challenge, enhanced plasma cholesterol clearance, and decreased despair-like behavior and baseline corticosterone production (Mika & Fleshner, 2016). This early investigation demonstrates that treating metabolic and depressive-like behavioral abnormalities in mice with GABA-producing lactobacilli may improve metabolic and depressivelike behavioral abnormalities linked to metabolic syndrome. Changes in the gut microbiome can affect anxiety and depression, among other brain-related behavioral changes (Murota et al., 2018). The HPA axis, which depicts the connection between the hypothalamus, pituitary gland, and adrenal glands, is too sensitive for stressed germ-free mice, according to new research. The hypothalamus and pituitary gland are slightly above the brainstem, while the adrenal glands are on the top of the kidney (Mika & Fleshner, 2016). Supplementing mice with a single bacterial strain, *Bifidobacterium* infants reduced the overreaction of the HPA response (Mika & Fleshner, 2016). Chronic treatment of BALB/c mice with *Lactobacillus rhamnosus JB-1* was demonstrated in 2011 to reduce anxiety and antidepressant-related behavior, most likely through causing neurochemical changes. Changes in the expression of -aminobutyric acid receptors, including GABAA and GABAB receptors, across a range of brain areas were associated with decreased levels of anxiety in *L rhamnosus*-treated mice (Sarkar et al., 2016).

Conclusion

The gut microbiome has a variety of effects on brain health: Lipopolysaccharides, for example, are structural bacterial components that provide low-grade immune system activation. CNS inflammation can be caused by overstimulation or bacterial dysbiosis or intestine bacterial overgrowth (for example, Staphylococcus aureus bacteria can grow out of control and cause staph infection). Bacterial enzymes can synthesize neurotoxic compounds such as D-lactic acid, which lactobacillus bacteria produced and bacteria of the species Bifidobacterium (phylum Actinobacteria). Most living forms do not use D-lactic acid in their core metabolic activities. Overall, our results demonstrated that patients with diverse brain disorders have changed bacterial metabolites, as well as the possible neuroactive effects of gut-derived SCFAs, p-cresol, serotonin derivatives, and bacterial amyloids on disease onset and progression. The discoveries reported in this review may lead to more understanding of the gut-brain axis and, as a result, to possible diagnostic, therapeutic, or preventative measures for brain disorders.

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