

and GLP-1) and SCFAs that target receptors located on vagus fibers. Long chain fatty acids (LCFAs) also interact with vagus receptors through cholecystokinin-dependent mechanisms.

Direct measurements of EEC activities have been challenging due to their location in the gut wall. Recently, the lab of Reimann *et al.*^[55] has developed a method to directly investigate EEC activity by genetically tagging EECs with a fluorescent protein which expresses under the control of the promoter for a peptide hormone precursor proglucagon, GLP-1. Using this approach, they established the important role of G-protein coupled receptors (GPCRs) in chemosensing and their ability to activate EECs leading to the secretion of peptide hormones. GPCRs are critical for a variety of physiological functions, such as regulation of immune system, autonomic nervous system regulation, sensory (taste and smell) functions, and maintaining energy homeostasis. Recently, some GPCR chemoreceptors were found to be activated by bile acids, SCFAs, and LCFAs, which are also linked to EECs^[56]. It was shown that the LCFA receptors GPR40 and GPR120 and the bile acid receptor GPR131 (TGR5) are all expressed on the surface of EECs^[55]. In addition, Samuel *et al.*^[57] found that isolated EECs express GPR41, a receptor for SCFAs. It has been shown that these chemosensors are located on the basolateral membrane of EECs, which interact with the circulatory system^[58]. In addition, it is likely that GPCRs co-store and co-release with gut-derived hormones, which indicate that GPCRs may be regulated by associated intestinal hormones. SCFAs and LCFAs, released from gut microbiota or derived nutritionally, can activate release of CCK hormone, which can bind to CCK-A and CCK-B receptors (CCK-r) on vagal afferents that signal the brain^[59]. In response, the brain develops immune responses and triggers vagal efferent fibers to release acetylcholine (ACh), which is the principal parasympathetic neurotransmitter^[60]. These observations suggest that gut dysbiosis can result in pathological changes in the levels of gut hormones and metabolites, thus influencing GPCR function and dysregulating the vagus nerve and subsequent CNS activities.

The interactions between gamma-aminobutyric acid and vagus nerve

Gut microbiota also produce a number of neurotransmitters similar to mammalian physiological systems, including dopamine, norepinephrine, serotonin, and gamma-aminobutyric acid (GABA). GABA is the major inhibitory neurotransmitter in the CNS; however, GABA receptors are expressed throughout the body, including on the vagus nerve^[61]. In human intestines, GABA is produced by the microbiota populations *Lactobacillus brevis* and *Bifidobacterium dentium*. GF animals were shown to have reduced levels of GABA, suggesting that the gut microbiota is able to influence GABA levels. Furthermore, altered GABA levels have also been associated with neurological conditions, such as depression, anxiety, autism, and schizophrenia^[62,63]. For example, studies into rodents were found to have reduced depressive and anxiety-like behaviors after receiving chronic administration of the probiotic *Lactobacillus rhamnosus*, which was accompanied by decreases in GABA receptor subunit mRNA expression and corticosterone levels^[64]. The GABA-related reductions in behavioral effects did not occur in vagotomized rats and mice^[65]. Considering this effect existed only when the vagus nerve was intact, it suggests that intestinal microorganisms regulate GABA signaling through the vagus nerve. In support of this conclusion, animal studies by Takanaga *et al.*^[66] demonstrated that GABA produced by intestinal bacteria are able to cross the blood-brain barrier and influence CNS activities. In addition, the impairment of GABA-mediated neuronal inhibition associated with epilepsy might contribute to the therapeutic efficacy of vagus nerve stimulation, as was demonstrated in patients with drug-resistant partial epilepsy^[67].

Vagus nerve pathways in controlling inflammation

The microbiota-gut-brain interaction through the vagus nerve plays a major role in regulating inflammation. The anti-inflammatory properties of vagus nerve function is mediated through several debated pathways, such as the cholinergic anti-inflammatory pathway, the HPA axis and the splenic-sympathetic nerve anti-inflammatory pathway.

Previous studies demonstrated that the cholinergic anti-inflammatory pathway (CAP) plays a pivotal role in controlling neuroinflammation. The CAP modulates inflammation through vagal efferent fibers that

synapse onto enteric neurons surrounding the GI tract, which can release acetylcholine^[68,69]. Acetylcholine binds to α -7-nicotinic acetylcholine receptors on macrophages, including microglia, and inhibit the release of the pro-inflammatory cytokine TNF- α ^[70]. Other studies also illustrate the ability of the vagal nerve to regulate neuroinflammation by sensing increased peripheral pro-inflammatory cytokines^[71]. As a negative feedback loop, pro-inflammatory cytokine release is prevented if increased levels of inflammation are detected through the acetylcholine-mediated anti-inflammatory signaling system^[71]. Wang *et al.*^[72] observed that electrical stimulation of the vagus nerve can inhibit TNF synthesis in wild-type mice but not in α -7-nicotinic acetylcholine receptor-deficient mice. Collectively, these results support the critical role of the vagus nerve in regulating microglia activity and neuroinflammation through CAP signaling.

Studies of vagus nerve stimulation have provided additional evidence for vagus nerve afferent involvement in neuroimmune modulation. For example, non-invasive vagus nerve stimulation is widely used in the treatment of drug resistant depression and has been shown to increase levels of norepinephrine^[73,74]. The locus coeruleus is an aminergic brain stem nucleus which represents the main source of norepinephrine in the brain and plays a critical role as a neurotransmitter and neuroimmune modulator, including regulation of microglial activity. By activating β -receptors on the cell surface, norepinephrine affects microglia cell dynamics, which then influence neuronal activity^[75,76]. These observations indicate the potential of vagus nerve stimulation to regulate microglial activity.

Recently, the inflammatory reflex was found to be located where vagus afferent fibers activate vagus efferent fibers. Borovikova *et al.*^[77] reported that septic shock was prevented by vagus nerve stimulation of the distal end of the vagus nerve after injection of LPS. This effect is due to CAP activation and the binding of acetylcholine to α -7-nicotinic acetylcholine receptors in order to inhibit macrophages from releasing pro-inflammatory cytokines such as TNF- α ^[72]. However, the interaction between the vagus nerve and intestinal immune system is indirect because the vagus nerve does not directly interact with resident macrophages in the gut. Therefore, Rosas-Ballina *et al.*^[78] suggested that the vagus nerve tends to activate the splenic sympathetic nerve through a vago-sympathetic co-activation of ventricular contractility and heart rate^[78,79]. It is hypothesized that released norepinephrine from the distal end of the spleen can bind to the β 2 adrenergic receptor of splenic lymphocytes. Its binding leads to the release of acetylcholine, which in turn binds to α -7-nicotinic acetylcholine receptors on splenic macrophages and inhibits the release of TNF- α ^[80]. However, this hypothesis is still being debated due to the controversial interaction between the spleen and the vagus nerve^[81]. Furthermore, some studies demonstrate the spleen receives not only sympathetic inputs but parasympathetic inputs as well. The sympathetic inputs relay information to the spleen via the arteries while the parasympathetic inputs transfer signals at the tips of the spleen.

The vagus nerve also plays an important role within the neuroendocrine-immune axis, which can regulate coordinated neural, behavioral, and endocrine responses with the immune system in order to prevent chronic neuroinflammation. The vagus nerve recognizes peripheral pro-inflammatory cytokines released by macrophages, such as IL-1, IL-6, and TNF- α and conveys this information to the neurons within HPA pathway in order to decrease peripheral inflammation^[82]. Overall, the vagus nerve has anti-inflammatory properties both through its afferent end (activation of HPA axis) and through its efferent end (activation of CAP).

THE GUT AND THE ENDOCRINE SYSTEM

In addition to the vagus nerve, intestinal microbiota are able to communicate with the CNS through hormones secreted by glands within the endocrine system. Steroid hormones take part in many critical physiological processes in our body, such as survival of stress, injury, metabolism, inflammation, salt and water balance, immune functions, and development of sexual characteristics. Studies show that gut microbiota are also able produce and regulate these hormones to affect brain activity, including the state of microglia and neuroinflammation.

Glucocorticoids through HPA axis

The HPA axis is a complex set of direct pathways and feedback interactions which include the hypothalamus, the pituitary gland, and the adrenal glands. The hypothalamus produces and releases corticotropin-releasing hormone (CRH), which can induce the pituitary to release adrenocorticotrophic hormone (ACTH). ACTH then stimulates the adrenal cortex, producing glucocorticoid hormones. Each of these hormones can in turn act back on the hypothalamus and pituitary in a negative feedback cycle. Glucocorticoids are corticosteroids which bind to glucocorticoid receptors present in almost every vertebrate animal cell. They can reduce certain aspects of immune activities through a feedback mechanism. Cortisol is the most important human glucocorticoid which has a variety of cardiovascular, metabolic, immunologic, and homeostatic functions. The influence of microbiota on the HPA axis depends on many factors including bacterial strain, host age and sex, and different mouse strains^[83-89]. Individual strains of bacteria can regulate the HPA axis and the microbiota as a whole participate in developmentally programming stress responses^[90]. Conversely, microglial activity can also affect hormone release through HPA axis. In response to cerebral insults, microglia secrete a variety of inflammatory molecules, such as cytokines, stimulating neuronal activity within the paraventricular nucleus of the hypothalamus to activate the HPA axis anti-inflammatory feedback loop to reduce prolonged neuroinflammation.

Glucocorticoids released by the HPA axis bind to glucocorticoid receptors, which are highly expressed in neurons and microglia to affect cellular responses^[85,90]. Glucocorticoids work to suppress both stress and immune responses by binding to specific glucocorticoid receptors and mineralocorticoid receptors in CNS and immune cells^[91]. Studies have demonstrated that acute stress induced higher levels of ACTH and corticosterone in the serum of GF mice compared to conventionally-raised control mice^[85-87]. Recent targeted microarray analysis found 23 upregulated glucocorticoid receptor pathway genes in the hippocampus of GF mice compared to controls, of which six genes (*Slc22a5*, *Aqp1*, *Stat5a*, *Ampd3*, *Plekhf1*, and *Cyb561*) were confirmed by PCR validation^[87]. Among these six genes, two (*Stat5a* and *Ampd3*) were upregulated in *E. coli*-derived LPS-treated mice. The GF mice demonstrated reduced anxiety-like behaviors in response to acute stress, whereas LPS-treated control mice demonstrated anti-depressive but not anti-anxiety behavior and a decrease in the basal serum cortisol levels. LPS-induced abnormal behavior was consistent with previous findings that *E. coli* colonization in GF mice enhanced the HPA axis response to stress^[86]. In another study, plasma ACTH and corticosterone hormones were decreased in mice monocolonized with *Bifidobacterium infantis*, but were increased in *E. coli*-monocolonized mice. In addition, after receiving fecal samples from patients diagnosed with severe depression (“depression microbiota”), control mice exhibited anxiety- and depressive-like behaviors with parallel downregulation of *Stat5a* gene in their hippocampus compared with “healthy microbiota” recipient mice^[92]. *Stat5a* is a member of STAT family encoded transcription factors, mediating signals for a broad spectrum of cytokines. The JAK2-STAT5 signaling pathway plays a critical role in mediating IL-3-induced activation of microglia^[93]. Furthermore, STAT5 may play a protective role in damaged nerve cells and has been implicated in cellular functions of proliferation, differentiation, and apoptosis with relevance to processes including hematopoiesis and immunoregulation^[92]. Collectively, these observations suggest that microbiota related STAT5 levels may influence neuroinflammation and related disorders.

CRH and glucocorticoids from the HPA axis have been shown to directly affect microglia activity by binding to functional CRH-R1 receptors on microglia and initiate apoptosis of microglia^[94]. In that study, Ock et al.^[94] demonstrated that CRH-induced apoptosis did not induce nitric oxide production or increase expression of pro-inflammatory genes, which indicates that CRH does not affect inflammatory activation of microglia. This mechanism has been linked to the mitochondrial pathway and induction of reactive oxygen species (ROS) production, which can damage microglia cells and promote apoptosis^[95]. In support, the antioxidant *N*-acetyl cysteine inhibited CRH-induced microglial cell death suggesting that ROS was a main cause of apoptosis.

Glucocorticoid levels are strongly related to the activation of the HPA axis, and distinctively affect macrophage function. Low levels of corticosterone enhanced pro-inflammatory factors, while high corticosterone concentrations suppressed macrophage activation^[96]. Steroid hormones directly target mature microglia; glucocorticoids predominantly modulate expression of glucocorticoid receptors to regulate microglial inflammatory activity^[97]. Anti-inflammatory effect of glucocorticoids on microglia can reverse the pro-inflammatory function of CRH by attenuating the production of TNF- α , IL-6, and nitric oxide from LPS + IFN- γ -activated murine microglia. Physical or emotional stress may induce microglial activation in the brain as determined by changes in morphology^[98,99]. The stress-induced elevation of glucocorticoids can activate microglia in rats, and chronic stress can cause a marked transition from a resting to non-resting state^[100]. Temporal treatment of glucocorticoids can exhibit the opposite results^[101]. Stress and administration of glucocorticoids prior to peripheral immune stimuli exerted pro-inflammatory effects on microglia, while exposure to glucocorticoids after stimuli had anti-inflammatory effects in a rodent model^[101]. Corticosteroids limit microglial activation that occurs during acute stress, serving as an important endogenous suppressive signal limiting neuroinflammation^[98,99]. Moreover, glucocorticoid level increases and microglial morphological complexity decreases with aging^[88]. Increasing glucocorticoid levels in young mice enhanced microglial ramifications, pointing to their increased neuroprotective function. The opposite, amoeboid state of microglia renders them to move freely in the brain tissue and is indicative of inflammatory activation. Amoeboid microglia occur more frequently with aging. The effects of glucocorticoids or corticosteroids on microglia morphology are dependent on treatment time and concentration of glucocorticoids.

Estrogen through hypothalamic-pituitary-gonadal axis

The hypothalamic-pituitary-gonadal axis (HPG axis) plays an important role in the reproductive and immune systems, and controls development, reproduction, and aging in animal models. The hypothalamus secretes gonadotropin-releasing hormone, the pituitary gland produces luteinizing hormone and follicle-stimulating hormone, and the gonads release estrogen and testosterone. Although the HPG axis has not been as deeply studied as the HPA axis, strong evidence suggests that estrogen has the capacity to inhibit neuroinflammatory processes and can impact immune cells, including microglial functions.

Estradiol (E2) is an estrogen steroid hormone and the major female sex hormone. Studies show that 17 β -estradiol (E2) inhibits microglia activation^[102] and reduces the expression of inflammatory mediators^[102]. For example, E2 was able to inhibit A β -induced expression of scavenger receptor-A in microglia cells from an animal model of Alzheimer's disease^[102]. Ovarian hormone deprivation can alter the expression of major components of estrogen and neuronal inhibitory signaling, participating in the control of microglia reactivity^[103]. Moreover, aging is related to exaggerated responses to acute inflammatory stimuli, modulated by the duration of hormone deprivation. This deprivation is due to decreased estrogen receptor activity, which, despite the continuous synthesis of the receptors, induces neuroinflammation^[89].

SHORT-CHAIN FATTY ACIDS IN THE GUT AND NEUROINFLAMMATION

Microbiota are able to influence brain functions through the production of metabolites such as SCFAs. In addition to being derived from dietary sources, SCFAs are also produced by the microflora in the distal small intestine and colon through the fermentation of dietary fibers. The most abundant SCFAs in the human gut are acetate, propionate, and butyrate. Acetate is used for host synthesis of lipids and cholesterol, and propionate is mostly absorbed by the liver and serves as a substrate during gluconeogenesis. Butyrate functions as the main energy source for colonic enterocytes^[104]. SCFAs are mainly absorbed in both the small and large intestine through similar mechanisms, such as diffusion of the dissociated forms and through active transport by SCFA transporters^[105].

High doses of systemic or locally injected butyrate has been found to exert neuroprotective effects, such as memory enhancement and cognitive function restoration^[106,107]. Physiological levels of butyrate may

influence and improve neuroinflammation through different mechanisms. Butyrate is a known inhibitor of histone deacetylases (HDACs)^[108,109], which control the innate inflammatory system by regulating the number of microglia cells and astrocytes^[110]. Histone acetylation is a post-translational modification through epigenetic process and causes the chromatin structure to loosen by weakening electrostatic attraction between the histone proteins and DNA backbone. Activation of microglia are suppressed by this process. Therefore, increased HDACs have been shown to be involved in neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases^[110,111].

Butyrate is one of the most important microbial end-products of the human colon fermentation process which displays several physiological effects via different mechanisms. One function is mentioned above: butyrate is a well-established HDAC inhibitor. In addition to having a significant impact on the transcriptional system, butyrate also serves as the energy substrate. Butyrate is the primary source of energy in the colon and microbiome, which accounts for nearly 70% of ATP produced. It may appear that metabolic events in the colon are disconnected with that of the brain. However, it is impossible to ignore the immense energy demand of the brain. In this regard, energy imbalance in the brain has been noted at early stages of neurodegenerative disease such as Alzheimer's disease^[112]. Another function of butyrate is its ability to activate GPCRs, as described in detail above, within the vagus nerve system section^[113]. Butyrate can signal through GPR109a, which is widely expressed in colonocytes, T cells and has also been found in microglia. Butyrate is sensed by FFA2 (previously GPR43) and FFA3 (previously GPR41), which modulate the relationship between SCFAs and gut, as well as the whole body energy use^[114,115].

Many studies have shown that butyrate can serve as an anti-inflammatory agent, improving gut barrier function, protecting against colon cancer and neurodegenerative diseases, such as Alzheimer's disease^[116-118]. These studies demonstrate that treatment with butyrate inhibited pro-inflammatory cytokines (IFN- γ , TNF- α , IL-1 β , IL-6, and IL-8) and upregulated anti-inflammatory cytokines (IL-10 and TGF- β). This effect may be partly due to the inhibition of transcription factor NF- κ B that controls the transcription of DNA, cytokine production, and cell survival. Aguilar *et al.*^[119] demonstrated that butyrate suppressed the NF- κ B signaling pathway by rescuing the redox machinery and controlling ROS, which also regulate NF- κ B activation. In addition, butyrate is known to enhance and repair barrier function of intestinal epithelial cells. *In vitro* experiments have illustrated that butyrate plays an important role in the maintenance of gut-barrier integrity in order to block the translocation of LPS, which can cause immune activation^[120]. For instance, butyrate leads to the upregulation of mucin 2, the most prominent mucin protein, and enhances the protection of the mucosal layer^[121]. These effects of butyrate were demonstrated in Caco-2 cell cultures, which are human epithelial colorectal adenocarcinoma cells, and can form confluent monolayers *in vitro* that both structurally and functionally resemble the small intestinal epithelium. For instance, butyrate leads to the upregulation of mucin 2, the most prominent mucin protein, and enhances the protection of the mucosal layer^[121].

Gut dysbiosis and reduced levels of SCFAs have been observed within neurological disease, including Pelizaeus–Merzbacher disease^[122]. Unger *et al.*^[123] found changes in gut microbiota and SCFAs in patients diagnosed with Parkinson's disease. Fecal SCFA concentrations were significantly reduced in Parkinson's patients compared to controls. This was associated with reduced microbiota populations of *Bacteroidetes* and *Prevotellaceae*^[123]. Furthermore, some studies have demonstrated beneficial effects of SCFAs during neuronal pathologies, such as against formation of neurotoxic A β aggregation, which occurs during the pathogenesis of Alzheimer's disease^[124]. SCFAs have been reported to increase the expression level of retinoic acid in the GI tract, which inhibits Th17 cell differentiation and promotes Treg proliferation, limiting prolonged neuroinflammation^[125]. SCFAs, especially butyrate, are able to modulate immune cells and influence cell proliferation and apoptosis. For example, high concentration of butyrate induces cell apoptosis while low concentration will enhance cell proliferation^[126]. Collectively, these observations support the ability of SCFAs to have a therapeutic effect on many neurodegenerative disorders.

MICROBIOME-TARGETED THERAPEUTICS ADDRESSING NEUROLOGICAL DISEASES

The conclusion of the 10-year NIH Human Microbiome Project has been integral in providing resources, methods, and discoveries linking humans and their microbiomes to health and disease^[127]. The study utilized a combination of shotgun metagenomics, untargeted metabolomics, and immunoprofiling to determine host-microbiota interactions manifest in largely diverse ways, and sampling large population sizes is critical for accurately determining potential mechanisms of microbiome-linked diseases^[127]. They demonstrated that microbiome composition alone was not always an accurate representation of host phenotype, and necessitated the consideration of microbial functions of the microbiota ecosystem as they interacted with host immunity, metabolism, and other interconnected activities^[128]. Through this accomplishment, microbiome-targeted strategies have begun to gain interest in both studying mechanistic relationships within animal models and in the treatment of pathologies, including those related to the gut-brain axis.

Antibiotics: non-absorbable “eubiotic” rifaximin

Beyond their bacteriostatic and bactericidal effects in treating GI infections, antibiotics have been shown to negatively affect the intestinal flora, a phenomenon considered “collateral damage”. Antibiotic treatment can have long-lasting negative effects on the GMB, which has been shown to decrease diversity and reduce beneficial bacteria, leading to increased susceptibility to pathogens, such as *Salmonella* and *Clostridium difficile*^[129,130]. Alternatively, rifaximin, a broad-spectrum, non-absorbable antibiotic, prescribed to treat irritable bowel syndrome and traveler’s diarrhea caused by *E. coli*, has shown unique qualities related to the GMB and symptoms beyond the GI tract^[131]. The mechanism of rifaximin action to reduce pathogens is through binding the β -subunit of microbial RNA polymerase and inhibition of bacterial RNA synthesis^[132]. However, unlike other antibiotics which commonly reduce microbiota diversity and promote dysbiosis, rifaximin exerts anti-inflammatory properties and has the “eubiotic” ability to enrich beneficial microbiota populations^[133]. For example, Maccaferri *et al.*^[134] found that *in vitro* treatment with rifaximin increased levels of *Bifidobacteria*, *Atopobium*, and *Faecalibacterium prausnitzii* cultured from colonic samples of patients with Crohn’s disease. These changes were also accompanied by increases in SCFAs, microbial metabolites known to be important in host health, metabolism, and immune homeostasis^[135]. In a rodent model of ankylosing spondylitis spinal joint inflammation, rifaximin treatment was able to inhibit TLR-4/NF- κ B signaling and decrease levels of pro-inflammatory cytokines, such as TNF- α , IL-6, IL-17A, and IL-21^[136]. Another important commensal GMB population and producer of the SCFA lactate, *Lactobacillus*, was increased in a rat model of visceral hyperalgesia with rifaximin treatment^[137]. Furthermore, hepatic encephalopathy is a common complication of patients with acute or chronic liver disease that is detected through neuropsychological testing and presents as neurocognitive decline: forgetfulness, confusion, irritability, and coma at its most severe forms^[138]. These symptoms are mainly a result of elevated levels of ammonia. Rifaximin was able to reduce levels of ammonia-producing intestinal bacteria without decreasing GMB diversity, while also significantly reducing hospital stay, mortality rate, and improving psychometric test performance in patients with mild and severe hepatic encephalopathy compared to other treatments^[139]. These observations support alternate uses for rifaximin which may be related to beneficial changes in microbiota and SCFAs, including its indication for CNS-related disorders.

Microbial-derived metabolites: sodium butyrate

Beyond directly targeting and supplementing live bacteria in the GMB, the Human Microbiome Project stressed the importance of microbiota functions in influencing host immunity and pathologies. As a HDAC inhibitor, sodium butyrate can change the balance between two types of enzymes, histone acetylase and HDACs^[140]. These two enzymes control acetylation, which is an important process in chromatin structure and gene expression associated with many diseases, such as diabetes, Alzheimer’s disease, and various cancers^[141-143]. Physiological doses of sodium butyrate (0.25-4.00 mM) were observed to inhibit glioblastoma cell proliferation and induce cancer cell senescence *in vitro*^[143]. Pharmacological treatment of sodium

butyrate was also shown to significantly increase survival rate and delay the neuropathological sequelae in the R6/2 transgenic mouse model of Huntington's disease^[106]. The findings of Arnoldussen *et al.*^[144] demonstrated the beneficial effect of dietary butyrate intervention on the detrimental effects of high fat diet, including relieving high fat diet-induced cognitive impairment and dementia in humans. In addition to serving as a therapeutic agent in some specific diseases, sodium butyrate can have complementary effects when administered with other agents, such as metformin. Metformin is the most prescribed oral anti-diabetic agent, whose potential benefit in many diseases has been investigated. Recent research demonstrates that metformin is able to increase butyrate-producing populations within the gut microbiome^[145,146]. Additional data indicate metformin and butyrate have anti-inflammatory effects in relation to physiological functions, including transcription, replication, and repair in the process of tumorigenesis^[147]. Other SCFAs also have therapeutic effects. For example, glatiramer acetate serves as immunomodulator to reverse detrimental immune reactivity in two murine models of irritable bowel disorder. Collectively, these findings point to the therapeutic potential of sodium butyrate and other SCFAs in the treatment of various pathologies including neurological disorders.

Targeting the vagus nerve

Lewy body aggregates, constituted mainly by α -synuclein and ubiquitin, and GI dysfunctions are physiopathological characteristics of early development of Parkinson's disease^[148]. Braak *et al.*^[149] hypothesized that these early biomarkers initiate within the gut and then progress to the CNS via the vagus nerve and spinal cord. In support, vagus nerve-mediated brain migration of α -synuclein injected into the intestinal wall has been found in a rodent model^[150]. Sander and his colleagues further indicated the correlation between the vagus nerve and cognitive fatigue in multiple sclerosis patients^[151]. It is thought to be the result of the vagus nerve stimulation due to the pro-inflammatory cytokines causing changes in neural activity in brainstem and hypothalamus^[152]. Furthermore, the stimulation of the vagus nerve is used in the treatment of drug resistant depression, which is the major factor for developing Alzheimer's disease. Experiments in APP/PS1 (a murine model of Alzheimer's disease) animals were performed to induce morphological changes in microglia towards a neuroprotective phenotype, which was mediated by vagus nerve activation^[153]. Therefore, due to its important role in regulating the gut-brain axis through transferring microbial metabolites and neurotransmitters, such as SCFAs and GABA, manipulation of vagus nerve signaling may play a key role in modulation of some neurological conditions, including Parkinson's disease, Alzheimer's disease, and multiple sclerosis.

LIFE-STYLE INTERVENTIONS

Lifestyle interventions can affect gut microbiome composition, which influence brain activity and immune responses. Since neuroinflammation is strongly linked to neurodegenerative diseases, lifestyle alterations, such as dietary supplement and exercise, are able to play an important role in improving disease states.

Pre-/probiotic supplementation

Probiotics are living beneficial microorganisms (bacteria and yeasts), and prebiotics are the indigestible fibers which feed them^[154]. Probiotics have been widely marketed and consumed as dietary supplements or as functional foods, such as "live" yogurts^[154]. Probiotic treatments with *Lactobacillus acidophilus*, *L. casei*, and *L. rhamnosus* were able to affect transcription of host genes related to mucosal immunity in healthy human volunteers, supporting the ability of live bacterial cultures to affect host activities^[155]. D'Mello *et al.*^[26] demonstrated a probiotic mixture, VSL#3, was able to reduce "sickness behavior" by increasing novel social investigation in a liver inflammation rodent model, which was related to an increase in circulating G-CSF, reduction in TNF- α , and a decrease in activated microglia. In an *in vitro* study, peripheral blood mononuclear cells isolated from patients with Parkinson's disease were co-cultured with probiotic bacteria, *Lactobacillus* and *Bifidobacterium*, to investigate changes in innate immune cell release of inflammatory signaling markers. Probiotic strains were able to significantly reduce pro-inflammatory (TNF- α , IL-6, and IL-17A) and increase

anti-inflammatory cytokines (IL-4 and IL-10)^[156]. In another study of a randomized, double-blind trial, patients diagnosed with Alzheimer's disease given a probiotic mixture for 12 weeks, exhibited a significant score improvement on the mini-mental state examination compared to controls^[157].

High fiber prebiotic with or without probiotic supplementation can be a non-invasive strategy to treat neurological conditions. High fiber diets can affect gut microbiota abundance. For example, inulin is a prebiotic fiber and inulin-type fructan supplementation on the fecal microbiota is able to selectively change abundance of specific colon bacteria strains, such as *Anaerostipes*, *Bilophila*, and *Bifidobacterium*^[158]. As such, high fiber supplementation has been shown to counter age-related microbiota dysbiosis^[159]. Feeding mice with inulin has been shown to beneficially alter gut microbiome resulting in improved neurological outcomes through affecting gut microbiota-produced SCFAs. In support, high fiber diets, in which SCFAs can be derived, have numerous reported health benefits in reducing risk of type 2 diabetes, obesity, stroke, and cardiovascular disease. High fiber diets have been shown to increase circulating levels of butyrate, which may affect CNS function directly^[160]. Collectively, these studies provide exciting evidence and demonstrate the need for further investigations into the ability of live bacteria with or without prebiotic supplementation to treat inflammation and neurological pathologies.

Diet

The microbiota composition and diversity are sensitive to host dietary habits^[23,161]. Dietary factors may have pro-inflammatory or anti-inflammatory effects^[162], which can indirectly affect gut microbiota by providing multiple nutrients and specific compounds. For example, data suggest that the modified Mediterranean-ketogenic diet can modulate the gut microbiome and metabolites in association with improved Alzheimer's disease biomarkers in cerebrospinal fluid^[163]. The abundance of *Enterobacteriaceae*, *Akkermansia*, *Slackia*, *Christensenellaceae*, and *Erysipelotriaceae* increases while that of *Bifidobacterium* and *Lachnobacterium* reduces after modified Mediterranean-ketogenic diet treatment in subjects. A bad dietary habit, such as chronic alcohol intake, can induce neuroinflammation and neurodegeneration. Reduction of intestinal bacterial load was able to attenuate alcohol-associated CNS and gut inflammation^[164]. Alcohol activated microglia and modified its cell morphology, taking on an amoeboid shape with enlarged soma and shortened peripheral processes^[164].

Exercise

Exercise is considered as a protective treatment for neurodegenerative diseases^[165]. Both voluntary and controlled exercise can alter the gut microbiota^[166]. The microbiota composition of exercised rats was notably different from the sedentary rats with a significantly higher butyrate concentration^[167]. Voluntary running has neuroprotective effects in an α -synuclein rat model of Parkinson's disease^[168]. It can protect rats against neuronal loss, increase enteric glial expression, and modify gut microbiome composition in the Parkinson's disease model^[169]. Exercise is also considered to enhance immune system. The vagus nerve regulates gastrointestinal inflammatory tone. Parasympathetic neuroimmune reflex depends on vagal afferent neurons for the local release of intestinal inflammatory mediators in response to pathogenic gut bacteria. For this reason, elevated vagal tone and parasympathetic influence in the resting state of athletes foster a preferential anti-inflammatory milieu through conditionally influencing microbial composition^[170].

CONCLUSION AND FUTURE DIRECTIONS

Recent discoveries link the GBM and neurological disorders through the microbiota-gut-brain axis. It is also increasingly recognized that disruptions in the GBM ecosystem and its function may directly or indirectly impact CNS disease states, implicating the involvement of microglial-induced neuroinflammation and neurodegeneration. In this respect, there is bidirectional communication between the GBM and the brain, which is achieved through several pathways [Figure 1]. This communication involves the immune system, which not only supports the tolerance towards the microbiome ecosystem residing in the GI

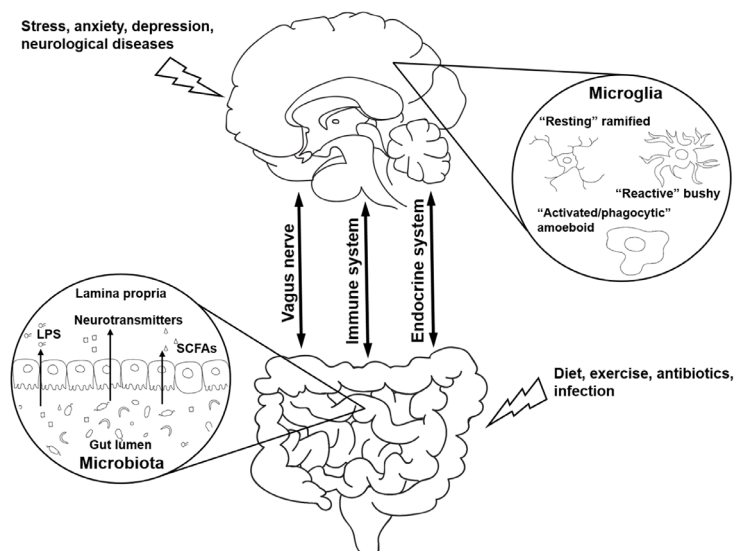


Figure 1. A schematic summarizing the pathways of gut-brain bidirectional communication with the emphasis on the immune system, the vagus nerve, and the endocrine system. The importance of the gut bacterial metabolites in this communication as well as lifestyle changes that affect microglia functioning in normal physiology and during neurological diseases with neuroinflammatory component are indicated. LPS: lipopolysaccharide; SCFAs: short-chain fatty acids

tract but also can react to dysbiosis and “leaky” gut, thus relaying this information to the CNS. On the other hand, there is the involvement of the vagus nerve in the microbiota-gut-brain interactions, which have several afferent and efferent pathways involving a variety of factors such as gut endocrine cells, neurotransmitters, and receptors. Importantly, the vagus nerve plays an important function in controlling inflammation through cholinergic and splenic-sympathetic anti-inflammatory pathways and the HPA axis. The role of hormones in the microbiota-brain bidirectional communication is also deemed important through regulation of the HPA and HPG axes. In addition, microbiota-derived metabolites, such as SCFAs and LCFAs, are integral in maintaining intestinal health and have been shown to also impact neurological health.

The GMB’s critical influence on host development, immune homeostasis, and metabolism as well as involvement in the development of the CNS disorders, makes it an ideal candidate for novel preventative therapies and treatments. These strategies include the use of beneficial “eubiotic” antibiotics or other means such as lifestyle interventions (diet and exercise) aimed at reversing microbiota “dysbiosis” by targeting microbiota and their metabolites. Although in its infancy, studies into the efficacy of the microbiome-targeted manipulation and FMT to treat diseases, including those beyond the GI tract, promise interesting insights into the importance and impact of the vast and diverse microcosm residing within us every day of our lives from birth to old age and death.

Certainly, we are still in the beginning of the research trying to reveal the causative links between the GMB and brain function as it relates to neurological disorders. There is a huge untapped potential in this area of microbiome in human health and disease, which will be more appreciated with the improvement of new technologies and methods of GMB research.

DECLARATIONS

Authors’ contributions

Designed the focus and scope of the review and substantially contributed to the bulk of the manuscript: Reyes REN, Asatryan L

Contributed to different sections of the review and all participated in editing and finalizing the manuscript: Reyes REN, Zhang Z, Gao L, Asatryan L

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Ethical approval and consent to participate

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Consent for publication

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