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1354 *Current Neuropharmacology,* **2021**, *19,* **1354-1366**

REVIEW ARTICLE

Gut Microbiota Regulate Astrocytic Functions in the Brain: Possible Therapeutic Consequences

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ARTICLE HISTORY

Received: November 28, 2020
Revised: February 03, 2021
Accepted: February 11, 2021

DOI:
10.2174/1570159X19666210215123239

Abstract: Astrocytes are essential for maintaining the homeostasis of the central nervous system (CNS). Astrocytic dysfunction has been implicated in the progression of several neurodegenerative and psychiatric diseases; however, a multitude of factors and signals influencing astrocytic activity have not been entirely elucidated. Astrocytes respond to local signals from the brain, but are also indirectly modulated by gut microbiota. Previous studies revealed that most of the CNS diseases triggered by astrocytic dysfunction are closely associated with the dysbiosis of gut microbiome. Emerging data from preclinical and clinical studies suggest that the maturation and functioning of astrocytes rely on gut microbiota, which plays a pivotal role in the decrease of astrocytic activation and may alleviate symptoms of brain diseases. Herein, we discuss the most recent advances concerning the complex connections between astrocytes and gut microbiota, which are involved in the immune, neurotransmission and neuroendocrine pathways. Deciphering these pathways will facilitate a better understanding of how perturbed gut microbiota contributes to the dysfunction of astrocytes and open therapeutic opportunities for the treatment of brain diseases.

Keywords: Astrocytes, gut microbiota, central nervous system, brain diseases, gut-brain axis, neurodegenerative diseases, psychiatric diseases.

1. INTRODUCTION

Astrocytes account for approximately 20-40% of all glial cells in the central nervous system (CNS) [1]. They are coupled to each other by gap-junctions, which allow the exchange of ions and small cytosolic components, supporting the generation of glial networks [2]. Astrocytes enwrap with their cellular processes synaptic structures [3, 4] and thereby establish the so called "tripartite synapse" consisting of these processes, presynaptic nerve terminals and postsynaptic dendritic specializations modulating neuronal circuits [5]. In addition to participating in neuroinflammation by a phenomenon called astrogliosis [6], astrocytes also exert vital effects on synapse formation during development and adult neurogenesis [7]. By their end-feet they regulate the vascular tone [8] and participate in the establishment of the blood-brain barrier (BBB) [9, 10]. Astrocytes possess multiple receptors, activated by neurotransmitters/signaling molecules such as glutamate, serotonin, ATP, and cytokines, widely recognized to contribute to the dysfunction of the brain under pathological conditions [11]. Therefore, astrocytes have important roles in neurodegenerative disorders (*e.g*. neuropathic and chronic pain [12]. Parkinson's disease (PD) [13, 14], Alzheimer's disease (AD) [15, 16], epilepsy [17]) as well as psychiatric illnesses (*e.g*. major depressive disease (MDD) [18], autism spectrum disorders (ASD) [19, 20].

Gut microbiota is a general term to define various microbial communities colonizing the host's gastro-intestinal tract, involved in the balance of enteric microecology [21-23]. Abundant experimental data from the Human Microbiome Project (https://www.hmpdacc.org/) suggest that gut microbiota may regulate brain function and behavioral phenotype of hosts *via* an inextricable communication network known as the "gut-brain axis", underlying the communication between the enteric and central nervous systems [24]. The interaction of microbiota with the gut-brain axis has been implicated to mainly include neuroendocrine and immune pathways and direct nerve afferents, by which microbiota could modulate the activity of neurons and glial cells in the CNS, thereby affecting the host's behavior or emotion.

Astrocytes were recently proposed to be implicated in the pathways of microbiota/gut-brain axis in MDD [25, 26], ASD [27, 28], PD [29, 30], AD [31, 32], *etc*. Therefore, revealing the effects of the gut-brain axis on astrocytic activity may facilitate the investigation of potential therapeutic targets for various neurological diseases. In this review, we will

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1570-159X/21 $65.00+.00

evaluate recent advances in our knowledge on the interaction between astrocytes and the gut-brain axis, and the consequent implications for brain homeostasis. According to our knowledge, this review is filling a gap in the considerable amount of papers discussing the neuron-microbiota interrelationship.

2. GUT MICROBIOTA AND METABOLITES

Gut microbiota has been recently considered to be a crucial endocrine organ which is able to produce bioactive molecules to maintain the host's undisturbed functioning [33, 34]. These molecules consist of an array of metabolites produced at the interface between gut microorganisms and the host; they mainly include the essential aromatic amino acid tryptophan, short-chain fatty acids (SCFAs) manufactured by the microbes from the fermentation of dietary fibers, and bile acids produced in the liver and transformed by gut microbiota [33, 34]. Emerging sequencing data suggests that the gut is a complex ecosystem which contains mostly obligatory anaerobes like Bacteroides, Eubacterium, Bifidobacterium, Ruminococcus, Clostridium, and Lactobacillus in the ileum, and to a minor extent of aerobic bacteria or facultative anaerobes, such as *Escherichia coli* and Streptococcus [35-38]. Unabsorbed carbohydrates, proteins and peptides support these microbiota activities, and are metabolized into amino acids, fatty acids, organic acids, phenols, phenyl and its derivatives, indole, *etc*. Moreover, the metabolites derived from microbial fermentation of dietary fibers (like acetic acid, propionic acid and butyric acid), and the metabolites of tryptophan (like serotonin, kynurenine and indole) have been revealed to play vital roles in gut-brain interactions.

3. GUT MICROBIOTA MODULATE ASTROCYTES IN BRAIN

3.1. Gut Microbiota Influence Maturation and Function of Astrocytes

Gut microbiota in embryonic and early postnatal development appear to be key regulators of the maturation and function of astrocytes. Astrocytes and other glial cells are massively increased in number during the early postnatal period [39]. This growth, together with the corresponding growth in the number of neurons results in a continuous and dramatic expansion of brain volume amounting to three- to four-fold in humans from birth to age six, and more than six-fold in rats from birth to adulthood [39, 40]. This postnatal neurodevelopment is most likely affected by genetic and environmental factors. Latest evidence indicates that gut microbiota in early life has emerged as an environmental factor, acting directly or indirectly on development, maturation and function of the CNS [41]. For instance, early in the ontogenetic development of rat astrocytes, dietary treatment with lactic acid, a product of Lactobacilli, plays an important role [42].

3.2. Gut Microbial Dysbiosis Affects Astrocytes in the Brain

Interestingly, between brain and gut microbiota exists a mutual relationship in that gut microbiota factors are among the most potent modulators of astrocytic number, morphology and functions. Astrocyte abnormalities have a crucial role in the neuroinflammatory pathophysiology, and have been regularly observed in disorders accompanied by gut dysbiosis. Astrocytes constantly survey their local microenvironment for signals of injury and danger arising *i.e*. from intestinal microbiota disorders. For example, it is well-established that negative emotional states emerge from activity in the central amygdala. It was reported that neuroinflammatory genes, notably Tnf encoding tumor necrosis factor-α (TNF-α), were upregulated in the opioid withdrawal condition in highly active astrocytes of the amygdala, and in parallel, a decreased Firmicutes to Bacteroides ratio indicated gut dysbiosis [43]. Additionally, an increase in the number of S100β-immunopositive astrocytes in the brain of ASD children and a misbalance of certain bacteria in their guts was shown to develop simultaneously [20]. In rats subjected to chronic unpredictable mild stress (CUMS), with the aim to induce depression-like behavior, hippocampal astrocytes were activated, as indicated by an increased number of glial fibrillary acidic protein (GFAP)-immunopositive cells; this was accompanied by the destruction of gut microbiota (altered ratio of Lactobacillus to Clostridium) [44]. Treatment with finasteride which is known to decrease the synthesis of the dihydrotestosterone, also caused depressive-like behavior in male rats and elevated the number of GFAP-immunoreactive astrocytes in the hippocampal dentate gyrus, and caused dysbiosis in their gut [45]. Furthermore, the detection of activated astrocytes after traumatic brain injury (TBI) [46], AD [47, 48] and PD [49] was accompanied by alterations of gut microbiota, suggesting that gut microbiota contributes to astrocyte number, activation and function in the brain.

Another biologically and therapeutically important proof for the existence of a gut-brain axis is that diet regulates the number and properties of astrocytes in the brain *via* gut microbiota. Astrocytic density decreased in the hypothalamus of female mice fed with high fat, high sugar diet, alongside Bacteroidetes and Firmicutes abundance in their guts [50]. Ingestion of a certain type of bioactive food decreased the astrocytic/microglial activation in the brain of 3xTg-AD mice and consequently improved β-amyloid (Aβ) aggregation/tau hyperphosphorylation; this was found to be due to a restoration of healthy gut microbiota resulting in less lipopolysaccharide (LPS) production [51]. Altogether, these data confirm an important role of astrocytic functions regulated by the microbiota-gut-brain axis, in light of dietary content determining intestinal microenvironment.

It is of equal importance that some metabolites of gut microbiota, such as SCFAs have also been found to play a key role in astrocytic activation. The dopaminergic neurotoxin MPTP selectively damages dopamine neurons of the substantia nigra pars compacta. Sodium butyrate, an abnormal metabolic product of SCFAs, significantly increased the number of activated astrocytes, decreased dopamine and 5-HT levels, exacerbated declines of dopaminergic neurons, and finally aggravated neuroinflammation in the brain of MPTP-treated mice [52]. *In vitro*, sodium butyrate also exerted a strong anti-inflammatory effect against LPS-induced responses in neural co-cultures of microglial cells, astrocytes

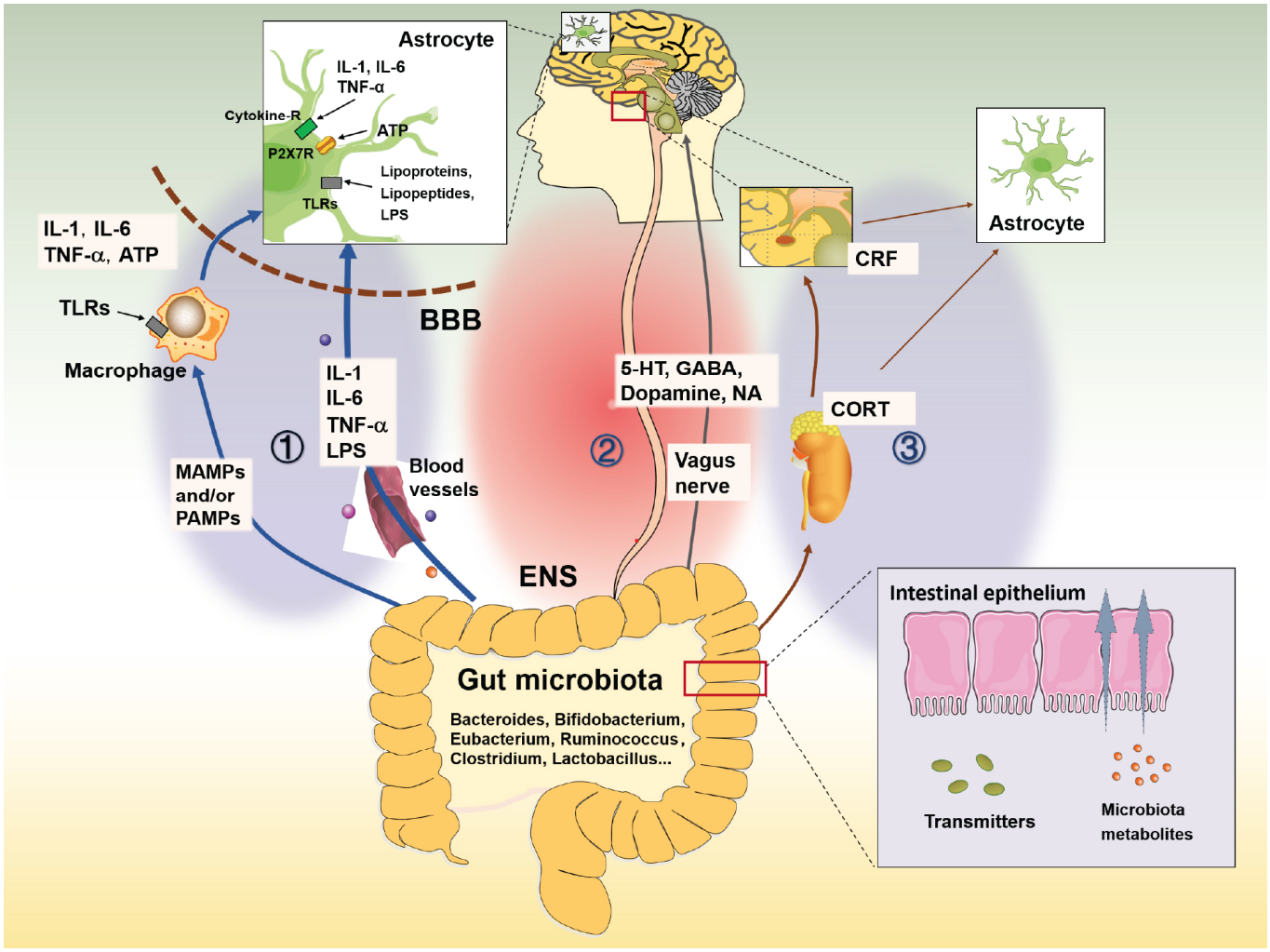

Fig. (1). Gut microbiota modulate astrocytic functions in the brain. Recovery of normal gut microbiota by antibiotics, dietary measures and fecal microbiota transplantation can regulate the number of astrocytes and their activity in the CNS. Communication between gut microbiota and astrocytes is mediated directly and indirectly by immune, neuronal and endocrine pathways. (1) Altered composition of gut microbiota may increase the permeability of the BBB, allowing cytokines and microbiota metabolites to enter the brain. MAMPs and PAMPs stimulate macrophages to secrete a range of cytokines and cellular damage releases ATP into the extracellular space. (2) Enteric neurons located in the intestinal wall, send information to the brain through synapsing spinal cord or vagal nerve afferents. (3) Hormones of the hypothalamic-pituitary-adrenal axis regulate the morphology and function of central astrocytes in endocrine and paracrine ways. Inset "Astrocyte": These cells possess receptors for cytokines, LPS and ATP. Inset "Intestinal epithelium": Transmitters (*e.g.* 5-HT, histamine) as well as microbiota metabolites (*e.g.* short-chain fatty acids, phenols, indol) increase the trans-cellular and para-cellular permeability of these cells. BBB, blood-brain-barrier; CORT, corticosteroids; CRF, corticotropin releasing factor; ENS, enteric nervous system; LPS; lipopolysaccharide; MAMPs, microbe-associated molecular patterns; PAMPs, pathogen-associated molecular patterns. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

and cerebellar granule neurons [53]. Myxobacteria produce a wide range of bioactive metabolites; in fact their extracts protected human primary astrocytic cultures from oxidative stress by increasing the glutathione level in cells [54].

Astrocytes do not require mitochondria to satisfy energy demand, but alterations in mitochondrial function determine astrocyte activity and regulatory effects [55]. The SCFA, butyrate, is an important regulator of mitochondrial function across different cell types [56]. This is mediated by a number of effects, including the upregulation of the melatonergic pathway, epigenetic histone deacetylase inhibition, and the optimization of mitochondrial function, partly *via* an increase in oxidative phosphorylation [57, 58]. Such effects seem to arise from increasing pyruvate dehydrogenase complex activity, and therefore the conversion of pyruvate to acetyl-CoA, which regulates the tricarboxylic acid (TCA) cycle and oxidative phosphorylation as well as the cytoplasmic and mitochondrial melatonergic pathway [59]. As astrocyte mitochondria are significant determinants of astrocytic function, it is important to mention that gut microbiome-derived SCFAs, such as butyrate, may have significant impacts on astrocytes *via* the regulation of their mitochondria.

Recent work in a rat model of ASD has suggested that propionic acid (PPA; an enteric bacterial metabolic product)

administered intracerebroventricularly caused neuroinflammation and reactive astrogliosis in hippocampus and white matter [60]. In addition, these rats displayed restricted behavioral interest to a specific object among a group of objects, impaired social behavior, and impaired reversal in a T-maze task, compared to controls. Astrocytes in the amygdala of naïve rats were also activated by a single relatively low dose of PPA and exhibited swollen and/or proliferating appearances under electron microscopic observation [61]. Both L-tryptophan and its metabolite L-kynurenine enhanced nerve growth factor (NGF) production in cultured mouse astroglial cells [62, 63].

3.3. Recovery of Gut Microbiota Composition Improve Astrocytic Dysfunction

Fecal microbiota transplantation, antibiotic therapy and probiotics reverse the composition of intestinal microbiota, and reverse the pathological activation of astrocytes. This is a beneficial therapeutic strategy not only in gastrointestinal diseases (*i.e.* inflammatory bowel disease and irritable bowel syndrome) but also in brain diseases (*i.e.* MDD, AD, PD), even if the underlying mechanism still remains to be explored. It was demonstrated that nucleotide-binding leucine-rich repeat, pyrin domain containing 3 (NLRP3) KO mice exhibited less depressive-like behavior in response to chronic unpredictable stress than the WT littermates [26]. This difference was accompanied by astrocyte dysfunction and altered microbiota composition in gut of the WT mice, which could be reversed by oral challenge with transplants of fecal microbiota taken from KO mice. Interestingly, perturbations in microbial diversity induced by life-long combinatorial antibiotic selection pressure in the APPswe/PS1ΔE9 mouse model of amyloidosis is commensurate with reductions in amyloid-β (Aβ) plaque pathology and plaque-localized gliosis [47, 48]. In experimental autoimmune encephalomyelitis, a rodent model of multiple sclerosis, both type I interferons and a gut metabolite of dietary tryptophan limit CNS inflammation *via* the activation of the aryl hydrocarbon receptor of astrocytes and the consequent suppression of the cytokine signaling 2 pathway [64].

Traumatic brain injury (TBI) causes dysbiosis and intestinal barrier disruption, which further exacerbate brain damage *via* an inflammatory pathway [65]. It was found that treatment of mice with the probiotic Lactobacillus acidophilus on the day of weight drop impact caused neuroprotection from traumatic brain injury. The neurological severity score, the increased concentrations of TNF-α and IL-1β, and the increased number of astrocytes/microglia were normalized by the probiotic. Although in this case the primary target of the beneficial effect was probably not the astrocyte, this cell type profoundly participated in the beneficial response to mechanical damage. 6-week dietary supplementation with prebiotics (fructo- and galacto-oligosaccharides) upregulated Atp1a2 and Pfkfb3 mRNA expression in the hippocampus of chronic psychosocial stress mice, which was the first report on influence of gut microbiota and prebiotics on mRNA expression of genes implicated in the metabolic coupling between neurons and astrocytes [58].

In conclusion, both microbiomic and metabonomic evidence strongly supports the idea that gut microbiota modulation can be a promising therapeutic strategy to improve astrocytic reactions and thereby, various neurodegenerative diseases.

4. HOW DO GUT MICROBIOTA MODULATE ASTROCYTIC FUNCTIONS

Over recent decades, accumulating data have provided a clue that commensal gut microbiota is implicated in modulating both the activation and function of astrocytes, thus influencing brain pathophysiology. Currently, microbiota is supposed to modulate the activity of astrocytes by the gut-brain axis, *via* immune, neuronal and neuroendocrine pathways.

4.1. Immune Activation and Inflammatory Mediators

Immune pathways are important components mediating the interaction of gut microbiota with astrocytes in the brain. The development and maturation of the immune system are accompanied by the formation of stable gut microbiota; the perturbation of microbiota equilibrium may trigger immune responses in both intestine and CNS. Intestinal lymphoid tissue, known as the largest immune organ of the human body, contains about 70%-80% of the total immune cells of the organism and provides the first barrier to microbiota influences on astrocytes in the brain [66, 67]. The antigen information of symbiotic and pathogenic bacteria is recognized by intestinal epithelial cells, and is then transmitted to antigen-presenting cells in the lymph node through transswallowing effects, thus inducing immune activation or tolerance. Meanwhile, enteric neurons in the lamina propria extend synapses directly to the junctions of intestinal epithelial cells to receive immune signals [68] and transmit them to the CNS. In a recent report, two distinct signals from gut microorganisms coordinately activate autoreactive T cells in the small intestine [69]. These cells respond specifically to myelin oligodendrocyte glycoprotein to act on the inflammation of extra-intestinal tissues, in which the family of Erysipelotrichaceae acts similarly to an adjuvant to enhance the responses of T helper 17 cells; a strain of Lactobacillus reuteri possesses peptides that potentially mimic myelin oligodendrocyte glycoprotein.

4.1.1. Cytokines

Pro-inflammatory cytokines derived from intestinal dysbiosis are vital immune signals for activating brain astrocytes directly. Microbiota and their products, mainly including SCFAs, 5-HT and aryl hydrocarbon receptor ligands, may stimulate intestinal epithelial cells and macrophages in the gastrointestinal tract, resulting in activation of immune response and release of inflammatory cytokines. Cytokines produced by monocytes/macrophages in the intestine (IL-1β, IL-6, TNF-α) can reach the brain *via* the systemic circulation, pass the BBB (probably by active transport), and are then recognized by astrocytes [70-72]. The activation of astrocytes and especially microglia induces neuroinflammation. What's more, it should be mentioned that the gut and astrocytes are integral aspects of the circadian system [73, 74], which can be dysregulated by an increase in gut permeability-derived LPS, inhibition of pineal melatonin production [75]. Pineal melatonin can also be suppressed by pro-inflammatory cytokines [76], indicating that pro-inflammatory cytokine induced gut permeability and gut

dysbiosis may be co-ordinated with circadian dysregulation, coupled to an increase in LPS that impacts on the function of astrocyte and other cells. This is of some importance to wider immune and glia regulation, as such inhibited pineal melatonin release will attenuate melatonin's resetting of immune and glia cells [58]. This gives an indication of the complexity of the wider interactions of the gut microbiome with astrocytes.

Microbe-associated molecular patterns (MAMPs) and pathogen-associated molecular patterns (PAMPs) from gut microbiota, are recognized by pattern recognition receptors (PRRs; mainly Toll-like receptors) located on monocytes/macrophages, microglia and natural killer (NK) cells in the periventricular apparatus and choroid plexus; this induces the release of inflammatory cytokines, which influence the activity of astrocytes [77, 78]. In an experimental autoimmune encephalomyelitis (EAE) mouse model of MS, it has been found that metabolites, released from the breakdown of dietary tryptophan by commensal bacteria, control signals between microglia and astrocytes to modulate pathogenesis. Transforming growth factor-α (TGF-α), a signal molecule released by activated microglia, limited astrocytes' pathogenic activities and their contribution to inflammation in EAE. Conversely, microglial vascular endothelial growth factor B (VEGF-B) promotes astrocytes' pathogenic activities and worsens inflammation and EAE progression [79]. Moreover, the latest study revealed that gut microbiota modulated the interferon-γ (IFNγ) expression in meningeal NK cells, thus driving the expression of astrocytic TRAIL, by which $LAMP1^+TRAIL^+$ astrocytes induced T cell apoptosis to limit CNS inflammation [80].

In addition, the above mentioned immune cells also produce ATP to activate astroglial P2X7 purinergic receptors, which allow Na^+/Ca^{2+} to enter and K^+ to leave cells, then inducing IL-1β release and neuroinflammation [81]. Additionally, aryl hydrocarbon receptor ligands from microbial metabolism of dietary tryptophan can regulate the activity of astrocytes indirectly by promoting microglia to produce TGF-α and VEGF-B [79]. However, gut microbiota can also limit astrocyte activities by generating aryl hydrocarbon receptor agonists [63, 82].

4.1.2. Toll-like Receptors (TLRs)

TLRs seem to be indispensable for the participation of gut microbiota in the modulation of host immune response. Multiple TLR subtypes, including TLR2, TLR3, TLR4, TLR5 and TLR9, have been described to occur on astrocytes, and to be involved in neuroinflammation [83, 84]. Particularly, TLR2 and TLR4 work as key mediators for the regulation of gut microbiota on astrocytes, since they can recognize bacterial components (*e.g.* lipoproteins, lipopeptides and LPS), and activate the downstream inflammatory pathways [85]. TLR engagement initially activates distinctive adaptor proteins, such as myeloid differentiation primary response gene 88 (MyD88) or toll-interleukin receptor (TIR) domain-containing adapter-inducing interferon-β (TRIF), and then delivers the signals to downstream inflammatory pathways. The downstream nuclear factor kappa-B (NF-κB) [86], mitogen-activated protein kinases (MAPK), and/or interferon-regulatory factor signaling pathways terminally regulate the expression of genes for inflammatory responses [87]. High-fat diet induces gut dysbiosis disrupt the intestinal barrier function and elevate the circulating endotoxin level (*e.g.* LPS) [88], which activates brain astrocytes and triggers neuroinflammation [83, 84]. Meanwhile, high-fat diet has been reported to increase the expression of TLR2 and TLR4 at lymphocytes, indicating enhanced inflammation [88].

It is important to recognize that gut microbiota may influence the phenotype and activity of astrocytes to modulate brain inflammatory responses *via* immune pathways. Further studies will hopefully explore the microbiota-derived factors and metabolites responsible for immune signaling, thus promoting insight into the complex dialogue between gut microbiota and astrocytes in health conditions and neurodegenerative disorders.

4.2. Neurotransmitters

A number of neurotransmitters are responsible for integrating intestinal motility with endocrine and immune activity signals, which can rapidly enter the brain, participating in astrocytic activity regulation. The neuronal connections converging on enteric neurons constitute the neurotransmission pathway of the gut-brain axis. Thus, these extrinsic enteric-associated neurons identify microbial dysbiosis, and transfer corresponding information to the brain through vegetative ganglia (sensory nodose ganglion, dorsal root ganglia). A microbially-responsive subset of viscerofugal neurons in the ileum and colon, responsive to microbial colonization, sends axons to the prevertebral ganglia and is poly-synaptically connected to the liver and pancreas, to modulate feeding and glucose metabolism [89].

Furthermore, a range of G protein-coupled receptors expressed on unmyelinated vagal afferents have been characterized to respond to microbiome-derived metabolites, lipids and inflammatory factors, as the fastest pathway to deliver the information on intestinal homeostasis to the CNS [90]. The vagus nerve forms direct contacts with endocrine and immune cells as well as with enteric neurons; thus, the sensory, immune and endocrine signals are rapidly transferred from gut to brain *via* vagus nerve afferents [91]. For example, it is proposed that the shift of gut microbiota induced by high energy-containing diet disrupts vagal gut-brain communication resulting in microglia activation, and increased body fat accumulation [92].

However, our understanding of the regulation by gut microbiota through the vagus nerve of astrocytic functions is still incomplete, although neurotransmitters released from gut microbiota have been shown to modulate nervous system activity and behaviors [93].

4.2.1. 5-Hydroxtryptamine (serotonin)

90–95% of serotonin is produced in the gastrointestinal tract, especially by epithelial enterochromaffin cells [94], which can directly or indirectly influence the function of astrocytes [95, 96]. Selective serotonin reuptake inhibitors (SSRI) significantly increase vagal activity. SSRI increases the excitability of intrinsic primary afferent neurons in the myenteric plexus through an intestinal epithelium dependent

mechanism, and alter diversity of gut microbiota. Subdiaphragmatic vagotomy, blocking vagal signaling from gut to brain, abolishes the anti-depressive effect of oral SSRI treatment [97]. The SSRI paroxetine can ameliorate the reactive microglia-mediated inflammatory responses in astrocytes, partially *via* inhibition of the NF-κB pathway [98]. Fluoxetine, another SSRI, has been suggested to protect astrocytes in mice, subjected to chronic unpredictable mild stress, by promoting autophagosome formation and increasing clearance of injured mitochondria [99]. Furthermore, fluoxetine inhibited activation of astrocytes by ameliorating neurotoxicity in and APP/PS1 mouse model of AD [100].

4.2.2. Dopamine

Dopamine, noradrenaline and adrenaline are major catecholamines in the CNS. In a number of cases, these catecholamines in bacterial cells appear to be more abundant than in higher order animal cells [101], which suggests that the ability of commensal microbiota to secrete dopamine and noradrenaline allows them to communicate with the host body, especially *via* the nervous system. When mice were treated with non-absorbable antibiotics to reduce gut bacteria, enhanced sensitivity to cocaine reward and locomotor-sensitizing effects of repeated cocaine administration was observed [102]. Since euphoria caused by cocaine consumption is known to depend on the release of dopamine in the mesocortico-limbic system of the brain, the depletion of gut microbiota by antibiotics was assumed to act *via* this system. In fact such treatment was shown to cause significant depression of monoamine levels in brainstem and gut microbiota [103] and elevation of dopamine D2 receptor signaling in the nucleus accumbens [104]. The above data indicate that the effect of gut microbiota on brain dopamine was capable of modulating the activity of astrocytes through distinctive receptors [104, 105], thus inducing their morphological transformation [106, 107] and eventually neuroinflammation [108, 109].

4.2.3. γ-Aminobutyric Acid (GABA)

Commensal microbiota are potentially involved in GABAergic regulation of astrocytes [110, 111]. Lactobacilli in the gut have the capability of consuming or producing GABA, thereby ameliorating metabolism and depressive-like behavior in a mice model of the metabolic syndrome [112]. Oral Lactobacillus increased brain GABA and glutamate levels [113]. Human gut microbiota also produce GABA, and the brain signatures referring to MDD, a disease associated with an altered GABAergic response, negatively correlated with the relative abundance of levels of fecal Bacteroides [114]. Oral supplementation of Bifidobacterium dentium engineered to produce GABA, reduced the sensitivity to visceral pain in a rat model [115].

4.3. Neuroactive Hormones

Hormones are another important component of the gut-brain axis to participate in the regulation of astrocyte morphology and function. More than 20 kinds of endocrine cells are found in the intestine. Lines of evidence have verified that gut microbiota is implicated in regulating the activity of these peripheral endocrine cells, thus affecting the biosynthesis of neuroactive hormones to protect brain homeostasis. Especially hormones of the hypothalamic-pituitary-adrenal axis (HPA) are important in this respect.

The corticotropin-releasing factor/hormone (CRF/CRH) secreted in the hypothalamus stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH), and then induces the adrenal cortex to release glucocorticoids (cortisol and corticosterone [CORT]) [116]. In turn, the massive release of CORT inhibits the secretion of CRH, thus forming a negative feedback cycle. Receptors for the individual hormones of the HPA axis are widely expressed on astrocytes indicating that this axis is capable of regulating astrocytic activities. CRF/CRH [117, 118] and CORT [119, 120] are directly targeted to their distinctive receptors on astrocytes, then stimulating Ca^{2+} influx [121], inducing astrocytic activity and proliferation [122], and resulting in inflammation [123, 124]. In addition, CORT could accelerate hypoxia- and cyanide-induced astrocyte ATP loss in the hippocampus [125], and damage interactions between neurons and astrocytes [126, 127], thus reducing astrocytic structural plasticity [128]. In a CORT-induced mouse model of MDD, the protrusion length and GFAP protein expression of astrocytes were decreased in the hippocampus [129]. Stress-induced CRH not only acts on astrocytes, but also, *via* TNF release from enteric mast cells, increases gut permeability [130]. This would indicate some CRH-driven co-ordination of astrocytes and the gut.

Accumulating evidence implies that the HPA axis has considerable importance in mediating CNS responses to microbiota in the intestine [131, 132]. In response to open-field stress, serum corticosterone concentrations were higher in germ-free (GF; gut microbiota is missing) than in specific pathogen-free rats. Simultaneously, GF rats were less active in the social interaction test than their specific pathogen-free counterparts and displayed a lower number of visits to the aversive central area of the open-field [133]. Chronic restraint stress also induced a greater increase of CRH, ACTH and CORT levels in GF mice than in the specific pathogen-free ones, resulting in an anxiety-like behavioral phenotype [134]. These differences in the behavioral responses to psychosocial stress of the two strains of mice were primarily due to the effects of microbiota on the expression of genes involved in HPA axis regulation [135]. Furthermore, GF mice showed antianxiety- and antidepressive-like behaviors, while "depression microbiota" recipient mice (fecal samples of severe depressive patients were transferred to GF mice) exhibited anxiety- and depressive-like behaviors [136]. In addition, six glucocorticoid receptor pathway genes were upregulated in GF mice. In addition, ingestion of a Bifidobacterium longum subspecies alleviated hyperactivity of the HPA axis response in chronic stress-induced depressive mice through reshaping gut microbiota [137].

Maternal probiotic intervention with Bifidobacterium and Propionibacterium has also been observed to increase neonatal CORT levels in female rats, as well as elevate the adult ACTH levels and alter neonatal microbiota comparable to that of maternal separation (being a massive stressful stimulus) [138]. These studies indicate a capability of gut microbiota to maintain the CNS homeostasis *via* modulating the activity of the HPA axis.

4.4. The Blood-Brain Barrier (BBB)

The BBB is a structural and functional barrier between the interstitial fluid of the brain and the blood to maintain a precisely controlled biochemical environment of the brain; it is formed by endothelial cells, macrophages, pericytes and astrocytes [139, 140]. Gut dysbiosis increased the permeability of BBB, allowing labeled antibodies and other substances to enter the brain parenchyma, suggesting that integrity and permeability of the BBB depend on the composition and diversity of the bacteria [141, 142]. The BBB permeability of GF mice after birth and during adulthood has increased compared with normal mice, by exhibiting a reduced expression of tight junction proteins. Similarly, exposure of GF adult mice to a pathogen-free gut microbiota reduces BBB permeability and up-regulates expression of tight junction proteins [143]. It follows that interaction between intestinal microbiota and BBB barrier begins in the embryonic stage and continues during the entire life cycle. On the other hand, circulating microbes and their toxins increase the expression of cell adhesion molecules, the release of cytokines/ chemokines, and the opening of the intercellular junctions, finally leading to the loosening of this barrier.

Microbiota metabolites like LPS, SCFAs, zymosan and others can pass through the BBB to activate astrocyte directly [144, 145]. LPS, zymosan and polyinosinic-polycytidylic acid (poly[I:C]) [146] down-regulate TLR4 and up-regulate TLR2, as well as the level of pro-inflammatory astrocytic cytokines (TNF-α, IL-1β, IL-6, IL-8) [147, 148]. Activated astrocytes and microglia induce tau phosphorylation (typical for AD), by activating glycogen synthase kinase 3β (GSK-3β) and stimulate the secretion of inflammatory cytokines (IL-1β, TNF-α) in the hippocampus [149].

CONCLUSION AND THERAPEUTIC CONSEQUENCES

Bidirectional communication along the gut-brain axis is a fundamental aspect of the synergy between microbiota and the host in accessing gut-brain signaling pathways to modulate host brain and behavior. Gut microbiota can influence the activity of astrocytes in the CNS, which in turn modulate neuronal circuits essential for behavior and emotional states. This review attempts to clarify the immune, neurotransmission and neuroendocrine pathways through which gut microbiota regulates astrocytic functions.

However, it would not be neglected that finding an association between gut dysbiosis and altered brain function does not establish a cause-effect relationship in either direction. This may be especially true for those experimental data that show concomitant alterations in gut microbiota composition and gene expression in various brain cell types (astrocytes, neurons, microglia) and/or behavior after administration/withdrawal of exogenous substances that may act concomitantly in the brain (altering neuronal connectivity), in the gut (altering motility, secretion, *etc*.) and, perhaps, on particular bacteria fila.

The studies mentioned above have evaluated how, through pharmacological and nonpharmacological means, gut microbiota may regulate astrocyte function [46, 47, 50, 150, 151]. In addition, gut microbiota modulates host's health and disease by the production of several substances, including LPS and SCFAs [60-62], among others. A recent new research has shown that melatonin increased SCFA production to protect DSS-induced neuroinflammation in the hippocampus and metabolic disorders in the liver of DSS rats [152]. Thus, a fascinating and hitherto neglected aspect of the field is how the recovery of a pathologically altered microbiota composition by selective antibiotic therapy, dietary measures, and transplantation of fecal microbiota may restitute healthy brain features.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This work was supported by grants from National Key R&D Program of China (2019YFC1709101), the Project First-Class Disciplines Development of Chengdu University of Traditional Chinese Medicine (CZYHW1901), and Science and Technology Program of Sichuan Province, China (2019YFH0108).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

We are grateful to Prof. Peter Illes for the correction and great comments on this manuscript.

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