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REVIEW

Gut microbes and metabolites as modulators of blood-brain barrier integrity and brain health

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ABSTRACT

The human gastrointestinal (gut) microbiota comprises diverse and dynamic populations of bacteria, archaea, viruses, fungi, and protozoa, coexisting in a mutualistic relationship with the host. When intestinal homeostasis is perturbed, the function of the gastrointestinal tract and other organ systems, including the brain, can be compromised. The gut microbiota is proposed to contribute to blood-brain barrier disruption and the pathogenesis of neurodegenerative diseases. While progress is being made, a better understanding of interactions between gut microbes and host cells, and the impact these have on signaling from gut to brain is now required. In this review, we summarise current evidence of the impact gut microbes and their metabolites have on blood-brain barrier integrity and brain function, and the communication networks between the gastrointestinal tract and brain, which they may modulate. We also discuss the potential of microbiota modulation strategies as therapeutic tools for promoting and restoring brain health.

Introduction

The gut microbiota play an essential role in the functioning of many organs in the body, including the brain. Our understanding of the composition and metabolism of the diverse ecosystem populating the gut, and the complex communication networks comprising the gut-brain axis are rapidly increasing in hand with advances in high-throughput 'omics-based technologies. This review summarises findings linking the gut microbiota and brain health, with a focus on the impact of gut microbes, and the metabolites they generate from dietary components, on blood-brain barrier integrity. We discuss how these metabolites travel throughout the body along bidirectional neural and circulatory routes, from the perspective of the current knowledge of specific mechanisms. We also highlight the potential therapeutic potential on brain health of manipulating the gut microbiota via delivery of prebiotics, probiotics, and fecal microbiota transplantation. Such approaches can be effective in treating gastrointestinal disorders, and while their suitability and efficacy to treat neurological and neurodegenerative conditions require investigation, they are promising tools that may open unexplored routes to disease treatment and prevention through precise microbiome-targeted therapies.

The intestinal microbiota in health and neurodegenerative diseases

The human microbiota consists of a diverse and dynamic population of microbes, including bacteria, archaea, viruses, fungi, and protozoa, that establish a mutualistic relationship with the host. More than 10^{14} bacteria cells populate the gastrointestinal (GI) tract the vast majority of which (10^{10}–10^{12} CFU/g of intestinal content) are located in the ileum and colon.[12] A taxonomically diverse intestinal microbiota is associated with integrity of the epithelial barrier, and maintenance of intestinal metabolic and immune homeostasis. Some species of *Lactobacillus* and *Bifidobacterium* genera are considered beneficial, with the presence of *Lactobacillus rhamnosus*, for example, associated with increased intestinal barrier function and

expression of epithelial tight junction proteins, and decreased serum levels of inflammatory cytokines.[3] By comparison, overgrowth of *Clostridium* is often a feature of intestinal microbial dysbiosis and increased intestinal permeability ("leaky gut syndrome"), a feature of inflammatory bowel diseases and other immune-related intestinal and extra-intestinal disorders.[4] Beyond the GI-tract, the microbiota may also play a role in the functioning of other organ systems including the brain.[5] Evidence for the GI-microbiota influencing the brain comes primarily from animal studies, in particular germ-free rodents, in which structural and functional attributes of the brain can be assessed prior to, and after, microbial exposure and colonization. The absence of gut microbes is associated with structural alterations in the blood-brain barrier (BBB), characterized by decreased expression of tight junction proteins, leading to increased permeability compared to conventional-specific pathogen free (SPF) mice.[6] Of note, con-ventionalizing germ-free mice using fecal material from SPF mice, decreases the permeability of the BBB,[6] providing evidence of a causal relationship between gut microbes and BBB integrity. Related experiments using chronically-administered anti-biotics to deplete the gut microbiota in mice resulted in object recognition impairment[7] and decreased hippocampal neurogenesis and memory retention, which were reversed by administering probiotic bacteria.

Recent studies suggest the gut microbiota may contribute to the development or progression of neurodegenerative diseases and dementia. Neurodegenerative diseases are characterized by impaired motor function and/or dementia, which is one of the major causes of disability and depen-dency among older people worldwide.[8] Dementia is a collection of symptoms used to categorize and diagnose the disease type. Common forms include Alzheimer's disease (AD), vascular dementia, fron-totemporal dementia, Parkinson's disease (PD), and dementia with Lewy bodies; all are chronic or progressive in nature and feature deterioration in memory, thinking, behavior, and the ability to perform everyday activities. A common feature of all dementias is chronic neuroinflammation, invol-ving overactivation and dysregulation of microglia,[9] the resident macrophage-like immune cells of the brain. When microglia are activated, their morphology changes in association with increased secretion of pro-inflammatory cytokines, such as IFN-γ, IL-6, and TNF-α, and the release of reactive oxygen and nitrogen species,[10] which can lead to neuronal cell death, loss of BBB integrity, and brain damage. Whether changes in BBB integ-rity are a cause or a consequence of neuroinflam-mation in patients is a major unresolved question.[11] This central question has been approached using animal models and, in particu-lar, genetically modified mice which develop fea-tures of AD or PD. Transgenic mice expressing the amyloid-β precursor protein (APP) develop fewer cerebral β-amyloid plaques when maintained under germ-free conditions compared to conven-tionalized mice.[12] Consistent with this finding, and supporting a role for the gut microbiota in the pathogenesis of neuroinflammation in this mouse model, antibiotic administration also limits β-amyloid pathology and neuroinflammation.[13] Possible links between specific commensal bacteria and neuroinflammation have been identified from microbiota taxonomic profiling in PD patients with alterations in populations of potentially ben-eficial bacteria (e.g. *Prevotella* genus) and patho-genic bacteria (e.g. members of the Enterobacteriaceae family).[14,15] Although these findings are intriguing and implicate the gut microbiota in neuroinflammation, they and other related studies have, to date, provided limited mechanistic insight and have been unable to iden-tify the pathways by which gut microbes can influ-ence, directly or indirectly, the BBB.

The blood-brain barrier

The term "blood-brain barrier" was first coined by Stern and Gautier,[16] who examined the penetra-tion or exclusion of compounds, such as morphine or India ink, between blood and brain, and pro-posed a role for the barrier in maintaining brain homeostasis. Later studies in the 1960s demon-strated that the BBB was located in the endothe-lium forming the walls of vessels in the brain.[17,18] Since these pioneering studies, the concept of the BBB as a static, impermeable barrier has evolved into the current view of a dynamic, highly regu-lated, specific cellular system,[19] with increasing

awareness of the contribution multiple cell types play in regulating dynamic BBB responses. The BBB is now considered to be part of a neurovascular unit (NVU) (Figure 1) comprising brain microvascular endothelial cells (BMEC), pericytes, astrocytes, neurons, microglia, and extracellular matrix (ECM),[20] which together contribute to regulating BBB stability and function. This organization is found in all brain regions, except for the circumventricular organs, which regulate the autonomic nervous system and endocrine glands and have fenestrations allowing the diffusion of molecules across vessel walls.[21]

BMECs are interconnected by protein complexes consisting of highly electrically-resistant tight junctions (*zonulae occludens*), which limit the paracellular flow of molecules between adjacent endothelial cells to maintain ionic homeostasis in the brain.[22] Joining the BMECs are several non-endothelial cells including pericytes that wrap around the capillary endothelium[23] and can modify vascular diameter and regulate transcytosis and immune cell trafficking across the BBB.[24] Astrocytes and their endfeet form a second physical, transport, and metabolic barrier around pericytes and endothelial cells, and communicate with neurons to establish an endothelium-neuron link.[25] Pericytes and astrocytes also transmit neuronal signals to the local vasculature, affecting barrier physiology by altering arteriolar dilation and blood flow.[26] While implicated in the regulation of

vascular growth during angiogenesis, the role of microglia in homeostatic BBB maintenance is not clear, but these cells are major players in the inflammation associated with neurodegenerative diseases, secreting pro-inflammatory cytokines and factors promoting BBB breakdown and neuronal loss. In inflammatory states, remodeling of BMEC tight junctions increases transcellular permeability, allowing circulating inflammatory cytokines and effectors into the brain. Inflammatory activation of vascular endothelium can induce BMEC expression of adhesion molecules and chemoattractants, allowing infiltration of neutrophils and effector Th1 and Th17 subsets of CD4$^+$ T cells which are implicated in the pathogenesis of multiple sclerosis (MS), AD and PD.[27,28] Astrocyte morphology and secretion of inflammatory cytokines and chemoattractants are altered in early stages of AD pathology.[26] Amyloid-β protein can induce BMEC activation and tight junction remodeling, and pericyte damage and loss leads to cognitive impairment, increased amyloid-β deposition, and tau pathology.[29] In summary, a combination of inflammation and changes in BBB component cell functions contribute to neurodegenerative disease-associated BBB breakdown. Infiltrating immune cells, microglial cells, and astrocytes may reciprocally activate each other, driving chronic inflammation and preventing BBB repair, with pericyte damage and neuronal loss further promoting cognitive decline. Preserving and restoring BBB integrity therefore
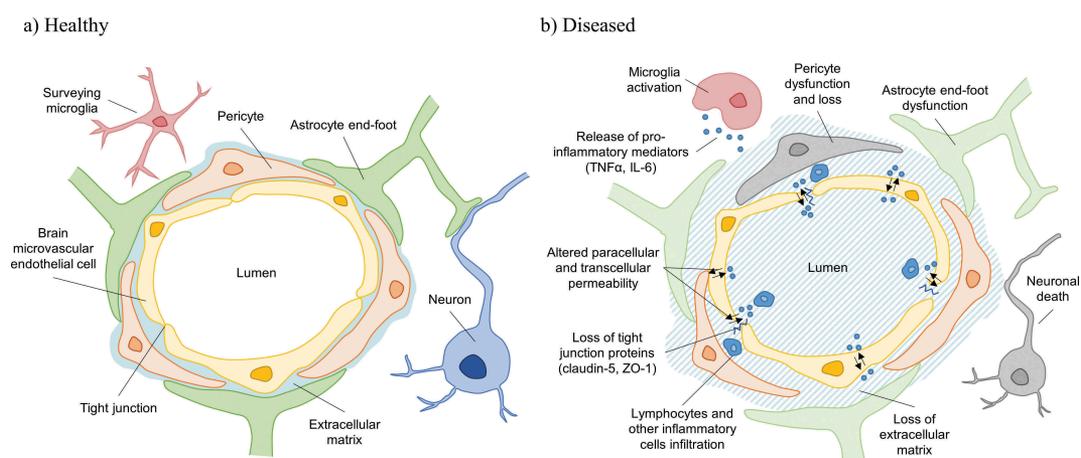

Figure 1. Schematic representation of the human blood-brain-barrier neurovascular-endothelial-unit in health (a) and disease (b) states. Increased permeability related to, for example trauma or infection, is associated with disruption of endothelial tight junctions leading to the ingress and translocation of blood-borne immune cells, and inflammatory mediators such as cytokines and microbes and their products that can activate microglia, resulting in local inflammation leading to loss of extracellular matrix and astrocyte, pericyte and neuronal cell dysfunction and death.

presents a primary target for developing neuroprotective strategies and interventions.

Gut microbiota-derived metabolites influencing BBB integrity and brain health

The gut microbiota transform dietary components, including macro- and micronutrients, fibs, and polyphenols, into a range of metabolites, including short-chain fatty acids, trimethylamines, amino acid derivatives, and vitamins. These microbial-derived metabolites and dietary components have essential metabolic and signaling functions which can modulate host homeostasis, including BBB integrity and brain function. Microbial metabolites affecting the BBB and brain are detailed below, and specific studies describing effects of some of these metabolites on BBB permeability are summarised in Table 1.

Short Chain Fatty Acids (SCFA): are small organic monocarboxylic acids, principally produced by colonic fermentation of dietary fib and complex plant-based polysaccharides, to generate energy and release carbon, permitting microbial growth. SCFAs are present at an approximate concentration of 100 mM in the colonic lumen at a ratio of 60:25:15 for acetate:propionate:butyrate, respectively.[34] The production of propionate is primarily restricted to members of the Clostridiales order of anaerobic bacteria, with production of acetate and butyrate being more broadly distributed.[35] Over 95% of SCFAs produced in the colon are absorbed by the mucosa of healthy individuals[36] with all three detectable in the peripheral blood at ratios different to those in the lumen (acetate, 22–42 μM; propionate, 0.9–1.2 μM; butyrate, 0.3–1.5 μM).[33] SCFAs stimulate colonic blood flow, upper-gut motility, influence water and salt uptake, and enhance satiety.[36] They can also access the BBB via the bloodstream to impact directly on its integrity.[37] For example, BBB permeability decreases in germfree mice after colonization with the butyrate producer *Clostridium tyrobutyricum* or, after oral administration of sodium butyrate, by upregulating tight junction proteins.[6] Following traumatic brain injury, intravenous or intraperitoneal administration of sodium butyrate can prevent BBB breakdown and promote neurogenesis.[30,31,38] It is therefore conceivable that modulating SCFA levels could be useful in preventing or treating neural decline. Intraperitoneal administration of butyrate or increased dietary soluble fib (inulin) intake improve neuroinflammation in aging mice,[39] and in CK-p25 transgenic mice, which exhibit synaptic and neuronal loss and learning, intracerebroventricular injections of butyrate modify histone acetylation in the hippocampus to improve memory and learning.[40] Protective, anti-inflammatory, and permeability-reducing effects of propionate treatment have also been described in a human brain endothelial cell culture model.[33] On the other hand, high brain levels of propionate can exacerbate symptoms in a mouse model of autism, but this can be mitigated with butyrate supplementation,[41] suggesting metabolite balance rather than individual metabolite levels may be important. The maturation of microglial cells, which regulate BBB integrity, neuroinflammation, and neurogenesis, is modified by SCFA in germfree mice, where the reduced microglia number, function and morphology can be rescued by 4-week delivery of an SCFA cocktail in drinking water.[42] Pending clinical trials on specific-optimized SCFA supplementations, it has been hypothesized

Table 1. Effects of gut microbes and their metabolites on blood-brain barrier permeability.

Method	Permeability modulator	Model	Effects on BBB	Reference
In vivo	*Clostridium butyricum*	Traumatic brain injury on C57Bl/6 mice	↑ TJ proteins expression ↓ Permeability	30
	Clostridium tyrobutyricum, *Bacteroides thetaiotaomicron* and sodium butyrate	Germ-free C57Bl/6 mice	↑ TJ proteins expression ↓ Permeability	6
	Sodium butyrate	Traumatic brain injury on C57Bl/6 mice	↑ TJ proteins expression ↓ Permeability	31
	Acetate/propionate/butyrate	α-synuclein overexpressing germ-free BDF1 mice	↑ Microglia activation	15
	Chenodeoxycholic acid and deoxycholic acid	Bile duct ligation on Sprague Dawley rats	↑ Permeability	32
In vitro	Propionate	hCMEC/D3 treated with LPS	↓ Paracellular permeability ↑ TEER	33
	Chenodeoxycholic acid and deoxycholic acid	RBMECs	↑ Permeability	32

that providing SCFA mixtures or simply increasing dietary fib could rescue the hypometabolism associated with neuronal dysfunction in neurodegenerative conditions including AD.[43] Intriguingly, a handful of recent studies in which bacterial, viral, and fungal-derived nucleic acids and proteins have been detected in post-mortem brains of AD sufferers[44,45] suggest microbial metabolites such as SCFAs could be produced locally, by brain-resident or infiltrating microbes. The possibility of a 'brain microbiome' remains controversial, but while consideration of possible contamination issues is needed in interpreting the detection of nucleic acids from low-abundance microbes in tissue samples, Carrasco and colleagues[46-48] provide supporting immunostaining data for various fungal species in post-mortem brain tissue from Alzheimer's patients. These included *Candida albicans,* which is commonly found in the mammalian gut but more rarely isolated from the environment,[49,50] and the detection of both budding and hyphal forms,[47,48] indicative of fungal growth within the living tissue. Whilst gut microbes can dictate the metabolite availability within the intestine and the brain via the circulation, whether they have a significant impact on SCFA availability within the brain as 'local' residents remains to be determined. Additional work is now needed to understand the optimum balance of SCFAs in the periphery and the brain which promote healthy aging, and further still how the microbiome of the gut (and potentially the brain) can be manipulated to achieve this balance and protect cognitive health.

Trimethylamines: are metabolites produced from gut microbial metabolism of dietary choline, lecithin, carnitine and trimethylamine-N-oxide (TMAO) that are present in foods such as eggs, nuts, dairy products, meat, and fish. Choline is degraded into trimethylamine (TMA), which is converted in the liver by flavin-containing monooxygenases (FMOs) into TMAO, and demethylated into dimethylamine and methylamine.[51] Gut-derived TMA is generated by bacteria of the genera *Anaerococcus, Clostridium, Escherichia, Proteus, Providencia*, and *Edwardsiella*.[52] The presence of TMAO in human brains indicates its ability to cross the BBB.[53] TMAs have been associated with both beneficial and detrimental health effects. High plasma levels of TMAO have been associated with increased

risk of colorectal cancer[54] and with risk of developing atherosclerosis and cardiovascular disease via effects on cholesterol metabolism.[55] This is of interest regarding neurodegenerative diseases including AD and vascular dementia, in which cardiovascular disease and altered cholesterol metabolism are strongly associated with increased risk. In individuals with a hereditary defect in FMO3, bacterial TMA production contributes to the symptoms of trimethylaminuria (TMAU) or fish-odor syndrome.[56] Therapy with archaebiotics and attempting to modulate the gut microbiota by administering specific strains of TMA metabolizing Archaea has been proposed as a treatment for cardiovascular diseases and TMAU. The methanogen, *Methanomassiliicoccales* can reduce TMA concentration in the gut by converting it to methane, thus decreasing the production of TMAO from TMA in the liver.[57,58] TMAO's beneficial effects include reducing endoplasmic reticulum stress and lipogenesis in adipocytes, increasing insulin secretion in pancreatic islets, and attenuating diet-induced impaired glucose tolerance.[59,60] Again, by extension, such therapies may also be beneficial in protecting against neurodegenerative disease as diabetes which is another dementia-associated risk-factor. More specific to AD, TMAO has also been shown to restore the ability of mutant tau protein to promote microtubule assembly[61,62] with microtubule disassembly and neuron death being hallmark pathological features of AD.[63] In addition to its potential use as an AD biomarker,[64] TMAO may also have a therapeutic effect in AD and other protein-misfolding conditions, by preferentially hydrating partially denatured proteins to correct folding defects and entropically stabilizing native conformations.[65,66]

Amino acid metabolites: the gut microbiota plays an essential role in amino acid catabolism the products of which can influence the balance between the production of excitatory and inhibitory neurotransmitters essential for correct brain functioning.[67] Species of the genera *Lactobacillus* and *Bifidobacterium* metabolize glutamate, the most abundant free amino acid and excitatory neurotransmitter in the brain, to produce γ-aminobutyric acid (GABA), a major inhibitory neurotransmitter.[68] Decarboxylases secreted by *Clostridium sporogenes* contribute to converting tryptophan, an essential amino acid found in a wide range of foods,[69] to the neurotransmitter

tryptamine, involved in the release of serotonin by cells of the enteroendocrine and enteric nervous systems.[70,71] Germfree mice display increased plasma tryptophan levels, which are normalized after conventionalization.[72] *Bifidobacterium infantis* can increase plasma levels of tryptophan.[73] Bacterial conversion of tryptophan to indoles, ligands for aryl hydrocarbon receptor (AHR), can decrease brain inflammation and limit disease severity in murine models of MS by activating astrocytes.[74] Tryptophan is a precursor of many other diverse microbial and host metabolites[75] including kynurenic acid, which has anti-inflammatory properties in the gastrointestinal tract[76] and is considered to be neuroprotective,[77] and quinolinic acid, which is a neurotoxin and a BBB modulator implicated in the etiology of psychiatric disorders and neurodegenerative diseases.[78,79] Tryptophan and glutamate-metabolizing microbes may therefore perform important BBB and brain-protective functions, but greater understanding and care are needed to harness their therapeutic potential while avoiding the effects of potentially harmful derivatives.

Vitamins: are essential micronutrients which humans must obtain from their diet and intestinal microbiota. Vitamin K is produced by *Escherichia coli, Klebsiella pneumoniae, Propionibacterium*, and *Eubacterium*; B2 (riboflavin) by *Bacillus subtilis* and *E. coli*; B9 (folic acid) by *Bifidobacterium, Lactococcus lactis* and *Streptococcus thermophilus*; and B12 (cobalamin) by *Lactobacillus reuteri* and *Propionibacterium freudenreichii*.[80] The uptake of microbe-derived vitamins occurs predominantly in the colon, in contrast to dietary vitamins, which are absorbed in the small intestine.[81] Vitamins have a variety of roles in maintaining and protecting intestinal and systemic health throughout life. Vitamin K, essential for the process of thrombosis,[82] is routinely administered to neonates shortly after birth to prevent hemorrhagic disease, prior to the establishment of their gut microbiota.[83] Low levels of vitamin K have been correlated with apolipoprotein Eε4 allele, a risk factor linked to AD.[84] Vitamin K has also been shown to have a beneficial role in the modulation of α-synuclein fibrillization, associated with PD.[85] Increased dietary vitamin K intake has been associated with less severe subjective memory complaints in the elderly.[86] Vitamin

B synthesis increases as the intestinal microbiota are being established[87] with deficiencies leading to serious neurological disorders including beri-beri, polyneuropathy and cerebellar ataxia.[88] Vitamin B9 has a preventive role in the development of neural tube defects, coronary heart disease, cancer, and neuropsychiatric disorders.[89] Folate deficiency has been associated with depression, with methylfolate being one of the only medical foods licensed for treating depression.[90,91] Folate intake below the Recommended Daily Allowance may also increase the risk for mild cognitive impairment and probable dementia among older women.[92] Similarly, high-dose B-vitamin treatment, including B6, B9, and B12, can decrease levels of homocysteine, a by-product of vitamin B, and slow the atrophy of specific regions of the brain associated with cognitive decline in AD.[93]

In summary, SCFAs and other microbial metabolites can act at the intestinal epithelial barrier, the blood-brain-barrier, directly on brain neurons, or by regulating the endocrine and immune systems to protect against the pathology and inflammation associated with ageing and disease, and may also protect against neurodegeneration by limiting the transit and influx of pathological microbes and their products into the brain.

Pathways of communication along the microbiota-gut-brain axis

Intestinal metabolic health status is relayed to the brain by both neural and circulatory routes (Figure 2). Bidirectional gut-brain neural relays control satiety signaling and appetite regulation.[94] Detection of luminal metabolites by intestinal enteroendocrine cells is communicated to the brain via activation of the vagus nerve,[95] by epithelial cell-derived hormones and neurotransmitters,[96,97] and via neural routes, including neuroepithelial connections.[98,99] Dietary metabolites and epithelial-derived soluble factors may also travel via the bloodstream to the BBB, where a variety of nutrient transporters and specific receptors expressed on BMECs[100,101] facilitate the translocation of specific nutrients (e.g. glucose, lactate) across the barrier into the brain parenchyma, and allow for binding of circulating peptide hormones and other factors which can modulate brain activity. The microbial metabolites
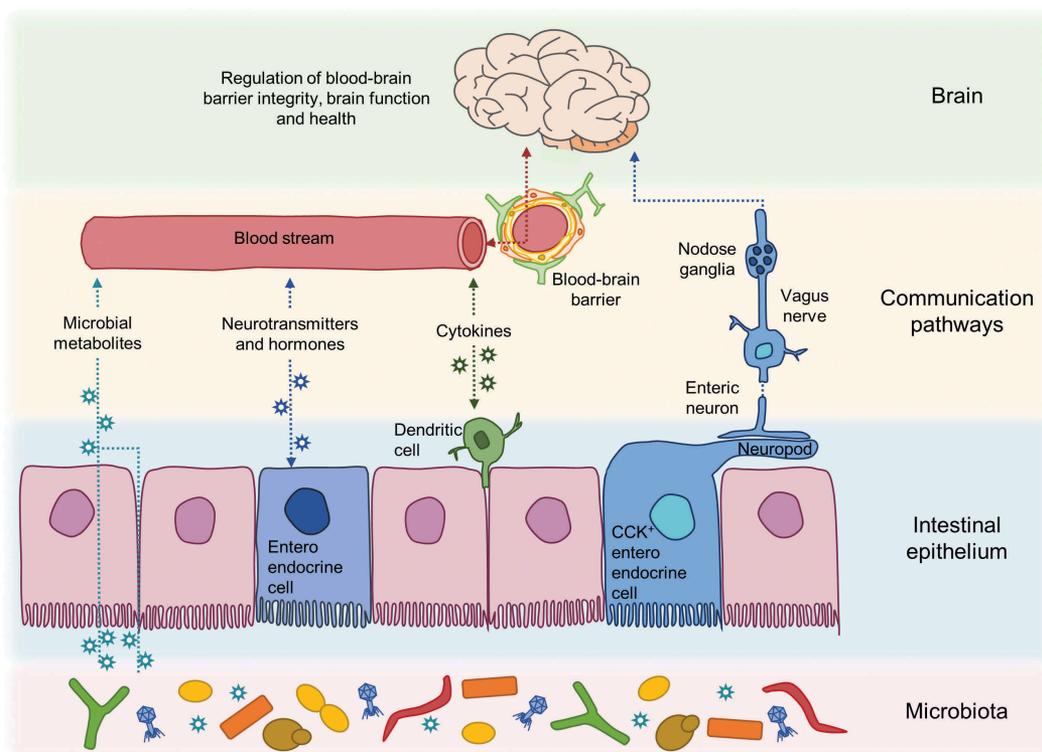
Figure 2. Pathways of communication along the gut-microbiota-brain axis. A complex interplay of epithelial, immune and neural cell signalling networks is involved in sensing and communicating changes in microbial metabolites in the gut and the brain involving both circulatory and neural routes.

discussed above including SCFAs, TMAs, amino acid metabolites, and vitamins can travel via or modulate these pathways to affect enteroendocrine, neuronal, and immune cells in the gut, liver, kidneys, pancreas, and brain.

Endocrine and neuroendocrine signaling

In the intestinal epithelium, specialized sensory enteroendocrine cells express a range of G-protein-coupled receptors (GPCR), transporters, and other receptors for fatty acids, carbohydrates, peptides, amino acids, and phytochemicals. Binding of bacterial products to these receptors induces the release of peptide hormones (including the incretin hormones GLP-1 and GIP, and neuropeptides CCK, PYY, and serotonin) which can act locally on enteric neurons, or enter the circulation and activate neurons innervating the portal vein, to signal to the brainstem via the vagus nerve. It is possible that some circulating hormones could reach and act directly on the brain. GLP-1 for example

may be able to reach the brain either by crossing the blood-brain barrier[102] or by acting at circumventricular structures.[103] However, the short half-life of peptide hormones in the circulation,[104] the excitation of enteric neurons and the vagus in response to metabolites and gut hormones,[105,106] and the speed of responses to nutrients,[107] reinforce the importance of neural signaling networks in communicating signals from the gut to the brainstem.[108] Enteric neurons express receptors for SCFAs[109] and bile acids[110] facilitating metabolite regulation of gastrointestinal motility[111] and allowing fast relay of information to the brain about metabolites crossing the epithelial barrier, and the concentrations of those metabolites in the gut lamina propria. For example, administration of luminal glucose activates both enteroendocrine cells and neural cells of the myenteric plexus, nodose ganglion and brainstem.[112]

Recent studies reveal direct physical associations between the epithelium and enteric nerves. Some enteroendocrine cells exhibit

'neuropod' processes which directly synapse with local neural networks, forming 'neuroepithelial units' which can and transmit chemical and electrical signals in response to metabolite binding.[99,113] At present, the relative balance and importance of the circulatory, neural, and neuro-epithelial routes in relaying luminal information to the brain are unknown. Given the complexity within the gastrointestinal tract luminal environment, the summation and combination of all routes may be required to accurately convey varying spatiotemporal conditions and fluctuating microbial and metabolic states.

Encouragingly, the ability to map connectivity between neurons manipulate neural activity in real time, and measure neural activity during behavior has produced a wealth of data approaching a "wiring diagram" of the bidirectional gut-brain control of appetite, able to describe and predict the effects of dietary nutrients, common hormones and regulators.[94] Building on this, recent studies are attempting to connect altered bacterial metabolism to specific neural signaling affecting brain functions. For example, Schretter and colleagues[114] describe how locomotor hyperactivity in germfree Drosophila (manifested as increased walking speed and daily activity) can be rescued by altering sugar metabolism, either by colonization with *L. brevis* or by administration of *L. brevis*-derived xylose isomerase. The behavioral hyperactivity effect in germfree flies was shown to be mediated by octapaminergic neurons, as specific stimulation of these neurons or exogenous administration of octopamine (the invertebrate counterpart of noradrenaline) prevented the rescue by xylose isomerase.[114] In mouse models, *in vivo* cell-connectivity tracing and enteroendocrine-neural co-cultures have shown that glucose stimulation of CCK-positive enteroendocrine cells activates vagal nodose neurons by glutamate-based neurotransmission.[99] What impact this signaling might have on regulation of BBB integrity and neurodegenerative disease remains to be determined, but it is an exciting step forward in connecting specific gut epithelial-neural circuits and developing the necessary understanding to trace microbe-to-brain communication.

Immune and neurotransmitter signaling

In addition to their actions on enteroendocrine and neural cells, metabolites can act via GPCR and other receptors to direct the development and normal functioning of the mucosal immune system; regulating the recruitment, development, maintenance, and activation of immune cells. The balance of dietary and bacterial metabolites is important for maintaining immune tolerance, and in directing inflammatory responses in the gut.

There are three main routes by which metabolite-immune cell interactions in the gut may be relayed to the brain. The first is via the secretion of cytokines and other immune signaling molecules into the bloodstream which ultimately reach the BBB. Breakdown of the epithelial barrier, resulting from dysbiosis, infection, damage, or age-associated degeneration allows ingress of bacteria, their metabolites, and other components such as toxins and lipopolysaccharides (LPS), triggering inflammatory immune responses and enteric neuronal damage.[115] If not resolved, continuous or remitting intestinal inflammation (a hallmark of inflammatory bowel disease) can promote a state of chronic systemic inflammation characterized by elevated serum TNF, IL-6, and IL-1β, disrupting the BBB by increasing the permeability of the BMEC layer[116] and allowing solutes and toxins into the brain. Increased systemic and brain inflammation also promotes immune cell extravasation[117] and stimulates inflammatory signalling by cells of the NVU and brain microglia,[118] perpetuating a vicious cycle of brain inflammation and neurodegeneration. *In vivo* infection models show that elevated TNF drives brain pathology in a Drosophila model of enterobacteria infection-aggravated AD.[119] In mice, blocking TNF uptake at the BBB by inhibiting TNF receptor 1 (TNFR1) can reduce immune cell infiltration and ameliorate disease severity in a model of MS.[120] Metabolite-immune cell interactions, intestinal barrier dysfunction, and bacterial infection can therefore be important early events in initiating neurodegenerative disease by altering gut-to-brain cytokine signaling and immune cell trafficking.

In the second route, metabolite induced secretion of immune cell cytokines and neurotransmitters may act locally on enteric neurons innervating

the gut and alter vagus nerve signaling to the brain. With advancing age, a primary risk factor for neurodegenerative diseases, a shift in the polarisation of intestinal macrophages and their cytokine production alters enteric neural responses to inflammatory signals and increases apoptosis and loss of enteric neurons.[121] Loss of enteric neurons not only alters intestinal functions but has implications for the ability of the gut to communicate with the brain. Furthermore, the cytokine milieu affects the functioning of enteric glial cells that support and regulate enteric neuronal functions by production of glial cell-derived neurotrophic factors (GDNFs). Glial cell GDNF production in response to microbial-immune cell signaling,[122] and potentially via SCFA-GPCR activation,[123,124] induces innate lymphoid type 3 (ILC3) cells to produce IL-22, promoting protection and restoration of the epithelial barrier.[125] These cells are therefore important in integrating microbial and host signalling in neuro-immune responses in the intestinal mucosa.

Along with immunoregulatory cytokines, binding of bacterial metabolites to intestinal cells can also trigger the release of local peptide neurotransmitters, including PYY and serotonin, for which enteric neurons express specific receptors.[126,127] For example, decarboxylation of tryptophan to tryptamine by *Clostridium sporogenes* induces enterochromaffin cells to release serotonin, which acts on enteric neurons to stimulate gastrointestinal motility.[128,129] Serotonin is also involved in regulating neurogenesis during development[130] but detangling its role in adult neurodegeneration is complicated by the multitude of serotonin receptor subtypes expressed in the mammalian brain.[131] Gut microbes may also trigger neurotransmitter release via Toll-Like Receptor (TLR) signaling on epithelial, immune and neuronal cells.[132,133] Finally, bacterial metabolites may act directly as neurotransmitters, acting locally and in the brain. *Lactobacillus* and *Bifidobacterium* can metabolize glutamate to produce GABA, a major inhibitory neurotransmitter of the brain[68,134] and modulator of gut functions.[135] Various enteric bacteria are also able to synthesize and release nitric oxide,[136] acetylcholine,[137] noradrenaline,[138] and dopamine.[139] The emerging field of "psychobiotics"[140,141] proposes to manipulate these neurotransmitter-producing bacteria to regulate gut and brain function.

In the third route, metabolite-activated immune cells may travel via the bloodstream to release soluble factors at the BBB which impacts its integrity and alters the inflammatory status of brain cells. Systemic inflammation and elevated circulating TNF promote extravasation of leukocytes and macrophages to the brain by upregulating adhesion molecules, chemokines, and matrix metalloproteases at the BBB and in the brain,[117,142] and by downregulating tight junctions. At steady state, during infection, and following brain injury, T cells from the gut can traffic to the brain.[143,144] Circulating immune cells may cross the BBB and choroid plexus to enter the brain and local draining lymph nodes[145,146] or infiltrate via meningeal vascular channels.[147] SCFA signaling may mitigate some of these effects, as altered lymphocyte migration from the gut in response to SCFAs can ameliorate uveitis[148] and modulation of the microbiota and its metabolites can impact neuroinflammation, and neurodegeneration.

Microbiota-gut-brain pathways in neurodegenerative disease

Multiple neurological and neurodegenerative disease are now being associated with gut dysbiosis, following infection, inflammation or antibiotic use, although the mechanisms of gut-brain transmission of pathology have so far remained elusive. PD is of particular interest in this regard as a proposed etiology has developed from a growing collection of animal and epidemiological studies which link PD with pathogenic alpha synuclein (αSyn) protein production and accumulation in the gastrointestinal tract. A proposed sequence of events involves age- infection-, or dysbiosis-driven αSyn accumulation in the intestine, leading to trans-synaptic transmission of pathological forms of αSyn from enteric neurons to the vagus nerve, and retrograde axonal transport along the vagus to the brainstem.[149-151] This model draws on autopsy studies of Lewy bodies, and observations that onset of gastrointestinal symptoms in PD patients, and detection of pathological α-synuclein (αSyn) in gastrointestinal tissues in animal models of PD, are seen prior to the

onset of motor symptoms. Also, rodent studies in which αSyn expression was chemically induced in enteric neurons, or in which recombinant αSyn was delivered to the gastric and/or duodenal wall, report subsequent αSyn detection in the vagal nerve and multiple brain regions.[152-155] The identification of αSyn also within intestinal enteroendocrine cells[156] is interesting in light of the recently described synaptic connections between subsets of these cells and vagal afferents,[113] providing a gut lumen-to brain communication pathway.

What events may trigger the initial generation of pathogenic αSyn in the gut, and whether αSyn propagation from the intestine to the vagus and/or brainstem occurs in humans and is causative in human PD pathology remain unknown. While transmission of αSyn via the vagal route has received the most attention, gut-brain transmission by other neural pathways (e.g. the splanchnic nerve innervating the colon, olfactory neurons[157]) or by trafficking immune cells is also possible. Moreover, vagal transmission is not absolutely required for PD development, as vagotomy delays but does not prevent PD-like pathology in mice[153] and while some human epidemiological studies suggest vagotomy is associated with lower risk of developing PD,[158] others do not.[159,160] The human appendix, which houses a diverse microbiome,[161] and in which pathology-associated αSyn can be also detected, has also been suggested as a site of gastrointestinal αSyn seeding.[162] While the history of appendectomy was associated with delayed onset of PD symptoms in a small late-onset cohort[163] a larger study found no effect,[164] and others find either no effect or a slightly increased risk of developing PD 5–10 years post-appendectomy.[165,166] As a reservoir of microbes and immune cells, the appendix could still have a role in modulating PD risk by influencing microbial and immune homeostasis. Given the interaction between gut microbes, enteroendocrine cells, enteric neurons and the enteric immune system discussed above, and recent evidence that bacterial proteins can enhance αSyn aggregation in animal models,[167] the activities of specific gut microbes or a more general 'microbial dysbiosis' could

conceivably play a role in the transition from benign to pathogenic αSyn states.

In summary, a complex interplay of signalling between epithelial, immune, and neural cell signalling networks is involved in translating microbial metabolite changes in the gut and the brain, and may be involved in the etiology of neurodegenerative disease. Progress is being made in trying to dissect these interactions, but a better understanding of microbe-brain communication now requires cross-disciplinary multi-organ-based investigations.

Modulation of the gut microbiota as a potential therapeutic tool for promotion and restoration of brain health

Disruption of the complex ecosystem of the intestinal microbiota is now implicated in multiple conditions and diseases of both the intestine and the brain, and some of the routes by which microbes may act on the gut-brain axis are beginning to be unravelled. Manipulating or shaping the microbiota is therefore attracting attention as a viable strategy to prevent or treat various extra-intestinal diseases. The beneficial effects of an 'optimized' gut microbiota would include immune and epithelial homeostasis, enteric nervous system regulation, and optimal digestion and metabolism. This would theoretically protect against neurodegenerative disease by preventing metabolic, cardiovascular and inflammatory conditions which are associated with neurodegeneration but, as discussed above, could also protect BBB integrity and brain function by more direct means. Current therapeutic approaches under consideration include modifying the existing microbial composition in the gut by: altering nutrient availability to promote the growth of particular classes or species of bacteria (prebiotics); introducing or expanding 'beneficial' species (probiotics); or by wholesale transplant of entire communities or portions of communities from other intestinal donors (faecal microbial transplantation and more selective stool transplants). Below we consider how some of these approaches are beginning to be tested, and the potential for their use in improving blood-brain-barrier homeostasis and brain health.

Promoting growth of beneficial microbes via prebiotics

Prebiotics are non-digestible short-chain carbohydrates that, when ingested selectively, stimulate the development of some health-promoting colonic bacteria.[168] The nutritional properties exhibited by prebiotics derive from their resistance to hydrolysis in the upper gastrointestinal tract and their fermentation in the large intestine by mainly anaerobic bacteria.[169] Common prebiotics include disaccharides (lactulose), oligosaccharides (fructooligosaccharides, FOS, galactooligosaccharides, GOS) and polysaccharides (inulin).[170] Other compounds that can also be considered as prebiotics are resistant starches, pectin, whole grains, and polyphenols.[171] Once in the gut, prebiotic compounds are metabolized by the host microbiota and resulting metabolites, such as SCFAs, act on the brain through different pathways contributing to an effect on BBB permeability and neurological health (described above). Several animal studies have analyzed the effect of prebiotics on brain function[172-176] including modulating mood and stress responses by activating or supressing the hypothalamic-pituitary-adrenal (HPA) or "stress" axis. Serum and salivary cortisol are reliable indicators of HPA-activation (stress) and can be modulated by pre- and/or probiotics. The raised levels of circulating cortisol in germfree rodents[177] are reduced following the administration of probiotics.[178] In healthy mice, supplementation with long-chain FOS or short-chain GOS, which promote the growth of beneficial species such as Bifidobacteria,[172] decreased anxiety-related behaviors and increased social behavior.[179] Few studies investigating the benefit of prebiotics on human brain function have been published to date, and are so far inconclusive. One example in healthy adult volunteers described reduced stress response (salivary cortisol awakening response) after GOS intake.[180] In preterm infants, supplementation with different prebiotics showed improvement in brain development when compared to a control group.[181] Synergistic combinations of prebiotics and probiotics (synbiotics) have been found to improve age-related memory impairment in rats[182] and are now being trialled in human clinical studies to promote intestinal health.[183,184] One simple goal arising from such studies is devising optimized healthy diets which include all the required nutrients and prebiotics needed to decrease the number of harmful gut microbiota, and to increase the concentration of microorganisms producing metabolites which have beneficial effects on immunologic, metabolic and brain function to maximize health.

Changing the gut microbiota composition via probiotics

Probiotics are non-pathogenic living microorganisms added to, or naturally occurring in, food products, that confer a health benefit to the host when administered in adequate amounts.[185] Examples include gut include species of the genera Lactobacillus, Bifidobacterium, Lactococcus, Streptococcus, and Enterococcus.[186] There is increasing interest in exploring the beneficial features of next-generation probiotics or live therapeutic products which include species not traditionally considered as probiotics, such as Akkermansia muciniphila,[187] Faecalibacterium prausnitzii,[188] species of the genus Bacteroides,[189] and genetically modified Lactococcus strains carrying beneficial traits.[190] Recent evidence suggests that probiotic bacterial viability is not necessary to develop health-promoting effects in the host.[191] The administration of inactivated probiotic microorganisms, known as paraprobiotics, has been shown to confer benefits to the host without the risk of enhanced inflammatory responses in immunocompromised individuals.[192,193] In line with this concept, the term postbiotics, also known as metabiotics or simply metabolites, emerged to refer to bioactive soluble factors secreted by live bacteria or released after bacterial lysis, reinforcing the idea that cell viability is not essential to induce healthy effects.[191]

Probiotic treatments have been associated with modulating mood and anxiety in animal models and humans. The first reported trial of using probiotic bacteria to treat mental health conditions was published in the early 20th century and described the use of lactic acid bacteria to successfully treat melancholia and constipation.[194] The term "psychobiotics" has since been coined to describe bacteria which, when ingested in adequate amounts, have a positive mental health effect.[140] Several human interventions provided evidence that psychobiotics can alter mental state. The

intake of *Lactobacillus helveticus* and *Bifidobacterium longum* reduced 24-hour urinary free cortisol, a biomarker for stress response, in healthy volunteers.[195] Healthy students consuming fermented milk containing *Lactobacillus casei* strain Shirota had lower plasma cortisol compared to placebo group on the day before an examination,[196] and a probiotic strain of *Lactobacillus rhamnosus* exhibited a protective effect on symptoms of postpartum depression.[197] One possible mechanism for the mood-altering effects of psychobiotics is by enhancing production of neurotransmitters, such as GABA and glutamate which control neural excitation-inhibition balance, and BDNF which is implicated in learning processes and control of fear.[198] Another possible mechanism is by altering the balance of circulating pro-and anti-inflammatory cytokines, restoring inflammation-induced BBB permeability, preventing potentially harmful material from entering the brain,[199] and promoting mental health and psychological resilience.[140]

Probiotic modulation has also shown promise in alleviating symptoms of PD. Delivery of some probiotic cultures has shown beneficial effects on gastrointestinal symptoms in PD patients,[200,201] while one study delivering a *Bifidobacteria/Lactobacilli* mix found improvements in motor scores.[202] Probiotics may also prove useful in treating AD. Delivery of *Bifidobacteria/Lactobacilli* mixtures has shown several benefits in mouse and rat models of AD, including improvements in memory and learning tests, reduced measures of oxidative stress, reduction in histopathological markers in the brain,[203,204] and restoration of neuronal cell proteolytic functions.[205] Some small-scale exploratory human studies comparing AD patients before and after probiotic supplementation, again using *Bifidobacteria/Lactobacilli* mixtures, report improved mini-mental state examination (MMSE) scores and improvement in some metabolic and inflammatory markers.[206,207] Two recent randomized, double-blinded, placebo-controlled clinical trials show improved MMSE cores, reduced serum C-reactive protein (an inflammatory marker) and improved insulin metabolism in patients receiving probiotic mixture containing *Bifidobacteria* and *Lactobacilli* species.[208,209] As with PD, the mechanisms of probiotic-promoted neuroprotective effects

in AD studies remain to be determined but may reflect positive effects on gut barrier health leading to improved immune and metabolic health (e.g. protection against type-II diabetes, decreased systemic inflammation), which in turn protects against BBB breakdown and neural pathology.

Changing the gut microbiota via fecal microbiota transplantation (FMT)

FMT is the therapeutic administration of fecal material containing gut microbiota from a healthy donor to a recipient with a dysbiosis-related condition, via enema, nasogastric, nasoenteric or endoscopic routes, to restore normal diversity and function in the microbial community.[210] FMT was first described in a medical manual for emergencies written by the Chinese alchemist Ge Hong in the fourth century, who reported that people suffering from food poisoning and diarrhea recovered after oral administration of fecal suspensions ('yellow dragon soup').[211] A more recent and well-documented use of FMT is the treatment of patients with *Clostridium difficile* infection, with efficacy rates of approximately 90%.[212] FMT has also been used to treat ulcerative colitis but with an effectiveness of lower than 25%.[213] The overall results of several randomized controlled trials using FMT to treat irritable bowel syndrome are so far inconclusive regarding efficacy in improving severity scores.[214] Due to the bidirectional signalling interactions along the microbiota-gut-brain axis, FMT has also been suggested as a potential treatment for extra-intestinal disorders, including neurological conditions. Bercik and colleagues[215] published one of the first studies using FMT to modulate brain function and modulate host behavior in mice. They colonized germfree BALB/c mice, usually a timid strain, with microbiota from the more exploratory NIH Swiss strain. The BALB/c mice displayed less timid and more exploratory behaviour after FMT, associated with higher levels of BDNF in the brain. In the reverse experiment, colonization of germfree NIH Swiss mice with BALB/c microbiota reduced exploratory behavior, suggesting the gut microbiota play a key role in behavior.[215] In support of this study, Zheng and colleagues[216] showed that germfree mice transplanted with microbiota from major depressive disorder patients displayed depression-like behavior.

Kelly and colleagues[217] also found physiological and behavioral features of depression in microbiota-depleted rats after transplantation with fecal microbiota from depressed patients, as well as a dysregulation in tryptophan metabolism, similar to that reported in autism, schizophrenia and neurodegenerative diseases.[218,219] In a disease model, FMT from normal mice has neuroprotective effects in a mouse model of PD, including reducing TNF-driven neuroinflammation and increasing brain levels of dopamine and serotonin, leading to improvement in motor symptoms.[220] Currently, studies focusing on the effect of FMT on the neurodegenerative disease in humans are lacking. Anecdotally, neurologic improvement in one patient with PD has been reported following FMT for chronic constipation.[221] Given the possible gut-brain propagation of pathogenic αSyn discussed above, the use of FMT to modulate the intestinal production of αSyn could be protective against PD by providing a 'protective' microbiota, which either does not promote aberrant protein folding or outcompetes pathogenic strains, or by maintaining immune, neural and epithelial barrier homeostasis such that any aberrant protein folding in the gut lumen is contained locally. However, safety remains a major concern in translating FMT research to humans. Stool donors and samples for FMT are currently tested for different potentially pathogenic bacteria, viruses, parasites, and other microorganisms,[222] but this is far from knowing the complete microbial composition of the sample to be transplanted, raising both safety concerns and issues over how to interpret results. The delivery of selective microbial mixtures, as in stool substitute transplant therapy (SSTT) or microbial ecosystem therapeutics (MET), in which purified beneficial intestinal bacterial cultures derived from a single healthy human donor are delivered into a patient's gastrointestinal tract, could minimize the potential risk of pathogenicity, not only due to infection but also to metabolic disease development or oncogenic potential. By inducing large-scale shifts in the intestinal microbiota by methods such as FMT and SSTT, metabolite production in the gut and subsequent availability in circulation may also be significantly altered. One recent study of African turquoise killifish (*Nothobranchius furzeri*) using metabolomic analysis of intestine, brain, liver, heart, skeletal muscle, serum, and stool, found important metabolic pathways are modified during killifish aging and that these changes could in part be reversed by gut microbiota transfers from young donors.[223] New work on metabolomics will be vital to understanding the complex metabolic interactions between host and microbes and how metabolic profiles are associated with health and disease. By harnessing such methods, and combining this information with microbial 'omics and systems biology approaches, it may be possible to identify beneficial vs detrimental microbial and metabolic profiles and pathways for gut and brain health, and to work towards optimized personal therapies to achieve beneficial conditions using a combination of microbial and dietary intervention. These and other improvements in our understanding of microbe–host interactions at the gut and brain barriers will hopefully accelerate research in the use of microbiota-modulating therapies to prevent and treat neurological and neurodegenerative disease.

Conclusions

Gut microbiome research is rapidly expanding, with recent advances in high-throughput 'omics technologies, providing us with a better understanding of the composition and functionality of such a complex ecosystem. Further investigation of bacterial metabolites and their effects on hormone production, immune signalling, and neural function will enable a fuller understanding of brain responses to age- and disease-associated alterations in the microbiota. Despite our current limited knowledge of specific mechanisms, dietary and microbial modulation are showing promise as potential strategies to tackle some neurodegenerative and neurological diseases. A deeper understanding of gut microbial ecology, metabolism, and signalling networks within the host may lead to a new generation of microbiome-targeted strategies, both for disease treatment and prevention.

Disclosure of interest

The authors report no conflict of interest.

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