HHS Public Access

Author manuscript

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2020 February 04.

Published in final edited form as:

Clin Gastroenterol Hepatol. 2019 January ; 17(2): 322–332. doi:10.1016/j.cgh.2018.10.002.

The Gut–Brain Axis and the Microbiome: Mechanisms and Clinical Implications

Vadim Osadchiy, **Clair R. Martin**, **Emeran A. Mayer**

G. Oppenheimer Center for Neurobiology of Stress and Resilience, Vatche and Tamar Manoukian Division of Digestive Diseases, University of California Los Angeles, Los Angeles, California

Abstract

BACKGROUND & AIMS: Based largely on results from preclinical studies, the concept of a brain gut microbiome axis has been established, mediating bidirectional communication between the gut, its microbiome, and the nervous system. Limited data obtained in human beings suggest that alterations in these interactions may play a role in several brain gut disorders.

METHODS: We reviewed the preclinical and clinical literature related to the topic of brain gut microbiome interactions.

RESULTS: Well-characterized bidirectional communication channels, involving neural, endocrine, and inflammatory mechanisms, exist between the gut and the brain. Communication through these channels may be modulated by variations in the permeability of the intestinal wall and the blood-brain barrier. Brain gut microbiome interactions are programmed during the first 3 years of life, including the prenatal period, but can be modulated by diet, medications, and stress throughout life. Based on correlational studies, alterations in these interactions have been implicated in the regulation of food intake, obesity, and in irritable bowel syndrome, even though causality remains to be established.

CONCLUSIONS: Targets within the brain gut microbiome axis have the potential to become targets for novel drug development for brain gut disorders.

Keywords

Irritable Bowel Syndrome; Early Life Influences; Diet

Based largely on studies with experimental animals, significant progress has been made in the past decade in illuminating the role of bidirectional interactions between the nervous system, the gastroin-testinal tract, and the gut microbiome. Studies performed using experimental animal models have confirmed the role of the gut microbiome in modulating affective, social, nociceptive, and ingestive behaviors. However, causality and translation of

Reprint requests Address requests for reprints to: Emeran A. Mayer, MD, G. Oppenheimer Center for Neurobiology of Stress and Resilience, Vatche and Tamar Man-oukian Division of Digestive Diseases, University of California Los Angeles, CHS 42-210, MC737818, 10833 Le Conte Avenue, Los Angeles, California 90095-7378. emayer@ucla.edu; fax: (310) 206-3343.

Conflicts of interest

This author discloses the following: Emeran A. Mayer is a member of the scientific advisory boards of Danone, Viome, Amare, Prolacta, Pharmavite, Axial Biotherapeutics, Bloom Science, Whole Biome, Ubiome, and Mahana, and a consultant for General Mills, Host Therabiotics, Kelloggs, Nestle, and Kevita. The remaining authors disclose no conflicts.

these findings into healthy human beings and patients with gastrointestinal or psychiatric disorders has been limited, and the effectiveness of specific gut microbiome-targeted treatments remains to be established. Despite these limitations, the new brain gut microbiome (BGM) science has spawned a considerable effort in academia and industry to determine if prebiotic, probiotic, and postbiotic interventions may be beneficial either as primary or adjuvant therapy in disorders such as irritable bowel syndrome (IBS) or obesity. Such therapies could be in the form of special diets, dietary supplements (prebiotics and probiotics), or novel molecules targeting or mimicking gut microbial signals (postbiotics). Here, we review key findings that show the existence of bidirectional signaling between the brain and gut microbiota, explore early life influences on brain and microbiota development, and then briefly discuss the potential role of BGM communication channels in 2 common gastrointestinal disorders.

Gut Microbiota to Brain Signaling

Communication from the gut microbiome to the central nervous system (CNS) primarily occurs through microbial-derived intermediates, with the best described examples including short-chain fatty acids (SCFAs), secondary bile acids (2BAs), and tryptophan metabolites.[1–3] Although some of these intermediates interact directly with enteroendocrine cells, enterochromaffin cells, and the mucosal immune system to propagate bottom-up signaling, other intermediates are able to cross the intestinal barrier to enter systemic circulation, and may even cross the blood-brain barrier.[3–5] It remains unclear whether these microbial-derived intermediates reach brain sites directly in sufficient regional concentrations to modify distinct brain circuits. Alternatively, microbial signals may communicate via neural pathways involving vagal and/or spinal afferents.[6,7] Table 1[3,8–18] outlines some of the best-characterized signaling channels driving bottom-up communication.

Microbiota Neuroimmune Interactions During Brain Development

A growing body of evidence has shown an important role for the gut microbiota in neuroimmune signaling. Preclinical models involving germ-free (GF) mice or mice exposed to broad-spectrum antibiotics consistently show deleterious effects on neurodevelopment and neurode-generative disease processes, often secondary to disrupted neuromodulatory signaling involving the gut microbiota.[19,20]

Perhaps the best-characterized example of the interaction between the microbiota and CNS involves microglial development. Comprising 10% to 15% of all glial cells, microglia are tissue macrophages of the brain, representing the most abundant resident innate immune cell of the CNS. These cells take on a diverse role because they are involved with CNS development early on, and with antigen presentation, phagocytosis, and modulating inflammation throughout life.[21] Microglia also maintain homeostatic function by continuously scanning the environment of the CNS and directly communicating with neurons, astrocytes, and blood vessels through processes extending from the cell body.[21,22]

Microbial-derived SCFAs have been shown to have an integral role in promoting microglial maturity and proper functioning.[23] GF and antibiotic-treated mice show an increased proportion of immature microglia, characterized by longer processes with more branching,

in addition to molecular markers associated with an immature phenotype.[23] Although an important role for SCFAs certainly has been implicated in modulation of microglial development and function, the exact mechanisms driving these changes, and the roles of potentially other microbial mediators, still are unclear. This is exemplified by a failure of microglial abnormalities to correct in response to GF colonization with a limited microbial community known to produce SCFAs.[23,24] Studies of microglial development also underscore the importance of the gut microbiome in developmental timing. Although GF mice show decreases in both microglial maturity and number, antibiotic-treated mice show decreased microglial maturity only.[23] These findings align with research showing differences in gene expression profiles of microglia between adult and newborn GF mice compared with controls.[25]

Another well-characterized interaction between the microbiota and CNS involves astrocytes. Astrocytes represent a functionally diverse group of glial cells, whose roles include ion homeostasis, neurotransmitter clearance, glycogen storage, maintenance of the blood brain barrier (BBB), and support of neuronal signaling, in addition to their prominent role in neuroinflammation.[26] Microbial metabolites can activate aryl hydrocarbon receptors (AhRs) to attenuate inflammation via regulation of type I interferon signaling in astrocytes.[27] Although many diverse mediators function as AhR modulators, including xenobiotics, indoles represent an important group of microbial-derived AhR agonists.[28,29] Most undigested dietary tryptophan in the gut lumen is converted to indole by the exclusively microbial enzyme tryptophanase.[30] Indoles then can be metabolized or modified further by microbial and hepatic enzymes, producing indole derivatives of varying affinities for AhR.[30–32]

Barriers to Bottom-Up Signaling

Signaling within the BGM axis is regulated by 2 dynamic barriers: first, the intestinal barrier, consisting of a basal monolayer of epithelial cells interconnected by tight junctions and a dynamic mucus layer containing secretory IgA and antimicrobial peptides[33]; and, second, the BBB consisting of cerebral endothelial cells interconnected by tight junctions.[34]

Intestinal Barrier

In response to specific microbial products, pattern recognition receptors in the gastrointestinal (GI) mucosa can activate enhanced antimicrobial defense, intestinal inflammation, and immunologic tolerance.[35,36] The intestinal epithelial barrier also plays an important role during healthy homeostatic conditions because micro-organisms and macromolecules are able to gain entry through microfold cells of the gut-and mucosa-associated lymphoid tissue, allowing for constant sampling of the gut luminal environment by immune cells.[37] The mucus layer, the outer layer of which is inhabited by commensal microorganisms, represents a dynamic barrier that maintains a glycoprotein-rich biofilm.[38] This protective biofilm can be degraded by microbes during periods of low dietary fiber, thereby increasing pathogen susceptibility.[39] The permeability of the intestinal barrier also can be influenced by inflammatory mediators and by sympathetic nervous system activity.[40,41]

Blood-Brain Barrier

The BBB represents a diffusion barrier between the circulatory system and the cerebrospinal fluid of the CNS. The gut microbiota can influence the permeability of this barrier by modulating expression of tight junction proteins.[34] Preclinical evidence suggests that SCFAs may act as a key signaling metabolite, regulating microbiota-influenced BBB development and maintenance through epigenetic modification.[42,43] Lipopolysaccharides also may play a role, although likely a more limited one, in disrupting the BBB through systemic immune activation.[44]

Brain to Gut Signaling

The CNS can influence the gut microbiota directly, through luminal secretion of endocrine mediators that interact with microbial receptors, and indirectly through modulation of the gut environment. Direct signaling often involves catecholamines, whose concentrations can be influenced by physical and psychological stress, whereas indirect signaling involves both branches of the autonomic nervous system (ANS).[45–47] The ANS can induce changes in gut physiology, thereby affecting microbial composition and function. As an example of this, changes in intestinal transit times influence water content, nutrient availability, and even bacterial clearance rates. Impaired migrating motor complex regularity can result in bacterial overgrowth, whereas increased intestinal transit times strongly correlate with stool microbial richness and composition.[48,49]The ANS also regulates the integrity of the intestinal mucus layer by modulating goblet cell function, as well as intercellular epithelial permeability. In a mouse model of brain injury, increased norepinephrine release contributed to decreased goblet cell abundance and mucoprotein production.[50] This resulted in changes to the gut microbiota, which correlated with the extent of injury.[50]

Because the majority of brain and brain gut disorders are characterized by enhanced stress responsiveness and altered ANS function, top-down modulation of the gut microbiome by the brain is likely to be an important contributor to the observed gut microbial signatures.

Early Programming of Gut Microbiome Brain Interactions

The first 3 years of life represent a particularly important developmental period for the CNS, with extensive synaptogenesis and myelination taking place.[51] In parallel, early life, including the prenatal period, also represents an important developmental period for the gut microbiota, and it has been suggested that calories harvested by microbes play an important part in brain development.[52] During this time, exposure to different microbes, diets, stressors, antibiotics, and other factors shape microbiota architecture and function, in addition to influencing communication with the developing CNS (Figures 1 and 2). In this way, multiple influences during early life events play a pivotal role in programing the gut microbiota and the brain, and may contribute to the etiology of several neurodevelopmental disorders.

Mode of Delivery

The infant microbiota is highly dependent on the mode of delivery because this represents the initial colonization of the gut.[53] During vaginal delivery, the neonate is colonized by

bacteria closely resembling the maternal vaginal microbiome (enriched in *Lactobacillus* and *Prevotella* species), as well as some fecal microbes.[53] The vaginal microbiome is dynamic and changes in response to maternal stress, which has been shown to influence the newborn gut microbiome and, more importantly, gut metabolome.[54] Maternal stress (infections, psychosocial stress) also has been shown to increase the risk for schizophrenia, autism, and attention deficit hyper-activity disorder in the newborn.[55,56] The neonate delivered by Cesarean section (C-section) instead is colonized by microbes enriched in *Staphylococcus* and *Corynebacte*rium.[53,57] Remarkably, differences in skin, gut, and naso-pharyngeal microbiome composition between vaginally delivered and C-section born infants exists up until the age of 2 years, during a period of intense brain development.[58,59] In a study of 2 million Danish term children, delivery by C-section was associated with an increased risk for the development of asthma, inflammatory bowel disease, immune deficiencies, and other chronic immune disorders.[60]

Early Nutrition

The gut microbiota also is influenced by whether the infant is breastfed or formula-fed, with breastfed infants showing better neurodevelopmental outcomes and a more complex *Bifidobacterium* microbiota relative to formula-fed infants.[61–63] A crucial factor in the development of the gut microbial architecture are the group of complex carbohydrates called *human milk oligosaccharides*.[64,65] These molecules are too large to be absorbed by the infant small intestine, and exclusively target the developing gut microbiome. Other factors shown to influence the development of the infant microbiota include genetics and gestational age.[66,67]

Early Brain Development

During the first 3 years of life,[68] extensive changes in brain architecture occur in parallel with the programming of the gut microbiome, with the end of the second year marking the establishment of an adult pattern of myelination[51] (Figure 2). A preclinical model of myelination suggests that early life commensal microbes are important in regulating proper myelination of the pre-frontal cortex. In this model, GF mice showed up- regulation of genes coding for structural components of myelin, contributing to the hypermyelination seen in these animals, relative to controls.[69] In addition, a study of 89 infants found that the gut microbial composition at 1 year of age was associated with cognitive performance a year later, further underscoring the importance of this early period in the interaction of the gut microbiome and the developing brain.[70]

Modulation of Brain Gut Microbiome Interactions in the Adult

Over time, the mature gut microbial architecture becomes more stable and relatively resistant to long-term perturbations.[71,72] Similarly, the basic architecture of neural networks also stabilizes, although continuous synaptic pruning and myelination continue throughout adulthood.[73] Despite the increased stability of the gut microbial community structure, the functional output to the CNS, via metabolites and signaling molecules, can be altered significantly throughout adult life by antibiotics, diet, prebiotics and probiotics, and by chronic stress.

Antibiotics

In adult rodents, long-term, broad-spectrum anti-biotic treatment was associated with changes in brain chemistry and behavior, in addition to the structure of the microbiome.[74] Antibiotic-treated mice showed decreases in serum concentrations of tryptophan and kynurenine, brain concentrations of serotonin metabolites, and hypothalamic concentrations of vasopressin and oxytocin.[74] These changes in signaling molecules likely contributed to the observed changes in anxiety, memory, and neurocognitive function in these animals.[74] Of note, a series of case-control studies from a large UK database found an association between recurrent anti-biotic exposure and an increased risk of depression and anxiety.[75] This may be related to an inability of the human gut microbiome, in some individuals, to completely recover after repeated antibiotic perturbation.[76]

Diet

Several human studies have shown transient diet-induced changes in the gut microbiome and gene expression patterns in adult subjects, whereas evidence has suggested that long-term changes are not observed.[77] It recently was shown in the Hadza hunter-gatherers of East Africa that seasonal variations in dietary patterns were associated with changes in the diversity, structure, and function of the gut microbiome.[78] These diet-associated changes in the gut microbiome also may be related to changes in brain structure. A preclinical study using machine learning classifiers found that diet-dependent changes in the gut microbiome were associated with changes in white matter architecture.[79] Long-term consumption of a low-fiber diet can have deleterious consequences on microbiota diversity and abundance, which is transferred over several generations, and cannot be reversed by a high-fiber diet.[80] Similarly, the lower-gut microbial diversity and SCFA production observed in North American infants can be reversed only partially by an increased fiber intake as an adult.[81]

Prebiotics and Probiotics

Several studies, mostly preclinical or a limited group of small clinical studies, have shown that prebiotic and probiotic ingestion in adults can modulate brain function and behavior, an observation that has led to the term *psychobiotics.* Table 2[82–95] highlights the increasing literature related to the effects of these psychobiotics, and underscores the sometimes conflicting data associated with these agents. These findings also are reflected in the similarly conflicting results of recent meta-analyses on the use of these agents in clinical trials for depression, anxiety, and stress.[96,97]

In summary, the basic gut microbial composition (including diversity and abundance of certain taxa), as well as BGM interactions, are established early in life, and once established are fairly stable, even in the presence of perturbations by antibiotics, gastrointestinal infections, or dietary changes. However, diet can influence both relative abundances as well as gut microbial functions in the adult within a certain bandwidth. When interpreting studies that explore perturbations in gut microbial structure, it is important to appreciate that the same protective (or deleterious) functional profiles can be generated by different microbial architectures.[98]

Clinical Implications and Brain Gut Disorders

Although preclinical studies clearly implicate the gut microbiome as a factor in modulating brain development, structure, function, and behavior in rodents, the demonstration of causal relationships in human beings remains challenging. Although no population-based studies have been reported on this topic, antibiotic treatment or total colectomies in the clinic are not known to be associated with significant changes in mood and affect. In addition, the effectiveness of prebi- otic and probiotic intake in the treatment of anxiety and depression remains to be determined by large, well-designed, randomized controlled trials. Largely unexplored is the role of early life influences on the evolving gut microbiome-brain communication network and its impact on gastrointestinal disorders with a strong developmental component. Based predominantly on preclinical studies, alterations in BGM interactions have been proposed as possible disease mechanisms in autism spectrum disorders,[19,99] attention-deficit hyperactivity disorder,[100] Parkinson's disease,[101] Alzheimer's disease,[102–104] stroke,[105,106] and epilepsy.[107] In addition, recent translational studies have shown that fecal microbiota transplantation from human donors with anxiety and depression can transmit some features of these conditions to recipient GF mice.[108–110]

BGM interactions likely also play an important role in healthy individuals, with 1 study identifying bacterial genus-based clusters in healthy females that were associated with functional brain profiles related to emotional regulation regions of the brain.[111] In the current review, we focus on 2 brain gut disorders with relevance to gastroenterology.

Irritable Bowel Syndrome

A large number of studies (n = 22 in a total of 827 subjects) have reported significant microbial shifts in fecal microbial community composition between healthy controls and IBS patients, based on disease subtypes (diarrhea-predominant IBS, constipation-predominant IBS, and IBS mixed subtype), age (pediatric vs adult), and compartment (mucosa vs stool).[112] Recent studies investigating gut microbial community structure have identified at least 2 subgroups of patients who meet Rome criteria for IBS. One subgroup, a eubiotic group, did not differ from healthy controls despite similar GI symptoms.[113,114] The dysbiotic IBS subgroup differed in regional brain volumes from the eubiotic group,[113] suggesting a relationship between microbial community structure and brain structure. Another recent study did not find a group difference in microbial composition between healthy controls and IBS, even though IBS symptom severity was correlated with dysbiosis.[115] Based on an analysis of fecal samples, regardless of analytical methodology used, a number of studies reported decreased relative abundance of the genera *Bifidobacterium* and *Lactobacillus,* and increased firmi-cutes:bacteroidetes ratios at the phylum level.[116,117] Because stress has been associated with a reduction in *Lactobacilli* in preclinical and clinical studies,[118–120] the reported IBS-related changes in community structure and resulting metabolism may represent alterations of ANS modulation of the gut, as described earlier.

Obesity

A dysregulation of feeding behavior (referred to as food addiction or hedonic eating behavior) plays a significant role in the current obesity epidemic.[121] By interacting with

enteroendocrine cells in the distal gut, the gut microbiota and its metabolites modulate satiety signals (see earlier) and eating behaviors.[1,122–124] In preclinical studies, fecal transplantation from hyperphagic obese mice to GF mice successfully induced hyperphagic behavior and weight gain in the recipients.[125,126] The gut microbiome also has been associated with changes in brain microstructure in obesity, with distinct microbial brain signatures capable of differentiating obese and lean subjects.[127] A handful of studies have pointed to a dramatic change in gut microbial composition after bariatric surgery.[128–132] Remarkably, fecal transplantation from subjects after bariatric surgery was able to transmit the weight loss effects of bariatric surgery to a GF nonoperated recipient, inducing weight loss and reduced food intake.[133,134]

Conclusions

Based on available, largely preclinical data, the emerging BGM science has the potential to improve conventional therapies for several brain gut disorders, including IBS and obesity. Although experimental animal studies have suggested a possible therapeutic role for certain probiotics (psychobiotics), well-controlled clinical trials in human beings are needed to confirm the therapeutic value of currently available microbiome-targeted therapies in brain gut disorders. Efforts are underway to identify unique gut microbial fingerprints in several GI disorders that may lead to personalized therapies, including diet, as well as prebiotics and probiotics based on individual patterns of dysbiosis. Similarly, there is a search to identify the role of individual gut microbial signaling molecules (postbiotics), which may be targeted for therapeutic benefits. Based on these efforts, novel personalized interventions may become useful as prophylactic or adjuvant therapies for common brain gut disorders. Finally, interventions during early life such as colonization with certain microbes or fecal microbial transplants may become a therapeutic strategy to reduce the risk for the development of disorders such as IBS, anxiety, and even autism spectrum disorders.

Acknowledgments

Funding

Supported by grants DK048351, DK064539, and DK096606 from the National Institute of Diabetes and Digestive and Kidney Diseases (E.A.M.).

Abbreviations used in this paper:

AhR	aryl hydrocarbon receptor
ANS	autonomic nervous system
BBB	blood-brain barrier
BGM	brain gut microbiome
C-section	Cesarean section
CNS	central nervous system
GF	germ-free

GI	gastrointestinal
IBS	irritable bowel syndrome
SCFA	short-chain fatty acid
2BA	secondary bile acid

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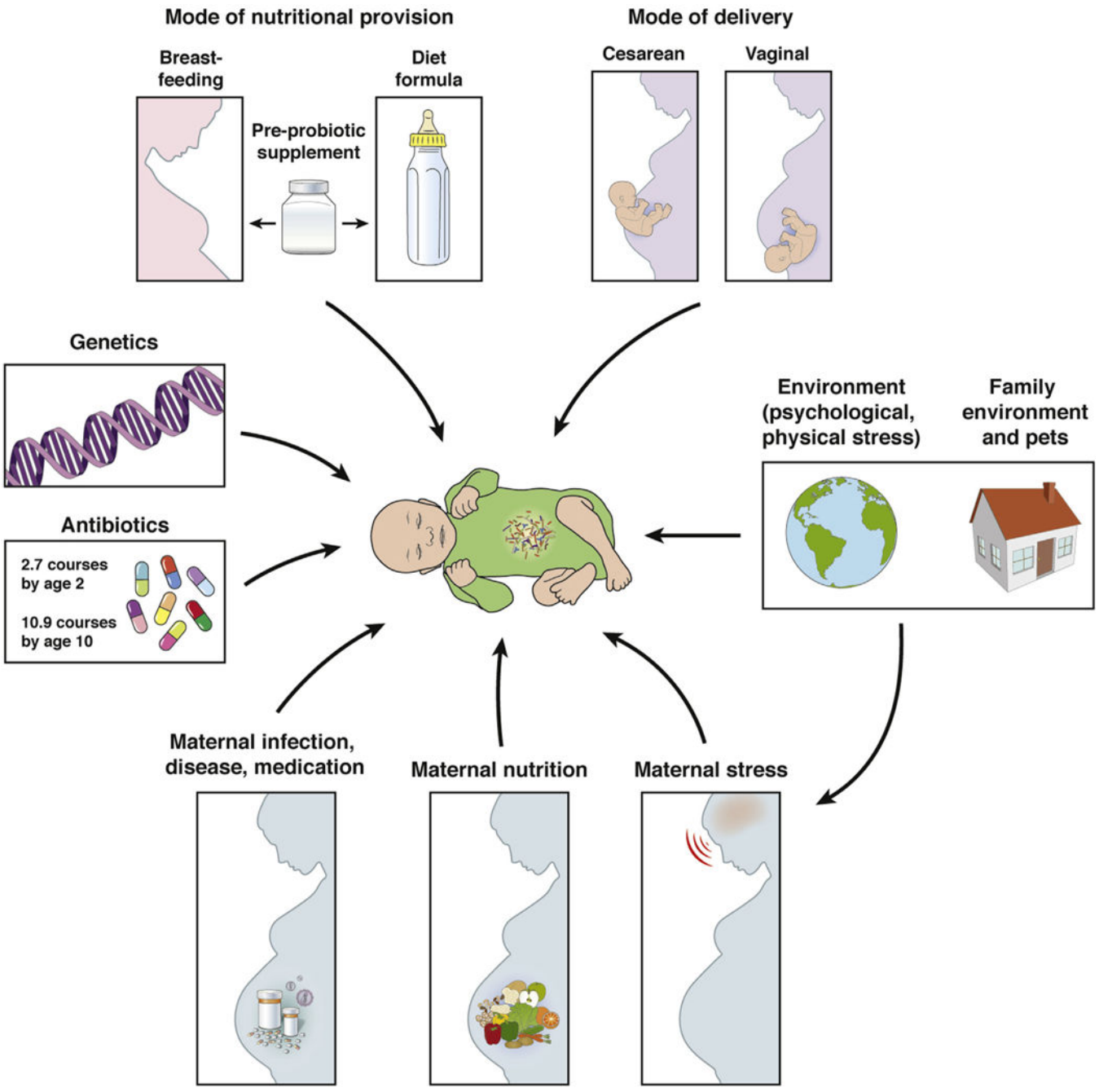

Figure 1.

Early life events and the development of the infant gut microbiota. Early life represents a particularly vulnerable period for the infant gut microbiome because it is highly responsive to numerous factors. In addition to genetics, prenatal influences (maternal nutrition, stress, overall health), mode of delivery, early life nutrition (breastfeeding, formula feeding), physical and psychological environment, and antibiotic use all influence the infant gut microbiome. Modified from Borre et al.[135]

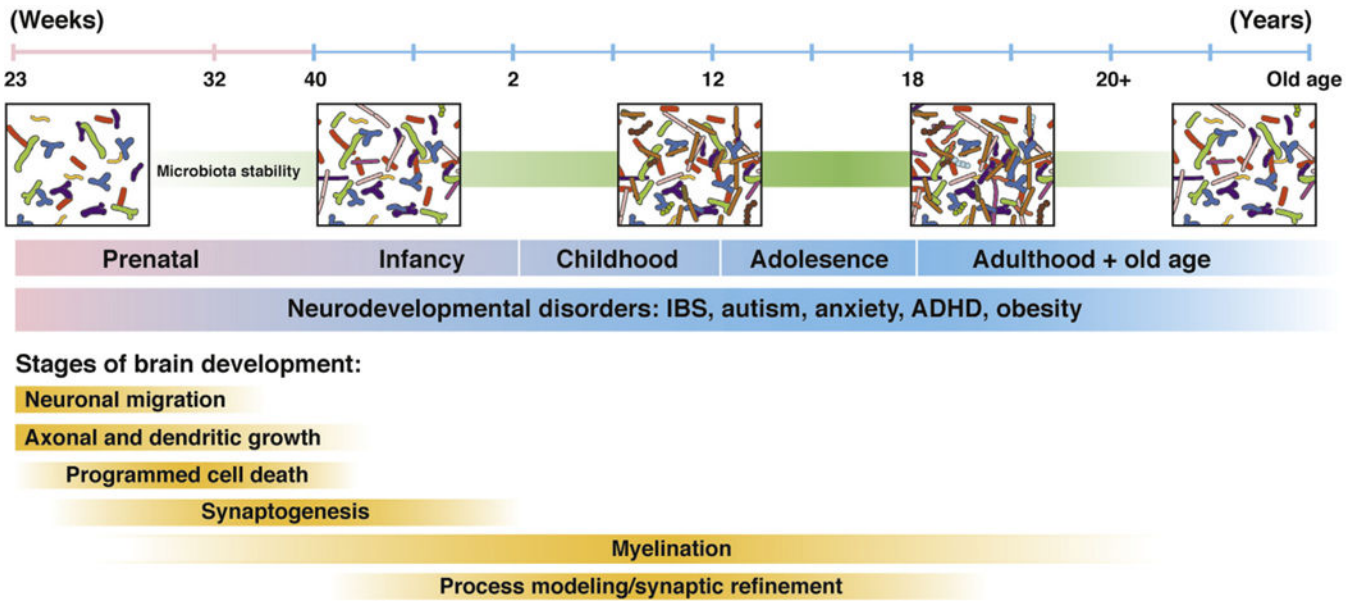

Figure 2.

The developing gut microbiome and brain. Gut microbiota and brain development begins during the prenatal period and continues throughout adulthood, with the first 3 years of life representing a particularly important developmental period. Disruptions in development can influence communication between these 2 systems and may contribute to the pathogenesis of neurodevelopmental disorders such as IBS, autism, anxiety, attention-deficit hyperactivity disorder (ADHD), and obesity. Modified from Borre et al.[135]

Table 1.

Selected Sample of Gut Microbiota to Brain Signaling Channels

Input	Output	Study
2BAs	Improved central regulation of glucose metabolism via production of FGF19	Marcelin et al[8]
		Ryan et al[9]
	Suppression of HPA axis via production of FGF19	Perry et al[10]
	GLP-1 and PYY release from L cells via TGR5 receptor	Bala et al[11]
	Synthesis and release of 5-HT from ECCs	Yano et al[3]
SCFAs	PYY, GLP-1, and GLP-2 release from L cells	Cani et al[12]
	Leptin production from adipocytes via GPR41	Xiong et al[13]
	Synthesis and release of 5-HT from ECCs	Yano et al[3]
Indole	GLP-1 secretion from L cells via interaction with voltage-gated potassium channels and mitochondrial NADH dehydrogenase	Chimerel et al[14]
	Kynurenine synthesis via activation of AhR	Vogel et al[15]
TLR ligands: LPS, flagellin, and so forth	CCK synthesis from EECs via TLRs	Palazzo et al[16]
	PYY expression in vitro from L cells via TLRs	Larraufie et al[17]
	5-HT release in vitro from ECCs via TLRs	Kidd et al[18]

NOTE. The table outlines well-characterized signaling channels driving bottom-up communication along the brain gut microbiota axis. Each input represents a microbiota-derived intermediate that results in a physiological output by interacting with host cells or host-derived signaling molecules.

5-HT, serotonin; CCK, cholecystokinin; ECC, enterochromaffin cell; EEC, enteroendocrine cell; FGF19, fibroblast growth factor 19; GLP, glucagon-like peptide; HPA, hypothalamic pituitary adrenal; LPS, lipopolysaccharide; NADH, nicotinamide adenine dinucleotide; PYY, peptide YY; TGR5, Takeda G-protein-coupled receptor 5; TLR, Toll-like receptor

Table 2.

Selected Sample of Studies Investigating Psychobiotics

Study	Design	Disease	Intervention	Conclusions
Tillisch et al[82]	Clinical; RCT	Healthy women	Probiotic	Probiotic changes functional connectivity of an emotional recognition network in the brain
Slykerman et al[83]	Clinical; RCT in pregnancy	Anxiety and depression	Probiotic	Probiotic significantly decreases postpartum anxiety and depression
Pinto-Sanchez et al[84]	Clinical; RCT in IBS	Depression	Probiotic	Probiotic reduces depression, increases quality of life; associated with changes in brain activation patterns
Romijn et al[85]	Clinical; RCT	Depression	Probiotic	No significant effect of probiotic on low mood or inflammatory biomarkers
Akkasheh et al[86]	Clinical; RCT	Depression	Probiotic	Probiotic reduces depression scores and improves insulin sensitivity
Takada et al[87]	Clinical; RCT	Stress	Probiotic	Probiotic suppresses cortisol hypersecretion and physical symptoms associated with stress
Allen et al[88]	Clinical; within-participant placebo-controlled trial	Stress	Probiotic	Probiotic reduces stress and improves memory
Kelly et al[89]	Clinical; RCT	Stress	Probiotic	No significant effect of probiotic on stress
Ostlund-Lagerstrom et al[90]	Clinical; RCT in older adults	Anxiety and stress	Probiotic	No significant effect of probiotic on stress
Schmidt et al[91]	Clinical; RCT	Anxiety	Prebiotic	Prebiotic is associated with anxiolytic properties
Wang et al[92]	Clinical; RCT	Stress	Rifaximin	Rifaximin shows stress-reducing effects
Burokas et al[93]	Preclinical	Stress	Prebiotic	Prebiotic improves stress-related behaviors
Desbonnet et al[94]	Preclinical	Depression	Probiotic	Probiotic normalizes markers associated with a rat model of depression
Tarr et al[95]	Preclinical	Anxiety	Prebiotic	Prebiotic improves stressor-induced anxiety behavior

NOTE. The table underscores the numerous studies, often with limited sample sizes, investigating the role of prebiotics, probiotics, and antibiotics to modulate anxiety, depression, stress, and other behavioral measures.

RCT, randomized controlled trial.