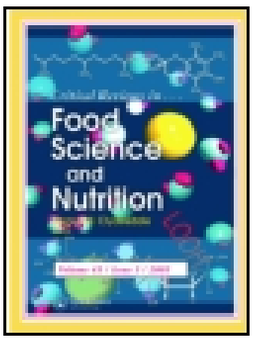

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REVIEW

The microbiota–gut–brain axis: A novel nutritional therapeutic target for growth retardation

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ABSTRACT

Growth retardation (GR), which commonly occurs in childhood, is a major health concern globally. However, the specific mechanism remains unclear. It has been increasingly recognized that changes in the gut microbiota may lead to GR through affecting the microbiota-gut-brain axis. Microbiota interacts with multiple factors such as birth to affect the growth of individuals. Microbiota communicates with the nerve system through chemical signaling (direct entry into the circulation system or stimulation of enteroendocrine cells) and nervous signaling (interaction with enteric nerve system and vagus nerve), which modulates appetite and immune response. Besides, they may also influence the function of enteric glial cells or lymphocytes and levels of systemic inflammatory cytokines. Environmental stress may cause leaky gut through perturbing the hypothalamic-pituitary-adrenal axis to further result in GR. Nutritional therapies involving probiotics and pre-/postbiotics are being investigated for helping the patients to overcome GR. In this review, we summarize the role of microbiota in GR with human and animal models. Then, existing and potential regulatory mechanisms are reviewed, especially the effect of microbiota-gut-brain axis. Finally, we propose nutritional therapeutic strategies for GR by the intervention of microbiota-gut-brain axis, which may provide novel perspectives for the treatment of GR in humans and animals.

KEYWORDS

Enteric nervous system; growth retardation; microbial metabolites; microbiota-gut-brain axis; probiotic

1. Introduction

Growth retardation (GR) is defined as the problem of individuals who display a significantly lower growth rate relative to healthy individuals, which is accompanied by metabolic disorder, systemic inflammation, or gut dysbiosis. GR is the underlying cause of high morbidity and mortality in children younger than 5 years (Muller and Krawinkel 2005). It affects approximately 20% of children globally, and children with GR are more susceptible to metabolic diseases and pathogen infection, and less likely to achieve their growth potential in adulthood (de Onis and Branca 2016; Vonaesch et al., 2018). Various factors including microbiota dysbiosis, neuro-inflammation, disordered endocrine secretion, malnutrition, maternal impact, and stress have been identified to have contributions to GR (Acosta et al., 2017; Qi, Tan, Wang, Li et al. 2019; Qi, Tan, Wang, Liao et al. 2019; Wells et al. 2020). Emerging perspectives from fecal microbiota transplantation (FMT) studies have suggested that the gut microbiota plays a role in the GR of both humans and animals (Bolte and Aagaard 2020; Mirzaei et al. 2020).

The microbiota residing in human bodies comprises bacteria, bacteriophages, and fungi, and outnumbers human cells by approximately 1.3:1 (Sender, Fuchs, and Milo 2016). Even at the genetic level, over 99% of the genes in human bodies are microbial genes, with a number exceeding 10 million (Cryan et al., 2019). The ecosystem of the gut microbiota is gradually established from birth to adulthood with the transfer of microbiota from the maternal and environmental sources (Mirzaei et al. 2020). The gut commensal microbiota plays essential roles in the modulation of nutrient absorption, immune response and metabolic function (Neuman et al. 2015; Torres-Fuentes et al. 2017).

GR has a complex and multifactorial etiology, and it is crucial to employ a systems biology-based approach to understand its pathophysiology and develop personalized strategies to achieve healthy growth and prevent GR (Nguyen et al. 2019). Emerging preclinical studies support the concept of bidirectional signaling within the microbiota-gut-brain-axis in the pathophysiology of GR, which is mediated by metabolic, endocrine, neural and immune system mechanisms (Osadchiy, Martin, and Mayer 2019). Perturbation of the

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microbiota-gut-brain axis system at any level may impair the mechanisms to lead to growth failure (Cryan et al., 2019). Sensing of microbial metabolites by gut specialized cells involving enteroendocrine cells (EECs) results in neural signaling to the brain and interactions with gut-based immune cells leading to local and systemic immune activation, or the microbial products may enter the blood circulation system for direct access into the brain circuits (Gupta, Osadchiy, and Mayer 2020). Signaling from brain induced by stress through the hypothalamic-pituitary-adrenal (HPA) axis disrupts many gut processes, resulting in abnormal gut motility, leaky gut, and lower microbial abundance, which play crucial roles in the occurrence of GR (Keita and Soderholm 2010; Yu et al. 2017). Our previous studies have demonstrated that pigs with GR displayed a decline in gut barrier function and nutrient absorption ability. These disorders are associated with alterations in the abundance of *Firmicutes*, *Lactobacillus* and *Ochrobactrum* in the small intestine and a decrease in the secretion of appetite hormones mediated by the brain (Qi, Tan, Wang, Liao, Li et al. 2020; Xiong et al. 2020). In this review, we discuss the changes of gut microbiota in GR, summarize the physiological factors related to the variations in microbiota-gut-brain axis, and then propose perspectives on several nutritional therapeutic strategies.

2. Microbiota-gut-brain axis in GR

The gut-microbiota-brain axis is important in maintaining homeostasis of the gastrointestinal, central nervous and microbial systems, thus promoting the growth and development of humans and animals (Cryan et al., 2019; Morais, Schreiber, and Mazmanian 2020). The signaling pathways include direct or indirect signaling via chemical transmitters, neuronal pathways, the immune system, and the HPA axis as described below. The depiction of the possible microbiota-gut-brain axis involved in GR is presented in Figure 1.

2.1. Role of gut microbiota in GR

2.1.1. Gr-associated gut microbiota

The establishment of the commensal gut microbiota strongly influences the development of the metabolic, digestive, neural, and immune systems in early postnatal life (Robertson et al. 2019). Abnormal microbial succession may cause retarded growth and development and then lifelong deficits (Tamburini et al. 2016; Robertson et al. 2019). The roles of microbiota in GR are summarized in Table 1. Stunted children tend to have more *Enterobacteriaceae*, *Escherichia coli* (*E. coli*), and *Campylobacter* spp. but less

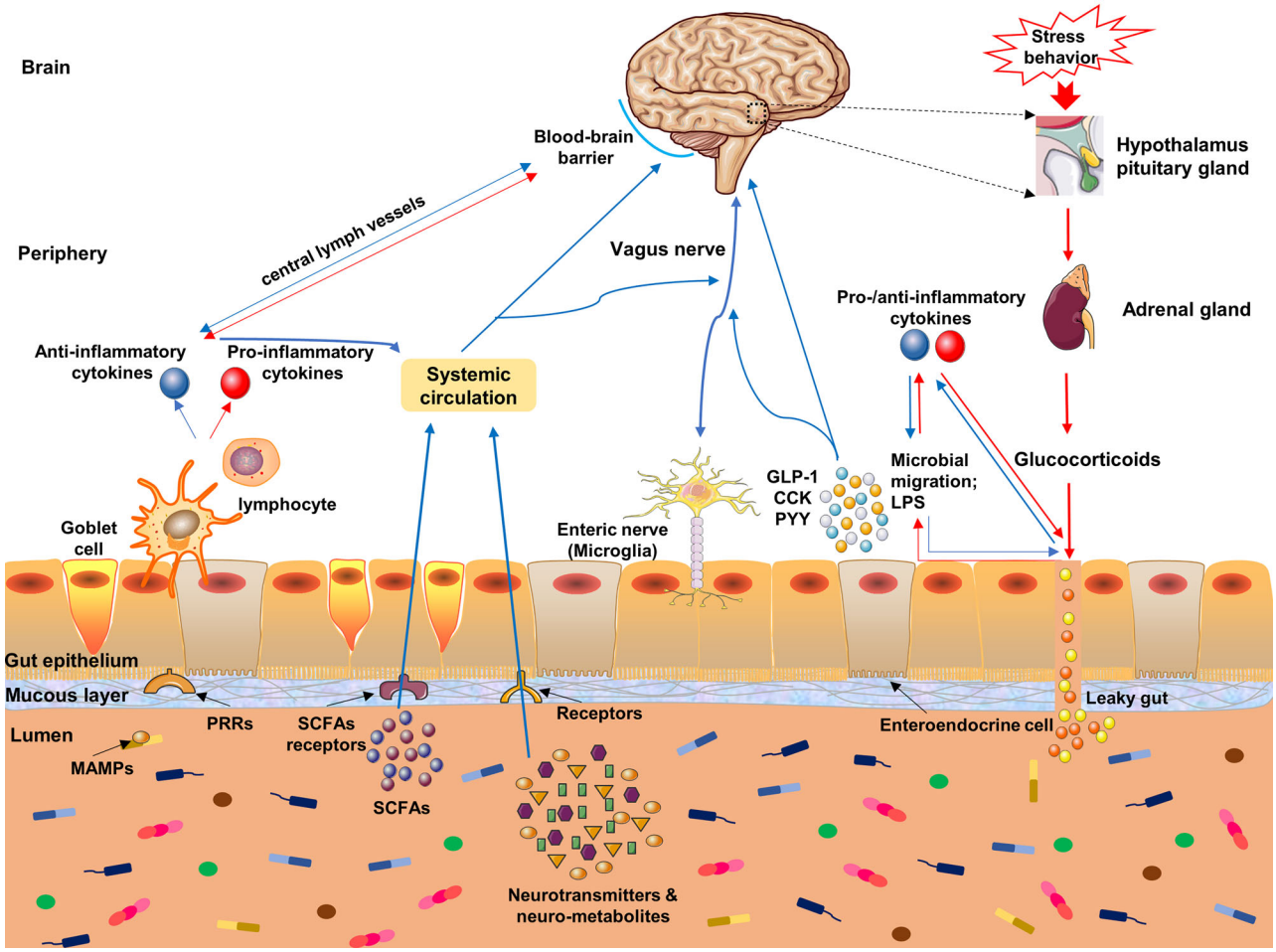

Figure 1. Systems-level overview of the various known bidirectional pathway of microbiota-gut-brain axis, including enteric nervous system, vagus nerve, enteroendocrine, immune-modulatory responses, hypothalamic-pituitary-adrenal axis, and microbial metabolites signaling. Blue arrows indicate beneficial physiological processes and effects, while red arrows indicate processes associated with leaky gut and inflammation. MAMPs, microorganism-associated molecular patterns; PRRs, pattern recognition receptors; SCFAs, short chain fatty acids; GLP-1, glucagon-like peptide-1; CCK, cholecystokinin; PYY, peptide YY; LPS, lipopolysaccharide.

Table 1. Gut microbiota in GR*.

Species	Microbial changes	Effects	References
Human, low birth weight infants	↑facultative anaerobic microorganisms such as *Enterobacteriaceae*, *Enterococcaceae*, *Escherichia coli*, *Enterococcus sp*, *Klebsiella pneumoniae*, and *Staphylococcus* sp;↓strict anaerobes such as *Bifidobacterium*, *Bacteroides*, etc in fecal samples.	Pathogenic and cause enterocolitis;↓production of SCFAs.	(Martin et al. 2016; Robertson et al. 2019)
Human, initial growth deficits	↑*Staphylococcus*;↓*Clostridium*, *Proteobacteria*, *Bacteroides fragilis*, and *Peptostreptococci* in fecal samples.	↓Amino acids fermentation;↓ability to produce essential vitamins.	(Dai, Wu, and Zhu 2011)
Human, stunted children	↑*Enterobacteriaceae*, *Escherichia coli*, and *Campylobacter spp.*;↓*Clostridia* in fecal samples.	↓digestive and absorptive functions;↑enteric inflammation.	(Subramanian et al. 2014; Vonaesch et al., 2018)
Human, undernutrition	↓*Ruminococcus gnavus* and *Clostridium symbiosum* in fecal samples.	Cause metabolic disorder such as↑serum acylcarnitines;↓bone development	(Blanton, Charbonneau et al. 2016)
Human, severe acute malnutrition	↑Anelloviridae and Circoviridae in fecal samples.	Still unclear.	(Reyes et al. 2015)
Human, undernourished children with diarrhea	↑*Faecalibacterium prausnitzii*, *Ruminococcaceae*, *Dorea*, and *Prevotella* in fecal samples.	↓Gut microbiota's resistance and resilience to diarrhea.	(Rouhani et al. 2020)
Human, early exposure to stress	↓*Bacteroides* and *Clostridium* spp in fecal samples.	↓Growth hormone production. Cause leaky gut.	(Skuse et al. 1996)
Human, undernourished individuals with anorexia nervosa	↓Total bacteria and obligate anaerobes (*C. coccoides* group, *B. fragilis*, *C. leptum*, and *Streptococcus*) in fecal samples.	↓Production of SCFAs; ↓appetite, and energy metabolism;↑level of methane.	(Morita et al. 2015)
Human, IBS patients with GR	↓*Bifidobacteria*, and *Lactobacillus*;↑*Escherichia Coli*, and *Enterobacter* in fecal samples.	Altered 5-HT metabolism such as↑plasma kynurenine levels and the ratio of kynurenine to tryptophan.	(Zhuang et al. 2017)
Mouse, low body weight	↓*Akkermansia muciniphila* in fecal samples.	Neuroinflammation and leaky gut;↓neurotrophin BDNF levels.	(Kimono et al. 2020)
Pig, postnatal GR	↓Genus *Alloprevotella* and *Oscillospira* in colon.	↓Ability to produce butyrate.	(Qi, Tan, Wang, Liao et al. 2020)
Pig, IUGR	↓Proteobacteria, *Ochrobactrum*, and *Lactobacillus* in jejunum; ↑Ruminococcaceae in ileum, and Firmicutes in jejunum.	↓Gut barrier function and nutrient absorptive ability.	(Xiong et al. 2020)
Sheep, low birth weight	↓*Saccharofermentans*, *Ruminococcus*;↑*Succiniclasticum* in ruminal digesta.	↓Ability to degrade saccharide and produce propionate.	(Xue et al. 2020)

*GR, growth retardation; SCFAs, short chain fatty acids; 5-HT, 5-hydroxytryptamine; IBS, irritable bowel syndrome; BDNF, brain- derived neurotrophic factor; IUGR, intrauterine growth retardation.

Clostridia in their fecal samples, which is highly associated with the impairment of digestive and absorptive functions and enteric inflammation (Subramanian et al. 2014; Vonaesch et al., 2018). It was further revealed that children with severe GR usually have poorer recovery from diarrhea and have prolonged dysbiosis, which further exacerbated the loss of microbial diversity (Rouhani et al. 2019). The GR phenotype can be transmitted via FMT to germ-free (GF) mice, pigs and humans. GR was observed in the GF piglets transplanted with a GR-associated microbiome that was deficient in *Ruminococcus gnavus* and *Clostridium symbiosum* (Smith et al. 2013; Blanton, Charbonneau et al. 2016). Supplementation of microbiota-directed complementary food to children with GR could restore the gut microbiota to a similar level compared with that in healthy children (Gehrig et al., 2019). The growth of mice with GR could be restored to a normal state after co-housing with mice receiving FMT from healthy individuals or administration with segmented filamentous bacteria (Blanton, Charbonneau et al. 2016; Wagner et al. 2016; Gehrig et al., 2019; Shi et al. 2019). In pigs and lambs with low birth weights, there were obvious perturbation of lipid metabolism and alteration of gut microbiota, such as the genera *Bifidobacterium* and *Subdoligranulum* (Lin et al. 2019; Huang et al. 2020). Notably, gut bacteriophages isolated from children with GR were infectious in vitro and could change the bacterial community in an age-specific manner (Mirzaei et al. 2020). Considering the role of microbiota identified in GR, a normal gut microbial profile should be critical for the healthy growth of neonates.

2.1.2. Ontogenesis of microbiota associated with body growth and development

An immature gut microbiota may cause significantly a lower weight gain in patients with GR. Previous studies have identified a variety of microbial signatures associated with either healthy growth or GR in the early postnatal period as summarized in Figure 2 (Mirzaei et al. 2020). In the first six months of life, children with GR showed lower abundance

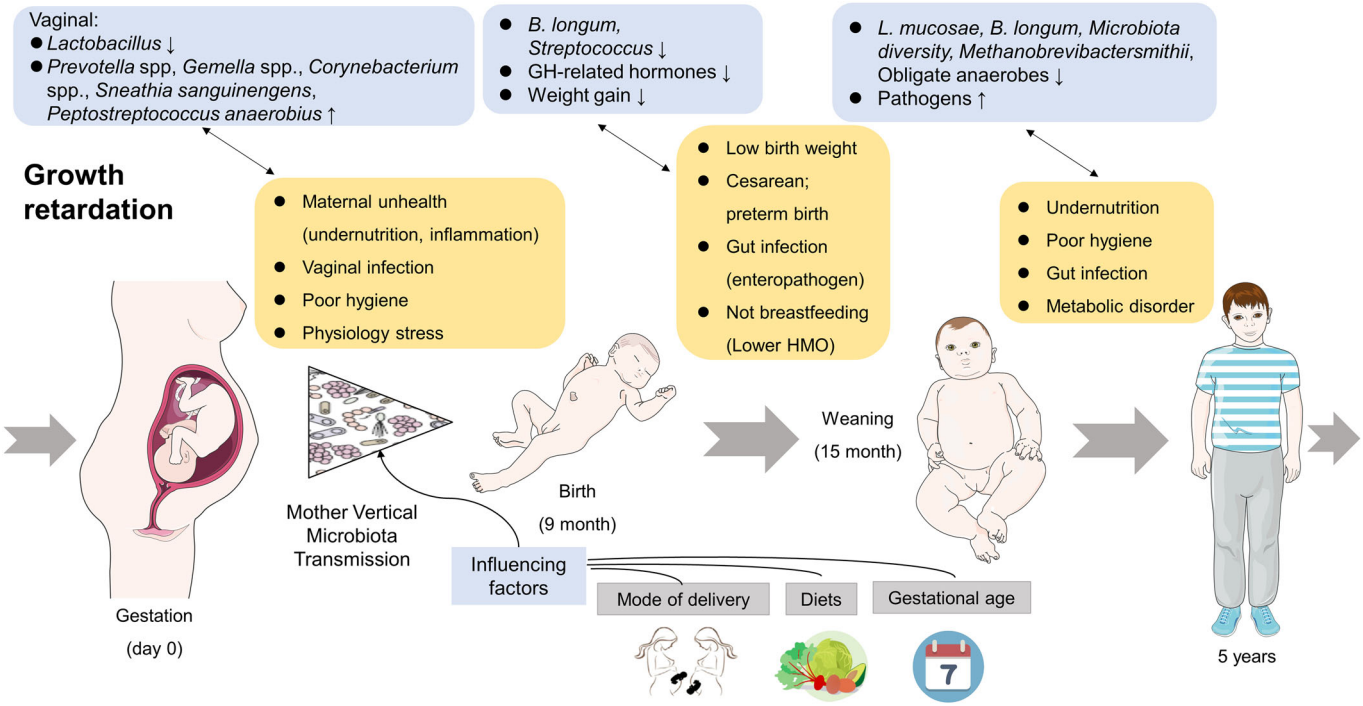

Figure 2. The dynamics of the key microbial taxa at different stages from pregnancy to childhood that contribute to growth retardation. During pregnancy, a vaginal microbiota with low diversity of *Lactobacillus* but high abundances of *Prevotella* spp., *Gemella* spp., and *Corynebacterium* is associated with reduced weight gain. Mode of delivery, diets, and gestational age are important factors affecting the maternal health, vaginal environment, and inflammatory state of infants. In the first 9 months of life, lower levels of *Bifidobacterium longum* and *Streptococcus*, accompanied by the decreased secretion of growth hormone-related hormones, may lead to lower body mass. In later childhood, *Lactobacillus mucosae*, *Bifidobacterium longum*, *Methanobrevibactersmithii*, and obligate anaerobes are associated with severe growth retardation. A two-way interaction exists between an immature microbiome and the risk factors contributing to growth retardation, whereby gut infection, nutrition, birth weight, and other factors both influence and are influenced by the "growth restricted" microbiome. GH, growth hormone; HMO, human milk oligosaccharide.

of *Bifidobacterium longum* (*B. longum*) and *Streptococcus thermophilus* but higher abundance of Gammaproteobacteria compared with healthy children (Blanton, Charbonneau et al. 2016). In particular, preterm birth is characterized by the overgrowth of *Staphylococcaceae*, *Enterococcus* and opportunistic pathogens, which can reduce the weight gain, delay the colonization of *Bifidobacteriaceae*, and cause higher susceptibility to colitis and diarrhea (Tirone et al. 2019). Administration of probiotics *Bifidobacterium* and *Lactobacillus* in preterm infants can significantly modify the gut microbial composition to make it close to that of full-term babies (Alcon-Giner et al. 2020). Healthy post-partum microbiota can support the proliferation and differentiation of intestinal epithelial cells and promote the maturation of the immune system (Yang et al. 2016). A clinical study has demonstrated that high levels of *Bacteroides fragilis* and low *Staphylococcus* in the gut in the first year of life contribute to a higher growth rate in later life (Vael et al. 2011). Additionally, breast milk provides many bioactive compounds for protection against enteropathogens and inflammation to maintain the healthy growth of children. A recent study has revealed that breastfed infants tend to have more *Lactobacilli*, *Bacteroides* and *Bifidobacterium* and fewer pathogens in the gut, which will contribute to a greater growth rate relative to formula-fed infants (Martin et al. 2016). A markedly lower abundance of sialylated human milk oligosaccharides (HMOs) in maternal breast milk can cause severe growth failure of infants. Supplementation of sialylated HMOs could promote microbiota-dependent growth in infants with GR, which may be explained by the higher abundance of *Bifidobacteriaceae* in the infant feces (Charbonneau et al., 2016; Berger et al. 2020).

In later childhood, increases in the abundance of *Faecalibacterium prausnitzii*, *Akkermansia muciniphila* (*A. muciniphila*), *Lactobacillus* and obligate anaerobes were observed in healthy children, while higher levels of *E. coli*, *Staphylococcus aureus* and other species were found to be associated with GR (Robertson et al. 2019). During postnatal development, microbiota-dependent processes greatly affect the transcription of epithelial genes, which are primarily involved in immune pathways and endocrine metabolic processes (Pan et al., 2018). A bidirectional interactive effect between an immature microbiota and various adverse factors may finally cause GR.

The gut microbiota can influence linear growth by altering hormone secretion. Recent studies have shown that the modulation of ghrelin receptors by short-chain fatty acids (SCFAs) affects both the central nervous system (CNS) and the peripheral nervous system, which is involved in the regulation of weight gain (Torres-Fuentes et al. 2019). Another study revealed that microbial alteration of insulin-like growth factor-1 (IGF-1) levels could restore the linear growth in a *Drosophila* and GF mouse model (Shin et al. 2011; Schwarzer et al. 2016). However, SCFAs can inhibit growth hormones in cows by affecting the expression of genes involved in the cAMP/PKA/CREB signaling pathway (Wang et al. 2013). Furthermore, somatostatin derived from bacteria is a known inhibitor of growth hormones, and the

perturbation on the somatotropic axis stability is associated with linear growth (Neuman et al. 2015). Overall, the gut microbial profile undergoes gradual changes from birth to childhood, which may be affected by the preterm birth or breast feeding.

2.1.3. Multiple factors interact with gut microbiota to affect growth

The interactions of gut microbiota with maternal effects, birth delivery, host genetics, environmental factors and diet play crucial roles in the pathophysiology of GR (Figure 3). Maternal effects and the type of birth delivery significantly influence the gut microbiota, and further affect the growth in later life of humans and animals. Intervention on the gut microbiota during early life period exerts profound effects on the development of the host, because the early colonization of microbiota is more readily modulated than the increasingly resistant gut microbiota of adults (Figure 2). During pregnancy, fetal growth and development are mainly influenced by the *in utero* environment. The GR *in utero* is related to maternal and placental inflammation and infection as well as dramatic changes in host hormone levels, suggesting a prenatal role of the microbiota-brain axis in fetal growth (Robertson et al. 2019). In general, there are significant increases in hormones such as estrogen and leptin while decreases in adiponectin and pituitary hormones with increasing gestational age (Neuman et al. 2015). Specifically, in the third trimester, the composition of the gut microbiota undergoes dramatic changes, leading to increases in low-grade inflammation and decreases in insulin allergic response. This phenotype was found in GF mice, as the GF mice receiving microbiota in the third trimester exhibited a greater inflammatory response than those receiving microbiota in the first trimester (Goltsman et al. 2018). Maternal gut carriage of *Prevotella copri* during pregnancy may promote the development of immune tolerance in the offspring, such as reduced allergic disease in the infants (Vuillermin et al. 2020).

Different modes of delivery (spontaneous vaginal delivery vs. cesarean section delivery) will lead to differences in microbial diversity in infants. Compared with the infants born via spontaneous vaginal delivery, those born through cesarean section tend to have lower gut bacterial diversity and density, delay of immune system development and higher risk of postnatal diarrhea, and thus are more susceptible to GR in later life of humans and domestic animals (Siggers et al. 2008; Robertson et al. 2019). In addition, the healthy vaginal microbiota helps to establish the gut microbial community of infants at birth during vaginal delivery. The vaginal microbiota with low diversity or dominated by *Lactobacillus* is associated with healthy postnatal growth. However, a more diverse vaginal microbiota, especially with high abundance of *Prevotella* spp., *Gemella* spp. and *Corynebacterium*, is associated with postnatal GR, which may be attributed to vaginal infection, poor hygiene, or maternal malnutrition (Robertson et al. 2019).

It is generally believed that mother-to-infant vertical microbiota transmission significantly influences infant growth trajectories. Thus, the maintenance of maternal

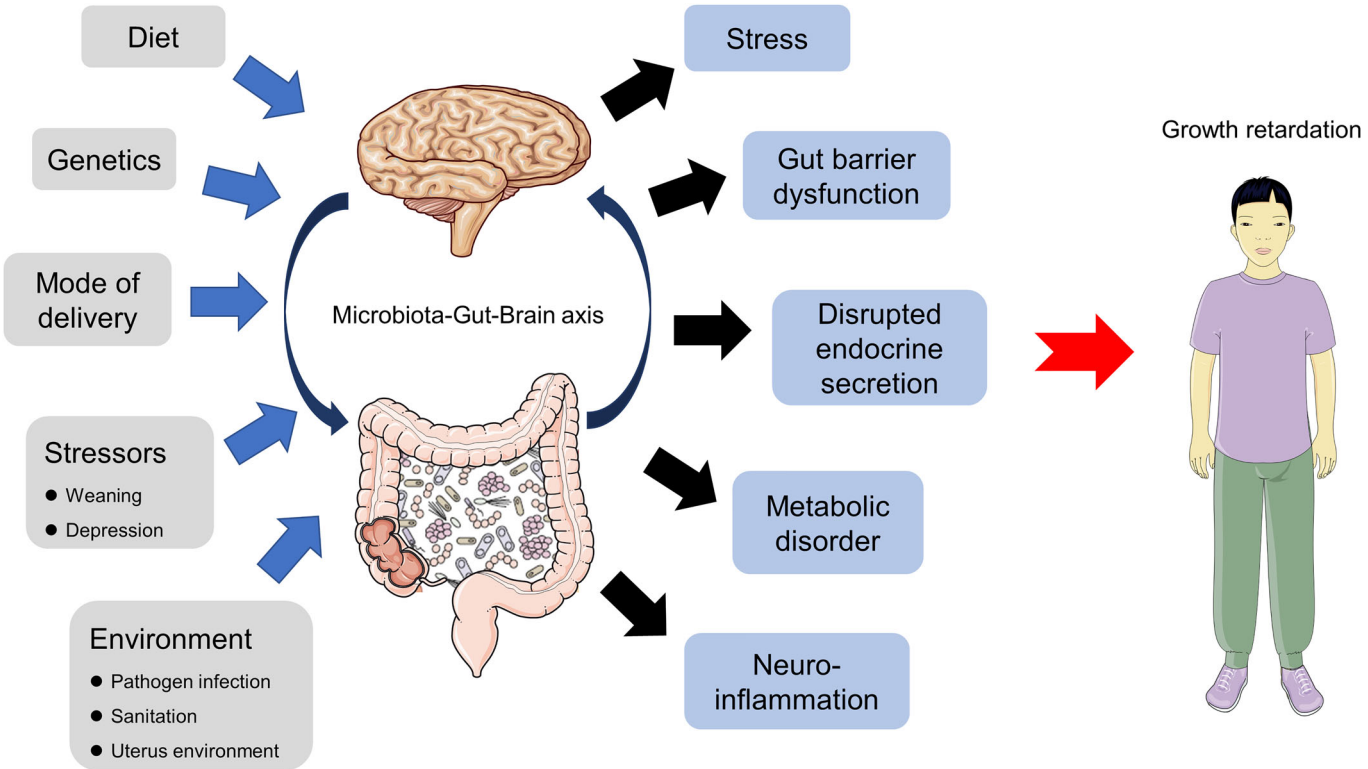

Figure 3. Illustration identifying common factors known to affect microbiota-gut-brain axis, including diet, congenital heredity, mode of delivery, stressors involving weaning and depression, and environmental impact involving pathogen infection, sanitation, and uterus environment, as well as various behaviors known to be interfered by microbiota-gut-brain perturbation, including social stress, gut barrier dysfunction, disrupted endocrine secretion, metabolic disorder, and neuroinflammation, which may result in growth retardation.

microbial homeostasis is crucial for the prevention of metabolic disorders and growth impairments in subsequent generations (Neuman et al. 2015). Maternal microbiota dysbiosis caused by leaky gut will induce a severe inflammatory response and hormonal imbalance, accompanied by the development of diseases such as polycystic ovary syndrome, which will negatively affect fetal growth (Neuman et al. 2015). Adverse factors such as unhealthy maternal diet during pregnancy impact the maternal endocrine system and gut microbiota acquisition of the infants. For instance, a high-fat diet during gestation significantly decreases the colonization of *Bacteroides*, *Sutterella*, *Parabacteroides* and *Comamonas* in the gut of newborn infants, and the effect will last for about one month after birth (Chu et al. 2016). However, the mechanism through which the maternal pregnancy diet alters the microbiota of the offspring remains unclear.

Apart from maternal effects and birth delivery discussed above, different genetic backgrounds also shape the microbial composition, immune response and host metabolism, which are crucial in growth and development. *Nod2*-depletion mice, which were deficient in apoptosis and antifungal immunity, had a low abundance of gut bacteria and was susceptible to pathogen infection. Besides, *Card9*-knockout mice (deficient in immune responses) were prone to display hindgut dysbiosis. In general, these gene-edited mice were prone to developing GR (Rehman et al. 2011; Lamas et al., 2016). Environmental factors such as sanitation, weaning and infection affect the gut microbial profile as well. Unsanitary conditions will cause leaky gut, infection and bacterial translocation, which further lead to GR in children (Owino et al. 2016). Microbial changes in response to disrupted weaning contribute to delayed maturation of intestinal barrier and increased susceptibility to allergic inflammation, which may result in GR later (Al Nabhani et al. 2019; Beaumont et al. 2020). Furthermore, an "ecogroup" of 15 bacterial taxa with consistent variations in fecal samples was identified in Peru children with GR under 5 years of age (Raman et al., 2019).

Collectively, obvious changes in microbial profile can be observed under GR. A mature gut microbial profile can help to maintain a mature immune system and a normal level of growth hormone through communication with the brain, which may be affected by various factors associated with maternal conditions, birth delivery, host genetics, and environment. The mechanisms underlying the interaction of gut microbiota with the brain under GR are also summarized in this review.

2.2. Chemical signaling between the gut and brain in GR

The gut microbiota can modulate the immune system and metabolic homeostasis of host through direct or indirect chemical communications with the nerve system, which play an important role in the healthy growth and development of humans and animals.

2.2.1. Scfas directly influence CNS

The microbiota ferments undigested carbohydrates as the main substrate to produce SCFAs in the gut, including acetic acid, propionic acid and butyric acid, which constitute more than 95% of the total SCFA content (Sun et al. 2017). The primary SCFA-producing bacteria include *Firmicutes*, *Bacteroides*, *Eubacterium*, *Bifidobacterium*, *Clostridium*, *Propionibacterium*, *Lactobacillus*, *Roseburia*, and *Prevotella* (O'Callaghan et al., 2016). SCFAs enter the circulatory system from the gut to CNS, and serve as signaling molecules to modulate the host metabolism and immunity-related processes, which can significantly influence the growth and development of individuals (Long-Smith et al. 2020). Chronic administration of exogenous sodium butyrate could significantly ameliorate GR caused by acute stress by altering the expression of a neuronal factor of brain, namely brain derived neurotrophic factor (BDNF), in a mouse model (Schroeder et al. 2007). Butyrate that enters into the CNS could decrease lipopolysaccharide (LPS)-induced neuroinflammation in the primary microglia and hippocampus of rats, and further down-regulate systemic pro-inflammatory cytokines and alleviate GR (Varatharaj and Galea 2017). These findings suggest that SCFAs may directly influence the brain by crossing the blood-brain barrier (BBB), which may in turn influence the host homeostasis.

Fecal levels of SCFAs may be utilized to predict GR. Decreases in fecal SCFA level have been associated with various GR-induced disorders, such as anorexia, inflammatory bowel diseases (IBD) and neuroinflammation in human studies (Morita et al. 2015; Sun et al. 2017; Cryan et al., 2019). A lower fecal SCFA production was also observed in children with severe GR under the infection of gut pathogens. However, SCFA levels increased in parallel with fecal microbiota amount during recovery (Monira et al. 2010). Thus, it may be speculated that administration of SCFAs into the circulatory system has multiple functions to directly influence CNS, which can alleviate GR caused by neuroinflammation or gut dysbiosis.

2.2.2. Microbial-derived neurotransmitters directly influence CNS

The gut microbiota modulates the concentrations of neurotransmitters in model systems, which regulates the growth and development of humans and animals. Gut microorganisms can synthesize neurotransmitters by themselves and can also induce the production of neurotransmitters by their hosts. For example, several microorganisms (*Bacteroides*, *Bifidobacterium*, *Lactobacillus* and *Escherichia* spp.) are known to produce the neurotransmitter γ- aminobutyric acid (GABA) (Strandwitz et al. 2019). Oral administration of these microbes significantly increased the serum levels of GABA and the expression of GABAα receptor in the brain, which in turn improved intestinal health, stress-like behaviors and growth performance in mouse and pig models (Strandwitz et al. 2019). Thus, microbial-derived neurotransmitters directly interact with their receptors in the brain to boost healthy growth.

2.2.3. Other microbial metabolites directly influence CNS

Other microbial metabolites such as bile acid (BA) and trimethylamine N-oxide (TMAO) directly communicate with the nerve system for the maintenance of host growth and development. The gut microbiota affects BA metabolism during the process of detoxification and the gut immune response (Connors et al. 2020), which relies on the conversion of primary bile acids (PBAs) into secondary bile acids (SBAs) by the host and microbiota, and this process is known as a crucial mediator of host health involving gut homeostasis and energy metabolism (Wang et al. 2019). Subsequently, BAs are reabsorbed in the distal gut through BA receptors such as farnesoid X receptor (FXR) and G protein-coupled receptor TGR5 (also known as G protein-coupled bile acid receptor 1 (GBAR1)). Impaired vagus nerve and suppressed BA synthesis were observed in rats with GR caused by the deterioration of mucosal function, while agonistic FXR changed the BA levels and composition to promote growth (Wang et al. 2018). Another study revealed that restoration of the intestinal BA pool in mice with undernutrition-induced GR could increase the number of intestinal intraepithelial lymphocytes (IELs) such as RORγt^{+} Treg cells, and reduce the risk of neuroinflammation, thus enhancing the growth performance (Song et al. 2020). Additionally, dysbiosis of the gut microbiota would cause SBA deficiency in patients with IBD-induced GR and amplify the pro-inflammatory state in CNS, which was reverted by SBA supplementation relying on TGR5 (Quraishi et al. 2020; Sinha et al. 2020). Moreover, intrauterine growth restriction (IUGR) mice showed lower plasma BAs, glucose intolerance and gut dysbiosis, which could be rescued by supplementation of PBAs (Ma et al. 2017). In addition to BAs, TMAO, which is mainly generated from the metabolism of choline and betaine by the gut microbiome, also modulates growth through direct impact on CNS. A clinical study has revealed that GR in children is associated with low serum choline levels and high betaine-choline and TMAO-choline ratios, accompanied by decreases in the secretion of growth hormone, but the exact mechanism remains unclear (Semba et al. 2016). Further studies are needed to determine whether the enhancement of choline intake or metabolism can improve the growth and development of children with GR. Collectively, these findings suggest that specific gut microbiota and the corresponding metabolites can directly communicate with the nerve system through the circulatory system to alleviate GR in humans and animals.

In addition to direct communication, gut microbiota can indirectly communicate with the nerve system by affecting EECs to produce hormones or neurotransmitters, further modulating the growth of individuals.

2.2.4. Microbial metabolites promote EECs to secret appetite hormones

Gut microbiota can indirectly communicate with CNS through interacting with EECs for the secretion of appetite hormones. Eating and metabolic disorders are important factors to cause the delay of growth (Clark et al., 2014). In a clinical study, low birth weight (LBW) infants exhibited poorer digestive tolerance than healthy infants, which was associated with different development of gut microbiota (Jacquot et al. 2011). Our previous study also revealed the aberrant energy status in the intestinal mucosa of pigs with GR (Qi, Wang, Tan, Liao, Long et al. 2020). Mice that received FMT from stunted children showed a significant weight loss, accompanied by impairment of glucose, lipid, and amino acid metabolism, which was attributed to alterations of the bacterial species *Ruminococcus gnavus* and *Clostridium symbiosum* (Smith et al. 2013).

Microbial metabolites including SCFAs, BAs and indole affect the secretion of gut-derived satiety hormones such as cholecystokinin (CCK), peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) in EECs, as summarized in Figure 4 (Cryan et al., 2019). These hormones can activate vagal and spinal gut-derived signals, which are then integrated into the nucleus solitary tract, and induce a signal in the hypothalamic arcuate nucleus (ARC). In the ARC, the main appetite-suppressing proteins, pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), induce the production of melanocortins and promote a negative energy balance. Neuropeptide Y (NPY) and agouti-related protein (AGRP) are appetite-stimulating neurotransmitters, which also inhibit POMC expression. These hormones are crucial in the modulation of food intake and maintenance of glucose homeostasis to facilitate the normal growth of humans and animals (Torres-Fuentes et al. 2017; Lach et al. 2018). Patients with marked weight loss were found to have excessive activation of the POMC neurons and inhibition of the NPY/AGRP neurons (Bauer, Hamr, and Duca 2016). Our recent study revealed a decrease in the mRNA expression of *AGRP* in the gut and a lower level of plasma AGRP in piglets with postnatal GR (Qi, Tan, Wang, Liao et al. 2019). Mice with GR induced by microbial clearance exhibited a decrease in the secretion of satiety hormones, which was associated with a decreased ability of the gut to sense nutrients and transmit satiety signals via the gut-brain axis (Duca et al. 2012).

The increase in SCFAs could modulate EECs and their secretion of PYY and GLP-1 via GPR41 and GPR43 in the mouse model, thus improving food intake and gut homeostasis (Overduin et al. 2013; Cluny et al. 2015). Administration of *B. animalis*, *B. bifidum* and oligofructose could promote the colonization of beneficial bacteria and production of SCFAs, which can facilitate growth by stimulating GLP-1 secretion (Cryan et al., 2019). In addition, microbiota-derived bile acids can activate FXR and TGR5 expressed on EECs to promote the release of GLP-1 and PYY, which are essential for the regulation of glucose tolerance and insulin sensitivity in the intestine and liver (Katsuma, Hirasawa, and Tsujimoto 2005; Thomas et al. 2009; Torres-Fuentes et al. 2017). A clinical study reported that patients with type 2 diabetes had significant weight loss, which was linked with alterations of bile acid metabolism and low serum levels of GLP-1, while supplementation with bile acid could improve the glucose tolerance (Staels and Fonseca 2009). The transplantation of gut dominant genus

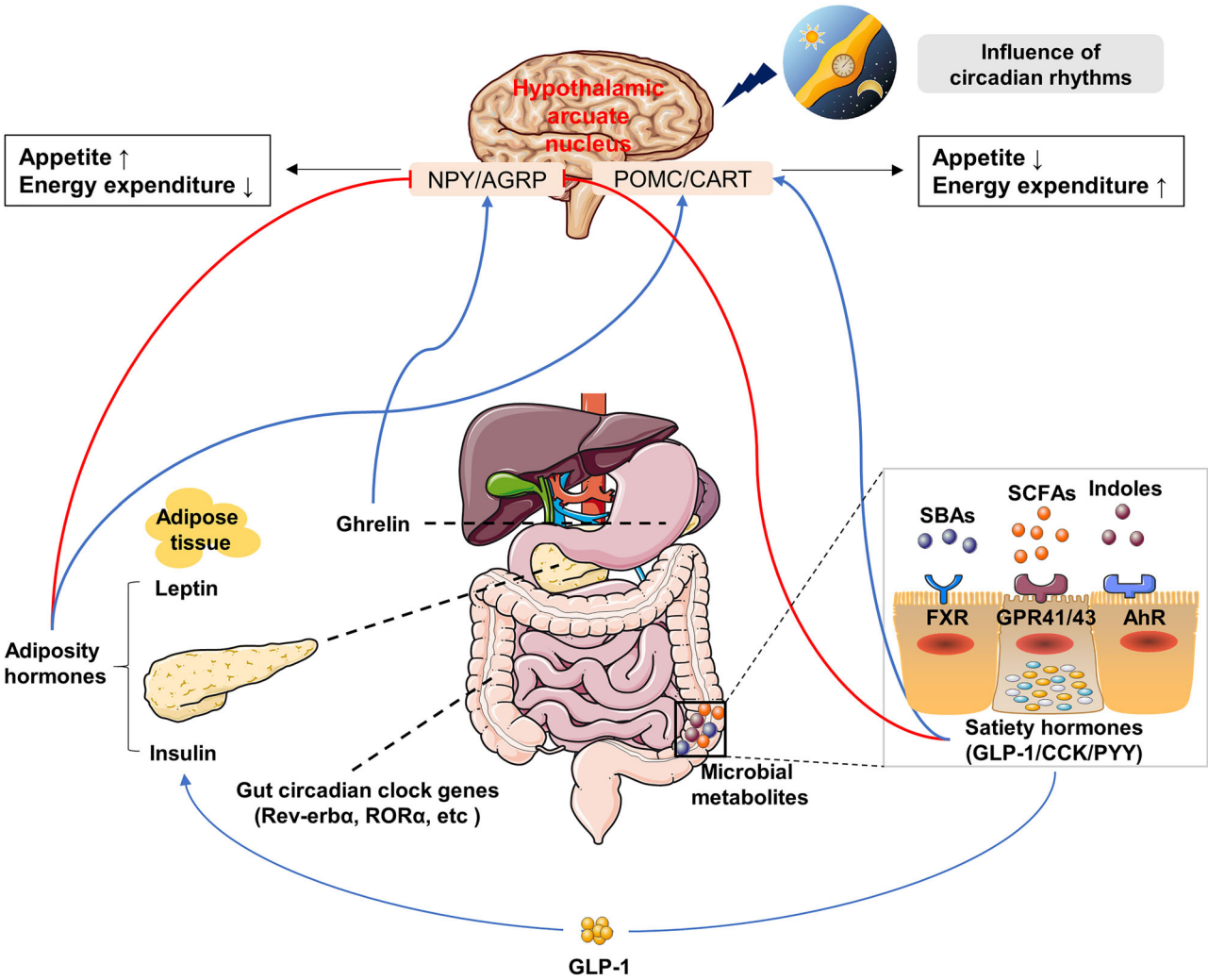

Figure 4. The microbiota-gut-brain axis affecting appetite and energy metabolism. Satiety and adiposity hormones are secreted in the gut and adipose tissue, directly or indirectly affecting NPY/AGRP- and POMC/CART-associated neurons located in the hypothalamic arcuate nucleus. The activation of NPT/AGRP signaling promotes food intake, whereas the activation of POMC/CART neurons has an anorexigenic effect. Circadian rhythms also influence host energy metabolism. CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; NPY, neuropeptide Y; AGRP, agouti-related protein; CART, cocaine- and amphetamine-regulated transcript; POMC, pro-opiomelanocortin; PYY, peptide YY; GPR41, G-protein coupled receptor 41; GPR43, G-protein receptor 43; SBAs, secondary bile acids; FXR, farnesoid X receptor; SCFAs, short chain fatty acids; AhR, aryl hydrocarbon receptor.

Prevotella copri increased gut SBA levels, and recovered the secretion of satiety hormones, thus improving glucose tolerance in rats with GR (Parseus et al. 2017; Pean et al. 2020). Moreover, indole and derivatives were found to improve energy metabolism through activating aryl hydrocarbon receptor (AhR) expressed on EECs, and stimulate the secretion of NPY/AGRP in the ARC of humans and mice with GR by activating the vagus nerve (Lee, Wood, and Lee 2015; Rastelli, Cani, and Knauf 2019). Furthermore, bacterial components can mediate the host metabolism by stimulating the secretion of GLP-1 from EECs. Caseinolytic protease B (ClpB) acts as an anorexigenic and anxiogenic neuropeptide (Arnoriaga-Rodriguez et al. 2020). It can regulate satiety, energy metabolism and growth, as manifested by the result that GR mice immunized with ClpB showed improvement of food intake and growth (Tennoune et al. 2014). Compared with that of ClpB-deficient *E. coli*, the administration of ClpB-producing *E. coli* in patients with eating disorders would increase the food intake and body weight in the short term through communication with EECs (Tennoune et al. 2014). A clinical study revealed that bacteria-derived N-acyl amide, one type of bioactive lipids, affects the host glucose metabolism by triggering GLP-1 secretion in EECs, and further promotes growth (Cohen et al. 2017).

Emerging evidence suggests that the microbiota-gut-brain axis and circadian rhythms act in concert to regulate the energy metabolism of the host. Genetic models with aberrant circadian clock genes, such as *Bmal1*$^{-/-}$ and *Per1/2*$^{-/-}$ mice, exhibited a marked reduction of gut microbiota circadian rhythmicity and an increment in the plasma level of leptin, resulting in disordered lipid metabolism and weight loss (Liang, Bushman, and FitzGerald 2015). In addition, the key circadian clock genes regulated by microbiota, *RORα* and *Rev-erbα*, promote nutrient uptake and lipid absorption (Kuang et al. 2019). *Rev-erbα*$^{-/-}$ mice were prone to develop GR with severely impaired formation of brown fat and adiposity, which may be associated with gut microbial dysbiosis (Wang et al. 2017). Collectively, these findings suggest that gut microbiota or microbial products can

indirectly activate appetite-related proteins in ARC through modulating the secretion of GLP-1 or PYY by EECs, further improving appetite and eating habits in patients with GR. It is reasonable to speculate that the intervention that modulates the interaction between microbial products and gut hormones may be an effective treatment strategy for GR.

2.2.5. Microbiota affects the production and secretion of serotonin by EECs

In addition to appetite hormones, gut microbiota indirectly communicates with the nerve system by affecting the secretion of serotonin (5-HT) from EECs. 5-HT production and secretion by EECs are affected by certain bacterial species or microbial products including indole, SCFAs and tryptophan (Morris et al. 2017). Inhibition of neural 5-HT synthesis was found to cause GR and a high mortality rate in the early postnatal life of mice (Alenina et al. 2009). Mice with GR caused by a low diversity of bacteria showed a decrease in 5-HT biosynthesis, which could be rescued by inoculation with spore-forming bacteria to enhance the tryptophan metabolism by enterochromaffin cells (Ma et al. 2020). Notably, spore-forming bacteria from healthy human gut microbiota have similar effects when transplanted into mice with GR, indicating that gut microbiota can improve tryptophan metabolism to promote the growth across mammals (Ma et al. 2020). Administration of *Clostridium ramnosum* could improve the 5-HT biosynthesis in colonic EECs of mice and humans, and further promote the growth (Yano et al. 2015; Mandic et al. 2019). Tryptophan hydroxylase is expressed in some commensal bacteria, which controls the rate-limiting reaction to utilize tryptophan for the synthesis of 5-HT. These commensal bacteria include *Lactococcus*, *Lactobacillus*, *Enterococcus*, *E. coli*, *Streptococcus*, and *Klebsiella* (O'Mahony et al., 2015; Sarkar et al. 2016). In human studies, some GR-associated disorders, such as irritable bowel syndrome (IBS), are associated with impaired tryptophan metabolism (Agus, Planchais, and Sokol 2018). Indole and SCFAs can facilitate the secretion of 5-HT in EECs, and then modulate the secretion of GLP-1 and PYY after feeding. In a study with a murine model, fetal GR was associated with decreases in fecal SCFA levels and gut 5-HT production, which had negative effects on brain development and appetite (Ranzil et al. 2019).

Regarding the importance of 5-HT in the regulation of gut motility via the ENS, a clinical study demonstrated different compositions of microbiota between constipation- and diarrhea-predominant IBS patients. Dysregulated 5-HT synthesis and transport, together with decreases in the expression of 5-HT transporters (e.g., SERT) and receptors (e.g., 5-HT_3), were observed in IBS patients compared with the healthy control (Kerckhoffs et al. 2012). The majority of 5-HT is produced in the gut, but 5-HT cannot bypass BBB. However, mice with GR induced by low abundance of microbiota exhibited decreases in the levels of 5-HT and its metabolic precursor tryptophan in the hippocampus, suggesting that gut microbiota plays a mediating role in 5-HT signaling pathways in the CNS (Clarke et al. 2013). It remains to be determined how the interaction between the gut microbiota and 5-HT production in the brain affects growth.

In summary, these findings demonstrate that gut microbiota may influence body growth through direct or indirect communication with the nerve system in chemical signaling. In fact, it remains to be determined to which extent microbial metabolism influences the activity of the CNS, partly because the general ratio of microbial metabolites that are transported into the brain remains unknown. Apart from chemical signaling, the interaction of the gut microbiota with the nerve system in neuronal pathways may also result in GR.

2.3. Neuronal pathways for gut-brain interactions in GR

The neuronal pathways involve the vagus nerve, which extends from the brainstem to innervate the gut and the ENS. Here, we will review the effects of microbiota and its metabolites on the activity of ENS and the function of the vagus nerve in humans and animals with GR.

2.3.1. Microbiota-ENS interaction affects growth

The gut differs from all other peripheral organs with the evolution of its own intrinsic nervous system, namely the ENS, which is called the "second brain" in the body. The interaction between ENS and the gut microbiota regulates various gut functions, including peristalsis, gastric acid secretion, permeability, nutrient absorption, and interaction with the immune and endocrine systems of the gut (Furness 2012). Children with GR usually exhibit gut motility disorders due to microbial dysbiosis and immature ENS (Chumpitazi and Nurko 2008).

Gut microbiota can regulate the development and electrophysiological activity of the ENS (Sarkar et al. 2016). GF mice with growth failure showed an immature ENS with decreases in nerve density and excitability in the jejunal and ileal myenteric plexuses, whereas colonization of normal microbiota could revert these deficits, suggesting a direct regulatory effect of the microbiota on ENS development in the GR phenotype (Collins et al. 2014; De Vadder et al. 2018).

Gut microbiota influences the development of enteric glial cells (EGCs), which are important for the maintenance of gut homeostasis and neuronal networks (Morais, Schreiber, and Mazmanian 2020). The gut microbiota regulates the neurogenic program of gut motility by mediating the AhR expressed on EGCs. Microbiota-induced expression of AhR acts as a biosensor in enteric neural circuits, as revealed by the finding that gut neuron-specific deletion of *AhR* would lead to damage of the peristaltic function of the colon and further cause GR in a mouse model (Obata et al. 2020). Impaired production of AhR agonists by the gut microbiota would aggravate GR-related metabolic syndrome by increasing systemic inflammation in mice, while GR was observed in $AhR^{-/-}$ mice (Esser 2009; Natividad et al., 2018). Improvement of EGC function could facilitate nutrient absorption and ameliorate bacterial or inflammatory

challenges, further promoting the growth, and vice versa (Sharkey 2015). GF mice displayed defects in renewal of EGCs accompanied by a low appetite, while reconstitution of GF mice with normal microbiota improved the density of EGCs and gut physiology, including digestive function and motility (Kabouridis et al. 2015). The interaction between the gut microbiota and group 3 innate lymphoid cells (ILC3s) under the mediation by cytokine signaling in EGCs could alleviate gut inflammatory response and promote growth. In mice with GR due to gut dysfunction, reconstruction of the microbial profile prevented pathogen infection in the gut through the activation of neural regulation signals by EGC to secrete IL-22 (Ibiza et al. 2016). In addition, the microbiota maintains the development and function of ENS via Toll-like receptors (TLRs). Mice with *Tlr2*-deficiency (*Tlr2*$^{-/-}$) in EGCs were prone to develop GR, as characterized by the abnormal neurotransmission of the ENS and disorder of the microbial profile, and ingestion of TLR2 agonist rescued the phenotype (Anitha et al. 2012; Brun et al. 2013).

Microbial products have also been shown to influence ENS activity and gut motility in GR (Morais, Schreiber, and Mazmanian 2020). In patients with metabolic syndrome, low body weight can be rescued by administration of SCFA-producing gut microbiota, which helps to suppress the ENS-induced gut contraction (Muller et al. 2020). *B. longum* NCC3001 metabolites promoted gut recovery by reducing the action potentials of ENS in response to electrical stimulation in patients with IBS (Meyer and Vassar 2018). Overall, these findings shed light on the role of gut microbiota and its metabolites in the alleviation of GR by modulating the ENS pathways of the gut-brain axis.

2.3.2. Microbiota communicates with the vagus nerve to affect growth

Gut microbiota can communicate with the vagus nerve to achieve healthy growth. Vagus nerve fibers can innervate the muscle and mucosa layers of the gastrointestinal tract, sense intestinal molecules such as microbial metabolites, gut hormones and neurotransmitters, and are responsible for transmitting the information on gut function to the CNS (Thayer and Sternberg 2009). Stimulation of the vagus nerve occurs through the activation of mechanoreceptors triggered by mechanical and chemical stimuli (including hormones, microbial metabolites and neurotransmitters) produced by EECs, which may themselves be affected by the gut microbiota (Muller et al. 2020). In patients with GR, mechanical ablation of the vagus nerve, a treatment formerly used for peptic ulcers, will lead to a higher incidence of psychiatric-related disorders, accompanied by a disturbed microbial profile in feces (Browning and Houseworth 1953). Additionally, in mice with GR caused by disordered secretion of satiety hormones, EECs failed to transduce sugar stimuli to the vagus nerve due to the inhibition of neurotransmitter glutamate synthesis, suggesting that the interaction of neurotransmitters with vagus nerve can modulate growth (Kaelberer et al. 2018). Rats with GR experienced a loss of vagal sensitivity to satiety-related hormones, gut contraction and changes in eating habits, while injection of acetate, propionate and butyrate could reverse these phenotypes (Esser 2009). It was shown that the interaction of SCFAs with the vagus nerve regulates the eating behavior and gut motility to promote growth (Kentish and Page 2015; Vaughn et al. 2017). Furthermore, the vagus nerve has been identified as a therapeutic target for GR-associated disorders, such as leaky gut and metabolic syndrome, through its anti-inflammatory effects and promotion of mucosal barrier function (Pavlov and Tracey 2012; Kentish and Page 2014; Olson et al. 2018). Inhibition of the vagus nerve can suppress the function of macrophages to cause IBD, which may further lead dto GR in humans (Mulak and Bonaz 2004). Reduced vagal activity was found to be accompanied by increases in bacterial overgrowth and bacterial translocation in the small intestine, which led to marked inhibition of growth (Van Felius et al. 2003).

Collectively, these findings reveal that gut microbiota and microbial metabolites are crucial factors that modulate the activity of ENS and the vagus nerve, transmit signals of the gut to the brain, and then regulate the systematic immune function and metabolism to boost healthy growth of human and animal models.

2.4. Microbiota-gut-brain signaling through the immune system

The gut microbiota interacts with the immune system to affect the CNS. Impairment of the gut microbiota-immune system affects the immunological sensory function of intestinal neurons (Blanton, Barratt et al. 2016; Jarret et al., 2020). Patients with GR were reported to have increased exposure to enteropathogens, which perturbed gut microbial composition, and was associated with the disruption of the innate and adaptive immune system, leading to inflammation in both the gut and the brain (Liu et al., 2016). Our group previously found that the deterioration of intestinal immunological barrier function is associated with gut dysbiosis using a GR pig model (Qi, Tan, Wang, Liao, Li et al. 2020). The gut microbiota mediates the development and function of the immune system by activating microglia and IELs or circulating cytokines (Morais, Schreiber, and Mazmanian 2020).

2.4.1. Microglia-mediated immune programming

The gut microbiota and metabolites communicate with the immune system through interaction with microglia to achieve healthy growth. Microglia cells in the gut are innate immune cells that have been suggested to sense subtle changes in gut microbial profiles and subsequently modulate the neuroinflammatory response in individuals with GR or the associated disorders (Tremblay et al. 2011; Vuong et al. 2017; Abdel-Haq et al. 2019). GF mice experienced deficits in microglia maturation and function, such as a deteriorated immune response to pathogen infection, which could be restored by transplantation with healthy gut microbiota (Erny et al. 2015; Thion et al., 2018). These results illustrate the necessity of maintaining gut microbial homeostasis for

healthy microglia function. The gut microbiota activates microglia cells, which subsequently recruit CNS-regulated peripheral monocytes to protect the cells and clear cell debris (Cryan et al., 2019). Microbial metabolites modulate the development and function of microglia. Administration of SCFAs could maintain a normal microglia population and anti-neuroinflammatory function in microbiota-depleted mice with GR (Erny et al. 2015). In GR-associated disorders, patients with IBS exhibited a different bacterial composition and impairment of tryptophan metabolisms, which can suppress the NF-κB pathway and regulate TGF-α and VEGF-B production in microglia (Brown, Kenny, and Xavier 2019). A lower VEGF-B abundance in the gut would reduce the activity of inflammatory astrocytes, thus recruiting local immune cells and aggravating gut inflammation (Brown, Kenny, and Xavier 2019). The cytokine milieu stimulated by SCFAs affects the function of EGCs, which support enteric neuronal functions by producing glial cell-derived neurotrophic factors (GDNFs). GDNFs are produced in response to microbiota immune signaling, which promotes the production of IL-22 by ILC3 cells and improves the restoration of the epithelial barrier, thus alleviating GR caused by gut dysfunction (Rosenbaum et al. 2016; Godinho-Silva et al. 2019; Parker, Fonseca, and Carding 2020). Furthermore, some specific microbiota may be necessary for the proper function and development of microglia in GR. In a previous study, feeding of low-body-weight mice with four *Bifidobacterium* spp. showed that these bacteria could promote growth performance, which may influence the development and activation of microglia through transcriptional mechanisms (Luck et al. 2020). Therefore, microbiota and microbial metabolites maintain the maturation and function of microglia, and then alleviate neuroinflammatory response in GR.

2.4.2. Gut microbiota interacts with the brain by circulating cytokines

In addition to activating microglia, the gut microbiota also induces active immune responses by modulating the production of pro-/anti-inflammatory cytokines in GR. Active immune defense in GR requires the monitoring, coordination and response to microbial changes by the host disturbed cells, which are achieved by pattern recognition receptors (PRRs) (Burgueno and Abreu 2020). PRRs recognize abnormal microbes via microorganism-associated molecular patterns (MAMPs), including lipopolysaccharides (LPS), flagellin, peptidoglycan, formyl peptides, and unique nucleic acid structures (Boyapati et al. 2016; Hernandez, Huebener, and Schwabe 2016; Rooks and Garrett 2016). The gut microbiota communicates with the ENS and innate immune system through crosstalk between MAMPs and PRRs expressed along the lumen, and these interactions are responsible for the transmission of inflammatory information about the changes in microbial profile to the host with GR (Sarkar et al. 2016). The expression of TLR in intestinal epithelial cells (IECs), one type of PRR, is strongly linked with the presence of bacteria and responsible for the maintenance of gut homeostasis. The expression of TLR1 and TLR2 was downregulated in mice with GR, accompanied by a low diversity of microbiota (Obata and Pachnis 2016). In normal mice, the expression of TLRs was higher in colons with the most abundant microbiota compared with in the small intestine (Lundin et al. 2008; Hormann et al. 2014; Kamdar et al. 2018; Price et al. 2018). Perturbation of the TLR pathway by infection of pathogens such as *Yersinia enterocolitica* was observed in GR-associated disorders such as gut dysbiosis (Kamdar et al. 2016). Disturbed TLR2 signaling triggered spontaneous colitis in mice, and transplantation with gut microbiota from IBD patients led to faster development of colitis than in healthy individuals, exhibiting an amplified negative effect on growth (Nagao-Kitamoto et al. 2016; Gunasekera et al. 2020). Overexpression of TLR4 in the intestinal epithelium has been shown to increase bacterial translocation and the risk of colitis, which could be transmitted to co-housed wild-type mice through fecal microbiota. GR phenotype was then observed in the recipient mice (Dheer et al. 2016; Burgueno and Abreu 2020).

Breakdown of the epithelial barrier resulting from GR-associated disorders, such as dysbiosis, infection and damage, allows the ingress of bacteria, their metabolites, toxins and LPS to induce inflammatory responses and enteric neuronal damage (Zhao et al. 2017). Continuous intestinal inflammation can trigger chronic systemic inflammation characterized by increases in blood pro-inflammatory cytokines in mice with GR (Mark and Miller 1999). It is known that the access of pro-inflammatory cytokines into the CNS can increase the permeability of the BBB, permitting the access of potential pathogens and toxins (Parker, Fonseca, and Carding 2020). The deteriorated BBB further causes systemic inflammation and disorders in hormone secretion. In GR, administration of probiotics such as *Lactobacillus plantarum DR7* (*L. plantarum DR7*) could promote the growth by mediating the level of pro- and anti-inflammatory cytokines (Cryan et al., 2019). The MAMP-PRR interaction modulates the production of pro-/anti-inflammatory cytokines under GR or its associated disorders. The MAMPs of beneficial microbiota promote the secretion of anti-inflammatory cytokines via activating the PRRs expressed in IECs, which can alleviate gut dysbiosis-induced growth failure (Sarkar et al. 2016). *L. rhamnosus GG* supplementation attenuated tumor necrosis factor-α (TNF-α)-induced gut barrier impairment and stress behavior by downregulating pro-inflammatory cytokines in the blood and brain (Donato et al. 2010). Inoculation of growth retarded piglets with microbiota from healthy human infants elevated the levels of IL-6 and IL-10 in ileal mononuclear cells and promoted the development of the neonatal immune system, thus exerting a growth promotion effect (Zhang et al. 2014). However, depletion of IL-18, a pro-inflammatory cytokine, from enteric neurons disturbed MAMP-PRR interaction and AMP production, making the mice susceptible to invasive *Salmonella typhimurium* infection and develop GR (Jarret et al., 2020). The mechanism underlying the intricate interactions between PRRs, MAMPs and the inflammatory response remains to be fully uncovered. It was proposed that beneficial microbiota may directly eliminate pathogenic

MAMPs in the lumen or competitively bind to them (such as LPS) and thus impede them from activating the expression of ileal PRR in rats (Zhou et al. 2015). Thus, gut microbiota and microbial products can be recognized by PRRs on IECs, and modulate the systemic levels of pro- and anti-inflammatory cytokines to improve deteriorated BBB induced by cytokines.

2.4.3. Microbiota-IELs interaction in GR

The gut microbiota can also interact with IELs, further alleviating the inflammatory response in GR. The perturbation of microbial colonization would inhibit the development of the IELs, which may contribute to the development of GR in humans and animals (Huang et al. 2020; Mirzaei et al. 2020). GF mice showed reduction in the activities of T cells and B cells, as well as a smaller population of $CD4^+$ T cells, which was accompanied by obvious growth failure (Belizario, Faintuch, and Garay-Malpartida 2018). *Rag2*$^{-/-}$ mice with GR that lacked mature B and T lymphocytes displayed reduction of stress and improvement of social behavior when lymphocytes were transferred from stressed mice (Brachman et al. 2015). In addition, administration of *Lactobacillus reuteri* facilitated the recruiting of intraepithelial lymphocytes and stimulated the reprogramming of intraepithelial $CD4^+$ T cells into immunoregulatory T cells in response to stress in mice with GR (Cervantes-Barragan et al. 2017). *Rag1*$^{-/-}$ mice with deficiency in adaptive immunity showed impaired growth performance accompanied by depression-like behavior, which could be reversed by the colonization of *L. rhamnosus* and *L. helveticus* (Smith et al. 2014). These findings reveal that the gut microbiota can affect the adaptive immune system and thus influence the behavior in response to GR-associated disorders. Furthermore, adaptive immunity can be activated by specific microbial metabolites or microbial antigens from diets, indicating that intervention in dietary composition can be a potential strategy for alleviating GR associated disorders, such as IBS and arthritis in humans (Cryan et al., 2019). The gut microbiota mediates immune tolerance to dietary antigens through affecting the production of regulatory T cells (Kim et al. 2016). Regulatory T cells could prevent immunogenic reactions to daily nutrient intake, while GF mice exhibited excessive immune responses to dietary antigens and experienced IBS (Kim et al. 2016). Commensal viruses maintain the growth and development of healthy humans by modulating the homeostasis of IELs via their cytosolic viral RNA-sensing receptor (RIG-I) expressed in antigen-presenting cells (Liu et al. 2019). Microbial metabolite-activated immune cells can travel via the blood to release soluble factors at the BBB, impacting its integrity and changing the inflammatory status of brain cells. In GR-associated disorders, systemic inflammation causes extravasation of leukocytes and macrophages to the brain through activation of adhesion molecules, chemokines and matrix metalloproteases at the BBB and in the brain and through downregulation of tight junctions (Parker, Fonseca, and Carding 2020). The mechanisms by which SCFA signaling influences CNS include inhibiting histone deacetylases (HDACs) and serving as binding ligands for G protein-coupled receptors (GPCRs) in both the gut and brain. SCFA-driven inhibition of HDACs has anti-inflammatory effects in macrophages and dendritic cells (DCs) located on the gut by suppressing the nuclear factor-κB (NF-κB) signaling pathway, which may alleviate inflammation-induced GR in patients. It was also reported to suppress the activity of forkhead box P3 $(FOXP3)^+$ Treg cells and thus attenuate colitis and promote colonic homeostasis in mice with low body weight (Singh et al. 2010; Chang et al. 2014; Rooks and Garrett 2016). Considering the anti-inflammatory effects of SCFAs, intestinal and systemic inflammations and fecal SCFA levels are used to predict the mortality of acute undernutrition-induced GR patients (Attia et al. 2016). The activation of GPCRs is important for SCFA-induced Treg cell homeostasis and anti-inflammatory function of monocytes (Tan et al. 2014). The binding of SCFAs to GPR43 is required for the maintenance of microglia homeostasis and glucose control through the gut-brain neural circuit involving GPR41 (De Vadder et al. 2014; Erny et al. 2015). Stress-induced GR disturbs the microbial profile, and alters the polarization of intestinal macrophages. The harmful metabolites of microbiota and cytokine production impair enteric neural responses to inflammatory signals and increase the apoptotic rate of enteric neurons (Becker et al. 2018). The loss of enteric neurons not only alters the intestinal function but also affects the ability of the gut to communicate with the brain. Colitis patient-derived *Enterococcus faecium* impaired the development of the BBB in the mouse host genetically susceptible colitis, resulting in severe gut dysbiosis and GR in the recipient mice (Seishima et al. 2019). Thus, gut microbiota interacts with IELs via specific receptors and then activates immune response.

To sum up, these results reveal that specific microbiota or microbial metabolites can modulate the development of microglia, IELs and systematic levels of pro/anti-inflammatory cytokines, thus influencing the growth of individuals. Further studies are required to investigate the possible role of the gut microbiota in shaping such immune-brain communication in GR-associated immune disorders, and more clinical studies are needed.

2.5. Signaling from brain through HPA axis influences growth

Signaling from the brain through HPA axis influences gut homeostasis and hormone secretion in GR, and the causal environmental factors have also been shown to result in GR. Early exposure to chronic and acute stress can reduce gut microbiota diversity, such as decreases in *Bacteroides* and *Clostridium* spp. abundance and production of growth hormones, by directly activating the HPA axis, thus leading to GR in children (Skuse et al. 1996). The HPA axis serves as a crucial integrative system in the adaption of organisms to stress by stimulating the secretion of glucocorticoids (GCs) (Bermudez-Humaran et al. 2019). The link between the gut microbiota and the HPA axis was established in the studies of GF mice. In response to stress, male GF mice showed a

hyperresponsive HPA axis, as evidenced by a higher level of plasma GCs (Sudo et al. 2004). The high level of GCs can lead to gut dysfunction and further cause GR. In humans, IBD patients with GR exhibited higher levels of adrenocorticotropin hormone (ACTH) and GCs in response to corticotropin-releasing hormone (CRH) infusion, accompanied by alterations of the microbiota (Dinan et al. 2006). Overexposure to GCs *in utero* was postulated to induce IUGR or postnatal GR in humans and rats (Lesage et al. 2001). Additionally, microbiota from stressed individuals could transmit stress by regulating the GC production of the recipient, which is supported by the result that inoculation with the vaginal microbiota from the stressed mother would increase the corticosterone levels and gut microbiota dysbiosis in rat pups not exposed to stress *in utero* (Jasarevic et al. 2018). Importantly, recipients of microbiota transfer had similar corticosterone levels to the original offspring who were stressed prenatally (Jasarevic et al. 2018). Maternal stress and depression could alter the microbial composition and aggravate gut symptoms and allergic responses in the offspring, who were prone to develop GR (Rondo et al. 2003; Zijlmans et al. 2015). Moreover, stress and depression can increase the risk of poor eating habits and leaky gut, which further affect the growth of individuals. A longitudinal study in Australia reported that those with existing depressive episode had poor diets, accompanied by various degrees of IBD (Bear et al. 2020). Another study of 339 adults demonstrated that chronic stress influences the level of insulin, as well as glucose and cortisol responses, which would further lead to abnormal eating patterns and weight gain (Chao et al. 2017).

Immunity-HPA axis interactions are critical in a variety of stress and inflammatory disorders, which impair the individual's growth and development. Chronic stress in adulthood can impair gut permeability and increase enteric oxidative stress and inflammation, thus negatively affecting the growth of humans and animals (Cryan and Dinan 2012; Westfall et al. 2017). In animal models under psychological stress, high levels of GCs would disrupt the gut barrier function, including impairment of intestinal epithelial integrity and induction of bacterial dysbiosis, such as an increase in *Proteobacteria* and *E. coli* (Krishna et al. 2018; Schepper et al., 2019). Exposure to bacteria and bacterial antigens could induce the secretion of pro-inflammatory cytokines and ultimately activate the HPA axis (Misiak et al. 2020). Ampicillin-treated mice showed anxiety and colitis, and their microbiota could transfer the same behaviors to GF mice by increasing the levels of blood GCs and pro-inflammatory cytokines (Jang et al. 2018). Notably, from the neonatal period to early childhood, a first increase and then a decrease in GC levels as well as disturbance of intestinal function were observed in children with IUGR, which may be associated with rapid developmental changes in the gut microbiota (de Weerth 2017; Iwata et al. 2019).

Collectively, environmental factors such as stress can activate the HPA axis by stimulating the secretion of GCs, and then disturb the microbial composition, which is accompanied by leaky gut and poor eating habits in GR. Although there has been increasing evidence showing that the microbiota may be associated with the mood and behavior in humans with GR, the mechanisms are still not fully understood, and there is a lack of clinical relevance.

3. Nutritional therapeutic strategies for GR

Previous insights into the key role of the gut microbiota in modulating social behavior, host metabolism, immune response, development and growth have contributed to novel nutritional therapeutic strategies for GR. The nutritional intervention involves microbiota-targeted treatments, such as beneficial microbiota (probiotics) or the prebiotics that enhance the growth of such beneficial microbiota, to alleviate GR by affecting the microbiota-brain relationship (Sarkar et al. 2016).

3.1. Probiotics

Probiotics are live microorganisms that confer health benefits to the host when introduced in appropriate amounts (Butel 2014). Previous studies have highlighted the potential effect of probiotics in the treatment of GR and its related diseases (Table 2). As reviewed in the above sections, the growth promotion effects of probiotics may be attributed to the competition with pathogens for PRR binding, enhancement of gut mucosal barrier function, microbial modulation of stress responses, balance of pro- and anti-inflammatory cytokines, and production of neurotransmitters via the CNS. A mixture of *L. rhamnosus* R0011 and *L. helveticus* R0052 was found to alleviate colitis and weight loss though reduction of HPA activity and recruitment of anti-inflammatory lymphocytes in mice (Rodrigues et al. 2012). In humans, probiotics have been reported to have certain promoting effects on the growth of children with GR in double-blind efficacy randomized controlled trials (Agarwal and Bhasin 2002; Kerac et al. 2009). The widely used probiotics for growth promotion are *Bifidobacterium*, *Lactobacillus* and/or *Streptococcus* genera. *B. breve* has been shown to induce substantial weight gain, especially in children with undernutrition (Kitajima et al. 1997). Recently, *A. muciniphila* and *Enterococcus faecium* have been regarded as beneficial bacteria that can improve lipid metabolism, gut inflammation, and insulin resistance (Xu et al. 2020). However, inconsistent clinical results have been obtained about the effects of some probiotics on the growth of LBW infants. An intervention randomized controlled prospective trial revealed that infants receiving *L. rhamnosus GG* (*LGG*) exhibited increases in body length and weight gain relative to those receiving a placebo (Vendt et al. 2006). On the contrary, in another intervention study, no effect of *LGG* was observed on the weight gain of LBW infants (Chrzanowska-Liszewska, Seliga-Siwecka, and Kornacka 2012). For *Bifidobacteria*, contradictory clinical results were also observed in the effect of *B. bifidum*, *B. lactis* and *B. breve* on the growth of LBW infants (Patole et al. 2014; Totsu et al., 2014; Hays et al. 2016). These inconsistent clinical results of probiotic administration indicate a very complicated role of the gut

Table 2. Probiotic studies of microbiota-gut-brain axis in GR*.

Species, models	Probiotic	Treatment duration	Effects	References
Metabolic syndrome, human, ♂ ♀ (n = 21)	*Lactobacillus reuteri* (ingestion of 10^{10} b.i.d.)	4 wk	↑ Glucose-stimulated GLP-1 and GLP-2 release by 76% and 43%, respectively.	(Simon et al. 2015)
Very low birth weight infants, human, ♂ ♀ (n = 91)	*Bifidobacterium breve* (distilled water containing about 0.5×10^9 live bacteria)	8 wk	↑ Wight gain (increased 12% of body weight of low birthweight infants). ↓ Apirated air volume from the stomach.	(Kitajima et al. 1997)
IBS, human, ♂ ♀ (n = 44)	*Bifidobacterium longum NCC3001* (orally gavage at a dose of 1.0E + 10 colony-forming units/1 g powder with maltodextrin)	6 wk	↓ Depression scores of 2 points or more. ↑ Quality of life score.	(Pinto-Sanchez et al., 2017)
IBS, human, ♂ ♀ (n = 77)	*Lactobacillus salivarius* UCC4331 and *Bifidobacterium infantis* 35624 (orally gavage at a dose of 1×10^{10} live bacterial cell)	8 wk	Normalization of the ratio of IL-10 to IL-12 to those for healthy volunteer.	(O'Mahony et al. 2005)
Stress, human, ♂ ♀ (n = 111)	*Lactobacillus plantarum* DR7 (orally gavage at a dose of 1×10^9 CFU/day)	12 wk	↓ Stress and anxiety measures (decreased 6 stress score using DASS-42 questionnaires). ↓ Plasma cortisol (decrease 1 μg/dl), pro-inflammatory cytokines, ↑ anti-inflammatory cytokines in young adults. ↑ Speed needed for social emotional cognition and verbal learning and memory in normal adults over 12 wk. ↑ Serotonin, IL-4, IL-10.	(Chong et al. 2019)
Type 2 diabetes, human, ♂ ♀ (n = 60)	*Capsule: L. acidophilus, L. casei, B. bifidum, L. fermentum, vitamin D3* (50,000 IU vitamin D every 2 weeks plus 8×10^9 CFU/ g probiotic)	12 wk	↓ anxiety and depression (improved beck depression inventory, beck anxiety inventory, general health questionnaire scores by decreasing average 2 more scores compared with placebo group)	(Raygan et al. 2018)
Stress-induced anxiety and colitis, mouse, ♂ (n = 42)	*Lactobacillus reuteri* NK33 and *Bifidobacterium adolescentis* NK98 (orally gavage at a dose of 1×10^9 CFU/day)	4 wk	↓ Depression (mitigation of open arms in the elevated plus maze task to 80% versus 38% of control mice) ↓ Pro-inflammatory cytokines, microglia activation, corticosterone secretion to those for control mice.	(Jang, Lee, and Kim 2019)
Eating-disorder, mouse, ♂ ♀ (n = 14)	*Lactobacillus johnsonii* Q1-7 (orally gavaged with 5×10^9 CFU six days a week)	9 wk	↑Food intake (twice than control group), and body mass (more than 20% of origin weight). Recovered anxiety hormones secretion to those for control mouse.	(Chagwedera et al. 2019)
Undernutrition, mouse, ♂ (n = 10)	*Ruminococcus gnavus* and *Clostridium symbiosum* (colonized recipient mice 27% and 2.6% relative abundance, respectively)	5 wk	Amelioration of growth (5% of initial weight more than control group) and metabolic abnormalities (↑ acylcarnitines in cecal samples).	(Blanton, Charbonneau et al. 2016)
Chronic undernutrition, mouse, ♂ (n = 28)	*Lactobacillus plantarum* (intragastric gavage of 2×10^8 CFU)	8 wk	↑ Serum IGF-1 (2.5 times more than control group), bone development (20% more length compared with control group). Promotion of growth (52% more weight compared with control group).	(Schwarzer et al. 2016)

(*continued*)

Table 2. Continued.

Species, models	Probiotic	Treatment duration	Effects	References
Citrobacter rodentium-induced colitis, mouse, ♀ (n = 48)	*Lactobacillus rhamnosus R0011* and *Lactobacillus helveticus R0052* (10^9 CFU/mL in drinking water)	1 wk	↑ Body mass (more than 10% of original body weight than colitis mouse). ↓ Gut inflammation (normalization of levels of pro-inflammatory cytokines to healthy group), HPA activity	(Rodrigues et al. 2012)
Immunodeficient mouse, ♂ (n = 32)	*Lactobacillus rhamnosus* and *Lactobacillus helveticus* (10^9 CFU/mL in drinking water)	8 wk	Normalized the behavior deficiency (restored explorative ability compared with immunodeficient mice). Restored c-Fos expression in immunodeficient mice.	(Smith et al. 2014)
Chronic gut inflammation, mouse, ♂ (n = 24)	*Lactobacillus rhamnosus* NCC4007 and *Bifidobacterium longum* NCC3001 (orally gavage at a dose of 1×10^{10} CFU)	1 wk	↓ Anxious behavior and normalized *BDNF* mRNA abundance. No significant reduction in any pro-inflammatory cytokines.	(Bercik et al. 2010)

*CFU, colony forming units; IBS, irritable bowel syndrome; DASS, depression, anxiety, and stress; BDNF, brain-derived neurotrophic factor; HPA, hypothalamic-pituitary-adrenal.

microbiota in neonatal growth. Perhaps because LBW infants suffer from early gut dysbiosis, the interaction between probiotics and preexisting microbiota will determine the influence of microbiota on the weight gain of LBW infants. Further studies are required to elucidate the causality between the effect of probiotics and changes in the brain. Furthermore, the time courses of these effects have not been clarified in human or animal models.

3.2. Prebiotics

Prebiotic administration can promote the colonization of beneficial microbiota and suppress pathogen infection (Table 3). Prebiotics are defined as non-digestible substrates, which are selectively utilized by the host gut microbiota for healthy benefits (Bindels et al. 2015). According to this definition, prebiotics mostly comprise dietary carbohydrates including RS, oligosaccharides (e.g., inulin), galacto-oligosaccharides (GOS), and fructo-oligosaccharides. Administration of prebiotics leads to the reduction of pro-inflammatory cytokines, regulation of ENS-mediated endocrine secretion, and improvement of gut absorptive ability. Specifically, a randomized clinical study found that a high-RS diet could significantly increase the ratio of Firmicutes to Bacteroidetes, along with the improvement of digestive enzyme activities and lipid metabolism in the gut of humans (Maier et al. 2017). Dietary inulin supplementation remarkably increased serum IGF-1 concentration and fecal SCFA production, improved nutrient absorption, and promoted the growth of beneficial bacteria, leading to favorable changes of host metabolism in human and animal studies (Dewulf et al. 2013; Wang, Tan, Liao, Long et al. 2020). Moreover, administration of fiber-rich diets increased the abundance of *Bifidobacterium* and *Lactobacillus* spp., reduced endotoxemia, improved intestinal barrier function, and decreased circulating pro-inflammatory cytokines in patients with GR (Torres-Fuentes et al. 2015). Prebiotics also modulate the HPA axis via regulating the expression of hippocampal brain-derived neurotrophic factor and alleviate stress-induced disorders (Cryan et al., 2019). In humans, a small-scale placebo-controlled study demonstrated that administration of GOS reduced waking salivary cortisol levels, and improved the stress handling ability of healthy individuals (Schmidt et al. 2015). In an animal model, administration of fructo-oligosaccharides and GOS reduced stress-induced GCs release and altered SCFA concentration, which ameliorated neuroinflammation and microbial dysbiosis to further attenuate GR in mice (Burokas et al. 2017). However, current results from clinical studies are still insufficient for the proposal of recommendations for the general population (Cuevas-Sierra et al. 2019).

3.3. Postbiotics

The notion of "postbiotics" has been recently proposed and tentatively defined as beneficial microbial metabolic byproducts that can modulate the fermentation process (Malagon-Rojas et al. 2020). Therefore, postbiotics can comprise constituents such as SCFAs, microbial cell fractions, functional proteins, teichoic acid, cell lysates, and pili-type structures (Table 3). In clinical trials, administration of heat-killed *L. acidophilus* or *L. paracasei* CBA L74 reduced the risk of diarrhea in children younger than 5 years compared with that of placebo (Malagon-Rojas et al. 2020). In animal models, postbiotics from *B. breve* C50 and *Streptococcus thermophilus* 065 promoted dendritic cell maturation, interacted with microglia, and produced high IL-10 through TLR2 in mice (Wegh et al. 2019). Indole-3-propionic acid has also been shown to facilitate the reconstruction of the gut mucosal barrier and alleviate neuroinflammation in rats (Jennis et al. 2018). However, the activity of postbiotics and the host response to postbiotic compounds are largely dependent on the efficient and viable postbiotic production

Table 3. Prebiotic and postbiotic studies of microbiota-gut-brain axis in GR*.

Species, models	Types	Treatment duration	Effects	References
Prebiotic				
IBS, human, ♂ ♀ (n = 79)	Short chain FOS (5 g / d)	4 wk	↓ Hospital Anxiety Depression scores (1/4 of placebo group).	(Azpiroz et al. 2017)
Insulin-resistance, human, ♂ ♀ (n = 39)	Resistant starch (4 g amylose in low diet; 66 g amylose in high diet)	4 wk	↑ Fecal butyrate-producing bacteria *Faecalibacterium*, *Roseburia*, and *Ruminococcus*; ↓ gut microbiota of participants with type 2 diabetes mellitus. ↑ Lipases activity (such as colipase, pancreatic triglyceride lipase, and bile salt-stimulated lipase). ↑ Lipid metabolism (pathways for fatty acid metabolism, primary and secondary bile acid biosynthesis, and bile acid secretion; less abundant in three fatty acids, namely hexadecanoic acid, octadecadienoic acid, and octadecenoic acid).	(Maier et al. 2017)
Type 2 diabetes mellitus, human, ♀ (n = 55)	Resistant dextrin (Nutriose®06; 10 g/d)	8 wk	↓ Depression, anxiety, and stress (DASS, −38.4%). ↓ Cortisol (-20.9%), KYN, KYN/TRP ratio (-29.1%). Altered peripheral immune markers (↑ CD8, 6.1%; IL-10, 21.6%. ↓ LPS, −17.8%; IFN-γ, −26.8%).	(Farhangi et al. 2018)
Weaning stress, pig, ♂ (n = 32)	Inulin (diet containing 2.5, 5.0 and 10.0 g/kg)	3 wk	↑ Serum IGF-1 (110% concentration of control group in insulin-supplemented group). ↑ Gut integrity (protein expression of tight junction increased twofold). ↑ Absorptive ability (sucrase activity increased twofold). ↑ SCFAs production (acetic acid and butyric acid increased twofold). ↑ Microbiota numbers (*Lactobacillus* abundance increased).	(Wang, Chen et al. 2020)
Stress-induced anxiety, mouse, ♂ (n = 50)	3′-Sialyllactose and 6′-sialyllactose (5% of the diet)	3 wk	↓ Anxiety-like behavior (↓ time spent in the dark zone in light/dark preference test, and latency to enter the center of the open filed). Restoration of DCX^+ immature neurons.	(Tarr et al. 2015)
LPS-challenged, mouse, ♂ (n = 18)	GOS (drinking water containing 1.3%, w/v)	3 wk	↓ Pro-inflammatory cytokines IL-1β, IL-6, and TNF-α in frontal cortex (2/3 of concentrations of control group). ↓ Cerebral cortex 5-HT_{2A} receptor expression. ↑ Social behavior (↑ twofold time spent in the light section).	(Savignac et al. 2016)
Depression and chronic stress, mouse, ♂ (n = 40)	FOS, GOS, or both FOS and GOS (drinking water for 0.3-0.4 g/mouse/day)	3 wk	↓ Plasma glucocorticoid (60% of levels of control group). ↓ Neuroinflammation (↓ plasma IL-6 and TNF-α levels).	(Burokas et al. 2017)

(*continued*)

Table 3. Continued.

Species, models	Types	Treatment duration	Effects	References
			Alteration in SCFAs production (↑ cecal acetate and propionate levels; ↓ isobutyrate levels).	
Diet-induced metabolic syndrome, mouse, ♂ (n = 32)	Citrus polymethoxyflavones (intragastric gavage of 30, 60, or 120 mg/kg)	8 wk	Restoration of serum BCAAs, blood fat. Improvement in insulin resistance, microbial community (↑ commensal bacterium *Bacteroides ovatus*).	(Zeng et al. 2020)
Aβ1-42-induced neurotoxicity, rat ♂ (n = 72)	Chitosan oligosaccharides (200 mg/kg, 400 mg/kg, and 800 mg/kg)	2 wk	↓ Hippocampal neuronal apoptosis by 50%. ↓ Hippocampal levels of TNF-α, and IL-1β by 73%, and 71%, respectively.	(Jia et al. 2016)
Postbiotics				
Eating-disorder, mouse, ♂ (n = 32)	Bacterial ClpB (50 μg per mouse)	2 wk	↑ Food intake by 20%. Improvement of emotion (↓social insecurity, bulimia, and maturity fears).	(Tennoune et al. 2014)
Diet-induced inflammation, mouse, ♂ (n = 60)	β-hydroxy-β-methylbutyrate (0.5, 1.0, 1.5, and 2.0% (wt/vo) in drinking water)	24 wk	↑ Propionic acid production by 60%. Restoration of microbial profile (↓ *Firmicutes*; ↑ *Bacteroidetes*). Improvement of lipid metabolism (↓ serum glucose, triacylglycerol, and total cholesterol. ↓ mRNA expression of ACC, SREBP2, LXRα in liver, and ↑mRNA expression of UCP1, CPT-1β, CD36 in brown adipose tissue).	(Duan et al. 2019)
IBD, mouse, ♂ (n = 42)	Sodium butyrate (5 g/L in drinking water)	6 wk	↓ Pro-inflammatory cytokines IL-6 and TNF-α production. ↑ Gut barrier function (↓ colon damage score, permeability; ↑ protein expression of tight junction).	(Chen et al. 2018)
db/db, mouse, ♂ (n = 16)	Myristoleic acid (5 mg/kg)	8 wk	↓ Adiposity by activation of brown adipose tissue and beige fat formation (↑ UCP1 expression and mitochondrial oxphos protein expression).	(Quan et al., 2019)
Acute colitis, mouse, ♂ (n = 20)	Amuc_1100 (3 μg)	2 wk	↑ Gut barrier function (↑ intestinal epithelial cell proliferation; ↓ apoptosis and DNA damage). ↑ $CD8^+$ cytotoxic T lymphocytes. ↓ Pro-inflammatory cytokines TNF-α.	(Wang, Tang et al. 2020)
High-fat diet induced inflammation, mouse, ♂ (n = 16)	Indole-3-propionic acid (20 mg/kg)	1 wk	↑ Gut integrity (half of FITC-dextran levels in vehicle group), mRNA expression of metabolic-related genes. ↓ Pro-inflammatory cytokines IL-6 and IL-1β.	(Jennis et al. 2018)

*FOS, fructooligosaccharide; GOS, galactooligosaccharides; IBS, irritable bowel syndrome; DASS, depression, anxiety, and stress; KYN/TRP, kynurenine-to-tryptophan ratio; BCAAs, branched-chain amino acids.

process and accurate delivery of the active ingredients to the desired location in the gut.

3.4. FMT

FMT contributes to the restoration of normal gut microbial profiles, and thus improves host growth and development (Torres-Fuentes et al. 2017). In humans, FMT from healthy individuals to patients with metabolic syndrome increased microbial diversity and butyrate-producing bacteria as well as improved insulin sensitivity (Vrieze et al., 2012). In an animal model, FMT from donor chickens with high feed efficiencies improved the growth performance of those with low feed efficiencies by promoting the development of

intestinal villus and secretion of growth-related hormones (Metzler-Zebeli et al. 2019). Additionally, recent studies have shown that fecal virome transplantation could significantly alter bacterial and viral composition, plasma metabolites, and the expression of type 2 diabetes-related genes, which could improve glucose tolerance to alleviate GR in metabolic disorder mice (Mirzaei et al. 2020; Rasmussen et al. 2020). However, FMT also faces several challenges in clinical therapeutic treatment. Donor-recipient compatibility is critical for the successful colonization of donor microbiota in the recipient's gut. In addition, a stool bank for FMT is in urgent need (Cryan et al., 2019).

4. Conclusion and perspectives

Gut microbiota-host interactions are crucial for the maintenance of host homeostasis. GR is always accompanied by metabolic disorders, systemic inflammation, or gut dysbiosis, and commonly occurs in childhood. Emerging evidence from animal models and clinical studies highlights the key role of the microbiota in the gut-brain axis and the implications in GR. The microbiota interacts with the nervous system mainly in three ways, including regulation on the metabolism (mainly through hormones and neurotransmitters), modulation of the immune response, and direct mediation of neurons or neuronal signaling. Although correlations between changes in the microbiota-gut-brain axis and physiological effects on GR have been observed, these studies have highlighted that the focus of microbiome studies should be shifted from associations to causality relationships (Zhao and Zhao 2020). The majority of studies were performed in rodent models, and there have been few mechanistic studies in humans. Thus, further validation is required before the application to clinical trials. In addition, inter-individual variations in microbiota composition and drug sensitivity can be significant, suggesting that a standardized treatment of the microbiota may not be appropriate for every patient with GR. Precise nutrition is required in the intervention of microbiota-gut-brain axis. An approach that integrates multi-omics analyses, including metagenomics, metatranscriptomics, metaproteomics and metabolomics, in well-phenotyped human populations facilitate the discovery of microbial signature of GR. Besides, a variety of studies have been focused on the growth promotion effect of bacteria through the gut-brain axis; however, the effects of the remaining members of the microbiota such as the gut virome and mycobiome have not been elucidated, since they not only affect the commensal bacteria but also directly influence host health. Further, it is still highly challenging to screen efficient microbiota to boost growth through the administration of pre/pro/postbiotics, and the treatment cycle, production technology and efficacy all remain to be explored. In conclusion, a healthy gut microbial profile is essential to the promotion of the growth and development of individuals. The perturbation of the microbial community is associated with disturbed communication between the microbiota and brain, which would result in ENS- and CNS-mediated GR. Targeted regulation of the microbiota-gut-brain axis may represent great opportunities for the development of strategies to alleviate GR in humans and animals. Deeper insights into the correlation between the gut microbiota and the brain may pave the way for these novel nutritional therapies.

Author's contributions

We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript. The authors' responsibilities were as follows—MQ, BT, and YY: conceived this review; MQ, JW, SL, and YD: discussed this review; MQ: prepared this review; PJ, TS, AZ, and BT: revised this review; and all authors: read and approved the final manuscript.

Disclosure statement

The authors report no declarations of interest.

Abbreviations used

GR	growth retardation
CNS	central nervous system
ENS	enteric nervous system
HPA	hypothalamic-pituitary-adrenal
FMT	fecal microbiota transplantation
GF	germ-free
SCFAs	short chain fatty acids
ARC	arcuate nucleus
EGCs	enteric glial cells
ILC3s	group 3 innate lymphoid cells
TLRs	Toll-like receptors
AhR	aryl hydrocarbon receptor
ECs	enterochromaffin cells
HDCAs	histone deacetylases
FXR	farnesoid X receptor
PRRs	pattern recognition receptors
CCK	cholecystokinin
PYY	peptide YY
GLP-1	glucagon-like peptide-1
IUGR	intrauterine growth restriction
GOS	galacto-oligosaccharides
FOS	fructo-oligosaccharides
IGF-1	insulin-like growth factor-1
BDNF	brain-derived neurotrophic factor
BBB	blood-brain barrier

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