



Review Article

Insights into host-microbe interaction: What can we do for the swine industry?

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ABSTRACT

Recent discoveries have underscored the cross-talk between intestinal microbes and their hosts. Notably, intestinal microbiota impacts the development, physiological function and social behavior of hosts. This influence usually revolves around the microbiota-gut-brain axis (MGBA). In this review, we firstly outline the impacts of the host on colonization of intestinal microorganisms, and then highlight the influence of intestinal microbiota on hosts focusing on short-chain fatty acid (SCFA) and tryptophan metabolite-mediated MGBA. We also discuss the intervention of intestinal microbial metabolism by dietary supplements, which may provide new strategies for improving the welfare and production of pigs. Overall, we summarize a state-of-the-art theory that gut microbiome affects brain functions via metabolites from dietary macronutrients.

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1. Introduction

As an active player in host physiology, intestinal microbiota affects functions of the intestine and surrounding organs. Notably, through host-microbe dialogues, especially along the microbiota-gut-brain axis (MGBA), gut microbiome is involved in brain function and behavior through microbial metabolites (Gheorghe et al., 2019). For example, short-chain fatty acids (SCFA) fermented from dietary fiber in the colon directly or indirectly regulate brain function owing to their properties of neuroactivity and their impacts on cellular signaling pathways (Clarke et al., 2014; Stilling et al., 2016). Another example in the lexicon of host-microbial cross-talk is tryptophan because of the important physiological implications of microbial metabolism of

tryptophan both in the gut and brain (Lee et al., 2015; Roager and Licht, 2018). As meat quality and product safety are the priority of the swine industry, the health and welfare of pigs are of universal importance for all swine producers (Lyte and Lyte, 2019). Interestingly, a stable and diverse flora structure is essential for the health and welfare of pigs. Here, with especial focusing on the information from pigs, we reviewed the establishment of intestinal microbes and their effects on hosts, highlighting dietary fiber and tryptophan metabolite-mediated MGBA. We propose a strategy to modify the microbiome through dietary intervention to enhance growth performance and well-being of pigs.

2. Variations in gut microbiota: factors from the host

Gut microbiota performs various functions in hosts, including nutrient metabolism, immunomodulation and protection against pathogens. Intestinal flora begins to colonize early in life, and its composition and distribution has a strong spatiotemporal specificity. In adulthood, the symbiotic core microbiota remains relatively stable, but differs between individuals. Although it is difficult to define the optimal composition of gut microbiota, the balance of host-microorganism is essential for metabolic and immune functions and prevention of intestinal diseases.

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2.1. Physiological stage

Mammals were traditionally regarded as sterile during the fetal period, which has been questioned over recent years (Perez-Munoz et al., 2017). Analysis of meconium samples collected within 6 h after farrowing indicates that microbiome acquisition likely begins in utero, and meconium microbiome is likely to be vertically transmitted from the sows (Wang et al., 2019b). Another compelling study also provides evidence of bacterial colonization during the human fetal period (Collado and Segata, 2020). Although these studies provide evidence of the origin of intestinal microbiome, whether mammals are germ-free in fetal period is in debate, and the biological impact of intra-uterine microbial colonization on host development remains to be uncovered.

In contrast to the situation in the fetal period, it is widely accepted that gut microbe colonizes in neonates in an orderly manner after they are exposed to a wide variety of microorganisms (Von Mutius, 2017). Aerobic and facultative anaerobes such as *Enterobacter*, *Enterococcus* and *Staphylococcus* are first colonized in the intestine (Li et al., 2018; Huang et al., 2019). With the consumption of oxygen, the micro-environment of the gut gradually changes into an anaerobic state, which provides unique conditions for the colonization of specific anaerobes (Heinritz et al., 2013). During lactation, *Lactobacillus* and *Streptococcus* are dominant in the small intestine of piglets, but the intestinal environment changes abruptly after weaning, resulting in reconstruction of the microflora. For example, there is a clear difference in the α diversity of gut microbiota during weaning, and the α diversity increases even further after feeding a plant diet (Freshe et al., 2015).

Besides diversity, there is a significant alteration in the fecal microbiota composition during weaning. Gut microbial communities include Firmicutes, Bacteroidetes, Proteobacteria, Spirochaetes and Tenericutes at the phylum level, which are 54.00%, 38.70%, 4.20%, 0.70% and 0.20%, respectively, at the pre-weaning period, and are 35.80%, 59.60%, 1.00%, 2.00% and 1.00%, respectively, at the post-weaning period (Pajarillo et al., 2014). In each situation, and even in growing-finishing pigs, the most abundant phyla are Firmicutes and Bacteroidetes, which account for more than 90% of the community (Kim et al., 2012; Kim and Isaacson, 2015). At the family level, relative abundances of Bacteroidaceae and Enterobacteriaceae decline gradually, but Veillonellaceae, Prevotellaceae, Lactobacillaceae and Ruminococcaceae increase in weaned piglets (Alain et al., 2014). At the genus level, weaning is associating with the reduction in *Bacteroides*, and increases in *Lactobacillus* and *Prevotella* (Guevarra et al., 2018). The possible reason is that *Bacteroides* use the monosaccharides and oligosaccharides in breast milk, and *Prevotella* degrades plant polysaccharides in plant diets (Lamendella et al., 2011). After weaning, the changes of intestinal microflora continue until the market (Wang et al., 2019b). Collectively, the intestinal tract of newborns rapidly changes from a basically sterile state to a dense microbial population, and eventually to a relatively stable, established microbial community (Alain et al., 2014).

2.2. Intestinal environment

The intestinal environment is one of the strongest determining factors for microbial colonization (Parker et al., 2018). The gut tract is composed of a series of connected specialized segments with certain amounts of physiological pressures that affect bacterial colonization. Microbial communities of different niches of swine intestine have spatial heterogeneity (Looft et al., 2014; Donaldson et al., 2016) due to local environmental variations (Espey, 2013; Tropini et al., 2017; Zhang et al., 2018).

Owing to the rapid transformation of luminal contents and presence of digestion enzymes, the proximal small intestine is not suitable for bacterial colonization (Donaldson et al., 2016). Thus, there are relatively low numbers of bacteria, and the most abundant genera are *Lactobacillus* (45.79% and 36.75%, respectively) and *Clostridium* (25.64% and 29.67%, respectively) in the duodenum and jejunum. Bacterial growth in the distal ileum is possible owing to the neutral pH value, reduced oxygen availability, and lowered concentrations of compounds that challenge microbial growth. *Streptococcus* (17.73%) and the unspecified genera of the Clostridiaceae family (17.10%) are the most abundant genera in the ileum. In the colon, the most dominant genus is *Prevotella*, representing 40.90% and 34.99% in the proximal and distal parts respectively (Zhang et al., 2018).

Differences in microbial distribution are not only reflected in the longitudinal structure of the digestive tract, but in the direction of axial (Zhang et al., 2018). This is due to the response of microbial populations to different physicochemical conditions (Stearns et al., 2011). For example, an oxygen-abundant micro-environment is created in mucosa because of the diffusion of oxygen from the epithelial capillary to intestinal mucosa (Albenberg et al., 2014), thus, microaerophilic Helicobacteraceae and Campylobacteraceae are enriched, whereas obligate anaerobic bacteria from Prevotellaceae, Lachnospiraceae, Ruminococcaceae, and Veillonellaceae are abundant in the lumen of the cecum (Kelly et al., 2017; Zhang et al., 2018). Although it is accepted that intestinal microbes have the characteristics of compartmentalization in composition and function, there are various unanswered questions. For example, it is interesting to know whether the flora colonized in different ecological niches communicate and interact with each other.

2.3. Dietary factors

Besides host genotype, immune status and intestinal environment, diet also affects gut microbiota (David et al., 2014; Goodrich et al., 2014; Carmody et al., 2015; Pereira and Berry, 2017; Rothschild et al., 2018). Alterations in diet, like carbohydrates and proteins, cause rapid changes in gut microbial profiles (David et al., 2014). Although it cannot be digested by animal endogenous digestive enzymes (Raninen et al., 2011), dietary fiber regulates the abundance of the microbial community (Jha and Berrocoso, 2015; Liu et al., 2018; Tan et al., 2018; Wang et al., 2018a), and maintains the homeostasis of the intestinal environment (Tian et al., 2017; Luo et al., 2018; Che et al., 2019). Thus, there is a growing interest in the usage of fiber in feed to optimize the intestinal health of pigs, however, it should be noted that the effects of dietary fiber with different sources, types and levels differ.

The quantity and quality of protein also have direct effects on intestinal microbiota (Fan et al., 2015; Singh et al., 2017). Diets that contain high levels of protein result in longer intestinal transit time and higher microbiota diversity (Macfarlane et al., 1986). Low-protein diets affect pig microbiota by increasing Lachnospiraceae, Prevotellaceae, and Veillonellaceae (Chen et al., 2018; Qiu et al., 2018), while decreasing ammonia, which is one kind of microbial metabolite (Luo et al., 2015).

3. Local effects of major microbial metabolites

Since the intestinal microbiota in pigs currently includes 9,623,520 non-redundant genes (Xiao et al., 2016; Wang et al., 2019a), it is regarded as a second genome with functions that the host cannot perform in most situations (Backhed et al., 2005; Guevarra et al., 2019). Gut microbiota is pivotal for the health and well-being of animals (Stokes, 2017), which is largely dependent on microbial metabolism (Human Microbiome Project, 2012). The

well-known metabolites in the colon are SCFA from dietary fiber fermentation, including acetate, propionate and butyrate (Pascale et al., 2018; Koh et al., 2016; Oliphant and Allen-Vercoe, 2019). Interestingly, the chemical structure of the fermentable fibers determines the production of SCFA, for example inulin is propionigenic, and resistant starches are more butyrogenic (Rastelli et al., 2019). SCFA have lots of effects in gut functions. Mechanistically, SCFA are rapidly transported by monocarboxylate transporters (MCT) to enter the citric acid cycle (Dalile et al., 2019). Other possible mechanisms include G protein-coupled receptors (GPR)-mediated cellular signaling and histone deacetylase (HDAC)-mediated epigenetic modifications (Yang et al., 2018). SCFA are also transported into portal circulation as an energy substrate for hepatocytes (Schonfeld and Wojtczak, 2016) and into the circulatory system (Dalile et al., 2019) to perform microbiota-gut-brain cross-talk (Sarkar et al., 2016).

In contrast to carbohydrate metabolism by the gut microbiota, proteolysis is less extensively researched. It should be noted that microbial fermentation of proteins produces a variety of metabolites, which are generally considered to be harmful to intestinal integrity and metabolism (Nyangale et al., 2012; Zhao et al., 2018). For example, the microbial metabolite of histidine, imidazole propionate, has been shown to be a major risk factor for insulin resistance and type 2 diabetes (Koh et al., 2018). However, microbial metabolites from tryptophan have benefits for health (Agus et al., 2018). Tryptophan is mainly metabolized through the kynurenine pathway, 5-hydroxytryptamine (5-HT) pathway and indole/aryl hydrocarbon receptor (AHR) pathway (Alkhalaf and Ryan, 2015; Agus et al., 2018). Although most of tryptophan ingested is digested and absorbed in the small intestine, tryptophan reaches the colon (Morales et al., 2016; Yao et al., 2016) to be degraded by a series of symbiotic bacteria into effective immunomodulating products (Islam et al., 2017).

Indole is a major tryptophan metabolite that is metabolized by many species of Bacteroides and Enterobacteriaceae (Roager and Licht, 2018). The function of indole includes affecting the integrity of intestinal epithelial barrier (Bansal et al., 2010), regulating intestinal immunity (Lamas et al., 2016), preventing death after chemical colitis (Shimada et al., 2013), as well as affecting lifespan of the host (Sonowal et al., 2017). Tryptamine is a neurotransmitter that activates the 5-HT₄ receptor expressed in colon epithelial cells to control colonic transport (Bhattarai et al., 2018; Cryan et al., 2018). Tryptamine also enhances immune surveillance and inhibits the expression of pro-inflammatory cytokines (Tourino et al., 2013; Islam et al., 2017). Indole 3-propionate affects host intestinal inflammation (de Mello et al., 2017; Tuomainen et al., 2018), glucose metabolism, gut barrier and immune response (Zhang and Davies, 2016; Dodd et al., 2017).

4. Indirect effects of major microbial metabolites: microbiota-gut-brain axis

Currently, the MGBA has been well-established, and the microbiota is an important regulator in this axis (Cryan et al., 2019). Metabolites of intestinal flora impact brain function via the vagus nerve, blood-brain barrier (BBB) and immune system (Fig. 1) (Borre et al., 2014; Forsythe et al., 2014; Erny et al., 2015; O'Mahony et al., 2015; Dalile et al., 2019; Silva et al., 2020).

4.1. Vagus nerve

The vagus nerve contains sympathetic and parasympathetic nerves, including about 80% of the afferent nerve fibers and 20% of the efferent nerve fibers (Napadow et al., 2012). This anatomical structure makes the vagus nerve a bridge between

the intestine and central nervous system (CNS) (Bonaz et al., 2018). Vagal nerve fibers express receptors of 5-hydroxytryptamine and free fatty acid receptors (FFAR) (Nohr et al., 2013, 2015), resulting in ideally transmitted signals from the gut to the brain (Bonaz et al., 2018). Notably, gut microbes, such as *Bifidobacterium longum* NCC3001, *Lactobacillus rhamnosus* JB-1 and *Lactobacillus reuteri*, fail to affect brain functions after vagotomy (Bercik et al., 2011; Bravo et al., 2011; Poutahidis et al., 2013; Buffington et al., 2016; Sherwin et al., 2019), suggesting that the vagus nerve plays an important role in gut microbiota-brain cross-talk (Fulling et al., 2019). However, not all communication signals between microorganisms and the brain are mediated by the vagus nerve (Mayer et al., 2015). The anxiety behavior of mice caused by mild gastrointestinal infection is still obvious after vagotomy, indicating that the vagus nerve is not the only way of mediating the anxiety caused by gastrointestinal infection (Chu et al., 2019).

4.2. Blood brain barrier

The BBB is a kind of semi-permeable structure segregating peripheral blood from the brain (Rustenhoven and Kipnis, 2019). As MCT expressed in endothelial cells of BBB, SCFA may go through the BBB (Vijay and Morris, 2014; Perez-Escuredo et al., 2016; Dalile et al., 2019). Besides crossing the BBB, SCFA appear to be strategic in maintaining the integrity of the BBB. For example, germ-free mice exhibit low expression of tight junction proteins, resulting in increased permeability of the BBB (Braniste et al., 2014). Notably, the integrity of the BBB can be restored by replanting complex flora or a single bacterium that produces pro SCFA (Braniste et al., 2014). Similarly, propionate treatment alleviates the permeability of cerebral vascular endothelial cells after exposure to lipopolysaccharide (Hoyle et al., 2018).

4.3. Immune system of central nervous system

The nervous immune system is related to a series of processes including the development, function, aging and injury of the CNS (Hickman et al., 2018). Microglia are the main neuroimmune cells (Hong et al., 2016; Chu et al., 2019; Wilton et al., 2019). The metabolism of gut microorganisms regulates the maturation as well as function of microglia (Erny et al., 2015; Colpitts and Kasper, 2017). Microglia from germ-free mice or antibiotic-treated mice exhibit an immature phenotype compared with microglia from normal mice (Reemst et al., 2016). Interestingly, in both cases, oral administration of a mixture of the 3 major SCFA are sufficient to promote the maturation of microglia (Reemst et al., 2016), suggesting that SCFA regulate the homeostasis of microglia. Similarly, germ-free mice with GPR43 deficiency also show microglial defects (Erny et al., 2015), suggesting that SCFA and GPR43 are required to maintain the homeostasis of microglia. In addition, the alterations of intestinal microbial diversity induced by antibiotics affect neuroinflammation and change the morphology of microglia (Jang et al., 2018). Interestingly, sodium butyrate reduces the activation of microglia and the secretion of pro-inflammatory cytokines after lipopolysaccharide challenge (Wang et al., 2018b; Yamawaki et al., 2018). Likewise, acetate treatment reduces inflammatory responses in primary microglia (Soliman et al., 2012). Indole is also increasingly considered to be essential in the cross-talk of microbiota and a host, especially the brain immune responses (Dodd et al., 2017; Agus et al., 2018). For example, indole crosses the BBB and decreases pro-inflammatory activities via activating AHR in astrocytes (Rothhammer et al., 2016).

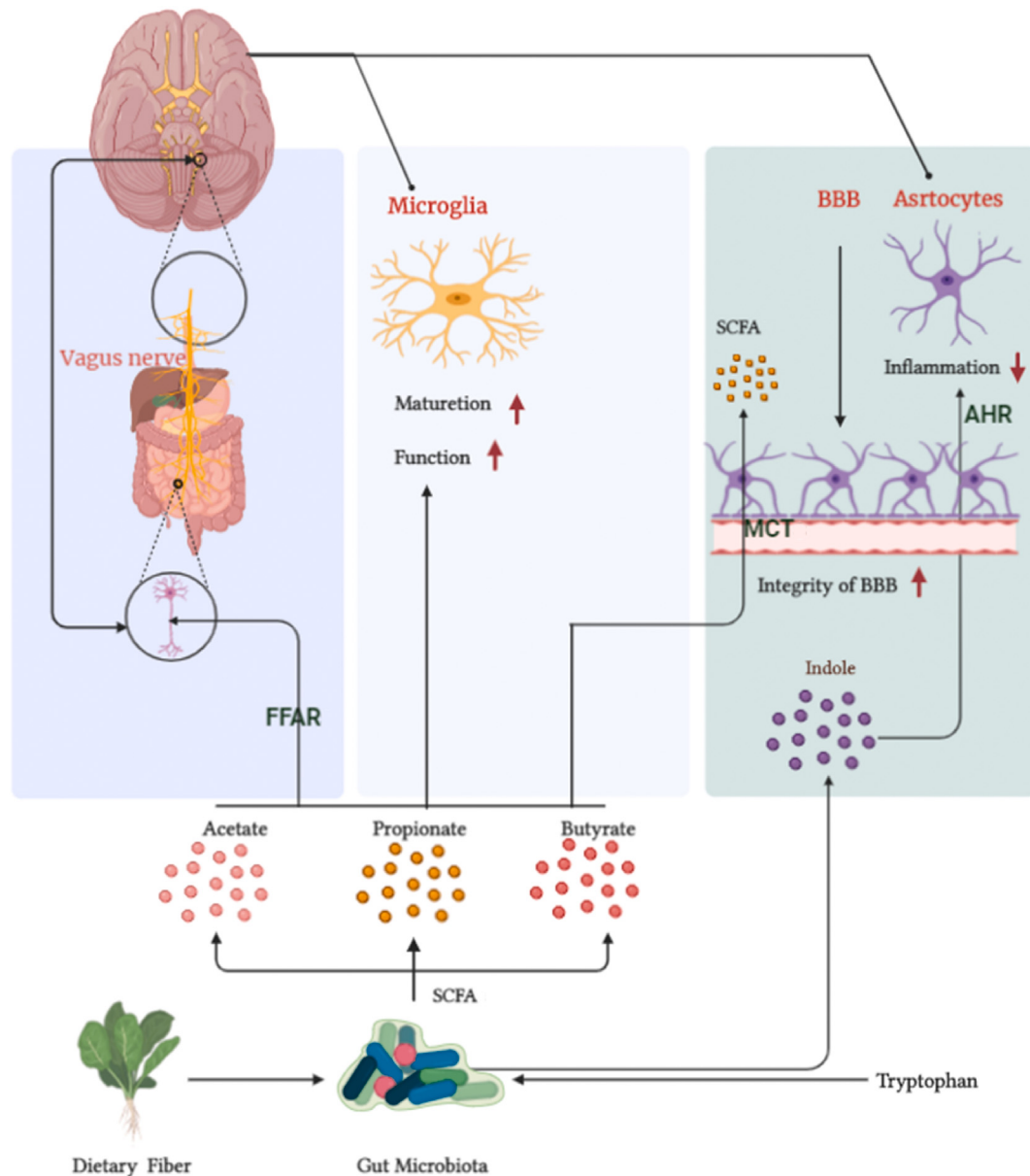


Fig. 1. Pathways that SCFA and tryptophan affect MGBA. Fermentation of dietary fiber and tryptophan by symbiotic gut microbes leads to the production of SCFA and indole derivatives, respectively. SCFA bind the FFAR of vagal nerve fibers to transmit signals to the CNS. SCFA pass through the BBB via MCT and affect the integrity of the BBB. SCFA affect the maturation and function microglia. Indole crosses the BBB and decreases pro-inflammatory responses by activating AHR in astrocytes. SCFA = short-chain fatty acids; MGBA = microbiota-gut-brain axis; FFAR = free fatty acid receptors; CNS = central nervous system; BBB = blood–brain barrier; MCT = monocarboxylate transporters; AHR = aryl hydrocarbon receptor.

5. Summary and future directions

Under the modern intensive breeding model, pigs are usually kept in barren environments, resulting in various psychological problems. These psychological problems in pigs may lead to weight loss, accumulation of subcutaneous fat and poor meat quality, resulting in severe economic losses in swine production. Given that the metabolites of tryptophan and dietary fiber regulate behavior and CNS function, such as cognitive function, it could be fruitful to alleviate the psychological problems in pigs with these metabolites. However, cautious should be exercised when we apply this knowledge to pigs because our current understanding of MGBA is mainly derived from mouse models, and there are different physiological and metabolic characteristics between mice and pigs. Thus, a thorough understanding of the mechanism in which those

metabolites participate, and the complex gut-brain interaction, especially in pigs, may help to propose new strategies for improving swine health. Fortunately, our scientific community has conducted seminal studies in this field. For example, intestinal perfusion with mixed antibiotics and corn starch in fistula pigs affects the concentrations of aromatic amino acids, serotonin and dopamine in the hypothalamus and regulates the expression of neurotransmitters in the brain (Gao et al., 2018, 2019). In addition, dietary tryptophan supplementation increases reproductive performance and milk yield of sows (Miao et al., 2019), while reducing the time and times of fighting among piglets, and the stress responses of weaned piglets after mixed herd rearing (Koopmans et al., 2005). Dietary fiber also affects the welfare and behavior of piglets (de Leeuw et al., 2008; Superchi et al., 2017; Jiang et al., 2019). Overall, the research on the interaction between the host and gut microbes

allows us to see the huge regulatory potential of microbial metabolites for host health.

Author contributions

Lijuan Fan: writing-original draft preparation, visualization; Bingnan Liu and Ziyi Han: writing-reviewing and editing; Wenkai Ren: conceptualization, methodology, writing-reviewing and editing.

Conflict of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work.

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