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Gut Brain Axis and Its Microbiota Regulation in Mammals and Birds

Jan S. Suchodolski, MedVet, DrMedVet, PhD, DACVM

KEYWORDS

• Microbiota • Microbiome • Bacteria • Gut-brain-axis • Serotonin

KEY POINTS

- The intestine harbors a highly complex microbial ecosystem consisting of bacteria, fungi, viruses, and parasites.
- Bacterial culture and fecal cytology does not allow proper assessment of intestinal bacteria, and molecular-based methods are now standard in the assessment of bacterial microbiota.
- The intestinal microbiota is a highly active immunologic and metabolomic system that is crucial to host health.
- Various microbiota-derived metabolites contribute to neuroendocrine pathways that provide signaling to the brain via the gut-brain axis.

INTESTINAL MICROBIOTA AND ITS FUNCTION

The intestinal microbiota is defined as the collection of all living microbes (bacteria, fungi, protozoa, and viruses) residing in the gastrointestinal (GI) tract. Until a decade ago, bacterial culture was the most commonly used technique to describe bacteria within the mammalian and avian GI tract. The recent advance of molecular tools, especially next-generation sequencing technologies that allow to inexpensively amplify, sequence, and thereby identify which bacterial taxa are present in a sample, has revolutionized understanding and revealed that the GI microbiota of mammals and birds is much more species-rich than previously thought.[1] In mammals, it is estimated that 100 trillion bacterial cells populate the GI tract and the total sum of bacteria is approximately 10 times more than the number of host cells. The collective genome of all these microbes (referred to as microbiome) exists in close relationship with the host and, through its immunologic and metabolic function, this highly complex microbial-host ecosystem has a crucial impact on host health, including the nervous system.

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Small Animal Medicine, Gastrointestinal Laboratory, Department of Small Animal Clinical Sciences, Texas A&M University, 4474 TAMU, College Station, TX 77843-4474, USA
E-mail address: Jsuchodolski@cvm.tamu.edu

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Resident bacteria provide many beneficial mechanisms, such as fending off transient enteropathogens, aiding in nutrition and harvesting energy from diet, providing metabolites that feed enterocytes, and stimulating the host immune system. Although most data about the functions of the intestinal microbiota are derived from studies in mammals and fewer data are available in avian species, it is likely that many microbiota–host interactions are evolutionary and conserved across various animal species. For example, in mammals, complex fibers obtained through the diet (eg, starch, cellulose, pectin) are fermented by intestinal bacteria. The end products of this bacterial fermentation are short-chain fatty acids (SCFA). These are partially absorbed and serve as an energy source for the host (eg, propionate, acetate), regulate intestinal motility, and are also used as important growth factors for the intestinal epithelial cells. SCFA are also important stimuli for maintaining intestinal barrier function, thereby minimizing bacterial translocation.[2,3] SCFA are also immunomodulatory by activing regulatory T cells in the intestine.[4] Although SCFA are the most studied bacterially derived metabolites, novel metabolomics approaches have revealed various other metabolites that are produced by intestinal microbiota, such as indole, a byproduct of tryptophan degradation, which is anti-inflammatory and enhances intestinal barrier function.[5] Of importance is that bacterial metabolism and immunologic stimulation in the intestine have consequences that reach far beyond the GI tract. It is now well-recognized that a gut-brain connection exists that is modulated by gut microbes. Modulation of gut microbiota is an exciting emerging area of research with the potential for better understanding of pathophysiology and treatment of various intestinal and metabolic, as well as neurologic diseases.

ASSESSMENT OF INTESTINAL MICROBIOTA

Until a decade ago, most information about the composition of the intestinal microbiota was obtained using traditional culturing techniques. Bacterial culture is a useful tool for determination of an active infection of known pathogens (eg, *Salmonella*, *Campylobacter*) and antibiotic susceptibility testing in clinical specimens. Individual isolates and their virulence factors can be typed for epidemiologic surveys of specific strains. It is now well-recognized that there are several limitations associated with bacterial culture of intestinal samples. Bacterial culture widely underestimates the total bacterial numbers in the intestines. Most gut bacteria cannot be isolated on routinely used laboratory media because not enough information is available about their optimal growth requirements. Most microbes in the gut are strict facultative anaerobes, hindering their successful isolation in vitro. It is estimated that less than 10% of intestinal bacteria can be cultured on routine media and only a small fraction can be correctly classified using classic morphologic and biochemical criteria. Therefore, clinical examination of intestinal samples by culture is currently biased toward the minor cultivable portion of the gut microbiota.

Because of these limitations, the use of molecular tools is now standard. The principle is that DNA is extracted from intestinal samples and 16S ribosomal RNA (rRNA) genes are amplified using universal bacterial primers. This approach allows in theory amplification of DNA from all known and unknown bacterial species present in a sample. To identify the phylotypes present in the sample, the PCR amplicons can be subsequently sequenced by high-throughput sequencing platforms.[6] These platforms allow for analysis of several thousand sequences within a few hours, yielding a deep identification of the intestinal microbiota. If the sequence for a particular phylotype is known, specific PCR assays can be designed for its detection. Real-time polymerase chain reaction (PCR) assays (with universal-specific, group-specific, or

species-specific primers) can be used for quantitative analysis. Fluorescent in situ hybridization (FISH) allows visualization of the location of bacteria with regard to the epithelium (ie, intracellular, adherent, or invasive).[7]

INTESTINAL MICROBIOTA OF MAMMALS

Humans, Mice, Dogs, Cats

Most data are available about the microbiota of humans and their animal models and, in veterinary medicine, about dogs and cats. These data are briefly summarized here as a reference for comparison with exotic and avian species. There is a remarkable similarity in the predominant bacterial phyla present in the GI tract across carnivores and omnivores, and also along the length of the GI tract.[8] The predominant phyla in the feces of healthy dogs, cats, and humans are Bacteroidetes, Firmicutes, Fusobacteria, and Proteobacteria.[1,8,9] On lower phylogenetic levels, the small intestine of dogs harbors predominantly Clostridia, Lactobacillales, and various classes of Proteobacteria, whereas the large intestine harbors almost exclusively anaerobic species from the orders of Clostridiales and Bacteroides, the families Ruminococcaceae and Lachnospiraceae, and the genera *Prevotella* and *Fusobacteria*.[8] Members of the Clostridiales order are especially highly abundant and it is thought that the bacterial species within this order perform major functions in the large intestine, such as the production of SCFA, indole metabolism, vitamin synthesis, and amino acid synthesis.[10] Although the intestine also harbors various resident fungi[6,11] and viruses,[1] little is currently known about their contribution to health and disease.

Rabbits, Ferrets, and Hamsters

Fewer studies have been reported characterizing the intestinal microbiota of other animal species, and even less is known about the metabolic functions of these gut communities compared with the previously described animal species. Studies characterizing the microbiota of rabbits have described mostly bacteria in fecal or cecal samples, and only limited information is available about the bacterial composition in the stomach and small intestine. Some of these studies observed many yet uncharacterized bacterial sequences in the rabbit's large intestine, suggesting that rabbits have a more unique microbial ecosystem compared with other animal species. Given the emerging importance of the gut microbiota for host health, there is need for more comprehensive descriptive studies cataloging the intestinal microbiota and their functional capacity in exotic animals. Rabbits are hindgut fermenters and seem to have microbiota similar to horses because both harbor large proportions of *Streptococcus* and Verrucomicrobia in fecal samples.[12,13] Published studies describing the known bacterial taxa reported the predominance of Clostridia (especially Ruminococcaceae and Lachnospiraceae), Bacteroidetes, and *Akkermansia* in rabbits.[14–17]

In a recent study, the fecal microbiota of ferrets was analyzed using the bacterial cultivation method. The predominant bacterial groups were *Clostridium acetobutylicum*, *Helicobacter* spp, and *Lactobacillus* spp.[18] To the author's knowledge, no molecular-based study was reported in literature describing the intestinal microbiota of ferrets. Therefore, it is likely that the intestinal microbiota of ferrets harbors many others besides the reported bacterial taxa. One study described the cecal microbiota of hamsters and found that Firmicutes, especially Clostridiales (families Ruminococcaceae and Lachnospiraceae) were most abundant.[19] Of interest is that fasting, but not hibernation, led to significant changes in gut microbiota, especially increases in the abundance of mucin-degrading bacteria such as *Akkermansia muciniphila*.[19] It has also been recently shown in dogs that prolonged fasting has a very strong impact

on the small intestinal microbiota.[20] These initial studies describing the intestinal microbiota of small mammals suggest that the microbiota is as complex as in larger mammals, warranting more in-depth studies evaluating the intestinal microbiota across various diseases, and before and after nutritional interventions.

INTESTINAL MICROBIOTA OF PARROTS AND PSITTACINES

Compared with the many studies that have been performed in humans and other mammalian species, little information is yet available about the intestinal microbiota of birds beyond chickens. Similarly, very little information is available about the differences in microbiota composition along the intestinal tract and luminal versus mucosal-adherent bacterial populations. In one of the first molecular-based studies, the cloacal microbiota of 16 parrots (mealy Amazon parrot and macaws) was analyzed: 8 parrots were free-ranging in southeastern Peru and 8 parrots were living in captivity in a colony in Texas.[21] In this initial small-scale study, there was a trend for clustering of the captive birds versus the wild birds and, in the captive birds, based on the species and/or aviary they came from. Four predominant phyla were present across these cloacal samples in descending order of abundance: Firmicutes, Proteobacteria, Actinobacteria, and Bacteroidetes. On lower phylogenetic levels, the bacterial families Lactobacillaceae and Staphylococcaceae were predominant. In a recently reported large-scale study, the fecal microbiota of 3 different avian species (budgerigars, cockatiels, and domestic canaries) was analyzed by next-generation sequencing of 16S rRNA genes.[22] Firmicutes were the most abundant bacterial phylum, followed by Proteobacteria and Actinobacteria. *Lactobacillus* spp was the most abundant genus across all birds. Of interest was that the microbiota composition tended to be more similar for each bird species, suggesting that birds within an avian species have more similar microbiota compared with birds of other avian species.[22] Similarly, a recent study described the fecal microbiota of captive cockatiels, and reported that Firmicutes were most abundant, comprising mostly Erysipelotrichaceae, *Clostridium* and *Lactobacillus* spp, respectively.[23] These studies suggest that avian species have, in part, a different microbiota compared with mammals because they appear to have relative higher abundances of *Lactobacillus* spp.

To better understand the microbiota composition and its contribution for immune regulation, nutrition, and metabolism of birds, more descriptive studies are clearly needed about the intestinal microbiota (especially across the various avian species) and about the microbiota along the intestinal tract. In a study (Rossi and colleagues, unpublished data, 2014) from the author's laboratory, initial data suggest that crop and cloaca harbor similar species richness but very distinct microbial communities (ie, different makeup of bacterial taxa). Proteobacteria were significantly more abundant in the crop compared with the cloaca, whereas Firmicutes (mostly *Lactobacillus* spp) and Actinobacteria were more abundant in the cloaca. This distribution is similar, at least in part, to that described in mammals, in which aerobic bacteria, such as Proteobacteria, are more abundant in more proximal parts of the GI tract, and Firmicutes are more abundant more distally.[8] The reader is referred to other review articles that provide an overview about microbiota composition across other bird species.[24–26]

EXAMPLES OF GUT-BRAIN AXIS INTERACTIONS ACROSS ANIMAL MODELS

Until recently, the main focus for examining intestinal bacteria was to search for potential enteropathogens associated with various intestinal diseases. Just as with the appreciation of the close relationship between intestinal microbiota and the host,

the investigators realized that gut microbiota composition also influences organ systems beyond the GI tract, and is associated with changes in cognition, behavior, stress, and other disorders of the nervous system.[27,28] One potential pathway is the direct immunologic stimulation through cell-to-cell contact affecting the enteric nervous or immune system that then further provides stimulatory signals to the brain. Another potential pathway is the production of endocrine metabolites by the intestinal microbiota that, in turn, stimulate the nervous system. Although those stimuli are physiologic and beneficial, negative effects can occur when there are imbalances in commensal microbiota because they may occur through external triggers (eg, use of antibiotics), through nutritional imbalances, and also through intestinal inflammation, which, in turn, affects microbiota composition. Examples from the literature across different animal models are summarized here to provide a broad overview about the current knowledge in the field.

Specific members of the microbiota have been shown to directly produce neurotransmitters, such as gamma-aminobutyric acid (GABA) or acetylcholine, under in vitro conditions. It is likely that this may also occur within the GI tract.[29] It was reported that there is a significant difference in the production of neuroendocrine substances (eg, catecholamines, norepinephrine, and dopamine) between mice that are born under normal conditions with a commensal microbiota versus mice that were born and remained germfree (ie, mice that were never exposed to intestinal microbes). These neuroendocrine substances were detected in the normal mice at regular concentrations but at much lower concentrations in the germfree mice, suggesting that the intestinal microbiota produces significant amounts of these neuroendocrine substances.[30] On the other side, neuroendocrine substances produced by the host during periods of stress may modulate the virulence of enteropathogens in vivo, providing evidence how host neuroendocrine substances have also an effect on gut microbiota.[31]

There is also clear evidence that GI colonization with potential enteropathogens can alter the behavior of the infected animals.[32] For example, in 1 study, mice were inoculated with *Campylobacter jejuni*, leading to mild subclinical infection that did not lead to measurable activation of the immune system (ie, no alterations in proinflammatory cytokine expression).[32] Nevertheless, the infected mice showed increases in anxiety, which manifested itself through a decrease in exploratory behavior, suggesting that the microbiota directly activated neural pathways.[32] Subsequent follow-up work by the same investigators revealed that the colonization with *C jejuni* indeed activated the nucleus of the solitary tract and the lateral parabrachial nucleus in the brainstem, supporting evidence that the gut reacts to the subclinical infection and then further signals to the brain.[33]

Some neurologic disorders have been associated with changes in the global commensal microbiota composition, rather than an infection with an external pathogen. For example, multiple sclerosis in humans has repeatedly been linked to altered microbial communities in the gut,[34] especially increases in *Methanobrevibacter* and *Akkermansia* and decreases in *Prevotella*.[35] Similarly, a recent study analyzed the fecal microbiota of dogs with meningoencephalomyelitis of unknown origin (MUO), which is an immune-mediated condition of dogs that has been suggested as a potential model for studying the pathophysiology of multiple sclerosis in humans.[36] Fecal samples were obtained from 20 dogs that were diagnosed with MUO and the microbiota was compared with the 20 control dogs accurately matched for breed, age, and gender. As observed in humans with multiple sclerosis, Prevotellaceae were significantly less abundant in dogs with MUO, providing additional evidence that presence of Prevotellaceae at higher abundances are associated with reduced risk for developing immune-mediated brain disease.[36]

Autism spectrum disorders (ASDs) are other neurodevelopmental diseases with emerging evidence for the role of the gut microbiota.[37] Human patients with ASD exhibit neurologic and, often, GI disorders. Several studies have reported alterations in gut microbiota in people with ASD compared with controls.[37,38] Furthermore, therapeutic manipulation of the gut microbiota in children with ASD revealed improvements in GI and behavioral symptoms of ASD.[39] In a small open-label pilot study, 18 children diagnosed with ASD received an initial 2-week treatment with a nonabsorbable antibiotic, followed by a bowel cleanse. These children then received fecal microbiota transplantation daily for 7 to 8 weeks.[39] The symptoms of children improved during therapy with lasting effect even after completion of therapy, suggesting a prolonged change in gut microbiota associated with improvement of ASD.

Bacterial components have also been shown to directly modulate brain development and, subsequently, behavior. For example, in 1 study, bacterial peptidoglycan (PGN) was derived from the commensal gut microbiota and it was shown that PGN was able to translocate into the brain and was sensed by specific pattern-recognition receptors within the innate immune system.[40] Furthermore, the absence of these bacterial factors was associated with increased risk for autism-like behavior in a mouse model. Similarly, in mice, polysaccharide A from the capsule of the commensal bacterium *Bacteroides fragilis* was protective of experimental autoimmune encephalomyelitis, which is the experimental model of human multiple sclerosis.[41] The proposed mechanism was due to induction of immunoregulatory T cells by the polysaccharide A capsule. Of importance is that this protective effect was not induced by all strains of *B fragilis* but only by the specific strain *B fragilis* (ATCC 9343).[42] The effect is believed to be due to enhancement of gut barrier function.

Nutrition also plays a role by modulating gut microbiota, which, in turn, affects cognition and behavior. For example, feeding of resistant starch to mice revealed that animals developed more pronounced anxiety-like behavior.[43] Mood disorders have been associated with dietary sensitivities that were hypothesized to be caused by increased gut permeability due to infectious agents such as *Toxoplasma gondii*, influenzavirus, and coronavirus.[44] Nutrition and carbohydrate catabolism due to microbial metabolism in the small intestine was also associated with autism syndrome disorders in humans.[45] There are a variety of changes at the genus and species level found in the duodenal microbiota in children with autism that could potentially be caused by carbohydrate malabsorption. These observations may represent a pronounced and enduring dysbiosis that results in formation of metabolites that affect the behavior of autistic children.[45]

SUMMARY

Studies have shown strong evidence for a bidirectional link between gut microbiota and the brain. So far, most studies have shown mechanistic links in mouse models of disease. However, the first therapeutic pilot trials in children with autism provide support for the notion that manipulation of gut microbiota may be an important pathway for future therapies. This is an exciting area of research and highlights the need for more comprehensive studies to better define the intestinal microbiota in mammals and avian species. Future therapeutic trials will be necessary to evaluate how diet, probiotics, and even fecal microbiota transplantation may be used for establishing an optimal microbiota. Also, recent studies have shown the detrimental long-term impact of antibiotics on the gut microbiota, which should alert clinicians to use antibiotics more judiciously.

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