The Gut Microbiome – Taking a Nutritional Approach to Modify Disease

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KEY MESSAGES

- Microbiota of dogs and cats should be considered a key aspect of animal health and nutrition.
- Gut microbiota influences many areas of dog and cat health from nutritional benefits, modulation of immune system, and protection of host against pathogens.
- The benefits of microbiota to the host are mediated through postbiotics, or products of microbial metabolism with biological effects.
- A dysbiotic state of the gut microbiota is associated with inadequate diet and in pathological conditions of gastrointestinal tract in dogs and cats.
- Prebiotics in the diet produce a lasting and positive impact on microbiota, resulting in a number of health benefits.

Have you been wondering why the word microbiome has been an increasingly popular topic in human and veterinary medicine? This is because scientists began to uncover that the microbes living on and in the body are not just a random cluster of germs originating from the environment that can make an individual sick. Nor are the gut microbes only important to herbivores to help them extract energy from food. In fact, the gut microbiota is a living ecosystem of commensal microorganisms that provides lots of benefits to every mammal, from maintaining gut health to regulating distant organs. In return, the mammalian host (dog or cat) provides the microbiota with nutrients and a stable environment. Research is clear that harboring a healthy microbiota in the gut offers many of health benefits to dogs and cats.

What is the size of gut microbiota of dogs and cats?

Gut microbiota is the entire habitat of living microorganisms, including not only anaerobic and aerobic bacteria but also fungi, protozoa, and viruses. They have been evolving for billions of years and there are thousands of diverse species known. It is estimated that the intestine of mammals contains approximately $10^{10}$ to $10^{14}$ microorganisms, which is 10 times more than the number of cells within the body.\footnote{1} Due to the small size of microbes and presence in high density, the microbial mass is not as large and heavy when compared to the rest of the body. The total bacterial counts increase along the gastrointestinal (GI) tract of dogs and cats, with numbers being lowest in the stomach and highest in the colon.

What benefits do dogs and cats get from the microbiota?

Traditionally, the gut microbiota are known to be a key player in digestion of foregut and hindgut fermenters like ruminants, horses, or rabbits, helping them to extract energy from otherwise indigestible feed by fermentation. In fact, ruminants are totally dependent on microbial fermentation to survive. Although the energy derived from fiber fermentation in omnivores and strict carnivores is much
less, dogs and cats have the capacity to ferment undigested material in their colon for their benefit, including pathogen resistance, modulation of immune system, and synthesis of nutrients. Additionally, even in a true carnivore like the cat, microbes inhabiting the feline hindgut have been shown to be very active and have fermentative functions similar to those found in dogs, pigs, and humans.\(^2\)

**Where do dogs and cats get their microbiota?**

Puppies and kittens are born virtually without GI microbiota and their intestines are colonized by microorganisms from the birth canal and from the environment within 24 hours from birth. Those microbes are necessary to the newborn to establish an oral tolerance to commensal bacteria and food antigens, which ensure that the gut immune system will ignore them and will not initiate an inflammatory response. Throughout life, a balanced intestinal ecosystem continues to collaborate with the immune system and among multiple other roles, serves as the defense against invading intestinal pathogens.

**Is the gut microbiota of dogs and cats unique?**

While microbiota of individual dogs and cats has similar functions, recent studies conducted have shown that each dog and cat harbors a very unique and individual microbial profile.\(^3,^4\) The main difference is in bacterial species and strains with minor overlap between individual animals. In one study, 84% of cats harbored *Bifidobacterium* species but only a minor percentage of cats harbored the same species of Bifidobacteria.\(^4\)

In spite of existing differences in microbial species between individual dogs or cats, the metabolic end products formed do not markedly differ. This is because several members of the microbial community are able to perform similar functions, and if one microbial group is displaced, other members of the community are capable of substituting that function and stabilizing the entire ecosystem. As a result, there is a large similarity in the products of microbial fermentation among individual dogs and cats, in spite of large differences of bacterial species involved in the process. Using an analogy, it doesn't matter what kind of builders construct the house (or what bacteria do the work), as long as the house (or products of microbial metabolism) is built.

**Why does the gut microbial ecosystem matter to dogs and cats?**

Intestinal microbiota plays an important role in the health of dogs and cats (table 1). Most of its action is located in the colon where the flow of ingesta slows down, providing the ideal environment for the microbes to grow and multiply. Microbes are excreted with each defecation, which means that this ecosystem is in a dynamic and constant state of turnover, growth, and replenishment. The microbial community is capable of competitively excluding pathogenic bacteria through various cooperative strategies developed by the microbes, which maintains the balance of this ecosystem.
Table 1. Examples of functional contributions of the gut microbiota

<table>
<thead>
<tr>
<th>Function</th>
<th>Products</th>
<th>Benefits of products</th>
</tr>
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<tbody>
<tr>
<td>Harvest of otherwise inaccessible nutrients and</td>
<td>Production of short chain fatty acids (SCFA; acetate, propionate,</td>
<td>Acetate and propionate are energy substrates for microbial growth but are also absorbed from the colon and provide source of energy for the body. Butyrate is important energy fuel for colonocytes. SCFA facilitate the absorption of sodium and water in the colon.</td>
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<td>energy from the diet</td>
<td>butyrate)^2</td>
<td></td>
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<tr>
<td>Release and metabolism of fiber-bound plant</td>
<td>Release and metabolism of fiber-bound plant polyphenols^4</td>
<td>Polyphenols are molecules from fruits and vegetables with antioxidant and anti-inflammatory properties.</td>
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<td>Synthesis of vitamins</td>
<td>Microbial synthesis of vitamin K and water soluble B vitamins^6,7</td>
<td>Vitamin K is a fat soluble vitamin involved in blood coagulation and in binding calcium in growing bones. B vitamins are a class of water-soluble vitamins that play important roles in cell metabolism and help the body to utilize energy from food.</td>
</tr>
<tr>
<td>Development and activity of the immune system</td>
<td>Intestinal bacteria present early in life is necessary to establish oral tolerance to commensal bacteria and food antigens^8,9</td>
<td>In healthy animals, the microbiota and the immune system maintain a balance so that excessive immune and inflammatory responses are avoided.</td>
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<td>Protection against harmful microbial species</td>
<td>1. The microbiota induces gut immune system to produce IgA^10</td>
<td>Ig A limits local epithelial bacterial colonization and prevents penetration of bacteria through the epithelial layer. The secreted antibacterial activity is confined to the mucus layer, which provides physical and antibacterial barrier while allowing the presence of luminal microbiota^24</td>
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<td></td>
<td>2. The microbiota stimulate intestinal secretory cells to produce antimicrobial compounds (beta-defensins, cathelicidins, bactericidal/permeability-increasing protein and chemokine^11,12</td>
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<tr>
<td></td>
<td>3. Beneficial bacteria competitively exclude pathogens by occupying receptor sites, competing for space and nutrients^13</td>
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<td>Improved integrity of the mechanical mucosal</td>
<td>The microbiota stimulates the mucus layer^15 and alters the mucin chemical composition^16</td>
<td>Mucins (highly glycosylated macromolecules) form the first barrier between the gut contents and epithelial cells, protecting them from direct contact with commensal bacteria and their components.</td>
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What are some problems associated with an unhealthy gut microbiota?

Most of the commensal bacteria in the canine and feline gut are symbiotic; however, after translocation through the mucosa or under specific conditions, such as immunodeficiency, commensal bacteria could cause or contribute to disease pathogenesis. A state when the bacterial populations within the GI tract become imbalanced is called dysbiosis. Clinical disturbances of dysbiosis include indigestion, anorexia, diarrhea, and malabsorption of nutrients. Dysbiosis in dogs and cats has a number of causes and has been associated with both acute and chronic GI diseases, antibiotic administration, or can be diet-induced. In people, dysbiosis is also associated with atopy, obesity, liver disease, or GI malignancy. Conversely, normal gut microbial equilibrium is associated with health.

Evidence is accumulating that supports the gut microbiome as a central player in the gut-kidney axis. Some microbial products, such as phenols and indoles, are uremic toxins which are absorbed into the circulation and cleared by normal-functioning kidneys. In kidney disease, these products can accumulate and may contribute to the uremic load and increased morbidity.

Bacteria in the gut also play a role in whether or not an individual becomes obese. This is linked to the ability of the intestinal biome to extract additional energy from undigested food and to regulate energy expenditure and storage.

Growing evidence also supports that there is a gut microbe and brain communication. Neuroscientists are probing the idea that intestinal microbiota might influence brain development and behavior, as well as anxiety. More research is needed to investigate this relationship in dogs and cats.

What is the best way to maintain gut microbial health in dogs and cats?

Microbial growth in the gut is influenced by multiple factors but the major determinant is the substrate for their nourishment, such as dietary fiber, residuals of undigested food, sloughed mucosal cells, or enzymes released into the gut lumen. Altogether, gut microbes use these substrates for their own benefit and growth. In return, they manufacture and release a number of compounds called postbiotics, with many of them providing benefits to the host.

Gut microbiome of dogs and cats can be modulated with diet composition, antibiotics, prebiotics, probiotics, or synbiotics. Prebiotics, probiotics, or synbiotics can be administered as dietary supplements or added to commercial pet food. Because dogs and cats have to eat every day, choosing complete and balanced foods specifically designed to promote healthy microbial fermentation with a blend of active fiber ingredients is the most practical way to nourish healthy gut microbiota from day to day.

Prebiotics

Inclusion of active fiber ingredients into the food offers the most practical and lasting strategy to positively influence the intestinal microbiome. Not every prebiotic fiber is created equal, however. Fibers with prebiotic benefits commonly found in pet foods include beet pulp, flaxseed, fruit fiber, rice fiber, fructooligosaccharides, inulin, oats, or barley.
Many fruits, vegetables and fibers derived from them are excellent source phytonutrients called polyphenols. These phytonutrients are thought to have powerful antioxidant and antiinflammatory activity when consumed in the diet. When included in the diet many can be measured in feces. Those which are fiber-bound are unable to be used by the host until cleaved by enzymes held only by resident bacteria in the colon, resulting in the release of the active polyphenol that may then benefit the host both locally in the colon and systemically if absorbed.

Different prebiotic substances exert different effects on the composition of intestinal microbiota in canine. For example, lactitol and pectin were shown to reduce concentrations of coliforms and Clostridium perfringens, while fructooligosaccharide and beet pulp increased concentrations of beneficial Lactobacilli and Bifidobacteria in dogs.

It should be noted that the background food formulation may impact the mechanism of fiber modulation of microbial metabolism. Jackson et al formulated two test foods with added mixture of fiber and bound-polyphenols, with each of these foods having a different nutrient profile background composition. One was a hydrolyzed meat food and the other was a grain-rich food. In both foods fiber inclusion improved stool quality, lowered stool pH, increased beneficial gut microbes, and changed microbial metabolites to indicate improved colonic health. However, the background composition affected the microbial production of SCFA, beneficial compounds that improve host health. In the hydrolyzed meat food, the addition of fiber increased the SCFA (acetate, propionate, butyrate) while the addition of fiber to the grain-rich food decreased all potentially detrimental branched short chain fatty acids (BCFA). It was concluded that there was a difference in the degree to which the fiber-bound polyphenols could impact microbial endpoints depending upon the background formulation fed.

**Postbiotics**

Postbiotic is a relatively new term that refers to the metabolic product or byproduct secreted by live commensal bacteria, or released after bacterial lysis (e.g., enzymes, peptides, polysaccharides, cell surface proteins, organic acids) which are responsible for many of the biological effects.

The major postbiotic products generated by canine and feline intestinal microbiota are short chain fatty acids (SCFA) acetate, propionate and butyrate. They are mainly products of carbohydrate and fiber fermentation by microbes with saccharolytic function. Acetate and propionate are energy substrates for microbial growth but are also absorbed from the colon of the dog and provide a source of energy for the body. Butyrate is an important energy fuel for colonocytes. Interestingly, up to 7% of the metabolic energy of dogs, and to a lesser extent in cats, is produced by microbial fermentation in the colon. Without the presence of gut microbes, these energy substrates would never form and the energy would remain trapped within the fiber and lost in the feces. It is generally accepted that carbohydrate and fiber fermentation results in beneficial effects for the host due to generation of SCFA.

Anaerobic degradation of undigested protein in the colon is a process called putrefaction. Bacterial proteases and peptidases break the protein down to peptides and amino acids, and release of NH$_3$ through deamination. Although SCFA are the major end products from carbohydrate fermentation, they
are also produced from many amino acids. Other metabolites of proteolysis include branched chain fatty acids (BCFA) from fermentation of branched amino acids, phenolic and indolic compounds from aromatic amino acids, and hydrogen sulfide (H₂S) from sulfur containing amino acids. Finally, decarboxylation of amino acids results in the appearance of amines in the gut. Microbiome products, such as phenols and indoles, are absorbed into the circulation but are cleared by normal-functioning kidneys. In chronic kidney disease, these products may become toxic and can contribute to the uremic load and increased morbidity.²⁴

Researchers at Hill’s Pet Nutrition did show that feeding dogs food enriched with fiber-bound polyphenols improved fecal stool quality, increased saccharolytic postbiotic concentration, decreased microbial putrefaction and decreased polyamine concentration, when compared to dogs fed food without fiber-bound polyphenols.²⁷

In conclusion, while some postbiotic products from protein fermentation are beneficial, others can be potentially harmful. Inclusion of fiber-bound polyphenols appears to promote healthy gut microbiome in dogs.

**Probiotics**

Probiotics are live microorganisms that when administered in adequate amounts, confer a health benefit on the host. How well a probiotic will work depends on how specific it is to the host. The adhesion receptors on the lining of the intestine for example may not fit the probiotic bacteria looking to adhere if they are bacteria from another species rather than a bacteria that co-evolved with that particular species. Thus they may not be able to out compete a pathogenic species that did evolve with that host. For example, if the probiotic bacteria were isolated from a human, co-evolved with a human, it would be most likely to adhere and survive in that host species. Currently, few canine and feline probiotics on the market are actually isolated from the species and they have some evidence for management of chronic, acute diarrhea or as an adjunct therapy with antibiotics. Nevertheless, while probiotics induce microbiota changes in the large intestine, these changes are minor, transient and dose dependent. High doses over prolonged periods of time are required to maintain viable counts of probiotic species. In summary, it appears that prebiotics are a better and more sustainable way to influence the microbiome and provide long-term health benefits to pets when compared to probiotics.

**Effect of macronutrients**

The macronutrient ratios of the foods ingested by individuals can have profound effects on their gut microbiota. Undigested fibers that enter the colon undergo saccharolytic fermentation to produce beneficial postbiotics such as SCFA. However, if protein is not digested fully in the small bowel and is bypassed to the large intestine, the fermentation can result in putreactive products. Therefore, the protein to carbohydrate ratio in the food of companion animals has been examined to better understand specific effects on the gut microbiota, microbially-derived end products, and the health of the animal itself.
Conclusion

Traditional viewing on gut microflora in veterinary medicine has focused mainly on the role of microbes to ferment herbivorous diets and help herbivorous animals extract energy from poorly digestible plant matter. However, research has shown that omnivores (e.g., dogs) and true carnivores (e.g., cats) benefit from having a balanced ecosystem in their gut. Gut microbiota is an important living ecosystem within the body, which influences both gut health and extra-intestinal organs. Gut microbes metabolize and ferment substances that travel to the hindgut in the form of undigested substrate. The composition of the intestinal microbiota ecosystem and postbiotics produced are strongly affected by dietary patterns. Composition of the diet and inclusion of prebiotic fiber represent a long-lasting strategy to consistently maintain balance of gut microflora and deliver health benefits.

Glossary

Commensal microorganisms - live in a relationship in which one organism derives food or other benefits from another organism without hurting or helping it. Commensal bacteria are part of the normal gut flora.

Microbiome – the collective genomes (set of genes or genetic material) of the micro-organisms in a particular environment.

Microbiota – the community of micro-organisms.

Short chain fatty acids – fatty acids with two to six carbon atoms that are produced by bacterial fermentation of carbohydrates and dietary fibers.

Dysbiosis – a term for a microbial imbalance or maladaptation on or inside the body, such as an impaired gut microbiota.

Prebiotic – a dietary prebiotic is an ingredient selectively fermented that results in specific changes in the composition and/or activity of the gastrointestinal microbiota thus conferring benefit(s) upon host health.

Probiotics – live bacteria and yeasts that, when administered in a viable for and in adequate amounts, are beneficial to animal health.

Postbiotic - a relatively new term that refers to the metabolic product or byproduct secreted by live commensal bacteria, or released after bacterial lysis (e.g., enzymes, peptides, polysaccharides, cell surface proteins, organic acids) which are responsible for many of the biological effects.

Synbiotics – contain a mixture of prebiotics and probiotics.
**Polyphenols** – naturally occurring micronutrients found in plants with anti-oxidant and anti-inflammatory activity when consumed in the diet. Some are fiber bound and unable to be used by the host until cleaved by enzymes held only by resident bacteria in the colon.

References:


