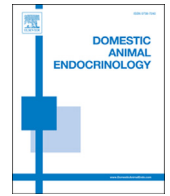




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## Domestic Animal Endocrinology

journal homepage: [www.domesticanimalendo.com](http://www.domesticanimalendo.com)

# The gut microbiome as a virtual endocrine organ with implications for farm and domestic animal endocrinology

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## ARTICLE INFO

## Article history:

Received 24 August 2015

Received in revised form 6 May 2016

Accepted 11 May 2016

## Keywords:

Gut microbiome

Endocrinology

Stress

Tryptophan

Behavior

Animal

## ABSTRACT

The gut microbiome exerts a marked influence on host physiology, and manipulation of its composition has repeatedly been shown to influence host metabolism and body composition. This virtual endocrine organ also has a role in the regulation of the plasma concentrations of tryptophan, an essential amino acid and precursor to serotonin, a key neurotransmitter within both the enteric and central nervous systems. Control over the hypothalamic-pituitary-adrenal axis also appears to be under the influence of the gut microbiota. This is clear from studies in microbiota-deficient germ-free animals with exaggerated responses to psychological stress that can be normalized by monocolonization with certain bacterial species including *Bifidobacterium infantis*. Therapeutic targeting of the gut microbiota may thus be useful in treating or preventing stress-related microbiome-gut-brain axis disorders and metabolic diseases, much the same way as redirections of metabolopathies can be achieved through more traditional endocrine hormone-based interventions. Moreover, the implications of these findings need to be considered in the context of farm and domestic animal physiology, behavior, and food safety.

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## 1. Introduction

Research in the area of microbiome science has in recent years received a large amount of interest. This has been supported by major advances in the methods used for the characterization and identification of microbes typically not culturable by traditional plate-culturing methods. Such advancements in technology include the development of sequencing-based measurements, genetic fingerprinting, fluorescent-labeled oligonucleotide probes, quantitative PCR, multilocus gene typing, and metagenomic-sequencing

approaches [1–3]. The new discoveries emerging from such substantial investment in this field has prompted a changing perception of the importance of this symbiotic relationship between a host and the trillions of microbes that make up its microbiome [4,5].

The gut microbiota has a wide range of functions of a protective, structural, and metabolic nature influencing the health of the host by aiding the processing of foods, synthesis of vitamins (such as B<sub>12</sub> and K), prevention of pathogen colonization, digestion and harvest of energy from complex carbohydrates ingested but not digestible by the host [6,7]. As noted [8], mammals in particular lack an enzymatic stock to efficiently harvest energy and nutrients from plant structural carbohydrates. This is especially important in ruminants on a herbivorous diet. Indeed through the use of compartmentalization, the microbiome of the ruminants' gastrointestinal tract (GIT) aids in the

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digestion of this plant material with the fermentation products yielding up to 70% of total dietary energy [9]. The gut microbiota also has effects on the intestinal epithelium by supporting the growth of intestinal microvilli [10] and has been shown to play an essential role in the development of innate and adaptive immune responses mediated by a number of signaling molecules and metabolites derived from the microbiota [7,10].

The gut microbiota has also been shown to impact the function of distal systems and organs via the production of potent hormones that are released into the bloodstream through interstitial tissue and then transported to act not just locally in the enteric nervous system (ENS) but also at remote sites such as the liver [11,12] and even the brain [13]. The use of microbiota-deficient germ-free animals in particular has been the catalyst behind some fundamental advances in our grasp of the extent to which the gut microbiota influences brain and behavior [14]. This expanding repertoire currently includes anxiety-like behaviors [15–17], regulation of the stress response [18], social development [19,20], neurotransmitter synthesis and precursor availability [21,22], microglia activation [23], neurogenesis [24], neurotrophic support [25], transcriptional regulation [26], and maintaining the integrity of the blood brain barrier [27]. This impact is likely achieved by recruitment of the scaffolding provided by the gut-brain axis, a bidirectional communication system with immune, endocrine, and neural infrastructure [28]. Lagging behind our expanding knowledge of the key roles played by the gut microbiota in health and disease are mechanistic insights into how it achieves such a vast range of functions. Conceptualizing the gut microbiota as a virtual organ, attributed to its vast metabolic activity, regulatory potential and ability to influence the function of local and nonlocal organs and systems, provides a framework to help understand this complex area [6,29–31]. For example, an increased understanding of how the neonatal microbiome of animals is developed and maintained can help clarify and promote its function in influencing health effects on the host, such as the mucosal immune system [8]. This extends to a major role in orchestrating the communication between the immune and neuroendocrine systems, key to the maintenance of homeostasis across the lifespan [32].

In this review, we discuss this endocrine capacity and the main features of the gut microbiome that facilitate its impact on host physiology, brain, and behavior. To date, research efforts have been concentrated on the importance of the gut microbiota in human health and disease, ably supported by parallel laboratory animal studies. We also consider the substantial relevance and implications from this emerging field for farm and domestic animal physiology and behavior.

## 2. The gut microbiome as a virtual endocrine organ

Typical endocrine organs or systems have the capability to produce a single or small number of hormones. Conversely, the gut microbiota has the potential to produce a plethora of different hormonal products, which have the ability to affect the status of the gut and when taken up by the bloodstream and transported throughout the body,

these hormones can have an effect on the function of remote organs and systems [6] (see Fig. 1). Although the gut microbiome is multicellular with numerous constituent genomes [33], it does satisfy many of the classical criteria required for consideration as an organ. This includes the fact that microbes in the GIT are responsive to signals from other organs and in turn influence the function of other organs within the host [34] (see Fig. 2).

The gut microbiota from a morphologic and biochemical viewpoint is much larger and more heterogeneous than that of any other endocrine organ in man, even exceeding the biochemical complexity of the brain [35]. A comprehensive review by Smith et al [36] on the use of germ-free (GF) animals has further demonstrated the numerous effects this essential organ can have on host health and quality of life. This enormous biochemical capacity results from the vast and diverse array of microbial cells that are located within the gut. It is worth mentioning however, owing to its functions being derived from its diverse microbial composition, perhaps the gut microbiota should be considered as a system instead, much like the immune system is composed of different cells with various functions and roles [30]. Nevertheless, a functional understanding of key microbiota genes is essential to beneficially exploit the endocrine features of the gut microbiota in promoting host health.

## 3. The gut microbiome: development, composition, and functional relevance

After birth, the human GIT is colonized with  $10^{13}$  to  $10^{14}$  microorganisms [37,38]. The microbiome is a diverse environment, which is dominated by bacteria mainly consisting of strict anaerobes but also contains viruses, protozoa, archaea, and fungi. Simpson et al [39] described the differing microbiota between food animal species. The gut microorganisms of monogastric animals such as pigs, chicken, rabbits, and humans are dominated by *Bacteroides*, *Clostridium*, *Bifidobacterium*, *Eubacterium*, *Lactobacillus*, *Enterobacteriaceae*, *Streptococcus*, *Fusobacterium*, *Peptostreptococcus*, and *Propionibacterium*. On the other hand, polygastric animals including cows and sheep, the rumen is dominated with fiber degrading species of *Fibrobacter*, *Ruminococcus*, *Butyrivibrio*, and *Bacteroides* with other major groups including *Prevotella*, *Selenomonas*, *Streptococcus*, *Lactobacillus*, and *Megasphaera*, in addition to a large presence of methanogens in the rumen [40]. Given the dietary differences as well as the disparate mechanics and adaptations of the respective digestive processes, such differences are not surprising. Although the rumen microbiome has been extensively studied in isolation, integration of this knowledge with the findings of newly emerging concepts from rodent and human microbiome research is a neglected area of research. The challenges in translating the microbiome findings even between monogastric species has been noted [41] such that further extrapolation to ruminants will undoubtedly be a difficult process. Nevertheless, there are sufficient similarities in terms of establishment, development, and core functions to suggest this is a viable prospect [42]. Moreover, there are indications that specific bacterial members of the rumen microbiome are associated with high and low milk

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