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## Symposium review: Microbial endocrinology—Why the integration of microbes, epithelial cells, and neurochemical signals in the digestive tract matters to ruminant health<sup>1</sup>

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### ABSTRACT

The union of microbiology and neurobiology, which has been termed microbial endocrinology, is defined as the study of the ability of microorganisms to produce and respond to neurochemicals that originate either within the microorganisms themselves or within the host they inhabit. It serves as the basis for an evolutionarily derived method of communication between a host and its microbiota. Mechanisms elucidated by microbial endocrinology give new insight into the ways the microbiota can affect host stress, metabolic efficiency, resistance to disease, and other factors that may prove relevant to the dairy industry.

**Key words:** epithelium, microbiology, infection, microbiota-gut-brain axis

### CONNECTION BETWEEN THE GUT MICROBIAL COMMUNITY AND STRESS

Animals experience a variety of stressors that occur when they transition between physiological conditions, when they are exposed to changing environments, and when these and other stressors interact. Environmental stress, particularly heat stress, has long been established as influencing dairy animal performance in measures including growth, reproduction, and lactation (Collier et al., 2006). Heat stress during the transition to lactation can be especially detrimental to dairy cattle performance (Baumgard and Rhoads, 2012, 2013). Acclimation to stress in ruminants includes numerous endocrine changes, such as reduced aldosterone secretion, reduced glucocorticoid secretion, increased epinephrine,

and increased progesterone secretion by the adrenal glands; decreased thyroxine secretion by the thyroid gland; increased leptin secretion by adipose tissue; decreased somatotropin and increased prolactin secretion by the anterior pituitary; and decreased estrone sulfate secretion by the placenta (Bernabucci et al., 2010). Although extensive studies of rumen microbial ecology and the effect of dietary alterations on microbial communities, nutrient supply, and animal performance have been conducted, investigations into the effects of animal stressors on the microbiome of ruminants are in their infancy (Malmuthuge and Guan, 2017). Initial work has identified alterations in rumen microbiota when heifers were heat stressed (Uyeno et al., 2010), when cows were subjected to intravenous challenges with LPS (Jing et al., 2014), and when cows transition to lactation, especially when the rumen becomes acidotic (Wetzels et al., 2016). Given that links between stress, the neuroendocrine system, and the microbiota are well established, even if not completely understood in other mammals (Furness et al., 2013; Furness, 2016; Schroeder and Backhed, 2016), it is likely that similar relationships will be identified in ruminants.

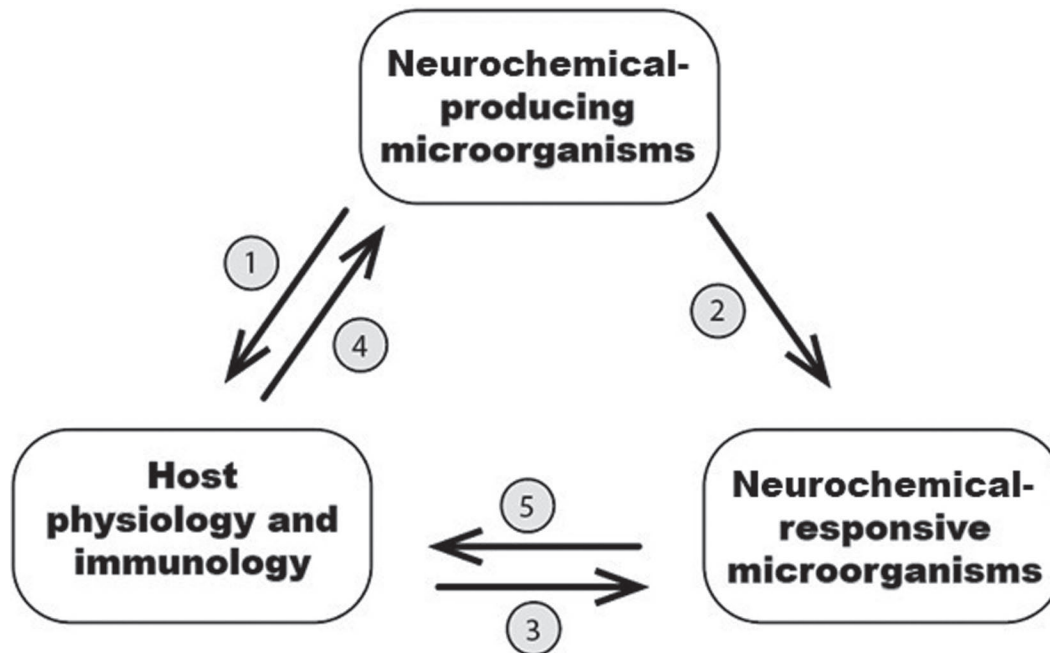
Stress can act through the central nervous system and effect changes to the microbiota through the sympathoadrenal and hypothalamic-pituitary-adrenal axes (Lyte, 2016b). These neurochemical axes release chemicals that can act on and change the microbiota. Changes in the host's microbiota may then feedback onto the host through the gut-brain axis to effect further changes. Simply stated, the microbiota and host are intimately linked in a bidirectional way (Figure 1). A physiological model drawn from our understanding of the interactions of microbes with the endocrine and enteric nervous systems has been developed and is termed the microbiota-gut-brain axis. Food ingested by the host can be metabolized by the microbiota in ways that generate specialized metabolites that have the potential to modulate host health (Sharon et al., 2014). Neurochemical metabolites can be taken up into

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**Figure 1.** Bidirectional nature of microbial endocrinology in which neurochemicals produced by the host and microbiota can influence each other. Neurochemicals produced by the microbiota can influence the host (1) as well as responsive microorganisms within the overall microbial community in the alimentary tract (2). The host response to neurochemicals may include physiological changes (intestinal motility, water reabsorption, secretory), behavioral changes (appetite, mood), or immunological states (i.e., inflammation). Similarly, the microbiota can respond to neurochemicals secreted from either the host (such as during periods of stress; 3) or other microorganisms (2) through altered physiology (i.e., infection, secretion, or environmental tolerance). Physiological changes in the host may feedback onto the neurochemical producers of the microbiota (4). Neurochemical responsive members of the microbiota also have the capacity to generate a response that affects the host (5). Together these pathways have the capacity to lead to reciprocal responses, as indicated by the paired arrows, and are part of the more generalized microbiota-gut-brain axis (Lyte, 2014).

the circulation or interact with the host locally at the level of the enteric nervous system. Some signals may be transduced to the brain, where they can influence cognition and behavior, whereas other signals may result in changes in the enteric system, which feedback on the microbiota in a bidirectional way.

Among many potential signals that can pass between a host and the microbiota, the catecholamine molecule norepinephrine (NE) is considered to be of particular importance. For the purposes of this limited review, NE will serve as a prototypical example for the manner in which bacterial-neuroendocrine interactions function within the larger context of microbial endocrinology. Norepinephrine normally functions as a neurotransmitter in the digestive tract, but can act as a hormone as well when it is released from the adrenal medulla in response to a stressful stimulus and carried through the blood to the ruminal and intestinal epithelia. Norepinephrine is among several chemical mediators that may play an important role in modulating host-bacteria interactions (Hughes and Sperandio, 2008). Although many investigations of NE actions on the intestinal mucosa have been carried out, the majority of these have

used rodent, rabbit, or guinea pig models and only a relatively small number have been conducted with livestock species, and those have been performed mainly on the porcine intestine. As few analogous studies exist in cattle, we reviewed host-bacteria interactions at the intestinal mucosa surfaces and NE-host-bacteria interactions, citing relevant studies in cattle when available.

### INTERDOMAIN COMMUNICATION IN THE INTESTINAL MUCOSA

Through the production and release of chemical signals or by physical or structural interactions, the various members of the ruminal and intestinal microbial communities are capable of communicating with each other across taxonomic boundaries, including interdomain signaling between prokaryotes (bacteria) and eukaryotes (e.g., fungi). This microbial signaling extends to cells of the host as well, which is the subject of the emerging field of microbial endocrinology. In the rumen, bacteria have been observed to make direct contact with the stratum corneum of the stratified, squamous ruminal epithelium as well as rumen

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