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Review: Microbial endocrinology: intersection of microbiology and neurobiology matters to swine health from infection to behavior

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From birth to slaughter, pigs are in constant interaction with microorganisms. Exposure of the skin, gastrointestinal and respiratory tracts, and other systems allows microorganisms to affect the developmental trajectory and function of porcine physiology as well as impact behavior. These routes of communication are bi-directional, allowing the swine host to likewise influence microbial survival, function and community composition. Microbial endocrinology is the study of the bi-directional dialogue between host and microbe. Indeed, the landmark discovery of host neuroendocrine systems as hubs of host–microbe communication revealed neurochemicals act as an inter-kingdom evolutionary-based language between microorganism and host. Several such neurochemicals are stress catecholamines, which have been shown to drastically increase host susceptibility to infection and augment virulence of important swine pathogens, including Clostridium perfringens. *Catecholamines, the production of which increase in response to stress, reach the epithelium of multiple tissues, including the gastrointestinal tract and lung, where they initiate diverse responses by members of the microbiome as well as transient microorganisms, including pathogens and opportunistic pathogens. Multiple laboratories have confirmed the evolutionary role of microbial endocrinology in infectious disease pathogenesis extending from animals to even plants. More recent investigations have now shown that microbial endocrinology also plays a role in animal behavior through the microbiota–gut–brain axis. As stress and disease are ever-present, intersecting concerns during each stage of swine production, novel strategies utilizing a microbial endocrinology-based approach will likely prove invaluable to the swine industry.*

Keywords: neurotransmitters, pig, microbiota–gut–brain axis, stress, behavior

Implications

The microbiota constitutes microorganisms found on virtually the pig's entire body sites exposed to the environment, including the gastrointestinal tract and lung, each with unique potential to affect pig health and production. Microbial endocrinology, the study of bi-directional communication between microbiota and host, provides an evidence-based conceptual framework immediately applicable in swine research for the design of testable hypotheses. Here we draw on microbiota research in swine and other animals, as well as agriculture, to introduce a new mechanistic way to understand how the microbiota may improve pig health and performance.

Introduction

Microbial endocrinology represents the union of two seemingly disparate fields; microbiology and neurophysiology (Lyte, 2016b). It is based on the recognition and production of neurochemicals that are common to both microbe and host, allowing these small molecules to serve as a common evolutionary-based language for bi-directional communication (Lyte, 2014). Indeed, the acquisition of the cell-based communication system that underpins the nervous system of vertebrates has been hypothesized to have occurred in large part due to horizontal gene transfer from bacteria (Iyer *et al.*, 2004). The central 'take home' message of this review is that microbial endocrinology-based mechanisms mediate the ability of bacteria and host to interact with each other in a bi-directional manner ultimately influencing host physiology ranging from susceptibility to infectious disease to behavior. In the latter case of behavior, such interactions which involve both gut and brain occur through what has become known as the microbiota–gut–brain (MGB) axis (Lyte and Cryan, 2014).

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It should be recognized at the outset that neurochemicals are widely dispersed throughout nature. Neurobiological concepts, such as those involving stress, are often perceived to be mainly relevant to animals. Stress, as experienced by plants, is of course well-recognized. However, how many porcine physiologists would be aware that in response to stress many plants make the exact same stress-related neurochemicals, namely the catecholamines norepinephrine and epinephrine, that pigs make (Kulma and Szopa, 2007)? In fact, plant-based processes from pollen germination to the stimulation of flowering utilizes neurochemistry (Roshchina, 2001). Further, catecholamines have also been shown in insects (Pitman, 1971) and fish (Guerrero et al., 1990).

More surprising, however, is that bacteria have been recognized for decades to be capable of producing quantities of neurochemicals that could affect host physiology. For example, the production of histamine by starter bacterial cultures used in the production of fermented meats such as sausages is a well-known food safety-related issue that has to be monitored during the production process (Restuccia et al., 2015). Indeed, the ability of bacteria that are often used as probiotics to produce acetylcholine goes back decades (Stephenson et al., 1947). The range of neurochemicals and neurohormones isolated from microorganisms is extensive and additionally have been demonstrated to show biological activity in mammalian cells. These include serotonin (Sridharan et al., 2014); catecholamines, such as norepinephrine and dopamine (Asano et al., 2012) (Tsavkelova et al., 2000; Malikina et al., 2010); progesterone (Schar et al., 1986); somatostatin (LeRoith et al., 1985); and even the primary inhibitor neurotransmitter in the brain, γ amino butyric acid (GABA) (Barrett et al., 2012). For a more complete discussion of the ubiquitous presence of neurochemicals throughout the various biological kingdoms see the comprehensive review (Roshchina, 2016).

Thus, it is increasingly being recognized that neurochemicals produced from both host and microbes represent a common language for communication enables the design of experiments to rigorously test mechanistic pathways of host–microbe communication. Further, it is critical to understand that the neurochemicals produced by both host and microbes, such as the biogenic amines, are *exactly* the same in structure as those that are constitutively produced by pigs' own neurophysiological system.

Given that both host and microbiota possess many of the same neurochemicals as well as the receptors with which to recognize them (Lyte and Brown, 2018), host health and microbe viability are therefore mutually affected by the evolutionary-based, bi-directional, neurochemical language which unites the two. This evolutionary bridge also provides for one of the mechanisms (and certainly not the only one) which composes the ability of the microbiota to influence host behavior through the MGB axis. It should be noted that the reader should expressly *not* draw the conclusion that microbial endocrinology is being proposed as the central inter-kingdom language of host–microbe dialogue. Multiple mechanistic pathways that are beyond the scope of this review, such as those involving immune-based mechanisms, are also critically involved in host–microbe interactions such as the MGB axis which has been shown to influence behavior (Lyte and Cryan, 2014).

At every stage of swine production microorganisms influence swine health. Hindgut microbiome viability is affected by swine nutrition, and microbial metabolites are influential of swine health. Incidence of gastrointestinal and respiratory infections as well as other diseases caused by pathogenic and opportunistic pathogenic microorganisms can be initiated by swine host stress. In 1930, growth of Clostridium perfringens, a human and pig pathogen, was perhaps the first microorganism to be reported to be affected by the host-derived catecholamine epinephrine. Since that time, there have been several clinical and literature reports of the effect of host neuroendocrine molecules on disease pathogenesis (Lyte, 2016a). Multiple reports in swine have likewise shown neurochemicals, including catecholamines, to strongly influence swine-specific pathogen growth and infectious processes in vivo, ex vivo and in vitro. Microbial metabolites, such as short-chain fatty acids (SCFA) from swine microbiota fermentation of dietary sources have the potential to affect stress physiology systems such as the hypothalamic–pituitary–adrenal (HPA) axis.

The pathways by which neuroendocrine molecules signal microorganisms to influence viability are diverse. For example, dopaminergic antagonists have been shown to prevent catecholamine-induced growth in Escherichia coli O157:H7, Salmonella enterica and Yersinia enterocolitica (Lyte, 2016a). Recently, it was demonstrated that probiotic strains of Lactobacillus spp. express transporter-systems which uptake environmental norepinephrine and serotonin (Lyte and Brown, 2018), further elucidating the mechanisms by which host-derived neurochemicals are able to signal responses by microorganisms. Lactobacillus spp. are commonly employed as probiotics in swine production (Valeriano et al., 2017), thereby warranting a microbial endocrinological approach to improve efficacy of these treatments in swine and tease apart the underlying mechanisms. Distinct actions of different catecholamines on swine pathogens can effect robust changes in microbial genetic expression and alter the conditions under which pathogens can survive. Norepinephrine and epinephrine induce 158 and 105 genes, respectively, of which only 18 are common to both catecholamines, in the porcine respiratory pathogen Actinobacillus pleuropneumoniae (Li et al., 2012). Norepinephrine can change Campylobacter jejuni, a foodborne pathogen, from a microaerotolerant to an aerotolerant organism (Bowdre et al., 1976). As stress is an everyday factor for swine from birth until slaughter, so is the constant bi-directional communication between swine host and microbiota. Microbial endocrinology will continue to prove important in the development of novel strategies in the improvement of swine health.

Microbial endocrinology-based mechanisms in infectious disease

Housing methodology
Housing methodology and animal handling are strong determinants of stress and therefore can profoundly affect

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swine health and meat quality. Through the lens of microbial endocrinology, stress physiology pathways represent avenues of bi-directional communication between the swine host and the animal's microbiome. As host stress results in the production of a trove of neuroendocrine-immune changes that can drive functional change in the microbiome, including opportunistic pathogens and transient microorganisms, to impact host health, it is important to understand how in the pig host–microbiome crosstalk may mediate swine health following housing and handling-related stressors. It is important to note that in this section, the terms 'indoor' and 'outdoor' housing are frequently employed. As it is impossible to strictly characterize these two systems into a dichotomy of stressors as many variants of both systems exist which can drastically alter swine stress (i.e. indoor slatted barren pens v. enriched-environment; freezing/hot v. optimal outdoor conditions), general comparisons between indoor and outdoor systems are avoided as much as possible.

Environmentally acquired infections

Canonical stress pathways in the pig, including the HPA axis and sympathoadrenal-medullary (SAM) system can be activated by environmental stressors which reflect on housing conditions. The reduction of housing stress through environmental enrichment has multiple positive effects on swine welfare, including improved behavior and lowering of disease susceptibility. Such beneficial effects are likely, in part, due to host–microbe communication as the stimulation of the HPA axis and SAM leads to the production of catecholamines which, at the site of the intestinal epithelium, can drive bacterial invasion and affect host behavior. The positive effect of norepinephrine on enteric bacterial pathogenesis and growth, first mechanistically described in rodents, as well as the role of norepinephrine in mediating susceptibility of host intestinal environment to infection has been observed in swine intestinal tissue. As the swine gut is a reservoir for *E. coli* O157:H7, a major source of foodborne illness in humans, it is important to understand what mediates the adherence and infection of pathogenic *E. coli* in swine. *Escherichia coli* O157:H7 adherence to the mucosa of swine cecal and colonic explants increased in the presence of norepinephrine in a concentration-dependent manner (Green *et al.*, 2004). Although swine infected with *E. coli* O157:H7 and other Shiga toxin-producing strains do not develop disease (Booher *et al.*, 2002), fecal shedding of this organism represents a route of exposure and transmission between infected and naïve animals (Cornick and Vukhac, 2008). It was separately shown that *Salmonella typhimurium* could be detected in the feces of naïve pigs following 2 h of exposure to a novel environment containing *S. typhimurium* (Hurd *et al.*, 2001). Interestingly, pigs orally administered norepinephrine or 6-hydroxydopamine, which causes the release of peripheral norepinephrine, resulted in increased fecal shedding of *S. typhimurium* and fecal load of this organism (Pullinger *et al.*, 2010), suggesting stress hormones released into the gastrointestinal tract affect swine enteric pathogens. Temporary housing conditions, including transport and lairage are well known to elicit stress reactions in swine and to increase fecal shedding of both enteropathogenic *Salmonella* spp. and *E. coli*. Hence, sanitation of housing conditions and swine stress likely interact to mediate transmission and infection of *E. coli* and *Salmonella* spp. in the swine intestinal tract.

Indoor v. outdoor housing: unique microorganismal food safety concerns

When presented with a purchasing decision between pork labeled produced from swine raised indoor or outdoor, consumers identified the outdoor production sourced pork to be more desirable (Edwards, 2005). Consumer preference includes international audiences as consumer panels in multiple European countries preferred outdoor to indoor-raised labeled pork despite being unable to discriminate the flavor of these two products (Dransfield *et al.*, 2005). Swaying of consumer purchasing decision based on perceived animal welfare has increased viability and created opportunity for outdoor pig production systems (Park *et al.*, 2017). It is important to consider that indoor and outdoor production may expose the pig to unique microbial organisms which can result in distinct swine microbiomes (Mulder *et al.*, 2009) which pose unique food safety concerns. *Campylobacter coli* and *C. jejuni* readily colonize the swine intestinal tract, with *C. coli* typically dominant in abundance to *C. jejuni*. Although poultry remain the primary source of *C. jejuni* in the incidence of human foodborne illness, there is concern that naturally occurring prevalence of *C. jejuni* in an outdoor environment may expose outdoor-reared pigs to this organism thereby decreasing food safety. In a study examining the detection of *C. jejuni* in the feces of outdoor-raised swine, 29.8% of all pigs in the study tested positive for *C. jejuni,* with considerable seasonal variation where 79% of pigs in the August trial were positive for *C .jejuni* (Jensen *et al.*, 2006). Campylobacteriosis foodborne illness in people from poultry also exhibits greatest incidence in the summer season (Schielke *et al.*, 2014). This presents the consideration of outdoor stress, such as heat during the summer in affecting the swine gut environment to be more hospitable to *C. jejuni.* In normal pigs (Stefanovic *et al.*, 1970) and those which suffer from malignant hyperthermia (Williams *et al.*, 1985), experimental heat stress induces strong release of catecholamines, including norepinephrine. Interestingly, at concentrations as low as 1.2×10^{-5}M, norepinephrine can convert *C. jejuni* from a strict microaerophilic organism to one that is aerotolerant (Bowdre *et al.*, 1976). Given that the mechanism of intestinal infection by *C. jejuni* involves the infiltration of intestinal epithelial cells, and that oxygen gradient increases greatly in a transverse-sense from intestinal lumen toward the epithelium, exposure of *C. jejuni* within the intestinal tract of a heat-stressed pig may encounter greater norepinephrine concentrations, becoming aerotolerant, which would allow it to infiltrate through the mucosa to establish infection.

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Microbial endocrinology: more than just the gut

Host epithelial surfaces are sites of constant interaction with the outside world. Distinct microbial communities have been identified on epithelia, such as the lung, external to the gastrointestinal tract. Respiratory infections in swine are of significant economic concern (Maes *et al.*, 2018). Like the gastrointestinal tract, the lung contains several functionally distinct layers including an overlying mucosa, is innervated by adrenergic and noradrenergic nerve fibers, and due to its function in gas exchange, is supplied with both oxygenated and de-oxygenated blood. The alveolus is the functional unit of gas exchange between the lung and blood in mammals, including the human and pig (Massaro and Massaro, 2002). The alveolar space is a site of bacterial invasion where the alveolar lining fluid (e.g. mucosa) overlies the lung epithelial cells. Intraalveolar catecholamine concentrations determined in the human lung demonstrated the presence of nor-epinephrine and epinephrine (Dickson *et al.*, 2015). Lung catecholamine concentrations were positively associated with incidence of respiratory infection. Catecholamines sti-mulate the growth of several swine respiratory pathogens, including *A. pleuropneumoniae* (Li *et al.*, 2012), *Mycoplasma hyponeumoniae* (Oneal *et al.*, 2008), *Bordetella bronchisepta* (Anderson and Armstrong, 2006) and *Pseudomonas aerugi-nosa* (Hegde *et al.*, 2009). Indeed, environmental enrich-ment, a factor which can reduce swine stress, can lessen swine susceptibility and improve clinical outcome (van Dix-hoorn *et al.*, 2016) to respiratory infectious agents. This would indicate that swine producers should apply the fra-mework of microbial endocrinology to diverse sites of host–microbe interactions, not just in the porcine gut.

Microbial endocrinology-based mechanisms of bi-directional brain-to-gut communication

The intimate association between the host central nervous system (CNS), which is composed of the brain and spinal cord, and the enteric nervous system (ENS), enables rapid changes in the neuroendocrine environment of the gut in response to stressors which originate outside of the gastro-intestinal tract. It is not well appreciated that the ENS represents a division of the nervous system that is composed of over 500 million neurons innervating the entire length of the alimentary canal (Furness *et al.*, 2014). Further, elements of the ENS project directly to the tips of the intestinal villi providing a means by which sensing of the external envir-onment, namely the lumen, is communicated to the CNS (Green *et al.*, 2003; Powley *et al.*, 2011). The longest nerve in the body, the vagus, provides one of the means by which the ENS maintains constant communication with the CNS. The role of the ENS as a sensory organ that plays a critical role in maintaining health has been amply demonstrated (for review, see Furness *et al.*, 2013).

It can therefore be hypothesized that a shared evolutionary-based language between microbe and host would also potentially involve elements of the host's nervous system and by extension host behavior which is under the control of the neuronal elements including those coming from the gut. Such interaction of microbiota with host gut and brain neurophysiology (Goyal *et al.*, 2015) would have implications extending from brain development to the behavior of adult animals including those in farm production settings.

The gut epithelium contains diverse chemosensory path-ways that detect neuroactive molecules found in the lumen, including bacterial metabolites, and enable bi-directional communication between host and microbiota (Breer *et al.*, 2012). Interaction between the gut and brain, an area of study which has received significant attention, is relevant in mediating changes in mental health by enteric pathologies (Lyte, 2013b). The inclusion and recognition that micro-organisms interact with elements of the ENS and thereby contribute to the information that is received by the brain concerning the physiological state of the gut has led to the use of the term the MGB axis. However, it should not be supposed that the recognition that the gut microbiota could impact host behavior is a relatively new field of study. In fact, the recognition of a role for the gut microbiota in behavior is very old (Bested *et al.*, 2013).

Intestinal fluid exchange, permeability and Yersinia enterocolitica infection

In the pig, common examples include the multifactorial environmental stressors which can cause diarrhea or predis-pose a pig to infection (Rhouma *et al.*, 2017). Central ner-vous system-initiated changes in the gastrointestinal tract, lung and other mucosal epithelial sites via neuroendocrine or sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) pathways can likewise cause func-tional and compositional changes in the microbiome. Many of the advances made in the understanding of the multiple routes of brain-to-gut-to-microbiota communication were discovered in studies utilizing rodents but hold value to swine as greater understanding of such pathways in the pig may provide novel strategies in improving pig welfare and production.

Stress can alter autonomic output from the CNS to the gut generally via regulation of the SNS and PNS activation. Mammalian sympathetic preganglionic neurons originate in the thoracic–lumbar regions of the spinal cord and synapse on, among other sites, post-ganglionic neurons within the sympathetic trunk. Like in other mammals, in the pig post-ganglionic axons ramify in the intestinal serosa and, at the nerve terminal, synthesize a variety of neuroendocrine molecules, including the catecholamine norepinephrine (Skobowiat *et al.*, 2010). Catecholaminergic signaling plays a critical role in the immediate response to stress, termed the 'fight-or-flight response' to affect gut motility as well as fluid secretion and uptake. Projection of sympathetic nerve fibers into the porcine cecal and colonic mucosa (Chen *et al.*, 2006) has implications for stress-induced diarrhea in swine as norepinephrine has been shown to stimulate chloride secre-tion in pig colonic explants.

Relatedly, SNS and PNS pathways are likely related to the stress-induced increase in swine intestinal permeability. 90%

of intestinal mucosal mast cells (IMMC), a type of leukocyte which affects intestinal permeability located in the lamina propria of the enteric mucosa, are either in direct contact or within 2 μm of a nerve fiber (Stead *et al.*, 1989). Sympathetic activation in response to acute stress has been shown to suppress degranulation of IMMC (Befus *et al.*, 1987) but increase IMMC histamine content (Eutamene *et al.*, 2003), whereas parasympathetic vagal activation (Bani-Sacchi *et al.*, 1986) during the recovery from stress can cause IMMC release of histamine and other cell-mediators, which is associated with increased intestinal permeability (Santos *et al.*, 2001). Prevention of mast cell degranulation blocked changes in piglet intestinal permeability following early weaning stress (Moeser *et al.*, 2007). Perturbations in pig intestinal permeability during chronic social stress (Li *et al.*, 2017) may then be suggested to be related to the repeated activation and degranulation of IMMC.

Together, the stress-induced cycle of sympathetic and parasympathetic activation which can cause norepinephrine spillover into the gut and histamine release via mast cell degranulation may be suggested to influence *Y. enterocolitica* infection in a brain-to-gut-to-microbiota microbial endocrinological mechanism. *Yersinia enterocolitica* contamination of swine is a major food safety concern (Virtanen *et al.*, 2012) and may occur in the period before slaughter (Fredriksson-Ahomaa *et al.*, 2000) which can include stresses of transport and social re-grouping. Norepinephrine can cause the growth of *Y. enterocolitica* (Lyte, 2016a), and this organism can induce host transcription of histidine decarboxylase (Handley *et al.*, 2006), which synthesizes histamine from ʟ-histidine. Histamine activation of histamine-2 (H2) receptor is associated with increased survival in response to *Y. enterocolitica* infection in mice (Handley *et al.*, 2006). The interplay between norepinephrine and histamine production in the gut and its relation to *Y. enterocolitica* infection is therefore likely complex, the exploration of which may prove important in managing infection in swine.

Neuroendocrine-immune brain-to-gut-to-microbiota communication

Regional variation of the porcine gastrointestinal tract can point to region-dependent mechanisms by which CNS-stress signals changes in the gut which alter the behavior of enteric pathogens. Porcine gut-associated lymphoid tissue in the small intestine is likewise innervated by sympathetic varicosities which synthesize catecholamines (Kulkarni-Narla *et al.*, 1999). Microfold (M)-cells within jejunal and ileal Peyer's patches sample gut intraluminal content and are exploited as sites of invasion by enteric pathogens such as *Salmonella* spp. Norepinephrine was demonstrated to increase internalization of *S. enterica* serovar Choleraesuis in porcine jejunal Peyer's patches *ex vivo* (Green *et al.*, 2003). This microbial endocrinological effect may be dependent on the bacterial strain as invasion of porcine Peyer's patches in jejunal explants by multi-drug resistant *S. enterica* serovar Typhimurium DT104 was not significantly affected by norepinephrine (Brown and Price, 2008). Pathogen exposure to norepinephrine before host contact can also determine catecholamine-induced changes in infectivity. As swine feces contains norepinephrine, pathogen-contaminated norepinephrine-rich feces from stressed pigs may expose naïve pigs to a more virulent pathogen. In a series of experiments where pigs were nasally inoculated with *S. enterica* serovar Typhimurium χ4232 grown in media with or without norepinephrine, compared to the pathogen grown without norepinephrine the pathogen grown with norepinephrine was found in greater concentration in ileocecal lymph nodes, colon, cecal contents and the cecum *in vivo* 24 h post-infection (Toscano *et al.*, 2007). In this same study, norepinephrine was also found to increase pathogen survival in the swine stomach environment *ex vivo*.

Catecholamines synthesized outside of the gastrointestinal tract in response to stress can also reach the gut lumen via bloodstream (Marra *et al.*, 2005) flow into capillaries within the gut wall. Indeed, epinephrine and norepinephrine effect distinct responses in enteric pathogen motility, growth and other genes important in the colonization and invasion of the host intestinal epithelium (Bearson, 2016). Norepinephrine in the gut may effect different immune-related changes in the intestinal mucosa which impact on the microbiota depending on whether the catecholamine is a product of neuronal stimulation or derived from an extra-gastrointestinal site, such as the adrenal medulla. Electrical stimulation of nerves in *ex vivo* porcine ileal tissue resulted in decreased luminal secretion of secretory immunoglobulin A (sIgA) (Schmidt *et al.*, 1999). Conversely, contraluminal application of norepinephrine in Ussing chamber-mounted porcine intestinal tissue stimulated the luminally directed secretion of sIgA (Schmidt *et al.*, 2007). Epithelial cell release of sIgA is important in modulating the mucosal microbial population and in the prevention of pathogen migration through the mucosa.

Microbial endocrinology-based mechanisms in behavior

Infection and behavior

Although pigs can serve as reservoirs of *E. coli*, this microorganism does not always cause overt signs of intestinal or systemic disease following challenge by certain pathogenic *E. coli* (Booher *et al.*, 2002). As such, it is interesting to speculate that the clinical demonstration of illness is not required in order to modulate pig behavior via a gut-to-brain mechanism even at the initial stages of infection. As adherence of *E. coli* to the swine intestinal mucosal epithelium represents the first stage of infection, in rodents it was shown that within 7 h following exposure to *Citrobacter rodentium*, a rodent colonic pathogen, mice developed anxiety-like behavior via vagal afferent signaling along the MGB axis (Lyte *et al.*, 2006). Likewise, behavior of pigs infected with *S. enterica* differed from non-infected pigs despite the absence of clinical symptoms of disease (Rostagno *et al.*, 2011). As *S. enterica* serovars *typhimurium* and

enteritidis can cause clinical disease in swine (Kim and Isaacson, 2017), and to negatively affect swine behaviors including animal movement and feed intake (Ahmed, 2015), a microbial endocrinological framework may identify novel gut-to-brain pathways of sub-clinical and symptomatic infections. Together, these results suggest that a reduction in swine stress may inhibit not only intestinal adherence and infiltration by enteric pathogens encountered in housing environments, but also neurocentric effects on the pig itself, such as alterations in behavior which can impair animal weight gain.

A role for microbial endocrinology in swine stress during early life

As pigs raised in indoor or outdoor environments have distinct gut microbiota compositions (Mulder *et al.*, 2009), rearing in an outdoor piggery may expose piglets to a unique set of factors, including distinct microbial organisms. Examination of the infection process and colonization dynamics of *C. jejuni* in the early life piglet intestinal tract revealed that *C. jejuni* genes encoding for motility and chemotaxis were critical for successful infection (de Vries *et al.*, 2017). Interestingly, epinephrine and norepinephrine have been shown to positively affect expression of chemotactic genes in several Gram-negative bacteria (Lyte and Ernst, 1992 and 1993), including *C. jejuni* (Xu *et al.*, 2015). Early life, typically classified as the pre-weaning stage, is widely appreciated to be a critical window wherein the developing neuroendocrinological-immune systems which regulate stress, including the HPA axis are highly plastic and dramatically affected by the gut environment. As the gastrointestinal tract is a continuation of the external environment, the quality of indoor and outdoor swine production systems likely have the potential to uniquely determine the developmental trajectory of stress resilience in the piglet and at later life stages in the pig. Indeed, plasma cortisol concentrations at baseline and following ear-piercing stress of piglets raised in an indoor piggery were greater than piglets raised in an outdoor space at 4 weeks/age (Yonezawa *et al.*, 2012). Moreover, piglets born in indoor standard farrowing crates displayed characteristics of chronic social stress in adulthood whereas these negative effects were absent in piglets born in an enriched environment (De Jonge *et al.*, 1996). Acute social stress in indoor-raised piglets causes an increase in norepinephrine (Bacou *et al.*, 2017), however, in the construction of this review no study was identified investigating acute stress-induced norepinephrine in outdoor-raised piglets. Germ-free rodents (i.e. rodents born in sterile conditions and completely lacking a microbiota) display exaggerated HPA axis response, including corticosterone, the rodent analog to cortisol, in response to acute stress (Sudo *et al.*, 2004). Exposure to a non-sterile environment during early life partly corrected the abnormal stress response, indicating early life as a time-sensitive window in which the gut microbiome strongly influences host stress physiology well into later life. It would be therefore of interest to examine whether piglet catecholaminergic response to stress is altered by indoor or outdoor rearing environment, and whether this affects susceptibility to intestinal infection by potential foodborne pathogens such as *C. jejuni*.

Relatedly, Yonezawa *et al.* reported that once outdoor-raised piglets reached 6 months/age, they were harvested and, in a taste panel, the meat of the outdoor-raised pigs was preferred (Yonezawa *et al.*, 2012). Although the authors did not attempt to demonstrate causation or correlation between early life stress response and meat quality, biochemical measures of pre-slaughter stress, including cortisol have been repeatedly shown to affect muscle chemistry and pork quality (Dokmanovic *et al.*, 2015). As such, it would be interesting to evaluate how early life stress management via the piglet microbiome attained in an outdoor housing system may affect the development of stress resilience potentially beneficial toward meat quality.

Social aspects of housing

Housing is strongly modulatory of social stress as decrease in space allowance per pig has been associated with increased aggressive behavior, skin injuries and cortisol (Hemsworth *et al.*, 2013). Moreover, the stress of mixing unfamiliar pigs which can cause re-structuring of hierarchal dominance/subordinance, can be reduced if increased floor space is given right after re-grouping (Hemsworth *et al.*, 2016). Swine intestinal transepithelial fluid transport is altered by chronic social stress as well as stress catecholamines. Pigs subjected to chronic social stress by re-grouping and reductions in pen floor space were shown to have increased ileal and colonic permeability (Li *et al.*, 2017). Norepinephrine, which increases following social stress (Koopmans *et al.*, 2005), differentially affects transepithelial ion exchange in the porcine small intestine and colon. In pig intestinal explants, chloride absorption in the small intestine increased via norepinephrine binding to enteric submucosal neuronal α-2-adrenergic receptors, whereas binding to α-1 adrenergic receptors in the colonic epithelium causes chloride secretion (Brown and O'Grady, 1997). Together these actions have been hypothesized to affect the composition and thickness of the small and large intestinal mucosae (Lyte *et al.*, 2018). Alterations to the integrity of the intestinal mucosa may affect enteric pathogen infection as the mucosal layer is an important barrier which inhibits migration of pathogens from lumen toward epithelial cells. As social stress has been shown to increase fecal shedding of *Salmonella* spp. in piglets (Callaway *et al.*, 2006), it is necessary to understand how social dynamics at different stages of life alter the intestinal neuroendocrine environment to affect host-pathogen interaction.

Microbial endocrinology-based mechanisms in nutrition

Environmental enrichment as a microbial mediator of host stress and neuroendocrine pathways

Aggression in pigs is of economic concern as social conflict can cause chronic stress, injury and reduced growth.

Substrates used in swine indoor-environmental enrichment include consumable products such as straw which serve as fermentable substrates into SCFA by hindgut bacteria. Straw as environmental enrichment has been reported to lessen (Lyons, 1995), have no effect (Arey, 1995) and even increase aggression in pigs (Morgan, 1998). Within indoor-production systems pens with a slatted floor or those with straw bedding as an environmental enrichment differentially altered the gut microbiota composition of sows (Kubasova et al., 2017), an outcome which the authors suggested was due to sow ingestion of straw. Butyrate, a microbial SCFA, has been shown affect host stress catecholamine pathways, including tyrosine hydroxylase which is the rate-limiting enzyme in the synthesis of dopamine, norepinephrine and epinephrine (DeCastro et al., 2005) and at high concentrations initiate a host HPA axis stress response (Gagliano et al., 2014). The variable effect of straw on aggression in swine is likely due to several factors among which may exist a role for microbe–host interaction, whereby the question of whether the pig chooses to ingest straw, and the amount of straw consumed may determine an effect of microbial butyrate production on host stress. It would be interesting to understand how indoor-housing enrichment materials, such as straw, may mediate a gut-to-brain pathway of behavioral regulation in the pig. As the pig colonic epithelium expresses monocarboxylate transporter (MCT)-1 (Ritzhaupt et al., 1998), which transports butyrate from the colonic lumen into circulation, it would be warranted to investigate if the pig blood brain barrier (BBB) also contains MCT-1 since endothelial cells of the rodent BBB express MCT-1 which transports butyrate from the circulation into the brain (Gerhart et al., 1997).

Microbial endocrinology and nutrition

The concept of a shared, evolutionary-based, language founded on the prevalence of common neurochemicals in the host, microbiota and foods enables a new microbial endocrinology-based perspective to be proposed by which nutrition can affect host health and behavior (see Lyte, 2013a review). Food contains a wealth of substrates that serve as neurochemical precursors and can be used by the gut microbiota to produce neurochemicals. For decades, it has been known that amino acids such as tyrosine are used in the biosynthesis of catecholamines and other biogenic amines, such as tyramine, which are found in foods (Rice et al., 1976). Fermented foods can also contain significant concentrations of microbial-produced biogenic amines which pose health hazards if consumed (Innocente and D'Agostin, 2002). For example, ingestion of foods which have utilized microorganisms as part of the manufacturing process can contain histamine and tyramine. Consumption of microbial-produced histamine or tyramine containing foods carries the risk of anaphylactic shock (Silla Santos, 1996) and hypertensive episodes (McCabe, 1986), respectively. Catechols found in foods have also been shown to increase the growth of foodborne bacterial pathogens, such as E. coli, as well as the enteric pathogen S. enterica (Freestone et al., 2007). Further, changes in the neuroendocrine environment of the gastrointestinal tract can elicit changes in the

microbiome as the release of catecholamines in vivo was demonstrated to cause compositional changes at the species-level of the gut microbiome (Lyte and Bailey, 1997). This highlights the bi-directional nature of host–microbial interactions that are part of a microbial endocrinology-based approach. As such, there is abundant evidence that neuroendocrine molecules and their precursors consumed via diet, as well as changes in host neuroendocrine physiology, can affect the microbiome.

Nutrition-dependent effects

Alteration in nutrition can dramatically impact the composition of the microbiota (Flint et al., 2017). However, whether nutritional-mediated changes in taxa result in altered production of neurochemicals by the microbiota within the gut has not yet been extensively studied. The ability of neurochemicals, produced by bacteria as part of a nutrition-based process, to influence host behavior has been shown. For example, fermentation of black bean soymilk using Lactobacillus spp. produced high levels of GABA that when fed to rats was as effective as fluoxetine in alleviating depressive-like behavior in a forced swim test (Ko et al., 2013). As such, it can be proposed that supplementation of diets with known neurochemical substrates can lead to the increased production of neurochemicals by relevant bacterial taxa. Identifying taxa capable of producing biogenic amines and designing a diet supplemented with appropriate substrates may provide a means by which the MGB axis may be enhanced to influence cognition, ameliorating the deleterious consequences of stress on behavior and cognition. It should be noted that it is beyond the scope of this review to fully address the role of nutrition as concerns microbial endocrinology. The reader is directed to a recent review on the subject (Lyte, 2013a).

Microbial endocrinology-based mechanisms in society and culture

Stress and disease in swine are of universal importance for all swine producers, yet these concerns are uniquely shaped, and sometimes aggravated by the socio-cultural and economic factors which differently govern swine production in different countries. Such external influences are relevant to swine host-microbe interaction and should therefore be considered in the application of microbial endocrinology to swine production. This section is presented within the Supplementary Material S1 of this manuscript.

Conclusions and future directions

Novel approaches which address stress and disease in swine are urgently needed as the intensification of global swine production to meet increasing consumer demand must also satisfy unprecedented consumer attention to food safety and safeguard herds from known and emerging infectious agents. The application of microbial endocrinology to swine production will likely help address these concerns as the effect of stress on swine neuroendocrine-immune physiology

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has been repeatedly demonstrated to affect swine susceptibility to disease and modulate pathogen virulence, both which feedback to affect host welfare and behavior. Indeed, a greater understanding of the bi-directional communication between host and microbiome not just within the gut but at other sites such as the lung could foster novel treatments against swine gastrointestinal, respiratory and other site-specific pathogens. Microbial endocrinological mechanisms that affect host-pathogen interaction are also of direct relevance to consumers as reduced pre-slaughter contamination can lead to increased food safety. As several major issues facing the swine industry involve the microbiome, a microbial endocrinology-based approach to understanding relevant host–microbe interactions will help inform strategies to tackle current concerns and prevent future problems.

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1751731119000284

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