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

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**Supplementary Material S1: Microbial endocrinology-based mechanisms in society and culture**

Non-nutritional feed additives are frequently regulated by governmental bodies, which impose strict no-tolerance policies of considerable economic impact on the import of pork tainted by banned substances. Ractopamine, one such non-nutritional feed additive, is banned in mainland China and the European Union but permitted in the United States, Japan, and some other countries. A beta-adrenergic agonist, ractopamine offers numerous benefits of economic value to the swine producer, including improved carcass leanness and feed efficiency (Apple, 2007). The effects of ractopamine on different stress parameters in swine, including norepinephrine and epinephrine are inconsistent. For example, although in-feed ractopamine treatment has been reported to more than double porcine resting plasma catecholamine concentrations (Marchant-Forde *et al.*, 2003), others have reported no such effect (Poletto *et al.*, 2010, Puls *et al.*, 2015). Moreover, dose-dependent effects of ractopamine were found to increase epinephrine but not norepinephrine following a stressor, such as handling or transport. After 34 days of in-feed ractopamine treatment, pigs were experimentally infected with *Salmonella typhimurium* and studied for 4 days post-infection (Edrington *et al.*, 2006). Interestingly, fecal shedding of *S. typhimurium* was lower each day post-infection in ractopamine-fed pigs compared to control animals which did not receive ractopamine. In addition, the authors found non-statistically significant effects of ractopamine on reducing *Salmonella*-positive ileocecal lymph nodes and liver samples. Importantly, *in vitro* incubation with 2μg/mL ractopamine was found to increase the growth of *S. choleraesuis* but not *S. typhimurium* in pure culture, an effect which likely requires further investigation in a medium similar to the porcine gastrointestinal *in vivo* environment. Not a single study was identified in the construction of this review which examined an effect of ractopamine on the swine microbiome, either from a compositional or functional standpoint.

Relatedly, one of the world’s largest pork producers, Smithfield Foods, once an American company was recently acquired by WH Group, formerly known as Shuanghui International Holdings Ltd., a Chinese entity. While Smithfield still receives ractopamine-fed pigs from outside suppliers, on the Smithfield company site it is stated that ractopamine has been eliminated entirely from the feed of company-owned animals (Smithfield Foods, 2015). Although ractopamine is officially banned in China, Chinese swine can be exposed to other, likewise banned, in-feed beta-adrenergic agonists such as clenbuterol (Yan, 2015). Like ractopamine, clenbuterol provides economic incentive to swine producers as it increases lean gain in pigs. Clenbuterol has been shown to increase norepinephrine in swine (Mersmann, 1989), however any effect on host-microbe interaction, pathogen growth or invasion, or microbiome is unknown. Therefore, unique socio-cultural and economic motivations in different countries may expose swine to distinct in-feed non-nutritive additives which can impact porcine stress physiology and potentially alter host-microbe interactions.

Farm structure and feed supply sources can vary significantly between countries. This is important as the nutritional composition of grains, soybeans, and other feed components may differ depending on crop growing conditions, and the effect of diet on microbiome composition and function is well-known. Global and regional leaders in pork production often source feed supplies from vastly different geographical origins. For example, within the European Union, France and Germany export feed grain to the Netherlands which has been estimated to import approximately 90% of its feed grain whereas 80% of feed grain in Denmark is domestically-sourced (Willems, 2016). China utilizes several feed components, including maize, dried distiller’s grains, wheat, soybean, and others which rely on both domestic-production and importation (Hoste *et al.*, 2013). Although little is known regarding how the chemical compositions of feed components grown in China vary between domestic regions (Li *et al.*, 2015) and compare to those grown in other countries (Huang, 2017), such comparisons may illuminate a relationship between incidence of swine disease and feed composition. Indeed, several naturally-occurring amino acids, minerals, prebiotic carbohydrates, and other components of feed ingredients have demonstrated roles in affecting host stress (Shen *et al.*, 2012), immune response (Medardus *et al.*, 2014, Schulte *et al.*, 2016), as well as microbiome composition (Umu *et al.*, 2015).

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