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Nutrition and pathology of weaner pigs: Nutritional strategies to support barrier function in the gastrointestinal tract☆

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ABSTRACT

Factors including sub-optimal nutrient and energy intake associated with lowered digestion and absorption, immature immune function, and psychosomatic factors caused by weaning can compromise intestinal barrier function through mucosal damage and alteration of tight junction integrity. As a consequence, pigs at weaning are highly susceptible to pathogenic enteric diseases such as post-weaning colibacillosis (PWC) caused by enterotoxigenic *Escherichia coli*. Dietary components such as protein, non-starch polysaccharides, and minerals are known to influence microbial growth in the gastrointestinal tract as undigested nutrients then become available for bacterial growth. This article reviews the association between dietary components, intestinal bacterial growth, intestinal barrier function, and enteric disease in weaner pigs with special emphasis on PWC. Evidence presented in this review indicates that the pathogen-originated diseases such as PWC are closely associated with dietary components and intestinal barrier functions can be maintained through manipulation of dietary protein, non-starch polysaccharides (NSP) and mineral levels. Especially, the use of a reduced protein diet for at least 7 days immediately after weaning, limitation of viscosity-increasing soluble NSP content while including 20–80 g/kg insoluble NSP source in the diet, and limitation of iron to 100 mg/kg are important dietary strategies to maintain intestinal barrier function and to minimise PWC.

1. Introduction

Weaning is the most significant event in the life of pigs as they are abruptly forced to adapt to nutritional, immunological and psychological disruptions. Sows' milk that is highly digestible and high in protein, fat and lactose is replaced by a dry and less-digestible starch-based diet (Williams, 2003) causing significantly reduced energy intake for maintenance of epithelial structure (Pluske et al., 1996), reduced transmucosal resistance (Spreeuwenberg et al., 2001; Boudry et al., 2004) and increased secretory activity in the small intestine (Boudry et al., 2004). Damage to the epithelial layers also decreases nutrient digestibility which provides more substrates for pathogen proliferation (Pluske et al., 2002), increases production of epithelial irritants such as ammonia (Heo et al., 2010), and increases pathogen attachment and penetration through the

Abbreviations: AA, amino acid; AGP, antibiotic growth promotants; BCFA, branched-chain fatty acids; CMC, carboxymethylcellulose; CP, crude protein; *E. coli*, *Escherichia coli*; ETEC, enterotoxigenic *E. coli*; FCR, feed conversion ratio; GIT, gastrointestinal tract; N, nitrogen; NDF, neutral detergent fibre; NO, nitric oxide; NSP, non-starch polysaccharides; PE, proliferative enteropathies; PIS, porcine intestinal spirochaetosis; PWC, post-weaning colibacillosis; SD, swine dysentery; TEER, transepithelial electrical resistance; ZnO, zinc oxide; ZO, zonula occludens.

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transcellular and paracellular pathways (Moeser and Blikslager, 2007). Innate and adaptive immune system of weaner pigs are yet to be fully developed and specialized while passive immunity from the sows' secretions are depleted at weaning (King and Pluske, 2003; Gallois et al., 2009). Young pigs also have to cope with psychological stressors at weaning such as separation from the sows, mixing with unfamiliar littermates and establishment of the social hierarchy within the group, which are known to increase cortisol release and corticotrophin-releasing factor receptor expression in the intestine of weaned pigs (Moeser et al., 2007). These stressors can increase paracellular and transcellular permeability and therefore eventually increases translocation of antigen and bacterial lipopolysaccharides across the mucosal barrier (Moeser et al., 2007; Smith et al., 2010). Since the ban of antibiotic growth promotants (AGP) in the European Union, numerous additives, management and dietary strategies have been studied to address the abovementioned consequences at weaning without AGP, and a substantial number of review papers dealing particularly with the range of feed additives available have been published (*e.g.,* Gallois et al., 2009; Lalles et al., 2009). Also, associations between amino acids and immune function are reviewed by Li et al. (2007), Ball (2008) and Seve et al. (2008).

Nevertheless, pigs at weaning remain susceptible to a number of bacterial and viral diseases but the most significant diseases that at least partly associated with the dietary components at weaning are the pathogenic bacteria-originated diseases, which can cause diarrhoea after weaning. These diseases include post-weaning colibacillosis (PWC) caused by serotypes of enterotoxigenic *Escherichia coli* (ETEC), the proliferative enteropathies (PE), caused by *Lawsonia intracellularis*, salmonellosis caused by *Salmonella* S., porcine intestinal spirochaetosis (PIS) caused by *Brachyspira piloscicoli*, and swine dysentery (SD) caused by *Brachyspira hyodysenteriae*. Among these pathogen-originated diseases PWC occurs in the first 2 weeks post-weaning period while others are generally occurs 4–6 weeks after weaning. While the ETEC and *Lawsonia intracellularis* specifically affect the small intestine, *Brachyspira piloscicoli* and *Brachyspira hyodysenteriae* are known to colonize in the large intestine (Hampson and Pluske, 2004; Pluske and Hampson, 2009). Therefore, different dietary components depending on their solubility, digestibility, viscous-forming ability and acid buffering ability can prevent or promote proliferation and colonization of these pathogens in the different part of the intestine. Although the data predominantly generated from the grower–finisher pig studies, including detailed aetiology of these disease and relationships between dietary treatment and onset, development and severity of the diseases are described elsewhere (Pluske et al., 2002; Hampson and Pluske, 2004; Pluske and Hampson, 2009) and will not be repeated in this review. Moreover, the pathogenic bacterial-originated diseases that are known to be influenced by dietary components but not common at immediate post-weaning period, such as PIS, SD and stomach ulcers caused by *Helicobacter S.* will also be excluded. Also, evidence for relationships between the PE and dietary components are not explored yet at a meaningful level and reviewed recently (Pluske and Hampson, 2009). Therefore, this review will concentrate on the role of nutrition on PWC at immediate post-weaning period (i.e., first 2 weeks after weaning) and will review recent evidence concerning the effects of dietary components that are responsible for intestinal barrier function under ETEC infection.

2. Intestinal barrier function

The mucosal epithelium is the primary 'barrier' between the internal milieu and the so-called "external environment", which consists of nutrients and harmful elements such as pathogens and antigens. This epithelial 'barrier' is protected externally by the unstirred water layer and mucus, and internally by the tight junctions between enterocytes. These external and internal barriers regulate selective passage of molecules, thereby protecting entry of pathogens and antigens into the system. Although, roles of the unstirred water layer as a barrier are generally not well understood, it is known that the unstirred water layer acts as a diffusion barrier and is known to limit the entry of fat-soluble components, except forms that are solubilized by micelles (Farhadi et al., 2003).

Underneath the unstirred water layer, a high molecular weight mucus layer covers the enterocytes and prevents damage by endogenous and bacterial proteases and acidic damage in the stomach and duodenum. In addition to this physical protection, the mucus layer is known to selectively block entry of macromolecules such as enzymes and antigens while being permeable to nutrients, and provides pathogen colonization resistance by adhesion of commensal bacteria in the luminal surface (Montagne et al., 2004). Therefore, mucus-bound commensal microbes are important for competitive exclusion of intestinal pathogens. For example, feeding probiotic strains such as *Bifidobacterium lactis* and *Lactobacillus rhamnosus* inhibited mucosal adhesion of *E. coli*, *Salmonella enterica* serovar Typhimurium and *Clostridium difficile* in the pig's small and large intestine via pathogen exclusion, displacement and competition *in vitro* (Collado et al., 2007). Also, the quantity and maturity of mucins covering the epithelial surface are important factors for optimum pathogen resistance. For example, as neutral mucins mature, sulphate and sialic acids are detected and these mature mucins are more acidic and viscous and are highly resistant to the bacterial proteases (Allen et al., 1982; Rhodes, 1989; Montagne et al., 2004). In a rat study, both experimental suppression of mucus production from goblet cells using colchicine and thinning mucous gel layer using mucolytic agent N-acetyl cysteine increased small intestinal permeability of fluorescein isothiocyanate dextran, showing the importance of mucous layer thickness and mucin production for intestinal barrier function (Boshi et al., 1996).

Enterocytes are adjoined by a paracellular diffusion barrier called a tight junction. Tight junctions consist mainly of the transmembrane protein complexes claudins and occludins and the cytosolic proteins zonula occludens (ZO-1, ZO-2 and ZO-3), which join the transmembrane proteins to the cytoskeletal actins. These structural proteins provide connections between the cytoskeletons of adjacent enterocytes (Mitic et al., 2000; Anderson, 2001). Alterations of tight junction protein formation and distribution through dephosphorylation of occludins, redistribution of ZO, and alteration of actomyosin