

## BOARD INVITED REVIEW

# Effects of dietary fatty acids on gut health and function of pigs pre- and post-weaning

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## Abstract

Fatty acids (FA) play a major role in relation to mucosal immune responses, epithelial barrier functions, oxidative stress, and inflammatory reactions. The dietary FA composition and the molecular structures (chain length and number of double bonds) influence digestion, absorption and metabolism, and the bioactivity of the FA. Piglets post-weaning having an immature intestine and not fully formed immune functions are very vulnerable to invading microorganisms. Manipulation of the milk FA composition via sow nutrition, or inclusion of dietary fat sources in the feed for newly weaned pigs, may be used as a strategic tool to enhance pig performance and their gut health and function pre- and post-weaning. Medium-chain fatty acids (MCFA) are absorbed directly into the portal blood and may contribute to immediate energy for the enterocytes. In addition, the MCFA, similarly to the short-chain fatty acids (SCFA), possess antibacterial effects and may thereby prevent overgrowth of pathogenic bacteria in the gastrointestinal tract. The essential FA, linoleic (LA) and  $\alpha$ -linolenic (ALA) FA, form the building blocks for the long-chain polyunsaturated  $n$ -3 and  $n$ -6 FA. The conversion of ALA and LA into  $n$ -3 and  $n$ -6 eicosanoids, respectively, influences the molecular structures of metabolites and inflammatory reactions and other immune responses upon bacterial challenges. Dietary manipulation of the lactating sow influences the transfer of the  $n$ -3 and  $n$ -6 polyunsaturated fatty acids (PUFA) from the sow milk to the piglet and the incorporation of the FA into piglet enteric tissues and cell membranes, which exerts bioactivity of importance for immune responses and the epithelial barrier function. Especially, the  $n$ -3 PUFA present in fish oil seem to influence the gut health and function of pigs, and this is of importance during the transition periods such as post-weaning in which piglets are prone to inflammation. The proportion of unsaturated FA in the cell membranes influences the susceptibility to oxidative stress. Oxidative stress accompanies infectious diseases, and the development of lipid peroxides and other reactive oxygen products may be harmful to the epithelial barrier function. Fatty acid peroxides from the feed may also be absorbed with other lipid-solubles and thereby harm the intestinal function. Hence, antioxidative protection is important for the enteric cells. In conclusion, manipulation of the dietary FA composition can influence the gut health and function in pigs and may support a normal immune system and modulate resistance to infectious diseases during especially stressful phases of a pig's life such as post-weaning.

**Key words:** barrier function, fatty acids, immunity, inflammation, microbiota, piglets

## Abbreviations

ALA	$\alpha$ -linolenic acid
BSH	bile salt hydrolase
CEH	carboxylic ester hydrolase
CLA	conjugated linoleic acid
COX-2	cyclooxygenase 2
DHA	docosahexanoic acid
EPA	eicopentanoic acid
ETEC	Enterotoxigenic <i>Eschericia coli</i>
FA	fatty acids
FFA	free fatty acids
GIT	gastrointestinal tract
LA	linoleic acid
LCFA	long-chain fatty acids
LCTG	long-chain triglycerides
LPS	lipopolysaccharide
lysoPC	lysophosphatidylcholine
MAG	monoacyl-glycerides
MCFA	medium-chain fatty acids
MCTG	medium-chain triglycerides
NOD2	nucleotide-binding oligomerization domain-containing protein 2
PFAD	palm oil fatty acid distillates
PL	phospholipid
PUFA	polyunsaturated fatty acids
ROS	reactive oxygen species
SCFA	short-chain fatty acids
TG	triglycerides
TLR4	toll-like receptor 4
TNF	Tumor necrosis factor

## Introduction

The interest in lipids for swine nutrition has historically emphasized the effects of dietary fat on the performance during various stages of production. For reproducing swine, quite a number of studies were performed on the influence of dietary *n*-3 polyunsaturated fatty acids (PUFA) in relation to sperm quality of boars as reviewed in NRC (2012). For gilts and sows during late gestation and lactation, focus has been given to the influence of lipid supplementation on milk production, milk lipid content, and performance and livability of the piglets (Pettigrew, 1981; Verstegen et al., 1998). For growers, effort has been devoted to the digestibility and energy value of lipids (Jørgensen and Fernandez, 2000) and the manipulation of the pork nutritional quality, emphasizing the FA composition to meet with the human health recommendation (Jakobsen, 1999; Wood et al., 2004). In addition, the impact of dietary level, type, and rate of inclusion of oil has been studied with regard to the meat quality of finishing pigs (Lauridsen et al., 2000; Wisemann et al., 2000). More recently, the interest in maximizing the use of supplemental lipids for pigs has increased because of the ever-increasing energy costs. Nutritionists strive to increase the dietary energy density to meet the requirements of the high-performing contemporary pigs via dietary lipids, and the lipid supplement can be obtained from various sources. However, an efficient utilization of the supplied lipid by the pig requires a proper gut function for the digestion and absorption. Furthermore, there is a potential in enhancing the knowledge of the role of fatty acids (FA) in early nutrition of pigs in relation to their gut development. Preterm birth of pigs which occur due to the large litter size of hyperprolific sow lines compromises gut structure, function, and immunology (Sangild, 2006) and

gut colonization (Kamal et al., 2019). The first objective of the present review was, therefore, to emphasize how the digestion, absorption, and metabolism of lipids are influenced by the composition of the dietary FA and the digestive capacity by the piglet. The intestine must adapt to dramatic shifts in nutrient supplies and profiles during critical phases such as during transition from the prenatal to the postnatal environment, and from suckling to weaning, and the second objective of this review was to study how the fatty acid composition of sow milk and weaner feed influence the transfer of FA to the piglet.

Research and commercial interests in pig nutrition currently focus on the gastrointestinal functionality and optimal immune function and regulation of microbiota, especially emphasizing on the period post-weaning, in which high antibiotic consumption is used to prevent enteric diseases (DANMAP, 2017). However, little focus has been devoted to the impact of lipid nutrition, and specifically the role of dietary FA, on gut health and development of pigs. The term ‘Gut health of pigs’ has been addressed in the recent reviews (Celi et al., 2017; Pluske et al., 2018). A general conclusion was that this term is defined not only by the lack of enteric diseases but also by the intestinal function in which key factors are diet, effective structure of the gastrointestinal barrier, the host interaction with the intestinal microbiota, effective digestion and absorption of feed, and effective maturation and development of innate and acquired immune functions. With this current understanding and interpretation of gut health in pigs, the aim is to provide a literature review of the current knowledge of lipid nutrition and the impact on gut health and function of pigs, specifically addressing how dietary FA can influence intestinal microbiota, immune function, and epithelium function of the piglet.

## Lipid Digestion, Absorption, and Metabolism

Most of the dietary FA are bound to triglycerides (TG), which is quantitatively the most important lipid fraction of the pig diet contributing with more than 95% of the dietary fat. In addition, the dietary fat consists of phospholipid (PL), commonly present as lecithin, and minor contents of cholesterol, cholesteryl esters, and fat-soluble vitamins. However, the PL and cholesterol present in the digestive tract are derived not only from the diet but also from the bile. Further, it should be mentioned that short-chain fatty acids (SCFA, i.e., acetate, propionate, butyrate), which can be added as feed additives, are produced via microbial fermentation of nondigestible carbohydrates and digestible starch in the hindgut and contribute with energy supply for the host and the colonocytes (Sciascia et al., 2016). It should be noted that the absorbed energy is much higher from glucose than from SCFA (Bach Knudsen, 2011); however, the SCFA are a bioavailable energy source for the colonocytes (Bach Knudsen, 2005).

A proper gastrointestinal function is a prerequisite for the digestion and absorption and metabolism of FA in monogastrics as can be described elsewhere (Lauridsen, 2017). In brief, the digestion of dietary lipids begins with an emulsification in the stomach in which partial degradation of the TG is performed. The enzymes involved are lingual lipase, secreted from the salivary gland, and gastric lipase, secreted by the gastric mucosa. These enzymes are, however, incapable of hydrolyzing PL. Both enzymes hydrolyze the FA in the sn3-position of the TG molecule giving diacylglycerol and FA (e.g., non-ionized long-chain FA).

The major digestion of TG results from hydrolysis with pancreatic lipase. The lipid emulsion enters the small intestine

as fine lipid droplets, and the combined action of bile and pancreatic juice brings about a marked change in the chemical and physical form of the ingested lipid emulsion. Most of the digestion of TG is brought about by pancreatic lipase in the upper part of the small intestinal lumen, implying a general conservation of approximately 75% of the FA located in the sn2-position (Mu and Høy, 2004). The overall target of the lipid digestion is the formation of lipid emulsions, which can be further processed for uptake (absorption) by the enterocytes. Mixed micelles are formed upon the presence of bile to the lipid emulsion, facilitating the transport of the lipid components into the enterocytes. PL in the intestinal lumen will distribute between the mixed micelles and the TG droplets and by the action of pancreatic phospholipase A<sub>2</sub> at the sn-2 position of the PL, yielding an FA and a lysophosphatidylcholine (lysoPC).

Fat-soluble vitamins, commonly supplemented to the feed in their ester forms, must be completely hydrolyzed within the intestinal lumen to their alcohol forms which can be taken up by enterocytes (Lauridsen, 2017). The hydrolysis requires the catalytic action of enzymes present in the pancreatic juice, and the enzyme, which appears to be mainly responsible for the hydrolysis of the ester bond of vitamin E and vitamin A, is the carboxylic ester hydrolase (CEH) (Lauridsen et al., 2001).

During normal gut function conditions of the pig, the digestion and absorption of TG are very efficient. However, stress related to the weaning of pigs from the sow and preterm birth may compromise the intestinal functional capacity for digestion, absorption, and metabolism of the dietary lipids. While the apparent digestibility of lipid by suckling piglets is high (96%; Cranwell and Moughan, 1989), it decreases after weaning from 65% to 80% (Cera et al., 1988). The reason is probably due to the function of gastric lipase, which is responsible for 10% to 30% of the hydrolysis of the dietary TG. The enzyme plays an important role in the lipid digestion, particularly in neonates provided with milk lipid which is completely digested due to the gastric lipolysis. Compromised pancreatic function may also result in reduced pancreatic lipase production leading to maldigestion and malabsorption of lipids as demonstrated in a young porcine exocrine pancreatic insufficient model (Goncharova et al., 2014).

The uptake of the various lipid components by enterocytes, which is both passive and active, is reviewed in detail by Iqbal and Hussain (2009). To be absorbed into the enterocytes, the lipid fractions have to cross two barriers: the unstirred water layer and the brush border membrane. The solubility of FA and monoacyl-glycerides (MAG) in an aqueous medium is extremely low, and very few molecules will, therefore, gain access to the brush border membranes. However, the micellar solubilization of MAG and FA (together with TG- and PL-residues, lysoPC, lipid-soluble vitamins, free cholesterol, and bile acids) greatly enhances the number of molecules available for uptake by the enterocytes.

Digestion, absorption, and metabolism of dietary lipids are affected by the FA composition of the dietary-derived lipids, specifically the degree of saturation of the FA and the carbon chain length, as well as the position of the FA on the TG molecule. In general, unsaturated dietary lipids are more digestible in pigs than saturated lipids, which can be attributed to the feasibility by which lipase can get access to the TG as explained by Ravindran et al. (2016). Hence, saturated long-chain fatty acids (LCFA) may exert inhibitory effects and unsaturated LCFA may increase lipase activity, and hence influence the lipid digestion.

Odle (1997) summarized the general contrast of the utilization of medium-chain triglycerides (MCTG) and long-chain triglycerides (LCTG) and claimed that the differences in

their digestion, absorption, and metabolism stem largely from the differences in physical chemistry. To recapitulate the major differences, the hydrolysis of MCTG is more rapid and complete than the hydrolysis of LCTG. MCFA exert less inhibitory effect on the pancreatic lipase, and medium-chain-2-monoacyl glycerides (MC-2-MAG) isomerize more rapidly than those of the long-chain length, thereby facilitating rapid and complete hydrolysis. Further, for LCTG to penetrate mucosal cells, the LCTG must be emulsified, then hydrolyzed within the gut lumen, and then the resulting LCFA and 2-MAG must be mixed with bile salts to form mixed micelles to be absorbed through the unstirred water layer and into the enterocyte. Overall, the discrepancy means that FA with a chain length of 12 carbon (C) or below will be absorbed via the portal blood, whereas FA with a chain length of 14 C or above are absorbed via the lymph. Hence, MCFA being saturated, and FA with 6 to 12 C, which occur naturally in the form of MCTG in milk fat and some vegetable fat sources, such as coconut and palm kernel oils, represent immediately available sources of energy. FA with more than 14 C and above are re-esterified to triglycerides within the enterocyte and delivered to the lymph. That is, with the increasing length of FA in the dietary fat, an increasing proportion of the FA can be absorbed into the lymph and less into the portal blood. In the case where only free fatty acids (FFA) are administered, more FA are transported via the portal system, whereas more FA are transported via the lymphatics when both FFA and MAG are administered (Mu and Høy, 2004). When lipids are given in the form of TG rather than FFA, less FA are transported via the portal vein (Mu and Høy, 2004). Milk TG contains a high proportion of C16:0 and over 70% of this FA is esterified to the sn-2 position. In comparison, the C16:0 in vegetable and nonmilk fats is predominantly esterified in the 1,3 positions, while mono- and polyunsaturated FA are usually esterified at the 2-position of the TG. Hence, hydrolysis of the TG milk by lipases results in the formation of 2-monopalmitin, whereas hydrolysis of vegetable fat sources produced unesterified C16:0 (Innis et al., 1997). When considering lipid sources for the development of milk formula for piglets, or special diets for premature or low-birth-weight piglets, the impact of TG structure can be considered in terms of lipid digestibility.

Digestibility of dietary lipids can be assessed by determination of the apparent or true digestibility in which the difference between ingested lipid in feed and excreted lipid in feces is assessed. This gives an estimate of the amount of digestible lipids originating from the diet because of the exclusion of endogenous losses of fat. The endogenous loss occurs due to loss of bile acids, desquamated cells, structural lipids from mucosa, and cholesterol and may vary not only with dry matter intake but also with source and level of dietary lipid (Kil et al., 2010). The apparent total tract lipid digestibility varies between 25% and 77% (Noblet and Van Milgen, 1994) and is limited to the true total tract digestibility rather than ileal digestibility, which ignored the microbial synthesis of FA in the gut. The level of endogenous fat was determined in a study using increasing levels of dietary fat for ileal-fistulated pigs (Jørgensen et al., 1993), and it was concluded in their study that the digestibility of fat increased with increasing levels of fat and that only small differences between ileal and fecal digestibility of FA were present. Addition of lipid to diets can, furthermore, enhance protein digestibility due to the slowing of the passage rate in the intestine by lipid, which is in contrast to the effect of fiber (Kil et al., 2010). As recommended in NRC (2012), more lipid research is needed to determine the standardized ileal digestibility of lipid sources

in pigs, especially in nursery pigs (NRC, 2012). Due to changes in the intestinal microbiota as described below, exclusion of antibiotic growth promoters from diets for pigs may, in fact, influence the digestibility of lipid and lipid-soluble vitamins in broilers (Knarreborg et al., 2002, 2004), which may in fact also apply for pigs.

While many studies on lipid digestibility have been conducted with growing pigs, fewer studies are available concerning pig during the weaning period (Christensen, 2005). Therefore, the bioavailability of various lipid sources was assessed by the determination of the apparent digestibility of pigs during the weaner and the grower period (Table 1; Christensen, 2005). The same pigs entered in total six consecutive balance periods, and in total 48 pigs from eight litters with an initial weaning weight at 28 d of age of 8.3 kg were used. The experiment used six different lipid sources at a level of 5%, and lipid in diets and feces was extracted after modification of Bligh and Dyer (1959) method before acid hydrolysis (Lauridsen et al. 2005, 2007a). Surprisingly in this experiment, the digestibility of fat was higher in the pigs during the weaner phase than during the growing phase (Table 1). This result was in contrast to other studies showing that lipid digestibility is reduced during the first week post-weaning but increases with age and gradually returns to a 90-% range by 4 to 6 wk post-weaning (Azain, 1993). Furthermore, when considering lipid digestibility, rapeseed oil and coconut oil were good alternatives to animal fat for the weaner pigs while palm oil fatty acid distillates (PFAD) and palm oil had similar lipid digestibility as animal fat, and fat blend and the vegetable oil mix (consisting of 50% palm oil mix and 50% palm oil) were not suitable (Lauridsen et al., 2005 and Table 1). Dry matter digestibility was also affected, while no significant effects of dietary treatments were obtained on protein digestibility (Table 1) or the growth performance of the pigs in the digestibility trial (Christensen, 2005). More recently, a number of studies have been performed to evaluate the lipid digestibility and energy value of fat blends with varying proportions of FFA for young pigs (Liu et al., 2014; Kerr et al., 2016; Lindblom et al., 2017). Some of these studies have included not only measures of lipid digestibility and energy value of the dietary lipid sources but also the impact on gut health and function as will be addressed below.

In summary, the composition of FA as well as the positional distribution on the TG affect the digestion, absorption, and metabolism, and these factors exert impact for the transfer of the various FA to the piglets as described in the next section.

## Transfer of FA to Piglets

Piglets' digestibility of the lipid in sows colostrum and milk is >90% (Azain, 2001), and colostrum and milk are as such an efficient vehicle in the transfer of FA. Supply of lipids via colostrum and milk is an important energy source for the newborn piglet, as it should be remembered that 95% of the energy in the TG is attributed to the FA, while the glycerol part contains 5% energy. Lipid nutrition is important for porcine growth and development, and the FA are crucial components of biological membranes, are involved in cell signaling, and act as substrates for various enzymes. Irrespective of the genetic changes (e.g., development of hyperprolific sows), only minor changes in sow colostrum and milk content of macronutrients have appeared over the past 30 yr, and, for the total lipid content, an increase from 6.5% to 7.5% has been reported (from the 1980s to 2010s) (Zhang et al., 2018). While many research studies were performed with the aim to enhance the total lipid content in colostrum and milk of sows to improve litter performance, more recent interest has been devoted to the colostrum and milk FA composition and more specific biological responses. The FA present in the sow's colostrum and milk are commonly the LCFA (C14:0, C16:0, C16:1, C18:0, C18:1, C18:2). The mechanisms involved in the FA uptake by porcine mammary epithelial cells are still largely unknown (Zhang et al., 2018); however, the sow milk FA composition is highly influenced by the dietary FA composition (Lauridsen and Danielsen, 2004). Therefore, it may be possible to transfer specific FA into sow milk and colostrum via dietary manipulation, for instance, the presence of MCFA (C8:0, C10:0, C12:0) and the long-chain PUFA (eicopentanoic acid [EPA] and docosahexanoic acid [DHA]) on the expense of some of the commonly present FA. In addition, the inclusion of dietary lipids in lactational diets influenced the FA profile of the tissues of the progeny during suckling, and the effect was in fact maintained on the FA composition during the post-weaning period (Lauridsen and Jensen, 2007). According to the metabolism of MCFA by the liver and the limited inclusion in chylomicrons, supplementing lactating sows with MCTG would be unlikely to markedly impact the milk MCFA content as a means of supplementing suckling pigs (Zentek et al., 2011). However, supplementation of coconut oil (8%) to lactational diets increased the proportion of C12:0 (with 0.5% to 1.3% unit increase) in adipose tissue of the piglets during suckling and post-weaning, whereas this MCFA was not detectable in the liver of the piglets (Lauridsen and Jensen, 2007). From the same animal experiment of this study, a tendency to improved litter

**Table 1.** Effect of supplemental lipid sources on apparent fecal digestibility (%) of dry matter, fat, and protein (N × 6.25) in weaned and in growing pigs<sup>1</sup>

	Animal fat	Palm oil mix	Palm oil	Vegetable oil mix	Coconut oil/Fat blend <sup>2</sup>	Rapeseed oil	SE
<b>Weaners</b>							
Dry matter <sup>3</sup>	86.2 <sup>b</sup>	87.9 <sup>a</sup>	87.8 <sup>a</sup>	87.2 <sup>ab</sup>	87.5 <sup>a</sup>	87.6 <sup>a</sup>	0.4
Fat <sup>4</sup>	75.1 <sup>bc</sup>	77.0 <sup>ab</sup>	76.4 <sup>b</sup>	72.8 <sup>c</sup>	80.0 <sup>a</sup>	80.2 <sup>a</sup>	1.1
Protein <sup>3</sup>	84.2	85.3	85.0	84.6	85.0	84.3	0.7
<b>Growers</b>							
Dry matter <sup>3</sup>	81.2	82.0	81.7	81.2	80.2	82.2	0.5
Fat <sup>4</sup>	65.5 <sup>bc</sup>	67.8 <sup>b</sup>	64.0 <sup>bc</sup>	59.1 <sup>d</sup>	62.1 <sup>c</sup>	73.5 <sup>a</sup>	1.5
Protein <sup>3</sup>	76.9	77.5	76.7	75.9	75.1	76.5	1.2

<sup>1</sup>A total of six balance periods were included in the study: For weaned pigs, balance periods were from days 30 to 35, days 37 to 42, days 44 to 49. For growing pigs, the three balance periods were initiated when pigs weighed 51.7 kg, 67.0 kg, and 82.1 kg, respectively.

<sup>2</sup>Coconut oil was used for weaned pigs and fat blend for growing pigs.

<sup>3</sup>Unpublished data (Christensen, 2005).

<sup>4</sup>Lauridsen et al. (2005, 2007a).

<sup>a,b,c,d</sup>Means with different letters within a line are significantly different (P<0.05)

weight gain was obtained when feeding the lactating sows with coconut oil rather than fish oil (Lauridsen and Danielsen, 2004). Furthermore, oral supplementation of coconut oil to low-weight piglets tended to increase body weight during the first week (Manzke et al., 2018), and in another experiment of this study oral supplementation of rice-bran oil to pigs increased the weaning weight (Manzke et al., 2018). Unpublished data (C.L., personal communication) showed that feeding sows with lipid sources at a level of 8% of octanoic acid (4%) in combination with fish oil (4%) increased the sow milk concentration of C8:0, which was present with 0.12%, whereas when other dietary treatments (8% of either coconut oil, fish oil, or sunflower oil) were provided, the relative proportion of C8:0 was 0.04%. Feeding coconut oil (8%) to sows increased the concentration of C12:0 (present with approximately 5%) and a slight influence on the concentration of C10:0, and the concentration of EPA and DHA was increased in sows' milk when the fish oil treatment was provided. In addition, the dietary fatty acid composition positively affected the concentration of immunoglobulins in colostrum and milk, which may be attributed to the immunomodulatory effects of the FA (Quesnel and Farmer, 2019). In the same animal experiment, a low mortality of piglets suckling sows fed the 4% octanoic acid plus 4% fish oil was found, and, in general, the performance was positively influenced by sow's intake of MCFA and negatively with LCFA (Hansen et al., 2012). Likewise, comparison of the feeding of MCTG with LCTG to sows in the late gestation phase showed an increased survival rate of neonatal piglets (Azain, 1993; Jean and Chiang, 1999). Survival rate was highest in piglets with a birth weight of less than 900 g due to feeding of MCTG (Azain, 1993). As obtained in the study by Hansen et al. (2012), Lauridsen and Danielsen (2004) also obtained lower performance in terms of litter weight gain by the inclusion of fish oil (8%), compared with other dietary lipid treatments, and ascribed this to impaired milk production in sows fed the LCTG from fish oil. In a more recent study by Jin et al. (2017), however, the inclusion of soybean oil and fish oil (around 3% to 4%) in diets for sows during late gestation and lactation resulted in improved growth performance of nursing piglets by increasing milk fat input (when compared with no fat inclusion or palm oil). The authors concluded that fish oil consumption might benefit the piglets via increasing bioavailability of *n*-3 FA and immunoglobulins (IgG and IgM) secretion.

Not only in suckling pigs but also in weaned pigs, the difference in chain length of dietary FA seems to influence the performance of the piglets (Azain, 1993) as explained by the complexity in the digestion and absorption. This may be even more challenging upon weaning and especially during weaning of piglets at an early age or low weight. During the immediate post-weaning period, piglets may suffer from reduced activities of enzymes important for the digestion and hydrolysis of the FA from the dietary TG. As shown by Jensen et al. (1996), there was a dramatic reduction in lipase, colipase, and CEH in pancreatic tissue during the first 2 wk post-weaning (when pigs were weaned at 28 d of age). Little is known about the possibilities of influencing the lipid absorption capacity of piglets post-weaning via manipulation of the maternal diet. However, assessment of the lipid absorption capacity in terms of pancreatic enzyme activity, hormonal regulation, and bile salt concentration in piglets showed no effects of differences in dietary fat source (coconut oil, rapeseed oil, fish oil, or sunflower oil) but high differences in age of piglets (Lauridsen et al., 2007b). More studies have focused on dietary lipid manipulation for pigs post-weaning in order to enhance lipid bioavailability. Combined

dietary supplementation of MCTG with different lipases can be a strategy to enhance lipid bioavailability. In weaned pigs, this combination improved the daily live weight gain (Dietrick et al., 2002), and, as concluded by subsequent reviews (Zentek et al., 2011; Hanczakowska, 2017), the inclusion of MCTG and MCFA in pig nutrition seems to improve piglet performance. It should be noted, however, that free MCFA have a strong odor (i.e., an intense, goatish smell of nonesterified FFA), which may have a negative impact on the feed intake. This challenge may be overcome by using MCTG, potentially combined with lipases to enhance enzymatic release of MCFA in situ in foregut. Other dietary strategies for enhanced FA transfer could involve the addition of emulsifiers to the diets, whereby a bridge between water- and fat-soluble materials is formed, leading to improved fat utilization. The endogenous produced emulsifiers in the gut are primarily bile acids and salts, which can reduce the tension of the oil-water interface and also activate pancreatic lipase, while a long list of nutritional emulsifiers includes lecithins and mono- and diglycerides (Ravindran et al., 2016). Crude lecithin is a complex mixture of various species of surface active phospholipids, consisting of hydrophobic and hydrophilic portions, and has gained interest to improve fat digestibility and energy efficiency in pigs and broilers (Upadaya et al., 2019); however, the obtained effects seem to depend on the physiological status of the pig, that is, young pigs or pigs with compromised gut function may obtain more benefits of natural lecithin provision than older or more mature pigs. With regard to the transfer of EPA and DHA, provision via seaweed or algae biomass may be a more sustainable dietary strategy than fish oil (Schmid et al., 2018) and more bioavailable if these LCFA are present in the form of PL rather than TG, such as in some marine sources (e.g., krill oil) (Schmid et al., 2018).

Although it can be concluded that inclusion of MCTG in early nutrition of piglets is an important energy supply and has been shown to improve pig performance, there is a great interest in long-chain PUFA, as these FA are incorporated into the cell membranes and thereby can have a major impact on the piglet's gut health and function. The essential FA (linoleic acid [LA] and  $\alpha$ -linolenic acid [ALA]) cannot be synthesized endogenously by the animals and must, therefore, be provided exogenously from dietary sources. The parent compounds of the *n*-6 and *n*-3 FA families are LA (C18:2*n*-6) and ALA (C18:3*n*-3) which are present at a rich amount in many plant oils. LA and ALA are the essential FA from which arachidonic acids, DHA, and EPA are formed by desaturation and chain elongation; however, the conversion efficiency is in fact considered limited (Lauridsen and Danielsen, 2004; Lauridsen, 2017). In a recent study, the transfer of FA from hemp oil provided sows to piglets was studied, and the maternal supply of especially ALA and stearidonic acids via the hemp oil, in fact, showed that piglets were able to convert these FA to longer-chained PUFA (C20:5*n*-3 and C22:5*n*-3) (Vodolazska and Lauridsen, 2020). Well-documented effects of fish oil (characterized by the presence of the longer chained *n*-3 PUFA) in relation to the health and immunity of humans (Calder, 2017) have inspired to research in relation to pigs' health and immunity. Thus, many studies have been performed on the effect of dietary sources of fish oil (Møller and Lauridsen, 2006; Lauridsen et al., 2007c) for sows and piglets to enhance incorporation of EPA and DHA into membranal phospholipids and the effect on immune cell responses. In general, alteration of dietary PUFA intake substantially influences membrane structure through incorporation into cellular membrane phospholipids in many tissues, including the intestine of newborn piglets; an effect

that seems to be dose and time dependent (Hess et al., 2008). Lauridsen (2010) studied the comparison of tallow, sunflower, and fish oil at a 5-% inclusion to piglet diets from weaning (day 28 of age) until euthanized at 56 d of age and found a significant increase in the concentration of C20:5 and C22:6n-3 in the intestinal epithelium and mucosa of pigs fed fish oil when compared with other dietary treatments.

Hence, via early nutrition, it is possible to transfer FA to the piglet pre- and post-weaning, and the efficiency in the transfer of the FA may be enhanced via different nutritional tools. While TG composed of SCFA and MCFA may benefit piglet growth due to their immediate uptake into the blood, the early nutrition with LCFA can affect intestinal tissues' and cell membrane FA composition. Before describing the impact of the various FA for the host's responses, the interplay between the gut microbiota and the FA present in the gut digesta is explained.

## Intestinal Microbiota

Pigs are born sterile but quickly develop an established microbiota which is acquired from the oral-fecal transmission in their post-birth environment and via the milk and feed. After the initial colonization, the gut microbiota remains relatively stable until weaning. However, when the sow milk is no longer available, profound and marked microbial changes are reported, appearing during the first 7 to 14 d after weaning (Heo et al., 2013). One of the most important factors affecting the total population and diversity of the intestinal microbiota is the diet composition; however, little is known regarding the effect of dietary lipid on the microbiota composition in pigs. Comparing treatments using either a combination of bovine fat and milk fat globule membranes or vegetable fat in a study using pig as model for human infants, Huërou-Luron et al. (2018) showed increased *Proteobacteria* and *Bacteroides* while decreased *Firmicutes* phyla in fecal samples of piglets when milk fat rather than exclusively vegetable lipids was provided to the newborn piglets.

Most research in pig nutrition focusing on changes in the microbiota via dietary lipids has so far been attributed to the SCFA and MCFA, which are well-described to exhibit antibacterial effects and were initially used in the preservation of feed (e.g., protecting feed from microbial and fungal destruction or to increase the preservation effect of fermented feed; Woolford, 1975). Several studies have been performed to study the effect of applying organic acids such as lactic-, formic-, and propionic acid to the diet to reduce the pH of the intestinal digesta in order to reduce pathogenic overgrowth and in that way to control post-weaning diarrhea in pigs (Metzler et al., 2005; Vondruskova et al., 2010). When compared with the mature pig having a pH range of 2.0 to 3.0, the gastric pH in suckling and weaned piglets ranged between 2.6 and 5.0. It is important to maintain a low gastric pH not only to prevent the overgrowth of pathogens but also to optimize nutrient digestibility (Canibe et al., 2001). Following dietary intake, organic acids are only recovered from the proximal part of the pig's gastrointestinal tract (GIT; stomach and small intestine), but the antibacterial activities are important for limiting the risk of infection of *Escherichia coli*. The organic acids are capable of diffusing across the cell membrane of bacteria, and, once inside the bacteria, they will dissociate to produce protons and anions that disrupt the pH inside the bacterial cell. However, where more neutral pH conditions prevail, the acids will dissociate into potentially toxic anions and protons; the latter may compromise bacterial energy generation by disrupting the transmembrane proton gradient

(Heo et al., 2013). Elevated cell cytoplasmic pH has lethal consequences on the cell by affecting the integrity of purine bases and denaturing essential enzymes. Likewise, the MCFA are also characterized by having a strong antibacterial activity due to their ability to penetrate the semi-permeable membrane of bacteria and damage their internal structures (Hanczakowska, 2017). An overview on the effect of caprylic (C8:0) and capric acids (C10:0) on gram-positive and gram-negative bacteria in vitro studies is provided elsewhere (Zentek et al., 2011). Lastly, the combination of SCFA and MCFA has been studied for the antimicrobial activity and feeding a blend of organic acids and MCFA (0.2% to 0.4%) to *E. coli*-challenged piglets around weaning reduced the incidence of diarrhea (Lei et al., 2017).

The general conclusion regarding the impact of dietary FA on the intestinal microbiota seems to be that especially SCFA (organic acids) and MCFA are described to have antimicrobial properties. Also, dietary strategies using these lipids to inhibit the growth of common pathogens like *E. coli* and *Salmonella* in digesta of pigs post-weaning may limit the risk of infectious diseases in the gut. Marine n-3 FA might also affect the bacterial diversity of colonic microbiota to create a less inflammatory environment for the colonic mucosa during human health and disease treatment (Calder, 2019). However, very little is known regarding the effect of n-3 LCFA or fish oil on porcine bacterial composition. Varying dietary n-6 to n-3 ratios for weaned pigs had no influence on fecal microbial counts (Upadhaya et al., 2019), and it would be of interest to know if the LCFA play a role for the mucosal bacterial composition in the upper part of the intestine, where lipid absorption takes place. Novel findings in mice indicated an interplay between gut microbiota and host energy metabolism via metabolites of LCFA in the ileum (Miyamoto et al., 2019).

Another area of interest is how enteric microbiota manipulation affects lipid digestibility and absorption and metabolism. The growth-promoting effect of antibiotic growth promoters has been partly correlated with the decreased activity of bile salt hydrolase (BSH) (Lin, 2014), which is an intestinal bacteria-produced enzyme catalyzing de-conjugation of conjugated bile acids in the intestine (Begley et al., 2006). The conjugated bile acids are more efficient as biological detergents than unconjugated bile acids to emulsify and solubilize lipids for digestion. Hence, higher activity of BSH exerts a negative impact on host lipid digestion and utilization. Oral administration of low-dose antibiotics affected diversity and relative abundance of gut microbiota (Lin, 2014), and, as shown in broilers, also affected the digestibility of lipids and fat-soluble vitamins (Engberg et al., 2000; Knarreborg et al., 2002). Removal of antibiotic growth promoters in the pig production seems to influence the microbiota composition, which may have consequences for the digestion and absorption and metabolism of the dietary lipids.

To summarize, SCFA and MCFA expose antibacterial activity in the gut and can be used as a dietary tool to limit the exposure of pathogens in the gut. Further, manipulation of the intestinal microbiota can influence digestion and absorption of the FA, and novel results seem to indicate the role of the intestinal microbiota in the metabolism of LCFA. In the next section, the impact of the FA for immune function in pigs is described.

## Immune Function

The GIT is not only an important organ for digestion, absorption, and metabolism of dietary nutrients, but it is also the largest

immune organ of the body, compromising more than 70% of the body's immune cells (Blikslager et al., 2007). The pigs encounter numerous pathogenic and nonpathogenic challenges post-weaning, which results in activation of the gastrointestinal immune system. While a healthy GIT is considered to be in a constant state of "controlled" inflammation, intestinal infections caused by pathogenic bacteria such as *E. coli* and *Salmonella* may drastically amplify inflammatory responses. However, stress in connection with weaning may also induce inflammation (Gresse et al., 2017). During the activation of the GIT immune system, a number of pro-inflammatory cytokines are produced, and overproduction of these cytokines results in intestinal injury and dysfunction. FA play a critical role as immune modulators via their contributors as a major energy source, their important components in cell membranes, being metabolic substrates in many biochemical pathways, and in cell-signaling molecules.

A lot of research on other animal species is available regarding the ability of LCFA to improve immune function and health. Probably because of the focus obtained in human health, the most widely researched LCFA group is the *n*-6 and *n*-3 FA: The ratio of *n*-6 and *n*-3 FA appears to modulate the immune response, and, according to Simopoulos (2008), Western-like diets for humans with a ratio of 20:1 of *n*-6 to *n*-3 FA have been shown to increase the production of pro-inflammatory mediators, whereas diets with a ratio of approximately 1:1 are considered protective against inflammation (Simopoulos, 2008). In this context, it should be noted that a dietary intake of LA is recommended in pig nutrition but not that of ALA (NRC, 2012). However, pig diets are often based on corn or wheat and barley, making the natural content of LA high, and additional vegetable oils such as sunflower oil or soybean oil would probably result in diets giving an overall high ratio of *n*-6 to *n*-3. Focusing on prevention of enteric diseases in pigs and broilers, Lauridsen (2019) described the influence of early nutrition with dietary *n*-6 and *n*-3 FA to these animals on the synthesis of long-chain

PUFA and eicosanoids developed from the metabolism of LA and ALA, including the mechanisms for inflammatory responses and oxidative stress. Table 2 gives a broader summary of the effect of early exposure of *n*-6 and *n*-3 LCFA on intestinal health and immunity of pigs. While the impact of dietary fish oil for immune function and health and disease in relation to humans is well described (Calder, 2017), the optimal *n*-6 and *n*-3 FA ratio is still to be determined in pig nutrition. Reduction of the dietary *n*-6 to *n*-3 in the study by Huber et al. (2018) had a positive influence on parameters such as growth performance during the early nursery period and immunity (as measured by an attenuation of acute-phase protein production and reduction of hyper dermal IgG response) of weaned piglets upon challenge. However, the optimal ratio between *n*-6 and *n*-3 FA for response parameters related more specifically to pig gut immunity and health is not known.

Other dietary FA have been ascribed for their impact on gut immunity and should be mentioned. Conjugated linoleic acid (CLA) is a group of positional and geometric isomers of LA, and the effect of dietary CLA has been studied with regard to gene expression and lipid metabolism in growing and finishing pigs (Lauridsen et al., 2005; Tous et al., 2012). Moreover, supplementation of 2% CLA for sows from mid-gestation reduced the intestinal inflammation and increased the concentration of immunoglobulins of piglets compared with piglets weaned from control sows after enterotoxigenic *E. coli* challenge of piglets (Patterson et al., 2008). Hence, in this study (Patterson et al. (2008) as well as in the study by Lauridsen and Jensen (2007), a carry-over effect was obtained, that is, the dietary FA treatment of sows influenced the suckling piglet via the sow milk FA composition, and the effect persisted in the form of enhanced immunity in the piglet post-weaning.

It should be pointed out that several studies have researched the role of SCFA on inflammatory reactions and immune parameters in the colon of piglets. However, as these studies are focusing mostly on human gut health, it is beyond the scope of this review to address this aspect further. A study by Xu et al. (2016) on early oral intervention with sodium butyrate showed a modulation of ileal inflammatory cytokine responses of the neonatal pigs, but with little impact on the bacterial community in the ileum and colon. Thus, dietary sodium butyrate may exert potential beneficial properties in gut health via modulation of the immune system in neonatal pigs.

To summarize, especially LC *n*-3 and *n*-6 PUFA have been researched in relation to the gut immune function of piglets, and in the next section, the link to the epithelial barrier function is described.

## Intestinal Epithelium Function

Various intestinal disease conditions damage intestinal epithelium and consequently cause poor absorption of nutrients. In general, *E. coli* infection can decrease villus height (villus atrophy), increase in crypt depth (crypt elongation), and has detrimental effects on the villus height: crypt depth ratio, the villus area, and the villus volume, and may, in fact, destroy the villus. In addition, infection of intestinal epithelial cells with Enterotoxigenic *Escherichia coli* resulted in an impaired barrier function and aberrant tight-junction protein complexes (Muza-Moons et al., 2004). During an infectious disease challenge, the mitochondrial reactive oxygen species (ROS) development may lead to oxidative stress (Lauridsen, 2019), and the oxidative stress can lead to disruption of the intestinal barrier function

**Table 2.** Effects of early exposure of *n*-6 and *n*-3 FA on intestinal health and immunity of piglets

Studied responses	References
Increase in intestinal tissue and cell membrane <i>n</i> -6 and <i>n</i> -3 FA via dietary supplementation of <i>n</i> -6 and <i>n</i> -3 FA	Hess et al. (2008) Lauridsen (2010)
Effect on pro-inflammatory eicosanoids (decrease with <i>n</i> -3 (fish oil) relative to <i>n</i> -6 FA upon ex vivo stimulation of immune cells)	Møller and Lauridsen (2006) Lauridsen et al. (2007c)
Decrease in cell-mediated immune response via <i>n</i> -3 (fish oil supplementation) upon LPS mediation	Møller and Lauridsen (2006)
Reduction in liver intestinal tocopherol content	Lauridsen et al. (2013)
Alteration in the expression of inflammatory COX-2 and TNF- $\alpha$ proteins	Walter et al. (2019) Zhang et al. (2019)
Alteration in the expression of genes related to lipid metabolism	Duran-Montgé et al. (2009)
Influence on antibodies (e.g., immunoglobulins) and other immune parameters (e.g., cytokine responses)	Bontempo et al. (2004) Swiatkiewicz et al. (2015) (review) Huber et al. (2018) Upadhaya et al. (2019) Calder (2019)
Effect on bacterial diversity by fish oil	

(Shuting et al., 2018). This was shown in pigs where oxidative stress was induced via a challenge with diquat (Cao et al., 2018). Weaning in itself can also exert deleterious effects on the intestinal morphology in pigs (Gresse et al., 2017) and, for example, measure of pro-inflammatory cytokines coincidence with significant changes in intestinal morphology during the first week post-weaning of pigs (Hu et al., 2013). Reduced feed intake (which is often observed in pigs during the first days upon weaning) may, in fact, induce inflammation and changes in the intestinal epithelium. The process may be very fast; actually, Hampson (1986) demonstrated that the villus height rapidly decreased about 25% to 35% of the pre-weaning height within the first 24 h in pigs weaned at day 21 of age, and the reduction in villus height continued until about 5 d after weaning when villi were approximately only half of the initial height. Besides the high cell turnover in the intestinal epithelium, oxidative stress and lipid oxidation products can also disturb the barrier function of the epithelial monolayer. Fortunately, and even in overt inflammation, replacement of the intestinal epithelium is a process that occurs rapidly with cells proliferating in the crypts, maturing along the villus axis and being exfoliated from the villus tip with a turnover rate of 3 to 5 d (Potten et al., 1997). Turnover of the intestinal epithelium is an important mechanism of innate defense, which is highly affected by the microbial colonization (Willing et al., 2013). The rates of cell loss and proliferation are highly determined by the activation of the GI immune mechanisms associated with commensal bacteria. Thus, in addition to the digestive and absorptive function, inflammation may exert detrimental effect on the intestinal barrier function, that is, dampen the prevention of the penetration of luminal bacteria and dietary allergens into the mucosa (Blikslager et al., 2007).

FA, mainly MCFA and LCFA, influence the gut morphology and epithelial barrier functions via different mechanisms (Liu, 2015). Inflammation often results in the repartitioning of the host's energy to functions other than digestion. An immediate energy supply in the form of various oils supplemented to newborn piglets had no influence on gut morphology (Manzke et al., 2018). The impact may be more pronounced in post-weaning pigs, as MCFA can be directly utilized by the enterocytes for energy production and thereby maintain the integrity of the intestinal tissue (Guillot et al., 1993). Further, the feeding of MCTG to rats positively influenced the intestinal morphology, resulting in an augmentation of the mucosa, a higher phospholipid/protein ratio in jejunal mucosal villus lipids, longer intestinal villi, and shorter crypts, and increased activity of membrane-bound enzymes (Takase and Goda, 1990). Using a source of MCFA in the form of *Cuphea* seeds (which contain 70% C8:0 and 20% C10:0) with a lipase supplement in the diet for piglets, Dierick et al. (2003) obtained a significantly greater villus height and lesser crypt depth and a trend toward improved performance parameters. Benefits were also obtained for villus height when using capric acid, while no significant effect was obtained for caprylic acid in pigs (Hanczakowska, 2017).

Liu et al. (2012) demonstrated in weaned pigs under an inflammatory condition (*E. Coli* lipopolysaccharide [LPS] challenge) that dietary fish oil improved the intestinal integrity by alleviating intestinal inflammatory LPS, which is sensed by cells of the immune system through the toll-like receptor 4 (TLR4). Activation of the TLR4 by LPS will induce an inflammatory response of the immune cells. The long-chain *n*-3 PUFA highly present in fish oil can interfere with the TLR4 activation and thereby ameliorate this inflammatory signal (Childs et al.,

2019), as also shown in the pig study using fish oil (Liu et al., 2012). Fish oil supplementation to the pigs during inflammation was associated with inhibition of TLR4- and NOD2-signaling pathways (Liu et al., 2003, 2012).

Oxidation of dietary polyunsaturated FA may, on the other hand, impair the function of the intestinal epithelium. Fatty acid peroxides arising from the feed may be present during the digestion of lipid as a means to access the intestinal absorptive membrane. In addition, hydrolysis of the TG molecule provides the free form of PUFA which are more vulnerable to peroxidation than if esterified. Once the fatty acid hydroperoxides are formed, they may potentially damage absorptive membranes (Lauridsen et al., 1995), as the formed micelles are sufficiently small to enter the unstirred water layer (Moran, 2017), coalescing on the absorptive membranes. ROS and lipid peroxidation products are able to disrupt the tight-junction protein complex, the active cytoskeleton, and the adherent junctions (Degroote et al., 2019). Blends of fat sources, especially those including high content of FFA, may enhance the risk of oxidative stress and inflammation and hence impair gut integrity (Zhu et al., 2012). However, lipid composition of diets containing 10% soybean oil, choice white grease, palm oil, distillers' corn oil with approximately 5% FFA, or distillers' corn oil with approximately 10% FFA appeared to have inconsistent effects on gut integrity and measures of oxidative stress (Lindblom et al., 2017). Dietary challenge of piglets during weaning with peroxidized oil did not affect the small intestinal histomorphology (Degroote et al., 2019); however, the impact of dietary antioxidants in that study cannot be ignored, as malondialdehyde levels in plasma and liver of the piglets also remained unaffected. Feeding thermally peroxidized soybean oil to grower pigs had little impact on gut permeability measured as urinary lactulose:mannitol ratio (Overholt et al., 2018). As reviewed recently, vitamins E and A and trace elements provide via their antioxidative mechanisms significant protection from hydroperoxide abuse of membranes (Moran, 2017; Dalgaard et al., 2018; Lauridsen, 2019). Hence, manipulation of dietary fatty acid composition should take into consideration the risk of oxidative processes of the cell membranes. The integration of  $\alpha$ -tocopherol between the FA of the membranous PL (Lauridsen and Jensen, 2012) is of high structural importance for the intestinal barrier function.

## Conclusion and Perspectives

The literature discussed in this review indicates that lipid nutrition encompasses a wide range of bioactive FA which may offer beneficial effects for pigs pre- and post-weaning. The antimicrobial lipids (SCFA and MCFA) have promising antibacterial activities and can supply immediate energy for the host. In contrast, digestion and absorption of the LCFA are more complex, but these FA exert via their incorporation into membranes' bioactive effects of importance for the inflammatory reactions. Both antibacterial and immunological properties of the epithelium are important for its barrier function. Dietary *n*-3 PUFA and especially the LCFA present in fish oil can decrease acute and chronic inflammatory immune reactions of importance for enteric health and robustness. It can be concluded that during the challenging phases of gut development and function, such as in low-birth-weight pigs and in pigs suffering from weaning stress, the strategic use of FA could potentially optimize the growth, function, and health of the pig's gut.



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## Conflict of interest statement

The author declares no conflict of interest.

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