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Review Article

Dietary fatty acids in gut health: Absorption, metabolism and function

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ABSTRACT

In biological responses, fatty acids (FA) are absorbed and metabolized in the form of substrates for energy production. The molecular structures (number of double bonds and chain length) and composition of dietary FA impact digestion, absorption and metabolism, and the biological roles of FA. Recently, increasing evidence indicates that FA are essentially utilized as an energy source and are signaling molecules that exert physiological activity of gut microbiota and immune responses. In addition, FA could serve as natural ligands for orphan G protein-coupled receptors (GPCR), also called free fatty acid receptors (FFAR), which intertwine metabolic and immune systems via multiple mechanisms. The present review explores the recent findings on FA absorption and its impact on gut health, particularly addressing the mechanism by which dietary FA potentially influences intestinal microbiota and epithelial functions. Also, this work attempts to uncover research ideas for devising future strategies for manipulating the composition of dietary FA to regulate gut health and support a normal immune system for metabolic and immune disorders.

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1. Introduction

Fatty acids (FA) are critical reservoirs of energy for a large number of body tissues and exert several functions during the life cycle. FA are organics that show as long aliphatic hydrocarbon chains containing one carboxyl group at one end. Based on the length of hydrocarbon chain, FA can be divided into 3 classes: short chain fatty acids (SCFA), with aliphatic tails fewer than 6 carbons; middle chain fatty acids (MCFA), which have aliphatic tails of 6 – 12 carbons; and long-chain fatty acids (LCFA), having aliphatic tails with more than 12 carbons (Burdge and Calder, 2015). FA are important components to form lipids, such as triglycerides (TAG), phospholipids, cholesteryl esters, plant sterols and so on (Wang et al., 2013), which mainly contribute to energy metabolism, stability of the cell membrane and modulation in various cell processes (Glatz and Luiken, 2015).

FA and the associated ligands, including peroxisome proliferator-activated receptors (PPAR) potentially regulate the expression of associated genes contributing to the synthesis of fatty acids, oxidation, energy partitioning, glucose utilization, lipogenesis, insulin sensitivity, reverse cholesterol transport, thermoregulation, cholesterol synthesis, growth and differentiation, inflammatory responses (Grygiel-Gorniak, 2014; Hoppenbrouwers et al., 2019; Sekikawa et al., 2019), and low-density-lipoprotein-receptor expression. Our previous study found that gut immunity and microbiota dysbiosis are associated with altered fatty acids metabolism in LPS-challenged piglets (Xiao et al., 2021; Zong et al., 2019b). Accumulating evidence has shown the cardioprotective

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activity of monounsaturated fatty acids (MUFA) in dietary fat (Gillingham et al., 2011), especially with essential FA docosahexaenoic acid (Hammad et al., 2016). Further, conjugated linoleic acids have proved to be beneficial in preventing and managing several diseases, such as cancer, obesity, cardiovascular diseases, and diabetes (Fuke and Nornberg, 2017). Because of the inability to synthesize essential FA by bodies, these FA or their precursors must be ingested from dietary fat. Therefore, an understanding of FA absorption is essential.

Based on the current understanding, 3 groups of proteins (plasma membrane fatty acid-binding proteins [FABP] and free fatty acid receptors [FFAR]) potentially detect the type and presence of fatty acids whether in the cytosol, extracellular medium, or the nuclear matrix (Hara et al., 2013). Within the plasma membrane, FA activate G protein-coupled receptors (GPCR), also called FFAR. Independently, they are taken by FABP and channeled to specific metabolic pathways or subcellular structures in the cytosol. Eventually, nuclear receptors PPAR mediate the regulatory functions of fatty acids within the nucleus (Zolezzi and Inestrosa, 2013). The particular spatiotemporal expression pattern and multiple co-expression of isoform from each protein family in one cell depict a sensory and modulatory platform of cellular response to the presence of various FA, for instance, cell adaptation to functional or developmental needs. Thus, the signaling or regulatory functions of FA have widely been implicated in various pathological and physiological processes.

With this current understanding and interpretation of FA, the aim is to highlight recent discoveries related to FA absorption and the impact on health, particularly addressing the mechanisms by which dietary FA alters intestinal microbiota and epithelium function.

2. Absorption and metabolism of FA

2.1. Overview of dietary lipid digestion

As shown in Fig. 1, dietary fat and other food ingredients form a bolus by chewing and stirring of the tongue. This bolus goes through the esophagus and hydrolyzes into diglycerides and free FA in the stomach by gastric lipase or lingual lipase (Hamosh and Scow, 1973). Following the gastric pre-digestion, the bolus enters the duodenum and the major digestion of TAG takes place here by hydrolysis with pancreatic lipase. Bile salts act as vehicles for TAG, diglycerides, cholesteryl esters, and other lipids to form micelles that can make fat contact with the water-phase as much as possible (Maldonado-Valderrama et al., 2011). Colipase helps pancreatic lipase to bind to the emulsion/water interface, which can highly facilitate the digestion of fat (van Tilbeurgh et al., 1999). Eventually, the digestion of fat results in monoglycerides (MAG) and free FA. The FA chain length influences the rate of dietary fat digestion. It will decrease with increasing FA chain length, i.e. the rate is in this order: short chain TAG > medium chain TAG > long chain TAG (Guo et al., 2017).

2.2. The uptake of FA into enterocytes

The absorption of solutes by the gut depends on the amount of solutes that can get to the brush-border membrane (BBM), and the delivery of solute to the BBM depends upon the efficiency of luminal stirring (Levitt et al., 1990). There would be a permeability barrier between the digesta and brush border which is called the unstirred water layer (UWL) (Kono et al., 2016; Korjamo et al., 2009). The UWL exerts a significant function in the membrane transport process; transporting the rapidly penetrating solutes across membranes can be wholly or partly rate regulated by UWL (Thomson and Dietschy, 1984).

2.2.1. The uptake of SCFA in colonocytes

The absorbed SCFA, such as acetate, are sources of energy to the mammals, which can be rapidly absorbed, recycled and metabolized into the body to make the body functional (Latymer et al., 2010). Many researchers disagree about how SCFA get into the gut cells. Some hold the view that SCFA go through the cell membranes by simple diffusion, but others think it may need some proteins to transport SCFA. One study showed that formic, acetic and propionic acid permeate via the lipid bilayer membranes owing to nonionic diffusion as well as the permeability pattern, which is similar to other nonelectrolytes in lipid bilayers (Walter and Gutknecht, 1984). Researchers found that apical membrane vesicles obtained from rat distal colon uptake butyrate, which is a representative SCFA, by a bicarbonate gradient dependent, were pH-dependent, and carrier-mediated anion exchange process (Mascolo et al., 1991; Stein et al., 2000), which supports the latter opinion. The carrier is called monocarboxylate transporter (MCT), SLC5A8. A large volume of evidence has proven that the uptake of SCFA will be various in different situations. The uptake of SCFA monomers is limited by the BBM; however, the diffusion via the

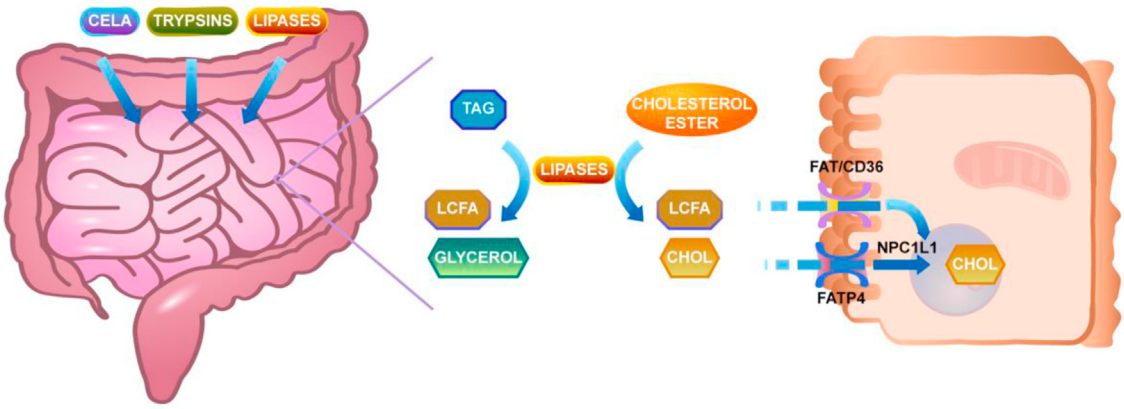

Fig. 1. Intestinal fatty acids absorption. Dietary lipids are emulsified with bile salts and are hydrolyzed by different pancreatic lipases, resulting in the generation of free fatty acids and cholesterol. These products are taken up by the enterocytes involving various transporters and transported to the endoplasmic reticulum, where they are used for the synthesis of triacylglycerols. TAG = triglyceride; LCFA = long-chain fatty acids; CHOL = cholesterol.

UWL is increasingly rate limiting with an increase in the chain length (Sallee and Dietschy, 1973; Thomson et al., 1993).

2.2.2. The uptake of MCFA and LCFA in enterocytes

The uptakes of MCFA and LCFA in enterocytes are similar, but some small differences exist. For LCFA and cholesterol, any passage across the UWL is rate-limiting, but not for MCFA. The rate liming step for MCFA is passaging across the brush-border membrane (Thomson et al., 1993).

SCFA and MCFA uptake by enterocytes do not require FA transporters, but LCFA require fatty acid transport proteins (Stahl et al., 2001), plasma membrane-embedded fatty acid translocase (FAT/CD36) (Drover et al., 2008), FABP (Gajda and Storch, 2015) and other proteins (Stremmel et al., 2017) for their cellular uptake (Schonfeld and Wojtczak, 2016). After entry into the enterocytes, FA and MAG are moved to the membrane of the endoplasmic reticulum (ER) by FABP; here, they resynthesize TAG to form the hydrophobic core of chylomicrons (CM) (Yen et al., 2015) in the cytoplasmic lipid droplets within the enterocytes (D'Aquila et al., 2016). TAG and other neutral lipids together with apolipoprotein (apo) B-48s and microsomal triglyceride transferases form pre-CM, which transport from ER to the Golgi complex by the pre-CM transport vesicles to form mature CM (Black, 2007). The mature CM exit the Golgi complex and fuse with the basolateral membrane, after which they are secreted into the lamina propria (Mansbach and Gorelick, 2007; Sabesin and Frase, 1977).

2.3. The metabolism of FA

Of note, FA are primarily synthesized in animals from carbohydrates in the adipose tissue, lactating mammary glands and liver (Hillgartner et al., 1995; Rinaldo and Matern, 2002). First, the most critical step in how carbohydrates are converted to FA, is the generation of carbohydrates to pyruvate through glycolysis (Olson, 1966). Then, pyruvate is decarboxylated, which forms acetyl-CoA within the mitochondria. Notably, the acetyl-CoA must be transported to the cytosol, the FA synthesis site. For cytosolic acetyl-CoA generation, the citrate released through acetyl-CoA condensation with oxaloacetic acid is eliminated from the citrate cycle. It is then taken to the cytosol via the inner mitochondrial membrane. At this point, it is cleaved to oxaloacetate and acetyl-CoA and catalyzed by ATP ci-tratelyase. Oxaloacetic acid is then taken back to the mitochondria in the form of malic acid (Ferre and Foufelle, 2007). Acetyl-CoA carboxylase mediates the carboxylation of cytosolic acetyl-CoA to malonyl-CoA; notably, this forms the initial committed step in FA synthesis. Malonyl-CoA participates in iterative reactions that prolong the FA chain by 2 carbons at a time. Consequently, nearly all natural FA exhibit an even number of carbon atoms. When the synthesis is complete, FA, in most cases, bind to glycerol (3 FA bind to 1 glycerol molecule) and form triglycerides, the main storage form of FA, thereby it produces the main energy source in animals. Also, synthesized FA are a crucial component of phospholipids, forming essential phospholipid bilayers in establishing the cell membranes.

Within the circulating plasma, FA are derived through lipolysis from reserved triglycerides (Zechner et al., 2005). Owing to the insoluble nature of FA in water, their transportation is aided by binding to plasma albumin. Consequently, the presence of albumin binding sites is limited by plasma FA levels. Besides, FA may be absorbed from circulating plasma by all mitochondria-containing cells, then are metabolized through β-oxidation and broken down to water and CO_2 within the mitochondria. As a result, large quantities of energy are released in the form of ATP via the citric acid cycle and β-oxidation (Mcgarry and Foster, 1980). Thus, FA serve as an energy source in tissues. Cells in the central nervous system (CNS) have mitochondria; however, glucose is the primary source of energy in the mammalian brain. FA synthesis from carbohydrates takes place in CNS cells; this enhances the production and maintenance of the required phospho-lipids for organelles and cell membranes. At the same time, the transport mechanisms of FA from the plasma to the brain via the blood–brain barrier is dependent on the carbon length of FA (Tsuji, 2005; Vijay and Morris, 2014). For instance, FA obtained from dietary fat ingestion or from the triglycerides secreted in adipose tissue are distributed to cells, acting as a fuel source for systemic metabolism and muscle contraction.

3. Physiological functions of FA on gut health

Notably, FFA serve as essential energy sources and signaling molecules regulating distinct physiological functions and cellular processes, but that is dependent on the length of their carbon chain.

3.1. Impact of dietary FA on gut immune function

3.1.1. SCFA

Studies have revealed that SCFA are significantly crucial in improving intestinal health and limiting intestinal inflammation. The low potential of intestinal mucosa in the oxidation of butyrate has been described in ulcerative colitis pathogenesis (Scheppach et al., 1992). A study by Fang et al. (Fang et al., 2014) found that dietary supplementation of sodium butyrate (1 g/kg feed) remarkably lowered cases of diarrhea in weaned piglets from 15% to 11%. Further, there was enhanced immune function due to high serum IgG concentration and IgA^+ cell count in the jejunum, which lowered the adverse impacts of weaning stress and maintained the intestinal mucosa integrity. There is a close correlation of the beneficial roles of butyrate with elevated proliferation and decreased apoptosis of enterocytes (Bartholome et al., 2004; Kien et al., 2007). Elsewhere, Hou et al. (Hou et al., 2014) demonstrated that 0.1% tributyrin dietary supplementation alleviated intestinal injury through inhibition of apoptosis, enhanced tight-junction establishment and activation of epidermal growth factor receptor signaling in a piglet colitis model induced via intrarectal acetic acid administration. With the intestinal porcine enterocytes J2 (IPEC-J2) cell model, we revealed that SCFA and their analogs induced porcine host defense peptide gene expression (Xiong et al., 2016). Collectively, dietary SCFA supplementation, in particular, butyrate, is key to intestinal health and attenuation of inflammation of the intestines.

3.1.2. MCFA and LCFA

MCFA and LCFA have been suggested to improve the gut morphology and epithelial barrier functions through distinct ways (Liu, 2015). Inflammation, in most cases, causes the repartitioning of the host's energy to other functions apart from digestion. Our study revealed that the absorption of LCFA is closely related to intestinal barrier function (Zong et al., 2019a). Also, MCFA is absorbed directly by the enterocytes to produce energy, thus supporting the intestine integrity (Jia et al., 2020). For instance, relative research has provided evidence that MCFA can induce the production of host defense peptides, such as β-defensins (Wang et al., 2018; Zhou et al., 2019). A diet with 0.5% capric acid fed to pigs could significantly protect against cyclophosphamide-induced intestinal inflammation, oxidative stress, and gut barrier function (Lee and Kang, 2017).

Reports have suggested MCFA or LCFA potentially improve gut health in inflammatory conditions. Sam et al. (2021) demonstrated that SCFA and MCFA have divergent immunomodulatory propensities. MCFA down-attenuated host pro-inflammatory IL-1β, IL-

6, and TNFα response predominantly through the TLR2 pathway. Bertevello et al. (Bertevello et al., 2012) showed that partial substitution of n-6 fatty acids with MCT enhanced damage in experimental colitis of rats but improved colon cytokine response. Also, Papada et al. (Papada et al., 2014) revealed that a MCT-rich diet lowered the levels of intercellular adhesion molecule-1 (ICAM-1), IL-6, IL-8 and glutathione S-transferase (GST) activity, thus inducing anti-inflammatory functions in trinitrobenzenesulfonic acid (TNBS) induced colitis. Besides, in an *Escherichia coli* (ETEC) infected pig model, they found MCFA-protected sodium butyrate and heptanoate additive did not lead to reduce ETEC colonisation, but enterobacterial counts and goblet cell numbers in the ileum were increased and this followed higher serum TNF-α concentrations (Lopez-Colom et al., 2020). These observations reveal that adopting MCFA or MCT as supplements in attenuating intestinal inflammation may offer a promising strategy.

3.1.3. PUFA

The synthesis of essential fatty acids (EFA) in animals cannot take place endogenously; thus, they are availed exogenously from dietary reservoirs (Beare-Rogers et al., 2001). Two EFA families have been described: n-6 (ω-6) and n-3 (ω-3). Notably, linoleic acid (LA; C18:2n-6) and α-linolenic acid (ALA; C18:3n-3) represent the sourcing factors for n-6 and n-3 families, respectively (Swick, 2019). Numerous plant oils, such as soybean oils, sunflower, and corn, contain excellent n-6 fatty acid sourcing, primarily as LA. The diet-derived ALA/LA in pigs is processed into long-chain PUFA, for example, eicosapentaenoic acid (EPA; C20:5n-3), arachidonic acid (ARA; C20:4n-6), together with docosahexaenoic acid (DHA; C22:6n-3). However, there are limitations in the conversion efficiency owing to the low activity of desaturase (Jacobi et al., 2011; Xie and Innis, 2008).

Currently, researchers have shown immense interest in the mechanisms by which long-chain PUFA influence intestinal function. Through clinical trials and animal models, a wealth of literature reports have proven n-3 PUFA has positive functions over inflammatory bowel conditions (Scaioli et al., 2017). For instance, the long-chain n-3 PUFA, abundant within fish-oils, could reduce inflammation signaling transductions, especially the TLR4 pathway (Childs et al., 2019). Similarly, Liu et al. (Liu et al., 2012) revealed that dietary fish oil enhanced the integrity of the intestines through inhibiting TLR4 and NOD2 signaling pathways within breastfed developing porcines post-LPS confrontation. Interestingly, n-3 PUFA, mainly EPA, are able to alleviate LPS-induced Kupffer cells pyroptosis via abolishing NLRP3 inflammasome activation, thus inhibiting subsequent release of cytokines (Fan et al., 2021).

A few reports have demonstrated that n-6 PUFA, particularly, ARA in addition to its metabolites, enhances the recovery process for damaged intestinal mucosa (Lauridsen, 2020). Adrian et al. (Bartoszek et al., 2020) assessed the anti-inflammatory effect of walnut oil within dextran sulfate sodium (DSS)-induced colitis murine studies, and found that walnut oil treatment could increase the expression of tight junction proteins (TJ), decrease pro-inflammatory cytokines, and restore colonic wall permeability. Additional experiments using pigs revealed that dietary supplementation of prostanoids triggers the rapid recovery of barrier function, reduces inflammatory response, together with enhancing intestinal tight junction proteomic levels (Hu et al., 2020). In addition, Patterson et al. (Patterson et al., 2008) revealed that weaning piglets using 2% CLA-augmented sows led to lower intestinal inflammatory responses, together with elevated serum IgG/IgA levels, in comparison to control sows, following ETEC challenges. Additional health effects were found upon the provision of dietary intake of n-6/n-3 PUFA, Paleolithic-/Mediterranean-supplementations could be linked to reduced systemic inflammatory/oxidative stress responses within humans (Whalen et al., 2016). Thus, use of PUFA as a supplement is a practical means for improving the overall gut health, and should be considered as an immune-resolving approach.

3.2. Impact of dietary FA on intestinal microbiota

Diet composition is among the highly significant factors influencing the total diversity and population of the intestinal microbiota. Previous investigations highlighted influences by selected diet-derived FA sub-groups, including LCFA, MCFA, MUFA and PUFA, upon intestinal microbiomes (Castonguay-Paradis et al., 2020). A high-fat diet is known to impact on the composition of gut microbiota and its function; however, the majority of studies focus on the colonic or faecal microbiota (Zong et al., 2020). Furthermore, high-fat dietary regimes carrying palm oil were found to reduce microbiotic diversification (Mujico et al., 2013).

Information on diet-derived lipid influences over microbiotic composition is scanty. Mozes et al. ((Mozes et al., 2008) and other groups (Sefcikova et al., 2010), using 2-week-aged rat pups (overfed high-fat-content milk), showed through fluorescent *in situ* hybridization (FISH), that such a diet regulated the number of *Bacteroidetes* (*Bacteroides*/*Prevotella*) while exacerbated *Firmicutes* (*Lactobacillus/Enterococcus*) populations within jejuni. Other than altering spatial distribution/microbial counts, high-fat dietary regimes severely impacted the microbiota constitution, with exacerbation of *Firmicutes* (appearance of *Erysipelotrichia*), *Proteobacteria* (*Desulfovibrionales)* and *Verrucomicrobia,* together with reductions in *Bacteroidetes* (Chang and Martinez-Guryn, 2019). Through a comparison of the dietary effects, antibiotic cocktails and broad-spectrum antibiotics, Poteres et al. (Poteres et al., 2020) revealed that antibiotics impacted the murine small intestine, faeces and caecum microbiota make-up, whereas dietary intake highly influenced caecum and jejunum microbiota, implying that dietary intake exerts specific and localized effect over gastrointestinal microbiota. Thus, future exploration on how lipids influence the microbial content in human jejunum is needed to decipher the detailed relationship between microbiota, host, and diet.

Generally, it is concluded that the influence of dietary FA on the intestinal microbiota is dependent on SCFA (organic acids, e.g. formic, propionic, and lactic acids) and MCFA, which have been proved to exhibit antimicrobial properties. Moreover, dietary strategies with such lipids impede the survival of common pathogens such as *Salmonella* and *E. coli* within porcine digested matter post-breastfeeding; this could reduce possibility for gastrointestinal infections (Gunness et al., 2016; Yang et al., 2021). The effect of capric acids (C10:0) and caprylic (C8:0) on Gram-negative and Gram-positive bacterial organisms through non-animal investigations has been described (Zentek et al., 2011). Further, MCFA/SCFA tandem effects were explored based administering a mixed-feed containing MCFA (0.2% to 0.4%) and organic acids, and the antimicrobial activity over *E. coli*-confronted young porcines during breast-feeding lowered diarrheal cases (Lei et al., 2017). Also, marine n-3 potentially influences the diversity of the bacteria (colonic microbiota), creating a limited inflammatory condition within colon intestinal lining for such medical management (Calder, 2019). Notwithstanding, information on the fish oil/n-3 LCFA influences over composition of porcine bacteria remains scanty. Variation in diet-derived n-6-content: n-3-content in breastfed porcines does not affect the fecal microbial counts (Upadhaya et al., 2019); thus, there is an urgent need to explore whether the LCFA has significant effects on the composition of mucosal bacteria colonizing the upper intestinal portion, which is the lipid absorption site. Further, novel reports in mice demonstrated an existing interplay of intestinal-

based microbial populations with the organism's energetic processing through LCFA ileal metabolytes (Miyamoto et al., 2019).

It is interesting to elucidate the mechanism by which enteric microbiota manipulates lipid absorption, digestibility, and processing. Antibiotic-based development enhancers shows a partial correlation with low bile salt hydrolase (BSH) activity (Lin, 2014); such gut microbiota-secreted enzymatic agent catalyzes splits within bound intestinal bile acids (Begley et al., 2006). Of note, such bound bile acids have higher efficiency as bio-detergents, compared to unbound bile acids, especially in the emulsification and solubilization of lipids. Thus, higher BSH activity negatively impacts the digestion and utilization of the host lipid. Orally administering low-dose antibiotics also influences intestinal-based microbial distribution, density and population strain (Lin, 2014). Similar to broilers, this additionally influenced degree of breakdown for fat-soluble vitamins/lipids (Engberg et al., 2000; Knarreborg et al., 2002). Eliminating antibiotic-based development enhancers from porcine rearing potentially influences microbiota make-up; this may consequently affect the breakdown, uptake, and processing for diet-derived fat.

Collectively, MCFA and SCFA modulate intestinal-antimicrobial roles, being instrumental in dietary regimes for reducing intestinal pathogenic risks. Additionally, manipulating gut-based microbial populations may alter FA breakdown/uptake; however, novel observations illustrate the LCFA metabolic functions of the intestinal microbiota.

4. Mechanism of action of FA: GPCR

Studies have reported numerous orphan GPCR as FA receptors. Notably, the receptors GPR120 and GPR40 are activated by LCFA and MCFA, whereas GPR43 and GPR41 are activated by SCFA (Fig. 2) (Delzenne et al., 2011; den Besten et al., 2013; Donohoe et al., 2011; Liou et al., 2013). GPCR are seven transmembrane receptors that constitute an extensive protein family of receptors vital in the detection of extracellular molecules. They initiate the activation of intracellular signal transduction pathways, and eventually induce cellular responses (Lagerstrom and Schioth, 2008; Marinissen and Gutkind, 2001).

4.1. GPR40

By 2003, GPR40 was eventually described as the receptor activated by LCFA and MCFA (Briscoe et al., 2003; Itoh et al., 2003). Unsaturated FA potentially activate GPR40 but not saturated FA; notably, DHA shows the highest potency as a GPR40 agonist among unsaturated FA (Grundmann et al., 2021). The activation of GPR40 by saturated FA is dependent on the carbon-chain length, while palmitate (C16) acts as a robust binding factor for saturated FA (Offermanns, 2014). GPR40 was initially found to be a Gq-proteomic-coupled receptor (Itoh et al., 2003; Shapiro et al., 2005), which activated phospholipase C, increasing the intracellular Ca^{2+} levels diacylglycerol-induced or IP3 protein kinase C (PKC) phosphorylation (Fig. 2). Extra-cellular signaling-modulated kinases (ERK1/2) activation was revealed to be part of down-stream GPR40-Gq protein signaling cascades (Itoh et al., 2003). Thus, GPR40 signaling may seem more complex than anticipated. Further exploration is necessary to elucidate the actual mechanism and satisfactory clinical demands.

4.2. GPR120

Unlike for GPR40, there are no confirmed reports on GPR120 coupling onto Gi/Gs proteomic players. Hirasawa et al. (Hirasawa et al., 2005) de-isolated GPR120 to be a secondary FFAR, revealing its strong affinity to LCFA. Also, they described how GLP-1 discharge could be enhanced through FFA, through GPR120 triggering within STC-1 cellular structures, with high plasma insulin/GLP-1

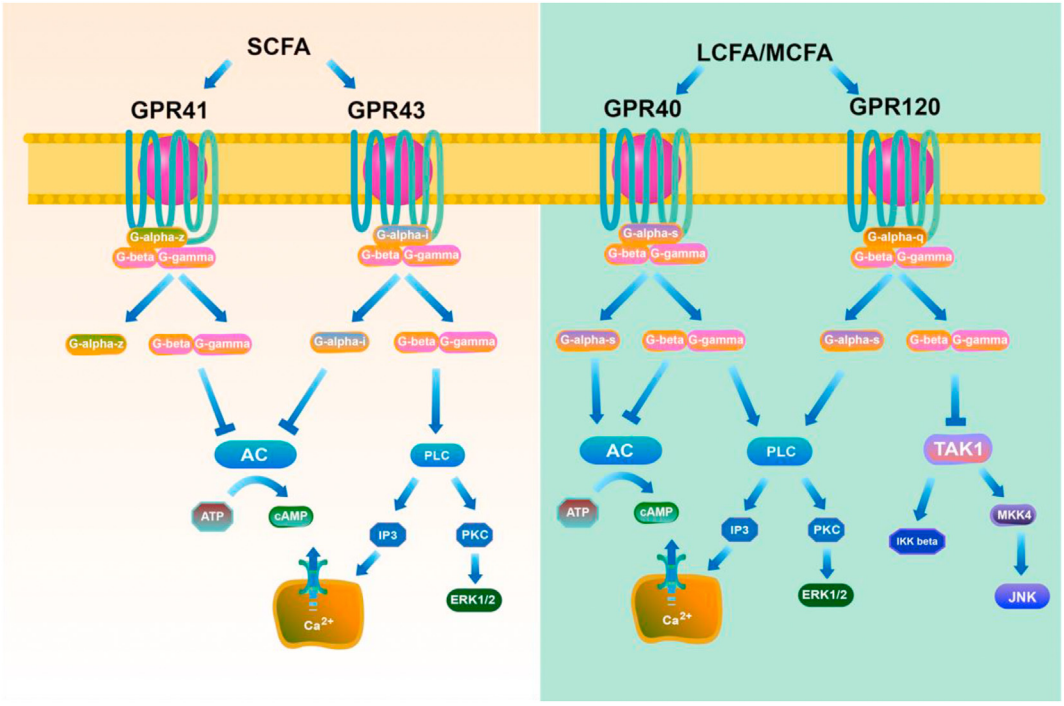

Fig. 2. Signaling pathways and G protein-coupled receptors (GPCR) ligand specificity of fatty acids. LCFA and MCFA activate GPR40 and GPR120, whereas short chain fatty acids (SCFA) activate GPR41 and GPR43. An illustration of the signaling pathways downstream of each receptor is shown. LCFA = long-chain fatty acids; MCFA = middle chain fatty acids; AC = adenylate cyclase; DAG = diacylglycerol; IP3 = inositol trisphosphate; PKC = protein kinase C; PLC = phospholipase C.

concentrations occurring within murines subjected to oral ALA treatment. GPR120/GPR40 each have 10% homology in AA sequencing (Hirasawa et al., 2005; Itoh et al., 2003); however, binding factor function (FA into GPR120) is similar to that of GPR40. GPR120 has a preference for C18 PUFA as internally-derived binding factors, following 50% effective concentration values generated, employing GPCR protein over-expressing cell lines (Ichimura et al., 2014). With downstream signaling, phospho-inositide 3-kinase (PI3K) and ERK1/2 activation have been reported after GPR120 activation within restricted investigational situations. Such a defined cascade, however, is elusive (Fig. 2) (Katsuma et al., 2005).

4.3. GPR43

Following reports on the structure–activity relationship, GPR43 prefers to be activated by acetate (C2) as well as other SCFA, including butyrate (C4) and propionate (C3) (Brown et al., 2003; Nilsson et al., 2003). GPR43 activation by SCFA through the Gi/o family impedes the generation of cAMP, also triggering ERK cascading system. Further, GPR43 triggering through SCFA, using Gq family members, elevates Ca^{2+} levels and induces MAPK cascade activation (Fig. 2) (Hudson et al., 2012; Hudson et al., 2013). Moreover, GPR43 signaling impeded the nuclear NF-κB translocating processes, thus down-regulating inflammation-related cytokines, including IL-6/IL-1β, within GPR43-transfected HeLa cellular populations (Fig. 2) (Lee et al., 2013). Of note, SCFA receptors GPR41/GPR43 bind onto pertussis toxin-sensitive Gi/o proteomic family; GPR43 binds onto pertussis toxin-insensitive Gq proteomic family (Bolognini et al., 2016; Hudson et al., 2011; Le Poul et al., 2003). Notwithstanding, the physiological parts played by such duet-combined signal transduction pathways via GPR43 are unclear.

4.4. GPR41

GPR41, which regulates energy homeostasis (Samuel et al., 2008b; Xiong et al., 2004), was deorphanized in 2003 and described as a SCFA receptor (Brown et al., 2003; Le Poul et al., 2003). GPR41 is activated by SCFA, including valerate (C5), butyrate (C4) and propionate (C3), all synthesized through microbial fermenting activity over colon-based diet-derived fiber-content (Brown et al., 2003; Le Poul et al., 2003). However, GPR41 exerts more robust reactions towards extended SCFAs, for example, valerate/caproate (C6) in comparison to GPR43 (Brown et al., 2003; Le Poul et al., 2003). GPR41 stimulation with SCFA promotes phosphorylation of ERK1/2 and impedes cAMP release. Additionally, these responses are managed using pertussis toxin, an implication of GPR41 coupling to Gi/o (Bolognini et al., 2019; Hudson et al., 2011) (Fig. 2). Reports show that GPR41 expression occurs in various body structures, including adipose tissue, immune cells, together with the peripheral nervous system, and orchestrates overall energetic balance through SCFA-driven signaling (Brown et al., 2003; Kimura et al., 2011; Le Poul et al., 2003; Samuel et al., 2008a). Of interest, one previous investigation utilizing bimolecular fluorescence complementation (BiFC), fluorescence resonance energy transfer (FRET), and proximity ligation assays demonstrated that the GPR43-GPR41 heteromer displays distinct signaling from its parent homomers (Ang et al., 2018).

Even though combining GPR43/GPR41 in any manner depicts differing signal transduction routes, defined functions for this are still unclear. Thus, further studies should probe additional pathophysiological functions for such receptors, elucidating if receptor heteromerizing activities are crucial, or otherwise, to develop such bespoke signal transduction roles.

5. Conclusion and perspectives

Based on the literature reports reviewed in the present study, fat-feeding covers multiple biologically important FAs with potential positive functions on gut health. The antibacterial fats (SCFA and MCFA) could provide rapid host energetic boosts. Contrarily, there is complexity in LCFA breakdown/uptake, though such FA function through inserting within membrane-based biologically-important functions tied to inflammation responses. Epithelial immunological and antimicrobial capacities become crucial for its barrier function. These findings demonstrate redundancy as a remarkable aspect of GPCR and FA for maintaining receptor triggering within specific levels. Although the role of GPCR over positive contributions by selected dietary regimes are still elusive, uncovering such mechanistics by which diet correlates with health may offer new therapeutic strategies. Finally, with the strategic use of FA gut development and function in the challenging phases, growth, function, and health of the gut could be optimized.

Author contributions

E. Xu: investigation, original draft preparation. **Chao Chen, Jie Fu, Luoyi Zhu, and Junlan Shu:** investigation, revision and reviewing. **Minliang Jin:** reviewing and editing. **Yizhen Wang and Xin Zong:** original draft preparation, writing, supervision, validation.

Conflict of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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