The pro- and anti-inflammatory activity of fatty acids

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Abstract

Inflammation is crucial to maintain homeostasis in the body. The contribution of fatty acids to the inflammatory process is exerted through a variety of mechanisms leading to cell surface modifications, activation of intracellular receptors that control inflammatory signaling processes, and changes in gene expression patterns. While long-chain saturated fatty acids induce NFkB pathway activation through TLR-4 binding, unsaturated fatty acids, such as monounsaturated, polyunsaturated and conjugated fatty acids anti-inflammatory ability is mediated through PPARs or GPR120. Moreover, these unsaturated fatty acids, especially omega-3 fatty acids, have immunomodulatory and cytoprotective potential, which is highly relevant for diseases with a neuroinflammatory component, such as obesity, Alzheimer's disease, multiple sclerosis and schizophrenia.

Keywords

Bioactive lipids; fatty acids; pro-inflammatory; anti-inflammatory; neuroinflammation; omega-3

Abbreviations

2-arachidonoylglycerol (2-AG); Alpha-linolenic acid (ALA); Alzheimer's disease (AD); Arachidonic acid (AA); Arachidonoylethanolamide (AEA); Blood-brain barrier (BBB); Ceramide 1-phosphate (C1P); Cyclooxygenase (COX); Conjugated linoleic acid (CLA); Conjugated linolenic acid (CLNA); Damage-associated molecular patterns (DAMPs); Docosahexaenoic acid (DHA); Eicosapentaenoic acid (EPA); Endocannabinoids (eCBs); G protein coupled receptors (GPRs); G protein receptor 120 (GPR120); high-fat diet (HFD); Insulin receptor substrate (IRS); Linoleic acid (LA); lipopolysaccharide (LPS); lysophosphatidic acid (LPA); lysophosphatidilinositol (LPI); lysophosphaditylcholine (LPC); Long-chain saturated fatty acids (LC-SFAs); Monounsaturated fatty acids (MUFAs) ; Multiple Sclerosis (MS); Myeloid differentiation primary response 88 (Myd88); nuclear factor kappa B (NFkB); inhibitory subunit (IκB); Palmitoylethanolamide (PEA); Pathogen-associated molecular patterns (PAMPs); Peroxisome proliferator activated receptors (PPARs); Polyunsaturated fatty acids (PUFAs); Prostaglandins (PGs); Polyunsaturated fatty acids (PUFAs); Saturated fatty acids (SFAs); Specialized pro-resolving mediators (SPMs); sphingosine 1-phosphate (S1P); Tetrahydrocannabinol (THC); TGF-β activated kinase 1 (TAK1); TGF-β activated kinase binding protein 1 (TAB1); T helper cells (Th); Tumor necrosis factor (TNF); Toll-like receptors (TLR); type-1 and type-2 cannabinoid receptors (CB1 and CB2)

1. Introduction: inflammation

Inflammation is defined as the process through which the immune system recognizes and removes harmful and foreign stimuli and begins the healing process (Fritsch & Abreu, 2019; Michels da Silva et al., 2019; Xufei Zhang et al., 2019). It comprises an intricate network of cellular and molecular events, where newly synthesized mediators are produced to obtain a temporal and spatial response (Chiurchiù et al., 2018). Inflammation can be either acute or chronic. On one hand, acute inflammation is a rapid and often severe process that occurs following tissue damage, microbial invasion, or exposure to noxious compounds which symptoms may last for a few days. On the other hand, chronic inflammation is a slow, long-term inflammation that can last for prolonged periods (several months to years) (Pahwa et al., 2021). The self-regulation of the inflammatory response relies on the activation of several negative feedback mechanisms, that when lost result in increased concentration of inflammatory mediators and activated inflammatory cells both at the site of tissue damage and in the systemic circulation, leading to excessive and irreparable damage in host tissues (Calder, 2012a).

1.1. The role of lipids as inflammatory mediators

Lipids are one of the most important inflammatory mediators: they are involved in all phases of inflammation and in the regulation of several important inflammatory processes. Thus, due to their importance in immune regulation, inflammation and maintenance of tissue homeostasis, several lipids have been classified as bioactive lipids. Bioactive lipids are generally divided into four main families according to their biochemical functions: classical eicosanoids, specialized pro-resolving mediators (SPMs), lysoglycerophospholipids/sphingolipids and endocannabinoids (eCBs). These lipids are generated from omega-6 or omega-3 essential polyunsaturated fatty acids (PUFAs) precursors, that are esterified into membrane lipids and act by binding to and activating specific G protein coupled receptors (GPRs) (Chiurchiù et al., 2018).

In the presence of an inflammatory stimuli, such as tissue insults or infections, granulocytes and monocytes/macrophages (innate immune cells) are recruited to the site of injury and generate a class of lipids mediators, eicosanoids, which are responsible for acute inflammation (Nathan, 2002). Classical eicosanoids lipids are highly pro-inflammatory and signal via autocrine and paracrine mechanisms. During the last stage of inflammation when there is resolution of inflammation, innate immune cells switch the production of eicosanoids lipids to another class of bioactive lipids, the SPMs (Chiurchiù et al., 2018). SPMs terminate inflammation and drive the restoration of full tissue homeostasis (Basil & Levy, 2016; Serhan, 2014). In cases when the inflammation is not resolved, it turns into a chronic inflammation state (or histophlogosis) resulting in aberrant tissue remodeling and organ dysfunction (Nathan & Ding, 2010). In such context, other bioactive lipids, such as lysoglycerophospholipids/sphingolipids and eCBs, mediate several cellular processes promoting cell and tissue adaption to the inflammatory millieu (Chiurchiù et al., 2015; El Alwani et al., 2006).

1.1.1. Eicosanoids

Eicosanoids are a class of bioactive lipids derived from 20-carbon PUFAs, most frequently from the omega-6 arachidonic acid (AA), which is released from membrane phospholipids. This class of molecules include the prostaglandins (PGs), thromboxanes, leukotrienes and lipoxins. Such molecules usually act on short distances and time periods, autocrinally, in the cells that produce them, or paracrinally in neighboring cells (Macouzet et al., 2010).

Prostaglandins, specifically, seem to be involved in the sustained inflammation that causes the transition to chronic inflammation by enhancing cytokine production (Aoki &

Narumiya, 2012; Narumiya & Furuyashiki, 2011). Indeed, prostaglandins induce chronic inflammation through enhancement of the pro-inflammatory release cascade (Honda et al., 2006), amplification of innate immunity response to pathogen- and damage-associated molecular patterns (PAMPs and DAMPs) (Hirata & Narumiya, 2012), activation of specific pro-inflammatory subsets of T helper (Th) cells (Q. Chen et al., 2010; Yao et al., 2009), recruitment of immune cells associated with chronic inflammation, such as macrophages, T and B cells, by synergistically acting with chemokines (Aoki & Narumiya, 2012) and by increasing the expression of pro-inflammatory genes induced by cytokines (Chiurchiù et al., 2015).

1.1.2. Lysoglycerophospholipids/sphingolipids

Lysoglycerophospholipids and sphingolipids are bioactive lipids with glycerol or sphingosine as backbones, respectively. They can link with other molecules, such as ethanolamine, choline, inositol, serine or/and fatty acids to form many different compounds distributed in plasma membranes. Importantly, lysophospholipids are derived from membrane phospholipids by removal of one or both fatty acids, being lysophosphaditylcholine (LPC) and lysophosphatidilinositol (LPI) as well as their byproduct lysophosphatidic acid (LPA) the most biologically active. Such lipids are important signaling molecules involved in relevant aspects of cellular and tissue biology, including plasma membrane shaping, cell growth and death, and inflammatory cascades. LPC and LPA modulate immune responses by controlling distribution, trafficking and activation of immune cells (Chiurchiù et al., 2018; D'Aquilio et al., 2007; Knowlden & Georas, 2014; Piñeiro & Falasca, 2012; Sevastou et al., 2013). Moreover, their sustained activation has been linked with several chronic inflammatory diseases like obesity and diabetes (Heimerl et al., 2014; Moreno-Navarrete et al., 2012), cancer (Piñeiro & Falasca, 2012), atherosclerosis (H. Lee et al., 2002) and rheumatoid arthritis (Fuchs et al., 2005; Nikitopoulou et al., 2012).

Regarding sphingolipids, the main active ones are ceramide and their byproducts ceramide 1-phosphate (C1P) and sphingosine 1-phosphate (S1P). Sphingolipids are important bioactive lipids participating in numerous inflammatory processes including intracellular trafficking and signaling, cell growth, adhesion, vascularization, survival, and apoptosis (Chiurchiù et al., 2018). As reviewed by (Chiurchiù et al., 2018) the role of sphingolipids in chronic inflammation has been widely assessed and most studies have associated it with immunodependent and vascular-related chronic inflammatory diseases (*e.g.* diabetes and obesity, neuroinflammatory disorders, chronic obstructive pulmonary disease and inflammatory bowel disease). Indeed, excessive ceramide signaling is associated with the development of adipose tissue inflammation and insulin resistance which ultimately leads to obesity and type 2 diabetes. C1P enhances both acute and chronic inflammatory responses by promoting phospholipase A2-mediated eicosanoid storm and by inducing cytokine production. However, ceramide and C1P have also been shown to negatively regulate some proinflammatory cytokines. In addition, ceramide and its metabolites are also involved in the physiological regulation of endothelial/vascular integrity and function, and alterations in these sphingolipids are associated with vascular dysfunctions and therefore with chronic inflammatory states. Regarding S1P, it is an important mediator for lymphocyte trafficking between lymphoid and non-lymphoid tissues allowing the egress of effector T and B cells from lymph nodes, thymus, bone marrow, and spleen and blocking the ability of immature dendritic cells to migrate. This is highly relevant since T and B cells are important initiators of many chronic inflammatory conditions and autoimmune diseases.

1.1.3. Endocannabinoids

eCBs are a group of bioactive lipids that are endogenously produced by humans and animals and are recognized due to their ability to bind and activate the same receptors as the Δ9-

tetrahydrocannabinol (THC), the main psychoactive component of marijuana, the type-1 and type-2 cannabinoid receptors (CB1 and CB2) (Chiurchiù et al., 2018). Besides CB1 and CB2 cannabinoid receptors, peroxisome proliferator activated receptors (PPARs) and GPR55 are also engaged by some cannabinoids (Lu & Mackie, 2016). The eCBs molecules as well as their enzymes and receptors constitute the eCBs system, which serves as a homeostatic system controlling several physiopathological states. Indeed, this system is a widespread neuromodulatory system that plays important roles in CNS development, synaptic plasticity and the response to endogenous and environmental insults (Chiurchiù et al., 2018; Lu & Mackie, 2016).

The two best studied members of eCBs family are arachidonoylethanolamide (commonly known as amandamine, AEA) and 2-arachidonoylglycerol (2-AG). 2-AG-ehter, O-arachidonoylethanolamine, palmitoylethanolamide (PEA) are also members of the eCBs family. Such molecules are ubiquitously produced by most tissues and immune cells, which are capable of metabolize them with a specific set of enzymes (Chiurchiù et al., 2018). AEA and PEA are mostly anti-inflammatory, and 2-AG acts both as pro- and anti-inflammatory.

The eCBs are amongst the most potent immunoregulatory compounds capable of regulating the function of several cell subsets of either innate or adaptive immunity. In consequence, perturbations in all members of the eCBs system occur during every chronic inflammatory process, from cancer, metabolic, and gastrointestinal diseases to autoimmune and neuroinflammatory disorders. Moreover, the modulation of this system has been shown to be beneficial by attenuating inflammatory processes.

2. The pro-inflammatory actions of fatty acids

Fatty acids are carboxylic acids presenting a long aliphatic chain. Such chain can be straight or branched and saturated (only single bond) or unsaturated (one or more double bond). These molecules, which are naturally occurring constituents of diet, have metabolic, structural and functional roles in the human body. They are usually used as energy sources: β-oxidation of the fatty acids is a well-known process, mostly used by the heart and the muscular tissue to obtain energy (Nagy & Tiuca, 2017a). Nevertheless, different fatty acids can present different biological activities. The influence of fatty acids on inflammation has been widely studied and it is known to be exerted through a variety of mechanisms. Indeed, fatty acids can act at the cell surface, as intracellular receptors that control inflammatory signaling processes, and can influence gene expression patterns. Besides, fatty acids are important players in cell membrane function and modification in the fatty acid composition of the cell membrane can impact its fluidity, lipid raft formation and cell signaling, which can ultimately result in altered gene expression and in alterations in lipid and peptide's mediators production (Calder, 2012b; Nagy & Tiuca, 2017b). Thus, it is widely accepted that fatty acids can affect inflammatory cell function and consequently inflammatory processes; for instance, they can act directly in surface or intracellular receptors, they can be incorporated in the membrane phospholipids of inflammatory cells and they can act as precursors of extracellular signaling molecules such as PGs, as mentioned in the previous section (Calder, 2012b).

2.1. Long-chain saturated fatty acids

Long-chain saturated fatty acids (LC-SFAs) are fatty acids with 14 or more carbon atoms, with no double bonds. In general, saturated fatty acids (SFAs) are important energy sources, used as building blocks for structural elements, protein modification and regulation of gene transcription. Adipose tissue and liver are able to *de novo* synthesize and store SFAs, namely palmitic acid (C16:0) from precursors such as glucose (Ruiz-Núñez et al., 2016a). The role of SFAs, namely dietary SFAs, as pro-inflammatory molecules was unraveled because obesity was

found to be associated with a low-grade inflammatory state, both in adipose tissue and hypothalamus. Thus, the mechanisms causing this inflammation were widely studied and the role of high-fat diet (HFD), specifically LC-SFAs, elucidated. It was found that the SFA excess, itself a characteristic of obesity, triggers cellular stress and the activation of pro-inflammatory pathways mediated by JNK and nuclear factor kappa B (NFkB) (Ellulu et al., 2017). This raises the circulating levels of several acute-phase proteins and inflammatory cytokines contributing to the chronic low-grade inflammation state (Gómez-Hernández et al., 2016; Longo et al., 2019). Moreover, several studies have identified toll-like receptors (TLR)-4, widely known for binding bacterial lipopolysaccharide (LPS), as the mediator responsible for the activation of innate immune response initiated by SFA (O'Neill, 2006). TLRs are known to be expressed in several cells: macrophages, dendritic cells, adipocytes, hepatocytes and muscle. In addition, TLR- 2 and -4 are also recognized binding sites for LC-SFAs in the hypothalamus. Indeed, studies have shown that HFD significantly increases the expression level of TLR gene expression (Nam et al., 2017). It is known that when activated, TLRs are responsible for the NFkB pathway activation, by facilitating the NFkB translocation to the nucleus (Kawai & Akira, 2006; Ruiz-Núñez et al., 2016b). Considering this and the ability of LC-SFAs to bind TLR-4, these SFAs have been shown to induce NFkB activation in several *in vitro* models: endothelial cells (Harvey et al., 2010), mHypoA-POMC/GFP-2 neurons (Tse & Belsham, 2018), cocultures of 3T3-L1 adipocytes and RAW264 macrophages (Takayoshi et al., 2007), skeletal muscle cells (Hommelberg et al., 2009), L6 muscle cells differentiated into myotubes (Nisr et al., 2019), among others. Under normal conditions NFkB is associated with its inhibitory subunit (IκB) remaining inactive in the cytosol. The phosphorylation of IκB by IKKβ, results in IκB dissociation from NFkB, allowing NFkB to translocate into the nucleus to initiate transcription of its target genes (Xiaoqing Zhang et al., 2008). Regarding NFkB pathway activation by LC-SFAs through TLR-4, this process is mediated by myeloid differentiation primary response 88 (Myd88) activation. The activation of Myd88 leads to TGF-β activated kinase 1 (TAK1) activation and consequent interaction with TGF-β activated kinase binding protein 1 (TAB1) resulting in NFkB activation (as reviewed by (Salsinha et al., 2021)). Recently, the role of Myd88 role on HFD on hypothalamic inflammation was elucidated in an astrocyte specific Myd88 knockout mice model: in the knockout mice the HFD or SFAs-induced inflammation was ameliorated (Jin et al., 2020).

Besides their direct effect on NFkB pathway activation, SFAs can be incorporated into specific lipid rafts domains of the plasma membrane. Such incorporation enhances TLR-4 dimerization, important for its activation (Wong et al., 2009) as well as the activation of downstream signaling pathways, such as JNK/AP-1 (Ruiz-Núñez et al., 2016b). Moreover, SFAs are known to be involved in the *de novo* synthesis of ceramides (mentioned in the introductory section): serine and palmitoyl-CoA are condensed to form 3-ketosphingamine via a synergistic signaling of TLR-4 and LPS (Schilling et al., 2013). Despite strong evidences in the role of TLR-4 and -2 in inducing LC-SFAs induced inflammatory responses, the direct binding of SFAs to TLR-4 has been challenged (Erridge & Samani, 2009; Ruiz-Núñez et al., 2016b; Salsinha et al., 2021). Pal and colleagues (Pal et al., 2012) suggested that SFAs may interact with TLR-4 through fetuin A. Fetuin-A (alpha-2 Heremans-Schmid glycoprotein) is extensively expressed in the kidney, brain, skin, gastrointestinal tract, and in the liver, from where is predominantly secreted in adults. Importantly, both proinflammatory and anti-inflammatory roles have been attributed to it, and due to its proinflammatory role this glycoprotein has been associated with several inflammatory diseases, including metabolic syndrome, nonalcoholic fatty liver disease, atherosclerosis, coronary artery disease, and is considered to be an important predictor of cardiovascular morbidity in diabetes (as reviewed by (Mukhopadhyay et al., 2014)). Indeed, fetuin A can interact with a variety of receptors including TLRs (Mukhopadhyay et al., 2014). It was shown that fetuin A binds and activated TLR-4 and can also play an important role in

polarizing adipose tissue M2 macrophages towards the pro-inflammatory M2 phenotype (Chatterjee et al., 2013).

The proinflammatory potential of the mentioned fatty acids is summarized in Figure 1.

2.2. Omega-6 fatty acids

Polyunsaturated fatty acids (PUFAs) are unsaturated fatty acids which present two or more double bonds. They can be classified accordingly to the position of the first double bound relative to the methyl-end group: omega-6 fatty acids have the double bound 6 carbons atoms away from the terminal methyl group and omega-3 fatty acids have the double bound 3 carbons away from the terminal methyl group. Omega-3 PUFAs are synthesized from the essential fatty acid alpha-linolenic acid (ALA) (C18:3 *c*9,*c*12,*c*15) and omega-6 PUFAs from the linoleic acid (LA) (C18:2 *c*9,*c*12). Although humans and other animals can metabolize these essential fatty (ALA and LA), they are not able to synthesize them (Brenna et al., 2009; Burdge & Wootton, 2002; Mišurcová et al., 2011; Orsavova et al., 2015; Proust et al., 2014). Thus, they have to be obtained through dietary sources (Ander et al., 2003). The balance of omega-6 to omega-3 obtained through diet is very important to human health since overabundance of one type of fatty acids will interfere with the metabolic production of the other type and even limit it.

Besides LA, arachidonic acid (AA) is the other most important omega-6 fatty acid. AA can be synthesized by the conversion of LA after desaturation and elongation reactions (B. Chen et al., 2012). Along with omega-3 eicosapentaenoic acid (EPA), AA is a precursor of the eicosanoids (mentioned in the introductory section). In general, eicosanoids derived from n-6 PUFA are proinflammatory while eicosanoids derived from n-3 PUFA are anti-inflammatory (Patterson et al., 2012). Besides eicosanoids, ARA is a precursor of other potent pro-inflammatory mediators, such as PGs and leukotrienes. Considering this, several anti-inflammatory drugs targeting the ARA pathway are used to control inflammatory processes in different diseases. It was reported that higher dietary intake of omega-6 fatty acids, namely ARA or LA, leads to increased inflammatory processes (Patterson et al., 2012). Diets, such as the western diet, with high intake of omega-6 fatty acids, should in principle exacerbate the inflammatory response. This diet results in increased omega-6:omega-3 ratios, resulting in augmented production of mediators and regulators of inflammation and immune responses (Patterson et al., 2012). However, studies in healthy humans have showed that increased intake of ARA or LA does not increase concentrations of several inflammatory markers (Innes & Calder, 2018). Indeed, the pro-inflammatory profile associated with western-pattern diet has been increasingly associated with the overconsumption of LC-SFAs and not with the omega-6: omega-3 ratio, as discussed below.

3. The anti-inflammatory potential of bioactive lipids

In contrast to what is observed for HFD, it has been noticed that some diets, such as the Mediterranean diet, are associated with lower risk of developing overweight and obesity (Notario-Barandiaran et al., 2020). Such observations lead to the understanding that in contrast to LC-SFAs, others fatty acids may possess beneficial effects on human health. In fact, the beneficial effects of the Mediterranean diet are strongly related with unsaturated fatty acids consumption, namely monounsaturated fatty acids (MUFAs) olive oil-based diet. Indeed, a MUFA rich diet was shown to reduce macrophage infiltration and to allow the shift to a more anti-inflammatory profile with production of anti-inflammatory cytokines IL-10 and IL-4 (Montserrat-de la Paz et al., 2019). Other study, aiming at addressing the impact of the omega-7 palmitoleic acid (C16:1 *c*9) MUFA on atherosclerosis in mice, has shown that palmitoleic acid supplementation reduces the expression of IL-1β and tumor necrosis factor (TNF)-α genes (Z. Yang et al., 2020). It has been suggested that this anti-inflammatory effect is mediated by PPAR-γ, since it was observed that MUFA diet induces the expression of the corresponding gene (Montserrat-de la Paz et al., 2019).

Importantly, PPAR α, β/δ and γ are nuclear receptors that translate nutritional and/or pharmacologic stimuli into changes in gene expression and are involved in the regulation of inflammation, immunity and epithelial cell differentiation. (Bassaganya-Riera, Reynolds, Martino-Catt, Cui, Hennighausen, Gonzalez, Rohrer, Benninghoff, Hontecillas, et al., 2004; Cunard et al., 2002; Jones et al., 2002; Natarajan & Bright, 2002; P Tontonoz et al., 1994; Peter Tontonoz et al., 1994; Y. L. Wang et al., 2002; Zakaria, 2014). While LC-SFAs induce NFkB activation through TLR-4, the palmitoleic acid MUFA was shown to downregulate NFkB pathway through PPAR-γ stimulation (de Souza et al., 2018). Nonetheless, *in vivo* studies have shown that palmitoleic acid interacts with G protein receptor 120 (GPR120) receptor and that its activation is responsible for the resolution of palmitic acid-induced inflammation (Hirasawa et al., 2005; Ichimura et al., 2012). Thus, it has been suggested that MUFAs can inhibit NFkB through direct binding of PPARs or GPR120, inhibiting its activation by SFAs (Ravaut et al., 2021).

Similarly to MUFAs, PUFAs are widely known for their anti-inflammatory potential, thought to be mediated through the GPR120 receptor. In fact, some PUFAs, mostly omega-3 fatty acids - ALA, docosahexaenoic acid (DHA) and EPA – are proven activators of GPR120 (Oh et al., 2010). It has been suggested that activation of GPR120 by these omega-3 fatty acids leads to the recruitment of β-arrestin 2, and to the formation and subsequent internalization of a GPR120-β-arrestin 2 complex. Such complex interacts with TAB1, inhibiting its interaction with another protein, the TAK1. This inhibition is highly relevant since their interaction mediates downstream inflammatory processes by activating NFkB and JNK pathways. Thus, GPR120 activation by omega-3 fatty acids inhibits the activation of pro-inflammatory pathways, reverting the inflammatory action of SFAs via TLR 4 receptors (Salsinha et al., 2021; Talukdar et al., 2011). Importantly, GPR120 is highly expressed in adipocytes and macrophages suggesting a potential anti-inflammatory action of PUFAs in several tissues and a possible therapeutical role in several inflammatory diseases. In addition, DHA was able to inhibit cyclooxygenase (COX)-2 gene expression in macrophages bearing constitutively active TLR-4 but not in those bearing constitutively active Myd88 - used by TLR-4 to activate NFkB -, suggesting that the effects of DHA on the NFkB pathway produce a direct effect on TLR-4 signaling (Calder, 2012b; J. Y. Lee et al., 2001). Additionally, EPA and DHA dietary intake increase their proportion in cell membranes. Such effect decreases the generation of pro-inflammatory molecules derived from omega-6 PUFAs (Martínez Leo et al., 2019).

Other PUFAs, namely conjugated fatty acids – conjugated linoleic acid (CLA) and conjugated linolenic acid (CLNA) – are also known for their anti-inflammatory potential. It was observed that CLA – a group of positional and geometric isomers of LA – exerts a PPAR-γ anti-inflammatory action on colitis, by repression of TNF-α expression and NFkB activation, while inducing the expression of the immunoregulatory cytokine TGF-β1 (Bassaganya-Riera, Reynolds, Martino-Catt, Cui, Hennighausen, Gonzalez, Rohrer, Benninghoff, & Hontecillas, 2004). Regarding CLNA, the punicic acid isomer, was associated with suppression of NFkB activation and TNF-α expression. Such action was also mediated by PPAR-γ, since loss of PPAR-γ impaired the ability of dietary punicic acid to suppress inflammation (Hontecillas et al., 2009).

4. Bioactive lipids and brain: role of fatty acids on neuroinflammation

The role of PUFAs in the brain especially during early development is widely recognized: they play important biological roles, including receptor binding, neurotransmission, signal transduction and eicosanoid synthesis. In fact, PUFAs represent 35% of total lipids in adult brain. Specifically, AA, DHA and EPA play important roles during brain development and in the maintenance of normal brain structure and function. DHA, for instance, accounts for 30 to 40%

of fatty acids in the gray matter of the cortex, being particularly concentrated in synaptic membranes (Chew et al., 2020; Lauritzen et al., 2016; Liu et al., 2015).

Moreover, the bioactive fatty acids obtained from dietary intake can cross the blood-brain barrier (BBB) and reach the CNS where they accumulate (Nadjar et al., 2016). Interestingly, *in vivo* studies in mice showed that high-SFA diet altered the levels of several lipids, and increased the levels of palmitic acid (LC-SFA) in brain. Later, the authors demonstrated that after entering the brain, SFAs are transported into the hypothalamus and are taken up by microglia cells (Valdearcos et al., 2014).

4.1. Obesity and neuroinflammation: the dietary fatty acids role

There is an increasing interest in obesity that despite being a preventable disease has currently reached a worldwide pandemic level and plays a central role in the development of non-communicable diseases. As reviewed by Salsinha and colleagues (Salsinha et al., 2021) hypothalamus inflammation triggered by diet has been showing to play a relevant role in the onset and progression of this disease. Several studies have reported that HFD, particularly LC-SFAs, is responsible for inducing inflammatory processes in both CNS and peripheral tissues, including the adipose tissue (Argente-Arizón et al., 2015; Valdearcos et al., 2014). In fact, 1 to 3 days of HFD consumption is sufficient to elevate inflammatory markers in *in vivo* models (Thaler et al., 2012). Importantly, the inflammatory potential of these fatty acids is associated with a persistent elevation of microglia reactivity and consequent TNF-α secretion (Yi et al., 2017). The LC-SFA palmitic acid induces proinflammatory activation of microglia (Duffy et al., 2015; Valdearcos et al., 2014; Z. Wang et al., 2012) via TLR-4 mediated NFkB pathway induction (Duffy et al., 2015; Milanski et al., 2009; Z. Wang et al., 2012). The effects of LC-SFAs on IKKβ and JNK have been associated to insulin resistance (Ono, 2019). HFD-induced inflammation leads to increased activation of the intracellular kinases JNK and NFkB, through IKKβ (Lawrence, 2009), which induces phosphorylation of the insulin receptor substrate (IRS) on its serine residues and inhibits phosphorylation on its tyrosine residues, critical to the transmission of the insulin signal to downstream effectors and for biological outcomes (Rorato et al., 2017). Insulin resistance causes disruption of insulin signaling processes in the CNS and suppresses the effect of insulin on food intake. Moreover, besides the homeostatic imbalance caused by such processes, insulin resistance is also described as the common link between obesity and the development of type 2 diabetes (W. Chen et al., 2017).

On the other hand, omega-3 fatty acids, through dietary supplementation, have been showing promising results in ameliorating the obesity effects caused by the HFD, specifically by LC-SFAs. Several of the omega-3 beneficial effects have been attributed to their anti-inflammatory potential (Pimentel et al., 2012; Viggiano et al., 2016) thought to be mediated through the GPR120 receptor (Oh et al., 2010). It has been suggested that activation of GPR120 by omega-3 fatty acids abrogates NFkB and JNK pathway activation (Talukdar et al., 2011). Furthermore, Oh Da et al. (2010) reported that DHA stimulation of GPR120 inhibits both TLR 2/3/4 and the TNF-α proinflammatory cascade. Recently, DHA intracerebroventricular injection in male C57BL/6J mice ameliorated the HFD-induced hypothalamic inflammation (Cheng et al., 2020). Some *in vitro* studies have also reported relevant results in microglia cell lines: DHA was able to reverse LPS inflammatory effects in N9 microglia cells (Chang et al., 2015; De Smedt-Peyrusse et al., 2008).

Other PUFAs are also recognized for their anti-inflammatory potential, namely conjugated fatty acids. For instance, CLA has been showing interesting results regarding HFD-induced obesity symptoms, including normalization of serum leptin levels (Ryan et al., 2011; Y.-M. Wang et al., 2005; Yanagita et al., 2005) and positive energy balance (Ryan et al., 2011). CLA isomers incorporation into the brain has been detected in few cases at very low concentrations

(Alasnier et al., 2002; Murru et al., 2021). C18:2 *c*9,*t*11 and C18:2 *t*10,*c*12 were demonstrated to be actively incorporated into the rat brain and in *in vitro* astrocyte cultures (Fa et al., 2005). Since it is known that CLA is an activator of PPARs, specifically PPAR-α, it has been suggested that CLA anti-inflammatory actions in the CNS are possibly connected to the activation of such factors. Indeed, PPAR-α anti-inflammatory action is mediated through repression of many activated transcription factors, such as NFkB, among others. The same anti-inflammatory potential was attributed to CLNA. A study demonstrated that pomegranate seed oil (a source of punicic acid CLNA isomer) affected the morphology of activated BV-2 microglia cells. The authors suggested an immunomodulatory and cytoprotective potential comparable to that of omega-3 PUFAs, in neuroinflammatory disease caused by obesity (Račková et al., 2014).

Besides PUFAs, the possible beneficial role of MUFAs on brain, was recently assessed both *in vitro* and *in vivo*, using microglia cells (BV-2 cell line) and C57BL/6J mice, respectively. In both models using an olive oil source, MUFAs enhanced the microglia anti-inflammatory phenotype, while SFAs polarize microglia towards a pro-inflammatory profile (Toscano et al., 2020). Such results suggest a potential positive impact of olive oil MUFAs (particularly oleic acid) in neuroinflammation.

4.2. Alzheimer's disease

Epidemiological and clinical research studies have shown that a high dietary intake of PUFAs is associated with lower risk for Alzheimer's disease (AD) and related dementias. Moreover, high intake of fish and unsaturated fatty acids are associated with reduced cognitive decline (Gustafson et al., 2020). Importantly, DHA plays an important role in the maintenance of optimal membrane functions and is known to reduce amyloid deposition. This is highly relevant since amyloid deposits are present in AD patients (Gustafson et al., 2020). In addition, increased ratios of omega-6: omega-3 fatty acids have been associated with a higher risk of AD (MacDonald-Wicks et al., 2019). In addition, SPMs, synthesized from omega-3 fatty acids DHA and EPA, are important to resolve inflammation through inhibition of polymorphonuclear leukocytes and lowering vascular permeability. It has been suggested that this process is impaired in AD (Chew et al., 2020; Whittington et al., 2017). Moreover, many studies have also reported alterations to the eicosanoid pathway in AD (Biringer, 2019). Considering omega-3 fatty acids role on SPMs and eicosanoids and their potential in resolving the inflammatory processes underlying this disease, they have attracted a great deal of interest (Martínez Leo et al., 2019).

Importantly, in the CNS the activation of microglia and its associated cytokine production are responsible for inflammatory responses. Unregulated inflammation, excessive cytokine production and failure to resolve inflammatory responses, contribute to chronic neuroinflammation, which is a hallmark of many neurodegenerative diseases, including AD (as reviewed by (Chew et al., 2020)). Omega-3 supplementation inhibits microglial activation and the subsequent inflammatory response by regulating the translocation and nuclear secretion of high mobility group protein B1 (HMGB1). This factor is important since it mediates microglia activation through the TLR4/ NF-κβ pathway, responsible for neuroinflammation after neuronal injury (Martínez Leo et al., 2019).

4.3. Multiple Sclerosis

Multiple sclerosis is considered an autoimmune disorder first described in 1868 by Jean-Martin Charcot. The French neurologist framed the disease as *sclérose en plaques*, which meant multiple sclerosis (MS) in French. MS is characterized by myelin loss (demyelination), accompanied by inflammation within the CNS, which are called the plaques or lesions (Kihara, 2019). The development of MS depends on both genetic and environmental factors, but several studies have reported that impairment of Th cells are involved (Rezapour-Firouzi, 2017). In

summary, Th1 and Th2 cells are the major type of Th cells; the formers produce IL-2 and TNF-α. Th2 cells produce IL-4, IL-5, IL-10 and IL-13,6,7. It is the balance between Th1 and Th2 cells that is considered one of the risk factors of MS. Indeed, altered cytokine profiles in CNS tissue and peripheral blood mononuclear cells have been discovered in MS patients (Imitola et al., 2005). It has been reported that in MS several Th1 cytokines levels are increased, while Th2 cytokines levels are decreased (Rezapour-Firouzi, 2017).

In 1952, Swank suggested that the variations in MS geographical distribution is related with the amount and the type of fat consumption (*1952-Swank-Multiple-Sclerosis-In-Rural-Norway*, 2010). Nowadays, several studies demonstrated that abnormalities of polyunsaturated fatty acids (PUFAs) synthesis may be involved in this disease. Indeed, increased risk for MS development was associated with HFD (Ghadirian et al., 1998). Moreover, when comparing the values between normal and MS patients the saturated/ unsaturated fatty acids ratio is significantly higher in the latter (OLIVEIRA et al., 2019). The increased concentrations of lysolecithin and its SFAs is being appointed as a possible explanation for some changes in MS patients, namely in the platelet behavior.

Moreover, a relation between dyslipidemia and early stages of MS has been found. Indeed, there is a correlation between high density lipoprotein-cholesterol and inflammatory cytokines in MS, confirming the existence of a relationship between lipid metabolism and inflammation (Rádiková et al., 2020). Furthermore, omega-6 fatty acids have been associated with the pathogenesis as well as treatment of MS. Studies evidenced that there is a disturbance in omega-6 fatty acid metabolism in MS and that this disturbance has been linked with dysregulation of cytokines. Indeed, the disturbance of omega-6 metabolism originates an important loss of membrane omega-6 fatty acids LA and AA, which was associated with a decrease in TGF-β. Moreover, the loss of these fatty acids also impact CNS structure and function and, in the long term, can lead to neurological deficits associated with MS (Harbige & Sharief, 2007).

Omega-3 supplementation was first demonstrated in 1995, to being able to modulate some immune functions altered in MS patients (Gallai et al., 1995). Recently, as reviewed by (Labuschagne & Blaauw, 2018) although omega-3 fatty acids seem to have a relative low influence on disease progression they reduce the frequency of relapsing episodes. Moreover, fish oil supplementation was also effective in the reduction of pro-inflammatory cytokines and nitric oxide levels in patients with relapsing-remitting MS (Ramirez-Ramirez et al., 2013). Nevertheless, in 2017 the European Society for Clinical Nutrition and Metabolism stated that there is not enough evidence regarding a positive effect of omega-3 to recommend such supplementation in multiple sclerosis patients (Burgos et al., 2018).

4.4. Schizophrenia

Schizophrenia is a neuropsychiatric disorder with disabling symptoms and a lower life expectancy (Ouyang et al., 2020).

The association between an abnormal lipid content in peripheral tissues and violence in patients with schizophrenia has been reported: low blood levels of total cholesterol and low-density lipoproteins, as well as higher blood triglycerides levels, were associated with violence and a higher suicide risk in schizophrenia patients. Furthermore, disturbance of PUFA metabolism was also associated with schizophrenia, where omega-3 deficits is related with psychiatric symptoms in schizophrenia (as reviewed by (Ouyang et al., 2020)). In fact, low levels of EPA and DHA as well as the ratio of EPA/ AA in red blood cells are associated with hostile behaviour in schizophrenia patients (Watari et al., 2010). Such effects are related with the fact that omega-3, mainly DHA, is important to membrane integrity. Its deficiency alters the structure and function

of membranes and induce dysfunctions in neurotransmission of serotonin and dopamine (Chalon, 2006; Healy-Stoffel & Levant, 2018; Ouyang et al., 2020)

Besides, neuroinflammation has been suggested to play an important role in the pathogenesis of schizophrenia. Uncontrolled microglia activation increases the production of pro-inflammatory factors, which ultimately result in neuronal impairments. Omega-3 fatty acids can control inflammation. Indeed, omega-3 PUFAs, such as EPA and DHA, have anti-inflammatory properties since they can produce resolvins and cytokines and have an inhibitory effect on microglia activation.

5. Conclusion

Fatty acids are important cellular mediators which act on cell membrane integrity and function, as intracellular signaling molecules and can influence gene expression. Thus, they are important mediators in several inflammatory processes. Different fatty acids have different roles in the human organism. For instance, TLR-4 was identified as the mediator responsible for the activation of the innate immune response initiated by LC-SFAs, ultimately resulting in NFkB activation. While LC-SFAs have a pro-inflammatory profile, the MUFAs and conjugated fatty acids, CLA and CLNA, were shown to downregulate NFkB pathway through PPAR-γ stimulation. Furthermore, *in vivo* studies have shown that MUFAs along with PUFAs interact with the GPR120 receptor and that its activation is responsible for the inhibition of NFkB activation. Thus, it has been suggested that these unsaturated fatty acids can inhibit NFkB through direct binding of PPARs or GPR120, blocking its activation by LC-SFAs. Notably, neuroinflammation plays an important role in the pathogenesis of schizophrenia, AD, obesity and MS. For instance, uncontrolled microglia activation increases the production of pro-inflammatory factors, which ultimately results in neuronal impairments. Indeed, omega-3 PUFAs, such as EPA and DHA, anti-inflammatory properties have an modulatory effect on microglia, inhibiting their activation and the subsequent inflammatory response.

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7. Conflicts of interest

The authors declare no conflict of interest.

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10. References

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Table 1 – Summary of some relevant studies available since 2017 regarding fatty acids' effects on Alzheimer's disease (AD).

Fatty acids studied	Study's objectives	Experimental model	Main results	Reference
Dietary short-, medium-, and long-chain fatty acids.	Determine the associations between AD risk and dietary fatty acid intakes.	Multiethnic, longitudinal, population study from the Washington Heights-Hamilton Heights-Inwood Columbia Aging Project (WHICAP). Dietary intake was measured using a food frequency questionnaire.	Higher intake of DHA and EPA are protective for AD.	(Gustafson et al., 2020)
Long-chain fatty acids particularly omega-6 fatty acids.	Evaluate whether a range of dietary long-chain fatty acids are associated with cognitive performance in older men and women.	Data from the Hunter Community Study (HCS) (older men and women of Newcastle Australia); comparing dietary data from a validated Food Frequency Questionnaire with validated cognitive performance measures.	A higher intake of total omega-6, but not other types of fatty acids, was associated with better cognitive performance.	(MacDonald-Wicks et al., 2019)
Fish oil (rich in omega-3 polyunsaturated fatty acids).	Determined the dynamic alterations of blood-brain barrier transport function in the early disease stage of AD.	APPswe/PS1dE9 C57BL/6J (APP/PS1) transgenic mice	Supplementation with fish oil significantly enhanced the expression level of LRP-1 - a main efflux transporter of blood-brain barrier -, promoted Amyloid-β (Aβ) plaques clearance from the brain to circulation, inhibited NFkB activation, reduced the expression of interleukin-1β and tumor necrosis factor-α and suppressed the glial activation in mice.	(Yan et al., 2020)
Unsaturated fatty acids: linoleic acid, linolenic acid, DHA, EPA, oleic acid and arachidonic acid.	Metabolic profiling of brain tissue samples from AD individuals (57 to 95 y old) to assess how the abundance of omega-3 and omega-6 fatty acids species is affected by differing levels of disease pathology.	Autopsy sample of the Baltimore Longitudinal Study of Aging (BLSA) forming three groups: AD, controls and "asymptomatic Alzheimer's disease", *i.e.*, individuals with significant AD neuropathology at death but without evidence for cognitive impairment during life.	Unsaturated fatty acid metabolism is significantly dysregulated in the brains of patients with varying degrees of Alzheimer pathology.	(Snowden et al., 2017)
Fish oil supplementation	Determine the impact of supplemental xanthophyll carotenoids plus omega-3 fatty acids on disease progression in patients with AD.	Three trials: supplementation of AD patients with xanthophyll carotenoids; combined supplementation of xantophyll and fish oil; subjects free of AD supplemented with xantophyll.	Preliminary results suggest positive outcomes for patients with AD who consumed a combination of xanthophyll carotenoids plus fish oil.	(Nolan et al., 2018)
Omega-3 or olive oil supplementation	Determine the effect of omega-3 PUFA supplementation on behavioral performances and hippocampal neurogenesis, volume, and astrogliosis.	Aged mice subjected to a selective depletion of basal forebrain cholinergic neurons- valuable model to mimic one of the most reliable hallmarks of early AD neuropathology.	Omega-3 polyunsaturated fatty acids can counteract behavioral deficits and hippocampal neurodegeneration in the experimental model.	(Cutuli et al., 2020)

Table 2 - Summary of some relevant studies available since 2017 regarding fatty acids' effects on Multiple Sclerosis (MS).

Study's objectives	Experimental model	Main results	Reference
Evaluate the lipid profile characteristic of MS present in cerebrospinal fluid and plasma.	Preliminary untargeted qualitative lipidomics analysis comparing cerebrospinal fluid and plasma samples from patients with MS, other inflammatory neurological diseases and idiopathic intracranial hypertension.	Cerebrospinal fluid and plasma from patients with MS present a unique lipid signature that can be useful as a diagnostic biomarker.	(OLIVEIRA et al., 2019)
Determine the association between lipoprotein subfractions and inflammatory status in early stages of MS.	Lipoprotein profile analysis in 19 newly diagnosed MS patients	Male MS patients might be at higher risk of atherosclerosis development. Presence of subtle dyslipidemia in early stages of the disease. Observation of mutual links between systemic inflammation and lipid metabolism in early MS with low inflammatory activity.	(Rádiková et al., 2020)
Investigate the role of environmental lipids in shaping the tissue resident Treg (regulatory T cells) phenotype.	*Ex vivo* computational analyses and *in vitro* experimental assays with human Tregs isolated from peripheral blood and adipose tissue.	Oleic acid concentrations were reduced in patients with MS. Exposure of MS Tregs to oleic acid restored defects in their suppressive function.	(Pompura et al., 2021)
Investigate the association between dietary intake of polyunsaturated fatty acids and MS risk.	Assessment of 80,920 women from Nurses' Health Study (1984–2004) and 94,511 women from Nurses' Health Study II (1991–2009) dietary intake from a validated food frequency questionnaire every 4 years. Identification of 479 incident MS cases during follow-up.	Higher intake of total polyunsaturated fatty acids at baseline was associated with a lower risk of MS. Low dietary polyunsaturated fatty acids intake may be another modifiable risk factor for MS.	(Bjørnevik et al., 2017)
Analyze possible changes in the lipidome (namely fatty acids) of MS patients.	Lipidomic approach to analyze the cerebrospinal fluid of MS patients diagnosed with relapsing-remitting MS.	Unique cerebrospinal fluid lipidomic signature in MS patients at the time of diagnosis that might be considered as a potential diagnostic tool.	(Nogueras et al., 2019)
Optic neuritis is an acute inflammatory demyelinating disorder of the optic nerve and is an initial symptom of MS. Address a possible role of fatty acids diet supplementation in counteracting optical neuritis, namely retinal ganglion cell degeneration.	Experimental autoimmune encephalomyelitis mouse model of MS, a well-established model for optic neuritis.	Dietary supplementation with Neuro-FAG (nFAG®), a balanced mixture of fatty acids (FAs), counteracted inflammatory and gliotic processes in the retina.	(Dal Monte et al., 2018)

Table 3 - Summary of some relevant studies available since 2017 regarding fatty acids' effects on Schizophrenia.

Study's objectives	Experimental Model	Main results	Reference
Scan the free fatty acids pattern and elucidate the characteristics of lipid metabolic abnormality in schizophrenia patients.	110 patients with schizophrenia and 109 healthy controls.	Monounsaturated fatty acids and omega-6 polyunsaturated fatty acids were significantly increased in schizophrenia. Desaturation from saturated fatty acids to monounsaturated fatty acids and β-oxidation were enhanced. These results suggest that lipolysis and β-oxidation are upregulated in this disease, presumably resulting from insufficient brain energy supply.	(X. Yang et al., 2017)
Determine if omega-3 fatty acids may be of value in enhancing BDNF levels and improving cognitive function in patients with schizophrenia and metabolic syndrome.	12-week randomized placebo-controlled trial: 80 patients with both schizophrenia and Metabolic syndrome.	Omega-3 treatment improves cognitive function in schizophrenia patients with metabolic syndrome. Omega-3 enhanced BDNF levels after 12 weeks of treatment through suppressing TNF-α levels.	(Tang et al., 2020)
Investigate if the levels of oxidative markers are increased in schizophrenia compared with healthy controls and if they are associated with the levels of membrane polyunsaturated fatty acids and symptom severity.	51 control patients and 55 patients with schizophrenia spectrum disorders, assessed during an acute phase and 5 years later during a stable phase.	Redox regulation is dynamic and changes during different phases of the disorder. Abnormal levels of antioxidants (α-tocopherol) in the stable phase indicate persisting redox dysregulation. Changes in α-tocopherol were associated with polyunsaturated fatty acids levels in the acute phase.	(Solberg et al., 2019)
Examine the relationship between omega-3 fatty acids with cognitive function, social function, and psychiatric symptoms in patients with schizophrenia.	30 patients with schizophrenia or schizoaffective disorder. Psychiatric symptoms, cognitive function, and social function were assessed using the Positive and Negative Syndrome Scale, the Brief Assessment of Cognition in Schizophrenia (BACS), and the Social Functioning Scale (SFS), respectively.	Reduced blood omega-3 fatty acids are associated with cognitive impairment, which then impacts social functioning outcomes in schizophrenia.	(Satogami et al., 2017)
Determine the differences in polyunsaturated fatty acids nutritional status and metabolism between patients with schizophrenia and healthy individuals.	80 participants (40 in each group).	Different metabolisms of fatty acids in schizophrenia. The diminisched anti-inflammatory response could be a component connecting GPR120 insensitivity with schizophrenia.	(Rog et al., 2020)

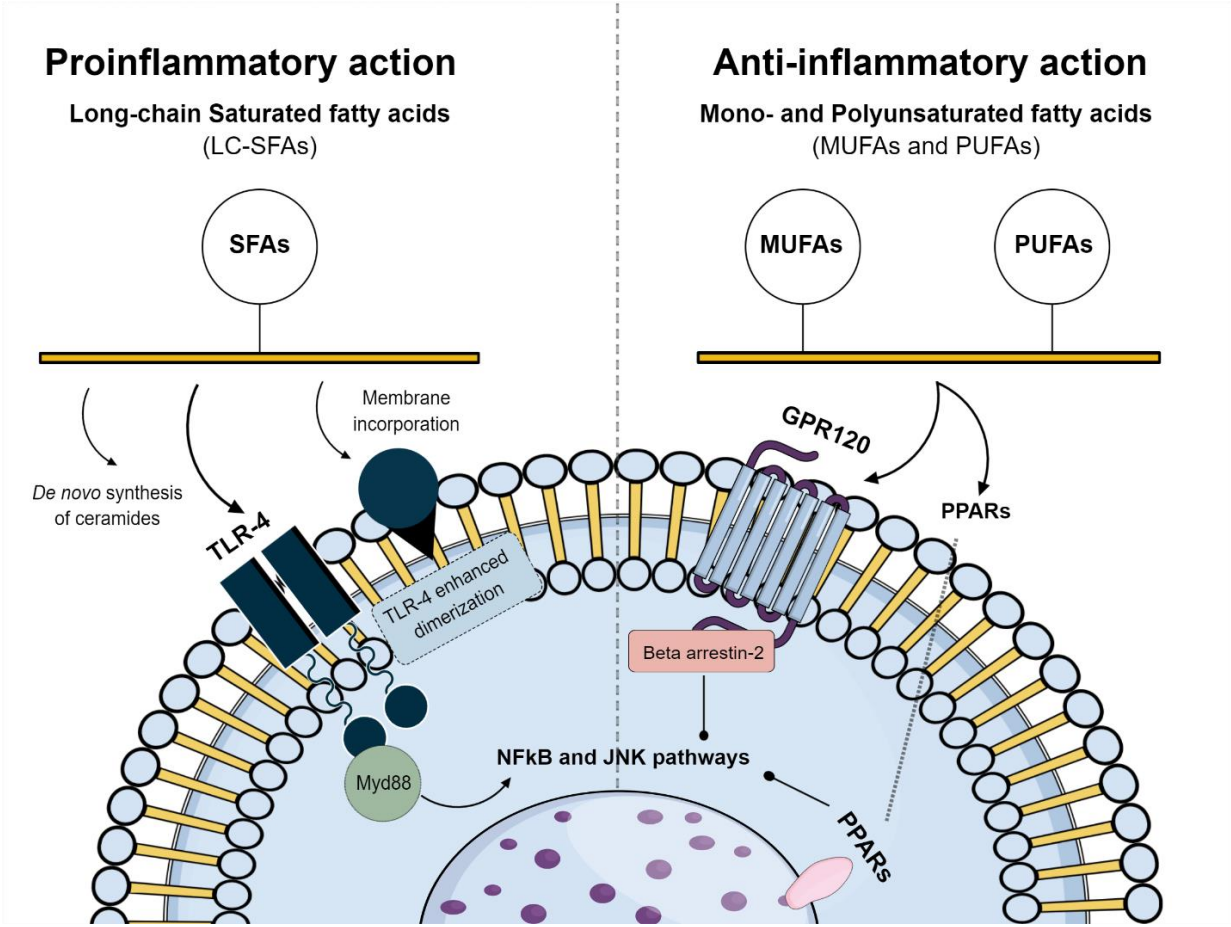

Figure 1 - Pro- and anti-inflammatory action of different fatty acids: Long-chain saturated fatty acids present a proinflammatory potential mediated by TLR-4 and Myd88 activation, ultimately leading to the activation of NFkB and JNK pathways. These saturated fatty acids can be incorporated in specific lipid rafts domains of the plasma membrane where they enhance TLR-4 dimerization, important for its activation. Besides, they are known to be involved in the *de novo* synthesis of ceramides. On the other hand, monounsaturated and polyunsaturated fatty acids through GPR120 and/or PPARs (like PPAR-γ) can repress the activation of NFkB and JNK by saturated fatty acids. Created with Mind the Graph (mindthegraph.com).