Direct and indirect effects of lipids on microglia function

Quentin Leyrolle, Sophie Layé, Agnès Nadjar

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Leyrolle Q[1], Laye S[1], Nadjar A[1]

[1]INRA, Nutrition et Neurobiologie Intégrée, UMR 1286, 33076 Bordeaux, France; Univ. Bordeaux, Nutrition et Neurobiologie Intégrée, UMR 1286, 33076 Bordeaux, France

Abstract

Microglia are key players in brain function by maintaining brain homeostasis across lifetime. They participate to brain development and maturation through their ability to release neurotrophic factors, to remove immature synapses or unnecessary neural progenitors. They modulate neuronal activity in healthy adult brains and they also orchestrate the neuroinflammatory response in various pathophysiological contexts such as aging and neurodegenerative diseases. One of the main features of microglia is their high sensitivity to environmental factors, partly via the expression of a wide range of receptors. Recent data pinpoint that dietary fatty acids modulate microglia function. Both the quantity and the type of fatty acid are potent modulators of microglia physiology. The present review aims at dissecting the current knowledge on the direct and indirect mechanisms (focus on gut microbiota and hormones) through which fatty acids influence microglial physiology. We summarize main discoveries from *in vitro* and *in vivo* models on fatty acid-mediated microglial modulation. All these studies represent a promising field of research that could promote using nutrition as a novel therapeutic or preventive tool in diseases involving microglia dysfunctions.

Keywords: Microglia; Fatty acids; Obesity; Gut microbiota; Hormones, Inflammation

Introduction

Microglia are the resident macrophages of the brain. They have been studied for decades for their role as primary immune cells of the central nervous system (CNS)[1]. They orchestrate the local inflammatory response to maintain tissue homeostasis. Exaggerated activation of microglial inflammation is yet observed in several disorders such as Alzheimer's Disease (AD), Parkinson's Disease (PD), Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS) or obesity, where it can lead to further damage[2]. Microglia are also involved in the resolution phase of inflammation by phagocyting dying cells or debris and by releasing cytokines and some lipid mediators exerting anti-inflammatory and pro-repair properties[3,4].

More generally, microglia are extremely sensitive to their local environment, which they continuously scan with highly motile processes[5,6]. One reason for that is the wide array of receptors microglia expressed at their membrane, known as "microglia sensome", that give them the ability to "sense" and respond to lots of endogenous as well as exogenous signals[7]. Among all receptors identified, several of them can bind to lipids, including membrane phospholipids such as phosphatidylserine (PS) or oxidized lipids. This can promote phagocytosis of myelin, spines, apoptotic cells, protein aggregates, etc. More generally, many factors including nutrition can modulate microglia functions through the activation of their sensome[3,8]. Depending on the brain structure, sex and the type of environmental stimulus, microglia acquire diverse phenotypes characterized by singular transcriptomic signatures[9–12]. The combination of several studies helped to draw the gene profile of microglia, so-called "Disease Associated Microglia" or DAM[13–15]. Interestingly, some of these genes, such as *trem2, apoe, lpl* are related to lipid transport and metabolism [13–15]. Likewise, diseases such as obesity and metabolic disorders, characterized by profound alterations in lipid metabolism, display microglial inflammatory activation [16–19]. Overall, regulation of brain homeostasis is likely to involve some lipid-mediated mechanisms aimed at modulating microglia functions.

A new field of research has hence emerged, aiming at deciphering how lipids affect microglia using a wide variety of protocols (*in vitro* lipid application or *in vivo* dietary approaches) and analyzing outcomes such as inflammation, phagocytosis, density, proliferation, etc.[20,21]. While *in vitro* experiments address a potential direct effect of fatty acids on microglial function, *in vivo* experiments must considered indirect actions of lipids through "secondary actors", including hormones, peripheral immune cells or gut microbiota, that in turn affect microglia function. This review summarizes the current knowledge on direct and indirect effects of lipids on microglial cells and highlights different aspects of this complex relationship.

1. Direct effect of fatty acids on microglia function

Several lines of evidence suggest a link between microglia and fatty acids: 1) Fatty acids are present at high amount in cellular membranes, including microglial cells[22], and many of them can be metabolized into bioactive derivatives [23,24], modulate proteins localization and function as well as downstream signaling pathways[23]. 2) Microglia express many lipid-sensitive receptors such as TREM2, CD36, Toll-Like Receptors (TLRs), receptors for fatty acids derivatives such as endocannabinoids, oxylipins, etc.[25]; 3) Macrophages can store fatty acids within lipid droplets, that are known to control their inflammatory response and phagocytic activity [26], suggesting that lipids are potential regulators of microglial function[20]. All these observations suggest a potential role of fatty acids on microglial physiology.

Three main families of fatty acids have been studied, based on the number of double bonds: the saturated (SFA), monounsaturated (MUFA) or polyunsaturated (PUFA) fatty acids. Subfamilies are distinguished by the position of unsaturation and the length of the hydrocarbon chain. In the following chapters, we extensively review the literature on the effects of SFA, MUFA and PUFA on microglial cells.

1.1. Microglia and SFA

SFA are present in great quantities in obesity-inducing diets, among which palmitate (C16:0) is the most abundant. Hence, high-fat diet (HFD) intake rises brain SFA levels, and more specifically those of palmitate[19]. Several studies showed that HFD modulates brain inflammatory status[27], in a body weight-independent [19,28] and microglia-dependent fashion[16,19,29,30]. **This supports the newly developed concept that microglia act as nutrient sensors within the brain in basal conditions, so that when levels of dietary nutrients suddenly rise, these cells are among the first to react, long before metabolic alterations occur[31]. Once obesity develops, the increase in adiposity and associated metabolic disturbances and inflammatory processes will contribute to the second phase of microglial microglia activation[27].** Microglial activation and neuroinflammatory processes are initiated within the hypothalamus, before spreading to other structures such as amygdala, hippocampus and cerebellum[32–34].

In terms of mechanisms, the pioneer study of Valdearcos and colleagues revealed that in animals fed a SFA-rich diet, fatty acids, including palmitic acid, are rapidly conveyed to the brain after ingestion. There, they are directly taken up by microglia within the hypothalamus

to trigger an inflammatory response[19]. Palmitic acid in return induces central insulin and leptin resistance and impairs **glucose and lipid** metabolism[35,36]. *In vitro* studies on microglial cell cultures confirmed the ability of SFA to initiate an inflammatory reaction, characterized by the production of pro-inflammatory cytokines and oxidative stress response[19,37–40]. However, a more recent study using a lower dose of palmitate showed that application of this fatty acid on BV2 and IMG cells, two immortalized microglial cell lines, induces an anti-inflammatory response[41]. This study pinpoints the potential neuroprotective action of palmitate-treated microglia, that release interleukin-13 (IL-13) and in turn induce an anti-inflammatory response in co-cultured hypothalamic neurons[41]. Beyond the fact that the relevance of *in vitro* models of microglia, and especially the use of cell lines, must be questioned[42], these results highlight the importance of the dose, duration of treatment and type of SFA considered when studying their effects on microglial physiology[41,43]. Moreover, none of these studies ever considered and/or studied potential modulations of lipid transport into the brain, as well as their local synthesis and metabolism within the CNS.

How SFA affect microglial phagocytosis is still a matter of debate. While a BV2-based study showed that palmitate enhances phagocytosis[38], this has been recently challenged by another study using primary microglia culture[40]. In the latter, they showed that application of palmitate does not increase basal phagocytic activity and suppresses interferon-γ (IFN-γ) induced phagocytosis[40]. Of note, these two groups used different experimental conditions: palmitate dissolved in ethanol *vs* methanol, different doses (125 µM *vs* 100-200µM), different duration of phagocytic assays (5h *vs* 1h). Further studies are thus needed to understand how palmitate and other SFA, if they do, modulate microglial phagocytosis.

Of importance, a recent study conducted on macrophages highlighted various pitfalls in palmitate studies [43]. Indeed, fatty acids require specific carriers (e.g. BSA) or solvents (e.g. ethanol) to increase their solubility, both factors having a strong effect on cellular activity. Moreover, Bohlen et al. demonstrated that the composition of culture medium is a potent modulator of microglial function, hence adding another potential bias to *in vitro* studies[44]. Overall, combining different approaches (*in vitro*, *ex vivo* and *in vivo*) as well as using cell components (dead neurons, synaptosomes) in phagocytic assay rather than beads seems essential to conclude on the (direct) effects of SFA on microglia function.

1.2. Microglia and MUFA

The beneficial inflammation in BV2 cells[45,46]. Based on the same microglial cell line, Debabbi and collaborators reported that oleate **(18:1)** prevents7-ketocholesterol-inducedcytotoxicity[47].

In microglia primary cultures, oleic acid does not trigger pro-inflammatory cytokines release while SFA do[19]. MUFA have greater affinity than SFA for the transcription factor peroxisome proliferator-activated receptor (PPAR), that mainly promotes anti-inflammatory processes[48]. Thus, it could represent a mechanism through which oleate exerts its anti-inflammatory effects. Data also show that the oleate derivatives oleamide increases phagocytic activity of microglia towards amyloid beta (Aβ) particles both *in vitro* and *in vivo*[49].

1.3. Microglia and polyunsaturated fatty acids (PUFA)

We focus here on the two main PUFA families, n-3 and n-6 PUFAs, that differ by the position of the first double-bound[23]. The main PUFA that constitute the mammalian brain are the long chain (LC) fatty acids arachidonic acid (AA) and docosapentaenoic acid (DPA, **22:5 n-6**) from n-6 family and docosahexaenoic acid (DHA, **22:6 n-3**) from the n-3 group[50]. The n-3 PUFA eicosapentaenoic acid (EPA, **20:5 n-3**) is present at very low oncentration in the CNS, yet it is enriched in the membrane of microglial cells[22]. LC-PUFA are either biosynthesized from their dietary precursors, respectively linoleic acid (18:2n-6 or LA) and α-linolenic acid (18:3n-3 or ALA) or can be directly sourced from the diet (mainly meat and dairy products for AA/DPA, fat fishes for DHA/EPA)[51,52]. PUFA are mainly esterified into phospholipids within cell membranes[23]. They can also be released from these membranes in a phospholipase A2-dependent manner. Once free from the membrane, PUFA can act directly on specifics targets or can be enzymatically metabolized, leading to the production of a wide variety of derivatives, such as docosanoids, eicosanoids or endocannabinoids[3]. PUFA and their bioactive mediators exert numerous biological properties, from immunomodulation to neuronal plasticity or regulation of gene expression[3].

Westernization of dietary habits not only led to an increase in SFA intake but also to a decrease of the n-3/n-6 PUFA ratio (both from a decrease in n-3 PUFA consumption and an increase in n-6 PUFA)[53]. Consequently, AA brain concentration rose while DHA content diminished[3,53]. Moreover, our data show that lifelong dietary n-3 PUFA deficiency specifically alters microglia composition in mice[22]. Numerous groups also studied the effect of PUFA on microglia inflammatory activity *in vitro*, knowing that n-3 PUFAs and their derivatives are considered rather anti-inflammatory while n-6 PUFAs and their derivatives are anti-inflammatory[3]. DHA, and to a lesser extent EPA, decrease the production and release of pro-inflammatory cytokines, oxidative stress and NO production after treatment with LPS, cytokines or Aβ[54–58]. *In vivo* studies confirmed that DHA and/or EPA attenuate neuroinflammation and microglial activation triggered by various inflammatory challenge

(HFD, LPS, aging, maternal immune activation)[59–68]. Among the pathways activated by n-3 PUFA, DHA and EPA have been shown to inhibit the inflammatory signaling cascades NFκB, and MAPK and to activate the anti-inflammatory factors PPAR, retinoid X receptor (RXR) and the G-protein coupled receptor 120 (GPR120) [3,54,57,58]. Another property of DHA is to remodel lipid bodies inside microglia cells, counteracting the effect of inflammation by restoring mitochondrial function[69,70].

PUFA can also modulate the phagocytic activity of microglia. Two *in vitro* studies observed similar results, i.e. an increase in phagocytic activity against Aβ particles and myelin debris in response to EPA or DHA application[55,71]. Moreover, we showed *in vivo* that perinatal dietary n-3 PUFA deficiency increases microglia-mediated phagocytosis of synaptic elements in the CA1 region and of apoptotic neurons in the dentate gyrus of juvenile mice[72]. Altogether, these data suggest that n-3 PUFA differentially regulates the phagocytic response of microglial cells depending on the context (physiology vs pathology, cellular elements vs exogenous stimuli, etc.). Further studies are needed to clarify how the n-3/n-6 PUFA balance controls microglial phagocytic activity, such as exploring the role of PUFA derivatives that are known to influence microglial function as well[3].

PUFA derivatives are produced through a wide range of enzymatic and non-enzymatic pathways[3]. A positive correlation between DHA and EPA intake and blood level of their derivatives has been observed, meaning that dietary PUFA intake directly influences the amount of bioactive compounds[73,74]. Oxylipins such as n-6 PUFA-derived prostaglandins, thromboxanes or lipoxins and n-3 PUFA-derived resolvins, maresins or neuroprotectin are synthesized by the cyclooxygenase (COX), lipoxygenase (LOX), cytochromes P450 (CYP) and epoxide hydrolase (EH)[3,24,75]. A differential expression of lipid mediators is observed across inflammation in parallel of cytokine expression [24,76]. Decreasing n-3 PUFA-derived pro-resolutive species might have detrimental effects, leading to chronic inflammation[24]. Resolvins from the D- (DHA-derived) or the E-series (EPA-derived) decrease neuroinflammation and counteract microglial activation[77–80]. The release of neuroprotectins and maresins also protect from microglial inflammatory activation. Moreover, maresins facilitate phagocytosis of Aβ by microglia[81,82]. The situation is more complex for n-6 PUFA derivatives. While prostaglandins can be either pro- or anti-inflammatory, thromboxanes and leukotrienes promote microglial activation and neuroinflammation[3]. AA-derived prostaglandin E2 (PGE2) for instance has been shown to decrease microglia phagocytosis of Aβ through its receptor EP2[83]. Likewise, AA-derived lipoxin A4 is anti-inflammatory in various models of CNS inflammation[84–86].

PUFA can also be metabolized into endocannabinoids. Microglia possess all the machinery to produce these molecules and express their receptors, namely CB1 and CB2[3,87]. The most abundant AA-derived endocannabinoids, anandamide and 2-arachidonoylglycerol, dampen microglial inflammation[88]. Endocannabinoids can also be produced from DHA and EPA. The DHA-derived DHEA (or synaptamide) and EPA-derived EPEA exert anti-inflammatory activity on microglial cells, yet only few data are available in the literature[89,90]. Overall, and regardless of their precursor, endocannabinoids are likely to exert anti-inflammatory action on microglia notably through CB2 receptors but more extensive studies are needed to decipher the mechanisms underlying these effects[87,88].

1.4. Microglia and other lipids

Other lipids modulate microglia function. Cholesterol, lipoproteins, lipid-related enzymes or receptors can control microglia phenotype and phagocytic activity. As we described above, DAM are characterized by altered expression of lipid transport and metabolism related genes such as *apoe*, *trem2* or *lpl*[13–15]. In this part, we explore the literature linking microglia functions with these factors.

Trem2 and APOE. TREM2 is specifically expressed by microglial cells in the brain. It binds to phospholipids, LPS, lipoproteins such as LDL, and apolipoproteins including APOE and APOJ [7,91,92]. Interaction of TREM2 with apoliporoteins is involved in microglia-mediated Aβ phagocytosis and could explain why mutations in *trem2* and *apoe* have been associated with neurodegenerative diseases[91,92]. APOE is also pivotal in the polarization of microglial phenotype during development, aging and neurodegenerative disorders[42,93]. Concomitantly, its expression is high during development and decreases across brain maturation[42]. APOE and TREM2 both promote microglia protective effects in contexts such as neurodegenerative diseases, stroke, MS or brain development[15,91,92,94–100]. While the specific mechanisms are not fully understood, several reports suggest that these molecules are necessary for microglia reactivity to injuries, by controlling their inflammatory response and metabolism[91,101–103].

Lipoprotein lipase (LPL). Another lipid-related gene that appears to modulate microglia phenotype and function is *lpl*[14,17]. This gene encodes the protein LPL, which hydrolyzes triglycerides that are bound to lipoproteins. In mice models of neurodegenerative and neuroinflammatory diseases, *lpl* expression is increased[14,104]. These observations were confirmed in brain samples of AD patients[14,105]. Increased expression of *lpl* has been observed

during remyelination and its role in promoting microglia phagocytosis has also been revealed[104,106–108]. Inhibition or suppression of LPL skews microglia phenotype towards pro-inflammation and decreases their phagocytic activity[104,107]. HFD increases *lpl* expression in hypothalamic microglia[17]. In this context, inhibiting LPL activity aggravates HFD-induced metabolic alterations[17].

Cholesterol. Cholesterol is synthesized *de novo* in the brain, mainly by astrocytes[109,110]. It is then transferred to surrounding cells through APOE, the main cholesterol-carrier of the CNS, that is expressed by both astrocytes and microglia[111,112]. Cholesterol uptake by microglia, that follows APOE-TREM2 interaction, ensures survival of cultured cells[44,92]. Even though the mechanisms remain unclear, cholesterol metabolism modulates microglial phagocytic capacity[44,109,113]. When present at high concentration, engulfed cholesterol (cellular debris, myelin), can no longer be digested by microglia so that it accumulates within lipid bodies or cholesterol crystals[114]. Cholesterol efflux capacity is overwhelmed in these conditions[114], impairing the normal induction of remyelination processes in a context of lysolecithin-induced demyelination in aged mice[114]. This maladaptive immune response (cholesterol efflux impairment) could explain why alterations in the expression of genes like *apoe* or *trem2* are associated with greater risks of neurodegenerative disorders.

Cholesterol can be metabolized in bioactive derivatives, namely oxysterols. These latter modulate microglial inflammatory response *in vitro* as well as MS and AD brains[111,115,116]. Many oxysterols are anti-inflammatory as they decrease LPS-induced inflammatory response in microglia primary culture[116]. Conversely, 25-hydroxycholesterol (25-OH) promotes neuroinflammation in a model of adrenoleukodystrophy[117]. Mechanisms through which oxysterols modulate brain inflammation remain unknown. Some reports suggest that they could act through LXRs[116,117]. Interestingly, LXRs activation is beneficial in AD progression as it decreases Aβ burden and as a consequence cognitive impairments[118–120]. Oxysterols have been recently showed to stimulate microglial expression of ABCA1 and APOE, two targets of LXR signaling, hence favoring cholesterol efflux[121–123].

Other lipid carriers have been studied for their ability to control microglia function. A recent paper highlighted the role of Apolipoprotein A-I binding protein (AIBP) in microglial activation in a context of neuropathic pain[124]. HDL and APOA-I, its principal protein component, are known to bind AIBP which interacts with TLR4, leading to cholesterol efflux

and remodeling of lipid rafts[124,125]. Overall AIBP and cholesterol efflux exert anti-inflammatory action on microglia and macrophages[124,126,127].

2. Indirect effects of lipids on microglia function

The levels of body lipids are controlled by two main factors: 1) dietary intake and 2) endogenous lipid synthesis and metabolism, which are themselves regulated by a wide variety of genetic or environmental factors[128]. Some reports suggest that peripheral lipids can influence microglia function as well, through indirect mechanisms including microbial-derived metabolites, hormonal control and inflammation. In a second part, we are summarizing current knowledge on the potential candidates involved in lipid-mediated indirect modulation of microglial activity. We concentrate on experimental contexts in which lipid intake and/or metabolism are disturbed such, as HFD feeding, obesity and n-3 PUFA deficiency. We more specifically discuss the role of hormones and gut-derived messengers in these aspects (as the role of inflammation has been extensively reviewed in the past).

2.1. Microglia and gut physiology

Microbiota and their metabolites. Diet is one of the main modulator of gut microbiota composition and function. Relative intake of proteins, lipids and carbohydrates as well as fiber consumption not only controls the diversity of microbial species but also their activity (e.g. metabolites production)[129–133]. More specifically, the quantity and quality of lipid intake can modulate intestinal permeability, low-grade inflammation, fat storage and endocrine activity[132,134–136,134,137,138]. Conversely, microbiota controls fat absorption, storage and metabolism[139,140]. Furthermore, microbiota composition and function influences behavior, neuronal activity and neuroinflammatory processes [12,141–147].Notably, microbiota transfer from HFD-fed mice to standard chow-fed animals triggers behavioral deficits and neuroinflammation in the acceptor mice[148]. Recent studies have shown that microglia are sensitive to microbial activity[12,142,145,149]. In a pioneering study, Erny and colleagues showed that germ-free mice display alterations in microglial morphology [142]. Knocking-out TLR receptors did not reverse the phenotype, suggesting that the effect of microbiota on microglia is independent of microbial ligands recognition [142]. Authors also showed that short-chain fatty acids (SCFA), which are bacterial metabolites, are involved in gut-microglia communication through activation of the free-fatty acid receptor 2 (FFAR2)[142]. More recently, Thion et al. showed that microbiota modulates microglia transcriptome in a sex and age-dependent manner[12]. Moreover, they revealed that maternal microbiota influences the maturation of fetal

microglia [12]. Overall, these studies highlighted for the first time the role of gut bacteria and associated metabolites on microglia phenotype. Rothhammer and colleagues showed that tryptophan-derived metabolites produced by the commensal flora limits microglial inflammatory activation in the experimental autoimmune encephalomyelitis (EAE) mouse model of MS. Specific removal of aryl hydrocarbon receptor (AHR) receptor from microglia, a receptor for tryptophan metabolites, worsened microglial inflammation and subsequent outcomes of EAE [148]. These 3 pioneering studies lay the foundations for a new field of research on the microbiota-microglia axis[141,149]. Yet, previous studies had already shown that microbiota-derived molecules (SCFA, AHR ligands) modulate neuroinflammation and microglia function. SCFA levels are altered in obese subjects, among which butyrate can counteract most of the side-effects of HFD including lipogenesis and inflammation[150,151]. Butyrate also decreases LPS-mediated microglial activation *in vitro*, by blocking NFκB pathway and by promoting apoptosis in these cells[152–155]. *In vivo,* butyrate and high-fiber diet (which increases SCFA levels) dampen neuroinflammation in mice models of aging, stroke and acute LPS injection[155–157]. The microbiota can also generate conjugated fatty acids from dietary fatty acids. A recent study showed that 10-oxo-trans-11-octadecenoic acid and 10-hydroxy-cis-12-octadecenoic acid, two LA derivatives produced by lactobacillus plantarum, exert anti-inflammatory effects in BV2 cells[158]. Beyond these studies, only little is known about the mechanisms involved. Yet, it was shown that brain concentration of gut-derived tryptophan metabolites, such as the indole family, increases following systemic administration of these compounds, suggesting that they can reach the CNS after production by the microbiota[159]. Moreover, butyrate is likely to exert its effect by binding to several types of receptors: the above-mentioned FFARs but also GPR109a (or HCAR2) and GPR164 (or Olfr558)[160].

Bile acid. Bile acid (BA) synthesis and recycling depends on the tight collaboration between the liver and the gut[161,162], BA being released by the liver and controlling lipid absorption in the intestine. The microbiota control liver-derived BA pool size. Moreover, reduced BA levels in the gut are associated with bacterial overgrowth and inflammation[163]. Two main receptors are thought to mediate their effects, namely the nuclear farnesoid X receptor (FXR) and the Takeda G protein-coupled receptor 5 (TGR5). BA-mediated activation of these receptors modulates metabolism (lipid and carbohydrate metabolism, energy expenditure) and inflammatory processes[161,162,164]. Their role in the control of microglia function has been highlighted by recent studies showing that BA *per se* or targets of BA receptors control

microglial activation in animal models of neuroinflammation (hepatic encephalopathy, retinal degeneration, LPS or Aβ injection, HFD)[165–172]. BA is likely to indirectly act on the brain by activating TGR5 in enteroendocrine cells that in turn release GLP-1, a known modulator of brain function[173].

Overall, all these studies suggest that the microbiota communicates with the brain using various, direct and indirect, pathways. If most of above-mentioned gut-derived metabolites can theoretically reach the brain, it remains unclear how they modulate microglia function in return. Moreover, most of these molecules may act peripherally, by modulating neurotransmitter release in the gut, by stimulating vagus nerve terminals or by acting on peripheral organs that would lead to the release of secondary messengers (e.g. hormones, cytokines or chemokines).

2.2. Hormones and microglia

Both the quantity and quality (SFA, MUFA, PUFA, short- or long-chain, etc.) of lipids can modulate metabolic outcomes including insulin resistance, adiposity, inflammation and hormones levels[19,174,175]. PUFA for instance, especially from the n-3 series, decrease triglyceridemia, insulin resistance or inflammation[176–180]. A recent study showed that the transplantation of microbiota from Fat-1 mice (genetically enriched in n-3 PUFA) prevents metabolic disorders triggered by HFD exposure in WT littermates[181]. This suggests that the beneficial effects of n-3 PUFA on metabolic deficits are mediated by the microbiota, at least partially. Moreover, dietary lipids modulate hormone release by peripheral organs such as the gut, liver, stomach and pancreas[178,182]. In this part, we will discuss the link between circulating hormones, metabolic status and microglia function as a potential indirect mechanism by which lipids may regulate neuroinflammation.

Insulin. Obesity and SFA intake induce insulin resistance and hyperinsulinemia[27]. If the effects of insulin on neurons have been extensively studied, how this hormone might regulate microglia remains largely unknown. One *in vitro* study revealed that insulin application on microglial cells decreases LPS-induced NO and TNF-α production, and potentiates their phagocytic activity, in a dose-dependent manner[212]. Overall, insulin might exert anti-inflammatory and pro-repair effects, yet this needs to further studies.

Insulin like growth factor 1 (*IGF-1).* IGF-1 is a growth factor that shares structural similarities with insulin. Its blood concentration is decreased in metabolic syndrome and obese subjects, while PUFA (both n-6 and n-3 series) can increase it[185,186]. Specific microglial populations can synthesize and release IGF-1[187–190]. These cells usually support neurodevelopmental processes such as neuron survival and myelination among others.

Glucagon-like peptide-1. The peptide GLP-1 is mainly synthesized by enteroendocrine L cells. It promotes insulin sensitivity and reduces food intake, plasma glucose levels and body weight[191]. Both the type and amount of lipids modulate GLP-1 release[192,193]. Moreover, microbiota can also increase GLP-1 levels through the activity of its metabolites[160]. When produced, GLP-1 has a very short lifetime as it is rapidly degraded by dipeptidyl-peptidase 4. Hence, it is thought that peripheral GLP-1 is mainly acting on brain vagal signaling[194]. However, neurons and microglia can also sense and release GLP-1[194,195]. Microglial GLP-1 production is blunted in LPS-treated microglia or in the context of obesity[195,196]. Moreover, administration of GLP-1 receptor agonists (e.g. liraglutide, lixisenatide, exendin-4 or NLY01) prevents microglial activation[197,198]. Yun and colleagues recently showed that NLY01 displays neuroprotective properties in a model of α-synucleinopathy by preventing microglia-mediated conversion of astrocytes into an A1 (inflammatory) phenotype[198]. The same neuroprotective effect of GLP-1 receptor activation has been observed in a wide variety of neuroinflammation models[195,199–203].

Leptin. Leptin originates from the adipose tissue. It is an anorexigenic hormone whose production is increased in obese patients (combined to leptin resistance), while a supplementation with n-3 PUFA can decrease it[27,204]. Leptin is structurally close to interleukins and influences neuroinflammatory processes[205,206]. Under SFA-enriched diet, microglia decreases leptin signaling in the hypothalamus as shown by depleting these cells with the CSF1R inhibitor PLX5622[19]. Microglia express the leptin receptor and respond to the hormone by mounting a proinflammatory response[205–208]. Deletion of microglial leptin receptor recapitulates many symptoms observed in mice lacking leptin receptor (db/db mice) especially in the context of obesity[209]. Moreover, this specific deletion alters microglia morphology and decreases its phagocytic activity[209].

Amylin. Amylin is a pancreatic peptide that shares several biological effects with GLP-1 and exerts neuroimmunomodulatory activity[191]. Amylin treatment regulates microglia

inflammatory response, as its application stimulates IL-6 production by microglia which in turn increases the sensitivity to leptin, giving amylin the role of "leptin sensitizer"[210,211].

Adiponectin. Adiponectin originates from adipocytes. Its production is decreased in obese patients and increased by n-3 PUFA intake[204,212]. This hormone exerts anti-inflammatory effects on microglial cells through its receptor AdipoR1[212–214]. Song and colleagues also suggested that adiponectin promotes neuroprotective phenotype of microglia by activating PPAR-γ[214].

Ghrelin. Ghrelin is an orexigenic hormone produced by the stomach and the duodenum[212]. Obesity is known to decrease the overall ghrelin levels while it increases its active form, namely acyl-ghrelin[212,215]. Ghrelin exerts anti-inflammatory and anti-oxidative effects on LPS-stimulated microglia[216]. Moreover, its neuroprotective action has been observed in many models of neuroinflammation[205,217–219]. The mechanisms through which ghrelin decreases microglial activation remain elusive since these cells do not express the ghrelin receptor. Some studies indicate that inhibition of endothelial cells-derived MMP-3 release could represent one mechanisms[219,220].

Conclusion

All these data demonstrate that dietary lipids affect microglia function, either directly or through indirect mechanisms. Yet, many questions remain:

1- Considering other factors (genetic and environmental) that can influence lipid transport and metabolism, including the production of bioactive metabolites.

2- Using large-scale analyses of microglia, such as lipidomics and transcriptomics, to help understanding how lipids regulate microglial function in a wide range of pathophysiological situations.

3- Addressing if and how the peripheral alteration of lipid homeostasis (inflammation, metabolic disturbances and gut microbiota alterations) could either alleviate or reinforce the effects of fatty acids on microglial cells.

4- Exploring further whether circulating hormones and gut microbiota composition/function represent interesting targets to understand the co-morbidities between metabolic diseases (obesity, diabetes) and neuroinflammation.

5- Defining the impact of other nutrients such as carbohydrates and **proteins on microglia function especially regarding its role in neuroinflammation**.

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