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Fatty acid metabolism in the progression and resolution of CNS disorders

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Abstract

Recent advances in lipidomics and metabolomics have unveiled the complexity of fatty acid metabolism and the fatty acid lipidome in health and disease. A growing body of evidence indicates that imbalances in the metabolism and level of fatty acids drive the initiation and progression of central nervous system (CNS) disorders such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease. Here, we provide an in-depth overview on the impact of the β-oxidation, synthesis, desaturation, elongation, and peroxidation of fatty acids on the pathophysiology of these and other neurological disorders. Furthermore, we discuss the impact of individual fatty acids species, acquired through the diet or endogenously synthesized in mammals, on neuroinflammation, neurodegeneration, and CNS repair. The findings discussed in this review highlight the therapeutic potential of modulators of fatty acid metabolism and the fatty acid lipidome in CNS disorders, and underscore the diagnostic value of lipidome signatures in these diseases.

Keywords

Central nervous system, lipids, neuroinflammation, immunometabolism, neurodegeneration, remyelination.

Declaration of interest

None

Abbreviations

ABCD1, ATP-binding cassette subfamily D member 1; ACC, acetyl CoA carboxylase; ALA, α-linolenic acid; ARA, arachidonic acid; CNS, central nervous system; CPT1, carnitine palmitoyl transferase 1; Δ4,5,6,9D, delta-4,5,6,9 desaturase; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EAE, experimental autoimmune encephalomyelitis; EPA, eicosapentaenoic acid; ELOVL, elongation of very long chain fatty acids proteins; FASN, fatty acid synthase; FAO, fatty acid β-oxidation; HNE, 4-hydroxy-trans-2-nonenal; LA, linoleic acid; LCFA, long-chain fatty acid; TLR, toll-like receptor; MCFA, medium-chain fatty acid; mTORC1, mammalian target of rapamycin complex 1; MUFA, monounsaturated fatty acid; NSPC, neural stem and progenitor cell; OPC, oligodendrocyte precursor cell; PUFA polyunsaturated fatty acid; Th1/Th17, T helper 1 cell; Treg, regulatory T cell; SCD, stearoyl-CoA desaturase; SCFA, short-chain fatty acid; SFA, saturated fatty acid; SPM, specialized pro-resolving mediator; SREBP, sterol regulatory element binding protein; VLCFA, very-long chain fatty acids; X-ALD, X-linked adrenoleukodystrophy.

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Content

1. Introduction

Fatty acid metabolism consists of anabolic and catabolic processes that are necessary for energy homeostasis as well as the formation of metabolic intermediates required for the maintenance of cell membrane structure and function, storage of energy, and cell signaling. Recent advances in technologies used to dissect and study fatty acid profiles and metabolism have shed light on the pathogenic and protective role of fatty acid metabolism in health and disease. Not surprisingly, given the abundance of fatty acids in the central nervous system (CNS), emerging evidence indicates that fatty acid metabolism influences the pathophysiology of neurological disorders, such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease. Alongside the direct impact on neuronal and oligodendrocyte differentiation, function, and integrity, fatty acid metabolism is key in driving both the disease-promoting and –resolving features of peripheral and CNS-resident immune cell subsets. Based on these properties, modulation of fatty acid metabolism is increasingly being recognized as a promising therapeutic strategy to suppress neuroinflammation, prevent neurodegeneration, and even stimulate CNS repair. Here, we summarize and discuss the current knowledge on the impact of fatty acid β-oxidation, synthesis, desaturation, elongation, and peroxidation, on the pathology of CNS disorders. Moreover, we will discuss if functional modulation of proteins and enzymes involved in these metabolic processes is of therapeutic interest for CNS disorders. Finally, we will elaborate on the inflammatory, neurotoxic, and neuroprotective features of individual fatty acids, as well as the emerging role for their downstream bioactive lipid mediators called specialized pro-resolving mediators in health and disease.

2. Fatty acid β-oxidation

Mitochondrial fatty acid β-oxidation (FAO) is an essential process for cellular energy production, especially during fasting and intensive exercise. For FAO to initiate, fatty acids

first need to be activated to fatty acyl-CoAs by a family of acyl-CoA synthetases (Figure 1). Fatty acyl-CoAs are subsequently converted to acyl carnitine derivatives and transported into the mitochondrial matrix, reactions driven by the enzymes carnitine palmitoyl transferase 1 (CPT1) and carnitine-acylcarnitine translocase, respectively. Within the mitochondrial matrix, CPT2 removes carnitine to regenerate fatty acyl-CoA esters, which are then repeatedly cleaved to produce acetyl-CoAs. Acetyl-CoAs are fed into the Krebs cycle and produce reducing equivalents for oxidative phosphorylation.

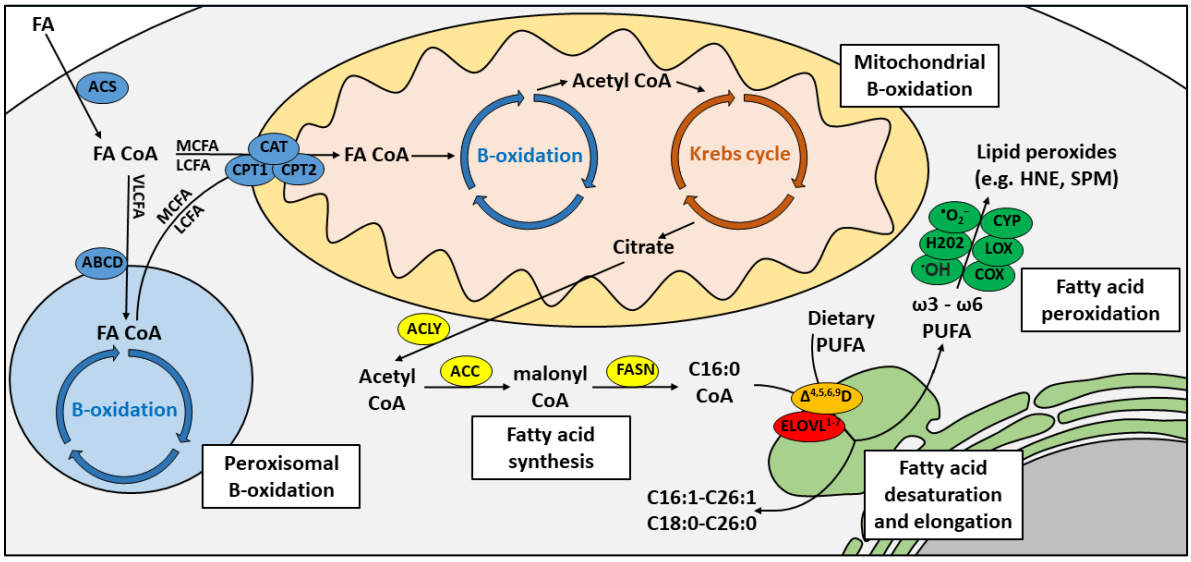

Figure 1. Schematic illustration of fatty acid anabolism and catabolism. The β-oxidation of very long-chain fatty acids (VLCFAs) and medium- and long-chain fatty acids (MCFAs and LCFAs) is initiated in peroxisomes and mitochondria, respectively. For the initiation of fatty acid β-oxidation, fatty acids are converted to fatty acyl-CoAs (FA-CoAs) by a family of acyl-CoA synthetases (ACS). While ATP-binding cassette subfamily D (ABCD) transports VLCFA-CoAs into peroxisomes, carnitine palmitoyl transferases (CPT) and carnitine-acylcarnitine translocases (CAT) transport MCFA-CoAs and LCFA-CoAs into the mitochondrial matrix. Fatty acid synthesis starts in the cytosol with the conversion of acetyl-CoA to malonyl-CoA, a reaction driven by acetyl CoA carboxylases (ACCs) and ATP citrate lyase (ACLY, citrate to acetyl-CoA conversion). Fatty acid synthase (FASN) elongates FA-CoAs, which results in the formation of C16:0-CoA, the initial product of fatty acid synthesis. Subsequent elongation and desaturation steps, catalysed by elongases (ELOVL1-7) and desaturases (Δ4,5,6,9D), form fatty acids of different carbon lengths and degrees of saturation. Lipid peroxidation products are formed as a consequence of oxidative stress (e.g. $^{\bullet}O_2^-$, H_2O_2, and $^{\bullet}OH$) or after enzymatic conversion by cyclooxygenases

(COX), lipoxygenases (LOX), and cytochrome P450 (CYP). The peroxidation of unsaturated fatty acids, especially PUFAs, results in formation of lipid peroxyl radicals and hydroperoxides, such as 4-hydroxy-trans-2-nonenal (HNE), and specialized pro-resolving mediators (SPMs).

2.1 Fatty acid β-oxidation in neuroinflammation

In the last decade, it has become clear that pro-inflammatory immune cell subsets, such as classically-activated M1 macrophages and T helper 1 (Th1) and 17 (Th17) cells, primarily use aerobic glycolysis for sustaining their effector functions [1]. In contrast, regulatory T cells (Tregs), alternatively activated M2 macrophages, and memory T cells largely rely on FAO for sustaining their energy needs [1]. In line with this dichotomy, inactivation of aerobic glycolysis markedly reduces neuroinflammation in animal models for Guillain-Barré syndrome, ischemic brain injury, and multiple sclerosis [2-4]. Likewise, shifting microglia energy metabolism from anaerobic glycolysis to oxidative phosphorylation alleviates neuroinflammation and Aβ burden in two animal models of Alzheimer's disease [5]. Counterintuitively, mice treated with etomoxir, an inhibitor of CPT1 and thus FAO, show reduced CNS inflammation and demyelination in the experimental autoimmune encephalomyelitis (EAE) model, an animal model of multiple sclerosis [6]. Here, etomoxir reduced inflammation by promoting apoptosis of effector T cells, in particular upon glucose deprivation [6]. The mechanisms accounting for the pro-apoptotic effect of etomoxir remain poorly understood. It has been proposed that inhibition of FAO results in perturbations in proteins of the anti-apoptotic B cell lymphoma 2 family [7]. Another explanation is that etomoxir causes T cell apoptosis by reducing ATP production and inducing oxidative stress [8]. Altogether, these studies indicate that FAO impacts immune cell physiology, thereby likely affecting neuroinflammation.

2.2 Fatty acid β-oxidation in neurodegeneration and demyelination

While glucose is the main energy substrate in the CNS [9], increasing evidence supports a role for FAO in neuronal and glial cell development and function. With respect to the latter, FAO

contributes up to 20% of the total brain energy requirement [10], and fatty acid-binding proteins and carnitines are present in the CNS [11]. A recent study demonstrated that quiescent neural stem and progenitor cells (NSPCs), which give rise to neurons and oligodendrocytes, rely on FAO for survival and proliferation [12]. On that same note, functional peroxisomal FAO is necessary to maintain glial cell integrity [13]. In X-linked adrenoleukodystrophy (X-ALD), mutations in the fatty acid transporter ATP-binding cassette subfamily D member 1 (ABCD1) lead to a reduced import of very-long chain fatty acids (VLCFAs) into peroxisomes and decreased peroxisomal FAO. The resulting increase in intracellular VLCFAs induces oligodendrocyte cell death and causes demyelination [13]. While these studies support a protective role of FAO in maintaining NPSC and oligodendrocyte integrity and cell number, a recent study showed that FAO can negatively impact glial cell and neuronal function as well. In a mouse model of peripheral neuropathy, remodelling of lipid metabolism away from fatty acid synthesis and towards oxidation depletes Schwann cells of important lipid myelin components such as cerebrosides and sulfatides [14]. Furthermore, elevated FAO markedly increased the formation of long-chain acyl carnitines that increased axonal calcium levels and promoted axon degeneration [14]. Collectively, these studies indicate that FAO is essential for the function of neurons, glial cells, and NPSCs.

While modulation of FAO holds promise for treating neurological disorders, future studies should address the abovementioned contradictions. Why does the induction of T cell apoptosis by etomoxir outweigh its inflammatory impact on immune cell function, and does this still hold up in experimental models that do not rely solely on T cells for induction? How does FAO exactly impact the physiology of different CNS-resident cell types, and does the contribution of FAO in these cells change in neurological disorders? In addition, given the reported off-target effects of the golden standard FAO inhibitor etomoxir [15], there is also an urgent need to develop more specific FAO inhibitors.

3. Fatty acid synthesis

The synthesis of fatty acids is a critical anabolic pathway in mammals. It occurs in the cytosol and initiates with the carboxylation of acetyl-CoA to malonyl-CoA (Figure 1). This irreversible reaction is the rate-limiting step in the synthesis of fatty acids and catalysed by acetyl CoA carboxylases (ACCs). The serial condensation of seven malonyl-CoA molecules and one acetyl-CoA by fatty acid synthase (FASN) eventually forms palmitate, the initial product of fatty acid synthesis. Subsequent elongation and desaturation steps will produce fatty acids of different lengths and degrees of desaturation, as described in section 4 and 5.

3.1 Fatty acid synthesis in neuroinflammation

Emerging evidence indicates that *de novo* fatty acid synthesis controls the fate of inflammatory and immunosuppressive immune cell subsets. For instance, the inflammatory activation of macrophages is closely associated with elevated fatty acid synthesis [16-20]. Similar, impeding fatty acid synthesis, through inhibition of ACC1 and FASN, restrains the development of Th17 cells and instead favors the induction of Tregs [21, 22]. In line with these studies, inhibition of ACC1 and FASN attenuates the neuroinflammatory burden in the EAE model by reducing the number of Th17 cells [21, 23]. Likewise, genetic depletion of ACC1 in $CD4^+$ T cells or pharmacological inhibition of ACC1 reduces neuroinflammation and infarct volume after middle cerebral artery occlusion by altering the Treg/Th17 balance [24]. Indirect evidence also supports a role for fatty acid synthesis in driving neuroinflammation and disease activity in Alzheimer's, Huntington's, and Parkinson's disease. In particular, the mammalian target of rapamycin (mTOR), a master regulator of fatty acid lipogenesis [25], is highly active in these disorders, and inhibition of mTOR complex 1 (mTORC1) signaling reduces the neuroinflammatory burden and disease severity in preclinical models of these neurodegenerative diseases [26-29]. However, given the pleiotropic functions of mTOR,

more research is warranted to define the relative contribution of reduced fatty acid synthesis in the immunosuppressive and neuroprotective impact of mTOR inhibitors in these disorders.

3.2 Fatty acid synthesis in remyelination

Oligodendrocytes support signal transmission in the CNS by enwrapping axons with myelin, which contains an exceptionally high content of fatty acid-containing glycolipids and phospholipids [30]. Accurate formation of myelin is not only essential for proper developmental myelination but also during remyelination that follows pathological demyelination in diverse CNS disorders. While dietary fatty acids can be utilized to form myelin sheaths, increasing evidence supports a role for fatty acid synthesis in this process. By depleting FASN in oligodendrocyte precursor cells (OPCs), fatty acid synthesis was found to be essential for both developmental myelination and remyelination after lysolecithin-induced focal demyelination [31]. Likewise, while oligodendrocyte-specific deficiency of mTORC1 leads to developmental hypomethylation [32], inhibition of mTOR using rapamycin impairs remyelination in the cuprizone-induced remyelination model [33]. Conversely, oligodendrocyte-specific hyperactivation of mTORC1 results in the formation of thinner myelin sheaths during development and does not improve remyelination after lysolecithin-induced demyelination [25, 34]. This suggests that a precisely balanced regulation of mTORC1 in oligodendrocytes is pivotal for CNS myelination and remyelination. In addition to affecting oligodendrocytes directly, astrocytic fatty acid lipogenesis is key in providing OPCs with lipids for full myelin membrane synthesis [35], which points towards the importance of horizontal lipid flux in supplying OPCs with the necessary fatty acids for myelin formation. Collectively, these findings indicate that fatty acid synthesis in oligodendrocytes and astrocytes controls the formation of myelin, thereby likely influencing remyelination in CNS disorders.

3.3 Fatty acid synthesis in neurogenesis and dendritogenesis

Proper (re)myelination ensures efficient neuronal function and can protect axons from degeneration in CNS disorders. Hence, by affecting the physiology of myelin-producing oligodendrocytes, fatty acid synthesis can impact neuronal functioning. However, several studies indicate that fatty acid synthesis not only changes neuronal function indirectly but also in a cell-autonomous manner. For instance, FASN expression and activity is high in proliferating NSPCs and its inhibition decreases NPSC proliferation [36]. By crossing tamoxifen inducible nestin-promoter driven Cre mice with FASN-flox mice, the authors further show that adult NSPCs require high levels of *de novo* lipogenesis for accurate neurogenesis *in vivo*. Alongside promoting neurogenesis, fatty acid synthesis controls neuronal dendrite expansion. Genetic knockdown of sterol regulatory element binding protein (SREBP), a crucial regulator of fatty acid production, in dendritic arborization neurons decreases dendritic branch length and the number of terminal endpoints, and promotes axon loss [37]. In summary, these studies argue for fatty acid synthesis being essential for neuronal development, function, and integrity.

The abovementioned studies indicate that pharmacological inhibition of fatty acid synthesis, using FASN, ACC1, or mTORC1 inhibitors, may hold therapeutic promise to suppress inflammation in CNS disorders. However, by doing so, one risks perturbing neurogenesis, neuronal function, and remyelination, processes that are essential to prevent neurodegeneration and stimulate CNS repair.

4. Fatty acid elongation

Fatty acid elongation occurs in the endoplasmic reticulum and relies on specific elongases (Figure 1). Similar to cytosolic fatty acid synthesis, malonyl CoA is the source of added carbons during elongation. In the first rate-limiting step, fatty acyl-CoAs are condensed with malonyl-CoA, a reaction catalysed by elongases (elongation of very long chain fatty acids proteins,

ELOVL). Mammals have seven elongases (ELOVL1–7) that exhibit a tissue-specific expression pattern and characteristic substrate specificity to different fatty acyl-CoAs. Commonly, ELOVL1, 3, 5, 6, and 7 are involved in the elongation of monounsaturated (MUFAs) and saturated fatty acids (SFAs), and ELOVL2 and 5 strictly elongate polyunsaturated fatty acids (PUFAs). ELOVL4 catalyzes the formation of VLCFAs (>C26) [38, 39]. While literature regarding the precise role of ELOVLs in CNS disorders is scarce, mutations in ELOVLs are associated with CNS disorders such as Parkinson's disease [40], spinocerebellar ataxias [41], and neuro-ichthyotic syndrome [42]. Moreover, the expression and activity of ELOVLs is closely linked to the pathophysiology of Alzheimer's disease [43], X-ALD [44], and multiple sclerosis [45].

4.1 Fatty acid elongation in neuroinflammation

Several studies indicate that elongases control the balance between pro- and anti-inflammatory immune responses. While ELOVL1 is positively associated with the inflammatory status of astrocytes in X-ALD [44], ELOVL6 reduces the inflammatory burden in preclinical models of type 2 diabetes [46], non-alcoholic liver steatosis [47], and dermatitis [48]. These studies suggest that inhibition of ELOVL1 and ELOVL6 may be an attractive therapeutic strategy to reduce neuroinflammation. In contrast, ELOVL2-mediated synthesis of the ω3 PUFA docosahexaenoic acid (DHA) keeps macrophage and T cell polarization in check by suppressing Th1/Th17 differentiation and M1 macrophage activation, and sustaining the number and function of Tregs and M2 macrophages [49, 50]. Finally, the induction of T cell proliferation is closely associated with an elevated expression of ELOVL5 [51]. However, despite this elevated expression, ELOVL5 silencing does not impact T cell proliferation, viability, or activation [51]. These studies indicate that the different elongases have a divergent impact on immune cell function and that elongase-specific modulation is required to modulate neuroinflammation.

4.2 Fatty acid elongation in neurodegeneration and demyelination

Increasing evidence points towards elongases being essential in controlling oligodendrocyte and neuronal physiology in health and disease. In X-ALD patients, ELOVL1 is highly expressed in oligodendrocytes and has been identified as the single elongase responsible for catalyzing the toxic accumulation of VLCFAs [13, 52]. In accordance, the VLCFA-lowering and neuroprotective impact of Lorenzo's oil in X-ALD partially depends on its suppressive action on ELOVL1 activity [53]. In concert with the pathogenic impact of VLCFA in CNS disorders, oligodendrocyte-specific *Dicer* mutant mice show abundant demyelination and neuronal degeneration in the brain [54]. Elevated ELOVL7 activity was identified as one of the primary molecular processes involved in driving the phenotype in these mice [54]. Of interest, saturated VLCFAs formed by ELOVL4 were recently reported to prevent epileptogenesis and neurodegeneration, and control presynaptic release kinetics [55, 56]. Collectively, these studies indicate that excessive ELOVL1 and ELOVL7 activity promote demyelination and neurodegeneration, and that ELOVL4 activity is essential to maintain synaptic transmission.

To date, the impact of fatty acid elongation on CNS disorders remains poorly understood. While it is becoming clear that the divergent elongases impact immunity differently, the underlying molecular mechanisms and fatty acids remain largely unresolved. In addition, while inhibition of ELOVL1 and ELOVL7 represents a viable option to prevent neurodegeneration and demyelination, its impact on CNS repair (e.g. remyelination and neuroregeneration) remains to be determined. The absence of specific inhibitors of the different elongases, as well as the fact that ELOVL1 and ELOVL4 knockout mice die shortly after birth [57, 58], likely explains the lack of research on elongases.

5. Fatty acid desaturation

The desaturation of fatty acids is essential for the biosynthesis of UFAs (Figure 1). It relies on specific desaturases, which require molecular oxygen and two electrons to insert double bonds at specified positions within fatty acyl chains [59]. In mammals, four classes of desaturases are described: delta-4 (Δ4Ds), delta-5 (Δ5Ds), delta-6 (Δ6Ds), and delta-9 desaturases (Δ9Ds), each catalyzing the formation of a cis-double bond at the Δ4, Δ5, Δ6, and Δ9 position of fatty acyl-CoAs, respectively. The Δ4Ds, Δ5Ds and Δ6Ds are required for the formation of PUFAs, such as DHA, eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and arachidonic acid (ARA), from the dietary fatty acids linoleic acid (LA) and α-linolenic acid (ALA) [60]. The formation of these PUFAs requires the successive actions by elongase and desaturase enzymes [60]. The Δ9Ds, also called stearoyl-CoA desaturases (SCD), catalyze the formation of MUFAs (palmitoleoyl- and oleoyl-CoA) from SFAs (palmitoyl- and stearoyl-CoA) [61]. Unlike lower animals and plants, mammals lack the Δ12Ds and Δ15Ds, which are needed to catalyse the formation of linoleic acid (LA) and α-linolenic acid (ALA) [59]. Therefore, LA and ALA acid are known as dietary essential fatty acids.

5.1 Fatty acid desaturation in neuroinflammation

Similar to the oxidation, synthesis, and elongation of fatty acids, fatty acid desaturation impacts immune cell physiology. Deficiency of the Δ9D SCD1 augments the inflammatory features of effector T cells and macrophages [62-64]. Alternatively, while Δ5D (FADS1) deficiency reduces the number of Th17 cells in a colitis mouse model [65], it promotes and suppresses the induction of M1 and M2 macrophage activation programs, respectively [66]. Alterations in the levels of immunomodulatory ω3 and ω6 PUFAs, and pro-resolving and inflammatory lipid mediators formed from these PUFAs (see section 8), likely underlie the impact of Δ5Ds on immune cell function and differentiation [65-67]. Several studies also reported a role for fatty acid desaturases in controlling neuroinflammation. Transcriptomic analysis identified that amyloid-β uptake by macrophages increases SCD1 expression in addition to a set of pro-

inflammatory genes [68]. In line with these findings, we found that myelin internalization increases SCD1 expression in macrophages and that inhibition of SCD1 counters the inflammatory phenotype of these cells *in vitro* and *in vivo* (unpublished data). Despite the importance of ω3 and ω6 PUFAs in driving immune cell function (see section 7), it remains unclear how changes in Δ4D, Δ5D, and Δ6D activity influence neuroinflammation in CNS disorders.

5.2 Fatty acid desaturation in neurogenesis and neurodegeneration

MUFAs and PUFAs are essential nutrients and fundamental components of neurons and oligodendrocytes. Not surprisingly, desaturase activity correlates closely with the physiology of these cells in health and disease. With respect to Δ9D activity, SCD1 promotes the formation of astrocytic oleic acid, which enhances neuron migration, and axon and dendrite growth [69, 70]. In contrast, while constitutive expression of human SCD5 promotes proliferation of mouse Neuro2a cells, it suppresses retinoic acid-induced neuritogenesis and maturation [71]. These findings indicate that SCD1 and SCD5 impact neuronal growth and maturation differently. In yet another study, a direct link between SCD1 inhibition and synucleinopathies such as Parkinson disease was demonstrated [72]. Here, inhibition of SCD1 enhanced the survival of human neurons in the presence of toxic α-synuclein. To what extent these findings also hold up for other CNS disorders characterized by the accumulation of toxic protein aggregates remains to be determined. Yet again, while dietary supplementation with ω3 and ω6 PUFAs is well-known to impact the integrity of neuronal and glial cells (see section 7), the importance of *de novo* formation of PUFAs by Δ4D, Δ5D, and Δ6D in this process remains unresolved. The relative inactive desaturation in neurons as compared to endothelial cells and astrocytes might indicate that neurons rely mainly on horizontal lipid fluxes for PUFAs [73], rendering Δ4Ds, Δ5Ds, and Δ6Ds redundant in these cells.

As clarified in the abovementioned paragraphs, the Δ9D SCD1 represents a promising therapeutic target to suppress neuroinflammation and neurodegeneration, and promote CNS repair processes. Several small molecule inhibitors of SCD1 already progressed to early clinical development for the treatment of metabolic disorders and cancer [74-76]. However, clinical success remains to be attained, partially due the difficulty of translating lipid metabolism from rodents to humans. Moreover, the accumulation of inflammatory SFAs poses a problem upon prolonged treatment with SCD1 inhibitors [77]. Co-administration of PUFAs has been proposed to prevent or reduce the deleterious side-effects stemming from this accumulation SFAs [77]. In contrast to Δ9Ds, evidence for the therapeutic applicability of Δ4Ds, Δ5Ds, and Δ6Ds to treat CNS disorders is rather limited. It is clear that the body converts the essential fatty acids AL and ALA into the much needed ω3 and ω6 PUFAs. However, the relative contribution of Δ4Ds, Δ5Ds, and Δ6Ds in controlling ω3 and ω6 PUFAs levels in CNS-resident and immune cells, as compared to dietary-derived ω3 and ω6 PUFAs, is poorly understood.

6. Fatty acid peroxidation

The process of lipid peroxidation occurs when oxidants such as free radicals interact with fatty acids containing carbon-carbon double bonds, especially PUFAs (Figure 1). This interaction involves hydrogen detachment from a carbon and oxygen insertion, and results in the formation of lipid peroxyl radicals and hydroperoxides [78]. Peroxidation can also be mediated by enzymes such as lipooxygenases, cyclooxygenases, and cytochrome P450 [78] (Figure 1). Fatty acid peroxidation products have both cytotoxic/inflammatory and cytoprotective/anti-inflammatory effects. The eventual cellular outcome depends on the fatty acid substrate (e.g. ω3 versus ω6 PUFAs) and pathway involved (e.g. enzymatic versus non-enzymatic) [78, 79].

6.1 Fatty acid peroxidation in neuroinflammation

The early observation that lipid peroxidation products are generated in atherosclerosis suggested a link between fatty acid peroxidation and inflammation [80]. Indeed, aldehydes derived from fatty acid peroxidation are implicated in a number of oxidative stress-induced inflammatory conditions including diabetes [81], liver and kidney toxicity [82], cancer [83], metabolic syndrome [84], aging [85], and ischemia [86]. Lipid peroxidation products can act as precursors of important bioactive mediators of inflammation, such as the prostaglandins, thromboxanes, and leukotrienes, following enzymatic conversion by cyclooxygenases, lipoxygenases, and cytochrome P450 [87]. Likewise, 4-hydroxy-trans-2-nonenal (HNE), a major lipid peroxidation-derived aldehyde, stimulates the inflammatory response in macrophages and contributes to disease progression of atherosclerosis by inducing cyclooxygenase 2 activity, prostaglandin formation, and NF-kβ activation [88, 89]. Alternatively, some of the lipid mediators generated from multistage enzymatic oxidation of ω3 PUFAs, such as resolvins, protectins, and maresins, support the resolution of inflammatory processes (discussed in section 8) [90, 91]. Furthermore, reactive lipid oxidation products can activate the anti-inflammatory peroxisome proliferator-activated receptor γ (PPARγ) in immune cells, thereby transrepressing inflammatory responses [92, 93]. In the EAE model, the generation of oxidative-stress induced lipid peroxidation products seems mainly pro-inflammatory as treatment with antioxidants ameliorates disease severity [94, 95]. Accordingly, oxidative stress induced by lipid peroxidation precedes the inflammatory response in multiple sclerosis patients [96]. Collectively, these studies indicate that lipid peroxidation products likely affect neuroinflammation in CNS disorders. However, more research is needed to define the fatty acid substrates and pathways involved in driving the formation of pro- and anti-inflammatory lipid peroxidation products in CNS disorders.

6.2 Fatty acid peroxidation in neurodegeneration and CNS repair

The high level of PUFAs in the brain makes it particularly vulnerable to oxidative stress and fatty acid peroxidation [97]. With respect to the latter, relapsing-remitting multiple sclerosis patients display heightened levels of biochemical markers of peroxidation, such as malondialdehyde [96]. Lipid peroxidation products are also abundantly present in the brain, cerebrospinal fluid, and plasma from patients with Alzheimer's disease [85]. Here, amyloid β causes oxidative stress through its interaction with transition metal ions, such as Cu^{2+} and Zn^{2+}. These metals are enriched in senile plaques ultimately leading to the formation of aggregates. Hydrogen peroxide can be generated by Cu^{2+}- or Zn^{2+}-bound amyloid β using other electron donors such as PUFAs, leading to the generation of toxic lipid peroxidation products such as HNE [98]. An increase in lipid peroxidation products is also apparent in the substantia nigra in Parkinson's disease [99]. Oligomeric α-synuclein was found to induce ROS production and the peroxidation of PUFA residues within lipid membranes. The subsequent increase in lipid peroxidation products is integral to α-synuclein-induced neuronal damage and neuronal death [100]. Interestingly, lipid peroxidation products can be transported from neurons to neighbouring astrocytes for detoxification or storage in lipid particles [101]. Horizontal transfer of toxic lipid metabolites likely retains neuronal homeostasis in health and disease, but may eventually also contribute to disease pathology in CNS disorders. While these studies show that accumulation of oxidative stress-induced lipid peroxidation products causes neurodegeneration, emerging evidence indicates that the enzymatic formation of oxygenated pro-resolving mediators, such as resolvins, maresins, and protectins, reduces neuroinflammation and supports CNS repair (discussed in section 8). On that same note, oxygenated derivates of ω3 PUFAs called elovanoids were recently found to counteract oligomeric β-amyloid-induced gene expression and protect photoreceptors [102]. Moreover, elovanoids protected neuronal cultures undergoing either oxygen/glucose deprivation or receptor-mediated excitotoxicity, and were neuroprotective in an experimental ischemic stroke model [103]. Therefore, increasing the level

of pro-resolving mediators and elovanoids, and decreasing that of oxidative stress-induced lipid peroxidation products is considered a promising strategy to reduce neurodegeneration and promote CNS repair.

7. Fatty acid chain length and saturation

In the previous sections, we focused on the impact of enzymes and proteins involved in the metabolism of fatty acids on CNS disorders. In the next sections, we will summarize and discuss the current knowledge on the impact of individual fatty acid species, formed through the anabolism and catabolism of fatty acids, obtained through the diet, or synthesized by the gut microbiota, on CNS disorders. We subdivided fatty acids based on their aliphatic carbon chain length. According to the chain length, fatty acids are classified as short-chain fatty acids (SCFAs, C1-6), medium-chain fatty acids (MCFAs, C7-12), long-chain fatty acids (LCFAs, C13-22), and very-long chain fatty acids (VLCFAs, > C22).

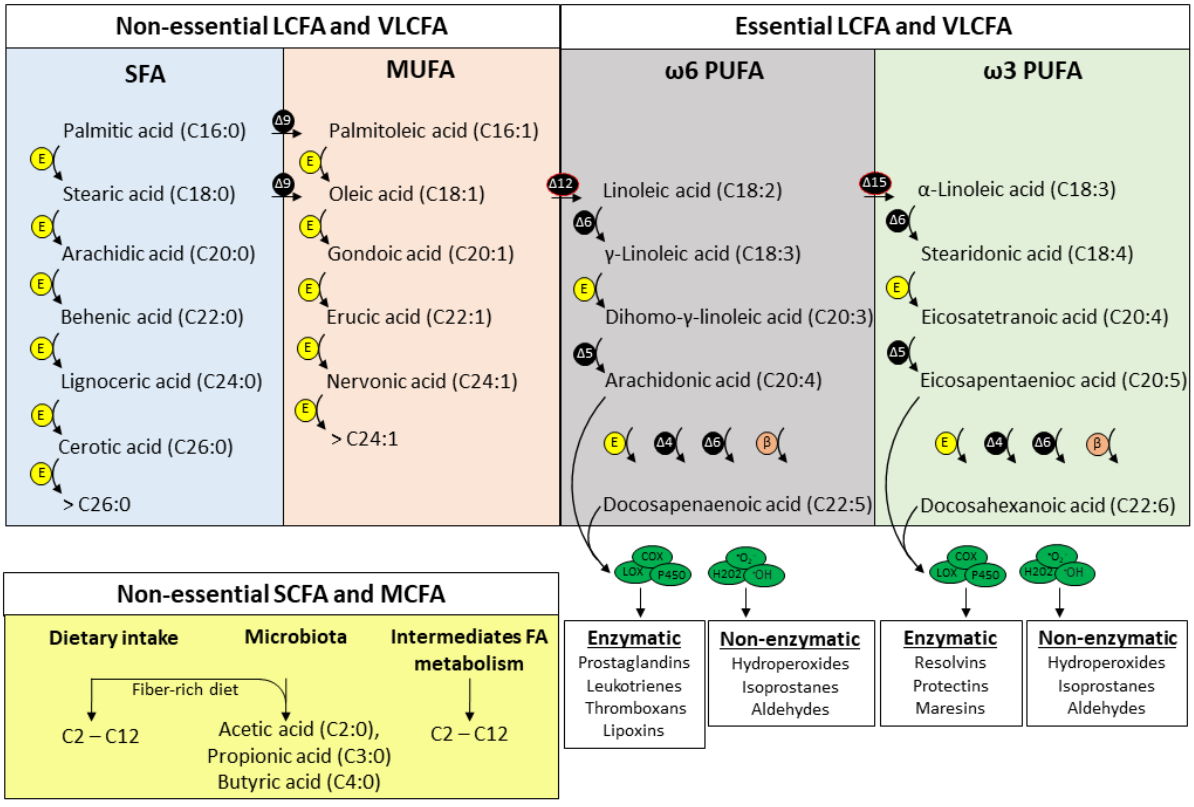

Figure 2. Simplified figure of the origin and formation of individual fatty acids in the human body including key enzymes involved in their synthesis. Non-essential LCFAs and VLCFAs can be obtained from a variety of dietary sources or endogenously synthesized from other fatty acids through successive desaturation (delta-9 desaturases, Δ9D) and elongation (E, ELOVL1, 3, 4, 6, and 7) steps. Non-essential SCFAs and MCFAs are acquired through the diet, formed by the gut microbiota, or endogenously synthesized as intermediates during the anabolism and catabolism of fatty acids. Given the lack of delta-12 and delta-15 desaturases (Δ12D and Δ15D) in humans, ω3 and ω6 PUFAs can only be obtained through the diet and, therefore, are called essential fatty acids. Successive elongation (ELOVL2, 5, and 7), desaturation (Δ4D, Δ5D, and Δ6D), β-oxidation (β), and peroxidation (enzymatic and non-enzymatic) steps result in the formation of complex polyunsaturated lipid species.

7.1 Short-chain fatty acids

SCFAs, such as acetic (C2:0), propionic (C3:0), and butyric acid (C4:0), are the primary end-products of gastrointestinal fermentation of complex polysaccharides, found in fiber-rich diets (Figure 2) [104]. Recent evidence indicates that these microbiota-derived SCFAs closely regulate CNS homeostasis and neuroinflammation by affecting microglia activation and Treg expansion [105, 106]. Furthermore, in experimental models of Alzheimer's disease, Parkinson disease, stroke, traumatic brain injury, and infectious CNS disorders, SCFAs and derivatives thereof were found to reduce amyloid β aggregation [107], protect neurons and oligodendrocytes from cell death [108-111], restore blood-brain barrier permeability [112], suppress neuroinflammation [111, 113], and improve memory and locomotor deficits [108, 111, 114, 115]. The neuroprotective impact of SCFAs likely depends in part on their ability to reverse disease-associated reductions in histone deacetylation [108-111, 114-116]. Interestingly, multiple sclerosis patients display a depletion of bacterial species belonging to clostridia XIVa and IV cluster, which produce SCFAs, such as propionate and butyrate [117]. Likewise, changes in gut microbiota are associated with a reduced presence of SCFAs in patients with Parkinson's disease [118]. These microbial imbalances might promote the neuroinflammatory burden in multiple sclerosis and Parkinson's disease. To what extent

478 microbial imbalances in these CNS disorders originate from environmental factors or disease-
479 associated processes remains to be determined. Collectively, these findings stress the beneficial
480 impact that gastrointestinal bacteria-derived SCFAs have on the healthy, inflamed, and
481 damaged CNS.

482 **7.2 Medium-chain fatty acids**

483 MCFAs, such as caprylic (C8:0), nonanoic (C9:0), capric (C10:0), and lauric acid (C12:0), are
484 mainly acquired through our diet by consumption of milk fat, coconut oil, and pelargonium oil
485 (Figure 2). MCFAs markedly increase the differentiation of Th1 and Th17 cells, and decrease
486 that of Tregs *in vitro* [106]. A lauric acid-rich diet mimics these immunological changes *in vivo*
487 and enhances CNS autoimmunity in the EAE model [106]. Gut microbiota were found to be
488 crucial in driving changes in the immunological landscape in these animals, likely by increasing
489 the concentration of MCFAs and LCFAs, and decreasing that of SCFAs. Aside from having a
490 direct impact on T cell polarization, caprylic acid can enhance the neuroinflammatory burden
491 by disrupting blood-brain barrier integrity [119]. While *in vivo* evidence is largely lacking,
492 MCFAs might boost neuroinflammation by activating the G-protein coupled receptor 84
493 (GPR84) [120]. GPR84 is highly expressed by T cells, neutrophils, macrophages, and microglia
494 [121], and its activation enhances the pro-inflammatory properties of these cells [120, 122-126].
495 Moreover, ample evidence indicates that GPR84 is highly expressed on activated microglia in
496 diverse animal models of CNS pathologies [122, 126-128]. Unexpectedly, while GPR84
497 deficiency reduces microgliosis, it accelerates the number of degenerating dendrites in
498 APP/PS1 mice [128]. The latter study indicates that GPR84, and thus likely MCFAs, are crucial
499 in maintaining dendritic homeostasis. In line with this protective role of MCFA, nonanoic and
500 capric acid enhance seizure control activity and provide protection against neuronal loss in
501 *in vitro* seizure and *in vivo* epilepsy models [129, 130]. These findings can partially explain
502 the therapeutic efficacy of a medium-chain triglyceride ketogenic diet on childhood epilepsy

[131], Alzheimer's disease [132, 133], and Huntington disease [134]. In summary, while MCFAs promote inflammation, studies indicate that they maintain neuronal and oligodendrocyte integrity in CNS disorders as well.

7.3 Long-chain fatty acids

LCFAs can be obtained from a variety of dietary sources or endogenously synthesized from other fatty acids (Figure 2). The impact of LCFAs on neuroinflammation and neurodegeneration largely depends on their saturation level. Hence, LCFAs were subdivided into saturated, monounsaturated, and polyunsaturated LCFAs.

7.3.1 Saturated long-chain fatty acids

Saturated LCFAs such as myristic (C14:0), palmitic (C16:0), stearic (C18:0), arachidic (C20:0), and behenic acid (C22:0) are generally regarded to promote the proliferation and differentiation of inflammatory T cell, astrocyte, and microglia/macrophage subsets [106, 135-140]. In accordance, dietary supplementation with saturated LCFAs promotes neuroinflammation in diverse experimental animal models [106, 137, 140, 141]. Given the structural similarity between saturated LCFAs and the lipid portion of bacterial lipopolysaccharide (LPS), they are suggested to impact inflammation by ligating the toll-like receptor (TLR) 2 and 4 [138-140]. Several studies demonstrated that saturated LCFAs reduce neuronal and glial cell integrity in health and disease as well. For instance, palmitic acid reduces the survival of NSPCs and hypothalamic neurons, and negatively impacts hippocampal neurogenesis [142, 143]. Similar, palmitic and stearic acid induce hyperphosphorylation of tau in cortical neurons by affecting the secretory profile of astrocytes [144]. Finally, diets high in saturated fatty acids increase the level of neurotoxic α-synuclein and amyloid β, and reduce the number of OPCs and mature oligodendrocytes in experimental mouse models [145-147]. Altogether these studies provide evidence that saturated LCFAs are inflammatory and neurotoxic, explaining the positive

correlation between LCFAs and disease progression in multiple sclerosis and Alzheimer's disease [148, 149].

7.3.2 Monounsaturated long-chain fatty acids

In contrast to saturated LCFAs, the majority of studies report that monounsaturated LCFAs such as palmitoleic (C16:1), oleic (C18:1), gondoic (C20:1), and erucic acid (C22:1) are anti-inflammatory *in vitro* [150-153], and reduce neuroinflammation *in vivo* [154-156]. While direct evidence is lacking, monounsaturated LCFAs may impact neuroinflammation through activation of the anti-inflammatory receptors GPR120 and PPARs [156-159]. Oleic and palmitoleic acid have also been extensively scrutinized for their neuroprotective effects. Astrocytic oleic acid promotes neuronal differentiation and migration as well as oligodendroglial myelination during brain development [35, 69, 70, 160]. On that same note, oleic and palmitic acid increase the viability, proliferation, and stemness of embryonic neural stem cells [161]. Finally, in experimental animal models of Alzheimer's disease, oleic acid supplementation increases the non-amyloidogenic cleavage of amyloid precursor protein and reduces amyloid β plaque load in the brain [162]. Despite of these protective properties, monounsaturated LCFAs have neurotoxic features as well. By using a yeast proteinopathy model, oleic and palmitoleic acid were found to promote α-synuclein toxicity [72]. Furthermore, they stimulate the assembly of amyloid β and tau filaments, and the cytotoxic aggregation of amyotrophic lateral sclerosis-linked superoxide dismutase 1 mutants *in vitro* [163-165]. Collectively, these findings indicate that monounsaturated LCFAs can reduce neuroinflammation and promote CNS repair. However, they can also stimulate the formation of cytotoxic protein aggregates in CNS disorders. Future studies should correlate reported changes in oleic acid levels in patients with Alzheimer's disease and multiple sclerosis to disease progression and remission in these disorders [166-170].

7.3.3 Polyunsaturated long-chain fatty acids

In contrast to saturated and monounsaturated LCFAs, the brain primarily maintains levels of polyunsaturated LCFAs via the uptake from dietary sources through diffusion over the blood-brain barrier [171]. The general consensus is that ω3 PUFAs, such as ALA (C18:3), EPA (C20:5), and DHA (C22:6), are anti-inflammatory in CNS disorders. Dietary supplementation with these ω3 PUFAs reduces the neuroinflammatory burden in diverse experimental models [172, 173], likely by suppressing the activation of the NLRP3 inflammasome [174], the differentiation of Th17 cells [175], and the migratory capacity of leukocytes [176]. Accordingly, ω3 PUFA supplementation is associated with a reduced inflammatory burden in Alzheimer's disease [177], Parkinson disease [178], and multiple sclerosis [179]. Similar to monounsaturated LCFAs, ω3 PUFAs are hypothesized to reduce inflammation by activation of GPR120 and PPARs [180, 181]. However, the anti-inflammatory effects of ω3 PUFAs may also be explained by the fact that they act as precursors of anti-inflammatory specialized pro-resolving lipid mediators (discussed in section 8) [182, 183]. As opposed to ω3 PUFAs, ω6 PUFAs were for a long time considered to promote the inflammatory features of immune and glial cells, mainly because ARA (C20:4) is a precursor of pro-inflammatory eicosanoids, such as prostaglandins, thromboxanes, and leukotrienes [65, 184-187]. Indeed, by using the fat-1 mouse model, in which ω3 PUFAs are endogenously formed from ω6 PUFAs, a reduced neuroinflammatory burden in experimental models for Alzheimer's disease and depression was observed [188, 189]. Conversely, oral feeding of ω6 PUFAs attenuates the disease course of acute and chronic EAE [190], and emerging evidence indicates that ω6 PUFAs have anti-inflammatory properties in cardiovascular disorders [191, 192]. In concordance with these studies, a Cochrane review of randomized dietary trials for multiple sclerosis did not observe a significant effect of ω6 PUFA supplementation on disease progression and relapse rate in multiple sclerosis patients [193]. The latter findings might be explained by the wide variety of the eicosanoids produced by ω6 PUFAs, some of which possess pro-inflammatory features

577 [184]. Moreover, a biphasic activity of ω6 PUFAs has been reported, with ω6 PUFAs having a
578 role in both the initiation and resolution of inflammation and tissue repair [194], a process called
579 lipid mediator class switching [195] . Finally, stable isotope studies defined limited conversion
580 of dietary LA supplementation to AA in humans [196].

581 Approximately one-third of the lipids in the CNS are polyunsaturated LCFAs. Not surprisingly,
582 changes in the levels of these lipid species impact the formation, integrity, and function of glial
583 and neuronal cells in health and disease. For instance, ω3 PUFAs promote the differentiation
584 of neurons [197-199], and support neurite growth in hippocampal, cortical, and sensory neuron
585 cultures [200, 201]. DHA was further found to stimulate oligodendrocyte progenitor maturation
586 and prevent the maturational arrest induced by TNFα [202, 203]. In accordance with these
587 studies, by using the fat-1 mouse model or dietary intervention, an increase in ω3 PUFAs
588 improves neuronal and oligodendrocyte survival, and attenuates remyelination in experimental
589 animal models [188, 204-209]. In contrast to ω3 PUFAs, ω6 PUFAs such as ARA can induce
590 neuronal cell death through lipoxygenase- and cytochrome P450-catalyzed pathways [210].
591 Cellular release of ARA was even found to underlie neuronal cell death upon exposure to
592 soluble amyloid β peptides [210, 211]. An early study further demonstrated that ARA is also
593 an effective inhibitor of sodium currents and synaptic transmission in cultured striatal neurons
594 [212], which might cause maladaptive neurotransmission in CNS disorders. In support of these
595 studies, dietary ARA supplementation amplifies Aβ oligomer neurotoxicity and promotes
596 cognitive decline in animal models of Alzheimer's disease [213, 214]. However, ω6 PUFAs are
597 also reported to have neuroprotective features. ARA supplementation can compensate for
598 changes in ω6 PUFA levels and deficits in motor activity and coordination during development
599 in Δ6D deficient mice [215, 216]. Even more, maternal ARA supplementation improves
600 neurodevelopment in young adult offspring [217]. These studies suggest that ω6 PUFAs are

601 neurotoxic in excess but necessary for early brain development. On the other hand, these
602 findings might merely reflect the dual role that ω6 PUFAs have on cell physiology [184, 194].

603 **7.4 Very long-chain fatty acids**

604 Saturated and monounsaturated VLCFAs, such as nervonic (C24:1), montanic (C28:0), and
605 cerotic acid (C26:0), are primarily derived through elongation of LCFAs. Polyunsaturated
606 VLCFAs are formed through the elongation and desaturation of the essential fatty acids ALA
607 and LA. Given the highly elevated levels of VLCFAs in X-ALD patients [218, 219], most
608 evidence concerning the role of VLCFAs in CNS disorders originates from studies in these
609 patients and analogous experimental models. For example, elevated plasma and CNS levels of
610 VLCFAs correlate with the level of inflammatory mediators in X-ALD patients [220, 221]. As
611 VLCFA metabolism is primarily affected in monocytes in X-ALD patients [222], the observed
612 inflammatory changes are likely due to an elevated inflammatory status of these cells.
613 Correspondingly, macrophages exposed to VLCFAs or deficient in ABCD1, the causative gene
614 in X-ALD, display an inflammatory phenotype, increased level of intracellular ROS, and
615 accumulation of inflammatory crystalline structures [223-226]. A number of studies further
616 demonstrated that the intracellular accumulation of VLCFAs promotes astrocytic generation of
617 TNF, IL1β, NO, and ROS [227, 228]. Collectively, these studies provide evidence that
618 excessive accumulation of VLCFAs promotes the inflammatory activation of macrophages,
619 microglia, and astrocytes.

620 VLCFAs are well-documented to negatively impact neuronal and oligodendrocyte physiology.
621 Exposure to high levels of VLCFAs, such as C24:0 and C26:0, induces mitochondrial,
622 lysosomal, and peroxisomal dysfunction, and stimulates neuronal, astrocyte, and
623 oligodendrocyte cell death [229-232]. Of all CNS-resident cell types, oligodendrocytes are most
624 vulnerable to the cytotoxic effect of VLCFAs [13, 231, 232]. Interestingly, treatment with a
625 histone deacetylase inhibitor corrects the derangement of VLCFA levels and counteracts

oligodendrocyte loss [13, 232]. While these studies indicate that organelle dysfunction and aberrant histone acetylation underlie the cytotoxic features of VLCFAs, other studies suggest that VLCFAs can directly destabilize and permeabilize membranes [233], thereby promoting necroptosis, a programmed form of necrosis [234]. Necroptosis is a common pathological feature in CNS disorders, including multiple sclerosis, Alzheimer's disease, and Parkinson's disease [235]. In line with the detrimental impact of VLCFAs on neuronal and glial cells *in vitro*, extensive demyelination and neurodegeneration is apparent in the CNS of X-ALD patients and associated animal models [236]. Although direct evidence for a disease-promoting role of VLCFAs in other CNS disorders is lacking, VLCFA levels are increased in the serum and CNS of patients suffering from multiple sclerosis and Alzheimer's disease [45, 237, 238]. Moreover, emerging evidence links peroxisomal dysregulation to these and other neurological disorders [239]. Interestingly, while the latter studies indicate that long-term increases in VLCFAs in the CNS can initiate or promote neurodegenerative events, recent studies indicate that ω3 PUFA-derived elovanoids and saturated VLCFA formed through ELOVL4 are neuroprotective and essential for proper synaptic transmission [55, 56, 102, 103]. Future studies should define whether the abundance of these newly identified protective VLCFA is associated with disease remission in CNS disorders.

8. Specialized pro-resolving mediators

Fatty acids, and in particular essential PUFAs, are themselves precursors for a variety of bioactive lipid mediators that have a broad range of biological functions. One of the most important function is that they play a pivotal role in the control of both acute and chronic inflammatory responses, a process known as the resolution of inflammation [90]. This counteractive and tissue protective process is orchestrated by a new genus of bioactive lipids called specialized pro-resolving mediators (SPMs), including lipoxins, resolvins, maresins, and protectins [90, 240]. The biosynthesis of SPMs is initiated by the enzymatic addition of oxygen

651 to four dietary fatty acids, namely, ω6 AA, ω3 EPA, ω3 DHA, and ω3 DPA, by means of the
652 concerted action of lipoxygenase isozymes, cyclooxygenase 2, and, to a lesser extent,
653 cytochrome P450 (Figure 2) [240]. Initially, the resolution phase was thought to be a passive
654 process, but is now recognized as an active event initiated at the start of an inflammatory
655 response [241]. Similar to Virchow's cardinal signs of inflammation, like rubor (redness), calor
656 (heat), tumor (swelling), dolor (pain) and functio laesa (loss of function), there are five cardinal
657 signs of resolution [183, 242]. One of the key cardinal signs of resolution is cell clearance, in
658 which neutrophil apoptosis occurs and, as a consequence, efferocytosis through recruited
659 monocyte-derived macrophages ensues [243, 244]. The other four cardinal signs are cessation
660 of leukocyte recruitment, counter regulation of pro-inflammatory mediators, transition from
661 classical activated macrophages to a more alternative phenotype, restoration of vascular
662 integrity and re-entering of leukocytes in the vasculature and lymphatics [183, 242]. In general,
663 SPMs are potent resolution agonists that extinguish the eicosanoid-induced inflammation by
664 activating local resolution programs [245], via five separate G protein-coupled receptors;
665 ALX/FPR2, GPR32/DRV1, ChemR23/ERV, BLT1 and GPR18/DRV2 [246]. During
666 resolution of inflammation, the very same cells recruited to the inflammatory milieu, undergo
667 a temporal lipid mediator class switch, whereby they stop producing classical eicosanoids from
668 ω6 AA and start to biosynthesize SPMs [195]. In addition, SPMs are produced in coordinated
669 waves, with lipoxins appearing earlier and resolvins, protectins, and maresins being produced
670 later during an inflammatory response [246]; therefore, they act in a time- and cell-dependent
671 manner.

672 Since the identification of SPMs in human samples relies on liquid chromatography-tandem
673 mass spectrometry (LC-MS-MS)-based approaches and internal standards have only recently
674 become available [247], it is now possible to consider that a failed resolution response may be
675 a universal cause of chronic (neuro-)inflammatory disorders [248]. For example, it has recently

been shown that LXA_4 is decreased in the brain and CSF of patients with Alzheimer's disease, and that LXA_4 and RvD1 levels in the CSF positively correlate with mini-mental state examination scores [249]. In line with these findings, levels of MaR1, PD1, and RvD5 are reduced in the entorhinal cortex of patients with Alzheimer's disease [250], thereby providing more evidence of a disturbed resolution pathway in Alzheimer's disease [251]. Moreover, our recent findings indicate that such resolution defects are also apparent in multiple sclerosis and that SPM signatures can be used to stratify patients according to their disease phase [252]. Further human studies are needed to reveal resolution defects in other neurological disorders that are characterized by uncontrolled or chronic inflammation to facilitate clinical translation of SPM supplementation. Results from preclinical disease models are encouraging and suggest that treatment of inflammation-associated diseases might be possible with SPM agonists that stimulate resolution and protect organs from collateral damage [253]. Moreover, in experimental animal models of spinal cord injury, lamellar keratectomy, and Alzheimer's disease, exogenous administration of SPMs, such as MaR1, PD1, and LXA_4, results in reduced neuroinflammation, decreased levels of amyloid beta and phosphorylated-tau, neuroprotection, and functional neurological recovery [254-257]. These studies indicate that treatment with SPMs represents a promising therapeutic strategy to reduce neuroinflammation and stimulate CNS repair simultaneously.

9. Advances and challenges in lipidomics

In contrast to genomics, transcriptomics, and proteomics, progress in developing global lipidomics has fast-tracked only recently due to considerable advancements in the lipidomic 'pipeline'. Great progress has been made in defining solvents that recover lipid classes that differ in polarity and abundance [258-260], and internal standards for uncommon lipid classes are becoming available [247]. Also, the generation of publically available lipid databases and tools to place lipidomics data in a biological context has been essential for progress in the field

[261-263]. Furthermore, the development of soft ionization mass spectrometry techniques, such as electrospray ionization (ESI) [264], desorption electrospray ionization (DESI) [265], and matrix-assisted laser desorption/ionization (MALDI) [266], has spurred the advent of lipidomics. Soft ionization mass spectrometry techniques enabled researchers to quantitatively and qualitatively define an unprecedented number of lipids species in biological samples, even in crude lipid extracts without prior chromatographic separation, so called 'shotgun' lipidomics [267]. Moreover, MALDI mass spectrometry imaging (MALDI-MSI) is becoming an important tool to unravel the spatial distribution of lipid species in health and disease, and an increasing number of studies apply MALDI-MSI to establish the regional distribution of lipids in the CNS [268, 269]. In future studies, MALDI-MSI will undoubtedly be invaluable to confirm reported brain region-specific differences in the presence and incorporation of ω3 PUFA and phospholipids in health and disease [270-273]. So far, the relatively low spatial resolution has hampered single-cell analysis using MALDI-MSI. However, we recently managed to obtain lipid spectra from pixels as small as 6 µm in human post-mortem brain tissue [269]. This high spatial resolution will pave the way for extensive single cell lipidomics in the healthy and diseased brain in the near future.

Despite of these advances, there are still many hurdles to overcome. A first challenge is associated with the immense complexity and structural diversity of lipids, and relates in part to the inability of existing extraction, separation, and fractionation methods to fully resolve individual lipids species in complex lipid extracts [274]. With respect to the latter, any single extraction, separation, and fractionation procedure is bound to generate a bias toward particular lipid species at the expense of others. Another challenge is related to the inability of current mass lipidomics techniques to provide sufficient structural detail and resolution to distinguish isomeric lipid populations and the location of double bonds [274, 275]. To date, this shortcoming has prohibited the annotation of complex lipids including glycerophospholipids.

On a similar note, current mass spectrometry methods are not inherently quantitative, as lipid ion abundance does not necessarily match its concentration but is also affected by experimental factors, such as sample preparation and mass spectrometry steps [274]. Finally, there remains substantial methodological diversity amongst different laboratories, and efforts to align methodologies have proven challenging [276]. By overcoming the abovementioned challenges, lipidome coverage and reproducibility between laboratories will significantly increase.

10. Summary and therapeutic possibilities

Advances in lipidomics and metabolomics have unveiled the complexity of fatty acid metabolism and the fatty acid lipidome in CNS disorders. However, despite of these advances, it remains challenging to modulate fatty acid metabolism in such as a way that it reduces neuroinflammation and neurodegeneration, and simultaneously promotes CNS repair. For instance, while inhibitors of fatty acid β-oxidation (CPT1a), synthesis (ACC1 and FASN), and desaturation (SCD1) hold great therapeutic promise to suppress neuroinflammation, studies found that they also reduce neuronal and oligodendrocyte differentiation and integrity. By using liposomes or nanoparticles, one could specifically target immune cells, thereby circumventing the neurotoxic properties of these inhibitors. Alternatively, it would be worthwhile to define whether the absence or accumulation of particular fatty acid species underlies the detrimental impact of the abovementioned inhibitors on neuronal and oligodendrocyte physiology. Combinatorial therapies might prove to be a promising strategy to correct for such detrimental changes in the fatty acid lipidome. With respect to the latter, co-administration of ω3 PUFAs has been proposed to prevent or reduce the deleterious side-effects originating from the accumulation SFAs upon treatment with an SCD1 inhibitor [77].

As touched upon in this review, fatty acids can have both beneficial and detrimental effects on CNS disorders, depending on the carbon chain-length and degree of desaturation. SCFAs,

monounsaturated LCFAs, ω-3 PUFAs, elovanoids, and SPMs are suggested to resolve neuroinflammation, prevent neurodegeneration, and even stimulate CNS repair. Hence, dietary supplementation with these fatty acids may reduce disease severity in CNS disorders. In contrast, given their inflammatory and neurotoxic features, excessive consumption of MCFAs, saturated LCFAs, and VLCFAs should be avoided. However, one should keep in mind that these findings stem primarily from *in vitro* and *ex vivo* culture models, and *in vivo* animal models. As species-specific differences in fatty acid metabolism are reported, care should be taken when extrapolating findings to humans. To illustrate, despite abundant evidence in experimental models, a systematic review found that ω6 PUFA and ω3 PUFA supplementation does not significantly impact disease progression in multiple sclerosis patients [193]. In addition, emerging evidence indicates that the lipid class in which fatty acids are incorporated (e.g. phospholipids, sphingolipids, and ceramides) affects their impact on CNS disorders. Hence, future studies should define to what extent fatty acids present in different lipid classes modulate the pathology of CNS disorders. Finally, while CNS disorders show considerable overlap in their lipidome signatures, disease-associated changes in particular fatty acid-containing lipid species are reported. These lipid imbalances might call for disease-specific dietary interventions or lipid-based therapies.

To date, numerous randomized, double-blinded, placebo-controlled clinical trials have been undertaken to study the impact of fatty acid supplementation on neurodegenerative disorders, often with mixed results. To illustrate, in Parkinson's disease, supplementation with ω3 PUFAs from fish oil (180 mg EPA and 120 mg DHA) in combination with vitamin E reduced depressive symptoms but did not impact the level of disability [277]. Conversely, supplementation with ω3 PUFAs (1000 mg total) from flaxseed oil in combination vitamin E did reduce the level of disability Parkinson's disease patients [278]. In subjects with mild to moderate Alzheimer's disease, daily ω3 PUFAs supplementation (1720 mg DHA and 600 mg

EPA) did not improve cognitive function but ameliorated depressive symptoms in non-APOEε4 carriers [279, 280]. By using different doses and source of ω3 PUFA, other clinical trials studied either corroborated or contradicted these studies [281-284]. Of interest, supplementation with Souvenaid, a complex mixture including ω3 PUFAs and choline, improved memory performance in drug-naïve Alzheimer's disease patients but not in an alike patient population taking FDA-approved symptomatic treatments [285-289]. Also in multiple sclerosis and Huntington disease, clinical trials reported conflicting outcomes on the impact of ω3 PUFAs on pathological and disability measures [193, 290, 291]. Potential causes for the controversial outcome of the abovementioned clinical trials, as well as those using other fatty acid containing lipid species such as ω6 PUFAs, phospholipids, and ketogenic diets [292, 293], include differences in 1) the source (*e.g.* plant versus animal) and dosing of lipids, 2) supplementation of co-factor mixtures, 3) patient population characteristics (*e.g.* age, disease status, and treatment regime), 4) trial duration and clinical endpoint measures, and 5) potential disease-associated disturbances in lipid metabolism. Also, the relatively small patient populations used in the majority studies makes it challenging to draw meaningful conclusions. Another major issue concerns the relative lack of knowledge about the spatial distribution of lipids in the healthy and diseased CNS. Increasing evidence indicates brain region-specific differences in the presence and incorporation of fatty acids in disease and following dietary supplementation, respectively [270-273]. An extensive analysis of region- and cell-specific lipidome signatures using MALDI-MSI in the healthy and diseased CNS is likely to enable researchers to pinpoint exact lipid requirements and formulate well-founded, disease-specific dietary formulas.

Changes in the fatty acid lipidome are apparent in plasma and CSF samples of patients with neurological disorders, as discussed in sections 7 and 8. Hence, fatty acid profiling has the potential to become a viable method to monitor the prognosis, diagnosis, and response to therapies in these disorders in the near future. However, gender-, ethnic-, gut microbiota-, and

diet-induced alterations in fatty acid composition complicate the identification of disease- and therapy-specific lipidome signatures. Moreover, applying lipidomics to monitor these disease- and therapy-associated changes in the clinic requires the development of standard operation procedures (e.g. protocols, lipid standards, data handling and quantification). However, to date, there remains substantial methodological diversity amongst different laboratories, and efforts to align methodologies have been rather limited [276]. Once these methodological issues are resolved, lipidomics will become an important diagnostic approach in the clinic.

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