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25 Abstract

Recent advances in lipidomics and metabolomics have unveiled the complexity of fatty acid 26 metabolism and the fatty acid lipidome in health and disease. A growing body of evidence 27 indicates that imbalances in the metabolism and level of fatty acids drive the initiation and 28 progression of central nervous system (CNS) disorders such as multiple sclerosis. Alzheimer's 29 disease, and Parkinson's disease. Here, we provide an in-depth overview on the impact of the 30 β -oxidation, synthesis, desaturation, elongation, and peroxidation of fatty acids on the 31 pathophysiology of these and other neurological disorders. Furthermore, we discuss the impact 32 of individual fatty acids species, acquired through the diet or endogenously synthesized in 33 mammals, on neuroinflammation, neurodegeneration, and CNS repair. The findings discussed 34 in this review highlight the therapeutic potential of modulators of fatty acid metabolism and the 35 fatty acid lipidome in CNS disorders, and underscore the diagnostic value of lipidome 36 signatures in these diseases. 37

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39 Keywords

40 Central nervous system, lipids, neuroinflammation, immunometabolism, neurodegeneration,41 remyelination.

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43 **Declaration of interest**

44 None

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49 Abbreviations

ABCD1, ATP-binding cassette subfamily D member 1; ACC, acetyl CoA carboxylase; ALA, 50 α-linolenic acid; ARA, arachidonic acid; CNS, central nervous system; CPT1, carnitine 51 palmitoyl transferase 1; Δ 4,5,6,9D, delta-4,5,6,9 desaturase; DHA, docosahexaenoic acid; 52 DPA. docosapentaenoic acid: EAE. experimental autoimmune encephalomvelitis: EPA. 53 eicosapentaenoic acid; ELOVL, elongation of very long chain fatty acids proteins; FASN, fatty 54 acid synthase; FAO, fatty acid β-oxidation; HNE, 4-hydroxy-trans-2-nonenal; LA, linoleic 55 acid; LCFA, long-chain fatty acid; TLR, toll-like receptor; MCFA, medium-chain fatty acid; 56 mTORC1, mammalian target of rapamycin complex 1; MUFA, monounsaturated fatty acid; 57 NSPC, neural stem and progenitor cell; OPC, oligodendrocyte precursor cell; PUFA 58 polyunsaturated fatty acid; Th1/Th17, T helper 1 cell; Treg, regulatory T cell; SCD, stearoyl-59 CoA desaturase; SCFA, short-chain fatty acid; SFA, saturated fatty acid; SPM, specialized pro-60 resolving mediator; SREBP, sterol regulatory element binding protein; VLCFA, very-long 61 chain fatty acids; X-ALD, X-linked adrenoleukodystrophy. 62

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104 **1. Introduction**

Fatty acid metabolism consists of anabolic and catabolic processes that are necessary for energy 105 106 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 107 advances in technologies used to dissect and study fatty acid profiles and metabolism have shed 108 light on the pathogenic and protective role of fatty acid metabolism in health and disease. Not 109 110 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 111 112 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 113 acid metabolism is key in driving both the disease-promoting and -resolving features of 114 peripheral and CNS-resident immune cell subsets. Based on these properties, modulation of 115 fatty acid metabolism is increasingly being recognized as a promising therapeutic strategy to 116 117 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, 118 synthesis, desaturation, elongation, and peroxidation, on the pathology of CNS disorders. 119 Moreover, we will discuss if functional modulation of proteins and enzymes involved in these 120 metabolic processes is of therapeutic interest for CNS disorders. Finally, we will elaborate on 121 the inflammatory, neurotoxic, and neuroprotective features of individual fatty acids, as well as 122 123 the emerging role for their downstream bioactive lipid mediators called specialized proresolving mediators in health and disease. 124

2. Fatty acid β-oxidation

126 Mitochondrial fatty acid β-oxidation (FAO) is an essential process for cellular energy
127 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.



136 Figure 1. Schematic illustration of fatty acid anabolism and catabolism. The β -oxidation of very long-chain 137 fatty acids (VLCFAs) and medium- and long-chain fatty acids (MCFAs and LCFAs) is initiated in peroxisomes 138 and mitochondria, respectively. For the initiation of fatty acid β -oxidation, fatty acids are converted to fatty acyl-139 CoAs (FA-CoAs) by a family of acyl-CoA synthetases (ACS). While ATP-binding cassette subfamily D (ABCD) 140 transports VLCFA-CoAs into peroxisomes, carnitine palmitoyl transferases (CPT) and carnitine-acylcarnitine 141 translocases (CAT) transport MCFA-CoAs and LCFA-CoAs into the mitochondrial matrix. Fatty acid synthesis 142 starts in the cytosol with the conversion of acetyl-CoA to malonyl-CoA, a reaction driven by acetyl CoA 143 carboxylases (ACCs) and ATP citrate lyase (ACLY, citrate to acetyl-CoA conversion). Fatty acid synthase (FASN) 144 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 (Δ 4,5,6,9D), 145 146 form fatty acids of different carbon lengths and degrees of saturation. Lipid peroxidation products are formed as a 147 consequence of oxidative stress (e.g. 'O2-, H2O2, and '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-2nonenal (HNE), and specialized pro-resolving mediators (SPMs).

151 **2.1 Fatty acid β-oxidation in neuroinflammation**

In the last decade, it has become clear that pro-inflammatory immune cell subsets, such as 152 classically-activated M1 macrophages and T helper 1 (Th1) and 17 (Th17) cells, primarily use 153 aerobic glycolysis for sustaining their effector functions [1]. In contrast, regulatory T cells 154 (Tregs), alternatively activated M2 macrophages, and memory T cells largely rely on FAO for 155 sustaining their energy needs [1]. In line with this dichotomy, inactivation of aerobic glycolysis 156 markedly reduces neuroinflammation in animal models for Guillain-Barré syndrome, ischemic 157 158 brain injury, and multiple sclerosis [2-4]. Likewise, shifting microglia energy metabolism from anaerobic glycolysis to oxidative phosphorylation alleviates neuroinflammation and A^β burden 159 in two animal models of Alzheimer's disease [5]. Counterintuitively, mice treated with 160 etomoxir, an inhibitor of CPT1 and thus FAO, show reduced CNS inflammation and 161 demyelination in the experimental autoimmune encephalomyelitis (EAE) model, an animal 162 model of multiple sclerosis [6]. Here, etomoxir reduced inflammation by promoting apoptosis 163 of effector T cells, in particular upon glucose deprivation [6]. The mechanisms accounting for 164 the pro-apoptotic effect of etomoxir remain poorly understood. It has been proposed that 165 inhibition of FAO results in perturbations in proteins of the anti-apoptotic B cell lymphoma 2 166 family [7]. Another explanation is that etomoxir causes T cell apoptosis by reducing ATP 167 production and inducing oxidative stress [8]. Altogether, these studies indicate that FAO 168 impacts immune cell physiology, thereby likely affecting neuroinflammation. 169

170 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 rolefor 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 173 174 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 175 FAO for survival and proliferation [12]. On that same note, functional peroxisomal FAO is 176 necessary to maintain glial cell integrity [13]. In X-linked adrenoleukodystrophy (X-ALD), 177 mutations in the fatty acid transporter ATP-binding cassette subfamily D member 1 (ABCD1) 178 179 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 180 oligodendrocyte cell death and causes demyelination [13]. While these studies support a 181 182 protective role of FAO in maintaining NPSC and oligodendrocyte integrity and cell number, a 183 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 184 185 acid synthesis and towards oxidation depletes Schwann cells of important lipid myelin components such as cerebrosides and sulfatides [14]. Furthermore, elevated FAO markedly 186 increased the formation of long-chain acyl carnitines that increased axonal calcium levels and 187 promoted axon degeneration [14]. Collectively, these studies indicate that FAO is essential for 188 189 the function of neurons, glial cells, and NPSCs.

190 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 191 by etomoxir outweigh its inflammatory impact on immune cell function, and does this still hold 192 up in experimental models that do not rely solely on T cells for induction? How does FAO 193 exactly impact the physiology of different CNS-resident cell types, and does the contribution 194 195 of FAO in these cells change in neurological disorders? In addition, given the reported offtarget effects of the golden standard FAO inhibitor etomoxir [15], there is also an urgent need 196 to develop more specific FAO inhibitors. 197

198 **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.

206 3.1 Fatty acid synthesis in neuroinflammation

Emerging evidence indicates that *de novo* fatty acid synthesis controls the fate of inflammatory 207 208 and immunosuppressive immune cell subsets. For instance, the inflammatory activation of 209 macrophages is closely associated with elevated fatty acid synthesis [16-20]. Similar, impeding fatty acid synthesis, through inhibition of ACC1 and FASN, restrains the 210 211 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 212 EAE model by reducing the number of Th17 cells [21, 23]. Likewise, genetic depletion of 213 ACC1 in CD4⁺ T cells or pharmacological inhibition of ACC1 reduces neuroinflammation and 214 215 infarct volume after middle cerebral artery occlusion by altering the Treg/Th17 balance [24]. 216 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 217 mammalian target of rapamycin (mTOR), a master regulator of fatty acid lipogenesis [25], is 218 219 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 220 neurodegenerative diseases [26-29]. However, given the pleiotropic functions of mTOR, 221

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

224 **3.2 Fatty acid synthesis in remyelination**

Oligodendrocytes support signal transmission in the CNS by enwrapping axons with myelin, 225 which contains an exceptionally high content of fatty acid-containing glycolipids and 226 phospholipids [30]. Accurate formation of myelin is not only essential for proper developmental 227 myelination but also during remyelination that follows pathological demyelination in diverse 228 CNS disorders. While dietary fatty acids can be utilized to form myelin sheaths, increasing 229 230 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 231 developmental myelination and remyelination after lysolecithin-induced focal demyelination 232 [31]. Likewise, while oligodendrocyte-specific deficiency of mTORC1 leads to developmental 233 hypomethylation [32], inhibition of mTOR using rapamycin impairs remyelination in the 234 235 cuprizone-induced remyelination model [33]. Conversely, oligodendrocyte-specific 236 hyperactivation of mTORC1 results in the formation of thinner myelin sheaths during development and does not improve remyelination after lysolecithin-induced demyelination [25, 237 34]. This suggests that a precisely balanced regulation of mTORC1 in oligodendrocytes is 238 pivotal for CNS myelination and remyelination. In addition to affecting oligodendrocytes 239 directly, astrocytic fatty acid lipogenesis is key in providing OPCs with lipids for full myelin 240 membrane synthesis [35], which points towards the importance of horizontal lipid flux in 241 supplying OPCs with the necessary fatty acids for myelin formation. Collectively, these 242 findings indicate that fatty acid synthesis in oligodendrocytes and astrocytes controls the 243 formation of myelin, thereby likely influencing remyelination in CNS disorders. 244

245 3.3 Fatty acid synthesis in neurogenesis and dendritogenesis

Proper (re)myelination ensures efficient neuronal function and can protect axons from 246 247 degeneration in CNS disorders. Hence, by affecting the physiology of myelin-producing oligodendrocytes, fatty acid synthesis can impact neuronal functioning. However, several 248 studies indicate that fatty acid synthesis not only changes neuronal function indirectly but also 249 in a cell-autonomous manner. For instance, FASN expression and activity is high in 250 proliferating NSPCs and its inhibition decreases NPSC proliferation [36]. By crossing 251 252 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 253 in vivo. Alongside promoting neurogenesis, fatty acid synthesis controls neuronal dendrite 254 255 expansion. Genetic knockdown of sterol regulatory element binding protein (SREBP), a crucial regulator of fatty acid production, in dendritic arborization neurons decreases dendritic branch 256 length and the number of terminal endpoints, and promotes axon loss [37]. In summary, these 257 258 studies argue for fatty acid synthesis being essential for neuronal development, function, and integrity. 259

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.

265 **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 270 271 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 272 (MUFAs) and saturated fatty acids (SFAs), and ELOVL2 and 5 strictly elongate 273 polyunsaturated fatty acids (PUFAs). ELOVL4 catalyzes the formation of VLCFAs (>C26) 274 [38, 39]. While literature regarding the precise role of ELOVLs in CNS disorders is scarce, 275 276 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 277 activity of ELOVLs is closely linked to the pathophysiology of Alzheimer's disease [43], X-278 279 ALD [44], and multiple sclerosis [45].

280 4.1 Fatty acid elongation in neuroinflammation

Several studies indicate that elongases control the balance between pro- and anti-inflammatory 281 immune responses. While ELOVL1 is positively associated with the inflammatory status of 282 283 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 284 suggest that inhibition of ELOVL1 and ELOVL6 may be an attractive therapeutic strategy to 285 reduce neuroinflammation. In contrast, ELOVL2-mediated synthesis of the $\omega 3$ PUFA 286 docosahexaenoic acid (DHA) keeps macrophage and T cell polarization in check by 287 suppressing Th1/Th17 differentiation and M1 macrophage activation, and sustaining the 288 number and function of Tregs and M2 macrophages [49, 50]. Finally, the induction of T cell 289 proliferation is closely associated with an elevated expression of ELOVL5 [51]. However, 290 despite this elevated expression, ELOVL5 silencing does not impact T cell proliferation, 291 292 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 293 neuroinflammation. 294

4.2 Fatty acid elongation in neurodegeneration and demyelination

296 Increasing evidence points towards elongases being essential in controlling oligodendrocyte and neuronal physiology in health and disease. In X-ALD patients, ELOVL1 is highly 297 298 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 299 and neuroprotective impact of Lorenzo's oil in X-ALD partially depends on its suppressive 300 301 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 302 neuronal degeneration in the brain [54]. Elevated ELOVL7 activity was identified as one of the 303 304 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 305 neurodegeneration, and control presynaptic release kinetics [55, 56]. Collectively, these studies 306 indicate that excessive ELOVL1 and ELOVL7 activity promote demyelination and 307 neurodegeneration, and that ELOVL4 activity is essential to maintain synaptic transmission. 308

309 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 310 molecular mechanisms and fatty acids remain largely unresolved. In addition, while inhibition 311 of ELOVL1 and ELOVL7 represents a viable option to prevent neurodegeneration and 312 demyelination, its impact on CNS repair (e.g. remyelination and neuroregeneration) remains to 313 be determined. The absence of specific inhibitors of the different elongases, as well as the fact 314 that ELOVL1 and ELOVL4 knockout mice die shortly after birth [57, 58], likely explains the 315 lack of research on elongases. 316

317 5. Fatty acid desaturation

The desaturation of fatty acids is essential for the biosynthesis of UFAs (Figure 1). It relies on 318 319 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 320 described: delta-4 (Δ 4Ds), delta-5 (Δ 5Ds), delta-6 (Δ 6Ds), and delta-9 desaturases (Δ 9Ds), each 321 322 catalyzing the formation of a cis-double bond at the $\Delta 4$, $\Delta 5$, $\Delta 6$, and $\Delta 9$ position of fatty acyl-CoAs, respectively. The Δ 4Ds, Δ 5Ds and Δ 6Ds are required for the formation of PUFAs, such 323 324 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 325 formation of these PUFAs requires the successive actions by elongase and desaturase enzymes 326 327 [60]. The Δ 9Ds, also called stearoyl-CoA desaturases (SCD), catalyze the formation of MUFAs (palmitoleoyl- and oleoyl-CoA) from SFAs (palmitoyl- and stearoyl-CoA) [61]. Unlike lower 328 animals and plants, mammals lack the $\Delta 12Ds$ and $\Delta 15Ds$, which are needed to catalyse the 329 330 formation of linoleic acid (LA) and α-linolenic acid (ALA) [59]. Therefore, LA and ALA acid are known as dietary essential fatty acids. 331

332

5.1 Fatty acid desaturation in neuroinflammation

Similar to the oxidation, synthesis, and elongation of fatty acids, fatty acid desaturation impacts 333 immune cell physiology. Deficiency of the Δ 9D SCD1 augments the inflammatory features of 334 effector T cells and macrophages [62-64]. Alternatively, while $\Delta 5D$ (FADS1) deficiency 335 reduces the number of Th17 cells in a colitis mouse model [65], it promotes and suppresses the 336 induction of M1 and M2 macrophage activation programs, respectively [66]. Alterations in the 337 levels of immunomodulatory w3 and w6 PUFAs, and pro-resolving and inflammatory lipid 338 mediators formed from these PUFAs (see section 8), likely underlie the impact of Δ 5Ds on 339 immune cell function and differentiation [65-67]. Several studies also reported a role for fatty 340 acid desaturases in controlling neuroinflammation. Transcriptomic analysis identified that 341 amyloid-ß uptake by macrophages increases SCD1 expression in addition to a set of pro-342

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 ω 3 and ω 6 PUFAs in driving immune cell function (see section 7), it remains unclear how changes in Δ 4D, Δ 5D, and Δ 6D activity influence neuroinflammation in CNS disorders.

349 5.2 Fatty acid desaturation in neurogenesis and neurodegeneration

MUFAs and PUFAs are essential nutrients and fundamental components of neurons and 350 351 oligodendrocytes. Not surprisingly, desaturase activity correlates closely with the physiology of these cells in health and disease. With respect to Δ 9D activity, SCD1 promotes the formation 352 of astrocytic oleic acid, which enhances neuron migration, and axon and dendrite growth [69, 353 70]. In contrast, while constitutive expression of human SCD5 promotes proliferation of mouse 354 Neuro2a cells, it suppresses retinoic acid-induced neuritogenesis and maturation [71]. These 355 356 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 357 Parkinson disease was demonstrated [72]. Here, inhibition of SCD1 enhanced the survival of 358 human neurons in the presence of toxic α -synuclein. To what extent these findings also hold up 359 for other CNS disorders characterized by the accumulation of toxic protein aggregates remains 360 to be determined. Yet again, while dietary supplementation with $\omega 3$ and $\omega 6$ PUFAs is well-361 known to impact the integrity of neuronal and glial cells (see section 7), the importance of de 362 *novo* formation of PUFAs by Δ 4D, Δ 5D, and Δ 6D in this process remains unresolved. The 363 relative inactive desaturation in neurons as compared to endothelial cells and astrocytes might 364 indicate that neurons rely mainly on horizontal lipid fluxes for PUFAs [73], rendering Δ 4Ds, 365 Δ 5Ds, and Δ 6Ds redundant in these cells. 366

As clarified in the abovementioned paragraphs, the Δ 9D SCD1 represents a promising 367 368 therapeutic target to suppress neuroinflammation and neurodegeneration, and promote CNS repair processes. Several small molecule inhibitors of SCD1 already progressed to early clinical 369 development for the treatment of metabolic disorders and cancer [74-76]. However, clinical 370 success remains to be attained, partially due the difficulty of translating lipid metabolism from 371 rodents to humans. Moreover, the accumulation of inflammatory SFAs poses a problem upon 372 373 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 374 SFAs [77]. In contrast to Δ 9Ds, evidence for the therapeutic applicability of Δ 4Ds, Δ 5Ds, and 375 376 Δ 6Ds 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 $\omega 3$ and $\omega 6$ PUFAs. However, the relative 377 contribution of Δ 4Ds, Δ 5Ds, and Δ 6Ds in controlling ω 3 and ω 6 PUFAs levels in CNS-resident 378 379 and immune cells, as compared to dietary-derived ω 3 and ω 6 PUFAs, is poorly understood.

380

6. Fatty acid peroxidation

The process of lipid peroxidation occurs when oxidants such as free radicals interact with fatty 381 acids containing carbon-carbon double bonds, especially PUFAs (Figure 1). This interaction 382 383 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 384 enzymes such as lipooxygenases, cyclooxygenases, and cytochrome P450 [78] (Figure 1). Fatty 385 acid peroxidation products have both cytotoxic/inflammatory and cytoprotective/anti-386 387 inflammatory effects. The eventual cellular outcome depends on the fatty acid substrate (e.g. ω 3 versus ω 6 PUFAs) and pathway involved (e.g. enzymatic versus non-enzymatic) [78, 79]. 388

389 6.1 Fatty acid peroxidation in neuroinflammation

The early observation that lipid peroxidation products are generated in atherosclerosis 390 391 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 392 inflammatory conditions including diabetes [81], liver and kidney toxicity [82], cancer [83], 393 metabolic syndrome [84], aging [85], and ischemia [86]. Lipid peroxidation products can act as 394 precursors of important bioactive mediators of inflammation, such as the prostaglandins, 395 thromboxanes, and leukotrienes, following enzymatic conversion by cyclooxygenases, 396 lipoxygenases, and cytochrome P450 [87]. Likewise, 4-hydroxy-trans-2-nonenal (HNE), a 397 major lipid peroxidation-derived aldehyde, stimulates the inflammatory response in 398 399 macrophages and contributes to disease progression of atherosclerosis by inducing cyclooxygenase 2 activity, prostaglandin formation, and NF-kβ activation [88, 89]. 400 Alternatively, some of the lipid mediators generated from multistage enzymatic oxidation of 401 402 ω 3 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 403 activate the anti-inflammatory peroxisome proliferator-activated receptor γ (PPAR γ) in 404 immune cells, thereby transrepressing inflammatory responses [92, 93]. In the EAE model, the 405 generation of oxidative-stress induced lipid peroxidation products seems mainly pro-406 407 inflammatory as treatment with antioxidants ameliorates disease severity [94, 95]. Accordingly, oxidative stress induced by lipid peroxidation precedes the inflammatory response in multiple 408 sclerosis patients [96]. Collectively, these studies indicate that lipid peroxidation products likely 409 410 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-411 inflammatory lipid peroxidation products in CNS disorders. 412

413 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 414 415 fatty acid peroxidation [97]. With respect to the latter, relapsing-remitting multiple sclerosis patients display heightened levels of biochemical markers of peroxidation, such as 416 malondialdehyde [96]. Lipid peroxidation products are also abundantly present in the brain, 417 cerebrospinal fluid, and plasma from patients with Alzheimer's disease [85]. Here, amyloid β 418 causes oxidative stress through its interaction with transition metal ions, such as Cu^{2+} and Zn^{2+} . 419 420 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 421 donors such as PUFAs, leading to the generation of toxic lipid peroxidation products such as 422 423 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 424 peroxidation of PUFA residues within lipid membranes. The subsequent increase in lipid 425 426 peroxidation products is integral to α-synuclein-induced neuronal damage and neuronal death [100]. Interestingly, lipid peroxidation products can be transported from neurons to 427 neighbouring astrocytes for detoxification or storage in lipid particles [101]. Horizontal transfer 428 of toxic lipid metabolites likely retains neuronal homeostasis in health and disease, but may 429 430 eventually also contribute to disease pathology in CNS disorders. While these studies show that 431 accumulation of oxidative stress-induced lipid peroxidation products causes neurodegeneration, emerging evidence indicates that the enzymatic formation of oxygenated pro-resolving 432 mediators, such as resolvins, maresins, and protectins, reduces neuroinflammation and supports 433 434 CNS repair (discussed in section 8). On that same note, oxygenated derivates of ω 3 PUFAs called elovanoids were recently found to counteract oligomeric β-amyloid-induced gene 435 expression and protect photoreceptors [102]. Moreover, elovanoids protected neuronal cultures 436 undergoing either oxygen/glucose deprivation or receptor-mediated excitotoxicity, and were 437 neuroprotective in an experimental ischemic stroke model [103]. Therefore, increasing the level 438

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.

442 **7. Fatty acid chain length and saturation**

In the previous sections, we focused on the impact of enzymes and proteins involved in the 443 metabolism of fatty acids on CNS disorders. In the next sections, we will summarize and discuss 444 the current knowledge on the impact of individual fatty acid species, formed through the 445 anabolism and catabolism of fatty acids, obtained through the diet, or synthesized by the gut 446 microbiota, on CNS disorders. We subdivided fatty acids based on their aliphatic carbon chain 447 length. According to the chain length, fatty acids are classified as short-chain fatty acids 448 (SCFAs, C1-6), medium-chain fatty acids (MCFAs, C7-12), long-chain fatty acids (LCFAs, 449 C13-22), and very-long chain fatty acids (VLCFAs, > C22). 450



452 Figure 2. Simplified figure of the origin and formation of individual fatty acids in the human body including 453 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-9 454 455 desaturases, Δ 9D) and elongation (E, ELOVL1, 3, 4, 6, and 7) steps. Non-essential SCFAs and MCFAs are 456 acquired through the diet, formed by the gut microbiota, or endogenously synthesized as intermediates during the 457 anabolism and catabolism of fatty acids. Given the lack of delta-12 and delta-15 desaturases (Δ 12D and Δ 15D) in 458 humans, $\omega 3$ and $\omega 6$ PUFAs can only be obtained through the diet and, therefore, are called essential fatty acids. 459 Successive elongation (ELOVL2, 5, and 7), desaturation (Δ 4D, Δ 5D, and Δ 6D), β -oxidation (β), and peroxidation (enzymatic and non-enzymatic) steps result in the formation of complex polyunsaturated lipid species. 460

461 **7.1 Short-chain fatty acids**

SCFAs, such as acetic (C2:0), propionic (C3:0), and butyric acid (C4:0), are the primary end-462 products of gastrointestinal fermentation of complex polysaccharides, found in fiber-rich diets 463 (Figure 2) [104]. Recent evidence indicates that these microbiota-derived SCFAs closely 464 regulate CNS homeostasis and neuroinflammation by affecting microglia activation and Treg 465 expansion [105, 106]. Furthermore, in experimental models of Alzheimer's disease, Parkinson 466 disease, stroke, traumatic brain injury, and infectious CNS disorders, SCFAs and derivatives 467 thereof were found to reduce amyloid β aggregation [107], protect neurons and 468 oligodendrocytes from cell death [108-111], restore blood-brain barrier permeability [112], 469 suppress neuroinflammation [111, 113], and improve memory and locomotor deficits [108, 111, 470 114, 115]. The neuroprotective impact of SCFAs likely depends in part on their ability to 471 reverse disease-associated reductions in histone deacetylation [108-111, 114-116]. 472 Interestingly, multiple sclerosis patients display a depletion of bacterial species belonging to 473 clostridia XIVa and IV cluster, which produce SCFAs, such as propionate and butyrate [117]. 474 Likewise, changes in gut microbiota are associated with a reduced presence of SCFAs in 475 patients with Parkinson's disease [118]. These microbial imbalances might promote the 476 neuroinflammatory burden in multiple sclerosis and Parkinson's disease. To what extent 477

478 microbial imbalances in these CNS disorders originate from environmental factors or disease479 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 mainly acquired through our diet by consumption of milk fat, coconut oil, and pelargonium oil 484 (Figure 2). MCFAs markedly increase the differentiation of Th1 and Th17 cells, and decrease 485 486 that of Tregs in vitro [106]. A lauric acid-rich diet mimics these immunological changes in vivo and enhances CNS autoimmunity in the EAE model [106]. Gut microbiota were found to be 487 crucial in driving changes in the immunological landscape in these animals, likely by increasing 488 the concentration of MCFAs and LCFAs, and decreasing that of SCFAs. Aside from having a 489 direct impact on T cell polarization, caprylic acid can enhance the neuroinflammatory burden 490 491 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 (GPR84) [120]. GPR84 is highly expressed by T cells, neutrophils, macrophages, and microglia 493 [121], and its activation enhances the pro-inflammatory properties of these cells [120, 122-126]. 494 Moreover, ample evidence indicates that GPR84 is highly expressed on activated microglia in 495 diverse animal models of CNS pathologies [122, 126-128]. Unexpectedly, while GPR84 496 deficiency reduces microgliosis, it accelerates the number of degenerating dendrites in 497 APP/PS1 mice [128]. The latter study indicates that GPR84, and thus likely MCFAs, are crucial 498 in maintaining dendritic homeostasis. In line with this protective role of MCFA, nonanoic and 499 500 capric acid enhance seizure control activity and provide protection against neuronal loss in in vitro seizure and in vivo epilepsy models [129, 130]. These findings can partially explain 501 the therapeutic efficacy of a medium-chain triglyceride ketogenic diet on childhood epilepsy 502

503 [131], Alzheimer's disease [132, 133], and Huntington disease [134]. In summary, while 504 MCFAs promote inflammation, studies indicate that they maintain neuronal and 505 oligodendrocyte integrity in CNS disorders as well.

506 7.3 Long-chain fatty acids

507 LCFAs can be obtained from a variety of dietary sources or endogenously synthesized from 508 other fatty acids (Figure 2). The impact of LCFAs on neuroinflammation and 509 neurodegeneration largely depends on their saturation level. Hence, LCFAs were subdivided 510 into saturated, monounsaturated, and polyunsaturated LCFAs.

511 **7.3.1 Saturated long-chain fatty acids**

Saturated LCFAs such as myristic (C14:0), palmitic (C16:0), stearic (C18:0), arachidic (C20:0), 512 513 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 514 accordance, dietary supplementation with saturated LCFAs promotes neuroinflammation in 515 516 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 517 suggested to impact inflammation by ligating the toll-like receptor (TLR) 2 and 4 [138-140]. 518 519 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 520 hypothalamic neurons, and negatively impacts hippocampal neurogenesis [142, 143]. Similar, 521 palmitic and stearic acid induce hyperphosphorylation of tau in cortical neurons by affecting 522 523 the secretory profile of astrocytes [144]. Finally, diets high in saturated fatty acids increase the 524 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 525 evidence that saturated LCFAs are inflammatory and neurotoxic, explaining the positive 526

527 correlation between LCFAs and disease progression in multiple sclerosis and Alzheimer's528 disease [148, 149].

529 7.3.2 Monounsaturated long-chain fatty acids

In contrast to saturated LCFAs, the majority of studies report that monounsaturated LCFAs 530 such as palmitoleic (C16:1), oleic (C18:1), gondoic (C20:1), and erucic acid (C22:1) are anti-531 inflammatory in vitro [150-153], and reduce neuroinflammation in vivo [154-156]. While direct 532 evidence is lacking, monounsaturated LCFAs may impact neuroinflammation through 533 activation of the anti-inflammatory receptors GPR120 and PPARs [156-159]. Oleic and 534 535 palmitoleic acid have also been extensively scrutinized for their neuroprotective effects. Astrocytic oleic acid promotes neuronal differentiation and migration as well as 536 oligodendroglial myelination during brain development [35, 69, 70, 160]. On that same note, 537 oleic and palmitic acid increase the viability, proliferation, and stemness of embryonic neural 538 stem cells [161]. Finally, in experimental animal models of Alzheimer's disease, oleic acid 539 540 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, 541 monounsaturated LCFAs have neurotoxic features as well. By using a yeast 542 proteinopathy model, oleic and palmitoleic acid were found to promote α -synuclein toxicity 543 [72]. Furthermore, they stimulate the assembly of amyloid β and tau filaments, and the cytotoxic 544 aggregation of amyotrophic lateral sclerosis-linked superoxide dismutase 1 mutants in vitro 545 [163-165]. Collectively, these findings indicate that monounsaturated LCFAs can reduce 546 neuroinflammation and promote CNS repair. However, they can also stimulate the formation 547 of cytotoxic protein aggregates in CNS disorders. Future studies should correlate reported 548 changes in oleic acid levels in patients with Alzheimer's disease and multiple sclerosis to 549 disease progression and remission in these disorders [166-170]. 550

551 7.3.3 Polyunsaturated long-chain fatty acids

In contrast to saturated and monounsaturated LCFAs, the brain primarily maintains levels of 552 553 polyunsaturated LCFAs via the uptake from dietary sources through diffusion over the bloodbrain barrier [171]. The general consensus is that ω3 PUFAs, such as ALA (C18:3), EPA 554 (C20:5), and DHA (C22:6), are anti-inflammatory in CNS disorders. Dietary supplementation 555 with these ω 3 PUFAs reduces the neuroinflammatory burden in diverse experimental models 556 [172, 173], likely by suppressing the activation of the NLRP3 inflammasome [174], the 557 differentiation of Th17 cells [175], and the migratory capacity of leukocytes [176]. 558 Accordingly, ω 3 PUFA supplementation is associated with a reduced inflammatory burden in 559 Alzheimer's disease [177], Parkinson disease [178], and multiple sclerosis [179]. Similar to 560 561 monounsaturated LCFAs, w3 PUFAs are hypothesized to reduce inflammation by activation of GPR120 and PPARs [180, 181]. However, the anti-inflammatory effects of ω 3 PUFAs may 562 also be explained by the fact that they act as precursors of anti-inflammatory specialized pro-563 564 resolving lipid mediators (discussed in section 8) [182, 183]. As opposed to ω 3 PUFAs, ω 6 PUFAs were for a long time considered to promote the inflammatory features of immune and 565 glial cells, mainly because ARA (C20:4) is a precursor of pro-inflammatory eicosanoids, such 566 as prostaglandins, thromboxanes, and leukotrienes [65, 184-187]. Indeed, by using the fat-1 567 568 mouse model, in which ω 3 PUFAs are endogenously formed from ω 6 PUFAs, a reduced 569 neuroinflammatory burden in experimental models for Alzheimer's disease and depression was observed [188, 189]. Conversely, oral feeding of $\omega 6$ PUFAs attenuates the disease course of 570 acute and chronic EAE [190], and emerging evidence indicates that $\omega 6$ PUFAs have anti-571 572 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 573 significant effect of $\omega 6$ PUFA supplementation on disease progression and relapse rate in 574 multiple sclerosis patients [193]. The latter findings might be explained by the wide variety of 575 the eicosanoids produced by $\omega 6$ PUFAs, some of which possess pro-inflammatory features 576

577 [184]. Moreover, a biphasic activity of ω 6 PUFAs has been reported, with ω 6 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].

Approximately one-third of the lipids in the CNS are polyunsaturated LCFAs. Not surprisingly, 581 changes in the levels of these lipid species impact the formation, integrity, and function of glial 582 and neuronal cells in health and disease. For instance, $\omega 3$ PUFAs promote the differentiation 583 of neurons [197-199], and support neurite growth in hippocampal, cortical, and sensory neuron 584 cultures [200, 201]. DHA was further found to stimulate oligodendrocyte progenitor maturation 585 and prevent the maturational arrest induced by $TNF\alpha$ [202, 203]. In accordance with these 586 studies, by using the fat-1 mouse model or dietary intervention, an increase in ω 3 PUFAs 587 improves neuronal and oligodendrocyte survival, and attenuates remyelination in experimental 588 animal models [188, 204-209]. In contrast to ω 3 PUFAs, ω 6 PUFAs such as ARA can induce 589 590 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 an effective inhibitor of sodium currents and synaptic transmission in cultured striatal neurons 593 594 [212], which might cause maladaptive neurotransmission in CNS disorders. In support of these studies, dietary ARA supplementation amplifies Aß oligomer neurotoxicity and promotes 595 cognitive decline in animal models of Alzheimer's disease [213, 214]. However, ω6 PUFAs are 596 also reported to have neuroprotective features. ARA supplementation can compensate for 597 changes in ω 6 PUFA levels and deficits in motor activity and coordination during development 598 599 in $\Delta 6D$ deficient mice [215, 216]. Even more, maternal ARA supplementation improves neurodevelopment in young adult offspring [217]. These studies suggest that $\omega 6$ PUFAs are 600

601 neurotoxic in excess but necessary for early brain development. On the other hand, these 602 findings might merely reflect the dual role that $\omega 6$ PUFAs have on cell physiology [184, 194].

603 7.4 Very long-chain fatty acids

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

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

oligodendrocyte loss [13, 232]. While these studies indicate that organelle dysfunction and 626 627 aberrant histone acetylation underlie the cytotoxic features of VLCFAs, other studies suggest that VLCFAs can directly destabilize and permeabilize membranes [233], thereby promoting 628 necroptosis, a programmed form of necrosis [234]. Necroptosis is a common pathological 629 feature in CNS disorders, including multiple sclerosis, Alzheimer's disease, and Parkinson's 630 disease [235]. In line with the detrimental impact of VLCFAs on neuronal and glial cells in 631 632 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 633 role of VLCFAs in other CNS disorders is lacking, VLCFA levels are increased in the serum 634 635 and CNS of patients suffering from multiple sclerosis and Alzheimer's disease [45, 237, 238]. 636 Moreover, emerging evidence links peroxisomal dysregulation to these and other neurological disorders [239]. Interestingly, while the latter studies indicate that long-term increases in 637 VLCFAs in the CNS can initiate or promote neurodegenerative events, recent studies indicate 638 that ω 3 PUFA-derived elovanoids and saturated VLCFA formed through ELOVL4 are 639 neuroprotective and essential for proper synaptic transmission [55, 56, 102, 103]. Future studies 640 should define whether the abundance of these newly identified protective VLCFA is associated 641 642 with disease remission in CNS disorders.

643 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

to four dietary fatty acids, namely, $\omega 6$ AA, $\omega 3$ EPA, $\omega 3$ DHA, and $\omega 3$ DPA, by means of the 651 652 concerted action of lipoxygenase isozymes, cyclooxygenase 2, and, to a lesser extent, cytochrome P450 (Figure 2) [240]. Initially, the resolution phase was thought to be a passive 653 process, but is now recognized as an active event initiated at the start of an inflammatory 654 response [241]. Similar to Virchow's cardinal signs of inflammation, like rubor (redness), calor 655 (heat), tumor (swelling), dolor (pain) and functio laesa (loss of function), there are five cardinal 656 657 signs of resolution [183, 242]. One of the key cardinal signs of resolution is cell clearance, in which neutrophil apoptosis occurs and, as a consequence, efferocytosis through recruited 658 monocyte-derived macrophages ensues [243, 244]. The other four cardinal signs are cessation 659 660 of leukocyte recruitment, counter regulation of pro-inflammatory mediators, transition from classical activated macrophages to a more alternative phenotype, restoration of vascular 661 integrity and re-entering of leukocytes in the vasculature and lymphatics [183, 242]. In general, 662 663 SPMs are potent resolution agonists that extinguish the eicosanoid-induced inflammation by activating local resolution programs [245], via five separate G protein-coupled receptors; 664 ALX/FPR2, GPR32/DRV1, ChemR23/ERV, BLT1 and GPR18/DRV2 [246]. During 665 resolution of inflammation, the very same cells recruited to the inflammatory milieu, undergo 666 667 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 waves, with lipoxins appearing earlier and resolvins, protectins, and maresins being produced 669 670 later during an inflammatory response [246]; therefore, they act in a time- and cell-dependent 671 manner.

572 Since the identification of SPMs in human samples relies on liquid chromatography-tandem 573 mass spectrometry (LC-MS-MS)-based approaches and internal standards have only recently 574 become available [247], it is now possible to consider that a failed resolution response may be 575 a universal cause of chronic (neuro-)inflammatory disorders [248]. For example, it has recently

been shown that LXA4 is decreased in the brain and CSF of patients with Alzheimer's disease, 676 677 and that LXA₄ 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 678 reduced in the entorhinal cortex of patients with Alzheimer's disease [250], thereby providing 679 more evidence of a disturbed resolution pathway in Alzheimer's disease [251]. Moreover, our 680 recent findings indicate that such resolution defects are also apparent in multiple sclerosis and 681 682 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 683 that are characterized by uncontrolled or chronic inflammation to facilitate clinical translation 684 685 of SPM supplementation. Results from preclinical disease models are encouraging and suggest 686 that treatment of inflammation-associated diseases might be possible with SPM agonists that stimulate resolution and protect organs from collateral damage [253]. Moreover, in 687 688 experimental animal models of spinal cord injury, lamellar keratectomy, and Alzheimer's disease, exogenous administration of SPMs, such as MaR1, PD1, and LXA4, results in reduced 689 neuroinflammation, decreased levels of amyloid beta and phosphorylated-tau, neuroprotection, 690 and functional neurological recovery [254-257]. These studies indicate that treatment with 691 SPMs represents a promising therapeutic strategy to reduce neuroinflammation and stimulate 692 693 CNS repair simultaneously.

694 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 701 702 as electrospray ionization (ESI) [264], desorption electrospray ionization (DESI) [265], and matrix-assisted laser desorption/ionization (MALDI) [266], has spurred the advent of 703 704 lipidomics. Soft ionization mass spectrometry techniques enabled researchers to quantitatively and qualitatively define an unprecedented number of lipids species in biological samples, even 705 706 in crude lipid extracts without prior chromatographic separation, so called 'shotgun' lipidomics 707 [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 708 number of studies apply MALDI-MSI to establish the regional distribution of lipids in the CNS 709 710 [268, 269]. In future studies, MALDI-MSI will undoubtedly be invaluable to confirm reported brain region-specific differences in the presence and incorporation of $\omega 3$ PUFA and 711 phospholipids in health and disease [270-273]. So far, the relatively low spatial resolution has 712 713 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 714 spatial resolution will pave the way for extensive single cell lipidomics in the healthy and 715 diseased brain in the near future. 716

717 Despite of these advances, there are still many hurdles to overcome. A first challenge is 718 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 719 720 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 721 722 lipid species at the expense of others. Another challenge is related to the inability of current 723 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 724 725 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.

732 **10. Summary and therapeutic possibilities**

Advances in lipidomics and metabolomics have unveiled the complexity of fatty acid 733 metabolism and the fatty acid lipidome in CNS disorders. However, despite of these advances, 734 it remains challenging to modulate fatty acid metabolism in such as a way that it reduces 735 736 neuroinflammation and neurodegeneration, and simultaneously promotes CNS repair. For instance, while inhibitors of fatty acid β-oxidation (CPT1a), synthesis (ACC1 and FASN), and 737 738 desaturation (SCD1) hold great therapeutic promise to suppress neuroinflammation, studies 739 found that they also reduce neuronal and oligodendrocyte differentiation and integrity. By using liposomes or nanoparticles, one could specifically target immune cells, thereby 740 circumventing the neurotoxic properties of these inhibitors. Alternatively, it would be 741 742 worthwhile to define whether the absence or accumulation of particular fatty acid species underlies the detrimental impact of the abovementioned inhibitors on neuronal and 743 744 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-745 746 administration of ω 3 PUFAs has been proposed to prevent or reduce the deleterious side-effects originating from the accumulation SFAs upon treatment with an SCD1 inhibitor [77]. 747

As touched upon in this review, fatty acids can have both beneficial and detrimental effectson 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 750 751 neuroinflammation, prevent neurodegeneration, and even stimulate CNS repair. Hence, dietary supplementation with these fatty acids may reduce disease severity in CNS disorders. In 752 contrast, given their inflammatory and neurotoxic features, excessive consumption of MCFAs, 753 saturated LCFAs, and VLCFAs should be avoided. However, one should keep in mind that 754 755 these findings stem primarily from *in vitro* and *ex vivo* culture models, and *in vivo* animal 756 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 757 758 experimental models, a systematic review found that ω 6 PUFA and ω 3 PUFA supplementation 759 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 760 (e.g. phospholipids, sphingolipids, and ceramides) affects their impact on CNS disorders. 761 762 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 763 overlap in their lipidome signatures, disease-associated changes in particular fatty acid-764 containing lipid species are reported. These lipid imbalances might call for disease-specific 765 dietary interventions or lipid-based therapies. 766

To date, numerous randomized, double-blinded, placebo-controlled clinical trials have been 767 undertaken to study the impact of fatty acid supplementation on neurodegenerative disorders, 768 769 often with mixed results. To illustrate, in Parkinson's disease, supplementation with ω 3 PUFAs from fish oil (180 mg EPA and 120 mg DHA) in combination with vitamin E reduced 770 771 depressive symptoms but did not impact the level of disability [277]. Conversely, 772 supplementation with ω 3 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 773 moderate Alzheimer's disease, daily w3 PUFAs supplementation (1720 mg DHA and 600 mg 774

EPA) did not improve cognitive function but ameliorated depressive symptoms in non-APOEɛ4 775 776 carriers [279, 280]. By using different doses and source of ω 3 PUFA, other clinical trials studied either corroborated or contradicted these studies [281-284]. Of interest, supplementation with 777 Souvenaid, a complex mixture including ω 3 PUFAs and choline, improved memory 778 performance in drug-naïve Alzheimer's disease patients but not in an alike patient population 779 taking FDA-approved symptomatic treatments [285-289]. Also in multiple sclerosis and 780 781 Huntington disease, clinical trials reported conflicting outcomes on the impact of ω 3 PUFAs on pathological and disability measures [193, 290, 291]. Potential causes for the controversial 782 783 outcome of the abovementioned clinical trials, as well as those using other fatty acid containing 784 lipid species such as $\omega 6$ PUFAs, phospholipids, and ketogenic diets [292, 293], include differences in 1) the source (e.g. plant versus animal) and dosing of lipids, 2) supplementation 785 of co-factor mixtures, 3) patient population characteristics (e.g. age, disease status, and 786 787 treatment regime), 4) trial duration and clinical endpoint measures, and 5) potential diseaseassociated disturbances in lipid metabolism. Also, the relatively small patient populations used 788 789 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 790 791 healthy and diseased CNS. Increasing evidence indicates brain region-specific differences in 792 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 793 using MALDI-MSI in the healthy and diseased CNS is likely to enable researchers to pinpoint 794 795 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 diseaseand 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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