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FORUM REVIEW ARTICLE

Essential Dietary Bioactive Lipids in Neuroinflammatory Diseases

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Abstract

Significance: Under physiological conditions, neurons and glia are in a healthy, redox-balanced environment; when injury perturbs this equilibrium, a neuroinflammatory state is established by activated microglia that triggers pro-inflammatory responses and alters the oxidant/antioxidant balance, thus leading to neuronal loss and neurodegeneration. In neurodegenerative diseases (such as Alzheimer's disease, Parkinson's disease, amyothrophic lateral sclerosis, and multiple sclerosis), the brain is in a constitutively self-sustaining cycle of inflammation and oxidative stress that prompts and amplifies brain damage.
Recent Advances: Recently, an increasing amount of scientific data highlight the ability of specific nutrients to cross the blood-brain barrier, and to modulate inflammatory and oxidative pathways. Therefore, nutritional approaches may contribute to restore the lost equilibrium among factors accounting for neurodegeneration.
Critical Issues: Herein, we critically examine how essential lipids (including fatty acids, liposoluble vitamins and phytosterols) might contribute to accelerate or prevent the onset and progression of such pathologies. In particular, we highlight that experimental and clinical findings, although promising, are still inadequate to draw definitive conclusions.
Future Directions: More research is warranted in order to establish the real impact of lipid intake on brain health, especially when redox balance and inflammatory responses have been already compromised. In the future, it would be hoped to gain a detailed knowledge of chemical modifications and dynamic properties of such nutrients, before planning to exploit them as potential therapeutics. *Antioxid. Redox Signal.* 29, 37–60.

Keywords: fatty acids, liposoluble vitamins, neuroinflammation, nutrition, phytosterols

Introduction

In the past decades, an ever-growing body of evidence has emphasized the existence of an intricate cross-talk between neurons and immune cells, which maintains and guarantees brain homeostasis (26). When injury perturbs this delicate equilibrium, inflammatory responses that originated in the central nervous system (CNS) give rise to the so-called ''neuroinflammation.'' In this context, glia (non-neuronal cells, including microglia and astrocytes) represent the main source of neurotoxic molecules [*i.e.*, inflammatory mediators and reactive oxygen (nitrogen) species], responsible for progressive loss of the structure and function of neuronal cells, thus leading to functional and mental impairment (32, 205). Neuroinflammation is, indeed, continuously emerging as a critical factor in the pathogenesis and progression of neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS) (63, 72, 73, 76, 88, 186, 221). The self-sustaining cycle of neuroinflammation and neurodegeneration, characterized by dying neurons that activate microglia that, in turn, release factors killing additional neurons, suggests that the neuroinflammatory cascade might have a causal role in disease pathogenesis.

During the past decades, many epidemiological studies have increasingly pointed out the role of diet as one of the major modifiable determinants of Western diet-associated diseases, such as obesity, diabetes, cardiovascular disease, hypertension, stroke, and some types of cancer. Food, indeed, due to the

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coexistence of specific components, appears to have significant effects (both positive and negative) on well-being throughout life. Importantly, dietary adjustments and the so-called ''personalized nutrition'' may not only influence existing health but also determine whether or not an individual will eventually develop such diseases (167).

Some of the specific dietary components that increase or decrease the probability of occurrence of neurodegenerative diseases in any subject, and interventions to modify their impact, have been identified (1, 146, 193). Among them, bioactive lipids have been intensely studied, as modulators of redox state and inflammation in the CNS. Along with a structural function, indeed, lipids may also contribute to neuronal processes by influencing various signaling pathways directing neuronal survival or death. For instance, different lipids have been shown to act as both pro- and anti-apoptotic second messengers, to modulate innate and adaptive immunity, and to trigger or resolve inflammation (8, 38, 40).

Extensive studies have revealed that these bioactive lipids mainly act at the level of lipid rafts, which are privileged platforms for lipid–lipid and lipid–protein interactions at the plasma membrane. These dynamic membrane domains (enriched in certain neutral and acidic glycosphingolipids, sphingomyelin, and sterols) modulate signaling receptors and ion channels, thus regulating the cross-talk between the extracellular and intracellular milieu (102). Dysfunction of lipid rafts leads to abnormal neuronal and glial functions, so that it represents a pathogenic factor for several neurodegenerative diseases (8). The relevance of bioactive lipids in neurodegeneration is further supported by the finding that lipid changes occur in early stages of neuronal pathologies: In an experimental model of PD, for instance, 19 lipid species (from phosphatidylcholine and lysophosphotidylcholine lipid classes) were found to be downregulated, whereas lysophosphatidylcholine (16:0) and lysophosphatidylcholine (18:1), both important for neuroinflammatory signaling, appeared to be upregulated within the substantia nigra (61).

In this study, we provide an overview of the role in neuroinflammatory responses of some of the most widely studied dietary lipids. For the sake of clarity, we have chosen to focus on essential lipids with antioxidant and anti-inflammatory properties, which are polyunsaturated fatty acids (PUFAs) and lipophilic vitamins. After a brief description of the main hallmarks (misfolding, redox stress, and neuroinflammation) shared by the mentioned pathologies, the potential effects exerted by dietary lipids on microglia and astrocyte functions, referring to the most relevant *in vitro*, *in vivo*, and clinical studies, are discussed. Although not essential nutrients, phytosterols are also mentioned, as they represent the most powerful exogenous cholesterol-lowering agents in the CNS, for prevention or delay of most late-onset CNS diseases.

Hallmarks of Neurodegeneration

Even though each neurodegenerative disease has its own clinical features, common hallmarks can be identified (Fig. 1) (103, 127). First, all of them share the accumulation of abnormally folded, disease-specific proteins that damage and kill neurons. Protein misfolding occurs in PD, where α-synuclein (αSyn) forms proteinaceous cytoplasmic inclusions (named Lewy bodies), whose accumulation leads to death of dopaminergic neurons in the substantia nigra of the basal ganglia. Similarly, several ALS-associated proteins [superoxide dismutase 1 (SOD1), TAR DNA binding protein, or Fused-in-Sarcoma protein] are embodied in inclusions present in motor neurons, as a result of defects in protein degradation. Finally, in AD, abnormally folded β-amyloid (Aβ) peptide deposits outside neurons in formations known as senile plaques, and hyper-phosphorylated Tau protein aggregates in intracellular neurofibrillary tangles (103, 127).

Misfolded proteins are strictly linked to two other common features of neurodegenerative diseases, which are oxidative (nitrosative) stress and inflammation. Under normal conditions, reactive oxygen species (ROS) and reactive nitrogen species (RNS) regulate physiological functions of the CNS, including the process of learning and memory; however, when redox balance is impaired, oxidative (nitrosative) stress elicits neurotoxicity by altering redox-sensitive signaling cascades and triggering oxidation and misfolding of key proteins (103). Just as an example, ROS and RNS increase the phosphorylation of Tau and the activity of β-secretase, thus stimulating the amyloidogenic process; whereas in PD, oxidation and nitration of αSyn promote its oligomerization and, in the meanwhile, reduce the clearance of this aberrant protein by proteasome and autophagy (77, 103). The scenario is further worsened by the fact that misfolded proteins can lead, by themselves, to ROS and RNS accumulation. For instance, by activating different pathways and interacting with metal ions, Aβ stimulates the production of superoxide and hydrogen peroxide (11, 25, 103, 110). Interestingly, common hallmarks of neurodegenerative diseases have been found to target mitochondria, thus triggering mitochondrial dysfunction and subsequent ROS generation. This is of particular relevance if one keeps in mind that neurons, because of high oxygen consumption, can accumulate more ROS than any other cell and, therefore, are more sensitive to oxidant unbalance (103). Aging is another contributor to oxidative stress, and unsurprisingly neurodegenerative diseases occur in aged individuals: When getting older, loss of endogenous antioxidant defenses [including SOD, heme oxygenase-1 (HO-1), and γ-glutamyl cysteinyl synthetase] occurs, leading to increased free radical production (13). Weakened cellular antioxidant defenses, together with increased ROS and RNS generation, activate redox-sensitive transcription factors, including nuclear factor-κB (NF-κB) and activator protein-1, both of which upregulate the expression of many genes involved in neurodegeneration, including pro-inflammatory mediators.

Progressive deposition of misfolded proteins and oxidative (nitrosative) stress converge into a common signaling pathway, which leads to chronic activation of immune cells (77, 108, 161). In this context, microglia, CNS-resident immune cells, play a pivotal role (Fig. 2), as they are involved in the defense of the brain against pathogens and cellular debris, as well as in providing factors that support tissue maintenance and plasticity of neuronal circuits (20, 107). Once activated by pathological stimuli (*e.g.*, neuronal death or protein aggregation), microglial cells migrate to the site of injury and trigger pro-inflammatory responses that lead to damage and loss of neurons, through: (1) release within the brain of pro-inflammatory cytokines [interleukin (IL)-1β, IL-6, tumor necrosis factor alpha (TNFα), and interferon gamma (IFNγ)]; (2) recruitment of peripheral immune cells; (3) increase in free radicals and eicosanoids; (4) impairment of blood–brain barrier (BBB) permeability; and (5) leukocyte invasion (45,

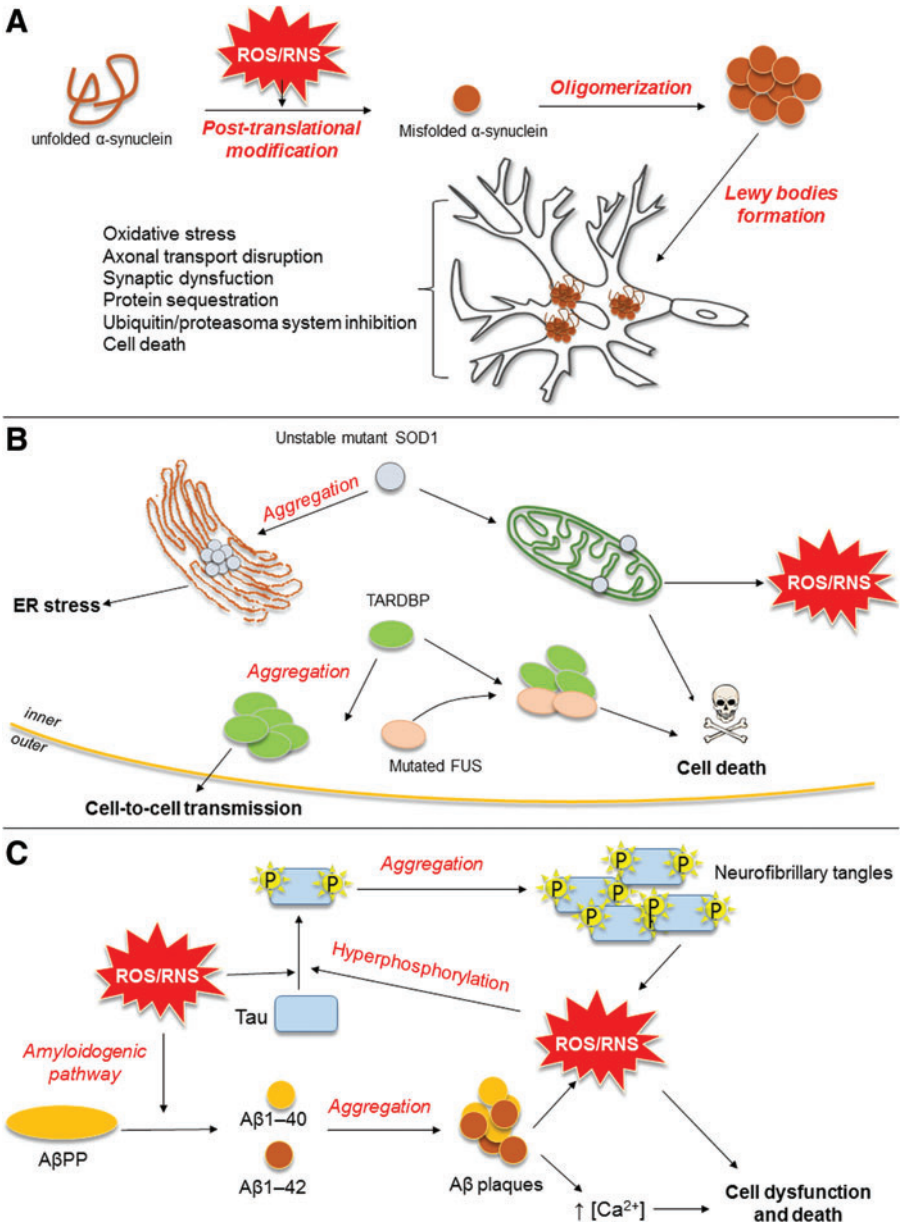

FIG. 1. Schematic representation of three common protein misfolding diseases. **(A)** Causal relationship between oxidative/nitrosative stress and misfolded αSyn in Parkinson's disease. Oxidative and nitrosative stress is mainly responsible for the misfolding process of αSyn. ROS and RSN, indeed, induce αSyn post-translational modifications that promote its oligomerization. αSyn oligomers, in turn, form cytoplasmic inclusions, termed Lewy bodies, whose accumulation leads to dysfunction and death of dopaminergic neurons in the substantia nigra of the basal ganglia. **(B)** Potential mechanisms triggered by mutated SOD1, TARDBP, and FUS proteins in amyotrophic lateral sclerosis. Unstable mutant SOD1 proteins form misfolded protein aggregates, which abnormally locate in ER (where they trigger ER stress), as well as in the mitochondrial outer membrane, where they cause mitochondrial dysfunction and activate apoptotic cascades. Cytosolic aggregation of mutated or dysregulated TARDBP (normally localized in the nucleus, where it modulates RNA metabolism) may have cell-to-cell transmitting ability. TARDBP can also form a toxic complex with FUS (another RNA processing protein), thus sequestering essential components for motoneuron survival. **(C)** Relationship among Aβ deposition, hyper-phosphorylated Tau aggregation, and neurotoxic mechanisms involved in the pathogenesis of Alzheimer's disease. Oxidative and nitrosative stress triggers accumulation of potentially neurotoxic Aβ peptide by activating the β-secretase-dependent amyloidogenic process of AβPP and secretion of Aβ1-40 and Aβ1-42. Aβ oligomers formed by toxic misfolded Aβ peptides and ROS production exacerbate oxidative stress and mitochondrial dysfunction, thus triggering Tau protein hyperphosphorylation and its aggregation into neurofibrillary tangles. All these events converge to dysfunction and death of neuronal cells. αSyn, α-synuclein; Aβ, β-amyloid; AβPP, amyloid β protein precursor; ER, endoplasmic reticulum; FUS, Fused-in-Sarcoma; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD1, superoxide dismutase 1; TARDBP, TAR DNA binding protein. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

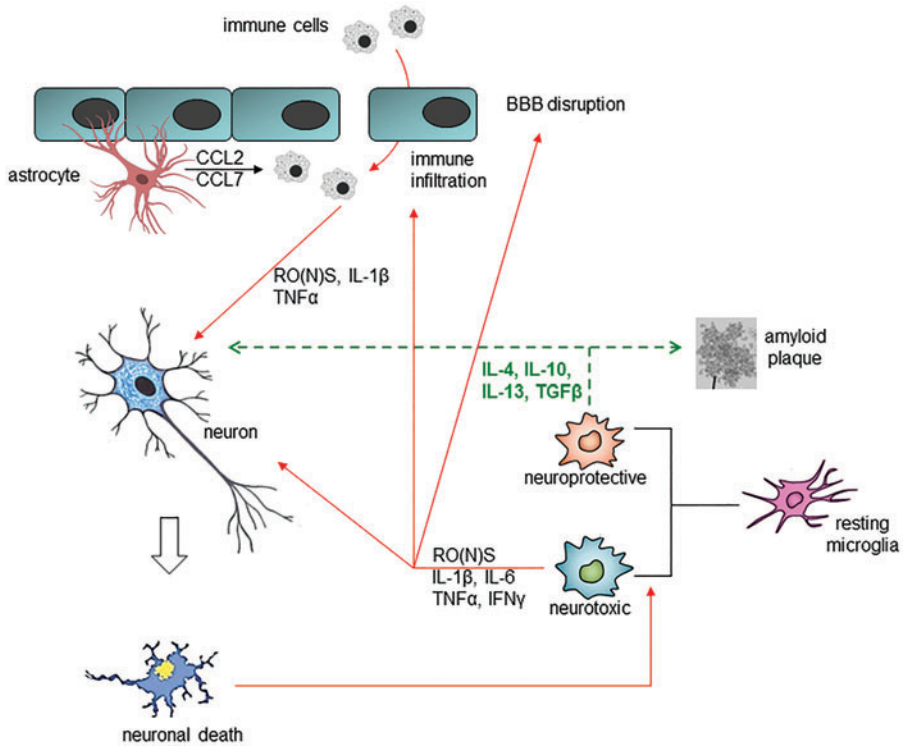

FIG. 2. Cross-talk between glial cells and neurons under physiological and pathological conditions. Neurotoxic pathways are depicted with *red lines*; neuroprotective pathways are depicted with *green dashed lines*. Misfolded proteins and oxidative (nitrosative) stress lead to chronic activation of microglia: once activated, microglial cells and astrocytes release pro-inflammatory cytokines and free radical species, triggering neuronal death, impairment of blood-brain barrier permeability and leukocyte invasion. Conversely, microglia might also acquire a neuroprotective phenotype, characterized by the ability of releasing anti-inflammatory cytokines and increased phagocytic capacity. BBB, blood–brain barrier; CCL, chemokine (C-C motif) ligand; IFN-γ, interferon gamma; IL, interleukin; TGFβ, transforming growth factor beta; TNFα, tumor necrosis factor alpha. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

121, 176). Besides this neurotoxic potential (M1 phenotype), microglia might also acquire a neuroprotective M2 phenotype, which is characterized by the ability of releasing anti-inflammatory cytokines [including IL-10, IL-4, IL-13, and transforming growth factor beta (TGFβ)] and increased phagocytic capacity, thus favoring angiogenesis, remodeling, and tissue repair (72). The balance between M1 and M2 phenotypes is finely tuned and sensitive to type and duration of stimulus, state of disease, involved brain regions, and interaction with other cells.

Astrocytes are also responsible for brain health, representing a source of different molecules that orchestrate a multitude of central events such as growth of axons, synaptogenesis, formation and maintenance of BBB, and neurotransmission (205, 211). In addition, astrocytes actively participate in inflammatory responses, due to: (1) the presence on their membrane surface of a wide range of receptors for pro-inflammatory cytokines (especially IL-1β and TNFα), chemokines, and damage signals [including toll-like receptor (TLR) ligands]; (2) the ability to release pro- and anti-inflammatory cytokines; and (3) the ability to produce ROS from the mitochondrial respiratory chain (60).

From the information already provided, it seems apparent that at least three factors (proteostasis, redox stress, and inflammation) contribute toward maintaining the brain in a constitutively reactive, unhealthy state. A vicious circle is, therefore, established whereby single contributors influence each other, exacerbating the pathological signs. This phenomen is evident during AD pathogenesis, where activated microglial cells are responsible for clearance of Aβ and Tau aggregates (216), but on the other hand the prolonged release of pro-inflammatory cytokines further induces Tau hyper-phosphorylation and neuronal loss, thus worsening the disease (209, 210).

It remains to be clarified as to what the impact of each factor is during the onset and progression of neurodegenerative diseases, and whether one is more prevalent than others during the different stages. Indeed, chronic treatment of humans with low levels of cyclooxygenase (COX) inhibitors (nonsteroidal anti-inflammatory drugs) has been shown to reduce the risk for AD (207), but clinical trials with celecoxib or naproxen failed to give positive results in AD patients (3, 4, 48). Further, although blockade of IL-12/IL-23 signaling attenuates amyloid burden and cognitive defects (208), anti-inflammatory strategies targeting IL-10 signaling have recently been shown to have negative effects on Aβ proteostasis, thus exacerbating AD-related pathology (33, 69).

Finally, it should be stressed that redox stressors are listed among factors that induce glial senescence. Oxidative stress and mitochondrial dysfunction trigger all markers of cellular senescence, such as over-expression of cell-cycle inhibitors and of the lysosomal enzyme β-galactosidase, loss of proliferation, formation of DNA damage foci, chromatin remodeling, and, more importantly in the case of glia, induction of a secretory pro-inflammatory phenotype (209).

Essential Dietary Bioactive Lipids

Epidemiological studies have shown that the Mediterranean diet may be useful for the prevention of cognitive decline and dementia in later life (179). The beneficial effects appear to be related to the presence, at least in part, of different bioactive lipids, including PUFAs and lipophilic vitamins. These belong to the class of ''essential nutrients,'' as they cannot be synthesized by mammals (including humans) and, therefore, must be supplied with diet.

Linoleic acid (LA; 18:2 $\Delta^{9,12}$) and α-linolenic acid (ALA; 18:3 $\Delta^{9,12,15}$) are the precursors of all members of the two non-convertible families, that is, ω6- and ω3-PUFAs. Both LA and ALA can be elongated and desaturated by human cells to more highly unsaturated members, mainly the ω6 arachidonic acid (AA; 20:4 $\Delta^{5,8,11,14}$), and the ω3 eicosapentaenoic acid (EPA; 20:5 $\Delta^{5,8,11,14,17}$) and docosahexaenoic acid (DHA; 22:6 $\Delta^{4,7,10,13,16,19}$) (Fig. 3, upper panel).

LA is found in the seeds of most vegetables, including corn, soybean, canola, sunflower, and safflower, whereas AA is present in most meats and products from animals fed corn-based diets that are high in ω6-PUFAs. Green leafy vegetables, such as purslane and spinach, and seeds of flax, linseed, walnuts, and others are the predominant sources of ALA, whereas fish is the main source of EPA and DHA (183). Once taken up by cells, PUFAs are incorporated into membrane phospholipids, from where they can be released by the action of phospholipase A_2 (PLA_2) enzymes, on specific stimuli; nonetheless, up to 90% of AA, DHA, and EPA are rapidly re-esterified to phospholipids, and only <10% act as cell mediators or are enzymatically converted into pro- or anti-inflammatory products (10). Indeed, through the action of distinct lipoxygenase (LOX) and COX isozymes (Fig. 3, lower panel), DHA and EPA may undergo oxidative metabolism, leading to generation of anti-inflammatory (ω3-derived eicosanoids) and pro-resolving mediators (resolvins, neuroprotectins, and maresins) (173); whereas oxidative metabolism of AA, except for generation of lipoxins (LXs), leads to production of pro-inflammatory mediators [leukotrienies and prostaglandins (PGs)] (154). Finally, it should be recalled that non-oxidative

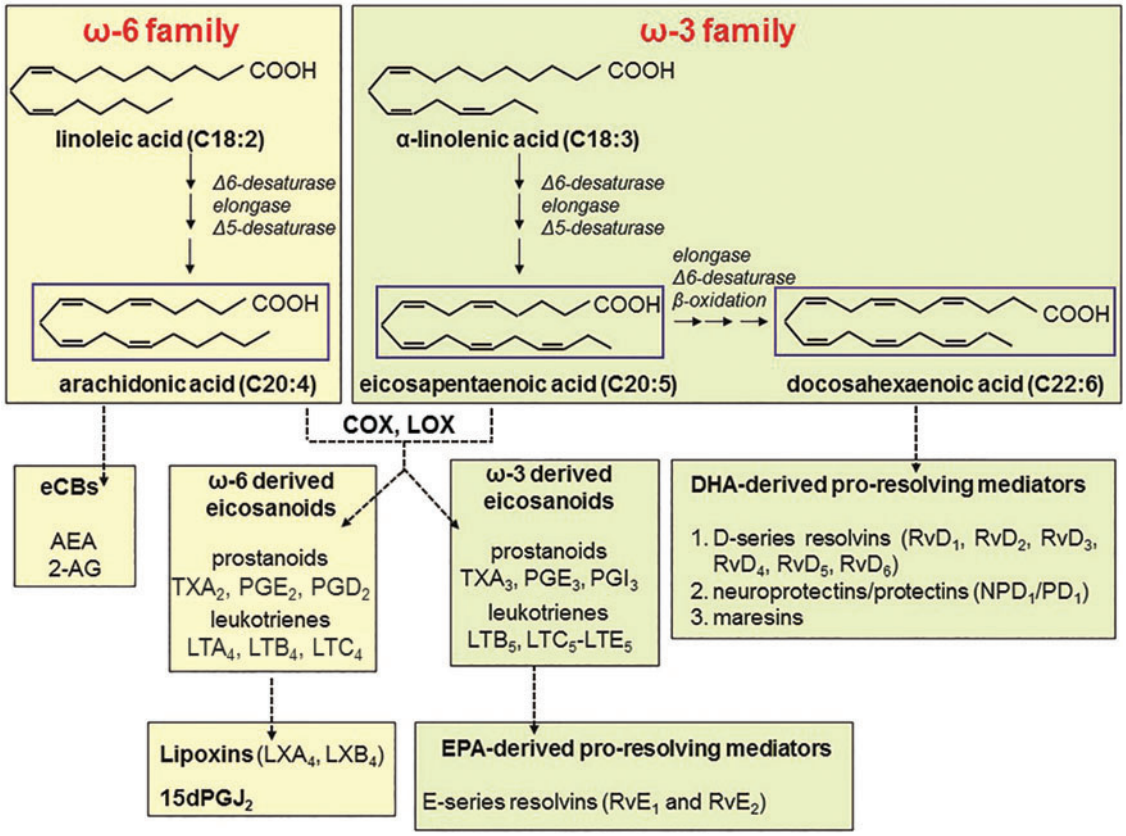

FIG. 3. PUFAs and their derivatives. *Upper panels*: ω3 and ω6 families. *Lower panels*: oxidative and non-oxidative derivatives of ω3 and ω6 series. After the action of LOX and COX enzymes, AA gives rise to pro-inflammatory leukotrienes (LTB_4 and LTC_4) and prostaglandins (PGE_2 and PGD_2), respectively. AA can also be responsible for originating anti-inflammatory and pro-resolving lipid mediators, including lipoxins LXA_4 and LXB_4 (derived from LTA_4 and LTB_4 by the sequential action of 5-LOX and 15-LOX, respectively), and 15-deoxy-prostaglandin J_2 ($15dPGJ_2$; formed from PGD_2 by the action of prostaglandin D_2 synthase). In addition to ω3-derived eicosanoids, EPA and DHA lead to the formation of anti-inflammatory, pro-resolving mediators. This class encompasses the E-series resolvins (RvE_1 and RvE_2) derived from EPA, and the D-series resolvins (RvD_1, RvD_2, RvD_3, RvD_4, RvD_5, RvD_6), the neuroprotectins/protectins (NPD_1/PD_1), and the maresins originated from DHA. 2-AG, 2-arachidonoylglycerol; AA, arachidonic acid; AEA, *N*-arachidonoyl-ethanolamine; COX, cyclooxygenase; DHA, docosahexaenoic acid; eCBs, endocannabinoids; EPA, eicosapentaenoic acid; LOX, lipoxygenase; LX, lipoxin; PUFA, polyunsaturated fatty acid; Rv, resolvin. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

metabolism of AA gives rise to another class of compounds, collectively known as endocannabinoids (eCBs), whose main representative members are *N*-arachidonoyl-ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) (111).

Among lipophilic vitamins, A and E are the most relevant for prevention of inflammation and neurodegeneration, due to their potent antioxidant activity. In this context, the action of vitamin A (be it retinal, retinol, and retinoic acid) is fundamental for immune system functionality, as its deficiency mainly correlates with defects in adaptive immunity (168). This vitamin is obtained from eggs, liver, bottled milk, or fortified cereals, as well as from foods enriched in retinyl esters, which represent ~75% of vitamin A. In addition, vegetables (such as tomato, carrot, or spinach) represent the most abundant source of carotenoids, which are vitamin A precursors. This group of pigments, widely distributed in nature, confers distinct colors to fruits and flowers, and it plays critical roles in plant growth and development (134). More than 700 carotenoids have been identified, and they are divided into two groups: carotenes, which are polyunsaturated hydrocarbons (*e.g.*, α- and β-carotene, lycopene), and xanthophylls, which are oxygenated forms of carotenoids (*e.g.*, lutein, β-cryptoxanthin, astaxanthin).

Vitamin E is the collective term for two natural groups of lipid-soluble bioactive compounds: saturated tocopherols and poly-unsaturated tocotrienols, which are also known as tocols. Corn, soybean, and olive oil are the primary dietary source of tocopherols, whereas rice bran, palm, and barley oils are particularly rich in tocotrienols; the latter substances are, however, much less prevalent than tocopherols (84). Vitamin E is recognized as the major chain-breaking antioxidant in the body, which is able to protect the integrity of membranes by inhibiting both lipid peroxidation (101) and low-density lipoprotein oxidation (195).

On a final note, phytosterols deserve to be mentioned, although they are not essential nutrients. Indeed, these compounds are often used as cholesterol-lowering agents in the CNS, which represents the most cholesterol-rich organ by weight, able to accumulate ~23% of total free cholesterol (56, 80). Phytosterols are a heterogeneous class of natural compounds, including plant sterols (β-sitosterol, stigmasterol, campesterol, fucosterol) and their saturated stanol derivatives (spinasterol, schottenol, sitostanol), whose biochemical structure resembles cholesterol in mammals (Fig. 4). These substances are abundantly present in vegetables, fruits, nuts, and cereals; a daily non-vegetarian diet contains ~250 mg of phytosterols, whereas a vegetarian diet contains more than 500 mg (188).

PUFAs in Neuroinflammation

As already described, PUFAs and their metabolic products play important roles in coordinating immunity and inflammation; their direct engagement in neuroinflammation is currently receiving a great deal of attention, especially in the light of evidence that the brain contains significantly high amounts of both ω6- and ω3-PUFAs. Igarashi *et al.* (80) found that, in the human brain, ω6- and ω3-PUFAs are 16.9% and 12.1% of total FA content, respectively, with AA representing 8.6% and DHA representing 11.5% of total FAs. EPA is maintained at a much lower brain concentration (0.4% of total FAs), most likely because of a very rapid breakdown by β-oxidation. Noticeably, the endogenous synthesis of AA, EPA, and DHA is low within the brain if compared with the uptake of unesterified FAs from the plasma pool (52, 53). In the brain, PUFA uptake is mainly mediated by fatty acid transport proteins 1 and 4 and fatty acid translocase/CD36, concomitantly with passive diffusion across the BBB (34, 156). The uptake does not appear to be selective, as the different PUFAs show a very similar chemical structure, and they accumulate to a similar extent. Once taken up, PUFAs are either committed toward β-oxidation or stored into brain membranes, where they compete for the incorporation of phospholipids at the same *sn*-2 position (34, 156). Altogether, these findings suggest that the brain maintains PUFA levels

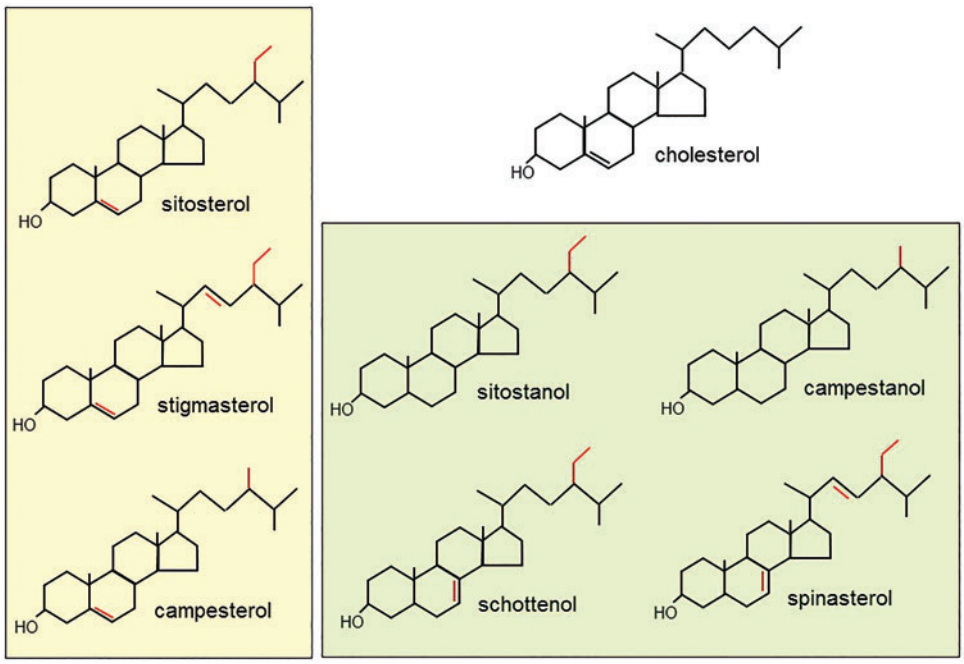

FIG. 4. Chemical structure of plant sterols and stanols. The structure of cholesterol is also shown for comparison. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

TABLE 1. RELEVANT *IN VITRO* STUDIES ON ω3-POLYUNSATURATED FATTY ACID EFFECTS IN NEUROINFLAMMATION-RELATED DISEASES

	Experimental protocol	*Main findings*	*References*
Neuroinflammation	Murine BV2 or rat primary microglia treated with 30 μ*M* DHA for 6 h	↑ HO-1 activity	Lu *et al.*(106)
	Murine primary microglia pre-treated with 20 μ*M* EPA or DHA for 24 h before 2.5 ng/mL LPS for 24 h	↓ M1 microglia activation ↑ M2 microglia activation	Chen *et al.*(35)
	Murine primary microglia pre-treated with 20 μ*M* EPA alone or combined with other nutrients for 24 h before 50 ng/mL LPS for 24 h	↑ IL-10	Kurtys *et al.*(97)
	Murine primary microglia pre-treated with 20 μ*M* DHA (6.67 μ*M* when combined with other nutrients) for 24 h before 50 ng/mL LPS for 24 h	↓ NO and IL-6	
	Murine BV2 microglia pre-treated with 10 n*M* RvD_1 or RvE_1 for 30 min before 1 μg/mL LPS for 6 and 24 h	↓ IL-1β, TNFα, IL-6	Rey *et al.*(157)
	Neonatal rat microglia pre-treated with RvD_2 for 1 h before 0.1 ng/mL LPS for 24 h	↓ IL-18, IL-6, NO, TNFα, IL-1β ↓ iNOS ↓ ROS levels	Tian *et al.*(194)
AD	Human CHME3 microglia treated with 1 μg/mL Aβ plus 0.1–1 μ*M* EPA or DHA up to 24 h	↓ M1 microglia activation ↑ Aβ phagocytosis	Hjorth *et al.*(74)
	Human CHME3 microglia treated with 1 μg/mL Aβ plus 0.1–1 μ*M* DHA up to 24 h	↑ M2 microglia activation	
	Human neuronal-glial cells treated with 5 μ*M* Aβ plus 50 n*M* NPD_1 for 48 h	↓ Apoptosis ↓ COX-2, B-94, TNFα	Zhao *et al.*(227)
	Human neuronal-glial cells overexpressing APP treated with 500 n*M* NPD_1	↓ β-secretase-1 ↑ α-secretase ADAM10	
MS	Primary murine immature dendritic cells pre-treated with 50 μ*M* DHA for 24 h before 0.1 μ*M* LPS for 24 h	↓ Dentritic cell maturation and cytokine production ↓ Dendritic cell-dependent $CD4^+$ T cell activation ↓ T cell differentiation into Th1/Th17 subsets	Kong *et al.*(96)
	Murine primary microglia pre-treated with 20 μ*M* EPA or DHA for 24 h before 5 ng/mL INFγ plus 1–10 μg/mL myelin for 24 h	↓ NO and TNFα	Chen *et al.*(35)
	Murine primary microglia pre-treated with 20 μ*M* EPA or DHA for 24 h before labeled myelin	↑ Myelin phagocytosis	
PD	Rat primary mesencephalic neurons pre-treated with 100 n*M* NPD_1 for 5 min before 100 n*M* rotenone, 100 μ*M* MPP^+, or 100 μ*M* MPTP up to 48 h	↑ Cell survival ↓ Dendrite retraction	Calandria *et al.*(29)
	Microglial cells from neonatal rats pre-treated with RvD_2 for 60 min before 100 ng/mL LPS for 24 h	↑ Neuronal survival in SNpc ↓ Glial cell activation	Tian *et al.*(194)

↓ decrease; ↑ increase; Aβ, β-amyloid; AD, Alzheimer's disease; APP, amyloid precursor protein; COX-2, cyclooxygenase-2; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HO-1, heme oxygenase-1; IL, interleukin; INFγ, interferon gamma; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MPP^+, 1-methyl-4-phenylpyridinium ion; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; NO, nitric oxide; NPD_1, neuroprotectin D_1; PD, Parkinson's disease; ROS, reactive oxygen species; Rv, resolvin; SNpc, substantia nigra pars compacta; TNFα, tumor necrosis factor alpha.

mainly *via* dietary uptake, and, therefore, PUFA content mainly depends on intrinsic and extrinsic factors, including ω3/ω6 PUFA ratio in food, PUFA bioavailability, and quality and quantity of different lipoproteins.

EPA, DHA, and their metabolites have emerged as major players in resolution of inflammation. This finding, together with the fact that DHA is the most abundant ω3-PUFA in the brain, calls for a better understanding of ω3-PUFA potential in preventing and/or counteracting CNS inflammatory states. Despite available data being often contradictory, it seems fair to state that both *in vitro* and *in vivo* findings appear to be rather promising (Table 1). In primary and immortalized microglial cells, both DHA and EPA have been shown to reduce the expression of inducible nitric oxide synthase (iNOS) [*via* upregulation of phosphoinositide 3 kinase (PI3K)/protein kinase B (Akt) signaling, and subsequent HO-1 activity], COX-2, IL-6, and TNFα, otherwise activated by different stimuli such as IFNγ, myelin, Aβ, and lipopolysaccharide (LPS) (35, 89, 106, 120). EPA and DHA counteract the cellular inflammatory state through different, yet complementary, mechanisms: DHA attenuates the pro-inflammatory response by inhibiting nitric oxide (NO) and IL-6, whereas EPA increases the anti-inflammatory response by enhancing IL-10 production (97).

Accumulating evidence attributes to resolvins and neuroprotectins the pro-resolution action of their ω3-PUFAs precursors, in both central and peripheral inflamed tissues. For instance, BV-2 cells express receptors for resolvin (Rv)D_1 and RvE_1 (*i.e.*, LXA_4 receptor/formyl peptide receptor 2 for RvD_1 and chemokine-like receptor 1 for RvE_1, respectively), as well as the enzymes responsible for their synthesis (*i.e.*, 5- and 15-LOX) (157). On LPS stimulation, the expression of receptors and enzymes in BV-2 cells increases, so that accumulation of RvD_1 and RvE_1 reduces the expression of the pro-inflammatory cytokines IL-1β, TNFα, and IL-6 (157). In a recent study, RvD_2 was found to reduce microglial inflammation *via* inhibition of LPS-triggered expression of NF-κB, TNFα, IL-1, IL-18, IL-6, IL-1β, and iNOS (194). In addition, in human neuronal-glial cells and in 3xTg-AD mice (a triple transgenic model of AD), neuroprotectin D_1 (NPD_1) downregulates Aβ42-triggered expression of COX-2 and of the TNFα-inducible pro-inflammatory element B-94. Moreover, it promotes the amyloid precursor protein (APP) non-amyloidogenic pathway, by downregulating β-secretase-1 and activating the α-secretase ADAM10 (227). Finally, NPD_1 preserves the integrity of the dendritic arbor and reverts the dendrite retraction induced in dopaminergic neurons by 1-methyl-4-phenylpyridinium ion (MPP^+), an inhibitor of mitochondrial complex I that is widely used to elicit a severe PD-like syndrome (29).

As a result of their anti-inflammatory action, ω3-PUFAs powerfully modulate the M1/M2 microglial balance. Both EPA and DHA decrease pro-inflammatory M1 markers CD40 and CD86, and they enhance Aβ phagocytosis by human

Table 2. Relevant *In Vivo* Studies on ω3-Polyunsaturated Fatty Acid Effects in Neuroinflammation-Related Diseases

	Experimental protocol	*Main findings*	*References*
AD	3xTg-AD mice	↓ Hippocampal NPD_1 and DHA	Zhao *et al.*(227)
	3xTg-AD mice fed with fish oil microcapsule containing DHA:EPA (4:1; 0.6% DHA w/w)	↑ Cell capacitance Improvement of cognition Prevention of dysfunction of entorhinal cortical neurons	Arsenault *et al.*(7)
	APP/PS1 rats fed for 4 months with safflower oil-based diet supplemented with DHA 0.6% (w/w) from algae	↓ Hippocampal Aβ plaque density ↑ Fibrillar Aβ oligomerization ↓ Prefibrillar Aβ oligomerization Improvements on behavioral testing	Teng *et al.*(192)
AD/aging	Aged rats fed for 4 weeks with EPA (125 mg/rat/die) before intracerebroventricular injection of 20 μM Aβ	↓ Long-term potentiation impairment ↓ Hippocampal IFNγ and IL-1β	Lynch *et al.*(109)
MS	Mice fed with DHA-enriched diet (0.22%, DHA w/w) for 5 weeks before EAE induction	↔ EAE onset ↓ EAE severity and mortality ↓ Th1/Th17 cells	Kong *et al.*(96)
	Mice fed with a regular diet containing 0.2% cuprizone plus 15 μg/kg DHA and EPA for 5 weeks	↑ Myelin phagocytosis ↓ M1 microglia activation ↑ M2 microglia activation Improvement of motor and cognitive functions	Chen *et al.*(35)
PD	Rats fed from 21 to 90 days of life with fish oil before injection of 4 μg 6-OHDA in medial forebrain bundle	↓ Lipid peroxidation ↑ Dopaminergic neuron turnover ↔ Motor deficits ↓ Dyskinesia	Delattre *et al.*(50)
	Maternal supplementation with 3.0 g/kg of fish oil (18% EPA +12% DHA) during pregnancy: (1) Rat offspring prenatally (at gestation day 11) exposed to 1 mg/kg LPS	↓ Dopaminergic neuron damage	Delattre *et al.*(49)
	(2) Stereotaxic re-exposure of rat offspring (at day 90) to 1 μg LPS	↔ Dopaminergic neuron apoptosis ↓ Glial cell activation Amelioration of learning and memory deficits	
	Rats pre-treated with 25–100 ng/kg RvD_2 for 3 days before and after LPS injection (30 days in total)	↓ Numbers of apo-morphine-induced rotational cycles	Tian *et al.*(194)
ALS	G93A-SOD1 mice	↓ DHA-phosphatidylcholine in spinal cord at terminal stage	Arima *et al.*(6)
	G93A-SOD1 mice fed with: (1) EPA-enriched diet (300 mg/kg/die) for 7 days at pre-symptomatic stage or	(1) ↑ Lipid peroxidation; ↑ Disease progression	Yip *et al.*(225)
	(2) EPA-enriched diet (300 mg/kg/die) for 7 days at disease onset	(2) ↑ Lipid peroxidation; ↔ Disease onset, progression, and survival	

↓ decrease; ↑ increase; ↔ no change; 6-OHDA, 6-hydroxydopamine; ALS, amyotrophic lateral sclerosis; EAE, experimental autoimmune encephalomyelitis; PS1, presenilin 1.

microglia. In particular, DHA also shows a stimulatory effect on the anti-inflammatory M2 marker CD206 (74). Moreover, RvD_1 has been found to enhance M2 polarization in BV-2 microglial cells, through a mechanism that is possibly related to activation of signal transducer and activator of transcription 6 (STAT6) and peroxisome proliferator-activated receptor (PPAR)γ signaling pathways (104). By the same mechanism (*i.e.*, a shift in microglial polarization toward the beneficial M2 phenotype), ω3-PUFAs enhance myelin phagocytosis and improve motor and cognitive functions in the cuprizone mouse model of MS (35).

As yet, *in vivo* data on the impact of ω3-PUFA supplementation on neurodegenerative diseases are still scant and often unclear (22), although they seem to speak in favor of a beneficial role in alleviating disease symptoms (Table 2). By employing 6-hydroxydopamine-treated rats, which develop a PD-like syndrome, Delattre *et al.* (50) reported that prolonged (from the post-weaning period until adulthood) ω3-PUFA ingestion efficiently reduced lipid peroxidation and dyskinesia; however, it did not ameliorate motor deficits, much likely through stimulation of dopaminergic turnover in the remaining terminals of the lesioned striatum. By using another experimental model of neurodegeneration, the same authors have recently reported that dopaminergic damage could also be reverted *via* maternal ω3-PUFA supplementation of prenatally LPS-exposed offspring; the positive effect was not linked to inhibition of apoptotic death in dopaminergic cells, but rather to maintainance of neurochemical integrity in remaining neurons, thus ameliorating learning and memory deficits (49). In 3xTg-AD mice, chronic supplementation with DHA-rich fish oil improves cognition and prevents dysfunction of entorhinal neurons in the cortex, one of the brain regions that develop early neurofibrillary tangles and Aβ plaques in AD patients (7). In another transgenic APP/presenilin 1 rat model of AD, DHA supplementation can modulate Aβ aggregation, as it reduces hippocampal Aβ plaque density by increasing the less toxic fibrillar Aβ oligomers and decreasing the more toxic prefibrillar Aβ oligomers (192). In aged rats, EPA treatment can attenuate the Aβ-induced impairment in long-term potentiation, by decreasing hippocampal concentrations of IFNγ, which are known to trigger microglial activation and amyloidogenic processing of APP (109, 223). In experimental autoimmune encephalomyelitis (EAE) mice, an animal model of MS, DHA improves clinical symptoms by acting on dendritic cell-dependent T-lymphocyte activation (96). In addition, in mice fed with cuprizone-enriched food, both DHA and EPA attenuate the copper chelator-mediated demyelination, *via* a series of anti-inflammatory responses, among which microglial phenotype switching is the most evident (35). Since M1 to M2 phenotype shift usually occurs at the beginning of remyelination (122), ω3-PUFAs may not only reduce demyelination but also favor the remyelination process in MS. Clearly, further studies are deemed necessary to investigate the therapeutic potential of these FAs for MS patients.

Detrimental rather than beneficial effects of dietary ω3-PUFAs on glial activation, and thus on disease progression and survival of G93A-SOD1 mice, a mouse model of ALS, have been reported (225). EPA-enriched diet does not affect either ALS onset and survival or the course of motor deficit, when administered at disease onset, whereas it accelerates disease progression if used at a pre-symptomatic stage. The main mechanism accounting for this negative action lies in lipid peroxidation that damages tissue vacuolization. Incidentally, the spinal cord of ALS patients shows reduced DHA levels (81), and G93A-SOD1 mice have low amounts of DHA-containing phosphatidylcholines in their spinal cords at terminal stages of the disease, but not in the pre-symptomatic or early stages (6).

Likewise, both positive and negative effects have been reported in human studies (Table 3). A cross-sectional population-based study among 1613 subjects, ranging from 45 to 70 years, documented that fatty fish consumption inversely correlated with the risk of impaired overall cognitive function (87). Consistently, a multi-center incident case–control study reported a significant decrease in first clinical diagnosis of CNS demyelination risk, in subjects with high ω3-PUFA intake, particularly from fish (75), and five large prospective cohort studies suggest that ALA and marine ω3-PUFAs intake reduces risk of developing ALS (64). A recent systematic review, summarizing data from population-based longitudinal observational studies, demonstrated that fish consumption significantly reduces cognitive decline rates and incidence of AD (139). Moreover, several epidemiological studies suggest that ω3-PUFA supplementation is also positively associated with clinical outcomes in MS patients (83). Finally, an interventional study that enrolled relapsing-remitting MS patients showed that chronic ω3-PUFA supplementation (12 months of fish oil) significantly reduced serum levels of TNFα, IL-1β, and IL-6 (155), without any effect on the glutathione redox system (182). Nonetheless, other studies have emphasized the positive effect of ω3-PUFA supplementation on cognitive decline in healthy, but not in diseased people. Indeed, a 24-week supplementation with 900 mg/die DHA improved age-related cognitive decline in 485 healthy adults, suggesting potential benefits of purified DHA to treat cognitive decline in the normal elderly (226). A 24-week ω3-PUFA supplementation ameliorated mild cognitive impairment (MCI), but it failed to improve cognitive performance in mild AD patients (36). Correspondingly, a randomized, double-blind, placebo-controlled trial showed that DHA supplementation (2 g/die for 18 months) did not slow the rate of cognitive and functional decline in individuals with mild-to-moderate AD (151). Finally, the OmegAD study reported beneficial effects in mild, but not in advanced AD patients after 6 months of ω3-PUFA treatment (65). Taken together, these findings suggest that high ω-3 PUFAs intake may be useful for preventing or delaying cognitive decline and/or dementia, but it seems uneffective in the late stages of neurodegeneration. A possible explanation can derive from the observation that, due to the presence of double bonds, DHA and EPA are the most susceptible PUFAs to free radical attack, so that they can generate neurotoxic reactive products (*e.g.*, *trans*-4-hydroxy-2-hexenal and F_4-neuroprostanes from DHA, and F_3-isoprostanes from EPA), whose levels are raised during neurodegenerative diseases (66, 126, 130, 169, 175). Therefore, if on the one hand ω3-PUFAs are beneficial for the diseased brain by counteracting neuroinflammation, on the other hand they might represent a harmful pro-oxidative stimulus that can exacerbate disease progression.

As for ω-3 PUFAs, AA (derived either from dietary intake or from endogenous synthesis from its LA precursor) represents the second most abundant PUFA after DHA (80), and it

Table 3. Relevant Human Studies on ω3-Polyunsaturated Fatty Acid Effects in Neuroinflammation-Related Diseases

	Experimental protocol	*Main findings*	*References*
Cognitive functions	1613 middle-aged subjects self-administered food-frequency questionnaire	Risk of impaired cognitive function inversely correlated with fish consumption	Kalmijn *et al.*(87)
AD	23 AD and 23 MCI patients orally receiving 1.8 mg/die ω3-PUFA for 24 weeks	↔ Cognitive performance in AD patients ↑ Cognitive performance in MCI patients	Chiu *et al.*(36)
	204 AD patients orally receiving 1.7 g/die DHA and 0.6 g/die EPA for 6 or 12 months	↔ Cognitive performance in advanced AD patients ↑ Beneficial effects in mild AD patients only after 6 months	Freund-Levi *et al.*(65)
	DHA supplementation (2 g/die) in 171 individuals with mild-to-moderate AD for 18 months	↔ Cognitive and functional decline in AD patients	Quinn *et al.*(151)
Age-related cognitive decline	485 healthy older adults with mild memory complaints orally receiving 900 mg/die DHA for 24 months	↑ DHA plasma levels Improvement of learning and memory function	Yurko-Mauro *et al.*(226)
MS	1493 relapsing-remitting MS patients self-administered food frequency questionnaire	Quality of life directly correlated with frequent consumption of fish and/or ω3-PUFA supplementation. Disease activity and disability inversely correlated	Jelinek *et al.*(83)
	50 relapsing-remitting MS patients orally receiving 4 g/die of fish oil (0.8 g EPA and 1.6 g DHA) for 12 months	↓ Serum levels of TNFα, IL-1 β, IL-6, ↓ NO metabolites	Ramirez-Ramirez *et al.*(155)
		↑ ω3-PUFA ↓ ω6-PUFA ↔ Glutathione reductase activity ↔ GSH/GSSG ratio	Sorto-Gomez *et al.*(182)
ALS	995 definite or probable patients (age 18–81 years) self-administered food frequency questionnaire about ω3-PUFA daily intake	ALS risk inversely correlated with ω3-PUFA intake	Fitzgerald *et al.*(64)

↓ decrease; ↑ increase; ↔ no change; GSH/GSSG, reduced GSH/oxidized GSH; MCI, mild cognitive impairment.

has been recognized as a risk factor for age-associated neurodegenerative diseases. Indeed, AA can be hydrolyzed from brain membrane phospholipids by specific PLA_2 isozymes, and then it can be converted into pro-inflammatory mediators by the action of selected COX or LOX isozymes, which produce PGs and thromboxanes or leukotrienes, respectively (10). In neurodegenerative diseases, increased activation of these enzymes usually occurs, leading to increased production of eicosanoids and activation of microglia and astrocytes. Consistently, the use of synthetic PLA_2 inhibitors, as well as of phytochemical-based inhibitors such as curcumin or *Ginkgo biloba* extracts, has been shown to be useful for the treatment of oxidative stress and neuroinflammation associated with cognitive impairment (137, 228).

Less clear is the therapeutical efficacy of blocking AA oxidative metabolism. As already mentioned, the beneficial effects of COX inhibitors observed *in vitro* have not been confirmed in human studies (3, 4, 48, 207). Nonetheless, dual inhibitors that are able to block the action of COXs and 5-LOX that are over-expressed in experimental MS animal models and human patients (92, 217) have recently been investigated. Such an inhibitor, flavocoxid, exerts protective effects by reducing pro-inflammatory cytokine release in MS and AD mice, as well as Aβ plaques, learning and memory loss in AD models (19, 95).

It should be recalled that AA can also generate, through an alternative 5-LOX pathway, protective compounds such as LXA_4, which acts as a ''stop signal'' of inflammatory processes (172). In Tg2576 transgenic AD mice, aspirin-triggered LXA_4 has been shown to reduce Aβ and phosphorylated Tau levels, as well as microglial and astrocyte reactivity, while promoting clearance of Aβ aggregates and enhancing cognitive performance (57, 117, 172). Also orally administered, mushroom-derived LXA_4 was able to upregulate LX levels in cortex and hippocampus, and to activate vitagenes (encoding for members of the heat shock protein family, HO-1, the thioredoxin/thioredoxin reductase system, and LXA_4 itself) involved in the cellular stress response triggered by proteotoxic stresses and accumulation of misfolded proteins (196, 197). The vitagene system, therefore, is emerging as an integrated system, cooperating with the proteostasis network to counteract aggregation of misfolded proteins and to promote cellular stress tolerance. These data, together with the finding that LXA_4 levels are reduced with age and in postmortem brain tissue and cerebrospinal fluid samples from AD patients, may suggest that activation of LXA_4 signaling and modulation of vitagene proteins are promising targets for novel cytoprotective interventions against oxidative stress-driven neuroinflammation and neurodegenerative diseases (28, 57, 117, 215, 196, 197).

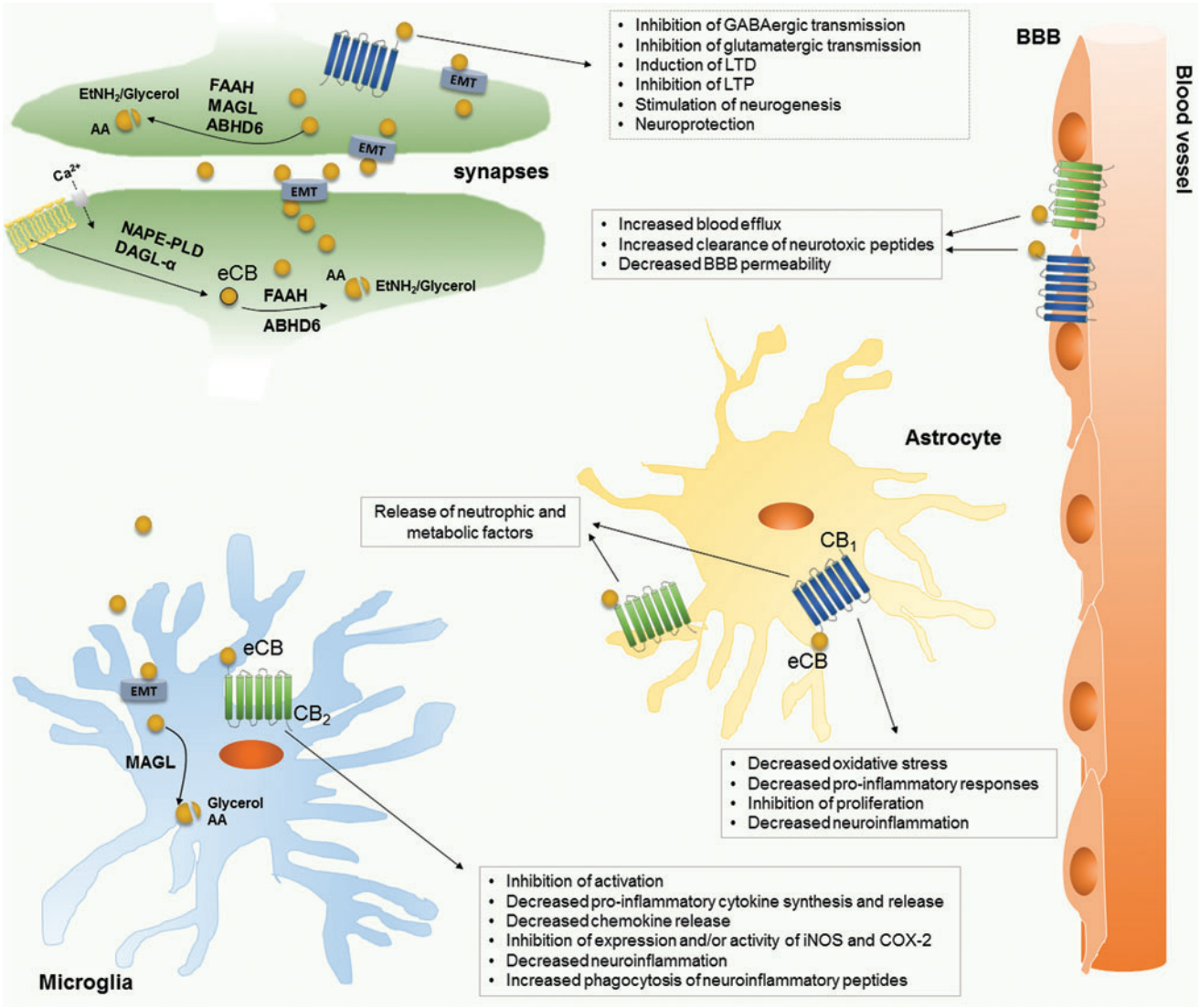

FIG. 5. Schematic representation of eCB actions in the CNS, in physiological conditions and during neuroinflammation. Anandamide (AEA) and 2-AG are produced on demand from AA-containing phospholipids, *via* multiple biosynthetic pathways requiring (among others) the catalytic activity of NAPE-PLD (especially present in presinaptical terminals) for AEA, and of the sn-1-specific DAGL-α (in dendritic spines of excitatory synapses) for 2-AG. In CNS, eCBs are post-sinaptically produced and exported through the EMT; once in the synaptic space, eCBs (mainly 2-AG) bind the CB_1 receptor to inhibit, in a retrograde manner, neurotransmitter release. The eCB biological action is stopped by hydrolysis catalyzed by either FAAH (for AEA) and MAGL (for 2-AG) or ABHD6 that selectively recognizes 2-AG. In microglia and astrocytes, eCBs activate CB_1 and CB_2 receptors, playing distinct and often ovarlapping effects; in neuroinflammatory conditions, they exert neuroprotective effects by inhibiting pro-inflammatory cytokine release and increasing the production of anti-inflammatory mediators. Also, the effect of eCBs on BBB is reported here, by highlighting their protective effect on BBB integrity and functionality. ABHD6, alpha/beta-hydrolase domain containing 6; CNS, central nervous system; DAGL-α, diacylglycerol lipase-α; EMT, endocannabinoid membrane transporter; $etNH_2$, ethanolamine; FAAH, fatty acid amide hydrolase; iNOS, inducible nitric oxide synthase; LTD, long-term depression; LTP, long-term potentiation; MAGL, monoacylglycerol lipase; NAPE-PLD, *N*-acyl-phosphatidylethanolamines-hydrolyzing phospholipase D. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

Finally, non-oxidative products of AA such as the eCBs AEA and 2-AG are emerging as new players in neurodegeneration (Fig. 5). eCBs, whose levels are regulated by the activity of metabolic enzymes, as well as by AA availability, bind to and functionally activate G protein-coupled type-1 and type-2 cannabinoid (CB_1 and CB_2) receptors (15). Within the CNS, eCBs reduce excitotoxicity and modulate adult neurogenesis and oligodendrocyte formation, through activation of CB_1 (111). Instead, by acting at CB_2, they regulate the reactivity of glial cells, stimulate cell migration, and inhibit release of pro-inflammatory cytokines (40, 62). Moreover, eCBs provide trophic and metabolic support to neurons, by astroglial CB_1/CB_2 activation, or limit oxidative stress and inflammatory responses through interactions with nuclear factor (erythroid-derived)-like 2 (Nrf-2), NF-κB, and PPARs (40, 62).

The time- and brain region-specific alterations of eCB signaling during neuroinflammation and neurodegeneration

have been investigated in detail (16, 38, 39, 79, 204). Changes in both AEA and 2-AG levels have been found in several disorders, together with negative or positive modulation of their biosynthetic and degradative enzymes. For example, in amyloidosis and AD animal models, eCB concentrations are modulated during disease progression, so that pharmacological or genetic regulation of metabolic (mainly degradative) enzymes can be viewed as a novel therapeutical target for reducing disease hallmarks (113, 200, 204). The protective role of eCB upregulation seems to be particularly relevant in MS (31, 218), with protective pathways ranging from downregulation of IL-23 and IL-12 release by microglial cells (42) to inhibition of cytokine production by myeloid, but not plasmacytoid, dendritic cells in MS patients (37). More recently, in monocytes obtained from both relapsing-remitting MS patients and healthy controls, AEA has been shown to suppress the viral TLR activation-mediated production of IL-12p40 and IL-6 (38).

From the data already summarized, it can be hypothesized that tissue concentrations, and biological activity thereof, of AA derivatives might be modulated by dietary AA content. Indeed, several studies have highlighted that FAs, and even more the ω3-/ω6-PUFA ratio, might be diet modulators of AA-derivative levels. Overall, it appears that PUFAs show immunomodulatory properties in the brain, with ω3-PUFAs being mainly anti-inflammatory and ω6-PUFAs being more prone to enhance inflammation. Depending on which PUFA is present in the diet, neuroinflammation will be reduced or enhanced, and subsequently, well-being in the elderly will be either improved or worsened. Both AA and DHA are incorporated into brain membranes and, therefore, their abundance may define which inflammatory mediator will be produced. Indeed, DHA competes with AA as a substrate of COXs and LOXs, so that the synthesis of inflammatory eicosanoids is counteracted by the production of anti-inflammatory metabolites (30, 98). In Western diet, the ω3/ω6 PUFA ratio is heavily biased (usually 1 to 10–20) toward ω6-PUFAs (177), so that the excess of ω6 precursors promotes the formation of AA that, in turn, increases the risk for chronic inflammatory diseases (98). In this context, ω3-enriched diets may be recommended to reduce neuroinflammation. For instance, a high intake of DHA or EPA has been shown to reduce AA concentrations in the brain, and especially in glial cells, thus exerting neuroprotective effects (98). These results were confirmed through genetic engineering, whereby mice genetically modified to produce high amounts of endogenous ω3-PUFAs were shown to respond to an immune challenge better than their wild-type counterparts, in terms of anti-inflammatory phenotype of microglia and cognitive performances (51).

On a final note, when considering personalized nutrition, it should be always kept in mind that several studies have demonstrated that ω3-PUFA intake, and especially that of DHA supplements, may improve cognitive development only during infancy, whereas it does not increase cognitive performance in children, adults, elderly, nor in AD subjects (85, 145). Therefore, any nutritional intervention should be planned at a very early point in anybody's life.

Vitamin A and Carotenoids

An intriguing aspect of the potential benefits of vitamin A and carotenoids in certain CNS illnesses has been underlined by several studies on the ability of these bioactive lipids to modulate oxidative stress and inflammatory reactions in astrocytes and microglia. In murine astrocyte primary cultures, retinoic acid efficaciously inibited the release of chemokines, including chemokine (C-C motif) ligand (CCL)2, CCL3, CCL5, and chemokine (C-X-C motif) ligand (CXCL)1 and CXCL2, which attract and activate monocytes and neutrophils across the BBB (201). In primary microglia cells, vitamin A, in combination with ω3-PUFAs and vitamin D, has been shown to inhibit LPS-induced release of inflammatory mediators (such as NO and IL-6); this convergence between different nutrients is encouraging for the design of a dietary intervention that is aimed at reducing neuroinflammation, for prophylactic or therapeutic purposes (97). Tomato-derived lycopene (a carotenoid without pro-vitamin A activity) has been proved to drive glial cells toward a neuroprotective M2 phenotype, by *in vitro* suppression of the expression of COX-2 and inflammatory mediators, *via* the adenosine monophosphate-activated protein kinase-α1/HO-1 pathways. This finding was confirmed *in vivo*, as lycopene administration mitigated microglial activation and motor coordination dysfunction caused by an intraperitoneal LPS injection (105). More recently, Wu *et al.* (220) have highlighted the neuroprotective effects of astaxanthin (naturally occurring in algae, crustaceans, shellfish, and various plants) also in neurons: By stimulating HO-1 expression, this xanthophyll has, indeed, been shown to protect neuronal cultures against Aβ- or MPP^+-induced cytotoxicity (212, 224).

The beneficial effects on AD and PD have been further supported by *in vivo* studies. In haloperidol-treated rats, a model of tardive dyskinesia, lycopene supplementation leads to a dose-dependent: (i) decrease of lipid peroxidation and nitrite levels; (ii) elevation of glutathione content; and (iii) attenuation of the oxidative stress-dependent release of neuroinflammatory mediators (such as TNFα, IL-1β, and IL-6) in the striatum; all these effects were accompanied by significant amelioration of motor activity (47). The latter study is in agreement with other reports documenting similar protective effects of lycopene (as well as of the other carotenoid lutein) on dopaminergic neurons against cytotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Indeed, by enhancing antioxidant defense and diminishing mitochondrial dysfunction and apoptotic death, these carotenoids improve behavioral deficits and motor abnormalities that are induced by the neurotoxin (133, 149, 178). Lycopene has also been suggested as an adjuvant in AD therapy, since *in vivo* studies demonstrated a dose-dependent improvement of Aβ-induced spatial learning and memory impairment, maybe linked to the ability of lycopene to downregulate the expression of pro-inflammatory cytokines (namely TNFα, TGFβ, and IL-1β), to prevent mitochondrial dysfunction and ROS generation, and to decrease the apoptotic rate (150, 163).

Finally, epidemiological, observational, and supplementation studies have underlined the ability of both vitamin A and carotenoids to cross the BBB and to counteract the oxidative-inflammatory state within the brain, thereby reducing the risk of neuropathology. A healthy human cohort study (10 men and 28 women, average age 53 ± 20 years) has revealed a correlation between plasma carotenoid levels and markers of inflammation and oxidative stress, as well as NAD^+ stores; in particular, an inverse, age- and sex-dependent correlation has been found between carotenoid concentrations and plasma and cerebrospinal fluid IL-6 levels

(68). A positive association has also been found between α and β carotenoid levels and plasma total antioxidant capacity, as well as between α carotenoids and cerebrospinal fluid TNFα levels (68). In the latter case, TNFα levels found in the cerebrospinal fluid were consistent with the finding that, when present below the physiological range, this multifunctional, pleiotropic cytokine exerts positive neuromodulatory effects, rather than acting as a pro-inflammatory and neurotoxic agent (142, 206). Therefore, it is conceivable that α carotenoids may exert a positive role against neuroinflammation by promoting the healthy neuromodulatory function of TNFα. Finally, the positive association between lycopene and central NAD^+ stores (68), together with the ability of carotenoids to quench ROS and restore poly(adenosine diphosphate-ribose) polymerase-1 activity (82), supports the hypothesis that these phytonutrients may be beneficial in reducing DNA damage.

Defects in retinoid metabolism may predispose to degeneration of motor neurons, thus leading to muscle weakness and atrophy, whereas activation of different retinoid receptors (RAR and RXR isoforms) has been proved to slow down loss of motor neurons at both pre-symptomatic and early symptomatic stages of the disease (41, 94, 159). It is not surprising, therefore, that vitamin A deficiency correlates with dysregulation of immune tolerance and pathogenic immune cell production in MS. Coherently, several observational studies documented vitamin A deficiency in MS patients, whereas high concentrations of plasma retinol correlate with outcome improvement in MS patients (158). In this context, the regulation of different T cell subsets and BBB function deserves mention. Retinoic acid modulates the balance between T helper (Th)1/Th2 and Th17/T regulatory (Treg) cells, as well as dendritic and B cell functions, thus re-establishing the balance between pathogenic and immunoprotective cells as well as increasing tolerance of autoimmunity (2, 158). In addition, retinoic acid can be listed among the astrocyte-derived factors halting MS lesion progression, as it is able to limit inflammatory damage and loss of BBB integrity (124). Several vitamin A supplementation studies further support the protective role of this vitamin in MS progression. A controlled, randomized clinical trial (enrolling 101 patients, aged 20–45 years) reported that 1-year retinyl palmitate supplementation significantly improved clinical progression and psychiatric signs (including fatigue and depression) of MS, although no changes were seen for number of relapses and brain lesions (17, 18). In a clinical trial of 36 relapsing-remitting MS patients who received 25,000 IU retinyl palmitate, over a 6-month period, vitamin supplementation was proven to upregulate TGFβ and Forkhead box P3 gene expression in peripheral blood cells, thus re-establishing Th17/Treg balance (162). More recently, another randomized, double-blind controlled trial, where 39 relapsing-remitting MS patients (aged 20–45 years) were supplemented with retinyl palmitate for 6 months, showed that treatment significantly reduced the expression of transcription factor T-box expressed in T cells, the key transcription factor committing $CD4^+$ T cells to the Th1 lineage (189) and, thus, inhibiting the expression of Th1-secreted IFNγ (125).

Vitamin E, Tocopherols, and Tocotrienols

Although all tocols are active vitamers, for a long time α-tocopherol has been recognized as the most important and active form of the vitamin, mostly due to its abundance (it is presently at a 1:1000 ratio in cell membrane lipids) and to mechanisms of transport and inactivation (23, 99). α-Tocopherol, indeed, has higher binding affinity for the α-tocopherol-binding protein (responsible for preferential retention of α-tocopherol and discrimination against other vitamers) and lower propensity to be metabolized by cytochrome P450 and β-oxidation pathways (84, 140, 181). Recent *in vitro* and *in vivo* studies, combined with epidemiological studies, have changed this concept, showing how the other vitamers may have biological properties that are distinct from α-tocopherol. Tocotrienols appear to be more powerful agents than tocopherols, by virtue of their cholesterol-lowering property and better antioxidant activities (129, 152, 153). Structural and dynamic studies have shown that tocotrienols are more mobile within biological membranes and are recycled by other antioxidants more efficiently than tocopherols, thereby more powerfully scavenging free radicals (187); a more efficient cellular uptake for tocotrienols with respect to tocopherols has also been reported, as is the case of astrocytes that intracellularly transport γ-tocotrienol more efficiently than α-tocopherol (171).

Several experimental and clinical studies highlight the central role of vitamin E in preserving neurological structure and function, under both physiological and pathological conditions: (i) α-tocotrienol and α-tocopherol protect primary neuronal cells against toxicity induced by glutamate (as well as by a number of other toxins) (138, 170); (ii) orally supplemented vitamin E isomers reach the cerebrospinal fluid and the brain (203), with tocotrienols being more bioavailable than tocopherols (their unsaturated hydrocarbon tails allow for better penetration into fatty tissues) (91); (iii) primary vitamin E deficiency is associated with certain neurological diseases (136, 198); (iv) γ-tocopherols reduce the concentration of nitrogen dioxide that is involved in several neurological diseases (86), as well as they reduce NO release by LPS-stimulated microglia (191); and (v) an inverse correlation between incidence of dementia/AD and plasma levels or dietary intake of all vitamers has been reported (21, 54, 112, 114, 128, 148, 160, 222).

Despite these findings, the role of vitamin E in neuroinflammation remains somewhat controversial and not well defined. Some *in vitro* and *in vivo* models of PD have shown that low concentrations of δ-tocotrienol protected neurons against MPTP-induced cytotoxicity, *via* a mechanism that was dependent on the estrogen receptor β-PI3K/Akt pathway (131, 132). Nonetheless, several authors reported negative outcomes, maybe linked to alternative pathways that are activated by vitamin E at supra-physiological doses (>400 IU/die). For example, Miyamoto *et al.* (123) reported that a very high dose of α-tocopherol activated microglia in spontaneously hypertensive rats, and it significantly increased the expression of glial fibrillary acidic protein, a hallmark of astroglial activation. Khanna *et al.* (90) showed that, in mice fed with α-tocopherol-enriched diet (used at the equivalent human dose of 1680 IU/die), α-tocopherol exacerbated microglial activation and oxidative stress, as well as the neuroinflammatory signaling observed after stroke-induced brain injury. Similarly, high concentrations of γ-tocotrienol, but not of α-tocopherol, were cytotoxic for primary astrocytes in culture (115). Accordingly, healthy human volunteers who received a dose of 596 IU/die of α-tocopherol for 4 weeks showed increased levels of lysophosphatidycholine (219),

representing both a general marker of inflammation (213) and a pro-inflammatory mediator that is able to trigger processing and secretion of mature IL-1β in activated brain microglia (185). Finally, several randomized, double-blind controlled clinical trials provided strong evidence that vitamin E does not slow the progression of cognitive deterioration in aging people. In particular, vitamin E supplementation (1000 IU twice daily) for 3 years does not improve cognition or function in Down Syndrome patients older than 50 years of age (166), nor does it delay clinical progression to AD in 769 subjects with amnestic MCI (143).

Discrepancy among different studies and lack of definitive conclusions can be explained by considering that vitamin E is a general antioxidant, whose molecular mechanisms are not yet fully elucidated. In addition, vitamin E seems to have a hormetic profile, showing a typical inverted U-shaped dose–response curve, characterized by a low-dose protective effect and a high-dose harmful effect (27). Hormesis is an endogenous protective mechanism accounting for adaptability and plasticity of biological systems; the typical biphasic dose–response curve displayed by hormetic compounds may explain the limits experienced with numerous nutritional (including vitamin E supplementation studies) and pharmacological interventions (27). Finally, most of the studies underlining the vitamin E-dependent modulation of microglia neuroinflammatory cascades employed stabilized rice bran extract (RBE) as a vitamin E-enriched food (14, 70, 71, 180). It should, however, be recalled that, in addition to tocols, RBE contains other antioxidant compounds, including carotenoids, γ-oryzanol (a mixture of ferulic acid esters, triterpene alcohols, and phytosterols), and polyphenols (180); therefore, it is conceivable that the potential value of RBE as a nutraceutical for prevention of neuroinflammatory diseases may result from the synergistic interaction of multiple bioactive agents, rather than from the exclusive action of vitamin E.

Phytosterols

In the CNS, cholesterol mainly localizes in myelin sheaths surrounding the axons ($\sim$70% of total cholesterol) and only a minority (the remaining 30%) resides within the plasma membrane of neurons and glial cells (55, 184); by modulating membrane fluidity and functionality, cholesterol plays a crucial role in cell-to-cell cross-talk, intracellular signaling, and synapse formation (144). The finding that impairment in cholesterol homeostasis is involved in neuroinflammatory disorders, together with the ability of plant sterols to cross the BBB, has powered research on the role of phytosterols in healthy and diseased CNS.

Sterols with a lower molecular side-chain complexity (*e.g.*, campesterol) can easily cross the endothelial barrier and, then, are incorporated within lipid rafts of CNS parenchymal cells (202). By lowering the cholesterol content in lipid rafts, plant sterols (i) counteract oxidative stress (*via* estrogen receptor, PI3K, and glycogen synthase kinase-3β), by stimulating the expression of antioxidant molecules, such as glutathione transferase, glutathione peroxidase, and glutamyl cysteine ligase (174); (ii) prevent the proteolytic processing of APP, by inhibiting β- and γ-secretases, by decreasing β-site amyloid precursor protein cleaving enzyme 1 internalization to endosomal compartments, and by promoting migration of APP toward non-raft regions (24, 214).

The therapeutic potential during disease-related cognitive impairment can also be ascribed to the anti-inflammatory action, as reported in MS animal models, where plant sterol (60% sitosterol, 25% campesterol, and 15% stigmasterol) intake upregulates the expression of anti-inflammatory IL-10 and inhibits the expression of pro-inflammatory factors (CCL2, TNFα, IL-6, and IFNγ) (199). Phytosterols (including sitosterol, stigmasterol, schottenol, and fucosterol) inhibit inflammatory pathways in CNS infiltrating and resident immune cells, by activating liver X receptors (LXRs) that suppress inflammatory responses and, moreover, promote (together with activation of RXRγ) CNS repair processes and remyelination (59, 78, 100, 147). Impairment of LXR signaling has been shown to lead to progressive degeneration of motor neurons: At 7 months of age, LXRβ knock-out mice develop severe motor impairment closely resembling ALS (5). The strict link among LXR signaling, phytosterol/cholesterol metabolism, and neuroinflammatory diseases is also underlined by the finding that frequency of sporadic ALS seems to be higher among statin users with respect to nonusers (58). Likely, statins impair LXR signaling, which, in turn, regulates the Niemann-Pick C1-like 1 protein (responsible for both cholesterol and phytosterol intestinal absorption) and adenosine triphosphate-binding cassette type 5 and 8 (responsible for efflux of cholesterol and phytosterols from enterocytes to the gut lumen), in an opposite manner (12). Therefore, LXR-dependent perturbations of cholesterol/phytosterol metabolism in the CNS will occur, and this might explain the increased risk of ALS observed in statin-treated patients (44, 119). Based on these data, a phytosterol-mediated activation of LXRs might be an interesting therapeutic tool for neurodegenerative and neuroinflammatory diseases, as natural sterols do not elicit the severe side-effects (*i.e.*, hepatic hypertriglyceridemia and liver steatosis) that are usually observed with synthetic LXR agonists (67). However, more research is needed since the transfer of different plant sterols to the CNS is limited.

It should be recalled, however, that some phytosterols (in particular, β-sitosterol) may shift the balance between neuroprotective and neurotoxic effects, after structural modifications. For example, β-sitosterol protects neurons and glial cells from oxidative stress and lipid peroxidation (174), but its oxidative or glycosylated derivatives are neurotoxic, *via* glutamate excitotoxicity, ROS generation, and cell death (118, 141, 190). In particular, glycosylation hampers the binding and activation of LXRs, thereby masking the neuroprotective effect of phytosterols. In line with this hypothesis, administration of β-sitosterol worsened the ALS-like phenotype in LXR$\beta^{-/-}$ mice (93) and excessive dietary intake of β-sitosterol-β-D-glucoside present in cycad seeds (*Cycas circinalis*) was implicated as the cause of ALS/parkinsonism-dementia complex observed in specific geographic areas (116, 190).

Conclusions

A wealth of literature data highlight the crucial role played by essential lipids in maintaining brain health, as they modulate both neuronal plasticity and immune activity of glial cells, so that dysfunction in lipid metabolism contributes to the onset and progression of neurodegenerative diseases that are characterized by neuroinflammatory pathways (Fig. 6). For

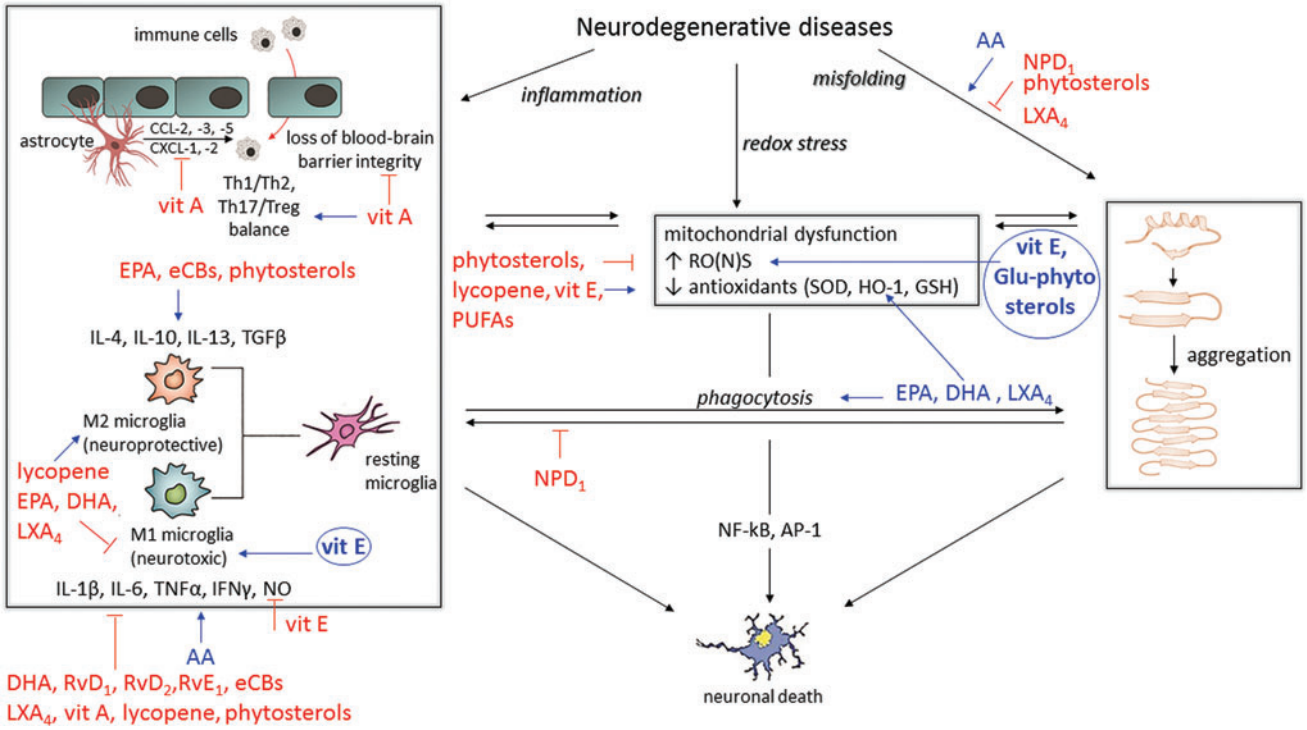

FIG. 6. Main effects of dietary bioactive lipids on hallmarks of neurodegeneration. The three major culprits of neurodegenerative diseases (inflammation, redox stress, and protein misfolding) are depicted in *black boxes*. Stimulating effects of different lipids are shown in *blue*; inhibitory effects of different lipids are shown in *red*. *Circles* represent potential harmful effects that are derived from either elevated concentrations or chemical modifications. AP-1, activator protein-1; CXCL, chemokine (C-X-C motif) ligand; Glu-phytosterols, glycosylated phytosterols; GSH, glutathione; HO-1, heme oxygenase-1; NF-κB, nuclear factor-κB; vit, vitamin. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

example, epidemiological data indicate a higher risk of cognitive decline in people who have lower intake or blood levels of ω3-PUFAs (46), and an inverse association between plasma EPA and lower gray matter atrophy and slower cognitive decline has been reported in aged people (164, 165).

Based on these findings, different studies have suggested that a nutritional approach might be useful to prevent and/or treat such pathologies. Nonetheless, available data are somewhat controversial and far from being conclusive. Regarding ω3-PUFAs (which are the best investigated), traditionally there has been a lack of discrimination between different compounds, so that effects have been broadly attributed to this group of molecules as a whole. This is the case for the majority of clinical trials enrolling healthy older adults, individuals with MCI or AD: In these trials, mixed EPA and DHA preparations and at different ratios have usually been used (85). Though this approach does not allow one to discriminate among different compounds, one has to take into account that dietetic sources contain a mix of all PUFAs; therefore, to formulate a nutritional approach for preventing/curing neuroinflammatory diseases, it may not be central to understand what is doing what, also because a synergistic action between the different compounds may actually do the job. In addition, many questions about the ideal ω3/ω6-PUFA ratio remain to be addressed before drawing conclusions: What is the real link between AA and DHA? May bioavailability of different FAs account for selective incorporation into brain phospholipids? As they show somewhat overlapping effects, may an increase of dietary DHA limit the AA-induced neurodegenerative effects? Answering these questions is deemed necessary to fully understand the involvement of ω3/ω6-PUFAs in the onset and progression of neurodegeneration.

In addition, some useful effects of antioxidant vitamins and phytosterols need to be better clarified, before translating *in vivo* data to clinical practice. In the first case, the positive activation of the RXR receptor has led to a consideration of its synthetic agonist bexarotene, already approved by the U.S. Food and Drug Administration for cancer treatment, as a candidate for AD clinical trials. Although bexarotene possesses documented beneficial effects in AD animal models (where it facilitates intracellular Aβ clearance, reduces neuron loss, upregulates markers of synaptic integrity, and improves cognition), multiple failures have been reported, particularly in the context of apolipoprotein E genotype representing one of the most potent risk factors for AD (9, 43, 135). These negative data highlight, once again, the complexity of molecular mechanisms underlying neurodegenerative diseases, so that the synergistic action of dietary antioxidant vitamins should be more effective than direct activation of a single target with a synthetic drug. With respect to plant sterols, another caveat should be kept in mind, that is, detailed knowledge of its chemical structure and

dynamic properties before planning to exploit it as a potential therapeutic.

Although there is no doubt that a nutritional strategy would be advisable to ameliorate the quality of life of patients, other factors are involved in the pathogenesis of neuroinflammatory diseases. The overall picture is, therefore, more complex than expected, and nutritional intervention should simply accompany pharmacological therapies, to obtain beneficial effects in diseased people.

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Abbreviations Used

αSyn = α-synuclein
2-AG = 2-arachidonoylglycerol
6-OHDA = 6-hydroxydopamine
AA = arachidonic acid
Aβ = β-amyloid
AβPP = amyloid β protein precursor
ABHD6 = alpha/beta-hydrolase domain containing 6
AD = Alzheimer's disease
AEA = *N*-arachidonoyl-ethanolamine
Akt = protein kinase B
ALA = α-linolenic acid
ALS = amyotrophic lateral sclerosis
AP-1 = activator protein-1
APP = amyloid precursor protein
BBB = blood–brain barrier
CB = cannabinoid
CCL = chemokine (C-C motif) ligand
CNS = central nervous system
COX = cyclooxygenase
CXCL = chemokine (C-X-C motif) ligand
DAGL-α = diacylglycerol lipase-α
DHA = docosahexaenoic acid
EAE = autoimmune encephalomyelitis
eCBs = endocannabinoids
EMT = endocannabinoid membrane transporter
EPA = eicosapentaenoic acid
ER = endoplasmic reticulum
$etNH_2$ = ethanolamine
FAAH = fatty acid amide hydrolase
FUS = Fused-in-Sarcoma
GSH/GSSG = reduced GSH/oxidized GSH
HO-1 = heme oxygenase-1
IFN-γ = interferon gamma
IL = interleukin
iNOS = inducible nitric oxide synthase
LA = linoleic acid
LOX = lipoxygenase
LPS = lipopolysaccharide
LTD = long-term depression
LTP = long-term potentiation
LX = lipoxin
LXR = liver X receptor
MAGL = monoacylglycerol lipase
MCI = mild cognitive impairment
MPP^+ = 1-methyl-4-phenylpyridinium ion
MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MS = multiple sclerosis
NAPE-PLD = *N*-acyl-phosphatidylethanolamines-hydrolyzing phospholipase D
NF-κB = nuclear factor-κB
NO = nitric oxide
NPD_1 = neuroprotectin D_1
PD = Parkinson's disease
PG = prostaglandin
PI3K = phosphoinositide 3 kinase
PLA_2 = phospholipase A_2
PPAR = peroxisome proliferator-activated receptor
PS1 = presenilin 1
PUFA = polyunsaturated fatty acid
RBE = rice bran extract
RNS = reactive nitrogen species
ROS = reactive oxygen species
RXR = retinoid X receptor
SNpc = substantia nigra pars compacta
SOD1 = superoxide dismutase 1
TARDBP = TAR DNA binding protein
TGFβ = transforming growth factor beta
Th = T helper
TLR = toll-like receptor
TNFα = tumor necrosis factor alpha
Treg = T regulatory