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Review

Lipid peroxidation in neurodegeneration

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ABSTRACT

Neurodegenerative diseases have great social and economic impact and cause millions of deaths every year. The potential molecular mechanisms in these pathologies have been widely studied and implicate lipid peroxidation as an important factor in the development of neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases. Data indicates that pathologic mechanisms specifically involve ferroptosis and mitochondrial dysfunction. Here we review the molecular mechanisms related to the lipid peroxidation that involve the development of neurodegeneration, as well as the utility of some biomarkers in diagnosis, prognosis and evaluation of new therapies for neurodegenerative diseases.

1. Introduction

1.1. Neurodegeneration development

The loss of neuronal function and/or structure leading to cell death is a common characteristic in neurodegenerative diseases [1]. Although neurodegenerative diseases (amyotrophic lateral sclerosis, Parkinson's, Alzheimer's and Huntington's disease) are incurable, they show similarities at a molecular level [2,3]. It is clear, however, that further research is warranted to comprehensively identify and describe the main stages in molecular neurodegeneration.

Alzheimer Disease (AD) and other dementias are the fifth leading cause of death worldwide being even more prevalent in developed countries [4]. In general, the number of deaths associated with neurodegenerative diseases, as well as other diseases that could involve neurodegenerative processes (e.g. diabetes mellitus) have drastically increased, [5]. In addition, it is important to highlight that these disabling conditions pose a great economic and social burden affecting patients' and families' quality of life for years [6,7]. The causes originating the neurodegeneration processes are not yet clear, but some risk factors are widely accepted, such as ageing [8] and genetics [9,10]. Apart from physiological neurodegeneration that occurs spontaneously, there are external factors that produce neuronal loss, such as nutrition [11], environment pollution [12], hazardous wastes in water or aliments (e.g. pesticides) [13], and alcohol consumption [14]. Alcohol abuse generates neurodegeneration through increasing lipid peroxidation products and producing cAMP response element-binding brain derived neurotrophic factor (CREB-BDNF) [15]. In this sense, curcumin has been tested as a treatment against alcohol-induced neurodegeneration [15].

The most studied molecular pathways involved in neurodegeneration are inflammation [16], oxidative stress [17], lipid peroxidation [18,19,20] and DNA damage [21].

In this review, we focus on the important role of lipid peroxidation in the pathogenesis of neurodegeneration. Brain has a high lipid content and high oxygen consumption [22], both factors leading to accumulation of lipid peroxidation byproducts in brain and peripheral systems.

1.2. Oxidative stress

Oxidative stress is described as an imbalance between oxidant and antioxidant species in favour of oxidants [23]. It may be generated as a

Abbreviations: A-Syn, Alpha-synuclein; AD, Alzheimer Disease; Akt/GSK3, Protein kinase B/Glycogen synthase kinase 3; ALS, Amyotrophic Lateral Sclerosis; aMCI, Amnestic mild cognitive impairment; APP, Amyloid precursor protein; BDNF, Brain derived neurotrophic factor; CREB-BDNF, cAMP response element-binding-brain derived neurotrophic factor; GFAP, Glial fibrillary acidic protein; GLP-1, Glucagon-like peptide 1; GPX4, Glutathione peroxidase 4 ; HD, Huntington Disease; HNE, Hydroxynonenal; ICAM, Intercellular Adhesion Molecule; iNOS, Inducible nitric oxide synthase; iPSC, Induced pluripotent stem cells; JDP2, Jun Dimerization Protein 2; MafK, MAF BZIP Transcription Factor K; MDA, Malondialdehyde; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NF-Kb, Nuclear factor kappa B; 6-OHDA, 6-hydroxydopamine; PANK2, Pantothenate kinase 2; PD, Parkinson Disease; PUAFs, Polyunsaturated fatty acids; RNS, Reactive Nitrogen Species; ROS, Reactive Oxygen species; α-Syn, α-Synuclein; TBARS, Thiobarbituric Acid Reactive Substances; TDP-43, Transactive response to DNA-binding Protein 43; TNF-α, Tumour Necrosis Factor

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consequence of antioxidant molecules decrease or inactivation, an increase of reactive oxygen species (ROS) and other oxidant molecules, as well as an increase of endogenous metabolites capable of autoxidation [24]. Among oxidant species, ROS and Reactive Nitrogen Species (RNS) (e.g. superoxide anion, hydrogen peroxide, hydroxyl radical, nitric oxide) are produced predominantly in the mitochondria from molecular oxygen and nitrogen [25]. Other sources of ROS are the endoplasmic reticulum, and nuclear or plasmatic membranes, as well as, oxidases enzymes (xanthine oxidase, NADPH) [24]. Glutathione (GSH) is the most abundant non-enzymatic antioxidant in the human body, being able to avoid damage caused by ROS to important cellular components. In general, oxidative stress is involved in most of chronic diseases, such as cancer [26], respiratory diseases [27], and also in neurodegeneration [28]. Therefore, oxidative stress mechanisms have been largely studied to clarify the pathogenesis of neurodegeneration.

Oxidative stress causes oxidation of biomolecules such as proteins, DNA, or lipids. The latter are extremely relevant because lipid peroxidation generates cellular damage and new oxidizing molecules [29], altering membrane lipids and circulating lipids, and also cellular functions [30]. The lipid peroxidation process consists of a 3-phase chain reaction (initiation, propagation, termination) [31], in which the generated radicals alter the membranes structure and function, as well as receptors.

Previous studies have shown that lipid peroxidation is involved in the development of neurodegeneration [22]. However, there is a lack of studies evaluating the specific molecular mechanisms related to lipid peroxidation. Therefore, we have included in the present review studies that reported on the molecular implications of lipid peroxidation in the development of neurodegenerative diseases.

2. Lipid peroxidation mechanisms implied in neurodegeneration development

Scheme 1 summarizes the assessment of lipid peroxidation in neurodegeneration from different points of view (experimental models, treatments, diagnosis, mechanisms). In fact, some experimental studies in literature consisted in the assessment of lipid peroxidation products to evaluate treatment efficacy [32–35]. Specifically, toxins, such as arbin, generate neurodegeneration, by means of lipid peroxidation or acetylcholinesterase enzyme inhibition [36]; methylmercury generates a loss of neurons and astrocytes, as well as an increase of lipid peroxidation levels, and a reduction of antioxidant capacity [37]; and acrylamide generates neurodegeneration that could be reduced using farnesol, an organic compound present in numerous plant essential oils, which reduces gliosis and lipid peroxidation by means of a down-regulation of glial fibrillary acidic protein (GFAP), and ionization of calcium-binding adapter molecule-1 [38]. Hypoxia has also been related to the pathogenesis of neurodegeneration. In this sense, dihydromyricetin, a flavonoid with antioxidant activity, showed an improvement in neurodegenerative damage produced by hypoxic altitude, specially by reducing lipid peroxidation [39]. In addition, retina neurodegeneration models showed an increase in lipid peroxidation that was accompanied by neuron loss [40]. In retinal degeneration, overexpression of cytochrome *b*5 protected against lipid peroxidation and light-induced oxidative damage, constituting a promising therapeutic target [41].

Among the mechanisms implied in neurodegeneration processes, it has been shown that high enzymatic activities of acetylcholinesterase and butylcholinesterase lead to increased lipid peroxidation [42]. Also, p75 neurotrophin receptor is involved in neurodegeneration mediating hydroxyl-nonenal (HNE) induced neuronal loss [43]. In addition, 6-hydroxydopamine (6-OHDA) hemi-lesioned rat model generated by Falcone et al., showed an increase of 4-HNE two weeks after the induction of the lesion [44]. This lipid peroxidation product that showed activity in the regulation of proteins from autophagy and mitochondrial pathways [45], could be targeting the proteasome [46]. Moreover, 4-HNE could trigger α-Syn aggregation that is commonly associated to some neurodegenerative diseases, as well as increasing the secretion of extracellular vesicles containing α-Syn [47]. Therefore, it is not clear if lipid peroxidation products are the consequence or the cause of neurodegenerative processes [48].

2.1. Mitochondrial dysfunction in neurodegeneration

Among the molecular mechanisms involved in the development of neurodegeneration, mitochondrial dysfunction is highlighted, since it could trigger lipid peroxidation processes and promote altered protein accumulations. In fact, aggregation of different proteins is involved in the most prevalent neurodegenerative diseases [49]. In addition, this dysfunction could lead to an imbalance of energetic status, increasing free radicals' production and promoting lipid peroxidation.

Mitochondrial dysfunction associated with neurodegeneration has been largely studied in cell cultures and different animal models. In fact, iPSC (induced pluripotent stem cells) -derived neuronal cell models showed that this dysfunction could lead to the accumulation of lipid peroxidation products, and subsequent neurodegeneration [50]. It could be explained by a reduction in pantothenate kinase 2 (PANK2) levels found in impaired neurons [50]. Also, mitochondrial dysfunction could be related to an accumulation of lipid droplets in glial cells generating an early lipid peroxidation process [51]. Some treatments tested in animal models against neurodegeneration (e.g. propofol) showed beneficial effects by its action on mitochondrial activity and lipid peroxidation levels [52]. In addition, animal models for Amyotrophic Lateral Sclerosis (ALS) showed that mitochondrial aerobic metabolism is involved in the disease development, especially in the presynaptic compartment [53]. In the same sense, an AD mouse model showed a mitochondrial dysfunction that preceded the manifestations of the pathology [54].

A possible explanation for the connexion between lipid peroxidation and mitochondrial dysfunction in neurodegenerative diseases could be the alteration in mitochondrial membrane fluidity [55].

2.2. Ferroptosis

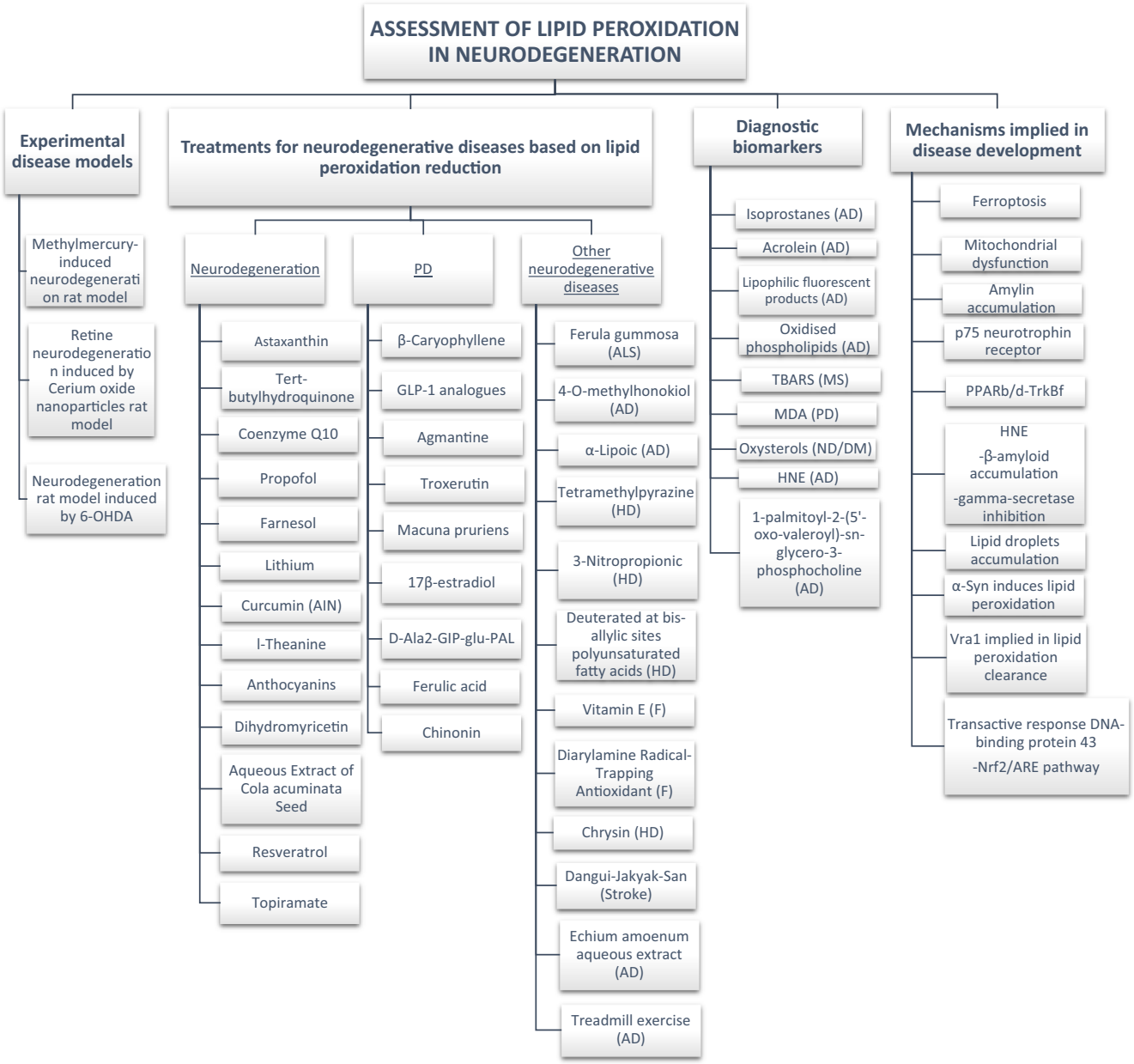
Ferroptosis is a recently discovered mechanism of programmed cell death, which is mainly caused by the accumulation of lipid peroxidation byproducts. It is mediated by the loss of glutathione peroxidase 4 (GPX4) activity, which is inhibited by iron chelation and alpha-tocopherol supplementation [56,57]. Pesticides, such as paraquat or maneb, could induce ferroptosis [58], while vitamin E treatment reduce this neuronal death, and the inhibition of 15-lipoxygenase is able to reduce lipid peroxidation products [59]. In addition, diarylamine radical-trapping antioxidant could revert this type of cell death inhibiting lipid peroxidation [60]. In the same way, the ferroptosis inhibition by means of liproxstatin-1 reduced the hippocampal lipid peroxidation, so it could be a potential treatment for neurodegeneration [61].

2.3. Ubiquitin-proteasome system

The ubiquitin-proteasome system (UPS) is a cellular machinery that mediates selective protein degradation and the impairment of UPS could be implicated in the genesis of neurodegenerative diseases [62,63]. Hence, the end-product of lipid peroxidation, 4-HNE could modify the proteasome and chaperone proteins promoting protein aggregations and contributing to neurodegenerative processes [64].

2.4. Lipid peroxidation and genetics in neurodegenerative diseases

Together with lipid peroxidation, genetic alterations constitute an important risk factor in the development of neurodegenerative diseases. Alteration in genes, like PLA2G6 (calcium-independent phospholipase A2 beta enzyme that selectively hydrolyses glycerophospholipids to



Scheme 1. Approach to lipid peroxidation assessment in neurodegeneration from different points of view.

release free fatty acids) could lead to mitochondrial dysfunction and lipid peroxidation. These findings in a drosophila model suggested that an alteration in this gene could involve neurodegeneration [65].

Specifically, familiar AD cases are related to different gene mutations, among which apolipoprotein E and presenilin stand out. Fibroblasts and lymphocytes samples from patients with presenilin 1 (PS1) and amyloid precursor protein (APP) mutations showed higher levels of lipid peroxidation markers (e.g. MDA, 4-HNE) than controls [66] [67]. Also, mutant mouse apolipoprotein E gene-deficient (ApoE −/−) showed increased lipid peroxidation levels [68]. In this sense, ApoE could play an important role in 4-HNE clearance. Different ApoE isoforms showed different union capacity, showing the allele Ɛ4 lower affinity [69]. However, McKracken et al., demonstrated that the ApoE genotype did not influence the 4-HNE immunoreactivity [70]. On the other side, patients with AD that had a mutation for hereditary hemochromatosis (HFE) gene showed elevated levels of isoprostanes (F2-IsoP). In fact, mutations on this gene could promote iron accumulation and lipid peroxidation related to AD [71].

Regarding Parkinson Disease (PD), the gene Leucine-rich repeat kinase 2 (LRRK2) seems to be implied in the relationship between lipid peroxidation and neurodegeneration. *Drosophila* knock down for LRRK2 showed resistance against impairment induced by paraquat and lower lipid peroxidation levels. Therefore, the expression of LRRK2 could explain the development of parkinsonism mediated by oxidative stress and lipid peroxidation [72]. In addition, a mutant LRRK2 expressed in *Caenorhabditis elegans* showed an increase of lipid peroxidation. Therefore, LRRK2 could be implied in mitochondrial dysfunction associated to neurodegenerative diseases [73].

Friedrich's ataxia is a genetic disease generated by a mutation in frataxin gene. Mouse model for this pathology leaded to an alteration in mitochondrial dysfunction with an increase of oxidative stress, and consequently, an increase of lipid peroxidation. In fact, when lipid peroxidation is reduced by the treatment, neuronal death is reduced [74].

In general, the study of these mutations related to lipid peroxidation leading to neurodegeneration could open a promising field in

personalized medicine, reducing the impairment in this group of pathologies.

3. Neurodegenerative disease and lipid peroxidation

3.1. Alzheimer Disease

Increased levels in plasma and CSF of some lipid peroxidation products (e.g. acrolein) have been correlated with the development of AD [75]. Also, the biomarker 1-palmitoyl-2-(5′-oxo-valeroyl)-sn-glycero-3-phosphocholine showed higher levels in AD patients, and these levels were not reduced with carotenoids as potential treatment [76]. Arimon et al., showed that lipid peroxidation products, such as 4-HNE, were involved in the accumulation of β-amyloid, the most important histopathological hallmark of AD. In addition, 4-HNE was involved in the inhibition of γ-secretase activity inducing conformational changes in presenilin 1, which were directly related to the formation of the insoluble β-amyloid peptide [77]. The susceptibility to lipid peroxidation is increased in AD, especially at its initial stages compared to healthy controls and other neurodegenerative diseases, such as ALS. So, it seems that oxidative stress and lipid peroxidation are important mechanisms in early stages of the disease [78].

The relationship between AD and Diabetes Mellitus has also been a matter of study. A potential mechanism explaining this correlation could be the accumulation of amylin. It could cause membrane lipid peroxidation, and as a consequence, it could form adducts with HNE [79].

Regarding potential AD treatments, some of them are focused on the reduction of characteristic protein accumulations (tau and β-amyloid) and reducing lipid peroxidation. For example, α-lipoic showed beneficial effects against AD by reducing tau hyperphosphorylation, lipid peroxidation, neuronal loss and ferroptosis mechanisms [80]. Moreover, 4-*O*-methylhonokiol improved cognitive impairment in an AD mouse model by reducing lipid peroxidation levels and β-amyloid accumulation [81].

3.2. Parkinson Disease

PD is also related to Diabetes Mellitus. This relationship could be explained by the effect of analogues of glucose dependent insulinotropic polypeptide, such as, D-Ala2-GIP-glu-PAL that reduced neuronal loss, lipid peroxidation levels and increased BDNF [82]. Similarly, the major sign of the PD pathology, the oligomeric α-Syn, produces an increase of oxidative stress and lipid peroxidation. This increase of lipid peroxidation is inhibited by isotope-reinforced polyunsaturated fatty acids, and it also reduces cell death induced by α-Syn [83].

Regarding potential PD treatments, Gene Vra1 includes a protein that clears lipid peroxidation producing a neuroprotective effect against dopaminergic loss, one of the main mechanisms involved in the development of the disease [84]. Hormones derivatives, such as 17β-estradiol, protect against dopaminergic loss in a mouse model of PD decreasing lipid peroxidation levels [85]. In addition, treatment with *Mucuna pruriens* reduces the increase lipid peroxidation levels produced by the intoxication with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. The intoxicated mouse showed increased levels of NF-κB, TNF-α, iNOS, ICAM and GFAP, which were reduced after the treatment [86]. Moreover, chinonin showed neuroprotective effect against MPTP neurodegeneration induction, reducing lipid peroxidation and dopaminergic neuron loss in a PD model [87]. Rotenone has been commonly used in the generation of PD mouse models showing an increase in lipid peroxidation levels [88]. Treatments applied in this model (e.g. ferulic acid, β-caryophyllene, agmantine) inhibited lipid peroxidation and produced a reduction in microglia and astrocytes activation, generating neuroprotective effects [88] [89] [90].

3.3. Other neurodegenerative diseases

Other neurodegenerative diseases are also associated to high lipid peroxidation levels. In this sense, Friedrich Ataxia's mouse model showed a dysregulation of neuronal mitochondria that leads to a lipid peroxidation increase. A reduction of lipid peroxidation in this disease produces a decrease of cell death [74].

In ALS, cell lines with altered transactive response to DNA-binding protein 43 (TDP-43) play an important role. They showed an increase of lipid peroxidation and produced a shortening of axons. The effect of TDP-43 impairment is mediated by Nrf2/ARE pathway trough MAF BZIP Transcription Factor K (MafK) and Jun Dimerization Protein 2 (JDP2) proteins [91]. In addition, in ALS the glutamate neurotransmitter could lead to neurodegeneration. Some treatments, such as *Ferula gummosa*, showed neuroprotection against glutamate-induced damage, reducing lipid peroxidation levels and apoptotic cells [92].

In Huntington Disease (HD) an increase of 4-HNE levels in different brain areas was observed, and this lipid peroxidation biomarker co-localized with mutant huntingtin protein that characterizes the pathology [93]. The increase of lipid peroxidation that takes place in the pathology was reduced by deuterated at bis-allylic sites polyunsaturated fatty acids (D-PUFA) in mouse model [94]. Also, 3-nitropropionic acid reduced lipid peroxidation and increased antioxidants, improving locomotor activity in HD [95]. Moreover, tetra methylpyrazine protects against HD-like symptoms induced by 3-nitropropionic acid reducing malondialdehyde (MDA) levels and increasing antioxidant biomarkers [96].

4. Lipid peroxidation biomarkers for neurodegenerative disease diagnosis

In general, lipid peroxidation biomarkers accompanied histological lesions produced in neurodegenerative diseases, such as, ischemic stroke or AD. In a previous study, it was shown that lipid peroxidation triggered by ischemic stroke was followed by grey matter lesion [97]. In addition, Benseny-Cases et al., found a co-localization between β-amyloid plaque and lipid peroxidation products in human brain [98].

Lipid peroxidation by-products have been investigated as potential biomarkers for diagnosis in different neurodegenerative diseases (see Table 1). In Scheme 1, we can see some lipid peroxidation biomarkers evaluated as diagnostic biomarkers in neurodegeneration. In AD, 4-HNE and MDA showed high levels in blood samples being potential diagnostic biomarkers for the disease [99]. Specifically, MDA showed higher levels in AD and MCI patients compared to healthy controls [100], being able to differentiate these patients from other pathologies, such as, vascular dementia, with which it shares similar clinic features [101]. Also, MDA showed increased levels in Scrapie and Rett syndromes [102,103]; lipophilic fluorescent products were increased in erythrocytes and plasma from AD patients, and also in patients with amnestic mild cognitive impairment (aMCI) [104,105]. In addition, oxidised phospholipid biomarker 1-palmitoyl-2-(5′-oxo-valeroyl)-sn-glycero-3-phosphocholine showed higher levels in serum from AD patients than in controls [76].

Our group has developed some analytical methods to determine a panel of lipid peroxidation biomarkers in different biological samples (urine, plasma, saliva) [18,19,106]. These determinations would allow to distinguish quite accurately between healthy control and early AD patients (AUC_ROC 0.82) [19], constituting a promising screening test for non-invasive or minimally invasive AD diagnosis [18,20]. Isoprostanes have been studied as potential diagnosis biomarkers by Mufson et al., but no relationship with AD pathology was found [107], while Seet et al. found different levels for F2-IsoPs and hydroxyeicosatetraenoic acid products (HETEs), cholesterol oxidation products and neuroprostanes between PD and healthy participants [108]. Previous studies carried out in AD showed higher acrolein levels in plasma and CSF samples from patients than healthy controls [75].

Table 1
Potential biomarkers for the diagnosis and therapy evaluation in neurodegenerative diseases.

Reference	Sample	Disease	Method	Biomarkers	Results	Biomarkers utility
19	Plasma	AD	HPLC-MS	Isoprostanes	Diagnosis model for AD based on isoprostanes	Diagnosis
32	Rat model	Neurodegeneration	Spectrophotometry	MDA	↓ MDA by topiramate mediated by BDNF	Therapy evaluation
33	Rat model	neurodegeneration	Spectrophotometry	MDA	↓ MDA by topiramate	Therapy evaluation
34	Mouse model	Neurodegeneration	Spectrophotometry	MDA	↓ MDA by l-theanine	Therapy evaluation
39	Rat model	Neurodegeneration	Spectrophotometry	MDA	↓ MDA by dihydromyricetin	Therapy evaluation
75	Plasma Urine CSF	AD	LC-MS Western	Acrolein-related metabolite	↑ Acrolein-conjugated protein were higher in plasma and CSF of AD patients ↓ 3-hydroxypropyl mercapturic acid (3-HPMA) in AD patients.	Diagnosis
76	Serum	AD	ESI-MS ELISA	Oxidised phospholipid biomarker 1-palmitoyl-2-(5′-oxo-valeroyl)-sn-glycero-3-phosphocholine (POVPC)	↑ POVPC in AD patients compared to controls	Diagnosis
96	Rat model	HD	Spectrophotometry	MDA	↓ MDA with tetramethylpyrazine	Therapy evaluation
99	Blood	AD	HPLC Spectrophotometry	Hydroxynonenal (HNE) Malondialdehyde (MDA)	↑ HNE and MDA in AD patients compared to healthy controls	Diagnosis
100	Serum	AD	Spectrometry	MDA	↑ MDA in MCI and AD	Diagnosis
101	Serum	AD	Spectrometry	MDA	↑ MDA in AD compared to controls, but ↓ compared to vascular dementia	Diagnosis
102	Mouse model	Scrapie	Spectrophotometry	MDA 4-hydroxyalkenals	↑ MDA 4-hydroxyalkenals precede the prion pathology in the brain	Diagnosis
103	Plasma	Rett syndrome	Spectrophotometry	MDA	↑MDA in Rett syndrome	Diagnosis
104	Blood	AD	fluorescence spectroscopy	LPF	↑ LPF in AD	Diagnosis
105	blood	AD	fluorescence spectroscopy	Lipophilic fluorescent products	↑ lipophilic fluorescent products in erythrocytes and plasma of AD dementia and aMCI patients versus controls	
107	Plasma and urine	AD	GC/MS	F2-isoprostane	Not differences between AD and control groups	Diagnosis
108	Plasma	PD	GC/MS	F(2)-isoprostanes hydroxyeicosatetraenoic acid products (HETEs) cholesterol oxidation products neuroprostanes	↑ F(2)-IsoPs, HETEs, F(4)-NPs in PD	Diagnosis
109	Spinal cord horse	Neuroaxonal dystrophy/equine degenerative myeloencephalopathy	HPLC	F_2-IsoP F_4-NeuroP Oxysterols	↑ [7-ketocholesterol], [7-hydroxycholesterol], and [7-keto-27-hydrocholesterol] in equine neuroaxonal dystrophy/equine degenerative myeloencephalopathy horses ↓[24-ketocholesterol] No differences for F_2-IsoP F_4-NeuroP	Diagnosis
110	Plasma	Multiple sclerosis	Spectrophotometry	TBARS	↑ TBARS in plasma from MS	Diagnosis
111	Plasma	AD	Spectrometry	TBARS	↑ TBARS in AD	Diagnosis
112	Plasma	PD	HPLC	MDA	↑ MDA in PD patients	Diagnosis
113	plasma	AD	Fluorescence spectroscopy	ipofuscin-like pigments (LFPs)	Differences were found for various intensities of LPF between control, MCI and AD groups	Diagnosis
114	Brain	AD	GC/MS	4-hydroxyhexenal (HHE)	↑ HHE in AD progression	Diagnosis
115	Mouse model	Neurodegeneration	Spectrophotometry	MDA	↓ MDA with Astaxanthin	Therapy evaluation
116	Cell culture	Neurodegeneration	Spectrophotometry	MDA	↓ MDA by S. lavandulifolia essential oils	Therapy evaluation
117	Cell culture	A beta toxicity	Spectrophotometry	TBARS	↓ TBARS by Pycnogenol against b amyloid induced toxicity	Therapy evaluation
118	Cell culture	Neurodegeneration	Spectrophotometry	TBARS	↓ TBARS by Phenserine	Therapy evaluation

(*continued on next page*)

Table 1 (*continued*)

Reference	Sample	Disease	Method	Biomarkers	Results	Biomarkers utility
119	Cell culture	Nuerodegeneration	Spectrophotometry	Conjugated dienes (CDs) MDA	↓ CDs and MDA by biotin	Therapy evaluation
120	Cell culture	Neurodegeneration	Western blot	HNE	↓ HNE by aldehyde dehydrogenase 1A1	Therapy evaluation
121	Cell culture	AD	Spectrophotometry	Lipid hydroperoxide (LH)	↓ LH by puerarin	Therapy evaluation
122	Cell culture	PD	Spectrophotometry	MDA	↓ MDA by Allicin	Therapy evaluation
123	Cell culture	PD	Enzyme inmunoassay	8-isoprostane	↓ 8-isoprostane by Phloroglucinol	Therapy evaluation
125	Cell culture	Neurodegeneration	Spectrophotometry	MDA	↓ MDA by CoenzimeQ10	Therapy evaluation
126	Cell culture	Neurodegeneration	Spectrophotometry	MDA	↓ MDA by Tert-butylhydroquinone	Therapy evaluation
127	Mouse model	Neurodegeneration	Spectrophotometry	MDA	↓ MDA and LH by vanillin	Therapy evaluation
128	Mouse model	Neurodegeneration	Spectrophotometry	MDA	↓ MDA by Fisetin	Therapy evaluation
129	Mongolian gerbils model	Neurodegeneration	Spectrophotometry	MDA	↓ MDA by tetanus toxin C	Therapy evaluation
130	Rat model	Neurodegeneration	Spectrophotometry	MDA	↓ MDA by Topiramate	Therapy evaluation
132	Mouse model	Multiple sclerosis	Spectrophotometry	MDA	↓ MDA by resveratrol	Therapy evaluation
133	Mouse model	ALS	HPLC-MS/MS	4-HNE	↑ 4-HNE by omega-3 fatty acid eicosapentaenoic acid	Therapy evaluation
134	Rat model	HD	Spectrophotometry	MDA	↓ MDA by Chrysin	Therapy evaluation
135	Rat model	Neurodegeneration (ischemic stroke)	Spectrophotometry	MDA	↓ MDA by Danggui-Jakyak-San	Therapy evaluation
136	Drosophila model	PD	Spectrophotometry	TBARS	↓ TBARS by cabergoline alginate	Therapy evaluation
137	Drosophila model	PD	Spectrophotometry	TBARS	↓TBARS by apigenin.	Therapy evaluation
138	Rat model	PD	Spectrophotometry	MDA	↓ MDA by ACS84 (hydrogen sulfide-releasing L-Dopa derivative)	Therapy evaluation
139	Rat model	AD	Inmunofluorescence Spectrophotometry	4-HNE MDA	↓MDA production and 4-HNE immunoactivity by Methylene blue	Therapy evaluation
140	Rat model	Neurodegeneration	Spectrophotometry	MDA	↓ MDA by Aqueous Extract of *Cola acuminata* Seed	Therapy evaluation
141	Rat model	AD	Spectrophotometry	MDA	↓ MDA by Echium amoenum aqueous extract	Therapy evaluation
142	Mouse model	Neurodegeneration	Spectrophotometry	MDA	↓ MDA by Farnesol	Therapy evaluation
143	Mouse model	PD	Spectrophotometry	MDA	↓ MDA by *Mucuna pruriens*	Therapy evaluation
144	Rat model	PD	Spectrophotometry	MDA	↓ MDA by Troxerutin	Therapy evaluation
145	Mouse model	PD	Western blot	4-HNE	↓4-HNE by GLP-1 analogues	Therapy evaluation
146	Rat model	AD	Immunofluorescence	4-HNE	↓ 4-HNE by treadmill exercise	Therapy evaluation

(*continued on next page*)

Table 1 (*continued*)

Reference	Sample	Disease	Method	Biomarkers	Results	Biomarkers utility
147	Mouse model	Neurodegeneration	Inmunofluorescence	4-HNE	Piperlongumine did not produce reduction of 4-HNE	Therapy evaluation

AD: Alzheimer Disease; ALS: Amyotrophic Lateral Sclerosis; aMCI: Amnestic mild cognitive impairment; BDNF: Brain derived neurotrophic factor; GLP-1: Glucagon-like peptide 1; HD: Huntington Disease; HNE: Hydroxynonenal; MDA: Malondialdehyde; PD: Parkinson Disease; TBARS: Thiobarbituric Acid Reactive Substances.

Other neurodegenerative diseases showed altered levels of lipid peroxidation products that could serve as diagnostic or prognostic biomarkers. For instance, spinal cord oxysterols showed impaired levels in neuroaxonal dystrophy/equine degenerative myeloencephalopathy [109]. In addition, thiobarbituric acid reactive substances (TBARS) were elevated in plasma from multiple sclerosis patients [110] and AD [111], while plasmatic MDA showed high levels in PD patients compared to healthy participants [112].

Lipid peroxidation by-products not only showed differences among pathologies but also along disease stages, as it occurs with lipofuscin-like pigments in AD [113]. In addition, 4-HNE showed a significant correlation with AD progression, showing different levels in the different stages of the disease [114].

Lipid peroxidation is evident since early stages of different neurodegenerative diseases, and the corresponding biomarkers could be useful in early diagnosis. In addition, some compounds could predict the disease progression since these levels change along the disease stages.

5. Treatments reducing lipid peroxidation in neurodegenerative diseases

Attending to the implications of lipid peroxidation in the development of multiple neurodegenerative diseases, some studies search for treatments focusing on these metabolites and pathways as targets. Considering the key role of lipid peroxidation in neurodegeneration, some potential treatments try to reduce levels of these products in order to avoid their consequences in brain. The evaluation of different products (e.g. MDA, TBARS) is commonly used in order to evaluate effectiveness against neurodegeneration and neurodegenerative diseases [96] [115].

Different treatments tested in cell models of neurodegeneration showed beneficial effects reducing lipid peroxidation biomarkers, such as, *Salvia lavandulifolia* essential oils, phenserine, biotin or aldehyde dehydrogenase 1A [116–120]. Other treatments tested in cell models for degenerative diseases, such as AD or PD, showed a decrease of lipid peroxidation biomarkers, such as, lipid hydroperoxide, MDA or isoprostanes [121–123]. Generally, lipid peroxidation decrease is accompanied by an improvement of cognitive functions. The cell line (SH-SY5Y) was used to evaluate lithium neuroprotective effects, and it may be associated to lipid peroxidation reduction, although it is not statistically significant [124]. Also, lipid peroxidation caused by H2O2-induced neurotoxicity in cell culture was reduced by coenzyme Q10 [125]. In addition, the tert-butylhydroquinone treatment reverted iron-induced lipid peroxidation increase and apoptosis through Nrf2/ARE pathway [126].

Also, different animal models have been used in order to evaluate treatment effectiveness against neurodegeneration [127–129]. Topiramate showed similar effects and its neuroprotection role was attributed to its function in CREB/BDNF and protein kinase B/Glycogen synthase kinase 3 (Akt/GSK3) signalling pathways [32,33,130]. Also, resveratrol, an important antioxidant molecule, tested to reduce oxidative stress produced in AD [131], showed beneficial effects in a multiple sclerosis mouse model [132]. By contrast, omega-3 fatty acid eicosapentaenoic acid treatment produced an increase of 4-HNE and promoted the pathology progression [133]. In addition, L-theanine showed a reduction of lipid peroxidation by-products in a cadmium-induced neurodegeneration mouse model that showed a reduction in tau phosphorylation [34]. Some treatments, such as dihydromyricetin, showed neuroprotective effects against hypobaric hypoxia-induced neurodegeneration, decreasing lipid peroxidation and stimulating mitochondria biogenesis that improve its activity [39]. In addition, chrysin reduced MDA and apoptosis in a mouse model with HD-like pathology induced by nitropropionic acid [134]. Dangui-Jakyak-San showed neuroprotective effects against stroke neurodegeneration by means of the reduction of apoptosis and a decrease of MDA [135]. PD

drosophila models showed a reduction of TBARS by cabergoline alginate and apigenin [136,137], while a mouse model for this pathology showed a reduction of MDA by a hydrogen sulfide-releasing L-Dopa derivative (ACS84) [138]. Also, an AD mouse model showed a reduction of MDA production and 4-HNE immunoactivity by methylene blue treatment [139].

Natural treatments (e.g. aqueous extract of *Cola acuminata* Seed, echium amoenum aqueous extract) were tested, they showed neuroprotection by their action against acetylcholinesterase and butyrylcholinesterase activities, so lipid peroxidation levels were reduced [140] [141]. Apoptosis is one of the main causes of neurodegeneration, and treatments focused on interfering in this cascade have shown neuroprotective effects accompanied by a reduction of oxidative stress levels [142]. Other potential treatments tested in PD were *Mucuna pruriens* and Troxerutin. They reduced lipid peroxidation products regulating iNOS and phosphatidylinositol 3-kinase/estrogen receptor β pathways [143] [144]. Moreover, PD glucagon-like peptide 1 (GLP-1) analogues and astaxanthin caused a decreased 4-HNE and MDA levels, producing an improvement in motor impairment and memory, respectively [115] [145].

Other kind of therapeutic measures commonly studied in AD is the physical exercise that caused an improvement not only in cognition, but also in lipid peroxidation levels, having effects against mitochondrial dysfunction and inflammation [146]. Nevertheless, other treatments, such as Piperlongumine, improved cognitive impairment in a neurodegeneration mouse model, in spite of its inability to reduce 4-HNE levels [147], corroborating the fact that lipid peroxidation is not the only mechanism implied in neurodegeneration and neurodegenerative diseases.

6. Conclusions

Lipid peroxidation is closely related to neurodegeneration and neurodegenerative diseases, such as Alzheimer, Parkinson or Huntington Disease. Among the mechanisms that are related to lipid peroxidation in these pathological conditions both mitochondrial dysfunction and ferroptosis play an essential role. Nowadays, it is not clear if lipid peroxidation is the cause or the consequence of neurodegeneration processes. However, this relationship could be useful, since lipid peroxidation biomarkers are good indicators of the effectiveness of different treatments and they could serve as diagnostic and/or prognostic biomarkers. Nevertheless, in some cases a reduction of lipid peroxidation levels does not imply necessarily an improvement in neurodegeneration, histological markers, or cognitive function, revealing, a multifactorial etiology. Further research in this line is required.

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Disclosure

The authors declare not having anything to disclose in relation with the present manuscript.

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