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REVIEW ARTICLE

Mitochondria and lipid peroxidation in the mechanism of neurodegeneration: Finding ways for prevention

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Abstract

The world's population aging progression renders age-related neurodegenerative diseases to be one of the biggest unsolved problems of modern society. Despite the progress in studying the development of pathology, finding ways for modifying neurodegenerative disorders remains a high priority. One common feature of neurodegenerative diseases is mitochondrial dysfunction and overproduction of reactive oxygen species, resulting in oxidative stress. Although lipid peroxidation is one of the markers for oxidative stress, it also plays an important role in cell physiology, including activation of phospholipases and stimulation of signaling cascades. Excessive lipid peroxidation is a hallmark for most neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and many other neurological conditions. The products of lipid peroxidation have been shown to be the trigger for necrotic, apoptotic, and more specifically for oxidative stress-related, that is, ferroptosis and neuronal cell death. Here we discuss the involvement of lipid peroxidation in the mechanism of neuronal loss and some novel therapeutic directions to oppose it.

Abbreviations: AA, arachidonic acid; CoQ, coenzyme Q; COX, cyclooxygenase; CYPs, cytochrome p450s; GSH, glutathione; LOX, lipoxygenase; LP, Lipid peroxidation; ND, Neurodegeneration; NOX, NADPH oxidase; PUFAs, polyunsaturated fatty acids.

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KEYWORDS

free radicals, lipid peroxidation, mitochondria, neurodegeneration, Nrf2, PUFAs, ROS

1 | INTRODUCTION

Although the brain is relatively small and isolated by the highly effective brain–blood barrier (BBB), this organ consumes about 20% of total oxygen and glucose. Importantly, the rate of lipid metabolism in the brain is also highest in the body and cells use part of the energy for membrane lipid replacement. The high metabolic rate in mitochondria and the availability of oxygen, both prompt the production of free radicals and specifically of the reactive oxygen species (ROS). One of the major producers of ROS in brain cells in resting conditions is mitochondria, predominantly due to the leakage of electrons out of the electron transport chain.[1] Contrary to mitochondria, in the cytosol, ROS are mostly produced by the NADPH oxidase (NOX) and, depending on the conditions, by other enzymes including xanthine

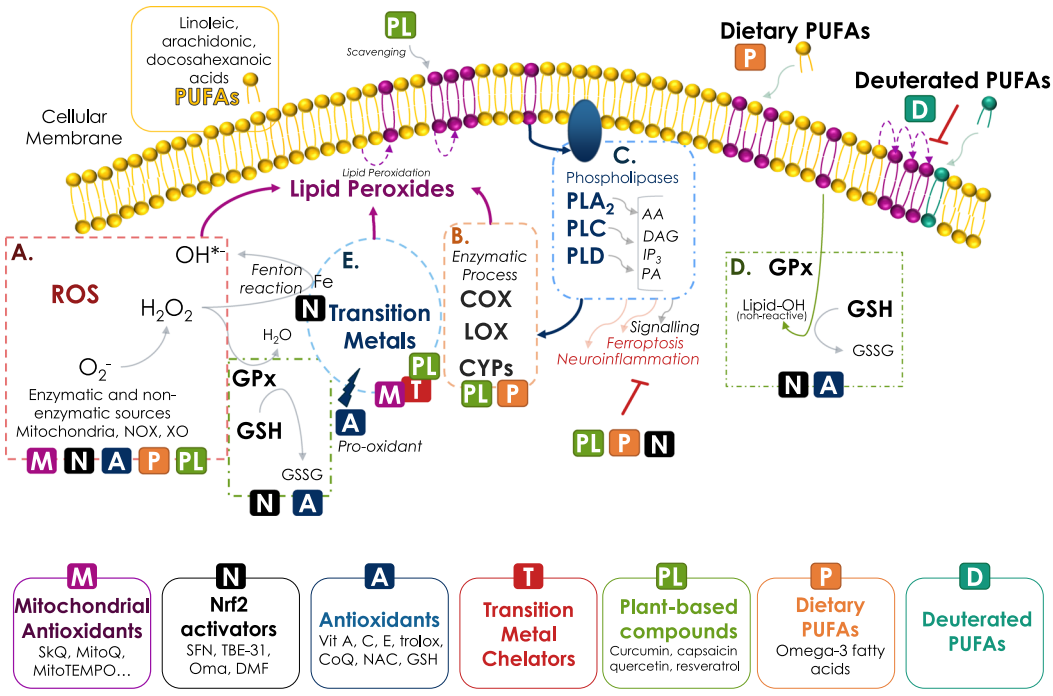

FIGURE 1 Lipid peroxidation in neurodegeneration and major protective pathways. A, Lipid peroxidation can occur in a nonspecific (via ROS) or (B) enzymatically assisted reaction (through COX, LOX, and CYPs) and affects preferentially polyunsaturated fatty acids (PUFAs) in the cellular membranes. E, Fe and other transition metals are also involved in the process, directly and indirectly. C, Lipid peroxidation induces the activation of phospholipases and their products, which are involved in cell signaling but also in pathogenic processes such as ferroptosis or neuroinflammation. D, Glutathione peroxidases (GPx) are able to terminate the reaction and reduce peroxides to the corresponding alcohol, using glutathione (GSH) as a substrate. The main mechanisms of protection of mitochondrial antioxidants (M), Nrf2 activation (N), antioxidants (A), transition metal chelators (T), plant-based bioactive compounds (PL), dietary PUFAs (P), and deuterated PUFAs (D) in lipid peroxidation are indicated in the graph. CoQ, coenzyme Q; COX, cyclooxygenase; CYPs, cytochrome p450s; DMF, dimethyl fumarate; LOX, lipoxygenase; NAC, *N*-acetyl cysteine; Nrf2, nuclear factor erythroid 2-related factor 2; Oma, omaveloxone; ROS, reactive oxygen species; SFN, sulforaphane [Color figure can be viewed at wileyonlinelibrary.com]

oxidase.[2–4] There are a number of enzymatic sources of ROS in the brain, including the enzymes of the tricarboxylic acid (TCA) cycle, monoamine oxidases, and others (Figure 1). The majority of the enzymatic producers initially generate superoxide anion which, due to its short lifetime (~1 ns), oxidizes molecules in close proximity, and is neutralized by antioxidant systems or is converted to other types of ROS including hydrogen peroxide (H_2O_2) in the superoxide dismutase (SOD). H_2O_2 is more stable, therefore less reactive, and is a form of ROS that could be used as a signaling molecule. On the other hand, in higher amounts, it is also more toxic and induces the oxidation of nearby located biomolecules. Furthermore, it can be converted in Fenton reaction to hydroxyl anion OH^{*-}, which is highly reactive and damaging to the surrounding molecules; it oxidizes the lipid constituents of the membrane to generate lipid hydroperoxides (Figure 1A). The process of product formation of oxidized lipid membranes, called lipid peroxidation, occurs in a nonspecific way, such as random effects of ROS (Figure 1A) or in an enzymatically assisted reactions by cyclooxygenases (COXs), cytochrome p450s (CYPs), and lipoxygenases (LOXs; Figure 1B).[5,6] Lipid peroxidation targets preferentially polyunsaturated fatty acids (PUFAs), including linoleic acid, arachidonic acid (AA), and docosahexaenoic acid (DHA). Interestingly, the brain, as in the case with oxygen and glucose, consumes 20% of all PUFAs of the body which suggests a high level of lipid turnover in this organ. Products of lipid peroxidation are constantly generated and used for signaling and housekeeping needs.[7–9] The products of lipid peroxidation are utilized enzymatically to hydroxyl acids by glutathione peroxidase, using glutathione (GSH) as a cosubstrate to reduce lipid peroxides to the corresponding alcohols[10] or, to aldehydes[6,11] (Figure 1D). However, lipid peroxidation dramatically induces the activation of phospholipases PLA_2, PLC, PLD, and their products[12,13] (Figure 1C), which suggests the involvement of LP in many signaling cascades, but also that phospholipases—the housekeeping enzymes of our membranes—use as a substrate predominantly oxidized lipids.[9] Any signaling event that produces lipid radicals will then stimulate phospholipases and will have physiological response.[1,7,12] AA which has been found to be present in the cell in an active radical form, has been shown to have multiple direct effects as well, such as the effects on the nearby ion channels,[14,15] and it has been appointed a role for the arachidonic hydroperoxides in the initiation of the processes of ferroptosis and inflammation.[16]

2 | MITOCHONDRIA AND LIPID PEROXIDATION IN NEURODEGENERATIVE DISORDERS

The involvement of oxidative stress in the development of many neurodegenerative diseases (Alzheimer's disease [AD], Parkinson's disease [PD], Huntington's disease [HD], amyotrophic lateral sclerosis [ALS], frontotemporal dementia [FTD], etc.) has been well-documented.[17,18] Neurodegeneration is a complex multifactorial type of disorder and as such it justifies a combined therapeutic approach. In both familial and sporadic forms of neurodegeneration, aggregation of misfolded proteins, mitochondrial dysfunction (affecting mitochondrial bioenergetics, transmembrane potential, calcium handling, dynamics, and maintenance), and oxidative stress are accepted to be the cause for neuronal loss in human and animal models.

2.1 | Alzheimer's disease

A high level of lipid peroxidation is shown in patients with AD. Interestingly, it can be detected in serum[19] and it correlates with the dramatic decrease of the major lipid-soluble antioxidant α-tocopherol.[20] More importantly, elevated levels of the products of lipid peroxidation were also found in the brain of AD patients.[21,22] This renders lipid peroxidation metabolites suitable for a potential novel biomarker for diagnosis, prognosis, and therapy.[23] However, due to the involvement of lipid peroxidation in the number of diseases and the controversy of some methods for the detection of lipid peroxidation metabolites, using them as a biomarker is still far from clinics. Lipid peroxidation is mainly to be the result of excessive ROS production in NOX upon its activation with oligomeric β-amyloid in astrocytes and neurons[23–27] or in microglia.[28] There is more and more evidence that in addition to apoptosis and necrosis, neuronal death in AD involves ferroptosis, an iron- and lipid peroxidation-dependent form of regulated necrosis.[29]

2.2 | Parkinson's disease

Production of ROS in familial and sporadic forms of PD has been shown to have multiple sources including mitochondrial electron transport chain, monoamine oxidase, NOX, and even the oligomeric α-synuclein itself.[3,30–33] Considering this, lipid peroxidation in PD can be induced by a number of factors and may occur in the membrane of various organelles, including mitochondria.[18] We have recently shown that lipid peroxidation specifically, but not ROS production in general, is the mechanism of α-synuclein-induced neurotoxicity in PD.[17,18] Lipid peroxidation has been shown to be involved in the triggering of the mitochondrial permeability transition pore,[4,18] mitophagy,[34] ferroptosis,[35] and many others.

2.3 | Other neurodegenerative diseases

In almost all neurodegenerative diseases, ROS production and lipid peroxidation have been shown to be a hallmark of pathology, for example, FTD[36,37] or ALS, where excessive levels of metabolites of lipid peroxidation have been found in the blood of patients.[38] In tauopathy, activation of lipid peroxidation can be induced by mitochondrial ROS production or by activation of NOX.[39,40]

In in vitro or in cellular model experiments, positive effects of various antioxidants have been described.[4] However, none of the ND clinical trials with antioxidants has been yet successful, due to the low bioavailability of synthetic antioxidants in the brain or "side effects," probably developed by the direct inhibition of the ROS- and LP-mediated physiological signaling processes (Figure 1). Moreover, some antioxidants could act as pro-oxidants, depending on the redox status of the local environment.

In this article, we aim to point to the reader's attention to the multiple sources and types of free radicals and ROS that all ultimately lead to lipid peroxidation that is causal for neurodegeneration. Furthermore, we will accentuate the different stages where lipid peroxidation could be counteracted and the tailor-made approaches towards finding a solution for successful treatment.

3 | NOVEL APPROACHES FOR NEURODEGENERATIVE DISEASE TREATMENT

3.1 | Mitochondria-targeted antioxidants

After the discovery of triphenylphosphonium ability to shuttle any small molecules to the mitochondrial matrix, the intracellular application of antioxidants, directly to their source in mitochondria became possible.[41]

Based on this, a variety of mitochondria-targeted free radical scavenger have been developed over the last 40 years, for example, *SKQ* (plastoquinone), *MitoQ* (ubiquinone), *MitoVitE* (vitamin E), *MitoTEMPO* (SOD mimetic), MCAT (catalase), MitoPBN (coenzyme Q [CoQ] and phenyl tertbutylnitrone conjugate), to name a few. As such these are effective in preventing superoxide-induced lipid peroxidation, scavenging all sorts of free radicals, specifically produced in mitochondria,[42] where the major source of oxidative stress is complex-I-related pathology,[43] for example, in PD.[44,45]

3.2 | Nuclear factor erythroid 2-related factor 2 activators

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor able to induce the expression of different endogenous antioxidants and detoxifying enzymes. Moreover, some of its target genes include mediators of

iron/heme, intermediate and GSH metabolism, NOX and fatty acid (FA) β-oxidation, all of which contribute to the specific defense against ROS generation and lipid peroxidation.[46–48] Nrf2 levels are tightly controlled in a mechanism involving the adaptor molecule Keap1, which targets Nrf2 for continuous proteasomal degradation under basal conditions. Keap1 contains highly reactive Cys residues that act as sensors that are modified by electrophilic or oxidative signals under stress conditions. This prevents Nrf2 ubiquitination and degradation, thus allowing its translocation to the nucleus and the transcription of its target cytoprotective genes.

Activation of Nrf2 represents an exceptional therapeutic strategy for neurodegenerative disorders, in which oxidative stress and mitochondrial dysfunction are key features of the pathology.[49] The most studied pharmacological tools aiming to activate Nrf2 are small electrophilic molecules that react with Cys residues in Keap1 (Figure 1). These include the naturally occurring sulforaphane, able to cross the BBB,[50] the potent tricyclic compound TBE-31,[51] the fumaric acid ester dimethyl fumarate (approved for the treatment of relapsing–remitting multiple sclerosis),[52] or omaveloxolone (RTA 408), also able to cross the BBB and currently in a clinical trial in Friedreich ataxia (FRDA) patients.[53] Work from our group has shown the cytoprotective activity of these compounds in animal models of epilepsy[54] and cellular models of neurodegenerative diseases such as ALS/FTD, PD, or FRDA.[55–57] Nrf2 activation in these studies has successfully improved mitochondrial function and bioenergetics reduced ROS production and lipid peroxidation and/or prevented cell death and neurodegeneration.

Recent approaches to activate Nrf2 are focusing on the development of nonelectrophilic compounds aiming to disrupt Nrf2–Keap1 interaction, which would reduce the off-target effects of the nonspecific alkylation of Cys residues caused by electrophilic compounds.[58] Animal studies have shown the neuroprotective activity of this type of compounds in cerebral ischemia and its effectiveness in preventing oxidative stress-induced DNA damage and lipid peroxidation.[59] As recently reviewed by Cuadrado et al.,[60] multiple Nrf2 activators are currently under development and clinical trials, which will provide essential advances in the near future.

3.3 | Natural and synthetic antioxidants

Given the consequences of free radical overproduction—lipid peroxidation and oxidative stress, significant efforts have been made in search of possibilities to control this reaction. Many natural and synthetic agents have been discovered to have antioxidant properties: retinol (vitamin A), ascorbic acid (vitamin C), α-tocopherol (vitamin E) and its water-soluble derivative trolox, calcipherol (vitamin D3), *N*-acetyl cysteine, GSH, uric acid, ubiquinol (CoQ), to name a few (Figure 1). Despite the initial hype following positive results in cellular models and in vitro,[61–63] soon, it becomes recognizable that these antioxidants often have pro-oxidant activities, depending on the metabolic or redox status of the cell/organism.[14,15] For example, ascorbic acid can reduce transition metal ions to generate very potent radical hydroxyl radical ($HO^{\cdot-}$) in the so-called Fenton reaction. Uric acid and homocysteine can enter similar reactions in the presence of copper or iron ions and yield pro-oxidant effects. These observations have led to the recent description of the highly disputable concept of "reductive stress" as a counterpart of oxidative stress and another type of redox dysbalance that ultimately leads to cytotoxicity.[64,65]

3.4 | Transition metal chelators

Metals with dynamic valence, that is, transition metals (iron, copper, zinc, manganese, etc.) have been shown to play an initiating role in the induction of lipid peroxidation (Figure 1E). The transition metal-catalyzed breakdown of lipid hydroperoxides can end by yielding toxic products such as aldehydes or, alternatively, could give rise to the generation of alkoxyl or peroxyl radicals that reinitiate lipid peroxidation by redox cycling of the latter metal ions.[66]

In relation to the development of neurodegenerative diseases, transition metals are involved in the formation of cytotoxic protein aggregates from misfolded proteins as shown for PD, AD, HD, and ALS.[67–72] Moreover, transition metal accumulation and metal metabolism dysfunction have been shown for *postmortem* brain tissue of PD and AD patients.[73–75] Besides, a role for the accumulation of heavy metals like mercury or aluminum into the etiopathology of neurodegeneration has been discussed.[76,77] In this sense, metal chelating therapy has been proven to be largely effective, especially in the prevention of lipid peroxidation in cellular ND models[32,78,79] as well as in hit doses in vivo or in ND patients.[80,81] However, prolonged usage of metal chelating agents could be detrimental to many physiological processes.[82–84]

3.5 | Plant-based bioactive compounds

Plant mono- and polyphenols, alkaloids, and flavonoids are naturally occurring plant components present in foods of plant origin such as fruits, vegetables, tea, cocoa, and wine, which have been used by humanity for ages.

Curcumin is a natural polyphenol, present in turmeric (*Curcuma longa*) used for centuries for its anti-inflammatory activity. Recently, it has been reported a wide range of antioxidant and neuroprotective actions.[85] It has a direct inhibitory effect on lipid peroxidation.[86] Its bioavailability and effect is further enhanced by the addition of the alkaloid *piperine* from (*Piper nigrum*), and both exhibit a synergetic effect which results in neuroprotection in an ND rat model.[87] Curcumin has been shown to be neuroprotective and have great potential for the prevention or treatment of neurological disorders like HD and PD.[88] Further, curcumin protects against oxidative stress, neurodegeneration and memory impairment via Nrf2/toll-like receptor 4/receptor for advanced glycation endproducts regulation.[89]

Resveratrol, the major antioxidant in grape (*Vitis vinifera*) skins, is a stilbenoid polyphenol found to inhibit the nuclear factor kappa B (NF-κB), activator protein-1, and COX-2 pathways and activates peroxisome proliferator-activated receptor, endothelial NOS, and sirtuin 1.[90] Moreover, resveratrol directly inhibits the process of lipid peroxidation mainly by scavenging lipid peroxyl radicals within the membrane.[91]

Capsaicin (*Capsicum* sp.), is an alkaloid that has been found to be a selective inhibitor of transient receptor potential cation channel subfamily V member 1 (TRPV1) is a nonselective cation channel with high specificity for Ca^{2+}. It is activated by chemical and physical stimuli, such as heat, low pH, capsaicin, and certain inflammatory mediators. In addition, capsaicin has been reported to inhibit COX-2 activity, iNOS expression, and the NF-κB pathway in a TRPV1 independent way.[92] For example, capsaicin is reported to reduce metal-catalyzed lipid peroxidation. Moreover, it has been shown to be neuroprotective in a PD model.[93]

Epigallocatechin-3-gallate (EGCG) is a polyphenol isolated from the green tea plant (*Camellia sinensis*) with reported multiple anti-inflammatory, antioxidant, anticancer, antiangiogenic, and chemopreventive effects.[94,95] Furthermore, it inhibits the expression of COX-2.[96] It has been reported that EGCG can protect neurons in AD models by reducing the activity of β- and γ-secretases through inhibiting ERK and NF-κB,[97] reducing amyloid plaques by stimulating α-secretase activity which results in cleavage of APP.[98] For PD, it has been found that EGCG increases GSH and this, in turn, activates cAMP response element-binding protein and B-cell lymphoma 2,[99] which in final leads to survival of tyrosine hydroxylase-positive neurons in *substantia nigra* through phosphoinositide 3-kinase/protein kinase B[100] and through Nrf2/antioxidant responsive element (ARE) pathways.[101]

Quercetin is a flavonoid found in many foods, including apples, grapevines, berries, onions, etc. It exerts a large variety of biological actions: anti-inflammatory, antioxidant,[102] and neuroprotective.[103] Quercetin is a scavenger of reactive oxygen and nitrogen species and targets prominent proinflammatory pathways, such as signal transducer and activator of transcription 1, NF-κB, and mitogen-activated protein kinase.[104,105]

Caffeine is an alkaloid that directly attenuates the lipid peroxidation in[106] and modulates metal-induced oxidative stress and cognitive impairment through regulating Nrf2/heme oxygenase-1.[107]

Salicylate is a lipophilic monohydroxybenzoic acid, a plant-based nonsteroid anti-inflammatory drug historically derived from *Salix* sp., which is an inhibitor of inflammatory cascades and in particular of the lipid oxidizing enzymes LOX, COX, and P450. Recently, it has been reported that an aspirin derivative blocks neuronal cell death associated with AD, PD, and HD.[108]

Naringenin is a flavanone derived mainly from grapefruit (*Citrus paradisi*) and other citrus fruits, possesses strong antioxidant, and neuroprotective activity, and also anti-inflammatory effects in mammals. It has been proven efficient in hereditary spastic paraplegia type of neurodegeneration[109] and has beneficial effects on learning and memory in the AD model through the mitigation of lipid peroxidation and consequently of apoptosis/ferroptosis.[110] Similarly, regarding the role of naringenin in PD, it was described being effective,[111] also through the activation of Nrf2/ARE pathway[112] and through the inhibition of c-Jun N-terminal kinase/p38/which leads to the inhibition of caspase-3 and the apoptosis, respectively.[113]

3.6 | Endogenous, dietary, and reinforced FAs

PUFAs are highly susceptible to oxidation due to the presence of a weaker C–H bond at the *bis*-allylic position. These hydrogen atoms are easily removed to form multiple types of lipid radical products that are responsible for the development of various diseases, including neurodegenerative diseases.[114,115] Oxygenated PUFAs may play various signaling roles in physiological processes.[1,7,116] Plant- and animal-derived omega-3-FAs have shown a high potential of reducing oxidative stress and inflammation (Figure 1).

3.6.1 | Dietary FAs

α-Lipoic acid is a natural organosulfur derivative from octanoic acid, essential for the energy turnover in mammals, serving as a cofactor of several TCA enzymes. It has been as well shown to be protective in reducing lipid peroxidation damage in several animal models, as well as in *postmortem* brains with of ND pathology.[34,117,118]

3.6.2 | Dietary PUFAs

A source of natural PUFA with beneficial health effects is the cod (*Gadidae*) liver oil, containing the essential omega 3-FAs DHA and eicosapentaenoic acid, as well as high doses of vitamin A and vitamin E. An alternative plant source of omega-3-FAs is the flaxseed (*Linum sativum*) oil, containing α-linolenic acid and linoleic acids, with proven positive effects on the reduction of lipid peroxidation.[17] Dietary sources of γ-linoleic acids, which is able to inhibit LOX, COX, and CYP450 are borage (Figure 1; *Borago officinalis*) and evening primrose (*Oenothera biennis*) oils.[119] Long-chain dietary PUFAs are shown to be beneficial as in the proper development as well as in the proper functioning of the nervous system.[120]

3.6.3 | Deuterated PUFAs

Recently, site-specific isotope-reinforced PUFAs, termed D-PUFAs, where *bis*-allylic hydrogens of PUFAs have been replaced with deuterium atoms, are very powerful in inhibiting PUFA peroxidation and confer solid cell protection against oxidative stress[121] (Figure 1). D-PUFAs function like lipid-radical traps, unlike antioxidants, and are able to prevent redox cycling of lipid radicals and therefore successfully cease the lipid-radical chain reaction.

D-PUFAs have been shown to be effective in multiple cell models of disease, involving lipid peroxidation,[17,122–125] as well as clinically successful in several neurological disorders, like INAD or FRDA.[126]

3.7 | Gene therapy

Recently, the intervention in the ND patient genome has been proposed as a potent tool to directly correct photogenic mechanisms (protein misfolding, enzyme dysfunction, etc.), milder and alleviate symptoms, restore damaged neuronal circuits, prevent the neuronal cell death. Modified viral vectors (adeno-associated viruses are used to deliver the genes of interest), for example, glutamic acid decarboxylase (which opposes the hyperactivity in STN) or aromatic L-amino acid decarboxylase (the rate-limiting enzyme of dopamine biosynthesis) for PD patients.[127,128] In addition, neurotrophic factors as a glial-derived neurotrophic factor or neurturin could be delivered intracerebrally for neurorestorative purposes to attempt to replace defect cellular functions.[129,130]

3.8 | Antisense oligonucleotides

Antisense oligonucleotides (ASO) are small fragments of messenger RNA (mRNA) that are complementary to and target the "sense" mRNA of a DNA transcript.

When applied, ASOs can lead to complete inhibition of the target protein synthesis. This type of intervention is a very promising gene therapy of neurodegeneration[131] that allows for the massive reduction of the misfolded protein levels that otherwise target plasma and mitochondrial membranes and lead to massive ROS production (in the cytoplasm or in mitochondria) or high levels of lipid peroxidation.[18,32,131] For example, ASOs-based clinical studies have shown very promising results in HD, ALS, spinocerebellar ataxia 2 and TDP-43-related FTD.[132–135]

3.9 | Genome editing

The novel CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats) gene-editing tool has been very effective in the development of more exact disease models. However, due to its high efficacy, simplicity and adaptability, it holds immense potential to correct almost any kind of disease, including neurodegeneration. To achieve results in the ND field, the potentially important targets for CRISPR/Cas9-based research should be focused on aberrant protein aggregation and redox mechanisms and pathways. These relate to proteins and enzymes from the redox metabolism, mitochondrial bioenergetics and transport, and the regulated cell death programs, that have all been identified as strongly associated with the pathogenesis of neurodegeneration.[136–138]

4 | CONCLUSION

Lipid peroxidation plays an essential part in the mechanism of neurodegeneration. It can potentially be one of the most promising targets for the development of novel therapeutic strategies for the treatment of major neurodegenerative disorders. One of the main challenges is to distinguish oxidative stress in general, from lipid peroxidation. Thus, the majority of research works are predominantly based on the establishment of ways to protect cells from oxidative stress, based on the usage of antioxidants. To avoid this problem, a tailor-made strategy should be developed, which can target the specific source of oxidative stress, that is, certain enzymatic pathways or specifically inhibit lipid peroxidation in brain cells.

Oxidative stress and part of this process—lipid peroxidation is widely accepted to be one of the triggers for neurodegeneration and is shown to be involved in most of the neurodegenerative disorders. However, there is more and more evidence that lipid peroxidation can play an important role in the regulation of physiological processes in different parts of the body, including the brain. The importance of lipid peroxidation in physiology and pathology is confirmed by the fact that lipid peroxidation is a major factor in a recently described new form of cell death—ferroptosis. The involvement of lipid peroxidation and its products in neurodegeneration has been shown in various disease models but also in patient tissue and in *postmortem* brains. Lipid peroxidation in some of these diseases is induced by the general production of ROS (AD and PD), some of them due to the accumulation of high levels of transition metals (NBIA and FRDA) or inhibition of phospholipase activity (INAD–PLAG6). Considering this, lipid peroxidation intermediates are actively studied as a pathological marker for various diseases including most common neurodegenerative disorders, that is, AD and PD. This direction of research is potentially very promising and important considering all the difficulties in the early diagnosis of neurodegenerative disorders.

There is a general skepticism about antioxidant therapy for the treatment of neurodegenerative disorders because of a paradox: oxidative stress is shown to be involved in almost all pathologies and antioxidants are very effectively protective in cellular models of these diseases, but none of the antioxidants have shown to be effective in clinical trials. Lipid peroxidation is controlled by lipid-soluble antioxidants but there are several other mechanisms, which we described in this review, which potentially could be developed in therapeutic strategies in the treatment of neurodegenerative disorders and neurological diseases in general. Thus, nonantioxidant strategy with excessive lipid peroxidation by using PUFAs in a special diet, transition metal chelators, and activation of general antioxidant pathways via Nrf2 quench the excessive lipid peroxidation without issues typical to the application of antioxidants. We also discuss here the role of polyphenols and some other natural compounds isolated from various plants or animals, which can be effective in the reduction of lipid peroxidation and oxidative stress in general.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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