7

PATHOGENESIS OF NEURODEGENERATIVE DISEASES: CONTRIBUTION OF OXIDATIVE STRESS AND NEUROINFLAMMATION

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7.1 INTRODUCTION

Neurodegenerative diseases are characterized by slow death of specific neuronal populations and synapses in brain and spinal cord. In neurodegenerative diseases, the degenerating neuronal population modulates thinking, skilled movements, decision making, cognition, and memory [1, 2]. These diseases are characterized by chronic cellular processes that lead to cumulative insults to the nervous system. Neurodegenerative diseases include Alzheimer disease (AD), Parkinson disease (PD), Huntington disease (HD), amyotrophic lateral sclerosis (ALS), and prion diseases. In AD, neurodegeneration mainly occurs in the nucleus basalis. In PD, neuronal demise takes place in the substantia nigra. Neurodegeneration of striatal medium spiny neurons contributes to the pathogenesis of HD, and ALS is characterized by the death of motor neurons in the brain and spinal cord. Although it is not clear when the neurodegenerative process actually starts and how long it takes for neuropathological symptoms to appear, it is becoming increasingly evident that old age, positive family history, unhealthy lifestyle, and exposure to toxic environment may contribute to the pathogenesis of neurodegenerative diseases (Fig. 7.1) [3–5]. As stated above, most neurodegenerative diseases are accompanied by the premature and slow death of specific neuronal populations, increase in oxidative stress, and neuroinflammation. These processes contribute to the modulation of brain function through not only alterations in levels of phospholipid, sphingolipid, and cholesterol-derived lipid mediators but also accumulation of misfolded and aggregated proteins, which threaten neuronal viability [6]. Despite the important differences in clinical manifestation and progressive cell loss of specific neuronal populations in a specific region, neurodegenerative diseases share some common features, such as excitotoxicity, synaptic dysfunction, and the accumulation of intracellular or extracellular cerebral deposits of misfolded protein aggregates with a β-sheet conformation, such as β-amyloid (Aβ) in AD, α-synuclein in PD, huntingtin in HD, and mutation in Cu/Zn-superoxide dismutase (SOD) in ALS (Table 7.1) [6]. In addition to the above alterations, neurodegenerative diseases also share some terminal neurochemical common processes including excitotoxicity, oxidative stress, and inflammation [7]. It remains controversial whether these processes are the cause or the consequence of a neurodegenerative process [8, 9]. The onset of neurodegenerative diseases is often subtle and usually occurs in middle to late life, and their progression depends not only on genetic but also on environmental factors [1]. Although a number of indices of oxidative stress and neuroinflammation such as protein oxidation and nitrosylation, lipid peroxidation, DNA oxidation, and 3-nitrotyrosine formation as well as diminished levels of antioxidants such as SOD

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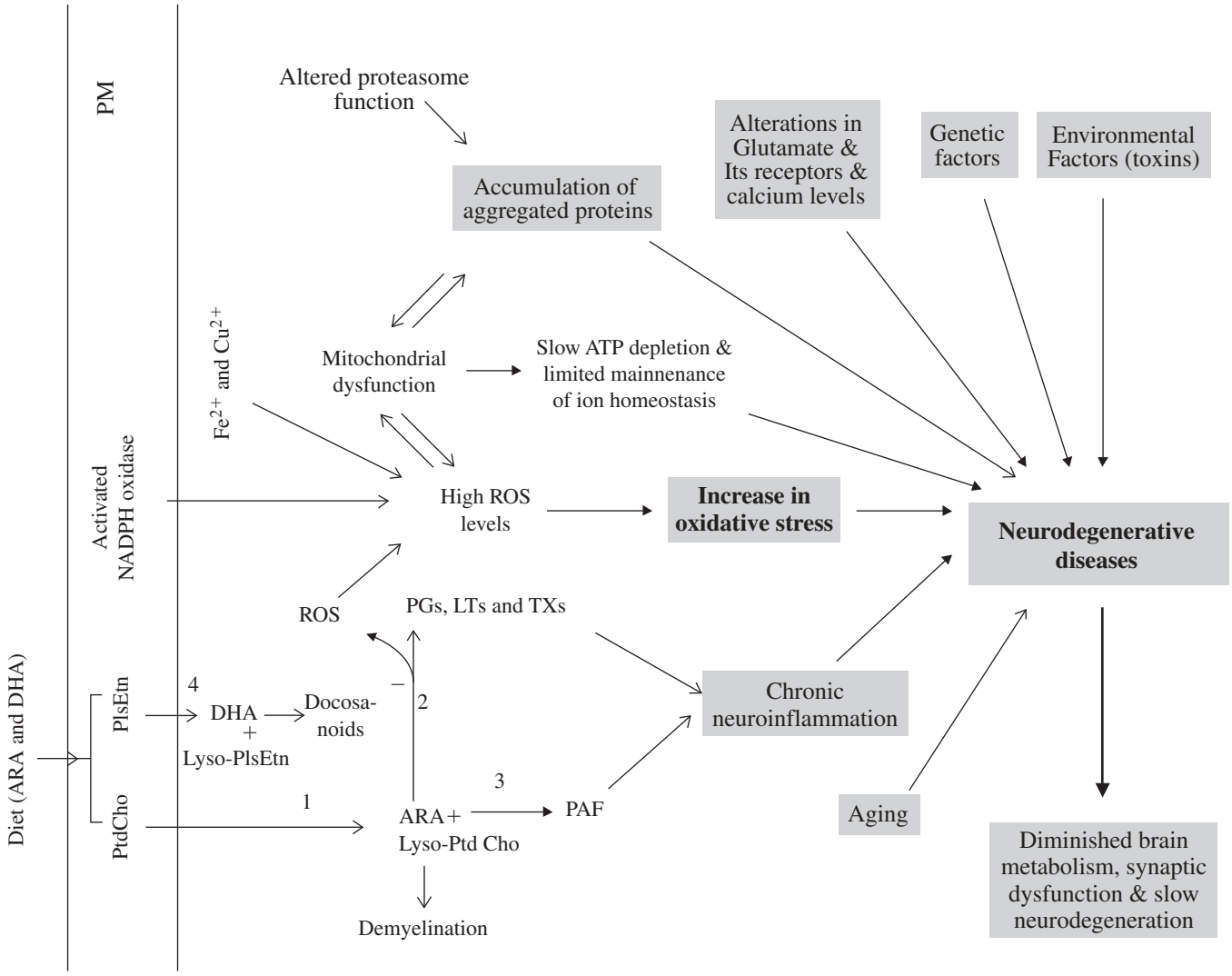

Fig. 7.1 Factors modulating neurodegenerative diseases: cytosolic phospholipase A_2 (1); cyclooxygenases and lipoxygenases (2); acetyltransferase (3); plasmalogen-selective phospholipase A_2 (4). ARA, arachidonic acid; DHA, docosahexaenoic acid; PtdCho, ARA-containing phosphatidylcholine; PlsEtn, DHA-containing ethanolamine plasmalogen; lyso-PtdCho, lyso-phosphatidylcholine; lyso-PlsEtn, lysoplasmalogen; ROS, reactive oxygen species; PGs, prostaglandins; LTs, leukotrienes; TXs, thromboxanes; PAF, platelet-activating factor. DHA-derived docosanoids inhibit the generation of eicosanoids (PGs, LTs, and TXs).

and increased expression of proinflammatory cytokines have also been reported to occur in neurodegenerative diseases [6, 10], very little information is available on timing, selective cellular vulnerability, and progression of neurodegenerative diseases.

7.2 OXIDATIVE AND NITROSATIVE STRESS IN NEURODEGENERATIVE DISEASES

Oxidative stress is defined as a cytotoxic process that occurs in the cell when antioxidant mechanisms are overwhelmed by reactive oxygen species (ROS), which are atoms or molecules possessing one or more unpaired electrons in the outer orbit and therefore prone to react chemically [11]. Thus oxidative stress is characterized by a major increase in the amount of oxidized cellular components. ROS include superoxide anions ($O_2^{\bullet -}$), hydroxyl ($^{\bullet}OH$), alkoxyl ($RO^{\bullet -}$), and peroxyl radicals ($ROO^{\bullet}$), and hydrogen peroxide (H_2O_2). The major sources of ROS include the mitochondrial respiratory chain, xanthine oxidase, myeloperoxidase in cytoplasm, oxidation of arachidonic acid (ARA) by cyclooxygenase (COX), lipoxygenase (LOX), and epoxygenase (EPOX) in cytoplasm, and NADPH oxidase in plasma membranes. NADPH oxidase generates superoxide radical by the one-electron reduction of oxygen, using NADPH as the electron donor. In neurons and neuroblastoma cells,

TABLE 7.1 Status and levels of lipid mediators, excitotoxicity, oxidative stress, and neuroinflammation in neurodegenerative diseases

Parameter	AD	PD	HD	ALSALS
Neurodegeneration site	Nucleus basalis and hippocampus	Substantia nigra	Striatum	Motor neurons in anterior spinal cord
Glu/Glu receptor levels	Altered	Altered	Altered	Altered
Ca^{2+} levels	Increased	Increased	Increased	Increased
Cytokine expression	Increased	Increased	Increased	Increased
Oxidative stress	Increased	Increased	Increased	Increased
Neuroinflammation	Increased	Increased	Increased	Increased
Aggregated protein accumulation	Aβ levels increased	α-Synuclein	Huntingtin increased	Cu^{2+}/Zn^{2+} SOD increased
Mitochondrial function	Abnormal	Abnormal	Abnormal	Abnormal
4-HNE	Increased	Increased	Increased	Increased
Isoprostanes	Increased	Increased	Increased	Increased
Ceramide	Increased	Increased	Increased	Increased
Hydroxycholesterols	Increased	Increased	Increased	Increased
Apoptosis	Increased	Increased	Increased	Increased
BBB permeability	Abnormal	Abnormal	Abnormal	Abnormal

Information adapted from references [4, 6, 30, 72]

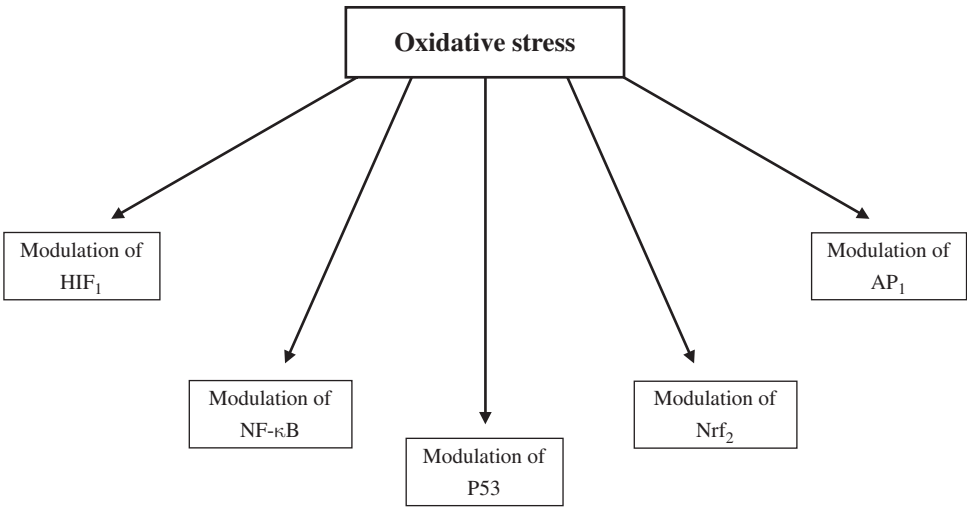

Fig. 7.2 Modulation of transcription factors by oxidative stress.

NADPH oxidase-mediated ROS synthesis is implicated in redox signaling mechanisms, which are modulated by the aging process in brain [12, 13]. The ability of NADPH oxidase inhibitors to ameliorate ROS-mediated cytotoxicity provides strong support for the role of this enzyme in regulation of neuronal excitatory activity. In the presence of metal ions, such as Fe^{2+} and Cu^{2+}, H_2O_2 is also transformed into hydroxyl radical ($^{\bullet}OH$) through the Fenton reaction. Hydroxyl radicals can attack polyunsaturated fatty acids in neural membrane phospholipids, forming the peroxyl radical ($ROO^{\bullet}$), and then propagate the chain reaction of lipid peroxidation. ROS production plays an important role in cell signaling. During normal aerobic metabolism, ROS generation is kept under tight control through the activities of antioxidant defense systems. The disruption of this tight control by high ROS levels results in oxidative stress. Low levels of ROS are needed for fundamental cellular functions, such as growth and adaptation responses. Specifically, ROS are implicated in mitogen-activated protein kinase (MAPK) pathways, which induce activation of various nuclear transcription factors, such as nuclear factor (NF)-κB, activator protein-1 (AP-1), hypoxia-inducible factor (HIF)-1α, and sterol regulatory element binding proteins (SREBPs) [14] (Fig. 7.2). These transcription factors occur in cytoplasm. Generation of high ROS in neural

cells facilitates their translocation from cytoplasm to the nucleus, where they facilitate the expression of proinflammatory enzymes, cytokines, chemokines, growth factors, cell cycle regulatory molecules, adhesion molecules, and antiinflammatory molecules (Fig. 7.3). NF-κB is associated with initiation and orchestration of inflammatory pathways through the production of TNF-α, IL-1β, and adhesion molecules. AP-1 is involved in increased expression of adhesion molecules and inflammatory cytokines. HIF-1α activates a broad range of genes protecting cells against hypoxia. Induction of HIF-1α during oxidative stress represents the response of neurons suffering from hypoxic/ischemic insult. In addition, HIF-1α binds to p53 and also activates the expression of various genes including Bax (a proapoptotic member of the Bcl-2 family) [15]. Bax inactivates Bcl-2 by forming a heterodimer. The balance between levels of bcl-2 and bax can serve as an indicator of cell survival or death [16]. The transcription factor NF-(erythroid-derived 2)-related factor (Nrf2) is associated with regulation of basal and inducible expression of numerous antioxidant stress genes and plays an important role in neuroprotection against oxidative stress in many animal models of neurodegenerative diseases.

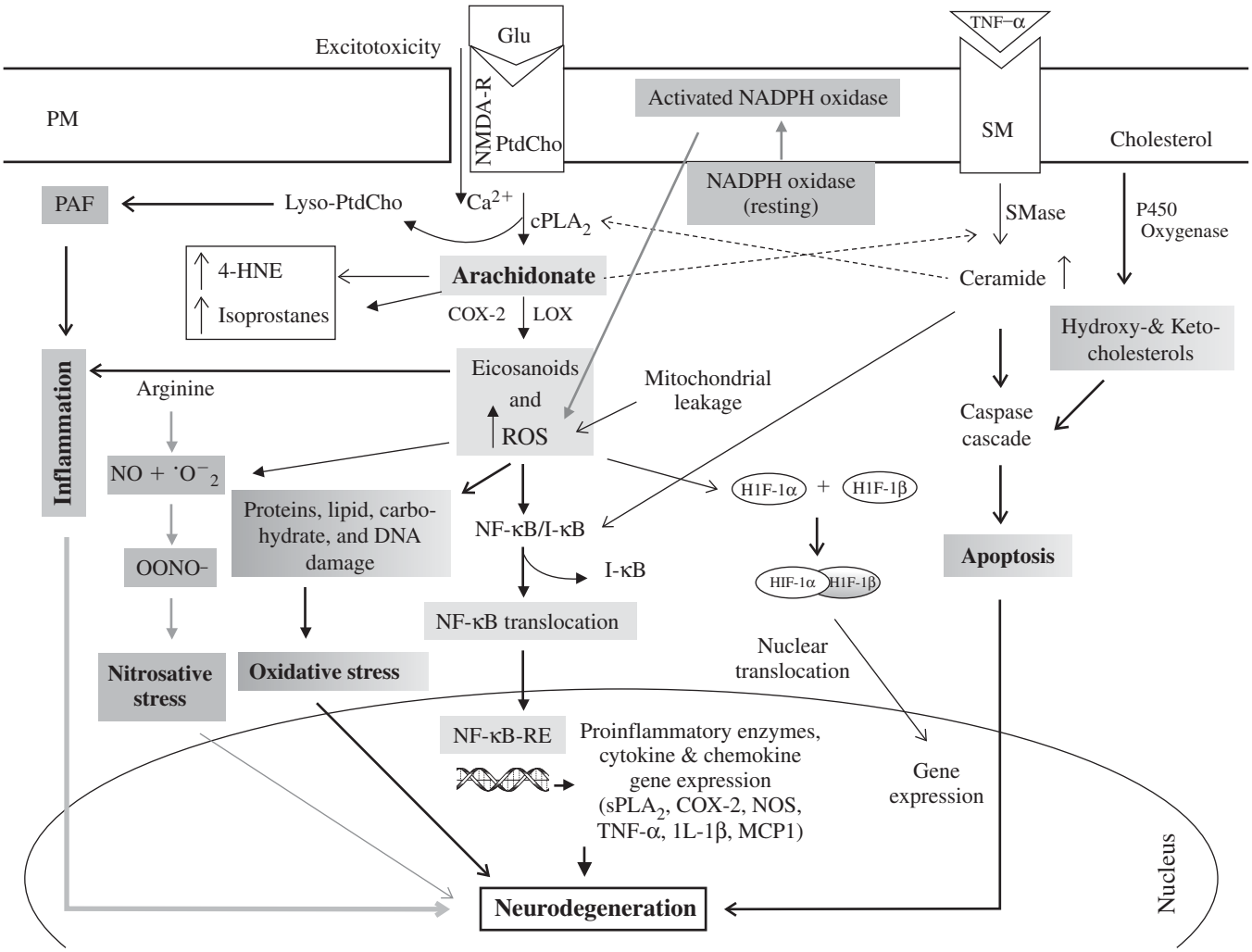

Fig. 7.3 Generation of lipid mediators and interactions between excitotoxicity, oxidative stress, and neuroinflammation in neurodegenerative diseases. $cPLA_2$, cytosolic phospholipase A_2; $sPLA_2$, secretory phospholipase A_2; COX-2, cyclooxygenase-2, LOX, lipoxygenase; NOS, nitric oxide synthase; SMase, sphingomyelinase; TNF-α, tumor necrosis factor-α; IL-1β, interleukin 1β; lyso-PtdCho, lyso-phosphatidylcholine; ROS, reactive oxygen species; HIF-1, hypoxia-inducible factor-1; 4-HNE, 4-hydroxynonenal; NO, nitric oxide; $OONO^-$, peroxynitrite; PAF, platelet-activating factor. Activation of NF-κB by ROS leads to its translocation to the nucleus, where it facilitates the transcription of proinflammatory enzymes ($sPLA_2$, COX-2, NOS, and SOD) and proinflammatory cytokines (TNF-α and IL-1β). These cytokines upregulate activities of $cPLA_2$ and $sPLA_2$ through a positive loop mechanism in cytoplasm and neural membranes. Furthermore, 4-HNE and isoprostanes promote neurodegeneration. Red arrows indicate increase in levels of metabolites. *(See color insert.)*

In neurodegenerative diseases enhanced ROS levels contribute to neuronal membrane damage not only by attacking neural cell membrane components (polyunsaturated fatty acids, sulfhydryl groups of proteins, bases of nucleic acids, and carbohydrates), but also by altering activities of various transcription factors (NF-κB, AP-1, HIF-1, and Nrf2). It is important to stress that ROS-mediated damage to the above neural membrane components is cumulative and not amenable to repair, particularly in postmitotic cells such as neurons. Reactions between ROS and cellular components can alter cell membrane properties such as fluidity, ion transport, loss of enzyme activity, protein cross-linking, inhibition of protein synthesis, and DNA damage eventually leading to neural cell apoptosis, a type of cell death that commonly occurs in neurodegenerative disease [6]. In addition, oxidative damage to mitochondrial DNA (mtDNA) not only leads to mutation but also triggers proapoptotic protein release from mitochondria into the cytoplasm, further contributing to impairment of cell viability.

In neurodegenerative diseases, excessive generation of nitric oxide (NO) due to the overactivation of NMDA receptor in neurons (excitotoxicity) [17] or induction of nitric oxide synthase (NOS) in the neighboring glia (microglial cells and astrocytes) results in generation of NO. The covalent reaction between NO and thiol groups of specific protein is called *S*-nitrosylation. Nitrosylation modifies function of many proteins by altering the hydrophobicity, hydrogen bonding, and electrostatic properties within the targeted protein. *S*-nitrosylation also contributes to protein misfolding of many proteins including redox-sensitive enzyme, disulfide isomerase, and dynamin-related protein 1 (SNO-Drp1) [18–20] in the endoplasmic reticulum, promoting neurodegeneration [21]. Nitrosylation of perkin, which is catalyzed by E3 ubiquitin ligase, may promote the pathogenesis of PD. Inhibition of nitrosylation produces neuroprotective effects [19, 21, 22].

Brain tissue from AD, PD, and ALS contains many nitrated proteins [23–27]. Recent studies using proteomics in brain from mild cognitive impairment subjects and AD patients indicate that many other proteins like peroxiredoxin 2, triose phosphate isomerase, glutamate dehydrogenase, neuropolypeptide h3, phosphoglycerate mutase1, H^+-transporting ATPase, α-enolase, and fructose-1,6-bisphosphate aldolase are also covalently modified through nitration [28]. In addition, interaction between NO and superoxide anion leads to the formation of the powerful oxidant species peroxynitrite ($ONOO^-$). The activation of NAD^+-consuming enzyme poly(ADP-ribose) polymerase-1 (PARP-1) is another likely mechanism for NO-mediated energy failure and neurotoxicity [29, 30]. NO also binds to cytochrome *c* oxidase and is able to inhibit cell respiration in a process that is reversible and in competition with oxygen. This action leads to the release of more superoxide anion from the mitochondrial respiratory chain.

In neural membranes, the hydrophobic environment maximizes the formation of reactive nitrogen species (RNS) [31, 32]. In addition to proteins, RNS react with unsaturated fatty acids (e.g., oleic acid) generating nitrooleic acid, a highly reactive electrophilic compound that can modulate a variety of cellular targets, including thiol residues and peroxisome proliferator-activated receptor (PPAR)γ [33–35].

Unlike 4-hydroxynonenal (4HNE), which is generated from the peroxidation of free arachidonic acid [36], nitrooleic acid remains esterified in the neural membrane phospholipids [37]. It is proposed that esterified nitrated fatty acids represent a sink of bioactive mediators, which are produced during nitrative stress leading to cellular dysfunction after release from the membrane by phospholipase A_2 [34]. Free nitrooleic acid is a stimulator of somatosensory and visceral nociceptors. It acts through the selective and direct activation of transient receptor potential cation channel, subfamily A1 (TRPA1) channels in a concentration-dependent manner [32]. Although the role of nitrooleic acid in neurodegenerative diseases is not fully understood, several studies indicate that 9- and 10-nitro-9-*cis*-octadecenoic acid is a potent ligand for PPARs at physiological concentrations [32, 37]. PPARγ agonists prevent Aβ neurotoxicity in hippocampal neurons. In addition, based on concentration-response analysis in both neurons and hTRPA1-HEK cells, it is suggested that nitrooleic acid is the most potent endogenous TRPA1 agonist. Emerging evidence suggests that nitrated fatty acids comprise a class of NO-derived, receptor-dependent, cell signaling mediators that act within physiological concentration ranges. Their levels are increased in neurodegenerative diseases, which are accompanied not only by a higher degree of ROS and NO production but also by diminished functions of mitochondria, endoplasmic reticulum, and the proteasome system, which are responsible for the maintenance of the normal protein homeostasis of neural cells [29, 30, 38].

7.2.1 Oxidative Stress-Mediated Damage to Neural Membrane Components in Neurodegenerative Diseases

It is well known that neural membranes are composed of phospholipids, sphingolipids, cholesterol, and proteins [6]. Arachidonic acid (ARA) and docosahexaenoic acid (DHA) are major polyunsaturated fatty acids found in neural membrane glycerophospholipids. Under normal conditions, isoforms of phospholipase A_2 (PLA_2) liberate ARA and DHA. Small amounts of ARA and DHA are

oxidized to eicosanoids (prostaglandins, leukotrienes, thromboxanes, and lipoxins) [39] and docosanoids (resolvins, neuroprotectins, and maresins) (Fig. 7.4) [40–42], respectively, by cyclooxygenases (COXs) and lipoxygenases (LOXs), whereas the majority of ARA and DHA are reincorporated into neural membrane phospholipids [39, 43].

Lysophosphatidylcholine (lyso-PtdCho), the other product of PLA_2-catalyzed reaction, is converted into platelet-activating factor (PAF), another proinflammatory lipid mediator. In neurodegenerative diseases, stimulation of PLA_2 isoforms (Table 7.1) and accumulation of ARA not only lead to the uncoupling of oxidative phosphorylation, resulting in mitochondrial dysfunction [4], but also trigger an uncontrolled "arachidonic acid cascade." This sets the stage for increased production of ROS that enhance oxidative stress [6]. Furthermore, nonenzymic peroxidation of ARA and DHA produces 4-HNE and 4-hydroxyhexenal (4-HHE), respectively. 4-HNE is a nine-carbon α, β-unsaturated aldehyde (Fig. 7.5), which is one of the major end products of ARA peroxidation and an important mediator of neural cell damage because of its ability to covalently modify proteins, which are important cellular functions [30, 44, 45]; 4-HNE reacts with lysine, cysteine, and histidine residues in proteins [44]. The C3 position of 4-HNE is a highly reactive site that undergoes a Michael addition reaction with cellular thiols and hence readily forms adducts with glutathione or proteins containing thiol groups.4-HNE not only inhibits key membrane proteins including glucose transporter, glutamate transporter, and sodium, potassium ATPases [45–49], but also inhibits rat brain mitochondrial respiration, blocks neurite outgrowth, disrupts neuronal microtubules, and modifies cellular tubulin, which may contribute to the cytoskeletal changes in neurons undergoing a neurodegenerative process [50, 51]. Collective evidence suggests that 4-HNE triggers multiple signaling cascades that variably affect cell growth, differentiation, and apoptosis [52]. 4-HNE inhibits DNA and RNA synthesis. Nonenzymic oxidation of DHA generates 4-HHE (Fig. 7.5). Like 4-HNE, 4-HHE reacts readily with nucleophiles such as thiols and amines, while the carbonyl group forms Schiff bases with amino groups such as the N-termini of proteins and the ε-amino group of lysine. 4-HHE binds to proteins. These carbonyl derivatives are potential markers of oxidative stress [30, 53].

In neurodegenerative diseases nonenzymic oxidation of esterified ARA also results in the generation of isoprostanes, which are prostaglandin-like mediators (Fig. 7.5) [54, 55]. The molecular mechanism of F_2-isoprostanes involves the formation of positional

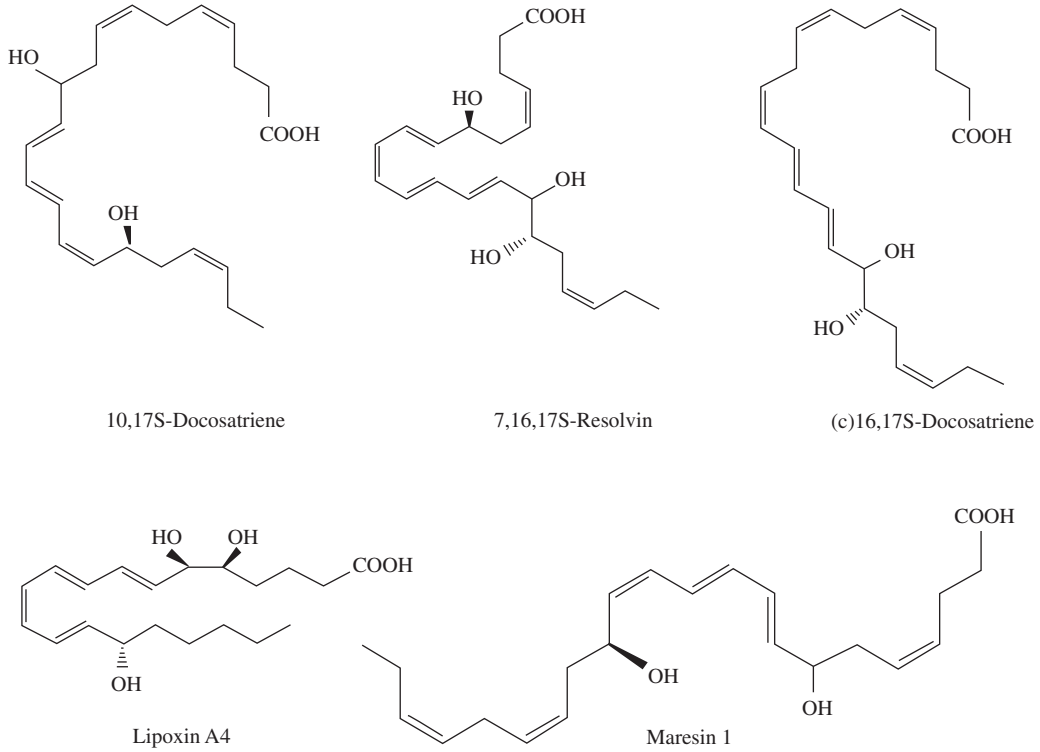

Fig. 7.4 Chemical structures of DHA-derived lipid mediators: 10,17S-docosatriene; 7,16,17S-resolvin; 16,17S-docosatriene; lipoxin A4 (this mediator is derived from ARA); and Maresin 1.

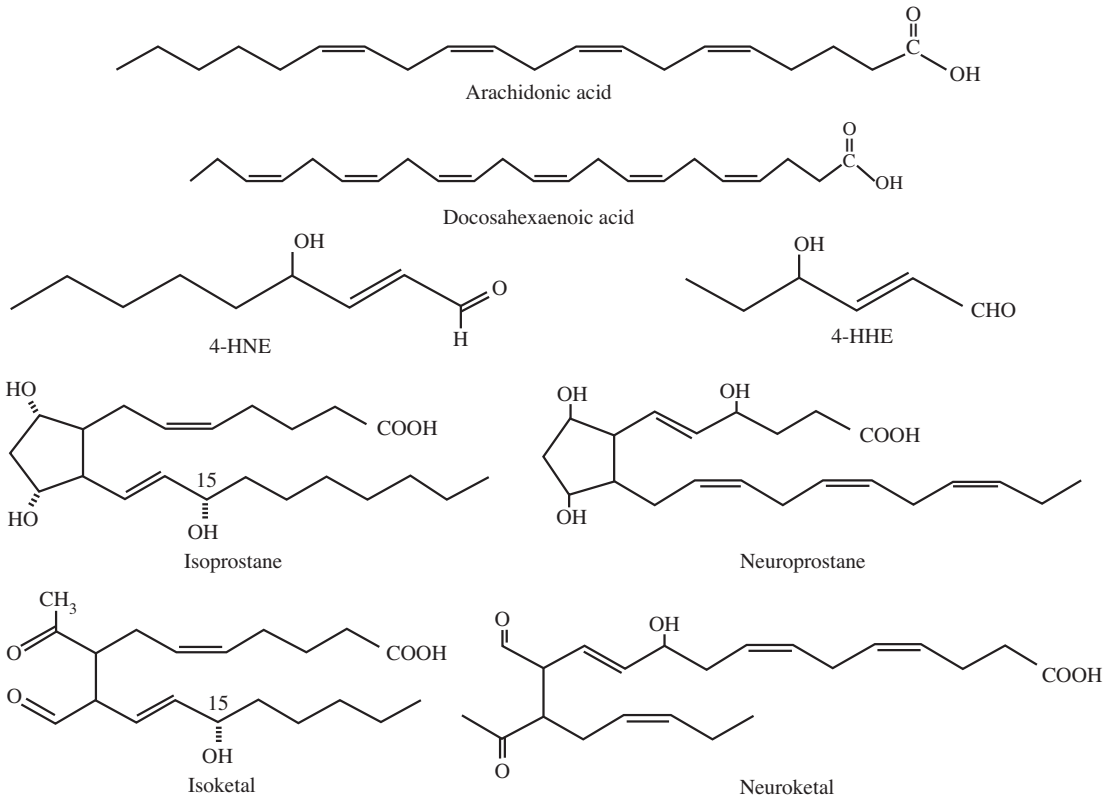

Fig. 7.5 Chemical structures of nonenzymic lipid mediators derived from ARA and DHA.

peroxyl radical isomers of ARA, which undergo endocyclization to form PGG_2-like compounds. These compounds are reduced to PGF_2-like compounds. F_2-isoprostane (F_2-IsoP) is subsequently released in free form by the action of PLA_2 [56–58]. F_2-IsoP modulates the p38 MAPK pathway during monocyte adhesion [59]. Isoprostane-mediated monocyte adhesion does not depend on VCAM-1 but involves protein kinases, such as protein kinase A and mitogen-activated protein kinase kinase 1. Thus F_2-IsoP not only affects vascular and bronchial smooth muscle function but also modulates cellular proliferation [57]. In addition to the above metabolites, nonenzymic oxidation of ARA produces isofurans and isoketals. Similarly, nonenzymic lipid mediators of DHA oxidation include neuroprostanes, neurofurans, and neuroketals. All these mediators are reliable indices of oxidative stress in vivo [6, 30, 52].

Ceramide and sphingomyelin are major components of lipid rafts in neural membranes. In neurodegenerative diseases, ceramide and ROS modulate intracellular ion channels, cell proliferation, and apoptotic cell death [52]. Ceramide triggers the generation of ROS and increases oxidative stress in many mammalian cells and animal models of neurodegenerative diseases [30, 38] (Fig. 7.3). Moreover, inhibition of ROS-generating enzymes or treatment of antioxidants impairs sphingomyelinase activation and generation of ceramide. Ceramide-enriched raft platforms are important redox signaling platforms that amplify activation of ROS-generating enzymes (e.g., NADPH oxidase family enzymes) and sphingomyelinases [52].

The brain is the richest source of cholesterol in the body. Most brain cholesterol is present in myelin sheets and in cellular membranes. The presence of cholesterol in neural membranes is necessary for optimal fluidity, neural plasticity, and synaptic transmission. The structure of cholesterol makes it susceptible to a variety of radical attacks because of the 5,6-double bond and the concomitant vinylic methylene group at C-7 in the B ring. In addition, at C-17, cholesterol has an isooctyl side chain, which undergoes enzymic oxidation largely by cytochrome *P*450-dependent oxygenases, but this site of oxidation is typically not a target for ROS relevant to cellular biochemistry [60, 61]. ROS-mediated oxidation of cholesterol results in formation of three major products, cholesta-4,6-dien-3-ol, cholesta-4,6-dien-3-one, and cholesta-3,5-dien-7-one. In brain cytochrome *P*450-dependent oxygenases transform cholesterol into 24-hydroxycholesterol, 25-hydroxycholesterol, and 27-hydroxycholesterol. Cholesterol is also oxidized to cholesterol oxides and converted into cholesterol ester via acyl-CoA:cholesterol acyltransferase [62, 63].

Transformation of cholesterol into 24-hydroxycholesterol, 25-hydroxycholesterol, and 27-hydroxycholesterol is an important mechanism for the excretion of cholesterol from the brain. It promotes the maintenance of brain cholesterol homeostasis [64, 65]. Hydroxycholesterols produce apoptotic cell death in the brain through the activation of caspases [63, 64]. It should be noted that metabolism of phospholipid, sphingolipid, and cholesterol are closely interrelated and interconnected. For example, glycerophospholipid-derived lipid mediators (ARA and PGs) regulate sphingolipid metabolism by modulating SMase activity, and sphingolipid-derived lipid mediators (ceramide, ceramide phosphate, and sphingosine) regulate phospholipid metabolism by stimulating PLA_2 activity [6, 66] (Fig. 7.3). Moreover, many cell stimuli modulate more than one enzyme at the same time; this adds complexity to the regulation of phospholipid, sphingolipid, and cholesterol metabolism. Under physiological conditions, homeostasis among phospholipid, sphingolipid, and cholesterol metabolism and activities of PLA_2, COX, LOX, SMase, and cytochrome *P*450 oxygenases are based not only on levels of lipid mediators and organization of signaling network but also on the complexity and interconnectedness of their metabolism. In neurodegenerative diseases, elevations in PLA_2, COX, LOX, SMase, and cytochrome *P*450 oxygenases and marked alterations in levels of lipid mediators disturb the signaling networks, resulting in loss of communication among glycerophospholipid, sphingolipid, and cholesterol metabolism. This process threatens the integrity of neural cell lipid homeostasis, resulting in neural cell death [6, 51, 66, 67].

7.3 INFLAMMATION AND NEURODEGENERATIVE DISEASES

Inflammation is a protective mechanism, which not only isolates injured brain cells from uninjured cells but also destroys injured neurons and initiates the repair of the extracellular matrix [67]. Although the main mediators of neuroinflammation are microglial cells, recent studies indicate that astrocytes, neurons, and oligodendrocytes also contribute to inflammatory response. In the normal healthy brain, resting microglial cells have a ramified morphology (a small cell soma and numerous branching processes) and are associated with monitoring their microenvironment in the brain. In neurodegenerative diseases, the resting microglia are activated and transformed into activated microglia, which are characterized by amoeboid morphology. Activated microglial cells migrate rapidly to the site where the neurodegenerative process is taking place. They not only engulf dead cells but also clear cellular debris. Thus activated microglial cells act as immunocompetent macrophage-like cells in the injured or infected brain. They not only mediate the innate defense system but also interact with cellular debris through scavenger receptors. These receptors bind to cellular debris, and microglial phagocytic receptors signal via immunoreceptor tyrosine-based activation motif-containing adaptor proteins that promote phagocytosis of extracellular material. Insufficient clearance by microglia appears to be prevalent in neurodegenerative diseases such as AD [68, 69]. Similarly, in neurodegenerative diseases astrocytes also undergo activation in the areas showing the accumulation of aggregated proteins and may release a variety of signaling molecules, such as cytokines, chemokines, and growth factors. They also show increased expression of glial fibrillary acidic protein, vimentin, and nestin [70]. Thus astrocytes provide homeostatic control of the extracellular environment of the neurons and respond to various stimuli such as disease and chemical or physical damage.

In neurodegenerative diseases, the chronic activation of microglia promotes neuronal damage through the release of glutamate, ROS, NO, proinflammatory cytokines, proteinases, and complement proteins [67, 71, 72], which can exert deleterious as well as beneficial effects on the surrounding tissue. These factors propagate and maintain neuroinflammation by a number of mechanisms, including the activation of multiple forms of PLA_2, COX, and LOX, generating PAF, and proinflammatory prostaglandins [39]. Thus at the molecular level in neurodegenerative diseases, inflammation is accompanied by the activation of isoforms of PLA_2, COX, LOX, SMases, and cholesterol hydroxylases, increase in expression of proinflammatory cytokines (TNF-α, IL-1β, and IL-6) and chemokines, and production and accumulation of prostaglandins, leukotrienes, thromboxanes, ceramides, and hydroxyl- and ketocholesterols. Some prostaglandins and leukotrienes produce proinflammatory effects by interacting with their receptors, whereas others (prostaglandin J_2 and lipoxins) cause anti-inflammatory and antiapoptotic effects in the brain [30, 52]. Emerging evidence suggests that activated microglia and astrocytes take part in neuroinflammation, which is different from nonneural (peripheral) inflammation due to the involvement of a complex network of neural cells, signaling molecules, and lipid mediators that occur within the brain. As mentioned above, neuroinflammatory responses include microglial and astroglial cell proliferation and migration of microglia and astrocytes toward the site where aggregated proteins are accumulating and the release of cytotoxic and inflammatory mediators (cytokines and chemokines, advanced glycation end products; Fc fragment of antibodies, and other complement factors) [10, 30, 38, 66, 67, 73, 74].

PAF (1-*O*-alkyl-2-acetyl-*sn*-glycerophosphocholine), another potent proinflammatory mediator, is synthesized from a specific subclass of PtdCho that contains an ether bond at the sn-1 position of the glycerol backbone during oxidative stress [75–77]. PAF exerts its neurochemical effects by activating the PAF receptors on neural cell surfaces [75, 77]. Stimulation of PAF receptors promotes transcriptional activation of a number of genes including immediate-early genes including c-fos, c-jun, and krox-24, cytokines, enzymes such as cyclooxygenase-2, and growth factors [78, 79]. The activation of these genes by PAF can be blocked by the PAF antagonist BN 52021 [80]. Excessive levels of PAF have been implicated in inflammatory syndrome, epileptic seizures, bacterial meningitis, multiple sclerosis, prion diseases, Miller–Dieker lissencephaly, and HIV replication associated with AIDS dementia complex [77, 81]. PAF has also been implicated in the neuronal damage in AD. Although the mechanisms linking neural cell injury to PAF levels are fully understood, the activation of PAF receptors is accompanied by the mobilization of calcium through calcium channels and from intracellular stores and enhanced turnover of PtdCho, PlsEtn, and PtdIns [82] via the activation of phospholipases and generation of ROS through the oxidation of ARA. These ROS interact with NF-κB/IκB complex in the cytoplasm [30, 67, 83]. Upon stimulation IκB is rapidly phosphorylated, ubiquinated, and then degraded by proteasomes, resulting in the release and subsequent nuclear translocation of active NF-κB [84]. In the nucleus, NF-κB mediates the transcription of many genes implicated in inflammatory and immune responses (Fig. 7.3). These genes include COX-2, intracellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), E-selectin, TNF-α, IL-1β, IL-6, $sPLA_2$, inducible nitric oxide synthase (iNOS), and matrix metalloproteinases (MMPs). Expression of these proteins may promote neuronal growth cone collapse and neurodegeneration in neurological disorders [77, 85].

At the molecular level, neuroinflammation includes two phases. One phase is associated with the generation of proinflammatory lipid mediators such as eicosanoids and platelet-activating factor, and the other phase is called resolution of inflammation, a turning off mechanism by which neural cells limit tissue injury [66, 86]. Resolution involves the synthesis of proresolving and anti-inflammatory eicosanoids. The molecular mechanism of resolution remains elusive [87]. However, lipoxins [88], PGD_2 and PGJ_2 [89], and docosanoids (resolvins, neuroprotectins, and maresins) [40, 41, 86] (Fig. 7.4) have been reported to play an important role during resolution. Resolvins, neuroprotectins, and lipoxins are potent anti-inflammatory and proresolving molecules that act through specific G protein-coupled receptors, which suppress the expression of proinflammatory cytokines. In addition, studies on the effect of nitrooleic acid on cultured dorsal root ganglion (DRG) neurons indicate that this lipid mediator is present in normal and inflamed mammalian tissues at up to micromolar concentrations and exhibits anti-inflammatory signaling actions [90].

Emerging evidence suggests that neuroinflammation includes not only long-standing activation of glial cells (microglia and astrocytes) and subsequent sustained release of the above-mentioned inflammatory mediators but also elevation in oxidative and nitrosative stress [91]. The sustained release of inflammatory mediators is required for the neuroinflammatory cycle, activating additional microglia and promoting their proliferation, which promotes the further release of inflammatory factors. Sustained nature of the neuroinflammation often facilitates abnormalities in the blood-brain barrier (BBB), which increases infiltration of peripheral macrophages into the brain parenchyma to further intensify the neuroinflammation [92, 93]. The duration and intensity of neuroinflammatory response dictate whether neuroinflammation is detrimental or beneficial.

7.4 SIGNIFICANCE OF INTERPLAY AMONG EXCITOTOXICITY, OXIDATIVE STRESS, AND NEUROINFLAMMATION

It is well known that intensity of excitotoxicity, oxidative stress, and neuroinflammation are significantly increased in normal aged brain compared to adult brain [67]. The onset of many neurodegenerative diseases is associated not only with increased intensity but prolonged duration of interactions among excitotoxicity, oxidative stress, and neuroinflammation [4, 94]. Initially, the coordinated and controlled interplay among excitotoxicity, oxidative stress, and neuroinflammation in normal aged human brain may cause some abnormalities in motor and cognitive performance, but in neurodegenerative diseases an enhanced rate of interplay among excitotoxicity, oxidative stress, and neuroinflammation may turn on specific genes that affect only a specific neuronal population in a particular region where neuronal degeneration occurs (Fig. 7.6) [94, 95]. This proposal is supported by the hypothesis that the nature of neuron-neuron connections as well as interactions between neurons and glial cells is essential for determining the selective neuronal vulnerability of neurons in neurodegenerative diseases [66, 67, 96]. This interplay may be a common mechanism of brain damage in neurotraumatic diseases (stroke, spinal cord injury, and traumatic head injury) as well as neurodegenerative diseases such as AD, PD, HD, and ALS [6, 7]. In neurotraumatic diseases,

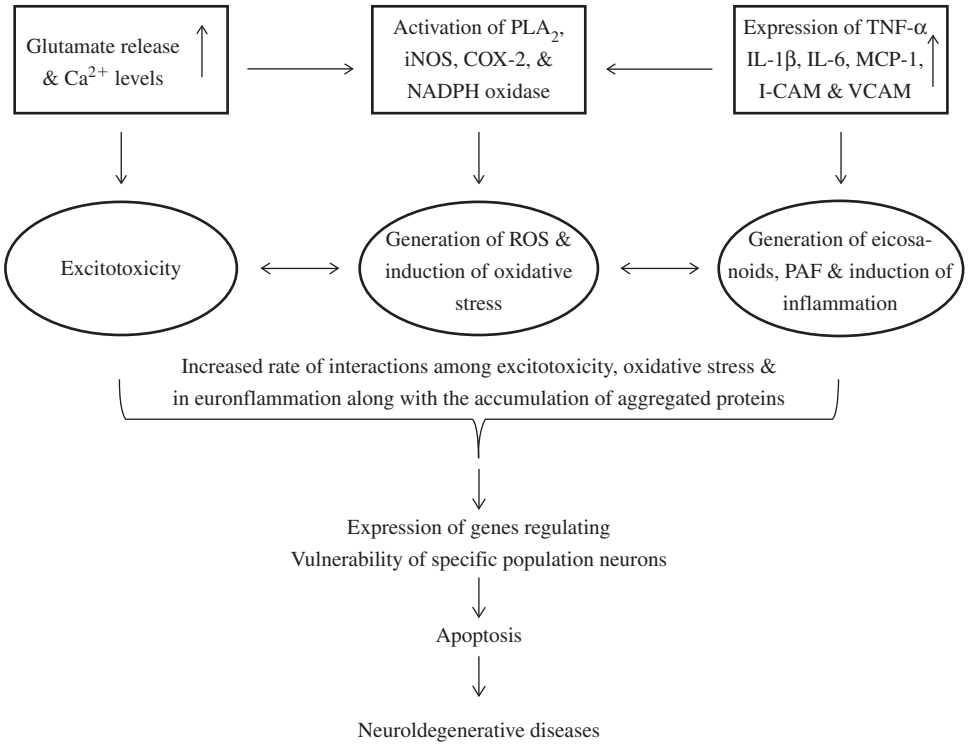

Fig. 7.6 Interactions among excitotoxicity, oxidative stress, and neuroinflammation in neurodegenerative diseases.

neurons die rapidly (within hours to days) because of sudden lack of oxygen, reduction in ATP, and sudden collapse of ionic gradient along with an acute inflammatory response that is accompanied by increased production of cytokines, chemokines, acute-phase proteins, and complement factors. In contrast, in neurodegenerative diseases some oxygen, nutrients, and ATP are available to neurons, and ionic homeostasis is maintained to a limited extent. These processes, along with consistent and continuous chronic inflammatory response and oxidative stress, result in a neurodegenerative process that takes several years to develop. Little is known about the rate of neurodegeneration and clinical expression of neurodegenerative diseases with age. As stated above, neurodegenerative diseases commence late in life and are accompanied by the loss of specific neuronal populations, synapses, and accumulation of misfolded protein aggregates [2, 4, 30]. The chemical nature of the misfolded protein aggregate is different in each neurodegenerative disease. Furthermore, each neurodegenerative disease has a separate etiology with distinct morphological and pathophysiological characteristics. However, they share similar common terminal neurochemical processes such as excitotoxicity, oxidative stress, and inflammation [6, 7]. Importantly, increased intensity and prolonged duration of interplay among excitotoxicity, oxidative stress, and neuroinflammation impair neurogenesis, a process involved in the maturation of stem cells into new functional neurons, supporting the view that adult neurogenesis may be involved in regenerative attempts and the neuroplasticity of the nervous system [97]. In addition in neurodegenerative diseases, it is proposed that neurons increase their defenses by developing compensatory responses (oxidative strength) [98, 99] aimed to avoid or at least reduce cellular damage caused by the interplay among excitotoxicity, oxidative stress, and neuroinflammation. This hypothesis is supported by studies on Aβ deposition in AD. It is stated that Aβ may not be the initiator of AD pathogenesis, but rather a downstream protective adaptation mechanism developed by cells in response to coordinated and upregulated interplay among excitotoxicity, oxidative stress, and neuroinflammation [98–100]. A proposal on the neuroprotective role of Aβ explains why many aged individuals, despite having a high number of senile plaques in their brain, show little or no alteration in cognitive function. Accumulating evidence suggests that more studies are required on neurochemical aspects of neurodegenerative diseases in patients with neurodegenerative diseases.

7.5 CONCLUSION

ROS are generally generated in normal physiological conditions at low levels and are scavenged by endogenous antioxidants, such as superoxide dismutase,

glutathione peroxidase, catalase and small molecules such as vitamin C and E. Oxidative stress refers to the pathological states in which increased ROS production exceeds the antioxidant capacity of brain tissue to neutralize ROS. Although low levels of ROS are needed for normal neural cell function, high ROS levels damage neuronal plasma membrane and membranes of subcellular organelles directly (e.g., through peroxidation). ROS react with metals, nitrogen, or carbon to form intermediates that react with proteins (e.g., through nitration and nitrosylation). Oxidative stress also damages DNA or RNA, including mtDNA. Neuroinflammation is a neuroprotective process, in which the brain responds to infections, diseases, and injuries. Microglial cells play a major role in inducing and maintaining the intensity and duration of neuroinflammation through the release of glutamate, ROS, proinflammatory cytokines, and NO. Inhibition of microglial activation leads to the amelioration of neurodegeneration. It is becoming increasingly evident that increase in intensity and duration of interactions among excitotoxicity, oxidative stress and neuroinflammation, alterations in calcium homeostasis, mitochondrial and proteasomal dysfunction, and ROS-mediated protein aggregation play a crucial role in the development and progression of many neurodegenerative diseases.

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