Redox regulation of mitochondrial fission, protein misfolding, synaptic damage, and neuronal cell death: potential implications for Alzheimer's and Parkinson's diseases

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Abstract Normal mitochondrial dynamics consist of fission and fusion events giving rise to new mitochondria, a process termed mitochondrial biogenesis. However, several neurodegenerative disorders manifest aberrant mitochondrial dynamics, resulting in morphological abnormalities often associated with deficits in mitochondrial mobility and cell bioenergetics. Rarely, dysfunctional mitochondrial occur in a familial pattern due to genetic mutations, but much more commonly patients manifest sporadic forms of mitochondrial disability presumably related to a complex set of interactions of multiple genes (or their products) with environmental factors ($G \times E$). Recent studies have shown that generation of excessive nitric oxide (NO), in part due to generation of oligomers of amyloid-β (Aβ) protein or overactivity of the NMDA-subtype of glutamate receptor, can augment mitochondrial fission, leading to frank fragmentation of the mitochondria. *S*-Nitrosylation, a covalent redox reaction of NO with specific protein thiol groups, represents one mechanism contributing to NO-induced mitochondrial fragmentation, bioenergetic failure, synaptic damage, and eventually neuronal apoptosis. Here, we summarize our evidence in Alzheimer's disease (AD) patients and animal models showing that NO contributes to mitochondrial fragmentation via *S*-nitrosylation of dynamin-related protein 1 (Drp1), a protein involved in mitochondrial fission. These findings may provide a new target

for drug development in AD. Additionally, we review emerging evidence that redox reactions triggered by excessive levels of NO can contribute to protein misfolding, the hallmark of a number of neurodegenerative disorders, including AD and Parkinson's disease. For example, *S*-nitrosylation of parkin disrupts its E3 ubiquitin ligase activity, and thereby affects Lewy body formation and neuronal cell death.

Keywords *S*-Nitrosylation · Mitochondrial fragmentation · Dynamin-related protein 1 · β-Amyloid · Alzheimer's disease

Introduction

Brains with neurodegenerative diseases often manifest excessive generation of reactive nitrogen species (RNS) and reactive oxygen species (ROS), which can contribute to neuronal cell injury and death via a series of redox reactions [1–5]. While many intra- and extracellular molecules may participate in neuronal injury, accumulation of nitrosative stress due to excessive generation of nitric oxide (NO) appears to be a potential factor contributing to neuronal cell damage and death [6, 7]. A well-established model for NO production entails a central role of the *N*-methyl-D-aspartate (NMDA)-type glutamate receptors in nervous system. Excessive activation of NMDA receptors drives Ca^{2+} influx, which in turn activates neuronal NO synthase (nNOS) as well as the generation of ROS [8, 9]. Accumulating evidence suggests that NO can mediate both protective and neurotoxic effects by redox reactions with cysteine residues of target proteins to form *S*-nitrosothiols (SNOs), a process termed *S*-nitrosylation because of its effects on the chemical biology of protein function.

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Importantly, normal mitochondrial respiration may also generate free radicals, principally ROS, and one such molecule, superoxide anion (O_2^-), reacts rapidly with free radical NO to form the very toxic product peroxynitrite ($ONOO^-$) [10, 11].

Production of NO from inducible NOS (iNOS) can also contribute to the pathogenesis of neurodegenerative diseases, including Alzheimer's disease (AD) [12, 13]. A classic feature of AD pathology is the generation of β-amyloid ($A\beta$) peptides. Recently, several lines of evidence have suggested that soluble oligomers of $A\beta$ represent the most toxic form of the peptide [14]. Consistent with this notion, $A\beta$ oligomers, but not fibrillar $A\beta$, induce high expression of iNOS in astrocytes and thus generation of NO [15]. Additionally, $A\beta$ is known to inhibit glutamate re-uptake, at least in part via generation of ROS; this can lead to pathological activation of NMDA receptors, thereby disturbing synaptic function in AD [16–18]. Excessive stimulation of NMDA receptors also leads to activation of nNOS, as discussed above, thus representing another source of NO emanating from $A\beta$ oligomers.

Dysfunction in mitochondria represents another hallmark of neurodegenerative diseases. For example, patients with early stage AD regularly exhibit declining mitochondrial energy metabolism and ATP production, which may subsequently cause synaptic loss and neuronal damage [19–21]. Interestingly, neurons in AD and other neurodegenerative brains often display abnormal mitochondrial morphology [22, 23].

Normally, mitochondria are known to continuously undergo fission and fusion (known as mitochondrial dynamics) to generate smaller organelles or elongated, tubular structures, respectively. This normal mitochondrial fission and fusion can facilitate formation of new mitochondria (biogenesis), repair of defective mitochondrial DNA through mixing, and redistribution of mitochondria to sites requiring high-energy production [24–26]. Conversely, an imbalance in fission or fusion initiates malfunctions in mitochondrial morphology and bioenergetics, and may thus contribute to neuronal injury during neurodegeneration [26–28]. Dysfunction in mitochondrial dynamics can result from either (i) rare genetic mutations in fission- or fusion-related genes, as occurs in Charcot-Marie-Tooth (CMT) Disease and Autosomal Dominant Optic Atrophy (ADOA) [29, 30], or (ii) posttranslational changes to the fission or fusion proteins. In particular, a posttranslational modification engendered by nitrosative/oxidative stress may well account for the more common sporadic cases of the disease [31, 32]. Hence, a key theme of this article is the hypothesis that excessive accumulation of nitrosative stress contributes to abnormal mitochondrial morphology in brains of neurodegenerative patients. In this review, we discuss a specific example, showing that S-nitrosylation of the mitochondrial fission protein dynamin-related protein 1 (Drp1) contributes to excessive mitochondrial fission/fragmentation, synaptic injury, and neuronal apoptosis in neurodegenerative diseases such as AD. We also review evidence that S-nitrosylation of critical proteins can cause protein misfolding and contribute to the aggregation of aberrant proteins seen in many neurodegenerative disorders, including AD and Parkinson's disease (PD).

Mitochondrial fission/fusion machinery in nerve cells

Neurons are particularly vulnerable to mitochondrial defects because they require high levels of energy for their survival and specialized function. Mitochondrial biogenesis is required in regions that demand high concentrations of ATP, especially the synapse. The distribution of mitochondria at the nerve terminal can control synaptic transmission and structure [24, 33, 34].

In healthy neurons, the fission/fusion machinery proteins maintain mitochondrial integrity and insure their presence at critical locations. These proteins includes Drp1 and Fis1, acting as fission proteins, and Mitofusin (Mfn) and Opa1, operating as fusion proteins [35]. In both familial and sporadic neurodegenerative conditions, abnormal mitochondria regularly appear in the brain as a result of dysfunction in the fission/fusion machinery. Genetic mutations in Mfn2 can cause CMT disease, a hereditary peripheral neuropathy that affects both motor and sensory neurons [30, 36]. Mutations in Opa1 cause ADOA, characterized by the loss of retinal ganglion cells and the optic nerve, representing their axons [29]. Recently, Waterham et al. described a heterozygous, dominant-negative mutation of Drp1 in a patient whose symptoms were broadly similar to those of CMT neuropathy and ADOA [37]. Drp1 includes four distinct structural domains: an N-terminal GTPase domain, a dynamin-like middle domain, an insert B domain, and a C-terminal GED domain. The mutation (Ala 395 to Asp) was found in the middle domain of Drp1. This case study further suggested that a defect in mitochondrial fission may have more severe consequences than those of fusion defects, since the Drp1 mutation caused a much earlier onset (prenatal) and fatal outcome. Additionally, it is apparent that the balance between fission and fusion is critical for normal function of mitochondria and determination of phenotype in disease. These fission/fusion proteins are widely expressed in human tissues, clearly supporting the notion that neurons are particularly sensitive to mitochondrial dysfunction.

Dysregulation of mitochondrial dynamics in AD

An estimated 26 million people globally have AD, which is thought to be the most common form of dementia. In AD

brains, neuronal loss in the hippocampus and cerebral cortex mainly accounts for the cognitive decline. Degenerating AD brains contain aberrant accumulations of misfolded, aggregated proteins—Aβ and tau—which can adversely affect neuronal connectivity and plasticity, and trigger cell death signaling pathways. These aggregates are recognized as either intracellular neurofibrillary tangles, which contain hyperphosphorylated tau, or extracellular plaques, which contain Aβ. β-Secretase and γ-secretase proteolytically cleave amyloid precursor protein (APP) in its transmembrane region to generate Aβ. It is currently thought that soluble oligomers of misfolded protein are pathogenic and that the large aggregates may actually be an attempt by the cell to wall off the aberrant proteins (although such aggregates could potentially be toxic by location or if not contained by the proper chaperones). Interestingly, a recent study showed that an N-terminal fragment of APP may also contribute to neurodegeneration in AD models [38].

Emerging evidence suggests that mitochondrial dysfunction plays a prominent role in the pathogenesis of AD [39]. Analyses of autopsy and biopsy samples revealed that mitochondria isolated from AD brains exhibit diminished respiratory capacity [20], and that AD neurons contain a number of mitochondria with fractured cristae [40]. Additionally, electron-microscopic studies have described an increase in mitochondrial fragmentation in human AD brains [22, 23]. In cell-based experiments, Aβ production resulted in the appearance of fragmented and abnormally distributed mitochondria [27, 41], suggesting that Aβ (possibly in the form of soluble oligomers) may trigger excessive mitochondrial fission in AD patients. Pathological forms of tau may also contribute to mitochondrial fragmentation in AD brains since expression of caspase-cleaved tau induced mitochondrial fission in a calcineurin-dependent manner [42].

Similarly, dysfunction in mitochondrial integrity is associated with PD [43]. For instance, the Parkinsonian neurotoxins, rotenone and l-methyl-4-phenyl-pyridinium ion (MPP$^+$), which inhibit complex I of the mitochondrial electron transport chain, can induce excessive mitochondrial fragmentation and cell death [27]. Additionally, multiple groups recently observed that a deficiency in familial PD-related proteins, such as parkin and PINK1, led to the appearance of mitochondrial pathology [44–47]. Exogenous expression of mitochondrial fusion proteins, Mfn2 and OPA1, or dominant negative Drp1 rescued the altered mitochondrial morphology, suggesting that parkin or PINK1 deficiency promoted mitochondrial fragmentation [46]. Interestingly, Drp1 seems to activate autophagy/mitophagy pathways for morphologic remodeling of mitochondria in PINK1-deficient neuroblastoma cells [48]. Taken together, dysregulation of mitochondrial dynamics may contribute to a common pathway leading to the pathogenesis of several neurodegenerative diseases, including AD and PD.

NMDA receptor signaling pathways induce generation of RNS/ROS

The amino acid glutamate is the major excitatory neurotransmitter in the brain. Excitatory neurotransmission plays an important role in the normal development and plasticity of synapses, and for some forms of learning or memory; however, excessive activation of glutamate receptors is implicated in neuronal damage in many neurological disorders ranging from acute hypoxic-ischemic brain injury to chronic neurodegenerative diseases. Among several families of glutamate receptors, the NMDA receptor has long attracted attention because it has several properties that set it apart from the other receptors. One such characteristic is that NMDA receptor-coupled channels are highly permeable to Ca^{2+}, triggering Ca^{2+} entry after ligand binding if the cell is first depolarized in order to relieve channel block by Mg^{2+} [49, 50]. Subsequent binding of Ca^{2+} to various intracellular molecules can lead to many significant consequences. In particular, excessive activation of NMDA receptors leads to the production of damaging free radicals (e.g., NO and ROS) and other enzymatic processes, contributing to cell injury and death [6, 11, 51–54]. It is currently thought that overstimulation of extrasynaptic NMDA receptors mediates this neuronal damage, while, in contrast, synaptic activity predominantly activates survival pathways [55–57]. Intense hyperstimulation of excitatory receptors leads to necrotic cell death, but milder or chronic overstimulation can result in apoptotic or other forms of cell death [53, 54, 58]. Furthermore, Aβ oligomers induce neuronal synaptic damage via an NMDA receptor-dependent mechanism [59].

Excessive activation of glutamate receptors has been implicated in neuronal damage in many neurological disorders. John Olney coined the term "excitotoxicity" to describe this phenomenon [60, 61]. This form of toxicity is mediated at least in part by excessive activation of NMDA-type receptors [6, 7, 62], resulting in excessive Ca^{2+} influx through a receptor's associated ion channel. Increased levels of neuronal Ca^{2+}, in conjunction with the Ca^{2+}-binding protein CaM, trigger the activation of nNOS and subsequent generation of NO from the amino acid L-arginine [8, 63]. NO is a gaseous free radical (thus highly diffusible) and a key molecule that plays a vital role in normal signal transduction but in excess can lead to neuronal cell damage and death. The diversity of NO effects on neuronal survival can also be caused by the formation of different NO species or intermediates: NO radical (NO$^{.}$),

nitrosonium cation (NO$^+$), nitroxyl anion (NO$^-$, with high energy singlet and lower energy triplet forms) [11].

Nitrosative stress regulates protein misfolding and neuronal cell death

Early investigations indicated that NO participates in cellular signaling pathways, which regulate broad aspects of brain function, including synaptic plasticity, normal development, and neuronal cell death [51, 64–66]. In general, NO exerts physiological and some pathophysiological effects via stimulation of guanylate cyclase to form cyclic guanosine-3′,5′-monophosphate (cGMP) or through S-nitros(yl)ation of regulatory protein thiol groups [9, 11, 67–70]. S-Nitrosylation is the covalent redox reaction of an NO group with a critical cysteine thiol/sulfhydryl (RSH or, more properly, thiolate anion, RS$^-$) to form an S-nitroso-thiol derivative (R-SNO). Such modification modulates the function of a broad spectrum of mammalian, plant, and microbial proteins. In general, a consensus motif of amino acids comprised of nucleophilic residues (generally an acid and a base) surround a critical cysteine, which increases the cysteine sulfhydryl's susceptibility to S-nitrosylation [71, 72]. Our group first identified the physiological relevance of S-nitrosylation by showing that NO and related RNS exert paradoxical effects via redox-based mechanisms— NO is neuroprotective via S-nitrosylation of NMDA receptors (as well as other subsequently discovered targets, including caspases), and yet can also be neurodestructive by formation of peroxynitrite (or, as later discovered, reaction with additional molecules such as MMP-9, parkin, peroxiredoxin II, Drp1, protein-disulfide isomerase (PDI), and GAPDH) [11, 73–80]. Over the past decade, accumulating evidence has suggested that S-nitrosylation can regulate the biological activity of a great variety of proteins, in some ways akin to phosphorylation [11, 72, 79–92]. Chemically, NO is often a good "leaving group," facilitating further oxidation of critical thiols to disulfide bonds among neighboring (vicinal) cysteine residues or, via reaction with ROS, to sulfenic (−SOH), sulfinic (−SO$_2$H), or sulfonic (−SO$_3$H) acid derivatization of the protein [79, 82, 83, 93]. Alternatively, S-nitrosylation may possibly produce a nitroxyl disulfide, in which the NO group is shared by close or vincinal cysteine thiols [94].

In prior work, analyses of mice deficient in either nNOS or iNOS confirmed that NO is an important mediator of cell injury and death after excitotoxic stimulation; excessive NO generated from nNOS or iNOS is detrimental to neuronal survival [95, 96]. In addition, inhibition of NOS activity ameliorates the progression of disease pathology in animal models of AD, PD, and Amyotrophic Lateral Sclerosis, suggesting that excess generation of NO plays a pivotal role in the pathogenesis of several neurodegenerative diseases [97–100].

A common theme in many neurodegenerative disorders is the finding of abnormal aggregates of misfolded proteins. Recent findings have implied that NO-related species may significantly participate in the process of protein misfolding through protein S-nitrosylation under degenerative conditions. Specifically, we and others recently mounted physiological and chemical evidence that S-nitrosylation modulates the (i) ubiquitin E3 ligase activity of parkin [81, 82, 101], and (ii) chaperone and isomerase activities of PDI [83], contributing to protein misfolding and neurotoxicity in models of neurodegenerative disorders (Fig. 1). Mutations in the parkin gene can cause autosomal recessive juvenile Parkinsonism (ARJP), accounting for some cases of hereditary PD manifest in young patients with onset beginning anywhere from the teenage years through the 40s [102–104]. As an E3 ubiquitin ligase, parkin catalyzes formation of polyubiquitin chains on substrate proteins (e.g., synphilin-1 and Pael-R); these ubiquitin chains represent the signal for proteasomal degradation of the proteins. Clearance of misfolded or aberrant proteins requires, at least in part, the activity of the ubiquitin-proteasome system (UPS). We and others found evidence for S-nitrosylation of parkin (forming SNO-parkin) not only in rodent models of PD but also in the brains of human patients with PD and the related α-synucleinopathy, diffuse Lewy body disease (DLBD). SNO-parkin initially stimulates ubiquitin E3 ligase activity, resulting in enhanced ubiquitination as observed in Lewy bodies, followed by a decrease in enzyme activity, producing a futile cycle of dysfunctional UPS [82, 101, 105]. Moreover, S-nitrosylation appears to compromise the neuroprotective effect of parkin [81]. These mechanisms involve S-nitrosylation of critical cysteine residues in the first RING domain of parkin [82]. Nitrosative and oxidative stress can also alter the solubility of parkin via posttranslational modification of cysteine residues, which may concomitantly compromise its protective function [106–108].

During protein folding in the ER, PDI can introduce disulfide bonds into proteins (oxidation), break disulfide bonds (reduction), and catalyze thiol/disulfide exchange (isomerization), thus facilitating disulfide bond formation, rearrangement reactions, and structural stability [109]. In many neurodegenerative disorders as well as in cerebral ischemia, the accumulation of immature and denatured proteins results in ER dysfunction [110–113], and upregulation of PDI represents an adaptive response known as the unfolded protein response (UPR), which promotes protein refolding and may contribute to neuroprotection [111, 114–116]. In a recent study, we reported that the S-nitrosylation of PDI (to form SNO-PDI) disrupts this neuroprotective role [83]. We found that PDI is
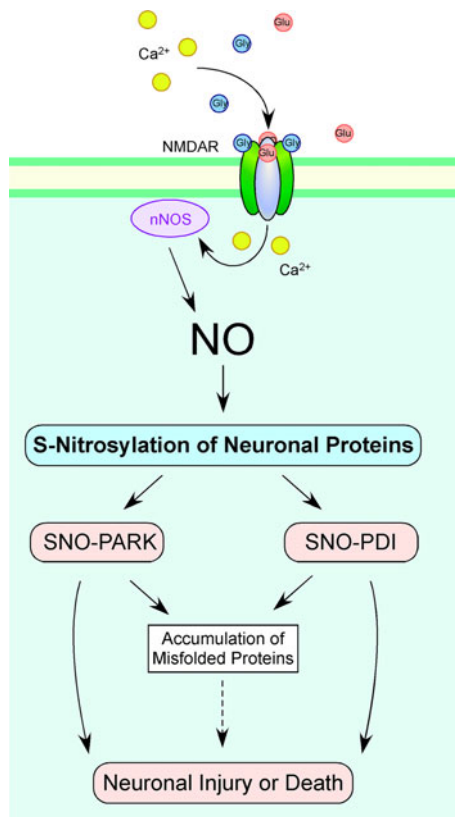
Fig. 1 Schema of *S*-nitrosylated species contributing to the accumulation of aberrant proteins and neuronal damage. NMDAR hyperactivation triggers generation of NO/ROS. *S*-Nitrosylation of parkin (forming SNO-PARK) and PDI (forming SNO-PDI) can contribute to neuronal cell injury in part by triggering accumulation of misfolded proteins

S-nitrosylated in the brains of virtually all cases examined of sporadic AD and PD. SNO-PDI formation led to the accumulation of polyubiquitinated/misfolded proteins and activation of the UPR. Moreover, *S*-nitrosylation abrogated the inhibitory effect of PDI on aggregation of proteins observed in Lewy body inclusions [83, 117]. *S*-Nitrosylation of PDI also prevented its attenuation of neuronal cell death triggered by ER stress, misfolded proteins, or proteasome inhibition.

Nitrosative stress can also result in defects in mitochondrial function. For example, NO affects mitochondrial respiration by reversibly inhibiting complexes I and IV [118, 119]. Mitochondria thus compromised will release ROS, and this in turn could contribute to brain aging and/or pathological conditions associated with neurodegenerative diseases. Additionally, increased nitrosative and oxidative stress can elicit dysfunction of mitochondrial dynamics (fission and fusion events) [27, 120, 121]. However, until recently little was known regarding the molecular and pathogenic mechanisms by which NO contributes to the formation of fragmented mitochondria. Our recent findings
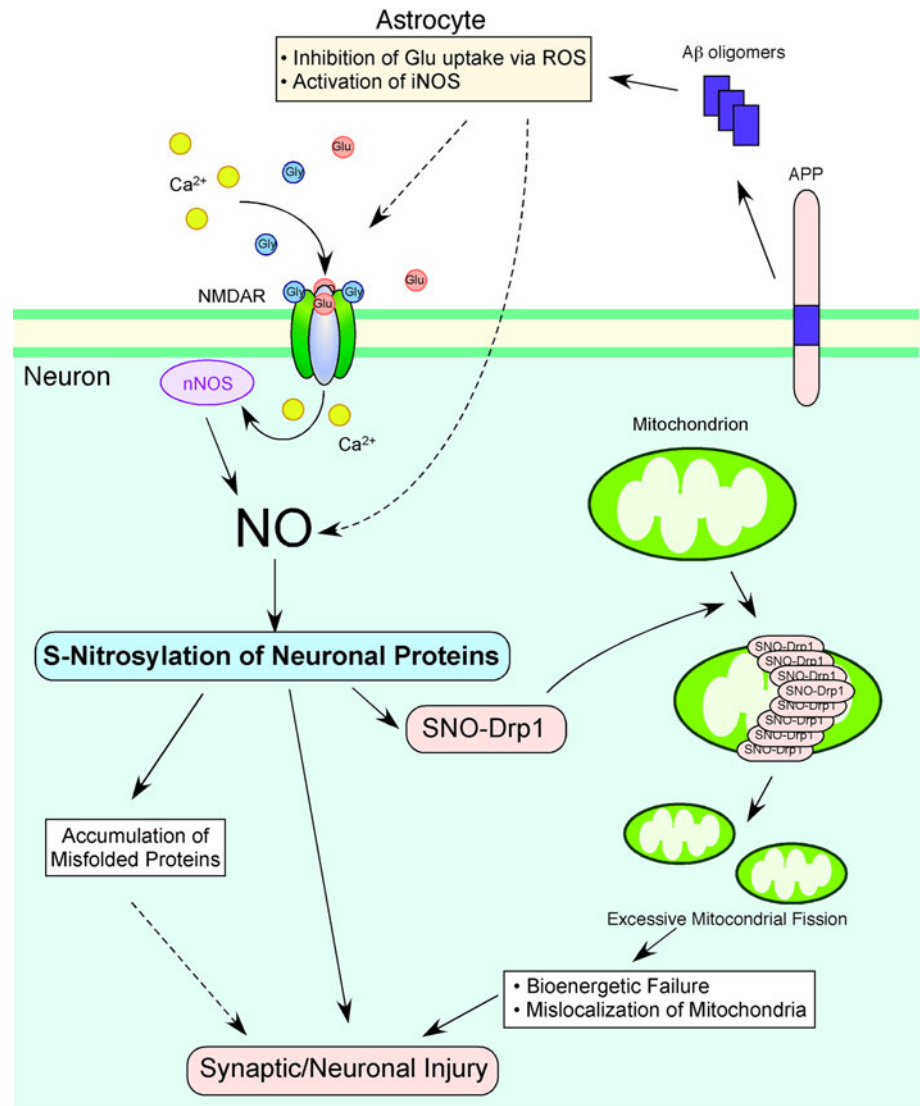
have shed light on the molecular events underlying this relationship, particularly in AD. Specifically, we recently discovered physiological and chemical evidence that *S*-nitrosylation modulates the GTPase activity of Drp1, thus contributing to mitochondrial fragmentation, bioenergetic impairment, synaptic damage, and eventually frank neuronal loss in models of AD.

S-Nitrosylation of Drp1 mediates mitochondrial fission and neurotoxicity in cell models of AD

In addition to the rare genetic mutations seen in the genes encoding mitochondrial fission and fusion proteins, recent studies have demonstrated that posttranslational modification of these molecules can contribute to altered mitochondria dynamics. For example, phosphorylation, ubiquitination, sumoylation, and proteolytic cleavage of Drp1 regulate mitochondrial fission by affecting Drp1 activity, at least in cell culture systems [122–129]. Excessive activation of mitochondrial fission or fusion proteins by posttranslational modification was posited to contribute to neurodegeneration by compromising mitochondrial function. Interestingly, along these lines, we recently reported that excessive NO can also lead to *S*-nitrosylation of Drp1 at Cys644 [31]. Cys644 resides within the GTPase effector domain (GED) of Drp1, which influences both GTPase activity and oligomer formation of Drp1 [130–133]. *S*-Nitrosylation of Drp1 (forming SNO-Drp1) induces formation of Drp1 dimers, which function as building blocks for tetramers and higher order structures of Drp1, and activates Drp1 GTPase activity; however, substitution of Cys644 to Ala (C644A) abrogated these effects of NO.

We further demonstrated that exposure to oligomeric Aβ peptide results in formation of SNO-Drp1 in cell culture models (Fig. 2). Moreover, we and others have observed that Drp1 is *S*-nitrosylated in the brains of virtually all cases of sporadic AD [23, 31]. In order to determine the consequences of *S*-nitrosylated Drp1 in neurons, we exposed cultured cerebrocortical neurons to the physiological NO donor, SNOC, or to Aβ oligomers and found that both induced SNO-Drp1 formation and led to the accumulation of fragmented mitochondria. Moreover, mutation of a specific cysteine residue in Drp1 (C644A) prevented these effects of SNOC or Aβ on mitochondrial fragmentation, consistent with the notion that SNO-Drp1 triggered excessive mitochondria fission or fragmentation. Finally, in response to Aβ, SNO-Drp1—induced mitochondrial fragmentation caused synaptic damage, an early characteristic feature of AD, and eventually apoptotic neuronal cell death. Importantly, blockade of Drp1 nitrosylation (using the Drp1(C644A) mutant) prevented Aβ-mediated synaptic loss and neuronal cell death,

Fig. 2 Possible mechanism whereby *S*-nitrosylated species contribute to excessive mitochondrial fragmentation and neuronal damage. NMDAR hyperactivation triggers generation of NO and subsequent *S*-nitrosylation of neuronal proteins, contributing to synaptic damage and eventually neuronal death. Soluble oligomers of A*β* oligomers, known to be a key mediator of AD pathogenesis, can facilitate neuronal NO production in both NMDAR-dependent and -independent manners. *S*-Nitrosylation of Drp1 (forming SNO-Drp1) can contribute to synaptic damage and neuronal cell death by triggering excessive mitochondrial fission and bioenergetic impairment

suggesting that SNO-Drp1 may represent a potential therapeutic target to protect neurons and their synapses in AD.

In addition to AD, SNO-Drp1 may affect the pathogenesis of other neurodegenerative disorders, such as Huntington's disease (HD), as we have recently observed nitrosylation of Drp1 in HD brains as well as in AD brains. An expanded CAG repeat in the huntingtin (htt) gene is the cause of HD. A potential mechanism for neurodegeneration in HD that is triggered by mutant Htt (mtHtt) involves mitochondrial dysfunction. Evidence for this includes reduced activity of respiratory complexes, decreased mitochondrial membrane potential, and changes in mitochondrial ultrastructure [134, 135]. Interestingly, expression of mtHtt induces mitochondrial fragmentation in Hela cells [136], and exposure to the mitochondrial complex II inhibitor 3-NP, which reproduces many of the pathological features of HD, leads to mitochondria fission [137]. Furthermore, accumulating evidence suggests that excitotoxic

pathways, which increase NO, may contribute to the pathophysiology of HD [138]. Hence, it is tempting to postulate that SNO-Drp1 may be involved in the mitochondrial fragmentation and neuronal injury observed in HD.

Conclusions

Excessive nitrosative and oxidative stress triggered by overstimulation of NMDA receptors and/or A*β* production may result in mitochondrial dysfunction, thus contributing to synaptic damage and neuronal loss in sporadic forms of neurodegenerative diseases. Additionally, nitrosylation reactions can lead to aberrant and misfolded proteins in neurodegenerative conditions. For example, *S*-nitrosylation of parkin and PDI can contribute to the accumulation of such aggregated proteins. Our recent identification of

SNO-Drp1, triggered by oligomeric Aβ, provides a mechanistic link between free radical production, abnormal mitochondrial morphology, and neuronal cell injury in neurodegenerative disorders such as AD. Elucidation of this new pathway may lead to the development of additional therapeutic approaches to prevent excessive mitochondrial fission by targeted disruption or prevention of SNO-Drp1.

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