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Forum Review

Expanding Insights on the Involvement of Endoplasmic Reticulum Stress in Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disease characterized by selective loss of dopaminergic neurons and the presence of Lewy bodies. The pathogenesis of PD remains incompletely understood. Environmental factors, oxidative damage, misfolded protein aggregates, ubiquitin–proteasome system impairment, and mitochondrial dysfunction might all be involved. Recent studies point to activation of endoplasmic reticulum (ER) stress-mediated cell death linked to PD. Accumulation of unfolded and/or misfolded proteins in the ER lumen induces ER stress. To withstand such potentially lethal conditions, intracellular signaling pathways collectively termed the unfolded protein responses (UPR) are activated. The UPR include translational attenuation, induction of ER resident chaperones, and degradation of misfolded proteins through the ER-associated degradation. In case of severe and/or prolonged ER stress, cellular signals leading to cell death are activated. Accumulating evidence suggests that ER stress induced by aberrant protein degradation is implicated in PD. Here the authors review the emerging role of ER stress in PD and related disorders, and highlight current knowledge in this field that may reveal novel insight into disease mechanisms and help to provide novel avenues to potential therapies. *Antioxid. Redox Signal.* 9, 553–561.

INTRODUCTION

PARKINSON'S DISEASE (PD) is the most common neurodegenerative movement disorder among elderly people. The classical symptoms of the disease include rigidity, resting tremor, bradykinesia, and postural instability. The pathological hallmarks underlying the clinical phenotypes are characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), together with the presence of intraneuronal inclusions termed Lewy bodies (7). Although the molecular mechanisms underlying neurodegeneration remain elusive, its pathogenesis begins to be considered as a multifactorial cascade of deleterious factors. Mitochondrial dysfunction, protein aggregation, impairment of the ubiquitin–proteasome system (UPS), and activation of the stress kinase signaling pathways have been supposed to be involved in the pathogenesis of PD. Recently, emerging lines of evidence from familial forms of PD, coupled with those findings from toxin-induced PD models, raise the possibility of widespread involvement of unfolded protein responses [UPR, also known as endoplasmic reticulum (ER) stress responses], the term given to an imbalance between the cellular demand for ER function and ER capacity (2, 43, 44), in the pathogenesis of this disease.

Neuronal loss in both familial and sporadic forms of neurodegenerative disorders is often accompanied by formation of inclusion bodies and aggregation of misfolded proteins (45). Upregulation of ER stress markers has been observed in postmortem brain tissues and cell culture models of many neurodegenerative diseases including PD, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and expanded polyglutamine diseases such as Huntington's disease and spinocerebellar ataxias (4, 26). Several chaperones ameliorate the accumulation of misfolded proteins triggered by oxidative or nitrosative stress, or of mutated gene products (26, 40, 58). The hypothesis that ER dysfunction plays an important role in the development of dopaminergic neuronal

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loss in PD has recently been put forward by observations that parkin has been associated with ER stress-induced cell death. Mutations in the *PARK2* gene coding for parkin cause autosomal recessive juvenile Parkinsonism (AR-JP), the most common form of familial PD. This review summarizes new observations implying that impairment of ER functioning is a common denominator of neuronal death in PD.

ER STRESS AND ER STRESS RESPONSES

Besides calcium storage and signaling, a central function of the ER is quality control for membrane or secretory proteins, which comprise nearly one-third of all cellular proteins (29). The importance of the ER for normal cell function is highlighted by the observation that blocking of the protein folding or processing reactions can be lethal for cells. Indeed, in various cases such as depletion of ER calcium stores, blocking the proteasome that is required for degradation of unfolded proteins, or genetic mutations resulting in proteins that cannot be properly folded, the ER functions are impaired and unfolded proteins accumulate in the ER. Accumulation of unfolded proteins in the ER is a severe form of stress that will induce apoptosis if ER function cannot be restored. To cope with conditions associated with impairment of ER function, cells activate highly conserved stress response, the UPR (2, 43, 44). The main purpose of UPR is to remove aberrant substrates and restore the ER to an efficiently operating maturation compartment. The UPR pathway functions as a tripartite signal that comprises (i) inhibition of general translation to attenuate the load of proteins to the ER, (ii) transcriptional activation of ER chaperones to increase protein folding and processing capacity; (iii) activation of ER-associated degradation (ERAD) to promote degradation of terminally misfolded proteins. However, when the ER stress is severe or prolonged, the cells eventually activate apoptotic signals, leading to cell death (5, 29) (Fig. 1).

Cells have developed two pathways for removing unfolded proteins from the lumen of the ER, increasing folding capacity through upregulation of ER chaperones (Fig. 2A) and promoting degradation of terminally misfolded proteins through activation of ERAD (Fig. 2B). The ERAD pathway is

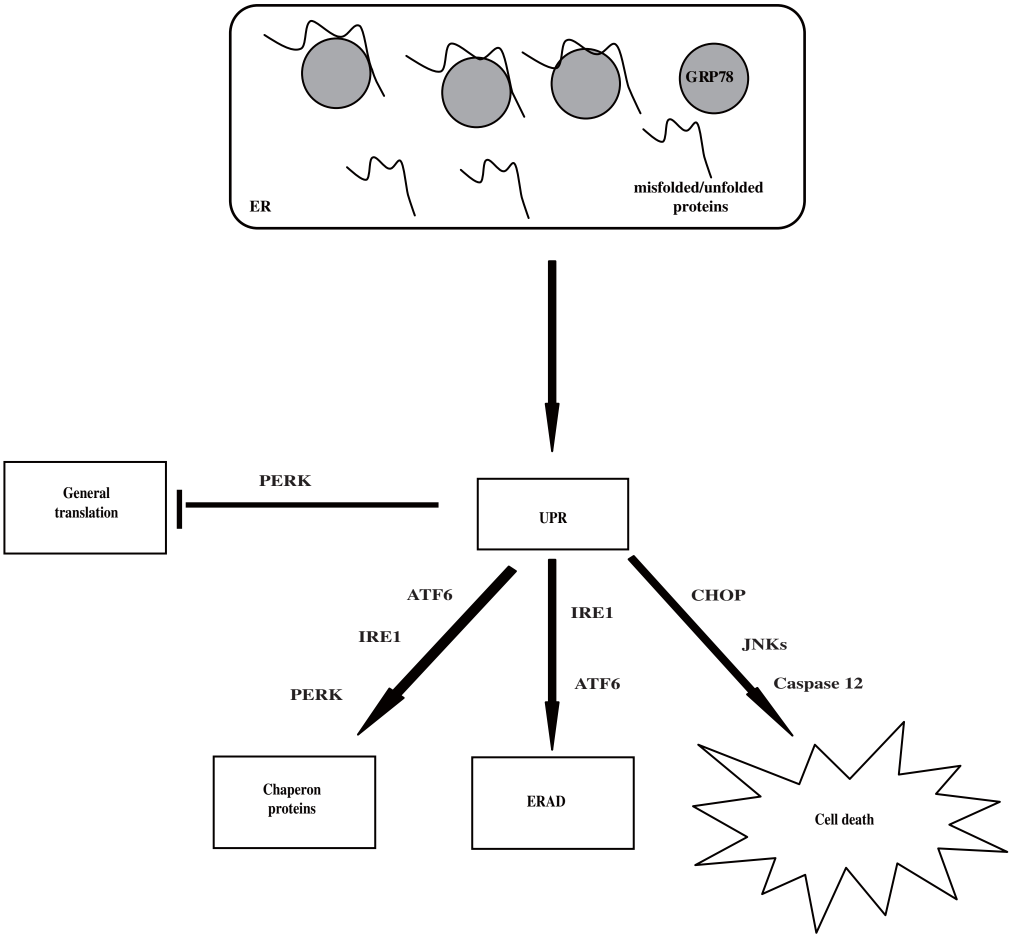

FIG. 1. The tripartite unfolded protein response. Three primary transducers of the unfolded protein response (UPR) signal, known as ATF6, IRE1, and PERK, seek to relieve ER stress through suppression of translational initiation, increased folding capacity of ER, and degradation of terminally misfolded proteins until the aberrations have been alleviated. However, severe or prolonged ER stress eventually activates apoptotic pathway.

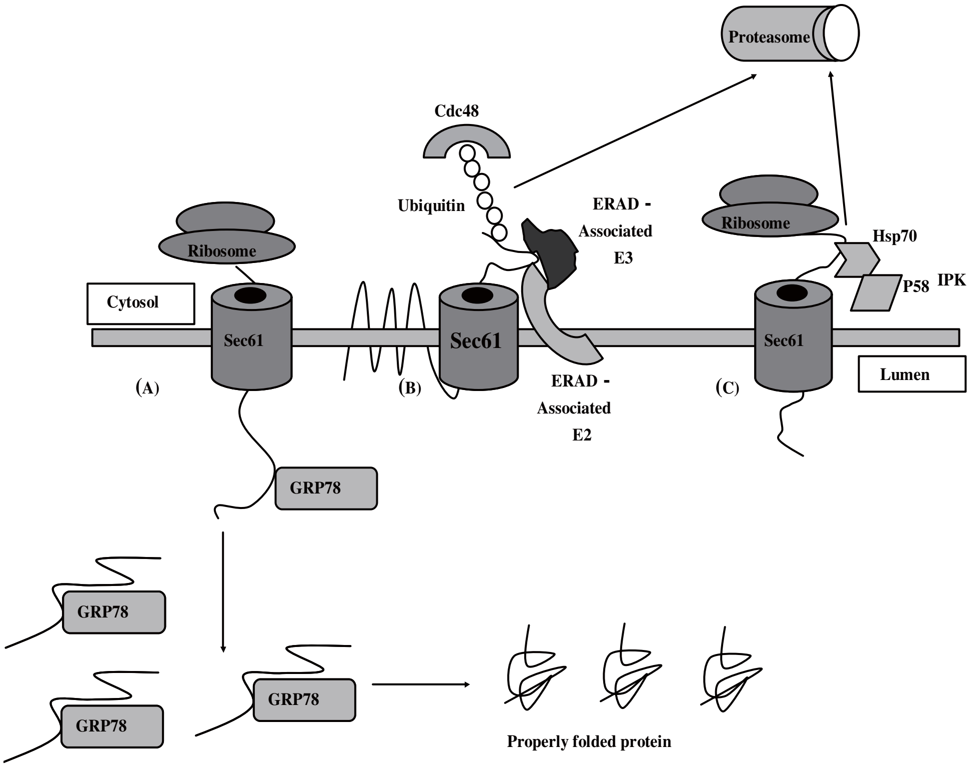

FIG. 2. The pathways related to clearance of unfolded proteins upon ER stress. Under ER stress conditions, cells develop three pathways to clear unfolded proteins in the ER. (**A**) ER chaperones such as GRP78 are upregulated to facilitate proper substrate folding. (**B**) Activation of ER associated degradation (ERAD)-mediated degradation of terminally unfolded proteins. (**C**) Cotranslational degradation of newly synthesized proteins trapped in the Sec61 translocon to decrease load burden to the ER.

characterized by the polyubiquitination and subsequent degradation of misfolded proteins (36–38). With the aid of the cytosolic AAA-ATPase p97/Cdc48, the misfolded ER protein is extruded through the ER membrane conduit Sec61, where it is then polyubiquitinated and delivered to the proteasome for degradation in the cytosol (Fig. 2B).

A recent study has revealed a new layer in the UPR pathway that permits the cotranslocational degradation of secretory proteins involving P58^{IPK}/DNAJC3, which collaborates with cytosolic chaperone networks and appears to assist in the co-translational/translocational degradation of nascent polypeptide chains that are stalled in ER translocons (Fig. 2C). This function diminishes the biosynthetic burden on the ER by degrading proteins at a stage earlier than previously envisioned. This protective effect might reflect a reduction in protein flux into the stressed ER's lumen. Alternatively, intervention early in the protein biogenesis by P58^{IPK}/DNAJC3 might allow the maturation and quality control machinery to focus its attenuation on the pre-existing improperly folded proteins that triggered the initial UPR signal (34).

ER STRESS IN FAMILIAL FORMS OF PD

As in most cases of PD, the degeneration is idiopathic, the etiology of the disease remains unknown. The recent identification of genetic mutations in familial cases of PD has advanced our understanding of the molecular mechanisms that cause the neurodegeneration. So far, six PD-associated genes have been identified.

Autosomal dominant forms of PD

Three rare missense mutations in the α-*synuclein* gene (A30P, E46K, and A53T) cause autosomal dominant familial PD (23, 39). Although the function of α-synuclein is still unclear, the discoveries that α-synuclein is a main component of Lewy bodies (48) and that its overexpression and gene triplication can cause neurodegeneration (1, 46) suggest that abnormalities of α-synuclein might be crucial for the pathogenesis of both familial and sporadic forms of PD. α-Synuclein transgenic mouse or *Drosophila* at least partially recapitulated PD phenotype including α-synuclein positive aggregate formation, although no obvious dopaminergic neuronal loss was observed in transgenic mice (12, 49). Lentivirus-mediated overproduction of α-synuclein in rat substantia led to significant cell death (27). Leucine-rich repeat kinase 2 (LRRK2) has recently been added to the list of genes that are implicated in autosomal dominant PD (35, 59). LRRK2 is a GTP/GDP-regulated protein kinase, and increased kinase activity appears to be implicated in neurodegeneration (47). Another gene, ubiquitin carboxyl-terminal esterase L1 (UCHL1), has been associated with the dominantly inherited disease, but the genetic evidence for its pathogenicity is not established since only a single mutation with low penetrance has been identified in one family (39).

Autosomal recessive forms of PD

Three recessive forms of parkinsonism have been identified, including mutations in the genes that encode parkin, DJ1, and PTEN-induced kinase 1 (PINK1).

Mutations in the *parkin* gene were originally discovered from the linkage study of Japanese AR-JP families, the most frequent type of familial PD (20). Thereafter its mutations have been found worldwide. Parkin is a 465 amino acid protein characterized by a ubiquitin-like domain at its NH2-terminus, as well as two RING (really interesting new gene) finger domains flanking a domain known as the IBR (in-between RING) at its COOH-terminus (RING–IBR–RING). Like many other proteins containing a RING domain, parkin has been found to function as an ubiquitin ligase (E3) (Fig. 3). E3s are part of the cellular machinery that tags proteins with ubiquitin, thereby targeting them for degradation by the proteasome. The UPS plays a major role in many vital cellular processes, and its dysfunction has been implicated in the pathogenesis of neurodegenerative disorders including sporadic PD. Parkin mutants associated with AR-JP reduce or abolish its E3 activity. Therefore, the most straightforward mechanism by which the dysfunction of parkin would cause neurodegeneration is accumulation of some neurotoxic substrate protein(s), which leads to dysfunction and eventually the death of susceptible neurons.

Mutations in *PINK1* were initially identified in three large consanguineous families with autosomal recessive forms of PD (52). Mutations in *PINK1* have differential effects on protein stability, localization, and kinase activity (3). As the kinase domain is the hot spot of mutations, disruption of the kinase activity is the most probable disease mechanism. Although functional data are limited, wild-type PINK1 protected neurons from mitochondrial dysfunction and apoptosis induced by oxidative stress (11), supporting an involvement of mitochondria in the pathogenesis.

A third gene linked to recessively inherited albeit rare PD is *DJ-1* (6). DJ1 has been assigned various functions, but perhaps the most relevant function in terms of the pathogenesis of PD is its potential role in oxidative stress response, either as a redox sensor or antioxidant protein (8).

In this review, rather than attempting to overview the entire picture, we focus on potential involvement of ER stress in this disease according to published data.

ER stress in α-synuclein-associated PD

In a *Drosophila* model of PD engineered to express wild-type and mutant α-synuclein, expression of molecular chaperone heat shock protein 70 (Hsp70) prevented dopaminergic cell loss mediated by accumulation of α-synuclein (1). However, Hsp70 is not directly activated in the UPR. A recent study provided direct evidence indicating the implication of ER stress in α-synuclein-mediated cell death (47). In a mammalian cell culture model, induction of the expression of A53T α-synuclein induced ER stress, as evidenced by the elevation in expression of CHOP and GRP78, increased phosphorylation of eIF2α, and activation of caspase-12. Furthermore, decrease of eukaryotic initiation factor 2α (eIF2α) phosphorylation by inhibitor, or knockdown of caspase-12 levels by RNA interference partially protected against cell death (47), indicating that ER stress at least partially contribute to A53T α-synuclein-induced cell death. Overexpression of mutant forms of α-synuclein in cultured neuronal cells leads to decrease in proteasome activity (51). The mechanism underlying mutant α-synuclein-induced impairment of proteasome activity remains to be identified. α-Synuclein is reported to be degraded through several different pathways including macroautophagy, chaperone-mediated autophagy, and proteasome (10, 50, 53). Since α-synuclein interacts with a subunit of proteasome regulatory complexes (15), it is possible that mutant α-synuclein directly affects the proteasome complex. It is of interest that an important means of removing misfolded proteins from the ER is their degradation by proteasomes. In addition, it has been reported that partial inhibition of the proteasome activity by poly-Q was sufficient to cause ER stress in primary neurons (33). Therefore, ER stress observed in overexpression of mutant forms

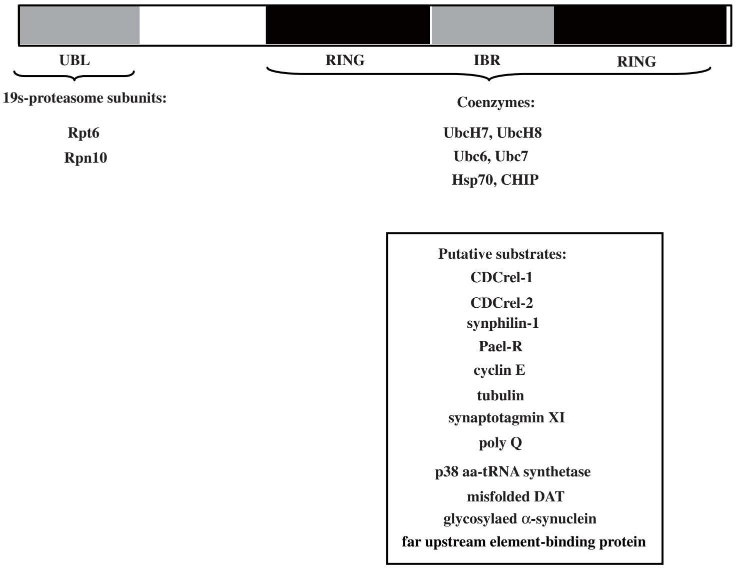

FIG. 3. Modular structure of parkin. Parkin has a modular structure, containing a ubiquitin-like (UBL) domain at the amino-terminus and two real interesting new gene (RING) fingers at its carboxy-terminus. In addition, an in-between RING (IBR) domain is inserted in the middle portion between two RING finger motifs. The two RINGs and IBR are named as a RING box. Furthermore, the linker region is located between UBL and RING box. The UBL binds to 19S proteasome subunits, and the RING–IBR–RING domain binds to specific co-enzymes and substrates (except for glycosylated α-synuclein, which binds to the UBL domain).

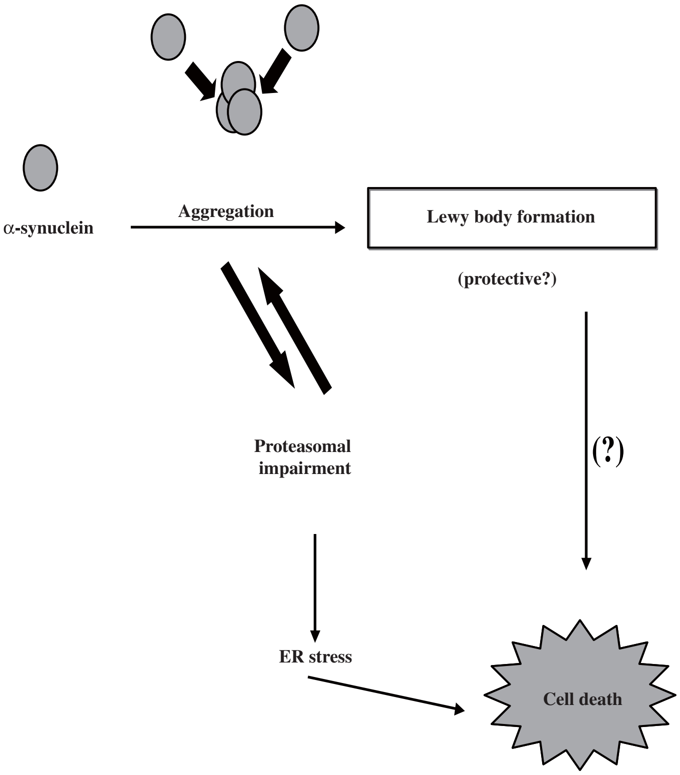

FIG. 4. Hypothetical mechanism of ER stress-mediated cell death induced by α-synuclein. The insidious loop feedback between α-synuclein aggregation and proteasomal impairment induces ER stress, which at least in part contributes to α-synuclein-mediated cell death.

of α-synuclein in cultured neuronal cells possibly derive from disruption of proteasome activity (Fig. 4).

ER stress in parkin-associated PD

Evidence supporting the involvement of ER stress in parkin mutations-induced cell death is more potent. Parkin is an E3 enzyme that interacts with Hsp70 and CHIP and plays a general role in protein degradation during ER stress (17–19). In line with this notion, cognate E2 (ubiquitin conjugating enzyme) partners of parkin include Ubc6 and Ubc7, which are ER-associated E2s involved in ERAD, indicating parkin is a component of ERAD machinery. It is easily conceivable that disruption of parkin function directly leads to ER stress, since ERAD and ER stress are coordinately regulated and deletion of ERAD components results in ER stress (13).

Given that accumulation of the substrate of parkin might play a key role in the neurodegenerative process, identification of parkin substrates has therefore been a major focus of many laboratories working on parkin. Typically, one expects an E3 to be highly specific for one or possibly a small number of substrates. Unexpectedly, a large number of putative parkin substrates have been reported (Fig. 3). Interestingly, several parkin substrates are misfolded or aggregation-prone proteins and are components of Lewy bodies. Considering that misfolded proteins, associated molecular chaperones, and proteasomal subunits are accumulated in Lewy bodies, the substrates of parkin may represent a subset of misfolded proteins. The C-terminus of Hsc70 interaction protein (CHIP), a U-box containing E3, has been shown to recognize misfolded protein through the heat-shock protein Hsp70 and is proposed to be a “quality control E3” that is contributed to the clearance of misfolded proteins (31). Given that parkin also binds to Hsp70, parkin may have a similar function to CHIP in dealing with misfolded proteins.

Among these substrates of parkin, one of the best-characterized parkin substrates, Pael-R underscores the ER stress-mediated cell death in the pathogenesis of AR-JP (18). Pael-R is a multipass G protein-coupled transmembrane protein with homology to the endothelin receptor type B, the function of which is unknown. Folding of Pael-R is a formidable challenge to cells. When overexpressed in cultured cells, Pael-R tends to become unfolded and insoluble; at the early stage of Pael-R accumulation, ER chaperones showed transcriptional upregulation, indicating that accumulation of Pael-R actually induced ER stress. Interestingly, CHIP serves as a cofactor of parkin. When Pael-R misfolding exceeds the cellular chaperone capacity, CHIP is upregulated, which sequesters Hsp70 and facilitates parkin-mediated ubiquitination of Pael-R (17). Under these conditions, parkin apparently acts as part of the ERAD machinery, utilizing the ER associated E2 enzymes Ubc6 and Ubc7 as the collaborating partners.

The UPR induces upregulation of parkin mRNA per se, and cells overexpressing parkin, but not mutant parkins found in AR-JP patients, are particularly resistant to unfolded protein-induced cell death (19**).** Furthermore, when astrocytes and neurons were exposed to conditions associated with ER stress, parkin protein levels were upregulated in astrocytes

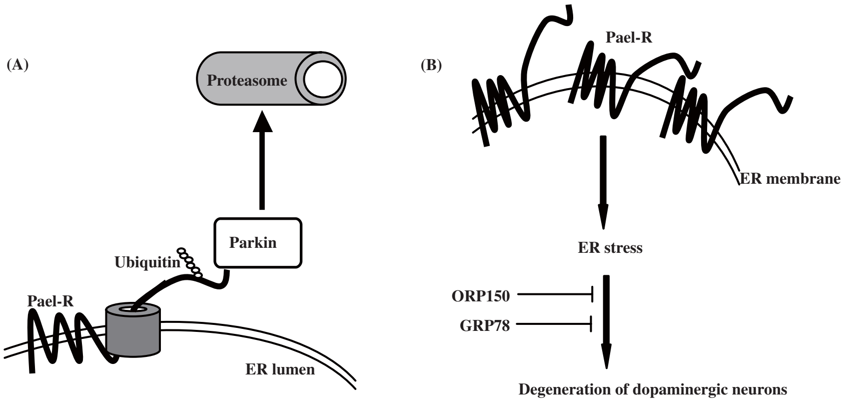

FIG. 5. Implication of ER stress in Pael-R-induced neuronal degeneration. (**A**) Pael-R is a difficult protein to be folded, and parkin ubiquitinates misfolded Pael-R and facilitates its degradation by UPS. (**B**) When dysfunction of parkin or overexpression of Pael-R, unfolded Pael-R accumulates in the ER and causes ER stress. ER chaperones, GRP78 and ORP150, suppress Pael-R-induced neuronal degeneration, possibly through enhancing the folding capacity of the ER.

but not in neurons (25). In the brain, Pael-R is primarily expressed in oligodendrocytes and shows little expression in neurons, except for a few distinct subpopulations of neurons, including hippocampal neurons and dopaminergic neurons in the SNpc. This implies that dopaminergic neurons of patients suffering from AR-JP are less well protected from neurotoxicity arising under conditions of Pael-R accumulation-induced ER stress. Thus, the inability of neurons to respond to ER stress by activating the expression of parkin and distributional pattern of Pael-R may contribute to the high vulnerability of dopaminergic neuronal cells. Using a transgenic *Drosophila* expressing human Pael-R, Yang *et al*. (55) found that this fly model revealed the age-dependent selective degeneration of dopaminergic neurons in spite of pan-neuronal expression of Pael-R. This Pael-R mediated dopaminergic neuronal loss was suppressed by the coexpression of human parkin and exacerbated by knockdown of endogenous parkin in the *Drosophila* by RNA interference. Recent *in vivo* observations in mice further highlights the important role of ER stress in Pael-R-mediated toxicity (21). Adenovirus-mediated overexpression of Pael-R in dopaminergic neurons induced ER stress and degeneration. This Pael-R-mediated neuronal death was suppressed by increased GRP78 or oxygen regulated protein 150 (ORP150), whereas cell death was exacerbated by downregulation of parkin or ORP150 (Fig. 5). Furthermore, a complicated interplay between ER stress and dopamine toxicity might present a mechanism underlying Pael-R-induced selective dopaminergic neuronal death, as evidenced by a neuroprotective effect of a tyrosine hydroxylase (TH) inhibitor (21).

ER STRESS IN TOXIN-INDUCED PD MODELS

Mitochondria toxins, 6-OHDA, rotenone, and MPP^+, are believed to contribute to dopaminergic neuronal death. These reagents can promote the generation of reactive oxygen species (ROS) via the inhibition of mitochondrial complex I or their oxidative function (14). Using functional genomics approaches to identify transcriptional alterations, numerous changes in genes associated with UPR were identified (42). Notably, a major target of the UPR pathway, the transcription factor CHOP, was dramatically upregulated by these reagents, as well as numerous markers of UPR including GRP78, splicing of XBP1, PERK, and the JNKs pathway. The assumption that ER dysfunction may play a role in the pathological process resulting in PD is corroborated by the observation that exposing cells to 6-OHDA, rotenone, or MPP^+, which are cellular models mimicking pathological disturbances associated with PD, induces a striking increase in transcripts associated with UPR (16, 42, 54). A number of reports have shown that both proteasome inhibition and ROS can trigger ER stress-mediated cell death pathways. One possible mechanism of ER stress induced by these mitochondria toxins is that accumulation of damaged oxidized proteins by the effects of these reagents on mitochondrial respiration causes ER stress (13). Alternatively, oxidative stress can directly compromise proteasomal components (41). However, the oxidative stress caused by the effects of these agents on mitochondrial respiration may not be totally attributable since a nonselective oxidant does not trigger ER stress. In addition, neurons lacking expression of PERK are defective in ER response and are significantly more sensitive to the death-promoting effects of PD mimetics (42). Thus, not only do mitochondria toxins provoke ER stress, but neurons lacking the capacity to deal with this by inducing an appropriate UPR are at greater risk of death, suggesting that ER stress is likely to play a causative role in neuronal cell death induced by these mitochondria toxins. Coupled with evidence from familial forms of PD, the induction of UPR and ER stress in these generally used neurotoxin models raise the possibility of widespread involvement of ER stress-mediated cell death in the pathogenesis of PD and other related disorders (Fig 6).

CROSSTALK OF ER STRESS WITH OXIDATIVE STRESS IN PD

PD has been closely associated with oxidative stress and mitochondrial dysfunction. In addition, dopaminergic neurons are particularly subjected to increased oxidative stress due to production of free radicals during dopamine autooxidation and dopamine metabolism (24). ER stress is intricately connected to oxidative stress. As described above, oxidative stress can directly or indirectly induce ER stress (13, 41). Evidence is also accumulating for a converse

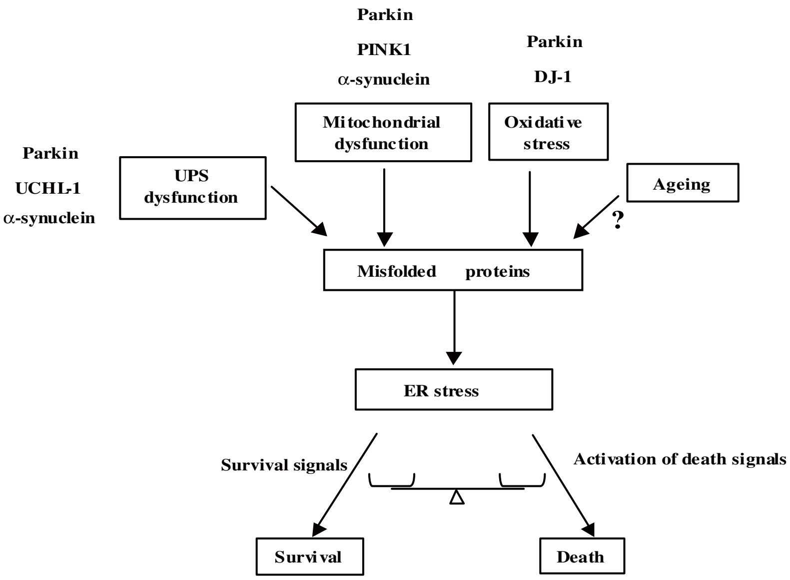

FIG. 6. Widespread involvement of ER stress in the pathogenesis of Parkinson's disease. In Parkinson's disease, proteasome dysfunction, oxidative stress, mitochondrial dysfunction, and possibly aging could directly or indirectly cause accumulation of misfolded proteins in the ER, thus induce ER stress. Cells counteract ER stress by activation of unfolded protein responses (UPR), which activates protective signals to eliminate misfolded proteins. However, when UPR fails to eliminate misfolded proteins, cells undergo apoptosis.

mechanism, whereby ER stress can result in secondary oxidative damage. One target of CHOP is ER oxidoreductase ERO1α, which participates in protein disulfide bond formation during protein refolding in the ER to help relieve ER stress, but in doing so also promotes production of ROS (28). The interplay between ER stress and oxidative stress might be mediated in part by parkin. Parkin is itself sensitive to oxidative stress, and is inactivated by nitric oxide-mediated nitrosylation or dopamine, which could lead to a simultaneous ER stress and oxidative damage (9, 24, 56). Inactivation of parkin is likely to create a feed-forward amplification loop, rendering dopaminergic cells more susceptible to oxidative and ER stress.

CONCLUSIONS

Evidence has been presented in various experimental studies that impairment of ER function may be involved in the neuronal cell death in PD. Environmental toxins, oxidative damage by dopamine itself, and mitochondrial abnormalities are all believed to play a role in sporadic PD (30). All these affect protein folding in the cytoplasm and lead to ER stress by compromising the process of ERAD (4). Alternatively, a genetic defect such as parkin mutation could impair the ability of cells to adapt to ER stress through impairment of its E3 activity. Since some novel components of the canonical UPR are expressed in a cell type-specific fashion, different types of cells may have unique responses for adaptation to ER stress (22, 32, 57). It is noted that parkin is upregulated in astrocytes, but not in neurons upon ER stress (25), suggesting parkin may represent as another unique response for adaptation to ER stress. Further investigation of parkin regulators will improve our chances of identifying novel targets for designing effective therapeutic strategies to impede the pathological processes.

ABBREVIATIONS

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AR-JP, autosomal recessive juvenile Parkinsonism; bZIP, basic leucine zipper; CHIP, C-terminus of Hsc70 interaction protein; CHOP, C/EBP homologous protein; E2, ubiquitin conjugating enzyme; E3, ubiquitin ligase; eIF2α, eukaryotic initiation factor 2α; ER, endoplasmic reticulum; ERAD, ER-associated degradation; ERO1α, ER oxidoreductase 1α; GRP78, glucose regulated protein 78; Hsp70, heat shock protein 70; IBR, in-between RING; JNK, c-Jun NH2-terminal kinase; Pael-R, parkin associated endothelin like-receptor; ORP150, oxygen regulated protein 150; PINK1, PTEN-induced kinase 1; PD, Parkinson's disease; RING, really interesting new gene; ROS, reactive oxygen species; SNpc, substantia nigra pars compacta; TH, tyrosine hydroxylase; UPR, unfolded protein response; UPS, ubiquitin–proteasome system.

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