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Review Article

Roles of endoplasmic reticulum stress and activating transcription factors in Alzheimer's disease and Parkinson's disease

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Abstract

Endoplasmic reticulum (ER) is a crucial organelle associated with cellular homeostasis. Accumulation of improperly folded proteins results in ER stress, accompanied by the reaction involving triggering unfolded protein response (UPR). The UPR is mediated through ER membrane-associated sensors, such as protein kinase-like ER kinase (PERK), inositol-requiring transmembrane kinase/endoribonuclease 1α, and activating transcription factor 6 (ATF6). Prolonged stress triggers cell apoptotic reaction, resulting in cell death. Neuronal cells are especially susceptible to protein misfolding. Notably, ER and UPR malfunctions are linked to many neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), delineated by accumulation of misfolded proteins. Notably, ATF family members play key roles in AD and PD pathogenesis. However, the connection between ER stress, UPR, and neuropathology is not yet fully understood. Here, we discuss our present knowledge of the association between ER stress, the UPR, and neurodegeneration in AD and PD. We also discuss the roles of ATF family members in AD and PD pathogenesis. Moreover, we provide a mechanistic clarification of how disease-related molecules affect ER protein homeostasis and explore recent findings that connect the UPR to neuronal plasticity.

Keywords: *Activating transcription factor family, Alzheimer's disease, Endoplasmic reticulum stress, Parkinson's disease*

Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) are described by advanced detriment of function in the nervous system, terminating in serious impairment. Although each disease has specific neuropathophysiology, they have a similar pathologic characteristic: misfolded protein aggregates [1,2]. Since the progression of pathology in AD and PD is related to a specific misfolded protein aggregate, these diseases are frequently characterized as protein misfolding disorders [3].

Under the physiological state, chaperones in the cell provide the accurate protein folding and recognize improperly folded proteins and promote protein degradation through lysosome or autophagy pathways [4]. The protein homeostasis [5] is essential for the preservation of cell function since it inhibits improperly folded protein aggregates. In protein misfolding disorders, improperly folded protein aggregates complicate the maintenance of cellular protein homeostasis [6] and leads to endoplasmic reticulum (ER) stress [7]. ER stress triggers a fast and integrated biochemical reaction, termed as the unfolded protein response (UPR). Growing evidence indicates that ER stress and UPR play important pathophysiological role in AD and PD; nevertheless, the molecular mechanism of ER and UPR involved in pathology of AD and PD is still unknown.

Endoplasmic reticulum stress and unfolded protein response

The ER controls numerous important cellular processes. Notably, it modulates the protein synthesis and is the major Ca^{2+} storage organelle that supplies Ca^{2+} for intracellular signaling. ER homeostasis is primarily regulated by the UPR, a complicated signaling system that modulates translation and transcription in response to demand and enhances the ER's protein-folding ability [8]. Various conditions – such as reduced calcium in the ER lumen and mutations in proteins that are trafficked through the secretory pathway – can lead

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to ER dysfunction and ER stress, thereby triggering the UPR [9]. Activation of the UPR in cells can prompt three types of actions: initial adaptation, alarm signaling, and cell apoptosis [10,11]. Under stress, UPR modulates cellular adaption by increasing the ER's protein-folding ability and concurrently decreasing the synthetic load [12].

UPR is regulated by sensor proteins, such as RNA-activated protein kinase-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring transmembrane kinase/endoribonuclease 1α (IRE1α). In the physiological state, these proteins bind with immunoglobulin heavy-chain binding protein (BiP). Under ER stress, these sensor proteins release BiP, enabling PERK and IRE1α dimerization and autophosphorylation, respectively, and modulated ATF6 proteolysis. These actions lead to the induction of UPR. PERK activation triggers the phosphorylation of eIF2α, and phosphorylated eIF2α decreases global protein synthesis and induces ATF4 translation, which increases the expression of apoptosis-related genes. The endoribonuclease activity of IRE1α enables the splicing of XBP1u protein to the spliced XBP1 (XBP1s). XBP1s increase transcription of numerous genes related to ER-associated degradation and UPR. In unstressed cells, ATF6 was located in ER. Under ER stress, it translocates to the Golgi, where it is cleaved consecutively by the enzymes S1P and S2P. Active ATF6 translocates into nucleus, then it binds promoters of various UPR-related genes, including GADD34, CHOP, BiP, and XBP1 [1,13,14] [Figure 1].

Endoplasmic reticulum stress in Alzheimer's disease

AD is a destructive degenerative condition affecting many people. It is described by a significant decrease in memory and cognitive tasks. The mechanisms leading to AD are complex and involve alterations in increased ER stress, calcium imbalance, synaptic transmission, and chronic neuroinflammation [15]. Neuropathological traits of AD include the plaques of amyloid-β (Aβ) peptides and accumulation of hyperphosphorylated tau [15,16]. While tau normally stabilizes neuronal microtubules, its phosphorylated form (p-tau) accumulates into neurofibrillary tangles [17]. Neurotoxic Aβ peptides result in neurodegeneration [18] [Table 1]. During the process of AD development, persistent aggregation of Aβ or p-tau leads to ER calcium dyshomeostasis, ER stress, and aberrant protein folding. Tau reportedly inhibits the ER-associated degradation pathway, resulting in improperly folded protein aggregates in the ER [19]. The neurotoxicity of Aβ peptides is associated with ER stress-modulated apoptosis through JNK activation [20].

Table 1: Protein misfolding in Alzheimer's disease and Parkinson's disease

Disease	Protein misfolding
AD	Deposits of intracellular tau aggregate to form neurofibrillary tangles
	Extracellular aggregates of amyloid-β form amyloid plaques
PD	Formation of protein inclusion bodies, known as Lewy bodies, that contain aggregated α-synuclein and ubiquitin
	Accumulation of tau deposits

AD: Alzheimer's disease, PD: Parkinson's disease

Various studies have reported dysregulated ER stress in the brains of AD patients. During moderate ER stress, UPR plays a protective role. However, prolonged ER stress triggers the proapoptotic pathway of the UPR, potentially leading to neurodegeneration. Increased levels of BiP and other chaperones, including Hsp72, Hsp73, and glucose-regulated protein 94 (Grp94), have been found in the cerebrospinal fluids and brains of AD patients [21,22]. In addition, AD brains show substantial upregulation of p-PERK and p-eIF2α, which can be induced by tau aggregates [13,23]. This phosphorylation is induced by tau accumulates [21]. Activation of PERK is linked to increased expression of ATF4 and BACE1 [24]. ATF4 is an important modulator of neuronal plasticity and spatial memory [25].

IRE1 activation in human brain tissue is positively associated with the progression of AD. IRE1 deleted the RNase domain in the nervous system, decreased Aβ oligomer content, and led to recovery of memory capacity and learning in mouse AD model [26]. In addition, XBP1 promoter polymorphism increases a risk factor for it [27]. XBP1 can decrease BACE1 expression through HMG-CoA reductase degradation 1, resulting in a reduction of Aβ plaques [28]. ATF6 reduces APP expression level, thereby inhibiting Aβ levels, decreasing the expression of BACE1 and promoter activity, and facilitating the spatial memory retention in mouse AD model [29].

In the brains of AD patients, CHOP, caspase-12 and GADD34, linking ER stress to apoptosis, is increased [30]. An increase in CHOP results in the production of reactive oxygen species (ROS), elevated levels of Aβ oligomers, and ultimately, cell death [31].

Sadleir *et al*. found that 5XFAD transgenic mice (with familial AD) showed increased expressions of APP and presenilin 1 (PS1; the most common cause of familial AD). These mice did not show UPR activation and did not exhibit increased expressions of sensor proteins, suggesting that the role of ER stress in AD is still controversial [32]. In summary, ER and UPR appear to be important factors in the development of AD [Figure 2].

Endoplasmic reticulum stress in Parkinson's disease

PD is a serious neurodegenerative disease portrayed by both motor and nonmotor symptoms, eventually resulting in immobility [33,34]. The pathogenic factors involved in PD remain largely unclear. Most cases of PD are sporadic with an unknown etiology, while only 10%–15% result from mutations in several genes, such as PRKN, SNCA/PARK1, and PINK1 [35].

PD is typically identified by two major features: the impairment of dopaminergic neurons in the substantia nigra and the aggregation of improperly folded alpha-synuclein (α-SYN) in neuronal somas (Lewy bodies) or within axons and dendrites (Lewy neurites) [36] [Table 1]. High α-SYN expression is detected in the presynaptic terminals of neurons

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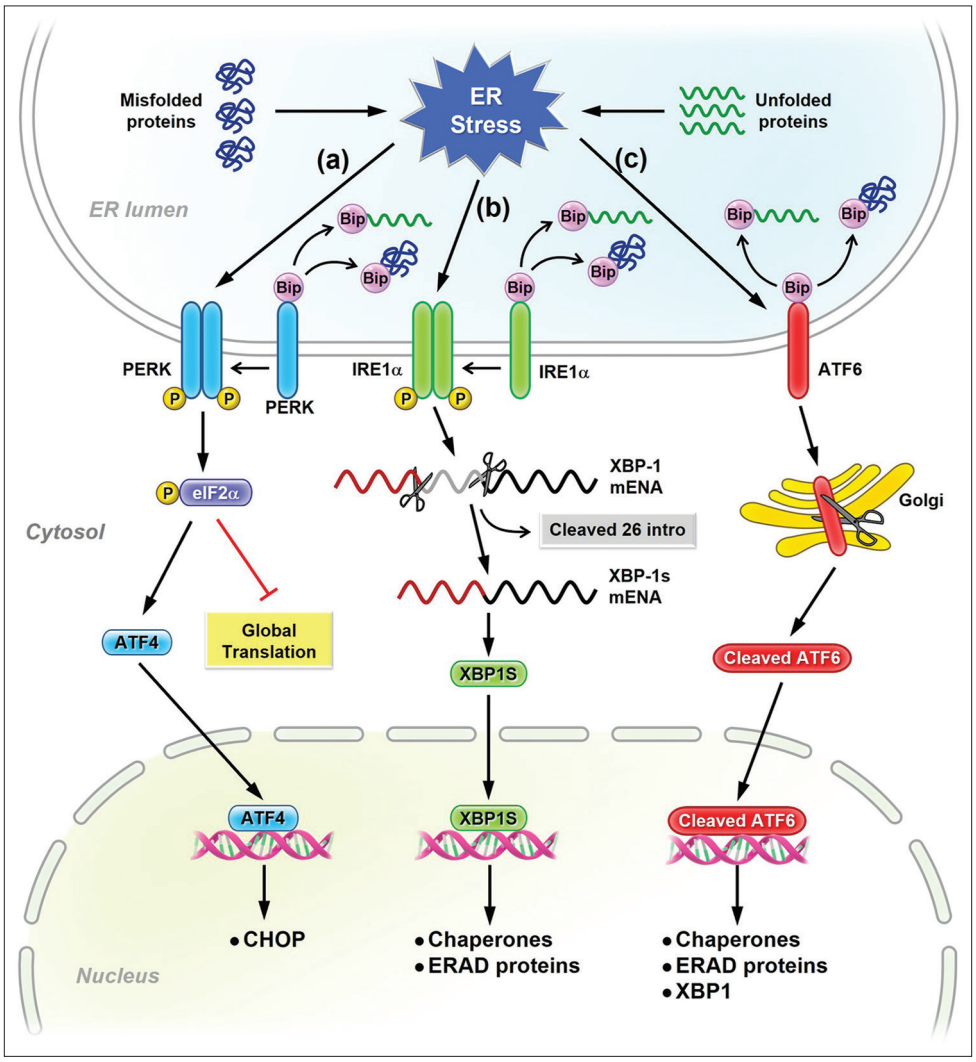

Figure 1: Diagrammatic illustration of the sensor proteins of unfolded protein response (UPR). The principle UPR pathways after binding protein dissociated from sensor proteins when Endoplasmic reticulum (ER) stress happens: (a) protein kinase-like ER kinase (PERK)/eIF2α/ATF4 pathway: trans PERK auto-phosphorylation results in p-eIF2α, then reducing protein translation and upregulates ATF4 translation which increases the expression of gene related to apoptosis, including CHOP, (b) inositol-requiring transmembrane kinase/endoribonuclease 1α (IRE1α)/XBP1 pathway: IRE1α with RNase activity cuts out 26 intronic nucleotides of the XBP1 mRNA, leading to the XBP1s, which is accountable for inducing gene expression related to chaperones and ER-associated degradation, (c) activating transcription factor 6 (ATF6) pathway: Active ATF6 translocates to the nucleus and promotes the expression of genes related to chaperone, ER-associated degradation, and XBP-1

but can also be found in blood and tissues [37,38]. SNCA gene mutations, including A53T, A30P, and E46K, are recognized as inherited causes of PD [39-41]. α-SYN is prone to accumulate, and their β-sheet form extends into insoluble fibrils [42].

Numerous studies indicate that ER stress acts a key role in α-SYN toxicity and modulates the death of dopaminergic neurons. α-SYN accumulation interacting with BiP results in UPR signaling pathway [14,43]. α-SYN is reportedly more plentiful in the ER/microsome fractions of brain tissue from mice and humans with PD, compared with non-PD controls [44]. In addition, ER stress markers, including p-PERK and p-eIF2α, have been detected in the dopaminergic neurons of PD patients [45].

α-synucleinopathy was positively correlated with the activation of ER chaperones and aberrant UPR in pathological neurons of A53T transgenic mouse model. This correlation is validated by the upregulated accumulation of polyubiquitin chains and caspase-12 triggering [44]. Notably, lack of glucose caused α-SYN-induced cell apoptosis in dopaminergic differentiated SH-SY5Y cells. α-SYN plays a role in stress detection; lack of glucose results in α-SYN overexpression, leading to interaction with BiP, and subsequent triggering of the PERK/ATF4/cAMP response element binding protein-2 (CREB-2) pathways [14].

Controversy remains regarding the IRE1-XBP1 pathway involved in ER stress in PD. In neurotoxin 6-hydroxydopamine-induced PD model animals, the active form of XBP1 is reportedly neuroprotective [46]. However, in a PD model fruit fly, IRE1 induce cell loss in photoreceptor neurons, in an XBP1-unrelated way [47]. Moreover, in yeast, α-SYN aggregate induces ER stress through suppressing ER-to-Golgi transport [48,49]. This trafficking damage is reportedly induced by RAB1 GTPase, or by ATF6 [48,50].

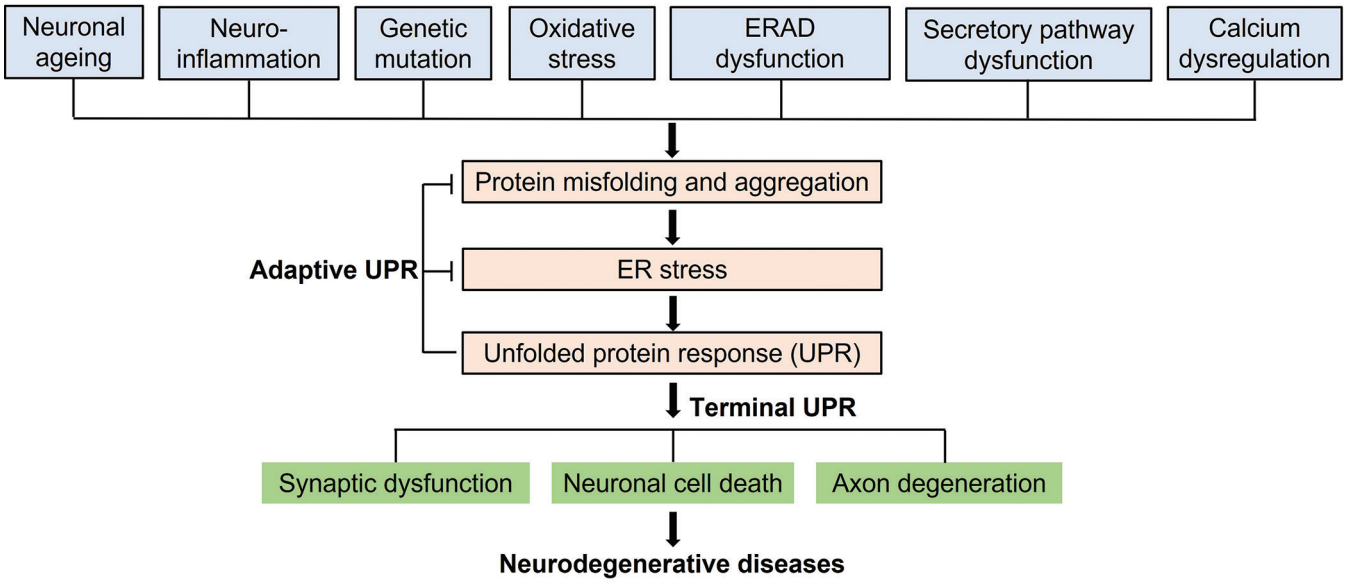

Figure 2: Endoplasmic reticulum (ER) stress and unfolded protein response (UPR) in neurodegeneration. Neuronal ageing, neuro-inflammation, genetic mutations, and other stimuli may trigger improperly folded protein accumulation and aggregation resulting in ER stress. In order to rescue ER stress, the response via UPR is triggered. However, long-lasting ER stress triggers apoptosis influencing neurons and synaptic function, thereby resulting in neurodegenerative

Notably, the coexpression of RAB1 with α-SYN has recovered the damage of dopaminergic neurons in animal models [48].

In addition, α-SYN suppresses ATF6 activation through coat COPII-modulated ER-Golgi trafficking, triggered on ER stress, resulting in induction of apoptosis [51]. In addition, ER stress triggered by α-SYN accumulation is through destabilized ER Ca^{2+} homeostasis. α-SYN accumulation stimulates ER calcium pump SERCA protein in neurons, resulting in changes of calcium metabolism and apoptosis [52]. Knockout mice of the CaBP-9k gene showed upregulation of α-SYN and activation of apoptosis in neurons. CaBP-9k knockout mice treated with ER stress inhibitor tauroursodeoxycholic acid restored ER stress markers and cleaved caspase-12 to regular levels [53]. In conclusion, UPR and ER stress-related pathways appear to be a novel target for PD treatment [Figure 2].

Activating transcription factor family in Alzheimer's disease and Parkinson's disease

ATF family acts significant roles in the neuropathogenesis of AD and PD. ATFs contain a basic leucine zipper-like domain that enables the execution of critical transcriptional modulatory functions [54,55]. The ATF family includes ATF1-7 [56,57], and these transcription factors exhibit differential expression in human tissues [58]. Notably, ATF-2, -4, and -6 are highly expressed in the brain compared to other tissues, while ATF-1, ATF-3, ATF-5, and ATF-7 are expressed at lower levels in the brain relative to other tissues.

ATF-1 binds with CREB to exert beneficial effects on neurons [59] and modulate several stress responses [60]. ATF-2 is involved in DNA damage and apoptosis [61,62] and can regulate the inflammation in microglia cells, which is related to AD [63]. ATF-2 exhibits cytoplasmic localization in brain tissue from AD patients, suggesting that the pathogenesis of AD may involve altered subcellular localization of ATF-2 [64]. Kang *et al*. found that metformin activates ATF-2/CREB/PGC-1α pathway, resulting in neuroprotection. PGC-1α, CREB, and ATF-2 appear important for cell viability against mitochondrial stress, as SH-SY5Y cells with knockdown of these genes are susceptible to MPP+ toxicity [65]. In addition, in dopaminergic neuron-specific conditional ATF-2 mutant mice, MPTP-triggered neurodegeneration was significantly mitigated, suggesting that ATF-2 activation acts a harmful function in PD neuropathogenesis [66].

ATF-3 expression is low under normal situations but is rapidly induced by multiple stresses [67]. ATF-3 binds to the cyclic AMP response element, typically decreasing the expressions of various target genes, and ATF-3-mediated responses can be adaptive or maladaptive [67,68]. ATF-3 is increased in damaged neurons to help neuronal regeneration [69]. Upregulation of ATF3 is linked to neuroprotection and regeneration [70]. ATF3 protects neurons from death and rebuilds synaptic links after neurotoxic injury [71]. In the peripheral nervous system, ATF3 is also involved in axonal regeneration [70].

López-Cerdán *et al*. highlighted sex-based different mechanisms in PD hallmarks, including inflammatory reaction, mitochondrial malfunction, and oxidative stress. In female PD patients, specific transcription factors were activated with normalized enrichment scores of >0 including ATF-3, B-cell lymphoma 6, and Polycomb Group Ring Finger 2, which have been previously linked to neurodegenerative diseases or cognitive disabilities [72]. In addition, a PD model exhibited alterations of ATF-3 in response to ROS production and neurological damage [73]. Moreover, in a mouse model of PD, suppression of the ROS/ATF-3/CHOP pathway mitigates cell apoptosis in neurons, as ATF-3 activation induces CHOP expression, ultimately leading to cell apoptosis [73].

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Francis *et al*. reported that ATF3 overexpression protects rat neurons from kainic acid-triggered neurotoxicity, having antiapoptotic effects on cells [74]. Although these results are contradictory, they suggest that ATF-3 is implicated in apoptosis. Accordingly, it is possible that ATF-3 activation or overexpression might modulate AD or PD through regulation of apoptosis.

ATF-4 is generally expressed at low levels but is increased on stimulation. It can be as both a transcriptional repressor and activator [75]. ATF-4 is involved in cell apoptosis [76], redox homeostasis, mitochondrial function, and amino acid metabolism in neurons [77,78]. ATF-4 is also involved in cell death [79,80]. The AD brain shows a significantly increased protein level of ATF-4 [81]. This may be related to the finding that ATF-4 may function as the downstream effector of Aβ and an upstream initiator for the neuropathological features in AD [82]. It is possible that increased ATF-4 is related to upregulated phosphorylation of tau, through protein phosphatase 1 kinases and glycogen synthase kinase 3, which could result in neuronal damage. Sun *et al*. found that human PD brain samples showed intense ATF-4 immunostaining [83]. Aimé *et al*. found that the drug adaptaquin blocks ATF-4/CHOP-dependent pro-death Tribbles pseudokinase 3 induction and protects in cellular and mouse models of PD [84]. Wang *et al.* found that verbascoside suppresses the progress of AD through downregulating PERK-eIF2α-ATF-4-CHOP axis triggered by ER stress in U251 glioma cells and in APP/PS1 transgenic mice [85].

ATF-5 is an opposing modulator of differentiation in neurons [86]. A decrease of ATF-5 is necessary to enhance neural cell cycle exit and neuronal differentiation [86,87]. ATF-5 can suppress apoptosis [88]. ATF-6 activates the UPR in response to ER stress [89]. The first line of defense against ER stress, the UPR can preserve ER homeostasis, although its activation may also lead to cell death [90]. ATF-6 is involved in the UPR pathway and can decrease ER stress [91,92]. When lasting presence of stimuli damages ER function, the ATF-6 pathway triggers the ER stress-regulated apoptosis, stimulating the expression of caspase-12 and CHOP to provoke apoptotic pathway [93,94]. In summary, ATFs act an important role in modulating cell repair, injury, and regeneration in neurons.

Conclusion

ER stress acts a critical role in AD and PD characterized by improperly folded protein aggregates. However, it is not yet completely clear how the UPR is involved, and related mechanisms through which ER stress leads to neuropathogenesis are unknown, and may have opposite effects. This may explain the interaction between ER stress, UPR, and neuroinflammation. As previously reviewed, studies using both *in vitro* and *in vivo* neurodegenerative disease models have demonstrated that the disease-related aggregates of improperly folded protein result in synaptic and neuronal dysfunction. Targeting ER- and UPR-related pathways appears to be a promising approach to treat neurodegenerative diseases. A comprehensive understanding of the cellular signaling pathways and physiological roles of ER- and UPR-related proteins will assist to guide the development of new therapeutic strategies. It will be important to discover novel drugs that can regulate ER stress and UPR signaling in various cell and animal models, which will provide substantial information regarding how the ER and UPR are involved in AD and PD progression.

Here, we also summarized the roles of ATFs in the neuropathogenesis of AD and PD. Since ATF expressions are significantly changed during AD or PD, it can be suggested that ATFs family may be the causative genes for AD or PD. ATFs play diverse roles during AD and PD and may be involved in these diseases through several pathways, including modulation of ER stress and apoptosis. Thus, ATFs may act as a potential target for the therapy of AD and PD. However, there are presently few drugs that target ATFs to treat AD or PD, and there remains a need for further research to investigate the particular mechanism of ATFs in AD and PD.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

Dr. Ching-Feng Cheng, an editorial board member at *Tzu Chi Medical Journal*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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