The Role of IRE1 Signaling in the Central Nervous System Diseases

Haibo Ni1,*, Qin Rui2,#, Di Li3,#, Rong Gao1 and Gang Chen4

1Department of Neurosurgery, The First People’s Hospital of Zhangjiagang City, Suzhou, Jiangsu, P.R. China; 2Department of Laboratory, The First People’s Hospital of Zhangjiagang City, Suzhou, Jiangsu, P.R. China; 3Department of Translational Medicine Center, The First People’s Hospital of Zhangjiagang City, Suzhou, Jiangsu, P.R. China; 4Department of Neurosurgery & Brain and Nerve Research Laboratory, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, P.R. China

Abstract: The accumulation of misfolded or unfolded proteins in endoplasmic reticulum (ER) lumen results in the activation of an adaptive stress process called the unfolded protein response (UPR). As the most conserved signaling branch of the UPR, Inositol-requiring enzyme 1 (IRE1) possesses both Ser/Thr kinase and RNase activities operating as major stress sensors, mediating both adaptive and pro-apoptotic pathways under ER stress. Over the last three decades, a mounting body of evidence has shown that IRE1 signaling dysfunction is involved in the pathology of various neurological disorders. Targeting this pathway has emerged as a promising therapeutic strategy against these diseases. In this review, we provide a general overview about the expression and physiological function of IRE1 signaling and its pathophysiological roles in the central nervous system diseases.

Keywords: Inositol-requiring enzyme 1, X box-binding protein 1, diseases, central nervous system, Alzheimer’s disease, Parkinson’s disease, ischemic stroke.

1. INTRODUCTION

Endoplasmic reticulum (ER) is an important subcellular organelle for proper folding and sorting of proteins. The function of the ER can be disrupted by various physiological and pathological stimuli, including glucose deprivation, perturbation of calcium homeostasis, and exposure to free radicals [1]. Under such conditions, the accumulation of unfolded proteins or disturbance of Ca2+ homeostasis in the ER would trigger ER stress-induced apoptosis [2]. Inositol-requiring protein 1 (IRE1) has been long believed to be a proximal ER stress sensor and plays an important role in transducing the stress signals [3]. However, when cells are exposed to excess levels of stimuli causing ER stress, the apoptotic IRE1 signaling pathway is activated [4]. Over the last three decades, a mounting body of evidence has shown that IRE1 signaling dysfunction is involved in the pathology of various neurological disorders, such as Alzheimer’s disease (AD) [5], Parkinson’s disease (PD) [6], Huntington’s disease (HD) [7], ischemic stroke [8], spinal cord injury [9] and glioma [10]. In this review, we provide a general overview of IRE1 signaling in these central nervous system diseases. In the first section, we describe the localization, structure of IRE1 and the function of IRE1 signaling pathways under ER stress. In the second section, we summarize the roles and possible mechanisms of IRE1 signaling pathways in different neurological disorders.

2. ER STRESS AND IRE1

ER is the main subcellular organelle in eukaryotic cells, which plays essential roles in protein folding and secretion, in addition to lipid synthesis and calcium storage [11]. A wide range of external factors, such as ischemia-reperfusion injury, oxidative stress, calcium disturbances and imbalances, and the inhibition of protein glycosylation, can disturb ER homeostasis, leading to ER stress [12-14]. To alleviate ER stress, cells activate an adaptive signaling cascade known as the unfolded protein response (UPR), which aims to re-establish ER proteostasis by decreasing the load of misfolded proteins [15]. The UPR is essentially initiated by three classes of sensors, (i) PERK (PKR-like ER kinase), (ii) IRE1 and (iii) ATF6 (activating transcription factor 6). The activation mechanism of these proteins has not been totally resolved but it is known that certain molecular chaperones of ER lumen, e.g. glucose-regulated protein (GRP78), are involved in the activation of these effector proteins. Among the three UPR branches, IRE1, a serine-threonine kinase and endoribonuclease located at the ER membrane, is the most conserved ER stress sensor [16]. It has two isoforms: IRE1α and IRE1β; IRE1α is ubiquitously expressed in most cells.
and tissues while IRE1β is limited to gastrointestinal epithelial cells [3]. IRE1 comprises a serine/threonine protein kinase domain and an endoribonuclease (RNase) domain and is activated upon dimerization and autophosphorylation.

3. IRE1 SIGNALING PATHWAYS

At the initial phase of ER stress, IRE1 is bound by GRP78 and is subsequently activated by dimerization following separation from GRP78. The activated IRE1 cleaves a 26-nucleotide intron from the coding region of the transcription factor X box-binding protein 1 (XBP1) [17]. This unconventional splicing event leads to a shift of the coding reading frame of the mRNA, resulting in the expression of a more stable and active transcription factor, termed XBP1s, which is also an indicative activation of UPR [17, 18]. Subsequently, XBP1s translocates into the nucleus and binds to the promoters of its target genes such as encoding molecular chaperones and proteins contributing to ER-associated degradation.

Although the IRE1-XBP1 pathway has neuroprotective effects, activated IRE1 also mediates the crosstalk with other stress pathways as a scaffold by binding to tumor necrosis factor receptor associated factor 2 (TRAF2), forming a compound which separates TRAF2 from pro-caspase-12. This activates caspase-12 and JUN N-terminal kinase (JNK), which are closely associated with autophagy and apoptosis [19]. Caspase-12, specific to apoptosis induced by ER stress, leads to cell apoptosis through the activation of downstream caspase-9 and caspase-3 as well as the induction of DNA fragmentation [20-22]. JNK can phosphorylate and inhibit the anti-apoptotic activity of Bcl-2 and Bcl-xL or activate the pro-apoptotic function of Bim and Bid [23, 24]. In addition, the RNAase activity of IRE1 is also involved in the degradation of mRNAs, rRNAs and microRNAs through a process called regulated IRE1-dependent decay (RIDD), which selectively degrades certain mRNAs encoding for proteins located in the ER and then initiates apoptosis [25, 26].

4. IRE1 SIGNALING IN CENTRAL NERVOUS SYSTEM DISEASES

IRE1 signaling has been extensively studied in the past decades and its dysfunction in the brain is linked to the occurrence of several central nervous system (CNS) diseases. As summarized in Table 1, the impairment of IRE1-XBP1 branch plays a role in the development of many neurological disorders, such as AD, PD, HD, post-traumatic stress disorder (PTSD), glioma, and spinal cord injury. Meanwhile, the pro-apoptotic function of IRE1 signaling has been shown to be involved in ischemic stroke and epilepsy. Thus, IRE1 signaling may play quite different roles in CNS diseases, as discussed in more detail below.

4.1. IRE1 Signaling in Alzheimer’s Disease

AD is a progressive neurodegenerative disorder that affects almost 480 billion individuals worldwide. Pathologically, the clinical manifestation of AD is characterized by two hallmarks: intracellular aggregates of tau in the neurofibrillary tangles (NFTs) and extracellular aggregates of β-amyloid (Aβ) in the senile plaques [27, 28]. In the hippocampus of AD patients, it was found that a large quantity of phosphorylated IRE1 accumulated in granules associated with granulovacuolar degeneration in pyramidal neurons [29]. Higher XBP1 levels were also observed in cortical areas of patients with AD than those in normal subjects [30]. In addition, a latest study which was assessed among 276 AD patients and 254 matched healthy individuals in China demonstrated a possible association between polymorphism in XBP1 promoter and risk of AD development. There was a significant difference in genotype and allele frequencies between AD patients and control subjects, suggesting that the -116C/G polymorphism of XBP1 might be a risk factor to develop AD in the Chinese population [31]. In light of the common belief that the abnormal deposition of both Aβ and tau proteins is critical for the pathobiology of AD, it has been shown that targeting IRE1 signaling represents a significant pathway for protection against all cardinal features of AD pathology, leading to reduced amyloid deposits, improved cognitive and synaptic function, and attenuated astrogliosis [5]. Moreover, growing evidence indicates that XBP1s prevents the Aβ neurotoxicity and phosphorylated tau in neurons and it has the ability to improve cognitive impairment in AD mouse models [5, 32]. In both drosophila and mammalian cell culture models of AD, XBP1 overexpression down-regulates ryanodine receptors 3 expression, which in turn prevents free Ca2+ accumulation in the cytosol, a key cellular mediator of Aβ cytotoxicity [33, 34]. In contrast, silencing endogenous XBP1 using small interfering RNA results in a decrease in cell viability for Aβ toxicity [32]. Although these observations suggest that IRE1 signaling may participate in AD, its direct function to AD pathogenesis remains to be established.

4.2. IRE1 Signaling in Parkinson’s Disease

PD, following AD, is the second most common neurodegenerative disease and affects about 1% of the elderly population [35]. PD is typically characterized by the selective loss of dopaminergic neurons in the substantia nigra pars compacta (SN) and the accumulation of α-synuclein in Lewy bodies [36, 37]. Growing evidence from studies in human PD, genetic or toxicological models, indicates that ER Stress is an important contributor to the pathogenic processes, ultimately leading to aggregated protein accumulation and dopaminergic neurons loss in PD [38]. In the disease model induced by unilateral intrastriatal injection of 6-hydroxydopamine (6-OHDA), developmental ablation of XBP1 protected dopaminergic neurons against a PD-triggering neurotoxicity. This survival effect was accompanied by the up-regulation of UPR-responsive chaperones calreticulin and the disulfide isomerase Erp72 in dopaminergic neurons of the SN, but not in other brain areas [39]. Similarly, in Drosophila and mouse models of AD, a mild dose of the ER stress agent tunicamycin selectively induced activation of the IRE1-XBP1 pathway but not pro-apoptotic factor CHOP expression, providing protection for dopaminergic neurons against 6-OHDA [40]. By contrast, knockdown of XBP1 in nigral dopaminergic neurons of adult mice triggered chronic ER stress with CHOP induction, which led to spontaneous neurodegeneration [39]. In the same study, the potential therapeutic effect of targeting XBP1 in a neurotoxin-based model of PD was explored using a gene therapy
Table 1. Published studies on expression and effects of IRE1 signaling in central nervous system diseases.

| Disease Name                  | Study Models                        | Molecules in IRE1 Signaling Analyzed | Conclusions                                                                                     | Refs.   |
|------------------------------|-------------------------------------|-------------------------------------|-------------------------------------------------------------------------------------------------|---------|
| Alzheimer’s disease (AD)     | Clinical patients                   | IRE1-XBP1                           | Phosphorylated IRE in hippocampal neurons and XBP1 in cortical areas are overexpressed in AD patients; The -116C/G polymorphism in XBP1 promoter is identified as a risk factor to develop AD in the Chinese population. | [29-31] |
|                              | In-vivo mouse model                 | IRE1-XBP1                           | Targeting IRE1 leads to reduced amyloid deposits, improved cognitive and synaptic function, and attenuated astrogliosis; XBP1s prevents the Aβ neurotoxicity. | [5, 32] |
|                              | In-vitro cell culture               |                                     | Protective activity of XBP1 can be mediated by the downregulation of ryanodine receptors 3.       | [32]    |
| Parkinson’s disease (PD)     | In-vivo drosophila, rat and mouse model | IRE1-XBP1                           | XBP1 KO triggers the degeneration of dopaminergic neurons; XBP1 transgene promotes dopaminergic neurons and neural stem cells survival and improves the symptoms of PD. | [39-42] |
| Huntington’s disease (HD)    | Clinical patients                   | IRE1-XBP1                           | phosphorylated IRE1 is increased in striatal tissues of HD patients; XBP1 is overexpressed in the striatum of HD patients. | [7, 44] |
|                              | In-vitro cell culture               | IRE1-TRAF2                          | Activation of IRE1-TRAF2 stimulates Htt aggregation and induces death of neuronal cells.        | [44]    |
| Ischemic stroke              | In-vivo rat model                   | IRE1-TRAF2 and IRE1-XBP1            | IRE1-TRAF2-JNK/p38 pathway mediates ischemia-reperfusion-related neuronal injury; XBP1 and GRP78 are overexpressed in injured brain regions. | [8, 50, 53, 55] |
| Post-traumatic stress disorder (PTSD) | In-vivo rat model                   | IRE1-XBP1                           | IRE1-XBP1 pathway is activated in the mPFC and locus coeruleus of PTSD models; IRE1 inhibitor treatment attenuates neuronal apoptosis in response to single-prolonged stress stimulation. | [58, 60, 61] |
| Glioma                       | Clinical patients                   | IRE1-XBP1                           | XBP1 is overexpressed in human glioma tissues.                                                  | [66]    |
|                              | In-vivo mouse model                 | IRE1-XBP1                           | IRE1 KO reduces tumor growth and angiogenesis through inhibition of hypoxia or glucose deprivation induced VEGF-A expression. | [62, 63] |
|                              | In-vitro cell culture               | IRE1-XBP1                           | IRE1 KO reduces hypoxia or glucose deprivation induced VEGF-A expression; IRE1 KO relieves extracellular matrix protein SPARC, sustains circadian clock protein PER1 and then decreases tumor growth, infiltration and invasion; XBP1 KO protects glioma cells against oxidative stress via up-regulating catalase. | [63-65] |
| Mesial temporal lobe epilepsy (MTLE) | Clinical patients                   | IRE1-TRAF2                          | IRE1-TRAF2-ASK1-JNK pathway is activated in temporal neocortex of MTLE; XBP1 is overexpressed in MTLE hippocampi. | [67, 68] |
| Amyotrophic lateral sclerosis | In-vivo mouse model                 | IRE1-XBP1                           | XBP1 KO enhances clearance of the mutant superoxide dismutase-1 protein via autophagy.          | [69]    |
| Spinal cord injury (SCI)     | In-vivo mouse model                 | IRE1-XBP1                           | XBP1 deficiency attenuates locomotor recovery after SCI whereas XBP1s gene transfer into the SCI site enhances locomotor recovery. | [9]     |
| Cerebral malaria             | In-vivo mouse model                 | IRE1-XBP1                           | IRE1-XBP1 pathway is activated in experimental cerebral malaria and then protects against neuronal cell death. | [70]    |

Abbreviations: IRE1, Inositol-requiring enzyme 1; XBP1, X box-binding protein 1; Aβ, β-amyloid; KO, knock out; TRAF2, tumor necrosis factor receptor associated factor 2; Htt, huntingtin; JNK1/2, JUN N-terminal kinase 1/2; GRP78, glucose regulated protein; mPFC, medial prefrontal cortex; VEGF-A, vascular endothelial growth factor-A; ASK1, Apoptosis signal-regulating kinase 1.
approach. XBP1 active form (XBP1s) was delivered into the SN of adult mice using adeno-associated viral vectors (AAVs), conferring neuroprotective effect in dopaminergic neurons against 6-OHDA-mediated neurotoxicity [39]. In another study, the XBP1s transgene also prevented the degeneration of striatal dopaminergic neurons in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse model, which is one of the most commonly used PD models [41]. In addition to neuroprotective effect in dopaminergic neurons, a recent study also suggested that XBP1 transfection increased neural stem cells survival and improved behavior in a rotenone-induced rat model of PD [42].

4.3. IRE1 Signaling in Huntington’s Disease

HD is the most common inherited neurodegenerative disease characterized by motor abnormalities, and onset of psychiatric symptoms and dementia in early- to mid-adult life. The mutation responsible for HD leads to an abnormally long polyglutamine (polyQ) expansion in the huntingtin (Htt) protein, which confers one or more toxic functions to mutant Htt leading to neuronal loss in the striatum [43]. Recent clinical research showed that the expression levels of phosphorylated IRE1 were increased in striatal tissues of HD patients compared with controls by Western blot analysis [44]. Further evidence supported that the activity of IRE1-TRAF2 is necessary to stimulate Htt aggregation and induce neuronal cells death in vitro [44]. In addition, another study reported elevated protein expression of XBP1s in the striatum of HD patients compared with control subjects, while no detectable changes were observed in cortex and cerebellum samples from the same individuals [7]. Interestingly, the authors provided correlative evidence indicating that XBP1 deficiency might improve motor performance and neuronal survival, which is in contrast to its traditional role in CNS diseases pathology. These beneficial effects of XBP1 deficiency could be in part explained by the upregulation of FoxO1-dependent autophagy associated with reduced accumulation of mHtt aggregates in the striatum, but it is more likely that continuous improved degradation of the soluble forms of the protein prevents its organization into aggregates in these animals [7, 22]. Thus, additional research is warranted to better understand the complex role of IRE1 signaling in HD pathogenesis.

4.4. IRE1 Signaling in Ischemic Stroke

Acute ischemic stroke is among the leading causes of death and long-term disability in elders [45, 46]. Ischemia and hypoxia resulting from arterial occlusion or hypotension in patients lead to major damage to the brain with glucose deprivation, which causes endoplasmic ER stress and neuronal death [47-49]. Recent research suggested that neuronal ischemic injury increased cell cytotoxicity and apoptosis, which occurred via the activation of IRE1-TRAF2 pathway and downstream kinases which further activated JNK and p38 MAPK [50-52]. However, additional research showed that IRE1 signaling also exerted neuroprotective effect in a rat model of focal cerebral ischemia by middle cerebral artery occlusion. A marked increase in the expression of XBP1 and GRP78 mRNA was found both in the striatum and cortex of injured brain regions [8, 53, 54]. Similarly, another study using immunofluorescence staining also showed the temporal profile of GRP78 expression in ischemic neurons [55]. These findings support that IRE1-XBP1 pathway seems to be pro-survival in ischemic stroke by activating the transcription offer chaperones. However, more robust clinical and scientific studies are required to reveal the relationship between IRE1 signaling and ischemic stroke and also to determine the functional roles of correlative IRE1 pathways in the pathogenesis of ischemia/reperfusion injury.

4.5. IRE1 Signaling in Post-Traumatic Stress Disorder

PTSD is a delayed and long-term psychiatric disorder that may develop after exposure to a serious life-threatening trauma [56, 57]. PTSD shows four Cardinal symptoms: re-experiencing of the traumatic event, numbness, negative alteration in cognition and mood, and symptoms of avoidance and hyperarousal [58, 59]. The medial prefrontal cortex (mPFC) is considered as the critical area of cognition about stress information. Recent studies have shown that there were abnormal expansion of ER and upregulations of IRE1 and XBP1 in the mPFC of rats exposed to single-prolonged stress (SPS), which is a reliable model of PTSD [58, 60], suggesting that the activation of the IRE1-XBP1 pathway is involved in the pathogenesis of PTSD. Furthermore, another study has shown that the IRE1 pathway was significantly activated in the locus coeruleus of a rat PTSD model [61]. Treatment with STF-083010, an IRE1 RNase-specific inhibitor, could attenuate the IRE1 activation, specific splicing of XBP1, increased GRP78 expression and neuronal apoptosis in response to SPS stimulation [61]. Taken together, above data illustrate that the IRE1-XBP1 pathway is involved in PTSD, which suggests a new therapeutic target for the disease.

4.6. IRE1 Signaling in Glioma

Malignant gliomas are the most frequent primary brain tumors and their treatment still remains a challenging issue. An increasing body of evidence indicates a functional link between IRE1 signaling and glioma growth/progression [10]. Indeed, impairing IRE1 signaling in human glioma cells reduced tumor growth and angiogenesis both in vitro and in vivo through mechanisms dependent on inhibition of hypoxia or glucose deprivation induced VEGF expression [62, 63]. Furthermore, In-vitro study has been shown that inactive IRE1 in glioma cells relieved the post-transcriptional repression of an important modulator of astrocytoma cell migration, SPARC. This in turn led to decreased tumor growth, infiltration and invasion in a Rho-dependent way [64]. Similarly, the inhibition of IRE1 signaling by either siRNA or a dominant-negative strategy resulted in sustained expression of circadian clock PER1 which was associated with reduced tumorigenesis in the U87 model [65]. In addition, the IRE1 substrate XBP1 has been shown to protect glioma cells against oxidative stress via up-regulating antioxidant molecules such as catalase [66]. This report also showed an increased expression of XBP1 in human glioma tissues, as compared with normal brain tissues, supporting the obstruction of IRE1-XBP1 pathway as a novel therapeutic for glioma.
4.7. IRE1 Signaling in Other CNS Diseases

As an ER stress sensor, IRE1 signaling is associated with many other diseases affecting the CNS. IRE1-ASK1-JNK signaling cascade is activated in resected temporal neocortex of mesial temporal lobe epilepsy (MTLE) patients [67]. Simultaneously, XBP1 is also overexpressed and activated in MTLE hippocampi [68], suggesting that both IRE1-mediated pro and anti-apoptotic signaling pathways might be involved in epileptic brain damage. In mouse models of amyotrophic lateral sclerosis, XBP1 deficiency leads to augmented autophagy, which enhances clearance of the mutant superoxide dismutase-1 protein and decreases its toxicity [69]. In contrast, XBP1 is required for locomotor recovery after spinal cord injury [9]. In addition, the activation of IRE1-XBP1 pathway also plays an important role in protecting neuronal cell death in experimental cerebral malaria by Plasmodium berghei ANKA infection in mice [70].

CONCLUSION

Taken together, there are clear indications that IRE1 signaling is involved in a range of neurological disorders and plays important roles in pathological processes (Fig. 1). In brief, IRE1 mediates both adaptive and pro-apoptotic pathways in CNS diseases. Under ER stress, IRE1-XBP1 axis mainly serves neuroprotective and anti-apoptosis effects by inducing the production of UPR gene Bip, up-regulation of antioxidant molecules such as catalase [66], and inhibition of Caspase-3 activation and free calcium accumulation in the cytosol [32]. In addition, IRE1 also acts on promoting apoptosis by activating the JNK/p38 pathway and downstream pro-apoptotic factors (e.g. Caspase-4/12 [3, 4], CHOP [3] and calcrin [5]) through a direct interaction with TRAF2. Up to date, however, the intrinsic factors which determine the role of IRE1 in CNS diseases have been less investigated and remain unclear. A well-established hypothesis is that the switch between anti-apoptotic and pro-apoptotic signaling of activated IRE1 might be dependent upon the ER stress intensity or duration [71]. At the initial phase, IRE1-XBP1 pathway is triggered to protect cells against cytotoxicity. Nevertheless, if the stress is intensive or prolonged, the IRE1-XBP1 pathway may fade out gradually and instead the IRE1-TRAF2 axis contributes to the transition to an apoptotic phase.

PROSPECTIVE

Despite the fact that IRE1 signaling is now widely recognized as a new therapeutic target against CNS diseases, what remains to be discovered is how successful strategies that target on this signaling will be applied to the clinical treatment. However, to translate the current knowledge of IRE1 signaling into clinical therapeutics for CNS diseases is still
The Role of IRE1 Signaling in the Central Nervous System Diseases

challenging. Rather than using natural products with pleiotropic effects, the development and testing of specific IRE1 signaling targeting molecules, such as small molecules targeting IRE1 or XBP1 [72], is warranted to examine the IRE1 signaling as a promising target for therapy in patients of CNS diseases.

CONSENT FOR PUBLICATION
Not applicable.

CONFLICT OF INTEREST
The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS
Declared none.

REFERENCES
[1] Diehl, J.A.; Fucho, S.Y.; Kuemmins, C. The cell biology of the unfolded protein response. Gastroenterology. 2011, 141(1), 38-41. e31-32. [http://dx.doi.org/10.1053/j.gastro.2011.05.018]

[2] Chinta, S.J.; Rane, A.; Poksay, K.S.; Bredesen, D.E.; Andersen, J.K.; Rao, R.V. Coupling endoplasmic reticulum stress to the cell death program in dopaminergic cells: effect of paraquat. Neuronmol. Med. 2008, 10(4), 333-342. [http://dx.doi.org/10.1007/s12070-008-0047-9] [PMID: 18773310]

[3] Tirasophon, W.; Weinhinda, A.A.; Kaufman, R.J. A stress response pathway from the endoplasmic reticulum to the nucleus requires a novel bifunctional protein kinase/endonuclease (Ire1p) in mammalian cells. Genes Dev., 1998, 12(12), 1812-1824. [http://dx.doi.org/10.1101/gad.12.12.1812] [PMID: 9637683]

[4] Lin, J.H.; Li, H.; Yasumura, D.; Cohen, H.R.; Zhang, C.; Panning, B.; Shokat, K.M.; Lavail, M.M.; Walter, P. IRE1 signaling affects cell fate during the unfolded protein response. Science, 2007, 318(5852), 944-949. [http://dx.doi.org/10.1126/science.1146361] [PMID: 17991856]

[5] Duran-Aniotz, C.; Cornejo, V.H.; Espinoza, S.; Ardiles, A.O.; Medina, D.B.; Salazar, C.; Foley, A.; Gajardo, I.; Iwawaki, T.; Scheper, W.; Soto, C.; Walter, P.; Ron, D. The unfolded protein response enhances mitochondrial function in brain of mice with ischemic stroke through Akt-mediated mTOR pathway. Transl. Stroke Res., 2016, 7(6), 497-511. [http://dx.doi.org/10.1007/s12975-016-0441-7] [PMID: 25750795]

[6] Sano, R.; Reed, J.C. ER stress-induced cell death mechanisms. Biochim. Biophys. Acta, 2013, 1833(12), 3460-3470. [http://dx.doi.org/10.1016/j.bbamcr.2013.06.028] [PMID: 23850759]

[7] Qi, Z.; Dong, W.; Shi, W.; Liu, S.; Zhang, C.; Zhao, Y.; Ji, X.; Liu, K.J.; Luo, Y. Bcl-2 phosphorylation triggers autophagy switch and reduces mitochondrial damage in limb remote ischemic conditioned rats after ischemic stroke. Transl. Stroke Res., 2016, 7(3), 193-200. [http://dx.doi.org/10.1007/s12975-015-0393-y] [PMID: 25744447]

[8] Nakka, V.P.; Gusein, A.; Raghuram, R. Endoplasmic reticulum stress plays critical role in brain damage after cerebral ischemia/reperfusion in rats. Neurotox. Res., 2010, 17(2), 189-202. [http://dx.doi.org/10.1007/s12008-009-9110-5] [PMID: 19763736]

[9] Valenzuela, V.; Colley, E.; Armentano, D.; Parsons, G.B.; Court, F.A.; Hetz, C. Activation of the unfolded protein response enhances motor recovery after spinal cord injury. Cell Death Dis., 2012, 3, e272. [http://dx.doi.org/10.1038/cddis.2012.8] [PMID: 22337234]

[10] Peharanda Fajardo, N.M.; Meijer, C.; Krutz, F.A. The endoplasmic reticulum stress/unfolded protein response in gliomagenesis, tumor progression and as a therapeutic target in glioblastoma. Biochem. Pharmacol., 2016, 118, 1-8. [http://dx.doi.org/10.1016/j.bcp.2016.04.008] [PMID: 27106078]

[11] Sitia, R.; Braamka, I. Quality control in the endoplasmic reticulum protein factory. Nature, 2003, 426(6968), 891-894. [http://dx.doi.org/10.1038/nature02262] [PMID: 14685249]

[12] Hotamisgil, G.S. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. Cell, 2010, 140(6), 900-917. [http://dx.doi.org/10.1016/j.cell.2010.02.034] [PMID: 20303879]

[13] Liutus, V.A.; Alfaro-Martinez, F.; Bedoya, F.; Chung, C.C.; Pimentel, D.A.; Novak, V. Intravenous insulin and insulin-Like Growth Factor 1 as neuroprotectants in acute ischemic stroke. Transl. Stroke Res., 2015, 6(4), 264-275. [http://dx.doi.org/10.1007/s12975-015-0409-7] [PMID: 26404023]

[14] Shenoda, B. The role of Na+/Ca2+ exchanger subtypes in neuronal ischemic injury. Transl. Stroke Res., 2015, 6(3), 181-190. [http://dx.doi.org/10.1007/s12975-015-0395-9] [PMID: 25860439]

[15] Walter, P.; Ron, D. The unfolded protein response: from stress pathway to homeostatic regulation. Science, 2011, 334(6059), 1081-1086. [http://dx.doi.org/10.1126/science.1209038] [PMID: 22116877]

[16] Koizumi, N.; Martinez, I.M.; Kiyama, Y.; Kohno, K.; Sano, H.; Chrispeels, M.J. Molecular characterization of two Arabidopsis IRE1 homologs, endoplasmic reticulum-located transmembrane protein kinases. Plant Physiol., 2001, 127(3), 949-962. [http://dx.doi.org/10.1104/pp.010592a] [PMID: 11760177]

[17] Calfon, M.; Zeng, H.; Urano, F.; Till, J.H.; Hubbard, S.R.; Harding, H.P.; Clark, S.G.; Ron, D. IRE1 couples endoplasmic reticulum load to secretory capacity by processing the XBP-1 mRNA. Nature, 2002, 415(6867), 92-96. [http://dx.doi.org/10.1038/415059a] [PMID: 11780124]

[18] Yoshida, H.; Matsu, T.; Yamamoto, A.; Okada, T.; Morita, M.; Kondo, T.; Uchi, A. ER stress and Parkin-associated autophagy pathway. Disentangling Alzheimer’s disease. Lancet Neurol., 2012, 11(9), 701-717. [http://dx.doi.org/10.1016/S1474-4422(11)70171-5] [PMID: 21802368]

[19] Kurata, T.; Fukata, K.; Kozuki, M.; Wada, D.; Miyazaki, K.; Morimoto, N.; Ohta, Y.; Deguchi, T.; Yamashita, T.; Hishikawa, N.; Matsuizono, K.; Ikeda, Y.; Kamiya, T.; Abe, K. Long-term effect of telmisartan on Alzheimer’s amyloid genesis in SHR-SR after
modified neural stem cells for treatment of Parkinson’s disease. J. Neurosci., 2008, 31(9), 454-463. [PMID: 18675468]

[50] Chen, J.H.; Kuo, H.C.; Lee, K.F.; Tsai, T.H. Global proteomic analysis of brain tissues in transient ischemia brain damage in rats. Int. J. Mol. Sci., 2015, 16(6), 11873-11891. [PMID: 26016499]

[51] Maier, P.J.; Zemoura, K.; Acuña, M.A.; Yévenes, G.E.; Zielhofer, H.U.; Benke, D. Ischemia-like oxygen and glucose deprivation mediates down-regulation of cell surface γ-aminobutyric acidB receptors via the endoplasmic reticulum (ER) stress-induced transcription factor CCAAT-enhancer-binding protein (C/EBP)-homologous protein (CHOP). J. Biol. Chem., 2014, 289(18), 12896-12907. [PMID: 25000542]

[52] Paschen, W.; Aufenberg, C.; Hotop, S.; Mengesdorf, T. Transient cerebral ischemia activates processing of xbp1 messenger RNA indicative of endoplasmic reticulum stress. J. Cereb. Blood Flow Metab., 2003, 23(4), 449-461. [PMID: 1289722]

[53] Koh, S.H.; Park, H.H. Neurogenesis in Stroke Recovery. Transl. Stroke Res., 2017, 8(1), 3-13. [PMID: 2897222]

[54] Zhang, H.Y.; Wang, Z.G.; Lu, X.H.; Kong, X.X.; Wu, F.Z.; Lin, L.; Tan, X.; Ye, L.B.; Xiao, J. Endoplasmic reticulum stress: relevance and therapies in central nervous system diseases. Mol. Neurobiol., 2015, 57(3), 1343-1352. [PMID: 26048984]

[55] Valdés, P.; Mercado, G.; Vidal, R.L.; Molina, C.; Parsons, G.; Court, F.A.; Martínez, A.; Galleguillos, D.; Arambarri, D.; Schneider, B.L.; Hetz, C. Control of dopaminergic neuron survival by the unfolded protein response transducer water- and intermediate hydrogen gas exposure, but not lactulose or continuous hydrogen gas exposure, prevent 6-hydroxydopamine-induced Parkinson’s disease in rats. Med. Gas. Res., 2012, 2, 15. [PMID: 22602009]

[56] Fournet, A.; Levet, C.; Virgone, A.; Robin, M.; Dourlen, P.; Rieusset, J.; Belaidi, E.; Ovize, M.; Touret, M.; Nataf, S.; Mollereau, B. ER stress inhibits neuronal death by promoting autophagy. Autophagy, 2012, 8(6), 915-926. [PMID: 22466027]

[57] Sado, M.; Yamashita, O.; Iwanaga, T.; Onaka, Y.; Ibuki, T.; Nishihara, S.; Mizuguchi, H.; Momota, H.; Kishibuchi, R.; Hashimoto, T.; Wada, D.; Kitagawa, H.; Watanabe, T.K. Protective effect against Parkinson’s disease-related insults through the activation of XBP1. Proc. Natl. Acad. Sci. USA, 2014, 111(18), 6804-6809. [PMID: 24753614]

[58] Fouillot, A.; Levet, C.; Virgone, A.; Robin, M.; Dourlen, P.; Rieusset, J.; Belaidi, E.; Ovize, M.; Touret, M.; Nataf, S.; Mollereau, B. ER stress inhibits neuronal death by promoting autophagy. Autophagy, 2012, 8(6), 915-926. [PMID: 22466027]

[59] Sado, M.; Yamashita, O.; Iwanaga, T.; Onaka, Y.; Ibuki, T.; Nishihara, S.; Mizuguchi, H.; Momota, H.; Kishibuchi, R.; Hashimoto, T.; Wada, D.; Kitagawa, H.; Watanabe, T.K. Protective effect against Parkinson’s disease-related insults through the activation of XBP1. Proc. Natl. Acad. Sci. USA, 2014, 111(18), 6804-6809. [PMID: 24753614]

[60] Sado, M.; Yamashita, O.; Iwanaga, T.; Onaka, Y.; Ibuki, T.; Nishihara, S.; Mizuguchi, H.; Momota, H.; Kishibuchi, R.; Hashimoto, T.; Wada, D.; Kitagawa, H.; Watanabe, T.K. Protective effect against Parkinson’s disease-related insults through the activation of XBP1. Proc. Natl. Acad. Sci. USA, 2014, 111(18), 6804-6809. [PMID: 24753614]

[61] Si, L.; Xu, T.; Fang, F.; Liu, Q.; Cui, M. X-box-binding protein 1-modified neural stem cells for treatment of Parkinson’s disease. Neural Regen. Res., 2017, 10(9), 736-740. [PMID: 25737695]

[62] Bossy-Wetzel, E.; Petrilli, A.; Knott, A.B. Mutant huntingtin and mitochondrial dysfunction. Trends Neurosci., 2008, 31(12), 609-616. [PMID: 18951640]

[63] Lee, H.; Noh, J.Y.; Oh, Y.; Kim, Y.; Chang, J.W.; Chung, C.W.; Lee, S.T.; Kim, M.; Ryu, H.; Jung, Y.K. IRE1 plays an essential role in ER stress-mediated aggregation of mutant huntingtin via the inhibition of autophagy flux. Hum. Mol. Genet., 2012, 21(1), 101-114. [PMID: 21954231]
The Role of IRE1 Signaling in the Central Nervous System Diseases

[62] Auf, G.; Jabouille, A.; Guérin, S.; Pineau, R.; Delugin, M.; Bouche-careilh, M.; Magnin, N.; Favereaux, A.; Maitre, M.; Gainer, T.; von Deimling, A.; Czbanka, M.; Vajkoczy, P.; Chevet, E.; Bikfalvi, A.; Moenner, M. Inositol-requiring enzyme I alpha is a key regulator of angiogenesis and invasion in malignant glioma. Proc. Natl. Acad. Sci. USA, 2010, 107(35), 15553-15558. [http://dx.doi.org/10.1073/pnas.0914072107] [PMID: 20702765]

[63] Drobat, B.; Auguste, P.; Nguyen, D.T.; Bouche-careilh, M.; Pineau, R.; Nalbantoglu, J.; Kaufman, R.J.; Chevet, E.; Bikfalvi, A.; Moenner, M. IRE1 signaling is essential for ischemia-induced vascular endothelial growth factor-A expression and contributes to angiogenesis and tumor growth in vivo. Cancer Res., 2007, 67(14), 6700-6707. [http://dx.doi.org/10.1158/0008-5472.CAN-06-3235] [PMID: 17638880]

[64] Dejeans, N.; Pluquet, O.; Lhomonod, S.; Grise, F.; Bouche-careilh, M.; Juin, A.; Meynard-Cadars, M.; Bidaud-Meynard, A.; Gentil, C.; Moreau, V.; Saltel, F.; Chevet, E. Autocrine control of glioma cells adhesion and migration through IRE1 alpha-mediated cleavage of SPARC mRNA. J. Cell Sci., 2012, 125(Pt 18), 4278-4287. [http://dx.doi.org/10.1242/jcs.099291] [PMID: 22718352]

[65] Pluquet, O.; Dejeans, N.; Bouche-careilh, M.; Lhomonod, S.; Pineau, R.; Higa, A.; Delugin, M.; Combe, C.; Loriot, S.; Cubel, G.; Dugot-Senant, N.; Vital, A.; Liseau, H.; Gosline, S.J.; Taouji, S.; Hallett, M.; Sarkaria, J.N.; Anderson, K.; Wu, W.; Rodriguez, F.J.; Rosenbaum, J.; Saltel, F.; Fernandez-Zapico, M.E.; Chevet, E. Posttranscriptional regulation of PER1 underlies the oncogenic function of IRE1. Cancer Res., 2013, 73(15), 4732-4743. [http://dx.doi.org/10.1158/0008-5472.CAN-12-3989] [PMID: 23752693]

[66] Liu, Y.; Zhang, X.; Liang, Y.; Yu, H.; Chen, X.; Zheng, T.; Zheng, B.; Wang, L.; Zhao, L.; Shi, C.; Zhao, S. Targeting X box-binding protein-1 (XBP1) enhances sensitivity of glioma cells to oxidative stress. Neuropathol. Appl. Neurobiol., 2011, 37(4), 395-405. [http://dx.doi.org/10.1111/j.1365-2990.2010.01155.x] [PMID: 21138464]

[67] Liu, G.L.; Wang, K.Y.; Guo, H.; Zhao, S.J.; Shen, Y.; Zhao, Y.B. Inositol-requiring protein 1 alpha signaling pathway is activated in the temporal cortex of patients with mesial temporal lobe epilepsy. Neuron Sci., 2013, 34(3), 357-364. [http://dx.doi.org/10.1007/s10072-012-1008-y] [PMID: 22419015]

[68] Liu, G.; Guo, H.; Guo, C.; Zhao, S.; Gong, D.; Zhao, Y. Involvement of IRE1 alpha signaling in the hippocampus in patients with mesial temporal lobe epilepsy. Brain Res. Bull., 2011, 84(1), 94-102. [http://dx.doi.org/10.1016/j.brainresbull.2010.10.004] [PMID: 20965234]

[69] Hetz, C.; Thielen, P.; Matus, S.; Nassif, M.; Court, F.; Kiffin, R.; Martinez, G.; Cuervo, A.M.; Brown, R.H.; Glimcher, L.H. XBP1 deficiency in the nervous system protects against amyotrophic lateral sclerosis by increasing autophagy. Genes Dev., 2009, 23(19), 2294-2306. [http://dx.doi.org/10.1101/gad.1830709] [PMID: 19762508]

[70] Anand, S.S.; Babu, P.P. Endoplasmic reticulum stress and neurodegeneration in experimental cerebral malaria. Neurosignals, 2013, 21(1-2), 99-111. [http://dx.doi.org/10.1159/000336970] [PMID: 22584375]

[71] Wu, J.; He, G.T.; Zhang, W.J.; Xu, J.; Huang, Q.B. IRE1 alpha Signaling pathways involved in mammalian cell fate determination. Cell. Physiol. Biochem., 2016, 38(3), 847-858. [http://dx.doi.org/10.1159/000463029] [PMID: 26910807]

[72] Pampandreu, I.; Denko, N.C.; Olson, M.; Van Meers, H.; Lusty, S.; Tam, A.; Solow-Cordero, D.E.; Bouley, D.M.; Offner, F.; Niwa, M.; Koong, A.C. Identification of an Ire1alpha endonuclease specific inhibitor with cytotoxic activity against human multiple myeloma. Blood, 2011, 117(4), 1311-1314. [http://dx.doi.org/10.1182/blood-2010-08-303099] [PMID: 21081713]