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Invited review

Endoplasmic reticulum stress in cerebral ischemia

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ABSTRACT

The endoplasmic reticulum (ER) stress is an essential step in the progression of brain ischemia/reperfusion (I/R) injury. It is possible that the timing of events for ER stress signaling regulation is important for the balance of life and death such that ER stress is initially protective, aiming to restore ER homeostasis, whereas prolonged periods of ER stress can be deleterious and damaging. Nevertheless, modulation of ER stress exerts a remarkable protective effect on the ischemic brain and offers the prospect of new stroke therapies. As ER stress is not devoid of deleterious side effects, a better understanding of the reciprocal interaction between the ER and the ischemic brain is essential to harness the full therapeutic potential of ischemic stroke.

1. Introduction

The World Health Organization estimates that every year, 15 million people suffer a stroke, a devastating illness second only to cardiac ischemia as a cause of death worldwide. Despite this, interventions to treat stroke remain extremely limited (Moskowitz et al., 2010). Recent developments have revealed that endoplasmic reticulum (ER) stress is an essential signaling event for neuronal injury resulting from ischemia/reperfusion (I/R) (Ma and Hendershot, 2004; Anelli and Sitia, 2008; Osada et al., 2012; Nakka et al., 2010). Ischemic preconditioning protects against I/R injury, which is associated with reduction of excessive ER stress during subsequent fatal ischemia (Sheng et al., 2012; Mahfoudh-Boussaid et al., 2012). Certain stimuli such as ischemia, hypoxia, and hypertension might trigger the accumulation of unfolded proteins in the ER lumen, leading to the unfolded protein response (UPR) which involves expansion of ER membranes, accelerated degradation of unfolded proteins, increased translation of folding chaperones, and inhibition of other protein synthesis (Kaufman, 1999; Herrmann et al., 2013). After ER stress induced by oxygen and glucose depriva-

Abbreviations: ER, endoplasmic reticulum; I/R, ischemia/reperfusion; UPR, unfolded protein response; OGD, oxygen and glucose deprivation; PERK, double-stranded RNA-dependent protein kinase-like ER kinase; IRE1, inositol requiring enzyme-1; ATF6, activating transcription factor 6; GRP78, glucose regulated protein 78; BIP, binding immunoglobulin protein; HSP5A, heat shock protein 5A; ERAD, ER-associated degradation; CHOP, CCAAT/enhancer binding protein homologous protein; GADDl53, growth arrest and DNA damage inducible gene/protein 153; GADD34, growth arrest and DNA damage inducible gene/protein 34; JNK, c-Jun N-terminal kinase; MCAO, middle cerebral artery occlusion; BDNF, brain-derived neurotrophic factor; COX-2, cyclooxygenase-2; bcl-2, B-cell lymphoma-2; bax, bcl-2 associated X protein; BIK, bcl-2-interacting killer; ORP150, 150 kDa oxygen-regulated protein; SMCs, smooth muscle cells; oxLDL, oxidized low-density lipoprotein; eIF2α, eukaryotic initiation factor 2α; PSI, protein synthesis inhibition; ATF4, activating transcription factor 4; ATF/CREB, activating transcription factor/cyclic AMP response element binding protein; bZip, basic region-leucine zipper; CRE, cAMP responsive element; CREB, cAMP response element binding factor; XBP1, X-box-binding protein 1; ERSE, ER stress-response elements; NOS, nitric oxide synthase; nNOS, neuronal NOS; iNOS, inducible NOS; NO, nitric oxide; OGD/R, oxygen and glucose deprivation/reoxygenation; TRAF2, tumor necrosis factor receptor associated factor 2; ROS, reactive oxygen species; p38 MAPK, p38 mitogen-activated protein kinase; TG, thapsigargin; BFA, brefeldin A; ICE, interleukin-1β converting enzyme; NMDA, N-methyl-D-aspartate; MAPKs, mitogen-activated protein kinases; ERKs, extracellular signal-regulated kinases; SAPK, stress-activated protein kinase; ASK1, apoptosis signal-regulating kinase 1; MPAP3K, mitogen-activated protein kinase kinase kinase; JIK, C-jun-N-terminal-inhibiting kinase; AP-1, activator protein 1; EAE, experimental autoimmune encephalomyelitis; AD, Alzheimer's Disease; PG, prostaglandin; IFN-γ, interferon-γ; IL-6, interleukin-6; IP_3R, inositol 1,4,5,-triphosphate receptor; RyR, ryanodine receptor; PTP, permeability transition pore; MMP, mitochondrial membrane potential; MAMs, mitochondria-associated membranes; PACS-2, phosphofurin acidic cluster sorting protein-2; BBB, blood–brain barrier; PD, Parkinson's disease.

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tion (OGD), ER appears swelling. A larger ER volume enables larger numbers of misfolded proteins to be incorporated within the ER membrane and reduces the concentration of protein intermediates, thus reducing the risk of protein aggregate formation and increasing cellular capacity to deal with abundant protein damage (Herrmann et al., 2013; Schuck et al., 2009; Apetri and Horwich, 2008). Cerebral ischemia might perturb ER function resulting in accumulation of unfolded proteins in the ER lumen, a condition referred to as ER stress. It then triggers the UPR to restore ER functions via activation of three ER transmembrane receptors namely double-stranded RNA-dependent protein kinase-like ER kinase (PERK), inositol requiring enzyme-1 (IRE1), activating transcription factor 6 (ATF6), respectively (Kim et al., 2008). In the physiological state, IRE-1, PERK, and ATF-6 are inhibited by binding to glucose regulated protein 78 (GRP78), an ER chaperone, also known as binding immunoglobulin protein (BIP) and as Heat shock protein 5A (HSP5A). Under conditions associated with the perturbation of ER functions, GRP78 dissociates from these ER transmembrane proteins, initiating UPR. The UPR is initially a protective response aimed to restore ER functions predominantly through translational attenuation of proteins, up-regulation GRP78 and ER-associated degradation (ERAD) of unfolded proteins. If the stress is severe or prolonged, UPR can eventually result in promotion of pro-apoptotic pathways mediated by CCAAT/enhancer binding protein homologous protein (CHOP), caspase-12 and c-Jun N-terminal kinase (JNK) (Ferri and Kroemer, 2001; Paschen and Mengesdorf, 2005; Szegezdi et al., 2006). There are some potential drugs that have been proved to attenuate ER stress after experimental cerebral ischemia, which may become a strong candidate as a therapeutic agent in the treatment of ischemic brain disease of human stroke patients in the near future. For instance, dantrolene, a ryanodine receptor antagonist, significantly decreases infarct volume and provides neuroprotective effect on rats after transient middle cerebral artery occlusion (MCAO) by reducing ER stress-mediated apoptotic signal pathway activation in the ischemic area (Li et al., 2005); (−)-epigallocatechin-3-gallate (EGCG), the predominant constituent of green tea, has been demonstrated to be neuroprotective against stroke in rats through inhibition of ER stress-related markers and apoptosis (Yao et al., 2014); Cocaine and amphetamine regulated transcript (CRAT), a neuropeptide, is functional in inhibiting the cerebral I/R-induced ER stress and neuronal apoptosis by facilitating the transcription, synthesis and secretion of brain-derived neurotrophic factor (BDNF) in a cAMP response element binding factor (CREB)-dependent way (Qiu et al., 2013); Sodium phenylbutyrate, a chemical chaperone by targeting ER stress, ameliorates brain I/R damage associated with comorbid type 2 diabetes by reducing ER stress and DNA fragmentation (Srinivasan and Sharma, 2011); Edaravone, a free radical scavenger, can protect against ER damage induced by cerebral ischemia through inhibiting the eukaryotic initiation factor 2α (eIF2α) phosphorylation, CHOP induction and caspase-12 activation (Qi et al., 2004). In conclusion, drugs specific to ER stress signaling may be useful therapeutic approaches for cerebral ischemia.

2. ER stress signaling

2.1. GRP78

GRP78, widely used as a sentinel marker for ER stress under pathologic conditions, binds transiently to newly synthesized proteins translocated into the ER and more permanently to unfolded or misfolded proteins (Yoshida et al., 1998). Upon UPR activation, GRP78 is released to facilitate protein folding, prevent the aggregation and facilitate the proteasome degradation of misfolded proteins (Jin et al., 2000). Accumulating evidence emphasizes that the induction of GRP78 prevents neuronal death induced by ER stress (Yuan et al., 2011; Lehotsky et al., 2009; Ye et al., 2013). It has been reported that GRP78 can restore proteins to their correct conformation, maintain the homeostasis of internal environment, provide protection for cell survival and can also help neurons withstand the stressful conditions during ischemic stroke (Rao et al., 2004; Lee, 2001; Liu et al., 1997). A recent study indicated that GRP78 functions an anti-apoptotic molecule under ER stress, as the up-regulation of GRP78 promotes the expression of the pro-survival protein, B-cell lymphoma-2 (bcl-2), and inhibits the expression of the pro-apoptotic protein, bcl-2 assaciated X protein (bax) after cerebral ischemic injury (Wang et al., 2013). One previous study reported that increased expression of GRP78 decreases bcl-2-interacting killer (BIK) binding to bcl-2 at the ER (Zhou et al., 2011). However, it is debatable whether GRP78 is actually involved in the up-regulation of bcl-2 as it is also reported that GRP78-mediated ER stress can down-regulate the bcl-2 protein, which mediates mitochondria-dependent cell death (Su et al., 2011). Nevertheless, GRP78 is involved in the down-regulation of the expression of bax. The mRNA expression of GRP78 is negatively correlated with the mRNA expression of bax and the reduction in GRP78 protein expression causes the increased expression of the bax protein, thus promoting apoptosis. However, the mechanism by which GRP78 inhibits bax activation is presently unknown. GRP78 might interfere with bax activation by an alternative mechanism (Sun et al., 2012; Ranganathan et al., 2006). GRP78 are Ca^{2+}-dependent proteins hence disturbance in calcium homeostasis significantly impairs the ER protein folding function. Moreover, the biosynthesis and biological functions of GRP78 also depends on the 150 kDa oxygen-regulated protein (ORP150), an ER-resident chaperone, up-regulated by hypoxia and prevents ischemia-induced cell death. A defect of ORP150 reduces the SMCs (smooth muscle cells) self-protective capacity against ER stress. SMCs are isolated from both $ORP150^{+/-}$ and $ORP150^{+/+}$ mice. The former proves more vulnerable to tunica-mycin-induced ER stress than the latter (Takizawa et al., 2007). A previous study pointed out the ability of ORP150 to maintain calcium homeostasis as a crucial mechanism of its protective effect against oxidized low-density lipoprotein (oxLDL)-induced apoptosis, since the activation of calpain and the mitochondrial apoptotic pathway were completely blocked (Sanson et al., 2008). Recently, researchers demonstrated that after focal cerebral ischemia, administration of parecoxib, a novel cyclooxygenase-2 (COX-2) inhibitor, protects brain from I/R injury, which is associated with the up-regulation GRP78 and ORP150 expression (Ye et al., 2013). Additionally, the increased expression of GRP78 attenuates the induction of CHOP during ER stress and reduces ER stress-induced apoptosis (Liu et al., 2013). To this end, a thorough analysis of the regulation of GRP78 could provide insight into the homeostatic role of ER stress, thus may lead to new therapeutic approaches for this ischemic stroke.

2.2. PERK

UPR should be conceptualized as consisting of two signal transduction cascades, resulting in suppression of protein synthesis at the initial step and induction of the expression of genes coding for ER stress proteins. In the first step, PERK and IRE1 are activated by autophosphorylation. In the neuronal homeostasis, autophosphorylation of PERK and IRE1 is suppressed by GRP78 protein binding to both kinases. Under ER dysfunction, GRP78 dissociates from PERK, ATF6, and IRE1, inducing the oligomerization, autophosphorylation and thus activation of these enzymes. PERK is a transmembrane ER stress-sensor protein, first