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ER Stress, CREB, and Memory: A Tangled Emerging Link in Disease

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Abstract

The brain undergoes several changes at structural, molecular, and cellular levels leading to alteration in its functions and these processes are primarily maintained by proteostasis in cells. However, an imbalance in proteostasis due to the abnormal accumulation of protein aggregates induces endoplasmic reticulum (ER) stress. This event, in turn, activates the unfolded protein response; however, in most neurodegenerative conditions and brain injury, an uncontrolled unfolded protein response elicits memory dysfunction. Although the underlying signaling mechanism for impairment of memory function following induction of ER stress remains elusive, recent studies have highlighted that inactivation of a transcription factor, CREB, which is essential for synaptic function and memory formation, plays an essential role for ER stress-induced synaptic and memory dysfunction. In this review, current studies and most updated view on how ER stress affects memory function in both physiological and pathological conditions will be highlighted.

Keywords

memory and synapse; CREB; brain injury; ER stress; Akt

Proteostasis and ER Stress Signaling Pathways

The biogenesis, folding, trafficking, and degradation of proteins are controlled inside a cell through a process of proteostasis where biological pathways integrate to regulate gene expression, stress signaling, quality control mechanisms, protein localization, and protein degradation systems (Balch and others 2008). This process serves as an underlying mechanism to maintain the functional proteome and prevention of abnormal aggregation (Balch and others 2008). The endoplasmic reticulum (ER) is an organelle where several proteins are expressed, which assist in protein folding, maturation, quality control, and degradation. The synthesis and folding of 30% of the proteome in eukaryotic cells, including all plasma membrane channels and receptors essential for synaptic function, are coordinated via ER. If the protein were unable to fold correctly, these proteins could be degraded through

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the ER-associated degradation (ERAD) pathway. Several shreds of evidence suggest that multiple transmembrane regions, are likely to misfold and aggregate during maturation spontaneously and about 10% of the total cargo does not reach its final destination (Balch and others 2008).

Exposure of extrinsic and intrinsic distresses to a cell causes an imbalance in proteostasis in the ER and induces the accumulation of misfolded proteins in the lumen of the ER by modifying the commitment of the proteome generating a stress state that is known as ER stress (Walter and Ron 2011). The ER stress is essential to maintain the quality of proteins under physiological condition; however, uncontrolled ER stress leads to the pathological condition. During the ER stress, several signaling transduction mechanisms were up-regulated to cope with the ER stress known as the unfolded protein response (Walter and Ron 2011). The UPR transduces information about the protein folding status from the ER lumen to the cytosol and nucleus to initiate a stress response that restores cellular proteostasis (Walter and Ron 2011) and sustains cell's function (Hetz and Saxena 2017).

The protein folding varies as the rate the protein synthesis altered inside cells. Thus, to control transcription and translation of a proteins cells have developed the “unfolded protein response” (UPR). Under physiological condition, UPR coordinate rates of protein synthesis with nutrient and energy stores, and regulate neuronal differentiation to survive nutrient-limiting conditions or to produce large amounts of secreted products such as neurotrophins. However, proteins have different ATP requirements for protein folding before export during pathological conditions. Thus, it has been proposed that the threshold for UPR activation might differ depending on their energy stores and the amount and nature of the secretory proteins they produce during stress conditions (Hetz and Mollereau 2014; Kaufman 2002; Kaufman and others 2002). In essence, the threshold for disease sensitivity can be varied on the severity and mode of neurode-generation and brain injury and the age. In the aged brain, there is a progressive loss of ER proteostasis, which causes an attenuation of stress responses and lowers the threshold for disease sensitivity (Hetz and Mollereau 2014; Kaufman 2002; Kaufman and others 2002).

Under chronic or irreversible ER stress, the UPR triggers apoptosis involving multiple cellular and molecular components (Urrea and others 2013). This pathway includes the activation of three dominant type I ER trans-membrane proteins known as inositol-requiring enzyme 1a (here termed IRE1) and 1b, PKR-like ER kinase (PERK), and activating transcription factor 6 (ATF6) a and b (Hetz and others 2011; Hetz and Papa 2018; Urrea and others 2013; Walter and Ron 2011) (Fig. 1).

IRE1 is composed of two subunits. Despite IRE1 α express ubiquitously, the expression of IRE1 β is restricted within gut and lung. The active IRE1 α (henceforth referred to as IRE1) is originated from splicing the mRNA encoding the transcription factor X-Box-binding protein 1 (XBP1) (Walter and Ron 2011) and upregulates the expression of target genes that are essential to restoring global proteostasis under ER stress (Lee and others 2003). Moreover, IRE1 degrades a subset of mRNAs and microRNAs, having an essential regulatory function on inflammation, apoptosis and other pathways (Maurel and others 2014). IRE1 also associates with adapter proteins, like TRAF2, to engage alarm pathways

including ASK1 and JNK that regulates autophagy and apoptosis (Hetz and others 2015; Hetz and Glimcher 2009).

ATF6 is an ER stress–regulated transmembrane transcription factor that activates the transcription of ER molecular chaperones. On ER stress, ATF6 is transported to the Golgi apparatus, where it is cleaved by site one protease (S1P) and S2P, releasing the cytosolic ATF6 fragment (ATF6a). ATF6a functions as a transcription factor that regulates a cluster of genes, including ERAD components and XBP1 (Yamamoto and others 2007; Yoshida and others 2001). Also, XBP1s and ATF6a heterodimerize and drive a specific transcriptional program (Shoulders and others 2013).

The ER kinase PERK also serves as another ER stress sensor, and on ER stress, PERK oligomerizes and phosphorylates the α -subunit of eukaryotic initiation factor 2 (eIF2 α) at serine 51 (Walter and Ron 2011). This event leads to reduce the overload of misfolded proteins (Harding and others 2000; Harding and others 2003) by inhibiting global protein translation. On the other hand, phosphorylation of eIF2 α increases the translation of a transcription factor, ATF4, which transcribes genes for autophagy and proteins involved in the regulation of the redox and metabolic status of the cell (Harding and others 2003). Most important, ATF4 transcribes another transcription factor CHOP, GADD34, and several members of Bcl2 family, which plays an essential role in cell death (Tabas and Ron 2011; Urrea and others 2013). Phosphorylated eIF2 α can be dephosphorylated by GADD34 in a feed-forward loop to shut down PERK signaling (Tsaytler and Bertolotti 2013). Collectively, the activation of these transcription factors to mitigate the ER stress depends on the nature extrinsic or intrinsic stimuli that can induce ER stress as well as crosstalk with other signaling pathways that regulate gene expressions such as c-Jun or NF κ B and the status of chromatin (Hetz and others 2015). In this review, the importance of ER stress in synaptic plasticity and memory formation under physiological and brain injury was highlighted.

Role of ER Stress in Synaptic Plasticity and Memory under the Physiological Condition

The up-regulation of an ER stress–induced transcription factor XBP1 has been well correlated with learning behavior, and it has been shown that behavioral stress induces splicing of Xbp1 mRNA in the hippocampus (Toda and others 2006) and exercise can augment its level (Kim and others 2010; Park-York and others 2012; Toda and others 2006). Recently, a conditional mouse model of XBP1 was generated, and it was observed that synaptic function and memory formation was impaired in this transgenic knockout mouse. As a part of the mechanism, it was shown that depletion of XBP1 affects the brain-derived neurotrophic factor (BDNF) level, which is necessary for memory function. Furthermore, supplementation of XBP1 in the hippocampus of this transgenic mice rescue the loss of memory function; although heterozygous XBP1 did not exhibit a significant deficit in behavioral tests. This data suggests that depletion of both alleles of XBP1 is required for impairment of memory function; the loss of partial function of XBP1 is not sufficient to induce memory impairment may be due to functional supplementation from other signaling

pathways relevant to memory formation (Martinez and others 2016; Takata and others 2010).

The importance of phosphorylation of eIF2 α in synaptic plasticity has been explored extensively but remains controversial. It was shown that impaired protein synthesis due to reduced eIF2 α phosphorylation leads to an improvement in spatial memory, which was evident by an increase in long-term potentiation (LTP). On the other hand, activity-dependent reduction in long-term hippo-campal depression was enhanced by triggering eIF2 α phosphorylation (Costa-Mattioli and others 2007; Di Prisco and others 2014; Jiang and others 2010). eIF2 α can be phosphorylated by several kinases such as GCN2, PKR, or PERK at Ser 51 (S51) residue. Thus, blocking phosphorylation of eIF2 α by mutating serine to alanine or deleting the responsible kinase, such as GCN2 for phosphorylation of eIF2 α enhances long-term memory formation (Costa-Mattioli and others 2005; Costa-Mattioli and others 2007; Jiang and others 2010; Ounallah-Saad and others 2014; Zhu and others 2011).

In contrast, deletion of PERK in the brain affects repetitive behaviors (Trinh and others 2012). Thus, it is possible that PERK regulates memory function independent of eIF2 α . Following the same notion, recently, it was identified that PERK mediates its effect through phosphorylation of cAMP response element binding protein (CREB) and a postsynaptic protein PSD95 following brain injury (Sen and others 2017). The signaling pathway and their influence on memory will be discussed more in detail in the subsequent section.

Considering that the phosphorylation of eIF2 α critically regulates the expression of ATF4, previous studies reported that the deletion of GCN2, which is responsible for the phosphorylation of eIF2 α , reduces ATF4 expression. As a result, synaptic function and associated memory functions were improved significantly (Costa-Mattioli and others 2005; Costa-Mattioli and others 2007). Considering that PERK as another kinase to phosphorylate eIF2 α , the depletion of PERK causes a reduction in ATF4 and improves memory function (Ounallah-Saad and others 2014). However, it is essential to consider that both GCN2 and PERK has another large set of proteins which can be phosphorylated by these kinases. Thus, it is not clear whether the neuroprotective functions executed by a depletion in GCN2 or PERK is exclusively through suppression of ATF4 expression. Moreover, it has not been fully elucidated whether blocking their catalytic activities exclusively result in similar outcomes.

The importance of ATF4 in synaptic function was further evidenced in another study where blocking ATF4 expression with its dominant negative form in the fore-brain enhances gene expression which is mostly governed by a transcription factor CREB, and this event facilitates LTP and long-term memory (Chen and others 2003). Consistent with these data, it was shown that inhibition of ATF4 using its ortholog improves synaptic function in correlation with memory formation (Bartsch and others 1995). However, the question remains unanswered whether the transcriptional activity or the presence of ATF4 affects the memory function. A recent study shows that depletion of ATF4 using RNAi in the hippocampus blocks memory functions (Pasini and others 2015), which suggests that transcriptional activity of ATF4 contributes more toward memory dysfunction. To further

confirm this finding, it is important to test its role in memory function using conditionally transgenic mice where the DNA-binding domain of ATF4 will be impaired.

CREB Is a Critical Regulator of Synaptic Function and Memory Formation

CREB is a nuclear protein and expresses ubiquitously in a variety of tissues, including the brain. CREB functions as a family of leucine zipper transcription factor, and it can homodimerize or heterodimerize with either it is repressor, cAMP response element modulator (CREM) or activates transcription factor (ATF) to form a functional dimer. The DNA-binding domain of CREB recognizes and binds to the promoter cAMP response element (CRE) sequences. However, the transcriptional activity of CREB is significantly regulated by phosphorylation of a serine residue (S133) in its kinase-inducible domain. Phosphorylation of CREB at S133 is essential to recruit the coactivators to form the active transcription complex. Several kinases have been identified that can regulate phosphorylation of CREB at S133; for example, cAMP-protein kinase A (PKA), the MAP kinase signalling pathway (MEK/ERK), the calcium-CaMKII/IV cascade, as well as phospholipase C (PLC), protein kinase B (Akt) (De Cesare and others 1999; Johannessen and others 2004; Montminy 1997; Sakamoto and others 2011). A change in the level of phosphorylation of CREB has been identified in patients suffering from depression (Dwivedi and others 2006) and neurodegeneration such as Alzheimer's disease (AD) or Parkinson's disease (PD).

In addition to S133-phosphorylation, the functionality of CREB can be affected via an array of additional phosphorylation events, which have complicated, and context-specific effects on CREB transactivation. For example, the phosphorylation of Ser 142 (S142) by CaMKII has been shown to represses CREB transactivation by triggering the dissociation of the CREB dimer and, in turn, inhibiting CBP recruitment (Kornhauser and others 2002; Wu and McMurray 2001). Other than S133 and S142, CREB was shown to be phosphorylated at S129 residue by glycogen synthase kinase-3 β (GSK3 β), which has been implicated in neurodegenerative and psychiatric disorders. Unlike phosphorylation of CREB at S133, phosphorylation of CREB at S129 suppresses its transcriptional activity (Bullock and Habener 1998; Fiol and others 1994; Grimes and Jope 2001). The direct correlation between ER stress and CREB was recently evidenced in one study where administration of tunicamycin (TM), a recognized ER stress inducer, has shown to impair transcriptional activity of CREB by facilitating its phosphorylation at S129 through activation of GSK3 β . Simultaneous inhibition of GSK3 β attenuated TM-induced UPR and spatial memory impairment by suppressing GSK3 β phosphorylation at S129 and synaptic plasticity (Lin and others 2018).

The interaction between CREB and an acetyltransferase CBP/p300 is essential to form the active transcriptional complex and phosphorylation of CREB at S271 by protein kinase 2 (HIPK2) regulates its interaction with CBP/p300 (Sakamoto and others 2010). Recently, it was shown that the interaction between a histone deacetylase, HDAC4, and CREB suppresses its transcriptional activity after exposure of anesthetics to developing brain (Sen and Sen 2016). Although CREB cannot be directly acetylated in vivo, the interaction of CREB with TORC1 is mostly depended on the acetylation status of TORC1 (Jeong and

others 2011; Li and others 2009b). It was shown that deacetylation of TORC1 by SIRT1 facilitates its interaction with CREB and augments its transcriptional activity (Jeong and others 2011). In Figure 2, the general signaling pathway responsible for activation and inactivation of CREB in the brain was summarized. However, it is not clear how phosphorylation of CREB at either S133 or S129/142 affects its interaction with either TORC1 or HDAC4. Also, it is also not fully understood whether ER stress affects the formation of an active transcriptional complex with CREB by modifying the acetylation status of its coactivators.

Molecular Mechanism Involved in the Regulation of Synaptic Function and Memory Formation by CREB

Protein synthesis is an essential step for long-term memory formation (Davis and Squire 1984), and work in some model systems has established an underlying role for CREB/CRE-mediated transcription in this process (Dash and others 1990; Kaang and others 1993; Schacher and others 1988) in invertebrate animals. This study provides a platform to explore the role of CREB in synaptic plasticity and memory formation in vertebrate animals. It was shown that knock out mouse of CREB showed impaired memory formation in contextual fear conditioning, and the spatial memory formation (Bourtchuladze and others 1994; Graves and others 2002; Lamprecht and others 1997; Pittenger and others 2002; Yin and others 1994). To further confirm whether phosphorylation of CREB at S133 mediates its transcriptional activity in vivo, it was shown that overexpression of a dominant negative form of CREB (i.e., CREB-S133A) induces deficit in synaptic function (Guzowski and McGaugh 1997; Jancic and others 2009; Kida and others 2002). On the contrary, gain-of-function of CREB function in VP16-CREB mice, neuronal plasticity, and memory function was improved significantly (Barco and others 2002; Viosca and others 2009); suggests that balanced activation of CREB is required for synaptic function and memory formation. The importance of phosphorylation of CREB was further confirmed by another study where dephosphorylation of CREB by Ser-/Thr-specific protein phosphatases type 1 (PP1) and 2A (PP2A) suppress the transcriptional activity of CREB (Flores and others 1994; Wadzinski and others 1993).

In healthy brains, synaptic activity induces specific genes in neurons to turn on or off, which in turn leads to the long-lasting synaptic changes that underlie learning and memory. The central CREB target-gene expression related to memory consolidation and LTP are c-fos, activity-regulated cytoskeleton-associated protein (Arc), and BDNF (Alberini and Kandel 2014; Miyamoto 2006). A neurotrophic factor, BDNF is essential for neuronal growth, and it functions as a neuroprotective protein with numerous effects in the brain. BDNF levels are low in the brains of people with the AD and AD mouse models (Phillips and others 1991), and a deficiency of BDNF is associated with cognitive decline (Li and others 2009a). More excitingly, BDNF has demonstrated therapeutic potential for an AD in animal models (Blurton-Jones and others 2009; Nagahara and others 2009). BDNF has also emerged as an essential regulator of synaptogenesis and synaptic plasticity mechanisms underlying learning and memory in the adult CNS. The effects of BDNF on neuronal excitability may also be in part mediated by the regulation of Arc/Arg3.1 activity. BDNF regulates the expression of the immediate early gene *Arc/Arg3.1* (Yin and others 2002; Ying and others 2002).

Role of ER Stress in Memory Impairment in Neurodegeneration and Brain Injury

The impact of ER stress on synaptic function and memory formation under neurodegenerative condition was mostly explored in the field of AD research. AD is the most frequent age-related neurodegenerative disorder, mostly affecting individuals at 65 years or older (Ballard and others 2011). AD is characterized by an accumulation of amyloid plaques and neurofibrillary tangles, which are composed by extracellular deposition of misfolded amyloid beta peptide and intracellular hyperphosphorylated Tau, respectively (Gomez-Isla and others 2008; Lee and others 2003; Lee and others 2001). Both events independently or in combination induce synaptic dysfunction and memory impairment due to neuronal loss and induction of the neuro-immune system. Recent studies have shown that ER stress can modulate the deposition of misfolded amyloid peptides in the brain and subsequently affects cognitive processes (Halliday and Mallucci 2015). To explore the underlying mechanism, it was found that activation of PERK is directly responsible for deficiency in cognitive function in the AD (Duran-Aniotz and others 2014) by affecting active protein synthesis through modulation of phosphorylation of eIF2 α (Costa-Mattioli and others 2005; Costa-Mattioli and others 2009; Jiang and others 2010). Consistent with this study, studies from another independent group have suggested that either suppression of PERK expression or blocking phosphorylation of eIF2 α phosphorylation by targeting the responsible kinases such as GCN2 and PKR using RNAi restores learning and memory deficits in AD (Devi and Ohno 2013; Zhu and others 2011). It was shown that the β -amyloid (A β) peptide, which plays a crucial role in the pathogenesis of AD, alters hippocampal-dependent synaptic plasticity and memory and mediates synapse loss through the CREB signaling pathway. Mechanistically, A β causes a decrease in phosphorylation of CREB at S133 residue and affects its transcriptional activity (Saura and Valero 2011). As a result, the level of neurotrophic factor like BDNF was decreased which ultimately leads to neuronal loss and synaptic dysfunction in AD. However, more studies are needed to fully explore the correlation between ER stress and memory deficits, including the underlying mechanism for the inactivation of CREB during the progression of the AD. In contrast to AD, in hypoxia, CREB was activated by ER stress, and activation of CREB and the UPR pathway occurred in a coordinated manner. In fact, it was shown that depletion of CREB decreased the expression of IRE1 α and PERK, two critical UPR signaling molecules. Promoter analysis and a chromatin immunoprecipitation assay indicated that CREB binds to the promoter region of these genes and regulates their expression (Kikuchi and others 2016).

Traumatic brain injury (TBI) is the leading cause of death and disability around the world and affects 1.7 million Americans each year. The induction of a TBI not only causes direct damage to tissue but also triggers a delayed sequence of cellular and molecular events that result in secondary injury (Bramlett and Dietrich 2007; Stoica and Faden 2010; Truettner and others 2007). The direct damage to cellular proteins and folding mechanisms exacerbates aberrant protein accumulation and thus ER stress (Larner and others 2006; Truettner and others 2007). The expression of CHOP is a hallmark of ER stress and ER-associated programmed cell death (Oyadomari and Mori 2004). In the controlled cortical impact model, increased levels of CHOP were observed in the ipsilateral hemispheres of

mouse brains 6 hours after a sustained TBI and remained elevated 14 days post-TBI (Krajewska and others 2011).

Moreover, UPR activation was also observed in distant regions from the injured area, indicating that the ER stress response in the spinal cord injury model is broad and can have far-reaching deficits in motor-related activities (Valenzuela and others 2012). The mechanisms underlying these broad ER stress responses are unknown; however, pro-inflammatory factors from the lesion site could propagate the events to surrounding tissues (Mahadevan and others 2011; Valenzuela and others 2012). These studies suggest that ER stress contributes to neuronal cell death after TBI. GADD34 has been shown to bind the eukaryotic serine/threonine protein phosphatase, PP1 to direct eIF-2 α dephosphorylation (Connor and others 2001; Novoa and others 2001) and suppress the UPR (Connor and others 2001). Recently, a study has shown that augmentation of GADD34 directly facilitates TBI-induced cell death in a controlled cortical impact model of TBI in mice. ER stress generated by TBI elicits a transcriptional increase in GADD34, enabling it to bind TRAF6 in competition with Akt. The ubiquitin E3 ligase, TRAF6, can ubiquitinate Akt and promote its translocation to the plasma membrane, where it becomes phosphorylated at the T308 position. In cells lacking TRAF6, it was shown that ubiquitination, membrane localization, activation and signaling of Akt is impaired in response to treatment with growth factors (Yang and others 2009). The binding of GADD34 to TRAF6 prevents TRAF6-mediated ubiquitination of Akt and subsequently prevents membrane translocation and phosphorylation of Akt at T308 position (Farook and others 2013) (Fig. 3). Depletion of GADD34 in the cerebral cortex reduces TBI-induced cell death, suggesting that GADD34's binding to TRAF6 is critical for TBI-induced neurotoxicity. Akt is one of the critical kinase involved in neuronal survival and synaptic functions in the brain (Wang and others 2003) and predominantly, it mediates its effect via phosphorylation of CREB at S133 residue (Du and Montminy 1998; Li and others 2011). Thus, it is being anticipated that inactivation of Akt due to a reduction in its phosphorylation at T308 will result in an inactivation of CREB and this event will, in turn, affects synaptic plasticity and memory function in the brain. In fact, attenuation of the catalytic activity of Akt has been shown to be associated with several neurodegenerative conditions such as AD and PD (Greene and others 2011; Kitagishi and others 2014; Sakamoto and others 2011). Thus, more studies are needed to understand whether blocking this neurotoxic signaling pathway can result in an improvement in transcriptional activity of CREB and upregulate synaptic function and memory formation following brain injury and neurodegeneration.

In another effort, Dr. Sen and his associates have shown that induction of ER stress is directly involved in memory loss through PERK phosphorylation. Multiple studies have shown that significant loss of synapses in the days after brain injury (Gao and Chen 2011; Gao and others 2011) are responsible for memory deficits after TBI. Dendritic spines are the postsynaptic protrusions through which neurons receive most of their excitatory input. Recently it has been shown that in a mouse model that, after TBI, there are fewer dendritic synaptic spines in the cortex and hippocampus (Gao and others 2011). The formation of synapses and spine density depends on the level of the postsynaptic scaffold protein PSD95 and the BDNF level, which can be transcribed by CREB (Fig. 4).

Strikingly, recent studies showed that inhibition of PERK phosphorylation rescued the memory loss without affecting the phosphorylation of eIF2 α ; although a substantial number of studies focused on the fact that PERK attributes its function through phosphorylation of eIF2 α . These data suggest that PERK phosphorylation may function independently of the phosphorylation of eIF2 α , but did not exclude the importance of eIF2 α in synaptic function. For example, aberrant eIF2 α phosphorylation was associated with synaptic pathophysiology and memory dysfunction after AD (Ma and others 2013). In essence, phosphorylation of PERK and eIF2 α both contribute to the deterioration of synaptic plasticity, but their contribution varies from context to context. In fact, a recent data is consistent with the previous finding where it was shown that inhibition of PERK activity did not affect downstream PERK signaling such as phospho-eIF2 α , ATF, or CHOP protein levels in the pancreas (Atkins and others 2013). Considering that the initiation factor eIF2 α can be phosphorylated by several kinases other than PERK, such as GCN2, PKR, and HRI (Ohno 2014), it is possible that preventing phosphorylation of PERK does not necessarily block phosphorylation of eIF2 α .

These data forced us to rethink what are the other substrates that can be targeted by PERK to execute its effects on the functional aspects of synapse and memory. Recently, it was found that PERK phosphorylates CREB directly at the S129 residue without altering its phosphorylation status at S133. To further elucidate the underlying mechanism, it was shown that phosphorylation of CREB at S129 prevents its interaction with a coactivator, CBP, that leads to its transcriptional inactivation and downregulation of BDNF. Conversely, PSD95, a significant scaffold protein of PSD that promotes synaptic strength, can be phosphorylated by PERK at the T19 residue (Sen and others 2017). Previously it was shown that phosphorylation of PSD95 affects stability in dendritic spines, which can be reversed by overexpression of the T19A mutant of PSD95 (Nelson and others 2013). A recent study showed that phosphorylation of PSD95 by PERK leads to its degradation (Sen and others 2017). Taken together, inactivation of CREB and substantial reduction in the level of PSD95 affects dendritic spine density and pruning following TBI. These events ultimately lead to impairment in memory functions following TBI. Collectively, this study provided a novel mechanism in which PERK phosphorylation impairs memory by inactivating CREB and downregulation of PSD95 after TBI. Inhibiting PERK phosphorylation rescues spine density and dendritic outgrowth after TBI. The molecules in ER stress/CREB signaling, which contribute to memory impairment mostly in AD and TBI have been highlighted in Table 1.

In recent years, many chemical compounds and small molecules which are capable of alleviating or inducing ER stress through different mechanisms have been elegantly described in review articles published by Dr. Kaufman (Wang and Kaufman 2014) and others (Remondelli and Renna 2017). Thus, in this review article, we highlight the compounds that mostly function via ER stress/CREB signaling axis to regulate memory. A substantial number of preclinical studies have revealed that the PERK/eIF2 α phosphorylation axis is the most relevant in the occurrence of neurodegenerative diseases. Thus, PERK-specific inhibitors such as GSK2606414 abolished translation attenuation and counteracted neurodegeneration (Moreno and others 2013). The high selectivity of GSK2606414 and its ability to cross the blood-brain barrier render such a molecule a promising therapeutic tool for neurodegenerative disorders. Therefore, they are becoming an attractive model to investigate

the self-propagating properties of protein mis-folding in neurodegenerative diseases, a common feature of the AD, PD, and amyotrophic lateral sclerosis (Goedert and others 2010; Soto 2012). Also, treatment with PERK inhibitor improves transcriptional activation of CREB, and memory deficit by rescuing BDNF level after brain injury (Sen and others 2017).

Other than GSK2606414, a potent drug-like small molecule, ISRIB (integrated stress response inhibitor) also can prevent PERK activation and inhibit eIF2 α phosphorylation under persistent ER stress (Sidrauski and others 2013; Sidrauski and others 2015) to improve cognitive function in rodents. As a part of the mechanism, it was shown that inhibition of PERK signaling pathway would reduce ATF4 and CHOP expression, which is known to function as a repressor of memory and long-term synaptic plasticity. On the other hand, ISRIB activates eIF2 β by stabilizing eIF2 β -activated dimers to ameliorate the cognitive defects that develop from neuro-degenerative diseases (Sidrauski and others 2015). Another group has shown that ISRIB has also been proven effective in a mouse model of prion-related disease with reduced toxicity as compared with the PERK inhibitor GSK2606414 (Halliday and others 2015). More recently, a Food and Drug Administration–approved drug, trazodone hydrochloride, currently under clinical trial as an anticancer drug, prevented brain cell damage and restored memory in frontotemporal dementia mouse models (Halliday and others 2017). A neurosteroid, progesterone can suppress neuroinflammation by down-regulating PERK/eIF2 α signaling (Hong and others 2016) and improve memory functions (Barros and others 2015).

Concluding Remarks

A substantial number of intensive research on the impact of ER stress in neurotoxicity have been performed; however, more insightful studies are required to elucidate the importance of ER stress in synaptic function and memory formation under either healthy condition or neurodegenerative conditions. Of course, a few elegant studies have been demonstrated to shed light in this end some, but controversies arose in the field. This could be due to the difference in their functions as a protein or kinase. Depletion of either PERK or eIF2 α will affect not only their interaction with other proteins but also the phosphorylation status of their downstream substrates. The phosphorylation eIF2 α mostly depends on two factors: (1) eIF2 α can be phosphorylated directly by PERK on induction of ER stress and (2) interaction of eIF2 α with other proteins such as a deacetylase SIRT1, which negatively regulates its phosphorylation status (Ghosh and others 2011). Considering SIRT1 has a significant influence on learning by itself (Cao and others 2017; Michan and others 2010), disrupting the interaction between eIF2 α and SIRT1 by knocking down eIF2 α will influence the memory formation, which may or may not resemble the effect executed by phosphorylation mutant of eIF2 α . Thus, to understand the influence of phosphorylation of eIF2 α in learning, it will be better to target phosphorylation of eIF2 α directly, instead of deleting its level. Thus, it is essential to have a conditional transgenic mouse where the catalytic function of these kinases will be explicitly compromised. The availability of these transgenic mice will provide more in-depth insights into how the kinase activity of these proteins contributing to synaptic functions and memory formation.

A recent study has shown that in adolescents, whose brains are still developing, aerobic exercise of moderate-to high-intensity levels seems to have a positive effect on levels of serum BDNF (synthesized mostly via transcriptional activation of CREB), at rest and on cognitive functioning (Jeon and Ha 2017). In contrast, another group has shown that maximal intensity exercise in children and adolescents may result in both beneficial and detrimental cognitive effects, including transient impairment in verbal learning. Cognitive functions applying short-term memory improve following a recovery period. Parents, educators, and coaches should consider these changes in memory and attention following high-intensity exercise activities in children (Samuel and others 2017). No direct study has been published yet to narrow down the role of ER stress in exercise-induced memory formation in the brain. However, an elegant study was performed in skeletal muscle (the tissue requires a large amount of energy like the brain), where it was shown that high-intensity exercise training resulted in increased mitochondrial bio-genesis, and decreased ER stress and apoptotic signals such as a decrease in XBP1 mRNA in the skeletal muscle tissue of rats. It is important to mention that there was no significant change in the spliced XBP1 mRNA between the groups of mice performing high- and low-intensity exercise (Kim and others 2014); this suggests that exercise-induced reduction in XBP1 mRNA is not dependent on the intensity of exercise. If we extrapolate these data into the brain, and combine the results obtained from cognitive functioning resulted from that high-intensity exercise, we can conclude that exercise, ER stress, and BDNF may function in an orchestrated manner to influence memory in an age-dependent manner.

Thus far, most of the studies mostly focused on the function of the hippocampus to study long-term memory. However, more studies are needed to understand whether ER stress affects synaptic functions in the amygdala, striatum, nucleus accumbens and frontal cortex, which are responsible for either short-term memory, fear memory, and drug-induced memory. It would be ideal to have a transgenic mouse where the catalytic activity of ER stress signaling molecules will be compromised in the specific region of the brain.

In the past decade or so, a growing number of studies have appreciated the importance of microglial cells in memory functions. In healthy condition, microglia secrete BDNF and other anti-inflammatory cytokines such as IL4, and IL10 which positively contribute to synaptic function and memory formation (Ferrini and De Koninck 2013; Parkhurst and others 2013). However, in a neurodegenerative condition, activated microglia secrete pro-inflammatory cytokines which cause toxicity in neurons. However, it is not clear whether ER stress has any role in regulating population and activation of microglial cells under the healthy or diseased brain. Thus, it is reasonable to anticipate that within the next several years, new developments will emerge that will transform current thinking about the role of ER stress in the synaptic function and memory formation in the brain. Also, knowledge gained from these studies will provide a platform that can be exploited to tackle unmet medical needs in the diseased brain.

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References

- Alberini CM, Kandel ER. 2014 The regulation of transcription in memory consolidation. *Cold Spring Harb Perspect Biol* 7(1):a021741. [PubMed: 25475090]
- Atkins C, Liu Q, Minthorn E, Zhang SY, Figueroa DJ, Moss K, and others. 2013 Characterization of a novel PERK kinase inhibitor with antitumor and antiangiogenic activity. *Cancer Res* 73(6):1993–2002. [PubMed: 23333938]
- Balch WE, Morimoto RI, Dillin A, Kelly JW. 2008 Adapting proteostasis for disease intervention. *Science* 319(5865):916–9. [PubMed: 18276881]
- Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. 2011 Alzheimer's disease. *Lancet* 377(9770):1019–31. [PubMed: 21371747]
- Barco A, Alarcon JM, Kandel ER. 2002 Expression of constitutively active CREB protein facilitates the late phase of long-term potentiation by enhancing synaptic capture. *Cell* 108(5):689–703. [PubMed: 11893339]
- Barros LA, Tufik S, Andersen ML. 2015 The role of progesterone in memory: an overview of three decades. *Neurosci Biobehav Rev* 49:193–204. [PubMed: 25434881]
- Bartsch D, Ghirardi M, Skehel PA, Karl KA, Herder SP, Chen M, and others. 1995 Aplysia CREB2 represses long-term facilitation: relief of repression converts transient facilitation into long-term functional and structural change. *Cell* 83(6):979–92. [PubMed: 8521521]
- Blurton-Jones M, Kitazawa M, Martinez-Coria H, Castello NA, Muller FJ, Loring JF, and others. 2009 Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. *Proc Natl Acad Sci U S A* 106(32):13594–9. [PubMed: 19633196]
- Bourtchuladze R, Frenguelli B, Blendy J, Cioffi D, Schutz G, Silva AJ. 1994 Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. *Cell* 79(1):59–68. [PubMed: 7923378]
- Bramlett HM, Dietrich WD. 2007 Progressive damage after brain and spinal cord injury: pathomechanisms and treatment strategies. *Prog Brain Res* 161:125–41. [PubMed: 17618974]
- Bullock BP, Habener JF. 1998 Phosphorylation of the cAMP response element binding protein CREB by cAMP-dependent protein kinase A and glycogen synthase kinase-3 alters DNA-binding affinity, conformation, and increases net charge. *Biochemistry* 37(11):3795–809. [PubMed: 9521699]
- Cao Y, Yan Z, Zhou T, Wang G. 2017 SIRT1 regulates cognitive performance and ability of learning and memory in diabetic and nondiabetic models. *J Diabetes Res* 2017:7121827. [PubMed: 29164153]
- Chen A, Muzzio IA, Malleret G, Bartsch D, Verbitsky M, Pavlidis P, and others. 2003 Inducible enhancement of memory storage and synaptic plasticity in transgenic mice expressing an inhibitor of ATF4 (CREB-2) and C/EBP proteins. *Neuron* 39(4):655–69. [PubMed: 12925279]
- Connor JH, Weiser DC, Li S, Hallenbeck JM, Shenolikar S. 2001 Growth arrest and DNA damage-inducible protein GADD34 assembles a novel signaling complex containing protein phosphatase 1 and inhibitor 1. *Mol Cell Biol* 21(20):6841–50. [PubMed: 11564868]
- Costa-Mattioli M, Gobert D, Harding H, Herdy B, Azzi M, Bruno M, and others. 2005 Translational control of hippocampal synaptic plasticity and memory by the eIF2alpha kinase GCN2. *Nature* 436(7054):1166–73. [PubMed: 16121183]
- Costa-Mattioli M, Gobert D, Stern E, Gamache K, Colina R, Cuellar C, and others. 2007 eIF2alpha phosphorylation bidirectionally regulates the switch from short- to long-term synaptic plasticity and memory. *Cell* 129(1):195–206. [PubMed: 17418795]
- Costa-Mattioli M, Sossin WS, Klann E, Sonenberg N. 2009 Translational control of long-lasting synaptic plasticity and memory. *Neuron* 61(1):10–26. [PubMed: 19146809]

- Dash PK, Hochner B, Kandel ER. 1990 Injection of the cAMP-responsive element into the nucleus of Aplysia sensory neurons blocks long-term facilitation. *Nature* 345(6277):718–21. [PubMed: 2141668]
- Davis HP, Squire LR. 1984 Protein synthesis and memory: a review. *Psychol Bull* 96(3):518–59. [PubMed: 6096908]
- De Cesare D, Fimia GM, Sassone-Corsi P. 1999 Signaling routes to CREM and CREB: plasticity in transcriptional activation. *Trends Biochem Sci* 24(7):281–5. [PubMed: 10390618]
- Devi L, Ohno M. 2013 Deletion of the eIF2 α kinase GCN2 fails to rescue the memory decline associated with Alzheimer's disease. *PLoS One* 8(10):e77335. [PubMed: 24146979]
- Di Prisco GV, Huang W, Buffington SA, Hsu CC, Bonnen PE, Placzek AN, and others. 2014 Translational control of mGluR-dependent long-term depression and object-place learning by eIF2 α . *Nat Neurosci* 17(8):1073–82. [PubMed: 24974795]
- Du K, Montminy M. 1998 CREB is a regulatory target for the protein kinase Akt/PKB. *J Biol Chem* 273(49):32377–9. [PubMed: 9829964]
- Duran-Aniotz C, Martinez G, Hetz C. 2014 Memory loss in Alzheimer's disease: are the alterations in the UPR network involved in the cognitive impairment? *Front Aging Neurosci* 6:8. [PubMed: 24523695]
- Dwivedi Y, Rizavi HS, Conley RR, Pandey GN. 2006 ERK MAP kinase signaling in post-mortem brain of suicide subjects: differential regulation of upstream Raf kinases Raf-1 and B-Raf. *Mol Psychiatry* 11(1):86–98. [PubMed: 16172610]
- Farook JM, Shields J, Tawfik A, Markand S, Sen T, Smith SB, and others. 2013 GADD34 induces cell death through inactivation of Akt following traumatic brain injury. *Cell Death Dis* 4:e754. [PubMed: 23907468]
- Ferrini F, De Koninck Y. 2013 Microglia control neuronal network excitability via BDNF signalling. *Neural Plast* 2013:429815. [PubMed: 24089642]
- Fiol CJ, Williams JS, Chou CH, Wang QM, Roach PJ, Andrisani OM. 1994 A secondary phosphorylation of CREB341 at Ser129 is required for the cAMP-mediated control of gene expression. A role for glycogen synthase kinase-3 in the control of gene expression. *J Biol Chem* 269(51):32187–93. [PubMed: 7798217]
- Flores E, Roy G, Patel D, Shaw A, Thomas ML. 1994 Nuclear localization of the PEP protein tyrosine phosphatase. *Mol Cell Biol* 14(7):4938–46. [PubMed: 7516475]
- Gao X, Chen J. 2011 Mild traumatic brain injury results in extensive neuronal degeneration in the cerebral cortex. *J Neuropathol Exp Neurol* 70(3):183–91. [PubMed: 21293299]
- Gao X, Deng P, Xu ZC, Chen J. 2011 Moderate traumatic brain injury causes acute dendritic and synaptic degeneration in the hippocampal dentate gyrus. *PLoS One* 6(9):e24566. [PubMed: 21931758]
- Ghosh HS, Reizis B, Robbins PD. 2011 SIRT1 associates with eIF2- α and regulates the cellular stress response. *Sci Rep* 1:150. [PubMed: 22355666]
- Goedert M, Clavaguera F, Tolnay M. 2010 The propagation of prion-like protein inclusions in neurodegenerative diseases. *Trends Neurosci* 33(7):317–25. [PubMed: 20493564]
- Gomez-Isla T, Spires T, De Calignon A, Hyman BT. 2008 Neuropathology of Alzheimer's disease. *Handb Clin Neurol* 89:233–43. [PubMed: 18631748]
- Graves L, Dalvi A, Lucki I, Blendy JA, Abel T. 2002 Behavioral analysis of CREB α mutation on a B6/129 F1 hybrid background. *Hippocampus* 12(1):18–26. [PubMed: 11918283]
- Greene LA, Levy O, Malagelada C. 2011 Akt as a victim, villain and potential hero in Parkinson's disease pathophysiology and treatment. *Cell Mol Neurobiol* 31(7):969–78. [PubMed: 21547489]
- Grimes CA, Jope RS. 2001 CREB DNA binding activity is inhibited by glycogen synthase kinase-3 β and facilitated by lithium. *J Neurochem* 78(6):1219–32. [PubMed: 11579131]
- Guzowski JF, McGaugh JL. 1997 Antisense oligodeoxynucleotide-mediated disruption of hippocampal cAMP response element binding protein levels impairs consolidation of memory for water maze training. *Proc Natl Acad Sci U S A* 94(6):2693–8. [PubMed: 9122258]
- Halliday M, Mallucci GR. 2015 Review: modulating the unfolded protein response to prevent neurodegeneration and enhance memory. *Neuropathol Appl Neurobiol* 41(4):414–27. [PubMed: 25556298]

- Halliday M, Radford H, Sekine Y, Moreno J, Verity N, le Quesne J, and others. 2015 Partial restoration of protein synthesis rates by the small molecule ISRIB prevents neurodegeneration without pancreatic toxicity. *Cell Death Dis* 6:e1672. [PubMed: 25741597]
- Halliday M, Radford H, Zents KAM, Molloy C, Moreno JA, Verity NC, and others. 2017 Repurposed drugs targeting eIF2 α -P-mediated translational repression prevent neuro-degeneration in mice. *Brain* 140(6):1768–83. [PubMed: 28430857]
- Harding HP, Zhang Y, Bertolotti A, Zeng H, Ron D. 2000 Perk is essential for translational regulation and cell survival during the unfolded protein response. *Mol Cell* 5(5):897–904. [PubMed: 10882126]
- Harding HP, Zhang Y, Zeng H, Novoa I, Lu PD, Calfon M, and others. 2003 An integrated stress response regulates amino acid metabolism and resistance to oxidative stress. *Mol Cell* 11(3):619–33. [PubMed: 12667446]
- Hetz C, Chevet E, Oakes SA. 2015 Proteostasis control by the unfolded protein response. *Nat Cell Biol* 17(7):829–38. [PubMed: 26123108]
- Hetz C, Glimcher LH. 2009 Fine-tuning of the unfolded protein response: assembling the IRE1 α interactome. *Mol Cell* 35(5):551–61. [PubMed: 19748352]
- Hetz C, Martinon F, Rodriguez D, Glimcher LH. 2011 The unfolded protein response: integrating stress signals through the stress sensor IRE1 α . *Physiol Rev* 91(4): 1219–43. [PubMed: 22013210]
- Hetz C, Mollereau B. 2014 Disturbance of endoplasmic reticulum proteostasis in neurodegenerative diseases. *Nat Rev Neurosci* 15(4):233–49. [PubMed: 24619348]
- Hetz C, Papa FR. 2018 The unfolded protein response and cell fate control. *Mol Cell* 69(2):169–81. [PubMed: 29107536]
- Hetz C, Saxena S. 2017 ER stress and the unfolded protein response in neurodegeneration. *Nat Rev Neurol* 13(8): 477–91. [PubMed: 28731040]
- Hong Y, Wang X, Sun S, Xue G, Li J, Hou Y. 2016 Progesterone exerts neuroprotective effects against A β -induced neuro-inflammation by attenuating ER stress in astrocytes. *Int Immunopharmacol* 33:83–9. [PubMed: 26878478]
- Jancic D, Lopez de, Armentia M, Valor LM, Olivares R, Barco A. 2009 Inhibition of cAMP response element-binding protein reduces neuronal excitability and plasticity, and triggers neurodegeneration. *Cereb Cortex* 19(11):2535–47. [PubMed: 19213815]
- Jeon YK, Ha CH. 2017 The effect of exercise intensity on brain derived neurotrophic factor and memory in adolescents. *Environ Health Prev Med* 22(1):27. [PubMed: 29165142]
- Jeong H, Cohen DE, Cui L, Supinski A, Savas JN, Mazzulli JR, and others. 2011 Sirt1 mediates neuroprotection from mutant huntingtin by activation of the TORC1 and CREB transcriptional pathway. *Nat Med* 18(1):159–65. [PubMed: 22179316]
- Jiang Z, Belforte JE, Lu Y, Yabe Y, Pickel J, Smith CB, and others. 2010 eIF2 α Phosphorylation-dependent translation in CA1 pyramidal cells impairs hippocampal memory consolidation without affecting general translation. *J Neurosci* 30(7):2582–94. [PubMed: 20164343]
- Johannessen M, Delghandi MP, Moens U. 2004 What turns CREB on? *Cell Signal* 16(11):1211–27. [PubMed: 15337521]
- Kaang BK, Kandel ER, Grant SG. 1993 Activation of cAMP-responsive genes by stimuli that produce long-term facilitation in Aplysia sensory neurons. *Neuron* 10(3):427–35. [PubMed: 8384857]
- Kaufman RJ. 2002 Orchestrating the unfolded protein response in health and disease. *J Clin Invest* 110(10):1389–98. [PubMed: 12438434]
- Kaufman RJ, Scheuner D, Schroder M, Shen X, Lee K, Liu CY, and others. 2002 The unfolded protein response in nutrient sensing and differentiation. *Nat Rev Mol Cell Biol* 3(6):411–21. [PubMed: 12042763]
- Kida S, Josselyn SA, Pena de Ortiz S, Kogan JH, Chevere I, Masushige S, and others. 2002 CREB required for the stability of new and reactivated fear memories. *Nat Neurosci* 5(4):348–55. [PubMed: 11889468]
- Kikuchi D, Tanimoto K, Nakayama K. 2016 CREB is activated by ER stress and modulates the unfolded protein response by regulating the expression of IRE1 α and PERK. *Biochem Biophys Res Commun* 469(2):243–50. [PubMed: 26642955]

- Kim K, Kim YH, Lee SH, Jeon MJ, Park SY, Doh KO. 2014 Effect of exercise intensity on unfolded protein response in skeletal muscle of rat. *Korean J Physiol Pharmacol* 18(3):211–6. [PubMed: 24976760]
- Kim Y, Park M, Boghossian S, York DA. 2010 Three weeks voluntary running wheel exercise increases endoplasmic reticulum stress in the brain of mice. *Brain Res* 1317:13–23. [PubMed: 20045396]
- Kitagishi Y, Nakanishi A, Ogura Y, Matsuda S. 2014 Dietary regulation of PI3K/AKT/GSK-3 α pathway in Alzheimer's disease. *Alzheimers Res Ther* 6(3):35. [PubMed: 25031641]
- Kornhauser JM, Cowan CW, Shaywitz AJ, Dolmetsch RE, Griffith EC, Hu LS, and others. 2002 CREB transcriptional activity in neurons is regulated by multiple, calcium-specific phosphorylation events. *Neuron* 34(2):221–33. [PubMed: 11970864]
- Krajewska M, Xu L, Xu W, Krajewski S, Kress CL, Cui J, and others. 2011 Endoplasmic reticulum protein BI-1 modulates unfolded protein response signaling and protects against stroke and traumatic brain injury. *Brain Res* 1370:227–37. [PubMed: 21075086]
- Lamprecht R, Hazvi S, Dudai Y. 1997 cAMP response element-binding protein in the amygdala is required for long-but not short-term conditioned taste aversion memory. *J Neurosci* 17(21):8443–50. [PubMed: 9334416]
- Larner SF, Hayes RL, Wang KK. 2006 Unfolded protein response after neurotrauma. *J Neurotrauma* 23(6):807–29. [PubMed: 16774469]
- Lee AH, Iwakoshi NN, Glimcher LH. 2003 XBP-1 regulates a subset of endoplasmic reticulum resident chaperone genes in the unfolded protein response. *Mol Cell Biol* 23(21):7448–59. [PubMed: 14559994]
- Lee VM, Goedert M, Trojanowski JQ. 2001 Neurodegenerative tauopathies. *Annu Rev Neurosci* 24:1121–59. [PubMed: 11520930]
- Li G, Peskind ER, Millard SP, Chi P, Sokal I, Yu CE, and others. 2009a Cerebrospinal fluid concentration of brain-derived neurotrophic factor and cognitive function in non-demented subjects. *PLoS One* 4(5):e5424. [PubMed: 19412541]
- Li S, Zhang C, Takemori H, Zhou Y, Xiong ZQ. 2009b TORC1 regulates activity-dependent CREB-target gene transcription and dendritic growth of developing cortical neurons. *J Neurosci* 29(8):2334–43. [PubMed: 19244510]
- Li XY, Zhan XR, Liu XM, Wang XC. 2011 CREB is a regulatory target for the protein kinase Akt/PKB in the differentiation of pancreatic ductal cells into islet β -cells mediated by hepatocyte growth factor. *Biochem Biophys Res Commun* 404(2):711–6. [PubMed: 21156158]
- Lin L, Cao J, Yang SS, Fu ZQ, Zeng P, Chu J, and others. 2018 Endoplasmic reticulum stress induces spatial memory deficits by activating GSK-3. *J Cell Mol Med* 22(7):3489–502. [PubMed: 29675957]
- Ma T, Trinh MA, Wexler AJ, Bourbon C, Gatti E, Pierre P, and others. 2013 Suppression of eIF2 α kinases alleviates Alzheimer's disease-related plasticity and memory deficits. *Nat Neurosci* 16(9):1299–305. [PubMed: 23933749]
- Mahadevan NR, Rodvold J, Sepulveda H, Rossi S, Drew AF, Zanetti M. 2011 Transmission of endoplasmic reticulum stress and pro-inflammation from tumor cells to myeloid cells. *Proc Natl Acad Sci U S A* 108(16):6561–6. [PubMed: 21464300]
- Martinez G, Vidal RL, Mardones P, Serrano FG, Ardiles AO, Wirth C, and others. 2016 Regulation of memory formation by the transcription factor XBP1. *Cell Rep* 14(6):1382–94. [PubMed: 26854229]
- Maurel M, Chevet E, Tavernier J, Gerlo S. 2014 Getting RIDD of RNA: IRE1 in cell fate regulation. *Trends Biochem Sci* 39(5):245–54. [PubMed: 24657016]
- Michan S, Li Y, Chou MM, Parrella E, Ge H, Long JM, and others. 2010 SIRT1 is essential for normal cognitive function and synaptic plasticity. *J Neurosci* 30(29):9695–707. [PubMed: 20660252]
- Miyamoto E. 2006 Molecular mechanism of neuronal plasticity: induction and maintenance of long-term potentiation in the hippocampus. *J Pharmacol Sci* 100(5):433–42. [PubMed: 16799259]
- Montminy M. 1997 Transcriptional regulation by cyclic AMP. *Annu Rev Biochem* 66:807–22. [PubMed: 9242925]

- Moreno JA, Halliday M, Molloy C, Radford H, Verity N, Axten JM, and others. 2013 Oral treatment targeting the unfolded protein response prevents neurodegeneration and clinical disease in prion-infected mice. *Sci Transl Med* 5(206):206ra138.
- Nagahara AH, Merrill DA, Coppola G, Tsukada S, Schroeder BE, Shaked GM, and others. 2009 Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. *Nat Med* 15(3):331–7. [PubMed: 19198615]
- Nelson CD, Kim MJ, Hsin H, Chen Y, Sheng M. 2013 Phosphorylation of threonine-19 of PSD-95 by GSK-3 β is required for PSD-95 mobilization and long-term depression. *J Neurosci* 33(29):12122–35. [PubMed: 23864697]
- Novoa I, Zeng H, Harding HP, Ron D. 2001 Feedback inhibition of the unfolded protein response by GADD34-mediated dephosphorylation of eIF2 α . *J Cell Biol* 153(5):1011–22. [PubMed: 11381086]
- Ohno M. 2014 Roles of eIF2 α kinases in the pathogenesis of Alzheimer's disease. *Front Mol Neurosci* 7:22. [PubMed: 24795560]
- Ounallah-Saad H, Sharma V, Edry E, Rosenblum K. 2014 Genetic or pharmacological reduction of PERK enhances cortical-dependent taste learning. *J Neurosci* 34(44):14624–32. [PubMed: 25355215]
- Oyadomari S, Mori M. 2004 Roles of CHOP/GADD153 in endoplasmic reticulum stress. *Cell Death Differ* 11(4):381–9. [PubMed: 14685163]
- Park-York M, Kim Y, York DA. 2012 Cage food location alters energy balance and endoplasmic reticulum stress in the brain of mice. *Physiol Behav* 106(2):158–63. [PubMed: 22336738]
- Parkhurst CN, Yang G, Ninan I, Savas JN, Yates JR 3rd, Lafaille JJ, and others. 2013 Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. *Cell* 155(7):1596–609. [PubMed: 24360280]
- Pasini S, Corona C, Liu J, Greene LA, Shelanski ML. 2015 Specific downregulation of hippocampal ATF4 reveals a necessary role in synaptic plasticity and memory. *Cell Rep* 11(2):183–91. [PubMed: 25865882]
- Phillips HS, Hains JM, Armanini M, Laramée GR, Johnson SA, Winslow JW. 1991 BDNF mRNA is decreased in the hippocampus of individuals with Alzheimer's disease. *Neuron* 7(5):695–702. [PubMed: 1742020]
- Pittenger C, Huang YY, Paletzki RF, Bourtschouladze R, Scanlin H, Vronskaya S, and others. 2002 Reversible inhibition of CREB/ATF transcription factors in region CA1 of the dorsal hippocampus disrupts hippocampus-dependent spatial memory. *Neuron* 34(3):447–62. [PubMed: 11988175]
- Remondelli P, Renna M. 2017 The endoplasmic reticulum unfolded protein response in neurodegenerative disorders and its potential therapeutic significance. *Front Mol Neurosci* 10:187. [PubMed: 28670265]
- Sakamoto K, Huang BW, Iwasaki K, Hailemariam K, Ninomiya-Tsuji J, Tsuji Y. 2010 Regulation of genotoxic stress response by homeodomain-interacting protein kinase 2 through phosphorylation of cyclic AMP response element-binding protein at serine 271. *Mol Biol Cell* 21(16):2966–74. [PubMed: 20573984]
- Sakamoto K, Karelina K, Obrietan K. 2011 CREB: a multi-faceted regulator of neuronal plasticity and protection. *J Neurochem* 116(1):1–9. [PubMed: 21044077]
- Samuel RD, Zavdy O, Levav M, Reuveny R, Katz U, Dubnov-Raz G. 2017 The effects of maximal intensity exercise on cognitive performance in children. *J Hum Kinet* 57:85–96. [PubMed: 28713461]
- Saura CA, Valero J. 2011 The role of CREB signaling in Alzheimer's disease and other cognitive disorders. *Rev Neurosci* 22(2):153–69. [PubMed: 21476939]
- Schacher S, Castellucci VF, Kandel ER. 1988 cAMP evokes long-term facilitation in *Aplysia* sensory neurons that requires new protein synthesis. *Science* 240(4859):1667–9. [PubMed: 2454509]
- Sen T, Gupta R, Kaiser H, Sen N. 2017 Activation of PERK elicits memory impairment through inactivation of CREB and downregulation of PSD95 after traumatic brain injury. *J Neurosci* 37(24):5900–11. [PubMed: 28522733]

- Sen T, Sen N. 2016 Isoflurane-induced inactivation of CREB through histone deacetylase 4 is responsible for cognitive impairment in developing brain. *Neurobiol Dis* 96:12–21. [PubMed: 27544482]
- Shoulders MD, Ryno LM, Genereux JC, Moresco JJ, Tu PG, Wu C, and others. 2013 Stress-independent activation of XBP1s and/or ATF6 reveals three functionally diverse ER proteostasis environments. *Cell Rep* 3(4):1279–92. [PubMed: 23583182]
- Sidrauski C, Acosta-Alvear D, Khoutorsky A, Vedantham P, Hearn BR, Li H, and others. 2013 Pharmacological brake-release of mRNA translation enhances cognitive memory. *Elife* 2:e00498. [PubMed: 23741617]
- Sidrauski C, McGeachy AM, Ingolia NT, Walter P. 2015 The small molecule ISRIB reverses the effects of eIF2 α phosphorylation on translation and stress granule assembly. *Elife* 4:e05033.
- Soto C2012 Transmissible proteins: expanding the prion heresy. *Cell* 149(5):968–77. [PubMed: 22632966]
- Stoica BA, Faden AI. 2010 Cell death mechanisms and modulation in traumatic brain injury. *Neurotherapeutics* 7(1):3–12. [PubMed: 20129492]
- Tabas I, Ron D. 2011 Integrating the mechanisms of apoptosis induced by endoplasmic reticulum stress. *Nat Cell Biol* 13(3):184–90. [PubMed: 21364565]
- Takata A, Kakiuchi C, Ishiwata M, Kanba S, Kato T. 2010 Behavioral and gene expression analyses in heterozygous XBP1 knockout mice: possible contribution of chromo-some 11qA1 locus to prepulse inhibition. *Neurosci Res* 68(3):250–5. [PubMed: 20692302]
- Toda H, Suzuki G, Nibuya M, Shioda K, Nishijima K, Wakizono T, and others. 2006 Behavioral stress and activated serotonergic neurotransmission induce XBP-1 splicing in the rat brain. *Brain Res* 1112(1):26–32. [PubMed: 16889758]
- Trinh MA, Kaphzan H, Wek RC, Pierre P, Cavener DR, Klann E. 2012 Brain-specific disruption of the eIF2 α kinase PERK decreases ATF4 expression and impairs behavioral flexibility. *Cell Rep* 1(6):676–88. [PubMed: 22813743]
- Truettner JS, Hu B, Alonso OF, Bramlett HM, Kokame K, Dietrich WD. 2007 Subcellular stress response after traumatic brain injury. *J Neurotrauma* 24(4):599–612. [PubMed: 17439344]
- Tsaytler P, Bertolotti A. 2013 Exploiting the selectivity of protein phosphatase 1 for pharmacological intervention. *FEBS J* 280(2):766–70. [PubMed: 22340633]
- Urra H, Dufey E, Lisbona F, Rojas-Rivera D, Hetz C. 2013 When ER stress reaches a dead end. *Biochim Biophys Acta* 1833(12):3507–17. [PubMed: 23988738]
- Valenzuela V, Collyer E, Armentano D, Parsons GB, Court FA, Hetz C. 2012 Activation of the unfolded protein response enhances motor recovery after spinal cord injury. *Cell Death Dis* 3:e272. [PubMed: 22337234]
- Viosca J, Lopez de Armentia M, Jancic D, Barco A. 2009 Enhanced CREB-dependent gene expression increases the excitability of neurons in the basal amygdala and primes the consolidation of contextual and cued fear memory. *Learn Mem* 16(3):193–7. [PubMed: 19237641]
- Wadzinski BE, Wheat WH, Jaspers S, Peruski LF Jr, Lickteig RL, Johnson GL, and others. 1993 Nuclear protein phosphatase 2A dephosphorylates protein kinase A-phosphorylated CREB and regulates CREB transcriptional stimulation. *Mol Cell Biol* 13(5):2822–34. [PubMed: 8386317]
- Walter P, Ron D. 2011 The unfolded protein response: from stress pathway to homeostatic regulation. *Science* 334(6059):1081–6. [PubMed: 22116877]
- Wang M, Kaufman RJ. 2014 The impact of the endoplasmic reticulum protein-folding environment on cancer development. *Nat Rev Cancer* 14(9):581–97. [PubMed: 25145482]
- Wang Q, Liu L, Pei L, Ju W, Ahmadian G, Lu J, and others. 2003 Control of synaptic strength, a novel function of Akt. *Neuron* 38(6):915–28. [PubMed: 12818177]
- Wu X, McMurray CT. 2001 Calmodulin kinase II attenuation of gene transcription by preventing cAMP response element-binding protein (CREB) dimerization and binding of the CREB-binding protein. *J Biol Chem* 276(3):1735–41. [PubMed: 11013247]
- Yamamoto K, Sato T, Matsui T, Sato M, Okada T, Yoshida H, and others. 2007 Transcriptional induction of mammalian ER quality control proteins is mediated by single or combined action of ATF6 α and XBP1. *Dev Cell* 13(3):365–76. [PubMed: 17765680]

- Yang WL, Wang J, Chan CH, Lee SW, Campos AD, Lamothe B, and others. 2009 The E3 ligase TRAF6 regulates Akt ubiquitination and activation. *Science* 325(5944):1134–8. [PubMed: 19713527]
- Yin JC, Wallach JS, Del Vecchio M, Wilder EL, Zhou H, Quinn WG, and others. 1994 Induction of a dominant negative CREB transgene specifically blocks long-term memory in *Drosophila*. *Cell* 79(1):49–58. [PubMed: 7923376]
- Yin Y, Edelman GM, Vanderklish PW. 2002 The brain-derived neurotrophic factor enhances synthesis of Arc in synaptoneurosomes. *Proc Natl Acad Sci U S A* 99(4):2368–73. [PubMed: 11842217]
- Ying SW, Futter M, Rosenblum K, Webber MJ, Hunt SP, Bliss TV, and others. 2002 Brain-derived neurotrophic factor induces long-term potentiation in intact adult hippocampus: requirement for ERK activation coupled to CREB and upregulation of Arc synthesis. *J Neurosci* 22(5):1532–40. [PubMed: 11880483]
- Yoshida H, Matsui T, Yamamoto A, Okada T, Mori K. 2001 XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. *Cell* 107(7):881–91. [PubMed: 11779464]
- Zhu PJ, Huang W, Kalikulov D, Yoo JW, Placzek AN, Stoica L, and others. 2011 Suppression of PKR promotes network excitability and enhanced cognition by interferon- γ -mediated disinhibition. *Cell* 147(6):1384–96. [PubMed: 22153080]

Figure 1.

Signaling pathways involved on induction of endoplasmic reticulum (ER) stress. The misfolded proteins can be degraded through proteasomal ERAD pathway. However, accumulation of misfolded proteins activates three ER stress sensors: activating transcription factor-6 (ATF6), inositol-requiring transmembrane kinase/endoribonuclease 1 (IRE1), and double-stranded RNA-dependent protein kinase (PKR)-like eukaryotic initiation factor 2α (eIF2α) kinase (PERK). Activation of IRE1 leads to splicing of XBP1-mRNA and the spliced XBP1 accumulated inside the nucleus and activates gene expression that is required for ERAD pathway. In the Golgi apparatus, ATF6 can be cleaved by S1P or S2P. The fragmented ATF6a translocate to the nucleus and function as a transcription factor to synthesize mRNA for ER chaperones and XBP1. On ER stress, PERK phosphorylates and dimerizes; the activated PERK phosphorylates eIF2α to shut down protein synthesis and increases the expression of ATF4, which translocates to the nucleus to function as a transcription factor to synthesize mRNA for ER-chaperones and GADD34, which blocks ATF4 in a feedback loop.

Figure 2.

Signaling pathways involved in activation and inactivation of CREB. On activation, CREB can be phosphorylated at S133 residue by either Akt, MAPK, PKA, CAMKII; however, it can be dephosphorylated by PP1. Phosphorylated CREB forms the active transcription complex inside the nucleus with an acetyltransferase CBP/p300 and TORC1. The interaction between TORC1 and CREB depends on the acetylation status of TORC1. On deacetylation by SIRT1, TORC1 can interact with CREB. If CREB is phosphorylated by GSK3B at S129 residue or interacts with HDAC4, it cannot interact with CBP, and as a result, the activation complex cannot be formed.

Figure 3.

Signaling pathway how PERK activation affects Akt-activation and synaptic function. Traumatic brain injury (TBI) activates endoplasmic reticulum (ER) stress, which in turn phosphorylates PERK and subsequently induces GADD34 expression by triggering ATF4. GADD34 interacts with an E3 ligase TRAF6 can interact with Akt to facilitate the phosphorylation of Akt at T308. The interaction between GADD34 and TRAF6 prevents the interaction between TRAF6 and Akt, and as a result, the phosphorylation of Akt was decreased significantly after TBI. Since Akt is essential for cell survival, the decrease in its phosphorylation leads to its inactivation and induces neuronal death and synaptic dysfunction after TBI.

Figure 4.

Signaling pathway explains how PERK activation affects CREB signaling and memory impairment. The phosphorylation of PERK is critical for memory dysfunction following traumatic brain injury (TBI). The phosphorylated PERK, in turn, phosphorylates a postsynaptic protein PSD95 and a transcription factor CREB which plays a critical role in cognitive function in the brain. PERK phosphorylates CREB at its S129 residue and prevents the interaction between phosphorylated CREB with CBP and blocks the active transcriptional complex formation in the nucleus to attenuate the transcription of mRNA responsible for BDNF, c-fos, and Arc which are essential for early memory genes. On the other hand, phosphorylation of PSD95 by PERK at its T19 residue leads to its degradation. Since PSD95 functions as a scaffold protein, the absence of PSD95 affects the surface expression of AMPAR and NMDAR. In digest, inactivation of CREB and loss of expression of PSD95 affects dendritic spine formation and ultimately compromises memory function following TBI.

Table 1.

Diseases	Responsible Molecules in ER Stress/CREB Signaling to Induce Memory Impairment	References
Alzheimer's disease	PERK	Duran-Anioz and others (2014)
	eIF2 α	Costa-Mattioli and others (2005); Costa-Mattioli and others (2009); Jiang and others (2010)
	IRE1 α and PERK	Kikuchi and others (2016)
Traumatic brain injury	CHOP	Oyadomari and Mori (2004); Krajewska and others (2011)
	PERK	Sen and others (2017)
	GADD34	Farook and others (2013)