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Translational Control by eIF2α Kinases in Long-lasting Synaptic Plasticity and Long-term Memory

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Abstract

Although the requirement for new protein synthesis in synaptic plasticity and memory has been well established, recent genetic, molecular, electrophysiological, and pharmacological studies have broadened our understanding of the translational control mechanisms that are involved in these processes. One of the critical translational control points mediating general and gene-specific translation depends on the phosphorylation of eukaryotic initiation factor 2 alpha (eIF2α) by four regulatory kinases. Here, we review the literature highlighting the important role for proper translational control via regulation of eIF2α phosphorylation by its kinases in long-lasting synaptic plasticity and long-term memory.

Keywords

protein synthesis; translation initiation; synaptic plasticity; learning; memory; knockout mouse; eIF2; GCN2; PERK; PKR; HRI

Introduction

One of the more remarkable features of the brain is the ability to acquire and store new information as lasting memory traces. This continuous capacity to learn and remember allows one to process changes in the environment, retain new information, and adapt to behavioral choices over time. A fundamental question remains that intrigues modern neuroscientists: how are memories formed and stored at the cellular and molecular level? Behavioral studies performed in mice treated with the protein synthesis inhibitor puromycin provided the first molecular clue that protein synthesis is required for long-term memory (LTM) formation, but not for task acquisition and short-term memory (STM) formation (Flexner et al., 1963). Since then, a plethora of pharmacological and genetic studies have highlighted the critical role for *de novo* gene expression and protein synthesis in LTM formation (Kandel, 2001; McGaugh, 2000).

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Neurons can alter their molecular and physiological characteristics in response to temporaland activity-dependent changes in their environment. Synaptic plasticity refers to the ability of the brain to change the efficacy (strengthening or weakening) of synaptic connections between neurons and is hypothesized as the cellular basis for learning and memory (Bliss and Collingridge, 1993; Malenka and Nicoll, 1999). These persistent, activity-dependent, changes in synaptic strength are triggered by *de novo* protein synthesis (Klann and Sweatt, 2008). Evidence indicating a role for protein synthesis at local synaptic sites stem from observations that neuronal dendrites and their spines contain polyribosomes (Steward and Levy, 1982), translation factors (Tang and Schuman, 2002), and mRNA (Crino and Eberwine, 1996) that can be translated into proteins to support synaptic activity. Consistent with this notion, local protein synthesis was shown to be necessary for long-lasting increases in synaptic strength induced by brain-derived neurotrophic factor (BDNF; Kang and Schuman, 1996). Similarly, rapid, local protein synthesis also was required for long-lasting decreases in synaptic strength induced by activation of group I metabotropic glutamate receptors (mGluR; Huber et al., 2000). Together, these findings indicate that protein synthesis can be triggered locally at activated synapses and is required for persistent, activity-dependent forms of synaptic plasticity, which in turn is thought to be essential for memory formation.

Although the initial report fromFlexner et al. (1963) and other early studies identified new protein synthesis as a molecular requirement for memory formation, they offered little in the way of molecular translational control mechanisms because they relied mostly on the administration of general translation inhibitors into animals. In the last 10 years, however, a vast amount of genetic, biochemical, pharmacological, and physiological studies have increased our knowledge of the precise translational control mechanisms underlying long-lasting synaptic plasticity, memory formation, and cognitive function (Costa-Mattioli et al., 2009; Kelleher et al., 2004; Richter and Klann, 2009). In this review, we specifically discuss the functional role of eIF2α kinases and their regulation of activity-dependent synaptic plasticity and cognitive function, including learning and memory.

Translational Control by eIF2α Phosphorylation

Translational control can be defined as a change in either the efficiency or rate of mRNA translation. The process of mRNA translation can be divided into three main steps: initiation, elongation, and termination. Although regulation can occur at each step, translational control primarily occurs at the rate-limiting initiation step when the small 40S ribosomal subunit is recruited to the mRNA and positioned at the initiation codon (Jackson et al., 2010). Translation initiation itself can be further divided into three key steps. First, the initiator methionyl transfer RNA (Met-tRNA$_i^{Met}$) binds to the small 40S ribosomal subunit, forming the 43S preinitiation complex. This is followed by the binding of the 43S complex to the mRNA so that it can find the initiation codon, thereby forming the 48S complex. Finally, the large ribosomal subunit joins the 48S complex to generate an 80S translational-competent ribosome, which can subsequently proceed with elongation (Jackson et al., 2010; Pestova et al., 2007).

One highly conserved mechanism of translational control in eukaryotic cells involves phosphorylation of eukaryotic initiation factor 2 (eIF2). In this early step in translation initiation, eIF2, a heterotrimer consisting of α, β, and γ subunits, binds Met-tRNA$_i^{Met}$ and GTP to form the stable 43S preinitiation complex (eIF2-GTP-Met-tRNA$_{i\ Met}$). Exchange of GDP for GTP is promoted by eIF2B, a guanine-nucleotide exchange factor that is required to regenerate the active GTP-bound eIF2 that is required for new rounds of translation. The guanine-nucleotide exchange on eIF2 serves as a critical translational control point and is regulated via phosphorylation. Specifically, the phosphorylation of eIF2 on its α subunit at

serine 51 (Ser51) converts eIF2 to a competitive inhibitor of eIF2B, which blocks the GDP/GTP-exchange and causes a decrease in general translation initiation (Pestova et al., 2007; Sonenberg and Dever, 2003).

Although eIF2α phosphorylation inhibits general translation, it also selectively increases the translation of a subset of mRNAs that contain upstream open reading frames (uORFs) in their 5' untranslated region (UTR). uORFs are present in nearly half of rodent and human transcripts (Iacono et al., 2005; Matsui et al., 2007; Mignone et al., 2002), but despite their prevalence, they are less frequent than expected by chance (Iacono et al., 2005), and also are highly conserved (Neafsey and Galagan, 2007).

Probably the best characterized example of gene-specific translational control via eIF2α phosphorylation is that of the yeast transcriptional activator GCN4 (Hinnebusch and Natarajan, 2002). When general translation was inhibited by eIF2α phosphorylation, GCN4 translation, as well as the translation of the transcriptional modulator ATF4 (activating transcription factor 4; also termed CREB2) was enhanced (Harding et al., 2000; Vattem and Wek, 2004). Additional uORF-containing mRNAs have been shown to be translated under conditions resulting in enhanced eIF2α phosphorylation, including the CAAT/enhancer binding proteins C/EBPα and β (Calkhoven et al., 2000) and the β-site β-amyloid precursor protein (APP)-cleaving enzyme BACE1 (De Pietri Tonelli et al., 2004; Lammich et al., 2004). Notably, in multiple species ATF4 and its homologs act as repressors of cAMP-responsive element binding protein (CREB)-mediated gene expression, which is known to be required for long-lasting changes in synaptic plasticity and LTM (Abel et al., 1998; Bartsch et al., 1995; Chen et al., 2003). Thus, eIF2α phosphorylation controls both general and gene-specific translation that regulates CREB-mediated transcription, two distinct processes that are required for long-lasting synaptic plasticity and LTM formation.

eIF2α Kinases

eIF2α phosphorylation is regulated by four serine/threonine (Ser/Thr) protein kinases, each of which phosphorylate eIF2α on Ser51. The four eIF2α kinases are heme-regulated inhibitor (HRI), the double-stranded (ds) RNA activated protein kinase (PKR), the general control non-derepressible-2 (GCN2), and the PKR-like endoplasmic reticulum (ER) resident protein kinase (PERK). These four eIF2α kinases share a conserved kinase domain, but respond differentially to various cellular stressors due to divergent regulatory domains (Dever et al., 2007). For example, HRI is activated by conditions of heme deficiency (Mellor et al., 1994), PKR is activated by double-stranded RNA (dsRNA; Meurs et al., 1990), GCN2 is activated by amino acid deprivation as well as UV irradiation (Deng et al., 2002; Sood et al., 2000), and PERK is activated by an accumulation of misfolded proteins in the ER (Harding et al., 1999; Shi et al., 1998). Thus, depending on the particular cellular stimuli, specific eIF2α kinases become active and phosphorylate eIF2α to control both general and gene-specific translation (Fig. 1). There is very little information concerning whether these kinases are activated under normal physiological conditions, especially in neurons.

All eIF2α kinases are abundantly expressed in the mammalian brain (Berlanga et al., 1999;Harding et al., 1999; Meurs et al., 1990; Shi et al., 1998; Sood et al., 2000; Trinh et al., 2012;Zhu et al., 2011), with the exception of HRI whose expression is relatively low (Crosby et al., 1994; Mellor et al., 1994). We will describe the most salient aspects of GCN2, PKR, and PERK because they are known to play important roles in protein-synthesis dependent synaptic plasticity and cognitive function, including learning and memory.

GCN2 is present in all eukaryotes (Dever et al., 2007; Hinnebusch et al., 2004; Sood et al., 2000) and is activated in response to amino acid starvation via the accumulation of

uncharged tRNAs. GCN2's structure is complex and contains five domains: (1) an N-terminal domain that binds to GCN1 and is required for activation, (2) a pseudokinase domain, (3) an eIF2α kinase domain, (4) a regulatory domain resembling histidyl-tRNA synthetase (HisRS), containing a conserved sequence (motif 2), which is thought to bind all deacylated tRNAs with similar affinity, and (5) a carboxy-terminal domain that dimerizes, enhances tRNA binding, and mediates ribosomal binding (Dever et al., 2007). In contrast to the monomers PKR and PERK that require dimerization for activation, GCN2 exists constitutively as a dimer where the HisRS domain interacts with both the kinase domain and the carboxy-terminal domain to maintain it in inactive state. In response to amino acid starvation, uncharged tRNAs accumulate and bind to the HisRS domain, which results in the release of these inhibitory interactions and the subsequent activation of GCN2 (Dever et al., 2007). GCN2 also is activated by UV irradiation, high salinity, rapamycin, and glucose limitation (Deng et al., 2002; Hinnebusch, 2005). Interestingly, these stress stimuli could not activate a GCN2 mutant lacking a functional HisRS domain (Hinnebusch, 2005; Wek et al., 1995). All together, these findings indicate that uncharged tRNA is the main activator of GCN2.

PKR is expressed widely in vertebrates and activated in response to dsRNA produced during viral infection (Dever et al., 2007). Compared to GCN2 and PERK, the structure of PKR is relatively simple with an N-terminal dsRNA-binding domain (dsRBD), which consists of two dsRNA binding motifs (dsRBMs), and a carboxy-terminal kinase domain. Direct binding of dsRNA to the dsRBMs induces a conformational change exposing the kinase domain of PKR, which subsequently promotes dimerization and kinase activation (Carpick et al., 1997; Patel and Sen, 1998; Zhang et al., 2001). PKR and PERK regulate protein synthesis during viral infection and ER stress, respectively, but also regulate the levels of specific proteins via degradation (Baltzis et al., 2007; Raven et al., 2008). A growing body of evidence indicates that protein synthesis as well as degradation plays a critical role in synaptic plasticity and memory (Bingol and Sheng, 2011; Kaang and Choi, 2012). Thus, it seems likely that activation of eIF2α kinases control not only protein synthesis, but also other cellular processes that are important for changes in protein expression that regulate synaptic and cognitive function. Moreover, several neurological conditions including status epilepticus (Carnevalli et al., 2006), Alzheimer's disease (Couturier et al., 2010; Dumurgier et al., 2013; Peel and Bredesen, 2003), Huntington's disease (Bando et al., 2005; Peel et al., 2001), Parkinson's disease (Bando et al., 2005), and Creutzfeldt-Jakob's disease (Paquet et al., 2009) have been linked to activation of the PKR-eIF2α axis, suggesting a role for PKR-regulated translational control pathologies associated with neurological disorders.

PERK has been identified in both vertebrates and invertebrates and becomes activated in response to an accumulation of misfolded proteins in the ER (Harding et al., 1999; Shi et al., 1998; Wek and Cavener, 2007). PERK contains four domains, including a signal peptide, an N-terminal regulatory region, a transmembrane domain, and a cytoplasmic kinase domain. Normally, the ER chaperones BiP (GRP78) and GRP94 bind to PERK, keeping it inactive as a monomer (Bertolotti et al., 2000). During ER stress, BiP and GRP94 dissociate from PERK, which results in dimerization, autophosphorylation, and activation of the kinase. Previous studies showed that mutations in the human PERK gene (*EIF2AK3*) causes Wolcott-Rallison syndrome (WRS), a rare autosomal recessive disorder characterized by permanent neonatal diabetes, multiple epiphyseal dysplasia, liver dysfunction, and pancreas insufficiency (Delepine et al., 2000; Julier and Nicolino, 2010; Rubio-Cabezas et al., 2009). Consistent with these findings, molecular and genetic studies have shown that these pathologies are recapitulated in PERK-deficient mice (Harding et al., 2001; Wei et al., 2008; Zhang et al., 2002; Zhang et al., 2006). In some cases of WRS, patients have been reported to develop clinical features associated with mental retardation (Delepine et al., 2000; Reis et al., 2011; Senee et al., 2004; Thornton et al., 1997). In addition, cell lines lacking either of

the tuberous sclerosis complex (TSC) proteins, TSC1 or TSC2, and both mouse and human tumors from TSC model mice and patients, respectively, exhibited activation of PERK-eIF2α signaling (Ozcan et al., 2008). Finally, a single nucleotide polymorphism in *EIF2AK3* has been identified that is associated with progressive supranuclear palsy, a movement disorder with prominent tau neuropathology (Hoglinger et al., 2011). Collectively, these findings suggest that PERK is a key factor in severe pathologies associated with dysregulated protein synthesis.

In higher eukaryotes, the dynamic regulation of eIF2α phosphorylation is critical for cell survival. For example, PERK is rapidly activated by ER stress, but within minutes of the restoration of ER homeostasis, PERK is dephosphorylated and inactivated (Ma and Hendershot, 2003; Ron and Walter, 2007). Genetic screening studies in somatic cells have identified two phosphatase complexes that independently dephosphorylate eIF2α. The first complex consists of the eIF2α-specific regulatory subunit CReP (constitutive repressor of eIF2α phosphorylation) and PPIc (protein phosphatase I catalytic subunit; (Jousse et al., 2003). The second complex consists of the related regulatory subunit GADD34 (growth arrest and DNA damage-inducible gene 34) and PPIc (Connor et al., 2001; Jousse et al., 2003; Novoa et al., 2001). CReP is constitutively expressed and is thought to contribute to baseline eIF2α dephosphorylation, whereas GADD34 is transcriptionally induced by eIF2α phosphorylation and serves within a negative feedback loop to restore protein synthesis (Ma and Hendershot, 2003).

GCN2 Controls L-LTP and LTM

As previously mentioned, distinct eIF2α kinases phosphorylate eIF2α to control two fundamental processes that are crucial for the consolidation of long-term memories: *de novo* protein synthesis and CREB-mediated gene expression via the memory repressing factor ATF4. Evidence that regulation of eIF2α phosphorylation plays an important role in long-lasting synaptic plasticity and LTM was first provided by the observation that GCN2-deficient mice exhibit a lowered threshold for the induction of long-lasting late phase long-term potentiation (L-LTP) and the consolidation of long-term memory (Costa-Mattioli et al., 2005). The LTP phenotype observed in GCN2-deficient mice also has been observed in mice lacking other translational repressors such as 4E-BP2 (Banko et al., 2005) and TSC2 (Ehninger et al., 2008). Consistent with these findings, heterozygous eIF2α knockin mice with a mutation on Ser 51 of eIF2α also have a decreased threshold for the induction of L-LTP (Costa-Mattioli et al., 2007). Moreover, decreased eIF2α phosphorylation in GCN2-deficient mice and heterozygous eIF2α knockin mice was associated with enhanced LTM in multiple tasks using training paradigms that normally do not elicit LTM (Costa-Mattioli et al., 2005; Costa-Mattioli et al., 2007). In contrast, hippocampal infusion with Sal003, an inhibitor of eIF2α dephosphorylation (Boyce et al., 2005), prevented the induction of both L-LTP and LTM (Costa-Mattioli et al., 2007). Taken together, these findings indicate that GCN2-dependent phosphorylation of eIF2α is required for the expression of L-LTP and LTM.

A possible mechanism for gene-specific translation via GCN2-dependent phosphorylation of eIF2α in L-LTP and LTM involves the translation of ATF4 mRNA, which then would block the CREB-dependent transcription of synaptic plasticity-related genes and hence, L-LTP and LTM formation. Evidence supporting this hypothesis is provided by the observation that basal levels of eIF2α phosphorylation and ATF4 expression were decreased in GCN2-deficient mice, which were associated with a lower threshold for activation of CREB-mediated gene expression (Costa-Mattioli et al., 2005). Therefore, it is possible that the effect of GCN2 on long-lasting LTP and memory is mediated by the modulation of ATF4/CREB activity. Although the threshold for L-LTP is decreased in GCN2-deficient mice,

normal L-LTP-inducing stimulation failed to elicit L-LTP (Costa-Mattioli et al., 2005), suggesting that additional inhibitory factors may be upregulated due to the lack of translational repression and consequently block L-LTP and LTM in these mice. For instance, L-LTP-inducing stimulation may increase the levels of IMPACT, a GCN2 inhibitor, whose expression is enriched in the mammalian brain (Pereira et al., 2005). Furthermore, although the threshold for inducing LTM is decreased in the GCN2-deficient mice, robust training paradigms that normally produce LTM fail to elicit it in these mice (Costa-Mattioli et al., 2005). Collectively, these findings suggest that GCN2-dependent regulation of ATF4 translation must be tightly controlled for the normal expression of L-LTP and LTM.

Genetic deletion of GCN2 appears to affect LTP, but not LTD. In contrast to LTP, mGluR-LTD, which was enhanced in 4E-BP2 knockout mice (Banko et al., 2006), was unaffected in GCN2-deficient mice (Costa-Mattioli et al., 2005). As will be discussed in more detail later, LTP, which has a lower threshold for induction in GCN2-deficient mice, was unaffected in mice with a forebrain specific disruption of PERK (PERK cKO; Trinh et al., 2013 *in revision*). Furthermore, mGluR-LTD, which is protein synthesis-dependent and unaffected in GCN2-deficient mice, was enhanced in PERK cKO mice (Trinh et al., 2013 *in revision*), suggesting the interesting possibility that distinct pools of mRNA may be differentially translated during protein synthesis-dependent forms of LTP and LTD. Thus, these findings suggest that the regulation of CREB-dependent gene expression via GCN2-dependent ATF4 translation is specific to LTP.

PKR Controls Gene-specific Translation, L-LTP, and LTM

Using a novel pharmacogenetic mouse model,Jiang et al. (2010) demonstrated that a selective increase in PKR-mediated eIF2α phosphorylation in CA1 hippocampal neurons impairs L-LTP and LTM. Accordingly, the increase in eIF2α phosphorylation was associated with an increase in ATF4 translation and the suppression of CREB-dependent gene expression (Jiang et al., 2010), including that of BDNF, a key protein involved in L-LTP and the consolidation of LTM (Bekinschtein et al., 2008). It should be noted that although general protein synthesis was not altered, ATF4 translation was increased in CA1 neurons from these mice, suggesting that gene-specific translation of ATF4 is required for the suppression of L-LTP and LTM. Consistent with these findings, Sal003, which increases eIF2α phosphorylation, failed to inhibit L-LTP in hippocampal slices from ATF4-deficient mice (Costa-Mattioli et al., 2007). Collectively, these findings indicate that precise control of specific mRNAs (such as ATF4 or BDNF), rather than general translation, is required for the proper expression of long-lasting synaptic plasticity and long-term memory.

Recent pharmacological and genetic studies confirm an important role for endogenous PKR in the control of neural networks and normal cognitive function. For example, pharmacological inhibition of PKR in the gustatory cortex of mice and rats enhanced both positive and negative forms of long-term taste memory (Stern et al., 2013). In addition, either genetic deletion or pharmacological inhibition of PKR results in hyperexcitability of cortical and hippocampal networks, facilitated L-LTP, and enhanced LTM (Zhu et al., 2011). It was proposed that PKR regulates these processes via interferon gamma (IFN-γ)-mediated disinhibition at the synapse. Indeed, IFNγ mRNA normally activates PKR in the cell to specifically inhibit its own translation (Ben-Asouli et al., 2002; Cohen-Chalamish et al., 2009). Subsequently, it was shown that when PKR activity was inhibited, IFNγ mRNA translation was increased, resulting in a loss of GABAergic transmission, enhanced neuronal excitability, and improved cognitive performance (Zhu et al., 2011). Thus, these findings indicate that PKR activation plays a key role in modulating activity-dependent changes in synaptic strength, network rhythmicity, and cognition.

PKR also has been proposed to be a cognitive decline biomarker in patients suffering from Alzheimer's disease (AD) based on correlations between cognitive and memory test scores with activation and dysregulation of PKR-mediated translation (Damjanac et al., 2009). Moreover, recent studies showed that PKR activity and eIF2α phosphorylation was increased in mice overexpressing ApoE4, a model for sporadic AD, as well as in aging rodents (Segev et al., 2013).These findings suggest that PKR-eIF2α signaling may contribute to the aging-related cognitive decline associated with sporadic AD.

PERK Controls ATF4 Translation, mGluR-LTD, and Behavioral Flexibility

Using mouse behavioral genetics and biochemistry, it was demonstrated that PERK plays a crucial role in regulating behavioral flexibility (Trinh et al., 2012). Previous studies showed that global inactivation of PERK results in severe developmental abnormalities (Wei et al., 2008; Zhang et al., 2002). To rule out the possibility that the effects of PERK on synaptic and cognitive function occur during development, mice were generated in which PERK was selectively removed in the forebrain at approximately 3 weeks of age (Trinh et al., 2012). Although general protein synthesis was unaltered in the prefrontal cortex (PFC) of PERK cKO mice, both eIF2α phosphorylation and ATF4 expression were reduced significantly (Trinh et al., 2012). Interestingly, these molecular changes in the PERK cKO mice were associated with multiple phenotypes consistent with impaired information processing and behavioral flexibility (Trinh et al., 2012). For example, PERK cKO mice exhibited reduced paired pulse inhibition, a type of sensorimotor-gating that restricts the processing of sensory information (Bitsios et al., 2006; Braff et al., 2001). In addition, PERK cKO mice showed enhanced preference for the familiar object compared with the novel object when tested in the novel object recognition task (Trinh et al., 2012). Furthermore, although PERK cKO mice exhibited normal task acquisition and spatial memory in the Morris water maze, they displayed enhanced perseveration for the originally learned platform position, even after it has been moved to the opposite quadrant. Similarly, PERK cKO mice displayed severe behavioral inflexibility in the Y-water maze choice reversal task (Trinh et al., 2012) in which the mice are trained to shift their response pattern when the platform position is relocated to the other arm of the maze. This type of inhibitory learning is usually called reversal learning. One possible explanation for these results is that PERK plays an important role in regulating frontal and temporal cortex-dependent sensory information processing. Hence, in the absence of PERK, mice are unable to inhibit responses to sensory and cognitive information, which causes enhanced perseveration, impaired reversal learning, and behavioral inflexibility. Moreover, PERK cKO mice displayed impaired fear extinction (Trinh et al., 2012), indicating an equally important role for PERK in PFC-dependent updating of behavior. Collectively, these findings suggest that in the postnatal adult forebrain, PERK-directed translational control of ATF4 is critical for normal behavioral flexibility.

The behavioral studies with the PERK cKO mice suggest that eIF2α phosphorylation is normally altered during reversal learning. Indeed, wild-type mice exhibited reduced eIF2α phosphorylation 30 minutes after reversal learning (Trinh et al., 2012). Although basal eIF2α phosphorylation was reduced, there was no further reduction in the PERK cKO mice, suggesting that reversal learning normally is associated with decreased phosphorylation of eIF2α phosphorylation. However, unlike PERK cKO mice, GCN2-deficient mice exhibited normal reversal learning (Trinh et al., 2012), suggesting the interesting possibility that behavioral flexibility is controlled specifically by a pool of eIF2α that is normally phosphorylated by PERK. All together, these findings suggest that reversal learning normally decreases eIF2α phosphorylation and that PERK phosphorylates a specific pool of eIF2α, which stimulates the translation of ATF4, to regulate behavioral flexibility. It should be noted that in addition to ATF4, other genes recently have been identified that are

preferentially translated by eIF2α phosphorylation, which suggests that additional factors may participate downstream of PERK to regulate cognitive control functions (Dey et al., 2010; Jackson et al., 2010).

Interestingly, it was shown that PERK and ATF4 expression are reduced in the frontal cortex of human schizophrenic patients (Trinh et al., 2012). In addition to schizophrenia, cognitive and information processing deficits have been implicated as core features of several other mental illnesses, including bipolar disorder, attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) (Bora et al., 2009; Goos et al., 2009; Lesh et al., 2011; Solomon et al., 2009). In contrast to schizophrenic brains, PERK and ATF4 levels were unaltered in the frontal cortex of bipolar patients compared to normal control patients (Trinh et al., 2012). Together, these findings suggest that disruption of PERK-regulated translation of ATF4 in the frontal cortex contributes to the pathophysiology of schizophrenia. Future studies examining PERK and ATF4 expression in the frontal cortex of patients with other mental illnesses are needed to determine how broadly or specifically PERK-directed translation is involved in mental illnesses.

More recently, it was demonstrated that PERK regulates eIF2α phosphorylation and ATF4 translation during hippocampal mGluR-dependent LTD. *Cre*-mediated deletion of PERK in hippocampal area CA1 was associated with reduced eIF2α phosphorylation and ATF4 expression (Trinh et al., 2013 *in revision*). Interestingly, although PERK cKO mice exhibited enhanced mGluR-LTD, both E-LTP and L-LTP remained unchanged (Trinh et al., 2013 *in revision*). Moreover, in wild-type mice mGluR-LTD was associated with increased phosphorylation of eIF2α, which was absent in the PERK cKO mice. In contrast, L-LTP was associated with decreased phosphorylation of eIF2α. Together, these findings support the notion that bidirectional changes in synaptic transmission, namely LTP and LTD, use distinct mechanisms to regulate eIF2α phosphorylation and suggest that PERK-mediated phosphorylation of eIF2α may be specific to mGluR-LTD. Moreover, these results suggest that disruption of PERK-directed translational control following activation of group I mGluRs may serve as a possible mechanism for the behavioral phenotypes observed in the PERK cKO mice (Trinh et al., 2012).

Conclusions and Future Directions

It is now evident that eIF2α kinases and their ability to impact translational control via the phosphorylation of eIF2α are critical for long-lasting plasticity of synaptic connections and for cognitive functions that rely on such plasticity in the brain. One intriguing insight from the studies of the role of eIF2α kinases in synaptic plasticity thus far is that eIF2α phosphorylation is divergently regulated during LTP and LTD. Moreover, these studies suggest that eIF2α kinases, such as PERK and GCN2, modulate eIF2α phosphorylation in order to regulate the translation of distinct sets of mRNAs to enable the expression of either LTP or LTD. An important next step would be to establish the identity of the mRNAs whose translation is locally regulated by eIF2α kinases, perhaps with either microarray studies of polysome fractions or proteomic and bioinformatic analyses.

Studies investigating the role of eIF2α kinases in synaptic plasticity and memory have primarily focused on pyramidal neurons of the hippocampus and prefrontal cortex (in the case of PERK), but little is known about their function in other brain regions and cell types. For instance, mechanisms of translational control by eIF2α kinases in cortical or striatal GABAergic interneurons have not been explored. Thus, future studies characterizing the role of eIF2α kinases in different brain regions and cell types will be necessary to provide a comprehensive analysis of how proteins are synthesized throughout the brain in response to diverse stimuli. Furthermore, it will be important to investigate the biochemical signaling

cascades that couple neurotransmitter and neurotrophin receptors to the activation/inactivation of eIF2α kinases. By identifying the upstream pathways that impinge on translational control by eIF2α kinases, one should be able to determine how these specific pathways couple receptor activation to trigger distinct forms of synaptic plasticity and multiple cognitive processes.

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Research Highlights

eIF2 kinases control general and gene-specific translation

eIF2 kinases are required for hippocampal synaptic plasticity

eIF2 kinases are required for various forms of long-term memory

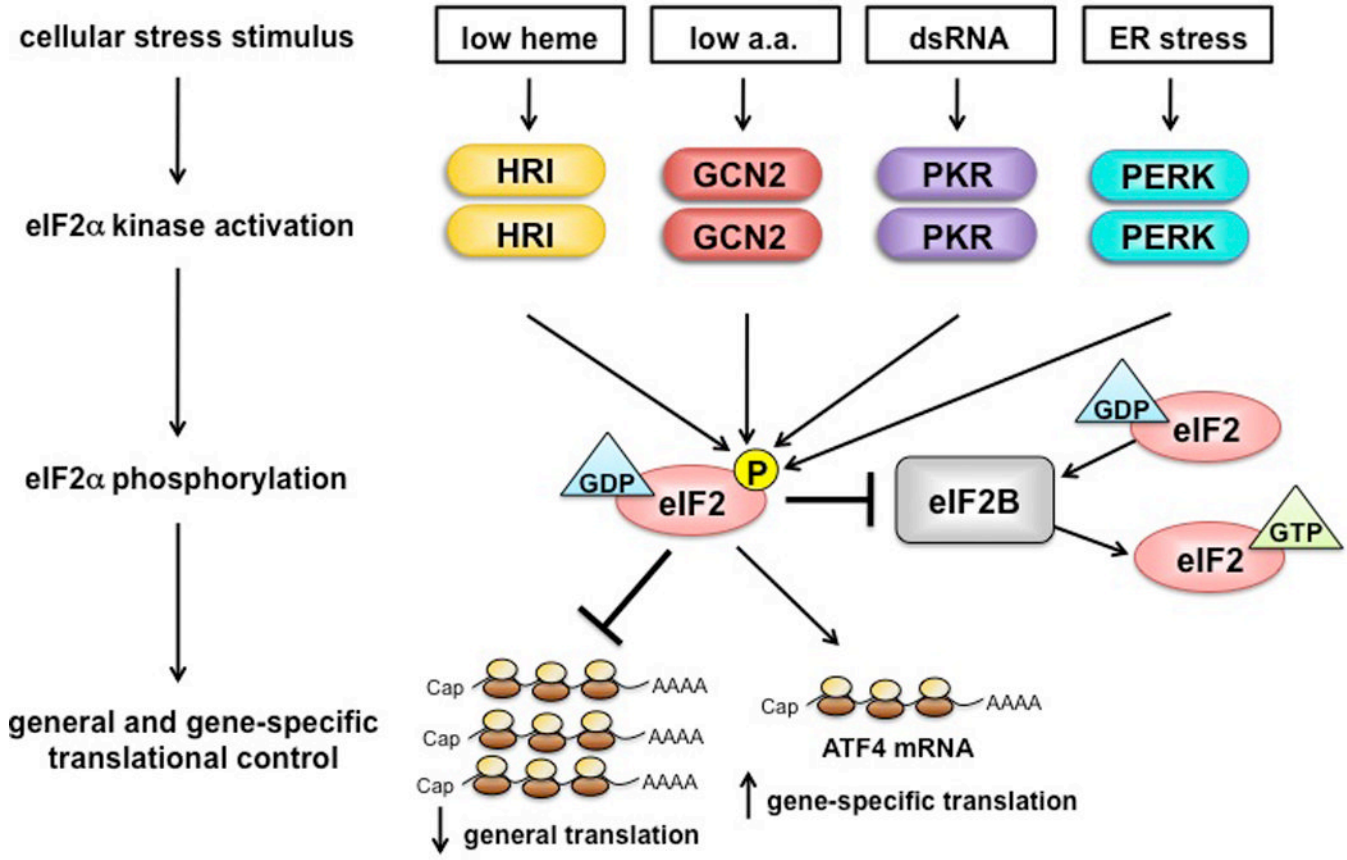

Fig. 1. Schematic representation of translational control by eIF2α kinases

In response to distinct cellular stress stimuli, four eIF2α kinases become activated and phosphorylate the α subunit of eIF2. The guanine nucleotide exchange factor eIF2B catalyzes the exchange of inactive GDP for active GTP-bound eIF2, a process required for new rounds of translation initiation. Phosphorylation of eIF2 inhibits eIF2B activity, which blocks GDP/GTP-exchange, resulting in the reduction of general translation and the stimulation of gene-specific translation of uORF-containing mRNAs (for example, ATF4).