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Emotional modulation of the synapse

Jayme R. McReynolds and

Department of Behavioral and Brain Sciences, The University of Texas at Dallas, 800 West Campbell Road, Richardson, TX 75080, USA

Christa K. McIntyre[*]

Department of Behavioral and Brain Sciences, The University of Texas at Dallas, 800 West Campbell Road, Richardson, TX 75080, USA

Abstract

Acute stress and emotional arousal can enhance the consolidation of long-term memories in a manner that is dependent on β-adrenoceptor activation in the basolateral complex of the amygdala (BLA). The BLA interacts with multiple memory systems in the brain to modulate a variety of classes of memory. However, the synaptic mechanisms of this interaction remain unresolved. This review describes the evidence of modulation of memory and synaptic plasticity produced by emotional arousal, stress hormones, and pharmacological or electrophysiological stimulation of the amygdala. The amygdala modulation of local translation and/or degradation of the synaptic plasticity-related proteins, activity-regulated cytoskeletal-associated protein and calcium/calmodulin-dependent protein kinase II α, is offered as a potential mechanism for the rapid memory consolidation that is associated with emotionally arousing events. This model shares features with synaptic tagging and the emotional tagging hypotheses.

Keywords

amygdala; Arc; CaMKIIα; local translation; memory; synaptic plasticity

Introduction

Emotional arousal modulates the consolidation of long-term memories (McGaugh, 2004). Experiences that produce acute stress, fear, or excitement are typically remembered better than emotionally neutral experiences. This effect is observed in both humans (Cahill et al., 1994, 1996; Cahill and Alkire, 2003; Kuhlmann and Wolf, 2006) and nonhuman animals (Gold et al., 1975; Cahill and McGaugh, 1996; Quirarte et al., 1998; Ferry et al., 1999b; McIntyre et al., 2002; Okuda et al., 2004). Both the invasive studies in animals and the imaging studies in humans corroborate a role for the amygdala in this memory enhancement (Cahill et al., 1994; Ferry et al., 1999b; Roozendaal, 2000; McGaugh and Roozendaal, 2002; Cahill and Alkire, 2003; Roozendaal et al., 2006a, 2008a). More generally, the stress hormones epinephrine (adrenalin) and cortisol (corticosterone in rats) are released by the adrenal glands into the bloodstream to enhance the fight-or-flight response that may be

[*]Corresponding author: Christa K. McIntyre, christa.mcintyre@utdallas.edu.

important for survival. These stress hormones also modulate the storage of memories of events that have a bearing on survival through mechanisms involving the activation of β-adrenoceptors in the basolateral complex of the amygdala (Quirarte et al., 1997; Ferry and McGaugh, 1999; Ferry et al., 1999a; Miranda et al., 2003; Roozendaal et al., 2006c). The evidence implicating this pathway stems from an original finding by Liang et al. (1986) indicating that the infusions of the β-adrenoceptor antagonist propranolol into the basolateral complex of the amygdala (BLA) blocked the memory-enhancing effect of posttraining, systemic administration of epinephrine in rats. Many subsequent studies have supported this finding and have demonstrated that the glucocorticoid effects on memory also require β-adrenoceptor activation in the amygdala (Quirarte et al., 1997; Roozendaal et al., 2002, 2004, 2006a, 2006b, 2006c, 2007, 2008b).

A relatively unchallenged assumption in the field is that memory is supported by changes that occur in the brain at the level of the synapse. Molecular and cellular processes contribute to synaptic changes, which likely influence larger brain systems and the local circuitry. Whereas emotional memory-related synaptic changes are seen within the lateral nucleus of the amygdala (Rodrigues et al., 2004), there is also evidence indicating that the cellular processes in the amygdala influence cellular processes in efferent brain regions and, in so doing, may modulate synaptic plasticity in a distributed manner (McGaugh, 2004). Accordingly, amygdala modulation of synaptic plasticity in the hippocampus and cortex contributes to the contextual and sensory features of an emotionally arousing memory.

Packard et al. (1994) were among the first to identify the amygdala as a modulator of multiple memory systems. They observed that posttraining administration of amphetamine into the dorsal hippocampus or caudate nucleus enhanced the consolidation of a spatial or cued version of the water maze task, respectively. Posttraining infusions of amphetamine into the amygdala enhanced consolidation of both versions of the water maze task. Importantly, inactivation of the amygdala prior to testing 24 h after training did not affect the memory enhancement produced by posttraining intra-amygdala amphetamine treatment, indicating that the amygdala was not the locus of the memory trace but instead a modulator of memory consolidation that likely interacted with the hippocampus and caudate nucleus to exert its effects. Since this influential discovery, many have observed interactions of the amygdala with other brain regions that play a role in memory consolidation. These regions include, but are not limited to, the nucleus accumbens (Setlow et al., 2000), the entorhinal cortex (Roesler et al., 2002), the insular cortex (Miranda and McGaugh, 2004), the rostral anterior cingulate cortex (Malin et al., 2007), and the medial prefrontal cortex (Roozendaal et al., 2009). Given the evidence that the amygdala is not the locus of hippocampus- or caudate nucleus-dependent memory but can modulate its consolidation, most of this research considers the influence of the amygdala on efferent structures. However, a role for the amygdala in the modulation of processing in efferent brain regions does not exclude the possibility of a critical feedback or feed-forward modulation of the amygdala (Rodrigues et al., 2009; Roozendaal et al., 2009). The amygdala sends extensive projections to cortical and subcortical regions (McDonald and Jackson, 1987; Price, 2003); however, a monosynaptic connection is not a requirement of this model of amygdala modulation of synaptic plasticity.

In this review, research examining the influence of emotional arousal, stress hormones, and electrical or pharmacological manipulations of the BLA on synaptic plasticity in downstream brain regions is described. The preponderance of evidence for amygdala modulation of efferent plasticity comes from studies of the hippocampus. Research examining the influence of electrical or pharmacological stimulation of the amygdala on hippocampal long-term potentiation (LTP) and expression of synaptic plasticity-related proteins is discussed, with particular emphasis on the synaptic plasticity-related proteins activity-regulated cytoskeletal-associated protein (Arc) and calcium/calmodulin-dependent kinase II α (CaMKII α). Both synaptic tagging and emotional tagging hypotheses are considered in light of evidence of amygdala modulation of synaptic plasticity-related proteins in the hippocampus. The aim of the proposed model is to expand the current thinking about the effects of emotional arousal on synaptic plasticity.

BLA influence on synaptic plasticity

Many of the mechanisms of LTP are shared with mechanisms required for memory. Just as memory formation can be separated into encoding and consolidation phases, LTP can be separated into induction and maintenance phases. The maintenance of LTP is comparable to the consolidation phase of memory in that both are protein synthesis dependent and both exhibit similar biochemical changes, such as changes in the phosphorylation state of the GluR1 subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (Davis and Squire, 1984; Kelleher et al., 2004; Whitlock et al., 2006). The study of LTP has facilitated our understanding of the influence of BLA activation on synaptic strength in the efferent regions of the brain, particularly the hippocampus. The nuclei of the BLA (lateral and basolateral) project directly to the hippocampus and also to the entorhinal cortex (Price, 2003). Stimulation of the BLA enhances, and lesions of the BLA impair, perforant path stimulation-induced LTP in the dentate gyrus (Ikegaya et al., 1994, 1996). The effect of BLA stimulation on dentate gyrus synapses can be replicated by the stimulation of the lateral perforant path, implicating the BLA-entorhinal cortex pathway in dentate gyrus plasticity (Nakao et al., 2004). The early phase of LTP (lasting ~4 h) can be converted to longer-lasting late-phase LTP with stimulation of the BLA (Frey et al., 2001). This late phase of LTP is dependent on protein kinase A activation (Huang et al., 1995; Abel et al., 1997), indicating a role for catecholamines. More specifically, bath application of norepinephrine (NE) facilitates CA1 LTP in a time-dependent manner (Hu et al., 2007). Furthermore, administration of a β-adrenoceptor agonist to dendrites of the stratum radiatum, paired with subthreshold stimulation of the Schaffer collaterals, promotes late-phase LTP. This effect remains when the dendrites are mechanically separated from the cell body layer, indicating that NE can modulate LTP through protein synthesis-dependent mechanisms that are independent of the soma (Gelinas and Nguyen, 2005). Noradrenergic activation in the BLA also plays a role in hippocampal LTP. Blockade of BLA β-adrenoceptors impairs perforant path stimulation-induced LTP in the dentate gyrus of the hippocampus (Ikegaya et al., 1997). In the intact animal, the stress response would promote locus coeruleus activation (Abercrombie and Jacobs, 1987) and increase release of NE in both the amygdala (McIntyre et al., 2002) and the hippocampus (Rosario and Abercrombie, 1999). Indeed, emotional arousal influences the maintenance of LTP. After induction in

freely moving rats, LTP in the hippocampus can be reinforced with aversive or appetitive stimuli, and this reinforcement is dependent on β-adrenoceptors in the BLA as it is blocked with the β-adrenoceptor antagonist propranolol (Seidenbecher et al., 1997). Although NE application to the bath is sufficient to influence LTP in hippocampal slices, NE activation of β-adrenoceptors in the BLA appears to play a necessary role in the enhanced hippocampal plasticity that results from emotional arousal in the intact animal. Furthermore, lesions of the locus coeruleus or blockade of β-adrenoceptors in the medial septum block the BLA-influenced transformation of early to late-phase LTP in the dentate gyrus (Bergado et al., 2007), suggesting that systems, including the medial septum-hippocampus and the BLA, work in concert to enhance the storage of emotionally arousing events.

Synaptic tagging and emotional tagging

Over a decade ago, Frey and Morris (1997) identified ‘synaptic tagging’ as an explanation for the synapse specificity of LTP. The more recently proposed ‘ behavioral tagging’ and ‘emotional tagging’ hypotheses (Richter-Levin and Akirav, 2003; Ballarini et al., 2009) incorporated an element of memory specificity to the tagging concept. Synaptic tagging is based on the observation that the induction of LTP creates the potential for, but not commitment to, lasting changes in synaptic efficacy. This is similar to memory formation in that experiencing an event creates the potential for, but not commitment to, a long-lasting memory for the experience. The core components of synaptic tagging are (1) the setting of a local tag at a synaptic location where long-lasting changes may occur and (2) the synthesis of plasticity-related proteins that are captured by tagged synapses to produce lasting changes in synaptic strength (Redondo and Morris, 2011). The emotional tagging hypothesis is based on the observation that irrelevant information, which would normally be rapidly forgotten, is stored as long-term memory when associated with emotional arousal (Bergado et al., 2011). According to the emotional tagging hypothesis, the activation of the hippocampus by experience sets the local synaptic tag that is reinforced by emotional arousal, resulting in lasting synaptic modifications that support long-term memories. Given that emotional arousal increases NE in the amygdala, and the β-adrenoceptor activation in the BLA is critically involved in the memory-enhancing effects of stress and stress hormones on memory consolidation, the BLA is a likely participant in the emotional tagging process. Here, we discuss evidence indicating that the BLA influences the expression of plasticity-related proteins, promoting the maintenance of long-lasting synaptic modifications in the hippocampus.

BLA influence on expression of plasticity-related proteins in the hippocampus

Although hundreds of known plasticity-related proteins are expressed in the hippocampus, this review will focus on two proteins: CaMKIIα and Arc. These dendritically localized plasticity-related proteins share some similar characteristics. Cap-dependent initiation is a common mechanism triggering translation, requiring the formation of a eukaryotic initiation factor complex to bind ribosomal subunits to the 7-methyl-GTP cap structure at the 5′ end of the messenger RNA (mRNA; Klann and Dever, 2004). However, *Arc* and *CaMKIIα* also

have internal ribosomal entry sites (IRES) that undergo translation initiation in a cap-independent manner, which may confer a translational advantage (Pinkstaff et al., 2001). The decreased availability and dephosphorylation of the cap-dependent initiation factor eIF4E can result in a switch from predominantly cap-dependent initiation to a cap-independent initiation of translation of mRNAs that have IRES sequences (Dyer et al., 2003; Svitkin et al., 2005). *CaMKIIα* and *Arc* protein appear specifically in stimulated regions of dendrites and in spines of hippocampal neurons (Steward et al., 1998; Mori et al., 2000; Moga et al., 2004; Lee et al., 2009). Knockout models have demonstrated that *CaMKIIα* and *Arc* are important for long-term memory formation and long-term plasticity in the hippocampus (Silva et al., 1992a,b; Plath et al., 2006). In fact, dendritic targeting of *CaMKIIα* mRNA is essential for synaptic plasticity and memory. A mutation of the *CaMKIIα* gene preventing dendritic localization and restricting *CaMKIIα* mRNA to the soma results in reduced late-phase LTP as well as impairments in spatial memory, associative fear conditioning, and object recognition memory (Miller et al., 2002). This result demonstrates the importance of local translation for plasticity and memory. Arc can also be translated in synapses. Both LTP-inducing stimuli and long-term depression (LTD)-inducing stimuli increase the expression of Arc protein in isolated synapses *in vitro* (Yin et al., 2002; Waung et al., 2008). These data suggest that there might be a group of dendritically localized plasticity-related genes whose local translation contributes to long-term plasticity and memory consolidation (Sutton and Schuman, 2006).

The translation of *Arc* mRNA appears to be an important event for hippocampal plasticity and memory. Arc protein expression is necessary in the dorsal hippocampus, the rostral anterior cingulate cortex, and the lateral amygdala for the optimal consolidation of long-term memory (McIntyre et al., 2005; Ploski et al., 2008; Holloway and McIntyre, 2011). Intrahippocampal infusions of anti-sense oligodeoxynucleotides block the expression of Arc and impair the maintenance of hippocampal late-phase LTP without affecting induction. This blockade of hippocampal Arc expression also impairs consolidation but not acquisition of spatial memory (Guzowski et al., 2000). These data, combined with the fact that the knockout of the *Arc* gene resulted in intact short-term memory but impaired long-term memory, suggest a role for Arc in the consolidation of synaptic plasticity and memory (Plath et al., 2006).

The role of Arc protein in modifying synaptic strength has been well reviewed by others (Bramham et al., 2008, 2010; Korb and Finkbeiner, 2011; Shepherd and Bear, 2011). Briefly, Arc is implicated in actin polymerization (Messaoudi et al., 2007) and AMPA receptor endoytosis (Chowdhury et al., 2006; Rial Verde et al., 2006). It is necessary for LTD (Waung et al., 2008) as well as for potentiation and appears to influence spine shape and density (Peebles et al., 2010). According to one view, Arc expression maintains synaptic homeostasis in a dynamic environment (Shepherd et al., 2006).

The BLA modulates the expression of Arc in the hippocampus. We found that memory-enhancing infusions of a β adrenoceptor agonist into the BLA after training on an aversive inhibitory avoidance task increased Arc protein expression in the hippocampus without influencing mRNA levels (McIntyre et al., 2005). These data suggest that the BLA modulates the synaptic plasticity-related protein Arc in the hippocampus through a post-

transcriptional mechanism. Huff et al. (2006) reported that infusions of musicmol into the BLA following contextual fear conditioning attenuated training-induced increases in Arc protein expression in the hippocampus; however, this group observed a reduction in *Arc* mRNA as well. The apparent discrepancy in hippocampal *Arc* mRNA measurements across studies may indicate that the BLA can exert a transcriptional influence and a posttranscriptional influence on Arc expression in the hippocampus. Alternatively, our method for mRNA analysis (fluorescence *in situ* hybridization with densitometry) may not have been sensitive enough to detect a difference in mRNA levels. However, we did detect an increase in *Arc* mRNA as a result of training. In support of the evidence for a posttranscriptional influence of the BLA on hippocampal Arc expression, Ren et al. (2008) reported that the memory-impairing anesthetic proprofol decreased hippocampal Arc expression, but intra-BLA infusions of musicmol reversed the effect on Arc protein, but not mRNA, in the hippocampus. Using real-time PCR to detect *Arc* mRNA, this group found evidence in support of BLA modulation of hippocampal Arc expression through a posttranscriptional mechanism. Taken together with evidence of local translation of Arc *in vitro*, these findings suggest that the BLA may modulate long-term memory for the inhibitory avoidance task by a mechanism that involves posttranscriptional modulation of Arc in the hippocampus through an influence on local synthesis of Arc at the synapse. In support of this theory, the posttraining administration of a memory-enhancing dose of the stress hormone corticosterone increases Arc protein expression in hippocampal synaptoneurosomes and this effect is attenuated by the blockade of BLA β-adrenoceptors (McReynolds et al., 2010).

In recent years, our research has focused on understanding the limitations of this BLA-modulated effect. We have examined the influence of BLA β-adrenoceptors on Arc expression in areas beyond the hippocampus, including the medial prefrontal and rostral anterior cingulate cortex. We have also addressed the issue of whether the effect is limited to Arc expression that is associated with emotional arousal. Finally, we have begun to investigate other plasticity-related proteins, such as CaMKIIα. The results indicate that the posttraining activation of the β-adrenoceptors in the BLA increases both Arc and CaMKII α protein expression in the rostral anterior cingulate cortex (Holloway-Erickson et al., 2012). The influence of the BLA on Arc protein expression at the synapse is not limited to aversive training, as we have observed a similar increase in Arc protein expression in hippocampal synapses following an appetitive conditioned cue preference task (unpublished observations). Therefore, it appears that the BLA may contribute to the long-lasting synaptic changes that support memory by modulating plasticity-related proteins, such as Arc and CaMKIIα, at the synapses that are activated by that particular event.

According to our working model, a novel context activates specific synapses in the hippocampus resulting in mRNA transport to those synapses. If this context exposure is coupled with emotional arousal, the noradrenergic activation of the BLA will influence the expression of plasticity-related proteins, such as Arc and CaMKIIα, at the synapse. This may occur through an influence on transport of the mRNA, local translation, or degradation of the protein. Figure 1 illustrates the proposed interaction of the stress hormones and the BLA on synaptic expression of Arc in the hippocampus.

Potential mechanisms for regulation of plasticity-related proteins

The BLA appears to influence Arc expression in the hippocampus in a posttranscriptional manner, although the mechanism of this effect is not known. Arc expression is tightly regulated and there are a multitude of different stages at which synaptic Arc expression in efferent brain regions may be influenced by the BLA. Here, some of the stages of the expression of Arc and other plasticity-related proteins that may be regulated by the BLA are addressed. The mechanisms of regulation of the transcript and the protein product of Arc have been reviewed extensively elsewhere (Korb and Finkbeiner, 2011; Shepherd and Bear, 2011). We will focus on the transport of dendritically localized mRNA to the synapse, the translation of the mRNA, and the degradation of the mRNA and protein.

Transport

Although it appears that the BLA does not influence *Arc* mRNA levels in the hippocampus, the influence of the BLA may result in increased availability of dendritically localized mRNAs at the synapse through an influence on their packaging and transport to the dendrites. The exact machinery involved in this transport has not been fully elucidated. However, many of the individual components involved in the packaging of the dendritically localized mRNAs into messenger ribonucleoprotein complexes (mRNPs) and the transport of those mRNPs out to the dendrites have been investigated. *Arc* and *CaMKIIα* mRNAs have a conserved dendritic targeting sequence called the A2 response element (A2RE). This *cis*-acting sequence is the target of a *trans*-acting RNA-binding protein, hnRNP-A2, which appears to be involved in packaging the mRNA into granules for transport to the dendrites (Gao et al., 2008). The A2RE sequence is sufficient for dendritic targeting, and the deletion of this sequence prevents the dendritic targeting of *Arc*, *CaMKIIα*, neurogranin, and *MAP2 in vitro* (Gao et al., 2008). In addition, there appears to be a competition for space within the mRNP, as the overexpression of one mRNA reduces the amount of the other mRNAs in the mRNP (Gao et al., 2008). Another *trans*-acting factor that seems to target the *cis* -acting A2RE sequence is CBF-A, which facilitates the dendritic transport and the localization of *Arc*, brain-derived neurotrophic factor (*BDNF*), and *CaMKIIα* (Raju et al., 2011). This suggests that there may be multiple components that target the same sequence to facilitate the packaging into mRNPs and the transport out to the dendrites.

Staufen-2 is an RNA-binding protein that is necessary for mRNPs to be trafficked out to the dendrites (Tang et al., 2001; Barbee et al., 2006; Johnson et al., 2006; Kim and Kim, 2006). In addition, Staufen-2 is regulated by extracellular signal-regulated kinase 1/2 (ERK 1/2), a component of the mitogen-activated protein kinase (MAPK) signaling pathway. Staufen-2 has a docking site for ERK 1/2 and the deletion of that site both reduces the amount of Staufen-2-containing mRNPs in the dendrites and completely abolishes the depolarization-induced increase in the amount of Staufen-2-containing mRNPs (Nam et al., 2008). Indeed, both actin polymerization and ERK phos-phorylation are required for *Arc* mRNA to be targeted to activated synaptic sites (Huang et al., 2007). This suggests that ERK phosphorylation may be one potential target of the BLA for the regulation of plasticity-related protein expression at the synapse. In fact, manipulations of the BLA influence the phosphorylated levels of ERK in memory-related brain regions such as the medial prefrontal

cortex (Roozendaal et al., 2009). There are a number of different components in the mRNPs that mediate the transport and localization of the dendritically localized mRNAs and it remains to be seen whether these components can be influenced by the BLA.

Translation

It is well established that both LTP and long-term memory require *de novo* protein synthesis (Davis and Squire, 1984; Kelleher et al., 2004). The translation of proteins is composed generally of three main stages: initiation, elongation, and termination.

The initiation stage of protein translation is a complex process and a likely target for regulation (Klann and Dever, 2004). As discussed previously, BLA stimulation produces a protein synthesis- and NE-dependent effect on hippocampal LTP, converting it from early-phase to late-phase LTP. *Arc* and *CaMKIIα* mRNAs are transported to the stimulated regions of dendrites and can be translated in isolated synapses *in vitro*. Taken together with the evidence that activation of β-adrenoceptors in the BLA enhances memory and produces a posttranscriptional effect on Arc expression, and increases both Arc and CaMKIIα protein in synaptoneurosomes, these findings suggest that an influence on the initiation of local translation is a plausible mechanism for BLA modulation of memory consolidation. In support of this hypothesis, the same posttraining activation of β-adrenoceptors in the BLA that increases the expression of Arc and CaMKIIα does not appear to modulate the expression of the somatic activity-dependent protein c-Fos (McIntyre et al., 2005; Holloway-Erickson et al., 2012).

Here, we discuss two of a number of translation initiation factors that are involved in long-term plasticity and memory. The fragile X mental retardation protein (FMRP)-mediated repression of translation has been identified as a translational repressor for both Arc and CaMKIIα, and it plays a critical role in the metabotropic glutamate-mediated plasticity in the hippocampus (Huber et al., 2002; Zalfa et al., 2003). Another potential target for modulation is the eukaryotic initiation factors eIF2 α and eIF4E. The mechanisms for translational regulation in synaptic plasticity and memory have been reviewed extensively elsewhere (Klann and Dever, 2004; Costa-Mattioli et al., 2009; Richter and Klann, 2009). Finally, the role of the elongation factor, eukaryotic elongation factor 2 (eEF2), in the translation of plasticity-related proteins such as Arc is described.

Initiation—A potential influence on local translation is the removal of a translational repressor. There are a number of different RNA-binding proteins that are studied for their role in translational repression, but here we focus on FMRP. In purified synaptoneurosomes taken from mice lacking the *Fmr1* gene, Arc and CaMKIIα protein expression is elevated and association of the mRNA with polyribosomes is increased, indicating active local translation (Zalfa et al., 2003). FMRP may repress translation by interacting with the noncoding neuronal RNA BC1. The noncoding neuronal RNA BC1 interacts with the initiation factor eIF4A and the poly(A)-binding protein to inhibit the formation of a complex important for translation initiation. Furthermore, BC1 may increase FMRP interaction with CYFIP1/ Sra-1, a recently identified neuronal eIF4E-binding protein (4E-BP), which would also prevent the formation of a complex important for initiation (Zalfa et al., 2003; Napoli et

al., 2008). It remains to be seen whether manipulations of the BLA influence FMRP expression or its association with CaMKIIα, Arc, and other target mRNAs in memory-related efferent brain regions.

The initiation of translation is typically composed of three main stages: the formation of the 43S preinitiation complex, the binding of mRNA to the 43S preinitiation complex, and the formation of the 80S ribosomal complex (Klann and Dever, 2004). There are a number of different initiation factors that are involved in these processes, although two of the most commonly studied in plasticity and learning and memory are the eukaryotic initiation factors eIF2 α and eIF4E. The initiation factor eIF2 is involved in the formation of the 43S preinitiation complex and the phosphorylation at the serine51 site in the α-subunit prevents normal recycling of eIF2 and results in a decrease in general translation (Klann and Dever, 2004). The phosphorylation/dephosphorylation of this initiation factor is important for plasticity and memory. If the serine51 site is mutated and the phosphorylation is reduced, the threshold for eliciting LTP is reduced and the memory is enhanced. Conversely, if dephosphorylation of eIF2α is prevented by a small-molecule inhibitor, which would correspond to a decrease in general translation, LTP can be induced but not maintained and long-term memory is impaired (Costa-Mattioli et al., 2007). It is suggested that the phosphorylation/dephosphorylation of eIF2 α might serve as a bidirectional biochemical switch between short-term and long-term memory (Costa-Mattioli et al., 2007). Therefore, the phosphorylation and dephosphorylation of eIF2 α provide a possible target for a BLA influence on translational regulation in a manner that would influence synaptic plasticity and memory, although this effect may not be specific to the plasticity-related proteins.

A cap-binding complex is required for cap-dependent translation and is thought to promote the binding of the mRNA to the 43S preinitiation complex to form a 48S complex (Klann and Dever, 2004). This cap-binding complex binds to a 7-methyl-GTP cap structure at the 5′ end of the mRNA and contains initiation factors such as eIF4E, eIF4G, and eIF4A, which together form the eIF4F complex (Klann and Dever, 2004). The eukaryotic initiation factor eIF4E is a target for translational regulation. The interaction between eIF4E and eIF4G is important for cap-dependent translation and learning and memory. A small-molecule inhibitor of cap-dependent translation 4EGI-1, which inhibits the interaction between eIF4E and eIF4G, given into the amygdala blocks the consolidation of fear memory (Hoeffer et al., 2011). This suggests that the cap-dependent initiation of translation is necessary for long-term memory formation. In addition, high-frequency stimulation, which induces LTP and Arc protein expression, increases the levels of phosphorylated eIF4E and eIF2α in an ERK-dependent manner (Panja et al., 2009). However, control of translation is also necessary for proper memory formation. The 4E-BPs are translational regulators that compete with eIF4G for binding of eIF4E and, when bound to eIF4E, prevent eIF4F complex formation. The failure of eIF4F complex formation would result in the inhibition of general protein synthesis. Figure 2 illustrates the influence of phosphorylated 4E-BPs on eIF4E formation and translation. When the 4E-BPs are hyper-phosphorylated, they no longer bind to eIF4E and the initiation factor is free to form the cap-binding complex, thus facilitating eIF4F formation (Klann and Dever, 2004). The controlled regulation of translation is necessary for proper memory formation and the 4E-BPs are important for that regulation. Mice that are lacking 4E-BP2, and should therefore have increased protein translation, show normal

acquisition and short-term memory but impaired long-term memory for spatial and conditioned fear associative tasks. These findings suggest that unregulated increases in translation do not provide an advantage for memory consolidation. Rather, the controlled regulation of translation is necessary for long-term memory formation (Banko et al., 2005).

As discussed previously, the packaging and transport of mRNAs to dendrites involve ERK signaling. In addition, ERK signaling plays a role in the initiation of translation. The initiation factor eIF4E is phosphorylated by MAPK-interacting kinase (Mnk), which is a substrate of ERK 1/2 (Klann and Dever, 2004). It is suggested that the phosphorylation of this initiation factor is correlated with enhanced binding of eIF4E to capped mRNA (Minich et al., 1994). The pharmacological inhibition of Mnk1 blocks high-frequency stimulation-induced eIF4F formation and eIF4E phosphorylation (Panja et al., 2009). The pharmacological inhibition of Mnk1 also has a posttranscriptional effect on Arc expression as it blocks Arc translation without affecting Arc transcription (Panja et al., 2009). This is similar to the effect that is seen in the hippocampus following BLA manipulations. Cap-dependent translation can be influenced by neuromodulators as well. The stimuli that would only result in E-LTP, when paired with the bath application of a β-adrenoceptor agonist to hippocampal slices, produce L-LTP as well as the activation of eIF4E and Mnk1 and the inhibition of 4E-BP (Gelinas et al., 2007). These data suggest that the machinery involved in the cap-dependent initiation of translation may be involved in the BLA influence on expression of plasticity-related proteins at the synapse.

Elongation—One target for regulation of the elongation stage of translation is eEF2. Figure 3 illustrates the impact of phosphorylation of this elongation factor on translation. When eEF2 is phosphorylated by eEF2 kinase (eEF2K), the elongation stage of translation is inhibited and protein translation is slowed (Ryazanov et al., 1988). The phosphorylation state of eEF2 is influenced by behavioral testing with dephosphorylation seen in the hippocampus and amygdala following a fear conditioning test (Im et al., 2009). Interestingly, although the phosphorylation of eEF2 slows down general translation, it increases the translation of some dendritically localized mRNAs such as *Arc*, *CaMKIIα*, and *BDNF* (Chotiner et al., 2003; Sutton et al., 2007; Park et al., 2008; Verpelli et al., 2010). The slowing down of general translation could increase the availability of initiation factors for mRNAs that might otherwise be poorly translated. In accordance with this supposition, general protein synthesis is decreased 1 h after high-frequency stimulation, but Arc protein expression and eEF2 phosphorylation are increased (Chotiner et al., 2003). Therefore, the BLA may influence a select group of plasticity-related proteins through an influence on eEF2 phosphorylation.

Degradation—Another way that expression of plasticity-related proteins may be increased at the synapse is through regulation of mRNA and protein degradation. After the stop codon, *Arc* and *CaMKIIα* have exon-exon junction complexes that allow the mRNA to undergo nonsense-mediated decay (NMD) after a single round of translation. These mRNAs are upregulated when a component of the exon-junction complex, eIF4AIII, or a component of the NMD machinery, Upf1, is blocked by RNA interference (Giorgi et al., 2007). Therefore, if the interaction of the mRNA with the exon-junction complex is impeded, or if the NMD

machinery is interfered with, *Arc* mRNA would likely remain available for additional rounds of translation. This would be one way in which the processes within the BLA may influence the expression of Arc at a posttranscriptional level, although it is not known at this time if training on learning and memory tasks or manipulations of the BLA can influence components of the NMD process.

Protein degradation is just as critical to synaptic plasticity as protein synthesis. There is a balance between synthesis and degradation, as the blockade of either synthesis or degradation results in impaired L-LTP but not if both synthesis and degradation are blocked (Fonseca et al., 2006). There is evidence for local degradation of proteins as components of the ubiquitin-proteasome system, such as ubiquitin and proteasome subunits and associated enzymes, are found at synapses and at the postsynaptic density (Bingol and Schuman, 2005). Furthermore, synaptic stimulation results in an N-methyl-D-aspartate receptor-dependent redistribution of proteasomes from dendritic shafts into synaptic spines (Bingol and Schuman, 2005). Recently, the E3 ligase for Arc was identified. Ube3a is an ubiquitination ligase whose loss is implicated in Angel-man syndrome and whose expression is activity dependent (Greer et al., 2010). Arc contains a Ube3a-binding domain and undergoes activity-dependent ubiquitination by Ube3A. Mice lacking Ube3A show greater Arc protein expression in response to kainic acid or an enriched environment, and this effect was greatest for synaptic Arc protein expression levels. Because some of the changes were only seen with 6 h of treatment, it has been suggested that Ube3A serves a role of returning Arc to baseline levels following activity and, consequently, controlling AMPA receptor endocytosis (Greer et al., 2010; Korb and Finkbeiner, 2011). Whether learning and memory events change the levels of Ube3A or its association with Arc remains an intriguing area of study.

Concluding remarks

Although the role of the BLA in the modulation of emotional memory consolidation and the regulation of local expression of plasticity-related proteins such as Arc have been extensively studied separately, little is known about the exact mechanisms of the BLA influence on synaptic plasticity and the expression of plasticity-related proteins in efferent brain regions. The activation of the BLA does not appear to simply produce a general increase in neuronal activity in these efferent brain regions as β-adrenoceptor activation increases the expression of plasticity-related proteins, Arc and CaMKIIα, but not a common neuronal activity marker, c-Fos, in the anterior cingulate cortex (Holloway-Erickson et al., 2012). These findings suggest that the BLA preferentially influences the dendritically localized, synaptic plasticity-related proteins. An influence of the BLA on plasticity-related protein expression has been observed in efferent brain regions such as the hippocampus, the prefrontal cortex, and the rostral anterior cingulate cortex. How the BLA is able to exert its effects remains to be determined. One possibility is that a coincidence of the stimuli-induced ‘ synaptic tag ’ together with the modulatory effect produced by an emotional event and mediated by the BLA is required for the increase in plasticity-related protein expression at the synapse for the conversion of short-term plasticity and memory into long-term plasticity and memory. These two separate events must converge somewhere inside the cell through intracellular signaling pathways to elicit increases in specific sets of proteins. Future

research aimed at determining where this convergence occurs may elucidate the mechanisms underlying the rapid and long-lasting storage of emotionally arousing memories.

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Biographies

Jayme R. McReynolds completed her Bachelor of Science degree at the University of California, Irvine, where she examined stress effects on learning and memory in the laboratory of Dr. James L. McGaugh. She went on to complete her PhD in cognition and neuroscience at the University of Texas at Dallas under the guidance of Dr. Christa McIntyre. Her graduate research was focused on the role of the basolateral complex of the amygdala in modulating emotionally arousing memory and expression of plasticity-related proteins in efferent brain regions. She is now a postdoctoral fellow in Dr. John Mantsch's laboratory at Marquette University studying the influence of stress on addictive behavior.

Christa K. McIntyre is an Assistant Professor of Cognition and Neuroscience in the School of Behavioral and Brain Sciences at the University of Texas at Dallas. She earned her PhD at the University of Virginia under the mentorship of Dr. Paul Gold and did her postdoctoral work with Dr. James L. McGaugh at the University of California, Irvine. Her research examines the neurobiology of memory consolidation, with a focus on the influence of

emotional arousal on memory and synaptic plasticity. Together with her graduate students, Christa McIntyre studies the effects of the autonomic nervous system on interacting brain systems with the aim of understanding how events of a single emotionally arousing experience are stored as long-term memories, whereas memories of nonarousing events are lost forever.

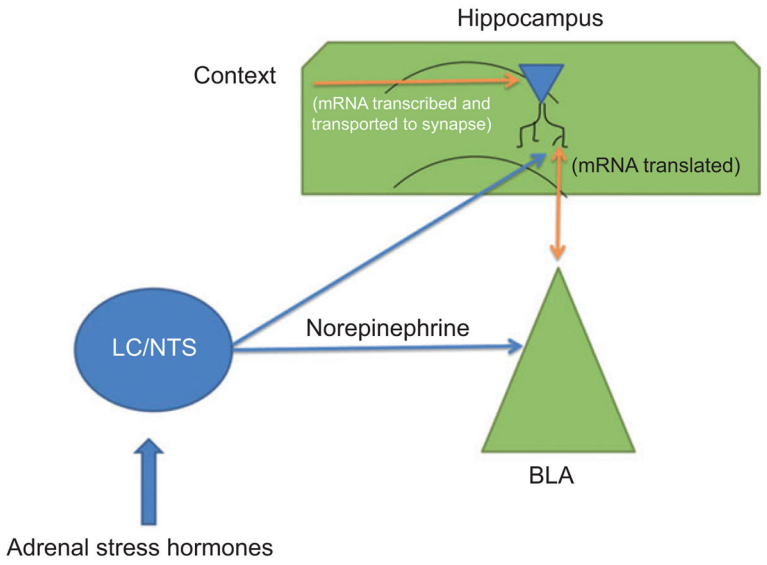

Figure 1.

A novel context produces the transcription of *Arc* mRNA and the transport to stimulated synapses in the hippocampus. Stress enhances memory through noradrenergic actions on the BLA, which, in turn, influences the translation of the transcript that is already present in the appropriate synapses. Arrows indicate the connections between brain regions, but they are not necessarily monosynaptic.

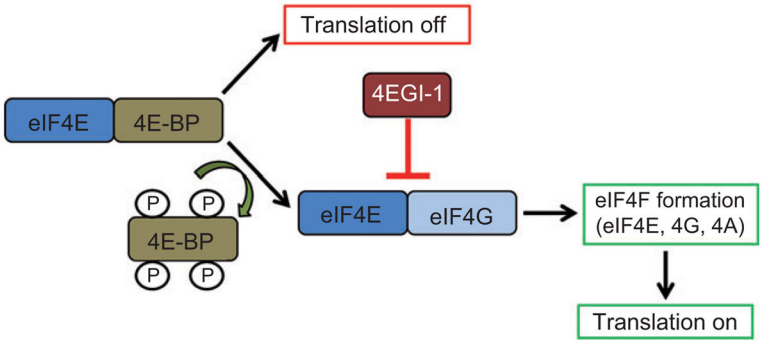

Figure 2. Translational machinery

When the 4E-BPs are hyperphosphorylated, they no longer bind to eIF4E, leaving the initiation factor to form the eIF4F complex and promote cap-dependent initiation of translation. 4EGI-1 is a small molecule that inhibits cap-dependent translation by interfering with the interaction between eIF4E and eIF4G.

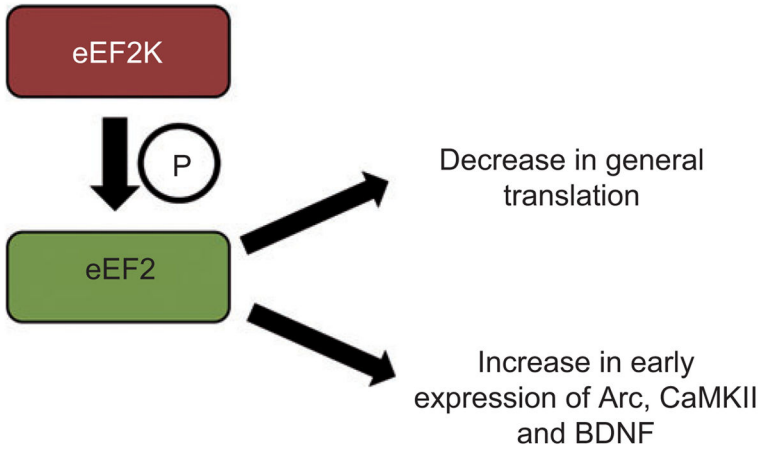

Figure 3. Elongation

When the eukaryotic elongation factor, eEF2, is phosphorylated by the eEF2K, the elongation stage of translation is slowed and general protein synthesis is decreased. Although the general protein synthesis is decreased, the early expression of Arc, CaMKIIα, and BDNF is increased.