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Invited review

Molecular mechanisms controlling protein synthesis in memory reconsolidation

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ABSTRACT

It is currently well established that the synthesis of new proteins (mRNA translation) is required for long-lasting synaptic plasticity and memory formation. Translation in the brain is regulated primarily at the initiation stage by general as well as by gene-specific mechanisms. Stored memories can become sensitive to interference upon reactivation, through a process termed reconsolidation, which depends on protein synthesis. Here, I examine the role of translation control mechanisms, focusing particularly on the mechanistic target of rapamycin complex 1 (mTORC1), in reconsolidation.

1. Introduction

The need for protein synthesis, also called mRNA translation, for the formation of enduring memories has been supported by evidence for over 50 years (Davis & Squire, 1984). Increases in de novo protein synthesis result from changes in gene expression triggered by learning-induced activation of neuronal receptors, intracellular signaling pathways, and epigenetic mechanisms (Alberini, 2009; Kandel, Dudai, & Mayford, 2014; McGaugh, 2000). Translation inhibitors are effective in impairing synaptic plasticity and long-term memory, particularly if given around the time of training or at a second time window 3–4 h after training, suggesting a biphasic pattern of requirement (Bourtchouladze et al., 1998; Grecksch & Matthies, 1980; Quevedo et al., 1999). The large body of evidence showing the need for protein synthesis in long-term memory has been subjected to reexamination, given that widely used translation inhibitors such as anisomycin have been shown to display non-specific effects, including alterations in neurotransmitter release (Canal, Chang, & Gold, 2007; Gold, 2008). However, the use of different inhibitors, the temporal specificity of their effects, and complementary approaches including genetic manipulations, provide compelling evidence supporting the interpretation of findings as impairments caused by protein synthesis inhibition (Alberini, 2008; Hernandez & Abel, 2008). More recently, attention has been given to mechanisms that regulate protein synthesis, including local translation in dendrites, during memory formation (Buffington, Huang, & Costa-Mattioli, 2014; Costa-Mattioli, Sossin, Klann, & Sonenberg, 2009; Kelleher, Govindarajan, & Tonegawa, 2004; Santini, Huynh, & Klann, 2014).

Through the process known as consolidation, newly learned memories can, within a limited time window, initially be disrupted or enhanced by different types of manipulations, and then become increasingly stable and resistant to interference to be stored as stable and lasting traces (McGaugh, 2000; Roesler & McGaugh, 2010). This traditional view of memory formation has been reexamined after the emergence of findings suggesting that, when a memory is reactivated by retrieval, it can again become labile and require a new protein synthesis-dependent stabilization phase (Nader, Schafe, & Le Doux, 2000). The nature and functions of the reconsolidation process are somewhat controversial and have been extensively debated elsewhere (Alberini, 2011; Alberini & Ledoux, 2013; Besnard, Caboche, & Laroche, 2012; Fernández, Boccia, & Pedreira, 2016; McGaugh, 2004; McKenzie & Eichenbaum, 2011; Nader & Hardt, 2009; Rodriguez-Ortiz & Bermúdez-Rattoni, 2007; Sara, 2000). I share the view that the phenomenon known as reconsolidation may be considered part of a long-lasting, dynamic consolidation process during which memories can be weakened, strengthened, or updated (Alberini, 2011; Alberini, Johnson, & Ye,

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2013; Amaral, Osan, Roesler, & Tort, 2008; Dudai & Eisenberg, 2004; Lee, 2013; Roesler & McGaugh, 2010). In this article, I will use an operational definition, considering experiments investigating reconsolidation those where memory retention of a behavioral task was modified by interventions given around the time of a reactivation session, provided that the findings were not interpreted as changes in memory extinction. Under this criterion, here I review studies describing the role of general mechanisms controlling protein synthesis in reconsolidation.

2. Translational control in memory formation

Protein synthesis from mRNA translation in eukaryotes can be divided into initiation, elongation, and termination phases, each being regulated by eukaryotic initiation factors (eIFs), elongation factors (EFs), and release factors, through the formation of regulatory complexes with several other proteins (Jackson, Hellen, & Pestova, 2010). Initiation factors control ribosomal recruitment to mRNA 5′ cap, which is recognized by the initiation factor eIF4E, which in turn associates with eIF4G. This interaction is inhibited by eIF4E binding to the eukaryotic initiation factor 4E binding protein 1/2 (4E-BP1/2). Phosphorylation of 4E-BP releases eIF4E, enabling ribosomal recruitment. Several of these molecular components have been shown to play a role in neuronal protein synthesis regulation, synaptic plasticity, and memory consolidation (Buffington et al., 2014; Costa-Mattioli et al., 2009; Gal-Ben-Ari et al., 2012; Kelleher et al., 2004; Santini et al., 2014) (Fig. 1). In addition to these general mechanisms, which apply to many or all RNAs and are the focus of this review, gene-specific mechanisms target a subset of mRNAs. Gene-specific control involve *cis*-acting sequences in mRNA, for instance cytoplasmic polyadenylation elements (CPEs) located in the end of distal UTRs of mRNAs, which are recognized by the binding protein CPEB. When CPEB is phosphorylated, it leads to dissociation of the translational repressor Marskin, polyadenylation, and recruitment of the initiation factor eIF4G, stimulating mRNA translation. These mechanisms play a role in controlling local protein synthesis in dendrites involved in synaptic plasticity (Kelleher et al., 2004; Macdonald, 2001; Mayford, Baranes, Podsypanina, & Kandel, 1996). Emerging mechanisms of protein synthesis regulation in neurons also include non-coding RNAs, particularly of the microRNA class. In addition to acting on the chromatin at the epigenetic level, microRNAs control protein synthesis through binding to complementary sequences in target mRNAs, leading to reversible translational repression of mRNA degradation. Accumulating evidence implicates translational regulation by microRNAs in synaptic plasticity and memory formation (Bicker, Lackinger, Weiß, & Schratt, 2014; Griggs, Young, Rumbaugh, & Miller, 2013; Gao et al., 2010; Konopka et al., 2010; Saab & Mansuy, 2014; Thomas, Pascual, Maschi, Luchelli, & Boccaccio, 2014).

2.1. Mechanistic target of rapamycin (mTOR)

The target of rapamycin (TOR) is an evolutionary conserved eukaryotic serine/threonine kinase of the PI3K-related family (PIKK), found in combinations with other proteins as the catalytic subunit of two functionally distinct complexes, TOR complex I (TORC1) and TOR complex 2 (TORC2). The mammalian TOR, currently named mechanistic TOR (mTOR) is a protein with a predicted molecular weight of 280 kD) encoded by the *MTOR* gene. mTOR is a signaling node that integrates inputs from a variety of signals, including activation of neurotransmitter and growth factor

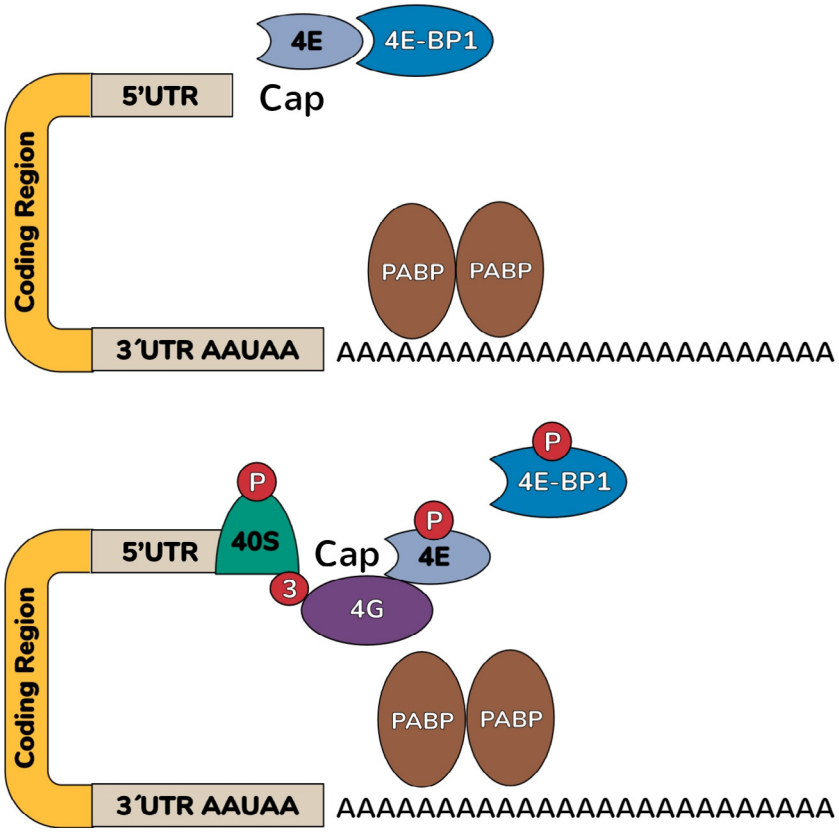

Fig. 1. Selected general mechanisms regulating protein synthesis. The initiation factor eIF4E recognizes mRNA 5′ cap, leading to recruitment of the 40S ribosomal subunit by associating with eIF4G. The interactions of eIF4E with cap and eIF4G are inhibited by 4E-BP1 and promoted by the poly(A)-binding protein (PABP). The ability of 4E-BP1 to sequester eIF4E is regulated by mTOR (Kelleher et al., 2004).

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