



Macromolecular synthesis, distributed synaptic plasticity, and fear conditioning

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Abstract

Recent work from a number of laboratories has provided new and important insights about how gene expression is altered by experience and how these molecular changes may provide a substrate for the long-term storage of new memories. Here, we review a series of recent studies using aversive Pavlovian conditioning in rats as a well characterized model system in which experience-dependent alterations in gene expression can be manipulated and quantified within a specific neural circuit. We highlight some of the issues involved in using broad-spectrum inhibitors of mRNA and protein synthesis to study cellular changes underlying the formation and long-term stability of memory and discuss the idea that these changes occur over widespread, behaviorally-defined, networks of cells. We also discuss the idea that the maintenance of memory and its susceptibility to disruption after retrieval may relate to local protein synthesis in dendrites. Finally, a series of recent experiments from our laboratory studying the role of a specific signaling pathway (mTOR) which regulates translational processes and memory formation in the amygdala and hippocampus during fear conditioning are reviewed.

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1. Introduction

Over the last 60 years or so the general idea that the cell biological substrate for long term memory storage critically involves the synthesis of new mRNA and protein has enjoyed increasingly widespread support. While the initial evidence for this position was often drawn from studies using large systemic doses of broad-spectrum inhibitors and a variety of species and behavioral paradigms, more recent experimental work has been able to go a bit deeper into describing the relationships between macromolecular synthesis and the consolidation of long-term memory.

Pavlovian fear conditioning (FC) in rodents has emerged as one of the more productive approaches to understanding the neurobiology of learning and memory. This robust form of learning is rapidly acquired, straightforward to measure, and relies on a fairly well-described

neural circuit that includes cortical and subcortical elements. Similar training procedures can be used in laboratory animals and human volunteers and current data suggest a large degree of similarity in neural mechanisms across species. A number of excellent recent reviews are available providing more detailed treatment of various aspects of the anatomy, physiology, and molecular biology of FC than space here permits (e.g., Blair, Schafe, Bauer, Rodrigues, & LeDoux, 2001; Davis, 2000; Fanselow & Poulos, 2005; Goosens & Maren, 2002; Kim & Jung, 2006; Maren, 2001; Pare, Quirk, & Ledoux, 2004; Stork & Pape, 2002).

It is generally accepted that the amygdala plays a critical role in the formation of memory for aversive events although important details regarding the nature of its involvement are still a matter of some debate (McGaugh, 2004). Pioneering studies by LeDoux and colleagues showed that cells in the basolateral subdivision (BLA), including the lateral and basolateral amygdaloid nuclei (c.f., de Olmos, Alheid, & Beltramino, 1985), are necessary

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for normal learning in FC. BLA cells receive inputs capable of representing both auditory and contextual signals for shock (conditional stimuli, CS) as well as diencephalic projections that may help encode the shock unconditional stimulus (UCS). Electrophysiological studies have shown that unit responses in BLA are consistent with processing relevant presynaptic inputs and appropriate stimulation regimens result in long-term potentiation (LTP) at BLA synapses both *in vitro* and *in vivo*. Because of the large amount of systematic work being done on this region of the amygdala, a clear and detailed picture of the molecular and cellular events underlying FC-related synaptic plasticity in this structure is emerging (Blair et al., 2001; Goosens & Maren, 2002; Maren & Quirk, 2004).

While the BLA is thought by many to be a site of critical synaptic plasticity in FC, the expression of fear-related conditional responses (CR) during subsequent behavioral performance based on this learning is thought to depend on intrinsic amygdaloid connections from BLA to the central nucleus (CeA) and from there to a widespread series of target structures more specifically involved in the generation of particular behavioral and physiological elements of the fear response. Expression of FC involves multiple simultaneous outputs and systems-level analyses have identified various unique contributions to components of this response. Early work showed that specific lesions of the CeA or destruction of major output pathways from the CeA to the brainstem results in general suppression of multiple CRs (Helmstetter, 1992a, 1992b; Hitchcock & Davis, 1991). Autonomic CRs appear to require CeA projections to the lateral hypothalamus (LH) but not projections to the periaqueductal gray or rostral medulla (e.g., Helmstetter & Tershner, 1994; LeDoux, Iwata, Cicchetti, & Reis, 1988). Freezing behavior, on the other hand, is disrupted by manipulation of the PAG (e.g., Amorapanth, Nader, & LeDoux, 1999; Kim, Rison, & Fanselow, 1993) while changes in pain sensitivity in response to a CS for shock rely on a polysynaptic pathway from the CeA to subpopulations of cells in PAG and medulla (e.g. Bellgowan & Helmstetter, 1998; Helmstetter, Tershner, Poore, & Bellgowan, 1998).

BLA neurons receive multiple sensory inputs from cortical and subcortical sites. LeDoux's early work was the first to show that direct input to the LA from the medial portion of the medial geniculate nucleus (MGm) was sufficient to support auditory FC. Subsequent studies have confirmed the importance of MGm and its projections to the amygdala. Conditioning to a contextual CS, on the other hand, appears to rely on a specific role of the hippocampus in processing contextual stimuli (Anagnostaras, Gale, & Fanselow, 2001; Rudy & O'Reilly, 1999, 2001). Certain manipulations targeting the hippocampus show a time-limited and selective effect on learning about context without disrupting acquisition of tone-evoked CRs. While a role for the hippocampus in context processing seems clear at this point, the specific contribution of this structure to FC acquisition and the extent to which auditory CRs are

really independent of the structure still needs to be worked out completely. Recent work by Rudy and others strongly supports the idea that hippocampal contributions to context FC reflect a more general role of this structure in forming mnemonic representations of complex multi-modal stimuli. In auditory FC when tones and shocks are presented in a distinctive context, potentially important learning-related changes in physiology simultaneously take place in hippocampal, neocortical, and thalamic inputs to the amygdala (see below).

2. Gene expression and fear conditioning

As the technology to quantify and anatomically localize alterations in gene expression in brain tissue became available it was applied to the study of memory formation generally, and to the neurobiology of FC specifically. Early work in this area focused largely on the expression of immediate early genes (IEGs) as potential markers for cellular activity and plasticity. Campeau and colleagues (1991) were the first to show that exposure to the training procedures used in FC was sufficient to produce an elevation in mRNA in the amygdala, in this case for *c-fos*. This basic training effect was later confirmed at the protein level and quantitative assays of FOS protein have been shown to correlate with behavioral performance (e.g., Radulovic, Kammermeier, & Spiess, 1998). Importantly, synthesis of new protein can also be driven by the recall/retrieval/behavioral expression of FC as well as during the consolidation of new learning (Hall, Thomas, & Everitt, 2001). Early studies also identified a specific role for *zif268/egr-1* in the lateral amygdala in the formation of new memory (Malkani & Rosen, 2000; Rosen, Fanselow, Young, Sitzeske, & Maren, 1998). More recent work using DNA microarrays or related approaches with multiple probes assessed in parallel has shown, not surprisingly, that a rather large number of genes are likely to alter their expression following fear conditioning in the amygdala and hippocampus alone (e.g., Levenson et al., 2004; Ressler, Paschall, Zhou, & Davis, 2002; Stork, Stork, Pape, & Obata, 2001). Within this group one can find multiple functional classes including a variety of glutamate receptor subunits, IEGs, transcription factors and growth regulators as well as structural proteins.

The presence of new transcripts or proteins in a particular brain region (or at particular location within neurons) during the period after training, even if these molecules are only present in the cells of animals that learn compared to appropriate behavioral controls, obviously does not indicate the degree to which this change in gene expression is actually necessary for new memory to be formed. Similarly, evidence for training-related activity in various protein kinases and transcription factors thought to be contributing to synaptic modification does not mean that they are actually needed or specifically involved in memory formation *per se*. Direct manipulation of these gene products restricted to specific aspects of the training experience or

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