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BUILDING UP AND KNOCKING DOWN: AN EMERGING ROLE FOR EPIGENETICS AND PROTEASOMAL DEGRADATION IN SYSTEMS CONSOLIDATION

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Abstract—Memory formation is a protracted process in which recently acquired events are consolidated to produce stable and specific associations. Initially, newly acquired information undergoes cellular consolidation in the hippocampus, which transiently supports the storage of recently acquired memories. In contrast, remote, or ''old'' memories are maintained in the cortex and show almost complete independence from the hippocampus. Memories are transferred from the hippocampus to the cortex through a process termed systems consolidation. Emerging evidence suggests that recurrent activation, or ''training'' of the cortex by the hippocampus is vital to systems consolidation. This process involves prolonged waves of memory-related gene activity in the hippocampus and cortex long after the learning event has terminated. Indeed, molecular events occurring within hours and days of fear conditioning are essential for stabilizing and eventually transitioning the memory to the cortex. It is increasingly evident that molecular mechanisms that exhibit a capacity for prolonged activation may underlie systems consolidation. Processes that have the capacity to control protein abundance over long time scales, such as epigenetic modifications, are prime candidates for the molecular mechanism of systems consolidation. Indeed, recent work has established two types of epigenetic modifications as integral for systems consolidation. First, localized nucleosomal histone variant exchange and histone modifications are integral for early stages of systems consolidation, whereas DNA methylation appears to be utilized to form stable marks that support memory maintenance. Since systems consolidation also requires discrete and time-sensitive changes in protein abundance, additional mechanisms, such as protein degradation, need also be considered, although their role in systems consolidation has yet to be investigated. Here, we discuss the role of molecular mechanisms in systems consolidation and their implications for understanding how memories persist over time.

Key words: epigenetics, recent memory, remote memory, systems consolidation, ubiquitin proteasome system, memory maintenance.

Contents

INTRODUCTION

Memory formation is a complex process that requires several rounds of molecular and cellular modifications within neurons that form the memory trace (Zovkic and Sweatt, 2013). These modifications occur at multiple and interacting levels that shift neurons from a pre-learning state, characterized by high levels of memory suppressor genes (Abel et al., 1998) to a consolidation state, characterized by high levels of memory-promoting genes (Zovkic and Sweatt, 2013). Such shifts require coordinated activity of machinery involved in both protein degradation and gene transcription, and indeed, interference with either of these processes is detrimental to memory

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Abbreviations: ACC, anterior cingulate cortex; IEGs, immediate early genes; LTP, long-term potentiation; MBNs, mushroom body neurons; OFC, orbitofrontal cortex; PFC, prefrontal cortex; TET, ten-eleven-translocation; TSS, transcription start site; UPS, ubiquitin proteasome system; VTA, ventral tegmental area.

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(Frick, 2013; Zovkic et al., 2013; Jarome and Helmstetter, 2014). However, these processes tend to be studied independently and very little is known about the ways in which they interact. Moreover, the relative function and contribution of each level of regulation may change over the protracted time course of memory formation, which is characterized by modifications occurring in different brain regions at different points in time (Frankland and Bontempi, 2005; Miller et al., 2010; Lesburgueres et al., 2011; Zovkic et al., 2014). Here, we review the literature pertaining to the molecular mechanisms of systems consolidation, focusing particularly on epigenetic modifications that regulate the induction of gene activity and in protein degradation that is involved in resetting cellular states. Additionally we speculate how these mechanisms may be generalized to inter-regional communication, specifically systems consolidation.

Human case studies initially identified the hippocampus as a critical site for memory acquisition (Milner, 2005), but evidence for sparing of older, remote memories in patients with hippocampal lesions suggested that the hippocampus may have a time-limited role in memory (e.g., Rosenbaum et al., 2000; Squire and Bayley, 2007; Huijgen and Samson, 2015). Indeed, a growing number of studies in animal models indicate that many forms of memory are transiently dependent on the hippocampus and are subsequently transferred to the cortex for long-term storage and maintenance (Frankland and Bontempi, 2005; Preston and Eichenbaum, 2013). This process is referred to as systems consolidation to reflect the temporally graded and multi-regional characteristics of memory consolidation (Frankland and Bontempi, 2005; Preston and Eichenbaum, 2013). Recent studies have tremendously expanded our understanding of the molecular basis of hippocampal memory consolidation, but very little is known about the molecular mechanisms involved in network reorganization and long-term memory storage. This review will focus primarily on newly emerging studies of the molecular basis of systems consolidation and the open questions needed to understand the prolonged, multi-regional process of memory stabilization and storage.

Evidence for systems consolidation in animal models

Various lines of evidence demonstrate that memories undergo systems consolidation in rodents, including behavioral outcomes of localized lesions, time- and region-dependent changes in molecular markers, and morphological changes time-locked to different stages of memory formation. Some of the best characterized data come from lesion studies in the hippocampus and the cortex (reviewed in Frankland and Bontempi, 2005). In general, transient inactivation or permanent lesions of the hippocampus shortly after training (immediately or after 24 h) impair both recent (24 h–2 days) and remote ($\geqslant$7 days after training) memory, whereas hippocampal lesions at later time points have no impact on remote memory (e.g., Kim and Fanselow, 1992; Maviel et al., 2004), suggesting that remote memories do not require the hippocampus for recall once they are established. In contrast, inactivation of the prefrontal cortex (PFC) or the anterior cingulate cortex (ACC) shortly before testing selectively impair remote memory without impacting recent memory (Frankland et al., 2004; Maviel et al., 2004), supporting the hypothesis that memory is initially dependent on the hippocampus and is subsequently downloaded to the cortex for maintenance.

Molecular evidence. Consistent with evidence from lesion studies, molecular and imaging experiments have found shifts in activity from the hippocampus to the cortex during the recall of recent and remote memory, respectively, providing naturalistic support for data from lesion studies. For example, functional imaging studies in mice showed that the hippocampus is highly active when recalling recent radial arm maze memory, whereas high levels of ACC activity come online during remote (25 days) memory recall (Bontempi et al., 1999). Using a molecular approach, Maviel et al. (2004) showed that the recall of recent memory for a baited arm in a five-arm maze increased the expression of immediate early genes (IEGs) *Egr1* and *cFos* in the hippocampus and not in the cortex, whereas the recall of remote memory selectively activated these IEGs in the prefrontal, ACC, and retrosplenial cortices. Similar results were obtained for water maze training and contextual fear conditioning, wherein *Egr1* and *cFos* expression increased in the ACC, infralimbic, prelimbic and temporal cortices after remote (36 days), but not recent (1 day) memory recall (Frankland et al., 2004; Teixeira et al., 2006). Interestingly, memory recall at remote time points has been associated with reduced IEG expression in the hippocampus compared to the recent time point, suggesting that memory reorganization may involve active inhibition of the hippocampus during remote memory recall (Maviel et al., 2004).

There is some evidence to suggest that increased IEG expression in the cortex at remote time points is blocked in α-CaMKII$^{+/-}$ mutant mice, which have a specific deficit in remote memory (Frankland et al., 2001). Indeed, α-CaMKII$^{+/-}$ mice exhibit a dissociation between recent and remote memory, wherein memory for conditioned fear and the water maze is normal at recent and impaired at remote time points (Frankland et al., 2001). These mice have normal long-term potentiation (LTP) in the CA1 subregion of the hippocampus and impaired LTP in the cortex (visual and temporal) (Frankland et al., 2001), providing further support for the preferential role for the cortex in remote memory.

Morphological evidence. Consistent with the time course of molecular changes in the hippocampus and the cortex, spine density in the hippocampus increases rapidly and transiently after learning, whereas increased spine density in the ACC emerges more slowly (within 8 days of training) and persists for at least 48 days (Restivo et al., 2009; Vetere et al., 2011). Inhibiting the early growth of spines in the ACC impairs training-induced increase in spine density and memory recall 48 days after training (Vetere et al., 2011), indicating that changes in spine density support the maintenance of remote memory. Interestingly, MEF2, a negative regulator