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The role of protein synthesis in memory consolidation: Progress amid decades of debate

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Abstract

A major component of consolidation theory holds that protein synthesis is required to produce the synaptic modification needed for long-term memory storage. Protein synthesis inhibitors have played a pivotal role in the development of this theory. However, these commonly used drugs have unintended effects that have prompted some to reevaluate the role of protein synthesis in memory consolidation. Here we review the role of protein synthesis in memory formation as proposed by consolidation theory calling special attention to the controversy involving the non-specific effects of a group of protein synthesis inhibitors commonly used to study memory formation *in vivo*. We argue that molecular and genetic approaches that were subsequently applied to the problem of memory formation confirm the results of less selective pharmacological studies. Thus, to a certain extent, the debate over the role of protein synthesis in memory based on interpretational difficulties inherent to the use of protein synthesis inhibitors may be somewhat moot. We conclude by presenting avenues of research we believe will best provide answers to both long-standing and more recent questions facing field of learning and memory.

Keywords: Protein synthesis; RNA synthesis; Consolidation; Memory; Amnesia; Reconsolidation; Protein synthesis inhibitor; Sleep; Gene expression; Transcription; Translation; Knockout; Synaptic; Systems; Side effects; Rescue; Hippocampus; Learning; LTP; cAMP; CREB; NMDA; Tagging; Post-translational modification

1. Introduction

> *I sometimes feel, in reviewing the evidence on the localization of the memory trace, that the necessary conclusion is that learning is just not possible* (Lashley, 1950).

One of the most puzzling questions facing psychologists and neurobiologists alike is one that was posed centuries ago: what is the nature of memory? How does wakeful experience alter neural circuits within the brain in such a precise and meaningful way that even decades later we are able to invoke a remarkably detailed percept of our own history? Indeed, the formation of cognitive associations between external stimuli or between our actions and their consequences can be demonstrated with relative ease. However, it is considerably more difficult to causally connect cellular and molecular events to the instantiation of such associations. Nevertheless, we are now equipped with sophisticated molecular and genetic techniques that afford us the opportunity to probe deeper than ever before into the molecular underpinnings of memory.

In the first section of this review, we examine the emergence of consolidation theory—the idea that memories are stabilized over time—recalling several important findings that were seminal to its development and continuing evolution. We then examine the basis of the long-standing debate regarding the validity of a major tenet of consolidation theory: that new proteins must be synthesized to stabilize newly acquired memories. Indeed, this debate, although ignored by many, has never been resolved to the satisfaction of some. We then briefly summarize the

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remarkable progress that has been made in understanding consolidation in spite of this debate and present promising new approaches being developed to address some old questions as well as questions that have arisen along the way. Lastly, we conclude by addressing a few alternatives or addendums to consolidation theory that merit consideration.

2. The emergence of consolidation theory: The role of studies using protein synthesis inhibitors

Early empirical forays investigating memory function began in 1878 when Hermann Ebbinghaus introduced the concept of "retroactive interference". Using sequentially memorized lists of nonsense syllables, Ebbinghaus showed that "forgetting" could be attributed to the interfering effects of subsequently learned matter (Ebbinghaus, 1885), thereby establishing the existence of temporal constraints on memory formation and storage. In 1900, using improved methodology and controls, Müller and Pilzecker confirmed that memory for verbal material was susceptible to disruption if new material was introduced too soon after the initial acquisition period. Thus, they proposed that new memories required a period of "consolidation" to fixate or become resistant to disruption (Lechner, Squire, & Byrne, 1999; Müller & Pilzecker, 1900).

Support for Müller and Pilzecker's consolidation theory came a half-century later when it was observed that memory in rats could be retroactively disrupted by applying an electroconvulsive shock near the time of training (Duncan, 1949) or through head injuries involving the hippocampus and related structures (Russell & Nathan, 1946). In both forms of retrograde amnesia, memory loss varies inversely with the age of the memory where new memories are more susceptible to disruption. The amnesia described by Russell and Nathan, which can extend for years prior to the actual neural insult, led to the hypothesis that memories are formed and stored in the hippocampus temporarily but are then transferred to distal cortical sites for permanent storage. This relatively slow process is now referred to as *systems consolidation* (McGaugh, 2000; Squire & Bayley, 2007). This is in contrast to the relatively faster processes of stabilization revealed by verbal interference, electroconvulsive shock, and pharmacological experiments (described below) thought to occur on a cellular or synaptic or level (McGaugh, 1966). Parenthetically, the precise time course during which synaptic consolidation occurs is unclear but has been reported to range anywhere from 500 ms to hours depending on the type of memory being examined, the training procedures, and the amnestic agent used to probe memory (Miller & Matzel, 2006).

This review focuses primarily on the role of protein synthesis during synaptic consolidation largely because the vast majority of cellular and molecular research has targeted the more accessible processes occurring immediately after novel learning situations. However, the existence of systems consolidation must also dictate to an equal extent how we envision and study memory storage over extended periods of time (Frankland & Bontempi, 2005).

Another major step in the evolution of consolidation theory that changed the way the field would conceptualize the consolidation of memory on a cellular level also occurred in 1949 when Hebb introduced his "dual-trace hypothesis" of memory formation. Hebb proposed that reverberation of activity within assemblies of neurons was the essence or trace of short-term memory and that if maintained long enough some growth processes at the level of the synapse could lead to long-term memory (Hebb, 1949). Indeed, disruptions in neuronal reverberation was seen as an attractive explanation of the mechanism by which retrograde amnesia might occur (Glickman, 1961; McGaugh, 1999; Misanin, Miller, & Lewis, 1968; Schneider & Sherman, 1968).

Further support for consolidation theory was offered in the late 1950s, after Scoville and Milner described the memory deficits experienced by the famous patient H.M. After bilateral resection of the medial structures of the temporal lobe to treat epilepsy, it was evident that H.M. had severe short-term memory deficits, unable to form new hippocampus-dependent long-term memories (Scoville & Milner, 1957). Importantly, when tested in delayed matching and delayed comparison tasks, H.M.'s performance worsened as the delays increased leading Milner to conclude, in support of Hebb's view of consolidation, that a distinction exists between the initial processing of memory that decays rapidly and a later, secondary process that is responsible for long-term storage of information (Milner, 1972).

Yet, while great progress was being made in understanding memory from observations from both human and animal studies, direct evidence of the mechanisms by which experience produced long-lasting neural changes was still lacking. This would all change when, in considering how memory traces might be instantiated within neural circuitry on a molecular level Monné, as well as Katz and Halstead, hypothesized that protein molecules were somehow required (Katz & Kalstead, 1950; Monné, 1948; Sutton & Schuman, 2006). At last, after a decade or so of speculation, Flexner and colleagues demonstrated memory for a discriminative avoidance task (performed in a Y-maze) could be disrupted in mice using the protein synthesis inhibitor puromycin (Flexner, Flexner, Stellar, De La Haba, & Roberts, 1962; Flexner, Flexner, & Stellar, 1963). Additionally, some cortical specificity in memory formation was evident in that only bilateral temporal injections affecting the hippocampus and adjacent temporal cortex consistently disrupted memory for recently acquired memories. Consistent with the notion of systems consolidation, temporal infusions in combination with infusions more rostral and caudal were required to disrupt more remote memories (e.g.,11–43 days old), indicating the establishment of a more distributed trace over time (Flexner et al., 1963). A flurry of reports investigating the role