An accumulating body of evidence shows that reactivated long-term memory undergoes a dynamic process called reconsolidation, in which de novo protein synthesis is required to maintain the memory. These findings open up a new dimension in the field of memory research. However, few studies have shown how once-consolidated memory becomes labile. The authors’ recent findings have demonstrated that pre-existing long-term memory becomes unstable via the ubiquitin/proteasome-dependent protein degradation pathway and that this labile state is required for the reorganization of fear memory. Here, the authors review this finding and focus on the labile state that is critical for the reorganization of memory triggered after memory retrieval.

Keywords: Memory reorganization; reconsolidation; labile state; protein degradation; ubiquitin; proteasome

Long-Term Memory Can Fall Into a Labile State by Synaptic Protein Degradation

Memories generally have common processing stages. When an individual experiences a variety of information about the world and attends to it, the information is conveyed to a short-term memory trace that is sensitive to disruption. Then, through a consolidation process, the information is gradually stored in a long-term memory trace that is thought to be relatively insensitive to disruption; when we encounter the appropriate cues, we can retrieve that information (Fig. 1; modified from Bower 1967). It is well known that the consolidation process is dependent on de novo mRNA and protein synthesis and involves synaptic structural changes (Kandel 2001). In the consolidation process, time is required to activate the molecular cascade responsible for long-term memory formation, including activation of the N-methyl-d-aspartate (NMDA) receptor, several kinases, and transcription factors (Milner and others 1998). Therefore, memories are in a labile state shortly after learning and before the consolidation process, whereas long-term memories are insensitive to disruption (Montarolo and others 1986; Nader and others 2000a). For a long time, it was widely accepted that once consolidated, a memory is maintained permanently (Nadel and Land 2000). However, the consolidation theory has been challenged on occasions, especially in recent years (Misanin and others 1968; Nader and others 2000b). In particular, Nader and others (2000b) provided evidence that challenges the consolidation theory. In their experiments, they tested rats in a cued fear conditioning paradigm. In this task, when they infused the protein synthesis inhibitor anisomycin into the rat basolateral amygdala just after memory retrieval, the preexisting fear memory was impaired. The injection of anisomycin itself, without memory retrieval, did not affect memory persistence. Nader and others (2000) suggested that a consolidated fear memory becomes labile again after memory retrieval and that protein-synthesis-dependent reconsolidation processes are required to maintain the original memory (Fig. 1). These studies have provided new insight to the investigation of consolidated memory dynamics.

Since this report (Nader and others 2000a) was made, similar phenomena have been observed in a variety of animals and memory tasks. In contextual fear conditioning in mice, the administration of a protein synthesis inhibitor (either systemically or by intrahippocampal infusion), before or immediately after retrieval, disrupted the original memory (Debiec and others 2002; Suzuki and others 2004). In the rat, a reactivated inhibitory avoidance memory was impaired by protein synthesis inhibition (Lopez-Salon and others 2001). In the mouse, chick, and crab, passive avoidance memories were also disrupted by protein synthesis inhibition after reactivation (Alberini 2005; Tronson and Taylor 2007).

However, the question of how the consolidated memory becomes labile after memory retrieval remains
unclear, as does the biological nature of the labile state. Our recent study focused on these two questions (Lee and others 2008). First, we hypothesized that de novo protein synthesis is required to rebuild the original memory because preexisting proteins, which constitute the memory-encoding synapses, are degraded after memory retrieval. Our results showed that protein degradation is activated in the synaptic region after memory retrieval. The degradation of specific synaptic proteins such as Shank and guanylate kinase-associated protein (GKAP) increased, whereas the postsynaptic density protein PSD-95 was not degraded at all (Lee and others 2008). The endogenous levels of Shank decreased in accordance with its polyubiquitination and were lowest 2 h after memory retrieval, returning to the basal level by 6 h after retrieval (Fig. 2). This reduction in Shank appears to reflect the increased activity of proteasomes, because clasto-lactacystin-β-lactone (β-lactone), a specific inhibitor of proteasomes, blocked the reduction of Shank after retrieval. This result suggests that synaptic destabilization followed by restabilization is triggered after the memory retrieval process and that postsynaptic protein degradation underlies the labile state after memory retrieval.

What is the physiological role of protein degradation induced by memory retrieval? To address this question, we blocked protein degradation after memory retrieval using a pharmacological method. When we infused β-lactone and anisomycin into the hippocampal CA1 area, we found that the memory impairment caused by anisomycin infusion after memory retrieval was blocked by the infusion of β-lactone (Fig. 3) (Lee and others 2008). This suggests that the ubiquitin/proteasome pathway is involved in forgetting a pre-existing fear memory. In contrast, β-lactone treatment alone did not affect memory persistence after retrieval. Collectively, these data support the idea that protein degradation after memory retrieval is critical for the destabilization of a pre-existing fear memory, rather than for the restabilization of the retrieved memory. Furthermore, β-lactone infusion immediately after training did not suppress the memory impairment caused by the anisomycin infusion, which is known to block the consolidation process (Fig. 4). This result also supports the idea that the increase in protein degradation after memory retrieval plays a major role in the destruction of the previously formed memory.

Recently, it was reported that NMDA receptor activation is required to destabilize a consolidated fear memory (Mamou and others 2006). Other reports have also shown that glutamatergic transmission activates the ubiquitin/proteasome system in cultured neurons (Ehlers 2003; Bingol and Schuman 2006; Guo and Wang 2007). It has also been reported that L-type voltage-gated calcium channels (LVGCCs) or central cannabinoid (CB1) receptors are required for the initial destabilization of reactivated memory (Suzuki and others 2008). Therefore, the NMDA receptor, LVGCCs, or CB1 receptors may be upstream molecules involved in ubiquitin/proteasome-dependent protein degradation and may trigger the destabilization of the retrieved memory. These propositions require further investigation.

**Reorganization of Consolidated Memory by Synaptic Protein Degradation**

What are the roles of the destruction and reconstruction processes after memory retrieval? Are these processes futile? If not, what is their function? One
Figure 3. Proteasome inhibitor blocks the anisomycin-induced fear memory impairment after retrieval. Vehicle, β-lactone, anisomycin, or β-lactone with anisomycin was infused into the hippocampus CA1 region immediately after the first retrieval (retrieval 1). Then, the fear level was retested 24 h after the drug infusion (retrieval 2). The fear memory of the anisomycin group was impaired at retrieval 2. However, concurrent infusion of β-lactone with anisomycin prevented the anisomycin-induced fear memory impairment.

Figure 4. Protein degradation has no effect on the fear memory consolidation. Vehicle, β-lactone, anisomycin, or β-lactone with anisomycin was infused into the CA1 region immediately after the conditioning. The fear level was retested 24 h after the drug infusion. The infusion of β-lactone had no effect on the anisomycin-induced memory impairment during memory acquisition as well as on the memory acquisition itself.
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would be destroyed eventually after retrieval. Our results also demonstrate that the memory reconsolidation and extinction processes share common molecular mechanisms, at least in part, at the synaptic level. It should be stressed, however, that a different mechanism, so-called relearning, underlies certain forms of memory extinction. For example, inhibitory neurons from the prefrontal cortex as well as within the amygdala are involved in extinction of a cued fear memory (Herry and others 2008; Likhtik and others 2008; Quirk and Mueller 2008).

The fact that PSD95 is not degraded by retrieval, whereas GKAP and Shank are degraded, provides insight into how synaptic structures are rearranged in the memory reactivation process (Lee and others 2008). PSD95 is a major neuronal scaffold protein that associates with a number of receptors and cytoskeletal proteins to maintain the synaptic structure (Kim and Sheng 2004). Even with the synaptic protein degradation induced by memory retrieval, the main structure of the pre-existing synapse might be maintained to some extent in the presence of the PSD95 scaffold. Therefore, the entire synaptic structure is easily restored by reconsolidation or relearning processes, whereas the degradation of synaptic proteins, such as GKAP and Shank, is required to change the synaptic structures to unlearn or update them with new information. The question of how the synaptic structures are rearranged by retrieval-induced protein degradation and the behavioral relevance of these structural changes will be addressed in a future study.

Conclusions

There exists experimental evidence that consolidated memory undergoes destabilization and rebuilding processes after memory retrieval, which offers a new perspective on the memory consolidation theory that has developed over several decades. Our recent findings suggest that ubiquitin/proteasome-dependent protein degradation contributes to the destabilization (“unlearning”) of consolidated long-term memory, whereas protein synthesis contributes to the restabilization (“relearning”) of the original memory. These findings imply that destabilization and restabilization processes are required for memory reorganization, allowing pre-existing memories to incorporate new information. These results provide us with both the fundamental mechanism for memory reorganization and a basis for therapeutic targets in the treatment of mental disorders, such as posttraumatic stress disorder and addiction to alcohol or drugs.
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