Memory Extinction, Retrieval and Consolidation: An Overview

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Abstract

This paper presents an overview for the mechanisms of memory extinction, retrieval and consolidation. Memory extinction may result from the inhibition of NMDA receptors by the tubulin/CRMP2 complex, which could bind to the GluN2B subunit at Serine 1166 (S1166), a phosphorylation site of protein kinase A (PKA). Phosphorylation of S1166 by PKA may cause dissociation of tubulin/CRMP2 from GluN2B, thereby facilitating retrieval, whereas dephosphorylation of S1166 by calcineurin promotes extinction. It has been well documented that memory retrieval often leads to memory consolidation. According to the Microtubule Track hypothesis, the "very long-term memory" (> 1 month) is stored in specific microtubule tracks directing PSD-95 trafficking from the soma toward potentiated spines. Therefore, memory consolidation should involve remodeling of microtubule tracks, which can be achieved by tubulin and CRMP2 dissociated from GluN2B, as they are known to play a pivotal role in microtubule polymerization. During consolidation, PKMζ is required to maintain an elevated level of synaptic AMPARs, for otherwise the memory would not be retrieved and consolidated, even after tubulin/CRMP2 dissociates from GluN2B.

Introduction

"Forgetting" could arise from two possibilities: (1) the physical memory traces have gone forever, or (2) the memory still exists but could not be retrieved at a given moment. In the first case, the memory is said to be "erased". The word "**extinction**" refers to the second case. It has been well established that strong synaptic potentiation is often accompanied by

microtubule invasion into the stimulated spines (reviewed in Dent, 2017). Paper 16 proposes that microtubules may transport tubulin and CRMP2 into spines to inhibit NMDA receptors (NMDARs), which would attenuate synaptic strength. Such attenuation, however, is reversible. The synaptic strength can be recovered as tubulin and CRMP2 dissociate from NMDARs. Therefore, memory extinction and retrieval could be fundamentally governed by the interaction between tubulin/CRMP2 and NMDARs.

Memory consolidation, the process that converts short-term memory into long-lasting memory, is closely linked to memory retrieval. For instance, the spontaneous memory retrieval at the hippocampus, known as "hippocampal replay", has been shown to play an important role in memory consolidation (Carr et al., 2011). The retrieval of a previously consolidated memory can also induce reconsolidation (Tronson and Taylor, 2007). What exactly the brain is doing during memory consolidation?

According to the Microtubule Track (MTT) hypothesis, the "very long-term memory" (> 1 month) is stored in specific microtubule tracks directing PSD-95 trafficking from the soma toward potentiated spines (Lee, 2013a; Lee, 2013b). On the basis of this hypothesis, memory consolidation should involve creating and/or modifying MTTs, in which both tubulin and CRMP2 play a pivotal role (Wilson et al., 2014). The newly created and/or modified MTTs may lead to alteration in dendritic branching, where CRMP2 is also implicated (Niisato et al., 2013; Zhang et al., 2016). These results support the view that memory consolidation could originate from memory retrieval induced by the dissociation of tubulin/CRMP2 from NMDARs. The dissociated tubulin/CRMP2 then participate in the remodeling of microtubule tracks and dendritic branching.

The Mechanism of Extinction

The tubulin/CRMP2 complex interacts only with the GluN2B (also known as NR2B) subunit, not GluN2A (Paper 15). The specific binding site in GluN2B can be identified as S1166, which has been demonstrated to be the phosphorylation site of protein kinase A (PKA) (see Paper 16). Tubulin is a highly negatively charged protein while phosphorylation is a process that adds a negatively charged phosphate group PO_4^{3-} to a protein. Hence, phosphorylation of this site should disrupt tubulin binding, consequently

increasing the open probability of GluN2B-containing NMDARs and facilitating memory retrieval.

On the other hand, calcineurin (protein phosphatase 2B) has been shown to compete with PKA for the same site in NMDARs (Raman et al., 1996). While PKA prevents tubulin inhibition of the GluN2B-containing NMDARs, dephosphorylation of S1166 by calcineurin (CaN) should have the opposite effects. Indeed, calcineurin activation has been demonstrated to reduce NMDAR currents (Raman et al., 1996), and play an important role in promoting memory extinction (Lin et al., 2003). Therefore, the regulation of memory extinction and retrieval by tubulin boils down to the competition between PKA and CaN for the phosphorylation state of S1166 located at the cytoplasmic domain of GluN2B (NR2B). Phosphorylation of S1166 by PKA facilitates retrieval whereas dephosphorylation of S1166 by CaN promotes extinction.

In the resting state, NMDARs are phosphorylated (presumably at S1166 of GluN2B) by basally active PKA (Raman et al., 1996), which prevents tubulin inhibition. During excitatory transmission, the Ca^{2+} influx through GluN2B-containing NMDARs may stimulate the CaN anchored to GluN2B via AKAP79/150 (Paper 17), resulting in S1166 dephosphorylation, which would allow tubulin to bind to the GluN2B-containing NMDARs, thereby leading to extinction. The extinction process may take 5 - 15 minutes, as manifested in the short-term potentiation (Paper 16). In contrast, the desensitization process reflected in the falling phase of NMDAR currents during agonist binding takes less than a second (Erreger et al., 2005).

GluN2A-containing NMDARs will never be extinguished, because the tubulin/CRMP2 complex does not interact with GluN2A. The macroscopic memory extinction is a combined result of microscopic states in NMDARs. Since GluN2A-containing NMDARs do not have the microscopic extinction state, the macroscopic memory extinction should also depend on the GluN2B/GluN2A ratio in the dendritic branches that encode the memory. The higher the ratio, the memory is more likely to become extinguished. This explains why the brain-derived neurotrophic factor (BDNF) promotes memory extinction, as BDNF is known to enhance the localization of GluN2B-containing NMDARs to the dendritic membrane (see this article).

In cortical neurons, both GluN2A and GluN2B increase with age. In the hippocampus, however, GluN2A increases whereas GluN2B declines with age (Dong et al., 2006). The GluN2B-GluN2A switch has been proposed to underlie the mechanism of **infantile amnesia** - the inability of adults to recall events from early childhood (Travaglia et al., 2016). This hypothesis is consistent with the present model. At early childhood, GluN2B dominates in both cortical and hippocampal neurons. Therefore, the childhood memories should be encoded predominately by the neurons enriched with GluN2B-containing NMDARs, which are prone to extinction.

The Mechanism of Retrieval

As mentioned above, phosphorylation of S1166 by PKA facilitates retrieval, because it can cause dissociation of tubulin/CRMP2 from GluN2B. The activity of PKA depends on the binding of cyclic AMP (cAMP), whose level is regulated by adenylyl cyclase (AC) that catalyzes the conversion from ATP to cAMP. The activity of AC is under the regulation of various pathways. For instance, norepinephrine may bind to the β_1 adrenergic receptors, triggering G-protein-coupled signaling to enhance AC activity (Zhang et al., 2013). In addition to this pathway, the AC subtype 1 (AC1) can also be activated by calcium-calmodulin (Wong et al., 1999) to enhance PKA activity. Hence, AC1 provides a shortcut for Ca^{2+} to increase PKA activity. This pathway is very important as PKA is anchored to GluN2B via AKAP79/150 (Paper 17), permitting the Ca^{2+} influx through GluN2B-containing NMDARs to efficiently activate PKA and augment long-term potentiation (LTP). This also explains why AC1 contributes to LTP in the neocortex of adult mice (Chen et al., 2014; Yamanaka et al., 2017).

A number of studies have provided evidence for the critical role of PKA in memory retrieval:

1. Disruption of PKA anchoring to AKAP79/150 promotes extinction of contextual fear memories (Nijholt et al., 2008).
2. The activators of PKA block fear extinction (Corcoran et al., 2015).
3. The GluN2B-mediated PKA inhibition prevents retrieval of remote memory (Corcoran et al., 2013).

4. Norepinephrine promotes retrieval via the stimulation of β_1-adrenergic receptors, the production of cAMP, and the activation of PKA (Zhang et al., 2013).
5. Blockade of the M1 type muscarinic acetylcholine receptors (M1-AChRs) impairs the retrieval of well-trained memory (Soma et al., 2014).
6. The serotonin 2A receptors (5-HT2ARs) control the retrieval of recognition memory in rats (Bekinschtein et al., 2013).

Activation of M1-AChRs or 5-HT2ARs may trigger signaling cascades to increase Ca^{2+} level, thereby activating PKA. Details will be discussed in Paper 20. The following figure summarizes the proposed mechanisms for memory extinction, retrieval and consolidation.

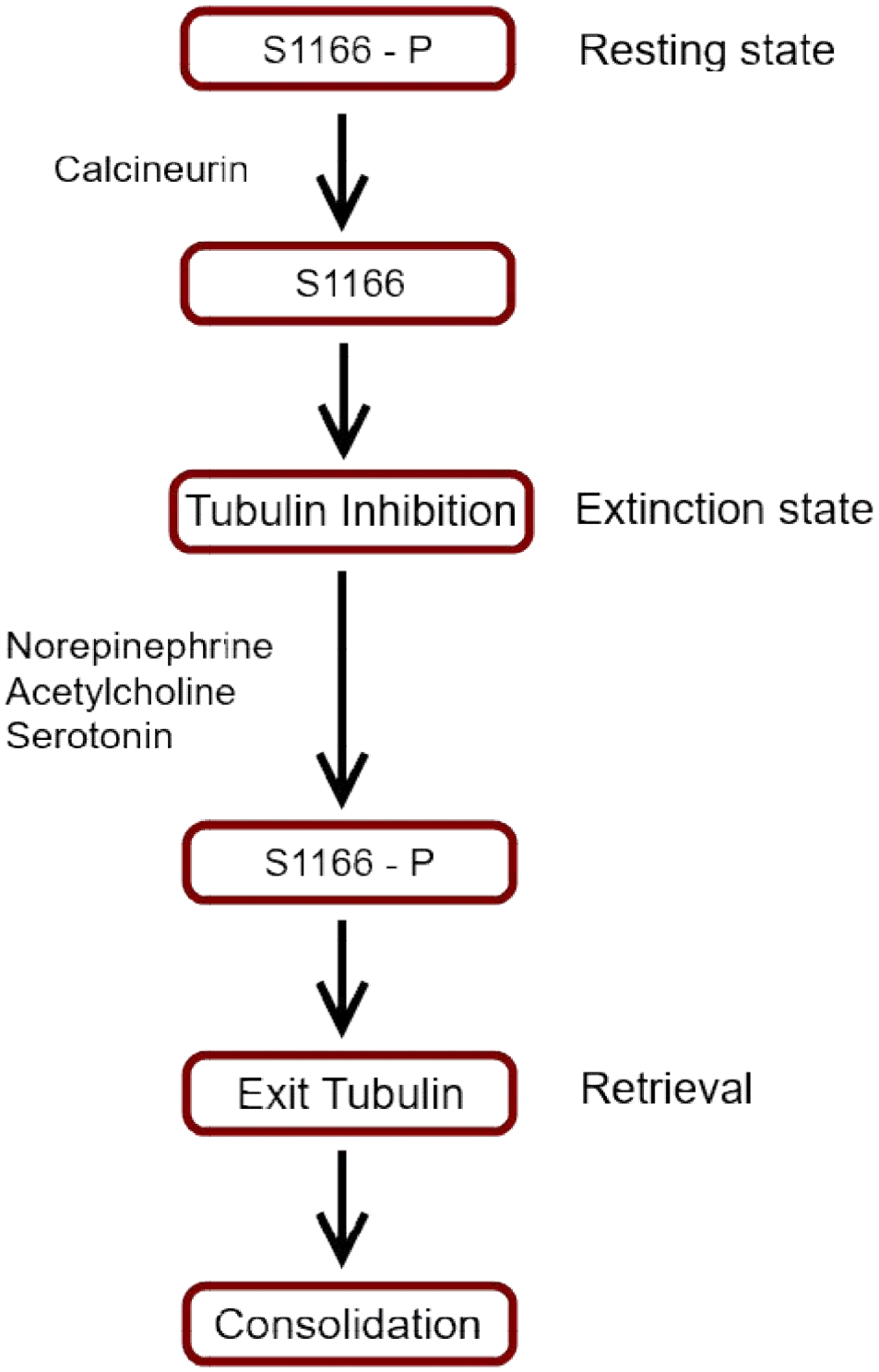

Figure 1. The proposed mechanisms of memory extinction, retrieval and consolidation.
(1) In the resting state, S1166 of GluN2B is phosphorylated by PKA, preventing NMDAR inhibition by tubulin.
(2) The Ca^{2+} influx through GluN2B-containing NMDARs may

activate calcineurin to dephosphorylate S1166.
(3) S1166 dephosphorylation allows NMDAR inhibition by tubulin.
(4) Neurotransmitters, such as norepinephrine, acetylcholine and serotonin, may trigger signaling cascades to activate PKA, resulting in S1166 phosphorylation, consequently leading to the dissociation of tubulin from NMDARs.
(5) The dissociated tubulin and CRMP2 may participate in the remodeling of microtubule tracks for memory consolidation.

The Necessity of PKMζ During Consolidation

Paper 18 suggests that the primary function of PKMζ is to maintain an elevated level of synaptic AMPARs while the memory is being consolidated. Why is this necessary? In addition to tubulin and CRMP2, the consolidation may also require retrieval to induce Ca^{2+} influx through NMDARs. Suppose during the consolidation phase, the level of synaptic AMPARs is very low (e.g., by using ZIP to inhibit PKMζ), then the initially potentiated synapses cannot be reactivated and the encoded memory would not be retrieved and consolidated, even after tubulin/CRMP2 dissociates from GluN2B.

After the consolidation is complete, PKMζ is no longer necessary (Hales et al., 2015; Hales et al., 2016), because the remodelled MTTs should be able to transport plasticity-related proteins (particularly PSD-95) to potentiated spines.