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Review article

Synaptic plasticity during systems memory consolidation☆

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ABSTRACT

After learning, memory is initially encoded in the hippocampus but subsequently stabilized in other brain regions such as the cortex for long-lasting storage. This process is known as systems memory consolidation, and its cellular mechanism has long been a fundamental question. Synaptic plasticity is the major cellular mechanism underlying learning and memory, and is therefore considered a key function in the process of systems memory consolidation. Therefore, many studies have aimed to establish a causal link between synaptic plasticity in the brain and memory-associated behaviors. In this review, I discuss the various lines of research showing the function of synaptic plasticity, mainly in the hippocampus and cortex during memory consolidation.

1. Synaptic plasticity in learning and memory

Learning and memory are represented by vastly interconnected neural circuits; the connections are mediated by synapses that enable a neuron to pass an electrical or chemical signal to another neuron. The efficacy of a synapse is strengthened or weakened over time, and this phenomenon is called synaptic plasticity. Therefore, synaptic plasticity is postulated to be an important cellular substrate for learning and memory. The phenomenon has been indeed documented in a variety of learning-associated brain areas including the hippocampus, cerebral cortex, cerebellum, amygdala, and striatum (Frankland and Bontempi, 2005; Lüscher and Malenka, 2012; Tonegawa et al., 2018).

Learning can be distinguished into two forms of memory: declarative and procedural. Declarative memory can be stated and recalled in the conscious mind as an image (episodic information) or language (semantic information). It is typically stored in the medial temporal lobes (MTL), a region that includes the hippocampus (Frankland and Bontempi, 2005). On the other hand, procedural memory cannot be recalled in a conscious mind or described through language. Synaptic plasticity is important in both declarative and procedural memories (Frankland and Bontempi, 2005; Kreitzer, 2009). However, patients with hippocampal damage and deficits in declarative memory do retain intact learning of certain motor, perceptual and cognitive skills (Squire et al., 2004; Corkin, 2002), suggesting the processes of these two forms are considered separate. In this review, I focus on declarative memory and discuss the functions of synaptic plasticity responsible for this process.

2. The molecular and cellular mechanisms underlying synaptic plasticity

Different areas of the brain exhibit various forms of synaptic plasticity. One of the important types of synaptic plasticity in the hippocampus, and thus in systems memory consolidation, is the long-term potentiation (LTP) of excitatory synaptic transmission, a long-lasting experience-dependent strengthening in the efficacy of synaptic transmission (Lüscher and Malenka, 2012). In particular, NMDA-type glutamate receptor (NMDAR)-dependent LTP in the hippocampal CA1 region and other forebrain regions has been well-characterized. Therefore, in this section, I will briefly provide an overview of the molecular mechanisms underlying NMDA receptor-dependent LTP.

An excitatory synapse is formed on a small mushroom-like protrusion on dendrites called dendritic spines. During LTP induction, an influx of Ca^{2+} to the postsynaptic compartment through NMDARs leads to the activation of calcium/calmodulin-dependent kinase II (CaMKII) resulting in subsequent phosphorylation of a number of proteins, including AMPA-type glutamate receptors (AMPARs) (Derkach et al., 1999). The phosphorylation of AMPAR subunits can cause an increase in the conductance of AMPAR channels. In addition, the increase in CaMKII activity contributes to the insertion of AMPARs, leading to potentiation of synapses (Hayashi et al., 2000). At the same time, new dendritic spines are formed, and the volume of existing ones increases (Engert and Bonhoeffer, 1999; Okamoto et al., 2004; Maletic-Savatic et al., 1999; Matsuzaki et al., 2004). The size of the spine and density of AMPARs are

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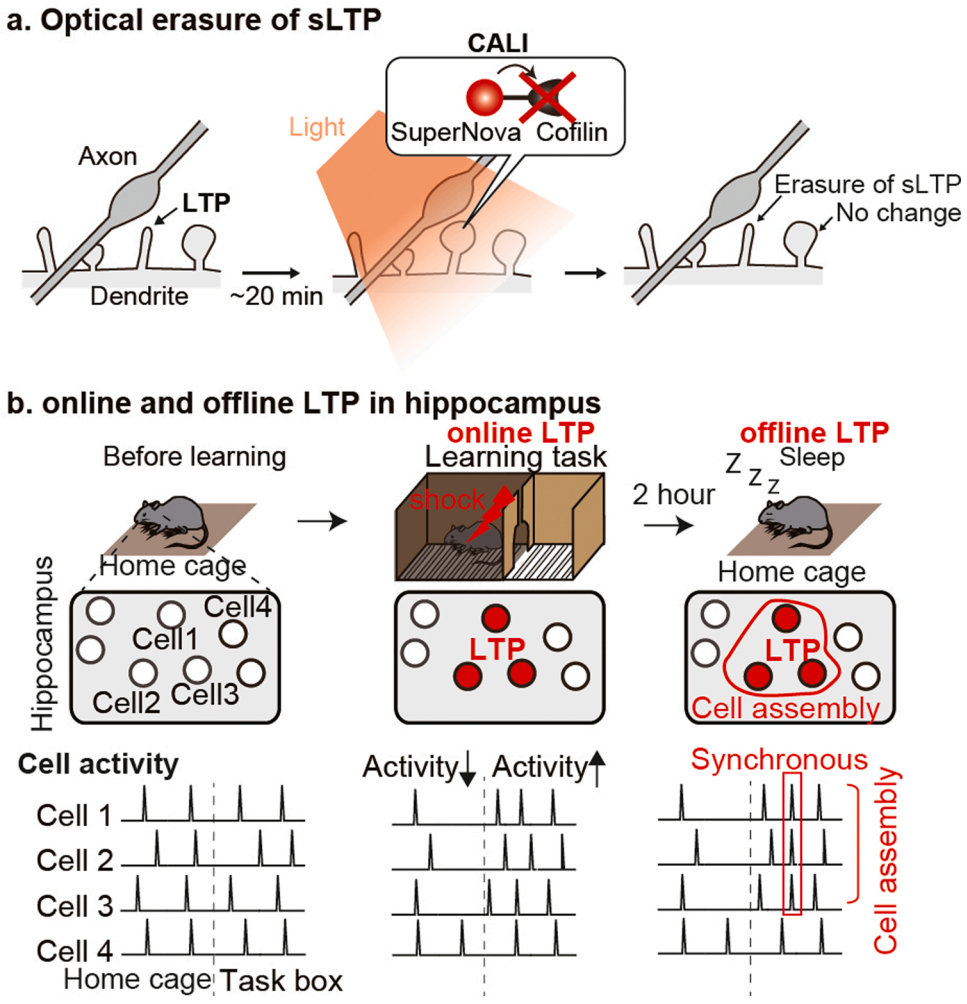

Fig. 1. (a): Scheme of an optogenetics tool that allows for optical erasure of specific memory by chromophore-assisted light inactivation (CALI) (Goto et al., 2021). SuperNova (SN) is a photosensitizer that generates reactive oxygen species (ROS) upon illumination. SN fuses with cofilin (CFL), which is a critical protein for memory formation. Illumination of this fusion protein induces CALI and inactivates CFL. Since CFL is highly accumulated in the spine that undergoes sLTP, illumination of the fusion protein specifically erases sLTP. sLTP is erased within 20 min of its induction; thus, this method enables spatiotemporal analysis of neuronal circuits responsible for memory formation. **(b):** Formation and neural activity of hippocampal cell assembly. Two steps of LTP, immediately after learning (online LTP) and during subsequent sleep (offline LTP), lead to synchronous firing in cell assembly.

positively correlated (Matsuzaki et al., 2004), indicating that the changes in the spine structure lead to modification of synaptic function. This structural change in LTP is known as structural LTP (sLTP). sLTP is mainly mediated by actin filaments, which are the principal cytoskeletal component of the spine (Okamoto et al., 2009, 2004). Actin exists in dynamic equilibrium between two forms: the monomeric globular (G-actin) and the filamentous (F-actin). This equilibrium is bidirectionally modulated by several actin binding proteins. In particular, actin depolymerization factor ADF/cofilin forms a complex with F-actin thereby stabilizing it rather than destabilizing, which is critical for spine enlargement (Bosch et al., 2014).

NMDAR-associated Ca^{2+} influx also promotes synthesis of both mRNA and protein (Kandel et al., 2014). Changes in gene expression and protein synthesis are thought to contribute to postsynaptic structural changes, as well as to increased sensitivity to neurotransmitters leading to the long-term stabilization of synaptic transmission. For example, an increase in the postsynaptic scaffolding proteins PSD-95 and Homer1c has been shown to correlate with stabilization of synaptic enlargement (Meyer et al., 2014).

Immediate-early genes (IEG), such as *Arc*, *c-fos*, and *egr-1*, are induced in specific brain regions during neuronal activity associated with learning (Minatohara et al., 2015). Therefore, IEGs are widely used as markers of neurons involved in learning. Although the biological and physiological effects of IEG on synaptic plasticity remain unclear, some IEGs are known to regulate LTP (Jones et al., 2001).

3. Synaptic plasticity in hippocampus during systems memory consolidation

The process underlying LTP described above completes within hours and involves the stabilization of changes in synaptic connectivity in the local circuits. For instance, LTP can be readily reversed by giving a depotentiation stimulus consisting of prolonged low frequency pulses 20 min after the induction. However, it becomes more resistant to depotentiation after 100 min (Fujii et al., 1991). This process is called synaptic consolidation which can be explained by protein synthesis-dependent transport of PSD scaffolding proteins to the synapses (Bosch et al., 2014; Frankland and Bontempi, 2005). However, storage of memory does not end there, and consolidation of memory can also occur at a system level. The brain regions that support memory gradually reorganized over time and neuronal network becomes more stable at the systems level. This process is called system consolidation. Fast process of synaptic consolidation in each local circuit may play critical role during slow process of systems memory consolidation.

The idea of systems memory consolidation was originally described in early psychological studies; recently formed memories were more susceptible to disruption than those formed remotely (Frankland and Bontempi, 2005). This indicates that declarative memories become consolidated and resistant to decay over time. This concept was supported by the reports on patients with MTL damage. MTL damage preferentially affects recent but not remote declarative memories. In the most well-known case, patient H.M., who had parts of the MTL removed to alleviate severe epilepsy, showed impaired ability to form new

declarative memories (anterograde amnesia). H.M. also lost recent declarative memories (retrograde amnesia) but retained memories from his early childhood. This led to the perception that the hippocampus is essential for the formation and early retrieval of episodic memories, and has a time-limited role in the storage and retrieval of memory.

Although the timeline of hippocampal function in memory retrieval continues to be controversial (Tonegawa et al., 2018), studies have consistently shown that LTP in the hippocampus is important for the formation and retrieval of short-term memory. In an early study of LTP in the hippocampus, researchers attempted to find evidence of LTP in the brain after learning using pharmacological or genetic approaches. After blockade of synaptic plasticity in the hippocampus by injecting the NMDAR antagonist (APV), APV-treated rats showed significant impairment in memory (Morris et al., 1986). Hippocampal CA1-specific knockout mice of NMDAR1 showed impairment in spatial memory, indicating that synaptic plasticity in the hippocampus plays an essential role in the acquisition of spatial memory (Tsien et al., 1996). These studies provided evidence that LTP is required for the formation of recent memories *in vivo*.

Direct evidence of LTP in behavioral memory was reported in 2006 (Whitlock et al., 2006). This study showed that learning the inhibitory avoidance (IA) task in rats induced the same changes in hippocampal glutamate receptors as the induction of LTP in slice experiments and even caused a spatially restricted increase in the amplitude of evoked synaptic transmission in CA1 *in vivo*.

3.1. Online hippocampal synaptic plasticity in memory formation

Although many studies have shown that hippocampal synaptic plasticity is necessary for memory formation, the precise spatiotemporal profile of hippocampal synaptic plasticity remains unclear. This was primarily due to the lack of appropriate experimental techniques to detect and modify synaptic plasticity in a precise spatiotemporal manner. Therefore, Goto et at. (2021) attempted to develop a new optogenetics tool that could detect the timeframe in which LTP is induced (Fig. 1) (Goto et al., 2021). They focused on the actin-binding protein cofilin (CFL), which is important for reorganization and stabilization of the actin cytoskeleton in spines during sLTP (Bosch et al., 2014). Since CFL is highly accumulated in the spine that undergoes sLTP, they reasoned that impairing the function of CFL would specifically impair sLTP. Toward this, they fused CFL to a photosensitizer protein, SuperNova (SN), which generates reactive oxygen species (ROS) upon exposure to particular wavelengths of light and inactivates a fused protein, a phenomenon known as chromophore-assisted light inactivation (CALI) (Takemoto et al., 2013). CFL-SN was expressed in pyramidal neurons in cultured rat hippocampal slices and sLTP was induced by glutamate uncaging. Though glutamate uncaging drove spine enlargement, the subsequent induction of CALI reversed this effect, thus erasing sLTP. The effect of CALI on sLTP was limited to 30 min following sLTP induction. Importantly, it did not alter the basal transmission or interfere with future LTP.

The authors further examined the effects of LTP erasure on memory formation *in vivo* by expressing CFL-SN in the mouse hippocampal region CA1 using an adeno-associated virus (AAV) vector. CALI was induced in CA1 after IA task training. They documented that the CALI of the CFL-SN, immediately after training in the IA task, impaired memory recall. The study demonstrated that LTP is induced in the hippocampus immediately after the memory task and that such local synaptic plasticity event is necessary for short-term memory formation.

3.2. Offline hippocampal synaptic plasticity in memory formation

Sleep improves various forms of memory (Gais and Born, 2004). The activity of hippocampal place cells during spatial exploration is repeated when the animal is asleep (without any sensory input) (Ji and Wilson, 2007; Skaggs and McNaughton, 1996). Such reactivation of event-specific activity is known as replay and occurs during brief high-frequency bursts in the hippocampus, that is known as sharp wave-ripples (Karlsson and Frank, 2008; Kudrimoti et al., 1999; Nádasdy et al., 1999). This indicates memories can be reactivated during either 'online' (such as during training of memory task) or 'offline' states (such as during sleep or rest period after the task). The strength of reactivation correlates with subsequent memory expression (Dupret et al., 2010; Nakashiba et al., 2009), and preventing replay by electrically disrupting sharp wave-ripples following learning impairs the subsequent expression of that memory (Ego-Stengel and Wilson, 2010; Girardeau et al., 2009; Jadhav and Frank, 2009). Therefore, replay is essential for systems memory consolidation.

Offline hippocampal reactivation likely induces synaptic plasticity in the hippocampus. Genetic disruption of NMDAR function in the CA1 region of the hippocampus immediately following training, blocks memory consolidation (Shimizu et al., 2000). Another study showed *Zif268*, which is involved in LTP was upregulated in rats hippocampus after they had explored a novel environment during subsequent sleep (Ribeiro et al., 1999). These studies demonstrated that offline hippocampal synaptic plasticity is important for systems memory consolidation. However, it remains unclear whether such offline synaptic plasticity occurs during sleep. Therefore, Goto et al. used optogenetics tool and revealed a more precise time window for hippocampal LTP in the offline state (Fig. 1)(Goto et al., 2021). They canceled LTP during extended periods following learning (from to 2–8 h after training) by inducing CALI in the hippocampus expressing CFL-SN and found that memory recall was impaired on the subsequent day. Importantly, this effect was specific to sleep period; the erasure during wakefulness had no effect on memory. Memory was not erased when CALI was induced more than one day after the shock. The study showed that LTP takes place during the subsequent sleep period (offline LTP) in addition to during or immediately after the event (online LTP), and that these two forms of local hippocampal LTP events are necessary for memory formation.

3.3. Differential roles of online and offline LTP on the formation of hippocampal cell assembly

Goto et al. (2021) further examined whether these two forms of hippocampal LTP shape memory representations in different ways (Goto et al., 2021). They performed calcium imaging using a head-mounted microscope during an IA task and examined the effect of cancellation of online and offline LTP on neuronal activity. They discovered that online LTP is crucial for the establishment of selective neuronal firing related to the learning context. This selective firing in the learning context is consistent with the results of a previous study (Tanaka et al., 2018). In contrast, the offline LTP that occurs later during sleep on the same day enables these neurons to fire in a synchronized manner during memory recall. This indicates that an offline LTP is required for synchronous firing. According to Hebb's theory, learning strengthened the synaptic connections between neurons, thereby facilitated the formation of neuronal ensembles (cell assemblies), and those neurons fire together at the time of learning and again during memory retrieval (Josselyn et al., 2015). This study showed that offline LTP, which may be induced by offline reactivation in the hippocampus on the same day as learning, is required for the formation of synchronous activity (cell assembly). This was the first study showing that two steps of synaptic plasticity (online and offline LTP) are required for the formation of cell assembly, which fire together and encode hippocampal memory.

4. Synaptic plasticity in cortex during systems memory consolidation

Although memories are initially dependent on the hippocampus as described above, they gradually become dependent on the cortex. (Kim and Fanselow, 1992; Frankland and Bontempi, 2005). Systematic

mapping of the brain regions involved in the retrieval of recent or remote memory in mice was accomplished using ^{14}C-2-deoxyglucose to measure regional levels of glucose metabolism (Bontempi et al., 1999). The study identified several cortical regions, including the frontal and temporal cortices, that showed higher activity following retrieval 25 days post-learning than that retrieved 5 days after learning. The prefrontal cortex consists of several highly interconnected regions, including the anterior cingulate (ACC) and prelimbic and infralimbic cortices. These regions are reciprocally connected to the sensory motor and limbic cortex (Uylings et al., 2003), and are therefore thought to integrate and synthesize information from multiple cortical regions (Miyashita, 2004).

The necessity of cortical synaptic plasticity in memory consolidation has been reported (Frankland and Bontempi, 2005; Tonegawa et al., 2018). Mice that are heterozygous for a null mutation of α-CaMKII have global deficits in cortical plasticity but normal hippocampal plasticity (Frankland et al., 2004, 2001). These mice have deficient remote contextual fear memory but normal recent memory. A similar pattern of memory loss was observed in mice overexpressing a dominant-negative mutant form of p21-activated kinase, which is critical for spinal structure and synaptic function (Hayashi et al., 2004). These studies suggest that cortical synaptic plasticity plays an increasingly important role in memory expression over time during systems memory consolidation.

Subsequent studies have attempted to reveal a more specific cortical region whose synaptic activity is involved in the formation and recall of remote memory. IEGs (*Zif*268 and *c-fos*) are elevated in multiple cortical regions, such as the ACC, prefrontal and temporal cortex, following remote memory recall (Frankland et al., 2004). Suppression of synaptic plasticity by blockade of NMDAR in the medial prefrontal cortex (mPFC) subregions results in impairment of the retrieval of remote but not recent memory (Takehara-Nishiuchi et al., 2006). Likewise, blocking synaptic activity by injecting a competitive AMPAR antagonist (CNQX) or an NMDAR antagonist (APV) into the orbitofrontal cortex (OFC) also prevents the formation of remote memory (Lesburgueres et al., 2011). The retrosplenial cortex, which is connected to the hippocampus and mPFC, is also important for memory consolidation and shows greater IEG, which is involved in synaptic plasticity, such as *Zif*268 and *Arc* (Gusev and Gubin, 2010; Maviel et al., 2004).

4.1. *Rapid formation of cortical memory trace through synaptic plasticity during systems memory consolidation*

According to prevalent models of systems memory consolidation, storage site of episodic memory shift from hippocampus to neocortical networks during the post-encoding period (Tonegawa et al., 2018). Some studies have shown that memory traces are rapidly formed through synaptic plasticity in the frontal cortical area, as in the hippocampus. A study using the social transmission of food preference paradigm for the learning task (Lesburgueres et al., 2011) showed that blockade of synaptic plasticity in the OFC during the training period by injecting CNQX or APV prevents the formation of remote memory. Another study showed that pharmacological or genetic blockade of the NMDAR subunit NR2B in the cingulate cortex impairs the formation of early contextual fear memory (Zhao et al., 2005). As the NR2B subunit is important for cingulate LTP, this study showed that synaptic plasticity within the prefrontal cortex is important both during and shortly after learning for contextual fear memory. One more study inhibited spine growth using myocyte enhancer factor 2 (MEF2), which is a transcription factor shown to negatively regulate spine growth *in vivo* (Vetere et al., 2011). Increasing MEF2-dependent transcription in ACC neurons immediately following training, but not at later time points, blocked both increase in spinal growth and consolidation-associated memory. The authors demonstrated that rapid structural remodeling (spine growth) in the ACC after learning is critical for the subsequent gradual process of systems memory consolidation. Quick induction of synaptic plasticity in the mPFC after training has also been reported in paired-associate memory when new learning occurs against a background of established prior knowledge (Tse et al., 2007). The subsequent study further showed that some IEG involved in synaptic plasticity (such as *Zif*268 and *Arc*) in the prelimbic cortex of the mPFC were upregulated after hippocampal-dependent learning of new paired associates (Tse et al., 2011). Pharmacological interventions for synaptic activity in the mPFC prevent systems memory consolidation. Other groups have found a subset of mPFC neurons strongly expresses c-fos (Kitamura et al., 2017; Ye et al., 2016) and Arc (Ye et al., 2016) during the learning of contextual fear conditioning. They further tagged c-Fos-positive neurons with ChR2 or ArchT to activate or inhibit these neurons, respectively (Kitamura et al., 2017). Optogenetic reactivation can induce memory retrieval as early as one day after training and until at least 2 weeks after learning. The findings of the study indicate that memory traces in the mPFC are generated quickly on the day of training, and memory is retrievable from these cells through optogenetic stimulation, but not by natural recall cues, one day after training (thus referred to as silent engrams).

4.2. *Maturation of cortical memory trace through synaptic plasticity during systems memory consolidation*

The cortical memory trace in silent or inactive state in early stage of the memory formation should become active as the memory maturates. Many studies hypothesized that offline hippocampal activity is required for maturation of cortical memory trace during systems memory consolidation (Frankland and Bontempi, 2005; Tonegawa et al., 2018). Similar to the requirement of hippocampal reactivation and the resultant offline LTP in the formation of hippocampal synchronous activity (cell assembly) as described above, hippocampal reactivation is thought to also induce cortical synaptic activity which is required for the maturation of the cortical memory trace. This is supported by the study which showed that the output of the hippocampal dentate gyrus engram, as defined by c-fos positive cells after training, to mPFC cells one day after training is required for the increase in the dendritic spine density of mPFC engram cells and for activation of silent engram cells. (Kitamura et al., 2017). Therefore, after the initial generation of memory traces in the cortex, the memory trace is assumed to mature through offline reactivation of hippocampal input into the cortex over days or weeks.

Many studies further hypothesized that replay in high-frequency oscillatory hippocampal activity promotes the strengthening of synaptic connections in the cortex as well as in the hippocampus (Frankland and Bontempi, 2005). This has led to studies examining whether recurrent hippocampal reactivation in replay is involved in cortical synaptic modifications and essential for systems memory consolidation. Sharp-wave ripples in the hippocampus are temporally correlated with cortical slow-wave spindles (SWS) recorded in the mPFC (Siapas and Wilson, 1998). As replay predominantly occurs during hippocampal sharp-wave ripples and cortical SWS, such coordinated replay in hippocampal-cortical (Qin et al., 1997) and cortico-cortical (Hoffman and McNaughton, 2002) networks could promote the gradual stabilization of memory in the cortex, allowing new memories to become independent of the hippocampus and gradually integrate with pre-existing cortical memories (Frankland and Bontempi, 2005).

There are reports that show that offline hippocampal reactivation during sleep promotes gradual remodeling of hippocampal-cortical circuits that support memory. *Zif268* is a transcription factor that regulates long-term plasticity and stabilization of retrieved memories (Jones et al., 2001). Upregulation of *Zif268* was documented in rats after they had explored a novel environment during subsequent sleep in the hippocampus as well as in various cortical regions, such as the piriform and frontal cortices (Ribeiro et al., 1999). Similarly, the induction of LTP in the dentate gyrus in awake behaving rats led to the upregulation of *Zif268* during subsequent sleep in various cortical regions, including the entorhinal, auditory, somatosensory, and frontal cortices (Ribeiro et al., 2002). Inactivation of the hippocampus prior to the onset of sleep blocks

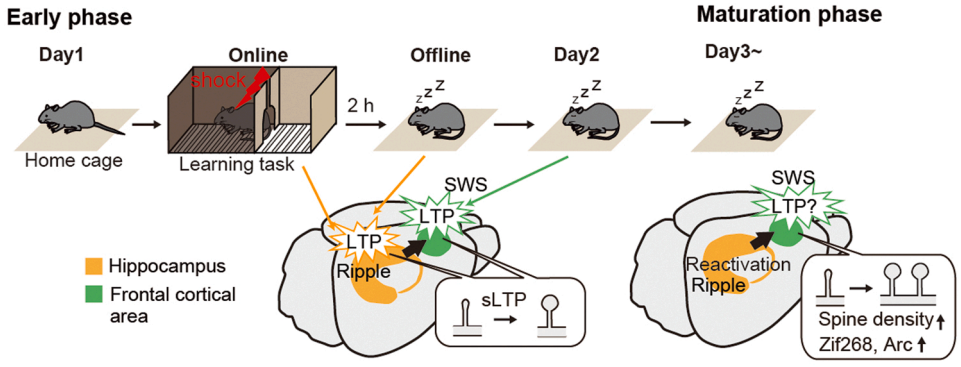

Fig. 2. Timeline of hippocampal and cortical synaptic plasticity during systems memory consolidation. Stepwise LTP events in hippocampus and frontal cortical area occur in early phase of systems memory consolidation. In maturation phase, hippocampal reactivation in replay (ripple) occurs in temporal correlation with cortical activity in slow-wave spindles, and such coordinated activity promote the gradual stabilization of memory in the cortex.

the upregulation of *Zif268* in these cortical regions. These observations suggest that offline hippocampal activity during sleep (replay during SWS) leads to cortical synaptic plasticity event and stabilization of the cortical networks (Ribeiro et al., 2004).

To identify a more precise time window of cortical synaptic plasticity during systems memory consolidation, Goto et al. (2021) conducted a spatiotemporal analysis of synaptic plasticity in the ACC after learning (Goto et al., 2021). When the CALI of the CFL-SN was induced in the ACC on the day of training, memory was not erased. However, when CALI was induced a day after training, memory was erased. This implies that the memory trace was rapidly formed through synaptic plasticity in the ACC. Furthermore, they found that the effect of memory cancellation was specific to sleep period, with LTP erasure during wakefulness having no effect on memory. The findings indicates that sLTP in the ACC occurs one day after learning during sleep, which is consistent with a study that showed that rapid structural remodeling (spine growth) in the ACC after learning is critical for subsequent and gradual processes of memory consolidation (Vetere et al., 2011). The rapid structural remodeling in the ACC that occurs during sleep is was most likely induced during replay during SWS. This implies that cortical synaptic plasticity during replay is important for both rapid generation and maturation of memory traces in the ACC during systems memory consolidation. As described above, the study also showed that LTP occurs during sleep in the hippocampus on the day of training, indicating that there are distinct LTP events during sleep in the hippocampus and ACC, and that both LTP events during sleep are necessary in the early phase of systems memory consolidation (Fig. 2). This study suggests that even at this early point in systems consolidation, cortical circuits can play a role in memory recall. This is inconsistent with a previous study (Kitamura et al., 2017) in that cortical memory trace was first silent and not involved in recall of recent memory. The discrepancy between these studies is not clear at this point, but it may be due to differences in the method of inactivation (tetanus toxin to block output *versus* CFL-SN to erase LTP while leaving basal activity intact). Although involvement of rapid cortical trace in memory is still controversial, these two studies suggest structural change occur quickly after the training, but subsequent synaptic activity (such as increase in spine density) is also required for system memory consolidation.

4.3. Perspectives

In this review, I discuss the role of synaptic plasticity in memory consolidation, particularly in the hippocampus and cortex. However, some areas such as the basolateral amygdala that are involved in memory consolidation have not be discussed. Likewise, layer Va cells of the medial entorhinal cortex project to the mPFC that are important for memory consolidation (Kitamura et al., 2017) has not be included in this review.

Recently, optogenetics approaches using ChR2 have been widely used to reveal neural circuits underlying memory consolidation, and a protocol that allows for the manipulation of LTP and LTD has also been reported (Nabavi et al., 2014). Furthermore, new optogenetics approaches that allow for high spatiotemporal manipulation of LTP have been developed, such as AS-PARac, PA-AIP, eosin-tagged AMPA receptor antibody, and CALI on the CFL-SN (Goto et al., 2021; Hayashi-Takagi et al., 2015; Murakoshi et al., 2017; Takemoto et al., 2016). Therefore, further understanding of the spatiotemporal aspects of synapses in a wide area of the brain related to memory consolidation can be expected in the near future.

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