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The tired hippocampus: The molecular impact of sleep deprivation on hippocampal function

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Abstract

Memory consolidation, the process by which information is stored following training, consists of synaptic consolidation and systems consolidation. It is widely acknowledged that sleep deprivation has a profound effect on synaptic consolidation, particularly for memories that require the hippocampus. It is unclear, however, which of the many molecular changes associated with sleep deprivation directly contribute to memory deficits. In this review, we highlight recent studies showing that sleep deprivation impairs hippocampal cAMP and mTOR signaling, and ultimately causes spine loss in CA1 neurons in a cofilin-dependent fashion. Reversing these molecular alterations made memory consolidation resistant to the negative impact of sleep deprivation. Together, these studies have started to identify the molecular underpinnings by which sleep deprivation impairs synaptic consolidation.

Introduction

Memory consolidation is the process of storing information in the brain after the initial acquisition. The consolidation of memories consists of two processes, synaptic consolidation and systems consolidation, both of which are modulated by sleep and sleep loss. Synaptic consolidation refers to the growth of new synaptic connections and restructuring of existing synaptic connections, a process that occurs in the first few hours following training. Systems consolidation is usually a slower process and refers to the gradual reorganization of the brain regions that support memory. In this review, we will focus on the molecular underpinnings of synaptic consolidation and highlight more recent studies aimed at defining which

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alterations in signaling processes are necessary and sufficient to cause the consolidation of hippocampal memories to go awry under conditions of sleep deprivation.

Sleep deprivation affects molecular signaling in the hippocampus that is important for synaptic plasticity

Learning induces a series of molecular events that together contribute to the consolidation of memories at the synaptic level. Calcium entry through NMDA receptors initiates a series of events, including the activation of calcium-dependent adenylate cyclases (Figure 1). The rise in intracellular cAMP levels then leads to the activation of the PKA signaling pathway and phosphorylation of the cyclic AMP-response element binding protein (CREB), a critical regulator of gene transcription [1,2]. Protein synthesis is also essential for long-term memory storage with translation initiation through mTOR signaling being the rate-limiting step [3,4] controlled by multiple signaling pathways[5]. Indeed, disrupting these signaling cascades attenuates memory consolidation for tasks that critically depend on the hippocampus [1,6,7] (Figure 1). It is important to note that temporal inhibition of cAMP-PKA signaling and translational processes is most effective during two specific windows in the first few hours following training [8] suggesting that the contribution of these signaling pathways to the process of synaptic consolidation is highly temporally regulated.

Interestingly, just like the aforementioned signaling events, sleep deprivation has the biggest impact on memory consolidation in the first few hours following training [9,10]. Indeed, even a brief 3-hour period of sleep deprivation commencing 1 hour after training impaired the formation of spatial memories [11]. This window corresponds with the second wave of cAMP signaling and protein synthesis which supports structural changes in neuronal connectivity [12] (Figure 2) and may relate to neuronal replay [13]. Such memory impairments due to a brief period of sleep deprivation cannot be attributed to sleepiness, as a 3-hour sleep deprivation period directly after training leaves memory consolidation undisturbed [11]. Further, even a delayed period of sleep deprivation (*i.e.* starting sleep deprivation at 5 hours following training) leaves memory consolidation undisturbed [9].

While these studies in rodents have helped to identify the time windows during which sleep deprivation affects memory consolidation, defining the signaling events that contribute to memory deficits has remained challenging. Even a brief period of sleep deprivation impacts a wealth of signaling events in the hippocampus including, transcriptional and translational processes [14,15], alterations in second messenger pathways such as the cAMP-PKA signaling pathway [16–18], glutamate receptor composition [19], and synaptic structure [17] (Figure 1). Sleep deprivation even affects gliotransmission [18,20], the release of transmitters from astrocytes (Figure 1). For an in-depth review about the pathways affected by sleep deprivation, see [21]. To directly relate the alterations in specific signaling events to deficits in memory and plasticity deficits caused by sleep deprivation, attempts have been made to modulate the affected molecular pathways in the hippocampus of sleep-deprived mice. We now describe some of these recent studies, which have identified some of the critical pathways impacted by sleep deprivation.

Phosphodiesterases cause memory deficits by degrading cAMP in the hippocampus of sleep-deprived mice

A few hours of sleep deprivation perturbs cAMP-dependent forms of synaptic plasticity such as long-lasting forms of long-term potentiation (LTP) and memory consolidation in tasks that require the hippocampus [8,16,22]. Bath application of hippocampal slices with the PDE4 inhibitor rolipram prevents these deficits in long-lasting forms of LTP in hippocampal area CA1 [16]. Likewise, systemic delivery of rolipram during sleep deprivation made the consolidation of contextual-fear memories resistant to the impact of sleep loss [16]. These observations raised two important questions. First, would restoring cAMP signaling selectively in hippocampal neurons prevent the long-term memory deficits caused by sleep deprivation? Second, which PDE4 isoform(s) contribute to the endophenotypes associated with sleep deprivation?

To transiently modulate cAMP levels selectively in hippocampal excitatory neurons, we used viral approaches to express G α s-coupled octopamine receptors from *Drosophila*, selectively in hippocampal excitatory neurons [22]. We found that transiently increasing cAMP levels in this subset of hippocampal neurons selectively during sleep deprivation was sufficient to prevent long-term deficits in object-location memories [22]. Because the formation of object-location memories critically depends on proper hippocampal function [23], these findings indicate that sleep deprivation leads to memory deficits by misregulating cAMP signaling in hippocampal excitatory neurons. Using biochemical assays, Vecsey *et al* [16] identified PDE4A5 as the only PDE4 isoform that was upregulated at the protein level in the hippocampus of sleep-deprived mice. This observation raised the intriguing question of whether the PDE4A5 isoform critically contributed to the endophenotypes associated with sleep deprivation. To address this question, a catalytically inactive version of PDE4A5 (PDE4A5^{catnul}), which targets the same complexes as endogenous PDE4A5 but does not degrade cAMP, was expressed in hippocampal excitatory neurons [17]. Mice expressing PDE4A5^{catnul} formed proper spatial memories regardless of sleep deprivation, suggesting that PDE4A5^{catnul} in hippocampal excitatory neurons preserved memory consolidation despite 5 hours of sleep deprivation [17]. The isoform-unique N-terminal domain of individual PDE isoforms orchestrates the targeting of a unique set of protein complexes and intracellular domains leading to the compartmentalized regulation of cAMP within the cell [24]. If PDE4A5 mediated its effects on memory and plasticity by targeting protein complexes through the isoform-unique N-terminal domain, then expression of a truncated form of PDE4A5^{catnul} lacking the N-terminal region should not prevent the memory deficits associated with sleep deprivation. If PDE4A5 exerts its effects through common targets that interact with other domains of the isoform, then expression of the N-terminal lacking PDE4A5^{catnul} should still prevent the memory impairments under conditions of sleep deprivation. Expression of a truncated form of PDE4A5^{catnul}, which lacked the isoform-unique localization domain, failed to prevent the memory deficits under conditions of sleep deprivation. These findings suggest that PDE4A5 targets a unique set of cAMP-containing complexes through its N-terminal domain that are critical for memory consolidation and susceptible to sleep loss. Consistent with these observations, overexpression of full-length wild-type PDE4A5 mimicked the long-term memory and synaptic plasticity deficits

associated with sleep deprivation [25]. Without the N-terminal unique domain, overexpression of the wild-type isoform failed to impact memory processes [25], further emphasizing the importance of the isoform unique N-terminal domain in the modulation of cAMP-dependent processes [24] critical for synaptic plasticity and memory.

Because these findings suggested that sleep deprivation attenuates cAMP signaling in a compartmentalized fashion, a critical question was which cAMP-dependent signaling processes were modulated by PDE4A5 and ultimately responsible for the endophenotypes associated with sleep deprivation. Identifying specific processes is challenging as the cAMP pathway modulates various neuronal processes, including the phosphorylation of GluA1-containing AMPA receptors and cAMP response element binding protein (CREB), both of which are affected by sleep deprivation [16,26–29] (Figure 1). A less well-known target of the cAMP-PKA signaling is LIM kinase (LIMK) which modulates spine dynamics through suppression of the filamentous actin-degrading protein cofilin [30] (Figure 1). We next describe recent work examining the mechanisms by which sleep deprivation affects structural plasticity and the role of cAMP signaling in this process.

Sleep deprivation attenuates the cAMP-PKA-LIMK pathway leading to spine loss in the hippocampus

Changing the number of dendritic spines and the efficacy of existing spines is an essential component of synaptic plasticity that can occur rapidly after training [31]. To assess whether sleep deprivation affected the LIMK-cofilin pathway in a PDE4A5-dependent fashion, we determined whether sleep deprivation reduced LIMK phosphorylation by PKA, with and without PDE4A5^{catnull} expression. Indeed, sleep deprivation attenuated LIMK phosphorylation by PKA and also reduced cofilin phosphorylation. Importantly, suppressing PDE4A5 function through PDE4A5^{catnull} expression normalized hippocampal LIMK and cofilin phosphorylation levels to those observed in non-sleep-deprived animals. Because reduced cofilin phosphorylation corresponds to high cofilin activity [32], and recent work revealed that sleep deprivation following learning leads to spine loss in the motor cortex [33], these findings raised the possibility that sleep deprivation causes spine loss in the hippocampus. Indeed, five hours of sleep deprivation affected the number of detectable dendritic spines of CA1 neurons [17], a finding in line with a previous study using a longer period of sleep deprivation [34]. Importantly, viral overexpression of an inactive version of cofilin (cofilin^{S3D}) selectively in hippocampal excitatory neurons not only prevented the sleep deprivation-induced spine loss in CA1 neurons, it also prevented deficits in a long-lasting form of LTP and the consolidation of spatial memories. Furthermore, expression of a constitutively active version of cofilin (cofilin^{S3A}) in hippocampal neurons was sufficient to mimic the spatial memory deficits that accompany sleep deprivation. Together these studies indicate that increased cofilin activity is necessary and sufficient to cause deficits in hippocampal memory consolidation. They also suggest that misregulation of cAMP signaling through the PDE4A5 isoform directly affects structural plasticity in the hippocampus. It should be noted, that the study does not exclude the possibility that sleep loss merely leads to spine shrinkage (*i.e.* partial retraction) rather than the absolute loss of the spines including the breakdown of the postsynaptic densities of mature spines. While

multiple days of sleep deprivation can reduce postsynaptic density 95 (PSD95) protein levels [35], to our knowledge it remains to be examined whether such changes also occur after a single brief period of sleep deprivation.

The synaptic homeostasis hypothesis for sleep function proposes that sleep acts to downscale synaptic strength that has accumulated as a result of neuronal activity during wakefulness [36]. The majority of hippocampal studies (for extensive review see [21]) and the work described in detail above suggest that the impact of sleep deprivation and sleep on the hippocampus is at odds with this theory. In fact, 3 hours of recovery sleep following sleep deprivation restores CA1 spine numbers to levels observed in non-sleep-deprived animals rather than decreasing them further as predicted by the theory. This discrepancy could be due to the fact that synaptic plasticity is highly prominent in the hippocampus relative to other brain regions or due to the existence of many distinct forms of synaptic plasticity that mediate hippocampal function. That being said, the hippocampus is not the only region at odds with the synaptic homeostasis hypothesis. Indeed, recent work suggests that both the visual cortex and motor cortex also do not always act in accordance with the sleep homeostasis hypothesis [33,37]. Altogether, it is important to realize that sleep deprivation has region- and cell-type specific effects rather than a uniform impact on the brain as a whole. To date it is unclear what causes these responses that contradict the sleep homeostasis hypothesis, but the origin may relate to changes in glutamate release during prolonged wakefulness [38] as proposed by the theory.

Sleep deprivation attenuates translational mechanisms through the mTORC1 pathway

Protein synthesis is essential for hippocampal synaptic plasticity and hippocampus-dependent long-term memory formation [3,4] with translation initiation being the rate-limiting step. The kinase complex mammalian target of rapamycin (mTOR) complex 1 (mTORC1) regulates protein synthesis through the inhibition of the eukaryotic translation initiation factor 4E-binding protein 2 (4EBP2). Because sleep modulates translational regulators [39], promotes protein synthesis in the rat and primate brain [40,41] as well as in the feline brain mediated by an mTORC1-dependent process [42], a critical question is whether sleep deprivation attenuates translational processes. Indeed, five hours of sleep deprivation reduces protein synthesis, and additional in depth biochemical analyses revealed that sleep deprivation attenuated mTORC1 signaling in the hippocampus [14,15].

To test whether the changes in mTORC1 signaling directly impacted memory consolidation, Tudor and colleagues [15] virally increased protein levels of 4EBP2 in hippocampal excitatory neurons *in vivo* before sleep deprivation. Increasing 4EBP2 protein levels restored hippocampal mTORC1 signaling in sleep-deprived mice and was sufficient to prevent memory deficits associated with sleep loss. These findings emphasize that dysregulation of translational processes in the hippocampus critically contributes to the memory deficits associated with sleep deprivation and complements previous work showing that sleep deprivation affects the translational processes in the visual cortex [42]. It is interesting to note that BMAL1, in addition to regulating transcription, also modulates translational

processes through the interactions with the mTOR pathway [43]. The latter does not exclude the possibility that sleep deprivation affects translational processes through misregulation of the circadian system.

Conclusion and future directions

The recent work highlighted in this review has started to provide a deeper understanding of the causal mechanisms that underlie the impact of sleep deprivation on synaptic consolidation, demonstrating that restoring one of the affected molecular pathways is sufficient to overcome the deficits. These observations, however, also raise further questions. For example, are the observed changes in structural plasticity and translational processes interrelated or are these processes affected by sleep deprivation in a parallel but independent fashion? What sets all of these molecular changes in motion? How do these molecular findings relate to the recent observation that theta activity during REM sleep plays a critical role in the consolidation of hippocampal memories [44]? And, finally, why is the hippocampus so susceptible to sleep deprivation? Addressing these questions may eventually not only lead to a better understanding of how sleep deprivation impacts the brain, it may also pave the way to better and more sophisticated pharmacological and therapeutic approaches to combat the negative impact of sleep deprivation on brain function, which is becoming ever more important in a society where social and economic demands create pressure to spend less and less time asleep.

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Highlights

Restoring hippocampal cAMP levels prevents sleep deprivation-induced memory deficits

Blocking hippocampal PDE4A5 function prevents memory deficits caused by sleep loss

Cofilin causes spine loss in CA1 neurons under conditions of sleep deprivation

Attenuating cofilin activity prevents sleep deprivation-induced memory impairments

Restoring hippocampal mTORC1 signaling prevents sleep loss-induced memory deficits

Figure 1. The molecular impact of sleep deprivation

A schematic overview of hippocampal signaling pathways whose modulation by sleep deprivation may contribute to effects on memory formation. Sleep deprivation has been reported to reduce glutamatergic signaling while increasing adenosine levels. Sleep deprivation also attenuates cAMP signaling, CREB-mediated gene transcription, translational processes through mTOR signaling, and structural plasticity through modulation of the PKA-LIMK-cofilin pathway. All of these molecular events are shown in a single connected pathway in order to demonstrate how the effects of sleep deprivation could potentially interact to impact learning and memory. Dashed black lines and blue arrows pointing down indicate attenuation of the signaling pathway. Red lines and upward pointing arrows indicate an increase of the signaling pathway.

Figure 2. Sleep deprivation affects hippocampus-dependent memory consolidation in a specific time window following training

Sleep deprivation has the biggest impact on hippocampal memory consolidation in the first few hours following training when it overlaps with the second wave of cAMP signaling, transcription, and protein synthesis critical for increasing synaptic efficacy and memory storage.