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Circadian Rhythms and Memory: Exploring the Mechanisms of Synaptic Plasticity, Hormonal Modulation, and Cognitive Function

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Abstract. Circadian rhythms influence memory formation, consolidation, and retrieval. The suprachiasmatic nucleus coordinates the internal circadian timing with external environmental signals, serve as the central pacemaker. This alignment influences the timing and efficiency of synaptic plasticity across various brain regions, particularly the hippocampus. Normal circadian regulation affects hippocampus-dependent processes such as long-term depression and long-term potentiation, contributing to time-of-day variations in memory consolidation. These activities are governed by core clock genes, which interact with signaling pathways like the cAMP-MAPK-CREB cascade. Additionally, circadian rhythms are modulated by hormones such as cortisol and melatonin, which help regulate sleep cycles and memory processing. Sleep deprivation or disruptions in circadian rhythms, like irregular light exposure, can impair cognitive function and hinder memory performance. Understanding the mechanisms linking circadian rhythms and memory could provide new treatment approaches for memory dysfunctions associated with disrupted circadian control.

Keywords: Circadian rhythms, memory formation, synaptic plasticity, clock genes.

1. Introduction

Memory is a vital cognitive function that enables organisms to recall and store information, supporting learning, decision-making, and adaptation to environmental changes. Memory formation involves a series of neurochemical stages includes encoding, consolidation, and retrieval. These processes are dynamic, intricately intertwined with anabolic and catabolic consumption, and are highly influenced both internally (via neural activity) and externally. Encoding is the process of converting sensory inputs, such as visual, auditory, olfactory, or tactile stimuli, into a neuronal format that can be stored in the brain. The strength of memory storage is influenced by factors like emotional importance, attention, and repetition [1,2]. During consolidation, the encoded information is organized and solidified in long-term memory, which helps protect it from interference or decay [3]. Sleep is vital for memory consolidation, as it relies on synaptic plasticity and neural connections, which are often strengthened during sleep [4,5]. Retrieval refers to the process of accessing and reactivating and repetition long-term storage stored information for use in cognitive tasks with its success depending on the proper activation of neural pathways, influenced by context and external conditions [6].

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Circadian rhythm controls a variety of behavioral and physiological activities in a 24-hour cycle, such as eating patterns, temperature regulation, and the secretion of hormones [7]. These rhythms allow organisms to adjust to changes in their environment by influencing internal mechanisms like exposure to light, food intake, and body temperature [8]. In the hypothalamus, the suprachiasmatic nucleus (SCN) acts as the primary circadian clock, communicates with different brain regions, including those related to memory, such as the hippocampus and amygdala [7]. Recent studies indicate that circadian rhythms influence memory functions, with the circadian clock potentially regulating the timing and accuracy of memory formation [9]. Disruptions caused by disturbed sleep (e.g., shift work, jet lag) or irregular light exposure can weaken circadian rhythms and lead to cognitive deficits [10]. While there is clear evidence of circadian timing's influence on memory, the exact mechanisms behind memory processes that vary depending on the time of day remain unknown. This paper examines the complex connection between circadian rhythms and memory, focusing on how the circadian clock affects cognitive functions

2. The role of circadian genes in memory

Intracellularly, circadian rhythms are controlled by a sophisticated molecular mechanism involving core clock genes and proteins. In mammals, it relies on the interaction between the circadian locomotor output cycles kaput (CLOCK)and brain and muscle ARNT-like(BMAL1) proteins, which form a heterodimer responsible for initiating the transcription of key genes such as period (PER) and cryptochrome (CRY) [11]. In the cytoplasm, accumulation of PER and CRY proteins to a certain threshold, leading to phosphorylation via casein kinase Iε (CKIε), resulting in heterodimer formation [12]. After heterodimer enters the nucleus, it attaches to and inhibits the transcriptional acitivity of CLOCK-BMAL1 complex and creates a negative feedback loop that regulates the production of these proteins [11].

2.1. PER gene

The PER gene was first identified as a key circadian rhythm regulator in *Drosophila melanogaster*, where mutations in *per* affected the timing of eclosion and locomotor rhythms. Studies indicate that *per* has important functions in memory formation across different species. Adult flies with *per0* mutants lose rhythmic activity and exhibit impaired long-term memory (LTM) in behavioral tasks like courtship conditioning [13]. This memory deficit can be rescued by re-expression of a functional *per* gene, with constitutive expression of *per* even enhancing LTM [13]. Mutations in CREB also reduce *per* gene expression and circadian behaviors, as well as the transcriptional activity of genes involved in memory in flies [14]. In mammals, data generated in recent years indicate that PER1 is fundamental in controlling memory-related hippocampal signaling pathways. Specifically, PER1 regulates cAMP response element-binding (CREB) protein phosphorylation in a time-of-day-dependent manner [15]. It is well established that the adenylyl cyclase-mediated circadian induction of CREB activity requires PER1 to form a kinase complex with pP90RSK for signaling [16]. Consistent with this, studies show that the *per* gene promoter in mice binds with CREB protein [17]. Altogether, the results suggest a possible functional collaboration between PER and CREB in regulating circadian rhythms in both flies and mammals. These mechanisms not only regulate circadian rhythms but also influence cognitive functions such as synaptic plasticity and memory formation, pointing to the dual role of these signaling pathways.

2.2. CRY gene

The CRY genes, particularly CRY1 and CRY2, plays an important role in the circadian rhythm system and have been found to affect numerous physiological functions, such as memory performance. Mice with a double knockout of Cry1 and Cry2 (Cry1−/−Cry2−/−) exhibit significant deficits in behaviors that depend on circadian timing, such as time-place learning. In these tasks, mice learn to associate certain locations with specific times of day in order to avoid an aversive stimulus (like a mild footshock) while seeking a food reward [18]. In contrast, wild-type mice are able to successfully form these time-place associations, highlighting CRY proteins'effect on linking the circadian clock to memory processes [18].

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Interestingly, the double knockout mice did not show impairments in general learning abilities. They performed normally on tasks that did not require temporal information. This suggests that CRY genes play a specific role in circadian-dependent memory tasks, rather than in overall cognitive function [18]. CRY proteins regulate memory formation by maintaining circadian-modulated hippocampal plasticity, a process essential for stabilizing long-term memories [18]. Without CRY proteins, this modulation is disrupted, impairing the mice's ability to use circadian cues to optimize memory retrieval and learning at certain times of the day [18]. The involvement of CRY1 and CRY2 in hippocampal time-place learning underscores their role in synchronizing memory formation with the body's internal clock, ensuring that cognitive processes are aligned with optimal physiological states throughout the day.

2.3. CLOCK and BMAL1 genes

Two of the most important genetic components contributing to the circadian regulation of memory storage are the *CLOCK* and *BMAL1* genes. They influence hippocampal-dependent tasks such as contextual fear conditioning and spatial memory. Studies on *Clock* mutant mice indicate that alterations in *CLOCK* activity result in impairments in tasks that depend on long-term potentiation (LTP) and synaptic plasticity, which are both necessary for memory consolidation [19]. The essential role of circadian regulation in these cognitive behaviors is emphasized by loss in spatial learning and memory retention observed in *Clock* knockout mice [19]. Similarly, *Bmal1* knockout mice display significant defects in memory consolidation tasks, such as contextual fear conditioning and novel object recognition, which are hippocampus-dependent [9]. *BMAL1* is also necessary for circadian regulation of signaling pathways important for synaptic plasticity, including cAMP and CREB phosphorylation, both of which are essential for memory formation [20]. *BMAL1* knockout experiments demonstrated the disruption of circadian oscillation in these pathways, resulting in impaired memory consolidation [21]. Together, *CLOCK* and *BMAL1* synchronize memory formation with the circadian clock, ensuring that cognitive processes occur at optimal times of the day. Their roles in regulating gene expression and signaling pathways involved in synaptic plasticity highlight their importance in maintaining cognitive health and memory function.

3. The role of hormones in memory

The central clock in the suprachiasmatic nucleus (SCN) in the hypothalamus, and additional peripheral oscillators distributed across other tissues, regulates the mammalian circadian rhythm in a hierarchical system [22]. The SCN synchronizes internal processes by interpreting environmental signals, such as light, through the retinohypothalamic tract (RHT) [7]. Intrinsically photosensitive retinal ganglion cells (ipRGCs) in the retina perceive light and transform it into electrical impulses.These signals are then sent via the RHT to the SCN, where they regulate circadian rhythms across the body [23,24].

In this context, melanopsin, a photopigment present in ipRGCs, is essential to circadian rhythms and influences memory in two key ways: by directly modulating neurophysiological processes and through indirect pathways involving hormonal regulation and sleep cycles. Melanopsin directly regulates circadian light input, which can influence hippocampal activity. In particular, hippocampal-dependent tasks are highly sensitive to circadian timing, significantly affecting spatial memory and contextual learning [25]. Disruptions in light exposure or irregular light cycles have been shown to impair hippocampal function, affecting long-term potentiation (LTP), the primary mechanism underlying synaptic plasticity and memory storage [26]. The indirect effects of melanopsin on memory occur largely through its regulation of hormonal cycles and its influence on sleep, which is crucial for memory consolidation.

After photic signals reach the SCN, they are relayed through the subparaventricular zone (sPVz) to other hypothalamic regions involved in sleep-wake regulation, including the dorsomedial hypothalamus (DMH), lateral septum (LSep), ventrolateral preoptic area (VLPO), dorsal raphe nucleus (DRN), lateral hypothalamus (LH), and paraventricular nucleus (PVN) [27]. Key brain regions involved in memory formation, such as the hippocampus and amygdala, do not receive direct projections from the SCN.

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Instead, they are influenced by circadian regulation through intermediary pathways or hormonal signaling [24,28].

The temporal organization of behavioral and cognitive functions is linked to synchronized hormonal fluctuations, optimizing memory formation and synaptic plasticity at specific times of day. This suggests that circadian rhythms play a crucial role in regulating long-term potentiation. This intricate system highlights how circadian rhythms help coordinate various biological and cognitive functions in the body.

3.1. Cortisol

Cortisol, a glucocorticoid hormone, follows a robust circadian rhythm, peaking shortly after awakening and gradually declining throughout the day[29-30]. The SCN organizes this rhythmic pattern of cortisol release, ensuring that cortisol secretion is closely aligned with the day-night cycle[31]. The SCN regulates the hypothalamus, which releases corticotropin-releasing hormone (CRH), activating the hypothalamic-pituitary-adrenal (HPA) axis and causing the adrenal cortex to release cortisol.This rhythmic cortisol release prepares the body for the day's demands and helps regulate cognitive processes, particularly memory[32].

Cortisol's impact on memory differs based on its levels, the timing of exposure, and the particular memory process affected. Moderate cortisol levels, particularly in the morning are associated with improved retrieval of emotionally salient stimuli. Laboratory studies have shown that individuals with elevated morning cortisol levels generally perform better on memory tasks, particularly those involving emotional content, compared to those tested in the evening[33]. This enhancement is thought to result from cortisol's influence on attention and emotional processing during heightened arousal, thereby facilitating memory recall.On the other hand, elevated cortisol levels—often induced by stress—can impair hippocampal-dependent memory retrieval, particularly for spatial and episodic memories[34]. Studies have consistently shown that cortisol administered prior to a memory task significantly reduces recall accuracy. For instance, experimental studies have demonstrated that cortisol administration before retrieval impairs memory performance, with participants performing nearly half a standard deviation below placebo controls. The damaging effects are especially pronounced 25-90 minutes after stress stimulation when cortisol levels peak. This aligns with research showing that stress exposure leading to high cortisol levels diminishes hippocampal neuron responsiveness, thereby impairing processes such as memory retrieval and emotional memory consolidation[35].

Interestingly, cortisol's effect on memory retrieval is region-specific within the brain. Notably, hippocampal-dependent memories (e.g., episodic and spatial memories) are more affected by cortisol fluctuations than perirhinal cortex-dependent memories, which underlie familiarity-based recognition[36-37]. This region-specificity is due to variations in receptor distribution and the intricate interactions between the circadian clock and HPA axis. Beyond its negative effects on memory retrieval, the fluctuations in cortisol levels throughout the day are also significant. Wolf (2017) emphasized that in healthy young adults, there is a rapid increase in cortisol levels right after waking up, referred to as the cortisol awakening response (CAR). This is linked to better working memory and episodic memory retrieval. This underscores the importance of circadian rhythms and diurnal fluctuations in stress hormone function concerning cognitive performance[38]. Together, these results support the idea that moderate morning cortisol concentrations facilitate memory consolidation and retrieval while high levels of cortisol related to hippocampal dysfunction impair these processes.

3.2. Melatonin

All mammals produce melatonin in the pineal gland, using the amino acid tryptophan as a precursor. Melatonin has a half-life of less than 30 minutes and is released into the bloodstream immediately after production. Its production follows a circadian pattern, with higher levels synthesized at night and lower levels present in the plasma, blood, and other bodily fluids during the day[39]. After circulating in the body, melatonin is metabolized either in the liver or within the central nervous system (CNS), where it is converted into N1-acetyl-N2-5-methoxykynuramine (AFMK), a kynuramine derivative of melatonin [40]. These metabolic pathways and its rapid processing allow melatonin to be efficiently utilized and

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cleared by the body. Melatonin is able to pass through all cell membranes, including the blood-brain barrier, as it is a small, lipophilic molecule [12]. This property allows it to exert its effects throughout the body, particularly in brain regions with high concentrations of melatonin receptors, including the prefrontal cortex and hippocampus, both of which are essential for memory, are key targets. By interacting with these regions, melatonin has been associated with the regulation of cognitive processes, such as learning and memory.

Melanopsin regulates the suppression of melatonin during daylight in humans after light exposure, helping to maintain the sleep-wake cycle and support memory consolidation. For example, disruption of light exposure to disrupt melanopsin signaling is shown to impair memory related processes like memory retrieval and spatial learning. Research also shows that melatonin's effects on the hippocampus are time dependent. Studies using functional MRI have revealed that memory-related activity in the hippocampus fluctuates with endogenous melatonin levels [7]. For instance, at night (when melatonin levels are naturally higher), activation in the hippocampus is reduced compared to afternoon levels, indicating a circadian rhythm in hippocampal responsiveness. This reduction in hippocampal activity correlates with melatonin levels, suggesting that melatonin's influence on memory is maximized when its endogenous levels are highest, during the evening and night[25]. Additionally, the presence of melatonin receptors in the hippocampus, as well as its ability to modulate synaptic plasticity, further emphasizes its critical role in memory function [32].

Melatonin's anti-phase relationship with memory performance in circadian regulation is consistent across both diurnal and nocturnal species. Lower melatonin levels are associated with higher performance in memory tasks for both nocturnal and diurnal species across vertebrates and several invertebrate groups. For example, in diurnal species such as zebrafish (*Danio rerio*), learning and memory formation are enhanced during their active phase (daytime)[18]. In contrast, in nocturnal species like the fruit fly and the mouse, memory performance reaches its peak during the inactive phase (nighttime) of their circadian rhythm, indicating that species-specific activity patterns play an adaptive role in determining the optimal timing for memory processin[12-13]. These findings highlight the intricate relationship between circadian rhythms, melatonin secretion, and memory consolidation across various organisms.

4. Synaptic plasticity

Synaptic plasticity describes the brain's capacity to modify the strength of synaptic connections in response to previous neural activity. This plasticity provides the underpinnings of memory, learning, and cognitive flexibility [8]. Long-term potentiation (LTP) and long-term depression (LTD) are the primary types of synaptic plasticity. LTP enhances synaptic connections, improving communication between neurons, whereas LTD diminishes synaptic efficiency, helping to regulate synaptic activity and avoid network overload [5].

4.1. LTP

LTP refers to the sustained increase in synaptic strength following repeated stimulation of a synapse. It is triggered by the activation of NMDA(N-methyl-D-aspartate) receptors, leading to calcium ion influx into the postsynaptic neuron, which activates cAMP/PKA and MAPK signaling pathways and ultimately phosphorylates CREB, promoting the recruitment of AMPA receptors and triggers the transcription of genes necessary for the structural growth and synaptic stabilization. LTP is crucial for memory encoding and consolidation, enhancing synaptic transmission and the efficiency of neural circuits involved in specific memories[6]. Synaptic changes induced by LTP are fundamental to hippocampus-dependent memories, such as spatial learning and episodic memory. Studies show that blocking LTP in the hippocampus impairs spatial learning and memory consolidation, highlighting its role in maintaining long-term memory[10].

LTP is among the most extensively studied forms of synaptic plasticity and is considered essential for the consolidation of memories. By strengthening the synapses involved in a specific memory, LTP enables neural circuits to be more efficiently activated during repeated use. It enhances the postsynaptic

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cell's response to future stimuli by increasing both the sensitivity and the quantity of AMPA receptors on the postsynaptic membrane, thus enhancing memory retrieval. These synaptic changes are thought to underlie hippocampus-dependent memories, including spatial learning and episodic memory, with LTP serving as a key cellular mechanism for information storage[8].

Studies have shown that inhibiting LTP negatively affects spatial learning and memory consolidation associated with the hippocampus. Blocking NMDA receptors, which prevents LTP, results in impaired performance in the Morris water maze, a task that relies on spatial memory. Moreover, mice with mutations in critical signaling molecules necessary for LTP, like CREB, exhibit impairments in long-term memory while short-term memory remains unaffected, emphasizing LTP's distinct function in the stabilization and retention of long-term memories.

4.2. LTD

LTD involves a prolonged decrease in synaptic efficiency triggered by low-frequency stimulation, acting as a counterpart to LTP by diminishing synaptic strength. It usually arises after partial activation of NMDA receptors, leading to a moderate calcium ion influx. LTD is essential for preventing synaptic saturation, ensuring flexibility within the neural network, and is involved in memory modification processes such as forgetting and extinction[9]. LTD also plays a key role in fine-tuning synaptic connections during associative learning and fear conditioning .

LTD is crucial for preventing synaptic overload by weakening inactive or redundant synapses, thereby maintaining neural network flexibility and allowing the formation of new memories. It also plays a significant role in memory modification processes, such as extinction and forgetting, where previously established memories are selectively weakened. Moreover, studies have shown that LTD is involved in fine-tuning synaptic connections during fear conditioning and associative learning.

4.3. Circadian modulation of LTP and LTD

LTP is modulated by circadian rhythms, with time-of-day variations observed across different species and hippocampal subregions. In rodent models, such as rats, hamsters, and mice, LTP follows a time-of-day pattern that aligns with the animal's diurnal or nocturnal activity [31]. For instance, in rats, LTP in the dentate gyrus is more prominent during the dark phase, whereas in the CA1 region, it is more pronounced during the light phase. Similarly, LTP in the SCN is stronger during the day than at night, demonstrating that circadian effects on synaptic plasticity vary by species and brain region.

In hamsters, LTP is most pronounced when hippocampal tissue is collected during the light phase and assessed in the dark phase, demonstrating a direct circadian effect on synaptic plasticity, even in isolated tissues. This metaplastic regulation of LTP, where previous conditions affect plasticity, has been observed in several rodent species. For example, nocturnal mice show decreased LTP in the CA1 region during the light phase but exhibit enhanced LTP when hippocampal tissues are collected in the light phase and tested during the dark phase. These results highlight the importance of internal circadian oscillators in controlling synaptic plasticity, even in the absence of external environmental signals.

5. The cAMP-MAPK-CREB pathway

The cAMP-MAPK-CREB signaling pathway is crucial for the consolidation of long-term memory, particularly in the hippocampus, a brain region central to learning. This pathway is activated by the production of cAMP, which sets off a cascade by activating protein kinase A (PKA). PKA then initiates the MAPK (Mitogen-Activated Protein Kinase) pathway, ultimately leading to the phosphorylation of the transcription factor CREB. Upon phosphorylation, CREB attaches to specific DNA sequences, driving the transcription of genes essential for synaptic plasticity and memory formation. This pathway is highly influenced by circadian rhythms, with its activity fluctuating throughout the day. Research shows that the cAMP-MAPK-CREB pathway is most active during the day, suggesting that the body's internal clock optimizes memory consolidation at certain times. Additionally, this pathway shows increased activity during REM sleep, a phase essential for memory consolidation [9]. The alignment of circadian rhythms with REM sleep enhances memory retention, as key molecular processes like gene

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transcription and protein synthesis occur at their peak during this time [9]. Disruption of this pathway, particularly during REM sleep or misalignment of circadian rhythms, can impair hippocampus-dependent memories consolidation, underscoring the importance of this pathway in both sleep and memory function.

6. Conclusion

This review emphasizes the profound impact circadian rhythms have on memory processes such as formation, consolidation, and retrieval, which are regulated by key clock genes including PER, CRY, CLOCK, and BMAL1. Disruptions to corcadoam rhythms, usually caused by factors like sleep deprivation or irregular work schedules, can negatively affect memory function. Circadian rhythms are key in regulating sleep timing and quality, which subsequently affect synaptic plasticity and the consolidation of memories. Deepening our knowledge of the molecular pathways linking circadian rhythms and memory could lead to novel therapies for cognitive impairments associated with circadian disturbances. Continued research in this area is vital for enhancing cognitive health and improving memory function in both clinical and everyday contexts.

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