

Influences of Circadian Rhythm on Memory Formation and Underlying Neuronal Regulatory Mechanisms

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Abstract. Circadian Rhythm disruption in modern society damages the hippocampus and leads to memory loss. However, the existing interventions for the central clock have not restored hippocampal rhythms and cognition. Therefore, this paper systematically summarizes the neural circuits and molecular feedback loops of the mammalian circadian system, analyzes the regulatory effects of environmental zeitgebers on central and peripheral rhythm entrainment, and elaborates the multi-layer mechanisms of memory impairment mediated by reduced hippocampal neurogenesis, disrupted synaptic plasticity and epigenetic dysregulation of clock genes. REV-ERB α (nuclear receptor subfamily 1 group D member 1, NR1D1) is a required molecular hub that coordinates the regulation of circadian rhythms and neural function and whole-body metabolism, according to a second proposal. This paper presents an organised theoretical system for the study of circadian regulation of memory and offers a reference for screening intervention targets in rhythm-related cognitive disorders. Research will be conducted on hippocampus-specific targeting strategies to improve the therapeutic effect of circadian rhythm disorders for memory next.

Keywords: Circadian rhythm, Memory, Hippocampus, REV-ERB α , Neural regulatory mechanism

1. Introduction

Endogenous circadian rhythms are evolutionarily conserved biological adaptations found in almost all eukaryotes that align internal physiological activities with the 24-hour cycle of sunlight on Earth. The mammalian circadian system is a multi-oscillator, hierarchical organisation system. Rhythms are produced by the cooperation of a central pacemaker and behaviourally induced rhythms.

Physiological and Gene Expression in Peripheral Tissues [1]. Functionally, the master pacemaker in the suprachiasmatic nucleus (SCN) regulates the downstream hypothalamic network of the subparaventricular zone (SPZ) and dorsomedial hypothalamus (DMH) to drive rhythmic glucocorticoid secretion via the hypothalamic-pituitary-adrenal (HPA) axis, and thus connects central circadian signals with hippocampal memory function [2]. At the molecular level, cell-autonomous circadian oscillations are driven by a conserved transcriptional-translational feedback loop: CLOCK-BMAL1 heterodimers activate the expression of Period and Cryptochrome genes, and their protein products subsequently inhibit CLOCK-BMAL1 activity to generate ~24-hour rhythms of clock-controlled gene expression in various tissues.

Circadian rhythms are the rhythms of life for all living things, and they affect the body and behaviour of people in different ways. Nowadays, young people are often too tired from studying or working late, or they sleep in. Memory loss due to the above circadian rhythm disorder is a relatively frequent problem. Adolescents are a particularly vulnerable group; social jet lag is widespread among this group, and chronic circadian disruption during this stage of development leads to deficiencies in spatial memory, short-term object recognition and social memory, as well as abnormal oscillations of clock genes and synaptic plasticity-related molecules in the hippocampus [3].

It has been confirmed that the Circadian Rhythm System is related to health and disease. In 2007, the International Agency for Research on Cancer (IARC) designated shift work that disrupts the body's circadian rhythm as possibly carcinogenic to people. Circadian Rhythm disturbances can also cause damage to the hippocampus and change gene expression [3].

Researchers have identified several factors affecting the neurons in the hippocampus and regulating hormone release that have been exposed to light cycles and sleep rhythms to date [3]. Disruption of circadian rhythms is associated with altered function and other traits of the hippocampus in memory. At present, the interventions to address circadian misalignment and related memory impairment generally include timed bright-light exposure, sleep time adjustment and melatonin supplementation. However, the above strategies have shown limited practical effectiveness; they mainly aim to regulate the central SCN pacemaker but often fail to restore synchrony in peripheral clocks of the hippocampus and cannot fully alleviate cognitive impairments caused by chronic circadian disruption.

The purpose of this paper is to introduce the regulatory system for circadian rhythms, examine in detail the effects and changes in memory that occur due to non-circadian factors such as sleep and wakefulness at the neurological and physiological levels, and put forward countermeasures to regulate circadian rhythms and mitigate memory decline caused by circadian disruption. To find effective countermeasures, all potential causes and how they occur need to be identified first, and then an all-around investigation should be conducted.

2. Neural regulatory mechanisms of circadian rhythms

2.1. Environmental factors affecting circadian rhythms

The mammalian circadian system is generally entrained to the 24-hour cycle of the external world by time-givers, and among these, the light-dark (LD) cycle is the most common [4, 5]. Light signals are recognised by intrinsically photosensitive retinal ganglion cells in the retina and then transmitted directly to the central pacemaker via the retinohypothalamic tract [1]. In addition to light, feeding-fasting cycles are also strong synchronisers for peripheral circadian clocks in metabolically active tissues; thus, if misaligned with the central pacemaker, they can be desynchronised. Many methods for causing controlled circadian disruption in experiments include constant light exposure, repeated phase shifts and non-24-hour light-dark cycles [6].

Light-dark cycles, feeding behaviour and other external time-givers work together to coordinate the entrainment of both central and peripheral circadian clocks, and thus organise all sorts of bodily and brain functions in time. Based on the accumulation of evidence, interruptions in these environmental time-signalings and the resulting circadian dysregulation may spread to damage the central pacemaker and other neural circuits, thereby altering learning and memory.

2.2. Neural circuits and molecular mechanisms of circadian regulation

The Suprachiasmatic Nucleus (SCN) in the hypothalamus is considered the main clock in the mammalian circadian system, and other clocks in the body are regulated by it.

Circadian rhythms at the molecular level are caused by interconnected transcriptional-translational feedback loops. The positive regulator CLOCK and BMAL1 heterodimerize to bind to E-box motifs in the promoters of Period (*Per1/2/3*) and Cryptochrome (*Cry1/2*) genes to promote their expression. PER and CRY proteins accumulate in the cytoplasm, form a complex, translocate to the nucleus, and inhibit CLOCK/BMAL1-mediated transcription by closing a negative feedback loop. Additional regulatory loops involving REV-ERB (reverse erythroblastosis virus-related) and ROR (retinoic acid receptor-related orphan receptor) nuclear receptors modulate *Bmal1* expression and stabilize the oscillator [1].

Circadian Signals are transmitted to the lower brain areas by different neural pathways. The hippocampus is not directly innervated by the SCN with circadian signals; instead, they are transmitted through the medial septum via GABAergic signalling and cholinergic networks. This Septo-hippocampal connection is required for memory formation. SCN regulates the HPA axis through the paraventricular nucleus to promote cyclical secretion of glucocorticoids and thus alter clock gene expression and synaptic function in both the hypothalamus and hippocampus [3]. Clock genes are expressed in an organised manner in the suprachiasmatic nucleus (SCN) and many other parts of the brain, such as the hippocampus, and they also regulate local processes such as synaptic plasticity and neurogenesis.

2.3. Etiology of circadian disruption

Circadian disruption is the state in which a person's body clock fails to synchronize with the external environment or when oscillators in different tissues become uncoordinated. An acute disorder of jet lag caused by cross-meridian travel is generally short-lived and reversible; the circadian system will gradually re-synchronise with the new environment. Chronic circadian disruption, on the other hand, is caused by prolonged exposure to misalignment, such as rotating night-shift work, irregular sleep patterns, and persistent social jetlag in adolescents and adults [5].

Circadian rhythm disturbances in experimental animals can be induced by various ways, such as repeated phase shifts of the light-dark (LD) cycle to simulate jet lag, inversion of the LD cycle to mimic shift work, non-24-hour LD cycles, and constant light exposure. Constant light exposure abolishes cyclic LD cues and impairs hippocampal neurogenesis and spatial memory in mice, for example [6]. Chronic sleep restriction and delayed sleep-wake cycles also disrupt circadian gene expression in peripheral tissues and the brain significantly, even when the SCN pacemaker is relatively undisturbed [1]. Adolescence is a high-risk period for development; continuous phase shifts in this stage (youth jet lag) cause prolonged changes in clock gene expression and cognition [3].

Together, both acute and chronic circadian misalignment due to lifestyle factors and standardised experimental conditions have repeatedly disrupted clock gene expression and internal synchronisation in the central nervous system and peripheral tissues. In particular, an increased susceptibility of the hippocampus to circadian disruption provides an additional route for damage to the circadian timing system to cause prolonged impairment of learning and memory and other cognitive functions.

3. Effects of circadian rhythms on memory

3.1. Physiological functions of circadian rhythms

The circadian system keeps most changes in the body during a 24-hour period regulated, such as the sleep-wake cycle, hormone release and energy utilisation, immune defence, etc [1]. Synchronised circadian rhythms of all organs in the body help to maintain a state of homeostasis; a disturbance in this coordination can cause severe diseases such as metabolic syndrome, weakened immunity and cognitive decline.

Circadian Rhythms in the Central Nervous System regulate all cell- and organ-level processes of memory. First, the genes for core clocks show strong circadian rhythms in the hippocampus; this area is required for space and explicit memory. These local hippocampal clocks drive the rhythmic expression of genes involved in synaptic function, such as those for glutamate receptors, BDNF/TrkB neurotrophic signalling components and endocannabinoid system mediators, and together regulate long-term potentiation (LTP), a core cellular mechanism of memory formation [3].

Second, hippocampal neurogenesis in the dentate gyrus exhibits circadian rhythmicity under normal LD conditions; disruption of this rhythmicity by constant light reduces neural progenitor cell proliferation and impairs spatial learning [6]. Thirdly, circadian regulation of dendritic spine morphology in the subregions of the hippocampus provides the dynamic synaptic alteration necessary for memory encoding and consolidation. Notably, both the extent of LTP and behavioural memory performance differ under light-dark cycle conditions, and thus circadian timing directly impacts mnemonic processing [3].

Together, the circadian system regulates the hippocampus at multiple levels, including transcriptional oscillations of core clock genes and synaptic signalling molecules, as well as rhythmic adult neurogenesis and daily remodelling of dendritic spine morphology.

In cooperation, these coordinated cellular rhythms regulate the induction of long-term potentiation and affect the efficiency of memory encoding and consolidation; thus, an undisturbed circadian system is required for normal memory function.

3.2. Ion channel-mediated excitability rhythms in the SCN circadian clock

The suprachiasmatic nucleus (SCN) in the brain of mammals serves as the master clock to produce stable approximately 24-hour rhythms of spontaneous action potential firing that regulate all parts of circadian behaviour and coordinate peripheral clocks. Although the core transcriptional-translational feedback loops (TTFLs) can be used to regulate gene expression over time, dynamic and state-dependent changes in ion channel function are required to generate rhythmic electrical signals. Among these ion channels, large-conductance Ca^{2+} - and voltage-activated K^+ (BK) channels are typical effectors that regulate the diurnal cycle of SCN neuronal excitability [7].

BK channel currents in SCN neurons show a distinct day-night difference: the size of the steady-state BK current is relatively small during the day and larger at night; thus, the firing frequency is lower in the daytime and more easily excited at night. The reason for this rhythm is that N-type BK channels are inhibited by the auxiliary $\beta 2$ subunit. Most of the SCN BK currents are rapidly inactivated during the day (known as BK_i currents); an N-terminal "ball-and-chain" domain of the $\beta 2$ subunit closes the channel pore shortly after opening and thus reduces steady-state K^+ conductance. BK currents are non-inactivating sustained currents at night; they cause large outward K^+ currents that inhibit action potential generation. Genetic deletion of the $\beta 2$ subunit eliminates all BK_i currents in SCN neurons, abolishes the diurnal difference in BK current density, and

significantly reduces the circadian amplitude of SCN circuit-level firing. On the other hand, intracellular delivery of the isolated $\beta 2$ N-terminal peptide is sufficient to restore inactivation, rescue daytime BK current levels, and reinstate normal daytime firing rates in $\beta 2$ knockout neurons; thus, inactivation gating per se—rather than other gating properties of the full $\beta 2$ subunit—drives the diurnal switch in excitability [7].

BK inactivation alters the subthreshold membrane properties of SCN neurons and changes the daytime "upshift" caused by a modification in peak current amplitude. Neurons that express BK currents have more depolarised resting membrane potentials and a higher input resistance than neurons without BK currents because inactivation closes subthreshold BK conductance that would otherwise hyperpolarise the membrane and shunt excitatory drive. The change in passive membrane properties is closer to the action potential threshold, and thus the high-frequency spontaneous firing of daytime SCN neurons can occur. At the behaviour level, $\beta 2$ knockout mice have reduced amplitude of circadian rhythm in locomotor activity, faster re-entrainment to phase shifts of the light-dark cycle, and enhanced phase resetting in response to nocturnal light pulses; thus, BK channel inactivation is a cellular mechanism that directly affects organismal circadian rhythmicity. In short, the above results have identified ion channel inactivation gating as a biophysical switch that converts molecular clock signals into rhythmic electrical output in the SCN and provides a fundamental link between the core clockwork and neural circuit function and behaviour.

3.3. Epigenetic regulation of circadian clock genes in hippocampal memory processing

Although the SCN regulates the circadian rhythm of the entire body, local expressions of key clock genes in the memory region of the brain, such as the hippocampus, can have cell-autonomous effects on cognition independently of the central pacemaker. Epigenetic modifications to histone acetylation have been identified as one of the regulatory factors affecting age-related changes in hippocampal clock gene expression and memory [8].

Histone deacetylase 3 (HDAC3) is a strong transcriptional repressor that removes acetyl groups from histone tails to condense chromatin; thus, it serves as a negative regulator of long-term memory formation and synaptic plasticity in the hippocampus.

Dysregulation of HDAC3 in older animals results in a more repressive chromatin structure that suppresses gene expression induced by experience and thus causes age-related cognitive decline.

Among the genes directly targeted by HDAC3 in the hippocampus is the core circadian clock gene *Period1* (*Per1*). In young mice, hippocampus-dependent learning tasks, such as object location memory (OLM) training, rapidly increase the expression of *Per1* in the dorsal hippocampus, but this experience-dependent induction is lost in aged animals. Genetic deletion or enzymatic inhibition of HDAC3 restores *Per1* expression by increasing acetylation of histone H4 at lysine 8 (H4K8Ac) in the promoter region of *Per1*, and this molecular rescue is associated with the amelioration of age-related deficits in long-term memory and long-term potentiation (LTP) at Schaffer collateral-CA1 synapses [8].

Per1 from the hippocampus is a memory-modulating gene that does not follow the circadian rhythm. Focal manipulation of HDAC3 or *Per1* in the dorsal hippocampus does not change the circadian locomotor activity pattern; therefore, the cognitive improvement observed is likely due to local clock gene function rather than global circadian disruption.

Direct evidence for a local, memory-relevant role of *Per1* comes from targeted loss- and gain-of-function experiments: siRNA-mediated knockdown of *Per1* selectively in the dorsal hippocampus impairs long-term OLM in young mice, and viral overexpression of *Per1*—either through lentiviral cDNA delivery or CRISPR/dCas9-mediated transcriptional activation—rescues age-related memory

deficits in aged mice. At the level of signalling, PER1 is proposed to gate memory consolidation by regulating the nuclear translocation of p90RSK and subsequent phosphorylation of the transcription factor CREB, a master regulator of activity-dependent gene expression required for long-term memory formation [8].

Therefore, the circadian effect on memory may not be solely due to the output of the SCN. Instead, they support a model of epigenetically regulated expression of local clock genes in the hippocampus to provide a cell-autonomous mechanism for gating memory formation during the day-night cycle. Age-related dysregulation of HDAC3-mediated repression of *Per1* is thus a molecular link between circadian dysfunction and cognitive decline in ageing, and epigenetic modulators and hippocampal clock genes have been identified as potential therapeutic targets for age-associated memory impairment.

4. Therapeutic approaches targeting REV-ERB α

REV-ERB α is one of the necessary components of the circadian regulatory system in the nucleus, and at the same time, it also functions as a tissue-specific transcription factor that links circadian rhythm to all sorts of other physiological functions, such as metabolism, cognition and emotion [9]. As a heme-sensing transcriptional repressor, REV-ERB α binds to RORE DNA elements in the promoters of target genes and recruits the NCoR-HDAC3 corepressor complex to repress transcription. REV-ERB α directly represses *Bmal1* and *Clock* expression in the core clock circuitry, forms a stabilizing secondary feedback loop, and thus enhances the robustness of the primary PER/CRY-based TTFL. REV-ERB α has many other targets in the body besides the core clock and is responsible for regulating many other output pathways to integrate circadian and systemic information.

REV-ERB α modulates various regions of neural function in the brain outside of SCN pacemaking. Genetic ablation of *Rev-erb α* causes dysregulation of dopamine turnover in the midbrain, deficits in hippocampal-dependent memory formation, and an increased anxiety-like behaviour. Pharmacological activation of REV-ERB with synthetic agonists reduces anxiety-like behaviour in rodents, and thus this pathway is also a target for treating neuropsychiatric disorders [9].

REV-ERB α has many functions in the peripheral metabolic tissues and includes inhibiting *Ucp1* expression to reduce thermogenesis in brown adipose tissue during rest, promoting a rapid decrease in REV-ERB α protein levels after cold exposure to enhance a thermogenic response, regulating lipid homeostasis by repressing *Lpl* in white adipose tissue and skeletal muscle to adjust fatty acid uptake and oxidation capacity, and regulating the circadian rhythm of lipogenesis, cholesterol metabolism, and bile acid synthesis through target genes such as *Srebf1*, *Fasn*, and *Cyp7a1* in the liver.

The development of synthetic REV-ERB agonists, such as SR9009 and SR9011, has facilitated in vivo pharmacological dissection of REV-ERB function and provided a proof-of-concept for therapeutic targeting of the circadian clock [10]. Systemic administration of these compounds changes the circadian locomotor behaviour, reduces the amplitude of SCN *per2* bioluminescence oscillations, and alters the circadian expression pattern of core clock genes in the hypothalamus. REV-ERB agonists increase whole-body energy expenditure by upregulating fatty acid and glucose oxidation in skeletal muscle, reduce hepatic lipogenesis and cholesterol synthesis, and decrease triglyceride storage in white adipose tissue metabolically. Chronic administration of REV-ERB agonists decreases fat mass and ameliorates dyslipidaemia and blood glucose/insulin levels in diet-induced obese mice without reducing food intake. Given the above metabolic benefits and the

capacity to regulate circadian behaviour, REV-ERB ligands are now being explored as new treatment options for metabolic diseases, sleep disorders and jet lag.

REV-ERB α is also a sensor of the metabolic status of cells, and its repressive function is regulated by endogenously produced ligand heme; thus, under different conditions in the cell, its amount will be different. Metabolic gating is used to align the circadian gene expression programme with nutrient status, and thus energy conservation and storage are temporally regulated. REV-ERB α has two roles that make it suitable for acting as a master clock and tissue-specific metabolic regulator; thus, it likely regulates the circadian rhythm, neuronal function and whole-body metabolism at the molecular level.

5. Conclusion

In conclusion, Circadian rhythms function to organise time in most of the body's physiology and neurons, and prolonged disruption of these rhythms due to modern life has been identified as a general risk factor for hippocampal-dependent memory decline. Many studies have shown a hierarchy of circadian systems and their cognitive effects; however, the exact way in which desynchronisation of the central and peripheral clocks leads to memory loss remains unknown, and practical prevention and management strategies for chronic rhythm-related cognitive decline have not been proposed.

The current research has identified several components in the study of circadian rhythms that influence memory, such as altered ion-channel-dependent neuronal-excitability rhythms, epigenetic regulation of local hippocampal clock genes, and changes in systemic glucocorticoid signalling pathways. REV-ERB α is a molecular centre that regulates the circadian clock and neuronal plasticity and metabolism.

This work provides all-encompassing mechanistic support for the development of chronotherapy in memory preservation. In the future, one will explore the translational path of the candidate molecular target and build tissue-specific intervention strategies to mitigate memory impairment caused by chronic circadian rhythm disorders.

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