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What Role do Circadian Rhythms Play in Learning and Memory?

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Abstract

Circadian rhythmicity in gene expression and physiological process has been observed both in the central nervous system and in the periphery, including the hippocampus. As a center for memory formation and storage, the hippocampus shows circadian rhythmicity in clock gene expression and synaptic plasticity. Circadian variation in performance of hippocampus-dependent memory task suggests a link between clock gene oscillation and behavioral response. Yet the discrepancy in time scale between fast information encoding during memory acquisition and much slower circadian oscillation in cellular processes casts doubt on the underlying mechanism of circadian regulation of learning and memory. This short review suggests that instead of being a modulator of learning process and memory formation, the time-of-day information itself could be integrated as a component of episodic memory for later consolidation and retrieval.

Keywords: Circadian rhythm; Suprachiasmatic nucleus; Learning; Memory; Hippocampus

Introduction

Circadian rhythms are basic biological phenomena conserved in a variety of organisms. Endogenous circadian oscillators modulate a range of physiological and behavioral activities observed throughout phylogeny. Animals need intact learning ability and well-maintained memory to survive varying environmental conditions. However, the relationship between circadian rhythm biology and memory formation is far from well understood. This short review first summarizes the basic organization and functionality of circadian machineries in the central nervous system and in the periphery. It then reviews current knowledge about circadian modulation of learning and memory. Finally, it raises the question: Is circadian rhythmicity a modulator of learning and memory, or it is a component integrated into episodic memory during learning? I suggest that the time-of-day information could be encoded as a component of episodic memory rather than being an active modulator of learning and memory.

Circadian clocks exist in the central nerve system and in the periphery

Circadian rhythms are biological activities that oscillate under constant environmental conditions with a ~24 hour period. Circadian rhythms regulate the biological processes of diverse organisms ranging from prokaryotes to mammals [1-4]. Patterns of brain activity, hormone production, cell regeneration and many other biological activities are linked to this 24-hour cycle [5-7]. Circadian rhythms are endogenously driven: organisms maintain their behavioral and physiological rhythms even under constant environmental conditions.

In mammals, the master circadian center is located in the suprachiasmatic nucleus (SCN) of the hypothalamus [8,9]. In individual SCN cells, circadian machinery is self-sustained and maintained by a cellular feedback loop. In the positive feedback phase, two transcription activators, CLOCK and BMAL1, dimerize and bind to E-box motifs in promoter segments and stimulates transcription of clock genes [1,10]. In the negative feedback phase, two clock gene (Per and Cry) products, Period and Cryptochrome proteins, form a heterodimer complex and inhibit CLOCK:BMAL1-mediated transcription through direct protein–protein interaction [11]. This inhibition down-regulates the transcription of clock genes including their own. The ensuing decline in Period and Cryptochrome protein levels eventually leads to reactivation of CLOCK/BMAL1-induced clock gene transcription and reinitiation of the cycle. Individually oscillating SCN cells use neuropeptide communication (primarily vasoactive intestinal peptide (VIP) [12-14]) and gap junctions [15,16] to promote synchronization and coordination among them.

Rhythmic clock gene expression underlies the rhythmic electrical activity, such as spontaneous firing rate, of SCN neurons [17,19]. In nocturnal rodents, spontaneous firing rate of SCN neurons show circadian rhythmicity with an elevated firing rate in subjective daytime [20-22]. It is possible that there is direct transcriptional regulation of ion channel proteins or regulatory factors affecting channel activity by CLOCK/BMAL1. Clock genes may also regulate electrical activity indirectly via clock controlled genes (CCGs), such as vasopressin, which appears to augment the magnitude of the electrical activity rhythm in the SCN through a receptor-mediated excitation of SCN neurons [23,24].

The SCN outputs are thought to synchronize a number of circadian oscillators in the periphery, such as lungs [25], pancreas [26,27], adipose tissue [28], adrenal glands [29,30] and ovaries [31,32]. Furthermore, independent circadian oscillators exist in the periphery, including the food-entrainable oscillator in the liver [33-35] and oscillator in the olfactory bulb [36,37].

Circadian fluctuations in clock gene expression and synaptic plasticity exist in the hippocampus

The hippocampus is a region in the brain critical for learning and memory formation. Interestingly, some clock genes are expressed in

the hippocampus and their expressions oscillate in a robust circadian manner. For instance, the Per1 and Per2 genes are reported to oscillate in both the dentate gyrus and CA1 regions of the hippocampus [38]; the oscillation of the latter in the dentate gyrus can be abolished by lesion of the SCN [39]. In addition to circadian fluctuations in gene expressions at the cellular level, time-dependent synaptic strengthening has been observed in rodent SCN. Stimulation of the optic nerve elicited long-term potentiation (LTP) only during the day [40]. This time-dependent LTP finds its parallel in the hippocampus. In both hamsters and mice, LTP was elevated in slices containing hippocampal CA1 prepared during light phase but tested during dark phase [41,42]. Conversely, in hippocampal slices prepared during dark phase but tested during light phase, LTP exhibited opposing activities [42]. These data raise the possibility that hippocampal LTP is dependent on the time of testing; they also support the hypothesis that an independent circadian center controls the hippocampal plasticity since the possible association between the SCN and the hippocampus was abolished in vitro.

Circadian modulation of learning and memory

The influence of circadian rhythm on learning and memory has long been studied. Circadian effects on different stages of memory formation have been postulated in various paradigms [43,44]. Chaudhury and Colwell showed that recall of contextual and cued fear memory in mice peaks in the early daytime [45]. They also showed that mice displayed the same periodicity of peak memory when housed under constant darkness condition and this peak memory is independent of the time of training. In contrast, other studies suggest that memory formation is dependent upon time of training [46-49]. Rats demonstrate better acquisition and performance on an operant task when trained during the dark phase. Spatial learning ability assessed by Morris water maze was not affected by the time of training; but better long term spatial memory was achieved if animals were originally trained during the dark phase [47]. These studies indicate that the time of training, rather than an endogenous circadian system, appears to be the critical factor for memory formation.

Given that some clock genes have been found in hippocampus, it is natural to ask whether the circadian regulation of learning and memory formation are attributed to hippocampus-specific clock gene fluctuation; or one might think that circadian machineries may exert their functions through other neuronal processes and, therefore, affect learning and memory indirectly. Most manipulations of the circadian clock also lead to sleep disruption, which is a major cause of learning deficits and memory dysfunctions. As a result, the cellular mechanisms of circadian regulation of learning and memory remain vague. Using a non-invasive means in Siberian hamsters, Ruby et al. recently showed that circadian system is involved in memory function independent of sleep [50].

It is worth noting that the presence of clock genes in the hippocampus does not necessitate them for hippocampus-dependent learning and memory. To elucidate the link between circadian clock and hippocampus-dependent learning and memory, region-specific alterations of circadian clock machinery in the hippocampus would be necessary. Rather than the coarse ablation of the SCN area, spatially restricted manipulations of clock genes in subregions of the hippocampus would allow us to determine whether disruptions of circadian clock affect learning and memory at cellular as well as behavioral level. With the advent of novel biotechnologies, including cell type-specific genetic manipulation and optogenetics [51,52], questions such as which group of cells that express clock genes undergo activation after learning can be addressed.

Mechanisms underlying circadian regulation of learning and memory

The aforementioned evidence along with other experimental results point to the notion that different stages of memory formation along with their cellular substrates are under the modulation of circadian rhythms. However, whether the time-dependent LTP observed in hippocampus and/or the circadian modulated memory formations are SCN-dependent are questions to which answers remains largely elusive. Anatomically, the SCN has connections with many brain regions [53-55]. Of particular interest is its projections to the hippocampus, both directly [55] and indirectly via the locus coeruleus [56], which in turn mediates hippocampal activation [57]. Whether these connections are responsible for the circadian expressions of clock genes in hippocampus, or hippocampal synaptic plasticity is not known. Since the LTP has been thought the cellular basis of long-term memory formation [58,59], it would be premature to propose that hippocampus-dependent learning and memory is modulated by the SCN pacemakers until it can be confirmed that disruptions of SCN-hippocampus connection lead to memory dysfunctions.

The circadian clock could regulate learning and memory through hormonal signalling. For instance, melatonin administration inhibits LTP in the hippocampus [60,61]. In rats, melatonin modulates memory in a phase-specific manner [62]. Genetic deletions of melatonin receptors in mice lead to enhanced cognitive performance [63]. Glucocorticoid is another hormone that has been shown to exert rhythmic regulation of neuronal plasticity. High glucocorticoid levels increase learning-induced spine formation, while low glucocorticoid levels do not [64]. Meanwhile, prolonged exposure to high glucocorticoid levels disrupts previous memories and eliminates new spines induced by learning [64].

But is the link between hormones and learning and memory direct? Or do hormones regulate learning and memory indirectly via affecting neuronal plasticity in general? Most learning processes take place at a time scale much smaller than 24-h period, rendering the former possibility less likely. Recent findings of time cells in hippocampus [65,66] suggest that a subset of hippocampal cells can keep track of temporal elapses independent of pacemaker cells in the SCN. During the acquisition phase, the time-of-day information could be encoded as a contextual component, therefore becoming a time "tag" of episodic memory. This would ensure that during later test phases, animals demonstrate significantly better memory performance at the same time of training [67,68]. This encoding process can be SCN-independent so that animals with lesioned SCN demonstrate similar performance in memory tasks as their wild-type counterparts [69].

Conclusion

Circadian rhythmicity in cell physiology is conserved across a wide variety of organisms. The presence of circadian variations in gene expression and synaptic plasticity in hippocampal cells, as well as in learning and memory formation, indicates an inherent link between cellular activities and behaviors of the whole animal. However, the mechanism by which the activity of a group of pacemaker cells is translated into behavioral responses is still poorly understood. Anatomical and physiological evidence summarized above and many other studies indicate that pacemaker cells in the SCN may modulate

circadian variations in learning and memory formation directly and/or indirectly. However, contemporary theories of memory consolidation suggest that newly-acquired episodic memories are replayed during ripples for consolidation at tens of millisecond time scale, both immediately after learning and remotely during sleep [70-72]. How could cellular processes oscillating at ~24 h cycles influence the memory encoding at such finer time scales? It is more plausible that during learning, the time-of-day information is embedded as a component of episodic memory which is consolidated along with other memory components during subsequent replays. This time "tag" of episodic memory could be encoded independent of the SCN or local circadian center in the hippocampus. However, the elucidation of the relationship between circadian rhythms and memory formation warrants further research.

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