Circadian oscillations within the hippocampus support memory formation and persistence

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INTRODUCTION

Circadian rhythms are oscillations that occur with approximately 24-h periodicity. These rhythms persist throughout the body and play essential roles in physiology. Single cell oscillators interact within specific tissues to drive tissue-specific activities, which in turn provide information for the rest of the body (Schibler and Sassone-Corsi, 2002). Neurons of the central nervous system are among the single cell oscillators in the body and these coordinate function within specific brain regions to direct activities as disparate as melatonin secretion, thermoregulation, and memory formation and maintenance. As a region devoted to short-term to long-term memory conversion, the hippocampus provides a pivotal node for the intersection of circadian rhythms and memory formation.

The circadian clock is organized hierarchically. The suprachiasmatic nucleus (SCN) of the brain provides synchronization of circadian clocks throughout the body and lesions of the small bilateral nuclei that make up this region produce molecular and circadian clocks throughout the body and lesions of the small asymmetrical nucleus (SCN) of the brain provides synchronization of formation.

The ability to sustain memories over long periods of time, sometimes even a lifetime, is one of the most remarkable properties of the brain. Much knowledge has been gained over the past few decades regarding the molecular correlates of memory formation. Once a memory is forged, however, the molecular events that provide permanence are as of yet unclear. Studies in multiple organisms have revealed that circadian rhythmicity is important for the formation, stability, and recall of memories (Gielen et al., 2009). The neuronal events that provide this link need to be explored further. This article will discuss the findings related to the circadian regulation of memory-dependent processes in the hippocampus. Specifically, the circadian-controlled mitogen-activated protein kinase (MAPK) and cAMP signal transduction pathway plays critical roles in the consolidation of hippocampus-dependent memory. A series of studies have revealed the circadian oscillation of this pathway within the hippocampus, an activity that is absent in memory-deficient, transgenic mice lacking Ca^{2+}-stimulated adenylyl cyclases. Interference with these oscillations proceeding the cellular memory consolidation period impairs the persistence of hippocampus-dependent memory. These data suggest that the persistence of long-term memories may depend upon reactivation of this signal transduction pathway in the hippocampus during the circadian cycle. New data reveals the dependence of hippocampal oscillation in MAPK activity on the suprachiasmatic nucleus, again underscoring the importance of this region in maintaining the circadian physiology of memory. Finally, the downstream ramifications of these oscillations in terms of gene expression and epigenetics should be considered, as emerging evidence is pointing strongly to a circadian link between epigenetics and long-term synaptic plasticity.

Keywords: circadian, hippocampus, memory, mitogen-activated protein kinase, adenylyl cyclase
FIGURE 1 | Long-term memory formation is linked to circadian time and the suprachiasmatic nucleus. Activity oscillations within the MAPK pathway are dependent on the SCN, ultimately linking them to external zeitgebers such as light. Oscillations of the MAPK pathway depend on the rhythmic activation of Ras activity as well as that of the calcium-stimulated adenylyl cyclases and ultimately control downstream signaling events including de novo transcription and translation. Rhythmicity within this cascade controls not only the efficiency with which memories are formed but also their persistence once forged.

for many hours in vivo, exhibit firing rates of a sinusoidal nature and with a 25-h period (Murrin and Bilkey, 2011). Fluctuations in synaptic plasticity that depend on diurnal luminescence have also been observed in the visual cortex. The induction of LTP and LTD in areas 2/3 of the primary visual cortex after stimulation of the dorsal lateral geniculate nucleus shows a strong dependence on the lighting cycle. Interestingly, while low frequency stimulation of 3 Hz can generate LTD in light-exposed animals, the same stimulus generates LTP in dark-exposed animals (Dusov and Manahan-Vaughan, 2007). While the idea that synaptic plasticity in the visual cortex would be affected by circadian fluctuations in lighting may seem obvious, it provides an example of just how disparate neuronal responses can be – even after the same stimulus – depending on the basal firing state of the integrating network.

DEPENDENCE OF CIRCADIAN RHYTHMICITY AND HIPPOCAMPAL LONG-TERM MEMORY ON MAPK ACTIVATION

While the mechanisms underlying the circadian effects on LTP are still being explored, some pathways implicated in synaptic plasticity, particularly those associated with hippocampal potentiation, have been explored in detail. Among the singling events known to be important for the induction of hippocampal LTP is the activation of the mitogen-activated protein kinase (MAPK) cascade. Activation of this pathway is necessary for both the transcriptional and the translational events underlying long-term memory formation in the hippocampus (Figure 1) (Atkins et al., 1998; Davis et al., 2000; Kelleher III et al., 2004). The MAPK cascade encompasses important proteins in signal transduction. The MAPKs are highly conserved across all eukaryotes and their roles extend beyond the cytoplasm to the nucleus, where they can directly modulate gene transcription. The MAPK cascade generally consists of three-tiered kinase proteins. The kinase upstream of MAPK is typically referred to as the MAPK kinase, MKK, or MEK protein. These kinases lie downstream of a third activator kinase, the MAPK kinase kinase, MEK or MKKs. Five MAPK cascades have been identified including the ERK1/2, JNK, ERK5, and the atypical MAPK proteins which include ERK3 and ERK4 among others (reviewed in Gaestel, 2008). The ERK1/2 pathway is well known to regulate cell differentiation and growth while the JNK and p38 pathways are involved in stress response (reviewed in Schaeffer and Weber, 1999). Several mitogens and growth factors are known to activate these pathways. In neurons (unlike many other cell types), however, the activation of calcium-sensitive adenylyl cyclases appears to be important for the transduction of membrane stimulation to activation of the MAPK cascade (Impyey et al., 1998; Dugan et al., 1999). While the contribution of MAPK to memory consolidation is largely based on the administration of inhibitors (which are often dirty and impair the function of additional relevant pathways), the administration of MAPK antisense oligonucleotides in area CA1 of the hippocampus underscores the importance of this kinase in hippocampal plasticity (Wu et al., 1999).

The role of the MAPK pathway in circadian rhythmicity is beginning to be established. The p44/42 MAPK pathway is light responsive in neurons of the rodent SCN (Obrietan et al., 1998; Butcher et al., 2002) and several MAPK isoforms have been implicated in cellular timekeeping in a variety of other organisms (de Paula et al., 2008). While cAMP levels are antagonistic to MAPK phosphorylation and activation in some cell types, in neurons the activation of the MAPK is tightly coupled to increases in cAMP. This coupling appears to be important for clock time
keeping in the brain. Circadian oscillations in cAMP are essential modulators of SCN rhythmicity and infusion of adenylyl cyclase agonists or antagonists into the third ventricle can alter the phase of rhythmic gene expression in the SCN (O’Neill et al., 2008). cAMP has also been observed as oscillatory in the hippocampus where its reliance on the calcium-sensitive adenylyl cyclase seems to be critical for its oscillatory presence (Eckel-Mahan et al., 2008).

DEPENDENCE OF HIPPOCAMPAL LONG-TERM MEMORY FORMATION AND PERSISTENCE ON NORMAL CIRCADIAN RHYTHMICITY

Recent work centered on the role of hippocampal P-ERK oscillations has maintained the SCN as a pacemaker for hippocampal oscillations – at least in this signaling cascade, are not intrinsic to this region, and rather rely on a network of neurons that provide circadian information from the SCN. This is supported by the idea that constant light ablates circadian fluctuations in hippocampal cAMP activity (Eckel-Mahan et al., 2008). What remains to be seen is whether memory training can function as a zeitgeber for the hippocampus and other memory-associated areas such as the cortex and the amygdala. For example, in the liver feeding restriction can restore rhythmicity to a liver rendered arrhythmic by loss of SCN and the amygdala. For example, in the liver feeding restriction can restore rhythmicity to a liver rendered arrhythmic by loss of SCN and the amygdala. For example, in the liver feeding restriction can restore rhythmicity to a liver rendered arrhythmic by loss of SCN and the amygdala. For example, in the liver feeding restriction can restore rhythmicity to a liver rendered arrhythmic by loss of SCN and the amygdala.

REFERENCES

Angelo-Castellanos, M., Amaya, J. M., Sabado-Delgado, R., Pena, B. M., and Escobar, C. (2011). Sceduling food进食s re-entrainment more than melatonin does after a 6-8 phase advance of the light-dark cycle in rats. J. Biol. Rhythms 26, 324-334.

Makino, C. M., Soldati, J. C., Ferraris, J. L., Tzounis, J. M., and Swart, J. D. (1998). The MAPK cascade is required for mammalian associative learning. Nat. Neurosci. 1, 602–609.

Butcher, L. G., Deren, J., Okamura, H., Collemere, M., Burgong, P W., and D’Olevenstein, K. (2008). pE244 nitogen-activated protein kinase pathway couples pletic input to circadian clock entrainment. J. Biol. Chem. 277, 29518–29526.

Chadbury, D., Wong, L. M., and Gahwiler, C. S. (2005). Circadian regulation of hippocampal long-term potentiation. J. Biol. Rhythms 20, 274–281.

Dumasia, F., Le Mink, N., Prudent, N., Kermans, P., Henley-Ollo, F., and Schleier, U. (2008). Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. Genes Dev. 14, 2950–2961.

Davis, S., Vardenout, P., Pages, C., Gahwiler, J., and Lecoeur, S. (2006). The MAPK/ERK cascade targets both Erk-1 and cAMP response element-binding protein to control long-term potentiation-dependent gene expression in the dentate gyrus in vivo. J. Neurosci. 26, 4572–4577.

de Paula, R. M., Lamm, E. M., Bennett L., and Bell-Polenden, D. (2008). A connection between MAPK pathways and circadian clocks. Cell Cycle 7, 2630–2634.

Dogan, I. L., Kim, J. S., Zhang, Y., Bart, R. D., Sum, Y., Hofmann, D. M., and Martin, D. H. (1991). Differential effects of cAMP in neurons and astrocytes. Role of B-atal. J. Biol. Chem. 276, 5062–5068.

Eastman, C. I., Minberger, R. E., and Rechtschaffen, A. (1984). Suprachiasmatic nucleus lesions eliminate circadian temperature and sleep rhythms in the rat. Physiol. Behav. 32, 357–368.

Elk-Mahan, K. L., Phan, T., Han, S., Bartoli, D., and Gilestro, G. F., Tonino, G., and Cardi, C. (2006). Widespread changes in circadian and memory formation and maintenance. As the concept that synaptic plasticity and therefore cognition are greatly influenced by the circadian clock has become empirically validated, it becomes necessary to address the role of circadian rhythmicity in behavioral studies.

Becoming increasingly clear is that baseline synaptic plasticity is not a static phenomenon but rather changes over time with the circadian cycle. These changes are dependent on the time of day – as discussed here – but also on the previous state of sleep and wakefulness in an organism (Vyasozvnyi et al., 2008; Gilastro et al., 2009). Such changes in synaptic plasticity ultimately rely on intracellular fluctuations in small molecules (such as cAMP and calcium), circadian changes in enzyme activity (i.e., adenylyl cyclase, and MAPK activity), and circadian changes in gene transcription. As oscillating circadian events, such changes can be essential modifers of memory formation and maintenance. As the concept that synaptic plasticity and therefore cognition are greatly influenced by the circadian clock has become empirically validated, it becomes necessary to address the role of circadian rhythmicity in behavioral study design.
nuclear translocation. Neuron 21, 869–882.

Ng, A., Lomn, S., Porzcha, N., Schwengler, H., Selbach, O., Dehghani, F., and Stahl, J. H. (2010). Temporal dynamics of mouse hippocampal clock gene expression support memory processing. Hippocampus 20, 377–388.

Ng, A., Moos, J., Weaver, D. R., Korf, H. W., Stahl, J. H., and von Gall, C. (2005). Rhythms in clock proteins in the mouse pars tuberalis depend on MT1 melatonin receptor signalling. J. Neurosci. 25, 2845–2854.

Kalinic, R. J., Ilvy, Godin stor, A., Jung, H. Y., Kang, H., and Tonsgaard, S. (2004). Transcriptional regulation of clock proteins in the mouse pars tuberalis depend on MT1 melatonin receptor signalling. J. Neurosci. 25, 404–408.

Munn, R. G., and Bilkey, D. K. (2011). The firing rate of hippocampal CA1 place cells is modulated with a circadian period. Hippocampus. doi: 10.1002/hipo.20969

Obrietan, K., Impey, S., and Storm, D. R. (1998). Light and circadian rhythm regulate MAP kinase activation in the suprachiasmatic nucleus. Nat. Neurosci. 1, 893–901.

O'Neill, J. S., Mynowska, E. S., Cheatham, J. E., Zakharov, J. S., and Hartings, M. H. (2008). AMP-dependent signalling as a core component of the mammalian circadian pacemaker. Science 320, 940–953.

Pantazopoulos, H., Dolanbash, H., and Darn, E. C. (2011). A fear-inducing odor alters PER2 and e-Fos expression in brain regions involved in fear memory. PLoS ONE 6, e20818. doi:10.1371/journal.pone.0020818

Phan, T. X., Chan, G. C., Sindreu, C. B., Eckel-Mahan, K. L., and Storm, D. R. (2011). The diurnal oscillation of MAP (mitogen-activated protein) kinase and adenylyl cyclase activities in the hippocampus depends on the suprachiasmatic nucleus. J. Neurosci. 31, 10640–10647.

Prolo, L. M., Takahashi, J. S., and Herzog, E. D. (2005). Circadian rhythm generation and entrainment in astrocytes. J. Neurosci. 25, 404–408.

Schibler, U., and Sassone-Corsi, P. (2002). A web of circadian pacemakers. Cell 111, 919–922.

Stephan, F. K., and Zucker, I. (1972). Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. Proc. Natl. Acad. Sci. U.S.A. 69, 1585–1586.

Stokkan, K. A., Yamaoka, S., Ts, H., Sakaki, Y., and Menaker, M. (2001). Entrainment of the circadian clock in the liver by feeding. Science 291, 490–493.

Vuazensky, V. V., Cirelli, C., Pfister-Genikou, M., Fatigoni, U., and Tononi, G. (2008). Molecular and electrophysiological evidence for net synaptic potentiation in waking and depression in sleep. Nat. Neurosci. 11, 200–208.

Wu, S. P., Lu, K. T., Chang, W. C., and Gean, P. W. (1999). Involvement of mitogen-activated protein kinase in hippocampal long-term potentiation. J. Neurosci. 19, 4550–4554.