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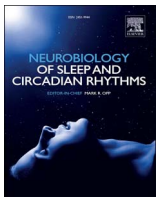

Sleep and clocks – implications for brain health

Sleep and circadian homeostasis are important for overall well-being. Increasing evidence points to a specific pivotal role that sleep and circadian system play in brain health (Abbott and Videnovic, 2016; Musiek and Holtzman, 2016). Neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases are common neurological disorders, and are become more prevalent as the population ages. These conditions share disturbed sleep as a common and yet frequently overlooked manifestation. Further, disrupted sleep and circadian rhythms frequently predate the onset of cardinal features of these disorders. Sleep and circadian system are therefore positioned as important potential therapeutic targets for improving function and quality of life of patients affected by neurodegenerative disorders. This special issue is centered on the interface of sleep, circadian biology and neurodegeneration, and incorporates a combination of original research papers and comprehensive reviews on this rapidly evolving and promising avenue of investigation.

Sleep and circadian rhythms disturbances in Alzheimer's Disease (AD) have long been appreciated (Ancoli-Israel et al., 1997; Loewenstein et al., 1982). Disruptions of sleep and circadian rhythms take a great toll on patients and their caretakers, and are among the most common symptoms leading to institutionalization of patients (Bianchetti et al., 1995). Studies from a number of groups have demonstrated severe sleep abnormalities, including sleep fragmentation and decreased slow-wave sleep, as well as pronounced degradation of circadian rhythms, in patients with AD dementia(Ancoli-Israel et al., 1997; Hatfield et al., 2004; Ju et al., 2014). Resulting symptoms such as increased nocturnal activity, increased daytime napping, fatigue, and increasing confusion in the late afternoon/early evening (termed “sundowning”) carry significant morbidity for AD patients and their caretakers.

The specific cause of these disturbances in AD is not clear, though several studies have described degeneration of neurons in sleep-regulating nuclei, as well as loss of neuropeptidergic neurons in the suprachiasmatic nucleus (SCN), the brain's “master circadian clock” (Lim et al., 2014; Swaab et al., 1985; Wang et al., 2015; Zhou et al., 1995). Thus, neurodegeneration in AD ultimately leads to sleep and circadian disruption, though the upstream mechanisms remain unknown. Moreover, a potential causative role for sleep and circadian dysfunction in AD pathogenesis is emerging. Sleep deprivation in mice greatly accelerates the accumulation of amyloid plaque pathology, a hallmark of AD (Kang et al., 2009). Conversely, promoting sleep with orexin antagonist drugs, or by deletion of the orexin gene, prevents plaque accumulation in mice (Kang et al., 2009; Roh et al., 2014). Thus, it appears that sleep regulates amyloid-beta pathology in mouse models of AD. In their review in this issue, Holth and Holtzman discuss how sleep may influence AD pathogenesis beyond its effect on amyloid-beta, including how sleep might interact with another arbiter of neurodegeneration, tau. Also in this issue, Dissel et al. describe learning and memory impairments in a drosophila model of AD generated by overexpression of human amyloid precursor protein, beta-secretase, and tau. They demonstrate that pharmacological augmentation of sleep in these mice rescues deficits in learning and memory and prevents synapse loss, in part by restoring normal cAMP signaling. These two papers point to new horizons in our understanding of the role of sleep in AD, and new strategies for using sleep to combat the disease.

Similar to AD, disorders of sleep and alertness are very common in movement disorders, and affect majority of patients during the course of their disease. Parkinson's Disease (PD) is a prototype disease in this category and is the second most common neurodegenerative disorder that affects over one million individuals in the United States alone. In his seminal monograph “Essay on the Shaking Palsy”, published two centuries ago, James Parkinson provided astute descriptions of disturbed sleep among his six patients with “paralysis agitans”, a disorder later to be named after him (Parkinson, 2002). Despite these early reports of disturbed sleep in PD, it is only over the past few decades that sleep dysfunction in PD and other movement disorders have attracted attention of medical and scientific community.

All categories of sleep disorders have been associated with movement disorders such as PD and Huntington disease (HD) (Morton, 2013; Videnovic and Golombek, 2013). Many sleep disorders exhibit unique features when co-expressed with movement disorders. This is likely reflective of specific interactions between underlying neurodegenerative processes and sleep-wake regulation mechanisms. Some sleep disorders precede the onset of movement disorders and may represent early pre-motor markers of neurodegeneration. The best example is REM sleep behavior disorder (RBD), that is of clinical and basic physiological importance, since individuals diagnosed with RBD have an approximately 80% risk of developing Parkinson's disease (PD) or other α-synuclein-related disorders within one decade of being diagnosed with RBD (Iranzo et al., 2014).

The function of the circadian system in movement disorders has not been systematically studied until recently. Over the past decade several important basic and clinical investigations targeting circadian function in PD and HD have been reported (Breen et al., 2014; Morton et al., 2005; Videnovic et al., 2014b; Willison et al., 2013). These studies point to significant modification of circadian timekeeping in movement disorders, link circadian disruption with manifestations of these diseases, and suggest potential bidirectional relationships between circadian disruption and the primary neurodegenerative process. These studies also provide a foundation for exploration of the circadian system as an important therapeutic target in movement disorders.

This special issue contains several articles that continue to explore relationships between the circadian system, sleep homeostasis, and PD and HD. Videnovic and Golombek provide a comprehensive review on the function of circadian system in PD. The review summarizes knowledge about

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the function of the circadian system in PD, and encompasses both basic and clinical research investigations on the topic.

Colwell and colleagues report beneficial effects of supplemental light exposure on the BACHD and Q175 mice models of HD. Animals were exposed daily for 3 months to 6 h to blue-enriched light at the beginning of their daily light cycles. The intervention resulted in improvements in locomotor activity rhythms and motor performance without change in sleep in both animal models of the disease. Further, blue-enriched light alters the expression of HD relevant markers in the cortex and striatum. In another study published in this special issue, Morton and colleagues report effects of prolonged day light exposure on daytime activity and circadian behavioral rhythms in R6/2 mice model of HD that demonstrated profound alterations in circadian rhythms by the age of 16 weeks. A long day photoperiod (16 h light/8 h dark) was associated with improved survival and circadian strength, while short day photoperiod had a negative impact on survival in this animal mode of HD. These two investigations further strengthen the notion that circadian based interventions may be a novel approach in the symptomatic treatment and modification of neurodegenerative process itself. The studies align with several other investigations that reported beneficial effects of circadian interventions in movement disordered in both patients and animal models of these disorders (Pallier et al., 2007; Paus et al., 2007; Willis and Turner, 2007).

While not typically considered neurodegenerative disorders, both traumatic brain injury (TBI) and stroke lead to degeneration of neurons, and can be associated with sleep and circadian deficits (Baumann et al., 2007; Meng et al., 2008). TBI shares common molecular mechanisms with AD, including tau aggregation, and is characterized by ongoing synapse loss, inflammation, and neurodegeneration well after the initial injury(McKee and Daneshvar, 2015). TBI patients frequently experience disabling disturbances of sleep and circadian rhythm, and these deficits can be modeled in animals (Baumann et al., 2007; Boone et al., 2012; Grima et al., 2016; Lim et al., 2013; Shekleton et al., 2010). In this issue, Yue et al. describe circadian fluctuations in the Glasgow Coma Scale in TBI patients, suggesting that the time of day at which an injury occur may effect severity and ICU admission rate. Two other original research papers in this issue provide novel insights into the effects of TBI on sleep and wakefulness. Thomasy and colleagues present evidence that TBI causes an increase in non-REM sleep and diminished nighttime wakefulness in mice, an effect associated with specific loss of orexin/hypocretin and cholinergic neurons. Modarres et al. demonstrate that TBI in both humans and mice is associated with increased amounts of slow wave activity and desynchronized slow waves during wakefulness, offering a potential biomarker of TBI-related impairment in humans. While the incidence of ischemic stroke and the sensitivity of tissue to ischemic damage are both influenced by the time of day (Bassetti and Aldrich, 1999; Elliott, 1998; Karmarkar and Tischkau, 2013), sleep may also play a role in healing of the brain after infarction. Duss et al. examine the evidence linking sleep to synaptic plasticity and sleep deprivation to impaired brain recovery following stroke. They suggest that augmenting sleep in the post-stroke period might be a strategy to promote rewiring of the brain and functional recovery after stroke.

Sleep and circadian rhythms influence a wide variety of physiologic processes in the brain and periphery, many of which are critical to brain health. However, the cellular and molecular mechanisms linking sleep, circadian function, and neurodegeneration are just beginning to be uncovered (Musiek and Holtzman, 2016; Videnovic et al., 2014a). The contributions in this special issue of *Neurobiology of Sleep and Circadian Rhythms* reveal the cutting edge in this field, and illustrate what we know and how much we have to yet to understand. These studies keenly demonstrate the importance of research on sleep, rhythms, and neurodegenerative disorders, and provide several unique examples of how sleep and circadian systems might be targeted to ameliorate these terrible diseases.

Conflicts of interest

None.

References

Abbott, S.M., Videnovic, A., 2016. Chronic sleep disturbance and neural injury: links to neurodegenerative disease. Nat. Sci. Sleep 8, 55–61.

Ancoli-Israel, S., Klauber, M.R., Jones, D.W., Kripke, D.F., Martin, J., Mason, W., Pat-Horenczyk, R., Fell, R., 1997. Variations in circadian rhythms of activity, sleep, and light exposure related to dementia in nursing-home patients. Sleep 20, 18–23.

Bassetti, C., Aldrich, M., 1999. Night time versus daytime transient ischaemic attack and ischaemic stroke: a prospective study of 110 patients. J. Neurol. Neurosurg. Psychiatry 67, 463–467.

Baumann, C.R., Werth, E., Stocker, R., Ludwig, S., Bassetti, C.L., 2007. Sleep-wake disturbances 6 months after traumatic brain injury: a prospective study. Brain 130, 1873–1883.

Bianchetti, A., Scuratti, A., Zanetti, O., Binetti, G., Frisoni, G.B., Magni, E., Trabucchi, M., 1995. Predictors of mortality and institutionalization in Alzheimer disease patients 1 year after discharge from an Alzheimer dementia unit. Dementia 6, 108–112.

Boone, D.R., Sell, S.L., Micci, M.A., Crookshanks, J.M., Parsley, M., Uchida, T., Prough, D.S., DeWitt, D.S., Hellmich, H.L., 2012. Traumatic brain injury-induced dysregulation of the circadian clock. PloS One 7, e46204.

Breen, D.P., Vuono, R., Nawarathna, U., Fisher, K., Shneerson, J.M., Reddy, A.B., Barker, R.A., 2014. Sleep and circadian rhythm regulation in early Parkinson disease. JAMA Neurol. 71, 589–595.

Elliott, W.J., 1998. Circadian variation in the timing of stroke onset: a meta-analysis. Stroke 29, 992–996.

Grima, N., Ponsford, J., Rajaratnam, S.M., Mansfield, D., Pase, M.P., 2016. Sleep disturbances in traumatic brain injury: a meta-analysis. J. Clin. Sleep. Med. 12, 419–428.

Hatfield, C.F., Herbert, J., van Someren, E.J., Hodges, J.R., Hastings, M.H., 2004. Disrupted daily activity/rest cycles in relation to daily cortisol rhythms of home-dwelling patients with early Alzheimer's dementia. Brain 127, 1061–1074.

Iranzo, A., Fernandez-Arcos, A., Tolosa, E., Serradell, M., Molinuevo, J.L., Valldeoriola, F., Gelpi, E., Vilaseca, I., Sanchez-Valle, R., Llado, A., Gaig, C., Santamaria, J., 2014. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. PLoS One 9, e89741.

Ju, Y.E., Lucey, B.P., Holtzman, D.M., 2014. Sleep and Alzheimer disease pathology–a bidirectional relationship. Nat. Rev. Neurol. 10, 115–119.

Kang, J.E., Lim, M.M., Bateman, R.J., Lee, J.J., Smyth, L.P., Cirrito, J.R., Fujiki, N., Nishino, S., Holtzman, D.M., 2009. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science 326, 1005–1007.

Karmarkar, S.W., Tischkau, S.A., 2013. Influences of the circadian clock on neuronal susceptibility to excitotoxicity. Front. Physiol. 4, 313.

Lim, A.S., Ellison, B.A., Wang, J.L., Yu, L., Schneider, J.A., Buchman, A.S., Bennett, D.A., Saper, C.B., 2014. Sleep is related to neuron numbers in the ventrolateral preoptic/intermediate nucleus in older adults with and without Alzheimer's disease. Brain 137, 2847–2861.

Lim, M.M., Elkind, J., Xiong, G., Galante, R., Zhu, J., Zhang, L., Lian, J., Rodin, J., Kuzma, N.N., Pack, A.I., Cohen, A.S., 2013. Dietary therapy mitigates persistent wake deficits caused by mild traumatic brain injury. Sci. Transl. Med. 5 (215ra), 173.

Loewenstein, R.J., Weingartner, H., Gillin, J.C., Kaye, W., Ebert, M., Mendelson, W.B., 1982. Disturbances of sleep and cognitive functioning in patients with dementia. Neurobiol. Aging 3, 371–377.

McKee, A.C., Daneshvar, D.H., 2015. The neuropathology of traumatic brain injury. Handb. Clin. Neurol. 127, 45–66.

Meng, H., Liu, T., Borjigin, J., Wang, M.M., 2008. Ischemic stroke destabilizes circadian rhythms. J. Circadian Rhythm 6, 9.

Morton, A.J., 2013. Circadian and sleep disorder in Huntington's disease. Exp. Neurol. 243, 34–44.

Morton, A.J., Wood, N.I., Hastings, M.H., Hurelbrink, C., Barker, R.A., Maywood, E.S., 2005. Disintegration of the sleep-wake cycle and circadian timing in Huntington's disease. J. Neurosci. 25, 157–163.

Musiek, E.S., Holtzman, D.M., 2016. Mechanisms linking circadian clocks, sleep, and neurodegeneration. Science 354, 1004–1008.

Pallier, P.N., Maywood, E.S., Zheng, Z., Chesham, J.E., Inyushkin, A.N., Dyball, R., Hastings, M.H., Morton, A.J., 2007. Pharmacological imposition of sleep slows cognitive decline and

reverses dysregulation of circadian gene expression in a transgenic mouse model of Huntington's disease. J. Neurosci. 27, 7869–7878.
Parkinson, J., 2002. An essay on the shaking palsy 1817. J. Neuropsychiatry Clin. Neurosci. 14, 223–236, (Discussion 222).
Paus, S., Schmitz-Hubsch, T., Wullner, U., Vogel, A., Klockgether, T., Abele, M., 2007. Bright light therapy in Parkinson's disease: a pilot study. Mov. Disord. 22, 1495–1498.
Roh, J.H., Jiang, H., Finn, M.B., Stewart, F.R., Mahan, T.E., Cirrito, J.R., Heda, A., Snider, B.J., Li, M., Yanagisawa, M., de Lecea, L., Holtzman, D.M., 2014. Potential role of orexin and sleep modulation in the pathogenesis of Alzheimer's disease. J. Exp. Med. 211, 2487–2496.
Shekleton, J.A., Parcell, D.L., Redman, J.R., Phipps-Nelson, J., Ponsford, J.L., Rajaratnam, S.M., 2010. Sleep disturbance and melatonin levels following traumatic brain injury. Neurology 74, 1732–1738.
Swaab, D.F., Fliers, E., Partiman, T.S., 1985. The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. Brain Res. 342, 37–44.
Videnovic, A., Golombek, D., 2013. Circadian and sleep disorders in Parkinson's disease. Exp. Neurol. 243, 45–56.
Videnovic, A., Lazar, A.S., Barker, R.A., Overeem, S., 2014a. The clocks that time us-circadian rhythms in neurodegenerative disorders. Nat. Rev. Neurol. 10, 683–693.
Videnovic, A., Noble, C., Reid, K.J., Peng, J., Turek, F.W., Marconi, A., Rademaker, A.W., Simuni, T., Zadikoff, C., Zee, P.C., 2014b. Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease. JAMA Neurol. 71, 463–469.
Wang, J.L., Lim, A.S., Chiang, W.Y., Hsieh, W.H., Lo, M.T., Schneider, J.A., Buchman, A.S., Bennett, D.A., Hu, K., Saper, C.B., 2015. Suprachiasmatic neuron numbers and rest-activity circadian rhythms in older humans. Ann. Neurol. 78, 317–322.
Willis, G.L., Turner, E.J., 2007. Primary and secondary features of Parkinson's disease improve with strategic exposure to bright light: a case series study. Chronobiol. Int. 24, 521–537.
Willison, L.D., Kudo, T., Loh, D.H., Kuljis, D., Colwell, C.S., 2013. Circadian dysfunction may be a key component of the non-motor symptoms of Parkinson's disease: insights from a transgenic mouse model. Exp. Neurol. 243, 57–66.
Zhou, J.N., Hofman, M.A., Swaab, D.F., 1995. VIP neurons in the human SCN in relation to sex, age, and Alzheimer's disease. Neurobiol. Aging 16, 571–576.

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