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Commentary and hypothesis: Circadian and/or sleep disruption may cause negative conditioning in the brain

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The concept of tolerance and pre-conditioning states that sublethal insults induce endogenous protective mechanisms that defend the cell against subsequent potentially lethal insults. An emerging idea suggests that "negative conditioning" may also exist, i.e., prolonged exposure to stress may degrade endogenous protective capacities and render the cell or organism more vulnerable to subsequent insults. Here, we propose the hypothesis that disruptions in sleep and/or disruptions in entrainment by the circadian clock may lead to perturbations in cellular and physiologic homeostasis that increase brain vulnerability to injury and disease, and decrease resilience.

Keywords: Circadian rhythm, Sleep disruption, negative conditioning, dementia, neurodegeneration

Tolerance and preconditioning are well documented in neurobiology and vascular biology (Gidday, 2006; Koch et al., 2012; Jiang et al., 2018; Chong et al., 2019). For example, exposing the brain to short periods of ischemia mitigates injury after subsequent prolonged ischemia and stroke (Pignataro et al., 2008; Zhao, 2009; Cuomo et al., 2018). Molecular mechanisms underlying this phenomenon have been extensively investigated and involve multifactorial pathways including hypoxia-inducible factor (HIF), mitogen-activated protein kinase (MAP kinase), nuclear factor-kappa B (NF-kappa-B), and mitochondrial and endoplasmic reticulum signaling (Gidday, 2006; Yang et al., 2017; Cuomo et al., 2018; Yu et al., 2018). In contrast to the beneficial "positive" effects of pre-conditioning, "negative conditioning" may also exist, whereby prolonged exposure to stress degrades homeostasis, downregulates cellular pathways of endogenous protection, and leads to increased vulnerability of the brain (Pignataro et al., 2019). This is an emerging concept, and mechanisms remain to be defined. One hypothesis would be that positive and negative conditioning are mediated by the same molecular components, and differences in outcome depend on the intensity, duration, or timing of the stimulus or stressor. For example, brief activation of extracellular signal-regulated kinases (ERK) MAP kinase (Choi et al., 2006) or HIF (Mesa-Ciller, 2019) triggers protective responses, whereas prolonged activation of ERK or HIF signaling leads to cytotoxicity (Subramaniam and Unsicker, 2010; Choi et al., 2016). Alternatively, positive versus negative conditioning may be induced by different types of stimuli or stress.

Aging and common clinical comorbidities provide obvious examples for negative conditioning (Pignataro et al., 2019; Selvaraji et al., 2019; Jiang et al., 2021). In animal models of focal cerebral ischemia, antioxidant systems are downregulated and reactive oxygen species (ROS)-mediated damage is amplified in aged brains compared to younger ones (Ritzel et al., 2018; Fan et al., 2019). Similarly, in hypertension or diabetes, prolonged vascular and metabolic stress may exacerbate neuroinflammation after stroke (Shukla et al., 2017). In this context, is it possible that negative conditioning may also be triggered by other types of stress that disrupt physiology? It has been proposed that sleep is a form of beneficial pre-conditioning for the brain (Pincherle et al., 2017), therefore

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prolonged disturbances in sleep or circadian disruption may be detrimental.

The term circadian (from the latin "circa diem") refers to near-24-h cycles of physical and behavioral changes regulated by phylogenetically and evolutionarily conserved endogenous systems (Allada and Bass, 2021). The circadian clock regulates a variety of critical cellular processes, including inflammation (Scheiermann et al., 2018), blood flow (Pulido et al., 2020), metabolism (Han et al., 2021), and redox homeostasis (Wang et al., 2012; Chhunchha et al., 2020). Hence, circadian biology may interact with mechanisms of central nervous system (CNS) disease and neuroprotection, and disruption of clock-regulated rhythmicity may induce molecular, cellular, and metabolic stress that render the brain more vulnerable to neurodegeneration (Videnovic et al., 2014; Logan and McClung, 2019; Esposito et al., 2020; Lo et al., 2021; Nassan and Videnovic, 2021).

Emerging studies point to interactions between circadian clock-regulated biology and neurodegeneration (Musiek and Holtzman, 2016). Patients with dementia often display fragmented sleep/wake patterns; they frequently fall asleep during the day and wake up during the night (Peter-Derex et al., 2015; Cordone et al., 2021), and fragmentation precedes and even predicts increased risk of cognitive decline (Targa et al., 2021). Circadian rhythm disruptions are not surprising since these patients may have degeneration of the neurons of the suprachiasmatic nucleus (SCN) of the hypothalamus, decrease in SCN volume and cell number (Swaab et al., 1985; Hu et al., 2013). The SCN is the location of the central mammalian circadian pacemaker, which is responsible for temporal organization of sleep-wake patterns and for coordinating hormonal and behavioral rhythms (Morin, 2013). In patients with dementia, daily rhythm disruption occurs before onset of typical clinical symptoms, suggesting that in addition to being a symptom of neurodegeneration, it might also be a potential risk factor for developing disease. Moreover, studies have found correlations between circadian disruption and severity measures of Alzheimer's disease (AD) (Leng et al., 2019).

A critical question is whether circadian rhythm disruptions are in part responsible for CNS disease or a consequence of it, or both. There are many potential pathways by which circadian rhythms and sleep can affect the pathology of dementia. Sleep deprivation or disruption perturbs amyloid-beta (Aβ) dynamics (Rothman et al., 2013), increases neuroinflammation, alters the glymphatic clearance of toxic proteins (Xie et al., 2013), and abolishes rhythms in the synaptic proteome and synaptic phosphorylation (Bruning et al., 2019; Noya et al., 2019). Neuronal circadian clocks may be involved in brain oxidative stress, metabolic function, and synaptic homeostasis (Musiek et al., 2013; Noya et al., 2019). Daily rhythms are also observed in astrocytes and microglia, and these glial mechanisms may regulate the blood-brain barrier (BBB), inflammation, and synaptic function (Chi-Castaneda and Ortega, 2016). Furthermore, genes implicated in neurodegeneration may interact with genes regulating the circadian clock (Lim and Allada, 2013; Lananna et al., 2020). Finally, outside the brain, circadian clocks in peripheral cells and tissues regulate the immune system and the gut microbiome, and these elements of systemic biology may in turn, modify mechanisms of CNS disease (Druzd et al., 2017; Murakami and Tognini, 2019).

CNS disease may also induce dysregulations in circadian biology and sleep. As noted above, there is a loss in SCN neurons in some patients with dementia (Swaab et al., 1985). In some mouse models of AD, disease progression is accompanied by disruptions in circadian rhythms (Nassan and Videnovic, 2021). In cell cultures, Aβ peptide can induce degradation of the transcription factor aryl hydrocarbon receptor nuclear translocator-like protein-1 (BMAL1) (Schmitt et al., 2017), one of the central clock genes. An initial study suggested that fibroblasts from AD patients show altered methylation of the BMAL1 promoter, leading to altered BMAL1 expression (Cronin et al., 2017). Therefore, it is likely that signaling pathways that connect CNS disease and circadian biology will be bidirectional (Wang and Holtzman, 2020); circadian and sleep disruptions enhance CNS pathophysiology, and in turn, neurodegeneration perturbs sleep and the circadian clock.

Clinical evidence for the potential role of circadian and sleep disruption as a stressor and negative conditioner in the brain may be found in observational studies that have attempted to link disturbed sleep/wake cycles or short sleep duration with the increased risk of cognitive decline and dementia (Li et al., 2020). However, most studies to date have a follow-up of less than 10 years, whereas pathophysiological progression in dementia typically occurs over longer periods of time (Westwood et al., 2017). In this regard, a new study that followed patients for over 20 years beginning at middle-age, may offer additional insights (Sabia et al., 2021). Seven thousand nine hundred and fifty-nine patients were recruited at 50 years of age, and then follow-ups were performed at the age of 60 and 70. Among these participants, 521 developed dementia over a mean follow-up period of 24.6 years. Seven hours of sleep per night was considered normal sleep duration for this study, while short duration was defined as $\leq$ 6 hours and long duration as $\geq$ 8 hours. The lowest incidence of dementia was observed among those who slept 7 hours per night, independently of the age at which sleep duration was measured. In contrast, short sleep duration was associated with the highest risk of dementia at all ages. Although this study cannot prove causality, these associations between sleep at middle age and the risk of dementia at later age suggest that chronic short sleep duration may comprise a potential form of negative conditioning that renders the brain more susceptible to disease.

Other epidemiological studies document that shift-work or night-work, which typically are associated with circadian disruption (and sometimes sleep loss) because they require the individual to be awake at night and try to sleep during the day, are associated with multiple negative cardiovascular and CNS outcomes (Vyas et al., 2012; Morris et al., 2016), including increased risk of dementia (Bokenberger et al., 2018), ischemic stroke (Li et al., 2016), and migraine headaches (Sandoe et al., 2019).

Mechanisms of CNS disease and neurodegeneration are often linked with aging and inflammation. Recent studies suggest that these pathways may also be modulated by circadian rhythms. There are diurnal patterns in the regulation of immune cells and the amplitude of circadian rhythms may be dampened in older adults. Interestingly, a recent study demonstrated that with aging, there are losses in diurnally rhythmic innate immune responses and monocyte trafficking from bone marrow to blood that underlie maladaptive responses of the aging immune system (Blacher et al., 2021). Another paper showed that aging of the immune system alters neutrophil trafficking and these perturbations may underlie the circadian susceptibility of older mammals to cardiovascular disease (Adrover et al., 2019). Altogether, these emerging studies suggest that feedback between disruptions of circadian rhythms and loss of immune homeostasis may play a causal role in driving systemic ageing (Yousefzadeh et al., 2021). Thus, a deeper investigation into these complex mechanisms may lead to new therapeutic targets not only for neurodegeneration but also for extending brain resilience and healthy aging.

Although this commentary mostly focuses on neurodegeneration, circadian and sleep mechanisms may also contribute to other forms of CNS disease. Sleep disturbances have been implicated as a risk factor for stroke (Kostenko et al., 2016; Lo et al., 2021), and after traumatic brain injury, circadian disruption may be involved in the progression of

injury and recovery (Ayalon et al., 2007). Of course, acute brain injury after stroke and trauma involves many mechanisms that differ from neurodegeneration, and there will also be important differences even within the spectrum of neurodegeneration itself (e.g., AD versus Parkinson's disease). However, it is also likely that common pathways may exist that underlie the complex balance between beneficial and deleterious stimuli in the context of molecular and cellular tolerance and conditioning.

Taken together, the emerging literature may be consistent with the hypothesis that circadian and sleep disruptions comprise a form of negative conditioning that renders the brain more vulnerable to various subsequent insults. Some data indeed suggest connections between circadian biology and molecular mechanisms of tolerance. For example, studies have found that remote ischemic pre-conditioning is dependent on Bmal1 (Brager et al., 2016), mitochondrial pre-conditioning requires signaling pathways involving RevErb-alpha (Sengupta et al., 2016), preconditioning-mediated protection of the BBB involves genes that are modulated by the circadian clock (Cuddapah et al., 2019; Hong et al., 2019), and benefits of exercise pre-conditioning may be subject to circadian clock regulation (McGinnis and Quindry, 2020). It is important to note, however, that there may be a complex balance between positive versus negative effects of circadian disruptions, perhaps dependent on intensity, duration, and timing. One experimental study suggests that mild sleep deprivation prior to ischemia could act as a protective pre-conditioning stimulus in a rodent model of focal stroke (Cam et al., 2013). Finally, there may be interactions with other negative conditioners since circadian clocks are altered in aging and comorbidities such as hypertension and metabolic disease (Sladek et al., 2012; Lemmer and Oster, 2018). Further studies are warranted to investigate this hypothesis of negative conditioning and define mechanisms in circadian biology and sleep that may lead to novel therapeutic targets for CNS injury and disease.

Declaration of conflicting interests

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