EBioMedicine 62 (2020) 103142

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

Circadian rhythm sleep-wake disorders (CRSWDs): Linking circadian misalignment to adverse health outcomes.

Krista K Ingram

Department of Biology, Colgate University, United States

ARTICLE INFO

Article History:
Received 9 November 2020
Accepted 9 November 2020
Available online xxx

Sleep comprises roughly one-third of our lives and is vital to human health. Disruptions to behavioural sleep-wake cycles are becoming increasingly common and can lead to adverse health outcomes, including psychiatric and metabolic disorders, cardiovascular disease, and cancer [1,2]. An estimated 15–30% of US adults suffer from the negative effects of dysregulation of sleep, contributing to over $411 billion annual losses or approximately 2.3% of the US gross domestic product [3]. For decades, circadian biologists and sleep researchers have made significant advances in understanding the environmental and biological factors affecting circadian rhythms and sleep disorders in parallel but independently. Though the two-process model of sleep regulation integrates the two fields in theory [4], efforts to understand the molecular mechanisms linking the sleep homeostat and the circadian clock are in their infancy.

The timing of sleep is regulated by both homeostatic factors (an increase in sleep drive with hours of wakefulness) and the endogenous circadian system (rhythmic oscillations of clock genes in the brain). Normally, sleep occurs about two hours after the onset of melatonin secretion, a physiological marker of circadian rhythms. In some individuals, this intrinsic circadian clock may cycle later or earlier than socially scheduled sleep time, resulting in a delayed or advanced sleep-wake phase relative to the social environment, a form of social 'jet lag'. Circadian misalignment with the external environment, *e.g.*, as occurs in shift work, can lead to negative health outcomes, with the most common sleep conditions collectively termed circadian rhythm sleep–wake disorders (CRSWDs). CRSWDs are often misdiagnosed as insomnia or other sleep-related issues—a serious problem as treatments to alleviate sleep issues are ineffective and potentially harmful in patients whose disorders have a circadian etiology [5].

Disentangling circadian factors from sleep issues in a clinical setting is difficult and labor-intensive, yet critical to identifying the correct medical treatment. To date, clear diagnostic standards for CRSWDs are still in development, as is the search for effective therapeutic targets. In a recent article in *EBioMedicine*, Akashi and colleagues outline an innovative method for solving the former issue [6]. Utilizing the ubiquity of circadian clock function in many peripheral tissues, they demonstrate the use of a non-invasive measure of circadian gene oscillations in hair follicle cells to estimate the phase of an individual's circadian cycle. This intrinsic circadian phase can then be compared relative to behavioural sleep parameters, *e.g.*, what time an individual goes to sleep or what time they wake up, to distinguish whether an individual has a circadian-related sleep condition. In typical CRSWDs, circadian-driven sleepiness is synchronized to habitual sleep timing, but desynchronized to social time schedules. In this study, the authors identify a novel type of CRSWD, referred to as latent circadian-related sleep-wake disorder (LSCRWD). In cases of LCRSWDs, individuals force synchronization of habitual sleep timing to coincide with daily social activities *against* circadian-driven sleepiness, which causes additional sleep problems.

To characterize the circadian-coupling of LSCRWD, Akashi and colleagues discovered a prototypic diagnostic standard for LCRSWD—the interval between the peak expression of the clock gene Period 3 (Per3) and the wake time on a work or school day (GUw). This interval represents the degree of misalignment between the intrinsic circadian rhythm and the socially-influenced sleep-wake cycle; individuals suffering from sleep problems due to a delayed circadian phase have a value of GUw-Per3 peak that is lower than the mean - SD value for the control group. The diagnostic criteria described in the article are required but not sufficient for the development of sleep problems, suggesting additional factors contribute to the development of LCRSWD. To validate the diagnostic criteria, the authors tested whether circadian amelioration (via increased exposure to morning sunlight, decreased exposure to light-emitting devices before bedtime, and stabilization of wake times across work/school days and free days), altered sleep symptoms and the interval of Per3 and GUw. Albeit with a small sample size, the demonstration of improved sleep disturbance scores and an advance in phase (timing of peak Per3 expression) following circadian treatment underscores the utility of using *in vivo* circadian phase as a means of evaluating potential therapeutic interventions.

Reliable *in vivo* measures of circadian phase are of significance to both clinicians and researchers of basic science. Given that up to one-

https://doi.org/10.1016/j.ebiom.2020.103142

third of the adult urban population suffers from 2 h or more of social jet lag and that younger generations are exposed to considerably higher levels of bright or blue lights during the evening from modern electronic devices, the number of people suffering from LCRSWD is likely to be substantial [6,7]. By testing for *in vivo* circadian phase, clinicians can easily and reliably diagnosis circadian disorders from those due to chronic sleep loss or ineffective sleep, and subsequently tailor effective therapies based on the cause and even the type of circadian disorder. Treatmentstrategies for many CRSWDs are based on additional exposure to bright or blue light at appropriate times (morning for delayed and afternoon for advanced phase disorders) and/or prescribed doses of melatonin (*e.g.*, taking oral melatonin one hour prior to bedtime for delayed phase disorder) [5,8]. Once correctly diagnosed, treatments for LCRSWD are both inexpensive and effective, underscoring the significance of accurate diagnostic criteria.

Importantly, this study heralds a significant research tool for addressing the outstanding questions at the intersection of the fields of chronobiology and sleep research. Circadian misalignment has been implicated in a number of health problems, ranging from mild, temporary outcomes, ie, those due to travel jet lag or daylight savings, to severe, chronic problems leading to mental health issues, sleep disturbance, and other physiological disorders. Yet, we are still lacking a clear understanding of the molecular mechanisms underlying circadian misalignment and its associated outcomes. Furthermore, it is not known why some individuals who experience circadian misalignment are more susceptible to negative health outcomes than others with similar phase advances or delays. The ability to reliably measure *in vivo* circadian phase allows researchers to begin to tackle these important questions. Understanding how sleep- and circadian-mediated synchronization of diverse behavioural, metabolic and physiological systems contributes to health resilience and well-being is the next frontier in basic research to improve personalized medicine, pharmacotherapies, mitigation of disease risk and general public health.

Contributors

The author confirms sole responsibility for the conception and preparation of this invited Commentary.

Declaration of Competing Interest

KI declares no conflicts of interest.

References

[1] Kiley JP, Twery MJ, Gibbons GH. The national center on sleep disorders research-progress and 5, promise. Sleep 2019;42(6):zsz105. doi: 10.1093/sleep/zsz105.
[2] Walker WH, Walton JC, DeVries AC, Nelson RJ. Circadian rhythm disruption and mental health. Transl Psychiatry 2020;10:28 https://doi.org/10.1038/s41398-020-0694-0.
[3] Hafner M, Stepanek M, Taylor J, Troxel W, Van Stolk C. Why sleep matters-the economic costs of insufficient sleep: a cross-country comparative analysis. RAND Health Q 2017;6(4):11.
[4] Borbély AA, Daan S. Wirz–Justice A and Deboer T, The two–process model of sleep regulation: a reappraisal. J Sleep Res 2016;25:131–43. doi: 10.1111/jsr.12371.
[5] Pavlova KM, Latreille V. Sleep Disorders. Am J Med 2019;132(3):292–9. doi: 10.1016/j.amjmed.2018.09.021.
[6] Akashi M, Sogawa R, Matsumura R, Nishida A, Nakamura R, Tokuda IT, Node T. A detection method for latent circadian rhythm sleep-wake disorder. EBioMedicine 2020;62 https://doi.org/10.1016/j.ebiom.2020.103080.
[7] Roenneberg T, Allebrandt KV, Merrow M, Vetter C. Social jetlag and obesity. Curr Biol 2012;22(10):939–43.
[8] Faulkner SM, Bee PE, Meyer N, Dijk DJ, Drake R. Light therapies to improve sleep in intrinsic circadian rhythm sleep disorders and neuro-psychiatric illness: a systematic review and meta-analysis. Sleep Med Rev 2019;46:108–23 https://doi.org/10.1016/j.smrv.2019.04.012.