Dear editors,

The seminal, discoveries by Jeffrey Connor Hall, Michael Rosbash and Michael Warren Young have earned the Nobel Prize in Physiology and Medicine 2017 for revealing a crucial physiological mechanism explaining biological clock, with important implications for human health and diseases. The work explains the interplay between the biological clock, the transcriptional feedback loop, and neuroscience, where they identified genes and proteins that work together both in humans and other animals. This article describes the link between biological clock disruption and consequent neurodegeneration and also highlights the significance of biological clock modulators for possible clinical interventions in neurological disorders.

The biological clock of ~24 hours is an internal timekeeping mechanism which controls most of the body functions. The hypothalamic suprachiasmatic nucleus (SCN) is the master regulator of the biological clock, which coordinates functioning of various organs viz., brain, liver, kidney, and heart. Variations in sleep, metabolism, and hormone together determine daily circadian oscillation patterns. Disruption of the biological clock (e.g., people working in night shift) significantly increases the risk of developing various diseases such as neurodegenerative disorders, metabolic disorders, cardiovascular disease, and cancer (Cermakian and Boivin, 2003), which suggests that biological clock-controlled actions play indispensable roles in human physiology.

Clock disruption correlates with progressive neurodegeneration: Studies have shown that patients with neurodegenerative brain disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) are associated with disrupted biological clock (Musiek, 2015). The biological clock abnormalities comprised delayed sleep, impaired cortisol and thermoregulation rhythm, the reduction of melatonin levels during the night, and impaired expression of the CLOCK genes (e.g., Bmal1, Rev-Erb, Per1, Per2, Cry1 and Cry2). As shown in Figure 1, the biological clock is controlled at molecular level via feedback loop mechanism by a group of CLOCK genes in ~24 hours. The CLOCK genes control a variety of biological functions viz., sleep-wake cycle, cognitive functions, immune responses, and response to oxidative stress. Importantly, disruption of the CLOCK leads to increased oxidative stress, inflammation and synaptic loss that contribute directly to neurodegeneration and loss of cognitive functions. In this context, Karatosoreos and coworkers have demonstrated a connection between clock dysfunction and neurodegeneration, wherein chronic disruption of CLOCK in mice via shifting light-dark (20:4) cycles leads to loss of cognitive functions, suggesting that impaired biological clock contribute in neurodegeneration (Karatosoreos et al., 2011). The findings are supported by the loss of expression and mutual correlations of the CLOCK genes in clinical and preclinical AD (Wu et al., 2006). Functional disruption of the SCN might be responsible for the loss of expression patterns of the CLOCK genes (Wu et al., 2006). Studies have shown that during AD the melatonin levels are profoundly depleted while its supplementation provides neural protection in experimental ischemia, AD, and PD (Reiter et al., 2004). A report by Song et al. (2015) showed that five familial AD mutations (5XFAD) mice (an experimental model of AD) have abundant amyloid deposits in their brain, and the amyloid β (Aβ) critically induce impairment of the biological clock. In addition, the biological clock also controls the functioning of lymphoid tissues viz., spleen, lymph nodes, and resident macrophages (e.g., microglia). In our study, we demonstrated that Aβ and lipopolysaccharide initiate neurotoxic inflammatory response through microglial activation, and we proposed that TLR4 antagonism, inhibition of JNK/p38-MAPK and CD40 stimulation could provide neuroprotection (Gaikwad et al., 2017). Further, evidences suggest a tight interplay between immune system and biological clock can control the disease outcome (Dumbell et al., 2016). In this complex scenario, it is possible that the microglia-mediated excessive production of inflammatory cytokines could have an influence on biological clock and sleep, which might play a role in regulation of neurodegenerative disorders. However, more detailed investigation of this system is warranted.

Clock dysfunction influences the pathogenesis of neurological disorders: Pathophysiological mechanisms of impairment of biological clock and neurodegeneration have been well documented in the AD (Musiek, 2015). Neuronal loss in the SCN and loss of melatonin production by pineal gland are the major contributors in impairment of biological clock in the AD patients (Wu et al., 2006). It is clear that the prolonged disrupted biological clock negatively influences health via impairment of immune responses, stress responses and metabolism in the brain (Musiek, 2015), which may exacerbate the pathogenesis of neurodegenerative disorders. Notably, single nucleotide polymorphisms (SNPs) of Bmal1 and per1 are associated with increased risk of PD. Furthermore, the clock genes (e.g., presenilin-2) regulate the expression of other genes that have direct implication in the pathogenesis of neurodegenerative disorders. Evidence suggests that the impaired biological clock may contribute to pathogenesis of neurodegenerative disorders through impaired metabolism and increased oxidative stress in the brain, a well-known contributor for neurodegeneration. The biological clock regulates oxidative stress via melatonin, an efficient scavenger of free radicals (Reiter et al., 2004). Restoration of the biological clock in a mouse model of neurodegenerative disease using pharmacological intervention, scheduled-feeding as well as management of sleep-wake cycles shown to rejuvenate oscillation of CLOCK genes in the SCN which leads to improvements in neurological function (Pallier et al., 2007; Maywood et al., 2010). These observation affirms that impairment of biological clock contributes to the pathogenesis of neurodegenerative disorders.

Clock targeted intervention for neurodegenerative disorders: As the impaired biological clock is involved in the pathogenesis of neurodegenerative disorders, restoring the biological clock could ameliorate the symptoms, or prevent the disease. In this context, a number of biological clock targeted therapies have been investigated for possible therapeutic interventions. In patients with PD, daily light exposure has shown to improve sleep/wake rhythms through reducing daytime sleepiness and increasing daytime activity (Videnovic et al., 2017). Further, light exposure regimens lead to improvements in daily living activities in patients with PD and severe dementia (Forbes et al., 2014). Timed light therapy achieves improvements in cognitive functions mechanistically via master clock restoration, which helps protect against oxidative stress and inflammation (Figure 1). Strategies directed at normalizing biological clock might provide novel therapeutic interventions. Therefore, the biological clock could be a novel therapeutic target and regulators of the master clock (e.g., light, melatonin, food intake pattern) could be
The biological clock: future of neurological disorders therapy.

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Accepted: 2017-12-05

doi: 10.4103/1673-5374.228764.

The study was financially supported by DST-SERB (PDF/2016/001369). The Author acknowledges Dr. Birendra Prusty, Dr. A. Raj Kumar Patro and Dr. Dwaker Singh for helpful discussion.

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This article is a perspective on the influence of the biological clock with neurological alterations. The article is principally very interesting, well-organized and correctly written.

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