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The Central Clock in Patients With Parkinson Disease

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To the Editor

The regulation of sleep-wakefulness behavior involves 2 physiological processes. A circadian process, based in the suprachiasmatic nucleus, is responsible for the timing of sleep and wakefulness, and a homeostatic process that monitors and responds to the quality and quantity of prior sleep and wakefulness.[1] In patients with Parkinson disease (PD), sleep disturbances are among the most debilitating nonmotor symptoms.[2] The underlying neuropathology is multifactorial and involves complex disease-medication interactions.[2] Given this complex pathophysiology, the contribution of a dysfunctional suprachiasmatic nucleus clock has remained elusive.

In a study published in *JAMA Neurology*, Breen et al[3] assessed sleep architecture and the circadian profile of cortisol, melatonin, and peripheral clock gene expression in 30 patients diagnosed as having PD. In addition to confirming the well-established alterations of sleep in PD,[2] a significant reduction in the amplitude of melatonin secretion, hypercortisolemia, and altered peripheral clock gene expression were found in patients with PD. Videnovic et al[4] also reported a 4-fold reduction in the amplitude of melatonin secretion in 20 patients with PD housed in a constant-routine protocol. Videnovic et al[4] went further by showing that patients with PD with excessive daytime sleepiness had a significant 2.5-fold reduction in the melatonin rhythm amplitude compared with patients with PD without excessive daytime sleepiness.

However, in both the Breen et al[3] and Videnovic et al[4] studies, no alterations in the markers of the circadian phase were reported in patients with PD. This is surprising given that in both studies, patients with PD were receiving dopaminergic therapy. Previous studies that investigated the phase of the melatonin rhythm in medicated and unmedicated patients with PD found a phase-advanced melatonin rhythm in patients receiving dopamine therapy.[5] Indeed, Bolitho et al[6] confirmed the alteration of the phase angle of entrainment of the melatonin rhythm in 16 treated compared with untreated de novo patients with PD and healthy control participants. Additionally, Bolitho et al[6] reported a 3-fold increase in melatonin secretion, contrasting the decrease reported by Breen et al[3] and Videnovic et al.[4] The reasons behind these discrepancies are not clear. As stated by Videnovic et al,[4] the

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experimental protocols of the earlier studies did not control for environmental conditions. Consequently, the melatonin rhythm phase and amplitude may have been influenced by external factors such as light exposure. However, this may not account for the results of Bolitho et al[6] given that melatonin samples were collected under controlled conditions. A more plausible explanation is that these differences reflect an intrinsic neuropathophysiological variability in the PD cohorts investigated. This conclusion is supported by significant differences in multiple features of the sleep/wake cycle between patients studied by Breen et al[3] and Bolitho et al.[6] Furthermore, the patients in both studies did not show an increase in total sleep duration, which departs from the hypersomnia characterizing sleep in PD.[2]

Collectively, these studies show that alterations in the circadian system are a potential causative factor in disturbed sleep in PD. However, a remaining question is whether alterations in peripheral circadian markers reflect a dysfunctional central clock. The reported alterations in hormonal and molecular markers measured to assess the circadian system could also reflect dysfunctional efferent or afferent pathways of the suprachiasmatic nucleus. Detailed assessments of the different components of the neuronal networks governing circadian rhythms regulation using, for example, functional magnetic resonance imaging, are needed to resolve this remaining conundrum.

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