Circadian control of the peripheral vestibular organs in rodents and humans

Circadian rhythms are fundamental for maintaining physiological homeostasis, influencing processes such as sleep-wake cycles, metabolism, and hormonal regulation. The suprachiasmatic nucleus (SCN) serves as the master clock, synchronizing peripheral clocks throughout the body. The vestibular system, responsible for balance and spatial orientation, has been implicated in circadian regulation, yet its intrinsic clock machinery remains unexplored. Previous studies suggest vestibular input influences circadian rhythms, as evidenced by altered locomotor activity and temperature control in animals with vestibular dysfunction. Additionally, vestibular disorders in humans display time-dependent patterns, further supporting a vestibular-circadian interaction. Our study investigates the presence of an autonomous circadian clock in the peripheral vestibular organs (semicircular canals SCC, saccule, utricle and vestibular ganglia) by assessing core clock gene and protein expression in vestibular structures of mice and humans. Using PERIOD2::LUCIFERASE (PER2::LUC) bioluminescence assays from mouse tissues, we observed self-sustained oscillations in SCC, saccule, and utricle, with differential amplitudes and phase relationships. RNA scope (*Bmal1*and *Per2*) and immunohistochemistry (Bmal1, Cry1, Per1, and Per2) confirmed the rhythmic expression of in the peripheral vestibular organ from mice and humans, corroborating their functional circadian regulation. Furthermore, we explored the impact of cisplatin, a chemotherapeutic agent, on vestibular clock rhythms. Cisplatin administration disrupts PER2 oscillations in vestibular explants in a time-dependent manner, mirroring the cochlear findings where the day or night timing of drug delivery modulates drug response. Our findings provide the first direct evidence of a clock within the peripheral vestibular organ of rodents and humans, highlighting its potential role in modulating vestibular function and responses to pharmacological interventions. These findings suggest that vestibular disorders may follow a daily pattern, which could help explain why symptoms worsen or improve at different times of the day. This could lead to better treatment strategies for millions of people affected by vestibular dysfunction. These results underscore the importance of considering circadian timing in vestibular research and therapeutic strategies.