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EDITORIAL

Immune-Mediated Denervation of the Pineal Gland: a Potential Mechanism for Sleep Disturbance in Cardiac Disease

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In a typical human physiology, the sleep–wake cycle is strictly regulated by the circadian release of melatonin, aligning seamlessly with the Earth's diurnal cycle. The genesis of melatonin takes place within the pineal gland, which is under the regulatory influence of sympathetic neurons projecting from the superior cervical ganglia (SCG). Interestingly, the SCG also houses neurons that influence cardiac function [1]. Sleep anomalies, marked by diminished melatonin concentrations, altered sleep–wake patterns, and sympathetic disruptions, are frequently observed in patients with cardiac diseases, often correlating with escalated morbidity and mortality [2]. The specific etiology of these sleep interruptions in the context of cardiac diseases remains elusive, and the role of pineal gland innervation has not been addressed.

Recent insights emerge from a study led by Stefan Engelhardt's team at the Technical University of Munich, disseminated in the journal "Science." This groundbreaking research elucidates that sleep–wake disruptions in cardiac disease patients are precipitated by immune-triggered denervation of the pineal gland, which is the epicenter of melatonin production [3].

Acknowledging the central role of the pineal gland and its sympathetic regulation in maintaining diurnal rhythms and the frequent disruptions observed in chronic cardiac conditions, the researchers hypothesized that the neuronal regulation of the pineal gland might be abnormal in patients with cardiac diseases. They validated this hypothesis by labeling the sympathetic nerves via tyrosine hydroxylase staining and detected a remarkable decline in axonal density within the pineal gland tissue from the patients with cardiac diseases. The team extended their investigation to murine models of cardiac hypertrophy and failure, utilizing a transverse aortic constriction (TAC) model. The results revealed that cardiac hypertrophy and heart failure induced a significant reduction in plasma melatonin concentration and disruption of diurnal rhythmicity. To visualize the sympathetic neurons and their axons, the researchers crossbred dopamine-β-hydroxylase (Dbh)-Cre mice with tdTomato^{flox} mice. It was found that mice with chronic cardiac disease and heart failure appeared reduced sympathetic axonal density in the pineal glands. Meanwhile, they observed fibrotic scarring and hypertrophy of the SCG in both mice and humans with heart failure.

To dissect and quantitatively assess the cellular basis for the histomorphologic alterations of the SCG, the researchers performed a single-cell and single nuclei RNA sequencing (scRNA-seq and snRNA-seq, respectively). In total, 20,780 cells passed quality checks and were used for subsequent computational analysis. Five main cell types in the SCG were identified, including sympathetic neurons, Schwann cells, fibroblasts, endothelial cells, and immune cells. Notably, through snRNA-seq and spatial sequencing, a subset of sympathetic neuron category manifested melatonin receptor 1A

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Comment on Ziegler K, Ahles A, Dueck A, Esfandyari D, Pichler P, Weber K, Kotschi S, Bartelt A, Sinicina I, Graw M, Leonhardt H, Weckbach L, Massberg S, Schifferer M, Simons M, Hoeher L, Luo J, Erturk A, Schiattarella G, Sassi Y, Misgeld T, and Engelhardt S, Immune-mediated denervation of the pineal gland underlies sleep disturbance in cardiac disease. Science, 2023. 381(6655): p. 285–290. https://doi.org/10.1126/science.abn6366.

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(*Mtnr1a*) expression, earmarked as the genuine pineal gland-innervating neurons. Further investigations using the macrophage marker CD68 revealed an intensified macrophage infiltration alongside a decline of pineal-innervating neurons in the backdrop of chronic cardiac conditions.

Lastly, to understand the effects of pineal gland denervation on melatonin-regulated diurnal rhythm, surgical SCG extractions were performed, and the researchers found that pineal gland denervation resulted in the disruption of diurnal rhythmicity, which could be restored by melatonin supplementation. This reaffirmed the instrumental role of the pineal gland and melatonin in modulating the sleep–wake cadence. To further investigate the role of macrophages in this process, transcriptomic analyses detected perturbed cellular communication between macrophages and sympathetic neurons in the early cardiac disease phase. Administering the macrophage inhibitor clodronate reduced macrophage numbers, which prevented pineal denervation and functional impairment, resulting in increased sympathetic axonal density and elevated melatonin levels in the pineal gland. This suggests that macrophages play a significant role in the interaction between sympathetic neurons and the pineal gland. The study proposes that ganglion-targeted anti-inflammatory interventions and melatonin supplementation could be potential treatments for sleep disturbances in cardiac diseases.

In summary, this study combining immunostaining, RNA sequencing, and animal models finds that sleep–wake anomalies in patients with chronic cardiac diseases predominantly stem from pineal gland denervation and consequent melatonin disruptions. The research highlights the immune-driven sympathetic neuron degradation as a central mechanism. Targeting immune responses, particularly macrophage accumulation in the SCG, may emerge as a promising therapeutic avenue.

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Declarations

Research Involving Human Participants and/or Animals This article does not contain any studies with human participants or animals performed by any authors.

Consent to Participate This article does not contain any studies with human participants.

Conflict of Interest The authors declare no competing interests.

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