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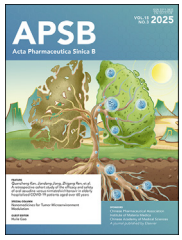

HIGHLIGHT

Monocytes in the brain−heart crosstalk control sleep under myocardial infarction

KEY WORDS

Myocardial infarction;
Slow wave sleep;
Monocytes;
TNF signaling

Communication between the brain and the heart is finely tuned by numerous factors, with sleep being particularly crucial. It is well known that sleep plays a vital role in cardiovascular health, and poor sleep can exacerbate myocardial infarction (MI) by interfering heart energy metabolism and triggering oxidative stress[1]. However, it remains unclear whether the immune system conveys information about cardiac homeostasis to the brain. A recent study[2], published in *Nature*, has addressed this question by demonstrating immune-mediated pathways that connect acute ischemic cardiac injury to the brain's sleep circuits, subsequently impact in the sympathetic outflow from the brain to the heart to govern cardiac healing and recovery, which may be a potential therapeutic target for drug development to MI therapy.

The brain−heart interaction theory, first proposed by Roger Sperry, is pivotal in the context of many cardiovascular and cerebrovascular diseases, including atherosclerosis, heart failure, and cerebral ischemia[3,4]. The central autonomic nervous network, a key component of the brain−heart axis, modulates cardiac vascular function and myocardial metabolism *via* the autonomic nervous system and hormonal regulation[5,6]. Similarly, the heart's normal function impacts the physiological activities of tissues and organs throughout the body, with a particular influence on the brain[7]. Furthermore, brain nuclei, such as the amygdala and hippocampus, significantly regulate cardiac physiological functions through the hypothalamic−pituitary−adrenal axis and the sympathetic nervous system[8]. Recent evidence has uncovered intricate neural and immune-mediated circuits, like sleep-regulating signals from the hypothalamus that modulate immune cell production in atherosclerosis, thereby allowing the sleeping brain to influence the biological processes underlying cardiovascular disease[9,10]. However, it remains unclear whether cardiovascular injury affects sleep and its brain circuits through interoceptive heart-to-brain signaling, and if these sleep alterations subsequently influence brain outputs and neuronal innervation of the heart.

In the study by Huynh et al.[2], the sleep of mice with and without atherosclerosis was compared. The mice with atherosclerosis exhibited an increase in slow wave sleep (SWS) and a decrease in sleep rhythmicity compared to the healthy counterparts. To further investigate this effect, they created MI mouse models and monitored the sleep patterns. In the week following MI, the mice spent more time asleep, with an increase in SWS characterized by longer SWS episodes, fewer transitions between sleep and wakefulness, and reduced time in both wakefulness and rapid eye movement (REM) sleep. Moreover, spectral analysis of electroencephalography (EEG) signals demonstrated that MI led to an increase in delta wave (0.5−4 Hz) power during the initial seven days post−MI, suggesting a specific enhancement in the pressure and drive for SWS. These observations suggest that MI is associated with an increase in sleep time and a change in sleep pattern.

Monocytes were recruited into the brain after MI by microglia. Single-cell sequencing analysis of the brain tissue revealed a significant upregulation of markers for microglial activation—such as Trem2, Apoe, Itgax, Spp1, and Il3ra—as well as chemokine signaling genes including Ccl2, Ccl5, Ccl8, Ccl3, Ccl4, Cxcl2, and Cxcl12. This transcriptional shift was not observed in non-microglial macrophages. Interestingly, monocyte number was elevated in the brain of MI mice, and remained up to three days, without any changes in other types of immune cells including neutrophil, T cell, or microglia counts. Lineage tracing and imaging system demonstrated that post−MI, the monocytes

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were recruited to the brain, predominantly localizing to the choroid plexus of the third ventricle and the thalamic region. The deletion of IL-3Rα in microglia, a key regulator of chemokines, halted the MI-induced rise in CCL2 levels and the subsequent monocyte infiltration into the brain, suggesting that microglia are responsible for attracting peripheral monocytes to the choroid plexus and thalamus following MI. In MI mice, the expression of CCR2, the receptor for CCL2, was notably increased in the third ventricle and thalamus. The administration of a CCR2 antagonist not only reduced monocyte infiltration into the brain post−MI but also mitigated the sleep disturbances arising from cardiovascular pathology, much like CCR2 gene knockout. Moreover, the injection of monocytes from MI model mice into the cerebrospinal fluid of healthy mice led to an increase in SWS and sleep disturbances, indicating that the monocytes recruited to the brain post−MI contribute to sleep disorders. These findings collectively reveal that MI augments sleep through microglia-mediated monocyte recruitment into the brain.

Glutamatergic neurons were activated by the monocytes through secretion of tumor necrosis factor (TNF). The scRNA-seq data revealed that genes significantly enriched in the monocytes following MI injury are predominantly associated with the TNF signaling pathways. Flow cytometry experiments found an increase in TNF production by the brain monocytes after MI, without TNF elevation in the peripheral blood levels. Intriguingly, when anti-TNF antibodies were injected into the cerebrospinal fluid of MI model mice, there was no change in the number of monocytes in the brain; however, sleep disturbances were markedly alleviated. Similarly, TNF knockout mice did not exhibit increased sleep after receiving monocytes from MI model mice. Additionally, in thalamic lateral posterior nucleus (LPN), a class of neurons, 80% of which are glutamatergic neurons, highly express the TNF receptor (TNFR1). Selectively knocking out *Tnfrsf1a* in LPN neurons significantly alleviated the sleep disturbances induced by MI. Together, these findings suggest that after MI, the recruited monocytes in the brain exert their influence on glutamatergic neurons in the LPN through the TNF−TNFR1 signaling axis.

Augmented sleep reduces cardiac inflammation and promotes healing after MI. To detect the physiological correlation between cardiac injury and sleep, mice were either permitted unrestricted sleep or subjected to sleep fragmentation (SF) after MI. It was demonstrated that mice with MI that experienced SF exhibited a significantly higher mortality rate compared to those allowed to sleep freely. Simultaneously, monocytes, neutrophils, macrophages, and fibroblasts were markedly accumulated in the infarcted area, with macrophages and fibroblasts lasting for seven days. These findings suggest that unrestricted sleep post−MI reduced cardiac monocyte recruitment and ameliorated inflammation. Additionally, macrophages in the infarcted area of mice with SF differentially enriched genes related to chemokine signaling and expressed the adrenergic β2 receptor (ADRB2). In these mice, plasma corticosterone levels remained unchanged, but cardiac expression of dopamine-β-hydroxylase (DβH, a key enzyme in norepinephrine synthesis) was elevated. Knocking out ADRB2 or pharmacologically blocking it significantly reduced monocyte aggregation in the heart and improved cardiac ejection function in MI model mice after SF. Moreover, knockdown of *Tnfrsf1a* in glutamatergic neurons increased cardiac DβH and the accumulation of monocytes and macrophages in the infarcted heart. These results reveal that increased sleep stimulated by MI help to restrict cardiac sympathetic tone and limit monocyte influx and cardiac inflammation, thereby contributing to the healing process.

Collectively, this research reveals a monocyte-mediated signal in the heart−brain axis for MI-induced sleep after MI. Specifically, monocytes are recruited into the brain by activated microglia secreting chemokines, and subsequently engaged in activation of glutamatergic neurons in the thalamic LPN through the TNF−TNFR1 axis, inducing increased sleep. Conversely, increased sleep alleviates cardiac inflammation and promotes healing by restricting cardiac sympathetic innervation. This study not only reveals the mechanism by which monocytes migrate to the brain to promote deep sleep after MI, but also provides new perspectives and potential therapeutic targets for clinical practice. On the one hand, the cardiac sympathetic innervation may be a target for drug development in the control of MI. On the other hand, by monitoring sleep patterns after MI, patients with sleep disorders can be identified early and interventions can be implemented promptly, which may help prevent further deterioration of cardiac function and reduce the complications. In addition, it's demonstrated that microglia recruit monocytes to the brain by releasing chemokines, such as CCL2, so targeting these chemokines or their receptors may help regulate the migration of monocytes, thereby improving sleep and cardiac function. Moreover, recruited monocytes produce TNF, which increases deep sleep by activating glutamatergic neurons, therefor, targeting TNF or its receptors (such as TNFR1) may help regulate sleep, reduce cardiac inflammation, and promote cardiac healing.

However, this research has some limitations. Firstly, while the study identifies that monocytes are actively recruited to the brain after MI to augment sleep, the precise mechanisms by which these monocytes are specifically directed to the thalamic lateral posterior nucleus remain unaddressed. Further investigation into the molecular signals and pathways that guide monocytes to this specific region could provide deeper insights into the neuro-inflammatory response post−MI. Understanding these mechanisms could also reveal potential therapeutic targets for modulating this response. Secondly, the study primarily focuses on the acute phase following MI. It would be valuable to explore the long-term effects of sleep augmentation on cardiac recovery and remodeling. Questions such as whether sustained increase in sleep continues to provide benefits beyond the initial healing phase, or if there are potential adverse effects of prolonged sleep augmentation, could be addressed. This would help in understanding the optimal duration and timing of sleep interventions post−MI for maximal therapeutic benefit. Thirdly, this study highlights the importance of sleep in limiting inflammation and promoting heart healing after MI. However, the direct impact of sleep quality on myocardial regeneration and the regeneration of cardio myocytes remains an open question. Investigating how different aspects of sleep quality, such as sleep depth, continuity, and circadian alignment, affect the regenerative processes in the heart could provide crucial information for developing targeted sleep-based therapies to enhance cardiac repair.

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Author contributions

Meng Mao and Hailong Bing drafted the manuscript. Jianping Ye, Zhengyuan Xia and Qinjun Chu provided the concept and revised the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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