Neuron
Previews

CellPress

"Goodnight" from the heart: A cardiovascular circuit that promotes sleep

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https://doi.org/10.1016/j.neuron.2022.11.005

The baroreflex is essential for blood pressure homeostasis. In this issue of *Neuron*, Yao et al.[1] uncover a novel role of brainstem barosensitive neurons in promoting non-REM (NREM) sleep, providing a direct link between the cardiovascular system and sleep-wake states.

It is well appreciated that sleep-wake cycles potently affect cardiovascular functions.[2] Cardiac activity is high during wakefulness, while heart rate slows and blood pressure falls during sleep. Hemodynamics is also precisely regulated within different sleep stages: lower during non-rapid eye movement (NREM) sleep and higher during REM sleep. Disrupting physiological sleep patterns in various sleep disorders and sleep deprivation can lead to cardiovascular complexities. The fluctuations of cardiac activity during sleep-wake cycles are largely modulated via the autonomic nervous system through the balance of sympathetic vagal tones. Previous studies have uncovered some essential brain regions and underlying neural circuits from sleep centers to premotor sympathetic and vagal neurons for cardiovascular control during sleep-wake cycles. On the other hand, cardiovascular diseases are often associated with altered sleep patterns,[3] suggesting that the link between sleep process and the cardiovascular system might be bidirectional. However, little evidence supporting the existence of this heart-sleep pathway has been found so far. The underlying neural mechanism remains to be elucidated. This exciting work presented by Yao, Dan, and colleagues in this issue of *Neuron* uncovers a cardiovascular circuit that also promotes NREM sleep, providing strong and direct evidence for the connection between the heart and sleep control.[1]

The baroreflex is a pivotal inhibitory cardiovascular reflex that maintains blood pressure at nearly constant levels. Fluctuation of arterial blood pressure is detected by mechano-sensitive ion channels PIEZO1 and PIEZO2 through specialized fine "end-net" endings of baroreceptor neurons in the vagus and glossopharyngeal nerves from the aorta and carotid sinus.[4,5] Inputs from baroreceptor neurons are projected to the nucleus tractus solitarius (NTS) in the brainstem and regulate cardiovascular functions through two downstream circuits. The parasympathetic NTS-nucleus ambiguus (Amb, parasympathetic preganglionic vagal neurons) pathway regulates heart rate, while the sympathetic NTS-rostral and caudal ventrolateral medulla (RVLM and CVLM, respectively, premotor neurons)-intermediolateral nucleus of the spinal cord (sympathetic preganglionic neurons) pathway modulates both heart rate and vasomotor tone.[6] The baroreflex is bidirectional, providing beat-to-beat control of cardiac hemodynamics. Differential modulation of the baroreceptor sensitivity at various sleep cycles has also been well documented.[2] Undoubtedly the baroreflex is one of the best characterized cardiovascular reflexes. In this regard, Yao et al. examined whether activating the baroreflex can affect the sleep-wake brain status.

To gain genetic access to barosensitive NTS neurons, Yao et al. first performed activity-dependent labeling after injection of phenylephrine, a vasoconstrictor commonly used to induce the baroreflex, using TRAP2 mice that express tamoxifen-inducible Cre recombinase under Fos promoter.[7] Fluorescence RNA *in situ* hybridization (FISH) revealed that the majority of labeled neurons (referred to as $NTS^{PE-TRAP}$) are glutamatergic, and a large fraction of them also express *Cartpt*. The barosensitivity of $NTS^{PE-TRAP}$ neurons was further confirmed *in vivo* with channelrhodopsin-assisted optrode recordings in freely moving animals. The firing rate of $NTS^{PE-TRAP-ChR2}$ neurons, identified based on their response to optogenetic stimulation, closely followed heart rate and blood pressure fluctuations, with their spiking activity significantly time-locked to each heartbeat at a sub-second level. Similar to $NTS^{PE-TRAP}$ neurons, NTS Cartpt$^+$ (NTS^{CART}) neurons are activated by phenylephrine as revealed by fiber photometry-based calcium imaging, and their activity is positively correlated with cardiac hemodynamics, which is consistent with FISH results. Rabies-based neuronal tracing showed that both $NTS^{PE-TRAP}$ and NTS^{CART} neurons are directly connected to putative baroreceptor vagal sensory neurons expressing *Piezo1* and/or *Piezo2*. Together, both functional and anatomical data suggest that $NTS^{PE-TRAP}$ neurons are barosensitive.

Surprisingly, activating $NTS^{PE-TRAP}$ and NTS^{CART} neurons with chemogenetics in freely moving animals not only decreases heart rate and blood pressure but also, as revealed by electroencephalogram and electromyogram, reduces wakefulness while increasing NREM sleep. Optogenetic activation of these neurons led to similar outcomes. The effects on hemodynamics happen very rapidly and interestingly are brain-state independent. On the other hand, inhibiting $NTS^{PE-TRAP}$ and NTS^{CART} neurons with the inhibitory opsin iC++ induces an opposite effect with reduced NREM sleep

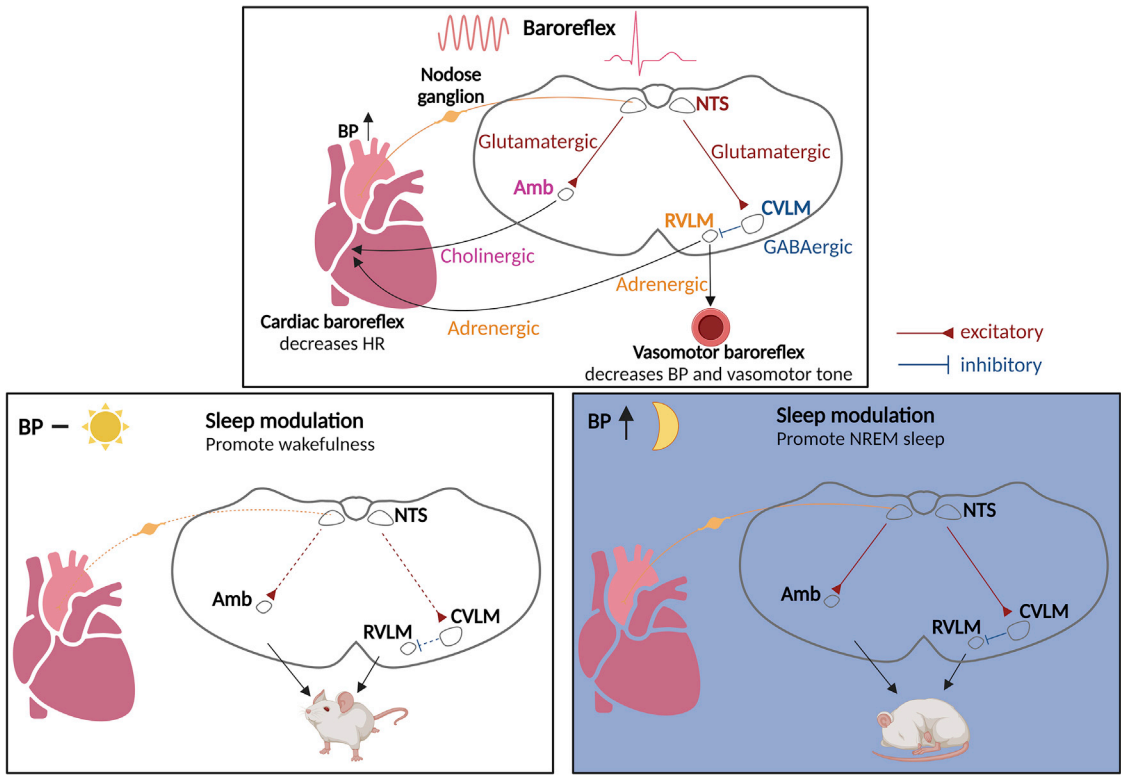

Figure 1. A novel role of the baroreflex circuit in sleep control

The brainstem baroreflex circuit consists of a parasympathetic cardiac branch that decreases the heart rate (NTS-Amb) and a sympathetic vasomotor branch (NST-CVLM-RVLM) that decreases the vasomotor tone and blood pressure. NTS, nucleus tractus solitarius; CVLM, caudal ventrolateral medulla; RVLM, rostral ventrolateral medulla; Amb, nucleus ambiguus. Yao et al.[1] discover a novel function of the baroreflex circuit in sleep control. Activating barosensitive NTS neurons and their downstream targets in both parasympathetic and sympathetic branches leads to increased non-rapid eye movement (NREM) sleep in addition to cardiac regulation, providing a direct link for the bidirectional interaction between the cardiovascular system and sleep-wake brain states. Illustration made using BioRender.

and increased wakefulness. The inhibitory experiment suggests that the endogenous activity of these neurons also contributes to sleep regulation. It is worth noting that a strong correlation between changes of sleep states and of heart rate and blood pressure was always observed, in both directions, suggesting that they are likely regulated by the same neurons through the same pathways. Taken together, this study clearly demonstrated that barosensitive NTS neurons can regulate both the somnogenic and cardiovascular functions, with primary cardiovascular regulation happening regardless of brain states. Whether the somnogenic effect is through direct neuronal circuits or indirect pathways will need to be addressed in future studies.

The authors next mapped two downstream neural pathways that connect the cardiovascular circuit to sleep regulation. The first one is the NTS (glutamatergic)-CVLM (GABAergic)-RVLM (adrenergic) vasomotor pathway, as sympathoexcitatory neurons in the RVLM are known to promote wakefulness, so the GABAergic inhibition from CVLM would, in turn, suppress wakefulness and promote sleep. Using pseudo-rabies-based transsynaptic tracing, Yao et al. confirmed that some NTS^{CART} neurons directly synapse onto GABAergic CVLM neurons. Optogenetically activating CVLM neurons or inhibiting RVLM neurons increases NREM sleep while decreasing wakefulness, and vice versa. The RVLM-locus coeruleus (LC) pathway has been previously characterized in sleep regulation; therefore, it is likely that LC might be involved in this heart-sleep regulation circuit. The second pathway is the NTS (glutamatergic)-Amb (cholinergic) parasympathetic cardiac pathway. Similarly, there is a monosynaptic connection between NTS^{CART} neurons and the Amb, and chemogenetic activation of Amb cholinergic neurons decreases blood pressure and heart rate, increases NREM sleep, and decreases wakefulness. Unlike the sympathetic NTS-CVLM-RVLM pathway, the Amb has not been linked with sleep control in previous studies, and how Amb activation promotes NREM sleep remains to be explored. Nevertheless, these studies demonstrate that both sympathetic and parasympathetic branches of the baroreflex are involved in sleep regulation.

In sum, Yao et al. uncovered a novel role of the well-characterized cardiovascular baroreflex and beautifully demonstrated its previously underappreciated contribution to sleep-wake regulation (Figure 1). By combining specific activity-dependent genetic labeling with state-of-the-art neural imaging and manipulations, this study provides a comprehensive and convincing story of

how cardiovascular circuit activation promotes sleep. Importantly, all experiments mentioned above were carried out in freely moving animals, which is vital in studying sleep-wake behaviors. This exciting study also forms a critical foundation for future investigations and raises many questions. One question that remains to be answered is whether and how circadian cycle affects the outcome of this heart-sleep pathway. For instance, in the daytime, barosensitive NTS$^{PE-TRAP}$ neurons will be activated by the increase of blood pressure during active exercise or escape from predators. Will this activation promote sleep? It seems counterintuitive to think that we will feel sleepy every time blood pressure increases. One possibility is that this circuit is more active at night. Indeed, barosensitive neurons have a significantly lower set point and are more sensitive toward blood pressure increase at nighttime.[2,8] The tight correlation between changes in cardiac function and sleep states observed by Yao et al. during various manipulations raises another question as to whether cardiac control and sleep regulation can be separated at any point of this heart-sleep circuit. Identifying such branching points would enable function-specific regulation and facilitate the design of more specialized treatments to better target cardiovascular and sleep disorders. This study also provides important data for understanding interoceptive coding in the brainstem. The sensory vagus nerve is organized into parallel streams using a multidimensional coding architecture.[9] How parallelly presented visceral information is coded in the NTS remains to be elucidated. While Yao et al. clearly show that genetically defined NTS neuron subtypes may code specific cardiovascular information, in other cases, as beautifully demonstrated in a recent study using *in vivo* NTS imaging, various visceral signals from the lung and gut are coded by spatially segregated NTS neurons across multiple subtypes,[10] suggesting that multiple coding strategies might be used in the NTS.

The cardiovascular system is vital to the whole body. Many studies have shown cross organ interaction networks that couple the heart with other organ systems like the lung, kidney, liver, and gut. Now Yao et al. provided an intriguing perspective to correlate the cardiovascular function and animal behavior/state that share the same neural circuit. This study thus provides a beautiful example of how a simple design can be employed to regulate multiple functions and orchestrate cross-organ homeostasis.

ACKNOWLEDGMENTS

We thank NIH for funding (R01HL150449 and R01AT012041).

DECLARATION OF INTERESTS

The authors declare no competing interests.

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