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# Autonomic Dysfunction in Sleep Disorders: From Neurobiological Basis to Potential Therapeutic Approaches

Hakseung Kim[a]
Hee Ra Jung[b]
Jung Bin Kim[c]
Dong-Joo Kim[a,c,d,e]

[a]Department of Brain and Cognitive Engineering, Korea University, Seoul, Korea
[b]Department of Psychological and Brain Sciences, Washington University in St. Louis, St. Louis, MO, USA
[c]Department of Neurology, Korea University College of Medicine, Seoul, Korea
[d]Department of Artificial Intelligence, Korea University, Seoul, Korea
[e]NeuroTx, Co., Ltd., Seoul, Korea

Sleep disorder has been portrayed as merely a common dissatisfaction with sleep quality and quantity. However, sleep disorder is actually a medical condition characterized by inconsistent sleep patterns that interfere with emotional dynamics, cognitive functioning, and even physical performance. This is consistent with sleep abnormalities being more common in patients with autonomic dysfunction than in the general population. The autonomic nervous system coordinates various visceral functions ranging from respiration to neuroendocrine secretion in order to maintain homeostasis of the body. Because the cell population and efferent signals involved in autonomic regulation are spatially adjacent to those that regulate the sleep-wake system, sleep architecture and autonomic coordination exert effects on each other, suggesting the presence of a bidirectional relationship in addition to shared pathology. The primary goal of this review is to highlight the bidirectional and shared relationship between sleep and autonomic regulation. It also introduces the effects of autonomic dysfunction on insomnia, breathing disorders, central disorders of hypersomnolence, parasomnias, and movement disorders. This information will assist clinicians in determining how neuromodulation can have the greatest therapeutic effects in patients with sleep disorders.

**Keywords** sleep disorders; autonomic nervous system; pathology; neurobiology.

## INTRODUCTION

Sleep promotes neuronal connectivity and preserves the networks involved in a vast array of biological functions. Since sleep plays a vital role in synaptic plasticity, alterations in sleep patterns can attenuate emotion regulation, memory consolidation and retrieval, and even autonomic activities.[1,2] Recent studies have found that 16.6% to 56.0% of the general population experiences sleep problems, and a sixfold increase in the prevalence of sleep problems has been observed over the past decade.[3-5] Sleep problems include insomnia, breathing disorders, central disorders of hypersomnolence, parasomnias, and movement disorders.

Sleep disorders contribute to an extensive range of diseases, from neuropsychiatric to neurodegenerative diseases, and including autonomic impairments. Sleep-promoting neurons are scattered in the vicinity of the central autonomic network, and their control of sleep cycles induces profound changes in the autonomic nervous system (ANS).[6] This results in autonomic impairments with an imbalanced sympathetic drive occurring secondarily to abnormal sleep. To the extent that sleep architecture exerts direct effects on autonomic regulation, autonomic dysfunction may conversely induce sleep disturbance. The ANS is a control system for homeostatic functions and visceral adjustments that is functionally divided into parasympathetic and sympathetic branches, which are involved in secretory activities that mediate sleep.[7] It is often reported that sleep disorders manifest as symptoms of autonomic impairment, suggesting that autonomic factors modulate sleep physiology.

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**Correspondence**
Dong-Joo Kim, PhD
Department of Brain and Cognitive Engineering, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Korea
**Tel** +82-2-3290-5929
**Fax** +82-2-3290-3970
**E-mail** dongjookim@korea.ac.kr

The interconnection between sleep disorders and autonomic dysfunction suggests that sleep and autonomic regulation have a bidirectional relationship or shared pathology. Identifying the causality of these conditions is significant for understanding the underlying mechanism and therefore could also provide opportunities for optimizing clinical therapies. Addressing the types of neuromodulation that result from autonomic neuropathy may have positive effects on sleep complications, and vice versa. In this review we describe the function and architecture of sleep and the ANS, and consider the mechanisms underlying the interdependence between sleep disorders and autonomic impairments in order to understand the potential impacts of cross-therapeutic interventions.

## SLEEP AND THE ANS

A dynamic shift in physiological processes occurs during sleep that enhances synaptic plasticity, and thereby eventually contributes to development, performance, energy conservation, brain waste clearance, immune responses, emotion, cognition, and other integrated activities.[8] These effects include significant changes in autonomic regulation, such as temperature regulation, blood pressure, and heart-rate variability.[9] Since the cell population and efferent signals are spatially adjacent to those involved in sleep, the ANS coordinates bodily functions in distinct ways during different stages of sleep.

Sleep comprises two distinct states: non-rapid-eye-movement (NREM) sleep and rapid eye movement (REM) sleep. NREM sleep is further divided into three different stages characterized by the relative depth of sleep: N1, N2, and N3. REM sleep has two states: tonic and phasic. While tonic REM sleep is a unique phase accompanied by low muscle tone throughout the body, sympathetically driven phasic REM sleep is intermittently accompanied by rapid eye movements and cardiorespiratory fluctuations during the dream state. Parasympathetic tone increases as sleep progresses from NREM N1 sleep to the deeper stages, while sympathetic tone simultaneously decreases.[10] This change leads to reductions in heart rate, arterial blood pressure, and peripheral vascular resistance, which lessens the burden on the cardiac output and induces autonomic stability.[11] The autonomic balance shifts from parasympathetic to sympathetic dominance when sleep enters the REM stage, and the heart rate and blood pressure increase abruptly.[10,12,13]

These changes in autonomic dominance during sleep suggest that they have autonomic-related functions. The progressive reduction in cardiovascular control during NREM-sleep phases promotes regular respiration and gas exchange, which aids metabolic recovery.[10] Specifically, chemoreceptors in the lateral medulla recognize minor fluctuations in $O_2$ and $CO_2$ levels and adjust the breathing rate and depth via neurotensin pathways.[14] This observation suggests that NREM sleep contributes to autonomic stability. Additionally, parasympathetic activities during phasic REM sleep are accompanied by cholinergic neuronal discharges in the pedunculopontine tegmentum (PPT) and laterodorsal tegmentum (LDT) of the cholinergic arousal pathway.[10] Indeed, the PPT and LDT are responsible for muscle atonia, including that of the upper airway muscles such as the genioglossus.[14] This finding suggests that REM-sleep-specific muscle recruitment is related to respiration and other autonomic regulation processes.

## PHYSIOLOGY OF THE BIDIRECTIONAL RELATIONSHIP BETWEEN SLEEP AND AUTONOMIC ACTIVITY

While autonomic observations during sleep and arousal demonstrate a correlation between sleep architecture and autonomic regulation, the mechanism underlying this relationship remains unclear. Identifying the contributing elements requires examinations of the neuroanatomy of these systems. The cell populations involved in sleep and arousal are spatially adjacent to autonomic cell populations in the upper brainstem.[10] Working in close proximity, the sleep-wake system and ANS communicate with each other both chemically and mechanically via efferent and afferent signals.

### Hypothalamus and carotid baroreceptors

The sleep and wake systems promote a sleep status and wakefulness, respectively. The mutual inhibition of the sleep and arousal circuitry leads to switching properties that produce a sharp transition from sleep to wakefulness[15] (Fig. 1). Sleep-inducing neurons are found in the ventrolateral preoptic nucleus (VLPO) in the hypothalamic area. These neurons secrete inhibitory γ-aminobutyric acid (GABA) and inhibitory neuropeptide galanin to produce drowsiness.[16] Contrary to the sleep state, the waking state begins with inhibition of the VLPO. When neurons release the neuropeptide orexin, the firing of VLPO neurons ceases since the VLPO does not contain orexin receptors. This process indirectly reinforces different arousal pathways, including the cholinergic pathway, monoaminergic pathway, and glutaminergic neurons[15] (Fig. 2).

Orexin is heavily involved in the ascending arousal pathways of the sleep-wake system. The related neurons are located predominantly in the hypothalamus, which is a major regulator of autonomic functions in addition to sleep and wakefulness. Areas of the hypothalamus are spatially organized by their functions, and the lateral region participates in autonomic regulation, including inflammatory and reward re-

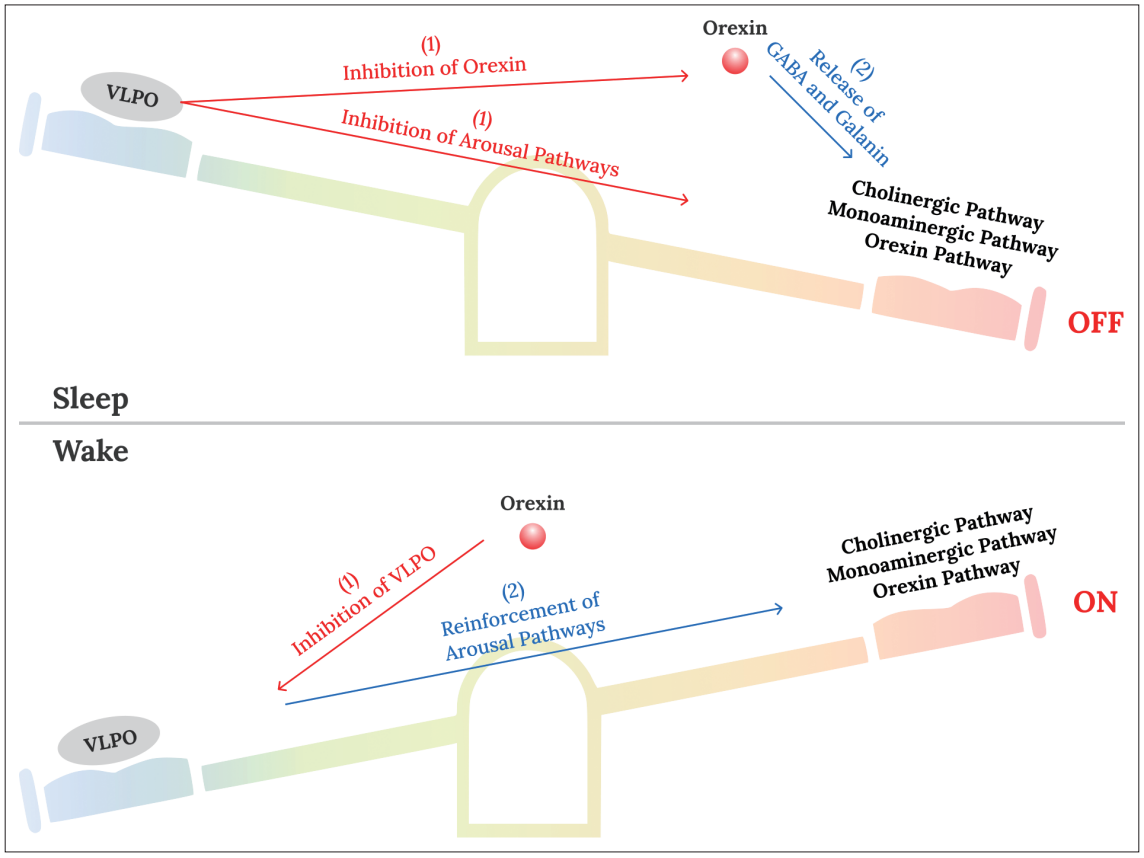


**Fig. 1.** Flip-flop switch model of sleep-wake regulation. Sleep and wakefulness are shown in the upper and lower panels, respectively. Red and blue indicate inhibition and stabilization, respectively. VLPO, ventrolateral preoptic nucleus.

sponses.[19,20] The lateral hypothalamus contains autonomic neurons that diffusely relay inputs to the nucleus of the solitary tract (NTS) in the lateral medulla oblongata, which contains not only efferent pathways from the hypothalamus but also afferent pathways that involve various mechanoreceptors.[21] The mechanoreceptors that carry afferent signals are stretch receptors in the wall of the carotid sinuses called carotid baroreceptors. Whereas the hypothalamus contributes to autonomic regulation in the sleep-wake system, baroreceptors affect sleep and arousal by relaying afferent signals. They sense and regulate the systemic blood pressure and variability therein, providing robust beat-to-beat negative feedback to the blood pressure and its variability that reduces short-term fluctuations in the arterial blood pressure.[22] An increase in blood pressure mechanically stretches the baroreceptors, which enhances the glutamatergic afferent tone of the NTS. This increases parasympathetic outflow to cardiac and vasomotor smooth muscles, and reduces sympathetic discharges. Conversely, a decrease in afferent arterial discharge leads to baroreceptor closure, leading to parasympathetic inhibition and sympathetic activation. This triggers reflexive increases in heart rate, cardiac contractility, vascular resistance, and venous return.[23]

Autonomic commands regarding the set point and balance of the baroreflex may promote differences in baroreflex sensitivity as the sleep stages proceed (Fig. 3). Baroreflex modulation permits simultaneous reductions in heart rate, blood pressure, and peripheral muscle sympathetic nerve activity during NREM sleep. The subsequent baroreflex intervention rapidly increases heart rate, blood pressure, and sympathetic activity, inducing the REM sleep stage. This baroreflex control is evident during intrinsic changes in the brain or in response to external stimuli. Upon arousal, central autonomic commands load baroreceptors to generate a rapid transition in the plasticity of baroreflex dynamics from low sympathetic activity to permissive tachycardia.[22] This positive feedback loop plays a crucial role in the pathophysiology of diseases associated with alterations in the cardiovascular and sleep-wake cycle, including obstructive sleep apnea (OSA) with baroreflex impairment and insomnia associated with hypertension.[24] These disorders are discussed in detail in the next section.

## Norepinephrine

Norepinephrine is involved in the sleep-wake system and changes in autonomic tone. Norepinephrine is secreted from

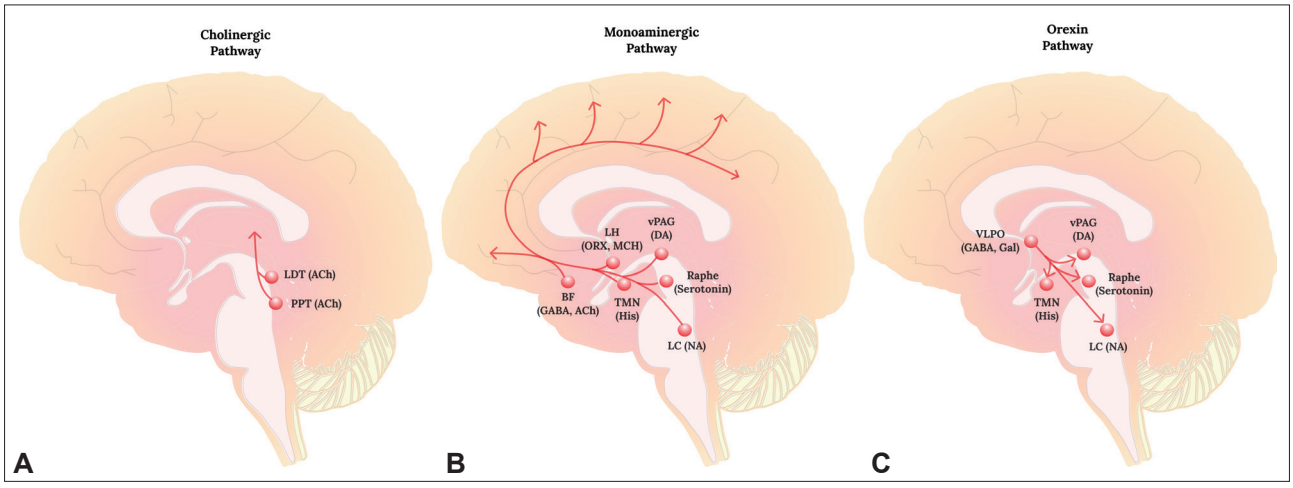


**Fig. 2.** Cell populations involved in the sleep and arousal systems. The ventrolateral preoptic nucleus (VLPO), located in the hypothalamic area, releases γ-aminobutyric acid (GABA) and galanin (Gal) to promote drowsiness. This field also innervates one-third of all arousal pathways. A: The first arousal pathway is the cholinergic pathway, in which cholinergic cell populations located in the pedunculopontine tegmentum (PPT) and laterodorsal tegmentum (LDT) of the pons provide most of the input to the reticular nuclei of the thalamus. Indeed, the paraventricular nucleus of the thalamus, which originates from the reticular formation, is densely innervated by orexin (ORX) fibers.[16,17] B: The monoaminergic pathway integrates inputs from monoaminergic cells, including noradrenaline (NA) from the locus coeruleus (LC), serotonin from the raphe nucleus (Raphe), histamine (His) from the tuberomammillary nucleus (TMN), and the dopamine (DA) from periaqueductal gray (vPAG). The relay projects to the lateral hypothalamus (LH) to coordinate a homeostatic response while also receiving ORX and melanin-concentrating hormone (MCH) from the LH and basal forebrain (BF) neurons, which contain GABA and acetylcholine (ACh).[15] C: The third arousal system consists of glutaminergic neurons and hypocretin neurons or ORX. Starting from the VLPO, these neurons extend to all monoaminergic populations from the second pathway to stimulate the release of neurotransmitters.[18] This contributes to the flip-flop switch model, which highlights the role of ORX in inhibiting the VLPO and thereby relieving the inhibition of monoaminergic cells.[15]

postsynaptic nerve terminals of noradrenergic sympathetic neurons in the locus coeruleus, and this alters sleep latency and arousal regulation.[26] The firing rate of sympathetic neurons is reduced firing rate during NREM sleep, and their conduction velocity is reduced during tonic REM sleep. During phasic REM sleep, the firing rate increases along with an increase in norepinephrine release or greater reuptake inhibition. These changes induce a dramatic surge in blood pressure, which is a risk factor for patients with OSA.[11] At the time of arousal, neuronal discharge activity increases to contribute to the maintenance of arousal levels associated with spontaneous waking.[27]

In a highly divergent efferent projection system, the locus coeruleus supplies norepinephrine for autonomic regulation. Norepinephrine is a catecholamine whose signaling pathways are activated during fight-or-flight responses. The hyperadrenergic feedback from norepinephrine increases blood pressure, cardiac output, and glucose levels, relaxes smooth muscles, and induces metabolic changes to reinforce sympathetic tone.[28] While rapid norepinephrine responses allow the coordination of cardiac and adrenal medullary functions, sustained elevation of circulating norepinephrine can result in pathological conditions such as heart failure and cardiac hypertrophy, as well as various psychiatric and neurodegenerative disorders.[29] Thus, norepinephrine levels should be closely monitored when a patient exhibits both sleep disorders and autonomic abnormalities.

## PRIMARY SLEEP DISORDERS AND AUTONOMIC DYSFUNCTION

The complex interdependence between the sleep-wake system and autonomic regulation supports the presence of bidirectional causality. With an understanding of the neuroanatomical mechanisms involved, addressing sleep disorders associated with autonomic dysfunction may lead to improved clinical treatments for both conditions. This section reviews the evidence for bidirectional interactions between sleep disorders and autonomic impairments, with a focus on the contribution of primary sleep disorders to an increased risk of developing cardiovascular autonomic impairments such as OSA, insomnia, narcolepsy, REM-sleep behavior disorder (RBD), periodic leg movement disorder (PLMD), and restless legs syndrome (RLS) (Fig. 4).

### Obstructive sleep apnea

OSA is a common breathing disorder in which respiration stops involuntarily for a brief period during sleep. OSA involves frequent arousals and excessive daytime sleepiness (EDS), as well as cardiovascular complexities. It has been estimated that

5%–10% of the general population suffers from the disorder.[30]

Individuals affected by OSA undergo repeated complete (apnea) or partial (hypopnea) airflow obstruction, which may have significant autonomic consequences. During apnea, a prolonged increase in negative intrathoracic pressure caused by inhaling against a partially closed glottis inhibits pulmonary

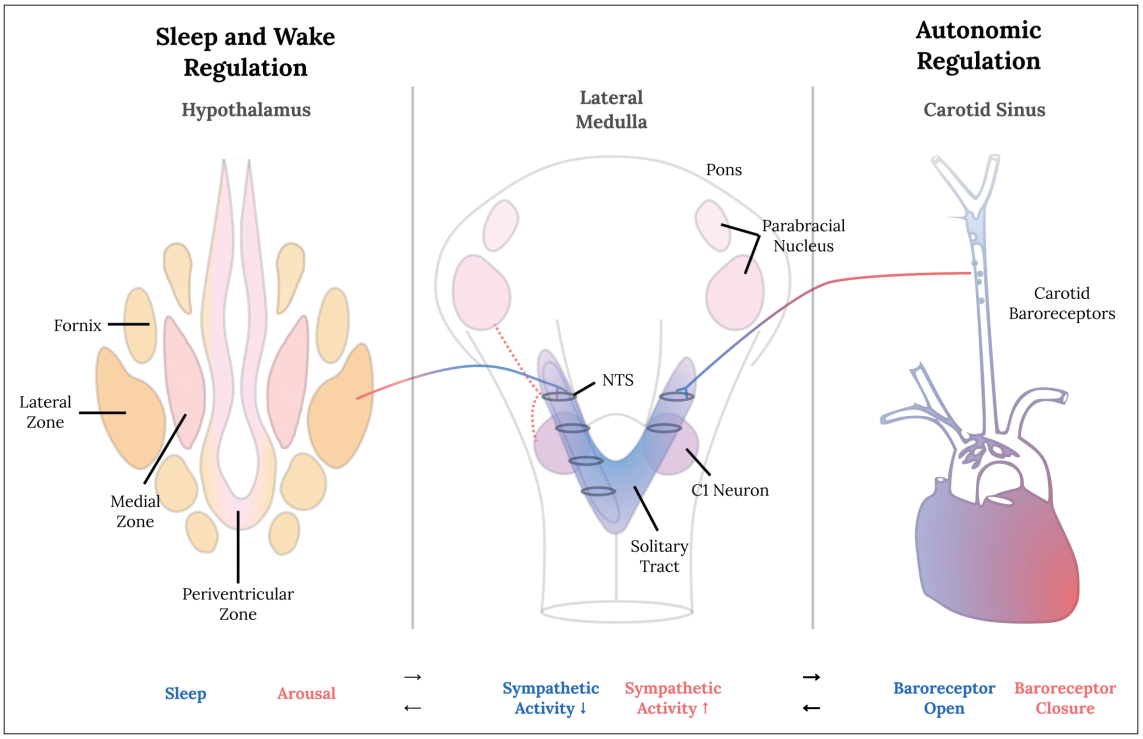


**Fig. 3.** Interactions between the hypothalamus and carotid baroreceptors via the lateral medulla. The nucleus of the solitary tract (NTS) and adrenergic C1 neurons of the lateral medulla and the parabrachial nucleus of the pons mediate the bidirectional interactions between the baroreflex and the sleep-wake system, facilitating autonomic commands and coordinating sleep states and arousal.[25] Blue and red indicate sleep and arousal mechanisms, respectively.

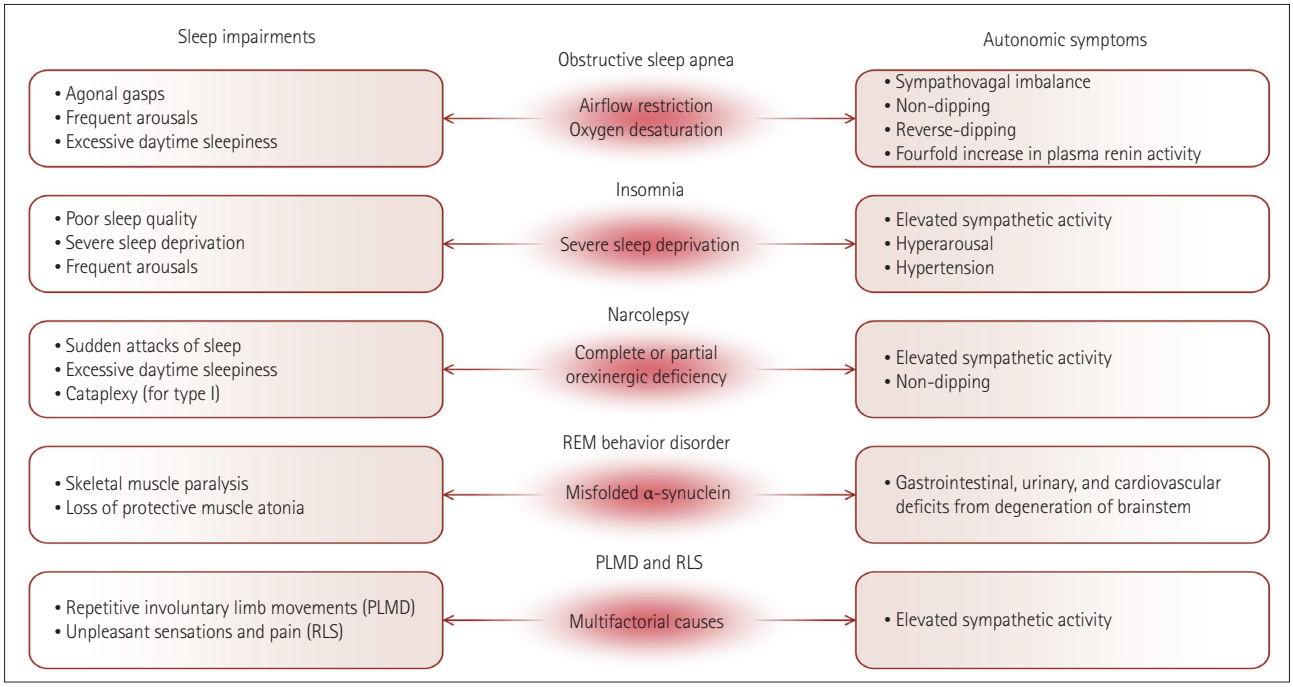


**Fig. 4.** Bidirectional interactions between sleep disorders and autonomic impairments. PLMD, periodic limb movement disorders; RLS, restless legs syndrome.

autonomic afferents, reduces baroreceptor sensitivity, and eventually causes intermittent hypoxemia.[31] This results in peripheral vasoconstriction along with hypoxia or hypercapnia.[32] Hypoxemia triggers a driving reflex, which is a protective mechanism that preserves the cardiac and cerebral blood flows.[33] This progressive sympathetic dominance provokes transient bradycardia, leading to the absence of systolic reduction during sleep, a phenomenon called nocturnal dipping. However, a "nondipping" status (i.e., a reduced decrease in blood pressure during sleep) significantly increases the risk of cardiovascular and cerebrovascular mortality in patients.[34] Another risk comes when breathing resumes after apnea, and cardiac output increases during sleep.[35] Driven by a higher level of systemic arterial pressure, tachycardia produces "reverse dipping" in which both sympathetic activity and catecholamine levels increase. This adrenergic drive after abrupt waking continues during the early morning hours, contributing to cardiovascular events including hypertension.[36,37] These consecutive abnormal dipping patterns have an additive effect on systolic blood pressure,[13] and repeated episodes of apnea may lead to a chronic elevation in the mean blood pressure as well as a fourfold increase in the plasma renin activity.[38] Similarly, the intermittent hypoxemia caused by an increase in the severity of OSA is sufficient to cause cardiovascular morbidity.

Autonomic responses to impaired nocturnal dipping patterns may be present in sleep-related breathing syndromes other than OSA. Airflow restriction and oxygen desaturation from apnea and hypopnea facilitate interactions between parasympathetic and sympathetic activities, resulting in different values of autonomic indices.[39] In patients with upper airway resistance syndrome (UARS), reduced airway diameter manifests during NREM sleep, whereas a normal blood pressure pattern begins with increased parasympathetic activity. Restriction of the inspiration flow results in hyperactivation of the parasympathetic nervous system, inducing irregularities in blood pressure control.[40] In contrast to UARS, sleep-related alveolar hypoventilation does not involve significant airflow restriction or oxygen saturation. Instead, it reduces parasympathetic activity, which reduces the high-frequency (HF) component (0.15–0.40 Hz) of the heart-rate variability and increases its low-frequency (LF) component (0.04–0.15 Hz).[41] This finding provides further evidence that frequent arousals may serve as a potent trigger of sympathetic activity as well as cardiovascular risk, and vice versa. This further highlights the importance of understanding the bidirectionality of sleep disorders and autonomic dysfunction.

## Insomnia

Insomnia is a chronic dissatisfaction with sleep quality and duration, conventionally characterized by difficulty falling asleep or early morning awakenings. Reportedly 6%–18% of the general population is affected by insomnia.[42]

Insomnia is accompanied by an increased cardiovascular risk. Nondipping status, hyperarousal, elevated blood pressure, and reduced heart-rate variability are frequently observed.[43] Moreover, the frequent arousals associated with sleep disorders can lead to tachycardia or bradycardia, followed by increased sympathetic and baroreceptor tone that may impair the ANS.[44,45] Indeed, a cardiovascular study demonstrated the connection between severe sleep deprivation and sympathovagal imbalance.[46] That study found that patients with a sleep duration of less than 6 hours have elevated mean heart-rate variability metrics and reduced parasympathetic activities compared with the normal population. Other studies have also provided evidence of autonomic dysfunction in the form of hyperarousal, which is the "tired but wired" condition that prevents patients from falling asleep despite being exhausted. Positron-emission tomography in insomnia patients has revealed hypermetabolism in the hypothalamus and the relevant efferent projections of arousal networks as well as excessive cortical activity during sleep, which ultimately contribute to hypertension.[47] Likewise, people with sleep deprivation may develop an unusual sympathetic drive that increases their susceptibility to autonomic complications.

## Narcolepsy

Narcolepsy is a chronic sleep disorder that involves sudden attacks of sleep and overwhelming daytime sleepiness, with the immediate occurrence of REM sleep upon sleep onset. Cataplexy (episodes of muscle weakness) occur in narcolepsy type 1 but not type 2. The present study highlights narcolepsy type 1, which has a prevalence of 14 per 100,000 people.[48]

Narcolepsy originates from a complete or a partial deficiency in orexinergic neurons in the lateral hypothalamus, which project to the reticular activating system (RAS) that regulates sleep and arousal. During sleep, RAS activity decreases, promoting atonia and separating sleep from wakefulness. The RAS suppresses GABA and releases dopamine, norepinephrine, serotonin, and histamine, which inhibits REM sleep. However, this mechanism is unable to achieve a stable transition between sleep and wakefulness without a sufficient amount of orexin.[48] As a result of abnormal sleep architecture, narcolepsy patients are unlikely to exhibit slow tonic firing with either increased sympathetic drive or parasympathetic withdrawal. They eventually develop a nondipping status and lose the ability to modulate their blood pressure. While the nondipping profile observed in the 24-hour blood pressure pattern of narcolepsy patients is not correlated with cerebrospinal fluid orexin levels, it does explain elevated heart rates throughout all stages

of sleep and a blunted heart rate response to awakening in narcolepsy patients.[49,50] In short, the loss of orexin disrupts sleep and wake progression, contributing to increased cardiovascular risk in patients with narcolepsy.

### REM-sleep behavior disorder

RBD is a parasomnia characterized by skeletal muscle paralysis and loss of protective muscle atonia during REM sleep. Susceptible individuals appear to physically act out vivid dreams by talking, yelling, thrashing about, or punching while asleep. Although its prevalence is difficult to evaluate, approximately 1% of the general population is thought to be affected by RBD.[51]

RBD derives from a relatively small but ubiquitously expressed protein called α-synuclein (aSyn), which is capable of progressively spreading and accumulating throughout the nervous system. The concomitant deposition of misfolded aSyn fuels the neurotoxic cycle and has a deleterious impact on neurons that creates appropriate conditions for neurodegenerative comorbidities.[52] Approximately 80% of idiopathic RBD patients eventually develop α-synucleinopathies such as Parkinson's disease, Lewy body dementia, or multiple-system atrophy, as well as autonomic impairments.[10,53-55] α-Synucleinopathy also impairs both sleep and autonomic tone. aSyn-mediated neurodegeneration of brainstem nuclei leads to RBD and other sleep complications, whereas aSyn-related neurodegeneration of the central and peripheral autonomic areas causes autonomic failure. The prevalence of such cases has led RBD and autonomic failure to be frequently regarded as prodromal markers of neurodegenerative disorders.[55,56] Indeed, RBD is frequently comorbid with some degree of autonomic impairment.[14] A systematic assessment of autonomic symptoms performed as part of a multicenter case–control study found that gastrointestinal, urinary, and cardiovascular deficits were greater in idiopathic RBD patients than in controls.[57] Furthermore, attenuated heart-rate variability and abnormal blood-pressure decreases during active standing and sudden arousals are common manifestations.[58,59] While there is no single aSyn-related contributor to this correlation, autonomic dysfunction is integrally linked to RBD via several mechanisms. Degeneration of the pontine nuclei, cholinergic REM-sleep nuclei, and autonomic nuclei and their projections in the brainstem occur in RBD. Degeneration of the pontine nuclei, which are involved in both REM-sleep regulation and locomotion, induces abnormal REM sleep and motor regulation.[60] Meanwhile, degeneration of the cholinergic REM-sleep nuclei and the autonomic nuclei also occurs with the deposition of aSyn progressing from the lower brainstem to the cortex.[61,62] While the shared pathogenesis of neurodegeneration explains the bidirectionality between sleep disorders and autonomic dysfunction in RBD patients, more investigations of these correlations are needed to fully understand the diagnostic, prognostic, and therapeutic implications.[63]

### PLMD and RLS

PLMD and RLS are sleep-related chronic sensorimotor disorders. Whereas PLMD is a condition involving repetitive involuntary leg movements during sleep that sometimes lead to arousal, RLS patients experience unpleasant sensations and pain in their legs that worsen while resting.[64] Most RLS patients complain of periodic leg movements, but RLS is a distinct clinical syndrome that affects an estimated 5%–10% of the population.[65]

Both PLMD and RLS provide insights into the correlation between pathological movements and autonomic profiles with the presence of elevated sympathetic activity. However, the correlation is complex since there is no consensus regarding the pathophysiology underlying the effects of PLMD and RLS on heart-rate variability.[14] A study found no differences in heart-rate variability during periods without leg movements or arousals between patients with PLMD and control subjects. This implies that leg movements and arousal responses play a role in cardiac dysregulation in patients with PLMD, which is consistent with the increased responses of the heart rate and arterial blood pressure to rapid bradycardia during the onset of PLMD. This also validates the theory that periodic leg movements are due to reduced subcortical inhibition of pacemaker cells in the brainstem that support the autonomic network.[64] Another study found that the magnitude of cardiac changes was larger during periodic leg movements with microarousals than during those without microarousals.[66] The cardiovascular response appeared to depend on the intensity of central activation rather than on somatomotor changes. A similar anomaly is observed in RLS patients: blood pressure increases to satisfy the criteria for systolic prehypertension and mild sympathetic adrenergic impairment in RLS patients, but this response is evident only at rest in a supine position.[67] The dopamine dysfunction hypothesis states that this condition is caused by restriction of dopaminergic inhibitory drive disinhibiting the spinal somatosensory pathways, thereby increasing sympathetic tone and cardiovascular activity.[68] While the pathophysiology of PLMD and RLS has yet to be elucidated, the inconsistent findings may have multifactorial causes, including the intermittent arousals caused by different degrees of leg movements.

## NEUROMODULATION FOR SLEEP THERAPEUTICS

Sleep disorders may affect autonomic functions, while autonomic impairments alter the physiology of sleep. However, nei-

ther the diagnosis and prognosis of sleep disorders nor treatments for sleep disorders have been systematically investigated with a focus on this bidirectional interaction. Medicinal interventions are conventionally used to treat sleep disorders, with the goal of helping patients fall asleep by increasing their GABA levels. However, these medications abnormally modify the autonomic tone, and their long-term use magnifies the decrease in systolic blood pressure and increases the heart rate.[69] Current methods of neuromodulation are effective for normalizing sleep patterns without the risk of addiction. Repetitive transcranial magnetic stimulation reduces cortical hyperexcitability and rebalances neurotransmitter release by activating the local neural network with alternating currents, whereas LF (25 Hz) deep-brain stimulation of the PPT increases the duration of REM sleep. However, these types of neuromodulation fail to balance turbulent autonomic shifts associated with impaired sleep physiology.[70-72] Other noninvasive clinical methods of brain stimulation for sleep disorders are currently being developed, with a focus on optimizing the most appropriate neural target, stimulation protocols, and candidate symptoms to treat.[73] While the currently available approaches that induce only restricted cross-therapeutic effects, this section reviews the neurostimulation research in the fields of both sleep medicine and autonomic modulation.

## Vagus nerve stimulation

The vagus nerve is the longest of the cranial nerves originating from the brainstem, and it serves as an interface between higher central nervous system (CNS) circuits and ANS circuitry. It provides an extensive afferent and efferent network of innervation to the esophagus, bronchi, and heart. Vagus nerve stimulation (VNS) was recently approved by the US Food and Drug Administration for therapeutic use; it modulates the CNS and peripheral organs, driving cardiorespiratory and gastrointestinal autonomic tone.[74] Although the involved signaling pathways and the mechanisms of VNS are not completely understood, VNS is a promising option for a wide range of therapeutic interventions in the field of clinical sleep medicine.

Transcutaneous auricular VNS (taVNS) has been reported to improve the clinical symptoms of primary insomnia. taVNS enhances sleep onset latency, sleep quality, and sleep behaviors, and it also directly attenuates autonomic nerve imbalance, including hypersensitivity to external stimuli and negative mood.[75] taVNS currents trigger brain regions involved in ascending sleep-related projections, including the locus coeruleus, periaqueductal gray, hypothalamus, and thalamus. It promotes the secretion of melatonin and GABA to induce a sedative effect that facilitates the effortless transition to a sleep state.[76] VNS also reaches the cholinergic anti-inflammatory pathway, mediating cholinergic neuronal discharges in the PPT and LDT. The resulting acetylcholine (ACh) release induces the pharmacological blockade of acetylcholinesterase. This elicits antinociceptive effects for pain management, thereby directly improving sleep quality and behavior.[77-79] The stimulation additionally inhibits the areas of the brain associated with sensitivity and emotion regulation. It blocks projections to the visual cortex, which are hyperactivated in patients with insomnia, while suppressing the amygdala and default mode network and their altered intranetwork connections. Furthermore, taVNS significantly decreases the excitability of the hypothalamic–pituitary–adrenal axis, a stress system involved in chronic depression. This alleviates hypersensitivity to light during sleep and the emotional circuits associated with insomnia.[80-83] However, the performance of taVNS varies markedly between individuals. One study found that 80% of insomnia patients had elevated heart-rate variability with a significant autonomic contribution, whereas another revealed that insomnia was alleviated in only 69% of these individuals.[75,84,85] This inconsistency might be due the differences in the sensitivity of the vagus nerve to external stimulation, but this needs to be confirmed to support the development of a standard treatment and reduce medical costs.[75]

Chronic VNS (cVNS) has shown efficacy in alleviating the symptoms of other sleep disorders, while selective VNS (sVNS) adjusts cardiac and respiratory autonomic dysfunctions. cVNS reduces both the occurrence of narcolepsy and the severity of RLS. Stimulation attenuates BHT-920, a cataplexy-aggravating alpha-2 agonist, while enhancing anticonvulsive inhibitory mechanisms. Unfortunately, this has only been investigated in case studies of two genetically narcoleptic dogs and an elderly female with RLS.[86,87] Other positive results have been restricted to preclinical studies in rats, which have not been confirmed in human subjects. Although findings from several human studies are available, these were performed using a left cervical vagal cuff with the stimulation settings being restricted by regulatory constraints.[88] Regardless, the described effects provide new possibilities for nonmedical treatment across several domains. Additionally, sVNS lowers the blood pressure and respiratory rates without major side effects. It activates baroreceptors in the carotid sinus through bipolar stimulation, thereby adjusting baroreflex sensitivity. Since the baroreflex is a multifactorial control system that is affected by the combination of pulse amplitude, frequency, and width values employed, its adjustment promotes a significant reduction in the heart rate and respiratory rate.[89] Although the study that provided this evidence used a rat model, the sVNS-induced steady decreases in heart and respiratory rates suggest that this modality could be used as an alternate antihypertensive treatment for therapy-resistant patients with hy-

pertension and related autonomic impairments.

VNS therapy is not a panacea, since it may induce sleep disorders or worsen preexisting sleep conditions. Moreover, individuals are more inclined to develop OSA and stridor during VNS activation. Both central and peripheral mechanisms are postulated as underlying OSA.[90] Intermittent stimulation of the vagus nerve modifies central projections to the reticular formation and baroreceptors of the brainstem. An inability of the body to overcome the inhibitory effect of stimulation can lead to an increased respiratory rate and decreases in the respiratory amplitude, tidal volume, and oxygen saturation. These changes in respiratory patterns all decrease the airflow as well as increase REM sleep in most patients, causing more frequent apnea and hypopnea episodes along with diminished airflow.[78,90,91]

Stimulation of the vagus nerve also mediates peripheral projections to motor efferents. The peripheral shift alters neuromuscular transmission to the upper airway muscles of the pharynx and the larynx, eventually narrowing and obstructing the upper airway.[90] Reversible sleep-related stridor induced by VNS has similarly been reported. A female without a preclinical history of respiratory complications received VNS therapy for refractory partial epilepsy and developed sleep-related stridor during the course of parameter titration.[92] While the underlying mechanism has yet to be clarified, that report expands the spectrum of breathing disorders associated with VNS therapy. While VNS is a prospective neuromodulation technique that has been investigated in a range of preclinical studies, VNS-induced sleep-disordered breathing problems remain an unsolved issue. A decrease in the VNS output current may relieve breathing symptoms but may also exacerbate seizure activity.[93] As long as this therapeutic dilemma persists, risk factors for OSA and stridor need to be closely screened before applying VNS.

### Carotid baroreceptor stimulation

The carotid sinus is an area of expansion of the internal carotid artery, and consists of baroreceptors that collectively regulate autonomic activity to maintain a constant blood pressure during sleep. The baroreceptor reflex adjusts cardiac output to meet the demands of the arterial blood pressure, inducing parasympathetic and sympathetic activities across sleep stages[94] (a more detailed explanation of baroreceptors is provided in Section 3-1). Given their cardiovascular homeostatic function, interventions involving the baroreceptor reflex may have therapeutic potential in patients with sleep disorders via an effect called the depressor response.[95]

Carotid baroreceptor stimulation (CBS) is a type of electric-field stimulation applied to carotid baroreceptors in which the intra-arterial blood pressure is monitored while altering the sympathetic tone to produce a cardiovascular homeostatic balance.[96] This approach mediates sympathetic inhibition to elicit the depressor response (i.e., an acute decrease in arterial blood pressure).[95] CBS-induced alterations in baroreceptor afferents may exert a bottom-up effect on the sleep-wake cycle, since altered modulation of the sleep-wake system accounts for the onset of autonomic complications.[97] In patients with OSA, the ongoing occurrence of obstructive events during sleep leads to permanent sympathetic overactivity, characterized by spontaneous sensitivity to baroreflex assessments.[98-100] Selective impairment of the sympathetic response to changes in the baroreflex in OSA patients has been found, but the results may depend on the methodology used to quantify baroreflex control of the heart rate.[101] Furthermore, patients with EDS exhibit reduced baroreceptor sensitivity and an increased LF/HF power ratio, indicating elevated sympathetic activity throughout various sleep stages.[102] It has been speculated that chronic sympathetic overactivation changes the afferent regulation of baroreflex NTS neurons in these patients, attenuating the inhibitory effects on sympathoexcitatory neurons in the lateral medulla.[97] If CBS can induce the depressor response to sympathetic overactivation in these patients, alleviation of the cardiovascular risk can be expected. To date there has been no clinical trial of CBS in patients with OSA or EDS. However, the inhibition of hypertension and atrial fibrillation with a low level of baroreceptor stimulation has been reported in a pig model of sleep apnea, suggesting that CBS could be used therapeutically to reduce the susceptibility to related diseases in patients with OSA.[103] Regardless, CBS remains a potential therapeutic option for OSA and other sleep disorders that are associated with cardiovascular dysregulation.

## CONCLUSION

There is a bidirectional relationship between the sleep-wake system and the ANS. Chronic disruptions throughout the different stages of sleep lead to dysregulation of autonomic functions, while dysfunction in autonomic coordination impairs the initiation and maintenance of sleep. This bidirectionality may result in cross-therapeutic effects in various sleep disorders, with their symptoms being complicated by sympathetic drive and hyperarousal. Improving cardiovascular autonomic homeostasis may prevent the development of significant morbidity, especially in patients with OSA, insomnia, narcolepsy, RBD, PLMD, and RLS. Given these effects, it is hoped that the present description of how neuromodulation is related to both sleep and autonomic regulation will help clinicians optimize care for patients with these conditions.

## Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

## ORCID iDs

Hakseung Kim https://orcid.org/0000-0001-5407-293X
Hee Ra Jung https://orcid.org/0000-0002-4246-7173
Jung Bin Kim https://orcid.org/0000-0002-8013-9349
Dong-Joo Kim https://orcid.org/0000-0002-0988-2236

## Author Contributions

Conceptualization: Hakseung Kim, Dong-Joo Kim. Funding acquisition: Dong-Joo Kim. Investigation: all authors. Project administration: Dong-Joo Kim. Resources: Dong-Joo Kim. Supervision: Dong-Joo Kim. Visualization: Hee Ra Jung. Writing—original draft: Hakseung Kim, Hee Ra Jung. Writing—review & editing: all authors.

## Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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## REFERENCES

1. Krueger JM, Obal F Jr. Sleep function. *Front Biosci* 2003;8:d511-d519.
2. Shin HY, Han HJ, Shin DJ, Park HM, Lee YB, Park KH. Sleep problems associated with behavioral and psychological symptoms as well as cognitive functions in Alzheimer's disease. *J Clin Neurol* 2014;10: 203-209.
3. Stranges S, Tigbe W, Gómez-Olivé FX, Thorogood M, Kandala NB. Sleep problems: an emerging global epidemic? Findings from the INDEPTH WHO-SAGE study among more than 40,000 older adults from 8 countries across Africa and Asia. *Sleep* 2012;35:1173-1181.
4. Léger D, Poursain B, Neubauer D, Uchiyama M. An international survey of sleeping problems in the general population. *Curr Med Res Opin* 2008;24:307-317.
5. Alexander M, Ray MA, Hébert JR, Youngstedt SD, Zhang H, Steck SE, et al. The National Veteran Sleep Disorder Study: descriptive epidemiology and secular trends, 2000–2010. *Sleep* 2016;39:1399-1410.
6. Cortelli P, Lombardi C. Sleep and autonomic nervous system dysfunction. In: Gastone GC, editor. *Handbook of Clinical Neurophysiology.* Vol 6. Amsterdam: Elsevier, 2005;343-353.
7. Bassi A, Bozzali M. Potential interactions between the autonomic nervous system and higher level functions in neurological and neuropsychiatric conditions. *Front Neurol* 2015;6:182.
8. Zielinski MR, McKenna JT, McCarley RW. Functions and mechanisms of sleep. *AIMS Neurosci* 2016;3:67-104.
9. Miglis M. Sleep and the autonomic nervous system. In: Mitchell M, editor. *Sleep and Neurologic Disease.* Amsterdam: Elsevier, 2017;227-244.
10. Miglis MG. Autonomic dysfunction in primary sleep disorders. *Sleep Med* 2016;19:40-49.
11. Van de Borne P, Nguyen H, Biston P, Linkowski P, Degaute JP. Effects of wake and sleep stages on the 24-h autonomic control of blood pressure and heart rate in recumbent men. *Am J Physiol* 1994;266: H548-H554.
12. Caples SM, Somers VK. Autonomic dysregulation during REM sleep. In: Larry RS, editor. *Encyclopedia of Neuroscience.* Amsterdam: Elsevier, 2009;817-823.
13. Van Dort CJ, Zachs DP, Kenny JD, Zheng S, Goldblum RR, Gelwan NA, et al. Optogenetic activation of cholinergic neurons in the PPT or LDT induces REM sleep. *Proc Natl Acad Sci U S A* 2015;112:584-589.
14. Fink AM, Bronas UG, Calik MW. Autonomic regulation during sleep and wakefulness: a review with implications for defining the pathophysiology of neurological disorders. *Clin Auton Res* 2018;28: 509-518.
15. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature* 2005;437:1257-1263.
16. Otake K, Ruggiero DA. Monoamines and nitric oxide are employed by afferents engaged in midline thalamic regulation. *J Neurosci* 1995; 15:1891-1911.
17. Kirouac GJ, Parsons MP, Li S. Orexin (hypocretin) innervation of the paraventricular nucleus of the thalamus. *Brain Res* 2005;1059: 179-188.
18. Grimaldi D, Silvani A, Benarroch EE, Cortelli P. Orexin/hypocretin system and autonomic control: new insights and clinical correlations. *Neurology* 2014;82:271-278.
19. Goudreau JL, Lindley SE, Lookingland KJ, Moore KE. Evidence that hypothalamic periventricular dopamine neurons innervate the intermediate lobe of the rat pituitary. *Neuroendocrinology* 1992;56:100-105.
20. Pearson CA, Placzek M. Development of the medial hypothalamus: forming a functional hypothalamic-neurohypophyseal interface. *Curr Top Dev Biol* 2013;106:49-88.
21. Saper CB. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. *Annu Rev Neurosci* 2002;25:433-469.
22. Lanfranchi PA, Somers VK. Arterial baroreflex function and cardiovascular variability: interactions and implications. *Am J Physiol Regul Integr Comp Physiol* 2002;283:R815-R826.
23. Eckberg DL, Sleight P. Human Baroreflexes in Health and Disease. Oxford: Oxford University Press, 1992.
24. Baust W, Heinemann H. The role of the baroreceptors and of blood pressure in the regulation of sleep and wakefulness. *Exp Brain Res* 1967;3:12-24.
25. Silvani A, Calandra-Buonaura G, Benarroch EE, Dampney RA, Cortelli P. Bidirectional interactions between the baroreceptor reflex and arousal: an update. *Sleep Med* 2015;16:210-216.
26. Hunsley MS, Palmiter RD. Altered sleep latency and arousal regulation in mice lacking norepinephrine. *Pharmacol Biochem Behav* 2004;78:765-773.
27. Berridge CW. Noradrenergic modulation of arousal. *Brain Res Rev* 2008;58:1-17.
28. Tank AW, Lee Wong D. Peripheral and central effects of circulating catecholamines. *Compr Physiol* 2011;5:1-15.
29. Jansen AS, Nguyen XV, Karpitskiy V, Mettenleiter TC, Loewy AD. Central command neurons of the sympathetic nervous system: basis of the fight-or-flight response. *Science* 1995;270:644-646.
30. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002;165:1217-1239.
31. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995;96: 1897-1904.
32. Lanfranchi PA, Somers VK. Cardiovascular physiology: autonomic control in health and in sleep disorders. In: Kryger MH, Roth T, Dement WC, editors. *Principles and Practice of Sleep Medicine.* 5th ed. Amsterdam: Elsevier, 2010;226-236.

33. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. *Am J Cardiol* 1983;52:490-494.
34. Fagard RH, Celis H, Thijs L, Staessen JA, Clement DL, De Buyzere ML, et al. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension* 2008;51:55-61.
35. Moon J, Choi KH, Park JH, Song TJ, Choi YS, Kim JH, et al. Sympathetic overactivity based on heart-rate variability in patients with obstructive sleep apnea and cerebral small-vessel disease. *J Clin Neurol* 2018;14:310-319.
36. Cortelli P, Parchi P, Sforza E, Contin M, Pierangeli G, Barletta G, et al. Cardiovascular autonomic dysfunction in normotensive awake subjects with obstructive sleep apnoea syndrome. *Clin Auton Res* 1994;4:57-62.
37. Taylor KS, Murai H, Millar PJ, Haruki N, Kimmerly DS, Morris BL, et al. Arousal from sleep and sympathetic excitation during wakefulness. *Hypertension* 2016;68:1467-1474.
38. Fletcher EC, Bao G, Li R. Renin activity and blood pressure in response to chronic episodic hypoxia. *Hypertension* 1999;34:309-314.
39. Kim JB, Seo BS, Kim JH. Effect of arousal on sympathetic overactivity in patients with obstructive sleep apnea. *Sleep Med* 2019;62:86-91.
40. Lin C, Lo MT, Guilleminault C. Exploring the abnormal modulation of the autonomic systems during nasal flow limitation in upper airway resistance syndrome by Hilbert–Huang transform. *Front Med (Lausanne)* 2017;4:161.
41. Palma JA, Urrestarazu E, Lopez-Azcarate J, Alegre M, Fernandez S, Artieda J, et al. Increased sympathetic and decreased parasympathetic cardiac tone in patients with sleep related alveolar hypoventilation. *Sleep* 2013;36:933-940.
42. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002;6:97-111.
43. Nano MM, Fonseca P, Vullings R, Aarts RM. Measures of cardiovascular autonomic activity in insomnia disorder: a systematic review. *PLoS One* 2017;12:e0186716.
44. Blasi A, Jo J, Valladares E, Morgan BJ, Skatrud JB, Khoo MC. Cardiovascular variability after arousal from sleep: time-varying spectral analysis. *J Appl Physiol (1985)* 2003;95:1394-1404.
45. Carter JR, Durocher JJ, Larson RA, DellaValla JP, Yang H. Sympathetic neural responses to 24-hour sleep deprivation in humans: sex differences. *Am J Physiol Heart Circ Physiol* 2012;302:H1991-H1997.
46. Jarrin DC, Ivers H, Lamy M, Chen IY, Harvey AG, Morin CM. Cardiovascular autonomic dysfunction in insomnia patients with objective short sleep duration. *J Sleep Res* 2018;27:e12663.
47. Nofzinger EA, Buysse DJ, Germain A, Price JC, Miewald JM, Kupfer DJ. Functional neuroimaging evidence for hyperarousal in insomnia. *Am J Psychiatry* 2004;161:2126-2128.
48. Slowik JM, Collen JF, Yow AG. *Narcolepsy*. StatPearls. Treasure Island: StatPearls Publishing, 2020.
49. Grimaldi D, Calandra-Buonaura G, Provini F, Agati P, Pierangeli G, Franceschini C, et al. Abnormal sleep-cardiovascular system interaction in narcolepsy with cataplexy: effects of hypocretin deficiency in humans. *Sleep* 2012;35:519-528.
50. van der Meijden WP, Fronczek R, Reijntjes RH, Corssmit EP, Biermasz NR, Lammers GJ, et al. Time- and state-dependent analysis of autonomic control in narcolepsy: higher heart rate with normal heart rate variability independent of sleep fragmentation. *J Sleep Res* 2015;24:206-214.
51. Haba-Rubio J, Frauscher B, Marques-Vidal P, Toriel J, Tobback N, Andries D, et al. Prevalence and determinants of rapid eye movement sleep behavior disorder in the general population. *Sleep* 2018;41:zsx197.
52. Visanji NP, Lang AE, Kovacs GG. Beyond the synucleinopathies: alpha synuclein as a driving force in neurodegenerative comorbidities. *Transl Neurodegener* 2019;8:28.
53. Postuma RB, Gagnon JF, Vendette M, Montplaisir JY. Markers of neurodegeneration in idiopathic rapid eye movement sleep behaviour disorder and Parkinson's disease. *Brain* 2009;132:3298-3307.
54. Boeve BF, Silber MH, Ferman TJ, Lin SC, Benarroch EE, Schmeichel AM, et al. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. *Sleep Med* 2013;14:754-762.
55. Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, et al. MDS research criteria for prodromal Parkinson's disease. *Mov Disord* 2015;30:1600-1611.
56. Kaufmann H, Norcliffe-Kaufmann L, Palma JA, Biaggioni I, Low PA, Singer W, et al. Natural history of pure autonomic failure: a United States prospective cohort. *Ann Neurol* 2017;81:287-297.
57. Ferini-Strambi L, Oertel W, Dauvilliers Y, Postuma RB, Marelli S, Iranzo A, et al. Autonomic symptoms in idiopathic REM behavior disorder: a multicentre case-control study. *J Neurol* 2014;261:1112-1118.
58. Sorensen GL, Kempfner J, Zoetmulder M, Sorensen HB, Jennum P. Attenuated heart rate response in REM sleep behavior disorder and Parkinson's disease. *Mov Disord* 2012;27:888-894.
59. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. *Sleep Med* 2013;14:744-748.
60. Saponjic J, Radulovacki M, Carley DW. Respiratory pattern modulation by the pedunculopontine tegmental nucleus. *Respir Physiol Neurobiol* 2003;138:223-237.
61. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24:197-211.
62. Hijaz BA, Volpicelli-Daley LA. Initiation and propagation of α-synuclein aggregation in the nervous system. *Mol Neurodegener* 2020;15:19.
63. Sunwoo JS, Kim YJ, Byun JI, Kim TJ, Jun JS, Lee ST, et al. Comorbid depression is associated with a negative treatment response in idiopathic REM sleep behavior disorder. *J Clin Neurol* 2020;16:261-269.
64. Sforza E, Nicolas A, Lavigne G, Gosselin A, Petit D, Montplaisir J. EEG and cardiac activation during periodic leg movements in sleep: support for a hierarchy of arousal responses. *Neurology* 1999;52:786-791.
65. Ghorayeb I, Tison F. Epidemiology of restless legs syndrome. *Rev Neurol (Paris)* 2009;165:641-649.
66. Pennestri MH, Montplaisir J, Colombo R, Lavigne G, Lanfranchi PA. Nocturnal blood pressure changes in patients with restless legs syndrome. *Neurology* 2007;68:1213-1218.
67. Izzi F, Placidi F, Romigi A, Lauretti B, Marfia GA, Mercuri NB, et al. Is autonomic nervous system involved in restless legs syndrome during wakefulness? *Sleep Med* 2014;15:1392-1397.
68. Clemens S, Rye D, Hochman S. Restless legs syndrome: revisiting the dopamine hypothesis from the spinal cord perspective. *Neurology* 2006;67:125-130.
69. Ford GA, Hoffman BB, Blaschke TF. Effect of temazepam on blood pressure regulation in healthy elderly subjects. *Br J Clin Pharmacol* 1990;29:61-67.
70. Nardone R, Sebastianelli L, Versace V, Brigo F, Golaszewski S, Pucks-Faes E, et al. Effects of repetitive transcranial magnetic stimulation in subjects with sleep disorders. *Sleep Med* 2020;71:113-121.
71. Du X, Xu W, Li X, Zhou D, Han C. Sleep disorder in drug addiction: treatment with transcranial magnetic stimulation. *Front Psychiatry* 2019;10:848.
72. Sharma VD, Sengupta S, Chitnis S, Amara AW. Deep brain stimulation and sleep-wake disturbances in parkinson disease: a review. *Front Neurol* 2018;9:697.

73. Fisicaro F, Lanza G, Bella R, Pennisi M. "Self-neuroenhancement": the last frontier of noninvasive brain stimulation? *J Clin Neurol* 2020;16:158-159.
74. Johnson RL, Wilson CG. A review of vagus nerve stimulation as a therapeutic intervention. *J Inflamm Res* 2018;11:203-213.
75. Wu X, Zhang Y, Luo WT, Mai RR, Hou XY, Xia ZQ, et al. Brain functional mechanisms determining the efficacy of transcutaneous auricular vagus nerve stimulation in primary insomnia. *Front Neurosci* 2021;15:609640.
76. Badran BW, Dowdle LT, Mithoefer OJ, LaBate NT, Coatsworth J, Brown JC, et al. Neurophysiologic effects of transcutaneous auricular vagus nerve stimulation (taVNS) via electrical stimulation of the tragus: a concurrent taVNS/fMRI study and review. *Brain Stimul* 2018;11:492-500.
77. De Couck M, Nijs J, Gidron Y. You may need a nerve to treat pain: the neurobiological rationale for vagal nerve activation in pain management. *Clin J Pain* 2014;30:1099-1105.
78. Rawat JK, Roy S, Singh M, Guatam S, Yadav RK, Ansari MN, et al. Transcutaneous vagus nerve stimulation regulates the cholinergic anti-inflammatory pathway to counteract 1, 2-dimethylhydrazine induced colon carcinogenesis in albino wistar rats. *Front Pharmacol* 2019;10:353.
79. Naser PV, Kuner R. Molecular, cellular and circuit basis of cholinergic modulation of pain. *Neuroscience* 2018;387:135-148.
80. Zhao B, Bi Y, Li L, Zhang J, Hong Y, Zhang L, et al. The instant spontaneous neuronal activity modulation of transcutaneous auricular vagus nerve stimulation on patients with primary insomnia. *Front Neurosci* 2020;14:205.
81. Rong P, Liu J, Wang L, Liu R, Fang J, Zhao J, et al. Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: a nonrandomized controlled pilot study. *J Affect Disord* 2016;195:172-179.
82. Luo M, Qu X, Li S, Zhao J, Zhao Y, Jiao Y, et al. Transcutaneous vagus nerve stimulation for primary insomnia and affective disorder:a report of 35 cases. *Zhongguo Zhen Jiu* 2017;37:269-273.
83. O'Keane V, Dinan TG, Scott L, Corcoran C. Changes in hypothalamic-pituitary-adrenal axis measures after vagus nerve stimulation therapy in chronic depression. *Biol Psychiatry* 2005;58:963-968.
84. Chapleau MW, Sabharwal R. Methods of assessing vagus nerve activity and reflexes. *Heart Fail Rev* 2011;16:109-127.
85. Sacha J. Interaction between heart rate and heart rate variability. *Ann Noninvasive Electrocardiol* 2014;19:207-216.
86. Fujiki N, Yoshida Y, Shiba T, Parnis S, Nishino S. Vagus nerve stimulation modulates cataplexy in narcoleptic dogs. *Sleep Biol Rhythms* 2003;1:191-193.
87. Merkl A, Brakemeier EL, Danker-Hopfe H, Bajbouj M. Vagus nerve stimulation improves restless legs syndrome associated with major depression: a case report. *J Clin Psychiatry* 2007;68:635-636.
88. Val-Laillet D, Aarts E, Weber B, Ferrari M, Quaresima V, Stoeckel LE, et al. Neuroimaging and neuromodulation approaches to study eating behavior and prevent and treat eating disorders and obesity. *Neuroimage Clin* 2015;8:1-31.
89. Gierthmuehlen M, Plachta DT. Effect of selective vagal nerve stimulation on blood pressure, heart rate and respiratory rate in rats under metoprolol medication. *Hypertens Res* 2016;39:79-87.
90. Ebben MR, Sethi NK, Conte M, Pollak CP, Labar D. Vagus nerve stimulation, sleep apnea, and CPAP titration. *J Clin Sleep Med* 2008;4:471-473.
91. Parhizgar F, Nugent K, Raj R. Obstructive sleep apnea and respiratory complications associated with vagus nerve stimulators. *J Clin Sleep Med* 2011;7:401-407.
92. St Louis EK, Faber K. Reversible sleep-related stridor during vagus nerve stimulation. *Epileptic Disord* 2010;12:76-80.
93. Upadhyay H, Bhat S, Gupta D, Mulvey M, Ming S. The therapeutic dilemma of vagus nerve stimulator-induced sleep disordered breathing. *Ann Thorac Med* 2016;11:151-154.
94. Lai Y, Yu L, Jiang H. Autonomic neuromodulation for preventing and treating ventricular arrhythmias. *Front Physiol* 2019;10:200.
95. Heusser K, Tank J, Engeli S, Diedrich A, Menne J, Eckert S, et al. Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. *Hypertension* 2010;55:619-626.
96. Doumas M, Guo D, Papademetriou V. Carotid baroreceptor stimulation as a therapeutic target in hypertension and other cardiovascular conditions. *Expert Opin Ther Targets* 2009;13:413-425.
97. Cortelli P, Lombardi C, Montagna P, Parati G. Baroreflex modulation during sleep and in obstructive sleep apnea syndrome. *Auton Neurosci* 2012;169:7-11.
98. Parati G, Di Rienzo M, Bonsignore MR, Insalaco G, Marrone O, Castiglioni P, et al. Autonomic cardiac regulation in obstructive sleep apnea syndrome: evidence from spontaneous baroreflex analysis during sleep. *J Hypertens* 1997;15:1621-1626.
99. Bonsignore MR, Parati G, Insalaco G, Marrone O, Castiglioni P, Romano S, et al. Continuous positive airway pressure treatment improves baroreflex control of heart rate during sleep in severe obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 2002;166:279-286.
100. Bonsignore MR, Parati G, Insalaco G, Castiglioni P, Marrone O, Romano S, et al. Baroreflex control of heart rate during sleep in severe obstructive sleep apnoea: effects of acute CPAP. *Eur Respir J* 2006;27:128-135.
101. Narkiewicz K, Pesek CA, Kato M, Phillips BG, Davison DE, Somers VK. Baroreflex control of sympathetic nerve activity and heart rate in obstructive sleep apnea. *Hypertension* 1998;32:1039-1043.
102. Lombardi C, Parati G, Cortelli P, Provini F, Vetrugno R, Plazzi G, et al. Daytime sleepiness and neural cardiac modulation in sleep-related breathing disorders. *J Sleep Res* 2008;17:263-270.
103. Linz D, Hohl M, Khoshkish S, Mahfoud F, Ukena C, Neuberger HR, et al. Low-level but not high-level baroreceptor stimulation inhibits atrial fibrillation in a pig model of sleep apnea. *J Cardiovasc Electrophysiol* 2016;27:1086-1092.