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Autonomic regulation during sleep and wakefulness: a review with implications for defining the pathophysiology of neurological disorders

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Abstract

Cardiovascular and respiratory parameters change during sleep and wakefulness. This observation underscores an important, albeit incompletely understood, role for the central nervous system in the differential regulation of autonomic functions. Understanding sleep/wake-dependent sympathetic modulations provides insights into diseases involving autonomic dysfunction. The purpose of this review was to define the central nervous system nuclei regulating sleep and cardiovascular function and to identify reciprocal networks that may underlie autonomic symptoms of disorders such as insomnia, sleep apnea, restless leg syndrome, rapid eye movement sleep behavior disorder, and narcolepsy/cataplexy. In this review, we examine the functional and anatomical significance of hypothalamic, pontine, and medullary networks on sleep, cardiovascular function, and breathing.

Keywords

Autonomic nervous system; Breathing; Sleep; Sympathetic; Parasympathetic

Introduction

Seventeenth-century philosophers were fascinated with sleep [1, 2]. Descartes grappled with an uncertain human existence during unconsciousness, concluding that the sleeping brain continues to *think* [1]. Locke separated the awake and sleeping minds, suggesting the latter state to be inactive and—by extension—with limited purpose [2]. By the 1950s, however, discoveries about *paradoxical* sleep (a sleep stage with rapid movements of the eyes and cortical activity resembling wakefulness) challenged the notion that the sleeping brain was inactive [3]. Modern definitions acknowledge that many biologic processes are active during sleep, particularly networks regulating the autonomic nervous system (ANS).

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Compliance of ethical standards

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Understanding the neural mechanisms regulating sleep and autonomic function is important for defining the relationship between sleep disorders and cardiovascular (CV) morbidity. The purpose of this review was to examine neural networks differentially controlling the ANS during wakefulness versus sleep. The review also summarizes knowledge about the following clinical disorders: insomnia, sleep apnea, restless leg syndrome (RLS), rapid eye movement (REM), sleep behavior disorder, and narcolepsy/cataplexy.

Neural networks

Knowledge about central nervous system (CNS) networks is important for determining relationships between the CNS sleep/wake control circuitry and the pathways regulating autonomic function. Evidence from preclinical and clinical studies indicates that the modulation of ANS reflexes is dependent on behavioral state (i.e., sleep vs. wake). The key CNS nuclei associated with these functions are summarized in Table 1.

Cardiorespiratory regulation and CNS activities during wakefulness

During wakefulness, particularly during periods of physical activity, there are significant fluctuations in cardiac output and respiratory flow. The brainstem reflexively responds to afferent signals communicating these changes from peripheral baroreceptors, chemoreceptors, and the cardiac sympathetic nerves. The nucleus of the solitary tract (NTS) and the rostral ventrolateral medulla (RVLM) are the primary regulators of CV adjustments [4]. Baroreceptors in the aortic arch sense blood pressure (BP) changes and relay this information to the NTS via the vagus nerve [5]. When the BP is elevated, NTS efferents decrease sympathetic outflow to the heart while simultaneously increasing vagal tone [6]. NTS neurons project to gamma-aminobutyric acid (GABA)-ergic neurons in the caudal ventrolateral medulla, which provides inhibitory inputs to the RVLM, thereby reducing sympathetic outflow to the kidney [7]. Pre-motor neurons in the RVLM project to the intermediolateral column of the spinal cord, which synapse with renal post-ganglionic neurons [8]. Via this neural network, RVLM neurons regulate renal blood flow, sodium and water reabsorption, and excretion, as well as the activity of the renin–angiotensin system [9].

Baroreceptor activation also reduces respiratory rate, a response attributed to the activation of neurons in the Bötzinger complex, a cluster of neurons in the RVLM and ventral respiratory column. The Bötzinger complex receives projections from the NTS and innervates respiratory control centers [10, 11]. In the RVLM, sympathetic neurons are intermingled with respiratory-modulating neurons [7]. Chemoreceptors in the carotid body provide another afferent signal to the NTS in response to hypoxia. Low levels of arterial oxygen increase afferent discharge via the glossopharyngeal nerve; this chemosensory information is relayed to the NTS, and the NTS neurons excite central respiratory centers, including the retrotrapezoid nucleus/parafacial respiratory group and Bötzinger complex [11]. The chemoreflex enhances respiratory drive and sympathoexcitation.

In circuits originating from the midbrain and pons, the *fast* neurotransmitters glutamate and GABA play critical roles in maintaining alertness [12]; these midbrain/pontine networks also influence cardiorespiratory activities, possibly via efferents to the NTS or RVLM. In

addition, several modulatory CNS circuits exist to regulate wakefulness. A cholinergic pathway (originating from the laterodorsal tegmentum and pedunculopontine tegmentum [PPT]) promotes arousal. The cholinergic projections innervate the thalamus, promoting the transmission of sensory input to the cortex [12]. Monoaminergic neurons (originating from the parabrachial nucleus, periaqueductal grey [PAG], locus coeruleus, and raphe nuclei) project to the cortex, lateral hypothalamus, and basal forebrain and also modulate alertness [13]. Orexinergic neurons in the lateral hypothalamus represent another system promoting wakefulness; these neurons provide excitatory projections that activate the ascending monoaminergic system and brainstem cholinergic systems [14]. Collectively, these pathways activate the cortex and contribute to the low-voltage, high-frequency electroencephalogram (EEG) pattern occurring during wakefulness. Glutamatergic neurons in the parabrachial nucleus of the rostral pons are preferentially active during wakefulness [15, 16]; projections from the parabrachial nucleus to the NTS may represent a mechanism for adjusting BP between wakefulness and sleep. Increased parabrachial nucleus activity may inhibit the baroreflex [17–19], representing a mechanism for maintaining higher BP during wakefulness compared with sleep.

Networks regulating sympathetic/respiratory activities during sleep

During non-REM sleep, parasympathetic drive increases, with an associated reduction in cardiac sympathetic activity [20]. The decline in sympathetic drive accounts for the *dipping phenomenon*, which is an approximately 10% decrease in mean arterial pressure compared with that during wakefulness. BP dipping represents a healthy cardiovascular response; non-dipping, rising, or extreme-dipping is associated with elevated CV disease risk [21]. Non-REM sleep is also accompanied by decreased muscle tone and reduced respiratory rate [22].

Hypothalamic nuclei, specifically the ventrolateral preoptic nucleus (VLPO) and median preoptic nucleus, promote non-REM sleep via descending GABAergic projections to the arousal systems of the hypothalamus and brainstem. These sleep-promoting pathways are regulated by neuromodulators, such as adenosine, that accumulate during wakefulness to increase the physiologic pressure to sleep [23]. Activity of the preoptic nuclei may also influence ANS functions. For example, anatomical evidence suggests that non-REM sleep-promoting neurons in the VLPO inhibit the hypothalamic structures with pressor and sympathoexcitatory functions. For example, Uschakov and colleagues demonstrated the presence of an inhibitory projection from the VLPO to the paraventricular nucleus of the hypothalamus in rats [24, 25]. Inhibition of the paraventricular nucleus may account for a reduction in sympathetic drive, taking into account the possible impact on vasopressin synthesis/secretion. Vasopressin, synthesized by the paraventricular nucleus, is an important neurotransmitter/hormone for maintaining BP. As a potent vasoconstrictor, vasopressin contributes to elevated BP, in addition to its role in increasing fluid reabsorption from the filtrate in the nephron [26].

The occurrence of non-REM sleep requires inhibition of the wake-promoting networks, which is dependent on neurotransmission involving GABA and galanin [12]. Inhibition of the networks exciting the cortex results in a slower-frequency, higher-voltage EEG pattern during non-REM sleep, although *slow waves* are not uniformly distributed across the

cortical surface [27]. The VLPO of the anterior hypothalamus plays an important role in promoting the transition from wake to sleep [28]. VLPO neurons fire rapidly during sleep; via GABAergic and galaninergic efferents, the VLPO inhibits the discharge of wake-promoting monoaminergic cells [28, 29]. Data also support a possible role for the preoptic area in promoting REM sleep, as evidenced by firing rates of the VLPO and the median preoptic nucleus increasing during both non-REM and REM sleep in rats [30]. REM sleep is a *paradoxical* stage consisting of a high-frequency and low-amplitude EEG pattern (similar to the EEG pattern observed during wakefulness) with muscle atonia.

Unlike non-REM sleep, REM sleep involves an increase in cholinergic activity in the pons, particularly in the PPT and laterodorsal tegmentum [31]. The EEG features of REM sleep and the rapid eye movements are controlled by neurons in the sublaterodorsal region of the pons [12]. Skeletal muscle paralysis, a key feature of REM sleep, is associated with increased glutamatergic neuron activity in the dorsal pons [29]. Typically, REM sleep bouts are preceded by longer periods of non-REM sleep. A network of CNS nuclei regulates the timing of REM sleep. REM-promoting neurons in the pons are inhibited by GABAergic projections from the PAG and VLPO, as well as by the wake-promoting structures of the lateral hypothalamus [12, 32]. Inhibition of REM sleep may also involve serotonergic input from the raphe nuclei, albeit this connection is incompletely understood [33].

Autonomic instability with fluctuations in BP and respiratory rate have been reported during REM sleep [34–36]; these events may be related to the activities of pontine nuclei, such as the PPT, that have connections with sympathetic/respiratory control centers (NTS and RVLM) [37, 38]. Functional and anatomical data from rat studies support a role for the PPT in regulating sympathetic nerve activity. For example, studies in anesthetized rats demonstrated the ability to increase renal and splanchnic sympathetic nerve activity by stimulating neurons in the PPT [39, 40], which also evoked respiratory dysrhythmia [39]. Sympathetic activity in different vascular beds as modulated by the PPT, however, has yet to be examined during non-REM and REM sleep. The irregular breathing patterns associated with REM sleep may be attributed to chemoreflex and baroreflex control [41]. During non-REM sleep, chemoreceptors promptly recognize small fluctuations in oxygen and carbon dioxide, which results in minor adjustments in breathing rate and depth via NTS pathways [11]. Non-REM sleep is therefore associated with stability in respiration and BP, but chemo- and baroreflex response time may be altered during REM sleep. For example, transitions from non-REM to REM sleep evoke increases in mean arterial pressure in humans [42] and in rats [43, 44], and these BP fluctuations may lead to baroreflex instability. These observations suggest that an increase in the *loop gain* of these feedback systems may accompany REM sleep. Loop gain measures the propensity for a feedback system to become unstable [45, 46]. Although REM sleep is associated with skeletal muscle atonia, results from several studies have challenged the notion that upper airway muscles lose tone during REM sleep. For example, Fraigne and Orme demonstrated that genioglossus muscle activity increased in rats during REM sleep compared with non-REM sleep, suggesting the possibly that REM-specific muscle recruitment could contribute to changes in respiration [47].

Features of the cortical EEG relevant to understanding state–dependent cardiorespiratory patterns

Figures 1 and 2 illustrate examples from our laboratory of polysomnography in freely moving rats. Our procedures conformed to the American Physiological Society's Guiding Principles for the Care and Use of Vertebrate Animals and were approved by the University of Illinois at Chicago Institutional Animal Care and Use Committee. In Fig. 1, non-REM sleep is associated with a high-amplitude/low-frequency cortical EEG pattern (Fig. 1a), and a transition from non-REM sleep to wakefulness shifts the EEG to a lower amplitude/higher frequency pattern accompanied by adjustments in BP (Fig. 1b). With the transition from non-REM sleep to REM sleep, the EEG shifts to a high-frequency/low-amplitude pattern (similar to wakefulness), while the electromyogram (EMG) signal provides evidence of skeletal muscle paralysis, a defining characteristic of REM sleep (Fig. 1c). Figure 2 illustrates a non-REM to REM sleep transition in a rat. An increase in the EEG frequency with low EMG tone signifies the transition to REM sleep, a sleep stage in which respiratory rate can be irregular (Fig. 2 a, c). Both rodent and human sleep demonstrate alternating patterns of non-REM and REM sleep, which can be accompanied by fluctuations in BP, heart rate, ventilation, and arterial concentrations of oxygen and carbon dioxide.

Pathophysiology of sleep disorders associated with ANS dysfunction

Insomnia

Insomnia is accompanied by hyperarousal, elevated BP, and reduced heart rate variability [48]. To understand ANS dysfunction with insomnia, autonomic parameters have been examined in individuals with objective short sleep duration (< 6 h) and in those with genetic disorders causing severe sleep loss and hyperarousal (e.g., fatal familial insomnia [FFI]). Jarrin and colleagues demonstrated that, compared with controls with normal sleep duration (≥ 6 h), short sleep duration was associated with elevated mean heart rate and with heart rate variability metrics indicating reduced parasympathetic activity and sympathovagal imbalance [49]. In FFI, a progressive, inherited (autosomal-dominant) neurodegenerative disease, the inability to sleep leads to unbalanced autonomic control, coma, and death [50]. No single CNS anomaly is linked with FFI, but dysfunction of the sleep- and autonomic-regulating systems of the thalamus, hypothalamus, parabrachial nucleus, PAG, and NTS have been investigated. FFI is characterized by severe sympathetic over-activity (tachycardia, hypertension, and hyperthermia), which is hypothesized to involve impaired inhibition of the baroreflex, possibly resulting from over-excitation of the RVLM [51].

Sleep apnea and airway resistance syndromes

Sleep apnea involves a complex group of disorders causing adverse CV and metabolic consequences in addition to excessive daytime sleepiness. Sleep-disordered breathing can cause intermittent hypoxia and chronic activation of the sympathetic nervous system—two mechanisms hypothesized to link sleep apnea with an elevated risk for CV diseases, such as hypertension and stroke [52]. Patients experience frequent arousals from sleep, resulting from increased respiratory effort in response to hypoxia or hypercapnia [53]. Respiratory events can be apneas (defined as the absence of inspiratory flow for ≥ 10 s) or hypoapneas

(shallow, slow respiration lasting ≥ 10 s), leading to EEG arousals and varying degrees of arterial oxygen desaturation [52]. The etiology of these respiratory events may be obstructive or central. Obstructive sleep apnea (OSA) involves repetitive airway blockage caused by the surrounding soft tissue and can be correlated with obesity; central sleep apneas result from reduced neural output of the brainstem neurons innervating the upper airway and thoracic inspiratory muscles [52]. Many patients, however, experience both obstructive and central events [54]. Interestingly, treating airway obstruction with positive airway pressure or tracheostomy results in central apnea, suggesting that underlying CNS neural mechanisms are implicated in both types of apnea and contribute to complex sleep apnea phenotypes [55, 56].

Sleep apnea disrupts sleep architecture, evoking frequent arousals and modifying sleep stage-dependent interactions between sympathetic and parasympathetic tone [57]. In OSA, hypoxia is a powerful stimulus for increasing sympathetic drive via the chemoreflex [58–60]. In humans, obstructive sleep apnea has been associated with an impaired nocturnal dipping pattern in BP. Mokhlesi and colleagues demonstrated a dose–response risk for developing systolic and diastolic non-dipping BP with increasing severity of sleep apnea [61]. Experiments in rats have demonstrated how repetitive apneas have an additive effect on widening pulse pressure and increasing BP; these responses activate CNS ascending arousal systems, increase respiratory muscle effort, cause changes in intrathoracic blood volume, and activate sympathetic activity [59, 60, 62]. Data from rat models of chronic intermittent hypoxia have also provided evidence for renal mechanisms in the development of chronically elevated BP. Rats with renal sympathetic denervation did not demonstrate hypertension in response to chronic intermittent hypoxia, but sham-operated rats exhibited a 10 ± 3 mmHg increase in mean arterial pressure after 5 weeks of hypoxia exposure. Plasma renin activity increased fourfold in the latter group but remained at baseline levels in denervated rats [63]. It remains to be determined whether afferents from state-regulating nuclei, such as the PPT, that have projections to the RVLM exert a pathophysiologic influence on renal function or sympathetic nerve activity. Other candidates for understanding CV morbidity with sleep apnea include the pontine and medullary respiratory control systems, which receive projections from the PAG. As explained above, in addition to regulating wakefulness/arousal, the PPT modulates respiratory patterns [64], and PAG neuronal activity is synchronized with respiratory cycles [65]. Therefore, dysfunction of these nuclei could contribute to central sleep apneas and sympathetic consequences.

Investigators have examined airflow restriction and oxygen desaturation to determine how autonomic responses depend on the degree of airway obstruction, sleep disruption, or oxygen desaturation. Normally, parasympathetic activity increases as a patient transitions from wakefulness to non-REM sleep, but this response may be overactive or reduced depending on the type of sleep-related breathing disorder. For example, Lin and colleagues studied beat-to-beat heart rate (RR intervals) and finger photoplethysmography in patients with upper airway resistance syndrome (UARS); these patients had reduced airway diameter during sleep, but airway restriction had a very limited effect on oxygen saturation. During non-REM sleep, patients with UARS demonstrated parasympathetic nervous system hyperactivation with inspiratory flow limitation/increased respiratory effort. Chronic vagal stimulation during sleep may, therefore, evoke irregularities in BP control with UARS [66].

Patients with sleep-related alveolar hypoventilation (SRAH), however, have oxygen desaturation without significant limitations in airflow. Palma and colleagues found SRAH to be associated with two autonomic abnormalities: (1) an increase in the low-frequency component of the heart rate variability spectrum (0.04–0.15 Hz) and (2) a decrease in the high-frequency component (0.15–0.40 Hz). These findings suggest a reduction in parasympathetic activity, and the researchers found that this abnormality was particularly evident during REM sleep [67]. These studies emphasize the importance of considering that different autonomic profiles, with different underlying mechanisms, are associated with sleep-related breathing disorders, depending on how the disease involves airflow limitation and changes in oxygenation.

Patients with postural tachycardia syndrome (POTS) often undergo evaluation for sleep-disordered breathing. POTS is defined by orthostatic intolerance; when patients move from the recumbent sleeping position, they demonstrate syncope and excessively elevated heart rate [68]. Patients with POTS have markedly elevated sympathetic outflow in response to hypotensive challenges and enhanced activation of the parasympathetic nervous system [69]. The presence of sleep-disordered breathing and changes in sleep architecture are controversial with POTS, considering that several studies reported no polysomnographic changes compared with controls [69, 70]. When mild airflow limitations accompany POTS, they may not cause significant oxygen desaturation but still appear to contribute to significant autonomic impairment. This may be of greatest concern when POTS is diagnosed in patients with disorders affecting connective tissue flexibility, such as Ehlers–Danlos syndrome, which contribute to airway collapse during sleep [71].

Restless leg syndrome

Restless movements of the legs are monitored during polysomnography and have provided insights into how these pathological movements correlate with heart rate variability metrics. The pathophysiology may be complex because some studies demonstrate no impact of leg movements on heart rate variability [72], while others indicate the presence of elevated sympathetic activity during non-REM sleep [73]. Inconsistencies among study findings may result from the observation that not all leg movements cause arousals from sleep. For example, patients with RLS are kept awake by their leg movements. In contrast to RLS, patients with periodic limb movement disorder exhibit involuntary movement during sleep. Barone and colleagues demonstrated that periodic limb movement disorder is associated with sympathetic over-activity during non-REM sleep, a finding not associated with the autonomic profile of RLS [73]. These observations underscore the importance of measuring sleep—and arousals from sleep—to characterize the etiology of autonomic dysfunction with restless leg movements.

REM sleep behavior disorder

Skeletal muscle paralysis normally accompanies REM sleep. With REM sleep behavior disorder, however, muscle paralysis is incomplete or absent, resulting in forceful movements during REM sleep. Dreams may also be intense and vivid. REM sleep behavior disorder has been associated with CNS neurodegenerative diseases, and the presence of comorbid neurodegeneration and REM sleep behavior disorder is associated with a greater degree of

autonomic impairment [74]. The neurobiology of REM sleep behavior disorder remains incompletely defined, but the role of CNS REM sleep circuitry has been investigated. For example, degeneration of the sublaterodorsal region of the pons and the associated projections to spinal interneurons have been proposed to contribute to abnormal REM sleep and motor regulation [74]. Pontine nuclei involved in REM sleep regulation, such as the PPT, are also implicated in regulating balance, locomotion, and gain [64]. Although the findings of some investigations are equivocal, studies of patients with REM sleep behavior disorders have revealed reduced variability in heart rate in addition to abnormal heart rate responses to arousals from sleep [75].

Narcolepsy/cataplexy

Narcolepsy is a rare disease involving excessive daytime sleepiness, uncontrollable bouts of sleep, the presence of REM sleep immediately upon sleep onset, and/or episodes of muscle weakness (cataplexy). The condition results from the partial or complete destruction of orexinergic neurons in the hypothalamus, which project to the CNS nuclei regulating arousal and wake–sleep switching [14, 76]. Data from mouse models indicate that, during wakefulness, orexinergic neurons exhibit slow tonic firing, and these neurons are not active during non-REM sleep [77]. There is evidence suggesting that narcolepsy affects the ability to modulate BP during sleep. For example, Grimaldi and colleagues demonstrated different 24-h BP patterns in patients with narcolepsy compared with controls. Narcolepsy was associated with a nighttime non-dipping pattern, although it remains unknown whether this pattern contributes to CV disease development in this population [78]. Sieminski and colleagues also observed a non-dipping profile with narcolepsy; BP, however, did not correlate with cerebrospinal fluid orexin levels or sleep characteristics [79]. Findings from other studies indicated reduced sympathetic drive during wakefulness with narcolepsy [80, 81]. For example, Fronczek and colleagues found evidence of reduced sympathetic tone in a small group of men with narcolepsy [81]. Collectively, these findings suggest that the loss of orexinergic neurons affects BP in a manner that differs according to sleep–wake states.

Conclusions and future directions

Networks of CNS nuclei play critical roles in differentially regulating autonomic CV function during wakefulness, non-REM sleep, and REM sleep. Dysfunction of these networks underlies sleep and autonomic disorders. The etiologies are complex and can involve neurodegeneration of CNS nuclei, genetic factors, and plasticity of the nervous system. Arousals, hypoxia, and other stimuli may contribute to chronic changes in neuronal signaling, promoting an imbalance in sympathetic and parasympathetic drive. Conditions that arouse a patient from sleep (e.g., insomnia, OSA) evoke hyperarousal of the CNS networks promoting wakefulness and sympathetic parameters (e.g., thalamus, hypothalamus, parabrachial nucleus, PAG, and NTS). Short sleep duration contributes to elevated heart rate and sympathovagal imbalance, and in severe forms of the disease (e.g., fatal familial insomnia), severe dysfunction of CV reflexes contributes to mortality. Diseases that disrupt sleep architecture (e.g., OSA, UARS, RLS) also alter the sleep stage-dependent interactions of the sympathetic and parasympathetic nervous systems. The existing literature indicates that it is important to differentiate patients with different phenotypes of a sleep disorder

(e.g., OSA vs. UARS, RLS vs. periodic limb movement disorder) because their autonomic profiles may differ depending on the disease-specific neural mechanisms. There is a critical need to devise animal models and obtain clinical data to understand disorders associated with progressive neuron destruction (e.g., REM sleep behavior disorder, narcolepsy/cataplexy) given that there is evidence linking these conditions with widespread/progressive neurodegeneration, chronic autonomic impairment, and impaired quality of life.

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Abbreviations

ANS	Autonomic nervous system
BP	Blood pressure
CNS	Central nervous system
CV	Cardiovascular
EEG	Electroencephalogram
EMG	Electromyogram
FFI	Fatal familial insomnia
GABA	Gamma-aminobutyric acid
NTS	Nucleus of the solitary tract
OSA	Obstructive sleep apnea
PAG	Periaqueductal grey
POTS	Postural orthostatic tachycardia syndrome
PPT	Pedunculopontine tegmentum
REM	Rapid eye movement
RLS	Restless leg syndrome
RVLM	Rostral ventrolateral medulla
SRAH	Sleep-related alveolar hypoventilation
UARS	Upper airway resistance syndrome
VLPO	Ventrolateral preoptic nucleus

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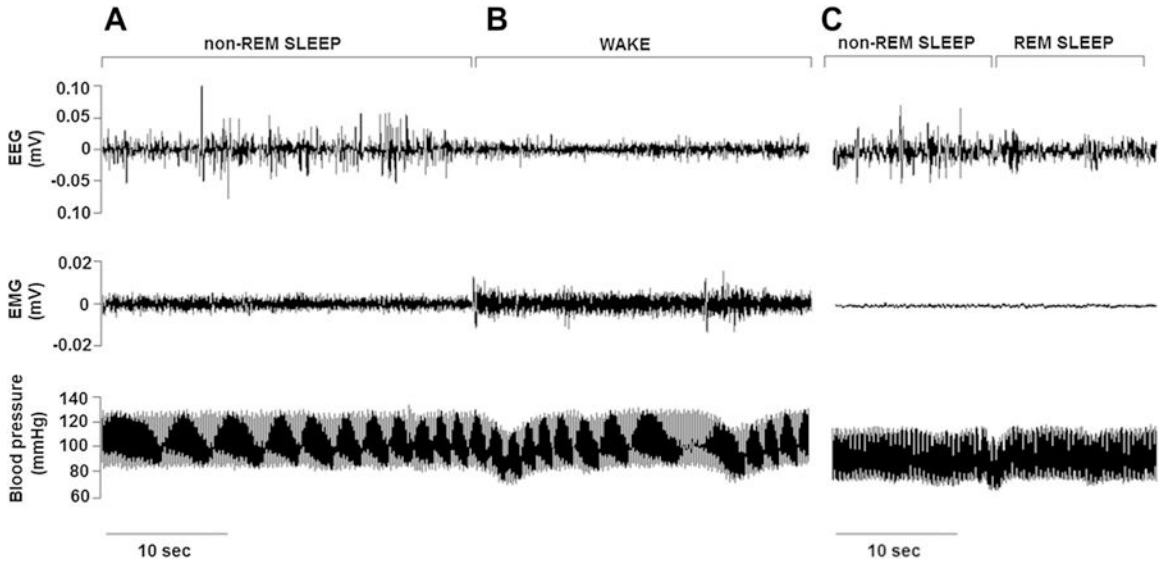

Fig. 1.

Cardiovascular and electroencephalogram/electromyogram (*EEG*/*EMG*) characteristics of non-rapid eye movement (*REM*) sleep, wakefulness, and REM sleep in the rat. EEG, EMG, and blood pressure (BP) patterns during sleep and wakefulness in an adult male Wistar-Kyoto rat are shown. During non-REM sleep (**a**), BP and heart rate were stable. The non-REM sleep EEG demonstrated a lower frequency, higher amplitude pattern compared with wakefulness. When the rat awoke (**b**), BP became less stable, and the EEG pattern shifted to a lower amplitude/increased frequency waveform; the increased EMG indicated skeletal muscle activity. **c** Illustration of a transition occurring 2 h later in the same rat; from non-REM sleep, the rat transitioned to REM sleep, which is demonstrated by a lower amplitude/higher frequency EEG with muscle atonia. The latter is indicated by the very low EMG tone. Data were acquired using the Data Sciences International (Minneapolis, MN) implantable telemetry system (transmitter models 4ET/HDS-11; 500 Hz sampling rate). Data were graphed using Igor Pro version 6.3 (WaveMetrics Inc.)

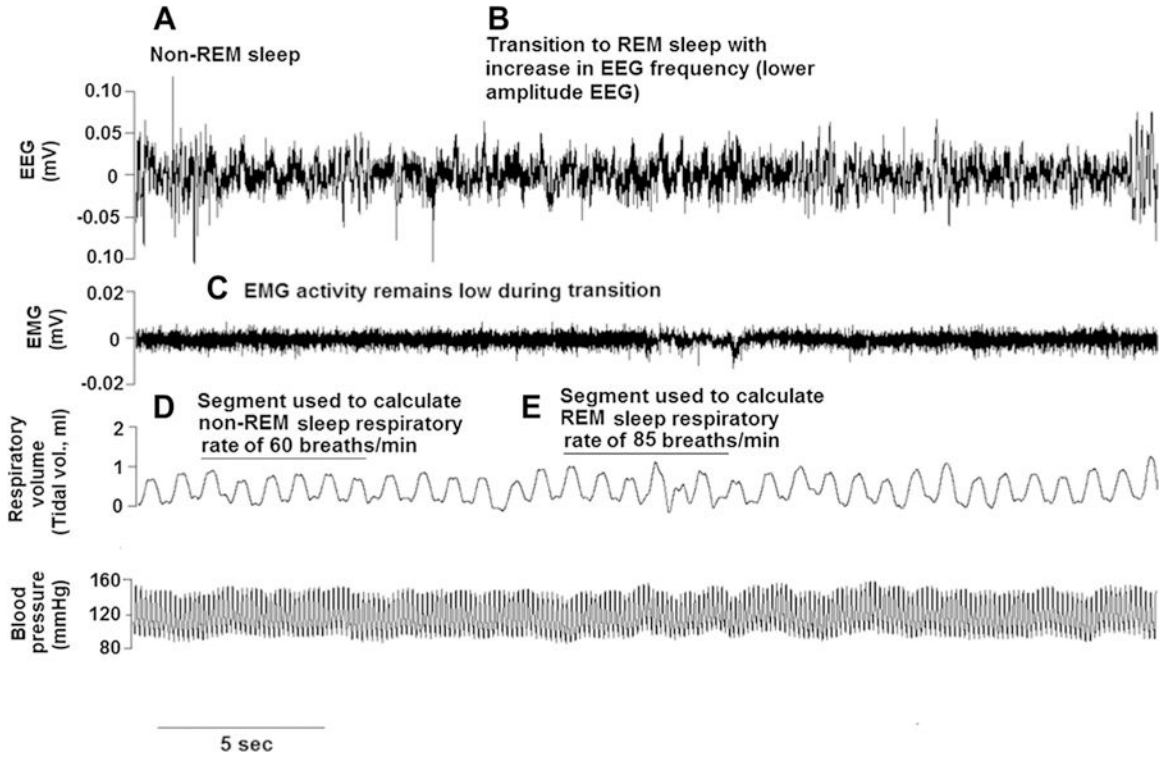

Fig. 2.

Cortical EEG, respiratory, and BP activities during a sleep transition in the rat. Patterns in EEG, EMG, breathing, and BP in an adult male Sprague–Dawley rat are shown. **a**–**c** A transition from non-REM to REM sleep (**a**, **b**) is illustrated by increasing frequency in the EEG while EMG tone remains unchanged (**c**). Non-REM sleep is typically associated with stability in respiratory and CV parameters (**d**). Compared with non-REM sleep, REM sleep can evoke more variability in breathing and/or BP. In this example, the respiratory rate increased [from approx. 60 breaths/min to 85 breaths/min during the transition (**e**)]. BP remained relatively stable in this rat. Data were acquired using implantable telemetry system and analyzed using Neuroscore software (Data Sciences International, Minneapolis, MN)

Table 1

Summary of the major central nervous system mechanisms regulating autonomic and sleep/wake functions

CNS region	CNS nuclei	Important anatomical connections	Functional significance
Hypothalamus	Preoptic area (VLPO)	Provides GABAergic projections to hypothalamic monoamerinergic systems [30]	Inhibits wakefulness [30]
		Provides a GABAergic projection to the paraventricular nucleus [24, 25]	Inhibits vasopressin synthesis, possibly leading to blood pressure reduction [26]
	Subparaventricular zone	Receives efferents from the suprachiasmatic nucleus [32]	Integrates signals regulating body temperature, locomotion, and level of alertness [30]
	SCN	Provides polysynaptic GABAergic input to pineal gland and receives light signals from retinal ganglion cells [32]	Regulates melatonin secretion from the pineal gland; contributes to regulation of circadian rhythms [32]
Midbrain and pons	Parabrachial nucleus	Provides inhibitory projections to the NTS [17]	Suggests a role in baroreflex modulation.
	PPT	Provides cholinergic projections to the thalamus [12]	Promotes/modulates sensory input to the cortex (alertness) and contributes to the EEG activity of REM sleep [12]
		Provides cholinergic projections to RVLM [37, 40]	Suggests a role in sympathetic/CV regulation
	PAG	Provides GABAergic projections to pontine REM-regulating neurons [12]	Regulates the timing of REM sleep [12, 32]
		Provides input to the parabrachial nucleus [13]	Suggests a role in baroreflex modulation
Medulla	NTS	Receives afferent signals from peripheral baroreceptors, chemoreceptors, cardiac sympathetic nerves, and vagus nerve [5]	Regulates sympathetic outflow to the heart
	Bötzinger complex	Receives projections from NTS [11]	Innervates the respiratory control centers [11]
	Caudal ventrolateral medulla	Provides GABAergic projections to RVLM [7]	Regulates sympathetic outflow to the kidney [7]
	RVLM	Pre-motor neurons project to the intermediolateral column of the spinal cord, which synapse with renal post-ganglionic neurons [8]	Regulates renal blood flow, sodium and water reabsorption and excretion, and renin–angiotensin system [7, 9]

CNS Central nervous system, *VLPO* ventrolateral preoptic nucleus, *SCN* suprachiasmatic nucleus/nuclei, *PPT* pedunculopontine tegmentum, *PAG* periaqueductal grey, *NTS* nucleus of the solitary tract, *RVLM* rostral ventrolateral medula, *GABA* gamma-aminobutyric acid, *REM* rapid eye movement, *EEG* electroencephalogram