Autonomic Neuroscience: Basic and Clinical 218 (2019) 54–63

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Review

Control of the cardiovascular and respiratory systems during sleep

Eduardo E. Benarroch*

Department of Neurology, Mayo Clinic, Rochester, MN, United States of America

ARTICLE INFO

Keywords:
Sleep
Parabrachial
Rostral ventrolateral medulla
Retrotrapezoid
Sympathetic
Cardiovagal

ABSTRACT

Sleep and arousal from sleep are associated with profound changes in cardiovascular and respiratory functions. Fluctuations of arterial blood pressure (ABP), heart rate (HR), and respiration occur both during non-rapid eye movement (NREM) and REM sleep and during transitions between sleep and behavioral arousal. These changes reflect complex, state-dependent interactions among several neuronal groups in the hypothalamus and brainstem. These neurons utilize the excitatory amino-acid L-glutamate or the inhibitory amino acid γ-aminobutyric acid (GABA) and are modulated in a state-dependent manner by inputs from cholinergic, monoaminergic, and hypothalamic orexin/hypocretin and melanin-concentrating hormone (MCH) neurons. These different neuronal populations mediate continuous interactions between cortical state and subcortical circuits modulating sympathetic and cardiovagal output, respiratory pattern, and chemosensitivity. Reciprocally, brainstem areas involved in these functions promote behavioral arousal in the setting of hypoxia, hypercapnia, or other stressors. Studies in rodents using optogenetic and other approaches for selective activation or inactivation of specific neuronal groups identified by their unique neurochemical markers, combined with recording of cortical activity, cardiovascular responses, and respiration, have provided new information on the brainstem mechanisms controlling arousal, wake-sleep cycle, cardiovascular and respiratory control (Luppi et al., 2017; Saper and Fuller, 2017; Scammell et al., 2017; Dampney, 2016; Del Negro et al., 2018; Guyenet, 2006; Guyenet and Abbott, 2013; Smith et al., 2013). These findings also provide further insight into the pathophysiology of sleep-related cardiovascular and respiratory disorders including sleep apnea, narcolepsy, congenital central hypoventilation syndrome, sudden infantile death syndrome, and sudden unexpected death in epilepsy.

1. Cardiovascular and respiratory phenomenology during sleep and wakefulness

The different stages or sleep are defined by distinct patterns of electrocortical activity reflected in the electroencephalogram (EEG) and associated changes in motor and autonomic functions. NREM sleep is associated with reduction of muscle tone, and different EEG patterns that define 3 stages; stage 1 (N1) at the beginning of sleep; stage 2 (N2) characterized by sleep spindles; and deep or stage 3 sleep (N3) characterized by low frequency (0.5–2 Hz) delta waves. NREM sleep is punctuated by spontaneous or stimulus-induced Microarousals detected by spontaneous increase in EEG frequencies, K complexes, or delta bursts. REM sleep is associated with low amplitude mixed frequency in the EEG and absent muscle tone; tonic EMG is interrupted by phasic phenomena characterized by muscle brief irregular distal muscle twitches, rapid eye movements, and arousal reflected by increases in EEG frequency and muscle tone. There are state-related changes in sympathetic output, ABP, HR, baroreflex sensitivity, respiratory rhythm, chemosensitivity, and airway tone during sleep (Somers et al., 1993; Douglas et al., 1982a; Douglas et al., 1982b; Silvani and Dampney, 2013; Schafer and Schlafke, 1998; Dempsey et al., 2004; Orem et al., 2000). These interactions among pontomedullary circuits directly involved in the wake-sleep cycle, cardiovascular and respiratory reflexes and modulatory inputs from the hypothalamus and other rostral regions (Fig. 1).

1.1. Cardiovascular changes

The cardiovascular changes during sleep in experimental animals have been comprehensively reviewed (Silvani and Dampney, 2013). In humans, like in experimental animals, during NREM sleep there is a progressive reduction of ABP reflecting decrease in sympathetic vasomotor activity; there is also a progressive increase in cardiac parasympathetic modulation associated with reduced HR (Somers et al., 1993).

In rats, sympathetic nerve activity to both skeletal muscles and kidneys decreases in NREM sleep compared with that during wakefulness (Silvani and Dampney, 2013). There is also an increase in skin

* 200 Third Street SW, Rochester, MN 55905, United States of America.
E-mail address: Benarroch.eduardo@mayo.edu.

https://doi.org/10.1016/j.autneu.2019.01.007
Received 4 September 2018; Received in revised form 28 January 2019; Accepted 28 January 2019
1566-0702/ © 2019 Published by Elsevier B.V.

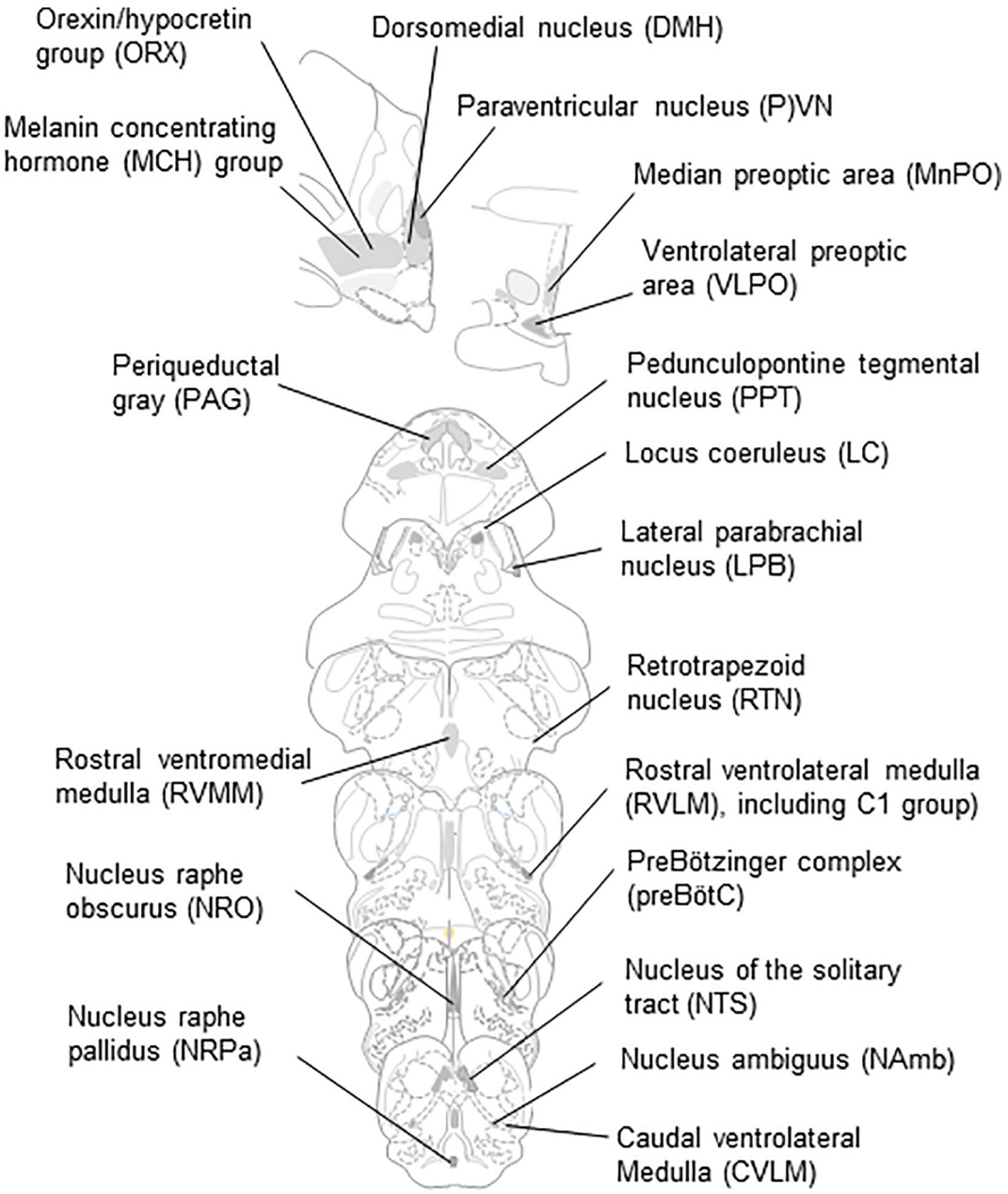

Fig. 1. Brainstem and hypothalamic areas involved in control of cardiovascular and respiratory functions.
Several areas of the hypothalamus and brainstem participate in control of arousal, sleep-wake cycle, cardiovascular and respiratory functions. Where these areas have been primarily identified in experimental animals, particularly rodents, their putative location in human brain are shown. Among the hypothalamic areas, the ventrolateral preoptic (VLPO) and median preoptic (MnPO) areas are primarily involved in transition from wakefulness to non-rapid eye movement (NREM) sleep; the melanin concentrating hormone (MCH) neurons in the posterior later hypothalamus are also active during both NREM and particularly REM sleep. In contrast, the orexin (ORX)/hypocretin neurons are active primarily during active wakefulness and stabilize the wake state. The paraventricular nucleus (PVN) mediates responses to internal stressors whereas the dorsomedial nucleus (DMH) initiates responses to external stressors as well as cold. These effects are mediated by premotor sympathoexcitatory neurons in the rostral ventrolateral medulla (RVLM) including the C1 group, which are critical for responses to hypoxia and other internal stressors, and neuron of the rostral ventromedial medulla (RVMM) and medullary raphe nuclei, including the nucleus raphe obscurus (NRO) and raphe (pallidus) that are involved in response to externals stressors and thermoregulatory responses to cold. Activity of sympathoexcitatory neurons in the RVLM is regulated by baroreceptor and chemoreceptor inputs relayed by the nucleus of the solitary tract (NTS). Baroreflex inputs to NTS neurons trigger inhibition of sympathoexcitatory RVLM neurons via a relay in the caudal ventrolateral medulla (CVLM) and activation of cardiovagal neurons of the nucleus ambiguus (NAmb). Components of the central respiratory network, including the retrotrapezoid nucleus (RTN) that responds to hypercapnia and indirectly (via the chemoreceptors) to hypoxia, and the preBötzinger complex (preBötC), which is the inspiratory pattern generator, interacts with cardiovascular control areas. The activity of brainstem cardiovascular and respiratory groups is controlled during wakefulness (and REM sleep) by neurons in the lateral parabrachial nucleus (LPB) and pedunculopontine tegmental nucleus (PPT). Neurons in the locus coeruleus (LC) participate in behavioral arousal and contribute to cardiovascular and respiratory responses during this state via interactions with other brainstem areas. All these wake-active regions are stimulated by ORX neurons and inhibited by MCH neurons (not shown).

temperature, particularly at distal sites, during NREM sleep; this is presumably due to reduced vasoconstrictor sympathetic nerve input to skin blood vessels (Silvani and Dampney, 2013). Microarousals during NREM sleep are accompanied by transient cardiovascular manifestations referred to autonomic arousals. They manifest with a stereotyped sequence: of increase in HR, followed by an increase in ABP, and then returns of HR to or below baseline level followed by return of ABP to baseline (Silvani and Dampney, 2013). This sequence of cardiovascular activation also occurs spontaneously during wakefulness and during episodes of periodic leg movements of sleep (Silvani and Dampney, 2013). REM sleep is characterized by bursts of skin and muscle sympathetic nerve activity and elevated ABP and HR (Somers et al., 1993). During REM sleep, ABP and HR return toward values similar to those during wakefulness (Silvani and Dampney, 2013). Studies in experimental animals indicate that, in contrast with NREM sleep and wakefulness, there is a highly differentiated change in sympathetic outflow during REM sleep. There is an increase in activity in lumbar sympathetic nerves supplying the skeletal muscle, whereas there is a decrease in mesenteric and renal sympathetic nerve activity (Silvani and Dampney, 2013). Baroreflex sensitivity also varies across the sleep-wake cycle, reaching a maximum during deep NREM sleep and resulting in lower short-term variability of ABP and HR than in wakefulness (Silvani and Dampney, 2013). Cross-correlation studies show that the pattern of coupling between the spontaneous fluctuations of heart period (reciprocal of HR) and systolic ABP varies among wake-sleep states in normal subjects, reflecting variable contribution of baroreflex and central command mechanisms (Silvani et al., 2008). Overall, during the night, there is a normal 10–20% reduction of BP (dipping), which primarily reflects reduced sympathetic output to resistance vessels (Seravalle et al., 2018).

1.2. Respiratory changes

There is reduced respiratory chemosensitivity during sleep (Douglas et al., 1982a; Douglas et al., 1982b; Schafer and Schlafke, 2001). The hypoxic ventilatory drive is minimal during REM sleep whereas the hypercapnia ventilatory drive varies during sleep. Hypercapnia is a much more potent stimulus for arousal than hypoxemia (Douglas et al., 1982a; Douglas et al., 1982b). Behavioral respiratory drive is minimal during deep NREM sleep and may be activated intermittently during REM sleep, either erratically or by dream contents (Schafer and Schlafke, 1998). This leads to irregular breathing patterns with short breathing pauses and phases of rapid shallow breathing that are independent of variations in chemoreceptor or vagal afferent activity (Orem et al., 2000). Bursts of rapid eye movements are associated with increased breathing frequency and reduced tidal volume even in the setting of hypercapnia (Schafer and Schlafke, 1998). During transition from wakefulness to sleep and throughout sleep stages there is reduced tonic activation of dilator muscles of the upper airway particularly during REM sleep, which predisposes to obstructive sleep apnea (Mezzanotte et al., 1996).

2. Control of arousal and sleep states

The changes in cardiovascular and respiratory functions during sleep reflect the influences of multiple neuronal cell groups that regulate arousal and transitions between sleep stages. These neurons are distributed in the basal forebrain, hypothalamus, and brainstem. Whereas medullary neurons mediate feedback cardiovascular and respiratory reflexes, inputs from more rostral areas involved in control of arousal and sleep-wake cycle provide a state-dependent, feedforward modulation of these reflexes (Fig. 2). Thus, a short discussion review of these areas is appropriate in this context. There are several excellent reviews on this topic (Luppi et al., 2017; Saper and Fuller, 2017; Scammell et al., 2017).

2.1. Brainstem arousal circuits

Recent evidence in rodents indicates that the parabrachial nucleus (PB) in the dorsal pons is a primary wake-promoting area (Saper and Fuller, 2017). Studies in rats showed that integrity of the basal forebrain is critical for cortical arousal and this involves input from glutamatergic neurons in the medial parabrachial nucleus and adjacent precoeruleus area; cell-specific lesions in this region produced behavioral unresponsiveness a monotonous slow cortical EEG (Saper and Fuller, 2017). A study using selective deletion of vesicular glutamate transporter gene in the external lateral PB subdivision showed that glutamatergic neurons in this region have a critical role in arousal in response to elevated CO_2 (Kaur et al., 2013).

The basal forebrain contains cholinergic, glutamatergic, and GABAergic neurons that promote arousal via inputs to the cerebral cortex. Recordings from channelrhodopsin-2 tagged neurons showed that three cell types - cholinergic, glutamatergic, and parvalbumin-positive GABAergic neurons - were more active during wakefulness and REM sleep than NREM sleep and activation of each cell type rapidly induced wakefulness (Xu et al., 2015). The pedunculopontine tegmental nucleus (PPT) contains intermingled populations of glutamatergic and cholinergic neurons that promote wakefulness and suppress low-frequency electroencephalogram rhythms during NREM sleep (Kroeger et al., 2017). Monoaminergic brainstem groups, including noradrenergic neurons of the locus coeruleus (LC) and serotonergic neurons of the dorsal raphe nuclei, together with histaminergic neurons of the tuberomammillary nucleus, are active during arousal, reduce their activity in NREM sleep and become essentially silent in REM sleep (Hobson and Pace-Schott, 2002). All wake-promoting glutamatergic, cholinergic, and monoaminergic neurons are activated by inputs from orexin/hypocretin neurons of the posterior lateral hypothalamus (Kuwaki and Zhang, 2010). Orexin neurons fire during active wakefulness and via their brainstem targets have major role in coordinating arousal with cardiovascular and respiratory activation (Grimaldi et al., 2014; Kuwaki and Zhang, 2010; Nattie and Li, 2012), as discussed below. The posterior hypothalamus also contains a population of glutamatergic neurons in the supramammillary nucleus that promote wakefulness (Luppi et al., 2017; Saper and Fuller, 2017; Scammell et al., 2017).

2.2. Transition from wakefulness to sleep

The transition from wakefulness to sleep primarily depends on GABAergic neurons in the core region of the ventrolateral preoptic area (VLPO) and in the median preoptic area (Saper and Fuller, 2017). The sleep-promoting neurons of the VLPO also produce galanin and send inhibitory projections to all wake-promoting neuronal groups of the brainstem and hypothalamus. Low-frequency photostimulation of these neurons in mice promotes sleep whereas their optogenetic inhibition reduces sleep. Chemogenetic activation of these neurons also reduced body temperature, and induced short-latency sleep in an animal model of insomnia (Kroeger et al., 2018). The lateral hypothalamus contains a population of MCH neurons that also synthesize GABA and promote sleep in part via inhibition of wake-active neurons (Jego et al., 2013; Konadhode et al., 2013; Tsunematsu et al., 2014). A study in rodents led to identification of group of medullary neurons located lateral and dorsal to the facial nerve (named parafacial zone by the authors) that participate in initiation of slow wave sleep (Anaclet et al., 2014). These neurons project to the wake-promoting medial PB nucleus and are sleep active; their lesion leads to increases in daily wakefulness at the expense of slow-wave sleep (Anaclet et al., 2014). Studies in transgenic mice showed that the majority of these neurons are GABA/glycinergic; genetically targeted activation and optogenetically based mapping showed that inhibitory connections between these medullary neurons and basal forebrain projecting medial PB glutamatergic neurons form a circuit that can trigger slow wave sleep and modulate the cortical EEG

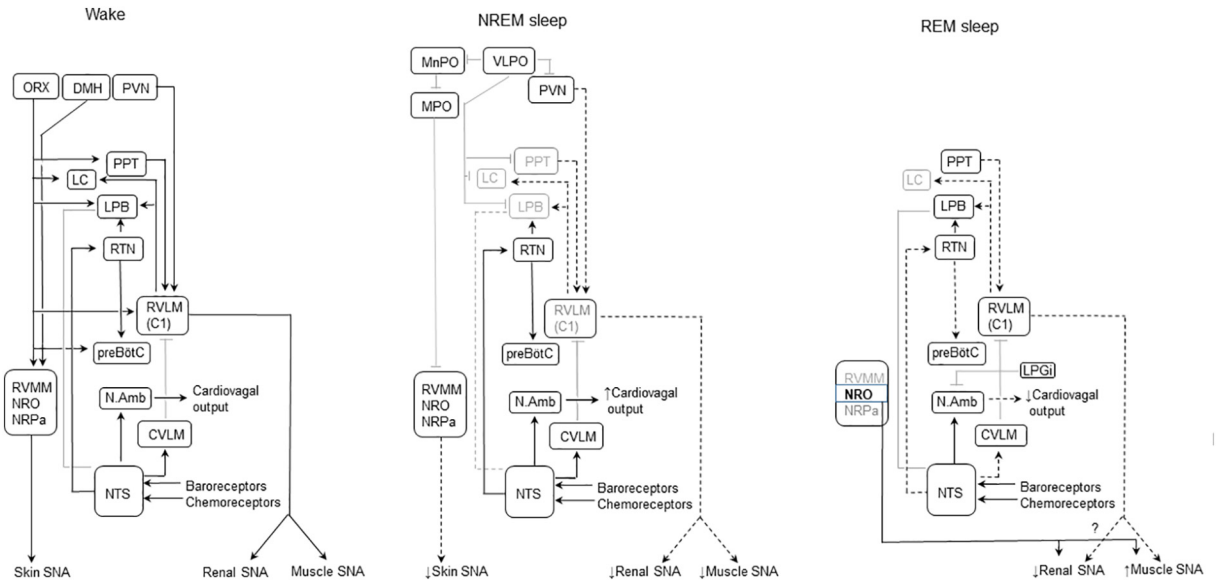

Fig. 2. Interactions among brainstem and hypothalamic areas involved in control of cardiovascular and respiratory functions during wakefulness and sleep. (A) During wakefulness there is activation of hypothalamic orexin (ORX) neurons and several brainstem groups, including the lateral parabrachial nucleus (LPB) and pedunculopontine nucleus (PPT) that, together with neurons of the locus coeruleus (LC) maintain arousal and promote sympathetic activity via inputs to the rostral ventrolateral medulla (RVLM) including the C1 group and respiration via inputs to the preBötzinger complex (preBötC). During wakefulness, as well as non-rapid eye movement (NREM) sleep the respiratory rhythm is regulated by neurons of the retrotrapezoid nucleus (RTN) that respond to CO_2. The RVLM provides premotor sympathoexcitatory neurons that trigger increase in muscle and splanchnic, including renal, sympathetic nerve activity (SNA). The nucleus of the solitary tract (NTS) relays baroreceptor and chemoreceptor inputs to the RVLM, nucleus ambiguus (NAmb), lateral PB and RTN. The LPB provides a reciprocal input to the NTS that reduces baroreflex responses during arousal, including those mediated by sympathoinhibitory neurons of the caudal ventrolateral medulla (CVLM). In responses to internal stressors, neurons of the PVN activate sympathoexcitatory responses via the RVLM. In response to internal stressor and cold exposure, neurons of the dorsomedial nucleus of the hypothalamus promote sympathoexcitatory responses via inputs to the rostral ventromedial medulla (RVMM), nucleus raphe obscurus (NRO) and raphe pallidus, including increase in skin SNA. (B) During NREM sleep there is a progressive reduction of arterial blood pressure that reflects reduced muscle and renal SNA, reduced in heart rate and increased baroreflex sensitivity. This may in part reflect reduced inhibitory influence of the LPB on baroreceptive NTS neurons as well as reduced input from sympathoexcitatory hypothalamic neurons such as ORX and PVN neurons. The ventrolateral preoptic area (VLPO) and median preoptic are (MnPO) participate in NREM sleep induction and thermoregulation. Increased activity of neurons in the medial preoptic nucleus (MPO) may result in decreased activity of medullary raphe neurons, including those in the RPa that elicit skin SNA in response to cold. This may explain the skin vasodilation during NREM sleep. The influence of the RTN on preBötC continues to drive the respiratory rhythm, although the sensitivity of the respiratory network is reduced compared to NREM sleep, in part reflecting reduced activating neuromodulatory drive from sleep-active groups, such as the LC and PPT. (C) During REM sleep there is increased in skeletal muscle SNA and decreased in renal SNA These changes may in part reflect the activity of REM-sleep active nonserotonergic neurons in the nucleus raphe obscurus, which include putative sympathoinhibitory and sympathoexcitatory populations. In the sympathoexcitatory effects of C1 neurons is blunted during REM sleep. The periaqueductal gray consist of a lateral column containing REM-active sympathoexcitatory and a ventrolateral column containing REM-inactive sympathoinhibitory neurons that regulate sympathetic output to different vascular beds via their effect on the RVLM and could potentially contributed to the hemodynamic pattern in REM sleep (not shown). REM-active neurons in the LPB may contribute to sympathetic excitation. REM-sleep active GABAergic neurons in the nucleus reticularis paragigantocellularis (NPGi) inhibit these cardiovagal neurons in brain slices; this may contribute to increase in heart rate during REM sleep. During this state, the RTN does not drive inspiration via the preBötC and therefore the hypercapnic drive to increase respiratory frequency is absent.

in behaving animals (Anaclet et al., 2014).

Sleep initiation is determined both by circadian and homeostatic influences. The suprachiasmatic nucleus of the hypothalamus is the master circadian oscillator and sends direct or indirect signals to hypothalamic areas involved in wake-sleep transition, thermoregulation, and control of ABP and HR (Saper, 2013). They include the sleep-promoting neurons of the VLPO and median preoptic nucleus, warm-sensitive neurons of the medial preoptic nucleus (MPO), and sympathoexcitatory neurons of the paraventricular nucleus (PVN) and dorsomedial nucleus (DMH) (Saper, 2013).

2.3. Non REM-REM sleep transition

Onset of REM sleep depends on a group of glutamatergic REM-on neurons located ventral to the LC in the dorsal pons and referred to as subcoeruleus region (sublaterodorsal region in rodents) (Boeve et al., 2007). These neurons trigger muscle atonia via projections to the nucleus reticularis gigantocellularis in the ventromedial medulla, which sends projections that inhibit the spinal motor apparatus (Luppi et al., 2013b). The NREM-REM sleep transition depends on a putative flip-flop mechanism that involves reciprocal GABAergic inhibitory interactions between REM-on neurons of the subcoeruleus region REM-off neurons located in the ventrolateral periaqueductal gray (PAG) and adjacent pontine tegmentum (Lu et al., 2006; Luppi et al., 2013a; Luppi et al., 2013b). The REM-on/REM-off switch is modulated by cholinergic, monoaminergic, and hypothalamic influences (Scammell et al., 2017). Cholinergic neurons of the PPT are REM-on neurons that facilitate REM sleep in part via inputs to the subcoeruleus area; monoaminergic neurons of the LC and dorsal raphe are REM-off neurons that inhibit REM sleep in part via inputs to the PPT (Hobson and Pace-Schott, 2002). A group of neurons in the ventrolateral medullary tegmentum, corresponding to the nucleus reticularis paragigantocellularis, promote REM sleep by sending GABAergic inhibitory projection to REM-off neurons (Weber et al., 2015). The hypothalamus has an important role in controlling NREM-REM sleep transitions (Luppi et al., 2013b). Orexin neurons inhibit REM sleep by activation of LC and dorsal raphe neurons (Hasegawa et al., 2014). In contrast, the MCH neurons of the posterolateral hypothalamus activate the REM-on and inhibit REM-off neurons (Varin et al., 2018; Torterolo et al., 2015).

3. Mechanisms for cardiovascular control during sleep

Both during wakefulness and across sleep stages the control of ABP and HR occurs primarily at the level of the medulla and results from the interaction between feedback control via reflexes triggered by cardiovascular and respiratory afferents, and feedforward modulation by inputs primarily from the hypothalamus and PAG activated during different behavioral states (Dampney, 2016; Guyenet, 2006; Silvani and Dampney, 2013) (Fig. 2).

3.1. Brainstem Targets for cardiovascular modulation during the wake-sleep cycle

The main target for both reflex and behavioral control of ABP are the premotor sympathoexcitatory glutamatergic neurons of the rostral ventrolateral medulla (RVLM), including the C1 group. The RVLM sends excitatory inputs to a subset of spinal preganglionic neurons that activate noradrenergic neurons in the sympathetic ganglia that elicit vasoconstriction of splanchnic and skeletal muscle blood vessels. This pathway has a primary role in mediating tonic and reflex control of peripheral vascular resistance and thus ABP (Guyenet, 2006; Dampney, 2016). C1 neurons utilize L-glutamate and epinephrine; they innervate both sympathetic and parasympathetic preganglionic neurons, the PVN, and many brainstem areas involved in autonomic regulation, arousal and stress, including the lateral PB and LC. Optogenetic C1 stimulation increases ABP and mimics the effect of various internal stressor that increase sympathetic nerve activity (Stornetta and Guyenet, 2018). Studies using archaerhodopsin loss-of-function optogenetics showed that photoinactivation of C1 neurons reduced sympathetic nerve activity and ABP in anesthetized rats but resulted in only a small ABP reduction in conscious animals under normoxic conditions (Wenker et al., 2017). The sympathoinhibitory effects of C1 inactivation were substantially enhanced during hypoxia or after sino-aortic denervation. These results indicate that C1 neurons have low activity under normoxia, but their function is important to maintain stability of ABP during hypoxia or anesthesia and is a major contributor to hypertension caused by baroreceptor deafferentation (Wenker et al., 2017). Channelrhodopsin-2 mediated photostimulation of C1 neurons also caused arousal from NREM sleep associated with intense cardiorespiratory activation; the arousal response was less reliably obtained during REM sleep and the cardiorespiratory activation was dramatically reduced during REM compared to NREM sleep and wakefulness (Abbott et al., 2013; Burke et al., 2015).

The rostral ventromedial medulla (RVMM) and medullary raphe, including the serotonergic neurons of nucleus raphe pallidus and raphe obscurus, contain premotor sympathoexcitatory neurons that are critical for thermoregulatory responses to cold; these neurons elicit skin vasoconstriction and lipolysis in the brown fat (Nakamura and Morrison, 2011). These neurons also elicit tachycardia in response to external stressors (Dampney, 2015, 2016).

The third major target of state-dependent cardiovascular control is the cardiac vagal preganglionic neurons located in the ventrolateral portion of the nucleus ambiguus (McAllen and Spyer, 1978; Gourine et al., 2016). These neurons inhibit the automatism of the sinus node and provide for a beat-to-beat control of the heart rate (Gourine et al., 2016).

3.2. Hypothalamic commands and cardiovascular changes during NREM sleep

There is evidence that central commands are primarily responsible for the changes in ABP and HR that occur during transition from wakefulness to sleep (Silvani and Dampney, 2013). The VLPO core, which is critical for induction of NREM sleep, sends GABAergic inputs to the PVN; this inhibitory connection may contribute to decrease sympathetic nerve activity during this sleep stage (Uschakov et al., 2006). Warm sensitive neurons of the medial preoptic area are also activated during NREM sleep (Alam et al., 1995) and send inhibitory projections to cold-sensitive neurons of the median preoptic nucleus and medullary raphe, including the nucleus raphe pallidus. As mentioned above, neurons of the nucleus raphe pallidus are responsible for skin vasoconstrictor responses to cold (Nakamura and Morrison, 2011); reduced activity these neurons may thus contribute to skin vasodilation occurring in NREM sleep (Silvani and Dampney, 2013).

3.3. Baroreceptor reflex and its modulation during sleep

The baroreceptor reflex (baroreflex) is the principal mechanism for short-term regulation of ABP (Dampney, 2016; Guyenet, 2006). Baroreceptor afferents provide a monosynaptic excitatory input to a group of neurons of the caudal portion of the nucleus of the solitary tract (NTS), triggering a disynaptic sympathoinhibitory pathway mediated by a group of GABAergic neurons in the caudal ventrolateral medulla that inhibit the RVLM neurons, and a monosynaptic cardioinhibitory pathway mediated by cardiovagal neurons of the nucleus ambiguus resulting in bradycardia (Dampney, 2016; Guyenet, 2006). There is a continuous modulation or resetting of the baroreflex during each phase of the sleep-wake cycle (Silvani et al., 2015; Silvani and Dampney, 2013). Baroreflex sensitivity increases during NREM sleep due to increases responsiveness of NTS to baroreceptor input (Tang and Dworkin, 2010). This may reflect reduced inhibition of the NTS from the lateral PB (Silvani et al., 2015). The lateral PB projects to the NTS (Herbert et al., 1990) and its activation reduces sympathoinhibitory baroreflex sensitivity during wakefulness (Hayward and Felder, 1998) and also reduces cardioinhibitory baroreceptor sensitivity during defence responses (Hayward, 2007). Lateral PB neurons that are active during wakefulness are inhibited during NREM sleep and this may promote baroreflex responses via disinhibition of the NTS in his stage (Silvani and Dampney, 2013).

3.4. Putative brainstem mechanisms for cardiovascular changes during REM sleep

As mentioned above, during the tonic period of REM sleep there are highly differentiated changes in sympathetic nerve activity, with increased in skeletal muscle and decreased in renal and mesenteric vascular resistance. These effects are mediated by brainstem mechanisms driving changes in activity of premotor sympathetic neurons at the transition from NREM to REM sleep (Fig. 2) (Silvani and Dampney, 2013). The central mechanisms that drive these cardiovascular changes are incompletely understood. The caudal portion of the nucleus raphe obscurus contains REM-sleep active nonserotonergic neurons that include putative sympathoinhibitory and sympathoexcitatory groups (McCall and Clement, 1989; Morrison and Gebber, 1984); stimulation of this region elicited an increase in muscle sympathetic activity and decreased in renal sympathetic activity similar to that observed in REM sleep (Futuro-Neto and Coote, 1982). The REM-on neurons of the subcoeruleus (sublaterodorsal tegmental) nucleus project to the lateral paragigantocellular nucleus in the medulla (Sirieix et al., 2012), which also contains REM-sleep active neurons that overlap the sympathoexcitatory regions in the RVLM and RVMM (Dampney, 1994); neurons in these areas could potentially increase sympathetic nerve activity during REM sleep. Whereas C1 neurons in the RVLM are unlikely to contribute substantially to the increased skeletal muscle sympathetic nerve activity as their cardiovascular effects are blunted during REM sleep (Abbott et al., 2013).

The PAG consist of a lateral column containing sympathoexcitatory and a ventrolateral column containing sympathoinhibitory neurons, these PAG columns regulate sympathetic output to different vascular beds via their effect on the RVLM (Bandler et al., 2000). Neurons of the ventrolateral PAG are inhibited, whereas those in the lateral PAG are activated during REM sleep (Luppi et al., 2013a; Saper et al., 2010),

these opposite changes in PAG neuronal activity could contribute to the increase in skeletal muscle and the decrease in renal sympathetic nerve activity via changes in the firing rate of RVLM neurons (Silvani and Dampney, 2013). The lateral PB contains a substantial number of neurons that are more active during REM sleep than during quiet wakefulness and NREM sleep (Saito et al., 1977) and may contribute to resetting of the baroreflex and subsequent increase in sympathetic nerve activity during REM sleep. Similarly, the PPT contains cholinergic neurons that are more active during wakefulness and REM sleep than during NREM sleep (Hobson and Pace-Schott, 2002). These neurons integrate motor, sympathoexcitatory, and respiratory commands and provide excitatory inputs to the RVLM (including the C1 area), resulting in increased sympathetic activity (Padley et al., 2007; Topchiy et al., 2010; Fink et al., 2017). Thus, these cholinergic PPT neurons may contribute to trigger the burst of sympathetic activity, increased ABP, HR and respiration during REM sleep. Conversely, reduced activity of these neurons may contribute to the progressive reduction of ABP and HR during NREM sleep. Neurons in the medial vestibular nucleus show burst discharges synchronized to bursts of rapid eye movements (Bizzi et al., 1964) and, via their projections to the NTS, lateral PBN, and PPT may contribute to transient cardiovascular changes, particularly baroreflex modulation during phasic REM sleep (Horowitz et al., 2005). During phasic REM sleep, there are irregular bursts and trains of respiratory activity; in this state the central respiratory drive may modulate the activity of sympathetic premotor RVLM neurons in part via inputs from GABAergic barosensitive neurons in the caudal ventrolateral medulla (Mandel and Schreihofer, 2006). Activity of cardiovagal neurons of the nucleus ambiguus may also be affected during sleep stages. In addition to the beat-to-beat excitatory drive from the baroreceptive neurons of the NTS, these cardiovagal neurons are also strongly modulated by respiration, primarily via influences from neurons in the neighboring respiratory oscillator but also from peripheral afferent inputs via the NTS (Ben-Tal et al., 2012) Increased activity of these cardiovagal neurons may explain the progressive reduction of the HR and increased respiratory HR modulation during NREM sleep. In contrast, REM-sleep active GABAergic neurons in the nucleus reticularis paragigantocellularis inhibit these cardiovagal neurons in brain slices; this may contribute to increase in heart rate during REM sleep (Dergacheva et al., 2010).

4. Brainstem respiratory circuits and sleep

The respiratory central pattern generator is located in the lower brainstem and includes several rhythm-generating components that drive downstream premotor neurons innervating spinal respiratory and cranial motoneurons (Del Negro et al., 2018; Smith et al., 2013). These pattern generators respond to stimuli from central and peripheral chemoreceptors that trigger ventilatory responses to maintain optimal alveolar ventilation and gas exchange (Nattie and Li, 2012). These central and peripheral chemoreceptor inputs interact to regulate the pattern of respiration and also trigger sympathoexcitatory and cardiovagal responses to maintain optimal tissue oxygenation.

4.1. Respiratory pattern generators

Breathing at rest is characterized by 3 phases, active inspiration, post-inspiration, and passive expiration. Periods of increased respiratory demand or hypercapnia engages active expiration, which increases the tidal volume of the subsequent breath and thus ventilation to meet the O_2 demands or to correct PCO_2. The different phases of the respiratory rhythm are driven by 3 coupled oscillators (Del Negro et al., 2018; Smith et al., 2013). The preBötzinger Complex (preBötC) located in the ventrolateral medulla is the critical pattern generator of inspiration and provides glutamatergic inputs to all pontine and medullary premotor respiratory regions (Smith et al., 2013). Other preBötC promote arousal via projection to the LC and other rostral areas. Active expiration is driven by a group of neurons located rostral to the preBötC and lateral to the facial nerve nucleus and referred to as the parafacial respiratory group (Pisanski and Pagliardini, 2018). These neurons are close or correspond to neurons of the retrotrapezoid nucleus (RTN), the primary chemosensitive area, as discussed below. A group of cholinergic and glutamatergic interneurons located medial to the RTN/parafacial nucleus, referred to as postinspiratory complex (Anderson et al., 2016) may constitute an independent oscillator that controls postinspiration; post-inspiration retards lung deflation, promotes gas exchange, and reduces the risk of upper airway collapse during sleep (Del Negro et al., 2018; Smith et al., 2013).

4.2. Central chemosensitive zones

There is abundant experimental evidence that the primary central chemosensitive zone is the RTN (Guyenet and Bayliss, 2015). The RTN contains glutamatergic neurons that express the transcription factor paired-like homeobox 2 B (PHOX2B) and are activated by increased PCO_2, both via intrinsic proton receptors and paracrine signals from astrocytes (Guyenet and Bayliss, 2015). These neurons also receive input from peripheral chemoreceptors activated by hypoxia via a relay in the NTS and thus integrate central and peripheral chemosensitive signals (Guyenet and Bayliss, 2015). Whereas under hypocapnia RTN neurons are silent and the hypoxia-triggered excitatory input from the carotid bodies is suppressed., silencing RTN neurons optogenetically quickly triggers a compensatory increase in carotid body activity (Guyenet et al., 2017). Optogenetic studies using channelrhodopsin photoactivation show that stimulation of RTN neurons elicits an immediate increase in ventilation without changes in ABP or arousal (Burke et al., 2015). Glutamatergic RTN neurons stimulate respiration via inputs to the preBötC and other brainstem respiratory groups. Optogenetic activation of RTN neurons in wake rodents increases breathing frequency and inspiratory amplitude, entrains the breathing cycle, elicits active expiration, and reduces expiratory flow immediately following inspiration (expiratory brake) (Burke et al., 2015; Guyenet et al., 2017). The effects of optogenetic activation of RTN on breathing depend on the state of vigilance. These studies show that RTN neurons regulate breathing frequency during quiet rest and NREM sleep when inspiration is driven rhythmically by the preBötC. In contrast, phasic RTN stimulation ceases to influence breathing frequency during REM sleep (Burke et al., 2015). Selective optogenetic inhibition of RTN neurons profoundly reduces breathing rate and amplitude during NREM sleep and reduces inspiratory amplitude during REM sleep (Burke et al., 2015). Active expiration during REM sleep may reflect excitatory effects of cholinergic inputs from REM-on neurons of the PPT (and laterodorsal tegmental nucleus) to the RTN/parafacial area (Boutin et al., 2017; Pisanski and Pagliardini, 2018). The RTN/parafacial area is also site of coordination of central respiratory activity with rhythmic oscillations in sympathetic discharge. In normal conditions, sympathetic bursts occur primarily during inspiration; under hypercapnia or hypoxia there is phasic activation of expiratory muscles, which is accompanied by synchronous discharges in sympathetic nerve activity (Molkov et al., 2014).

Respiratory chemosensitivity also involves serotonergic neurons of the medullary raphe, including the nucleus raphe pallidus and nucleus raphe obscurus (Hodges and Richerson, 2010; Corcoran et al., 2015). These neurons detect changes in PCO_2 as well as hypoxia, and exert a global excitatory effect on the brainstem respiratory network, including the preBötC and phrenic motoneurons (da Silva et al., 2011; Morinaga et al., 2018; Barnett et al., 2017). Whereas C1 neurons are activated by hypoxia, neurons of the LC are activated by hypercapnia and also have an excitatory effect on brainstem respiratory neurons (Nattie and Li, 2012; Doi and Ramirez, 2010). The respiratory network controls the phasic activity of muscles that the control upper airway via inputs to the nucleus ambiguus, hypoglossal, trigeminal, and facial nuclei. These cranial motor nuclei also receive modulatory serotonergic and

catecholaminergic inputs that promote patency of the upper airway. For example inputs from the nucleus raphe pallidus excite neurons of the nucleus ambiguus innervating the posterior cricoarytenoid muscle (Arita et al., 1995); and inputs from the C1/A1 area activate neurons of the hypoglossal nucleus innervating the genioglossus muscle (Rukhadze et al., 2017). A decrease of these monoaminergic influences during NREM, and particularly REM sleep, may contribute to reduced tone of muscles opening the upper airway and increase susceptibility to obstructive sleep apnea.

4.3. Nucleus of the solitary tract and integrated respiratory and cardiovascular responses

The caudal portion of the NTS has a major role in coordinating respiratory and sympathetic activities (Zoccal et al., 2014; Molkov et al., 2014; Guyenet, 2014). The NTS is the first synaptic station of all cardiorespiratory afferents, including those from peripheral chemoreceptors, baroreceptors, cardiac receptors and pulmonary stretch receptors (Subramanian et al., 2007).

These afferents are excitatory (glutamatergic) and participate in complex synaptic interactions at the level of the NTS, in part via local inhibitory neurons (Zoccal et al., 2014). The NTS conveys chemoreceptor inputs to the RTN, RVLM (including C1 neurons) and cardiovagal neurons of the nucleus ambiguus (Guyenet, 2014). Activation of peripheral chemoreceptors stimulates ventilation and elicits sympathetic vasoconstriction and decrease of the heart rate. The NTS is also a site of interaction between inputs from baroreceptors and chemoreceptors (Zoccal et al., 2014). For example, baroreceptor inputs result in perturbation of the respiratory pattern via transient activation of inspiratory neurons in the BötC; these neurons participate in the respiratory modulation of sympathetic nerve activity, thereby providing and additional pathway for the sympathetic baroreflex (Zoccal et al., 2014).

4.4. Parabrachial/Kölliker Fuse complex: arousal, respiratory, and cardiovascular control

The PB, together with the adjacent Kölliker-Fuse (KF) nucleus, forms a complex referred to as pontine respiratory group that participates in multiple mechanisms controlling ventilation, upper airway caliber, and cardiovascular responses. Selective microsimulation at different sites the PB/KF generates distinct respiratory patterns and changes in the upper airway (Chamberlin and Saper, 1994). As mentioned earlier in this paper, studies in rodents indicate that glutamatergic neurons of the external lateral PB have a critical role in arousal in response to elevated CO_2 (Kaur et al., 2013). These neurons receive excitatory inputs from chemosensitive neurons of the RTN and medullary raphe and project to forebrain regions mediating arousal, including the orexin group (Niu et al., 2010). These connections may provide an anatomical substrate for the role of the external lateral PB in hypercapnic arousal (Chamberlin, 2013; Kaur et al., 2013). A study combining c-Fos immunohistochemistry with in situ hybridization or retrograde tracing showed that glutamatergic neurons in the external lateral, lateral crescent, and KF subnuclei of the PB complex that are activated by hypercapnia project to several respiratory groups (Yokota et al., 2015; Yokota et al., 2016). They include the ventrolateral medullary premotor respiratory column, the hypoglossal motor nuclei, and in the case of the KF also the phrenic nucleus in the spinal cord (Yokota et al., 2015; Yokota et al., 2016). The lateral PB is also connected to the RTN (Li and Song, 2001). All these connections may provide for the effects of hypercapnia in promoting respiration and stabilizing the upper airway. The lateral PB receives inputs from arterial baroreceptors and cardiac receptors via the NTS and projects back to the NTS and to the RVLM, including the C1 group. Via these projections, different portions of the lateral PB may exert either excitatory or inhibitory influences on baroreflex responses and sympathetic output (Chamberlin and Saper, 1992; Davern, 2014).

5. Integrated control of arousal, cardiovascular and respiratory control

The multiple interactions among neuronal groups controlling arousal, cardiovascular, and respiratory functions provide for an integration among these functions across behavioral states.

5.1. Brainstem mechanisms

One typical example of state-dependent integration is provided by the brainstem cholinergic and monoaminergic groups. Despite their opposite activity and influences on REM sleep, both cholinergic and monoaminergic neurons promote arousal, sympathetic activity, ventilation, and patency of the upper airway. Neurons of the lateral PB and the C1 area are also important examples of such integrative function. Glutamatergic neurons of the external lateral PB receive overlapping inputs from the RTN and C1 area, mediate hypercapnic arousal from sleep, and together with cholinergic PPT neurons, promote sympathoexcitatory and ventilatory responses during wakefulness and REM sleep. C1 neurons respond to hypoxia via chemoreceptor inputs relayed by the NTS, and elicit arousal from NREM sleep, sympathetically mediated increase in ABP, and increase in ventilation (Abbott et al., 2013; Guyenet and Abbott, 2013). These multiple effects reflect their widespread glutamatergic and adrenergic connections (Stornetta and Guyenet, 2018; Wenker et al., 2017). C1 neurons provide glutamatergic input to preganglionic sympathoexcitatory neurons (Dampney, 2016; Guyenet, 2006), preBötC inspiratory neurons (Malheiros-Lima et al., 2018) and LC neurons promoting behavioral arousal (Abbott et al., 2012). C1 neurons also send adrenergic inputs to orexin neurons promoting arousal (Bochorishvili et al., 2014), to RTN/parafacial region neurons generating active expiration (Malheiros-Lima et al., 2017) and to local inhibitory interneurons of the nucleus ambiguus, promoting tachycardia (Boychuk et al., 2011). In contrast to lateral PB neurons, the effects of C1 neurons are blunted during REM sleep (Abbott et al., 2013; Burke et al., 2015). There is evidence that substantial increases or decreases in baroreceptor activity in physiological conditions cause arousal in animal models and human subjects. For example, in conscious subjects, baroreflex deactivation during head-up tilt increased sleep latency and fast EEG activity indicating cortical activation (Cole, 1989) and increase of ABP by 10–20 mm Hg in response to pharmacological stimuli causes arousal from sleep in humans (Kesler et al., 1999). The interactions between the baroreflex and arousal in both humans and experimental animals have been recently reviewed (Silvani et al., 2015). Both lateral PB and C1 neurons may also participate in the modulation of the state of arousal by the baroreflex. Increased baroreceptor activity could promote arousal via NTS-mediated activation of the lateral PB; upon arousal the lateral PB could reduce activity of baroreceptive NTS neurons leading to disinhibition of C1 neurons; this in turn would further promote arousal and sympathoexcitation (Silvani et al., 2015).

5.2. Role of hypothalamic neurons

As briefly reviewed above, the hypothalamus contains several neuronal groups that participate in maintenance of arousal, promote transition between wakefulness and sleep, and/or contribute to regulation of REM sleep. Two salient examples of integration between these effects and control of cardiovascular and respiratory functions are provided by orexin and MCH neurons. These neuronal groups provide widespread inputs to brainstem areas cardiovascular and respiratory areas and exert opposite effects on these functions. Orexin neurons fire during active wakefulness, primarily during behavioral states such as stress or reward. They decrease their firing during quiet wakefulness, are virtually silent during NREM sleep, and are almost silent, with

occasional discharges, during REM sleep. Orexin increases sympathetic activity, ABP and HR primarily via excitatory effects on the RVLM (including C1 neurons), and also activates neurons in the medullary raphe nuclei, pontine A5 (noradrenergic) group, and PVN (Grimaldi et al., 2014). Orexin neurons provide collateral input to the NTS and nucleus ambiguus and contribute to state-dependent modulation of the cardioinhibitory baroreflex. Brain extracellular levels of orexins do not tightly correlate with different wake-sleep states and may thus contribute to modulation of cardiovascular and respiratory functions during sleep (Grimaldi et al., 2014). Studies on knockout mice indicate that orexin is necessary for the normal changes of ABP and HR that occur upon transitions between wakefulness, NREM sleep, and REM sleep (Grimaldi et al., 2014). Orexin neurons also innervate brainstem respiratory pattern generators and chemosensitive areas, including the PB/KF complex, preBötC, and RTN/parafacial region; via these projections orexin promotes ventilatory responses to hypercapnia during behavioral arousal (Shahid et al., 2012; Yokota et al., 2015; Yokota et al., 2016). Orexin may also facilitate baseline neural ventilatory output in response to acidosis in part via increased chemosensitivity of medullary serotonergic neurons (Corcoran et al., 2015). In contrast, sleep-active MCH neurons exert widespread control of autonomic and respiratory functions that are largely opposite to those of orexin. For example, activation of MCH neurons facilitate the baroreflex, reducing ABP and HR (Brown et al., 2007); and inhibit the hypercapnia-induced chemoreflex (Li et al., 2014).

6. Conclusions

Recent experimental findings provide a pathophysiological basis for combined cardiovascular and respiratory abnormalities functions in sleep-related disorders, including development of hypertension in patients with obstructive sleep apnea and increased cardiovascular risk in patients with narcolepsy. These disorders are further discussed in other reviews in this Issue and only few examples will be briefly mentioned here to emphasize the interactions among sleep, cardiovascular, and respiratory disturbances in these and other disorders. Conditions such as chronic intermittent hypoxia, an experimental model of obstructive sleep apnea (OSA), are associated with plastic changes in the medullary respiratory network including the RTN/parafacial region that promote active expiration associated with an additional bursts of sympathetic activity that may provide a mechanism for development of hypertension (Barnett et al., 2017; Lemes et al., 2016). Plastic changes in the NTS elicited by chronic intermittent hypoxia also contribute to increased chemoreceptor input to sympathoexcitatory areas, providing an additional mechanism for hypertension in OSA. Carotid body hyperactivity occurs not only in animal models of OSA, essential hypertension, and heart failure. Unlike these animal models, in humans with OSA, essential hypertension, or mild to moderate congestive heart failure sympathetic tone and ABP are elevated but resting ventilation under normoxia is unchanged. It has been proposed that in humans in the waking state, a mild and sustained rise in carotid body activity may have little effect on breathing because a simultaneous reduction in central chemoreceptor (RTN) activity (Guyenet et al., 2017). Increased sympathetic activity could be sustained in these conditions due to reduced activity of the baroreflex resulting from activation of the carotid bodies and/or direct chemoreceptor reflex driven activation of sympathoexcitatory neurons of the RVLM (Guyenet et al., 2017).

Orexin knockout mice have blunted decrease in ABP on passing from wakefulness to NREM sleep and an exaggerated increase in ABP on passing from NREM to REM sleep. These findings suggest that physiologic concentrations of orexins may modulate sympathetic function to amplify the sleep-related fall in ABP (Grimaldi et al., 2012). Impairment of orexin signaling may prevent the normal ABP dipping during sleep and thus constitute a cardiovascular risk factor in patients with narcolepsy (Grimaldi et al., 2014).

The complex interactions among key brainstem areas involved in arousal, cardiovascular control, and automatic respiration also explain the life-threatening manifestations of disorders such as multiple system atrophy (MSA) and congenital central hypoventilation syndrome. For example, loss of C1 neurons in MSA may manifest not only with orthostatic hypotension but also reduced respiratory chemosensitivity and arousal responses to hypoxia. Loss of neurons in the preBötC, lateral PB and medullary raphe may contribute to sleep apnea, respiratory dysrhythmia, impaired arousal responses to hypercapnia, laryngeal stridor, and death during sleep in these patients Congenital central hypoventilation syndrome associated with *PHOX-2B* mutations is characterized by loss of hypoxic or hypercapnic ventilatory reflexes, abnormal fluctuations of arterial PCO2 and, in severe cases, fatal respiratory failure during sleep. Phox2B expression is necessary for differentiation of carotid body afferents and several brainstem nuclei including the RTN, NTS/dorsal vagal complex, and medullary catecholaminergic (including C1) neurons. A defect in hypercapnia/hypoxia induced arousal due to impaired activity of medullar serotonergic neurons may contribute to some cases of sudden infant death syndrome and sudden unexplained death in epilepsy.

References

Abbott, S.B., Kanbar, R., Bochorishvili, G., Coates, M.B., Stornetta, R.L., Guyenet, P.G., 2012. C1 neurons excite locus coeruleus and A5 noradrenergic neurons along with sympathetic outflow in rats. J. Physiol. 590, 2897–2915.

Abbott, S.B., Coates, M.B., Stornetta, R.L., Guyenet, P.G., 2013. Optogenetic stimulation of c1 and retrotrapezoid nucleus neurons causes sleep state-dependent cardiorespiratory stimulation and arousal in rats. Hypertension 61, 835–841.

Alam, M.N., McGinty, D., Szymusiak, R., 1995. Neuronal discharge of preoptic/anterior hypothalamic thermosensitive neurons: relation to NREM sleep. Am. J. Phys. 269, R1240–R1249.

Anaclet, C., Ferrari, L., Arrigoni, E., Bass, C.E., Saper, C.B., Lu, J., Fuller, P.M., 2014. The GABAergic parafacial zone is a medullary slow wave sleep-promoting center. Nat. Neurosci. 17, 1217–1224.

Anderson, T.M., Garcia III, A.J., Baertsch, N.A., Pollak, J., Bloom, J.C., Wei, A.D., Rai, K.G., Ramirez, J.M., 2016. A novel excitatory network for the control of breathing. Nature 536, 76–80.

Arita, H., Ichikawa, K., Sakamoto, M., 1995. Serotonergic cells in nucleus raphe pallidus provide tonic drive to posterior cricoarytenoid motoneurons via 5-hydroxytryptamine2 receptors in cats. Neurosci. Lett. 197, 113–116.

Bandler, R., Keay, K.A., Floyd, N., Price, J., 2000. Central circuits mediating patterned autonomic activity during active vs. passive emotional coping. Brain Res. Bull. 53, 95–104.

Barnett, W.H., Abdala, A.P., Paton, J.F., Rybak, I.A., Zoccal, D.B., Molkov, Y.I., 2017. Chemoreception and neuroplasticity in respiratory circuits. Exp. Neurol. 287, 153–164.

Ben-Tal, A., Shamailov, S.S., Paton, J.F., 2012. Evaluating the physiological significance of respiratory sinus arrhythmia: looking beyond ventilation-perfusion efficiency. J. Physiol. 590, 1989–2008.

Bizzi, E., Pompeiano, O., Somogyi, I., 1964. Vestibular nuclei: activity of single neurons during natural sleep and wakefulness. Science 145, 414–415.

Bochorishvili, G., Nguyen, T., Coates, M.B., Viar, K.E., Stornetta, R.L., Guyenet, P.G., 2014. The orexinergic neurons receive synaptic input from C1 cells in rats. J. Comp. Neurol. 522, 3834–3846.

Boeve, B.F., Silber, M.H., Saper, C.B., Ferman, T.J., Dickson, D.W., Parisi, J.E., Benarroch, E.E., Ahlskog, J.E., Smith, G.E., Caselli, R.C., et al., 2007. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain 130, 2770–2788.

Boutin, R.C., Alsahafi, Z., Pagliardini, S., 2017. Cholinergic modulation of the parafacial respiratory group. J. Physiol. 595, 1377–1392.

Boychuk, C.R., Bateman, R.J., Philbin, K.E., Mendelowitz, D., 2011. alpha1-adrenergic receptors facilitate inhibitory neurotransmission to cardiac vagal neurons in the nucleus ambiguus. Neuroscience 193, 154–161.

Brown, S.N., Chitravanshi, V.C., Kawabe, K., Sapru, H.N., 2007. Microinjections of melanin concentrating hormone into the nucleus tractus solitarius of the rat elicit depressor and bradycardic responses. Neuroscience 150, 796–806.

Burke, P.G., Kanbar, R., Basting, T.M., Hodges, W.M., Viar, K.E., Stornetta, R.L., Guyenet, P.G., 2015. State-dependent control of breathing by the retrotrapezoid nucleus. J. Physiol. 593, 2909–2926.

Chamberlin, N.L., 2013. Brain circuitry mediating arousal from obstructive sleep apnea. Curr. Opin. Neurobiol. 23, 774–779.

Chamberlin, N.L., Saper, C.B., 1992. Topographic organization of cardiovascular responses to electrical and glutamate microstimulation of the parabrachial nucleus in the rat. J. Comp. Neurol. 326, 245–262.

Chamberlin, N.L., Saper, C.B., 1994. Topographic organization of respiratory responses to glutamate microstimulation of the parabrachial nucleus in the rat. J. Neurosci. 14, 6500–6510.

Cole, R.J., 1989. Postural baroreflex stimuli may affect EEG arousal and sleep in humans. J. Appl. Physiol. 67, 2369–2375.

Corcoran, A.E., Richerson, G.B., Harris, M.B., 2015. Functional link between the hypocretin and serotonin systems in the neural control of breathing and central chemosensitivity. J. Neurophysiol. 114, 381–389.
da Silva, G.S., Giusti, H., Benedetti, M., Dias, M.B., Gargaglioni, L.H., Branco, L.G., Glass, M.L., 2011. Serotonergic neurons in the nucleus raphe obscurus contribute to interaction between central and peripheral ventilatory responses to hypercapnia. Pflugers Arch. 462, 407–418.
Davern, P.J., 2014. A role for the lateral parabrachial nucleus in cardiovascular function and fluid homeostasis. Front. Physiol. 5, 436.
Dampney, R.A., 1994. Functional organization of central pathways regulating the cardiovascular system. Physiol. Rev. 74, 323–364.
Dampney, R.A., 2015. Central mechanisms regulating coordinated cardiovascular and respiratory function during stress and arousal. Am. J. Phys. Regul. Integr. Comp. Phys. 309, R429–R443.
Dampney, R.A., 2016. Central neural control of the cardiovascular system: current perspectives. Adv. Physiol. Educ. 40, 283–296.
Del Negro, C.A., Funk, G.D., Feldman, J.L., 2018. Breathing matters. Nat. Rev. Neurosci. 19, 351–367.
Dempsey, J.A., Smith, C.A., Przybylowski, T., Chenuel, B., Xie, A., Nakayama, H., Skatrud, J.B., 2004. The ventilatory responsiveness to CO(2) below eupnoea as a determinant of ventilatory stability in sleep. J. Physiol. 560, 1–11.
Dergacheva, O., Wang, X., Lovett-Barr, M.R., Jameson, H., Mendelowitz, D., 2010. The lateral paragigantocellular nucleus modulates parasympathetic cardiac neurons: a mechanism for rapid eye movement sleep-dependent changes in heart rate. J. Neurophysiol. 104, 685–694.
Doi, A., Ramirez, J.M., 2010. State-dependent interactions between excitatory neuromodulators in the neuronal control of breathing. J. Neurosci. 30, 8251–8262.
Douglas, N.J., White, D.P., Weil, J.V., Pickett, C.K., Martin, R.J., Hudgel, D.W., Zwillich, C.W., 1982a. Hypoxic ventilatory response decreases during sleep in normal men. Am. Rev. Respir. Dis. 125, 286–289.
Douglas, N.J., White, D.P., Weil, J.V., Pickett, C.K., Zwillich, C.W., 1982b. Hypercapnic ventilatory response in sleeping adults. Am. Rev. Respir. Dis. 126, 758–762.
Fink, A.M., Dean, C., Piano, M.R., Carley, D.W., 2017. The pedunculopontine tegmentum controls renal sympathetic nerve activity and cardiorespiratory activities in nembutal-anesthetized rats. PLoS One 12, e0187956.
Futuro-Neto, H.A., Coote, J.H., 1982. Desynchronized sleep-like pattern of sympathetic activity elicited by electrical stimulation of sites in the brainstem. Brain Res. 252, 269–276.
Gourine, A.V., Machhada, A., Trapp, S., Spyer, K.M., 2016. Cardiac vagal preganglionic neurones: an update. Auton. Neurosci. 199, 24–28.
Grimaldi, D., Calandra-Buonaura, G., Provini, F., Agati, P., Pierangeli, G., Franceschini, C., Barletta, G., Plazzi, G., Montagna, P., Cortelli, P., 2012. Abnormal sleep-cardiovascular system interaction in narcolepsy with cataplexy: effects of hypocretin deficiency in humans. Sleep 35, 519–528.
Grimaldi, D., Silvani, A., Benarroch, E.E., Cortelli, P., 2014. Orexin/hypocretin system and autonomic control: new insights and clinical correlations. Neurology 82, 271–278.
Guyenet, P.G., 2014. Regulation of breathing and autonomic outflows by chemoreceptors. Compr Physiol 4, 1511–1562.
Guyenet, P.G., 2006. The sympathetic control of blood pressure. Nat. Rev. Neurosci. 7, 335–346.
Guyenet, P.G., Abbott, S.B., 2013. Chemoreception and asphyxia-induced arousal. Respir. Physiol. Neurobiol. 188, 333–343.
Guyenet, P.G., Bayliss, D.A., 2015. Neural Control of Breathing and CO2 Homeostasis. Neuron 87, 946–961.
Guyenet, P.G., Bayliss, D.A., Stornetta, R.L., Kanbar, R., Shi, Y., Holloway, B.B., Souza, G., Basting, T.M., Abbott, S.B.G., Wenker, I.C., 2017. Interdependent feedback regulation of breathing by the carotid bodies and the retrotrapezoid nucleus. J. Physiol.
Hasegawa, E., Yanagisawa, M., Sakurai, T., Mieda, M., 2014. Orexin neurons suppress narcolepsy via 2 distinct efferent pathways. J. Clin. Invest. 124, 604–616.
Hayward, L.F., 2007. Midbrain modulation of the cardiac baroreflex involves excitation of lateral parabrachial neurons in the rat. Brain Res. 1145, 117–127.
Hayward, L.F., Felder, R.B., 1998. Lateral parabrachial nucleus modulates baroreflex regulation of sympathetic nerve activity. Am. J. Phys. 274, R1274–R1282.
Herbert, H., Moga, M.M., Saper, C.B., 1990. Connections of the parabrachial nucleus with the nucleus of the solitary tract and the medullary reticular formation in the rat. J. Comp. Neurol. 293, 540–580.
Hobson, J.A., Pace-Schott, E.F., 2002. The cognitive neuroscience of sleep: neuronal systems, consciousness and learning. Nat. Rev. Neurosci. 3, 679–693.
Hodges, M.R., Richerson, G.B., 2010. The role of medullary serotonin (5-HT) neurons in respiratory control: contributions to eupneic ventilation, CO2 chemoreception, and thermoregulation. J. Appl. Physiol. 108 (1985), 1425–1432.
Horowitz, S.S., Blanchard, J., Morin, L.P., 2005. Medial vestibular connections with the hypocretin (orexin) system. J. Comp. Neurol. 487, 127–146.
Jego, S., Glasgow, S.D., Herrera, C.G., Ekstrand, M., Reed, S.J., Boyce, R., Friedman, J., Burdakov, D., Adamantidis, A.R., 2013. Optogenetic identification of a rapid eye movement sleep modulatory circuit in the hypothalamus. Nat. Neurosci. 16, 1637–1643.
Kaur, S., Pedersen, N.P., Yokota, S., Hur, E.E., Fuller, P.M., Lazarus, M., Chamberlin, N.L., Saper, C.B., 2013. Glutamatergic signaling from the parabrachial nucleus plays a critical role in hypercapnic arousal. J. Neurosci. 33, 7627–7640.
Kesler, B., Anand, A., Launois, S.H., Weiss, J.W., 1999. Drug-induced arterial pressure elevation is associated with arousal from NREM sleep in normal volunteers. J. Appl. Physiol. 87, 897–901.
Konadhode, R.R., Pelluru, D., Blanco-Centurion, C., Zayachkivsky, A., Liu, M., Uhde, T., Glen Jr., W.B., van den Pol, A.N., Mulholland, P.J., Shiromani, P.J., 2013. Optogenetic stimulation of MCH neurons increases sleep. J. Neurosci. 33, 10257–10263.
Kroeger, D., Ferrari, L.L., Petit, G., Mahoney, C.E., Fuller, P.M., Arrigoni, E., Scammell, T.E., 2017. Cholinergic, glutamatergic, and GABAergic neurons of the pedunculopontine tegmental nucleus have distinct effects on sleep/wake behavior in mice. J. Neurosci. 37, 1352–1366.
Kroeger, D., Absi, G., Gagliardi, C., Bandaru, S.S., Madara, J.C., Ferrari, L.L., Arrigoni, E., Munzberg, H., Scammell, T.E., Saper, C.B., et al., 2018. Galanin neurons in the ventrolateral preoptic area promote sleep and heat loss in mice. Nat. Commun. 9, 4129.
Kuwaki, T., Zhang, W., 2010. Orexin neurons as arousal-associated modulators of central cardiorespiratory regulation. Respir. Physiol. Neurobiol. 174, 43–54.
Lemes, E.V., Aiko, S., Orbem, C.B., Formentin, C., Bassi, M., Colombari, E., Zoccal, D.B., 2016. Long-term facilitation of expiratory and sympathetic activities following acute intermittent hypoxia in rats. Acta Physiol (Oxford) 217, 254–266.
Li, Q., Song, G., 2001. Afferent projection to the retrotrapezoid nucleus from respiratory related structures in the brainstem of rabbit–a retrograde CB-HRP tracing study. Sheng Li Xue Bao 53, 401–404.
Li, N., Nattie, E., Li, A., 2014. The role of melanin concentrating hormone (MCH) in the central chemoreflex: a knockdown study by siRNA in the lateral hypothalamus in rats. PLoS One 9, e103585.
Lu, J., Sherman, D., Devor, M., Saper, C.B., 2006. A putative flip-flop switch for control of REM sleep. Nature 441, 589–594.
Luppi, P.H., Clement, O., Fort, P., 2013a. Paradoxical (REM) sleep genesis by the brainstem is under hypothalamic control. Curr. Opin. Neurobiol. 23, 786–792.
Luppi, P.H., Clement, O., Valencia Garcia, S., Brischoux, F., Fort, P., 2013b. New aspects in the pathophysiology of rapid eye movement sleep behavior disorder: the potential role of glutamate, gamma-aminobutyric acid, and glycine. Sleep Med. 14, 714–718.
Luppi, P.H., Peyron, C., Fort, P., 2017. Not a single but multiple populations of GABAergic neurons control sleep. Sleep Med. Rev. 32, 85–94.
Mandel, D.A., Schreihofer, A.M., 2006. Central respiratory modulation of barosensitive neurones in rat caudal ventrolateral medulla. J. Physiol. 572, 881–896.
McAllen, R.M., Spyer, K.M., 1978. Two types of vagal preganglionic motoneurones projecting to the heart and lungs. J. Physiol. 282, 353–364.
McCall, R.B., Clement, M.E., 1989. Identification of serotonergic and sympathetic neurons in medullary raphe nuclei. Brain Res. 477, 172–182.
Mezzanotte, W.S., Tangel, D.J., White, D.P., 1996. Influence of sleep onset on upper-airway muscle activity in apnea patients versus normal controls. Am. J. Respir. Crit. Care Med. 153, 1880–1887.
Malheiros-Lima, M.R., Takakura, A.C., Moreira, T.S., 2017. Depletion of rostral ventrolateral medullary catecholaminergic neurons impairs the hypoxic ventilatory response in conscious rats. Neuroscience 351, 1–14.
Malheiros-Lima, M.R., Totola, L.T., Lana, M.V.G., Strauss, B.E., Takakura, A.C., Moreira, T.S., 2018. Breathing responses produced by optogenetic stimulation of adrenergic C1 neurons are dependent on the connection with preBotzinger complex in rats. Pflugers Arch.
Molkov, Y.I., Zoccal, D.B., Baekey, D.M., Abdala, A.P., Machado, B.H., Dick, T.E., Paton, J.F., Rybak, I.A., 2014. Physiological and pathophysiological interactions between the respiratory central pattern generator and the sympathetic nervous system. Prog. Brain Res. 212, 1–23.
Morinaga, R., Nakamuta, N., Yamamoto, Y., 2018. Serotonergic projections to the ventral respiratory column from raphe nuclei in rats. Neurosci. Res.
Morrison, S.F., Gebber, G.L., 1984. Raphe neurons with sympathetic-related activity: baroreceptor responses and spinal connections. Am. J. Phys. 246, R338–R348.
Nakamura, K., Morrison, S.F., 2011. Central efferent pathways for cold-defensive and febrile shivering. J. Physiol. 589, 3641–3658.
Nattie, E., Li, A., 2012. Respiration and autonomic regulation and orexin. Prog. Brain Res. 198, 25–46.
Niu, J.G., Yokota, S., Tsumori, T., Qin, Y., Yasui, Y., 2010. Glutamatergic lateral parabrachial neurons innervate orexin-containing hypothalamic neurons in the rat. Brain Res. 1358, 110–122.
Orem, J., Lovering, A.T., Dunin-Barkowski, W., Vidruk, E.H., 2000. Endogenous excitatory drive to the respiratory system in rapid eye movement sleep in cats. J. Physiol. 527 (Pt 2), 365–376.
Padley, J.R., Kumar, N.N., Li, Q., Nguyen, T.B., Pilowsky, P.M., Goodchild, A.K., 2007. Central command regulation of circulatory function mediated by descending pontine cholinergic inputs to sympathoexcitatory rostral ventrolateral medulla neurons. Circ. Res. 100, 284–291.
Pisanski, A., Pagliardini, S., 2018. The parafacial respiratory group and the control of active expiration. Respir. Physiol. Neurobiol.
Rukhadze, I., Carballo, N.J., Bandaru, S.S., Malhotra, A., Fuller, P.M., Fenik, V.B., 2017. Catecholaminergic A1/C1 neurons contribute to the maintenance of upper airway muscle tone but may not participate in NREM sleep-related depression of these muscles. Respir. Physiol. Neurobiol. 244, 41–50.
Saito, H., Sakai, K., Jouvet, M., 1977. Discharge patterns of the nucleus parabrachialis lateralis neurons of the cat during sleep and waking. Brain Res. 134, 59–72.
Saper, C.B., 2013. The central circadian timing system. Curr. Opin. Neurobiol. 23, 747–751.
Saper, C.B., Fuller, P.M., 2017. Wake-sleep circuitry: an overview. Curr. Opin. Neurobiol. 44, 186–192.
Saper, C.B., Fuller, P.M., Pedersen, N.P., Lu, J., Scammell, T.E., 2010. Sleep state switching. Neuron 68, 1023–1042.
Scammell, T.E., Arrigoni, E., Lipton, J.O., 2017. Neural circuitry of wakefulness and sleep. Neuron 93, 747–765.
Schafer, T., Schlafke, M.E., 1998. Respiratory changes associated with rapid eye movements in normo- and hypercapnia during sleep. J. Appl. Physiol. 85, 2213–2219.

Schafer, T., Schlafke, M.E., 2001. Variability of CO2-sensitivity during sleep. Adv. Exp. Med. Biol. 499, 459–463.
Seravalle, G., Mancia, G., Grassi, G., 2018. Sympathetic nervous system, sleep, and hypertension. Curr. Hypertens. Rep. 20, 74.
Shahid, I.Z., Rahman, A.A., Pilowsky, P.M., 2012. Orexin A in rat rostral ventrolateral medulla is pressor, sympatho-excitatory, increases barosensitivity and attenuates the somato-sympathetic reflex. Br. J. Pharmacol. 165, 2292–2303.
Silvani, A., Dampney, R.A., 2013. Central control of cardiovascular function during sleep. Am. J. Physiol. Heart Circ. Physiol. 305, H1683–H1692.
Silvani, A., Grimaldi, D., Vandi, S., Barletta, G., Vetrugno, R., Provini, F., Pierangeli, G., Berteotti, C., Montagna, P., Zoccoli, G., et al., 2008. Sleep-dependent changes in the coupling between heart period and blood pressure in human subjects. Am. J. Phys. Regul. Integr. Comp. Phys. 294, R1686–R1692.
Silvani, A., Calandra-Buonaura, G., Benarroch, E.E., Dampney, R.A., Cortelli, P., 2015. Bidirectional interactions between the baroreceptor reflex and arousal: an update. Sleep Med. 16, 210–216.
Sirieix, C., Gervasoni, D., Luppi, P.H., Leger, L., 2012. Role of the lateral paragigantocellular nucleus in the network of paradoxical (REM) sleep: an electrophysiological and anatomical study in the rat. PLoS One 7, e28724.
Smith, J.C., Abdala, A.P., Borgmann, A., Rybak, I.A., Paton, J.F., 2013. Brainstem respiratory networks: building blocks and microcircuits. Trends Neurosci. 36, 152–162.
Somers, V.K., Dyken, M.E., Mark, A.L., Abboud, F.M., 1993. Sympathetic-nerve activity during sleep in normal subjects. N. Engl. J. Med. 328, 303–307.
Stornetta, R.L., Guyenet, P.G., 2018. C1 neurons: a nodal point for stress? Exp. Physiol. 103, 332–336.
Subramanian, H.H., Chow, C.M., Balnave, R.J., 2007. Identification of different types of respiratory neurones in the dorsal brainstem nucleus tractus solitarius of the rat. Brain Res. 1141, 119–132.
Tang, X., Dworkin, B.R., 2010. Baroreflexes of the rat. VI. Sleep and responses to aortic nerve stimulation in the dmNTS. Am. J. Phys. Regul. Integr. Comp. Phys. 298, R1428–R1434.
Topchiy, I., Waxman, J., Radulovacki, M., Carley, D.W., 2010. Functional topography of respiratory, cardiovascular and pontine-wave responses to glutamate microstimulation of the pedunculopontine tegmentum of the rat. Respir. Physiol. Neurobiol. 173, 64–70.
Torterolo, P., Scorza, C., Lagos, P., Urbanavicius, J., Benedetto, L., Pascovich, C., Lopez-Hill, X., Chase, M.H., Monti, J.M., 2015. Melanin-concentrating hormone (MCH): role in REM sleep and depression. Front. Neurosci. 9, 475.
Tsunematsu, T., Ueno, T., Tabuchi, S., Inutsuka, A., Tanaka, K.F., Hasuwa, H., Kilduff, T.S., Terao, A., Yamanaka, A., 2014. Optogenetic manipulation of activity and temporally controlled cell-specific ablation reveal a role for MCH neurons in sleep/wake regulation. J. Neurosci. 34, 6896–6909.
Uschakov, A., Gong, H., McGinty, D., Szymusiak, R., 2006. Sleep-active neurons in the preoptic area project to the hypothalamic paraventricular nucleus and perifornical lateral hypothalamus. Eur. J. Neurosci. 23, 3284–3296.
Varin, C., Luppi, P.H., Fort, P., 2018. Melanin-concentrating hormone-expressing neurons adjust slow-wave sleep dynamics to catalyze paradoxical (REM) sleep. Sleep 41.
Weber, F., Chung, S., Beier, K.T., Xu, M., Luo, L., Dan, Y., 2015. Control of REM sleep by ventral medulla GABAergic neurons. Nature 526, 435–438.
Wenker, I.C., Abe, C., Viar, K.E., Stornetta, D.S., Stornetta, R.L., Guyenet, P.G., 2017. Blood pressure regulation by the rostral ventrolateral medulla in conscious rats: effects of hypoxia, hypercapnia, baroreceptor denervation, and anesthesia. J. Neurosci. 37, 4565–4583.
Xu, M., Chung, S., Zhang, S., Zhong, P., Ma, C., Chang, W.C., Weissbourd, B., Sakai, N., Luo, L., Nishino, S., et al., 2015. Basal forebrain circuit for sleep-wake control. Nat. Neurosci. 18, 1641–1647.
Yokota, S., Kaur, S., VanderHorst, V.G., Saper, C.B., Chamberlin, N.L., 2015. Respiratory-related outputs of glutamatergic, hypercapnia-responsive parabrachial neurons in mice. J. Comp. Neurol. 523, 907–920.
Yokota, S., Oka, T., Asano, H., Yasui, Y., 2016. Orexinergic fibers are in contact with Kolliker-Fuse nucleus neurons projecting to the respiration-related nuclei in the medulla oblongata and spinal cord of the rat. Brain Res. 1648, 512–523.
Zoccal, D.B., Furuya, W.I., Bassi, M., Colombari, D.S., Colombari, E., 2014. The nucleus of the solitary tract and the coordination of respiratory and sympathetic activities. Front. Physiol. 5, 238.