Central control of cardiovascular function during sleep

Alessandro Silvani1 and Roger A. L. Dampney2

1Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy; and 2School of Medical Sciences (Physiology) and Bosch Institute for Biomedical Research, University of Sydney, Australia

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Silvani A, Dampney RA. Central control of cardiovascular function during sleep. Am J Physiol Heart Circ Physiol 305: H1683–H1692, 2013. First published October 4, 2013; doi:10.1152/ajpheart.00554.2013.—There is increasing evidence that cardiovascular control during sleep is relevant for cardiovascular risk. This review summarizes current knowledge on autonomic mechanisms of such control. This review summarizes current knowledge on autonomic features of sleep states [non-rapid-eye-movement sleep (NREMS) and rapid-eye-movement sleep (REMS)] and proposes some testable hypotheses concerning the underlying neural circuits. The physiological reduction of blood pressure (BP) during the night (BP dipping phenomenon) is mainly caused by generalized cardiovascular deactivation and baroreflex resetting during NREMS, which, in turn, are primarily a consequence of central autonomic commands. Central commands during NREMS may involve the hypothalamic ventrolateral preoptic area, central thermoregulatory and central baroreflex pathways, and command neurons in the pons and midbrain. During REMS, opposing changes in vascular resistance in different regional beds have the net effect of increasing BP compared with that of NREMS. In addition, there are transient increases in BP and baroreflex suppression associated with bursts of brain and skeletal muscle activity during REMS. These effects are also primarily a consequence of central autonomic commands, which may involve the midbrain periaqueductal gray, the sublaterodorsal and peduncular pontine nuclei, and the vestibular and raphe obscurus medullary nuclei. A key role in permitting physiological changes in BP during sleep may be played by orexin peptides released by hypothalamic neurons, which target the postulated neural pathways of central autonomic commands during NREMS and REMS. Experimental verification of these hypotheses may help reveal which central neural pathways and mechanisms are most essential for sleep-related changes in cardiovascular function.

Sleep; central autonomic commands; blood pressure; heart rate; sympathetic nerve activity; hypocretins/orexins

CARDBIOVASCULAR CONTROL DURING sleep is a relatively neglected field of investigation, particularly in regard to its physiological mechanisms. Nonetheless, nighttime sleep has long been known to confer protection from acute cardiovascular events compared with daytime wakefulness (61). Recent studies indicate that cardiovascular control during sleep also plays a substantial (8) and possibly causal (39) role in setting overall cardiovascular risk. A physiological understanding of sleep-related cardiovascular control is, however, lagging behind the rapid progress in clinical knowledge. This brief review aims to help bridge the gap between sleep and autonomic neuroscience. First, we will briefly summarize the somatic and autonomic features of sleep states and wakefulness. We will then consider the potential central mechanisms of sleep-related cardiovascular control.

Description of Different Sleep States

Sleep is a specialization of rest (79), characterized by lack of motor engagement with the external environment. In placental mammals, sleep is divided into two main states: non-rapid-eye-movement sleep (NREMS) and rapid-eye-movement sleep (REMS), the latter accounting for ~20% of total sleep time.

NREMS is associated with reduced muscle tone and characteristic EEG patterns including K complexes, sleep spindles, and high-amplitude low-frequency (0.5–2 Hz) delta waves (75). NREMS is further subdivided into three stages, defined according to the pattern of accompanying EEG changes. Stage 1 NREMS occurs mainly at the beginning of sleep, whereas stage 3 is deep NREMS, characterized by dominance of slow waves in the EEG (80). NREMS is punctuated by spontaneous or stimulus-induced arousals, which generally entail increased EEG frequency (11) but may also involve slower EEG waves such as delta wave bursts or K complexes (76).

REMS is usually preceded by NREMS and is associated with low or absent muscle tone. The EEG in REMS shows low-amplitude mixed-frequency activity in humans, whereas a synchronized theta rhythm (4–8 Hz) originating in the hippocampus prevails in rodents (75). A distinctive feature of REMS is the occurrence of transient neurophysiological events such as bursts of rapid eye movements, distal muscle twitches, acceleration of EEG theta rhythm (9), and ponto-geniculo-occipital (PGO) waves (12). REMS is also punctuated by
arousals, which are accompanied by increases in EEG frequency and muscle tone (11).

Sleep-Related Changes in Cardiovascular Function

During NREMS, blood pressure (BP) decreases by ≈10% compared with that during wakefulness in species as diverse as humans (84), rats (58), and mice (50) (Fig. 1, A and B). There is also an increase in heart period (HP) during NREMS, but it is not clear whether this decreases cardiac output (81). In rats, sympathetic nerve activity (SNA) to both skeletal muscles and kidneys decreases in NREMS compared with wakefulness (102) (Fig. 1D). Humans (26) and rats (4) also show increases in skin temperature particularly at distal sites (hands/feet, tail) during NREMS. This presumably occurs because reduced skin vasoconstrictor SNA decreases skin blood vessel tone in NREMS (44, 93).

During REMS, BP and HP return toward values characteristic of wakefulness (81, 97) (Fig. 1, A and B). In mice, this process of cardiovascular reactivation starts before the transition from NREMS to REMS and peaks in the first 50 s thereafter (50). In contrast with NREMS and wakefulness, the sympathetic outflow changes in a highly differentiated fashion during REMS, such that mesenteric and renal SNA decrease while lumbar SNA (supplying mainly blood vessels in hindlimb skeletal muscle) increases (102) (Fig. 1, C and D). Thus BP in REMS is apparently maintained by a balance between increases and decreases in the vascular resistance of different regional beds. The short-term variability of BP and HP is lower in REMS than in wakefulness and returns toward waking levels in REMS (84).

Brief arousals during NREMS are accompanied by transient cardiovascular changes that show a stereotyped sequence of events: first, HP decreases; then, BP rises reaching a peak; then, HP returns at or above baseline level; finally, BP also returns to baseline level. This is the same sequence that is associated with transient spontaneous BP increases in wakefulness and REMS (82, 83). In REMS, these transient cardiovascular activations are often associated with the transient neurophysiological events characteristic of this state (9).

Possible Mechanisms Causing Sleep-Related Changes in Cardiovascular Function

In most human subjects, BP and HP show diurnal changes under natural conditions, with a decrease (dip) in BP and an increase in HP during the rest period compared with the active period of the day (88). This raises the question as to whether these diurnal changes are primarily due to the sleep-wake cycle or to an endogenous circadian oscillator. Studies in both humans and mice indicate that when the circadian rhythm and sleep-wake cycle are dissociated, the BP dipping effect is primarily related to the sleep-wake cycle, particularly the periods when NREMS is predominant, rather than the endogenous circadian rhythm (7, 77).

Other possible mechanisms that might contribute to sleep-related cardiovascular changes are changes in posture or the decrease in somatic motor activity that accompanies sleep. A
change in posture in humans (i.e., from standing upright to lying down) cannot explain the decrease in BP during NREMS as compared with wakefulness, because BP decreases gradually during the different stages of NREMS following the onset of sleep, when the subjects remain in a recumbent position (13). Similarly, a study in mice has shown that BP decreases gradually for 1.5 min after transition from wakefulness to NREMS, whereas muscle tone changes rapidly at NREMS onset (50) (Fig. 1A). Thus it is unlikely that the BP reduction in NREMS is simply a consequence of decreased motor activity. In REMS, the increase in BP compared with NREMS is associated with no or very low muscle tone, and so in this state also the cardiovascular changes are clearly not due to increased motor activity. Furthermore, the differentiated changes in sympathetic activity that occur during REMS are also present in animals after neuromuscular blockade (29).

It therefore follows that sleep-related changes in cardiovascular function are primarily a consequence of central command, such that changes in the activity of central neurons that regulate the different sleep states lead to alterations in the activity of sympathetic preganglionic neurons in the spinal cord and/or cardiac vagal preganglionic neurons in the medulla. Such an effect could be mediated by connections from sleep-regulating neurons to hypothalamic paraventricular nucleus (PVN; Fig. 3) (58). In particular, sleep-related central commands shift baroreflex sigmoid functions toward lower values of BP and renal SNA and at higher values of HP compared with wakefulness (62) (Fig. 2C).

Similarly, the stereotypical temporal sequence of cardiovascular changes associated with arousals and other transient sleep events may be explained by the occurrence of transient central commands, which also alter baroreflex function (85). The analysis of spontaneous fluctuations of HP and BP indicates that the impact of these central commands on cardiac control markedly decreases during NREMS compared with REMS and wakefulness (84) (Fig. 2B).

In the following sections we shall discuss the central nuclei and pathways that might subserve sleep-related changes in cardiovascular function. Because sleep-related cardiovascular changes are so markedly different in NREMS and REMS, we shall consider each of these different sleep states separately.

**Neural Circuitries Potentially Involved in Cardiovascular Control During NREMS**

**Ventrolateral preoptic area.** There is considerable evidence that the ventrolateral preoptic area (VLPO; Fig. 3A) in the hypothalamus contains neurons that play an important role in the induction and maintenance of both REMS and NREMS (53, 75). In particular, neurons that are much more active during NREMS as compared with REMS and wakefulness are located preferentially within the core (cluster) part of the VLPO (51). Some neurons in the VLPO core project to the hypothalamic paraventricular nucleus (PVN; Fig. 3B) (98), which contains many neurons that regulate the sympathetic outflow (17). It is therefore interesting that approximately half of the PVN-projecting neurons in the VLPO core are activated during sleep (98). Many of these neurons contain GABA (32).
and it has been suggested that NREMS-active neurons in the VLPO core may decrease SNA via an inhibitory projection to sympathoexcitatory neurons in the PVN (98) (Fig. 4A).

Central thermoregulatory pathways. Skin vasodilation during NREMS may result from inhibition of the rostral medullary raphe (rMR; including the raphe pallidus and magnus and the parapyramidal nucleus; Fig. 3E), which is the key autonomic region involved in heat generation and retention (63). Neurons in the rMR also decrease HP and increase BP (63, 64). Inhibition of rMR neurons in NREMS may thus explain why distal skin vasodilation correlates with BP reduction during nighttime sleep (46). Neurons in the rMR are inhibited by warm-sensitive neurons in the hypothalamic medial preoptic area (MPO; Fig. 3A) (63). The activity of these MPO neurons increases during NREMS (3), consistent with rMR inhibition in this state. MPO activity during NREMS may itself explain why distal skin vasodilation correlates with BP reduction during nighttime sleep (46). Neurons in the rMR are inhibited by warm-sensitive neurons in the hypothalamic medial preoptic area (MPO; Fig. 3A) (63). The activity of these MPO neurons increases during NREMS (3), consistent with rMR inhibition in this state. MPO activity during NREMS may itself explain why distal skin vasodilation correlates with BP reduction during nighttime sleep (46).

As highlighted above, modulation of arterial baroreflex responses is a key feature of cardiovascular control during sleep (81). During NREMS, the baroreflex control is reset to lower levels of renal SNA (Fig. 2C) and BP and to higher levels of HP (62). Such resetting would also contribute to the reduction in BP and SNA and the increase in HP that occurs during NREMS compared with wakefulness (Fig. 1), but the central mechanism responsible for this resetting is unknown. The nucleus of the solitary tract (NTS; Fig. 3F) in the dorsal medulla is the site of termination of primary afferent fibers from the arterial baroreceptors and has long been regarded as a likely site at which modulation of the baroreflex may occur in different behaviors (5, 17). In fact, the response of NTS neurons to aortic depressor nerve stimulation increases with the slow EEG waves characteristic of NREMS (94). The NTS receives afferent inputs from several different brain regions including the cortex, amygdala, hypothalamic perifornical area and PVN, midbrain periaqueductal gray, pontine parabrachial nucleus (PBN) and A5 area, and ventrolateral medulla (17). Several lines of evidence point to the PBN (Fig. 4A).
reduced activity of PBN neurons during NREMS may disinhibit the baroreflex at the level of NTS neurons, thus explaining why baroreflex cardiac control is the most prominent and the least disrupted by central autonomic commands during NREMS (81).

**Command neurons in the pons and midbrain.** The pedunculopontine nucleus (PPT; Fig. 3C) in the rostral pons includes putative cholinergic neurons that have a high rate of firing during wakefulness and REMS, but a much lower activity during NREMS (22). In part, reduced activity of these neurons during NREMS may be because of inhibitory projections to the PPT from NREMS-active neurons in the VLPO (78). Neurons in the PPT project to the thalamus (35), thereby contributing to the activated thalamocortical mode of operation and EEG during wakefulness (89). A remarkable feature of the PPT is that it is one of two main regions in the brain (the other being the lateral hypothalamus) that contains neurons that have outputs to both the somatomotor system and the sympathetic system (47). Furthermore, 95% of these putative command neurons are cholinergic (47). The PPT is part of the classic locomotor region (31), and many PPT neurons are excited by static muscle contractions (69). Furthermore, activation of cholinergic inputs from the PPT to the sympathoexcitatory region of the rostral ventrolateral medulla (RVLM; Fig. 3E) increases BP and splanchnic SNA and reduces HP (65). It has been suggested, therefore, that the cholinergic command neurons in the PPT may contribute to the increases in SNA and the reduction in HP that occur during exercise and REMS (47, 65). It follows that a reduction in the activity of the PPT-RVLM pathway that accompanies behavioral disengagement from the environment may contribute to cardiovascular deactivation during NREMS (Fig. 4A).
Neural Circuitries Potentially Involved in Cardiovascular Control During REMS

Given the prominence of transient neurophysiological and cardiovascular activations in REMS, we shall discuss separately cardiovascular control during periods in which these activations do (phasic REMS) or do not (tonic REMS) occur.

**Tonic period of REMS.** As described above, during the tonic period of REMS there are highly differentiated changes in SNA, such that renal and mesenteric SNA decrease while skeletal muscle SNA increases (102). Both the sympathetic changes and the other features of REMS (e.g., muscle atonia) persist following decerebration (29, 53), and so the essential neural circuitry responsible for these effects must be located within the brainstem. The neurons driving the sympathetic changes at the transition from NREMS to REMS (Fig. 1C) are expected to alter their firing rate significantly at this transition point. The caudal midbrain and rostral pons contain neurons that exhibit either a rapid increase (REMS-on) or decrease (REMS-off) in firing rate at the onset of REMS. As reviewed recently (48, 65), there is considerable evidence for a mutually inhibitory interaction between REMS-on GABAergic neurons located in the sublaterodorsal nucleus (SLD; Fig. 3D) in the rostral pons and REMS-off GABAergic neurons located in the ventrolateral periaqueductal gray (vPAG; Fig. 3C) and the lateral pontine tegmentum (Fig. 3C) between the oral pontine nucleus and the PPT. This interaction is thought to be essential for NREMS-REMS transition (53, 75). According to this model, a separate group of excitatory glutamatergic REMS-on neurons in the SLD produce skeletal muscle atonia via multisynaptic projections to spinal cord motoneurons and receive inhibitory inputs from REMS-off cells in the vPAG/lateral pontine tegmentum (75).

Although the central mechanisms that drive cardiovascular changes during the transition from NREMS to REMS are not well understood, information is available that allows some hypotheses to be proposed. In an early study, Futuro-Neto and Coote (30) obtained evidence that activation of neurons within the caudal part of the nucleus raphe obscurus (NRO; Fig. 3F) in the midline medulla evoked a differentiated sympathetic response very similar to that observed in REMS (i.e., increased muscle SNA and decreased renal SNA). The region from which this response was evoked contains nonserotonergic neurons that are active in REMS (70, 100). Nonserotonergic neurons in the NRO include both putative sympatoexcitatory and putative sympathoinhibitory neurons (57, 60). At least a fraction of the former neurons project to the intermediolateral spinal cord column that includes sympathetic preganglionic neurons (57, 60). It is thus possible that REMS-active nonserotonergic neurons of the NRO contribute to the differential changes in regional SNA during REMS, as previously suggested by Morrison and Gebber (60) and Verret et al. (100) (Fig. 4B). The NRO also contains serotonergic neurons, but they are uniformly suppressed during REMS (42) and are thus unlikely to generate the differentiated sympathetic responses that occur in this state.

It is also possible that the REMS-on and/or REMS-off neurons in the brainstem contribute to the cardiovascular changes that occur at the onset of REMS. The SLD projects to the lateral paragigantocellular nucleus in the medulla, and neurons in the latter nucleus, as in the SLD, are strongly excited during REMS (86, 100). The lateral paragigantocellular nucleus overlaps the sympathoexcitatory regions in the RVLM and the more medially located rostral ventromedial medulla (RVMM; Fig. 3E) (17). This descending projection from the SLD to the RVLM/RVMM may thus activate premotor neurons that increase skeletal muscle SNA during REMS. It seems unlikely, however, that C1 neurons in the RVLM contribute substantially to the increased skeletal muscle SNA in this state, since the cardiovascular effects of optogenetic activation of these neurons is reduced during REMS (1). Furthermore, the inhibition of renal SNA during REMS would not be explained by activation of an excitatory projection from the SLD to the RVLM/RVMM.

As mentioned above, the vPAG contains neurons that are inhibited during REMS (53, 75), whereas other neurons located in the lateral periaqueductal gray (IPAG) may be activated during REMS (100). The vPAG and IPAG include distinct groups of sympatoexcitatory and sympathoinhibitory neurons, respectively, that regulate SNA to different vascular beds (including the renal and skeletal muscle vascular beds) via inputs to sympathoexcitatory neurons in the RVLM (14). It remains unclear whether the vPAG and IPAG neurons that change their activity during REMS correspond, at least in part, to those that modulate sympathetic outflow, or whether the former are connected to the latter by way of local interneurons. Thus changes in vPAG and IPAG activity in REMS could contribute to the increase in skeletal muscle SNA and the decrease in renal SNA in this state via changes in the firing rate of RVLM neurons.

Approximately 55% of neurons within the lateral PBN are most active during REMS, as compared with quiet wakefulness and NREMS (72), and these neurons may therefore contribute to resetting of the baroreflex and subsequent increase in SNA via their projection to the NTS (17, 28) (Fig. 4B). As remarked by Miki and Yoshimoto (58), however, the modulation of the baroreflex during REMS may occur in a differential manner, such that renal SNA is reduced while muscle SNA is increased. In any case, baroreflex modulation is not a critical factor in generating differentiated SNA changes during REMS, because these also occur during REMS in animals with denervated baroreceptors (29).

As previously discussed, the PPT contains neurons that are more active either during REMS only or during REMS and wakefulness than during NREMS (22). Some of these REM-on neurons may also be putative command neurons that have outputs to both the sympathetic and motor systems (47). These neurons could contribute to the cardiovascular activation that occurs in REMS even though skeletal motor output is prevented by muscle atonia in this state (53, 75) (Fig. 4B).

**Phasic periods of REMS.** Neurons in the medial (MVe; Fig. 3E) and inferior vestibular nuclei show phases of greatly increased firing during REMS, with burst discharges synchronized to bursts of rapid eye movements (10). These nuclei are necessary for the occurrence of bursts of rapid eye movements and the associated transient cardiovascular events during phasic REMS (59). The MVe may receive information on the tonic and phasic REMS state from the extended VLPO region (40, 52) and from the gigantocellular reticular formation (40, 99). In turn, the MVe projects to the NTS, lateral PBN, and PPT (40). Half of recorded NTS neurons increase firing in association with bursts of rapid eye movements during REMS (21). The
lateral PBN (72) and the PPT contain neurons whose firing precedes PGO waves, which are a characteristic transient neurophysiological event of REMS. Taken together, these data suggest that the projections from the MVe to the NTS, lateral PBN, and PPT may contribute to the transient cardiovascular changes and in particular to baroreflex modulation during phasic REMS.

During phasic REMS, there are also irregular bursts and trains of respiratory muscle activity (25). The central respiratory drive modulates the activity of sympathetic premotor neurons in the RVLM (54), at least in part via inputs from GABAergic barosensitive neurons in the caudal ventrolateral medulla (CVLM) (55). Thus transient changes in respiration may contribute to baroreflex modulation and cardiovascular variability during phasic REMS. However, optogenetic experiments recently demonstrated that the respiratory response to transient activation of the C1 and retrotrapezoid nucleus neurons of the RVLM is greatly reduced in REMS compared with either NREMS or wakefulness (1), suggesting that any effect of changes in respiratory activity on sympathetic activity during phasic REMS is mediated by neurons other than C1 and retrotrapezoid neurons. Further work is needed to determine whether medullary respiratory circuits contribute substantially to changes in cardiovascular activity during phasic REMS.

Orexins and the Physiological Modulation of Sleep-Related Neural Circuits

Neurons in the perifornical and lateral hypothalamus that release orexin (also known as hypocretin) peptides (20, 74) exhibit slow tonic discharge during quiet wakefulness and remain virtually silent during sleep except for transient discharges in REMS (92). These neurons are sufficient to cause arousal from NREMS or REMS (2) and are necessary for physiological behavioral state and motor control. Accordingly, death of orexinergic neurons causes narcolepsy/cataplexy, which is associated with daytime sleepiness, sudden loss of muscle tone during wakefulness, and frequent movement and awakening during sleep (18, 66). A similar phenotype is observed in mice lacking all orexinergic neurons (36) or lacking only orexin peptides (15). The behavioral effects of orexins are mediated by dense interconnections between orexinergic neurons and multiple structures involved in control of wakefulness and sleep (75).

Recent data indicate that orexinergic neurons are also necessary for normal physiological sleep-related changes in BP in mice and human subjects. In particular, mice lacking the whole orexinergic neurons or lacking solely the orexin peptides show a smaller decrease in BP between wakefulness and NREMS and a greater increase in BP between NREMS and REMS (6, 50). Narcoleptic patients lacking orexinergic neurons show a smaller decrease in BP between wakefulness and NREMS (34), greater values of BP during REMS (34), and a greater risk of a normotensive nondipper BP phenotype (19) compared with control subjects. Narcoleptic patients also show dysfunctions in cardiac control, which include reduced cardiac responses to leg movements and arousals during sleep (87) and reduced cardiac baroreflex sensitivity during wakefulness (83). However, sleep-related changes in the variability of BP and HP are preserved or only slightly altered in orexin-deficient mice (50, 82), suggesting that similar defects in humans are either species specific or not caused directly by orexin deficiency. Thus orexins may contribute to the decrease in BP during NREMS and REMS but not to the changes in cardiovascular variability associated with sleep. The mechanisms whereby orexins exert these effects are still unclear. Brain interstitial concentration of orexin shows little if any decrease between wakefulness and either NREMS or REMS (43), even though orexinergic neurons dramatically reduce firing during these sleep states (92). These data indicate that orexins may exert their physiological actions not only during wakefulness but also during NREMS and REMS. Thus one hypothesis to explain the cardiovascular changes recently observed on orexin-deficient mice (50, 82) and narcoleptic patients (19, 34) is that orexins physiologically amplify the activity of neural circuits that decrease BP during NREMS and REMS. Orexins have already been proposed to act as a gain controller (41), amplifying inputs to neurons regulating SNA and HP during wakefulness, such as in the course of defensive behavior (48).

Orexins bind to two specific excitatory metabotropic receptors (74). Activation of metabotropic receptors is known to modify fundamentally the cellular and network properties of the central pattern generators involved in locomotion (33, 56). It is thus conceivable that orexin receptors exert a similar modulation of central circuits involved in shaping autonomic outflow during sleep. Consistent with this, orexinergic neurons project to all of the structures that compose the circuits proposed in the previous sections (40, 45, 67). Although the critical orexin targets remain unknown, recent research has ruled out some of them. In particular, the effects of changes in ambient temperature on BP and HP are preserved in orexin-deficient mice, which show reduced effects of sleep on BP both at thermoneutrality and at cold ambient temperature (50). These data thus suggest that orexinergic modulation of central thermoregulatory pathways does not play any significant role in sleep-related cardiovascular control. Similarly, the preservation of sleep-dependent cardiovascular variability in orexin-deficient mice (82) suggests that orexins do not have a critical effect on the central pathways mediating the transient cardiovascular changes that occur during the phasic periods of REMS.

The effects of orexins may also be exerted indirectly via other transmitter systems. In particular, there are strong orexinergic projections to histamine neurons in the hypothalamic tuberomammillary nucleus (TMN), noradrenergic neurons in the locus coeruleus (LC), and serotonergic neurons in the dorsal raphe (DR) (23, 67). The firing rate of all of these neurons is highest during wakefulness, lower during NREMS, and lowest during REMS, and all have widespread projections to many other parts of the brain (42, 75, 90, 91, 95). The precise role of these different transmitter systems in cardiovascular regulation is poorly understood, but it is possible that they contribute to the cardiovascular changes accompanying different sleep states.

Summary and Conclusions

The cardiovascular changes that accompany the changes in state between wakefulness, NREMS, and REMS are very significant. Despite the fact that much is known about the central circuitry responsible for generating and maintaining the sleep-wake cycle, and also the central circuitry that subserves cardio-

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vascular control, very little is known about the mechanisms that link cardiovascular changes to sleep states. In this review we have attempted to identify some of the critical gaps in our knowledge and to propose some testable hypotheses concerning the neural circuits that might subserve these links. Hypotheses involving different neural pathways should not be regarded as mutually exclusive. Rather, sleep-related central commands may result from the summation of activity of different central pattern generators at the same time, in analogy with recent views on thermoregulation (71), and/or at different times, in agreement with recent evidence concerning the asynchronous development of the sleep process in different neuronal groups (68, 101). Although our hypotheses are based on the available evidence, much critical information is still lacking. Nevertheless, we hope that our hypotheses may lead to further investigations that will reveal the essential pathways and mechanisms responsible for sleep-related changes in cardiovascular function. This knowledge is likely to have considerable clinical significance, because of the link between abnormalities in cardiovascular control during sleep (e.g., a nondipping BP profile) and the risk of cardiovascular disease (8, 38, 39).

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Author contributions: A.S. and R.A.D. conceived and designed research; A.S. and R.A.D. prepared figures; A.S. drafted manuscript; A.S. and R.A.D. approved final version of manuscript; R.A.D. edited and revised manuscript.

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