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Abstract

The integrated activity of the autonomic nervous system (ANS) with the somatomotor and the neuroendocrine systems allows an animal to maintain internal homoeostasis and regulate its interaction with the external environment. Significant changes in ANS activity occur on passing from wakefulness to sleep, and this pattern of autonomic activation is profoundly different even between NREMS and REMS. While, during NREMS, the ANS works to maintain body homeostasis in accordance with the reduced metabolic needs of this state, during REMS ANS activity is greatly variable, and not visibly oriented to the maintenance of the stability of physiological variables. Sleep derangements determine an alteration of autonomic activity that can also extend to waking, favoring the development of pathological conditions. In this review, we summarize new insights into the impact of sleep derangements on ANS control of immune, respiratory and cardiovascular function, and into the role of ANS in thermoregulation and energy expenditure.

Autonomic nervous system: anatomy and function

The peripheral portion of the autonomic nervous system (ANS) consists of 3 subdivisions, the parasympathetic, the sympathetic, and the enteric nervous systems (ENS). While the ENS exclusively controls the function of the gastrointestinal system, the sympathetic and parasympathetic nervous systems i) control the activity of cardiac cells, smooth muscle cells, and exocrine and endocrine gland cells; ii) exert distinct metabolic effects, and iii) affect immune function. The sympathetic and parasympathetic nervous systems consist of preganglionic and postganglionic neurons. Sympathetic preganglionic neurons are located in the intermediate zone of the thoracic and lumbar (T1-L3) segments of the spinal cord, while postganglionic bodies lie in ganglia that are either lateral or anterior to the vertebral column; parasympathetic preganglionic neurons are located in the brainstem (midbrain, within the Edinger-Westphal nucleus; medulla, within the superior and inferior salivary nuclei, the dorsal motor nucleus of the vagus nerve and the nucleus ambiguous) and in the sacral segments (S2-S4) of the spinal cord, within its intermediate zone. Parasympathetic postganglionic bodies lie in ganglia located within or near the innervated organs. Sympathetic and parasympathetic visceromotor commands are controlled by a neural system that integrates autonomic visceral control, named the central autonomic network (CAN) [1]. The CAN includes limbic cortical and subcortical regions, as well as the hypothalamus and different brainstem nuclei; these regions are mutually interconnected and receive visceral sensory inputs, mainly through the nucleus of the solitary tract. Within the CAN, circuits involved in respiratory, cardiovascular, and thermoregulatory / metabolic regulation are largely overlapped, and their integrated activity, together with neuroendocrine and behavioral responses, operates to maintain body homeostasis, and to ensure the adaptation of visceral functions to environmental

demands (adaptation through change). CAN activity changes with wake and sleep states, while, in turn, CAN modulates centers for wake-sleep state control based on the afferent visceral sensory information it receives from internal and external environment [2].

ANS activity during wake and sleep

Wake and sleep are behaviors that are characterized by different levels of engagement with the external environment; accordingly, a consistent remodulation of autonomic nervous system (ANS) activity occurs on passing from wake to sleep [3]. Furthermore, sleep itself is a state that shows an intrinsic heterogeneity in terms of physiological control.

During non-rapid eye-movement sleep (NREMS), physiological regulation clearly operates according to the "homeostatic" modality. In accordance with the low somatic activity and the reduced metabolic needs of this sleep state, the ANS drives the physiological variables toward their lower limit, and they are maintained near to their fixed value by reflex mechanisms (baroceptive, chemoceptive, and thermoregulatory reflexes). Also, somatic activity allows the animal to find a proper posture in order to minimize any possible thermal discomfort [4].

During rapid eye-movement sleep (REMS), phasic cardiovascular and respiratory events occur, and thermoregulation is suspended or depressed [4]. Phasic central nervous commands are able to drive the cardiovascular variables beyond the normal control of the baroceptive reflex [5]. Moreover, muscle atonia does not allow the animal to adjust its posture according to different needs. This operative modality has been definied "poikilostatic", since it is not apparently oriented to the maintenance of internal stability, and it has been ascribed to a loss of the integrative capacity at a hypothalamic level [4]. However, findings showing that osmoregulation is maintained during REMS suggest that such a loss is specifically related to thermoregulation, and that at least part of the instability of cardiovascular variables during REMS is a consequence of the loss of thermoregulatory control [6].

Overall, compared to previous wakefulness, during NREMS parasympathetic activity prevails, while sympathetic activity is reduced, while during REMS the activity of the ANS displays a great variability, with phasic changes in sympathetic and parasympathetic discharge.

The ANS allows the body to cope with changes in the environment and to maintain body homeostasis also acting in a predictive manner, predisposing the organism to the occurrence of stimuli that recur regularly, and promoting the appropriate corrective responses in advance [7]. These predictive responses are controlled by peripheral circadian clocks synchronized by behavioral, neural, endocrine, and food-related cues that are under the coordination of the suprachiasmatic nucleus (SCN) in the anterior hypothalamus [8]. SCN neurons project to hypothalamic nuclei involved in the control of autonomic activity, and to hypothalamic neurons associated with the promotion of sleep (ventrolateral preoptic area, VLPO), thus producing a circadian modulation of physiological functions [9].

The aim of this review is to describe new insights into sleep-dependent changes in ANS activity, with particular emphasis on the impact of sleep derangement on ANS activity in its control of immune, respiratory and cardiovascular function, and on the role of ANS in the regulation of body temperature and energy expenditure.

Autonomic function, sleep disorders, and immune function

In physiological conditions, during NREMS an increase of parasympathetic activity is associated with a reduction in sympathetic activity. When the normal expression of NREMS is prevented, as in patients with insomnia or frequent nocturnal awakenings, the physiological reduction in sympathetic activity is also prevented. In these subjects, sympathetic activity is high during sleep and it remains high when they are awake [10]. A significant consequence of this derangement that has emerged in recent years is its relapse in immune function. There are reciprocal connections between the central nervous system (CNS), sleep and the immune system: sleep enhances immune defense and afferent signals from immune cells promote sleep [11]. The CNS modulates the immune system in two main ways: humorally, by activating the hypothalamic–pituitary–adrenal axis (HPA) to release glucocorticoids; and neurally, via the activation of the sympathetic

nervous system (SNS) [12]. SNS favors the activation of inflammatory response and the production of pro-inflammatory cytokines (IL1B, IL6 and TNF) [11]. Furthermore, the SNS alters the trafficking of innate immune cells, including the mobilization of haematopoietic stem cells, natural killer cells and splenic neutrophils, and monocytes [13]. Sleep disturbances may therefore lead to increased inflammation and may render the subject more susceptible to inflammatory challenge. Cytokines production is altered by sleep deprivation or sleep disruption [14] and, accordingly, sleep disruption exacerbates febrile response to LPS in mice [15] and impairs immune function in humans [16]. The relationship between sleep disturbances, sympathetic activation and immune response is further complicated by recent evidence that greater splanchnic nerves, which drive postganglionic sympathetic neurons, may represent the efferent arm of the "inflammatory reflex" [17]. The inflammatory reflex represents the neural pathway that reflexively monitors and adjusts the inflammatory response. The activation of this neural pathway inhibits an excessive release of inflammatory mediators in response to an immune challenge, avoiding an exaggerated response that can cause morbidity and mortality [18]. Thus, the SNS is believed, on one hand, to exert a pro-inflammatory effect, while on the other it is also thought to play a role in containing the inflammatory response. Further studies are needed to better characterize the role of sympathetic activation in determining alterations of immune responses associated with sleep disorders, and to develop a targeted pharmacological intervention. This goal appears to be particularly important given that the activation of inflammatory mechanisms linked to sleep disorders could also play a role in the development of neurodegenerative conditions such as Alzheimer's disease [19].

Autonomic function, sleep disorders, and cardiorespiratory function

During sleep, the main input controlling breathing is represented by signals coming from peripheral and central chemoreceptors. However, chemo-responsiveness is reduced in all stages of sleep compared with wakefulness: ventilatory responses to hypoxia decrease to two thirds of this waking value in NREMS, with a further significant decrease in REMS [20]; ventilatory responses to hypercapnia are also diminished, falling to less than 50 % of wakefulness during NREM sleep and less than 30 % during REM sleep [21], and the tolerance to high levels of CO_2 is increased. At the beginning of NREMS respiratory instability may appear, as a consequence of repeated fluctuations in arousal state [22]. Sleep onset is characterized by a decrease in minute ventilation (i.e., air volume inspired/exhaled per minute) and tidal volume (i.e., air volume exhaled with each breath), but substantial and rapid changes in these variables are associated with transitions between arousal, and stages N1 and N2 of NREMS, producing increases and decreases in depth of breath with a wavelength that usually varies between 60 and 90 sec [23]. During stable NREMS ventilation becomes regular, variability becomes very low and minute ventilation progressively decreases. The reduction in minute ventilation is accompanied by an increase in arterial pCO_2 of 3-8 mmHg. When arterial pCO_2 falls 2-6 mmHg below the normal stable sleep value (a value that broadly corresponds to normal arterial pCO_2 in wakefulness), apnoea threshold is reached and breathing stops [24]. During REMS, the respiratory rhythm becomes very irregular, displaying phasic changes in respiratory amplitude and frequency that parallel the occurrence of rapid eye movements and may include central apneas [24]. Rapid eye movements are also associated with inhibition of the upper airway dilator, favoring the occurrence of obstructive apneas [23]. The irregular respiratory pattern of REMS is a very robust phenomenon, and it is not eliminated by hypoxia, hypercapnia, chemodenervation or vagotomy [23]. Minute ventilation decreases compared to wakefulness, but it may increase in a temporal relationship with myoclonic twitches and other phasic events of REMS.

Autonomic regulation of cardiovascular function helps to match peripheral blood supply to metabolic requirements of the organs, depending on behavioral state. Moreover, changes in autonomic activity are also modulated by circadian influences. Hypothalamic SCN activity modulates circadian changes in vigilance state [9], and influences the cardiovascular system on a circadian basis, mainly via projections to pre-autonomic neurons of the hypothalamic paraventricular nucleus (PVN) [25]. Circadian fluctuations of blood pressure (BP) and heart rate (HR) have been described in mice [26, 27], and a circadian vagal influence on the heart has been reported in humans [28, 29]. In humans, however, the existence of circadian sympathetic changes is still controversial [30, 31]. Sleep-dependent changes in BP and HR are superimposed on these circadian fluctuations, and even if circadian changes are much smaller than changes linked to the wake-sleep cycle, a dysregulation of circadian rhythms can produce detrimental effects on cardiovascular function and may

increase cardiovascular risk [32]. BP and HR decrease when passing from wakefulness to NREMS, while on passing from NREMS to REMS they return towards the values they have during W [5]. In normal subjects, BP reaches its lowest levels during nighttime sleep, a phenomenon generally referred to as dipping. The "dipping profile" is considered to be protective for the cardiovascular system [33]. Increased values of BP during nocturnal sleep predict [34], and may even cause [35], higher cardiovascular risk and mortality [36]. Despite the scientific and clinical relevance of these cardiovascular effects of sleep, their autonomic mechanisms are still unclear. Recently it has been demonstrated that, at least in mice, the BP decrease during NREMS is mainly related to a decrease in sympathetic vasoconstriction, while HR reduction is obtained through both cardiac parasympathetic activation and sympathetic withdrawal [37]; during REMS, however, an increased sympathetic activity to the heart and blood vessels pushes the mean BP and HR to higher values than those present during NREMS, even if still lower than those recorded during wakefulness [37]. Central autonomic commands can control sympathetic and parasympathetic premotor neurons both directly and through a modulation of baroreflex, and a baroreflex reset contributes to decreasing BP and HR values during sleep [38]. The relationship between autonomic control and vigilance state is bidirectional, and baroreflex activation can in turn have an impact on sleep state, inducing cortical synchronization for a mild stimulation, or favoring arousal for a strong activation [2]. Therefore, sleep disorders can compromise cardiovascular regulation, favoring the development of hypertension, and the hyperstimulation of the baroreceptors produced by the increase in BP can have an impact on the quality of sleep, triggering a vicious circle. The overall reduction of sympathetic tone during sleep is interrupted by phasic sympathetic neural surges: external or internal stimuli may produce an autonomic activation associated with different degrees of arousal. Repeated phasic activations during the night, such as those produced by periodic limb movements during sleep (PLMS), prevent the normal sleep-dependent decline in BP and sympathetic nerve activity, and may thus represent a stressful condition for the cardiovascular system [39]. PLMS are linked to restless leg syndrome, but they are also observed in individuals with a variety of other sleep disturbances, such as obstructive sleep apnoea (OSA), narcolepsy, and REMS behavior disorder. Independently from PLMS occurrence, OSAs are associated with HR and BP surges, which peak at the end of the event, when airway patency is restored [40]; in OSA patients sympathetic nerve discharge remains very high even when they awaken [10]. The BP response to repeated arousals may prevent the physiological sleep-related reduction of BP, leading to a non-dipping hypertensive profile [41]. Insomnia represents another condition associated with derangements in cardiovascular regulation, and hypertension development. Recently muscle sympathetic neural activity was directly recorded in subjects with chronic insomnia. In this study an impaired sympathetic baroreflex function and heightened sympathetic reactivity to stress were found, providing a novel mechanicistic link between chronic insomnia and heightened cardiovascular risk [42].

Autonomic function, thermoregulation, and energy expenditure

Peripheral thermal signals from cutaneous thermoreceptors are transmitted by the lateral parabrachial nucleus [43] to the preoptic area of the hypothalamus (POA), where they are integrated with core body temperature information. The thermal input from the skin to the hypothalamic centers for sleep and temperature regulation could modulate sleep onset: the mild warming of the extremities shortens sleep latency in insomniac patients [44], and in mice the activation of warm-sensitive neurons in median and medial preoptic areas promotes both NREMS onset and body cooling [45]. During NREMS, the thermoregulatory responses that are active in wakefulness are substantially maintained, while they are suppressed in animals and depressed in humans during REMS [46]. Recently, a condition of "thermoregulatory inversion" was described in rats, characterized by an inhibition of BAT thermogenesis in response to skin cooling, whereas skin warming was shown to facilitate BAT heat production [47]. In this study, "inversion" was produced by either surgically or pharmacologically excluding, the influence of POA neurons from the neural network that mediates thermoregulatory responses. In this context, inverted thermoregulatory responses may also occur during the transition from NREMS to REMS, a condition in which POA thermosensitive neurons are inhibited [48] and the POA responses to thermal stimuli, which are normally active during wakefulness and NREMS, are abolished [49]. In fact, in animals exposed to a low ambient temperature, the entrance into REM sleep is

accompanied by a paradoxical inhibition of thermogenesis that can lead to hypothermia [46, 48]. Although more specific experiments are required, the Authors suggest that REMS includes an inhibition of the activity of a population of thermoregulatory neurons in the POA, resulting in the induction of a state of thermoregulatory inversion [47].

In humans the promotion of sleep onset is linked to circadian driven changes in body heat production and heat loss [50]. Core body temperature and energy expenditure progressively decrease in the first half of the night, and then remain stable until morning awakening [51]. Melatonin participates in the induction of peripheral vasodilation, even if it is not yet clear whether it acts through a direct effect on blood vessels or by modulating sympathetic activity [52]. In adults, body energy expenditure decreases during sleep. This sleep-related decrease is slight compared to quiet wakefulness, but it may become relevant for energy conservation in infants or small mammals, which present an unfavorable surface to volume ratio [50]. Moreover, in humans, energy expenditure during REMS is larger than during NREMS, an effect that is probably related to the relatively large size of the brain in humans, since brain energy metabolism is significantly higher in REMS than in NREMS. In small mammals, in which the size of the brain is reduced, the decrease in energy expenditure due to REMS muscle atonia is larger than the increase in brain metabolism and an overall decrease occurs in REMS compared to NREMS [46].

Autonomic Function and Sleep within the Frame of Physiological Regulation

The changes in ANS activity observed during sleep are part of the integrated somatomotor, autonomic and neuroendocrine pattern of activity, which characterizes the different states of waking and sleeping. While during NREMS physiological regulation clearly operates according to a “homeostatic” modality and is aimed at energy saving, during REMS the goal of such pattern of activity is not easily understandable. In particular, thermoregulation is suspended in laboratory animals or depressed in humans [4], but osmoregulation is still preserved [6]. REMS thus represents a unique transient heterothermic state, and it may be hypothesized that its function is linked to this peculiar condition, during which endotherms could fulfill some brain functional needs that are not compatible with thermoregulation[53]. According to this view, the coevolution between REMS and endothermy ([54] may have led thermoregulation and REMS to the sharing of brain regulatory areas [53], and to the consequent mutual exclusivity in their occurrence.

Funding
Professor Giovanna Zoccoli and Professor Roberto Amici are supported by University of Bologna research grants (RFO).

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[*11] In this review the current understanding of the relationship between sleep dynamics and immune mechanisms is discussed, with a focus on the role of neuroendocrine and autonomic pathways. Furthermore, the possibilities of a therapeutic intervention on these reciprocal mechanisms of sleep–immune regulation to mitigate the risk of diseases development is examined.

[*32] This review describes the role of circadian rhythms cardiovascular regulation, and it analyzes the contribution of chronic disruptions of the circadian clock to determine an increased cardiovascular risk. The importance of the circadian system to normal cardiovascular function and to cardiovascular disease is discussed, with the target to identify criteria for optimizing timing of medications in cardiovascular disease.

[*37] In this study, for the first time, the autonomic mechanisms of the cardiovascular effects of sleep have been assessed in mice. The results indicate a main role for the sympathetic nervous system in the control of cardiovascular changes, with a contribution of parasympathetic activation in determining the decrease of heart rate during NREM sleep.

[*42] This study compared muscle sympathetic neural activity recorded in subjects with chronic insomnia and in healthy controls. Chronic insomnia was associated with impaired sympathetic baroreflex function and heightened sympathetic reactivity to stress when compared with habitual good sleeper controls. These results provide novel mechanistic insight into the reported associations between chronic insomnia and heightened cardiovascular risk.

[*45] In this study, nitrergic/ glutamatergic neurons are identified in the MnPO-MPO hypothalamus, which after activity tagging by a warm external stimulus induce both sleep and hypothermia when reactivated. This suggests a strong relationship between sleep and body cooling, and it implies that one function of NREMS is to lower brain temperature and/or conserve energy.

[*53] In this paper the interaction between REMS and thermoregulation is discussed, and the central networks regulating REMS and body temperature, together with the areas in which they overlap, are described. Possible mechanisms of the reciprocal interaction between REMS and thermoregulation are analyzed, and a new hypothesis about REMS function is proposed.