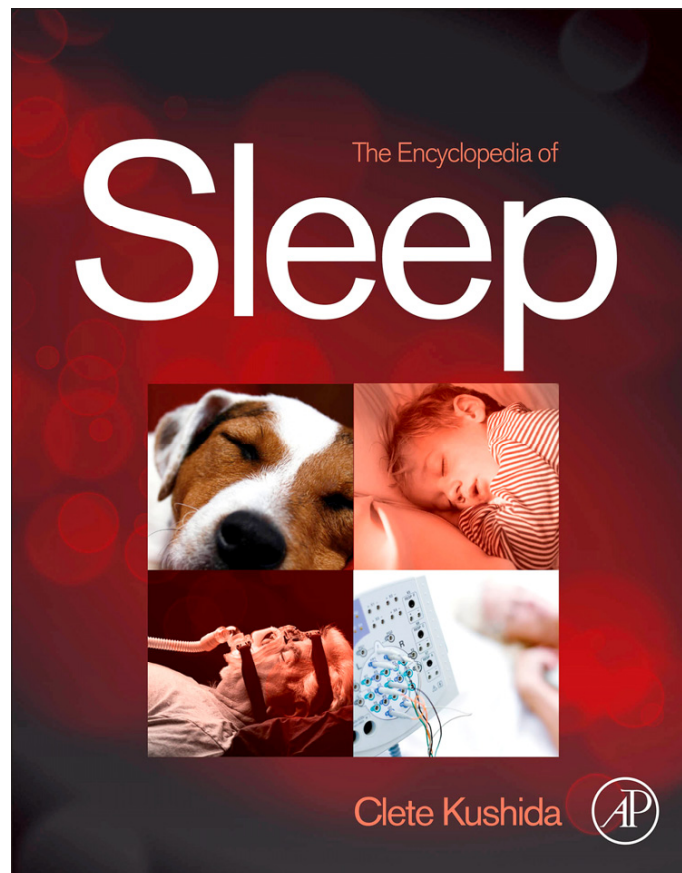


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ANATOMY, PHYSIOLOGY, AND PHARMACOLOGY OF SLEEP

Background

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Overview of Physiological Processes During Sleep

Chemical Neuroanatomy of Sleep–Wake Systems

Neurotransmitters and Neuropharmacology of Sleep/Wake Regulations

Overview of Physiological Processes During Sleep

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Glossary

Homeostasis: Maintenance of the stability of the physicochemical properties of the extracellular compartments that underlie the cellular survival.

Physiological regulation: Neural control mechanisms of the somatic and autonomic activity, which constitutes the 'behavior' of the organism.

The ultradian sleep cycle in mammals broadly consists of the single sequence of two behavioral states, which are usually called nonrapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep. To consider further subdivisions of sleep behavior would be outside the general scope intended for this article. In this context, the term *physiological regulation* refers to the neural control mechanisms of somatic and autonomic activity, which is defined here as the 'behavior' of the organism. To qualify the nature of physiological regulation in sleep not only is the study of the spontaneous activity of physiological functions necessary, but also the experimental testing of stimulus–response relationships in physiological mechanisms. In other words, it is necessary to verify whether the neural control is either adequate, that is, homeostatic, or inadequate, that is, poikilostatic, at maintaining the stability (homeostasis) of the physicochemical properties of the extracellular compartments that underlie cellular survival.

The study of the physiological aspects of the ultradian sleep cycle has shown that the principle of homeostatic physiological regulation does not apply to the whole cycle. In particular, NREM sleep is characterized by a homeostatic control and REM sleep by a poikilostatic control. The concept of a functional dichotomy in regulation does apply to systemic functions that fit the temporal dimensions of the states of the ultradian cycle. On this basis, the survey is restricted to the changes during

sleep of the physiological regulation of body temperature, circulation, and respiration, functions that have been studied in more depth than others in the most extensively studied terrestrial mammals.

Regulation of Body Temperature

In mammals, homeothermy is controlled by diencephalic integrative mechanisms that drive subordinate brainstem and spinal somatic and autonomic mechanisms eliciting the thermoregulatory effector responses. In particular, the preoptic area (POA) is considered the most important integrative center for thermoregulation.

The thermoregulatory responses to ambient thermal loads are present in NREM sleep and absent or depressed in REM sleep. For example, the drop in postural muscle tone during REM sleep is unrelated to ambient temperature. Moreover, notwithstanding a positive (warm) thermal load, tachypnea and heat exchanger vasodilation disappear in animals, and sweating in humans is at first abolished and then depressed during the episode of REM sleep. Likewise, under a negative (cold) thermal load, shivering, heat exchanger vasoconstriction, and piloerection are suppressed in animals during the REM sleep episode. Shivering also disappears during REM sleep

in a cold environment after pontine lesions producing REM sleep without muscle atonia. This result shows that the pontine inhibitory mechanisms eliciting muscle atonia do not underlie the suppression of this thermoregulatory response in REM sleep, and that such suppression depends on functional changes occurring in the neuronal network of the preoptic–anterior hypothalamic area. Moreover, the cold-defense function of the interscapular brown adipose tissue (BAT) is also altered, since its temperature sharply decreases in REM sleep, impairing the warming effect of this tissue. The thermoregulatory responses, elicited by positive and negative thermal loads applied directly to the thermosensitive preoptic–anterior hypothalamic area, are affected by the behavioral state in animals. Warming elicits tachypnea and heat exchanger vasodilation in NREM sleep but has no such effects in REM sleep. Likewise, cooling increases oxygen consumption and metabolic heat production in NREM sleep, whereas it is ineffective in REM sleep. Crucial proof of the behavioral state-dependent changes in the function of the preoptic thermostat has been provided by experiments of direct thermal stimulation of preoptic–anterior hypothalamic thermosensitive neurons across the behavioral states in animals. The changes in thermosensitivity of the majority of such neurons parallel the presence and abolition of thermoregulatory responsiveness to central thermal loads in NREM and REM sleep, respectively.

Experimental evidence shows that thermoregulatory mechanisms are operative in NREM sleep as they are in wakefulness. The only difference is that the set point of body and hypothalamic temperatures varies according to the level of the energy metabolism. In contrast, REM sleep is characterized by the lack of appropriate thermoregulatory responses to ambient thermal challenges. The result is that the temperature of the body varies qualitatively according to ambient temperature and quantitatively in relation to skin thermal insulation, the thermal inertia of body water, and the duration of the REM sleep episode.

Regulation of Circulation

Regulation of circulation during sleep has been studied in humans and animals. Despite the considerable amount of data published on the topic, a clear understanding of the underlying nervous control of the cardiovascular function has yet to be reached. The data presented in the scientific literature are inhomogeneous, showing species-dependent results with variable experimental environments and techniques. In part, this may also depend on the fact that early data may be biased by the use of non-telemetric measure systems which disturbed natural sleep behavior, and only the relatively recent availability of telemetric devices has allowed the recording of more reliable cardiovascular information. Nevertheless, species-specific variability persists.

NREM sleep is characterized by a downregulation of cardiovascular activity of variable degree, which depends on the previous level of cardiovascular activity during wakefulness and on the species. An overall decrease in arterial blood pressure generally occurs during the transition from wakefulness to NREM sleep, although it quantitatively varies in different individuals and species. The decrease in arterial pressure occurring during NREM sleep has been shown to reach statistical significance in

humans and small rodents, but not in other species. Moreover, it is unclear whether the occurrence of a deeper stage of NREM sleep triggers an additional reduction of arterial pressure.

Of the cardiac variables influencing cardiac output, namely, heart rate and stroke volume, a decrease in the first appears to be the most consistent experimental finding in all the species studied. Vascular conductance increases in skeletal muscle, skin, mesenteric, iliac, and renal beds while the baroreflex is normally operative. In conclusion, the cardiovascular changes in NREM sleep are consistent with a condition of postural and motor quiescence.

A variety of cardiovascular phenomena characterize REM sleep compared to NREM sleep. In general, arterial blood pressure may increase from NREM to REM sleep in humans and small rodents, but decreases or remains unchanged in other species; such changes are not always related to coherent and consistent changes in the underlying variables (i.e., heart rate and vascular conductance). Heart rate shows an increase in variability in relation particularly to phasic episodes of tachycardia or intense bradycardia, which can lead to asystolia and hypotension. Vascular conductance appears either to decrease or to increase in several beds depending on the species or the tissue (skin, mesenteric, iliac, and renal beds). Arterial blood pressure during REM sleep is modulated but still buffered by sinoaortic reflexes. Nevertheless, the relationship between changes in arterial blood pressure and cardiac output in REM sleep is, in general, inconsistent. In conclusion, the poor correlation between regional and systemic variables shows that the central integration of cardiovascular functions is altered in REM sleep. Concerning the control of brain integrative centers on cardiovascular function, the thermoregulatory vasomotion elicited by direct thermal stimulation of the preoptic–anterior hypothalamic area during NREM sleep is suppressed during REM sleep, in accordance with the reduced responsiveness of preoptic–anterior hypothalamic thermosensitive neurons.

In conclusion, functional variability is a most striking aspect of the cardiovascular function in REM sleep. The variability is in general loosely associated with bursts of rapid eye movements, myoclonic twitches, ponto–geniculo–occipital waves, and breathing irregularities. However, such variability is not only the direct result of central changes in the regulation of the autonomic outflow. It also depends on the indirect influences of a number of feedback loops activated by the centrally induced changes in the peripherally controlled variables. Therefore, the interaction between the central variability of autonomic control during REM sleep and the central influence of activated reflexes are main factors in the generation of cardiovascular regulation instability during REM sleep. The importance of such an interaction is also demonstrated by studies showing that the central generator underlying the rhythmicity of synchronized cardiac sympathetic nerve activity is subject to reflex modulation by baroreceptor inputs.

Regulation of Respiration

Conspicuous changes occur in the regulation of respiration across the behavioral states of sleep in humans and animals. The transition from wakefulness to NREM sleep is

characterized by the release of the automatic control mechanism of respiration from telencephalic influences. This transition (stages 1 and 2 of NREM sleep in humans) is characterized by some respiratory instability and the appearance of respiratory periodic phenomena. A regular breathing rhythm sets in with deep NREM sleep (stages III and IV in humans) when respiration is driven only by the automatic control mechanisms. The rate decreases and the tidal volume increases only slightly. As a result, ventilation decreases in humans and animals. A concomitant increase in alveolar and in arterial CO₂ partial pressure associated with a decrease in alveolar and arterial O₂ partial pressure has been observed. Airway resistance increases. These changes in respiratory variables are in agreement with a state of rest decreasing the metabolic rate. The operation of the automatic control mechanism is downregulated, but compensatory physiological responses to respiratory challenges are still maintained, since respiratory chemosensitivity to CO₂ is only moderately reduced, and the response to hypoxia is unaffected. Moreover, pulmonary inflation and deflation reflexes are active during NREM sleep. The responses to a mechanical respiratory load (airway occlusion, inspiration from a rigid container increasing respiratory work) are also practically identical to those observed during wakefulness, thus showing that proprioceptive reflexes of the intercostal muscles are normal during NREM sleep in humans.

The phenomena of REM sleep reveal a profound alteration in the activity of the automatic control mechanism of respiration. The respiratory rhythm is irregular, with the average frequency increasing or decreasing compared to the rate attained during NREM sleep in eupnea or polypnea, respectively. The respiratory activity of the intercostal muscles is diminished. In human infants, this intercostal muscle depression may even produce paradoxical chest collapse during inspiration. Ventilation variably increases, mostly in temporal relation to myoclonic twitches during REM sleep. The alveolar ventilation may underlie an average decrease or no change in alveolar CO₂ partial pressure. Such disturbances are of central origin, as they persist in animals after vagotomy, sectioning of the spinal cord at T₁₋₂, afferent denervation of the mid-thoracic chest wall, denervation of the carotid and aortic chemoreceptors and baroreceptors, as well as in hypercapnia and hypoxia. Upper airway resistance increases and respiratory load compensation is irregular and weak. The alteration of the automatic control mechanism of respiration during REM sleep is also shown by other phenomena. Respiratory responses to hypercapnia are depressed, while those to hypoxia are less affected. In contrast, the inflation reflex is practically abolished during REM sleep.

Depressed preoptic–anterior hypothalamic influence on respiration during REM sleep as compared to NREM sleep was shown by means of thermal or electrical direct stimulation of this diencephalic region in animals. Moreover, the depression in telencephalic control on respiration was also observed during REM sleep.

Neural Networks of Sleep and Physiological Regulation

The identification in the animal model of a neural network, which appears to be critically involved in sleep promotion and

maintenance, has not as yet clarified the neural mechanisms underlying the changes in the somatic and autonomic physiological regulation across sleep states.

However, the interaction between the mechanisms of sleep regulation and the mechanisms of somatic and autonomic regulation may occur in certain identified areas at the brainstem level, including the hypothalamus.

Concerning sleep regulation, recent studies in the mainstream of the pioneering studies by von Economo and Nauta have shown the presence of sleep-active neurons in the rostral hypothalamus at the level of the ventrolateral preoptic nucleus and the median preoptic nucleus, which are part of the POA. Both nuclei are reciprocally connected with different brain areas in which wake-active neurons are located. These include the monoaminergic neurons in the tuberomammillary nucleus, the dorsal raphe nucleus, and the locus coeruleus, the hypocretin neurons in the lateral hypothalamic area, and the cholinergic neurons in the dorsal pontine tegmentum and in the basal forebrain. Apparently, wake-active neurons keep sleep-active preoptic neurons inhibited during wakefulness, while the latter start inhibiting the former at sleep onset. This reciprocal inhibitory connection is thought to operate as a flip-flop switch for the maintenance of stable vigilance states. Hypocretin neurons in the lateral hypothalamic area apparently play a central role in the maintenance of wakefulness, since they also send excitatory inputs to the tuberomammillary nucleus, the dorsal raphe nucleus, and the locus coeruleus. The activation of preoptic sleep-active neurons and the inhibition of hypocretinergic and cholinergic wake-active neurons may depend on several 'hypnogenic' substances, such as adenosine, interleukin 1-β, and prostaglandin D₂.

A neural network underlying the switch from NREM to REM sleep has also been proposed. It has been suggested that the crucial role in promoting REM sleep belongs to a set of pontine REM-on neurons located in the sublateralodorsal nucleus. Projections from this area are considered to activate neural networks underlying both the cortical (electroencephalogram (EEG) desynchronization and hippocampal theta activity) and somatic (muscle atonia, twitches, and rapid eye movements) hallmarks of REM sleep. Some experimental evidence shows that REM-on neurons in the sublateralodorsal nucleus, which are apparently under a constant excitatory glutamatergic barrage from different brain areas, are kept tonically inhibited during wakefulness and NREM sleep by projections from the ventrolateral periaqueductal gray and the dorsal deep mesencephalic reticular nuclei. These REM-off neurons are excited by both hypocretin neurons in the lateral hypothalamic area and monoaminergic neurons in other wake-promoting areas. REM sleep onset apparently depends on the inhibition of these REM-off neurons carried out by (i) a subpopulation of GABAergic REM-on cells in the ventrolateral periaqueductal gray; (ii) GABAergic neurons in the dorsal paragigantocellular nucleus; and (iii) REM-on melanin-concentrating hormone neurons co-releasing GABA, located in the posterior and perifornical hypothalamus and in the lateral hypothalamic area. It is suggested that a contribution to the inhibition of these REM-off neurons is given by the suppression of an excitatory input from different wake-promoting areas. Wake-active neurons reduce firing during NREM sleep and cease firing during REM sleep. Melanin-concentrating

hormone neurons, which are also inhibited by wake-promoting neurons in the tuberomammillary nucleus, the dorsal raphe nucleus, and the locus coeruleus may contribute to the active inhibition of hypocretin neurons in the lateral hypothalamic area during REM sleep. Although other brainstem areas, among which the lateral paragigantocellular nucleus and the lateral parabrachial nucleus are strongly activated during REM sleep, the precise role of both areas in REM sleep regulation has not yet been clarified.

An anatomical site of possible interaction between sleep-regulatory processes and autonomic physiological regulation, and particularly thermoregulation, is represented by the POA. Information on shell and core temperature is apparently integrated at the level of POA warm-sensitive neurons, which have been proposed to control both cold- and heat-defense autonomic responses. Furthermore, the median preoptic nucleus represents a critical relay station of the extra-thalamic pathway from cutaneous thermal receptors to warm-sensitive neurons in the POA. Projections from POA are known to control, largely through the dorsomedial hypothalamus, the activity of the rostral ventromedial medulla (RVMM), where the sympathetic premotor neurons crucially involved in the central control of BAT thermogenic activity and of cardiovascular adaptation to bodily thermal needs are located. The neurophysiological analysis of the functional properties of the preoptic neurons has shown that a large number of warm-sensitive neurons are also sleep-active. This would explain the sleep-promoting effect of either direct POA warming or the induction of a mild increase in skin temperature at the lower extremities. In the median preoptic nucleus a set of osmosensitivity-related cells, apparently separated from GABAergic sleep-active neurons has also been observed by immunohistochemistry. This separation may underlie recent findings showing that the release of antidiuretic hormone (ADH) in response to central osmotic stimulation is substantially unaffected by the wake-sleep state, and in particular it is not different in REM sleep compared to NREM sleep. However, further studies are needed in order to clarify whether this apparent state of independence is a specific feature of such a phylogenetically old regulation or is common to all neuroendocrine hypothalamic responses.

The neural mechanisms responsible for the changes in cardiovascular regulation during sleep are still uncertain, although key areas of the central control of the cardiovascular function have been identified. The sympathetic premotor neurons controlling the smooth muscle of blood vessels are located in the rostral ventrolateral medulla (RVLM) and the putative sympathetic premotor neurons to the heart and to cutaneous blood vessels are to be found in the RVMM. The activity of RVLM neurons affecting arterial blood pressure appears to be modulated by two main influences. The information from the baroreceptors reaches the RVLM through synapses in the nucleus of the solitary tract and the caudal ventrolateral medulla and elicits the baroreflex. In addition, the so-called central commands are mostly mediated by neurons of the paraventricular nucleus of the hypothalamus. The activity of RVMM neurons, controlling heart rate and cutaneous vasomotion, appears to be mainly affected by the afference from the POA in connection with the dorsomedial hypothalamus. On this basis, the lack of consistent heat exchanger

vasomotion in response to preoptic-anterior hypothalamic thermal loads applied during REM sleep suggests that a state-dependent change in the activity of the neuronal network including the POA, dorsomedial hypothalamus, and RVMM may underlie the phenomenon.

The neural mechanisms underlying the changes in breathing during sleep are still only partially known. The respiratory phenomena of sleep suggest that the changes in the activity of the medullary respiratory neurons depend on the modification of several inputs from the control mechanism of breathing. On the basis of experimental studies, a decrease in NREM sleep of tonic excitatory drives from (i) the brainstem reticular formation, (ii) the monoaminergic brainstem nuclei, and (iii) the hypocretin neurons in the lateral hypothalamic area has been proposed. A decrease in the chemical reflex control of respiration during NREM sleep has also been postulated. In REM sleep, there is an endogenous excitation or inhibition of brainstem and telencephalic neuronal networks disrupting the normal respiratory function. This disorderly interaction underlies a variability of breathing in this state of sleep that apparently lacks a clear physiological purpose. In particular, the influence of the preoptic-anterior hypothalamic area on breathing is documented by experiments using electrical and thermal stimulation: inflation- and deflation-like responses and thermal tachypnea, respectively, are present during NREM sleep and absent during REM sleep.

A further hypothalamic substrate in which sleep-related processes and central control of autonomic function apparently interact is represented by hypocretin neurons in the lateral hypothalamic area. These neurons project to (i) the nucleus of the solitary tract and the RVLM; (ii) the RVMM; and (iii) the intermediolateral column of the spinal cord. Hypocretin neurons have been thought to play a role in cardiorespiratory adjustments underlying different motivated behaviors and, in particular, in the integrated autonomic response which characterizes the defense reaction. Moreover, BAT thermogenesis is enhanced by a chemical activation of the lateral hypothalamic area, possibly a result of direct action of the hypocretin neurons on RVMM. The release of both RVLM and RVMM from the hypocretinergic control may represent one factor responsible for the cardiovascular imbalance during REM sleep. Such an imbalance may be further aggravated by the impairment of the preoptic control on RVMM and, possibly, by a phasic central drive from preautonomic motor neurons in the paraventricular nucleus to RVLM.

Other possible sites of interaction between REM sleep-regulatory processes and autonomic function can be found at brainstem level. The chemical activation of different portions of the periaqueductal gray has been shown to induce three different types of defense reaction, which are defined on the basis of specific somatomotor, autonomic, and sensory changes. In particular, the so-called 'quiescence/hyporeactivity' response, which is characterized by the cessation of spontaneous motor activity, hypotension, and bradycardia, can be elicited by the stimulation of the ventrolateral periaqueductal gray, a region that, as previously discussed, is apparently crucially involved in controlling the onset of REM sleep episodes and, consequently, of REM sleep somatic and vegetative hallmarks. Finally, the lateral parabrachial nucleus may represent a site of interaction between sleep and thermoregulation, since

this nucleus is a fundamental relay station of the central afferent pathways of skin thermal receptors.

Conclusion

In NREM sleep, changes in autonomic regulation are consistent with somatic quiescence, as are the functional prevalence of parasympathetic activity over sympathetic activity, the lowering of metabolic heat production (decrease in muscle tone and in heart and breathing rates) and body temperature (vasodilatation of heat exchangers, sweating). Moreover, somatic and autonomic regulatory responses to endogenous and exogenous disturbances may be activated during NREM sleep in order to maintain homeostasis. In conclusion, the phenomenal stereotype of NREM sleep across mammalian species appears to be the coherent result of a common phylogenetic trend to develop a pattern of integrated automatic regulation minimizing energy expenditure. Mechanistically, the regulation of physiological functions during this state of sleep is led essentially by diencephalic structures, as shown particularly by the persistence of normal homeothermic regulation.

As far as REM sleep is concerned, it is difficult to establish a rational foundation of the observed functional phenomena in terms of a centrally integrated regulation. Their physiological aims escape a simple teleological explanation in behavioral terms. Remarkably, cause–effect relationships existing between variables during wakefulness and NREM sleep are suppressed or variable during REM sleep, yet the loss of the specific effects of stimuli during REM sleep is not associated with a loss of their nonspecific arousing influences. The arousal effect, however, requires a much higher stimulus intensity compared with that which normally elicits the specific regulatory response. Thus, REM sleep is characterized by the disintegration of the homeostatic physiological equilibrium, bringing about effector responses of great instability that are primarily of central origin but secondarily complicated by local autoregulation, altered reflex activity, or both.

The impairment of homeostatic control in REM sleep is more dramatic and evident in a function, such as temperature regulation in furry animals, that depends on effector mechanisms which are strictly subordinated to regulatory structures of the diencephalon (POA). In functions depending on more widely distributed control mechanisms, such as circulation and respiration, the features of functional impairment are rather more complex but less dramatic. This is a result of the persistence of more or less efficient reflex regulation or peripheral autoregulation in the presence of an altered central

command also due to the telencephalic endogenous activation in REM sleep. Nevertheless, it is evident that functional changes in REM sleep depend essentially on the suspension of the diencephalic integrated regulation that is operative in both wakefulness and NREM sleep, however, under functionally different homeostatic paradigms.

See also: **Extrinsic Factors Affecting Sleep Loss/Deprivation:** Effects of Light and Temperature on Sleep in Adults and the Elderly; **Intrinsic Factors Affecting Sleep Loss/Deprivation:** Thermoregulatory Changes; **Sleep and Other Systems:** Sleep and the Cardiovascular System; Sleep and the Peripheral Vascular System; Sleep in Cardiovascular Disease; **Sleep and the Nervous System:** Basic Sleep–Wake Mechanisms; NREM Sleep: Anatomy and Physiology; REM Sleep Anatomy and Physiology; Thermoregulation and Sleep; **Sleep and the Respiratory System:** Respiratory Physiology; Sleep and the Control of Breathing.

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