[Frontiers in Bioscience 8, s557-567, May 1, 2003]

THERMOREGULATION AND SLEEP

Pier Luigi Parmeggiani

Dipartimento di Fisiologia Umana e Generale, Piazza Porta San Donato 2, 40127 Bologna, Italy

TABLE OF CONTENTS

1. ABSTRACT

This review describes the systemic physiological phenomena characterizing the interaction between thermoregulatory and sleep processes in the adult mammal. Homeostatic thermoregulation is preserved across the behavioral states of quiet wakefulness and non-rapid eye movement sleep notwithstanding state-dependent differences in threshold and gain of effector responses to thermal loads. In many mammalian species rapid eye movement sleep is characterized by the suppression or depression of thermoregulatory responses to thermal loads. In human adults, however, rapid eye movement sleep is not as thermally altered as in other mammals. The experimental evidence shows that the interaction between thermoregulatory and sleep processes occurs at the level of the preoptic-hypothalamic thermostat. A main open question concerns the nature of the over-riding demand imposing on the central nervous system the temporary suspension of homeostatic integrative regulation in rapid eye movement sleep.

2. INTRODUCTION

The existence of a strong and even antagonistic interaction between thermoregulatory and sleep processes in the adult mammal was initially an unexpected observation (1), but is now established following major advances in the fields of sleep physiology and pathology during the second half of the last century. Albeit neither the

mechanisms nor the physiological purpose of this interaction are completely understood, researchers are aware of the fact that sleep is not a mere state of rest with respect to wakefulness. Sleep does not entail a quantitative change in a sole modality of physiological regulation shared with wakefulness, but rather a sequence of behavioral states each with its own specific paradigm of regulation (2). The critical epistemological revolution in the study of sleep was the discovery of a sleep state characterized by a desynchronized electroencephalogram (3). This discovery contradicted the previous belief, shared almost universally by sleep researchers, that a synchronized electroencephalogram was the most peculiar and essential feature of sleep. This belief had curiously neglected the many somatic and visceral phenomena characterizing the states of the behavioral continuum (4).

2.1. The behavioral state from the viewpoint of physiological regulation

A fundamental module of the behavioral continuum is the ultradian wake-sleep cycle that may be divided broadly into three behavioral states of different duration, which are currently named quiet wakefulness (QW), non-rapid eye movement sleep (NREMS) and rapid eye movement sleep (REMS). The physiological events conventionally selected in adult mammals to identify these states are the following: QW is characterized by a desynchronized electroencephalogram, high postural muscle tonus and stability of autonomic functions with sympathetic prevalence; NREMS is characterized by a synchronized electroencephalogram, low postural muscle tonus and stability of autonomic functions with parasympathetic prevalence; REMS is characterized by a desynchronized electroencephalogram, postural muscle atonia or hypotonia with myoclonic twitches, and highly unstable autonomic functions. In contrast, active wakefulness (AW), characterized by a desynchronized electroencephalogram, sympathetic prevalence and in various combinations by attention, orienting, exploring, feeding, mating, defense or attack behaviors, is so heterogeneous as to be unsuited to a balanced functional comparison with the behavioral states of sleep.

The behavioral states of the ultradian wake-sleep cycle are characterized by major qualitative and quantitative changes in physiological functions. An adequate description of such functions across the behavioral continuum of the cycle raises a conceptual problem with respect to the temporal dimension of such states. In fact, the problem of the identification of the behavioral state, on the basis of intrinsically variable physiological phenomena, is that the term “state” implies a temporal stability which is not always the case. Therefore, the need arose early to identify the state also from a global physiological viewpoint by means of truly stationary attributes. In other words, the question was whether the concept of state ought to be related either to a mere concomitance of physiological events or rather to specific control mechanisms underlying the systemic organization of such events (4). Since a conceptual link between physiological phenomena and generating mechanisms is implied by the abstract term “regulation”, the state could also be characterized by a qualitatively constant regulation paradigm. According to this line of thinking, the behavioral state may be identified not only by the temporal course and coincidence of a certain number of variables, but also by temporal limits determined by the duration of a specific regulation paradigm of physiological variables (4). In this respect, the quality of homeostatic or non-homeostatic (poikilostatic) regulation is a fundamental postulate of the operational definition of the behavioral state, for closed- and open-loop operations can be tested experimentally as real mechanistic counterparts of the concept of regulation. In order to implement this crucial test, stimulus-response studies of homeostatic functions, like thermoregulation, circulation, and respiration, have been carried out extensively at different integration levels of such functions (2).

Homeostasis is a teleological concept, conceived by C. Bernard (5) and developed by W. B. Cannon (6), underlying our current understanding of the purpose of physiological functions. Homeostasis is brought about by continuous changes in the activity of somatic and autonomic effectors, which maintain the values of the variables, directly affecting cellular activity and survival, within a conventional “normal” range. Two kinds of homeostatic regulation should be considered, namely reactive and predictive homeostasis (7). **Reactive homeostasis** encompasses all physiological responses to disturbances directly or indirectly influencing the controlled variables. Since the operations of reactive homeostasis differ depending on the behavioral state, as shown by the stimulus-response relationship, a comparative study between states encompassing the whole ultradian wake-sleep cycle was necessary to identify the changes in physiological regulation across the behavioral continuum. **Predictive homeostasis** is regulated by the circadian timing system and entails anticipatory adjustments of physiological functions, coping with periodic qualitative and quantitative changes in ambient influences and conditions, to improve the effectiveness of adaptation to the environment and decrease the energy expenditure for reactive homeostasis. On this basis, the circadian organization of the ultradian wake-sleep cycles may also be considered an expression of predictive homeostasis. This chronobiological aspect of sleep, however, is beyond the scope of this review.

3. BASIC ASPECTS OF THERMOREGULATION

This section briefly describes the basic aspects of temperature regulation in conformity with the definitions of the "Glossary of terms for thermal physiology" (8).

3.1. Homeothermy

The fact that the oscillations of body core temperature are small in mammals depends on the precise control of the balance between heat production and heat loss. A change in temperature may be quantitatively expressed as the ratio between the changes in heat content and the mass of the tissue multiplied by the specific heat of the tissue (deltaT = deltaQ/mc). Cellular metabolism continuously produces heat which is transferred to the

blood and carried to the systemic heat exchangers of the body where thermoregulatory mechanisms control heat dissipation to maintain the homeothermy of the body core. In theory, core temperature is constant when the heat content of the body is unchanged as the result of a perfect balance between heat production and heat loss to the environment. In reality, such a perfect homeothermy does not occur. A tachymetabolic organism is considered homeothermic when the cyclic variation in core temperature is maintained within arbitrarily defined limits (±2°C) despite much wider variations in ambient temperature. From a mechanistic point of view, such a regulatory system entails a set-range (fixed or variable) to define the error signal necessary to activate the different thermoregulatory responses. Afferent discharges from superficial and deep thermoreceptors of the body act as inputs to control the activity of the central thermostat, located in the preoptic-hypothalamic (POH) region, which drives subordinate brain stem and spinal mechanisms controlling systemic thermoregulatory responses (9). This region, moreover, is equipped with thermosensitive neurons, reacting selectively to central positive (warm) or negative (cold) thermal loads, which are direct feedback inputs to the central thermostat.

3.2. Effector mechanisms of thermoregulation

Thermoregulatory responses are either behavioral or autonomic. The rationale of this division is that **behavioral thermoregulation** influences passive heat loss by means of changes in posture (e.g., curling or sprawling) and/or location (to increase or decrease exposure to sun, wind, humidity, etc.) of the body with respect to the thermal environment and **autonomic thermoregulation** actively influences both heat production (shivering and non-shivering thermogenesis) and heat loss (vasomotion of heat exchangers, piloerection, thermal tachypnea, sweating). In other words, the first group of responses is aimed at establishing conditions appropriately affecting the heat exchange of the body with its environment and the second group at affecting the balance between the two variables underlying body core homeothermy, namely heat production and heat loss.

4. THERMOREGULATION DURING SLEEP

4.1. Behavioral thermoregulation

Behavioral thermoregulation is negatively affected by sleep since the motility related to the search for thermal comfort can only precede the onset of sleep. However, specific postures elicited by positive and negative thermal loads are static behavioral thermoregulatory responses during NREMS to maintain the balance between heat production and heat loss. In contrast, the drop in postural muscle tonus during REMS, occurring in all studied species including humans (10), is unrelated to ambient temperature and impairs postural thermoregulatory responses (11).

4.2. Autonomic thermoregulation

In this section, hormonal mechanisms of thermoregulation are not considered because the temporal course of many effects produced (e.g., long-term adaptation to thermal loads) is longer than the duration of the ultradian wake-sleep cycle.

4.2.1. Thermal vasomotion

Vasomotion of the systemic heat exchangers (ear pinna, upper airway mucosa, tail) in several mammalian furry species (cat, rabbit, rat) affects heat loss from the body to the environment. Thermoregulatory vascular control is, therefore, operative when vasodilatation and vasoconstriction occur and are maintained under positive and negative thermal loads, respectively. This is the case in QW and NREMS but not in REMS (12, 13, 14). During QW and NREMS, vascular heat exchangers are regulated by sympathetic outflow that varies depending on ambient and/or hypothalamic thermal loads. For instance, in a cold or warm environment, in the thermal zone of vasomotor regulation of body temperature (i.e., under moderate thermal loads), there is a respective increase or decrease in tonic vasoconstriction of the heat exchangers to reduce or enhance heat loss from the body. However, whatever the actual intensity of such tonic heat exchanger vasoconstriction may be, there is always a decrease in its intensity during NREMS with respect to QW as a sleep-dependent event. This is shown by an increase in heat exchanger temperature affecting heat loss and a related increase in selective brain cooling that lowers hypothalamic temperature during NREMS (15, 16, 17, 18). Thus, the actual intensity of heat exchanger vasoconstriction during NREMS is the result of an interaction between thermoregulatory and sleep processes, both influencing sympathetic outflow. In case thermoregulatory vasodilatation is already maximal, slight vasoconstriction may occur during NREMS as a result of a sleep-dependent decrease in vascular transmural pressure. None of the vasomotion phenomena observed during REMS appears to be consistent with the paradigm of homeothermy control since the autonomic regulation balancing vascular transmural pressure with smooth muscle tonus is altered in several vascular beds (2). This alteration particularly affects heat exchanger vessels showing the prevalence of transmural pressure over the decreased tonus of smooth muscle fibers in a cold environment and the prevalence of residual tonus of smooth muscle fibers over the decreased transmural pressure in a warm environment. Therefore, on the transition from NREMS to REMS, thermoregulatory vasoconstriction is replaced by vasodilatation at low ambient temperature and thermoregulatory vasodilatation by vasoconstriction at high ambient temperature. Such vasomotion is absent on the transition from NREMS to REMS, only at temperatures around ambient thermoneutrality (12, 13). This indifferent range of ambient temperatures, which varies in different species, reveals the persistence across the two behavioral states of an equilibrium between vascular transmural pressure and wall tension, as a result of proportionally consistent changes in such variables.

4.2.2. Shivering thermogenesis

Exposure to low ambient temperature (the critical temperature varies in different species and according to individual and seasonal factors) elicits shivering which is particularly evident in the electrograms of several neck,

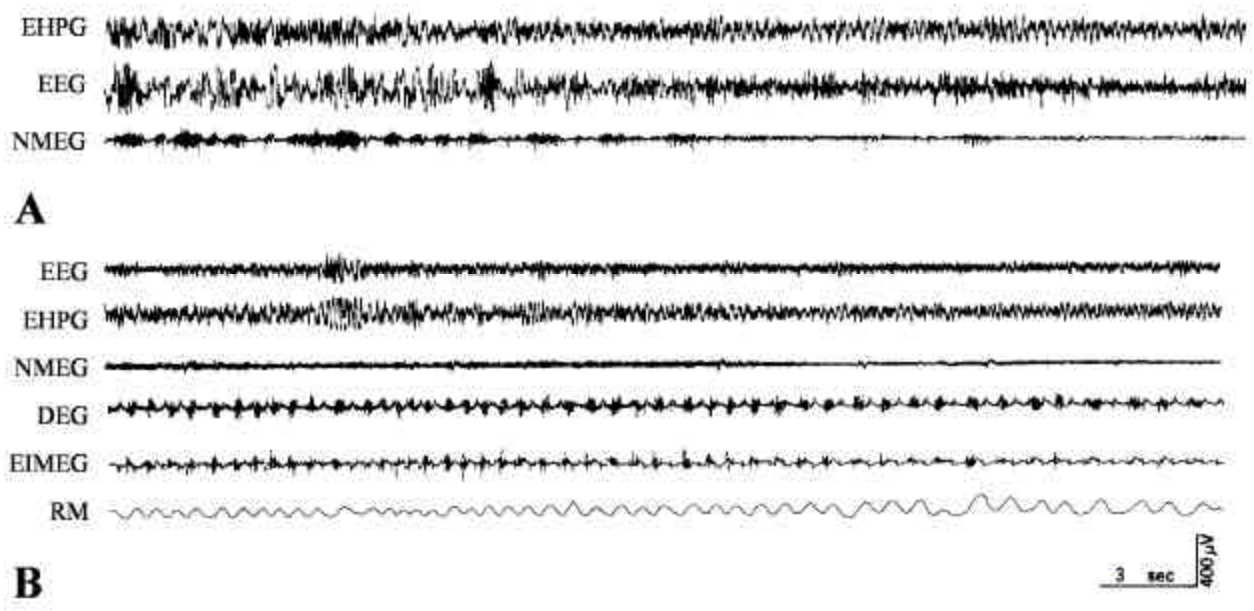

Figure 1. Influence of the behavioral state on thermoregulatory responses. A) At low ambient temperature (<10°C), shivering disappears on the transition from NREMS to REMS. EHPG, electrohippocampogram; EEG, electroencephalogram; NMEG, neck muscle electrogram. B) At high ambient temperature (>30°C), tachypnea disappears on the transition from NREMS to REMS. EEG, electroencephalogram, EHPG, electrohippocamprogram; NMEG, neck muscle electrogram; DEG, diaphragm electrogram; EIMEG, external intercostal muscle electrogram; RM, respiratory movements.

trunk and limb muscle groups in NREMS. On the transition from NREMS to REMS, the shivering activity disappears in cat (Figure 1A), armadillo and echidna and the absence of shivering lasts throughout the REMS episode (1, 11, 19, 20, 21, 22, 23, 24). The disappearance of shivering also occurs in cats with pontine lesions producing REMS without muscle atonia (23). This shows that the suppression of the thermoregulatory response in the normal animal does not depend on the pontine inhibitory mechanisms eliciting muscle atonia in REMS, but rather on behavioral-state dependent changes in the activity of the POH thermostat.

4.2.3. Non-shivering thermogenesis

Thermogenesis of brown adipose tissue (BAT) is an important cold-defense mechanism in the newborn (humans included) and, in some species, also in adulthood (e.g., rat). During NREMS in rats, interscapular BAT temperature is higher at low ambient temperature (4°C) than at normal room temperature (24°C) both before and after acclimation to cold. BAT temperature decreases steeply during REMS at low ambient temperature both before and after acclimation to cold. This decrease is subsequent to and negatively correlated with an increase in the temperature of the nasal mucosa enhancing systemic heat loss (cf. 4.2.1). Since only active BAT undergoes a remarkable cooling by such heat loss, as a result of its high flow rate of cooled arterial blood, BAT venous blood cannot maintain an adequate temperature gradient to warm the adjacent tissue. Thus, the cold-defense function of interscapular BAT is ineffective during REMS with respect to NREMS (25).

4.2.4. Thermal piloerection

Thermal piloerection is present in cats during NREMS and is suppressed during REMS (23).

4.2.5. Thermal tachypnea

Exposure to high ambient temperature (the critical temperature varies in different species and according to individual and seasonal factors) elicits tachypnea in cats during NREMS. The tachypnea disappears during the transition from NREMS to REMS (Figure 1B) and its absence lasts throughout the REMS episode (1, 11, 19). Only under conditions of severe hyperthermia (ambient temperature > 37°C) may the tachypnea not disappear during the REMS episode, probably as an effect of the direct activation of the thermo-chemosensitive region of the ventral medulla oblongata (11).

4.3. Thermoregulation during sleep in the human adult

The immature condition of the central nervous system in the human newborn raises complex phylogenetic and ontogenetic questions from the viewpoint of thermoregulatory and sleep processes that are beyond the scope of this review. The interested reader is referred to a recent review article (26).

4.3.1. Thermal sweating

Thermal sweating is observed during NREMS in a neutral or warm environment. Therefore, this sweating activity is consistent with both the down-regulation of body core temperature during NREMS with respect to QW and

the fact that thermoregulatory mechanisms are still able to elicit a proportional response to the thermal load. In contrast, thermal sweating is first suppressed (27) and then depressed during the REMS episode (27, 28, 29, 30, 31, 32) probably as a result of a decrease in the POH drive on subordinate sweating reflex mechanisms (cf. 4.3.4).

4.3.2. Thermal vasomotion

Skin vasodilatation at the onset of NREMS, indicating a state-dependent change in the central regulation of sympathetic outflow, is characterized by both a decrease and an increase in vasoconstrictor and vasodilator sympathetic discharge, respectively, in the lower extremities (33). In its turn, the resulting increase in skin temperature positively influences sleep propensity (34, 35, 36). This phenomenon, a result of the change in POH drive on sympathetic outflow, is analogous to the systemic heat exchanger vasodilatation occurring in furry species and eliciting a decrease in POH temperature during NREMS (cf. 5.3). During REMS, skin vasomotion in human adults is in general not inconsistent with thermoregulation except for forehead skin vasodilation at 21°C ambient temperature in naked humans (37).

4.3.3. Shivering thermogenesis

Shivering in naked humans at 21°C ambient temperature is present only in wakefulness and occasionally during stages 1 and 2 of NREMS. Since shivering is not present just before REMS episodes, the cessation of shivering cannot be assessed (10).

4.3.4. Inferences

A comparison of the results of studies of furry mammals with those of studies of naked human adults points to significant differences. However, they are not crucial enough to conclude that POH thermoregulation is not affected at all during REMS in human adults. Caution is justified by many constraints on methodology which impede an exhaustive study of the stimulus-response relationships of all the variables involved in thermoregulation in human adults during sleep. From the physiological viewpoint, moreover, there is a remarkable difference between humans and small furry mammals concerning thermal inertia and insulation, specific heat exchanger surface and skin area as source of sensory inputs. On the other hand, suppression and depression of sweating and forehead skin vasodilatation during REMS under positive and negative thermal loads, respectively, are changes suggesting at least a depression in the excitatory drive of the POH thermostat on the subordinate mechanisms: a drive necessarily underlying normal thermoregulatory responses. From a functional viewpoint, a reasonable inference is that a highly integrated autonomic thermoregulation is necessary in furry mammals characterized by small specific heat exchanger surfaces and small thermal inertia. In contrast, the lack of fur insulation and a large thermal inertia would be consistent with a less centralized thermoregulatory control based also on other mechanisms, located at lower levels of the neuraxis (9), for partially autonomous regional regulation of heat loss (sweating and vasomotion) and production (shivering) in the human adult. This view may be consistent also with the fact that thermal tachypnea is not preserved in human adults. Granted that sweating is a most effective cause of heat loss, the lack of thermal tachypnea is not really surprising since its preservation would also require such a strict POH integrative control (38) to conflict with other functions of breathing having higher priority in humans. In conclusion, it is reasonable to admit that an alteration of the POH regulation of homeothermy affects all the studied mammals during REMS, except that this event is less evident and dramatic in human adults than in other species as a result of a different hierarchical organization of thermoregulatory mechanisms (9, cf. 6.3).

5. THE POH THERMOSTAT DURING SLEEP

5.1. POH responsiveness to direct thermal stimulation

5.1.1. Regulation of heat loss

5.1.1.1. Thermal vasomotion

The effect of POH warming on ear pinna vasomotion was studied at neutral and low ambient temperatures in the cat (12). During NREMS ear pinna temperature increases indirectly indicating vasodilatation. This increased systemic heat loss is followed by a drop in POH temperature below the control level both at neutral and low ambient temperatures. In contrast, POH warming during REMS fails to elicit a specific increase in ear pinna temperature.

5.1.1.2. Thermal tachypnea

POH warming in cats elicits tachypnea during NREMS in the thermoneutral zone of ambient temperature (39, 40). The effect persists after the end of warming as long as the POH temperature is higher than the threshold temperature of tachypnea. Strong POH warming arouses the animal during NREMS. The tachypnea elicited by POH warming during NREMS immediately disappears with the advent of an episode of REMS even though the POH temperature is still above the NREMS threshold of the respiratory response. During REMS, POH warming of the same or higher intensity as that carried out during NREMS does not result in any significant respiratory response. However, on arousal of the animal at the end of the REMS episode, tachypnea appears immediately if POH temperature is still above threshold. In some cases, tachypnea may be elicited during REMS by strong POH warming without arousing the animal. Nevertheless, the increase in respiratory rate is significantly much smaller and shorter than that obtained by weaker warming during NREMS. In conclusion, whereas NREMS is characterized by a proportional threshold response to POH warming, during REMS neither a consistent threshold nor a proportional response are manifest (39, 40).

5.1.2. Regulation of heat production

POH cooling in the kangaroo rat and marmot during NREM sleep increases oxygen consumption and metabolic heat production. In comparison with W, not only the threshold temperature but also the gain of the proportional thermogenic response are slightly reduced. In

contrast, during REMS POH cooling eventually results in arousal but not in a thermogenic response (41, 42, 43).

5.2. Thermoresponsive neurons

Another proof of the behavioral state-dependent changes in the function of the central thermostat has been provided by experiments of direct thermal stimulation of neurons of POH and adjacent regions across the ultradian wake-sleep cycle in cats and kangaroo rats (44, 45, 46, 47, 48, 49, 50). The changes in thermoresponsiveness of the majority of such neurons parallel the changes in systemic effector responses to external (environment) or internal (body core) thermal loads during the cycle. Moreover, behavioral state-dependent changes in the firing rate of such neurons do not impair their thermoresponsiveness during QW and NREMS. In particular, the increase and decrease in thermosensitivity of warm-responsive and cold-responsive neurons, respectively, in NREMS (47, 48) is consistent with the down-regulation of body and brain temperatures (cf. 4.2.1). In contrast, state-dependent changes in neuron firing rate during REMS are associated with depression or suppression of thermoresponsiveness in a large number of neurons. The depression in thermoresponsiveness during REMS in furry mammals concerns either cold- and warm-responsive neurons (45, 47) or only cold-responsive neurons (49). Such partially conflicting results are less puzzling on considering that both thermal vasomotion (12) and tachypnea (39, 40) are responses to direct thermal stimulation of the POH thermostat which are nevertheless suppressed during REMS. It may well be that such neurons, sampled with different techniques, have different roles in the thermoregulatory network. On the other hand, the fact that panting during REMS may be observed in cats under heavy positive ambient thermal loads (11) and sweating is mainly depressed and only briefly suppressed in human adults during REMS (27) is not necessarily depending on warm-responsive POH neurons since a direct activation of more or less subordinate brain stem and spinal thermoregulatory mechanisms is possible (9, cf. 6.3). In conclusion, sleep processes in REMS evidently override the specific activity of the POH neuronal network underlying thermal homeostasis. In particular, other studies have shown that the differences in the spontaneous activity of cold- and warm-responsive neurons across QW, NREMS and REMS are consistent with the view of a direct involvement of such neurons also in sleep regulation (51, 52, 53). Particularly interesting are thermoresponsive neurons, also activated by peripheral thermoreceptors, which show increasing activity both at sleep onset and in response to increased core and/or skin temperatures. This may explain sleep promotion by mild positive thermal loads (cf. 6.2). On this basis, it is likely that different mechanisms would control behavioral state-related excitability and specific responsiveness in thermoresponsive neurons, which probably underlie several functions at the high integration level of POH structures (47). At present, the precise configuration of the neuronal network involved in this interaction is not yet established. One reason is that several neurons sampled by different researchers differ in size and firing rate, depending on the experimental techniques. Moreover, the resolution power of this approach in establishing whether the studied cells are either thermoreceptors or interneurons is rather weak. Also the role of excitatory and inhibitory neurotransmitters, which underlie the activity of such network, is a complicated issue.

5.3. Temperature of the POH thermostat across the ultradian wake-sleep cycle

In several mammalian species (e.g. cat, dog, goat, rabbit, rat, sheep), POH temperature undergoes small regular changes (a few tenths of a degree) in relation to the states of sleep, i.e. it decreases during NREMS with respect to QW, and increases during REMS with respect to NREMS regardless of exposure to a wide range of ambient temperatures (12, 13, 14, 54, 55) above and below ambient thermal neutrality (56). Such regular oscillations in POH temperature, an uppermost controlled variable, are small but raise the question as to the underlying mechanisms. Heat is produced by cellular metabolism and is transferred to the arterial blood which is maintained at a lower temperature than the POH tissue by heat loss from heat exchangers (15). In general, the metabolic heat production and flow and/or temperature of the arterial blood are the determinants of POH temperature. However, changes in metabolic rate would not be expected to contribute much to temperature variation since metabolism is indirectly coupled to heat clearance by blood flow (flow-metabolism couple) (15, 16, 17, 57). Therefore, changes in the amount and/or temperature of carotid and vertebral artery blood flowing into the circle of Willis become the fundamental points at issue.

Vertebral artery blood enters the circle of Willis at the same temperature as aortic arch blood, which has been cooled through the venous blood returning from the systemic heat exchangers (e.g., ear pinna, upper airway mucosa, tail, horn) of the whole body to the heart (systemic cooling). The carotid artery blood supply to the brain is thermally conditioned once more prior to entering the circle of Willis (selective cooling) by **countercurrent heat exchange** between a network of fine vessels (the carotid rete) and the cranial venous plexuses (e. g., cat, dog, sheep, goat) (15) or by **conductive heat exchange** (58) between basal brain, including the circle of Willis, and cranial venous lakes (e. g., rabbit, rat), both venous beds receiving cool blood from the systemic heat exchangers of the head (especially nasal mucosa). This explains the difference between the temperatures of vertebral artery blood (systemic cooling only) and carotid artery blood (both systemic and selective cooling) flowing into the circle of Willis. In practical terms, this difference may be indirectly appraised by computing the difference between pontine and POH temperatures, since they depend primarily on vertebral and carotid artery blood temperature, respectively (16, 17, 59). The presence of such difference also in species without the carotid rete (e.g, rabbit and rat) shows the efficacy for selective brain cooling of the mechanism of conductive heat exchange (58, 59).

During NREMS, the state-dependent decrease in tonic vasoconstrictor sympathetic outflow and the head-down posture (i.e. a decrease in the negative hydrostatic load which raises transmural pressure) concur to bring

Table 1. Thermoregulatory responses during wakefulness and sleep

RESPONSES		W	NREMS	REMS
	Behavioral	Locomotion		
		Posture	Posture	
Specific				
	Autonomic	Vasomotion	Vasomotion	
		Piloerection	Piloerection	
		Shivering Thermogenesis	Shivering Thermogenesis (+)	
		Non-shivering Thermogenesis	Non-shivering Thermogenesis	
		Thermal Tachypnea	Thermal Tachypnea (+)	
		Sweating	Sweating (+)	Sweating (0,–)
Non-specific		Vigilance	Arousal	Arousal

about a passive vasodilatation of systemic heat exchangers of the head which slightly increases systemic and selective brain cooling: pontine and POH temperatures are lower than during QW and their difference is increased (16, 17). From the functional viewpoint, behavioral state-dependent selective brain cooling may represent a thermal feedback involved in a mechanism of differential activation (uncoupling) of POH and extra-POH thermoreceptors during the homeothermic states (QW and NREMS) of the ultradian wake-sleep cycle (60). During REMS both POH and pontine temperatures increase, albeit differently, since the POH temperature approaches the pontine value. This appears to be the result of an increased supply of warmer (only systemic cooling) vertebral blood and a decreased supply of cooler (both systemic and selective cooling) carotid blood to the circle of Willis (16, 17, 61). The inference that REMS is characterized by a "steal" of carotid blood, producing a shift from the carotid artery to the vertebral artery (and probably also other arterial sources) in the amount of blood contributed to the circle of Willis, is supported by experiments of short-lasting bilateral common carotid artery occlusion. Such occlusion has little or no effect on the POH temperature rise in REMS in cats and rabbits (16, 61). The systemic hemodynamic changes, affecting blood flow in the carotid and vertebral beds during REMS, are consistent with the alteration in cardiovascular regulation characterizing this behavioral state (62).

6. SYSTEMIC INTERACTION BETWEEN THERMOREGULATORY AND SLEEP PROCESSES

There is a large body of evidence on the relationships between circadian oscillations of core temperature and sleep particularly in human adults, which is beyond the scope of this article dealing with the changes in physiological thermoregulation across the ultradian wake-sleep cycle.

6.1. Homeothermy versus poikilothermy in sleep

The stimulus-response experiments carried out during sleep in several mammalian species clearly showed that during NREMS thermoregulatory mechanisms are operative as in wakefulness, notwithstanding state-dependent differences in threshold and gain of effector responses to thermal loads. In particular, body and brain temperatures are down-regulated together with energy expenditure in NREMS with respect to QW. In contrast, REMS is characterized by events, which are not simply the result of state-dependent changes in threshold and gain of the different thermoregulatory responses, since the organism is not reacting adequately to external and internal thermal influences. This is shown by the suppression or depression of behavioral and autonomic thermoregulatory responses to thermal loads during this sleep state (table 1). The effector activity is not only functionally inconsistent with thermoregulation but also lacks a proportional relationship with the intensity of the thermal stimulus. The result is that body temperature (Tb) changes are positively correlated with ambient temperature (Ta), as expected in a poikilothermic species. For instance, the rate of change in body temperature of 0.0017°C/min·°CdeltaTb-Ta in a normal cat during REM sleep (63) is close (2/3) to the rate of change of 0.0027°C/min·°CdeltaTb-Ta in a poikilothermic pontine cat preparation (64). A good example of poikilothermy in REM sleep is given also by the small pocket mouse showing a positive correlation between core temperature, including brain temperature, with low and high ambient temperatures (65). As far as the brain is concerned, POH temperature increases during REMS within a wide range of ambient temperatures above and below ambient thermal neutrality in larger species (e.g. cat, rabbit, rat) with greater thermal inertia than the pocket mouse. This case is also a result of the state-dependent alteration in autonomic regulation which affects both circulation and thermoregulation (cf. 5.3). At all events, the organism is not endangered, since the duration of the REMS episode is in general short in relation to the thermal inertia of the body and the arousal mechanism is always ready to counteract an excessive drifting of core temperature by restoring POH thermoregulation (66).

6.2. Influence of thermoregulation on sleep

The influence of thermoregulation on sleep may be either synergic or antagonistic (66). During QW, thermal loads may induce or oppose the occurrence of NREMS, depending on whether sensory thermal influences (EEG synchronizing or desynchronizing) and thermoregulatory somatic and autonomic activities (posture, heat exchanger vasomotion, metabolic rate, circulatory and respiratory activity) are consistent or inconsistent with the specific somatic and autonomic patterns characterizing the latter sleep state. For instance, a moderately warm external or internal thermal load promotes NREMS (66, 67, 68, 69, 70, 71). In this case, the onset of sleep may be considered a synergic concomitant of thermoregulation in the adaptation

Table 2. Permutations in functional hierarchical arrays

RANK	MHA	FHA		
		QW	NREMS	REMS
I	T	T	D	R
II	D	D	R	T
III	R	R	T	D

MHA, morphological hierarchical array; FHA, functional hierarchical array; QW, quiet wakefulness; NREMS, non-rapid eye movement sleep; REMS, rapid eye movement sleep; D, diencephalon; R, rhombencephalon; T, telencephalon (Modified from 2, 79).

to a mild positive thermal load. However, NREMS may also occur under heavy thermal loads (72) since thermoregulation is still operative in this behavioral state. On the other hand, POH thermoregulatory activity strongly affects REMS occurrence. The surrender of the centralized homeostatic control in REMS is normally preceded by NREMS. During this highly homeostatic behavioral state, the probability of REMS onset depends on a successful down-regulation of core temperature, an event confined normally to harmless functional and/or ambient conditions (54, 66). Also the circadian propensity of REM onset around the minimum of body temperature, a reference of the functional condition of the POH thermostat, is indicative of a restraining POH influence (66). Therefore, REMS peaks within the ambient thermoneutral range, that is when thermoregulatory constraints are minimal. Outside of this range REMS is progressively depressed (11, 70, 73, 74, 75) and eventually suppressed for long periods until the accumulation of an increasing REMS debt produces a sufficient REMS pressure to overwhelm the thermoregulatory drive of the POH thermostat (11, 66, 73). In this case, REMS brainstem effector mechanisms escape from the normal POH control and thermoregulatory responses are suppressed. Nevertheless, the organism is not endangered since the loss of the specific effects of thermal stimuli is not associated with a loss of their non-specific arousing influence reestablishing the thermoregulatory function (table 1). Recently, two types of REMS episodes have been identified in rats: the “single episode”, preceded and followed by a long interval without REMS, and the “sequential episode”, occurring in clusters, that is in a sequence of REMS episodes separated by short intervals (76). The former type of REMS is less depressed than the latter type by a negative thermal load (77). This result indicates the complexity of the interaction between thermoregulation and sleep even in a case of clear-cut antagonism. In addition, the importance of non-specific stress effects of thermal loads ought to be considered concerning the changes in the structure of the ultradian wake-sleep cycle and particularly the decrease in REMS occurrence (66, 74, 75).

6.3. Influence of sleep on thermoregulation

In general, a regulation paradigm specific to each behavioral state of the ultradian wake-sleep cycle is also identifiable in other functions, like respiration and circulation (2, 62). The impairment of homeostatic control in REMS is more dramatic and evident in a function, such as temperature regulation in furry mammals, which depends on effector mechanisms strictly subordinated to regulatory structures of the POH region (78). In functions characterized by more widely distributed control mechanisms, such as circulation (62), respiration (38), and in the human adult thermal sweating, skin vasomotion and shivering (cf. 4.3), the features of POH functional impairment are rather more complex or even concealed as a result of the persistence of more or less efficient reflex regulation or peripheral autoregulation. Nevertheless, functional changes in REMS depend essentially on the suppression of a highly integrated homeostatic regulation which is operative in NREMS. In comparison with REMS, volitional and instinctive drives during AW may also impose a load on or interfere with homeostatic mechanisms at central and/or effector levels so as to overwhelm their regulatory power. However, the homeostatic mechanisms are still operative and capable of reestablishing the functional equilibrium which is the hallmark of QW and NREMS.

In all species, the somatic and visceral phenomena of NREMS are indicative of closed loop-operations, automatically maintaining homeostasis at a lower level of energy expenditure compared to QW. The operative paradigm is, however, unchanged. In contrast, the somatic and visceral activity of REMS is characterized in all species by the greatest variability as a result of non-homeostatic (open-loop) operations occurring in several physiological domains (2, 38, 62). Open-loop operations (effector excitation or inhibition) primarily of central origin, but secondarily complicated by local autoregulation, altered reflex activity, or both, prevail during REMS, so that the impairment of control mechanisms underlying homeostasis is the main physiological feature of this stage of sleep. Therefore, it is difficult to establish a rational foundation of the observed functional phenomena in terms of a centrally integrated regulation. Their physiological aim escapes a teleological explanation in behavioral terms. The differences in state-dependent physiological regulation disclosed with the help of the criterion of homeostasis emphasize the critical role of diencephalic and basal forebrain structures in the generation of the somatic and autonomic phenomena of the ultradian wake-sleep cycle (2, 38, 62).

A conceptual model of hierarchical permutations (table 2) can be surmised on the basis of the morphological and functional organization of the central nervous system as brought about by phylogenetic and ontogenetic processes. In particular, the states of the behavioral continuum are considered the functional landmarks of the discontinuous development of the mammalian encephalon characterized by the superimposition of increasingly complex integrative levels of physiological regulation. In mammals, the evolution of the ultradian wake-sleep cycle, from W to NREMS to REMS, would feature a stepwise functional regression of hierarchical dominance from telencephalon (QW) to diencephalon (NREMS) to rhombencephalon (REMS). The hierarchical array of the morphological organization is of course invariant, whereas the hierarchical array of functional dominance is behavioral state-dependent as a result of permutations occurring in the functional relationships among phylogenetically different

structures of the encephalon during the ultradian wake-sleep cycle (62, 79). Mechanisms that could underlie such hierarchical permutations are unknown at present, nevertheless the model may be useful as a conceptual frame encompassing both functional changes during ontogenesis and physiological differences between mammalian species.

7. PERSPECTIVES

The study of the interaction between thermoregulatory and sleep processes has revealed a number of systemic physiological phenomena of great consistency which have stood the test of time. However, important questions are raised by such observations. The changes in physiological regulation occurring during REMS may depend on mechanisms operative also in AW, in the latter case as a result of volitional and instinctive drives temporarily disrupting POH homeostatic integrative processes. Puzzling, however, is the fact that the physiological purpose of such events is clear in the latter behavioral state but absolutely obscure in the former. The non-homeostatic condition of REMS in the adult mammal, endowed with refined homeostatic mechanisms, may be regarded as a powerful expression of a basic and mysterious functional need of the nervous system, with which it is possible to cope only during a definite and well controlled behavioral state of sleep. Certainly, it is a difficult endeavor to dissect and identify a sleep-specific neuronal network in the brain which may be definitely considered as anatomically and functionally distinct from and hierarchically superimposed on the complex neuronal network underlying the systemic executive integration of somatic and autonomic physiological functions across the ultradian wake-sleep cycle. However, confidence in further analytical advances is warranted owing to the steadily increasing resolution power of experimental techniques.

8. ACKNOWLEDGMENT

The author is grateful to Dr. R. J. Berger for helpful information and indebted to his collaborators during many years of research. The studies carried out in the Institute of Physiology and later Department of Human and General Physiology of the University of Bologna were supported by grants of the Ministry of Education and the National Research Council.

9. REFERENCES

1. Parmeggiani P. L. & C. Rabini: Shivering and panting during sleep. *Brain Res* 6, 789-791 (1967)
2. Parmeggiani P. L.: Physiological regulation in sleep. In: Principles and practice of sleep medicine. Eds: Kryger M. H., Roth T., Dement W. C., Saunders, Philadelphia, pp 169-178 (2000)
3. Aserinsky E. & N. Kleitman: Regularly occurring periods of eye motility and concomitant phenomena during sleep. *Science* 118, 273-274 (1953)
4. Parmeggiani P. L.: Behavioral phenomenology of sleep (somatic and vegetative). *Experientia* (Basel) 36, 6-11 (1980)
5. Bernard C. : Lecons sur les phenomenes de la vie communs aux animaux et aux vegetaux., Museum, Paris, vol. I-II, (1878-1879)
6. Cannon W. B.: Organization for physiological homeostasis. *Physiol Rev* 9, 399-431 (1929)
7. Moore-Ede M. C.: Physiology of the circadian timing system: Predictive versus reactive homeostasis. *Am J Physiol* 250, R737-R752 (1986).
8. Glossary of terms for thermal physiology. *Pflügers Arch* 410, 567-587 (1987)
9. Satinoff E.: Neural organization and evolution of thermal regulation in mammals. *Science* (Washington DC) 201, 16-22 (1978)
10. Haskell E. H., J.W. Palca, J. M. Walker, R. J. Berger & H. C. Heller: Metabolism and thermoregulation during stages of sleep in humans exposed to heat and cold. *J Appl Physiol* 51, 948-954 (1981)
11. Parmeggiani P. L. & C. Rabini: Sleep and environmental temperature. *Arch ital Biol* 108, 369-387 (1970)
12. Parmeggiani P.L., G. Zamboni, T. Cianci & M. Calasso: Absence of thermoregulatory vasomotor responses during fast wave sleep in cats. *Electroencephalogr clin Neurophysiol* 42, 372-380 (1977)
13. Franzini C., T. Cianci, P. Lenzi & P. L. Guidalotti: Neural control of vasomotion in rabbit ear is impaired during desynchronized sleep. *Am J Physiol* 243, R142-R146 (1982)
14. Alfoeldi P., G. Rubicsek, G. Cserni & F. Obál Jr: Brain and core temperatures and peripheral vasomotion during sleep and wakefulness at various ambient temperatures in the rat. *Pflügers Arch* 417, 336-341 (1990)
15. Hayward J. N. & M. A. Baker: A comparative study of the role of the cerebral arterial blood in the regulation of brain temperature in five mammals. *Brain Res* 16, 417-440 (1969)
16. Azzaroni A. & P. L. Parmeggiani: Mechanisms underlying hypothalamic temperature changes during sleep in mammals. *Brain Res* 632, 136-142 (1993)
17. Azzaroni A. & P. L. Parmeggiani: Postural and sympathetic influences on brain cooling during the ultradian wake-sleep cycle. *Brain Res* 671, 78-82 (1995)
18. Azzaroni A. & P. L. Parmeggiani: Synchronized sleep duration is related to tonic vasoconstriction of thermoregulatory heat exchangers. *J Sleep Res* 4, 41-47 (1995)
19. Parmeggiani P. L. & L. Sabattini: Electromyographic aspects of postural, respiratory and thermoregulatory mechanisms in sleeping cats. *Electroencephalogr clin Neurophysiol* 33, 1-13 (1972)
20. Affanni J. M., E. Lisogorsky & A. M. Scaravilli: Sleep in the giant South American armadillo Priodontes giganteus (Edentata, Mammalia). *Experientia* (Basel) 28, 1046-1047 (1972)
21. Prudom A. E. & W. R. Klemm: Electrographic correlates of sleep behavior in a primitive mammal, the armadillo Dasypus novemcinctus. *Physiol Behav* 10, 275-282 (1973)
22. Van Twyver H. & T. Allison: Sleep in the armadillo Dasypus novemcinctus at moderate and low ambient temperatures. *Brain Behav Evol* 9, 107-120 (1974)

23. Hendricks J. C.: Absence of shivering in the cat during paradoxical sleep without atonia. *Exp Neurol* 75, 700-710 (1982)
24. Nicol S. C., N. A. Andersen, N.H. Phillips & R. J. Berger: The echidna manifests typical characteristics of rapid eye movement sleep. *Neuroscience Letters* 283, 49-52 (2000)
25. Calasso M., E. Zantedeschi & P. L. Parmeggiani: Cold-defense function of brown adipose tissue during sleep. *Am J Physiol* 265, R1060-R1064 (1993)
26. Bach V., F. Telliez, G. Krim & J. P. Libert: Body temperature regulation in the newborn infant: interaction with sleep and clinical implications. *Neurophysiol Clin* 26, 379-402 (1996).
27. Dewasmes G., B. Bothorel, V. Candas & J. P. Libert: A short-term poikilothermic period occurs just after paradoxical sleep onset in humans: characterization changes in sweating effector activity. *J Sleep Res* 6, 252-258 (1997)
28. Ogawa T., T. Satoh & K. Takagi: Sweating during night sleep. *Jpn J Physiol* 17, 135-148 (1967)
29. Takagi K.: Sweating during sleep. In: Physiological and behavioral temperature regulation. Eds: Hardy J. D. , Gagge A. P., Stolwijk J. A. J., Thomas, Springfield IL, pp 669-675 (1970)
30. Shapiro C. M., A. T. Moore, D. Mitchell & M. L. Yodaiken: How well does man thermoregulate during sleep? *Experientia* (Basel) 30, 1279-1281 (1974)
31. Henane R., A. Buguet, B. Roussel & J. Bittel: Variations in evaporation and body temperature during sleep in man. *J appl Physiol* 42, 50-55 (1977)
32. Sagot J. C., C. Amoros,V. Candas & J-P. Libert: Sweating responses and body temperatures during nocturnal sleep in humans. *Am J Physiol* 252, R462-R470 (1987)
33. Noll G., M. Elam, M. Kunimoto, T. Karlsson & B. G. Wallin: Skin sympathetic nerve activity and effector function during sleep in humans. *Acta Physiol Scand* 151, 319-329 (1994)
34. Krauchi K., C. Cajochen, E. Werth & A. Wirz-Justice: Warm feet promote the rapid onset of sleep. *Nature* 401, 36-37 (1999)
35. Krauchi K., C. Cajochen, E. Werth & A. Wirz-Justice: Functional link between distal vasodilation and sleep-onset latency? *Am J Physiol* 278, R741-R748 (2000)
36. Van Someren E. J. W.: More than a marker: interaction between the circadian regulation of temperature and sleep, age-related changes, and treatment possibilities. *Chronobiol Internat* 17, 313-354 (2000)
37. Palca J. W., J. M. Walker & R. J. Berger: Thermoregulation, metabolism, and stages of sleep in cold-exposed men. *J Appl Physiol* 61, 940-947 (1986)
38. Parmeggiani P. L.: Integrative aspects of hypothalamic influences on respiratory brainstem mechanisms during wakefulness and sleep. In: Central nervous control mechanisms in breathing. Eds.: Von Euler C., Lagerkrantz H., Pergamon Press, Oxford, pp 53-68 (1979)
39. Parmeggiani P. L., C. Franzini, P. Lenzi & G. Zamboni: Threshold of respiratory responses to preoptic heating during sleep in freely moving cats. *Brain Res* 52, 189-201 (1973)
40. Parmeggiani P. L., C. Franzini & P. Lenzi: Respiratory frequency as a function of preoptic temperature during sleep. *Brain Res* 111, 253-260 (1976)
41. Glotzbach S. F. & H. C. Heller: CNS regulation of metabolic rate in the kangaroo rat Dipodomys ingens. *Am J Physiol* 228, 1880-1886 (1975)
42. Glotzbach S. F. & H. C. Heller: Central nervous regulation of body temperature during sleep. *Science* 194, 537-539 (1976)
43. Florant G. L., B. M. Turner & H. C. Heller: Temperature regulation during wakefulness, sleep, and hibernation in marmots. *Am J Physiol* 235, R82-R88 (1978)
44. Parmeggiani P. L., A. Azzaroni, D. Cevolani & G. Ferrari: Responses of anterior hypothalamic-preoptic neurons to direct thermal stimulation during wakefulness and sleep. *Brain Res* 269, 382-385 (1983)
45. Glotzbach S. F. & H. C. Heller: Changes in the thermal characteristics of hypothalamic neurons during sleep and wakefulness. *Brain Res* 309, 17-26 (1984)
46. Parmeggiani P. L., A. Azzaroni, D. Cevolani & G. Ferrari: Polygraphic study of anterior hypothalamic-preoptic neuron thermosensitivity during sleep. *Electroencephalogr clin Neurphysiol* 63, 289-295 (1986)
47. Parmeggiani P. L., D. Cevolani, A. Azzaroni & G. Ferrari: Thermosensitivity of anterior hypothalamic-preoptic neurons during the waking-sleeping cycle: a study in brain functional states. *Brain Res* 415, 79-89 (1987)
48. Alam M. N., D. McGinty & R. Szymusiak: Neuronal discharge of preotic/anterior hypothalamic thermosensitive neurons: relation to NREM sleep. *Am J Physiol* 269, R1240-R1249 (1995)
49. Alam M. N., D. McGinty & R. Szymusiak: Preoptic/anterior hypothalamic neurons: thermosensitivity in rapid eye movement sleep. *Am J Physiol* 269, R1250-R1257 (1995)
50. Cevolani D. & P. L. Parmeggiani: Responses of extrahypothalamic neurons to short temperature transients during the ultradian wake-sleep cycle. *Brain Res Bull* 37, 227-232 (1995)
51. Alam M. N., D. McGinty & R. Szymusiak: Thermosensitive neurons of the diagonal band in rats: relation to wakefulness and non-rapid eye movement sleep. *Brain Res* 752, 81-89 (1997)
52. McGinty D., M. N. Alam, R. Szymusiak, M. Nakao & M. Yamamoto: Hypothalamic sleep-promoting mechanisms: coupling to thermoregulation. *Arch it Biol* 139, 63-65 (2001)
53. Szymusiak R., T. Steiniger, M. N. Alam & D. McGinty: Preoptic area sleep-regulating mechanisms. *Arch it Biol* 139, 77-92 (2001)
54. Parmeggiani P. L., L. F. Agnati, G. Zamboni & T. Cianci: Hypothalamic temperature during the sleep cycle at different ambient temperatures. *Electroencephalogr clin Neurophysiol* 38, 589-596 (1975)
55. Parmeggiani P. L., G. Zamboni, E. Perez & P. Lenzi: Hypothalamic temperature during desynchronized sleep. *Exp. Brain Res* 54, 315-320 (1984)
56. Altman P. L., D. S. Dittmer. In: Environmental biology, F.A.S.E.B., Bethesda, MA (1966)
57. Franzini C.: Brain metabolism and blood flow during sleep. *J Sleep Res* 1, 3-16 (1992)

58. Caputa M., A. Demicka, K. Dokladny & B. Kurowicka: Anatomical and physiological evidence for efficacious selective brain cooling in rats. *J Therm Biol* 21, 21-28 (1996)
59. Parmeggiani P. L., A. Azzaroni & M. Calasso: A pontine-hypothalamic temperature difference correlated with cutaneous and respiratory heat loss. *Respir Physiol* 114, 49-56 (1998)
60. Azzaroni A. & P. L. Parmeggiani: Changes in selective brain cooling across the behavioral states of the ultradian wake-sleep cycle. *Brain Res* 844, 206-209 (1999)
61. Parmeggiani P. L., A. Azzaroni & M. Calasso: Systemic hemodynamic changes raising brain temperature in REM sleep. *Brain Res* 940, 55-60 (2002)
62. Parmeggiani P. L.: The autonomic nervous system in sleep. In: Principles and practice of sleep medicine. Eds: Kryger M. H., Roth T., Dement W. C., Saunders, Philadelphia, pp 194-203 (1994)
63. Parmeggiani P. L., C. Franzini, P. Lenzi & T. Cianci: Inguinal subcutaneous temperature changes in cats sleeping at different environmental temperatures. *Brain Res* 33, 397-404 (1971)
64. Bard P., W. J. Woods & R. Bleier: The effects of cooling, heating and pyrogen on chronically decerebrated cats. In: Physiological and behavioural temperature regulation. Eds: Hardy J. D., Gagge A. P., Stolwijk J. A. J., Thomas, Springfield Ill., pp. 519-545 (1970)
65. Walker J. M., L. E. Walker, D. V. Harris & R. J. Berger: Cessation of thermoregulation during REM sleep in the pocket mouse. *Am J Physiol* 244, R114-R118 (1983)
66. Parmeggiani P. L.: Interaction between sleep and thermoregulation: An aspect of the control of behavioral states. *Sleep* 10, 426-435 (1987)
67. Euler von C. & U. Soederberg: The influence of hypothalamic thermoceptive structures on the electroencephalogram and gamma motor activity. *Electroncephalogr clin Neurophysiol* 9, 391-408 (1957)
68. Roberts W. W. & T. C. L. Robinson: Relaxation and sleep induced by warming of preoptic region and anterior hypothalamus in cats. *Exp Neurol* 25, 282-294 (1969)
69. Roberts W. W., E. H. Bergquist & T. C. L. Robinson: Thermoregulatory groming and sleep-like relaxation induced by local warming of preoptic area and anterior hypothalamus in opossum. *J Comp Physiol Psychol* 67, 182-188 (1969)
70. Sakaguchi S., S. F.Glotzbach & H. C. Heller: Influence of hypothalamic and ambient temperatures on sleep in kangaroo rats. *Am J Physiol* 237, R80-R88 (1979)
71. Obal F. Jr., I. Tobler & A. Borbely: Effect of ambient temperature on the 24-hour sleep-wake cycle in normal and capsaicin-treated rats. *Physiol Behav* 30, 425-430 (1983)
72. Parmeggiani P. L., C. Rabini & M. Cattalani: Sleep phases at low environmental temperature. *Arch Sci Biol* (Bologna) 53, 277-290 (1969)
73. Parmeggiani P. L., G. Zamboni, T. Cianci, L. F. Agnati & C. Ricci: Influence of anterior hypothalamic heating on the duration of fast-wave sleep episodes. *Electroencephalogr clin Neurophysiol* 36, 465-470 (1974)
74. Szymusiak R. & E. Satinoff: Maximal REM sleep time defines a narrower thermoneutral zone than does minimal metabolic rate. *Physiol Behav* 26, 687-690 (1981)
75. Haskell E. H., J. W. Palca, J. M. Walker, R. J. Berger & H. C. Heller: The effects of high and low ambient temperatures on human sleep stages. *Electroencephalogr Clin Neurphysiol* 51, 494-501 (1981)
76. Amici R., G. Zamboni, E. Perez, C. A. Jones, I. Toni, F. Culin & P. L. Parmeggiani: Pattern of desynchronized sleep during deprivation and recovery induced in the rat by changes in ambient temperature. *J Sleep Res* 3, 250-256 (1994)
77. Zamboni G., E. Perez & R. Amici: Biochemical approach to the wake-sleep cycle. In: Somatic and autonomic regulation of sleep. Eds: Lugaresi E., Parmeggiani P. L., Springer, Berlin, pp 3-24 (1997)
78. Parmeggiani P. L.: Temperature regulation during sleep: A study in homeostasis. In: Physiology in sleep. Research topics in physiology. Eds: Orem J., Barnes C. D., Academic Press, New York, pp 97-143 (1980)
79. Parmeggiani P. L.: Thermoregulation during sleep from the viewpoint of homeostasis. In: Clinical physiology of sleep. Eds: Lydic R., Biebuyck J. F., American Physiological Society, Bethesda MD, pp 159 –169 (1988)

Key Words: Thermoregulation, Heat, Temperature, Sleep, Mammal, Review

Send correspondence to: Pier Luigi Parmeggiani, M.D., Dipartimento di Fisiologia Umana e Generale, Piazza Porta San Donato 2, 40127 Bologna, Italy, Tel: +39 051 2091773, Fax: +39 051 251731, E-mail: plparm@biocfarm.unibo.it