Archives Italiennes de Biologie, 134: 101-107, 1995.

HYPOTHALAMIC HOMEOTHERMY ACROSS THE ULTRADIAN SLEEP CYCLE

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In the ambient thermal zone for the vasomotor regulation of body temperature (i.e. excluding heavy positive and negative thermal loads above and below ambient thermal neutrality) the hypothalamic temperature of mammals undergoes regular oscillations which, whilst being only a few tenths of a degree in magnitude, precisely mark the single behavioral states of the ultradian sleep cycle (19, 24). A basic question is whether or not this almost perfect homeothermy (cf. "Glossary of Terms for Thermal Physiology": Pflügers Arch. 410: 567-587, 1987) is achieved by specific thermoregulatory controls of heat production and heat loss driven by hypothalamic temperature itself. The hypothesis that hypothalamic temperature may act as the independent variable is conceptually reasonable since (i) the autonomic integrative mechanism for homeostatic temperature regulation is located in the hypothalamus (and in the adjacent preoptic region), (ii) the hypothalamus is known to contain specific thermosensitive neurons which are part of the neuronal network underlying thermoregulation, (iii) the thermosensitivity of such hypothalamic neurons varies in relation to the behavioral states of the ultradian sleep cycle. Therefore in order to have a better understanding of this issue, the mechanisms underlying the behavioral state-dependent changes in hypothalamic temperature should and, in this review, will be taken into consideration.

Without discussing the equally important state of quiet wakefulness (QW; characterized by a desynchronized electroencephalogram, high postural muscle tone and stability of autonomic functions with a sympathetic prevalence), the single sequence of two behavioral states of different duration, which are known as (i) quiet sleep (QS; characterized by a synchronized electroencephalogram, low postural muscle tone and stability of autonomic functions with a parasympathetic prevalence; other current acronyms: SS, synchronized sleep; SWS, slow wave sleep; NREM, non rapid eye movement sleep) and (ii) active sleep (AS; characterized by a desynchronized electroencephalogram, postural muscle atonia with myoclonic twitches, and the instability of autonomic functions; other current acronyms: DS, desynchronized sleep; PS, paradoxical sleep; REM, rapid eye movement sleep), is the basic pattern of the behavioral state organization of the ultradian sleep cycle in adult mammals. With respect to the efficiency of thermoregulation, the behavioral states of the ultradian sleep cycle are different, as AS, in contrast to QS, is characterized by a conspicuous impairment of thermoregulation (15, 16).

Fundamentally, hypothalamic temperature changes are the direct result of an

imbalance between heat production and heat loss. Heat is produced by cellular metabolism and is transferred to the perfusing arterial blood which is always maintained at a lower temperature than the hypothalamic tissue (14). Therefore, changes in metabolic heat production, the flow and the temperature of the arterial blood perfusing the brain may be considered as the principal determinants of hypothalamic temperature changes. However, changes in hypothalamic metabolic rate would not be expected to contribute much to temperature variation since metabolic heat production is coupled to heat loss by blood flow (cf. 9, 14). In fact, the basic variables, with respect to hypothalamic homeothermy across the behavioral states of the ultradian sleep cycle, are the temperature and flow of the vertebral and carotid arterial blood perfusing the brain, i.e., the mechanisms for brain cooling.

In several species the cooling of vertebral artery blood depends on systemic heat exchangers (ear pinna, upper airways mucosa) whereas the cooling of carotid artery blood depends not only on systemic heat exchangers but also on selective heat exchanging mechanisms (e.g., countercurrent heat exchange between the carotid rete and pterygoid venous plexus in the cat or conductive heat exchange between both the basal brain and the circle of Willis and cranial venous lakes in the rabbit) (7, 14). Thus, as result, vertebral artery blood is warmer than carotid artery blood (14).

This latter point has been recently confirmed in the cat, a species which has a carotid rete, by a study of the hypothalamic temperature changes produced by transient drops in carotid blood flow (2). As the result of a short (100s) bilateral common carotid artery occlusion, a sharp rise in hypothalamic temperature occurs in QS (fig. 1). Systemic baroreceptive reflexes and autoregulation of cerebral blood flow would buffer such drops in carotid blood flow by increasing the flow of vertebral blood (cf. 5). As the latter is warmer than carotid blood, hypothalamic temperature is raised. This rise in hypothalamic temperature does not depend on metabolic heat production, since on long lasting (300s) bilateral common carotid artery occlusion a plateau of hypothalamic temperature is attained early (2). In contrast, bilateral common carotid artery occlusion during AS, a sleep state which normally shows an increase in hypothalamic temperature, only enhances this spontaneous increase (Fig. 1). This would indicate that, during AS, carotid flow is spontaneously decreased, and that such a decrease would normally be buffered by an increase in the amount of vertebral blood flowing into the circle of Willis. Such mechanisms for systemic and selective brain cooling are affected by the changes in body posture and vasoconstrictor sympathetic outflow related to wake-sleep behavioral states (3, 4): a rise in hydrostatic transmural pressure weakens systemic brain cooling and enhances selective brain cooling, whereas an increase in tonic vasoconstrictor sympathetic outflow decreases both systemic and selective brain cooling (4).

Also in species lacking a carotid rete (e. g., the rabbit) the hemodynamic alterations in the common carotid bed during AS (10) are likely to impair the mechanism for selective brain cooling (i. e. a decrease of arterial blood flow to the circle of Willis and of venous blood flow from systemic heat exchangers to the pterygoid and ophthalmic plexuses) with the result that an increase in the supply

of vertebral blood to the circle of Willis occurs (2). This increased perfusion of the brain by vertebral blood in the presence of depressed conductive cooling is sufficient to raise hypothalamic temperature rapidly in rabbits since, also in this species, the vertebral blood is warmer than the carotid blood perfusing the hypothalamus (14). In contrast, the morphofunctional prevalence of the internal carotid blood supply in primates (8), due to the high degree of telencephalization, provides unfavourable hemodynamic conditions, particularly in humans (12), for a significant enhancement of vertebral blood perfusion of the hypothalamus during AS. In the case of primates, carotid blood temperature is an extremely (and probably the most) important determinant of hypothalamic temperature not only during QS but also during AS. In fact, systemic heat exchanger vasodilation during AS in the monkey has been

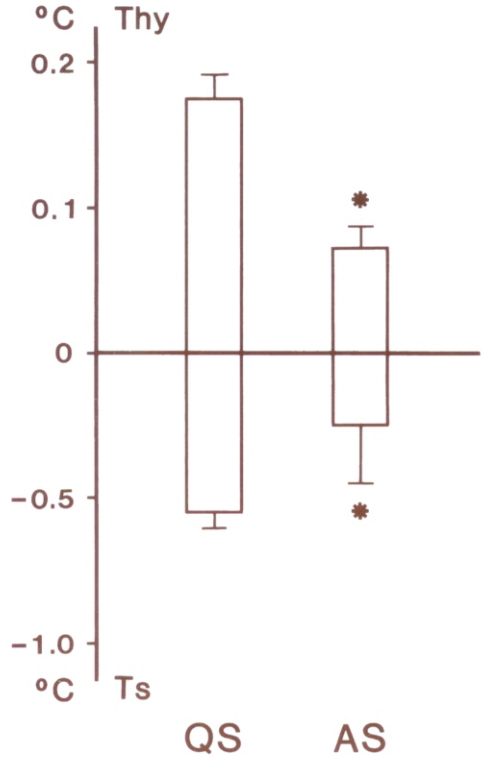

Fig. 1. - *Changes (mean ± S.E.M; *P<0.05, paired t-test) at neutral ambient temperature in hypothalamic temperature (Thy) and ear pinna temperature (Ts) elicited in the cat by the occlusion (duration, 100s) of both common carotid arteries by means of chronically implanted inflatable occluders.*

Zero represents the temperature (Thy or Ts) taken, as the reference, immediately before carotid occlusion. Such a procedure increased Thy more during QS than during AS; concomitantly, Ts was decreased more during QS than during AS. Thus, bilateral common carotid occlusion during AS contributed little in rising Thy and decreasing Ts, the spontaneous Thy increase and Ts decrease being only slightly enhanced. This result shows that during AS, the carotid blood flow perfusing the brain is already spontaneously decreased, and that such a decrease has already been buffered by an increase in the amount of vertebral blood flowing into the circle of Willis. Data from Ref. 2.

shown to be consistently associated with a decrease in hypothalamic temperature (13, 14) which is in contrast to that found for cats (23, 24), rabbits (10) and rats (1).

On the basis of this, it is possible to consider the different factors underlying the changes in hypothalamic temperature across the ultradian sleep cycle.

During QS, 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 about a vasodilation which increases systemic and selective brain cooling: vertebral and carotid blood temperatures are lower than during QW and their difference is increased (2, 4).

During AS, the autonomically regulated balance between transmural pressure and vasoconstriction is disturbed in several vascular beds, including the common carotid bed. In species with a carotid rete (e.g., the cat) the resulting alteration in the arterial blood perfusion of the circle of Willis, which receives an increased supply of warmer (only systemic cooling) vertebral blood to replace a decrease in the supply of the cooler (both systemic and selective cooling) carotid blood, weakens the influence of selective brain cooling on hypothalamic temperature. The result of this is an increase of hypothalamic temperature which rises to approach the same temperature as vertebral blood (2). Therefore, during AS, hypothalamic temperature is primarily influenced by the temperature of vertebral blood which, as observed previously, is dependent on the heat loss from systemic heat exchangers. Paradoxical changes (from the viewpoint of thermoregulation), as a result of the AS-dependent alteration in sympathetic regulation (cf. 18), occur in systemic heat exchanger vasomotion during AS, that is vasoconstriction at temperatures at and above ambient thermoneutrality and vasodilation at temperatures below ambient thermoneutrality (1, 2, 4, 10, 23, 24). At or above ambient thermoneutrality, the increase in hypothalamic temperature during AS is consistent with the systemic heat exchanger vasoconstriction occurring in response to a decrease in transmural pressure (cf. 2, 4, 23, 24). In concomitance with the impairment of the mechanism of selective brain cooling during AS, this vascular response may additionally influence hypothalamic temperature by raising systemic arterial blood temperature (and vertebral blood temperature) at a rate which is dependent on the thermal inertia of the whole body. However, a hypothalamic temperature increase during AS is observed even at low ambient temperatures (1, 10, 19, 23, 24) in spite of the systemic heat exchanger vasodilation (increasing systemic heat loss) due to the state-dependent suppression of thermoregulatory vasoconstriction (cf. 18). Also in this case, the effect of the impairment of selective brain cooling on hypothalamic temperature is associated with the effect of the thermal inertia of the whole body on the increased systemic heat loss. In fact, vertebral blood cooling during the short duration of AS is attenuated since the only influence on the temperature of vertebral blood comes from the long systemic venous return to the heart (2). Consequently, the increase in vertebral blood supply to the circle of Willis during AS (2) fails to raise hypothalamic temperature only when the systemic arterial blood temperature (and vertebral blood temperature), has been greatly lowered by excessive heat loss during the previous QS state in a very cold environment (cf.

24). In conclusion, within the ambient thermal zone for vasomotor regulation of body temperature hypothalamic temperature changes across the ultradian sleep cycle are primarily dependent on changes in systemic and selective heat loss affecting the temperature of the arterial blood perfusing the brain. However, such hypothalamic temperature changes are so small as to be subliminal as thermal feedback stimuli for thermoregulatory responses. This is particularly relevant in the case of QS, since this behavioral state is characterized by a normal hypothalamic thermosensitivity (11, 15, 16, 20, 21, 22). In contrast, a feedback role of the hypothalamic temperature during AS is simply unlikely for the reason that the responsiveness of the hypothalamic thermostat to direct thermal stimuli is strongly depressed (11, 15, 16, 20, 21, 22). The changes in hypothalamic temperature may, of course, interfere with the autonomic and somatic processes underlying sleep behavioral states but only when ambient temperature greatly deviates from the species-specific thermoneutral zone (cf. 17).

The mechanism maintaining the oscillations in hypothalamic temperature within a width of a few tenths of a degree across the ultradian sleep cycle may be considered as another example of "the wisdom of the body" (cf. 6). In fact, the stereotyped autonomic and somatic functional adjustments underlying the behavioral states of the ultradian sleep cycle entail heat production-heat loss imbalances which, however, scarcely affect the hypothalamic temperature since arterial blood temperature changes are temporarily but efficiently buffered, at a low energetic cost, by the thermal inertia of the mass of body water. This would imply that a phylogenetic pressure, associated with that of many other endogenous and exogenous factors (e. g. basal metabolic rate, skin thermal conductance, nutritional habits, ecological niche, predator-prey relationship), was operative early on in mammals in order to decrease the energy expenditure for thermoregulation by limiting the duration of the ultradian sleep cycle (particularly that of the AS stage, the behavioral state characterized by an impaired thermoregulation; cf. 15, 16) so as to fit the thermal inertia of the different masses of body water in mammals of different sizes (cf. 25).

Thus at present, experimental evidence would not support the hypothesis that hypothalamic temperature may act as the independent variable for thermoregulatory control of heat production and heat loss during the ultradian sleep cycle in the ambient thermal zone for the vasomotor regulation of body temperature.

SUMMARY

In the ambient thermal zone for the vasomotor regulation of body temperature hypothalamic temperature changes across the states of the ultradian sleep cycle are the result of state-dependent heat production-heat loss imbalances affecting the temperature of the arterial blood perfusing the brain. However, the changes in arterial blood temperature are efficiently buffered, at a low energetic cost, by the thermal inertia of the mass of body water. Thus, the oscillations in hypothalamic temperature are maintained within a width of a few tenths of a degree and are so

small as to be subliminal as thermal feedback stimuli for thermoregulatory responses. This passive hypothalamic homeothermy would support the hypothesis that a phylogenetic pressure was operative early on in mammals in order to limit the duration of the ultradian sleep cycle so as to fit the thermal inertia of the different masses of body water in mammals of different sizes.

Acknowledgement. - The author wishes to thank Dr Christine A. Jones for editing the English manuscript.

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