Autonomic Basis for the Rise in Brain Temperature during Paradoxical Sleep

Abstract. *The rise in brain temperature in the rabbit during paradoxical sleep originates in a temperature rise of the cerebral arterial blood. Heat loss from the ear is a major factor in the regulation of arterial blood temperature in the rabbit, and the primary thermal event in paradoxical sleep is a vasoconstriction of the skin of the ear which results in a rise in arterial blood and brain temperatures. These thermal correlates of paradoxical sleep are not present in a cold environment when the ear skin is already maximally vasoconstricted. The persistence of peripheral vasoconstriction during paradoxical sleep in a hot environment suggests a disturbance in autonomic thermoregulatory control.*

In the rabbit the temperature of the brain increases during paradoxical sleep because of intense peripheral vasoconstriction; this constriction causes a rise in the temperature of the cerebral arterial blood (*1*). Elevations in brain temperature in both the cat and the rabbit during paradoxical sleep have been attributed to increased neuronal heat production (*2*). We found no thermal evidence to indicate any local increases in central neural metabolism.

A body of experimental work, based upon studies of the electroencephalogram (EEG), cortical and subcortical unit activity, evoked potentials, d-c potentials, tissue impedance, and cerebral blood flow suggests that active processes are occurring in the central nervous system during paradoxical sleep (*3*). Brain temperature has been measured during sleep–waking cycles and after sensory stimulation in an attempt to clarify changes in local neuronal metabolism or blood flow which cannot be studied by conventional electrophysiological techniques (*4*).

The use of cerebral temperature measurements as indices of central neural function is founded on the assumption that local neuronal heat production and local blood flow are of primary importance in determining the temperature of a given brain site. However, studies in the monkey and the rat (*5*) have demonstrated that the major determinant of brain temperature is an extracranial one; in these species, changes in brain temperature which occur with changing behavioral states appear to originate in temperature fluctuations of the cerebral arterial blood. We undertook the present study to determine whether the elevation in brain temperature in the rabbit during paradoxical sleep might be the result of a rise in arterial blood temperature or whether this cerebral warming is a reflection of increased neuronal metabolism.

Sixteen mature female New Zealand white rabbits were studied. Under pentobarbital anaesthesia, copper-constantan arc-welded thermocouples in glass tubing (outside diameter, 0.7 mm) were implanted stereotaxically in the brainstem, on the midline, at frontal planes of the preoptic region, the mammillary body, and the basilar pons. Two or three thermojunctions were cemented in the same glass tube for measurements of temperature at different vertical levels in the same frontal plane. Probes were lowered into the subarachnoid space at the base of the brain in order to observe temperatures at the vessels of the arterial circle of Willis. Thermocouples in polyethylene tubing (outside diameter, 1 mm) were threaded to the arch of the aorta through the common carotid artery and fixed in place. Silicone elastic cannulae (outside diameter, 1 mm) were implanted in the right atrium through the external jugular vein for intravenous injections. The distal ends of the thermocouples were attached to miniature copper-constantan connectors cemented to a lucite platform elevated above the scalp on three epidural stainless steel screws. We used the elevated platform to avoid an artificial heat sink of dental cement over the cranium (*5*). The aortic thermocouple and venous cannula were threaded subcutaneously up the neck for attachment to connectors on the skull platform. Positions of the intracranial and intravascular probes were verified by postmortem gross and histologic examination. Temperatures of the skin were measured with bare thermojunctions taped to the dorsal surface of the ear or to the skin of the back; EEG was monitored over the parietal cortex between the two rear screws supporting the platform. We used an Offner type-R ink-writing oscillograph which provided continuous and simultaneous EEG and temperature records. Reference junctions in a distilled water–crushed ice bath were used, and thermopotentials were amplified with a chopper-stabilized d-c amplifier. The maximum sensitivity of the recording system was 0.025°C per millimeter of pen deflection. Unrestrained, afebrile rabbits in a sound-attenuated, temperature-controlled environmental chamber were studied at 25°C, 32°C, or 15°C ambient temperature. Animals were observed continuously through a one-way window. Our principal criterion for the identification of paradoxical sleep was a behavioral one, the fall of the head and ears, which accompanied EEG desynchronization (*3*, *6*).

Intracerebral temperature changes were correlated with similar thermal changes in the arterial blood both at the aortic arch (Fig. 1) and at the cerebral arteries (Figs. 1 and 2) at the base of the brain. We found all intracranial temperature changes to be the result of thermal changes in the blood perfusing the brain. Arterial blood enters the cranial cavity at aortic blood temperature levels and flows through the basal subarachnoid space cerebrospinal fluid essentially unchanged. As this arterial blood circulates through brain tissue, it becomes progressively warmed by the heat of local metabolism. The temperature levels of regional brain sites above the arterial blood depend upon the distance of the site from the circle of Willis in the basal subarachnoid space, with the exception that sites 5 to 7 mm from the dorsal surface of the skull are also influenced by environmental temperature. Temperatures measured in the cerebrospinal fluid at the anterior cerebral-middle cerebral artery junction, at the posterior cerebral artery, or at the basilar artery were at the temperature of the blood in the aortic arch and rapidly reflected changes in aortic blood temperature (Fig. 1). Deeper in the nervous tissue, temperature oscillations of the arterial blood appeared with a longer latency and a damping of the small fast changes in temperature (Figs. 1 and 2).

While the temperature of the skin of the back showed an inconstant relationship to blood temperature, we consistently found that the temperature of

the skin of the ear was inversely related to blood temperature. Therefore, heat loss from the ear appears to us to be a major factor in the regulation of blood temperature in the rabbit. Skin temperature is a good index of skin blood flow in the rabbit ear at ambient temperatures around 25°C (*7*). It is not surprising that changes in heat loss from the ear consequent to alterations in blood flow should be so well correlated with changes in central blood temperature in the rabbit, since the ear in this furred species is a large, naked, well-vascularized surface. Anatomical and physiological studies of the vascular innervation of the rabbit ear have demonstrated that vasoconstriction, with closure of the arteriovenous anastomoses, is a manifestation of sympathetic nervous activity (*8*).

At an ambient temperature of 25°C, our rabbits, at rest and habituated to their surroundings, maintained a relatively vasodilated ear skin, with a temperature 2° to 3°C below the arterial blood temperature. During long periods of slow sleep (high voltage EEG) or of wakefulness without vigorous somatic activity, the thermal relationships of ear, arterial blood, and brain

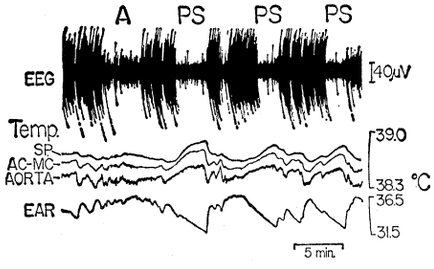

Fig. 1. Thermal changes in the arterial blood, the brain, and the skin during paradoxical sleep, slow sleep, and arousal in the rabbit. Periods of paradoxical sleep (*PS*), arousal (*A*), and slow sleep (unlabeled) in a freely-moving rabbit (R-2) at an ambient temperature of 25°C. Aortic blood temperature was identical to that of the cerebral vessels and has been lowered by 0.12°C for clarity. Note the dramatic cooling of the skin of the ear and the warming of the aortic and intracranial arterial blood and the brain which precede and accompany each episode of *PS*. Few thermal changes are associated with arousal or with slow sleep. The final period of *PS* is followed by arousal (not labeled). *EEG*, biparietal cortical electroencephalogram; *SP*, septal region; *Aorta*, arterial blood in the arch of the aorta; *AC-MC*, cerebral arterial blood at the junction of the anterior and middle cerebral arteries in the basal subarachnoid space; *Ear*, skin of the ear.

were relatively constant. But dramatic changes occurred during paradoxical sleep (Figs. 1 and 2). Ear temperature began to fall and the temperatures of the blood and brain began to rise seconds to minutes prior to EEG desynchronization and loss of tone in the posterior neck muscles. The ear temperature fell steadily, at a rate of about 1°C/minute, throughout the period of paradoxical sleep, regardless of duration, while the temperature of the arterial blood and the brain tended to reach a plateau in the longer paradoxical sleep episodes. At the instant that elevation of the animal's ears signalled the termination of paradoxical sleep, the ear temperature rose sharply and the temperatures of the arterial blood and brain fell (see Figs. 1 and 2).

We observed the ear temperature, aortic blood temperature, and several intracranial temperatures simultaneously in 91 episodes of paradoxical sleep which occurred at an ambient temperature of 25°C. The mean duration of these periods of paradoxical sleep, using the usual criteria of EEG desynchronization and atonia of the neck and ear muscles, was 2.6 minutes (range: 30 seconds to 7 minutes). In 72 of these episodes, the ear temperature began its decline before the EEG and behavioral signs occurred, preceding them by 48 seconds (10 seconds to 3 minutes). In the remaining 19 episodes, the EEG and behavioral signs of paradoxical sleep occurred at the same time as the drop in ear temperature began. The mean fall in ear temperature was 2.2°C (0.2° to 4.7°C) and the mean rise in aortic blood temperature was 0.2°C (0.05° to 0.4°C). The pattern of brain temperature rise depended on the cerebral site and the degree of "thermal inertia" (*9*) of the site. Brain regions only a few millimeters from the circle of Willis showed a temperature rise during paradoxical sleep which was very similar to the rise in arterial blood temperature, and which began within seconds of the blood temperature rise. Brain regions as far as 10 mm from the source of arterial blood (on the stereotaxic plane) exhibited temperature rises which were smaller than blood temperature rises and which lagged behind the changes in blood temperature by as much as 1 minute. We found that sites in the mammillary body, the preoptic region, and the septal area showed less thermal inertia and more closely reflected the rise in blood temperature, while sites in the midbrain and pontine reticular formations and the dorsal thalamus showed more thermal inertia (Figs. 1 and 2). Induced changes in the blood temperature helped to clarify these observations (*9*). A rapid intravenous injection of 4°C isotonic saline produced a sharp, deep fall in temperature at the circle of Willis, a slower, smaller decline in temperature in the preoptic, septal, and mammillary regions, and a very slight change in the temperature of pontine, mesencephalic, and thalamic sites.

In 100 percent of the episodes of paradoxical sleep observed in our rabbits at ambient temperatures of 25°C and 32°C, the same distinctive pattern of central and peripheral temperature changes occurred. The only other time that these associated thermal events occurred so dramatically was when the animal was stimulated by loud noises or by touch (*8*), and even under these conditions the ear temperature seldom fell as much as it did during paradoxical sleep. That the elevation in brain temperatures in paradoxical sleep does stem primarily from a decrease in peripheral heat loss (a decrease in ear blood flow), is demon-

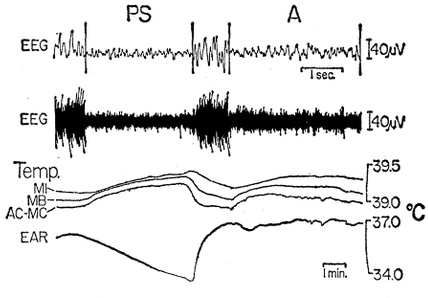

Fig. 2. Peripheral vasoconstriction and central temperature rise during paradoxical sleep in the rabbit. Slow sleep (unlabeled), paradoxical sleep (*PS*), and spontaneous arousal (*A*) in a freely-moving rabbit (R-17) at an ambient temperature of 25°C. Upper *EEG* trace at a faster speed is from similar sleep-waking periods in the same animal. Notice the continued cooling of the skin of the ear and the warming of the cerebral blood and brain throughout the period of activated sleep (*PS*), with an abrupt reversal of these temperatures upon transition to slow sleep. Elevation of intracranial temperatures during the arousal period without cutaneous vasoconstriction was associated with vigorous grooming and coprophagy. Labels are the same as in Fig. 1, except: *MI*, massa intermedia of the thalamus; *MB*, mid-mammillary body.

strated by our observation that, in a 15°C environment, periods of paradoxical sleep are not accompanied by rises in blood and brain temperatures. At this ambient temperature, although the rabbit is able to maintain a normal deep blood temperature (38.5° to 39.0°C), its cutaneous vessels are fully constricted so that the ear temperature remains near the ambient temperature. Thus, since the vessels of the skin of the ear are constricted maximally in response to the environmental thermal stimulus, there can be no further vasoconstriction during paradoxical sleep.

The experiments which we conducted at high ambient temperatures are perhaps the most interesting, pointing as they do to a disturbance in thermoregulation during paradoxical sleep. At an ambient temperature of 32°C, the rabbit, which can neither sweat nor pant effectively, is under severe thermal stress, its blood and brain temperatures elevated as much as 1°C. The skin of the ear is "clamped" in vasodilatation, allowing maximum heat loss, and even the usual small changes in temperature are absent; yet, in the face of hyperthermia, the skin of the ear shows a paradoxical vasoconstriction during paradoxical sleep, raising the central temperatures still higher. Thus these autonomic thermal correlates of paradoxical sleep in the rabbit are very persistent, superseding the thermoregulatory needs in a hot environment. This is clearly a disruption in the normal control of autonomic outflow. If the lower brainstem regions which have been postulated as necessary for the occurrence of paradoxical sleep (*3*) are initiating these autonomic events, the effect might be mediated through ascending influences on the preoptic-anterior hypothalamic region by activation of thermoregulatory neurons or through a change in the temperature "set point" (*10*). Alternatively, this autonomic response might represent an interference with descending thermoregulatory pathways, rhombencephalic regions acting more directly on preganglionic sympathetic effector neurons in the spinal cord. Other evidence of activity in the autonomic sphere during paradoxical sleep, such as lowered arterial blood pressure, irregularities in heart and respiratory rates, and changes in galvanic skin response and in pupillomotor control have been described (*3*).

Our studies confirm earlier reports (*2*) of 0.1° to 0.4°C elevations in brain temperature in paradoxical sleep, and our work shows that these elevations are due to a rise in the temperature of the cerebral arterial blood consequent to a vasoconstriction in the skin and a decrease in peripheral heat loss (*9*). Though our present thermal technique, which can be used to demonstrate large changes in heat production and blood flow in the brain (*5*), did not disclose such local events during paradoxical sleep, future studies using more sensitive temperature measurements may uncover such changes (*4*). The striking peripheral vasomotor activity which invariably accompanies paradoxical sleep in the rabbit suggests that further studies of vegetative phenomena might elucidate the role of the autonomic nervous system in paradoxical sleep.

MARY ANN BAKER
JAMES N. HAYWARD
Department of Anatomy and *Brain Research Institute, University of California, Los Angeles 90024*

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11. Supported in part by USPHS grant NB-05638. We thank E. Burrell for technical assistance and K. Tani for preparation of the figures.

10 July 1967

Discharge of Frontal Eye Field Neurons during Eye Movements in Unanesthetized Monkeys

Abstract. *Single unit activity was recorded from the frontal eye fields (area 8) in unanesthetized monkeys seated in a primate chair with the head restrained. The frontal eye field units were identified by antidromic response to stimulation of the cerebral peduncle. The findings indicate that most of the neurons discharge only after initiation of eye movements. These cells showed steady discharge when the eyes were immobile and oriented in a specific direction.*

The cerebral cortex of man and lower primates contains large regions concerned with eye movement. Among these is an area called the frontal eye field (usually homologized with area 8 of Brodmann), which lies in the frontal lobe along the anterior border of the arcuate fissure. Electrical stimulation applied to different points in the region evokes conjugate horizontal or vertical eye movement in primates (*1*). The importance of the area for the control of eye movement has further been seen in experiments involving lesions in both monkeys and man (*2, 3*). In spite of the fact that the reported effects of these lesions vary from a complete loss of voluntary eye movement (*2*) to a transient paresis of gaze (*4*), there is little doubt that subtle but lasting deficits of certain oculomotor functions occur following extirpation of the area (*3*). It has been found, for instance, that patients with lesions involving the frontal lobes show a prolongation of visual search time when required to use active head and eye movements in matching patterns (*3*).

While the methods of electrical stimulation and ablation which have thus far been employed in studies of the