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THE INFLUENCE OF THE NASAL MUCOSA AND THE CAROTID RETE UPON HYPOTHALAMIC TEMPERATURE IN SHEEP

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SUMMARY

1. In chronically-prepared sheep, intracranial temperatures were measured in the cavernous sinus among the vessels of the carotid rete and at the circle of Willis extravascularly, and in the preoptic area and in other brain stem regions. Extracranial temperatures were measured intravascularly in the carotid or internal maxillary arteries and on the nasal mucosa and the skin of the ear.

2. At 20° C ambient temperature, shifts in temperature of the hypothalamus and of other brain sites paralleled temperature shifts in the cerebral arterial blood which was cooler than central arterial blood. During periods of arousal and of paradoxical sleep, vasoconstriction of the nasal mucosa and the ear skin occurred and temperatures at the cerebral arteries and in the brain rose without a comparable rise in central arterial blood temperature.

3. Anaesthetic doses of barbiturate abolished the temperature oscillations in the cerebral arterial blood and the brain. When air was blown rapidly over the nasal mucosa in anaesthetized animals, temperatures dropped precipitously in the cavernous sinus, at the cerebral arteries, and in the brain, while central arterial temperature fell only slightly. Injections of latex into the facial venous system demonstrated a venous pathway from the nasal mucosa to the cavernous sinus.

4. When sheep were exposed to 45–50° C ambient temperature, respiratory rate increased 5–10 times and the temperature gradient between central and cerebral arterial blood widened.

5. It is concluded that venous blood returning from the nasal mucosa and the skin of the head to the cavernous sinus cools the central arterial blood in the carotid rete. This is an important factor in the maintenance of hypothalamic temperature in the wool-covered, long-nosed, panting

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sheep and undoubtedly affects hypothalamic thermoreceptors and temperature regulation in artiodactyls.

INTRODUCTION

The domestic sheep is an efficient homeotherm existing successfully in both hot and cold climates (Schmidt-Nielsen, 1964). This heavily-furred artiodactyl which relies primarily on panting to maintain a constant body temperature in the heat has been shown to be most tolerant of high environmental temperatures (Lee, 1950). The panting sheep maintains a lower deep body temperature in response to a standard heat exposure than many other mammals and does not exhibit neurological signs of hyperthermia until the rectal temperature is quite high. The factors responsible for panting and for the resistance to hyperthermia in sheep remain poorly understood. Bligh (1959) concluded that peripheral thermoreceptors are dominant in initiating thermoregulatory panting in sheep, but he assumed a direct association between carotid arterial blood temperature and the temperature of hypothalamic thermosensitive regions. Our studies in the cat (Baker & Hayward, 1967*b*) and the dog (Hayward, 1968) demonstrated that such an assumption is not valid for all species of mammals. We felt that studies of the factors influencing brain temperature in sheep were necessary as a first step in understanding the role which might be played by hypothalamic thermoreceptors in thermoregulation in this species.

Hemingway, Robinson, Hemingway & Wall (1966) found that hypothalamic temperatures in sheep were lower than rectal temperature, suggesting to us a dissociation between brain temperature and deep body temperature similar to that which we had observed in the cat and the dog. It was difficult to establish the brain–body temperature relationships in sheep from these data alone, because of the limitations of rectal temperature as an index of deep body temperature (Bligh, 1966). Our initial studies in the sheep (Baker & Hayward, 1968*a*, *b*, *c*) and those of Taylor (1966) in the goat, in which brain temperature and carotid arterial temperature were measured simultaneously, showed a dissociation between brain and carotid temperature and suggested that the mechanism of this dissociation might be heat exchange between warm arterial blood in the carotid rete and cool venous blood in the cavernous sinus surrounding the rete. We performed the present experiments in order to verify our hypothesis that counter-current heat exchange at the carotid rete is a major factor in the regulation of hypothalamic temperature in sheep and in order to examine the role of upper respiratory heat loss in this counter-current heat exchange.

METHODS

Thirteen ewes, of a Hampshire–Columbia cross, were used. The heads of eight adult animals were reserved for anatomical studies as described below, while the remaining five young (20 kg) animals were used for our physiological preparations. By developing a system of stereotaxic co-ordinates for these sheep and employing a modified dog head-holder (Hume & Ganong, 1956) we were able to implant probes in selected regions in the cranial cavity. With the animal anaesthetized (30 mg sodium pentobarbitone/kg), copper–constantan arc-welded thermocouples in glass tubing (o.d. 0·7 mm) were implanted in the brain stem, aimed for the mid line preoptic region or mid-brain reticular formation, or both. Two or three thermojunctions were cemented into each glass tube for measurement of temperature at different vertical levels in the same frontal plane, and the tubes were pushed through the brain into the basal subarachnoid space so that the thermojunction at the tip of the tube lay at the circle of Willis (Fig. 1). The rostral probes were located at the anterior cerebral arteries or at the junction of the anterior and middle cerebral arteries, and the caudal probes were at the posterior communicating or the basilar artery. We have established that temperature measured in the basal subarachnoid space near the cerebral arteries is a good index of temperature of arterial blood in the cerebral arteries (Hayward & Baker, 1968). In the rabbit (Baker & Hayward, 1967*a*) and the monkey (Hayward & Baker, 1968), cerebral arterial blood temperature measured in this way is the same as carotid arterial temperature and rapidly reflects both spontaneous and induced changes in carotid temperature. In the monkey, cerebral arterial blood temperature measured in this way is the same as temperature measured in the patent basilar artery. In two sheep, we measured temperature at the carotid rete with thermocouples in stainless-steel tubing (o.d. 0·5 mm) which had been stereotaxically implanted in the cavernous sinus to lie in the plexus of arteries forming the rete. Four to eight intracranial temperatures were measured in each animal.

Central arterial temperature, that is, the temperature of blood in the large extracranial arteries, was measured by thermocouples in polyethylene tubing (o.d. 1 mm) implanted through the inferior thyroid artery into the common carotid (three animals), the bicarotid trunk (one animal) or the internal maxillary (one animal) without occluding the flow of blood in these vessels. Thermocouples were implanted in the nasal cavity on the mucosa or were taped to the skin of the ear during recording sessions, with temperatures at these sites being used as indices of vasomotor activity. Silicone rubber cannulae (o.d. 1 mm) were implanted into the right atrium through the external jugular vein for intravenous injections of anaesthetic.

Thermocouples were made from enamelled 100 μ wires. The leads of the thermocouples were connected to miniature copper–constantan connectors (Thermoelectric Co., no. MX J-TX) which were cemented to a lucite platform elevated above the intact scalp on four epidural stainless-steel screws. Distal ends of the intravascular and nasal thermocouples and venous cannulae were threaded subcutaneously to the head where they were attached to the connectors or to a diaphragm-fitted Luer lock tip (Baker, Burrell, Penkhus & Hayward, 1968).

A cortical electroencephalogram was monitored between the two parietal epidural screws which supported the cranial platform. E.e.g. and temperatures were recorded simultaneously on an Offner Type-R ink-writing oscillograph. Reference junctions in a bath of distilled water and crushed ice were used, and thermopotentials were amplified with a chopper-stabilized DC amplifier (Offner 481 B preamplifier and 9806 A coupler). Before each experiment, thermocouples were calibrated over the expected temperature range against a Bureau of Standards thermometer in a constant-temperature bath. The maximum sensitivity of this recording system was 0·025° C/mm pen deflexion. The over-all accuracy of the system after calibration was $\pm 0{\cdot}05°$ C. In one experiment, a high gain DC preamplifier (Leeds and Northrup 9835-B) was used to amplify thermopotentials monitored at the carotid rete, and

the output registered on the oscillograph. Because of amplifier drift, the system was usually calibrated at hourly intervals and before and after each heating experiment.

After each animal had recovered from surgery as evidenced by its eating and drinking at preoperative levels, it was placed in a narrow pen specially constructed to allow it to stand or lie but not to turn around, and animal and apparatus together placed within a sound-attenuated, thermoregulated chamber with a one-way glass observation window. Relative humidity was measured (Bristol's Thermo-Humidograph, The Bristol Co., Waterbury, Conn., U.S.A.) but not controlled, varying between 20 and 50 %. Each animal was fed with 750 g alfalfa in the evening. Thirty-six experiments, from 1 to 5 hr in duration, were conducted at ambient temperatures of 20–25° C for a total of 195 hr. During these recording sessions, the temperature relationships among the various extracranial and intracranial sites were determined and the relationships between brain temperature and behaviour were observed.

In six experiments on two animals, anaesthetic doses of sodium pentobarbitone were administered while temperatures were being recorded, and in five of these experiments air was blown repeatedly into the nostril. In four animals, twenty-three experiments were conducted in which the ambient temperature was raised from 20–25 to 45–50° C in 1 hr and held there for 2 hr. In these experiments, the respiratory rate was counted against a stop-watch. Individual animals were studied for 26–40 days. At the end of the studies, the chronically prepared animal was anaesthetized and the patency of the extracranial arteries which contained thermocouples verified. The animal was then perfused through the carotids with saline followed by 10 % formol–saline. Positions of the intracranial and intravascular thermocouples were determined by gross dissection and examination.

The heads of eight freshly killed sheep were used for anatomical studies. After perfusion through the carotids with saline followed by formol–saline, coloured neoprene latex was injected under high pressure into one common carotid artery in each of two heads. In six other heads, the latex was injected centrally and distally into the angular vein of the face. These preparations were dissected and examined grossly to verify in our Hampshire–Columbia sheep the published descriptions of the carotid rete and the cerebral arterial system in sheep (Daniel, Dawes & Prichard, 1953), and to demonstrate the venous pathway reported to connect the nasal mucosa and the cavernous sinus in these animals (Foltz, Johnson & Nelson, 1966; May, 1964).

RESULTS

Temperature measured at the arteries of the circle of Willis (Fig. 1) in our sheep was always cooler than the carotid blood measured either high in the neck or near the aortic arch. Simultaneous temperature measurements in the cavernous sinus at the carotid rete and at the circle of Willis showed that temperature at the rete was almost identical with that at these cerebral arteries (Fig. 2). The only difference was that temperature oscillations in the cavernous sinus were slightly larger than those at the circle of Willis. Central arterial blood temperature tended to remain steady even at times when cerebral arterial temperature showed pronounced thermal shifts associated with cranial peripheral vasomotor activity consequent to behavioural activity.

Changes in cerebral arterial temperature were reflected by similar changes in temperature in the preoptic area and throughout the brain stem of the sheep, and a constant temperature difference was thus maintained between

each brain site and the cerebral arterial blood. A gradient of increasing temperature exists from the cerebral arteries in the basal subarachnoid space toward the centre of the brain stem. In general, the warmest brain sites are those which are farthest from the source of cool blood in the subarachnoid space surrounding the brain. Figure 1 shows the locations of the intracranial thermocouples in the sheep in this study. Table 1 shows the temperature gradients between various brain sites and the cerebral

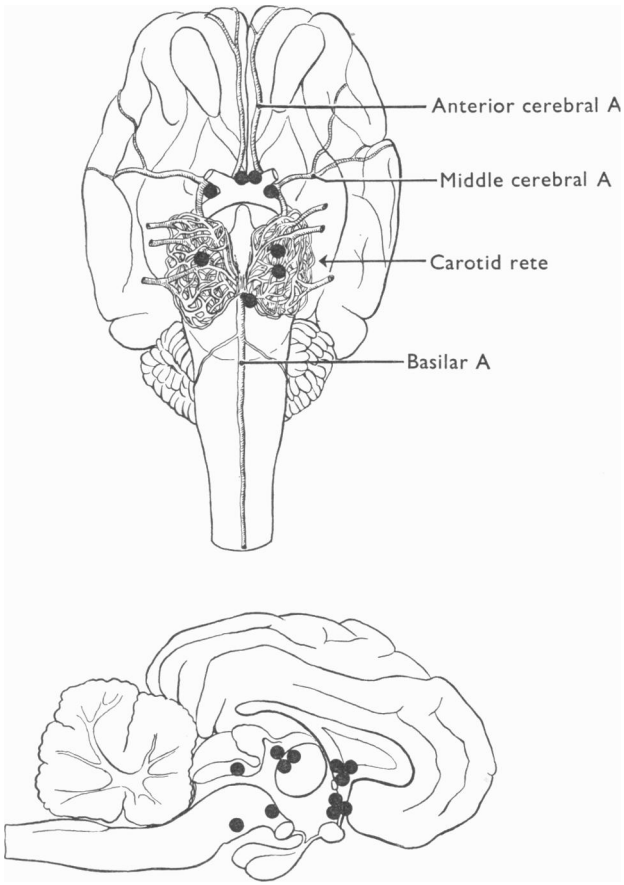

Fig. 1. The location of chronically-implanted intracranial thermocouples at the cerebral arteries and in the carotid rete (top) and in the brain stem (bottom) in five sheep. The thermocouples at the basal cerebral arteries were 2–4 mm outside the nervous tissue, and were no farther than 2 mm from the arteries themselves. The thermocouples in the rete were in the middle of the plexus of arteries, which has a dorsoventral extent of about 8 mm. Two thermocouples were placed at the posterior communicating arteries, and are not shown because they are below the rete in this drawing. The thermocouples in the brain stem were 1–4 mm off the mid line and have been projected on the mid-sagittal plane. See Table 1 for further description of thermocouple placements in individual animals.

arterial blood at the circle of Willis. These gradients were constant for as long as any animal was studied. The thermal inertia of cerebral structures caused the temperature gradient between the cerebral arterial blood and any brain site to be disturbed temporarily whenever a large, rapid change in blood temperature occurred. This resistance to a change in temperature was most marked in the warm, deep brain sites, as is evident in Fig. 2 and Fig. 3, and least marked in the cooler hypothalamus which is near the circle of Willis.

TABLE 1. Temperature gradients between brain and cerebral arterial blood in sheep

Brain site	Cerebral arterial blood reference site	Depth (mm)*	T_B–T_{CAB} (C)†	Range (C)	n‡	Animal
Preoptic region	Ant. cer. art.	5	0·25	—	1	1
Preoptic region	Post. comm. art.	4	0·23	0·20–0·25	7	5
Preoptic region	Post. comm. art	2	0·20	—	5	6
Subthalamus	Post. comm. art.	5	0·25	—	3	5
Cerebral peduncle	Post. comm. art.	4	0·23	0·20–0·25	6	6
Thalamus (ant. nuc.)	Ant. cer.-mid cer.	8	0·38	0·37–0·45	11	3
Septal region	Post. comm. art.	10	0·34	0·32–0·35	9	5
Septal region	Post. comm. art.	9	0·32	0·30–0·35	5	6
Thalamus (massa int.)	Basilar art.	8	0·35	0·30–0·40	11	4
Mid-brain ret. form.	Basilar art.	14	0·46	0·40–0·50	14	4
Thalamus (mid line)	Post. comm. art.	12	0·46	0·45–0·50	12	5
Thalamus (massa int.)	Post. comm. art.	11	0·46	0·45–0·50	8	6

* Depth (mm) is the distance of the site from the circle of Willis in the basal subarachnoid space.

† T_B–T_{CAB} is the temperature gradient (C) between the site and the cerebral arterial blood reference site.

‡ n is the number of observations, each representing a separate experimental day.

Vasomotor activity of the nasal mucosa and intracranial temperature shifts

Changes in posture. When our isolated, undisturbed sheep were relaxed and recumbent, as they usually were, the temperature at the cerebral arteries and at the carotid rete was as much as 1° C lower than the temperature in the large extracranial arteries, and nasal mucosal temperature was near the temperature of the central arterial blood. When the sheep were startled by noises or by handling, and when they stood up, the temperature of the nasal mucosa and of the skin of the ear fell, and cerebral arterial temperature rose toward central arterial temperature (Fig. 2). The central arterial blood temperature generally did not reflect behavioural changes. When the sheep stood up, however, there was usually a slight drop in central blood temperature, though a slight rise occurred in some instances (Fig. 2). In the aroused, standing animal, both cerebral and central arterial

temperatures were steady. When the sheep were recumbent and ruminating, only cerebral arterial temperatures oscillated. In twenty-five experiments on the five animals at an ambient temperature of 20° or 25° C, the mean temperature of the central arterial blood was 39·06 ± 0·35° C (S.D.). The mean temperature of the cerebral arterial blood in recumbent animals was 38·40 ± 0·33° C and in standing animals 38·88 ± 0·30° C.

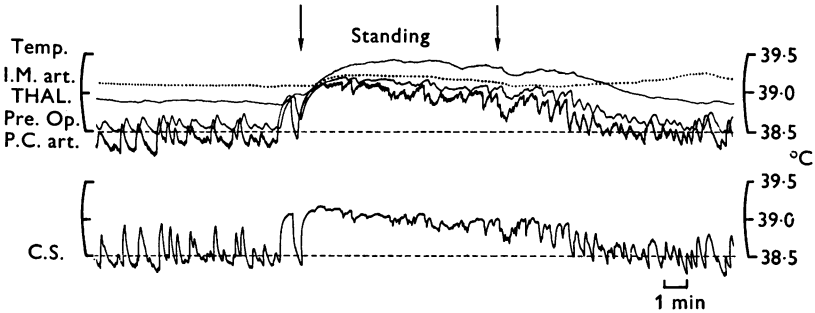

Fig. 2. The effect of standing on body temperatures in a sheep (no. 6) at 25° C ambient temperature. Central arterial blood temperature (dotted) is higher than cerebral arterial temperature, and the gradient between the two is reduced when the animal stands up. Notice that brain stem temperatures follow temperature oscillations in the cerebral arterial blood, with the cool preoptic region showing less thermal inertia than the warm thalamus. Temperature in the cavernous sinus among the vessels of the carotid rete is almost identical to that measured at the posterior communicating artery in the basal subarachnoid space. Note the dashed 38·5° C reference lines. Labels: I.M. art., patent internal maxillary artery, at the angle of the mandible; THAL., massa intermedia of the thalamus, 11 mm from the basal subarachnoid space; Pre. Op., preoptic region, 2 mm from the basal subarachnoid space; P.C. art., at the posterior communicating artery, in the basal subarachnoid space; C.S., in the cavernous sinus, among the vessels of the carotid rete.

Paradoxical sleep. At ambient temperatures between 20 and 25° C we observed thirty-five periods of paradoxical sleep, identified by the presence of cortical e.e.g. desynchronization, loss of tone in the neck muscles, and twitching of the eyes and facial musculature (D. Jouvet & Valatx, 1962; M. Jouvet, 1967). Vasoconstriction of the nasal mucosa and the ear skin and elevation of hypothalamic and other brain temperatures occurred during paradoxical sleep (Figs. 3 and 4). The mean duration of the paradoxical sleep episodes was 4·1 min (range, 1·5–7 min). The mean rise in cerebral arterial temperature during paradoxical sleep was 0·64° C (0·25–1·25° C) and the mean rise in central arterial temperature was 0·10° C (0·05–0·25° C). The concomitant temperature rise in any brain site was dependent upon the degree of thermal inertia of the site (compare preoptic area with septal area in Fig. 3). The reflexion of the large elevation in cerebral arterial temperature by a later, small rise in central arterial

temperature during paradoxical sleep (Fig. 4) suggests that cranial peripheral heat loss is an important factor in the regulation of deep body temperature in sheep.

Feeding and drinking. Arousing stimuli, such as startling or handling the sheep (Fig. 4), showing them food (Baker & Hayward, 1968*a*, see their Fig. 2) or feeding them also resulted in vasoconstriction of the nasal mucosa and a rise in cerebral arterial temperature. On five occasions, we recorded blood and brain temperatures of sheep during feeding. When the animal saw the food, there was a drop in temperature on the nasal mucosa and a

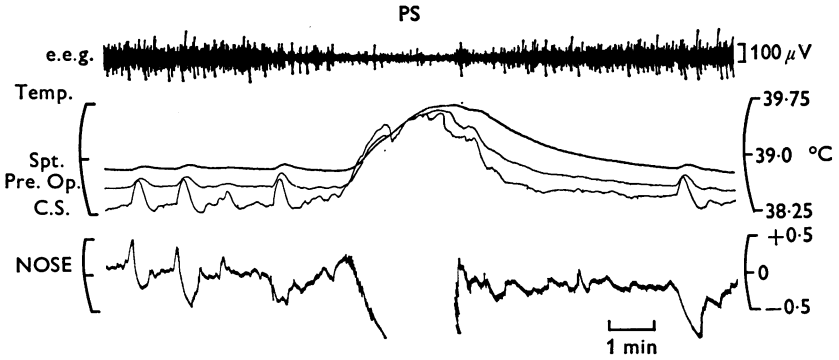

Fig. 3. Peripheral cranial vasoconstriction and intracranial temperature rise during paradoxical sleep in a sheep (no. 5). Ambient temperature 25° C. The animal is recumbent throughout the recording. During the episode of paradoxical sleep (PS), the cortical e.e.g. is desynchronized, vasoconstriction of the nasal mucosa occurs, and intracranial temperatures rise. Notice the rise in temperature in the cavernous sinus (C.S.) and the reflexion of this rise, with different degrees of thermal inertia, in the preoptic region and the septal region. Labels: e.e.g., biparietal cortical electroencephalogram; Spt., septal region, 10 mm from the basal subarachnoid space; Pre. Op., preoptic region, 4 mm from the basal subarachnoid space; C.S., in the cavernous sinus, among the vessels of the carotid rete; NOSE, anterior nasal cavity, on the nasal mucosa.

sharp rise in temperature at the carotid rete, at the circle of Willis, and in the brain. When it began to feed, intracranial temperatures remained elevated and central arterial temperature rose steadily during the feeding period. If the food were taken away, cerebral arterial blood and brain temperatures dropped when the animal began to relax, and central arterial temperature dropped gradually. The temperature elevation in the central arterial blood during feeding was the largest change we observed in deep body temperature in our sheep at neutral thermal environments. A rise in central blood temperature during feeding has been reported previously in the sheep (Mendel & Raghavan, 1964) and the ox (Findlay & Ingram, 1961).

Our animals were usually deprived of water during the recording periods,

but we recorded temperatures during drinking in eight experiments. When the sheep drank cool water, there was an immediate drop in temperature in the central arterial blood, the size of which was determined by the amount of water and its temperature. In some cases, the central arterial temperature drop was reflected by a similar temperature drop in the cerebral arterial blood, but in other cases there was no related thermal change in cerebral arterial blood.

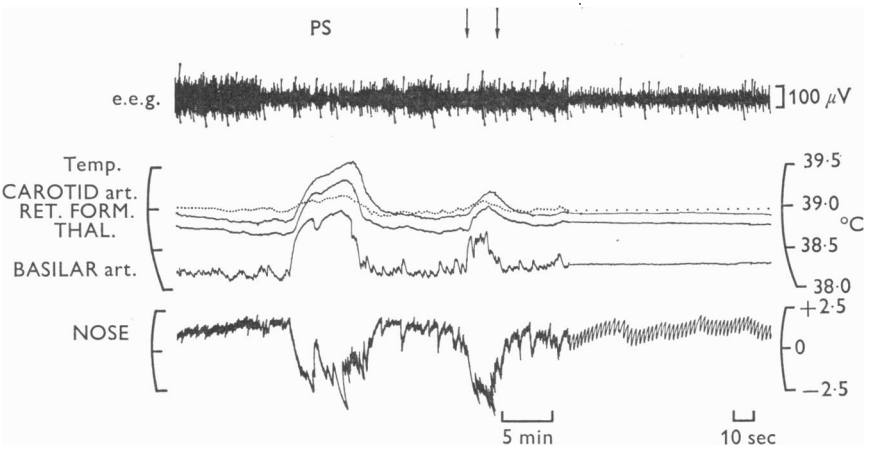

Fig. 4. Intracranial and extracranial temperature changes during sleep and arousal in a sheep (no. 4) at 25° C ambient temperature. Notice the vasoconstriction of the nasal mucosa and rise in cerebral arterial blood and brain temperatures during paradoxical sleep (PS) and arousal (arrows). The sheep was lying down throughout the recording, and between the arrows the door of the recording chamber was opened and the animal was touched by the experimenter. There is little correspondence between the temperatures of the central (dotted) and the cerebral arterial blood, except for the slight reflexion of prolonged cerebral arterial temperature changes in the central arterial blood. Basilar arterial blood has traversed the carotid rete, for blood flows caudally in the basilar artery of sheep (Baldwin & Bell, 1963). Labels: e.e.g., biparietal cortical electroencephalogram; CAROTID art., patent common carotid artery, at its origin from the bicarotid trunk; RET. FORM., mid-brain reticular formation, 14 mm from the basal subarachnoid space; THAL., massa intermedia of the thalamus, 8 mm from the basal subarachnoid space; BASILAR art., at the rostral basilar artery, in the basal subarachnoid space; NOSE, nasal cavity, on the nasal mucosa.

Effects of anaesthesia and nasal air flow on hypothalamic temperature

In the conscious sheep, two types of temperature oscillations occur in the cerebral arterial blood and in the hypothalamus and other brain stem regions. These are (1) the rapid, usually small temperature changes, having a period of about 30 sec, which occur almost continuously in the relaxed, recumbent animal (Figs. 2–4) and (2) the large, prolonged temperature changes associated with arousal, paradoxical sleep, and changes in posture

(Figs. 2–4). Anaesthetic doses of barbiturate abolish both types of temperature shifts. On five occasions, we administered 15–25 mg sodium pentobarbitone/kg intravenously to two sheep, injecting through a long tube from outside the recording chamber when the animals were lying down at 20° C ambient temperature.

Immediately following the injection the temperatures of the cerebral arterial blood and the brain became steady. There was usually a slight rise in all intracranial temperatures and in the central arterial blood temperature. Respirations became deep and regular. There were no changes in the temperature gradients between the cerebral arterial blood and the brain in these experiments. Hayward & Baker (1968) have observed a decrease in brain–blood temperature gradients in spontaneously breathing monkeys under deep barbiturate anaesthesia, due to respiratory depression, increased arterial P_{CO_2} and increased flow of cool blood through cerebral structures (Hayward, 1967).

In order to demonstrate that the evaporative surface of the nasal mucosa was an important source of the cool venous blood draining to the cavernous sinus to bathe the carotid rete, we conducted twenty experiments in two anaesthetized sheep in which room air at 25° C was blown into one nostril through a tube (i.d. 1 cm) inserted into the external nasal meatus and directed at the maxillary turbinates and nasal septum. A Harvard respiration pump, at 750 ml./stroke and 50 strokes/min was used to provide a high, intermittent rate of air flow.

We found that the onset of the high rate of air flow over the nasal mucosa was followed immediately by a drop in temperature at the carotid rete in the cavernous sinus, at the basal cerebral arteries, and in the brain stem, with a slight drop in central temperature in the longer experiments. Figure 5*A* shows two typical experiments. The size and rapidity of the temperature drop in any brain site was related to the thermal inertia of the site and the size of the temperature drop in the cavernous sinus. In seven experiments in one animal, in which air was blown into the right nostril for 1 min, the mean temperature drop in the right cavernous sinus was $1{\cdot}00 \pm 0{\cdot}31°$ C and in the left cavernous sinus was $0{\cdot}58 \pm 0{\cdot}38°$ C. Preoptic temperature fell $0{\cdot}46 \pm 0{\cdot}16°$ C, septal temperature fell $0{\cdot}27 \pm 0{\cdot}05°$ C and the temperature of the massa intermedia of the thalamus fell $0{\cdot}17 \pm 0{\cdot}05°$ C. There was no change in central arterial temperature. In two experiments lasting 5 min, a drop of 2° C occurred in the cavernous sinus of the same side, and central arterial temperature dropped 0·11° C. The cavernous sinus of the same side always showed a greater temperature drop than the opposite cavernous sinus when air was blown into one nostril. Deep brain sites 2–3 mm off the mid line showed a greater temperature drop when air was blown into the nostril of the same side than when it was blown into the

opposite nostril. Blowing air over the muzzle, the ears, and the top of the head had no effect on intracranial temperatures. Hunter & Adams (1966) reported a fall in hypothalamic temperature in the cat when air was drawn over the upper respiratory tract, but these investigators attributed the drop in brain temperature to direct coooling of the hypothalamus through the roof of the nasopharynx. We suggest that their observations in the cat were produced by the cooling of the cerebral arterial blood in the carotid rete by venous blood from the nasal mucosa.

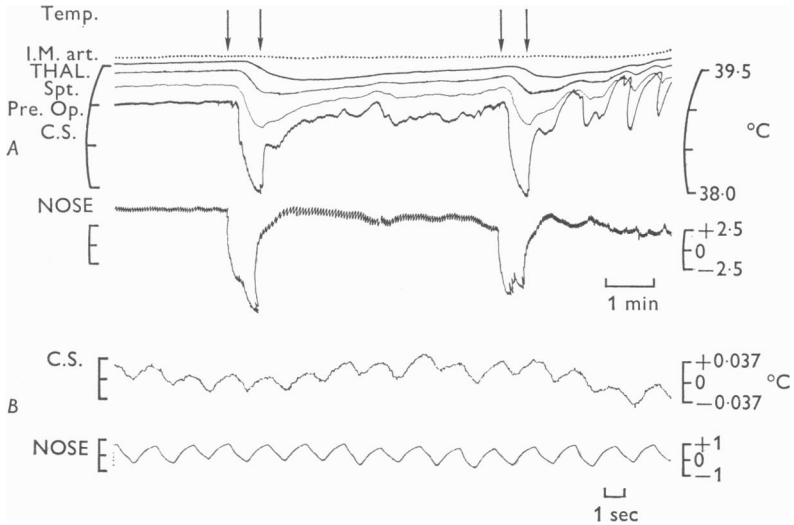

Fig. 5. The influence of upper respiratory evaporation on intracranial temperatures in an anaesthetized sheep (no. 6). *A*. Between the arrows, room air was blown into the right nostril with a Harvard respiration pump. Notice the fall in temperature in the right cavernous sinus, followed by temperature drops in the preoptic region, the septal region, and the thalamus, with varying degrees of thermal inertia. The increased upper respiratory evaporation has no effect on central arterial temperature (I.M. art., dotted). Cerebral arterial blood temperature (C.S.) is steady in the anaesthetized animal. At the end of the record, the animal begins to awaken, and thermal oscillations appear in the cerebral arterial blood and in the brain. *B*. Respiration-related temperature oscillations in the carotid rete of the same animal on another day. Labels: I.M. art., patent internal maxillary artery, at the angle of the mandible; THAL., massa intermedia of the thalamus; Spt., septal region; Pre. Op., preoptic area; C.S., right cavernous sinus, among the vessels of the carotid rete; NOSE, right nasal cavity, on the nasal mucosa.

In our sheep, when the respiration became deep and regular under anaesthesia, small temperature oscillations synchronous with the respiratory cycle appeared in the cavernous sinus. In one experiment, we amplified these oscillations with a high gain DC amplifier and recorded them simultaneously with nasal temperature, which gives an index of inspiration

and expiration. Inspiration of cool, dry air was accompanied by a fall in temperature in the cavernous sinus, and expiration of warm, moist air by a rise in temperature there (Fig. 5*B*).

Nasal venous drainage to the cavernous sinus

The anatomical basis for the thermal connexions between the nasal mucosa and the cavernous sinus lies in the connexions which exist between the cavernous sinus and the extracranial veins of the head. Our latex injections demonstrated a large venous pathway from the anterior portion of the nasal mucosa to the cavernous sinus via the dorsal and lateral nasal veins, angular vein, supraorbital vein and ophthalmic veins. Coloured latex injected distally into the angular vein entered the nasal cavity through the dorsal and lateral nasal veins and filled the superficial venous plexuses of the nasal mucosa (Dawes & Prichard, 1953) of the same side over the dorsal and ventral maxillary turbinates, the lateral wall and median septum, and portions of the ethmoturbinate. Latex injected centrally into the angular vein entered the supraorbital vein, which traverses the supraorbital canal and anastomoses with the ophthalmic veins in the back of the orbit, and filled the cavernous sinuses bilaterally. While these injection studies demonstrated one pathway for nasal venous drainage to the cavernous sinus, it is likely that the ethmoidal and sphenopalatine veins, which also drain the nasal mucosa in sheep (Dawes & Prichard, 1953), are also connected to the cavernous sinus. In man, these veins communicate with the cavernous sinus via the ophthalmic veins and the pterygoid venous plexus, respectively.

Thermal polypnoea and intracranial vascular heat exchange

In the relaxed sheep in a neutral thermal environment, heat exchange in the carotid rete cools arterial blood entering the cranial cavity. The brain of the sheep is thus cooler, with respect to the body, than are the brains of those animals in which no rete is present. Sheep have been reported to be able to withstand high rectal temperatures without gross behavioural disturbances better than many other mammals (Lee, 1950). Since the prevention of cerebral overheating is a most important aspect of thermoregulation in a hot environment, it appeared to us that the sheep, with its cool brain, might be in an advantageous position to withstand heat stress.

We subjected four of our chronically prepared animals to heat stress on twenty-three different days. In each heating experiment, blood and brain temperatures were monitored for 1–2 hr at ambient temperatures of 20 or 25° C, and then the temperature of the recording chamber was raised to 45 or 50° C and held there for 1 or 2 hr. The animals' temperatures were

recorded continuously. The rise in chamber temperature took from 45 to 50 min. Relative humidity was 20–40 % during heating. Respiratory rate of the isolated animal was counted by observation through the one-way glass, using a stop-watch. It was difficult to determine the rate of breathing when the animal was active or when it was nibbling at the chamber, and the observations of respiratory rate were made whenever the behaviour of the animal allowed it. These observations were necessarily approximate when the rates exceeded 200/min.

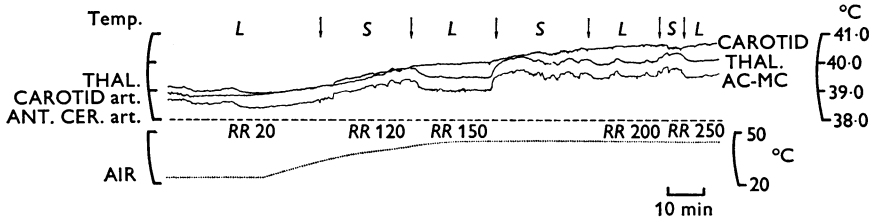

Fig. 6. Progressive dissociation between central arterial temperature and cerebral arterial temperature during thermal polypnea in a sheep (no. 3). This is a typical record selected from twenty-three experiments on four sheep. The arrows indicate a change in position. *L* is lying and *S* is standing. Brain temperature changes are reflexions of cerebral arterial temperature changes. The temperature gradient between the central and the cerebral arterial blood increases throughout the period of heating, as respiratory rate (*RR*) increases. Labels: THAL., anterior nucleus of the thalamus; CAROTID art., patent common carotid artery, at its origin from the bicarotid trunk; ANT. CER. art., at the junction of the anterior cerebral and middle cerebral arteries, lateral to the optic chiasm, in the basal subarachnoid space; AIR, temperature of the air in the recording chamber (dotted line). The dashed line at 38·0° C is a horizontal reference line.

The temperature dissociation between central and cerebral arterial blood, which is present in sheep in a cool environment, was accentuated in the heat. Cerebral arterial blood and brain temperatures reflected the behaviour of the animals, and were higher when the sheep were standing than when they were recumbent (Fig. 6). During heating, the central arterial blood temperature rose steadily, and tended to stabilize after 1½–2 hr in the heat. Cerebral arterial blood and brain temperatures also rose, but they rose less than central blood temperature, and the temperature gradient between central and cerebral arterial blood thus was increased during heating. In eighteen experiments, the mean temperature of the central arterial blood increased from $39{\cdot}00 \pm 0{\cdot}31°$ C during the control period to $40{\cdot}10 \pm 0{\cdot}58°$ C after 120 min of heating. The cerebral arterial blood temperature rose from $38{\cdot}48 \pm 0{\cdot}26°$ C to $39{\cdot}14 \pm 0{\cdot}46°$ C over the same period of time. The rise in central arterial temperature was significantly different from the rise in cerebral arterial temperature ($P < 0{\cdot}05$) over this time period. Table 2 shows the temperature gradients

between central and cerebral arterial blood and the respiratory rates in individual animals during heating. The values in the table represent measurements in recumbent animals; when the sheep were not lying down at the hourly intervals selected for measurement, the nearest period of lying was used. In every heating experiment, the temperature gradient between central and cerebral arterial blood increased as the environmental

TABLE 2. Temperature gradients between central arterial blood and cerebral arterial blood and respiratory rates in recumbent* sheep during heat stress

				Minutes of heating‡					
		Control†		60		120		180	
Animal	Experiment	T_A–T_{CAB}§	*RR*‖	T_A–T_{CAB}	*RR*	T_A–T_{CAB}	*RR*	T_A–T_{CAB}	*RR*
3	1	0·75C	35	0·90C	160	1·10C	—	—	—
	2	0·75	40	1·10	140	1·10	180	—	—
	3	0·25	20	0·50	150	1·00	200	—	—
	4	0·30	22	0·40	200	0·90	—	—	—
4	1	0·50	50	0·55	170	0·75	210	—	—
	2	0·40	30	0·60	—	0·65	200	0·75C	280
	3	0·50	25	0·50	180	0·70	200	—	—
	4	0·70	35	0·75	—	0·95	190	0·85	—
5	1	0·65	30	1·00	130	1·10	—	1·00	250
	2	0·50	32	0·65	100	0·75	170	—	—
	3	0·65	24	0·70	60	0·60	180	1·00	—
	4	0·50	30	0·60	—	0·85	190	1·00	—
	5	0·50	38	0·75	120	1·05	165	1·25	220
6	1	0·40	35	0·80	160	1·02	190	1·00	—
	2	0·30	60	0·70	200	0·70	250	—	—
	3	0·45	40	0·50	180	0·65	—	0·85	—
	4	0·25	40	0·70	—	0·70	275	—	—

* Measurements were made when the sheep were lying down.

† At 20° C–25° C ambient temperature.

‡ Air temperature was raised to 45° C–55° C over a 50 min period and held there for 1–2 hr.

§ T_A–T_{CAB} is the temperature gradient (*C*) between central arterial blood and cerebral arterial blood.

‖ *RR* is respiratory rate, the number of respirations/min.

temperature was raised and thermal polypnea ensued (Fig. 6). Cerebral arterial blood and brain temperatures were regulated at the lowest levels when the animals lay down and panted regularly and did not nibble or vocalize.

DISCUSSION

Studies of mammalian brain temperature in this laboratory began with the unanaesthetized monkey (Hayward, Smith & Stuart, 1966; Hayward, 1967; Hayward & Baker, 1968), in which the following observations were noted: brain temperature changes were reflexions of temperature changes

in the arterial blood; arterial blood was cooler than the brain and temperatures increased progressively toward the centre of the brain; temperatures at the circle of Willis were the same as temperature in the aorta or common carotid artery. Studies in the rabbit confirmed all of these observations (Baker & Hayward, 1967*a*). The regulation of brain temperature in the cat (Baker & Hayward, 1967*b*) was found to be similar to that in the monkey and the rabbit with a single exception: the temperature of arterial blood in the cat is altered as this blood traverses the carotid rete to enter the cranial cavity. Our preliminary studies in the sheep (Baker & Hayward, 1968*a*, *b*, *c*) demonstrated that, in this species too, the carotid rete acts as a heat exchanger. We wondered how heat exchange could occur in the carotid rete, which lies deep in the head in the cat and inside the cranial cavity in the sheep.

Our measurements of temperature in the cavernous sinus, providing an index of the temperature of the venous blood bathing the rete, demonstrated that the rete was exposed to cool blood the temperature of which was quite variable. The fact that temperature at the circle of Willis is the same as that in the cavernous sinus points to the efficiency of the rete as a heat exchanger. We feel that the nasal mucosa is the most important source of venous blood for heat exchange in the cavernous sinus. Scott (1954) has pointed out that the complex turbinates in many mammals provide an extensive surface area, and Dawes & Prichard (1953) demonstrated the vascularity of the nasal mucosa and the presence of artiovenous anastomoses there. The acceleration of heat exchange across the rete during thermal polypnea indicates that the venous blood in the cavernous sinus must be returning from an evaporative surface. Our experiments in which air blown over the nasal mucosa caused a dramatic temperature drop in the cavernous sinus are further evidence of the importance of the upper respiratory passages in regulating cerebral arterial blood and hypothalamic temperature in sheep. The sensitivity of vasomotor activity in the nasal mucosa to behavioural events suggests that the behavioural state of the animal is an important variable in studies of thermoregulation in artiodactyls.

The cooling of the cerebral arterial blood and brain which occurs in neutral thermal environments and which is accelerated during thermal polypnea in sheep must be advantageous in the prevention of cerebral overheating and may underlie, in part, the high heat tolerance of these animals. Lee (1950) reported that sheep do not develop the 'staggers' (muscular weakness and incoordination) until the rectal temperature reaches 110° F (43·3° C), while mice and rats stagger at a rectal temperature of 107° F (41·7° C). Investigators studying the carotid rete have marvelled at its presence in '. . . species so diverse in their habits as *Felidae*

and *Artiodactyla'* (Daniel *et al.* 1953). The function of the rete as a cranial heat exchanger might shed some light upon its significance, for a rete is often present in heavily furred animals which pant in order to lose heat at high ambient temperatures.

We have concluded from all of our studies that the changes in brain temperature which we observe in conscious mammals are not due to changes in local cerebral blood flow or in local neuronal metabolism, as other investigators have suggested (Serota, 1939; Hammel, Jackson, Stolwijk, Hardy & Strømme, 1963). We have never observed temperature changes in the brains of conscious animals which were not due to changes in temperature of the arterial blood perfusing the brain. Discounting shifts in direct heat exchange between the brain and the environment, the three factors which can cause a change in temperature in a local brain region are as follows: (1) a change in temperature of the arterial blood perfusing the brain; (2) a change in heat production by local neurons or glial cells; (3) a change in local blood flow. These studies in the sheep and our work on the monkey (Hayward & Baker, 1968), rabbit (Baker & Hayward, 1967*a*), cat (Baker & Hayward, 1967*b*) and dog (Hayward, 1968) demonstrate that the major factor producing changes in brain temperature is the temperature of the cerebral arterial blood. The presence of constant brain–blood temperature gradients suggests that heat production and blood flow are not dissociated—that is, that the rate of blood flow, tending to cool the brain, keeps pace with the rate of cellular metabolism, tending to heat the brain. *In vivo* studies of oxygen consumption and blood flow of the whole brain suggest that blood flow in the brain is adjusted to metabolic needs (Lassen, 1959), a suggestion which is supported by the well-known observation that CO_2, a metabolic by-product, is a most potent dilator of cerebral vessels (Sokoloff, 1959).

We have shown that our thermal method can be used to study changes in cerebral blood flow when there is no change in cerebral heat production (Hayward, 1967; Hayward & Baker, 1968). When the cerebral blood flow is increased, a decrease in the brain–blood temperature gradients occurs as the rate of flow of cool blood through cerebral tissues is accelerated. When the cerebral blood flow is decreased, an increase in the brain–blood temperature gradients occurs as the rate of flow of cool blood through cerebral tissues is lowered. In monkeys under deep barbiturate anaesthesia, a condition which produces a major depression of cerebral oxygen consumption and heat production (Sharpless, 1965), there is no change in the brain–blood temperature gradients when arterial P_{CO_2} is held constant. Any change in cerebral heat production will probably result in a simultaneous change in CO_2 production and pH. These metabolic by-products can act on local vessels to change blood flow and heat removal, thereby limiting

any temperature change which may be expected from such neural activity. If the rate of cerebral blood flow is adjusted to the rate of cellular heat production in local brain regions, then only a temporal dissociation of the heat-producing and heat-removing phases would allow thermal detection of changes in these parameters. We have seen no thermal evidence of such a temporal dissociation.

Our studies in sheep lead inevitably to the question of the thermoregulatory role which may be played by hypothalamic thermodetectors in those animals in which hypothalamic temperature is dissociated from deep body temperature. When thermosensitive regions were localized in the anterior hypothalamic region (Magoun, Harrison, Brobeck & Ranson, 1938; Hemingway, Rasmussen, Wikoff & Rasmussen, 1940), it was assumed that they might function in the regulation of deep body temperature by sensing the temperature of the arterial blood flowing from the body core to the brain (Euler, 1961; Hardy, 1961; Bligh, 1966). In the sheep, however, the temperature of the blood perfusing the hypothalamus is influenced not only by deep body temperature but also by evaporation and vasomotor activity on the nasal mucosa and the skin of the head. Large changes in cranial heat loss affect cerebral arterial blood temperature strongly and central arterial blood temperature weakly. Hypothalamic neurones may be exposed to a change in temperature if deep body temperature changes or if cranial vasomotor tone or evaporative heat loss changes.

While a shift in cranial heat loss can produce a large change in hypothalamic temperature, it is of little consequence for the regulation of deep body temperature. On the other hand, a small shift in deep body temperature, which may produce only a small change in hypothalamic temperature, may represent a thermal threat to the animal. We must assume that hypothalamic thermosensitive neurones involved in initiating thermoregulatory responses can distinguish between these two types of local temperature changes. This probably involves integration of the thermal input with a variety of neural inputs, including information from peripheral thermoreceptors (Bligh, 1959), auditory and visual systems, higher cerebral structures, and possibly feed-back from autonomic effectors. The analysis of the activity of individual hypothalamic neurones in conscious animals (Hellon, 1967; Findlay & Hayward, 1968) may provide some insight into the integrative activities of thermoregulatory nerve cells.

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