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SIGNIFICANCE OF CRANIAL CIRCULATION FOR THE BRAIN HOMEOTHERMIA IN RABBITS. II. THE ROLE OF THE CRANIAL VENOUS LAKES IN THE DEFENCE AGAINST HYPERTHERMIA

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Abstract. Chronic experiments were conducted on five freely moving rabbits at ambient temperatures of 0–42°C. The influence of nasal mucosal thermal changes on the venous blood temperature inside the pterygoid plexus and on the temperatures at three intracerebral sites were investigated against the background of the carotid arterial blood temperature shifts. A correlation was found between: (i) the fluctuations in the nasal mucosal temperature reflecting its vasomotor responses, (ii) temperature shifts of the pterygoid plexus venous blood, and (iii) of the ventral brain. Mucosal vasodilatation caused parallel drops in both the plexal blood and brain temperatures. However, mucosal vasoconstriction was accompanied by increases in temperatures at those sites. Intracranial thermal shifts were independent of the arterial blood temperature changes. During motor activity in normothermia nasal mucosal vasoconstriction was present, and in that case brain temperatures exceeded arterial blood temperature. During rest, mucosal vasodilatation appeared and brain base cooled below the arterial blood temperature. During panting in dry heat, the brain base was cooler than the arterial blood by as much as 0.5°C. The intensity of the selective brain cooling was directly proportional to deep body temperature. The blockade of the respiratory evaporation in heat elicited an increase of the plexal venous blood as well as brain temperatures above the arterial blood temperature. We conclude that the venous blood outflowing from the nasal mucosa exerts a cooling influence on the brain through the pterygoid plexus.

INTRODUCTION

According to the opinion of Baker and Hayward (1–4,8) the cerebral arterial blood circulation is the only way of eliminating large excess of metabolic heat from the brain. They found that the arterial blood tem-

perature was by a constant value lower than the temperature of a given point in the brain. Thus the arterial blood fullfils the function of a cerebral cooling fluid. Our previous paper (6), however, has shown that the thermal difference between the rabbit's brain and the internal carotid arterial blood is variable. Furthermore, fluctuations of the brain temperature were found to be correlated with the nasal mucosal vasomotor responses. Therefore we concluded that the cooling of the rabbit's brain is effected not only through the mediation of the arterial blood, but also and independently of it, through the venous blood returning from the nasal mucosa. As a result, under certain conditions, the brain base may be cooler than the arterial blood, which represents the average temperature of the trunk core (6). This phenomenon, well known in the animals possessing the carotid rete (1, 3, 4, 8, 11), is termed the selective cooling of the brain. We suggested (6) that this way of brain cooling in rabbits may be based on the heat exchange taking place through the neurocranial bottom between the ventral surface of the brain and the adjacent splanchnocranial venous lakes — the pterygoid plexus and ophthalmic sinus draining blood from the nasal mucosa.

The aim of the present study was to check directly the role of the pterygoid plexus in cooling the rabbit's brain.

MATERIALS AND METHODS

Animals. Experiments were performed on five freely moving rabbits of either sex, weighing 3–4 kg.

Surgery. Under general pentobarbitone anesthesia a stereotaxical implantation of the thermocouple in a glass tube (o.d. 0.4 mm) to the pterygoid plexus was performed. Coordinates: L6, P6, V25 mm. The thermocouple was placed inside a syringe needle, pushed through the brain and through the thin pterygoid bone layer into the plexus. Then the needle was withdrawn. Through the same trephine opening two thermocouples in glass tubes cemented together were stereotaxically lowered into the amygdala (coordinates: L7; P6, V18 mm) and area praesubicularis (coordinates: L6.5, P6, V22 mm) according to the atlas of Monnier and Gangloff (10). Additional thermocouples have been implanted (i) into the anterior hypothalamus, (ii) into mucosa inside the ventral nasal concha, (iii) into mucosa lining the nasal cavity above the central part of the concha, (iv) into respiratory sensor. Subsequently a polyethylene cannula was implanted into the wall of the internal carotid artery. The scheme of implantations is shown in Fig. 1. A detailed description of the surgery can be found in the previous paper (6).

Recordings. The temperatures of the hypothalamus, amygdala, area praesubicularis, carotid arterial blood, venous blood in the pterygoid plexus, and the mucosa lining the nasal cavity were recorded simultaneously with the sensitivity of 0.019°C/mm pen deflection. However, the temperatures of the ear pinnas, mucosa of the ventral nasal concha and environment were recorded with sensitivity of 0.2°C/mm pen deflection. The respiratory frequency and the relative air humidity were also registered. A detailed description of the temperature recording apparatus was supplied in the previous paper (6).

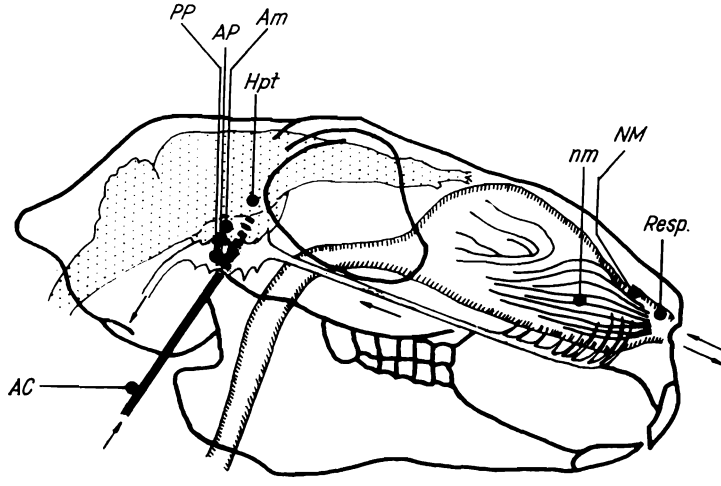

Fig. 1. The scheme of implantation. AC, cannula with thermocouple inserted into the wall of internal carotid artery. Intracerebral thermocouples: AP, area praesubicularis; Am, amygdala; Hpt, hypothalamus. Nasal thermocouples: nm, mucosa of the ventral nasal concha; NM, mucosa lining nasal cavity; Resp., breathing frequency sensor. PP, thermocouple inside the pterygoid plexus draining the venous blood from the nasal mucosa.

Experimental procedures. Altogether 96 chronic experiments were carried out at different ambient temperatures in the range 0–42°C over a period of 6 mo. They were begun at room temperature 20–25°C. After about 1 h the ambient temperature was raised or lowered for 10–30 min and the experiment was continued for another 4–8 h. In 10 experiments at ambient temperature of 40°C, after the animal had reached thermal equilibrium, the air humidity was raised from 30–35% to 95–100%. It was lowered to the initial value when the brain temperature approached 42°C, and the experiment was continued for the next 1–2 h in dry heat.

The localization of the implanted elements was checked histologically.

RESULTS

Influence of the pterygoid plexus blood temperature on the brain temperature in normothermia. Changes of the pterygoid plexus venous blood temperature in normothermia were recorded in 44 experiments. Shifts of the nasal mucosal temperature were clearly reflected by changes of the pterygoid plexus venous blood temperature (Fig. 2). Each increase of the former (due to dilatation of the mucosal vessels) was accompanied by the cooling of the pterygoid plexal blood. On the other hand, a decrease of the nasal mucosal temperature, induced by the constriction of its vessels, in each case elicited the warming of the plexal blood. The plexal temperature was always lower than the brain temperatures. Moreover, changes in the plexal blood temperature were always followed by similar shifts in brain temperatures, which were independent of thermal fluctuations of the arterial blood. Figure 2 shows

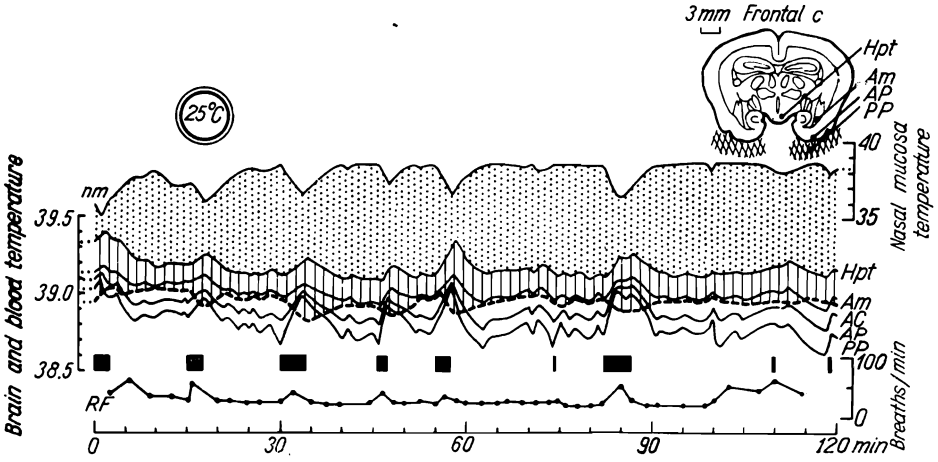

Fig. 2. A fragment of an experimental protocol carried out in room temperature 25°C. Temperature curves: nm, mucosa inside the ventral nasal concha; Hpt, hypothalamus; Am, amygdala; AC, blood of the internal carotid artery; AP, area praesubicularis; PP, pterygoid plexal venous blood; RF, respiratory frequency. Dotted area marks thermal correlation between the nasal mucosa and brain, while verticaly stripped area marks the hypothalamic-arterial blood temperature gradient. Black rectangles, periods of motor activity. Locations of brain thermocouples are indicated in brain frontal cross-section scheme. The outline of pterygoid plexus is shown by crossed area.

typical thermoregulatory responses. Evident thermal gradients increased in the sequence: area praesubicularis, amygdala, and hypothalamus — in relation to the pterygoid plexus blood temperature. Clearly, the brain temperatures increased gradually and proportionally to the distance

from the pterygoid plexus. It can be seen on the scheme of the brain frontal cross section in Fig. 2. In the same direction the inertia, expressed as lag in time and damping of changes in brain temperature augmented in comparison with the plexal thermal changes. Therefore it seems evident that in the normothermic rabbit the brain is cooled by the pterygoid plexal blood. The intensity of this cooling depends on the behavioral state of the animal. During motor activity lasting longer than 1 min (0–3rd min, 15th–18th min, 30th–35th min, 46th–48th min, 55th–58th min, and 83–87th min of the experiment) the pterygoid plexus and brain temperatures rose due to nasal mucosal vasoconstriction, exceeding the arterial blood temperature. In such moments the selective cooling of the brain base through the venous blood returning from the nasal mucosa to the pterygoid plexus was temporarily inhibited. Simultaneously the arterial blood temperature dropped as a result of ear pinnas vasodilatation. The widened brain-arterial blood thermal gradients suggest that brain cooling by arterial blood was intensified at such moments. In a resting animal vessels of the nasal mucosa dilated, which was reflected by a rise in the mucosal temperature. The result was the lowering of the pterygoid plexus temperature, causing a decrease in the brain temperatures to the level of the arterial blood temperature. Thus selective brain cooling was clearly noticeable.

In the above experiments the respiratory rate was relatively low. During rest it stayed at a level of about 25/min, but in certain periods of behavioral arousal with motor activity it increased slightly up to 60/min.

Influence of the pterygoid plexus blood on the brain temperature in hyperthermia. Forty two experiments were performed. In dry heat the selective brain cooling through the pterygoid plexal blood was in each case strongly enchanced. During the initial part of the experiment presented in Fig. 3, at ambient temperature of 25°C, the selective brain cooling was weakly pronounced. The pterygoid plexal blood was only insignificantly colder than the arterial blood. Yet the temperature of area praesubicularis, amygdala, and hypothalamus was higher than that of the arterial blood by 0.05–0.10°C, 0.10–0.25°C, and 0.25–0.35°C respectively. During that period the fluctuations of the pterygoid plexal blood and brain temperatures were elicited by the nasal mucosal vasomotor responses, just as in the experiment presented in Fig. 2. The respiratory rate stayed at a level of about 60/min.

The elevation of ambient temperature up to 42°C caused panting, which persisted to the end of the experiment. During the period between the 45th and the 80th min of the experiment the respiratory rate increased eightfold (from 60 to 475/min). Simultaneously the nasal mu-

cosa cooled from 38.5 to 37°C, probably due to increased respiratory evaporative heat loss from its surface. In the later part of the experiment the mucosal temperature remained at the lowered level. The frequent oscillations of the nasal mucosal temperature paralleled the breathing frequency shifts and reflected rapid changes in the rate of respiratory evaporation. Such steep shifts were not put into the respiratory frequency trace for clarity. Nasal mucosal temperature shifts

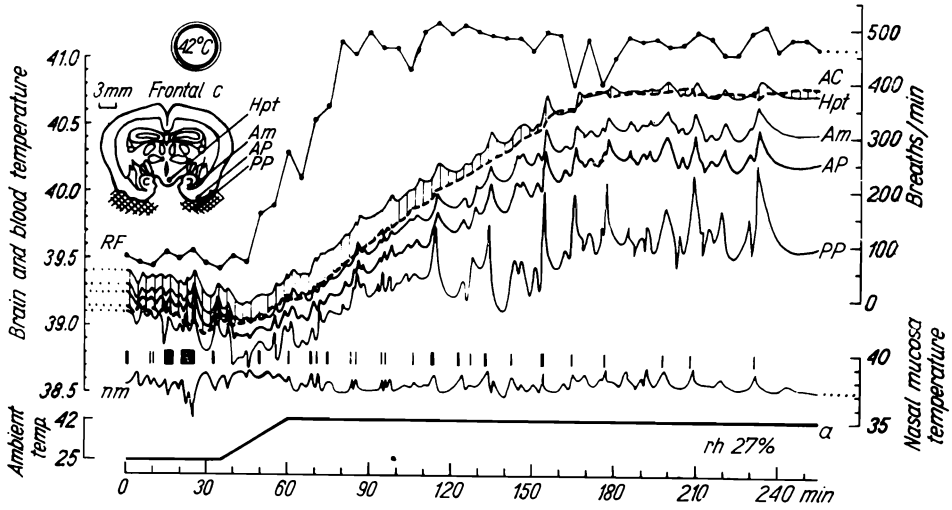

Fig. 3. A fragment of an experimental protocol carried out during transition from moderate temperature (25°C) to dry heat (42°C) and 27% relative humidity (rh), and in the heat stress condition. For remaining designations see previous Figures.

were in turn followed by parallel thermal changes in the pterygoid plexus blood and brain base — area praesubicularis, amygdala, and hypothalamus. The multiple and rapid increases of the mucosal, plexal blood and brain temperatures appeared only during periods of motor activity, which were always accompanied by a slow-down and arrhythmia of breathing, i.e., a cessation of panting. This shows that the respiratory evaporative cooling evidently weakens in rabbits during exercise. On the other hand, if the animal was in recumbent position during panting, the temperatures of the nasal mucosa, pterygoid plexus and brain decreased, and simultaneously the selective brain cooling intensified. A substantial increase of the deep body temperatures (cerebral, arterial) during the initial period of exposure to heat was elicited by frequent exercises. In the 155th min of the experiment, when the animal's motor activity was reduced, the temperatures of the pterygoid plexal blood, area praesubicularis, amygdala, and hypothalamus stayed at the level of: 39.65, 40.25, 40.45 and 40.75°C respectively. The arterial blood thermal equilibrium,

however, was not reached until the 175th min of the experiment, at a level of 40.75°C. At that time the arterial blood and hypothalamic temperatures were equal, but the temperatures of amygdala, area praesubicularis and plexal blood were lower by 0.3, 0.5, and 1.1°C respectively. Thus the increase of the arterial blood temperature proved by this experiment was higher by about 0.3, 0.5, 0.6 and 1.0°C than the rise of temperatures of the hypothalamus, amygdala, area praesubicularis and the plexal blood respectively. Moreover, the intracranial thermal gradients were significantly augmented during heat exposure.

Effect of respiratory evaporation blockade on the selective brain cooling. To eliminate heat loss from the nasal mucosa, the animals were exposed to saturated water vapor during heat stress. Saturated water vapor was introduced to the experimental chamber when steady state of brain temperature had been reached. This occurred usually in the 2nd or 3rd h of exposure to dry heat. During the initial half-hour phase of the experiment presented in Fig. 4 the animal was exposed to 40°C

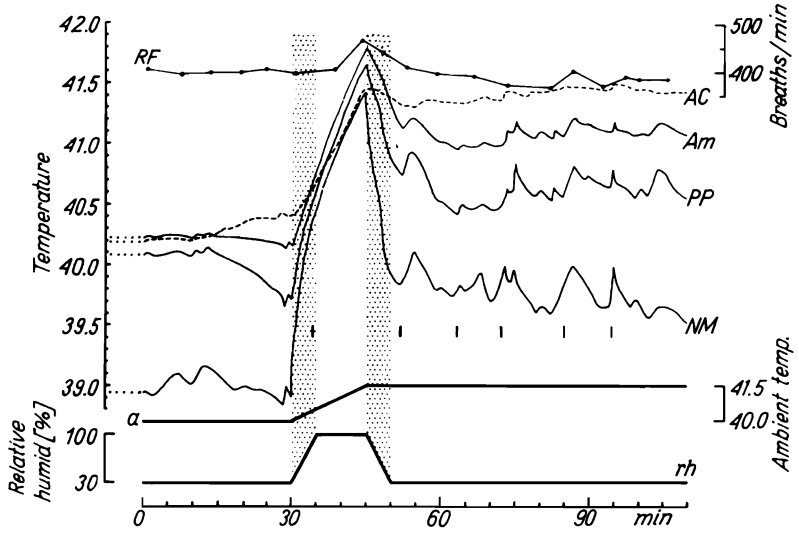

Fig. 4. A fragment of an experimental protocol showing a reversible break-down of rabbit brain thermoregulation in heat stress by saturated water vapor. Humid phase of the experiment is marked by dotted columns. For remaining designations see previous Figures.

ambient temperature and 30% relative air humidity, which caused panting with a frequency of 400/min. The arterial blood temperature gradually rose and the temperature of amygdala remained steady due to intensified selective brain cooling through the nasal mucosa and pterygoid

plexal blood. Just before air humidity was raised the temperatures of amygdala, pterygoid plexal blood, and nasal mucosa were lower than that of the arterial blood by 0.25, 0.7, and 1.5°C respectively. The increase of the relative air humidity up to 100% (30–35 min of the experiment) elicited an abrupt rise in the deep body (brain and blood) temperatures. In the humid phase of the experiment the ambient temperature was raised as the deep body temperatures increased. The saturated water vapor together with the lack of thermal gradient from the body to the environment allowed to eliminate entirely the heat loss from the nasal mucosa by dry means as well as by evaporation. Consequently, the nasal mucosal temperature increased abruptly reaching the arterial blood temperature level. The pterygoid plexus and amygdala temperatures, however, exceeded the arterial blood level by 0.2 and 0.35°C respectively. This may have been due to steadily intense cerebral metabolism, producing heat which had to cumulate under such conditions. In the hot humid air the thermal gradients between amygdala, pterygoid plexal blood, and nasal mucosa were reduced five times. Between the 45th and the 50th min of the experiment air humidity was decreased to the initial level, but the environmental temperature was maintained at 41.5°C to the end of the experiment. The restoration of respiratory evaporation elicited abrupt cooling of the nasal mucosa by 1.6°C for 6 min, in spite of the evidently high ambient temperature. Simultaneously, the pterygoid plexal blood and amygdala cooled by 0.9 and 0.7°C respectively. Arterial blood, on the other hand, cooled only by 0.15°C. It is particularly interesting to note that the pterygoid plexal blood and amygdala were once again cooler than the arterial blood. The motor activity in the 52nd, 72nd, 85th and 93rd min of the experiment elicited parallel but temporary rises in the temperatures of the nasal mucosa, pterygoid plexal blood and amygdala. But in general, from the 55th min an evident fall of the temperatures at those sites began, selectively in relation to the arterial blood. Till the end of the experiment temperatures of the amygdala and pterygoid plexus blood remained lower than the arterial blood by about 0.3 and 0.8°C respectively. Saturated vapor caused similar effects in nine other experiments of that series.

Regulation of intensity of the selective brain cooling. It is evident from the data of Figs. 3 and 4 that the selective brain cooling is enhanced strongly in the hyperthermic rabbit during exposure to dry heat. In order to define accurately the correlation between deep body temperatures and intensity of the selective brain cooling, the averaged values of the brain–arterial blood, and pterygoid plexus–arterial blood temperature differences were compared with the corresponding arterial blood temperatures. The data are presented in Fig. 5. Those differences have

positive values at the lowest possible values of the arterial blood temperature (left side of the Figure). However, in hyperthermia induced by dry heat (right site of the Figure) those differences have negative values. Therefore, the selective brain cooling is weakest at arterial blood temperature below 39°C. Under such conditions the brain base temperature in the area praesubicularis, amygdala, and hypothalamus was higher

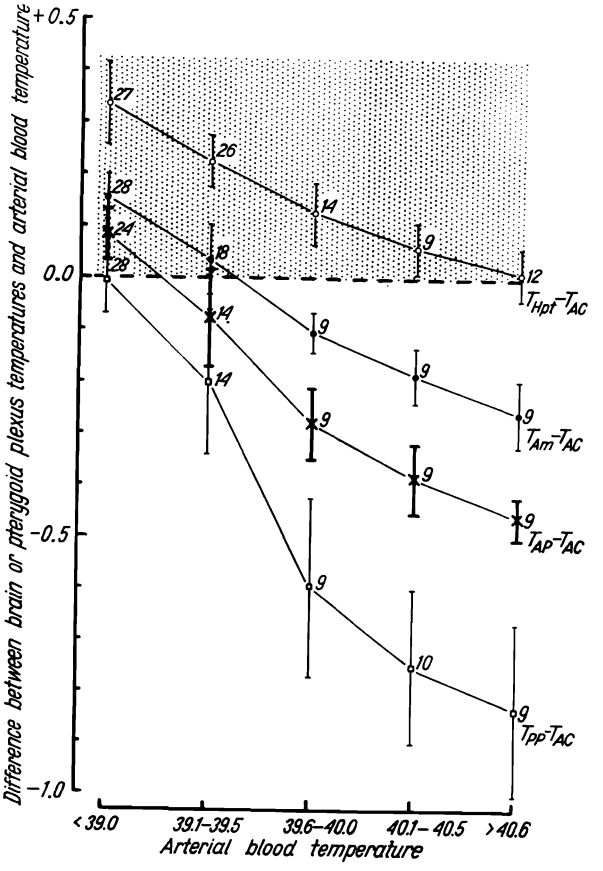

Fig. 5. Changes of average values (with double standard deviations) of temperature differences between: (i) hypothalamus and arterial blood (T_{Hpt}–T_{AC}), (ii) amygdala and arterial blood (T_{Am}–T_{AC}), (iii) area praesubicularis and arterial blood (T_{AP}–T_{AC}), (iv) pterygoid plexal blood and arterial blood (T_{PP}–T_{AC}), as a function of arterial blood temperature — on the abscissa. On the ordinate, temperature scale to show values of temperature gradients. 0.0, reference level of arterial temperature for every temperature gradient. Numbers by each vertical symbol denote amount of measurements in a thermal steady state of the rabbit. The shaded field at the top shows that intracranial sites were warmer than arterial blood, while those below — that they were cooler.

than that of the arterial blood by 0.08, 0.15, and 0.34°C respectively. On the other hand, the selective brain cooling is most intensive when the arterial blood temperature exceeds 40.6°C. Then the area praesubicularis and amygdala were colder than the arterial blood by 0.46 and 0.26°C respectively, whereas the hypothalamus was warmer, but only by 0.01°C. It follows that with regard to the increase in arterial blood temperature, the temperatures of area praesubicularis, amygdala, and hypothalamus were stabilized respectively by 0.54°C (0.08° + 0.46° = 0.54°), 0.41°C (0.15° + 0.26° = 0.41°), and 0.33°C (0.34° − 0.01° = 0.33°) more accurately than the blood.

Selective brain cooling weakens gradually with the distance of the measurement site from the pterygoid plexus, i.e., in the sequence: area praesubicularis–amygdala–hypothalamus. Worthy of notice is the gradually increasing separation of curves in Fig. 5, proportional to the increase of arterial blood temperature. It points out to enhanced resistance to selective brain cooling as the difference between the arterial blood and pterygoid venous blood temperature increases. This resistance appears to be elicited by an influx of some amount of heat with the arterial blood flowing into the brain, if the blood is warmer than the brain tissue. A substantial enhancement of the intensity of selective brain cooling occurs when the arterial blood temperature exceeds the level of 39.5°C. (Deflection of curves: T_{PP}–T_{AC}, T_{AP}–T_{AC}, and T_{Am}–T_{AC}).

DISCUSSION

The rabbit's splanchnocranium is surrounded by spacious venous lakes: the pterygoid plexus and ophthalmic sinus, which collect blood returning from the nasal mucosa (7). The mucosal surface is an important effector of heat dissipation in rabbits (9).

The results obtained in this study have shown that the pterygoid plexal venous blood has an important role in determining the temperature of the basal and probably also of other portions of the rabbit's brain. The plexal blood is always cooler than the brain tissue, because it returns from the nasal mucosal cooling area. Thermal oscillations in the plexal blood are produced by changes in the rate of heat loss from the nasal mucosa, and are always followed by parallel oscillations in the brain temperatures. Moreover, the brain temperature grows proportionally to the distance from the pterygoid plexus, and the lagtime of thermal changes extends in the same direction. This suggests that the brain temperature regulation in rabbits depends on uninterrupted removal of a good part of metabolic heat produced by the brain through

the pterygoid plexal, and probably through the ophthalmic sinus blood as well. This mechanism renders possible the selective brain cooling without arterial blood mediation. Therefore it has quite a different nature than that discovered previously in sheep (3, 8), Thomson's gazelle (11), cat (1,8) and dog (4,8).

The intensity of the selective brain cooling in rabbits is dependent on the behavioral state of the animal and on the deep body (cerebral, arterial) temperature. During rest in normothermia the nasal mucosal vessels dilate, respiratory heat loss increases, and brain base temperatures drop below the carotid arterial blood level. During exercise the mucosal vessels constrict as a result of arousal, and the brain temperature increases temporarily above the arterial blood level, due to the decrease of respiratory heat loss. It is a consequence of the drop of the nasal mucosal temperature, because evaporation rate is logaritmically dependent on temperature. There are similar dependences in sheep (3, 8), and cat (1, 8). Selective brain cooling in rabbits increases considerably in hyperthermia, but only in dry heat. Under these conditions the brain base temperatures in the vicinity of the pterygoid plexus may be lower even by 0.5°C than the arterial blood, which shows that in such a case the arterial blood does not exert its cooling influence on the brain, but even hampers the selective cooling carrying additional quantity of heat from the trunk into the brain. Consequently, the selective cooling of the hypothalamic region lying in the immediate vicinity of the arterial circle of Willis clearly arrested. In normothermic rabbit the arterial blood is slightly cooler than the brain. In that case the intracerebral thermal gradients are small (Fig. 5), due to the synergy in the brain cooling by the arterial blood and by the pterygoid plexal venous blood. In the hyperthermic rabbit the intracerebral thermal gradients are doubled (Fig. 5) as a result of antagonistic thermal actions of the arterial blood, which is warmer, and the pterygoid venous blood, which is colder than the brain. It is also interesting to note that the selective brain cooling increases significantly when the arterial blood temperature exceeds the rabbits normothermic level of 39.5°C (Fig. 5). This may be due to generalized thermal stimulation of the cerebral warm thermoreceptors.

In the monkey, cat, dog, and sheep the brain is cooled exclusively by arterial blood (1,3,4,8). Therefore the intracerebral thermal gradients in these species have steady values, irrespective of body temperature. Furthermore, the hypothalamus, lying in the close vicinity of the circle of Willis, is the coolest brain site in these species.

Blocking the respiratory heat loss in the heat stressed rabbit elicits

the vanishing of the selective brain cooling, and a significant narrowing of intracerebral thermal gradients. Simultaneously the brain temperature exceeds that of the arterial blood by 0.2–0.35°C. In our opinion cooling through the pterygoid venous blood effectively prevents brain hyperthermia in rabbits exposed to dry heat. Due to this mechanism of cooling the temperatures of the brain sites lying just above the pterygoid plexus (area praesubicularis, cortex of the pyriform lobe, amygdala, and ventral hippocampus) are maintained at a level 0.6–0.7°C lower than without the respiratory evaporative cooling. It is evident that hyperthermia induces severe disturbance of the brain function (5), and as a consequence desorganizes the animal's behavior.

Cooling the brain of the rabbit through the pterygoid plexal venous blood probably take place through the mediation of the cerebrospinal fluid. Its normal conductivity is undoubtedly greater than that of the neural tissue and it may readily undergo thermal movements. Therefore the whole cerebral cortex would be effectively cooled through the CSF. We have already started experiments to verify this assumption.

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