Cerebral Cooling During Increased Cerebral Blood Flow in the Monkey.* (31788)

JAMES N. HAYWARD (Introduced by Charles H. Sawyer)
Department of Anatomy, UCLA School of Medicine, Los Angeles, and Veterans Administration Hospital, Long Beach, Calif.

Deep cerebral temperatures are higher than arterial blood temperature in unanesthetized homoiotherms, with parallel fluctuations occurring in these temperatures during feeding, sleeping and arousal(1,2). An excellent means of studying the intracranial factors influencing brain temperature, namely local heat production and local blood flow, is to use the cooler arterial blood as a common thermal baseline. In the present experiments I have utilized an unorthodox "heated" thermocouple technique† (3,4) in which I compared the natural heat of the brain with this thermal baseline during alterations in blood flow associated with CO_2 inhalation in the monkey(5).‡

Materials and methods. Thermocouples (copper-constantan, 100 μ wires) were permanently implanted in deep brain sites and in the arterial blood at the arch of the aorta of 7 adult female monkeys *(Macaca mulatta)*. Stainless steel electrodes (EEG) were chronically placed. Silicon rubber tubing was inserted into the right atrium and into the aortic arch. Leads and tubing were carried under the skin for attachment to an elevated cranial platform. Animals were studied in a restraining chair in a thermoregulated chamber over several months. At repeated weekly intervals of several hours each, the trachea was intubated with a plastic tube and ventilation controlled with a pump at 20-25/min with the end-tidal CO_2 adjusted to 4-5%. A rapidly acting infra-red CO_2 analyzer was used. Gallamine triethiodide (3-8 mg/kg) and pentobarbital sodium (5-20 mg/kg) were given in most experiments to obtain full respiratory control. Simultaneous EEG, CO_2, temperature and blood pressure recordings were made on an Offner Type-R ink writing oscillograph, with the temperature being measured with a DC amplifier and an ice-bath reference junction, and the mean arterial blood pressure transduced by a Statham P23 strain gauge that was connected to the intra-aortic cannula by 6 feet of polyethylene tubing that damped pulse oscillations. Thermocouple and electrode positions were determined by gross and histologic examination.

Results. Thermocouples located in identical structures in the right and left cerebral hemispheres measured nearly identical temperatures. Thermocouples located at dissimilar sites in the same hemisphere often measured dissimilar temperatures (Fig. 1). In awake, spontaneously breathing monkeys, brain and blood temperatures showed similar fluctuations(1). Repeated observations over several months revealed that the temperature difference between brain and blood sites was maintained within narrow limits, thus providing a control level to which the thermal effects of changes in cerebral blood flow could be compared.

In artificially ventilated monkeys the spontaneous fluctuations in blood temperature were abolished. By maintaaining the end-tidal CO_2 between 4-5%, brain-to-blood thermal gradients were kept at control values of 0.2-0.5°C. Inhalations of 8-10% CO_2 in air cooled all brain sites, reducing the temperature difference with the arterial blood to 0.08-0.19°C. Changes induced by increased cerebral blood flow began 1 minute after onset of CO_2 inhalation, reached a low point in 4 minutes and continued at this level for the duration of CO_2 exposure, usually for 10 minutes but in some experiments for an hour. Upon return to air breathing, the brain temperatures began to increase in 1 minute and had returned to control levels by 7 minutes (Fig. 1B).

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† The orthodox heated thermocouple technique for qualitative blood flow measurements involves Joule heating of the thermoelement to a precise level above tissue temperature.

‡ Some of these results have been described in abstract form(6).

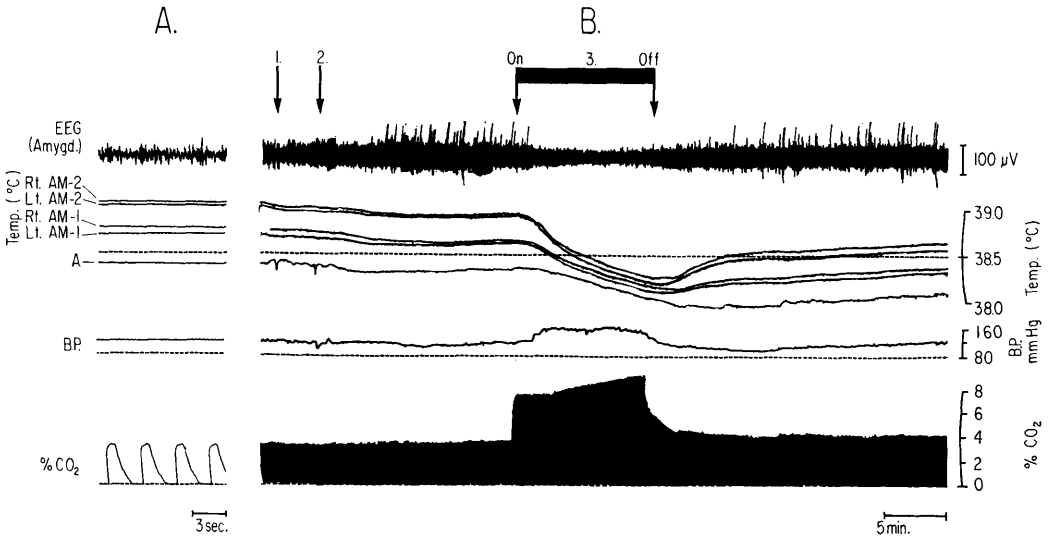

FIG. 1. Cerebral cooling during hypercapnia and increased cerebral blood flow. Air temperature 35°C. A. Fast paper speed. B. Slow paper speed; Arrow at 1, gallamine triethiodide, ("Flaxedil"), 20 mg, i.v.; at 2, pentobarbital sodium, 25 mg, i.v. (total accumulated dose, 10 mg/kg); at 3, breathing 8-10% CO_2 in air from a Douglas bag. Abbrev: EEG (Amygd.), amygdala electroencephalogram; Temp. (°C), temperature, degrees Celsius; Rt. AM-2, right globus pallidus; Lt. Am-2, left globus pallidus; Rt. AM-1, right amygdala; Lt. AM-1, left amygdala; A, arterial blood at the aortic arch; BP, mean aortic blood pressure; $\%CO_2$, percent end-tidal carbon dioxide.

During 3 consecutive weekly experiments in one monkey (Fig. 1), the mean level of right and left globus pallidus-blood temperature gradients for 5-minute periods during spontaneous breathing, during "normocapnia" (4-5% CO_2), and during hypercapnia (8-10% CO_2) were respectively ($\pm$ standard deviations) 0.50°C $\pm$ .05, 0.50°C $\pm$ .04 and 0.19°C $\pm$ .02. Similarly the right and left amygdala-blood temperature differences were respectively 0.25°C $\pm$ .05, 0.24°C $\pm$ .03 and 0.09°C $\pm$ .04. Hypothalamic-blood temperature differences were obtained in 3 other monkeys under conditions similar to those mentioned above, with temperature differences respectively 0.25°C $\pm$ .06, 0.26°C $\pm$ .05 and 0.08°C $\pm$ .05. During hypercapnia all values were statistically significantly different from the control values beyond the 0.01 level of confidence. Hyperventilation lowered the end-tidal CO_2 below 2% and caused an increase in all brain-to-blood temperature differences (Fig. 2). Typical cooling of the blood, lowering of the EEG voltage and elevation of the arterial pressure during hypercapnia are shown in Fig. 1B. Deeper levels of anesthesia modified many of these changes during hypercapnia.

Discussion. An understanding of the normal patterns of cerebral temperature and their relation to local changes in blood flow and heat production in the brain requires a better understanding of the role the arterial blood plays in determining cerebral temperature. One fact not widely recognized is that the arterial blood is cooler than the brain, thereby establishing a temperature difference between the brain and blood and allowing the blood to remove heat from the brain(1,7). Under conditions of increased blood flow the blood lowers brain temperature toward but not below the level of the perfusing arterial blood. A second essential fact is that fluctuations in brain temperature related to various behavioral states are associated with similar fluctuations in blood temperature(1,2). In the study of cerebral temperature it is necessary to measure brain and blood temperatures simultaneously in order to distinguish thermal changes due to warming or cooling of the arterial blood from those thermal changes due to altered neuronal metabolism or local blood flow in the brain.

To what extent the established intracer-

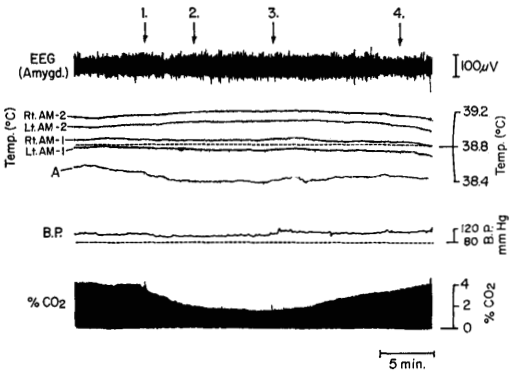

FIG. 2. Brain and blood temperatures during hypocapnia and decreased cerebral blood flow. Air temperature 35°C. Arrow at 1, respiratory rate gradually increased from 20/min to 40/min at 2; between 2 and 3 rate steady at 40/min; between 3 and 4 rate gradually decreased from 40/min to 20/min. Abbrev. as in Fig 1.

ebral temperature gradients are due to local differences in heat production and in blood flow is a problem still to be solved. The present thermal approach gives the algebraic sum of these two factors but does not give any quantitative measure of either blood flow or heat production in the brain. These relationships between cerebral blood flow and ventilation on the one hand, and cerebral and blood temperatures on the other, however, indicate that careful control of these extracranial factors is essential in any study of cerebral temperature in thermoregulatory or behavioral situations(8,9).

Since cerebral oxygen consumption is not appreciably affected by short term inhalation of 8-10% CO_2(5), the lowering of cerebral temperatures during the increased cerebral blood flow associated with hypercapnia is consistent with the concept that the cooler arterial blood serves an essential role in the removal of heat from the brain and in the establishment of intracerebral temperature gradients.

Summary. Temperature measurements were made simultaneously in the arterial blood and in deep brain strctures in 7 chronically prepared rhesus monkeys during both spontaneous ventilation and controlled ventilation. During normal breathing, cerebral temperatures were 0.2-0.5°C higher than the temperature of the arterial blood with identical sites in the right and left cerebral hemispheres showing nearly identical temperatures. During hypercapnia accompanied by increased cerebral blood flow, cerebral temperatures cooled to only 0.1-0.2°C above the arterial blood. During hypocapnia accompanied by decreased cerebral blood flow, brain-blood temperature gradients were increased above control levels. Intracerebral temperature gradients are basically dependent upon the rate of removal of heat from the brain by the arterial blood.

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1. Hayward, J. N., Smith, E., Stuart, D. G., Proc. Soc. Exp. Biol. and Med., 1966, v121, 547.
2. Abrams, R. M., Stolwijk, J. A. J., Hammel, H. T., Graichen, H., Life Sci., 1965, v4, 2399.
3. Gibbs, F. A., Proc. Soc. Exp. Biol. and Med., 1933, v31, 141.
4. Linzell, J. L., J. Physiol., 1953, v121, 390.
5. Kety, S. S., in: Handbook of Physiology, Sect. I. Neurophysiology, V. Hall, ed., Am. Physiol. Soc., Washington, D.C., 1960, 1751.
6. Hayward, J. N., The Physiologist, 1966, v9, 200.
7. McCook, R. D., Peiss, C. N., Randall, W. C., Proc. Soc. Exp. Biol. and Med., 1962, v109, 518.
8. Adams, T., Science, 1963, v139, 609.
9. Hull, C. D., Garcia, J., Gracchiolo, E., ibid., 1965, v149, 89.

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