ulins and complement, show a swelling after about 20 minutes affecting differently most, but not all, of the cells. This observation and the points mentioned above suggest that the action of antibodies is not always evident, in animal cells, as an "all or none" reaction.

The results presented here suggest that the metabolic changes observed after antibody action are not the consequence of a direct action on a given enzymatic system and that the study of glucose metabolism in cells submitted to antibody action is not always a useful indication of the cytotoxic effect of the latter.

Summary. The O_2 consumption of PF and KB cell suspensions cultivated *in vitro* and of Walker rat tumor and liver cells incubated with immune gamma globulins and complement, remains unchanged, while lactic acid production in aerobiosis by Walker tumor and liver cells, as a consequence of the action of anti-Walker gamma globulins and complement, shows a decrease. On the contrary, in the presence of specific antibodies and complement, an enhancement of aerobic glycolysis occurs in KB cells, while in PF cells no change is observed. It is suggested that some enzymatic systems may exhibit a different sensitivity to the altered metabolic exchanges occurring as a consequence of immune globulin adhesion to the cell surface.

1. Kalfayan, B., Kidd, J. D., *J. Exp. Med.*, 1953, v97, 145.

2. Miller, D. G., Hsu, T. C., *Cancer Res.*, 1956, v16, 306.

3. Flax, M. H., *ibid.*, 1956, v16, 774.

4. Goldberg, B., Green, H., *J. Exp. Med.* 1959, v109, 505.

5. Sugai, Y., Aizawa, K., *Nihon Univ. Med. J.*, 1959, v18/7, 1727.

6. Bickis, I. J., Quastel, J. H., Vas, S. I., *Cancer Res.*, 1959, v19, 602.

7. Defendi, V., Colter, G. S., *J. Nat. Cancer Inst.*, 1959, v23, 411.

8. Landy, M., Michael, J. G., Trapani, R. J., Achinstein, B., Woods, M. W., Shear M. J., *Cancer Res.*, 1960, v20, 1279.

9. De Gregorio, P., Terranova, T., Sabbatino, M., *Arch. Sci. Med.*, 1959, v108, 1.

10. McAllister, R. M., Grunmeier, P. W., Carriel, L. L., Marshak, R. R., *J. Nat. Cancer Inst.*, 1958, v21, 541.

11. Ellem, K. A. O., *Cancer Res.*, 1958, v18, 1179.

12. Green, H., Fleischer, R. A., Barrow, P., Goldberg, B., *J. Exp. Med.*, 1959, v109, 511.

13. Stambuk, B., Burk, D., *J. Nat. Cancer Inst.*, 1961, v26, 681.

14. Hanks, J. H., Wallace, R. E., PROC. SOC. EXP. BIOL. AND MED., 1949, v71, 196.

15. Umbreit, W. W., Burris, R. H., Stauffer, J. F., *Manometric Techniques and Tissue Metabolism*, Burgess Publ. Co., Minneapolis, 1951.

16. Barker, J. B., Summerson, W. H., *J. Biol. Chem.*, 1941, v138, 535.

17. Koch, F. C., Hanke, M. E., *Practical Methods in Biochemistry*, Williams & Wilkins Co., Baltimore, 1948.

18. Bucher, T., *Biochim. Biophys. Acta*, 1947, v1, 292.

19. Terranova, T., *Biochim. Appl.*, 1959, v6, 235.

20. Terranova, T., Feo, F., *Lo Sperimentale*, 1961, v111, 11.

Received September 19, 1961. P.S.E.B.M., 1962, v109.

Hypothalamic Temperatures and Blood Flow.* (27254)

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It is generally assumed that the hypothalamus is warmed by the arterial blood which perfuses it(1,2). This belief is associated with the concept that changes in hypothalamic temperature, and resultant thermoregulatory discharges from it, are dependent upon changes in the temperature of the perfusing arterial blood supply. However, it is well known(3) that the metabolic heat production of a unit mass of gray matter in the central nervous system is greater than that of most

* Support for this research has come from the following sources: Chicago Heart Assn. and from Nat. Inst. of Health grant.

TABLE I. Temperature Gradients between Anterior and Posterior Hypothalamus.

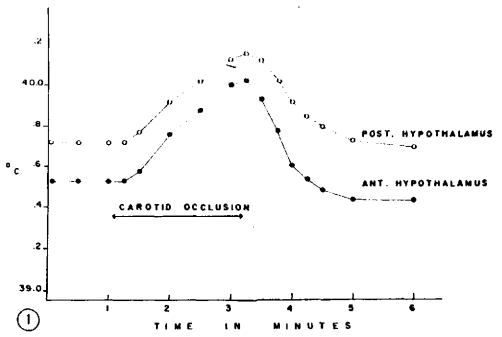
Cat No.	Hypothalamic temperature, °C Anterior	Posterior	ΔT
104	33.91	34.02	.11
105	38.00	38.20	.20
106	39.61	39.78	.17
111	39.71	39.85	.14
112	39.34	39.47	.13
113	38.30	38.42	.12
114	36.98	37.13	.15
Mean ΔT = .15°C		S.E. = .006°C	

tissues. The insulation of the brain by the relatively avascular bony cranium provides a limited heat loss by conduction and convection(4). Therefore, the temperature of the brain, and specifically the hypothalamus, should be determined by its rate of heat production and by the blood flow passing through it.

By use of small thermistors in 22 gauge needles or in fine polyethylene catheters, accurate measurements have been made of temperatures in the hypothalamus and in arterial blood in 9 cats under Sernyl† anesthesia. Temperatures were recorded by means of a bridge circuit and sensitive optical galvanometers. The probes are capable of detecting a change in temperature of 0.02°C. The hypothalamic temperatures were always recorded from probes inserted at identical stereotaxic coordinates, with the anterior probe at A14 and the posterior probe at A8(5). In all cases the probes were 1.5 mm to the right of the midline and 6 mm above the interaural line.

A consistent finding in these experiments was that posterior hypothalamic temperature was always higher than anterior hypothalamic temperature (Table I). If arterial blood actually warms the hypothalamus, total occlusion of the blood supply to the brain should result in a fall in these hypothalamic temperatures. Within 15-20 seconds following bilateral carotid occlusion (vertebrals intact), both anterior and posterior hypothalamic temperatures rose continuously for 2 minutes, reaching a maximum approximately 0.5°C higher than the pre-occlusion control

† The Sernyl was generously furnished by Parke Davis Co.



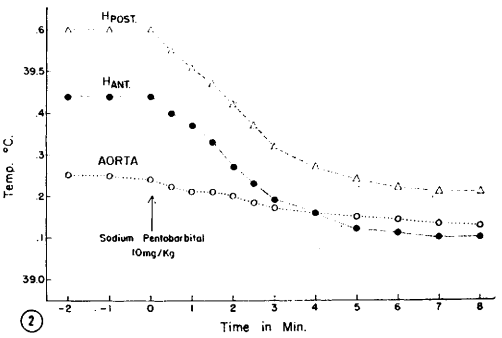


FIG. 1. Effect of bilateral carotid occlusion on temperatures in anterior and posterior hypothalamus of the cat.

FIG. 2. Effect of sodium pentobarbital on temperatures in anterior and posterior hypothalamus and in aorta.

level (Fig. 1). The extent and slope of the temperature rise would, of course, be greater if the vertebral arteries were also occluded. The slope of both curves was steeper following release than during occlusion. Since the slope of the temperature rise in the posterior hypothalamus following occlusion was not greater than that in the anterior hypothalamus, it is improbable that the higher posterior hypothalamic temperatures were due to greater heat production. It is more likely that this part of the hypothalamus has a lesser blood flow than the anterior hypothalamus. This is supported by the more rapid decline in anterior hypothalamic temperature following release of occlusion, and by anatomical evidence based on capillary counts which indicate a greater vascularity in the anterior hypothalamus(6).

It is quite clear, therefore, that arterial blood temperature must be lower than that of the hypothalamus and that the flow of blood through the highly vascular hypothala-

mus normally *cools* the thermosensitive elements. In a limited number of observations (6 animals) arterial blood was found to be from 0.34 to 0.75°C below posterior and 0.16 to 0.59°C below anterior hypothalamic temperature. This situation presumably does not obtain for other areas perfused by the same arterial supply, such as the sinuses and tympanic membrane. We believe that these areas supplied by the internal carotid artery are regions of low metabolic activity, where any gradient for heat flow is likely to be from the arterial blood to these tissues of low heat production. If this is true, then equating sinus or tympanic membrane temperatures with intracranial temperature(7) is unwarranted.

It is known that barbiturates depress central temperature regulating mechanisms(8), the *in vitro* metabolic rate of gray matter in the brain(9) and the *in vivo* oxygen consumption in monkey brain(10). Fig. 2 illustrates an experiment showing the effect of sodium pentobarbital on temperatures in the anterior and posterior hypothalamus, and in the aorta. At the time indicated by the arrow, 10 mg/kg of sodium pentobarbital was injected intravenously. Within 20 seconds, a dramatic fall in both anterior and posterior hypothalamic temperatures began, and continued for approximately 7 minutes, at which time the temperatures levelled off and remained at this new low level for a prolonged time. The maximum fall amounted to 0.35°C for anterior and 0.40°C for posterior hypothalamus. In other cats the temperature drop was as large as 0.75°C. Arterial blood temperature declined slowly during the same period to a a value 0.13° lower than the control level. Qualitatively similar responses have been obtained with doses of pentobarbital as low as 2.5 mg/kg. None of the injections was sufficient to reduce systemic blood pressure significantly.

Two possible mechanisms may be involved in this response. 1. Pentobarbital may cause a reduction in metabolic heat production in the hypothalamus. 2. Pentobarbital may cause an increase in hypothalamic blood flow. If there were a reduction in hypothalamic metabolism, one would expect a significantly decreased temperature rise during carotid artery occlusion after administration of pentobarbital. We found that this is not true. The temperature rise and decline are quite similar, both in magnitude and time course, to that which occurred before pentobarbital was administered. Thus there is no significant reduction of metabolic heat production in the hypothalamus following administration of sodium pentobarbital in doses from 2.5-10 mg/kg. It is more likely that the lowering of hypothalamic temperature is due to a significant increase in hypothalamic blood flow. Schmidt *et al.*(10) have reported that pentothal administration in the monkey results in a decreased cerebral blood flow and oxygen consumption. These observations are not inconsistent with our data, since it is possible that barbiturates decrease oxygen consumption and blood flow in the cerebral cortex. In the absence of changes in systemic arterial pressure, this could result in a shunting of blood from the cerebral cortex to the hypothalamus. This explanation is consistent with the findings of Donhoffer(11) that occlusion of the carotid blood supply in cats under barbiturate anesthesia results in elevated hypothalamic temperature, but a decreased cortical temperature.

Summary. Simultaneous temperature measurements in the hypothalamus and arterial blood reveal that the thermosensitive elements in the hypothalamus are normally cooled by the blood perfusing it. Posterior hypothalamic temperatures are consistently higher than those in the anterior hypothalamus. Occlusion of the common carotid arteries elicited a marked elevation in hypothalamic temperatures. Small i.v. doses (2.5 to 10 mg/kg) of sodium pentobarbital resulted in a prompt and sustained decline. The fall in temperature after pentobarbital appears to be due to a significant increase in hypothalamic blood flow.

1. Ranson, S. W., *Assn. Res. Nerv. Ment. Dis., Proc.*, 1940, v20, 342.

2. Magoun, H. W., Harrison, F., Brobeck, J. R., Ranson, S. W., *J. Neurophysiol.*, 1938, v1, 101.

3. Krebs, H. A., *Biochim. Biophys. Acta*, 1950, v4, 249.

4. Serota, H. M., Gerard, R. W., *J. Neurophysiol.*, 1938, v1, 115.

5. Jasper, H. H., Ajmone-Marsan, C., *A Stereotaxic Atlas of the Diencephalon of the Cat.* National Research Council of Canada, Ottawa, 1957.

6. Finley, K. H., *Assn. Res. Nerv. Ment. Dis., Proc.*, 1940, v20, 286.

7. Benzinger, T. H., *Fed. Proc.*, 1960, v19, Suppl. 5, 32.

8. Goodman, L. S., Gilman, A., *The Pharmacological Basis of Therapeutics.* The Macmillan Co., New York, 1955.

9. Fuhrman, F. A., Field, J., *J. Pharm. Exp. Therap.*, 1943, v77, 392.

10. Schmidt, C. F., Kety, S. S., Pennes, H. H., *Am. J. Physiol.*, 1945, v144, 33.

11. Donhoffer, S., Szegvari, G., Jarai, I., Farkas, M., *Nature*, 1959, v184, 993.

Received September 26, 1961. P.S.E.B.M., 1962, v109.

Canine Endotoxin Shock: Reversal with Aldosterone and Angiotensin II (Hypertensin) (27255)

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Previous studies from this laboratory have shown that a combination of hydrocortisone and metaraminol will reverse the lethal progress of canine endotoxin shock(1). Such steroid-pressor therapy has been employed in the management of patients with shock associated with bacteremia due to Gram-negative bacteria. A combination of aldosterone and metaraminol has also been found to be effective in reversing experimental endotoxin shock(2). The present report is concerned with the marked pressor activity of angiotensin II when used in combination with synthetic d-aldosterone to reverse endotoxin shock.

Methods. Forty-three mongrel dogs anesthetized with Na pentobarbital were used. A lipopolysaccharide suspension of *E. coli* endotoxin injected in a dose of 0.55 mg/kg into the femoral vein, initiated a state of shock that could be studied for 8 hours or until death of the animal. Systemic arterial pressure was measured continuously by a catheter placed in the femoral artery and recorded on a Sanborn twin-viso. Arterial blood pH and hematocrit were measured hourly. Urine outputs were determined at hourly intervals by means of an indwelling catheter in the urinary bladder. Sera from aldosterone-treated dogs were analyzed serially for sodium and potassium with the Baird flame photometer. D-aldosterone was given in a single intravenous dose of 0.2 mg.* One mg of angiotensin II in 100 ml of 5% dextrose and distilled water was administered as a slow intravenous infusion in amounts necessary to maintain blood pressure at approximately 100 mm Hg.* Permanent survivors were those animals alive 48 hours post-endotoxin.

Results. The combined results with 43 dogs given a lethal dose of endotoxin are shown in Table I. The average survival time for 13 control animals given endotoxin was 12.8 hours. These dogs showed marked hemoconcentration, acidosis, hypotension, and renal failure characteristic of this type of shock(3).

A second group of 10 animals given endotoxin were treated with angiotensin II at that point when the foregoing characteristics of otherwise irreversible shock appeared. Five of the 10 animals treated in this manner survived. An average dose of 650 γ of angiotensin II was required to maintain the blood pressure at approximately normal values. Some degree of acidosis was noted in these animals at about 2 hours post-endotoxin, but this had subsided at 4 hours post-endotoxin. An increase in hematocrit, from a control value of 42 to a maximum of 55, was seen 9 hours post-endotoxin. Oliguria and anuria were not observed; actually, diuresis occurred following therapy.

Two of the 10 dogs treated with aldoster-

* Supplied by Research Dept. of Ciba Pharmaceutical Products, Inc., Summit, N. J.