Cerebral oxygenation and metabolism during progressive hyperthermia

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NEMOTO, E. M., AND H. M. FRANKEL. Cerebral oxygenation and metabolism during progressive hyperthermia. Am. J. Physiol. 219(6): 1781-1788, 1970.—Cerebral blood flow (CBF), cerebral oxygen (CMR02) and glucose (CMRglu) consumption, and an aerobic index (OGI) were determined at rectal temperatures (Tre) of 38, 40, 42, and 43 C in dogs. At control Tre (38 C) mean values for these variables were 44.3 ± 3.1 ml/100 g per min, 3.8 ± 0.4 ml/100 g per min, and 7.8 ± 0.8 mg/100 g per min, and 73 ± 9%, respectively. When Tre was 42 C, CMR02 was increased significantly and CMRglu was not changed compared to control. At 43 C, CMR02 and CMRglu were reduced compared with values at 42 C. Aerobic index did not decrease at elevated Tre. From these results, it was concluded that cerebral hypoxia did not develop during progressive hyperthermia. Failure of cerebral metabolism in the absence of hypoxia could result from a limited supply of nucleotides required in cerebral glucose transport and is suggested as a possible model for further investigation.

METHODS

Male and female dogs (body wt 13.2-25.5 kg) were anesthetized with sodium pentobarbital (30 mg/kg). Cannulas were placed in the trachea, right femoral vein and artery, right brachial artery, and in the superior sagittal sinus. Rectal temperature (Tre) was monitored with a thermistor inserted approximately 10-15 cm into the rectum.

Cerebral blood flow was determined by a 4-iodoantipyrine-I1H technique using continuous infusion of isotope and external scintillation (43). The technique adapted for dog has been described elsewhere (37). Massive resection of temporal and associated musculature on the dorsal and lateral aspects of the skull was carried out to permit radioactive scanning of the skull.

At the end of each CBF determination, arterial and cerebral venous blood samples were obtained for Po2, Pco2, pH, and O2 and glucose content determinations. Glucose samples were deproteinized immediately after being drawn. All samples were stored in ice until determinations were made. Blood gas tension and pH were determined within 5 min of being drawn. Volumes of blood withdrawn were replaced with similar volumes of 6% dextran-saline solution drip infused intravenously.

Dogs were placed in a small control temperature chamber. For hyperthermic experiments the chamber was maintained 2-3 C greater than the Tre of the dog. In this manner Tre increased at a rate of approximately 2 C/hr. Measurements were made in hyperthermic dogs at normal Tre (38 C), and at Tres's of 40, 42, and 43 C. Control dogs were maintained normothermic and sampled for periods of time equal to, or greater than, the hyperthermic experiments (5-6 hr).
Measurements of $P_O_2$, $P_CO_2$, and pH were made at a temperature equivalent to the $T_c$ of the dog with appropriate electrodes housed in an Instrumentation Laboratory constant-temperature bath (model 127). Electrodes were calibrated before each set of determinations. Blood oxygen content was analyzed spectrophotometrically by the method of Nahas (36). Glucose was assayed using Glucostat reagent (Worthington Biochemical Corp.). All measurements were made in duplicate. Mean and standard error of the mean were calculated on all data. For the calculation of statistical significance each dog was used as its own control and changes from control value were compared. In the Student $t$ test a $P$ value of less than 0.05 was considered significant.

### TABLE 1. Blood gases, pH, and glucose in normothermic and hyperthermic dogs

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Approx. Time, hr</th>
<th>$T_c$, °C</th>
<th>Blood Sample</th>
<th>$P_O_2$, mm Hg</th>
<th>$P_CO_2$, mm Hg</th>
<th>pH</th>
<th>$P_CO_2$, mm Hg</th>
<th>$HCO_3^-$, mmol/l</th>
<th>Glucose, mg/dl</th>
<th>Cortisol, mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normothermic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I 0</td>
<td>37.7 ± 0.1</td>
<td>A 73</td>
<td>12.4 ± 1.9</td>
<td>7.37 ± 0.04</td>
<td>37</td>
<td>± 20.7 ± 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>37.6 ± 0.33</td>
<td>A 74</td>
<td>12.2 ± 1.8</td>
<td>7.38 ± 0.02</td>
<td>34</td>
<td>± 18.8 ± 0.5</td>
<td></td>
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</tr>
</tbody>
</table>

**RESULTS**

A) Arterial and venous blood composition. Arterial blood $P_O_2$, $P_CO_2$, $P_CO_2$, $P_CO_2$, and glucose content did not change significantly in dogs maintained normothermic for periods of up to 6 hr (Table 1). Except for a reduction of $P_O_2$ from 26 to 19 mm Hg appearing with the second sample (2 hr) and maintained through the fourth sample (5-6 hr) cerebral venous blood gas, pH, and glucose parameters were also stable. From these results we assumed the animals could be maintained physiologically stable for the time period of our hyperthermic experiments, viz., 4-5 hr.

Arterial blood composition changes during hyperthermia indicated the occurrence of hypocapnia. Arterial $P_CO_2$ pressure and $P_CO_2$ were significantly greater at $T_c$'s of 40 and 42°C than at control $T_c$. Arterial $P_CO_2$ pressure and $HCO_3^-$ were depressed at the same $T_c$ values. At 43°C $P_CO_2$ was decreased to control levels; $P_CO_2$ remained elevated and $HCO_3^-$ remained depressed. The pH response at 43°C was due to increased accumulation of fixed acids since $P_CO_2$ was still very low. This response supports findings of an increased fixed acid accumulation during hyperthermia (14). The $CO_2$ and pH changes in arterial blood were mirrored in cerebral venous blood samples. Ventricular $CO_2$ pressure and $HCO_3^-$ decreased and $pH$ increased. Arterial and cerebral venous $P_CO_2$ content did not change significantly with hyperthermia. It appeared that an adequate $O_2$ supply was maintained as a result of an elevated $P_CO_2$ plus the effects of decreased $P_CO_2$ and increased pH which counterbalanced the effect of elevated temperature to shift the $O_2$ dissociation curve to the right.

B) Cerebral blood flow. Cerebral blood flow appeared to decrease with time during periods up to 6 hr in normothermic dogs (Table 2). The decreased $P_CO_2$ during hyperthermia which would tend to decrease $CBF$ was counterbalanced by some other effect, possibly temperature per se.

### TABLE 2. Cerebral blood flow and cerebral $O_2$ and glucose metabolism in normothermic and hyperthermic dogs

<table>
<thead>
<tr>
<th>Run No.</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normothermic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_c$, °C</td>
<td>37.7 ± 0.21</td>
<td>37.5 ± 0.37</td>
<td>37.6 ± 0.46</td>
<td>37.7 ± 0.52</td>
</tr>
<tr>
<td>$CBF$, ml/100 g/min</td>
<td>46.3 ± 1.0</td>
<td>41.8 ± 1.1</td>
<td>39.7 ± 1.4</td>
<td>36.2 ± 1.3</td>
</tr>
<tr>
<td>$CMR_{O_2}$, ml/100 g/min</td>
<td>4.0 ± 0.3</td>
<td>3.9 ± 0.3</td>
<td>3.9 ± 0.3</td>
<td>2.8 ± 0.4</td>
</tr>
<tr>
<td>$GOI$, %</td>
<td>79 ± 8</td>
<td>59 ± 4</td>
<td>41 ± 3</td>
<td>36 ± 12</td>
</tr>
<tr>
<td><strong>Hyperthermic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_c$, °C</td>
<td>44.3 ± 3.1</td>
<td>44.3 ± 3.1</td>
<td>43.0 ± 0.06</td>
<td>44.3 ± 3.1</td>
</tr>
<tr>
<td>$CBF$, ml/100 g/min</td>
<td>44.3 ± 3.1</td>
<td>44.3 ± 3.1</td>
<td>42.1 ± 0.04</td>
<td>44.3 ± 3.1</td>
</tr>
<tr>
<td>$CMR_{O_2}$, ml/100 g/min</td>
<td>3.8 ± 0.4</td>
<td>3.9 ± 0.4</td>
<td>4.5 ± 0.4</td>
<td>3.4 ± 0.5</td>
</tr>
<tr>
<td>$GOI$, %</td>
<td>79 ± 8</td>
<td>59 ± 4</td>
<td>41 ± 3</td>
<td>36 ± 12</td>
</tr>
</tbody>
</table>

* Significantly different from control ($P < 0.05$).
so that CBF did not change significantly with increased $T_r$, up to 42 C. At 43 C CBF was decreased significantly. This response has been discussed in detail previously (37).

C) Cerebral oxygen and glucose metabolism. The initial mean value for cerebral oxygen consumption (CMRO$_2$) of 4.0 ml/100 g per min in normothermic dogs was essentially the same as the values reported by other investigators (34). In the second determination CMRO$_2$ decreased significantly in our normothermic dogs and remained at the lower value for the rest of the run (Table 2). In hyperthermic dogs, CMRO$_2$ was significantly elevated at a $T_r$ of 42 C. Values obtained at 43 C returned to essentially the same levels found in controls.

Cerebral glucose consumption (CMRGlu) at normal $T_r$ was the same value as that reported by Michenfield and Theye (34). It did not change significantly with time up to 6 hr in normothermic dogs (Table 2). The degree of variability in response was significantly greater in the latter two determinations made at normal $T_r$, however. The hyperthermic dogs showed a significant decrease in CMRGlu at 43 C compared to control. The value at 42 C was not significantly different than control. It was, however, elevated when compared to the value at 40 C.

D) Aerobic index. Oxygen glucose index (OGI) was calculated according to the equation:

$$\text{OGI} = \frac{100(A-V)O_2}{6(A-V)Glu}$$

where

$(A-V)O_2$ = arterial-cerebral venous oxygen difference in millimoles per liter

$(A-V)Glu$ = arterial-cerebral venous glucose difference in millimoles per liter

Aerobic index may be considered a representation of the percent aerobic metabolism of glucose (5). It was significantly reduced in the second and third samples drawn in normothermic dogs. At 38 C there was no significant difference in the values of control dogs and dogs that were to be heated (hyperthermic). In hyperthermic dogs OGI did not change significantly with increased $T_r$, although the mean value increased. When hyperthermic dogs were compared to control dogs at similar times, hyperthermic dogs had significantly higher values after the second sample.

DISCUSSION

Our data indicated cerebral metabolism was not markedly altered at body temperature up to 40 C. On the basis of the Arrhenius relation, assuming an activation energy of 11,000 (45), an increase of 12% could be expected in metabolic rate with an increase in temperature from 38 to 40 C. The standard error of the mean for CMRO$_2$ and CMRGlu in the present study was of the order of 10%. Thus a change of 12% would not be demonstrable. These findings were in agreement with those reported by Heyman et al. (24) in vivo and by Burger and Fuhrman (3) in vitro. At 42 C the theoretical increase in metabolism would be 26%, which would be demonstrable, and we did find a significant increase in CMRO$_2$. The fact that CMRO$_2$ increased but CMRGlu did not suggest an alteration in metabolic pathways at that temperature.

A further increase in metabolism would be expected at 43 C. However, in vitro studies of rat cerebral tissue metabolism indicated 42–42.5 C was a critical temperature above which CMRO$_2$ changed drastically (3, 28). The fact that CMRO$_2$ decreased to essentially the same level as control and CMRGlu was reduced below control in the present study can be considered evidence for cerebral metabolic dysfunction at a $T_r$ greater than 42 C. Alterations in metabolism have been suggested to explain the altered electrical activity of rabbit cerebral cortex at elevated $T_r$ (11). Either a thermal depression of metabolism per unit of tissue or a decrease in the total quantity of metabolizing tissue must have occurred at 43 C. Whichever alternate was correct the finding supports the view that at that $T_r$ brain function was impaired.

In addition to its ability to decrease cerebral blood flow (46), hypocapnia has been known to have a direct effect on tissue metabolism (7, 10). Waelsch et al. (47) have stated that "without a drain on the intermediates of the citric acid cycle, CO$_2$ fixation would correspond to the rate of decarboxylation and resynthesis of oxaloacetate . . . ." They suggested the rate of CO$_2$ fixation "may in part govern the rate of the citric acid cycle." Work by Pincus (38) gave evidence that the presence of 5% CO$_2$ in inspired gas, presumably resulting in increased arterial Paco$_2$, increased the rate of CO$_2$ fixation in rat brain. Hypocapnia has been reported to decrease cerebral glucose metabolism in vivo (2) and in vitro (7). The response was independent of pH. Thus, hypocapnia which was found at all $T_r$ greater than control could have directly affected metabolism during hyperthermia. However, CMRGlu was not decreased until a $T_r$ of 43 C. At that $T_r$ mean arterial glucose content was decreased 16% below control value compared to a 51% decrease in CMRGlu. Mean cerebral venous glucose levels were well above values that would indicate the brain had reached its limit in ability to extract glucose from blood (31). Glucose extraction ratios (A-V glucose content arterial glucose content) remained between 0.24 and 0.26, i.e., did not change significantly during hyperthermia. Since metabolic changes were demonstrable only at 42 C or higher and hypocapnia was found throughout hyperthermia, it was unlikely that decreased Paco$_2$ was directly responsible for cerebral dysfunction.

Although cerebral metabolism was altered, brain hypoxia most probably was not a primary response during progressive hyperthermia. Arterial Po$_2$ and O$_2$ content remained elevated up to 43 C so that adequate O$_2$ was found in the arterial blood supply (27). The O$_2$ extraction ratio O$_2$ content/arterial O$_2$ content) at 43 C, 0.57, was essentially the same as that found at 38 C, viz., 0.58. It was down from 0.65 at 49 C and 0.64 at 40 C. We have demonstrated that CBF was decreased at 43 C. If inadequate O$_2$ availability occurred at 43 C we would expect to see it represented by an increased O$_2$ extraction ratio, particularly with the decreased pH found favoring unloading of O$_2$ hemoglobin at that $T_r$. Our data indicated that decreased O$_2$ removal by brain tissue rather than an inadequate O$_2$ availability must have occurred. We ruled out histotoxic hy-
poxia because OGI increased with increased temperature, indicating an increase in aerobic glucose utilization.

The work of Geiger et al. (16, 17) suggested a possible sequence of events that could lead to decreased cerebral glucose metabolism at 43°C independent of the presence of hypoxia. Those workers demonstrated a requirement of cytidine diphosphate (CDP) and uridine diphosphate (UDP) for transport of glucose across the blood-brain barrier and consequently for normal glucose consumption by perfused brain in situ. The importance, in the whole animal, of protecting against excessive nucleotide degradation for survival to shock has been demonstrated (8). The liver is an important tissue for synthesis and degradation of nucleotides. Rawlinson et al. (41) have shown a rapid increase in the output of esterases, proteolytic enzymes, and alkaline phosphatase in isolated cat liver at 40–41°C. They concluded that in this temperature range heat injury occurred in the liver. Additional in vitro evidence of liver damage at 42°C and consequently for normal glucose consumption by the liver has been reported by others (33). Rat liver has been shown to have a greater metabolic response than brain at temperatures greater than 40°C (28). It has also been noted that temperatures in the splanchic regions were usually as high or higher than brain and aortic blood temperatures. On the basis of these findings it can be hypothesized that injury to the liver would decrease the availability of nucleotides, CDP and UDP, which in turn would limit cerebral glucose uptake. It is interesting to note that lethal brain temperature was reported to be 2–4°C lower in cats with the head alone heated when compared to cats with whole-body heating (44). Thus the interdependence of metabolism in two tissues rather than the specific failure of brain would be responsible for physiological failure in this model.

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