Temperature changes associated with forebrain ischemia in the gerbil

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Changes in brain temperature during and following ischemia have not been systematically examined in the gerbil. In this study, gerbils were subjected to a 5-min bilateral carotid artery occlusion. During surgery, skull and body temperatures were maintained with a heated water blanket and a homeothermic blanket unit, respectively. Rectal, skull and brain temperatures were monitored throughout ischemia and for up to 3 h in the post-ischemic period. Intra-ischemic brain temperature fell by approximately 1.5°C even though skull and rectal temperatures remained at normal values. Since brain temperature modulates the extent of ischemic injury it may not be sufficient to rely on skull and/or rectal temperature readings, especially during periods of anesthesia.

INTRODUCTION

Brief periods of global ischemia produce a profound loss of hippocampal CA1 neurons. It is thought that this cell loss is due to an excessive accumulation of intracellular calcium precipitated by elevated levels of glutamate during ischemia. Mild hypothermia (e.g. 29–33°C) during ischemia or in the early recirculation period can markedly reduce ischemic cell damage, possibly as the result of attenuating the ischemia-induced release of glutamate. Conversely, mild hyperthermia either during ischemia or in recirculation worsens ischemic outcome. In order to avoid the confounding effects of hypothermia when testing potential anti-ischemic agents, it is necessary to monitor temperature during surgery as well as in the post-ischemic period. For example, it has been shown that the reported protective action of MK-801 was largely due to hypothermia. Most investigators now rely on skull temperature to provide an approximation of brain temperature since rectal temperature does not always faithfully reflect brain temperature. In the rat, rectal, skull and brain temperatures have been compared during ischemia. However, little information concerning post-ischemic temperature is available. Brain temperature data have also been described in the gerbil, but no systematic comparisons of brain, rectal and skull temperatures were provided.

In this study, we used an FM transmitter-based brain temperature monitoring system (Mini-Mitter Inc., Sunriver, OR, USA) that allows continuous monitoring of brain temperature during surgery and in conscious, freely moving animals. This system does not require external cables that complicate other brain monitoring systems and avoids the stress associated with taking multiple rectal readings.

MATERIALS AND METHODS

Subjects

Ten female, Mongolian gerbils (High Oak Ranch Ltd., Goodwood, Ont., Canada), weighing between 75 and 115 g were used. Animals were housed under diurnal light conditions with food and water freely available.

Brain temperature monitoring

Five days prior to occlusion the gerbils were anesthetized with sodium pentobarbital (65.0 mg/kg, i.p.) and a 20-gauge stainless steel guide cannula was lowered to the dural surface overlying the frontal cortex and attached using dental cement and an anchoring screw. The cannulae were 6.0 mm in length, thereby permitting the 8.0-mm brain temperature probes (model XM-FH, Mini-Mitter, Sunriver, OR, USA) to sample cortical temperature. Two days prior to occlusion, the gerbils were anesthetized with 1.5% Halothane in a mixture of 30% O₂ and 70% N₂O and the...
brain probes were inserted into the guide cannula. Anesthesia was then discontinued and the gerbils were placed into small plastic cages resting on FM receivers (Mini-Mitter, Model CTR86-SA) interfaced to a computer. Brain temperature was recorded continuously for 3 h to provide baseline values. Temperature data were analyzed and plotted using Dataquest III software (Data Sciences, Inc., St. Paul, MN, USA).

**Cerebral ischemia**

Two days after baseline temperature was recorded, the gerbils were again anesthetized with 1.5% Halothane delivered through a mask equipped Fluovac Halothane Scavenger System (Stoelting Co., Chicago, IL, USA). Rectal temperature was monitored and maintained at approximately 37.5°C with a homeothermic blanket control unit (Harvard Apparatus, South Natick, MA, USA). Skull temperature was measured by a 30-gauge thermocouple probe (Omega Engineering, Stamford, CT, USA) inserted subcutaneously contralateral to the guide cannula. Skull temperature was maintained at 37.5°C by wrapping a heated water flow-through blanket snugly around the head. A small opening in the water blanket allowed passage of the brain temperature probe. This permitted brain temperature to be monitored without interfering with the water blanket heating system. Brain temperature was measured in 5 gerbils during surgery and in all animals after surgery.

Once all temperature probes were in place, the common carotid arteries were isolated and occluded for 5 min using micro-arterial clamps (Fine Science Tools, Vancouver, BC, Canada). At the end of occlusion the clamps were removed, the midline incision was sutured and anesthesia was discontinued. The entire procedure took approximately 20 min.

Following surgery rectal temperatures (Digi-Sense, Cole-Parmer, Chicago, IL, USA) were recorded at 0.5, 1, 2, and 3 h after ischemia. Recording of skull temperature was discontinued as soon as the animals displayed signs of discomfort.

Finally, brain temperature was monitored continuously for 3 h following occlusion.

**Histology**

Animals were sacrificed 10 days after surgery with an overdose of sodium pentobarbital. They were then transcardially perfused with 0.9% heparinized saline followed by 10% phosphate-buffered formalin. Brains were stored in the same fixative prior to being sectioned at 10 μm and stained with Cresyl violet.

Cell loss in medial, middle and lateral sectors of CA1 in each hemisphere was quantified using a 5 point rating scale. A rating score close to zero indicated near total CA1 cell loss whereas a score of 24 reflected a normal CA1 cell population.

**RESULTS**

The mean CA1 cell rating was 1.2 ± 1.14 S.D., indicating severe loss of CA1 neurons.

The mean brain temperature recorded 2 days prior to occlusion varied between 36.5–37.2°C (Fig. 1). During surgery, skull and rectal temperatures (Fig. 2 and Table I) were maintained near 37.5°C. However, brain temperature fell by 1.5°C during occlusion (Fig. 2) before quickly returning to normal values during reperfusion.

Rectal temperature recorded 30 and 60 min after occlusion was approximately 38°C. Thereafter (2 and 3 h post-ischemia), rectal temperature increased to nearly 39°C. After an initial decline at the end of occlusion, skull temperature quickly rose to approach 38°C. Brain temperature also increased above baseline values and was virtually identical to skull temperature at 30 min (Fig. 2). Brain temperatures recorded 30, 60, 120 and 180 min into the post-ischemic period were signifi-

**TABLE I**

<table>
<thead>
<tr>
<th>Time</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>30 min</th>
<th>60 min</th>
<th>120 min</th>
<th>180 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>37.51 ± 0.47</td>
<td>37.78 ± 0.26</td>
<td>37.44 ± 0.32</td>
<td>38.1 ± 0.44</td>
<td>37.91 ± 0.40</td>
<td>38.37 ± 0.34</td>
<td>38.9 ± 0.37</td>
</tr>
</tbody>
</table>
cantly higher than the median (36.7°C) pre-ischemic brain temperature \((t_q = -2.33\) to 3.20, \(P < 0.05\)).

DISCUSSION

Maintaining skull and rectal temperatures at normal values during occlusion did not prevent a 1.5°C fall in brain temperature. Therefore, skull and rectal temperatures do not appear to be accurate indices of brain temperature during ischemia. Similar decreases in brain temperature during ischemia have been noted in studies using rat \(^4,12\) and gerbil \(^14\). While it is desirable to maintain constant brain temperature during occlusion this is difficult to achieve unless surgery is performed in a temperature-controlled, humidified chamber to prevent evaporative heat loss \(^3\). It is likely that evaporative heat loss through the nasal and oral cavities coupled with cessation of cerebral blood flow accounted for the observed intra-ischemic decline in brain temperature. However, this small decline in brain temperature still resulted in a severe and consistent loss of CA1 neurons.

Skull temperature was 0.5–1.0°C above brain temperature during the first 15 min of reperfusion and at 30 min the two temperatures were nearly identical. Rectal temperature was also within approximately 1.0°C of brain temperature at the times sampled in the post-ischemic period. Thus in the absence of anesthesia or drugs with sedative actions (e.g. MK-801), both rectal and skull temperatures seem to provide a close approximation of brain temperature, especially 15 min or more into the reperfusion period. It may prove necessary to obtain temperature recordings continuously over several hours in the post-ischemic period since MK-801 and perhaps other compounds induce long-lasting temperature alterations that oscillate between hypothermia and hyperthermia \(^2,10\). Such oscillations could easily be missed by sampling rectal temperature at one or two arbitrary time points.

Several authors have noted post-ischemic hyperthermia in the gerbil as assessed with rectal, skull or brain probes \(^11,15,19\). The average increase in brain temperature has been reported to be about 0.7°C \(^15\) which corresponds well with the degree of brain hyperthermia (0.9°C) observed in the present study (Figs. 1 and 2).

In summary, our temperature monitoring system has shown that maintaining normal skull and/or rectal temperature during ischemia does not result in maintenance of normal brain temperature. If the head is not warmed during surgery, the drop in brain temperature may be greater than the 1.5°C decline noted in our experiment. Moreover, prolonged anesthesia may delay the recovery of brain temperature to normal levels (in preparation). A reduction in brain temperature during ischemia and the first few minutes of reperfusion can markedly attenuate glutamate release and reduce the severity of the ischemic insult \(^14\). This hypothemic blunting of the ischemic insult may in turn act synergistically or additively with neuroprotective drugs to yield a substantial, though somewhat artifactual, degree of protection. Our findings suggest that investigators who rely solely on rectal or skull temperatures to indicate normothermia should also determine the brain temperature of their animals so that any reduction in brain temperature during occlusion and reperfusion can be minimized and dissociated from true pharmacological attenuation of ischemic injury.

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