Effects of Reduced Regional or Body Temperatures on Responses of Pial Arterioles

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SUMMARY We have investigated the effects of a reduced regional or a reduced body temperature, on pial arteriolar response to a variety of vasoactive stimuli. This has been done by studying the effects of these stimuli on groups of mice with different body temperatures, or with different temperatures of the artificial cerebrospinal fluid (CSF) irrigating the pial surface. Responses in mice with body temperatures of 30° or 22°C showed little or no difference from responses in mice with body temperatures of 37°. This was so whether the surface irrigant was maintained at 37° or at 23°. On the other hand, significant reductions in pial vascular responses were observed when mice with “CSF” temperatures of 22° were compared with those having “CSF” temperatures of 37°. The data suggest that regional cooling is more effective than cooling the body in reducing the responses of pial arterioles. The data also indicate that marked reductions in body temperature would have to occur before a detectable effect on pial vascular responses is produced, at least in mice anesthetized with urethane.

WE DESCRIBE the effects of altering either the body temperature or the temperature of a cerebral surface irrigant on the response of cerebral surface arterioles (pial arterioles) to several vasoactive stimuli. The data indicate that even large changes in body temperature have little effect on vascular reactivity, while the changes in temperature of the irrigating solution produce pronounced alterations in reactivity.

Methods

Mice (ICR strain, Dublin Farms, females) were anesthetized with urethane, and a tracheotomy was performed followed by a craniotomy with stripping of the dura as previously described.1 An image splitter, coupled to closed circuit TV, was used to measure diameter of pial arterioles.4 The cerebral surface was irrigated by artificial cerebrospinal fluid (CSF) (Elliott’s solution5) at a thermostatically controlled temperature and maintained at a pH of 7.35 ± 0.05 (mean ± range). The pH of the cerebral surface was maintained throughout an experiment at a pH essentially that of the drop leaving the needle.

The animals were permitted to respire naturally or were paralyzed with gallamine and respired on a Harvard rodent respirator. Body temperature was monitored rectally by a Yellow Springs thermistor and telethermometer. Body temperature was manipulated by altering the temperature of water circulated through a metal mattress on which the mouse was placed.

Arterial blood gases were measured at 37°C with an ultramicroblood gas analyzer on samples of less than 100 μL obtained from the carotid artery. The blood gas and pH values were corrected back to the animal’s temperature and were expressed at that temperature.

In some experiments attempts were made to alter the blood gases of one group of mice to make them comparable to those of another group. This was done by adjusting the rate of respiration with the respirator. In some experiments all mice breathed 100% O₂.

Norepinephrine bitartrate, phentolamine mesylate and serotonin creatinine phosphate were diluted in Elliott’s solution and locally applied to the cerebral surface at the temperature and pH of the artificial CSF irrigating the cerebral surface. The doses of norepinephrine (NOR) and phentolamine are expressed as μg of base per milliliter of Elliott’s solution. The doses of serotonin (5HT) are expressed as μg of salt per milliliter. In addition, 5% BaCl₂ was utilized as a vasoconstrictor.1

All mice were tested with BaCl₂ and one other agent. The arterioles selected for study were 30–70 μm in diameter. The constrictors were given in 1 ml volumes and the response monitored through the point of maximum constriction and back to a steady baseline. The maximal change in diameter was measured and expressed as a percent of baseline diameter. Thus, if a 50 μ arteriole narrowed to 40 μ we expressed its constriction as 20% reduction in diameter. These constrictions were averaged and their means ±1 standard deviation tabulated below. Data were analyzed statistically with either a “t” test, analysis of variance or analysis of covariance depending upon the circumstances.

Results

1. Effects of Body Temperature on Response to Norepinephrine or BaCl₂

Several studies were performed under a variety of circumstances but because of the similarity in results of the several studies we have presented quantitative data for only the first.

Study #1-A

The surface irrigant was kept at 23° while body temperature was kept at 22°, 30° or 37°. Sixty mice were paralyzed with gallamine, and respired. Results are shown in table 1. Analysis of covariance showed no effect of temperature on the responses to NOR or
to BaCl₂. Covariates included arterial CO₂, O₂ and pH. There was a decline in arterial CO₂ levels, as expected, with hypothermia and this was paralleled by a rise in blood pH, omitted from the table for simplification. An expected decline in arterial O₂ was also observed.

**Study §1-B**

Seventy-five animals were treated as in study §1-A, except that they were artificially respired without being paralyzed. Assisted respiration was required because at 22° body temperature spontaneous respiration often ceased. Again, no effect of body temperature was found on either the response to NOR or to BaCl₂, nor was there an effect of Pao₂ or Paco₂.

**Study §1-C**

Mice with a body temperature of 37°C were compared with mice at a temperature of 22°C. As in study #2, the mice were not paralyzed, and their respiration were "forced" by placing them on the respirator pump. But instead of irrigating the pial vessels with a drip at 23°C, as in the first 2 studies, the irrigating Elliott's solution was now kept at 37°C. Also in contrast with the preceding study, the respirator rate was increased for the 37°C animals, in order to reduce their body temperature. The final diameter, expressed as a % of the original diameter, was related to final arterial CO₂ values to low levels like those found, and expected, in the cold animals. Arterial O₂ levels remained significantly higher in the 37°C mice, the lower levels in the cold animals also being expected as a manifestation of cooling. Analysis of covariance found no effect of either arterial CO₂ or O₂ on responses to NOR or to BaCl₂ and, again, there was no effect of body temperature on the response to NOR (three dose levels 1, 10, 100 µg/ml; 10 mice at each dose, with 5 at each temperature). However, at 37°C the constriction to BaCl₂ was larger than that elicited at 22° (a 70% reduction in size vs. 40% p < 0.01). This effect of body temperature on the response to BaCl₂ was never duplicated in any other study.

**(2) Additional Studies**

The responses to NOR (10 µg/ml) and BaCl₂ were further tested in 64 mice breathing an O₂ rich mixture. The ignorant was kept at 23°, the body temperature at 22° or 37°. No effect of body temperature was observed. In mice, respired but not paralyzed, serotonin (1, 10 or 100 µg/ml) was tested with an irritant at 37° and body temperature of either 37° or 22°. Body temperature failed to influence the response.

Phentolamine, an alpha-adrenergic blocker, was tested in 80 mice, either paralyzed or nonparalyzed, breathing either air or O₂-rich mixture. Doses of either 1, 10, 100 or 250 µg/ml were used with the irritant at 23° and body temperature of either 22° or 30°. No effect of body temperature was observed on the response to the drug, which had either no effect or produced a slight and inconsistent constriction at higher doses.

The response to an altered arterial CO₂ level was likewise unaffected by changes in body temperature. When a change in the respiratory rate produced a change in arterial diameter, the latter was linearly related to the final arterial CO₂ level and significantly correlated (p < 0.01) to the latter whether the body temperature was 22° or 37° (irritant at 23°) at either body temperature. The final diameter, expressed as a % of the original diameter, was related to final arterial CO₂ in the same way at each temperature (y = 83 + 0.4x at 22°, y = 78 ± 0.5x at 37°. CO₂ range 13 mm Hg to 110 mm Hg).

**(3) Effect of "CSF" Temperature on Response to Norepinephrine or BaCl₂**

The body temperature was maintained at 37° and the mice were respired but not paralyzed. The cerebral surface was irrigated with either 23° or 37° "CSF." A significant depressant effect of the low drip temperature was observed on both the response to NOR and to BaCl₂ (p < 0.001, p < 0.04; table 2).

### Table 1: Failure of Reduced Body Temperature to Affect Contractile Response* to Norepinephrine or BaCl₂

<table>
<thead>
<tr>
<th>Dose of NOR</th>
<th>22°</th>
<th>30°</th>
<th>37°</th>
<th>22°</th>
<th>30°</th>
<th>37°</th>
<th>22°</th>
<th>30°</th>
<th>37°</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 µg/ml</td>
<td>8 ± 5</td>
<td>8 ± 4</td>
<td>5 ± 8</td>
<td>16 ± 8</td>
<td>13 ± 6</td>
<td>12 ± 5</td>
<td>16 ± 5</td>
<td>34 ± 9</td>
<td>43 ± 6</td>
</tr>
<tr>
<td>1.0 µg/ml</td>
<td>8 ± 5</td>
<td>7 ± 7</td>
<td>7 ± 5</td>
<td>19 ± 6</td>
<td>21 ± 6</td>
<td>12 ± 2</td>
<td>20 ± 8</td>
<td>31 ± 11</td>
<td>50 ± 5</td>
</tr>
<tr>
<td>10.0 µg/ml</td>
<td>2 ± 8</td>
<td>17 ± 8</td>
<td>15 ± 9</td>
<td>20 ± 9</td>
<td>26 ± 4</td>
<td>18 ± 8</td>
<td>18 ± 8</td>
<td>29 ± 12</td>
<td>35 ± 8</td>
</tr>
<tr>
<td>100.0 µg/ml</td>
<td>13 ± 8</td>
<td>1 ± 18</td>
<td>12 ± 7</td>
<td>23 ± 10</td>
<td>22 ± 8</td>
<td>18 ± 6</td>
<td>18 ± 2</td>
<td>30 ± 6</td>
<td>37 ± 1</td>
</tr>
</tbody>
</table>

*Constriction expressed as a % of resting diameter. All values in table are mean from 5 mice ± one standard deviation. Analysis of covariance showed no effect of temperature on the response to either NOR or BaCl₂, and no effect of arterial CO₂ or other covariates (see text) on the response.

### Table 2: Reduction of Contractile Response to NOR and BaCl₂ Seen in Mice with Reduced "CSF" Temperature

<table>
<thead>
<tr>
<th>Dose NOR</th>
<th>23°</th>
<th>37°</th>
<th>23°</th>
<th>37°</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 µg/ml</td>
<td>10 ± 8</td>
<td>13 ± 10</td>
<td>14 ± 4</td>
<td>71 ± 33</td>
</tr>
<tr>
<td>10 µg/ml</td>
<td>11 ± 5</td>
<td>22 ± 18</td>
<td>11 ± 5</td>
<td>73 ± 28</td>
</tr>
<tr>
<td>100 µg/ml</td>
<td>11 ± 6</td>
<td>22 ± 9</td>
<td>11 ± 6</td>
<td>73 ± 27</td>
</tr>
</tbody>
</table>

*Constriction expressed as a % of resting diameter. All values as means from 5 mice ± one standard deviation. Analysis of covariance or variance showed a significantly (p < 0.04) smaller response to NOR in mice with a drip of artificial CSF at 23° compared with 37°, and a smaller response (p < 0.001) to BaCl₂ as well. Covariates such as vessel diameter, arterial CO₂ and O₂ values are not shown in order to simplify the table. There were no differences between groups, with respect to these covariates.
Essentially identical results were observed when the study was repeated but with mice at a body temperature of 22º and respired but not paralyzed.

When the study was again repeated at a body temperature of 37º, but without either paralysis or artificial respiration, the contractile response to BaCl₂ was again significantly depressed at a low irrigant temperature but the response to NOR was not as markedly reduced as before (p < 0.10).

Discussion

In our studies reduction of body temperature or of regional temperature produced constriction of the pial arterioles. However, these findings, which resemble those known to occur in other vascular beds,¹⁄² are not the subject of this report. Rather, these experiments tested the effects of temperature reduction on the response of pial arterioles to one or more of the following vasoactive stimuli: locally applied NOR, 5HT, BaCl₂ or phentolamine, and to changes in arterial CO₂ tension.

Our data revealed no significant effect of a change in body temperature on the responses to NOR, 5HT, phentolamine, or to an altered CO₂ tension and an inconsistent depressant effect of greatly reduced (22ºC) body temperature on the constrictions induced by locally applied BaCl₂. This effect of temperature on the response to BaCl₂ was only seen in 1 out of 4 studies.

In contrast to the meager effects of alterations in body temperature, the effects of changes in local temperature were more readily demonstrated, with both the responses to locally applied NOR or to locally applied BaCl₂ being significantly depressed in 2 out of 3, and 3 out of 3 studies, respectively. In these studies the temperature of the regional perfusate was reduced to 23ºC, 14º below normal body temperature. The effect of lesser reductions in suffusate temperature was not investigated.

The interpretation of these observations is complicated by the well known reductions in vascular diameter that follow reductions in either body or local temperature.¹⁄² Such reductions were readily demonstrated in our mice. If vessels are reduced in size by lowered temperatures, a greater change in diameter produced by vasoactive stimuli, should appear as a greater change when expressed as a percentage of the resting diameter. This effect will impair our ability to detect actual reductions in responsivity at lowered temperatures. Therefore, if diameters were reduced more by lowered body temperature than by lowered regional temperature one could explain the greater difficulty in detecting reduced responsivity produced by the lowered body temperature. In considering this possibility we analyzed the effect of diameter on our results and found that our results were independent of diameter. This conclusion is supported by our failure to detect an effect of arterial CO₂ tension on our results, in spite of the relationship between PACO₂ levels and diameter.

In other vascular beds, reduced local temperature has been reported both to decrease and to increase vasoactive responses.¹⁰ These experiments by others indicate that the effect of a lowered temperature on vascular responsiveness depends upon a complex interaction of many factors.

Our findings are relevant to two questions. First, what is the importance of maintaining either core or local temperature when studying vascular reactivity of pial vessels? The data suggest that reductions of core temperature to 30ºC may not produce detectable changes in responsivity, and even reduction to 22ºC may not significantly depress the response to a number of vasoactive agents. Of course this may be because the small size of the mouse brain enables an irrigant of constant temperature to maintain surface temperature quite well in spite of a fall in the temperature of the core. In any event, reduction of the temperature of the surface irrigant itself appeared much more effective as an inhibitor of pial arteriolar reactivity.

A second question concerns the possibility that hypothermia will alter the responsivity of cerebral blood vessels in a clinical situation. With these limitations in mind, our data suggest little effect of modest or moderate hypothermia on the responsivity of cerebral vessels, provided that surface temperature is maintained.

References

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