The relationship between traumatic brain injury-induced changes in brain temperature and behavioral and anatomical outcome

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Alteration of brain temperature, experimentally induced or spontaneous, has been shown to affect the symptoms resulting from a variety of cerebral insults. This study examined the effect of traumatic brain injury (TBI) on brain and body temperature in rats and the relationship between TBI-induced temperature changes, neuropathology, and behavioral recovery. Anesthesia, surgery and TBI all caused changes in brain and body temperatures. The level of brain (but not body) temperature at the time of TBI was positively correlated with the severity of hippocampal and thalamic pathology. In contrast, the measured levels of both brain and body temperatures after TBI were not related to behavioral or neuroanatomical outcome. Interestingly, the increase in brain (but not body) temperature from the time of TBI to 5 to 10 minutes after termination of anesthesia was negatively correlated with behavioral and anatomical outcome. Simply stated, the more rapidly brain temperature returned toward normal, the better the rats' behavioral and anatomical outcome. This rate of return toward normal brain temperature is not interpreted as causally related to outcome but rather as an index of the severity of brain injury.

Key Words • traumatic brain injury • hypothermia • hyperthermia • neuropathology • behavioral recovery

Both pathologically induced changes in and manipulations of brain temperature have been shown to affect many of the sequelae of cerebral insults. Numerous authors have demonstrated that raising or lowering brain temperature exacerbates or attenuates, respectively, many consequences of cerebral ischemia. Hypoxia and hypoglycemia similarly affect brain temperature and the sequelae of these insults are correspondingly affected by alterations of brain temperature.

Less thoroughly studied are the effects of brain temperature changes in animal models of traumatic brain injury (TBI). In 1991, Jiang, et al., using a fluid-perfusion model of TBI, reported no TBI-induced alteration of brain temperature at 10 minutes after TBI in anesthetized rats. In contrast, both body and brain temperature disturbances have been described in human patients with TBI (L. Sternau, et al. and DW Marion, unpublished data). In a second laboratory study using a fluid-perfusion model of TBI, Clifton, et al., found that increasing or decreasing post-TBI brain temperature affected the severity of locomotor deficits and weight loss in a manner similar to that observed in models of ischemia. However, this study may be confounded, since duration of anesthesia varied with the depth of induced hypothermia. As in this laboratory study, clinical reports indicate that posttraumatic hypothermia has some beneficial effects in humans with TBI.

Given the paucity of studies examining possible relationships between brain temperature and TBI, the current investigation studied TBI-induced changes in brain and body temperature and their relationships to behavioral and anatomical outcome in the rat. Weight-drop focal cortical impact was used to model TBI in this investigation because this method reliably produces locomotor deficits, cortical necrotic cavitation, hippocampal damage, and subcortical pathology (MP Weisend, et al., unpublished data). All of these sequelae have been reported to be affected by changes in brain temperature. In addition, brain and body temperature changes produced by the anesthetic agent and surgical technique necessary to produce TBI in this model were characterized and correlated with the outcome measures described above. Some of these data have been presented previously as an abstract.
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Materials and Methods

Animals

Twenty-six male Sprague-Dawley rats, each weighing between 300 and 360 g, on the day of surgery, were used in this experiment. The animals were individually housed in standard wire-mesh cages, maintained on a 12:12-hour light:dark cycle (lights on at 7:00 a.m.) and given access to food and water ad libitum, except for 12 hours of fasting before surgery. The rats were weighed every other day both before and after surgery.

Brain and Body Temperature Measurement

A thermistor placed in the brain for continuous measurement of actual brain temperature was impractical for this study since a rigid foreign object, such as a thermistor, located in the brain during TBI would likely cause local damage in addition to that caused by TBI. Hence, this study inferred brain temperature from a thermistor placed between the right temporal muscle and the lateral aspect of the skull. Both skull and temporal muscle temperatures are highly correlated with actual brain temperature; however, rapid fluctuations in brain temperature may be underestimated. Core body temperature was measured with a rodent rectal thermometer. Both brain and body temperatures were monitored using digital thermometers.

Conscious rats would not tolerate insertion of the thermists and freely moving animals would remove the thermostors after placement. Hence, insertion of thermostors was performed under brief halothane anesthesia and the rats were placed in a restraint jacket prior to regaining consciousness. Since restraint can affect temperature, the animals were habituated to restraint during the week prior to surgery. Specifically, habituation consisted of brief exposure to halothane (4% in O2 for 1 to 2 minutes), followed by placement in the restraint jacket for 30 minutes/day on 5 consecutive days.

After habituation to restraint and 24 hours prior to surgery, the effect of halothane anesthesia on body and brain temperatures was measured. To this end, the rats were anesthetized with halothane for 7 to 10 minutes while the thermostors were inserted and the restraint jacket fitted. For the measurement of brain temperature, the tissue-implanted thermistor was inserted with a hypodermic needle into the temporal muscle, as close to the skull as possible. Body temperature was measured by inserting the tip of the rectal probe approximately 5 cm into the rectum. Body and brain temperatures were recorded every 5 minutes for 2 hours after termination of anesthesia. Since both body and brain temperatures recovered to stable levels at 1 to 1.5 hours after termination of anesthesia, the mean levels at 2 hours after the termination of halothane anesthesia were considered normothermic. All rats underwent the measurement procedure but, due to technical problems (misplaced, broken, or migrated temporal muscle thermostors), acceptable temperature data were gathered in only 13 of the 26 rats during this phase of the experiment. Values from these 13 animals were used to determine baseline temperature only. The technical problems with the temporal muscle thermistor were corrected before the surgical phase of the experiment was begun. All 26 rats were included in the analyses of surgical and postsurgical temperatures.

On the day following measurement of temperature in the unoperated condition, the rats were pseudorandomly (random draws without replacement) assigned to one of the following surgical groups: scalp resection only (eight rats), scalp resection and craniotomy (eight rats), and scalp resection, craniotomy, and TBI (weight-drop focal cortical impact, 10 rats). In all surgically treated animals, both brain and body temperatures were recorded at 1-minute intervals from probe placement to discontinuation of anesthesia. After anesthesia was terminated, temperature readings were taken every 5 minutes for 1 hour and then every 15 minutes for an additional 5 hours. When temperature measurement was completed, the thermostors were removed, restraint was discontinued, and the rats were returned to their home cage in the colony.

Surgical Procedure

Surgery was performed under aseptic conditions. One objective of this study was to examine the effects of the weight-drop focal cortical impact procedure on body and brain temperatures; thus, no attempt was made to control brain or body temperature at any time during the experiment. Ambient temperature was maintained between 22° and 25°C to reduce variation in brain and/or body temperature that might be due to differences in room temperature.

Following induction of general anesthesia (1.5% to 2.5% halothane in O2 at 1.5 to 2.5 liters/min), the rats were placed in a stereotactic frame, the scalp and periosteum were resected, and the right temporal muscle was cut away from the lateral aspect of the skull. The thermistor from which brain temperature would be inferred was attached to the lateral aspect of the skull with bone wax. The temporal muscle, fascia, and skin were then returned to their natural position over the lateral aspect of the skull. This placed the bone wax containing the tip of the thermistor between the temporal muscle and the lateral aspect of the skull. The rectal thermistor probe was also inserted at this time. The surgical procedure to this point was the same for all rats. In the rats with scalp resection only, the skull remained exposed for 6 to 7 minutes before scalp closure was begun, to provide a time-matched control for the period during which scalp was open in the rats receiv-

* Rats supplied by Zivic Miller Laboratories, Zelienople, Pennsyl-

† Thermistor, Model IT-23, manufactured by Physitemp, Clifton, New Jersey.

‡ Rodent thermistor, Model L-08505-90, manufactured by Cole-

Parmer Instruments, Chicago, Illinois.

§ Digital thermometer, Model REX-C900, manufactured by RKC

Instrument Co., Tokyo, Japan.

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ing craniotomies and TBI. In all other rats, a circular craniotomy, 5 to 7 mm in diameter, was made over the right sensorimotor cortex. The dura remained exposed for 3 to 4 minutes before the bone flap was replaced, the cranium sealed with bone wax, and the scalp sutured. As before, this delay provided a time-matched control for the duration of skull opening in the rats receiving TBI.

Traumatic brain injury was produced using the weight-drop focal cortical impact method. Briefly, after completion of the craniotomy as described above, the footplate (4.5 mm in diameter) of the contusion device was stereotactically positioned over the right sensorimotor cortex, centered 2.5 to 3.0 mm posterior, and 2.5 to 3.0 mm lateral to the bregma. The guide tube was then lowered 2.5 mm below the point at which the footplate rested on the dura. This limited the depression of the cortical tissue underlying the footplate to 2.5 mm. When the footplate was in position, a 20-gm weight was dropped 20 cm through the guide tube, producing a “400 gm/cm” impact to the brain underlying the footplate. The footplate was removed from the craniotomy within 5 seconds after impact. Immediately after removal of the contusion device, the bone flap was replaced, the cranium sealed with bone wax, and the scalp sutured.

**Behavior-Testing Procedures**

**Beam Walking.** The locomotor deficits resulting from the cortical injury can be reliably evaluated on a beam-walking task. Briefly, the rats were trained to traverse a wooden beam 2.5 cm wide and 12.2 cm long. At the starting point on the beam, there was a lamp with a 60-W bulb and a tape recorder that played a white noise tape at 78 dB. At the other end of the beam, there was a darkened 24.5 × 18 × 20-cm goal box. During preoperative training and postoperative testing, the animal was placed on the beam and the light and noise were turned on until the animal traversed the beam and entered the goal box. The rats were allowed to remain in the darkened box for 30 seconds. Training consisted of one trial every day until the animal traversed the length of the beam with no more than two foot slips on three consecutive trials. Each traversal was scored according to a well-characterized rating scale (Table 1). Rats that did not attempt to traverse the beam within 30 seconds were tapped on the tail with a standard pencil until they moved down the beam or 90 seconds had elapsed. If the animal did not completely traverse the beam within 90 seconds, the trial was ended and a score of 2 was given. All rats were tested at 24 hours postsurgery and then every day until sacrifice.

**Wire Clinging.** The focal cortical contusion produced in this study damaged the cortical areas representing both the forelimb and the hindlimb. Since the rating scale for the beam-walking task assesses the function of only the contralateral hindlimb, the wire-grip test was used to examine forelimb function. The rats were hung by the forepaws from a wire (1 mm in diameter) 36 cm above a foam pad. Latency to release of the wire was measured for each forelimb. The animals were allowed to hang only by their forepaws. If the rats placed their teeth, tail, or hindpaws on the wire, the trial was restarted. The animals were tested 24 hours following surgery and then every other day until sacrifice.

**Histological Procedures**

Twenty-eight days after surgery, the rats were given an overdose of sodium pentobarbital and transcardially perfused with phosphate-buffered saline followed by phosphate-buffered 10% formalin fixative. The whole head was stored in fixative overnight to avoid artifactual staining. After extraction from the skull, the brain was again placed in fixative for approximately 1 week. Forty-eight hours before sectioning, the brain was immersed in a 20% sucrose/10% formalin solution. For sectioning, the brain was quick-frozen with CO₂ and cut into 40-μm coronal sections with a cryostat microtome. Every fifth section from the olfactory bulb to the posterior cerebellum was mounted on a glass slide and stained with thionine.

The dorsolateral striatum, hippocampal CA3 region, ventral posterior thalamic nuclei, and medial geniculate nucleus ipsilateral to the cortical impact exhibit selective neuronal death following weight-drop focal cortical impact. These structures were studied in tissue sections at three planes relative to the bregma (0.48, 3.8, and 5.8 mm) to rate neuronal death and/or gliosis on a four-point scale by a blind rater. The rating scale used to quantify neuropathology in the above structures was as follows: 0 = no detectable neuropathological reaction; 1 = mild neuropathological reactions, some detectable thinning of cells but no large gaps between cells with or without perceptible glial proliferation; 2 = moderate neuropathological reactions, notable cell thinning with large gaps between cells with glial proliferation; and 3 = severe neuropathological

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**Table 1**

<table>
<thead>
<tr>
<th>Score</th>
<th>Performance Characteristic</th>
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<tbody>
<tr>
<td>7</td>
<td>animal traverses the beam with no more than two foot slips</td>
</tr>
<tr>
<td>6</td>
<td>animal traverses the beam using the left hindlimb to aid more than 50% of its steps on the beam</td>
</tr>
<tr>
<td>5</td>
<td>animal traverses the beam using the left hindlimb to aid less than 50% of its steps on the beam</td>
</tr>
<tr>
<td>4</td>
<td>animal traverses the beam, placing the left hindfoot on the horizontal surface of the beam without using the left hindlimb to aid in forward locomotion</td>
</tr>
<tr>
<td>3</td>
<td>animal traverses the beam while dragging the left hindlimb or showing treading/stepping motions with the left hindlimb, but does not place the left hindfoot on the horizontal surface of the beam during traverse</td>
</tr>
<tr>
<td>2</td>
<td>animal fails to traverse the beam, but places the left hindfoot on the horizontal surface of the beam</td>
</tr>
<tr>
<td>1</td>
<td>animal fails to traverse the beam and does not place the left hindfoot on the horizontal surface of the beam</td>
</tr>
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reactions, general poverty of cells with prominent glial proliferation. The anterior hypothalamus was also examined for cell loss and gliosis since this area is thought to be important in temperature regulation.26

The volume of cortical cavitation necrosis was estimated by reconstructing the lesion from the thionine-stained serial sections. An image-analysis system with a computer-assisted morphometry program, interfaced with an Olympus microscope,1 was used to calculate the area (in sq mm) of cavitation necrosis in sections at 1-mm intervals through the lesion. The area of the lesion in each section was calculated by subtracting the area of the remaining cortical tissue ipsilateral to the cortical contusion from the area of cortical tissue contralateral to the cortical contusion. To estimate lesion volume, the areas of the lesion in individual sections were multiplied by the distance between serial sections (1 ± 0.2 mm) and these volumes were summed. The anterior and posterior extent of the lesion was also determined by matching coronal sections to a brain atlas.70

Statistical Analysis

Temperature Changes. The mean time between implantation of the temporal muscle thermistor and TBI was 4.2 minutes (range 3 to 6 minutes). Therefore, the temperature at 4 minutes after temporal muscle thermistor implantation in the rats with scalp incision and those with scalp incision and craniotomy was matched with the temperature measured at the time of injury in the rats that received TBI. This time point will hereafter be referred to as "preinjury," with the understanding that at least one group without TBI is always referred to for comparison. Temperature at this preinjury time point was compared between groups using t-tests to examine the effects of surgery and anesthesia.

Since each rat’s temperature at the time of TBI differed, temperature at postrauma time points was compared using analysis of covariance (ANCOVA) with pre-TBI temperature as the covariate. Where significant interaction terms (time × group) were observed, all individual time points were examined with pairwise comparisons to clarify the specific time points that contributed to the interaction term.

Relationship Between TBI-Induced Brain Temperature Change and Outcome. The purpose of this study was to determine the relationship between TBI-induced brain temperature changes and outcome. Thus, temperature change scores were used in the analysis of the relationship between postraumatic temperature and TBI-induced neuropathology, locomotor deficits, and weight loss. Change scores were calculated with the following formula: (postrauma temperature at time X) – (temperature at time of TBI). This index of temperature change was calculated for each time point at which postraumatic temperature was measured.

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Fig. 1. Graph showing the effect of surgery and anesthesia on rat brain and body temperature. Body and brain temperatures were within the normal range for conscious, unanesthetized rats. Body temperature was reduced by anesthesia but was unaffected by surgery. Brain temperature was lowered by anesthesia alone and reduced further by the surgical procedures used to produce traumatic brain injury.

The relationship between the temperature change and outcome (beam-walking deficits, wire-clinging, weight loss, cortical necrosis, and neuropathology in the ventral thalamic nuclei, hippocampus, and striatum) were examined using the Pearson r statistic.

Results

Effects of Anesthesia

Brain Temperature. Mean brain temperature (± standard error of the mean (SEM)) was 38.0 ± 0.1°C in unoperated, conscious, restrained rats. This falls within the normal range reported by other investigators inferring brain temperature from measurements of the temporal muscle or skull.43,57 In the same unoperated rats, 7 to 10 minutes of halothane anesthesia lowered brain temperature to 36.8° ± 0.05°C. This decrease in brain temperature was statistically significant compared to unoperated, conscious, restrained rats (t[12] = 15.82, p < 0.001; Fig. 1).

Body Temperature. Mean body temperature (± SEM) was 37.7° ± 0.1°C in unoperated, conscious, restrained rats. This falls within the normal range for body temperature in the rat (range 37° to 38.5°C, mean 37.6°C).35 There was no evidence of a stress-induced increase in body temperature due to restraint;62,63 thus, the procedure to habituate rats to restraint was successful. Similar to brain temperature, 7 to 10 minutes of halothane anesthesia lowered body temperature to 36.8° ± 0.05°C in unoperated rats. The reduction in body temperature by halothane anesthesia was statistically significant compared to unoperated, conscious, restrained rats (t[12] = 14.0, p < 0.001; Fig. 1).

Effects of Surgery

Brain Temperature. Brain temperature was lowered to 36.54° ± 0.18°C after scalp incision in anesthetized
rats. This 0.26°C reduction in brain temperature was not statistically different from that in the unoperated, anesthetized rats (Fig. 1).

The combination of scalp incision and craniotomy lowered brain temperature to 35.97° ± 0.28°C. Thus, craniotomy produced an additional 0.57°C reduction in brain temperature compared to that in the rats with scalp incision only. The combination of scalp incision and craniotomy produced a reduction of 0.83°C compared to the temperature in anesthetized, unoperated rats. However, neither reduction was statistically significant (Fig. 1).

In the anesthetized rats with scalp incision, craniotomy, and placement of the injury device on the dura, the mean brain temperature prior to injury was 35.48° ± 0.28°C. Thus, placement of the injury device, which was at room temperature, produced an additional 0.49°C lowering of brain temperature compared to the temperature in the rats with scalp incision and craniotomy. This reduction was not statistically significant. However, compared to the anesthetized, unoperated rats, the animals undergoing a combination of scalp incision, craniotomy, and placement of the injury device footplate on the dura experienced a 1.32°C reduction in brain temperature. This comparison reached statistical significance (t(9) = 4.46, p < 0.002; Fig. 1).

While there was no significant difference in brain temperature between rats with scalp incision only and those with scalp incision and craniotomy at the pre-injury time point, ANCOVA on the time-matched post-trauma time points revealed that craniotomy influenced brain temperature. There was no significant group effect (F[1,13] = 2.44, p < 0.142) but both the interaction (F[41,574] = 1.67, p < 0.006) and time (F[41,574] = 23.37, p < 0.001) effects were significant. The significant time effect indicates that temperature rose significantly over the 6-hour measurement period. Pairwise comparisons at each time point after surgery were employed to determine the differences that contributed to the significant interaction term and revealed that the rats with scalp incision had significantly (p < 0.05) higher mean brain temperatures than those with scalp incision and craniotomy from 2 to 4 hours after surgery. However, there were no significant differences between these groups by the end of the temperature measurement period.

**Body Temperature.** None of the surgical procedures used in this study had an effect on body temperature over and above those produced by anesthesia (Fig. 1). Likewise, craniotomy had no effect on body temperature after surgery.

**Effects of Traumatic Brain Injury**

**Brain Temperature.** Analysis of covariance revealed that, comparing the rats with scalp incision and craniotomy to the animals with TBI, brain temperature was influenced by TBI. There was no significant group effect (F[1,15] = 2.89, p < 0.110); however, both the interaction (F[41,656] = 5.80, p < 0.001) and time (F[41,656] = 24.14, p < 0.001) effects were significant. As previously discussed, the significant time effect is interpreted as a significant increase in temperature over the 6-hour measurement period. Again, pairwise comparisons at each time point after TBI were employed to determine the differences that contributed to the significant interaction term and showed that TBI caused an immediate, statistically significant reduction in brain temperature from 35.48° ± 0.28°C to 34.9° ± 0.45°C (p < 0.007). Furthermore, brain temperature in rats with TBI remained significantly lower than that in the rats with scalp incision and craniotomy for the first 5 minutes after injury (p < 0.027). Brain temperature in the brain-injured rats was not significantly different from that in the rats with scalp incision and craniotomy during the remainder of surgery. However, immediately following termination of anesthesia, brain temperature in the brain-injured rats rose above that in the rats with scalp incision and craniotomy and remained slightly, but consistently, elevated throughout the period of observation. Notably, these groups were significantly different only at 20 minutes after termination of anesthesia (p < 0.04; Fig. 2).

**Body Temperature.** Analysis of covariance was also used to examine changes in body temperature induced by TBI. All effects tested with ANCOVA for measures of body temperature were statistically significant: group (F[1,15] = 5.37, p < 0.035), interaction (F[41,656] = 1.90, p < 0.001) and time (F[41,656] = 6.27, p < 0.001). The significant group effect indicates that the brain-injured rats had a higher body temperature than the rats with scalp incision and craniotomy throughout the posttraumatic measurement period. The differences that contributed to the significant interaction term were examined with pairwise comparisons at each time point after TBI in the same manner as the data on brain temperature and showed that TBI did not change body temperature during anesthesia. However, body temperature, like brain temperature, rose above that in controls immediately after termination of anesthesia. Furthermore, 30 minutes after the termination of anesthesia, body temperature was significantly greater than that in rats with craniotomy and remained relatively (but not always significantly) hyperthermic compared to that in the rats with scalp incision and craniotomy (Fig. 2).

**Relationship Between Brain and Body Temperatures**

In addition to lowering both body and brain temperatures, anesthesia changed the relationship between these temperatures. In the normal unanesthetized rat, brain temperature is slightly higher than that of the body.1 In this study, mean brain and body temperatures in conscious, unoperated rats were 38.0° and 37.7°C, respectively. Prior to TBI, anesthesia alone eliminated this difference between body and brain temperatures. Furthermore, surgical procedures lowered brain (but not body) temperature (Fig. 1).

Likewise, TBI changed not only the levels of brain and body temperature, but also the relationship between these variables. In operated control animals, the normal 0.3°C difference between brain and body temperatures, which was eliminated or reversed by anesthesia and
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![Graph showing temperature changes over time after brain injury.](image)

**Fig. 2.** Graph demonstrating the effect of traumatic brain injury (TBI) on brain and body temperature. Brain temperature prior to weight-drop focal impact injury (Pre) was slightly lower in animals with craniotomy and placement of the footplate of the injury device on the dura than in those with craniotomy alone. Body temperature was the same in both groups. Traumatic brain injury caused an immediate drop in brain (but not body) temperature during the first 5 minutes after injury. Immediately following termination of anesthesia (arrow), both body and brain temperatures in brain-injured rats rose above that in animals with craniotomy. Body and brain temperature of brain-injured rats remained consistently elevated relative to control values. Also illustrated is the abnormal relationship between brain and body temperature in brain-injured rats. Note that approximately 3 hours after termination of anesthesia in the group with craniotomy, the difference between brain and body temperatures observed in conscious, unoperated rats is restored. However, this normal relationship between brain and body temperatures does not return during the 6-hour measurement period in rats with TBI.

surgery, returned by 3 hours after termination of anesthesia. In contrast, this normal difference had not returned by 6 hours in the rats that received TBI (Fig. 2).

**Correlation of Temperature With Measures of Outcome**

**Brain Temperature Change.** The levels of brain and body temperature were correlated with all outcome measures using the Pearson r statistic. However, this set of tests produced no identifiable pattern of correlations between the level of either brain or body temperature after TBI and any outcome measure. Only when the TBI-induced change in brain temperature was correlated with outcome was there an interesting pattern of results.

The change in brain temperature between the time of TBI and either 5 or 10 minutes after termination of anesthesia was predictive of several measures of outcome. Specifically, there was a significant correlation between the change in brain temperature from the time of TBI to 5 minutes after termination of anesthesia (15 to 20 minutes after TBI) and pyramidal cell loss in the ipsilateral hippocampal CA3 region (r = -0.8332, p < 0.003; Fig. 3 upper left). Similarly, neuronal loss and gliosis in the ipsilateral ventral posterior thalamic nuclei were related to the change in brain temperature from the time of impact to 5 minutes after termination of anesthesia (r = -0.7154, p < 0.020; Fig. 3 upper right). Figure 4 illustrates this hippocampal and thalamic pathology in the rat with the greatest change in brain temperature and in the rat with the smallest change in brain temperature (Fig. 4c and d). There was no significant relationship between duration of anesthesia and change in brain temperature at 5 minutes after termination of anesthesia.

At the next time point at which a temperature reading was taken (10 minutes after termination of anesthesia) the change in brain temperature was correlated with neuronal loss and gliosis in the ipsilateral medial geniculate nucleus (r = -0.7157, p < 0.020; Fig. 3 lower left) and the volume of cortical cavitation necrosis (r = -0.6860, p < 0.0285; Fig. 3 lower right). The cortical cavitation for the rat with the greatest change in brain temperature and the rat with the smallest change in brain temperature is illustrated in Fig. 5.

More importantly, functional measures of outcome including beam-walking performance deficits at 24 hours after injury (r = 0.7100, p < 0.021) and weight loss (r = -0.7066, p < 0.022) were significantly cor-
related with the change in brain temperature from the time of TBI to 10 minutes after termination of anesthesia (Fig. 6). The change in brain temperature 10 minutes after termination of anesthesia was not correlated with the duration of anesthesia.

None of several other measures of outcome, including neuropathology in the dorsolateral striatum, contralateral wire-clinging bias at 24 hours after TBI, time to recovery of baseline beam-walking performance, and number of behaviorally observable seizures, was related to temperature changes at either 5 or 10 minutes after termination of anesthesia. Moreover, only contralateral wire-clinging bias was related to brain temperature change at any time point after TBI. Contralateral wire-clinging bias, possibly analogous to the pathological grasp observed in human patients after cortical injury, was observed in all brain-injured rats at 24 hours after injury and was best predicted by the change in brain temperature at 60 minutes after termination of anesthesia. Brain temperature change between the time of impact and this time point was not related to any other measure of outcome.

Other Correlations. Mean brain temperature at the time of TBI was positively correlated with neuronal loss in the hippocampal CA3 region ($r = 0.7030, p < 0.023$) and gliosis in the ventral posterior thalamic nuclei ($r = 0.7255, p < 0.018$) but not with other measures of outcome. Unlike brain temperature change, the same measure of body temperature change after TBI produced no consistent pattern of significant correlations. No neuropathology was observed in any portion of the hypothalamus and thus temperature could not be correlated with neuropathology in this area.

Discussion

The present study examined the effects of TBI on brain and body temperatures and correlated TBI-induced brain and body temperature changes with several measures of outcome. The novel findings of this study are that TBI, produced by weight-drop focal impact trauma to the sensorimotor cortex, alters both brain and body temperatures and that brain temperature changes induced by TBI are correlated with some neu-
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Fig. 4. Photomicrographs illustrating the relationship between neuropathology ipsilateral to the weight-drop focal cortical impact and the rate at which brain temperature returned toward normal in rats with traumatic brain injury. Thionine. X 24. a: Specimen from a representative rat with scalp incision only. b: Specimen from a representative rat with scalp incision and craniotomy. c: Specimen from the rat with the most rapid return of brain temperature toward normal after TBI. d: Specimen from the rat with the slowest return of brain temperature toward normal after TBI.

ropathology, some locomotor deficits, and weight loss in this model. In addition, this study replicated the results of several others, confirming that anesthesia and surgery lower both brain and body temperatures, that TBI disrupts the normal relationship between brain and body temperatures, and that measures of brain temperature at certain times after trauma are not sensitive to the effects of TBI.

Effect of Traumatic Brain Injury on Temperature

Traumatic brain injury caused bidirectional changes in brain temperature. Immediately following TBI, brain temperature was reduced, with no corresponding effect on body temperature. The TBI-induced lowering of brain temperature was quite transient, lasting for only 5 minutes after impact. During the remainder of the surgical/anesthetic period, brain temperature in the rats with brain injury was not significantly different from that in the animals with craniotomy. However, within the first 10 minutes after the termination of anesthesia, both brain and body temperatures in the brain-injured rats rose above that in the rats with craniotomy. This relative hyperthermia of brain and body temperature in the brain-injured rats remained consistent, although not always statistically significant, throughout the 6-hour measurement period. Brain and body hyperthermia has also been observed in human patients after severe TBI (L. Sternau, et al. and DW Marion, unpublished data).

The effects of TBI on brain and body temperatures in this study are quite similar to those reported in models of cerebral ischemia. Ischemia, like TBI, induced an immediate drop in brain temperature which is not accompanied by a lowering of body temperature. Hypothermia during the ischemic period is followed by hyperthermia of both the body and the brain during recirculation. Furthermore, in this model of TBI and in ischemia, hyperthermia develops only after termination of halothane anesthesia.

The mechanism of the temperature changes observed after TBI is unknown. Because the effects of ischemia and trauma on both body and brain temperatures are quite similar and since temperature has been much more widely studied in ischemia than in trauma, the literature on ischemia was examined for information on the possible mechanisms of temperature change. The cooling of the brain during cerebral ischemia has been proposed to result from the lack of blood flow to the scalp, muscle, and skull surrounding the brain. The carotid artery occlusion used to produce cerebral ischemia also stops blood flow to the tissue surrounding the brain. By allowing these tissues to drop to room temperature, the conduction of heat from the deeper tissues to the environment increases, resulting in a lowering of brain temperature. This cannot be the case for TBI since the compromise of circulation to the tissues of the head is produced only by the surgical procedure and surgery alone did not cause the temperature fluctuations observed after TBI. Thus, other factors that contribute to temperature regulation must be examined to account for TBI-induced temperature changes.

One alternative mechanism for the changes in temperature observed after TBI is an imbalance between energy metabolism and blood flow. The maintenance of a constant temperature is critically dependent on a precise balance between energy metabolism and blood flow because in all deep body organs, including the brain, metabolic activity is the heat source and arterial blood the heat sink. Thus, temperature rises when the rate of metabolic heat production is greater than the rate of heat removal by the arterial blood; cooling results when the reverse is true.
Given this relationship between blood flow, energy metabolism, and temperature, it is reasonable to expect that TBI-induced changes in cerebral blood flow and metabolism will result in changes in brain temperature. The relationship between metabolism and blood flow has not been examined in this model of TBI during the period in which temperature was measured. However, in several other models of TBI and across diverse species, cerebral trauma induces large changes in both cerebral blood flow and energy metabolism beginning seconds after TBI and lasting hours after TBP.\textsuperscript{15,16,18–20,25,50,55,66–69,71,76,77,80,82,85,87,88,89} (MP Weisend, \textit{et al.}, unpublished data). While changes in cerebral blood flow and metabolism may be a mechanism of temperature change, the sequelae of TBI, such as neurochemical disturbances, hemorrhage, increased intracranial pressure, and secondary ischemia, are likely to be the cause of changes in cerebral blood flow and metabolism. Furthermore, changes in the neurochemistry, perfusion, and/or metabolism in structures critical for temperature regulation, such as the hypothalamus, could also contribute to the temperature disturbances observed after TBI, as has been proposed in ischemia.\textsuperscript{96}

Like the biphasic changes in brain temperature after TBI, the relative hyperthermia of body temperature observed after termination of anesthesia is likely to result from a combination of factors. Traumatic brain injury induces a prolonged period (days to weeks) of peripheral hypermetabolism in humans,\textsuperscript{18} during which body temperature is elevated.\textsuperscript{93} In addition, TBI can produce a massive release of peripheral catecholamines,\textsuperscript{73} which can cause thermogenesis.\textsuperscript{47} The peripheral metabolic response to brain injury has not been well studied in controlled laboratory experiments. It should be noted that the relative hyperthermia of the body core and brain are probably associated. A warmer core tempera-
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![Graphs showing relationship between temperature change and beam-walking score and weight loss.](image)

**Fig. 6.** Regression plots of the relationship between the rate of return toward normal of brain temperature and beam-walking ability or weight loss. **Left:** Relationship of postcontusion temperature change at 10 minutes after termination of anesthesia to beam-walking performance 24 hours after traumatic brain injury ($r = 0.7100$, $p < 0.021$). Lower scores mean greater impairment. **Right:** Relationship of postcontusion temperature change at 10 minutes after termination of anesthesia to weight loss ($r = -0.7066$, $p < 0.022$).

...ture will circulate warmer arterial blood to the brain and reduce the capacity of the arterial blood to dissipate heat generated in the brain.

**Relationship Between Brain Temperature and Outcome**

The second novel finding in this study was that several measures of outcome were correlated with the magnitude of the change in brain temperature induced by TBI. These same measures of outcome were not correlated with changes in body temperature or with the levels of brain or body temperature after TBI. Specifically, the increase in brain temperature measured from the time of TBI to 5 or 10 minutes after termination of anesthesia was correlated with beam-walking disability, weight loss, and several measures of neuropathology, including volume of cortical necrotic cavitation, pyramidal cell loss in the hippocampal CA3 region, gliosis in the ventral posterior thalamic nuclei, and neuronal loss in the medial geniculate nucleus. The nature of these relationships was unexpected. It was originally hypothesized that, with increased temperature after TBI, rats would be more behaviorally impaired and more anatomically damaged. However, the results of this experiment show that the rats that became warmer more quickly after termination of anesthesia had better outcomes for the measures discussed above, while those that had smaller increases in temperature had worse outcomes.

The observation that rats with greater increases in brain temperature following TBI are less behaviorally impaired and neuroanatomically damaged is quite surprising since hyperthermia worsens the sequelae of both ischemia and TBI. Notwithstanding, the increase in brain temperature from the time of TBI to shortly after termination of anesthesia can be thought of as the rate at which brain temperature returns toward normal. The rate at which a symptom abates or a function returns after a brain injury is thought to reflect the severity of the injury. Likewise, the data from this study indicate that differences in the rate at which brain temperature returns toward normal reflect the severity of the insult. Hence, the rate of brain temperature increase is probably not causally related to the severity of behavioral impairments and neuroanatomical damage. In simpler terms, the rate at which brain temperature returns toward normal is indicative of, but is not likely to influence, the severity of the TBI and thus predicts the ultimate outcome.

One alternative to this interpretation is that rats with more severe brain injuries regulate their brain temperature at a lower level. This idea is supported by the observation that animals spontaneously regulate their temperature at a lower level in response to toxins, hypoxia, and hypoglycemia. This presumably reflexive response increases the survival of animals under these conditions.

The data from this investigation cannot differentiate between an inability of the severely injured brain to return toward normal temperature and an actively suppressed temperature to protect against a severe brain injury; although in either case, our data can be interpreted to mean that prolonged depression of temperature indicates that a rat has sustained a more severe injury. These data should not be interpreted to mean that warming to normothermia is protective. In fact, if one entertains the possibility that rats with more severe injuries may be defensively lowering their brain temperatures, cooling to augment the reflexive response to TBI would be prudent.

Brain temperature at the time of TBI was significantly correlated with neuropathology in the hippocampal CA3 region and the ventral posterior thalamic nuclei, but not with any other neuroanatomical or neurological measure of outcome. The rats with lower brain temperatures at the time of TBI had less hippocampal CA3 and thalamic pathology. This is similar to the many other investigations showing that brain tem-

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perature is an important factor in the sequelae resulting from several cerebral insults, including TBI. Since the reduction in brain temperature at the pre-TBI time point resulted from anesthesia and the surgical technique used to produce TBI, procedurally induced alterations of brain temperature may be an important source of variability when modeling TBI.

Replication of Previous Findings

In addition to the novel findings discussed above, this study replicated the results of several other studies examining thermal responses to injury and anesthesia. Jiang, et al., 43 found no effect of cerebral fluid perfusion on brain temperature. Their conclusion was based on a single reading of brain temperature 10 minutes after fluid-perfusion brain injury in anesthetized rats. When the brain temperature data from this study are examined at 10 minutes after weight-drop focal impact (at which time the rats in this study were also anesthetized), the findings of this study (Fig. 2) are identical to those reported by Jiang, et al. Our data indicate that TBI-induced hypothermia abated by 10 minutes after cortical impact and that relative hyperthermia was present only after termination of anesthesia.

Jiang, et al., 43 also reported dissociation of body and brain temperature. The model of TBI in our study also produced a transient dissociation of body and brain temperatures immediately after impact. The more enduring effect on the relationship between brain and body temperatures in this study was not dissociation but extremely close association. In fact, the normal difference between body and brain temperatures (0.3°C) did not return within 6 hours after surgery in the brain-injured rats, but was present by 3 hours in all uninjured controls. Thus, this model of TBI produces disturbances in the relationship between body and brain temperatures similar to and different from those previously reported.

The data gathered in this investigation are similar to studies demonstrating that halothane anesthesia lowers both body and brain temperatures. 75 Halothane anesthesia probably lowered temperature by reducing energy metabolism while increasing superficial blood flow. 7,38,45,81 Surgery probably selectively lowered brain temperature by simply removing the insulating tissues, 34 causing excessive heat loss from the brain but not from the body. The thermal effect of surgery is much less frequently reported in the animal literature, although its importance in clinical work is recognized. 42

Conclusions

Our study results have important implications for those using animal models of TBI. Anesthesia combined with surgery to expose the dura lowered brain temperature to levels reported to be protective in models of ischemia and TBI. 11,17 These procedurally induced brain temperature changes were correlated with hippocampal and thalamic pathology resulting from TBI. Thus, procedurally induced changes in brain temperature in models of TBI are likely to be important sources of variability in the pathology observed after TBI, just as in models of ischemia. 5,21 Furthermore, TBI causes an immediate reduction in brain temperature, followed by hyperthermia (relative to control values). The rate at which brain temperature returns to normal is correlated with, but is unlikely to be causally related to, the neuroanatomical sequelae, beam-walking deficits, and weight loss resulting from TBI. Specifically, the rats in which the brain temperature returns to normal very rapidly have a better outcome than those with prolonged depression of brain temperature. Consequently, the magnitude of the TBI-induced brain temperature disturbance is interpreted as an index of the severity of the pathological processes induced by TBI, possibly perturbations of cerebral blood flow and metabolism.

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