Electrophysiological Properties of CA1 Neurons Protected by Postischemic Hypothermia in Gerbils

H. Dong, PhD; F. Moody-Corbett, PhD; F. Colbourne, PhD; Q. Pittman, PhD; D. Corbett, PhD

Background and Purpose—Recent studies show that prolonged (eg, 24-hour) postischemic hypothermia confers lasting histological and behavioral protection against severe global cerebral ischemia. However, functional abnormalities may be compensated for by undamaged brain regions and thus not detected by behavioral tests. To determine whether hypothermia preserves CA1 functional integrity, we measured synaptic and membrane properties of CA1 neurons in ischemic gerbils treated with postischemic hypothermia.

Methods—Gerbils were subjected to 5 minutes of forebrain ischemia and were either left untreated or exposed to 2 days of hypothermia (32°C for 24 hours and then 34°C for 24 hours). Sham animals were operated on but not made ischemic, then either allowed to recover at room temperature or subjected to hypothermia for 2 days. Approximately 5 weeks after ischemia or sham surgery, patch-clamp recordings were obtained from the CA1 region of hippocampal slices.

Results—There was approximately 95% CA1 cell loss in untreated ischemic animals, whereas ischemic gerbils treated with hypothermia had cell counts similar to sham animals. Resting membrane potential, action potential amplitude and duration, input resistance, and synaptic currents evoked by Schaffer collateral stimulation were similar between pyramidal cells obtained from ischemic gerbils treated with hypothermia and sham-operated animals ($P > 0.05$).

Conclusions—These data demonstrate that postischemic hypothermia preserves the measured electrophysiological properties of CA1 neurons in the absence of any apparent functional abnormalities. This study provides further support for the use of hypothermia as a treatment for cerebral ischemia. (Stroke. 2001;32:788-795.)

Key Words: cerebral ischemia, global ■ hippocampus ■ hypothermia ■ neuroprotection ■ gerbils

Prolonged (eg, 24-hour) postischemic hypothermia conveys permanent histological protection against global ischemia.1,2 Importantly, hypothermia also attenuates impairments in habituation and working memory that ordinarily accompany this type of injury.2,3 However, it is difficult to determine to what extent behavioral protection represents true preservation of CA1 neuronal function or instead reflects recovery/compensation mediated by undamaged nonhippocampal circuitry. Thus, while hypothermia largely prevents CA1 cell death, neuronal function could still be abnormal, albeit masked by recovery/compensatory processes intrinsic and distal to the CA1 sector of the hippocampus.4 Indeed, CA1 neurons salvaged by postischemic hypothermia are not always entirely normal with respect to ultrastructural features.5

One way to avoid these interpretative pitfalls is to assess the functional state of CA1 neurons by characterizing their electrophysiological properties. Previous electrophysiological studies6–12 have used this approach; however, they were concerned with identifying short-term (eg, <24 hours after ischemia) events related to irreversible CA1 injury in non-treated animals. In contrast, the goal of this study was to directly assess the membrane and synaptic properties of CA1 neurons that were protected by 48 hours of postischemic hypothermia in gerbils that were allowed to survive for a minimum of 30 days after ischemia. This was accomplished by using patch-clamp recording techniques in hippocampal slices harvested from sham-operated gerbils and from gerbils subjected to forebrain ischemia followed by hypothermia.

Materials and Methods

Animals
Twenty-four female gerbils from High Oak Farms (Baden, Ontario, Canada) weighing 50 to 60 g were used in the study. All animals were group housed in Plexiglas cages until the time of surgery, after which they were maintained individually. Food and water were freely available. All experimental procedures were approved by the Animal Care Committee of the University of Calgary and were in compliance with recommendations established by the Canadian Council on Animal Care.

Surgery and Temperature Control
Under sodium pentobarbital anesthesia (65.0 mg/kg IP), gerbils were implanted with a 5.0-mm stainless steel guide cannula as previously...
**TABLE 1. Groups Used to Generate Electrophysiological and Histological Data**

<table>
<thead>
<tr>
<th>Group</th>
<th>Patch-Clamp Recording</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham + hypothermic</td>
<td>n = 4</td>
<td>...</td>
</tr>
<tr>
<td>Sham</td>
<td>n = 5</td>
<td>n = 2</td>
</tr>
<tr>
<td>Ischemic + hypothermic</td>
<td>n = 7</td>
<td>n = 3</td>
</tr>
<tr>
<td>Ischemic</td>
<td>...</td>
<td>n = 3</td>
</tr>
</tbody>
</table>

Animals were exposed to >48 hours of hypothermia 1 hour after ischemia/sham surgery. Other animals were normothermic. n refers to the number of gerbils per group. See text for more details.

Described. Two days later, 8.0-mm brain temperature probes (model XM-FH, Mini-Mitter Co) were inserted to measure temperature from the dorsomedial striatum (approximately the same depth as the CA1 cell layer). Baseline temperature was recorded every 30 seconds for 24 hours while animals were individually housed in cages that rested on RPC-1 receivers (DataSciences, Int).

Ischemia or sham operation was performed 4 days after cannula implantation. Briefly, gerbils were anesthetized with halothane (2% in 70% air, 28% O2) followed by isolation of the common carotid cages that rested on RPC-1 receivers (DataSciences, Int). Baseline temperature was recorded every 30 seconds for 24 hours while animals were individually housed in cages. Ischemia/reperfusion was induced by occlusion of the common carotid arteries. Gerbils subjected to ischemia had their carotid arteries occluded with microaneurysm clips for 5 minutes. Sham animals were operated on but not made ischemic. Brain temperature was regulated near 36.4°C in all animals by an overhead infrared lamp that was servo-controlled.13 Arteries were visually inspected to ensure reflow after clip removal. After suturing of the neck wound, the gerbils had their back and abdomen shaved to facilitate postischemic temperature control. Anesthesia was then quickly discontinued, and animals were returned to their cages.

Sixteen of the gerbils were used solely for patch-clamp recording, while the other 8 animals were used for histological analysis (Table 1). The sham-operated animals were divided into 3 groups. One group was allowed to regulate its own postsurgical temperature and was therefore normothermic (n = 5). The second sham group (n = 4) was exposed to >2 days of mild hypothermia (Figure 1) starting 1 hour after sham operation, as described previously. The remaining 2 sham gerbils were used to provide normative CA1 cell counts. These animals regulated their own postischemic temperatures except during the first hour, when an infrared lamp was activated whenever the temperature fell below 37.0°C. This postischemic temperature regulation was rarely enabled because of the tendency of gerbils to display a mild degree (approximately 0.7°C) of postischemic hyperthermia immediately after recovery from anesthesia. The ischemic gerbils treated with postischemic hypothermia (ischemic + hypothermic group; n = 10) were similarly maintained during the first hour, after which hypothermia was induced and maintained for >2 days. Seven of these animals were used for electrophysiological experiments, and 3 were used to gauge the efficacy of hypothermia in protecting CA1 neurons. Hypothermia was produced in the awake animal by an automated system that uses infrared lamps to heat and fine-spray water misters and fans to cool.13 Finally, 3 gerbils made up an untreated (ie, normothermic) ischemia group for estimation of CA1 cell loss.

**Patch-Clamp Recording**

All electrophysiological experiments were performed by an individual unaware of the experimental treatment. After a minimum survival time of 30 days after surgery, ischemic + hypothermic (n = 7) and sham-operated gerbils (n = 8) were decapitated, and the brains were quickly removed and placed in ice-cold, artificial cerebrospinal fluid (aCSF) containing sucrose. The composition was as follows (in mmol/L): KCl 2.0, NaH2PO4 1.15, MgCl2 7.0, CaCl2 0.5, NaHCO3 26, glucose 11, and sucrose 250, bubbled with 95% O2/5% CO2 (pH 7.4). Transverse 300-µm slices were cut with a vibratome (Leica) and incubated in the aforementioned solution at room temperature (22°C) for at least 1 hour before recording. Slices were then transferred to a 500-µL recording chamber, where they were submerged and continuously perfused with warmed aCSF (34°C) bubbled with 95% O2/5% CO2 at a flow rate of 2 to 3 mL/min. The composition of the aCSF was as follows (in mmol/L): NaCl 126, KCl 2.5, NaH2PO4 1.2, MgCl2 1.2, CaCl2 2.4, NaHCO3 18, and glucose 11 (pH 7.3). To eliminate possible GABAergic contamination of the synaptic response, 50 µmol/L picrotoxin was added to the aCSF.

Nystatin perforated-patch recordings from hippocampal CA1 neurons were made with glass micropipettes (Garner Glass Co; tip resistances, 5 to 15 MΩ).4 Pipette tips were filled with nystatin-free internal recording solution (in mmol/L): K-acetate 120, MgCl2 5, EGTA 10, HEPES 40 (pH 7.3)) and back-filled with the same solution containing 450 µg/mL nystatin and Pluronic F-127 (dissolved in dimethyl sulfoxide). High-resistance seals (1 to 3 GΩ) were made with the use of an Axoclamp 2A amplifier, and access to the cell was obtained within 30 minutes after seal formation. Records were filtered at 1 kHz, and series resistance was not compensated. pClamp software (Axon Instruments) was used for data acquisition, voltage and current control, and data analysis.

Resting membrane potential and action potential amplitude and duration were recorded in current-clamp mode. To measure the properties of the action potentials, the cells were held near resting membrane potential (but below spike threshold), and current was injected in 40-pA increments (250-ms duration) until action potentials were elicited. The amplitude from baseline and the duration to the onset of the afterhyperpolarization were measured for the first action potential elicited by a depolarizing pulse. The threshold for generating action potentials was determined from ramps applied in current-clamp mode. From resting potential, a −0.3-mV current was introduced into the cell and ramped over 2 seconds to +0.5 mV. Input resistance was calculated from the steady state current measured in response to a hyperpolarizing 10-mV pulse (100-ms duration) from a holding potential of −70 mV.

To elicit synaptic responses, a bipolar silver wire electrode was placed in the stratum radiatum between CA3 and CA1. Schaffer collaterals were activated with monophasic pulses (1 to 8 V; 0.2 ms) applied to the stimulating electrode at 10-second intervals and recorded as inward currents under voltage clamp control from a holding voltage of −70 mV.

**Histology**

Additional gerbils (sham [n = 2], ischemic [n = 3], and ischemic + hypothermic [n = 3]) were perfused with saline followed by 10% buffered formalin. Brains were subsequently embedded in
paraffin before sectioning at 6.0 μm and staining with hematoxylin and eosin. The total number of normal-appearing CA1 cells was counted (×40) in 3 sectors (medial, middle, and lateral) of the rostral hippocampus (−1.7 mm posterior to bregma) from each hemisphere, as previously reported. Only neurons with a clearly defined cell membrane and nucleus were recorded. Eosinophilic cells, which were rarely present at these long survival times, were noted but not counted. Histological assessments were performed by an individual blinded to the treatment protocol.

Data Analysis
At the end of the experiments and after quantification of cell numbers and electrophysiological and synaptic properties, the code was broken, and data were assigned to the various treatment groups. A small number of animals (n=2 to 3) were used in each of the histological groups because we have repeatedly shown highly consistent levels of neuroprotection with long-duration postischemic hypothermia. Because of the small number of subjects, no statistical analysis was performed on these data. Electrophysiological data were compared between groups by Student’s t test or by repeated-measures ANOVA, as appropriate.

Reagents
All chemicals for the aCSF were obtained from Sigma, as were picrotoxin, nystatin, and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX). Pluronic F127 was obtained from BASF.

Results
The postischemic brain temperature profiles are shown in Figure 1. The temperatures of the sham animals closely approximated those of ischemic gerbils except for the brief period of mild postischemic hyperthermia observed in the latter group, which is characteristic of this model. The ischemic and sham gerbils were cooled effectively to the desired levels. Intraischemic temperatures were not significantly different among the treatment groups (range, 35.9°C to 36.0°C). The cooling procedure resulted in virtually complete histological protection of CA1 neurons (ischemic+hypothermic group=106% of sham counts), whereas untreated ischemic gerbils exhibited almost total loss (1.5% of sham counts) of these neurons (Figure 2). All animals tolerated the prolonged hypothermia without overt signs of malaise or stress, as noted previously.

A previous study has demonstrated a rapid loss (10 to 24 hours) of CA1 field potentials after 5 minutes of ischemia in the gerbil, followed by marked cell death between 48 and 72 hours. Since so few neurons remain after 30-day survival, no attempt was made to perform patch-clamp recordings in such animals. Good-quality, stable recordings of at least 30 minutes’ duration (but usually of 2 to 3 hours’ duration) were obtained from 78 cells in hippocampal slices obtained from 3 sham animals, 3 sham+hypothermic animals, and 6 ischemic+hypothermic animals. Inspection of the electrophysiological data from the sham and the sham+hypothermic animals indicated no differences, and therefore these data have been grouped. Resting and regenerative membrane properties are described in Table 2, and an example is shown in Figure 3. Recorded values did not differ between sham and ischemic+hypothermic cells. Under our recording conditions, resting membrane potential was approximately −64 mV in cells from both sham (n=35) and ischemic+hypothermic (n=43) groups; input resistance was 155 MΩ in the former and 130 MΩ in the experimental groups (P>0.05). Under current clamp, a series of hyperpolarizing pulses elicited a family of voltage deflections (from which input resistance was calculated), which revealed in most cells, both sham and experimental, a slight time-dependent sag in the voltage responses suggestive of an inward rectifier. No attempt was made to characterize this feature.

TABLE 2. Summary of Electrophysiological Data Collected in This Study

<table>
<thead>
<tr>
<th>Electrophysiological Properties</th>
<th>Sham Group</th>
<th>Ischemic+ Hypothermic Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting membrane potential, mV</td>
<td>−64.1±4.5</td>
<td>−64.4±4.4 (n=43)</td>
</tr>
<tr>
<td>Action potential amplitude, mV</td>
<td>78.4±9.4</td>
<td>80.5±10.0 (n=42)</td>
</tr>
<tr>
<td>Action potential duration, ms</td>
<td>3.4±.5</td>
<td>3.5±.5 (n=42)</td>
</tr>
<tr>
<td>Action potential threshold, mV</td>
<td>−49.8±4.6</td>
<td>−51.4±5.0 (n=43)</td>
</tr>
<tr>
<td>Input resistance, MΩ</td>
<td>155.6±52.2</td>
<td>130.3±60.3 (n=42)</td>
</tr>
</tbody>
</table>

None of the measured membrane properties (mean±SEM) differed between sham (n=10) and ischemic+hypothermic groups (n=7 gerbils; P>0.05, t test).
At resting potential, there was little spontaneous activity in either group, even in the presence of 50 μmol/L picrotinox. However, action potentials were obtained on depolarization in all cells. In preliminary experiments on hippocampi from untreated animals, performed without picrotinox in the bath, depolarization was associated with an initial couplet of action potentials, which were followed by several individual action potentials. In the presence of picrotinox, this pattern was still seen (Figure 3), although other cells from both sham and ischemic+hypothermic animals displayed depolarization-induced bursts of action potentials firing at approximately 100 Hz. Intervals between bursts were variable but usually were 100 to 200 ms in length. Whatever the pattern, action potential amplitude and duration were similar in the 2 groups. In a representative group of 14 ischemic+hypothermic and 12 sham-pretreated neurons, 64% of the former and 66% of the latter displayed an afterhyperpolarization. Thus, this feature did not differ between sham-operated gerbils at normothermic or hypothermic temperatures.

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Because we were interested in evaluating excitatory transmission without contamination of synaptic responses by either feed-forward or feedback inhibitory responses, we blocked GABAergic transmission. In preliminary experiments, we determined that 50 μmol/L picrotinox was sufficient to block GABAergic synapses, since an increase in the concentration to 100 μmol/L produced no further alteration in the synaptic responses. However, in the presence of 50 μmol/L picrotinox, we observed that inclusion of CNQX (10 μmol/L) completely abolished the remaining current, indicating that it was mediated by non-N-methyl-d-aspartate (NMDA)-type receptors (data not shown).

To facilitate comparisons between groups, synaptic currents were obtained from cells held at −70 mV. In both sham
(n=28) and ischemic+hypothermic (n=23) groups, a single peak inward current was elicited that, on visual inspection, showed similar rise and decay trajectories (Figure 5a and 5b). On occasion, a small outward current was seen that followed the inward current, but this was not a consistent feature of either sham or experimental cells, and the identity is unknown. Because of variability in slice orientation and proximity of the stimulating electrode to the recorded cell, there was considerable variability in the stimulus response characteristics of the excitatory postsynaptic current (EPSC). To determine whether this was similar in the 2 groups, stimulus intensity was varied in 1-V increments, and the size of the EPSC at its first appearance was measured. As can be seen in Figure 5c and 5d, the range of EPSC magnitudes elicited at "threshold" voltage for each cell is very similar between sham and ischemic+hypothermic groups. When we averaged these values, the EPSC size, at the threshold voltage, was identical in the 2 groups (Figure 6a). Another way to look at synaptic strength is to determine the magnitude of the inward current, but this was not a consistent feature of either sham or experimental cells, and the identity is unknown. Because of variability in slice orientation and proximity of the stimulating electrode to the recorded cell, there was considerable variability in the stimulus response characteristics of the excitatory postsynaptic current (EPSC). To determine whether this was similar in the 2 groups, stimulus intensity was varied in 1-V increments, and the size of the EPSC at its first appearance was measured. As can be seen in Figure 5c and 5d, the range of EPSC magnitudes elicited at “threshold” voltage for each cell is very similar between sham and ischemic+hypothermic groups. When we averaged these values, the EPSC size, at the threshold voltage, was identical in the 2 groups (Figure 6a). Another way to look at synaptic strength is to determine the magnitude of the stimulus to activate the synapse. We found that the average stimulus voltage required to elicit the first identifiable EPSC was identical in the 2 groups (Figure 6b; n=28 sham, n=23 ischemic+hypothermic; P>0.05, t test), as was the stimulus voltage at which the first action potential was elicited (Figure 6c). We also looked at 2 other features of the EPSC. A stimulus-response relationship was calculated for 5 cells in each group in which the initial EPSC elicited at 1-V stimulation strength was similar. With increasing stimulation voltage, the EPSC size increased in a similar manner in the sham and ischemic+hypothermic groups (Figure 7). In these experiments, holding potential was at −70 mV to prevent spiking.

The effect of driving force on the current magnitude was determined by eliciting the EPSC 50 ms after the membrane potential was clamped at various voltages between −60 and −100 mV. As expected, this caused a progressive increase in the size of the EPSC (Figure 8), and the relationship between holding potential and EPSC magnitude was similar in cells taken from sham and experimental animals (P>0.05, ANOVA). Thus, there was no evidence of alteration in synaptic properties in slices taken from sham gerbils or those subjected to ischemia plus hypothermia.

**Discussion**

Prolonged postschismic hypothermia (48 hours, delayed by 1 hour) conveyed essentially total histological protection of CA1 neurons against a severe global ischemic insult >30 days after occlusion. This confirms previous findings which indicated that hypothermia of varying duration is highly effective in rescuing neurons after ischemic insult.1,3,16–18 The present experiments are, to our knowledge, the first to provide the important additional information that hippocampal neurons from animals subjected to ischemia plus hypothermia retain electrophysiological features of undamaged tissue.

Electrophysiological recording was used to assess some of the functional properties of CA1 neurons exposed to ischemia and treated with hypothermia. This is important because a number of neuroprotective interventions have conveyed substantial histological protection in the presence of reduced functional preservation. For example, ischemic preconditioning largely attenuates CA1 ischemic cell death; however, CA1 field potentials and behavioral habituation profiles recorded from the same animals are abnormal.19,20 Similarly, the capase-3 inhibitor N-benzylxoyacarbonyl-Asp (OMe)-Glu (OMe)-Val-Asp (OMe)-fluoromethyl ketone (Z-DEVD-FMK) prevented CA1 cell loss, but the “protected” cells were abnormal, as shown by the inability to induce long-term potentiation.21 In the present study measurements of resting membrane potential and input resistance indicate normal membrane properties in CA1 neurons rescued by hypothermia. In fact, these values, taken at least 30 days after ischemia, were comparable to those recorded from sham gerbils. In addition, characteristics of action potentials, including amplitude and duration, were not significantly different between sham and ischemic gerbils treated with hypothermia. These results are in contrast to those obtained from CA1 neurons in untreated animals in the first 12 to 24 hours.
after ischemia, where there is a dramatic reduction in synaptic activity and elevated spiking threshold. In a rat model of global ischemia, in which a 5-minute occlusion produces limited CA1 damage, there were demonstrable reductions in action potential amplitude and membrane resistance. These indicators of subtle neuronal injury were not observed in any of the slices used in the present experiments. Our present findings of preserved electrophysiological function do not exclude the possibility that some salvaged neurons do not function normally, as suggested by recent ultrastructural findings. Given the limited sampling afforded by patch-clamp recording, it remains possible that some abnormal neurons escaped detection. Nonetheless, on the basis of multiple outcome measures (behavior, histology, and electrophysiology), the consensus is that postischemic hypothermia largely preserves hippocampal function.

Long-term sequelae of stroke frequently include the appearance of seizures, and this is sometimes suggested to be a potential complication of the gerbil model. While we did not systematically monitor this in the present study, in agreement with previous reports, neither untreated gerbils nor gerbils receiving ischemia plus hypothermia displayed overt evidence of seizure activity. In concordance with this, there was no suggestion of hyperexcitability of CA1 neurons in the ischemic+hypothermic animals, which, if present, might predispose the animals to seizures. Thus, at resting membrane potential, there was no evidence of paroxysmal depolarizing shifts or abnormal bursts such as have been reported in epileptic tissue. With inclusion of picrotoxin in the ACSF, we noted the expected increase in excitability in some of the cells, but this was not different in the sham and ischemic+hypothermic groups.

During an ischemic episode there is a massive release of glutamate in the hippocampus. Intensive activation of glutamate receptors in the hippocampus is often associated with a marked enhancement of synaptic transmission (long-term potentiation). Thus, in excitatory synapses surviving an ischemic episode, one might expect to see a similar enhancement of excitatory transmission. This is only one of a multitude of alterations in the hippocampus that have been documented after an ischemic episode. For example, there is a well-described alteration in the glutamate receptor subunit composition in the hippocampus that might be expected to alter the characteristics of the electrophysiological response to excitatory inputs. Likewise, NMDA-mediated responses have also been reported to be enhanced after ischemia. For these reasons, we paid particular attention to a
was not adequately assessed. In contrast, it is evident that efficacy of these drugs in preclinical studies with old animals. Recently, prolonged hypothermia has also been shown to convey lasting neuroprotection in 2 different focal ischemia models. While the electrophysiological competence of neurons rescued by hypothermia in the latter 2 models has not been evaluated, results from the present experiments suggest that the histological preservation of neurons by hypothermia is most likely accompanied by a similar preservation of electrophysiological function. These data provide encouragement for more detailed investigations of hypothermia by itself or in combination with neuroprotective agents in stroke patients.

**Acknowledgments**

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