Effect of a neuronal sodium channel blocker on magnetic resonance derived indices of brain water content during global cerebral ischemia

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Abstract

Diffusion-weighted magnetic resonance imaging (DWI) with calculation of the apparent diffusion coefficient (ADC) of water is a widely used noninvasive method to measure movement of water from the extracellular to the intracellular compartment during cerebral ischemia. Lamotrigine, a neuronal Na⁺ channel blocker, has been shown to attenuate the increase in extracellular concentrations of excitatory amino acids (EAA) during ischemia and to improve neurological and histological outcome. Because of its proven ability to reduce EAA levels during ischemia, lamotrigine should also minimize excitotoxic-induced increases in intracellular water content and therefore attenuate changes in the ADC. In this study, we sought to determine the effect of lamotrigine on intra- and extracellular water shifts during transient global cerebral ischemia. Fifteen New Zealand white rabbits were anesthetized and randomized to one of three groups: a control group, a lamotrigine-treated group, or a sham group. After being positioned in the bore of the magnet, a 12-min 50-s period of global cerebral ischemia was induced by inflating a neck tourniquet. During ischemia and early reperfusion there was a similar and significant decrease of the ADC in both the lamotrigine and control group. The ADC in the sham ischemia group remained at baseline throughout the experiment. Lamotrigine-mediated blockade of voltage-gated sodium channels did not prevent the intracellular movement of water during 12 min 50 s of global ischemia, as measured by the ADC, suggesting that the ADC decline may not be mediated by voltage-gated sodium influx and glutamate release.

1. Introduction

During cerebral ischemia, a compromised energy supply in the neurons leads to failure of energy-dependent ion exchange pumps. This results in anoxic depolarization of cells, a run-down in transmembrane ion gradients, a massive release of excitatory amino acids (EAAs), and a fluid shift from the extracellular to the intracellular compartment [29].

Numerous previous studies have demonstrated that diffusion-weighted imaging (DWI) and calculation of the apparent diffusion coefficient (ADC) of water molecules correlates with the changes of extracellular water volume [17,18,21]. Ischemia leads to a decline of the ADC with a return to normal values during reperfusion in global [5,10] and focal ischemia [22]. Measuring the ADC during ischemia allows for real-time, noninvasive monitoring of intra- and extracellular water movements, which may result from acute excitotoxicity [9,26]. DWI is therefore considered to be a powerful tool for evaluating ischemic damage during acute cerebral ischemia, and has been used to assess therapeutic drug effects in several animal models of focal cerebral ischemia [3,6,32,38].

The ability of lamotrigine, a neuronal Na⁺ channel blocker, to attenuate the release of EAAs has been shown in vitro [37], and various studies in animal models have...
demonstrated the ability of lamotrigine to attenuate EAA accumulation in the extracellular space and its resulting excitotoxicity after cerebral ischemia [1,7]. Recently, lamotrigine was shown to improve neurobehavioral and histologic outcome following global cerebral ischemia [20].

In the present study, we evaluated the use of an easily reproducible model of transient global cerebral ischemia in the rabbit. This animal model requires minimal surgical preparation and allows for single or multiple episodes of cerebral ischemia of any desired duration. Using this model, we investigated the effect of the preischemic intravenous administration of lamotrigine on ischemia-induced cytotoxic brain edema through serial monitoring of the ADC.

2. Materials and methods

2.1. Animals

This study was performed under a protocol approved by the Institutional Animal Care and Use Committee at the University of Texas Medical Branch. Fifteen New Zealand white rabbits, aged 4 months and weighing 3.5±0.25 kg (mean±S.D.), were randomly assigned to one of three groups: control (n=6), lamotrigine (n=6), or sham (n=3). The animals were fasted for 24 h before the start of the experiment and housed one per cage at the institutional Animal Resource Center where they received routine veterinary care.

2.2. Surgical procedure

The animals were anesthetized in a Plexiglas box with 5% halothane in oxygen. After loss of the righting reflex, endotracheal intubation was performed and the lungs were mechanically ventilated (FiO₂=1.0). The inspired halothane concentration was reduced to 1% as soon as mechanical ventilation was established. After infiltration with 0.25% bupivacaine, the groin was incised and PE-90 catheters were inserted into the femoral artery and vein. Mean arterial pressure (MAP) was measured throughout the study. Serial arterial blood samples were intermittently obtained during the experiment to measure pH, PO₂, and PCO₂ (1306 pH/Blood Gas Analyzer, Instrumentation Laboratory, Lexington, MA). Mechanical ventilation was adjusted to maintain the PCO₂ between 35 and 40 mmHg. Hemoglobin concentration was determined with a CO-oximeter (482 CO-Oximeter, Instrumentation Laboratory, Lexington, MA). Body temperature was monitored with a rectal temperature probe and maintained at 38°C with a circulating water heating pad (Gaymar Industries Inc., Orchard Park, NY) which was placed around the animal’s body throughout the experiment. An inflatable neck tourniquet (6 cm wide) was secured loosely around the rabbit’s neck for the later production of cerebral circulatory arrest. At the end of the experiment, the animals were euthanized by increasing the inspired halothane concentration to 5% and injecting an intravenous dose of potassium chloride.

2.3. Drug administration

Lamotrigine (Glaxo Wellcome Inc, Greenville, NC) was administered intravenously at a dose of 50 mg/kg diluted in 20 ml of deionized water in the lamotrigine group. This dose of lamotrigine has been shown to prevent any increase of glutamate during 10 min of ischemia [1], and improved neurobehavioral outcome after a 6.5 min ischemic episode [20]. The drug was infused over 20 min starting 90 min before the onset of ischemia. The animals in the control group received an identical volume of deionized water without lamotrigine. The infusion medium was prepared by an investigator not involved in image acquisition and data analysis. To avoid any biasing of the results, blinding of the investigators was maintained until data analysis was completed.

2.4. Induction of ischemia

After the animals had been positioned in the bore of the magnet, baseline images were recorded. Seventy minutes after completion of the lamotrigine infusion, the MAP was decreased to between 25 and 50 mmHg with an intravenous bolus of trimethaphan (5 mg). The neck tourniquet was inflated to a pressure of 700 mmHg within 0.5 s using a regulated source of compressed air. This protocol reliably results in profound cerebral ischemia as evidenced by the prompt (<30 s) appearance of an isoelectric electroencephalogram [1,20]. After 12 min and 50 s of ischemia, the neck tourniquet was deflated and MAP was restored to between 80 and 100 mmHg with a bolus of phenylephrine (5–10 μg given intravenously).

2.5. Brain temperature measurements

Brain temperature measurements were carried out in an additional two animals to monitor the actual change during cerebral ischemia while in the magnet. A burr hole, 2 mm in diameter, was drilled 4 mm posterior and 4 mm lateral to the bregma in order to place a temperature probe into the dorsal hippocampus. After securing the temperature probe with dental acrylic the animals were treated according to the protocol described above.

2.6. Magnetic resonance imaging

Following surgical preparation, the animals were secured in the prone position on a Plexiglas cradle. The head of the rabbit was fixed in a nonmagnetic head holder and positioned in the bore of the magnet. Magnetic resonance data were obtained using a 4.7 Tesla magnet (Oxford
Instruments Ltd., Oxford, UK) and a custom-built surface coil with a 9-cm diameter tuned to the ¹H resonance frequency (200.056 MHz). The magnetic field homogeneity throughout the sample volume was then maximized by shimming on the water free induction decay (FID) using a Varian Unity Inova NMR console coupled to a Sun Microsystems host computer (Ultra Sparc-Station 10) running VNMR 6.1B software (Varian Inc., Palo Alto, CA). Sagittal and coronal pilot scans were acquired for the selection of a set of five transverse imaging slices. DWIs were obtained using a multi-slice spin-echo diffusion sequence with a diffusion gradient applied along the transverse horizontal (‘X’) axis. Imaging acquisition parameters were as follows: five consecutive slices centered on the slice of interest, 1.6-mm slice thickness, repetition/echo times of 3000/65 ms, 10×10 cm field of view, using 128 phase encoding steps, and one echo was averaged per phase encoding step. For quantitative determination of the ADC, DWIs with different-weighting factors (b-values=0, 293, 661 s/mm²) were recorded before ischemia and after 10, 30, 60, and 90 min of reperfusion. To improve temporal resolution in the perischemic period, additional single DWIs (b=661 s/mm²) were acquired every 6 min and 25 s. These images and the unweighted spin echoes (b=0 s/mm²) of the previously recorded baseline measurements were used for calculation of the ADC during ischemia and early reperfusion.

Bolus track imaging was used to assess cerebral blood flow (CBF) during baseline and reperfusion. Two bolus tracking movies were acquired using a flash sequence with the following parameters: 50 single slices in rapid succession, total acquisition time per frame of 520 ms, repetition/echo time of 8/3 ms, and field of interest equal to 11×11 cm. The movies were recorded 25 min before ischemia and at the end of the experimental protocol. A bolus of 0.5 ml gadopentetate dimeglumine contrast agent (Magnevist®, Berlex Imaging Laboratories, Wayne, NJ) was injected intravenously during the sixth frame of each movie. A washout period of 30 min was used after each bolus tracking movie to reduce contrast agent concentration. The sequence of DWIs, bolus tracking movies, cerebral ischemia, and the measurement of physiologic variables are depicted in Fig. 1.

2.7. Data analysis

Computation of quantitative ADC images was performed on a Sun Microsystems computer (Ultra Sparc-Station 10). Regional evaluations of ADC mean values were carried out in two regions of interest (ROI’s), i.e., bilateral hippocampus (Fig. 2). Size and location of the ROI’s were selected with the reference to an atlas of the rabbit brain [34] and high-resolution images acquired using a conventional spin-echo sequence.

Phase files were made for each frame of the bolus tracking experiment. These were converted into individual frames of the bolus tracking movie in a proprietary format using an in-house developed software package (Transit). An artery (pixel) at the base of the brain and the sagittal vein (outlined) were then selected to provide arterial (A<sub>RT</sub>) and venous residue times (V<sub>WB</sub>). From these data the total signal observed (V<sub>AUC</sub>) was determined for each vessel. The parenchyma of the whole brain was then outlined and the average flow curve determined to give W<sub>B</sub> and parenchymal residue time (W<sub>B</sub><sub>WB</sub>). These data were then used to calculate the cerebral blood flow (CBF) before and after ischemia using the following method:

\[
\text{CBF (ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}) = \frac{V_{AUC} \cdot W_{B_{AUC}}}{W_{B} T - A_{RT}^{-1}}
\]

2.8. Statistical analysis

Data were analyzes using a commercially available...
computer program (StatView 5.0; SAS Institute Inc., San Francisco, CA). Physiologic parameters (pH, PO₂, PCO₂, hemoglobin, MAP, and body temperature) were compared with repeated-measures analysis of variance (ANOVA) and Scheffe’s test. ADC and CBF values were compared using factorial ANOVA and Dunnett’s test. A paired t-test was used to test for statistically significant changes between baseline and minimum ADC values as well as pre- and postischemic CBF values in both groups. Differences were considered statistically significant at P<0.05; data are presented as mean±S.D.

3. Results

3.1. Physiologic data

There were no significant differences in pH, PO₂, PCO₂, and hemoglobin among groups and no significant changes were observed over time (Table 1). Body temperature (rectal thermistor) was well maintained at 38°C in all groups during the entire experiment. Brain temperature measurements in two animals showed a 3.05±0.35°C decrease at the end of the 12 min and 50 s ischemic episode. As per the protocol, MAP during ischemia was lowered to 25 to 50 mmHg in the control and lamotrigine groups. After deflating the neck tourniquet, MAP returned to baseline values. No significant differences in MAP were observed between groups. CBF (ml/100 g/min) during baseline was 54±17 in the control group, 52±22 in the lamotrigine group, and 53±3 in the sham group. During reperfusion CBF was 54±4 in the control group, 49±12 in the lamotrigine group, and 57±5 in the sham group. There were no significant differences in CBF between groups or over time.

3.2. ADC — hippocampus

Fig. 3 shows ADCs versus time curves for each of the groups during the experiment. The mean value of the ADC within the hippocampus was 989±25×10⁻⁶ mm²/s in the control group vs. 998±24×10⁻⁶ mm²/s in the lamotrigine
and to baseline (paired P).

**Fig. 3.** Changes in the apparent diffusion coefficient (ADC) during the concentration, a subsequent loss of ion images. Solid bar represents a 12-min 50-s ischemic period. *p < 0.05 when compared with the sham group (analysis of variance, Dunnett’s test) and to baseline (paired t-test). Values are mean±S.D.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of physiologic data^a</th>
<th>Lamotrigine group</th>
<th>Sham group</th>
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<tbody>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>3.51±0.24</td>
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<td>Rectal temperature (°C)</td>
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<td>37.9±0.2</td>
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<td>Ischemia</td>
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<td>37.9±0.2</td>
<td>38.1±0.0</td>
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<tr>
<td>Early reperfusion</td>
<td>37.9±0.2</td>
<td>38.0±0.2</td>
<td>38.1±0.0</td>
</tr>
<tr>
<td>Late reperfusion</td>
<td>Baseline</td>
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<td>pH Base</td>
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<td>7.34±0.05</td>
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<tr>
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<td>7.34±0.06</td>
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<td>7.39±0.01</td>
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<tr>
<td><strong>PCO₂ (mmHg)</strong></td>
<td>Baseline</td>
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<td>35.4±1.5</td>
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<tr>
<td>Early reperfusion</td>
<td>38.2±2.1</td>
<td>35.7±1.4</td>
<td>38.8±2.6</td>
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<tr>
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<tr>
<td>Baseline</td>
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<td>377±50</td>
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<td>Early reperfusion</td>
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<tr>
<td>Late reperfusion</td>
<td>384±31</td>
<td>429±47</td>
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<td><strong>Hb (g/dl)</strong></td>
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<td><strong>MAP (mmHg)</strong></td>
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<td>71±3</td>
</tr>
<tr>
<td>Late reperfusion</td>
<td>72±3</td>
<td>66±10</td>
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<tr>
<td>CBF^a (ml/100 g⁻¹·min⁻¹)</td>
<td>Baseline</td>
<td>54±17</td>
<td>52±22</td>
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<tr>
<td>Reperfusion</td>
<td>54±4</td>
<td>49±12</td>
<td>57±5</td>
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</table>

^a Values are mean±S.D.

^b For the calculation method of CBF, see Materials and methods.

Hb, hemoglobin; MAP, mean arterial pressure; CBF, cerebral blood flow.

group and 950±7×10⁻⁶ mm²/s in the sham group. In the first ischemic image (I1), the ADC in the control group was numerically less (but not statistically so) than that for the lamotrigine group. In the second image during ischemia (I2), the mean ADC decreased to 87% of baseline in the control group and to 85% in the lamotrigine group. In the first image during reperfusion (Re1), ADCs continued to decline to 80% and 83% of baseline in the control and lamotrigine groups, respectively. The minimum observed ADC during ischemia was not different between control and lamotrigine groups. Twenty-five minutes of reperfusion returned mean ADCs to baseline. The mean ADC in the sham group remained at baseline throughout the entire experiment.

## 4. Discussion

This manuscript describes the use of a model of transient global cerebral ischemia ideally suited for use in MR studies. Using this model, we sought to investigate the effects of lamotrigine on ischemia-induced cytotoxic brain edema using DWI. Despite the expected ischemia-induced decrease in the ADC, there was no significant difference in the mean hippocampal ADC after 12 min and 50 s of global cerebral ischemia between the control or lamotrigine-treated groups. The ADC recovered to baseline following reperfusion within 25 min in both groups.

The validity of our ischemia model has been proven in several previous studies. Reproducible neurologic deficits [2,20] and histopathology [20], as well as a consistent increase in glutamate release [1] have been found using this model. In contrast to cardiac arrest or surgical arterial occlusion models, this model of transient global cerebral ischemia is easy to implement in the MRI environment and allows fine control of the duration of ischemia. Our ischemia model produced a reliable ADC decrease during ischemia in this study, and is therefore ideally suited for further MRI studies.

Although many neuroscientists have focussed their attention on drugs which may have neuroprotective properties when administered after an ischemic episode, there is a very large population of patients who are at significant risk for neurologic injury and who could benefit from preischemic drug therapy. Nearly 1 million patients undergo coronary artery bypass surgery every year [27]. Adverse cerebral outcome after coronary bypass continues to be a significant clinical problem, causing strokes in 1–5% of patients, transient ischemic attacks in 4–14%, and neurocognitive deficits in as many as 30–88% [25,27,30,36]. Preoperative treatment of these patients with an effective neuroprotective agent which has few side effects could dramatically improve outcome and reduce the high neurologic morbidity of this type of surgery.

Neuronal ischemia results in a rapid decrease in ATP concentration, a subsequent loss of ion homeostasis, and the release of excitatory amino acids and other neurotransmitters [29]. EAAs acting at postsynaptic receptors and depletion of ATP stores result in Na⁺/K⁺ pump...
dysfunction, increased Na\(^+\) influx, and cotransport of Cl\(^-\) and water, resulting in cytotoxic brain edema [14]. DWI and calculation of the ADC can detect changes in the brain tissue within minutes after the onset of ischemia. It is widely accepted that the ischemic ADC decrease is due to water protons moving from the extracellular to the intracellular compartments, which have different diffusion properties. Restricted intracellular proton diffusion occurs because of the high protein content and the presence of hydrophobic membranes hinder the free movement of water molecules within the cell [18].

Lamotrigine inhibits Na\(^+\) influx by blocking voltage-sensitive Na\(^+\) channels. The neuronal Na\(^+\) channel blockade decreases the frequency of action potentials, reduces presynaptic glutamate release, and diminishes accumulation of intracellular Na\(^+\). Reduced intracellular Na\(^+\) loading decreases the activity of energy-dependent 3Na\(^+\)/2K\(^-\) adenosine triphosphatase and preserves a sufficient Na\(^+\) gradient used for the Na\(^-\) glutamate uptake carrier, which forms an important reuptake mechanism, thus terminating glutamate or other EAA transmitter action. In addition, inhibition of Na\(^+\) influx also prevents the perischemic release of glutamate by reversed operation of the glutamate uptake carrier, which is the main mechanism of glutamate release during ischemia [31,35]. Glutamate acting at postsynaptic NMDA receptors is known to increase the movement of sodium and water into the postsynaptic neuron.

Lamotrigine has been approved for use in humans for the treatment of epilepsy. It has excellent bioavailability when taken orally and is associated with few side effects [11]. Several studies using our model of transient global cerebral ischemia in rabbits have proven the validity of this model and demonstrated that lamotrigine attenuates glutamate concentrations during 10 min of cerebral ischemia [1] and improves histological and neurobehavioral outcome [20]. Lamotrigine has also shown neuroprotective effects in a focal ischemia model measuring the lesion volume with DWI [28].

However, in this study, lamotrigine did not attenuate decreases in the ADC during ischemia. It may be that the duration of ischemia used in this study was excessively long for lamotrigine to demonstrate a beneficial effect. Suggestive evidence in support of this possibility is found in the numerically higher ADC in the lamotrigine group during the first ischemic image (II). Alternatively, our study may suggest that ischemic ADC changes are not simply mediated by glutamate activated, voltage-gated Na\(^+\) channels, given the fact that the same dose of lamotrigine prevented any increase in cerebral glutamate during 10 min of transient global cerebral ischemia [1]. This explanation is supported by a recent study [15] observing a decrease of the ADC of water during cerebral ischemia even before the onset of anoxic depolarization. Ischemic ADC decline may be a result of mechanisms contributing to intracellular acid–base regulation, which occur immediately after onset of ischemia, even before the loss of ion hemostasis and anoxic depolarization [15,33]. The Na\(^+\)/H\(^+\) exchange transporter, which is activated during cerebral ischemia [33], cycles Na\(^+\) into the cell and H\(^+\) to the extracellular compartment [19]. This active proton transfer causes an osmotic water shift into the cell. Other possible mechanisms for water movement into the intracellular compartment and subsequent ADC changes include generation of free radicals and membrane breakdown [19] or changes in the membrane water permeability [16].

To achieve better temporal resolution, ADC maps in this study were calculated using single DWIs (b=661 s/mm\(^2\)) acquired during ischemia and an additional previously recorded single DWI (b=0 s/mm\(^2\)). This enabled us to decrease acquisition time to approximately 6.5 min. To assure the validity of this method, which has already been used in previous studies [10], we calculated ADC maps using two different methods during baseline conditions and compared ADC values calculated from three different DWIs (b=0, 293, 661 s/mm\(^2\)) with the method described above in each of the animals. There was no difference between these ADC values indicating that our approach is valid.

The changes observed in the ADC measured during ischemia and the first reperfusion period could potentially be influenced by changes in the water T\(_1\) and T\(_2\) relaxation parameters. Using a similar period of transient global ischemia in rats it has been shown that T\(_2\) relaxation times remain constant during ischemia and reperfusion [12]. It may therefore be concluded that changes in T\(_2\) relaxation do not contribute to signal alterations of cerebral metabolites detected by DWI [12]. In this study it has also been demonstrated that no significant changes in major cerebral metabolite signal intensity occur during ischemia and reperfusion [12]. Apart from depletion of brain glucose pools and the accumulation of lactic acid, it has been previously demonstrated that levels of these metabolites remain unchanged during brief periods of transient global ischemia [4,24]. It can then be inferred that the water relaxation properties remain unchanged as well. This conclusion is supported by the fact that T\(_1\) and T\(_2\) relaxation times of water did not change during focal ischemia [13,23]. Hence, we believe that the changes we observed in the calculated ADC’s accurately reflect the internal environment of the cerebral tissue under study.

Other important factors that may affect the diffusion coefficient of water are brain temperature and CBF [17]. To quantify the influence of the brain temperature on ADC values, we measured brain temperature changes during ischemia. We found a mean maximum brain temperature decrease of 3°C during ischemia. In previous studies, an ADC drop of 10\(\times\)10\(^{-6}\) mm\(^2\)/s per 1°C was calculated for rats and cats [8]. Assuming the same value for the rabbit brain, a decrease of 30\(\times\)10\(^{-6}\) mm\(^2\)/s could be due to temperature change. Since the ADC drop was 190\(\times\)10\(^{-6}\)
mm²/s in the control group and 167×10⁻⁶ mm²/s in the lamotrigine group, only 15% to 17% of the mean ADC change during ischemia may have been caused by temperature decrease.

Because blood flow may also interfere with ADC measurements, we measured pre- and postischemic CBF. CBF values showed no difference, thus indicating adequate cerebral perfusion during baseline and reperfusion.

In this study, lamotrigine did not attenuate the decrease in ADC during ischemia despite the fact that an identical dose of lamotrigine in the same animal model prevented increases in extracellular glutamate during 10 min of ischemia [1]. This finding suggests either that the duration of ischemia exceeded the ability of lamotrigine to prevent excitotoxic-induced movement of water or that anoxic depolarization and elevation of glutamate levels do not necessarily need to precede changes in the ADC. In this case, mechanisms other than voltage-gated sodium influx and EAA release may be responsible for the observed ADC decline. Additional studies using the finer temporal resolution provided by echo planar imaging may help resolve these issues.

Acknowledgements

This study was supported in part by the National Institute of Health grant 2 RO1 NS 29403 to Dr Zornow, and a stipend from the Max Kade Foundation to Dr Koinig.

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[12] H. Fujimori, T. Michaelis, M. Wick, J. Frahm, Proton T2 relaxation in ADC during ischemia despite the fact that an identical CBF values showed no difference, thus indicating adequate cerebral perfusion during baseline and reperfusion.


