Effect of the 21-Aminosteroid Tirilazad on Cerebral pH and Somatosensory Evoked Potentials After Incomplete Ischemia

Yuichi Maruki, MD; Raymond C. Koehler, PhD; Jeffrey R. Kirsch, MD; Kathleen K. Blizzard, BS; and Richard J. Traystman, PhD

Background and Purpose: Postischemic evoked potential recovery correlates with acidosis during ischemia and early reperfusion. Acidosis promotes lipid peroxidation in vitro. We tested the hypothesis that the 21-aminosteroid tirilazad mesylate (U74006F), an inhibitor of lipid peroxidation in vitro, ameliorates somatosensory evoked potential recovery and acidosis during reperfusion after severe incomplete cerebral ischemia.

Methods: Cerebral perfusion pressure was reduced to 11±1 mm Hg (±SEM) for 30 minutes by cerebral ventricular fluid infusion in anesthetized dogs. Cerebral intracellular pH and high-energy phosphates were measured by magnetic resonance spectroscopy. Dogs were randomized to receive vehicle (citrate buffer; n=8) or tirilazad (1 mg/kg; n=8) before ischemia in a blinded study.

Results: Cerebral blood flow was reduced to 6±1 mL/min per 100 g during ischemia, resulting in nearly complete loss of high-energy phosphates and an intracellular pH of 6.0-6.1 in both groups. Initial postischemic hyperemia was similar between groups but lasted longer in the vehicle group. Tirilazad accelerated mean recovery time of intracellular pH from 31±5 to 15±3 minutes and of inorganic phosphate from 13±2 to 6±1 minutes. Recovery of somatosensory evoked potential amplitude was greater with tirilazad (49±3%) than vehicle (33±6%). Fractional cortical water content was less with tirilazad (0.819±0.003) than vehicle (0.831±0.002).

Conclusions: Tirilazad attenuates cerebral edema and improves somatosensory evoked potential recovery after incomplete ischemia associated with severe acidosis. Accelerated pH and inorganic phosphate recovery indicates that this antioxidant acts during the early minutes of reperfusion. (Stroke 1993;24:724-730)

Key Words • acidosis • cerebral blood flow • cerebral ischemia • evoked potentials, somatosensory • spectroscopy, nuclear magnetic resonance

Oxygen radicals are thought to make a significant contribution to ischemic/reperfusion injury in several major organs, but the magnitude of their role in brain injury is less clear.1 Whereas positive evidence based on markers of oxygen radical production and lipid peroxidation has been described,2-5 the changes are in some cases relatively small and spatially heterogeneous,6 gender dependent,7 and delayed by 24 hours.8 Administration of oxygen radical scavengers such as superoxide dismutase can limit the extent of infarction during focal ischemia,9,10 which may be contributed in part to a vascular effect of this large protein.11,12 With global ischemia significant protection has been reported with superoxide dismutase administration,13 although others have reported only modest effects14 possibly caused by poor penetration across the blood–brain barrier.15

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to follow changes in intracellular pH (pHi) and high-energy phosphates. We tested the hypothesis that pre-treatment with tirilazad mesylate improves SEP recovery and that improved SEP recovery correlates with accelerated pH and metabolic recovery during early reperfusion. A preliminary report has been presented.34

**Materials and Methods**

Male dogs weighing approximately 10 kg were anesthetized with fentanyl (50 μg/kg i.v.) and pentobarbital (10 mg/kg i.v.). Additional pentobarbital was infused continuously (3 mg/kg per hour) throughout the experiment. Lungs were mechanically ventilated with 25–30% O2, and end-tidal CO2 concentration was controlled. Femoral and axillary arteries were catheterized for cerebral blood flow (CBF) measurements with radiolabeled microspheres.30,31 Muscles were paralyzed with pancuronium bromide (0.3 mg/kg), and temporalis muscles were fully retracted. Through burr holes in the skull, catheters were inserted into the sagittal sinus and left lateral ventricle, and a thermistor was inserted into the epidural space. An electrode was secured in a burr hole in the skull over the right somatosensory cortex. Amplitude of the primary cortical wave complex of SEP with left foreleg stimulation was measured.30,31

Phosphorus MRS was performed with a 3.5-cm surface coil tuned to 32.5 MHz in a 1.89-T superconducting magnet (25-cm-bore diameter; Oxford Instruments, Oxford, UK) as previously described.27,30,31 Areas under the peaks corresponding to inorganic phosphate (P1), phosphocreatine, and the β-phosphorus of adenosine triphosphate (ATP) were measured by planimetry and normalized by the corresponding area of the preschismic spectra.30 Intracellular pH was calculated from the chemical shift of P1.30,35 Intracellular bicarbonate ion concentration ([HCO3−]) was estimated from the Henderson-Hasselbalch equation using the MRS-derived pH and sagittal sinus partial pressure of CO2 (Pco2) as an estimate of mean tissue Pco2.30,31,33

To maintain normothermia while in the magnet, the body of the dog was wrapped in plastic and placed on a blanket perfused with warm water. A blanket of fiberglass insulation was placed above the skull and surface coil to reduce radiant heat loss. Global incomplete ischemia was produced by infusion of artificial cerebrospinal fluid from a 38°C pressurized reservoir through a line in a 38°C water jacket and into the lateral ventricular catheter. Intracranial pressure was kept 10 to 15 mm Hg below mean arterial pressure while arterial pressure spontaneously changed. This procedure maintains CBF relatively constant throughout the ischemic period.31,33 After 30 minutes of ischemia, the fluid reservoir was disconnected, and intracranial pressure rapidly decreased. After 3 hours of reperfusion, the anesthetized dogs were killed by intravenous potassium chloride injection. A 200-μg sample of cortical gray matter was dried at 100°C for 48 hours to determine the fractional water content.

Phosphorus MRS spectra were analyzed in 15-minute epochs (225 free-induction decays) in duplicate before ischemia, in a 6-minute epoch followed by three 8-minute epochs during ischemia, in four 5-minute epochs during the first 20 minutes of reperfusion, and in 15-minute epochs for the remainder of reperfusion. Sagittal sinus Pco2 and SEP amplitude were measured at the midpoint of each MRS spectra. Arterial and sagittal sinus blood gases (ABL3, Radiometer, Copenhagen, Denmark), O2 content (CO-Oximeter 282, Instrumentation Laboratories, Lexington, Mass.), and glucose (23A, Yellow Springs Instrument Co., Yellow Springs, Ohio) were measured before ischemia, at 17 minutes of ischemia, and at 7.5, 30, 90, and 180 minutes of reperfusion. Radiolabeled microspheres (15±0.5-μm diameter; Du Pont-NEN Products, Boston, Mass.) were injected also at these time points, and CBF was calculated as previously described.30 Cerebral O2 consumption was calculated from the arterial-sagittal sinus O2 content difference and blood flow to the entire cerebrum.

Dogs were randomized into two groups. One group of eight dogs received 1 mg/kg of tirilazad mesylate (1.5 mg/mL) intravenously over a 10-minute period starting 20 minutes before ischemia. During 3 hours of reperfusion, tirilazad mesylate was continuously infused at a rate of 0.2 mg/kg per hour. A second group of eight dogs received the vehicle (0.02 M citric acid monohydrate, 0.0032 M sodium citrate dihydrate, 0.077 M NaCl, pH 3.0). Dogs with CBF values of less than 1 or greater than 14 mL/min per 100 g during ischemia were excluded. Investigators were blinded to the treatment and remained blinded until all data were analyzed and excluded dogs were replaced (two dogs in the vehicle group and one dog in the drug group).

Data were analyzed by two-way analysis of variance (ANOVA) in which group drug treatment was a between-subject factor and time was a within-subject factor. If there was a significant group effect or group×time interaction, mean values were compared between groups at individual time points using orthogonal contrasts. In addition, to obtain a measure of recovery rate based on all of the data of the recovery-time profile, mean recovery time of MRS-derived measurements was calculated by the stochastic approach of area/height, where area is the time integral of the difference between the recovery values and the preschismic value, and height is the difference between the end-ischemic and preschismic values.30 Mean recovery times were compared between groups by t test. Values of p<0.05 were considered significant in all tests. Values are presented as mean±SEM.

**Results**

Arterial blood gases were controlled during ischemia and reperfusion, and there were no differences between groups in arterial oxygen or glucose contents (Table 1). Arterial pH was slightly lower in the tirilazad group during reperfusion.

During ischemia, cerebral perfusion pressure was reduced to 11±1 mm Hg, CBF was reduced to 6±1 mL/min per 100 g, and cerebral O2 consumption was reduced to 0.6±0.1 mL O2 per minute per 100 g in both groups (Table 2). During reperfusion, cerebral perfusion pressure was rapidly restored to normal levels, and postischemic hyperemia at 7.5 minutes was equivalent in both groups. At 30 minutes of reperfusion, CBF remained elevated in the vehicle group but not in the tirilazad group. Delayed hyperperfusion was significant in both groups at 90 minutes. Cerebral O2 consumption recovered to preschismic levels, and there were no differences between groups. Epidural temperature was maintained at normothermic levels during ischemia and...
TABLE 1. Arterial Blood Analysis Before, During, and After 30 Minutes of Incomplete Ischemia

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Control</th>
<th>Ischemia</th>
<th>Reperfusion (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>Vehicle</td>
<td>7.39±0.01</td>
<td>7.32±0.02</td>
<td>7.30±0.01</td>
</tr>
<tr>
<td></td>
<td>Tirilazad</td>
<td>7.39±0.01</td>
<td>7.33±0.02</td>
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<tr>
<td></td>
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<td></td>
<td>7.31±0.01</td>
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<td>7.33±0.01</td>
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<tr>
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<td></td>
<td></td>
<td>7.33±0.02</td>
</tr>
<tr>
<td>Pco₂ (mm Hg)</td>
<td>Vehicle</td>
<td>37±1</td>
<td>42±2</td>
<td>40±1</td>
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<tr>
<td></td>
<td>Tirilazad</td>
<td>40±1</td>
<td>43±2</td>
<td>42±2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39±1</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>36±1</td>
</tr>
<tr>
<td>O₂ content (mL/dL)</td>
<td>Vehicle</td>
<td>121±5</td>
<td>114±6</td>
<td>112±6</td>
</tr>
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<td></td>
<td>Tirilazad</td>
<td>114±6</td>
<td>111±7</td>
<td>113±6</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>Vehicle</td>
<td>64±2</td>
<td>96±10</td>
<td>79±8</td>
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<td>Tirilazad</td>
<td>72±12</td>
<td>72±11</td>
<td>57±5</td>
</tr>
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</table>

Values are mean±SEM.
*p<0.05 different from vehicle group.

reperfusion. Intracranial pressure was significantly lower in the tirilazad group at 30 minutes of reperfusion. Fractional water content of cortical gray matter measured after 180 minutes of reperfusion was less in the tirilazad group (0.819±0.003) than in the vehicle group (0.831±0.002).

During incomplete ischemia, ATP and phosphocreatine were reduced nearly to undetectable levels (Figure 1). Recovery of ATP was rapid in both groups. However, two-way ANOVA indicated a significant treatment×time interaction for recovery of phosphocreatine and Pᵢ.

End-ischemic pHᵢ was 6.09±0.07 in the vehicle group and 5.98±0.08 in the tirilazad group (Figure 2). Estimated [HCO₃⁻], decreased to 1.7±0.3 mM in the vehicle group and to 1.5±0.2 mM in the tirilazad group. During reperfusion pHᵢ and [HCO₃⁻], eventually recovered to preischemic levels. However, two-way ANOVA indicated a significant effect of tirilazad on the pHᵢ and [HCO₃⁻], recovery profiles.

Recovery rates were analyzed by calculating mean recovery times, which integrate all data in the recovery profile. Mean recovery times of pHᵢ, [HCO₃⁻], and Pᵢ, were reduced by half with tirilazad treatment (Figure

TABLE 2. Cerebral Hemodynamics Before, During, and After 30 Minutes of Incomplete Ischemia

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Control</th>
<th>Ischemia</th>
<th>Reperfusion (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial pressure (mm Hg)</td>
<td>Vehicle</td>
<td>17±1</td>
<td>123±18</td>
<td>27±3</td>
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<td></td>
<td>Tirilazad</td>
<td>14±2</td>
<td>143±19</td>
<td>23±4</td>
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<tr>
<td>Cerebral perfusion pressure (mm Hg)</td>
<td>Vehicle</td>
<td>105±6</td>
<td>11±1</td>
<td>106±10</td>
</tr>
<tr>
<td></td>
<td>Tirilazad</td>
<td>105±7</td>
<td>11±1</td>
<td>128±13</td>
</tr>
<tr>
<td>Cerebral blood flow (mL/min per 100 g)</td>
<td>Vehicle</td>
<td>28±3</td>
<td>6±1</td>
<td>108±18</td>
</tr>
<tr>
<td></td>
<td>Tirilazad</td>
<td>30±3</td>
<td>6±1</td>
<td>112±23</td>
</tr>
<tr>
<td>Arteriovenous O₂ content difference (mL/dL)</td>
<td>Vehicle</td>
<td>12.0±0.7</td>
<td>8.6±1.4</td>
<td>5.0±1.2</td>
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<td>11.2±0.6</td>
<td>9.9±1.2</td>
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<tr>
<td>Cerebral O₂ consumption (mL/min per 100 g)</td>
<td>Vehicle</td>
<td>3.27±0.27</td>
<td>0.63±0.13</td>
<td>4.06±0.44</td>
</tr>
<tr>
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<td>Tirilazad</td>
<td>3.31±0.30</td>
<td>0.65±0.15</td>
<td>3.66±0.67</td>
</tr>
<tr>
<td>Epidural temperature (°C)</td>
<td>Vehicle</td>
<td>36.7±0.2</td>
<td>37.4±0.3</td>
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</tr>
<tr>
<td></td>
<td>Tirilazad</td>
<td>37.0±0.5</td>
<td>38.0±0.3</td>
<td>...</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
*p<0.05 different from vehicle group.
FIGURE 1. Line graphs show cerebral adenosine triphosphate (ATP), phosphocreatine, and inorganic phosphate (P_i) during 30 minutes of incomplete ischemia and 180 minutes of reperfusion in dogs pretreated with vehicle (n=8) or tirilazad (n=8). Bars represent SEM. Zero time indicates start of reperfusion. Time scale is compressed after 60 minutes to highlight early transients. Phosphocreatine was significantly greater at 12.5 and 17.5 minutes of reperfusion, and P_i was less at 2.5, 7.5, and 12.5 minutes of reperfusion in the tirilazad group.

FIGURE 2. Line graphs show intracellular pH and calculated intracellular bicarbonate ion concentration during 30 minutes of incomplete ischemia and 180 minutes of reperfusion in dogs pretreated with vehicle (n=8) or tirilazad (n=8). Bars represent SEM. Zero time indicates start of reperfusion. Time scale is compressed after 60 minutes to highlight early transients. Intracellular pH was significantly greater at 12.5 minutes of reperfusion, and intracellular bicarbonate was greater at 12.5 and 45 minutes of reperfusion in the tirilazad group.

3). Mean recovery times of ATP and phosphocreatine were not significantly reduced.

Baseline SEP amplitude was similar in the vehicle (86±19 μV) and tirilazad (98±12 μV) groups. In all dogs, SEP was isoelectric from 3 minutes through 30 minutes of ischemia. By 2.5 minutes of reperfusion, SEP waveforms were detectable in two of eight vehicle-treated dogs and five of eight tirilazad-treated dogs. Percent recovery of SEP amplitude was significantly greater in the tirilazad group at 90 minutes of reperfusion and thereafter (Figure 4). In individual data pooled from both groups, percent recovery of SEP amplitude at 180 minutes of reperfusion was correlated with mean recovery time of P_i (r=0.69), pH_i (r=0.53), and [HCO_3^-] (r=0.60), but not with that of ATP (r=0.11) or phosphocreatine (r=0.31).

Discussion

The principal findings of this randomized, blinded study on anesthetized dogs are that treatment with the 21-aminosteroid tirilazad before 30 minutes of severe incomplete global cerebral ischemia 1) doubles the recovery rate of pH_i, [HCO_3^-], and P_i during early reperfusion, 2) improves recovery of SEP amplitude, and 3) reduces cerebral edema. The drug does not appear to act by reducing the severity of the ischemic insult because the reductions in CBF, cerebral O_2 consumption, high-energy phosphates, pH_i, and SEP were equivalent in the vehicle and drug groups during ischemia. In addition, the effect of the drug was not attributable to hypothermia because epidural temperature was maintained in both groups.

Studies of the drug's properties indicate that tirilazad is a potent inhibitor of lipid peroxidation in vitro.16,17 In brain tissue homogenates tirilazad is a more potent inhibitor than vitamin E.18 The importance of lipid peroxidation as a mediator of ischemic/reperfusion injury in brain is unclear. Postischemic increases in conjugated diene formation have been reported,2,3 but the magnitude of these changes is often relatively small and spatially heterogeneous.6 On the other hand, postischemic depletion of vitamin E in gerbil is attenuated by tirilazad treatment.36 Indirect measurements of lipid peroxidation were not obtained in the present study.
However, our data demonstrating a doubling of pH, and P$_r$ recovery rates during the first half hour of reperfusion indicate that the effect of the drug is expressed during early reperfusion. If the drug’s mechanism of action in vivo is inhibition of lipid peroxidation, then our data indicate that lipid peroxidation can occur during early reperfusion after severe incomplete ischemia and that the magnitude of peroxidation is sufficient to exert a physiological effect on restoration of brain pH and on electrophysiological deficit. Moreover, the observation that pH$_r$ and [HCO$_3^-$], recovery can be accelerated by drug treatment implies that postischemic normalization of buffering capacity is not merely a passive process.

There are several potential explanations for more rapid pH$_r$ recovery. First, plasma membrane ionic conductance may be more rapidly restored by tirilazad, which would improve antipporter-dependent pH$_r$ recovery. The lower intracranial pressure at 30 minutes and lower cortical water content at 3 hours of reperfusion support the hypothesis of improved electrolyte recovery with tirilazad, consistent with observations during focal ischemia. Second, tirilazad may improve recovery of mitochondrial function and thereby reduce postischemic lactic acid production. Rapid recovery of ATP and cerebral O$_2$ consumption in both groups argues against major mitochondrial dysfunction in this model of normoglycemic ischemia. Nevertheless, dysfunction in a small portion of mitochondria undetected by global ATP and O$_2$ consumption measurements could give rise to substantial lactate accumulation in a subpopulation of cells. Because such a subpopulation would likely have elevated P$_r$ and because MRS measurements of pH$_r$ are heavily weighted by compartments containing most of the P$_r$, the more rapid recovery of pH$_r$ in our study may reflect rapid recovery in a subpopulation of selectively vulnerable neurons or selectively acidotic astrocytes.

Third, faster pH$_r$ recovery also might be attributable to more effective reperfusion. The lack of effect of tirilazad on global CBF during the early hyperemia or the delayed hypoperfusion argues against this possibility. However, tirilazad is concentrated in plasma membranes of brain endothelial cells in culture. In vivo, the drug’s hydrophobicity may limit diffusion to neurons beyond the endothelial membrane. Moreover, ischemia/reperfusion can cause superoxide dismutase–inhibitable changes in endothelial membrane fluidity. Superoxide anion is detectable in the extracellular space surrounding cerebral vessels and production is most prominent during early reperfusion. Thus, based on the site of oxygen radical production and on the hydrophobicity of tirilazad, our findings do not exclude the possibilities that 1) tirilazad acts by improving endothelial transport processes or control of capillary microflow undetected by microspheres, or 2) that release of toxic oxygen species from leukocytes and monocytes is inhibited, as reported for related 21-aminosteroids, which in turn could affect endothelial function or microflow.

After 10 minutes of carotid occlusion plus arterial hypotension in rats, Haraldseth et al. observed faster ATP and phosphocreatine but not pH$_r$ recovery with tirilazad treatment. The lack of effect on pH$_r$ recovery may be related to the less severe level of acidosis during ischemia in their model (pH$_r$, 6.55) than in our model (pH$_r$, 6.09). On the other hand, the lack of effect of tirilazad on ATP recovery rate in our study may be related to less temporal resolution associated with the lower magnetic field strength in our study (1.89 versus 4.7 T). Consistent with their data, we did find greater phosphocreatine during early reperfusion as indicated by the drug$	imes$time interaction with ANOVA. However, in our study much of this difference could be attributed to the effect of pH$_r$ on creatine kinase equilibrium. Despite some of these differences, our results are in general agreement with Haraldseth et al. that tirilazad exerts an effect during the early minutes of reperfusion. In addition, their observation that tirilazad was equally effective when administered either before or at the end of ischemia further supports the premise that the drug acts during reperfusion.

We also observed that recovery of SEP amplitude was improved by tirilazad and that this improvement correlated with mean recovery time of pH$_r$. A similar correlation was observed after complete ischemia of different
durations. Moreover, delaying pH recovery with acetazolamide or hypercapnic reperfusion resulted in depressed SEP recovery. These data taken together with the present results of accelerated pH recovery associated with improved SEP recovery are consistent with the hypothesis that part of the postischemic electrophysiological deficit is attributable to the magnitude and duration of acidosis during the reperfusion period. Acidosis promotes lipid peroxidation in vitro. By inhibiting initial lipid peroxidation and limiting the duration of severe acidosis, tirilazad may act to limit further lipid peroxidation and improve SEP conduction. Furthermore, resolution of postischemic hyperemia corresponds temporally to resolution of acidosis.

Thus, by SEP recovery are consistent with the SEP recovery may corresponded with the postischemic electrophysiological recovery may be more evident when the severity of metabolic acidosis is sufficient to reduce [HCO₃⁻] to less than 2 mM. This situation is prominent when incomplete ischemia is severe and prolonged.

Therefore, our results indicate that tirilazad exerts an effect on physiological recovery during early reperfusion as evidenced by accelerated pH recovery, greater SEP recovery, and attenuated edema. We suggest that this early effect is most prominent with severe acidosis accompanied by low [HCO₃⁻]. Our focus was on early reperfusion kinetics, and our results do not address the therapeutic impact of early improvement of SEP and pH recovery. Furthermore, these results do not exclude that tirilazad may also act later during reperfusion because improvement in neurological outcome after complete ischemia has been reported in some laboratories.

Acknowledgments

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References

In a carefully conducted, randomized, and blinded study, Maruki et al have shown that low doses of tirilazad mesylate (one of the 21-aminosteroid family) improve early metabolic and functional recovery after severe incomplete cerebral ischemia in the dog. Previously, they found no protection with tirilazad mesylate in total cerebral ischemia in dogs. The aminosteroids are hydrophobic and potent inhibitors of lipid peroxidation. They do not readily cross the blood-brain barrier, suggesting that the site of action involves the microvasculature. Similar conclusions have been reached with the superoxide scavenger polyethylene glycol-conjugated superoxide dismutase, which also does not readily cross the blood-brain barrier yet can reduce injury in cerebral ischemia. This growing literature strongly supports a role of oxygen radicals in microvascular injury to the brain. The low doses of tirilazad mesylate used in this study (1 mg/kg) are far too low to directly scavenge hydroxyl radical. The hydrophobicity of tirilazad suggests that the most likely mechanism involves lipid and fatty acid peroxidation products or possibly a direct attack on membrane proteins. The exciting challenge remains to identify how tirilazad mesylate protects in partial but not total ischemia in dogs.

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