Delayed treatment with magnesium: reduction of brain infarction and improvement of electrophysiological recovery following transient focal cerebral ischemia in rats

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Object. The authors examined whether delayed treatment with Mg \(^{2+}\) would reduce brain infarction and improve electrophysiological and neurobehavioral recovery following cerebral ischemia--reperfusion.

Methods. Male Sprague–Dawley rats were subjected to right middle cerebral artery occlusion for 90 minutes followed by 72 hours of reperfusion. Magnesium sulfate (750 μmol/kg) or vehicle was given via intracarotid infusion at the beginning of reperfusion. Neurobehavioral outcome and somatosensory evoked potentials (SSEPs) were examined before and 72 hours after ischemia–reperfusion. Brain infarction was assessed after the rats had died.

Before ischemia–reperfusion, stable SSEP waveforms were recorded after individual fore- and hindpaw stimulations. At 72 hours of perfusion the SSEPs recorded from ischemic fore- and hindpaw cortical fields were depressed in vehicle-injected animals and the amplitudes decreased to 19 and 27% of baseline, respectively (p < 0.001). Relative to controls, the amplitudes of SSEPs recorded from both ischemic fore- and hindpaw cortical field in the Mg \(^{2+}\)-treated animals were significantly improved by 23% (p < 0.005) and 39% (p < 0.001) of baselines, respectively. In addition, Mg \(^{2+}\) improved sensory and motor neurobehavioral outcomes by 34% (p < 0.01) and 24% (p < 0.05), respectively, and reduced cortical (p < 0.05) and striatal (p < 0.05) infarct sizes by 42 and 36%, respectively.

Conclusions. Administration of Mg \(^{2+}\) at the commencement of reperfusion enhances electrophysiological and neurobehavioral recovery and reduces brain infarction after cerebral ischemia–reperfusion. Because Mg \(^{2+}\) has already been used clinically, it may be worthwhile to investigate it further to see if it holds potential benefits for patients with ischemic stroke and for those who will undergo carotid endarterectomy.

Key Words • stroke • focal cerebral ischemia • neuroprotection • electrophysiological outcome • neurobehavioral outcome • magnesium • rat

Cerebral stroke is a potential complication following CA revascularization procedures. Ischemia induces neuronal depolarization that removes the voltage-dependent Mg \(^{2+}\) blockade from NMDA receptors and renders endogenous glutamate neurotoxic. Several antagonists of NMDA receptors have been found to decrease stroke lesions in animal models of ischemia, but at clinically active doses they usually produce sedation, respiratory depression, and cardiovascular and severe psychomimetic side effects in humans. As opposed to many experimental agents, Mg \(^{2+}\) offers the advantage of already being used clinically without major side effects. It has also been proposed that the systemic adverse effects caused by NMDA antagonists may be greatly reduced and neuroprotective efficacy greatly enhanced, when Mg \(^{2+}\) is administered directly via a proximal intraarterial infusion into the target organ.

Magnesium ion can readily cross the blood–brain barrier to bind specific receptors in the brain. It prevents excitotoxicity in blocking various subtypes of Ca \(^{2+}\) and NMDA channels and has proved to be neuroprotective in vitro and in vivo. Marinov et al. showed that pretreatment with Mg \(^{2+}\) reduces brain infarction following transient MCA occlusion. They stated that the neuroprotective action of Mg \(^{2+}\) is robust, dose dependent, and strongly related to the duration of ischemia. More recently, Mg \(^{2+}\) has been demonstrated to preserve energetic metabolism and to attenuate glutamate release during cerebral ischemia and early reperfusion periods in a gerbil model of transient ischemic stroke. Alternatively, we have shown that pretreatment with Mg \(^{2+}\) protects the brain against permanent focal cerebral ischemia. In a delayed treatment paradigm, intravenous administration of Mg \(^{2+}\) was shown in rats to offer a window of opportunity that extends up to 6 hours following embolic stroke, a model closer to permanent focal cerebral ischemia. Taken together, it is evident that Mg \(^{2+}\) has the ability to modulate cerebral bioenergetics during ischemia--

Abbreviations used in this paper: CA = carotid artery; ICoBF = local cortical blood flow; LDF = laser-Doppler flowmetry; MCA = middle cerebral artery; NMDA = N-methyl-D-aspartate; SEM = standard error of the mean; SI = primary somatosensory cortex; SII = secondary somatosensory cortex; SSEP = somatosensory evoked potential.
The scalp of each animal was incised along the midline, briefly, with the aid of an op-

erators, which was then removed at 90 minutes of MCA occlusion. Reperfusion was confirmed

Lack-

ragen were maintained at 37 °C by using a thermostatical-

reperfusion and events, and potential adverse effects, par-

ticularly with regard to intravenous administration of Mg2+

This has prompted us to assess whether delayed Mg2+

treatment, in the form of an intracarotid infusion given at an ear-

ily reperfusion time, would reduce brain infarction and im-

rope electrophysiological and functional neurobehavioral

in rats subjected to 90 minutes of MCA occlusion followed by 72 hours of reperfusion. Ad-

itionally, we compared spatial and temporal changes in ICoBF between Mg2+-treated animals and controls. Finally, we sought to determine which anatomical structure (cortex or striatum) of the ischemic MCA territory could be better salvaged by Mg2+ in the model.

Materials and Methods

All procedures that we performed were approved by the Subcommittee on Research Animal Care of the University Medical Center, whose standards meet the guidelines of the National Institutes of Health (Guide for the Care and Use of Laboratory Animals).

Animal Preparation, Anesthesia, and Monitoring

Male Sprague–Dawley rats, each weighing between 250 and 300 g, were supplied by the University Laboratory Animal Center and were allowed free access to food and water before and after surgery. Anesthesia was induced in these animals with a mixture of 1 to 2% halothane in 70% N2O/30% O2. During surgery, the rats’ body temperatures were maintained at 37 ± 0.5 °C by using a thermostatically controlled heating blanket and a rectal probe (Harvard Appara-
tus, South Natick, MA). The right femoral artery was cannulated over a flame and subsequently coated with silicone (Merck KGaA, Darmstadt, Germany), was advanced 17.5 to 19 mm from the exter-

nal CA into the internal CA until the suture tip occluded the origin of the MCA. After closure of the operative sites, the animals were al-

owed to awaken from anesthesia and were temporarily transferred to a cage with a heating lamp (ambient temperature 26 ± 1 °C). During another brief period of anesthesia, the sutures were removed at 90 minutes of MCA occlusion. Reperfusion was confirmed by an improvement in the ipsilateral ICoBF at a defined area of the ischemic core cortex to approximately 50% of baseline after an initial decrease to approximately 20% of baseline caused by MCA occlusion, as determined by LDF (Lasersfö BMP®, Vasamedics, St. Paul, MN). After the surgical procedures, the animals were kept in a cage containing a heating lamp, monitored for 4 hours, and then transferred to their home cages (ambient temperature ~ 24 ± 1 °C). Magnesium sulfate (Sigma Chemical Co., St. Louis, MO) was dis-

solved in saline. A fresh drug solution was prepared shortly before its administration. Each animal was given an intracarotid infusion containing either Mg2+ (750 μmol/kg, 12 rats) or vehicle (saline, 11 animals), over a 20-minute period starting at the initiation of reperfu-

sion (that is, 90–110 minutes after onset of ischemia). The dose of Mg2+ was based on the pharmacokinetic study of exogenous Mg2+ in rodents and on findings from neuroprotective dose–response stud-

ies of Mg2+ in a rat model of transient focal cerebral ischemia. Initial findings indicated that delayed treatment with Mg2+ conferred neuroprotection against cerebral ischemia–reperfusion; however, it also induced modest hypothermia, attenuating postisch-

emic hyperthermia. Given that hypothermia is a phenomenon well known to protect against ischemic brain damage, we also included an additional set of animals that received vehicle (saline, eight rats) at the beginning of reperfusion. These animals were used to clarify whether Mg2+-induced neuroprotection would be attributed to its at-

enuating effect on postischemic hyperthermia. These animals’ core temperatures were adjusted as closely as possible to temperatures ob-

served in the Mg2+-treated animals by externally applying alcohol two consecutive times during the first 2 hours of reperfusion and then twice daily, at 8-hour intervals, after 24 hours of reperfusion. These animals were transferred to a cage with a small ventilating fan, which maintained the ambient temperature at approximately 22 ± 1 °C, after 24 hours of reperfusion.

Monitoring of ICoBF

Laser Doppler flowmetry was used to obtain ICoBF measurements. The scalp of each animal was incised along the midline, and two 1.5-mm diameter areas in the bilateral parietal bones, 0.5 mm posterior and 7 mm lateral to the bregma, were thinned using a dental drill for placement of the LDF probes (model P436). The re-

region was located on the SII, which was close to the core of the infarc-

tion caused by MCA occlusion on the operated side. Another 1.5-
m diameter region in the right parietal bone, 2.5 mm lateral to the bregma, was thinned for additional ICoBF measure-

ments. This region is located on the posterior medial portion of the SI, which has been identified as a representative ischemic penumbral area in the model, based on the rat brain atlas and on data from previous studies on the measurements of cerebral blood flow.53,54 The ICoBF was serially measured before and during MCA occlusion and again 40 minutes after onset of reperfusion. The ICoBF data are expressed as percentages of baseline values.

Somatosensory Evoked Potential Recordings

Before the ischemic insult and again following a reperfusion peri-

od lasting between 70 and 72 hours, each animal was anesthetized and placed in a cage (60 × 45 × 45 cm) constructed of aluminum columns and copper meshes. The animal’s head was fixed in a ste-

terotactic frame that was adjusted so that the surface of the skull was level between the bregma and lambda. The cranium was then ex-

posed to create two 1.5-mm-diameter holes drilled above the SI for each hemisphere. Appropriate stereotactic coordinates were mea-

sured from the bregma and from the midline (~0.5 and ~2 mm in the anteroposterior direction for the forepaw receptive field and 4 and 2.5 mm laterally for the hindpaw receptive field).13,14 On exposure of the cortex, the dura mater was gently removed and the surface of the cortex was covered with warm saline. A metal microelectrode
Magnesium and poststroke electrophysiological recovery

(impedance 500 kW at 1000 Hz) was positioned 0.5 mm below the cortical surface. Signals were filtered with band-pass (10- to 2000 Hz) and notch (60-Hz) filters and were recorded digitally on a computer by using associated software (Medelec Synergy Suite EMG/EP; Oxford Instruments, UK). The somatosensory stimuli consisted of transcutaneous electrical stimulation (3 mA direct current, 1-msec duration, 1 Hz) of the fore- and hindpaws contralateral to the side of recording. A current stimulator and isolation unit constantly produced electrical pulses, which were delivered to the intraparenchymal needle electrode placed in the contralateral sensory cortex. Averaged records of at least 20 evoked potentials were computed online and stored on a computer disk. A custom-made software analysis provided measures of latency and amplitude potentials. The amplitude was defined in terms of the difference between the P and N peaks.

Neurobehavioral Testing and Body Weight Measurements

Body weight measurements were obtained daily. A neurological evaluation was conducted before and after the ischemia–reperfusion insult and on a daily basis up to 3 days after reperfusion by two observers unaware of the treatment protocol. Two neurological grading systems were used: 1) a sensorimotor grading scale modified from that previously published by Belayev, et al., methods15 which included five scores (0–4) for forward and sideways visual placement tests of the affected forelimb and five scores (0–4) for motor outcome;13,15,16 and 2) a neurobehavioral grading scale developed by Clark and colleagues17 for rodents with scores ranging from 0 to 28.14,16

Planned Death of the Animals and Quantification of Ischemic Damage

The animals were first anesthetized and then killed after 72 to 74 hours of survival. Their brains were rapidly removed, cut into 2-mm coronal sections by using a rat brain matrix (RBM 4000C; ASI Instrument, Inc., Warren, MI), and stained according to the standard coronal sections by using a rat brain matrix (RBM 4000C; ASI Instrument, Inc., Warren, MI), and stained according to the standard

Statistical Analysis

Neurobehavioral scores were expressed as medians ± 95% confidence intervals and were analyzed by performing nonparametric tests for independent groups, that is, the Kruskal–Wallis test and the Mann–Whitney U-test. Other data were expressed as means ± SEMs. A paired Student t-test was used to evaluate the response to a change in conditions, and a one-way analysis of variance with the Fisher protected least-significant difference post hoc comparison was used to evaluate differences between groups. Temperature, ICoBF, and SSEP values were analyzed among groups at each sampling time and location by performing repeated analyses of variance, followed by Fisher protected least-significant difference post hoc comparisons. A probability value less than 0.05 was selected for statistical significance.

Results

Throughout the course of the experiments, three animals (10%) died before completing the recovery protocol and were excluded from the analysis; two of the animals were in the vehicle-injected group and the third was in the Mg2+-treated group. Animals subjected to transient MCA occlusion invariably exhibited spontaneous hyperthermia.14 Their core temperatures reached 37.6 to 38.7˚C within 1 hour, remained high during the first 24 hours, and then gradually subsided. Relative to the vehicle-injected controls, the Mg2+-treated animals had a significantly reduced level of core temperatures, by 0.8˚C during the early reperfusion period. This temperature-lowering effect offered by Mg2+ was transiently lost during the 1st day, but reappeared between 48 and 72 hours of reperfusion (Fig. 1A). The postischemic core temperature, however, did not differ significantly at each sampling time interval between Mg2+-treated animals and temperature-adjusted controls. The other physiological parameters of the animals were kept within normal physiological limits during the course of experiments and did not differ significantly among the three study groups (Table 1).

Before the ischemia–reperfusion injury, stable SSEP waveforms containing two positive peaks and one intervening negative peak were consistently recorded after individual fore- and hindpaw stimulations (Fig. 2A–D, A'–D' and I–L). The amplitude between the P, and the N peaks and the P, latency did not differ significantly among the three study groups (Table 2). At 72 hours after onset of reperfusion, significantly depressed SSEPs were recorded from the ischemic fore- and hindpaw cortical fields of both groups of vehicle-treated controls and the P,–N, amplitude decreased to 18 to 20% and 26 to 28% of baselines, respectively (p < 0.001; Table 2 and Fig. 2E, F, E', and F'). These amplitudes did not differ significantly between the two groups of vehicle-injected animals, although Mg2+ significantly enhanced the P,–N, amplitude of the SSEPs recorded from the ischemic fore- and hindpaw cortical fields, by 22 to 24% and 38 to 40% of baselines, respectively (p < 0.005 and p < 0.001; Table 2 and Fig. 2M and N), relative to the two control groups.

Following 72 hours of reperfusion, animals in all three study groups displayed contralateral electrophysiological diaschisis, as indicated by a reduction in the P,–N, amplitudes measured in SSEPs recorded postischemia at the contralateral intact hindpaw cortical field, relative to their baseline values (p < 0.05; Table 2 and Fig. 2H, H', and P). Additionally, temperature-adjusted controls and Mg2+-treated animals had prolonged P, latencies in the SSEPs recorded from the ischemic forepaw and hindpaw cortical fields (p < 0.01; Table 2 and Fig. 2E', F', M and N), compared with their baseline values. These postischemic P, latencies of the ischemic cortical fields were, however, not significantly different among the three study groups. Moreover, the statistical analysis indicated that the amplitude and latency of the SSEPs recorded at 72 hours postischemia after individual right fore- or hindpaw stimulations were not significantly different among the three study groups (p > 0.05; Table 2).

The ipsilateral ICoBF recorded at the SII and the SI abruptly decreased to 15 to 18% and 36 to 40% of baselines, respectively, following onset of MCA occlusion. The decreased ICoBF values at the SII and SI subsequently im-
proved to 48 to 50% and 78 to 92% of baselines, respectively, after the initiation of reperfusion. In contrast, the contralateral lCoBF did not significantly change over time during the course of the experiments. Before and during the ischemic insult, recordings of lCoBF did not differ significantly among the three groups of animals (Fig. 1B–D; \( p > 0.05 \)). The Mg\(^{++} \) or mild temperature adjustments did not affect lCoBF values recorded either at the ipsilateral SI or SII or at the contralateral SII, as assessed within 40 minutes after treatment (Fig. 1B–D; \( p > 0.05 \)).

Transient MCA occlusion resulted in large ipsilateral cortical and striatal infarcts that were reproducible but variable in size. None of the three groups of animals displayed any hemorrhagic transformation after death. The animals that received an intracarotid injection of Mg\(^{++} \) (750 \( \mu \)mol/kg) demonstrated a significant reduction in brain infarct volumes by 41 to 46% \( (p < 0.01) \), but not in the index of ipsilateral brain swelling \( (p > 0.05) \), compared with the two groups of vehicle-injected controls (Fig. 3A and B). Cortical and striatal infarction lesions were reduced by 40 to 45% and 30 to 40%, respect-
Magnesium and poststroke electrophysiological recovery

**Table 1**

<table>
<thead>
<tr>
<th>Time &amp; Animal Group</th>
<th>No. of Rats</th>
<th>pH</th>
<th>PCO₂ (mm Hg)</th>
<th>PO₂ (mm Hg)</th>
<th>Hct (%)</th>
<th>Gluc (mg/dl)</th>
<th>MABP (beats/min)</th>
<th>HR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>preocclusion control</td>
<td>9</td>
<td>7.45 ± 0.01</td>
<td>41.9 ± 1.1</td>
<td>126.6 ± 9.1</td>
<td>37.4 ± 0.5</td>
<td>149 ± 8</td>
<td>89 ± 2</td>
<td>339 ± 9</td>
</tr>
<tr>
<td>temp-adjusted control</td>
<td>8</td>
<td>7.43 ± 0.01</td>
<td>39.8 ± 0.9</td>
<td>143.7 ± 6.6</td>
<td>37.9 ± 0.6</td>
<td>142 ± 5</td>
<td>90 ± 3</td>
<td>341 ± 12</td>
</tr>
<tr>
<td>Mg²⁺-treated postocclusion control</td>
<td>11</td>
<td>7.45 ± 0.01</td>
<td>41.2 ± 0.7</td>
<td>143.9 ± 9.8</td>
<td>36.5 ± 0.7</td>
<td>141 ± 9</td>
<td>92 ± 2</td>
<td>347 ± 8</td>
</tr>
<tr>
<td>temp-adjusted control</td>
<td>9</td>
<td>7.43 ± 0.01</td>
<td>43.6 ± 1.3</td>
<td>124.4 ± 7.1</td>
<td>36.7 ± 0.6</td>
<td>141 ± 9</td>
<td>96 ± 2</td>
<td>338 ± 8</td>
</tr>
<tr>
<td>Mg²⁺-treated 40 min of reperfusion control</td>
<td>8</td>
<td>7.42 ± 0.02</td>
<td>40.8 ± 1.8</td>
<td>146.5 ± 5.5</td>
<td>37.5 ± 0.6</td>
<td>144 ± 4</td>
<td>97 ± 4</td>
<td>348 ± 13</td>
</tr>
<tr>
<td>Mg²⁺-treated</td>
<td>11</td>
<td>7.44 ± 0.01</td>
<td>42.6 ± 1.0</td>
<td>134.5 ± 8.0</td>
<td>36.6 ± 0.6</td>
<td>140 ± 5</td>
<td>95 ± 4</td>
<td>349 ± 8</td>
</tr>
</tbody>
</table>

*Physiological data obtained from control and Mg²⁺-treated animal groups are represented as the means ± SEMs. Physiological parameters were normal and did not differ significantly among the three study groups. Abbreviations: Gluc = blood glucose; Hct = hematocrit; HR = heart rate; MABP = mean arterial blood pressure; temp = temperature.


datively, in the Mg²⁺-treated group (p < 0.05, respectively; Fig. 3C). Treatment with Mg²⁺ also significantly improved the sensory (p < 0.01), motor (p < 0.05), and 28-point neurological scores (p < 0.01) obtained 72 hours after the onset of reperfusion but did not attenuate the postischemic loss of body weight (p > 0.05; Table 3).

**Discussion**

This study confirmed that delayed treatment with Mg²⁺ was neuroprotective and could reduce both cortical and striatal infarctions induced by transient MCA occlusion. Additional novel findings were that Mg²⁺ improved neurobehavioral and electrophysiological outcomes in the model of cerebral ischemia–reperfusion, even when it was initiated as late as 90 minutes after onset of an ischemic insult. This neuroprotection cannot be accounted for by changes in hemodilution (as measured by the blood hematocrit levels), arterial blood pressure, heart rate, or differences in ICoBF because these were not significantly different when compared among the three study groups. Findings of previous

**Table 2**

<table>
<thead>
<tr>
<th>P1 Latency in msec (% of baseline)</th>
<th>P1–N1 Amplitude μV (% of baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time &amp; Animal Group</td>
<td>Rt Forepaw</td>
</tr>
<tr>
<td>preischemia control (9 rats)</td>
<td>14.8 ± 0.6</td>
</tr>
<tr>
<td>temp-adjusted control (8 rats)</td>
<td>14.4 ± 0.4</td>
</tr>
<tr>
<td>Mg²⁺-treated (11 rats) at 72 hours post-reperfusion control (9 rats)</td>
<td>14.9 ± 0.4</td>
</tr>
<tr>
<td>temp-adjusted control (8 rats)</td>
<td>18.1 ± 0.6</td>
</tr>
<tr>
<td>Mg²⁺-treated (11 rats)</td>
<td>16.8 ± 0.8</td>
</tr>
<tr>
<td>temp-adjusted control (8 rats)</td>
<td>17.7 ± 1.0</td>
</tr>
</tbody>
</table>

*Data on SSEPs are represented as means ± SEMs.
† p < 0.05 compared with preischemic data.
‡ p < 0.005 compared with two control groups.
§ p < 0.001 compared with two control groups.

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pharmacodynamic studies have indicated that systemic administration of Mg\(^{++}\) may lead to a dose-dependent decrease in both arterial blood pressure and heart rate.\(^{13,31}\) In this study, however, we found that the influence of an infusion of Mg\(^{++}\) on these hemodynamic parameters is not significant. The exact reason for this difference is not clear but may be due to the slower infusion rate via the intracarotid route, which may show less cardiovascular response.

Animals subjected to MCA occlusion for 90 minutes exhibited poststroke hyperthermia and this occurred most prominently within the first 24 hours of reperfusion. Treatment with Mg\(^{++}\), however, decreased the core temperature significantly by 0.8˚C 2.5 hours after MCA occlusion, compared with vehicle-treated animals. This Mg\(^{++}\)-induced temperature-lowering action was transiently obscured during the 1st day but reappeared during the subsequent 2 days. Interestingly, the neuroprotective potency of Mg\(^{++}\) has recently been linked to the presence of mild hypothermia in a rat model of global cerebral ischemia.\(^{14,46}\) Nevertheless, our results indicate that, relative to the vehicle-injected animals, temperature-adjusted controls did not achieve significant neuroprotection seen in infarct volume reductions or improvements in neurobehavioral and electrophysiological outcomes. Although postischemic hyperthermia is a factor accelerating the maturation of brain damage,\(^{10,17,34}\) it appeared that Mg\(^{++}\)-induced hypothermia might not be robust enough to confer effective neuroprotection in the model. Other mechanism(s) of action may actually underlie the neuroprotection actions observed with Mg\(^{++}\) following transient focal cerebral ischemia.

The two neurobehavioral scoring systems used in the current study are mainly designed to test postischemic sensorimotor integrity in rodents.\(^{14,13-16}\) Motor dysfunction is commonly observed in rats subjected to permanent and transient MCA occlusion but the mechanisms underlying sensorimotor dysfunction are not precisely known. Increasing evidence, however, has indicated that the efficacy of neuroprotectants, particularly with regard to functional recovery, is largely dependent on their ability to protect against both gray and white matter damage.\(^{15,23,42}\) It has been proposed that the lack of NMDA receptors in axons may restrict functional protection mediated through an exclusive NMDA receptor blockade.\(^{24}\) Magnesium ions, however, have many additional pharmacological properties, such as the ability to inhibit the deleterious importation of Ca\(^{++}\) into the intracellular space and to protect against oxidative radicals and their antiapoptotic effects, all of which have the potential to protect against ischemic white matter damage.\(^{5,26,27}\) Nevertheless, this remains elusive and needs further evaluation.

Impairment of sensorimotor function may substantially reflect a change in electrophysiological function and may not necessarily reflect a change in total infarct volumes or their percentages. It is well documented that extensive connections exist between the motor cortex and sensory cortex and between the cortex and subcortex.\(^{41}\) These structures are involved in the processing and integration of sensorimotor information. Thus, the beneficial effect on preserving more viable brain tissues in both ischemic penumbral cortex and striatum observed with Mg\(^{++}\) may be an important factor contributing to the improved electrophysiological and neurobehavioral functions observed here, because the SI and the medial caudoputamen ipsilateral to the MCA occlusion.
are two representative ischemic penumbral regions following cerebral ischemia–reperfusion. More important, Mg delivers a beneficial effect by preserving cerebral bioenergetics during ischemia and early reperfusion periods. The postischemic bioenergetic level is a key factor determining the electrophysiological recovery recorded at cortical fields at risk of infarction. Thus, the beneficial potential of Mg to prevent the depletion of adenosine triphosphate in the ischemic brain may also be one of the mechanisms underlying improved electrophysiological outcome, as observed here.

It is worthwhile to pursue studies of Mg as a neuroprotectant. Reasons for this include its posttreatment protection of the brain from infarction induced by transient MCA occlusion, as observed in this study, its consistent reductions in infarction volume and a wide therapeutic window of opportunity also reported in models of permanent and embolic MCA occlusion, and its marked reduction in systemic adverse effects. It should be noted that the post-insult administration of Mg within 12 hours after symptom onset failed to show efficacy in a clinical trial of ischemic stroke, although it may be helpful for lacunar strokes. The exact reason for this translation failure is not currently clear. It is possible that prolonged ischemia plus delayed spontaneous reperfusion events may have caused a fundamental change in NMDA-activated ion channels and other molecular events such that Mg is no longer able to block the succession of ischemic cascades, which subsequently causes irreversible neuronal damage and eventually neuronal death. Nevertheless, promising results in preliminary clinical studies support the validity of testing the efficacy of early Mg administration, despite the fact that these studies have comprised very few patients.

Although no neuroprotectant has been proven benefi-
cultural in the treatment of focal ischemic stroke in human beings, several currently available interventions have shown promising results in preliminary clinical trials. In particular, Mg\textsuperscript{++} offers an attractive potential therapy for stroke, because it is widely available, inexpensive, familiar to many clinicians, and can potentially be used by paramedics very early after onset of the insult.\textsuperscript{13} The results in the present study, combined with data we have previously reported,\textsuperscript{13} support the notion that Mg\textsuperscript{++} may have potential as an adjuvant therapy of intraarterial thrombolytic intervention for patients with ischemic stroke. It may also be worthwhile to investigate Mg\textsuperscript{++} further for its possible applicability in the field of CA revascularization, especially for those patients at risk of developing an ischemic stroke due to the poor vascular plasticity of the posterior communicating artery. Additional studies are needed, however, to decipher the molecular events through which Mg\textsuperscript{++} leads to neuroprotection of function, as observed here. Additional studies are also needed for evaluating the crucial therapeutic window of Mg\textsuperscript{++} and for verifying its potential benefit when combined with thrombolytic intervention (that is, extending the therapeutic window and/or reducing the rate of hemorrhagic transformation) in ischemic brain injury.

Conclusions

Delayed intraarterial administration with Mg\textsuperscript{++} at the initiation of reperfusion both enhances electrophysiological and neurobehavioral outcomes and reduces cortical and striatal infarction after cerebral ischemia–reperfusion. This neuroprotection cannot be attributed to its attenuating effect on posts ischemic spontaneous hyperthermia. Because Mg\textsuperscript{++} offers the advantage of already being used clinically, it is worthwhile to investigate it further to determine its potential benefits for those patients who will undergo carotid endarterectomy and for possible applications for patients suffering from ischemic stroke.

References


### TABLE 3

Comparison of sensorimotor behavioral scores and weight loss when Mg\textsuperscript{++} is given to rats with cerebral ischemia–reperfusion*

<table>
<thead>
<tr>
<th>Time &amp; Animal Group</th>
<th>Weight Loss in Grams (mean ± SEM)</th>
<th>Neurological Behavioral Score (median [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hrs postreperfusion control (9 rats)</td>
<td>40.1 ± 2.3</td>
<td>4.2 (3.6–4.1)</td>
</tr>
<tr>
<td>Mg\textsuperscript{++}-treated (11 rats)</td>
<td>39.4 ± 2.8</td>
<td>3.6 (3.2–4.0)††</td>
</tr>
<tr>
<td>48 hrs postreperfusion temp-adjusted control (8 rats)</td>
<td>33.9 ± 2.7</td>
<td>3.4 (3.0–3.8)</td>
</tr>
<tr>
<td>Mg\textsuperscript{++}-treated (11 rats)</td>
<td>39.4 ± 2.8</td>
<td>3.2 (2.8–3.6)</td>
</tr>
<tr>
<td>72 hrs postreperfusion control (9 rats)</td>
<td>64.0 ± 5.6</td>
<td>4.3 (3.7–4.9)††</td>
</tr>
<tr>
<td>Mg\textsuperscript{++}-treated (11 rats)</td>
<td>51.6 ± 2.6</td>
<td>3.6 (3.2–4.0)†</td>
</tr>
<tr>
<td>temp-adjusted control (8 rats)</td>
<td>58.6 ± 3.8</td>
<td>2.7 (2.3–3.3)††</td>
</tr>
<tr>
<td>Mg\textsuperscript{++}-treated (11 rats)</td>
<td>75.9 ± 8.0</td>
<td>4.3 (3.7–4.9)††</td>
</tr>
</tbody>
</table>

* Delayed Mg\textsuperscript{++} treatment improved sensorimotor behavioral scores and weight loss when Mg\textsuperscript{++} is given to rats with cerebral ischemia–reperfusion. Abbreviation: CI = confidence interval.

†p < 0.01 compared with two control groups.
‡p < 0.05 compared with two control groups.
Magnesium and poststroke electrophysiological recovery


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