Failure of MK-801 to Reduce Infarct Volume in Thrombotic Middle Cerebral Artery Occlusion in Rats

Hiroshi Yao, MD; Myron D. Ginsberg, MD; Brant D. Watson, PhD; Ricardo Prado, MD; W. Dalton Dietrich, PhD; Susan Kraydieh, BS; and Raul Busto, BS

Background and Purpose: We examined the effects of the noncompetitive N-methyl-D-aspartate receptor antagonist MK-801 using a newly developed stroke model of thrombotic distal middle cerebral artery occlusion under conditions of carefully controlled head temperature.

Methods: Male Sprague-Dawley rats were treated with 1 mg/kg of MK-801 or saline before the induction of ischemia. An argon laser–activated dye laser (562 nm) was used to cause thrombotic distal middle cerebral artery occlusion. In experiments 1 and 2, the single laser beam (20 mW) was separated into three beams. Each beam was positioned onto the distal middle cerebral artery at three sites along the vessel. The photosensitizing dye rose bengal (20 mg/kg) was administered intravenously over 2 minutes; the three points were then irradiated for 3 minutes. In experiment 3, higher power of the laser (three separate irradiations using a single beam of 20 mW) was used. The ipsilateral common carotid artery was occluded permanently, and the contralateral carotid artery was occluded for 60 minutes. Head temperature was controlled at 36°C in experiment 1 and not controlled in experiments 2 and 3. Three days after the ischemic insult, brains were perfusion-fixed and infarct volumes were determined.

Results: Head temperature was mildly hypothermic (34–35°C before ischemia, with a further decrease of 1–2°C during the initial 60 minutes of ischemia) in experiment 2. However, no differences were observed in head temperature between the MK-801-treated and control groups. Cortical infarct volume in experiment 1 was 89±29 mm³ (mean±SD) in the treated group, which was not different from the control value of 84±40 mm³. Infarct volumes were smaller (58±35 mm³ and 54±14 mm³) in the control groups of experiments 2 and 3, respectively. However, MK-801 also failed to reduce infarct volumes in experiments 2 and 3.

Conclusions: MK-801 is not effective in this stroke model of focal thrombotic infarction under conditions of either controlled (normothermic) or uncontrolled (mildly hypothermic) head temperature. (Stroke 1993;24:864–871)

KEY WORDS • cerebral ischemia • glutamates • MK-801 • photothrombosis • rats

Cerebral ischemia causes a massive release of glutamate from presynaptic terminals, which causes an abnormal influx of calcium ions into neurons through N-methyl-D-aspartate (NMDA) receptors and subsequently triggers detrimental responses in neurons, resulting in ischemic neuronal death. Blockade of the NMDA receptor with (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801) could potentially protect brain from ischemic stroke. This noncompetitive NMDA receptor antagonist is a lipophilic compound that readily crosses the blood–brain barrier, and binding to NMDA receptors is enhanced by the presence of glutamate (agonist dependence or use dependence). Although MK-801 is not effective in the face of severe ischemia, this drug has been reported to be unequivocally effective in the stroke models of middle cerebral artery (MCA) occlusion, in which a less dense ischemic region exists around the central core of severe ischemia. However, one of the most confounding factors in the studies using MK-801 is drug-induced hypothermia, which could attenuate ischemic insults in the settings of both global and focal ischemia. Furthermore, despite the fact that body temperature was well controlled in previous studies of focal ischemia that showed reductions of infarct volume by MK-801, we cannot exclude the possibility that mild hypothermia in the brain might have contributed to a synergistic protective action of MK-801 because brain temperature declines independently of body temperature during cerebral ischemia. Therefore, we examined the effects of

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MK-801 in a focal ischemia model of distal MCA occlusion with or without head temperature control.

Materials and Methods

Fifty-three male Sprague-Dawley rats (Charles River Laboratories, Inc., Wilmington, Mass.), weighing 260–410 g, which had been deprived of food overnight, were anesthetized with halothane (3% for induction, 1.5% during the surgical preparation with a face mask, 0.75% after intubation, and 0.5% for maintenance) in a mixture of 70% nitrous oxide and 30% oxygen. Under sterile surgical conditions, the right femoral artery and vein were cannulated using PE 50 tubing. The common carotid arteries were exposed through a ventral midline incision in the neck and loosely encircled with length of PE 10 tubings fitted within double-barreled Silastic tubings for later ligation. The rats were endotracheally intubated with a PE 240 tubing. Pancuronium bromide (0.3 mg) was injected intravenously; additional doses of 0.1 mg were administered every 30 minutes, and the rats were mechanically ventilated. Blood pressure was continuously monitored with a pressure transducer and Gould 2400 polygraph recorder. Blood gases and plasma glucose concentrations were measured before distal MCA occlusion and 10, 60, and 120 minutes after occlusion.

Rats were mounted on a stereotaxic head holder in the prone position, and a 2-cm incision was made vertically midway between the right orbit and the right external auditory canal; the temporalis muscle was separated and retracted to expose the zygoma and squamous bones. Under an operating microscope (model 30T, Carl Zeiss, Inc, Thornwood, N.Y.), a burr hole 3 mm in diameter was made with a high-speed drill 1 mm rostral to the anterior junction of the zygoma and squamous bones, revealing the distal segment of the distal MCA above the rhinal fissure. A thin bone layer was preserved to prevent injury to the brain and was removed carefully with forceps. The dura was left intact.

Rectal temperature was maintained by means of a rectal thermistor probe inserted 5 cm into the anal canal and a thermostatically regulated heating lamp (60 W) placed 10 cm above the body of the rat. In experiment 1, a thermocouple probe (CN 9000, Omega Engineering, Inc, Stamford, Conn.), which was calibrated against a mercury thermometer, was introduced beneath the skin in contact with the right side of the skull. Head temperature was thermostatically regulated at 36.0–36.5°C for at least 30 minutes before distal MCA occlusion and until 120 minutes after occlusion by means of another warming lamp (25 W), positioned 2 cm above the head and optically filtered to yield red light to eliminate any possible interaction between rose bengal dye and white light. In experiment 2, the positions of the two heating lamps were the same as in experiment 1, but the lamp over the head of the rat was turned off, and head temperature was then monitored but not controlled, while rectal temperature was strictly controlled as in experiment 1.

Infarct volumes in experiments 1 and 2 proved to be smaller, in particular in experiment 2, than in our previous study,27 in which a more powerful laser beam was used (i.e., three separate irradiations using a single laser beam of 20 mW). For these reasons, we also performed experiment 3, which was performed under exactly the same conditions as our previous study27 using higher laser power, without head temperature control and with the same duration of exposure to anesthesia.

In a preliminary study, three of four rats died after injection of MK-801 (5 mg/kg i.p.) because spontaneous respiration did not recover, despite maintenance of normal physiological variables (blood pressure, arterial gases, and plasma glucose level). Swan and Meldrum28 similarly observed that the mortality rate was high using a dose of 3 mg/kg i.p. in transient forebrain ischemia in Wistar rats. In previous focal ischemia studies, 0.5 mg/kg of MK-801 reduced infarct volume effectively in Sprague-Dawley15 and Fisher 344 rats.15 For these reasons, we decided on a dose of 1 mg/kg. MK-801 1 mg, freshly dissolved in 2 mL saline, or the same volume of saline (0.6–0.8 mL) vehicle, was injected intraperitoneally 30 minutes before distal MCA occlusion.

After exposing the distal MCA, three points for laser irradiation were determined according to essentially the same criteria as in our previous study.27 We excluded three rats, one with two MCAs and two with very low-Y-shaped bifurcations, all of which failed to satisfy our criteria.

An argon laser–activated dye laser at 562 nm (Innova 70, Coherent Inc., Palo Alto, Calif.) was used to irradiate the distal MCA at a power of 20 mW. In experiments 1 and 2, the single laser beam (20 mW) was separated into three beams by a Ronchi ruling. Each beam was separately positioned by a mirror onto a designated point on the distal MCA. The photosensitizing dye rose bengal (15 mg/mL in 0.9% saline, 20 mg/kg body wt) was administered intravenously over 2 minutes; then, the three points of the right distal MCA were simultaneously irradiated for 3 minutes. In experiment 3, one third of the total dose of rose bengal was injected intravenously over 30 seconds, and the most distal site among the three points was irradiated for 3 minutes using a single laser beam with a power of 20 mW. Then the second and third injections of rose bengal were followed by irradiations at the second and third vessel sites, respectively.

After distal MCA occlusion, the common carotid arteries were occluded bilaterally by tightening the snare ligatures. The ipsilateral (right) common carotid artery was permanently occluded, and the contralateral common carotid artery was occluded for 1 hour. One hour after release of the left common carotid artery, the neck and head wounds were closed, catheters were removed, and halothane was discontinued. The rats were extubated and returned to the home cage after regaining the ability to breathe independently.

Three days after MCA occlusion, the rats were transcardiostomized under 3–4% halothane anesthesia and mechanically ventilated after pancuronium bromide injection (1 mg i.p.). The brains were perfusion-fixed by transcardiac perfusion with physiological saline followed by a mixture of 40% formaldehyde, glacial acetic acid, and methanol (FAM) (1:1:8 by volume), which was delivered at 110 mm Hg for 20 minutes. The heads were immersed in FAM for at least 24 hours. The brains were then removed from the skull, and coronal brain blocks were embedded in paraffin. Brain sections 10 μm thick were prepared at 200-μm intervals. These sections were stained with hematoxylin and eosin. For morphometric study, eight coronal levels having readily identi-
TABLE 1. Physiological Variables in Experiment 1

<table>
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<tr>
<th></th>
<th>Control</th>
<th>MCAO+BCCAO</th>
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<tr>
<td></td>
<td>Before MCAO*</td>
<td>10 Minutes</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>101±19</td>
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<td>PCO2 (mm Hg)</td>
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<td>Glucose (mg/dL)</td>
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<td>Temperature (°C)</td>
<td>Rectum 37.0±0.2</td>
<td>37.1±0.3</td>
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<td></td>
<td>Head 36.3±0.3</td>
<td>36.1±0.4</td>
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<tr>
<td>MABP (mm Hg)</td>
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<td>119±23</td>
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<tr>
<td>PCO2 (mm Hg)</td>
<td>40±2</td>
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<td>PO2 (mm Hg)</td>
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<tr>
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<td>104±14‡</td>
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<td>Temperature (°C)</td>
<td>Rectum 37.0±0.1</td>
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<tr>
<td></td>
<td>Head 36.2±0.1</td>
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Values are mean±SD (n=8). MCAO, middle cerebral artery occlusion; BCCAO, bilateral common carotid artery occlusion; MABP, mean arterial blood pressure.

*20-30 minutes after saline or MK-801 1 mg/kg i.p.
†60 minutes after left common carotid artery release.
‡p<0.05 vs. control by unpaired t test with Bonferroni correction.

Results

Tables 1–3 demonstrate physiological variables in experiments 1–3, respectively. Blood pressure in the MK-801–treated group was slightly lower than that in the control group, but the difference did not reach statistical significance. Plasma glucose concentrations in the treated group were within the range of 82–134 mg/dL, and the mean concentration was significantly lower than in the control group at 10 minutes after distal MCA occlusion in experiment 1. Rectal temperature was controlled at 37°C in all three experiments. Head temperature in experiment 2 was 34.5±0.4°C and 34.4±0.4°C before ischemia in the treated and control groups, respectively, and decreased significantly by 1–2°C after distal MCA occlusion combined with bilateral common carotid artery occlusion. After release of the left common carotid artery, head temperature rose to the pre-ischemic level (Table 2). Because the respective values of head and rectal temperature were almost identical between MK-801–treated and untreated groups throughout the observation period, the values for two groups were combined and presented in Figure 1.

Rats treated with MK-801 could not be extubated until 3–4 hours after MK-801 administration. After extubation, the rats treated with MK-801 showed stereotyped repetitive head movements, ataxia on walking, and a poor righting reflex and subsequently became sedated on the second day. Two of the 10 MK-801–treated rats died at 5 hours and 2 days after the ischemic insult in experiment 1, and one of nine control rats died in experiment 2.

Figure 2 summarizes infarct volumes of the right cortex in experiments 1–3. Two treated rats in experiment 1 and one control rat in experiment 3 had bilateral infarcts. (We also observed occasional bilateral infarcts in our previous study.) The infarct volume in the contralateral hemisphere was not quantified. Infarct volume of the right cortex in the MK-801–treated group was 89±29 mm³ (n=8) in experiment 1 (head temperature controlled), which was not significantly different from the volume of 84±40 mm³ (n=8) of the control group. In experiments without head temperature control, infarct volumes were 66±46 mm³ (n=7) and 58±35 mm³ (n=8) in the treated and control groups in experiment 2 and 52±32 mm³ (n=6) and 54±14 mm³ (n=6) in the treated and control groups in experiment 3, respectively. The administration of MK-801 did not reduce the volumes of infarction in any series of the present experiments.

Discussion

Evidence for excitotoxicity in cerebral ischemia is briefly summarized as follows: 1) Glutamate, a major
excitatory amino acid, itself is neurotoxic. 2) Cerebral ischemia induces a massive increase in extracellular concentration of glutamate both in global and focal ischemia. 3) Destruction of glutamatergic afferent pathways protects against ischemic damage. Selective NMDA receptor antagonists are cerebroprotective. As will be discussed below, the consistent efficacy of NMDA antagonists such as MK-801 in focal ischemia models has been assumed to be strong evidence for excitotoxicity in cerebral ischemia and stroke.

Noncompetitive NMDA antagonists are lipophilic compounds that readily cross the blood–brain barrier. In addition, the phenomenon of agonist dependence or use dependence (i.e., MK-801 binding to NMDA receptors in vitro is enhanced by up to 700% under micro-}

molar concentrations of L-glutamate) may be of considerable advantage in pathological conditions such as cerebral ischemia, in which an excessive activation of NMDA receptor occurs. The in vivo uptake of MK-801 injected intravenously after transection of the MCA is greater, at 60 minutes after administration, in the ischemic cortex and striatum than in the contralateral hemisphere. The presence of increased levels of extracellular glutamate may also enhance the in vivo binding of MK-801.

The mechanism underlying the protective effect of MK-801 was investigated in vivo by Uematsu et al using a fluorescent cytosolic free calcium indicator, indo-1, which was superfused beneath a cortical window. MK-801 (2 mg/kg i.v. 5 minutes after MCA occlusion) attenuated both the increase in cytosolic free calcium

<table>
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<th>TABLE 2. Physiological Variables in Experiment 2</th>
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<td>Control</td>
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<td>MK-801</td>
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<td>MABP (mm Hg)</td>
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<td>Temperature (°C)</td>
<td>37.0±0.3</td>
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<tr>
<td>Rectum</td>
<td>34.5±0.4</td>
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<tr>
<td>Head</td>
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<td>Values are mean±SD (n=7–8). MCAO, middle cerebral artery occlusion; BCCAO, bilateral common carotid artery occlusion; MABP, mean arterial blood pressure. *20–30 minutes after saline or MK-801 1 mg/kg i.p. †60 minutes after left common carotid artery release.</td>
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and early histological damage caused by MCA occlusion in the cortex in cats. This drug also completely blocked the NMDA-induced increase in intracellular calcium.36 Interestingly, Gill et al36 demonstrated that cortical spreading depression, which was observed in the penumbral zone, was blocked by MK-801 in parallel with a significant reduction in cortical infarct volume, suggesting that blockade of cortical spreading depression and consequent attenuation of calcium overload on ischemic penumbral neurons may be a mechanism by which MK-801 reduces ischemic damage.

Although the situation is rather complicated in animal models of forebrain (global) ischemia and MK-801 would have no protective effects in the context of severe ischemia,7,11,12 studies of MK-801 in focal ischemia models have demonstrated 30–65% reductions in volumes of early (3–6 hours after MCA occlusion) ischemic changes in rats or cats and 18–32% reduction in cortical infarct volume determined at 24–48 hours after the ischemic insult in rats.13–21 Even in focal ischemia, however, MK-801 does not reduce infarct size of the striatum, which is an end-arterial territory and exhibits severe cerebral blood flow reduction.13–15,17,18,20 Furthermore, Roussel et al18 compared the pharmacological protection of MK-801 between spontaneously hypertensive rats and normotensive Fisher 344 rats under exactly the same experimental conditions and found a significant reduction in cortical infarct volume only in Fisher 344 rats. They concluded that the gradient of blood flow reduction between the collaterals and the ischemic core is more abrupt and the treatable zone is narrower in spontaneously hypertensive rats than in Fisher 344 rats. In our model, the contralateral common carotid artery was occluded for the initial 60 minutes, so that the initial reduction in perfusion pressure in the collaterally perfused MCA territory might be severe, resulting in a dense reduction in cerebral blood flow that could have blunted the protective effects of MK-801.

The volumes of infarction were substantially less in experiments without head temperature control than that in experiment 1 (32% reduction; statistics were not performed because of lack of concurrence between experiments). However, we assume that this reduction was caused by mild cranial hypothermia, which was shown in experiment 2 (Figure 1). The smaller infarct volume in experiment 3 than in our previous study might also be due to cranial hypothermia. Although we performed experiment 3 under the same conditions as our previous study, the positions of heat lamps might have been different and head temperature might thus have been normothermic in our previous study and mildly hypothermic in the present experiment 3. Reduction in infarct size by only about 3°C of hypothermia is remarkable but not surprising, because significant reduction in infarct volume with mild hypothermia has been reported in focal transient cerebral ischemia.25,26 Although the putative protective effect of MK-801 against global ischemia in gerbils appeared to be related to drug-induced hypothermia,22,23 body temperature was well controlled in previous studies of focal ischemia with MK-801, indicating that induced systemic hypothermia does not play a significant role in the neuroprotection of MK-801 in these studies.

Another confounding aspect of temperature control is that decreased brain temperature, which is induced by cerebral ischemia,24,25 could possibly provide an additive effect to that of NMDA antagonists. Combined therapy with hypothermia plus the NMDA antagonist dextromethorphan was more effective in mitigating ischemic neocortical injury produced by transient forebrain ischemia than was either hypothermia or dextromethor-
The ischemia-induced increase in the extracellular concentration of glutamate is temperature dependent,68,39 and greater when head temperature is not allowed to fall spontaneously during cerebral ischemia. Therefore, enhanced glutamate release might override the protective effects of MK-801, which might have caused the negative result of experiment 1. However, the results in experiments 2 and 3 were also negative, indicating that this drug is not effective under either normothermic or mildly hypothermic head conditions in this stroke model of focal ischemia.

In this study, the distal MCA was occluded thrombolytically by means of a photochemical technique developed in our laboratory.40,41 Thrombi were induced in the distal MCA segments by laser illumination after administration of the photosensitizing dye rose bengal. The occlusive thrombus is mainly composed of aggregated platelets, and a massive release of platelet-derived serotonin occurs in the blood during thrombus formation,42 which may cause cerebral blood flow and blood–brain barrier abnormalities.43,44 Furthermore, ischemia-induced serotonin release from neurons is proposed to be one of the major factors that causes ischemic hippocampal injury.45 In addition to neuron-derived serotonin, this substance secreted from platelets could potentially cause dysfunction or damage of neurons on diffusion into surrounding brain tissue through a disrupted blood–brain barrier.46,47 Therefore, one possible explanation for the negative result of the present study would be that mechanisms other than glutamate excitotoxicity (e.g., neurotoxicity caused by platelet secretory products) contribute to ischemic damage in this model.

In summary, the present study failed to demonstrate a protective effect of MK-801 in this focal thrombotic model with or without head temperature control. This negative result may be due to a severe reduction in cerebral blood flow in the collaterally perfused MCA territory or may be related to the thrombotic nature of this model. Although treatment with NMDA antagonists has theoretical benefits, the results of the present study do not support a profound protective effect of MK-801 in stroke therapy.

Acknowledgment
We wish to thank Carrie G. Markgraf, PhD, for her valuable advice during the course of this study.

References
Many studies have shown that selective antagonists of N-methyl-D-aspartate (NMDA) receptors such as MK-801 reduce infarct volume associated with middle cerebral artery occlusion. Recognition that MK-801 may provide neuroprotection secondary to systemic hypothermia led to subsequent studies in which rectal temperature was controlled. In the setting of focal ischemia and controlled rectal temperature, MK-801 was generally found to offer protection. However, brain temperature still decreases during focal ischemia even when rectal temperature is held constant because of locally reduced metabolic heat production. In addition, local hypothermia may be more pronounced in models using carotid occlusion in tandem with middle cerebral artery occlusion secondary to reduced blood flow to the insulating scalp and skull. Because a slight drop in brain temperature provides substantial neuroprotection, it is important to examine the potential interaction of MK-801 and brain temperature more closely during focal ischemia.

This issue is addressed in the study by Yao and colleagues in the preceding article. Using a model of thrombotic occlusion of the distal middle cerebral artery combined with permanent occlusion of the ipsilateral common carotid artery and 1-hour occlusion of the contralateral carotid artery, the authors examined the effect of MK-801 pretreatment on infarct volume. In one experiment, head temperature was controlled at normal levels, whereas in a second and third experiment with two different intensity durations of induced thrombosis, rectal temperature was controlled and head temperature was allowed to change spontaneously. As expected, infarction was smaller in the second and third experiments with lower head temperature. Surprisingly, however, MK-801 failed to reduce infarct size in this model whether or not head temperature was controlled. The authors conclude that although NMDA antagonists may have benefits on theoretical grounds, the protective effect of MK-801 is not profound.

These results are of interest because the model of thrombotic occlusion may produce effects relevant to human stroke that are not seen in many experimental models using vascular ligation or cauterization. For example, the platelet-rich thrombus may release considerable serotonin, which could exert vascular and neuronal effects and counter mitigating effects of MK-801. It is also conceivable that leukocyte involvement may occur at an earlier stage during ischemia in a thrombotic model and thereby amplify the injury process.

On the other hand, some aspects of the model differ from human stroke. For example, use of permanent ipsilateral carotid occlusion plus transient contralateral carotid occlusion may render a densely ischemic core with very low blood flow surrounded by a relatively thin rim of penumbral tissue with intermediate blood flow. In this case, the amount of tissue salvageable by MK-801 may be relatively small. When the reduction in blood flow becomes severe, such as in global models of severe ischemia with carotid occlusion and hypotension, non-NMDA glutamate receptor activation may predominate in the injury process.1 Likewise, voltage-gated calcium channels may also contribute to calcium entry when ischemia is severe, leading some investigators to support dual therapy of MK-801 plus a calcium channel blocker.2,5 Therefore, as the authors correctly discuss, efficacy of MK-801 alone may be limited to less severe ischemia.
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