The Neuroprotective Action of Ketamine and MK-801 after Transient Cerebral Ischemia in Rats

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The neuroprotective activity of two systemically administered N-methyl-D-aspartate (NMDA) receptor antagonists, ketamine and MK-801, were investigated in a long-term recovery model of near-complete forebrain ischemia in the rat. Doses of each drug were chosen on the basis of the known degree and time course of NMDA antagonism seen in vivo after their systemic administration. Ketamine, administered at a dose of 20 mg·kg⁻¹ iv, either immediately before or shortly after the 10-min ischemic period, failed to lessen neuronal damage in the selectively vulnerable hippocampal CA1 region. Increasing doses of ketamine administered over an increasing length of time in the postischemic period, however, did provide significant protection. MK-801 0.25 or 0.5 mg·kg⁻¹ iv administered before ischemia also resulted in significant protection. The results support the proposal that NMDA receptor-mediated events may contribute to neuronal damage in selectively vulnerable regions of the central nervous system after ischemia. (Key words: Anesthetics, intravenous ketamine. Antagonists, N-methyl-D-aspartate: ketamine; MK-801. Brain, ischemia: protection.)

ISCHEMIA OF THE BRAIN, and consequent neuronal damage, may occur as a result of diverse pathologic conditions. To date, however, no universally accepted pharmacologic neuroprotective therapy has emerged.¹

Within the central nervous system (CNS), neurons are the cells most susceptible to ischemic injury, and among neurons there is a further hierarchy of sensitivity, with hippocampal CA1 pyramidal cells being the most vulnerable.² Many factors are involved in the production of ischemic brain damage,³,⁴ but those that cause selective neuronal vulnerability remain unclear.⁵ Recent evidence, however, supports the involvement of excitatory amino acid (EAA) neurotransmitters.⁶⁻⁷ Thus, all brain areas selectively vulnerable to ischemia receive a profuse EAAergic input⁹ (transsection of which protects them from ischemic injury¹⁰), and transient ischemia results in a rapid increase in the extracellular levels of EAs in experimental animals¹¹ and in ventricular cerebrospinal fluid in humans.¹²

Activation of N-methyl-D-aspartate (NMDA) receptors is especially implicated in cerebral ischemic damage for a number of reasons. First, in brain they are largely confined to selectively vulnerable regions,¹³ where they have been shown to participate in synaptic transmission, particularly in circumstances of neuronal hyperactivity,¹⁴ as may be seen after ischemia. Second, unlike kainate or quisqualate receptors, their activation induces burst firing,¹⁵ which may account for ischemia-induced seizure activity.¹⁶ Third, the NMDA receptor-associated ionophore possesses a large Ca²⁺ conductance¹⁷; intracellular Ca²⁺ overload may contribute to cell death after ischemia.¹⁸ Finally, in contrast to quisqualate receptors, NMDA receptors exhibit no ischemia-induced desensitization¹⁹; their continued activation may thus occur after ischemia.

If the NMDA receptor-mediated hypothesis of ischemic damage is correct, NMDA antagonists should reduce neuronal loss in selectively vulnerable regions. NMDA antagonists do indeed attenuate acute changes in energy metabolism during ischemia,¹⁹ possibly by reducing NMDA receptor-stimulated Ca²⁺ influx.²⁰ Both competitive (e.g., 2-amino-5-phosphonovalerate)²¹ and noncompetitive (e.g., ketamine²²) NMDA antagonists effectively prevent anoxic neuronal death in vitro. Results obtained in vivo have, however, proved more conflicting. Thus, Simon and colleagues,²³ using an experimental protocol that did not allow for the development of delayed neuronal necrosis,²⁴ reported that intraarterioventricular injection of a competitive NMDA antagonist protected hippocampal CA1 pyramids from necrosis, whereas Pulssinelli and Block§ found no protection if a 3-day recovery period was permitted.

One particular difficulty is that presently available competitive NMDA receptor antagonists cross the blood–brain barrier only poorly. However, many systemically active phencyclidine (PCP) receptor agonists are also noncompetitive NMDA receptor antagonists²⁵,²⁶ and thus might be expected to ameliorate neuronal damage in vulnerable areas after ischemia. One such drug, (+)-5-methyl-10,11-dihydro-5H-dibenz[a,d]-cyclohepten-5,10-imine maleate (MK-801), which is a potent and long-lasting NMDA antagonist in vitro and in vivo,²⁷,²⁸ has recently

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been shown to protect against ischemia-induced CA1 pyramidal cell loss in gerbils.58 However, the propensity of this species to develop (subclinical) seizures after ischemia56—which may themselves produce neuronal damage—makes the wider applicability of these observations difficult to assess.

In these experiments we have therefore used a long-term recovery model of transient forebrain ischemia in the rat to examine and compare the neuroprotective efficacy of two systemically active PCP-like NMDA antagonist drugs, ketamine56 and MK-801, against neuronal loss in the selectively vulnerable hippocampal CA1 region.

Materials and Methods

The study was conducted under guidelines provided in the Cruelty to Animals Act, 1876.

Operative Procedures

These followed the methods of Smith et al.31,52 Anesthesia was induced in fasted Wistar rats (185–300 g) with 3% halothane in 70% N2O and balance O2. The trachea was intubated and, with the animal breathing 0.75% halothane in 2:1 N2O in O2, an external jugular vein was catheterized. Muscle paralysis was then induced (suc- cinylcholine chloride, 4 mg · kg\(^{-1}\) iv repeated every 20 min up to the induction of ischemia) and the lungs were ventilated with 0.75% halothane in 70% N2O and balance O2. Both common carotid arteries were gently exposed, a loose cotton suture being placed around each for subsequent manipulation, and a tail artery catheterized to allow continuous blood pressure recording. Halothane was then discontinued, and the animal was allowed to stabilize a period of 30 min during which the lungs were ventilated with 70% N2O and 30% O2. Throughout the experiment, PaCO\(_2\) was maintained above 12 kPa (90 mmHg), PaCO\(_2\), and end-tidal CO\(_2\) (EtCO\(_2\)) between 4.5–5.0 kPa (34–38 mmHg), and rectal temperature at 37.5 ± 0.5° C. Before the onset of ischemia, a small sample of blood was obtained for glucose estimation, and amoxycillin (75 mg · kg\(^{-1}\) im) and heparin (50 IU iv) were administered.

Experimental Groups and Treatment Regimens

There were eight experimental groups, each consisting of seven animals randomly assigned to each group. Animals in all groups had the operative procedures described above and, with the exception of sham-operated control animals, ischemia of 10 min duration followed by a 7-day recovery period (see below). The experimental groups were as follows:

Group A: Sham-operated (no ischemia, no treatment) control. The trachea of each of these animals was extu-

bated never less than 60 min after discontinuation of halothane after the completion of surgery, during which interval they were paralyzed with incremental doses of succinylcholine and ventilated with 70% N\(_2\)O:30% O\(_2\). They were then treated similarly to rats in the other groups.

Group B: Nontreated ischemic control.

Group C: Preischemia ketamine treatment. Animals received ketamine 20 mg · kg\(^{-1}\) iv 10 min before the onset of ischemia.

Group D: Postischemia ketamine treatment. Animals received ketamine 10 mg · kg\(^{-1}\) iv immediately postisch-

emia and at 45 min postischemia.

Group E: Preischemia and postischemia low-dose ket-

amine treatment. Animals received ketamine 5 mg · kg\(^{-1}\) iv at 10 min preischemia and at 0, 15, 30, 45, and 60 min postischemia plus ketamine 10 mg · kg\(^{-1}\) ip at 2, 4, and 8 h postischemia.

Group F: Preischemia and postischemia high-dose ket-

amine treatment. Animals received ketamine 10 mg · kg\(^{-1}\) iv at 10 min preischemia and at 0, 15, 30, 45, 60, and 90 min postischemia plus ketamine 20 mg · kg\(^{-1}\) ip at 2, 3, 4, 5, 6, 7, and 8 h postischemia.

Group G: Preischemia low-dose MK-801 treatment. Animals received MK-801 0.25 mg · kg\(^{-1}\) 15 min before ischemia.

Group H: Preischemia high-dose MK-801 treatment. Animals received MK-801 0.5 mg · kg\(^{-1}\) 15 min before ischemia.

The various protocols of ketamine (Ketalar\textsuperscript{®}, Parke Davis Medical) and MK-801\textsuperscript{1} administration were adopted on the basis of the known degree and time course of NMDA antagonism seen in vivo after their systemic administra-

tion. Thus, 5–20 mg · kg\(^{-1}\) ketamine iv (a sub-

anesthetic, relatively NMDA-selective dose in the rat) re-

sults in a 100% reduction of rat neuron responsiveness to iontophoretically administered NMDA.\textsuperscript{26} Recovery to control values takes from 30–120 min, depending on dose. This short duration of action requires that, with ketamine, repeated small doses must be given to achieve selective NMDA antagonism over a prolonged period of time. A similar reduction in responses to NMDA is seen after 0.1–

0.3 mg · kg\(^{-1}\) MK-801 iv, \textsuperscript{27} although recovery is far more prolonged, taking at least 4 h to reach even 40% of control values. A single dose of MK-801 will thus provide sub-

stantial NMDA antagonism for many hours. Drug admin-

istration, if prior to the onset of ischemia, was started at 10 min (ketamine) or 15 min (MK-801) preischemia to allow for the full development of NMDA blockade before the onset of ischemia.\textsuperscript{27,55} Test drugs were given slowly,
over a 5-min period at each administration, to minimize blood pressure changes.

**INDUCTION OF TRANSIENT ISCHEMIA**

After the 30-min stabilization period, hypotension was induced by a bolus of trimethaphan camsylate (8 mg·kg⁻¹ iv). When mean arterial pressure (MAP) reached 60–70 mmHg, both common carotid arteries were occluded and central venous exsanguination was performed by the jugular catheter to reduce MAP further to 50 ± 5 mmHg, at which point a timer was started. MAP was maintained at this level throughout the ischemic period by withdrawal or reinfusion of small volumes of blood. At the end of 10 min of ischemia, shed blood was rein infused and the carotid clamps removed. The venous and arterial cannulae remained in situ either until the final iv dose of test drug had been given or until MAP reached preischemic levels, whichever came last. The neck and tail incisions were then sutured, spontaneous respiration allowed to resume, and the trachea extubated. Some animals in the preischemia and postischemia high-dose ketamine treatment group received fluid iv (compound sodium lactate, 1–2 ml) in the postischemic phase to maintain MAP at preischemic levels. Intervals required for the resumption of spontaneous respiration were recorded, while the righting reflex were recorded. During the recovery period, animals were examined daily for evidence of upper respiratory tract obstruction, motor seizure activity, and motor neurologic deficit.

**ASSESSMENT OF NEURONAL NECROSIS**

After the 7-day recovery period, animals were reanesthetized with 2% halothane in 70% N₂O and balance O₂. An ascending catheter was inserted by an abdominal incision into the aorta, and, after injection of 50 IU heparin, the animals were perfused with buffered 4% formaldehyde (400 ml; pH 7.2). The brains were left in situ in fixative until the following day, when they were removed and stored in the same fixative. Preliminary experiments indicated that the degree of CA1 neuronal damage after 10 min of ischemia was bilaterally symmetric, in agreement with the findings of Smith et al.; the brains were therefore sagitally hemisected and the right hemispheres cut coronally into 6-mm blocks.

After dehydration and clearing, the blocks were embedded in paraffin wax, sectioned at 8-μm intervals, and adjacent sections stained with either cresyl violet or hematoxylin and eosin. Hippocampal CA1 and CA3 neuronal damage was quantified by direct visual counting (magnification ×200) of normal neurons (taken as those with prominent nucleoli in the absence of condensed cytoplasm) at three hippocampal levels, corresponding to 2.3, 2.8, and 3.3 mm caudal to bregma. No variability in CA1 or CA3 neuronal damage was detected at the various levels studied, and the results presented refer to those obtained at the single standardized level of 2.8 mm caudal to bregma, equivalent to level 2 of Smith et al. Observations were performed blind as regards experimental group. Five adjacent microscopic fields (diameter, 330 μm) in the mid-CA1 area and three adjacent fields in the mid-CA3 area were examined. Contamination of the CA1 and CA3 samples by CA2 pyramidal neurons, an area some consider to be ill-defined in the rat, was thus avoided. Counts of normal cells in the CA1 area from animals in each experimental group were pooled and expressed as the mean number of normal cells (±SEM) per microscopic field; normal neuron counts in the CA3 regions from animals in each experimental group were similarly treated.

**ANALYSIS OF DATA**

Physiologic variables were analyzed with the use of analysis of variance and a post hoc comparison with Newman-Keuls test. Histologic outcome was evaluated by the nonparametric Kruskal-Wallis procedure and a Mann-Whitney U-test comparing treated groups with nontreated ischemic controls. A P value of <0.05 was considered a statistically significant difference.

**Results**

Six animals were eliminated from the study. One each from the nontreated control, preischemia ketamine treatment, and preischemia and postischemia high-dose ketamine treatment groups had continuous seizures within 24 h of operation. One animal from the sham-operated control group and two from the postischemia ketamine treatment group had severe upper respiratory tract obstruction secondary to intubation trauma. They were killed with an overdose of pentobarbital.

**PHYSIOLOGIC VARIABLES**

There were no intergroup or intragroup differences in preischemia values for body weight, MAP, PaO₂, ETCO₂, or plasma glucose (10–13 mmol·l⁻¹). MAP at 1 min after the termination of ischemia was lower in all the treatment groups, with the exception of the preischemia and postischemia low-dose ketamine–treated group, than in the nontreated ischemic controls (table 1). Animals in these groups received MK-801 or ketamine ≥ 10 mg·kg⁻¹ as a single dose either before the ischemic insult or immediately upon termination of ischemia. At 5 min postischemia, only animals in the low-dose MK-801–treated group were significantly hypotensive, and by 15 min MAP in all groups was not statistically different from values in the nontreated ischemic controls. The onset of sponta-
neous respiration varied considerably between groups, as did the time to return of the righting reflex (table 1). Overall, the higher the total dose of ketamine administered, the longer the interval before resumption of spontaneous respiration. MK-801-treated animals resumed spontaneous respiration at a similar time to those in the nontreated ischemic control group, despite a considerable difference in histologic outcome. Rats in the postischemia ketamine and preischemia and postischemia low-dose ketamine-treated groups took more time to regain their righting reflex than those in the nontreated ischemic control group. This parameter was not recorded in the preischemia and postischemia high-dose ketamine- and MK-801-treated groups because of the presence of ataxia after operation. In ketamine-treated animals, ataxia was absent by 12 h after the final increment of the drug; MK-801-treated animals, in contrast, remained ataxic for up to 36 h. MK-801-treated rats resumed spontaneous respiration and reacted to painful stimuli more quickly than rats treated with high doses of ketamine, despite their persistent ataxia. After recovery from drugs, animals in all groups were neurologically indistinguishable, with no evidence of paraparesis or plegia.

### Neurohistology

Table 2 provides the quantitative histologic data obtained, and figure 1 depicts the histologic results schematically. No eosinophilic or shrunken neurons were seen in CA1 or CA3 in sections from the sham-operated control group. Extensive necrosis of selectively vulnerable hippocampal CA1 pyramids occurred in the nontreated ischemia group; normal pyramidal cells were completely absent from some microscopic fields. The relatively resistant CA3 sector (and dentate granule cells) was spared; CA3 neuronal counts were similar in all control and treatment groups, the border between the affected CA1 area and adjacent CA3 subfield being well demarcated. These findings are in general agreement with those of Smith et al.32

Ketamine did not affect CA1 histologic outcome at doses that would be expected to antagonize substantially the excitatory effects of NMDA either during (Group C) or for a short period after (Group D) 10 min of ischemia (fig. 2). However, as increasing doses of ketamine were administered over an increasing period of time in the postischemic period, improvement in CA1 outcome was seen. A cumulative dose of 60 mg·kg⁻¹ (Group E) or 210 mg·kg⁻¹ (Group F) ketamine over an 8-h period provided statistically significant protection (P < 0.01 and P < 0.001, respectively).

MK-801 0.25 or 0.5 mg·kg⁻¹ iv administered 15 min before 10 min of ischemia resulted in significant CA1 protection. At the 0.25 mg·kg⁻¹ dose, an overall 41% of CA1 neurons were histologically normal, greater in per-

### Table 1. Values (Mean ± SEM) for Physiologic Variables Measured at Intervals during the Experimental Procedures

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>MAPₑₑₑₑ (mmHg)</th>
<th>MAPₐₐₐₐ (mmHg)</th>
<th>MAPₕₕₕₕ (mmHg)</th>
<th>MAPₖₖₖₖ (mmHg)</th>
<th>Spont (min)</th>
<th>RR (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6</td>
<td>128 ± 3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>90 ± 3</td>
<td>NA</td>
</tr>
<tr>
<td>B</td>
<td>6</td>
<td>131 ± 7</td>
<td>130 ± 7</td>
<td>115 ± 7</td>
<td>121 ± 12</td>
<td>155 ± 4</td>
<td>73 ± 5</td>
</tr>
<tr>
<td>C</td>
<td>6</td>
<td>134 ± 10</td>
<td>81 ± 7*</td>
<td>117 ± 7</td>
<td>124 ± 12</td>
<td>143 ± 4</td>
<td>78 ± 8</td>
</tr>
<tr>
<td>D</td>
<td>5</td>
<td>131 ± 3</td>
<td>95 ± 15*</td>
<td>117 ± 9</td>
<td>106 ± 8</td>
<td>130 ± 8</td>
<td>139 ± 5*</td>
</tr>
<tr>
<td>E</td>
<td>7</td>
<td>125 ± 5</td>
<td>108 ± 8</td>
<td>119 ± 7</td>
<td>106 ± 8</td>
<td>147 ± 9</td>
<td>NA</td>
</tr>
<tr>
<td>F</td>
<td>6</td>
<td>130 ± 9</td>
<td>78 ± 7*</td>
<td>96 ± 9*</td>
<td>110 ± 3</td>
<td>147 ± 4</td>
<td>35 ± 3</td>
</tr>
<tr>
<td>G</td>
<td>7</td>
<td>141 ± 7</td>
<td>74 ± 7*</td>
<td>96 ± 9*</td>
<td>110 ± 3</td>
<td>147 ± 4</td>
<td>36 ± 4</td>
</tr>
</tbody>
</table>

7-day recovery period; MAP = mean arterial blood pressure (mmHg) before ischemia (MAPₑₑₑₑ) and at 1 min (MAPₐₐₐₐ), 5 min (MAPₕₕₕₕ), and 15 min (MAPₖₖₖₖ) postischemia; Spont = time in minutes from release of carotid clamps to onset of spontaneous respiration; RR = time in minutes from release of carotid clamps to establishment of righting reflex; NA = not applicable (see text).

* P < 0.05 for difference from nontreated ischemic control group.

### Table 2. Number of Histologically Normal Neurons in the CA1 and CA3 Regions of the Rat Hippocampus by Experimental Group (Expressed as Mean Count per 350 μm Diameter Field ± SEM)

<table>
<thead>
<tr>
<th>Group</th>
<th>CA1</th>
<th>CA3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>56 ± 3*</td>
<td>39 ± 2</td>
</tr>
<tr>
<td>B</td>
<td>4 ± 1</td>
<td>42 ± 2</td>
</tr>
<tr>
<td>C</td>
<td>7 ± 2</td>
<td>43 ± 3</td>
</tr>
<tr>
<td>D</td>
<td>4 ± 2</td>
<td>42 ± 3</td>
</tr>
<tr>
<td>E</td>
<td>10 ± 5*</td>
<td>39 ± 1</td>
</tr>
<tr>
<td>F</td>
<td>15 ± 4*</td>
<td>41 ± 2</td>
</tr>
<tr>
<td>G</td>
<td>28 ± 9*</td>
<td>39 ± 2</td>
</tr>
<tr>
<td>H</td>
<td>37 ± 7*</td>
<td>41 ± 1</td>
</tr>
</tbody>
</table>

Groups: A = sham-operated control; B = nontreated ischemic control; C = preischemia ketamine treated; D = postischemia ketamine treated; E = preischemia and postischemia low-dose ketamine treated; F = preischemia and postischemia high-dose ketamine treated; G = preischemia low-dose MK-801 treated; H = preischemia high-dose MK-801 treated.

* P < 0.001; †P < 0.01 for difference from nontreated ischemic controls.
aminoic, exhibits use dependency in vitro.\textsuperscript{27,28} Nevertheless, it is probable that a substantial degree of NMDA antagonism was achieved both during and for some hours after the ischemic insult in animals in the preischemic and post-ischemic high-dose ketamine-treated group, suggesting that additional factors may in part account for the observed differences in outcome between the two drugs.

Although derangement of NMDA receptor-mediated neurotransmission may be the final extracellular mediator of necrosis in selectively vulnerable regions in response to ischemia, as suggested by results in vitro, in the whole animal final outcome will be determined by many modifying influences, including metabolic disturbances, impaired regulation of cerebral blood flow, and altered activity of other neurotransmitter systems.\textsuperscript{5} Thus, the possession by a PCP-like compound of NMDA antagonist activity may not alone determine its neuroprotective efficacy in vivo; drugs that adversely affect these factors may worsen neurologic outcome even if they are also NMDA antagonists. In this regard, ketamine has a spectrum of activity, features of which may be disadvantageous after ischemia. First, it increases intracranial pressure, particularly in circumstances (e.g., after ischemia)\textsuperscript{4} in which it is already elevated\textsuperscript{38}; cerebral perfusion may thus be reduced.\textsuperscript{39} Second, it increases cerebral metabolism, particularly in regions that exhibit selective vulnerability\textsuperscript{40}; general metabolic uncoupling in these areas may thus be enhanced. Third, it has well-documented effects on many central transmitter systems apart from EAA-ergic ones; some of these actions may mask or limit any beneficial effect that may accrue from NMDA antagonism and may in themselves promote neuronal damage after ischemia. For example, dissociative anesthetics depress spontaneous firing of noradrenergic neurons in the locus coeruleus in vivo\textsuperscript{51} and inhibit NMDA-induced \(^{3}H\) norepinephrine release from hippocampal slices.\textsuperscript{42} Surgical lesions of the locus coeruleus projections to the forebrain aggravate ischemia-induced hippocampal CA1 pyramid necrosis.\textsuperscript{43} Ketamine, by pharmacologic deafferentation of the hippocampus from locus coeruleus input, might reduce the amount of protection provided by its simultaneous ability to antagonize the excitatory effects of NMDA. Indeed, this consideration may apply to all NMDA antagonists and may ultimately be found to limit the degree of neuroprotection that can be afforded by them.

Only limited information as yet exists as to which of the above properties of ketamine are also shared by MK-801, although some differences are already apparent. MK-801 is, for example, less potent than ketamine in inhibiting uptake of \(^{3}H\)-dopamine\textsuperscript{44,45}; increased levels of dopamine may promote neuronal loss after ischemia.\textsuperscript{46} It is thus tempting to speculate that MK-801 possesses fewer detrimental side effects than ketamine after cerebral isch-
emia, which allows beneficial NMDA antagonism to operate relatively unhindered and which results in improved neuroprotective activity. If this is indeed the case, it will be important to examine the neuroprotective actions of other PCP-like drugs with NMDA antagonist properties, many of which are already known to not share the same overall spectrum of activity on neurotransmitter systems. Dextromethorphan, for example, reduces the excitatory effects of NMDA on rat spinal neurons in vivo, attenuates hypoxic injury in neocortical cell cultures in vitro, and has recently been found to reduce neocortical ischemic neuronal damage in vivo.

We are unable to state whether a continued improvement in outcome with increasing dose might be seen with MK-801 or ketamine or whether a plateau of maximum protection might be found. We have tested higher doses of MK-801 (0.5 mg·kg⁻¹ before ischemia followed by 3 mg·kg⁻¹ in divided doses from 0 to 8 h postischemia, n = 4), but this treatment resulted in a long-lasting (>48 h) sedation during which the animals were unable to protect their pharyngeal reflexes. Despite intensive measures, two animals died and in the two survivors CA1 histologic outcome was worse than that seen after 0.5 mg·kg⁻¹ MK-801. However, given the compromised situation of these animals, it is impossible to assess whether higher doses of MK-801 are associated with poorer outcome per se or whether, for example, repeated episodes of postoperative respiratory obstruction might account for the relatively poor CA1 neuronal survival in these animals. The latter explanation appears more likely because MK-801 has been tested up to 10 mg·kg⁻¹ in acute nonrecovery ischemia models with good effect. Similar problems were also experienced with animals treated with higher doses of ketamine than the maximum reported here. Given these difficulties, meaningful results for direct comparison with other treatment groups could not be achieved with these treatments.

In conclusion, the present results demonstrate that systematically administered NMDA antagonists exert a neuroprotective effect in selectively vulnerable regions of the brain after transient near-complete forebrain ischemia. Recent results with MK-801 suggest that this neuroprotective effect may also be apparent after focal ischemia. However, it should be noted that the doses of ketamine or MK-801 required for significant protection in the present study engendered significant behavioral disturbances. This may limit both their prophylactic use before neurosurgery, for example, where accurate neurologic...
assessment may be of great importance immediately after operation, and their use in patients who are already debilitated.

References


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