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AMPA and NMDA Receptor Antagonists Do Not Decrease Hippocampal Glutamate Concentrations during Transient Global Ischemia

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Increased extracellular concentrations of glutamate during episodes of cerebral ischemia may be due in part to a positive glutaminergic feedback loop. We evaluated the effect of selective AMPA or NMDA receptor antagonists on hippocampal extracellular concentrations of excitatory amino acids during ischemia and reperfusion. Thirteen New Zealand white rabbits were subjected to 10 min of global cerebral ischemia produced by neck tourniquet inflation (20 psi) combined with systemic hypotension during halothane (1–1.5%) anesthesia. Hippocampal extracellular concentrations of glutamate, aspartate, and glycine were monitored using *in vivo* microdialysis. NBQX (a selective AMPA receptor antagonist), MK801 (a noncompetitive NMDA receptor antagonist), or 5% dextrose was administered starting 1 h before ischemia. The NBQX group (n = 4) received 5 mg · kg^{-1} of NBQX intravenously (dissolved in 5% dextrose) over 5 min followed by an infusion of 5 mg · kg^{-1} · h^{-1}. The MK801 group (n = 5) received 1 mg · kg^{-1} of MK801 (dissolved in 5% dextrose) over 5 min followed by 580 μg · kg^{-1} · h^{-1}. The 5% dextrose group (n = 4) received an equivalent volume of 5% dextrose. The peak concentrations of glutamate, aspartate, and glycine in the early reperfusion period were 5–8-fold, 9–10-fold, and 4–5-fold higher than preischemic values, respectively. There were no significant differences, however, among the three groups in the concentrations of glutamate, aspartate, or glycine at any time during the study. These results do not support the existence of a positive feedback loop for glutamate mediated *via* AMPA or NMDA autoreceptors in the hippocampus during transient global ischemia or reperfusion. (Key words: Animals: rabbit. Antagonists, AMPA receptor: NBQX. Antagonists, NMDA receptor: MK801. Brain. Brain: ischemia. Excitatory amino acids: aspartate; glutamate. Measurement techniques: microdialysis. Receptors: AMPA; NMDA.)

BRAIN INJURY due to episodes of transient cerebral ischemia constitute a major source of morbidity and mortality. Recently, the neurotoxic effects of endogenous excitatory amino acids (EAAs) have begun to be elucidated.[1,2] These neurotransmitters (*e.g.*, glutamate and aspartate) are present in low concentrations in the extracellular space of normal brain. However, in a variety of pathologic conditions, including ischemia,[3,4] hypoxia,[5] and hypoglycemia,[6] these agents may be released from neurons in excessive quantities. By subsequent overactivation of a variety of pre- and postsynaptic receptors (including those of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] and the N-methyl-D-aspartate [NMDA] receptor subtypes), EAAs may cause an influx of sodium, calcium, and water into neurons, initiating a cascade of events resulting in cell death.[7] One strategy to reduce ischemic brain damage has focused on the antagonism of the glutaminergic receptors. NMDA receptor antagonists such as MK801 have been demonstrated to reduce neuronal damage after focal ischemia.[8,9] Recently, an AMPA receptor antagonist (NBQX) has been reported to decrease neuronal damage after severe forebrain ischemia.[10–12] However, the mechanism of the successful protection with these antagonists is not fully understood.

There is now evidence from both *in vivo*[13,14] and *in vitro* studies[15–18] that there is a positive feedback loop in which glutaminergic neurons are stimulated to release additional glutamate into the extracellular space. During and after transient episodes of ischemia or hypoxia, increased extracellular glutamate, acting as an agonist at EAA receptors in nerve terminals of the same or other glutaminergic neurons, may produce an autoexcitation phenomenon leading to further elevations of extracellular glutamate. If the presynaptic effect is mediated by an AMPA or an NMDA receptor, then pretreatment with antagonists of these receptors might result in a decreased concentration of glutamate in extracellular fluid during ischemia and reperfusion.

Recently it has been recognized that glycine is an important facilitator of glutamate's action at the NMDA receptor.[19] Indeed, the presence of glycine at the NMDA receptor has been demonstrated to be essential for the functional activation of the receptor by glutamate.[20] Therefore, it is of some interest to know whether glutamate antagonists have any effects on the periischemic extracellular concentrations of glycine. Decreased levels of glycine after the administration of an AMPA antagonist or an NMDA antagonist may contribute to neuronal protection.

The effects of AMPA or NMDA receptor blockade on extracellular glutamate concentrations during transient cerebral ischemia have not been reported previously. The indicates that there was only a 3% chance of having com-

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present study was designed to determine whether the selective AMPA antagonist (NBQX) or the potent noncompetitive NMDA antagonist (MK801) reduces the concentrations of glutamate, aspartate, or glycine during or after 10 min of transient global ischemia in rabbits.

Materials and Methods

The protocol was reviewed and approved by the Animal Care Committee of the University of California, San Diego. Thirteen New Zealand white rabbits weighing 2.88 ± 0.37 (mean ± SD) kg were anesthetized in a Plexiglas box with 5% halothane in oxygen. After intubation of the trachea with a 4.0-mm uncuffed, wire-reinforced endotracheal tube, the animals' lungs were mechanically ventilated with 1–1.5% halothane in oxygen, to maintain normocapnia (Pa_{CO_2} 35–40 mmHg). Body temperature was monitored with an esophageal thermistor. After infiltration with 0.25% bupivacaine, a catheter (PE-90) was inserted into the femoral artery for measurement of arterial blood pressure and arterial blood gases. The femoral vein was also cannulated for the administration of drugs during inflation of the neck tourniquet. An ear vein catheter was inserted for the administration of fluids (0.9% saline) and drugs. All rabbits were initially hydrated with 0.9% saline solution (40 $ml \cdot kg^{-1}$) administered intravenously by an infusion pump over a 1-h period. This was followed by a maintenance infusion at 4 $ml \cdot kg^{-1} \cdot h^{-1}$ throughout the study. Monitored variables included mean arterial pressure, heart rate, arterial blood gases, hematocrit, blood glucose concentration, and the electroencephalogram (EEG).

The rabbit's head was positioned in a stereotactic frame, and a pneumatic tourniquet (8 inches in length, 2.5 inches in width) was secured loosely around the neck. After infiltration with 0.25% bupivacaine, the cranium was exposed and burr holes were made bilaterally over the dorsal hippocampus (4 mm posterior and 4 mm lateral to the bregma) for the insertion of microdialysis probes (CMA-10, Carnegie Medicin, Sweden). A third burr hole was made 4 mm anterior and 3 mm lateral to the bregma over the right hemisphere for the insertion of a thermistor (Physitemp® IT-23) into the epidural space. The epidural temperature was servocontrolled to 36° C with a heat lamp and a warming pad. Biparietal needle electrodes were placed into the scalp for continuous recording of the EEG.

Recovery rates for each microdialysis probe were determined in duplicate using 10^{-2} M dextrose solution *in vitro* before their insertion into the brain. *In vitro* samples (20 min duration) were collected and analyzed for dextrose concentrations by a glucose analyzer (Yellow Springs Instruments model 23A). The dura over the dorsal hippocampus was then incised, and microdialysis probes of concentric design (fiber length 4 mm, diameter 0.25 mm) were inserted vertically to a depth of 7 mm using micromanipulators. The probes were perfused with artificial cerebrospinal fluid (147 mM NaCl, 2.3 mM $CaCl_2$, 0.9 mM $MgCl_2$, 4.0 mM KCl) at a rate of 2 $\mu l \cdot min^{-1}$. After implantation into the brain, the probes were perfused for at least 1 h before baseline samples of brain tissue microdialysate were collected.

The rabbits were assigned randomly to one of the following groups. Group 1 (n = 4) received a 5-$mg \cdot kg^{-1}$ bolus of NBQX (dissolved in 5% dextrose) over 5 min followed by an infusion of 5 $mg \cdot kg^{-1} \cdot h^{-1}$ for 1 h before and after the ischemic episode. Group 2 (n = 5) received a 1-$mg \cdot kg^{-1}$ bolus of MK801 (dissolved in 5% dextrose) over 5 min followed by an infusion of 580 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 1 h before and after the ischemia. This dose was calculated to produce a plasma concentration of approximately 75 $ng \cdot ml^{-1}$ based on previously published kinetic data for MK801 in rabbits.[21] Group 3 (n = 4) received equal volume of 5% dextrose.

To induce global cerebral ischemia, the mean arterial blood pressure was lowered to less than 50 mmHg by using trimethaphan boluses (10 mg) and the application of positive end-expiratory airway pressure. The neck tourniquet was then inflated to a pressure of 20 psi for 10 min. A tendency to hypertension during the first 3 min of ischemia was treated with additional doses of trimethaphan as needed to keep the mean arterial pressure less than 50 mmHg. Global cerebral ischemia was verified in each rabbit by observation of an isoelectric EEG less

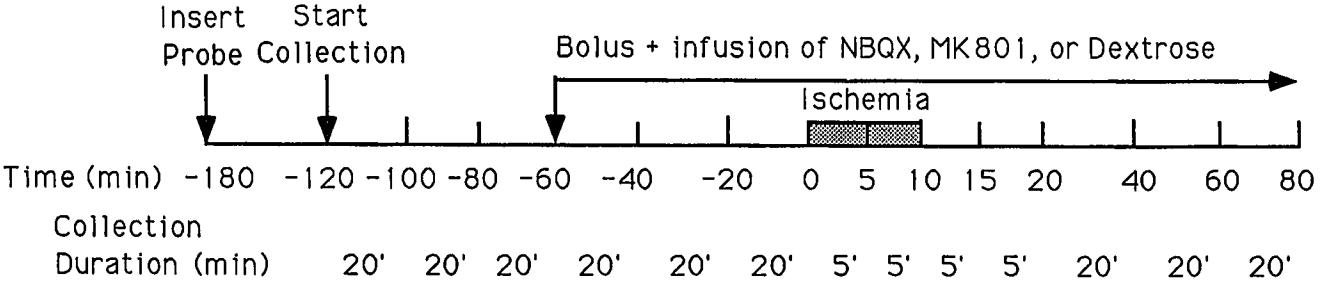

FIG. 1. Methods timeline. X-axis represents time in minutes referenced to the onset of ischemia at T = 0.

than 30 s after tourniquet inflation. Immediately upon deflation of the tourniquet, a bolus and then an infusion of phenylephrine was administered to restore the mean arterial pressure to 75 mmHg.

At the end of the study period, the microdialysis probes were removed, and 5 ml Evans blue dye (2%) was administered intravenously. The rabbits, still anesthetized, were then killed with an intravenous bolus of KCl. The brains were removed from the skull and sectioned coronally to identify the presence of a catheter track in the dorsal hippocampus as evidenced by Evans blue dye staining of the tissue.

Samples of microdialysate were collected as follows from the dorsal hippocampus. Three baseline samples (each of 20 min duration) were collected before administration of drugs (*e.g.*, NBQX, MK801, or 5% dextrose). After a bolus drug administration, three more samples (each of 20 min duration) were collected before ischemia, followed by two ischemia samples (each of 5 min duration), two immediate reperfusion samples (each of 5 min duration), and finally three reperfusion samples (each of 20 min duration) (fig. 1). All samples were collected on ice and immediately frozen and stored at −25° C until their analysis for amino acid content by high-performance liquid chromatography.

The dialysate from the dorsal hippocampus was analyzed for glutamate, aspartate, and glycine concentrations using high-performance liquid chromatography with phenylisothiocyanate derivatization on a reverse-phase C-18 column. Derivatives were detected fluorometrically, and peak areas were integrated and quantified based on linear calibration with known amino acid standards. This method has been shown to be sensitive to low picomolar concentrations of glutamate and aspartate.[22]

The means and SEMs for the concentrations of glutamate, aspartate, and glycine were calculated for each time period. Data for amino acid concentrations were analyzed by two-way analysis of variance (ANOVA) (groups *vs.* time). To determine whether ischemia had any effect on the concentrations of glutamate, aspartate, or glycine, paired *t* tests were used to compare basal (t = 60) *versus* peak concentrations of each of the amino acids. Physiologic data were tabulated and compared using two-way ANOVA (groups *vs.* time) or one-way ANOVA (doses of trimethaphan and phenylephrine) followed by multiple comparison tests when indicated. Differences associated with $P < 0.05$ were considered significant.

Results

Physiologic data are shown in table 1. There were no significant differences among the various groups for mean arterial pressure, heart rate, pH, Pa_{O_2}, Pa_{CO_2}, temperature, or blood glucose. The MK801 group required less

TABLE 1. Physiologic Data and Doses of Drugs

Group	Mean Arterial Blood Pressure (mmHg)	Heart Rate (beats/min)	pH	Pa_{CO_2} (mmHg)	P_{O_2} (mmHg)	Epidural Temperature (° C)	Esophageal Temperature (° C)	Blood Glucose (mg/dl)	Total Trimethaphan Dose (mg)	Total Phenylephrine Dose (μg)
NBQX (n = 4)									66 ± 10	197 ± 35
Baseline	67 ± 5	252 ± 7	7.37 ± 0.02	36.7 ± 1.1	526 ± 26	36.2 ± 0.1	37.2 ± 0.3	98 ± 7		
Postdrug	65 ± 4	258 ± 7	7.35 ± 0.01	35.8 ± 1.3	541 ± 16	36.3 ± 0.1	37.2 ± 0.3	122 ± 9		
Reperfusion 10 min	85 ± 6	192 ± 12	7.28 ± 0.02	37.6 ± 1.7	513 ± 29	36.2 ± 0.1	37.1 ± 0.3	131 ± 10		
Reperfusion 70 min	67 ± 4	234 ± 11	7.34 ± 0.01	39.1 ± 1.1	582 ± 22	36.3 ± 0.1	37.2 ± 0.3	112 ± 14		
MK801 (n = 5)									20 ± 3*	438 ± 53*
Baseline	71 ± 3	276 ± 11	7.35 ± 0.01	36.8 ± 2.2	529 ± 10	36.2 ± 0.1	37.9 ± 0.3	100 ± 9		
Postdrug	58 ± 2	246 ± 11	7.35 ± 0.01	36.7 ± 1.4	527 ± 18	36.5 ± 0.1	37.8 ± 0.2	120 ± 9		
Reperfusion 10 min	83 ± 6	204 ± 11	7.30 ± 0.01	38.5 ± 2.6	495 ± 25	36.4 ± 0.1	37.7 ± 0.1	119 ± 13		
Reperfusion 70 min	59 ± 2	198 ± 18	7.32 ± 0.01	38.1 ± 1.3	534 ± 29	36.4 ± 0.1	37.6 ± 0.1	107 ± 17		
Control (n = 4)									88 ± 23	268 ± 32
Baseline	66 ± 4	240 ± 13	7.37 ± 0.01	36.6 ± 0.9	510 ± 25	36.3 ± 0.1	37.8 ± 0.3	100 ± 10		
Postdrug	67 ± 3	228 ± 12	7.36 ± 0.01	35.4 ± 1.3	515 ± 21	36.4 ± 0.1	37.6 ± 0.3	125 ± 10		
Reperfusion 10 min	94 ± 4	228 ± 12	7.33 ± 0.03	39.9 ± 1.6	514 ± 15	36.3 ± 0.1	37.3 ± 0.1	131 ± 20		
Reperfusion 70 min	65 ± 4	204 ± 15	7.34 ± 0.01	38.7 ± 0.6	549 ± 12	36.5 ± 0.2	37.2 ± 0.2	117 ± 14		

Values are mean ± SEM.

* Significant difference from other two groups ($P < 0.05$).

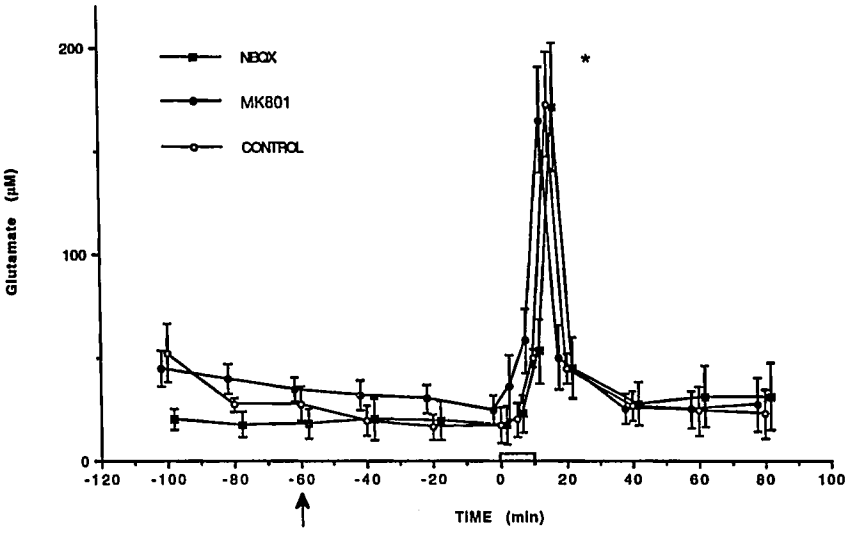

FIG. 2. Mean ± SEM corrected dialysate concentration of glutamate over time for NBQX (n = 4), MK801 (n = 5), and control (n = 4) group. There were no significant differences between the three groups by two-way ANOVA. *$P < 0.05$ different from baseline (t = −60) for all three groups by paired *t* test. Arrow indicates start of drug administration. Open bar = ischemia period.

trimethaphan but more phenylephrine than the other two groups to maintain the blood pressure within predefined limits. This difference was most likely due to the previously described hypotensive effects of MK801.[21] After the loading dose of MK801, a phenylephrine infusion was started to maintain mean arterial pressure greater than 50 mmHg before the onset of ischemia.

The time course of changes in concentrations of glutamate, aspartate, and glycine in the dialysate of hippocampal probes are illustrated in figures 2–4. Stable basal concentrations of extracellular glutamate (25 μM), aspartate (0.9 μM), and glycine (9 μM) were detected in the three consecutive samples collected before infusion of NBQX, MK801, or placebo. Subsequent administration of NBQX or MK801 had no effect on the preischemic concentrations of amino acids. In all three groups, ischemia resulted in significant elevations of hippocampal extracellular concentrations of glutamate (5–8-fold increase), aspartate (9–10-fold increase), and glycine (4–5-fold increase). These concentrations of glutamate and aspartate returned to baseline levels within 30 min after reperfusion. There were no significant differences among the three groups in the concentrations of glutamate, aspartate, or glycine either during ischemia or reperfusion. However, because of an apparent trend toward a difference among the groups for glycine concentrations, a power analysis of the glycine data was performed. The power of the two-way ANOVA for glycine was found to

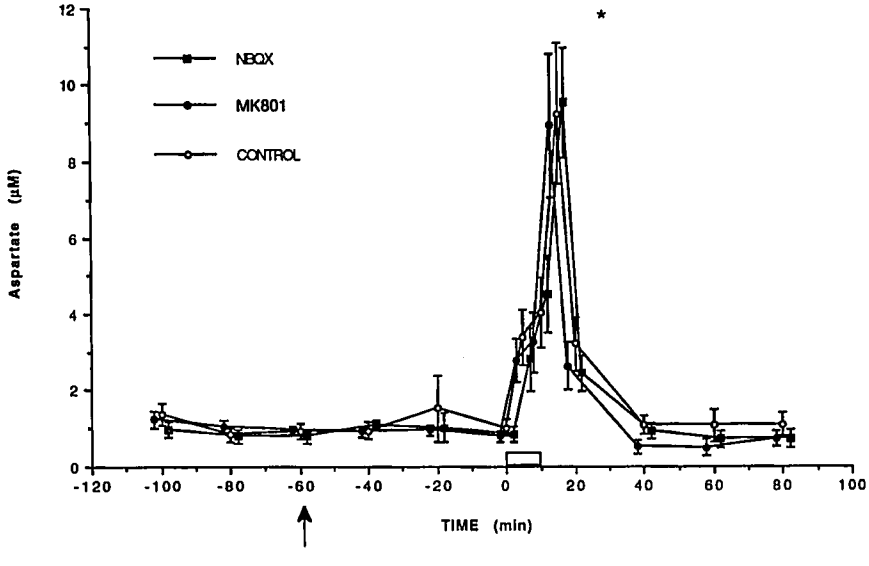

FIG. 3. Mean ± SEM corrected dialysate concentration of aspartate over time for NBQX (n = 4), MK801 (n = 5), and control (n = 4) group. There were no significant differences between the three groups by two-way ANOVA. *$P < 0.05$ different from baseline (t = −60) for all three groups by paired *t* test. Arrow indicates start of drug administration. Open bar = ischemia period.

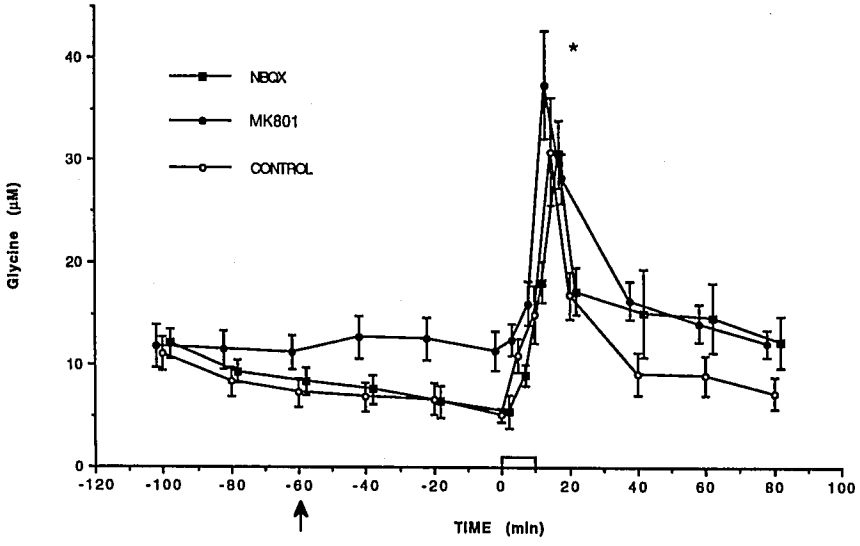

FIG. 4. Mean ± SEM corrected dialysate concentration of glycine over time for NBQX (n = 4), MK801 (n = 5), and control (n = 4) group. There were no significant differences between the three groups by two-way ANOVA. *$P < 0.05$ different from baseline (t = −60) for all three groups by paired *t* test. Arrow indicates start of drug administration. Open bar = ischemia period.

be 97% for data collected from t = 0 to t = 80 min. This indicates that there was only a 3% chance of having committed a type II error in this analysis (*i.e.*, 3% chance of erroneously concluding that no difference existed among the groups). No substantial differences were noted in the EEG among the three groups throughout the study period.

Discussion

Numerous studies have demonstrated significant increases in extracellular glutamate after episodes of cerebral ischemia.[3,4,23,24] Glutamate is a known neurotoxin which, in a dose-dependent fashion, may initiate a cascade of events eventually leading to neuronal death. Both *in vivo*[13,14] and *in vitro* studies[15–18] have suggested that there is a positive feedback loop for glutamate release *via* autoreceptors on glutaminergic neurons (fig. 1). This autoexcitation phenomenon might partially explain the significant increases in extracellular glutamate that have been documented after episodes of cerebral ischemia. Positive feedback loops using glutamate as the neurotransmitter have been demonstrated in the vertebrate visual system,[15] and NMDA-evoked release of glutamate has been demonstrated in rat striatum.[13] Furthermore, the ability to antagonize potassium-evoked release of glutamate *via* the administration of MK801 and other NMDA receptor antagonists has been demonstrated in hippocampal slice preparations.[16] Also, MK801 has been reported to prevent the massive release of glutamate and aspartate from rat striatum induced by 1-methyl-4-phenylpyridinium.[14]

The current study sought to determine whether a positive feedback mechanism mediated by an AMPA or an NMDA receptor subtype exists *in vivo* for glutamate release. Extracellular levels of EAAs are the result of a balance between release and reuptake. Most current evidence suggests that the increased extracellular levels of EAAs seen with ischemia are due to increased release from either transmitter pools or cytosolic sources. Given that there is no evidence for an effect of NBQX or MK801 on reuptake, it is logical to assume that possible differences in EAA levels after the administration of these drugs are a result of their action on release mechanisms.

This study used a well-characterized animal model of transient global cerebral ischemia. The effects of various durations of ischemia (5, 10, and 15 min)[24] and changes in temperature (37° C *vs.* 29° C)[23] on EAA concentrations in this model have been described. In the current experiment, the magnitude of the increases in glutamate, aspartate, and glycine were similar to what has been previously observed.[23,24] In the current study, the concentrations of EAAs in the microdialysate were corrected by using the *in vitro* recovery rate for dextrose. Although some authors question the use of *in vitro* recovery factors to estimate extracellular concentrations,[25,26] our purpose was simply to reduce the variability that may arise from differences in the condition of probe membranes.

This study demonstrates that neither NBQX nor MK801, at the doses administered, had any effect upon the periischemic extracellular concentrations of glutamate, aspartate, or glycine in the hippocampus. It is appropriate to wonder if the lack of effect of these drugs may simply represent an inadequate dose of these drugs. Neuroprotective effects have been demonstrated using NBQX (30 $mg \cdot kg^{-1}$ intraperitoneally) when administered before ischemic insults in gerbils.[10] Although the absolute amount of NBQX given in the current study was less than that given in this previous experiment, it was

administered as an intravenous bolus followed by a continuous infusion and may well have resulted in higher brain tissue concentrations during the ischemic period. The dose of MK801 administered in this study was calculated to produce a plasma concentration of 75 $ng \cdot ml^{-1}$.[21] This dose of MK801 was thought to be appropriate for study because smaller doses have been used to examine the protective effects of MK801 against cerebral ischemia.[27,28] Furthermore, this represents the maximum tolerable dose from a hemodynamic standpoint, as evidenced by the need to infuse phenylephrine in the MK801 group before ischemia.

Both NBQX and MK801 were administered before the ischemic episode by intravenous injection followed by a continuous infusion to maximize the likelihood that they would reach their potential sites of action in the central nervous system. There is good evidence, at least for MK801, that this drug rapidly penetrates the blood–brain barrier, as evidenced by its previously reported sedative and MAC-reducing effects.[21] Despite the previously cited evidence of the neuroprotective properties of NBQX and MK801 in other species, there is currently no evidence that these drugs are protective in this rabbit model of global cerebral ischemia. Had there been evidence of decreased release of either glutamate or aspartate in the current study, it would have provided a potent impetus for further investigation, including outcome studies with neurologic and histologic scoring.

The failure to demonstrate an effect with either NBQX or MK801 may involve the recent description of two additional glutamate receptor subtypes.[29] These are the metabotropic and kainate receptors. However, AMPA- and NMDA-mediated mechanisms have been investigated more thoroughly because specific and potent antagonists (*e.g.*, NBQX, MK801) have been available. Although details are still unclear about metabotropic and kainate receptors, metabotropic receptors are thought to be linked to inositol 1,4,5-triphosphate, leading to the mobilization of calcium from endoplasmic reticulum.[29] Recently it was reported that a receptor subtype at glutaminergic nerve terminals that may be involved in a positive feedback loop for glutamate is neither an AMPA receptor nor an NMDA receptor but a metabotropic type in rat cortex.[17] Metabotropic receptors are not antagonized by NBQX or MK801. This might explain in part why neither NBQX nor MK801 had any effect on the glutamate concentrations in our study. Unfortunately, there currently are no antagonists for the metabotropic receptor.

Another possible explanation why neither NBQX or MK801 had any effects on the concentrations of glutamate and aspartate in this study may be that the positive feedback loop simply does not play an important role in an elevation of glutamate during ischemia. In an ischemic period, glutamate may be released by two distinct mechanisms: a calcium-dependent release of a specific transmitter pool after an increase in cytosolic free calcium, or a calcium-independent efflux from the cytoplasm by reversal of the sodium-cotransport uptake pathway in the plasma membrane.[30] Receptor-mediated release of glutamate from nerve terminals requires high energy charge and is calcium dependent.[30–33] Adenosine triphosphate in the brain is close to its minimal value within 2 min of the sudden interruption of circulation.[34] *In vitro* synaptosome studies suggest that calcium-dependent glutamate release occurs in the first 2 min after the start of anoxia and then is inhibited because this release requires a high energy charge. Calcium-independent release of glutamate conversely increases with time because this release is energy independent.[32] The total amount of glutamate released by calcium-dependent mechanisms during anoxia has been reported to be much smaller than that by calcium-independent mechanisms in an *in vitro* study.[32] If this is also true *in vivo*, the positive feedback loop for glutamate that involves calcium-dependent mechanisms may account for only a very small fraction of the increase in glutamate concentration during ischemia. This might be part of the reason why NBQX or MK801 had no effect on glutamate, aspartate, or glycine concentration.

Choi *et al.* and others have hypothesized that a positive feedback loop for glutamate is initiated by a hypoxic insult and may be responsible for the delayed neuronal death.[2,7,35] They propose that the late release of glutamate, but not the abrupt massive release during ischemia, occurs both synaptically, from calcium-loaded and perhaps depolarized neurons, and nonsynaptically, from neurons damaged badly enough to leak EAAs.[2,7,35] Supporting evidence for such a sequence is provided by the recent findings suggesting that administration of NBQX 2 h postischemia protects the rat forebrain from severe ischemia.[10] Although further studies are needed, the concentration of glutamate might increase so slightly late in the reperfusion period that the increase is difficult to detect with present microdialysis technology.[36]

There is accumulating evidence that glycine plays an important role in the evolution of ischemic neuronal injury.[20,37] Baker *et al.* demonstrated that moderate hypothermia (29° C) prevented ischemia-induced increases in hippocampal glycine concentrations.[23] They suggested that persistent elevation of glycine in the postischemic period might explain glutamate's apparent ongoing toxicity.[23] In the current study, neither NBQX nor MK801 clearly affected the extracellular concentrations of glycine during either the ischemia or early reperfusion period. These results, considered together with the values for glutamate and aspartate, suggest that even if the preischemic administration of NBQX or MK801 ameliorates

ischemic neuronal damage, those effects are not due to the reduction of extracellular EAA concentrations during either the ischemic or early reperfusion periods. The reported neuroprotective properties of these drugs are presumably due to their ability to produce a functional blockade of the AMPA and NMDA receptors.

In conclusion, the preischemic administration of NBQX or MK801 had no effect on the extracellular concentrations of glutamate, aspartate, or glycine during periischemic period. If there is a positive feedback loop for glutamate release, it may operate *via* the metabotropic or kainate subclass of receptor. Investigation of this possibility awaits the synthesis of potent and specific antagonists of these receptor subtypes. These data do not support a role for AMPA- or NMDA-mediated antagonism in regulating the hippocampal extracellular concentrations of glutamate, aspartate, and glycine either during or up to 2 h after transient global ischemia.

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