YM872, a Highly Water-Soluble AMPA Receptor Antagonist, Preserves the Hemodynamic Penumbra and Reduces Brain Injury After Permanent Focal Ischemia in Rats

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Background and Purpose—We recently described an image analysis technique based on the temporal correlation mapping (TCM) of injected contrast agents that can be used to distinguish the hemodynamic core and hemodynamic penumbra after focal ischemia. In this study we used this technique for the first time to investigate the effects of the water-soluble AMPA receptor antagonist YM872 in permanent focal ischemia.

Methods—Fischer 344 rats were subjected to permanent occlusion of the middle cerebral artery. Approximately 30 minutes after ischemia, functional CT images were collected with the use of a dynamic scanning protocol with bolus injections of nonionic contrast agent iohexol (1 mL/kg). TCM analysis defined the distributions of hemodynamic core and hemodynamic penumbra. Cerebral perfusion indices were calculated on the basis of the area under the first-pass transit curves. One hour after ischemia, animals were randomly treated with YM872 (n=8, 20 mg/kg per hour over 4 hours) or normal saline (n=10). Twenty-four hours later, neurological deficits were evaluated, and conventional CT and triphenyltetrazolium chloride staining were used to define volumes of ischemic damage.

Results—At 24 hours after ischemia, hypodense lesions were visible on conventional CT scans that were highly correlated with triphenyltetrazolium chloride lesion volumes. YM872 improved neurological deficits and reduced volumes of ischemic damage in cortex (90±14 versus 170±16 mm³ in controls) but not striatum (57±14 versus 79±6 mm³ in controls). Comparison of early TCM images with conventional CT scans of ischemic injury showed that the hemodynamic core was always damaged in all rats. In controls, 54% of the tissue within the hemodynamic penumbra evolved into ischemic damage compared with 24% in YM872-treated rats. Furthermore, the perfusion index corresponding to the ischemic damage threshold was significantly reduced by YM872 (28±2% versus 37±2% in controls).

Conclusions—These results indicate that YM872 is a neuroprotective compound that ameliorates the deterioration of the hemodynamic penumbra after focal ischemia. (Stroke. 1998;29:2141-2148.)

Key Words: cerebral ischemia, focal n neuroprotection n penumbra n receptor antagonist, AMPA n tomography, emission computed n rats

In a wide variety of animal models of cerebral ischemia, AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptor antagonists have been shown to be neuroprotective. However, first-generation compounds were poorly soluble in water, which limited their use in patients. YM872 ([2,3-dioxo-7-(1H-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydro-1-quinoxalinyl]-acetic acid monohydrate) is a novel AMPA receptor antagonist that is highly water soluble. In in vitro experiments, YM872 significantly antagonized kainate neurotoxicity (IC₅₀=1.1 µmol/L) and decreased AMPA-induced intracellular calcium accumulation (IC₅₀=0.83 µmol/L) in rat hippocampal neurons. In addition, YM872 has been shown to reduce brain damage after focal ischemia in rats and cats. Recently, we described a class of image analysis techniques that are based on the temporal correlation mapping (TCM) of injected contrast agents into the brain. We showed that the TCM approach can quantitatively assess the hemodynamic gradients that are present after focal cerebral ischemia by segmenting perfusion patterns into a hemodynamic core and hemodynamic penumbra. In the present study we used this technique in a rat model of permanent ischemia to assess the effects of YM872 on cerebral perfusion and ischemic injury.
focal ischemia to test the hypothesis that neuroprotection by YM872 is accompanied by an attenuation of ischemic injury that otherwise occurs in the hemodynamic penumbra. Some of these data have been previously presented in abstract form.14

Materials and Methods

Rat Focal Cerebral Ischemia Model
All procedures were conducted following an institutionally approved protocol in accordance with guidelines set by the National Institutes of Health. Guide for the Care and Use of Laboratory Animals. Male Fischer 344 rats (weight, 260 to 330 g; Charles River) were subjected to focal cerebral ischemia under halothane anesthesia by means of face masks (induction, 1.5%; maintenance, 1% in 70% N2O/30% O2). The femoral artery was cannulated for monitoring mean arterial blood pressure and for sampling blood gases and pH. The jugular vein was cannulated for contrast agent injection and drug administration. Both arterial and venous catheters were then subcutaneously externalized through the dorsal neck region for easy access and drug delivery (see below). Rectal temperature was maintained at 37±1°C with a thermostatically controlled heating pad.

The proximal portion of the left middle cerebral artery (MCA) was permanently occluded by a microsurgical technique, as described by Tamura et al.15,16 Briefly, the temporal muscle was retracted through a trans-retro-orbital approach without removal of the temporal muscle and zygomatic arch, and a left subtemporal craniectomy was performed. The dura was incised with a sharp needle, and the stem of the MCA was electrocauterized just medial to the olfactory tract, then cut to ensure the completeness of the occlusion. Thirty minutes after MCA occlusion, rats were subjected to dynamic CT scanning to map the hemodynamic core and hemodynamic penumbra, as described above. Immediately after CT scanning, rats were returned to their cages. After recovery from anesthesia (1 hour after ischemia), rats were randomly treated with either YM872 (20 mg/kg per hour over 4 hours; n=8) or normal saline (n=10). In this dosing protocol, YM872 did not induce abnormal behavior including ataxia, hyperactivity, catalepsy, and agitation. Drug infusion was accomplished under conscious and freely moving conditions. After surgery, animals were placed in individual cages for drug administration. The tip of the catheter coming from the dorsal neck was connected to a cannula swivel device (375/23, Instech Laboratories, Inc) in the roof of the individual cage. This device was used to allow bidirectional rotation while fluid could be continuously passed between 2 cannulas. Polyethylene tubing (PE-50) extending from the other end of the device was joined to a disposable syringe that was fixed to an infusion apparatus (STC-525, Terumo). This was considered close to freely moving conditions since the rats could move in all 3 orthogonal directions. In addition, the cannula for monitoring blood pressure and blood gases was connected to a cannula swivel and joined to probe for monitoring blood pressure.

Dynamic CT Scanning Procedure
Rats were inserted into a custom-made head holder and placed into a slip-ring CT scanner (TCT-900S/X, Toshiba Medical Systems). All CT images were obtained with 150-mA and 120-kV settings. Sagittal scout images were collected to localize the brain, and 5 contiguous axial slices (2 mm thick, 150×150×μm in-plane resolution) were selected to cover the brain. A dynamic scanning protocol that has been previously described17,18 was used. Briefly, dynamic scans were collected at a rate of 1 image every second. A 1.0-mL/kg bolus of nonionic contrast agent iohexol (Omnipaque-350, Sterling-Winthrop) was injected through the jugular vein after 4 to 5 seconds of scanning, and images were collected for 35 seconds total. The same procedure was then repeated for each of the 5 axial slices. Therefore, for a typical 300-g rat, this entailed ~1.5 mL of total contrast administered. Image analysis was performed with DIPStation software (Hyphen Image Processing Group) with custom-designed modules on a Macintosh platform.

Behavioral Evaluation
Rats were allowed to survive 24 hours after ischemia. Neurological deficits were then evaluated as described by Bederson et al19 with some modifications. The following were assessed: (1) the degree of spontaneous activity, (2) right forepaw hemiplegia, (3) failure to extend right forepaw when the rat was lifted by its tail, (4) resistance to lateral push, (5) inclined posture to the right, (6) circling to the right, and (7) response to vibrissae touch. Each sign was scored according to the following criteria: grade 0, no abnormality; grade 1, mild abnormality; and grade 2, severe abnormality. The scores were summed into a total, with the lowest possible score of 0 and a highest possible score of 14.

Lesion Quantification with Triphenyltetrazolium Chloride Staining and Conventional CT Scanning
After behavioral observation at 24 hours after ischemia, rats were reanesthetized with 1.5% halothane in 70% N2O/30% O2 and placed in the CT ring for conventional CT scanning. As before, sagittal scout images were used to localize the brain, and 5 axial slices were imaged without contrast. Areas of ischemic damage were identified as hypodense lesions on these 24-hour CT scans and quantified as percent areas of ipsilateral hemisphere. Immediately after the end of conventional CT scanning, rats were killed with a lethal intravenous injection of sodium pentobarbital. Brains were removed, and the forebrains were sliced into 5 coronal (2-mm) sections with the use of a rat brain matrix (RBM-2000C, Activational System). Slices were placed in 2% triphenyltetrazolium chloride (TTC) solution, followed by 10% formalin overnight. Infarcted areas were visualized as regions lacking the typical brick-red staining of normal brain tissue.

These areas were quantified with an image analysis system (Bioquant IV; R&M Biometrics), and lesion volumes were calculated by integrating areas in all slices.

Quantitative Analysis of Dynamic CT Data
Each dynamic CT data set describes the cerebral transit profile of the injected iodinated contrast agent, which remains restricted to the intravascular compartment during the hyperacute phase of ischemia. Opening of the blood-brain barrier typically occurs within minutes of reperfusion after transient ischemia.19–20 With permanent ischemia, however, disruption of the blood-brain barrier as assessed by Evans blue permeability does not occur until much later, 12 to 24 hours after occlusion.12,21 In the present study, contrast CT was performed at a very early stage, 30 minutes after ischemia. No parenchymal leakage of contrast agents was observed in our experiments.

Alterations in cerebral hemodynamics after focal ischemia change the shape of the cerebral transit profile. These hemodynamic alterations were quantitatively analyzed with TCM, as previously described.12,13 Briefly, for each pixel in the brain, a normalized correlation coefficient was calculated with the transit profile from contralateral cortex used as a normal reference curve. Each pixel in the resulting TCM image thus has a value that quantifies how similar the shape of the transit profile is compared with normal transit profiles in unaffected brain. Statistical analysis was used to distinguish normal from abnormal hemodynamics. The first cutoff was set at the minimum value obtained from the contralateral hemisphere; any pixel in the ipsilateral hemisphere with correlation coefficients below the minimum level found in the contralateral side was deemed abnormal and thus part of the ischemic distribution. A second cutoff was selected on the basis of a P<0.01 threshold (1-tailed t distribution) comparing the shape of transit profiles from normal versus ipsilateral brain pixels. As previously described and validated, this approach defines the hemodynamic core as regions with no detectable transit profile and the hemodynamic penumbra as regions where bolus transit was not eliminated but delayed so that the shape of the transit profile was different from that in normal brain. The change in transit profile shape encompasses all aspects of the curve, including peak height, peak arrival time, and bolus width. Color look-up tables were constructed to display the TCM images with normal brain appearing green, the hemodynamic core appearing black, and the
hemodynamic penumbra appearing as an intermediate reddish zone surrounding the core.

In addition to the TCM analysis, a cerebral perfusion index for each image pixel was also calculated on the basis of the area under the first-pass transit curves. The index is expressed as a percentage of mean contralateral levels so that 100% is normal and 0% represents no flow. This approach has been widely used to indirectly estimate perfusion and includes both blood flow and blood volume influences. For our purposes, this index was used to compare the thresholds for ischemic damage between control versus treated rats.

**Laser-Doppler Flowmetry of Cerebral Blood Flow in Normal Brain**

In a separate set of experiments, the effects of YM872 on regional cerebral blood flow were determined in normal nonischemic brain with the use of laser-Doppler flowmetry. Under halothane anesthesia, catheters were placed into femoral arteries and veins in Fischer rats (**n**=10). Laser-Doppler fiberoptic flow probes (Omega FLO-N1, Neuroscience Instruments) were positioned onto the parietal cortex (from bregma: 3 mm lateral, 3 mm posterior). Care was taken to ensure that the probes were placed away from large surface vessels. These rats were then randomly infused with either normal saline or YM872 (20 mg/kg per hour over 4 hours). Changes in heart rate, mean arterial blood pressure, and laser-Doppler cerebral blood flow were monitored. Laser-Doppler blood flow values were expressed as a percentage of predrug baseline levels.

**Statistical Comparisons**

Data were expressed as mean±SEM. Comparisons of lesion size between controls and treated animals were performed with unpaired 2-tailed Student’s *t* tests. Multiple comparisons of systemic parameters were performed with ANOVA. Linear regression analysis was used to examine the relationship between conventional CT and TTC lesion volumes. Neurological scores were compared with nonparametric Mann-Whitney tests. Values of *P*<0.05 were considered statistically significant.

**Results**

**Systemic Parameters**

Physiological parameters including blood pressure, heart rate, blood gases, pH, and rectal temperature for both groups were within normal limits before MCA occlusion, 5 minutes after the end of drug administration, and 24 hours after MCA occlusion (Table). YM872 did not appear to have any effects on temperature or blood pressure.

**Volume of Ischemic Damage at 24 Hours**

YM872, when administered 1 hour after ischemia, significantly reduced the total volume of ischemic brain damage measured at 24 hours with TTC staining (*P*<0.01) (Figure 1). Most of the neuroprotection was found in the cortex, where ischemic damage was reduced by almost 47% (*P*<0.01). Lesion sizes were not significantly different in the striatum. Conventional CT scans also showed clearly demarcated regions of hypodensity that were highly correlated with TTC lesion areas (Figure 2).

**Neurological Deficits and Lack of Renal Precipitation of YM872**

Neurological deficits were reduced by YM872 treatment at 24 hours after MCA occlusion (5.7±0.8 versus 9.4±0.5 in controls; *P*<0.01). Specifically, YM872-treated animals showed improved right forepaw extension and posture and...
less hemiplegia. Under light microscopy of hematoxylin-eosin–stained sections, no crystals of YM872 were found in the kidney medulla or cortex in the rats tested.

**TCM and Perfusion Index Analysis**

TCM analysis showed high and stable correlation coefficients in the contralateral hemisphere where hemodynamics would be normal, as expected, and there were no differences in hemodynamic patterns between controls and YM872-treated rats. In the ipsilateral hemisphere, TCM images obtained at 30 minutes after ischemia showed hemodynamic core regions located primarily in the striatum and ventral cortex surrounded by regions of hemodynamic penumbra that typically extended into the overlying dorsolateral cortex (Figure 3 and Figure 4A and 4B). Comparison of early TCM images at 30 minutes after MCA occlusion with conventional CT scans of ischemic injury at 24 hours showed that the hemodynamic core was always damaged in all rats (Figure 3 and Figure 4A through 4C). In contrast, only 54±6% of the hemodynamic penumbra decayed into ischemic injury over 24 hours in untreated controls (Figure 4C). YM872 appeared to significantly (P<0.01) ameliorate this process so that only 24±6% of the hemodynamic penumbra became damaged in treated rats (Figure 4C).

In control rats, brain regions with a cerebral perfusion index <37±2% became damaged at 24 hours after ischemia. YM872 significantly lowered this threshold for ischemic damage to 28±2% (P<0.05) (Figure 5).

**Effects of YM872 on Normal Cerebral Blood Flow**

In normal nonischemic brain, YM872 did not alter cerebral blood flow as measured with laser-Doppler flowmetry (Figure 6). There were also no detectable effects on heart rates or mean arterial blood pressure. Heart rates were 444±5 in controls and 436±13 in YM872-treated rats. Blood pressures were 118±4 mm Hg in controls and 122±5 mm Hg in YM872-treated rats.

**Discussion**

Blockade of the AMPA-type glutamate receptor appears to be a promising approach for treating for acute ischemic stroke. However, most first-generation compounds were nephrotoxic as a result of their poor solubility in water. For example, NBQX (2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo-F-quinoxalone) has been shown to precipitate into the renal tubules after intravenous administration. The compound used in the present study, YM872, is a quinoxallinedione-type AMPA receptor antagonist that is highly water soluble. Others have previously shown that YM872 is neuroprotective after focal ischemia in rats and cats. Here we provide evidence that the neuroprotective properties of YM872 may be reflected by its ability to ameliorate the deterioration of the hemodynamic penumbra after permanent focal ischemia in rats. Moreover, YM872 also significantly decreased neurological deficits compared with untreated controls, suggesting that histological neuroprotection may be associated with functional improvement as well. Whether the changes we observed reflect a direct action of YM872 on the vasculature or indeed reflect AMPA receptor antagonist action in the parenchyma requires further study. However, YM872 did not alter blood flow in normal nonischemic brain.

The evolution of brain damage after focal ischemia follows a complex spatiotemporal profile. In central or core regions with severe deficits in cerebral blood flow, a rapid progression to irreversible pannecrosis typically occurs. However, in the peripheral or penumbral zones where the ischemic insult may be moderate or mild, tissue damage may evolve more slowly and gradually over several hours or even days. While salvage of the core may not be possible without the return of blood flow, targeting 1 or more steps in the ischemic cascade within
the penumbra constitutes a rational strategy for stroke therapy. It is therefore important to develop methods that can directly and quantitatively assess neuroprotection in the ischemic core and penumbra.

We have previously described an image analysis approach based on the TCM of injected boluses of contrast agents into the brain. Our previous studies showed that this approach was able to spatially resolve the hemodynamic core and the hemodynamic penumbra after focal ischemia. The hemodynamic core was operationally defined as regions with ischemia so severe that no detectable transit profiles of injected contrast agents were observed. The hemodynamic penumbra was operationally defined as regions where the shapes of the transit profiles were significantly different from those found in normal brain. In the hemodynamic penumbra, cerebral perfusion levels were typically in the 30% to 40% range compared with normal or contralateral levels. However, since the TCM approach measures alterations in overall hemodynamics and not absolute blood flow rates per se, it is likely that the hemodynamic penumbra will be mainly composed of regions where vasodilation and/or collateral recruitment have combined to compensate and alter the shape of the cerebral transit profile. This idea is supported in part by results obtained in knockout mice deficient in endothelial nitric oxide production. These animals show more severe ischemia and smaller hemodynamic penumbras than wild-type mice after focal ischemia. Nitric oxide generated by the endothelium promotes vasodilation and/or collateral recruitment, and removal of this source results in larger cores and...
more restricted hemodynamic penumbra in the knockout mice.

In the present study we coupled TCM analysis to dynamic CT scans with bolus contrast injections to examine the neuroprotective effects of the AMPA antagonist YM872 in a rat model of permanent focal ischemia. Infarct volumes at 24 hours assessed with both TTC staining and conventional CT imaging of hypodense lesions showed that treatment with YM872 at 1 hour after ischemia led to significant neuroprotection. When these late measurements were compared with the early (30 minutes after ischemia) TCM images, the tissue corresponding to entire hemodynamic core had completed the transition into ischemic damage in all 18 rats by 24 hours. In contrast, only 54% of the hemodynamic penumbra became damaged in control rats. In YM872-treated rats, preservation of the hemodynamic penumbra was evident; only 24% of the tissue had progressed to ischemic damage by 24 hours. When cerebral perfusion indices were calculated, the threshold corresponding to ischemic damage was also significantly reduced by YM872 from 37% in controls to 28% in treated rats. The perfusion threshold of 37% is higher than ischemic blood flow thresholds that have been measured by others in rat focal ischemia. Ginsberg and colleagues have reported that for a P<0.04 probability of ischemic damage, the flow threshold was <20% of contralateral levels. For a P<0.08 probability of ischemic damage, the threshold was higher, ie, 30% of contralateral levels. Two critical differences between this study and ours should be noted. First, Ginsberg’s group used a transient 2-hour occlusion, whereas we used a permanent occlusion of the MCA. Thus, it is conceivable that our thresholds are slightly higher since our ischemic insults were more severe. Second, our perfusion index includes a complex mix of blood flow and blood volume influences. Therefore, it cannot be directly compared with the “pure” measurements of blood flow that were conducted by Ginsberg and colleagues. This limitation of the dynamic bolus imaging approach is well known.

The results from this study are consistent with the idea that gradients in perfusion and tissue injury exist after focal ischemia, and these gradients can provide a useful index for assessing long-term tissue viability in the presence or absence of treatment. In a previous study we reached similar conclusions using a different analytical approach and imaging modality. Apparent diffusion coefficient probability distribution functions derived from diffusion-weighted MRI showed that gradients in cell swelling existed after focal ischemia in rats, and successful treatment with a glutamate antagonist ameliorated the worsening in apparent diffusion coefficient gradients over time.

The TCM method is highly sensitive to but not specific for each of the myriad hemodynamic effects of arterial occlusion. As discussed above, these include effects on blood flow and blood volume, compensatory vasodilation, and collateral recruitment. Therefore, the hemodynamic penumbra as defined here most likely differs from the penumbra defined with the use of absolute blood flow values. The high sensitivity of the technique may be one reason why, even in untreated rats, only ≈54% of the hemodynamic penumbra decays into regions of ischemic damage by 24 hours after ischemia. This may be due to an overestimation of what constituted a potentially lethal ischemic challenge, or alternatively, this may indicate that further delayed decay of the hemodynamic penumbra might occur over periods >24 hours. Many recent efforts have been aimed at obtaining truly quantitative in vivo imaging measurements of either blood flow or blood volume in the brain. It will be critical for future studies to assess neuroprotection in the penumbra using these quantitative blood flow and/or blood volume parameters in vivo.

In conclusion, we have demonstrated that early TCM analysis may be used to directly examine the effects of neuroprotective therapy in the hemodynamic penumbra. These findings provide evidence that the AMPA receptor antagonist YM872 ameliorates the deterioration of the hemodynamic penumbra after focal ischemia and reduces the perfusion threshold for ischemic damage.

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References

Pharmacological inhibition of glutamate receptors is a well-established experimental strategy for neuroprotection following cerebral ischemia. Glutamate receptors include NMDA, AMPA, kainate, and metabotropic receptors. NMDA receptor antagonists, while conferring substantial protection in animal models of focal cerebral ischemia, may be of limited clinical usefulness because of their psychomimetic effects. The discovery by Sheardown et al. that AMPA receptor antagonists reduce cerebral ischemic damage raised the possibility that inhibition of AMPA receptors could be useful in the therapy of ischemic stroke. However, the first generation of AMPA receptor antagonists were difficult to use in vivo because their poor water solubility resulted in precipitation in the kidneys and nephrotoxicity.

In the accompanying article, Shimizu-Sasamata and colleagues demonstrate that the water-soluble AMPA receptor antagonists reduce cerebral ischemic damage raised the possibility that inhibition of AMPA receptors could be useful in the therapy of ischemic stroke. However, the first generation of AMPA receptor antagonists were difficult to use in vivo because their poor water solubility resulted in precipitation in the kidneys and nephrotoxicity.
antagonist YM872 reduces brain damage and neurological deficits in a rat model of permanent focal cerebral ischemia. Using a recently introduced dynamic CT scanning technique, they were able to obtain a qualitative estimate of cerebral blood flow in the ischemic territory and to correlate the degree of flow reduction with tissue outcome in a topographic fashion. They found that in regions surrounding the ischemic core, comparable degrees of ischemia resulted in brain damage in untreated rats but not in rats treated with YM872. In addition, they demonstrated that YM872 does not influence resting cerebral blood flow in intact rats, indicating that effects of YM872 on postischemic blood flow are unlikely to play a role in the mechanism of the protection. These observations, collectively, suggest that YM872 renders the brain tissue more resistant to the deleterious effects of cerebral ischemia.

Activation of glutamate receptors is thought to contribute to ischemic injury by increasing intracellular calcium concentration, which in turn leads to cell death by activating an array of destructive enzymatic systems. However, only a small subset of AMPA receptors is highly permeable to calcium. Therefore, the mechanisms of the protection exerted by AMPA receptor antagonists is not entirely clear. One possibility is that activation of AMPA receptors increases intracellular calcium indirectly, for example, through voltage-gated calcium channels activated by depolarization or by reverse operation of the sodium-calcium exchanger. Increases in calcium permeability may also result from disruption of editing at the “Q/R” site of the GluR2 subunit of the AMPA receptor or from decreases in the expression of the GluR2 subunit itself. Irrespective of the mechanisms of the effect, the careful and well-controlled study of Shimizu-Sasamata et al provides convincing evidence that water-soluble AMPA receptor antagonists are promising compounds for the treatment of ischemic brain injury.

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