BW619C89, a Glutamate Release Inhibitor, Protects Against Focal Cerebral Ischemic Damage

M.J. Leach, PhD; J.H. Swan, PhD; D. Eisenthal, BSc; M. Dopson, LIBiol; M. Nobbs, PhD

**Background and Purpose:** The excitatory amino acid neurotransmitter glutamate is involved in excitotoxic brain injury and neurodegeneration after cerebral ischemia. Therefore, compounds that block the release of glutamate may be useful as cerebroprotective agents. The purpose of this study was to evaluate the cerebroprotective properties of a glutamate release inhibitor, BW619C89.

**Methods:** In the studies reported here, the effect of BW619C89 [4-amino-2-(4-methyl-1-piperazinyl)-5-(2,3,5-trichlorophenyl)pyrimidine] on neurotransmitter release (endogenous amino acids, \( \gamma \)-aminobutyric acid, and acetylcholine) from slices of rat brain cerebral cortex in vitro has been determined. The neuroprotective efficacy of BW619C89 has been evaluated using the middle cerebral artery occlusion model of focal cerebral ischemia in the Fischer 344 rat.

**Results:** In the in vitro studies, BW619C89 inhibited veratrine- (but not potassium-) evoked release of both endogenous glutamate and aspartate from rat cerebral cortex slices with IC\(_{50}\) values of approximately 5 \( \mu \)M. BW619C89 was approximately 10-fold less potent to inhibit veratrine-evoked \( ^3\)H-\( \gamma \)-aminobutyric acid release (IC\(_{50}\)=51 \( \mu \)M), fourfold less potent to inhibit \( ^3\)H-acetycholine release (IC\(_{50}\)=21 \( \mu \)M), and at 10 \( \mu \)M had only weak activity at excitatory amino acid (N-methyl-d-aspartate, kainate, and \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) binding sites. When administered intravenously to Fischer 344 rats 5 minutes after permanent middle cerebral artery occlusion, BW619C89 produced marked reductions of both total (cortex and basal ganglia) and cortical infarct volumes. Cortical infarct size was reduced by 20% at a dose of BW619C89 of 5 mg/kg (n=6, not significant); 43% at 10 mg/kg (n=8, P<.01); 59% at 20 mg/kg (n=8, \( P < .001 \)); 61% at 30 mg/kg (n=8, \( P < .001 \)), and 53% at 40 mg/kg (n=8, \( P < .001 \)). BW619C89 at doses of 20 and 30 mg/kg also significantly reduced noncortical (basal ganglia) infarct volumes, demonstrating that a proportion of this tissue also appears to be salvageable. Behavioral effects observed were dose related, generally minor, and at doses of 20 mg/kg IV and above consisted of body tremor and mild ataxia lasting approximately 2 hours.

**Conclusions:** These results suggest that glutamate release inhibitors such as BW619C89 may provide an alternative to excitatory amino acid receptor antagonists in the treatment of focal cerebral ischemia and stroke. (Stroke 1993;24:1063-1067)

**KEY WORDS** • cerebral ischemia • glutamates • neuroprotection

The involvement of the excitatory amino acid neurotransmitter glutamate in the neurotoxic events leading to cell death after cerebral ischemia and in various neurodegenerative disorders has prompted a plethora of investigations into the possibility of manipulating the glutamate neurotransmitter system and thereby providing protection to ischemic brain tissue. Glutamate acts on both N-methyl-d-aspartate (NMDA) and non-NMDA receptor sites to elicit its neurotoxic effect, with non-NMDA receptors possibly playing a more significant role in global ischemia and NMDA receptors in focal ischemia. Antagon-

**See Editorial Comment, page 1067**

onism at either of these postsynaptic sites has proved to be an effective therapy in reducing ischemic brain injury in a number of animal models of cerebral ischemia. The usefulness of an excitatory amino acid receptor antagonist as a therapy in humans, however, has been questioned recently by the discovery of undesirable behavioral and, in particular, morphological central nervous system side effects induced by the NMDA antagonist MK-801. The presynaptic blockade of glutamate release is an alternative approach to stroke therapy, potentially providing a more efficient intervention by preventing activation of both NMDA and non-NMDA receptor sites. Recently, the glutamate release inhibitor BW1003C87 [2,4-diamino-5-(2,3,5-trichlorophenyl)pyrimidine] has been reported to protect against both global and focal ischemia in the rat. BW1003C87 is unsuitable for development because it has antifolate properties, potentially inhibiting the enzyme dihydrofolate reductase. In
the study reported here, a structural analogue of BW1003C87 devoid of antifolate activity, BW19C89 [4-amino-2-(4-methyl-1-piperazinyl)-5-(2,3,5-trichlorophenyl)pyrimidine], has been evaluated in vitro against transmitter release and in vivo as a cerebroprotective agent using the rat middle cerebral artery (MCA) occlusion model of stroke.

Materials and Methods

Slices of rat brain cortex were prepared from adult male Wistar rats (200 to 250 g) and incubated essentially as described previously.\textsuperscript{8,9} to determine the effect of BW19C89 on endogenous amino acid release. Briefly, 0.4-mm slices were prepared using a McIlwain tissue chopper; they were prewashed and incubated for 10 minutes in Tyrode’s medium with or without veratrine (5 &micro;g/mL) or 50 mM potassium chloride and BW19C89. (Using this method, the veratrine-evoked amino acid release has previously been shown to be 95 to 100% tetrodotoxin sensitive and the potassium-evoked release markedly calcium dependent.\textsuperscript{8,9} The medium was recovered for amino acid analyzer using a Locarte amino acid analyzer. Amino acids were detected fluorometrically and calculated by reference to homocysteic acid as internal standard.

The effect of BW19C89 on \(^3\)H-\(\gamma\)-aminobutyric acid (GABA) and \(^3\)H-acetylcholine release from prelabeled brain slices was determined using previously described methods and a Brandel continuous superfusion system with sample collection every 5 minutes.\textsuperscript{10,11} Slices of rat brain cortex were incubated for 30 minutes at 37°C either in 10 mL Tyrode medium containing 10 &micro;m amino-oxyacetic acid to inhibit GABA metabolism and 100 nM \(^3\)H-GABA, or in medium containing 30 &micro;m eserine and 25 nM \(^3\)H-methylcholine to prelabel the tissue with \(^3\)H-GABA or \(^3\)H-acetylcholine, respectively, before transferring the slices to the superfusion apparatus.

The concentrations of veratrine used for the release studies (5 &micro;g/mL for endogenous amino acids; 15 &micro;g/mL for \(^3\)H-GABA; 75 &micro;g/mL for \(^3\)H-acetylcholine) were all previously determined to be suprathreshold concentrations. IC\(_{50}\) values were determined using three or more concentrations of BW19C89 and data fitted to a single-receptor hyperbolic curve-fitting model.

The receptor binding profile of BW19C89 was evaluated in the PANLABS Discovery Screen (PANLABS Inc, South Bothell, Wash). The screen incorporates \(^3\)H-kainate (NMDA, rat cortex); \(^3\)H-\(\gamma\)-aminobutyric acid (GABA, rat cerebro cortical); \(^3\)H-cyclopyrrolidine-1,3-dipropylxanthine (adenosine, whole rat brain); \(^3\)H-2-hydroxy-5-methyl-4-isoxazoolepropionic acid (AMPA, rat cerebral cortex); \(^3\)H-2,3,5-triphentlyzalolium chloride (2,3,5-triphentyltetrazolium chloride in saline infused through the left ventricle. After 5 minutes, the right atrium was unclamped, the perfusate drained, and the animals perfusion-fixed with 20 mL of 10% formalin in saline. The brain was removed and stored in formalin. Infarct size was determined (usually in 12 sections, starting at 5.00 mm anterior to the bregma and continuing through to 6.00 mm posterior to the bregma according to the atlas of Pellegrino and Cushman\textsuperscript{13} using an IBAS 2000 image analyzer (Kontron Electronics, Watford, England). Areas of both left and right cortex and basal ganglia regions were measured. Some infarcted tissue tended to be badly fixed, which rendered it difficult to handle, resulting in areas of dead tissue missing from the section. In these cases, the infarct area was reconstructed on the image analyzer using the hemispheric contour.

Some edema was usually present in the area of infarct in the left hand hemisphere. To negate the effect of edema on infarct volume, a simple equation was applied to the area measurement of each section for both total brain and cortex:

\[
\text{Left Hand Infarct Area} = \frac{\text{Right Hand Area}}{\text{Left Hand Area}}
\]

Infarct volume was calculated by summing the individual area measurements for each section. Data were expressed in cubic millimeters, and comparisons between treatment groups were made by analysis of variance incorporating both parametric and nonparametric testing with a 5% significance level.

4-Amino-\(n\)-[2,3,\(^3\)H]butyric acid (3.37 TBq/mmol; 91 Ci/mmol) and [methyl-\(^3\)H]choline chloride (2.78 TBq/mmol; 75 Ci/mmol) were obtained from Amersham International. 2,3,5-Triphenyl tetrazolium chloride was obtained from BDH, UK. BW19C89 was synthesized within the Department of Medicinal Chemistry, Wellcome Research Laboratories, Beckenham, Kent, UK. The receptor binding studies were provided by PANLABS Inc.
TABLE 1. Effect of BW619C89 on Veratrine-Evoked Release of Endogenous Amino Acids From Rat Cerebral Cortex Slices In Vitro

<table>
<thead>
<tr>
<th></th>
<th>Basal (5 mg/mL)</th>
<th>Veratrine + 0.3 μM BW619C89</th>
<th>Veratrine + 1 μM BW619C89</th>
<th>Veratrine + 3 μM BW619C89</th>
<th>Veratrine + 10 μM BW619C89</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taurine</td>
<td>212±36</td>
<td>337±59</td>
<td>314±56</td>
<td>273±48</td>
<td>304±52</td>
</tr>
<tr>
<td>Aspartate</td>
<td>78±11</td>
<td>294±31*</td>
<td>259±22</td>
<td>216±20*</td>
<td>206±28†</td>
</tr>
<tr>
<td>Threonine</td>
<td>78±11</td>
<td>108±10</td>
<td>111±8</td>
<td>95±7</td>
<td>94±11</td>
</tr>
<tr>
<td>Serine</td>
<td>257±34</td>
<td>315±14</td>
<td>359±28</td>
<td>306±21</td>
<td>295±29</td>
</tr>
<tr>
<td>Glutamate</td>
<td>80±9</td>
<td>507±32*</td>
<td>431±20</td>
<td>317±20†</td>
<td>349±26*</td>
</tr>
<tr>
<td>Glutamine</td>
<td>209±21</td>
<td>432±34*</td>
<td>347±39</td>
<td>313±38†</td>
<td>310±29†</td>
</tr>
</tbody>
</table>

Values are nmol/100 mg protein of endogenous amino acid released into the medium and are mean±SEM of 11-14 replicates per group (combined data from three separate experiments). BW619C89 and veratrine (5 μg/mL) were present together during the 10-minute incubation period. Statistical comparisons were made between basal and veratrine-treated groups and between veratrine- and BW619C89/veratrine-treated groups using analysis of variance. IC50 for inhibition of glutamate release was 5.3 (3.0-9.3) μM (mean, 95% confidence limits), and for inhibition of aspartate release was 5.1 (1.6-17.8) μM. IC50 values were determined by fitting to a single-receptor hyperbolic curve-fitting model.

*P<.001, †P<.05, ‡P<.01.

Results

The release of endogenous glutamate and aspartate from rat brain cortical slices evoked by veratrine (5 μg/mL) was inhibited by BW619C89 with IC50 values (95% confidence limits) of 5.3 (3.0-9.3) μM and 5.1 (1.6-17.8) μM, respectively (Table 1). There was no consistent inhibition of veratrine-evoked release of taurine, threonine, or serine (Table 1). BW619C89 did not inhibit basal release of any of the endogenous amino acids measured, nor did it inhibit potassium (50 mM)-evoked amino acid release (Table 2). BW619C89 was weaker as an inhibitor of veratrine (15 μg/mL)-evoked release of 3H-GABA with an IC50 of 51.7 (14.3-187.2) μM; potassium (50 mM)-evoked 3H-GABA release was weakly but significantly (P<.05) inhibited by 22% at 100 μM BW619C89 (Table 3). BW619C89 inhibited veratrine (75 μg/mL)-evoked 3H-acetylcholine release with an IC50 of 20.9 (13.2 to 33.1) μM (Table 3).

In studies in vivo, Po2, Pco2, and pH were not significantly altered after the administration of any dose of BW619C89 (control preocclusion and postocclusion data, respectively: Po2, 106±6, 111±9; Pco2, 36.2±1.8, 42.9±3.6; pH, 7.39±0.04, 7.41±0.06, n=8).

Intravenous injection of 5, 10, or 20 mg/kg BW619C89 caused an immediate, short-lasting decrease (5 to 10 mm Hg) in blood pressure, which rapidly returned to predrug levels within 10 minutes. After doses of BW619C89 of 30 and 40 mg/kg IV, the fall in blood pressure (15/16 mm Hg) observed at 10 minutes after infusion returned to normal at 20 and 50 minutes, respectively (Table 4). Reductions in heart rate returned to predrug levels by 20 minutes (20 and 30 mg/kg) and by 50 minutes (40 mg/kg) (Table 4).

After recovery from anesthesia (approximately 45 minutes), behavioral changes observed in rats receiving doses of BW619C89 of at least 20 mg/kg consisted of whole-body tremor and incoordination (ataxia) lasting approximately 2 hours.

Doses of BW619C89 (10 to 40 mg/kg IV) produced markedly significant reductions in both cortical and total brain infarct volume (Table 5) with a 43% reduction of total infarct volume at 10 mg/kg (P<.01); 57% at 20 mg/kg (P<.001), and a maximum reduction of total infarct volume of 62% at 30 mg/kg (P<.001). The dose-response relation for preservation of total (cerebral cortex plus basal ganglia regions) infarct volume appeared to be bell-shaped, with diminished but signifi-

TABLE 2. Effect of BW619C89 on Basal and Potassium-Evoked Release of Endogenous Amino Acids From Rat Cerebral Cortex Slices In Vitro

<table>
<thead>
<tr>
<th></th>
<th>Basal + 10 μM BW619C89</th>
<th>Potassium + 10 μM BW619C89</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taurine</td>
<td>151±14</td>
<td>218±56</td>
</tr>
<tr>
<td>Aspartate</td>
<td>165±18</td>
<td>113±11</td>
</tr>
<tr>
<td>Threonine</td>
<td>116±7</td>
<td>92±10</td>
</tr>
<tr>
<td>Serine</td>
<td>351±49</td>
<td>216±16</td>
</tr>
<tr>
<td>Glutamate</td>
<td>134±14</td>
<td>131±13</td>
</tr>
<tr>
<td>Glutamine</td>
<td>186±10</td>
<td>139±5*</td>
</tr>
</tbody>
</table>

Values are nmo1/100 mg protein of endogenous amino acid released into the medium and are mean±SEM of four replicates per group. BW619C89 was present throughout the 10-minute incubation period with or without 50 mM potassium chloride.

*P<.05 compared with basal release.

TABLE 3. Effect of BW619C89 on 3H-γ-Aminobutyric Acid and 3H-Acetylcholine Release From Rat Cerebral Cortex Slices In Vitro

<table>
<thead>
<tr>
<th></th>
<th>3H-GABA release (mean, % total tissue radioactivity)</th>
<th>3H-Acetylcholine release (mean, % total tissue radioactivity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10.75±0.44 (15)</td>
<td>18.15±0.90 (16)</td>
</tr>
<tr>
<td>100 μM</td>
<td>4.01±0.40 (12)*</td>
<td>14.13±0.97 (8)*</td>
</tr>
<tr>
<td>30 μM</td>
<td>6.14±0.65 (12)*</td>
<td>17.27±0.81 (7)*</td>
</tr>
<tr>
<td>10 μM</td>
<td>13.40±0.62 (6)</td>
<td>. . . . . . .</td>
</tr>
</tbody>
</table>

Values are mean±SEM of percent total tissue radioactivity released by a single 5-minute stimulus of veratrine (15 μg/mL, 3H-γ-aminobutyric acid (GABA); 75 μg/mL, 3H-acetylcholine) or potassium (50 mM). Combined data from paired control and test experiments were compared by analysis of variance. IC50 for BW619C89 to inhibit veratrine-evoked 3H-GABA release was 51.7 (14.3-187.2) μM, and for 3H-acetylcholine release was 20.9 (13.2-33.1) μM (mean, 95% confidence limits).

*P<.001, †P<.05 compared with control.
icant protection (40%, P<.01) still observed at the highest dose of BW619C89 (40 mg/kg).

Reduction of cortical infarct volume by BW619C89 appeared to plateau at 59% at 20 mg/kg (P<.001, Table 5); there was no indication of a bell-shaped dose-response relation, with no significant difference between cortical infarct volumes after doses of BW619C89 of 20, 30, or 40 mg/kg. Calculation of noncortical infarct volumes, however, revealed a bell-shaped inhibition curve with no significant protection with BW619C89 at 40 mg/kg, but significant reduction in noncortical infarct volume at doses of 20 mg/kg (54%, P<.05) and 30 mg/kg BW619C89 (63%, P<.05).

**Discussion**

NMDA and non-NMDA antagonists, adenosine A1 receptor agonists (which act presynaptically to decrease glutamate release), and platelet activating factor antagonists have all been reported to be neuroprotective in models of ischemic damage." Recently, BW1003C87 has been shown to block glutamate release both in vitro and in vivo as well as demonstrating neuroprotection in the rat MCA occlusion model of focal cerebral ischemia."

In the present study, we have evaluated the actions of BW619C89 (a novel pyrimidine analogue of BW1003C87), which we have now shown potently inhibits veratrine-evoked release of glutamate and aspartate in vitro. BW619C89 (10 μM) had weak affinity for excitatory amino acid binding sites inhibiting HCGS 19755 (NMDA ligand) binding by 24%, H-kainate binding by 12%, and H-AMPA binding by 17%. Also at 10 μM, BW619C89 had little or weak affinity for adenosine A1 (7%), A2 (8%), phenycyclidine (20%), and platelet activating factor (34%) binding sites. The site of action of BW619C89 is still under investigation, but like the chemically related analogues BW1003C87 and lamotrigine, BW619C89 inhibited veratrine- but not potassium-stimulated glutamate release, suggesting an action at voltage-gated sodium channels (also see Reference 17 for further discussion).

The rat MCA occlusion model of focal ischemia involves irreversible occlusion of a blood vessel supplying both the cerebral cortex and deeper brain structures. The Fischer 344 strain of rat used in this study is considered the normotensive rat strain of choice, with MCA occlusion producing a large and consistent infarct. In the hemisphere ipsilateral to the occluded MCA, infarcted tissue is most dense in the lateral caudate, which receives blood via striate end arteries. Thus, the cortical region is considered to be a metabolic penumbra, whereas the noncortical region (basal ganglia/striatum) contains the ischemic core.

BW619C89 (administered 5 minutes after MCA occlusion) produced a marked reduction in total infarct size with a maximal salvage of approximately 60%, being as effective as the NMDA antagonists in reducing total infarct volume in this model of focal ischemia. Protection was more evident in cortical rather than striatal regions. The behavioral side effects observed with BW619C89 at anti-ischemic doses were dose related and generally minor. Animals recovered rapidly from anesthesia (within 45 minutes), and at doses of 20 mg/kg IV and above, side effects consisted of a whole-body tremor and mild ataxia lasting approximately 2 hours and diminishing with time.

Only at the highest dose of BW619C89 (40 mg/kg) was there any indication of a bell-shaped dose-response relation when total (cortex and basal ganglia) infarct volume was assessed. Subsequent analysis of the cortical and noncortical infarct volumes revealed, however, that there was a significant sparing of noncortical tissue damage at doses of BW619C89 of 20 and 30 mg/kg, suggesting that a proportion of the basal ganglia region is not beyond salvage. However, this effect of BW619C89 on the tissue containing the ischemic core has not previously been observed for BW1003C87, using both histological assessment and 2-deoxyglucose measurements. Whether this reflects pharmacokinetic differences between the compounds is unclear but may relate to BW619C89 having a far higher brain-plasma partition ratio (greater than 30) compared with BW1003C87 (brain-plasma ratio, 3 to 4; Salmon J. 1993. Unpublished data), which may influence rapid drug

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**Table 4. Effect of BW619C89 on Blood Pressure and Heart Rate After Middle Cerebral Artery Occlusion**

<table>
<thead>
<tr>
<th>Treatment (mg/kg)</th>
<th>Predrug BP (mm Hg)</th>
<th>Predrug HR (bpm)</th>
<th>10 Min postdrug BP (mm Hg)</th>
<th>10 Min postdrug HR (bpm)</th>
<th>20 Min postdrug BP (mm Hg)</th>
<th>20 Min postdrug HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 (n=3)</td>
<td>93±2</td>
<td>318±2</td>
<td>92±4</td>
<td>280±10</td>
<td>105±4*</td>
<td>313±3</td>
</tr>
<tr>
<td>30 (n=4)</td>
<td>101±3</td>
<td>326±8</td>
<td>85±3*</td>
<td>280±16*</td>
<td>101±4</td>
<td>299±7*</td>
</tr>
<tr>
<td>40 (n=5)</td>
<td>107±2</td>
<td>317±9</td>
<td>88±7*</td>
<td>224±20*</td>
<td>104±1†</td>
<td>296±7†</td>
</tr>
</tbody>
</table>

Blood pressure (BP) and heart rate (HR) were determined before occlusion and at 10, 20, or 50 minutes after administration of BW619C89 (20, 30, and 40 mg/kg). Values are mean±SEM of three to five animals monitored from each treatment group. Statistical comparisons were made by analysis of variance. bpm, beats per minute.

*P<.05 compared with predrug.

†50 Minutes postdrug.

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**Table 5. Effect of BW619C89 on Infarct Volumes After Middle Cerebral Artery Occlusion**

<table>
<thead>
<tr>
<th>Treatment (mg/kg)</th>
<th>Total Infarct (cortex + basal ganglia)</th>
<th>Cortex Infarct</th>
<th>Noncortical Infarct (basal ganglia)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>161±11</td>
<td>56±12</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>164±29</td>
<td>79±17</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>92±19 (43%)†</td>
<td>35±8 (38%)†</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>20</td>
<td>69±12 (57%)†</td>
<td>26±6 (54%)‡</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>30</td>
<td>62±11 (62%)‡</td>
<td>21±4 (63%)‡</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>40</td>
<td>97±11 (40%)‡</td>
<td>48±10 (53%)</td>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>

Values are infarct volumes in cubic millimeters (see text) and are mean±SEM of six or eight animals per group. Figures in parentheses are percent reduction in infarct volume. BW619C89 (5-40 mg/kg) was administered intravenously within 5 minutes after occlusion. Statistical comparisons were made using analysis of variance.

*P<.01, †P<.001, ‡P<.05 compared with control.
distribution in ischemic tissue with a compromised blood supply. In the rat, BW619C89 has a plasma and brain half-life of 4 hours, with rapid penetration into brain, which may contribute to the salvage of deeper brain structures in this model (Salmon J. 1993. Unpublished data).

These results suggest that an agent such as BW619C89 acting presynaptically to decrease release of glutamate (and aspartate) may provide an alternative to the excitatory amino acid receptor antagonists in the treatment of ischemic brain damage. However, further studies are needed to determine the window of therapeutic opportunity of BW619C89 in this model of focal ischemia.

References

Editorial Comment

Glutamate receptor antagonists have been widely used to ameliorate neuronal injury after cerebral ischemia in many experimental settings. Most experimental strategies aimed at postsynaptic blockade use N-methyl-D-aspartate (NMDA) or non-NMDA receptor antagonists. However, postsynaptic antagonism may sometimes cause side effects that could limit the therapeutic potential of these compounds. In this article, Leach and colleagues have taken a fresh approach to ameliorating ischemic brain infarction through blocking the presynaptic release of glutamate. They have reported that BW619C89, an inhibitor of glutamate release in cortical slices, when administered 5 minutes after focal cerebral ischemia, reduces the infarct volume in rats. Cortical infarct size was reduced in a dose-dependent fashion at concentrations ranging from 5 mg/kg to 30 mg/kg IV. It reached a bell-shaped curve at higher concentrations. Although the 5 minutes postsischemia treatment does not provide the window of therapeutic opportunity in stroke, it nevertheless provides an alternative experimental strategy for ameliorating ischemic brain injury without the possible side effects of NMDA receptor antagonists. Since this drug has limited behavioral side effects and readily passes the blood-brain barrier, further detailed studies are warranted to determine the mechanisms underlying the mode of action on ischemic neurons as well as the window of therapeutic opportunity for this compound in focal stroke.

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References
BW619C89, a glutamate release inhibitor, protects against focal cerebral ischemic damage.
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*Stroke*. 1993;24:1063-1067
doi: 10.1161/01.STR.24.7.1063
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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