Inhibition of α4 Integrin Protects Against Transient Focal Cerebral Ischemia in Normotensive and Hypertensive Rats

Jane K. Relton, PhD; Kevin E. Sloan, MS; Erica M. Frew, BS; Eric T. Whalley, PhD; Steven P. Adams, PhD; Roy R. Lobb, DPhil

Background and Purpose—The present study was performed to determine the role of α4 (CD49d), a member of the integrin family of adhesion molecules, in ischemic brain pathology.

Methods—Male spontaneously hypertensive rats (SHR) or Sprague-Dawley rats underwent 60-minute middle cerebral artery occlusion (MCAO) followed by 23-hour reperfusion. Animals were injected intravenously with 2.5 mg/kg anti-rat α4 antibody (TA-2) or isotype control antibody (anti-human LFA-3 IgG1, 1E6) 24 hours before MCAO. Infarct volume was quantified by staining of fresh tissue with tetrazolium chloride and myeloperoxidase activity measured in SHR tissue homogenates 24 hours after MCAO. In SHR, mean arterial blood pressure was recorded before and after MCAO in animals treated with TA-2 and 1E6. Fluorescence-activated cell sorting analysis was performed on peripheral blood leukocytes before and after MCAO.

Results—TA-2 treatment significantly reduced total infarct volume by 57.7% in normotensive rats (1E6, 84.2 ± 11.5 mm³, n = 17; TA-2, 35.7 ± 5.9 mm³, n = 16) and 35.5% in hypertensive rats (1E6, 146.6 ± 15.5 mm³, n = 15; TA-2, 94.4 ± 25.8 mm³, n = 11). In both strains, TA-2 treatment significantly reduced body weight loss and attenuated the hyperthermic response to MCAO. In SHR, treatment with TA-2 significantly reduced brain myeloperoxidase activity. Resting mean arterial blood pressure was unaffected by treatment. Leukocyte counts were elevated in TA-2–treated rats. Fluorescence-activated cell sorting analysis demonstrated the ability of TA-2 to bind to CD3+, CD4+, CD8+, and CD11b+ cells in both naive animals and after MCAO.

Conclusions—These data demonstrate that inhibition of α4 integrin can protect the brain against ischemic brain injury and implicate endogenous α4 integrin in the pathogenesis of acute brain injury. The mechanism by which α4 integrin inhibition offers cerebroprotection is independent of blood pressure modulation and is likely due to inhibition of leukocyte function. (Stroke. 2001;32:199-205.)

Key Words: cerebral ischemia • inflammation • integrins • leukocytes

Infiltration of inflammatory cells is now established as a central component in the development of ischemic infarction in the brain.1,2 The temporal resolution of cellular infiltration has been characterized in various animal models of stroke,2–4 supporting the prevailing dogma that attributes brain inflammation to the detrimental actions of polymorphonuclear leukocytes (PMNs).5 These cells are reportedly the first to enter the brain after injury.5 The presence of monocytes, macrophages, and T cells in the brain after ischemia has also been documented.6,7 and manipulation of these immune-competent cell populations has been shown to protect the central nervous system (CNS) against ischemic injury.8,9

The trafficking of cells into the brain is dependent on the expression of adhesion molecules and their counter receptors on migrating cells and on the cerebrovascular endothelium.10 Three families of adhesion receptors have been identified: selectins, immunoglobulins, and integrins.10 The integrins are a group of heterodimeric glycoproteins consisting of α and β subunits.11 The integrin α4, first identified on T cells,12 forms a heterodimer with both β1 and β7 subunits. α4β1/Very late antigen-4 (VLA-4, CD49d/CD29) is constitutively expressed on all leukocyte subtypes and binds to vascular cell adhesion molecule-1 (VCAM-1) on inflamed endothelial cells, as well as macrophages and dendritic cells.13 The extracellular matrix protein osteopontin has also been identified as a ligand for α4β1.14 α4β7/Lymphocyte-Peyer’s patch adhesion molecule-1 (LPAM-1, CD49d/CD103) is expressed on almost all leukocyte subtypes and binds to mucosal addressin cell adhesion molecule-1 (MAdCAM-1), present in the gut, and to VCAM-1.13 Both α4β1 and α4β7 also bind to an alternately spliced form of the extracellular matrix protein fibronectin.13 Functionally, α4β7 is thought to be involved in lymphocyte homing to the gut, whereas α4β1 has been associated with lymphocyte recruitment in immune cell-
mediated disease pathology.\textsuperscript{13} At the blood-brain barrier, \(\alpha_4\) integrin/VCAM-1 adhesion interactions have been shown to play a crucial role in T cell migration into the CNS.\textsuperscript{13,15} In vitro VCAM-1 is markedly upregulated in response to inflammatory stimuli on murine and human cerebrovascular endothelial cells,\textsuperscript{16,17} neuronal cells,\textsuperscript{18} and astrocytes.\textsuperscript{19} Expression of mRNA for VCAM-1 occurs on the luminal surface of inflamed vessels and on perivascular cells after focal cerebral ischemia in the rat,\textsuperscript{6} and VCAM-1 protein is intensely expressed in ischemic brain tissue taken from stroke patients.\textsuperscript{20}

It was generally accepted that PMNs do not express \(\alpha_4\) integrin. However, recent studies have demonstrated the presence of \(\alpha_4\) on rat, mouse, and human neutrophils\textsuperscript{21} at a level sufficient to mediate binding to VCAM-1 and MAdCAM-1 under static or low-flow conditions.\textsuperscript{22} Under laminar flow conditions, few unstimulated PMNs bound to purified VCAM-1, but PMNs from rats in a chronic inflammatory state adhered more avidly.\textsuperscript{21} Inhibition of \(\alpha_4\) integrin decreased PMN infiltration through connective tissue fibroblast barriers\textsuperscript{23} and reduced adhesion to endothelial cells or extracellular matrix induced by chemotactic stimuli.\textsuperscript{24} In animal models, the functional role of \(\alpha_4\) integrin–mediated leukocyte adhesion has been demonstrated in several models of autoimmune/inflammatory disease.\textsuperscript{21}

The role of \(\alpha_4\) integrin in the brain after acute injury has not previously been investigated. The objective of this study was to determine whether \(\alpha_4\) integrin plays a functional role in the pathogenesis of ischemic brain damage in vivo. To address this question, we determined the effect of anti–\(\alpha_4\) integrin antibody (TA-2)\textsuperscript{25} treatment on brain damage in a rat model of transient focal cerebral ischemia. Inhibition of \(\alpha_4\) integrin significantly improved neurological outcome in both normotensive and hypertensive rats. Because of the relevance of hypertension to stroke pathology and in the interest of minimizing animal numbers, separate experiments to elucidate potential mechanisms of action of TA-2 were performed only on hypertensive rats. In spontaneously hypertensive rats (SHR), myeloperoxidase (MPO) activity was significantly reduced in the ischemic hemisphere of rats treated with TA-2 compared with 1E6-treated controls. Cerebroprotection was observed in the absence of alteration in blood pressure. Fluorescence-activated cell sorting (FACS) analysis of peripheral white blood cells (WBCs) demonstrated the ability of TA-2 to bind to circulating leukocytes. These data demonstrate that endogenous \(\alpha_4\) integrin plays a role in the generation of ischemic brain damage, probably via inhibition of leukocyte function.

Materials and Methods

Antibodies

In vivo studies used mouse anti-rat \(\alpha_4\) antibody (TA-2; Seikagaku America Inc) and isotype control mouse anti-human LFA-3 IgG\textsubscript{1} (1E6; Biogen Inc). For FACS analysis, fluorescein isothiocyanate (FITC)–labeled mouse anti-rat antibodies anti-CD3, anti-CD4, anti-CD8, and anti-CD11b were purchased from PharMingen, and phycoerythrin (PE)–labeled goat anti-mouse Ig was purchased from Jackson Immuno Research.

Middle Cerebral Artery Occlusion

All experiments were performed within the guidelines of the institutional animal care and use committee. Animals had free access to food and water and were on a 12-hour/12-hour light/dark cycle. Body weight was recorded before surgery and again before the animals were killed.

Male SHR (weight, 250 to 350 g; Taconic, Germantown, NY) or male Sprague-Dawley rats (weight, 270 to 300 g; Charles River, Wilmington, Mass) were injected intravenously with 2.5 mg/kg TA-2 (n=16 Sprague-Dawley rats, n=15 SHR) or 1E6 (n=17 Sprague-Dawley rats, n=11 SHR) 24 hours before induction of cerebral ischemia. Animals underwent 60 minutes of transient occlusion of the right middle cerebral artery (MCA) by the suture method, as described previously\textsuperscript{26}. Briefly, animals were anesthetized in 3% isoflurane (Fort Dodge Animal Health). A midline incision was made in the neck to expose the junction of the common and internal carotid arteries. Cerebral ischemia was induced by insertion of a poly-I-lysine coated 4.0 nylon monofilament (Ethicon Inc), with a rounded tip, up the internal carotid artery to the origin of the MCA. The incision was closed, and the animals were allowed to recover from anesthesia. One hour later the animals were reanesthetized, the incision was reopened, and the filament was retracted to allow reperfusion of the ischemic tissue. The incision was closed, and the animals were allowed to recover. Animals were tested for behavioral deficits at the time of reperfusion. Animals that did not exhibit marked behavioral deficits, namely, forelimb flexion and circling on bench indicative of hemiparesis, were excluded from the study.

Blood Pressure Measurement

In a separate study, naive SHR were anesthetized with thiobutabarbital (100 to 110 mg/kg IP; Inactin, RBI), and the femoral artery was cannulated with polyethylene tubing (PE50) to record resting blood pressure. Blood pressure was recorded for 30 minutes, and mean arterial blood pressure was taken as the average of the 30-minute recording. The same procedure was performed on separate groups of animals 24 hours after MCA occlusion (MCAO).
WBC Counts
Blood was drawn from SHR by cardiac puncture for measurement of WBC counts after either no treatment or surgery, 24 hours after treatment, or 24 hours after MCAO. Blood was collected in EDTA-coated tubes, and differential WBC counts were performed with an Abbott Cell Dyn 350 apparatus.

FACS Analysis
Differential WBC counts of fresh Li-heparin–anticoagulated whole blood from SHR were performed with an Abbott Cell Dyn 3500 apparatus. Red blood cells were lysed by hypo-osmotic shock. Remaining peripheral blood lymphocytes were washed twice and incubated with TA-2 (10 μg/mL) for 20 minutes at room temperature. Cells were washed and incubated with the secondary PE-labeled goat anti-mouse Ig (0.5 μg/mL) to localize the TA-2. Cells were washed again and incubated with FITC-labeled mouse anti-rat CD3, CD4, CD8, or CD11b or matched isotype (1 μg/mL). Cells were washed twice with FACS buffer, fixed in 1% paraformaldehyde, and analyzed on a FACScalibur unit (Becton Dickinson).

Staining was analyzed with the use of the CellQuest software package (Becton Dickinson), plotting FITC staining against PE staining.

Statistical comparisons between 2 groups were analyzed by unpaired Student's t tests. Multiple comparisons were made with repeated-measures 1-way ANOVA with Student-Newman-Keuls post hoc test. All results are expressed as mean±SEM.

Results
Transient MCAO resulted in reproducible infarction of the right hemisphere of the brain detected by TTC staining 24 hours after induction of cerebral ischemia in SHR and Sprague-Dawley rats. Damage was sustained to both cortical and subcortical regions and was more extensive in SHR than in Sprague-Dawley rats. These observations are consistent with previous reports.28

In SHR, pretreatment with anti-rat α4 antibody TA-2 (2.5 mg/kg IV) 24 hours before induction of cerebral ischemia significantly reduced total and subcortical mean infarct volume compared with animals treated with the same dose of an isotype control antibody, 1E6 (Figure 1; total, 146.5±15.5 versus 94.4±25.85 mm³, P<0.05; subcortical, 43.1±1.98 versus 30.47±4.57 mm³, P<0.01). Cortical infarction was reduced by a comparable extent, but this effect did not quite attain statistical significance (103.45±14.3 versus 63.9±21.8 mm³, P=0.053).

The degree of brain infarction in 1E6 antibody–treated animals was identical to that seen previously in PBS-treated animals (data not shown). In Sprague-Dawley rats, the same pattern of protection was observed in TA-2–treated rats as in SHR (Figure 1; total, 84.2±11.5 versus 35.7±5.9 mm³, P<0.001; cortical, 37.3±9.0 versus 23.6±5.7 mm³, P=0.1; subcortical, 36.6±3.7 versus 12.2±5.2 mm³, P<0.001).

Figure 1. Effect of TA-2 on infarct volume 24 hours after 60-minute MCAO in hypertensive (SHR) (1E6, n=15; TA-2, n=11) (A) and normotensive (Sprague-Dawley) rats (1E6, n=17; TA-2, n=16) (B). *P<0.05, **P<0.01, ***P<0.001 vs 1E6-treated control group.

Figure 2. Effect of TA-2 (n=11) on body weight loss over 24-hour experimental period (A) and hyperthermic response to MCAO, calculated as the increase in body temperature between arterial occlusion and reperfusion compared with 1E6-treated controls (n=15) (B). *P<0.05, **P<0.01 vs 1E6-treated control group. No other statistically significant differences between groups were observed.

Figure 3. Effect of TA-2 (n=6) treatment on MPO activity 24 hours after 60-minute MCAO in SHR compared with 1E6-treated controls (n=6). MPO activity in right (ischemic) and left (undamaged) hemisphere tissue homogenates is shown. *P<0.05 vs 1E6-treated control.
Body weight was recorded before surgery and again before the animals were killed. Treatment with TA-2 significantly reduced weight loss over the experimental period compared with 1E6-treated animals in SHR and Sprague-Dawley rats (Figure 2). In both strains body temperature was elevated from preischemic levels when recorded at the time of arterial reperfusion. TA-2 treatment significantly attenuated this increase in body temperature (Figure 2). In the absence of MCAO, TA-2 or 1E6 treatment had no effect on body temperature (data not shown).

PMN infiltration into ischemic tissue was quantified by MPO assay. Tissue homogenates from SHR treated with TA-2 had significantly reduced MPO activity compared with that measured in tissue homogenates from 1E6-treated rats (Figure 3).

Mean arterial blood pressure was comparable in 1E6- and TA-2–treated animals both before and after MCAO. Mean arterial blood pressure in naive SHR was comparable to that observed in the TA-2–treated group (Table 2). No significant differences between groups were observed in absolute PMN lymphocyte count was observed in all groups that had undergone MCAO compared with untreated animals that was not observed in the treatment groups (Table 1).

Total WBC counts were significantly elevated in TA-2–treated animals compared with untreated animals and animals treated with an isotype control antibody before and after MCAO (Table 2). Lymphocyte numbers were primarily responsible for the observed increase in circulating cell population in response to TA-2. A reduction in total WBC count and circulating lymphocyte count was observed in all groups that had undergone MCAO compared with unoperated animals. No significant differences between groups were observed in absolute PMN numbers; however, MCAO induced an increase in percentage of PMNs in untreated and 1E6-treated animals that was not observed in the TA-2–treated group (Table 2).

FITC-labeled cellular markers identifying CD3, CD4, CD8, and CD11b domains on peripheral blood leukocytes (PBLs), isolated from SHR before and after MCAO, were used to differentiate T cells (CD3); MHC II T cells, monocytes, and macrophages (CD4); MHC I T cells, T helper cells, and natural killer cells (CD8); and neutrophils and myeloid cells (CD11b).

PBLs were double labeled with PE/TA-2, and FACS analysis revealed TA-2 binding to all differentiated populations (Figure 4). In the absence of labeled antibodies to either cellular markers or TA-2, no fluorescence was observed. A significant increase in CD11b+/TA-2+ populations and a significant decrease in CD3+/TA-2+ and CD4+/TA-2+ populations were observed 24 hours after MCAO (Figure 4).

### TABLE 1. Mean Arterial Blood Pressure in SHR Before or After MCAO With or Without TA-2 Treatment

<table>
<thead>
<tr>
<th></th>
<th>No Antibody</th>
<th>1E6</th>
<th>TA-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before MCAO</td>
<td>168.1 ± 14.7 (n=4)</td>
<td>162.4 ± 12.0 (n=6)</td>
<td>151.5 ± 9.6 (n=6)</td>
</tr>
<tr>
<td>After MCAO</td>
<td>167.2 ± 8.0 (n=9)</td>
<td>159.6 ± 5.9 (n=5)</td>
<td>155.0 ± 4.9 (n=6)</td>
</tr>
</tbody>
</table>

Values are mean ± SEM (mm Hg). No significant differences were observed between treatment groups before or after MCAO (by 1-way ANOVA).

### TABLE 2. Leukocyte Counts Before and After MCAO in Whole Blood from 1E6- and TA-2–Treated SHR Compared With Untreated Controls

<table>
<thead>
<tr>
<th>n</th>
<th>Total WBC Count</th>
<th>PMN</th>
<th>% PMN</th>
<th>Lymphocytes</th>
<th>% Lymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>No Ab</td>
<td>8.9 ± 0.6</td>
<td>1.31 ± 0.19</td>
<td>14.4 ± 1.6</td>
<td>6.02 ± 0.41</td>
</tr>
<tr>
<td>(b)</td>
<td>No Ab/MCAO</td>
<td>5.94 ± 0.72</td>
<td>1.91 ± 0.15</td>
<td>35.9 ± 4.63</td>
<td>3.43 ± 0.67</td>
</tr>
<tr>
<td>(c)</td>
<td>1E6</td>
<td>5.37 ± 0.68</td>
<td>0.98 ± 0.12</td>
<td>17.8 ± 0.36</td>
<td>3.64 ± 0.57</td>
</tr>
<tr>
<td>(d)</td>
<td>1E6/MCAO</td>
<td>4.64 ± 0.34</td>
<td>1.5 ± 0.17</td>
<td>33.1 ± 3.85</td>
<td>2.53 ± 0.29</td>
</tr>
<tr>
<td>(e)</td>
<td>TA-2</td>
<td>10.66 ± 1.1</td>
<td>1.53 ± 0.24</td>
<td>14.3 ± 2.75</td>
<td>3.89 ± 1.13</td>
</tr>
<tr>
<td>(f)</td>
<td>TA-2/MCAO</td>
<td>9.71 ± 0.65</td>
<td>1.63 ± 0.13</td>
<td>17.2 ± 1.53</td>
<td>7.35 ± 1.83</td>
</tr>
</tbody>
</table>

Values are mean ± SEM (1000 cells/μL whole blood). Ab indicates antibody. Differential cell counts were performed with an Abbott Cell Dyn 350 apparatus. Statistical analysis was performed with 1-way repeated-measures ANOVA with Student-Newman-Keuls post hoc test. Superscript letters a through f denote P < 0.05 vs group (a) through (f).
demonstrated the protective effect of TA-2 treatment when administered 2 hours after MCAO.

A febrile response is often observed in response to brain injury both under experimental conditions and in the clinic and was observed here in response to 60-minute MCAO. A correlation between the degree of hyperthermia and clinical outcome has been established, and it has been proposed that fever may act as a surrogate marker for brain inflammation. In this study TA-2 treatment significantly attenuated the hyperthermic response of animals to MCAO. It is well established that hypothermia protects the brain against ischemic infarction, and the present data may be interpreted to suggest that the protective effect of TA-2 was due to attenuation of ischemia-induced hyperthermia. It is also plausible that this effect is due to a

![Figure 4. TA-2 binding in naive and stroked SHR. PBLs were isolated from naive SHR (n=10) and from rats 24 hours after 60-minute MCAO (n=6) and incubated with TA-2 and anti-CD3, anti-CD4, anti-CD8, or anti-CD11b. Sample size was consistent between groups (1.3 to 1.6×10⁴ cells). Mean±SEM percent double-positive PBLs are indicated for each panel. CD3+/TA-2+ and CD4+/TA-2+ percent double-positive cells were significantly reduced in stroked rats compared with naive rats (P<0.05, 1-way ANOVA). CD11b+/TA-2+ percent double-positive cells were significantly higher in stroked rats compared with naive rats (P<0.01, 1-way ANOVA).]
reduced degree of inflammation, which has been correlated with the severity of brain damage. The latter hypothesis is supported by the observations of Becker et al., who report inhibition of brain infarction but no effect of TA-2 on body temperature when the antibody was administered 2 hours after MCAO.

Leukocyte counts differed markedly between treatment groups, and elevated lymphocyte numbers were predominantly responsible for increased total leukocyte count in TA-2–treated groups. Peripheralization of hematopoietic cells in response to anti-ε4 treatment has been reported elsewhere. Elevated WBC count may be due to reduced lymphocyte adhesion and mobilization of lymphocytes from lymph nodes and spleen. Inhibition of leukocyte adhesion may reduce brain damage by prevention of the “no-reflow” phenomenon and postischemic hypoperfusion, in which WBCs physically plug and obstruct microvessels. This can result in the localized release of vasoactive mediators and direct injury of endothelial cells. Inhibition of adhesion also results in decreased cell trafficking into the injured CNS, as demonstrated by the ability of TA-2 to reduce MPO activity in ischemic tissue.

FACS analysis demonstrated ε4 expression and TA-2 binding to CD3+, CD4+, CD8+, and CD11b+ circulating blood cells both before and after MCAO. These findings are in agreement with previous reports describing ε4 expression on T cells, monocytes, macrophages, natural killer cells, and PMNs. All of these cell types have been implicated in ischemic brain pathology, and inhibition of their actions can protect against the development of infarction. The profound effect of TA-2 treatment on circulating lymphocyte numbers indicates inhibition of T cell adhesion to the vascular endothelium in all organs, including the brain. This may inhibit the potentially detrimental effects of T cell trafficking into the injured CNS, which in turn may protect against ischemic brain damage, in addition to the potentially beneficial effects of reduced PMN infiltration.

It is unclear from the present study whether the heterodimeric unit responsible for mediating ε4-dependent cell trafficking after focal cerebral ischemia is αβ1 (VLA-4) or αβ7. VCAM-1, which is upregulated in the cerebrovasculature in response to stroke or inflammatory stimuli, is the primary counter receptor for VLA-4. Lymphotoxins infiltrating the CNS during chronic inflammation bind to VCAM-1 but not MadCAM-1, the primary counter receptor for αβ7, and MadCAM-1 is reportedly not expressed on cerebrovascular endothelial cells in response to inflammatory stimuli. Osteopontin also acts as a counter receptor for VLA-4. Message for this protein is upregulated as early as 6 hours after permanent MCAO in SHR, but a role in glial scar formation, rather than the acute inflammatory response, was proposed. An alternately spliced form of the extracellular matrix protein fibronectin (CS-1) can also act as a ligand for αβ integrins, and synthetic CS-1 fibronectin peptides protected against ischemic injury after reversible MCAO. Taken together, current evidence suggests that after cerebral ischemia, ε4-dependent events are primarily mediated by VLA-4/VCAM-1 interactions. However, the promiscuous nature of integrin family members and their counter receptors permits redundancy in the system and does not allow one to attribute the actions of a ligand to a particular counter receptor.

Over recent years, inhibition of adhesion molecules has provided an attractive target for the development of novel therapeutics for the treatment of stroke. Interventions have focused on inhibition of PMN infiltration into the injured brain. Experimental results have been variable and clinical trials disappointing. Since αβ integrin is expressed on almost all leukocyte subtypes, the present results extend the pathological importance of leukocytes beyond the PMNs; consequently, inhibition of αβ integrin may offer advantages over therapies that selectively target PMN adhesion and transmigration after stroke.

In conclusion, the present data demonstrate a functional role for αβ integrin in the pathological responses to cerebral ischemia in normotensive and hypertensive rats. The mechanism by which TA-2 provides cerebroprotection appears not to be due to modulation of blood pressure. TA-2 bound to differentiated cell populations that are thought to be involved in ischemia-induced brain inflammation and injury caused a marked lymphocytosis and significantly reduced PMN infiltration into ischemic tissue. These findings support the hypothesis that TA-2 acts by inhibition of adhesion and transmigration of leukocytes into the brain.

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References


23. Gao J-X, Issekutz AC. The β1 integrin, very late activation antigen-4 on human neutrophils can contribute to neutrophil migration through connective tissue fibroblast barriers. *Immunology*. 1997;90:448–454.


Editorial Comment

It is now well established that the inflammatory response during stroke contributes significantly to the worsening of acute ischemic injury. For leukocytes to gain access to their target tissues, a variety of signaling proteins and adhesion molecules act in concert to permit chemotaxis, endothelial cell attachment, and transmigration. Among the most studied of these molecules are the intercellular adhesion molecules (ICAM), the selectins, and the leukointegrin CD11/CD18. Several prior experimental stroke studies have repeatedly shown that inhibition of 1 or more of these molecules reduces infarct size and improves neurological outcome. As a result, 2 clinical stroke trials emerged, only to fail at the phase 3 level.1 In their article, Relton et al show that antibody inhibition by TA-2 of a novel leukocyte target, the α4 integrin, not only reduces leukocyte infiltration into ischemic brain but attenuates injury in 2 different rat strains. A detailed analysis of TA-2 is provided, and the authors were careful to use an antibody-treated (1E6) control group. They also showed that TA-2 blunted the postischemic hyperthermic response. Given the potentially damaging effects of fever during stroke, there may be additional benefits to this treatment as well. However, the antibody was administered prior to ischemia onset; posttreatment administration would be more clinically relevant. Nevertheless, this paper suggests a novel new “antileukocyte” approach to treatment of acute ischemic stroke.

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Reference

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