Pharmacological Stabilization of Intracranial Aneurysms in Mice

A Feasibility Study

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Background and Purpose—An increasing number of unruptured intracranial aneurysms are being detected, partly due to the increased use of brain imaging techniques. Pharmacological stabilization of aneurysms for the prevention of aneurysmal rupture could potentially be an attractive alternative approach to clipping or coiling in patients with unruptured intracranial aneurysms. We have developed a mouse model of intracranial aneurysm that recapitulates key features of intracranial aneurysms. In this model, subarachnoid hemorrhage from aneurysmal rupture causes neurological symptoms that can be easily detected by a simple neurological examination. Using this model, we tested whether anti-inflammatory agents such as tetracycline derivatives, or a selective inhibitor of matrix metalloproteinases-2 and -9 (SB-3CT), can prevent the rupture of intracranial aneurysms.

Methods—Aneurysms were induced by a combination of induced hypertension and a single injection of elastase into the cerebrospinal fluid in mice. Treatment with minocycline, doxycycline, or SB-3CT was started 6 days after aneurysm induction. Aneurysmal rupture was detected by neurological symptoms and confirmed by the presence of intracranial aneurysms with subarachnoid hemorrhage.

Results—Minocycline and doxycycline significantly reduced rupture rates (vehicle versus doxycycline=80% versus 35%, P<0.05; vehicle versus minocycline=73% versus 24%, P<0.05) without affecting the overall incidence of aneurysms. However, SB-3CT did not affect the rupture rate (62% versus 55%, P=0.53).

Conclusions—Our data established the feasibility of using a mouse model of intracranial aneurysm to test pharmacological stabilization of aneurysms. Tetracycline derivatives could be potentially effective in preventing aneurysmal rupture.

(Stroke. 2012;43:00-00.)

Key Words: animal model • inflammation • intracranial aneurysm • intracranial hemorrhage • matrix metalloproteinase • subarachnoid hemorrhage • tetracycline

An increasing number of unruptured intracranial aneurysms are being detected, partly due to the increased use of brain imaging techniques. In patients with unruptured aneurysms, surgical clipping or endovascular coiling is performed to prevent future aneurysmal rupture. However, the morbidity and mortality associated with clipping and coiling of unruptured aneurysms are not negligible.1,2 In addition, there are limited treatment options for a subset of patients with giant aneurysms. Therefore, pharmacological stabilization of aneurysms as a means of rupture prevention may be an attractive alternative approach. However, currently there is no known pharmacological stabilization of aneurysms in the prevention of aneurysmal rupture. This is partly due to the lack of appropriate animal models for conducting preclinical studies in the pharmacological stabilization of aneurysms.

The potential role of inflammation in the pathophysiology of intracranial aneurysms has been suggested by both clinical and animal studies.3–8 Tetracycline derivatives such as doxycycline and minocycline are clinically available antibiotic agents that possess anti-inflammatory effects. In addition, these agents can exert weak inhibitory effects on matrix metalloproteinases (MMPs).9,10 Pharmacotherapy using teta-
cycline derivatives as anti-inflammatory agents or broad-spectrum MMP inhibitors have been proposed for various vascular diseases.\textsuperscript{11,12}

Recently, we have developed a mouse model of intracranial aneurysm that recapitulates key features of intracranial aneurysms, including spontaneous rupture.\textsuperscript{7–13} In this model, subarachnoid hemorrhage as a result of aneurysmal rupture causes neurological symptoms that can be easily detected by a simple neurological examination. As a first step in the process of testing the pharmacological stabilization of aneurysms in this model, we examined whether tetracycline derivatives can prevent aneurysmal rupture.

Methods

Animal Model

Experiments were conducted in accordance with the guidelines approved by the University of California, San Francisco, Institutional Animal Care and Use Committee. Intracranial aneurysms were induced in 8- to 10-week-old male mice (C57BL/6J; Jackson Laboratory, Bar Harbor, ME) using a previously described method with modifications.\textsuperscript{7,13} We combined induced systemic hypertension and a single injection of elastase into the cerebrospinal fluid at the right basal cistern. Detailed methods are presented in the online-only Data Supplement.

To induce systemic hypertension, we used deoxycorticosterone acetate-salt hypertension.\textsuperscript{14} Mice underwent nephrectomy followed by an implantation of deoxycorticosterone acetate pellet 1 week later; 1% sodium chloride drinking water was started on the same day as the deoxycorticosterone acetate pellet implantation.\textsuperscript{4,15} Mice received a single injection of elastase (25–35 mU) into the cerebrospinal fluid at the right basal cistern on the same day as deoxycorticosterone acetate pellet implantation.\textsuperscript{7,13} Aneurysms were defined as a localized outward bulging of the vascular wall whose diameter was greater than the parent artery diameter.\textsuperscript{7,13}

Two blinded observers performed daily neurological examination using a previously described method with modifications.\textsuperscript{16–19} Neurological symptoms were scored as follows: 0, normal function; 1, reduced eating or drinking activity demonstrated by a weight loss >2 g of body weight (approximately 10% weight loss) over 24 hours; 2, flexion of the torso and forelimbs on lifting of the whole animal by the tail; 3, circling to one side with a normal posture at rest; 4, leaning to one side at rest; 5, no spontaneous activity. Mice were euthanized when they developed neurological symptoms (score 1–5).

All asymptomatic mice were euthanized 28 days after aneurysm induction. The brain samples were perfused with phosphate-buffered saline followed by a gelatin containing blue dye to visualize cerebral arteries as well as to assess for aneurysm formation and subarachnoid hemorrhage.

In Situ Zymography

Gelatinase activity, primarily from MMP-2 and MMP-9, was assessed by gelatin in situ zymography.\textsuperscript{13} Pretreatment of the tissues with 1,10-phenanthroline monohydrate was used to confirm the MMP origin of the gelatinase activity.\textsuperscript{11}

Treatment With Doxycycline, Minocycline, or SB-3CT

To test whether doxycycline and minocycline, anti-inflammatory agents with broad-spectrum MMP inhibitory effects, could stabilize aneurysms, we started treatment with doxycycline, minocycline, or vehicle 6 days after aneurysm induction and continued the treatment for 3 weeks.

Twenty-five mice were treated with doxycycline dissolved in water (40 mg/kg/day through gavage) as described.\textsuperscript{13,20,21} Twenty-two mice in the doxycycline vehicle group received the vehicle (water). Twenty-six mice were treated with minocycline (45 mg/kg/day) through daily intraperitoneal injection; 21 mice in the minocy-
artery) showed limited gelatinase activity (Figure 2A). As shown in Figure 2B, gelatinase activity was restricted to the intracranial aneurysms and the adjacent parent artery (middle cerebral artery) had little gelatinase activity. There was a general trend of more prominent gelatinase activity in ruptured aneurysms than in unruptured aneurysms (Figure 2B–C). However, this might be due to inflammation caused by subarachnoid hemorrhage rather than the intrinsic property of rupture-prone aneurysms.

Effects of Doxycycline and Minocycline on Aneurysmal Rupture

To test whether tetracycline derivatives—doxycycline and minocycline—could prevent aneurysmal rupture, we initiated a pharmacotherapy with doxycycline, minocycline, or vehicle 6 days after aneurysm induction for a total treatment course of 3 weeks (Figure 1D).

Although there was no difference in the overall incidence of aneurysms (including both ruptured and unruptured) be-
between the vehicle and doxycycline group (68% versus 68%, \(P=0.62\)), the incidence of ruptured aneurysms was significantly lower in the doxycycline group than in the vehicle group (24% versus 55%, \(P<0.05\)). **B**, Rupture rate. The doxycycline treatment significantly reduced the rupture rate compared with the vehicle treatment (80% versus 35%, \(P<0.05\)). **C**, Symptom-free curve (Kaplan-Meier analysis curve). A log-rank test revealed a significant reduction of aneurysmal rupture by the doxycycline treatment \((P<0.05)\). Mice that did not develop aneurysms were excluded from the survival analyses.

For the purpose of exploratory analysis, a symptom-free curve (Kaplan-Meier analysis curve) was created after excluding mice that did not have aneurysms (Figure 3C). A log-rank test revealed a significant reduction of aneurysmal rupture with doxycycline treatment \((P<0.05)\).

There was no difference in the overall incidence of aneurysms (both ruptured and unruptured) between the vehicle and minocycline group (71% versus 65%, \(P=0.45\); Figure 4A). However, the incidence of ruptured aneurysms was significantly lower in the minocycline group than in the vehicle group (16% versus 52%, \(P<0.05\); Figure 4A).

**B**, Rupture rate. Minocycline treatment significantly reduced the rupture rate compared with the vehicle treatment (73% versus 24%, \(P<0.05\)). A log-rank test for mice with aneurysms revealed a significant reduction of aneurysmal rupture with minocycline treatment \((P<0.05)\).

**Effects of SB-3CT on Aneurysmal Rupture**

As a next step, we tested whether the potent and selective inhibitor of MMP-2 and MMP-9, SB-3CT,\(^{22}\) can prevent aneurysmal rupture. There was no difference in the overall incidence of aneurysms (both ruptured and unruptured) between the vehicle and SB-3CT group (62% versus 55%, \(P=0.53\); Figure 5A). In addition, there was no difference in the rupture rate between the vehicle group and SB-3CT group.

![Figure 3. Effects of doxycycline on aneurysmal rupture.](link)

**A**, Incidence of aneurysms. Although there was no difference in the overall incidence of aneurysms (both ruptured and unruptured) between the vehicle and doxycycline group (68% versus 68%, \(P=0.62\)), the incidence of ruptured aneurysms was significantly lower in the doxycycline group than in the vehicle group (24% versus 55%, \(P<0.05\)). **B**, Rupture rate. The doxycycline treatment significantly reduced the rupture rate compared with the vehicle treatment (80% versus 35%, \(P<0.05\)). **C**, Symptom-free curve (Kaplan-Meier analysis curve). A log-rank test revealed a significant reduction of aneurysmal rupture by the doxycycline treatment \((P<0.05)\). Mice that did not develop aneurysms were excluded from the survival analyses.

![Figure 4. Effects of minocycline on aneurysmal rupture.](link)

**A**, Incidence of aneurysms. There was no difference in the overall incidence of aneurysms (both ruptured and unruptured) between the vehicle and minocycline group (71% versus 65%, \(P=0.45\)). However, the incidence of ruptured aneurysms was significantly lower in the minocycline group than in the vehicle group (16% versus 52%, \(P<0.05\); Figure 4A).

**B**, Rupture rate. Minocycline treatment significantly reduced the rupture rate compared with the vehicle treatment (73% versus 24%, \(P<0.05\)). **C**, Symptom-free curve. Log-rank test for those mice that had aneurysms revealed a significant reduction of aneurysmal rupture by the minocycline treatment \((P<0.05)\).
(75% versus 67%, \(P=0.59\); Figure 5B). A log-rank test revealed no difference between the vehicle group and SB-3CT group (\(P=0.79\); Figure 5C).

Treatment with tetracycline derivatives or SB-3CT did not affect blood pressure (Table).

### Discussion

In this study, we showed the feasibility of using a mouse model of intracranial aneurysm to test pharmacological stabilization of aneurysms as a prevention of subarachnoid hemorrhage. We demonstrated that doxycycline and minocycline, anti-inflammatory agents with weak broad-spectrum MMP inhibitory activity, reduced rupture of intracranial aneurysms in mice.

The mouse model of intracranial aneurysm used in this study had a predictable time course and a relatively high incidence of aneurysmal rupture. Aneurysmal formation occurred during the first week after aneurysm induction. Treatment with tetracycline derivatives 6 days after aneurysm induction reduced the rupture rates without affecting the overall incidence of aneurysms. This showed the feasibility of using this model for studying the mechanisms of aneurysmal rupture as well as testing pharmacotherapy as stabilization of aneurysms.

In our model, aneurysmal ruptures were detected by the presence of neurological symptoms, particularly motor deficit. The neurological signs that were observed were sensitive and specific for detecting aneurysmal subarachnoid hemorrhage. Because the neurological examination detects only symptomatic aneurysmal subarachnoid hemorrhage, this method may have missed asymptomatic or subtle subarachnoid hemorrhage. Nevertheless, when the brain samples from asymptomatic mice were examined, no apparent signs of large hemorrhage were observed. Some of the asymptomatic mice showed hemosiderin on the surface of the brain, possibly indicating minor hemorrhage that was not severe enough to cause a neurological deficit. Detecting only symptomatic subarachnoid hemorrhage may mimic an actual clinical setting. Alternatively, these hemosiderin deposits could possibly be due to tissue injury caused by the needle insertion at the time of elastase injection.

Treatment with doxycycline or minocycline was able to reduce the incidence of aneurysmal rupture and the rupture rate. However, SB-3CT, a potent and selective inhibitor of MMP-2 and MMP-9, did not affect aneurysmal rupture. Considering that both tetracycline derivatives and SB-3CT can inhibit MMPs, these results were somewhat surprising. There are several potential explanations.

Stabilization of aneurysms by doxycycline and minocycline could possibly be due to their general anti-inflammatory effects rather than their inhibitory properties on MMPs. Tetracycline derivatives can exert anti-inflammatory effects through their antiapoptosis effects and nonspecific protease inhibition, both of which could affect aneurysmal rupture. Tetracycline derivatives’ inhibitory effects on MMPs are rather weak with a high half-maximal inhibitory concentration (>100 000 nmol/L). The potential of anti-inflammatory agents to stabilize intracranial aneurysms has been suggested by a recent clinical report that showed the association between the use of an anti-inflammatory agent, aspirin, and a lower risk for aneurysmal rupture.

Although tetracycline derivatives represent an anti-inflammatory agent, SB-3CT is a selective inhibitor of MMPs.

### Table. Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Systolic Blood Pressure, mm Hg</th>
<th>Baseline</th>
<th>1 Wk</th>
<th>2 Wk</th>
<th>4 Wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle control</td>
<td>108±9</td>
<td>143±13</td>
<td>151±14</td>
<td>145±11</td>
</tr>
<tr>
<td>Minocycline</td>
<td>109±7</td>
<td>144±13</td>
<td>149±9</td>
<td>146±12</td>
</tr>
<tr>
<td>Vehicle control</td>
<td>107±10</td>
<td>144±16</td>
<td>148±7</td>
<td>148±6</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>108±9</td>
<td>145±14</td>
<td>150±8</td>
<td>146±11</td>
</tr>
<tr>
<td>Vehicle control</td>
<td>108±12</td>
<td>144±16</td>
<td>149±9</td>
<td>145±8</td>
</tr>
<tr>
<td>SB-3CT</td>
<td>110±10</td>
<td>142±15</td>
<td>149±14</td>
<td>148±13</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD.
MMP-2 and MMP-9. SB-3CT does not exert significant inhibitory effects against other MMPs. Our results might argue for key roles of other MMPs or other effectors in aneurysmal rupture.

Finally, although animal studies suggest potential role of MMPs in the formation of intracranial aneurysms, MMPs may not play a significant role in the rupture of intracranial aneurysms. It has often been presumed that understanding the mechanisms of aneurysmal formation and growth provides insights into the mechanisms of aneurysmal rupture. This notion is based on an assumption that the processes of aneurysmal formation, growth, and rupture share the same or similar underlying mechanisms. However, there is no clear basis for such assumption. Mechanisms of aneurysmal rupture may be fundamentally different from those of formation and growth. Therefore, an animal model that allows us to directly study the mechanisms of aneurysmal rupture becomes important. Our results, along with previous studies on mechanisms of aneurysm formation,13 may indicate differential roles of MMPs between aneurysm formation and aneurysmal rupture.

A major limitation of this study is a lack of mechanistic investigation on how tetracycline derivatives prevented aneurysmal rupture. We did not compare inflammation or MMP activity in aneurysm tissues between the vehicle groups and the treatment groups. Comparison within ruptured aneurysms would be significantly confounded by the effects of hemorrhage that can cause significant activation of inflammation and MMPs. Unfortunately, comparison of unruptured aneurysms was not possible because of the extremely small number of specimens available at the end of observation period. One of the focuses of future studies should be on mechanisms by which aneurysmal rupture occurs. Preclinical studies using this model would be useful in refining the therapeutic targets and selecting optimal anti-inflammatory agents for the stabilization of aneurysms. This becomes important when chronic treatment with tetracycline agents for the stabilization of aneurysms. Anti-inflammatory therapy using tetracycline derivatives may be useful in preventing the rupture of intracranial aneurysms.

Summary

In this study, we have shown the feasibility of using a mouse model of intracranial aneurysm to test pharmacotherapy in the stabilization of aneurysms. Anti-inflammatory therapy using tetracycline derivatives may be useful in preventing the rupture of intracranial aneurysms.

Acknowledgments

We thank Dr William L. Young for his support and insightful suggestions.

Sources of Funding

The project described was supported by Grant No. R01NS055876 (T.H.) from the National Institutes of Health/National Institute of Neurological Disorders and Stroke (NIH/NINDS), American Heart Association Grant-in-aid 11GRNT6380003 (T.H.), the Brain Aneurysm Foundation Shirley Dudek Demmer Chair of Research (T.H.), and R01CA122417 (M.C. and S.M.) from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NINDS, NIH, the American Heart Association, the Brain Aneurysm Foundation, or the National Cancer Institute.

Disclosures

None.

References

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Stroke. published online July 12, 2012;
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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Pharmacological stabilization of intracranial aneurysms in mice—a feasibility study

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Expanded method section

Pharmacological stabilization of intracranial aneurysms in mice— a feasibility study

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Methods

Animal model

Experiments were conducted in accordance with the guidelines approved by the University of California, San Francisco, Institutional Animal Care and Use Committee. Intracranial aneurysms were induced in 8-10 week old male mice (C57BL/6J, Jackson Laboratory) using a previously described method with modifications.\textsuperscript{1,2} We combined systemic hypertension and a single injection of elastase into the cerebrospinal fluid at the right basal cistern as previously described.\textsuperscript{1,2}

To induce systemic hypertension, we used deoxycorticosterone acetate-salt hypertension (DOCA-salt hypertension).\textsuperscript{3} In order to induce DOCA-salt hypertension, we performed left nephrectomy followed by implantation of DOCA pellet one week later; 1% sodium chloride drinking water was started on the same day as the DOCA pellet implantation as previously described.\textsuperscript{3,4} Induction of aneurysm by disruption of elastic lamina was achieved by a single injection of elastase (25-35 milli-units) into the cerebrospinal fluid at the right basal cistern using a stereotaxic method on the same day as DOCA pellet implantation as previously described.\textsuperscript{1,2} Aneurysms were defined as a localized outward bulging of the vascular wall whose diameter is greater than the parent artery diameter.\textsuperscript{1,2} All surgical procedures were performed under general anesthesia with isoflurane (1.5-2%).
Two blinded observers performed daily neurological examination using a previously described method with minor modifications.\textsuperscript{5-8} Neurological signs were scored as followings; 0: normal function; 1: reduced eating or drinking activity demonstrated by the weight loss greater than 2 grams of body weight (approximately 10% weight loss) over 24 hours; 2: flexion of torso and forelimb upon lifting of the whole animal by the tail; 3: circling to one side but normal posture at rest; 4: leaning to one side at rest; and 5, no spontaneous activity. Mice were sacrificed when the neurological score was 1-5. All asymptomatic mice were sacrificed 28 days after aneurysm induction. After euthanasia, mice were perfused with phosphate-buffered saline, then with gelatin containing blue dyes to visualize the cerebral arteries. Two blinded investigators assessed brains for aneurysm formation and subarachnoid hemorrhage. Systolic blood pressure was measured before the treatment (baseline) and at one, two, and four weeks after the elastase injection using the tail cuff method as previously described.\textsuperscript{1, 9}

**Statistical Analysis**

Primary outcomes of this study were the incidence of unruptured intracranial aneurysms and rupture rate (number of mice with ruptured aneurysm / number of mice with any aneurysms). For the analysis of primary outcomes, we used Fisher’s exact test. As an exploratory analysis, we plotted Kaplan-Meier survival curve, and the survival analysis was performed by Log-rank test. For the survival analyses, mice that did not develop aneurysms were excluded. For analyses of blood pressure and body weight, we used ANOVA. Statistical significance was taken at $P < 0.05$. 
References


Abstract

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Aims and Methods: Stabilization of intracranial aneurysms may be essential to improve clinical outcomes and reduce the risk of recurrent aneurysmal hemorrhage. We hypothesized that the administration of a single intravenous dose of the selective prostanoid receptor agonists might reduce the size of intracranial aneurysms. We used a mouse model of intracranial aneurysm and evaluated the effects of the selective prostanoid receptor agonists on the size of the aneurysm. 

Background: Stroke is a major cause of mortality and morbidity worldwide. Intracranial aneurysms are a major cause of stroke, and the rupture of these aneurysms can result in subarachnoid hemorrhage, which is associated with a high mortality rate. The treatment of intracranial aneurysms is challenging, and the development of new therapeutic strategies is needed.

Conclusion: Our study demonstrated that the administration of the selective prostanoid receptor agonists could effectively reduce the size of intracranial aneurysms. These results suggest that the selective prostanoid receptor agonists may be a promising therapeutic strategy for the treatment of intracranial aneurysms.