Effect of subarachnoid hemorrhage on endothelium-dependent vasodilation

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The effect of subarachnoid hemorrhage (SAH) on endothelium-dependent vasodilation of the isolated rabbit basilar artery was examined using an isometric tension recording method. The SAH was induced by injecting 5 ml of fresh arterial blood into the cisterna magna. Sixty-two rabbits were separated into four groups according to the timing of sacrifice: control rabbits, and operated rabbits sacrificed on Days 2, 4, and 6 after SAH. Acetylcholine (ACh) ($10^{-7}$ M to $10^{-4}$ M) and adenosine triphosphate (ATP) ($10^{-7}$ M to $10^{-4}$ M) were used to evoke dose-dependent vasodilation of isolated arterial rings previously contracted by $10^{-6}$ M serotonin (5-HT). There were no significant differences in the vasodilatory response to ACh among these four groups. Relaxation to approximately 84% of the initial contractile tone occurred with $10^{-4}$ M ACh. On the other hand, the vasodilatory response to ATP was suppressed in the animals sacrificed 2 days after SAH; the relaxation of this group was approximately 52% at $10^{-4}$ M ATP, compared to a relaxation of 87% observed in the other groups of animals. One of the major causes of the impairment of endothelium-dependent vasodilation seems to be an inhibition of the production of endothelium-derived relaxing factor by endothelial cells.

After the relaxation studies, the dose-response curves for 5-HT were obtained. Serotonin caused significantly more contraction in the animals sacrificed 2 days after SAH than in the other groups. The present experiments suggest that impairment of the endothelium-dependent vasodilation following SAH, together with the potentiation of the contractile response to vasoactive agents in cerebral arteries, may play an important role in the pathogenesis of vasospasm.

KEY WORDS • acetylcholine • endothelium-dependent vasodilation • adenosine triphosphate • subarachnoid hemorrhage • rabbit

Cerebral vasospasm is the leading cause of morbidity and mortality in patients with subarachnoid hemorrhage (SAH) from aneurysm rupture. Despite extensive clinical and experimental studies, the pathogenesis of vasospasm is still controversial and poorly understood. The cause of vasospasm is presently considered to be multifactorial.

Several years ago, Furchgott and Zawadzki showed that the endothelium has an obligatory role in the relaxation of rabbit thoracic aorta strips in response to acetylcholine (ACh). Since then, many studies have confirmed the essential role of the endothelium in vasodilation induced by several pharmacological agents and in various preparations. In normal rabbit basilar arteries, we have recently demonstrated that ACh and adenosine triphosphate (ATP) induce endothelium-dependent vasodilation and that hemoglobin selectively inhibits this relaxation. Moreover, the results suggested that impairment of the endothelium-dependent relaxation mechanism by hemoglobin might be involved in the pathogenesis of vasospasm.

It has been reported that endothelial damage occurs frequently following SAH. Therefore, it seems quite possible that the endothelial damage caused by SAH could also result in impairment of the endothelium-dependent vasodilation. The present experiment was conducted to investigate the effect of SAH on the endothelium-dependent relaxation induced by ACh and ATP in the rabbit basilar artery in vitro.

Materials and Methods

Animal Preparation

Sixty-two New Zealand White male rabbits, each weighing 2.7 to 3.2 kg, were anesthetized by intramus-
cular injection of a mixture of ketamine (20 mg/kg), xylazine (5 mg/kg), and acepromazine (0.25 mg/kg) in a ratio of 8:1:1. The animals were intubated, and muscular paralysis was induced with intravenous pancuronium bromide (0.08 mg/kg). Ventilation was maintained with a Harvard dual-phase control respirator.*

The left ear artery of each animal was cannulated for monitoring blood pressure and withdrawing arterial blood. Arterial blood gases were checked, and arterial pH, PaCO2, and PaO2 were maintained within the physiological range.

A No. 23 butterfly needle was inserted percutaneously into the cisterna magna and connected to a three-way stopcock. One outlet was used for the injection of arterial blood, and the remaining outlet was connected to a pressure transducer through which intracranial pressure (ICP) was monitored before and immediately after the injection. Arterial blood pressure and ICP were monitored by means of a pressure transducer and were recorded on a chart recorder.†

The animals were separated into four groups as shown in Table 1. The SAH was produced by a single 5-ml injection of fresh autologous nonheparinized arterial blood over 10 seconds, following which the animals were tilted with the head down for 30 minutes to facilitate settling of the blood in the basal cisterns by gravity. Cisternal injection of 5 ml of arterial blood transiently elevated the ICP and the mean arterial pressure by about 200 mm Hg and 30 mm Hg, respectively. The animals were extubated when they were fully awake.

Artery Preparation and Tension Recording

On Days 2, 4, and 6 after SAH, the animals were reanesthetized with ketamine (60 mg/kg intramuscularly) and exsanguinated from the femoral arteries. Control animals without surgery were similarly prepared and sacrificed. The brain with the basilar artery in situ was removed and placed in a dissecting chamber filled with Krebs solution (composition (mM): NaCl 120; KCl 4.5; MgSO4 1.0; NaHCO3 27.0; KH2PO4 1.0; CaCl2 2.5; and dextrose 10.0). The basilar artery was dissected free under magnification, and 3-mm long arterial rings were prepared. Each specimen was suspended between L-shaped stainless steel rods in an organ bath with a 10-ml working volume, which was gassed with 95% O2 and 5% CO2. The pH of the solution ranged from 7.4 to 7.5. The resting tension was adjusted to 400 mg, since the best relaxation was obtained at this tension. The preparation was allowed to equilibrate at 37°C for 90 minutes before use. Isometric tension was recorded using a Grass FT.03 force-displacement transducer and was displayed on a Solutec 3418 chart recorder.‡

Initially, the contractile response to 40 mM KCl was obtained for each arterial ring. The preparation was then washed at least three times with 20 ml of Krebs solution and allowed to equilibrate for 45 minutes after each exposure to KCl or serotonin (5-HT). After confirming a consistent contractile response to KCl, experiments with 5-HT were begun.

For the relaxation studies, submaximal tone was first induced with 10-8 M 5-HT, after which ACh or ATP was added in a cumulative fashion. The relaxations induced by ACh or ATP were expressed as a percentage of the tonic phase of contraction induced by 10-6 M 5-HT. In the experimental series, a given arterial ring was exposed to only one drug: either ACh or ATP. However, in some arterial rings from the animals sacrificed 2 days after SAH, ACh was added following the addition of ATP in order to determine if ACh could still induce relaxation in arterial rings that had already been relaxed by 10-4 M ATP. In the relaxation studies with ATP, adenosine (8-PT), an 8-phenyltheophylline antagonist, was used to pretreat the arterial rings 5 minutes before application of 10-6 M 5-HT to exclude the effect of endothelium-independent relaxation by adenosine.

Following the relaxation studies, the contractile response to 40 mM KCl was obtained again. Later, the dose-response curves for 5-HT were obtained by the cumulative addition of the drug to confirm the effect of SAH on the contraction induced by 5-HT, since Lobato et al.23 have reported a denervation hypersensitivity of the cerebral artery to 5-HT following SAH. The maximal contraction induced by 40 mM KCl was assumed to be 100%.

An obligatory role of the endothelium in the vasodilation induced by ACh and ATP was confirmed again in the present experiments. The method for removal of the endothelial cells has been described elsewhere.14

Morphological Examination

Transmission and scanning electron microscopy were performed to assess the morphological changes of the arterial walls following SAH. In each group of rabbits, three animals were submitted to perfusion-fixation, apart from the in vitro experiment (see Table 1).

Perfusion-fixation was performed by transthoracic cannulation of the left ventricle and perfusion with a mixture of 2% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M phosphate buffer (pH 7.4), under a pressure of 120 cm H2O. The basilar arteries were removed from the brain and immersed in a cacodylate-buffered fixative (pH 7.4) for 5 hours at 4°C and then kept overnight at 4°C in 0.1 M sodium cacodylate buffer (pH 7.3).

† Pressure transducer, Model 78342A, manufactured by Hewlett-Packard, Co., Palo Alto, California.
‡ Force-displacement transducer, Model Ft.03, manufactured by Grass Instrument Co., Quincy, Massachusetts; chart recorder, Model 3418, manufactured by Solutec Corp., Sun Valley, California.

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### TABLE 1

<table>
<thead>
<tr>
<th>Animal Group</th>
<th>Relaxation Study</th>
<th>Morphological Study</th>
<th>Total</th>
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</thead>
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<td></td>
<td>ACh</td>
<td>ATP</td>
<td></td>
</tr>
<tr>
<td>control</td>
<td>6</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>SAH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>7</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Day 4</td>
<td>6</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Day 6</td>
<td>7</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>total no. of animals</td>
<td>26</td>
<td>24</td>
<td>12</td>
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</tbody>
</table>

* Rabbits in the experimental groups were sacrificed on Days 2, 4, and 6 after subarachnoid hemorrhage (SAH). ACh = acetylcholine; ATP = adenosine triphosphate.

For transmission electron microscopy, samples were post-fixed in 1% osmium tetroxide in 0.1 M phosphate buffer (pH 7.4), dehydrated in graded alcohol, and embedded in Epon 812. Ultrathin sections were stained with uranyl acetate and examined in a Hitachi HU-12A electron microscope. For scanning electron microscopy, the dehydrated specimen was immersed in isoamyl acetate, then critical-point dried and coated with palladium gold. The specimen was viewed and photographed on a JEOL JSM-35C scanning electron microscope. Immediately after the in vitro experiment the arterial rings were also examined with the transmission and scanning electron microscope to determine whether endothelial cells were injured during the in vitro studies.

#### Drugs

With the exception of 5-HT, stock solutions of ACh, papaverine, ATP, and 8-PT* were made by dissolving the drugs in distilled water. These drugs were diluted further in Krebs solution before use, such that volumes of less than 0.1 ml were added to the organ baths. The 5-HT was dissolved in 0.1 N HCl with 0.1% ascorbic acid.

#### Statistical Analysis

The data were expressed as means ± standard error of the means. Statistical analysis of the dose-response curves of ACh- or ATP-induced relaxation and of 5-HT-induced contraction was performed using general linear model procedures with the SAS (Statistical Analysis System) computer program, and Scheffé's test was used for subgroup analysis. Multiple comparisons of the contractile response to 40 mM KCl or 10⁻⁴ M 5-HT, of the vasodilatory response to ACh or ATP, and of the contractile response to 5-HT at each specific concentration were evaluated by Scheffé's test after analysis of variance. The values were considered to be significantly different if p was less than 0.05.

#### Results

**Effect of SAH on ACh- and ATP-Induced Relaxation**

Serotonin at a concentration of 10⁻⁶ M induced a phasic and tonic contraction complex. Acetylcholine (10⁻⁷ M to 10⁻⁴ M) caused dose-dependent vasodilation of the basilar arteries in each group of animals (Fig. 1). There were no significant differences in the vasodilatory response to ACh among these four groups, and ACh (10⁻⁶ M) produced relaxation to approximately 83% to 90% of the initial contractile tone induced by 10⁻⁶ M 5-HT (Fig. 2).

Adenosine triphosphate also induced dose-dependent vasodilation of the basilar arteries in each group of animals (Fig. 1). However, the vasodilatory response to ATP was significantly suppressed in animals sacrificed on Day 2 (Fig. 3). With ATP concentrations of 10⁻⁶ M to 10⁻⁴ M in Day 2 animals and 10⁻⁶ M in Day 4 and Day 6 animals, vessel relaxation was significantly inhibited when compared to control vessels. Relaxation of the arteries from Day 2 animals to 52% ± 4.8% of the initial contractile tone was recorded with 10⁻⁴ M ATP preparations. This compared to a relaxation to 87% of initial contractile tone seen in other groups.

Acetylcholine induced relaxation following the addition of 10⁻⁶ M to 10⁻⁴ M ATP to the precontracted arterial rings from the Day 2 animals (Fig. 4). At concentrations of 10⁻³ M to 10⁻⁴ M, ACh further relaxed the arterial rings previously relaxed by 10⁻⁴ M ATP (p < 0.01).

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* Hitachi electron microscope, Model HU-12A, manufactured by Hitachi, Tokyo, Japan.
† Scanning electron microscope, Model JEOL JSM-35C, manufactured by JEOL USA, Cranford, New Jersey.
* Drugs obtained from Sigma Chemical Co., St. Louis, Missouri.
FIG. 2. Effect of acetylcholine (ACh) on serotonin (5-HT)-induced contraction of rabbit basilar artery following subarachnoid hemorrhage. The addition of ACh induced a dose-dependent vasodilation. There was no significant difference among the dose-response curves of the four animal groups. Data are mean values expressed as a percentage of the contraction induced by 10\(^{-6}\) M 5-HT. Vertical bars indicate two standard errors of the mean; \(n\) refers to the number of specimens checked.

FIG. 3. Effect of adenosine triphosphate (ATP) on serotonin (5-HT)-induced contraction of rabbit basilar artery following subarachnoid hemorrhage (SAH). The addition of ATP evoked a dose-dependent vasodilation. Vasodilatory responses to ATP were impaired in the animals sacrificed 2 days (10\(^{-6}\) M to 10\(^{-4}\) M ATP) and 4 and 6 days (10\(^{-6}\) M ATP) following SAH. Data are mean values expressed as a percentage of the contraction induced by 10\(^{-6}\) M 5-HT. Vertical bars indicate two standard errors of the mean. * = \(p < 0.05\); ** = \(p < 0.01\) (vs. control values); \(n\) refers to the number of specimens checked.

### TABLE 2

**Effect of SAH in rabbits on isometric arterial contractions evoked by KCl and serotonin (5-HT)**

<table>
<thead>
<tr>
<th>Animal Group†</th>
<th>Acetylcholine</th>
<th>Adenosine Triphosphate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 mM KCl (gm)</td>
<td>10(^{-6}) M 5-HT (%)</td>
</tr>
<tr>
<td>control</td>
<td>1.03 ± 0.079</td>
<td>50.0 ± 7.46</td>
</tr>
<tr>
<td>(11)</td>
<td>(11)</td>
<td>(14)</td>
</tr>
<tr>
<td>SAH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>1.02 ± 0.068</td>
<td>106.2 ± 13.12†</td>
</tr>
<tr>
<td>(14)</td>
<td>(14)</td>
<td>(12)</td>
</tr>
<tr>
<td>Day 4</td>
<td>1.11 ± 0.089</td>
<td>61.9 ± 4.40</td>
</tr>
<tr>
<td>(11)</td>
<td>(11)</td>
<td>(12)</td>
</tr>
<tr>
<td>Day 6</td>
<td>1.13 ± 0.076</td>
<td>51.1 ± 3.48</td>
</tr>
<tr>
<td>(13)</td>
<td>(13)</td>
<td>(10)</td>
</tr>
</tbody>
</table>

* Contractions evoked by 40 mM KCl are expressed as an increase in the tension (grams) above baseline, and those evoked by 10\(^{-6}\) M serotonin (5-HT) are expressed as a percentage of the contraction elicited by a standard dose of 40 mM KCl. Data are shown as means ± standard error of the means. The number of arterial rings used for these experiments is given in parentheses. Initial contractile tone in the Day 2 group was significantly greater than that in any other group (‡ \(p < 0.01\)).

† Rabbits in the experimental groups were sacrificed on Days 2, 4, and 6 after subarachnoid hemorrhage (SAH).

The initial contractile tone induced by 10\(^{-6}\) M 5-HT in each group is shown in Table 2. Data are expressed as a percentage of the contraction elicited by a standard dose of 40 mM KCl. There was no significant difference between contractions among the four groups with the 40-mM dose of KCl. However, the initial contractile tone induced by 10\(^{-6}\) M 5-HT in Day 2 animals was significantly greater, by about two fold, than that observed in any other group.

**Effect of SAH on 5-HT-Induced Contraction**

The dose-response curves of the basilar arteries to 5-HT are shown in Fig. 5. Serotonin (10\(^{-8}\) M to 10\(^{-5}\) M) caused significantly more contraction in Day 2 animals than in any other group. The maximal contraction in this group was about twice that in the control group. In Day 4 animals, potentiation of the contractile tone was also seen (3 × 10\(^{-6}\) M to 10\(^{-5}\) M).

**Morphological Observation of the Basilar Arteries**

In Day 2 and Day 4 animals, thick subarachnoid clot was observed over the basal surface of the brain around
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Fig. 4. Upper: Effect of acetylcholine (ACh) on serotonin (5-HT)-induced contraction of rabbit basilar artery following the addition of $10^{-6}$ M to $10^{-4}$ M adenosine triphosphate (ATP) in the animals sacrificed 2 days after subarachnoid hemorrhage. The numbers with arrows indicate the log molar concentrations of ACh or ATP. Pap = $10^{-4}$ M papaverine. Lower: Typical pattern of the dose-response relationship of the basilar arteries to ACh and ATP. The addition of ACh significantly further relaxed the arterial rings that had previously been relaxed by $10^{-4}$ M ATP. Data are mean values expressed as a percentage of the contraction induced by $10^{-6}$ M 5-HT. Vertical bars indicate two standard errors of the mean. ** = p < 0.01 (vs. $10^{-4}$ M ATP).

On scanning electron microscopy, the basilar arteries from control animals showed a normal appearance, with normal inter-endothelial borders and normal endothelial cell shape and orientation. The basilar arteries from Day 2 animals showed convolution of the luminal surface with irregular endothelial borders and loss of orientation of the endothelial cells. In Day 4 and Day 6 animals, the endothelial cell shape was not uniform, but orientation of the endothelial cells was almost normal.

The arterial rings fixed immediately after the in vitro experiment showed no damage to the endothelial cells produced by these manipulations.

Discussion

It is well-established that the relaxation induced by ACh and other vasoactive agents, such as adenine nucleotides, substance P, bradykinin, and histamine, is mediated indirectly by the release of a
relaxant substance from the endothelial cells, which has been termed the "endothelium-derived relaxing factor" (EDRF).

The present experiments reveal that the endothelium-dependent relaxation of the basilar arteries induced by ATP is inhibited following SAH while that induced by ACh is not. Three major causes for this impairment of endothelium-dependent relaxation can be postulated: 1) denudation of the endothelium; 2) inhibition of the production mechanism of EDRF in the endothelium; or 3) a decrease in or lack of responsiveness of the smooth-muscle cells to EDRF, either by potentiation of the initial contractile tone or by degeneration or necrosis of the smooth-muscle cells. In the present experiments, impairment of the production mechanism of EDRF seems to be the most probable cause for inhibition of the relaxation by ATP.

According to Furchgott and Zawadzki, morphological studies performed immediately after pharmacological experiments in rabbits showed that vessel preparations giving good relaxation usually had about 60% to 75% of their endothelial cells still present, and that preparations with only a small percentage of these cells remaining still gave moderate relaxation. The relaxation induced by ATP was attenuated in animals sacrificed 2 days following SAH. In these animals, no loss of the endothelial cell layer or degenerative changes within these cells could be seen either with transmission or scanning electron microscopy despite the observation of corrugations and loss of cell orientation.

Decreased or absent responsiveness of the smooth-muscle cells to EDRF is another possible cause for inhibition of the relaxation response. Overt structural damage to smooth-muscle cells seems an unlikely cause for the impairment of the endothelium-dependent relaxation, since no such damage to the smooth-muscle cells was seen morphologically in the present studies, and since the smooth-muscle cells responded well to ACh and papaverine with good relaxation.

It has been reported that the percentage of relaxation by ACh of the initial contractile tone tends to decrease as the level of initial tone is increased. The contractile...
tone induced by $10^{-6}$ M 5-HT in the animals that were sacrificed 2 days after SAH was nearly twice as high as that seen in the other groups. In light of these findings, it was felt that the attenuated ATP-induced relaxation in the Day 2 animals might be due to the elevated initial contractile tone. However, there were no significant differences in the initial contractile tone in relaxation studies using either ACh or ATP. Moreover, the degree of relaxation of the arterial rings from Day 2 animals produced by ACh was not significantly different from that in control animals and was not affected by the initial contractile tone. In addition, ACh could still relax the arterial rings that had already been relaxed by $10^{-4}$ M ATP. It is therefore unlikely that the increased initial contractile tone resulted in decreased relaxation by ATP. The fact that the relaxation was inhibited at $10^{-6}$ M in Day 4 and Day 6 animals that showed no potentiation of contractile tone reinforces this hypothesis.

Based upon these results, inhibition of the endothelium-dependent relaxation by ATP could be attributed to impairment of the production mechanism of EDRF in the endothelium. Such impairment of the endothelium may be correlated with morphological change of the endothelium or with deformity of the endothelium due to convolution of the arterial wall, which was frequently seen in the present experiments.

Severe damage to the endothelium (such as marked degeneration and denudation of the endothelium), which was not seen in the present experiments, could be expected to further inhibit endothelium-dependent relaxation. Alternatively, lesser degrees of endothelial damage, which may not be apparent morphologically, could result in incomplete dysfunction of endothelium-dependent relaxation mechanisms. Thus, the persistence of vasodilation in response to ACh and in the absence of ATP-induced relaxation, as seen in the present study, may represent a partial injury of these mechanisms. To confirm these hypotheses would require further investigation using a different SAH model, perhaps one resulting in more severe vasospasm.

In the animals sacrificed on Days 4 and 6 after SAH, the relaxation produced by $10^{-5}$ M and $10^{-4}$ M ATP was almost equivalent to that in control animals. These findings, taken in light of the impaired relaxation seen in Day 2 animals, indicate early recovery from the hemorrhagic insult of the endothelium-dependent relaxation produced by ATP.

Although the chemical identity of EDRF is not known, there may be more than one such factor. It is controversial whether EDRF released by ATP is different from that released by ACh. Based on the fact that relaxations produced by ATP and ACh share a common susceptibility to inhibitory agents, Furchgott and Johtianandran concluded that EDRF released by ATP in rabbit aorta is similar to that released by ACh. On the other hand, De Mey and Vanhoutte demonstrated that, in the canine femoral artery, relaxation by ATP is mediated by a different "signal" (perhaps EDRF) than the signal that mediates relaxation by ACh, since relaxation by ATP, unlike that by ACh, was not susceptible to inhibition by eicosatetraynoic acid (an inhibitor of lipoxygenase as well as of cyclo-oxygenase) and quinacrine (an inhibitor of phospholipase A$_2$). In the present experiments, it was demonstrated that relaxation by ATP is more susceptible to SAH than is that by ACh, and that ACh can still relax the arterial rings that have been already partially relaxed by $10^{-4}$ M ATP. The present studies suggest the possibility that EDRF released by ATP is different from that released by ACh.

The animals sacrificed 2 days after SAH showed marked potentiation of the contractile response induced by 5-HT. Lobato, et al., reported that the increase in the vascular contractile response in cat cerebral arteries induced by SAH was similar to that seen after superior cervical ganglionectomy or intracerebral injection of 6-hydroxydopamine. They therefore postulated a denervation hypersensitivity of the cerebral artery to norepinephrine (NE) and 5-HT following these manipulations. Since that time, potentiation of the contractile tone induced by NE and 5-HT following SAH has been attributed by other authors as well to a denervation hypersensitivity of the cerebral artery.

It has recently been recognized that the presence of the endothelial cells has an obligatory role in preventing the artery from overconstriction. Cocks and Angus reported that removal of the endothelium potentiated the vasoconstriction responses to NE and 5-HT in coronary arteries isolated in greyhounds, mongrel dogs, and pigs. Their results with 5-HT have been supported subsequently by in vitro and in vivo studies of canine coronary arteries. Using perfused pial arteries from rabbit and cat brain, it has been recently demonstrated by Sercombe, et al., that the contractile tone induced by NE was potentiated in de-endothelialized arteries.

In our experiments, the animals sacrificed 2 days after SAH demonstrated impairment of endothelium-dependent vasodilation and morphological changes of the endothelium. Therefore, the possibility should be entertained that damage to the endothelium following SAH is associated with the potentiation of the contractile tone induced by 5-HT observed in the present experiments.

Endothelial damage often occurs following SAH, and it has been suggested that damage to the endothelial cells may play an important role in the pathogenesis of vasospasm. Endothelial damage following SAH brings about a decrease in the production of prostacyclin (a potent vasodilator) in the arterial wall, which results in impairment of vasodilation. The present experiments not only demonstrated the impairment of the endothelium-dependent relaxation in basilar arteries following SAH, but they suggest that damage to the endothelium might potentiate the contractile responses. Furthermore, hemoglobin released from the lysed erythrocytes also inhibits the endothelium-dependent vasodilation of cerebral arteries.
Based upon all these results, damage to the endothelium following SAH is strongly associated with the pathogenesis of vasospasm.

Conclusions
The present experiments demonstrate that SAH impaired the endothelium-dependent relaxation of the cerebral arteries. Subarachnoid hemorrhage also resulted in the potentiation of the contractile response to 5-HT, and it is suggested that endothelial damage might be associated with this potentiation by means of a denervation hypersensitivity. Together with potentiation of the contractile response in the cerebral artery, impairment of endothelium-dependent relaxation following SAH may play an important role in the pathogenesis of cerebral vasospasm.

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References
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