Selective Effects of Subarachnoid Hemorrhage on Cerebral Vascular Responses to 4-Aminopyridine in Rats

Lilly Quan, BSc(Hons); Christopher G. Sobey, PhD

Background and Purpose—We postulated that some abnormalities in cerebrovascular function after subarachnoid hemorrhage (SAH) may involve underlying alterations in K⁺ channel function. Thus, using pharmacological inhibitors, we assessed the influence of SAH on function of 2 types of K⁺ channel in regulation of basilar artery diameter in vivo and membrane potential (Eₘ) in vitro.

Methods—Rats were injected with saline (control) or autologous blood (SAH) into the cisterna magna. Two days later, effects of vasoactive drugs on the basilar artery were examined with a cranial window preparation. Vascular responses to 4-aminopyridine (4-AP), 3-aminopyridine (3-AP), tetraethylammonium (TEA), serotonin, acetylcholine, and adenosine were compared in control and SAH rats. Additional studies using intracellular microelectrodes evaluated the effects of 4-AP and serotonin on Eₘ of basilar arteries isolated from control and SAH rats.

Results—Baseline artery diameter was 236±5 μm in control rats and 220±7 μm in SAH rats (P<0.05). 4-AP, but not 3-AP, constricted the basilar artery in control rats, and responses to 4-AP were reduced in SAH rats. Constrictor responses to TEA or serotonin were unaffected by SAH. Vasodilator responses to acetylcholine were impaired in SAH rats, whereas responses to adenosine were not different. Resting Eₘ was −81±3 mV in control arteries and −79±3 mV in SAH arteries. Both 4-AP and serotonin depolarized the basilar artery, but only 4-AP-induced depolarization was impaired in SAH arteries.

Conclusions—These data suggest that 4-AP induces cerebral vasoconstriction in vivo through smooth muscle depolarization due to inhibition of voltage-dependent K⁺ channels. Furthermore, function of these K⁺ channels may be selectively reduced in the basilar artery after SAH and thus could contribute to cerebral vascular dysfunction. (Stroke. 2000;31:2460-2465.)

Key Words: 4-aminopyridine • basilar artery • potassium channels • tetraethylammonium ion • rats

Since the conductance to K⁺ ions effectively determines the membrane potential of vascular smooth muscle, any change in the resting K⁺ conductance (eg, via changes in activity of K⁺ channels) could alter regulation of vascular tone.1,2 Several types of K⁺ channels are expressed in cerebral arteries.2 Some K⁺ channels, such as voltage-dependent K⁺ channels3 and large-conductance calcium-activated K⁺ channels,4,5 appear to be active under basal conditions in large cerebral arteries in vivo.

K⁺ channel activity in cerebral arteries can be influenced acutely by a range of vasoactive stimuli, including both vasodilators and vasoconstrictors.2 Moreover, there is increasing evidence that K⁺ channel function may be variously altered in several disease states that predispose to stroke.6 For example, cerebral vasorelaxation in response to openers of ATP-sensitive K⁺ channels is impaired during chronic hypertension,7 diabetes,8,9 atherosclerosis,10 and after ischemia11 or brain injury12 but may be augmented after subarachnoid hemorrhage (SAH).13-15 In addition, the function of inwardly rectifying K⁺ channels is impaired after ischemia and reper-

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fusion,16 and activity of large-conductance calcium-activated K⁺ channels appears to be enhanced during chronic hypertension.14,17 Improved understanding of these complex changes in K⁺ channel function is therefore likely to be helpful in the understanding and treatment of cerebrovascular disease.

SAH is a unique cerebrovascular disorder and a major clinical problem that involves abnormalities in cerebral vascular function that may include depolarization, impaired vasodilatation, and increased vasoconstriction.18-21 Interestingly, it is thought that decreased membrane conductance of K⁺ ions may occur in cerebral vascular muscle after SAH,22 but whether the activity or function of specific K⁺ channels is altered in vivo after SAH is not known. Moreover, because dilator responses of the rat basilar artery to nitric oxide (NO) in vivo appear to involve activation of voltage-dependent K⁺ channels3 and large-conductance calcium-activated K⁺ channels5 and because NO responses are selectively impaired after
SAH, we postulated that the function of one or both of these K⁺ channels may be altered after SAH. An index of basal activity of K⁺ channels in vascular muscle can be obtained by recording the functional responses of cerebral arteries to pharmacological inhibitors of K⁺ channels. Thus, in the present study we used this approach in a cranial window preparation to investigate whether experimental SAH may alter activity of voltage-dependent and/or large-conductance calcium-activated K⁺ channels in the basilar artery in vivo. In addition, we measured effects of K⁺ channel inhibition on membrane potential of isolated basilar arteries from control and SAH rats.

**Materials and Methods**

Fifty-three male Sprague-Dawley rats (weight, 230 to 500 g) were studied. The rats were housed with a 12-hour light/dark cycle and had access to food and water ad libitum. The study was approved by the Animal Experimentation Ethics Committee of the University of Melbourne, Department of Pharmacology and Physiology in accordance with the guidelines of the National Health and Medical Research Council of Australia.

**Induction of SAH**

Rats (n = 26) were anesthetized with sodium pentobarbital (50 mg/kg IP) and treated with atropine (0.5 mg/kg IP; to inhibit respiratory secretions). The rats were then intubated and mechanically ventilated with room air and placed in a supine position on a heating pad. With the use of aseptic technique, the left femoral artery was cannulated for the removal of blood, the animal was placed in a stereotaxic device in a slight nose-down position (10°), and the atlanto-occipital membrane was exposed. A 27-gauge hypodermic needle was inserted 1.5 mm into the cisterna magna, and ~0.1 mL of cerebrospinal fluid (CSF) was gently aspirated. Freshly drawn autologous nonheparinized arterial blood (0.3 mL) was then injected into the CSF. The needle was removed after an additional 10 minutes, and the head incision was closed with the use of 5-0 silk sutures. After ligation of the femoral artery, the catheter was removed and the leg incision closed. The entire procedure was completed in ~1.5 hours; when necessary, anesthesia was supplemented with pentobarbital (10 to 20 mg/kg IP). Animals were fully awake 2 to 3 hours after the surgery and were studied 2 days later.

For comparison, control animals were either similarly injected with 0.3 mL of saline (n = 7), or naive control rats (no prior surgery, n = 20) were used. Since similar results were observed in saline-injected and naive control groups, data from the 2 control groups were combined (n = 27).

**Cranial Window Preparation (In Vivo)**

Two days after induction of experimental SAH or injection of saline, rats were again anesthetized with pentobarbital (50 mg/kg IP) for study of basilar artery reactivity in vivo. Anesthesia was supplemented throughout the experiment at 10 to 20 mg/kg per hour IV. A midline incision was made in the neck, a tracheostomy was performed, and the animals were mechanically ventilated with room air and supplemental O₂. Arterial blood gases were monitored and maintained within normal levels throughout the experiment (pH = 7.37 ± 0.01; PO₂ = 156 ± 5 mm Hg; PCO₂ = 38 ± 1 mm Hg). A catheter was placed in the right femoral artery to measure systemic arterial blood pressure and to obtain arterial blood. The right femoral vein was cannulated for injection of supplemental anesthetic. Rectal temperature was monitored and maintained at 37°C to 38°C with a heating pad. Gallamine triethiodide (60 mg IV) was administered to induce skeletal muscle paralysis and thus eliminate spontaneous respiratory movements. Depth of anesthesia was evaluated at least every 30 minutes by applying pressure to a paw and observing effects on heart rate or blood pressure. If any changes occurred, additional anesthetic was administered.

A craniotomy was performed over the ventral brain stem, as previously described. The cranial window was continuously superfused at 3 mL/min with artificial CSF (37°C to 38°C; ionic composition [mmol/L]: NaCl 132, KCl 2.97, d-glucose 3.69, CaCl₂ 1.71, MgCl₂ 0.64, NaHCO₃ 22.6) that was bubbled with 95% N₂/5% CO₂ (CSF sampled from the cranial window was as follows: pH = 7.35 ± 0.01; PO₂ = 117 ± 1 mm Hg; PCO₂ = 37 ± 1 mm Hg). Diameter of the basilar artery was monitored with a microscope equipped with a television camera coupled to a video monitor and was continuously measured with a computer-based tracking program (Diamtrack; Montech Australia).

**In Vivo Experimental Protocol**

After an equilibration period of at least 30 minutes to allow stabilization of vessel diameter and blood pressure, experimental vasoactive drugs were applied topically to the basilar artery within the CSF in a cumulative manner (3 concentrations per drug). Drugs studied were as follows: acetylcholine, an endothelium-dependent vasodilator that stimulates production of NO; adenosine, a vasodilator that stimulates production of cAMP by adenylate cyclase; 4-aminopyridine (4-AP), a selective inhibitor of voltage-dependent K⁺ channels at ≤1 mmol/L; 3-aminopyridine (3-AP), a relatively poor inhibitor of voltage-dependent K⁺ channels at ≤1 mmol/L; tetraethylammonium chloride (TEA), a relatively selective inhibitor of large-conductance calcium-activated K⁺ channels at ≤1 mmol/L; and serotonin, which was used as a control vasoconstrictor in these experiments. Diameter of the basilar artery was recorded under basal conditions and during application of each concentration of drug, and the steady state change in diameter, which was usually achieved within 5 to 6 minutes, was recorded. A recovery period of at least 15 minutes was allowed between applications of each drug. Except for 4-AP (see Results), there was no observed effect on arterial pressure of any drug applied to the cranial window. In each rat, 4 or 5 vasoactive drugs were studied in random order, except that the K⁺ channel inhibitor was always applied last. Not more than 1 K⁺ channel inhibitor was studied in each rat.

**Measurement of Membrane Potential in Basilar Artery Smooth Muscle (In Vitro)**

**Isolated Basilar Artery Preparation**

Rats (n = 21) were rendered unconscious by inhalation of 80% CO₂/20% O₂ and killed by decapitation. The brain was quickly removed and placed into cold artificial CSF solution. The basilar artery was carefully dissected from the brain and placed down in the Sylgard base of a 3.5 mL Petri dish and superfused constantly (4 mL/min) with CSF at 37°C. The artery was allowed to equilibrate in the chamber for 30 minutes before commencement of the experiment.

**Electrophysiological Measurements**

Capillary glass microelectrodes (borosilicate glass capillaries, GC 120-8 F-10) were made with the use of a Flaming/Brown micropipette puller (model P-87) and backfilled with KCl (0.5 mol/L). Microelectrodes with resistances between 80 and 180 MΩ were used. A Ag/AgCl electrode connected to a head stage (HS-2, Axon Instruments) was placed in the microelectrode to transmit changes in membrane potential, relative to a reference Ag/AgCl electrode present in the organ bath, to an amplifier (Axoprobe, Axon Instruments). Potentials were amplified (NeuroLog NL106), filtered (DC-3 kHz, Neurolog NL125), and observed on an oscilloscope (BWD645). The signal was digitized by an analog-to-digital converter (TL-1 DMA, Axon instruments) for recording and computer analysis.

Smooth muscle cells of the basilar artery segment were impaled with the microelectrodes by means of a Leitz micromanipulator. Successful electrode impalement was indicated by a rapid fall in membrane potential to approximately −45 mV or lower. Membrane potential was then allowed to stabilize over the next 5 to 7 minutes.

**In Vitro Experimental Protocol**

A 2-minute recording of resting membrane potential was made, and then 4-AP (0.1, 0.3, or 1 mmol/L) or serotonin (0.01, 0.1, or...
Effect of SAH on Vasodilator Responses to Acetylcholine and Adenosine

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Data are expressed as % change in diameter of the basilar artery. Baseline diameter was 213±7 μm in control and 199±13 μm in SAH rats. All values are mean±SE.

*P<0.05 vs control rats.

1 μmol/L was perfused over the basilar artery segment for 5 to 10 minutes. A washout period of at least 30 minutes followed before another concentration was tested.

Drugs

All drugs were obtained from Sigma Chemical Co and were dissolved and diluted in 0.9% saline.

Data Analysis

In vivo vascular responses are presented as percent change in basilar artery diameter over baseline diameter and are expressed as mean±SE. Changes in membrane potential are expressed in absolute terms. Student’s unpaired or paired t tests were used, as appropriate, to compare data. A *P value <0.05 was considered significant.

Results

In Vivo Studies

Mean arterial pressure was similar in control rats (97±4 mm Hg) and SAH rats (99±4 mm Hg). Baseline diameter of the basilar artery in control rats was 236±5 μm and was significantly smaller in SAH rats (220±7 μm; *P<0.05).

Responses to Acetylcholine and Adenosine

Acetylcholine and adenosine dilated the basilar artery in a concentration-dependent manner (Table). Vasodilator responses to acetylcholine were smaller in SAH rats (Table). In contrast, dilator responses of the basilar artery to adenosine were similar in control and SAH rats (Table).

Responses to 4-AP and 3-AP

4-AP produced concentration-dependent constriction of the basilar artery (Figure 1a). Responses to 4-AP were significantly smaller in SAH rats (Figure 1a). 3-AP had no significant effect on basilar artery diameter in either control or SAH rats (Figure 1b). The 2 higher concentrations of 4-AP (0.3 and 1 mmol/L) caused small decreases in mean arterial pressure (-4±1 and -8±2 mm Hg, respectively; n=21; *P<0.05; similar effects were seen in control and SAH groups [separate group data not shown]).

Responses to TEA and Serotonin

TEA produced concentration-dependent constriction of the basilar artery (Figure 2a). The response to the highest concentration of TEA (10 mmol/L) tended to be reduced after SAH (Figure 2a). Serotonin also produced concentration-dependent constriction of the basilar artery in control rats (Figure 2b). Responses to serotonin were not different in SAH rats (Figure 2b).

In Vitro Studies

Resting membrane potential was similar in arteries from control rats (281±3 mV, n=29 cells, 11 arteries) and SAH rats (279±3 mV, n=30 cells, 10 arteries).

Responses to 4-AP and Serotonin

4-AP produced concentration-related depolarization of basilar arteries from control rats that appeared to reach maximum at 0.3 mmol/L (Figure 3a). Responses to 4-AP were significantly smaller in SAH arteries (Figure 3a). Serotonin also produced concentration-related depolarization (Figure 3b), but SAH had no effect on these responses (Figure 3b).
have been reported to constrict cerebral arteries and/or modulate cerebral vasodilator responses in vivo (eg, References 17, 29–31), it seems likely that activity of large-conductance calcium-activated K⁺ channels also contributes to the regulation of cerebral vascular tone. Similarly, in this study we found that TEA caused constriction of the basilar artery. Interestingly, <10 mmol/L TEA produced relatively weaker vasoconstriction than 4-AP, perhaps reflecting a greater influence of voltage-dependent versus large-conductance calcium-activated K⁺ channels on resting diameter of the basilar artery.

**Effect of SAH on Basal K⁺ Channel Function**

SAH may cause various adverse changes to cerebral vascular function, including depolarization, decreased membrane conductance to K⁺ ions, vasoconstriction, and impaired vasodilation. 18–21 We found that vasodilator responses to acetylcholine, but not adenosine, were substantially reduced after SAH, thus confirming numerous reports of impaired cerebral vasorelaxation to endothelium-dependent and/or NO-dependent agonists after SAH (see References 18–21). Importantly, the impairment of endothelium-dependent relaxation after SAH appears to be partly due to decreased vascular responsiveness to NO, as distinct from altered biosynthesis or release of NO. 13,14,32–34 Under normal conditions, cerebral vasodilator responses to NO may be attenuated by inhibitors of voltage-dependent or large-conductance calcium-activated K⁺ channels. We reasoned that if changes in cerebrovascular function in vivo after SAH are related to altered basal activity of voltage-dependent and/or large conductance calcium-activated K⁺ channels, cerebral vascular responses to 4-AP and/or TEA may be abnormal in SAH rats. Consistent with this idea, we found that both depolarization and vasoconstrictor responses of the basilar artery to 4-AP were significantly reduced after SAH. Thus, because inhibition of 4-AP–sensitive K⁺ channel activity appears to have less effect in SAH rats, we suggest that this finding may reflect a diminished contribution of voltage-dependent K⁺ channels to basilar artery tone after SAH. Impaired function of voltage-dependent K⁺ channels in cerebral arteries would be expected to also result in enhanced vasoconstriction in response to depolarizing stimuli 24 and might thus further compromise cerebral perfusion following SAH.

The finding that mean diameter of the basilar artery was 5% to 10% smaller 2 days after SAH, as has typically been reported in rats, 13,38 is also compatible with decreased basal K⁺ channel activity. It was recently suggested that profound induction of heme oxygenase-1, an enzyme that participates in heme degradation, occurs in the rat basilar artery after SAH and may account for why subarachnoid blood is largely resolved within this species after 2 days. 38 Hence, greater levels of delayed vasospasm may occur in other species in which blood clots are less rapidly cleared. Nevertheless, despite the lack of development of profound vasoconstriction in the rat, the present data confirm that significant functional changes are present in the basilar artery of this model, which seems to be a valid and useful approach to investigate altered mechanisms of cerebral vascular reactivity in vivo after SAH. Information regarding the actual mediator(s) involved remains controversial, but there is evidence that hemoglobin and reactive oxygen species released from the

**Discussion**

In this study we tested the hypothesis that K⁺ channel activity is altered in cerebral arteries after SAH by examining the effects of K⁺ channel inhibitors on membrane potential and diameter of basilar arteries of control and SAH rats. The major new finding is that cerebral artery depolarization and constriction in response to 4-AP, an inhibitor of voltage-dependent K⁺ channels, is selectively impaired in SAH rats, consistent with a reduced function of that channel after SAH.

**Effects of K⁺ Channel Inhibitors on the Basilar Artery Under Normal Conditions**

Voltage-dependent K⁺ channels are present in cerebral arteries and have been proposed to play an important role in the regulation of vascular muscle membrane potential and thus contractile tone. 24,26–28 In this study topical application of 0.1 to 1 mmol/L 4-AP caused concentration-dependent constriction of the basilar artery in vivo. Because concentrations of ≤1 mmol/L 4-AP are believed to produce selective inhibition of voltage-dependent K⁺ channels, 1,24,26 this finding is consistent with an important contribution of basal activity of voltage-dependent K⁺ channels in modulating basilar artery tone in vivo and confirms our recent finding. 3 Furthermore, also consistent with an inhibitory action by 4-AP on voltage-dependent K⁺ channels, we observed depolarization of the isolated basilar artery in response to 4-AP. In contrast to 4-AP, 3-AP, which has little effect on voltage-dependent K⁺ channels at ≤1 mmol/L, 24,26 did not constrict the basilar artery. These latter 2 findings provide strong new evidence that the vasoconstrictor effect of 4-AP in the basilar artery in vivo is indeed related to inhibition of voltage-dependent K⁺ channels. 3 The slight hypotensive effects of applying 4-AP onto the brain stem probably result from actions on cardiovascular control centers in the medulla (see Reference 3 for discussion).

Large-conductance calcium-activated K⁺ channels are also expressed in cerebral arteries. 1,2 Because relatively selective inhibitors of these channels (eg, ≤1 mmol/L TEA, iberiotoxin)
aging clot might be key factors leading to delayed cerebrovascular dysfunction after SAH.\textsuperscript{19–21} Decreased voltage-dependent K\textsuperscript{+} channel function could conceivably be due to decreased expression of K\textsuperscript{+} channel proteins in vascular muscle cells (ie, fewer channels or channel subunits) or to decreased open probability of the channels (ie, less frequent or briefer channel openings) after SAH. In addition, altered signaling mechanisms such as increased CSF endothelin levels,\textsuperscript{39,40} increased intracellular calcium concentrations,\textsuperscript{41} and activation of protein kinase C\textsuperscript{42} could be involved in decreased voltage-dependent K\textsuperscript{+} channel activity after SAH. Future studies will be needed to investigate these possibilities.

In contrast to 4-AP, we found that vasocostrictr responses to \( \pm 1 \text{mmol/L} \) TEA were similar in control and SAH rats. Because TEA is thought to be a selective inhibitor of large-conductance calcium-activated K\textsuperscript{+} channels at these, but not higher, concentrations,\textsuperscript{1} our data imply that SAH has little or no effect on basal activity of this channel in cerebral arteries in vivo. Moreover, we found that the constrictor response to 10 mmol/L TEA tended to be reduced in SAH rats. This finding may reflect the fact that, at this concentration, TEA also produces substantial blockage of voltage-dependent K\textsuperscript{+} channels,\textsuperscript{3} such that this response may be partly due to inhibition of the 4-AP-sensitive K\textsuperscript{+} channel.

Responses to Serotonin and Adenosine

Previous in vitro studies have variously reported that cerebral vasocostrictr responses to serotonin may be augmented,\textsuperscript{43} attenuated,\textsuperscript{44} or preserved\textsuperscript{45} after SAH. In the present study serotonin elicited concentration-dependent constriction of the basilar artery in vivo that was similar in control and SAH rats. Similarly, depolarization of the isolated basilar artery in response to serotonin was not affected by SAH. Thus, our data imply that, in this model of SAH, cerebral vascular dysfunction may not be related to altered responsiveness to serotonin. Importantly, these findings confirm that the effects of SAH on responses to 4-AP were somewhat selective.

In vascular muscle, adenosine is likely to produce its relaxant effects by increasing the intracellular concentration of cAMP. In rat cerebral arteries in vivo, increases in cAMP levels may elicit vasodilatation in part by activation of large-conductance calcium-activated K\textsuperscript{+} channels.\textsuperscript{29,46} The preserved vasodilator responses to adenosine after SAH are therefore consistent with data from this and previous studies\textsuperscript{3–15} suggesting that the function of both these K\textsuperscript{+} channel types is not impaired after SAH.

In summary, to our knowledge, this is the first study to report evidence for altered function of voltage-dependent K\textsuperscript{+} channels in any cerebrovascular disease state. The findings suggest that depolarization and vasoconstriction in response to 4-AP are selectively reduced in SAH rats and may provide some insight into mechanisms of vascular dysfunction after SAH. Our data further support the emerging concept that altered K\textsuperscript{+} channel function in cerebral arteries may be associated with a diverse range of cardiovascular diseases.\textsuperscript{2,6}

Acknowledgments

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References

During the past decade, electrophysiological and pharmacological studies have demonstrated an important role for potassium (K⁺) channels in the control of vasomotor function in both peripheral and cerebral arteries. Improved understanding of the mechanisms underlying vasomotor reactivity in normal blood vessels provides a basis for studies involving diseased arteries. The pathogenesis of cerebral vasospasm following subarachnoid hemorrhage is very complex and involves alterations in function of the endothelium, smooth muscle cells, and perivascular nerves. Although our understanding of the mechanisms responsible for the development of vasospasm has improved, the exact sequence of events involved in chronic narrowing of cerebral arteries and reduction of cerebral blood flow is not known. The results presented in the study by Quan and Sobey provide evidence that selective impairment of voltage-dependent K⁺ channel function may contribute to the development of cerebral vasospasm in rats. Whether a similar mechanism is present in human cerebral arteries exposed to autologous blood is unknown and remains to be determined.

Activation of K⁺ channels in arterial smooth muscle cells causes vasodilatation and increase in blood flow. In contrast, inhibition of K⁺ channels in the vascular wall leads to vasoconstriction and reduction of blood flow. These effects are mediated by changes in the membrane potential such that hyperpolarization leads to vasodilatation, whereas depolarization causes vasoconstriction. In the present study the investigators used an in vivo pharmacological approach to demonstrate vasoconstriction of the rat basilar artery in response to a selective voltage-dependent K⁺ channel inhibitor, 4-aminopyridine. This effect was attenuated in arteries exposed to autologous blood, which suggests that these K⁺ channels are dysfunctional. Their pharmacological results were supported by measurements of membrane potential, which showed that the depolarizing effect of 4-aminopyridine was significantly reduced in arteries exposed to autologous blood, which suggests that these K⁺ channels are dysfunctional.

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Editorial Comment

The results presented by Quan and Sobey may help to explain the mechanisms underlying reduction in cerebral arterial diameter induced by subarachnoid hemorrhage. The presented findings support the hypothesis that inactivation of K⁺ channel function plays an important role in pathogenesis of vasospasm. However, identification of the specific K⁺ channels involved and elucidation of the precise mechanism responsible for the effect of blood on ion channel function in human cerebral arteries require further investigation.
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