Influx = \frac{4}{1 + 9} = 2 \mu\text{mol/min/g}

Total brain glucose = 6 \times 0.37 = 2.22 \mu\text{mol/g}

Correcting for cerebrospinal fluid and blood glucose contamination (see Footnote 1) to obtain net tissue glucose content:

net tissue content = (2.22) - (6 \times 0.105) = 1.59 \mu\text{mol/g}

E = 2 \mu\text{mol/min per g} - 1.59 \mu\text{mol/g} = 1.26 \text{ min}^{-1}

Table 2 predicts that the integral of brain glucose specific activity is about 95% of the plasma integral at 10 min. If greater accuracy is required or if a shorter time were necessary, brain glucose specific activity could be calculated as a function of time and used in equation 6 instead of plasma values. This latter approach would be analogous to that developed by Sokoloff and co-workers for "C-deoxyglucose."

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**Experimental Cerebral Vasospasm after Subarachnoid Hemorrhage**

**Participation of Adrenergic Nerves in Cerebral Vessel Wall**

**SHUNRO ENDO, M.D. AND JIRO SUZUKI, M.D.**

SUMMARY Distribution and morphology of nerves in basilar-artery-induced vasospasm were investigated electronmicroscopically. Small cored vesicles were transformed, decreased and disappeared gradually after development of vasospasm induced by blood-CSF mixture incubated 5-10 days. These changes were not induced by fresh arterial blood, lysed platelets in saline and mechanical stimulation. In the portion with severe vasospasm induced by incubated blood-CSF mixture, nerve distribution was rich and uniform in all portions of the adventitia. In the portion with slight vasospasm, nerves were extremely scanty in the innermost area of the adventitia, within 10\mu from the outer edge of the media. The severity of experimental vasospasm became definitely lighter and the duration shorter after bilateral cervical sympathectomy. These findings indicate that nerves, especially the adrenergic axon in the innermost area of the adventitia, may play an important role on the genesis of late vasospasm. The difference in nerve distribution may be a factor influencing individual differences in frequency or severity of vasospasm.

**Method**

Adult cats weighing 2.5-5.0 kg, were anesthetized with intramuscular pentobarbital, and placed on an electric temperature controlled surgical table. Tracheostomies were performed and spontaneous respiration permitted. Body temperature, femoral arterial pressure, respiratory rate and acid-base balance were measured.

By the transcilical approach, a bone window of about 2 x 2 cm was made in the clivus, and the dura was opened at the midline. About 2/3 of the proximal portion of the basilar artery was exposed. To induce vasospasm the following were used: fresh blood (10 cats), lysed platelets in saline with 1.2 \mu\text{g/ml} serotonin on the average (5 cats), and autogenous blood and CSF mixture incubated at 37°C for 5 days (10 cats), 7 days (17 cats), and 10 days (3 cats). In 5 cats the basilar artery was rubbed through the arachnoid membrane to induce vasoconstriction by mechanical stimulation. The sequential caliber change of the basilar artery was measured using photographs taken before and after spasm was induced. The severity of induced vasospasm was classified according to the degree of constriction as follows: Grade I, constriction less than 10%, Grade II, greater than 10 but less than 30%, Grade III, more than 30 but less than 50%, and Grade IV, more than 50%. In the 5 control cats, a mock operation exposing the basilar artery was performed and the sequential changes of caliber measured.

After the varying periods, these basilar arteries were fixed and removed for electronmicroscopic examination. In order to fix the basilar artery in situ with vasospasm, fixatives were injected through the right axial artery and applied on the arachnoid surface simultaneously. The aorta was cut off to stop the heart abruptly. In the 5 additional control cats without operation the brain was immediately removed and the basilar artery excised after anesthesia. The removed arterial segments were fixed in ice-cold 2%
To investigate the distribution of nerves at the arterial wall, the shortest distance between the outer edge of the media and the nerve fibers and endings in the cross sections were measured. The distribution of nerves is shown schematically below. SM: smooth muscle N: unmyelinated nerve fibers.

glutaraldehyde in Millonig's phosphate buffer for 30 min, and later fixed in ice-cold 1% osmium tetroxide in the same buffer for 2 h. Other specimens were fixed in ice-cold 3% permanganate in veronal acetate buffer for 2 h. They were dehydrated with ethanol and embedded in Epon 812. Sections were cut with glass knives transverse to the axis of the artery. Thick sections for light microscopy were stained with 1% toluidine blue, and the thin sections for electron-microscopy were stained with uranyl acetate and lead hydroxide. As the diameter of almost all the removed basilar arteries was less than 500 μ, as a rule, all parts of one arterial wall were included in a single section. In addition, some transverse sections were investigated so that no nerve fiber or ending would be overlooked.

For the investigation of synaptic vesicles in nerve terminals, permanganate fixation was used in 35 specimens better to show the dense components of small corded vesicles. Glutaraldehyde-osmium fixation was used for 25 specimens. Ten control arterial sections were obtained for each fixation. Vessels were removed immediately and at intervals of 10, 20, and 30 min, 1, 2, 5, 10, 24 and 48 h after vasospasm.

The distribution of nerves was investigated in the 5 control cats in which only mock operations were done and in 12 cats with vasospasm induced by blood and CSF mixture which had been incubated 5 to 10 days. To show the distribution of nerves in the adventitia of the basilar artery, the shortest distance between the outer edge of the media and the nerve fiber or ending was measured. The nerves enveloping a layer of basement membrane were counted as one (fig. 1). These investigations were performed on 3 or 4 portions of each arterial section, and in 2 more detailed observations were made on 15 serial sections at 1 mm intervals.

In another experiment using 5 cats, bilateral superior cervical ganglionectomy and perivascular sympathectomy of the cervical carotid arteries were performed. Seven days later, vasospasm of the basilar artery was induced by a blood and CSF mixture which had been incubated 7 days.

Results

In the 5 control cats, the sequential changes of caliber between 3 to 24 h varied from +3% to -4%. With induced vasospasm the caliber change of the basilar artery began immediately after the application of fresh blood, lysed platelets in saline, or blood and CSF mixture incubated 5 to 10 days. The constriction reached its peak 5 to 10 min later and then gradually decreased. Significant differences in the severity of vasospasm were seen (fig. 2). The mean maximum change of caliber was 8.3 ± 4.5% in the group treated with fresh blood, 20.1 ± 2.1% in the group treated with lysed platelets in saline, or blood and CSF mixture incubated 5 to 10 days. These values indicated significant constriction when they were compared with those from the control cases.

Differences in the duration as well as the severity of...
spasm were observed in the control and treated specimens. In the group treated with fresh blood or lysed platelets in saline, vasoconstriction almost completely disappeared 30 min after application. Vasoconstriction induced by the blood, CSF mixture, incubated for 5 to 10 days, continued longer. In this group, the mean caliber reduction was 37% at 30 min after the application, 21% after 1 h, and 22% after 5 h (fig. 2).

Mechanical stimulation caused the basilar artery to constrict immediately, with a mean maximum constriction of 70%. The duration of constriction was short and it disappeared between 5 and 10 min.

Abnormal changes in arterial blood pressure, body temperature, respiratory rate and acid-base balance were not observed in these experiments, but swelling of brain through the bone window in the clivus was observed beginning about 5 h after the application of vasoconstricting substances and increased gradually in cats which showed prolonged vasoconstriction of Grades III and IV. In experiments lasting more than 10 h, the condition of the experimental animals was maintained by infusions and pentobarbital.

Change Observed in Nerve Endings

In 10 control samples, small cored vesicles were observed in all portions of the adventitia and the number of axons with small cored vesicles and small clear vesicles was almost equal. The 2 methods of fixation were responsible for the differences in the configuration of small cored vesicles. The dense components stain more diffusely and strongly with permanganate than with glutaraldehyde-osmium fixation (figs. 3-1, 5). A definite and progressive change of nerve endings appeared in the small cored vesicle following the development of vasoconstriction induced by the blood and CSF mixture incubated 5 to 10 days.

These changes were clearly observable in the samples treated by permanganate fixation. In the specimens removed immediately after the application of the incubated mixture, the number and configuration of vesicles were almost identical to those in control specimens (fig. 3-2). Specimens removed 20, 30 and 60 min later showed a reduction, a shift to the vesicle membrane and the disappearance of dense components (fig. 3-3). These changes became progressively more definite and only 1 or 2 axons with vesicles metamorphosed. These were suspected of being small cored vesicles and were observed in any transverse section 5 to 10 h later (Fig. 3-4). In specimens from cats with vasoconstriction for 24 or 48 h, small cored vesicles were not observed at all, and only small clear and large cored vesicles were seen.

These findings were more prominent in specimens treated by glutaraldehyde-osmium fixation. Small cored vesicles were not observed in any portion of a specimen with vasoconstriction regardless of the duration of vasoconstriction (fig. 3-6). In 2 cats with localized vasoconstriction, small cored vesicles were observed in the portion with slight vasoconstriction (Grade I), but they were few in number and the distribution was limited to the distal part of the adventitia (fig. 3-7).

In 2 control cats in which only operations were performed without inducing vasoconstriction, small cored vesicles were observed. One cat was followed 24 h and the basilar artery fixed with permanganate. The other was followed 10 h with the basilar artery fixed with glutaraldehyde-osmium (fig. 3-8).

Change in nerve terminals including small cored vesicles was not seen in specimens with vasoconstriction induced by the application of fresh blood or lysed platelets in saline (fig. 3-10). Even following repeated applications of fresh blood for 5 h, the configuration of nerve terminals was almost normal (fig. 3-9). No change in small cored vesicles was observed in the cats the basilar arteries of which were subjected to mechanical stimulation (fig. 3-11).

Vasospasm and Nerve Distribution

The relationship between the severity of vasospasm and the distribution of sympathetic nerves was investigated in 12 cats with vasospasm induced by the application of a blood-CSF mixture incubated 5 to 10 days (fig. 4).

The types of vasospasm were classified into 3 groups. The first group exhibited a diffuse constriction of the basilar artery in the photographed area (diffuse type). The second group showed segmental constriction, even though the blood-CSF mixture has been applied equally along the artery (local type). The third group had diffuse and focal spasm (combined type).

In 6 out of 7 specimens with vasospasm of the local or combined type, no nerves were observed in the innermost area of the adventitia, (within 10 μ of the outer edge of the media) in the area with the vasoconstriction of less than 10 percent. Nerves were observed only in the peripheral portions of the adventitia. In the section with constriction of more than 10 percent, nerve distribution in the innermost area was rich. This contrast between the portions of the artery with or without vasospasm was significant.

Specimens from arterial sections showing the diffuse type vasospasm of Grades III and IV showed a uniform distribution of nerves in the all parts of the adventitia except for one cat (cat 9). All arteries with Grade III and IV constriction showed nerve distribution in the area within 5 μ from the outer edge of the media. Even in the one specimen which had only one nerve visible in the area within 10 μ, the nerve was 1.5 μ from the outer edge of the media.

To demonstrate the relationship between the severity of vasospasm and nerve distribution more clearly, the average number of nerves in the adventitia at 10 μ intervals from the outer edge of the media was calculated for each grade of vasospasm (fig. 5). In the innermost area, within 10 μ from the outer edge of the media, nerve distribution is rich with vasospasm of Grade III and IV, but is very scanty with Grade I. This tendency is similar in the area from 10 μ to 20 μ, but these differences were not seen in the area 20 μ from the outer edge. In 10 specimens from 5 control cats with operations that did not induce vasospasm,
only one specimen showed scant nerve distribution in the innermost area of adventitia and the average number of nerves seen was uniform and rich in all parts of the adventitia.

In 2 cats (8 and 11), the nerve distribution in the total length of the removed vessel was observed serially at about 1 mm intervals. Cat 8, with a diffuse type of spasm, showed a uniform and rich distribution of nerves in all portions of the specimen. In cat 11, with a combined type of spasm, nerve distribution was scanty in the innermost area of the adventitia in the portion with constriction of Grade II and it gradually became richer as the constriction became severer (fig. 6).

**Surgical Sympathectomy**

In 5 cats bilateral superior cervical gangliectomy and perivascular sympathectomy of the carotid artery were performed 7 days before vasospasm was induced. The effect of the blood-CSF mixture, incubated 7 days, was not completely suppressed, but the severity
Figure 3. Nos. 1 to 6 show the changes of small cored vesicles in the axon of basilar artery affected by induced vasospasm with incubated blood-CSF mixture. Small cored vesicles were transformed, decreased and disappeared gradually in the course of time after the development of the vasospasm. Permanganate fixation: 1. Control; Abundant small cored vesicles(s) are observed. X 30,000. 2. Immediately after the application of blood and CSF mixture; Small cored vesicles(s) and small clear vesicles(T) are observed similar to control cases. X 24,000. 3. 20 min after the application; Transformation of small cored vesicles(s) are observable. Dense component of vesicles became small, shift near the vesicle membrane and disappear in some vesicles. X 43,200. 4. 10 h after the application; Small cored vesicles are not seen, and only small clear vesicles (T) are observed. X 22,400.

Nos. 5 to 7 show the changes of small cored vesicles in the axon of basilar artery affected by induced vasospasm. Glutaraldehyde-osmium fixation. 5. Control; s: Small cored vesicles. X 38,400. 6, 7. 30 min after the application of mixture; small clear vesicles(T) and large cored vesicles(L) are observed. Small cored vesicles are not present in the severe vasospastic portion(6). Small cored vesicles(s) are in the slight vasospastic portion of Grade I(7). 6: X 36,000. 7: X 38,000.

No. 8 shows a nerve terminal of basilar artery without vasospasm. This vessel was removed 24 h after the only operation. Normal small vesicles(s) are observed. Permanganate fixation. X 30,000.

Nos. 9 to 11 show the small cored vesicles in the axon(s) of basilar artery affected by induced vasospasm with fresh arterial blood, lysed platelet in saline and mechanical stimulation. 9. 5 h after the first application of fresh arterial blood (repeated applications were done for 5 h); Changes of small cored vesicles are not observed. Permanganate fixation. X 30,000. 10. 20 min after the application of lysed platelet; Small cored vesicles are observed as in the nontreated cases. Glutaraldehyde-osmium fixation. X 30,000. 11. 5 min after the mechanical stimulation; Small cored vesicles are observed similarly to the nontreated cases. Permanganate fixation. X 30,000.

The mean caliber reduction was definitely less and the duration was shorter than in the cats without sympathectomy (fig. 7). The mean caliber reduction was 14.6 ± 5.2% in 5 cats with surgical sympathectomy and 44.3 ± 10.4% in 7 cats without sympathectomy. These values were significantly different (P < 0.01).

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Discussion

Many causes for the pathogenesis of vasospasm after subarachnoid hemorrhage have been considered, including mechanical factors and chemical factors such as catecholamines, serotonin and prostaglandins. In...
spite of many studies the true nature and causes remain unclear.

Recent reports have shown organic changes of the endothelium and muscle cells in the vessel wall after subarachnoid hemorrhage.\textsuperscript{1, 7, 15} These findings have been interpreted as the final changes in the vessel which had severe and continuous vasoconstriction. Presently, therapy is not effective at this stage.

A blood and CSF mixture incubated 5 to 10 days induced more severe and prolonged vasoconstriction than was induced by fresh arterial blood, lysed platelets in saline and mechanical stimulation. Reports of clinical and experimental research,\textsuperscript{12, 43, 44} have postulated that a substance contained in a blood and CSF mixture induces late vasospasm after the subarachnoid hemorrhage due to ruptured aneurysm.\textsuperscript{10, 29, 31, 44}

These experiments indicate that the vasoconstriction induced by this mixture can be regarded as the early stage of late vasospasm. The severity and type of vasospasm were not uniform, even though identical amounts of mixture were applied by the same methods. Such individual differences are also seen clinically.\textsuperscript{14, 42}

The investigation of nerve terminals and nerve distribution following induced spasm may be helpful in clarifying the pathogenesis of vasospasm and in explaining individual differences. Transformation, decrease, and disappearance of small cored vesicles were seen in the vessels with vasospasm induced by the

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**Figure 5.** Average number of nerves in the arterial adventitia are shown at 10μ intervals from the outer edge of the media in the grades of vasospasm respectively.

**Figure 6.** The nerve distribution in the arterial adventitia are observed at about 1 mm intervals throughout the removed vessel with combined type vasospasm (cat No. 11).
ADRENERGIC NERVES IN VASOSPASM AFTER SAH/Endo et al.

FIGURE 7. The effect of cervical sympathectomy on vasospasm: In 5 cats undergoing cervical sympathectomy 7 days before vasospasm induced by the blood and CSF mixture incubated for 7 days the vasospasm was lighter than non-treated cases.

Blood and CSF mixture incubated 5 to 10 days. These changes were limited to the dense component of the vesicles and only if the vesicle membrane was intact. This indicates that the release of catecholamines from sympathetic nerve terminals may take part in the development of vasospasm. The changes in nerve terminals are thought not to be an organic change but a transient functional one.

Changes of the vesicles in nerve terminals were not observed in the cats' basilar arteries when vasoconstriction was induced by fresh blood, lysed platelets in saline and mechanical stimulation. This indicates that the pathogenesis of early and late vasospasm may differ greatly.

The differences between permanganate and glutaraldehyde-osmium fixation are definite. Permanganate fixation is more suitable to demonstrating the changes of the small cored vesicles as mentioned by Machado.

The investigation of the relationship of nerve distribution and vasospasm induced by the blood and CSF mixture incubated 5 to 10 days, was interesting. In the cats with severe vasospasm, nerve distribution was uniform in all parts of the adventitia including the innermost area, that which is within 10 μ from the outer edge of the media. In the cats without or with slight vasospasm, the distribution was extremely scanty in the innermost area and the nerves were demonstrated only in the more distant parts of the adventitia. This relationship was remarkable, especially in cats with vasospasm of the local type.

The authors doubted whether the differences in nerve distribution were actual or only related to an irregular adventitial transformation due to vessel constriction. The thickness of the adventitia was 30 to 50 μ in all specimens and minimal differences were seen in respective vessels. In 5 control cats, only one portion of a basilar artery showed scant nerve distribution in the innermost area of adventitia — which is similar to that seen with vasospasm of Grade I. All other portions of the artery showed a uniform and rich nerve distribution similar to that seen with severe vasospasm. The frequency of local vasospasm in our experiments was low (14.3%) as reported previously. The fact that nerve distribution in the innermost area of the adventitia was scanty with vasospasm of Grade I or II was definite but it is rare. The majority of cats have a uniform and rich nerve distribution in all parts of the adventitia, with severe and diffuse vasospasm.

From these findings, it is believed that late vasospasm is initiated by the release of catecholamines from the nerve terminals located near vascular smooth muscle. The nerves, especially the adrenergic axons in the innermost area of adventitia, may play an important role in the genesis of late vasospasm. Late vasospasm does not appear with scant nerve distribution in the innermost area of the adventitia. The individual differences in vasospasm may be explained by the differences in nerve distribution. In patients with SAH abundant nerve distribution is seen in the vessels of the circle of Willis, especially near the bifurcation of the internal carotid artery, which is a frequent location of aneurysm. It is difficult to explain the pathogenesis of abnormal prolonged vasoconstriction as seen with late vasospasm by the function of nerve and muscle, but the results of this experiment show the importance of nerve action in the early stage of late vasospasm.

The existence of vascular nerves in intracranial arteries has already been confirmed by some methods. Reports emphasizing vascular nerves in the genesis of cerebral vasoconstriction are few. Bevan induced local vasoconstriction of the basilar artery by electrical stimulation and suspected that the differences in degree of vasoconstriction could be due to the differences in nerve

FIGURE 8. The effect of cervical sympathectomy on vasospasm: In 5 cats undergoing cervical sympathectomy 7 days before vasospasm induced by the blood and CSF mixture incubated for 7 days the vasospasm was lighter than non-treated cases.
distribution. Edvinsson reported the effect of sympathetic nerves on vasoconstriction. Peerless showed a decrease of catecholamine fluorescence in the sympathetic nerve terminals and an increase in the extraneuronal area in the vessels observed 3 days after subarachnoid hemorrhage. He also reported an increase of catecholamine fluorescence in the vessel wall following mechanical stimulation.

Rosenblum showed that the disappearance of catecholamine fluorescence after the subarachnoid hemorrhage could be the result of generalized stress of the operation. Our experiments indicated that there were no changes in the nerve terminals in cats undergoing mock operation or those where basilar arteries were subjected to fresh blood, lysed platelets in saline or mechanical stimulation. The changes in small core vessels, equivalent to the disappearance of catecholamine fluorescence, was observed only in the cats with vasospasm induced by the blood-CSF mixture incubated 5 to 10 days.

The participation of sympathetic nerves in the pathogenesis of late vasospasm has been believed to be inconsequential because the constrictive potential of basilar artery was not disturbed by bilateral superior cervical ganglionectomy. The perivasicular sympathetic nerves of the basilar artery originate chiefly from the superior cervical ganglia. The influence of the bilateral cervical sympathectomy observed in this experiment was definite and showed the importance of sympathetic nerves in the pathogenesis of late vasospasm.

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Effects of Hemorrhagic Hypotension on the Cerebral Circulation

I. Cerebral Blood Flow and Pial Arteriolar Caliber

ERIC T. MACKENZIE, PH.D., J. KEITH FARRAR, PH.D., WILLIAM FITCH, M.B., CH.B. PH.D., DAVID I. GRAHAM, M.B., CH.B. PH.D., PETER C. GREGORY, PH.D., AND A. MURRAY HARPER, M.D.

SUMMARY The relationship between local cerebral blood flow (measured by the hydrogen clearance technique) and stepwise reductions in mean arterial pressure was studied in 8 anesthetized cats. The relationship between pial arteriolar caliber and hypotension was studied in a further 5 cats. Hypotension was induced by graded hemorrhage. Autoregulation maintained a fairly constant cerebral blood flow over the arterial pressure range 60–120 mm Hg. At mean arterial pressures below 60 mm Hg, cerebral blood flow fell with decreasing arterial pressure. Pial arteriolar and arterial caliber increased as mean arterial pressure was decreased. In the smaller arterioles (<50 μm in diameter at a mean arterial pressure of 100 mm Hg), dilatation was maximal (average of 93%) in the arterial pressure range 30–39 mm Hg. The maximal dilatation was less (<50%) in the larger arterioles and small arteries (>50 μm in reference diameter), but occurred in the same arterial pressure range (30–39 mm Hg). Thus, the lower limit of cerebrovascular autoregulation (~65 mm Hg) occurred at a significantly higher pressure than that at which the pial vessels were maximally dilated (~35 mm Hg). Therefore, it would appear that the lower limit of autoregulation should not be equated with maximal pial vasodilatation, as it has tended to be in the past, but with the arterial pressure at which the cerebral dilatation responses can no longer compensate sufficiently for the decreasing perfusion pressure.

THE RELATIONSHIP between perfusion pressure and the cerebral circulation is of paramount importance in situations as diverse as hemorrhagic shock, deliberate hypotension during surgery, and raised intracranial pressure. This relationship is governed primarily by the phenomenon of autoregulation of cerebral blood flow, which may be defined as the intrinsic tendency of the brain to maintain a relatively constant blood flow in response to moderate variations in perfusion pressure (for review, see Lassen). The present communication relates changes in local cerebral blood flow and in pial arteriolar caliber to changes in mean arterial pressure induced by graded hemorrhagic hypotension. Such mechanisms and relationships have not previously been described systematically. In the accompanying communications, the vascular mechanisms will be related to changes in electrocortical function, and to the development of neuropathological changes in the cerebral parenchyma.
Experimental cerebral vasospasm after subarachnoid hemorrhage. Participation of adrenergic nerves in cerebral vessel wall.

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