Evidence that Neural Mechanisms Do Not Have Important Effects on Cerebral Blood Flow

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CEREBRAL blood flow may be regulated by four major factors: chemical stimuli (blood gases and extracellular fluid pH), autoregulation, metabolic factors, and neural stimuli. The first three factors are clearly important in control of cerebral vessels. In contrast, we propose that, despite many years of intensive study, there is no convincing evidence that neural control plays an important role in regulation of cerebral blood flow. Before accepting this conclusion, we must address three major questions, which will be the theme of this review.

First, why are cerebral vessels richly innervated if the innervation has no important function? In most vascular beds the density of adrenergic innervation correlates with responsiveness of vessels to neural stimuli. Because cerebral vessels are extensively innervated, one might expect important neural effects. If, however, the mechanism of neuromuscular transmission were unusual in cerebral vessels, the vessels might be relatively unresponsive to the neurotransmitter. There is good evidence that neuromuscular transmission is unusual and that cerebral vessels are relatively unresponsive to the adrenergic neurotransmitter, norepinephrine.

Second, if in fact neural stimuli do not have significant effects, why have numerous studies indicated important effects of neural stimuli on cerebral blood vessels? We suggest that, in the studies that have indicated important effects of neural stimuli on cerebral vessels, the methods for measuring cerebral blood flow and the experimental protocols have had serious limitations.

Third, could nerves have important cerebral vascular effects other than in regulation of blood flow? It is possible, for example, that nerves may affect capillary surface area without affecting blood flow significantly.

We suggest that nerves do not affect cerebral blood flow significantly under experimental conditions that have been examined to date. One might argue that, under other conditions, nerves may have important effects on cerebral blood flow. This argument cannot be refuted. In fact, one of the goals of this "controversy" is to stimulate further investigation which may identify conditions under which nerves have significant effects on cerebral blood vessels.

Our goal is to present the view that an important effect of nerves in the regulation of cerebral blood flow has not been proven. We are confident that the opposing view to be presented by Michael Purves, will provide the proper balance and perspective.

Innervation of Cerebral Vessels

Blood vessels in the brain are richly innervated by the sympathetic (adrenergic) nervous system. Sympathetic nerves to the cerebrum originate primarily in the ipsilateral superior cervical ganglion. Although the density of innervation appears to be greatest in large arteries, arteries as small as 15 μm in diameter receive adrenergic fibers. Although arteries on the surface of the brain also have cholinergic innervation, neither electron microscopy nor histochemistry has demonstrated cholinergic innervation in intraparenchymal cerebral vessels. Since a major portion of cerebral vascular resistance is accounted for by intraparenchymal vessels, the absence of innervation at this level must cast doubt on the functional significance of cholinergic innervation.

It has been proposed that a central noradrenergic (but nonsympathetic) pathway may originate in the medulla (primarily in the locus coeruleus), pass through brain parenchyma (in contrast to the perivascular course of sympathetic fibers), and innervate intracranial vessels. The pathway persists after removal of the superior cervical ganglion, which suggests a central origin of the system.

There is no doubt that this central pathway exists, but there is serious question whether the pathway innervates brain resistance vessels. A recent study suggests that the central pathway innervates brain capillaries. This interesting hypothesis needs to be confirmed.

It has been proposed that other central pathways may
affect cerebral vessels. The role of these other pathways also is controversial, but the evidence is preliminary and will not be considered in this paper.

Neuromuscular Mechanism: Studies of Isolated Cerebral Vessels

Can the dense sympathetic nerves on cerebral vessels release norepinephrine, activate α-receptors, and initiate physiologically important vasoconstriction? If so, one would expect to find that the vessels contract vigorously in response to transmural electrical stimulation and norepinephrine and that these contractions are blocked by α-adrenergic antagonists. However, recent studies suggest that the neuroeffector mechanism in cerebral vessels may be unconventional. These findings are important. They may help to resolve the paradox that cerebral vessels do not respond well to neural stimuli despite dense innervation.

α-Adrenergic receptors in cerebral arteries have several unusual characteristics. First, the receptors are relatively insensitive to norepinephrine. The basilar artery of the rabbit is about 1000 times less sensitive to norepinephrine than the saphenous artery. These same arteries are equally sensitive to serotonin. Second, the rabbit basilar artery exhibits little stereo-specificity (potency of d-norepinephrine is high relative to that of L-norepinephrine) and a very high dissociation constant for phenolamine. Third, isoproterenol can produce vasoconstriction which is mediated by α-adrenergic receptors, and phenolamine is a less potent vasoconstrictor agent than isoproterenol in cat middle cerebral artery.

These results suggest that the α-receptor in cerebral vessels is less discriminating and enormously less sensitive to agonists than the usual α-adrenergic receptor. These characteristics of the receptor would be expected to make cerebral arteries relatively insensitive to adrenergic neural stimuli.

It is possible that the responsiveness of cerebral arteries may be augmented under some circumstances. For example, histamine has been reported to potentiate α-adrenergic responsiveness of cerebral vessels. Thus, although cerebral vessels are remarkably insensitive to α-adrenergic stimuli, under some circumstances these stimuli may produce important responses.

If sympathetic nerves constrict cerebral arteries, one would expect that electrical stimulation of intramural nerves in isolated vessels would produce vigorous contraction which is blocked by α-adrenergic receptor antagonists. This is not the case. Transmural nerve stimulation produces much less constriction of isolated cerebral arteries than of saphenous arteries of rabbits. Responses to electrical stimulation of isolated basilar arteries in rabbits are abolished by chronic superior cervical ganglionectomy or guanethidine. This indicates that the vasoconstrictor response is mediated by sympathetic "adrenergic-like" neurons. Surprisingly, responses to electrical stimulation are not reduced by α-receptor antagonists, phenoxybenzamine and phenolamine, but, instead, are consistently augmented. The doses of α-blockers appear to be adequate, since they block constrictor responses to norepinephrine in cerebral vessels. The inability of α-blockers to block neurogenic responses in cerebral arteries might result from an unusually narrow neuromuscular cleft and inaccessibility of receptor sites to the blocking drugs. However, the cleft in the saphenous artery, in which responses to electrical stimulation are blocked by α-blockers, is narrower than the cleft in the basilar artery. This study raises the important question whether neuromuscular transmission in arteries of the brain is mediated by the conventional adrenergic receptor mechanism.

To summarize studies of isolated cerebral vessels, large cerebral arteries have dense adrenergic innervation, but they appear to have an unusual neuromuscular mechanism. The α-adrenergic receptor appears to be relatively insensitive and to have unusual characteristics. Responses to electrical stimulation suggest additional unconventional features in the neuroeffector mechanism. If these studies can be extrapolated to smaller cerebral vessels, they may provide an explanation for the minimal responses to sympathetic nerve stimulation in vivo. Preliminary observations suggest that small pial arteries (100 μm in diameter) as well as large arteries in the brain are relatively insensitive to norepinephrine and electrical stimulation.

Studies That Have Shown No Change in Blood Flow during Neural Stimuli

We will now examine results of in vivo studies that have attempted to determine whether neural stimuli affect cerebral blood flow. It is difficult to measure cerebral blood flow accurately, because there are numerous communications between intracranial and extracranial vessels. Because the question of methodology in measuring blood flow appears to be central to the controversy concerning neural control, we will review separately the results obtained with different methods.

The first of these involves the use of labeled microspheres. The microsphere technique has two fundamental advantages in measuring blood flow to the brain: (1) flow to the brain and to extracranial structures can be measured separately without ligating any vessels, and (2) flow to various regions of the brain (such as grey and white matter) can be measured repeatedly. Although the microsphere technique has not been compared with other techniques that have been used to measure cerebral blood flow, flow measurements obtained in other organs with the microsphere technique correlate well with results obtained by direct measurement.

Four basic assumptions must be satisfied before the microsphere method can be used to measure blood flow to an organ: (1) uniform mixing of the microspheres, (2) total extraction of the microspheres by the organ, (3) lack of adverse systemic or regional hemodynamic effects, and (4) absence of major distortion related to rheological properties of the microspheres. Studies in our laboratory have shown that, if 15-μm spheres are used, all of these assumptions are reasonably well satisfied for the brain. Thus, this technique seems to allow valid measurement of total and regional brain blood flow.

All of the studies that have used radioactive microspheres to measure cerebral blood flow have produced the...
same conclusion: neural effects are minimal, except during extreme hypertension. The results obtained with this technique are far more consistent than the results obtained with other techniques.

Several studies\textsuperscript{22-25} have indicated that sympathetic stimulation at normal levels of arterial pressure does not decrease total cerebral blood flow or redistribute flow within the brain (Table 1). The conclusions are strengthened by several aspects of the design of the studies: (1) Sympathetic pathways were stimulated on one side, so that responses could be compared in the stimulated and control hemibrain during the control period and during sympathetic stimulation. This approach should increase the sensitivity of the studies. (2) In our experiments,\textsuperscript{28} cerebral vessels constricted during hypocapnia; this indicates that the failure of the vessels to constrict during sympathetic stimulation was not the result of impairment of constrictor responses by the experimental preparation. (3) Sympathetic pathways were stimulated adequately in these studies, as manifested by ipsilateral pupillary dilation and vasoconstriction in ipsilateral cranial muscle.

We have observed that sympathetic denervation does not increase total or regional cerebral blood flow in anesthetized dogs over a wide range of arterial pressures or during hypocapnia.\textsuperscript{4} Our studies also indicate that physiological stimulation of carotid baroreceptors and chemoreceptors does not alter total blood flow to the brain or spinal cord or distribution of flow in the brain.\textsuperscript{28-30} Furthermore, denervation of carotid and aortic baroreceptors and chemoreceptors does not alter cerebral vascular responses to changes in arterial pressure or to hypoxia. The studies suggest that reflex stimuli do not have important effects on cerebral blood flow.

The only condition in which neural stimuli have been demonstrated to have appreciable effects on cerebral blood flow, as measured with microspheres, is severe hypertension. Bill and Linder\textsuperscript{29} reported that when mean arterial pressure in cats is acutely elevated to 170-310 mm Hg, sympathetic stimulation reduces blood flow in the ipsilateral hemibrain and protects the blood-brain barrier. In studies in dogs we have found that, when mean arterial pressure is raised to about 230 mm Hg, electrical stimulation of sympathetic pathways decreases blood flow to the ipsilateral cerebrum by 9\%.\textsuperscript{30} In additional studies on cats we have found greater responses to sympathetic stimulation during hypertension, since sympathetic stimulation reduced ipsilateral cerebral blood flow by 38\% when mean arterial pressure was about 210 mm Hg.\textsuperscript{30} These studies raise the possibility of a species difference in responses to sympathetic stimulation.

The physiological importance of these observations was not clear, since vasoconstrictor responses were observed only during intense electrical stimulation of the nerves.

### Table 1. Effect of Neural Stimulation on Cerebral Blood Flow, as Measured with Microspheres

<table>
<thead>
<tr>
<th>First author (ref. no.)</th>
<th>Species studied</th>
<th>Response</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alm (22)</td>
<td>Cat</td>
<td>No</td>
<td>No change during normo- or hypercapnia</td>
</tr>
<tr>
<td>Alm (23)</td>
<td>Monkey</td>
<td>No</td>
<td>One area (occipital gray) showed a 17% ↓ during stimulation; other areas showed no response</td>
</tr>
<tr>
<td>Meyer (24)</td>
<td>Dog and monkey</td>
<td>No</td>
<td>Stimulated distal to caudal cervical sympathetic ganglion</td>
</tr>
<tr>
<td>Authors (25)</td>
<td>Dog</td>
<td>No</td>
<td>No response during normo- or hypercapnia</td>
</tr>
</tbody>
</table>

**Electrical Stimulation of Cervical Sympathetic Nerves**

**Sympathetic Stimulation during Severe Hypertension**

| Bill (29)               | Cat             | Yes      | Electrical stimulation decreased flow during severe hypertension |
| Authors (30)            | Dog and cat     | Yes      | Responses to electrical stimulation were less in dog than cat; responses to physiological stimulation were modest and transient |

**Acute and Chronic Sympathetic Denervation**

| Authors (6)             | Dog             | No       | No change in response to alterations in Paco\textsubscript{2} or arterial pressure |

**Stimulation of Chemoreceptors and Baroreceptors**

| Authors (26–28)         | Dog and monkey  | No       | No response of cerebral or spinal cord vessels to chemoreceptor stimulation; no response to baroreceptor stimulation during normo- or hypercapnia |

**Denervation of Chemoreceptors and Baroreceptors**

| Authors (26, 27)        | Dog             | No       | No alteration in response to changes in Paco\textsubscript{2} |
during extreme hypertension. To determine the physiological significance of these findings, we observed responses in the barodenervated cat. Simultaneous barodenervation causes intense activation of sympathetic pathways and severe hypertension. We interrupted sympathetic pathways on one side and compared blood flow in the two hemispheres. At the peak of hypertension, mean arterial pressure was 230 mm Hg, but there was no difference in blood flow to the denervated and innervated hemisphere. Ten minutes later, blood flow to the denervated hemisphere was 17% greater than flow to the other hemisphere. Thirty minutes later, arterial pressure was normal and blood flow was similar on the two sides. This study indicates that, during severe hypertension, intense sympathetic activation of sympathetic pathways produces modest, transient cerebral vasocostriction, in contrast to marked, sustained vasocostriction in other vascular beds.

Rapela and coworkers' have measured cerebral blood flow by occluding both lateral sinuses to prevent communication between the intracranial and extracranial veins, collecting blood from the sagittal and straight sinuses and measuring cerebral venous blood outflow. These investigators have reported that the barodenervated cat. Simultaneous barodenervation causes intense activation of sympathetic pathways and severe hypertension. We interrupted sympathetic pathways on one side and compared blood flow in the two hemispheres. At the peak of hypertension, mean arterial pressure was 230 mm Hg, but there was no difference in blood flow to the denervated and innervated hemisphere. Ten minutes later, blood flow to the denervated hemisphere was 17% greater than flow to the other hemisphere. Thirty minutes later, arterial pressure was normal and blood flow was similar on the two sides. This study indicates that, during severe hypertension, intense sympathetic activation of sympathetic pathways produces modest, transient cerebral vasocostriction, in contrast to marked, sustained vasocostriction in other vascular beds.

Numerous studies have reported that neural stimuli affect cerebral vessels. In this section we will evaluate some of the limitations of measuring cerebral blood flow. One method for measuring cerebral blood flow is by determining the clearance of inert gases. We will first examine some of the limitations of measuring cerebral blood flow from the clearance of $\text{Xe}$ or $\text{Kr}$, after injection into the internal carotid artery, and then summarize the results that have been obtained.

These results suggest that measurements of internal carotid artery blood flow may have a significant component of flow to extracranial structures. Measurement of blood flow in the vertebral artery, which has numerous muscular branches, has similar limitations. Because extracranial structures are very responsive to neural stimuli, the responses to neural stimuli which have been observed in studies which have measured internal carotid or vertebral artery blood flow (and attributed to changes in brain blood flow) may be responses in extracranial structures.

Another method for measuring cerebral blood flow is by determining the clearance of inert gases. We will first examine some of the limitations of measuring cerebral blood flow from the clearance of $\text{Xe}$ or $\text{Kr}$, after injection into the internal carotid artery, and then summarize the results that have been obtained.

When neural stimuli alter the clearance of inert gases, it is assumed that the stimuli have altered cerebral blood flow. However, six factors in addition to cerebral blood flow may affect the value for blood flow which is calculated.
Table 2  Effect of Neural Stimulation on Cerebral Blood Flow, as Measured with Clearance of Inert Gases

<table>
<thead>
<tr>
<th>First author (ref. no.)</th>
<th>Species studied</th>
<th>Method of excluding flow to extracranial tissues</th>
<th>Response</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electrical Stimulation of Cervical Sympathetic Nerves</strong></td>
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<td></td>
</tr>
<tr>
<td>James (40)</td>
<td>Baboon</td>
<td>Lead shielding; ligate external carotid</td>
<td>Yes</td>
<td>Decreased cerebral blood (CBF) during normocapnia and hypercapnia</td>
</tr>
<tr>
<td>Harper (50)</td>
<td>Baboon</td>
<td>Ligate external carotid</td>
<td>1. No</td>
<td>1. Stimulation did not decrease CBF during normocapnia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Yes</td>
<td>2. Stimulation decreased CBF during hypercapnia</td>
</tr>
<tr>
<td>Kobayashi (51)</td>
<td>Cat</td>
<td>Craniectomy</td>
<td>Variable</td>
<td>Further statistical evaluation of results suggests small positive effect (ref. 59).</td>
</tr>
<tr>
<td><strong>Acute Denervation of Cervical Sympathetic Nerves</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>James (40)</td>
<td>Baboon</td>
<td>Lead shielding; ligate external carotid</td>
<td>Yes</td>
<td>Denervation increased CBF, especially at normal arterial pressure and during hypercapnia</td>
</tr>
<tr>
<td>Fitch (45)</td>
<td>Baboon</td>
<td>Scalp removal; ligate external carotid</td>
<td>1. No</td>
<td>1. Denervation did not increase CBF at normal arterial pressure</td>
</tr>
<tr>
<td>Harper (50)</td>
<td>Baboon</td>
<td>Ligate external carotid</td>
<td>1. No</td>
<td>1. Denervation did not increase CBF during normocapnia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. No</td>
<td>2. Denervation increased CBF 11% during hypercapnia</td>
</tr>
<tr>
<td><strong>Chronic Denervation of Cervical Sympathetic Nerves</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waltz (47)</td>
<td>Cat</td>
<td>Craniectomy</td>
<td>No</td>
<td>No alteration in response to changes in Paco2 or arterial pressure</td>
</tr>
<tr>
<td>Fitch (45)</td>
<td>Baboon</td>
<td>Scalp removal; ligate external carotid</td>
<td>No</td>
<td>No alteration in response to changes in arterial pressure</td>
</tr>
<tr>
<td>Eklof (46)</td>
<td>Monkey</td>
<td>Ligate external carotid</td>
<td>No</td>
<td>No alteration in response to changes in arterial pressure</td>
</tr>
<tr>
<td><strong>Stimulation of Carotid Chemoreceptors and Baroreceptors</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ponte (48)</td>
<td>Baboon</td>
<td>Scalp removal; lead shielding</td>
<td>Yes</td>
<td>Dilation of cerebral vessels during chemoreceptor stimulation and constriction during baroreceptor stimulation</td>
</tr>
<tr>
<td>James (49)</td>
<td>Dog</td>
<td>Craniectomy</td>
<td>Yes</td>
<td>Dilation of cerebral vessels during chemoreceptor stimulation and constriction during baroreceptor stimulation</td>
</tr>
<tr>
<td><strong>Denervation of Carotid Chemoreceptors and Baroreceptors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ponte (48)</td>
<td>Baboon</td>
<td>Scalp removal; lead shielding</td>
<td>Yes</td>
<td>Marked attenuation of responses to changes in Paco2, Pao2, and arterial pressure</td>
</tr>
<tr>
<td>James (49)</td>
<td>Dog</td>
<td>Craniectomy</td>
<td>Yes</td>
<td>Abolished response of cerebral vessels to stimulation of carotid chemoreceptors and baroreceptors</td>
</tr>
<tr>
<td>Eidelman (52)</td>
<td>Baboon</td>
<td>Ligate external carotid</td>
<td>1. Yes</td>
<td>1. Moderate attenuation of dilator response to ↑ in Paco2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. No</td>
<td>2. No alteration in response to changes in arterial pressure</td>
</tr>
<tr>
<td>Bates (53)</td>
<td>Cat</td>
<td>Scalp removal</td>
<td>No</td>
<td>No alteration in responses to changes in Paco2, Pao2, and arterial pressure</td>
</tr>
<tr>
<td><strong>Transection of 7th Cranial Nerve</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ponte (48)</td>
<td>Baboon</td>
<td>Scalp removal; lead shielding</td>
<td>Yes</td>
<td>Abolished response to hypoxia</td>
</tr>
<tr>
<td>Hoff (54)</td>
<td>Baboon</td>
<td>Scalp removal; lead shielding; ligate external carotid</td>
<td>No</td>
<td>No alteration in response to hypoxia</td>
</tr>
</tbody>
</table>

lated from the clearance of inert gases. First, when scalp and temporal muscle are not removed,40 the disappearance curve may reflect responses in these extracranial tissues.38 Second, capillary surface area affects the clearance of 133Xe after depot injection into skeletal muscle.41 We speculate that capillary surface area also may affect clearance from the brain, independently of blood flow. Third, blood flow is expressed per volume of distribution of the inert gas. Volume of distribution is not constant in the kidney29 and may not be constant in the brain. Fourth, partition coefficient is dependent on hematocrit,42 which may change during long, very invasive experiments. Fifth, diffusion bypass occurs at low rates of blood flow.43 Sixth, rate of injection of the inert gas affects the fast and slow components of the clearance curves. In theory, the gas should be delivered as a bolus,44 but in previous studies it...
has been injected in 1-3 seconds, 5-15 seconds, and 60 seconds, or the rate is not stated. We suggest that exaggeration of the first two factors by neural stimuli may have led to the conclusion that neural stimuli alter cerebral blood flow when, in fact, they have little effect, and that the last four factors may contribute to the variability of results that have been obtained with this method.

We should consider one other major problem with this method: the washout curve is multieponential. A fundamental assumption is that the curves are bimodal and that the fast and slow components correspond to gray and white matter blood flow, respectively. There are several findings that cast doubt on the validity of this assumption: First, although the number of exponential curves that can be derived from the washout curve is usually bimodal, the curves can be unimodal or they can have two rapid components and one slow component. In some species, such as the dog, two slow components may be present. After intracarotid injection of inert gases in man and baboons, multieponential curves are only rarely encountered. Second, blood flow is calculated as flow per volume of gray matter. Volume of gray matter is not actually measured, and when it is calculated from the clearance curves, it varies in the same animal. It should, of course, remain constant. Third, the estimate of volume of gray matter varies when isotopes with differing partition coefficients are used. Fourth, multieponential washout curves from the kidney have been analyzed in a similar fashion, and other techniques have suggested that the components do not reflect clearance from specific regions.

The results of investigations in which the inert gas clearance technique has been used to study neural control of the cerebral circulation are summarized in Table 2. Conflicting results have been reported with sympathetic stimulation and denervation and with reflex stimuli. Our view is that these conflicting results reflect the multiple determinants and limitations of the inert gas clearance method for measuring cerebral blood flow.

Cerebral blood flow also can be estimated by inserting heated probes into the brain and using a heat clearance technique. Sercombe et al. have reported that sympathetic stimulation or denervation produces profound changes in cerebral blood flow. The increase in blood flow with sympathetic denervation was much greater than the response to breathing 7% CO₂. It is likely that, despite histological evidence to the contrary, the thermal probes damage the tissue and disrupt the blood brain barrier, and that the technique as used is not valid. Many studies have shown that the cerebral vascular response to intra-arterial catecholamines is minimal, presumably because the blood-brain barrier prevents access to receptors. However, the thermal clearance technique suggests enormous responses to intravascular injections of catecholamines, probably because the blood-brain barrier is damaged.

Another explanation for the effects of neural stimuli on cerebral blood flow as measured by thermal clearance may be that the technique is influenced by variables in addition to blood flow, such as capillary surface area, and that neural stimuli may affect capillary surface area with little effect on total blood flow.

**Other Studies of Neural Stimuli in Vivo**

The measurement of pial artery diameter is the most direct method for measuring responses of cerebral vessels to neural stimuli. Studies that have used the pial window technique have demonstrated convincingly that stimulation of cervical sympathetic nerves constricts pial arteries. However, the magnitude of constriction is small. Wei et al. observed only a 7% decrease in diameter of large pial arteries and no change in diameter of small pial arteries during sympathetic stimulation. Kuschinsky and Wahl found a 12% decrease in diameter of large and small pial arteries. Our view is that the magnitude of this effect is small and, depending on the size of the arteries which constrict, may not be translated into a detectable change in blood flow. Observation of pial artery responses to stimulation of potential vasodilator pathways are few and difficult to interpret either because arterial pressure changed or because unilateral nerve stimulation produced bilateral responses.

**Studies on the Central Noradrenergic System**

An interesting hypothesis is that a central neural pathway, arising in the locus coeruleus and providing innervation to cerebral vessels, has important effects on small cerebral vessels. Stimulation of the locus coeruleus was reported to decrease cerebral blood flow and to increase capillary filtration; the latter change the authors attributed to an increase in capillary permeability. These observations must be considered preliminary because, although four monkeys were used for the study, only one monkey was studied during stimulation of the locus coeruleus.

**Summary, Speculation, and Recommendations for Future Studies**

Do sympathetic nerves affect cerebral blood flow? An important effect on flow is unlikely. Studies that have measured flow with microspheres have shown no effect except during extreme hypertension. Studies that have used monoclonal or microspheres have shown no effect, and studies that have used radioactive xenon have shown a decrease in flow rate. However, plethysmographic nerve fibers appear to be confined to large cerebral arteries and have not been demonstrated in small arteries. It seems unlikely that dilation of large arteries alone could account for large increases in blood flow. In support of this, studies that have used microspheres have shown no cerebral vascular response to reflex stimuli.

Could nerves affect cerebral vessels during some circumstances? This possibility cannot be denied. In the
presence of histamine or other endogenous substances, neural stimuli may have important effects.

Do nerves affect cerebral vessels without altering blood flow significantly? We are attracted to the possibility that neural stimuli may increase capillary surface area without increasing blood flow significantly. An increase in capillary surface area might account for increases in heat clearance and, possibly, cerebral blood volume after sympathetic denervation, and increases in capillary filtration during stimulation of central noradrenergic pathways. Could capillary surface area increase without a significant increase in blood flow? This could happen if essentially all of the resistance were provided by upstream vessels. If recruitment of capillaries occurs at a hierarchy of vessels that have a low pressure (i.e., they are downstream from the resistance vessels), capillary surface area could increase with a minimal change in resistance or blood flow. In skeletal muscle, vascular resistance and capillary surface area can respond differently to both pharmacological and neural stimuli. A similar phenomenon may occur in the brain.

We suggest that several approaches might be appropriate in attempting to resolve the question of neural control of cerebral vessels. Exploratory studies have been reported in relation to each of these approaches, and these studies should be extended:

1. Methods for measuring cerebral blood flow should be compared. A systematic evaluation and comparison of the various methods, during neural and non-neural stimuli, will clarify whether the conflicting results are produced by limitations in the methods or experimental protocols.

2. Experiments that examine parameters such as capillary filtration and cerebral blood volume may detect neural effects on cerebral vessels that are not detected by measuring blood flow.

3. It will be worthwhile to seek to uncover conditions under which vascular sensitivity may be increased. Although neural stimuli do not alter cerebral blood flow normally, it is possible that they have an important effect during ischemia, in disease states such as subarachnoid hemorrhage, or in the presence of histamine or other vasoactive substances. It is also possible that anesthesia may mask responses to neural stimuli. Furthermore, there may be species differences in cerebral vascular responses to neural stimuli.

4. Morphological and in vitro studies suggest that cholinergic and adrenergic nerves to cerebral vessels may interact. The physiological importance of this potential interaction needs clarification.

We conclude by suggesting that the evidence that nerves play an important role in control of cerebral blood flow is unconvincing. When responses to neural stimuli are observed, they are usually very small. It is likely that, if nerves actually have important effects on cerebral vessels, the effects are not manifested by physiologically significant change in blood flow.

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