Neurogenic Control of Cerebral Circulation

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Abstract: Neurogenic Control of Cerebral Circulation

A review of recent literature provides evidence that cerebral vessels are innervated with myelinated and nonmyelinated nerves. Among the latter, adrenergic nerves are readily demonstrated. Stimulation of cervical sympathetics produces a reduction in cerebral blood flow attributable to constriction of vessels in the neck and on the cerebral surface. In vitro experiments indicate that cerebral vessels possess a mechanism responsive to sympathomimetic agents. Evidence indicates that neurogenic influences can alter cerebrovascular diameter without necessarily playing a role in maintaining resting tone. Data are also available which suggest that neurogenic influences may modulate the response of cerebral vessels to other more potent stimuli. Cerebral vessels are less sensitive and less responsive to neurogenic influences than are vessels elsewhere. However, available data suggest that this characteristic of the cerebral vasculature reflects specialization of vascular muscle or of perivascular nerves, rather than a vestigial basis for the existence of these nerves.

ADDITIONAL KEY WORDS: nerves, arteries, veins, pial vessels, catecholamines, sympathetic nervous system, cholinergic nervous system, autonomic nervous system, norepinephrine, cerebral blood flow, brain stem, carbon dioxide, electron microscopy, fluorescence histochemistry.

One of the most troublesome questions concerning control of cerebral blood flow is whether or not cerebral vessels have a functional innervation. In the past this question arose in part because within the cranium the very existence of perivascular nerves was in doubt. When their existence was admitted, there remained a question as to whether they were branches of the somatic or of the autonomic nervous system. Moreover, even when the existence of perivascular autonomic nerves was admitted and autonomic nerves were stimulated, the response of cerebral vessels was small and difficult to reproduce. Similarly, the cerebral vasculature appeared to display only small and unreliable responses when exposed to substances normally released by perivascular nerves. The apparent paradox of a well-developed innervation but a small and unreliable vascular response to stimulation led some workers to believe that neurogenic control of cerebral blood flow is vestigial and without functional significance. In a previous review I have suggested that such a position was unwarranted. Six years have elapsed since that review, during which time new and pertinent studies have appeared. These newer data have established beyond doubt that portions of the cerebral vasculature have a rich adrenergic innervation. In addition, studies from several laboratories indicate that there is a functional adrenergic innervation to cerebral vessels, and also suggest that brain stem centers with unknown efferent pathways may exert a neurogenic influence on cerebral vessels. Some of the data seems to indicate that neurogenic stimuli may modulate vascular responses to other agents. Finally, negative experiments continue to appear, while some
workers, in spite of positive data, remain doubtful about the physiological significance of their own observations. The following review presents a selective summary of pertinent data appearing almost entirely during the last decade, and especially during the last six years. The author hopes that these data will lead others to the following conclusions: many cerebral vessels are innervated, including those under 160 micra in size; some cerebral vessels do possess a mechanism for responding to neurohumoral agents or neurogenic stimuli; the modulating effects of neurogenic influences are important areas for study.

**Morphology**

There is now no doubt that the major vessels supplying the brain, and many of the smaller branches on the cerebral surface (pial vessels), are supplied with a rich adrenergic innervation. This innervation is well demonstrated with a modern fluorescent histochemical technique for demonstrating norepinephrine, and the nerves have no features which would distinguish them from adrenergic nerves elsewhere in the body. The pial veins are not as well innervated as the arteries. However, pial arterioles as small as 15 microns O.D. may be innervated. Occasionally an adrenergic nerve may be seen on vessels which are actually within the brain, surrounded by the Virchow-Robin space; however, there may be regional differences with regard to the innervation of intracerebral vessels. Thus, Angelakos reports a significant innervation on vessels of the hypothalamus, although other workers have failed to make a similar observation. As is the case elsewhere in the body, the adrenergic nerves lie in the adventitia or at the medial adventitial junction rather than within the media. In addition to their perivascular distribution some adrenergic nerves have been observed to leave the pial vessels and to join the underlying molecular layer of the cerebral cortex.

Electron microscopy, in both human and animal vessels, has confirmed the presence of typical autonomic nerves on the cerebral vessels. These nerves display localized swellings containing dense vesicles which are thought to hold norepinephrine. Occasionally, these swellings are only separated from the vessels by a basement membrane. The gap between swelling and vessel wall is no smaller than 800 Angstroms, a gap similar to that seen in perivascular nerves elsewhere. Nerves were found on vessels as small as 20 microns.

The studies mentioned thus far pertain to primarily adrenergic nerves, although electron microscopic studies do not always permit one to distinguish these nerves from autonomic nerves utilizing some other transmitter. Techniques are available for differentiating cholinergic from adrenergic innervation, but only three reports concerning cholinergic innervation are known to me. The latter suggest that autonomic nonmyelinated cholinergic nerves are present on vessels. Myelinated nerves have also been reported, at least on the larger intracranial vessels, but there is little recent work concerning their origin or function.

**Responses to Neurotransmitters In Vitro**

Much of the argument concerning the importance of neurogenic stimuli has centered around the failure of certain workers to influence cerebral circulation by nerve stimulation or by application of neurotransmitters in an intact animal. Additional skepticism is engendered when different investigators obtain opposite effects in such experiments. Those workers who would deny the importance of neurogenic stimuli apparently prefer to believe that positive results are artifacts of the experimental situation, caused by variables not controlled by the investigators. In order to resolve this question it would seem advisable to test the response of cerebral vessels to neurotransmitters, after the vessels are removed from the brain or the brain removed from the body. Positive results of in vitro experiments cannot be ascribed to uncontrolled responses of the whole animal, or to responses of vessels in the neck, etc. Moreover, the demonstration of a dose-response curve in vitro can scarcely be dismissed as artifactual. Hence, in vitro data can provide us with evidence that cerebral vessels at least possess a contractile machinery which can be activated by neurotransmitters.

In vitro investigations have demonstrated that cerebral vessels constrict when exposed to serotonin and norepinephrine. Dose response curves have been obtained and responses have been inhibited by specific...
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blocking agents. Vessels as small as 60 μ O.D. have responded to these agents. Smaller vessels do not appear to have been studied in vitro. A dose-response curve to tyramine has also been demonstrated. This is of particular interest since the response to tyramine is largely due to release of norepinephrine from perivascular nerves. Thus the experiments with tyramine indicate that these nerves contain sufficient norepinephrine to produce a contractile response of at least some cerebral vessels. Moreover, responses to tyramine were larger than responses to norepinephrine itself. The authors make the interesting suggestion that exogenous norepinephrine may be rapidly bound to the nerves before much of it can reach the vessel. If this were so, and if norepinephrine were more avidly bound by these perivascular nerves than by perivascular nerves elsewhere in the body, this could account for the comparatively high threshold of the cerebral vascular response to norepinephrine. Such failures might be due to insufficient concentrations of the drug, or to some variable in the preparation of the vessel. In this regard it is of interest that when spiral strips of cerebral vessels were used, norepinephrine had no effect, while in the same laboratory the intact vessel constricted after application of norepinephrine. Another factor of importance may be the size of the vessel being observed. In the study with spiral strips vessels 200 to 300 μ O.D. were employed, while smaller vessels were observed when intact vessels were studied. Even in the latter investigation many vessels failed to respond. Vessels ranged from 50 to 250 μ O.D. One would like to know whether unreactive vessels tended to be of a certain size within this range. In extracerebral vascular beds, it is well known that smaller arterioles are more sensitive than larger ones to a variety of stimuli. It would also be of interest to know whether responsive vessels had perivascular nerves, and whether these had inadvertently detached from the unresponsive vessels during their preparation. Such data might be obtainable by applying the histochemical technique for adrenergic nerves after the experiment was terminated. In this connection workers have not been precise enough in specifying whether the vessels isolated from the brain were always pial vessels from the subarachnoid space where innervation is rich, or whether some or all of the vessels utilized were actually pulled out of the Virchow-Robin spaces within the brain itself, where innervation is sparse.

Responses to Neurotransmitters In Vivo

As in earlier years, a number of investigators continue to demonstrate a diminution of cerebral blood flow after intravenous injection of norepinephrine. Haggendal demonstrated that norepinephrine decreased gray matter flow in dogs. Norepinephrine will also increase blood pressure, but the accompanying increase in cerebrovascular resistance (CVR) could not have been due merely to autoregulatory responses since blood flow declined rather than remaining constant. Moreover, CVR increased even when blood pressure was held constant, or made to fall by controlled bleeding. These data are consistent with the in vitro results cited above, and indicate that cerebral vessels will constrict when exposed to a neurotransmitter. In the same experiments, metaraminol, a norepinephrine analog, also reduced gray matter flow, but less so than norepinephrine, a result in keeping with the concept that cerebrovascular smooth muscle is adopted to be most responsive to naturally occurring, vasoactive neurotransmitters. Similar data have been presented for man in that norepinephrine and epinephrine both have been shown to diminish total cerebral blood flow (CBF) and increase CVR after intravenous injection. Again, since CBF fell, the increased CVR cannot be ascribed merely to autoregulation but must represent an effect of catecholamines on cerebral vessels. Norepinephrine by itself will produce hyperventilation, and the resultant fall in CO₂ may cause cerebral vasocostriction; however, in Haggendal's canine experiments CO₂ was maintained between 30 and 50 torr, and norepinephrine increased CVR and reduced cortical blood flow even during slight hypercapnia.

Using different techniques for measuring flow and utilizing both intra-arterial and intravenous norepinephrine, other workers have not demonstrated decreased flow or increased CVR unless blood pressure was increased or CO₂ fell. However, in their...
studies flow was measured by a flowmeter placed on the internal carotid artery of patients who had previously undergone surgery for brain tumors within three weeks of the flow measurement. It would appear reasonable to suggest that cerebral hemodynamics and vascular responses may have been abnormal in such subjects. Moreover, once pressure rose and CO₂ fell, an increased CVR and decreased flow were observed. The authors assume that these changes were caused solely by the changes in pressure and CO₂ rather than by a direct action of norepinephrine on the vessels, but this remains to be proved in view of the contrary conclusion reached by Haggendal in experiments where these variables were controlled.

Using a flowmeter technique for measuring flow through the internal carotid, Meyer et al. observed data which totally contradict all the findings mentioned thus far. Meyer et al. found that norepinephrine and epinephrine each caused a sharp increase in flow. These results would appear to be explained best by assuming that flow was passively following pressure in animals with impaired autoregulation.

Rosendorff and Cranston have presented data which partially contradict the conclusion that norepinephrine decreases flow by causing vasoconstriction. These workers injected norepinephrine and also serotonin directly into the hypothalamus, and observed the effect on clearance of xenon also injected directly into that structure. Norepinephrine decreased hypothalamic blood flow only at higher doses, having an opposite effect at lower concentrations. The adrenergic blocking agent, phenoxybenzamine, prevented the constrictor effect, suggesting that a specific adrenergic constrictor mechanism was involved. Conscious rabbits were used and changes in BP or CO₂ levels could not account for the results. These experiments appear to contradict in vitro work cited earlier, which showed that serotonin constricted cerebral vessels of the rabbit and cat. However, Rosendorff and Cranston do not appear to have considered the possibility that in their experiments changes in hypothalamic flow were secondary to metabolic changes produced by injecting neurohormonal agents into the tissue.

The studies described above dealt with the effects of neurotransmitters on cerebral blood flow in vivo. In such studies, changes in diameter are inferred from changes in resistance, and the latter is calculated from measurements of flow and pressure. Although techniques are now available for measuring pressure in resistance vessels, this has rarely been done in the brain and never in connection with flow measurements in the same vessels. Thus calculations of resistance and conclusions about diameter changes are based on a pressure measurement made proximal to the resistance vessels. Such conclusions are really approximations since they are based on implicit assumptions concerning a one-to-one relationship between proximal pressures and pressures within the smaller vessels of the cerebral vasculature. Therefore, in addition to flow measurements, direct observations of diameter are also of great value. These observations can be made on the surface of the brain (pial vessels including large vessels entering or leaving the circle of Willis); however, such observations include those vessels responsible for a significant part of the pressure drop in the cerebral vasculature. The literature concerning diameter changes in response to neurohumoral agents was reviewed extensively in 1965. Since then, Kapp et al. have reported minute (4% to 7%) but definite constriction of the basilar artery to both epinephrine and norepinephrine in physiological concentrations. In addition, they found that serotonin produced much greater constriction (16% to 31%) of the basilar artery. In spite of the small response to catechols, these changes should not be dismissed as insignificant, since they would result in marked decrease in flow if they occurred over a large number of resistance vessels.

Other workers have shown no effect of norepinephrine on pial vascular diameter. Such failures may possibly be explained by rapid inactivation of norepinephrine or by avid uptake of norepinephrine by perivascular nerves. The latter possibility has been discussed earlier in this review.

Another study of drug effects on vascular diameter concerns possible cholinergic innervation of pial vessels, a subject of which there has been almost no investigation. In the latter study, atropine and other postganglionic cholinergic blocking agents inhibited the autoregulatory response of pial arterioles to changes in blood pressure. Blocking agents
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were effective when locally applied to the vessels as well as when given intravenously. The authors state that only autoregulatory vasodilatation was impaired, but their data indicate some impairment of constriction as well. Adrenergic blocking agents failed to interfere with autoregulation. The authors concluded that autoregulatory vasodilatation was mediated by cholinergic nerves to the vessels.

Effect of Nerve Stimulation or Nerve Section on Cerebral Vasculature

The effects of sympathetic stimulation have recently been reinvestigated by several workers. Meyer et al. utilized electromagnetic flowmeters in monkeys and reported a 30% decrease in flow through the internal carotid artery after sympathetic stimulation. Approximately half of the flow reduction could be attributed to constriction of the vessels in the neck, while half could be ascribed to constriction of the branches of the cerebral arteries on the surface of the brain or within the brain. The authors were careful to rule out constriction in the distribution of the external carotid as an explanation for their data. They also recalled that earlier workers described a greater sensitivity of vessels in the carotid distribution as compared with the vertebral distribution to the brain. In their own study Meyer et al. found that sympathetic stimulation did, indeed, have a lesser effect on flow through the vertebral artery. When the carotids were occluded, forcing the vertebrals to supply the entire brain, sympathetic stimulation had a much greater effect on vertebral flow, again indicating that stimulation was constricting smaller vessels in the distribution of the internal carotids. These decrements in flow could not be ascribed to blood pressure changes since pressure was almost always slightly elevated by sympathetic stimulation. Moreover, decrements in CO₂ could not account for the decrements in flow since the animals were artificially respired at a constant rate. Also, inhalation of 5% CO₂ did not alter the response to sympathetic stimulation. Finally, in this important study, the authors point out that, due to Poiseuille’s law, a mere 8% constriction would (if uniformly occurring throughout the system) account for a 30% fall in flow. Actually, only a 4% constriction would be needed to account for the 15% fall in flow which they could ascribe solely to constriction of vessels within the skull. It is of interest that Kapp et al., as indicated earlier in this review, observed a 4% to 7% constriction of the basilar artery produced by local application of sympathomimetic agents.

The preceding data were gathered on monkeys. Recent data from the cat also indicate that sympathetic stimulation decreases CBF and constricts cerebral arterioles. In these experiments by Kobayashi, Waltz and Rhoton, cortical blood flow was measured by recording clearance of beta activity from krypton 85. Sympathetic stimulation reduced flow ipsilaterally on 10 out of 13 occasions in nine animals. A confusing element was a decrement in flow on the contralateral side as well on ten occasions. However, because of the large variation between values determined with the krypton technique on successive measurements in the same animal, the authors consider changes significant only if they exceed 15%. By this criterion all of the ipsilateral decrements were significant, while only three of the ten contralateral decrements were significant.

The authors concluded that there was significant bilaterality of response, but only in a few animals, and they suggest that some cats may have contralateral as well as ipsilateral innervation from the same sympathetic trunk. In our opinion the interpretation of these data would benefit from a statistical analysis not provided by the authors. If changes of less than 15% on the contralateral side were due merely to random variations in blood flow or variability in the method of measurement, these small changes would be randomly distributed, in both an upward and a downward direction. Instead all the small changes are decrements in flow, and this is a significantly nonrandom distribution (p < 0.01 Sign test). Moreover, if paired t tests had been performed they would show that a significant decrement in flow appeared on the contralateral side as well as on the ipsilateral side (p = 0.01). Therefore, one cannot assume that small decrements in flow on the contralateral side were unrelated to the experimental manipulations, and since bilaterality of innervation in most animals is an hypothesis without proof, one must wonder whether the decrements in flow on the contralateral side were related at all to
neurogenic stimulation of cerebral vessels. Moreover, if such a doubt is cast on the contralateral observations, such a doubt must logically extend to the ipsilateral observations even though the decrements in flow were much larger on the ipsilateral side. Fortunately, in this study pial vessels were also observed, and observations of their diameter in ten animals indicated vasoconstriction on the ipsilateral side in nine of 15 experiments, but on the contralateral side in only two of 15 experiments. Again statistical analysis was not performed by the investigators. The Fisher test of exact probabilities shows that the incidence of ipsilateral constriction significantly exceeds the incidence of contralateral constriction (p = 0.05 two-tailed test). Consequently the evidence indicates not only a larger decrease in flow on the ipsilateral side (p = 0.05 Median test, one-tailed), but also a significantly greater incidence of vasoconstriction of small arteries on that side. These data cannot be explained on the basis of changes in CO₂ or blood pressure, since animals exhibiting such changes were eliminated from the study. Nor can the results be interpreted on the basis of nonspecific vasoconstriction of neck vessels occurring during the course of experimental manipulations of the animals. Such a suggestion was made by Kobayashi et al. in a footnote to their paper. But constriction of neck vessels would not lead to constriction of pial vessels; rather, dilatation of pial vessels would be expected due to autoregulation. Moreover, both hemispheres were exposed at surgery, and if autoregulation were impaired we have no reason to presume that it would be impaired to a much greater extent over the hemisphere ipsilateral to the stimulated nerve. In short, the data of Kobayashi, Waltz and Rhoton support the data of Meyer et al. in indicating that sympathetic stimulation diminishes cerebral blood flow by producing a constriction of smaller cerebral vessels. The small effect on the contralateral side remains unexplained, but a minor degree of bilateral innervation is further supported by the work of Yamaguchi and Waltz. Cerebral blood flow in cats was investigated by measuring clearance of labeled antipyrine with an autoradiographical technique. One sympathetic nerve was stimulated and flow on the stimulated side was compared with flow on the contralateral side. The authors state that meaningful decreases of CBF occurred after stimulation in seven regions in five animals. In addition, they state that following stimulation regional CBF values were, with rare exceptions, less on the ipsilateral side than on the contralateral side. The means of the values from the different regions were lower on the side of stimulation, but the difference was not statistically significant "because of the small number of animals." The authors point out that there appeared to be regional differences in the response to sympathetic stimulation, and express doubt that these differences could be brought about by nonspecific constriction of neck vessels.

It appears to this reviewer that greater statistical evidence for an effect of sympathetic stimulation could be obtained from the data of Yamaguchi and Waltz. For example, six out of seven animals showed an ipsilateral decrement in white matter flow after sympathetic stimulation. The other animal showed no change. These data are significant at the 0.03 level (Sign test). Seven out of seven animals showed an ipsilateral decrement in flow through at least two of the three cortical regions which were monitored. This result is significant at the 0.02 level (Sign test or Wilcoxon test). It seems clear then that a statistically significant decrease in flow occurred after sympathetic stimulation.

In still another recent paper cervical stimulation is reported to constrict the "larger intracerebral arteries." In this study the smaller vessels were not observed so an effect on them certainly cannot be eliminated. Therefore, it seems unnecessary for the authors of this particular paper to state that "in spite of the last observation, we have not been able to (convince ourselves) that the cerebral arterioles are under neurogenic control (in) our experiments." In reality, their data are perfectly consonant with those of the other recent publications showing an effect of sympathetic stimulation on cerebral vessels.

In addition to the data concerning stimulation of the sympathetics, a recent publication also presents data concerning the effect of interrupting the sympathetics. Waltz et al. extinguished the sympathetic ganglion in the cat and observed no consistent effect on cortical blood flow. As pointed out in an earlier review, failure of sympathectomy or sympathetic blockade to influence cerebral blood flow has been a major factor leading to the refusal
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of workers to believe that neurogenic influences play a physiological role in the control of the cerebral circulation. However, such negative data pertain only to the sympathetic nervous system. Moreover, the data merely indicate that sympathetic impulses play no role in maintaining the basal tone of cerebral vessels. Such data do not rule out an effect of the sympathetic nervous system on the vessels, such that stimulation of the nerves or an increase in nerve "traffic" results in vasoconstriction. Such an effect appears well demonstrated by the in vivo studies cited above, and by the in vitro studies cited earlier in the present review.

It should be pointed out that in recent and earlier studies the response of cerebral vessels to sympathetic stimuli is considerably smaller than the response of vessels in the distribution of the external carotid or elsewhere in the body. This difference in sensitivity or responsiveness is mirrored by the high threshold and small responses of cerebral vessels to neurohumoral agents, as described elsewhere in this review. Consequently, although many studies in the literature demonstrate an effect of sympathetic stimulation or sympathomimetic drugs, the cerebrovascular bed may still be distinguished from other vascular beds on the basis of the magnitude to its response or its sensitivity to these stimuli.

With respect to the magnitude of response, decreases in flow of 10% to 30% have been shown. These certainly cannot be dismissed as functionally insignificant. Some workers, in questioning the physiological significance of such experiments, have emphasized the unphysiological means required to stimulate the nerves. However, these may not really be the critical parameters. The important parameter would be current (amps) delivered to the nerve, and this depends on the resistance of the electrodes and of the surrounding tissues. High resistance could reduce large voltages to physiological currents. Data are not available concerning the actual current arriving at axons or ganglion cells in these experiments. Moreover, the means by which the investigator activates the nervous system is really not the important issue. What is important is whether there is impulse "traffic" in the perivascular nerves of the normal animal. The ideal experiment would monitor this traffic and regional or hemispheric flow in ambulatory animals.

With respect to measurements of vascular diameter, we have noted negative as well as positive reports concerning a vasoconstrictor influence of sympathetic stimuli or sympathomimetic drugs. As pointed out by Meyer et al., diameter changes of 4% to 8% could lead to flow changes of 15% to 40%. Such small changes in diameter could readily be overlooked or obscured by large standard errors of measurement. This is particularly true when macrophotography is used to measure these changes. Even with the compound microscope and higher power objectives it is exceedingly difficult to reliably detect changes of 2 micra or less (4% change in 50-micron vessel). Consequently, failure to observe vasoconstriction cannot really be taken as hard evidence against constriction of the small size required to produce the flow changes observed after sympathetic stimulation, or after treatment with sympathomimetic drugs.

Effect of Neurogenic Stimuli on the Reaction of Vessels to Other Agents

In the preceding section we have pointed out that neurogenic impulses might constrict vessels or alter resting tone without playing a role in maintaining resting tone. But in addition to directly altering the diameter or resting tone, stimuli of any kind may also interfere with, or increase the effects of, other stimuli. We wish to refer to this sort of interaction as a modulating effect, and to point out that there is recent evidence suggesting that neurogenic stimuli have modulating action.

Among the few papers in the literature dealing with cholinergic control of cerebral vessels, one recent study reports that postganglionic cholinergic blocking agents prevent autoregulatory vasodilatation in rabbits. With respect to the more commonly investigated sympathetic nervous system, Kobayashi, Waltz and Rhoton have reported that stimulation of the cervical sympathetic trunk in cats interferes with the response to CO₂. On eight occasions in six animals a change in CO₂ level resulted in only a negligible or an inappropriate change in cortical blood flow in the hemisphere ipsilateral to the stimulated nerve, while on the contralateral side flow changed greatly, or in the appropriate direction. Since ordinarily changes in CO₂ level produce large and reliable changes
in CBF, it is of great interest that a much weaker and unreliable stimulus could alter the response to CO₂. However, the validity of these results is somewhat clouded by a lack of reproducibility in these animals. Moreover, in five experiments on four additional cats, alterations in CO₂ resulted in appropriate changes in cortical flow on the side ipsilateral to sympathetic stimulation, and in some of these cases the ipsilateral hemisphere showed an even greater response than the contralateral. Because these features of their data make it difficult to interpret the observations of Kobayashi et al., confirmatory data should be sought. In this regard it is of interest that Meyer et al. were able to overcome the potent effects of CO₂ with the “weaker” sympathetic stimulus. They increased CO₂ and while CBF was rising they stimulated the sympathetics. This produced an abrupt fall in CBF, and the percentage decrement was identical to that observed after sympathetic stimulation during normocapnia. More recently, Harper et al. found that stimulation of the cervical sympathetics reduced the response of CBF to increments of CO₂. They preferred to interpret these results as being secondary to constriction of “major cerebral arteries,” rather than to a direct interference by sympathetic stimuli with the response to CO₂. Presumably they meant that by narrowing the large vessels, sympathetic stimulation limited the amount of blood entering the brain and hence diminished the increased flow produced by CO₂, an arteriolar dilator. However, Harper et al. do not report actually observing the pial vessels to determine whether or not dilatation was, in fact, unimpaired. Consequently, their data as they stand must be considered at least compatible with the observations of Kobayashi et al. and of Meyer et al., which indicate that sympathetic stimulation inhibits the response to CO₂.

One additional point should be raised concerning the localization of the response to CO₂, and the response to postulated neurogenic stimuli. Raper et al. have presented evidence to show that arterioles smaller than 50 µ are more sensitive to CO₂ than are the larger arterioles. On the other hand, the number of adrenergic nerves diminishes in the distal portion of the vascular tree. Thus, there is a real question as to whether adrenergic stimuli can exert a direct and potent influence on the sites which normally respond to CO₂. In order to investigate this question fully, the smaller arterioles should be directly observed during the experiments. Unfortunately, as pointed out earlier, many investigators use a so-called “operating microscope” which is not adapted to observation of diameter changes in vessels narrower than 50 µ. Moreover, with such a microscope accurate determination of diameter changes even in larger arterioles is difficult where such changes are less than 20 µ in magnitude. On the other hand, in larger mammals, the surface of the brain pulsates greatly unless the craniotomy is sealed with a window, and these pulsatile movements prevent observation with an ordinary microscope because of the relatively shallow depth of focus provided by the latter. Two solutions are available to this technological problem. Both employ a microscope designed for use with reflected light at higher magnifications and with greater resolution than the “operating microscope” can provide. The preferred microscope may then be used with an airtight window over the craniotomy, or with a very small mammal such as the mouse, where the pulsations of the exposed brain are not of sufficient magnitude to interfere with observations at moderately high magnifications.

General Summary

It is now clear that the large vessels supplying the brain are innervated and that this innervation is continued on the smaller pial arterioles, and apparently on the pial venules as well. Many of these nerves are now proved to be adrenergic. What proportion of them may be cholinergic, or somatic sensory rather than autonomic, remains to be elucidated. The existence of adrenergic nerves connecting pial vessels with the molecular layer of the cortex has also been reported. The existence of these nerves requires confirmation, and their functional significance demands further elucidation. In general, a very small number of arterioles within the brain parenchyma (Virchow-Robin space) are also innervated with adrenergic nerves. Whether more of these vessels are innervated by nerves other than adrenergic remains to be seen. Some regions of the brain may be exceptions to the general rule, and may contain larger numbers of innervated vessels. Chief among these exceptional regions may be the hypothalamus.
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Functional studies of the cholinergic innervation are extremely sparse. Flow studies indicate that sympathetic stimulation may diminish cerebral flow by up to 40%. Some portion of this diminution may be caused solely by constriction of neck vessels. However, the data indicate that another portion of the diminution in flow is due to constriction of vessels at the circle of Willis or beyond. Studies of vascular diameter indicate that small arterioles on the surface of the brain certainly can participate in the adrenergic response. In vitro experiments and in vivo studies also indicate that cerebral vessels have a contractile mechanism responsive to sympathomimetic drugs. A serious flaw in some studies is the failure to observe these vessels during the experiment. Moreover, the optical system most commonly used when the diameter of pial vessels is measured makes it difficult to observe changes of less than 10%. Yet such small changes are all that would be necessary to account for the moderate flow changes mentioned above. Small changes in diameter would therefore be physiologically “significant.” It should also be pointed out that the relative contribution of large and small vessels to the neurogenic response is not as important as the recognition that neurogenic stimuli can alter cerebral blood flow. What remains to be established is whether the body makes use of neurogenic pathways to help control cerebral artery flow, either during normal homeostatic reactions or during pathological states.

If the body does not utilize the nervous system to control cerebral blood flow, then the morphological pathways which do exist, and the contractile machinery which can respond to neurohumors and to neurogenic stimuli, may indeed be vestigial. The latter hypothesis is compatible with the fact that neurogenic stimuli and neurohumoral agents elicit cerebrovascular responses with greater difficulty than they elicit extracerebral responses. The “vestigial theory” is also compatible with the small size of the cerebrovascular response, in comparison with the size of extracerebral vascular responses. However, the higher threshold and smaller response of cerebral vessels seems better explained by an hypothesis which suggests that these vessels and/or their nerve supply are specially adapted to their particular location and to the needs of the brain. Data are now available which do point to specialized mechanisms that would limit neurogenic responses of cerebral vessels. Thus, cerebrovascular nerves may bind norepinephrine with a greater avidity than perivascular nerves elsewhere, and in this way increase the amount of drug or the size of the sympathetic discharge required to produce a given response. In short, specialization need not be synonymous with atrophy. The capacity to respond, albeit in a relatively modest manner, may still be of vital importance. Only if such a viewpoint is maintained will the search continue for those conditions, in either health or disease, where neurogenic response may play a vital role.

Finally, neurogenic stimuli may be capable of eliciting responses other than simple contraction or dilatation. They may also modulate or modify the effects of other vasoactive stimuli, which normally elicit large cerebrovascular responses. Evidence has been presented which suggests that such modulating effects do exist, perhaps originating from brain stem centers. If this is correct, then the importance of neurogenic influences cannot be measured simply in terms of the threshold or size of the direct response to such stimuli but must also be evaluated in terms of the degree to which other responses (e.g., responses to CO₂ or to changes in blood pressure) have been influenced.

Acknowledgment
The author wishes to thank Arthur Waltz, M.D., for encouragement in the preparation of this review, and for supplying copies of manuscripts still in press.

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