The Relevance of Peripheral Baroreceptors and Chemoreceptors to Regulation of Cerebral Blood Flow in the Cat

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SUMMARY The contribution of neural vasomotor reflexes to the control of cerebral blood flow (CBF) was investigated in 30 cats lightly anesthetized with pentobarbital. CBF was measured both by kinetic analysis and by the initial slope technique of the washout curve of a bolus of $^{133}$Xe. Autoregulation (18 cats) and responsiveness to alteration in arterial PCO$_2$ (Paco$_2$) (10 cats) and arterial Po$_2$ (Pao$_2$) (five cats) were assessed both before and after bilateral intracranial division of the 9th and 10th nerves. In an additional group (five cats), related changes in CBF to alteration of Paco$_2$ were recorded before and after unilateral section of the 7th and 8th nerves. Autoregulation was preserved after division of the 9th and 10th nerves and there was no significant change in the Paco$_2$ response curves. Section of the 7th and 8th cranial nerves did not produce conclusive results in the small number of cats studied. A conclusion that the facial nerves are not dominant in responses to hypercapnia seems justified, but a modulating role for these nerves is possible. These studies do not exclude a physiological role for these nerves in the autoregulation of CBF, but do indicate that the cerebral vascular bed apparently is capable of functioning normally after their division.

THERE IS considerable evidence that both the intraparenchymal and extraparenchymal cerebral blood vessels are supplied with adrenergic and cholinergic nerve fibers. Although not universally confirmed, it is accepted widely that cerebral vasoconstriction and vasodilation may be accomplished by electrical stimulation of the cervical sympathetic and facial nerve parasympathetic fibers, respectively. However, the importance of this neurogenic mechanism in the physiological control of cerebral blood flow (CBF) is unknown. It has been stated that, since nerve stimulation accomplishes only minor changes in vessel caliber and blood flow, the neural contribution to CBF regulation cannot be great. Conversely, the recent work of James et al. and Ponte and Purves has suggested that a neurogenic reflex with an afferent limb from the carotid baroreceptors and chemoreceptors and an efferent limb in the autonomic supply to the cerebral vessels exerts considerable control over CBF. It also has been suggested that disturbance of such neural control might be of importance in ischemic areas of brain and after subarachnoid hemorrhage.

Thus, the main problem is not whether the cerebral vessels are innervated or whether, by artificial stimulation, this innervation can dilate or constrict the vessels, but whether this phenomenon has any physiological or pathological role. The purpose of this study was to establish the role of such reflex control in response to physiological stimuli. This was achieved by assessing the response of the cerebral vessels to a variety of stimuli before and after destruction of the afferent limb of the proposed reflex arc and by observing the effect of section of the proposed parasympathetic efferent limb.

Much of the criticism of earlier studies has been directed at the trauma to cervical vessels incurred in surgery and the failure to achieve and confirm complete deafferentation of the brainstem vasomotor center. We therefore have used a technique involving a minimum of cervical surgery. Complete section of the fibers from the peripheral baroreceptors and chemoreceptors has been ensured by dividing the vagus and glossopharyngeal nerves at the level of the jugular foramen. In addition, we have studied the effect of division of the efferent parasympathetic fibers in the facial nerve on the reactivity of cerebral vessels.

Methods PREPARATION OF THE CATS

Thirty cats of either sex and weighing between 2.5 and 3.5 kg were used. They were anesthetized lightly with sodium pentobarbital, 20 mg/kg, intraperitoneally. Catheters were inserted into the right femoral artery and vein for monitoring blood pressure, sampling arterial blood gas, and administering drugs. A tracheostomy was performed and a PE 50 cannula was inserted into the left lingual artery so that its tip lay in the carotid artery. The skin, subcutaneous tissue, and muscle were excised bilaterally from the skull to the level of the zygoma.

Through a muscle-splitting incision in the posterior cervical muscles, the occiput and the first cervical vertebra were exposed. The atlantoccipital membrane was incised and a small craniotomy was performed in the occiput, enlarging the foramen magnum. The dura then was opened by a cruciate incision and tacked laterally to ensure a bloodless field. With the aid of an operating microscope (magnification = 10x), the vagus and glossopharyngeal nerves were identified and isolated as they passed through the jugular foramen (foramen lacerum posterior). In later
experiments the left facial and auditory nerves were identified at the internal auditory meatus. In all experiments, the isolation of the nerves was performed before measurement of control blood flows and their section was accomplished during the experiment without further dissection.

Blood loss during the preparation was minimal. The posterior craniotomy site remained open so that any blood that might accumulate in the posterior fossa drained away.

After surgery, the cat was paralyzed with d-tubocurarine (5 mg/kg of body wt) and ventilated with a mixture of oxygen, nitrogen, and carbon dioxide. Blood pressure was recorded constantly by a strain gauge transducer in the femoral artery catheter, and core temperature was monitored by a rectal thermometer and maintained at 37 ± 0.5°C by external warming. Analysis of arterial oxygen tension (PaO2), carbon dioxide tension (Paco2), and pH was performed immediately before each flow measurement. The hematocrit was measured at the beginning and end of each experiment. No significant change occurred and no hemolysis was detected.

The 9th and 10th nerves were divided with a sharp hook during each experiment. The glossopharyngeal nerve usually was defined as a single strand but the vagus comprised three to six fiber bundles which separated as they reached the medulla. In two of the 25 vagotomized preparations it was necessary to sacrifice the 11th nerve also. Section of the vagus and glossopharyngeal nerves resulted in an immediate rise in blood pressure to a mean arterial blood pressure (MABP) of 180-200 mm Hg, which persisted for 5-10 minutes and then declined to a level approximately 40 mm Hg higher than the presection level. Proof of adequate denervation was obtained by applying miniature vascular clips to the common carotid arteries bilaterally before and after section, in two cats in each experimental group (eight cats), and showing that the hypertension and tachycardia occasioned by this maneuver was abolished by nerve section. In addition, in those cats given phenylephrine HCl (Neo-Synephrine HCl) there was a loss of norepinephrine-induced brachycardia after deafferentation of the vasomotor center.

In five cats the 9th and 10th nerves were left intact and the 7th and 8th nerves were sectioned at the internal auditory meatus on the left. In all cats the completeness of nerve section was verified at autopsy.

MEASUREMENT OF CEREBRAL BLOOD FLOW

CBF was measured by the clearance of a 0.3-ml bolus of normal saline, containing 300 μCi of 133Xe, injected into the left lingual artery catheter. The detector was placed over the left parietal region of the skull at right angles to the bone and in the plane of the eyes. The sodium iodide detector, its collimation, and its calibration have been described in an earlier report.14 The isoresponse curve for the detector, when used on a cat skull with a diameter of 4 cm, is shown in Figure 1. It can be seen that the counting efficiency over the opposite hemisphere is less than 40% and is even lower in the more distal extracranial tissues. In addition, it has been demonstrated recently that, in a similar system, the amount of radioactivity in the contralateral hemisphere and extracranial tissue is less than 10% of that in the ipsilateral hemisphere. Thus the design of this experiment and the collimation of the detector is such that, essentially, only counts from the left hemisphere are recorded. The methods of recording used in this laboratory have been described18 and the system consistently has provided peak to background ratios of greater than 10 to 1, the background always being less than 2,000 counts/min and usually less than 1,000 counts/min.

Blood flow was estimated by the simplified initial slope technique18 and by kinetic analysis,19 λ for whole brain being taken as unity. The results are expressed as ml/100 g per min. The simplified initial slope technique (t0) and kinetic analysis (H/A) methods were used because they yield somewhat differing values for CBF and both are necessary for completeness.19 In the experimental animal, with 30 minutes between measurements, the kinetic analysis provides a measure of total CBF, and the long intermeasurement interval precludes inaccuracies due to residual activity. The t0 value overestimates total flow and, especially at high flow rates, tends to measure only the first exponential of gray matter flow. It therefore is more likely to show differences between the groups at such high rates of flow.

The data were statistically evaluated by Student's t-test for paired samples. The 0.05 level of probability was accepted as significant.

EXPERIMENTAL GROUPS

Surgical technique was standardized in a group of cats before its use in the experiments. Four groups then were created to assess each parameter.

Group 1. Response to Changes in Perfusion Pressure: Effect of Section of 9th and 10th Nerves. In the presence of an open craniotomy, the blood pressure is directly proportional to the perfusing pressure and is expressed as mean arterial blood pressure (MABP) ± SE. These experiments were performed in 10 cats, in which Paco2 and Pao2 were maintained at 40 ± 2 torr and 110 ± 20 torr, respectively. The Paco2 of 40 torr is slightly higher than the physiological Paco2 in this experimental animal (35 ± 2 torr) but control readings for CBF at the two levels differed little and Paco2
In five cats blood flow also was measured at the spontaneously hypertensive level (MABP = 165 ± 8 mm Hg) seen after vagotomy.

Group 2. 

Paco\textsubscript{2} Responsiveness: Effect of Division of 9th and 10th Nerves. In 10 cats the Paco\textsubscript{2} was maintained at 110 ± 20 torr and the Paco\textsubscript{2} was varied by altering the inspired gas tensions. An initial blood flow measurement was made at Paco\textsubscript{2} of 40 ± 2 torr, the Paco\textsubscript{2} was increased to 60 ± 2 torr, and, after allowing 15 minutes for equilibration of gases and maximum response to occur, the flow measurement was repeated. Paco\textsubscript{2} was reduced to 20 ± 2 torr for the third measurement and returned to 40 ± 2 torr for the fourth. The 9th and 10th nerves then were sectioned and, when the blood pressure had become stable, the pattern of blood gas tensions was repeated as shown in Figure 3.

Group 3. Paco\textsubscript{2} Responsiveness: Effect of Section of 9th and 10th Nerves. In the preliminary studies we found that little alteration occurred in CBF until the Paco\textsubscript{2} was reduced below 40 torr and, therefore, these experiments in five cats were designed to study reduced Paco\textsubscript{2} (to 30 ± 5 torr) while maintaining Paco\textsubscript{2} and pH constant. As shown in Figure 4, Paco\textsubscript{2} was initially held at normal levels (116 ± 7 torr) and a control CBF was estimated. Paco\textsubscript{2} was lowered to 28 ± 2 torr by replacing the inspired oxygen with nitrogen, and the flow was repeated. The third flow as assessed after Paco\textsubscript{2} had been restored to normal (100 ± 7 torr). The nerves then were sectioned and the pattern was repeated once the blood pressure had stabilized.

Group 4. Paco\textsubscript{2} Responsiveness: Effect of Facial Nerve
CEREBRAL BLOOD FLOW REGULATION/Bates and Sundt

In one cat, not included in the series, the blood pressure was lowered below the level of autoregulation (MABP = 35 mm Hg) and maintained at this level during measurement of CBF. The flow was unrecordably low (H/A value < 10 ml/100 g per min) and thereafter there was a loss of autoregulation and PaCO₂ responsiveness.

**PaCO₂ RESPONSIVENESS: EFFECT OF SECTION OF 9TH AND 10TH NERVES**

The results of the studies in these 10 cats are shown in Figure 3. CBF before deafferentation rose from a resting level of 46 ± 2 ml/100 g per min to 100 ± 13 ml/100 g per min at high PaCO₂, and then fell to 29 ± 1 ml/100 g per min at low PaCO₂, returning to 35 ± 2 ml/100 g per min as the PaCO₂ was restored to normal. After denervation, the values were 56 ± 8, 107 ± 14, 30 ± 3, and 46 ± 4 ml/100 g per min, respectively. The increased CBF after section may represent the increased blood pressure at this time and was not significantly different from the other flow rates at PaCO₂ of 40 torr (0.2 > P > 0.1). The blood flow measurements at PaCO₂ of 20 and 60 torr were significantly different from those at 40 torr (P < 0.01 in both cases). There was no significant difference between the blood flow rate before and after section at PaCO₂ of 20 torr (P > 0.6) or 60 torr (P > 0.7). Thus, the deafferentation of the vasomotor center does not appear to alter the CO₂ responsiveness of the cerebral vessels.

**Results**

The results of the studies are expressed graphically in Figures 2-5. Each diagram represents the results in one of the experimental groups.

**RESPONSIVENESS TO PERFUSION PRESSURE: EFFECT OF SECTION OF 9TH AND 10TH NERVES**

As shown in Figure 2, CBF remained virtually constant throughout the experiment. None of the flow rates was significantly different from the others (P > 0.2 for those with the greatest difference). Thus, autoregulation to blood pressures in the range of 130% to 70% of resting MABP is independent of the integrity of the peripheral baroreceptors. Those blood flows recorded at the spontaneously high blood pressures after vagotomy also were within normal limits (53 ± 6 ml/100 g per min).
Pao₂ RESPONSIVENESS: EFFECT OF 9TH AND 10TH NERVE SECTION

The results, shown in Figure 4, reveal a resting CBF of 39 ± 4 ml/100 g per min at normal Pao₂, with hypoxia this rose to 84 ± 8 ml/100 g per min and then returned to 42 ± 4 ml/100 g per min at a normal oxygen tension. After denervation, the corresponding values were 52 ± 9, 81 ± 6, and 48 ± 6 ml/100 g per min. The responses to the hypoxic stimuli were not significantly different (P > 0.7).

As can be seen in Figure 4, hypoxia before deafferentation caused a rise in MABP of about 25% (MABP = 118 ± 5 mm Hg, rising to 150 ± 13 mm Hg), but after nerve section a similar hypoxic stimulus caused a uniform fall in blood pressure of 25% (MABP = 132 ± 9 mm Hg, falling to 99 ± 13 mm Hg). The difference was significant at the 0.01 level.

During preliminary experiments, the level of hypoxia in one cat, after denervation, reached Pao₂ of 16 torr, whereupon an initial fall in blood pressure was followed by a sustained rise. The response to hypoxia and autoregulation was lost thereafter. It is possible that autoregulation may be somewhat impaired even at the level of hypoxia used in the experimental group, but if so, the uniform fall in MABP seen with hypoxia after nerve section would be expected to cause a fall in CBF. The absence of such a fall is evidence that this did not occur.

Paco₂ RESPONSIVENESS: EFFECT OF FACIAL NERVE SECTION

In the final five cats the response of CBF to hypercapnia before and after section of the left 7th and 8th nerves was studied (Fig. 5). The resting level of 46 ± 5 ml/100 g per min rose to 120 ± 6 ml/100 g per min at Paco₂ of 60 torr and then returned to normal levels. After denervation, a similar rise in Paco₂ caused the flow to increase to 101 ± 12 ml/100 g per min. There was, thus, a 20% decrease in the response to the vasodilating stimulus; this was seen in four of the five cats. But in the fifth cat there was a rise in CBF after section of the nerves and the difference, therefore, did not reach a significant level (0.2 > P > 0.1). Thus, although there is the suspicion of a fall in Paco₂ responsiveness, it cannot be supported by statistical analysis of the results.

Discussion

The evolution of present concepts of neural involvement in the responses of the cerebral blood vessels to changes in blood pressure, blood gas tension, and pH has been reviewed extensively by Purves and requires no further elaboration. In that review and one other, the persisting uncertainty as to the role of neural mechanisms in cerebral vascular regulation has been emphasized, although some reviewers have considered neural factors to be insignificant. In general, it has been accepted that the phenomena of autoregulation and responsiveness to Paco₂ and Pao₂ are intrinsic properties of the vessel wall or are related to local tissue metabolism. However, there is little doubt that stimulation of vasomotor nerves can influence CBF, despite the fact that such responses are not universally reported. The major question is the physiological relevance of such vasomotor responses.

If, indeed, neurogenic reflexes are involved in cerebral vascular control, the sites of the afferent limb of these reflexes are not defined. The position of the carotid and aortic baroreceptors and chemoreceptors and their known effects systemically have led some authors to suggest that they are involved in CBF regulation. Initial studies of pial vessels by Foskett suggested that the integrity of the vagi and the sinus and aortic nerves was not essential for cerebral vascular responsiveness. This finding was confirmed by others, measuring CBF rather than pial vessel diameter. However, James et al., in 1969, reported a significant reduction in cerebral vascular response after deafferentation of the brainstem vasomotor centers, and they criticized earlier studies for failure to control metabolic variables, excessive surgery, and inadequate denervation. These results were themselves criticized by Harper et al., who demonstrated that surgery in the region of the carotid vessels could cause significant vascular spasm and account for the earlier results. These last authors were unable to demonstrate a significant neural effect on CBF.

Most recently, Ponte and Purves, in an elaborate series of experiments in baboons, reported considerable changes in CBF in response to altered pressure, Paco₂, Pao₂, and pH of blood perfusing a vascularily isolated but neurally intact carotid bifurcation. They showed that denervation of these peripheral receptors then resulted in almost complete loss of responsiveness, and they suggested that all the responses to hypoxia, the majority to autoregulation, and two-thirds of the responses to hypercapnia were mediated reflexly. This study avoided many of the earlier criticisms but still involved considerable surgery and their preparations required infusion of 1 M bicarbonate at 1/2- to 1-hour intervals, to maintain pH.

The current study was designed to use an accepted method of studying physiological responses of CBF and to avoid excessive surgery to the cervical vessels and prolonged experimentation, both of which may alter vascular responses. The alterations in Paco₂, Pao₂, and MABP were not excessive and the reversibility of all changes in flow was ensured by measuring the blood flow repeatedly at normal parameters. The importance of this has been illustrated in studies showing that severe hypertensive, ischemic, or hypoxic stimuli can result in loss of normal vascular responsiveness. In our preparatory studies to design the experimental technique, it was noted that profound hypotension (MABP < 40 mm Hg) or hypoxia (Paco₂ < 20 torr) resulted in loss of autoregulation and metabolic responsiveness. It is possible that the loss of vascular responsiveness noted in earlier studies after denervation may have been due to excessive stimulation given immediately before or after nerve section.

This study has been concerned primarily with the afferent limb of a potential neurogenic reflex controlling CBF. The results of our experiments show that the ability of cerebral blood vessels to autoregulate to changes in MABP or to dilate and constrict in response to metabolic factors is not affected by deafferentation of the brainstem vasomotor center. Although this does not prove that these centers have no effect on the cerebral vessels, it makes untenable the belief that they are dependent on peripheral receptors. In addition, in those experiments in which dilatation of the cerebral vessels was assessed before and after division of the
auditory and facial nerves, no significant difference in response was detected. So it seems that, even if the facial nerve contributes toward vasodilation, it does not fill a dominant role in this phenomenon as has been suggested.12

Thus there is no evidence to suggest that the peripheral baroreceptors and chemoreceptors are essential for the physiological responsiveness of cerebral vessels, and it seems unlikely that the parasympathetic fibers in the facial nerve are important. These findings would be most compatible with the theories that such vascular control is mediated locally,26 although the possibility still exists that the peripheral baroreceptors and chemoreceptors are essential for the physiological responsiveness of cerebral vessels,26 perhaps acting via intrathecal pathways.1,31 If this latter possibility is true then the sites of receptors for such neural control are not defined and possibly may lie within the brainstem itself.30,31

In these experiments we noted that the main feature of the blood pressure after bilateral vagotomy and section of the glossopharyngeal nerves was not a severe, persisting hypertensive effect as noted in baboons13 but rather an increased lability that was most obvious in the experiments on autoregulation. Thus, although before nerve section it was necessary to withdraw 30-50 ml of blood to cause a fall of blood pressure to 70% of the basal level, after section a similar fall could be achieved with only a 5- to 10-ml withdrawal. Thus it appears that one of the major functions of the arterial baroreceptors may be to minimize variations in blood pressure rather than to set the chronic level.32

We also noted the paradoxical effect of hypoxia after section of the 9th and 10th nerves, in that a uniform hypertensive insufflament with damage to the blood-brain barrier. Stroke 6: 178-180, 1975


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