Response to "Do Vasomotor Nerves Significantly Regulate Cerebral Blood Flow?"

Michael J. Purves (MJP) has skillfully presented the view that neural mechanisms may play a major role in regulation of cerebral resistance. This view is in contrast to our review,¹ which deemphasized the importance of neural control except under unusual circumstances. We will expand on several points that MJP has made in his review.

Neuroeffector Mechanisms

There is no doubt that pial vessels have dense adrenergic and cholinergic innervation. Intracerebral vessels, however, have not been demonstrated to have cholinergic innervation and, although intracerebral vessels receive adrenergic innervation, the extent of innervation (i.e., the number of classical nerve terminals to cerebral vessels) is unclear.

MJP indicates that adrenergic innervation of cerebral vessels is not homogeneous, with denser innervation of the carotid arterial system than of the verteobasilar vessels. Similarly, it is possible that there are variations in characteristics of adrenergic receptors in cerebral vessels. The extremely unusual features of adrenergic transmission in cerebral vessels (including dilator responses to field stimulation in vitro and constrictor responses that are not blocked by alpha-adrenergic blocking drugs) have been described primarily in the basilar artery.² This pattern of regional differences in innervation and receptors suggests that sympathetic activation could reduce blood flow in the carotid but not verteobasilar distribution.

Recent studies³ which indicate that intense physiological stimulation of sympathetic pathways during hypertension in cats produces constriction of vessels in the cerebrum, but not the brainstem or cerebellum, may provide support for this concept.

Species Differences

MJP has proposed that species differences in effects of neural stimuli on cerebral blood flow may have contributed to the controversy. Since submitting our review,¹ we have obtained experimental evidence to support this concept. Electrical stimulation of sympathetic pathways, which does not decrease cerebral blood flow under normal conditions in dogs or cats, decreases cerebral blood flow by 26% in cynomolgus monkeys.⁴ This study and other work in vitro suggest that species differences may explain some of the conflicting results that have been obtained during neural stimuli.

Importance of Methodological Limitations

A point of agreement in both papers in this "Controversy" that should be emphasized is that the methods used to measure cerebral blood flow may measure different parameters and reflect different functions of flow. For example, the heat clearance method and possibly clearance of inert gases may reflect capillary surface area as well as blood flow.⁵ It will be important to attempt to define what each method measures, and to use techniques that measure a specific function rather than an integral of several determinants.

We have suggested that limitations in the methods for measuring cerebral blood flow may contribute to the discrepant results that have been obtained during neural stimuli. On the other hand, MJP has suggested that, except for methods that fail to prevent extracranial contamination, fundamental flaws in the methods used to measure flow do not contribute importantly to the discrepant results. Several points should be considered.

Many investigators who have used the inert gas clearance method to measure cerebral blood flow have reported conflicting results in response to neural stimuli. We have summarized several limitations of this method which may contribute to the variable results. Of particular concern is the contention that the fast and slow components of the washout curve correspond to blood flow to grey and white matter, respectively. In a recent study, we compared the ¹³³Xe clearance method with microspheres in measurement of cerebral blood flow and compared the two methods in measurement of blood flow to muscle with collection of venous outflow from muscle.⁶ Some conclusions of the study were (1) that slow and fast components of the clearance curve do not correlate well with grey and white matter blood flow measured with microspheres and (2) during severe hypercapnia and seizures, the microsphere technique indicated large increases in blood flow, but flow rates measured with ¹³³Xenon reached a plateau at 110 ml/min per 100 g. The correlation of values obtained with ¹³³Xe clearance and with the microsphere method or venous outflow improved when the ¹³³Xe clearance curves were analyzed with the height/area method, rather than separation into fast and slow components. Therefore, we recommend that ¹³³Xe clearance curves should not be analyzed by separation into components.

MJP suggested that sympathetic stimulation may produce more sustained constriction in pial vessels than in intracerebral vessels, that the fast component of clearance curves may reflect primarily responses in pial vessels, and that microsphere and venous drainage techniques measure total intracerebral flow. This interesting hypothesis could explain some of the conflicting results that have been obtained. However, the contribution of isotope within arteries to the clearance curve is minimized in most studies by adjusting the first 30 seconds of the curve from the analysis.

We will comment on another method which has...
been used to measure cerebral vascular responses to neural stimuli, i.e., measurement of pial vessel diameter through a cranial window. A recent study suggests that, when pial vessel diameter is measured, the milieu of pial vessels may be strikingly unphysiological unless the pial window is closed with a membrane. When pial vessels are covered with mineral oil, which has been done in most studies, the cerebrospinal fluid develops extreme alkalosis. Pial vasoconstrictor responses to norepinephrine are exaggerated during alkalosis. It may be very important to examine pial responses to neural stimuli in the closed preparation, to minimize alkalosis.

We want to suggest again that, in contrast to MJP’s view, limitations in the methods used to examine cerebral vascular responses to neural stimuli may contribute importantly to the controversy.

Conclusions

We suggest that several questions must be answered before one can conclude that nerves have physiologically important effects on cerebral blood flow. First, does reflex activation of neural pathways, as opposed to intense electrical stimulation, alter cerebral blood flow? Second, is the effect on flow trivial in magnitude, as in most experiments to this time, or are the effects of neural stimuli quantitatively important? Third, is the role of neural stimuli very circumscribed (e.g., only during severe hypertension), or do nerves play an important role during cerebral vascular responses to several physiological stimuli? When these questions are answered, significant progress will have been made toward resolving the controversy concerning the importance of neural mechanisms in control of cerebral blood flow.

Finally, we emphasize that nerves may have important cerebral vascular effects without altering blood flow significantly. It will be important to clarify the role of nerves in protection of the blood-brain barrier, in determining capillary surface area, and in affecting cerebral blood volume.

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