Cerebral Circulation: Effects of Sympathetic Nerves and Protective Mechanisms During Hypertension

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The first goal of this study was to examine bilateral effects of reflex activation of sympathetic nerves on the cerebral circulation. Seizures, which activate sympathetic nerves, were induced in animals with intact nerves and after bilateral cervical sympathetic denervation. Increases in cerebral blood flow (microspheres) and decreases in cerebral vascular resistance were similar in denervated and innervated animals. Thus, during intense metabolic stimulation, metabolic factors are the primary determinant of cerebral blood flow, and bilateral effects of sympathetic nerves are minimal. The second goal of this study was to examine the role of vascular hypertrophy in protection of the cerebral circulation. Cerebral perfusion pressure was decreased on one side by clipping one carotid artery in 4-week-old stroke-prone spontaneously hypertensive rats. Two to four months later, the clip was removed, and seizures were induced. Disruption of the blood–brain barrier in the cerebrum occurred predominantly on the clipped side. We suggest that reduction in perfusion pressure attenuates development of cerebral vascular hypertrophy and thereby increases susceptibility to disruption of the blood–brain barrier. Thus, hypertrophy of cerebral vessels during chronic hypertension may protect the cerebral circulation.

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Cerebral blood vessels are innervated by sympathetic nerves that originate primarily from the superior cervical ganglia. Several concepts have emerged recently that relate to effects of sympathetic nerves on the cerebral circulation. First, it has become apparent that bilateral activation of sympathetic nerves may have greater effects than unilateral activation on cerebral vessels under some conditions. Second, activation of sympathetic nerves attenuates increases in cerebral blood flow during acute hypertension. Third, sympathetic nerves exert a trophic effect on cerebral vessels and contribute to hypertrophy of vascular muscle during chronic hypertension. We have suggested that hypertrophy may protect cerebral vessels against stroke.

The present investigation examined two aspects of these concepts regarding regulation of cerebral vessels. Our first goal was to test the hypothesis that bilateral activation of sympathetic nerves, such as occurs during seizures, significantly attenuates cerebral vasodilatation during seizures. Our second goal was to examine the role of hypertrophy in protection of the cerebral circulation during chronic hypertension. We attempted to attenuate the development of cerebral vascular hypertrophy in hypertensive rats by reducing cerebral perfusion pressure. We tested the hypothesis that attenuation of vascular hypertrophy would increase susceptibility of the blood–brain barrier to disruption during acute hypertension or seizures.

Materials and Methods

Rats (300–400 g) were anesthetized with pentobarbital (50 mg/kg i.p.) or methohexital sodium (50 mg/kg i.p.) followed by chloralose (60–70 mg/kg i.v.). Animals were mechanically ventilated to maintain arterial blood gases and pH within the normal range (Pco2 = 34 ± 1 mm Hg, Po2 = 119 ± 6 mm Hg, and pH = 7.37 ± 0.01). Skeletal muscle paralysis was produced with gallamine triethiodide (10–20 mg/kg). Catheters were inserted into the brachial and femoral arteries, a femoral vein, and the left atrial appendage. Body temperature was monitored and maintained between 37°–38° C.

Experimental Protocols

Sprague-Dawley rats anesthetized with chloralose were used in the first series of experiments. The superior cervical ganglion was isolated bilaterally and was either left intact or removed bilaterally. Cerebral blood flow was measured using 15-μm radioactive microspheres. We have described our method in rats in detail. Blood flow was measured during control conditions and after induction of seizures with 1 mg/kg bicuculline (i.v.). During seizures, microspheres were injected at the peak of the increase in aortic blood pressure.

The second series of experiments was performed in stroke-prone spontaneously hypertensive rats (SHRSP) anesthetized with pentobarbital. In 4-week-old SHRSP, stenosis of one carotid artery was produced by placing a silver vascular clip with a gap of approximately 230 μm on the vessel to produce partial
occlusion and reduce cerebral perfusion pressure. Also, both superior cervical ganglia were removed at this time. The rats were studied 2 to 4 months later. Arterial pressure was measured proximal (aortic pressure) and distal to the clip, before and after removal of the clip. Pressure distal to the carotid clip was measured with a cannula inserted into the external carotid artery so the tip of the cannula was at the origin of the internal carotid artery. Seizures were induced with bicuculline (1 mg/kg i.v.). Disruption of the blood–brain barrier following seizures was evaluated using both Evans blue dye and albumin labeled with $^{125}$I as described in detail previously.¹¹

**Results**

**Bilateral Effect of Sympathetic Nerves**

We studied 9 rats with intact sympathetic nerves and 11 rats that had undergone bilateral cervical sympathetic ganglionectionomy. Aortic pressure was similar in the two groups during control conditions (97 ± 5 mm Hg in intact rats and 92 ± 7 mm Hg in denervated rats) and during seizures (184 ± 2 mm Hg in intact rats and 168 ± 8 mm Hg in denervated rats).

Resting cerebral blood flow was 74 ± 11 ml/min x 100 g (mean ± SEM) in rats with intact nerves and 79 ± 3 ml/min x 100 g in rats following bilateral sympathetic denervation. During seizures, increases in cerebral blood flow and decreases in cerebral vascular resistance were similar in innervated and denervated animals (Figure 1). Thus, bilateral sympathetic denervation had no effect on cerebral blood flow under control conditions or during seizures.

**Effect of Carotid Clipping on Disruption of the Blood–Brain Barrier**

With the carotid clip in place, a pressure gradient of 33 ± 5 mm Hg was present across the clip. Following removal of the clip, this gradient was reduced to 11 ± 7 mm Hg. After removal of the clip, seizures were induced to disrupt the blood–brain barrier. Evans blue dye was given in 16 rats.

In 12 of 16 rats, Evans blue dye was observed predominantly in the hemisphere ipsilateral to the clip (Figure 2), and in 4 rats, staining with Evans blue was similar in the two hemispheres. In 8 of these rats, we also gave $^{125}$I-albumin. Approximately twice as much $^{125}$I-albumin was present in the cerebral hemisphere ipsilateral to the clip than in the contralateral control side (tissue/plasma ratio was 2.2 ± 0.8 vs. 1.1 ± 0.3%, $p < 0.05$). Histologic examination of the brains provided no evidence of infarction or emboli.

**Discussion**

There are two new findings in the present study. First, during an intense metabolic stimulus, such as seizures, there are minimal effects on cerebral vessels of bilateral activation of sympathetic nerves. Second, we suggest that clipping one carotid artery, which reduced distal pressure, attenuates development of cerebral vascular hypertrophy and thereby increases susceptibility to disruption of the blood–brain barrier. These results suggest that hypertrophy of cerebral vessels during chronic hypertension protects the cerebral circulation.

**Effect of Sympathetic Nerves**

Cerebral blood vessels are innervated by sympathetic nerves that originate primarily from the superior cervical ganglia.¹² Activation of sympathetic nerves has important effects on cerebral microvascular pressure¹³ and on cerebral blood flow under conditions such as acute hypertermia⁶ and hypercapnia.³

Recently, it has become apparent that bilateral activation of sympathetic nerves has greater effects than unilateral activation on cerebral vessels.³ Under normal conditions, unilateral sympathetic stimulation has little effect on cerebral blood flow.⁶¹⁳ In contrast, bilateral stimulation of sympathetic nerves reduces cerebral blood flow by up to 40% during normocapnia.¹³ Responses to bilateral activation of sympathetic nerves are greater than responses to unilateral activation during hypercapnia and acute hypertension.³⁴ This concept initially was surprising because if nerves from sympathetic ganglia supply only ipsilateral cerebral vessels, then effects of bilateral stimulation would not be predicted to be greater than effects of unilateral stimulation. Blood vessels of the circle of Willis receive extensive bilateral innervation,¹ but vessels within the hemisphere are innervated predominantly from the ipsilateral ganglion. One explanation for the finding that bilateral stimulation has greater effects than unilateral stimulation may be that additive effects of bilateral sympathetic stimulation occur primarily at the circle of Willis and other large arteries and not at parenchymal vessels.

Seizures increase cerebral metabolism, increase cerebral blood flow greatly, and produce marked activation of sympathetic nerves. We have demonstrated that unilateral activation of sympathetic nerves during seizures has minimal effects on cerebral blood flow.¹⁴ In the present study, the hypothesis that bilateral activation of sympathetic nerves attenuates decreases in cerebral vascular resistance during seizures was tested. The results from this study suggest that bilateral activation of sympathetic nerves, like unilateral activation, has little effect on cerebral blood flow during seizures.

![Figure 1](http://cires.ahajournals.org/) Changes in cerebral blood flow and cerebral vascular resistance during seizures in rats with intact sympathetic nerves (•) and in rats following bilateral cervical sympathetic denervation (□).
We suggest that during an intense metabolic stimulus, such as seizures, metabolic factors are the primary determinant of cerebral blood flow, and effects of sympathetic nerves are minimal.

During severe hypertension, the autoregulatory capacity of cerebral vessels is surpassed and blood flow in different brain regions increases, but the changes are not uniform throughout the brain. Increases in blood flow to the cerebrum are greater than increases in blood flow to the brainstem (Figure 3). During pronounced increases in aortic pressure and breakthrough of autoregulation, pial arteriolar and pial venous pressure increase significantly, and the blood-brain barrier is disrupted. The extent of disruption of the blood-brain barrier during severe hypertension varies in different regions. Brain regions in which the greatest increases in blood flow occur during severe hypertension, such as the cerebrum, are most susceptible to disruption of the blood-brain barrier.

Two mechanisms appear to protect the cerebral circulation and the blood–brain barrier during acute hypertension. The first mechanism is protection by sympathetic nerves. Electrical stimulation of sympathetic nerves attenuates increases in cerebral blood flow during acute hypertension (Figure 3) and reduces disruption of the blood–brain barrier. These effects are most prominent in the cerebrum, particularly in gray matter.

There are regional differences in the degree of sympathetic innervation of cerebral vessels. Arteries of the anterior cerebral circulation (internal carotid, anterior, and middle cerebral arteries) are more densely innervated than arteries of the posterior circulation (vertebral, basilar, and posterior cerebral arteries). Functional consequences of these regional differences in sympathetic innervation are not established but may be important with regard to regional differences in regulation of blood flow during acute hypertension. Thus, activation of sympathetic nerves in regions such as the cerebrum, which are densely innervated, effectively extends the upper limit of autoregulation and protects the blood–brain barrier during acute hypertension.

The second protective mechanism during acute hypertension is autoregulation, which is very effective in the brainstem. Vascular resistance is higher in the brainstem than in the cerebrum during acute hypertension. As a result, increases in blood flow (Figure 3) and increases in pial venous pressure are less in the brainstem than in the cerebrum. Because elevation of pial venous pressure appears to be the primary mechanism for disruption of the blood–brain barrier during acute hypertension, attenuation of increases in pial
venous pressure by autoregulation of vessels upstream may be the mechanism of protection of the blood–brain barrier in the brainstem.  

Effect of Vascular Hypertrophy During Chronic Hypertension

Because blood pressure may be greatly increased during chronic hypertension, it might be predicted that cerebral blood flow would be elevated and the blood–brain barrier would be disrupted. Cerebral blood flow is normal and the blood–brain barrier is intact, however, in chronically hypertensive animals. Thus, cerebral vessels are protected more effectively during chronic hypertension than during acute hypertension.

The pressure drop between aorta and pial arterioles is greater in SHRSP than in normotensive rats. This finding suggests that an increase in large artery resistance in SHRSP protects small downstream vessels during chronic hypertension. Morphometric studies have shown that wall: lumen ratio of cerebral arterioles is increased in SHRSP, and hemodynamic studies indicate that cerebral vascular resistance is elevated in SHRSP during maximal dilatation. These results suggest that cerebral vessels undergo physiologically important hypertrophy during chronic hypertension.

In this study, we attempted to attenuate the development of cerebral vascular hypertrophy in hypertensive rats by reducing perfusion pressure to one cerebral hemisphere. Placing a clip on one carotid artery reduces perfusion pressure to the ipsilateral hemisphere. Our results suggest that this procedure attenuated the development of cerebral vascular hypertrophy and thereby increased susceptibility to disruption of the blood–brain barrier after the clip was removed. Thus, these studies provide evidence that hypertrophy of cerebral vessels during chronic hypertension protects the cerebral circulation.

The primary site of disruption of the blood–brain barrier in WKY during acute hypertension is cerebral venules. Disruption in venules is associated with, and presumably attributable to, increases in pial venous pressure. We speculate that, in chronic hypertension, hypertrophy of cerebral arteries and arterioles, which increases in cerebral vascular resistance, may protect the blood–brain barrier from disruption during acute hypertension by attenuating increases in pial venous pressure.

In conclusion, there is morphologic and physiologic evidence to suggest that cerebral vessels undergo hypertrophy during chronic hypertension. Our findings suggest that vascular hypertrophy protects the blood–brain barrier during chronic hypertension.

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References


**KEY WORDS** • blood-brain barrier • brainstem • seizures • autoregulation • hypertension
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