Effect of Sympathetic Stimulation on Permeability of the Blood-Brain Barrier to Albumin during Acute Hypertension in Cats

DONALD D. HEISTAD AND MELVIN L. MARCUS

SUMMARY Most studies concerning effects of neural stimuli on the cerebral circulation have focused on changes in cerebral blood flow (CBF). The purpose of this study was to examine effects of sympathetic nerves on permeability of the blood-brain barrier (BBB) to albumin, using a quantitative method, and to relate changes in blood flow to changes in permeability of the BBB. Permeability of the BBB was evaluated by measuring the accumulation of 131I-labeled serum albumin (RISA) in brain. RISA was injected intravenously, and the ratio of brain RISA to blood RISA was used as an index of permeability of the BBB. In normotensive cats, the BBB index in the cerebrum was 0.12 ± 0.04% (mean ± SE). During acute hypertension produced by intravenous norepinephrine, the BBB index in the cerebrum increased to 0.91 ± 0.20% (P < 0.05). Sympathetic stimulation during hypertension attenuated the increase in BBB index: the BBB index was 0.38 ± 0.10% and 1.01 ± 0.26% on the stimulated and unstimulated sides of the cerebrum, respectively (P < 0.05). CBF increased more than threefold during severe hypertension; sympathetic stimulation attenuated the increase in flow. Increases in flow and disruption of the BBB were most marked in cortical grey matter, and responses to sympathetic stimulation were also largest in cortical grey matter. Disruption of the BBB during hypertension was minimal in subcortical grey and white matter, and sympathetic stimulation had no detectable effect in these areas. In summary, these studies provide the first quantitative evidence that acute hypertension increases the permeability of the BBB to albumin and that sympathetic stimulation reduces disruption of the barrier. The regions of the brain that were most susceptible to disruption of the BBB were most responsive to the protective effect of sympathetic stimulation. Circ Res 45: 331-338, 1979

AFTER many years of uncertainty concerning the role of sympathetic nerves in regulation of cerebral blood flow (Heistad and Marcus, 1978; Purves, 1978), several recent studies suggest that, during severe hypertension, neural stimuli may have important effects on cerebral vessels. The experiments indicate that electrical (Bill and Linder, 1976; Boisvert et al., 1977; Edvinsson et al., 1976, 1977; Heistad et al., 1978; MacKenzie et al., 1977) or physiological (Gross et al., 1979) stimulation of sympathetic pathways attenuate the increase in cerebral blood flow during acute, severe hypertension.

During acute, severe hypertension, increases in cerebral blood flow are accompanied by disruption of the blood-brain barrier, with an increase in permeability to albumin (Johansson et al., 1970; Johansson et al., 1974). Recent studies suggest that, in addition to attenuating the increase in cerebral flow during acute hypertension, sympathetic stimulation also reduces disruption of the blood-brain barrier (Bill and Linder, 1976; Edvinsson et al., 1977; Gross et al., 1979; Heistad et al., 1978). In those studies, disruption of the barrier was estimated qualitatively with Evans blue dye. There have been no quantitative determinations of the effect of neural stimuli on disruption of the blood-brain barrier during acute hypertension.

In this study we have used radioiodinated serum albumin (131I-RISA) to measure the amount of albumin that passes the blood-brain barrier and enters the brain. The method is similar to that described by Lorenzo et al. (1972). The purposes of the study were, first, to determine whether disruption of the blood-brain barrier in different regions of the brain during acute hypertension occurred in the regions with the largest increases in blood flow and, second, to use a quantitative method to determine the effectiveness of sympathetic stimulation in protection of the blood-brain barrier during acute hypertension.

Methods
Thirteen mongrel cats (weight = 2-5 kg) were given sodium methohexital (30 mg/kg) intraperitoneally for initial anesthesia, and intravenous chlor-

From the Cardiovascular Division, Department of Internal Medicine and Cardiovascular Center, University of Iowa College of Medicine and Veterans Administration Hospital, Iowa City, Iowa.

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Address for reprint: Donald D. Heistad, M.D., Department of Internal Medicine, University of Iowa Hospital & Clinics, Iowa City, Iowa 52242.

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aloise and urethane (1:10) as needed during the experiment. The cats were intubated and ventilated with room air and supplemental oxygen. Heparin (500 U/kg, iv) and decamethonium bromide (0.3 mg/kg, iv) were administered for anticoagulation and skeletal muscle paralysis, respectively. Arterial blood gases and pH were measured frequently and maintained at normal levels by adjustment of the ventilatory rate and the flow rate of oxygen or by injection of small amounts of sodium bicarbonate.

After a left thoracotomy, a cannula was placed in the left atrium for injection of microspheres. Polyethylene catheters were inserted into brachial and femoral arteries for measurement of arterial blood pressure and for withdrawal of reference arterial blood samples during microsphere injection.

**Measurement of Cerebral Blood Flow**

Microspheres (15 µm mean diameter), labeled with $^{141}$Ce or $^{125}$I, were used for measurement of cerebral blood flow. Before each injection, the vial containing the spheres, which were suspended in 10% dextran, was sonicated or vigorously shaken for several minutes on a Vortex mixer. We injected 0.3 to 1.5 million spheres for each determination of blood flow. The spheres were injected slowly over a 20-second period and were flushed with 0.9% saline at 37°C. Beginning 30 seconds before injection of the spheres and continuing for 3 minutes after injection, reference arterial blood samples were obtained from the brachial and femoral arteries.

After each study, the cat was killed and the brain was dissected by region and tissue. Brain samples were classified as: right and left medulla,pons, and thalamus-midbrain, cerebral white matter (corpus callosum, centrum ovale, and optic chiasm), cerebral grey matter (caudate nucleus and cortical grey matter), multiple cerebral samples, and cerebellum. Samples of temporalis muscle also were obtained. The brain and muscle samples weighed 0.1–3g.

**Evaluation of Permeability of the Blood-Brain Barrier**

Two methods were used to evaluate disruption of the blood-brain barrier. A qualitative estimate of permeability of the barrier to albumin was obtained by injection of Evans blue dye intravenously. Evans blue dye binds to albumin and normally does not pass the blood-brain barrier. During acute hypertension, however, the brain becomes stained with blue dye when the barrier is disrupted (Johansson et al., 1979).
et al., 1970). Evans blue dye (2.5%, 3 ml/kg) was injected intravenously at the beginning of the experimental protocol, before measurements were obtained. At the end of each study, the brain was examined for superficial and deep staining by the dye. The extent of staining was graded as 0 (none), 1+ (minimal), 2+ (moderate), or 3+ (extensive). The grading was performed "blinded": i.e., by an observer who was not aware of the interventions in each cat.

A quantitative determination of permeability of the blood-brain barrier to albumin was obtained by injecting approximately 50 μCi of human 131I-RISA (Mallinckrodt Nuclear), intravenously. The 131I-RISA circulated for 10 minutes before and 10 minutes during interventions. After the cat had been killed, cerebral vessels were perfused with saline to remove 131I-RISA from the lumen of the vessel. Brain samples were counted with a gamma counter to determine the amount of 131I-RISA that remained in the brain. Permeability to albumin was calculated from the ratio of the amount of RISA in the brain to the RISA in the blood and was expressed as an index of permeability in percent.

After injection of 131I-RISA, we waited 10 minutes before experimental interventions were made. Venous blood samples that were obtained 10, 15, and 20 minutes after injection of RISA indicated only a small decrease in the level of circulating 131I-RISA. The venous blood samples were weighed, and radioactivity per unit weight was used as the reference value for the concentration of RISA in the brain.

The ascending aorta was cannulated immediately after the cat was killed, and the descending aorta was ligated. To remove RISA from the lumen of cerebral vessels, the brain was perfused with 0.9% saline for 5–10 minutes. To determine whether perfusion with saline dislodged microspheres, we measured the radioactivity of the effluent. The venous effluent did not contain detectable radioactivity from microspheres. To assess the efficacy of perfusion in removal of RISA from the lumen of cerebral vessels, samples of effluent were examined for radioactivity from RISA. Radioactivity in the last sample of effluent was 0.3 ± 0.1% (mean ± SE) of the 131I-RISA activity in venous blood.

A special approach was used in this study to separate the isotopes, because there were large differences in the radioactivity of 131I-RISA and the microspheres. Because only a small fraction (usually < 1%) of 131I-RISA in blood enters the brain, a relatively large quantity of 131I-RISA (50 μCi) was injected, so that the amount of 131I-RISA in the brain was sufficient to be quantified accurately. It was not difficult to separate the isotopes in the brain, even though the amount of 131I-RISA was not large. The specific energy of 131I-RISA is higher than the specific energy of 125I and 141Ce, so that virtually all of the radioactivity in the 131I window (300–400 keV) was from 131I. Radioactivity from 125I and 141Ce could be determined accurately in the brain, despite overlap of 131I to the lower energy windows, because the amount of 131I in the brain was not large. A special procedure was required, however, to separate the isotopes in the blood, because the amount of radioactivity from 131I-RISA was about 10-fold greater than the activity from the microspheres. This problem was circumvented with 141Ce-labeled microspheres by injecting the spheres before 131I-RISA was injected. Thus, there was no 131I-RISA in the reference arterial blood samples that contained 141Ce. The problem of separation was circumvented with 131I-labeled microspheres and RISA by separating the blood samples with centrifugation. The reference arterial blood samples were centrifuged at 5000 rpm for 5 minutes. Because the specific gravity of microspheres is 1.023 ± 0.05 g/ml, the microspheres precipitate during centrifugation. The supernatant, which contained RISA, was discarded and the precipitate was used as the reference blood sample for 131I microspheres.

We determined the amount of 131I that was not protein-bound in plasma and tissues of two cats during severe hypertension. The method of Lorenzo et al. (1972) was used to precipitate protein-bound 131I with trichloroacetic acid (TCA). Blood samples were obtained 10–20 minutes after injection of 131I-albumin. Plasma (0.1 ml) was mixed with 1.0 ml of 8% TCA. Samples of brain (cerebral cortex, cerebellum, and thalamus), kidney, and muscle (0.5–1.2 g) were mixed with 8% TCA and homogenized. The plasma samples were centrifuged at 7000 rpm for 20 minutes, and tissue samples were centrifuged at 10,000 rpm; radioactivity was determined in the supernatant and precipitate. In plasma, the amount of 131I that was not protein-bound was 0.6–2.1%; in brain, the amount of "free" 131I was 2.9–5.1%; in liver and muscle, the "free" 131I was 2.4–12.2%. Thus, in cats during acute hypertension as well as during seizures (Lorenzo et al., 1972), most of the 131I in blood and brain tissue is bound to a protein, presumably albumin.

Results

Blood-Brain Barrier and Blood Flow during Normotension

The amount of RISA in the brain in normotensive cats was small (Table 1). The brain was not stained by Evans blue dye in any cat. The amount of RISA tended to be larger in the cerebellum than in cerebrum or brainstem, but the values were not significantly different by analysis of variance. Sympathetic stimulation did not reduce the amount of RISA in the brain during normotension.

Sympathetic denervation and stimulation did not alter cerebral blood flow in normotensive cats (Table 1).
TABLE 1

Effect of Sympathetic Stimulation on Cerebral Blood Flow and Permeability of the Blood-Brain Barrier during Normotension

<table>
<thead>
<tr>
<th>Region</th>
<th>Control Unstimulated (ml/mm per 100 g)</th>
<th>Control Stimulated (ml/mm per 100 g)</th>
<th>Stimulation (ml/mm per 100 g)</th>
<th>Regional RISA index (%)</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemibrain</td>
<td>35 ± 5.4</td>
<td>35 ± 5.0</td>
<td>36 ± 7.7</td>
<td>0.14 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>Cerebrum</td>
<td>34 ± 5.4</td>
<td>35 ± 5.2</td>
<td>33 ± 6.7</td>
<td>0.11 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>Cortical grey</td>
<td>39 ± 5.0</td>
<td>36 ± 4.9</td>
<td>43 ± 10.8</td>
<td>0.12 ± 0.07</td>
</tr>
<tr>
<td></td>
<td>Caudate nucleus</td>
<td>35 ± 2.8</td>
<td>30 ± 3.9</td>
<td>31 ± 9.1</td>
<td>0.08 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>White matter</td>
<td>16 ± 6.6</td>
<td>17 ± 4.7</td>
<td>17 ± 7.6</td>
<td>0.01 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>Cerebellum</td>
<td>40 ± 7.2</td>
<td>36 ± 5.6</td>
<td>47 ± 10.0</td>
<td>0.28 ± 0.13</td>
</tr>
<tr>
<td></td>
<td>Brainstem</td>
<td>33 ± 4.6</td>
<td>34 ± 5.1</td>
<td>37 ± 9.7</td>
<td>0.15 ± 0.07</td>
</tr>
<tr>
<td></td>
<td>Thalamus-midbrain</td>
<td>34 ± 4.3</td>
<td>34 ± 4.6</td>
<td>38 ± 10.9</td>
<td>0.17 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>Pons</td>
<td>31 ± 5.4</td>
<td>36 ± 6.9</td>
<td>34 ± 7.9</td>
<td>0.13 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>Medulla</td>
<td>32 ± 5.5</td>
<td>31 ± 5.2</td>
<td>36 ± 8.8</td>
<td>0.12 ± 0.05</td>
</tr>
</tbody>
</table>

Values are mean ± SE in five cats. During control period, mean arterial pressure = 84 ± 8.0 mm Hg. arterial Pco2 = 36.0 ± 0.9 mm Hg, Po2 = 104 ± 11 mm Hg, and pH = 7.37 ± 0.02. During sympathetic stimulation, mean arterial pressure = 79 ± 8.5 mm Hg, arterial Pco2 = 35.4 ± 1.2 mm Hg, Po2 = 123 ± 8.9 mm Hg, and pH = 7.36 ± 0.01. There were no significant differences between the two sides of the brain.

Effect of Severe Hypertension on Blood Flow

In the hemibrain in which sympathetic nerves were not stimulated, the magnitude of the increase in cerebral blood flow during hypertension varied in different regions (Table 2). In the cerebrum there was a 6-fold increase in flow to cortical grey matter during hypertension but only a small increase in flow to subcortical grey matter (caudate nucleus) and white matter.

Sympathetic stimulation attenuated the increase in blood flow during hypertension (Fig. 1, Table 2). The effect of sympathetic stimulation on blood flow was statistically significant in cortical grey matter and medulla, which were the regions with the largest increase in blood flow during hypertension.

Effect of Severe Hypertension on the Blood-Brain Barrier

There was marked variation in different regions of the brain in the amount of disruption of the blood-brain barrier during hypertension (Table 2).

Comparison of Evans Blue Dye and RISA

The amount of RISA in cerebral grey matter was compared with the estimate of disruption of the blood-brain barrier obtained with Evans blue dye. The Spearman rank-order correlation coefficient...
Discussion

These studies provide quantitative evidence that acute hypertension increases the permeability of the blood-brain barrier to albumin and that sympathetic stimulation reduces disruption of the barrier. Sympathetic stimulation attenuated increases in blood flow and disruption of the blood-brain barrier in cortical grey matter. In subcortical areas of the cerebrum (caudate nucleus and white matter), increases in flow and disruption of the blood-brain barrier were small during hypertension, and sympathetic stimulation had no detectable effect.

Methods for Measuring Blood Flow and Permeability of the Blood-Brain Barrier

We have provided evidence that supports the validity of the microspheres method in measurement of cerebral blood flow (Marcus et al., 1976). A recent study suggests that microspheres can be used to measure cerebral blood flow during severe hypertension in cats (Heistad et al., 1978).

The method that we have used to measure the amount of albumin that passes the blood-brain barrier and enters the brain is similar to the method described by Lorenzo et al. (1972). Although the method is quantitative, it requires important assumptions. First, because RISA is an intravascular tracer, all of the RISA must be removed from the lumen of blood vessels in the brain to allow precise measurement of the amount of RISA in paren-
The disadvantage of the approach is that it circumvents the first two assumptions that we have discussed. The disadvantage of the approach is that it measures intravascular blood volume, as well as permeability of the blood-brain barrier. Lorenzo et al. (1972) perfused the brain with saline in some experiments, and did not perfuse the brain in other experiments, and arrived at the same conclusions with both approaches. Thus it appears that each method may be of value despite limitations of both.

Regional Blood Flow and Permeability of the Blood-Brain Barrier

Under normal conditions (Table 1), the amount of RISA in the brain was small. This observation is similar to that of Barlow et al. (1958) and Lorenzo et al. (1972).

During acute hypertension there were regional differences in susceptibility to "breakthrough" of autoregulation and disruption of the blood-brain barrier. Disruption of the barrier to albumin was most pronounced in regions with the largest increase in blood flow. Thus, increases in permeability and in blood flow were greatest in cortical grey matter and less in subcortical grey matter (caudate nucleus), white matter, and brainstem.

Effects of Sympathetic Nerves

Sympathetic stimulation attenuated the increase in blood flow and permeability of the blood-brain barrier during acute hypertension. In the cerebrum, in which sympathetic nerves supply ipsilateral vessels almost exclusively (Nielsen and Owman, 1967), the response to stimulation of one superior cervical ganglion occurred primarily in the ipsilateral hemisphere. In cortical grey matter, in which there was a large increase in blood flow and permeability during acute hypertension, sympathetic stimulation limited these increases. In the caudate nucleus and white matter, in which increases in blood flow and permeability were much smaller, sympathetic stimulation had no detectable effect. Thus, in the regions of the cerebrum that were most vulnerable to the effects of acute hypertension, sympathetic stimulation had the greatest effect. In the brainstem and cerebellum, increases in blood flow and permeability of the blood-brain barrier during acute hypertension tended to be less on the side ipsilateral to sympathetic stimulation.

Previous studies have indicated that sympathetic stimulation protects the blood-brain barrier during hypertension (Bill and Linder, 1976; Edvinsson et al., 1977; Gross et al., 1979; Heistad et al., 1978). Disruption of the barrier was estimated with Evans blue dye in those studies. Although previous studies with Evans blue dye did not allow quantification of disruption of the barrier in different regions of the brain, the results of this study support the validity of the method as a qualitative estimate of permeability to albumin. The estimate of the effectiveness of nerve stimulation in protection of the blood-brain barrier was similar with Evans blue dye and RISA (Fig. 3).

The blood-brain barrier restricts the rate of entry of water and inulin into the brain. Grubb et al. (1978) have reported that stimulation of the cervical sympathetic chain under normal conditions in mon-
keys increases permeability of the blood-brain barrier to water. Furthermore, Edvinsson et al. (1977) have observed that excision of the superior cervical ganglion in rats increases the uptake of inulin into the brain. Thus, these authors suggested that sympathetic nerves are involved in normal function of the blood-brain barrier. The mechanism of this effect is not clear. It is likely, however, that different mechanisms mediate the effect of sympathetic nerves on permeability to albumin during hypertension than regulate permeability to water and inulin during normotension.

**Speculation and Implications**

Kontos et al. (1978) have reported that large cerebral arteries constrict during acute hypertension, whereas small vessels remain unchanged or dilate. Thus the contribution of large cerebral arteries to total cerebral resistance increases during hypertension. Wei et al. (1975) have observed that sympathetic stimulation constricts large arteries more than small arteries. Rosenblum (1977) has discussed some implications of changes in the contribution of large and small arteries during hypertension, and the potential effect on responses to neural stimuli. We have suggested (Heistad et al., 1978) that autoregulatory constriction of large cerebral arteries, so that large arteries contribute relatively more to total cerebral resistance, accounts at least in part for the potentiation of responses to sympathetic stimulation during acute hypertension. A recent study of renal vessels (Carlson and Schramm, 1978) suggests that a shift in the contribution to total renal resistance by large and small arteries during autoregulation plays a role in altered responsiveness to sympathetic stimulation.

We have been unable to demonstrate constriction of large cerebral arteries during sympathetic stimulation in normotensive dogs (Heistad et al., 1977). It seems likely, however, that sympathetic stimulation may constrict large cerebral arteries during severe hypertension in cat. Constriction of large arteries could attenuate the rise in pressure in smaller distal vessels and thereby reduce disruption of the blood-brain barrier.

In this study we have not addressed the functional implications of increased permeability to albumin during acute severe hypertension. Although the increase in permeability is large, the amount of albumin that enters the brain is small. Albumin is degraded in the brain (Lorenzo et al., 1972), however, and it is possible that, as albumin is metabolized to smaller fragments, osmolarity of extracellular fluid would increase substantially. Johansson (1976) has been unable to detect an increase in water content after 30 minutes of hypertension in normocapnic rats. The functional importance of increased permeability of the blood-brain barrier to albumin during hypertension therefore must await clarification.

**Acknowledgments**

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Decreased Myocardial Contractility in Papillary Muscles from Atherosclerotic Rabbits

DARWIN W. PETERSON, DAVID W. GRIFFITH, JR., AND CHARLES A. NAPOLITANO

SUMMARY To determine the effect atherosclerosis has on myocardial contractility, we studied the contractile properties of right ventricular papillary muscles from 34 atherosclerotic and 17 control rabbits. We produced atherosclerosis by feeding for 2 to 8 months a diet of 5% lard, 5% peanut oil, 0.5% cholesterol, and 89.5% rabbit pellets. The controls received only rabbit pellets during the same time interval. Contracting isometrically 12 times per minute at 25°C, muscles from the atherosclerotic rabbits developed tension at a lower maximum rate (max dT/dt), had a longer latency, and required longer to develop tension at the maximum rate and to develop peak tension. In isotonic contractions, they shortened with lower maximum velocities and required longer to accelerate to maximum velocity and to shorten maximally. We found no evidence that developed tension or distance shortened differed between the two groups of muscles. Raising the contraction frequency to 24 contractions per minute brought performance of the two groups of muscles closer in both types of contraction. Norepinephrine (1.5 x 10^{-6} M) nearly abolished differences between performance of the two groups. The loss of contractility correlates poorly with coronary and aortic atherosclerosis. It occurred early in the feeding of the atherogenic diet. We think it was due to a lipid-induced defect in the cardiac cell’s handling of calcium. Circ Res 45: 338-346, 1979

MYOCARDIAL contractility is low in coronary artery disease. As measured during cardiac catheterization, the loss is proportional to the severity of the disease (Hamby et al., 1973; Moraski et al., 1975; Rackley and Russell, 1975). Some of the loss may be due to ischemia, because bypassing plaques with arterial grafts improves exercise tolerance and lessens angina (Kouchoukos et al., 1975). However, perhaps there is also a loss that is independent of the immediate presence of ischemia. To test for it, we performed the research described in this paper. Our results were obtained from isolated papillary muscles. Oxygen supply to the muscles depended,

Therefore, on diffusion, not on blood flow through atherosclerotic arteries. Some of our results have been reported in an abstract (Peterson et al., 1977).

Methods

Animals and Diets

We assigned male New Zealand laboratory rabbits randomly to two groups. One group received rabbit pellets for 2-8 months. Those in the other group received an atherogenic diet composed of 89.5% rabbit pellets, 5% lard, 5% peanut oil, and 0.5% cholesterol for the same length of time. At the start of the study the control rabbits weighed 2.42 ± 0.12 kg (mean ± se); those receiving the atherogenic diet weighed 2.42 ± 0.09 kg. We randomized the order the rabbits were used in experiments. A rabbit selected for an experiment was brought to a surgical plane of anesthesia with sodium pentobarbital (mean of 54 ± 1.7 mg/kg) given intravenously. We then quickly removed the heart, isolated a
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D D Heistad and M L Marcus

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