CORTICAL INJURY WITHOUT ISCHEMIA PRODUCED BY TOPICAL MONOAMINES

SHERMAN C. STEIN, M.D. AND ROGER Q. CRACCO, M.D.

SUMMARY Responses to monoamines perfused over the cortical surface through modified pial windows were monitored in 106 cats. Norepinephrine (NE) and serotonin (5-HT) were diluted in mock CSF to concentrations of 50 and 500 ng/ml respectively, levels at or near the maximum concentrations to which the cortical surface might be exposed in subarachnoid hemorrhage or damage to nearby neurons. Each cat had simultaneous one-hour perfusions of monoamine solution over one hemisphere and a control solution over the other hemisphere, thus serving as its own control.

The perfusion solutions were observed to be restricted to the area of the pial window, and minimal histological damage was seen with the perfusion technique. The 5-HT perfusions were associated with an almost 20% narrowing of small pial arteries and arterioles but no significant effect on regional cerebral blood flow (rCBF), cortical water content or cortical function as monitored by EEG and somatosensory evoked potentials (SEP). In contrast, NE caused cortical edema and changes in the EEG and SEP's without significant vascular effect. These results suggest a non-ischemic toxicity of NE released by subarachnoid hemorrhage or cerebral damage.

THERE has been considerable interest in recent years in the roles of two monoamines, norepinephrine (NE) and serotonin (5-hydroxytryptamine, 5-HT), in normal and pathological cerebral events. Both are present in the brain at concentrations adequate for physiological function and are widely considered to act as neurotransmitters.1-8 Fluorescent histochemical techniques have demonstrated NE and 5-HT in axon terminals of the cerebral cortex, to which they project from brainstem neurons.9-10

Some investigators have assigned a physiological role in cerebral blood flow (CBF) control to NE11,12 and 5-HT,13 and this concept has been supported by observed effects of both agents on pial vessel diameter.14-17 It has been suggested that these monoamines, released by subarachnoid hemorrhage, are responsible for arterial spasm, diminished CBF, and impaired neurological function.18-20 Disturbances in concentration and metabolism of these monoamines in the cerebral cortex and in the cerebrospinal fluid (CSF) have been found not only in subarachnoid hemorrhage21-23 but also in cerebral anoxia24-27 and in head trauma.28-31 It has been suggested that the release or redistribution of cortical NE and 5-HT are involved in the enlargement of ischemic and traumatic lesions.22,23-26

Attempts to study the effects of exogenous monoamines on the brain have been hampered by cerebral inaccessibility. Given parenterally, NE and 5-HT cross the blood-brain barrier (BBB) poorly or not at all.32-41 The value of monoamine injections and infusions into the ventricles and subarachnoid cisterns is limited by their rapid clearance with CSF flow42-44 and by the inability to control their distribution or to identify their sites of action.45 Direct cortical injection or implantation involves mechanical trauma and usually requires unphysiologically high concentrations to achieve demonstrable effects. Microiontophoresis is limited to studying the responses of single neurons and involves many possible artifacts related to dosage, anesthesia, etc.46-48 Effects of parenteral monoamines following opening of the BBB49-51 may be complicated by blood pressure changes or the presence of other substances accompanying monoamines through the barrier. In an effort to circumvent these obstacles, we chose to perfuse solutions over the surface of a local cortical area. For this, we chose a modification of the pial window, a device long used to observe surface cortical vessels52 but not previously applied in investigating cerebral function or blood flow.

Materials and Methods

One hundred and six adult male cats weighing 3-4.5 kg were anesthetized with 35 mg/kg intraperitoneal pentobarbital. A tracheostomy was performed and femoral arterial and venous catheters were inserted. The cats were paralyzed with gallamine triethiodide (Flaxedil) and artificially ventilated with an equal mixture of nitrous oxide and oxygen. Femoral arterial blood pressure was continuously monitored, and frequent arterial blood samples were taken to determine blood gas. The arterial pO2 was maintained at greater than 100 torr; arterial pCO2 was kept between 32 and 36 torr, the normal range for cats.49 The animals were then fixed in a stereotactic head holder. The scalp and temporalis muscles were reflected laterally from the underlying cranium. Symmetrical trephinations were made in the skull in the vicinity of the anterior and posterior sigmoid gyri and the underlying dura opened in a circular fashion. The dural edges were gently elevated at several points and lightly coagulated with bipolar electrocautery to prevent spread of solutions from the perfusion site.4 A modified pial window, designed to screw tightly into the trephine hole, was inserted on each side. Any experimental preparation in which cortical trauma or bleeding occurred was discarded.

Perfusions of the cortical surface under the pial window were done with solutions which had been warmed...
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FIGURE 1. Perfusion of the cortical surface, using modified pial windows. Monoamine solution is perfused through one window, mock CSF through the other. Symmetrical placement allows each animal to serve as its own control.

To 38°C, were all at the rate of 0.1ml/min and of one hour duration. NE perfusion solutions were prepared by diluting 0.2% levarterenol bitartarte in mock CSF* immediately prior to perfusion. Tartaric acid, 5-HT creatinine sulfate and creatinine sulfate were prepared as 0.2% solutions under sterile conditions from powders using doubly-distilled water and were diluted with mock CSF at the time of perfusion. Final concentrations of various solutions were NE base 50 ng/ml (3.0 × 10⁻⁷ M), 5-HT base 500 ng/ml (2.3 × 10⁻⁷ M), tartaric acid, and creatinine sulfate equimolar to their respective bases. pH measurements of the perfusion solutions varied somewhat but were always between 7.2 and 7.4. Each animal was perfused with a monoamine solution under one window and with a control solution (mock CSF alone or with tartaric acid or creatinine sulfate) under the other window. Thus, each cat served as its own control. Figure 1 shows a perfusion in progress.

In four animals, one hour perfusions were performed with 2% Evan's blue solution and the brains examined for abnormality by light microscopy.

Measurements of internal diameters of 10 pial arteries (5 cats) were made under green light from a fiber-optic source using a microscope with a Vicker's image-splitting eye piece at a combined final magnification of 40X. Serial measurements were taken during the perfusions. Upon completion of perfusions in 14 cats, 300 microcuries of ¹⁴C-antipyrine were infused intravenously over one minute. Each animal was then quickly sacrificed with intravenous KCl solution and regional cerebral blood flow (rCBF) determined using the method of Reivich and associates.¹⁶

Prior to cortical perfusion in 40 cats, epidural screw electrodes were inserted into the frontal, parietal, and occipital regions bilaterally for continuous EEG recording. Cerebral somatosensory evoked potentials (SEP) were induced with bipolar needle electrodes inserted into the vicinity of the median nerve in each forepaw. Stimulation pulses (duration 0.2 msec.) were generated by a Grass S88 stimulator* at rates of 9-10/sec. at supramaximal voltage, and recordings obtained from the metal housings of the pial windows. Nasal screw and knee cutaneous electrodes were used as reference electrodes. Input on the recording channels was filtered (−3 dB at 5KHZ) and led to differential amplifiers, averaged by a Nicolet Med 80 Computer,† and displayed on an X-Y plotter. Analysis times of 30 msec from stimulation were used for detailed inspection of cerebral potentials. Each recording run consisted of 1024 stimulations. Anesthesia for SEP's was induced with ketamine HCl, 35 mg/kg.


*Grass Medical Instruments, Quincy, Massachusetts.

†Nicolet Biomedical Instruments, Madison, Wisconsin.
and maintained with periodic ketamine and Flaxedil. Five cats perfused with NE and four with 5-HT were used.

In eight cats who were sacrificed with intravenous KCl immediately upon completion of the perfusion, the pia mater was stripped from the cortex in the areas of perfusion, and samples of gray matter were shaved from the cortical surface with a scalpel blade. The specimens weighed 50–100 mg. Water content of the cortical slices was determined by comparing their weights before and after 48 hours treatment in a heated vacuum dessicator. The integrity of the blood-brain barrier was assessed in another eight cats by intravenous infusion of 2% Evan's blue solution, 4 ml/kg, and by inspection of the cortex for evidence of extravasation. The Student's t test, adjusted for paired samples, was used to evaluate numerical data.

Results

Evan's blue solution perfused for one hour did not spread beyond the margins of the pial window in any of the four cats tested, confirming the focal nature of the perfusion technique (fig. 2). Cortical histology appeared entirely normal in six of the eleven control, two of six NE, and two of the five 5-HT perfusion sites. Changes to light microscopy, when they occurred, were restricted to small areas of superficial neuronal damage underlying the margins of the pial windows where they rested on the cortex.

Constriction of pial arteries, evident on gross visual inspection, was noted in 84% of the 38 5-HT perfusions. This was occasionally quite striking on microscopic examination (fig. 3). Obvious changes in vascular diameter were first noted after 15–50 minutes of perfusion, but were usually seen in the first 25 minutes. The extent and severity of the constriction varied from cat to cat, but in most cases involved all arteries in the field and persisted for the duration of the perfusion. Changes in pial vascular diameter observed during perfusions with NE and control solutions, when they occurred, were transient and of minor degree.

Accurate measurements of diameters and various-sized pial arteries in five cats (10 arteries) perfused with 5-HT confirms the above observations. Initial diameters of the vessels studied varied from 39.8 to 332.4 μ, the mean being 136.6 μ. The mean maximum constriction for the 10 arteries was 19.65 ± 1.47% of

Figure 2. Cortical surface after one hour Evan's blue perfusion through pial window. The window has been removed, as have the surrounding bone and dura mater. Cortical stain is restricted within the margins of the pial window.
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Figure 3. Microphotographs of pial vessels during 5-HT perfusion (original magnification 16X). a. Baseline appearance at onset of perfusion. b. Constriction of arteries and arterioles following 40 minutes of perfusion.

The resting diameter. In figure 4, the maximum constriction is plotted against the initial diameter of the vessels. There was no correlation between arterial size and the degree of constriction in response to 5-HT perfusion ($r = +0.27$, $P > .05$). The time to maximum constriction varied from five to thirty minutes with a mean of approximately nineteen minutes. There was no correlation between arterial diameter and speed of response.

The table summarizes rCBF values obtained after
TABLE 1  Effects of Perfusion Solutions on Regional Cerebral Blood Flow

<table>
<thead>
<tr>
<th>Perfusion solution</th>
<th>Cortex under perfusion port</th>
<th>Cortex remote from port</th>
<th>Subcortical white matter</th>
<th>Head of caudate nucleus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Superficial</td>
<td>Deep</td>
<td>Superficial</td>
<td>Deep</td>
</tr>
<tr>
<td>Mock CSF only (8)*</td>
<td>94 ± 4</td>
<td>95 ± 3</td>
<td>93 ± 4</td>
<td>99 ± 3</td>
</tr>
<tr>
<td>Tartaric acid (4)</td>
<td>98 ± 7</td>
<td>93 ± 6</td>
<td>96 ± 6</td>
<td>94 ± 7</td>
</tr>
<tr>
<td>Creatinine sulfate (4)</td>
<td>95 ± 7</td>
<td>90 ± 7</td>
<td>92 ± 7</td>
<td>89 ± 7</td>
</tr>
<tr>
<td>Norepinephrine (6)</td>
<td>94 ± 6</td>
<td>99 ± 7</td>
<td>90 ± 5</td>
<td>91 ± 5</td>
</tr>
<tr>
<td>Serotonin (6)</td>
<td>100 ± 5</td>
<td>96 ± 5</td>
<td>95 ± 6</td>
<td>93 ± 5</td>
</tr>
</tbody>
</table>

*Number of cerebral hemispheres tested.

one hour perfusion. For each animal, multiple determinations were made in superficial and deep cortex under the pial windows (perfusion ports), cortex remote from the ports, subcortical white matter, and the head of the caudate nucleus. rCBF was within normal limits in all preparations and no perfusion solution resulted in flow significantly different of those of mock CSF (p > .05). Fig. 5 is a representative autoradiograph in 5-HT perfusion.

Focal epileptiform activity was observed in 33% of the 42 NE perfusions. Spikes, occurring either singly or in paroxysms, were seen 9 to 56 minutes (mean time when present, 16 minutes) after perfusion was begun. There were electrical seizures in five animals, an example of which is shown in figure 6. Most of the remaining cats perfused with NE showed additional EEG abnormalities. However, the recording technique was not sufficiently standardized to analyze these changes with precision. EEG changes seen during perfusions with 5-HT and control solutions were rare and minor. Epileptiform activity was not seen with these agents.

Perfusions of 5-HT and control solutions had no significant effect on SEP's. When changes in signal latency and amplitude occurred, they were minor and/or transient. In contrast, the effect of NE on evoked responses was often striking. Four of the five cats perfused with NE demonstrated major shifts in latency or amplitude (fig. 7). Changes were restricted to waves occurring after 12 msec and presumably of cortical or immediately subcortical origin. Latency and amplitude changes varied in onset from 5 to 30 minutes following the start of the NE perfusion and followed no consistent pattern. Amplitude decreased in three cats and increased in one. Latency tended to be prolonged but was difficult to determine with accuracy when major changes in wave form occurred.

In 44% of NE perfusions, there was visible swelling.
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FIGURE 6. EEG during NE perfusion of left pial window, mock CSF perfusion on right. Paroxysmal spike discharges are localized to the region of the NE perfusion. (R = right, L = left, F = frontal, P = pial window, O = occipital EEG electrodes).

FIGURE 7. Somatosensory evoked potentials (SEP) in response to left median nerve stimulation and recorded from right pial window before and during NE perfusion on the right. Left knee reference electrode, shock artifact at t = 0. Two control tracings (each the average of 1024 stimulations) are superimposed to illustrate the stability of the preparation. Recordings at ten minute intervals illustrate latency and amplitude shifts of the later components of the SEP. Upward deflections represent negative potentials.

of the cortex underlying the pial window. Much milder apparent swelling was observed in 23% of the 5-HT and 11% of the control perfusions. Tartaric acid and creatinine sulfate solutions were not associated with greater swelling or EEG changes than was mock CSF; all three solutions are included in the control perfusion data. Water content of the superfused cortex was 83.7 ± 0.6% with NE (n = 4), 80.9 ± 0.4% with 5-HT (n = 4), and 80.4 ± 0.3% with control perfusion (n = 8), NE but not 5-HT being associated with significant edema (p < .01). None of the perfusion solutions influenced the blood brain barrier as determined by intravascular Evan’s blue solution. Intact and cut cortical surfaces showed no evidence of dye extravasation on low-power microscopic examination and ultraviolet illumination.

Discussion

The pial window technique avoids many of the pitfalls encountered in other pharmacological approaches to the cerebral cortex. The window is easily fabricated and inserted, and it is tolerated without significant cortical injury or dysfunction. Perfusions with control solutions do not cause cortical swelling or electrical abnormalities, and water content and regional cerebral blood flow of superfused cortex agree closely with normal values reported in the literature.63, 66 The blood-brain barrier does not interfere with delivery of monoamines by this route; indeed, it retards their egress from the parenchyma to the cerebral vessels.68 The distribution and site of action of the drugs are limited to the superfused cortex, and their concentrations are easily controlled.

Both NE and 5-HT penetrate the cortex from the pial surface, diffusing into deeper cortical layers within several minutes.7, 59, 61 Cortical penetration may be aided by diffusion along perivascular CSF channels.62 Distribution is predominantly to areas high in endogenous monoamines.63, 64 NE and 5-HT-containing nerve terminals are found mainly in the superficial cortical layers and are therefore easily accessible to topical monoamines.63, 66

The concentrations of NE and 5-HT used in this study are near the maximum levels achieved in peripheral blood, and hence represent the highest monoamine concentrations to which the cortex might be initially exposed in subarachnoid hemorrhage.67-70 The cortex might also come into contact with similar concentrations of monoamines released by axon terminals injured in mechanical or ischemic insults.71-76 The authors are aware that metabolic degradation of monoamines occurs in most physiologic solutions.76 However, we were reluctant to retard metabolism by adding acidifying or chelating agents to the perfusate because of the profound direct effect of these drugs on cerebral blood flow and function.77-80 That we observed pharmacological effects with our perfusions supports this decision. No such effects were seen during perfusions of tartaric acid or creatinine sulfate alone, suggesting that the monoamines themselves are the active agents.

The role of the pial microcirculation in regulating blood flow to the underlying cortex is the subject of debate.61, 81, 82 Although pial vascular diameters and
cortical rCBF both respond in the same direction to many stimuli, few studies have compared simultaneous reactions of both systems. Blair and Waltz* found similar decreases in pial arterial diameter and cortical blood flow following middle cerebral artery occlusion in cats. However, divergent responses have been reported following cervical sympathetic stimulation and experimental middle cerebral artery spasm.** Our finding that 5-HT produces pial vascular constriction without changes in rCBF to the underlying cortex is in agreement with the experience of Martins and associates,*** and provides further evidence against pial arterial control of cortical blood flow.

Subarachnoid hemorrhage (SAH) is often associated with spasm of major branches of the circle of Willis, areas of diminished rCBF, and focal neurologic abnormalities. Many investigators have considered vasospasm to be the major cause of both the circulatory and functional disturbances. Topical NE and especially 5-HT have been shown to cause constriction of major cerebral arteries.****,*****,*****,****** Nevertheless, there is no evidence that this constrictive effect of blood or its monoamine content is hemodynamically significant, either on large or small cerebral vessels. We have shown that at least one component of blood, NE, can adversely affect neuronal function without causing ischemia.

Many of our cats perfused with NE developed focal EEG abnormalities similar to those reported following cortical application of whole or hemolyzed blood.*** Kimishima, et al.***** found a lowered seizure threshold in rabbits after cisternal NE injection. The alterations in EEG and cortical evoked potentials during NE perfusions provide further evidence that exogenous NE in the cortical extracellular space can disrupt neuronal function. The lack of consistent changes in amplitude or latency is not readily explained but may result from variation in port placement and the huge and diverse neuronal populations exposed to the perfusate. However, the fact that such SEP and EEG changes were not seen when 5-HT and artificial CSF were perfused suggests a specific NE effect on cortical activity. It has been reported that NE and 5-HT in the CSF or free in the cerebral parenchyma disrupt the blood-brain barrier.*****,***** Our negative findings in this regard are in agreement with most recent studies.***** We have been unable to find previous descriptions of cortical edema produced by topical NE; reports on the effects of 5-HT are contradictory.*****,*****

Although previous studies have demonstrated an influence of NE on cortical neurons,*** single cisternal injections of monoamines have remarkably little neurological effect.*****,***** However, under conditions of normal CSF flow, injections are rapidly cleared from the CSF and hence maintain only brief contact with the cortical surface.*****,***** In subarachnoid hemorrhage, clotted and liquid blood may clog the subarachnoid pathways, retard CSF flow, and serve as a reservoir for monoamine release. This would ensure prolonged contact between blood-borne monoamines and the cerebral cortex, a situation approached in our experimental model. Under conditions of prolonged contact, we have demonstrated that NE in relatively low concentrations is capable of direct toxicity on cortical neurons without a concomitant change in regional cerebral blood flow or integrity of the blood-brain barrier.

A similar situation may exist in cortical trauma or ischemia. Although there are conflicting data regarding cortical concentration and metabolism of monoamines in these conditions,***,***,*****,****** there is clear evidence that NE and 5-HT are released by injured cortex.***,***,***,****** As pointed out by Wurtman and Zervas,*** monoamine release and redistribution may potentiate cerebral damage without necessarily changing their overall concentrations.

The normal NE concentration in the cerebral cortex of the cat is approximately 200 ng/g,***,***,*****,****** The NE and 5-HT content of the cortex is not homogeneous but is almost entirely restricted to terminal varicocities of projecting fibers, in which concentrations may reach 1 to 10 million ng/g.***,***** Free NE and 5-HT, such as might be released by subarachnoid blood or injured cerebral cortex, have been shown to enter neurons not normally exposed to these agents and possibly to disrupt neuronal function.***,***** Thus, indiscriminate neuronal effects of monoamines released by subarachnoid hemorrhage cortical damage may provide a clinical parallel to our experimental model.

In summary, exogenous NE is toxic to cortical neurons at a concentration which does not cause ischemia. On the other hand, 5-HT in concentrations which produce significant pial arterial constriction has no such toxic effects and no influence on flow to the underlying cortex.

The concentrations of both substances used in these experiments are those to which the cortex might be exposed in subarachnoid hemorrhage or neuronal damage secondary to trauma or infarction. The pial window technique provides an excellent model with which to study the role of various putative toxins on the progression of symptoms in these conditions.

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**Sympathetic Nerves Protect Against Blood-Brain Barrier Disruption in the Spontaneously Hypertensive Rat**

**SHIRLEY M. MUELLER, M.D., M.S., PHILLIP J. ERTEL, B.S., DAVID L. FELTEN, M.D., PH.D., AND J. MARC OVERHAGE, B.S.**

**SUMMARY** The cerebral vessels of spontaneously hypertensive rats (SHR) are reported to have an increased luminal size and decreased wall thickness after chronic sympathetic denervation. In order to evaluate a possible physiological significance of this observation, we studied blood-brain barrier protein transfer in two month old SHR and their normotensive controls, Wistar-Kyoto (WKY), during profound vasodilation stimuli one month after a unilateral superior cervical ganglionectomy. Our hypothesis was that during acute vasodilation, protein transfer, which is dependent on vessel tension (tension = pressure x radius/wall thickness), would be greater in the vasculature of the chronically denervated (De) than in contralateral innervated hemisphere (In). Vasodilation was induced with acute hypertension (norepinephrine) and seizures (bicuculline). Immediately prior, the cervical trunk to the innervated hemisphere was sectioned to prevent acute sympathetic neuronal effects. Protein transfer was assessed qualitatively with Evans blue dye and quantitatively with radioiodinated albumin. Successful chronic denervation was demonstrated by the absence of histofluorescence in De. Evans blue dye staining of SHR (n = 3) cerebral hemispheres was greater in De than in In. Radioiodinated albumin protein transfer was elevated in SHR De compared to In in each of eight animals studied (De-In = 0.16 ± 0.04%, *p < 0.01); WKY (n = 8) De protein transfer was not different from In (De-In = 0.07 ± 0.05%). These results suggest that the trophic influence of sympathetic nerves on SHR cerebral vessels contributes to protection of the blood-brain barrier during hypertension and seizures.

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CEREBRAL vessels of spontaneously hypertensive rats (SHR) undergo hypertrophy when compared to normotensive Wistar-Kyoto (WKY). This vascular hypertrophy of cerebral vessels in SHR has been interpreted as a protective adaptation which enhances vasoconstriction and attenuates microvascular pressure increases due to the hypertension. Hart et al. have suggested that sympathetic nerves enhance vascular hypertrophy based on their demonstration that a significantly decreased wall thickness is present in the intraparenchymal cerebral vessels of the stroke-prone subset of SHR after chronic sympathetic denervation. Intraparenchymal vessels provide the majority of vascular resistance in the intact cerebral vascular

bed. Thus, we hypothesized that a reduction in SHR intraparenchymal cerebral vessel wall thickness after chronic denervation could lead to a significantly enhanced wall tension (tension = pressure x radius/wall thickness) as blood pressure and vessel radius are increased. During basal conditions, a reduced wall thickness due to chronic sympathetic denervation would be expected to have little effect since cerebral vascular resistance is not altered over a wide range of arterial pressures or during hypocapnia after chronic sympathetic denervation. However, during profound vasodilation stimuli, such as an acute rise in arterial pressure and metabolic vasodilation, the effect of chronic sympathetic denervation may be unmasked as vessel wall tension rises. A number of consequences could follow including enhanced blood-brain barrier (BBB) permeability, cerebral edema and/or hemorrhage. To test this hypothesis, we determined vascular permeability to protein in the cerebral hemisphere and temporalis muscle of SHR and WKY during profound vasodilation induced with acute hypertension in conjunction with seizures. One side of the head of each of the rats was chronically sympathetically denervated. Thus, the tissue with normal...
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