Demonstration of Alpha and Beta Adrenergic Receptors in Canine Cerebral Vasculature

BY ROBERT F. LOWE, PH.D.* AND DAVID D. GILBOE, PH.D.†

Abstract:
Demonstration of Alpha and Beta Adrenergic Receptors in Canine Cerebral Vasculature

The cerebral vascular effects of various adrenomimetic agents were examined in 12 isolated canine brains perfused with blood at constant flow. Changes in cerebral vascular resistance (CVR) and the magnitude of pressor or depressor responses observed following drug injection were examined.

The presence of alpha adrenergic receptors in this vascular bed is indicated by the increased CVR observed when phenylephrine, norepinephrine, and epinephrine were administered and by the reduced or reversed pressor actions of these compounds following treatment with the alpha adrenergic blocking drug phenoxybenzamine HCl.

The presence of beta adrenergic receptors in this vascular bed is indicated by the decreased CVR noted when isoproterenol was given and by the reduced depressor actions of this compound following treatment with the beta adrenergic blocking drug propranolol. Further evidence for the presence of beta adrenergic receptors is demonstrated by the vasomotor reversal to epinephrine which was observed following alpha suppression with phenoxybenzamine.

As catecholamine blood levels in intact dogs are low in comparison to those achieved in these studies, it appears doubtful that circulating catecholamines play an important physiological role in the regulation of CVR. Possible explanations are considered for the lower response of the cerebral vasculature to catecholamines when this response is compared to that observed in other vascular beds.

ADDITIONAL KEY WORDS cerebral circulation phenoxybenzamine propranolol isolated brain catecholamines adrenoceptive sites

Introduction

The physiology of cerebral circulation has been studied extensively. While considerable information has been accumulated regarding the vasomotor effects of chemical compounds in this vascular bed, no general agreement has been reached with respect to the cerebral vascular actions of certain adrenomimetic agents. When applied to the surface of the dura or the pia these drugs have reportedly produced cerebral vasoconstriction, vasodilation, or no effect. Frequently effects different from those seen after topical application have been observed following systemic administration of these agents. The following studies were performed with an isolated, perfused canine brain preparation in an attempt to more clearly define the responses of the cerebral vasculature to adrenomimetic agents.

Methods

Twelve mongrel dogs were premedicated with morphine sulfate (60 mg, I.M.) 30 minutes prior...
to induction with the anesthetic methoxyflurane. The procedure for the isolation and perfusion of the canine brain, described elsewhere,2 involved the removal of the mandible, snout, and all extracranial soft tissue, leaving only the brain case intact. At the level of the second cervical vertebra a laminectomy was performed and the dura, spinal cord, and vertebral sinuses were ligated and transected. The internal carotid arteries and the anastomotic branch of the internal maxillary segment of the external carotid arteries supplied blood to the isolated brain in this preparation. Venous blood was returned to the oxygenator by gravity from a Luer connector placed through the bone covering the confluence of venous dural sinuses. Complete isolation of the canine brain by this method requires four to five hours. Such an extensive procedure can produce surgical shock. It has been shown that brain ATP levels are reduced in animals suffering from surgical shock and that this reduction in brain ATP can be prevented by administration of phenoxybenzamine.3 For this reason phenoxybenzamine HCl (0.5 mg/kg, I.V.) was administered to each animal at the time of anesthesia. A compatible donor was anticoagulated with heparin prior to infusion of 500 to 1,000 ml of 6% dextran to reduce the hematocrit.4 Between 400 and 500 ml of fresh blood were used to prime the Pemco micro disk oxygenator. Arterial blood was propelled by a variable speed roller pump, and passed through a dacron wool filter, a ten-tube heat exchanger, a manifold for injection of drugs and connection of a pressure transducer (Statham p23AA), and into the T-tubes placed in the common carotid arteries. At the time of isolation the roller pump was adjusted to deliver a constant flow of blood to the brain at approximately the mean aortic pressure observed just prior to isolation. The rate of blood flow was not altered during the course of the experiment. Perfusion pressure was monitored with the servo channel of a Gilson five-channel polygraph. A Grass eight-channel model III electroencephalograph was used to make intermittent recordings of brain electrical activity (EEG). Viability of the preparation was judged by the presence and quality of the EEG and the experiment was continued only if the brain exhibited a relatively normal EEG after isolation. The arterial inflow and the venous outflow temperatures were monitored with flexible thermistors placed in the line of blood flow. The blood was equilibrated with a mixture of 95% O2-5% CO2 and 100% O2 to achieve a Pco2 near 40 mm Hg. Arterial blood was sampled frequently to monitor pH, Pco2, and Po2. The gas mixture was adjusted and sodium bicarbonate (829 mEq/l) was injected as necessary in order to maintain a Pco2 of about 40

### Table 1

<table>
<thead>
<tr>
<th>Average Values for Measurements Made on the Isolated Perfused Canine Brain</th>
<th>Hematocrit</th>
<th>Po2 (mm Hg)</th>
<th>Pco2 (mm Hg)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>87.5 ± 4.0*</td>
<td>41.5 ± 9.12</td>
<td>44.5 ± 14.5</td>
<td>7.33 ± 0.06</td>
<td>597 ± 90.8</td>
</tr>
</tbody>
</table>

Values represent mean ± SD for 12 animals except Po2 values which were available only for nine dogs.
mm Hg and a pH of approximately 7.4. At the termination of each experiment the brain was removed from the skull and weighed. The pump was calibrated after each study so that flow/100 gm brain/min could be accurately calculated (table I).

The following drugs were used in these studies: /-phenylephrine (K & K Labs., Inc.), isoproterenol HCl (K & K Labs., Inc.), epinephrine HCl (K & K Labs., Inc.), norepinephrine bitartrate (K & K Labs., Inc.), phenoxybenzamine HCl (Smith, Kline & French), and propranolol (Ayerst). All drug dosages are expressed in terms of their base.

Drugs were rapidly injected into the perfusion system through the manifold. The dead space between the point of injection and the T tubes in the common carotid arteries was 34 ml. All drugs

Effects of drug injections on perfusion pressure in isolated canine brain. A: 0.9% NaCl injection followed by injection of phenylephrine (100 µg). B: norepinephrine injection (15 µg). C: epinephrine injection (15 µg). D: 0.9% NaCl injection after alpha suppression with phenoxybenzamine. E: phenylephrine injection (100 µg) after alpha suppression with phenoxybenzamine. Dog 2 (A-E), time as indicated in A. F: isoproterenol injection (20 µg). G: 0.9% NaCl injection followed by isoproterenol injection (20 µg) after beta suppression with propranolol. Dog 12 (F-G), time as indicated in F. Magnitudes of the pressor or depressor responses seen following injections were calculated by integration using Simpson's rule. Integration was begun following the injection artifact, just before drug-induced pressure changes were noted. Integration was terminated at the point where further changes in perfusion pressure were not apparent.
were prepared on the day of the experiment in 0.9% NaCl. Oxidation of the catecholamines was retarded by addition of 0.001% Na EDTA (K & K Labs., Inc.). Alpha adrenergic suppression was induced with phenoxybenzamine HCl (5 mg). Completeness of this blockade was tested 45 minutes after injection by administration of phenylephrine or norepinephrine. Beta adrenergic suppression was induced with propranolol (2 mg) and supplemented with additional doses of 1 mg given at ten-minute intervals. No more than three additional doses of propranolol were given. Completeness of this blockade was tested by administration of isoproterenol.

Alterations in perfusion pressure reflect changes in cerebral vascular resistance (CVR) because blood flow was held constant in each preparation. Pulsatile perfusion pressure was recorded and later converted to mean pressure for calculation of CVR (CVR = mean perfusion pressure [mm Hg]/cerebral blood flow [ml/min]). Since changes in perfusion pressure were usually small, the magnitude of the pressor or depressor responses was examined following injection of both 0.9% NaCl and adrenomimetic agents. In this context, magnitude refers to the area under the curve described by perfusion pressure following injection, and was calculated using Simpson's rule (fig. 1). Control injections of 0.9% NaCl uniformly produced a mild transitory drop in perfusion pressure (—0.6 ± 2.9 mm Hg). A similar response has been observed in other vascular beds and it is thought to reflect a decreased vascular resistance produced by transient alterations in blood viscosity. Since all drugs were made up in 0.9% NaCl, the areas calculated for individual drug injections in a given animal were corrected using the average value for all saline injections made in that animal.

Results

Phenylephrine
The effects of phenylephrine injections (50 to 200 µg) were determined in six dogs. Following injection the calculated CVR increased in every case. The magnitude of the pressor response, the area under a perfusion pressure curve, was positive in each case, giving further evidence that cerebral vasoconstriction had occurred. Following alpha adrenergic receptor suppression with phenoxybenzamine in four dogs, phenylephrine injections (100 µg) were less effective in increasing CVR than in corresponding control injections. The magnitude of each pressor response was also reduced when compared to its control (fig. 1A, D, and E, and table 2).

Isoproterenol
Seven isoproterenol injections (15 to 40 µg) were made in four dogs. Following injection the CVR decreased in each case. The negative areas observed following isoproterenol injections indicated that cerebral vasodilation had occurred. Following beta adrenergic receptor suppression with propranolol in three dogs, the changes in CVR and in the magnitude of the vasodilator responses to isoproterenol injections (15 to 40 µg) were reduced when compared to controls (fig. 1F and G, and table 2).

Norepinephrine
Thirteen norepinephrine injections (15 to 100 µg) were made in eight dogs. Calculated CVR increased and the area under the curve was positive in each case. Following alpha suppression in five dogs, the pressor effects of norepinephrine injections (15 to 100 µg) were reduced when compared to controls. In several cases negative areas and lowered CVRs indicated vasodilation had occurred (fig. 1B and table 2).

Epinephrine
Fourteen epinephrine injections (15 to 100 µg) were made in eight dogs. Calculated CVR increased and the area under the curve was positive in each case. Following alpha suppression in four dogs, the pressor effects of epinephrine injections (15 to 100 µg) were reduced when compared to controls. The calculated CVR decreased in all but one case and a number of negative areas were observed. In six of seven trials following beta suppression in four dogs, epinephrine injections (15 to 20 µg) increased both the CVR and the magnitude of the pressor response as compared to the corresponding controls (fig. 1C, table 2).

Discussion
An increase in cerebral blood flow has been observed following systemic administration of various catecholamines. Direct cerebral vascular effects of these agents could have been masked by transient passive vascular distention produced by increased systemic blood pressure or by cerebral vascular autoregulatory mechanisms which tend to oppose passive
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TABLE 2
The Effects of Adrenergic Receptor Suppression on the Vascular Actions of Adrenomimetic Agents in Isolated Canine Brain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (µg)</th>
<th>Control</th>
<th>Maximum or minimum observed</th>
<th>% change from control</th>
<th>Magnitude (areas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50(2)*</td>
<td>1.96 ± 0.31</td>
<td>+6.20 ± 4.23</td>
<td>+171.5 ± 65.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100(5)</td>
<td>2.41 ± 1.20</td>
<td>+8.33 ± 7.41</td>
<td>+330.4 ± 426.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200(2)</td>
<td>1.83 ± 0.32</td>
<td>+19.78 ± 7.38</td>
<td>+875.0 ± 298.4</td>
<td></td>
</tr>
<tr>
<td>After alpha suppression</td>
<td></td>
<td>3.59 ± 1.82</td>
<td>+0.20 ± 3.64</td>
<td>−45.0 ± 136.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100(3)</td>
<td>3.56 ± 1.83</td>
<td>3.57 ± 1.73</td>
<td>−180.0 ± 50.9</td>
<td></td>
</tr>
<tr>
<td>Isoproterenol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15(2)</td>
<td>1.79 ± 0.39</td>
<td>−5.52 ± 0.37</td>
<td>−779.0 ± 568.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20(3)</td>
<td>2.19 ± 0.43</td>
<td>−8.95 ± 3.37</td>
<td>−782.5 ± 233.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40(2)</td>
<td>2.27 ± 0.19</td>
<td>−5.86 ± 1.68</td>
<td>−139.0 ± 9.9</td>
<td></td>
</tr>
<tr>
<td>After beta suppression</td>
<td></td>
<td>3.68 ± 0.28</td>
<td>−4.07 ± 1.14</td>
<td>−94.6 ± 10.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15(1)</td>
<td>3.53 ± 0.26</td>
<td>3.52 ± 0.04</td>
<td>+1010.5 ± 23.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20(3)</td>
<td>3.22 ± 0.26</td>
<td>−0.58 ± 1.99</td>
<td>−94.6 ± 10.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40(1)</td>
<td>2.58 ± 0.24</td>
<td>−1.14 ± 1.13</td>
<td>−113 ± 113</td>
<td></td>
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<tr>
<td>Norepinephrine</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td>15(2)</td>
<td>2.79 ± 0.07</td>
<td>+12.05 ± 0.55</td>
<td>+512.0 ± 185.3</td>
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<tr>
<td></td>
<td>20(7)</td>
<td>2.27 ± 0.69</td>
<td>+6.02 ± 7.17</td>
<td>+403.5 ± 34.9</td>
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</tr>
<tr>
<td></td>
<td>30(2)</td>
<td>3.25 ± 0.26</td>
<td>+8.59 ± 7.64</td>
<td>+1010.5 ± 23.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60(1)</td>
<td>3.30 ± 0.26</td>
<td>+10.60 ± 2.60</td>
<td>+260 ± 260</td>
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<tr>
<td></td>
<td>100(1)</td>
<td>4.10 ± 0.39</td>
<td>+8.29 ± 1.44</td>
<td>+772 ± 772</td>
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</tr>
<tr>
<td>After alpha suppression</td>
<td></td>
<td>4.59 ± 0.25</td>
<td>−0.59 ± 1.71</td>
<td>+80.0 ± 87.7</td>
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<tr>
<td></td>
<td>20(4)</td>
<td>2.97 ± 0.84</td>
<td>−3.42 ± 5.64</td>
<td>−100.2 ± 156.5</td>
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</tr>
<tr>
<td></td>
<td>30(1)</td>
<td>4.56 ± 0.52</td>
<td>−0.68 ± 1.26</td>
<td>+126 ± 126</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60(1)</td>
<td>4.80 ± 0.34</td>
<td>+0.83 ± 1.96</td>
<td>+42 ± 42</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100(2)</td>
<td>4.61 ± 0.33</td>
<td>+4.95 ± 0.87</td>
<td>+273.0 ± 169.7</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15(3)</td>
<td>2.61 ± 0.50</td>
<td>+13.45 ± 1.63</td>
<td>+1232.3 ± 492.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20(5)</td>
<td>2.83 ± 1.14</td>
<td>+6.79 ± 2.55</td>
<td>+383.2 ± 293.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30(3)</td>
<td>2.90 ± 0.72</td>
<td>+13.21 ± 3.66</td>
<td>+802.3 ± 463.0</td>
<td></td>
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<tr>
<td></td>
<td>60(2)</td>
<td>2.90 ± 0.89</td>
<td>+10.63 ± 4.54</td>
<td>+392.5 ± 187.4</td>
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<tr>
<td></td>
<td>100(1)</td>
<td>4.42 ± 0.64</td>
<td>+11.59 ± 2.60</td>
<td>+900 ± 900</td>
<td></td>
</tr>
<tr>
<td>After alpha suppression</td>
<td></td>
<td>4.34 ± 0.23</td>
<td>−2.53 ± 1.23</td>
<td>+40 ± 40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20(1)</td>
<td>1.93 ± 0.86</td>
<td>−3.62 ± 1.60</td>
<td>−160 ± 160</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30(2)</td>
<td>4.93 ± 0.19</td>
<td>−9.06 ± 2.80</td>
<td>+63 ± 63</td>
<td></td>
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<tr>
<td></td>
<td>60(1)</td>
<td>4.80 ± 0.57</td>
<td>−4.79 ± 1.84</td>
<td>+67 ± 67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100(4)</td>
<td>3.24 ± 1.43</td>
<td>−0.60 ± 1.84</td>
<td>−54.5 ± 266.4</td>
<td></td>
</tr>
<tr>
<td>After beta suppression</td>
<td></td>
<td>3.82 ± 0.62</td>
<td>+11.51 ± 2.48</td>
<td>+1068 ± 1068</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20(6)</td>
<td>3.06 ± 0.62</td>
<td>+8.58 ± 2.48</td>
<td>+445.4 ± 410.8</td>
<td></td>
</tr>
</tbody>
</table>

*Number of injections at each dosage.
†Values represent the mean ± one standard deviation.

alterations in vascular diameter.¹⁴⁻¹⁸ Many communications exist between cerebral and extracerebral cranial vasculature;¹⁷,¹⁸ thus intra-arterial injection of vasoactive compounds into the cranial circulation could result in responses which reflect drug action on both vascular beds. It has also been shown that the extracerebral vasculature of the head is more responsive than the cerebral vasculature to many vasoactive compounds.¹⁹,²⁰ In these experiments isolation of the brain and perfusion at constant flow restricted drug action to
areas within the skull. The volatile anesthetic agent was discontinued following isolation. Consequently the variable effects of anesthesia on the brain and vasculature were minimized. Electroencephalographical activity, normal glucose uptake, and evidence that evoked potentials can be recorded from auditory and somatic sensory portions of the cerebral cortex are proof that the isolated canine brain preparation behaves normally in many respects.

These studies demonstrate that the cerebral vasculature is responsive to vasoactive catecholamines. The presence of alpha adrenergic receptors in this vascular bed is indicated by the fact that the usual increase in CVR that resulted from phenylephrine administration was reduced following treatment with the alpha adrenergic blocking agent phenoxybenzamine. Phenylephrine, a synthetic catecholamine, stimulates alpha adrenergic receptors while it is almost devoid of beta stimulating actions. The naturally occurring catecholamines, norepinephrine and epinephrine, possess alpha and beta stimulating properties on smooth muscle in a number of vascular beds, and were also found to increase CVR in this preparation. Their action was reduced or reversed following administration of phenoxybenzamine.

The changes in CVR were small in comparison to responses observed in other vascular beds following administration of large doses of pressor agents and were quite variable among animals. The magnitude of the response, as judged by the area under the perfusion pressure response curve, was equally variable among animals. The lack of a clear dose-response dependency may be the result of tachyphylaxis produced by the high blood levels of these agents which are not rapidly removed from the perfusion system in this preparation.

The presence of beta adrenergic receptors in this vascular bed is indicated by the fact that the usual decrease in CVR observed after isoproterenol administration was reduced following treatment with the beta adrenergic blocking agent propranolol. Isoproterenol is thought to stimulate only beta receptors. The vasomotor reversal to epinephrine and norepinephrine injections following alpha adrenergic receptor suppression further demonstrates the presence of beta receptors in this vascular bed. Cranial vasomotor reversal of a similar type was first demonstrated by Bouckaert and Jourdan with injections of adrenalin following treatment with ergotamine.

The results of these experiments substantiate the conclusions reached by a number of investigators. However, in many of the earlier studies it is not clear whether complete cerebral isolation was achieved; therefore, the possibility remained that drug effects on extracerebral vasculature of the head were interpreted as effects on cerebral vessels. Drug concentrations achieved in those studies probably were not sufficient to act through receptive sites in cerebral vessels, giving added support for this interpretation.

The results of the present studies are in disagreement with several more recent investigations, which have suggested that the agents used in this study have no effect on the intracranial vasculature. Compared to the drug doses used in the present study, the doses employed by those workers were low, and that could easily account for their failure to demonstrate the vasoactive properties of catecholamines on the cerebral vasculature. It is clear, however, that the cerebral vasculature is less responsive to catecholamines than other vascular beds. Structurally cerebral arteries contain smaller amounts of smooth muscle and are higher in elastic fiber content in comparison to vessels in other peripheral beds. Cerebral veins are composed mainly of connective tissue with no uniform number of layers. Innervation of these vessels is poorly developed and of questionable physiological significance. One recent study in the cat suggests that neuronal fibers are restricted to the adventitia of intracranial arteries and neuromuscular contacts to the border of the adventitia and the media. Innervation appears to be restricted to vessels larger than 50 $\mu$ in size. Electrical stimulation of the neuronal supply to the vessels of the pia produced a change in diameter of only 8%, whereas stimulation of vessels of similar size in the skin of the face produced an 80% change in diameter. In several studies, following topical application of epinephrine to the pia, only vessels larger than 50 $\mu$ in diameter were observed to constrict with any regularity. Thus, adrenergic receptors may be localized primarily in large vascular segments, and small
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changes in diameter produced by their stimulation may not alter CVR too much.

In the femoral vascular bed it has been shown that blood-born agents have difficulty interacting with receptors located in areas of neuromuscular contact. A similar situation may exist with respect to the vasculature of the brain. It is also possible that receptor populations are simply sparse in cerebral vessels.

Blood concentrations of catecholamines achieved in these experiments were much greater than would ever be expected to occur in the intact animal. One study has reported normal plasma levels of norepinephrine and epinephrine to be 2.09 ± 0.2 µg/ml and 0.29 ± 0.1 µg/ml respectively. In the same study stress produced by severe respiratory acidosis elevated norepinephrine and epinephrine levels to 9.04 ± 1.01 µg/ml and 5.44 ± 1.06 µg/ml. In our studies the lowest dose injected (15 µg), if diluted by the entire blood volume of the oxygenator, would have given a blood concentration of 30 µg/ml. Probably very little dilution took place from the time of injection to the time these agents reached the cerebral vasculature; consequently the vessels were undoubtedly exposed to much higher concentrations than 30 µg/ml.

Since large doses of vasoactive compounds are necessary to stimulate these receptors, it appears unlikely that naturally occurring catecholamines in the circulation play a major role in regulating CVR under physiological conditions. Furthermore, therapeutic administration of these agents to maintain the systemic blood pressure would be unlikely to reduce cerebral blood flow since autoregulatory mechanisms tend to maintain cerebral blood flow constant under conditions where systemic pressure is increased. It seems more likely that local metabolic factors in the brain are of greater importance in determining the level of CVR in the intact animal.

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