Effects of Cholinergic Nerves on Cerebral Blood Flow in Cats

DAVID W. BUSLIA AND DONALD D. HEISTAD

SUMMARY We studied the effects of parasympathetic nerves on cerebral blood flow (CBF). The greater superficial petrosal nerve, which apparently supplies cholinergic fibers to cerebral vessels and the lacrimal gland, was sectioned on one side at the internal auditory meatus in anesthetized cats. CBF was measured with 15-μm microspheres. Section of the petrosal nerve did not alter resting CBF. In addition, electrical stimulation of the distal cut end of the petrosal nerve had no effect on total CBF. In one area of the brain, the caudate nucleus, stimulation increased blood flow from 29 ± 2 to 36 ± 2 (mean ± sem) ml/min per 100 g. Lacrimal gland blood flow increased from 42 ± 7 to 198 ± 32 ml/min per 100 g during petrosal stimulation, which indicates that the stimulus was potent. In the same experiments, CBF increased 3- to 4-fold during hypercapnia; thus, cerebral vessels were responsive to another dilator stimulus. In other experiments, petrosal nerve section did not alter the response of cerebral vessels to hypercapnia (Pco2 > 50 mm Hg) or hypoxia (Po2 < 34 mm Hg). We conclude: (1) there is little or no resting vasodilator tone provided to cerebral vessels by the petrosal nerve; (2) petrosal nerve stimulation has a major effect on blood flow to the lacrimal gland but does not increase CBF; and (3) petrosal nerve section has little effect on the response of cerebral vessels to hypercapnia or hypoxia.


CEREBRAL vessels are richly supplied by both adrenergic and cholinergic nerves. It is clear that sympathetic nerves supplying cerebral vessels arise from the cervical sympathetic chain (Nielsen and Owman, 1967), but the origin of parasympathetic or cholinergic nerves is less well defined. One source of cholinergic fibers is thought to be the greater superficial petrosal nerve (Chorobski and Penfield, 1932; Cobb and Finesinger, 1932; Vasquez and Purves, 1979).

Effects of petrosal nerve stimulation or section on cerebral vessels have been controversial. Electrical stimulation of the petrosal nerve has been reported to increase pial vessel diameter (Cobb and Purves, 1932; Cobb and Finesinger, 1932; Vasquez and Purves, 1979). A recent study, however, failed to show a change in CBF during electrical stimulation of the petrosal nerve (Scremin et al., 1979). Section of the petrosal nerve has been reported to attenuate the response of cerebral vessels to hypercapnia (James et al., 1979) and hypoxia (Ponte and Purves, 1974) or to have no effect during these conditions (Bates and Bevan, 1979). Finally, responses to stimulation and section of stimulation. An additional feature of these studies was that we studied cats, a species with extensive cholinergic innervation of cerebral vessels and pronounced vasodilator responses to electrical stimulation in vitro (Duckles et al., 1977; Florence and Bevan, 1979). Finally, responses to stimulation and nerve section were studied under several experimental conditions: normocapnia, hypocapnia, hypercapnia, and hypoxia.

Methods

Twenty-eight cats (2.7-5.3 kg) were used. The cats were given sodium methohexital (30 mg/kg) intraperitoneally for initial anesthesia and intravenous chloralose (50 mg/kg) as needed during the experiments. They were intubated and ventilated with air and supplemental oxygen. A catheter was
placed into a femoral vein for the injection of drugs and fluids, and a catheter was inserted into a femoral artery for blood pressure recording and blood sampling. In some studies, heparin (500 U/kg i.v.) was given for anticoagulation. Body temperature was maintained at 37–38°C with a heating pad. After a left thoracotomy, a polyethylene catheter was placed into the left atrium over a 4- to 8-second period and the injection line was flushed with 5–7 ml of saline. The number of microspheres injected each time varied from 0.4 to 4.5 million. The nuclides used were \(^{46}\)Sc, \(^{95}\)Nb, \(^{85}\)Sr, \(^{113}\)Sn, \(^{141}\)Ce, and \(^{125}\)I. Withdrawal of reference blood samples began prior to microsphere injection and continued for 90 seconds afterward.

After each experiment, the cats were killed with intravenous KCl and the brain and lacrimal glands were removed. The brain was dissected according to region and tissue and placed in counting vials. Brain samples were classified as right and left cerebrum, cortical grey matter (sensory and visual areas), cerebral white matter (corpus callosum and centrum ovale), caudate nucleus, cerebellum, thalamus-midbrain, pons and medulla. Sample weights ranged from 0.1 to 2.0 g.

The tissues were counted in a 3-inch well-type \(\gamma\) counter after being weighed and placed in plastic test tubes. Blood samples were divided into aliquots so that counting geometry was similar to the tissue samples. The energy windows used were: \(^{46}\)Sc (400–750 keV), \(^{95}\)Nb (325–400 keV), \(^{85}\)Sr (230–275 keV), \(^{113}\)Sn (170–208 keV), \(^{141}\)Ce (65–80 keV), and \(^{125}\)I (18–34 keV). Polyspecific separation was performed using differential spectroscopy by the method of Rudolph and Heyman (1967).

Cerebral blood flow was calculated from the equation: 
\[
\text{CBF} = \frac{C_\text{B}}{C_\text{R}} \times \frac{100 \times \text{RBF}}{C_\text{B}}
\]
where CBF = cerebral blood flow in ml/min per 100 g, C_\text{B} = counts per g of brain, RBF = reference blood flow (rate of withdrawal of blood samples from reference arteries in ml/min), and C_\text{R} = total counts in the reference arterial blood samples. Lacrimal gland blood flow was determined in a similar fashion.

**Petrosal Nerve Isolation**

The scalp and external ear were removed to expose the tympanic membrane. The facial nerve was cut at the stylomastoid foramen, and the muscles attached to the lateral aspect of the tympanic bulla were separated from bone. The lateral side of the tympanic bulla was removed. In sham-operated sides, the surgery was stopped after removal of a portion of the lateral tympanic bulla. The facial nerve was placed along its course from the stylomastoid foramen to the internal auditory meatus. The greater superficial petrosal nerve, a branch of the nervus intermedius, travels with the facial nerve from the internal auditory meatus to the geniculate ganglion. Both nerves, and the vestibulo-cochlear nerve, were cut at the internal auditory meatus. The vestibulo-cochlear nerve was sectioned to prevent antidromic stimulation during petrosal nerve stimulation.

After the nerves were sectioned, the internal auditory meatus was sealed with bone wax. Bleeding from bone was stopped with bone wax and the area was kept dry with small surgical sponges. The petrosal nerve was activated by electrical stimulation of the entire nerve bundle containing the petrosal nerve and facial nerve proximal to the geniculate ganglion. Stimulation parameters were 5–20 V, 20 Hz, and 2–3 msec. Adequate stimulation activated the ipsilateral lacrimal gland.

**Denervation and Stimulation of Petrosal Nerve**

These studies were designed to determine if there is resting cholinergic tone to cerebral vessels and whether stimulation of the petrosal nerve increases CBF. In 13 cats, CBF and lacrimal gland blood flow were determined at the following times: (1) after unilateral section of the petrosal nerve, (2) after 20–30 seconds and 120–180 seconds of unilateral stimulation, and (3) during hypercapnia to determine if the cerebral vessels were responsive to a dilator stimulus. Arterial pH, PO\(_2\), and PCO\(_2\) also were determined at the time of each measurement.

We considered the possibility that, when cerebral vessels are constricted, the dilator response to stimulation would increase. CBF was measured during petrosal nerve stimulation during hypocapnia. In four cats, CBF and lacrimal gland blood flow were determined: (1) during normocapnia after unilateral petrosal nerve section, (2) during hypocapnia after unilateral nerve section, and (3) during hypocapnia after 20–30 seconds of unilateral stimulation.

**Temporal Response to Hypercapnia and Hypoxia**

These experiments were designed to determine if sectioning the petrosal nerve alters the temporal response of cerebral vessels to hypercapnia and hypoxia. In 13 cats, the petrosal nerve was sectioned on one side and sham surgery was performed on the other side (see above). Sham surgery was done on the side contralateral to nerve section because there was modest attenuation of CBF during hypercapnia on the operated side in the earlier studies (Table 1).

In seven cats, CBF was determined during normocapnia and after 40–60 seconds, 1½–2½ minutes, 3–4½ minutes, and 5–6 minutes of hypercapnia. Hypercapnia was induced by adding CO\(_2\) to the
inspired gas. In six other cats, CBF was determined during normocapnia and after 1–2 minutes and 8 minutes of hypoxia. Hypoxia was induced by ventilating the animals with 5% O₂ in N₂. During hypercapnia and hypoxia it was often necessary to tighten a ligature around the descending aorta to maintain arterial blood pressure at a normal level. In this group of animals, the femoral arterial catheter tip was confirmed by palpation. Tightening the ligature around the aorta did not dampen the blood pressure wave contour.

Statistical Analysis
All blood flow data were analyzed using paired t-test (one-tailed); the Bonferroni correction for α-level was used to maintain the overall α-level at 0.05 during multiple comparisons (Neter and Wasserman, 1974).

Results
Electrical stimulation of the petrosal nerve had only a small effect on CBF during normocapnia or hypocapnia despite a dramatic (4- to 6-fold) increase in ipsilateral lacrimal gland blood flow (Tables 1 and 2; Figs. 1 and 2). Blood flow to the caudate nucleus appeared to increase bilaterally (27%) at 25 seconds but returned to control levels by 90 seconds (Table 1). Sympathetic nerves have a bilateral distribution to some basal and medial areas of the brain (Nielsen and Owman, 1967), and it is possible that there is bilateral petrosal nerve innervation to the caudate nucleus in cats. The increase in caudate blood flow, however, was small. Blood flow to other areas of the brain did not change during stimulation, except flow to the medulla increased 14% with stimulation (Table 2) during hypocapnia.

Although petrosal nerve stimulation did not increase CBF, hypercapnia produced a 3- to 4-fold increase in flow in the same experiments (Table 1; Fig. 1). Thus, cerebral vessels were responsive to a dilator stimulus. During hypercapnia, flow tended to be less on the denervated side, compared to the intact side, probably because surgery to isolate the petrosal nerve reduced the capacity of cerebral vessels to respond during hypercapnia in a nonspecific fashion. Nonetheless, cerebral vessels were still very responsive during hypercapnia. Sham surgery, with an intact petrosal nerve, eliminated this side difference during hypercapnia (Table 3) and hypoxia (Table 4, Figure 3).

Comparison of CBF on the side with petrosal nerve section and the intact or sham-operated side in 30 control measurements during normocapnia and hypocapnia (Tables 1–4) indicate that there is little or no resting effect of this nerve on cerebral vessels.

Section of the petrosal nerve did not alter responses of cerebral vessels to hypercapnia (Table 3) or hypoxia (Table 4; Fig. 3). Cerebral blood flow was similar on the denervated and sham sides dur-

---

**Table 1** Petrosal Nerve Denervation and Stimulation (Normocapnia)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>25 sec</th>
<th>90 sec</th>
<th>Hypercapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>89 ± 3</td>
<td>81 ± 3</td>
<td>83 ± 6</td>
<td>86 ± 6</td>
</tr>
<tr>
<td>Arterial blood gases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pco₂ (mm Hg)</td>
<td>31 ± 0.8</td>
<td>32 ± 1</td>
<td>31 ± 0.6</td>
<td>54 ± 2*</td>
</tr>
<tr>
<td>pH</td>
<td>7.38 ± 0.01</td>
<td>7.38 ± 0.01</td>
<td>7.38 ± 0.01</td>
<td>7.15 ± 0.01*</td>
</tr>
<tr>
<td>P0₂ (mm Hg)</td>
<td>172 ± 12</td>
<td>171 ± 14</td>
<td>175 ± 24</td>
<td>132 ± 24</td>
</tr>
</tbody>
</table>

Blood flow (ml/min per 100 g):  

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Denervated</th>
<th>Intact</th>
<th>Stimulation</th>
<th>Intact</th>
<th>Stimulation</th>
<th>Intact</th>
<th>Denervated</th>
<th>Intact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrum</td>
<td>31 ± 2</td>
<td>34 ± 2</td>
<td>35 ± 2</td>
<td>37 ± 2</td>
<td>30 ± 2</td>
<td>32 ± 2</td>
<td>118 ± 27*</td>
<td>146 ± 36*</td>
</tr>
<tr>
<td>Cerebral grey matter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortex</td>
<td>46 ± 4</td>
<td>48 ± 4</td>
<td>50 ± 5</td>
<td>50 ± 5</td>
<td>50 ± 6</td>
<td>46 ± 6</td>
<td>185 ± 48*</td>
<td>196 ± 58*</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>29 ± 2</td>
<td>30 ± 2</td>
<td>36 ± 2*</td>
<td>39 ± 4*</td>
<td>34 ± 4</td>
<td>36 ± 5</td>
<td>82 ± 20*</td>
<td>88 ± 27*</td>
</tr>
<tr>
<td>Cerebral white matter</td>
<td>18 ± 2</td>
<td>20 ± 2</td>
<td>22 ± 4</td>
<td>22 ± 3</td>
<td>20 ± 2</td>
<td>23 ± 3</td>
<td>40 ± 10*</td>
<td>54 ± 12*</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>35 ± 2</td>
<td>36 ± 2</td>
<td>36 ± 3</td>
<td>38 ± 3</td>
<td>30 ± 2</td>
<td>32 ± 2</td>
<td>125 ± 29*</td>
<td>134 ± 30*</td>
</tr>
<tr>
<td>Brainstem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>32 ± 2</td>
<td>31 ± 2</td>
<td>38 ± 3</td>
<td>36 ± 3</td>
<td>32 ± 2</td>
<td>32 ± 3</td>
<td>114 ± 26*</td>
<td>126 ± 30*</td>
</tr>
<tr>
<td>Medulla</td>
<td>30 ± 2</td>
<td>28 ± 2</td>
<td>38 ± 3</td>
<td>32 ± 4</td>
<td>27 ± 2</td>
<td>30 ± 4</td>
<td>96 ± 22*</td>
<td>98 ± 28*</td>
</tr>
<tr>
<td>Pons</td>
<td>22 ± 2</td>
<td>27 ± 3</td>
<td>26 ± 3</td>
<td>30 ± 3</td>
<td>22 ± 3</td>
<td>28 ± 3</td>
<td>76 ± 22*</td>
<td>112 ± 25*</td>
</tr>
<tr>
<td>Thalamus-midbrain</td>
<td>34 ± 2</td>
<td>32 ± 2</td>
<td>39 ± 3</td>
<td>36 ± 3</td>
<td>36 ± 3</td>
<td>34 ± 4</td>
<td>130 ± 29*</td>
<td>142 ± 34*</td>
</tr>
<tr>
<td>Lacrimal gland</td>
<td>42 ± 7</td>
<td>30 ± 8</td>
<td>198 ± 32*</td>
<td>24 ± 7</td>
<td>264 ± 40*†</td>
<td>35 ± 7</td>
<td>26 ± 4</td>
<td>17 ± 2</td>
</tr>
</tbody>
</table>

| n                     | 13         | 10      | 7           | 6       |

Values are mean ± se.  
* Significantly different from control, P < 0.05.  
† Significantly different from intact side, P < 0.05.
TABLE 2  
**Petrosal Nerve Denervation and Stimulation (Hypocapnia)**

<table>
<thead>
<tr>
<th>Side</th>
<th>Control</th>
<th>Stimulation (25 sec)</th>
<th>Normocapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood gases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pco2 (mm Hg)</td>
<td>16 ± 0.5</td>
<td>14 ± 0.9</td>
<td>32 ± 2*</td>
</tr>
<tr>
<td>pH</td>
<td>7.62 ± 0.03</td>
<td>7.64 ± 0.04</td>
<td>7.35 ± 0.04*</td>
</tr>
<tr>
<td>Po2 (mm Hg)</td>
<td>174 ± 29</td>
<td>177 ± 29</td>
<td>153 ± 12</td>
</tr>
</tbody>
</table>

Blood flow (ml/min per 100 g):

<table>
<thead>
<tr>
<th>Side</th>
<th>Denervated</th>
<th>Intact</th>
<th>Stimulated</th>
<th>Intact</th>
<th>Denervated</th>
<th>Intact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrum</td>
<td>24 ± 3</td>
<td>24 ± 3</td>
<td>24 ± 2</td>
<td>24 ± 2</td>
<td>34 ± 3*</td>
<td>36 ± 2*</td>
</tr>
<tr>
<td>Cerebral grey matter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortex</td>
<td>32 ± 4</td>
<td>34 ± 3</td>
<td>31 ± 4</td>
<td>34 ± 3</td>
<td>48 ± 2*</td>
<td>50 ± 4*</td>
</tr>
<tr>
<td>Caudate</td>
<td>24 ± 3</td>
<td>21 ± 3</td>
<td>28 ± 3</td>
<td>25 ± 4</td>
<td>27 ± 2</td>
<td>28 ± 0.6</td>
</tr>
<tr>
<td>Cerebral white matter</td>
<td>12 ± 1</td>
<td>12 ± 6</td>
<td>16 ± 4</td>
<td>16 ± 6</td>
<td>18 ± 2</td>
<td>17 ± 3</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>25 ± 2</td>
<td>25 ± 3</td>
<td>28 ± 2</td>
<td>28 ± 2</td>
<td>36 ± 2*</td>
<td>41 ± 7*</td>
</tr>
<tr>
<td>Brainstem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>23 ± 4</td>
<td>23 ± 4</td>
<td>26 ± 4</td>
<td>24 ± 3</td>
<td>36 ± 3</td>
<td>36 ± 5</td>
</tr>
<tr>
<td>Medulla</td>
<td>21 ± 4</td>
<td>22 ± 4</td>
<td>24 ± 3*</td>
<td>24 ± 4</td>
<td>35 ± 2*</td>
<td>38 ± 4*</td>
</tr>
<tr>
<td>Pons</td>
<td>21 ± 6</td>
<td>20 ± 3</td>
<td>22 ± 4</td>
<td>18 ± 3</td>
<td>32 ± 7*</td>
<td>32 ± 4*</td>
</tr>
<tr>
<td>Thalamus-midbrain</td>
<td>24 ± 4</td>
<td>24 ± 4</td>
<td>26 ± 4</td>
<td>26 ± 4</td>
<td>36 ± 4</td>
<td>36 ± 6</td>
</tr>
<tr>
<td>Lacrimal gland</td>
<td>32 ± 7</td>
<td>31 ± 8</td>
<td>189 ± 34*†</td>
<td>26 ± 3</td>
<td>18 ± 1</td>
<td>14 ± 2</td>
</tr>
</tbody>
</table>

Values are mean ± SE.
* Significantly different from control, \( P < 0.05 \).
† Significantly different from intact side, \( P < 0.05 \).

Discussion

The major finding of these studies is that fibers of the greater superficial petrosal nerve have little effect on CBF under several experimental conditions. There is little or no resting vasodilator tone provided to cerebral vessels by the petrosal nerve, and intense electrical stimulation of the nerve has no significant effect on CBF during normocapnia or hypocapnia. In addition, section of the petrosal nerve does not attenuate the dilator response of cerebral vessels to hypercapnia or hypoxia. Our results, therefore, provide evidence that the petrosal nerve does not play an important role in the regulation of CBF. There are at least two possible explanations for our findings. First, contrary to the conclusion of several investigators, the petrosal nerve is not an important route of cholinergic nerves to cerebral vessels. Second, cholinergic nerves, provided by the petrosal nerve, are not important in the regulation of CBF under the conditions that we have studied. The discussion will focus on these two possibilities.

Cholinergic Innervation of Cerebral Vessels

Evidence provided from several methods suggest that cerebral vessels have a rich cholinergic innervation. First, electron microscopy demonstrates the presence of agranular vesicles, commonly associated with acetylcholine, in varicosities of nerve terminals on cerebral vessels (Edvinsson et al., 1972). In contrast to sympathetic nerves, however, cholinergic nerves appear to innervate only extra-
parenchymal vessels, and not intraparenchymal cerebral vessels. Second, specific biochemical assays (choline acetyltransferase concentration and high affinity choline uptake) demonstrate the presence of cholinergic nerves on large pial arteries in cerebral vessels. Although several investigators have reported that electrical or physiological activation of the petrosal nerve increases blood flow to all areas of the brain by 2 minutes of hypercapnia, Vasquez and Purves (1977) dem-

FIGURE 2. Comparison of the change in blood flow from control during petrosal nerve stimulation in the cerebrum, caudate nucleus and lacrimal gland. Values are means ± SE in 13 cats; *P < 0.05.

**TABLE 3** Response to Hypercapnia after Petrosal Nerve Section*

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>50 sec</th>
<th>2 min</th>
<th>4 min</th>
<th>6 min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arterial blood gases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pco2 (mm Hg)</td>
<td>31 ± 0.8</td>
<td>43 ± 2</td>
<td>52 ± 2</td>
<td>55 ± 2</td>
<td>59 ± 2</td>
</tr>
<tr>
<td>pH</td>
<td>7.42 ± 0.02</td>
<td>7.31 ± 0.04</td>
<td>7.22 ± 0.02</td>
<td>7.22 ± 0.03</td>
<td>7.18 ± 0.03</td>
</tr>
<tr>
<td>Po2 (mm Hg)</td>
<td>164 ± 8</td>
<td>105 ± 27</td>
<td>118 ± 16</td>
<td>116 ± 18</td>
<td>106 ± 15</td>
</tr>
</tbody>
</table>

Blood flow (ml/min per 100 g):

<table>
<thead>
<tr>
<th></th>
<th>Denervated</th>
<th>Sham</th>
<th>Denervated</th>
<th>Sham</th>
<th>Denervated</th>
<th>Sham</th>
<th>Denervated</th>
<th>Sham</th>
<th>Denervated</th>
<th>Sham</th>
<th>Denervated</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerebrum</strong></td>
<td>45 ± 6</td>
<td>44 ± 6</td>
<td>59 ± 12</td>
<td>58 ± 12</td>
<td>78 ± 9</td>
<td>76 ± 9</td>
<td>93 ± 6</td>
<td>92 ± 6</td>
<td>106 ± 8</td>
<td>105 ± 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cerebral grey matter</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortex</td>
<td>63 ± 8</td>
<td>58 ± 6</td>
<td>96 ± 16</td>
<td>92 ± 21</td>
<td>128 ± 16</td>
<td>119 ± 14</td>
<td>150 ± 14</td>
<td>150 ± 19</td>
<td>172 ± 19</td>
<td>168 ± 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>42 ± 6</td>
<td>44 ± 5</td>
<td>48 ± 8</td>
<td>51 ± 9</td>
<td>63 ± 6</td>
<td>64 ± 5</td>
<td>74 ± 3</td>
<td>73 ± 7</td>
<td>82 ± 7</td>
<td>76 ± 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral white matter</td>
<td>24 ± 3</td>
<td>21 ± 2</td>
<td>27 ± 6</td>
<td>22 ± 2</td>
<td>28 ± 2</td>
<td>26 ± 2</td>
<td>40 ± 4</td>
<td>33 ± 2</td>
<td>40 ± 4</td>
<td>30 ± 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>48 ± 6</td>
<td>46 ± 6</td>
<td>68 ± 12</td>
<td>68 ± 14</td>
<td>86 ± 8</td>
<td>83 ± 10</td>
<td>104 ± 7</td>
<td>102 ± 8</td>
<td>114 ± 6</td>
<td>114 ± 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Brainstem</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>40 ± 5</td>
<td>44 ± 6</td>
<td>63 ± 12</td>
<td>64 ± 12</td>
<td>76 ± 8</td>
<td>80 ± 9</td>
<td>94 ± 8</td>
<td>95 ± 6</td>
<td>102 ± 4</td>
<td>106 ± 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medulla</td>
<td>32 ± 4</td>
<td>30 ± 5</td>
<td>52 ± 10</td>
<td>60 ± 10</td>
<td>59 ± 6</td>
<td>71 ± 4</td>
<td>77 ± 6†</td>
<td>92 ± 4</td>
<td>82 ± 4</td>
<td>94 ± 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fons</td>
<td>31 ± 4</td>
<td>34 ± 6</td>
<td>50 ± 11</td>
<td>54 ± 12</td>
<td>60 ± 7</td>
<td>64 ± 10</td>
<td>74 ± 9</td>
<td>76 ± 6</td>
<td>76 ± 4</td>
<td>86 ± 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus-midbrain</td>
<td>46 ± 6</td>
<td>48 ± 6</td>
<td>72 ± 14</td>
<td>68 ± 14</td>
<td>87 ± 10</td>
<td>84 ± 10</td>
<td>106 ± 8</td>
<td>108 ± 7</td>
<td>116 ± 6</td>
<td>113 ± 8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE.

* Arterial blood pH decreased and Pco2 increased during hypercapnia. P < 0.05. Blood flow increased to all areas of the brain by 2 minutes of hypercapnia, except cerebral white matter at 2 and 4 minutes, P < 0.05.

† Significantly different from sham-operated side, P < 0.05.
TABLE 4  Response to Hypoxia after Petrosal Nerve Section*

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1½ min</th>
<th>8 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>86 ± 4</td>
<td>86 ± 6</td>
<td>94 ± 4</td>
</tr>
<tr>
<td>Arterial blood gases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pco2 (mm Hg)</td>
<td>32 ± 2</td>
<td>32 ± 1</td>
<td>32 ± 2</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 ± 0.04</td>
<td>7.37 ± 0.04</td>
<td>7.34 ± 0.06</td>
</tr>
<tr>
<td>Po2 (mm Hg)</td>
<td>155 ± 15</td>
<td>134 ± 4</td>
<td>30 ± 2</td>
</tr>
</tbody>
</table>

Blood flow (ml/min per 100 g):

<table>
<thead>
<tr>
<th></th>
<th>Denervated</th>
<th>Sham</th>
<th>Denervated</th>
<th>Sham</th>
<th>Denervated</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrum</td>
<td>31 ± 4</td>
<td>31 ± 4</td>
<td>64 ± 6</td>
<td>64 ± 6</td>
<td>89 ± 14</td>
<td>86 ± 15</td>
</tr>
<tr>
<td>Cerebral grey matter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortex</td>
<td>45 ± 6</td>
<td>46 ± 4</td>
<td>96 ± 9</td>
<td>96 ± 12</td>
<td>122 ± 24</td>
<td>122 ± 23</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>28 ± 2</td>
<td>28 ± 2</td>
<td>62 ± 4</td>
<td>60 ± 6</td>
<td>72 ± 8</td>
<td>74 ± 13</td>
</tr>
<tr>
<td>Cerebral white matter</td>
<td>19 ± 2</td>
<td>18 ± 3</td>
<td>26 ± 3</td>
<td>30 ± 4</td>
<td>32 ± 7</td>
<td>31 ± 4</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>36 ± 5</td>
<td>35 ± 5</td>
<td>74 ± 8</td>
<td>76 ± 8</td>
<td>100 ± 16</td>
<td>101 ± 17</td>
</tr>
<tr>
<td>Total</td>
<td>33 ± 4</td>
<td>32 ± 4</td>
<td>72 ± 8</td>
<td>71 ± 6</td>
<td>102 ± 20</td>
<td>102 ± 17</td>
</tr>
<tr>
<td>Medulla</td>
<td>30 ± 4</td>
<td>32 ± 5</td>
<td>63 ± 6†</td>
<td>71 ± 6</td>
<td>92 ± 18</td>
<td>101 ± 18</td>
</tr>
<tr>
<td>Pons</td>
<td>26 ± 4</td>
<td>26 ± 4</td>
<td>56 ± 4</td>
<td>55 ± 5</td>
<td>77 ± 11</td>
<td>71 ± 10</td>
</tr>
<tr>
<td>Thalamus-midbrain</td>
<td>36 ± 5</td>
<td>33 ± 4</td>
<td>78 ± 10</td>
<td>74 ± 6</td>
<td>111 ± 24</td>
<td>108 ± 18</td>
</tr>
</tbody>
</table>

Values are means ± SE.

* Arterial blood Po2 decreased during hypoxia, P < 0.05. Blood flow increased to all areas of the brain by early hypoxia, P < 0.05.
† Significantly different from sham-operated side, P < 0.05.

Figure 3  Effect of petrosal nerve section on the response of cerebral vessels to hypoxia. The petrosal nerve was sectioned on one side (O) and sham surgery was performed on the other side (●). The increase in blood flow to the cerebrum during hypoxia was the same on both sides. Values are means ± SE in 6 cats.
difference in flow between the denervated and sham sides if petrosal nerve pathways were activated during hypercapnia and hypoxia.

Experimental Conditions

If the increase in CBF during petrosal nerve stimulation is transient, as with the cerebral vasoconstriction during sympathetic stimulation in rabbits (Sercombe et al., 1979) and monkeys (Marcus et al., 1978), then it is possible that we missed the response. This possibility seems unlikely because we measured CBF during stimulation at 2 times: after 20-30 seconds (when effects of sympathetic nerves on CBF are maximal) and after 60-120 seconds of stimulation.

It is possible that the petrosal nerve supplies cerebral vessels but that major neural effects are detectable during conditions other than those we examined. Because cholinergic nerves appear to supply extraparenchymal but not intraparenchymal arteries (Edvinsson et al., 1972), dilation of these vessels during stimulation might not result in an increase in CBF. If large arteries dilate during petrosal nerve stimulation, downstream (intraparenchymal) arteries may constrict in response to increased intraluminal pressure. Although the proportion of total vascular resistance of each of these segments may change during stimulation, CBF may not change. This response would be analogous to that in cats during sympathetic stimulation. Although large pial arteries constrict during sympathetic stimulation in cats (Wei et al., 1975), CBF does not change (Heistad et al., 1978), probably because smaller downstream arteries dilate. We attempted to reduce the potential for "autoregulatory" constriction of downstream vessels during petrosal nerve stimulation by lowering arterial Pco2. During hypocapnia, however, there was little effect of stimulation on CBF.

Although we have found no effect of the petrosal nerve on CBF during normocapnia, hypocapnia, hypercapnia, or hypoxia, it is possible that major effects are detectable under other conditions. In this respect, the petrosal nerve may be analogous to sympathetic nerves. Effects of sympathetic nerves on CBF are detectable only under certain conditions. For example, electrical stimulation of sympathetic nerves has minimal effects on CBF during normal conditions but marked effects during sudden moderate increases in arterial pressure (Busija et al., 1980) and severe hypertension (Heistad et al., 1978). Thus, we cannot rule out a role for the petrosal nerve in the regulation of CBF.

Cholinergic nerves also may play a role in modulating effects of sympathetic nerves on cerebral vessels. There is a close anatomical relationship between cholinergic and sympathetic nerves (Edvinsson et al., 1972). Activation of nicotinic receptors on sympathetic nerves can attenuate the release of norepinephrine from cerebral vessels (Edvinsson et al. 1977) or reduce the effects of sympathetic nerve stimulation on CBF in rabbits (Aubineau et al., 1977). The primary effects of cholinergic nerves, then, may be in modulating effects of sympathetic nerves on cerebral vessels rather than direct effects.

Acknowledgments

We thank Lori Panther for technical assistance, Dr. William Clarke for assistance with the statistical analysis, Anita Riggan for typing the manuscript, and Drs. Melvin Marcus and Allyn Mark for critically reviewing the manuscript.

References


Effects of Intracoronary Administration of Bradykinin on the Impulse Activity of Afferent Sympathetic Unmyelinated Fibers with Left Ventricular Endings in the Cat

Federico Lombardi, Paolo Della Bella, Rodolfo Casati, and Alberto Malliani

SUMMARY In anesthetized and artificially ventilated cats, we recorded the impulse activity of 23 afferent sympathetic unmyelinated fibers with left ventricular endings, dissected from the left sympathetic rami T3 and T4. All fibers displayed a spontaneous discharge at a rate of 0.79 ± 0.2 impulses/sec. During constriction of the thoracic aorta, the discharge increased to 1.92 ± 0.2 impulses/sec. During myocardial ischemia, produced by interruption of left main coronary artery perfusion, supplied through an extracorporeal pump, the impulse activity increased to 1.73 ± 0.3 impulses/sec. The mean latency for this excitation was 16.5 ± 1.5 sec. The intracoronary administration of bradykinin (5 and 10 ng/kg) elicited a marked increase in impulse activity that, following 5 ng/kg, reached 2.06 ± 0.2 impulses/sec, after a latency of 18 ± 2 sec and in absence of significant hemodynamic changes. Myocardial ischemia and bradykinin never revealed the existence of silent afferent fibers included in the split nerve strand. The results obtained with this experimental model indicate that the ventricular endings of these afferent sympathetic unmyelinated fibers act as "polymodal" receptors. We hypothesize that the peripheral mechanism for cardiac nociception involves intensive excitation of fibers discharging spontaneously and not recruitment of silent fibers which are purely nociceptive in function.

Effects of cholinergic nerves on cerebral blood flow in cats.

D W Busija and D D Heistad

doi: 10.1161/01.RES.48.1.62

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/48/1/62