Sympathetic Cerebral Vasoconstriction Blocked by Adrenergic Alpha Receptor Antagonists

BY LOUIS G. D'ALECY, D.M.D., PH.D.*

Abstract:

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Alpha receptor adrenergic antagonists were used in chloralose-anesthetized dogs to block cerebral vasoconstriction elicited by stimulation of the sympathetic innervation of the cerebral vessels. A venous outflow technique was used to measure cerebral blood flow with an electromagnetic flow transducer. The brain's arterial supply was left undisturbed. The experiments were performed in both open and closed chest animals and in animals with open and closed craniums. The left sympathetic stellate ganglion was stimulated for 60 seconds at 15 Hz, 3 msec pulse duration, and 3 to 9 v intensity. Control stimulation produced a 65.8% decrease in cerebral blood flow. Dibozane, 1 or 2 mg/kg, or phentolamine, 2 mg/kg, was then administered, and stimulations were repeated with the same stimulus parameters. After alpha receptor blockade, cerebral blood flow decreased only 3.5% with sympathetic stimulation. The effective blockade by two different alpha receptor antagonists, of a different structure, indicated that an alpha receptor was responsible for the sympathetically mediated cerebral vasoconstriction. In conclusion, stimulation of the sympathetic innervation of the cerebral vessels results in a marked decrease in cerebral blood flow which is blocked by alpha receptor antagonists.

Additional Key Words: autonomic nervous system, dibozane, phentolamine, cervical sympathetic chain, neural vascular control

Previous studies have indicated that sympathetic stimulation produces a decrease in cerebral blood flow.1-6 Recent observations from our laboratory have indicated that sympathetic cerebral vasoconstriction is independent of changes in arterial carbon dioxide tension, oxygen tension, and pH.6 A sympathetic alpha receptor vasoconstriction mechanism has been described for vessels in muscle, heart, skin, and mesentery.7 It was desirable, therefore, to determine if adrenergic alpha receptor antagonists would block sympathetic cerebral vasoconstriction. Cerebral blood flow was continuously measured by a venous outflow technique, and the response to sympathetic stimulation was studied before and after the administration of the alpha receptor blocking agents phentolamine and dibozane.

Methods

GENERAL PREPARATION

Adult dogs of either sex weighing between 23 and 35 kg were anesthetized with alpha chloralose 100 mg/kg body weight IV and supplemented as required. Each animal was mechanically ventilated (Harvard Respiration Pump 607) via a tracheotomy or intratracheal tube at 15 breaths/min. The tidal volume was adjusted to give an end expiratory carbon dioxide tension between 4.6% and 5.4% as monitored by an infrared analyzer (Beckman LB-1). Central arterial pressure was measured in the arch of the aorta via a 75-cm polyethylene (260 Intramedic) cannula passed from the femoral artery. Heart rate was electronically determined from the arterial pressure pulse. Rectal temperature was controlled by heat lamp and pad to 39°C, and arterial pH was adjusted to approximately 7.4 pH by intravenous drip of 5 cc/kg/hr of 1.5% sodium bicarbonate.

The left stellate ganglion was stimulated in four closed chest and six open chest experimental animals. In the open chest animals the ganglion was exposed by left thoracotomy at the fourth intercostal space. Platinum electrodes were placed on the dorsal and ventral surfaces of the ganglion parallel to its long axis. In the four closed chest animals, electrodes were implanted one to two weeks previous to the experiment by left thoracotomy at the second interspace. Two loops of wire (Medwire Corporation, teflon coated, 0.002 inch, 316 stainless steel) were sutured around the ganglion approximately 1 cm apart, and the leads were fixed under the skin at the costochondral junction of the fifth and sixth rib.

Each stimulation was performed with a square wave stimulator (American Electronics Laboratories, Model 104A). The stimulus pulse was passed through a
ALPHA BLOCKED VASOCONSTRICTION

stimulus isolation unit (AEL, Model 112) to eliminate interference in the flow recording system. Stimulus parameters as monitored on the oscilloscope were rectangular square wave pulses 3 msec, 15 Hz, and 3 to 5 v in the open chest animals and 5 to 9 v in closed chest animals. The same stimulus parameters were used in the 60-second control stimulation as in the 60-second stimulation after the administration of the alpha receptor blocking agents.

Cerebral venous outflow pressure was measured by cannulation of the left superficial temporal vein just cranial to the location of the flow transducer (fig. 1). A 10-cm length of polyethylene tubing (PE 205, 1.57 mm ID, 2.09 mm OD) was inserted so that the tip lay within the retroglenoid vein. The cannula was connected by an 18-gauge needle to a strain gauge transducer (Statham P23 BB).

CEREBRAL BLOOD FLOW PREPARATION

The aim of this cerebral venous outflow preparation was to obtain an uncontaminated measurement of cerebral blood flow from the dorsal (cerebral) drainage system of the head without compromising flow in the ventral (extracerebral) drainage system. Separation of the two systems was accomplished by occlusion of the sigmoid sinuses. The arterial side of the cerebral circulation was left untouched.

Occlusion of Sigmoid Sinuses

The sigmoid sinuses were occluded within the occipital bone without opening the cranium (fig. 1). The skin and dorsal neck muscles were reflected from the occipital bone to expose the bony area over the sigmoid sinuses. A no. 20 round burr was used to thin the bone over the sigmoid sinuses so as to visually establish the lateral and medial margins of the sinus within the bone. The outer layer of dura was ruptured with a no. 11 round burr and the sinus was quickly packed with heparinized cotton pellets. The pellets were packed laterally and medially so as to occlude the sinus without damaging the inner layer of dura. The surface of the bony defect was then packed with dry cotton pellets. The occipital emissary veins and lesser auricular veins were cauterized during the reflection of the skin and dorsal neck muscles.

Isolation of Left Retroglenoid Flow

Ligation of the right retroglenoid vein diverted the blood from the anterior cranial fossa to the left retroglenoid vein (fig. 1). The ventral (extracerebral) drainage continued to drain the orbital plexus, palatal plexus, cavernous sinus, and ventral petrosal sinus via the internal jugular vein and the vertebral and condyloid sinuses.

The left retroglenoid vein was exposed by an incision along the posterior border of the masseter

CRANIAL VENOUS SINUSES - Posterior view

Schematic view of the cerebral venous sinuses depicting the preparation used to separate the dorsal and ventral drainage systems of the cranium. The points of occlusion and the placement of the flow transducer and pressure transducer are indicated. The labels on the left (italics) indicate principal vessels draining the brain. The labels on the right indicate vessels excluded from the outflow preparation.
Cerebral Blood Flow Transducer

Cerebral blood flow was measured with an electromagnetic flowmeter (Statham Instruments M-4000) using noncannulating Helmholtz coil transducers. In vivo flow calibration points were taken from each animal and grouped for computation of stepwise regression lines (calibration lines). Electrical zero was set before and checked after each experimental manipulation by mechanical occlusion of the vessel with a nonmetallic forceps. Drift of the occlusive zero more than 1.5% of full scale invalidated the flow measurement.

Sham stimulations were performed in four of the eight open chest experimental animals to test for electrical artifacts in the flow record during stimulation. The stimulating electrodes were placed on the muscle within 0.5 cm of the left stellate ganglion. No changes or artifacts were observed in the flow record during sham stimulations with the same voltage and frequency used for stellate stimulation.

VERIFICATION PROCEDURE FOR BLOOD FLOW PREPARATION

This procedure tests for the completeness of the dorsal-ventral venous sinus separation and for the presence of the anastomotic branch of the dorsal petrosal sinus. An anastomotic vein connecting the dorsal petrosal sinus to the cavernous sinus was observed in approximately one-third of the dogs examined. At the end of each experiment the animal was heparinized (750 units/kg body weight) and sacrificed by ventricular fibrillation. The head was removed from the atlas and all extracranial ligations and occlusions examined. The fascia around the external acoustic meatus was sectioned to expose the closed end of the lesser auricular vein. The palate, pterygoid fossa, jugular foramen, and internal maxillary vein were tied off. The principal vessels occluded were lesser auricular veins, palatine branches, mandibulo-alveolar branches, deep auricular, great auricular, and superficial temporal veins (fig. 1). An unbranched section of vessel was selected for the flow transducer placement. This section was dissected free of fascia and coated with papaverine hydrochloride (0.32 mg/ml) in order to avoid artifacts from vascular spasm.

The left retroglenoid vein was cannulated craniad to the body weight) and sacrificed by ventricular fibrillation. The brain weights were determined postmortem for each animal. The standard error of the mean was computed with nine degrees of freedom (ten animals). A paired t test and the simple sign test were used to compare the effects of stimulation before and after alpha receptor blockade.

Analog pressure and flow records were read at 30-second intervals for 120 seconds before the start of stimulation, at 10-second intervals from the start of stimulation until 30 seconds after the end of stimulation, and at 30-second intervals from 30 seconds after the end of stimulation until 150 seconds after the end of stimulation. Thus a total of 18 determinations per trial were taken and used for analysis.

Composite flow data were computed after normalizing individual flow determinations to percent of prestimulation flow level. Prestimulation flow level was determined for each trial by averaging the five flow determinations (—120, —90, —60, —30, and 0 seconds) taken during the 120-second period preceding stimulation. Flow during stimulation was taken as the average of five determinations (+20, +30, +40, +50, and +60 seconds) from 20 seconds after the start of stimulation until the end of stimulation. The average prestimulation flow and average stimulated flow are expressed in ml/min/100 gm by using in vivo calibration curves for each flow transducer and the brain weight within the anterior cranial fossa. The brain weights were determined postmortem for each animal. The standard error of the mean was computed with nine degrees of freedom (ten animals). A paired t test and the simple sign test were used to compare the effects of stimulation before and after alpha receptor blockade.
The percents, averages, and standard errors were calculated with the aid of a computer (CDC 6400 computer) (Biomedical Computer Program "BMD01D Simple Data Description," W. J. Dixon, ed., 1965).

Results

Stimulation Before Blockade

In the control, prior to alpha receptor blockade, stimulation of the left stellate ganglion produced a marked decrease in cerebral blood flow. End expiratory carbon dioxide tension, arterial blood pressure, and heart rate all increased during sympathetic stimulation. Cerebral venous outflow pressure decreased slightly (fig. 2). The average flow in ten animals was 44.7 ml/min/100 gm before stimulation and fell to 15.1 ml/min/100 gm during stimulation. When flow was expressed as percent of prestimulation levels, the average decrease in cerebral blood flow for the ten animals was 65.8% (fig. 3 and table 1).

Stimulation After Alpha Receptor Blockade

Alpha receptor blockade markedly attenuated the decrease of cerebral blood flow in response to sympathetic stimulation. End expiratory carbon dioxide tension, arterial blood pressure, and heart rate increased but to a lesser degree than those observed prior to blockade. Cerebral venous outflow pressure remained unchanged (fig. 4). The average flow in ten animals after the administration of the alpha receptor blocking agents was 44.5 ml/min/100 gm before stimulation and 43.3 ml/min/100 gm during sympathetic stimulation. When flow was expressed as percent of the flow in the prestimulation levels, the average decrease in cerebral blood flow for the ten animals during alpha receptor blockade was 3.5% (fig. 3).

Comparison of the stimulated flow level before and after alpha receptor blockade indicates there was a 94.7% reduction in the sympathetic cerebral vasoconstriction after alpha receptor blockade (165.8 - 3.5)/65.8 = 94.7%). The difference between the individual flow points during stimulation, before and after alpha receptor blockade, is statistically significant by both the paired t and the simple sign tests to a level of P less than 0.001.

Discussion

Anatomical evidence of the innervation of cerebral vessels has been accumulating since the time of Thomas Willis.9 As the various histological,10-14 histochemical,15-18 and electromicroscopic19-22 techniques have developed, so has the realization of the extent to which the cerebral vessels are innervated. In the 1940s and 1950s, cerebral vascular innervation was considered scanty and of little or no significance. More recent investigations using

<table>
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<tr>
<th>Table 1</th>
<th>Cerebral Blood Flow Before and After Alpha Receptor Blockade</th>
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<tbody>
<tr>
<td></td>
<td>Pre</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>30.7</td>
</tr>
<tr>
<td>2</td>
<td>45.2</td>
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<tr>
<td>3</td>
<td>28.6</td>
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<td>31.2</td>
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<tr>
<td>10</td>
<td>31.2</td>
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The individual flow data in the Pre and Stim columns are the averages of five observations/animal in the prestimulation and stimulation periods, respectively. The individual and composite flow data were obtained by averaging during corresponding time periods. The standard error of the mean was calculated with nine degrees of freedom (ten animals).
fluorescent histochemistry have revealed that the pial arteries have a "more extensive adrenergic nerve supply than any other arterial system in the body." As the anatomical evidence for innervation of the cerebral vessels accumulated, various physiological investigations probed the question of a possible

**SYMPATHETIC STIMULATION**

*(control)*

**CEREBRAL BLOOD FLOW (ml/min)**

<table>
<thead>
<tr>
<th>55.3</th>
<th>27.6</th>
</tr>
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<tbody>
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**EXPIRED CARBON DIOXIDE TENSION (mm Hg)**

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<th>24.8</th>
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**CEREBRAL VENOUS OUTFLOW PRESSURE (mm Hg)**

<table>
<thead>
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<th>50</th>
<th>25</th>
<th>0</th>
</tr>
</thead>
</table>

**ARTERIAL BLOOD PRESSURE (mm Hg)**

<table>
<thead>
<tr>
<th>300</th>
<th>175</th>
<th>50</th>
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</thead>
</table>

**HEART RATE (beats/min)**

<table>
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<tr>
<th>300</th>
<th>150</th>
<th>0</th>
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</table>

*Figure 2*

Stimulation of the left stellate ganglion prior to alpha receptor blockade for 60 seconds at 15 Hz, 4 V, and 3 msec pulse duration decreased cerebral blood flow, and increased end expiratory carbon dioxide tension, arterial blood pressure, and heart rate. The deflections at the beginning and the end of the flow and cerebral venous outflow pressure channels are caused by occluding the venous outflow to check the occlusive flow zero. This record was made with dog no. 9.
function for this innervation. Thermocouple techniques used by Schmidt, Krog, and Ludwigs and Schneider gave indirect indications of sympathetic vasoconstriction. The measurement of pial vessels by Forbes and Wolff, Mcchedlishvili, and others indicated that sympathetic stimulation will decrease pial vessel diameter. More recently James, Millar, and Purves used a washout technique of intra-arterially injected Xenon to measure cerebral blood flow during sympathetic stimulation. They observed that sympathetic stimulation attenuated the dilator effects of inspired carbon dioxide. Observations from our own laboratory indicate sympathetic stimulation results in a marked decrease in cerebral blood flow. This sympathetic vasoconstriction occurs independently from changes in arterial carbon dioxide tension, pH, and oxygen tension as well as changes in cerebral spinal fluid pressure.

Although previous studies were concerned with the function of the sympathetic innervation of the cerebral vessels, none has dealt with the question of the receptor involved in the vasoconstriction. In the present study we have demonstrated by the use of alpha receptor adrenergic blocking agents that sympathetic cerebral vasoconstriction is mediated by an alpha adrenergic receptor mechanism.

Kety and others have previously demonstrated using nitrous oxide and related techniques that there is little or no tonic sympathetic cerebral vasoconstriction. The present results confirm these observations inasmuch as the unstimulated blood flow levels before and after alpha blockade were essentially the same (44.7 versus 44.5 ml/min/100 gm). The alpha receptor blockade therefore was principally effective in attenuating the vasoconstriction elicited by activation of the sympathetic innervation of the cerebral vessels.

Cerebral vasoconstriction has been implicated in various pathological states, as, for example, in stroke and epilepsy. Cerebral vasoconstriction observed by stimulating the stellate ganglion in this and previous studies demonstrates the existence of a sympathetic control mechanism capable of decreasing cerebral blood flow. Whether such events take place in the pathological conditions mentioned has not been established. If sympathetic vasoconstriction is involved in stroke, etc., the present study demonstrates that alpha receptor blocking agents may be therapeutically useful.

In summary, a sympathetic adrenergic mechanism capable of decreasing cerebral blood flow which
is blocked by alpha receptor antagonists has been observed; its role in the physiological and pathologica-
cal regulation of the brain's blood supply has yet to be determined.

**SYMPATHETIC STIMULATION**

( **alpha blocked** )

- **CEREBRAL BLOOD FLOW (ml/min)**
  - 55.3
  - 27.6
  - 0

- **EXPIRED CARBON DIOXIDE TENSION (mm Hg)**
  - 49.5
  - 24.8
  - 0

- **CEREBRAL VENOUS OUTFLOW PRESSURE (mm Hg)**
  - 50
  - 25
  - 0

- **ARTERIAL BLOOD PRESSURE (mm Hg)**
  - 300
  - 175
  - 50

- **HEART RATE (beats/min)**
  - 300
  - 150
  - 0

*Figure 4*

Alpha receptor adrenergic blockade with 2 mg/kg phentolamine blocked the decrease in cerebral blood flow produced by stimulation of the left stellate ganglion for 60 seconds at 15 Hz, 4 v, and 3 msec pulse duration. End expiratory carbon dioxide tension, arterial blood pressure, and heart rate are increased. The deflections at the beginning and the end of the flow and cerebral venous outflow pressure records are caused by the occlusive flow zeroes. This record was made with dog no. 9.
Acknowledgments

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References

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