Regional Blood Flow in Canine Brain During Nicotine Infusion: Effect of Autonomic Blocking Drugs*

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SUMMARY Radioactive microspheres (15 μ) were used to measure regional cerebral blood flow during intravenous infusion of nicotine (36 μg/kg/min) in anesthetized, open chest dogs. Experiments were conducted with uncontrolled mean aortic pressure and intact autonomic receptors (Series I; n = 9), and in four groups of dogs with mean aortic pressure held constant (Series II): 1) with intact autonomic receptors (n = 6), 2) after beta adrenergic blockade (n = 8), 3) after alpha and beta adrenergic blockade (n = 6), 4) after alpha and beta adrenergic and cholinergic blockade (n = 4). In Series I, nicotine raised mean aortic pressure (+72%) and increased flow in cerebral cortex (+67%), cerebellum (+38%), pons (+46%), medulla (+39%), and spinal cord (+48%). In all regions, but cortex, increases in vascular resistance limited nicotine-induced increases in flow. In Series II, nicotine changed flow only in cortex. Without blockade, nicotine increased cortical flow (+38%); but beta blockade abolished this increase in flow. After alpha and beta blockade nicotine again raised cortical flow (+29%); and additional cholinergic blockade had no effect on this response. It is concluded that nicotine causes predominant beta receptor mediated vasodilation in cerebral cortex, although it also activates alpha (vasoconstrictor) receptors and a non-adrenergic, non-cholinergic vasodilator mechanism in this region of brain.

The present studies were undertaken to evaluate changes in rCBF during intravenous infusion of nicotine and to define the contribution of the autonomic nervous system to these changes.

Methods

Thirty-three large, adult, mongrel dogs were anesthetized with sodium pentobarbital, 30 mg/kg initially and supplemented as required to maintain a stable plane of anesthesia. After tracheotomy and left thoracotomy, the animal was ventilated with room air (supplemented with 100% O₂, when necessary) to maintain physiological blood gases. A flow transducer was positioned on the ascending aorta, so that cardiac output (minus coronary blood flow) could be measured with an electromagnetic flowmeter, Micron RC1000 (Micron Instruments, Inc., Los Angeles, CA). The flow transducer was calibrated in vitro on a segment of aorta perfused with whole blood. Mean aortic, central venous, and left atrial pressures were monitored through catheters connected to Statham pressure transducers, model P23Db (Gould Inc., Oxnard, CA). Limb lead II of the electrocardiogram was used to drive a cardiotachometer. A record of blood pressures, aortic blood flow, electrocardiogram, and heart rate was made with a Beckman recorder, model R411 (Beckman Instruments, Inc., Schiller Park, IL). Succinylcholine (Anectine, 2 mg/kg i.v., supplemented as necessary; Burroughs Wellcome Co., Research Park, NC) was administered to prevent spontaneous respiratory movements during nicotine infusion. Heparin (500 U/kg i.v.) was used as an anticoagulant.

Regional CBF values were determined from tissue content of 15 ± 3 μ microspheres administered into the left atrium. The microspheres were labeled with gamma-emitting radionuclides (⁵⁷Co, ⁵⁷Co, ⁸⁵Sr, ¹¹¹Sn; New England Nuclear, Boston, MA, and 3M Co., St. Paul, MN). Prior to injection, the microspheres were dispersed by agitation in an ultrasonic bath and with a vortex mixer. Approximately 10⁶ microspheres were
administered for each flow determination. These determinations had no detectable effect on monitored hemodynamic parameters. Upon injection of microspheres, duplicate reference samples of arterial blood were withdrawn from two different sites in the aorta at a constant rate (approximately 7.5 ml/min) for 2 min, so that regional blood flows could be computed. Similarity of radioactivity in duplicate reference samples verified adequate mixing of microspheres. Each dog received two injections of differently labeled microspheres to measure rCBF values under the pre-nicotine control condition and during intravenous infusion of nicotine (see Experimental Design).

After the final dose of microspheres, the dog was killed by intravenous injection of potassium chloride. The skull was opened and the brain plus a cervical segment of the spinal cord were removed. Samples of tissue were cut from the frontal and occipital lobes of the cerebral cortex, the cerebellum, the pons, the medulla, and the spinal cord. These tissue samples and the reference arterial blood samples were analyzed for radioactivity in a gamma counter equipped with a multichannel analyzer (Packard Instrument Co., Downer Grove, IL). Isotope separation was accomplished by standard techniques of gamma spectroscopy with the aid of a PDP/8E minicomputer (Digital Equipment Corp., Maynard, MA).

Experimental Design

Series I Effect Of Nicotine With Uncontrolled Aortic Pressure

In nine dogs, control measurements of hemodynamic parameters and of rCBF were first obtained after sufficient time for stabilization of experimental preparation. These dogs, with intact autonomic receptors, then received intravenous infusion of nicotine (36 µg/kg/min). This rather high dose of nicotine was chosen throughout the study, so that hemodynamic responses were pronounced and modifications of these responses by autonomic blockers were readily detectable. Nicotine caused marked arterial hypertension, and, at the peak of this hypertensive response, a second injection of microspheres was made to measure again rCBF values. The nicotine infusion was continued for two minutes after this injection of microspheres.

Series II Effect Of Nicotine With Constant Aortic Pressure

In order to eliminate the contribution of nicotine-induced increases in aortic blood pressure to changes in rCBF, studies were conducted in four groups of animals whose aortic pressure was held constant. Aortic pressure was controlled by connecting a 500 ml, pressurized reservoir bottle to the left subclavian artery, which had been ligated and then cannulated with wide-bore tubing. Reservoir pressure was maintained equal to mean aortic pressure with compressed gas. During infusion of nicotine, vascular constriction caused blood to be translocated from the dog's circulation to the reservoir, allowing aortic blood pressure to be maintained within 5 mm Hg of the control blood pressure. In these constant pressure studies, microspheres were injected when reservoir volume had reached its maximum, thus indicating that pressor mechanisms were maximally activated.

Group 1 Without Autonomic Blockade

In six dogs with intact autonomic receptors, control measurements of hemodynamic parameters and rCBF by the microsphere technique were first obtained. Nicotine was then infused and hemodynamic parameters were recorded and a second injection of microspheres was made at peak reservoir volume.

Group 2 After Selective Beta Adrenergic Blockade

In eight dogs, after control measurements of hemodynamic parameters were obtained, a bolus injection of propranolol (Inderal; Ayerst Laboratories, New York, NY), 1 mg/kg was administered intravenously to block beta adrenergic receptors. Beta adrenergic blockade was verified by the absence of inotropic and depressor responses to a bolus injection of isoproterenol (Ipoprenol; Vitarine, New York, NY), 5 µg i.v. Hemodynamic parameters were recorded and radioactive microspheres were injected to define a new control condition prior to nicotine infusion. Nicotine was then infused and a second injection of microspheres was made at peak reservoir volume.

Group 3 After Combined Alpha And Beta Adrenergic Blockade

In six dogs, after control measurements of hemodynamic parameters were obtained, alpha adrenergic blockade was produced with phenoxybenzamine HCl (Dibenzyline; Smith Kline and French Laboratories, Philadelphia, PA), 2 mg/kg in 300 ml isotonic saline infused intravenously over 45 min. Alpha adrenergic blockade was verified by absence of pressor response to a bolus injection of methoxamine (Vasoxyl; Burroughs Wellcome Co., Research Park, NC), 4 mg i.v. Beta adrenergic blockade was then produced and verified as described for Group 2. In dogs subjected to combined alpha and beta adrenergic blockade, arterial blood pressure was maintained near the pre-blockade condition by addition of blood from a donor dog. Radioactive microspheres were injected to define the pre-nicotine control condition subsequent to combined alpha and beta adrenergic blockade. Following this injection, nicotine was infused and at peak reservoir volume, hemodynamic parameters were recorded and a second injection of microspheres was made.

Group 4 After Combined Alpha And Beta Adrenergic And Cholinergic Blockade

In 4 dogs, after control measurements were obtained, alpha and beta adrenergic blockades were produced and verified as described above. Then cholinergic blockade was produced with atropine sulfate (Elkins-Sinn, Inc., Cherry Hill, NJ), 1 mg i.v. This dose of atropine sulfate was adequate to prevent the transient, vagally-mediated bradycardia which occurs initially upon intravenous infusion of nicotine. Radioactive microspheres were injected to define new pre-nicotine control flows subsequent to autonomic block-
ade. Nicotine was then infused, and hemodynamic parameters were recorded, and a second injection of microspheres made at peak reservoir volume.

Statistical Analyses

Effects of nicotine alone and of nicotine after autonomic blocking drugs were tested with a randomized block analysis of variance and the Student-Newman-Keuls test. A value of $P > 0.05$ was considered to reflect statistically significant differences throughout this study.

Results

Series I With Uncontrolled Aortic Pressure

Under control conditions (before nicotine infusion) systemic hemodynamic parameters were unremarkable (table 1) and CBF values showed regional heterogeneity (cerebral cortex > cerebellum > pons; medulla; spinal cord) (table 2).

Nicotine infusion increased mean aortic pressure (+72%), heart rate (+11%), and mean left atrial pressure (+112%), but it had no significant effect on mean central venous pressure or aortic blood flow (table 1). Nicotine caused a significant increase in rCBF throughout brain (Table 2); flow increased 67% in cerebral cortex, 38% in cerebellum, 46% in pons, 39% in medulla, and 48% in spinal cord. This regional variation in increases in rCBF during nicotine infusion was not statistically significant.

Regional blood flow is determined by the regional arteriovenous blood pressure gradient and by the regional vascular resistance [vascular resistance = (mean aortic pressure - mean central venous pressure)/ blood flow]. Since nicotine-induced increases in CBF values were accompanied by changes in the arteriovenous blood pressure gradient, vasoactive effects of nicotine in brain were assessed by comparing calculated values for regional vascular resistance. Nicotine infusion did not change significantly vascular resistance in cerebral cortex, but it increased significantly vascular resistance in cerebellum (+29%), pons (+24%), medulla (+30%), and spinal cord (+14%) (fig. 1).

Series II With Aortic Pressure Constant

With aortic pressure held constant without autonomic blockade (Group 1), nicotine reduced mean left atrial pressure (−50%) and mean aortic blood flow (−52%), but it had no other systemic hemodynamic effects (table 3). Under these constant pressure conditions, nicotine raised significantly flow in cerebral cortex (−39%), but it did not affect flow in any other region of brain (table 4).

With pressure held constant after selective beta adrenergic blockade (Group 2), nicotine caused significant reductions in mean left atrial pressure (−39%), mean central venous pressure (−32%), and mean aortic blood flow (−49%) (table 3), but it had no effect on rCBF values (table 5).

With pressure constant after combined alpha and beta adrenergic blockade (Group 3), nicotine caused a significant reduction in mean aortic blood flow, but it did not change other systemic hemodynamic parameters (table 5). Under these conditions, nicotine increased significantly flow in cerebral cortex (+29%) while it had no significant effect on flow in any other region of brain (table 6). Additional cholinergic blockade (Group 4) did not cause further changes in either systemic hemodynamic parameters (table 3) or CBF values (table 7) during nicotine infusion.

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Effect of nicotine on regional cerebral vascular resistance with uncontrolled aortic pressure and intact autonomic receptors ($n = 9$).
**Table 3** Effect of Nicotine on Systemic Hemodynamic Parameters with Aortic Pressure Held Constant Without Autonomic Blockade, After Selective Beta Adrenergic Blockade, After Combined Alpha and Beta Adrenergic Blockade, and After Combined Alpha and Beta Adrenergic and Cholinergic Blockade

<table>
<thead>
<tr>
<th>Without autonomic blockade (n = 6)</th>
<th>After beta adrenergic blockade (n = 8)</th>
<th>After alpha and beta adrenergic blockade (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Control (pre-blockade)</td>
<td>Control (post-blockade)</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>99.2 ±0.8</td>
<td>100.0 ±5.5</td>
</tr>
<tr>
<td>Mean left atrial pressure (mm Hg)</td>
<td>4.8 ±0.8</td>
<td>4.6 ±0.6</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>211 ±9</td>
<td>155 ±12</td>
</tr>
<tr>
<td>Mean central venous pressure (mm Hg)</td>
<td>4.1 ±1.1</td>
<td>3.4 ±0.6</td>
</tr>
<tr>
<td>Aortic blood flow (ml/min)</td>
<td>977 ±161</td>
<td>1238 ±132</td>
</tr>
</tbody>
</table>

*p < 0.05, effect of nicotine; †p < 0.05, effect of blockade. Findings after blockade served as control values for determining effect of nicotine in group. Values are mean ± SE.

**Discussion**

Radioactive microspheres, 15 μ in diameter, were used to measure rCBF. This method of flow measurement is particularly useful in brain because of 1) the complex anatomical arrangement of cerebral circulation, 2) the difficulty in separating intracranial and extracranial sources of flow, and 3) the marked structural and functional heterogeneity of the organ.21 For the microsphere method to measure accurately rCBF, the following conditions must be fulfilled: 1) The microspheres must be uniformly distributed in the left ventricular output. 2) The microspheres must not cause any systemic or local hemodynamic effects. 3) The microspheres must be trapped completely in brain during their initial passage and those that are not trapped in other organs must undergo entrapment in the lungs so they do not re-circulate. These conditions were fulfilled in the present study. Firstly, radioactivity of duplicate samples of arterial blood collected from the aorta as the bolus of microspheres passed through that vessel differed by less than 10%, indicating mixing of microspheres in the left ventricular output. Secondly, no change in heart rate, aortic blood pressure, or aortic blood flow was detected following left atrial injection of microspheres. Finally, arteriovenous shunting of 15 μ spheres is negligible in the cerebral and pulmonary circulations.

Increases in blood flow in all regions of the brain were observed during nicotine infusion in dogs with uncontrolled aortic pressure. But with the exception of cerebral cortex, these increases in flow were less than proportional to increases in aortic pressure, thus indicating vasoconstriction (fig. 1). In light of the well-documented capability of the regional cerebral circulations for pressure-flow autoregulation,13 a role for this mechanism in the cerebral vasconstriction during nicotine infusion could not be dismissed. Thus, in order to distinguish nicotine-induced vasconstriction per se from autoregulatory vasconstriction secondary to elevated aortic pressure, studies were conducted in which aortic pressure was maintained at normotensive levels

**Table 4** Effect of Nicotine on Regional Cerebral Blood Flow with Mean Aortic Pressure Held Constant without Adrenergic Blockade

<table>
<thead>
<tr>
<th>Regional cerebral blood flow (ml/min per 100 g)</th>
<th>Control</th>
<th>Nicotine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral cortex</td>
<td>37 ± 6</td>
<td>51 ± 4*</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>36 ± 5</td>
<td>36 ± 3</td>
</tr>
<tr>
<td>Pons</td>
<td>33 ± 5</td>
<td>35 ± 2</td>
</tr>
<tr>
<td>Medulla</td>
<td>29 ± 4</td>
<td>30 ± 4</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>16 ± 4</td>
<td>18 ± 4</td>
</tr>
</tbody>
</table>

**Arterial blood parameters**

| PO2 (mm Hg) | 152.3 ± 18.3 | 104.8 ± 11.4* |
| PCO2 (mm Hg) | 32.3 ± 4.4 | 31.7 ± 1.7 |
| pH           | 7.40 ± 0.01 | 7.39 ± 0.02 |
| Hematocrit (%) | 33.8 ± 2.3 | 37.5 ± 7.5 |

*p < 0.05, effect of nicotine. Values are mean ± SE in 9 dogs.

**Table 5** Effect of Nicotine on Regional Cerebral Blood Flow with Mean Aortic Pressure Held Constant Following Beta Adrenergic Blockade

<table>
<thead>
<tr>
<th>Regional cerebral blood flow (ml/min per 100 g)</th>
<th>Control (post-blockade)</th>
<th>Nicotine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral cortex</td>
<td>35 ± 5</td>
<td>34 ± 2</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>33 ± 5</td>
<td>35 ± 5</td>
</tr>
<tr>
<td>Pons</td>
<td>27 ± 3</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>Medulla</td>
<td>26 ± 5</td>
<td>23 ± 3</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>20 ± 2</td>
<td>18 ± 1</td>
</tr>
</tbody>
</table>

**Arterial blood parameters**

| PO2 (mm Hg) | 166.1 ± 15.7 | 153.8 ± 18.8 |
| PCO2 (mm Hg) | 37.8 ± 1.8 | 32.2 ± 1.9* |
| pH           | 7.37 ± 0.02 | 7.41 ± 0.03* |
| Hematocrit (%) | 35.7 ± 3.8 | 37.1 ± 3.5 |

*p < 0.05, effect of nicotine. Values are mean ± SE in 8 dogs.
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Table 3 (Continued)

<table>
<thead>
<tr>
<th>Control (pre-blockade)</th>
<th>Control (post-blockade)</th>
<th>Nicotine</th>
</tr>
</thead>
<tbody>
<tr>
<td>108.0 ± 6.8</td>
<td>96.3 ± 1.8</td>
<td>95.3 ± 1.9</td>
</tr>
<tr>
<td>3.3 ± 0.7</td>
<td>6.0 ± 1.0†</td>
<td>4.6 ± 0.6</td>
</tr>
<tr>
<td>179 ± 23</td>
<td>129 ± 10†</td>
<td>130 ± 9</td>
</tr>
<tr>
<td>2.6 ± 0.6</td>
<td>4.4 ± 0.4†</td>
<td>3.1 ± 0.9</td>
</tr>
<tr>
<td>1182 ± 402</td>
<td>1108 ± 226</td>
<td>730 ± 178</td>
</tr>
</tbody>
</table>

Values are mean ± SE in 6 dogs.

Table 7 Effect of Nicotine on Regional Cerebral Blood Flow with Mean Aortic Pressure Held Constant Following Combined Alpha and Beta Adrenergic Blockade

<table>
<thead>
<tr>
<th>Regional cerebral blood flow (ml/min per 100 g)</th>
<th>Control (post-blockade)</th>
<th>Nicotine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral cortex</td>
<td>38 ± 4</td>
<td>49 ± 5*</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>35 ± 4</td>
<td>39 ± 5</td>
</tr>
<tr>
<td>Pons</td>
<td>32 ± 3</td>
<td>38 ± 5</td>
</tr>
<tr>
<td>Medulla</td>
<td>35 ± 5</td>
<td>39 ± 6</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>19 ± 3</td>
<td>21 ± 4</td>
</tr>
</tbody>
</table>

Values are mean ± SE in 4 dogs.

During nicotine infusion. With pressure controlled, nicotine had no effect on blood flow (or vascular resistance) in any region of brain, except cerebral cortex, where a hyperemic response persisted. These results indicate that vasoconstriction in cerebellum, pons, medulla, and spinal cord during nicotine infusion in dogs with uncontrolled aortic pressure was due to pressure-flow autoregulation and not due to vasomotor mechanisms activated by nicotine per se. Furthermore, they indicate that nicotine aroused a vasodilator mechanism in cerebral cortex which was sufficiently potent to override autoregulatory vasoconstriction in that region. This latter finding is consistent with the report of Hall24 that intravenous injection of nicotine caused reduction in cortical vascular resistance in anesthetized cats.

Nicotine is known to activate the sympathoadrenal system by stimulation of neurons in the central nervous system,14-16 of autonomic ganglia including the adrenal medulla,25,26 and of the arterial chemoreceptors.27,28 Since histochemical, histological, and electromicroscopic studies have demonstrated that cerebral vessels are well endowed with sympathetic nerve terminals associated with both alpha and beta adrenergic receptors,29 it was possible that the effect of nicotine on blood flow in cerebral cortex was adrenergically mediated. Thus, in order to define the role of the sympathoadrenal system in cerebral vascular responses during nicotine infusion, studies were conducted with adrenergic blocking drugs. In these studies aortic pressure was maintained at normotensive levels to eliminate autoregulatory adjustments in rCBF during nicotine infusion.

Although dogs were paralyzed and artificially ventilated, nicotine infusion with aortic pressure held constant following selective beta adrenergic blockade with propranolol caused a 15% reduction in arterial carbon dioxide tension (table 5), probably due to a decrease in whole body oxygen consumption.30 While arterial hypocapnia has been demonstrated to cause cerebral vasoconstriction,31 these past studies indicate that the fall in carbon dioxide tension during nicotine following propranolol in the present study would have been insufficient to prevent by itself the increase in cortical flow before propranolol. Thus, it appears that propranolol eliminated the increase in cortical flow during nicotine because it blocked stimulation of cerebral beta adrenergic receptors. Whether cortical vasodilation by nicotine in dogs with intact adrenergic receptors was due to direct stimulation of vascular beta receptors or secondary to a beta receptor mediated increase in cortical metabolism cannot be ascertained from the present study.

The present finding of an increase in cortical flow during nicotine after both propranolol and phenoxybenzamine indicates that nicotine stimulates alpha as well as beta adrenergic receptors in cerebral cortex, although alpha-mediated vasoconstriction is masked by beta-mediated vasodilation in unblocked dogs. Since alpha receptors were not blocked when propranolol was used alone, a nicotine-induced decrease in
cortical flow might have been expected. However, the finding of no change in cortical flow in these dogs with intact alpha receptors suggests activation of a non-adrenergic vasodilator mechanism (see below) which balanced alpha-mediated vasoconstriction.

Inasmuch as catecholamines penetrate only poorly the blood-brain barrier, 32, 33 it is highly probable that norepinephrine, released locally from sympathetic nerve terminals, and not epinephrine, released into the systemic circulation from the adrenal medullae, stimulated cortical adrenergic receptors during nicotine infusion. This is consistent with the present finding of predominant beta adrenergic vasodilation in cerebral cortex, since although norepinephrine causes vasoconstriction in most organ beds, its local effect in brain is beta receptor mediated vasodilation, 32 because of unusually low sensitivity of alpha adrenergic receptors in brain. 34

The literature is replete with conflicting data relating to the ability of the sympathetic nerves to cause cerebral vasoconstriction. 35, 36 Because of apparent species differences in cerebral vascular responses to sympathetic stimulation, 37 studies most relevant to the present investigation will be discussed, namely those performed in anesthetized dogs.

D’Alecy 38 reported a marked decrease in cerebral blood flow during electrical stimulation of the left sympathetic stellate ganglion, which was nullified by alpha receptor blockade with either dibozane or phentolamine. Lang and Zimmer 39 obtained similar results in the isolated canine brain during stimulation of the vagosympathetic trunk before and after alpha adrenergic blockade with phentolamine. On the other hand, in a series of studies, Heistad et al. 37, 40, 41 have accumulated a body evidence arguing against sympathetic control of cerebral vascular resistance. They have shown that electrical stimulation of left stellate and superior cervical ganglia 1) did not reduce or redistribute cerebral blood flow 42, 2) did not constrict large cerebral vessels significantly, 40 and 3) produced only a 9% reduction in cerebral blood flow during severe arterial hypertension. 37 Furthermore, they reported no effect of stimulation of carotid chemoreceptors with nicotine or hypoxic or hypercapnic blood on total or regional cerebral blood flow. 41 We can propose no definite explanation for the discrepancy between our findings and those of Heistad et al. Perhaps, in the studies of Heistad et al alpha (vasoconstrictor) and beta (vasodilator) mechanisms were simultaneously activated by sympathetic nerve stimulation and had negating influences on cerebral blood flow which were interpreted as indicating no effect. Another possibility is that, in the present study, nicotine itself, or a vasoactive substance activated by nicotine, altered the sensitivity of cerebral vascular smooth muscle to the vasoconstrictor effects of sympathetic stimulation.

Nicotine would be expected to activate additional vasoconstrictor mechanisms whose effects on cerebral vascular resistance also warrant address. These include 1) angiotensin, because stimulation of the renal sympathetic nerves should increase renin release from the kidney, 42 and, in turn, raise plasma concentration of angiotensin, and 2) vasopressin, because it has been demonstrated that nicotine accelerates release of vasopressin from the posterior pituitary gland. 6, 7 A role for plasma angiotensin appears unlikely in light of its difficulty in diffusing across the blood-brain barrier. 13 On the other hand, a role for blood-borne vasopressin cannot be discounted. Firstly, a recent report indicated a significant, although modest, reduction in cerebral blood flow when, in conscious dogs, vasopressin was infused to raise the plasma level to that associated with osmotic stimuli. 10 Furthermore, intravenous infusion of pharmacologic doses of vasopressin increased cerebral vascular resistance in anesthetized rats. 11 Currently studies are being conducted in this laboratory to determine whether plasma levels of vasopressin during nicotine infusion were sufficient to constrict cerebral vasculature.

Because of the ability of nicotine to stimulate parasympathetic ganglia 3 and of the demonstrated cholinergic innervation of cerebral vasculature, 29 we evaluated whether the parasympathetic nervous system was responsible for masking of alpha receptor vasoconstriction in cerebral cortex during nicotine after beta blockade and for the nicotine-induced increase in cortical flow in dogs after combined alpha and beta adrenergic blockade by attempting to prevent the latter response with atropine. The finding of no effect of atropine on nicotine-induced cerebral vascular responses following combined alpha and beta adrenergic blockade indicates no important role for the parasympathetic nervous system in changes in rCBF during nicotine infusion.

We can only speculate about the nature of the non-adrenergic mechanism causing vasodilation in cerebral cortex during nicotine infusion. It has been demonstrated that nicotine causes direct arousal of the central nervous system 14-16 and it is possible that the vasodilation was at least in part a metabolically-linked response. Another possibility is that nicotine caused locally non-adrenergic, non-cholinergic relaxation of cerebral vascular smooth muscle, a mechanism which has been demonstrated in vitro in helical strips of dog cerebral arteries. 17

Regions of brain other than cerebral cortex were insensitive to vasomotor effects of intravenous nicotine. This may reflect regional variation in sympathetic innervation and/or adrenergic receptor density in brain. 33, 44

Acknowledgments

The technical assistance of Arthur G. Williams, Rebecca A. Holton, and Robert F. Scarbough is acknowledged together with the secretarial assistance of Olive Fagala. Ayerst Laboratories and Smith Kline and French Laboratories generously contributed propranolol and phenoxybenzamine, respectively.

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Stroke. 1983;14:941-947
doi: 10.1161/01.STR.14.6.941

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