An Analysis of the Effects of Nicotine on the Cerebral Circulation of an Isolated, Perfused, in situ Cat Brain Preparation

BY ALPHONSE J. INGENITO, PH.D., JAMES P. BARRETT, PH.D., M.D.,* AND LEONARD PROCITA, PH.D.

Abstract:
An Analysis of the Effects of Nicotine on the Cerebral Circulation of an Isolated, Perfused, in situ Cat Brain Preparation

To determine the effects of nicotine HCl on the cerebral circulation of the cat, without the complicating actions of the drug at other sites in the body, the drug was perfused at concentrations of 1, 10 and 100 μg/ml through a vascularly isolated, perfused in situ cat brain preparation. Cats having selective section of cranial nerves 9, 10, 11 and 12 and the cervical sympathetic trunks comprised various experimental groups. Nicotine was also perfused through an isolated, denervated hindlimb of the same cat for comparative purposes. Nicotine caused only a mild and transient vasoconstriction of the cerebral circulation, mediated primarily by stimulation of the superior cervical ganglia, and a small direct cerebral vasoconstrictor component. An acute tolerance to the cerebral vasoconstrictor effects of repeated increments of nicotine was also observed. The cerebral vasoconstrictor effect of nicotine was diminished in the presence of intact vagi, suggesting a cerebral vasodilator role for these nerves. In contrast, the effect of nicotine on the denervated hindlimb vasculature was a weak but sustained vasodilation. The mechanism of action of nicotine on the cerebral circulation is discussed along with the relevance of these findings to the potential health hazards of tobacco smoking in individuals with cerebrovascular insufficiency.

ADDITIONAL KEY WORDS
innervation of cerebral circulation
smoking and cerebral ischemia
nicotine and hindlimb circulation

Introduction
Despite occasional speculation as to the relationship between cerebrovascular disease and smoking1-3 and the suggestion that smoking be discouraged in patients with cerebral vascular insufficiency,4 relatively little is known of the effects of smoking or nicotine on the cerebral circulation.5, 6 Some studies in man have shown little or no effect of cigarette smoking or intravenously injected nicotine (in "smoking" doses) on cerebral blood flow and cerebrovascular resistance (CVR).5-9 Larson et al.5 cite a number of older studies on experimental animals in which cerebral blood flow was measured directly or by visual observation of exposed cortical vasculature following tobacco smoke inhalation or systemically injected nicotine. In most of these studies the action of nicotine was either vasodilator or
The surgical method for isolation of the cerebral circulation from that of the body was as previously described by Barrett et al. This study demonstrated the completeness of isolation of the cerebral circulation from that of the body and the ability of such perfused brains to take up glucose and oxygen from the perfusing blood, to maintain normal A-V differences in perfusion blood pH and to exert tonic and reflex neurogenic control over the peripheral circulation. The brain was perfused via both common carotid arteries with the following major and a number of other accessible minor branches of the common and external carotid arteries being ligated: the dorsal muscular branch, superior thyroid, lingual, external and internal maxillaries and the buccinator. Other arteries in the head, neck and thoracic regions were also ligated as previously described. The rather extensive arterial isolation notwithstanding, the key to the vascular isolation was, however, from the venous side, where the internal and external jugular veins, the vertebral venous sinuses and their interconnections with the jugular veins and a number of other veins in the head, neck and thoracic regions were ligated or occluded, as previously described. The proper occlusion of the vertebral venous sinuses at the level of the foramen magnum by specially constructed clips is critical to this preparation as it has been stated that these sinuses, rather than the jugular veins, carry the major part of the venous drainage from the brain. In addition, the entire cervical muscle masses were ligated with strong nylon cord at the level of the second cervical vertebra. The venous return was obtained from the transverse sigmoid cranial sinuses through two 14-gauge needles with one-fourth inch shanks inserted into bilateral openings drilled through the occipital bone. It is important to note that perfusion blood reached the area of the carotid sinuses and bodies and also reached the superior cervical ganglia so that any effect of the drug on these structures that might influence the cerebral circulation were manifest in the results unless they were obviated by prior nerve section, as described below.

Our criteria for an effective isolation of the cerebral circulation, apart from the extensive ligations and other anatomical considerations previously set forth, reside in the results of latex perfusion studies of these brains and in the lack of significant blood loss from the extracorporeal circuit during perfusion. Careful dissection studies following latex perfusion have shown none of this material in extracerebral tissue except for the orbital contents and the dura. In the cat, the internal carotid artery is nonpatent and blood is supplied to the circle of Willis mainly by the external carotid artery via the external and internal rete mirabile. These latter structures also supply the orbit and render exclusion of the orbital contents from the perfusion technically
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unfeasible. Since there is minimal (<0.5 ml/min) or no blood loss from the extracorporeal perfusion circuit during perfusion, as monitored by the level of a calibrated reservoir, and since the venous return is obtained from the dural venous sinuses, which drain mainly intracranial tissues, it is unlikely that there is any significant perfusion of extracranial tissues by this method.

The details of the isolation and perfusion of the hindlimb were as previously described. Briefly, the perfusion included the vascular bed supplied by the femoral artery, with the superior circumflex, deep femoral and medial muscular arteries and veins being ligated. The leg muscles were tightly ligated with nylon cord at the level of the inguinal ligament, the sciatic and femoral nerves being excluded from the ligations, but later were sectioned prior to addition of nicotine to the perfusing blood. The vascular bed perfused was a mixture of skeletal muscle and the skin of the paw region.

With regard to the cardiovascular reflex innervation of the perfused brain and possible vasomotor innervation of the cerebral circulation, three different groups of cats were employed: (1) CN 10 and other cardiovascular reflex afferents intact; (2) CN 10 sectioned bilaterally in the cervical region but with the cervical sympathetic trunks and other CN left intact; and (3) CN 9, 10, 11 and 12 and the cervical sympathetic trunks sectioned bilaterally at the jugular foramina. This latter procedure eliminated all conventionally known cardiovascular reflex afferent pathways and eliminated sympathetic vasomotor tone to the cerebral circulation coming by way of the cervical sympathetic trunks and the superior cervical ganglia. The basis for making these nerve sections related primarily to previous studies on the effects of nicotine on the central and reflex control over the peripheral circulation. Because of technical difficulties involved in sectioning of the above nerves after the animal's head was fixed in position for perfusion and also because an acute tolerance to the effects of nicotine on the cerebral circulation develops after one exposure, as later described, it was not possible to determine the effect of the drug prior to and after nerve sectioning in the same animal.

EXTRACORPOREAL CIRCULATION

The perfusion medium employed for both brain and hindlimb was defibrinated beef blood obtained fresh weekly from a local abattoir. The hematocrit (30%), glucose, Na⁺ and K⁺ concentrations, and pH corresponded, or were adjusted, to values closely approximating those in cat blood. Heparin sodium, 2,500 units/liter, were added to insure against formation of microemboli. The essential elements of the extracorporeal perfusion apparatus for both brain and hindlimb included a falling-film type of oxygenator, a calibrated 100 ml reservoir, a Sigmamotor Model T-8 finger pump, an unbleached muslin blood filter and a heat exchanger (set at 37°C). The total volume of blood in each extracorporeal circuit was 250 ml. The unbleached muslin filter effectively removes microemboli and fibrin strands and contributes to the stable brain perfusion pressures obtained, varying from cat to cat over a range of 50 to 100 mm Hg. The pumps were adjusted to provide a constant flow (variable pressure) of 13 to 15 ml/min for the brain and 6 to 8 ml/min for the hindlimb. This blood flow for brain amounts to 52 to 60 ml/min/100 gm brain and corresponds well to the flow rates reported for brains of a variety of mammalian species in the studies cited by Lassen. The hindlimb flow employed approximates that which we have found previously for resting hindlimb in the cat. Blood flows in each organ bed were determined by timed collection of the venous effluent in a graduated cylinder.

For oxygenation of the perfusion blood, humidified air containing 2.5% CO₂ was supplied to the oxygenator. This mixture was selected because it produced arterial P₀₂, P₀₂, and pH values in the perfusing blood which are close to those which we have found in the body of the chloralose-anesthetized cat prior to cerebral perfusion. In some experiments 98% O₂-2% CO₂ was used for purposes of comparison. Blood gases were routinely measured on a Radiometer gas monitor with P₀₂ and P₀₂ electrodes and pH on a Beckman Expandomatic pH meter with blood microelectrodes. The mean (±S.E.) P₀₂ and P₀₂ (mm Hg) and pH values of arterial blood in the perfusion circuit were, respectively, using air-2.5% CO₂: 116 ± 6, 41 ± 5 and 7.35 ± 0.03; and for 98% O₂-2% CO₂: 410 ± 37, 38 ± 4 and 7.41 ± 0.02. Equivalent mean P₀₂, P₀₂, and pH values obtained from the venous return of the brains were, respectively, for air -2.5% CO₂: 51 ± 3, 59 ± 5 and 7.27 ± 0.03, and for 98% O₂-2% CO₂: 48 ± 3, 58 ± 6 and 7.31 ± 0.02.

Cerebral and hindlimb perfusion pressures were recorded on a Beckman Type R Dynograph from Statham P23AA transducers connected to short side-arms off the arterial inlets to the perfused vascular beds.

NICOTINE CONCENTRATIONS

Nicotine hydrochloride, purchased from Pfaltz and Bauer, Inc., Flushing, New York, was employed throughout these studies. The stated concentrations in the perfusing blood are in terms of the hydrochloride salt and were obtained by adding the appropriate amount of a 2.5 mg/ml solution in saline to the 100 ml perfusion reservoir.
and mixing. A concentration of 10 μg/ml of nicotine HCl was selected for the main body of the study because this concentration gave the most consistent results while still falling within the range of "smoking" doses. However, in many experiments, similar results were obtained with final concentrations of 1 μg/ml. The dynamics of the perfusion circuit were such that it took approximately four minutes from the time the drug was added to the reservoir until it reached the brain, and slightly longer for the hindlimb. Some recent chemical determinations of perfusion blood nicotine by us indicate that the nicotine concentrations, which perfused the brain within the first five minutes after reaching the brain, were considerably below the stated 10 μg/ml concentration amounting to about 1 or 2 μg/ml. When 1 μg/ml was selected as the final perfusing concentration, the levels initially perfusing the brain were approximately one-tenth this value. Total mixing in the perfusion circuit volume (250 ml) to achieve the stated final concentration occurred only after 15 minutes had elapsed from the time of addition to the reservoir. Since the effects observed on the cerebral circulation occurred almost immediately after the drug reached the brain (the maximal effect was achieved in two minutes), these effects were obtained at concentrations considerably below those stated in the text, as finally attained in the perfusion circuit.

STATISTICAL ANALYSES

The effects of nicotine on the cerebral and hindlimb vasculatures were expressed and tabulated as resistance units, calculated from perfusion pressure (mm Hg)/blood flow (ml/min). Due to the variation in basal cerebrovascular resistance (CVR) and hindlimb vascular resistance (HLVR) between animals, it was necessary to use paired data in the statistical analyses, in which each animal served as its own control. A paired t test, as described by Steel and Torrie, was employed to determine the probability of chance variability in the differences of CVR or HLVR from predrug control values in each animal two or 15 minutes after the drug. The two-minute and 15-minute times after drug intervals were used in the analysis because at approximately two minutes after reaching the brain the nicotine effect on CVR was maximal, and the effect on HLVR had reached a maximal level at approximately 15 minutes. It must be emphasized that although mean values are listed in table 1 of the Results section, comparison of these means did not constitute the statistical analyses. It was, rather, the variability of the differences between control and drug values in each animal that constituted the analyses. The null hypothesis tested was whether the sample population mean of these changes differed from a mean of zero. To evaluate the statistical significance of the differ-
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ences in mean percent change in CVR, following the drug, between groups having different CN status, Student's t test was employed using the absolute changes in resistance values in each animal from its own control figure. In all tests described above, the probability level selected for statistical significance was p ≤ 0.05.

Results

The effects of perfusion of nicotine HCl on the cerebral vasculature of the vascularly isolated, perfused, in situ cat brain and on the vascularly isolated, denervated, perfused cat hindlimb are illustrated in figure 1. This figure contains records of the cerebral perfusion pressures (mm Hg) from four cats in which the integrity of CN 9, 10, 11 and 12 differed, and a record of the perfusion pressure in the denervated hindlimb of a fifth cat. In all cases, the final concentration of nicotine HCl in the perfusion system was 10 μg/ml. It took approximately four minutes for the drug to reach the brain from the time of its addition to the perfusion system reservoir. On reaching the brain, the drug effect was almost immediate, and was, in each case excepting the hindlimb, qualitatively similar, that is, a transient increase in CVR as indicated by the resistance unit values given above each tracing. Quantitatively, however, the response differed depending upon the status of cranial nerve section. Trace A is from a cat having CN 9, 10, 11 and 12 intact. In trace B, which was taken from a cat in which CN 10 was sectioned bilaterally in the cervical area, the response is seen to be greater than in trace A. In trace C, in which CN 9, 10, 11 and 12 had been sectioned bilaterally at the jugular foramina, but in which the superior cervical ganglia remained intact, the response is smaller than that of B, resembling that of A. In trace D, CN 9, 10, 11 and 12 were sectioned bilaterally at the jugular foramina and the cervical sympathetic trunks were cut rostral to the superior cervical ganglion, eliminating cervical sympathetic vasomotor tone from the cerebral circulation. In this latter case, the change in CVR is barely detectable and is considerably less than in A, B and C. Trace E is from the vascularly isolated and denervated hindlimb and indicates only a weak but sustained vasodilating effect of the nicotine. At the concentration employed, we have never observed vasoconstriction to occur in the denervated hindlimb vasculature following

<table>
<thead>
<tr>
<th>Condition</th>
<th>Oxygenating gas</th>
<th>Resistance of the isolated, perfused, in situ cat brain (% change)</th>
<th>Absolute change in resistance (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN 10 intact</td>
<td>Air</td>
<td>6.0 ± 0.9</td>
<td>6 ± 0.5</td>
</tr>
<tr>
<td>CN 10 sectioned</td>
<td>Air</td>
<td>5.7 ± 0.5</td>
<td>6.4 ± 0.5</td>
</tr>
<tr>
<td>CN 9, 10, 11, 12 and sup.</td>
<td>Air-2.2% CO₂</td>
<td>6.2 ± 0.6</td>
<td>6.6 ± 0.6</td>
</tr>
<tr>
<td>CN 9, 10, 11, 12 and sup.</td>
<td>Air-2.5% CO₂</td>
<td>6.2 ± 0.5</td>
<td>6.6 ± 0.5</td>
</tr>
<tr>
<td>CN 9, 10 sectioned</td>
<td>Air-2.5% CO₂</td>
<td>6.2 ± 0.5</td>
<td>6.6 ± 0.5</td>
</tr>
<tr>
<td>CN 10 sectioned</td>
<td>Air</td>
<td>6.2 ± 0.5</td>
<td>6.6 ± 0.5</td>
</tr>
<tr>
<td>CN 10 sectioned</td>
<td>Air-2.5% CO₂</td>
<td>6.2 ± 0.5</td>
<td>6.6 ± 0.5</td>
</tr>
</tbody>
</table>

Values are given ± S.E., in terms of resistance units calculated as arterial perfusion pressure (mm Hg)/flow (ml/min).

*Indicates statistical difference from controls (p < 0.05) by t test.

The differences in control values between groups are not statistically significant (i.e., p > 0.05).
nicotine. Conversely, we have never observed nicotine to produce vasodilation in the cerebral circulation at any CN status cited above, even when the nicotine concentration was lowered to 1 μg/ml or raised to 100 μg/ml. At these latter two concentrations, the effect remained vasoconstrictor.

In a number of brain perfusion experiments, the effect of a second exposure to nicotine was determined either by adding another increment to the perfusion reservoir without having removed the first concentration or by having removed the first by replacing it with drug-free blood. Representative samples of the results obtained in preparations having only CN 10 sectioned are illustrated in figure 2. Traces A and B show the diminished effect of repeated additions of nicotine HCl to the reservoir without an intervening washout with fresh blood, while in trace C, a similar effect was observed even when the first was removed by washing the system with fresh, drug-free blood. Thus, an acute tolerance develops to the cerebral vascular constricting effect of nicotine in which the effect of a second exposure to the drug, at even ten times the initial concentration, may be completely eliminated. We have not investigated this phenomenon further as to its duration or mechanism.

Tables 1 and 2 summarize the results of experiments with 10 μg/ml of nicotine HCl on the cerebral and hindlimb vascular resistances. Because of the variability in control resistance values between animals, it was necessary to use paired data in the statistical analyses as previously explained in the Methods section. Therefore, although the means and standard errors are listed in the tables, these were not employed in the statistical analyses by the paired t test. In using this test, the differences from control values in each animal were analyzed and the mean percent changes from controls are listed in the tables, along with the probability level associated with these changes. The tabulated results indicate the following: (1) The effect of nicotine on the cerebral circulation of the cat, under the stated conditions, quantitatively is altered by the presence or absence of sympathetic vasomotor and cardiovascular reflex afferent nerves, being
maximal when the cervical sympathetic innervation is present and CN 10 is sectioned, and being less when CN 10 is intact or when CN 9, 10, 11 and 12 and the superior cervical ganglion are sectioned. In a few preparations, one of which is shown in trace C of figure 1, the cervical sympathetic trunks and superior cervical ganglia remained intact, but CN 9, 10, 11 and 12 were sectioned. In such preparations the response to nicotine was greater than when CN 9, 10, 11 and 12 and the ganglia were sectioned. From the foregoing, it would appear that the superior cervical ganglia play a prominent role in the vasoconstriction, but also an extraganglionic vasoconstrictor component exists which may result from an action of the drug on the walls of the cerebral blood vessels.

Discussion

The present data indicate that the effect of nicotine on the cerebral circulation is not particularly striking, consisting of a mild and transient vasoconstriction. It is likely that this vasoconstriction is due principally to stimulation of the superior cervical ganglia, since the effect was considerably reduced on decentralization of the ganglia. The fact that the effect is relatively small is not surprising, since electrical stimulation of the cervical sympathetic trunk has been reported to have only a small vasoconstricting effect on the cerebral circulation of a variety of species.\(^6\)\(^{19}\) The transience of the vasoconstrictor effect may relate to two aspects of nicotine's action. Firstly, there is the likelihood that although the initial vasoconstricting effect is due to ganglionic stimulation, this is soon superseded by ganglionic blockade, a well-established character of nicotine's action.\(^6\) Secondly, in the absence of secondary ganglionic blockade, there is the possibility that an acute tolerance develops to the ganglionic stimulating action and to the directly mediated vasoconstriction, such as we have observed following a second exposure to the drug after a washout period or following the addition of greater concentrations to the perfusion reservoir. Although acute tolerance to a variety of cardiovascular effects of nicotine have occasionally been mentioned,\(^5\) to our knowledge this has not been reported previously for the cerebral circulation. Our failure to observe a decrease in cerebral perfusion pressure following nicotine, even at 100 \(\mu\)g/ml, a concentration that would be expected to cause ganglionic blockade, presumably relates to the existence of only a minimal of sympathetic vasomotor activity to the cerebral circulation.\(^5\)\(^{10}\)

The mechanism of the extraganglionic cerebral vasoconstriction caused by nicotine is not apparent from the present data but would appear to be due to a direct action of the drug on the vascular smooth muscle, possibly mediated by a local release of catecholamine stores in the vessel walls by the drug, as has been described previously in isolated, perfused arterial segments and in the perfused rabbit ear.\(^6\) This direct cerebral vasoconstricting effect is in contrast to the direct vasodilating effect which it has on the vasculature of the denervated hindlimb. If these direct effects relate to local release of catecholamines in the vessel wall by the drug, the difference in effects on these two vascular beds might have a basis related to the difference in effects of epinephrine, which dilates skeletal muscle vasculature and constricts other beds.

We have not found any studies in the literature in which an attempt was made to confine nicotine to the cerebral circulation except that of Solli et al.,\(^20\) who used slug injections of 0.5 mg into the arterial input to the head of a recipient dog in cross-circulation dog experiments. In these latter studies, no change in cerebral blood flow in the recipient dog was observed following the nicotine, but it is not possible to compare these results to the present study as the manner of drug administration, the characteristics of the cerebral perfusion and many other experimental conditions differed between the two studies. The results with nicotine in the numerous studies

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cited by Larson et al. in which various isolated organ beds were perfused with nicotine are difficult to reconcile with one another since vasoconstriction, vasodilation, both (in either order), or no effect at all have been observed following the drug. Aside from dosage considerations, which differed widely in these studies, and other experimental variables, in general, nicotine was most apt to cause a directly mediated vasoconstriction in isolated aortic strips, in visceral organs, and in skin, and most likely to cause directly mediated vasodilation in skeletal muscle vasculature. The direct cerebral vasoconstriction observed in our studies would, therefore, more closely resemble the direct actions of nicotine on a majority of vascular beds other than skeletal muscle.

Our findings that the presence of intact vagi can reduce the nicotine-induced cerebral vasoconstriction prompted us to consider the nature of this interaction and raised the possibility that afferents from CN 10 may directly or reflexly mediate cerebral vasodilation. This was a subject of considerable controversy some years ago, but the present consensus denies or minimizes a cerebral vasodilator role for the vagus. One possible explanation for the enhancing effect of CN 10 section on nicotine’s action in the present investigation is that afferent impulses traveling cephalad along these nerves ordinarily exert a vasodilating influence on the cerebral circulation which tends to antagonize the pressor effect of nicotine. In a previous study, however, we did not observe any change in cerebral perfusion pressure following faradic stimulation of the central end of the cut vagus nerve in the cervical area. An alternative, yet less plausible explanation might relate to the ability of nicotine to augment efferent vagal activity by a central mechanism in preparations having CN 10 intact. In fact, in vagally intact preparations we have often observed a centrally induced vagal bradycardia following nicotine. Such effects may in some way activate visceral afferent reflexes which can dilate the cerebral circulation through pathways which have been speculated upon but whose actual existence is uncertain.

Finally, the relevance of our findings to the effects which tobacco smoking might have on the cerebral circulation and the possible health hazards resulting therefrom deserves some comment. Because of the possible differences in reactivity to nicotine between the cerebral circulation of the isolated, perfused cat brain and that of the smoking human, it would be inappropriate to make a strict analogy between the two situations. Based on our experimental results, however, some conjectural generalizations would seem to be warranted. Nicotine concentrations measured in the blood of smokers has been found to range from 0.1 to 10 μg/ml, depending on a host of factors within the individual in addition to the extent of smoking. These levels approximate, or are in excess of, the concentrations necessary to produce mild cerebral vasoconstriction in the present study, taking into account the dynamics of drug presentation in our perfusion system (see Methods section). We do not believe that the magnitude and duration of this vasoconstriction is sufficient to compromise appreciably blood flow to the brain, a conclusion which the limited studies on the smoking human seem to bear out. In terms of the nicotine content of tobacco smoke, then, the hazards of tobacco smoking in the human with cerebrovascular insufficiency would appear to be minimal. Further, the demonstrated acute tolerance to the cerebrovascular effects of nicotine in our studies would also tend to minimize the importance of this effect in habitual smokers. However, since tobacco smoke contains many other pharmaceutically active agents, including carbon monoxide, oxides of nitrogen and the materials collectively referred to as "tars," none of which have been investigated with respect to the cerebral circulation, we must still be circumspect regarding the cerebrovascular health hazards of tobacco smoking. Some preliminary studies in this laboratory with serum extracts of cigarette smoke which produce perfusion blood nicotine levels of 1 to 5 μg/ml indicate that the pattern of response of the cerebrovasculature to nicotine is somewhat different when other tobacco constituents are also present in the blood. In this case the pressor response appears to be somewhat slower in developing and has a more prolonged duration than with nicotine alone. There is also some indication that the cerebrovascular pressor effect of subsequently administered nicotine may be enhanced by a prior exposure to
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cigarette smoke. Further studies in this laboratory with smoke and smoke constituents are being planned to discern the effects of these agents on the cerebral circulation and their interactions with the known effects of nicotine.

Conclusions

From the above data we would conclude that the effect of nicotine HCl on the cerebral circulation of the perfused cat brain is a small and transient vasoconstriction mediated mainly via stimulation of the superior cervical ganglia, since when the cervical sympathetic trunks are sectioned rostral to the ganglia the vasoconstrictor effect is considerably reduced. The presence of a residual vasoconstrictor component following ganglion section suggests a direct action of the drug on the vascular wall, as has been reported for various other circulatory beds other than skeletal muscle vasculature. The results also indicate that afferent vagal impulses can reduce the cerebral vasoconstrictor effect of nicotine mediated via ganglionic stimulation, since the vasoconstriction is reduced in the presence of intact vagi. Since studies were not made with selective sectioning of CN 9, 11 or 12, the role of these nerves in the above effects of nicotine cannot be assessed by the present data.

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References

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