Further Evidence for a Muscarinic Component to the Neural Vasodilator Innervation of Cerebral and Cranial Extracerebral Arteries of the Cat

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SUMMARY. Transmural electrical stimulation of segments of lingual and cerebral (basilar, middle and posterior cerebral) and also other cranial arteries of the cat results after a long latency in a dilator response. The response may be resolved into two components—an initial transient atropine-sensitive component and a slower more ponderous one that is atropine-resistant. The variability in pattern of dilation responses from segments of different vessels or even those from the same segment of different cats is considerable. Some responses are entirely atropine-sensitive and others atropine-resistant; however the vast majority show a dilation that can be considered to be made up of both components. The latencies of the atropine-sensitive and atropine-resistant components are not different. The effect of atropine on the lingual but not the cerebral arteries is frequency dependent, being proportionately greater at low than at high frequencies. In both vessels, the effect of atropine is independent of train length at 1 Hz. Physostigmine potentiates significantly the dilation of the lingual artery but not that of the cerebral arteries. The potentiation is reversed by atropine. The endogenous acetylcholine level was measured in a series of vessels. It can be correlated with the activity of choline acetyltransferase and the presence of neurogenic dilation. It is proposed that there are two transmitters released in parallel from nerve(s) in the walls of cerebral, lingual, and, possibly, other cranial arteries to cause vasodilation. It seems likely that one of these is acetylcholine. (Circ Res 51: 421-429, 1982)

THE vasculature of many tissues in the head receives a vasodilator innervation that is independent of the sympathetic outflow and which has been frequently found to be atropine-resistant. Observations of this innervation of the circulation to the nose, tongue, and salivary glands are reasonably consistent: see for example Emmelin (1968), Darke and Smaje (1972), Eccles and Wilson (1973), Anggärd (1974), Stjernschantz and Bill (1980), and Lundberg (1981). By contrast, there is disagreement concerning the vasodilator innervation of the pial circulation (see Heistad and Marcus, 1978; Purves, 1978, for synopses of much of the relevant literature). Although the dilator innervation frequently has been reported to be atropine-resistant, this does not necessarily mean that it is uninfluenced by atropine. This drug in conventional dosage often diminishes but does not completely block neurogenic dilation (see, for example, Eccles and Wilson, 1973). Such findings suggest that there may be a component of dilation mediated by a muscarinic receptor. More recent evidence of a cholinergic mechanism in cerebral and extracerebral cranial arteries has been found. This includes choline acetyltransferase, a high affinity choline uptake system, and diminution of neurogenic dilation in vitro by atropine (Florence and Bevan, 1979; Bevan et al., 1981, 1982). Such observations strongly imply the presence of a postganglionic cholinergic link in some of the cranial vascular beds.

Our recent conclusion that atropine diminishes neurogenic vasodilation in segments from the cerebral vasculature represents a reversal of position (compare Lee et al., 1978, with Bevan and Buga, 1981; Bevan et al., 1981, in press). Because of this, and in view of the conflicting results of Duckles (1979) and the results of a variety of in vivo studies (see above), the effect of atropine on the neurogenic dilation in selected cranial artery segments was pursued in more detail. In addition, measurements of two other features of cholinergic transmission that help to establish acetylcholine as an effective transmitter in the vessel wall—endogenous acetylcholine content of the blood vessel wall and the potentiating effects of physostigmine on neurogenic responses in vitro—are included in this paper.

It will be argued that a component of the neurogenic dilation seen in segments from cerebral and lingual and, by implication also, other cranial arteries is effected through a functional cholinergic link.

Methods

Arteries were obtained from adult cats of either sex of varying and unknown age. After anesthesia by pentobarbital (40 mg/kg) given by intraperitoneal injection, they...
were exsanguinated. The required arteries were rapidly removed and placed in Krebs bicarbonate solution, the composition of which was (mM): Na⁺, 144.2; K⁺, 4.9; Ca²⁺, 1.6; Mg²⁺, 1.2; Cl⁻, 126.7; HCO₃⁻, 25.0; SO₄⁻, 1.19; glucose, 11.1; and calcium disodium ethylenediamine tetracetae, 0.023. The vessels were dissected clean of surrounding tissue, utilizing a dissection microscope.

Ring segments (4 mm long) of the arteries were mounted in isolated tissue baths containing 50 ml of Krebs bicarbonate solution at room temperature according to the method of Bevan and Osher (1972). Ten minutes after artery segments were set up, the temperature of the Krebs bicarbonate solution was increased gradually over a 15-minute period and maintained at 38°C. Resting tension was adjusted to 0.5 g for pial and 1.0 g for other arteries, and a period of 1 hour was allowed for equilibration. A pair of stimulating electrodes was arranged, one on either side of the vessel, for transmural nerve stimulation (TNS).

After equilibration, a contractile response to an approximate EC₅₀ concentration of norepinephrine (NE; 10⁻⁷-10⁻⁵ M), the precise level depending on the segment, was elicited. After washing, the tissue was incubated in guanethidine (5 × 10⁻⁶ M) for 30 minutes to inactivate neuronal adrenergic mechanisms—as confirmed in each experiment by the absence of a contractile response to electrical transmural nerve stimulation (TNS) in the absence of muscle tone. Guanethidine was maintained in the tissue bath throughout the experiment. After equilibration, smooth muscle tone was induced by prostaglandin PGF₂α, 5 × 10⁻⁴ M and TNS was applied as 20-second trains of 0.3-msec pulses at 1, 2, 4, and 8 Hz at the lowest voltage that caused a dilator response and was blocked by tetродotoxin (3 × 10⁻⁶ M). A low source impedance device to the stimulating electrodes was utilized (Duckles and Silverman, 1980).

The latency between the start of transmural nerve stimulation and the commencement of dilation was measured with a stop watch. In separate studies, when the commencement of stimulation was registered together with an amplified tension trace on fast moving paper, this method was shown to be accurate within less than 0.25 second.

When testing for pharmacological blockade with atropine, control TNS responses were elicited in the presence of PGF₂α-induced tone. After the tissue was washed, atropine was added, and 15-20 minutes later, tone was reestablished with the prostaglandin and the sequence of TNS was repeated. In many of the experiments, to act as a control, an adjacent tissue segment was treated in an identical manner except that no atropine was added to the tissue bath. The peak dilation was expressed as a percentage of the level of active tone and/or g tension decrease.

The following arteries were included in the study: basilar, common carotid, external and internal maxillary, lingual, middle and posterior cerebral, posterior auricular, posterior inferior cerebellar, and radial.

Endogenous acetylcholine levels were determined in vessel segments after they had been dissected and quickly weighed. They were homogenized in 2 ml 15% aqueous formic acid (v/v) containing (Hg) ACh as internal standard. Samples were extracted as described by Freeman et al. (1975) and the concentration of ACh determined by gas chromatography mass spectrometry (Jenden et al., 1973).

Results

Two Components of Neurogenic Dilation

A survey of 607 dilator responses to transmural nerve stimulation (TNS) recorded from 84 different cat arterial segments including lingual (44), basilar (11), middle cerebral (7), posterior cerebral (5), internal maxillary (6), external maxillary (4), parotid (4), superficial temporal (3), and the modification of many of these responses by atropine (5 × 10⁻⁷ M) reveals that they vary widely in magnitude and time course. We propose that the dilator response is compounded of an initial transient and a subsequent more prolonged relaxation component whose absolute and relative magnitude vary in the same segment from different animals and between different segments from the same animal. The experimental evidence in support of this proposal is summarized below. In some instances only a transient (Figs. 1, 2, and 4) and in others only a slow prolonged recovery from dilation is seen (Figs. 3 and 4). However, the majority of responses seem to be a composite of two components: (Figs. 2, 4, and 9), although this distinction cannot always be made. This degree of variability in the size and shape of the neurogenic dilator response was quite different from our own past experience in studying adrenergic neuroeffector mechanisms in many types of blood vessels from a variety of species. The early parts of the dilator responses at 4 Hz from a consecutive series of experiments on the cat lingual and cerebral arteries are shown in Figure 4, together with the magnitude of the peak dilation expressed in relation to the level of tone. In experiments in which artery segments were used as controls for the study of drug action, the pattern of dilator response was seen to remain very similar during the course of a day's experiment.

Atropine-Sensitive and -Insensitive Dilator Components

A survey of responses of all arteries and their modification by atropine shows that the initial transient component is atropine-sensitive and the later prolonged part of the response atropine-resistant (Figs. 1, 2, and 4). In some instances, this distinction is not possible. Such responses may be considered to

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**FIGURE 1.** Selected tracings from a record showing responses of cat internal maxillary arteries to transmural nerve stimulation at 2, 4, and 8 Hz and the effect of atropine (5 × 10⁻⁷ M). The tissue was pretreated with guanethidine (3 × 10⁻⁴ M), tone induced by PGF₂α (5 × 10⁻⁴ M): its extent was shown by papaverine (10⁻⁵ M).

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Selected tracings from a record showing responses of \( \text{at lingual artery to TNS at 2, 4, and 8 Hz and the effect of atropine (5 \times 10^{-7} \text{M})} \). Tissues were pretreated with guanethidine (3 \times 10^{-6} \text{M}), tone induced by PGF\(_{2\alpha} \) (5 \times 10^{-8} \text{M}).

There are occasions when the later slow component is fairly large compared to the early transient phase or when the latter may be entirely absent (see Figs. 1, 3, 4, and 9 for examples of this variation).

Latency of Dilation

In Figure 5, the latencies of the constrictor and dilator responses of cat lingual arterial segments are shown. The latency for dilation is considerably longer than for constriction at the same frequency. Atropine (5 \times 10^{-7} \text{M}) and physostigmine (5 \times 10^{-8} \text{M}) plus atropine had no effect on dilator latency. This suggests that a cholinergic link is not a rate-limiting event in the processes leading to smooth muscle relaxation.

Effect of Stimulus Train Length and Frequency

In Figure 6, the effect of atropine on the size of the dilation obtained from cerebral and lingual arterial segments stimulated at varying frequencies is illustrated. Not all stimulation frequencies were examined on all vascular segments. This illustrates quite clearly that the atropine-sensitive and -insensitive components of the dilator response occur at all frequencies tested. The data for the cerebral and lingual arteries at 4 \text{Hz} correspond to the detailed results shown in Figure 4. In the lingual but not the basilar artery, the effect of atropine was frequency-dependent. At 1 \text{Hz}, more than 60\% of the lingual artery response is atropine-sensitive compared with only 10\% at 8 \text{Hz}. Since, in these studies, train length was held constant at 20 seconds, the number of pulses applied varied with frequency. This raises the possibility that part of the frequency dependency seen in the lingual artery may be due to variation in numbers of pulses in the stimulus train.

The influence of train length alone on the atropine-sensitivity of the lingual and basilar arteries stimulated at 1 \text{Hz} is shown in Figure 7. At this frequency, when the atropine-sensitive component of the lingual artery dilator response is greatest, the dilations recorded after 5, 10, 20, and 40 stimuli were reduced to the same degree by atropine. The proportionate change in response with atropine after 20 pulses was not significantly different from those after 5, 10, and 40 pulses.

Effect of Physostigmine

In the classical pharmacological characterization of cholinergic transmission, particularly at muscarinic receptor sites, the measurement of the effect of anticholinesterases takes only second place to the study of atropine. In Figure 8, physostigmine (5 \times 10^{-8} \text{M}) is shown to increase mean peak responses of the lingual artery to TNS. In this series of experiments carried out on arterial segments (28 segments from 23 cats) which were different from those used in the study of atropine alone (see above), the increase in relaxation was potentiated significantly at 2, 4, and 8 \text{Hz}. At each frequency, the potentiation was reversed by atropine (5 \times 10^{-7} \text{M}) added in the presence of physostigmine, suggesting the specificity of the physostigmine potentiation (see Fig. 8). Physostigmine preferentially potentiates the early transient phase of relaxation; it was this phase that was antagonized upon atropine addition (Fig. 9). Although the mean responses of the cerebral arteries were increased by physostigmine, the increase was not significant.

Effect of Atropine and Physostigmine on the Level of Prostaglandin-Induced Tone

The possible effect of these cholinergic drugs on the level of tone achieved in various vessels in response to PGF\(_{2\alpha} \) was tested either by preincubating the vessels prior to addition of the prostaglandin, or by their addition to the tissue bath after tone has been achieved. No evidence for a consistent effect of either agent on any artery tested was found.

Endogenous Acetylcholine Levels

The presence of two biochemical markers of cholinergic function—ChAT and high affinity choline uptake only in those vessels that exhibit neurogenic dilation (Florence and Bevan, 1979; Bevan et al., 1981)—strongly suggests that acetylcholine is involved in this phenomenon. To strengthen the credibility of this possibility, particularly in view of early...
negative or equivocal pharmacological evidence (Lee et al., 1978; Lee, 1980), endogenous levels of acetylcholine were measured in selected cranial vascular segments. A positive correlation was found between mean acetylcholine content and mean ChAT activity in a group of vessels that spans both cerebral and extracerebral arterial beds (r = 0.87; P = < 0.005; Fig. 10). Because of tissue size limitations, acetylcholine content and ChAT activity could not be measured in the same animal. Only those vessels with levels of acetylcholine in excess of approximately 15 pmol/mg protein exhibit neurogenic dilation (Bevan et al., 1982).

Discussion

Evidence presented in this paper derived from the study of cat cerebral (basilar, middle, and posterior cerebral) and lingual arteries supports the conclusion that the neurogenic vasodilation seen after guanethidine pretreatment and after induction of smooth muscle tone can be considered to be a composite of two separate components. We have observed a similar biphasic pattern of dilation in comparable studies of other cranial vessels, specifically the internal and external maxillary, the carotid and superficial temporal arteries. That these are two separate and distinct components becomes clear, when a large number of responses are studied. The components differ in their time course, relative size, and atropine-sensitivity. The latencies of the initial transient atropine-sensitive and prolonged atropine-resistant components are not significantly different but are considerably longer than their neurogenic constriction. A partial reduction of the neurogenic dilation of the basilar, middle cerebral, internal maxillary, and lingual arteries has been reported previously (Bevan et al., 1982). The atropine-sensitive component comprised a proportionately greater part of the dilation at lower frequencies in the lingual but not the cerebral arteries. The proportional effect of atropine was the same when the stimulus train lengths varied between 5 and 40 pulses in both cerebral and lingual arteries.

Comparable atropine-sensitive vasodilator characteristics have been reported for other tissues of the head on the basis of in vivo measurements. In cranial tissues where atropine-resistant neurogenic vasodilation has been described, it was not always absolute. There was often a residue of effect that persisted after atropine administration; for example the nose (Eccles and Wilson, 1973), tongue (Stjernschantz and Bill, 1980), and salivary glands (Darke and Smaje, 1972).
Bevan et al. / Cholinergic Vasodilation

Control
Atropine
Phystostigmine

**FIGURE 5.** Latency between beginning of transmural nerve stimulation of lingual artery segments and neurogenic response. Latencies to stimulation of the segments in the absence of tone led to constriction. Dilator responses were elicited in the presence of guanethidine (3 × 10⁻⁶ M) and PGF₂α (5 × 10⁻⁶ M). In one series of experiments, only the effect of atropine (5 × 10⁻⁷ M) was tested (left); in the other, first the effect of physostigmine (5 × 10⁻⁸ M) and, subsequently, of atropine (5 × 10⁻⁷ M) was determined.

Furthermore, there are reports that it is the earlier component of dilation—that seen at low frequencies—that is atropine-sensitive (Emmelin et al., 1968; Darke and Smaje, 1972; Anggård, 1974; Lundberg et al., 1981b). It is difficult to understand why the atropine-sensitive components should be greater at low frequencies. In cholinergic systems, transmitter release per pulse has been found to be independent of stimulation frequency (Paton and Aboozar, 1968). If two substances are released from the same varicosity—which is one possible explanation of the two phases of dilation (see below), in the same proportion, which seems the most likely event—then it must be the effector cell-disposition mechanism system that confers frequency-dependent characteristics. After chronic sympathectomy, the remaining neuronal varicosities in the lingual artery appear homogeneous with respect to their vesicle population (Rowan et al., unpublished result), and this is also true of cerebral arteries (Lee, 1981). On the other hand, if two substances are released from different nerve terminals, there is no reason to expect that the frequency-release characteristics should be the same.

The concentration of atropine used in this study is equal to or less than that used by others to characterize peripheral muscarinic systems and to determine specificity in receptor binding studies with muscarinic ligands (Frey and McLsaac, 1981; Heilbronn, 1978; Yamamura and Snyder, 1974). Furthermore, the concentration of atropine had no effect on the dilation of these vessels to papaverine and nitrite (Bevan et al., 1982). With regard to physostigmine, the concentration used (5 × 10⁻⁸ M) is one-tenth or less that used by others in comparable experiments (Yamamura and Snyder, 1974; Hutchinson and Kosterlitz, 1976; Dietrich et al., 1976). There is no reported action of physostigmine at this dose that would account for potentiation of neurogenic dilation, other than its anticholinesterase activity. We selected doses of both of these drugs that are equal to or lower than those commonly used in this type of study, to avoid the criticism of nonspecificity of action. Thus, the extent of atropine and physostigmine sensitivity in this study may be quantitatively underestimated. Why an effect of physostigmine was noted in the lingual but not the basilar artery and why the response of the former but not the latter vessel was frequency-dependent cannot be explained. It could reflect the fact that the variation of the basilar artery responses was considerably greater than the lingual. There are many factors that contribute to the relationship between nerve traffic frequency and effector response, most of which are unknown or unestablished in these vessels.

We have, on several occasions, commented on the reversal of our earlier position of complete atropine-resistance for neurogenic vasodilation in the cat basi-
CEREBRAL ARTERIES

LINGUAL ARTERY

Figure 7. Effect of varying stimulation train length on size of the dilator response to transmural stimulation at 1 Hz, of cat cerebral (basilar: n = 4, and middle cerebral: n = 5) and lingual arteries and the effect of atropine (5 × 10⁻⁷ M).

The latency of the neurogenic dilation is 2 to 3 orders of magnitude greater than that found at other cholinergic sites. In autonomic ganglia, neuromuscular junction, and at some other postganglionic parasympathetic synapses, latencies have been established to be 0.5 msec (Katz and Miledi, 1965), 0.3-0.5 msec (Coombs et al., 1956), and 50-100 msec (Ursillo, 1961), respectively. A latency of up to 15 seconds, as we have observed in the external maxillary artery (Bevan, unpublished data), has not been previously described for a mammalian neuroeffector system at 38°C, and suggests an unusual mechanism. The similar latency of the atropine-sensitive and atropine-resistant responses favors the release of two transmitters, one of which is acetylcholine, in parallel. It seems unlikely that one transmitter is responsible for the release of the second. However, this possibility is not absolutely excluded, as the first substance which might be responsible for one of the components of dilation could, in turn, release the second transmitter. Similar latencies do not necessarily negate such a hypothesis, since

Figure 8. The effect of physostigmine (5 × 10⁻⁸ M) and atropine (5 × 10⁻⁷ M) in the presence of physostigmine on the neurogenic response of cat lingual artery segments in the presence of guanethidine (3 × 10⁻⁷ M). Tone was induced by PGA₃ (5 × 10⁻⁶ M).

Relaxation is expressed in grams. At each frequency, the dilation in the presence of physostigmine was greater than control, and the subsequent dilation in the presence of physostigmine plus atropine was significantly smaller than that with physostigmine alone.
a long delay could occur at any point(s) on the complex series of events that eventually lead to relaxation of the smooth muscle cells. Since atropine and physostigmine have no significant effect on latency, the majority of the delay at any rate does not occur at a cholinergic step. Since latency was not a function of the magnitude of dilation, it seems likely that the method of establishing latency is appropriate to these relatively slow events.

The results presented in this paper satisfy several more of the requisite criteria for the existence of cholinergic transmission in the arterial wall. This evidence, at least for the cat vessels, is very strong and can be summarized as follows: (1) choline acetyltransferase is present in high amounts only in vessels that exhibit neurogenic dilation (Bevan et al., 1982); (2) in a small series of vessels, a high affinity choline uptake system has been shown whose extent parallels ChAT activity levels (Florence and Bevan, 1979); (3) endogenous Ach content parallels ChAT activity in a number of cranial vessels; (4) Ach is released on transmural nerve stimulation of the basilar artery (Duckles and Jenden, 1980) and from the lingual artery (unpublished results by present authors); (5) acetylcholinesterase is present in cerebral (Edvinsson et al., 1972) and other vessels of the head (Lundberg et al., 1979); (6) in the lingual and cerebral arteries, the neurogenic dilator response is reduced by atropine, and in the lingual is potentiated by physostigmine. However, the obvious implications of this listing must be tempered. It is quite possible that there are two cholinergic sites in the walls of the arteries—ganglionic and postganglionic. The evidence is consistent with the conclusion that the initial component of dilation is associated with a muscarinic receptor. This classically is parasympathetic—however, it need not be, as a similar muscarinic component has been noted associated with the sympathetic outflow (Beck et al., 1966; Zimmerman, 1968; Pollard and Beck, 1971). The other choline-related features could be either pre- or postganglionic, or both. Our own survey has failed to reveal ganglion cells in the wall of the segment of lingual artery used in this in vitro study, (Rowan et al., unpublished result), but this does not unequivocally exclude such a possibility.

Although acetylcholine is generally reported as a vasoconstrictor of large blood vessels, more recent studies show that in small concentrations it dilates and in larger constricts (Edvinsson and Owman, 1976; Lee, 1980). This complex action may explain the variation in response shape and the effect of atropine (Fig. 4). Furchgott and Zawadzki (1980) contend that the muscarinic receptors leading to dilation in blood vessels are found exclusively in the intima. We have confirmed that this is also the case for cat lingual and basilar arteries. Our own results suggest that the innermost cell layers must be intact for neurogenic dilation to occur in these vessels (Bevan et al., in press).

The cause of the second more ponderous component of dilation, the atropine-resistant phase, is unknown. Our preliminary studies (Bevan et al., in press) suggest that vasoactive intestinal polypeptides (VIP) may in some way be associated with dilator events. Such a conclusion is consistent with the studies of Lundberg et al. (1979), who found an association between cholinergic systems and VIP, especially in blood vessels and also in the material released from perfused submandibular gland and nasal mucosa (Lundberg et al., 1981a) during parasympathetic nerve stimulation.

Whether or not the two transmitter substances are released from the same or different neurons cannot be resolved at the moment. The possibility that two transmitters may co-exist in the same nerve terminal is not in conflict with the original Dale postulate. It has been proposed that two classical transmitters or one classical and a putative transmitter may be present in the same neuron at different times during development or even in the adult neuron at the same time in the same neuron (Burnstock, 1976; Patterson, 1978). As dilation was not studied after chronic nerve section, the origins of the neurons involved in this dilation are not known. Quite clearly, they occur after adrenergic varicosity inactivation, but this does not define their anatomical origins.

In the introduction to this paper, references were limited to a few of those pertaining to dilator systems to cranial vessels. There is some evidence from ChAT distribution patterns that these form a cohesive outflow (Bevan et al., 1982). However, it should be emphasized that noncholinergic dilator pathways are known for some noncranial parts of the body. These include the vasculature to hind limb (Beck et al., 1966; Brody and Shaffer, 1970), intestine (Burch, 1899; Kure et al., 1931), kidney (Goldberg, 1975), paw (Zimmer-
man, 1968; Abboud, 1972), and the portal vein (Hughes and Vane, 1967).

Two or more components of vasodilation, one of which is sensitive to atropine, have been described in the hindlimb of cats and dogs following stimulation of the sympathetic trunk (for early work, see Beck and Brody, 1961; Beck et al., 1964; Abboud and Weinberg, 1965). The effect was unmasked by adrenergic neuronal blockade. It showed variability from animal to animal at least in the cat. Beck et al. (1966), Zimmerman (1968), and Pollard and Beck (1971), who investigated this dilation in some detail, showed that it was the transient component that was atropine-sensitive and that the sustained component was atropine-insensitive and occurred after a long latency. In many respects, this dilation in the hindlimb is similar to that described in the present paper, in the cranial vasculature. It is also interesting that, in the giant petrel, the vasodilator response to nerve stimulation of the foot is also considered to be a composite of two components: a short-lasting response blocked by atropine and a second longer-lasting component which is unaffected by this drug (Johansen and Milnor, 1981). It is clear from the study of the literature that the neural vasodilator innervation of the circulation is not homogeneous and that generalization can be made only with caution.

Research described in this paper was supported by U.S. Public Health Service Grants HL 15805, 20581, and MH 17691. We thank Dr. Donald J. Jenden for the use of the GCMS facility.

A preliminary account of these findings was previously published: Bevan, JA, Bevan RD, Buga GM (1982) The evidence for a peripheral cholinergic component to the neurogenic vasodilator control of cat cerebral and cranial arteries. Fed Proc 41: 1117.

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Received November 30, 1981; accepted for publication June 17, 1982.

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INDEX TERMS: Neurogenic dilator • Atropine • Acetylcholine • Cranial arteries
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Circ Res. 1982;51:421-429
doi: 10.1161/01.RES.51.4.421

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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