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Morphology of the rat carotid sinus nerve. I. Course, connections, dimensions and ultrastructure

DONALD M. McDONALD

The Cardiovascular Research Institute and The Department of Anatomy, University of California San Francisco, San Francisco, California 94143, USA

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Summary

An analysis of the morphology of the carotid sinus nerve in 39 rats revealed that the nerve emerged from the glossopharyngeal nerve (nerve IX) 0.6–1.0 mm beyond the distal extent of the petrosal ganglion. In 68% of cases the nerve consisted of a single bundle of axons; two bundles were present in the other nerves. Near the rostral pole of the carotid body, the nerve divided into multiple bundles of axons. Most axon bundles entered the carotid body, but some instead joined sympathetic nerves from the superior cervical ganglion. Some of the latter group of sinus nerve axons innervated the wall of the carotid sinus. Other presumptive baroreceptor axons reached the carotid sinus from the sinus nerve by first traversing the carotid body.

The sinus nerve had an average length of 2.0 ± 0.13 mm (mean ± S.E.M., range = 1.3–2.9 mm, $N = 15$) and was elliptical in cross-section (major axis = 77 μm, minor axis = 46 μm). The nerve contained an average of 625 axons, 86% of which were unmyelinated. The perineurial sheath that enveloped the circumference of the nerve was comprised of 3 or 4 layers of cells interconnected by gap junctions and tight junctions. Near the carotid body, the perineurium extended into the nerve where it compartmentalized fascicles of axons. The endoneurium consisted mainly of collagenous fibres (mean diameter 40 nm) that were only half the size of those outside the perineurium. Endoneurial connective tissue cells were sparse, being only 5% as numerous as Schwann cells. The one blood vessel in the nerve (mean luminal diameter 12.4 ± 1.2 μm) usually arose from vessels in nerve IX and terminated in a venule at the rostral surface of the carotid body.

Ganglion cells were located in nerve IX near the origin of the sinus nerve and along the length of the sinus nerve itself. All ganglion cells examined were postsynaptic to vesicle-containing nerve terminals, and therefore were presumed to be autonomic rather than sensory. Ganglion cells were more numerous in terminal branches of the sinus nerve on the ventral surface of the carotid body. Most other ganglion cells in the carotid body were located among axons of the ganglioglomerular nerve, although some were associated with a small branch of the vagus nerve. Paraganglia were located within the sinus nerve in 15% of cases, and in another 10% of cases they were found nearby in nerve IX. The paraganglia, which measured approximately 50 × 50 × 100 μm, were innervated by axons that resembled sensory nerves of the carotid body.

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Introduction

The carotid sinus nerve (also known as the intercarotid nerve, nerve of Hering or simply the sinus nerve) is the branch of the glossopharyngeal nerve (nerve IX) that innervates structures in the region of the bifurcation of the common carotid artery. From experiments done by Hering (1924), de Castro (1926, 1928), Heymans and his coworkers (1930) and many others after them, the sinus nerve is known to contain chemoreceptive axons from the carotid body and baroreceptive axons from the carotid sinus.

The sinus nerve also is a route for visceral efferent (autonomic) axons. In the rat and certain other species, the sinus nerve carries parasympathetic axons destined to end on ganglion cells and blood vessels of the carotid body (de Castro, 1926; McDonald & Mitchell, 1975, 1981). This pathway may mediate the increase in carotid body blood flow produced by electrical stimulation of the carotid sinus nerve (Neil & O'Regan, 1971). The sinus nerve also contains sympathetic axons (de Castro, 1926; Eyzaguirre & Uchizono, 1961; Mishra & Hess, 1978), and there is physiological evidence of a nonsympathetic efferent pathway in the nerve that modifies the sensitivity of chemoreceptors (Biscoe & Sampson, 1968; also see reviews by Majcherczyk *et al.*, 1980; McDonald & Mitchell, 1981).

Gross anatomical relationships of the sinus nerve have been described for many species (reviewed by Adams, 1958), but information on the composition of the nerve has come mainly from studies of the cat (Gerard & Billingsley, 1923; de Castro, 1951; Ask-Upmark & Hillarp, 1961; Eyzaguirre & Uchizono, 1961; Fidone & Sato, 1969). The sinus nerve of the rat has not been studied as extensively as that of the cat, in spite of the considerable attention that has been given to the rat carotid body and carotid sinus (reviewed by McDonald, 1981). De Castro (1926) and others (Chiarini, 1965; McDonald & Mitchell, 1975; Sapru & Krieger, 1977; Yates & Chen, 1980) have described certain aspects of the course and branches of the nerve, yet there is only limited information on the composition of the nerve (Mishra & Hess, 1978; McDonald, 1981, p. 111).

This paper reports a study of the morphology of the sinus nerve in the rat. The specific objectives were: 1. to define the path of the nerve from its origin from nerve IX to the carotid body and carotid sinus; 2. to determine where the nerve gives rise to branches, and to identify other nerves that have connections with the sinus nerve; 3. to measure the dimensions of the nerve; 4. to elucidate the blood supply of the nerve; 5. to characterize the connective tissue sheaths of the nerve; and 6. to analyse the ultrastructure of ganglion cells and paraganglia present in the nerve. The number and size of axons in the sinus nerve are described in a companion paper (McDonald, 1983).

Materials and methods

The 39 female rats (Long-Evans strain; body weight 200–250 g) used in the study were anaesthetized with sodium methohexital (75 mg/kg) injected intraperitoneally, ventilated with 100% O_2 through a tracheal cannula attached to a Harvard rodent respirator, and then perfused via the left ventricle with one of the solutions described below.

STUDIES OF THE COMPOSITION AND DIMENSIONS OF THE SINUS NERVE

Tissue preparation

The 31 rats used for determining the dimensions of the sinus nerve and for light and electron microscopic studies of the components of the sinus nerve were perfused with a fixative containing glutaraldehyde and hydrogen peroxide as described previously (McDonald & Mitchell, 1975). Sinus nerves with the carotid body at one end and a segment of nerve IX at the other end were dissected free of most adjacent structures, treated with osmium tetroxide and uranyl acetate, and embedded in epoxy resin (McDonald & Mitchell, 1975).

Quantitative methods

The length of whole sinus nerves embedded in epoxy resin was measured with a calibrated eyepiece in a compound microscope. The interval measured extended from the point of origin at nerve IX to the point of branching of the sinus nerve at the rostral pole of the carotid body.

To determine cross-sectional dimensions of the sinus nerve and its blood vessel, the nerves embedded in epoxy resin were photographed as whole mounts, cut transversely with a saw at a specified distance from nerve IX, and then rephotographed. The photographs recorded the interval from the block face to nerve IX. Then cross-sections (50–60 nm in thickness) of sinus nerves were cut for electron microscopy and mounted on single slot grids. Measurements of the sinus nerve were made on electron micrographs (magnification approximately × 5000) by using a digitizing tablet (Talos Model 614B, Scottsdale, Arizona) interfaced with a Hewlett-Packard Model HP 9815S computer (Loveland, Colorado). The average diameters of vessels and nerves (assuming a circular profile) were calculated from measurements of their cross-sectional areas. The major and minor axes of sinus nerves were measured point-to-point on the micrographs. The variability of measurements about their average value was expressed as the mean ± S.E.M. (standard error of the mean).

STUDIES OF ANATOMICAL RELATIONSHIPS OF THE SINUS NERVE

The sinus nerve's site of origin, course, branching pattern, blood supply, association with other nerves, and relation to the carotid body and carotid sinus were elucidated by examining serial sections, specimens stained with methylene blue, and whole mounts of tissues prepared for electron microscopy.

The four rats used for preparing serial sections were perfused for 1 min with 0.9% NaCl containing 4% polyvinylpyrrolidone (PVP, MW 40 000) and then for 5 min with Bouin's fixative which also contained PVP. The carotid sinus nerves were removed in a block of tissue that included all structures in the region of the carotid bifurcation. In two cases the roots of the glossopharyngeal and vagus nerves and portions of the brain stem were included as well. Tissues were embedded in paraffin, cut into serial 7 μm sections, and stained with iron haematoxylin and aniline blue.

The four rats used to study the innervation of the carotid sinus were injected intravenously with heparin (250 units), perfused with a buffered salt solution (McEwen, 1956) for 1 min at 120 mmHg, and then perfused with 0.01% methylene blue chloride in phosphate buffer at pH 5.0 for 10 min (Richardson, 1969). Carotid bifurcations were removed immediately and immersed in ammonium molybdate fixative at 4° C for 24–48 h (Richardson, 1969). Specimens consisting of the carotid sinus nerve, carotid body, carotid sinus and superior cervical ganglion were rinsed in water, flattened between two glass slides, dehydrated in alcohol, and mounted in Permount.

Before being sectioned, tissues prepared for electron microscopy were examined as whole mounts by transillumination in a compound microscope (McDonald & Blewett, 1981).

Reconstructions of the sinus nerve and adjacent structures were made from the serial sections and from methylene blue-stained preparations enlarged to a scale of 300:1 by using a Zeiss camera lucida attached to a compound microscope.

Results

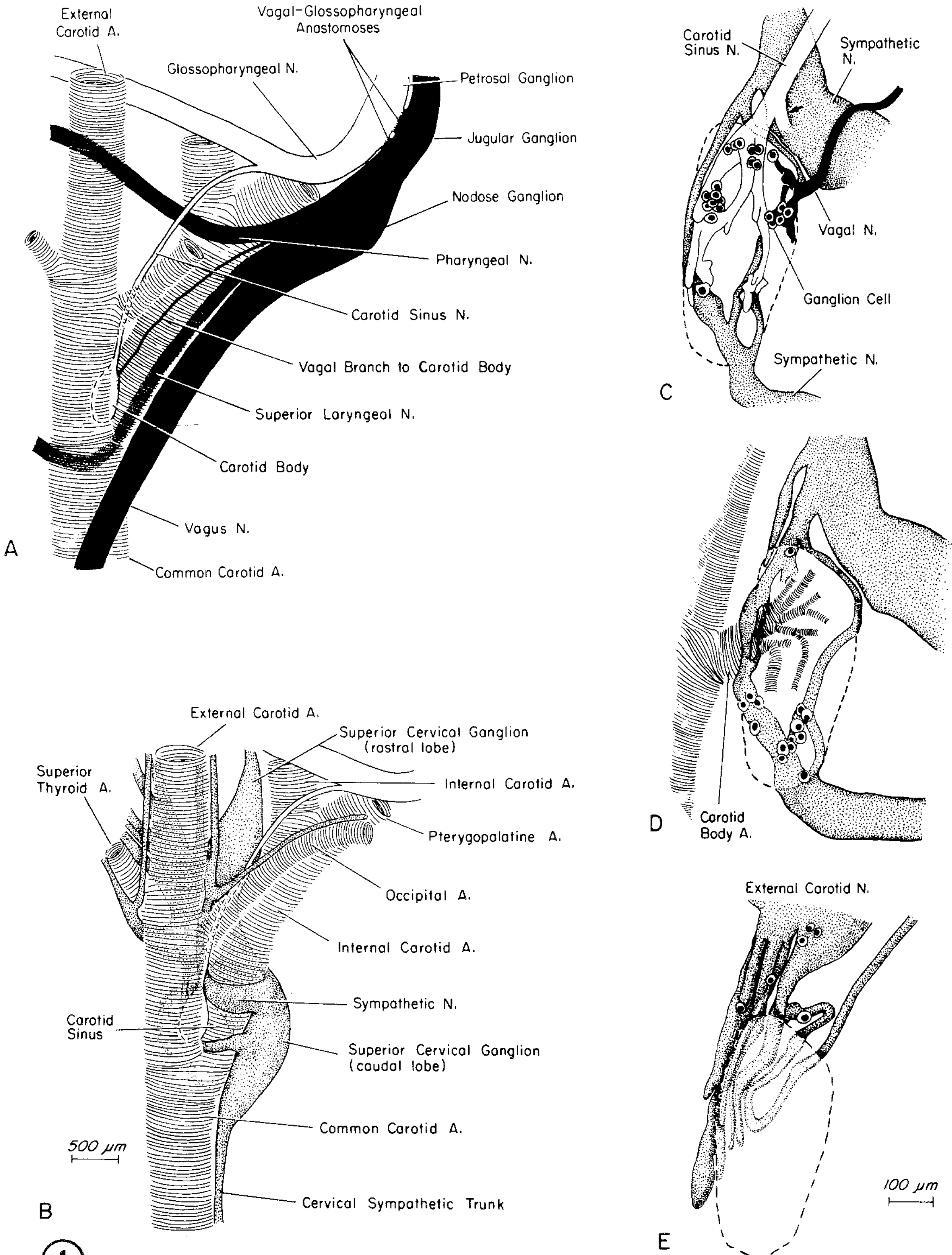
ORIGIN OF THE CAROTID SINUS NERVE

The carotid sinus nerve was the second major branch of nerve IX, the first being the tympanic nerve that emerged directly from the petrosal ganglion (inferior sensory ganglion of nerve IX). The sinus nerve arose from the caudal aspect of nerve IX at a point some 0.6–1.0 mm beyond the distal extent of the petrosal ganglion. The borders of the petrosal ganglion were difficult to define precisely because at some points it was in continuity with the jugular ganglion (superior ganglion) of the vagus nerve (Fig. 1A). Because the petrosal ganglion itself protruded about 1 mm beyond the surface of the skull, the total distance from the origin of the sinus nerve to the jugular foramen was 1.6–2.0 mm. Nerve IX, after emerging from the jugular foramen, followed a looping trajectory (dorsal to ventral and then lateral to medial) toward the pharynx.

At its origin the sinus nerve was ventral to the pterygopalatine artery near the site where the artery arose from the internal carotid artery (Fig. 1B). The origin of the sinus nerve was near the distal portion of the occipital artery at a site dorsal to the hypoglossal nerve about 0.4 mm proximal to the origin of the descendens hypoglossi. The sinus nerve arose at a point dorsal to the posterior belly of the digastric muscle and the stylohyoid muscle.

The sinus nerve emerged at an angle of 90°–140° with respect to the proximal portion of nerve IX. In 68% of cases (19 of 28) the sinus nerve consisted of a single bundle of axons enveloped by a perineurial sheath. In the other cases two discrete nerves were present. Curiously, 78% (7 of 9) of the double nerves were on the right side (an equal number of left and right nerves were examined).

Fig. 1. (A, B) Drawings of the ventrolateral aspect of the bifurcation of a left common carotid artery showing the major nerves (N) and ganglia in the region of the sinus nerve. Both drawings show the glossopharyngeal nerve, carotid sinus nerve and carotid body. In addition, Fig. 1A shows the jugular and nodose ganglia and branches of the vagus nerve (black) and Fig. 1B shows the superior cervical ganglion and its major branches (stippled). The names of arteries (A) present in both drawings are given in Fig. 1B. Reconstruction from serial sections. Approximate magnification × 17. (C–E) Drawings of the carotid body (broken line) shown in Figs. 1A and B illustrating here additional features of the relationship of the sinus nerve, sympathetic nerves and a branch from the vagus nerve. Also shown are the locations of ganglion cells associated with each of the nerves. Fig. 1C shows nerves near the ventrolateral third of the carotid body, Fig. 1D shows the middle third, and Fig. 1E shows the dorsomedial third. The arrow in Fig. 1C marks an anastomosis between the sinus nerve and a sympathetic nerve. Fig. 1D illustrates the sympathetic nerves that surround the carotid body artery. Fig. 1E shows the ganglioglomerular nerve as branches of the external carotid nerve that project to the carotid body. Approximate magnification × 80.


External Carotid A.
Vagal-Glossopharyngeal Anastomoses
Glossopharyngeal N.
Petrosal Ganglion
Jugular Ganglion
Nodose Ganglion
Pharyngeal N.
Carotid Sinus N.
Vagal Branch to Carotid Body
Superior Laryngeal N.
Carotid Body
Vagus N.
Common Carotid A.
A
Carotid Sinus N.
Sympathetic N.
Vagal N.
Ganglion Cell
Sympathetic N.
C
Carotid Body A.
D
External Carotid A.
Superior Cervical Ganglion (rostral lobe)
Superior Thyroid A.
Internal Carotid A.
Pterygopalatine A.
Occipital A.
Internal Carotid A.
Sympathetic N.
Carotid Sinus
Superior Cervical Ganglion (caudal lobe)
Common Carotid A.
500 µm
Cervical Sympathetic Trunk
B
External Carotid N.
100 µm
E

(1)

COURSE OF THE SINUS NERVE

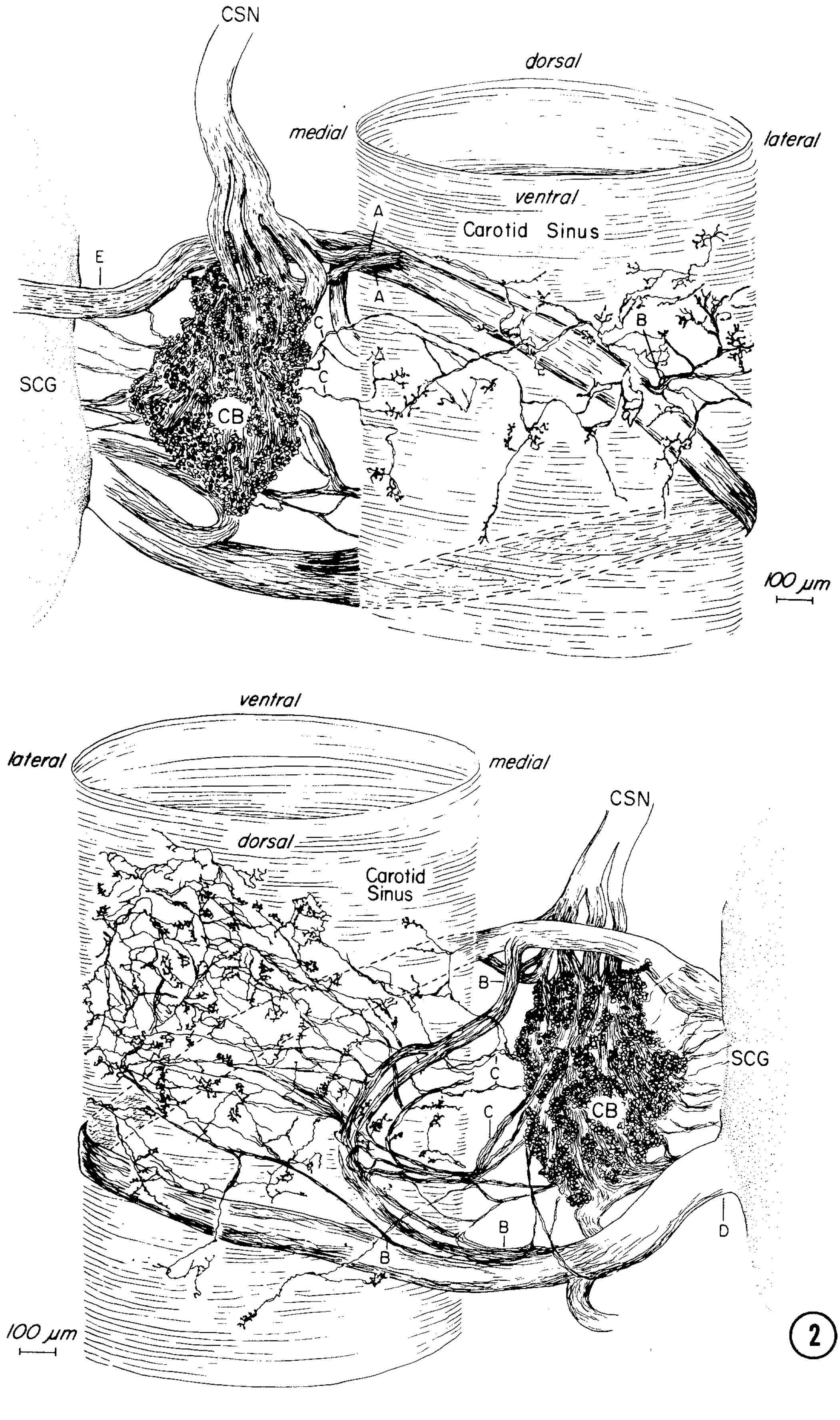
En route to the region of the carotid bifurcation, the sinus nerve followed a gradually curving path in a ventromedial and caudal direction (Fig. 1A). The sinus nerve initially tended to parallel the occipital artery, the nerve maintaining a more dorsal and medial position. The sinus nerve crossed the dorsal surface of the hypoglossal nerve, then passed at a right angle to and immediately ventral to the pharyngeal branch(es) (hereafter called the pharyngeal nerve) of the vagus nerve (Fig. 1A). The intersection with the pharyngeal nerve occurred about midway along the sinus nerve's course to the carotid body. Just before reaching the rostral pole of the carotid body, the sinus nerve crossed the dorsal surface of the occipital artery and the ventral surface of a nerve from the superior cervical ganglion (Figs. 1B, 1C, 2).

Because the point at which the occipital artery arose from the external carotid artery varied (0.2–2.4 mm from the carotid bifurcation), some carotid bodies were caudal to the occipital artery whereas others were adjacent to the dorsal surface of the vessel. The caudal pole of the carotid body typically was 0.5 to 2 mm rostral to the carotid bifurcation.

BRANCHES OF THE SINUS NERVE

The sinus nerve had no major branches before reaching the vicinity of the carotid body. However, in all specimens examined nerve bundles some 10–15 μm in diameter left and/or entered the sinus nerve near the level of the pharyngeal nerve. The small nerve bundles resembled morphologically the remainder of the sinus nerve (they did not contain the large myelinated axons typical of the pharyngeal nerve). Some of the small nerve bundles entered the carotid body. One of the small branches was found to join the external carotid nerve (the sympathetic nerve on the external carotid artery). Another branch accompanied sympathetic nerves distally on the external carotid artery. Most of the small nerve branches apparently did not join the pharyngeal nerve, but their destination was not established in all cases.

Fig. 2. Camera lucida drawings of nerves associated with a left carotid body and carotid sinus stained with methylene blue. The upper drawing shows the ventral surface and the lower drawing shows the dorsal surface. A sympathetic nerve, which emerges from the superior cervical ganglion (SCG) at a point marked D in the lower drawing, encircles the carotid sinus, and then passes over the ventral surface of the SCG at point E in the upper drawing. Other sympathetic nerves enter the carotid body (CB) directly from the ganglion. In the upper drawing, two branches of the carotid sinus nerve (CSN) join a sympathetic nerve at points marked A. Sinus nerve axons leave the sympathetic nerve at points B in both drawings, and then form characteristic baroreceptive-type nerve endings in the adventitia of the carotid sinus. Other baroreceptive axons enter the carotid sinus from the carotid body at points C. Some of the latter axons could be followed through the carotid body to the sinus nerve. Note that baroreceptive nerve endings are most numerous on the dorsolateral surface of the carotid sinus. In these figures, the carotid body is displaced some 100–200 μm from the SCG and the wall of the carotid sinus to show neural connections. Approximate magnification $\times$ 60.


CSN
dorsal
medial
lateral
ventral
Carotid Sinus
A
A
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SCG
CB
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ventral
lateral
medial
CSN
dorsal
Carotid Sinus
B
SCG
C
C
CB
B
B
D
100 μm

2

The sinus nerve split into four or more finger-like bundles of axons just before reaching the rostral pole of the carotid body at a point just medial to the carotid sinus (Figs. 1C, 2). Most of the nerve bundles continued on to the ventrolateral surface of the carotid body where they divided further and entered the organ (Figs. 3, 4). In all carotid bodies examined in serial sections or after staining with methylene blue, at least one of the sinus nerve bundles deviated from the course of the other bundles and joined a nerve from the superior cervical ganglion (see below).

ASSOCIATION OF OTHER NERVES WITH THE SINUS NERVE

The sinus nerve crossed the paths of three nerves en route to the carotid body: the hypoglossal nerve, the pharyngeal nerve, and one or more sympathetic nerves. No evidence was found of a communication between the sinus nerve and the hypoglossal nerve, but the sinus nerve did have connections with the other nerves. It was also associated with a small nerve coming directly from the vagus nerve.

Pharyngeal nerve

A branch from the pharyngeal nerve joined the sinus nerve in 43% of cases (6 of 14). This branch was distinctive because it contained myelinated axons larger than those in the sinus nerve itself (Fig. 4; see McDonald, 1983). It also contained unmyelinated axons. The branch when present became associated with the sinus nerve at a point between the pharyngeal nerve and the carotid body. However, most of the large axons in the branch remained separate from the sinus nerve axons, ultimately diverged from the sinus nerve, and did not end in the carotid body. Although the destination of the large axons was not established in most cases, in at least two cases they joined the external carotid nerve.

Sympathetic nerves

The close association of the sinus nerve with postganglionic branches from the superior cervical ganglion was conspicuous in all cases examined in serial sections and in specimens stained with methylene blue. Nerves from the superior cervical ganglion were abundant near the carotid body and the carotid sinus, and formed a neural network considerably more extensive than that derived from the sinus nerve itself

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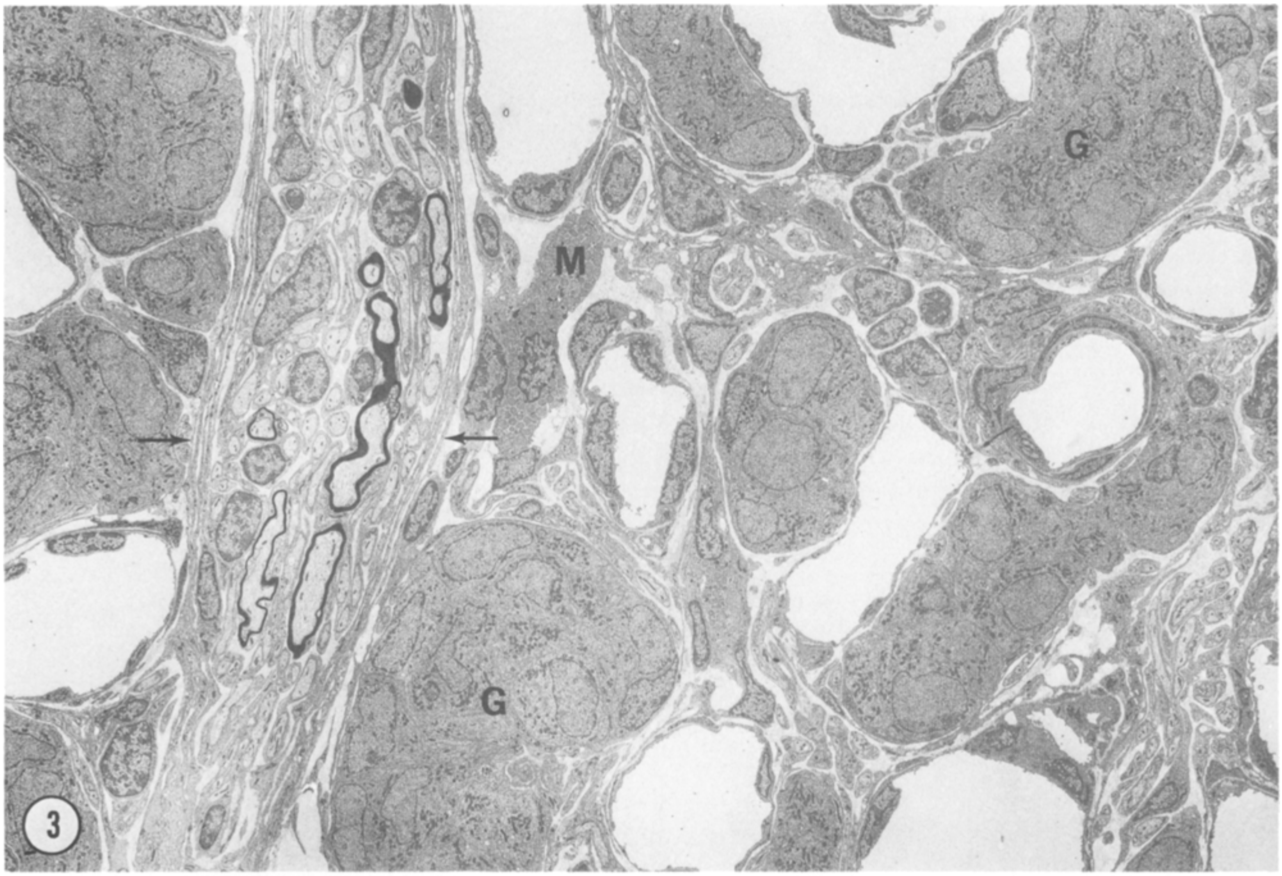
Fig. 3. Electron micrograph of a superficial region of a carotid body showing a bundle of sinus nerve axons still enveloped by perineurium (arrows) and located near clusters of glomus cells (G). Note that no myelinated axons are located outside the axon bundle. M, mast cell. × 1400.

Figs. 4, 5. Sections of carotid bodies which compare the morphology of three types of nerves. Fig. 4 shows a branch of the sinus nerve (small arrows) associated with a group of glomus cells (G) and a small bundle of axons (large arrow) from the pharyngeal branch of the vagus nerve. Myelinated axons in the latter bundle are larger than most axons in the sinus nerve. Fig. 5 shows sympathetic ganglion cells (arrows) within bundles of unmyelinated sympathetic axons (S) near the dorsomedial surface of the carotid body. Toluidine blue-stained 0.5 μm sections. × 650.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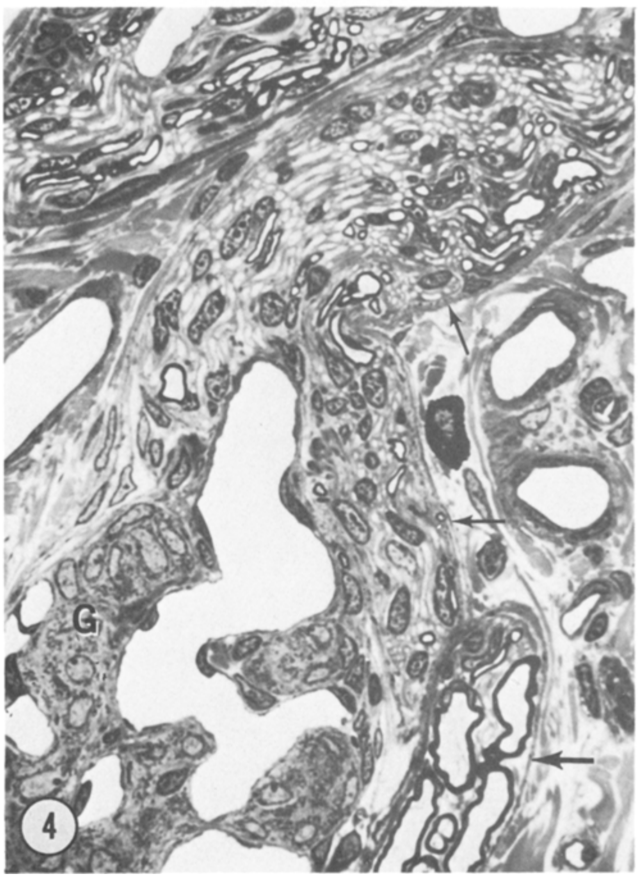
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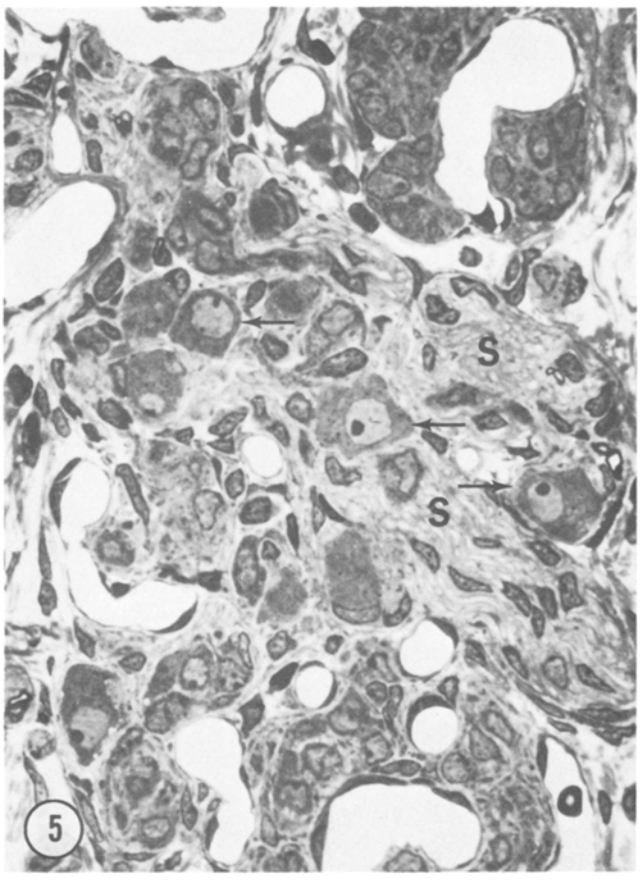
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(Figs. 1B–E). The numerous bundles of sympathetic axons that comprised the ganglioglomerular nerve were located on the dorsomedial surface of the carotid body near the external carotid nerve (Figs. 1E, 5). Bundles of sympathetic axons enveloped the carotid body artery (Fig. 1D) and were located elsewhere on the perimeter of the carotid body except for the ventrolateral surface. Most sympathetic nerves that did not enter the carotid body or did not encircle the carotid sinus joined the nerve plexus associated with the external carotid artery and its branches.

A division of the sinus nerve typically joined a sympathetic nerve at the rostral pole of the carotid body (Figs. 1C, 2). This sympathetic nerve was distinctive because it emerged from the lateral aspect of the superior cervical ganglion, wrapped around the carotid sinus in a dorsal to ventral trajectory, passed just dorsal to the sinus nerve, and then joined the sympathetic nerves on the external carotid artery (Figs. 1B, 2). The symphathetic nerve bundles (as much as 100 μm in width) that traversed the carotid sinus typically were much larger than the bundles of sinus nerve axons that joined them (less than 20 μm in width). In most cases these sympathetic nerves came from the rostral portion of the ganglion in the region adjacent to the carotid body. The nerves arose from the caudal portion of the ganglion in one case (Fig. 1B). [In about half of the rats examined, the superior cervical ganglion had two distinct lobes (rostral and caudal lobes as shown in Fig. 1B), which were joined by the thin portion of the ganglion that wrapped around the dorsal aspect of the internal carotid artery. This feature was seen as easily in living rats as in fixed preparations. The caudal lobe of the ganglion was not present in other rats.]

Vagus nerve

All carotid bodies examined in serial sections and after methylene blue staining received one to three branches directly from the vagus nerve. Invariably, these were small (10–20 μm in diameter). The vagal branch arose from the medial aspect of the nodose ganglion at a level between the origins of the pharyngeal and superior laryngeal nerves (Fig. 1A). En route to the carotid body, the branches from the vagus traversed the ventral surface of the internal carotid artery near the carotid sinus (Fig. 1A). Some of the axons appeared to terminate in the adventitia of the carotid sinus, but most ended in the carotid body or continued on to the superior cervical ganglion. The vagal branch(es) usually entered the dorsolateral aspect of the carotid body (Fig. 1C), but in two cases they entered the caudal surface.

INNERVATION OF THE CAROTID SINUS

The carotid body invariably was located next to the ventromedial surface of the carotid sinus portion of the internal carotid artery. From descriptions in the literature I anticipated finding a major division of the sinus nerve that bypassed the carotid body and innervated the carotid sinus directly. However, this was not observed. Instead, most axons that reached the carotid sinus passed through the carotid body or joined sympathetic nerves en route to the sinus.

Although most axons of the sinus nerve entered the carotid body, approximately ten small branches of the nerve, each containing some 1 to 20 axons, traversed the carotid body and entered the adventitia of the carotid sinus (Fig. 2). Some of the larger branches emerging from the carotid body could be traced as a unit back to the sinus nerve. Other branches appeared to be consolidations of dispersed axons within the carotid body. It was not clear whether sympathetic axons contributed to these nerve bundles.

The other route to the carotid sinus was by way of sympathetic nerves that some sinus nerve axons joined at the rostral pole of the carotid body (see above). After travelling a short distance in a sympathetic nerve, the sensory axons emerged in groups and ramified in the wall of the carotid sinus (Fig. 2). The proportion of sinus nerve axons that reached the carotid sinus by way of sympathetic nerves varied from rat to rat. When the proportion was small, a larger number of axons went to the carotid sinus via the carotid body.

Sensory nerve endings were most concentrated in the dorsolateral half of the sinus in the region furthest from the carotid body (Fig. 2). This plexus of sensory nerve endings was produced by the arborization of as few as 60 to 100 axons. However, the precise number of axons involved is uncertain because the proportion of axons stained by methylene blue is not known. The sympathetic nerve bundle that enveloped the carotid sinus passed superficial to the plexus of sensory nerves.

DIMENSIONS OF THE SINUS NERVE

The sinus nerve had an average length of 2.0 mm measured from its origin at nerve IX to the rostral pole of the carotid body (Table 1). The shortest of 15 nerves measured was

Table 1. Dimensions of the carotid sinus nerve.

	Left	*Right*	*All nerves*
Length (mm)	2.1 ± 0.24 (1.5–2.9)	1.9 ± 0.15 (1.3–2.5)	2.0 ± 0.13 (1.3–2.9)
Cross-sectional dimensions (μm or μm^2)			
Diameter	63 ± 3.4	62 ± 3.3	62 ± 2.2
Area	3088 ± 334	3069 ± 320	3078 ± 218
Major axis	80 ± 8.3	74 ± 8.7	77 ± 5.8
Minor axis	50 ± 6.2	43 ± 4.0	46 ± 3.7

Mean ± S.E.M.; values for length obtained from 15 sinus nerves (6 left, 9 right); ranges are in parentheses. Cross-sectional measurements were made from sections cut at a level 0.5 mm from the junction with nerve IX (10 sinus nerves from 5 rats). In the two cases in which two branches of the sinus nerve were present, major and minor axes of the larger branch are shown, whereas combined dimensions for both branches are given for area and diameter. Diameter was calculated from the cross-sectional area by assuming a circular profile.

1.3 mm, and the longest was 2.9 mm. Nerves from the left side were not appreciably different in length from those from the right side (Table 1).

When examined in cross-section, the sinus nerve tended to be elliptical in shape (Fig. 6). At a level 0.5 mm from its origin from nerve IX, the nerve had an average major axis of 77 μm and a minor axis of 46 μm (Table 1). The ratio of the two axes at this level was 1.7 ± 0.3 ($N = 10$). Distal to this level the nerve was more flattened at two points: in the region next to the occipital artery and near the carotid body where the nerve divided into multiple fascicles of axons (Figs. 1C, 2).

COMPOSITION OF THE SINUS NERVE

The main constituents of the sinus nerve were: 1. unmyelinated and myelinated axons; 2. Schwann cells that enveloped the axons; 3. endothelial cells, pericytes and in some cases smooth muscle cells of the blood vessel in the nerve; 4. connective tissue cells that formed the endoneurium, perineurium and epineurium; 5. a few ganglion cells; and, in a small proportion of sinus nerves, 6. the cells of a paraganglion.

Axons

The sinus nerve contained an average of 536 unmyelinated axons (mean size = 0.78 μm) and 89 myelinated axons (mean total fibre diameter = 2.7 μm) (examples shown in Figs. 6, 7). A detailed analysis of the number and size of the axons is reported in a companion paper (McDonald, 1983).

Blood vessel of the sinus nerve

Origin and course. A single blood vessel traversed the length of all 20 sinus nerves examined (Fig. 8). In 7 of the 9 sinus nerves in which two discrete nerve trunks were present, only the larger trunk had a blood vessel. A small vein usually ran parallel to the sinus nerve, but it was outside the perineurium (Fig. 8).

The sinus nerve vessel followed a straight, unbranched course between nerve IX and the carotid body. Proximally the vessel was connected with vessels in nerve IX, and distally it was in continuity with vessels of the carotid body. Only in the three cases in which paraganglia were present did vessels enter or leave along the length of the nerve.

In most sinus nerves the vessel joined a venule at the rostral pole of the carotid body where the nerve split into finger-like branches (Fig. 8). This suggests that blood flows toward the carotid body. However, exceptions may exist because in some cases the

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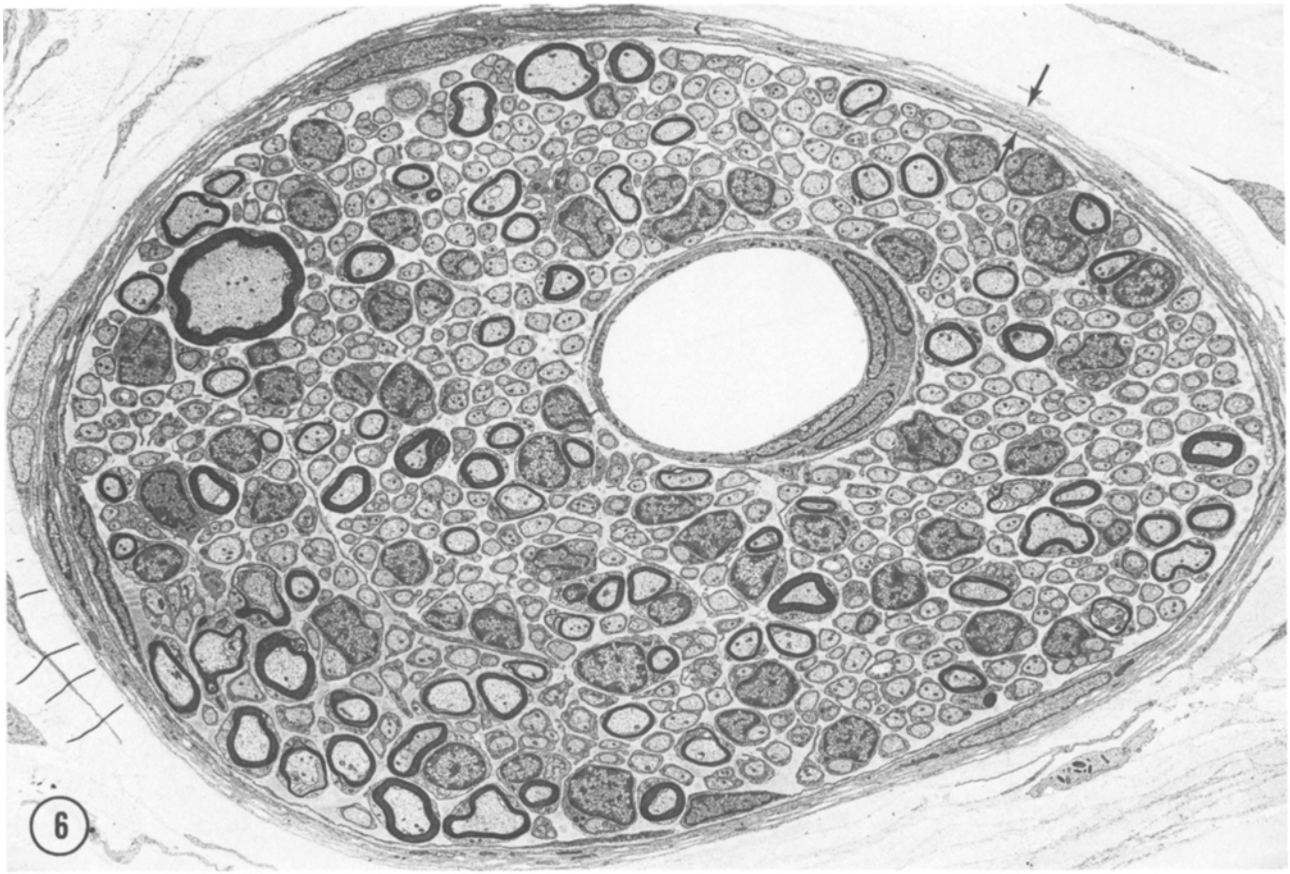
Fig. 6. Cross-section of a left sinus nerve at a level 0.5 mm from nerve IX. Note the single blood vessel, uniform dispersal of myelinated and unmyelinated axons, and envelopment of perineurium (arrows). × 2100.

Fig. 7. Unmyelinated axons and a myelinated axon in the nerve illustrated in Fig. 6 are shown here at higher magnification. Collagenous fibres occupy much of the space between axons. A portion of an endoneurial cell (E), which lacks a basal lamina, can be distinguished from processes of Schwann cells, which have a distinct basal lamina (arrows). × 26 300.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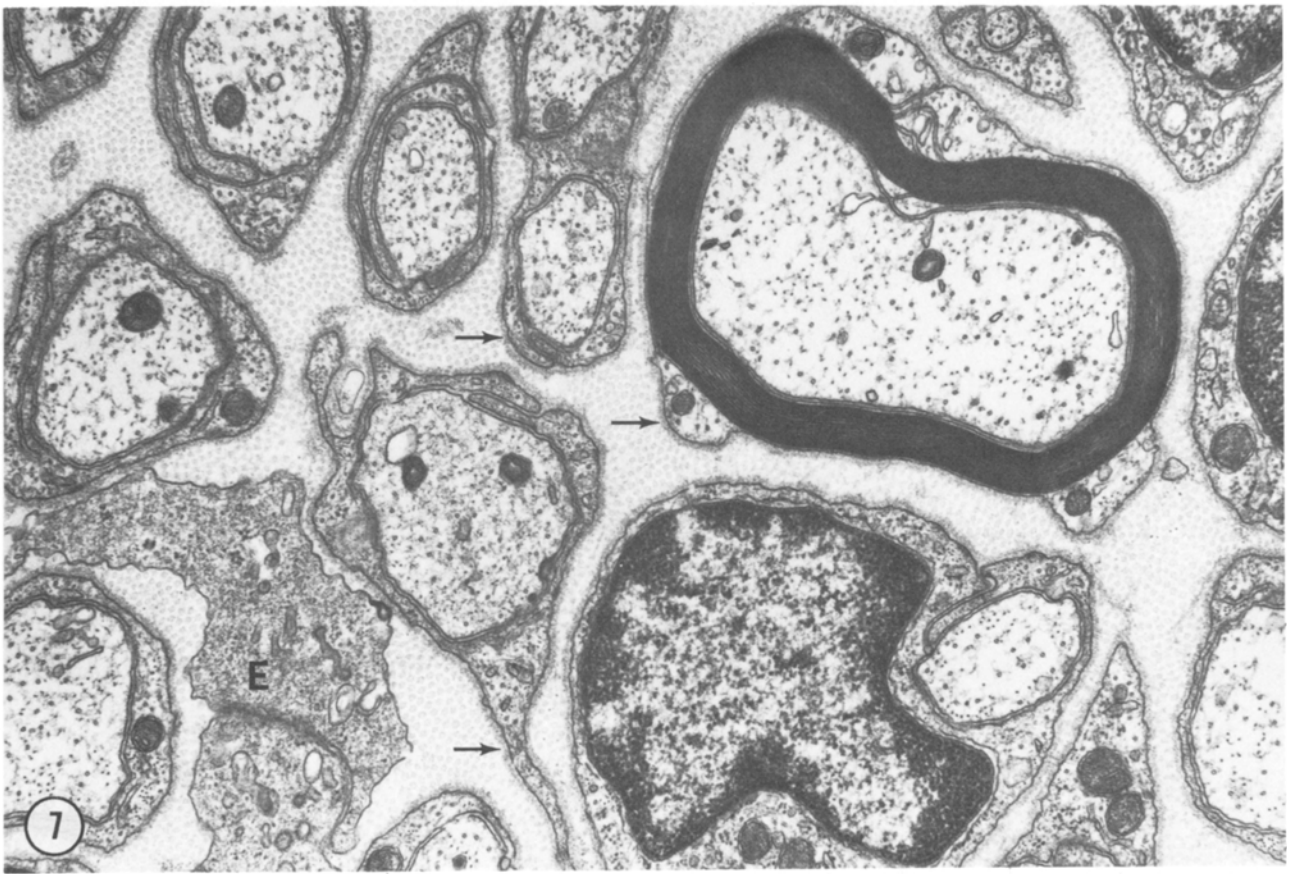
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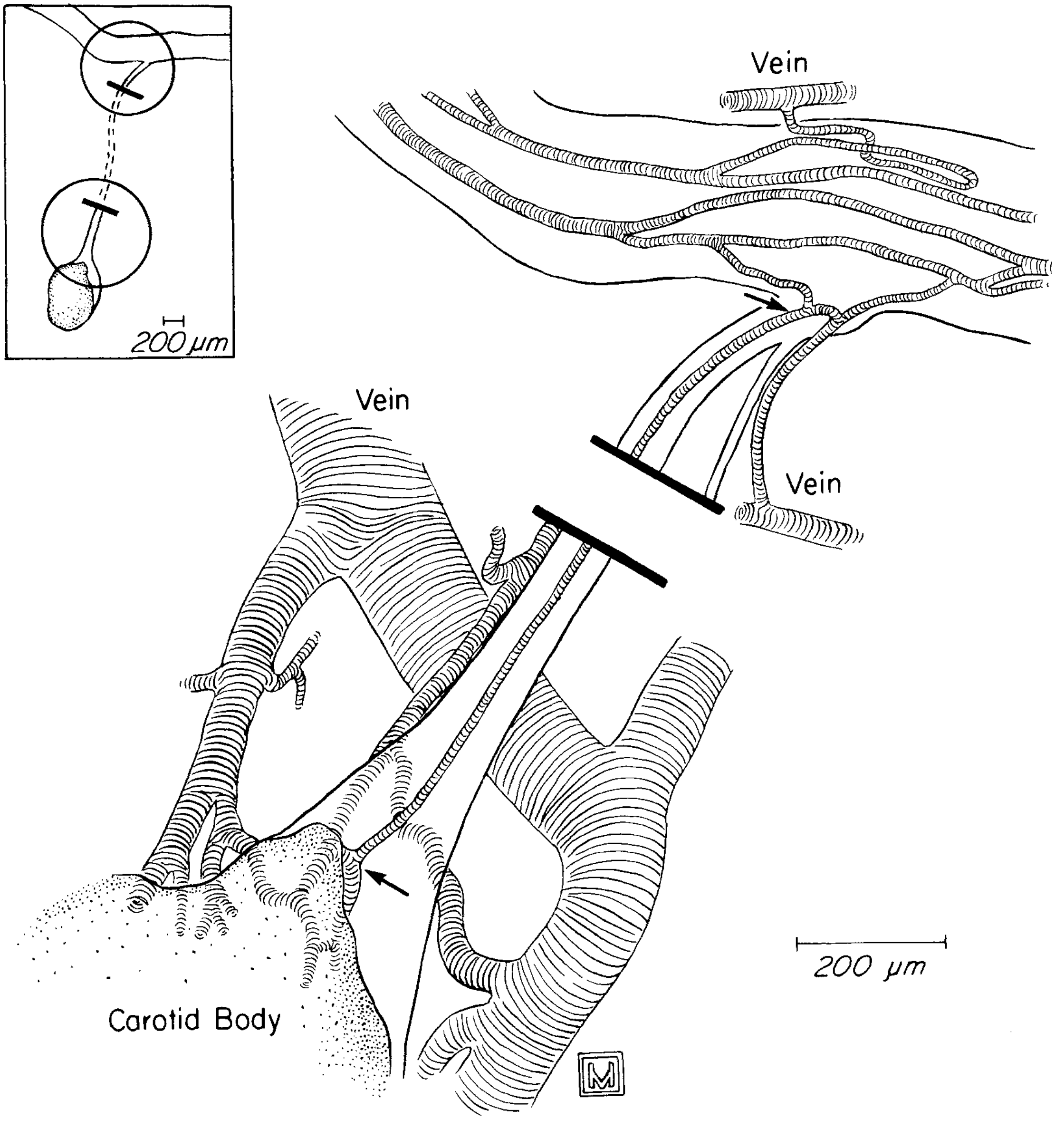

Fig. 8. A camera lucida drawing of a whole mount showing the ventrolateral aspect of blood vessels (contoured) in the region of a left sinus nerve. Arrows mark the apparent origin of the sinus nerve vessel from vessels in the glossopharyngeal nerve (upper right) and its termination in a venule at the surface of the carotid body (lower left). The sinus nerve vessel was unbranched throughout its length. The inset shows the two regions (circles) illustrated in the main drawing. Approximate magnification of main drawing × 120.

distal portion of the vessel had a layer of smooth muscle and resembled an arteriole (Figs. 12, 13), but the proximal portion had no smooth muscle and appeared to be a capillary or venule.

In each of the 20 cases examined, one or two branches of a vessel in nerve IX extended into the proximal portion of the sinus nerve, joined the sinus nerve vessel, and at that point left the nerve and joined a vein nearby (Fig. 8). When two vessels from nerve IX entered the sinus nerve (3 cases), they joined with one another or with the sinus nerve vessel (Fig. 8), but otherwise the pattern was identical to that found in the other nerves. The level at which the sinus nerve vessel arose and the parent vessel left was 350 ± 75 μm from nerve IX (range = 0–800 μm, N = 14).

Vessels in nerve IX at the level of the sinus nerve were in continuity with the vasculature of the petrosal ganglion. The ganglion received most of its blood supply from branches of the occipital artery. Although no arterioles entered the proximal portion of nerve IX from outside its perineurial sheath, I did not determine whether arterioles that enter the distal part of nerve IX contribute to the blood supply of the proximal portion.

Vessel dimensions and structure. Blood vessels in sinus nerves averaged 12.4 ± 1.2 μm (N = 19) in luminal diameter at a level 0.5 mm from nerve IX. However, the vessels had a bimodal size distribution: approximately 21% had a diameter of less than 6 μm, 5% were in the range 6–12 μm, and the remaining 74% were greater than 12 μm (mean diameter of largest vessels = 14.9 μm).

The wall of the smaller vessels consisted of endothelium, basal lamina and pericytes (Fig. 6). Half (7 of 14) of the larger vessels (37% of all vessels) had one layer of smooth muscle cells in their wall instead of pericytes (Figs. 12, 13). Autonomic nerve endings filled with synaptic vesicles were located next to the smooth muscle in four of the seven vessels with smooth muscle (example in Fig. 13).

Connective tissue sheaths

The *endoneurium* consisted mainly of longitudinally oriented collagenous fibres that occupied much of the space between the axons (Figs. 7, 9, 10). Attenuated connective tissue cells that lacked a basal lamina lined the inner aspect of the perineurium, formed a thin, incomplete sheath around the blood vessel, and were scattered among axons in the interior of the nerve (Fig. 9). Such cells were only about 5% as numerous as Schwann cells at a level 0.5 mm from nerve IX. In each nerve cross-section there were an average of 2.2 ± 0.5 endoneurial cell nuclei (0.071 cells/100 μm^2 of nerve) and 47 ± 5 Schwann cell nuclei (1.7 cells/100 μm^2 of nerve, N = 10).

All sinus nerves were surrounded by three or four thin, closely apposed layers of cells that constituted the *perineurium* (Figs. 6, 9). The plasma membrane of attenuated extensions of these cells had numerous caveoli. The cells were covered by a basal lamina and were interspersed by collagenous fibres (Fig. 10). Adjacent cells were joined by gap junctions (Fig. 11) and tight junctions. The perineurium enveloped the blood vessel in distal portions of the nerve (Figs. 12, 13), but not proximally (Figs. 6, 9). Perivascular perineurium invariably was present in the region where the blood vessel emerged from the sinus nerve. In the distal portion of the nerve near the carotid body, perineurial cells not only were present at the perimeter but also extended into the interior of the nerve (Fig. 13). In doing so, the perineurial cells compartmentalized groups of axons that formed the terminal branches of the nerve more distally (Fig. 14).

Cells of the *epineurium* were dispersed and blended with connective tissue surrounding the sinus nerve (Fig. 6). As has been observed in somatic nerves (Thomas, 1963), collagenous fibres outside the perineurium of the sinus nerve had a cross-sectional diameter twice as large (80 ± 1.7 nm, $N = 50$) as that of fibres within the perineurial and endoneurial compartments (40 ± 0.5 nm, $N = 50$) (Fig. 10).

Ganglion cells

Ganglion cells invariably were present in nerve IX near the origin of the sinus nerve (Figs. 15, 16) and one or two ganglion cells typically were located along the length of the sinus nerve (Fig. 17). All five ganglion cells examined by electron microscopy were postsynaptic to vesicle-containing nerve terminals (example in Fig. 18). At the surface of the carotid body, ten or more ganglion cells were associated with major branches of the sinus nerve (Fig. 1C).

The proximity of ganglion cells to various nerves that end in the carotid body was

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Fig. 9. Cross-section of a sinus nerve showing the paucity of endoneurial connective tissue cells (arrows), even near the blood vessel (upper right), at a level 0.5 mm from nerve IX (compare with Figs. 12, 13). The overlap of sizes of unmyelinated and myelinated axons is evident also. × 4500.

Fig. 10. Layers of sinus nerve perineurium (between arrows), each of which is covered by basal lamina. An endoneurial cell (E) on the inner surface of the perineurium has no basal lamina. Note that transverse sections of collagenous fibres (unstained circles) within the perineurium and endoneurium (right) are half the size of those in the epineurium (left). × 40 000.

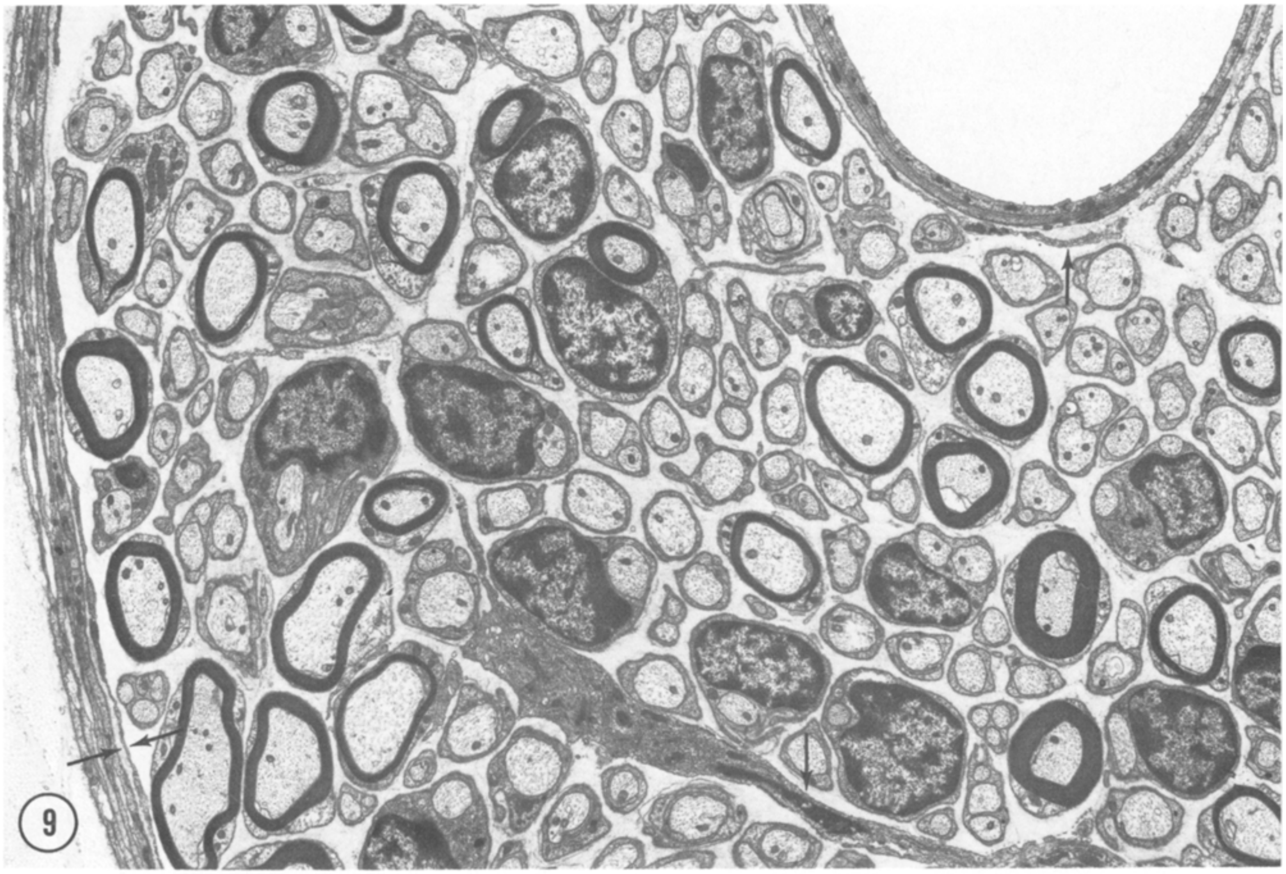
Fig. 11. A gap junction (arrows) between two cells of the sinus nerve perineurium. × 140 000.

Figs. 12–14. Cross-sections of a left sinus nerve at levels 1.0 mm (Fig. 12) and 1.3 mm (Fig. 13) from nerve IX. The morphology at the 1.0 mm level resembles that at more proximal levels (compare with Fig. 6) except for the envelopment of the blood vessel by perineurium (small arrows). However, at the 1.3 mm level the perineurium (small arrows) has begun to segregate groups of axons into fascicles. The total length of this sinus nerve was 2.0 mm. The large arrow in Fig. 13 marks unmyelinated axons and vesicle-containing axonal varicosities that innervate the blood vessel. × 2000. Fig. 14 shows at higher magnification the compartmentalization of axons at the 1.3 mm level. × 4000.

Figs. 15, 16. Two of a series of longitudinal sections through nerve IX showing the origin of the sinus nerve (large arrows). A vessel (1) in nerve IX gives rise to the sinus nerve vessel (2) and also is connected to a venule (3) outside the nerve. Two ganglion cells (small arrows) and a paraganglion (P) are present in this portion of nerve IX. Note that many myelinated axons in nerve IX are larger than those in the sinus nerve. Toluidine blue-stained 0.5 μm section. × 650.

Fig. 17. An autonomic ganglion cell (C) located in the endoneurium of a sinus nerve. × 2400.

Fig. 18. A synaptic nerve terminal (arrow) indenting the surface of a ganglion cell (C) in nerve IX near the origin of the sinus nerve. × 40 000.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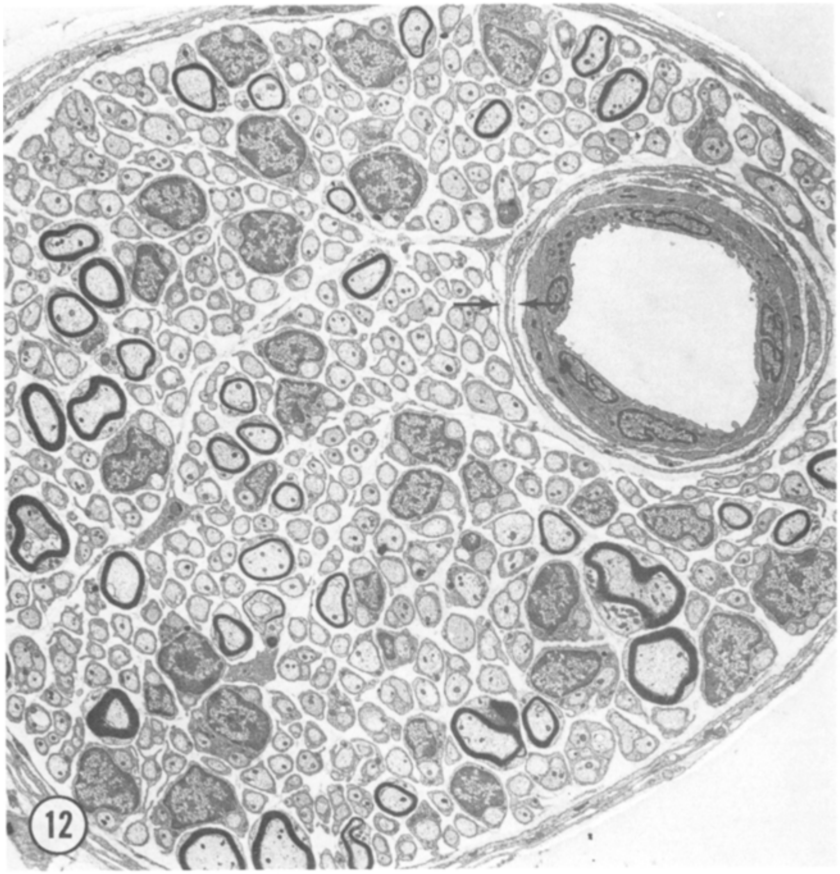
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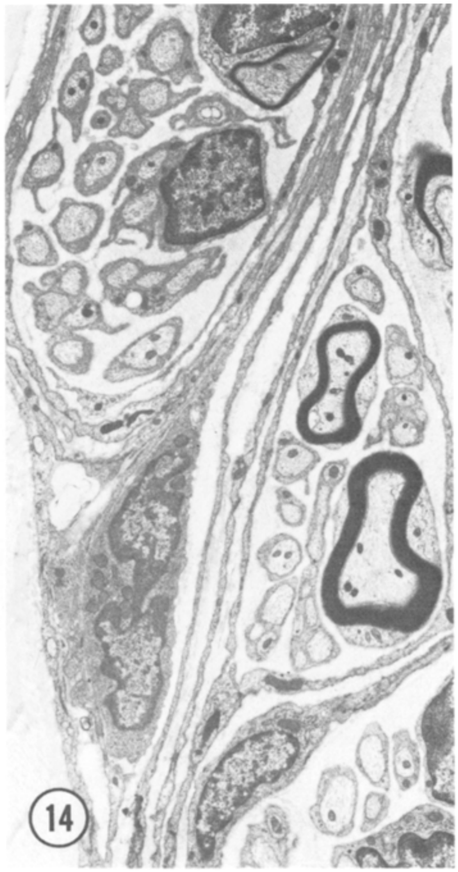
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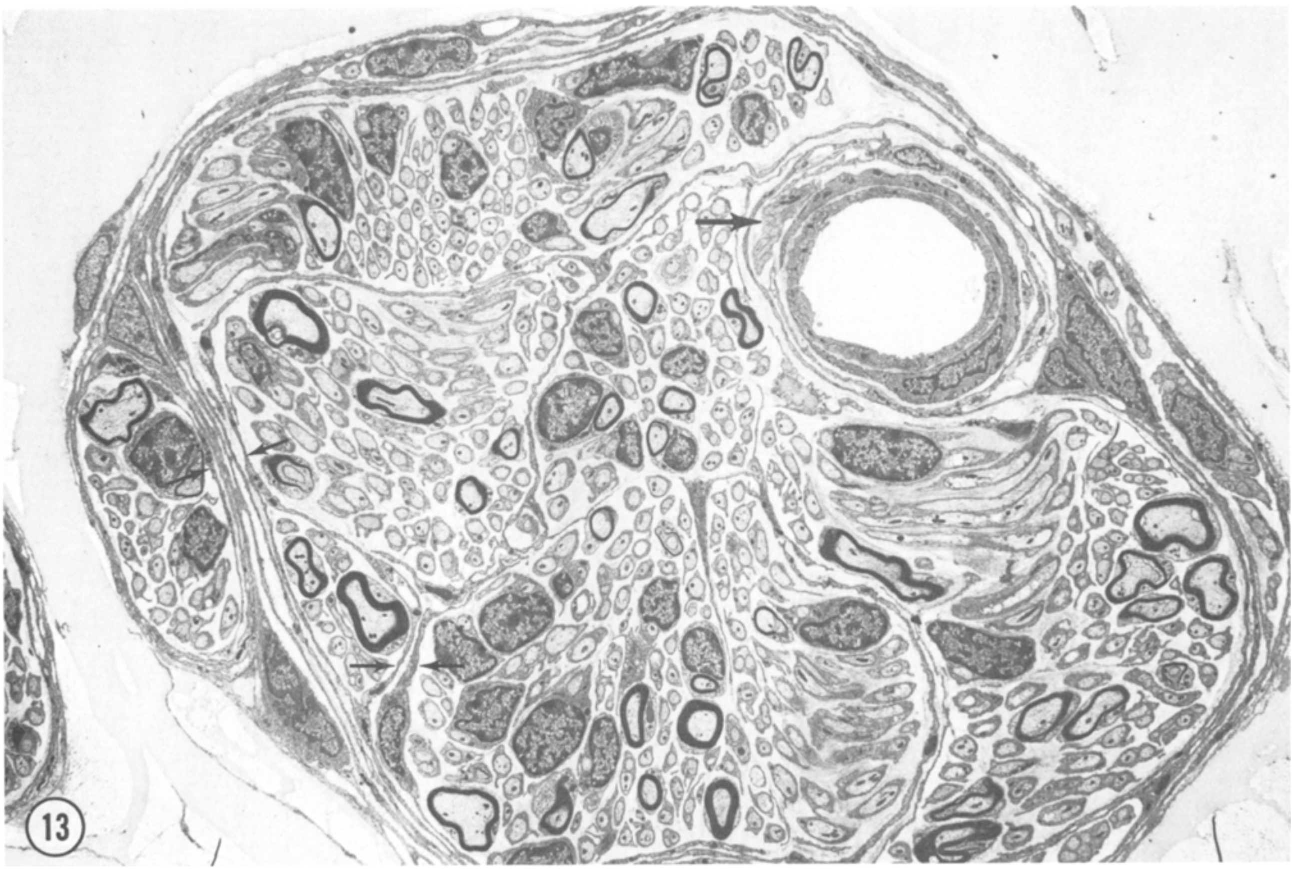
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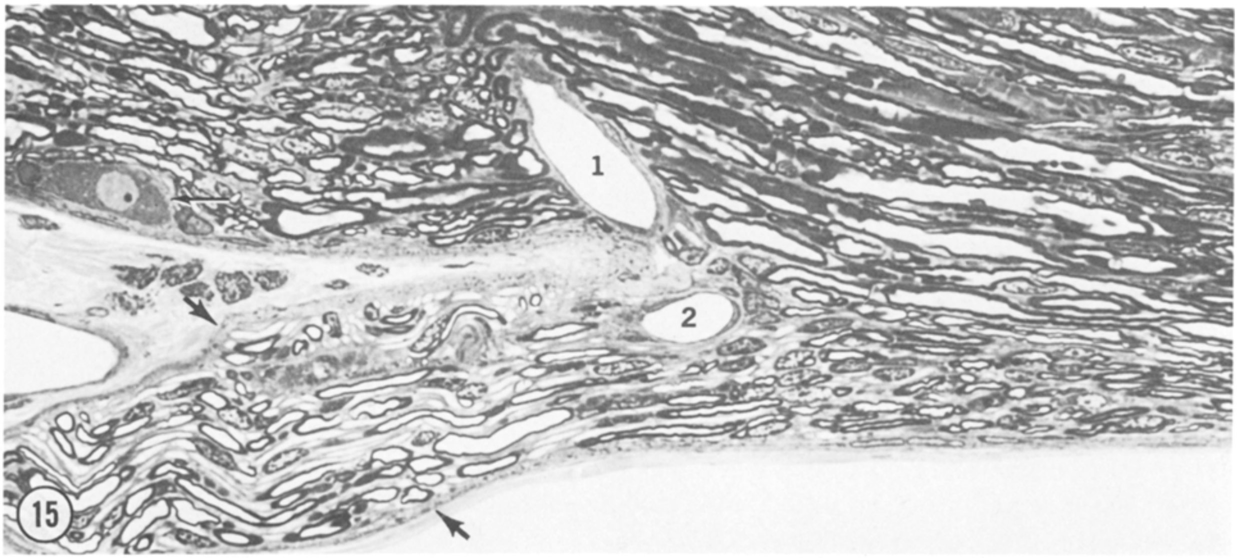
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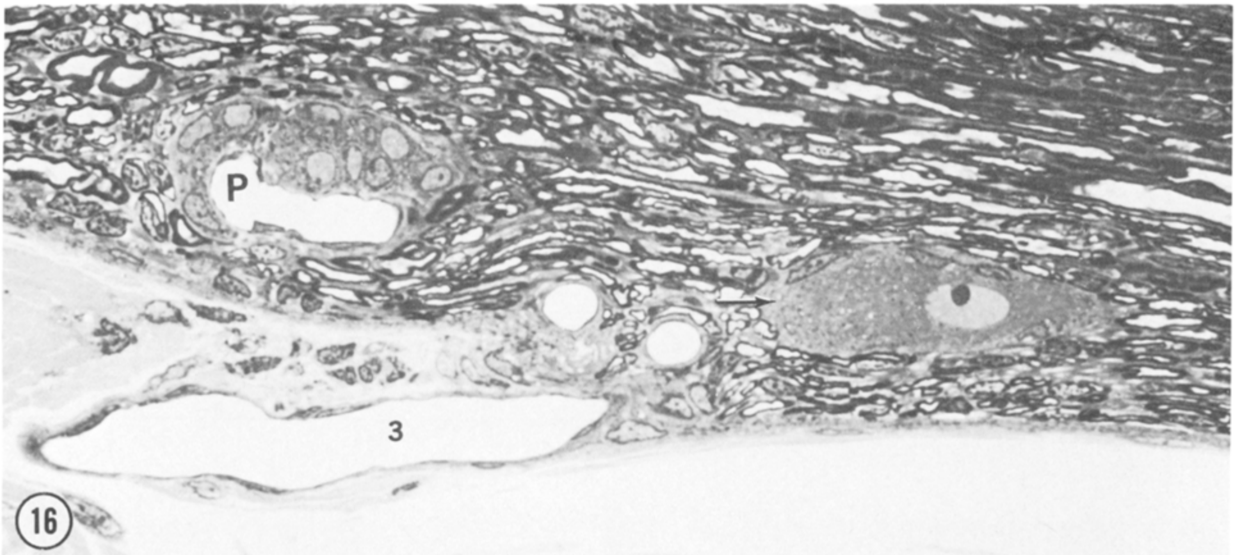
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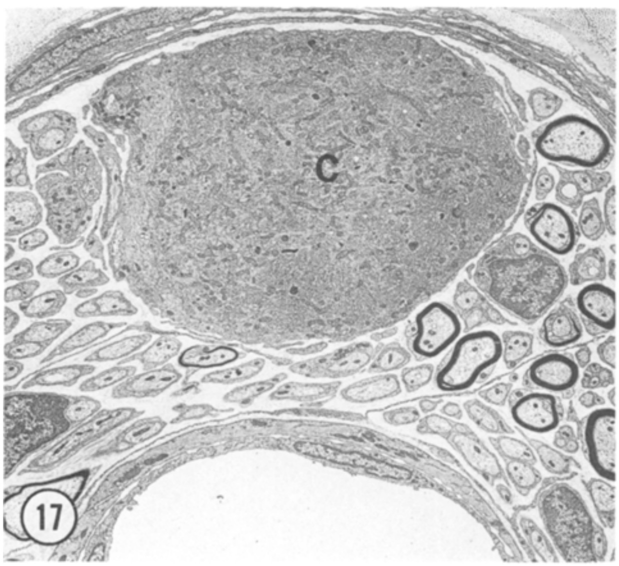
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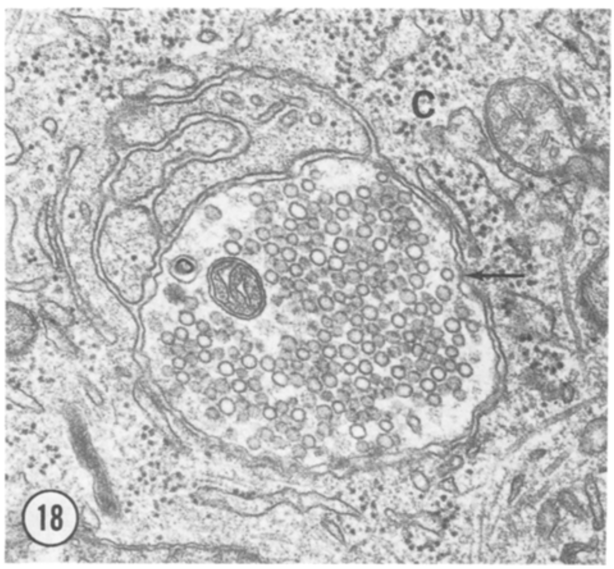
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particularly well illustrated in the case shown in Figs. 1C–E. Of the 42 ganglion cells located in or near this carotid body, 6 were associated with a branch of the vagus nerve, 16 were located in branches of the sinus nerve, and 20 were distributed among branches of the ganglioglomerular nerve. All ganglion cells were at the periphery of the carotid body near the point of entry of the nerve with which they were associated. Consequently ganglion cells associated with the sinus nerve (Fig. 1C) tended to be located ventrolaterally, whereas those associated with sympathetic nerves (Figs. 1D, E, 5) had a dorsomedial position.

Paraganglia

Paraganglia were present in nerve IX near the origin of the sinus nerve in 2 of 20 cases (example in Fig. 16) and were located within the sinus nerve itself in 3 of 20 cases (Figs. 19, 20). The paraganglia measured about 50 × 50 × 100 μm and were readily identified in whole mounts of the nerves because they had numerous blood vessels and they displaced the axons. The tiny organs were located within the perineurium of the sinus nerve. Most portions of the paraganglia were encapsulated by their own thin sheath of perineurium (Fig. 22). Where the encapsulation was lacking, the paraganglion cells were adjacent to sinus nerve axons (Fig. 20).

By their tortuosity (Fig. 19), thin fenestrated endothelium and envelopment of pericytes (Fig. 23), blood vessels of paraganglia resembled vessels of the carotid body (Figs. 3, 4) but were conspicuously different from the main vessel of the sinus nerve (Figs. 6, 12, 13, 19). Paraganglion cells, like carotid body glomus cells, had abundant large dense-cored vesicles (Fig. 21). Nerve endings on paraganglion cells (Figs. 24, 25) were similar in ultrastructure to sensory nerve endings of the carotid body (McDonald & Mitchell, 1975). Some profiles of nerve endings were presynaptic to paraganglion cells (Fig. 24), whereas others were postsynaptic to the cells (Fig. 25).

Fig. 19. A paraganglion (P) within a sinus nerve. The paraganglion cells are clustered around a tortuous thin-walled blood vessel. V, main vessel of the sinus nerve. Toluidine blue-stained 0.5 μm section. × 650.

Fig. 20. In this paraganglion, some of the principal cells (G) are adjacent to unmyelinated axons (arrows) of the sinus nerve. × 4600.

Fig. 21. A cluster of paraganglion cells enveloped by processes of a sheath cell (SC). The paraganglion cells contain dense-cored vesicles that are uniformly distributed and resemble vesicles of carotid body glomus cells. Paraganglion of nerve IX. × 7200.

Fig. 22. A portion of a paraganglion cell (G) separated from an axon (A) in nerve IX by a thin sheath of perineurium (arrows). × 30 000.

Fig. 23. A paraganglion cell (G) next to a blood vessel (V) with a fenestrated endothelium. Sinus nerve paraganglion. PC, pericyte. × 30 000.

Figs. 24, 25. Nerve endings (N) next to cells (G) of a nerve IX paraganglion. The nerve ending in Fig. 24 is presynaptic (arrow) to the paraganglion cell, whereas that in Fig. 25 is postsynaptic (arrow) to such a cell. × 45 000.


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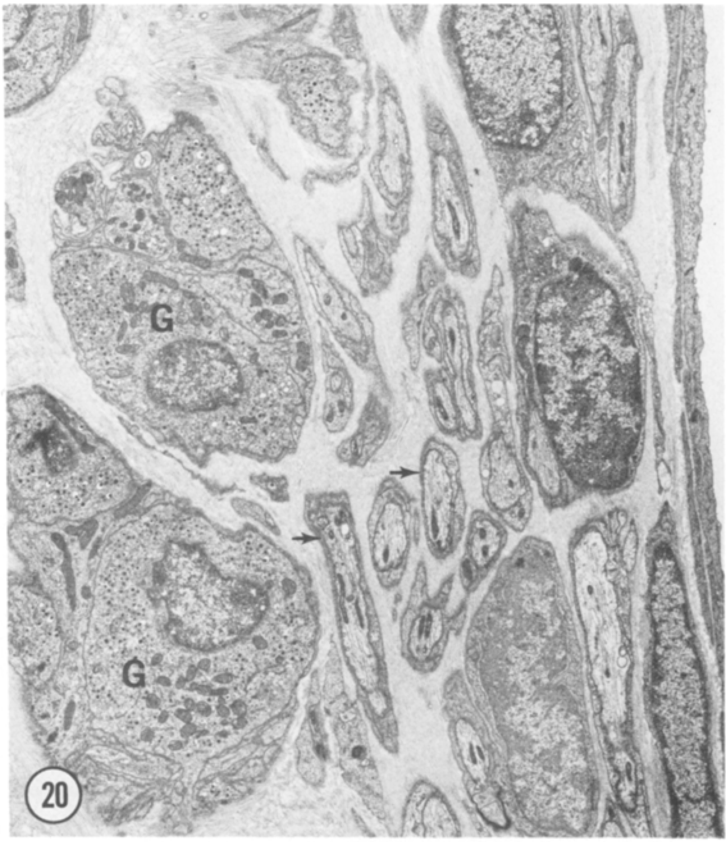
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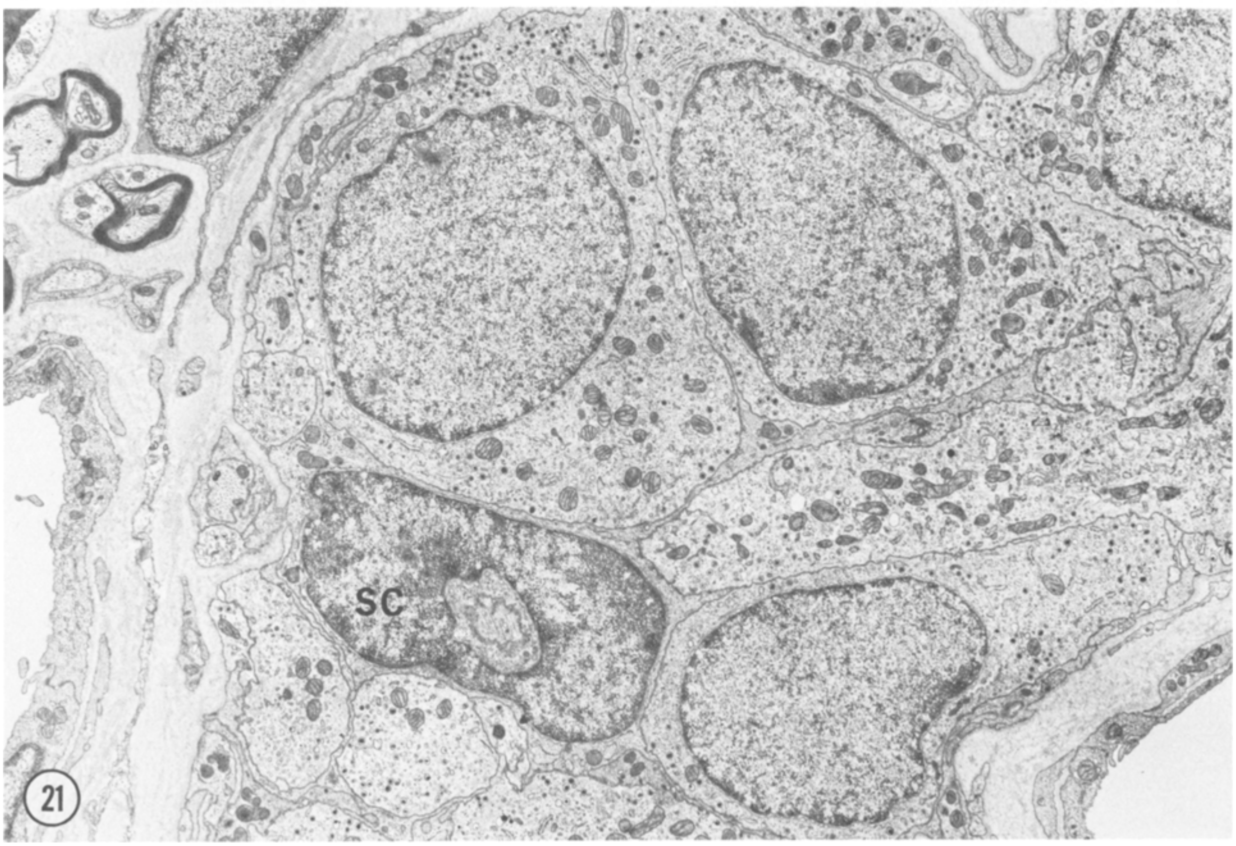
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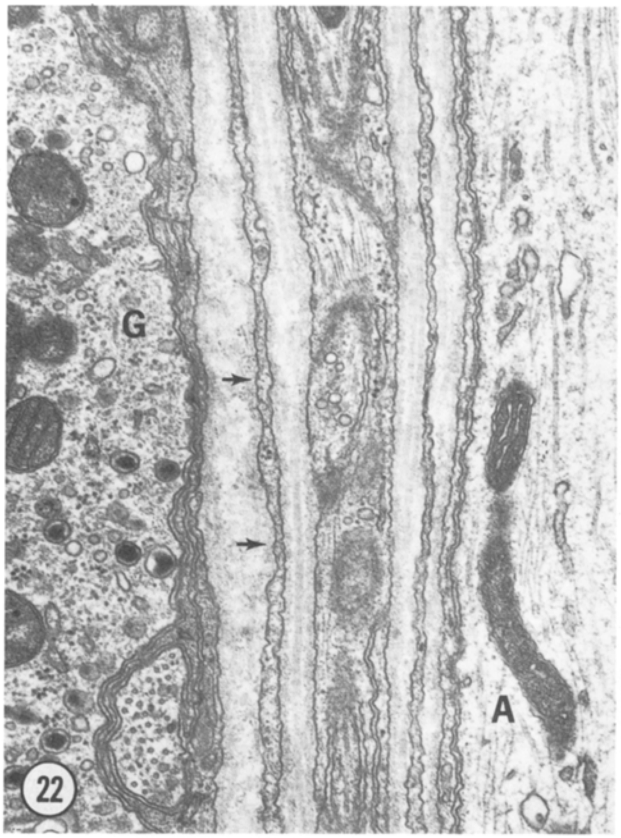
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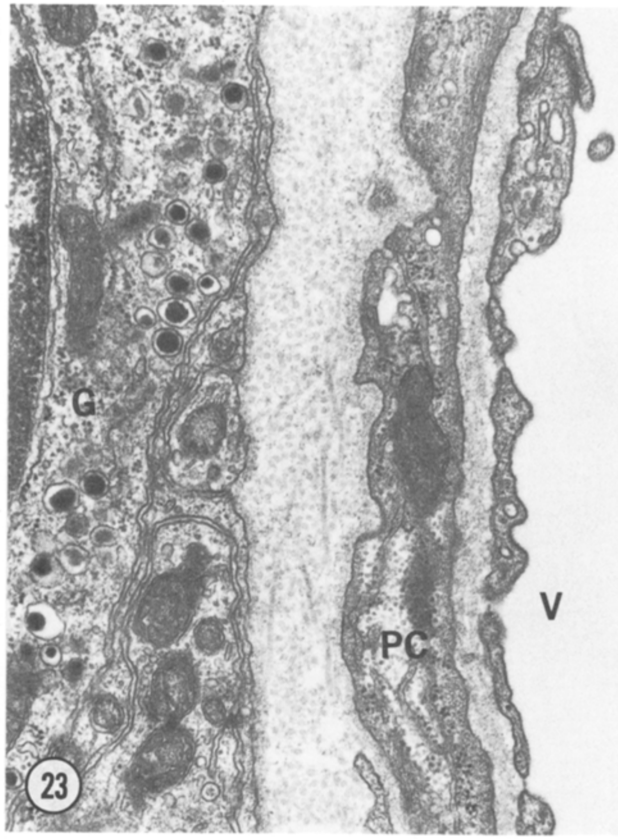
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Discussion

The present study revealed several distinctive features of the carotid sinus nerve in the rat. 1. Chemoreceptive axons in the sinus nerve enter the *carotid body* directly, whereas baroreceptive axons in the nerve reach the *carotid sinus* either by way of anastomoses with sympathetic nerves or by traversing the carotid body. 2. Anastomoses with sympathetic nerves interconnect the sinus nerve with the superior cervical ganglion. 3. Autonomic ganglion cells are located at the origin and along the length of the sinus nerve but are most numerous in terminal branches of the nerve on the surface of the carotid body. 4. In a small proportion of rats, paraganglia are located within the sinus nerve. These paraganglia are innervated by nerves that resemble the sensory nerves of the carotid body. 5. The blood supply of the sinus nerve consists of only one vessel, which usually arises from vessels in nerve IX and ends in a venule at the surface of the carotid body.

INNERVATION OF THE CAROTID BODY AND CAROTID SINUS

The carotid sinus nerve usually is depicted as dividing distally, with one branch innervating the carotid body and the other branch innervating the carotid sinus (see Adams, 1958). Such branches to the carotid sinus have been described in the cat, dog, guinea pig, rabbit and rat (Eyzaguirre & Uchizono, 1961; Rees, 1967a; Sapru & Krieger, 1977; Yates & Chen, 1980). In humans, the bifurcation of the sinus nerve reportedly makes it possible to remove both carotid bodies surgically without disrupting carotid baroreceptor function (Winter, 1972). However, in the present study of the rat no such direct projection from the sinus nerve to the carotid sinus was found.

Sinus nerve axons to the carotid body

At the rostral pole of the carotid body, the sinus nerve divides into multiple fascicles of axons. In the rat nearly all sinus nerve axons, apart from those joining sympathetic nerves (see below), enter the carotid body. De Castro (1926, p. 402) estimated that two-thirds of these axons end on glomus cells. Although the validity of this estimate is difficult to assess, it is clear that nearly all of these axons innervating glomus cells are sensory (de Castro, 1928; also see review by McDonald, 1981). After entering the carotid body, some axons of the sinus nerve end on ganglion cells or innervate blood vessels (de Castro, 1926; McDonald & Mitchell, 1975, 1981). Some axons continue on through the carotid body to end in the wall of the carotid sinus, whereas others may go to the superior cervical ganglion.

The predominance of the carotid body among the sinus nerve's target organs is exemplified by the vasculature. The route of the nerve's single blood vessel follows the path of most of the axons to the rostral pole of the carotid body.

Sinus nerve axons to the carotid sinus

The sinus nerve supplies more than 90% of the sensory innervation of the carotid sinus (de Castro, 1951; Rees, 1967a). Other sensory axons reach the carotid sinus through tiny branches of the vagus nerve (de Castro, 1926, 1928, 1951).

In the rat, small groups of sensory axons leave the sinus nerve in anastomoses that link the sinus nerve with a sympathetic nerve. Where the sympathetic nerve encircles the carotid sinus, sensory axons emerge from the nerve and ramify in the adventitia of the sinus.

In the cat some branches of the ganglioglomerular nerve project to the carotid sinus (Eyzaguirre & Uchizono, 1961). These branches in the cat and certain other species are the source of noradrenergic nerves that innervate the carotid sinus (Rees, 1967b; Reis & Fuxe, 1968) and influence baroreceptor sensitivity (Kezdi, 1954; Koizumi & Sato, 1969; Sampson & Mills, 1970; Wurster & Trobiani, 1973; Bolter & Ledsome, 1980). The branches also provide a route for afferent axons that project to the superior cervical ganglion from the carotid sinus (Tuttle & McCleary, 1982). The present observations of a sympathetic nerve bundle that encircles the carotid sinus of the rat are consistent with the findings of de Castro (1926, p. 406) and Yates & Chen (1980). Although catecholamine-containing nerve endings are sparse in the carotid sinus of the rat (Reis & Fuxe, 1968; Stanton & Hinrichsen, 1980), some afferent axons from the carotid sinus may reach the superior cervical ganglion through this nerve bundle.

The other route taken by sinus nerve axons to the carotid sinus adventitia is through the carotid body. This pathway has been observed previously (de Castro, 1926; Rees, 1967a) and is one manifestation of the intimate association of the carotid body and carotid sinus (discussed by Boyd, 1937, p. 24; Adams, 1958, p. 45). Another manifestation is the interconnection of the blood supplies of the two organs (McDonald & Larue, 1983).

SINUS NERVE–SYMPATHETIC NERVE INTERCONNECTIONS

Sinus nerve axons to the superior cervical ganglion

A close association of the sinus nerve with branches of the sympathetic nerve plexus near the carotid body is present in most species (Adams, 1958) and is evident early in embryonic development (Smith, 1924; Boyd, 1937). De Castro (1926, p. 399) observed in the mouse, rat, dog, cat and human that some axons of the carotid sinus nerve join the external carotid nerves from the superior cervical ganglion. This projection of the sinus nerve initially was interpreted by de Castro as consisting of preganglionic axons. However, this conclusion was reached before he discovered the large proportion of sensory axons in the sinus nerve (de Castro, 1928). More recent reports of SIF cells of the superior cervical ganglion that have nerve endings resembling sensory nerves of the carotid body (Matthews, 1976; Kondo, 1977; Grillo, 1978) favour the possibility that some sensory axons of the sinus nerve end in the sympathetic ganglion.

Sympathetic axons in the sinus nerve

De Castro (1926) reported that postganglionic sympathetic axons enter the sinus nerve. Consistent with this observation, Mishra & Hess (1978), using axonal degeneration techniques, found that some of the smallest unmyelinated axons in the sinus nerve of the rat come from the superior cervical ganglion. In the cat carotid sinus nerve, sympathetic axons run in both directions. One group of sympathetic axons enters the sinus nerve from the ganglioglomerular nerve (Eyzaguirre & Uchizono, 1961) and accompanies the sensory axons rostrally toward nerve IX (Eyzaguirre & Levin, 1961). A second group of sympathetic axons from the superior cervical ganglion enters nerve IX and then projects toward the carotid body in the sinus nerve (Biscoe & Sampson, 1968).

SINUS NERVE–PHARYNGEAL NERVE INTERCONNECTIONS

In the rat a branch of the pharyngeal nerve is associated frequently with the sinus nerve. In some cases axons of the two nerves are intermixed (de Castro, 1926, p. 405). Such a vagal input to the sinus nerve, though small, is consistent with observations that some axons in the sinus nerve remain intact when nerve IX is cut and the superior cervical ganglion is removed (Mishra & Hess, 1978). De Castro (1926) found that axons in this branch from the pharyngeal nerve were destined for such structures as the pharynx, superior cervical ganglion and carotid sinus.

GANGLION CELLS

De Castro's (1926, p. 382) extensive analysis of the distribution and innervation of ganglion cells in the vicinity of the carotid body revealed that the neurons are located at the periphery of the organ and within nerve trunks that innervate it. His axonal degeneration studies done on cats revealed that ganglion cells located within the sinus nerve and along its branches at the surface of the carotid body receive a preganglionic innervation from nerve IX. Ganglion cells associated with sympathetic nerves, however, are innervated by preganglionic sympathetic nerves. Results of experiments on the rat carotid body (McDonald & Mitchell, 1975) are in general agreement with these findings of de Castro.

PARAGANGLIA

The carotid body is the largest but not the only paraganglion in the region of the carotid bifurcation (de Castro 1926, 1962). The number and distribution of paraganglia vary among different species (Clarke & Daly, 1981) and among different individuals of the same species (McDonald & Blewett, 1981). In the rat, paraganglia are located in nerve IX and in nerves from the superior cervical ganglion (McDonald & Blewett, 1981). De Castro (1926) showed that many paraganglia in this region, even those in sympathetic nerves, are innervated by axons of nerve IX. The ultrastructure of axons in paraganglia located within nerve IX and within the sinus nerve is similar to that of sensory axons of the carotid body (McDonald & Mitchell, 1975) and other paraganglia in this region (McDonald & Blewett, 1981).

The results of the present study emphasize that the carotid sinus nerve is a complex thoroughfare for axons of numerous functions and sources: 1. sensory axons mediating chemoreception in the carotid body; 2. sensory axons mediating baroreception in the carotid sinus; 3. preganglionic parasympathetic axons from the brain stem; 4. postganglionic parasympathetic axons from ganglion cells in the glossopharyngeal and sinus nerves; 5. axons of unknown types from the pharyngeal branch of the vagus nerve, and via connections with nerves from the superior cervical ganglion; 6. postganglionic sympathetic axons; and 7. possibly sympathetic afferent axons.

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