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Structure of rat aortic baroreceptors and their relationship to connective tissue

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Summary

The ultrastructure of fibres and sensory terminals of the aortic nerve innervating the aorta between the left common carotid and left subclavian arteries was investigated in the rat. This is the region from which most baroreceptor responses are recorded electrophysiologically. The fibres of the aortic nerve enter the adventitia and separate into bundles generally containing one myelinated fibre and four or five unmyelinated fibres of various sizes. The bundles pursue a roughly helical course through the adventitia; when they are close to the aortic media, the myelinated fibre loses its myelin sheath. A complex sensory terminal region is formed, as both the unmyelinated and 'premyelinated' axons become irregularly varicose. The concentration of mitochondria becomes very dense and cytoplasmic deposits of glycogen are observed. Both unmyelinated and premyelinated axons branch, and the unmyelinated axons wind irregularly around the premyelinated axon. The latter may have several loops and small holes. The terminal regions of both types of axon contain clusters of clear 40 nm vesicles. Part of the surface of each terminal region is ensheathed by Schwann cells, but the rest of the axolemma is directly exposed to extracellular connective tissue. There are often several layers of basal lamina around the sensory terminals and parts of the axolemma and Schwann cell membranes are attached to it by fine fibrillar material. The basal laminae are also attached to fibroblasts, fibroblast-like perineurial cells and elastic laminae, and the whole cellular and extracellular system appears to be tightly bound together. No differences between baroreceptors of spontaneously hypertensive and normal rats were found.

Introduction

Although aortic baroreceptors have been studied by several investigators at the light microscopic level (Ábrahám, 1969; Aumonier, 1972), very little electron microscopy of these baroreceptors has been done. Yamauchi (1976) has briefly described the ultrastructure of rat and dog aortic baroreceptors, but a thorough study of their structure has not been reported. The present study includes observations of serial sections of the sensory terminal region of a bundle of presumptive baroreceptor axons in one rat as well as shorter series of sections of baroreceptor sensory terminals from other rats, including six-month-old spontaneously hypertensive rats

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(SHRs). The SHR is now being studied intensively as an animal model for essential hypertension. In rabbits with induced renal hypertension (Angell-James, 1973) and humans with hypertension (Ábrahám, 1967), degenerative changes have been observed by light microscopy in aortic baroreceptors. The research reported here was undertaken to provide a structural foundation for understanding how these baroreceptors are stimulated and how they are affected by hypertension.

Methods

The animals used were male, Wistar–Kyoto strain, normotensive rats (NTRs) and Okamoto–Aoki strain SHRs, 14–24 weeks old. They were anaesthetized with ether, then with sodium pentobarbital (Nembutal, 30–40 mg/kg) administered intraperitoneally. The aortic arch and nerve were dissected as described by Brown *et al.* (1976).

For whole mounts, the aortic arch and nerve were rinsed in 0.9% NaCl and placed in a small acrylic chamber containing 0.01% methylene blue in Krebs–Henseleit buffer (120 mM NaCl, 4.8 mM KCl, 1.2 mM $MgSO_4$, 1.1 mM $CaCl_2$, 1.2 mM KH_2PO_4, 25 mM $NaHCO_3$, and 5.5 mM dextrose). The staining solution was maintained at 37° C throughout the staining process. Due to the thickness of the connective tissue and fat deposits around the nerve fibres, it was necessary to dissect carefully away some of this material about every hour until the whole nerve plexus was stained. After several hours the preparation was rinsed in 0.9% saline and placed in a vial with cold saturated ammonium molybdate (Weddell and Zander, 1950). It was left overnight at 5° C, then rinsed in tap water for 30 min, dehydrated in cold absolute ethanol for two 10 min changes, placed in benzene for a few minutes, and immersed in Pro-Texx mounting medium (Scientific Products, McGraw Park, Illinois). The aortic arches from three animals of each strain were used for whole mounts.

For light and electron microscopy, aortic arches were fixed by immersion in 3% glutaraldehyde in 0.1 M piperazine-N, N′-bis(2-ethane sulphonic acid) (PIPES) buffer, pH 7.4 (Baur and Stacey, 1977). Specimens were left overnight in fixative at 5° C, then rinsed in PIPES buffer, postfixed in 1% OsO_4 in 0.1 M PIPES, dehydrated in ethanol series and embedded in Epon. Specimens were embedded so that the aortic nerve protruded and could be followed in thick sections (0.5–1.0 μm). When a favourable area for electron microscopy of sensory terminals was found, thin (silver) sections were cut. Serial sections were placed on slot grids coated with Formvar. Thick sections were stained with *p*-phenylenediamine and thin sections were stained with uranyl acetate and lead citrate.

Serial sections were photographed at two different magnifications, 3900 and 10 000 (the latter was sometimes necessary for location of boundaries between, for example, sensory terminals and Schwann cells). The higher magnification micrographs were used to outline sensory terminal profiles on the lower magnification prints. Tracings of these outlines were fastened together in groups of 15 sections. A composite tracing of each group was made, including connective tissue markers such as elastic laminae, Schwann cell nuclei and basal laminae. For the longest series of sections, a clay model was made by following the composite drawings, in order to represent the general structure of the sensory terminal region.

One part of this series was used to examine the detailed surface structure of the sensory terminals of one axon. Tracings of all sections in this partial series were glued to cardboard, cut out, stacked to correspond with connective tissue markers and glued together.

The sensory terminals arising from at least 18 fibre bundles from two NTRs and 13 bundles from two SHRs were examined.

Results

The left aortic depressor nerve in the rat has two main branches, dorsal and ventral (Fig. 1), each of which contains about 15—20 myelinated fibres and several times as many unmyelinated fibres. The ventral branch innervates the base of the left subclavian and left common carotid arteries as well as the rostral part of the ventral surface of the aorta, while the dorsal branch appears to spread over a large area of the dorsal surface of the aorta. The present study has been concentrated on the ventral branch of the nerve. On the ventral side of the aorta, stimulation of the region innervated by this branch is most likely to elicit baroreceptor responses in the aortic nerve (Saum, personal communication).

The ventral branch separates into progressively smaller bundles of fibres as it approaches and enters the outer layer (adventitia) of the aorta wall. Many, if not all of these bundles are associated with blood vessels. Finally most bundles contain only one or two myelinated and four or five unmyelinated fibres. Some myelinated fibres do not appear to be associated with unmyelinated fibres and some are joined by additional unmyelinated fibres which are assimilated into the bundle.

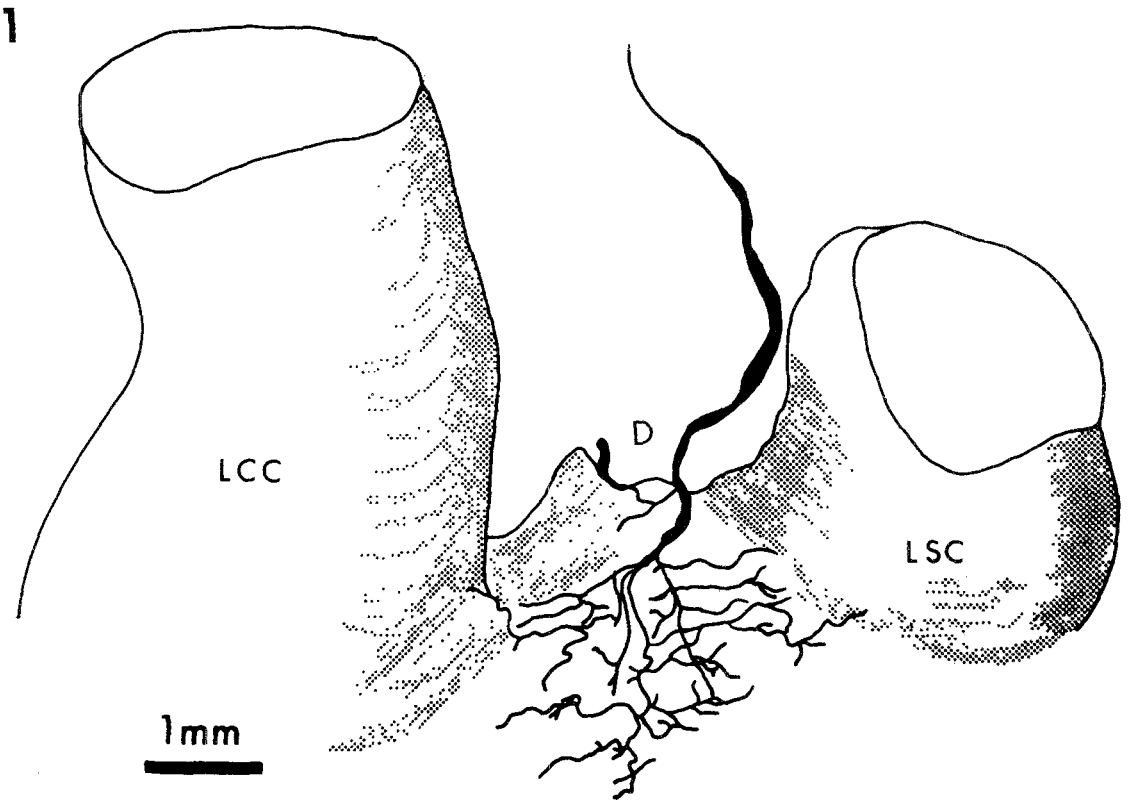


Fig. 1. Drawing of a methylene blue-stained NTR aortic nerve whole mount, as seen through the dissecting microscope. Part of the dorsal branch (D) is visible, along with the ventral branch. LCC, left common carotid artery; LSC, left subclavian artery. Drawing by Gary Matsuoka and Jo Long.

Each bundle is surrounded by a perineurium consisting of fibroblast-like processes separated by collagen (Fig. 2). Each myelinated fibre and group of unmyelinated fibres is surrounded by a Schwann cell and embedded in collagen. A basal lamina is associated with every cellular surface exposed to extracellular connective tissue. The unmyelinated fibres vary somewhat in size.

Distal to the formation of individual bundles, serial sections show that the myelinated fibres lose their myelin sheaths (but not at the same time if there are two myelinated fibres). Distal to this point they are called 'premyelinated' axons (Rees, 1967). At varying distances (usually tens of μm) from the point of myelin loss, the premyelinated axon gives way to premyelinated sensory terminal regions characterized by axonal swellings, fine processes and a generally irregular surface. These terminals branch and are sometimes connected by short (a few μm) axonal segments, usually where the neuron penetrates a fenestration in an elastic lamina. The unmyelinated axons also begin to branch and give way to sensory terminal regions at

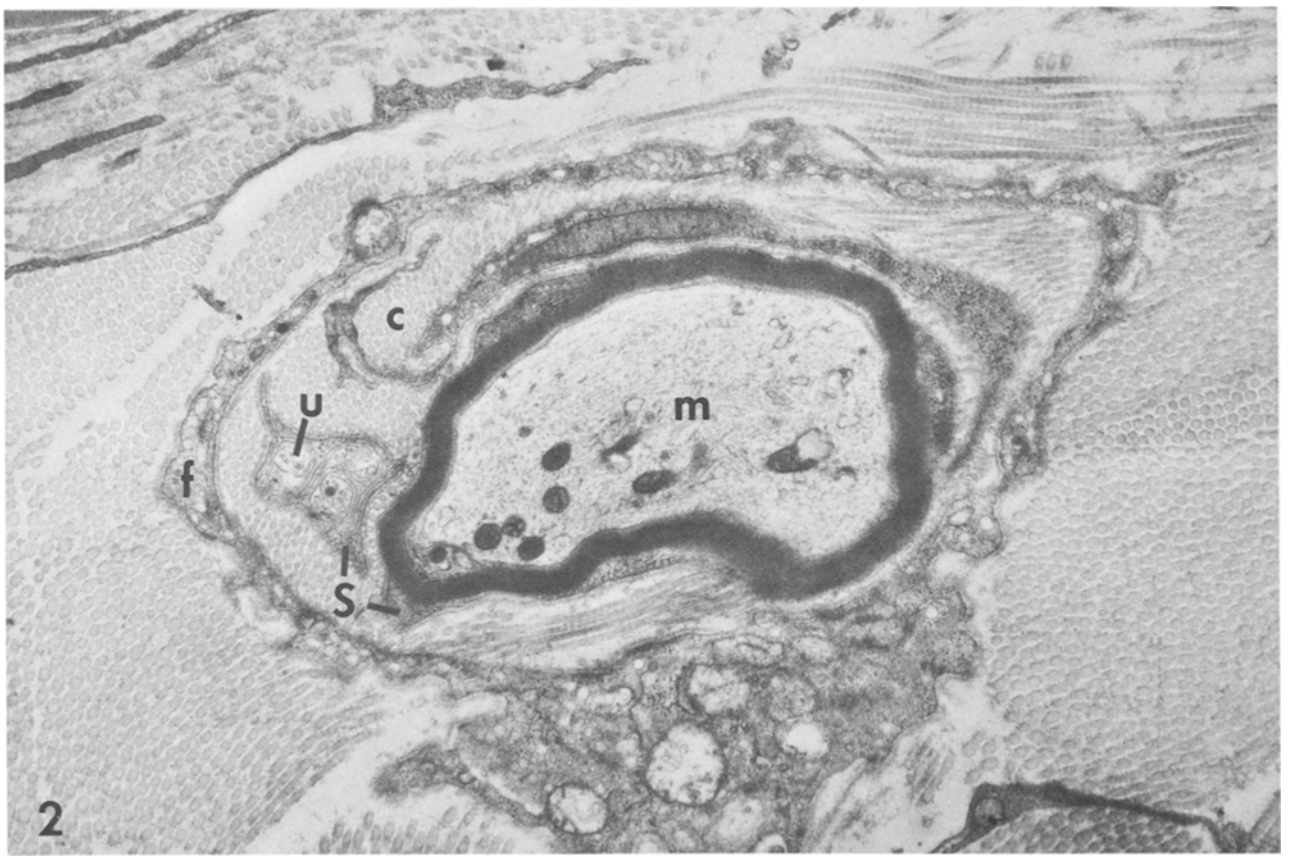


Fig. 2. A 'typical' fibre bundle in the outer adventitia from an NTR. It is bounded by fibroblast-like perineurial processes (f). A group of unmyelinated fibres (u) and a myelinated fibre (m) are sheathed in Schwann cells (S) and embedded in collagen (c).

frequent intervals, although the variation in diameter along the axons is much less than that along the premyelinated axon and the unmyelinated axons do not appear to have fine processes. The unmyelinated axons wind irregularly around the branches of the premyelinated axon. (The configuration of unmyelinated and premyelinated axons in bundles containing two premyelinated axons is unknown.)

Fig. 3 was drawn from a clay model of a long series of sections of the axons and

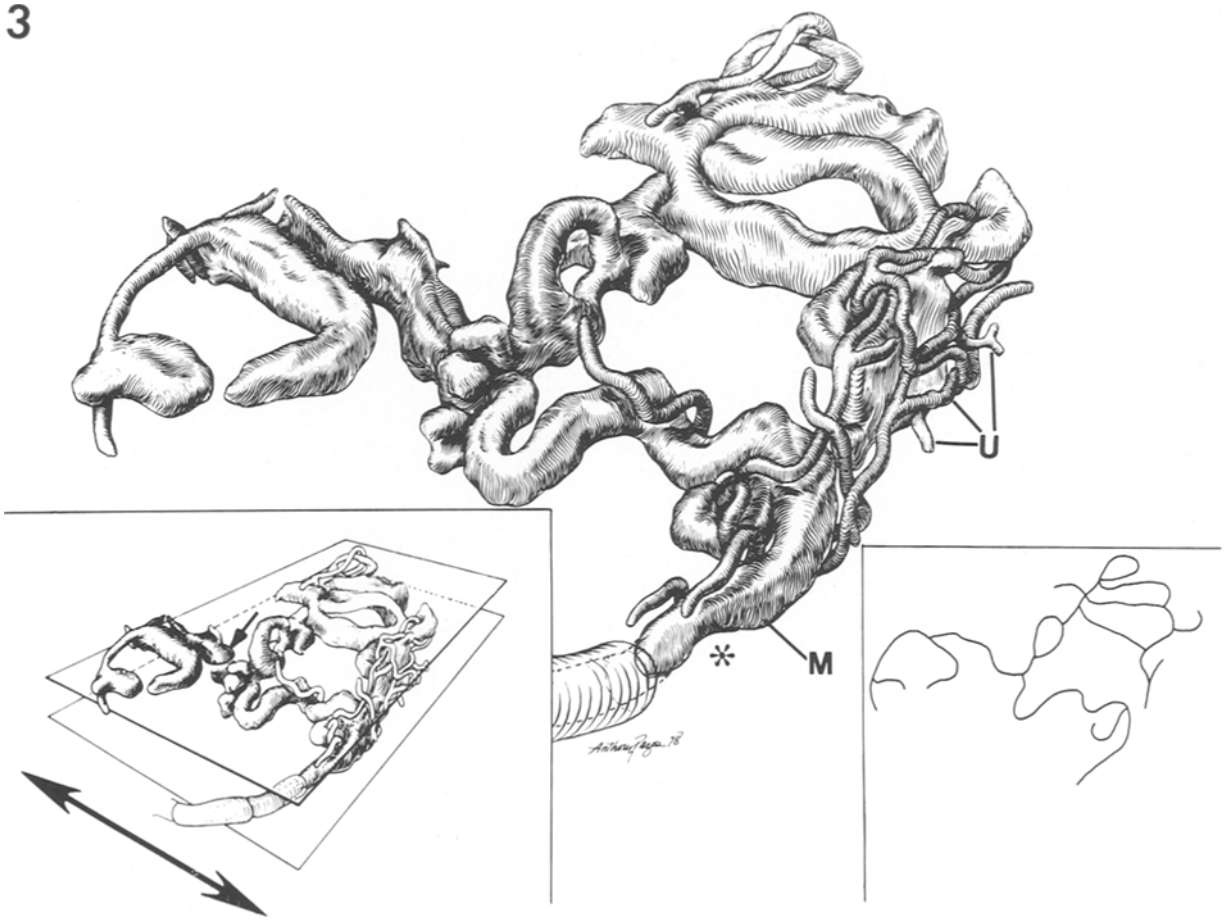
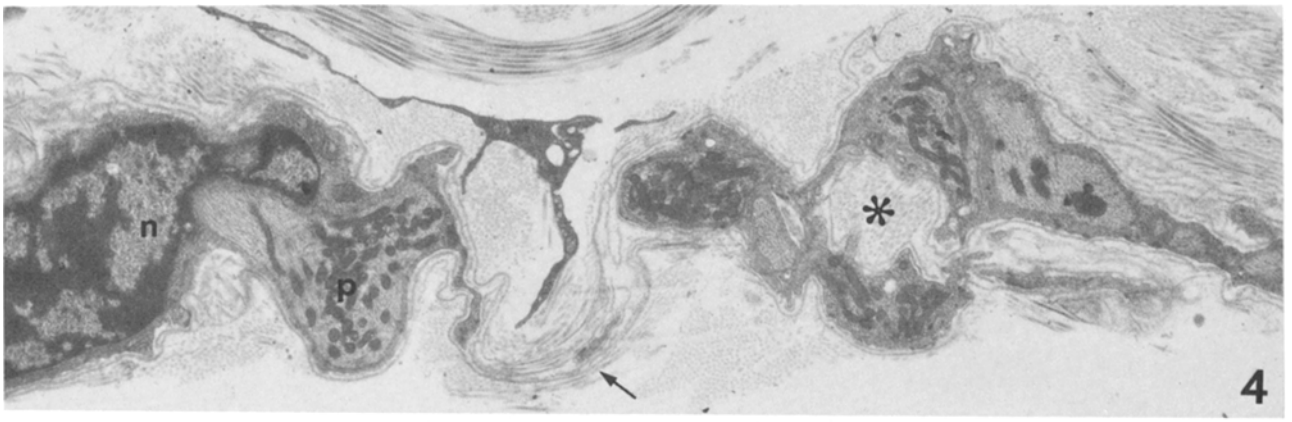


Fig. 3. Drawing (by Anthony Pazos) of a clay model of serial sections of the sensory terminal region arising from one fibre bundle consisting of a myelinated fibre (M) and several unmyelinated fibres (U). Terminal ultrastructure first appeared in the region marked by an astérisk. Myelin is drawn in for orientation purposes, but the distance between the loss of myelin and the beginning of the sensory terminal region was actually much greater than the distance shown here. The premyelinated axon has several branches and loops, shown more clearly in the inset at right. Parts of the unmyelinated axons are shown; these could not be followed in all sections. As shown in the inset on the left, most of the terminal portions of the premyelinated axon are located between two sheets of elastic lamina, but one branch goes through a fenestration (small arrow) into another layer of adventitia. The double-headed arrow indicates the presumed direction of stimulation. The bundle is magnified about 2000 times.



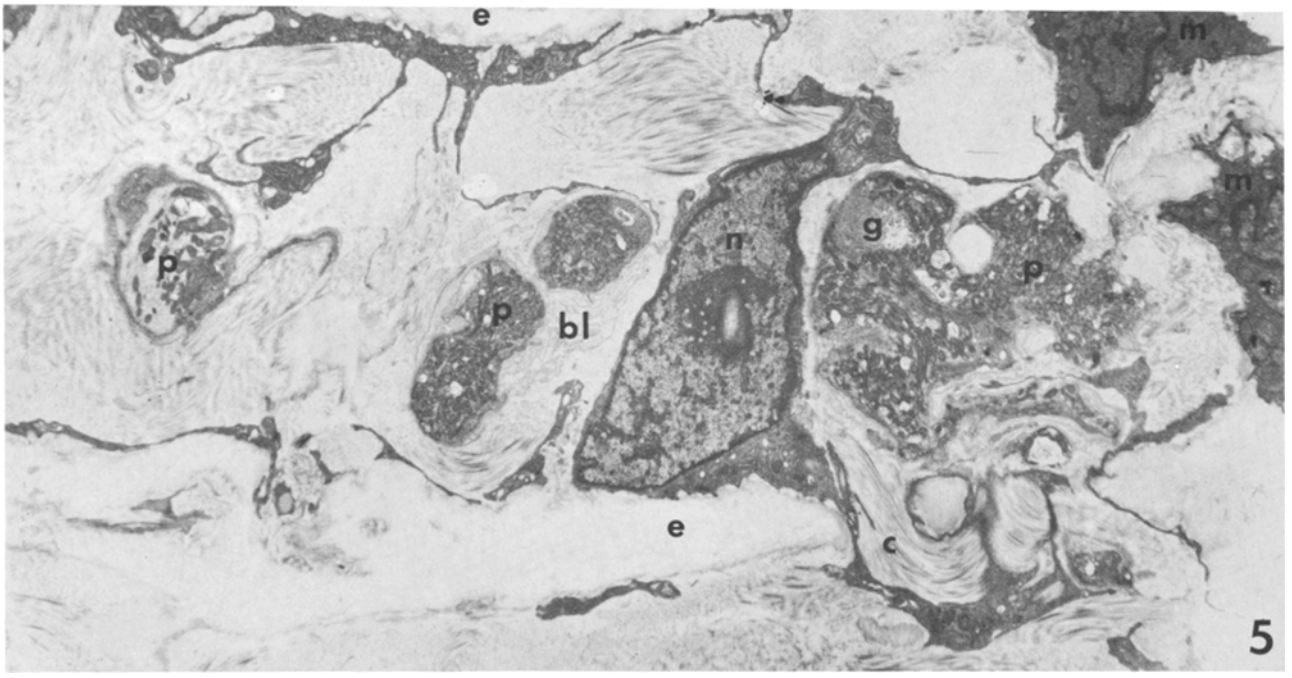


Fig. 4. Part of a premyelinated axon (p), from an SHR, showing a coiled pattern and what is believed to be a ring (the asterisk is in the centre of the ring). Note the curving basal lamina and collagen in a region (arrow) connecting two axon profiles. n, Schwann cell nucleus. x 9400.
Fig. 5. Longitudinal section of a very short premyelinated axon and its sensory terminals (p) innervating the base of the left subclavian or left common carotid artery from an NTR. The proximal end is toward the left, where parts of two coils of the helical axon can be seen. Distally the axon enlarges and its surface becomes highly irregular. Note the swirling collagen bundles (c), masses of glycogen (g), basal lamina (bl), and nucleus (n) of a fibroblast-like perineurial cell. This cell is attached to two elastic laminae (e). Smooth muscle cells (m) of the media are also visible. x 5000.

sensory terminal regions of one bundle from an SHR. Shorter series of sections of bundles of both NTR and SHR baroreceptors agree in general with this model. The terminal portions of the unmyelinated axons were difficult to follow because of their small size, and only portions of them are shown in Fig. 3. The premyelinated axon is coiled in a complicated manner with some parts of the sensory terminal regions forming helices (Figs. 3, 4 and 5). Reconstruction of serial sections has shown that these sensory terminals form loops and have small holes filled with Schwann cell processes: their surface is irregular, with a number of projections and 'grooves' running longitudinally along the surface. The inset on the right is a simplified diagram of the premyelinated axon.

Most of the structure in Fig. 3 extends between two elastic laminae, but as shown in the inset on the left, the premyelinated axon penetrates through a fenestration in one elastic lamina and its sensory terminals continue in another layer of adventita.

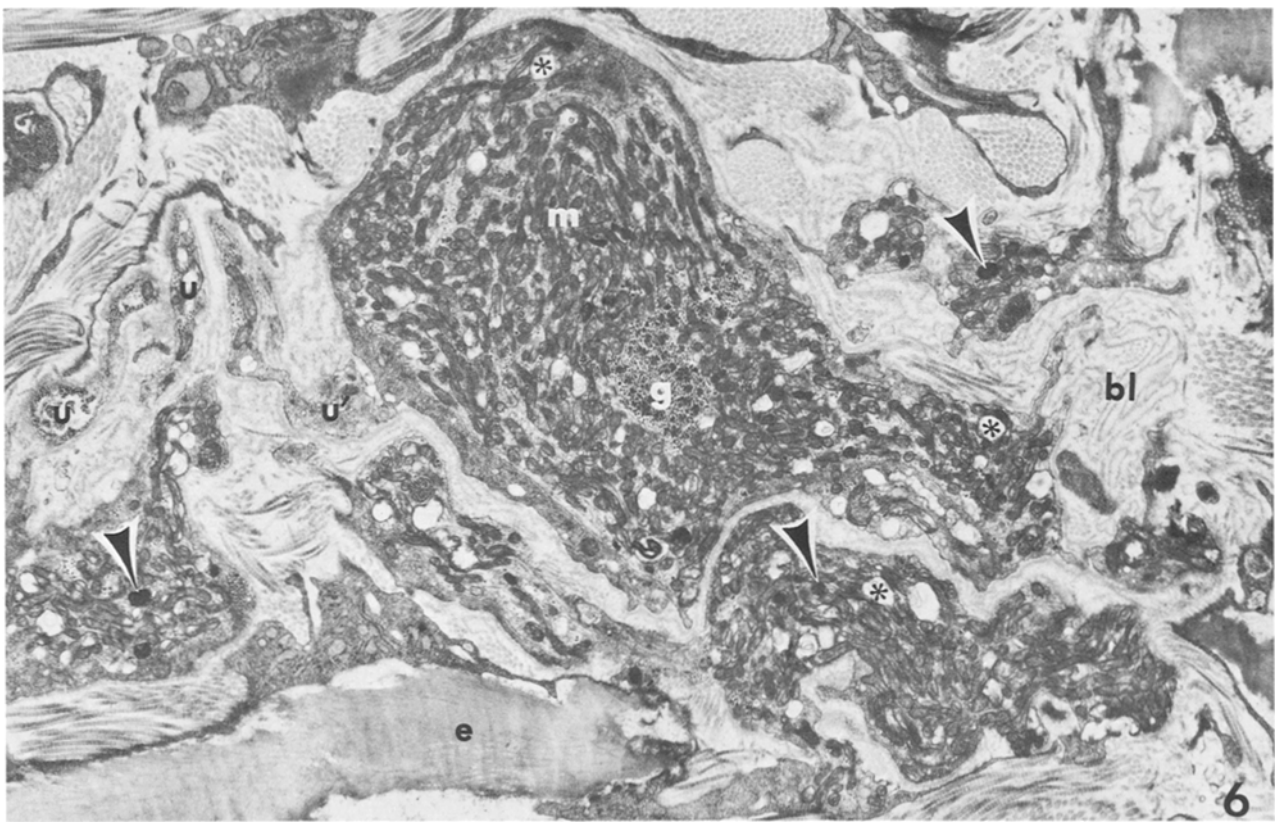


Fig. 6. Sensory terminals of the bundle of baroreceptor axons to which the premyelinated axon in Fig. 5 belongs. The three sensory terminal profiles at left are believed to be unmyelinated baroreceptors (u). The one on the right (u′) abuts the Schwann sheath covering a portion of the premyelinated axon. Part of the latter appears to be traversing a fenestration in the elastic lamina (e). g, glycogen; m, mitochondria of the premyelinated axon; bl, basal lamina; arrowheads, dense mitochondria; asterisks, vacuolar mitochondria. x 8400.

Although the sensory terminals of this particular axon approached the media, they did not appear to be part of the media but were part of an invagination of the adventitia into the media. Sensory terminals were not observed to penetrate the media.

The cytoplasmic features of the sensory terminals of unmyelinated and premyelinated baroreceptor axons are similar; the two types of axon are distinguished by their shape, as described above. While the axons contain few mitochondria proximal to the sensory terminal region, very high concentrations of mitochondria occur in the axoplasm in that region. In some of the swellings of the premyelinated axon, the axoplasm is almost entirely filled with mitochondria (Figs. 5 and 6). Masses of glycogen are also observed. Round, clear vesicles about 40 nm in diameter as well as a few larger dense-cored vesicles are found in the sensory terminals of both premyelinated and unmyelinated baroreceptor axons, often in clusters near the cell membrane or in projections as in Fig. 7. In such regions, 'thickened' areas of the cell membrane were often observed (arrowhead, Fig. 7). Some of the swellings of premyelinated axons contained larger vesicles (Fig. 8) and myelin figures (Fig. 9). These organelles were found in both NTRs and SHRs. Dense bodies and vacuolar mitochondria which may be comparable to the 'altered mitochondria', described by Knoche and Addicks (1976) and Knoche *et al* (1977) were observed; these are visible in Fig. 6 (arrowheads, asterisks). Large mitochondria with a large number of cristae, identical to those described by Böck and Gorgas (1976) were observed in the sensory terminals of one premyelinated axon.

Unmyelinated axons were sometimes observed to surround partially axons which were believed to be premyelinated (Fig. 10), and bundles of collagen (Fig. 11) were sometimes partially encircled by sensory terminal processes.

Whereas only one or two layers of basal lamina cover the sheath of each axon as long as the axons are roughly cylindrical, many layers of basal lamina are observed

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Fig. 7. A process of a premyelinated axon (NTR) containing many clear vesicles and two dense-cored vesicles. Note that the Schwann sheath (S) does not cover the process completely but the basal lamina (bl) does. Arrowhead, membrane 'thickening'. x 60 000

Fig. 8. A swelling of a premyelinated axon (SHR) containing a number of large vesicles and other organelles. x 35 000.

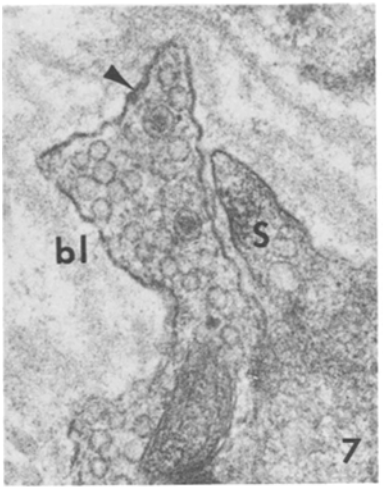
Fig. 9. Myelin figures (m) in a premyelinated axon from an NTR. Note also the large amounts of glycogen (g). x 9200.

Fig. 10. An unmyelinated axon (u) partially surrounds a portion of a premyelinated axon from an NTR. x 18 900.

Fig. 11. Processes of a sensory terminal (s) partially surround a bundle of collagen (c) and are separated from it by basal lamina (bl). From an NTR. x 12 600.

Fig. 12. A premyelinated sensory terminal from an NTR with part of its cell membrane attached to basal lamina (bl). The fibrillar attachments can be seen clearly in the circled region. The basal lamina is also attached to collagen (c). m, mitochondrion. x 96 600.

Fig. 13. Part of the sensory terminal region of the premyelinated axon (p) shown in Figs. 5 and 6. The club-shaped process is very close to a smooth muscle cell (sm) in the media. c, collagen; e, elastic lamina. x 23 000.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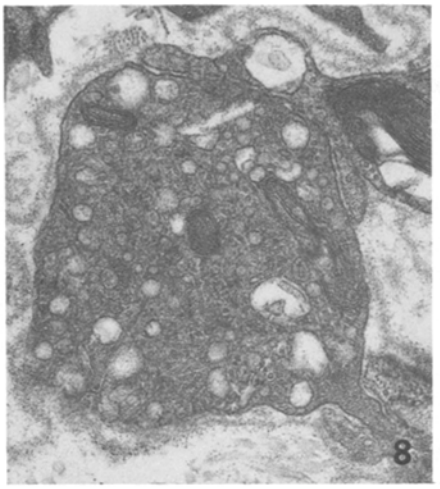
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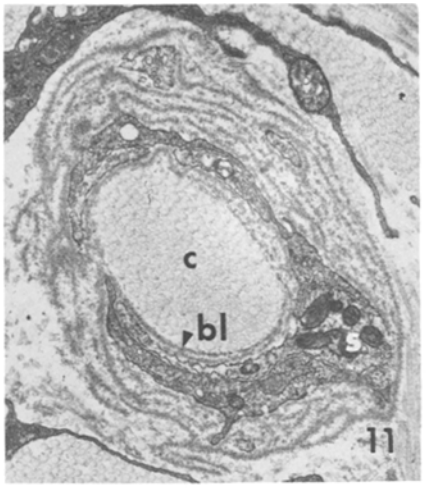
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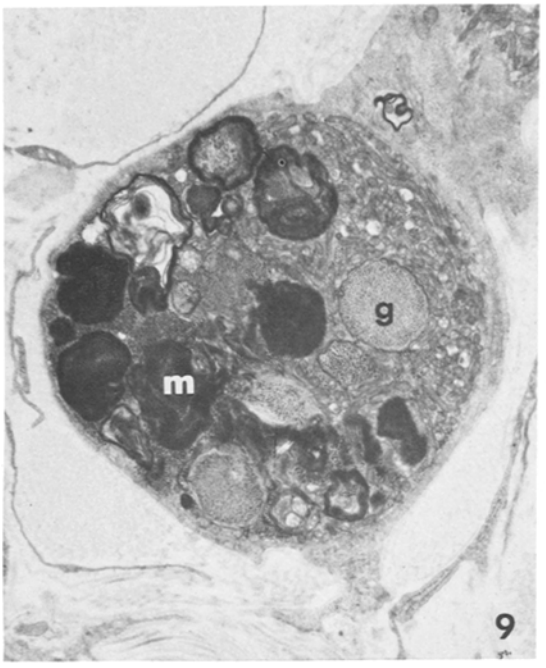
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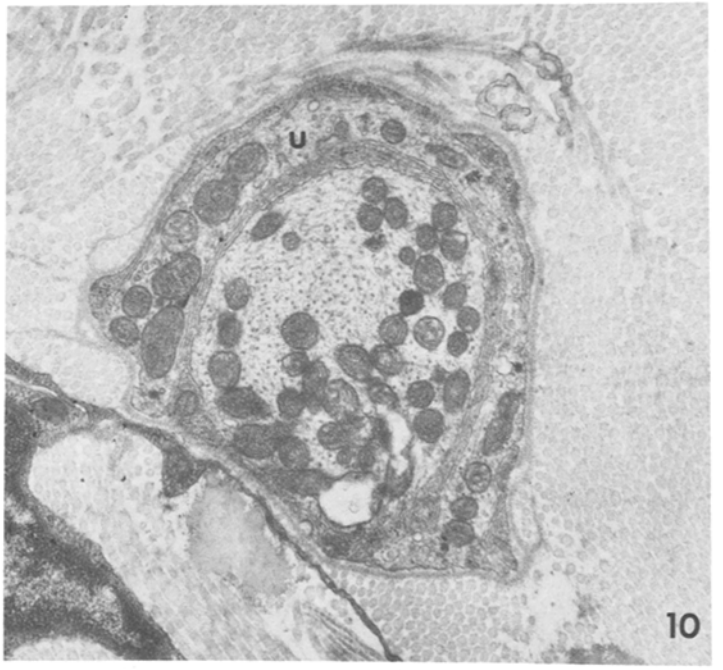
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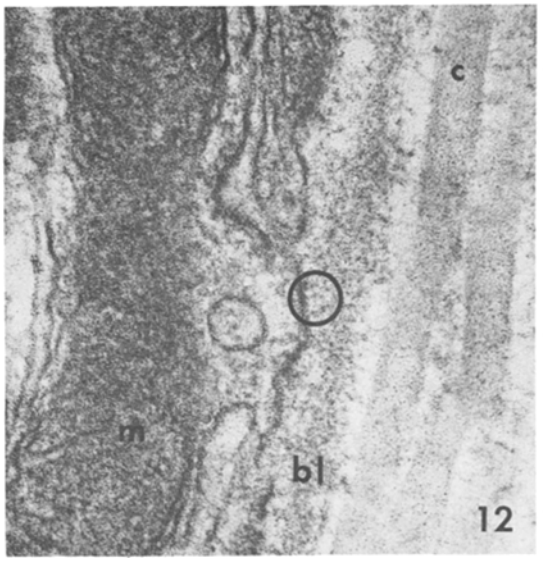
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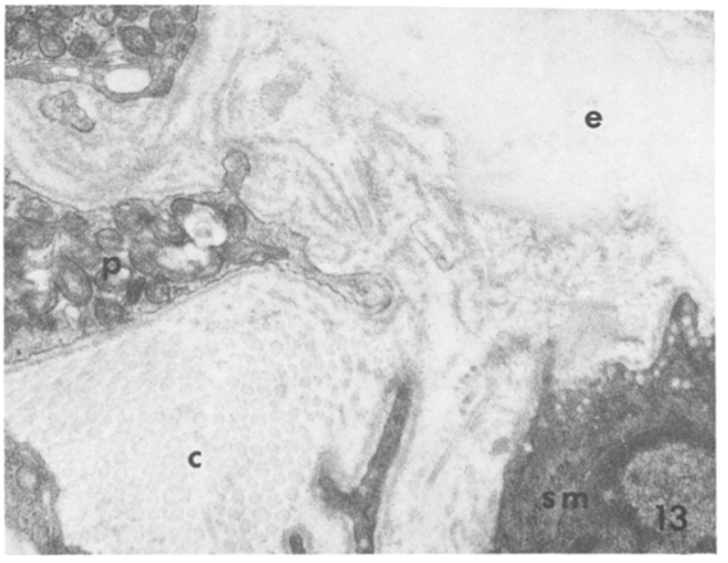
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around the sensory terminals (Figs. 5 and 6). Part of the sensory terminal surface is ensheathed by Schwann cells but a large portion of it (as much as 50%) is exposed directly to the extracellular connective tissue (Figs. 7, 10 and 11). Basal lamina always covers the sensory terminal membrane (premyelinated and unmyelinated) in these regions. At high magnification (Fig. 12) it can be seen that fibrillar material from the basal lamina is (apparently) attached to the nerve cell membrane.

It appears that the sensory terminals extend to but not into the media and the structures that are closest to the media are club-shaped processes of the sensory terminals of premyelinated baroreceptor axons (Fig. 13). These processes are surrounded by basal laminae which are attached to muscle cells in the media and to adjacent elastic laminae.

The cells of the adventitia and media appear to be bound to each other and to elastic laminae by the extensive system of basal laminae. The fibrous part of the elastic laminae appears to connect the latter to fibroblasts which lie along the laminae and to basal laminae (Fig. 5). The basal laminae are also attached to fibroblasts, fibroblast-like perineurial cells, Schwann cells and sensory terminals.

No structural differences in baroreceptors or connective tissue from NTRs and SHRs were observed.

Discussion

The sensory terminals described in this study have the distinguishing characteristics of baroreceptors (Böck and Gorgas, 1976) and are found in an area of the aorta wall where distortion produces responses in the aortic nerve. Very few of the fibres in this nerve respond to any other type of stimulus (Saum, personal communication). Therefore, these fibres are presumed to be baroreceptors.

Axons were observed only in the adventitia and in parts of the media into which the adventitia had apparently invaginated, a phenomenon noted by Ábrahám (1969) in ox, buffalo, sheep, pig and goat aortae. Baroreceptor terminals have, however, been found in the aortic media of rabbits, cats and dogs (Aumonier, 1972).

Some rather odd configurations, such as 'end plates' and 'end rings', of sensory terminals have been described in light microscopic studies of aortic baroreceptors (Ábrahám, 1969; Aumonier, 1972). The present study is the first in which a long series of thin sections has been used to reconstruct the sensory terminals of an arterial baroreceptor, and it has shown that these terminals do form 'rings' and 'reticula'. The location of sensory terminals mainly between two elastic laminae, sometimes with stepwise penetration through fenestrations, is similar to the configuration of the carotid baroreceptors described by Böck and Gorgas (1976).

Many of the ultrastructural characteristics of the sensory terminals described in the present study were identical to those of other sensory terminals presumed to be baroreceptors. Yamauchi (1976) also described a 'massive content of mitochondria', dense bodies and clear vesicles in presumptive aortic baroreceptors of the rat. The same features have been described in carotid baroreceptors of rat (Yates and Chen,

1978), cat (Knoche *et al.*, 1977), dog (Knoche and Addicks, 1976), guinea-pigs and mice (Böck and Gorgas, 1976); and in human myocardium (Chiba and Yamauchi, 1970) and mini-pig atrial endocardium (Tranum-Jensen, 1975). The distinguishing organelles are large numbers of mitochondria, some of which are wider than the others and have more cristae (Böck and Gorgas, 1976); osmiophilic bodies the same size as mitochondria (Knoche and Addicks, 1976); small, clear vesicles; occasional larger, dense-cored vesicles; glycogen accumulations; myelin figures; and lysosome-like dense bodies. It is interesting to note that vesicle and membrane 'thickenings' identical to those reported here have also been observed in varicosities of parasympathetic axons in the interatrial septum of the frog (McMahan and Kuffler, 1971).

The large number of mitochondria is generally interpreted as indicating a high metabolic rate of mechanoreceptors (Böck and Gorgas, 1976), probably necessary for operation of an electrogenic sodium pump (Krauhs and Mirolli, 1975). The 'modified' mitochondria, myelin figures, and lysosome-like bodies observed in our study are considered to indicate processes of degeneration, regeneration and perhaps reorganization occurring in the sensory terminals (Tranum-Jensen, 1975; Böck and Gorgas, 1976; Knoche *et al.*, 1977), possibly because of the (repeated) variations in pressure to which baroreceptors are subjected (Knoche and Addicks, 1976).

Although basal laminae coat other baroreceptors and the Schwann cells around them (Rees, 1967; Chiba and Yamauchi, 1970; Tranum-Jensen, 1975; Böck and Gorgas, 1976; Knoche *et al.*, 1977), these laminae seem to be particularly extensive and prominent around the rat aortic baroreceptors. The large number of layers of basal laminae around sensory terminals does not appear to have been described for any other sensory receptor.

The attachment of the basal lamina to sensory terminal and Schwann cell membranes by means of fibrillar material does not seem to have been emphasized by other authors, although contact of sensory terminals with elastic laminae (Knoche and Schmitt, 1964; Rees, 1967), collagen and smooth muscle (Rees, 1967) has been observed. Böck and Gorgas (1976) observed that the basal laminae sometimes 'intermingled with microfibrils' of elastic fibres in the carotid sinus. The identity of the fibrillar material projecting from the basal lamina is unknown, but the fibrils are similar to mucopolysaccharide-positive filaments that interconnect collagen fibrils (Myers *et al.*, 1973) and to 'bridging structures, presumably polypeptides' that attach the basement membrane to plasma membrane in the exocrine pancreas (Katsuyama *et al.*, 1977). The basal laminae are obviously not a unique feature of baroreceptors, but it appears likely that stresses on the connective tissue are transmitted through these laminae to the sensory endings. They also bind together all of the cells and the elastic (and perhaps collagenous) extracellular material in the aorta.

Landgren (1952) predicted that some baroreceptor terminals are in series and others in parallel with smooth muscle, and Rees (1967) interpreted his own findings as showing that regions of the carotid baroreceptor terminals 'related to' collagen and

smooth muscle in the adventitia were in series with smooth muscle, while 'elastin-related' baroreceptor terminals were in parallel. It is difficult to interpret the present findings in this manner. No direct connection between smooth muscle and baroreceptor terminals has been observed in the present study. One may imagine that when the elastic laminae are stretched, the sensory terminals are distorted circumferentially, in the direction shown in Fig. 3, and/or longitudinally.

The terminal portions of premyelinated axons in the rat aorta have a number of processes or protrusions which are probably comparable to the 'protrusions of mitochondria-free cytoplasm' described by Tranum-Jensen (1975). These were usually not covered or only partially covered by Schwann cell, protruded perpendicular to the longitudinal axis of the axon, and often contained small clear vesicles. Because of their configuration, they would appear to be more vulnerable to stimulation than the rest of the baroreceptor terminal. If the sensory terminal were distorted longitudinally, the angles between this axis and the protrusions would probably be changed and the membrane, particularly at the base of the protrusion, might be affected. Axon protrusions 'grasping' collagen fibre bundles have also been observed in the Golgi tendon organ (Schoultz and Swett, 1972).

The role of unmyelinated axon terminals in baroreception remains speculative. Tranum-Jensen (1975) found that thick and thin fibres appeared to be in the same end-organ in the mini-pig atrial endocardium; Knoche and Addicks (1976) and Böck and Gorgas (1976) have described unmyelinated efferent axons in the carotid baroreceptor region; and Rees (1967) has described unmyelinated as well as premyelinated axons in the carotid sinus.

Unmyelinated fibres in the rat aortic nerve have been studied electrophysiologically, and two types (as shown by their response characteristics) of afferent unmyelinated fibres were found (Thorén *et al.*, 1977; Brown *et al.*, 1978). These baroreceptor C fibres are believed to affect sympathetic activity (Akre and Aars, 1977), but the location of any sympathetic axon terminals in the aortic arch is unknown. No synapses or 'classical' efferent axons were observed in the present study. These electrophysiological and ultrastructural results indicate that the unmyelinated fibres in the fibre bundles described here are afferents. There was no obvious structural evidence for two types of unmyelinated fibre, although fibres of several different sizes were observed.

It is interesting to compare the structure of aortic and carotid baroreceptors. Both are found in elastic arteries, but some features of the aortic baroreceptors appear to be distinctive or at least have not been described in carotid baroreceptors. The latter do not seem to exhibit the large amount of coiling seen in the sensory terminals described here. This feature might be related to the rather large amplitude distension undergone by the aorta. The extensive basal laminae around rat aortic baroreceptors may help to protect the sensory terminals from the distending forces and/or distribute these forces over the fibres. It is possible that after more extensive studies of the carotid baroreceptors are done, particularly with long series of sections, these features will be discovered in them also.

No differences were found in the ultrastructure of baroreceptors from the NTRs and SHRs. This finding agrees with the results of Rees *et al.* (1978), who found no effects of experimental hypertension on ultrastructure of carotid sinus baroreceptors of dogs. As I have discussed above, the appearance of some baroreceptor organelles is taken to indicate the existence of continual degeneration, regeneration and possibly reorganization of the sensory terminals. Evidence for these processes was observed in both NTRs and SHRs. The present results, as well as other recent findings (Sapru and Wang, 1976; Andresen *et al.*, 1978), indicate that resetting of baroreceptors is the result of an increase in blood pressure and that the mechanism of resetting involves biochemical changes in the cell membrane before any gross changes in morphology occur.

Acknowledgements

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