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The blood–nerve barrier: an *in vivo* lanthanum tracer study

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INTRODUCTION

The blood–brain barrier has been the subject of numerous studies employing a wide variety of techniques (Cserr, Fenstermacher & Fencl, 1975; Rapoport, 1976; Bradbury, 1979; Eisenberg & Suddith, 1980). By contrast, the blood–nerve barrier has not been extensively investigated (Rapoport, 1976; Bradbury, 1979; Olsson, 1984). For example, for brain capillaries, endothelial cell junctional relationships have been evaluated using the freeze-fracture technique (Connell & Mercer, 1974; Dermietzel, 1975; Tani, Yamagata & Ito, 1977; Shivers, 1979*a*, *b*), vessels have been isolated for *in vivo* investigations (De Bault, 1982; Shivers, Betz & Goldstein, 1984; Nagy, Goehlert, Wolfe & Hüttner, 1985) and adluminal and abluminal cell membranes have been defined cytochemically, including their polarity, in terms of their enzymes, lectin receptors and surface charge (Inomata, Yoshioka, Nasu & Mayahara, 1984; Hardebo & Kåhrström, 1985; Schmidley & Wissig, 1986; Vorbrodt, Dobrogowska, Lossinsky & Wisniewski, 1986). No such studies appear to have been carried out on peripheral nerve vessels.

One area of investigation of the blood–nerve barrier has been thoroughly explored, largely by Olsson and his colleagues (Olsson, 1984). Thus a good morphophysiological correlation of vascular permeability has been achieved, at both the light and electron microscope levels, by the use of fluoroscein-labelled and electron-dense tracers. However even in this area the microscopic studies have been concerned almost exclusively with molecular tracers, either proteins or more recently dextrans, while physiological investigations have considered the permeability of the vasa nervorum in terms of both ionic and molecular tracers (Krnjevic, 1954; Welch & Davson, 1972; Bradbury & Crowder, 1976). We have therefore undertaken an electron microscope study of the permeability *in vivo* of the endoneurial vessels of the rat sural nerve to ionic lanthanum (Schatzki & Newsome, 1975).

MATERIALS AND METHODS

Animals and lanthanum microinjection

Eighteen male Sprague–Dawley rats weighing 200–480 g were used. The rats were anaesthetised with intraperitoneal sodium pentobarbitone (Sagatal) and inhalation of nitrous oxide and oxygen mixture at a rate of 1·0 and 0·3 litres respectively. After exposure in the popliteal fossa, the left sural nerve was microinjected with lanthanum in normal saline. Glass micropipettes (approximately 10 μm tip), attached to a glass tuberculin syringe (1·0 ml), were held in a micromanipulator and microinjection was

monitored by viewing with an operating microscope. Lanthanum solution (1 μl) was injected beneath the perineurium over a period of 1–3 minutes (in previous investigations we have demonstrated that injections of saline alone produced no apparent ultrastructural changes in endoneurial capillaries). The contralateral sural nerve was used as control tissue. In three animals the lanthanum solution was injected into the epineurium.

The lanthanum solutions used, as lanthanum nitrate in saline, were: 5 mM, 297 mOsm, pH 5·5; 10 mM, 319 mOsm, pH 5·9 and 7·4; 20 mM, 350 mOsm, pH 5·7. The rats were killed at 5, 10, 20 and 60 minutes post-injection. The use and limitations of lanthanum as an electron-dense tracer in the peripheral nerve and the avoidance of cytotoxic effects have been discussed previously (MacKenzie, Ghabriel & Allt, 1984; MacKenzie, Shorer, Ghabriel & Allt, 1984).

Tissue processing

The sural nerves were fixed either by immersion for 2 hours (7 animals) or by vascular perfusion followed by immersion for 2 hours (11 animals) with a 4% paraformaldehyde – 2% glutaraldehyde fixative in phosphate buffer (0·15 M). Vascular perfusion lasted for 5–10 minutes and 200–400 ml of fixative were used for each rat according to animal size, at a pressure equivalent to 80 mmHg. Segments of the left sural nerve (1·5 cm) with the injection site at its centre, and a corresponding portion of the right sural nerve, were excised. Tissue processing (aldehyde fixation, osmication, dehydration and embedding) was completed within 24 hours to limit loss of lanthanum from the tissues. For light microscopy, 1 μm sections were stained with 1% toluidine blue. Ultrathin sections for electron microscopy were unstained, stained lightly or conventionally stained with uranyl acetate and/or lead citrate. For further details of the histological techniques employed, see MacKenzie *et al.* (1984).

RESULTS

Lanthanum tracer was readily identified as electron-dense deposits in both unstained and stained sections (Figs. 1–5) from the microinjected nerves. No such deposits were ever seen in sections (Fig. 6) from the contralateral control nerves. In order to minimise the involvement of artefact resulting from the microinjection, the following description applies only to blood vessels sampled between 2·5 and 7·5 mm distally or proximally from the injection site (though no disrupted vessels were observed in the injected nerves).

The amount of tracer present in the endoneurial space varied markedly, probably being related to the distance, both radially and longitudinally, from the injection site. However, it did not appear to vary with the mode of fixation (perfusion or immersion). Irrespective of the amount of lanthanum present, the tracer was concentrated in the perivascular and subperineurial spaces, and this was especially evident at later time intervals (20 and 60 minutes). While there was usually more perivascular lanthanum at the 20 mM concentration than at 10 mM, and less still at 5 mM, most importantly the tracer was present in the inter-endothelial cleft (see below) at all three concentrations and all time intervals (5–60 minutes) used.

Endoneurial vessels often showed dense tracer deposits filling the spaces radially between endothelial layers (Figs. 1, 3*A*, 4*A*, *B*). Despite being so extensive radially, the tracer commonly extended only around part of the circumference of the vessel (Fig. 1) and less commonly around the whole circumference. The space between endothelial cell and pericyte was similarly occupied by tracer. The tracer formed discrete crystals

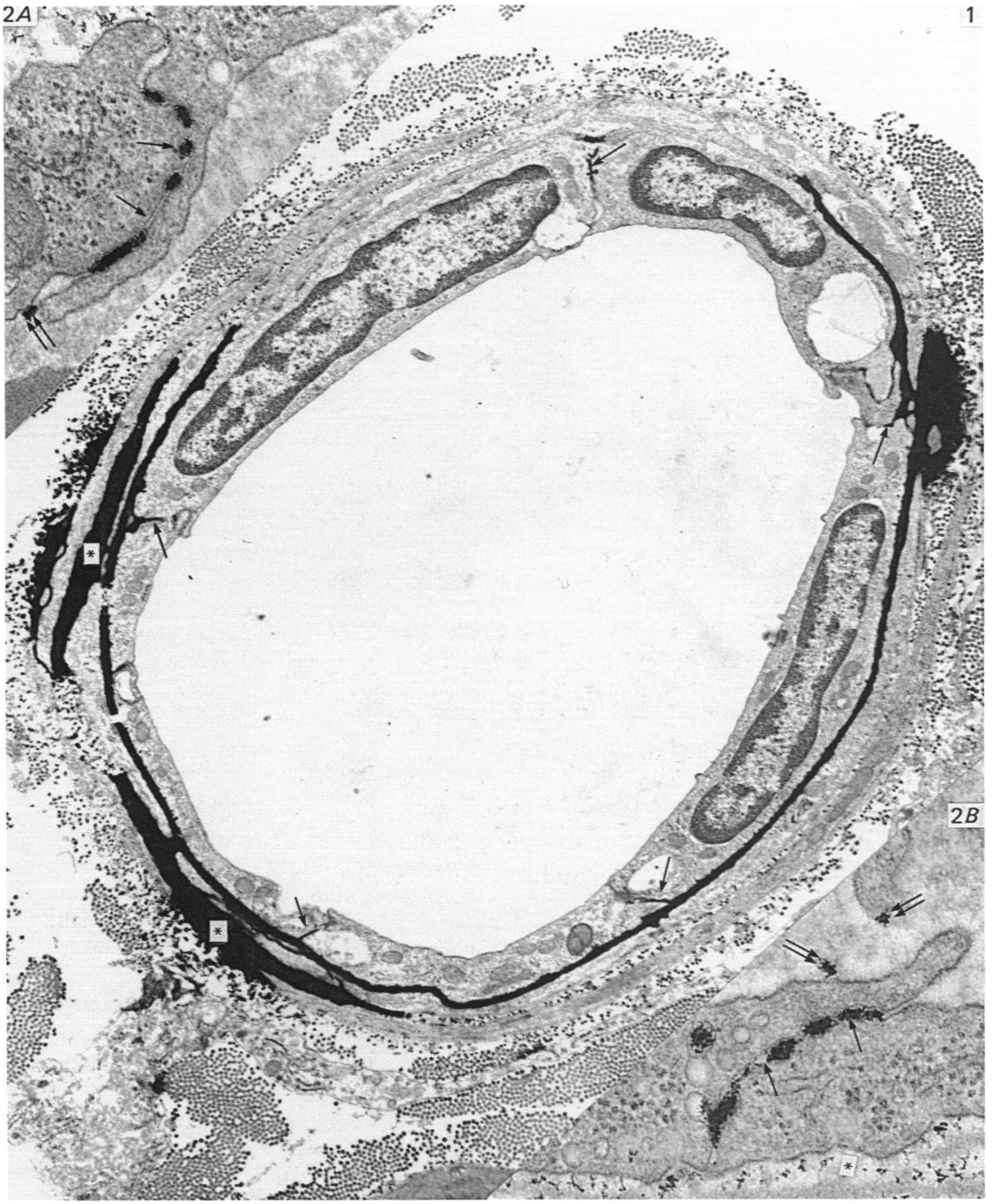


Fig. 1. An endoneurial vessel showing amorphous lanthanum between endothelial layers (asterisks) and within intercellular clefts (arrows). Endoneurium microinjected with 20 mM lanthanum solution followed by perfusion fixation after 5 minutes; stained with uranyl acetate for 15 minutes and lead citrate for 10 minutes. × 10600.

Fig. 2(*A–B*). Two intercellular clefts in an endoneurial vessel. Note lanthanum present in the lumen adjacent to the clefts (double arrows), in the diffuse, crystalline form between endothelial cell layers (asterisk) and discontinuously throughout the intercellular clefts (arrows). Endoneurium microinjected with 5 mM lanthanum solution followed by immersion fixation after 5 minutes; stained with lead citrate for 5 minutes. (*A*) × 45000; (*B*) × 56700.

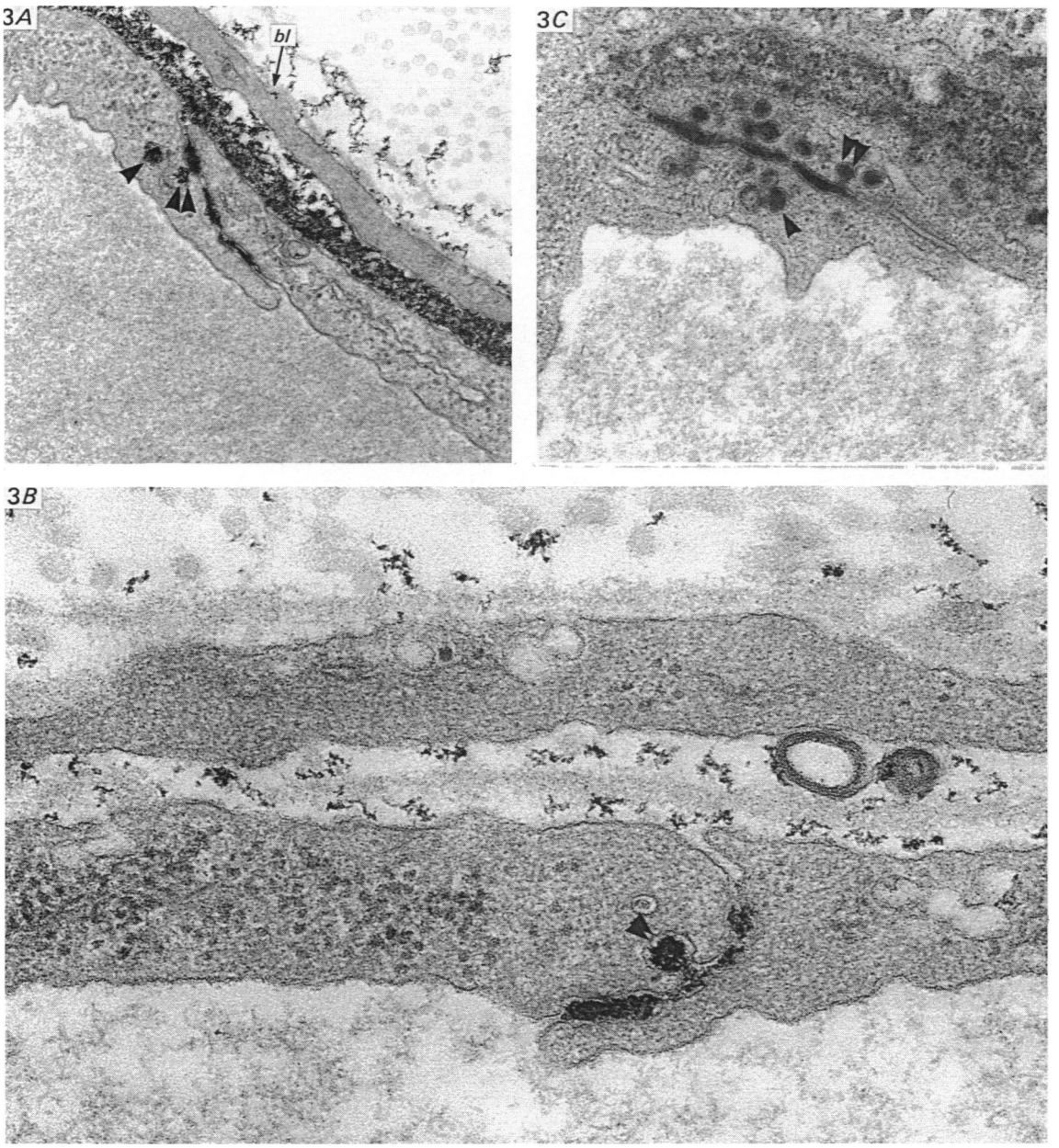


Fig. 3(*A–C*). Lanthanum tracer is present in cytoplasmic vesicles (single arrowheads) and caveolae (double arrowheads), adjacent to intercellular clefts containing lanthanum. Note, especially in (*A*), infiltration of the basal lamina (*bl*) by tracer. Endoneurium microinjected with 5 mM lanthanum solution (*A–B*) followed by immersion fixation after 10 minutes (*A*) or 20 minutes (*B*); (*C*) immersion in fixative containing 1% lanthanum nitrate and without lanthanum microinjected (see MacKenzie *et al.*1984). Stained with uranyl acetate for 30 minutes (*A*) or 1 minute (*C*) and lead citrate for 8 minutes (*A*) or 1 minute (*C*), or with lead citrate alone for 8 minutes (*B*)). (*A*) ×37000; (*B*) ×80400; (*C*) ×43200.

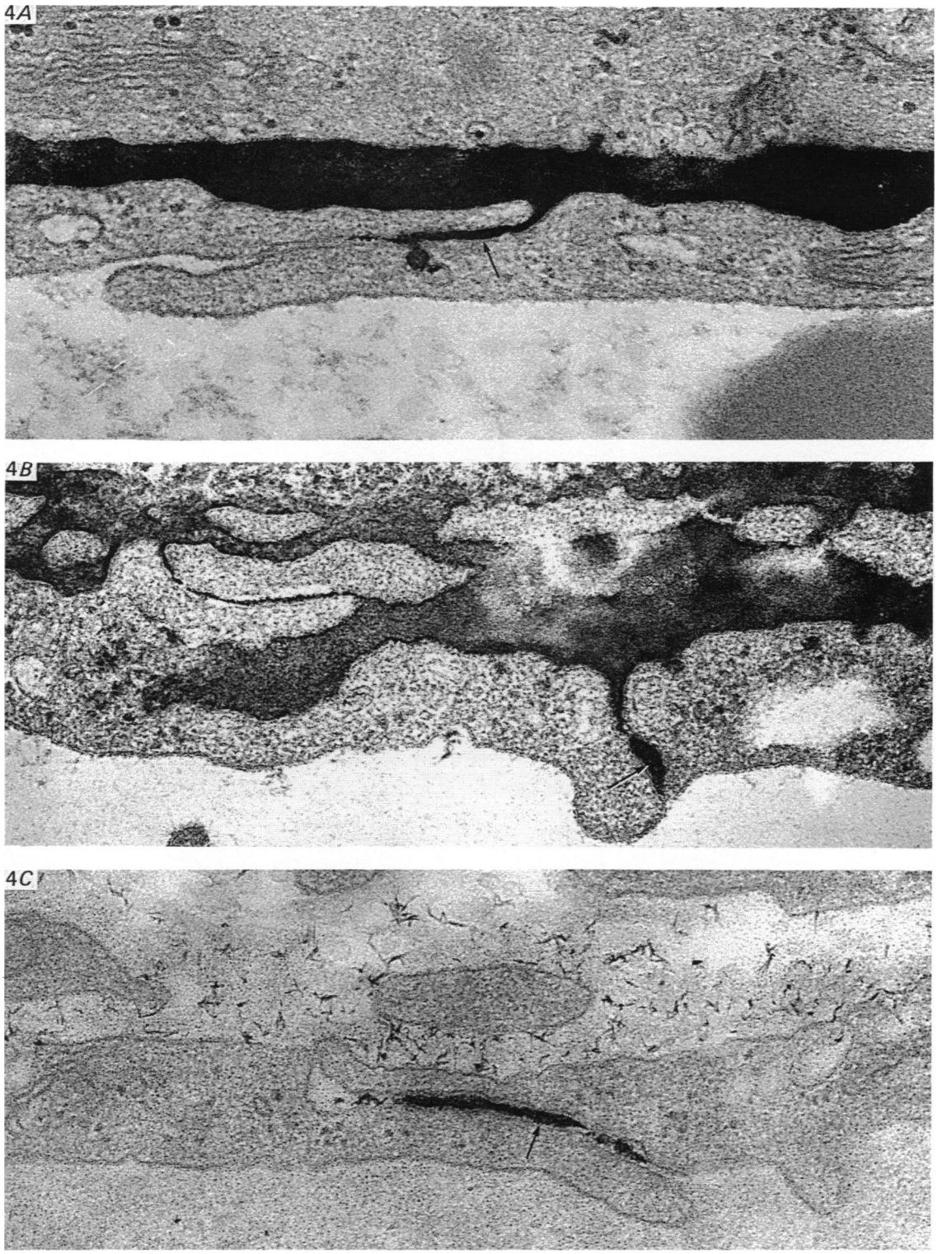
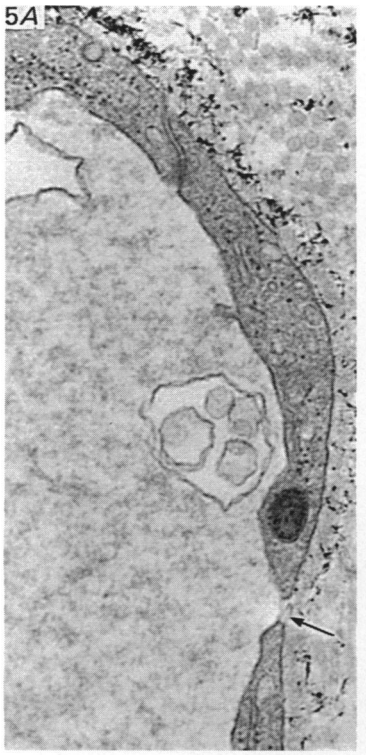


Fig. 4 (*A–C*). Lanthanum tracer is concentrated within the intercellular clefts (arrows) irrespective of whether it is present between cellular layers in the continuous amorphous form (*A*, *B*) or sparse crystalline form (*C*). Endoneurium microinjected with 10 mM (*A*, *C*) or 20 mM (*B*) lanthanum solution followed by perfusion fixation after 5 minutes (*A*, *B*, *C*); stained with uranyl acetate for 15 minutes and lead citrate for 10 minutes (*B*) or with lead citrate alone for 8 minutes (*A*) or 1 minute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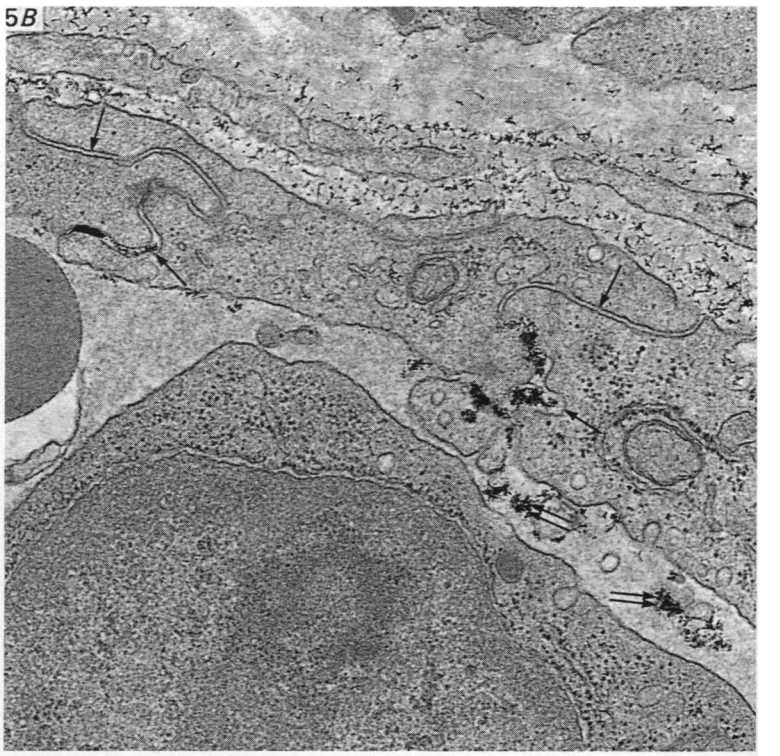
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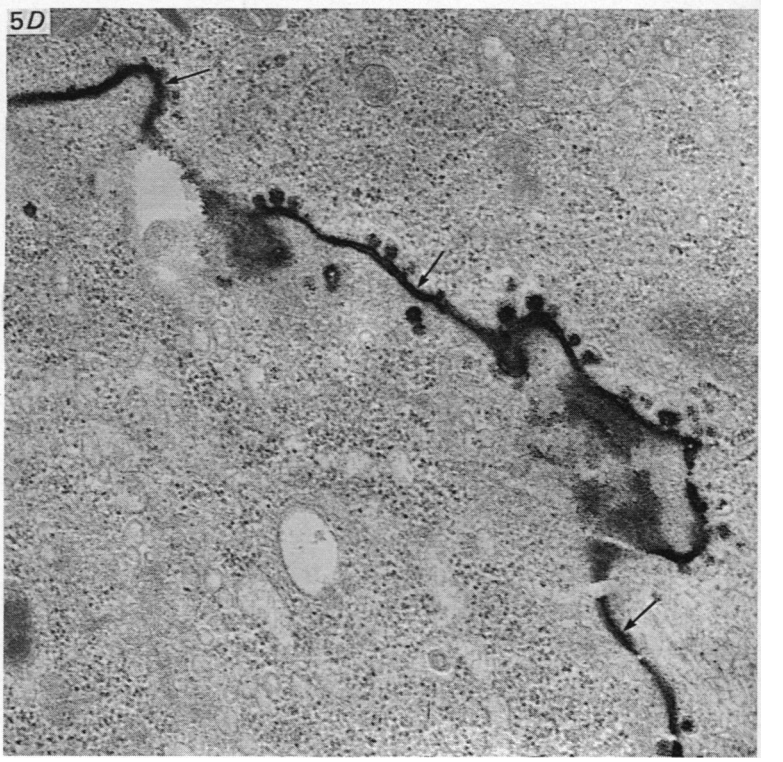
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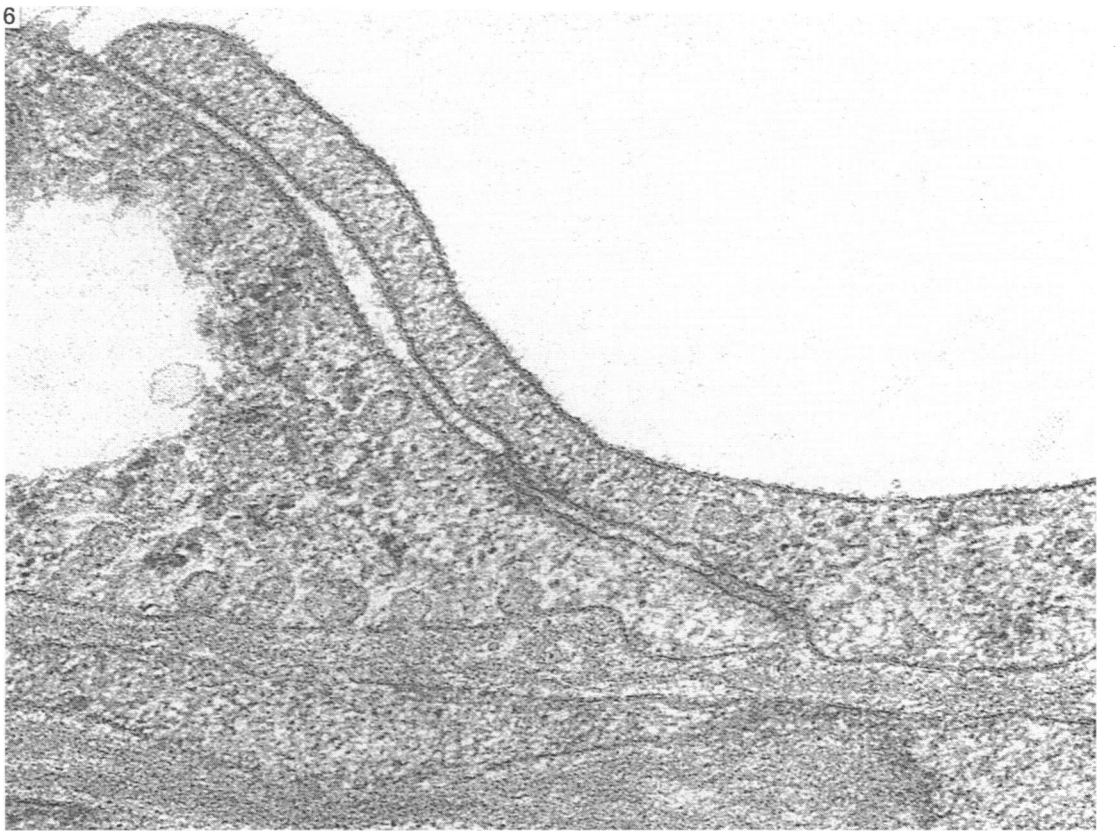

Fig. 6. Endoneurial endothelial cells from a control nerve showing no extracellular dense deposits similar to lanthanum. Perfusion fixation; stained with uranyl acetate for 30 minutes and lead citrate for 8 minutes. ×93600.

when it was less dense between endothelial cells (Fig. 4*C*). External to the pericyte or outermost layer of endothelial cells, the lanthanum commonly covered the outer (abluminal) surface of the cell, infiltrating the basal lamina but did not form a continuous amorphous layer as it frequently did between cells; instead it was present diffusely in the crystalline form (Fig. 3*A*). In the remainder of the perivascular space the tracer was much more sparsely distributed.

In the interendothelial clefts opening into the vessel lumen the tracer, when present, frequently occupied a portion of the cleft, either abluminally (Fig. 4*A*) or adluminally, was discontinous throughout the cleft (Figs. 2*A–B*, 3*A–B*, 4*C*) or less frequently occupied the entire cleft (Fig. 4*B*). Tracer could not be identified within cleft tight junctions themselves but was commonly present immediately adjacent to the putative tight junction both ab- and adluminally. Caveolae and vesicles in the endothelial cell

Fig. 5(*A–D*). Epineurial vessels showing fenestrations (*A*, arrow), intercellular clefts apparently without tight junctions (*B*, arrows) and lanthanum tracer within clefts (*B*, *D*, arrows) and vessel lumen (*B*, *C*, double arrows) and between endothelial layers (*C*, asterisks). Epineurium microinjected with 5 mM (*A*, *B*) or 10 mM (*C*, *D*) lanthanum solution followed by perfusion fixation after 60 minutes (*A*, *B*) or 8 minutes (*D*) or immersion fixation after 10 minutes (*C*); stained with lead citrate alone for 10 minutes (*A*, *B*) or 8 minutes (*D*) or unstained (*C*). (*A*) ×33000; (*B*) ×32000; (*C*) ×30400; (*D*) ×31200.

cytoplasm adjacent to the cleft (Figs. 3*A–C*, 4*A*) were sometimes filled with tracer (while some of the 'vesicles' may have opened into the cleft in a different plane of section, others were situated too far from the plasma membrane for this to have been likely).

Epineurial vessels (Fig. 5*A–D*) were characterised by endothelial cells which were usually attenuated, displaying few tight junctions at the intercellular clefts and containing fenestrations (Fig. 5*A*). Tracer was generally present in smaller quantities around epineurial vessels (probably related to the tracer being injected into a space which is not confined and enclosed like the endoneurial space). Consequently the tracer usually appeared in the diffuse crystalline form (Fig. 5*A–B*). Despite the small quantities of tracer, lanthanum was usually present in the vessel lumen (Fig. 5*B–C*) and in the intercellular clefts (Fig. 5*B*, *D*; where it was often sufficiently concentrated to appear as the amorphous form).

In animals fixed by vascular perfusion, tracer was not usually present in the vessel lumen (Figs. 1, 4*A–C*, 5*A*). In a minority of vessels, however, small quantities of tracer were present, especially adjacent to the intercellular cleft (Fig. 5*B*). In the seven animals fixed by immersion, tracer was found within the lumen (Figs. 2*B*, 5*C*) more commonly and in larger quantities. While the fine structure of vascular endothelial cells appeared to be equally well preserved by vascular perfusion (Figs. 1, 4, 5*A–B*, *D*, 6) and immersion (Figs. 2, 3, 5*C*) fixation, using the morphology of the myelinated fibres as the criterion, perfusion fixation was preferable.

DISCUSSION

The present study demonstrates that at least some and perhaps all endoneurial vessels of the rat sural nerve are permeable to ionic lanthanum when it is applied to their abluminal surfaces. By contrast, in the central nervous system of various species including the rat, lanthanum is prevented from entering cerebral capillaries from the neuropil or traversing the endothelium in the reverse direction, by inter-endothelial tight junctions (Brightman & Reese, 1969; Bouldin & Krigman, 1975; Rapoport, 1976; Bradbury, 1979; Nagy, Mathieson & Hüttner, 1979). These results, for the peripheral and the central nervous systems using an ionic electron-dense tracer, are compatible with the data from physiological experiments in which permeability coefficients were determined for radiolabelled ions (Welch & Davson, 1972). Using ^{24}Na and ^{36}Cl, capillaries in the sciatic nerve were approximately ten times more permeable than cerebral capillaries in the rabbit. However, as Bradbury & Crowder (1976) point out, the real difference is likely to be lower than this since a larger area of central versus peripheral nervous system endothelium was used in the determinations. It will be further lowered since epineurial vessels, with their lack of a blood–nerve barrier (Olsson, 1968), were included in the nerve sample. In addition caution should be exercised in the comparison of results from the rat and rabbit nervous systems, since species differences have been demonstrated for the permeability of endoneurial vessels (Olsson, 1971). Similarly, the results obtained for the sural nerve vasa nervorum in the present study cannot necessarily be extrapolated to other regions of the rat peripheral nervous system since topographical differences in vascular permeability have been demonstrated (Olsson, 1968).

For epithelia generally the intercellular junctions are the main transepithelial routes for water and ion flow (Rapoport, 1976). It is therefore of interest that in the central nervous system both the form of the zonulae occludentes between the vascular endothelial cells has been analysed (using the freeze-fracture technique; see Introduc-

tion) and the electrical resistance across the endothelium in isolated cerebral capillaries has been measured (Crone & Olesen, 1982; Olesen, 1986). Claude & Goodenough (1973) deduced that epithelia showing high transepithelial electrical resistance were characterised by tight junctions that showed many junctional ridges (P face) and complementary grooves (E face) in freeze-fracture replicas while for a lower electrical resistance there was a concomitant decrease in the number of ridges and grooves in the epithelium. However, exceptions to this correlation have been described in more recent studies (Martinez-Palomo & Erlij, 1975; Brightman, Anders & Rosenstein, 1980). In the capillaries of the central nervous system analysed so far, many complete, anastomosing ridges and grooves have been identified and the endothelia have shown a high electrical resistance, e.g. a mean of 1870 Ωcm^2, typical of 'very tight' junctions (Claude & Goodenough, 1973; Rapoport, 1976). It should be emphasised, however, that none of these studies made a direct correlation using the same capillaries. For the peripheral nervous system, endoneurial capillaries do not appear to have been examined using freeze-fracture or to have been isolated for use in electrophysiological determinations. It will therefore be of interest to compare both parts of the nervous system together with any further regional differences within them. On the basis of the results of the present study, together with physiological determinations of permeability coefficients of ions for the vasa nervorum, it may be predicted that endoneurial capillaries will have few ridges and grooves at tight junctions and a relatively low electrical resistance. In addition it is likely that endoneurial capillaries will be found to be relatively rich in contractile proteins since vessels of the peripheral nervous system show a marked increase in permeability in response to histamine and serotonin. The action of these pharmacological agents on vascular permeability is mediated, at least in part, via an actomyosin system which induces cell contraction and cell separation. By contrast cerebral capillary permeability to proteins appears to be less responsive to histamine and serotonin and the endothelial cells show a paucity of contractile proteins but there is enhanced vesicular transport in response to these vasoactive agents (Rapoport, 1976; Bradbury, 1979; Joó, 1986).

What is the functional importance of a greater ionic permeability in endoneurial compared with cerebral vessels? It is tempting to consider that endoneurial vessels in association with the perineurium (a diffusion barrier with its own zonulae occludentes) maintain a precise ionic *milieu* around nerve fibres as a prerequisite for continuous and saltatory conduction. However, against such a view of their homeostatic function it should be borne in mind that the perineurium is open-ended at some nerve terminations (Low, 1976; Rapoport, 1976; Thomas & Olsson, 1984), with apparently no restriction on ionic diffusion between the endoneurial and extraneural microenvironments. Such an apparently paradoxical situation is indicative of our need for new correlative data for the peripheral nervous system, by the application of techniques which have recently become available. It is now feasible to determine the ionic composition of the endoneurial matrix, and the properties of the perineurial and endoneurial capillaries as indicated by their transendothelial electrical resistance, permeability to ions and structure of zonulae occludents. Such techniques might shed more light on the significance of regional differences within the nervous system, and interspecies differences in the effectiveness of both the blood–nerve and blood–brain barrier to ions and molecules (Rapoport, 1976; Jacobs, 1978; Bradbury, 1979; Olsson, 1984). It remains to be determined whether the absence in the peripheral nervous system of any cells analogous to the perivascular astrocyte processes of the central nervous system is implicated in the differences in their vascular permeability.

SUMMARY

The permeability of the blood–nerve barrier was investigated using ionic lanthanum as an electron-dense tracer. The rat sural nerve was microinjected *in vivo* with lanthanum nitrate solution either into the endoneurial space or into the epineurium. Five to sixty minutes after injection the sural nerves were fixed by vascular perfusion or immersion. Using electron microscopy, lanthanum tracer was observed to be associated with endoneurial vessels in the perivascular spaces, in the inter-endothelial clefts and within the lumina. Furthermore, tracer was present in the spaces between adjacent endothelial cell layers and within vesicles and caveolae of endothelial cells. Epineurial vessels showed a similar distribution of tracer deposits but in greater quantities in inter-endothelial cell spaces and vessel lumina. The results are considered to demonstrate an absence of a blood–nerve barrier to ions as exemplified by lanthanum and are compatible with data from physiological experiments. The blood–nerve and blood–brain barriers are contrasted in their permeability to ions, their related fine structure and their physiological roles.

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