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Perivascular spaces in the basal ganglia of the human brain: their relationship to lacunes

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ABSTRACT

There is evidence for lymphatic drainage of interstitial fluid from the brain along perivascular spaces in a number of mammalian species. Ultrastructural studies suggest that there are similar drainage pathways in the human cerebral cortex. Perivascular spaces in the basal ganglia, however, differ from those in the cortex in that they dilate to form lacunes and rarely accumulate beta-amyloid (amyloid angiopathy) in Alzheimer's disease; in the cortex, lacunes are rare but amyloid angiopathy is common. The aim of the present study is to compare the structure of perivascular spaces in the basal ganglia and at the anterior perforated substance with perivascular spaces in the cerebral cortex. Eight postmortem brains from patients aged 23–80 years (mean 68 y) were examined by light microscopy, by scanning and transmission electron microscopy and by direct visualisation of etched paraffin blocks. The results show that arteries in the basal ganglia are surrounded by 2 distinct coats of leptomeninges separated by a perivascular space which is continuous with the perivascular space around arteries in the subarachnoid space. The inner layer of leptomeninges closely invests the adventitia of the vessel wall and the outer layer is continuous with the pia mater on the surface of the brain at the anterior perforated substance. Veins in the basal ganglia have no outer layer of leptomeninges and thus the perivascular space is continuous with the subpial space. The anatomy of the periarterial spaces in the basal ganglia differs significantly from that in the cerebral cortex where there is only a single periarterial layer of leptomeninges. Differences in structure of perivascular spaces around arteries may reflect relative efficiencies in the drainage of interstitial fluid from different sites in the brain. Futhermore, the structure of the perivascular spaces may contribute to the relatively high frequency of lacunes in the basal ganglia, and the low frequency of amyloid angiopathy at this site in Alzheimer's disease.

Key words: Vasculature; leptomeninges; interstitial fluid drainage; Alzheimer's disease.

INTRODUCTION

For many years it was thought that perivascular spaces in the brain connected directly with the subarachnoid space (Weed, 1923; Millen & Woollam, 1954). However, observations by scanning electron microscopy of animal (Krahn, 1982) and human brain (Hutchings & Weller, 1986) and of spinal cord (Nicholas & Weller, 1988) showed that the pia mater is reflected from the surface of the brain onto vessels in the subarachnoid space, thus separating the subarachnoid space from the perivascular spaces within the brain. Cells of the pia mater forming this barrier are joined by desmosomes and other intercellular junctions (Alcolado et al. 1988) and appear to be capable of pinocytosis (Feuer & Weller, 1991); in this way the pia mater forms a regulatory interface between the subarachnoid space and the surface of the brain and perivascular spaces.

Physiological and anatomical studies in a variety of mammalian species have emphasized the immunological role of perivascular spaces in the brain as

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lymphatic drainage pathways (Cserr et al. 1992; Weller et al. 1992, 1996; Kida et al. 1995; Knopf et al. 1995). Tracers injected into the grey matter of the rat brain drain along perivascular spaces which are lined by immunocompetent perivascular cells (Cserr et al. 1992; Zhang et al. 1992; Kida et al. 1993*b*). Within the subarachnoid space, tracers drain along perivascular spaces, via the circle of Willis to the olfactory bulbs and thence, through lymphatic channels in the cribriform plate and nasal submucosa to cervical lymph nodes (Kida et al. 1993*a*). This lymphatic drainage pathway plays a key role in the immunology of the central nervous system, such that removal of cervical lymph nodes significantly reduces immune reactions in the brain mediated by both B and T lymphocytes (Harling-Berg et al. 1989; Cserr et al. 1992; Knopf et al. 1995; Phillips et al. 1995, 1997; Weller et al. 1996).

Previous studies of perivascular spaces related to arteries in the human cerebral cortex have shown that these vessels are coated by a layer of leptomeninges which is subtended from the pia mater (Zhang et al. 1990) and, by this anatomical arrangement, the perivascular spaces of the intracortical arteries are in direct continuity with the perivascular spaces around arteries in the subarachnoid space. The lack of similar coating of leptomeningeal cells around veins in the cerebral cortex suggests that perivascular spaces around veins are in continuity with the subpial space (Zhang et al. 1990; Weller, 1995) and probably do not function as lymphatic drainage pathways in the same way as periarterial spaces.

The aim of the present study is to examine the structure of perivascular spaces in the basal ganglia and at the anterior perforated substance. Medial and lateral striate arteries are branches of the middle cerebral artery which enter the brain through the anterior perforated substance to supply the basal ganglia (putamen, globus pallidus and caudate nucleus) (Mohr, 1982). Lateral striate arteries ascend into the internal capsule and then turn medially across the putamen and internal capsule to supply the caudate nucleus. It is rupture of the largest ramus of the lateral striate artery that is thought to be most frequently involved in intracerebral haemorrhage (Weller, 1992). The anterior perforated substance is also the site at which the inferior striate veins converge; these vessels drain the ventral portion of the corpus striatum and, via the deep middle cerebral vein and basal vein, drain into the great cerebral vein of Galen (Truex & Carpenter, 1969).

In this study, we test the hypothesis that perivascular spaces in the basal ganglia differ from those in the cortex. This hypothesis is based upon the observations related to the ageing brain: firstly that lacunes, formed by the dilatation of perivascular spaces, are frequently seen in the basal ganglia in the aged human brain (Poirier & Derouesné, 1985) but are rarely present in the cerebral cortex; and secondly, that beta-amyloid accumulates in perivascular spaces around vessels in the cerebral cortex and overlying leptomeninges (amyloid angiopathy) with age and in Alzheimer's disease (Yamaguchi et al. 1992), but such amyloid accumulation is absent or rare in the basal ganglia (Mandybur, 1975; Braak & Braak, 1990). Differences in the structure of the perivascular spaces in relation to vessels in the cortex and basal ganglia could have implications for the efficiency of drainage of interstitial fluid and its constituent proteins from these different regions of the brain.

MATERIAL AND METHODS

A total of 8 postmortem human brains from patients without evidence of neurological disease and aged 23–80 y (mean 68 y) were studied. Postmortem delay was up to 24 h. Blocks of tissue from putamen, globus pallidus and from the anterior perforated substance were taken either fresh at postmortem and fixed in formalin (2 brains) or from 1 cm coronal slices of brain fixed for 4–5 wk in phosphate-buffered formalin (6 brains).

Light microscopy

One tissue block to include large blood vessels in the putamen and globus pallidus and 1 block from the anterior perforated substance were taken from each side of the 6 fixed brains (total of 24 blocks). The blocks, up to 5×3 cms in area and 1 cm thick, were dehydrated on a 12 d programme and embedded in paraffin wax. Sections, 5 μm thick, were stained with haematoxylin and eosin and by the Gordon & Sweet reticulin method.

The surfaces of the paraffin blocks were examined following the cutting of 5 μm sections and the etched vascular structures visible at the anterior perforated substance were photographed in oblique light using a Tessovar macro lens.

Scanning electron microscopy (*SEM*)

One block of putamen and 1 block of globus pallidus containing arteries, veins and their perivascular structures were selected from each side of the 6 formalin fixed brains (a total of 24 blocks), washed in

cacodylate sucrose buffer overnight and postfixed in 2% osmium tetroxide for 2 h. Tissue blocks were then stained with 1.5% uranyl acetate for 30 min for subsequent transmission electron microscopy. Following dehydration through graded alcohols, the blocks were dried in a Balzer's CPD 030 critical point drier and the surfaces to be studied were sputtercoated with gold and palladium in a Polaron SEM coating unit E1500 in an argon atmosphere. The specimens were then examined using a Hitachi 2800 scanning electron microscope at 15 kV.

Transmission electron microscopy (*TEM*)

For the histological and ultrastructural verification of structures examined by scanning electron microscopy, a total of 12 SEM blocks (from 6 brains) in which vessels and their coatings were well visualised were removed from the stubs, trimmed and placed in Histosol for 1 h, a 50/50 solution of Histosol and Spurr's resin, for approximately 5 h and then embedded in 100% Spurr's resin. Semithin sections (1 μm) were cut and selected ultrathin sections were prepared, contrasted with lead citrate and examined in a Hitachi 7000 transmission electron microscope with an accelerating voltage of 70 kV.

Eight sample blocks of formalin fixed brain obtained fresh at postmortem were also studied by transmission electron microscopy, without the prior scanning electron microscope stage. Such samples were washed in cacodylate buffer, postfixed in 2% osmium tetroxide, dehydrated and embedded in Spurr's resin.

RESULTS

Perivascular coats and spaces surrounding arteries and veins in the basal ganglia

Blocks in which there was distinct dilatation of the perivascular spaces in the globus pallidus were selected for study as the different structures around the vessels were widely separated and clearly demonstrated. Arteries 30–300 μm diameter were identified by their relatively thick walls and subsequently by histology. Figure 1 shows the arrangement of structures around an artery and its small branch in the globus pallidus. Endothelial cells line the lumina of the vessels and an intact layer of cells coats the outer surface of each vessel. A distinct, somewhat convoluted, thin sheet of cells surrounds both vessels but is separated from them by a wide perivascular space. Nuclei were visible by SEM in both the inner and outer sheets of cells. Quite independent of the outer cell layer, is a sheet of basement membrane which has become focally detached from the underlying brain. The appearances shown in Figure 1 were well demonstrated in at least 15 arteries and in no vessel was a different arrangement observed.

A different arrangement of cell layers was seen around veins. In Figure 2, a thin-walled vessel is lined by intact endothelium and coated by a layer of cells on its outer surface. The second sheet of cells, seen around arteries, is not present around veins and only a layer of basement membrane separates the perivascular space from the underlying brain. Again,the appearances shown in Figure 2 were well demonstrated in relation to at least 15 veins and in no vessel was a different arrangement observed.

Characterisation of perivascular coats around arteries

Cells forming the layers around arteries and veins were identified by a combination of SEM and subsequent TEM. Figure 3*a* shows an artery with a lumen, lined by endothelium, and a layer of cells on the adventitial surface. A distinct structure separates the perivascular space from the brain. TEM of the same vessel (Fig. 3*b*) reveals the fine structure of the wall of the vessel with endothelium lining the lumen and layers of smooth muscle cells forming the media. Separated from the media by adventitial collagen is a thin layer of cells lining the perivascular space. On the outer aspect of the perivascular space, a layer of cells is separated from the basement membrane of the glia limitans by subpial collagen. Artefactual separation of the basement membrane from the underlying brain in this way is commonly seen in scanning electron microscope preparations (Hutchings & Weller, 1986). Viewed at higher magnification (Fig. 3*c*), the inner and outer layers of cells encompasing the perivascular space form intact sheets. The presence of junctions between cells in both the inner and outer layers (Fig. 3*d*) suggests that they are leptomeningeal in origin (Alcalado et al. 1988). Many of the intercellular junctions were desmosomes, but others were less complex structures, as in Figure 3*d*, in which the outer lamellae of the cell membrane were in direct contact.

Characterisation of perivascular coats around veins

The arrangement of the leptomeninges around veins in the basal ganglia differed from that around arteries.

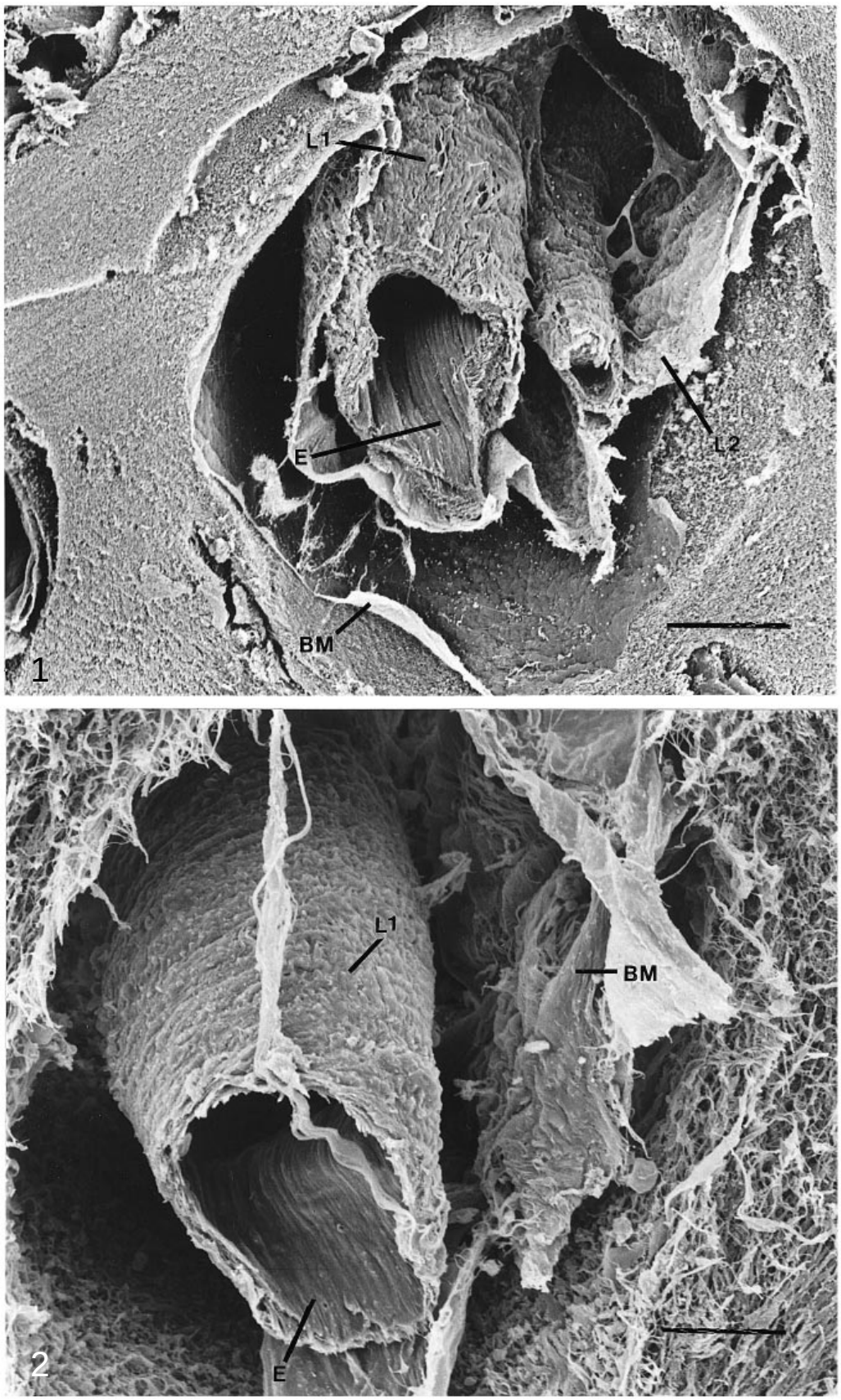

Fig. 1. Scanning electron micrograph of an artery and its branch in the globus pallidus of a 78-y-old subject. Endothelium (E) lines the lumen of the vessel and a layer of cells (L1) coats the outer surface of the vessel. Surrounding the perivascular space is a thin layer of cells (L2) which is separate from the basement membrane (BM) coating the surface of the brain. SEM. Bar, 330 μm.

Figure 4*a* shows a vein with endothelium lining the lumen, a thin wall and a perivascular space. The corresponding TEM of this vein reveals a thin layer of leptomeninges coating the outer aspect of the adventitia and forming the inner wall of the perivascular space (Fig. 4*b*). Cells in this layer are joined by intercellular junctions resembling desmosomes in leptomeninges. No outer layer of leptomeninges is observed around the veins, such that the outer wall of the perivascular space is formed by sheets of collagen overlying the basement membrane of the glia limitans (Fig. 4*b*).

Anterior perforated substance

The arrangement of leptomeninges in relation to the walls of the blood vessels at the anterior perforated substance was best visualised by observing the etched surfaces of paraffin blocks and examining the corresponding paraffin sections stained with the Gordon & Sweet reticulin technique. In Figure 5*a*, a small artery is seen at its point of entry into the brain. It is surrounded by a distinct perivascular space and an outer layer of leptomeninges which is continuous with the pia mater at the surface the brain. Thus, there is continuity between the perivascular space of the intracerebral portion of the artery and that around the artery in the subarachnoid space. A serial paraffin section from this block (Fig. 5*b*) shows continuity of the leptomeningeal coating of the artery as it penetrates the brain. The pia mater is attached to the outer surface of the perivascular leptomeningeal coat.

The delicacy of the leptomeninges on the surface of postmortem brains has, as yet, precluded adequate visualisation of the exact relationships between the pia mater and veins at the anterior perforated substance.

DISCUSSION

The results of the present histological and ultrastructural study allow a working hypothesis to be formulated regarding relationships between leptomeninges, perivascular spaces and vessels within the basal ganglia and at the anterior perforated substance of the human brain. Figure 6 summarises, in diagrammatic form, the relationships between leptomeninges and periarterial spaces in the basal ganglia and in the cerebral cortex. Two layers of leptomeninges coat arteries in the subarachnoid space at the anterior perforated substance and continue as arteries enter the brain. A similar arrangement is seen around arteries in the globus pallidus. The periarterial space is thus between 2 layers of leptomeninges and, in this way, differs from the perivascular space around arteries in the cerebral cortex (Fig. 6*b*). Cortical periarterial spaces are lined on the inner aspects by adventitia and smooth muscle cells and are confined on the outer aspect by a sheet of leptomeninges (Zhang et al. 1990; Weller, 1995).

Relationships of leptomeninges around veins in the basal ganglia differ from those around arteries. Veins lack the outer layer of leptomeninges which encompasses the perivascular space around arteries. Due to the fragility of the pia mater at the anterior perforated substance, it was not possible in this study to obtain adequate visualisation of the connections between leptomeninges and veins at this site. However, extrapolation from the anatomical arrangement in the basal ganglia would suggest that perivascular spaces around veins are continuous with the subpial space.

The anatomical arrangement of periarterial spaces in the basal ganglia described in this study may be significant *firstly*, in the formation of perivascular lacunes and, *secondly*, in their role as putative drainage pathways for interstitial fluid from the brain.

There has, in the past, been some confusion between perivascular lacunes and lacunar infarcts in the basal ganglia. However, Poirier and his coworkers have proposed a classification which clearly distinguishes lacunes formed due to dilatation of perivascular spaces from lacunar infarcts and haemorrhages (Poirier & Derouesné, 1985). Dilatations of perivascular spaces are described as regular cavities which always contain a patent artery. Such cavities are lined by a 'simple epithelium' but are not surrounded by gliosis and can be further divided into a number of subgroups including giant lacunes which may form space-occupying lesions within the brain (Homeyer et al. 1996). Such a description would suggest that perivascular lacunes are due to dilatation of perivascular spaces in the basal ganglia and that the 'simple epithelium' is the outer layer of leptomeninges (L2 in Fig. 6) identified in the present study.

A number of different theories regarding the pathogenesis of perivascular lacunes have been ad-

Fig. 2. Scanning electron micrograph of a vein in the globus pallidus of an 80-y-old subject. The lumen is lined by endothelium (E) and the adventitia is coated by a layer of cells (L1). Basement membrane (BM) separates the perivascular space from the underlying brain. SEM. Bar, 55 μm.

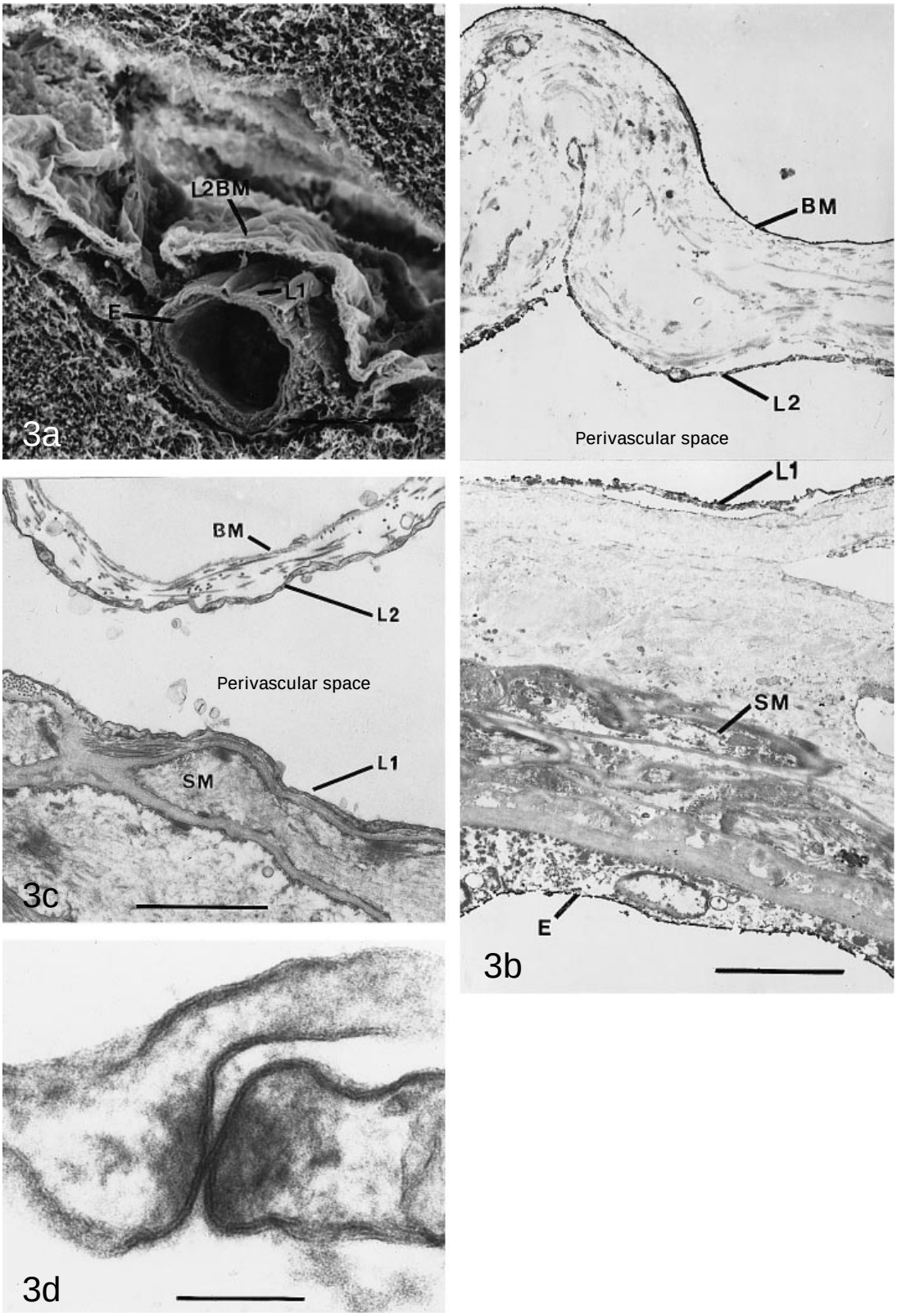

Fig. 3. SEM and TEM correlation of periarterial structures of a 79-y-old subject. (*a*) SEM of an artery in the globus pallidus. Endothelium (E) lines the lumen and a layer of cells (L1) coats the adventitial surface. A single structure identified in (*b*) as a layer of leptomeninges and basement membrane (L2 BM) separates the perivascular space from the brain. SEM. Bar, 105 μm. (*b*) TEM of the vessel wall shown in (*a*). The endothelium (E) lines the lumen and smooth muscle cells (SM) form the media. A layer of leptomeningeal cells (L1) coats the adventitia of the artery. A further layer of leptomeningeal cells (L2) forms the outer boundary of the perivascular space and is separated from the basement membrane (BM) of the glia limitans by bundles of collagen. TEM. Bar, 8 μm. (*c*) Higher magnification of a small artery in the globus pallidus showing the perivascular space bordered by inner (L1) and outer (L2) continuous, thin layers of cells similar in thickness

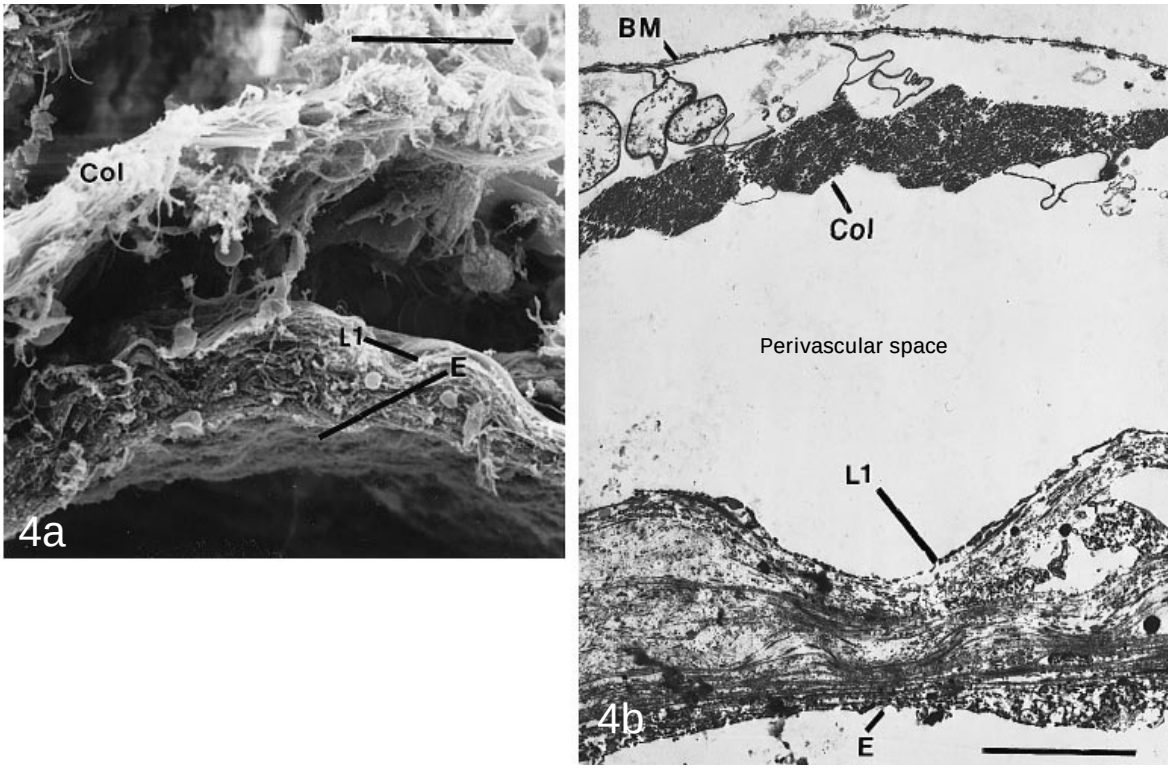

Fig. 4. SEM and TEM correlation of perivenous structures in a 78-y-old subject. (*a*) SEM of vein wall showing endothelium (E) lining the lumen and a layer of cells coating the adventitia (L1). Bundles of collagen (Col) separate the vessel from the brain. SEM. Bar, 24 μm. (*b*) TEM of the same vessel as in (*a*). Endothelium (E) lines the lumen and a layer of cells (L1) coats the adventitia. The outer aspect of the perivascular space is lined by bundles of collagen (Col) adjacent to the basement membrane (BM) of the glia limitans. TEM. Bar, 9 μm.

vanced. Enlargement of the perivascular space by coiling of the ageing artery, particularly in hypertension (Hughes, 1965), has been suggested as a mechanism for the formation of lacunes. However, there is usually little evidence of gliosis around such lacunes (Poirier & Derouesné, 1984) which would be against them forming in this traumatic way. Other theories suggest that there is an abnormality of the permeability of the arterial wall which allows fluid to leak out and overload the perivascular space to form lacunes in the cerebellum (Benhaïem-Sigaux et al. 1987). One factor in the formation of lacunes suggested by the putative function of the perivascular spaces as fluid drainage pathways (Cserr et al. 1992; Weller et al. 1992, 1996) may be fibrosis and obstruction of perivascular spaces along the length of arteries and consequent impedance of fluid flow. Macrophages containing blood pigment are frequently seen in perivascular spaces of patients with hypertension (Kalimo et al. 1997); such debris and subsequent scarring may be instrumental in blocking perivascular spaces. The formation of giant lacunes in nonhypertensive patients may be due to some other mode of obstruction in the drainage of interstitial fluid. Further study of perivascular spaces, particularly around the larger arteries in the subarachnoid space, may elucidate this problem.

Despite the information available from animal studies, the role of perivascular pathways in lymphatic drainage of the brain in man is still far from clear. There are reports of metastatic spread of glial tumours to cervical lymph nodes (Campora et al. 1993) but, as yet, the in vivo tracers that have been used for radiological definition of lymphatic drainage pathways of the brain in rabbits are not yet suitable for such studies in man (Hunter et al. 1995). Nevertheless, the continuity of periarterial spaces around vessels in the brain, at the anterior perforated substance, with

to pia mater (Alcolado et al. 1988). SM, smooth muscle of the artery wall. The basement membrane of the glia limitans (BM) is separated from L2 by strands of subpial collagen. TEM. Bar, 2 μm. (*d*) Intercellular junction between cells in the inner leptomeningeal layer (L1). The outer lamellae of the cell membranes are in direct contact. TEM. Bar, 125 nm.

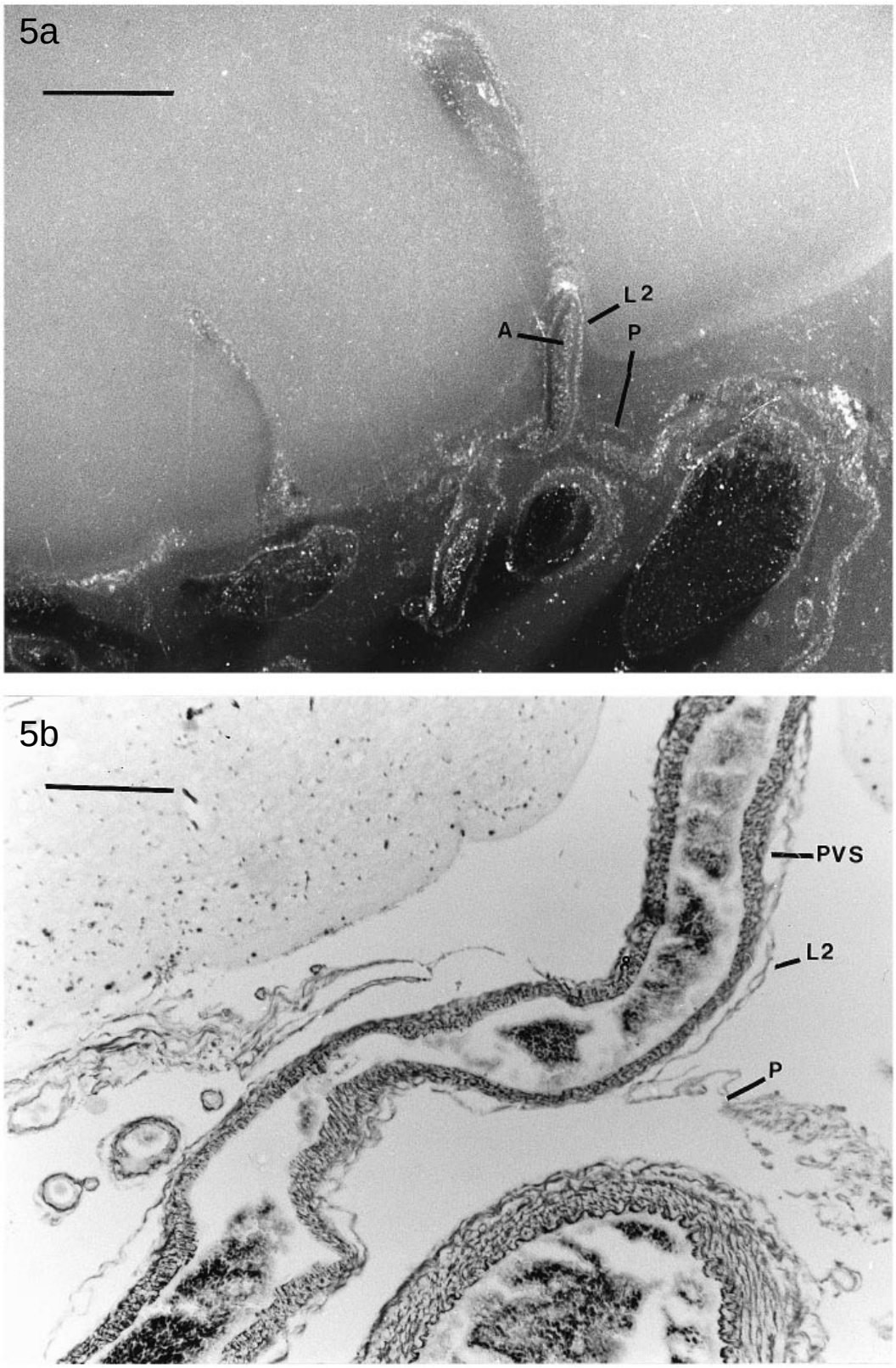

Fig. 5. Anterior perforated substance in an 80-y-old subject. (*a*) An etched paraffin block showing the arrangements of the meninges around a penetrating artery. The artery (A) passes from the subarachnoid space (below) into the brain (above). A layer of leptomeninges (L2) is continuous with the pia mater (P). The perivascular space separates L2 from the artery wall in the subarachnoid space and as the artery enters the brain. Bar, 2.8 mms. (*b*) Section taken from the paraffin block illustrated in (*a*). The artery in the subarachnoid space (below) enters the brain above. The pia mater (P) is continuous with the outer layer of leptomeninges (L2) as the artery enters the brain. The perivascular space (PVS) is seen between the artery and L2. Reticulin stain. Bar, 450 μm.

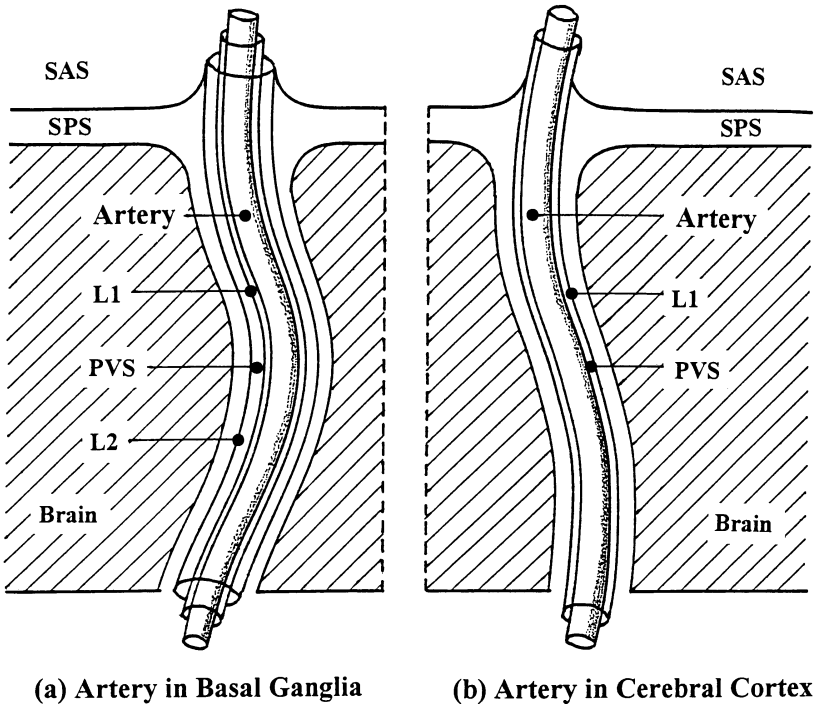

Fig. 6. Comparison of perivascular spaces in the basal ganglia and cerebral cortex—schematic representation. (*a*) An artery in the basal ganglia. The artery itself is closely invested by a sheet of leptomeninges (L1) and separated from the outer coat of the meninges (L2) by a perivascular space (PVS). L2 abuts on to the glia limitans of the underlying brain, and separates the perivascular space from the subpial space (SPS). The perivascular space in the brain continues to surround the artery in the subarachnoid space (SAS). Lacunes appear to form between L1 and L2. (*b*) An artery in the cerebral cortex. The artery is closely invested by a layer of leptomeninges (L1) which is continuous with the pia mater. Thus the perivascular space (PVS) in the cortex is continuous with that around the leptomeningeal arteries in the subarachnoid space (SAS). Data in diagram (*b*) are derived from previously published accounts (Zhang et al. 1990; Weller, 1995).

those outside the brain, in the subarachnoid space, could serve as perivascular fluid drainage pathways. Anatomical variations in the periarterial spaces between the cortex and basal ganglia may contribute to the high frequency of amyloid angiopathy in the frontal and temporal cerebral cortex in Alzheimer's disease and its reported infrequency in the corpus striatum (Mandybur, 1975; Braak & Braak, 1990). If amyloid is eliminated from the brain by interstitial fluid drainage pathways (Massey et al. 1997), the stucture of the perivascular spaces in the basal ganglia may allow amyloid peptides to drain relatively more efficiently from this region of the brain.

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