Filamentous contacts: the ultrastructure and three-dimensional organization of specialized non-synaptic interneuronal appositions in thalamic relay nuclei

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Abstract. Filamentous contacts are non-synaptic interneuronal junctions characteristic of thalamic relay nuclei. Symmetrical filamentous contacts occur between two dendrites, two somata or a dendrite and a soma; asymmetrical filamentous contacts occur between axon terminals and dendrites, or occasionally somata, chiefly between the large specific afferent axon terminals of the synaptic glomeruli and the shafts of relay cell dendrites. Both are arranged as extensive net-like (reticular) specializations. The strands of the network enclose fenestrae of variable shape and size and, in perpendicular thin sections, appear as stretches of slightly widened intercellular space containing an electron-dense material and bounded by plasma membranes, the cytoplasmic surfaces of which are coated by electron-dense material into which microfilaments appear to insert. The lamina of cytoplasmic material in dendrites and somata is thicker than that in axon terminals and contains distinct electron-dense sub-units. Regular synaptic junctions may be situated like islands within the territory of an asymmetrical filamentous contact, and small spot-like close membrane appositions resembling gap junctions are occasionally seen in the fenestrae adjacent to the strands of both varieties of contact. Bundles of neurofilaments running in different directions, but in a plane parallel to the plasma membrane, are prominent on either side of the symmetrical filamentous contact and on the dendritic side of the asymmetrical variety. The agranular reticulum also exhibits differences between the contact types. Because of their highly specialized ultrastructure and specific distribution, filamentous contacts probably do not serve a purely adhesive function. Their possible role in the establishment and maintenance of orderly connections between cells is discussed but not favoured. Filamentous contacts probably mediate some form of intercellular communication, possibly involving gap junctions.

Key words: Thalamus – Intercellular junctions – Synapse – Synaptic glomeruli – Agranular endoplasmic reticulum – Rat (Wistar)

Introduction

Intercellular adhering junctions associated with accumulations of paramembranous electron-dense material are generally classified into two basic categories: (1) the actin-microfilament-anchoring zonulae, fasciae and puncta adherentia and (2) the intermediate-filament-anchoring desmosomes. Rose et al. (1995) have recently reported that adhering junctions in cerebellar synaptic glomeruli differ fundamentally in their composition from other adhering junctions and do not fall into either of the two established categories. Their findings raise the possibility that adhering junctions are in reality a much more heterogeneous family of junctions (in terms of molecular organization and function) than is generally supposed and that the current classification could be an oversimplification.

In this context, we should like to direct attention to another specific and highly specialized class of intercellular junctions, the filamentous contact, the ultrastructure of which differs from that of most microfilament-anchoring junctions. Filamentous contacts are found in great abundance in thalamic relay nuclei. They were first identified and named by Colonnier and Guillery (1964) who described filamentous contacts as asymmetrical specializations between the terminals of retinal (optic) afferents and dendrites in the dorsal lateral geniculate nucleus (LGd) of the monkeys and as being characterized by (1) irregular (i.e. undulating) membranes with patches of electron-dense granular material along the cy-

toplasmic aspect of the dendritic plasma membrane, (2) the absence of presynaptic dense projections and (3) a concentration of neurofilaments in the dendritic cytoplasm below the paramembranous dense material. They interpreted the filamentous contact as a special variety of synaptic junction, perhaps concerned in the formation and maintenance of orderly contacts between retinal axons and geniculate neurons. Later, on the basis of further observations on cat LGd, Guillery (1967) described the presence of electron-dense material along the cytoplasmic aspect of the axonal plasma membrane and of intercellular dense material and extended the class of filamentous contacts to include similar specializations between two dendrites, at which paramembranous dense material and neurofilaments were symmetrically disposed on the two sides of the junction. These he referred to as symmetrical filamentous contacts.

These specializations have since been observed and commented upon in numerous studies of thalamic nuclei in various species, although they have not always been designated as filamentous contacts (see below, for references). The important additional features that have subsequently emerged concerning the organization of the filamentous contact are that it is arranged as an extensive lattice-like reticulum, and that it is associated with systems of agranular reticulum on either side of the interface (Lieberman and Spacek 1971; Brückner et al. 1972; Brauer et al. 1974; Spacek and Lieberman 1974, 1977; Kadota and Kadota 1979). In the present paper, we provide comprehensive details of the distribution, fine structure and three-dimensional organization of the asymmetrical and symmetrical filamentous contacts in relay nuclei of the rat thalamus and describe the associated systems of agranular reticulum and the relationships between asymmetrical filamentous contacts and synaptic contacts.

Materials and methods

Observations were made principally in three dorsal thalamic nuclei, the pars externa of the ventrobasal nucleus (VB), the pars lateralis of the posterolateral complex and the LGd, in young adult rats (Wistar) (body weight: 150–200 g). Most of the animals were perfused (under ether anaesthesia) through the left cardiac ventricle with a phosphate-buffered mixture of 4% paraformaldehyde and 0.5 % glutaraldehyde. Additional animals were perfused with 3% glutaraldehyde in phosphate buffer or with aldehyde mixtures of various composition in phosphate or cacodylate buffers. After postfixation in 1% or 2% osmium tetroxide in the appropriate buffer, tissue blocks from or including the selected nuclei were dehydrated through an ethanol series, stained in 1% uranyl acetate in absolute ethanol, passed through propylene oxide and embedded in Araldite, Durcupan or Epon-Durcupan.

In addition, blocks of VB were taken from unfixed brains removed rapidly from anaesthetized animals and immersed in 0.6% veronal-acetate-buffered potassium permanganate for 30 min. These specimens were treated subsequently like the aldehyde-osmium fixed specimens but block-staining in uranyl acetate was omitted.

Ultrathin sections were stained with uranyl acetate and lead citrate or with lead citrate alone and were examined in Siemens Elmiskop 1B, Philips 300 and Tesla BS 513 or 500 electron microscopes. More than 500 filamentous contacts were analysed.

Several reconstructions of filamentous contacts were made from series of 10–60 sections (see Spacek and Lieberman 1974; Spacek 1994). Series of sections perpendicular to the interface were used to confirm the reticular organization of the contact but accurate reconstructions from such series were difficult to achieve, because even the slightest compression defect displaced the strands relative to one another in adjacent sections. Moreover, the absence of internal reference guides in such an irregular reticulum, with strands whose width was in the same range as the section thickness, made reliable reconstruction onerous.

Results

Terminology

Non-synaptic specialized interneuronal junctions in rat thalamus fall into two broad classes: (1) puncta adherentia, which are small symmetrical plaque-like specializations (most common synonym: attachment plate or plaque; Gray 1961), have been described in all parts of the nervous system (Peters et al. 1991) and will not be considered further here; (2) filamentous contacts, so-called because of the conspicuous neurofilaments in the cytoplasm adjacent to them (Colonnier and Guillery 1964; Guillery 1967; Guillery and Collonier 1970). Over the years, they have been observed and referred to by numerous authors under a variety of other names, viz. dendritic attachment plaques (Szentágothai 1963), specialized contacts of type S (Karlsson 1966, 1967), non-synaptic interneuronal specializations (Pappas et al. 1966), desmosome-like specializations, desmosomoid attachment plaques or desmosomic contacts (Pappas 1965; Ralston and Herman 1969; Morest 1971; Hajdu et al. 1974; Rinvik and Grofova 1974; Harding and Powell 1977), maculae adherentes (Rinvik and Grofova 1974), adhesion plaques (Peters and Palay 1966; Jones and Powell 1969; Herman and Ralston 1970; Jones and Rockel 1971), symmetrische Kontaktzonen (Brückner et al. 1972) and non-synaptic symmetrical contacts or non-synaptic contact zones (Wong-Riley 1972; Mathers 1972). We prefer the original term, filamentous contacts, because this term aptly describes one of the conspicuous features of these specializations and because many of the other terms have been used promiscuously to designate both these and other, morphologically distinct, membrane specializations. As stated by Guillery (1967), filamentous contacts fall into two groups, those in which the paramembranous differentiations are asymmetrical (asymmetrical filamentous contacts) and those with a symmetrical organization (symmetrical filamentous contacts).

Location of filamentous contacts

The principal sites of filamentous contacts in thalamic relay nuclei are summarized in Fig. 1. In all nuclei, the filamentous contacts are most commonly observed within the glial-ensheathed clusters of neuronal processes referred to as synaptic glomeruli (Spacek and Lieberman 1974). Asymmetrical filamentous contacts (Figs. 1–15)
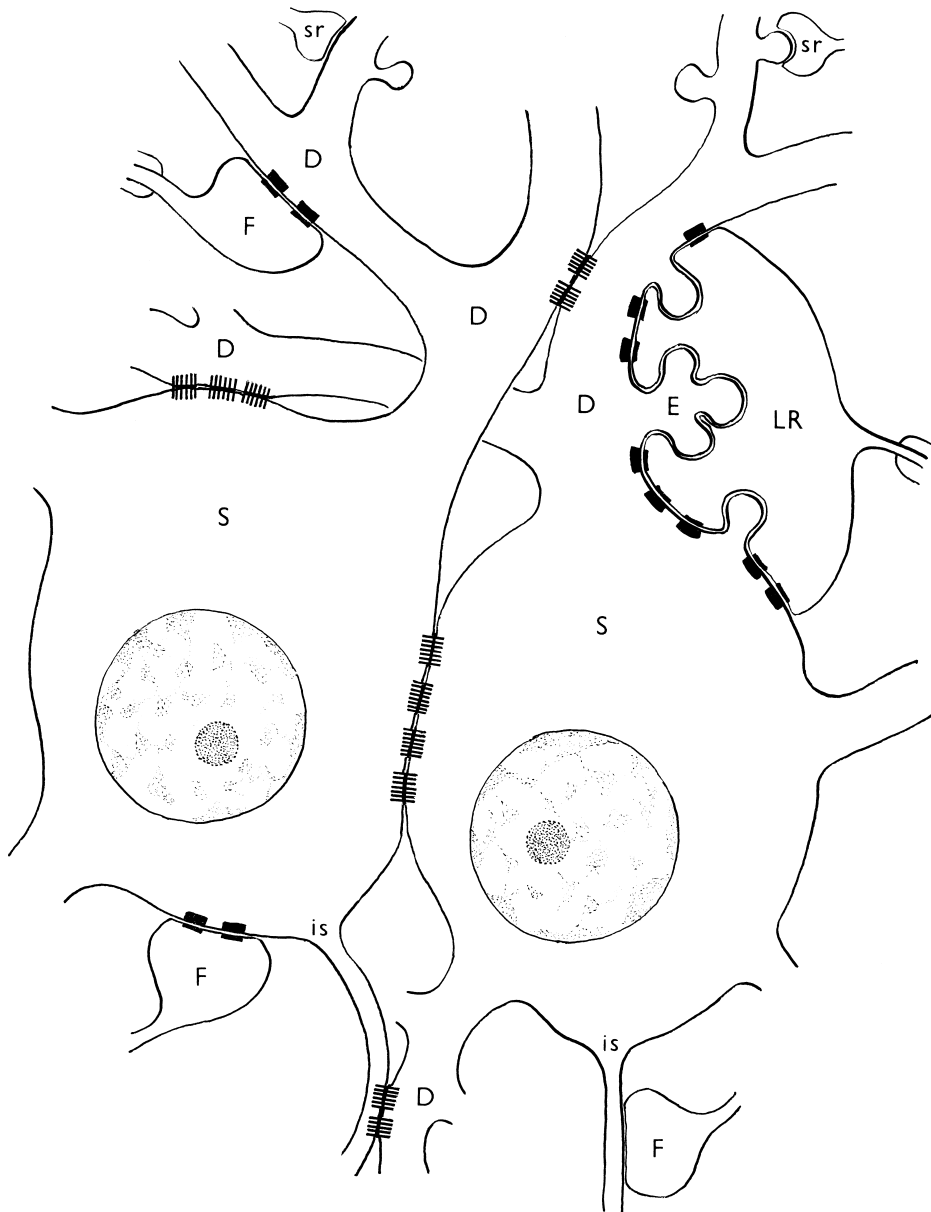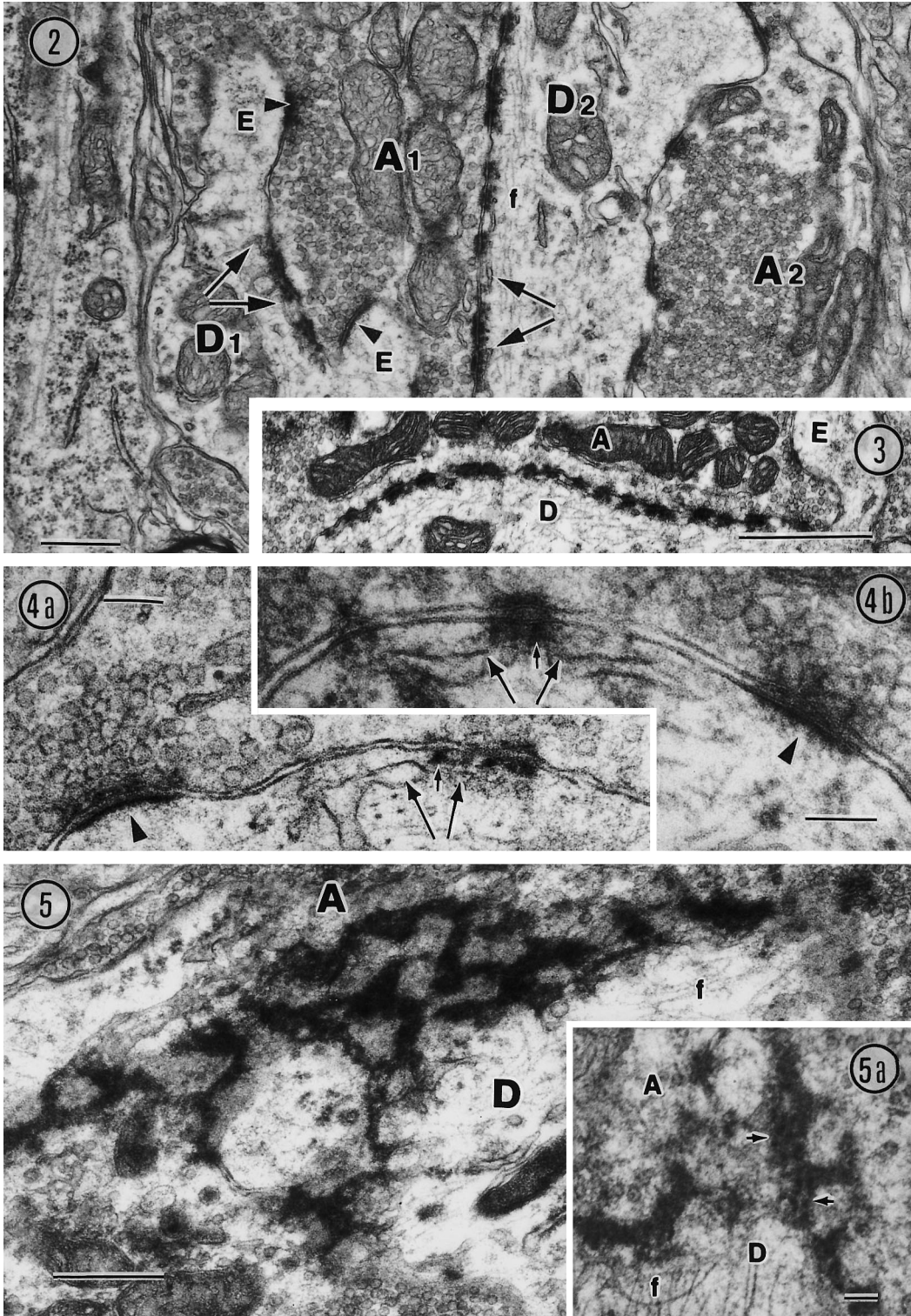
vesicle-containing axon terminals of the extraglomerular neuropil.

It is important to emphasize that asymmetrical filamentous contacts are formed exclusively between axon terminals and dendrites and only very rarely indeed between neural elements other than specific afferent terminals and proximal dendritic shafts of TCR cells at the sites of synaptic glomeruli. The symmetrical variety, in contrast, always involve dendrite-dendrite, soma-soma or dendrite-soma appositions. The initial segment-dendrite filamentous contact is also of the symmetrical type.

Asymmetrical filamentous contacts

General ultrastructural characteristics and three-dimensional arrangement. Filamentous contacts are almost invariably found along the interface between the axon terminals of specific afferents and the shaft of TCR cell dendrites at the sites of synaptic glomeruli and, in sections cut perpendicular to this interface, appear as a series of short specialized stretches, the individual components of which display a superficial similarity to adherens-like junctions or synaptic contacts (Figs. 2, 3, 6–9). Since the axon terminals are often very large, it is common in such planes of section to encounter filamentous contacts extending over several micrometers (e.g. Fig. 3). One such contact, along the interface between a dendritic shaft in VB and an elongated sausage-like lemniscal terminal, was 7 μm long in a single section, with 20 discrete specialized patches.

The criteria for distinguishing synaptic contacts from filamentous contacts are clearcut and unambiguous where membranes are cut perpendicularly. (1) Filamentous contacts are seldom associated with synaptic vesicles and even when vesicles are present in the immediate vicinity, they do not cluster around the axonal paramembranous dense material as at synaptic contacts (Figs. 2–4). (2) Synaptic contacts show apparently irregularly spaced distinct conical densities with their bases applied to the axon terminal plasma membranes (presynaptic dense projections). (3) The postsynaptic density at synaptic contacts is generally a continuous plaque-like structure with no obvious substructure. Synaptic and filamentous contacts are most readily compared when they occur side by side along the same interface (Figs. 4a, b). The length of the individual specialized stretches is variable, but in the range 60 nm to 800 nm, with most being in the lower part of the range. The interval between individual specializations is also variable but there are usually between 3 and 5 specializations per micrometer of interface. This variability in length and spacing of perpendicularly cut specializations is readily explained when the three-dimensional organization of the filamentous contact is reconstructed from serial sections (Figs. 19, 20) and from sections cut in the plane of or tangential to the interface (Figs. 5, 10). These sections reveal that the individual specializations seen in perpendicular sections are parts of an extensive continuous reticular contact. The anastomosing strands of the filamentous contact are usually 60–90 nm wide (but sometimes much thinner) and the fenestrae (areas of unspecialized apposition in the perpendicular sections) are irregular in size and shape, but commonly 120–270 nm in diameter. The lengths of individual stretches of specialized apposition and of intercalated non-specialized stretches of interface in perpendicular sections thus depends on the size and orientation, with respect to the plane of section, of the strands of the filamentous contact and the fenestrae enclosed by them.

Intermembranous and paramembranous dense material. The intercellular cleft between the specialized portions of the membranes is wider than usual (commonly 22–30 nm) and contains a finely granular electron-dense material, within which a thin, slightly more electron-dense band can sometimes be resolved, running parallel to the plasma membranes and approximately mid-way between them (Figs. 4b, 7, 8, 12). The paramembranous electron-dense cytoplasmic material extends on either side of the contact but in an asymmetrical manner, extending much deeper into the dendritic cytoplasm than into the axonal cytoplasm (approximately 30 nm vs 20 nm). This difference, which is seen very clearly in Figs. 2, 4, 6 and 8, allows such filamentous contacts to be classified as asymmetrical.

The paramembranous dense material is inhomogeneous: it comprises finely granular and filamentous material, which sometimes appears to consist of linear densities perpendicular to the plasma membrane, giving it a striated appearance, and within which are dispersed more electron-dense subunits (Figs. 4, 6–8). Sometimes, these subunits are globular or granular, about 20–30 nm in diameter, as originally described by Colonnier and Guillery (1964). Others appear to be bar-like and some have a more complex form (e.g. in Fig. 4a, b, small arrows indicate densities that appear to be tack-like, with a broad flat head facing outward and narrower neck in contact with the plasma membrane). These various "subunits" are more conspicuous on the dendritic side than on the axonal side of the contact and, in tangential sections, sometimes appear to be arranged in a hexagonal lattice with a centre-to-centre spacing of approximately 40 nm (Fig. 5a).

Fig. 2. Part of a synaptic glomerulus in rat LGd. Two dendrites (*D1*, *D2*) are associated with two large axon terminal profiles (*A1*, which is almost certainly a retinal afferent terminal, and *A2*), and both dendrites establish asymmetrical filamentous contacts with *A1*. Note that the excrescences (*E*) invaginating *A1* from *D1* make synaptic contacts (*arrowheads*) rather than filamentous contacts, and that neurofilaments (*f*) and agranular reticulum (*arrows*) are concentrated below the contact zones in both dendrites. ×24 000. *Bar:* 0.5 μm

Fig. 3. Extensive asymmetrical filamentous contact between a large presumptive lemniscal afferent axon terminal (*A*) and the primary dendrite (*D*) of a projection neuron in VB. Note the cluster of mitochondria in the axon terminal and the sheet of agranular reticulum enclosing them on the side facing the contact. A postsynaptic excrescence (*E*) protrudes from the dendrite. ×20 000. *Bar:* 1.0 μm

Fig. 4 a, b. Differences between axo-dendritic filamentous and synaptic contacts. Note the clustering of vesicles and the continuous postsynaptic densities at the synaptic contacts (*arrowheads*) and the dendritic agranular reticulum (*arrows*) and neurofilaments associated with the filamentous contacts. Some of the paramembranous electron-dense subunits on the dendritic side resemble a tack with the head facing into the dendritic cytoplasm (e.g. at *small arrows*). **a**, ×80 000; **b**, ×120 000. *Bars:* 0.1 μm

Fig. 5, 5a. Tangentially sectioned asymmetrical filamentous contacts between lemniscal axon terminals (*A*) and projection cell dendrites (*D*) in VB. The reticular arrangement of the filamentous contact is apparent (especially in **Fig. 5**) and so too is the presence of more electron-dense subunits in the paramembranous dense material (e.g. *arrows* in **Fig. 5a**). *f*, Neurofilaments. *Bars:* 0.5 μm in **Fig. 5** (×35 000) and 0.1 μm in **Fig. 5a** (×50 000)

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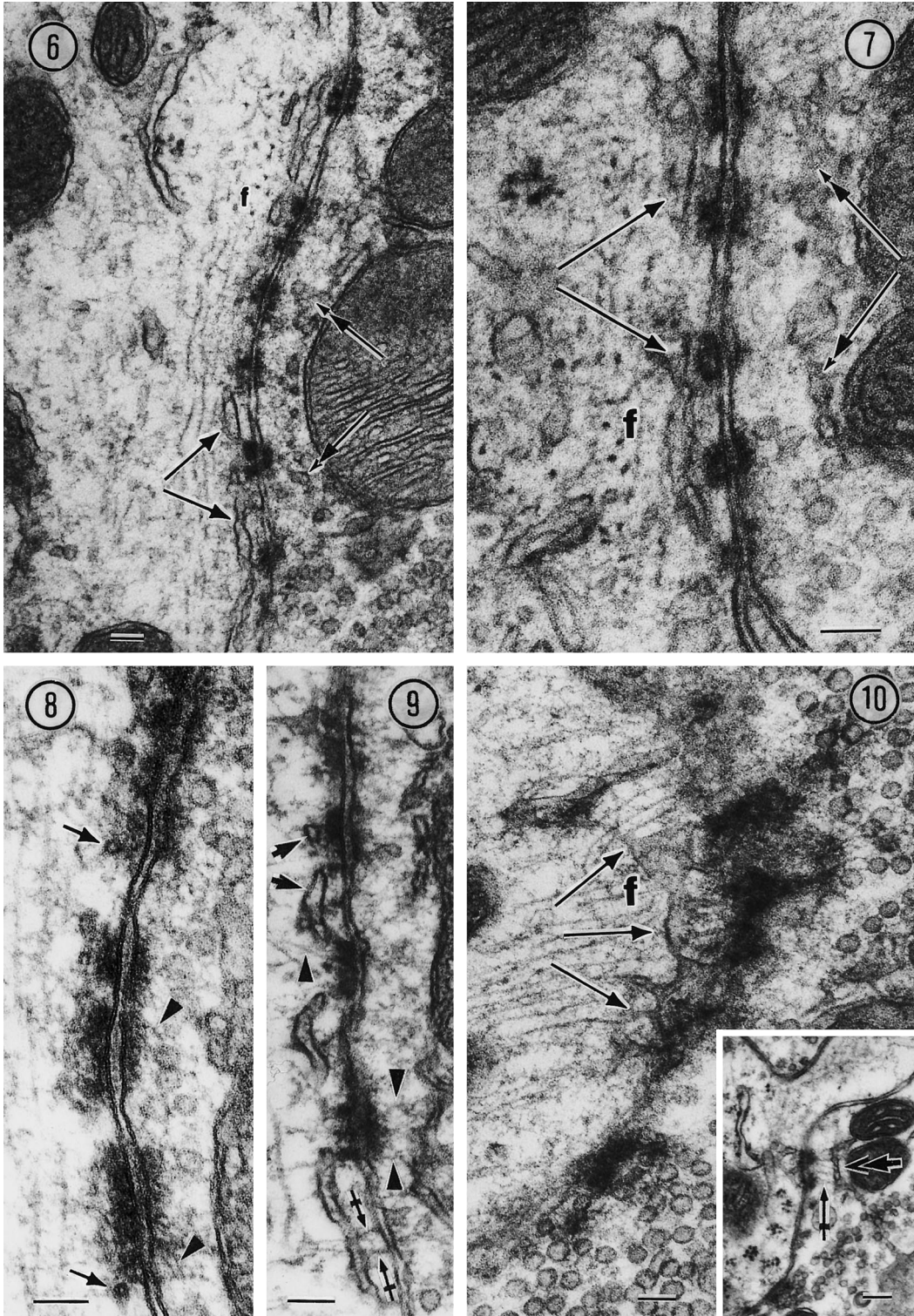
Figs. 6–10. Asymmetrical filamentous contacts in rat VB between projection cell dendrites and presumptive lemniscal axon terminals. The axon terminals are to the *right* in all figures. Electron-dense material is present in the intercellular cleft at the level of the paramembranous specializations (see especially **Figs. 7**, **8**). Note the very small diameter tubules of the dendritic agranular reticulum (*arrows*) in **Figs. 7** and **10** and the anastomosing elements in **Fig. 10** where the interface is cut tangentially. *Double-headed arrows*, Axonal agranular reticulum; *f*, dendritic neurofilaments. Note the smaller filaments, which appear to run perpendicular to the neurofilaments and to insert into the dense material on the dendritic side (*arrowhead* to the *left* of **Fig. 9** and see **Figs. 11, 12**) and similar microfilaments on the axonal side of the contact in **Figs. 8** and **9** (*arrowheads*). In **Figs. 9, 10**, and *inset*, note the thicker filaments (*crossed arrows*) that run between agranular reticulum elements and the dendritic plasma membrane (**Fig. 9**) or the paramembranous dense material on the axonal side of a filamentous contact (**Fig. 10**, *inset*). *Bars:* 0.1 μm. **Fig. 6** ×50 000; **Fig. 7** ×100 000; **Fig. 8** ×90 000; **Fig. 9** ×70 000; **Fig. 10** ×60 000; *inset* ×40 000
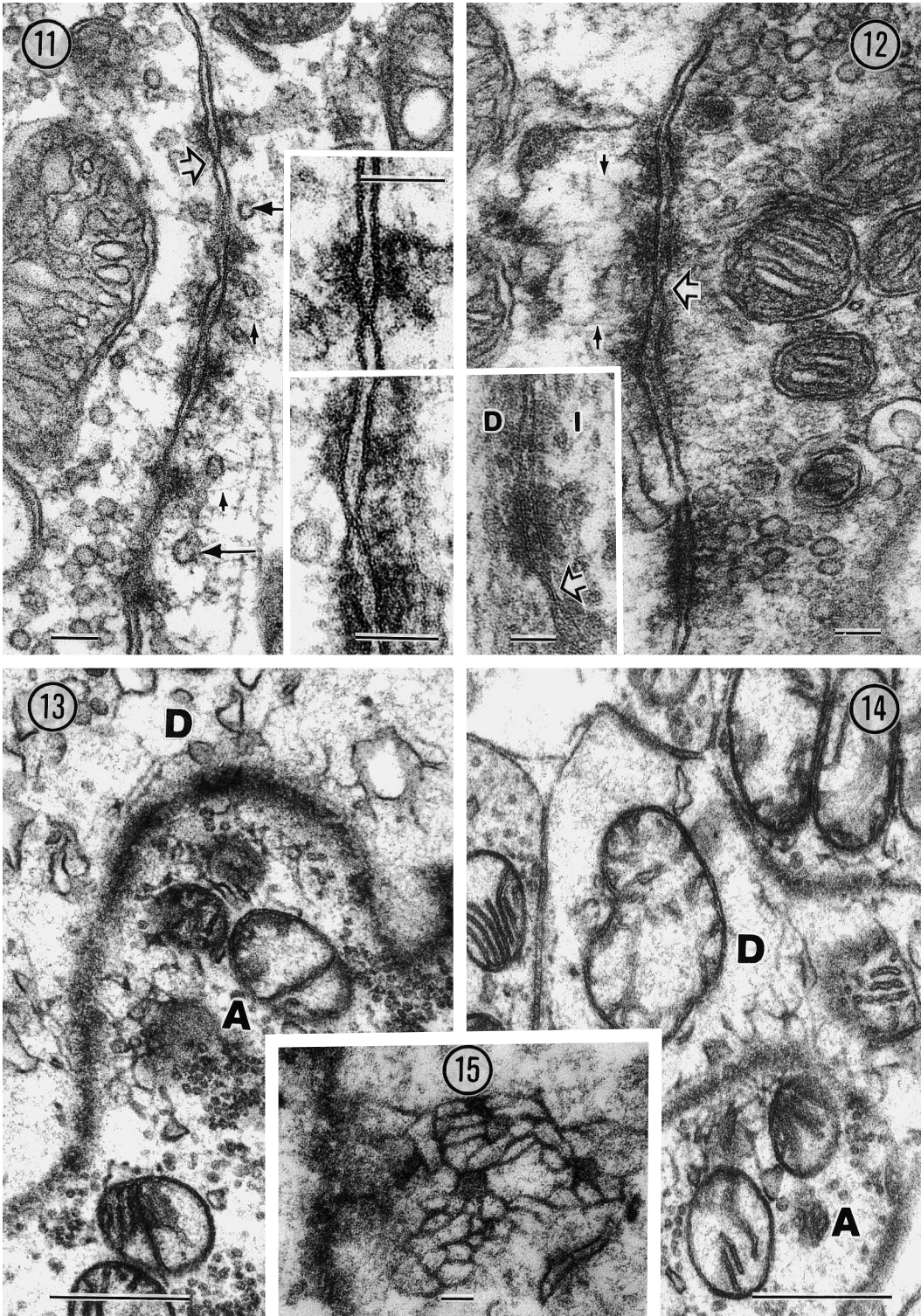
Figs. 11, 12. Spot-like regions of close apposition (*open arrows*) between axonal and dendritic plasma membranes in the interstices of the filamentous contact reticulum. *Insets* to **Fig. 11** show an enlargement of the arrowed apposition (*above*) and a similar close apposition from another specimen (*below*). *Inset* to **Fig. 12** shows part of a symmetrical filamenous contact between an axon initial segment (*I*) and a projection cell dendrite (*D*), which also exhibits a spot-like close membrane apposition (*open arrow*). *Bars:* 0.1 μm; ×70 000

Figs. 13, 14. Semi-tangentially sectioned asymmetrical filamentous contacts between large axon terminals (*A*) and dendrites (*D*) in VB. Tissue fixed with potassium permanganate. Fenestrated agranular reticulum is prominemt in both the axonal and dendritic components in **Fig. 14** and in the axon terminal in **Fig. 13**. *Bars:* 0.5 μm; ×42 000

Fig. 15. Tangential section of permanganate-fixed material showing an extensive array of dendritic agranular reticulum with narrow tubular elements and larger cisternal components. *Bar:* 0.1 μm; ×50 000

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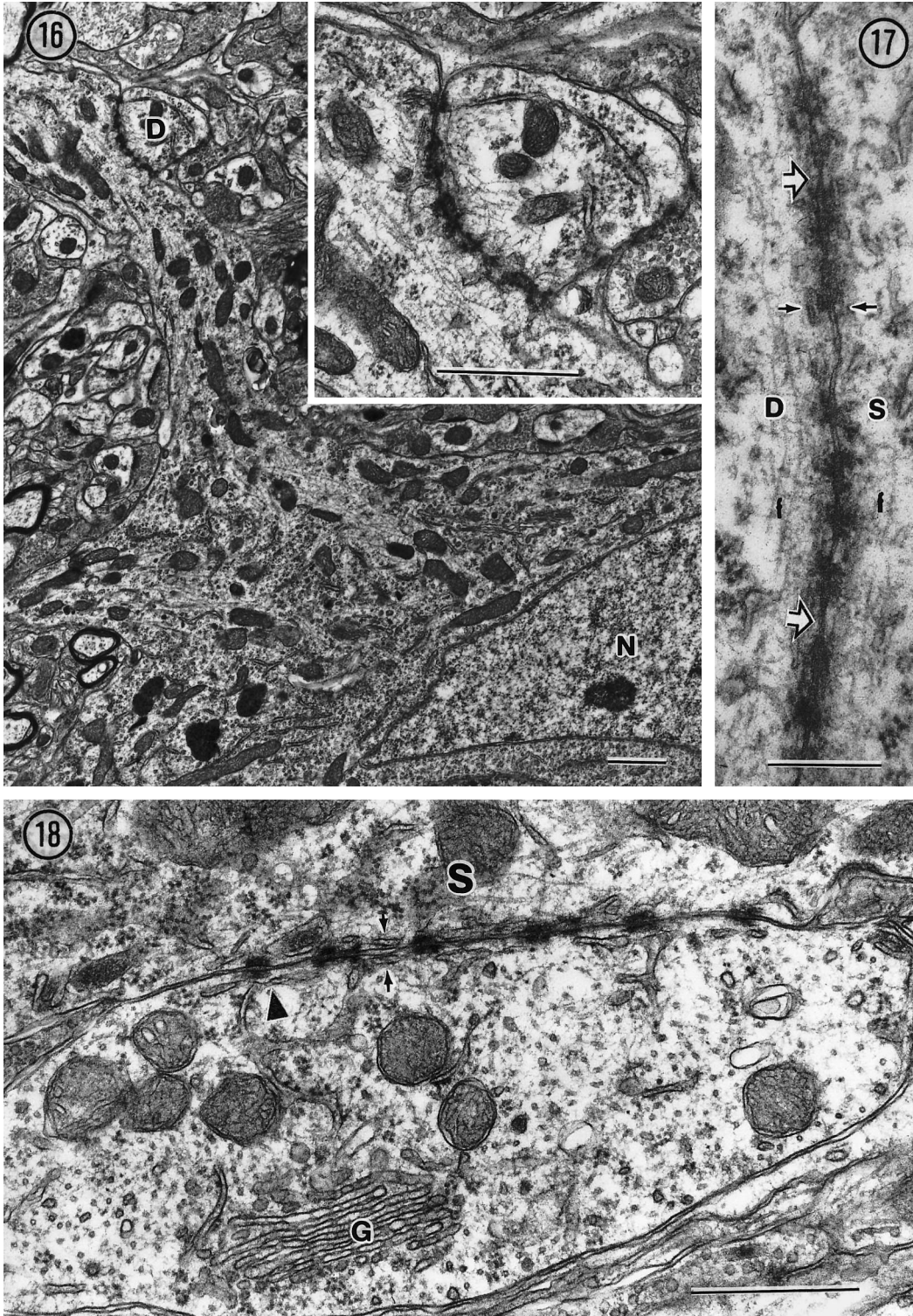
Fig. 16. Symmetrical filamentous contact, cut slightly obliquely, between the primary dendrite of a projection cell in mouse LGd and another similar dendrite (*D*). N, Nucleus. ×9000. *Inset*: Note the dense mat of neurofilaments on either side of the contact. Bar: 1 μm; ×20 000

Fig. 17. Symmetrical filamentous contact between the soma (*S*) and large proximal dendrite (*D*) of two projection neurons in VB. Note the neurofilaments (*f*), agranular reticulum (*arrows*) and areas of close membrane apposition (*open arrowheads*). Bar: 0.5 μm; ×33 000

Fig. 18. Symmetrical filamentous contact between a projection cell soma (*S*) and a large dendrite in LGd. The paramembranous densities are the same thickness on either side of the contact and the elements of agranular reticulum (*arrows*) are symmetrically disposed. *Arrowhead*, Paramembranous element of the agranular reticulum continuous with a more deeply situated granular reticulum. *G*, Golgi apparatus. *Bar:* 0.5 μm. ×50 000
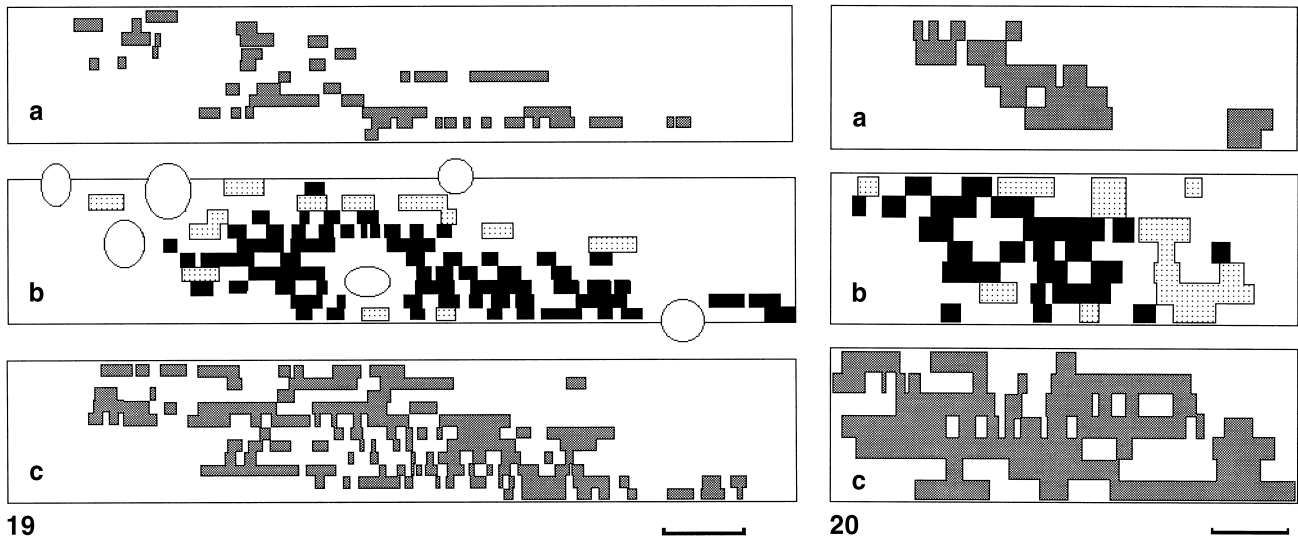
Figs. 19a-c, 20a-c. Reconstructions demonstrating, at three levels, the two-dimensional organization of filamentous contacts, synapses and endoplasmic reticulum at areas of intercellular contact between the dendritic shaft of a TCR neuron and a large principal axon terminal (**Fig. 19**) and between the same dendritic shaft and an axon terminal containing flattened vesicles (**Fig. 20**) in rat VB. The reticular arrangement of non-synaptic asymmetrical filamentous contacts (*black*) and their continuity with true synaptic contacts (*dotted*) is shown at the level of the interneuronal junction (**b**). *Empty rectangular area*, Non-specialized interneuronal contact. Circular origins of necks of dendritic spines are also visible in **Fig. 19b**. An extensive network of agranular reticulum (*grey*) lies just below the postsynaptic side of the contact (**c**). A similar but much less extensive network of agranular reticulum is apparent on the presynaptic side (**a**). *Bars:* 0.5 μm in **Fig. 20**, 0.4 μm in **Fig. 20**

Close membrane apposition. The plasma membranes of the axons and dendrites linked by filamentous contacts are kept apart and are parallel within the areas of paramembranous dense material. However, in the interstices of the reticulum, particularly at its margins, they commonly approach one another closely and small spot-like areas of close membrane apposition (Brightman and Reese 1969), resembling gap junctions, may be established (Figs. 11, 12, open arrows). Close appositions of this kind have not been seen at filamentous contacts of flat-vesicle-containing terminals but are occasionally observed at symmetrical filamentous contacts (Fig. 17) and at a filamentous contact between a dendrite and an axon initial segment (inset, Fig. 12).

Filaments. Neurofilaments (diameter 9–10 nm) are usually conspicuous on the dendritic side of the contact (Figs. 2, 3, 6). They run in a plane roughly parallel to the specialized plasma membrane. The predominant orientation of the neurofilaments is parallel to the long axis of the dendrite. Usually, however, neurofilaments coursing at 90° or other angles to the main bundle can also be identified (e.g. in Figs. 6, 7 and in the tangentially sectioned contacts in Figs. 5, 5a, 10) suggesting that some neurofilaments may change direction in the bundle.

Other finer filaments (5 nm or less in diameter) are also associated with both sides of the specialization and these microfilaments commonly appear to insert into the paramembranous dense material (e.g. arrowheads, Figs. 9, 11, 12). Occasionally, filaments of indeterminate character can be observed linking agranular reticulum elements to the paramembranous dense material or adjacent plasma membrane in the vicinity of a filamenous con-

tact. An example from the dendritic side is shown in Fig. 9 and from the axonal side in Fig. 10 (inset).

Agranular reticulum, mitochondria and multitubular bodies. Neural elements linked by filamentous contacts contain elaborate systems of agranular reticulum, the tubular and cisternal components of which run in a plane approximately parallel to the interface. In the case of asymmetrical filamentous contacts, the agranular systems are distinctly different on the two sides of the apposition. On the dendritic side, the agranular reticulum is situated close to the dendritic plasma membrane and immediately deep to the paramembranous dense material (e.g. Figs. 2–4, 6–9). The component elements are predominantly tubular, although cisternal elements, some of which are fenestrated, are also present. Most of the tubules are small (average diameter 50 nm) but many are approximately the same diameter as, or even smaller than, microtubules (Figs. 8, 10, 15). The tubules and cisterns are extensively interconnected to comprise a true reticulum, which is especially striking in tangential sections (Fig. 10), particularly in material fixed in permanganate (Figs. 13–15) or in reconstructions from serial sections (Figs. 19, 20). The paramembranous reticulum is continuous with other components of the agranular reticulum in the dendrite (Figs. 4a, 12, 14) and continuities have also been observed between this agranular reticulum and the outer membranes of mitochondria, which commonly appear to be concentrated in those portions of the dendritic shaft associated with filamentous contacts. Continuities could be traced between the agranular reticulum and the component tubules of multitubular bodies, which are highly specialized forms of the endoplasmic
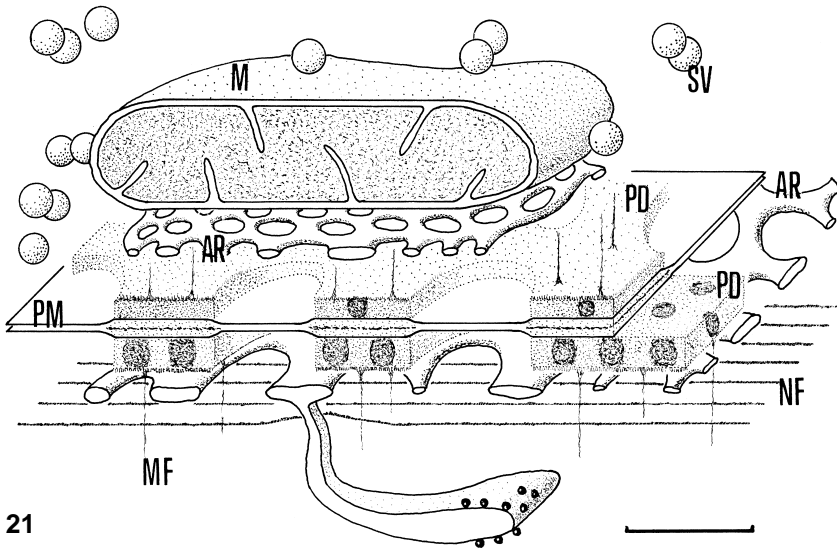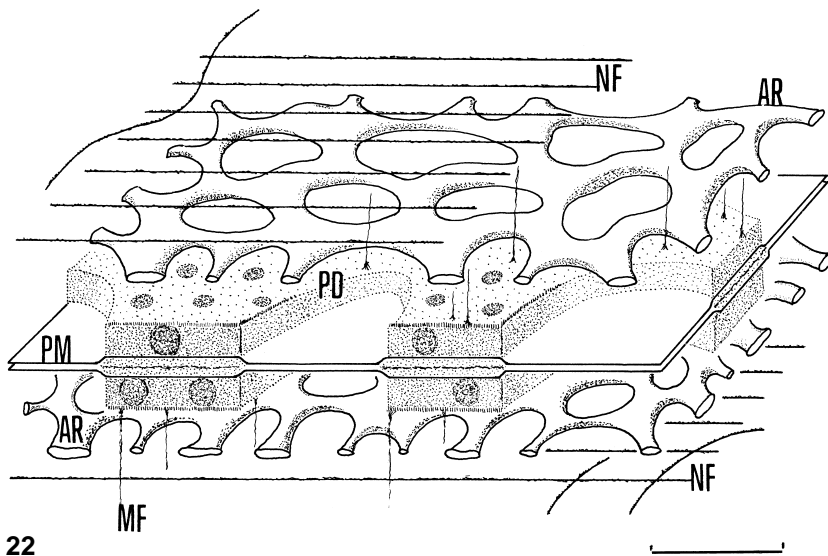
Figs. 21, 22. Diagrams summarizing the essential features of the asymmetrical filamentous contact (**Fig. 21**) and of the symmetrical filamentous contact (**Fig. 22**), based on observations of individual and serial sections in perpendicular and tangential planes. *AR*, Fenestrated cisterns and tubules of agranular reticulum in axon terminal and/or dendrites; *PD*, paramembranous electron-dense material in axon terminal and/or dendrites containing globular sub-units; an intercellular electron-dense material is arranged in register with the paramembranous densities; *MF*, microfilaments that appear to insert into the paramembranous dense material; *NF*, neurofilaments in the dendritic component(s) of the filamentous contacts run parallel to the interface; *SV*, synaptic vesicles; *M*, mitochondria; *PM*, plasma membrane. *Bar:* 0.2 μm

reticulum found in the cell bodies of TCR cells, and in their dendrites close to the sites of synaptic glomeruli (Lieberman et al. 1971). A comparable relationship between "adhesion plaques" and cytoplasmic laminated bodies (another form of modified endoplasmic reticulum) has been described in cat VB and posterior thalamic nuclei by Herman and Ralston (1970).

On the axonal side, the agranular elements are similar and again interconnected to constitute a reticulum (Figs. 7, 13, 14, 19, 20). Fenestrated cisterns are more commonly seen on the axonal side than on the dendritic side. Furthermore, the axonal reticulum consistently lies further from the contact zone than is the case for the dendritic reticulum (Figs. 6, 7). In addition, the axonal agranular reticulum elements tend not to be co-extensive with the filamentous contact but with the prominent cluster of mitochondria, which generally occupies the central portion of the specific afferent axon terminal (Figs. 2, 6, 7). In other words, the axonal reticulum is arranged as a loose and incomplete sheet around the part

of the periphery of the mitochondrial cluster that faces the filamentous contact. Although synaptic vesicles fill most parts of the axon terminal, few of them lie in the axoplasmic territory between the filamentous contact and the sheet of axoplasmic agranular reticulum (Figs. 2, 6, 7).

Relationships between filamentous and synaptic contacts. Although, as stated earlier, synaptic contacts between specific afferents and TCR cells are established principally on the dendritic excrescences of the latter, synaptic contacts are occasionally made on the dendritic shaft (Fig. 4a, b). Reconstructions of the interface in such cases show that the synaptic contacts are plaque-like and are enmeshed within the territory of a filamentous contact (Fig. 19). In the case of F-axons, synaptic contacts are normally made with the dendritic shaft and here again the synaptic contact may lie within or at the edges of an area of interface linked by a filamentous contact (Fig. 20).

Symmetrical filamentous contacts

These contacts (Figs. 16–18) are symmetrical not only with the respect to the paramembranous dense material but also with respect to the form and position of the neurofilaments and the sheets of agranular reticulum that lie equidistant from the specialized membranes (Figs. 17, 18). Most of the agranular reticulum appears to be in the form of larger and less conspicuously fenestrated cisterns than are usual at asymmetrical filamentous contacts. There is a further, slightly different sense in which they are also symmetrical, viz. they are established between similar parts of similar cells (i.e. the proximal dendrites and cell bodies of TCR cells). However, like the asymmetrical filamentous contacts, they comprise an often extremely extensive reticular contact and, in perpendicular section, the individual stretches of specialized membrane display variable length and spacing (Figs. 17, 18, 20). The essential similarities and differences between asymmetrical and symmetrical filamentous contacts are summarized in Figs. 21 and 22.

Discussion

Differences between asymmetrical and symmetrical filamentous contacts

Symmetrical and asymmetrical filamentous contacts exhibit many similarities and should probably be classified as varieties of intermediate junctions. Both are arranged in a lattice-like reticulum and show a similar arrangement of cleft and paramembranous dense material. In addition, the arrangement of neurofilaments and microfilaments and of agranular reticulum on the dendritic side of the asymmetrical contact is similar to that on both sides of the symmetrical contact. The principal difference between them is that the symmetrical filamentous contact is made between two similar neuronal processes and the asymmetrical contact between two dissimilar neuronal elements, viz. an axon terminal and a dendrite. The asymmetry in the latter case arises because, in the axon terminal, (1) the sheet of paramembranous dense material is not as wide as that in the dendrite, (2) there are no neurofilaments in the cytoplasm below the paramembranous thickenings and (3) the agranular reticulum lies further from the contact zone than is the case on the dendritic sides of the junction. Whether or not the differences in structure between symmetrical and asymmetrical filamentous contacts are reflected in functional differences between them is impossible to say, since the function of both varieties is at present obscure (see below).

Are filamentous contacts a specific feature of thalamic nuclei?

Non-synaptic interneuronal specializations characterized by the presence of electron-dense material on the cytoplasmic surfaces of apposed plasma membranes separated by a cleft of normal or increased width are widespread in the nervous system (Gray and Guillery 1966; Peters et al. 1991). For the most part, they appear to be simple plaque-like specializations, best classified as puncta adherentia, and are formed between almost any parts of contiguous nerve cells, between contiguous nonneuronal cells and between neurons and nonneuronal cells. At certain sites, however, specializations resembling puncta are particularly common and series of them may be observed along extensive appositions between nerve cells; these specializations show some similarities to perpendicularly sectioned interfaces with filamentous contacts. For example, extensive somato-somatic specializations of this sort occur between cells in the mesencephalic trigeminal nucleus (Hinrichsen and Larramendi 1968; Imamoto and Shimizu 1970) and other regions (e.g. Reid et al. 1975: red nucleus) and between large dendrites in the inferior olive of the cat (e.g. Sotelo et al. 1974). Punctum adherens-like junctions are also common wherever large axon terminals contact extensive areas of dendritic or perikaryal membrane (e.g. rabbit hippocampus: Hamlyn 1962; rat lateral vestibular nucleus: Mugnaini et al. 1967; Sotelo and Palay 1970; lamprey vestibular nuclei: Stefanelli and Caravita 1970; goldfish tangential (vestibular) nucleus: Hinojosa 1973; deep cerebellar nuclei: Angaut and Sotelo 1973; avian ciliary ganglion: Cantino and Mugnaini 1975), particularly along interfaces that are also characterized by the presence of chemical synapses and gap junctions (Sotelo and Palay 1970; Hinojosa 1973; Cantino and Mugnaini 1975; Sotelo and Korn 1978).

In none of the above studies, however, is a reticular character of the junctions or the subunit structure of the paramembranous material of the dendritic component(s) demonstrated and associated systems of agranular reticulum and neurofilaments either are not apparent or are much less conspicuous than at filamentous contacts in the thalamus. At the moment, therefore, but pending further detailed study of such non-synaptic membrane specializations at other sites, it is reasonable to conclude that filamentous contacts are either specific features of certain thalamic nuclei or, at least, are more common and more highly differentiated therein than elsewhere in the nervous system.

Functional considerations

We have no basis at present for deciding whether the structural dissimilarities between asymmetrical and symmetrical filamentous contacts are of any significance in functional terms, whether they are associated with substantially different functions, or whether they indicate a similar mode of functional interaction but one that is polarized or unidirectional at the asymmetrical contacts. Therefore, we shall consider the possible functions of both together in the following discussion. The two principal suggestions that have been made concerning the possible roles of filamentous contacts are: (1) that they have a mechanical role (Colonnier and Guillery 1964; Pappas et al. 1966); (2) that they are concerned in the

formation and maintenance of specific orderly connections between nerve cells (Colonnier and Guillery 1964; Guillery 1967).

Filamentous contacts as mechanical devices. The supposed mechanical role of filamentous contacts (and of other adherens-like junctions) is usually expressed in terms of an adhesive function. It is, however, difficult to understand why there should be a special requirement for adhesiveness between only certain elements in different types of neuropil. For example, filamentous contacts do not occur between contiguous axon terminals and, whereas filamentous contacts link large axon terminals to dendrites in the thalamus and similar contacts link large axon terminals to dendrites in the hippocampus, there is no consistent association between the presence of large axon terminals and adhering junctions with dendrites, a striking example being provided by the giant mossy fibre boutons of the turtle cerebellum, which are not characterized by more or larger "desmosomoid attachments" than their smaller counterparts in mammals (Mugnaini et al. 1974). Nor are extensive dendro-dendritic, somato-dendritic, somato-somatic or somato-dendritic appositions invariably linked by filamentous or other adhering contacts (e.g. Kerns and Peters 1974). On the other hand, the asymmetrical filamentous contacts may not be concerned with adhesiveness per se but in the maintenance of complex and possibly precise and functionally important configurations between the neuronal components of synaptic glomeruli. However, filamentous contacts and other adhering junctions are not as frequently observed in other sites containing glomeruli of comparable complexity in the central nervous system, for example the inferior olivary nucleus of cat (Sotelo et al. 1974) and rat (Gwyn et al. 1977) or the dorsal column nuclei of cat (Rustioni and Sotelo 1974) and rat (Tan and Lieberman 1974). The way in which the submembranous neurofilaments, the agranular reticulum and the connections between the latter and multitubular bodies and outer mitochondrial membranes are related to the supposed adhesive role of the junctions is unknown.

Finally, a current view of intermediate junctions is that they are transmitters of active forces between cells via the F-actin filaments inserted into the membrane (Staehelin 1974). However, it is difficult to associate precisely located junctions between specific partners in a deep and mechanically protected part of the brain with such a role. In any case, it has not been established that the microfilaments of filamentous contacts are of the F-actin type.

Filamentous contacts and the formation of specific connections between nerve cells. The possibility that asymmetric filamentous contacts play a role in the establishment and in the subsequent maintenance of precise connections between retinal and geniculate neurons and that, in a similar vein, symmetrical filamentous contacts are concerned in maintaining an orderly arrangement of cells within the geniculate nucleus has been suggested by Colonnier and Guillery (1964) and Guillery (1967). Since relay cells in LGd and the projections to and from

them show a very high degree of topographical organization, as is the case for all thalamic relay nuclei, this proposal is attractive. It is, however, unlikely to be true. For example, the topographical representation of the visual input is as important at the cortical as at the thalamic level but filamentous contacts do not occur in the cortex, where adhering junctions of any kind are rare. Furthermore, there are many other subcortical centres in which synaptic interactions occur between precisely ordered sets of connections in the absence of filamentous contacts or other types of adhering junction. On the other hand, adhering junctions probably play a role in the establishment or stabilization of precise connections between cells during development (Rees 1978) and they may subsequently regress at most sites but remain as a conspicuous feature of the adult organization in thalamic relay nuclei. Unfortunately, the data currently available on the development of synaptic and non-synaptic contacts in thalamic nuclei (e.g. Poppe et al. 1973; Mathews and Faciane 1977; J. Spacek and A. R. Lieberman, unpublished) are unable to tell us whether filamentous contacts appear before, at the same time as, or after synaptic contacts are established by the same elements. According to the study of Aggelopoulos et al. (1989), filamentous contacts in synaptic glomeruli of the rat LGd appear after synaptic junctions have been established. In the rat VB, they seem to be formed simultaneously with synaptic junctions (De Bias et al. 1996).

Nevertheless, adherens-like contacts of a much smaller extent, yet still resembling the main structural scheme of filamentous contacts, have been described over the last few years at adult neocortical and hippocampal axospinous synapses (Spacek 1985, 1987; Anthes and Petit 1995). These studies have shown that the membrane specializations of perforated synapses may be heterogeneous, some regions of the specialized interface being devoid of vesicle accumulations and resembling non-synaptic intermediate junctions of the punctum adherens type. They are usually not separated from, but are continuous with, the specialized interface of the chemical synapse, as shown by serial section analysis (Spacek 1985). A tendency for agranular reticulum, cytoskeletal components and mitochondria to be closely associated is apparent on both the pre- and postsynaptic sides of perforated synapses. This phenomenon has been interpreted as being a possible expression of synaptic plasticity, perhaps reflecting the addition of new material to an expanding synaptic contact. However, it could represent both the synthesizing machinery for the expansion of the synapse and a device for the maintenance of the precise configuration of pre- and postsynaptic elements.

Other possibilities. If filamentous contacts are not involved in the establishment of specific connections between neurons and do not have a purely mechanical function, could they perhaps play some as yet unrecognized role in communication between the neurons that they link? The consistent association of mitochondria and agranular reticulum with the filamentous contacts would certainly agree with the suggestion that some form of energy-dependent interaction occurs between

cells at the sites of filamentous contacts. A close association between mitochondria and cisterns or tubules of agranular reticulum has often been noted in nerve cells (see Peters at al. 1991) but this particular arrangement has not been clearly described in previous studies of asymmetrical filamentous contacts, although it may be readily recognized in many previously published micrographs (e.g. Fig. 8 of Karlsson 1966; Fig. 22 of Pappas et al. 1966; Fig. 7 of Guillery 1967; Fig. 32 of Jones and Powell 1969; Figs. 6, 12 of Guillery and Scott 1971; Fig. 4a of Brückner et al. 1972; Fig. 15b of Rinvik and Grofova 1974; Fig. 3a of Dekker and Kuypers 1976). It should also be noted that a similar arrangement can be seen in published electron micrographs of axon terminals in other regions of the nervous system that engage in the formation of adhering and gap junctions (e.g. Figs. 1, 5, 7, 18, lateral vestibular nucleus, Sotelo and Palay 1970; Fig. 8, motor nucleus of cat spinal cord, McLaughlin 1972; Fig. 16, magnocellular mesencephalic nucleus of a weakly electric fish, Sotelo et al. 1975; Fig. 19, avian ciliary ganglion, Cantino and Mugnaini 1975).

It is, however, extremely unlikely that the filamentous contacts could be involved in the exchange of ions or small molecules between nerve cells. Although it is not yet certain that all low-resistance pathways between cells involve gap junctions (Gilula 1978), there is no evidence that any junctions of the desmosome or adherens-like varieties are involved in such exchanges (Staehelin 1974; Gilula 1978). However, a consistent relationship between gap junctions, which do mediate such exchanges, and adherens-like junctions appears to be present: thus, adherens-like junctions and gap junctions commonly occur along the same interface and often a stretch of gap junction is delimited by puncta adherentia (Sotelo and Palay 1970; Sotelo and Llinas 1972; Sotelo et al. 1974, 1975; Cantino and Mugnaini 1975; Sotelo and Korn 1978). It is interesting, in the context of this common association, to recall the observations of rare spot-like regions of close membrane appositions resembling small gap junctions in the "windows" of the reticulum established by filamentous contacts, and that interneuronal apposition with gap junctions is commonly associated with paramembranous cisterns and vesicles of agranular reticulum (Sotelo and Korn 1978; Kensler et al. 1979). If indeed there are small gap junctions enmeshed by the filamentous contact, freeze-fracture studies should reveal them and, if such is the case, the paramembranous agranular reticulum could possibly have a role in the regulation of calcium ion concentration and thus of junctional permeability (Sheridan 1978). Aggregates of intramembrane particles, 10 nm in diameter, have been identified on the P-face in areas corresponding to the dense material of filamentous contacts in the cat medial geniculate body (Tatsuoka and Kadota 1984). So far, however, no particles typical of gap junctions have been found in this location in freeze-fracture studies. Nevertheless, De Zeeuw et al. (1995) have recently described dendritic lamellar bodies in the rat anterior olive and in other locations; these closely resemble specialized forms of endoplasmic reticulum observed in the

rat thalamus (Lieberman et al. 1971). De Zeeuw et al. (1995) have found them in bulbous dendritic appendages of projection neurons associated with regions in which these neurons form dendro-dendritic gap junctions. The lamellar bodies are specifically labelled by a new polyclonal connexin antiserum alpha 12B/18. Immunoreactivity first appears between postnatal day 9 and 15, i.e. in the period when neuronal gap junctions develop. The above mentioned (or: De Zeeuw et al. (1995)) authors suggest that the labelled lamellar bodies are involved in the synthesis of gap junctions.

Desmosomal or desmosome-like contacts accompanied by microfilamentous bundles, endoplasmic reticulum and/or mitochondria and resembling interneuronal filamentous contacts have been observed by many authors between epithelial cells in various tissues. For example, Bernstein and Wollman (1975, 1976) and Altorfer et al. (1974) have described such an association in the thyroid gland and in seminiferous epithelium, respectively. They suggest that endoplasmic reticulum is involved in the supply of proteins and ions, with mitochondria providing energy to these contacts, the significance of which, however, remains unknown. The smooth endoplasmic reticulum is a site of accumulation of calcium and, together with mitochochondria, plays an important role in the regulation of the concentration of intracellular calcium ions (for reviews, see Meldolesi et al. 1990; Miller 1992; Simpson et al. 1995). Calcium ions have been localized to presynaptic agranular reticulum intimately juxtaposed to mitochondria (McGraw et al. 1980) and a role in buffering the increased calcium levels associated with synaptic activity has been suggested for the agranular reticulum in this area. We also think it likely that extensive networks of agranular reticulum localized along both sides of filamentous contacts represent sites for the storage and release of calcium ions.

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