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Synaptic Targets of Thalamic Reticular Nucleus Terminals in the Visual Thalamus of the Cat

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ABSTRACT

A major inhibitory input to the dorsal thalamus arises from neurons in the thalamic reticular nucleus (TRN), which use gamma-aminobutyric acid (GABA) as a neurotransmitter. We examined the synaptic targets of TRN terminals in the visual thalamus, including the A lamina of the dorsal lateral geniculate nucleus (LGN), the medial interlaminar nucleus (MIN), the lateral posterior nucleus (LP), and the pulvinar nucleus (PUL). To identify TRN terminals, we injected biocytin into the visual sector of the TRN to label terminals by anterograde transport. We then used postembedding immunocytochemical staining for GABA to distinguish TRN terminals as biocytin-labeled GABA-positive terminals and to distinguish the postsynaptic targets of TRN terminals as GABA-negative thalamocortical cells or GABA-positive interneurons. We found that, in all nuclei, the TRN provides GABAergic input primarily to thalamocortical relay cells (93–100%). Most of this input seems targeted to peripheral dendrites outside of glomeruli. The TRN does not appear to be a significant source of GABAergic input to interneurons in the visual thalamus. We also examined the synaptic targets of the overall population of GABAergic axon terminals (F1 profiles) within these same regions of the visual thalamus and found that the TRN contacts cannot account for all F1 profiles. In addition to F1 contacts on the dendrites of thalamocortical cells, which presumably include TRN terminals, another population of F1 profiles, most likely interneuron axons, provides input to GABAergic interneuron dendrites. Our results suggest that the TRN terminals are ideally situated to modulate thalamocortical transmission by controlling the response mode of thalamocortical cells. J. Comp. Neurol. 440:321–341, 2001.

Indexing terms: gamma amino butyric acid; lateral geniculate nucleus; lateral posterior nucleus; medial interlaminar nucleus; pulvinar nucleus; perigeniculate nucleus

A major inhibitory input to the dorsal thalamus arises from the thalamic reticular nucleus (TRN), a sheet-like structure that surrounds the rostral and lateral borders of the thalamus. All cells in the TRN use gamma-aminobutyric acid (GABA) as a neurotransmitter (Houser et al., 1980; Oertel et al., 1983; Fitzpatrick et al., 1984; Yen et al., 1985; de Biasi et al., 1986; Rinvik et al., 1987; Rinvik and Ottersen, 1988; Spreafico et al., 1991) and are thought to function in the inhibition of the thalamocortical signals. In particular, reciprocal projections between the TRN and thalamocortical cells are thought to underlie a rhythmic firing of the thalamus, which may block the transfer of sensory signals during slow wave sleep (Livingstone and Hubel, 1981;

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McCormick and Feeser, 1990; Steriade and McCarley, 1990; McCormick and Bal, 1997).

More modality-specific functions of the TRN are suggested by the topographic projections of the TRN to individual thalamic relay nuclei. Based on the precision of these projections, the TRN can be divided into modality-specific sectors (Minderhoud, 1971; Jones, 1975; Montero et al., 1977; Steriade et al., 1984; Crabtree and Killackey, 1989; Conley and Diamond, 1990; Conley et al., 1991; Harting et al., 1991; Crabtree, 1992, 1996, 1998; Pinault and Deschenes, 1998). For example, the primary visual sector of the TRN, which includes the perigeniculate nucleus (PGN; a part of the TRN), projects topographically to the dorsal lateral geniculate nucleus (LGN), which relays visual signals from the retina to the visual cortex. Projections from the visual TRN to the LGN are also aligned with topographic projections from the retina and visual cortex (Montero et al., 1977; Crabtree and Killackey, 1989; Conley and Diamond, 1990; Harting et al., 1991; Coleman and Mitrofanis, 1996).

The visual sector of the TRN also projects to other visual thalamic nuclei, such as the pulvinar and lateral posterior (LP) nuclei. These nuclei receive visual information from more indirect sources such as the superior colliculus, pretectum, and a variety of visual cortical areas (Jones and Powell, 1971; Niimi et al., 1971; Kawamura et al., 1974; Berman, 1977; Berson and Graybiel, 1978, 1983; Graybiel and Berson, 1980; Robertson and Cunningham, 1981; Updyke, 1981; Raczkowski and Rosenquist, 1983; Rodrigo-Angulo and Reinoso-Suárez, 1995). The projections from the TRN to the pulvinar/LP complex appear to be more diffusely organized than the projections to the LGN (Rodrigo-Angulo and Reinoso-Suárez, 1988; FitzGibbon, 1994; FitzGibbon et al., 1995; Guillery et al., 1998) and may arise from distinct cells within the TRN (Sumitomo et al., 1988; Conley and Diamond, 1990).

To understand more fully the functions of the projections from the TRN to the visual thalamus, a detailed description of the synaptic organization of TRN terminals is needed. Several previous studies have reported that TRN terminals in the LGN contain flattened or pleomorphic vesicles and form symmetric synapses on dendrites and somata (Montero and Scott, 1981; Harting et al., 1991, Cucchiaro et al., 1991a). However, it has not been determined whether TRN terminals primarily contact thalamocortical cells or interneurons in visual relay nuclei of the thalamus. It is also not known whether the projections from the TRN to the various nuclei of the visual thalamus target different regions of the neuropil. To address this issue, we injected the visual sector of the TRN with biocytin to label TRN terminals by anterograde transport. By using the electron microscope, we examined the synaptic targets of TRN terminals in the A lamina of the LGN, the medial interlaminar nucleus (MIN), the lateral subdivision of the lateral posterior (LP) nucleus, and the pulvinar. Postembedding immunocytochemical staining for GABA was used to further characterize biocytin-labeled TRN terminals and to determine whether the postsynaptic targets were GABAergic (i.e., interneurons) or non-GABAergic (i.e., thalamocortical relay cells). Some of these results were previously published in abstract form (Bickford et al., 1994; Wang et al., 1999).

Abbreviations

A, AI, C	laminae of the LGN
F1	GABAergic profile with densely packed vesicles
F2	GABAergic profile with loosely packed vesicles
GABA	gamma-aminobutyric acid
IC	inferior colliculus
LGN	dorsal lateral geniculate nucleus
LP	lateral posterior nucleus
MGN	medial geniculate nucleus
MIN	medial interlaminar nucleus
OT	optic tract
PGN	perigeniculate nucleus
PUL	pulvinar nucleus
RL	large profile with round vesicles
RLP	large profile with round vesicles and pale mitochondria
RS	small profile with round vesicles
TRN	thalamic reticular nucleus
vLGN	ventral lateral geniculate nucleus

MATERIALS AND METHODS

Tracer injections

A total of 10 cats were used in this study. All procedures were conducted in accordance with NIH guidelines for the care and use of laboratory animals and were approved by the State University of New York at Stony Brook Animal Care and Use Committee and the University of Louisville Animal Care and Use Committee. Eight cats received bilateral injections of biocytin in the vicinity of the TRN. One cat received a biocytin injection in the right LGN and a biocytin injection in the left TRN. To inject the biocytin, cats were deeply anesthetized with an intravenous injection of sodium phenobarbital (initially 15 mg/kg, with 5- to 10-mg supplements when needed) and placed in a stereotaxic apparatus. The heart rate was monitored, and the rectal temperature was maintained at 38°C by means of a feedback-controlled heating blanket. A craniotomy was performed, and the dura was reflected. By using stereotaxic coordinates, a glass pipette (5- to 10-μm tip diameter) containing a solution of 5% biocytin (Sigma Chemical Company, St. Louis, MO) in saline was lowered vertically into the TRN overlying the LGN on each side. Iontophoresis was achieved by means of DC current (1.5 μA for 15 minutes), and the pipette was removed.

One cat received a unilateral injection of fluorescein-labeled latex microspheres in the pulvinar nucleus. The cat was initially anesthetized with an intramuscular injection of ketamine (10 mg/kg) and intubated for gas anesthesia (0.5–1% nitrous oxide and 1–2% halothane). The cat was then placed in a stereotaxic apparatus and prepared for sterile surgery. A small area of the skull overlying the pulvinar nucleus was removed, and the dura was reflected. A Hamilton syringe containing an undiluted solution of green fluorescent latex microspheres (Luma-Fluor, Naples, FL) was lowered vertically into the pulvinar nucleus, and a volume of 0.1 μl was injected.

Histology

Three hours after the biocytin injections, the cats were perfused through the aorta with saline followed by 2 liters of fixative solution (2% paraformaldehyde and 2% glutaraldehyde in 0.1 M phosphate buffer). One week after the microsphere injection, the cat was perfused by using a fixative solution of 4% paraformaldehyde. The brains were removed and immersed in the fixative solution overnight. The following day, the thalamus was cut into 50-μm-thick

sections by using a Vibratome and collected in 0.1 M phosphate buffer (PB; pH 7.4). Sections containing fluorescent microspheres were mounted on slides for examination under blue light.

Sections that contained biocytin were incubated overnight at 4°C in a 1:200 dilution of avidin and biotinylated horseradish peroxidase (Vector, Burlingame, CA) in phosphate-buffered saline (PBS; 0.01 M PB with 0.9% NaCl, pH 7.4), with 1% normal goat serum and 0.5% Triton added to sections used only for light level analysis. The next day, the sections were rinsed three times in PB (10 minutes each) and reacted with nickel intensified diaminobenzidine (DAB) for 30 minutes. After buffer washes, sections were either mounted on slides for light level examination or prepared for electron microscopy as described below.

Electron microscopy

Selected sections were post-fixed in osmium, dehydrated in an alcohol series, and embedded in Durcupan resin (Ted Pella, Redding, CA). Ultra-thin sections were cut, and every tenth section was collected on Formvar-coated nickel slot grids. Sections were stained for the presence of GABA by using previously reported postembedding immunocytochemical techniques (Patel and Bickford, 1997; Patel et al., 1999; Carden and Bickford, 1999; Datskovskaia et al., 2001). We used a rabbit polyclonal anti-GABA antibody (Sigma) at a dilution of 1:2,500. As in our previous studies, the GABA antibody was tagged with a goat anti-rabbit antibody conjugated to 15-nm gold particles (Amersham, Arlington Heights, IL). GABA-stained sections were examined by using an electron microscope, and biocytin-labeled terminals that also contained a high density of gold particles were photographed when sectioned through a synaptic contact. For comparison, we also photographed synaptic contacts made by terminals in the surrounding neuropil that contained a high density of gold particles but were not biocytin labeled.

Quantification of GABA labeling

We quantified the GABA labeling by using previous methods (Patel and Bickford, 1997; Carden and Bickford, 1999; Patel et al., 1999; Datskovskaia et al., 2001). Briefly, for presynaptic profiles, and profiles postsynaptic to them, we calculated the gold density by counting the overlying gold particles and measuring the profile areas by using a digitizing tablet. The density of gold particles within these profiles was then compared with the density of gold particles within small profiles with round vesicles (RS profiles), which are always GABA-negative in the LGN (Montero and Singer, 1985; Beaulieu and Cynader, 1992; Godwin et al., 1996; Erişir et al., 1997).

Computer-generated figures

The distribution of cells in the TRN labeled by the retrograde transport of biocytin or fluorescent latex microspheres was plotted by using a Minnesota Datametrics plotting system (Shoreview, MN), and the figure was composed by using Freelance Graphics (Cambridge, MA). To illustrate TRN injection sites, and the resulting cell and terminal distributions, sections were drawn by using a camera lucida attachment. The sketches were digitized by using an Arcus II flatbed scanner (AGFA, Woburn, MA) and composed by using Freelance Graphics. Light level photographs were taken by using a digitizing camera (Spot RT, Diagnostic Instruments Incorporated, Sterling Heights, MI). We used Photoshop software (Adobe Systems Incorporated, San Jose, CA) to adjust the brightness and contrast of the images.

Identification of terminal types

We identified five terminal types: three GABA-negative (RS, RL, and RLP) and two GABA-positive (F1 and F2). RS profiles are small; contain densely packed round vesicles; and form short, highly asymmetric, contacts. These terminals originate from brainstem sources (de Lima et al., 1985; Raczkowski and Fitzpatrick, 1989; Beaulieu and Cynader, 1992; Erişir et al., 1997; Patel and Bickford, 1997; Patel et al., 1999) or cortical layer VI (Jones and Powell, 1969; Vidnyánszky and Hámori, 1994; Erişir et al. 1997; Bourassa and Deschênes, 1995; Ojima et al., 1996; Erişir et al., 1997). RL profiles are large; contain moderately packed round vesicles; and form multiple, short, slightly asymmetric contacts. These terminals originate from cells in cortical layer V and are found in the pulvinar/LP complex (Mathers, 1972; Robson and Hall, 1977; Hoogland et al., 1991; Paré and Smith, 1996; Vidnyánszky et al., 1996). RLP profiles are large, contain moderately packed round vesicles, and pale mitochondria. Similar to RL profiles, they form multiple, short, slightly asymmetric contacts. These terminals originate from the retina (Guillery, 1969; Robson and Mason, 1979; Hamos et al., 1987) and are found in the LGN and MIN. It has been suggested that RL and RLP terminals are the same type found in the pulvinar/LP complex and LGN, respectively (Guillery, 1969; Hajdu et al., 1974).

F1 profiles contain densely packed, pleomorphic vesicles, and form symmetric contacts. F2 profiles contain more scattered, pleomorphic vesicles and form symmetric contacts. Based on studies of the LGN, these profiles likely represent the dendritic terminals of interneurons (Montero and Scott, 1981; Montero and Singer, 1984; Hamos et al., 1985). The main difference between the F1 and F2 terminals is the packing density of vesicles; this gives the F1 profiles a darker appearance when compared with the lighter F2 profiles. In addition, F2 profiles can be much larger than F1 profiles.

Sampling methods

The purpose of this study was to determine whether TRN terminals contact thalamocortical cells or interneurons. In addition, we determined the size of the profiles targeted by TRN terminals. To accomplish this, we examined tissue from the visual thalamus that contained labeled TRN terminals. We photographed the labeled TRN terminals if they were involved in a synaptic connection. If the size of the synaptic zones of TRN terminals varied with their location on the postsynaptic dendritic arbors, our sample would be biased in favor of the larger synaptic zones. To determine whether the synaptic zones of TRN terminals varied with location, we measured the length of the synaptic contacts and the diameter of the postsynaptic profiles and tested for statistically significant correlations by using the Pearson test.

This study did not attempt to determine the density of TRN terminals within a volume of tissue. Therefore, stereologic methods that have been developed to correct for sampling biases to determine an accurate count of neurons or terminals within a given volume of tissue were not appropriate for this study. Instead, we sampled the TRN

terminals that were labeled and determined their relative distribution on the dendritic arbors of thalamocortical cells and interneurons within the same blocks of tissue. Therefore, any shrinkage effects were applied equally to all postsynaptic profiles.

Similarly, we did not correct for the anatomic distribution of dendritic profiles within the visual thalamus. Although distal dendrites are more numerous than proximal dendrites and, therefore, will be encountered more often within a block of tissue, this finding simply reflects the morphology of thalamic neurons, and it is inappropriate to "correct" for this nonrandom distribution (Benes and Lange, 2001). Finally, it should be pointed out that our analysis of postsynaptic profiles was secondary to the sampling of TRN terminals. We did not sample a variety of dendrites to determine whether they were contacted by TRN terminals. Rather, we sampled TRN terminal synaptic zones and subsequently determined what type of profile was contacted. Therefore, any biases in our sampling methods would be introduced by variations in the size of the synaptic zones of the labeled TRN terminals and not by variations in the size of the postsynaptic profiles.

RESULTS

Location of TRN cells that project to the LGN and pulvinar nucleus

As illustrated in Figure 1, injections in the LGN or pulvinar label cells within the TRN overlying the LGN. Injections in the LGN label a restricted subset of TRN cells that, for the most part, directly overlie the injection site. In contrast, injections in the pulvinar (as previously reported by FitzGibbon, 1994) label cells throughout the rostrocaudal and mediolateral extent of the visual TRN. Thus, injections placed within restricted regions of the visual TRN should label terminals within a restricted region of the LGN, whereas labeled terminals in the pulvinar nucleus should be more widely distributed.

Morphology and distribution of label resulting from injections in the visual TRN

To examine the synaptic targets of TRN terminals in the visual thalamus, small injections of biocytin were placed in the TRN overlying the LGN. The injection sites were dorsal to the LGN and included both the outer tier of the TRN as well as the PGN. Figure 2 illustrates an example of an injection site and the resulting label in the visual thalamus in plots through a series of parasagittal sections. TRN injections resulted in dense columns of overlapping fibers labeled by anterograde transport and cells labeled by retrograde transport within the LGN, MIN, and the LP nucleus. The pulvinar and the ventral LGN contained sparser label.

Figure 3 shows examples of the anterograde and retrograde labeling that resulted from the biocytin injections in the TRN. Many thalamocortical cells were labeled in a Golgi-like manner (Fig. 3A), and two types of fibers were identified: fine fibers with short side branches ending in terminal boutons (Fig. 3B; type I; Guillery, 1966), most likely of cortical origin (Jones and Powell, 1969), and thicker fibers with beaded swellings (Fig. 3C–E), which likely arise from the TRN (Uhlrich et al., 1991).

Ultrastructure of labeled structures

At the ultrastructural level, three types of labeled profiles could be distinguished by their vesicle morphology and GABA staining. GABA-negative, biocytin-labeled terminals that contained round vesicles and made asymmetric synaptic contacts (RS or RL profiles; Fig. 4B) were presumed to be cortical in origin and are not considered further. GABA-positive, biocytin-labeled terminals that contained densely packed pleomorphic vesicles and made symmetric synaptic contacts (F1 profiles; Fig. 4A) were presumed to be TRN terminals and are the focus of the following results. Labeled cells and dendrites were also observed and were always GABA-negative. These structures are presumed to be labeled thalamocortical relay cells and are not considered further.

Synaptic targets of TRN terminals in the LGN

Lamina A. We limited our more detailed analysis of the TRN terminals in the LGN to the region of lamina A immediately ventral to the injection sites. We examined the synaptic targets of a total of 166 biocytin-labeled, GABA-positive terminals (111 from case 1 and 55 from case 2). In both cases, we found that the majority of TRN terminals contacted dendrites outside of glomeruli (Fig. 5). These findings included primary dendrites, distal dendrites, and dendritic appendages. However, the majority of dendrites postsynaptic to TRN terminals were of small caliber, and most unlabeled terminals that were found to make synaptic contacts with profiles that were also postsynaptic to TRN terminals were small GABA-negative terminals that contained round vesicles (RS profiles; Fig. 6).

We found that the overwhelming majority of the TRN contacts were made with GABA-negative profiles (Fig. 5A). In the first case, 103 of 111 (93%) of the postsynaptic targets were GABA-negative and, thus, originate from thalamocortical cells. Of these contacts, 14 of 103 (14%) of the targets were located on somata, and the remaining 89 (86%) were located on dendrites. In addition, 4 of 111 (3.5%) of the TRN terminals contacted GABA-positive dendritic shafts (Fig. 5B), and the remaining 4 (3.5%) contacted glomerular dendritic terminals of interneurons. The distribution of these contacts within the examined block of tissue is illustrated in Figure 7. Although there appeared to be some tendency for TRN terminals to contact more GABA-positive profiles toward the periphery of the column of label, this was not found in the second case. In the second case, we examined the synaptic contacts of 55 TRN terminals in both the center and the periphery of the column of label and found that all of them contacted GABA-negative extraglomerular dendrites.

Fig. 1. Cells in the visual sector of the TRN are labeled by retrograde transport after injections in the PUL or LGN. **A:** Plots of a series of coronal sections, arranged from rostral (top) to caudal (bottom), illustrate the distribution of cells labeled after an injection in the PUL. **B:** Plots of a series of parasagittal sections, arranged from lateral (top) to medial (bottom), illustrate the distribution of cells labeled after an injection in the LGN. Injections in the LGN label a restricted subset of TRN cells, whereas injections in the PUL label cells throughout the TRN. D, dorsal; L, lateral; C, caudal. For other abbreviations, see list. Scale bar = 5 mm.

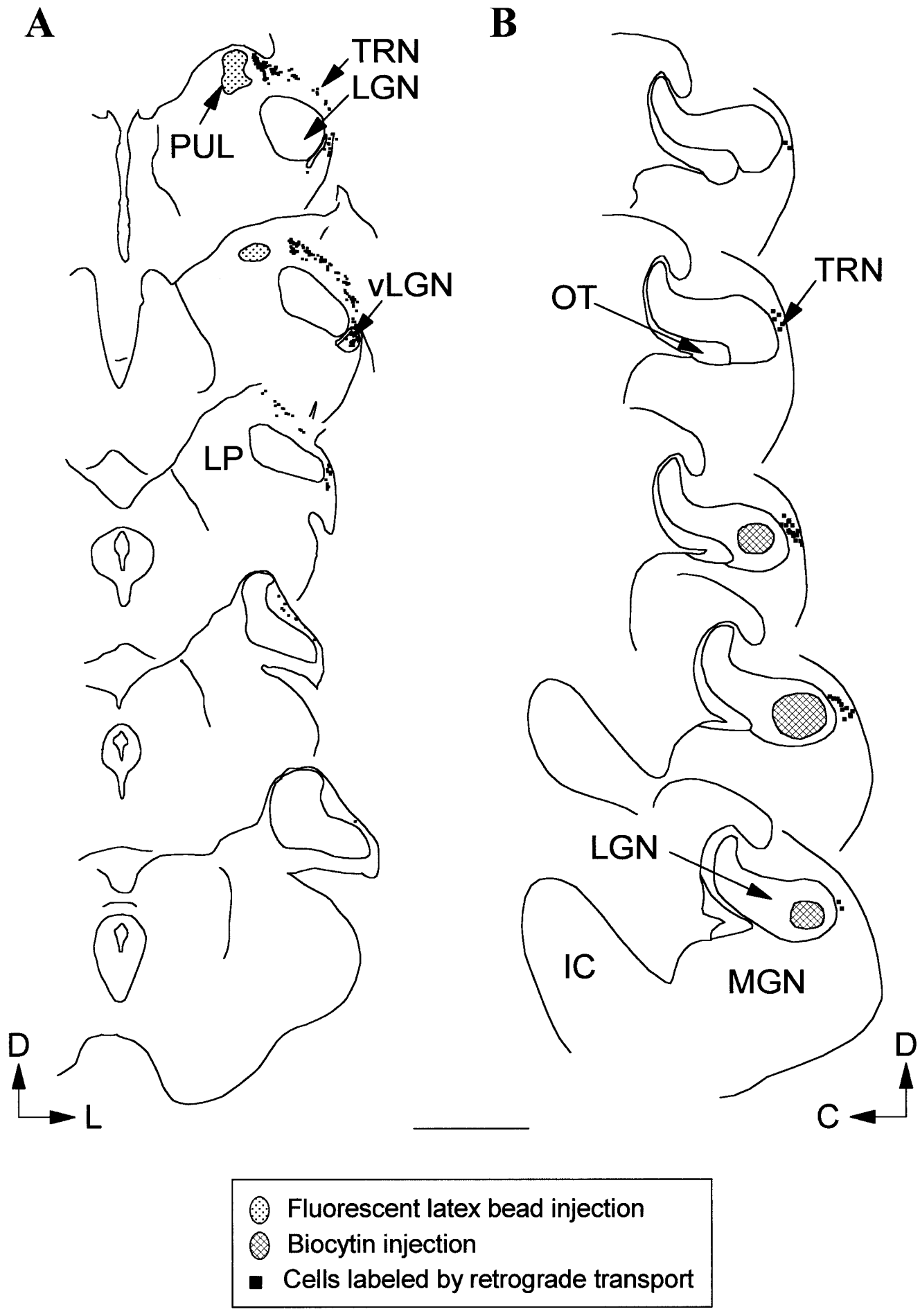
A
TRN
LGN
PUL
vLGN
LP
D
L
B
TRN
OT
LGN
IC
MGN
D
C
Fluorescent latex bead injection
Biocytin injection
Cells labeled by retrograde transport

Figure 1

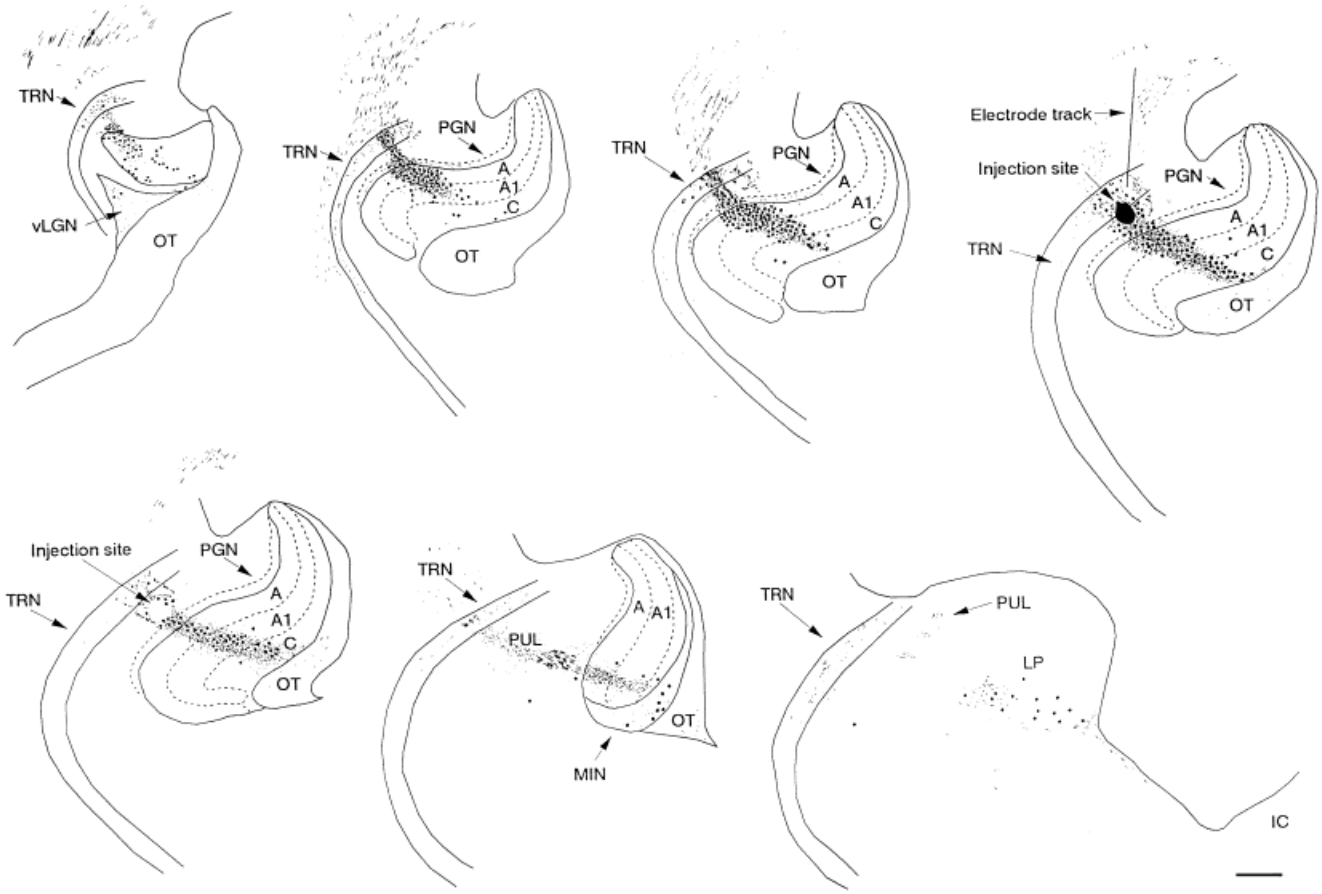

Fig. 2. Schematic diagram illustrates the distribution of labeled cells (black dots) and terminals (fine stippling) in the visual thalamus labeled by the retrograde and anterograde transport of biocytin injected in the TRN (case 1). The parasagittal sections are arranged from lateral (top left) to medial (bottom right). For abbreviations, see list. Scale bar = 1 mm.

MIN. We photographed a total of 108 TRN terminals making synaptic contacts in the MIN (53 in case 1 and 55 in case 2). As in lamina A, the majority of TRN terminals in the MIN contacted dendrites outside of glomeruli (Fig. 8). We observed two contacts (2%) on somata; the remainder were located on dendrites. Most terminals adjacent to TRN dendritic contacts were RS profiles (Fig. 6). Almost all (106 of 108 or 98%) of the TRN profiles contacted the GABA-negative dendrites or somata of thalamocortical cells. The remaining TRN terminals contacted the GABA-positive dendritic terminals of interneurons (2 of 108 or 2%).

Synaptic targets of F1 profiles in the LGN

Lamina A. To compare the synaptic targets of TRN terminals with the synaptic targets of all GABAergic axon terminals in lamina A, we also photographed synaptic contacts made by F1 profiles in the surrounding neuropil that contained a high density of gold particles but that were not biocytin-labeled (Fig. 9A). We examined the synaptic targets of 121 F1 profiles in case 1. As illustrated in Figure 10, in contrast to the TRN contacts, we found that only 50 (41%) of F1 profiles contacted GABA-negative thalamocortical cells: 46 contacts on dendrites and 4 contacts on somata. The remainder contacted GABA-positive dendritic shafts (41 of 121 or 34%), GABA-positive dendritic terminals (29 of 121 or 24%), or GABAergic somata (1 of 121 or 1%).

MIN. Within the surrounding neuropil of the MIN, we also photographed the synaptic contacts made by F1 profiles that were not biocytin-labeled. We examined the synaptic targets of 169 F1 terminals in the MIN (95 synaptic contacts in case 1 and 74 in case 2). Similar to the TRN contacts, most GABAergic terminals contacted GABA-negative dendrites that were also contacted by RS profiles (Fig. 9B). Contacts on somata were present, but rare (1 contact on a GABA-negative soma observed).

As illustrated in Figure 10, in contrast to the postsynaptic targets of TRN terminals, many of the postsynaptic targets of F1 terminals in the MIN are GABAergic profiles (20 of 95 or 21% in case 1 and 13 of 74 or 18% in case 2). Most of these postsynaptic GABAergic profiles contained vesicles (13 of 20 or 65% in case 1 and 11 of 13 or 85% in case 2). These vesicle-containing profiles are likely to be F2 terminals.

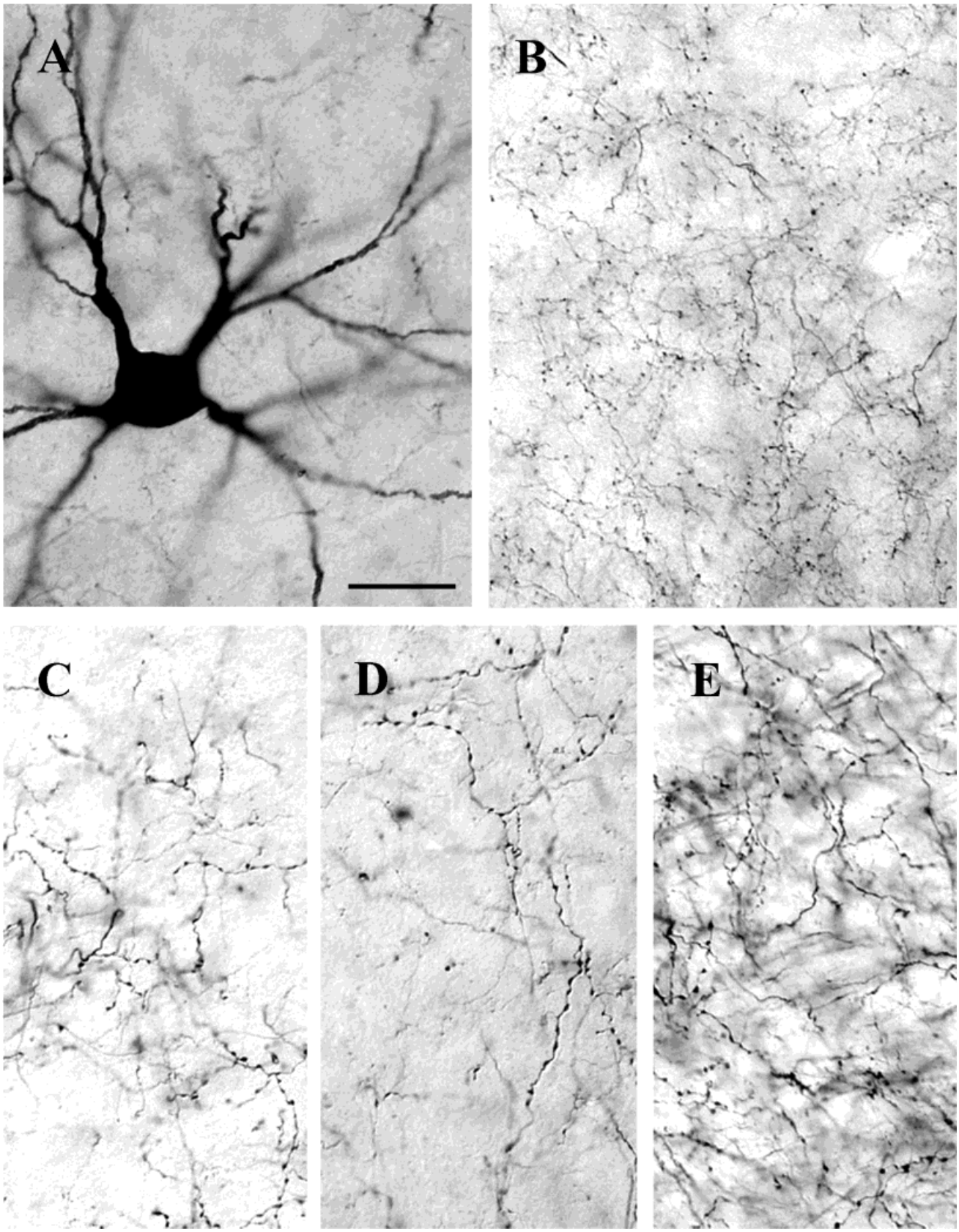

Fig. 3. Photomicrographs show examples of cells and fibers in the visual thalamus labeled by retrograde or anterograde transport after biocytin injections in TRN. **A:** A thalamocortical cell labeled by retrograde transport. **B:** Presumed corticothalamic axons labeled by anterograde transport. The fibers are thin and have "drumstick-like" terminal boutons. **C–E:** Presumed TRN fibers labeled by anterograde transport. The fibers are thicker and heavily beaded. For abbreviations, see list. Scale bar = 30 μm in A (applies to A–E).

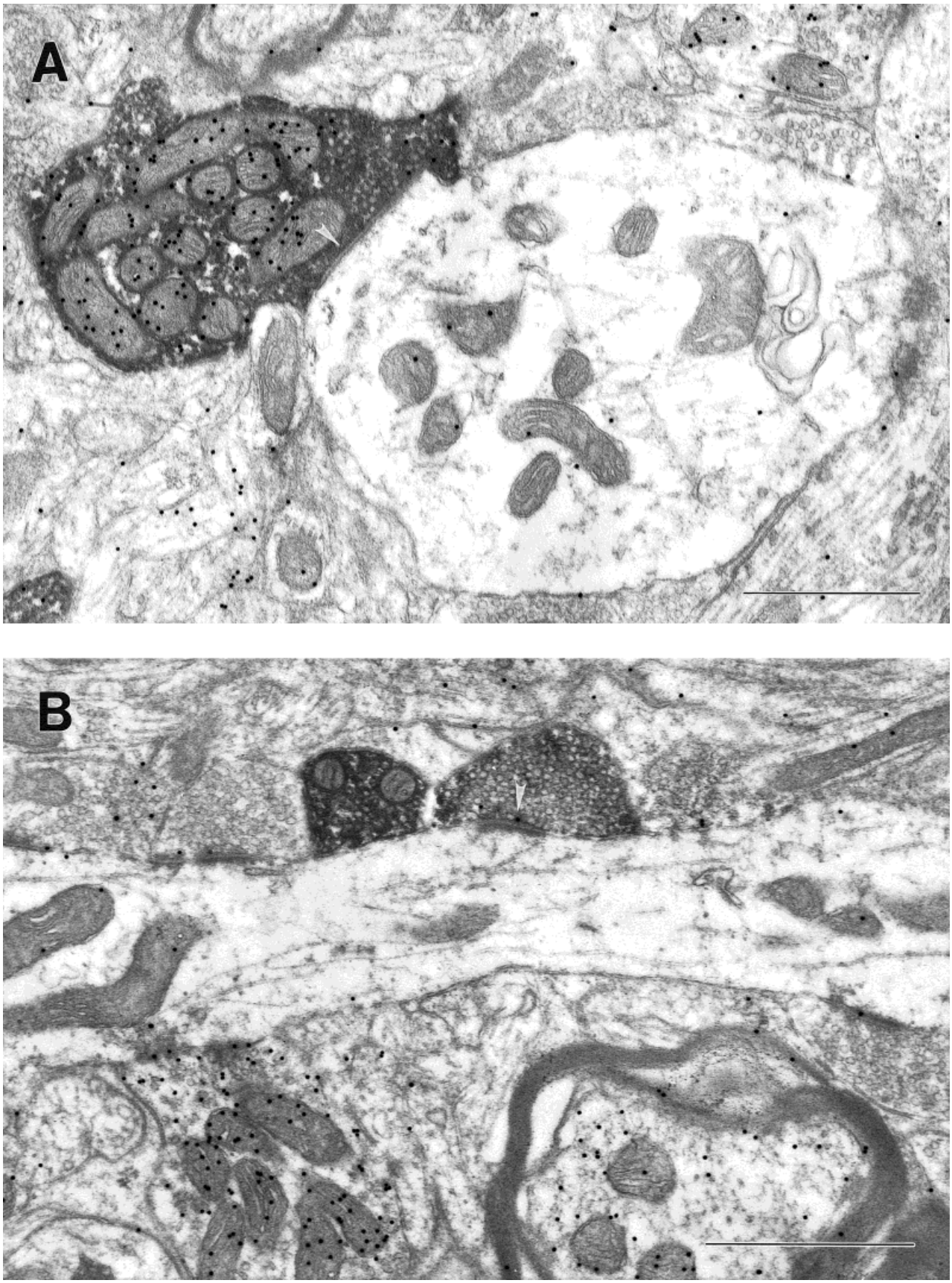

Fig. 4. Electron photomicrographs show examples of profiles in the visual thalamus labeled by anterograde transport after biocytin injections in the TRN. **A:** TRN terminals are identified as biocytin-positive (dark reaction product) and GABA-positive (high density of gold particles). This terminal contacts (white arrowhead) a GABA-negative dendrite. **B:** Small profiles that contain round vesicles (RS profiles) are presumed to be cortical in origin. They are biocytin-positive but GABA-negative (low density of gold particles). One of these profiles contacts (white arrowhead) a GABA-negative dendrite. For abbreviations, see list. Scale bar = 1 μm in A,B.

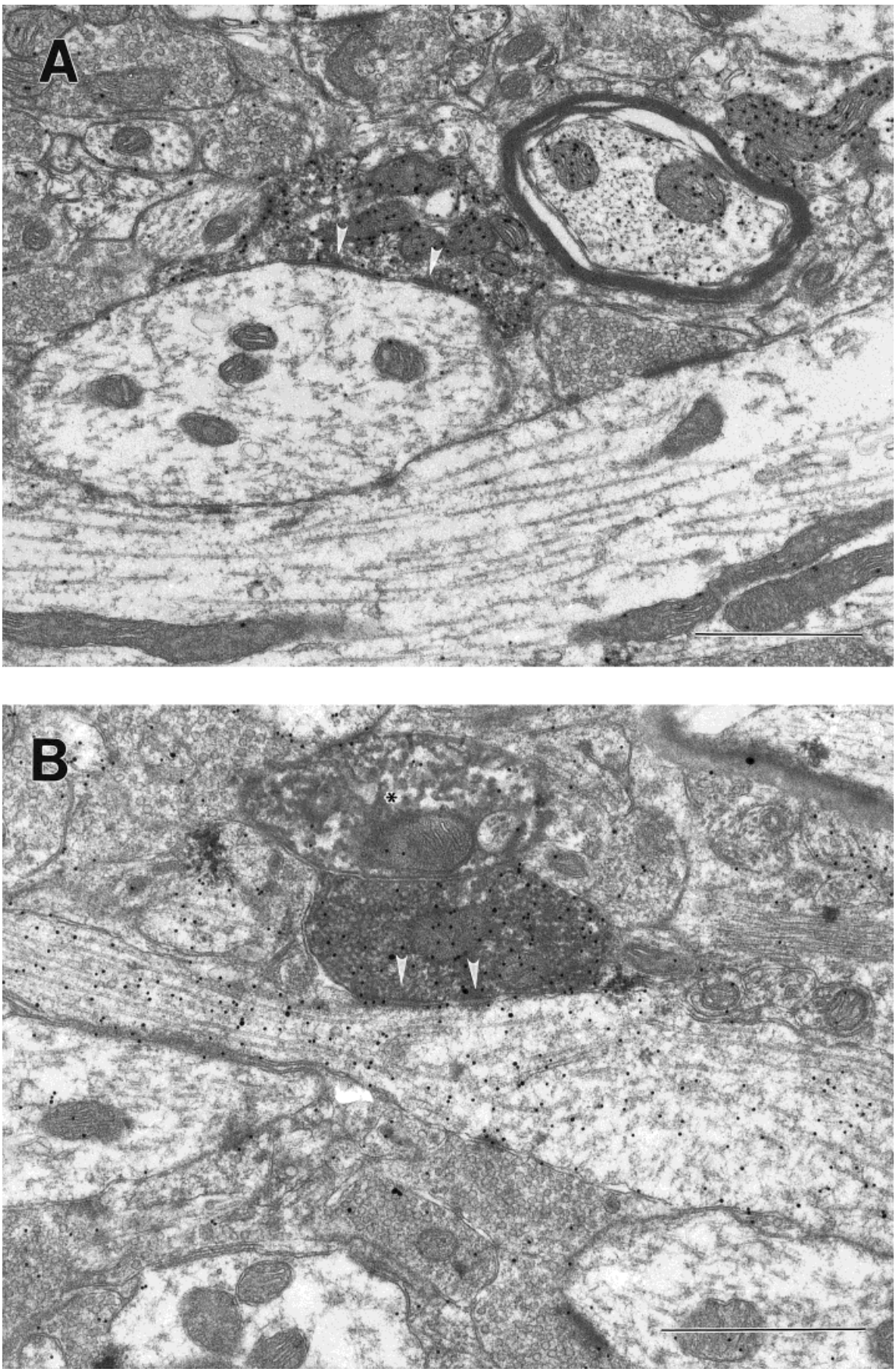

Fig. 5. Electron photomicrographs show examples of TRN terminals in the A lamina of the LGN. **A:** A TRN terminal contacts (white arrowheads) a thalamocortical cell dendrite. **B:** A TRN terminal contacts (white arrowheads) an interneuron dendrite. This terminal is adjacent to a biocytin-labeled thalamocortical cell dendrite (asterisk). For abbreviations, see list. Scale bar = 1 μm in A,B.

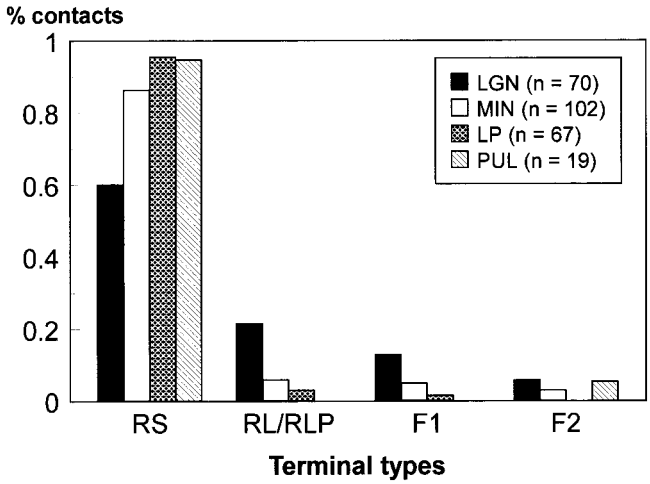

Fig. 6. Most terminals adjacent to TRN terminals are RS profiles. The histogram illustrates the number of RS, RL/RLP, F1, or F2 terminals that were found to make synaptic contacts on profiles that were also postsynaptic to TRN terminals. For abbreviations, see list.

Synaptic targets of TRN terminals in the lateral LP nucleus

We photographed a total of 112 TRN terminals making synaptic contacts in the lateral LP nucleus. As illustrated in Figure 11, almost all of these TRN terminals contacted extraglomerular, GABA-negative dendrites (case 1, 56 of 60 or 93%; case 2, 52 of 52 or 100%). The majority of terminals adjacent to TRN dendritic contacts were RS profiles (Fig. 6). We observed one contact on a GABA-negative soma. The remaining four terminals contacted GABA-positive dendritic terminals, three of which contained vesicles.

Synaptic targets of F1 profiles in the lateral LP nucleus

As illustrated in Figures 10 and 12, similar to the TRN terminals, the majority of F1 terminals in the surrounding neuropil of the lateral LP nucleus also contacted extraglomerular GABA-negative dendrites (case 1, 55 of 59 or 93%; case 2, 60 of 60 or 100%). Most of these dendrites were also postsynaptic to RS profiles. One GABAergic contact was observed on a GABA-negative soma, and three GABAergic contacts were made with GABA-positive, vesicle-containing dendrites.

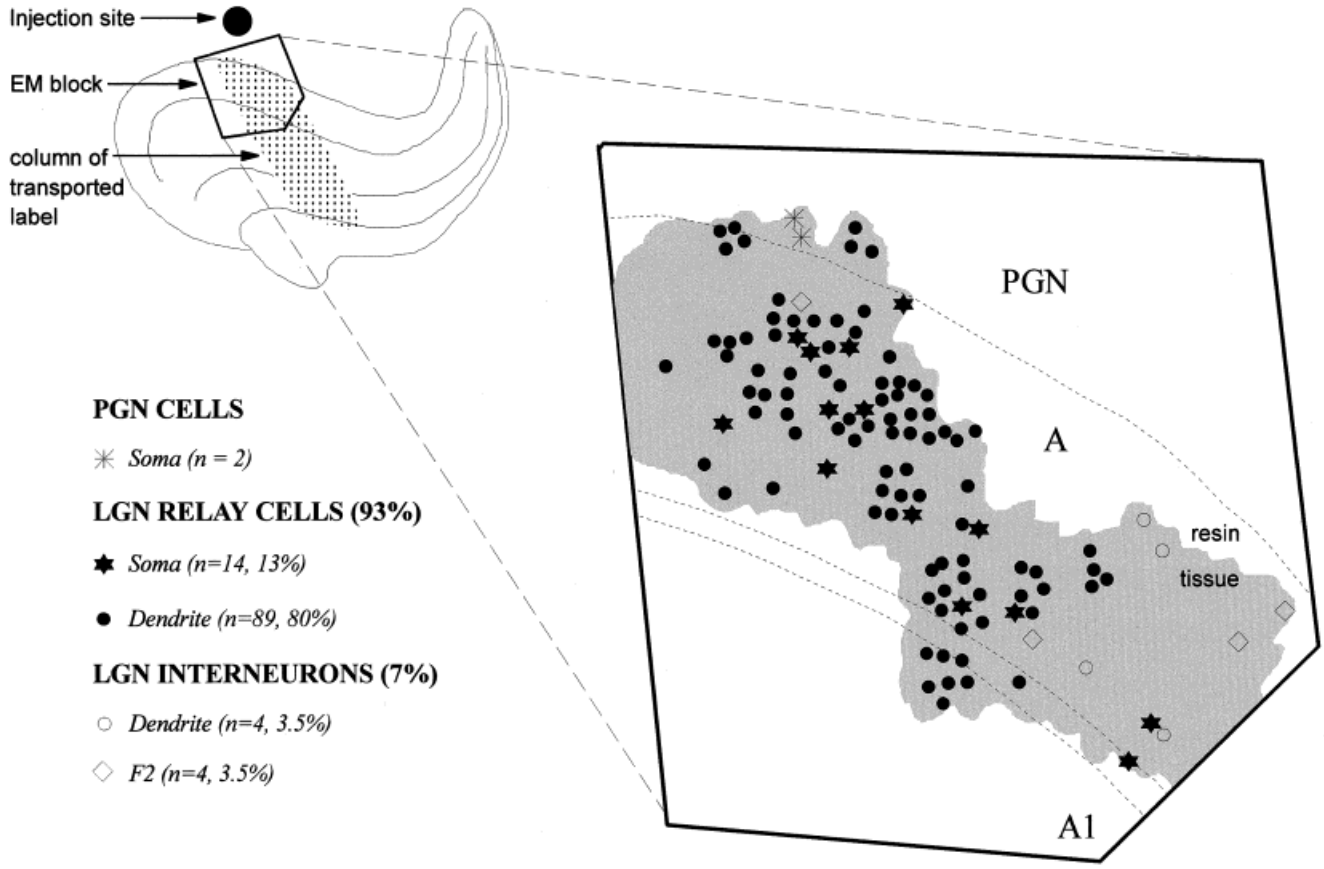

Fig. 7. The schematic diagram illustrates the distribution of postsynaptic targets of TRN terminals observed in case 1. For abbreviations, see list.

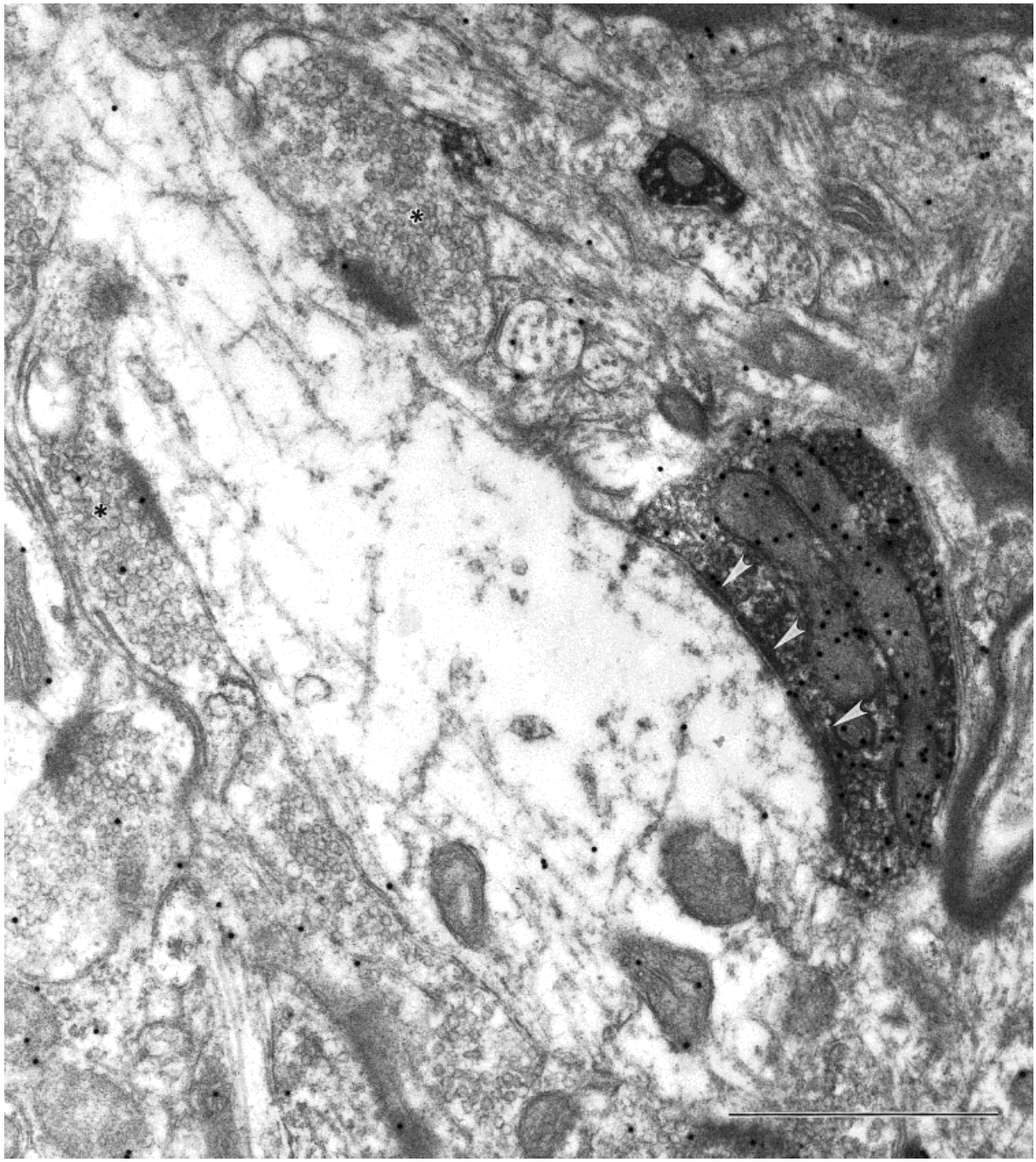

Fig. 8. A TRN terminal in the MIN contacts (white arrowheads) a thalamocortical cell dendrite. Adjacent contacts are RS profiles (asterisks). For abbreviations, see list. Scale bar = 1 μm.

Synaptic targets of TRN terminals in the pulvinar nucleus

Our TRN injections labeled a very sparse population of GABAergic terminals in the pulvinar nucleus. After examination of 48 sections in each case, we photographed a total of 24 synaptic contacts (9 in case 1 and 15 in case 2). All the synaptic targets were dendritic shafts outside of glomeruli (Fig. 13). None of these dendrites were GABA-positive, and none contained vesicles. Approximately half of these postsynaptic dendrites were also contacted by RS profiles (Fig. 8).

Evaluation of sampling methods

If size of the synaptic zones of TRN terminals varied with their presynaptic location, our sample would be biased in favor of the larger synaptic zones. To determine

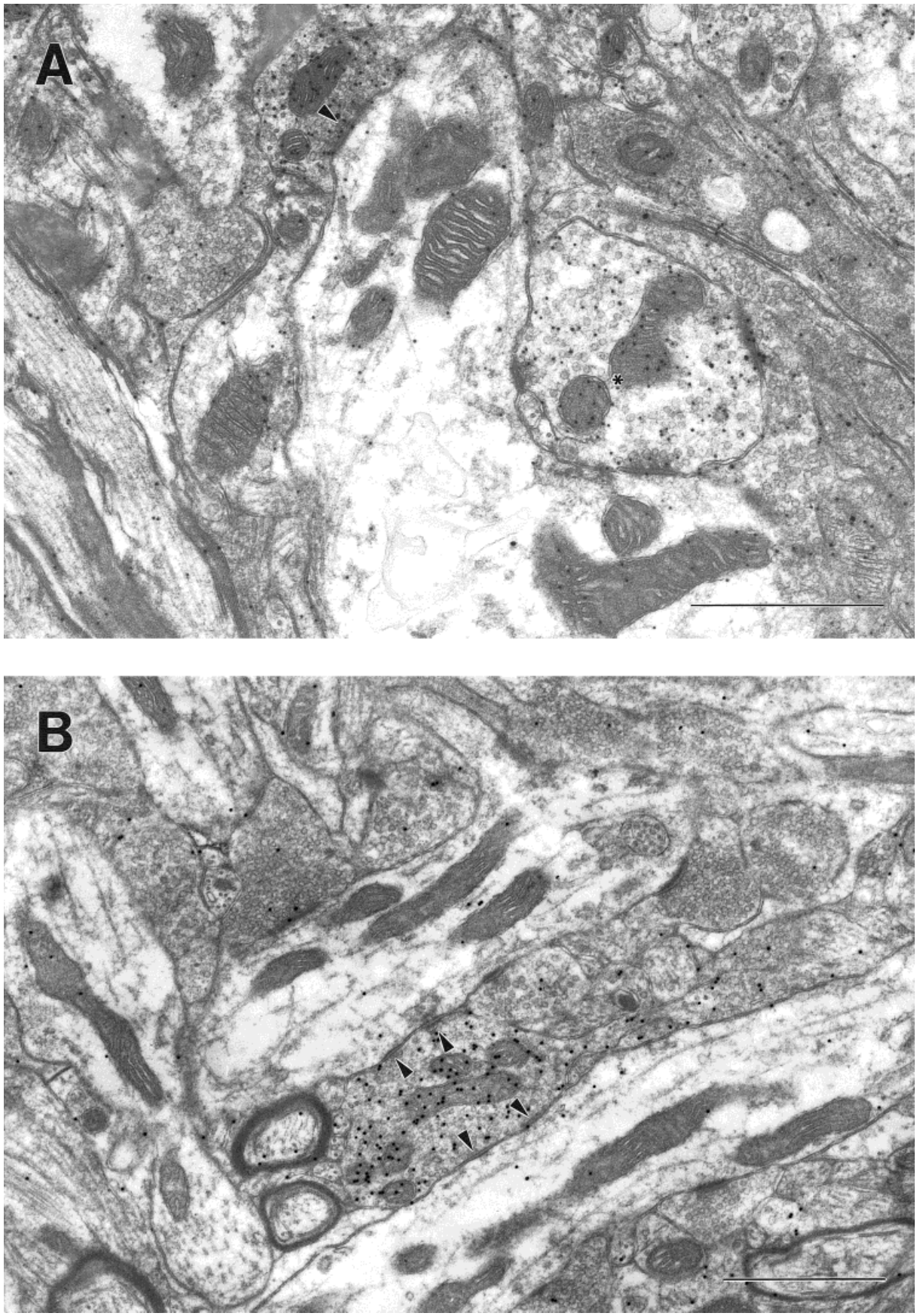

Fig. 9. Electron photomicrographs show examples of F1 terminals in the LGN. **A:** An F1 terminal in the A lamina contacts (black arrowhead) a thalamocortical cell dendrite. This dendrite is also contacted by an F2 profile (asterisk). **B:** An F1 terminal in the MIN contacts two (black arrowheads) thalamocortical cell dendrites. For abbreviations, see list. Scale bar = 1 μm in A,B.

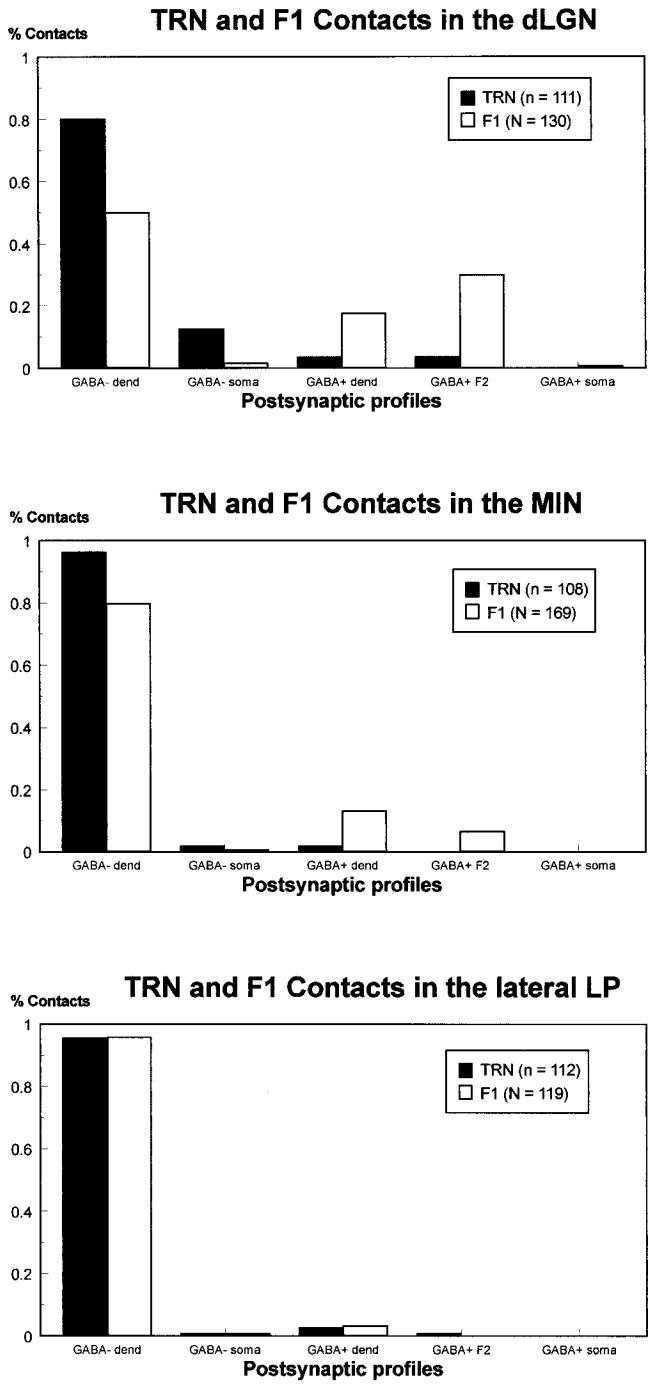

Fig. 10. TRN contacts do not account for all F1 contacts. The histograms compare the postsynaptic targets of TRN terminals and F1 terminals in the LGN A lamina, MIN, and LP. Most TRN terminals contact thalamocortical cell dendrites. F1 terminals contact more interneurons. For abbreviations, see list.

whether the size of the synaptic zones of TRN terminals was correlated with the size of the postsynaptic dendrites, we measured both of these parameters and tested for statistically significant correlations. As shown in Figure 14, in each nucleus, there was no correlation between the size of the synaptic zone and the size of the postsynaptic profile (Pearson test; LGN A lamina: r = 0.002, $P = 0.976$, n = 164; MIN: r = 0.048, $P = 0.621$, n = 109; LP: r = 0.036, $P = 0.704$, n = 112; PUL: r = 0.199, $P = 0.351$, n = 24). Therefore, with the assumption that the orientation of TRN terminal synaptic zones is random, our data suggest that the length of TRN terminal synaptic zones does not vary with presynaptic location. Therefore, our sampling methods did not bias our data in favor of small or large dendrites.

DISCUSSION

We have identified the synaptic targets of GABAergic TRN terminals throughout the visual thalamus. We examined the synaptic arrangements of TRN terminals in lamina A and MIN of the LGN, the lateral LP nucleus, and the pulvinar, and we found that, in all nuclei, the TRN provides GABAergic input primarily to thalamocortical relay cells (93–100%). The majority of this input appears targeted to peripheral dendrites outside of glomeruli, and this finding is summarized schematically in Figure 15. The TRN does not seem to be a significant source of GABAergic input to interneurons in the visual thalamus.

We also examined the synaptic targets of the overall population of GABAergic axon terminals (F1 profiles) within these same regions of the visual thalamus and found that the TRN contacts cannot account for all F1 profiles. In addition to F1 contacts on the dendrites of thalamocortical cells, which likely arise from the TRN, another population of F1 terminals provides input to GABAergic interneuron dendrites (either dendritic shafts or F2 profiles) and to glomeruli. The relative number of these contacts varies across nuclei, but it appears to be highest in the LGN. As discussed below, interneuron axons are a likely source of F1 contacts onto interneuron dendrites and within glomeruli.

Comparison with previous anatomic studies of the LGN

Previous studies have examined the synaptic targets of TRN terminals in the LGN of the rat (Ohara et al., 1980; Montero and Scott; 1981) and cat (Cucchiaro et al., 1991a), and, like the present study, these studies reported that the majority of postsynaptic targets of TRN terminals are dendrites. These dendrites were presumed to originate from thalamocortical cells, but definitive identification was not possible, because the tissue was not stained for GABA. By using postembedding staining for GABA, our study confirms that the vast majority of TRN terminals contact thalamocortical cells. In addition, the postembedding staining for GABA allowed us to examine only GABAergic axon terminals labeled from our injection sites. A preliminary study of the monkey LGN also used this technique and obtained similar results (Feig et al., 1998).

A previous study by Cucchiaro et al. (1991a) showed that the projections from the PGN, a subdivision of the TRN that is immediately dorsal to the LGN, terminate specifically in a column within the A laminae of the LGN where the majority contact small diameter, presumably distal dendrites. Our injection sites included both the PGN and TRN. The most significant difference between the present study and that of Cucchiaro et al. is our

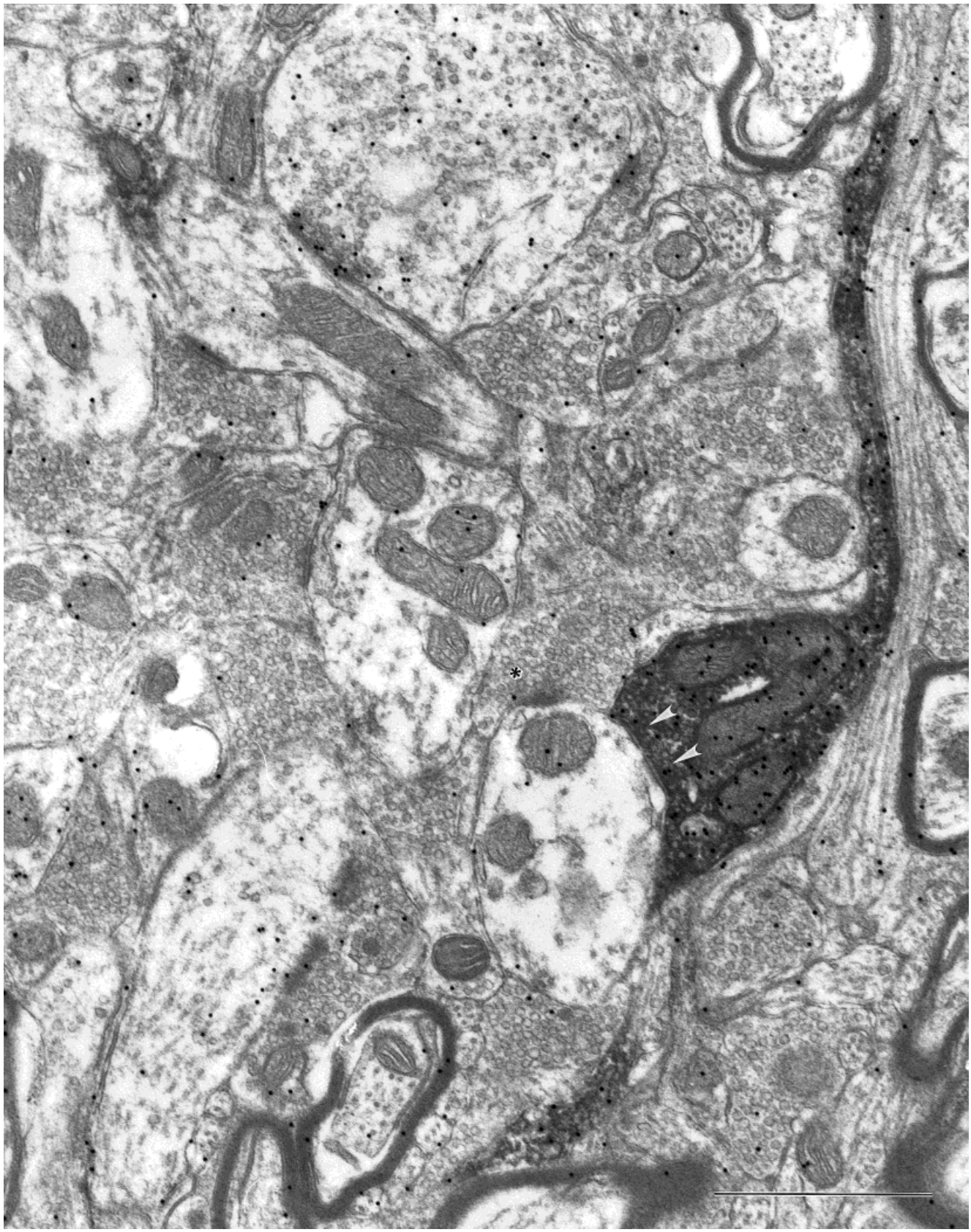

Fig. 11. A TRN terminal in the LP nucleus contacts (white arrowheads) a thalamocortical cell dendrite. An adjacent contact is an RS profile (asterisk). For abbreviations, see list. Scale bar = 1 μm.

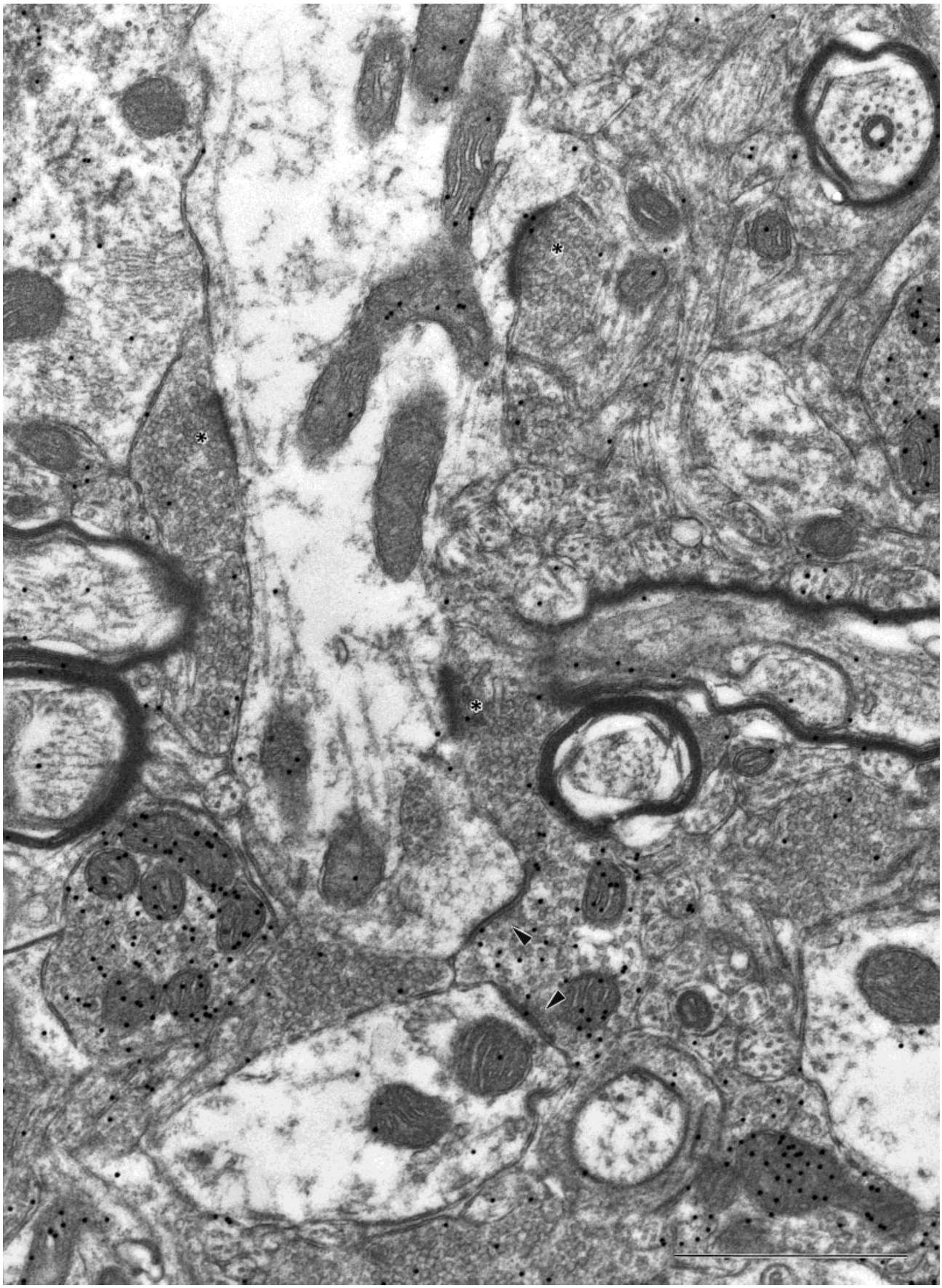

Fig. 12. Electron photomicrograph shows an example of an F1 terminal in the lateral posterior nucleus (LP) nucleus that contacts (black arrowheads) two thalamocortical cell dendrites. Adjacent contacts are RS profiles (asterisks). For abbreviations, see list. Scale bar = 1 μm.

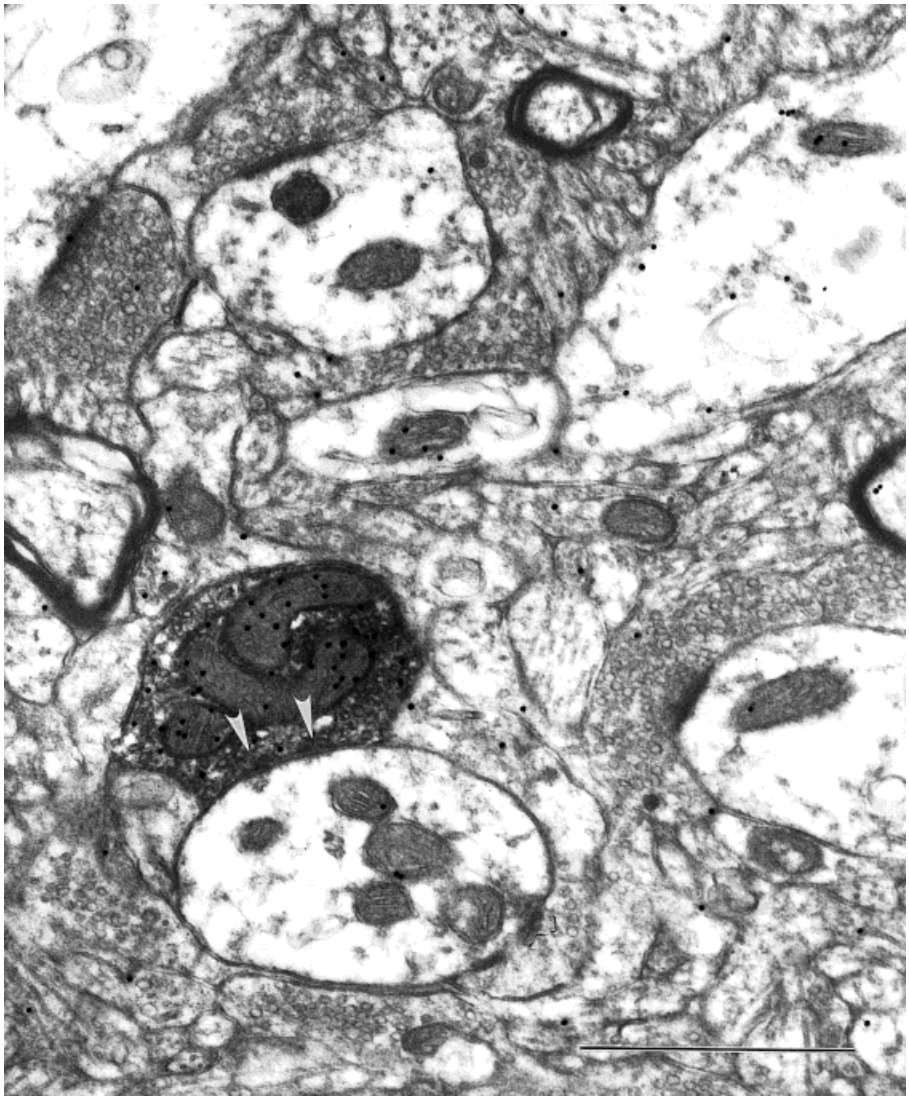

Fig. 13. Electron photomicrograph shows an example of a TRN terminal in the PUL that contacts (white arrowheads) a thalamocortical cell dendrite. For abbreviations, see list. Scale bar = 1 μm.

identification of axosomatic contacts. We also found somewhat more contacts from our injections on dendritic profiles in the retinal recipient zone, suggesting perhaps that the TRN terminals may occupy a more proximal position on the dendrites of thalamocortical relay cells than do the PGN terminals.

Our results also indicate that neither the PGN nor the outer tiers of the TRN are a significant source of GABAergic input to interneurons. In the LGN, other extrinsic GABAergic inputs to interneurons arise from the pretectum (Cucchiaro et al., 1991b). These terminals have been shown to contact interneuron dendritic terminals, which contact relay cell dendrites outside glomeruli (Cucchiaro et al., 1993). By process of elimination, we suggest that GABAergic inputs to interneurons within glomeruli may arise from interneuron axons. A similar conclusion was reached by Takács et al. (1991) based on a comparison of vesicle size within subpopulations of F1 terminals. This conclusion predicts that interneurons may form a network over which the TRN has little influence.

In contrast to F1 profiles, 48% of which contact interneurons, we noted that F2 profiles generally contact thalamocortical cell dendrites and that contacts between F2 profiles are quite rare. In fact, Van Horn et al. (2000) found that none of the synaptic targets of F2 profiles were interneurons. Accordingly, when F1 and F2 profiles are considered together, a much lower percentage is found to contact interneurons (13%; Erişir et al., 1998). Thus, it is likely that interneurons are primarily interconnected through axodendritic connections and not through dendrodendritic connections.

Comparison with previous studies of TRN sectors related to other sensory modalities

Data from other sensory systems suggest that the synaptic targets of TRN terminals are similar throughout the

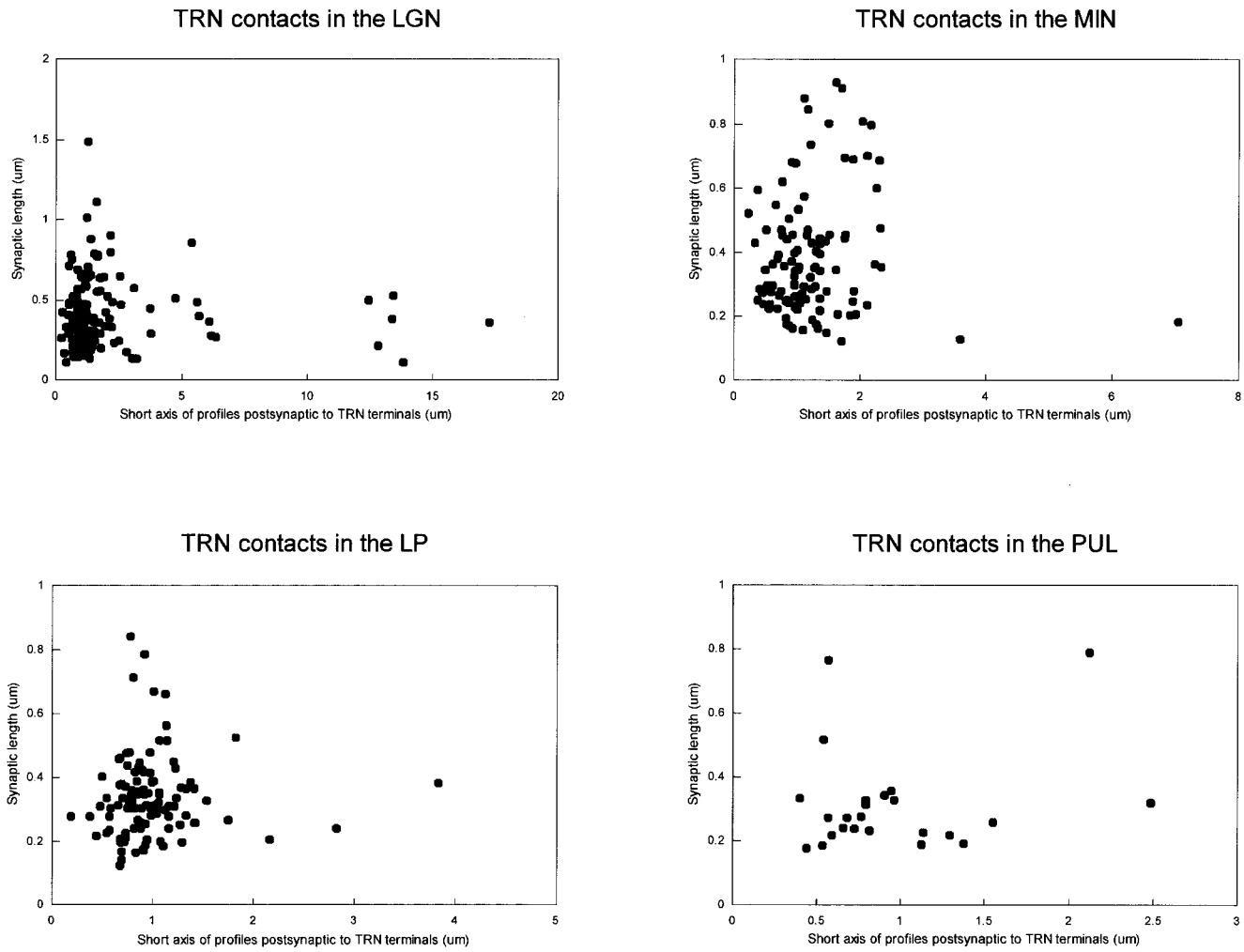

Fig. 14. The length of the synaptic contacts made by TRN terminals is plotted against the diameter of the postsynaptic dendrites in the LGN lamina A (**A**), MIN (**B**), LP nucleus (**C**), and PUL (**D**). No correlation was found between these two parameters (Pearson test). For abbreviations, see list.

dorsal thalamus. For example, Liu et al. (1995) examined the synaptic targets of TRN terminals within the cat ventroposterior nucleus labeled by the anterograde transport of *phaseolus vulgaris leucoagglutinin* injected into the somatosensory sector of the TRN. As in the present study, postembedding immunocytochemical labeling for GABA was used to identify thalamocortical cells and interneurons. With these techniques, they found that 82% of TRN terminals contacted thalamocortical cell dendrites, 9.3% contacted thalamocortical cell and interneuron somata, and 8.5% contacted the dendrites of interneurons. Thus, the somatosensory sector of the TRN also primarily targets thalamocortical cells. In addition, TRN terminals originating in the auditory sector of the rat TRN contact somata and dendrites of presumed thalamocortical cells in the medial geniculate nucleus (Montero, 1983). Thus, it seems likely that terminals originating from all the sensory sectors of TRN primarily contact the dendrites of thalamocortical cells.

In contrast, a much greater number of TRN terminals in the anterior, mediodorsal, and ventral anterior nuclei of the rhesus monkey contact interneurons (Kultas-Ilinsky et al., 1995; Tai et al., 1995; Ilinsky et al., 1999). By using methods similar to those in the current study, it was found that at least 50% of TRN terminals in these thalamic nuclei contact GABAergic interneurons. Thus, the projections of the TRN to the sensory thalamus are not representative of TRN projections to all dorsal thalamic nuclei.

Topography of TRN projections to the visual thalamus

Our results indicate that the visual TRN projects in a topographic manner to the LGN (including both the A-laminae and MIN) and LP nucleus. However, the projections from the TRN to the pulvinar nucleus appear to be organized differently than projections to the other visual thalamic nuclei we studied. As previously shown by FitzGibbon (1994), we found that injections in the pulvinar nucleus labeled cells throughout the rostrocaudal and mediolateral extent of the TRN. In addition, after injections within restricted regions of the TRN, we labeled only a small number of TRN terminals in the pulvinar nucleus.

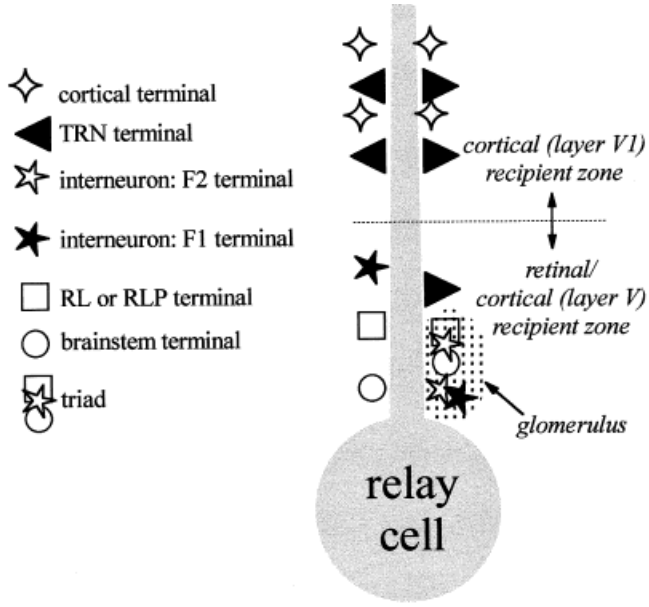

Fig. 15. Schematic diagram illustrates the distribution of terminals on thalamocortical cells within the LGN A lamina, MIN, LP, and PUL. TRN terminals are primarily distributed on distal dendrites adjacent to RS profiles. For abbreviations, see list.

FitzGibbon et al. (1995) also noted that TRN terminations in the pulvinar nucleus are not as prominent as those in the lateral posterior nucleus. This finding suggests that the axons of individual TRN cells project throughout the pulvinar nucleus, but that the terminations of each axon are sparse. This finding contrasts with the focused dense projections that have been identified after intracellular labeling of TRN cells that project to the LGN and LP nucleus (Uhlrich et al., 1991; Sanchez-Vives et al., 1996; Pinault and Deschênes 1998).

Data in the *Galago* suggests that the TRN cells that project to the LGN are distinct from those that project to the pulvinar nucleus and occupy distinct tiers within the TRN (Conley and Diamond, 1990). Although our data could not reveal an organization related to TRN tiers, it does suggest that cells in the TRN that project to the LGN are distinct from cells that project to the pulvinar nucleus. Thus, activity in one region of the TRN may have a widespread, but weak, influence on thalamocortical cells in the pulvinar nucleus and a more restricted, but strong, influence on thalamocortical cells of the LGN, MIN, and LP nuclei.

Functional implications

Role during sleep. During slow wave sleep, both thalamocortical relay cells and TRN cells are relatively hyperpolarized. In this state, both cell types tend to fire in synchronized, rhythmic bursts. A key factor in this pattern of activity is the activation of T channels (Jahnsen and Llinás, 1984a,b; Mulle et al., 1986; Avanzini et al., 1989; Bal and McCormick, 1993; Contreras et al., 1993). Burst firing of TRN cells produces large and long-lasting inhibitory postsynaptic potentials (IPSPs) in relay cells (Kim and McCormick, 1998). Because of the voltage dependency of the T channels, such IPSPs effectively deinactivate these channels, promoting burst firing as well in the relay cells. Interestingly, several studies have concluded that these T channels may be concentrated within the dendrites of thalamocortical cells (Zhou et al., 1997; Destexhe et al., 1998; Williams and Stuart, 2000; Zhan et al., 2000). Because we found that TRN terminals are primarily distributed on the dendrites of thalamocortical cells (see Fig. 15), it appears that TRN inputs are ideally arranged to control the inactivation state of T channels.

Additional evidence for a role of the TRN in synchronizing the activity of the thalamus during sleep comes from studies of connections between TRN cells. Dendrodendritic and/or axodendritic connections between neighboring and distant TRN cells have been identified in the cat (Deschênes et al., 1985) and rat (Pinault et al., 1997). Preliminary results also indicate that TRN cells may be electrically coupled (Landisman et al., 2000). These connections are thought to link the activity of cells in all sectors of the TRN and, in turn, synchronize the activity of all dorsal thalamic nuclei.

Role during wakefulness. The topographic nature of the projections from the TRN to the dorsal thalamus are thought to underlie an additional function that has been attributed to the TRN. That is, the TRN is thought to modulate the activity of the dorsal thalamus to maintain selective attention. Several different lines of evidence support this concept of TRN function. First, lesions of the TRN, either experimentally induced or resulting from cardiac arrest or head injuries, seem to impair the ability to attend to stimuli (Friedberg and Ross, 1993; Ross and Graham, 1993; Ross et al., 1993). Second, it has been found that C-FOS expression in the TRN is related to attention. Specifically, C-FOS expression is induced only in the sector of the TRN related to the sensory modality involved in attentional demands (Montero, 1997; McAlonan et al., 2000).

How the TRN might influence attention has yet to be determined. However, the pattern of terminations of TRN synapses offers a suggestion for the function of this pathway (see Fig. 15). It is interesting both that these terminals are prevalent on relay cells rather than interneurons, and that they synapse mostly on small caliber (presumably peripheral) dendrites outside of glomeruli. In addition, if we consider the LGN as an example, most terminals that are adjacent to TRN terminals are RS profiles and a smaller number are RLP profiles. This pattern is similar to the general distribution of terminals encountered in a random sampling of contacts on relay cells; even without correction for terminal size, relay cells are found to be contacted by more RS profiles (56%) than RLP profiles (15%; Van Horn et al., 2000). In addition, if one considers the dendritic arbors of relay cells, the volume occupied by small caliber, peripheral dendrites is much greater than that occupied by proximal dendrites. Thus, if TRN terminals are distributed fairly evenly across the dendritic arbors of relay cells, one would expect to encounter most of these terminals on distal dendrites adjacent to RS profiles.

This distribution suggests that, unlike GABAergic inputs from interneurons or cholinergic inputs from the brainstem that specifically target the retinorecipient zones of relay cell dendritic arbors within glomeruli (Hamos et al., 1985; Erişir et al., 1997), the TRN terminals do not appear to be distributed to influence the transfer of one type of input. Instead, the distribution of TRN termi-

nals might be better situated to affect response mode based on the inactivation state of T channels, which, as noted above, are concentrated on dendrites, including peripheral dendrites (Zhou et al., 1997; Destexhe et al., 1998; Williams and Stuart, 2000; Zhan et al., 2000). Recent evidence suggests that response mode is an important feature of thalamic relays in normal, waking function (Guido and Weyand, 1995; Ramcharan et al., 2000; Sherman, 2001). The TRN may function in the maintenance of selective attention by modulating the response mode of thalamocortical cells during the waking state.

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