# Two Systems of Giant Axon Terminals in the Cat Medial Geniculate Body: Convergence of Cortical and GABAergic Inputs

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ABSTRACT

The thalamus plays a critical role in processing sensory information that involves interactions between extrinsic connections and intrinsic circuitry. Little is known regarding how these different systems might interact. We found an unexpected nuclear convergence of two types of giant axon terminals, each of which must have independent origins, in the dorsal division of the cat medial geniculate body. The first class of giant terminal was labeled after injections of biotinylated dextran amines (BDA) in seven auditory cortical areas. A second type was found in sections immunostained for γ-aminobutyric acid (GABA); these endings had the same nuclear distribution, and they were numerous. The origin of this GABAergic terminal is unknown. The giant corticothalamic terminals were presumably those described in prior accounts using different tracers (Rouiller and de Ribaupierre [1990] Neurosci. Lett. 208:29–35; Ojima [1994] Cerebral Cortex 6:646–663), but with BDA they are labeled more fully. Clusters of such endings were often linked, and hundreds may occur in a single section. Their boutons formed a substantial proportion of the corticothalamic population. Other types of corticogeniculate axon terminals were also labeled, including two kinds that are much smaller and that match closely the classical descriptions of corticothalamic axons. The giant GABAergic endings were found in all dorsal division nuclei and in thalamic visual nuclei such as the lateral posterior nucleus. Like the giant cortical endings, the giant GABAergic terminals often encircled large, pale, immunonegative profiles that may be dendritic. This implies a close spatial, and perhaps a close functional, relationship between the populations of giant axon terminals. Insofar as physiological studies found that pharmacological inactivation of rat somatic sensory cortex suppresses peripheral information transmission through the posterior thalamus, corticofugal input may be essential for normal processing (Diamond et al. [1992] J. Comp. Neurol. 319:66–84). Our findings suggest that the giant corticothalamic endings could play an important role in descending control. Perhaps they are counterbalanced by a GABAergic system and affect thalamic oscillations implicated in shifts in vigilance and attention. J. Comp. Neurol. 413:181–197, 1999. © 1999 Wiley-Liss, Inc.

Indexing terms: corticofugal projections; corticogeniculate; γ-aminobutyric acid; inhibition; thalamus; axons

The thalamus is often referred to colloquially as a "relay" nucleus, which implies a passive role limited chiefly to sensory processing. Several lines of evidence suggest that this perspective underestimates the dynamic role of the thalamus in a wide array of physiological processes. These range from seizures (Bal and McCormick, 1996 [ferret lateral geniculate body]) to sleep (Steriade et al., 1991 [various sensory and motor nuclei; the species referred to is the cat unless noted otherwise]). These processes appear to be mediated by different families of neuronal oscillations (Steriade et al., 1993 [various systems and species]; Contreras and Steriade, 1996 [dorsal thalamus]). Little is known about the anatomical substrates for such events, nor is it clear how excitatory and inhibitory processes

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might interact in the thalamus. An unexpected convergence of two types of chemically specific giant axonal endings, which must have different origins, and which might contribute to a complex interplay of excitatory and inhibitory interactions, is the subject of this report.

The thalamus receives input from many sources. A powerful extrinsic influence arises from the cerebral cortex (Diamond et al., 1969; McCormick and von Krosigk, 1992 [guinea pig lateral geniculate body]). Such fibers have long been recognized as an integral part of the dorsal thalamus in general (Ramón y Cajal, 1911), and several types of corticothalamic axons have been described. Until recently, most corticothalamic axons were thought to be comparatively fine, with diffuse physiological actions appropriate for indirect modulation of thalamic activity (Jones, 1985). Slender axons (type I) with thin side branches and a dichotomous mode of division have been described in both the lateral (Guillery, 1966) and the medial (Morest, 1975) geniculate bodies and in the somatic sensory ventrobasal complex (Jones and Powell, 1969), using the Golgi method and in experimental degeneration studies. More recent descriptions of corticothalamic axon terminals in the lateral geniculate body, based on intraaxonal filling, characterize them as thin and having few boutons or as predominantly fine, with a rarer thick and beaded subtype (Robson, 1983). Although a population of large, ring-shaped corticothalamic axon terminals has been reported (Mathers, 1972 [squirrel monkey pulvinar]), their role in thalamic function is obscure. The subsequent discovery that corticothalamic giant axon terminals were present in different modalities and species (Rouiller and de Ribaupierre, 1990 [rat medial geniculate body]; Hoogland et al., 1991 [rat posterior thalamus]; Rockland, 1994 [monkey pulvinar]) challenged the view that the corticothalamic system is anatomically homogeneous and limited exclusively to a subsidiary role in thalamic sensory processing. This finding suggests that descending projections might have parallel streams, much like their ascending counterparts. Subsequent physiological studies have shown that corticothalamic giant (CG) axons are essential for transmission of somatic sensory information through the sensory thalamus and to the cortex (Diamond et al., 1992 [rat ventrobasal complex and posterior thalamus]).

A further insight into thalamic circuitry came from the discovery of widespread networks of γ-aminobutyric acidergic (GABAergic) neurons and axon terminals (Rinvik et al., 1987). These GABAergic influences arise from local (interneuronal) and remote sources. Intrinsic local circuit neurons (Rouiller et al., 1990) and extrinsic projections from the thalamic reticular nucleus (Conley et al., 1991 [prosimian primate medial geniculate body]; Cox et al., 1997 [rat ventrobasal complex]) or inferior colliculus (Winer et al., 1996) could counterbalance excitatory corticothalamic influences. Early reports on thalamic GABAergic axon terminals (puncta) noted some large terminals but tended to emphasize their overall uniformity (Rinvik et al., 1987). Substantial numbers of GABAergic puncta occurred, but they were not comparable in size to the corticogeniculate giant endings.

The present study addresses a possible relationship between giant corticothalamic and giant GABAergic axons in the dorsal division of the medial geniculate body, where we found many of each type of terminal in the course of independent connectional and immunocytochemical investigations. It is presumed that the corticothalamic and intrinsic systems are largely independent, and certainly no systematic relationship has been suggested between these axonal populations in the thalamus. The nuclear convergence reported here is unexpected and suggests that there must be processes unique to these thalamic nuclei, which might require complementary corticothalamic and GABAergic modulation. A preliminary report has appeared (Winer et al., 1998b).

## MATERIALS AND METHODS

Twenty-seven adult cats were used for connectional experiments (for a complete list, see Winer et al., 1998a) and 15 others for immunocytochemical purposes (for details, see Huang et al., 1996). They had clean auditory meati and no history of chronic ear disease; Siamese and blue-eyed males with white coats were excluded. All experimental procedures were administered under veterinary supervision following protocols approved by the Institutional Animal Care and Use Committee and current guidelines (Society for Neuroscience, 1991).

### Anesthesia, surgery, and perfusion

The animal was sedated with acepromazine (0.2 mg/kg s.c.; Aceproject® Vetus; Burns Veterinary Supply, Rock-

*Abbreviations*

| | | | |
|---|---|---|---|
| AAF | anterior auditory field | M | medial *or* medial division of medial geniculate body |
| AI | primary auditory cortex | MB | mammillary bodies |
| AII | secondary auditory cortex | Ov | *pars ovoidea* of the ventral division |
| ALLS | anterior lateral lateral suprasylvian area | P | posterior auditory field |
| APt | anterior pretectum | PLLS | posterior lateral lateral suprasylvian visual area |
| BDA | biotinylated dextran amines | PMLS | posterior medial lateral suprasylvian visual area |
| BIC | brachium of the inferior colliculus | PC | piriform cortex |
| C | caudal | R | rostral |
| CG | central gray | RN | red nucleus |
| CP | cerebral peduncle | SC | superior colliculus |
| D | dorsal *or* dorsal nucleus | SF/daz | suprasylvian fringe/dorsal auditory zone |
| DD | deep dorsal nucleus | Sgl | suprageniculate nucleus, lateral part |
| DCa | dorsal nucleus, caudal part | Sgm | suprageniculate nucleus, medial part |
| DS | dorsal superficial nucleus | Te | temporal cortex |
| EP | posterior ectosylvian cortex *or* gyrus | V | ventral *or* ventral division *or* ventral auditory field |
| EPD | posterior ectosylvian cortex, dorsal part | Vb | ventrobasal complex |
| GABA | γ-aminobutyric acid | VLEA | ventral lateral entorhinal area |
| Ins | insular cortex | VMEA | ventral medial entorhinal area |
| L | lateral | Vl | ventrolateral nucleus |
| LGB | lateral geniculate body | VP | ventral posterior auditory field |
| LP | lateral posterior nucleus | | |

ville, NY) and induced under isoflurane (1–3%; Vetus). When the animal was areflexic to nociceptive stimuli, an i.v. line and endotracheal tube were installed. Anesthesia was maintained under 1–3% isoflurane in $O_2$ and temperature was kept at 34–39°C with blankets and a recirculating warm water pad. Lactated Ringers with dextrose (10 ml/kg/hour; 4-hour-long experiment; i.v.) was given to maintain hydration. The physiological variables monitored routinely included rate of respiration, arterial $O_2$, temperature, and electrocardiogram. Atropine sulfate (0.05 mg/kg; i.p.; Anpro Pharmaceuticals, Arcadia, CA) was given as required to support cardiac output.

The surgical procedure was identical for the two tracers and used sterile technique. After a midline incision, the temporalis muscle was blunt dissected and retracted bilaterally to expose the skull overlying the cortical convexity. An approximately 8 × 10-mm craniotomy exposed parts of one or more major gyri or sulci, and the target was chosen with regard to the results from prior connectional and physiological work (Reale and Imig, 1980; Bowman and Olson, 1988a,b). The dura was reflected, and a glass pipette (bore diameter 35–50 µm) was used to deliver the tracer. Cortical deposits (1,800–2,000 µm beneath the pia) were designed to saturate layers V and VI in various areas as defined cytoarchitectonically (Winer, 1992).

Biotinylated dextran amines (BDA; 3K MW; Molecular Probes, Eugene, OR) was injected either by iontophoresis (10% BDA in saline, with a pipet with a 40 µm tip and 5 µA positive current for 30 minutes) or by pressure (20% BDA in distilled water, through a pipet with a 30–40 µm tip and pulses of 4.6 or 9.2 nl) using an electronically controlled hydraulic injector (World Precision Instruments, Sarasota, FL). Volumes for pressure injections were ≈0.08–1.1 µl with 7–28-day survivals.

To confirm the BDA experiments independently and to reveal the projections from larger expanses of cortex, we used wheat germ agglutinin conjugated to horseradish peroxidase (WGA-HRP; Sigma Chemical Co., St. Louis, MO; Mesulam, 1978). One or two unilateral deposits of 5% WGA-HRP in sterile saline were made with a nanoliter injector over 10–32 minutes (total volumes 0.15–0.4 µl in pulses of 4.6 or 9.2 nl/30–120 seconds). Buprenorphine (Buprenex® Reckitt & Colman Ltd., London, England) was administered postsurgically (0.00875–0.0125 mg/kg; s.c.) over the two-day survival in this procedure and for the initial 1–2 days in the other tract tracing experiments.

Animals were reanesthetized using sodium pentobarbital (Abbott Laboratories, North Chicago, IL; 26 mg/kg; i.v.) for perfusion. For BDA, a washout (0.12 M phosphate buffer [PB; the carrier in the following steps] and 0.001% lidocaine hydrochloride, 250–400 ml, 24°C) preceded the fixative (4% paraformaldehyde, pH 7.4, 2,250 ml). For WGA-HRP, the same washout was followed by a two-stage perfusion: a weak initial solution (0.5% paraformaldehyde/0.5% glutaraldehyde, 1,000 ml) preceded a stronger second fixative (1% paraformaldehyde/1.5% glutaraldehyde, 2,000 ml, 4–10°C). Cryoprotectant (10% sucrose, 500 ml) was perfused one hour later. Dissection, blocking in the frontal plane, photography for subsequent reconstruction, and immersion in another cryoprotectant (30% sucrose) for 1–3 days followed.

## Histology

Serial sections were cut in groups of six on a freezing microtome (Reichert; Warner Lambert Technologies, Inc., Buffalo, NY; 50 µm thick). For BDA, half the sections were placed in Triton X100 (0.4% in 0.1 M PB; 20 minutes), then incubated in avidin-biotinylated-peroxidase complex (ABC Elite reagent; 1:100; 60 minutes; Vector Laboratories, Burlingame, CA). The ABC signal was visualized with nickel/cobalt diaminobenzidine (Adams, 1981). A 1:3 series was stained with cresyl violet for Nissl substance, from which the nuclear boundaries were drawn independently of the distribution of labeled material.

The WGA-HRP sections were 60 µm thick; half were processed with tetramethylbenzidine (Mesulam, 1978), and one series was neutral red-counterstained to locate areal and laminar borders and to determine the limits of the injection(s). Other sections were developed with nickel-cobalt/DAB. A further series was DAB processed only, then Nissl stained; some sections were postfixed (10% formalin/PB; 5–10 days) before Nissl staining.

## Immunocytochemistry

For GABA immunocytochemistry, cats were anesthetized with sodium pentobarbital (50 mg/kg; i.p.) and perfused with PB saline (150 ml at room temperature), then 1% paraformaldehyde/3% glutaraldehyde in 0.1 M PB (2,000 ml; 4°C). Postfixation (10% sucrose/PB) was followed by Vibratome sectioning (TPI Inc., St. Louis, MO) at 50 µm (for free-floating immunocytochemistry) or at 100–200 µm (for slabs for plastic embedment before semithin postembedding immunocytochemistry). The thinner sections were treated with 5% normal goat blocking serum (60 minutes), then incubated in rabbit anti-GABA (courtesy of R.J. Wenthold; 1:2,000 or DiaSoria [Incstar], Clearwater, MN; 1:5,000; 4°C; overnight). Slabs for postembedding (Larue and Winer, 1996) were block stained (0.5–1% $OsO_4$; 1–3 hours), then dehydrated through graduated ethanols. They were next put into propylene oxide and epoxy (Araldite 6005) to which dibutylphthalate had been added to soften the consistency of the embedment, and finally polymerized (16 hours at 60°C). Blocks containing an entire thalamus were cut at 1–1.5 µm with 8-mm glass knives on an ultramicrotome (LKB Ultratome III; Bromma, Sweden). Sections were affixed to clean, uncoated slides, etched in ethanolic sodium hydroxide for 1–2 hours to dissolve the plastic, deosmicated (0.3% $H_2O_2$ in EtOH), rehydrated, and incubated in blocking serum on the slide (5% normal goat serum). Primary antiserum was used at twice the concentrations used for the free-floating procedure, and ABC reagents were used at twice the normal values. Alternatively, the streptavidinbiotin kit (Histomark®, Kierkegaard and Perry Inc., Gaithersburg, MD) was used at the ready-to-use concentration. The chromogen was cobalt/nickel-intensified DAB (Adams, 1981). Controls included omission trials in which specific immunoreactivity was absent.

Glutamic acid decarboxylase (GAD) immunostaining used the zinc-salicylate-formalin protocol (Mugnaini and Dahl, 1983). The wash-out was normal saline (≈500 ml) and the fixative contained 0.5% zinc salicylate/10% unbuffered formalin (200 ml; pH 6.5; 20°C). Fixative was washed out (10% sucrose/normal saline), and the brain was cryoprotected (30% sucrose/saline overnight at 4°C). Frozen sections 25 µm thick were collected in cold 0.5 M Tris buffer (pH 7.6), then placed in blocking medium (10% normal rabbit serum [NRS]; Sigma) and 0.1 M DL-lysine/0.5 M Tris (60 minutes; room temperature). We incubated, without washing, in GAD-1440 (sheep-derived anti-GAD; Oer-

tel et al., 1981) at 1:2,000 (0.5 M Tris with 1% NRS). For 60 minutes the sections were at room temperature, then at 4°C for 24–60 hours. A matching series was Nissl stained. Controls included omission trials or incubation in preimmune serum. Only background immunostaining was seen in control sections.

Both the ABC (Hsu et al., 1981) and the peroxidase-antiperoxidase (Sternberger and Joseph, 1979) methods were used. We preferred the ABC method with the Vectastain kit (Vector Laboratories) for its superior contrast. Rinses (three for 10 minutes each) in Tris (0.5 M; pH 7.6) were followed by incubation in biotinylated rabbit anti-sheep immunoglobulin (1:200; 30 minutes), then further rinses and incubation in ABC reagent (at the manufacturers' recommended dilution). More rinses preceded intensification (0.05% DAB/0.01% $H_2O_2$; 10–30 minutes). After further rinsing, sections were mounted from dilute (0.01–0.05 M) PB onto gelatinized slides. The osmium-thiocarbohydrazide-osmium method was used to intensify the DAB signal and enhance contrast (Willingham and Rutherford, 1984). Sections were dehydrated in alcohols, rehydrated, placed in 0.005% $OsO_4$, moved to 0.05% thiocarbohydrazide, and then the $OsO_4$ step was repeated (with 10-minute water rinses between each step). The tissue was then dehydrated in ascending alcohols, cleared in xylenes, and coverslipped.

### Data analysis

Representative drawings of BDA-labeled axons and of the GABAergic terminals were made with a planapochromatic lens, under oil immersion, using a drawing tube. The experiment was accepted for analysis only if the locus of the labeling matched the results from other, WGA-HRP experiments. The position of corticothalamic giant or GABAergic giant terminals (Fig. 3A–F: green dots) was plotted on a computer-driven microscope analysis system (Neurolucida; MicroBrightField, Colchester, VT). The architectonic borders drawn independently from nearby Nissl-stained sections were then overlaid. The schematic superimposition of three levels of analysis—cytoarchitecture, corticogeniculate giant terminals, and GABAergic giant endings—was used to compare their respective distributions (Fig. 3). The dimensions of giant axon terminals (Table 1) were determined by measurements with an ocular micrometer.

## RESULTS

### Corticothalamic giant axon terminals

We illustrate in detail the results from studies of AII (the second auditory cortical area); they provided many such corticothalamic giant terminals (Figs. 1A,C, 3: black dots, 5A) and were representative of the outcome in other experiments (Fig. 4). Injections of BDA were made in several auditory cortical areas, including the primary auditory cortex (AI; Fig. 4A), the anterior auditory field (AAF; Fig. 4B), and the posterior auditory area (P; Fig. 4C), as well as the posterior ectosylvian cortex (EP; Fig. 4D), insular cortex (Ins; Fig. 4E) and temporal cortex (Te; Fig. 4F). Deposits in each area labeled CG axons terminating almost entirely in the dorsal division.

Deposits of BDA in area AII (Downman et al., 1960) bulk-filled axons in specific parts of the medial geniculate body (Figs. 1A,C, 3G,H). A typical deposit was ≈2 mm in diameter (Fig. 1A: lower inset, star) and extended from the pia to the white matter (Fig. 3H: black) without encroaching onto subcortical axons. This region was classified as AII on the basis of cortical cytoarchitecture (Rose and Woolsey, 1949; Winer, 1992) and by its physiologically verified corticofugal connections with the inferior colliculus (Andersen et al., 1980a) and the auditory thalamus (Andersen et al., 1980b). The present study, which was connectional only, labeled nuclei in the dorsal division of the medial geniculate body (Fig. 1A: upper inset). In the dorsal nucleus, corticothalamic axons were present in large numbers (Fig. 3A–F). The variety of their terminal plexuses suggested that they represent a structurally diversified population. Most of these fibers had delicate terminals ≈0.5 μm in diameter in the neuropil (Fig. 1C: 3). A second type had much thicker preterminal trunks with oblique side branches that ended in swellings, which resemble axonal boutons (Fig. 1C: 2). These two varieties correspond closely to corticofugal axons previously identified in morphological, connectional, and ultrastructural studies of different thalamic nuclei, including the medial geniculate body (Ramón y Cajal, 1911; Guillery, 1966; Morest, 1975; Jones, 1985).

A third class, the corticogeniculate giant (CG) axons, was significantly larger still and had a far more complex configuration. As a framework for analyzing the terminal architecture of CG axons, they were subdivided into four

Fig. 1. Giant axonal endings and other auditory corticothalamic axons. **A**: Characteristic examples of corticothalamic giant (CG) axon terminals drawn from the dorsal nucleus of the medial geniculate body (**upper inset**, numbered circles). Several deposits of biotinylated dextran amines (BDA) were made in the second auditory cortical area (AII; **lower inset**, asterisk) and followed by a 21-day survival. The bulk-filled CG axons (1–4) were representative examples. A single section might contain hundreds of such endings (Figs. 4A, lower panel, 5B). For definitions of the various parts of giant axons, see the legend to Figure 5A. 1, The giant endings had an elaborate structure. They usually arose from a stem ≈2 μm thick, which, after emitting a few slender oblique branches, formed many terminal arrays. The most complex ones (such as this example) divided profusely, in circumscribed territories. Subsidiary branches arose from a large, rough-textured central core encrusted with fine (<1 μm in diameter), medium-sized (1–2 μm), or large (>3 μm) excrescences. The secondary trunks were sinuous and unbranched or had many clusters. The most elaborate endings might include up to 10 branches, many of which were transected (open circles at ends of processes) in these comparatively thin sections. 2, The simplest CG fibers had a substantial core and long, heterogeneous processes. 3, Giant ending with corkscrew, recurrent, and overlapping fibers that formed a local plexus. 4, A wide range of shapes in the central core arose from one preterminal fiber (lower right). 5, Representative, retrogradely labeled (coarse dots) thalamocortical tufted principal neurons, which were numerous in the dorsal nucleus (Winer and Morest, 1983b). Protocol for A–C: Planapochromat, N.A. 1.32, ×2,000. **B**: Characteristic rapid Golgi-impregnated type IV grumous axons redrawn from a previous study (Winer and Morest, 1984, their Fig. 4C) for comparison with the present, BDA-filled CG axons. 1, Parallels include several clusters arising from one stem. 2, Simpler endings like those in the BDA experiments (A: 2) were also present. 3, A lacuna was characteristic in the core of the CG terminals. 4, Another stellate terminal with a large core. **C**: Corticothalamic terminal field from the dorsal division (see A, upper inset, C) in which all the labeled axons were drawn to compare the various types. 1, Globular CG terminals were fragments of the large endings and had their characteristic structure. 2, Medium-sized preterminal fibers with acute, short lateral branches that ended in one bouton ≈2 μm in diameter. 3, Very fine fibers ≈0.5 μm thick formed a delicate meshwork among the coarser axons. Stippled profiles, unlabeled neurons. For abbreviations, see list.

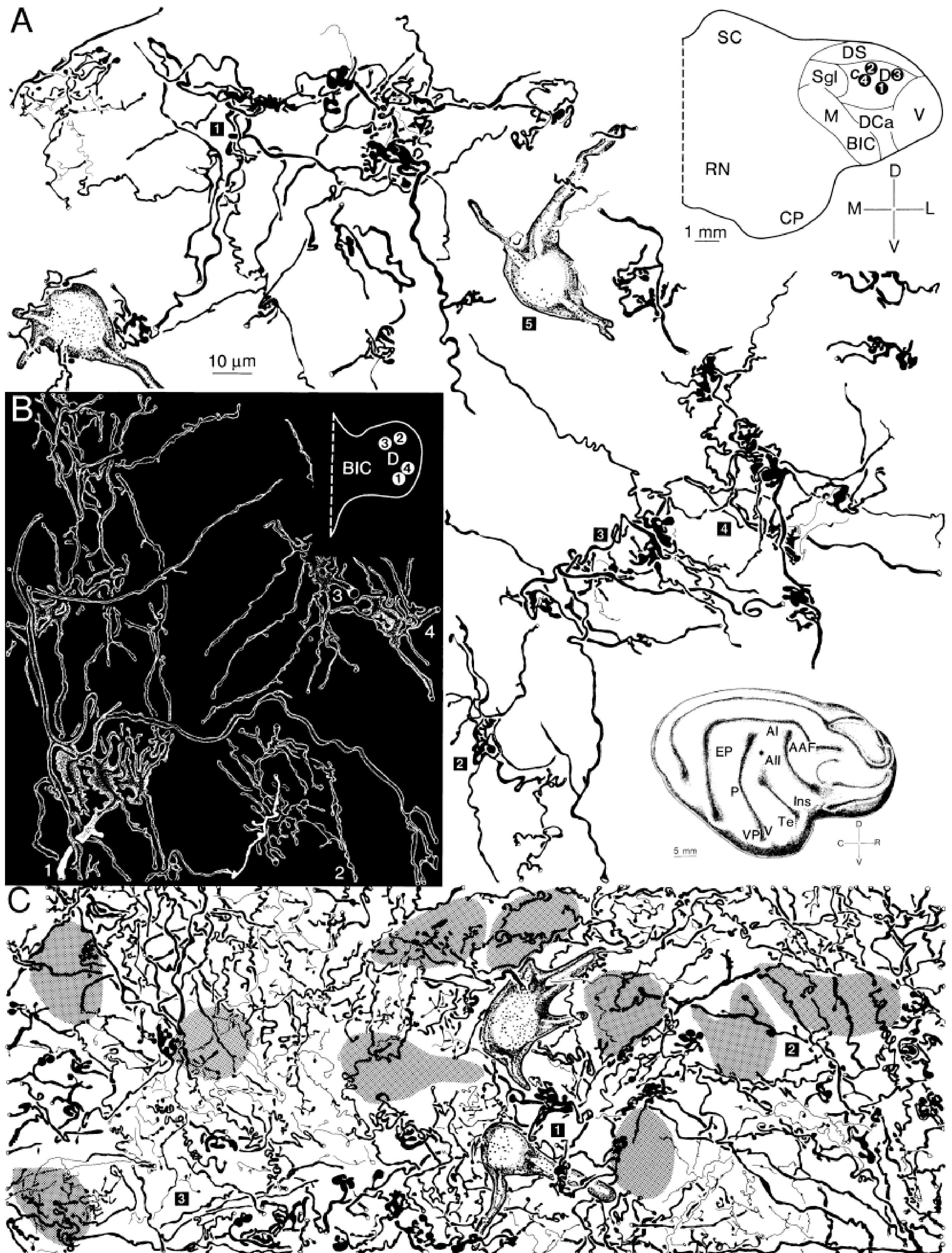


Figure 1

TABLE 1. Dimensions of Corticogeniculate Giant (CG) and GABAergic Giant (GG) Terminal Clusters

| | Mean diameter ± s.d.[3] (μm) | | Mean diameter ± s.d. (μm) | |
|---|---|---|---|---|
| | Minor axis | Range | Major axis | Range |
| CG terminals[1] | 5.4 ± 1.24 | 3.2–8.8 | 10.1 ± 3.2 | 4.8–18.4 |
| CG terminals[2] | 5.1 ± 1.1 | 3.2–8.0 | 8.1 ± 2.3 | 4.0–16.0 |

[1]A total of 100 clusters was collected from the medial geniculate subdivisions of the cases shown in Figures 3 and 4; they were measured as shown in Figure 5A. The sample was selected from the largest clusters in each case.
[2]A sample of 50 clusters was collected from the largest concentrations of labeling in the dorsal division of the medial geniculate body in 25-μm-thick GAD sections.
[3]Standard deviation.

parts in ascending order of complexity. The term bouton refers to individual swellings and dilatations ≈0.5–3 μm in diameter; these are located along the preterminal axonal segment or at the tip (Fig. 5A: i). An ending is formed by the boutons that arise from a single terminal strand (Fig. 5A: ii). A cluster contains several such terminal branches, each bearing boutons, and whose branches overlap; terminal strands in a cluster often are interconnected or apposed so closely that their individual strands cannot be resolved at the light microscopic level (Fig. 5A: iii). One or more clusters were present at least every 50 μm in regions with the heaviest labeling (Fig. 1C: 1), and they often had a patchy distribution. Finally, a complex consists of all the clusters that arise from a single corticothalamic preterminal trunk and that might extend through large territories of the caudo-rostral extent of a nucleus (see, for example, Fig. 3: DD, Vl). The full extent of a complex is unknown; the labeling approach in the present study marked thousands of axons and obscured the contribution of single fibers.

CG axonal endings had several unusual features (Fig. 1A). First, they were by far the largest axons in the auditory thalamus. Their principal axis was up to 18 μm long (Table 1) and the dimensions of the largest individual terminal clusters could approximate the somatic area of retrogradely labeled thalamocortical neurons (Fig. 1A: 5). The dimensions of a complex cannot be estimated accurately because the total number of clusters arising from one preterminal fiber is unknown. The CG endings were unique in the auditory thalamus, with a more elaborate terminal configuration than any axon known to be of midbrain origin (Jones and Rockel, 1971; Morest, 1975). Second, a preterminal fiber often gave rise to several clusters that were interconnected (Fig. 1A: 1, 3); these constitute the complex described above. Third, the plexus of terminal endings folded and wound sinuously upon themselves, with many hollows and spiral configurations. Fourth, the CG terminals closely resembled the profiles of a particular class of axon observed in rapid Golgi-impregnated material (Winer and Morest, 1983b, 1984: type IV grumous endings) and classified as giant terminals in the same nuclear territory (Fig. 1B).

## Giant GABAergic axon terminals

Immunostaining for GABA or GAD revealed a population of GABAergic giant (GG) terminals whose distribution overlapped substantially that of the giant corticogeniculate endings. The GG terminals were recognized readily, both in GABA- (Fig. 2A) and GAD-immunostained (Fig. 2B) preparations, including thick frozen and semithin postembedded material. The concordance between the results with different antisera to GABA was also substantial (not shown). One section through the dorsal division might contain several thousand GG terminals (puncta), whereas elsewhere in the medial geniculate body they were rare (Fig. 3A–F: green dots) or nonexistent (Fig. 5D).

The GG endings were so distinctive that even their fragments were recognized readily. The GG terminals had six definitive features. First, they were similar in size to the CG endings (compare Figs. 1A and 2A; see also Table 1). Second, they formed clusters of 5–25 endings (Fig. 2A: 1) interspersed in the neuropil between groups of immunonegative (Fig. 2: uniformly stippled profiles) and immunopositive (Fig. 2: shaded profiles) neurons. A third feature was their complex shape, often with elaborate lacunae (Fig. 2A: 2) and tortuous contours. This was marked even in the GABA material, where the immunopenetration was limited to the most superficial 2–4 μm of the tissue. It was still more striking in the GAD preparations, where enhanced reagent penetration revealed virtually entire, presumptive terminal segments (Fig. 2B: 1, 2). The

Fig. 2. Immunostained profiles in the dorsal division of the medial geniculate body demonstrated with antibodies to γ-aminobutyric acid (GABA) or glutamic acid decarboxylase (GAD). Shaded profiles, GABAergic cells. Stippled profiles, immunonegative neurons. **A**: GABA-immunostained axons (solid black outlines) from the upper 3–5 μm of the section were drawn from a representative specimen. Several types of puncta were present, but GABAergic giant (GG) terminals were noteworthy. Principal cells received moderate numbers of puncta near their somata; GABAergic neuronal perikarya were rarely so targeted. 1, Clusters of giant endings were prominent in the dorsal division neuropil. Individual endings were 4–16 μm in diameter (Table 1: GG terminals) and contained many fenestrated regions. These vacuolated areas closely matched the caliber of the major dendritic shafts of dorsal division projection neurons, and, in plastic material prepared for postembedding immunocytochemistry, these spaces contained profiles that may correspond to such dendrites (Fig. 5C: arrows). 2, The largest endings had an elaborate substructure, with overlapping and recurrent processes. 3, Most GG endings were in the neuropil and were rarely associated with the somata of immunopositive or immunonegative neurons. 4, Dendritic tips, nodes, or tufts were often surrounded by clusters of immunopositive axon terminals, some of which may be fragments of GG endings. 5, A few giant globular terminals had no lacunae. 6, Small GABAergic neuron. 7, Large GABAergic neuron. Insets: locus of observations and thalamic architectonic subdivisions. Protocol for A and B: Planapochromat, N.A. 1.32, ×2,000. **B**: GAD preparations confirmed many of the observations from the GABA material and revealed other facets of GG axonal structure. All the axon terminals from the depth of the 25-μm-thick section were drawn in this example, which accounts for the differential puncta density between the panels. 1, An entire terminal was sometimes contained in the section; single endings could be up to 30 μm long and 8 μm wide, with many blebs and irregularities. 2, The most complex examples resembled the most elaborate GABAergic specimens (A: 3). An unusual, perisomatic ending near an immunonegative cell (stippled). 3, Fragmented giant terminals, when sectioned through their long axis, had an elaborate internal structure. 4, Some fenestrations were associated with neural processes. 5, Endings in the neuropil had clusters of fine puncta that enveloped a thin process on an immunopositive neuron. 6, Clusters of tiny profiles could be the bouton-bearing elements from one or more giant GAD-positive ending, without the intervening, filamentous material in GABA preparations. Alternatively, these profiles may represent another type of terminal. The GAD-negative (stippled) neurons received many immunopositive puncta near their somata, whereas GAD-positive cells (shaded) had few such puncta except in rare instances (neuron above 1). 7, Small GAD-immunoreactive neuron. 8, Large GAD-immunoreactive neuron. Scale bar in A also applies to B.

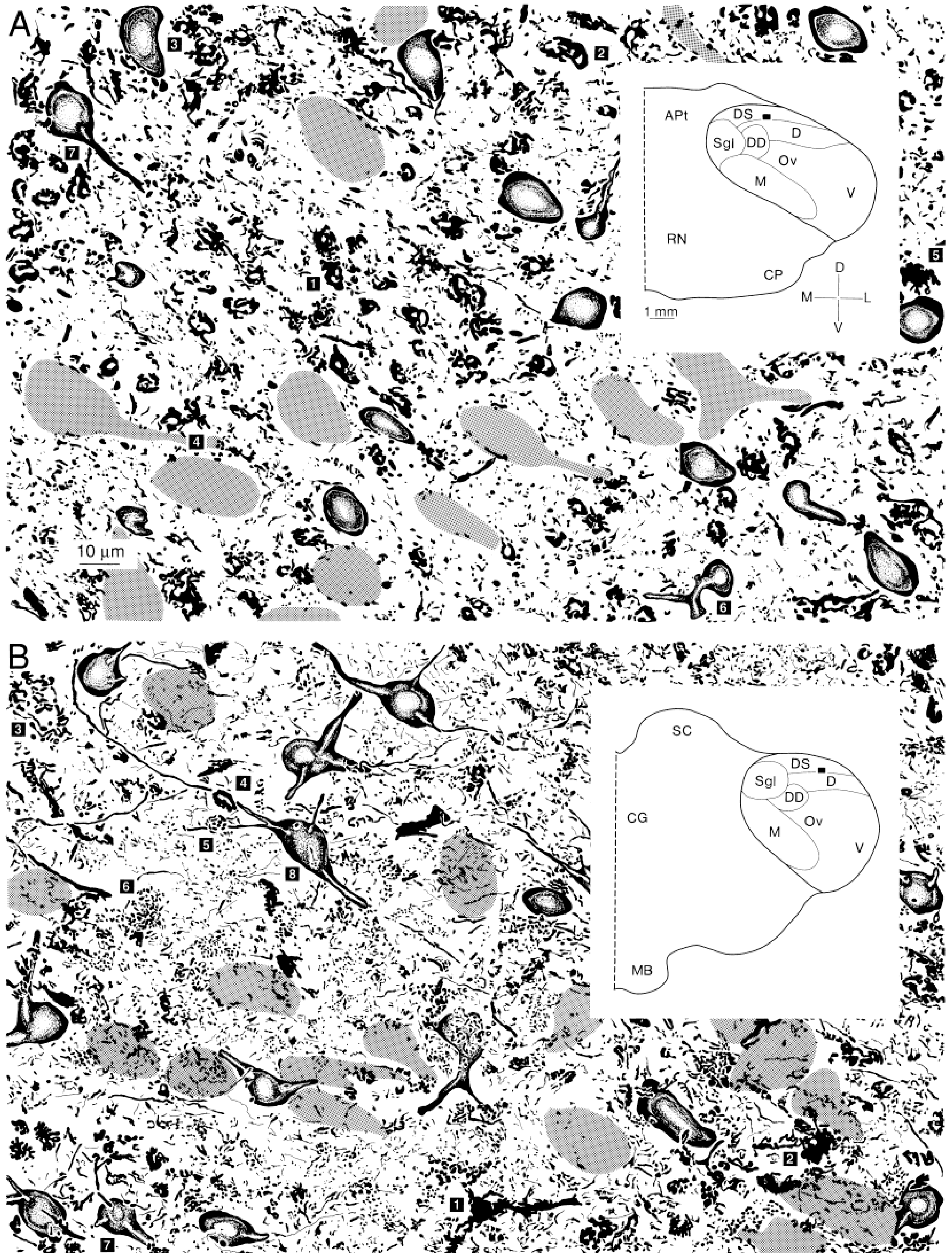


Figure 2

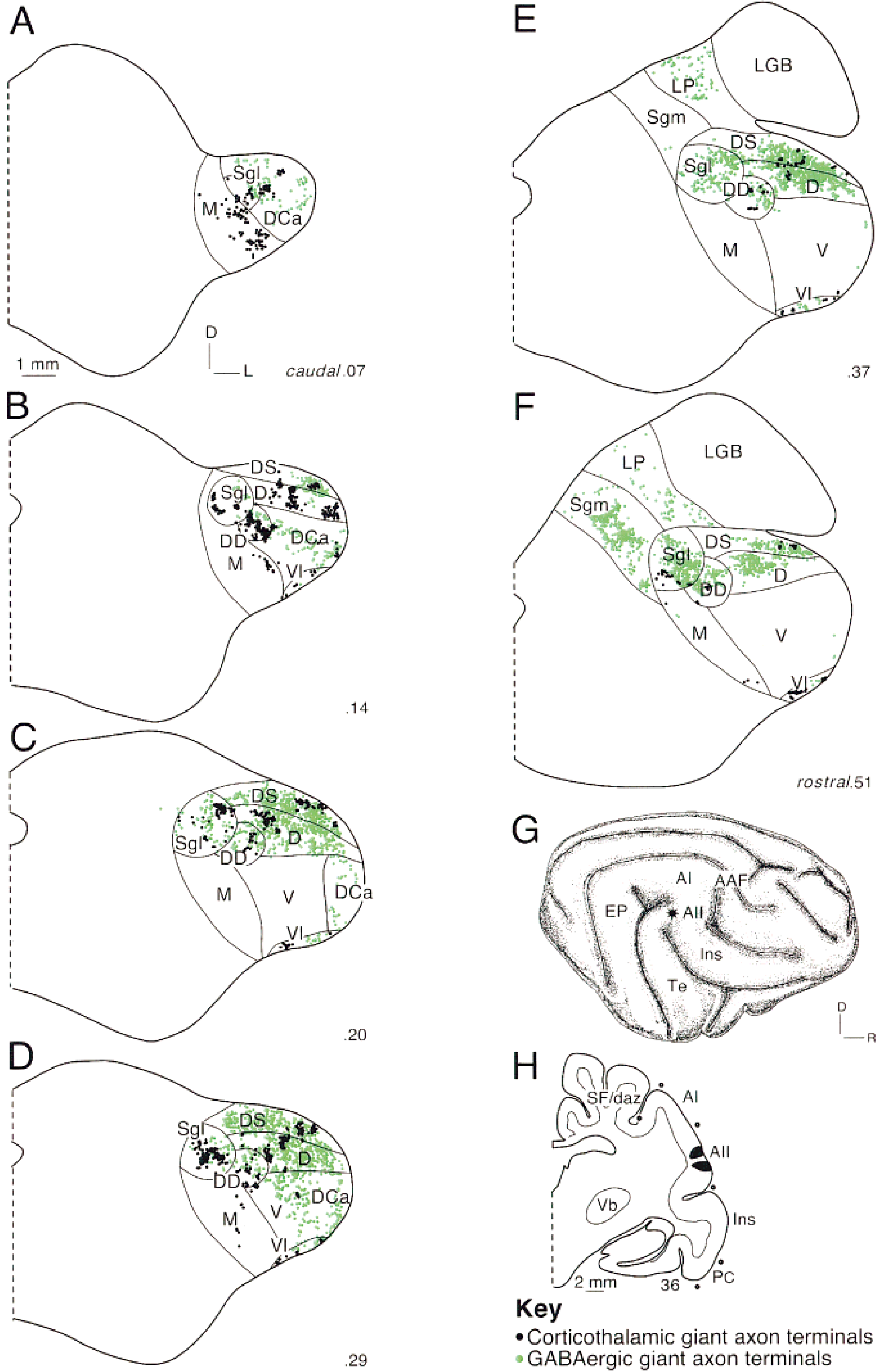


Figure 3

fragments noted above are a subset of these larger endings; all the other populations of puncta were far smaller and more granular. A fourth point was that these endings were associated overwhelmingly with neuropil and not with neuronal somata. Fifth, most GG puncta were found near dendrites (Fig. 2A: 4, 2B: 4), and rarely near neuronal somata (Fig. 2B: 2). In semithin plastic embedded material, these endings had a peridendritic affiliation as they surrounded clear, oval, or oblate profiles (Fig. 5C: arrows) that correspond in size (3–5 μm in diameter) and shape (round or oblate) to dendritic shafts sectioned en face (see Discussion; see also Peters et al., 1991). Finally, the internal structure of GG clusters as seen in GAD material had a more complex architecture than the profiles revealed in GABA-immunostained sections. In favorable GAD preparations, individual puncta were immunostained darkly, and intermediate axonal segments, devoid of terminals, were virtually transparent. This fine filamentous interposed material was difficult to draw and almost impossible to render photographically. Many of the focal clusters of fine GAD-positive terminals throughout the dorsal division (Fig. 2B: 6) could correspond to the individual segments in a GG ending. Including the intervening, puncta-poor segments results in images that correspond closely to those in the GABA preparations (Fig. 2A). In this material the terminals had distinct lobules, protrusions, and thorns, and they were fused into an apparently solid mass (Fig. 2A: 5).

There is also evidence for more than one population of GABAergic neuron in the dorsal division; many small (≈8–10 μm in diameter; Fig. 2A: 6, 2B: 7) and other much larger (≈12–15 μm; Fig. 2A: 7, 2B: 8) somata with appreciable dendritic immunostaining were noted (Huang et al., 1996). This point may be relevant when considering the source of the GG endings.

## Auditory thalamic distribution of giant axon terminals

The CG terminals in the auditory thalamus from a second BDA experiment involving AII were charted in one series of sections (Fig. 3A–F: black dots) and superimposed onto plots of the giant GABAergic terminals (Fig. 3A–F: green dots) from an independent, immunocytochemical preparation. The injection (Fig. 3G,H) was comparable in size and location to that in the other AII experiment (Fig. 1A: lower inset, asterisk), in which the foci of thalamic anterograde labeling were discrete and discontinuous. The sections with CG endings were chosen on the basis of labeling density. The number of such endings was conspicuous caudally (Fig. 3A: black dots), increased to its maximum in just a few sections (Fig. 3B,C) and then decreased (rostral to Fig. 3F). The dorsal division nuclei were involved principally. The projections formed independent patches; the topography of the groups of terminals was conserved between sections. Every dorsal division nucleus was involved. Even the ventrolateral nucleus, which was a compact region segregated spatially (Fig. 3B–F: Vl), was labeled consistently. Focal labeling was present within a nucleus (Fig. 3D: DS) and also crossed nuclear borders (Fig. 3B: DS, D, DD). Only a small part of AII was involved, so the projection may be highly divergent. The results from WGA-HRP studies (not illustrated) confirmed independently the nuclear distribution of auditory thalamic labeling present in the BDA experiments. Six further experiments, all involving BDA deposits in architectonically defined areas of primary and nonprimary auditory cortex (Fig. 4), produced labeling patterns virtually indistinguishable from the two AII deposits (Figs. 1, 3).

Giant GABAergic endings were found in virtually the same nuclei as the CG terminals. The GG endings (Fig. 3A–F: green dots) were plotted at levels corresponding closely to those with CG labeling; the concentration of GABAergic axon terminals continued rostrally (Fig. 3F). Superimposing the two types of endings for comparative purposes showed that their distributions were substantially similar (Fig. 3A–F). The strongest concordance was in the dorsal division nuclei, where even the ventrolateral nucleus contained both types of terminal in every section (Fig. 3B–F: Vl). Despite the much smaller number of CG terminals, their nuclear location matched well with that of the GG endings. Giant GABAergic terminals were usually present continuously through the caudo-rostral extent of a nucleus. Finally, GG terminals were relatively uniform in density (Fig. 2).

Fig. 3. Comparison of the distribution of the CG terminals (black dots) and giant GABAergic endings (green dots) in the auditory thalamus and adjoining nuclei. **A**: This was the only level at which the medial division (M) had many CG endings. Overall, there were comparatively few CG endings. **B**: The spatial correspondence between the two classes of giant terminals was substantial. **C**: The bulk of both types of terminal was concentrated in dorsal division nuclei. The focus in the ventral division included transitional parts of the caudal dorsal nucleus (DCa in B) that soon would be displaced by the ventral division (V in C–F), where there were few giant endings of either type. **D**: The characteristic pattern that will prevail in the remainder of the medial geniculate complex was present here. **E**: Giant GABAergic endings were found in the lateral posterior (LP) nucleus, and not in the lateral geniculate body (LGB). **F**: The medial part of the suprageniculate nucleus (Sgm), whose affiliations are visual and limbic (Benedek et al., 1997), had many GG endings. **G**: Lateral view of the hemisphere showing the locus of injection. **H**: Coronal section showing the injection site (black) and tracer diffusion (stippled) in area AII; the deposits here were remote from other areal borders and approached the junction with the white matter. Scale bar applies to G and H.

# DISCUSSION

## Comparison to previous studies of corticothalamic axons

Injections of *Phaseolus vulgaris* leucoagglutinin (Ojima, 1994) or biocytin (Bajo et al., 1995) in auditory cortex revealed many of the essential features of CG axons, which our results confirm. The points of agreement include origins from both primary and nonprimary auditory areas, a tendency for the terminals to form clusters, the complexity of single endings, the aggregations of these boutons in the dorsal division, the primarily peridendritic concentration of the terminals, and the several classes of corticogeniculate axon recognized on the basis of size and terminal configuration.

The new findings have various functional implications. These suggest that 1) CG axons are far more numerous than indicated by prior work, contributing thousands of such terminals to the dorsal division. They might therefore represent one of the principal, or even the dominant, corticofugal input. 2) All six dorsal division nuclei receive these endings. This implies that, at least within the dorsal division, a common function might be subserved by the giant endings of cortical origin. 3) Single terminals are more elaborate than suggested by prior studies using other

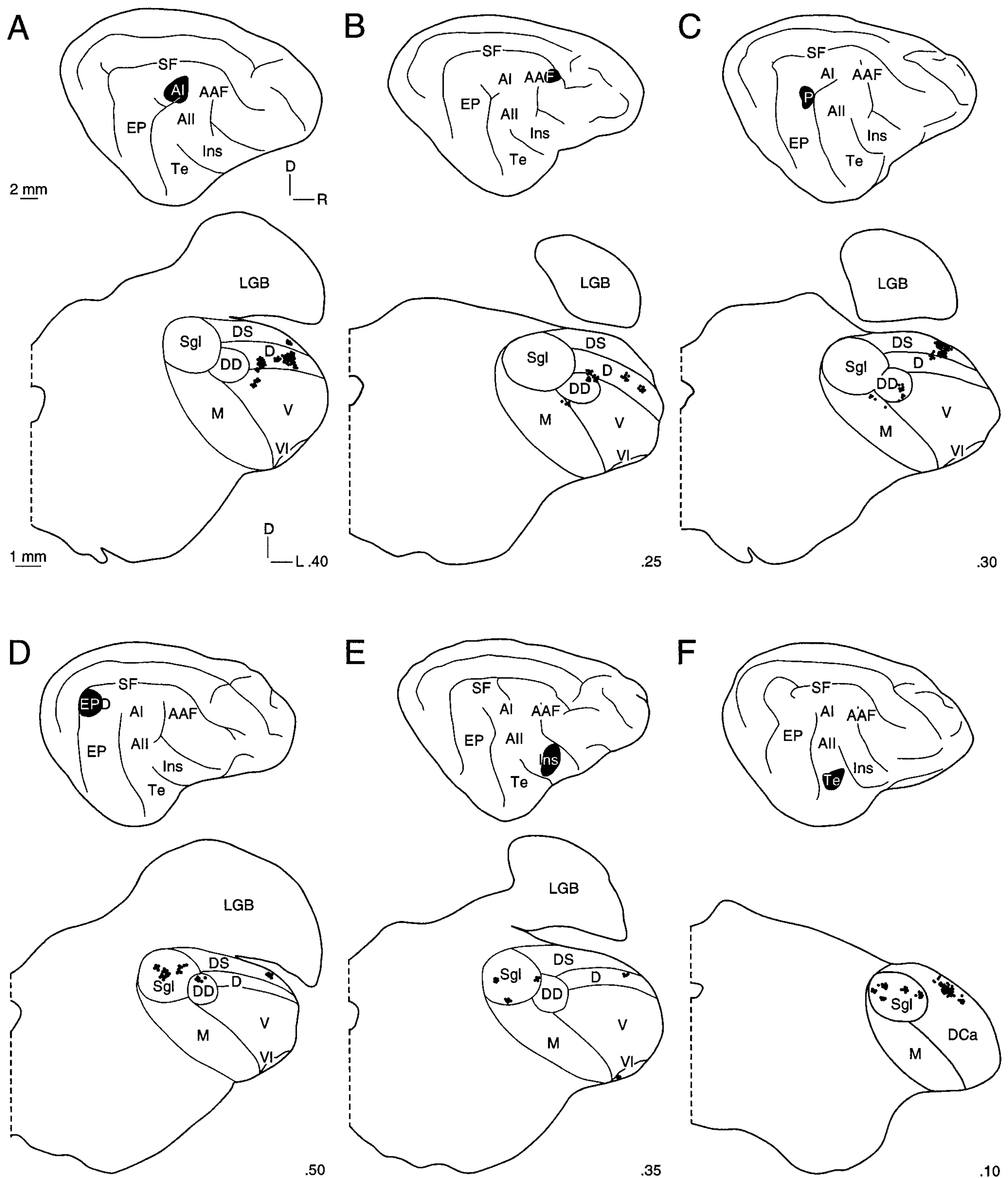


Fig. 4. Results from six further cortical BDA deposits (black regions in **upper panels**) and the ensuing distribution of corticogeniculate giant axon terminal clusters (dots in **lower panels**) from a representative section and centered at the heaviest concentration of such labeling. Other categories of corticogeniculate axon are not shown (see Fig. 1C). Single dots may represent more than one cluster (Fig. 5B). **A**: A deposit in the primary auditory cortical area (AI) labeled CG terminals clustered in the dorsal nuclei, with minor input to the ventral division at this level. **B**: Injections in the anterior auditory field (AAF) produced labeling virtually identical to the prior case. **C**: A deposit in area P involved more of the dorsal superficial nucleus and was otherwise similar to the preceding experiments. **D**: The projection from the dorsal part of the posterior ectosylvian gyrus (EPD) ended in the lateral part of the suprageniculate nucleus (Sgl), consistent with its perivisual and polysensory affiliations (see legend to Fig. 3F). **E**: The insular cortex (Ins), nearly 20 mm from the dorsal part of EP (see D), also had input to the suprageniculate nucleus (Sgl); this was the only experiment besides the AII deposits with labeling of CG axons in the ventrolateral nucleus (Vl) of the dorsal division. **F**: The foci of labeling after temporal cortex (Te) deposits were more caudal in the dorsal division yet as clustered and divergent as those from other experiments. Planapochromat, N.A. 0.70 × 475.

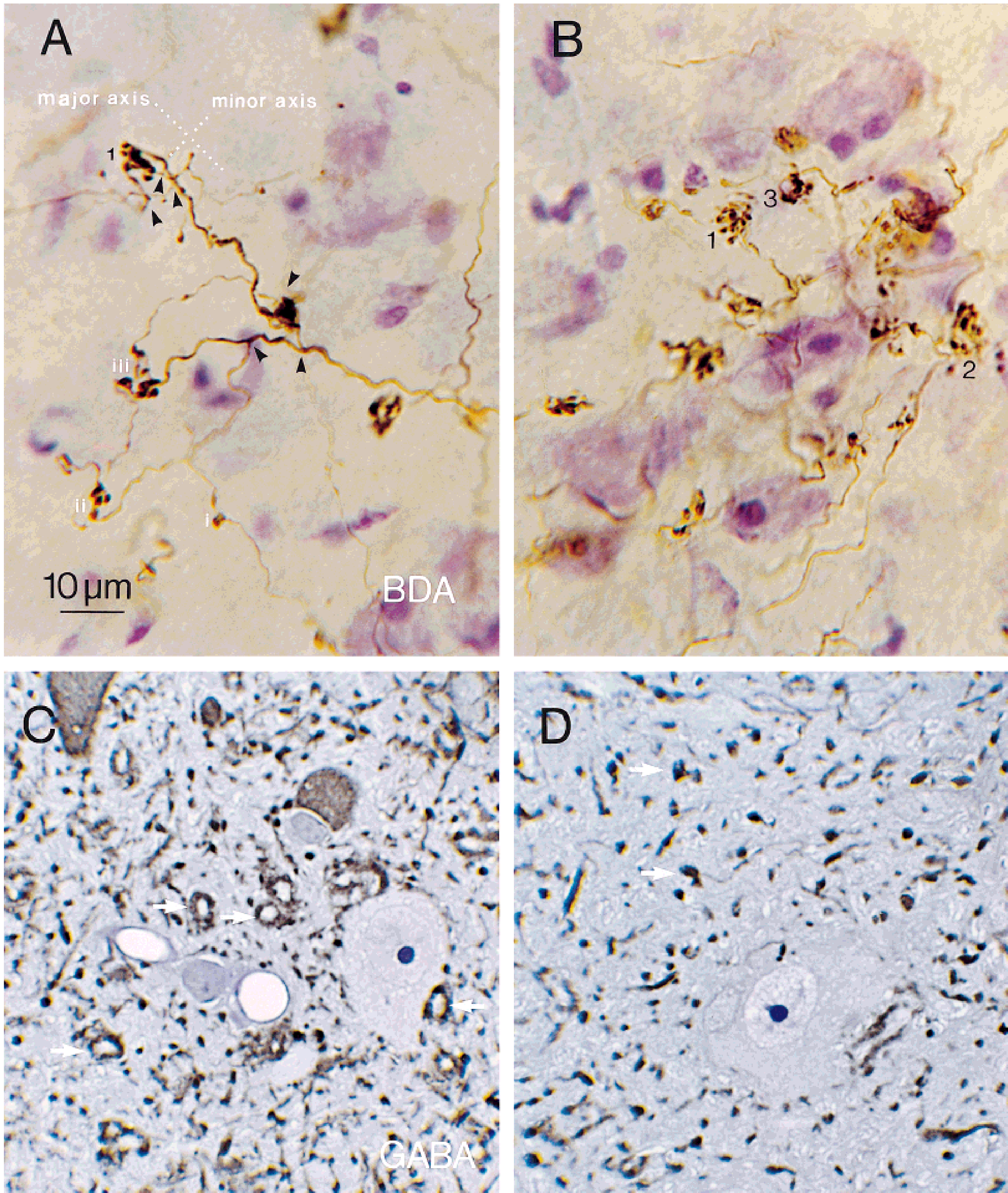


Fig. 5. Characteristic specimens of BDA-labeled CG axons (A,B) and of GG endings (C,D). Scale bar in A applies to all panels. **A**: Corticogeniculate giant axons consist of four subparts. Single boutons on a terminal branch (i) represent the smallest category, and many such branches make up an ending (ii); clusters of terminals (iii) in close proximity are the most conspicuous feature in the neuropil, whereas complexes (iv; not shown) contain many clusters that arise from one preterminal axon; their full extent is uncertain. 1, An axon and its terminal plexus in a counterstained preparation. The fiber branched at least 10 times in this section (some divisions are indicated with arrowheads) and had terminal forms ranging from globular (lower left) to fenestrated as well as single boutons de passage. None of the endings approached nearby neuronal somata. Protocol for A and B: frozen sections, 50-µm-thick, Nissl-counterstained; Edge Multiple Oblique microscope (Edge Scientific Instrument Co., Santa Monica, CA). Planapochromat, N.A. 1.0, ×1,000. **B**: Another BDA-labeled terminal plexus showing diverse endings. 1, Globular endings around a core with several vacuoles. 2, Complex terminal with heterogeneous boutons and among the largest endings in the neuropil. 3, Giant terminal with one large fenestration and some smaller ones. **C**: In the dorsal nucleus, the clasp-like, prospectively peridendritic (arrows) locus of many of the giant endings was clear. One ending (lower right arrow) encircled a dendrite and was apposed to the soma of an immunonegative neuron. Protocol for C and D: 1-µm-thick plastic-embedded sections (DiaSoria polyclonal rabbit anti-GABA, dilution 1:2,000), counterstained with toluidine blue. Planapochromat, N.A. 1.4, ×990. **D**: The ventral division had some club-shaped endings ≈2 µm in diameter, no GABAergic boutons near dendrites, and few if any giant terminals. In contrast, preterminal GABAergic fibers were plentiful.

tracers. Perhaps individual fibers form heterotypical endings, as do certain afferents in the cochlear nucleus (Kane, 1973). 4) Single CG axons may give rise to many terminal clusters, so that the activation of comparatively few corticothalamic projection cells may have both focal and widespread effects. The cortex might thereby influence functionally disparate types of neurons. 5) CG terminals in the dorsal division arising from AII projection neurons are much larger than their presumptive counterparts in the ventral division (Ojima, 1994). There may be regional differences in corticofugal influence that remain to be described. 6) The principal target of CG and of GG endings lies in the neuropil, principally upon dendrites. Such an arrangement might account for the dendritic complexity of dorsal division tufted neurons and could distinguish their electrotonic geometry from that of radiate principal cells. 7) Single CG clusters have a complex substructure, with many boutons. This could propagate cortical influence widely and rapidly onto ensembles of thalamic neurons. 8) The nuclear (and perhaps the synaptic) target of CG and GG axons coincides, with both concentrated preferentially in the dorsal division of the medial geniculate body. Such convergence suggests excitatory-inhibitory interactions that involve extrinsic and (possibly) intrinsic sources. 9) As many as three types of corticogeniculate axonal endings (small, large, and giant) are recognized. Perhaps the corticogeniculate system has parallel pathways analogous to those in the thalamocortical system. 10) The correspondence between type IV axons in rapid Golgi impregnations (Winer and Morest, 1984) and CG axons is sufficient to conclude that they are the same ending, as was suggested previously (Bajo et al., 1995). Because these endings are abundant in animals only a few weeks old, they represent an early specialization in the auditory thalamus. Finally, 11) CG axons arise from at least six other auditory cortical areas besides AII, and they are concentrated in the same dorsal division nuclei that have many GG endings. Both primary and nonprimary cortical fields contribute to this projection.

Giant corticogeniculate axon terminals also arise from rat auditory (Rouiller and Welker, 1991), somatic sensory (Hoogland et al., 1991), and sensory-motor (Rouiller et al., 1991) cortices and in the monkey visual corticofugal system (Rockland, 1994, 1996). In the rat medial geniculate body, these endings occur in a specific part of the dorsal division, whereas the somatic sensory giant corticofugal endings were found only in the posterior thalamic nucleus; in the primate, CG axons target the pulvinar nucleus. In each modality the giant axons thus seem to have a preferential origin (chiefly from nonprimary cortex) and a restricted set of targets (mainly in extralemniscal nuclei).

The fine structure of *Phaseolus vulgaris*-labeled CG fibers in rat posterior thalamus (PO) from cortical barrel field injections (Hoogland et al., 1991) is consistent with the present, high-resolution, light microscopic description in the cat medial geniculate body. Endings in PO concentrate in synaptic glomeruli, where they make abundant asymmetric synapses (and form about twice that number of puncta adhaerentia) onto what are probably dendritic spines (Hoogland et al., 1991). Large endings with a peridendritic distribution have also been seen in ultrathin sections from the rat dorsal division after auditory cortex tracer injections (Bartlett and Smith, 1995). Analogous glomerular endings in the monkey medial dorsal thalamic nucleus are labeled by frontal cortex injections of [$^3$H]leucine and [$^3$H]proline (Schwartz et al., 1991), suggesting that such terminals are not limited to primary sensory isocortex.

A parallel between prior work and this study is that the primary target of CG terminals is nearly always an extralemniscal thalamic nucleus. As was noted above, these parts of the thalamus are not well-understood; they are outside the topographically organized, modality specific, primary, or lemniscal pathway (Graybiel, 1972; Winer and Morest, 1983a; Jones, 1985). We shall return to this theme when we consider functional hypotheses about the CG endings.

## Sources of giant GABAergic terminals

The origin of the giant GABAergic endings is unknown. Three candidate sources—the thalamic reticular nucleus, the inferior colliculus, and Golgi type II cells—are considered in ascending order of our estimate of their likelihood (Fig. 6). Each prospective origin has different implications for the role of GG endings in auditory thalamic function.

The thalamic reticular nucleus projects to the principal thalamic visual, somatic sensory, and auditory nuclei (Jones, 1975). Reticular nucleus axon terminals typically are presynaptic to relay cell dendrites, and these endings have flattened or pleomorphic vesicles. The profiles of single reticular nucleus boutons in the electron microscope do not appear to be unusually large, but, without serial reconstructions, they cannot be excluded as a source of GG input (Montero, 1983 [rat]). Axon terminals from the thalamic reticular nucleus in the lateral geniculate body usually do not exceed 1 µm in diameter and are more diverse than corticogeniculate terminals (Ohara et al., 1980 [rat]). In the ventrobasal complex, no GG terminals are seen in serial ultrathin immunostained sections (Ohara et al., 1989 [monkey]). Insofar as thalamic reticular nucleus neurons are GABAergic (Houser et al., 1980), perhaps the GG axons from its auditory sector comprise two types: one with GG terminals that target the dorsal division, and a second variety that projects to the ventral and medial divisions and that forms smaller GABAergic endings. Despite evidence for thalamic reticular nucleus connectional specificity (Conley et al., 1991 [prosimian primate]), there are no reports of GG terminals, even in axon-filling experiments that reveal the wide range in the structure of axons ending in the ventrobasal complex (Cox et al., 1996 [rat]).

The inferior colliculus is another prospective source of GG axons. The largest neurons in the inferior colliculus are GABAergic (Oliver et al., 1994), and an immunoconnectional investigation demonstrated that many of these cells project to the auditory thalamus (Winer et al., 1996). Stimulation of the rat inferior colliculus evokes IPSPs in the medial geniculate body that arrive in advance of subsequent EPSPs (Peruzzi et al., 1997). It is unknown whether these responses depend on the giant axons. However, neither Golgi studies of midbrain axons terminating in the medial geniculate body nor electron microscopic analysis of the synaptic relations of such fibers has revealed any population of conspicuously large terminals that might represent the GG endings (Jones and Rockel, 1971; Morest, 1971, 1975). The latter studies, however, focused on material from the ventral division, where few if any of the largest terminals are present.

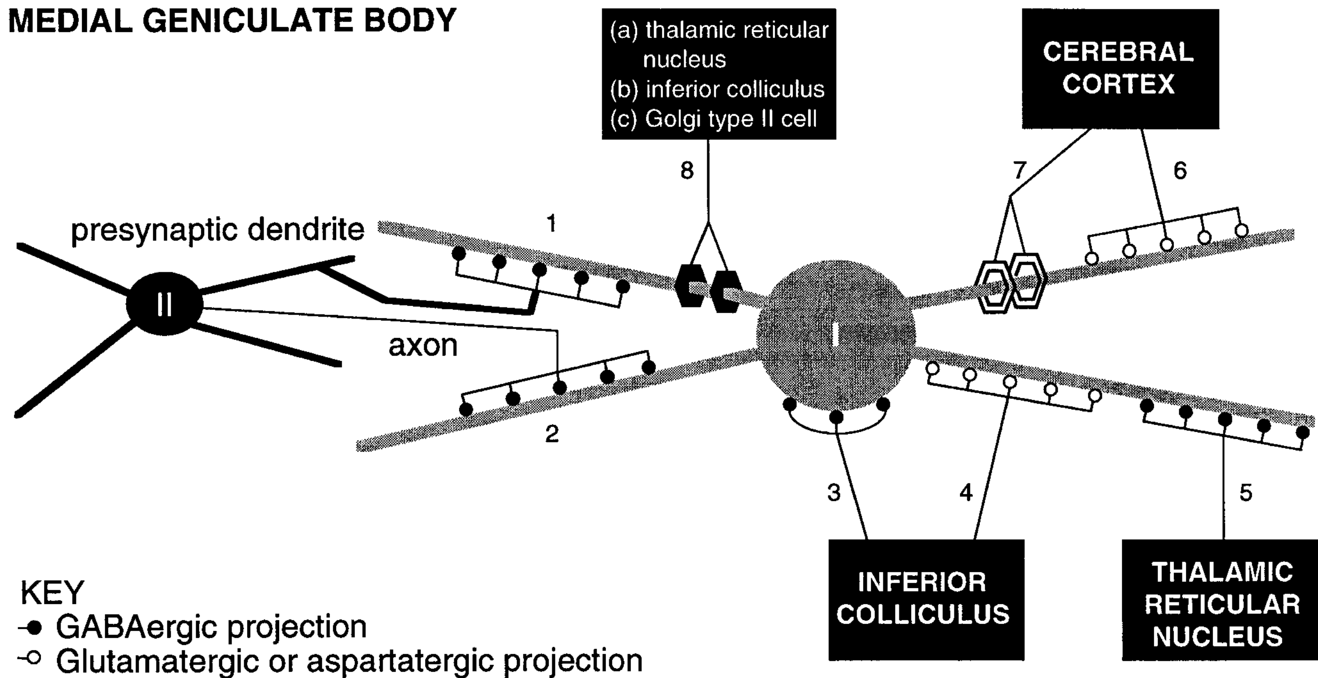


Fig. 6. Schematic summary of known and hypothetical circuit arrangements in the dorsal division of the cat medial geniculate body and related to the present results. 1, Golgi type II cell dendrites (II) may be presynaptic to those of principal cells (I; extrapolated from work on the ventral division; Morest, 1971). 2, The Golgi type II cell axon probably terminates on principal cell dendrites as well (Morest, 1975). 3, Inferior colliculus GABAergic neurons project to the medial geniculate body (Winer et al., 1996). A perisomatic input to type I cells is inferred, because their perikarya are studded with GABAergic axosomatic boutons (Winer et al., 1993) and no other source for such axosomatic endings is known. 4, Inferior collicular, presumptive glutamatergic/aspartatergic synaptic terminals may target intermediate dendrites (Jones and Rockel, 1971). 5, GABAergic projections from the thalamic reticular nucleus (Crabtree, 1998) terminate along intermediate and distal dendrites (Montero, 1983 [rat ventral division]). 6, Fine and medium-sized corticogeniculate axons interdigitate along the intermediate and distal dendrites with inferior collicular (4) and thalamic reticular nucleus (5) terminals. 7, Giant auditory corticogeniculate endings encircle the intermediate and proximal dendrites, often near branch points (not shown) where they would be situated ideally to influence $Ca^{2+}$-mediated dendritic spikes like those known to occur elsewhere (Deschênes, 1981; Pedroarena and Llinás, 1997 [guinea pig]). Although such spikes have not yet been demonstrated in the present neurons, their complex dendritic arbors, with many dichotomous branches (Winer and Morest, 1983b, 1984), would make them an appropriate candidate for such a role. If the CG endings contain many boutons, these could impose fine spatial and temporal constraints on dendritic excitability. Perhaps this serves as a pacemaker; one such preterminal axon may innervate many type I cells and thereby affect oscillations in several such neurons among small neural ensembles, as they seem to do in other systems (Walmsley and Bolton, 1994). 8, Giant GABAergic endings are slightly smaller than the corticogeniculate giant endings (Table 1), but they have the same dendritic target. Although the sources of these endings are unknown, three possible origins (a–c) are considered in the Discussion (Winer et al., 1993). The evidence is consistent with the idea that the large Golgi type II cell unique to the dorsal division is a candidate (Winer and Morest, 1983b, 1984; present results). The type I cells would receive three types of extrinsic excitatory (4, 6, 7, open circles) and five sources of inhibitory (1–3, 5, 8, solid circles) input.

GABAergic Golgi type II cell axons could be a source of GG terminals, though the evidence supporting this proposal is as indirect and incomplete as that for a thalamic reticular nucleus or an inferior collicular origin. The classic small stellate type II cells are unlikely contributors, because their axons are fine (Morest, 1975; Winer and Morest, 1983b, 1984). Indeed, such fibers from them as thin as 0.1 μm have been reported in the lateral geniculate body (Montero, 1987). The presynaptic dendrites of Golgi type II cells are distinct from the GG endings in size and structure (Morest, 1971). Moreover, they do not appear to be numerous enough to represent the entire population of GG terminals. A Golgi study of the dorsal division found a second, larger variety of local circuit neuron with a thicker axon than that of the smaller type II neuron (Winer and Morest, 1983b). Subsequent immunocytochemical studies found two populations of dorsal division GABAergic neurons—small and large—that resemble their Golgi-impregnated counterparts in size and somatodendritic shape (present results; Huang et al., 1996). The few examples of the larger intrinsic neuron and their axons in Golgi material constrain this argument. The absence of large type II/GABAergic neurons in the ventral division (Morest, 1975; Rouiller et al., 1990) and their relative rarity in the medial division (Winer and Morest, 1983a; Huang et al., 1996) are consistent with this idea, as is the absence of GG terminals in both (present results).

Another facet of dorsal division GABAergic organization supports the idea that the Golgi type II cell is the origin of the GG terminals. GABA studies in the rat (Winer and Larue, 1988, 1996) and mustache bat (Winer et al., 1992) dorsal division found no giant axon terminals and very few (<1%) immunostained neurons. The balance of the evidence favors the hypothesis that the large Golgi type II cell are a source of the GG terminals, though a more definitive treatment will entail intracellular filling studies and confirmation at the ultrastructural level. The main objection to this proposal is the comparative paucity of these neurons and the relatively high density of the GG endings.

## Giant axons in the vertebrate brain

Large or giant axon terminals are comparatively rare in the vertebrate central nervous system (Peters et al., 1991), and substantial numbers of these are concentrated in the lower auditory and primary vestibular nuclei (Ramón y Cajal, 1911). Here, high conduction velocity is at a premium for subsequent temporal coding (Kiang et al., 1973) or the rapid transmission of information critical for equilibrium (Wilson and Melvill Jones, 1979), respectively. In the auditory system the primary afferent fibers terminating as endbulbs of Held in the anteroventral cochlear nucleus upon spherical bushy cells (Ryugo and Fekete, 1982) form massive axosomatic endings, as well as axodendritic terminals (Ryugo and Sento, 1991). Likewise, cochlear nucleus axon terminals that arise from globular bushy cells (Smith et al., 1991) target principal cells in the medial nucleus of the trapezoid body and terminate as calyces of Held (Guinan and Li, 1990). The cardinal features of such axons are a thick (≈5 μm) preterminal fiber (Smith et al., 1991) immunoreactive for glutamate (Grandes and Streit, 1989) and terminals with many large, round synaptic endings and that form asymmetric pre- and postysynaptic membrane configurations (Smith et al., 1991). In the avian vestibular system, giant spoon endings (Peusner and Morest, 1977) arise from colossal vestibular afferent fibers (Peusner, 1980). These form axosomatic synapses in the tangential vestibular nucleus (Hinojosa and Robertson, 1967) whose terminal size closely matches that of both CG and GG endings. The main distinctions between the giant CG endings and the other classes of giant axons (endbulb, calycine, and spoon endings) are that the cortical axons are descending, numerous, have comparatively slender preterminal fibers, and appear to terminate chiefly in the neuropil as far as is known (Hoogland et al., 1991). This could exercise a permissive influence on the synaptic transmission of sensory information (Diamond et al., 1992). Too little is known about the GG terminals to permit definitive statements regarding their origin or synaptic targets. However, immunocytochemical analyses of neither the lateral geniculate body (Montero and Singer, 1985) nor the ventrobasal complex (Ohara et al., 1989; Ohara and Lieberman, 1993) have revealed such terminals.

## Possible functional correlates of giant axon terminals

Too few neurophysiological studies are available to permit firm conclusions about the role(s) of either class of giant axon terminal in the medial geniculate body. Results in other systems can serve as a frame of reference. Inactivating barrel cortex profoundly suppressed the response of thalamic cells in the medial part of the posterior thalamus (PO) to peripheral stimulation, while leaving intact the responsiveness of thalamic neurons in the adjoining ventral posterior medial nucleus (Diamond et al., 1992 [rat]). The cortex may thus allow information flow in the paralemniscal pathway, especially because the descending projections are denser than those ascending to POm. In contrast to rodent POm, the cat dorsal division receives abundant and widespread connections from the inferior colliculus (Calford and Aitkin, 1983) and from extralemniscal sources in the lateral tegmental system of the midbrain (Morest, 1965). In the primate visual system, striate cortex ablation profoundly altered inferior pulvinar receptive fields to movement orientation and direction, whereas superior colliculus lesions had far less impact (Bender, 1983). In certain nonprimary pathways, corticofugal control may be dominant at the expense of subcortical influences. A similar principle applies to the differential terminations of corticofugal and brainstem input to the inferior colliculus (discussed by Winer et al., 1998a).

Although no study has inactivated AII specifically and assessed changes in the dorsal division, temporary inactivation of cat primary auditory cortex affected medial geniculate subdivisions selectively. Dorsal division neurons showed decreased maximal firing rates and spontaneous discharge, with no appreciable change in signal-to-noise ratio (Villa et al., 1991). It was concluded that AI affected the dorsal division tonically. In the ventral division, only late reverberatory responses were affected (Ryugo and Weinberger, 1976). This supports the present, connectional results showing few CG endings from AI in the dorsal division (Fig. 4A). Cortical deactivation can also modulate classical associative conditioning in the medial division (Ryugo and Weinberger, 1978), suggesting important corticofugal effects even on nuclei outside the influence of CG axons.

Which physiological events might be affected by giant axonal endings in the dorsal division? One candidate is the temporally protracted, wave-like oscillations in global excitability (Aitkin et al., 1966). Such processes are not found elsewhere in the medial geniculate body (Aitkin and Dunlop, 1968; Aitkin and Prain, 1974). The broad tuning of single dorsal division neurons and their rather modest ability to encode temporal information, compared to that of the ventral division cells (Aitkin and Webster, 1972), suggests a role related more closely to changes in arousal and vigilance than to the explicitly sensory analysis that seems to be a hallmark of ventral division neurons. The large caliber and focal terminations of CG endings would support this idea.

Such a role might account for the two types of dorsal division projections. One is divergent and involves many subdivisions of auditory cortex (Winer et al., 1977), so that even a few thalamic neurons could reach remote cortical regions. The corticofugal neurons in these areas might affect dorsal division cells reciprocally (Winer and Larue, 1987 [rat]), depending on the degree of thalamocortical–corticothalamic coupling (Steriade, 1997). Area AII, a principal source of CG terminals, has considerable physiological plasticity (Diamond and Weinberger, 1984) that, unlike the case with area AI, may not require the participation of the nucleus basalis (Kilgard and Merzenich, 1998 [rat]). Perhaps the size and focal terminations of the giant terminals evoke rapid and regionally specific changes in the dorsal division. A second major dorsal division output arises in the suprageniculate nucleus and terminates in the frontal lobe (Kobler et al., 1987 [bat]; Kurokawa et al., 1990 [rat]). This would endow a multisensory nucleus (Benedek et al., 1997) with monosynaptic access to regions critical in cognition, long-term behavioral adaptations, and response control (Macmillan, 1992). It also underscores differences among dorsal division nuclei (Winer and Morest, 1983b, 1984). Dorsal division neurons project to the amygdala (Shinonaga et al., 1994) and are the target of input from the perirhinal cortex (Witter and Groenewegen, 1986), permitting important reciprocal relations between the limbic system and the auditory thalamus. A linkage between sensory information processing and pre-

motor planning could depend on suprageniculate projections to the caudate nucleus (Hu and Jayarman, 1986).

A triple role in cognitive, limbic, and motor responses would enable the sensory thalamus to influence behaviors critical for adaptive responses to sound, whereas local circuitry could modulate the structure of thalamic receptive fields. The giant axon terminals may provide a structural basis for rapid temporal and focal spatial control of thalamically mediated shifts in vigilance and attention that are integral to sensory processing.

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