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Descending projections to the inferior colliculus from the posterior thalamus and the auditory cortex in rat, cat, and monkey

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Abstract

Projections from the posterior thalamus and medial geniculate body were labeled retrogradely with wheat germ agglutinin conjugated to horseradish peroxidase injected into the rat, cat, and squirrel monkey inferior colliculus. Neurons were found ipsilaterally in the (1) medial division of the medial geniculate body, (2) central gray, (3) posterior limitans nucleus, and the (4) reticular part of the substantia nigra. Bilateral projections involved the (5) peripeduncular/suprapeduncular nucleus, (6) subparafascicular and posterior intralaminar nuclei, (7) nucleus of the brachium of the inferior colliculus, (8) lateral tegmental/lateral mesencephalic areas, and (9) deep layers of the superior colliculus. The medial geniculate projection was concentrated in the caudal one-third of the thalamus; in contrast, the labeling in the subparafascicular nucleus, substantia nigra, and central gray continued much further rostrally. Robust anterograde labeling corresponded to known patterns of tectothalamic projection. Biotinylated dextran amine deposits in the rat inferior colliculus revealed that (1) many thalamotectal cells were elongated multipolar neurons with long, sparsely branched dendrites, resembling neurons in the posterior intralaminar system, and that other labeled cells were more typical of thalamic relay neurons; (2) some cells have reciprocal projections. Similar results were seen in the cat and squirrel monkey. The widespread origins of descending thalamic influences on the inferior colliculus may represent a phylogenetically ancient feedback system onto the acoustic tectum, one that predates the corticocollicular system and modulates

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Abbreviations: AAF, anterior auditory field; AI, primary auditory cortex; AII, second auditory cortical area; APt, anterior pretectum; AvCN, anteroventral cochlear nucleus; BIC, brachium of the inferior colliculus; BICN, nucleus of the brachium of the inferior colliculus; BICN(c), contralateral nucleus of the brachium; Ca, caudate nucleus; Cb, cerebellum; CC, corpus callosum; CD, caudal dorsal nucleus; CeL, central lateral nucleus; CG, central gray; CIC, commissure of the inferior colliculus; CM, central medial nucleus; CN, central nucleus; CP, cerebral peduncle; Cu, cuneiform nucleus; D, dorsal nucleus *or* dorsal *or* dorsal division; DC, dorsal cortex of the inferior colliculus; DCN, dorsal cochlear nucleus; DD, deep dorsal nucleus; DH, dorsal hypothalamus; DNLL, dorsal nucleus of the lateral lemniscus; DS, dorsal superficial nucleus; EC, external cortex of the inferior colliculus; EPD, posterior ectosylvian gyrus, dorsal part; EPI, posterior ectosylvian gyrus, intermediate part; EPV, posterior ectosylvian gyrus, ventral part; EW, Edinger–Westphal nucleus; Ha, habenula; Hip, hippocampus; IC, inferior colliculus; IcT, intercollicular tegmentum; INLL, intermediate nucleus of the lateral lemniscus; Ins, insular cortex; IO, inferior olivary nucleus; III, oculomotor nucleus; IIIn, oculomotor nerve; I–IV, layers of the dorsal cortex of the inferior colliculus; I–VI, layers of the cerebral cortex; LD, lateral dorsal nucleus; LGB, lateral geniculate body; LL, lateral lemniscus; LMN, lateral mesencephalic nucleus; LN, lateral nucleus; LP, lateral posterior nucleus; M, medial division *or* medial; MB, mamillary bodies; MCP, middle cerebellar peduncle; MD, medial dorsal nucleus; mes V, mesencephalic nucleus of the trigeminal; MGB, medial geniculate body; MGBm, medial geniculate body, medial division; MLF, medial longitudinal fasciculus; MNTB, medial nucleus of the trapezoid body; MRF, mesencephalic reticular formation; P, posterior auditory field; PC, posterior commissure; Pd, posterodorsal nucleus; PL, posterior limitans nucleus; PN, pontine nuclei; Pol, lateral part of the posterior nucleus *or* rostral pole of the medial geniculate body; Pom, medial part of the posterior nucleus; Pul, pulvinar nucleus; Py, pyramidal tract; Ra, raphe nuclei; RN, red nucleus; RP, rostral pole of the inferior colliculus; Sa, sagulum; SC, superior colliculus; SCP, superior cerebellar peduncle; SCPX, decussation of the superior cerebellar peduncle; SF, suprasylvian fringe; SGI, superior colliculus, intermediate layers; Sgl, supragenicular nucleus, lateral part; Sg/M, supragenicular nucleus/medial division; SGP, superior colliculus, deep layers; SGS, superior colliculus, superficial layers; SNC, substantia nigra, compact part; SNL, substantia nigra, lateral part; SNR, substantia nigra, reticulated part; Spf, subparafascicular nucleus; Spfm, subparafascicular nucleus, medial part; SpN, suprapeduncular nucleus; St, subthalamic nucleus; Te, temporal cortex; TRN, thalamic reticular nucleus; V, ventral nucleus *or* ventral; Vb, ventrobasal complex; Ve, ventral auditory field; VI, abducens nucleus; VII, facial motor nucleus; Vl, ventrolateral nucleus; VNLL, ventral nucleus of the lateral lemniscus; VP, ventral posterior auditory area; ZI, zona incerta

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nonauditory centers and brainstem autonomic nuclei. Besides their role in normal hearing such pathways may influence behaviors ranging from the startle reflex to the genesis of sound-induced seizures. © 2002 Published by Elsevier Science B.V.

Key words: Thalamotectal; Posterior intralaminar system; Substantia nigra; Biotinylated dextran amine

1. Introduction

The inferior colliculus is a critical part of the ascending auditory system, and it is essential for normal hearing (Aitkin, 1986) and for accurate spatial orientation to sound (Jane et al., 1965). It receives afferent input from several medullary and pontine auditory nuclei (Beyerl, 1978). Its main upstream target is the medial geniculate body (LeDoux et al., 1987) and, to a lesser extent, the superior colliculus (Frisina et al., 1989). Classically, the thalamus has been seen as essentially a part of the ascending projection system, with little descending or reciprocal input to prethalamic nuclei (Schwartz, 1992). The primary descending projection instead arises in the auditory cortex (Andersen et al., 1980; Aitkin, 1986; Winer et al., 1998a). The absence of such reciprocal projections between the thalamus and the midbrain would seem to set the medial geniculate body apart since many collicular and subcollicular nuclei have descending interconnections with one another (Huffman and Henson, 1990). However, reports in several species find that the inferior colliculus receives modest descending input from various thalamic and perithalamic tegmental nuclei (Adams, 1980; Yasui et al., 1992; Frisina et al., 1997) and recent studies in the gerbil have documented the descending projections of single thalamic cells in tissue slices (Kuwabara and Zook, 2000). Estimates of the complete origin of such projections require sensitive retrograde tracers injected in the inferior colliculus. A second issue is the identity of morphological subtypes of thalamotectal neurons. This is pertinent to understanding the nature of the information that they might transmit to the midbrain. It is also unknown whether thalamotectal cells themselves receive ascending input from the inferior colliculus. If they operate independently, then their major synaptic influence may be cortical. Finally, it remains to establish whether the thalamotectal projection is similar in different mammals. Here, we report that these connections are more widespread and somewhat larger than expected, that they are concentrated in both sensory and intralaminar thalamic nuclei, that they involve different types of thalamotectal neurons in the sensory and posterior intralaminar systems, that some thalamotectal neurons are targets of complementary tectothalamic projections, and that this pathway has a similar organization in rodent, carnivore, and primate species. These features suggest that the descending thalamofugal system may have roles in auditory processing and extraauditory function that remain to be discerned.

2. Methods

Adult male rats (Wistar or Sprague–Dawley strain) weighing 275–350 g, and mature cats of either sex, weighing 3.5–5.5 kg and free of middle ear disease, were used. Adult squirrel monkeys (*Saimiri sciureus*) weighing 600–800 g were also studied. All experimental procedures were approved by the institutional animal care and use committee, and the postoperative status of experimental subjects was monitored by veterinary personnel as necessary.

2.1. Anesthesia, surgery, and perfusion

Rats were anesthetized with a mixture of ketamine (60.5 mg/ml), xylazine (6 mg/ml), and acepromazine (0.9 mg/ml) at a dosage (0.09 ml/100 g body weight; i.m.) which produced deep surgical anesthesia for about 60–90 min. Supplements at 10–50% the value of the original dose of ketamine were given as necessary to maintain analgesia. When areflexic to nociceptive stimuli, the rat was placed in a stereotaxic head holder (David Kopf, Tujunga, CA, USA) and a clean field was draped. A midline incision was made and a small craniotomy prepared rostral to the lambdoid suture and about 1.5–2 mm lateral to the midline. The dura was opened and a pipet (10–20 μm tip diameter) filled with 10% biotinylated dextran amine (BDA; Molecular Probes, Eugene, OR, USA) in saline was lowered stereotaxically through visual cortex into the inferior colliculus. Iontophoretic deposits were made by passing positive alternating current, 5–6.5 μA with a 7 s duty cycle for 15 min. The pipet remained in place for 5 min before withdrawal. Usually two deposits were made 0.5 mm apart along an injection track. The skin was closed and the animal recovered in a cage warmed by a heating pad. Postoperative analgesia was provided with buprenorphine (0.05 mg/kg, s.c.) and normal saline was given to maintain hydration.

Cats were sedated with acepromazine (0.2 mg/kg; i.m.) and induced with an inhalant anesthetic (isoflurane, ~3%). An endotracheal tube was inserted and the animal was maintained on 1–3% isoflurane in 1.0 l/min oxygen. When areflexic, the animal was mounted in a stereotaxic head holder (Kopf), a sterile field was pre-

pared, and a midline sagittal incision was made in the scalp. Lactated Ringer's solution was supplied intravenously and electrocardiogram, O_2 saturation, temperature, and respiration were monitored continuously throughout the procedure. A craniotomy $\sim 12 \times 12$ mm was made over the parietooccipital cortex and the dura was reflected. Visual cortex was removed using electrocautery and subpial aspiration until the underlying bony tentorium and inferior colliculus were exposed. The free margin of the tentorium was enlarged using a fine drill and/or rongeurs to reveal the posterolateral aspect of the inferior colliculus. Pressure injections of wheat germ agglutinin conjugated to horseradish peroxidase (WGA-HRP, 5%) in sterile saline were made in inferior colliculus subdivisions with a glass pipet with a 40 μm diameter tip and attached to a 1.0 μl syringe (Unimetrics, Shorewood, IL, USA). Deposits were made in 0.01 μl increments, 2 min apart. The pipet was withdrawn after 5 min and the exposure was cleaned and irrigated and the muscle and skin were closed. Buprenorphine (0.00875–0.0125 mg/kg; s.c.) was given before wound closure to ameliorate postoperative discomfort. A second dose was delivered after 12 h.

Young adult squirrel monkeys (2–3 years old) were induced by inhalation of isoflurane:nitrous oxide:oxygen (2:48:50%). Examination of the eardrums confirmed that the tympanic membranes were normal. Animals with ear disease and abnormal auditory thresholds were excluded from further study. Skin overlying the trachea, stereotaxic pin sites, and scalp was injected with lidocaine hydrochloride (2%) to augment general anesthesia. A tracheotomy secured the airway. After discontinuing the inhalation agents sodium pentobarbital (15–30 mg/kg, i.v.) was titrated to effect for the duration of the experiment. Normal saline with 1.5% dextrose and 20 mEq/l KCl was delivered at 6–8 ml/kg/h to support cardiovascular function. Core temperature was monitored with a thermistor probe and maintained at ~ 38°C with a feedback-controlled heated water blanket. Electrocardiogram and respiratory rate were monitored continuously through the experiment. The animals were maintained at a surgical plane of anesthesia for a survival period of 24–30 h.

The physiological mapping confirmed that the deposits were centered in a tonotopic division of the inferior colliculus. The limited neurophysiological data and studies now available in the squirrel monkey midbrain (Fitzpatrick, 1975; FitzPatrick and Imig, 1978) served as a frame of reference. Tungsten microelectrodes (FHC, Bowdoinham, MD, USA) with 1–2 MΩ impedance at 1 kHz were used for single and multiunit recordings. The characteristic frequency (CF) was estimated for each penetration using the quietest search tone burst frequency that evoked spike activity. Frequency–level response areas were recorded by presenting 675 pseudorandomized tone bursts at different frequency and sound pressure level combinations. The frequency–level pairs spanned 2.5–72.5 dB SPL in 5 dB steps, and 45 frequencies in logarithmic steps across a 2–4 octave range, centered on the neuron's estimated CF. One tone burst was presented at each frequency–level step. The derived tuning curve for CF measurement is more reliable than CF estimation by audio-visual technique. After completing extracellular recordings within the inferior colliculus, selected locations were injected with 150 nl of WGA-HRP delivered by pressure (nanoliter injector, World Precision Instruments, Sarasota, FL, USA) through a glass pipet with a tip 30 μm in diameter.

2.2. Histology

Rats survived for 4–5 days and were then sedated with the ketamine mixture, anesthetized with sodium pentobarbital (50 mg/kg; i.p.), and perfused transcardially with phosphate buffer (PB) followed by 1000 ml of freshly prepared paraformaldehyde (4%) in PB at room temperature. After 1 h, the fixative was flushed with 10% sucrose in fixative and the skull was dissected, the brain was blocked in the stereotaxic plane (Gergen and MacLean, 1962) and cryoprotected in 30% sucrose. Frozen sections 50 μm thick were cut and collected in PB. Sections were reacted for BDA using an ABC Elite kit (Vector Laboratories, San Mateo, CA, USA) and cobalt nickel intensified diaminobenzidine (DAB).

After a 24–48 h survival, cats were reanesthetized with sodium pentobarbital (26 mg/kg; i.v.) and perfused transcardially for HRP-tetramethylbenzidine (TMB) histochemistry. A wash with 0.12 M PB at room temperature for 2–3 min was followed by 1000 ml of paraformaldehyde (0.5%) and glutaraldehyde (0.5%) in PB, then 2000 ml of paraformaldehyde and glutaraldehyde (1 and 1.5%, respectively) in PB at 4–10°C. After 1 h, the fixative was washed out with 500 ml of 10% sucrose/PB and the brain was dissected, blocked in situ, then removed and placed in 30% sucrose in PB and refrigerated overnight or until equilibrated in the sucrose solution. Frozen sections 60 μm thick were cut on a sliding microtome and collected in PB. One series was reacted with TMB (Mesulam, 1982) and counterstained with neutral red, the other series was reacted with DAB and counterstained with cresyl violet. A similar procedure was followed for the squirrel monkeys.

2.3. Analysis

Sections were drawn from a microprojector and the locations of retrogradely filled cells charted using a drawing tube or on a computer connected to a micro-

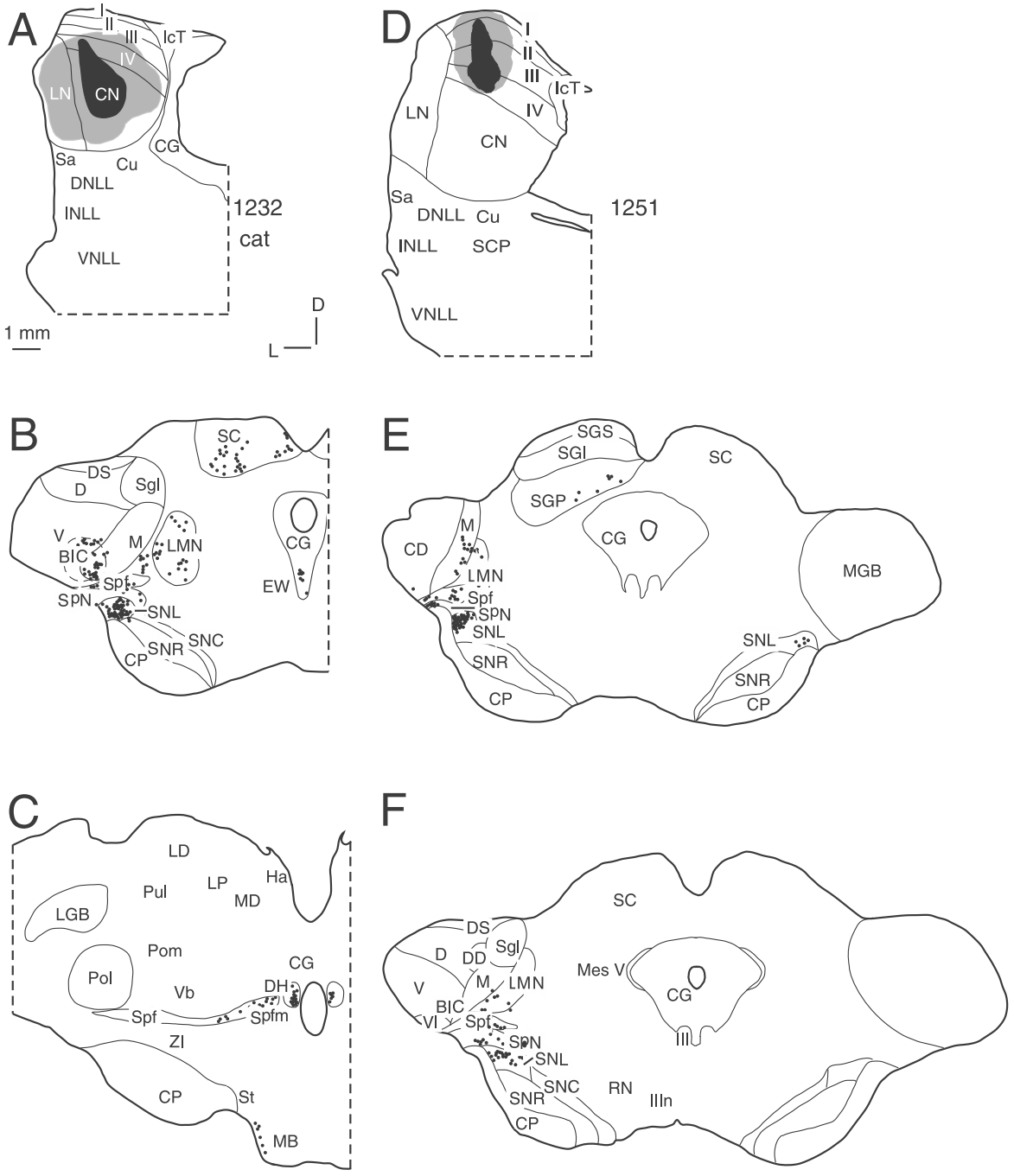


Fig. 1. Results from representative experiments in the cat; similar results were seen in the rat (Fig. 2A–C), squirrel monkey (Fig. 3), and mustached bat (not shown). (A) A large deposit of WGA-HRP in the central nucleus of the inferior colliculus (black) diffused slightly into the deep layers of the dorsal cortex (gray) and adjoining lateral nucleus. (B) Retrogradely labeled and/or bulk-filled neurons were concentrated in the substantia nigra (SN), superior colliculus (SC), and lateral mesencephalic nucleus (LMN). Neurons in the nucleus of the brachium of the inferior colliculus and the medial division were also labeled. (C) The rostral limb of the subparafascicular nucleus had retrogradely labeled cells in its medial portion. (D) In a second case the deposit was centered in the dorsal cortex. (E) Neurons in the LMN and the medial division were labeled. (F) The caudal, but not the rostral, parts of the posterior intralaminar system had labeled neurons.

scope (Neurolucida; MicroBrightField, Colchester, VT, USA). Cytoarchitectonic boundaries were determined in adjacent, Nissl stained sections and reconciled for differences in shrinkage with the experimental tissue.

3. Results

3.1. Cytoarchitecture

For the cat inferior colliculus, we followed an architectonic scheme based on Nissl, Golgi, and fiber stained material (Oliver and Morest, 1984) except in the lateral nucleus, which was defined as somewhat larger based on cytoarchitecture and corticocollicular input (Winer et al., 1998a,b). In the rat, our interpretation of the dorsal cortex is congruent with that of some accounts (Coleman and Clerici, 1987; Faye-Lund, 1985; Paxinos and Watson, 1998) and slightly larger than in other studies (Faye-Lund and Osen, 1985). Likewise, we follow accepted architectonic definitions of the external nucleus (Paxinos and Watson, 1998). Cat thalamic boundaries are derived from neuronal architecture (Morest, 1964), connectional data (Winer et al., 1998a), and atlas (Berman, 1968) results. Similarly, subdivisions of the rat thalamus follow cytoarchitectonic studies (Winer et al., 1999), connectional (LeDoux et al., 1985; Arnault and Roger, 1990; Yasui et al., 1992), chemoarchitectonical (Winer and Larue, 1988), and atlas (Paxinos and Watson, 1998) references. For the monkey inferior colliculus and medial geniculate body we followed standard architectonic schemes (Gergen and MacLean, 1962; Emmers and Akert, 1963).

The results from cases in two cats, one rat, and one monkey are presented; they are representative of others. In the cat WGA-HRP injections targeted either the central nucleus or the dorsal cortex of the inferior colliculus. The rat experiments used iontophoretic deposits of WGA-HRP, or of BDA, a tracer that labels bidirectionally by diffusion or bulk filling (Brandt and Apkarian, 1992) and by transport in some cases (Winer et al., 1998a). Monkeys received WGA-HRP deposits only.

3.2. Connections in the cat

Two experiments with cats are reported first (Fig. 1). One deposit (Fig. 1A: black represents the injection core, gray the spread of tracer) filled much of the central nucleus of the inferior colliculus, with lesser involvement of the deep layers of the dorsal cortex (Fig. 1A: CN); minor diffusion into the lateral nucleus and the medial part of the central nucleus is unlikely to have contributed substantively to tracer uptake. The ensuing retrograde labeling filled most of the ipsilateral medial superior olive (not shown), where low to middle frequencies are represented (Guinan et al., 1972). The retrograde labeling in the medial geniculate body was concentrated in the lateral and central parts of the ventral division, which contains a comparable range of characteristic frequency (Imig and Morel, 1984) and is virtually filled with axon terminals (not shown). As expected, the lateral part of the substantia nigra also had many retrogradely labeled cells (Olazabal and Moore, 1989).

Thalamotectal neurons were concentrated in the lateral mesencephalic nucleus adjoining the medial geniculate complex at approximately its caudal one-third (Fig. 1B: LMN) and in the peribrachial region (Fig. 1B: BIC). The lateral mesencephalic nucleus neurons were multipolar and had somata ~ 20 μm in diameter with three or four thick primary dendrites. These neurons were dispersed widely. The neuropil adjoining them there had a sparse concentration of diffuse terminal labeling (not shown). Some peribrachial neurons had a wider range of sizes and shapes and were embedded in a plexus of labeled axons terminating nearby.

A second focus of retrogradely labeled cells was in the anteromedial part of the subparafascicular nucleus (Fig. 1C: Spfm), which is a slender lamella interposed between the ventrobasal complex and the zona incerta (Fig. 1C: Vb, ZI) (Winer et al., 1988b). These neurons were smaller than those in the lateral mesencephalic nucleus and medial geniculate body, and they were oriented along the mediolateral axis with a primary dendrite at each pole. They were distinct from the still smaller cells of the nearby central gray, which clustered and were present bilaterally.

In another cat a deposit was centered in the deep layers of the dorsal cortex (Fig. 1D: III, IV), near the border with the central and lateral nuclei of the inferior colliculus but not crossing it. In contrast to the first case, the labeling in the cochlear nuclei and in the lateral and medial superior olivary nuclei was greatly reduced (not shown). As in the prior case, there were many cells labeled in the intermediate and ventral nuclei of the lateral lemniscus, and few in the contralateral dorsal nucleus.

Anterograde labeling in the ipsilateral medial geniculate body (not shown) involved all three divisions – ventral, dorsal, and medial – and it formed small, scattered foci, unlike the first experiment, where the labeling was virtually continuous. Input to the rostral pole, which was labeled extensively in the first case, was small.

The retrograde thalamotectal labeling also differed, with more in the medial geniculate body proper, especially the caudal part of the medial division (Fig. 1E: M). As in the monkey experiment (Fig. 3D), medial division neurons varied in size and shape. A second

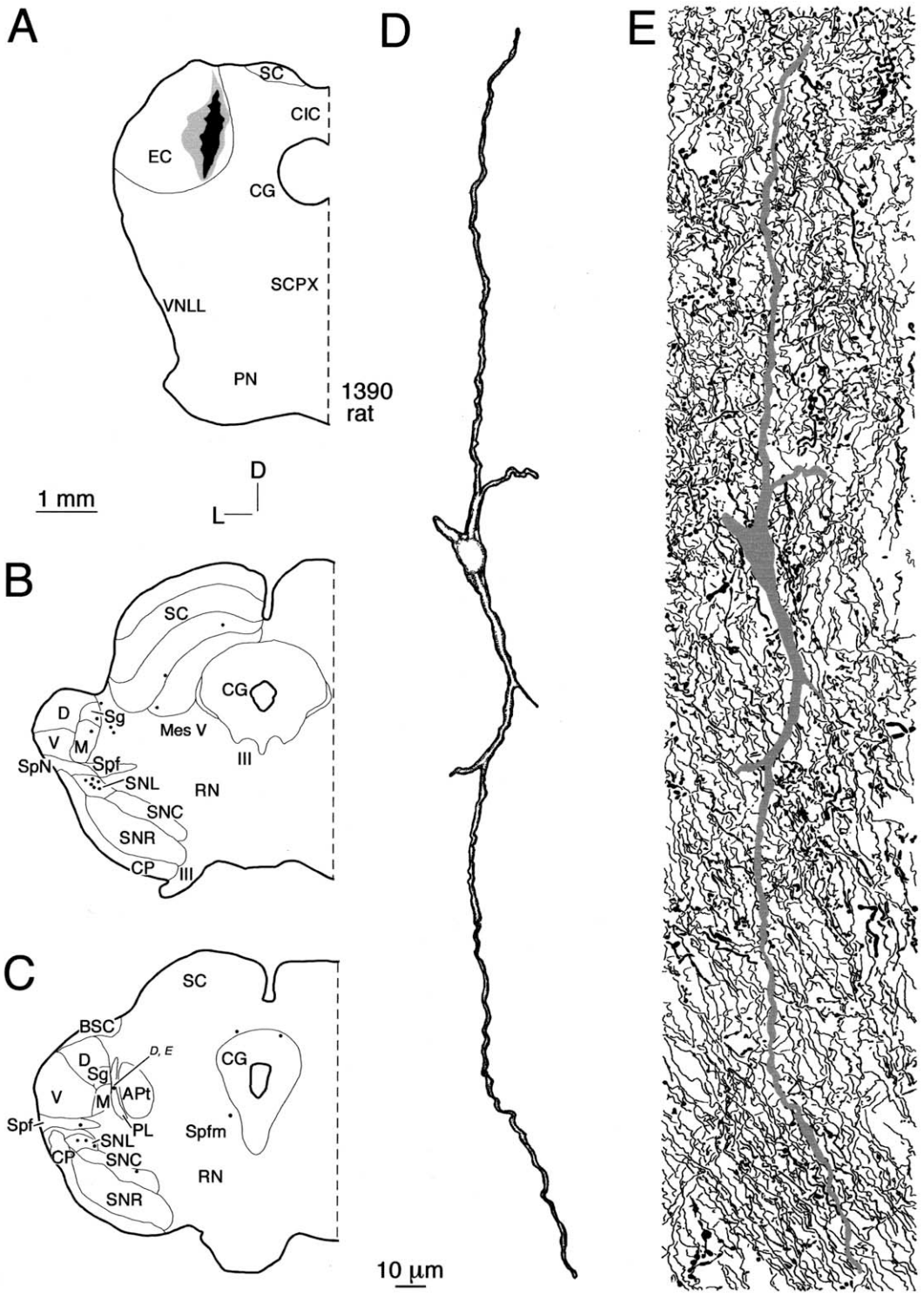


Fig. 2. (A) A tracer deposit in the rat external cortex. (B) The posterior thalamic labeling pattern is much like that in the cat (Fig. 1B). (C) Substantia nigra neurons were labeled by deposits in all inferior colliculus subdivisions. (D) An example of a bulk-filled neuron in the posterior limitans nucleus marked by this deposit. Many such cells have long, slender, sparsely branched dendrites reminiscent of tegmental, rather than specific sensory thalamic, neurons. (E) The same neuron (gray) embedded in a plexus of anterogradely labeled ascending axons. Protocol for D and E: planapochromat, N.A., 1,32*2000.

distinction was that the labeling in the intralaminar nuclei was concentrated in its caudal parts only (compare Fig. 1C and F: Spfm, Spf), with no involvement of the central gray.

3.3. Connections in the rat

In a representative experiment, a large deposit of tracer filled the medial aspect of the external cortex (EC) of the inferior colliculus (Fig. 2A: black and gray outlines). The BDA deposit resulted in comparatively few retrogradely labeled neurons and many well-filled axons. Such fibers were prominent in the ipsilateral olivary complex and throughout the lateral lemniscus, with intense anterograde labeling in the ipsilateral medial geniculate body in each division (not shown).

The thalamotectal neurons were found in the same nuclei as in the cat studies, including the medial division, abutting and sometimes within the suprageniculate nucleus, in the suprapeduncular nucleus, and in the central gray (Fig. 2B: M, Sg, SpN). Rostrally (Fig. 2C) the labeling declined abruptly and involved the rostral intralaminar nuclei only slightly (Fig. 1C: Spfm) as well as the central gray (Fig. 2C: CG).

3.4. Connections in the monkey

A large deposit targeted the central nucleus of the inferior colliculus (Fig. 3A) and labeled all divisions of the ipsilateral medial geniculate complex anterogradely, with weaker contralateral projections (not shown). In the subcollicular brainstem, the transport included many retrogradely labeled cells in the ipsilateral ventral nucleus of the lateral lemniscus and in the medial superior olive. There was a strong anterograde projection to the nucleus sagulum, and many labeled neurons in the contralateral lateral superior olive, and in the dorsal and anteroventral cochlear nuclei (Fig. 3A: DCN, AvCN).

Thalamotectal labeling was concentrated in both the medial geniculate body and the intralaminar nuclei. Within the auditory thalamus, most labeled cells were in the medial division or at its border with the overlying suprageniculate nucleus (Fig. 3B: Sg/M). These cells were noteworthy for their heterogeneity and included fusiform neurons <10 μm in diameter (Fig. 3D: 10), medium-sized multipolar neurons ~ 15 μm in diameter (Fig. 3D: 4,7), and magnocellular neurons >25 μm (Fig. 3D: 3). In contrast, neurons labeled in the posterior intralaminar system were more uniform, with spindle-shaped cell bodies ~ 15 μm in diameter and primary dendrites at their lateral and medial poles in transverse sections. Discrete foci of anterograde labeling sometimes closely abutted, but did not enter, the fields of retrogradely labeled neurons. This segregation of the tectal–intralaminar and thalamotectal systems suggests a surprising specificity in their connectivity, and confirms that retrograde–anterograde reciprocity (Fig. 2E) is not the sole organizing principle with respect to their projections. Moreover, some of the retrogradely labeled cells lay in small clusters (Fig. 3B,C), which argues as well against the notion of a diffuse projection.

The corticocollicular labeling was exclusively from layer V neurons in primary auditory cortex (AI), and consisted of small (~ 10 μm in diameter; Fig. 3E: 13, 16), medium sized (~ 15 μm; Fig. 3E: 1, 3), and large (>25 μm; Fig. 3E: 6, 15) pyramidal cells. Taken together, the data suggest that a broad range of cell types from auditory and non-auditory sources must converge onto the auditory midbrain (Figs. 2D, 3D,E, 4).

4. Discussion

4.1. Technical considerations

Given the few descriptions of thalamotectal projections available, it is pertinent to ask why studies that have injected retrograde axoplasmic tracers in the inferior colliculus have not detected this pathway. There are three plausible reasons: one is the relative insensitivity of autoradiography (Sousa-Pinto and Reis, 1975) or the inability of axonal degeneration to reveal small projections; a second is the unexpected origins of this input (Aitkin, 1986); finally, the small absolute size (perhaps a few hundred neurons in total) and diffuse nature of this pathway, which involves mainly neurons dispersed across subdivisions of the posterior thalamus whose identity is uncertain. Each of these factors militate against finding such a projection (Jones, 1985; Winer et al., 1988).

A related question is whether the present results could be artifactual, labeling some neural population that might be endogenously reactive (Mesulam, 1982) rather than particular thalamic neurons with specific midbrain connections. Evidence against this idea is the specificity of the locus of the labeled neurons, which was a systematic reflection of the site of injection, the volume of tracer deposited, and local variables such as the degree of damage and the spread of the tracer during injection. Another corroborative feature is the independence of anterograde and retrograde labeling. If both were always present in labeled areas, the possibility of transneuronal transport might arise (Spreafico et al., 1985; van der Want et al., 1997). The presence of clusters of neurons labeled without overlying masses of axon terminals, and aggregates of axon terminals without labeled neurons, suggests that the likelihood of neuron-to-neuron transfer was minimal (Herzog and Kum-

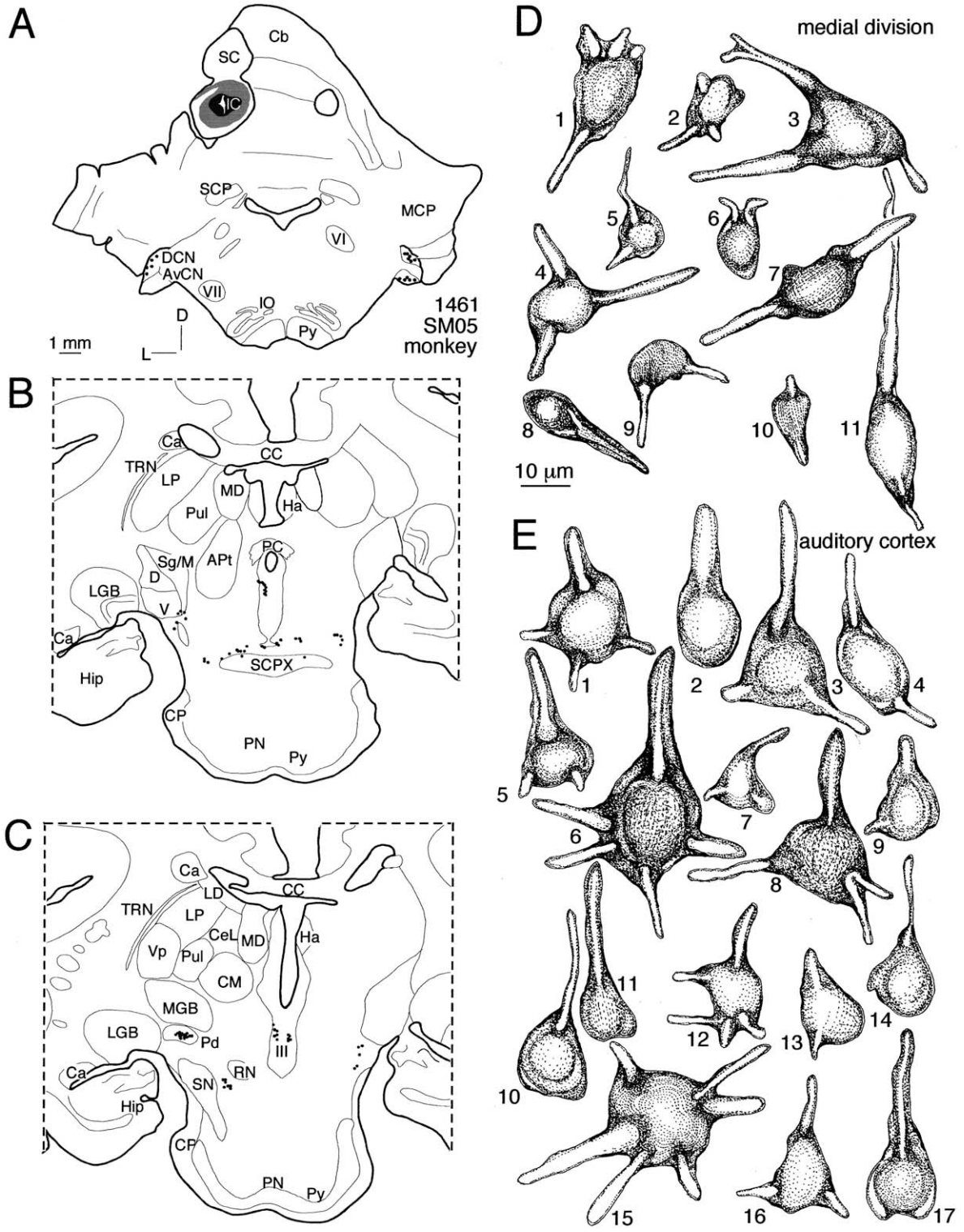


Fig. 3. Thalamotectal (A–D) and corticotectal cells (E) in a squirrel monkey. (A) The deposit entered the caudolateral inferior colliculus and extended about one-third of its length, filling the caudal cortex, much of the dorsal cortex, and possibly encroaching into the central nucleus. There was bilateral retrograde labeling in the cochlear nucleus. (B) The subcortical labeling had four foci: one at the ventromedial face of the medial geniculate complex, and a second small cluster bilaterally in much of the posterior intralaminar system. A third concentration lay in the central gray, with a fourth between the substantia nigra and the red nucleus. (C) The most rostral mass of thalamotectal cells was in the posterior dorsal nucleus, with a smaller focus bilaterally in the central gray, and a few neurons in the intralaminar nuclei ipsilaterally. (D) Characteristic medial division neurons included magnocellular (3), multipolar (4), and small (10) cells. (E) In the auditory cortex, all the labeled cells were pyramidal and in layer V, and they were diverse in form and size, ranging from classic large (6, 8) to small (11, 14) and medium (1, 3) pyramidal cells. Protocol for D and E: planapochromat, N.A. 1.32, $\times 2000$.

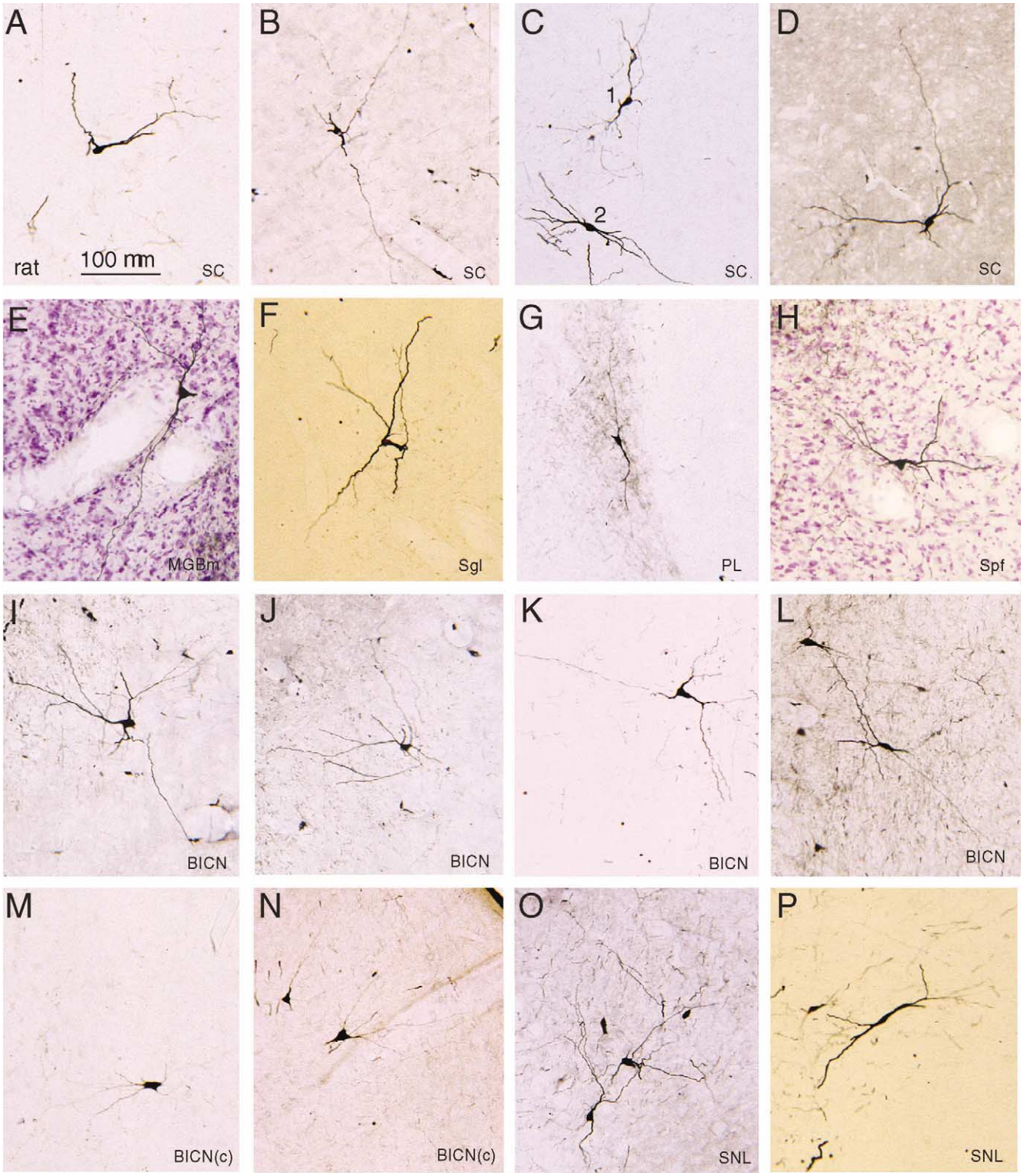
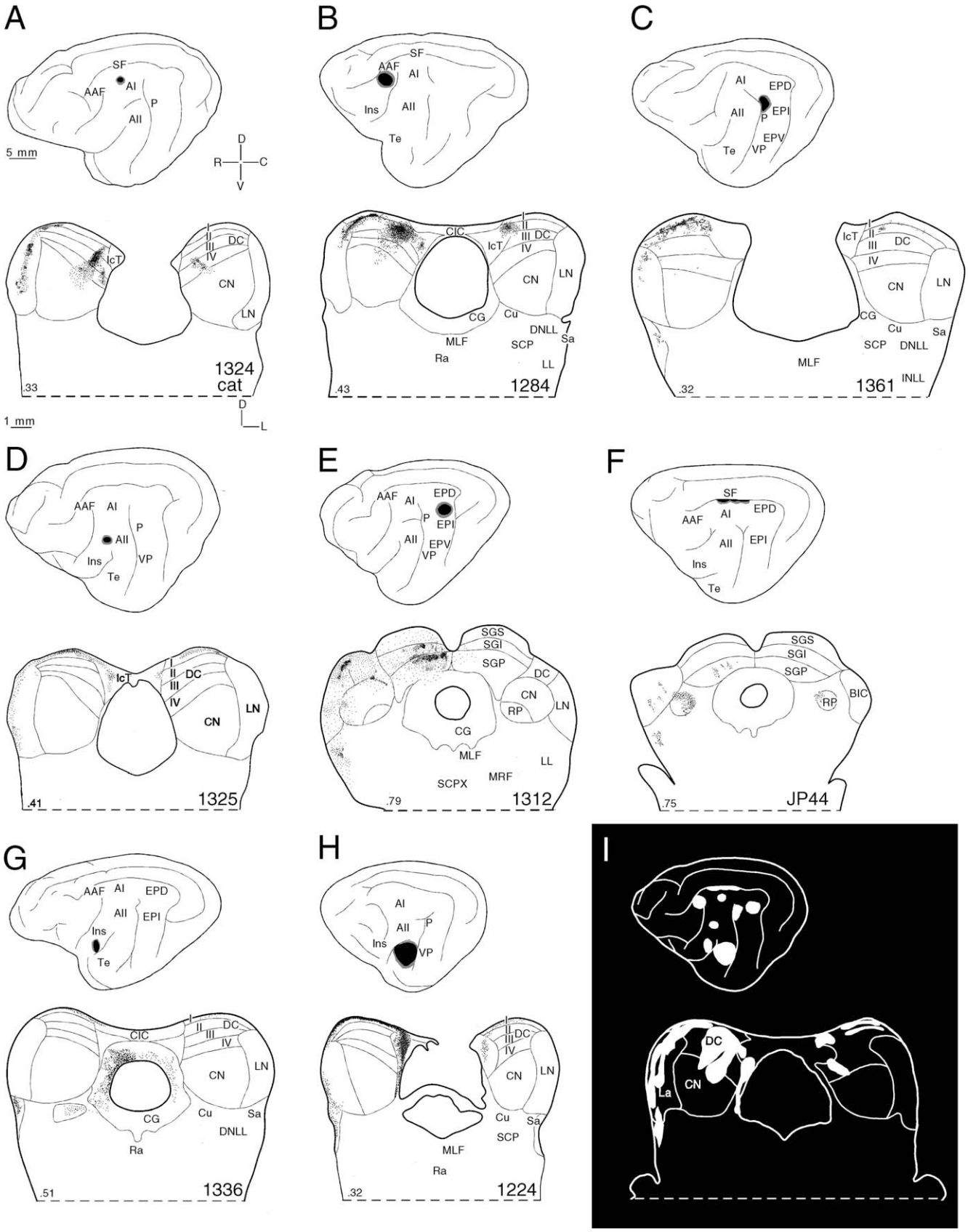


Fig. 4. Representative bulk-filled cells projecting to the rat inferior colliculus in (A–D) the superior colliculus, (E–H) posterior thalamus, and intralaminar nuclei (I–N) the brachium of the inferior colliculus contralaterally (c) and ipsilaterally, and (O,P) the substantia nigra. Most of the labeled cells resemble tegmental neurons (Ramón-Moliner and Nauta, 1966). Some superior colliculus cells have a vertical orientation (C: 1), while others are aligned parallel to the laminae (C: 2). Planapochromat, N.A. 0.32, ×125.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mel, 2000). For example, even after the largest deposits in the inferior colliculus, which result in massive anterograde labeling in the ipsilateral ventral division of the medial geniculate body, labeled neurons in the ventral division were absent, despite the powerful connections between the auditory midbrain and thalamus (Calford and Aitkin, 1983). Likewise, in the auditory cortex, where corticocollicular neurons were abundant, no axon terminals were found in cortical layers that normally are thalamic recipient (Burton and Jones, 1976; Huang and Winer, 2000). We saw no apparent difference in the number of labeled neurons with shorter (monkey) or longer (rat) survivals.

4.2. Comparison with previous reports

Limited data are available on the thalamotectal projection. An early study (Adams, 1980) noted that some cells of origin were in the medial division of the medial geniculate body and showed an example that matches closely certain neurons in the monkey (compare Adams's Fig. 1D with the present Fig. 3D: 3); no labeling in the posterior intralaminar system was noted. Later, brief reports described a pattern much like the present distribution in the cat (Paydar et al., 1993) and rat (Senatorov and Hu, 1999). The latter study used fluorescent tracers including latex microspheres and found labeling in the suprageniculate nucleus, peripeduncular area, and nucleus of the brachium.

The most complete analysis available (Kuwabara and Zook, 2000) used quasi-parasagittal tissue slices in the gerbil that included much of the medial geniculate body and inferior colliculus; in some experiments thalamotectal neurons were prelabeled with a fluorescent tracer deposited in the midbrain, then subsequently injected intracellularly with biocytin and lucifer yellow/biocytin to visualize their descending axons. Other animals received larger thalamic biocytin deposits to trace projection axons more directly. Most descending projections arose in the dorsal and medial divisions of the medial geniculate body, including medial division neurons resembling those seen in the present study. Such projections appeared to end predominantly in the external (lateral) nucleus of the inferior colliculus. This method, and its plane of section, would make the detection of labeled cells in the posterior intralaminar nuclei, which are long, slender lamellae running along the mediolateral axis, difficult.

4.3. Parallel descending systems

A comparison of the patterns of auditory corticocollicular terminations (Fig. 5) and thalamotectal origins (Figs. 1D, 2A) reveals that many of the same nuclei are involved in each projection. Thus, the lateral nucleus and the dorsal cortex of the inferior colliculus are the main target and chief origin, respectively, of cortical and thalamic projections. The data at this point are more problematic with regard to the central nucleus for two reasons: it is surrounded by other nuclei, such that any tracer deposit necessarily interrupts afferents and efferents entering and exiting it (Fig. 1A) and second, the question of a cortical projection to the central nucleus itself remains equivocal (Herbert et al., 1991; Herrera et al., 1994; Saldaña et al., 1996; Winer et al., 1998a). Thus the central nucleus may be either a subsidiary target of the corticocollicular system or it may operate more independently of the influence of the thalamotectal system than do other inferior colliculus divisions. Resolution of this question will require deposits of a tracer that is not incorporated by severed axons (Basbaum and Menetrey, 1987; Winer et al., 1996).

Irrespective of the status of a direct auditory cortical input to the central nucleus, there is a polysynaptic linkage between the auditory cortex and the intralaminar thalamic nuclei, on one hand, and the thalamocortical and corticocollicular systems on the other hand (Fig. 6). Thus, thalamotectal projections of the intralaminar nuclei appear to reach those subdivisions of the inferior colliculus that the auditory cortex also targets. Intralaminar nuclear projections to cortical layers I and VI could reach the apical dendrites of corticothalamic neurons, and the distal, basal dendrites of corticocollicular cells. The relationship with the corticocollicular cells of origin remains circumstantial. However, even if the intralaminar–corticocollicular relation were absent, these pathways converge at the level of the inferior

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Fig. 5. Patterns of corticocollicular input showing terminal labeling in many of the same nuclei that receive thalamotectal input. Representative deposit sites in subdivisions of cat auditory cortex (upper panels) and the ensuing anterograde transport (lower panels) in sections with characteristic WGA-HRP labeling. Deposit centers, solid black; zone of diffusion, stipple. Three patterns were discerned: a primary (tonotopic) arrangement for areas AI, AAF, and P (A–C), a nonprimary (nontonotopic) distribution for areas AII, EPD/EPI, SF and others (D–F), and a limbic-related disposition for Ins and Te cortex (G,H). A summary shows the global bilateral distribution of labeling (I). (A–C) Deposits in primary cortex target many of the same inferior collicular regions that receive thalamotectal projections. In particular, the lateral nucleus and the medial part of the dorsal cortex receive strong input. (D–F) For the deposits in nonprimary auditory cortex, the midbrain targets extend to the superior colliculus (E: SGI) and rostral pole nucleus of the inferior colliculus (F). (G,H) In contrast, deposits in limbic cortex terminate preferentially in the central gray (G) or along the perimeter of the inferior colliculus, including the superficial dorsal cortex (H) and the intercollicular tegmentum (Winer et al., 1998a).

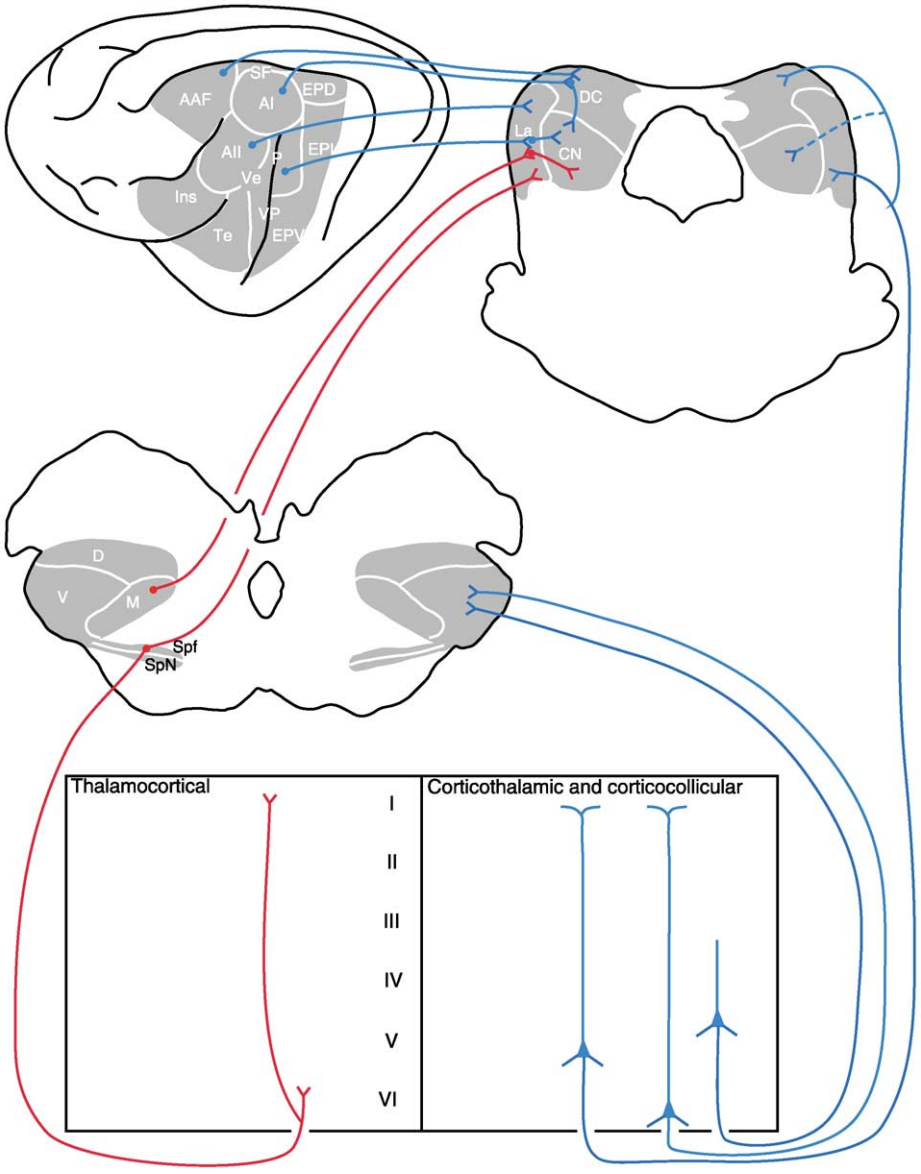

Fig. 6. Schematic summary showing inferior collicular convergence of cortical (upper left) and thalamofugal (lower left) input to the ipsilateral midbrain (upper right). The salient features are that such convergence allows the auditory cortex and the medial geniculate body access to all inferior colliculus subdivisions: input to the dorsal cortex and lateral nucleus is monosynaptic, while axons ending in the central nucleus have two projection modes: monosynaptic via thin corticocollicular fibers (dashed line, upper right) (J.A. Winer, unpublished observations) and polysynaptic via association pathways within the inferior colliculus (blue cells, upper left; unpublished observations by M.L. Chernock, J.J. Prieto and J.A. Winer). Some association pathways within the inferior colliculus may be represented by inhibitory neurons (red). Since the posterior intralaminar nuclei project to layers I and VI in sensory cortex (Herkenham, 1980), the basal dendrites of corticofugal neurons with axons terminating in the medial geniculate body or inferior colliculus (lower right) may themselves receive thalamic influence before projecting downstream. Such circuits could coordinate activity in the posterior intralaminar system, auditory cortex, amygdala, and inferior colliculus.

colliculus, where local circuitry permits descending information to reach extralemniscal and lemniscal limbs of the auditory midbrain.

If it can be assumed that the corticocollicular and thalamotectal systems are parallel, some implications follow. Even within this subdivision there may be finer functional distinctions. Thus, the thalamotectal projections themselves appear to involve two subsystems: one source is the medial division, whose neurons represent classic auditory thalamic cells in their dendritic architecture (Winer and Morest, 1983) and chemical organization (Winer, 1991). While the physiological nature and postsynaptic targets of these thalamotectal cells are unknown, the modest physiological data available for the medial division neurons suggest that they have broad tuning curves (Aitkin, 1973), may respond to input in more than one modality (Love and Scott, 1969), and that they might be important for physiolog-

ical plasticity (Edeline and Weinberger, 1992), and that they could participate in learned autonomic behaviors (LeDoux et al., 1986). The second source is the cells in the intralaminar thalamic nuclei, whose morphological properties recall those of tegmental rather than classic thalamic neurons (Winer et al., 1988). In contrast to medial division cells, their modality specificity is often related to nociceptive or limbic affiliations (Campeau and Watson, 2000), their firing patterns may involve burst-like activity (Seidenbacher and Pape, 2001), stimulation of them can evoke oscillatory discharges in the cortex (Sukov and Barth, 2001), and their functional role may be related more closely to arousal and vigilance than to higher order or cognitive function (Campeau et al., 1997). Collectively, these several differences imply that the thalamotectal system has more than one functional role, and that some process within the auditory midbrain requires convergent input of thalamic origin for its expression. Below, we speculate on the nature of such a process.

A third prospective parallel pathway involves the auditory cortex (Kelly and Wong, 1981), especially the layer V projection cells (Druga et al., 1997; Winer and Prieto, 2001), all of which are pyramidal (Coleman and Clerici, 1987) and whose axons terminate widely throughout the dorsal cortex, lateral nucleus, caudal cortex, intercollicular tegmentum, and rostral pole of the inferior colliculus (Games and Winer, 1988; Winer et al., 1998a,b). Some of these neurons are capable of bursting discharge behavior (Chagnac-Amitai et al., 1990; Hefti and Smith, 2000). Whether the corticocollicular neurons target the same types of postsynaptic cells as do thalamotectal neurons is unknown.

4.4. Speculation on the role of the thalamotectal system

Without explicit physiological data, the function of the thalamotectal system is unknown. The inputs to the lateral nucleus and dorsal cortex of the inferior colliculus suggest that at least some functions may not be exclusively auditory. Thus, the medial geniculate body subdivisions that receive the preponderant projections of the dorsal cortex and external (or lateral) nucleus (LeDoux et al., 1987) themselves terminate in the amygdala in the rat (LeDoux et al., 1984; Doron and LeDoux, 1999) and cat (Shinonaga et al., 1994) (Fig. 6). The projection to the amygdala may therefore affect smooth muscle ultimately (Davis et al., 1994). On the one hand, the inferior colliculus has an acknowledged role in spatial orienting behavior (Jane et al., 1965) and seizure genesis (Garcia-Cairasco and Sabbatini, 1991; Faingold et al., 1994). Moreover, its thalamic targets link it to circuits involved in the startle reflex (Rosen et al., 1991; Koch, 1999). Such diverse affiliations imply that the sensory midbrain mediates different facets of sound-related motor behavior. The most obvious of these is the integration of body positional information with the spatial locus of sound (Aitkin et al., 1978; Willard and Ryugo, 1979), including reflexive and preparatory skeletomotor adjustments (Ackermann et al., 1991). A second level pertains to the analysis of multisensory information, especially those involving to extrinsic frames of reference (Aitkin et al., 1981; Binns et al., 1995; Casseday and Covey, 1996). A third, and more indirect, influence is on smooth muscle either by multisynaptic brainstem pathways (Yeomans and Cochrane, 1993; Lingenhöhl and Friauf, 1994; Carlson and Willott, 1998) or through descending limbic forebrain circuitry (Endepols and Walkowiak, 1999). Each of these prospective influences implies a significant nonauditory role for descending pathways reaching the limbic system or the inferior colliculus.

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