# Chapter 5
# Intrinsic and Commissural Connections of the Inferior Colliculus

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## 1. INTRODUCTION

### 1.1. INTRACOLLICULAR CONNECTIONS

The inferior colliculus (IC) is regarded as a nearly obligatory relay center for the information ascending from subcollicular auditory centers. Few axons bypass the IC en route to the auditory thalamus (Ramón y Cajal 1904; Henkel 1983; Malmierca et al. 2002), and most lateral lemniscal fibers end in the IC. Because of these convergent projections, the complexity of the inputs to the IC (see Chapters 3 and 4) contrasts with the apparent simplicity of midbrain projections to the thalamus (see Chapter 7).

The rat IC contains approximately 350,000 neurons, almost five times that in auditory subcollicular nuclei, and five times the number in the medial geniculate body (MGB) (Kulesza et al. 2002). These numbers suggest that, before arriving at the MGB, auditory information is extensively processed in the IC. Such processing is shaped by interactions between IC neurons, which are mediated by intracollicular connections.

Intracollicular connections, which are the focus of this chapter, are monosynaptic interactions between ipsilateral or contralateral IC neurons. Connections between neurons in the same IC are intrinsic, whereas those between the colliculi are commissural and travel in the commissure of the IC (CoIC). In this account intrinsic and commissural connections are considered together, as most if not all IC neurons with commissural connections also have intrinsic connections. Moreover, intrinsic and commissural connections share similar patterns of distribution. The chapter also contains data about the organization of intracollicular connections of the cortical subdivisions of the rat IC, and the distribution of commissural IC neurons. All references are to the rat unless stated otherwise.

We use the now-classic cytoarchitectural parcellation of the rat IC (Faye-Lund and Osen 1985) with slight modifications (Saldaña and Merchán 1992). The IC contains a central nucleus (CN) surrounded dorsally and dorsocaudally by the dorsal cortex (DC), and rostrolaterally by the external cortex. For clarity, we
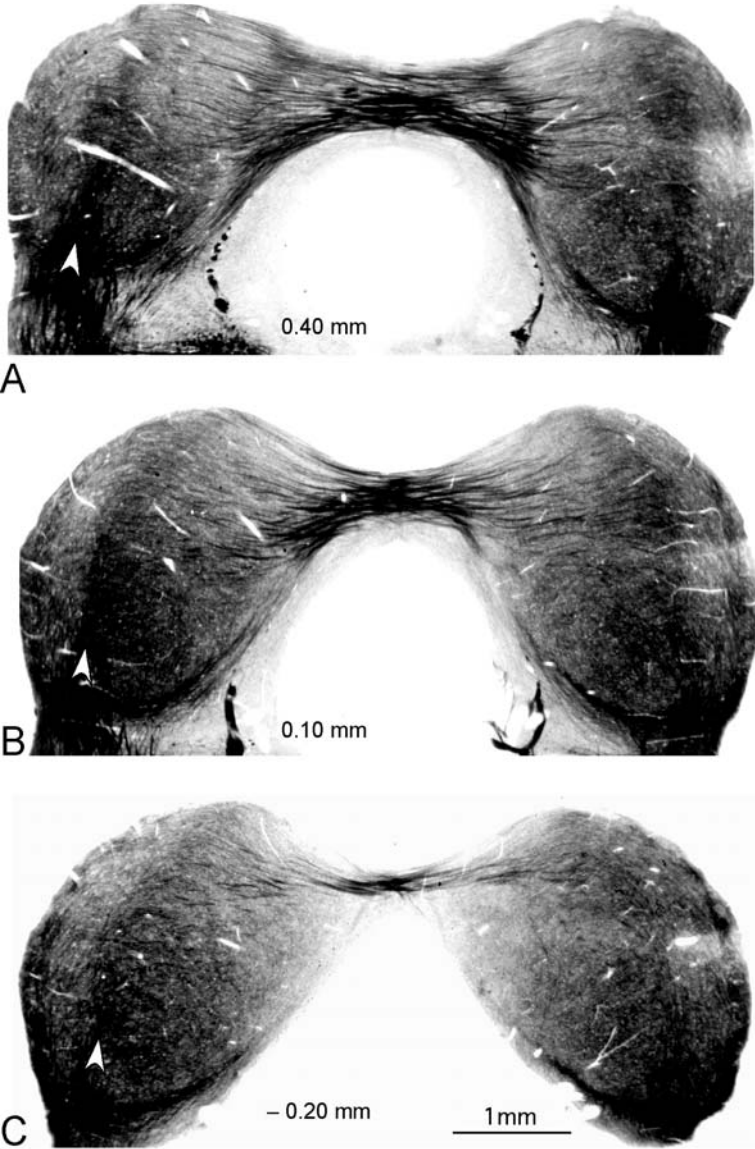
Figure 5.1. Micrographs of glutaraldehyde-fixed, 60-μm-thick coronal sections through the rat midbrain tectum. Sections were postfixed with osmium tetroxide, which stained myelinated fibers black. The numbers at the bottom of the section indicate the approximate rostrocaudal coordinate of the section in the interaural coronal plane. Fiber fascicles of CoIC are well defined and the IC neuropil is fiber rich, in contrast to the lightly stained periaqueductal gray matter. The *white arrowheads (left side)* indicate lateral lemniscal fascicles entering the IC.

refer to external cortex rostral to the CN as the rostral cortex (RC), and to the portion lateral to the CN as the external nucleus (EN).

## 1.2. THE COMMISSURE OF THE INFERIOR COLLICULUS

### 1.2.1. Anatomy and Topography

Despite subtle interspecies variations in volume and anatomical relationships, the main structural features of the CoIC are shared by most mammals (Figs. 5.1 and 5.2; see Chapter 22). The CoIC is a prominent transverse fiber tract that, at very caudal levels, consists of thin fascicles that constitute the roof of the recess of the fourth ventricle (Fig. 5.1C). Rostrally, it becomes a thick tract corresponding to the enlarged caudal portion of the tectal commissure (Faye-Lund and Osen 1985) and it is separated from the cerebral aqueduct by the thin rim of caudal periaqueductal gray matter (Fig. 5.1A, B). The CoIC is largest in the rostral third of the IC (Fig. 5.1A, B), where most commissural axons decussate. Whereas most CoIC axons project horizontally and in parallel, more caudal fascicles have variable, ascending or descending, oblique trajectories (Fig. 5.1C).

The rostral position of the CoIC is best seen in horizontal sections (Fig. 5.2) which show commissural axons traveling rostrally across the midline and then turning caudally in the contralateral IC. The horizontal plane shows that commissural axons cross in a nearly transverse plane (Fig. 5.2D), and that there is direct continuity between the rostroventral CoIC and the commissure of the superior colliculus (Fig. 5.2C).

### 1.2.2. Commissural Projections of the Inferior Colliculus

CoIC carries information bidirectionally (Held 1891, 1893; Moore and Goldberg 1966; van Noort 1969) and most CoIC axons belong to IC neurons. However, the CoIC contains some axons from other sources or destined for other targets. Tracer deposits in the MGB or the severed brachium of the IC (BIC) label projections to the contralateral MGB (Kudo and Niimi 1978; Aitkin and Phillips 1984; Oliver 1984; Hutson et al. 1991). Injection of anterograde tracers into the IC confirms crossed tectothalamic projections traveling in CoIC (Kudo and Niimi 1980; Andersen et al. 1980a; Hutson et al. 1991). It is unknown whether such axons also project in the contralateral IC before reaching the brachium.

The CoIC may contain also axons from subcollicular auditory centers (Ramón y Cajal 1904). Tracing studies in mice, rats, and cats suggest that the CoIC contains sagulum and/or lateral lemniscal fibers (González-Hernández et al. 1987; Henkel and Shneiderman 1988; Hutson et al. 1991; Bajo et al. 1993). Rat superior paraolivary nucleus cells project to the ipsilateral IC and proceed dorsomedially over the CoIC before ending in the contralateral DC (Fuentes et al. 1999). We are not aware of reports of axons in the CoIC from neural centers caudal to the superior olivary complex. The CoIC contains also auditory corticocollicular axons (Saldaña et al. 1996).
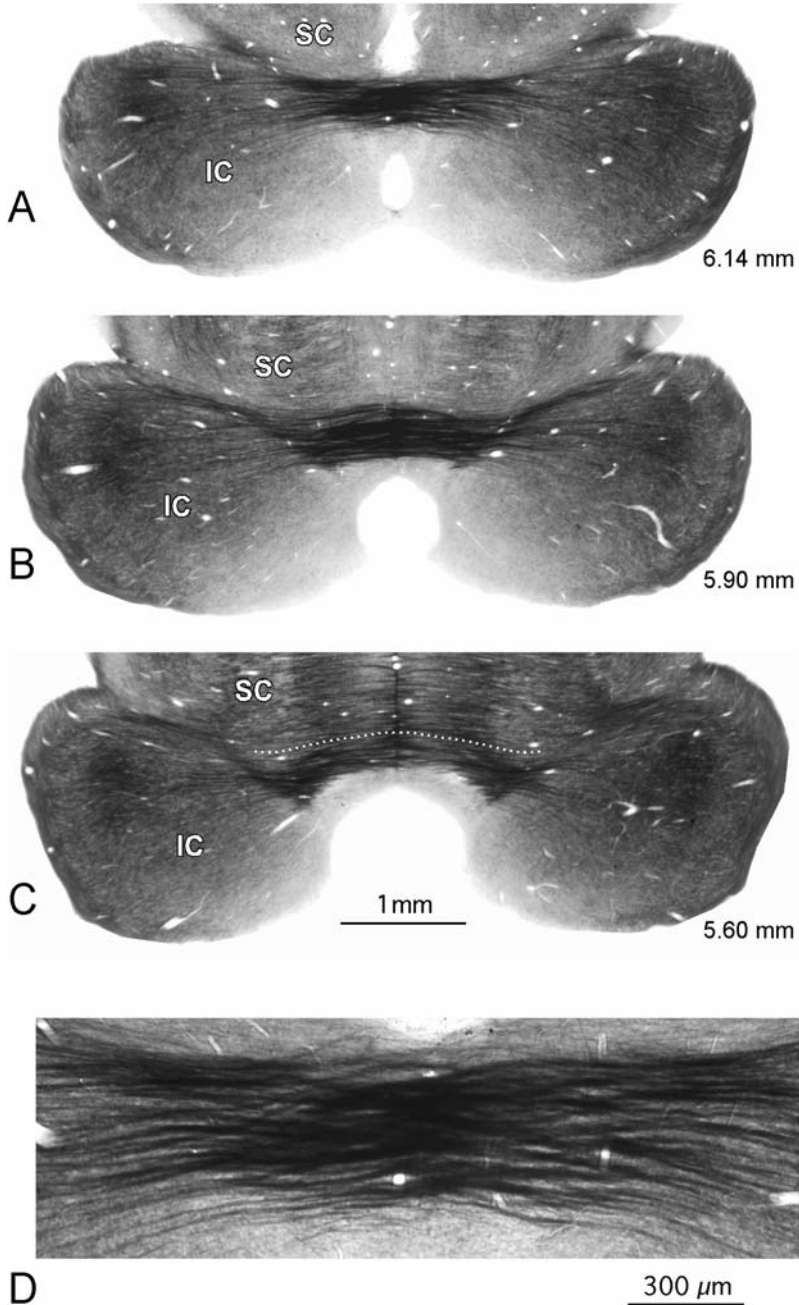
Figure 5.2. **(A, B)** Glutaraldehyde-fixed, 80-µm-thick horizontal sections of the rat midbrain tectum. Sections were postfixed with osmium tetroxide. Rostral is at the *top*. The *dotted white line* **(C)** indicates the border between the CoIC and the commissure of the superior colliculus. **(D)** Detail of the CoIC in the same section shown in **(A)**.

Whether the projections from different sources are segregated within the CoIC is unknown. There is rostrocaudal or dorsoventral topography for commissural IC axons with more rostral IC neurons crossing the CoIC more rostrally (Saldaña and Merchán, unpublished observations). Likewise, CN axons of neurons with low characteristic frequency (dorsolateral neurons) course more dorsally than higher characteristic frequency neurons (Saldaña and Merchán 1992; Figs. 5.5, 5.6).

## 2. Intracollicular Projections of the Central Nucleus and the Dorsal Cortex

### 2.1. Central Nucleus Projections

A study of the organization of the intrinsic and commissural connections of the albino rat (Saldaña and Merchán 1992) injected the anterograde tracer *Phaseolus vulgaris*-leucoagglutinin (PHA-L) into the CN. Axons (Fig. 5.3) from a discrete CN deposit formed two ipsilateral, rostrocaudally oriented laminar plexuses of terminal fibers in IC, a main (medial) plexus (iMP), and an external (lateral) plexus (iLP), and two more plexuses in the contralateral IC, a main (medial) plexus (cMP), and an external (lateral) plexus (cLP). Few terminals were outside the plexuses. The iMP extended dorsomedially and ventrolaterally from the injection site, parallel to the CN fibrodendritic laminae of the CN, a well-known cytoarchitectonic arrangement in which flattened terminal fields of incoming fibers intermingle with similarly oriented, flattened dendritic trees of the resident cells (see Chapter 2). This iMP was continuous in CN and DC and extended rostrally into the RC. The iLP was narrower than iMP and in the EN, iLP was nearly parallel to the surface of the nucleus, with its ventral pole deeper than its dorsal end. Each contralateral plexus was symmetrical with the ipsilateral plexus. The main and the external plexuses met caudally at their ventral poles, forming a dorsally open three-dimensional structure. The fiber density was variable in the plexuses: iLPs were most prominent.

These features were common to all experiments (Saldaña and Merchán 1992), irrespective of the CN injection site. Individual differences in plexus thickness, extent, position, and orientation were related to the features of the injection site. First, plexus size and density was a function of injection site size. Second, plexus size and shape depended on the deposit's location in the CN tonotopic axis (Fig. 5.4). Injections in the ventromedial CN, whose neurons have a high characteristic frequency, labeled the iMP ventromedially, near the IC–periaqueductal gray matter border, while the iLP was ventrolateral in EN, near the pial surface. With more dorsolateral injection sites at lower characteristic frequency, the iMP moved dorsolateral, and the iLP was more dorsal and more medial.

Such intracollicular projections are not unique to the rat, and a similar organization is present in the IC of mouse (González-Hernández et al. 1986; Frisina et al. 1997, 1998), gerbil (Doroshenko and Cant 1994), chinchilla (Caspary and
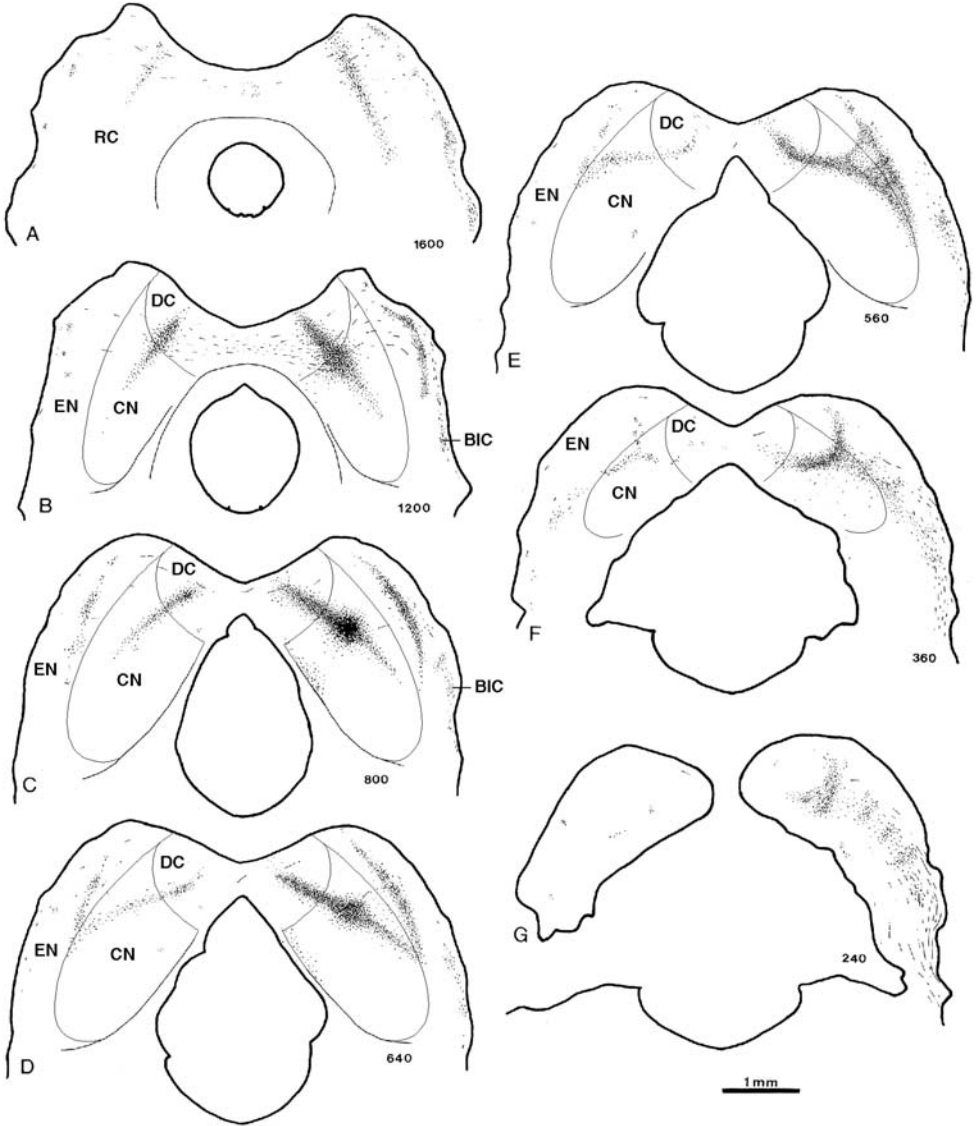
Figure 5.3. Camera lucida drawings of coronal sections showing the terminal intracollicular labeling pattern from a small PHA-L injection in the right CN. The numbers *(right side)* are the distance from the caudal pole of the IC in microns. In the IC, *lines* represent fibers of passage, and *stippling* denotes terminal fields. The injection site is near **C**. Intracollicular terminal fields are symmetrical, and the commissural labeling is weaker. The four axonal plexuses of terminal fibers span most of the IC rostrocaudally, and enter the RC. The iMP and cMP are continuous across the CN and DC. (Adapted from Saldaña and Merchán 1992. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)
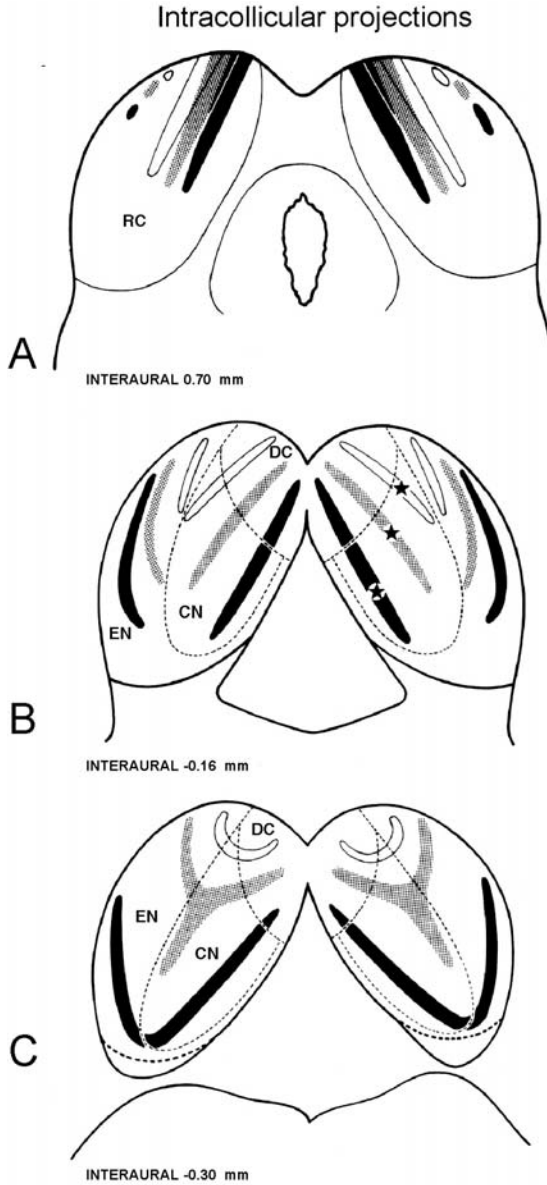
Intracollicular projections



Figure 5.4. Schematic representation of the topographic distribution of intracollicular connections of the CN. The *black, gray,* and *white* areas represent territories targeted by discrete groups of CN neurons (*star* in **B**). *Black areas:* territories with input from ventromedial (high-frequency) CN neurons. *Gray areas:* targets of central (medium-frequency) CN neurons. *White areas:* targets of dorsolateral (low-frequency) CN neurons. The distribution of intracollicular fibers suggest that the laminae cross the divisions and involve most of the IC. These fibrocellular laminae curve around a point located dorsally. (Adapted from Saldaña and Merchán 1992. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

Helfert 1993; Saint Marie 1996), guinea pig (Malmierca et. 1995), cat (Brunso-Bechtold et al. 1981; Malmierca et al. 1998), and bat (Vater and Feng 1990).

Intracollicular connections studied with biocytin deposits into physiologically identified CN loci showed a similar pattern of intracollicular CN projections in the guinea pig and the rat (Malmierca et al. 1995). Three-dimensional reconstructions of the plexuses provided a clearer picture of the near-concentric organization in IC (Fig. 5.5).

Further analysis of earlier results (Saldaña and Merchán 1992) and injections of PHA-L or biotinylated dextran (BDA) in rat CN show that plexuses labeled by injections in rostral isofrequency regions are denser rostrally than caudally, and the converse is true for the caudal deposits (Saldaña and Merchán, unpublished observations). Likewise, plexuses labeled by a ventral injection are denser ventrally. Thus, despite the widely divergent nature of the intracollicular projections of the CN, they involve preferentially neurons at rostrocaudal and dorsoventral levels near those of the parent cell bodies, a topographic arrangement whose functional significance will require further investigation.

## 2.2. DORSAL CORTEX PROJECTIONS

Because the ipsi- and contralateral targets of intracollicular fibers from the CN extend into the DC, it is of interest how DC intracollicular projections relate to those of CN. A PHA-L injection into rat central DC spared both the fiber-rich superficial layer of the DC and the CN (Fig. 5.6). It was centered at medium or medium-to-low characteristic frequency (CF). The labeled fibers created a medial and a lateral laminar plexus in each IC that spanned the IC rostrocaudally and merged caudally at their ventral ends, a pattern like that of the intracollicular CN projections. These plexuses were denser dorsally (compare Figs. 5.3 and 5.6). With more ventromedial (higher CF) or more dorsolateral (lower CF) DC injections, the plexuses resembled those labeled by injections in comparable CN tonotopic regions (Fig. 5.7A).

The organization of the DC intracollicular projections is remarkably similar to that of CN intracollicular projections, which accentuates the connectional parallels between the CN and the DC. Accordingly, the DC sends topographic (tonotopic) projections to all four ipsi- and contralateral IC subdivisions.

## 2.3. IMPLICATIONS FOR INFERIOR COLLICULUS ORGANIZATION

The pattern of intrinsic and commissural connections described in the preceding for CN and DC leads to several conclusions.

### 2.3.1. Strength of Intracollicular Inputs

Intracollicular projections are robust and may constitute one of the major inputs to IC neurons. They are an essential component of CN fibrodendritic laminae revealed by studies of the morphology of single intrinsic Golgi impregnated
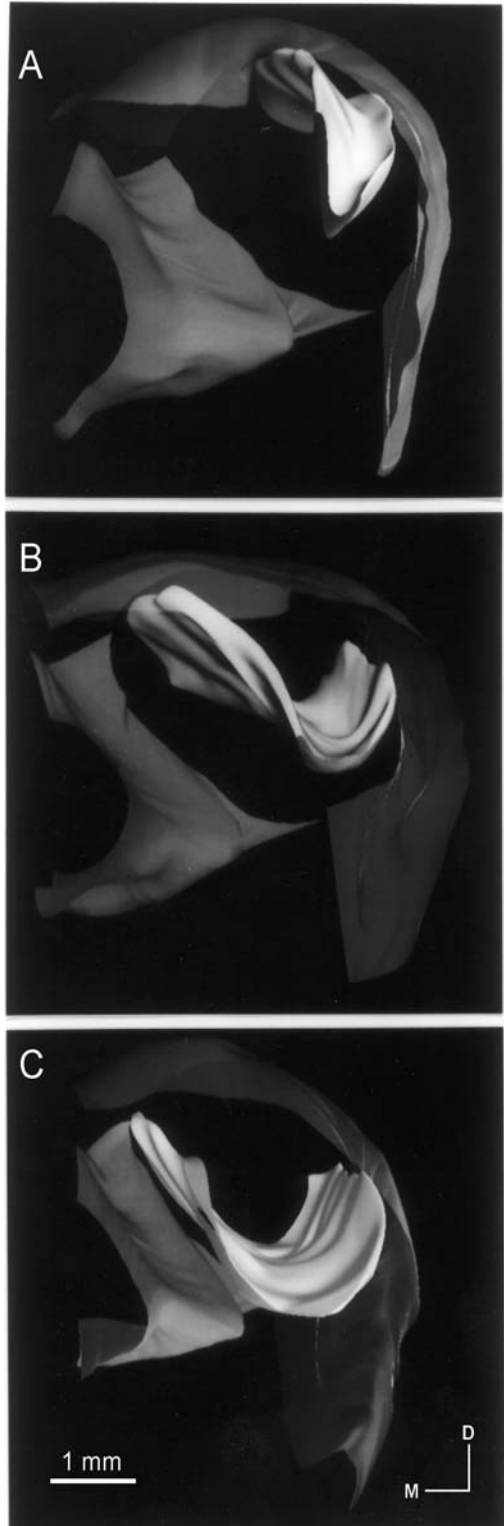
Figure 5.5. Three-dimensional reconstructions of guinea pig fiber plexuses of intrinsic CN axons at CFs of 0.5 kHz **(A)**, 6 kHz **(B)**, and 21 kHz **(C)**, respectively. The medial and lateral plexuses merge and form a complex, dorsally open structure. (Adapted from Malmierca et al. 1995. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

axons (Herrera et al. 1988, 1989) or neurons and axons filled with horseradish peroxidase (HRP) injected intracellularly (Oliver et al. 1991).

### 2.3.2. Divergence of Intracollicular Inputs

Neurons in specific CN and DC regions project divergently to the four divisions of the ipsi- and contralateral IC (CN, DC, EN, and RC), confirming the idea from retrograde tracing experiments that the commissural projections chiefly connect homotopic IC regions (Adams 1980; Schweizer 1981; Zook and Casseday 1982; Druga and Syka 1984; Tokunaga et al. 1984; Coleman and Clerici 1987; Ross et al. 1988; Ross and Pollak, 1989; Frisina et al. 1989; González-Hernández et al. 1996; Zhang et al. 1998). The commissural projection is more than merely reciprocal or homotopic because the contralateral IC targets includes areas homotopic to the iLPs (González-Hernández et al. 1986; Malmierca et al. 1995; Frisina et al 1998).

### 2.3.3. Topography of Intracollicular Inputs

The topographic (tonotopic) arrangement of the main plexuses show that CN and DC neurons project to CN and DC bilaterally at similar CF. We thus propose that the intracollicular projections enhance frequency specificity (see later), and that they may have other roles as well.

### 2.3.4. Possible Internal Topographies in Nuclei

The topography in the CN and DC projections to the EN raises the possibility that the EN possesses an unexpected tonotopic arrangement, whose isofrequency axes would parallel the IC surface, and whose main tonotopic axis is approximately mediolateral.

### 2.3.5. Contribution to Laminar Organization

The IC contains fibrocellular laminae. Each lamina is defined as the territory receiving input from CN and DC neurons with similar CF. Such laminae resemble the CN and DC plexuses or intracollicular input which curves around a point situated dorsally. Every fibrocellular lamina contains neurons and a precisely ordered axonal plexus. Fibrodendritic CN laminae may represent the central part of the fibrocellular laminae, but the latter are larger and extend into the other IC subdivisions. IC intrinsic and commissural projections are an essential component of the fibrocellular laminae, although other projection systems may also contribute. The distribution of the corticocollicular projections mimics that of the intracollicular connections (Fig. 5.7C), and this may apply to the cat (Andersen et al. 1980b).

Various lemniscal projections may follow a similar pattern, including those from the dorsal cochlear nucleus (Willard and Martin 1983; Malmierca et al. 2002) and the superior paraolivary nucleus (SPN) (Willard and Martin 1983; Fuentes et al. 1999). Input from the SPN forms two laminar plexuses in the
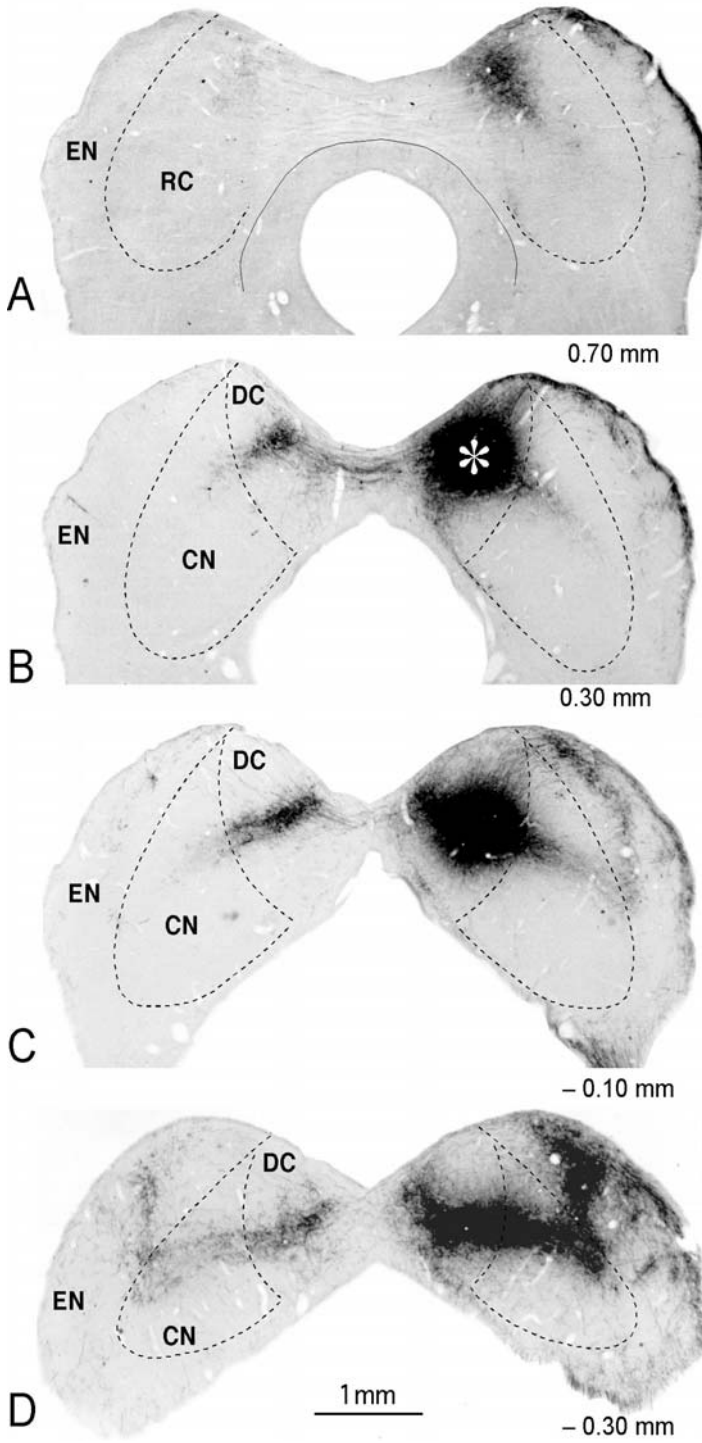
Figure 5.6. DC intracollicular projections after a small injection of PHA-L. **(A–D)** Micrographs of coronal sections. The numbers are the distance from interaural zero. The distribution of the terminal fibers plexus resembles that formed by CN axons (compare with Figs. 5.3 and 5.4).

ipsilateral IC, whose topography matches that of the iMP and iLP (Fig. 5.7B), and a weak CoIC projection. The SPN projection to the IC is topographic, and the size and shape of the terminal plexuses matches that of the intracollicular and corticocollicular projections. Thus, specific SPN cells project divergently to topographically matched neurons in the IC fibrocellular lamina.

# 3. Intracollicular Projections of the External Nucleus

Do EN neurons contribute to the same fibrocellular laminar distribution of intrinsic, commissural, ascending, and descending projections? The labeling in a representative experiment with a PHA-L deposit in EN (Fig. 5.8) showed terminal ipsilateral IC input to the EN extending rostrocaudally and dorsoventrally; in the DC and the dorsal part of the RC; and along the ventromedial IC border. Commissural terminal fields were sparser, and their distribution mirrored the ipsilateral projection. CN contained few fibers of passage bilaterally, and had few terminals. Thus, the EN projects to EN, DC, and RC bilaterally, and not to the CN. EN intracollicular projections do not contribute to the fibrocellular laminae of the IC, accentuating connectional differences between the medial (CN and DC) and the lateral (EN) IC.

Comparing PHA-L injections of EN with DC or CN deposits suggests that the intracollicular projections of the EN are weaker. That the EN innervates preferentially peripheral regions of the IC is of interest because these regions are the main recipients of the corticocollicular projections (Saldaña et al. 1996) and the EN is an early link in the "belt" auditory pathway.

The absence of significant projections from the EN to the CN is in partial agreement with studies using [³H]leucine in the cat (Kudo and Niimi 1980) and with work in the rat (Chernock and Winer 2003) that show few cells retrogradely labeled in rat EN after CN injections of gold conjugated to cholera toxin β subunit. In contrast, several accounts find abundant retrogradely labeled cell bodies in the ipsi- and/or contralateral EN following HRP injections into the CN (Willard and Martin 1983; Willard and Ryugo 1983; Druga and Syka 1984; Tokunaga et al. 1984; Coleman and Clerici 1987; Frisina et al. 1998). A parsimonious explanation may be methodological: HRP injection sites tend to be large, so the possibility that the tracer spread or was incorporated by fibers of passage cannot be dismissed.

# 4. Intracollicular Cells of Origin

## 4.1. Neurons with Intrinsic Connections

Golgi studies of the IC show that most neurons with well-impregnated axons have ipsilateral collaterals (cat: Rockel and Jones 1973a,b; rat: Herrera et al.
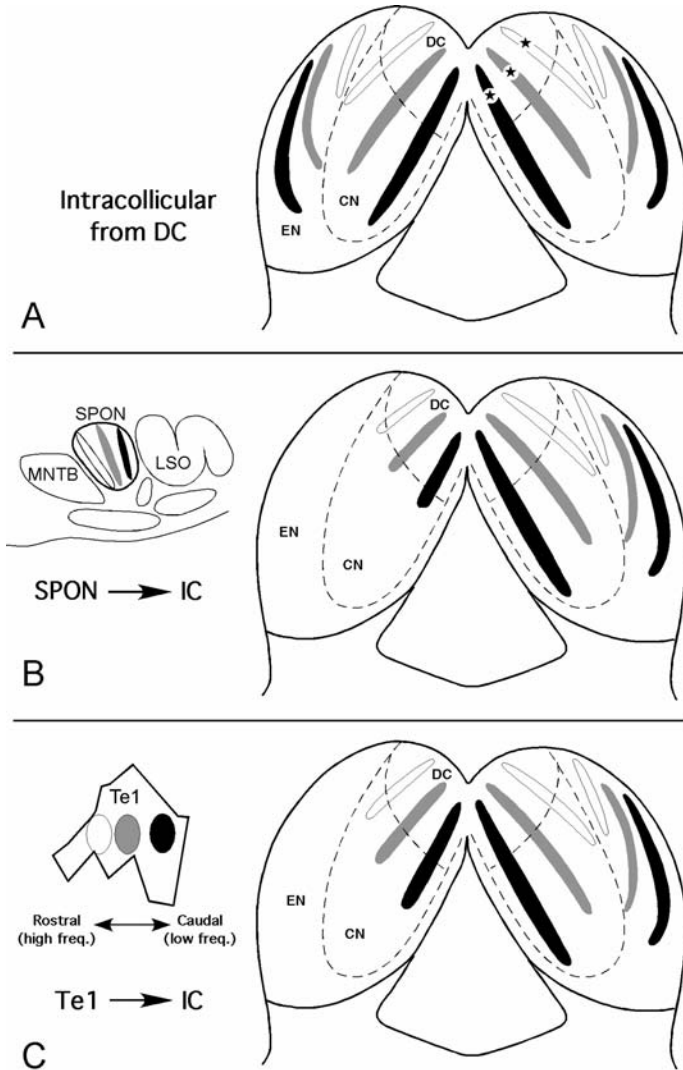
Figure 5.7. Schematic IC representation of the distribution of the terminal plexuses formed by axons from the right DC **(A)**, the right superior paraolivary nucleus **(B)**, and the right primary AC **(C)**. *Black, gray,* and *white areas* represent the IC territories targeted by a discrete group of neurons (*star* in the DC in **A**, *shadowing* in *insets* **B** and **C**). *Black areas:* territories receiving high-frequency projections. *Gray areas:* zones with medium-frequency input. *White areas:* loci targeted by low-frequency neurons. The distribution of IC ascending and descending projections mimics the topography of the CN and DC intracollicular projections except in the contralateral EN, which does not receive cortical or superior paraolivary nucleus input. (Adapted from Saldaña et al. 1996. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)
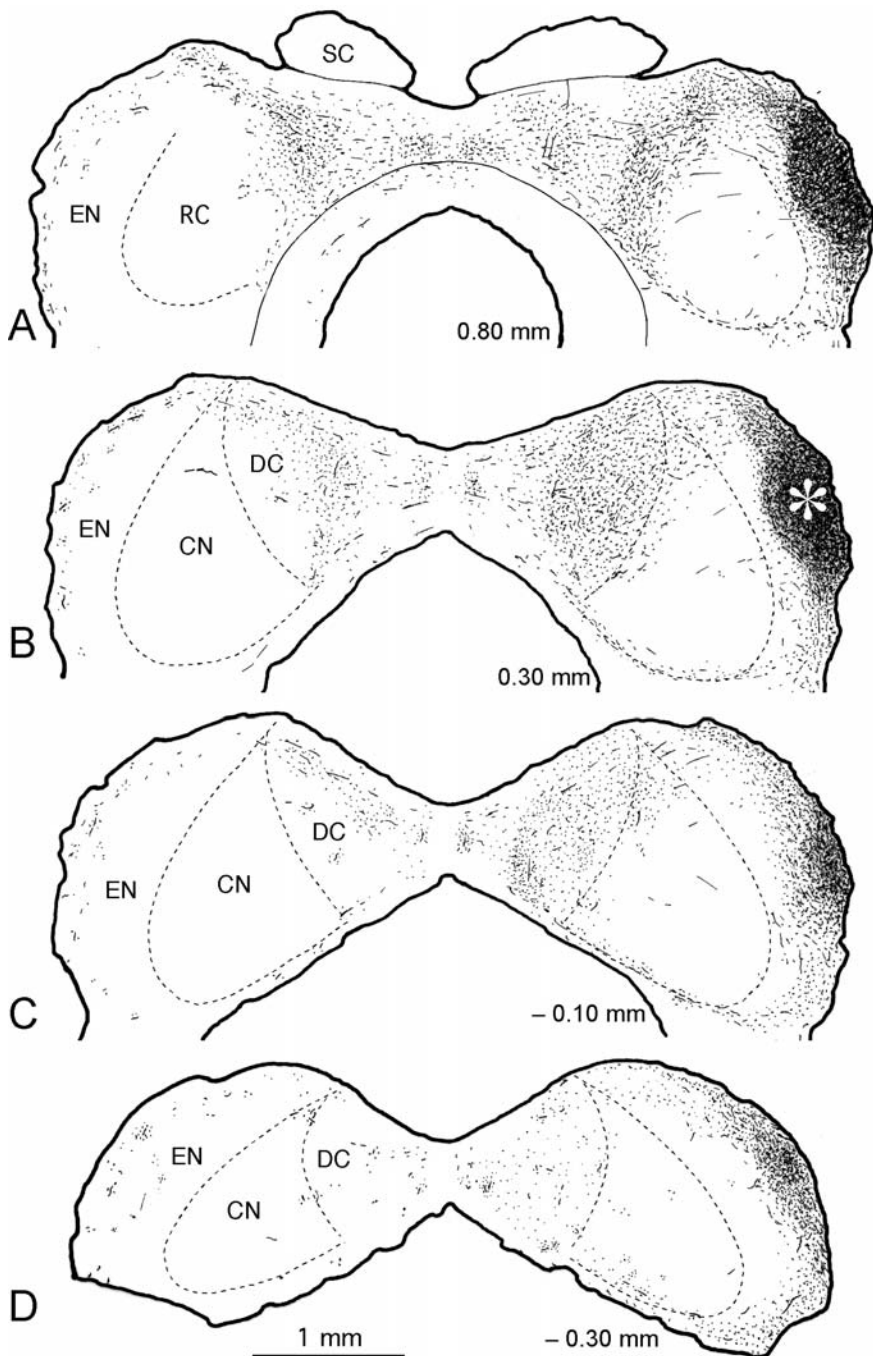
Figure. 5.8. Camera lucida drawings of bilateral coronal sections showing intracollicular terminal labeling from an EN PHA-L injection. *Numbers* are the rostrocaudal locus. *Lines* represent fibers of passage, stippling the terminal fields. The injection site center is marked *(asterisk).* **(B)** The main features are input to the ipsilateral EN, DC, and RC; a weak, symmetrical commissural projection; and no ipsi- or contralateral CN projection.

1988, 1989; González-Hernández et al. 1989). Intracellular injection in cats and rodents demonstrates that most IC neurons with filling of distal axon segments, including those whose axons enter the BIC, the CoIC or the lateral lemniscus, possess intrinsic axonal collaterals (Oliver et al. 1991; Smith 1992; Wagner 1994, 1996; Reetz and Ehret 1999; Peruzzi et al. 2000). Therefore, with the reservations imposed by the limited sample inherent to the Golgi method and to intracellular filling in mind, many if not all IC neurons have intrinsic connections. This is supported by the IC injection of retrogradely transported tracers, which label IC neurons belonging to virtually all morphologic types in rodents, bats, cats, and other small mammals (Tokunaga et al. 1984; Coleman and Clerici 1987; Saint-Marie 1996; Frisina et al. 1998).

Two conclusions can be drawn. Numerically, intrinsic connections may constitute the largest source of input to IC neurons, as the number of IC-projecting neurons in other auditory centers falls short of the number of labeled intrinsic IC neurons; and IC neurons with intrinsic connections are diverse in morphology, connections, neurochemistry, and physiology (see Chapter 2). This diverse morphology is evident in two representative cat IC neurons with very different intrinsic axonal arborization (Figs. 5.9 and 5.10) labeled by intracellular HRP injection (Oliver et al. 1991).

## 4.2. Neurons with Commissural Connections

Although there are no estimates of the total number of IC commissural neurons, nor has the number of CoIC axons been determined, the contralateral IC is surely among the main IC projection sources. For instance, the number of ferret IC neurons labeled after HRP injections in the contralateral IC was more than twice the number of neurons labeled in any other auditory center (Moore 1988).

Much like neurons with intrinsic connections, IC commissural neurons are heterogeneous in form and distribution. This is apparent in mammals as diverse as opossum (Willard and Martin 1983), mouse (González-Hernández et al. 1986; Frisina et al. 1998), rat (Druga and Syka 1984; Tokunaga et al. 1984; Coleman and Clerici 1987; González-Hernández et al. 1996), chinchilla (Saint Marie 1996), cat (Adams 1980), ferret (Moore 1988), and bat (Schweizer 1981). Although principal (disc-shaped) CN neurons have crossed projections, most commissural neurons are described as multipolar or stellate. While this trend may reflect differences in the relative proportion of different neuron types, multipolar neurons might also possess more extensive contralateral axonal arbors, or take up tracer more efficiently.

Four commissural neuron types were distinguished in the albino mouse on the basis of somatic size and their dendritic pattern: small-to-medium sized spiny cells, small-to-medium sized spineless cells, medium-sized sparsely spinous neurons, and large cells (González-Hernández et al. 1986). The profusion of intrinsic axon collaterals of the commissural neurons was also marked.

Commissural neuron projections may have various target nuclei. Rat IC contains some neurons that project to both the contralateral IC and the ipsilateral
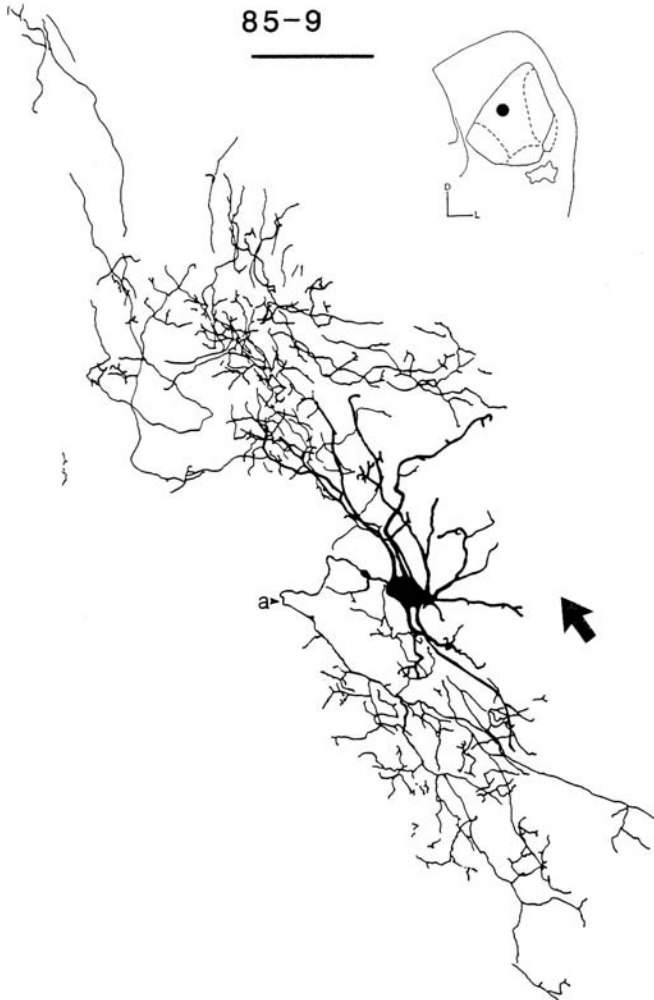
Figure 5.9. A cat CN neuron labeled in vivo by intracellular HRP injection. The neuron is shown in the coronal plane and its IC position is indicated *(inset)*. *Black arrow,* the orientation of CN fibrodendritic laminae. The highly oriented dendritic tree and the profusely ramified axonal arborization *(thinner lines)* both parallel the isofrequency laminae. The calibration bar represents 100 μm. (From Oliver et al. 1991. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

MGB (González-Hernández et al. 1991). The axonal branching of some mouse IC commissural neurons suggests that they project in the ipsilateral brachium and/or lateral lemniscus (Reetz and Ehret 1999). Some commissural axons send collaterals to CoIC to end in the tectal commissural column (Saldaña and Viñuela 2002).
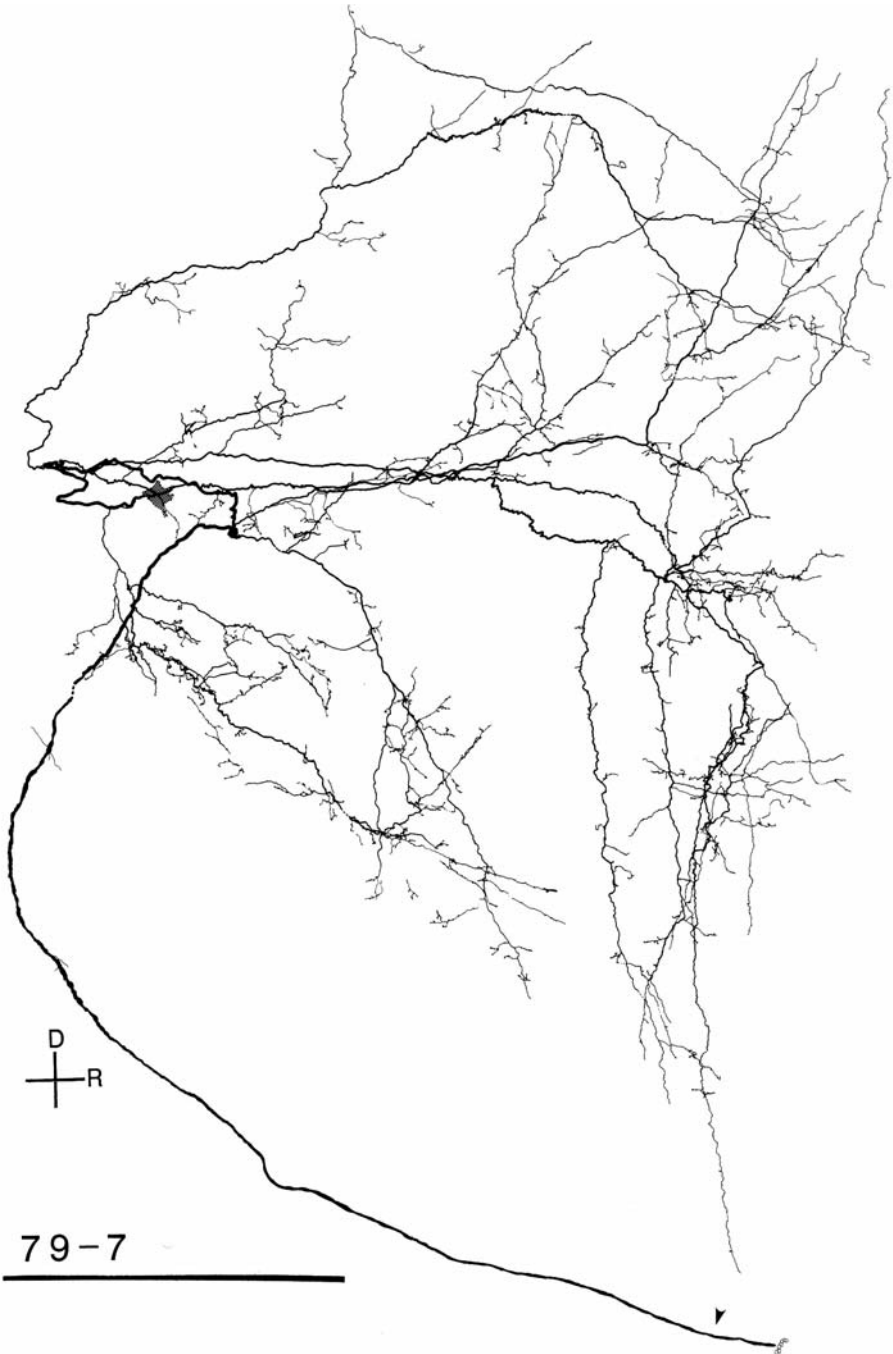
Figure 5.10. The axonal arborization of a cat CN neuron labeled by an intracellular injection of HRP in vivo. The neuron is shown in the sagittal plane, the cell body is *cross-hatched,* and the dendrites are omitted to reveal the axonal arbor. The main axon *(arrowhead)* courses laterally toward the brachium of the IC. This neuron's intrinsic axonal branches bear more than 2000 presumed synaptic boutons. The calibration bar represents 500 μm. (From Oliver et al. 1991. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

## 4.3. DISTRIBUTION OF COMMISSURAL NEURONS

Early degeneration studies speculated that the commissural projections might originate throughout the IC (van Noort 1969), a possibility now confirmed. Large HRP injections that fill most of the IC-labeled neurons retrogradely in all contralateral IC subdivisions (Schweizer 1981; Ross et al. 1988; Fig. 5.11). Experiments with discrete injection of retrograde tracers invariably found retrogradely labeled neurons in contralateral IC areas that included, but were not necessarily restricted to, the area homotopic to the deposit. Moreover, all anterograde transport experiments label contralateral IC fibers, irrespective of the location of the ipsilateral IC injection (Kudo and Niimi 1980; Malmierca et al. 1995).

Although all IC regions are a source of commissural projections, commissural neurons are distributed nonuniformly. To label all cat CoIC neurons retrogradely, HRP was deposited into a cut made in the CoIC (Aitkin and Phillips 1984; Hutson et al. 1991) and commissural neurons were concentrated ventrolaterally at posterior levels, and more dorsally at anterior levels. A similar trend is found in the rat (Fig. 5.11).

# 5. THE FUNCTION OF INTRACOLLICULAR CONNECTIONS

The density of intracollicular connections could enable IC neurons to modulate the activity of other collicular neurons. Many IC neurons may receive lateral lemniscal information through local connections rather than through lemniscal synaptic input (Smith 1992; Wagner 1996; Moore et al. 1998; Reetz and Ehret 1999).

It seems unlikely that the CoIC is associated with some aspect of sound localization, as transecting the CoIC and/or the corpus callosum of trained cats had little or no effect on the animal's ability to localize a sound source (Moore et al. 1974). This result is consistent with results in the ferret after unilateral IC ablation (Kelly and Kavanagh 1994).

## 5.1. THE PHYSIOLOGIC ROLE OF COMMISSURAL CONNECTIONS

The morphologic diversity of IC neurons with commissural projections suggests that they might be equally varied neurochemically and electrophysiologically, and the intrinsic and commissural projections of the IC may contain excitatory and inhibitory fibers (Saldaña and Merchán 1992). Preliminary immunoelectron microscopic results in the chinchilla suggested that the commissural axons are immunoreactive for γ-aminobutyric acid (GABA) and glutamate (Caspary and Helfert 1993). Later morphologic data disagree as to the neurochemical status of these projections. A combined tract tracing and the immunocytochemical approach found many double-labeled cells in the contralateral IC (González-Hernández et al. 1996). This is consistent with the presence of fibers immuno-
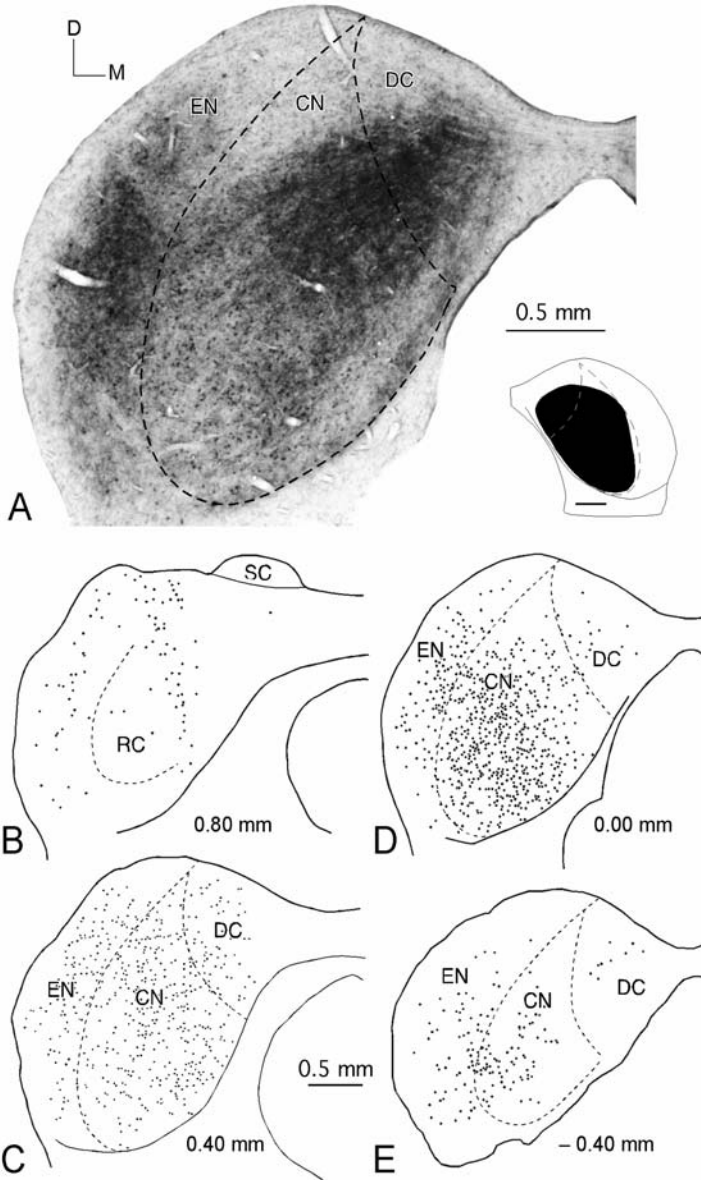
Figure. 5.11. Distribution of commissural neurons. *(Inset)* A BDA deposit *(black area)* spared only the lateral and dorsolateral CN and involved most of the DC. **(A)** A coronal section of the contralateral IC at the level of the injection site. Retrogradely labeled neurons are embedded in anterogradely labeled commissural fibers. **(B–E)** Commissural neurons in sections 400 μm apart. A *dot* represents one neuron; the position of each labeled cell body was noted. Drawing made at ×193 with a plan ×10 objective (numerical aperture 0.30).

reactive for glutamic acid decarboxylase, the synthesizing enzyme for GABA (Vetter and Mugnaini 1985). However, similar experiments combining retrograde transport of a fluorescent tracer and immunocytochemistry for GABA revealed no commissural double-labeled neurons, despite their abundance in the lateral lemniscal nuclei (Zhang et al. 1998).

Using a different approach, many chinchilla neurons are retrogradely labeled following deposits of D-[$^3$H]aspartate in the contralateral IC, which suggests that they are glutamatergic and that (at least some parts of) the commissural projections are excitatory (Saint Marie 1996). Some commissural neurons are immunopositive for enkephalin and neuropeptide Y (Nakagawa et al. 1995).

Support for a mixed excitatory–inhibitory commissural projection comes from electrophysiologic studies of living slices in vitro, which examined the effects on IC cells of electrical stimulation of the CoIC. DC neurons respond with an early inhibitory postsynaptic potential (IPSP) followed by a longer latency excitatory postsynaptic potential (EPSP); the pharmacologic evidence suggests that the IPSP reflects a direct, commissural GABAergic input, while the EPSP arises from direct, crossed input that activates non-$N$-methyl-D-aspartate-type (non-NMDA) glutamate receptors (Smith 1992). Similarly, most gerbil CN neurons receive both excitatory and inhibitory CoIC input, although GABAergic inhibition dominates (Moore et al. 1998). Furthermore, CoIC shock stimulation evokes short-latency PSPs in mouse IC, and these potentials may be excitatory or inhibitory (Reetz and Ehret 1999).

That the CoIC exerts both excitatory and inhibitory effects is corroborated by recent investigations in vivo. CN electrical stimulation and the injection of the glutamate-receptor agonist NMDA into CN both produced excitatory or inhibitory effects on the acoustically evoked activity of contralateral RC neurons, and this effect occurred in both normal and genetically epilepsy-prone rats (Chakravarty and Faingold 1997). These manipulations changed the neural discharge rate but did not affect sustained or onset discharge patterns. By the same token, silencing one IC reversibly by local microinjections of the glutamate receptor blocker kynurenic acid modified the spectral properties of contralateral IC neurons (Malmierca et al. 2003). In most neurons, blocking the contralateral IC increased the frequency response area to monaural (contralateral) or binaural stimulation, although decreased frequency response areas were also recorded (Fig. 5.12). One limitation of these in vivo studies is that they do not reveal if the neurons whose activity is modified by the contralateral IC manipulation receive direct commissural input or if other, interposed neurons are required. Moreover, IC stimulation or blockade alters the stream of information ascending to the cerebral cortex, and so may interfere with descending control of collicular activity.

## 5.2. NEOCORTICAL CONTROL OF INTRACOLLICULAR CIRCUITS

The corticofugal system modulates the sensitivity of IC neurons to sound frequency, amplitude, and duration (Suga and Ma 2003). For frequency selectivity,
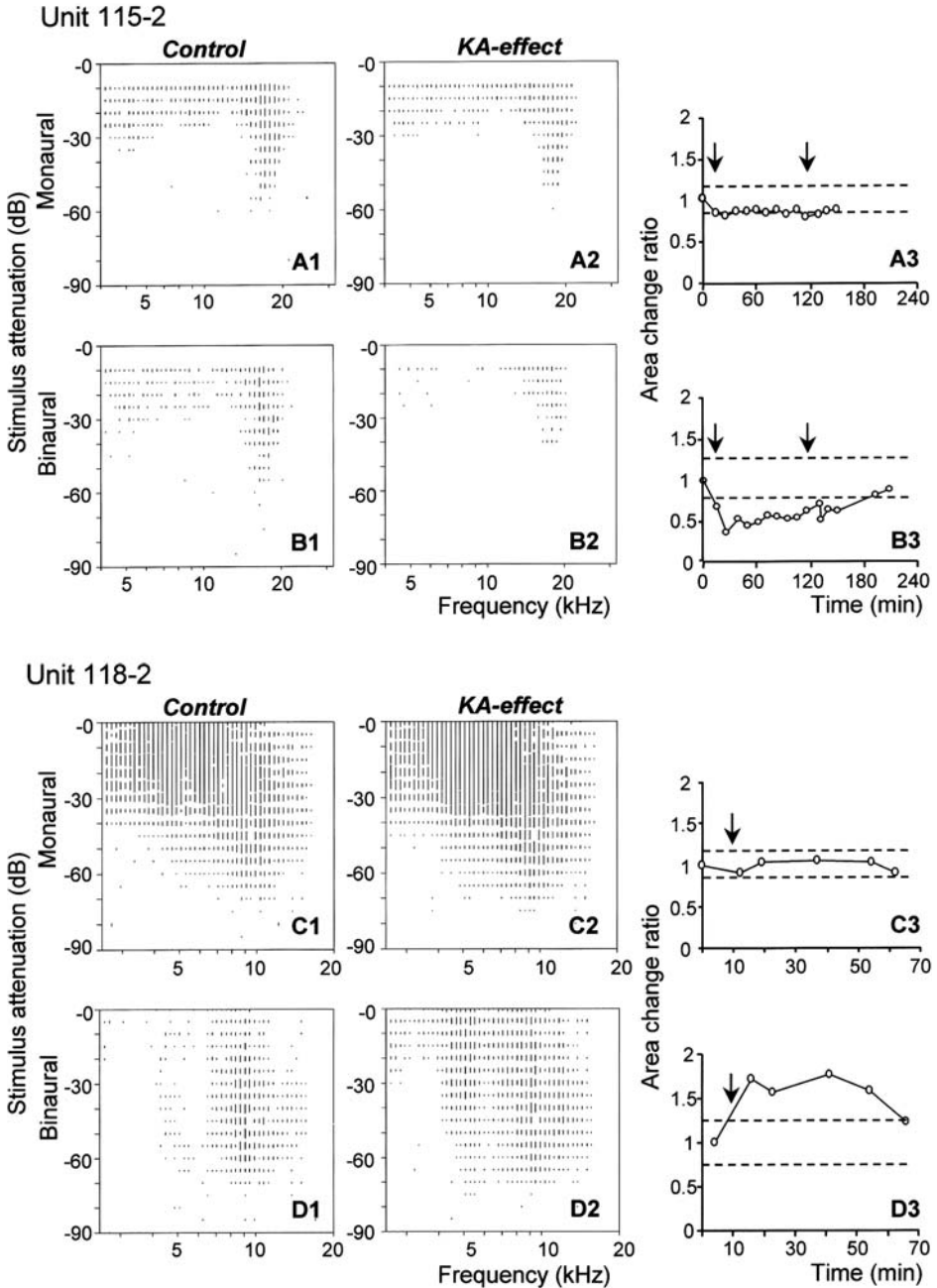
Figure. 5.12. Blocking reversibly the activity of one IC with kynurenic acid changes the frequency response area of commissural neurons. In unit 115-2 *(upper half)*, the contralateral blockade reduced the frequency response areas elicited by monaural (A1–A3) and binaural stimulation (B1–B3). In unit 118-2 (lower half), blockade increased the frequency response areas for monaural (C1–C3) and binaural stimulation (D1–D3). (Reproduced from Malmierca et al. 2003.)

the auditory neocortical activity evokes both facilitation and inhibition of auditory responses. The amount of facilitation and inhibition varies as a function of the relationship in frequency tuning between neocortical and IC neurons. A neuron's response is augmented at its CF and inhibited at other frequencies (see Chapter 8). Corticocollicular and intracollicular projections are topographically (tonotopically) matched (Andersen et al. 1980b; Saldaña et al. 1996). Corticocollicular projections are excitatory (Feliciano and Potashner 1995), and intracollicular projections have both excitatory and inhibitory effects (see Section 5.1), so that the facilitation and inhibition of IC neurons produced by auditory cortex activation can be best explained in terms of interactions mediated by intracollicular connections governed by corticocollicular modulation.

## 6. THEMES FOR DISCUSSION

1. Different IC neurons receive their main inputs from different sources. How do the IC intrinsic and commissural connections relate to the origin of their inputs?
2. Available data on the commissural connections come from bulk transport experiments. What is the morphology and distribution of individual commissural axons?
3. Within the IC, different afferent projections terminate preferentially on different parts of the target neurons (cell body, proximal or distal dendrites). For example, some lateral lemniscal inputs provide a significant input to more proximal portions of IC neurons, including cell bodies, than do corticocollicular fibers. What part(s) of the neuron is/are targeted preferentially by intracollicular connections?
4. The EN receives topographic ascending as well as intracollicular and descending projections. Are the efferent projections of the EN topographically organized?
5. The EN is usually regarded as a center for multisensory integration. How do the nonauditory projections intersperse within the EN with the topographic projection from the CN and the DC?
6. The CN has been implicated in the genesis of audiogenic seizures and the EN/RC in the propagation of the epileptic crises. Does the CN-to-EN projection play a role in the physiopathology of these seizures?
7. Neurons within an IC isofrequency region differ in other physiologic parameters. The distribution of some of these parameters within the IC is orthogonal to the isofrequency planes of the nucleus (Schreiner and Langner 1988). Is there a relationship between the orderly pattern of intracollicular connections and the representation of parameters other than frequency?
8. What information is conveyed by commissural fibers? What is the biologic significance of the CoIC?

9. The results reviewed here suggest that the IC consists of concentric fibrocellular laminae that involve all collicular subdivisions. Principal (disc-shaped) neurons are likely integral elements of these CN laminae. What neurons form the cellular substrate of the fibrocellular laminae in the cortical subdivisions of the IC?

10. Are there comparative variations in the organization of intracollicular projections? Some big brown bat EN neurons are excited by corticocollicular fibers and inhibit CN neurons, which are facilitated by corticofugal input (Jen et al. 1998). However, the morphologic data suggest that, in the rat, the EN does not project significantly to the CN.

# Acknowledgments

# Abbreviations

| | |
|---|---|
| BDA | biotinylated dextran amine |
| BIC | brachium of the inferior colliculus |
| CN | central nucleus of the inferior colliculus |
| CoIC | commissure of the inferior colliculus |
| DC | dorsal cortex of the inferior colliculus |
| EN | external nucleus of the inferior colliculus |
| EPSP | excitatory postsynaptic potential |
| GABA | γ-aminobutyric acid |
| GAD | glutamic acid decarboxylase |
| HRP | horseradish peroxidase |
| IC | inferior colliculus |
| IPSP | inhibitory postsynaptic potential |
| LSO | lateral superior olive |
| MNTB | medial nucleus of the trapezoid body |
| NMDA | $N$-methyl-D-aspartate |
| PHA-L | *Phaseolus vulgaris*-leucoagglutinin |
| RC | rostral cortex of the inferior colliculus |
| SC | superior colliculus |
| SPON | superior paraolivary nucleus |
| Te1 | primary auditory area of rat cerebral cortex |

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