

Chapter 2

Neuronal Organization in the Inferior Colliculus

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1. KEY ISSUES REGARDING INFERIOR COLLICULUS NEURONAL ORGANIZATION

An understanding of the neuronal organization of the inferior colliculus (IC) requires an exploration of how the types of neurons, the microcircuitry, and the synaptic organization of the IC interact to define functional zones. The IC was originally divided using anatomical methods to identify the neurons and their inputs with the hope that these subdivisions would correspond to functional zones. The central nucleus, the largest of the subdivisions, has been the focus of most studies of IC neuronal organization and its neuron types and the inputs are best known. Understanding the neuronal organization of the IC in terms of subdivisions has been a problem when it is uncertain how other parts differ from the central nucleus. Because IC subdivisions must be related to the constituent neurons and their inputs, the first part of this chapter discusses how the central nucleus and surrounding structures differ in this regard. One way to address the possible functional differences is through the study of IC microanatomy, our second topic. Within the central nucleus the microanatomical arrangements suggest that the inputs may create modules with specific combinations of inputs. Because a module may contain neurons performing similar types of processing, the types of functional zones present in each subdivision will define the function of that subdivision and clarify the differences between it and others. A third aspect of neuronal organization is the definition of the neuron type. Neurons have a functional as well as a morphological profile. Hence, neurons defined by their axonal targets, neurotransmitter content, and intrinsic membrane properties should reveal fundamental aspects of IC neuronal organization. The final facet of neuronal organization to be discussed is the synaptic organization—the types of synapses and patterns of synaptic input that are manifest on different neuron types or in different functional modules. Synaptic organization leads to the final question regarding neuronal organization. How is auditory processing influenced by the interaction of synaptic inputs with the intrinsic properties of the IC neurons?

2. THE PROBLEM OF SUBDIVIDING THE INFERIOR COLLICULUS

The IC is one of the largest structures in the mammalian midbrain. It forms the posterior half of the corpora quadrigemina in the midbrain tectum: four bulges on the dorsal surface of the midbrain (Fig. 2.1). Grossly, the IC is readily distinguished from the superior colliculus that constitutes the anterior half of the tectum. Likewise, it is distinguished from the midbrain tegmentum readily in frontal or transverse sections. Tectum and tegmentum develop from different stem cells (Senut and Alvarado-Mallart 1987). The tectum is an alar (sensory) plate derivative whereas the tegmentum is a basal plate derivative, which suggests a motor function.

Despite the ease with which the IC is distinguished from other midbrain structures, understanding the internal or functional organization of the IC has not been so obvious. Like many other brain structures, sharply defined internal boundaries are not always evident.

2.1. THE CENTRAL NUCLEUS AND A SURROUNDING CORTEX ARE THE MAJOR INFERIOR COLLICULUS SUBDIVISIONS

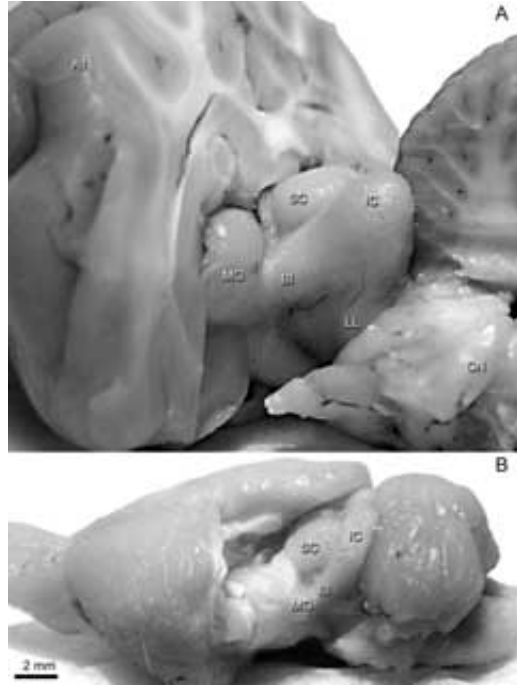
The simplest parcellation recognizes a central nucleus (ICC; Fig. 2.2) that is surrounded by a cortex. Most historical accounts as well as most modern studies follow this basic design. For example, Ramón y Cajal (1995) referred to a nucleus of the IC covered by a dorsal cortex (DC; Fig. 2.2) that includes the commissural connections. He described a lateral cortex (LC; Fig. 2.2) which is a thin layer of gray matter beside ICC that is covered by the brachium of the IC (BI; Fig. 2.2). The brachium contains axons that project to the medial geniculate body in the diencephalon and descending fibers to the IC from the neocortex. Although the name “central nucleus” has been in use for many years, the precise IC region associated with it has depended on the methodological approach and its interpretation.

The anatomical subdivisions of the cat (Oliver and Shneiderman 1991; Oliver and Huerta 1992) and human (Waitzman and Oliver 2002) IC have been reviewed and the references cited include a discussion of adjoining tegmental structures. Here, we address the IC structure from a comparative perspective and evaluate different views on the organization of the subdivisions.

2.2. MIDBRAIN SUBDIVISIONS REFLECT THE METHODS USED TO IDENTIFY THEM

Neuroanatomical studies have traditionally relied on Nissl stains or myelin stains to identify subdivisions (Figs. 2.2 to 2.4). These stains are complementary, as Nissl stains show cell bodies while myelin stains reveal axons, and increased

Figure 2.1. Gross anatomy of the cat (**A**) and rat (**B**) midbrain. *AI*, Primary auditory cortex; *BI*, brachium of the inferior colliculus; *CN*, cochlear nucleus; *IC*, inferior colliculus; *LL*, lateral lemniscus; *MG*, medial geniculate body; *SC*, superior colliculus. The scale bar represents 2 mm.



axon density usually reflects lower neuronal cell body density (Berman 1968; Olszewski and Baxter 1982; Paxinos and Watson 1998). Nissl and myelin stains, although widely used, can only hint at the functional subdivisions and internal complexity in the IC.

Golgi impregnations reveal details of IC neurons that are not discernible by other methods. They reveal more distinguishing features of unique neuron types, local differences in the structure of the neuronal distribution, and the differences in local dendritic neuropil organization. Golgi studies have been essential to identifying more specialized regions in the IC (Rockel and Jones 1973a,b; Fitzpatrick 1975; Oliver 1984b; Morest and Oliver 1984; Faye-Lund and Osen 1985; Meininger et al. 1986; Ramón y Cajal 1995). Unfortunately, Golgi stains are incompatible with many histological approaches. Thus, more refined methods that identify morphologically distinct cell types must be used to recognize subdivisions and to confirm their identity independently.

Molecular methods may ultimately identify subdivisions. For example, parvalbumin, a calcium binding protein, has a high concentration in ICC whereas calbindin and calretinin, other calcium binding proteins, concentrate in the dorsal cortex (ICD; see Section 2.6). Cytochrome oxidase, a metabolic marker, concentrates in the ICC (Dezso et al. 1993; González-Lima and Cada 1994; González-Lima et al. 1997; Poremba et al. 1997) rather than in the ICD.

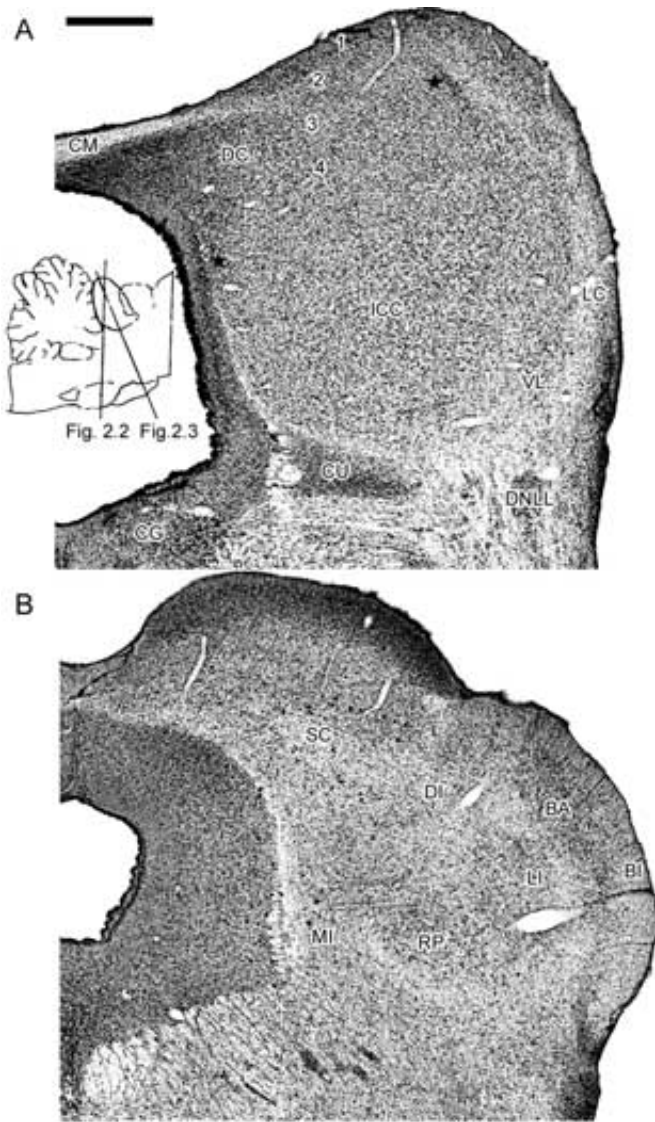
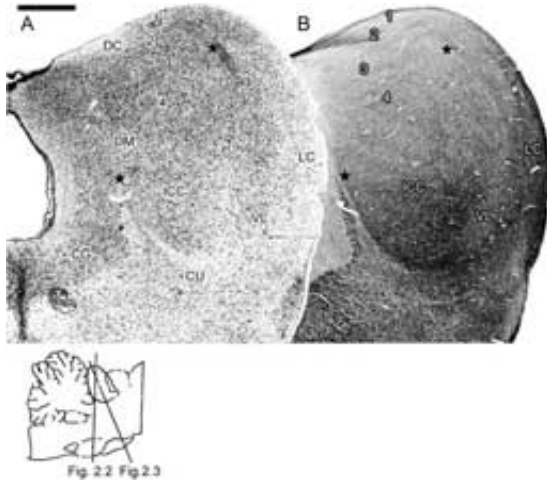


Figure 2.2. Nissl cytoarchitecture of the cat IC in the Horsley-Clarke stereotaxic plane. The *inset* shows the planes of section. **(A)** Mid-IC level through the DNLL. **(B)** A more rostral section at the level of the rostral pole nucleus (RP). BA, Nucleus of the brachium; BI, brachium of the inferior colliculus; CG, central gray; CM, commissural, commissure; CU, cuneiform nucleus; DC, dorsal cortex; DI, dorsal intercollicular tegmentum; DNLL, dorsal nucleus of the lateral lemniscus; ICC, central nucleus; LG, lateral cortex; LI, lateral intercollicular tegmentum; MI, medial intercollicular tegmentum; SC, superior colliculus; 1-4, layers of the dorsal cortex; VL, ventral lateral nucleus. The scale bar represents 1 mm.

Figure 2.3. Cat IC in the anatomical transverse plane of section. The *inset* shows the plane of #2. (A) Nissl stain. (B) Heidenhain fiber stain. The scale bar represents 1 mm.



Subdivisions can also be identified electrophysiologically. Microelectrode studies showed that ICC neurons had low thresholds and vigorous responses to simple acoustic stimuli, and their spectral properties and response latencies often distinguished them from ICD (see Chapter 11). ICC neurons have the sharpest tuning and shortest latencies (Aitkin et al. 1975), suggesting its functional primacy.

However, the presence of a tonotopic map does not distinguish the ICC from the surrounding cortex. In other brain regions there is often a reversal in the sequence of frequencies at a subdivision border. Such a reversal is found at the border of the ICC and lateral cortex but *not* at the border of the ICC and ICD or caudal cortex. This has frustrated any sharp distinction between the ICC and dorsal cortex in electrophysiological studies, as the best frequency of a neuron cannot conveniently determine electrode position relative to the ICC border. Electrophysiological methods must often be complemented by other independent methods such as post hoc histology to identify recording sites in smaller subdivisions.

Two methods combine elements of histological approaches and acoustic stimulation and may distinguish subdivisions. The first uses the accumulation of 2-deoxyglucose (2DG) in presynaptic endings during synaptic activity (Nudo and Masterton 1986). A second method is the detection of the Fos protein, a nuclear transcription factor, or its mRNA (Sheng et al. 1993; Fields et al. 1997). Both approaches can reveal activity evoked by acoustic stimuli in presynaptic endings (2DG) or in single neurons (Fos). The challenge in using these methods to identify IC subdivisions is the choice of an appropriate stimulus. One approach uses different spectral, temporal, and binaural features of acoustic stimuli to evoke differential responses in the ICC and surrounding structures.

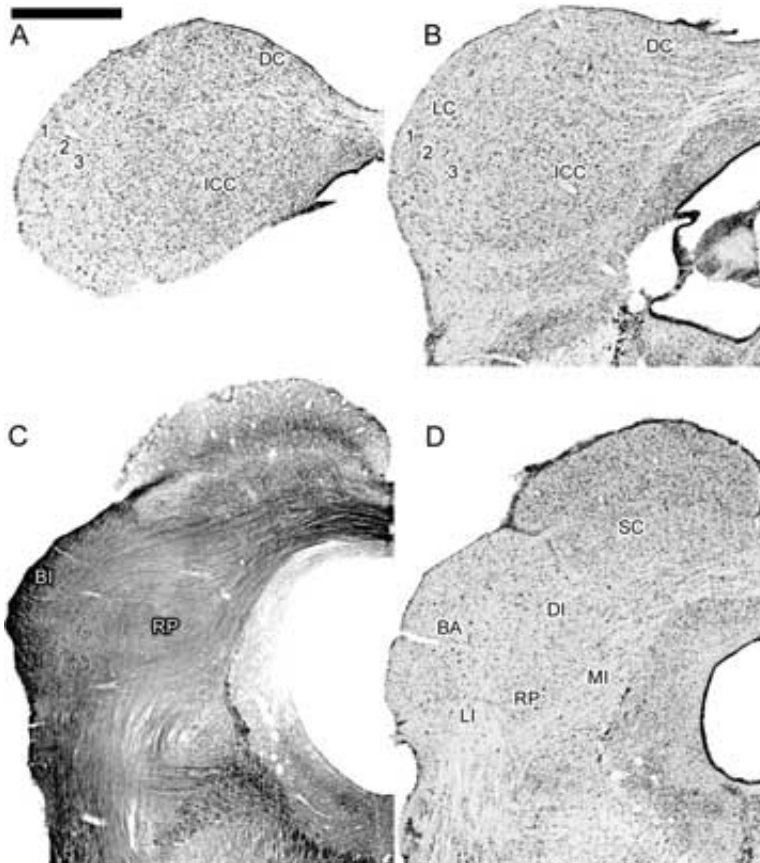


Figure 2.4. Rat IC. (A) Caudal central nucleus. 1–3, layers of the lateral cortex. (B) Rostral central nucleus. (C) Myelin stain at the level of rostral pole. (D) Nissl preparation. The scale bar represents 1 mm.

2.3. HOW IS THE CENTRAL NUCLEUS DEFINED?

The main subdivision of the mammalian IC is the central nucleus (Figs. 2.2 to 2.4). Its main feature is the fibrodendritic lamina, an entity comprised of disc-shaped neurons and the laminar plexus of afferent axons terminating in it.

2.3.1. Morphology of Central Nucleus Neurons

The main feature of ICC neurons is their highly oriented dendritic field. These disc-shaped neurons are by far the most common cell type and have been observed in almost every species studied. Similar neurons have been described in Golgi preparations of the cat (Oliver 1984b), mouse (Meininger et al. 1986), bat

(Zook et al. 1985), rat (Faye-Lund and Osen 1985; Malmierca et al. 1993. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.), and human (Geniec and Morest 1971) and after intracellular injections of horseradish peroxidase (Kuwada et al. 1997b; Oliver et al. 1991). In the cat most ICC neurons are disc-shaped and have dendritic fields parallel to one another (Figs. 2.5A and 2.6). This arrangement imparts a distinct appearance in Golgi stains that distinguishes the ICC. Disc-shaped neurons have dendritic

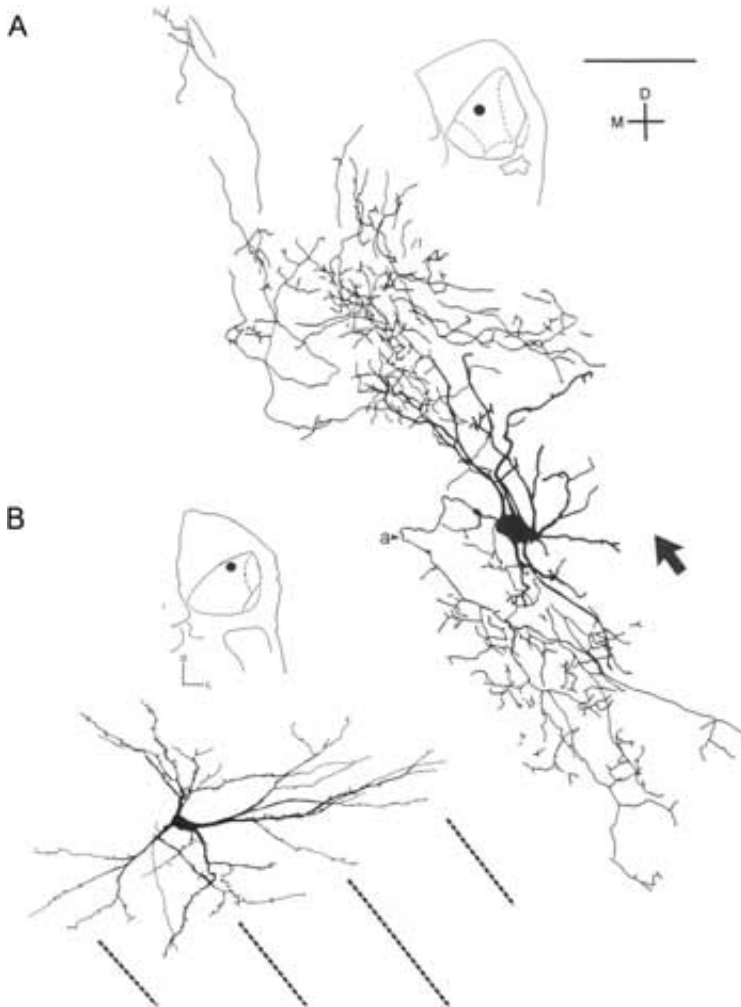


Figure 2.5. Disc-shaped (**A**) and stellate (**B**) cell types in the ICC labeled by intracellular injections of horseradish peroxidase in the adult cat. The approximate position of the cells is shown in the *inset* (closed circle). Laminar orientation is shown by arrow in (**A**) and by lines in (**B**). *a*, axon. The scale bar represents 100 μm. (From Oliver et al. 1991.)

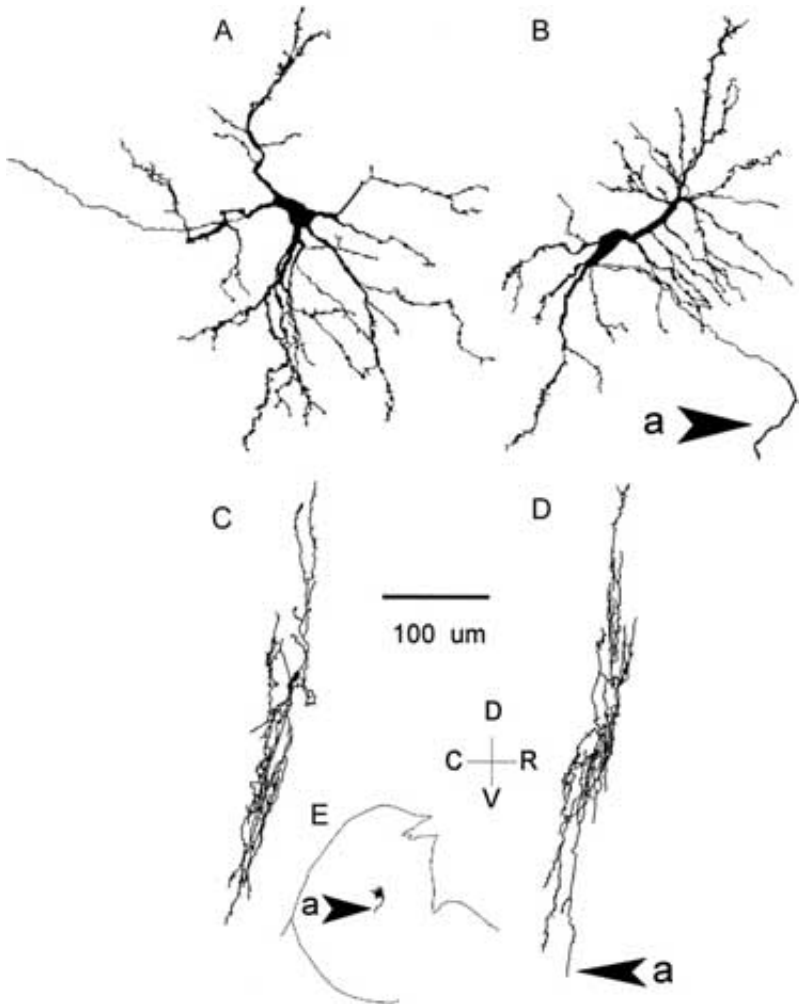


Figure 2.6. Two disc-shaped cells in the ICC of the cat after intracellular injection of horseradish peroxidase. (A, B) The cells are shown *en face* in the original parasagittal plane of section. (C, D) The same cells after 90° rotation to show the most highly oriented edge-on view of the dendritic field. (E) Location of the neuron. (From Kuwada et al. 1997.)

fields about 50 to 70 μm in diameter at the narrowest dimension although the longest axis may be a millimeter (Fig. 2.6). These dimensions may be species-specific. Disc-shaped cells form rows with cells stacked end-to-end or overlapping with long axes of the dendritic fields in parallel. In the rat the high-frequency part of ICC has layers where most disc-shaped neurons, called flat cells in that species, alternate with the less oriented less-flat cells (an oriented

stellate neuron is $100\text{ }\mu\text{m}$ in diameter) (Malmierca et al. 1993). Here, the laminar unit is proposed to be one flat cell and one less-flat neuron, yielding a laminar thickness of about 150 to $170\text{ }\mu\text{m}$ (Fig. 2.7). In the lower-frequency part in the rat and throughout the cat ICC, alternating cell types have not been observed and the laminar unit is likely a multiple of the diameter of the disc-shaped dendritic field. In Nissl stains the disc-shaped morphology is not apparent, as

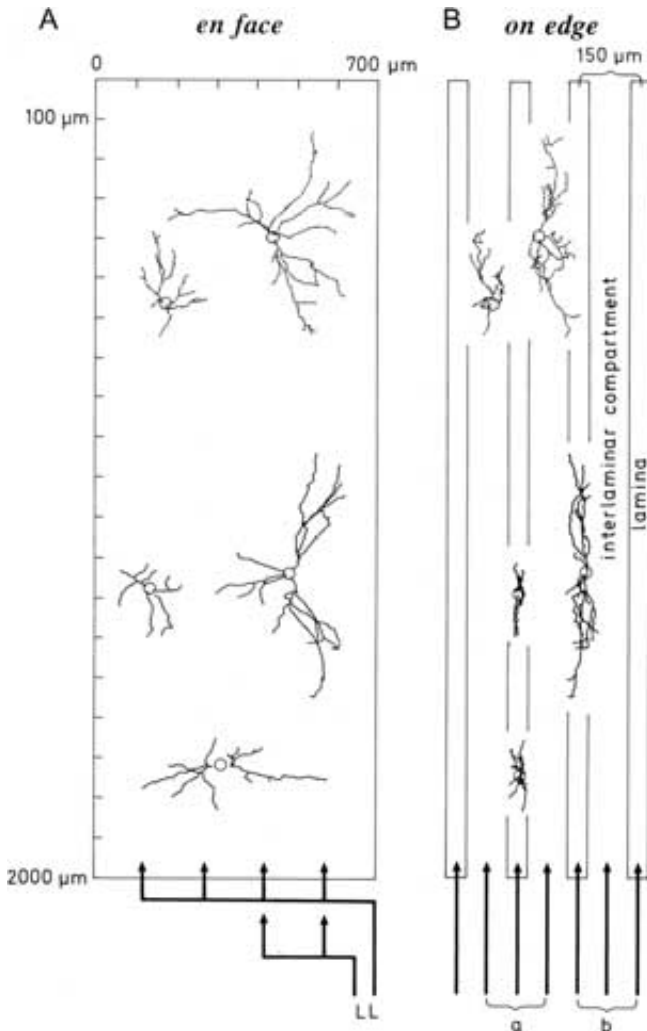


Figure 2.7. Alternating flat and less-flat cells create laminae in the rat central nucleus. (A) The *en face* view shows less-flat cells (*top*) and flat cells (*bottom*) with different-sized dendritic fields. (B) The on edge view shows the narrowest dimension of the neurons after 90° rotation. (From Malmierca et al. 1993.)

the dendrites are invisible but the somatic orientation is often still evident. Most ICC neurons have dispersed Nissl bodies (granular endoplasmic reticulum) and a smooth nuclear envelope, and presumably correspond to disc-shaped cells (Oliver 1984b; Ribak and Roberts 1986).

A second major cell type defined by morphology in ICC is the stellate (cat; Fig. 2.5B) or less-flat (rat; Fig. 2.7) neurons, which represent <25% of the population and often have radiating dendritic fields that are spherical. Dendrites typically extend beyond the single fibrodendritic lamina into adjacent laminae. Other cell types have ovoid dendritic fields oriented perpendicular to the long axis of the disc-shaped cells (cat) or parallel to the flat cells (the less-flat cells in rat). Nissl stains reveal that presumptive stellate cells have more Nissl bodies (stacks of granular endoplasmic reticulum) and an irregular or infolded nuclear envelope.

The identification of functionally relevant neuron types remains a challenge to research in this field. There are probably more than two types of ICC cells distinguished only on anatomical grounds. They can also be discriminated by size (disc-shaped cells are large to medium or small) and by the complexity of the dendritic branching (stellate cells have simple or complex dendritic branching patterns) (Malmierca et al. 1993). The incidence of dendritic spines (Paloff et al. 1992) and the number and types of axosomatic synaptic input may vary (Oliver 1984b; Ribak and Roberts 1986; Paloff et al. 1989). Observations on the neurotransmitter content, axonal targeting, and intrinsic membrane properties (see Section 4) support the notion that the definition of functional cell types must include data beyond classical morphological models.

2.3.2. Synaptic Inputs to the Central Nucleus

Inputs to the ICC ascend from neurons in the lower auditory brain stem, including the cochlear nuclear complex consisting of the dorsal (DCN; Figs. 2.8 and 2.9) anteroventral (AVCN) and posteroventral (PVCN) cochlear nuclei (see

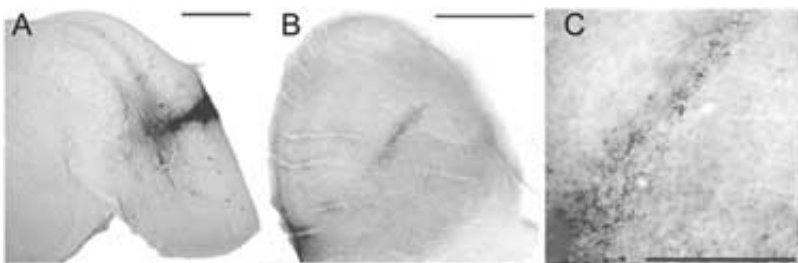
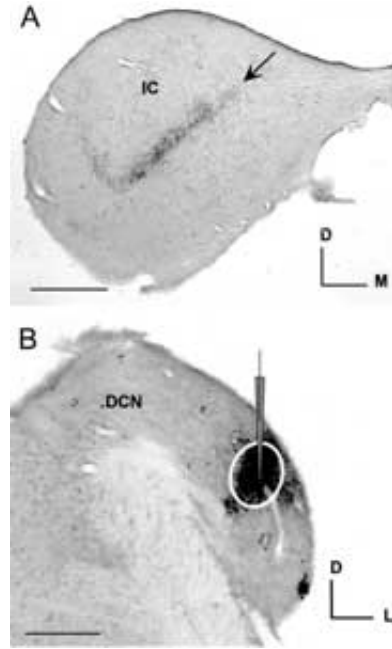


Figure 2.8. Projections from cat dorsal cochlear nucleus to the inferior colliculus. (A) Injection of biotinylated dextran amine in dorsal cochlear nucleus. (B) A single layer of dextran-labeled axons in the central nucleus of the inferior colliculus. (C) Higher magnification view of labeling. The scale represents 1 mm in (A, B); the scale bar represents 0.5 mm in (C). (From Oliver et al. 1997.)

Figure 2.9. Projection from dorsal cochlear nucleus (DCN) to the inferior colliculus in the rat. (A) Band of labeled axons in the ICC (arrow). The lateral band of axons in the external (lateral) cortex is orthogonal to the medial (lateral) band. (B) Injection of dextran in the 4.5 kHz region of dorsal cochlear nucleus. The scale bar represents 0.5 mm. (From Malmierca et al. 2002.)



Chapter 3), and from the superior olivary complex, which includes the medial superior olive (MSO; Fig. 2.10) and the lateral superior olivary nuclei (LSO; Chapter 4). Smaller inputs originate in the medial nucleus of the trapezoid body and from periolivary nuclei, including the superior paraolivary nucleus, and the lateral and ventromedial nuclei of the trapezoid body. The lateral lemniscal nuclei (dorsal and ventral nuclei; DNLL and VNLL, respectively) also provide many afferent axons to ICC (Brunso-Bechtold et al. 1981; Oliver and Shneiderman 1991) and represent the largest single source of input fibers. These projections have been described in small mammals (Merchán et al. 1994; Merchán and Berbel 1996; Malmierca et al. 1998).

Excitatory inputs to the ICC outnumber inhibitory inputs. Electron microscopic autoradiographic studies have identified the synaptic endings from different brain stem sources. These afferent endings are defined as excitatory inputs by the morphology of their synapses—their endings contain clear, round synaptic vesicles (R-type) that make asymmetrical synaptic contacts. It is possible to determine the relative prevalence of different types of axonal boutons from different sources. The MSO provides the largest single source of excitatory synaptic inputs (37%) in the cat followed by the ipsilateral LSO (26%), the contralateral LSO (18%) (Oliver et al. 1995), and the cochlear nucleus (DCN: 11%; AVCN: 13% to 18%) (Oliver 1984a, 1985, 1987). The sum of R-type endings from all sources is about 60% of the ICC axonal endings.

Inhibitory inputs are substantial and are a remarkable feature of ICC neuronal organization. Synaptic terminals that contain γ -aminobutyric acid (GABA) or

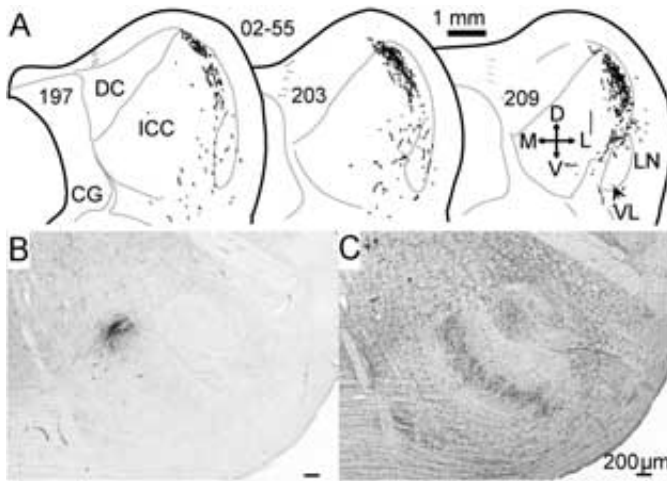


Figure 2.10. Medial superior olivary projections in the cat. **(A)** Plots of dextran-labeled axons terminating in the most dorsolateral ICC laminae corresponding to the lowest frequency representation. A few fibers cross the border into the dorsal cortex. Others may terminate in the most dorsal part of the ventrolateral nucleus. **(B)** Injection of dextran amines in the dorsal 150 Hz region of the medial superior olive. **(C)** Adjacent Nissl-stained section. (From Loftus et al. 2004.)

glycine as a neurotransmitter comprise 40% of the presynaptic endings (Oliver 2000). Electron micrographic studies find many endings with the morphology associated with inhibitory synapses—pleomorphic synaptic vesicles (PL-type) that make symmetrical synaptic contacts (Shneiderman and Oliver 1989). Many of these contain GABA (Shneiderman et al. 1993; Oliver et al. 1994) and originate in the DNLL (Hutson 1988; Shneiderman et al. 1988; Zhang et al. 1998; Chen et al. 1999) and they account for 26% of the PL-type endings (Shneiderman and Oliver 1989). A second source of inhibitory endings is the ipsilateral LSO projection, which contains glycine (Saint Marie et al. 1989; Saint Marie and Baker 1990; Glendenning et al. 1992) and also accounts for 26% of ICC endings (Oliver et al. 1995). A third and probably inhibitory projection is the VNLL, whose neurons contain both glycine and GABA (Saint Marie et al. 1997; Riquelme et al. 2001). These endings have not been identified at the electron microscopic level nor have the local axons from IC GABAergic neurons (see Section 4.2).

Although the inputs to ICC have been identified at the electron microscopic level, their synaptic role in processing auditory information remains an area of intense interest. For example, it is unclear whether these inputs are distributed homogeneously. Further evidence on ICC microanatomy suggests that inputs are segregated and raises the possibility that excitatory and inhibitory inputs have different densities in different functional modules (see Section 3.2.2). Likewise,

as the definitions of cell types expand to include transmitter content and intrinsic properties, it will be important to determine whether different cell types receive the same proportions of excitatory and inhibitory input.

2.3.3. Axonal Components of the Fibrodendritic Laminae

The major axonal components of the fibrodendritic laminae are lemniscal axons. Many axons in Golgi preparations run parallel to the dendrites of the disc-shaped neurons but the identity of these axons cannot be determined. In experimental material the contribution of the ascending fibers to the fibrodendritic laminae can be determined. Axons from lower brain stem sources form ventrolateral-to-dorsomedial oriented rows parallel to the dendritic fields of the disc-shaped neurons. Small injections of clusters of neurons in auditory brain stem structures with anterograde tracers (biotinylated dextran amines, [^3H]leucine) reveal axonal bundles that run from the caudal to rostral direction through much of the ICC (Figs. 2.8 to 2.10). In essence a single band of axons represents the narrowest laminar dimension, about 200 μm wide. In the cat the axonal laminae can extend 4 mm rostrocaudally and reach 2 mm in height (Fig. 2.11). These run from caudolateral-to-rostromedial at approximately 45° to the rostrocaudal plane and from ventrolateral to dorsomedial in the dorsoventral plane. The rostrocaudal laminar length may be species-specific. However, the width of single bands of axons from the DCN (compare Figs. 2.8 and 2.9) is similar in cat and rat and resembles that for AVCN and for cat LSO and MSO axons (Fig. 2.10).

A third component of the fibrodendritic laminae are axons from local IC neurons (see Chapter 5). Axons from both disc-shaped and stellate cells form local collaterals before leaving the IC. Disc-shaped cells injected with intracellular deposits of horseradish peroxidase (HRP) have axons that remain in the same lamina as the parent cell and the local axonal plexus is parallel to the dendritic field (Fig. 2.5A) (Oliver et al. 1991). IC neurons may also project to other ipsilateral laminae. Stellate neuron axons in Golgi impregnations in the cat or after intracellular filling in the rat contribute to fibrodendritic laminae other than the one in which the cell body resides (Fig. 2.12A). Thus, ICC neurons of all types have axons that contribute to ICC laminar organization. An important unresolved issue here is whether the ICC contains true interneurons with axons that are confined solely to the ipsilateral IC (see Chapter 22). Although there is evidence for local axonal collaterals, it is more difficult to prove that the axon remains within the ICC. No neuron with a unique morphology has been identified as a true interneuron and the evidence from HRP intracellular filling suggests that all neurons have axons with local collaterals, even those whose targets are outside of the IC or in the contralateral IC (Oliver et al. 1991).

A fourth component of the fibrodendritic lamina is commissural fibers (see Chapter 5). Small injections of *Phaseolus vulgaris* leucoagglutinin (PHA-L) or biotinylated dextran amines (BDA) on one side of the IC can label single contralateral laminae (Saldaña and Merchán 1992; Malmierca et al. 1995). The contralateral laminar labeling is at the same best frequency as the injected lam-

ina. Thus, the homotypical laminae on each side of the central nucleus appear to be interconnected.

2.4. *THE LATERAL CORTEx*

The lateral cortex is lateral to the central nucleus (LC; Fig. 2.2A) and has also been called the external nucleus (Berman 1968), external cortex (Faye-Lund and Osen 1985), and lateral zone (Geniec and Morest 1971). Part of it may receive input from the lateral lemniscal nuclei, but it lacks disc-shaped cells. In the cat and human the LC includes the lateral nucleus and the ventrolateral nucleus (Geniec and Morest 1971; Morest and Oliver 1984).

The LC has a fibrous outer layer 1 and a small-celled layer 2. In the cat it is easily defined relative to the low-frequency parts of ICC by its lower neuronal density (Fig. 2.2A: LC). The LC is also apparent in myelin stains because the fibers that become the brachium of the IC aggregate and the outer fibrous layer thickens rostrally (Fig. 2.3). Layer 2 of the LC is apparent in many species because of high acetylcholinesterase concentrations (rat: Paxinos and Watson 1998). The main inputs to the lateral nucleus are from the ipsilateral ICC, the auditory cortex, the spinal cord, and dorsal column nuclei of the somatic sensory system (Morest and Oliver 1984; Oliver and Huerta 1992). These terminate primarily in LC layer 2 and lateral lemniscus fibers do not enter layers 1 or 2 (Oliver et al. 1999) (see below).

In the cat and human the lateral cortex includes the ventrolateral nucleus (Figs. 2.2 and 2.3: VL) wedged between the ventral part of the lateral nucleus and the fibers of the lateral lemniscus as they enter the ventral central nucleus (also called the interstitial zone). VL has large and small cells and a cellular density intermediate to that in the central or lateral nuclei. Thus, it can appear as a third layer beneath the small-celled second layer of the lateral nucleus in the ventral IC. Rostrally, VL is usually segregated from ICC by the lateral lemniscal axons. More caudally, however, lemniscal fibers are fewer and the separation is less obvious. The cat VL receives lemniscal inputs from the cochlear nucleus and the MSO and LSO (Shneiderman and Henkel 1987). These are laminar projections. When labeled experimentally they form a “medial band” of axons in ICC parallel to the disc-shaped neurons, and a shorter “lateral band” in VL oriented orthogonal to those in ICC (Shneiderman and Henkel 1987).

In the rat the LC (Fig. 2.4A, B: LC) is called the external cortex (Faye-Lund and Osen 1985; Paxinos and Watson 1998). The many studies of rats make it useful to compare this region to that in the cat. The external cortex is a three-layered structure. Layers 1 and 2 resemble the cat LC, the fibrous layer and the small cellular layer, respectively. Layer 3 of rat LC corresponds to the ventrolateral nucleus. Studies of both the local connections and the lemniscal inputs to the IC in rat show laminated input to both the ICC and to layer 3 of the external cortex (see Chapter 5). As in the cat ICC and VL, the medial band of lemniscal fibers terminates parallel to the ICC laminae and the lateral band of fibers in the external cortex is nearly orthogonal (Fig. 2.9). Single lateral bands

are as wide as the medial bands. The lemniscal inputs to the external cortex are tonotopically organized with lower frequency bands located dorsally (Loftus et al. 2004b).

One explanation for the different appearances of the IC in the rat and cat is the absence of laminae in rat ICC and lateral cortex tuned to frequencies <1 kHz and the attenuation of laminae tuned to 1 to 5 kHz. In the rat, the ICC is separated from the lateral nucleus by the VL (layer 3 of LC). In contrast, in the cat the frequencies <5 kHz and especially <1 kHz occupy much of the dorso-lateral ICC. The portions of the IC lateral to this low-frequency ICC region have little or no ventrolateral nucleus intercalated between it and the lateral nucleus, and lateral bands of lemniscal axons tuned to frequencies <2 kHz diminish. Because in the rat few IC responses are <3 kHz (Clopton and Winfield 1973), the comparable low-frequency part of ICC is presumably absent or attenuated, perhaps explaining the species difference. A similar effect may be present in mice, whose low-frequency hearing is likewise minimal.

Questions remain concerning the LC particularly. Not least among these is the persistent use of different names for what may be the same structure. We propose that the term “lateral cortex” be adopted as a substitute for external cortex, as it clearly denotes this lateral portion of the IC, it distinguishes it from other rostral, medial, and dorsal regions, and it identifies its cortical affiliations.

The function of the LC is uncertain. This may be because observations from the deeper portion (VL nucleus, layer 3), which receives lemniscal inputs, are often combined with data from the superficial portion, which receives little ascending input but is a major target of ICC. Electrophysiological studies have not characterized these areas systematically and consequently there is little basis on which to compare their neuronal response properties. One possible function, suggested below, is that the lateral nucleus of the LC extends rostrally as the nucleus of the brachium of the IC and this amalgamated structure has a role in multimodal integration (Malmierca et al. 2002).

2.5. *STRUCTURES ROSTRAL TO THE CENTRAL NUCLEUS*

Rostral to the ICC the laminae disappear and the nucleus of the rostral pole (RP; Figs. 2.2B and 2.4C, D) emerges. In many species the RP receives the most anterior lemniscal fibers and these terminate on stellate neurons. The RP is evidently related to auditory function owing to its lemniscal inputs and it projects to the superior colliculus, providing auditory signals to the visual-motor system (Harting and Van Lieshout 2000). However, few studies have considered the responses of these neurons to sound stimuli.

The intercollicular tegmentum surrounds the RP (Figs. 2.2B and 2.4C, D) and it is named according to its location in the dorsal (DI), medial (MI), or lateral (LI) intercollicular tegmentum (Morest and Oliver 1984). These complex tegmental structures are the part of the mesencephalic reticular formation that separates the IC from the superior colliculus. The borders of ICC, RP and tegmental structures are best seen in sagittal or horizontal planes where the fibrous teg-

mental architecture contrasts with the denser cell packing of the ICC. The functions of the intercollicular tegmentum at the level of the IC remain obscure, but it may be involved with multimodal integration. Like the second layer of LC, the intercollicular tegmentum receives inputs from the somatosensory system (RoBards et al. 1976; RoBards 1979; Wiberg et al. 1987), from the auditory nerve root (Lopez et al. 1999), and more rostral portions of the mesencephalic reticular formation that are involved in visual-motor function (Waitzman and Oliver 2002). The intercollicular tegmentum may therefore be involved with multimodal integration.

The nucleus of the brachium of the IC (BI; Figs. 2.2B and 2.4C, D) may be involved in gaze control. Whereas the brachium of the IC (BI; Figs. 2.2B, 2.4C, D) contains the tectothalamic fibers from the IC and corticotectal fibers from the neocortex (Kudo and Niimi 1980; Winer et al. 1998), the BI is a cellular structure that receives inputs primarily from the IC. It is continuous caudally with the LC. The nucleus of the brachium projects in a reciprocal topographical manner to the superior colliculus (King et al. 1998; Doubell et al. 2000). The BI may also serve as an interface for routing auditory information from the ICC to the superior colliculus. Because of this role and its position in the auditory pathway the nucleus of the brachium (perhaps including the lateral nucleus) may be homologous to the “external cortex” as defined in the barn owl, where convergent inputs from ICC create a spatial map of sound location that is conveyed to the optic tectum (Knudsen 1983a,b). The nature of the auditory signals sent by BI to the superior colliculus in the mammal is unknown.

2.6. *STRUCTURES DORSAL AND CAUDAL TO THE CENTRAL NUCLEUS*

Dorsal to the ICC is the dorsal cortex (DC; Figs. 2.2A, 2.3, and 2.4B, C). Earlier studies (Berman 1968; Rockel and Jones 1973b) recognized a “pericentral nucleus” that is largely confined to the outer margin of the IC and resembles the LC in that it has a fibrous outer layer and a parvocellular inner layer. These layers correspond to layers 1 and 2 of the cat’s DC (Morest and Oliver 1984). The deeper layers of DC (layers 3 and 4; Figs. 2.2A and 2.3) were considered the dorsomedial part of ICC in some prior accounts (Rockel and Jones 1973b). Layer 3 is continuous with the fibers of the commissure of the IC and the deeper layers have successively larger cells. The caudal cortex is limited to the superficial 200 to 300 μm IC caudal to ICC (Morest and Oliver 1984; Oliver and Morest 1984). Much like the pericentral nucleus, it has two outer layers but the most superficial fibrous layer is less prominent. Where it is caudal to the DC in the dorsomedial IC, layer 2 of the caudal cortex borders layer 3 of the DC.

Golgi studies have shown that the deeper layers of DC continue beneath the pericentral region until it meets the ICC. Their border is clear, as the orientation of the dendritic fields shows disc-shaped neurons of the fibrodendritic laminae in the ICC ending at the border of the DC, where nonoriented neurons become prominent (see Fig. 11 in Morest and Oliver 1984). Fiber stains and anterograde

transport studies reveal the transition from the ICC, as the axonal populations change here. For example, DC neurons have unoriented axons while disc-shaped ICC neurons have axons confined to a lamina (Oliver et al. 1991). Inputs to ICC are primarily from the brain stem with minor (or no) inputs from the neocortex and a modest input from the contralateral IC (see earlier). This pattern is reversed in the deepest layer of dorsal cortex (layer 4), where the neocortical and commissural inputs are predominant (Chapters 5 and 8). Only modest inputs from the DCN and the DNLL reach DC layer 4 (Oliver 1984a; Shneiderman et al. 1988). These fibers are often smaller collaterals of the lemniscal axons whose principal terminal fields are in the ICC. Input to the DC from the SOC is absent.

Defining the dorsal border of ICC experimentally remains problematic and there is a question as to whether there is a sharp functional border. As noted earlier, there is no reversal of the tonotopic map at this border. However, changes in the populations of inputs and possibly in the intrinsic properties of the neurons (Smith 1992; Li et al. 1998) suggest that the response properties of neurons in these regions differ. For example, DC neurons have broader tuning than ICC neurons (Aitkin et al. 1975, 1994).

Certain histochemical stains and immunocytochemical probes may be useful to identify this border. In many species a high parvalbumin concentration delineates the ICC from the DC and the latter has high concentrations of calbindin and calretinin. Comparisons are available for human, gerbil, bat, guinea pig, macaque, dolphin, rat, and mouse (Seto-Ohshima et al. 1990; Ohshima et al. 1991; Coleman et al. 1992; Vater and Braun 1994; Yasuhara et al. 1994; Caicedo et al. 1996; Lohmann and Friauf 1996; Glezer et al. 1998; Idrizbegovic et al. 1999; Spencer et al. 2002; Tardif et al. 2003). Molecules such as cytochrome oxidase also have high concentrations in the ICC (Dezso et al. 1993; González-Lima and Cada 1994; González-Lima et al. 1997; Poremba et al. 1997) and NADPH-diaphorase is concentrated in the dorsal and lateral cortex (Paxinos 1999). These latter proteins may be expressed in the presynaptic lemniscal axons in the IC and these axons may not all terminate precisely at the ICC border, suggesting a concentration gradient at the DC border.

2.7. FUTURE RESEARCH ON DEFINING FUNCTIONAL SUBDIVISIONS IN THE INFERIOR COLLICULUS

Other endogenous proteins may better serve as architectonic guides to IC parcellation. The premise that IC subdivisions represent homogeneous functional zones based on either unique neuron types or fixed combinations of inputs suggests that cell-specific molecules or inputs may identify the subdivisions. At this point, however, single IC subdivisions remain to be identified by single molecules. Moreover, the premise that the identity of an IC subdivision is represented as a single functional module is tenuous.

A complementary approach that deserves attention is the molecular specificity of different IC cell types or cells of different lineage. Thus, if DC neurons originate from different stem cells or develop at different times than those in

the ICC it could explain why the dendrites of their neurons differentiate later (Morest 1969). Because ICC and DC neurons often differ in dendritic morphology, perhaps there are molecules related to this phenotype that would demarcate IC subdivisions. Different IC neurons have different patterns of ion channel expression, as suggested by firing patterns related to unique combinations of potassium and calcium currents (Sivaramakrishnan and Oliver 2001). Thus, probes for ion channel subunits or combinations of subunits may specify subdivisions.

3. MICROANATOMY OF THE CENTRAL NUCLEUS

There are units of IC neuronal organization finer than the subdivisions described earlier. The microanatomy within each subdivision may define functional modules that control important aspects of information processing. We have proposed that synaptic domains are functional modules formed by the segregation of in-

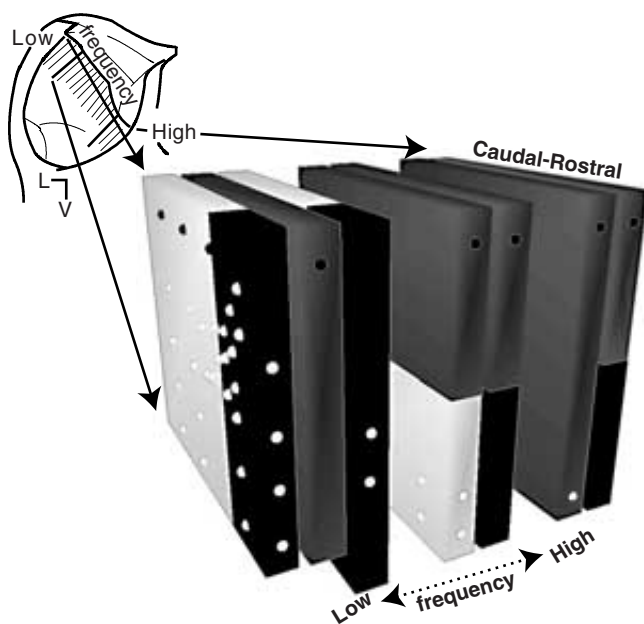


Figure 2.11. A model of ICC synaptic domains in the ICC. Each functional module is denoted by a different shade and represents a different excitatory brain stem input (*light gray*, medial superior olive; *dark gray*, cochlear nucleus; *black*, lateral superior olive). Inhibitory inputs (lateral superior olive, *white spheres*; dorsal nucleus of the lateral lemniscus, *black spheres*) terminate in particular domains and avoid others. The distribution of some modules is highly related to the tonotopic map since some inputs are absent at the ends of the frequency ranges.

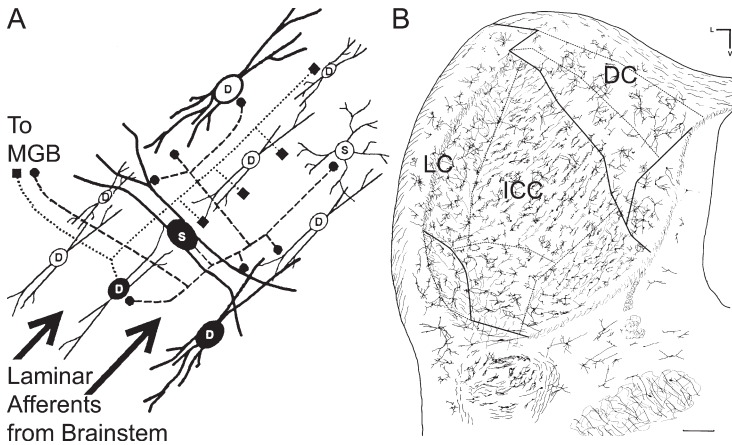


Figure 2.12. Microanatomy of ICC. **(A)** Disc-shaped neurons (D) align to form laminae that are reinforced by the local axons of these cells and parallel to the brain stem laminae afferents. Stellate cells (S) have dendrites and axons that interact with several laminae. Both disc-shaped and stellate cells can synthesize GABA (*black cells*) while others may be glutamatergic. GABAergic neurons can project to the medial geniculate body as do the nonGABAergic cells (*not shown*). **(B)** Golgi-impregnated section of the cat IC shows the subdivisions and ICC laminae at lower magnification. Most laminae run from ventrolateral to dorsomedial. For other abbreviations see Figs. 2.1 and 2.2. (From Oliver 1984. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.; Oliver et al. 1994.)

puts from different sources (Oliver and Huerta 1992; Oliver 2000). Synaptic domains are a basic feature of organization in the inferior and superior colliculus. Thus, small groups of neurons share a common set of synaptic inputs and are likely to share a similar function. In the ICC a single lamina may actually be composed of two or more synaptic domains (Fig. 2.11). Each DC layer may represent a functional module or a layer may contain multiple domains similar to the deep layers of the superior colliculus. Because the LC, VL, and RP nuclei also have unique combinations of inputs, they should be considered functional modules. Future study may show that they contain more than one domain. ICC functional modules have been the most thoroughly studied. Consequently, this section focuses on ICC modules and their role in processing auditory information.

The ICC has a three-dimensional organization defined by its microanatomy. Its laminae consist of arrays of disc-shaped neurons and parallel axons from brain stem and local sources (Fig. 2.12; cf. Section 2.3.2). In the cat the laminae are long sheets running obliquely to the rostrocaudal plane and several millimeters high. The bands of labeled axons seen after small injections in the brain stem or intracellular injections of single IC neurons suggest that single laminae are discrete units approximately 200 μm wide (Figs. 2.8 to 2.11). This unit organization is probably driven by the axonal components, as single dendritic

fields are usually one half to one third the diameter of the axonal bands (Oliver and Morest 1984; Malmierca et al. 1993).

Given this stereotyped ICC microanatomy, the synaptic domains may be related to the dimensions of a single lamina. The most obvious functional parameter related to the laminae is tonotopic organization. This varies in the dimension parallel to the width of the laminae. We first discuss the evidence that the spectral properties of ICC cells are related to the laminar microanatomy. Whether synaptic domains create other functional modules will be the second topic of this section.

3.1. WHAT IS THE STRUCTURAL BASIS OF TONOTOPIC ORGANIZATION?

The elementary organization of the ICC tonotopic map is clear from auditory physiology and experimental neuroanatomical studies. The lowest frequencies are represented dorsolaterally and the highest frequencies are ventromedial (Merzenich and Reid 1974; Schreiner and Langner 1997). Anatomical experiments show that brain stem neurons tuned to different frequencies project to corresponding positions of the ICC tonotopic map and these axonal laminae form discrete units approximately 200 μm wide.

Studies with 2DG show the activation pattern of axons activated by pure tones. Because 2DG is taken up by presynaptic axons during synaptic activity (Nudo and Masterton 1986), this method reveals the three-dimensional organization of the axons when they are activated by sound (Brown et al. 1997b). Their spatial pattern recapitulates the morphology of the axonal laminae. Most sound-activated axons are in the medial band in ICC and the lateral band in the VL is weaker or unlabeled. These studies also show that the width of the axonal band activated by tone increases with stimulus intensity (Brown et al. 1997a). The minimum width of the band activated by near-threshold stimuli should be related to the spatial dimensions of the axons. However, it is difficult to relate the activation pattern to the microanatomy of the laminae because 2DG labeling is usually performed with carbon-14 emission, producing substantial cross-scatter that reduces resolution of the method to a level too coarse to resolve single axons. Because the 2DG accumulates in the presynaptic axons only, the firing of single neurons is not detected.

Microelectrode recordings from single and multiple neurons provide higher resolution and are consistent with a frequency organization based on discrete laminae. The characteristic frequency changes in steps of $175 \pm 83 \mu\text{m}$ in penetrations perpendicular to the tonotopic axis (the dorsolateral to ventromedial direction) and each step is approximately 0.28 octaves (Schreiner and Langner 1997; see Chapter 11). Such frequency steps would constrain the maximum number of laminae available for ICC frequency coding. Thus, 35 to 40 laminae would be required to encode the 9 octaves audible in the cat (Schreiner and Langner 1997). This study suggests that an entire lamina may represent a narrow

range of characteristic frequencies, a “frequency-band lamina” rather than representing a single frequency, the “iso-frequency lamina” concept. However, this method does not address whether the laminar organization is effective in organizing the spectral properties of ICC at sound intensity levels above threshold.

It is now possible to relate the activity of the entire population of the ICC laminae to frequency coding using sound-activated Fos protein. Most neurons produce this nuclear transcription factor when stimuli induce regular bursts of firing for prolonged periods. The production of cFos mRNA and Fos protein is proportional to the amount of firing in the cochlear nucleus and dorsal root ganglion (Sheng et al. 1993; Fields et al. 1997; Saint Marie et al. 1999; Yang et al. 2003b). Consequently, the amount of protein reflects stimulus intensity (Yang et al. 2003b).

The sound activation of Fos protein can address whether the population of neurons activated by single tones is confined to a single lamina, independent of the stimulus intensity (Yang et al. 2003a). Interestingly the maximum band of neurons activated by a single sinusoidally amplitude modulated (SAM) tone (8 or 16 kHz; 14 Hz modulation) is limited to approximately 180 μm wide (Fig. 2.13A). The width of the band is virtually the same for 47- to 80-dB stimuli, although at 27 dB the band narrows (Fig. 2.13B, C). Because the laminar dimension is similar to that suggested by the microelectrode recordings in the cat,

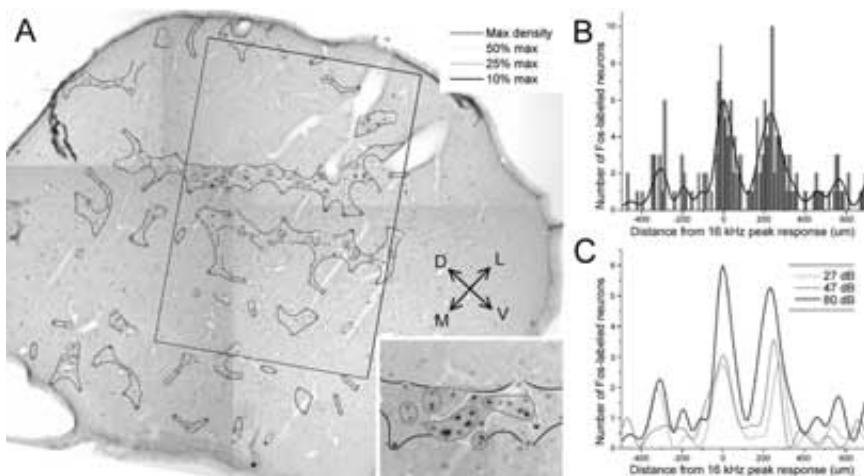


Figure 2.13. Fos protein in the rat IC activated by sounds of two different frequencies. (A) Montage showing Fos-immunopositive neural nuclei in the ICC, DC, and LC. The *inset* shows nuclei at higher magnification. Labeled ICC and LC neurons form bands. Isodensity contours show clusters of cells within bands activated by monaural 80-dB amplitude-modulated tones. (B) Histogram showing density of labeled cells in the box in A. Peaks correspond to the bands of labeled cells. (C) Smoothed curves fitted to the histograms generated by stimuli of different intensities. (From Yang et al. 2003a.)

the microanatomy of ICC laminae may constrain the spread of excitation in the frequency domain. Lateral inhibition may limit the number of neurons activated by a tone to those within the same lamina; however, the mechanisms for this inhibition are still unclear.

A second question addressed by sound activation of Fos is the laminar role in processing spectral information. For example, what frequency separation is necessary for two stimuli to activate independent ICC neural populations? Two populations of neurons were activated by two SAM tones (as above) one octave apart (Yang et al. 2003a, 2004). At levels from 27 to 80 dB the centers of the bands of labeled neurons were separated by 240 μm . Similarly two bands of neurons were evident after stimulation with 37 dB tones separated by 0.5 octave and their centers were half the distance of those in the one octave cases. However, when two tones were separated only by 0.25 octave at 27 to 37 dB the sound-activated neurons formed one band approximately 200 μm wide.

These experiments suggest that ICC laminar microanatomy may play an important role in spectral information processing and may be related to critical bands (Ehret and Merzenich 1985; Schreiner and Langner 1997). The laminae could permit independent neural populations to respond to stimuli separated by at least 0.5 octave across a relatively broad range of stimulus intensities. Two stimuli spectrally more separated are less likely to interact, as they activate discrete populations. For stimuli within 0.25 octave the activation is confined to a single population of neurons within a lamina. This population may respond to all stimuli within this range of frequencies while also encoding subtle differences in the activity pattern related to the stimulus spectrum. Stimuli that activate the same population of neurons in a lamina are likely to be identical perceptually because the neurons cannot distinguish them.

3.2. HOW DOES MICROANATOMY ORGANIZE INFERIOR COLLICULUS NEURONS WITH DIFFERENT BINAURAL RESPONSE PROPERTIES?

Because there is only one tonotopic map in the ICC, the processing of other types of auditory information faces a severe problem. All neurons with a similar best frequency (within 0.25 octave) may be within the same frequency-band lamina. Thus, all ICC neurons with similar tuning are at the same point on the tonotopic map. If each receives identical inputs from all of the lower auditory brain stem, they might have the same response properties. However, this is clearly not the case (see Chapters 11 to 14).

Functional classes of neurons have been identified using several sets of criteria. Early studies classified IC neurons based on interaural level differences (ILD) (EE: bilateral excitation; EI: ipsilateral suppression; EO: monaural only) (Semple and Aitkin 1979; Irvine 1986, 1992). Further studies have clarified the binaural response properties and enlarged the earlier classifications (Kelly and Sally 1993). Binaural neurons sensitive to interaural time disparity (ITD) com-

prise at least two types, both related to ITD sensitivity in the SOC. For peak-type neurons the ITD functions across frequencies align at or near maximal discharge (Kuwada and Yin 1983; Yin and Kuwada 1983a,b; Kuwada et al. 1984, 1987; Stanford et al. 1992) similar to those in MSO (Yin and Chan 1990; Batra et al. 1997a,b). In contrast, trough-type IC neurons align at or near the minimal discharge (Batra et al. 1993) like those in the LSO (Joris and Yin 1995; Joris 1996). In contrast, monaural neurons (Irvine 1986, 1992) must constitute a separate class, as a monaural response would be impossible with the convergence of monaural and binaural inputs. Spectral response properties have been used to classify these neurons (Ramachandran et al. 1999; Le Beau et al. 2001). The frequency-tuning curve shape (V-, I-, or O-shaped) may be correlated with certain binaural inputs (Ramachandran and May 2002). For example, low-BF neurons with V-shaped tuning curves often show peak-type responses, consistent with an input from MSO. I- and O-shaped response classes may receive their primary excitatory synaptic inputs from LSO and DCN, respectively (Ramachandran et al. 1999; Davis 2002).

A critical unresolved issue is how the combination of brain stem inputs contributes to the response properties of IC neurons. One clue is that the inputs to the IC differ by their frequency ranges. For example, MSO is a low-frequency structure with most of its neurons in the range from 100 Hz to about 5 kHz (Guinan et al. 1972). By comparison, the DCN is a high-frequency structure with little representation <1 kHz (Spirou et al. 1993). A particularly complex pattern is shown by the LSO, as the contralateral projection to the IC is heavier at high frequencies and the ipsilateral projection is stronger for low frequencies (Glendenning and Masterton 1983). Such differences in frequency range suggest one reason why synaptic domains across the IC will likely receive different combinations of inputs.

The synaptic domain hypothesis predicts that neurons with similar response properties will occupy the same functional module and receive similar brain stem inputs. For example, IC neurons aggregate when they have similar properties for coding interaural level differences (Roth et al. 1978; Semple and Aitkin 1979). The following sections consider the evidence for synaptic domains as defined by the major excitatory inputs to the IC from the MSO, LSO, and cochlear nucleus.

3.2.1. The Medial Superior Olivary Domain and the Representation of Azimuth

One type of synaptic domain in the ICC may be dominated by MSO input. MSO neurons compute ITD and their receptive fields indicate the location of azimuthal sound sources (Yin and Chan 1990; Batra et al. 1997a,b). The MSO projections neurons are the major source of ITD information to the midbrain. Despite the importance of this pathway, how ITD information is passed from the MSO to the IC is unclear. For example, if the ITD is mapped in the MSO along the rostrocaudal axis, as is often assumed, is this map transmitted to the

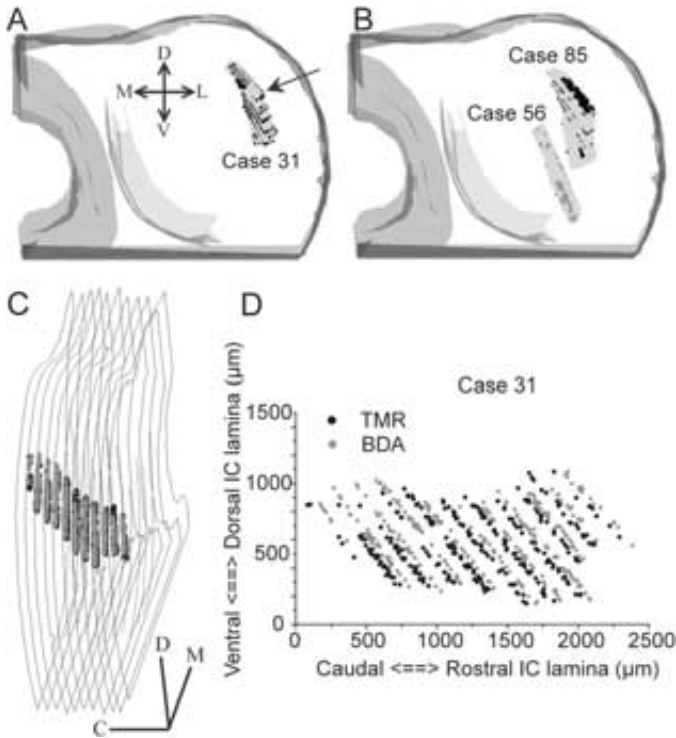


Figure 2.14. Three-dimensional reconstructions of MSO axonal boutons terminating in a lamina in the cat IC. **(A, B)** Single laminae from three animals. **(C)** Lateral view of boutons in a lamina. **(D)** *En face* view of the bouton distribution in **(C)** shows the absence of a simple density gradient related to injection site location. In **(A)**, **(C)**, and **(D)** the boutons are from two injections of different dextran anterograde transport markers in the same MSO at the same best frequency, one rostral and the other caudal. Boutons are labeled with either biotinylated dextran amines (BDA) or dextran labeled with tetramethylrhodamine (TMR). (From Oliver et al. 2003.)

rostrocaudal dimension of the IC laminae? The evidence for spatial topography in the MSO–IC projections was examined in the cat by making recordings of ITD sensitivity and small injections of BDA in different MSO locations and tracing the axons to the IC laminae (Figs. 2.14 and 2.15; Oliver et al. 2003). Two deposits in the same animal allow overlap and segregation of terminal fields to be studied. Different rostrocaudal locations on the same MSO frequency plane do not terminate at restricted points on the IC lamina. Instead, the MSO axons terminate along the length of a lamina (Figs. 2.14A to C, 2.15C). Within the lamina the axonal boutons are not distributed at uniform density or in a linear gradient (Fig. 2.14D). Consequently, there are neither point-to-point connections

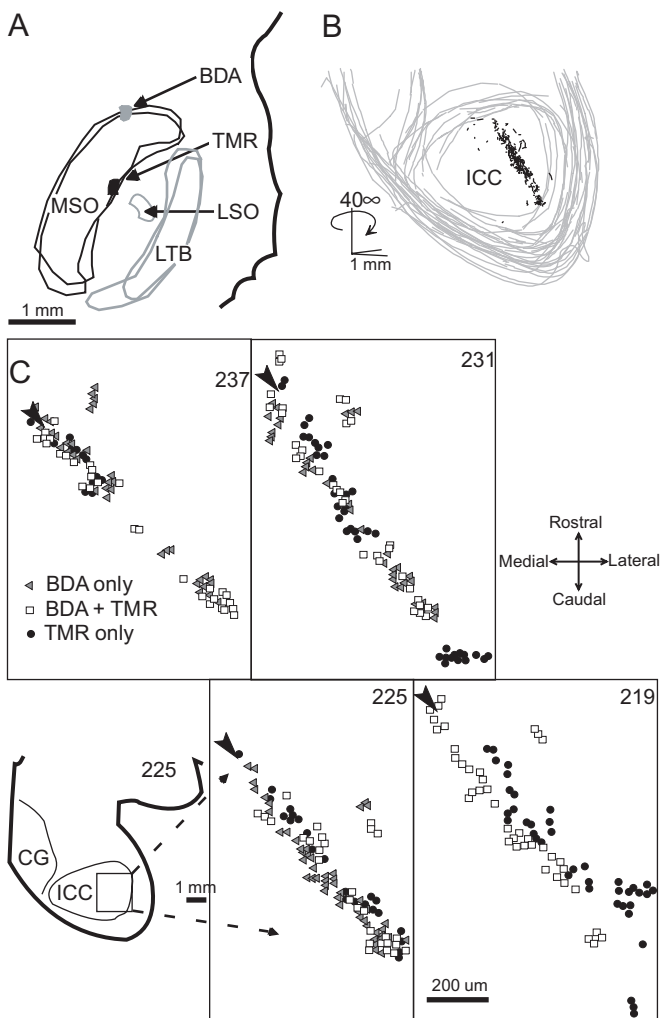


Figure 2.15. Axons from two points in the MSO with the same best frequency converge on the same IC lamina. **(A)** Injections of different dextrans. **(B)** Three-dimensional reconstruction of the colliculus to show the laminar labeling from these injections. **(C)** Axonal labeling in serial sections through the ICC (see *inset*). (From Oliver et al. 2003.)

nor a gradient of connections to convey information from a map of space in the MSO to a comparable map in the IC laminae.

These results suggest that the dimension of the lamina orthogonal to the frequency axis does not necessarily represent a monotonic spatial map of a sensory dimension. For the MSO projections to the IC, the transmission of information about azimuthal sound location does not rely on a rerepresentation of a spatial map of azimuth in the MSO that is conveyed to the IC. Consequently, the azimuthal response of an IC neuron may be unrelated to its laminar position. Instead, the results suggest that a complex nontopographical neural network codes the position of a sound source in the IC. The MSO domain is a key component of this network for the IC, as it identifies a population of neurons on a lamina that receive inputs and participate in the network to code sound location.

3.2.2. Lateral Superior Olivary Domain vs. the Medial Superior Olivary Domain

Do MSO inputs remain segregated from other major excitatory inputs to the ICC laminae? Excitatory LSO inputs have different binaural properties. As mentioned earlier, binaural response properties that mimic these inputs would be difficult to find in IC neurons if excitatory LSO and MSO inputs always converged on the same IC neuron. For example, peak-type ITD responses would be expected in IC neurons that receive excitatory inputs from MSO, but not excitatory trough-type ITD inputs from the LSO. To be consistent with the synaptic domain hypothesis, excitatory inputs from the MSO and the LSO should remain segregated. To test the hypothesis that the inputs from MSO and LSO would not converge in the same IC lamina, ITD-sensitive MSO and LSO cells with a similar characteristic frequency, but different binaural responses, were labeled with different anterograde tracers to trace the axons that project from these sites to the ICC.

The results suggest that the excitatory inputs from MSO and contralateral LSO remain separate (Loftus et al. 2002, 2004a). The MSO projections on one side were compared to the projections of the opposite LSO, as MSO axons project only to the ipsilateral IC, while the LSO excitatory projections are mostly contralateral. The LSO target in IC is more rostral than the MSO target (Fig. 2.11, black; Fig. 2.16A). The MSO termination zone is longer and has more boutons than the rostral LSO target (Fig. 2.11, light gray; Fig. 2.16B, C). This is consistent with injections of retrograde tracers in the caudal, low-frequency ICC, where neurons have peak-type ITD responses. Both the retrograde and anterograde labeling suggests that IC neurons with peak-type responses to ITD are in synaptic domains with excitatory inputs from the MSO whereas neurons with trough-type ITD responses are in another synaptic domain receiving mainly excitatory contralateral LSO input.

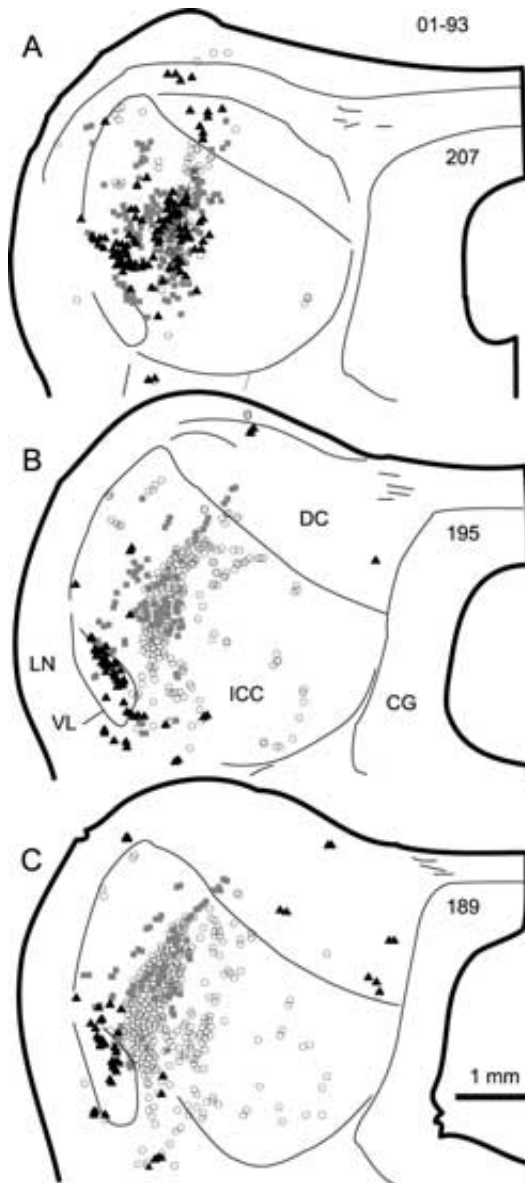


Figure 2.16. Summary of projections from the superior olives to the IC. One injection was made in the left MSO, and the second in the right LSO at an overlapping frequency range. Presumed excitatory ipsilateral MSO inputs (*open circles*) dominate (**B, C**) except in the most rostral levels (**A**) where excitatory inputs from the contralateral LSO dominate (*closed triangles*). Presumed inhibitory inputs from the ipsilateral LSO (*gray filled squares*) are superimposed on those from the medial superior olive. LN, Lateral nucleus; other labels as in Figs. 2.1 and 2.2. (From Loftus et al. 2004.)

These experiments also suggested that the MSO and LSO domains may have other forms of organization as well, including different inhibitory influences. The LSO projects to both the contralateral and ipsilateral IC, but only the contralateral projection is excitatory. The ipsilateral LSO projection is glycinergic. A comparison of both LSO projections was made by superimposing the bouton data from the right IC onto the left IC for each section. In contrast to the excitatory LSO and MSO inputs, which remained separate, the ipsilateral inhibitory LSO projection is denser, terminates in a broader area, and largely overlaps the MSO target zone (Fig. 2.16). Thus, there appears to be one synaptic domain with excitatory inputs from the MSO, and postsynaptic IC neurons also receive inhibitory input from the LSO. There appears to be a second synaptic domain where excitatory LSO inputs are prevalent. These are summarized in the model of the synaptic domains (Fig. 2.11) as the MSO domain (lightly shaded) and LSO domain (black). The inhibitory LSO input is shown as white spheres.

3.2.3. Comparing Central Nucleus Monaural and Binaural Domains

The third major excitatory input to the IC originates in the cochlear nucleus. It arises from multiple cell types in each major division of the cochlear nucleus. Although it is tempting to consider the cochlear nucleus inputs to the IC as a single entity, that would be a gross oversimplification (see Chapters 1 and 3) and DCN, AVCN, and PVCN neurons may not participate in the same synaptic domains. How the inputs from the divisions of the cochlear nucleus complex are related to each other in the IC remains an unresolved issue.

Because a proportion of IC neurons are monaural they likely receive direct input from the cochlear nucleus. They should lack input from binaural lower auditory brain stem neurons. This characteristic is most likely to occur in the high-frequency parts of ICC devoid of MSO afferents. In the rat IC cochlear nucleus axons were labeled with anterograde transport of BDA while tectothalamic IC neurons in the same animals were identified by retrograde transport from the medial geniculate body, and their dendrites were labeled by subsequent intracellular injection of Lucifer Yellow in formaldehyde-fixed brain slices. Cochlear nucleus inputs terminate directly on tectothalamic neurons (Oliver et al. 1999) and this synaptic input fulfills the first requirement for a monaural pathway extending from the cochlear nucleus to the thalamus.

The second requirement for a monaural pathway and for monaural IC neurons is a synaptic domain without binaural input. To address this issue the distribution of afferent axons from the DCN and LSO to the contralateral IC was compared (Oliver et al. 1997). DCN and LSO neurons were characterized by responses to monaural and binaural acoustic stimulation and a deposit was made in each structure with different markers. Both injection sites had cells with overlapping best frequencies. The results showed that DCN and LSO axons are superimposed in part of the contralateral ICC, in laminae in the ventral part of the central nucleus (Fig. 2.11, high frequency, black). However, in the dorsal part of the

same layer LSO axons are absent (Fig. 2.11, dark gray). These data suggest two types of synaptic domains in the high-frequency ICC laminae. One contains binaural neurons that combine the properties of inputs from the contralateral LSO and DCN. A second functional module may contain monaural neurons that have cochlear nucleus inputs and none from binaural structures.

3.3. UNRESOLVED ISSUES ABOUT MICROANATOMY AND FUNCTIONAL ZONES IN THE CENTRAL NUCLEUS

The synaptic domain hypothesis remains a viable explanation for the anatomical organization of the inputs to the ICC. Unresolved issues remain concerning the microanatomy and the organization of the inputs to functionally defined neuron types. Chief among them is the relative contribution of inhibitory inputs to the microanatomy and to each synaptic domain. It is not clear whether modules defined by excitatory inputs receive different combinations of inhibitory input. Inhibitory inputs to the IC are GABAergic axons from the DNLL and glycinergic axons from the ipsilateral LSO. Lemniscal and olivary nuclei influences on ITD sensitivity may differ (Kuwada et al. 1997). Some ITD-sensitive neurons receive predominantly DNLL inputs while others receive mostly ipsilateral LSO inputs. Future experiments will determine if separate groups of IC neurons are postsynaptic to these two inhibitory brain stem inputs.

The contribution of inhibitory inputs to monaural processing also remains unclear. The VNLL is actually a complex of nuclei whose neurons have predominantly monaural responses (Aitkin et al. 1970; Covey 1993; Batra and Fitzpatrick 1999), although one subregion has binaural responses (Batra and Fitzpatrick 2002). Many VNLL neurons contain glycine, GABA, or both and they represent a major input to the ICC that is probably inhibitory (Brunso-Bechtold et al. 1981; Merchán and Berbel 1996; Malmierca et al. 1998). Anatomical studies suggest that the ventral nucleus inputs are laminar rather than diffuse, as suggested earlier (Whitley and Henkel 1984). However, it is unclear to which synaptic domains they contribute.

The local components of the functional modules also remain uncertain. It is unknown how the synaptic domains relate to ICC local axons. Although the existence of Golgi type II interneurons is unresolved (see Section 2.3.2 and Chapter 22) there could be local intra- or intermodular input. It is also unclear how the local environment within a module influences the postsynaptic neurons that reside there. Perhaps the combination of inputs that define a module can also influence number and types of synaptic receptors and ion channels in the postsynaptic neurons (see below).

While synaptic domains are defined largely by the excitatory inputs from binaural or monaural sources, the present relationship of these zones to other facets of auditory processing remains to be clarified. Because inputs from different brain stem sources may differ in their spectral properties, the specific combination of inputs may be related to the spectral properties of single IC neurons. Likewise, the brain stem inputs to IC may differ in their ability to code

complex temporal patterns. Whether functional zones that differ in binaural properties also differ in their spectral and temporal properties remains an open question.

A final question is how ICC synaptic domains relate to functional modules in other subdivisions of IC. Because a frequency reversal does not mark the border between the ICC and the DC, other response properties may distinguish them from the upper tier of ICC synaptic domains. Only the basic inputs of these regions have been determined. The predominant inputs to the upper domains in the ICC are from the cochlear nucleus and nuclei of the lateral lemniscus. In contrast, the predominant input to the adjacent deep dorsal cortex is from the neocortex. Much remains to be learned about the microanatomy of the dorsal cortex and how it differs from that in the ICC.

4. FUNCTIONAL DEFINITIONS OF NEURON TYPES IN THE CENTRAL NUCLEUS

Up to this point the discussion of functional modules has focused almost exclusively on the inputs. However, the postsynaptic neurons in each module will integrate information from each input. Different types of IC neurons may influence how the inputs are integrated. Although IC neurons were originally defined primarily by their dendritic morphology into disc-shaped and stellate categories, this binary classification does not begin to account for all the functional properties observed. IC neurons also differ in their axonal targeting, the types of neurotransmitters produced, and in their electrical properties. These factors must be considered in any definition of IC neuron types to better understand their role in auditory information processing.

4.1. NEURON CLASSIFICATIONS BASED ON AXONAL TARGETING

One criterion for IC neuron types is a unique axonal target. The main IC target is the ipsilateral medial geniculate body (MGB) (see Chapter 7). ICC axons terminate primarily in the ventral division whereas axons from the dorsal cortex project to the deep part of the dorsal division. Some neurons from all subdivisions have axons that terminate in the medial division of MGB. Other IC targets are the ipsilateral nucleus of the brachium, the contralateral IC (see Chapter 5), and the contralateral MGB. Descending IC projections terminate in the periolivary nuclei of the superior olive and the cochlear nucleus (see Chapter 6).

Despite the fact that the targets of the IC are known, we have only a rudimentary knowledge of the cell types that participate in these connections. For example, both disc-shaped and stellate neurons project to the ipsilateral MGB (Oliver 1984b). It is not clear whether these two cell types carry the same information to the MGB and whether their termination patterns are similar. Even less is known about the cell types that participate in tectal or descending projections. Understanding which cell types participate in each IC projection will

allow us to determine whether the same information is transmitted from the IC to each target.

4.2. GABA PROJECTION NEURONS IN THE INFERIOR COLLICULUS

A second functional criterion for defining IC neurons is the neurotransmitter content. Two types of IC neurons project to the MGB. One type is excitatory and probably uses glutamate as the neurotransmitter. The second type is inhibitory and uses GABA as a neurotransmitter. In the cat about 20% of the IC projection neurons to the MGB are GABAergic (Winer et al. 1996). In the rat 40% of the IC neurons projecting to the MGB contain GABA (Peruzzi et al. 1997). GABAergic projection neurons are distributed throughout the IC subdivisions except in the caudal cortex and intercollicular tegmentum (Fig. 2.17). This matches the distribution of GABA immunostaining without reference to axonal target. Some of the IC neurons projecting to the contralateral IC also contain GABA (González-Hernández et al. 1996). However, all of the targets have not been investigated and it is not known whether these two populations of IC neurons project to other targets.

This dual population of GABAergic and presumed glutamatergic projection neurons is a distinctive feature of the IC. GABAergic neurons are often the largest neurons in the IC (Oliver et al. 1994). Most GABA-containing neurons are disc-shaped neurons although some with stellate morphology are also seen.

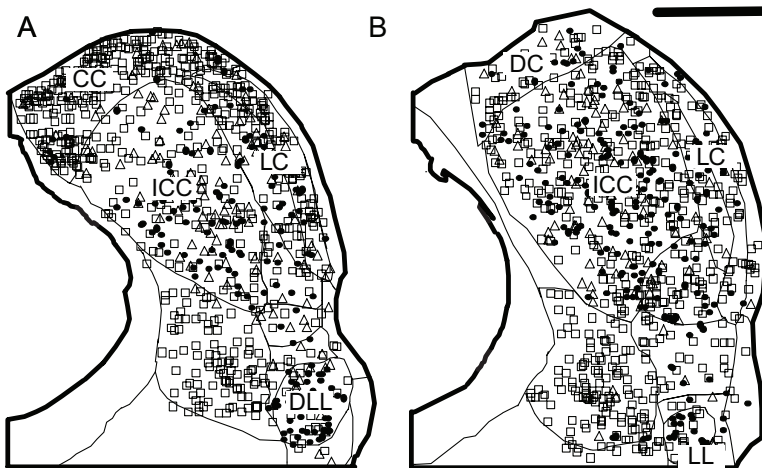


Figure 2.17. Distribution of GABAergic and nonGABAergic IC neurons projecting to the rat MGB. **(A)** Caudal section showing ICC and caudal cortex. **(B)** Section through middle ICC. Tectothalamic neurons are labeled by retrograde transport and are GABA-positive (black circles) or GABA-negative neurons (open squares); there are also GABA-positive neurons (open triangles) that are not retrogradely labeled. (From Peruzzi et al. 1997.)

However, the dendritic morphology of GABAergic neurons has not been correlated with projections. It is suspected that disc-shaped and stellate GABAergic neurons project from the IC to the MGB.

GABAergic IC neurons may have a special role in auditory processing at the thalamic level. Monosynaptic inhibitory postsynaptic potentials (IPSPs) from the IC often reach the MGB before the excitatory postsynaptic potentials (EPSP) (Peruzzi et al. 1997; Bartlett and Smith 2002). Additional IPSPs are seen after the EPSP. The fast IC GABAergic input may actively control the timing of the onset of excitation in the MGB and the slow GABAergic input may contribute to the suppression of firing along with other mechanisms such as GABAergic inhibition from the thalamic reticular nucleus. These data suggest that the IC projection to the thalamus is more complex than the thalamic inputs in other sensory systems (Bartlett et al. 2000). Retinal inputs to the lateral geniculate and the spinal cord or dorsal column inputs to the ventrobasal complex are assumed to be purely excitatory. Only in the thalamic motor nuclei is there a mixture of inhibitory and excitatory inputs and an interplay between them that seems to underlie the temporal responses of the thalamic neurons (Peruzzi et al. 1997).

There are several questions regarding GABAergic neurons. As mentioned earlier, there are both disc-shaped and stellate GABA-containing IC neurons. However, it is unknown if both project to the same MGB targets. Further, the GABAergic IC neuron and its role as an inhibitory neuron has not been related to the auditory responses of IC neurons. For example, in the context of binaural response types (see Section 2.3.2), it is unknown whether GABAergic neurons favor MSO domains, LSO domains, or monaural domains.

4.3. NEURON TYPES DEFINED BY INTRINSIC MEMBRANE PROPERTIES

A third basis for defining IC neurons is their intrinsic membrane properties. ICC neurons have distinct discharge patterns to intracellular current injection (Peruzzi et al. 2000) and their responses are correlated with distinctive current/voltage relationships (Sivaramakrishnan and Oliver 2001). Six physiological classes of IC cell are revealed by intracellular recording with either sharp electrodes or whole-cell patch-clamp techniques in rat brain slices. Neurons formed two groups based on their responses to the offset of hyperpolarizing currents. One group exhibits a rebound calcium-dependent depolarization in addition to sodium action potentials (Sivaramakrishnan and Oliver 2001), while the other group lacks the rebound response (Fig. 2.18). The rebound neurons form three subtypes based on their responses to depolarizing currents—a transient response (few action potentials, rapidly adapting), a sustained slowly adapting response, and a regular nonadapting response (Fig. 2.18, rebound). Nonrebound neurons also have three subtypes—an onset response with one spike (Fig. 2.18, onset), a sustained-regular response, and a pause-buildup response (Fig. 2.18, pause-buildup). The latter appears only when the depolarization is preceded by a hyperpolarization (see Chapter 10).

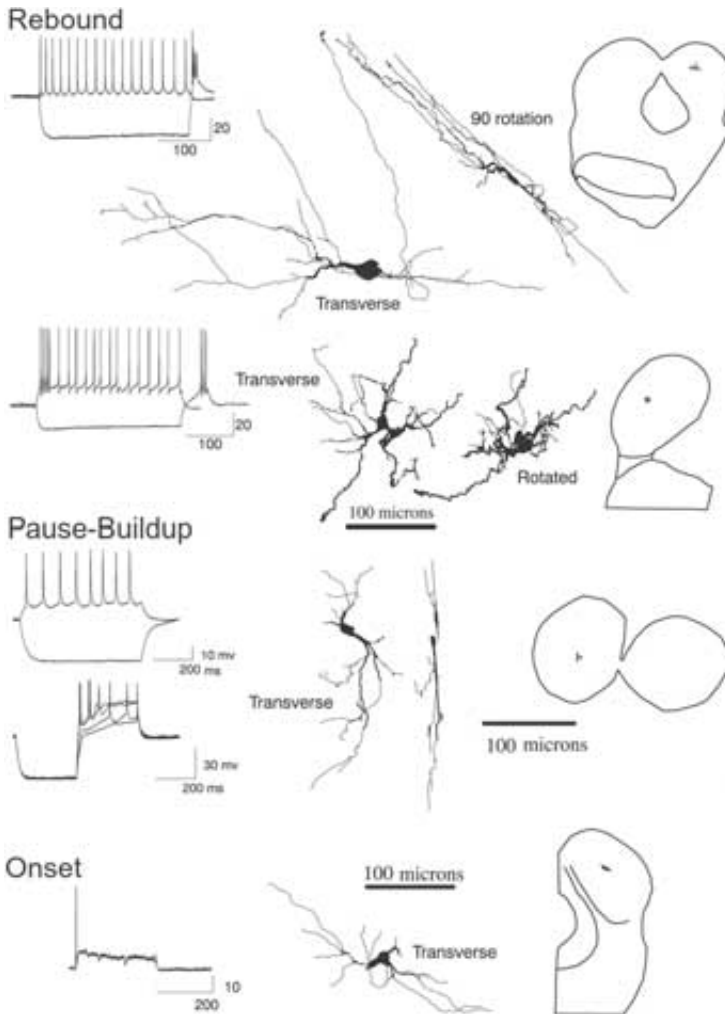


Figure 2.18. Firing patterns of neurons in the IC brain slice preparation. For each type the discharge pattern to depolarizing and hyperpolarizing intracellular current injections are shown (**left**). Neurons (**middle**) whose responses are shown were filled with neurobiotin (rebound onset) or Lucifer yellow (pause-buildup). IC location of the neuron appears on the inset (**right**). (From Peruzzi et al. 2000. Reprinted from Neuroscience with permission from Elsevier.)

The six IC firing patterns are generated by a unique K^+ current and set of cellular parameters (Sivaramakrishnan and Oliver 2001; cf. Chapter 10). For example, the IC rebound-adapting cell likely has an SK-type K^+ channel as it has a Ca^{2+} -activated K^+ current that is blocked by apamin. The rebound-transient cell also has a Ca^{2+} -activated K^+ current, but of the BK-type, as it is

blocked by charybdotoxin. Likewise, the pause-buildup cell has a response that can be directly related to an A-current K^+ current, while the onset response requires a high-threshold delayed rectifying K^+ current such as *Kv3.1* (Perney et al. 1992). The rebound-regular and the sustained-regular cells have primarily delayed rectifier currents and show no evidence for the additional currents mentioned earlier. However, the rebound-regular cell has a rebound response that may reflect a high density of a T-type Ca^{2+} channel that produces a Ca^{2+} influx after hyperpolarization offset.

The intrinsic properties of IC neurons entail several questions. There is little understanding of the molecular basis of these membrane properties and the distinct combinations of ionic currents are still poorly understood. Such currents likely depend on the precise subunit combinations that compose the channel and different subunit combinations may produce subtle differences in their current properties. Identification of expression patterns will have an enormous practical impact beyond the immediate issue of membrane properties, as they will identify intrinsic molecular markers for functional IC cell types.

The relationship of morphology to the firing patterns needs to be resolved. The cell types based on intrinsic properties do not correspond to the simple disc-shaped or stellate morphological classifications. Most neurons in the small sample were flat cells (Fig. 2.18) and the data suggests subtypes with different intrinsic properties (Peruzzi et al. 2000; Sivaramakrishnan and Oliver 2001). A small sample of less-flat rat stellate cells does not allow conclusions about the firing patterns. However, some morphological features besides dendritic orientation may be related to discharge pattern. Dendritic branching patterns, size, or the incidence of spines may be correlated with the intrinsic properties and the dendritic electrotonus of different cell types.

It is also not known how the firing patterns relate to the cell's projection. In some brain regions intrinsic properties are associated with cell types with different targets, as in the cochlear nucleus, where the spherical bushy cells project to the MSO while the stellate cells project to the IC, and octopus neurons project to the VNLL but not to the main targets of the other cells. In the midbrain the tectothalamic neurons may have a different firing pattern than cells projecting to the superior olive. One possible purpose of correlated firing properties and targeting is that each neuron type can convey different types of information to its target.

Finally, the relationship of the firing pattern to GABA needs to be clarified. Elsewhere in the nervous system GABAergic and glycinergic neurons often play a special role in the microcircuitry. If GABAergic neurons have firing properties that distinguish them from other cells, the temporal pattern of inhibition may differ from that of excitation. To resolve this issue the organization of the synapses of the types of IC cells must be determined.

5. SYNAPTIC ORGANIZATION OF CENTRAL NUCLEUS NEURONS

The previous section suggests that IC neurons are more complex physiologically than their early morphological designations indicated. If different types of neurons also receive different types of synaptic inputs it would further enhance the functional differences between them. Understanding synaptic inputs to the different IC neuron types and how the intrinsic membrane properties of these cells further modify the synaptic input to shape a neural response is vital.

5.1. DO INFERIOR COLLICULUS NEURON TYPES RECEIVE SIMILAR SYNAPTIC INPUTS?

Synaptic input is important for IC signal processing but little is known about the synaptic inputs to the different neuron types. Here synaptic input refers specifically to the excitatory or inhibitory postsynaptic current (EPSC or IPSC) elicited in the IC cell by stimulating the presynaptic ending and its interaction with ligand-gated receptors on the postsynaptic cell. IC neurons have various receptors for glutamate, glycine, and GABA (see Chapter 9) and the function of the synapses will depend on their subunit composition and their effect on the postsynaptic IC cell, as it does elsewhere in the brain (Barnes-Davies and Forsythe 1995; Wang et al. 1998; Gardner et al. 2001; Schmid et al. 2001). Thus, the GABA_A receptors are responsible for fast Cl⁻-mediated IPSCs at GABAergic IC synapses. The patterns of expression for GABA_A subunits provide the best evidence for neurons of different size having different combinations of GABA_A subunits (Shiraishi et al. 2001). Such differences suggest that there may be different types of GABA synapses in the IC just as in the neocortex (Gupta et al. 2000).

A related issue is activity-dependent changes in IC synapses that differ among the different IC cell types. Glutamate inputs to IC neurons can show long-term potentiation (LTP) (Zhang and Wu 2000; Wu et al. 2002) similar to *N*-methyl D-aspartate- (NMDA) dependent LTP elsewhere in the nervous system. It is important to resolve whether such changes are equally common to all cell types.

The important implication for IC neuronal organization is that synaptic properties are vital parameters for the function of neuron types. Each type of neuron must be defined by the interactions of multiple parameters—the location in a particular synaptic domain, the axonal target, the cell's morphology, the intrinsic membrane properties, and the types of synaptic input. Because of unique AMPA, NMDA, or GABA_A subunit compositions, activity could modify synaptic strength or the nature of the synaptic inputs, and consequently output could vary by the cell type. The relative number and location of glutamate, GABA, and glycine synapses also vary according to cell type. Each factor would contribute to the information processing carried out by the different IC neuron types.

5.2. CAN INTRINSIC AND SYNAPTIC PROPERTIES INTERACT TO CREATE THE RESPONSES OF INFERIOR COLLICULUS NEURON TYPES?

The cellular mechanisms that regulate synaptic integration are essential to understanding IC function in sound processing. Membrane properties can facilitate or degrade the temporal pattern of synaptic inputs evoked by sound and thus shape the synaptic inputs to which the cell ultimately responds. Neurons defined by different intrinsic properties may interact with the synaptic inputs in different ways that may especially influence the timing of responses.

The IC represents a transition stage for temporal coding in the auditory system. Timing here is better suited for coding the envelopes of complex signals (SAM tones; Batra et al. 1989), communication calls (Klug et al. 2002), and duration (Casseday et al. 2000) information than for coincidence detection (Fitzpatrick et al. 1997). Although the sources of input to IC neurons may phase lock and fire at high rates (Batra et al. 1997a,b; Spitzer 1998; Spitzer and Semple 1998), synaptic properties or intrinsic membrane properties of IC neurons could transform this information. Synaptic inputs may alter time codes because facilitation or depression occurs in some cell types, related perhaps to the relative contributions and kinetics of NMDA and AMPA components (see Chapter 10). Membrane properties are also important, as some IC cells follow stimuli at higher rates (Peruzzi et al. 2000).

We do not yet know the relative contributions of synaptic inputs and membrane properties to temporal processing in the different IC cells. Ultimately, the IC cell's response may reflect both the intrinsic membrane properties (voltage-gated and Ca^{2+} -activated ion channels) and synaptic inputs (presynaptic mechanisms and postsynaptic ligand-gated receptors). Ca^{2+} -activated conductances in particular can disrupt the normal cadence of neuronal firing in response to synaptic input, as they often enhance adaptation related to increased Ca^{2+} influx. The presence of Ca^{2+} -activated K^+ currents in some cell types suggests that their membrane properties may alter the response to synaptic input, transforming afferent input and shaping the temporal aspects of the response.

A final question relates to both synaptic inputs and intrinsic membrane properties and it is whether the neural responses to sound in vivo reflect different synaptic inputs or different membrane properties. The link between brain slice data, usually obtained from young animals, and sound processing in the adult is tenuous. Experiments are necessary in which IC cell types are identified in adult animals with the same criteria used in the brain slice experiments. Such an experiment may explain how the IC neuronal response is related to the cell-specific synaptic input and its sources.

6. SUMMARY

How are the types of IC neurons related to the synaptic domains? The synaptic domain hypothesis defines functional IC modules and seeks to establish a relationship between the auditory response properties of a neuron and the sources of its brain stem inputs. Within these domains the cell types are defined by their membrane properties, dendritic morphology, K^+ channel subunits, and transmitter content. Whether particular IC cell types are associated with specific synaptic inputs remains to be resolved in future experiments. If so, it suggests a special relationship between the sources of the brain stem projections, the synaptic inputs, and the postsynaptic IC cells that coexist within a synaptic domain.

Acknowledgments

The work in our laboratory has been supported by NIH grant DC00189. It could not have been accomplished without the outstanding contributions of Ms. Debbie Bishop, Ms. Gretchen Beckius, Drs. Shobhana Sivaramakrishnan, Ami Shneiderman, Dan Peruzzi, and William Loftus.

Abbreviations

a	axon
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazole propionate
AVCN	anteroventral cochlear nucleus
BI	brachium of the inferior colliculus
CG	central gray
DC	dorsal cortex
DCN	dorsal cochlear nucleus
2DG	2-deoxyglucose
DI	dorsal intercollicular tegmentum
DLL, DNLL	dorsal nucleus of the lateral lemniscus
EPSP	excitatory postsynaptic potential
GABA	γ -aminobutyric acid
IC	inferior colliculus
ICC	central nucleus of the inferior colliculus
ILD	interaural level differences
IPSP	inhibitory postsynaptic potential
LC	lateral cortex
LI	lateral intercollicular tegmentum
LL	lateral lemniscus
LSO	lateral superior olive
LTB	lateral nucleus of the trapezoid body

MGB	medial geniculate body
MI	medial intercollicular tegmentum
MSO	medial superior olive
NMDA	<i>N</i> -methyl-D-aspartate
PVCN	posteroventral cochlear nucleus
RP	rostral pole
SAM	sinusoidally amplitude modulated
VL	ventrolateral nucleus
VNLL	ventral nucleus of the lateral lemniscus

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The Inferior Colliculus

Winer, J.A.; Schreiner, C.E. (Eds.)

2005, XX, 705 p., Hardcover

ISBN: 978-0-387-22038-3