Chapter 3
Projections from the Cochlear Nuclear Complex to the Inferior Colliculus

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1. Introduction

The substantial projections from the cochlear nuclei to the inferior colliculus (IC) do not seem to have been generally recognized as a common mammalian characteristic until about the late 1960s. Although they were described in some of the earliest experimental studies of the auditory pathways (Woollard and Harpman 1940, q.v., for a discussion of the earlier literature on the subject; Barnes et al. 1943), the prevailing view appeared to be that most of the axons leaving the cochlear nucleus terminated in the superior olivary complex or nuclei of the lateral lemniscus and that the projections to the IC were sparse. Certainly, the matter appeared to be unresolved in 1953, as Stotler stated flatly in his influential article on brain stem auditory pathways in the cat that "all neurons reaching the level of the inferior colliculus are of the third order." It was not until the late 1960s and early 1970s that studies with sensitive degeneration techniques (cf. Nauta 1993) demonstrated conclusively that both the dorsal and ventral cochlear nuclei project directly to the contralateral inferior colliculus (cat: Warr 1966, 1969, 1972; Fernandez and Karapas 1967; van Noort 1969; Osen 1972; Rhesus monkey: Strominger and Strominger 1971; Strominger 1973; chimpanzee: Strominger et al. 1977; kangaroo rat: Browner and Webster 1975). In some cases, sparse ipsilateral projections were also reported.

Degeneration studies established that the main target of both the dorsal and ventral cochlear nuclei in the IC is the central nucleus, that the projections from these two sources overlap, and that they are topographically organized, with the cochlea systematically represented from apex to base. Since the late 1970s, neuroanatomical methods based on retrograde and anterograde axonal transport of various tracers have allowed detailed studies of the projections from the cochlear nuclei to the IC in a wide variety of species (Table 3.1). These tracing studies, supplemented by electron microscopy, have provided descriptions of both the cell types contributing to the projections and also the distribution and arborization patterns of their axons within the IC. An overview of the projections from the cochlear nuclei to the IC is presented in Section 2. The discussion is based mainly on the results of large injections of retrograde or anterograde tracers in

Table 3.1. Neuroanatomical studies of projections from the cochlear nucleus to the inferior colliculus by species, 1978–2003.

Species	Authors and year of study
CAT	Roth, Aitkin, Andersen, and Merzenich 1978 Adams 1979, 1983 Aitkin, Kenyon, and Philpott 1981 Brunso-Bechtold, Thompson, and Masterton 1981 Oliver 1984, 1985, 1987 Aitkin and Schuck 1985 Maffi and Aitkin 1987 Oliver and Beckius 1993 Oliver, Beckius, Bishop, and Kuwada 1997
RAT	Beyerl 1978 Druga and Syka 1984 Tokunaga, Sugita, and Otani 1984 Coleman and Clerici 1987 Alibardi 1998, 1999 Oliver, Ostapoff, and Beckius 1999
MOUSE	Ryugo, Willard, and Fekete 1981 Ryugo and Willard 1985 Frisina, Walton, Lynch-Armour, and Byrd 1998
MARSUPIAL	Aitkin and Kenyon 1981 Willard and Martin 1983 Aitkin, Byers, and Nelson 1986
GERBIL	Nordeen, Killackey, and Kitzes 1983a,b Moore and Kitzes 1985
FERRET	Moore 1988
MOLE	Kudo, Nakamura, Tokuno, and Kitao 1990
GUINEA PIG	Schofield and Cant 1996 Alibardi 2000
CHINCHILLA	Josephson and Morest 1998
BAT: Mustache bat	Zook and Casseday 1982, 1985, 1987 Ross, Pollak, and Zook 1988 Frisina, O'Neill, and Zettel 1989 Ross and Pollak 1989 Wenstrup, Mittmann, and Grose 1999
Horseshoe bat	Schweizer 1981 Vater and Feng 1990

the IC or cochlear nuclei, respectively. In Section 3, the laminar organization of inputs to the IC as revealed by small tracer injections is discussed.

2. Projections from the Cochlear Nucleus to the IC

2.1. Comparison with Other Sources of Ascending Input

The major sources of ascending auditory inputs to the IC are the cochlear nuclei, the nuclei of the superior olivary complex, and the nuclei of the lateral lemniscus (see Chapter 1). Some of the relevant neuroanatomical studies (those that contain information about the projections from the cochlear nuclei) are listed in Table 3.1. In some of these studies, counts were made of the numbers of neurons labeled in brain stem nuclei after large injections in the IC of retrograde tracers (substances that are taken up by axon terminals and transported through the parent axons back to the cell body of origin). Results from these studies have been replotted on common axes in Fig. 3.1 so that they can be compared directly. The figure shows that the pattern of labeling in the brain stem after large tracer injections is quite consistent across studies and species. (The results of small tracer injections are considerably more variable [see Section 3.3]). In terms of the numbers of neurons that are labeled, the projections from the contralateral cochlear nuclei are matched only by the projections from the ipsilateral ventral nucleus of the lateral lemniscus in most species. In the Japanese mole and the mustache bat (Fig. 3.1F, G), the number of labeled cells in the cochlear nuclei and superior olivary complex may be more nearly equal than in the other species, but the apparent differences among species could also be a function of differences in the sizes of the injection sites (see Section 4.3). The number of cells in the contralateral ventral cochlear nucleus that project to the IC is consistently larger than the number in the contralateral dorsal cochlear nucleus.

The contralateral projections are topographically organized. Cells in the ventral (low-frequency) parts of the cochlear nuclei project to the dorsolateral IC, and cells in the more dorsal (high-frequency) parts of the cochlear nuclei project to the ventromedial IC. Osen (1972) noted that the parts of the cochlear nucleus that represent middle frequencies project more caudally in the IC than do the parts with the lowest and highest frequency representations. In most species, a few cells in both the dorsal and ventral cochlear nuclei project to the ipsilateral IC. The ipsilateral projections appear to be mainly to the dorsolateral (or low-frequency) part (Nordeen et al. 1983a; Oliver 1984, 1987). In the chimpanzee, the ipsilateral projections were described as "substantial" (Strominger et al. 1977).

2.2. Cell Types that Project to the Inferior Colliculus

The cochlear nuclear complex contains a number of well-characterized cell types that can be distinguished based on a wide variety of criteria (reviewed by Cant

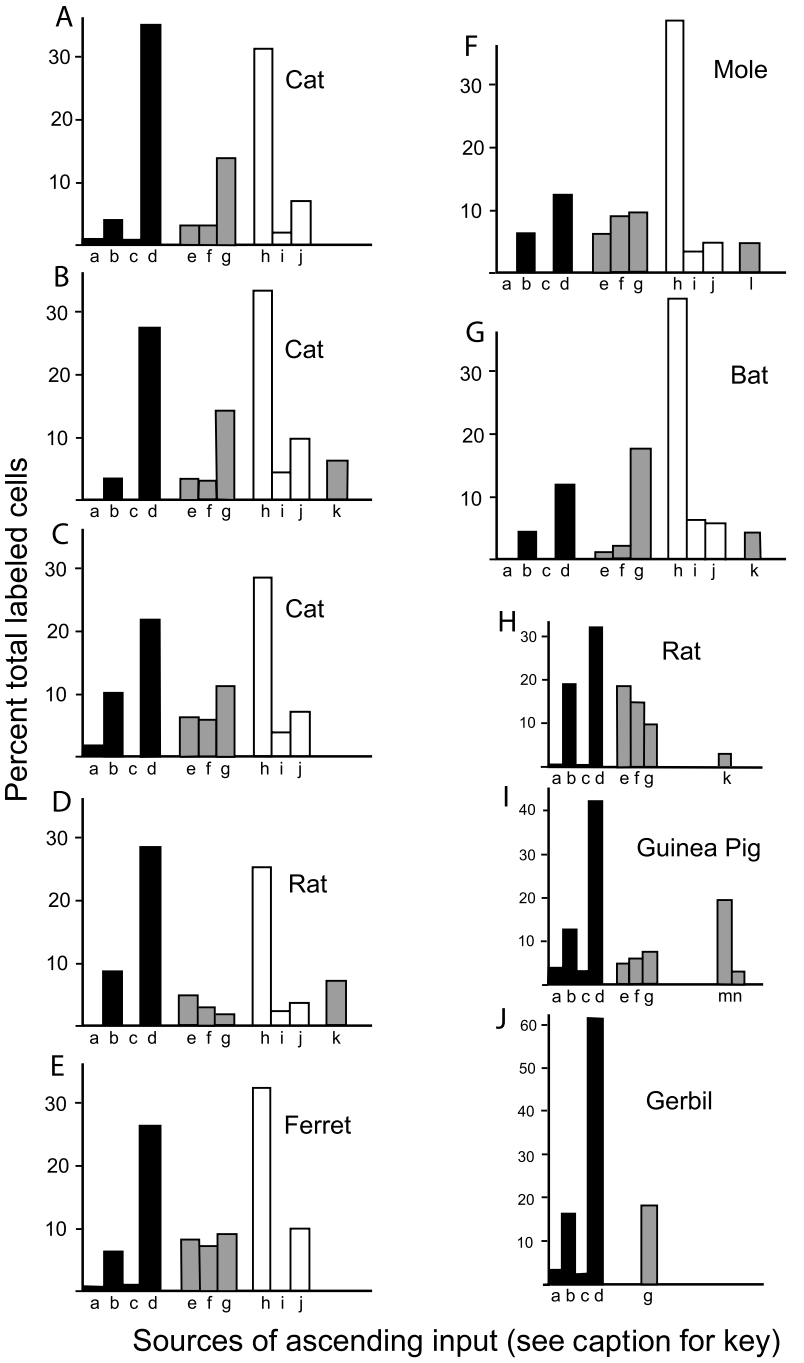
A
Cat
B
Cat
C
Cat
D
Rat
E
Ferret
F
Mole
G
Bat
H
Rat
I
Guinea Pig
J
Gerbil
Percent total labeled cells
Sources of ascending input (see caption for key)

Figure 3.1. Summary of results of 10 studies in seven species in which large injections of retrograde axonal tracers were placed in the IC. In each study, counts were made of the number of labeled cells in some or all of the sources of ascending inputs to the IC. For those studies in which the counts were reported as the numbers of labeled cells in each structure, the data have been converted to percent of total labeled cells counted in the structures shown. In some cases, counts were also made in other sources of input, such as the contralateral IC. If possible, these were not included in the calculation of the percent of labeled cells. **(A)** Cat (Adams 1979). The result from pressure injection of horseradish peroxidase (HRP) in ventral IC. Counts made in a sample of one twelfth of the total tissue; $N = 3799$. **(B)** Cat (Roth et al. 1978). The result from pressure injection of HRP in dorsal IC. The largest injection (in terms of numbers of labeled cells) in a series of six; 2-kHz region; counts made in 60% of the tissue; $N = 6305$. **(C)** Cat (Kudo and Nakamura 1988, quoted in Kudo et al. 1990). The result from a pressure injection of HRP conjugated to wheat germ agglutinin (HRP-WGA). Information about the counts not available. **(D)** Rat (Tokunaga et al. 1984). The result from pressure injection of HRP in the IC. The largest injection (in terms of numbers of labeled cells) in a series of four; counts made in every other section; $N = 4754$. **(E)** Ferret (Moore 1988). The result from multiple pressure injections of HRP-WGA in the IC. Counts made in every other section; numbers corrected for uncounted sections; $N = 41{,}605$. This does not include 15,435 neurons labeled in the contralateral IC; those cells were not included in the calculation of the percent labeled cells shown here. **(F)** Japanese mole (Kudo et al. 1990). The result from a pressure injection of HRP-WGA in IC. Counts made in every other section; average of counts from four different animals; total $N = 12{,}291$. **(G)** Mustache bat (Ross et al. 1988). The result from an iontophoretic injection filling most of the 60-kHz region of the IC. Counts made in every other section; estimated $N = 2000$–2300. A small percentage of the counted labeled cells were in the contralateral IC; data not included here. **(H)** Rat (Druga and Syka 1984). Pressure injection of HRP in the IC. Counts made in three animals and summed; sampling rate not given; total $N = 3608$. **(I)** Guinea pig (Schofield and Cant 1992). The result from a pressure injection of fluorescent tracers. Counts made in every sixth section; $N = 4122$. **(J)** Gerbil (Nordeen et al. 1983a). The result from a pressure injection of HRP in the IC. Counts in every other section; estimated $N = 4300$. For all panels, the *black bars* show the cell counts for the cochlear nucleus: *a,* ipsilateral dorsal cochlear nucleus (DCN); *b,* contralateral DCN; *c,* ipsilateral ventral cochlear nucleus (VCN); *d,* contralateral VCN. Gray bars *(middle)* show the cell counts for nuclei in the superior olivary complex: *e,* ipsilateral lateral superior olivary nucleus (LSO); *f,* contralateral LSO; *g,* ipsilateral medial superior olivary nucleus (MSO). *White bars* show the cell counts for nuclei of the lateral lemniscus: *h,* ipsilateral ventral nucleus of the lateral lemniscus; *i,* ipsilateral dorsal nucleus of the lateral lemniscus (DNLL); *j,* contralateral DNLL. *Gray bars* (end) show cell counts in other nuclei counted in specific studies: *k,* periolivary nuclei (PO); *l,* contralateral MSO (a substantial projection in the mole); *m,* ipsilateral PO; *n,* contralateral PO. Note the change in scale for panels **(H–J)**. Labeled cells in the nuclei of the lateral lemniscus were not counted in these studies, resulting in larger percentages in the other nuclei.

and Benson 2003). Even in studies based on degeneration techniques, it was recognized that only some of these cell types project to the inferior colliculus (Warr 1966, 1969, 1972; van Noort 1969). In all species studied (Table 3.1), it has been demonstrated that both fusiform and giant cells of the dorsal cochlear nucleus send axons to the IC. In fact, it appears that all of the large cells in the dorsal cochlear nucleus participate in the projection (Ryugo et al. 1981; Moore 1988). The projection from the ventral cochlear nucleus arises from neurons throughout its extent, including all but the most anterior part of the anteroventral cochlear nucleus and the octopus cell area in the posteroventral cochlear nucleus. It is generally agreed that multipolar (or stellate) cells are the major source of projections from the ventral cochlear nucleus, that octopus cells do not terminate in the IC, and that few if any globular cells or large spherical cells project that far. The case is less clear for small spherical cells in the anteroventral cochlear nucleus. A number of authors report that small, round cells in this part of the complex project to the IC, and some refer to these as small spherical cells, implying that they have a bushy cell morphology (cf. Cant and Benson 2003). Because the dendrites of the cells usually are not filled with the tracer, it is generally not possible to be sure that these really are spherical bushy cells, although Adams (1979) did illustrate one well-filled spherical bushy cell labeled after a large injection of horseradish peroxidase in the IC of the cat. Electron microscopic studies have provided no evidence for such a projection, however. In three species, all cells labeled retrogradely from the IC were identified in the electron microscope as type I stellate (or multipolar) cells (cat: Cant 1982; chinchilla: Josephson and Morest 1998; rat: Alibardi 1998). The cells that project from the ipsilateral cochlear nucleus have been identified as fusiform, giant, and multipolar cells (Adams 1979; Oliver 1984, 1987).

The ventral cochlear nucleus contains several types of multipolar cells. Those that project to the contralateral IC appear to be the type I multipolar cells (or type I stellate cells; cf. Cant and Benson 2003). It seems likely that most, if not all, of the type I cells participate in this projection (Josephson and Morest 1998). The same neurons in the ventral cochlear nucleus that project to the IC send collateral branches to the dorsal cochlear nucleus (Adams 1983). Multipolar cells in the ventral cochlear nucleus also give rise to projections to the superior olivary complex and the ventral nucleus of the lateral lemniscus (see Chapter 4). Although they have not been identified with certainty, the cells that give rise to these projections are probably also type I multipolar cells (Smith et al. 1993), but it is not known whether individual cells project to all of the targets. Some fusiform or giant cells in the dorsal cochlear nucleus may send axonal branches to both the ipsilateral and contralateral IC, but bilateral projections from cells in the ventral cochlear nucleus have not been described (Schofield and Cant 1996).

Axons arising from the fusiform and giant cells leave the cochlear nucleus in the dorsal acoustic stria. After crossing the midline, they enter the lateral lemniscus and travel in its medial part or in the adjacent tegmentum (Osen 1972; Willard and Martin 1983; Oliver 1984). The projections from the contralateral

ventral cochlear nucleus travel mainly in the trapezoid body, where they make up part of the thin fiber component, cross the midline, and enter the lateral part of the lateral lemniscus (Warr 1966; Osen 1972; Willard and Martin 1983). Ipsilateral projections from the cochlear nucleus travel in a small fiber bundle known as the lateral trapezoid body tract (Warr 1972).

2.3. Synaptic Terminals in the Inferior Colliculus

Electron microscopic studies of the terminals from both the anteroventral and dorsal cochlear nuclei in the IC demonstrate that they contain round synaptic vesicles and make asymmetrical contacts with their targets, the morphology associated with excitatory synapses (Oliver 1984, 1985, 1987). The fine structure of the inputs from the posteroventral cochlear nucleus to the IC has not been reported, but presumably they are also excitatory, as the collaterals of their axons that project into the dorsal cochlear nucleus (Adams 1983) give rise to terminals with round synaptic vesicles (Smith and Rhode 1989). Alibardi (1998) also concluded that the neurons in the posteroventral cochlear nucleus that project to the IC are excitatory, based on the variable presence of immunoreactivity for glutamate and the absence of immunoreactivity for the inhibitory neurotransmitters glycine and γ-aminobutyric acid (GABA). The ventral nucleus of the lateral lemniscus contains almost as many neurons that project to the IC as the cochlear nuclei (Fig. 3.1), but because a large proportion of the cells in the ventral nucleus of the lateral lemniscus are inhibitory (Riquelme et al. 2001), it is apparent that, in terms of numbers of neurons, the contralateral cochlear nucleus represents the major brain stem source of excitatory inputs to the IC.

Although the number of cells projecting to the IC from the cochlear nuclei may be much greater than the number of cells projecting from the main superior olivary nuclei, many of which are also excitatory (e.g., Oliver et al. 1995), the number of terminals that is made by axons from the different sources may be more comparable. For example, in areas where the terminals from the ipsilateral medial superior olivary nucleus terminate most densely, they may account for up to 36% of the terminals with round synaptic vesicles in that area. Terminals with round vesicles from the ipsilateral and contralateral lateral superior olivary nucleus can reach 26% and 18%, respectively. These values can be compared to the maximum density of terminals from the contralateral anteroventral cochlear nucleus (13%) and the contralateral dorsal cochlear nucleus (11%). Interestingly, in the lateral part of the central nucleus, the synapses formed by the ipsilateral anteroventral cochlear nucleus can contribute up to 18% of the terminals with round vesicles, although the number of neurons projecting from the ipsilateral cochlear nucleus is always very small (Fig. 3.1). It is not yet known how the regions with the maximum density of inputs from any one source overlap with those from other sources (see Section 3).

The inputs from the cochlear nuclei form synapses on the dendrites of both disc-shaped cells and stellate cells, the main types in the central nucleus (see Chapter 2). Occasionally, terminals are also found on the cell bodies of the

stellate cells. Little is known about differential innervation of different types of IC neurons (defined in terms of morphology, physiological response properties, neurotransmitter chemistry, connections, other sources of input, or any other criteria). Oliver et al. (1999) showed that at least some of the inputs from the contralateral cochlear nucleus terminate directly on neurons that project to the medial geniculate nucleus.

3. Distribution of Cochlear Nuclear Inputs within the Inferior Colliculus

The topography related to frequency is the most obvious organizational principle in the IC, and most, if not all, inputs to the IC are organized with respect to frequency. The part of each brain stem nucleus that represents the apex of the cochlea (low frequencies) projects to the dorsolateral IC and the part that represents the base of the cochlea (high frequencies) projects to the ventromedial IC, with a systematic progression of the intermediate regions (e.g., Osen 1972; Adams 1979). This topography has given rise to the concept that the IC is organized into a series of laminae, each of which receives inputs from a limited frequency range and is continuous across the major subdivisions of the IC (cf. Oliver and Morest 1984; Saldaña and Merchán 1992; Brown et al. 1997). Within this framework of tonotopic organization, however, there is evidence for other levels of organization. Some studies have focused on differences in the organization of inputs from one subdivision to the next, while others have provided evidence for partial segregation of inputs within the central nucleus of the IC.

3.1. Projections to the Major Subdivisions of the Inferior Colliculus

The main target of both the ventral and dorsal cochlear nuclei in the IC is the central nucleus, where the projections from these two parts of the cochlear nuclear complex appear to overlap almost completely (Osen 1972; Oliver 1984). In addition, both the dorsal and ventral cochlear nuclei send projections into the deep layers of the dorsal cortex, although the terminations appear to be more sparse than those to the central nucleus (Oliver 1984; Coleman and Clerici 1987; Zook and Casseday 1987). In the dorsal cortex, the projections from the ventral cochlear nucleus may arborize more widely than those from the dorsal cochlear nucleus (Oliver 1987). The dorsal cochlear nucleus also projects to the external cortex of the IC in rats (Coleman and Clerici 1987; Oliver et al. 1999), mice (Ryugo et al. 1981), and opossums (Willard and Martin 1983) but not in the cat (Aitkin et al. 1981). Like those to the central nucleus, the projections to both the dorsal and external cortices appear to be topographically organized (Ryugo et al. 1981; Oliver 1984, 1987).

Because the main sources of inputs to each subdivision of the IC are different (cf. Chapter 1), the inputs from the cochlear nuclei must converge with those from different sources in the various parts of the IC. For example, in the central nucleus, the projections from the cochlear nuclei overlap to a large extent with the projections from the superior olivary complex, the other major source of ascending excitatory inputs to the IC (Oliver et al. 1995; Oliver 2000; see Chapter 4). However, the superior olivary complex does not project into the dorsal or external cortices of the IC (Henkel and Spangler 1983; Shneiderman and Henkel 1987; Oliver et al. 1997) so that in some parts of the IC, inputs from the olivary nuclei and the cochlear nuclei may be convergent and in other parts, cells could be influenced by the cochlear nuclei but not by the olivary nuclei. Likewise, the main targets in the IC of the auditory cortex are the dorsal and external cortices (Chapter 8). Here, the neurons that receive inputs from the cochlear nuclei might be more subject to descending control than those in the central nucleus, which receives relatively little cortical input.

3.2. Organization Within the Central Nucleus

The proportion of labeled cells located in each source of ascending input to the IC is quite consistent both across studies and also across species after large injections of tracers (Fig. 3.1). However, when small (usually iontophoretic) injections of retrograde tracers are made into the central nucleus of the IC, the results are considerably more variable in terms of the proportions or even the presence of labeled cells in the different sources (Roth et al. 1978; Brunso-Bechtold et al. 1981; Aitkin and Schuck 1985; Maffi and Aitkin 1987; Ross and Pollak 1989; Wenstrup et al. 1999; cf. Oliver et al. 1995). For example, in some small regions, projections from the superior olivary nuclei may dominate. In the most extreme example reported, after an injection of a tracer in the lateral IC, 98% of the labeled cells were located in the ipsilateral medial superior olivary nucleus (Aitkin and Shuck 1985). In general, however, it is rare that so many labeled cells are located in only one source of input. In other cases, cells in the cochlear nuclei and nuclei of the lateral lemniscus might be labeled with little or no labeling in the superior olive. Across species and studies, almost every possible combination of inputs has been seen, although some are more common than others.

Studies with anterograde tracers also provide evidence for segregation of inputs within the central nucleus. Many inputs to the IC from the cochlear nucleus form bands that are parallel to the isofrequency laminae (Oliver 1984, 1987). In some cases, the bands from two sources overlap, as is the case for inputs from the contralateral dorsal cochlear nucleus and the contralateral lateral superior olivary nucleus (Oliver et al. 1997). Other inputs appear to lie in adjacent and possibly nonoverlapping bands, as is the case for the inputs from the ipsilateral and contralateral lateral superior olivary nuclei (Shneiderman and Henkel 1987). The inputs from the ipsilateral medial superior olivary nucleus and the ipsilateral cochlear nucleus may remain partially separate in the dorsolateral part of the IC

(Oliver and Beckius 1993). In that same part of the IC, some of the inputs from the contralateral and ipsilateral cochlear nuclei also appear to remain separate (C.G. Benson and N.B. Cant, unpublished results in the gerbil).

A dramatic example of segregation of inputs within a frequency lamina is provided by studies of the mustache bat, which exploited the fact that the 60-kHz "layer" is greatly expanded in this species (Wenstrup et al. 1986; Ross et al. 1988; Ross and Pollak 1989). When tracer injections filled most of the 60-kHz region, the pattern of labeling was very similar to that seen in other species (Fig. 3.1G), although more labeled cells were located in the nuclei of the lateral lemniscus than in the cochlear nuclei and the numbers of cells in the cochlear nucleus and the superior olivary complex were approximately equal (Ross et al. 1988). (Whether these differences from the common mammalian pattern are a result of specializations in the bat or occur because the injections are still relatively small is not clear.) However, when small, discrete injections were made systematically throughout the 60-kHz lamina, Ross and Pollak (1989) found different patterns of projections in four different regions that could be related to differences in the physiological response properties of the neurons in each region. Their results show that both connectivity and physiological response properties change systematically across this isofrequency representation.

In one of the first studies of projections to the IC employing tracer injections (and physiological recording), Roth and colleagues (1978) suggested that, "Within the cochleotopic and laminar framework of the central nucleus, it would seem that other rules of order must exist." Other investigators have reached the same conclusion. Maffi and Aitkin (1987) proposed that the central nucleus is made up of "core zones" in which inputs from specific brain stem nuclei are dominant. Based on their demonstration of a systematic difference in the proportions of labeled cells in the cochlear nuclei vs. the superior olivary complex when horseradish peroxidase injections were made in the caudal vs. rostral IC, Brunso-Bechtold and colleagues (1981) concluded that an organization based on "nucleotopy" was superimposed on the cochleotopic organization of the IC. The apparent differential organization of inputs forms the basis for the hypothesis that the central nucleus is organized into "synaptic domains" as put forth by Oliver and Huerta (1992; Oliver 2000). In this conception, the synaptic domains are defined as small groups of neurons that share the same populations of synaptic inputs. A given synaptic domain may lie next to another synaptic domain with the same frequency characteristics but with different sets of inputs and, presumably, different physiological properties (see Chapter 2).

Consistent with the conclusions based on neuroanatomical studies, the physiological response properties of IC neurons have been shown to vary with location, and neurons with similar properties tend to cluster together (Roth et al. 1978; Semple and Aitkin 1979; Wenstrup et al. 1986; Brückner and Rübsamen 1995). As noted earlier for the mustache bat, differences in the sources of inputs covary with differences in the physiological types found in various parts of the central nucleus. A similar progression of response types across isofrequency laminae was demonstrated in the gerbil (Brückner and Rübsamen 1995). The

properties of some unit types in the IC of the cat appear to reflect a dominant input from only one of the many brain stem sources of inputs (Davis et al. 1999; Ramachandran et al. 1999; Davis 2002).

4. Conclusions

Neurons in the IC receive inputs from a wide variety of brain stem, forebrain, commissural, and intrinsic sources. Learning exactly how these inputs are organized at the level of the individual neurons that make up the IC represents a major challenge for future studies. Although at the light microscopic level, many of the inputs overlap to a greater or lesser extent, it is not known whether individual cells receive synapses from all of the axons in their vicinity or only from some of them. Although the potential for convergence of multiple inputs at the level of the IC is generally emphasized, there is ample potential for divergence and segregation of inputs from different sources at the level of the individual cells, especially because the IC may contain over five times as many neurons as the cochlear nuclei, superior olivary complex, and nuclei of the lateral lemniscus combined (Kulesza et al. 2002).

Given the many sources of inputs to the IC, the possibilities for combinations of inputs to any particular neuron are staggering. Even if the inputs from the cochlear nuclei alone are considered, there are a number of possible combinations. The cell types in the cochlear nuclei that project to the IC—the fusiform and giant cells in the dorsal cochlear nucleus and multipolar cells in the ventral cochlear nucleus—each have different physiological response properties and appear to encode different types of information (Rhode and Greenberg 1992). It is curious that no major differences in the organization of the terminal fields of these three cell types have been described, but it is certainly possible that there are important differences at the level of the synaptic organization of the cells in the IC. Potential interactions between ipsilateral and contralateral inputs from the cochlear nuclei add to the number of possibilities, as all three major cell types that project contralaterally also project ipsilaterally. Although the number of cells projecting to the IC from the ipsilateral cochlear nucleus is small, they may provide a substantial proportion of the inputs in the dorsolateral region. The inputs from the cochlear nuclei to the IC could also be combined in many different ways with the ascending inputs from the superior olivary complex and nuclei of the lateral lemniscus (see Chapter 4), commissural connections (see Chapter 5), and descending projections from the forebrain (see Chapter 8).

Adding to the complexity of organization made possible by the multitude of inputs is the intrinsic complexity afforded by the many different cell types that make up the IC. As discussed elsewhere, neurons in the IC may differ in their morphology (see Chapter 2), projection targets (see Chapters 5 and 6), transmitter expression (see Chapter 9), biophysical properties (see Chapter 10), and physiological response properties (see Chapters 11 to 13). It is reasonable to expect that cell types defined based on these differences will also differ in their

sources of input and synaptic organization, but at present very little is known about the synaptic organization of any particular cell class.

Neuroanatomical methods based on axonal transport of tracers have constantly improved since their introduction in the 1970s, and can still be used profitably to address many of the outstanding questions about the auditory pathways. Double and triple labeling experiments, combined with electron microscopy or physiological recording and marking techniques, can answer many important questions about the specific sources of inputs to specific cell types and provide substantive hypotheses for further work. These are tried and true methods, but they are technically difficult and progress is slow. It is exciting, therefore, that in the near future, new methods based on work in genetics and molecular biology can be expected to have a major impact on our ability to examine neural circuitry. For example, transgenic mice have been produced that express axonally transported tracers under the control of cell-type specific promoters (Yoshihara et al. 1999). In these animals, the projections of one specific cell type may be studied in isolation from those of other cell types. Similar methods are already being applied to some sensory systems (Braz et al. 2002; Kinoshita et al. 2002), and there is every reason to expect that such technology will vastly improve our ability to trace specific circuits in the complex pathways of the auditory system.

Knowledge of the connectivity and synaptic organization of specific cell types is essential for advancing our understanding of how physiological response properties emerge and, ultimately, of how each pathway contributes to overall auditory function. Although questions remain that can be addressed with currently available neuroanatomical techniques, we can look forward to an exciting new era of investigations of brain stem auditory circuitry as new techniques of molecular biology are used to address these questions.

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