Chapter 19
Inferior Colliculus: Aging and Plasticity

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1. Introduction

Classic views and theories of the central nervous system (CNS) emphasized that mammalian neural circuitry formed during development remained essentially invariant in adulthood. No new neurons are added, and CNS damage entails neuron loss, resulting in permanent anatomical damage and enduring functional impairments. However, advances in the study of plasticity and aging in the CNS, including the central auditory system, reveal that neural systems can reconfigure themselves with age and in response to the loss of peripheral inputs from sensory end-organs. For instance, peripheral abnormalities induce unmasking, rewiring, or changes in functional responses in the central auditory system, sometimes termed "peripherally induced central changes" (Frisina et al. 2001). Alternatively, in the case of age-related changes in the central auditory system, deficits can occur independently of age-dependent alterations of the inner ear. Instances of these plastic and aging phenomena are presented in this chapter, focusing on those manifested in the inferior colliculus (IC).

2. Age-Related Functional Changes

2.1. Tonotopic Organization

Neuroanatomical and neurophysiological investigations revealed age-related tonotopic plasticity in the auditory midbrain in response to the loss of high-frequency input of cochlear origin (Willott 1984, 1986). The C57Bl/6 mouse strain suffers from accelerated peripheral age-related hearing loss, starting in the base of the cochlea. Like human age-related hearing loss (presbycusis), the C57 syndrome begins with an impairment of the high frequencies, which then spreads to the lower frequencies with age. The C57 high-frequency hearing loss is much more rapid than that of human presbycusis, even when correcting for the different absolute lifespans of mice and men. Specifically, young adult C57s about 6 months old have severe-to-profound high-frequency hearing losses and de-

velop profound deficits at all frequencies in their second year. Because a 6-month-old C57 mouse has an "old" ear but a young brain, it permits the dissection of aspects of presbycusis inherent in the inner ear and largely independent of the aging brain.

The IC tonotopic reorganization was documented by neurophysiological mapping in the central nucleus (ICC) across time in C57 mice (Willott 1984, 1986). In young adults, as in most mammals, there is a dorsoventral gradient of single-unit characteristic frequencies (CFs) orthogonal to the well defined neuroanatomical ICC laminae, with lower CFs dorsally and higher CFs ventrally. With age, high-CF units shift to lower frequencies, although the tuning curve tip sensitivity remains surprisingly good, indicative of a true CF shift and not merely a loss of the sensitive tips of high CF units (Fig. 19.1). Apparently, a development, strengthening, or enhancement process involving new synaptic connections occurs in the formerly high-frequency IC regions and/or its brain stem input nuclei, such that the low CFs become overrepresented in the tonotopic map.

In contrast to the C57, the CBA mouse strain has a slow, progressive age-related hearing loss that is similar (flat) across the auditory frequency range. This strain has been useful for studying age-related changes in the central auditory system when only moderate changes take place in the auditory periphery. Not surprisingly, in contrast to the C57 ICC reorganization, a tonotopic reorganization of the IC in aged CBA mice does not occur (Willott 1991a; Walton et al. 1998).

2.2. *Temporal Processing*

Sound temporal features are essential for effective processing and perception of biologically relevant acoustic stimuli such as speech, animal vocalizations, and music (see Chapters 12 and 14). In presbycusis, aged listeners often have auditory temporal processing deficits that contribute to their impairment in speech comprehension in the presence of background noise (Snell and Frisina 2000; Frisina et al. 2001). Temporal processing deficits may be due to a sloping hearing loss of peripheral origin. When aged persons have good peripheral sensitivity, speech perception problems may involve temporal processing deficits caused by brain stem auditory pathology, including the IC (Frisina and Frisina 1997; Frisina et al. 2001).

Gap stimuli and amplitude-modulated stimuli are two of the most commonly utilized sounds for investigating auditory temporal processing deficits in cases of hearing loss, including presbycusis (Frisina 2001a). Gap detection paradigms involve measuring the minimum detectable silent interval between two sounds. These sounds are sometimes referred to as "markers," or the "masker" and the "target," and may be pure tones or wideband noise bursts. Gap detection experiments assess the smallest gap that a human listener, behaving animal, or single neuron can perceive, encode, or process. Temporal envelope features are represented by amplitude-modulated (AM) sounds. The most common AM stimulus

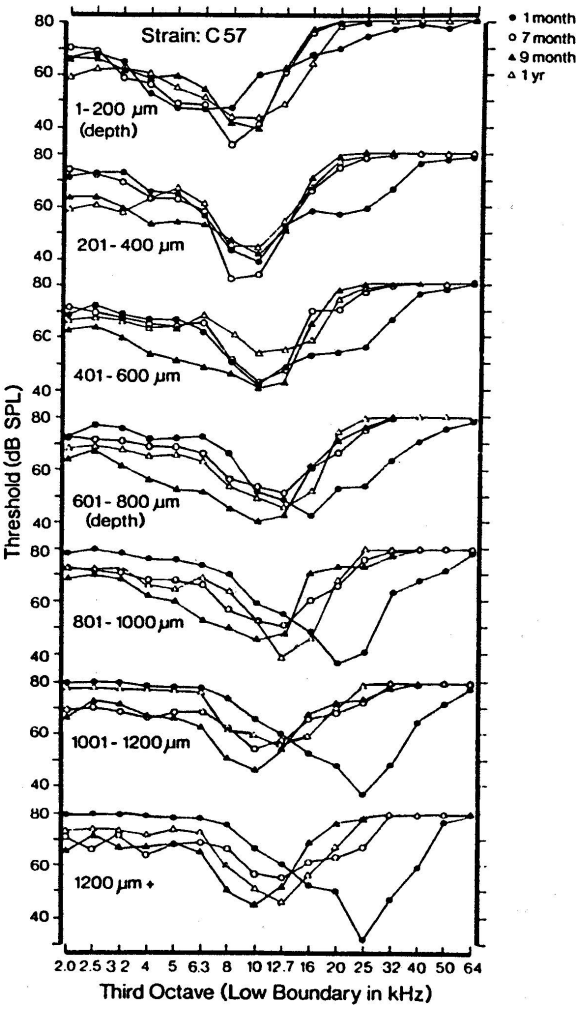


Figure 19.1. The tonotopic (cochleotopic) map of CFs in the C57 mouse IC reorganizes after an age-related decline in inputs from the high-frequency region (basal turn) of the cochlea. Group average frequency-threshold tuning curves (MTCs) for units, as a function of age and dorsoventral ICC depth, show a statistically significant CF shift from high (25 kHz) to middle (10 to 12 kHz) frequencies at the three lowest depths for the 7- to 12-month old subjects relative to the young adults. The number of single-unit tuning curves comprising each of the group average MTCs is: 1 month, $n = 90$; 7 months, $n = 74$; 9 months, $n = 50$; 12 months, $n = 56$. (From Willott 1986.)

envokes a periodic, usually sinusoidal, fluctuation in a tone's or wideband noise's envelope. Here, the threshold for the minimal depth of modulation can be measured or, more commonly in physiological experiments, the strength of the response of a single-unit or multiunit cluster is determined, either in terms of number of action potentials (rate) or timing of the action potentials (synchrony) in response to the AM (see Chapter 12). Both gap and AM coding can change with age in the IC.

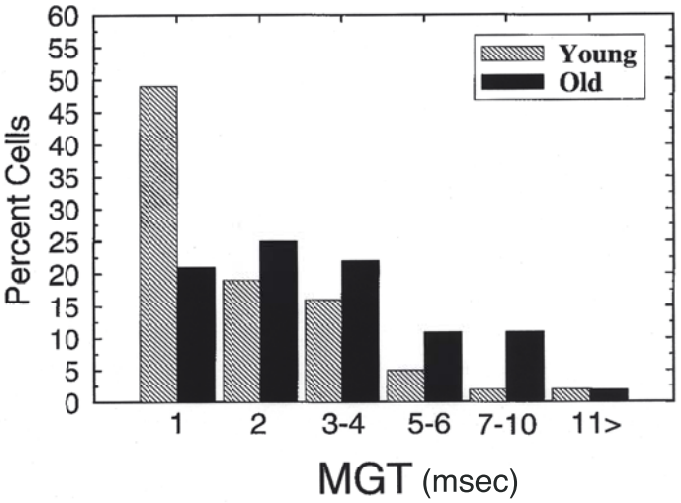
2.2.1. Sound Gaps

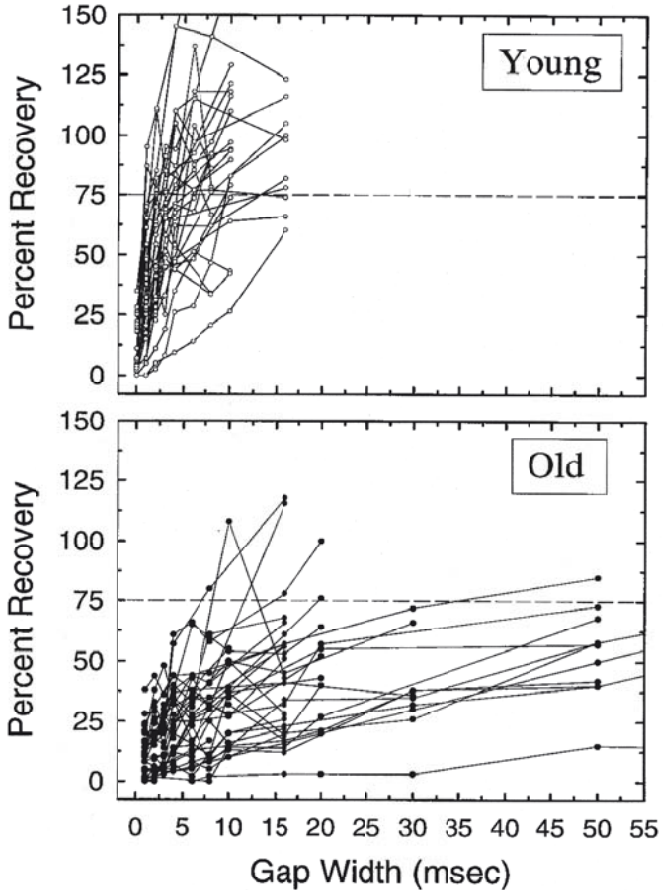
Single-unit gap encoding in the ICC of unanesthetized CBA mice is consistent with behavioral gap detection, both of which degrade with age, starting in middle age (Walton et al. 1997, 1998). Specifically, units with short gap detection thresholds decline, and the strength of their gap responses decreases in the ICC of aged CBA mice (Fig. 19.2). It is unknown what portion of this age effect occurs within the ICC and in brain stem nuclei that project to the ICC. It is likely that much of this age-related temporal processing decline occurs at ICC, as the coding of gaps there is of a different nature than that at subcollicular sites. For instance, at the auditory nerve and cochlear nucleus, gaps are encoded by a decrease in single-unit firing rate during the gap. In contrast, ICC neurons respond to gaps with an increase in neural firing at the end of the gap, and it is this response that declines with age in CBA mice with relatively good peripheral hearing sensitivity.

2.2.2. Amplitude Modulation

The neural encoding of ongoing auditory temporal features is investigated in AM experiments. Using monaural stimuli in anesthetized rats, there were no dramatic changes in ICC sinusoidal AM coding with age, no significant declines in the upper cutoff frequencies of the modulation transfer functions, or any marked changes in other temporal and rate measures of AM coding. However,

Figure 19.2. The proportion of single units in the unanesthetized CBA mouse IC with short gap thresholds decreases in old animals. The percentage of units in young adult and old CBA mice with minimum gap thresholds (MGTs) from 1 to >11 ms for young adult (*hatched, n* = 78) and aged mice (*solid, n* = 108). The distribution shows longer gap thresholds for aged animals. IC cells in young adult units encode gaps with higher firing rates. Neural recovery functions for 30 phasic units in young adult *(top)* and aged *(bottom)* animals. Recovery *(vertical axis)* was measured by computing the number of spikes elicited by the noise burst following the gap, divided by those to the noise burst preceding it, ×100. This calculation included all gap durations for each unit. A 100% recovery *(horizontal dashed line)* designates equal discharges to both bursts. Gap response recovery to the post-gap noise burst is 75% by <10 to 15 ms for almost all young adult units, whereas most aged units do not reach this criterion at even the longest gaps. (From Walton et al. 1998.)


Young
Old
Percent Cells
60
55
50
45
40
35
30
25
20
15
10
5
0
1
2
3-4
5-6
7-10
11>
MGT (msec)


Young
Old
Percent Recovery
150
125
100
75
50
25
0
0
5
10
15
20
25
30
35
40
45
50
55
Gap Width (msec)

there was a significant shift in the shape distribution of modulation transfer functions, with a decline in band-pass, and an increase in the low-pass shape, with age, in both the ICC and the external nucleus of the IC. This was interpreted as consistent with the hypothesis that IC inhibition contributes to the formation of band-pass AM transfer functions in young adult animals, and if this inhibition declines with age (see later), then band-pass specificity of AM coding will also degrade (Shaddock-Palombi et al. 2001).

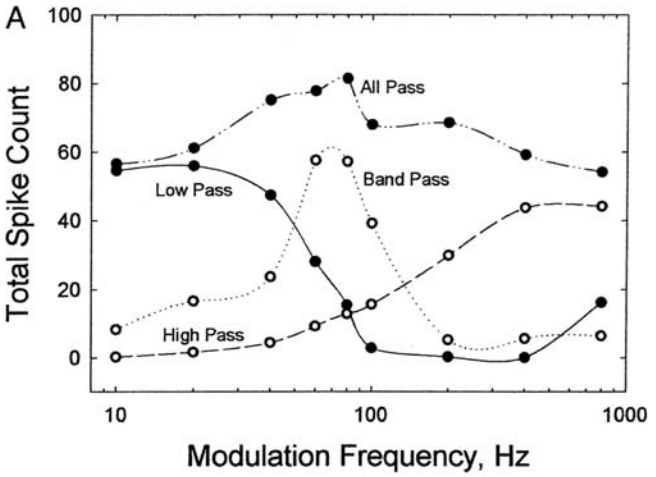
Subsequent sinusoidal AM studies in the unanesthetized mouse ICC used free-field stimuli and also demonstrated the age-related shift from band-pass to low-pass modulation transfer function shapes, originally found in the aged rat (Walton et al. 2002). The various shapes of modulation transfer functions characteristic of the mammalian IC (Fig. 19.3A) shift from a preponderance of band-pass transfer functions in young CBA mice to more low-pass in old mice (Fig. 19.3B). Other aspects of AM processing change with age, such as declining upper cutoff and best modulation frequencies (Fig. 19.3C) of rate modulation transfer functions, and the increased spike rate for pure tone stimulation was amplified in old animals in response to AM stimuli, further supporting a loss of IC inhibition with age.

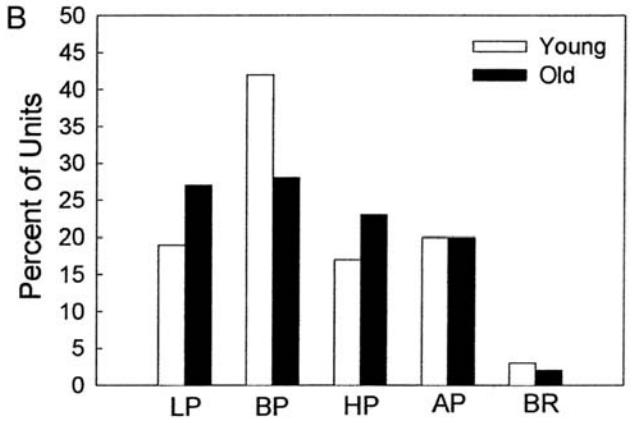
2.3. *Spatial Processing*

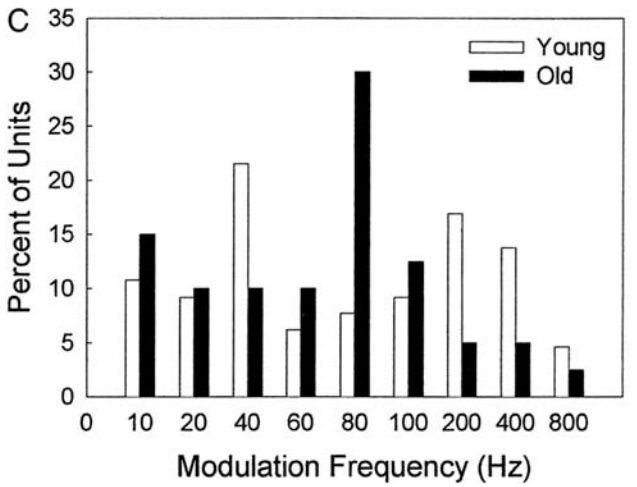
The auditory system uses different neural mechanisms for separating signals of interest, such as speech, from interfering acoustic clutter, such as ambient noise. Spatial localization of a speaker of interest in the context of noise from other speakers is a critical auditory adaptation for enhancing the signal-to-noise ratio in complex acoustic environments. It has been postulated, from clinical research, that this ability degrades with age (Willott 1991b). Consistent with the initial behavioral experiments with human subjects and patients, animal experiments found that sound localization abilities decline with age in C57 mice, and in a manner independent of their high-frequency hearing loss that occurs between young adulthood and middle age (Heffner et al. 2001).

What is the neural basis for age-related declines in the ability of the brain stem auditory system to separate signals from noise spatially? Single IC units in middle-aged C57 mice did not benefit from moving background noise sources away from signal locations, as do cells in young adult C57 mice. At a given

Figure 19.3. Age-related effects on rate encoding of envelope periodicities for IC single units. **(A)** Four different single-unit amplitude modulation transfer functions (MTF) types showing the scheme for MTF filter shape classification. Five categories occur: low-pass with a maximum synchronization index (SIm) of 0.889; band-pass, SIm 0.939; high-pass, SIm 0.946; all-pass, SIm 0.703; band-reject, example not shown. **(B)** Young adult *(open bars)* and aged *(filled bars)* units with each rate MTF filter shape. **(C)** Young adult *(open bars)* and old *(closed bars)* mice units with rate BMFs at each of the nine AM frequencies tested. (From Walton et al. 2002 with permission.)


A
Total Spike Count
All Pass
Band Pass
Low Pass
High Pass
Modulation Frequency, Hz


B
Percent of Units
Young
Old
LP
BP
HP
AP
BR


C
Percent of Units
Young
Old
Modulation Frequency (Hz)

azimuthal location, the amount of masking from the background noise was greater in the older mice, a change that peripherally induced threshold shifts with age could not account for and that implicates age-related declines in the mammalian brain stem auditory spatial localization analysis system (McFadden and Willott 1994a,b).

3. Neuroanatomical and Chemical Changes with Age

3.1. Changes in Input Pathways

Do IC brain stem connections also change in aged mice and, if so, is altered connectivity implicated in this syndrome? A neuroanatomical retrograde tracer, horseradish peroxidase, was injected into the centers of the IC regions from which recordings were obtained in temporal processing experiments (Frisina et al. 1998; Frisina and Walton 2001a,b). Inputs from all three divisions of the contralateral cochlear nucleus, the ipsilateral anterolateral periolivary nucleus, and portions of the ventral nucleus of the lateral lemniscus, each decline with age. These inputs likely contribute to the normal IC temporal processing abilities in young adult animals. As inputs age and decline, the balance of excitatory and inhibitory inputs to IC principal cells may become disrupted and precise temporal processing is diminished, leading to degradations in gap coding. These declines in brain stem inputs to the IC begin in middle-aged mice who have relatively normal auditory sensitivity as measured with auditory brain stem responses (ABRs), a finding consistent with the human mid-life psychophysical declines in temporal processing, even in subjects with otherwise normal audiograms (Snell and Frisina 2000).

3.2. Changes in Inhibitory System

GABA (γ-aminobutyric acid) is one of the main auditory brain stem neurotransmitters, and it is prominent in ICC neurons and synaptic endings where it has been implicated in many aspects of sound processing, including temporal and spatial coding. A study of IC GABAergic systems found that many aspects decline with age (Caspary et al. 1995). Quantitative analyses of GABA immunolabeling in IC perikarya in young and aged Fischer 344 rats found a 36% reduction with age (Caspary et al. 1990) and a reduced basal and K^+-evoked GABA release, in contrast to the normal values in control excitatory neurotransmitter levels and in acetylcholine release. Using quantitative receptor autoradiography, it was shown that declining $GABA_B$ receptor binding occurs in all three divisions of the aged rat IC (Milbrandt et al. 1994) while cerebellar tissue was unchanged. In contrast, $GABA_A$ receptors increased with age, perhaps in compensation for the $GABA_B$ decline (Milbrandt et al. 1996). Immunogold electron microscopy demonstrates that rat IC excitatory and inhibitory synapses

decrease in density with age (Helfert et al. 1999), just as does synaptic density in the IC of C57 mice (Kazee et al. 1995), although not in aged CBA mice (Kazee and West 1999). In conclusion, in rats, most aspects of GABA neurotransmitter biochemistry degrade with age, perhaps causing an imbalance of excitation and inhibition in the IC and concomitant functional impairments such as deficits in auditory signal extraction in background noise.

3.3. Activity-Dependent Changes in Calcium-Binding Proteins

Several competing theories and models address age-related neural degeneration and cell death in the mammalian CNS. These include processes such as calcium excitotoxicity; apoptosis; and damage caused by the harmful by-products of oxidative phosphorylation such as free radicals, stress/inflammatory responses in the brain, and others. Calcium excitotoxicity can result from concentration imbalances in intracellular calcium-binding proteins such as calbindin, calretinin, or parvalbumin. Age-related changes in calcium-binding proteins have been found in the IC (Zettel et al. 1997; Frisina 2001b,c). Antibodies for calbindin and calretinin reveal an age-related decline in IC calbindin immunostaining of CBA and C57 strains. For calretinin, up regulation occurs in the aged CBA IC, but not in aged C57 mice. Perhaps the age-related up regulation of calretinin in CBA mice reflects sound-evoked IC activity, as this up regulation was absent in aged, deaf C57s. This hypothesis was confirmed in CBA mice deafened as young adults and compared to the aged controls (Zettel et al. 2001). Calretinin up regulation in aged, hearing CBAs was absent in the mice deafened as juveniles (Fig. 19.4).

4. Plasticity in the Adult Mammalian Inferior Colliculus Caused by Altered Cochlear Outputs

Plasticity in the IC has been studied at many time points in the lives of experimental animals. This section examines studies in the adult, but not aged, mammalian IC.

The mature IC possesses the neural machinery that, at other brain sites, plays important roles in neural plasticity, including the *N*-methyl-D-aspartate (NMDA) glutamate receptors, the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptor, and $GABA_A$ receptors (Caspary et al. 2002; Kelly and Zhang 2002; Ma et al. 2002; Pollak et al. 2002). Many neuromodulators such as acetylcholine, serotonin, and noradrenaline (Habbicht and Vater 1996; Hurley et al. 2002) are present and can influence neuronal response plasticity in specific brain areas. IC cells express long-term potentiation (LTP), a synaptic phenomenon that is an important form of neural plasticity (Buonomano and Merzenich 1998). Various chemical levels in IC show immediate

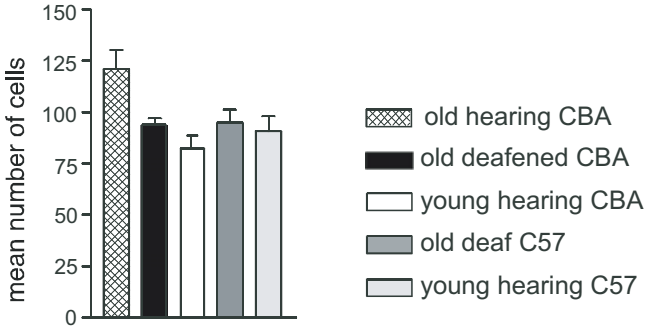


Figure 19.4. Mean cell density of calretinin-stained (CR+) cells per 100 μm² in the dorsomedial IC of aged, deafened CBA mice, aged hearing CBA, young adult hearing CBA, and young adult hearing C57 mice. Aged deafened CBA mice do not show the statistically significant increase in CR+ cells discovered in the aged hearing CBA mice. There was no significant difference between the cross-sectional areas of the dorsomedial IC in any of the ages or strains tested (not shown). Error bars denote standard errors of the mean. (From Zettel et al. 2001.)

changes as well as long-term changes after major alterations in afferent input. It is therefore surprising that, except in aging, there are very few demonstrations of physiological response plasticity in the adult mammalian IC.

An important distinction is made between plasticity and "unmasking" of latent inputs. As noted in the somatosensory CNS after damage or other manipulations to the receptor surface, CNS plasticity cannot simply mean the expression of latent, functionally dormant inputs once these have been released from inhibition (i.e., "unmasked") after removal of a dominant input (Calford and Tweedale 1988, 1991). Instead, plasticity must involve the conversion of implicit but unexpressed inputs into explicit responses expressed as part of the cell's normal suprathreshold repertoire, whereas unmasking entails the expression of explicit inputs that are otherwise blocked by other dominant (often inhibitory) inputs. Plasticity must involve changes in synaptic weights (Calford and Tweedale 1988, 1991; Buonomano and Merzenich 1998) that would not occur in unmasking. This distinction between plasticity and unmasking has been made in auditory cortex (Rajan 2001) and in the IC (Snyder et al. 2000) and will guide this exposition. It does not mean that the IC only has a stereotyped repertoire of hard-wired responses unaltered by major alterations of afferent or efferent input, or that unmasking does not produce functionally important response changes. However, it does provide a conceptual context for thinking about these changes and their causes. Finally, studies of IC plasticity in adults are confined to ICC unless otherwise stated.

4.1. Inhibitory Neurochemistry in the Inferior Colliculus after Cochlear Damage

IC neurochemistry has been examined often after cochlear ablation or total inactivation, and for focal cochlear damage with acoustic trauma. Although the former type of manipulation is not representative of most clinical conditions, it allows assessment of IC neurochemical reorganization after large changes in afferent input.

Many studies examined the effects on $GABA_A$ receptors, as hyperactivity or increased spread of activity often follows cochlear damage (Ryan et al. 1992; Bledsoe et al. 1995; Nagase et al. 2000; Salvi et al. 2000). IC cells express LTP only after blocking of some, if not most, inhibitory inputs such as $GABA_A$ receptors (Hosomi et al. 1995). LTP required NMDA and $GABA_B$ receptor activation—the latter likely acting presynaptically on GABAergic neurons to reduce postsynaptic inhibitory potentials mediated through $GABA_A$ receptors—and blocking of glycinergic receptors (Zhang and Wu 2002). LTP also occurs in brain slices in which GABAergic and glycinergic inhibition was routinely suppressed pharmacologically (Wu et al. 2002). These studies provide the rationale for examining changes in inhibition-related parameters in IC after cochlear damage.

There are considerable changes in GABAergic indices in IC after alterations of cochlear outflow. An immediate (Milbrandt et al. 2000; immediately after, and 42 hours after focal acoustic trauma) or rapid (Mossop et al. 2000; 24 hours and 7 days post-cochleotomy, but not 4 hours post) decrease in levels of glutamic acid decarboxylase (GAD), the rate-limiting enzyme in GABA synthesis, occurs in both membrane and cytosolic fractions (Milbrandt et al. 2000). Return to normal GAD levels follows 30-day (Milbrandt et al. 2000) or 1-year survivals (Mossop et al. 2000). However, GAD levels (primarily GAD67, the GAD isoform of molecular mass 67,000 kDa) in the entire IC increased immediately after focal acoustic trauma (Abbott et al. 1999), returned to near normal levels 2 days post-trauma, then dropped significantly below control levels at 30 days with a permanent hearing loss of 20 to 25 dB in auditory brain stem response thresholds. A similar trend occurs for GAD-immunoreactive cells in all IC divisions, although these changes were rarely significant and 30 days post-trauma the number was similar to that of normal animals. When salicylate was chronically administered in drinking water for 4 weeks or 4 months to produce a very small elevation in rat auditory brain stem evoked response (ABR) thresholds (Bauer et al. 2000), there was a marginal increase in GAD65 levels at 4 weeks treatment and a significant increase at 4 months.

Variability occurs in other indices of GABAergic function. A significant decrease in evoked GABA release occurs 21 days after ototoxic drug-induced bilateral deafness (Bledsoe et al. 1995). Evoked GABA release exceeded control levels in the contralateral IC 2 to 5 days after unilateral cochleotomy or ossicular removal, fell to normal at 59 days, and increased again at 145 days, with no

changes ipsilaterally. There were small decreases in GABA uptake in both ICs after cochleotomy only after the 145-day survival, in contrast with an immediate increase followed by a return to normal (ipsilateral) or subnormal (contralateral) levels after ossicle removal (Suneja et al. 1998). $GABA_A$ receptor function shows similar variability: increased binding when tested with muscimol (Milbrandt et al. 2000) and a small decrease in binding sites but increased receptor affinity to muscimol and not other $GABA_A$ ligands (Bauer et al. 2000). Thus, these studies do not show that a decrease in cochlear outflow consistently reduces IC GABAergic levels or expression.

Glycine is present in low amounts in the IC compared to GABA and has received correspondingly less attention. Little change in glycine release was seen 21 days after ototoxic drug-induced bilateral deafness in rats (Bledsoe et al. 1995). In guinea pigs a small and transient increase in glycine receptor binding occurred only in dorsal cortex (ICD) and the lateral nucleus (LIC) 2 days after unilateral cochleotomy and became normal 31 days later, decreased slightly in all three IC divisions at 60 days, and returned to normal at 147 days. The pattern was similar bilaterally (Suneja et al. 2000a).

4.2. Excitatory Transmitters and Calcium-Related Inferior Colliculus Proteins After Cochlear Damage

Changes in glutamate after unilateral cochleotomy in adult guinea pigs were assessed by measuring the number and/or activity of intracellular AMPA-type glutamate receptors. There was a small, significant decrease in AMPA receptor binding in contralateral IC 2 days post-lesion, a gradual increase to above average 60 days later, and a return to normal at 147 days. The ipsilateral pattern showed a significant decrease starting at 31 days, then followed the contralateral pattern. These changes were predominantly in the ICC and the ICD but not in LIC (Suneja et al. 2000b).

Given the established role of high calcium levels in excitotoxic neuronal cell death, a few studies have examined changes in calcium-related proteins; different effects have been reported for different proteins. Parvalbumin was unchanged from immediately after focal acoustic trauma to 30 days later (Abbott et al. 1999). After unilateral cochleotomy in adult rats, increased immunostaining was found for calbindin, which regulates intracellular calcium and may act as a cytoplasmic calcium buffer and thereby exert a neuroprotective effect. Changes were found only in the IC contralateral to the ablated cochlea, with immunoreactivity increasing from about 23 days post-lesion to a plateau only by 18 weeks (Förster and Illing 2000). Both cochleotomy and focal acoustic trauma also upregulate GAP 43, a growth and plasticity-associated phosphoprotein that binds to calmodulin and acts a substrate of protein kinase C, in IC neurons (Illing et al. 1997; Michler and Illing 2002). GAP 43 influences early synaptogenetic processes and decreases to near-zero levels with maturation; thus, GAP 43 expression after cochlear damage represents its trauma-induced reemergence

and occurs only from day 10 post-lesion and increases to day 30; the ipsilateral increase is greatest until day 30 when contralateral expression predominates. Immediately after acoustic trauma there is a reactive transient decrease in the phosphorylated form of the cyclic adenosine monophosphate (cAMP) response element binding protein (phospho-CREB) in ipsilateral IC and a contralateral increase that persists for up to 239 days and exceeded any subsequent ipsilateral changes. These changes in calcium-related proteins and in CREB are indicative of reactive changes but not plasticity, unless the latter is loosely defined as any change in the parameter under measurement (Michler and Illing 2003).

4.3. Changes in Inferior Colliculus Physiology After Cochlear Damage

Focal cochlear damage, quantified by changes in the compound action potential (CAP) audiogram, was created with acoustic trauma (Popelář and Syka 1982; Syka and Popelář 1982) or by spiral ganglion cell lesions (Snyder et al. 2000; Snyder and Sinex 2002), or lesions to the base of the cochlear partition (Irvine et al. 2003). Several indices, from potentials evoked at the IC surface to the responses of single neurons, before and after lesions, were assessed (Salvi et al. 1992; Wang et al. 1996). Responses were recorded from multineuron clusters across the dorsolateral-to-ventromedial tonotopic IC axis before and after cochlear lesions at similar depths (Snyder et al. 2000). Chronic implanted IC electrodes were used to assess neural responses from multineuron clusters pre- and post-lesion (Snyder and Sinex 2002). Multineuron responses several moths after cochlear lesions were compared to normal animals (Irvine et al. 2003). The results from these studies are presented below according to the type of IC response measured.

4.4. Changes in Evoked Potentials

In the IC contralateral to a damaged cochlea, changes in evoked potential (EP) amplitudes and thresholds to stimulation of the undamaged ipsilateral cochlea and to stimulation of undamaged parts of the contralateral test cochlea were obtained, although not in the same study. After unilateral cochlear deactivation with an ototoxic drug, the IC ipsilateral to the intact ear was now as sensitive and responsive to stimulation as the contralateral IC, whereas normally the contralateral IC is more sensitive. The decreased laterality differences were specifically due to changes in the IC responsiveness ipsilateral to the intact cochlea and occurred with a lag: the difference persisted at 1 to 2 days post-lesion and decreased at 7 days (Popelář et al. 1994).

A second effect was elicited by acoustic trauma (Salvi et al. 1992). Thirty days post-trauma a focal permanent hearing loss was seen with a peak of a 20- to 30-dB loss in CAP thresholds, and EP amplitude enhancement to frequencies below the peak of the cochlear hearing loss occurred, even at nearby frequen-

cies with deficits resembling the peak loss. Enhanced EP amplitude occurred at threshold and at mid-to-high stimulation intensities (>50 dB SPL). At frequencies above and below that of peak cochlear hearing loss, there was a decrease in EP amplitude in the IC at 8 hours post-lesion but not after 1 hour. Deficits could occur at frequencies at which CAP amplitudes (and EP amplitudes from cochlear nucleus) were below normal, or when CAP amplitudes had recovered but the amplitude of the cochlear nucleus EP was still depressed. These results were interpreted as due to relatively rapid, but not instantaneous, changes local to the IC or at least proximal to the cochlear nucleus (Salvi et al. 1992).

In contrast to these EP enhancement effects, other studies (Popelář et al. 1987) found none in awake guinea pigs after white noise trauma, even when the trauma caused a permanent hearing loss. Instead, EP amplitude was depressed and gradually recovered. That study (Popelář et al. 1987) also found EP enhancements in the auditory cortex, but not in the IC, when acoustic trauma was administered when the animals were awake but not when anesthetized. The absence of EP enhancement in the IC cannot simply reflect the use of a click stimulus, as the enhancement was found in the auditory cortex in the same animals. No EP enhancement occurred in the IC after acute noise trauma although the decrease of EP amplitude with increasing tone burst duration was slower in the lesioned animals, an effect mimicked by application of a $GABA_A$ blocker in controls (Szczepaniak and Møller 1995).

4.5. Changes in the Response Properties of Single Neurons

The reduced ipsilateral–contralateral differences after deactivation of one cochlea (Popelář et al., 1994) indicate recruitment of more IC neurons ipsilateral to the intact ear to the ipsilateral stimulus, possibly through a decreased inhibition on binaural input. In keeping with this hypothesis, increased IC neurons responsive to ipsilateral stimulation occur in adult cats with partial high-frequency contralateral cochlear damage (Snyder and Sinex 2002; Irvine et al. 2003) and in adult ferrets after unilateral cochleotomy (Moore et al. 1993). The change was larger after cochlear lesions causing broad high-frequency losses extending over the entire frequency range with 26% to 100% increase in ipsilateral responsive sites in IC (Irvine et al. 2003) than the changes ensuing after more focal damage and <50% increase (Snyder and Sinex 2002).

Any increase in EP amplitudes at frequencies below the peak of cochlear damage in a focally damaged cochlea (Salvi et al. 1992) could indicate a recruitment of more neurons, and a plausible mechanism for such recruitment is decreased monaurally acting inhibition evoked by stimulating a partially damaged cochlea. Discounting for the moment the varied effects of cochlear damage on GABA function in the IC noted earlier, a decrease in such function should affect the frequency-bandwidth of the response areas (tuning curves) because inhibition can shape this property of central auditory neurons (Vater et al. 1992;

Yang et al. 1992; Suga 1995; Palombi and Caspary 1996; Rajan 1998). Consistent with the idea that cochlear damage reduced inhibition in IC cells and could thereby unmask responses in them, 21 days after ototoxicity-induced cochlear deafness, there was decreased IC GABA release and fewer IC cells were inhibited by electrical stimulation of the contralateral cochlea (Bledsoe et al. 1995). Another study, using the same technique and duration of cochlear deafening (Nagase et al. 2000), found more Fos-immunoreactive cells activated by an intense electrical stimulus to the basal cochlea (and fewer activated by a near-threshold stimulus). These results predict that, after cochlear damage, there should be changes in the profile of the response area and/or other response properties of IC neurons that do not simply mimic the peripheral desensitization changes seen in auditory nerve responses. Analyses of response properties (Wang et al. 1996; Snyder et al. 2000; Snyder and Sinex 2002) found changes in response area profiles consistent with a decrease in inhibition after cochlear damage. Acoustic trauma at frequencies above the characteristic frequency (CF) of individual neurons created cochlear hearing losses above the high-frequency edge of the IC neuron's response area (Wang et al. 1996). In essence, rapidly after acoustic trauma there was addition of excitation to the low-frequency side of the response area in about 40% of cells, and this was more likely to occur in mustached bat IC cells whose response areas are shaped by GABAergic inhibition than in neurons whose response areas were less influenced or uninfluenced by GABA. Most often the change was manifest as decreased thresholds in the low-frequency tails of the neuron's response area and occasionally as a broadening of bandwidth along the low-frequency slope between the CF tip and the low-frequency tail of the response area, with no change in the neuron's CF (Yang et al. 1992; Fig. 19.5).

The posttrauma effects (Wang et al. 1996) resemble those seen on tuning curves after applying $GABA_A$ blockers to mustached bat IC neurons (Yang et al. 1992). Following the earlier model (Yang et al. 1992), tuning curve changes were interpreted as an unmasking of low-frequency excitatory inputs normally suppressed by inhibitory inputs tuned to a higher CF than that of the IC neuron under study (Wang et al. 1996). They postulated that the cochlear hearing loss at frequencies higher than the response area of an IC neuron under study, desensitized inhibitory neurons with CFs above that of the IC neuron, thereby unmasking lower threshold responses on the low-frequency side (mainly in the tail) of the IC cell's response area (Fig. 19.5).

Unmasking responses and changes in the response area profile also occurred after focal cochlear damage in IC neurons that previously had (Snyder and Sinex 2002), or would have had (Snyder et al. 2000), a CF at or near frequencies sustaining cochlear hearing losses. A withdrawal of lesion-induced afferent drive at the appropriate frequencies in the response area and addition of excitation at other frequencies, could shift the tuning curve CF. The rapidity of unmasking shows that the IC physiology can change soon after alteration in afferent outflow and argues that the effect cannot be a form of adaptive plasticity (Snyder et al. 2000).

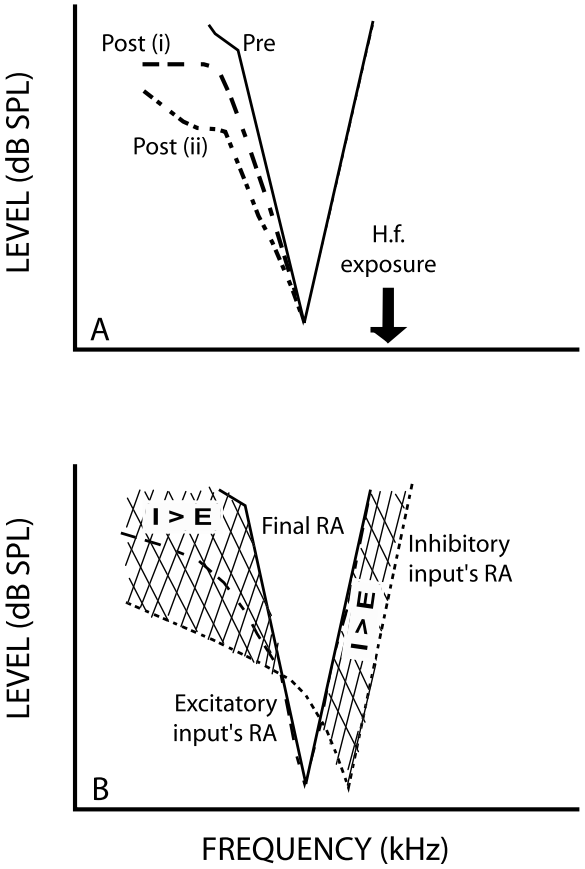


Figure 19.5. Rapid unmasking in the CNIC. **(A)** Prototypical changes in the tuning curves of level-tolerant CNIC neurons after a brief high-frequency loud tone (H.f. exposure) at a frequency above the high-frequency boundary of the IC neuron's tuning curve. (From Wang et al. 1996.) *Pre* is the response area boundary before the loud sound. The two *Post* curves show schematically two common changes seen immediately after the loud tone. In *Post (i)* the major change was the "addition" of a low-frequency "tail" at high intensities, whereas in *Post (ii)* the low-frequency "tail" occurred at lower intensities. *Post (ii)* shows another feature sometimes seen: a broadened response area width toward low frequencies at intensities nearer threshold. There is no change at the characteristic frequency (CF). **(B)** Schematic representation of the model (Wang et al. 1996). The final response area (*Final RA*) of the level-tolerant IC neuron is modeled as consisting of excitatory and inhibitory inputs; for clarity, only one of each input is shown. Both inputs have the same general profile but the inhibitory input is tuned to a higher frequency. In the hatched regions, the inhibitory input has a lower threshold than the excitatory input, and is therefore modeled to be a stronger input ($I>E$) at suprathreshold levels, thus suppressing excitatory input at these frequencies. In the area *Final RA,* excitation is stronger than excitation as is observed with extracellular recording. If a high-frequency loud tone exposure elevated the inhibitory input thresholds, and if this effect was greater on the low-frequency side, low-frequency excitation would be unmasked to produce the *Post* curves in **(A)**.

The physiological unmasking is consistent with a reduction in inhibition; however, studies of IC neurochemistry demonstrate that cochlear damage can decrease or increase indices of GABAergic inhibition (see Section 4.1). The difference does not appear to be methodological: focal acoustic trauma in a single neuron study (Wang et al. 1996) caused immediate physiological unmasking, probably from reduced inhibition, while similar trauma increased GAD levels across the entire IC (Abbott et al. 1999). Perhaps small decreases in inhibitory gain suffice to unmask physiological responses, but these may not be detectable neurochemically, and certainly physiological unmasking was not seen in all cases (Wang et al. 1996; Snyder and Sinex 2002), nor was the pattern of unmasking related to the locus of cochlear damage (Snyder and Sinex 2002).

Other studies (Popelář et al. 1978; Popelář and Syka 1982) found no unmasking of new components in IC neural tuning curves after acoustic trauma, but only threshold elevation which, like the data in studies of unmasking, were obtained in the same neurons before and after acoustic trauma.

Changes in the maximum firing rate of single IC neurons have also been reported after cochlear damage. Acoustic trauma, targeted to produce hearing losses at frequencies in the response area of IC neurons, found a few neurons with an increased maximum firing rate at the CF (Lonsbury-Martin and Martin 1981). Even with acoustic trauma targeted at frequencies above the tuning curve of IC neurons, 70% increased their maximum response rate at CF, possibly through decreased suprathreshold inhibition. Because the same study reported response area changes in about 40% of neurons after acoustic trauma, in at least 30% of neurons, GABA-mediated IC inhibition does not play a significant role in shaping the threshold response area (Wang et al. 1996), although it may have effects at high intensities (Yang et al. 1992; Rajan 2001).

4.6. Relationship of Single-Unit Changes to Evoked Potential Shifts

Does the unmasking of new components in single neuron response areas account for the EP amplitude enhancement after cochlear trauma? Prior work did not provide a definitive answer because the principal unmasking took place at tail frequencies in neurons with CF below the frequency range with hearing loss (Wang et al. 1996). Because EP enhancement occurs (Wang et al. 1996) even for frequencies with significant hearing loss (frequencies near, but below, the peak hearing loss), the unmasking effects (Wang et al. 1996) are at frequencies too far from the damaged frequencies in the EP studies to provide the single-neuron basis for EP enhancement. Unmasking provides a more likely candidate, as it was found in neurons with CF at a frequency with hearing loss. Further, unmasking could often be at low frequencies very near to the pre-lesion CF of the IC neuron (Snyder and Sinex 2002).

Despite this, unmasking of new parts of the response area is unlikely to account for the EP amplitude enhancement because it does not occur as reliably or predictably as does the EP amplitude enhancement (Salvi et al. 1992). The

other factor likely to play a role—and probably a more important role since it appears to be a more common effect than unmasking in the response area profile—is the increase in IC neural maximum firing rates after cochlear damage (Salvi et al. 1992; Snyder and Sinex 2002).

4.7. Cochleotopic Map Changes After Cochlear Damage

This issue has been examined using paradigms described earlier to create focal cochlear hearing losses, assessed subsequently by changes in the CF progression across the dorsolateral-to-ventromedial tonotopic IC axis, examined by multineuron mapping before, and within hours after, a small focal lesion in the basal cochlea. Post-lesion there was a normal CF progression in dorsal IC regions receiving CF input from cochlear frequency regions below the lesion-affected region. Further ventrally there were discontinuities in the CF progression within and adjacent to the region receiving CF input from cochlear frequencies with hearing losses (Snyder et al. 2000). The term *lesion projection zone* (LPZ) denominates the region of a CNS structure that once received input from a receptor region that is now lesioned (Schmid et al. 1996). Despite the awkwardness of the term, because a lesion cannot project anywhere, it suffices as a short and easily remembered descriptor of such a region.

Two types of discontinuities were observed (Fig. 19.6). In one type, starting near the ventral edge of the LPZ, successive points had CFs at the low-frequency edge of the cochlear lesion, indicating an expanded CF map from the low-frequency margin of the cochlear lesion. Next, a succession of points occurred with CF at a frequency at the high-frequency edge of the cochlear lesion, representing an expanded CF map at the high-frequency margin of the cochlear lesion. Further ventrally in IC, there was a normal CF progression. The second type of discontinuity had an LPZ with an expanded CF frequency map at the low-frequency edge of the cochlear lesion and this enlarged map persisted throughout the depth of the IC even when exiting the LPZ and entering regions that, pre-lesion, had CF at frequencies without hearing losses. Thresholds at the new CFs in the expanded CF representations (in the map discontinuities) resembled, and were even more sensitive than, thresholds at the same CF(s) in neurons in the normal parts of the map.

Others have concluded (Snyder et al. 2000) that the rapid changes embody unmasking of suppressed inputs (see Section 4.5) and cannot represent adaptive use-dependent plasticity consequent on sensory deprivation. In the mapping study unmasking resulted in more homogeneous CF representation in the LPZ than would be predicted (see Section 4.4) from the wide scattering of CF with unmasking (Snyder and Sinex 2002). This may relate to the fact that the latter study produced much larger CAP losses (up to 60 dB); it would be interesting to determine whether rapid map changes of the sort seen in the first study, with small CAP losses, would have occurred in the second study.

This issue is particularly germane because further study found that only rarely could an expanded CF map of a lesion-edge frequency be interpreted as not

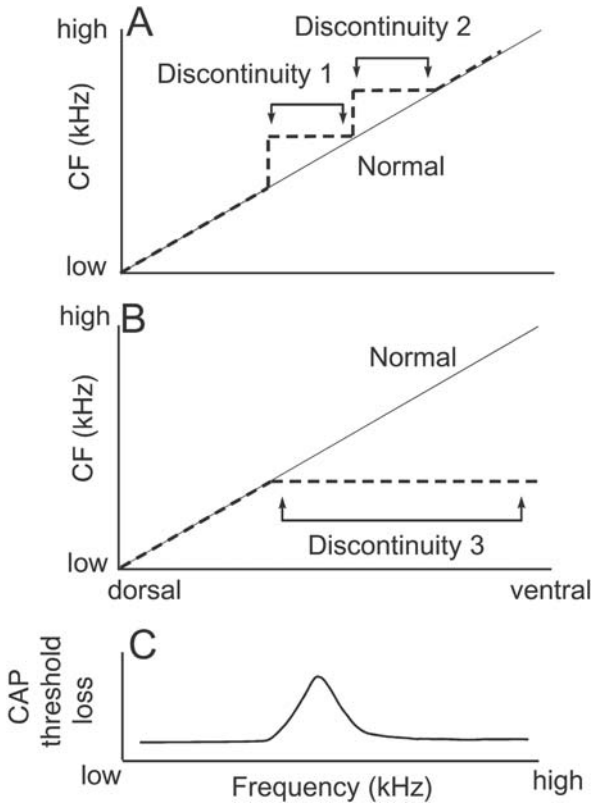


Figure 19.6. Changes in the frequency gradient curves (Snyder et al. 2000) in the CNIC after cochlear lesions. **(A, B)** Schematics of the frequency progression in CNIC when an electrode passes from dorsolateral to ventromedial and characteristic frequencies (CFs) are recorded at regular intervals. The *light line* (*Normal* in **B**) is the normal CF progression across the CNIC frequency axis. The *dashed line* shows the CF progression seen after a cochlear lesion produced a focal hearing loss (shown in **C** as elevations in cochlear compound action potential thresholds). In **(A)**, two discontinuities in CF progression are observed, and in both CFs remain about the same for some distance. Discontinuities include an expanded CF at the low-frequency edge of the cochlear lesioned range, and a CF over-representation at the high-frequency edge. **(B)** A single CF discontinuity at the low-frequency edge of the cochlear lesioned range extended across the remainder of the IC depth.

simply the residue of pre-lesion inputs to the LPZ (Irvine et al. 2003). In this residue argument (Rajan et al. 1993; Rajan and Irvine 1998) thresholds should increase across the expanded CF map in the LPZ (Fig. 19.6). Twenty sequences of recordings in the IC of 8 chronically lesioned animals found that the residue argument accounted for effects in almost every case when CFs were defined from the late component of multineuron responses to tones (time window from 35 ms after tone onset to the end of the 150-ms tone) (Irvine et al. 2003). CFs defined from the onset component (time window 5 to 35 ms after tone onset) were comparable to the 50-ms time window in other studies (Snyder and Sinex 2002; Snyder et al. 2000) for 50-ms duration tones. For two thirds of the sequences the effects were consistent with responses in the LPZ being simply the residue of pre-lesion responses at those sites. Reservations as to why even the remaining one third may not represent plasticity of the type seen in studies in auditory cortex in the same experimental paradigm led to the conclusion that, if IC tonotopic map plasticity occurs, it is rare, unrelated to intersubject variability, and limited to the early responses to tonal stimuli (Irvine et al. 2003).

5. Summary and Conclusions

Despite differences in techniques used to alter cochlear outflow and to record from the IC, and in physiological responses measured in the IC, similar conclusions follow from most such studies: the changes in IC physiology after altering cochlear outflow are best explained as a post-lesion expression of preexisting inputs, either through unmasking of previously suppressed inputs or as the residue of pre-lesion inputs. These studies suggest that there is little native capacity for plasticity in IC physiology in the adult mammal in response to large changes in cochlear outflow, at least in the limited context of the few experimental paradigms available. This conclusion is at odds with the effects seen in IC physiology with presbycusis, and with the dramatic changes in IC physiology seen after neonatal cochleotomy (Moore et al. 1993), or following large and extensive perinatal cochlear lesions with ototoxic drugs (Harrison et al. 1998). The plasticity in the latter two instances may reflect developmental phenomena, as massive cochlear lesions made with ototoxic drugs in adult life do not produce the IC plasticity seen after similar neonatal lesions (Harrison 2001).

Abbreviations

AI	primary auditory cortex
AM	amplitude modulation of sound envelopes
AP	all pass
BF	best frequency
BP	band-pass
C57	C57Bl/6 mouse strain

cAMP	cyclic adenosine monophosphate
CAP	compound action potential
CBA	CBA mouse strain
CF	characteristic frequency
CNS	central nervous system
CR+	calretinin-stained cells
CREB	(phospho-CREB) cyclic adenosine monophosphate response element binding protein
EP	evoked potential
GABA	γ-aminobutyric acid
GAD	glutamic acid decarboxylase
GAP 43	growth associated protein 43
HP	high pass
IC	inferior colliculus
ICC	central nucleus of inferior colliculus
LIC	lateral nucleus of the inferior colliculus
LPZ	lesion projection zone
LTP	long-term potentiation
LP	low-pass
MGT	minimum gap threshold
MTC	frequency-threshold tuning curve
MTF	modulation transfer function
NMDA	*N*-methyl-D-aspartate
SIm	synchronization index maximum

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