

Research paper

Dorsal cochlear nucleus response properties following acoustic trauma: Response maps and spontaneous activity

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Abstract

Recordings from single neurons in the dorsal cochlear nucleus (DCN) of unanesthetized (decerebrate) cats were done to characterize the effects of acoustic trauma. Trauma was produced by a 250 Hz band of noise centered at 10 kHz, presented at 105–120 dB SPL for 4 h. After a one-month recovery period, neurons were recorded in the DCN. The threshold shift, determined from compound action-potential audiograms, showed a sharp threshold elevation of about 60 dB at BFs above an edge frequency of 5–10 kHz. The response maps of neurons with best frequencies (BFs) above the edge did not show the typical organization of excitatory and inhibitory areas seen in the DCN of unexposed animals. Instead, neurons showed no response to sound, weak responses that were hard to tune and characterize, or “tail” responses, consisting of broadly-tuned, predominantly excitatory responses, with a roughly low-pass shape similar to the tuning curves of auditory nerve fibers with similar threshold shifts. In some tail responses whose BFs were near the edge of the threshold elevation, a second weak high-frequency response was seen that suggests convergence of auditory nerve inputs with widely separated BFs on these cells. Spontaneous rates among neurons with elevated thresholds were not increased over those in populations of principal neurons in unexposed animals.

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1. Introduction

Acoustic trauma damages hair cells in the cochlea (Liberman and Kiang, 1978; Liberman and Beil, 1979), producing a lesion that decreases the quality of the auditory neural representation of simple and complex sounds (Salvi et al., 1982; Geisler, 1989; Palmer and Moorjani, 1993; Miller et al., 1997). Although the lesions produced by acoustic trauma are in the cochlea, secondary effects in the central nervous system may be important in determining the perceptual consequences of trauma (reviewed by Syka, 2002). Central effects of cochlear damage or abla-

tion include degeneration of axons and neurons (Born and Rubel, 1988; Morest et al., 1998; Redd et al., 2000; Muly et al., 2002), formation of new synaptic connections (Kim et al., 2004a; Muly et al., 2004), rewiring of central circuits (Nordeen et al., 1983; Rajan et al., 1993; Leake et al., 2000), and changes in synaptic strength to favor excitation over inhibition (Suneja et al., 1998a; Abbott et al., 1999; Milbrandt et al., 2000; Mossop et al., 2000; Oleskevich and Walmsley, 2002; Vale and Sanes, 2002; Kim et al., 2004a). Each of these could influence substantially the central representation of sound.

The perceptual changes due specifically to central auditory plasticity following cochlear damage are still unclear, but there are at least two areas in which a relationship between changes in the auditory CNS and abnormal perception of sound have been hypothesized. The first is recruitment, the abnormal growth of loudness in damaged

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ears. Because the basilar membrane input/output function is steeper with outer hair cell damage (Ruggero et al., 1997), it has been suggested that recruitment results from a steepened growth of discharge rate with sound level in auditory nerve fibers (Harrison, 1981; Moore, 1995). However, such a change has not been observed following acoustic trauma (Heinz and Young, 2004; Heinz et al., 2005). At the same time, studies have provided evidence for steeper growth of overall neural response in central auditory neurons, in the inferior colliculus or cortex for example, following damage to the cochlea (Szczepaniak and Moller, 1996; Gerken et al., 1984; Popelar et al., 1987; Salvi et al., 1990). These data suggest that recruitment could reflect an enhanced response in central neurons in the face of decreased input from the auditory nerve.

Tinnitus is a second perceptual phenomenon that is thought to have a central origin, in part because tinnitus perception is not eliminated when the auditory nerve is severed (reviewed by Kaltenbach et al., 2005). There are several reports of elevated spontaneous activity in the dorsal cochlear nucleus (DCN) after an acoustic trauma that is sufficient to produce behavioral signs of tinnitus in animals (Brozoski et al., 2002; Kaltenbach et al., 2004; but see Chang et al., 2002; Brozoski and Bauer, 2005), suggesting that DCN is the generator site for tinnitus. In addition, DCN principal cells receive excitatory and inhibitory inputs from a superficial granule-cell associated system (Mugnaini et al., 1980; Berrebi and Mugnaini, 1991) that carries non-auditory information from the somatosensory, vestibular, and other systems (Itoh et al., 1987; Burian and Gstoettner, 1988; Shore et al., 2000; Ohlrogge et al., 2001). Its somatosensory components have characteristics consistent with the phenomenon of somatic tinnitus, in which manipulation of deep tissues in the face and jaw can modulate tinnitus (Levine, 1999; Kanold and Young, 2001). However, the identity of the DCN neurons producing the observed elevated spontaneous rates and/or the tinnitus percept is not clear.

Although the effects of acoustic trauma on auditory-nerve fibers are well known, the effects of trauma on central auditory neurons have received little detailed study. Here, we report on the response properties of single neurons in the DCN following acoustic trauma. The response types of DCN neurons are well-characterized and their relationships to the underlying neural circuit are understood (reviewed by Young and Davis, 2001). DCN neurons display strong inhibitory responses, which should be particularly affected by acoustic trauma, based on studies in other auditory nuclei (Bledsoe et al., 1995; Vale and Sanes, 2002; Rajan, 2001; Wang et al., 2002). Thus, the DCN is an ideal site for studies of the functional reorganization of central circuits following damage to the ear. The goal of this study was to determine the response characteristics of DCN neurons following acoustic trauma, especially the extent of inhibition in response maps, the quality of tuning, and spontaneous discharge rates. These data will form a basis for quantitative study of phenomena like recruitment and tinnitus.

2. Materials and methods

2.1. Animal care

Experiments were done using nine healthy adult male cats obtained from Liberty Labs. Animals were exposed either once or twice to acoustic trauma and allowed to recover for at least 28 days (range 28–98 days, median 41 days) after the last exposure before the acute single-neuron recording session. At the end of the recording session, the animals were killed with sodium pentobarbital (200 mg/kg, i.v., to effect). The animal protocol was approved by the Johns Hopkins University's Animal Use and Care Committee.

2.2. Acoustic trauma

Animals were anesthetized with ketamine (35–45 mg/kg, i.m.) and xylazine (0.5–0.7 mg/kg, i.m.), supplemented with half the initial dose every hour, as needed. Atropine was given (0.03 mg/kg, i.m.) to reduce secretions. Each ear was examined to confirm clear tympanic membranes. The animal was positioned on sound-damping foam 10–15 cm below a speaker. The exposure signal was a 250 Hz band of noise centered at 10 kHz (the stopband is down 100 dB and the transition bands are ≈ 1 Hz wide) at 105–120 dB SPL for 4 h. After exposure, cats were allowed to recover from anesthesia and then returned to the animal care facility. In two cases, post-exposure auditory-brainstem responses (ABRs) suggested that the trauma had not produced a hearing loss and a second exposure was performed. In two additional cases, the ABRs suggested that a loss had occurred, but no threshold shift was apparent in the recording session.

2.3. Surgery and recording procedures

At least 28 days after the final sound exposure, single neuron recordings were done in the DCN. Cats were anesthetized with ketamine and xylazine as described above, with supplemental doses as needed to maintain anesthesia during surgery. Atropine (0.03 mg/kg, i.m.) was administered daily to reduce secretions. At the start of the surgery, dexamethasone (1–1.3 mg/kg, i.m.) was administered to reduce edema. The cat's airway was maintained with a trachea tube, body temperature was maintained at 38.5°C with a heating pad on a feedback controller, and fluids were maintained with an i.v. drip of 5% dextrose in lactated Ringers. The skull was exposed and opened over the caudal cortex; the animal was decerebrated by cutting the brain between the thalamus and the superior colliculus using an aspirator under visual observation. After decerebration, anesthesia was discontinued. The DCN was exposed by opening the posterior fossa and aspirating the caudo-lateral portion of cerebellum. The fluid level over the free surface of the DCN was maintained by CSF flow, supplemented with heparinized saline.

A scalpel was used to open a small hole into the bulla through which a Teflon-coated silver-wire electrode was inserted. The electrode was placed on the bone near the round window and glued in place; a length of PE tubing was inserted through a second hole then both holes were sealed with modeling clay. The round-window electrode was used to record compound-action-potential (CAP) responses to 10 ms tone pips (1 ms rise–fall times, presented once per 100 ms). Threshold was determined by recording CAP amplitudes at three near-threshold sound levels, separated by 5 dB, and interpolating to a fixed amplitude clearly above noise level.

CAP and single neuron recordings were performed in a double-wall IAC chamber. Sound was produced by an electrostatic driver and presented via hollow earbars. Probe tube calibration of the acoustic system was done in each experiment with the probe tip about 2 mm from the eardrum. Single neurons were recorded extracellularly with platinum iridium microelectrodes placed in the DCN under visual control. Neurons were characterized with responses to 200 ms stimuli presented once per second.

2.4. Analysis of neural responses

Neurons' best frequencies (BFs) were estimated as the frequency that produced either an excitatory or inhibitory response at the lowest sound level. For broadly-tuned neurons, BF were estimated from response maps; these are plots of discharge rate in response to constant-attenuation tone bursts presented across a range of frequencies, usually spaced logarithmically at 25 stimuli/octave, and attenuations spaced at 5 or 10 dB intervals. The frequency producing the largest rate change at the lowest sound level presented was taken as BF; however, for neurons in animals with significant threshold shift, this criterion was modified slightly as described in Section 3.

Response types were classified using the scheme developed for the DCN in unexposed animals (Shofner and Young, 1985; Young et al., 1995); this scheme is based on identifying areas of excitation and inhibition (increase or decrease in rate from spontaneous, respectively). The types are briefly defined later in Fig. 2. Spontaneous rates were calculated from 10 min recordings with no stimulus presented. Exceptionally, the spontaneous rates were computed from the last 500 ms of the stimulus-off period in the tone and noise presentations. Comparison data from unexposed animals were obtained from archival data that have been published previously (Nelken and Young, 1994; Davis and Young, 2000; Reiss and Young, 2005).

3. Results

3.1. Threshold audiograms

Seven of the nine animals exhibited threshold shifts suggestive of noise-induced trauma. The remaining two animals exhibited near normal CAP thresholds and DCN

response properties typical of responses in unexposed animals; data from these two animals are not considered further in this paper. CAP thresholds for the seven animals exhibiting threshold shifts are shown in Fig. 1. Fig. 1A shows CAP thresholds versus tone frequency for exposed animals (light solid lines), compared to unexposed animals (dashed and dotted lines). In four of the seven animals, the exposure produced hearing loss functions with steeply sloped threshold elevations at frequencies between 5 and 10 kHz. In two other animals, the exposure produced more gradual losses that extended to lower frequencies; the remaining animal exhibited only a very high frequency hearing loss, significant at frequencies of 13 kHz and above.

To show the effects of the threshold shift, subsequent figures are plotted against frequency relative to the edge of

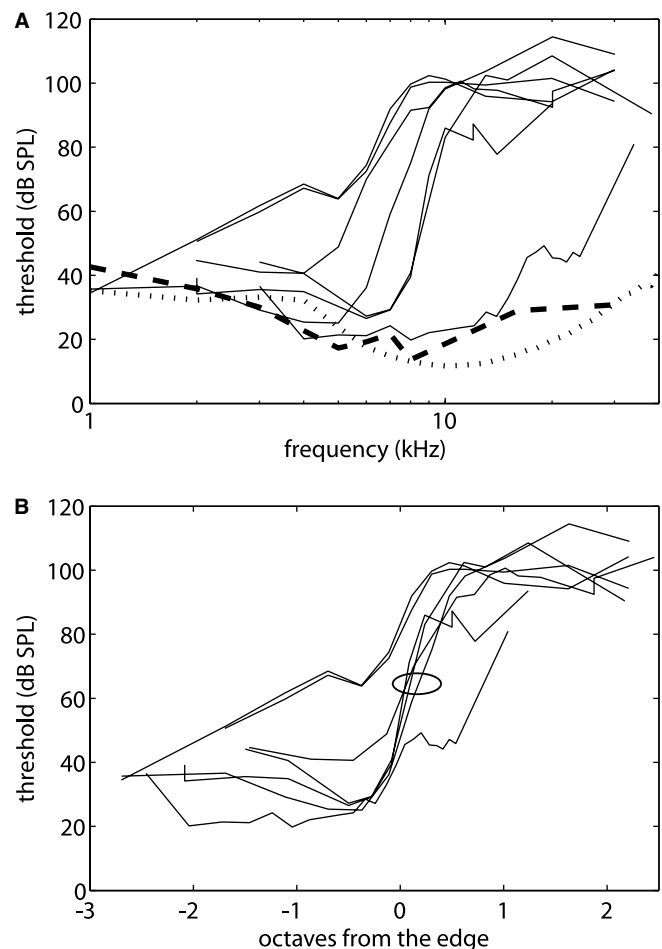


Fig. 1. (A) CAP threshold functions for cats exposed to acoustic trauma (light solid lines), compared to thresholds from unexposed animals (dashed and dotted lines). CAP threshold is plotted versus frequency for CAPs studied at the beginning of each experiment. The heavy dashed line is from one unexposed animal studied in our lab; the dotted line is the average CAP audiogram from three animals reported by Rajan and Irvine (1998). (B) Threshold audiograms from the exposed cats shifted along the frequency axis to align the steepest portions of the audiograms. The abscissa is frequency relative to the steepest point, in octaves. The circle identifies four similar threshold functions; data from these experiments are shown separately in Fig. 4A.

the threshold audiogram, where the edge is defined as the center of the steepest-slope segment of the audiogram. For this calculation, the threshold functions in Fig. 1A were shifted to align them on the steepest slope. The shifted threshold functions are shown in Fig. 1B. Four of the experiments had similar threshold functions, which are circled in Fig. 1B.

3.2. Response maps of DCN neurons

Response maps for neurons in the DCN of decerebrate animals have been described in detail (Young and Brownell, 1976; Spirou and Young, 1991; Spirou et al., 1999). Examples of response maps that have both normal and abnormal shapes are shown in Fig. 2 and a summary of the numbers of neurons of each type is given in Table 1. The left column of Fig. 2 shows examples of four DCN response map types that are typical of unexposed animals. These maps are actually taken from exposed animals, but are at BFs with little or no threshold shift. The right column shows response maps at BFs with substantial threshold shift.

Type II response maps (Fig. 2A) show narrowly-tuned excitatory regions with substantial inhibitory areas at surrounding frequencies; because these neurons lack spontaneous activity the inhibitory areas are only seen in the presence of background activity produced by a second tone, as plotted here (a “two-tone” response map). Type II responses are recorded from vertical cells (Young, 1980; Rhode, 1999), which are one source of inhibition to DCN principal cells (Voigt and Young, 1990). The remaining examples, types III, IV-T, and IV are probably recorded from DCN principal cells (Young, 1980; Rhode and Kettner, 1987; Davis et al., 1996; Ding et al., 1999). They vary in the amount of inhibition, from Type III responses (Fig. 2B) which show no signs of inhibition at BF, but are inhibited away from BF, to type IV responses (Fig. 2D) which have a large inhibitory area centered at or just below BF. Type IV-T (Fig. 2C) responses are intermediate. Types III, IV-T, and IV are thought to form a continuum with differing degrees of inhibitory input. To support this hypothesis, a neuron’s response map can be changed from type IV to type III by anesthesia (Joris, 1998; Anderson and Young, 2004) and in the reverse direction by GABA_A antagonists (Davis and Young, 2000). Most neurons in decerebrate cat DCN fall into types II, III or IV, although there are other types (I/III and V, see Young et al., 1995), not shown in the figure but summarized in Table 1.

Neurons with BFs at frequencies that showed substantial CAP threshold shift usually had different response properties, illustrated in the right column of Fig. 2. Many of the responses fall into a category called “tail responses” in this paper. They are characterized by poorly-tuned responses extending broadly to low frequencies, resembling the tail of an auditory nerve fiber tuning curve. The extent of inhibition in these responses varies, as described below,

but in most tail responses, the broad tail appears within 30–40 dB of threshold.

The most common tail response (class A, Fig. 2E) consists of broadly-tuned excitatory responses at and below an upper cutoff frequency (22 kHz in Fig. 2E). The upper frequency edge of the response is sharp at all levels with inhibition sometimes visible at higher frequencies. Auditory nerve fibers in ears with acoustic trauma often show tuning curves with similar low-pass behavior, appearing to be derived from the tails of the original tuning curve (Lieberman and Dodds, 1984). Because of the similarities in the response areas of class A tail responses to these auditory nerve fiber responses, the BFs of tail responses are assigned near the upper frequency edge of the excitatory area (after Liberman, 1984). Consistent with this, there was often a narrowly-tuned region within 10–20 dB of threshold (as in Fig. 2E) that clearly defined BF as being near the upper frequency edge.

Tail responses sometimes showed inhibitory areas both above and below BF, as in the example of Fig. 2F. The dashed lines show the single-tone response map of this neuron, which is similar to Fig. 2E, consisting of excitatory responses on a background of zero spontaneous rate. The difference between Figs. 2E and F is that the latter has a tail 40–50 dB above threshold, which is a high value for the cases classed as tail neurons. When a background rate was produced by adding a low-level tone at BF, inhibitory areas were seen in the resulting two-tone response map, the filled-in response maps shown in Fig. 2F. The inhibitory areas occur at frequencies where the single-tone response map had rate dips or zero rate. This sort of inhibition was often seen in tail responses.

A second type of tail response (class B, Figs. 2G and H) has a broad excitatory response area as in the class A response, but shows an additional excitatory area above BF at higher sound levels (the arrows in Figs. 2G and H). These high-frequency responses are often weak, but are unmistakable as rate increases and consistent across frequency. They usually do not provide evidence for a BF at higher frequencies in that they are not tuned. For that reason, the BF of class B neurons was placed at the high-frequency edge of the low-threshold portion of the response map. As with class A tail responses, class B neurons sometimes had entirely excitatory response maps (Fig. 2G) but could show substantial inhibitory areas (Fig. 2H).

A small group of tail responses (class C, not shown) showed only inhibitory responses to sound. The general shapes of these response maps were like those of class A neurons, except inhibitory. They differ from entirely inhibited neurons sometimes encountered in unexposed animals by having broader inhibitory areas.

Table 1 summarizes the response types for all the neurons encountered in the seven experiments. Counts are shown separately for neurons in the BF region below the edge of the lesion (left column) and in the region with elevated thresholds above the edge (center column). In the

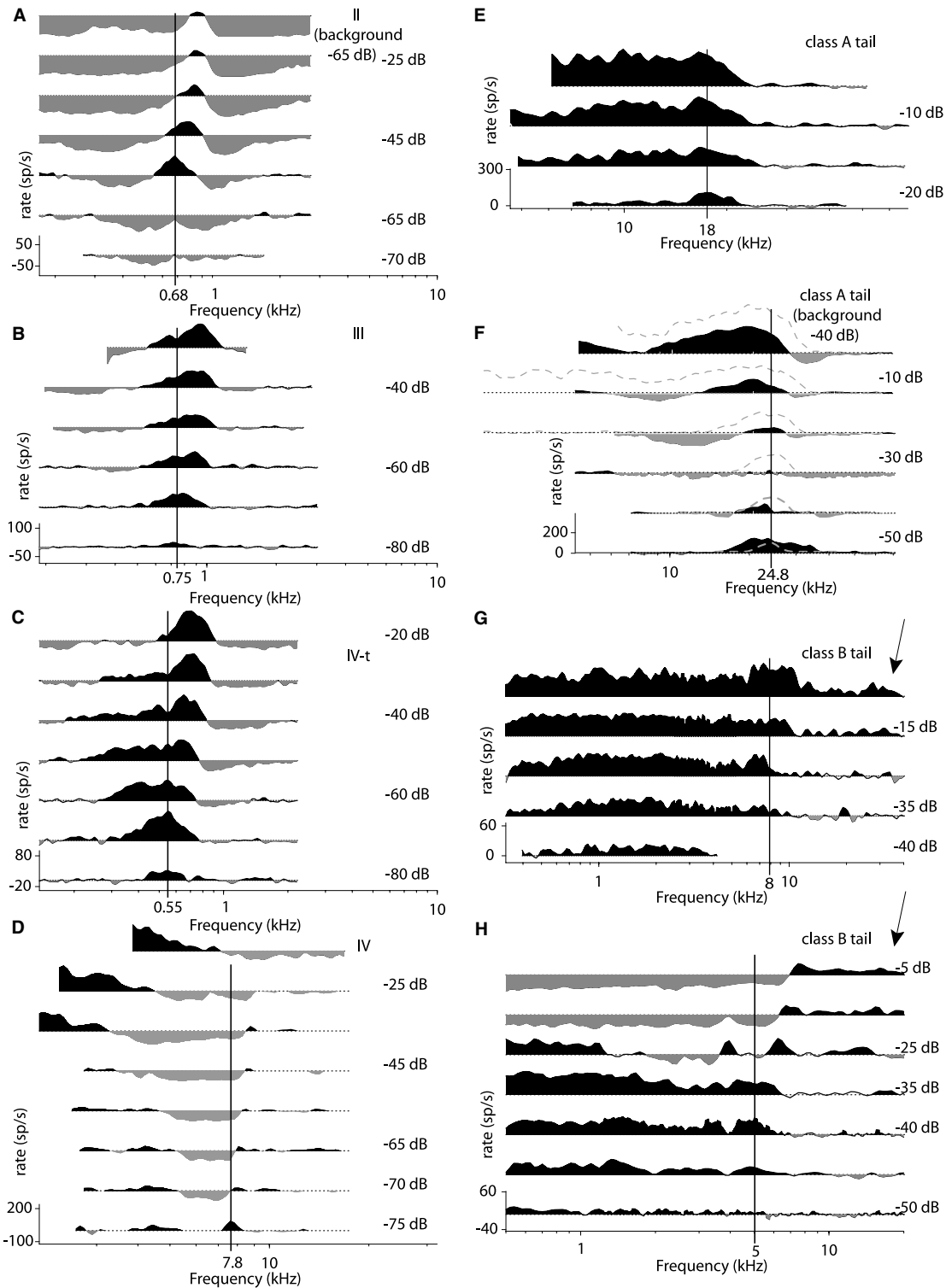


Fig. 2. Response maps of DCN neurons typical of non-exposed (left column) and exposed (right column) animals. Response maps show discharge rate versus frequency at a succession of fixed attenuations (the sound level at 0 dB attenuation is approximately 100 dB SPL). The horizontal lines are spontaneous rate or background rate in two-tone maps. The vertical solid lines show the BFs assigned to the neurons. Regions colored black are excitatory, meaning an increase in rate over spontaneous, and regions colored gray are inhibitory, meaning a decrease in rate. The maps are based on responses to one repetition of a 200 ms tone, so should be interpreted qualitatively. They have been smoothed with a three-point filter. For neurons without spontaneous activity, two-tone response maps are shown (A and F). In these cases, a second tone a few dB above threshold at the BF of the neuron was presented along with the response-map tone. The second tone produces enough background activity that inhibitory responses can be seen. (A) Type II two-tone map (the second tone was 0.68 kHz at -65 dB, 36 dB SPL). (B) Type III map. (C) Type IV-T map. (D) Type IV map. (E) Class A tail response map showing no clear inhibition for a neuron with spontaneous activity. (F) Class A tail response map showing inhibition; both single-tone (dashed line) and two-tone (filled map) response maps are shown. the horizontal line is the spontaneous rate (zero) for the single-tone map and is the driven background rate for the two-tone map. The second tone was 24.8 kHz at -40 dB, 72 dB SPL. (G) Class B tail response. Note the low level of activity extending to high frequencies at the highest level (arrow). (H) Class B tail response with inhibition.

Table 1
Numbers of neurons of various response types from seven exposed animals

Response type	BF < (edge – 0.5 oct.)	BF ≥ (edge – 0.5 oct.)	Shofner and Young (%)
Normal			
I/III	6	1	23
II	6	1	19
III	6	5	23
IV-T	4	1	4
IV	4	3	31
V	0	1	–
Tail response			
A	6	44	
B	2	8	
C	3	1	
Not classified	11	25	
Not classified, BF not known		12	
Not responsive to sound		30	

The percentages in the last column show the fractions of response types reported by Shofner and Young (1985) in unexposed animals.

range of BFs below the edge of the lesion, response types found in the normal DCN were common, with a numerical distribution consistent with the fraction of various response types in normal animals (right column). For neurons with BFs above the edge of the lesion, the most common response type was the class A tail response.

The bottom three rows of Table 1 summarize the neurons with response maps that could not be classified. Thirty neurons were spontaneously active but did not respond to sound, up to the maximum level available from our sound system (≈ 100 dB SPL). An additional 48 neurons had response areas that could not be fit into any of the schemes, either for exposed or unexposed animals. Sometimes these were simply cases in which not enough data were obtained during the experiment, either because contact with the neuron was lost or the threshold was so high that the response map was insufficient. Other neurons had response maps with weak and inconsistent responses, so that a BF could be assigned but a response map type could not; the example in Fig. 3 is of this type. In 12 cases, neurons had thresholds well within the range of the sound system, but the responses were so weak that BFs could not be established with certainty.

3.3. Distributions of response types by BF

Neurons with tail responses were found only at BFs where the threshold was elevated or at the edge of the elevated-threshold region. Fig. 4A shows the thresholds of all the neurons studied in the four experiments with similar sharp threshold transitions, for which audiograms are shown in Fig. 1B. Here, the BF is plotted relative to the edge of the threshold shift. The CAP audiograms are plotted in light gray lines for reference and the legend defines

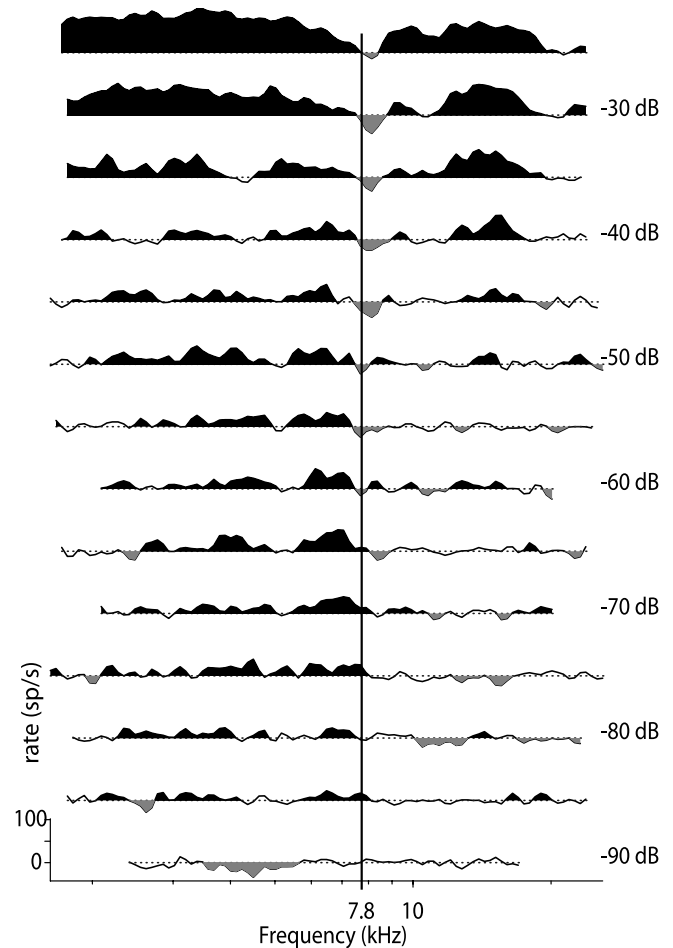


Fig. 3. Response map of a neuron that gave weak non-specific responses. Such neurons were not classified, although a BF could often be found, as here.

the response map types. For BFs below the edge region ($\text{BF} < -0.5$ on the abscissa, to the left of the dashed lines), neurons with near-normal thresholds (< 30 dB) had response maps typical of the unexposed DCN (circular, triangular or square symbols).

At the threshold-shift edge, from -0.5 to 0.5 octave on the abscissa (between the dashed lines), the neurons showed mainly tail responses or were not classified. All three types of tail responses were found here, but class B tail responses (*) were mainly found here, suggesting that class B tail responses are associated with the edge of the threshold shift. Note that tail responses are seen in neurons with thresholds from about 20 dB SPL, in the normal range, to over 80 dB SPL. Thus, threshold alone does not predict the occurrence of tail responses.

At BFs in the damaged region above the edge (> 0.5 on the abscissa, to the right of the dashed lines) the responses were mainly class A tail responses (+). All of the neurons within this BF range showed severely degraded response characteristics.

Fig. 4B shows the neurons recorded from all seven animals, again plotted as BF relative to the edge. Here, some neurons with elevated thresholds were seen at BFs below

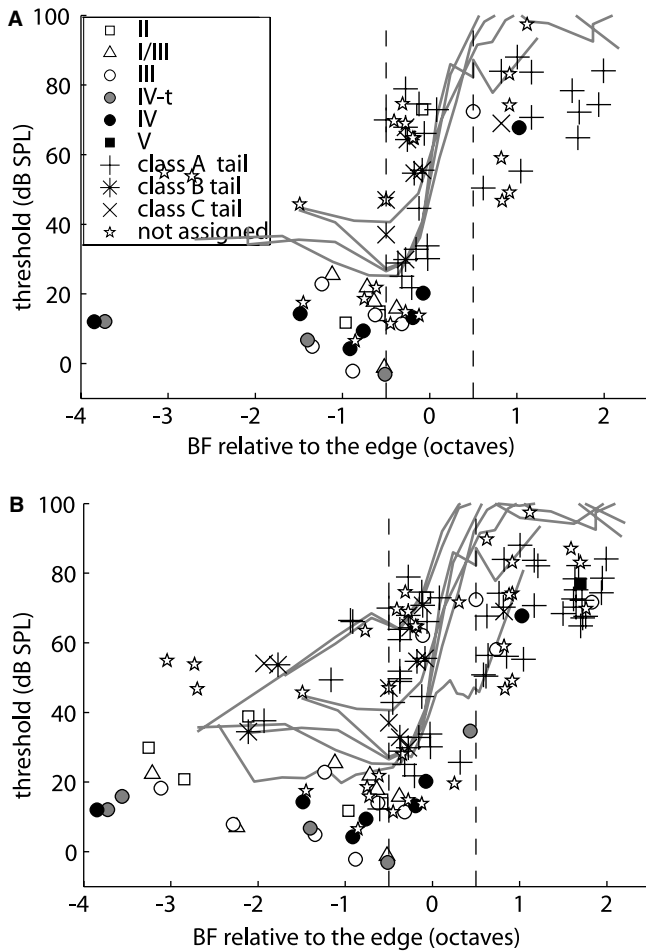


Fig. 4. (A) Threshold at BF versus BF, plotted as octaves relative to the edge of the threshold shift. In most cases, thresholds were obtained from rate versus level functions for BF tones in 1 dB intensity steps. Only data from the four experiments with similar sharp threshold shifts, circled in 1B, are shown. CAP threshold audiograms are plotted in light gray. Symbols define different response map types, defined in the legend. “not assigned” means neurons in which the BF could be determined, but the response type could not. The dashed lines mark the edge region, from -0.5 to 0.5 octave relative to the steepest point on the threshold functions. (B) The same plot using data from all seven animals.

-0.5 octaves relative to the edge. These neurons showed mainly tail responses (+, \times , and $*$) or were not classified (stars) and were exclusively from the two animals with gently sloping CAP audiograms showing elevated thresholds at low BFs.

3.4. Bandwidths of excitatory regions

Tail responses are defined by having a broad low-frequency response area at sound levels within 30–40 dB of threshold. Fig. 2 suggests that the excitatory bandwidths of tail neurons are larger than in the usual DCN response types. The extent of the response area for the entire population is shown quantitatively in Fig. 5, which plots the Q s of the excitatory areas of response maps at 10 (Fig. 5A) and 40 (Fig. 5B) dB above threshold. For comparison, the approximate boundaries of auditory nerve and DCN Q

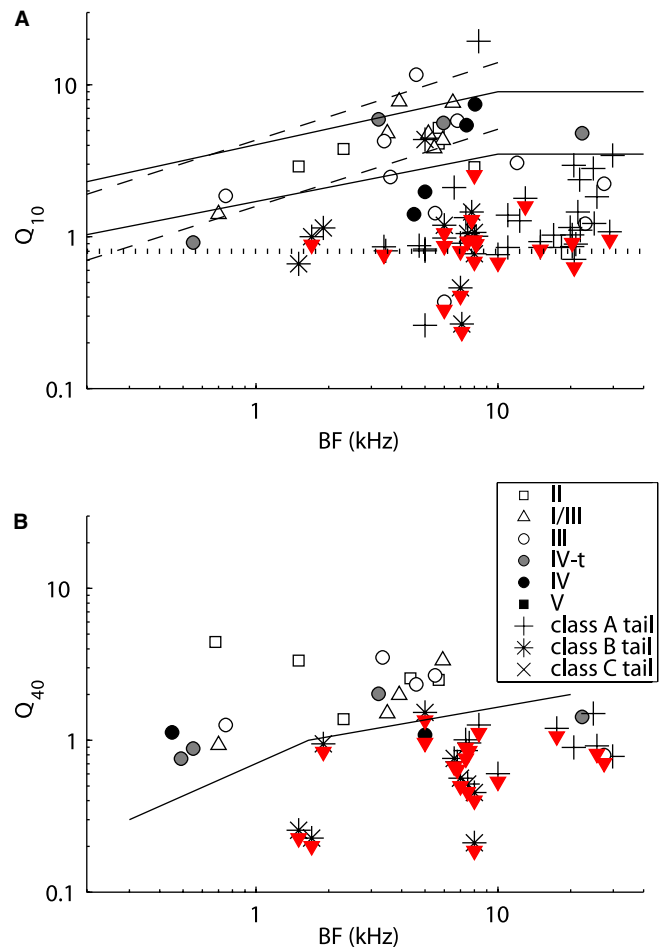


Fig. 5. Bandwidths of excitatory response areas plotted as Q values, defined as $\text{BF}/\text{bandwidth}$. The bandwidth is for excitatory responses only and bandwidths were not measured at sound levels where inhibitory areas encroached on BF. The legend identifies response types. (A) Q_{10} , based on bandwidth 10 dB above threshold. The shaded down-pointing triangles are plotted just below points for which the bandwidth was not fully determined in the response map, usually because the frequencies studied did not extend far enough at the low frequency end. In these cases, the Q value is actually less than the position plotted. The dashed lines bound the Q_{10} data in auditory-nerve fibers from unexposed cats (Miller et al., 1997) and the solid lines are from Liberman and Dodds (1984). The dotted line shows the minimum Q_{10} in auditory-nerve fibers with 40–60 dB threshold elevation from acoustic trauma, also from Miller et al. (1997). (B) Q_{40} , based on bandwidth 40 dB above threshold. The line is a lower bound on auditory nerve (Liberman, 1978) and DCN (Young and Voigt, 1982) values in unexposed cats.

values in unexposed cats are shown by the lines (Liberman, 1978; Young and Voigt, 1982; Liberman and Dodds, 1984; Miller et al., 1997). Generally it is not possible to measure bandwidths for type IV responses at 40 dB because of the inhibitory areas, so Fig. 5B shows mainly data from type II, type III, and tail neurons, whose bandwidths were measured from the excitatory areas of single-tone response maps.

The response types typical of non-exposed animals (i.e. types II, III, IV-T and IV), with a few exceptions, show Q values comparable to the data from unexposed animals (lines) in both Figs. 5A and B. By contrast, tail responses

clearly have Q_s that are less than the range seen in unexposed animals.

As a further comparison, the dotted line in Fig. 5A shows the approximate minimum Q_{10} seen in auditory-nerve tuning curves in animals with 40–60 dB threshold shifts following acoustic trauma (Miller et al., 1997). The majority of tail responses are above this line, meaning that their bandwidths are similar to those that would be expected of auditory-nerve fibers from damaged ears. Others are below the line, but such very low Q_{10} s are also seen in cats following acoustic trauma that produces threshold shifts in the 60–80 dB range (K. Franck and T. Ji, unpublished data).

As expected, Q values were higher for tail responses from neurons with lower thresholds (not shown). Using data from tail neurons with BFs in the edge region (-0.5 to 0.5 octaves re the edge), the correlations between $\log(Q)$ and threshold were $r = -0.55$ for Q_{10} ($P < 0.02$) and $r = -0.76$ for Q_{40} ($P < 0.005$).

3.5. Spontaneous activity

The distribution of spontaneous activity by BF is shown in Fig. 6A. The small dots show spontaneous rates of DCN neurons of response types III, IV-T, and IV from three previously reported data sets in unexposed animals (Nelken and Young, 1994; Davis and Young, 2000; Reiss and Young, 2005). The symbols show data from the present experiments, as defined in the legend. The spontaneous rates of the comparison data are somewhat heterogeneous in that the ranges of BFs and mean spontaneous rates differ among the three groups. To illustrate, of the 13 comparison neurons (dots) with spontaneous rates above 110/s, 11 came from early experiments in one of the comparison studies in which the animals were from a different supplier than we now use. Those neurons were otherwise typical of DCN response types.

There is a tendency for spontaneous rate to increase at higher BFs in Fig. 6A, in that the largest spontaneous rates are higher at higher BFs. The gray lines show smoothed estimates of the median (center line) and the 20% and 80% percentiles of the comparison spontaneous rates in 1/3 octave bins. When examined in this way, the median spontaneous rates of the comparison data do not change significantly with BF; the same result is obtained with mean values (for both, $r < 0.1$, NS). However, the interquartile range (difference between the upper and lower gray lines) shows the same increase as the maximum rates. These tendencies are similar in exposed and unexposed animals.

Fig. 6B shows a comparison of the spontaneous rates of exposed and unexposed animals. This figure plots the spontaneous rates from the exposed animals on a normalized scale in which 0 is the median rate in unexposed animals and $+1$ and -1 are the upper and lower quintile. Thus, the points in Fig. 6B are plotted as rate minus median unexposed rate, scaled to be a fraction of the range from the median to the 80th or 20th percentile. This method

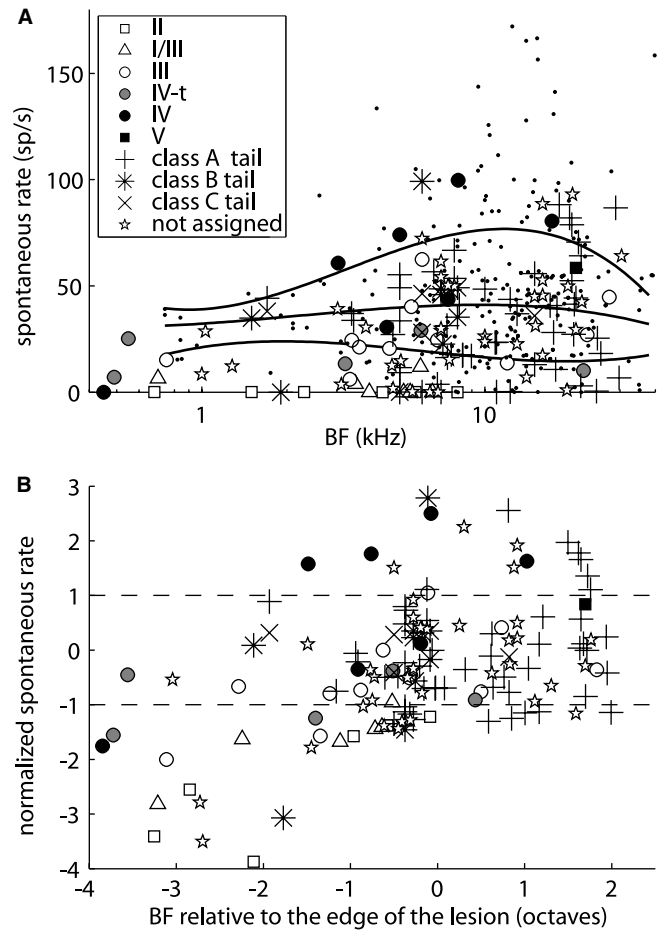


Fig. 6. (A) Spontaneous rate plotted versus BF for all neurons with BFs in the seven experiments. The symbols identify response map types and are defined in the legend. The dots show spontaneous rates of type III, IV-T, and IV neurons from three previous studies in non-exposed animals, as a comparison. The median rates and 20th and 80th percentiles were determined from the comparison group in non-overlapping 1/3 octave bins. The lines are best-fitting third-order polynomials (as rate versus $\log(\text{BF})$) fit to the medians and quintiles. (B) Spontaneous rates for the data from the seven experiments plotted versus BF, on a scale of octaves re the edge of the threshold shift. The rate scale is normalized to the smoothed medians and quintiles from A, such that the ordinate in B is $(\text{rate} - \text{median rate}) / (\text{quintile rate} - \text{median rate})$. The 20% line was used for rate $<$ median and the 80% line was used for rate $>$ median. The medians and quintile were computed from the polynomials shown in A. The horizontal dashed lines should contain 60% of the data in any group of neurons with a spontaneous rate distribution similar to the comparison data.

was adopted because the spontaneous rate distributions are not Gaussian and because the correspondence of response types between unexposed and exposed animals is not clear, making summary statistical comparisons dubious. The abscissa is BF relative to the edge of the lesion, to show the relationship of the hearing loss and the spontaneous rates.

If the exposed and unexposed populations have the same spontaneous-rate distributions, then about 20% of the data in Fig. 6B should be above the upper solid line and 20% below the lower solid line. Only about 12% (17/138) of the data from exposed animals are above the upper

line. Confining the analysis to the neurons with tail responses, 12.5% (8/64) are above the upper line and confining the analysis to unclassified neurons, 11% (4/36) are above the line. By contrast the number of tail and unclassified neurons with spontaneous rates below the 20% line are larger (19%, 12/64 and 25%, 9/36). Thus, there is no tendency for the any group of neurons with non-normal responses in exposed animals to have elevated spontaneous rates.

4. Discussion

4.1. Source of tail responses

The main result of this paper is that the distribution of excitatory and inhibitory areas that define neuronal response types in the decerebrate cat DCN is lost following acoustic trauma. Response type classification has long been a feature of the study of the functional properties of the cochlear nucleus (Pfeiffer, 1966; Evans and Nelson, 1973; Godfrey et al., 1975; Young and Brownell, 1976). The purpose of classification, of course is to describe the responses in a way that allows them to be associated with their anatomical generators and allows functional relationships, as between inhibitory interneurons and principal cells, to be established. This program has been successful in the cochlear nucleus, both in ventral and dorsal divisions (summarized by Rhode and Greenberg, 1992 and by Young and Oertel, 2003).

In the exposed animals studied here, the typical DCN response types were generally seen only in BF regions where thresholds were near normal (Fig. 4). Within the impaired regions, three groups of “non-normal” neurons were recorded (Table 1): (1) many neurons were unresponsive to sound at levels up to 100 dB; these neurons were often spontaneously active at rates somewhat below those of neurons that did respond to sound (median 16.25/s); (2) a second group of neurons responded to sound, but did so weakly or broadly and with low discharge rates that made it difficult to locate BF and also difficult to demarcate excitatory and inhibitory areas (e.g., Fig. 3); (3) a third group of neurons showed vigorous responses to sound and the characteristics described above as tail responses.

Tail responses were described qualitatively as broadly tuned and mostly excitatory response maps. It is apparent from Fig. 2 that this description, while clearly appropriate for some neurons (e.g., Figs. 2E, G, and H), is not quite right for others. For example, the neuron in Fig. 2F clearly has the tail characteristics if studied with single tones (dashed lines), albeit with a tail that develops only at relatively high sound levels. However, in the two-tone response map, the tail characteristics are interrupted by inhibition. The data in Fig. 4 quantify the excitatory bandwidths of tail responses. At both 10 and 40 dB re threshold, Q_s are low, usually less than 1, and are less than the comparison data from the auditory nerve and the DCN of unexposed animals. Thus, the qualitative notion of broad tuning based

on looking at response maps survives quantitative test in that tail neurons are more broadly tuned than normal, some much more so.

It is not possible to be certain about the anatomical sources of tail responses, although they probably include most DCN cell types. Tail responses were recorded at all depths below the surface, from those appropriate to the fusiform layer to the deep DCN. Based on recordings at BFs with near-normal thresholds (the left column of Table 1), our electrodes recorded from both principal-cell and interneuron response types, with about half the recordings from principal cell types (III, IV-T, IV, 14/26); this compares well with the 50–60% fraction of principal-cell response types typically reported in previous studies that used unbiased searching (right column of Table 1, Shofner and Young, 1985; Joris, 1998). Assuming that the relative numbers of principal-cell and non-principal cell types are the same in regions with elevated thresholds, we conclude that about half of the neurons with tail or non-classifiable responses were recorded from principal cells. The remainder would therefore come from vertical cells, which give type II responses in non-exposed animals, or type I/III neurons, whose anatomical sources are diverse and unknown, but probably include some principal cells (Ding et al., 1999; Spirou et al., 1999; Anderson and Young, 2004).

Complex action potentials of the type associated with cartwheel cells (Zhang and Oertel, 1993; Manis et al., 1994; Parham and Kim, 1995; Davis and Young, 1997) were noted rarely in the neurons studied here. Neurons with complex action potentials are, if anything, more prevalent in DCN slices cut from animals following acoustic trauma and they have non-zero spontaneous discharge rates (Chang et al., 2002). Thus, cartwheel cells should have been active in our preparations and should have presented recognizable spike patterns, even though we did not record from them.

4.2. Mechanisms of the tail response

In order to account for the broadened tuning exhibited by tail responses, it seems sufficient to consider as the cause the broadened tuning of auditory nerve fibers following acoustic trauma (Lieberman and Dodds, 1984). The dotted line in Fig. 5A allows a comparison of the tuning in tail responses (the data points) with the tuning of auditory nerve fibers following a similar acoustic trauma (Miller et al., 1997). In the auditory nerve data, the trauma was induced at 2 kHz and produced a 40–60 dB threshold shift. That threshold shift is somewhat less than the shifts produced here (60 dB or more) and is at a different BF. Nevertheless, it is inescapable that the tail portion of tail responses could simply reflect the tail-like shape of the tuning curve of the afferent auditory nerve fibers.

A second component of tail response maps is their relative lack of inhibition. Weakened inhibition is evident from the low prevalence of predominantly inhibited response types (IV-T and IV) at BFs with elevated thresholds as well

as in the tail response maps themselves. Weak inhibition is important to broad low-frequency responses because inhibition can limit the excitatory bandwidth of such responses (Wang et al., 1996). This is exemplified by the low-frequency side of the excitatory response at -20 dB in Fig. 2F, where the drop in rate in the single-tone response map appears to correspond to an inhibitory area in the two-tone response map. Thus, the low prevalence of inhibition in tail responses contributes to their broad excitatory responses.

A decrease in inhibitory strength is expected from previous studies of the effects of cochlear damage on inhibitory synapses in the cochlear nucleus and inferior colliculus, mentioned in the introduction. Many of the studies on this subject have used cochlear ablation or degeneration and have concluded that the strength of inhibition relative to excitation is decreased (e.g., Suneja et al., 1998b; Mossop et al., 2000; Potashner et al., 2000). More relevant to the present work are studies in which acoustic trauma was used. Following trauma, degeneration of axons and cells in the cochlear nucleus occurs (Bilak et al., 1997; Muly et al., 2002; Kim et al., 2004b; Muly et al., 2004). The initial loss includes both excitatory and inhibitory synapses, but there is a return of excitatory synapses and of glutamate release and uptake, without a corresponding increase in inhibitory synapses. These results are consistent with results in other auditory centers showing reduced immunostaining and receptor binding for molecules associated with inhibitory synapses accompanying aging (Willott et al., 1997) and following acoustic trauma (Abbott et al., 1999; Milbrandt et al., 2000).

In order to evaluate the changes in inhibition in DCN following trauma, it will be important to link responses to their anatomical generators. For example, vertical-cells are glycinergic, but are themselves under strong inhibitory control via GABAergic synapses (Davis and Young, 2000). Thus, the net effect on principal cells of weakening inhibitory synapses could be either excitatory or inhibitory, depending on which synapses are weakened more.

4.3. Implications of class B responses

The major diversity among tail responses is the difference between class A and class B, the difference being the excitatory area at high sound levels and high frequencies in the latter. Tuning curves similar to these two groups of response maps have been shown previously in DCN after acoustic trauma (Kaltenbach et al., 1992). In the present work, class B responses were almost exclusively found in the edge region, near the lower frequency boundary of the threshold shift (Fig. 4). These response maps seem to require two sources of excitatory inputs from the auditory nerve. First, there must be an input from fibers with BFs near the edge which can produce the low-frequency part of the class B response map. However, the tuning of such fibers should be strictly low-pass, and therefore it is unlikely that this input can account for the high frequency por-

tion of class B response maps. Instead, those seem to require a second input from fibers with high BFs, BFs that are within the region of substantial threshold elevation and therefore produce a weak, poorly tuned response at high frequencies.

This model seems to require plasticity in reorganizing DCN circuits after acoustic trauma. DCN neurons are relatively well tuned in unexposed animals and do not show evidence of multiple excitatory inputs from fibers with BFs that differ by an octave or more, as seems to be required for class B responses. Thus, we propose that a part of the regrowth of synaptic connections demonstrated in the DCN (Kim et al., 2004b) involves formation of new connections to DCN neurons from fibers with BFs relatively remote from the neuron's own BF; most likely this would be low-BF fibers making contact with formerly higher-BF DCN neurons. Previous studies of the tonotopic organization of the DCN following cochlear damage have not found evidence for plasticity of this type and have specifically ruled it out (Kaltenbach et al., 1992; Rajan and Irvine, 1998). The argument used in those studies is based on the distribution of thresholds at BF and does not apply to responses like the class B response maps. Such response maps would probably have been analyzed only for their BF responses in the low frequency part of the response map by Rajan and Irvine, who did not comment on the shapes of response maps away from BF.

4.4. Spontaneous discharge rate

The generators of spontaneous rate in the DCN are not well understood, but must include both auditory nerve fibers and parallel fibers (Hirsch and Oertel, 1988). Following acoustic trauma, both sources of spontaneous activity could contribute to DCN neurons' spontaneous spiking. The average spontaneous rates should be lower in auditory nerve fibers following acoustic trauma (Lieberman and Kiang, 1978), but the spontaneous rate in parallel fibers is not known. The ultimate spontaneous rate of DCN cells must depend on both the altered spontaneous activity in their inputs and any changes in synaptic strength that occur.

Studies of the DCN aimed at evaluating its possible role in tinnitus have reported elevated spontaneous discharge rate following acoustic trauma similar to that used here. Most of the physiological data has been from multi-unit recordings in the superficial layers of the DCN, in which the overall spiking rate of unspecified populations of neurons was measured (Kaltenbach and McCaslin, 1996; Kaltenbach et al., 1998, 2000, 2002, 2004). The elevation in spontaneous rate was significant, as much as a factor of 2, and developed over several days' time after the acoustic trauma. The extent of the elevation was proportional to the threshold shift, to the extent of outer hair cell loss, and is correlated with a behavioral test for tinnitus in the same animals. Elevated spontaneous rate has also been reported in single neurons, presumed principal cells in the DCN,

after a relatively mild acoustic trauma that produced 20–30 dB of temporary but no permanent threshold shift (Brozoski et al., 2002). In contrast to these data, Fig. 6 shows that we saw no evidence for elevated spontaneous rates in the preparations studied here. Chang and colleagues (2002) also did not report elevated spontaneous rate in recordings in slice preparations of the DCN after acoustic trauma.

It is difficult to hypothesize why some studies have reported a relationship between acoustic trauma and spontaneous rate whereas others have not. One uncertainty is that there is insufficient knowledge about the neural elements whose spontaneous rates are being recorded, especially in the multi-unit studies. Heterogeneous populations, like those in the DCN, may show complex changes in properties such as spontaneous rate in response to acoustic trauma. For example, if inhibitory inputs to type II neurons, which probably maintain their spontaneous rates near zero (Spirou et al., 1999), weaken following acoustic trauma then the spontaneous rates of type II neurons could increase. This could cause the spontaneous rates of type IV neurons to decrease or increase, depending on the change in the strength of the inhibitory connection from type II to type IV neurons. Independent of such complex changes, the variation in the range of spontaneous rates with BF shown in Fig. 6A means that the BFs of the populations that are compared must be controlled. Further work is needed to resolve these questions.

5. Conclusions

There are some important reservations to the interpretation of the data presented here. Most important, it is necessary to establish which DCN neurons are being recorded. Given the differences in the synaptic circuitry associated with principal cells and interneurons, the interpretation of modified responses will depend on the cellular sources of the responses, whether they are principal cells or inhibitory interneurons, for example. Second, more recordings from cartwheel cells are likely to be interesting because they are an important inhibitory interneuron in DCN and are a potential source of the elevated multiunit spontaneous activity reported in the superficial DCN. Finally, the status of the granule-cell associated circuitry in the superficial DCN may be important to an understanding of the post-trauma state of the DCN, when auditory inputs are modified and non-auditory inputs, such as somatosensory ones, are not. For example, a shift in the predominance of auditory versus non-auditory sources of spontaneous firing could be relevant to the phenomenon of tinnitus.

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