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RESEARCH ARTICLE

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Effects of contralateral sound stimulation on unit activity of ventral cochlear nucleus neurons

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Abstract The cochlear nucleus (CN) commissural connection represents the first opportunity for convergence of binaural information in the auditory brainstem. All major neuron types in the ventral CN (VCN) are innervated by a diverse population of cells in the contralateral VCN. This study examined the effect of contralateral sound stimulation on the spontaneous rates (SRs) of neurons in the VCN. Unit activity was recorded with silicon-substrate multichannel probes which allowed recordings from up to 16 sites simultaneously. On average, 30% of units showed short-latency (often only 2 ms greater than the latencies of ipsilateral sound-evoked responses) inhibition of SR by wideband contralateral noise bursts. Fewer units (4.5%) were excited by contralateral noise at sound levels low enough to exclude excitation by acoustic crossover. Both regular and irregular units in the anterior VCN (AVCN) and posterior VCN (PVCN) were inhibited by contralateral sound. Decrements in SR followed a monotonic function with increases in contralateral sound level, except where responses could be attributed to acoustic crossover. Restricting the contralateral noise bandwidth resulted in a frequency-specific inhibition, dominated by frequencies at and below the ipsilateral BF of the unit, consistent with anatomical findings of the tonotopic organization of the CN commissural pathway. The latencies of these effects are compatible with mono, di and tri-synaptic connections reflecting CN commissural pathway effects.

Keywords Auditory · Auditory brainstem · Single unit physiology · Neural pathways · Commissural pathway

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Introduction

Connections between the cochlear nuclei (CN) were originally suggested by the responses of dorsal cochlear nucleus (DCN) neurons to acoustic stimulation of the contralateral ear (Klinke et al. 1969; Mast 1973; Young and Brownell 1976). The latencies of these inhibitory responses ranged widely, some in the range of hundreds of milliseconds, while others were compatible with only one synaptic delay (Pfalz 1962; Pirsig and Pfalz 1967; Pirsig et al. 1968; Hochfeld 1973). Subsequent anatomical studies have demonstrated the existence of a CN commissural connection that is comprised primarily of large, type II, glycinergic multipolar cells, but also small, multipolar cells and possibly bushy cells (Cant and Gaston 1982; Wenthold et al. 1987; Shore et al. 1992; Schofield and Cant 1996b; Shore and Moore 1998; Alibardi 2000).

Only two physiological studies have focused on the ventral cochlear nucleus (VCN) as a binaural nucleus: Electrical stimulation of contralateral VIIIth nerve in an in vitro preparation (Babalian et al. 1999, 2002) produced IPSPs in up to 70% of principal cells in the VCN. These effects were blocked by strychnine (Babalian et al. 2002) supporting the anatomical evidence of a primarily glycinergic CN commissural projection. Most latencies were suggestive of mono-, di- and tri-synaptic connections. All principal cell types were affected.

Although CN commissural neurons project to all divisions of the contralateral cochlear nucleus (Shore et al. 1992; Schofield 2001), in vivo studies have focused only on responses in the DCN. This study examined the effect of contralateral sound stimulation on the spontaneous rates (SRs) of neurons in the VCN.

Materials and methods

Experiments were performed on healthy female, adult pigmented guinea pigs (NIH outbred strain) with normal Preyer's reflexes, weighing 250–350 g. All procedures were performed in accordance with the NIH guidelines for the care and use of laboratory animals

(NIH publication No. 80–23), and guidelines provided by the University of Michigan (UCUCA).

Surgical preparation

Guinea pigs were anesthetised with ketamine (120 mg/kg) and xylazine (16 mg/kg) and held in a stereotaxic device (Kopf) with hollow ear bars for the delivery of sounds. Rectal temperature was monitored and maintained at 38±0.5°C with a thermostatically controlled heating pad. For cochlear destruction, the round window membrane was exposed by a lateral surgical approach. The bone overlying the cerebellum and posterior occipital cortex was removed to allow placement of a recording electrode into the VCN, after aspirating a small amount of cerebellum to visualize the surface of DCN.

Histology

To mark electrode tracks, the recording and stimulating electrodes were dipped in di-I (10%) or Fluorgold (2%) before being inserted into the brain. The brain was subsequently cryosectioned at 40–60 μm, and examined under epifluorescence for evidence of recording electrode locations.

Recordings

All unit recordings were made in a sound-attenuating double-walled booth. Sixteen-channel electrodes fabricated by the University of Michigan Electrical Engineering and Computer Science Department were used for recording responses at a number of sites, enabling us to record from many units simultaneously. The 16-channel multi-electrode array was connected via a 16-channel amplifier to a Plexon data acquisition system which provided filtering (bandwidth 300–10 k), programmable gain, and analogue-to digital (A/D) conversion. A/D conversion was performed by simultaneously sampling 12-bit converters at 40 kHz per channel. Signals were then routed to multiple digital signal processor boards for computer-controlled spike waveform capture and sorting. The processors were controlled from a Pentium III 500 MHz, PC using a dual monitor display. Units were sorted using Plexon software both on and off line, depending on the experiment. It was possible to sort waveforms from more than one unit per channel, thus increasing our yield of individually isolated units. In some cases it was not possible to sort spikes belonging to a single unit. In these cases, multi-unit data is presented.

In order to identify unit types, digitized acoustic stimuli (20, 50 or 100 ms, 1.5 ms rise-fall times) presented at the unit's best frequency (BF), were delivered to the ear via calibrated speakers coupled to hollow ear bars. A Tucker Davis System II was used for signal generation and attenuation. Units were classified on the basis of their spontaneous rates (SR), coefficients of variation (CV), and poststimulus time (PST) patterns (Godfrey et al. 1975; Rhode and Smith 1986a; Young 1998a, 1998b).

Controls

To assess levels at which acoustic crossover might occur, we mechanically destroyed the contralateral cochlea by inserting a probe through the round window. We then assessed levels at which we saw contralateral excitation in the ipsilateral VCN. Any excitation observed under these conditions must necessarily be due to crossover, since there would be no commissural neural pathway for activation of CN cells by the contralateral sound. After cochlear destruction, all inhibition disappeared and the number of units in which excitation occurred increased, suggesting that crossover excitation is normally masked to some extent by the inhibition. The level at which excitation occurred was 70 dB SPL. Thus, any excitation elicited by contralateral sounds with levels above 70 dB SPL is considered due to acoustic crossover. It is possible, in other animals, that crossover could occur at lower sound levels, as reported by others (Gibson 1982). In this study we have only considered excitatory responses in cases where crossover can be ruled out.

Results

Data were obtained from 40 healthy, pigmented guinea pigs. Units were included in the study if unit thresholds to toneburst stimulation were within normal limits (Shore 1995) and histological reconstructions revealed that the electrode was located in VCN. Results are based on responses from 800 units. Approximately 70% of these units were multi unit recordings and the other 30% were sortable into single units. Only those units which were sorted into single units were classified according to unit type. Population data utilized both single and multiunit

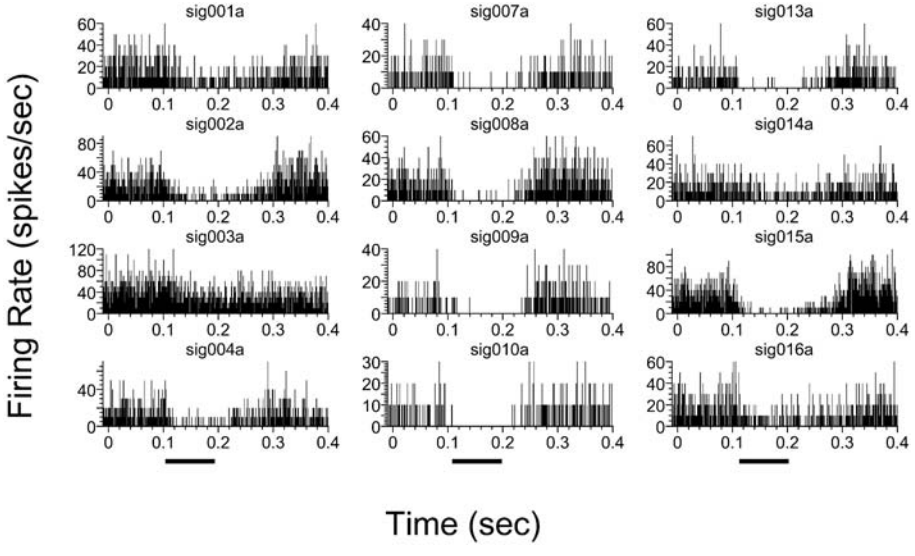

Fig. 1 Inhibition of spontaneous rate: poststimulus time histograms (PSTHs) of responses from 12 units on a Michigan probe to a 70-dB SPL 100-ms contralateral BBN (signal onset —100 ms). Fifty presentations, bin width 1 ms. Signal onsets and durations are indicated by *bar below graph*

recordings, which are not distinguished unless unit typing was the object. This study focused on the effects of contralateral sound stimulation on the spontaneous activity of VCN units. Ipsilateral BF toneburst stimulation was used only to type the units that responded to contralateral sound stimulation.

Contralateral noise stimulation elicits primarily inhibitory responses

Contralateral broadband noise (BBN) stimulation elicited primarily inhibitory responses from VCN neurons. An example of these responses for 12 units (from a 16-channel probe) during one penetration into VCN is shown in Fig. 1. For this penetration, inhibition was observed in almost every unit. On average, across animals, 30% of units showed inhibition of spontaneous rate. The rise to maximum inhibition, and the duration of inhibition varied among units and could be a function of unit type (see below). Firing rate decreased monotonically below spontaneous rate as a function of contralateral noise level (Fig. 2A), sometimes ceasing completely at high levels (Fig. 1). The latency of inhibition by contralateral noise ranged from 5 to 9 ms, as compared with a range of 3 to 5 ms for ipsilateral stimulation (Fig. 2B).

Thresholds for contralateral inhibition, determined from rate-level functions as a 10% decrease below spontaneous rate, showed considerable variability, ranging from as low as 10 dB SPL to as high as 75 dB SPL (Fig. 3A). No relationship was found between threshold for contralateral inhibition and unit BF or electrode depth. A comparison of thresholds for excitation by ipsilateral BBN with those for inhibition by contralateral BBN is shown in Fig. 3B. In all cases where normal thresholds were found for ipsilateral BBN, the threshold for contralateral inhibition was higher. The range of differences in these thresholds extends from a few dB to as much as 59 dB (Fig. 3B).

Contralateral inhibition is frequency specific

The frequency specificity of contralateral inhibition was assessed using narrow band noise bursts. Presentation of 1/3 octave noise bursts resulted in the greatest decrement of firing rate when the center frequency of the noise burst was below the BF of the unit (Fig. 4). In the unit shown in Fig. 4A, the rate-level functions for frequencies below BF show a continuous decrement in rate as the level of the narrow band noise burst is raised. At BF, however, the rate decreases at first and then increases sharply at high levels, suggesting excitation, perhaps due to acoustic crossover. In contrast, for frequencies below BF the rate continues to decrease as sound level increases. The tendency for inhibitory effects to peak below unit BF was evident for units with low and high BFs (Fig. 4B). In all units shown in this figure, response rate decrements to the noise burst was maximum at frequencies below the units' BFs.

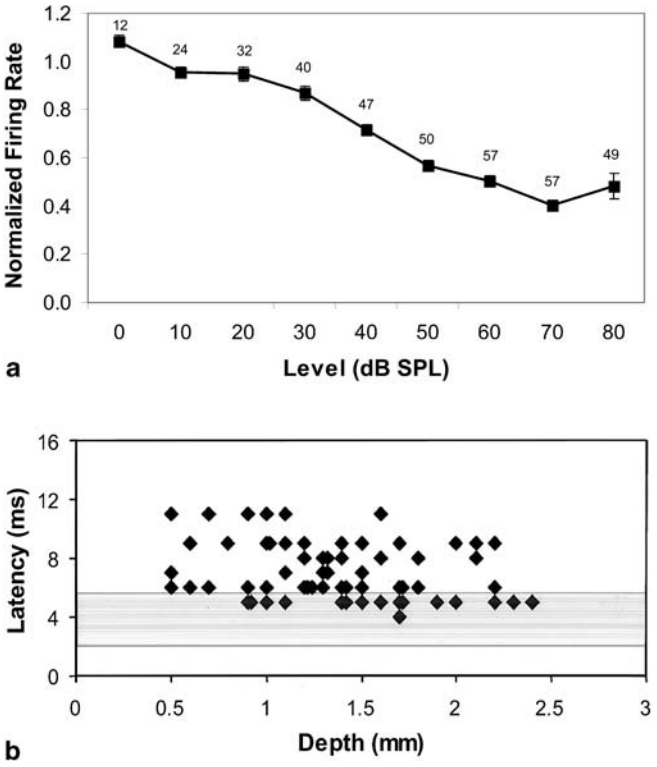

Fig. 2. a Mean rate-level functions computed from PSTHs in response to 100-ms contralateral BBN bursts. Firing rate is normalized over the spontaneous rate for a unit. *Numbers above the graph* indicate the number of units across five animals used to calculate each point. **b** Latencies of inhibition by contralateral sound for 62 units. Latency was estimated from visual inspection of PSTHs obtained in response to 100 presentations of a 70-dB SPL, 100-ms, contralateral BBN noise burst. The *shaded area* indicates the latency range of these units in response to ipsilateral toneburst stimulation with 50-ms, BF tonebursts presented at 30 dB SL

Contralateral inhibition is observed among different VCN unit types

Unit types showing contralateral sound inhibition included: primary-like (PL), primary-like with notch (PL-N), transient chopper (CT), onset chopper (OnC) and onset L (OnL). Figure 5 shows poststimulus time histograms of responses from three of these cell types in response to ipsilateral and contralateral sound stimulation. Units showed varying recoveries from inhibition with contralateral stimulation. The PL unit in Fig. 5A showed slower recovery from inhibition than either of the other units (Fig. 5B, C).

Contralateral sound stimulation elicits excitatory responses

Excitation was also elicited in response to contralateral sound stimulation. An example is shown in Fig. 6. The top unit has an excitatory response to a 60 dB SPL, contralateral BBN. For comparison, a unit showing inhibition in response to the same tone is shown in the lower panel. This could not have been due to crossover,

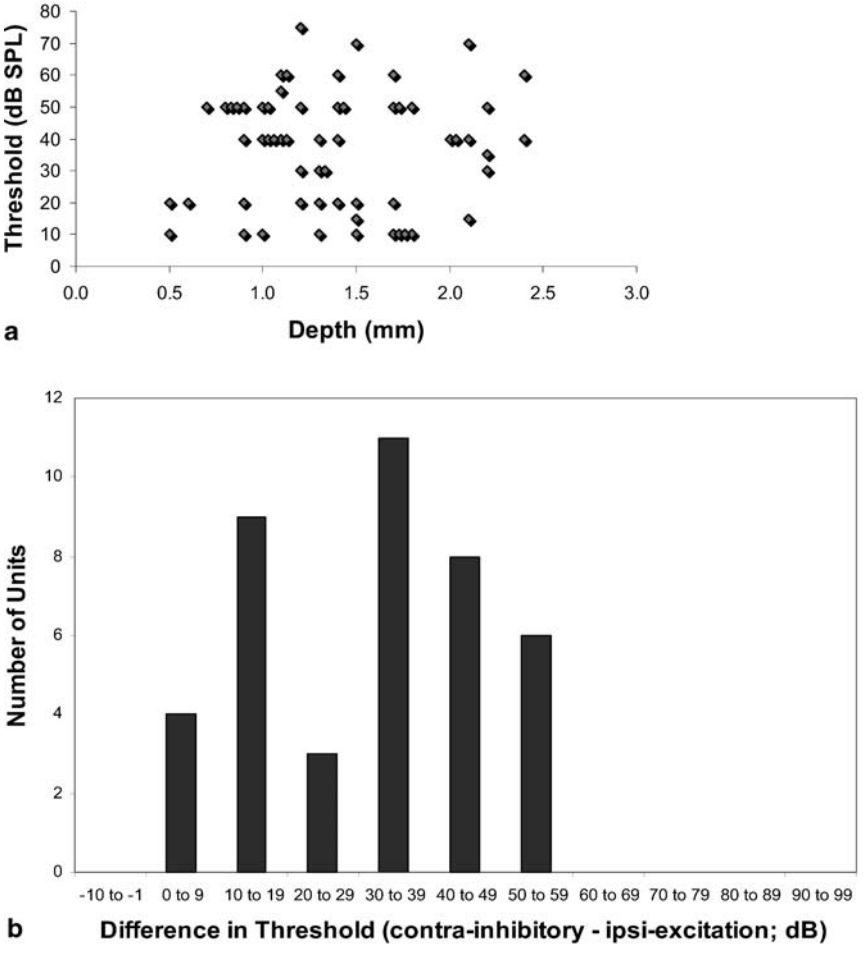

Fig. 3. a Thresholds for inhibition by contralateral BBN shown as a function of electrode depth in VCN (mm below surface of CN). Thresholds were defined as a 10% decrease in firing rate below spontaneous. **b** Histogram of threshold differences between ipsilateral excitation and contralateral inhibition in response to BBN (i.e. contralateral inhibition minus ipsilateral excitation threshold). Absolute thresholds for ipsilateral excitation range from 10 to 40 dB SPL for the units shown in this figure

since there was not response to a 70 dB SPL ipsilateral BBN. Figure 7 summarizes the thresholds of units for a number of penetrations to ipsilateral and contralateral BBN stimulation. Note that almost all cases of contralateral excitation (47/224 or 21%) have thresholds at levels well above the ipsilateral thresholds (see right side of Fig. 7), and are above 70 dB SPL. Excitation cannot be distinguished from acoustic crossover at these levels, as demonstrated in our control experiment in which the contralateral cochlea was destroyed (see METHODS). The remainder (10/224 units or 4.5%) of excitatory responses occur at levels below the thesholds for ipsilateral stimulation (see left side of Fig. 7) and therefore cannot be due to acoustic crossover. These cases of "contralateral-synaptic" excitation are observed only in high-threshold units (i.e. units with ipsilateral thresholds above 60 dB SPL) and have latencies that range from 5 to 14 ms, overlapping the latency range for contralateral inhibition.

Discussion

This study has demonstrated that contralateral sound stimulation produces inhibitory responses in approximately 30%, and excitatory responses in a much smaller percentage (4.5% in this sample) of VCN neurons. The relatively short latencies of these responses compared to ipsilateral latencies, suggest that they may be mediated by fibers of the CN commissural connection (Shore et al. 1992; Schofield and Cant 1996b).

Inhibitory responses

The results of the present study demonstrate less contralateral inhibition of CN neurons than previously shown. In DCN, most units appear to be inhibited by contralateral sound (Joris and Smith 1998). The lower percentages of inhibition of VCN units (30% observed in the present study compared to those of Babalian et al. (1999, 2002) could be due to differences in the effects of electrical and acoustic stimulation, the latter perhaps producing an underestimate of inhibition because of excitation caused by acoustic crossover. Additionally, the IPSPs that Babalian et al. were recording may not always have resulted in a reduction in action potentials.

Contralateral inhibition of VCN units in the present study, although tuned, showed stronger inhibition for noise bands centered below ipsilateral BF. Multipolar type II cells, which comprise much of the commissural projection (Schofield and Cant 1996b), may provide the contralateral short-latency inhibition that was observed in this study and

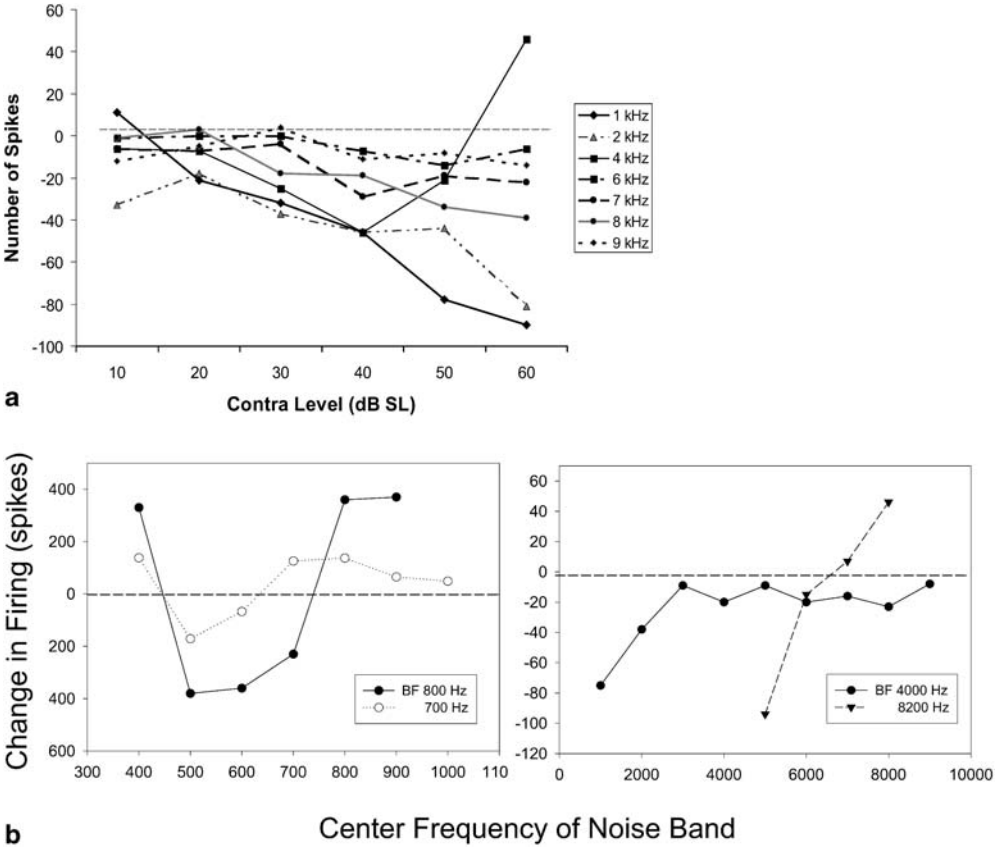

Fig. 4a, b Contralateral inhibition is frequency specific: **a** Firing rate of a PL unit (CF 4 kHz) in VCN to 1/3 octave noise bands of different center frequencies and sound levels presented to the contralateral ear. Firing rate is expressed relative to spontaneous rate (*dashed line*). Responses to 200 stimulus presentations are shown. **b** Response rates for 4 VCN regular (i.e. most likely PL) units after 1/3 octave noise bands of different frequencies were presented to the contralateral ear (60 dB SPL). Responses for two low BF units are shown *on the left*; high BF units *on the right*. Firing rate is expressed relative to spontaneous rate (shown at zero by *dashed line*), as a function of the center frequency of the noise band. Maximum decrement in firing rate always occurred when the center frequency of the contralateral noise band was below the BF of the unit

also demonstrated in DCN neurons (Joris and Smith 1998). Multipolar type II cells are innervated by numerous VIIIth nerve fibers with different BFs. Thus, they are broadly tuned. They show OnC responses to acoustic stimulation, and are capable of transmitting rapid, temporally precise signals (Smith and Rhode 1989; Ostapoff et al. 1997). They are believed to be inhibitory (Ostapoff et al. 1997), and considered to be a possible source of the ipsilateral short-latency inhibitory responses observed in bushy, stellate and pauser-buildup cells (Lorente de No 1933; Wu and Oertel 1984; Wickesberg and Oertel 1990; Saint Marie et al. 1991; Shore et al. 1991; Young 1998a). The primarily inhibitory nature of the responses of VCN neurons to contralateral sound in the present study is consistent with the primarily glycinergic composition of the CN commissural projection (Wenthold et al. 1986; Babalian et al. 2002). The dominance of contralateral inhibition below the ipsilateral BF could be due to the wide response area of OnC cells. However, the asymmetrical nature of auditory nerve tuning might itself produce this response to band limited noise. In addition, the wider tuning curves observed for low BF units could explain the greater amount of inhibition demonstrated in low BF units as compared with high BF units (see Fig. 4B). The wider low BF tuning curves would more easily accommodate the full extent of the 1/3 octave noise bursts used in this study. OnC units fire mostly at the beginning of a BF pure tone. Noise stimuli would be expected to provide more sustained responses in OnC cells (Rhode and Smith 1986b; Winter and Palmer 1995). However, this cannot explain the slow recovery of some units from a putatively glycinergic, i.e. fast inhibition. This could be produced by synapses in which more than one neurotransmitter is co-contained, introducing longer-lasting inhibition (Altschuler et al. 1993). The possibility of inputs from a more diverse population of cells, including those descending from the superior olivary complex and inferior colliculus (Spangler et al. 1987a) cannot be excluded. Units of all types (primarylike, choppers, and onset) in all central VCN regions could be inhibited by contralateral sound. This heterogeneous distribution is consistent with anatomical findings demonstrating that CN commissural fibers innervate all regions of the CN (Shore et al. 1992; Schofield and Cant 1996b). Preliminary findings suggest that units were inhibited over a different time course depending on their unit type (see Fig. 5). More units need to be studied in order to substantiate this suggestion.

Contralateral sound stimulation has been shown to suppress VIIIth nerve activity (Liberman and Brown 1986; Gummer et al. 1988; Brown 1989). These suppressive effects, present in almost all units, have latencies close to 200 ms, durations longer than 200 ms, and are maximal if the contralateral tone is at BF. Cutting the olivocochlear bundle (OCB) removes the suppression (Warren and Liberman 1989a, 1989b) which has thus been assumed to be due to OCB innervation of the outer hair cell system. Some OCB neurons themselves have a long-latency response to sound (Liberman and Brown 1986; Gummer et al. 1988; Brown 1989), while others have a short-

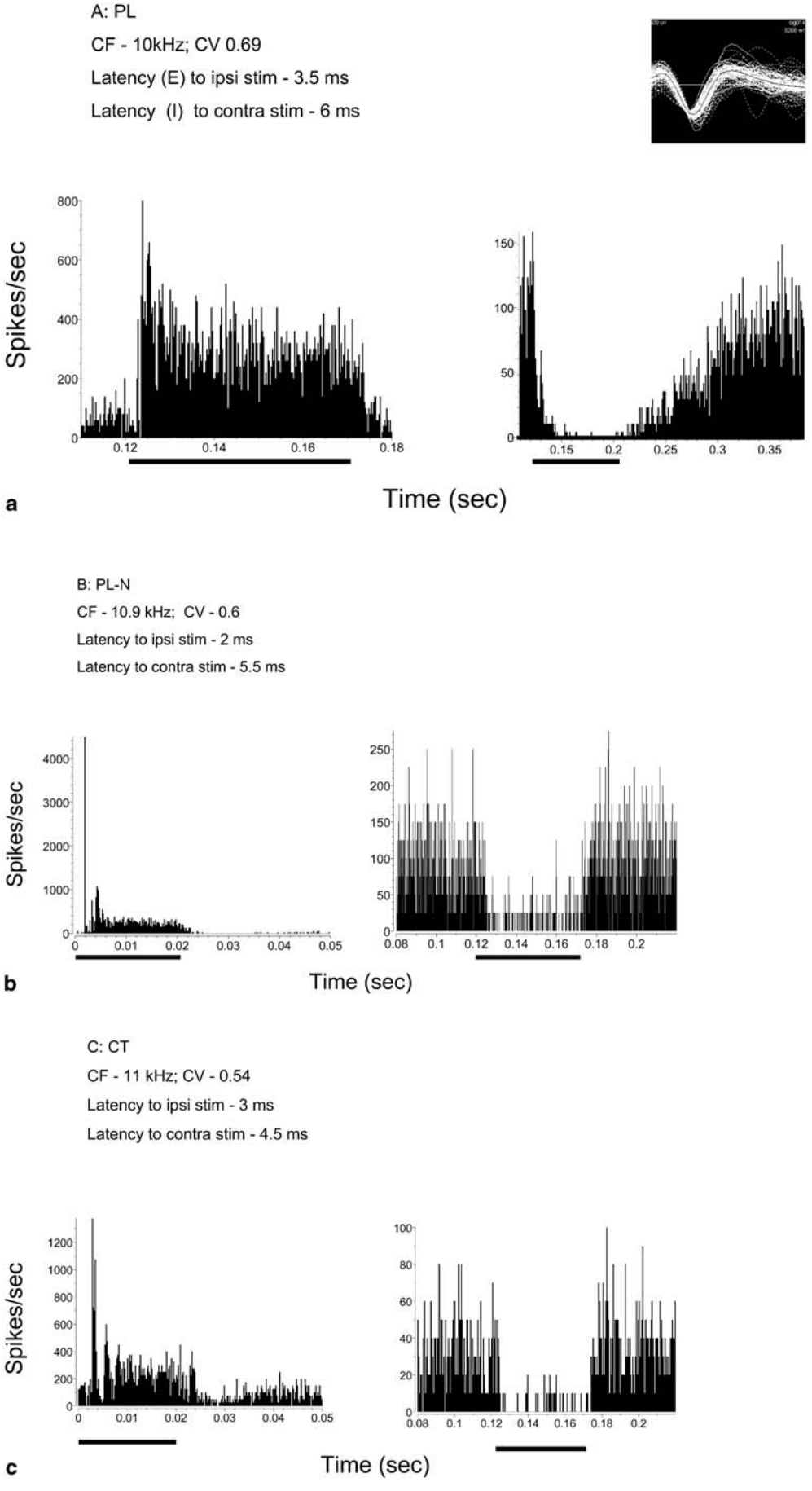

Fig. 5a–c Responses of different unit types to 200 presentations of ipsilateral (20 or 50 ms BF toneburst, 30 dB SL) and contralateral sound (100 ms BBN burst, 70 dB SPL) stimulation: **a** PL; **b** PL-N; **c** CT. PSTHs are shown to ipsilateral (*left panel*) and contralateral stimulation (*right panel*). Signal onsets and durations are indicated by *bar below graph*. Bin counts are divided by the number of reference events*bin width to yield instantaneous firing rate in each PSTH. Bin width 0.25 ms. *Inset in* **A** is an example of a sorted unit waveform

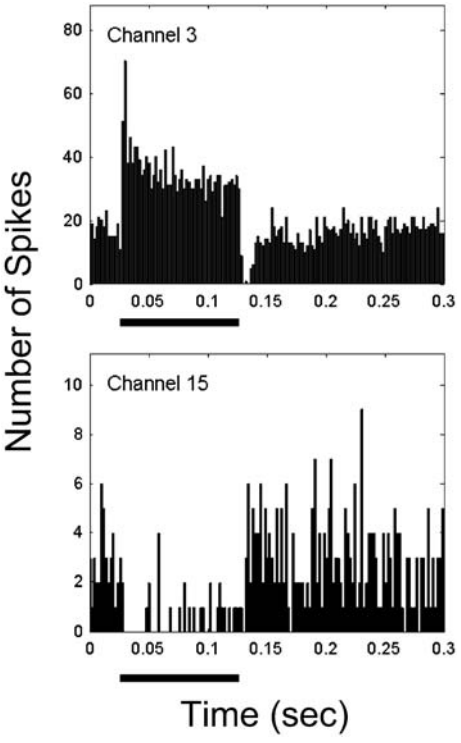

Fig. 6 PST histograms of responses of 2 units on a Michigan Probe. Responses to 50 presentations of a 100-ms contralateral BBN are shown at 60 dB SPL. The threshold for ipsilateral excitation for unit 3 is above 70 dB SPL. The threshold for ipsilateral excitation on unit 15 is 20 dB SPL. Signal onsets and durations are indicated by *bar below graph*. Bin width: 2 ms

latency response (Brown et al. 2002). In contrast, only about 30% of VCN units in the present study are inhibited by contralateral sound, the effects are orders of magnitude faster, durations are often equal to the stimulus duration, and effective frequencies are at and below BF. Thus, it is unlikely that the OCB projection to the cochlea contributes to the results described in this study. However, *collaterals* of the OCB send a projection to the CN which has been postulated to be excitatory (Benson and Brown 1990; Brown et al. 1991; Brown and Benson 1992; Brown 1993). Additionally, stimulation of OCB axons results in both excitation and inhibition of CN neurons (Robertson et al. 2002). It is therefore possible that this pathway could be responsible for some of the contralateral inhibition and excitation (see below) described in this study, although, in most cases, the latencies observed here are shorter than those expected with OCB stimulation.

Excitatory responses

A small percentage (4.5%)of units showed excitation after contralateral stimulation which could not be attributed to acoustic crossover. These responses are consistent with findings that the CN commissural pathway is additionally comprised of smaller multipolar type I and perhaps globular bushy cells (Spangler et al. 1987b; Shore et al. 1992; Schofield and Cant 1996b; Alibardi 1998). The principal projections of multipolar type I neurons are excitatory to the contralateral inferior colliculus. Globular bushy cells send an excitatory connection to the MNTB. However, these cells also contribute minor components to the CN commissural projection. They may therefore be responsible for excitatory responses to contralateral sound stimulation observed in this study, and in neurons of the deep DCN (Mast 1973; Adams 1979a, 1979b). Alternatively, the existence of neurons with latencies at the upper end of the latency range of these excitatory responses suggests that other descending pathways may be involved (Shore et al. 1991; Schofield and Cant 1992; Schofield 2001). Another possibility is that the excitation in VCN

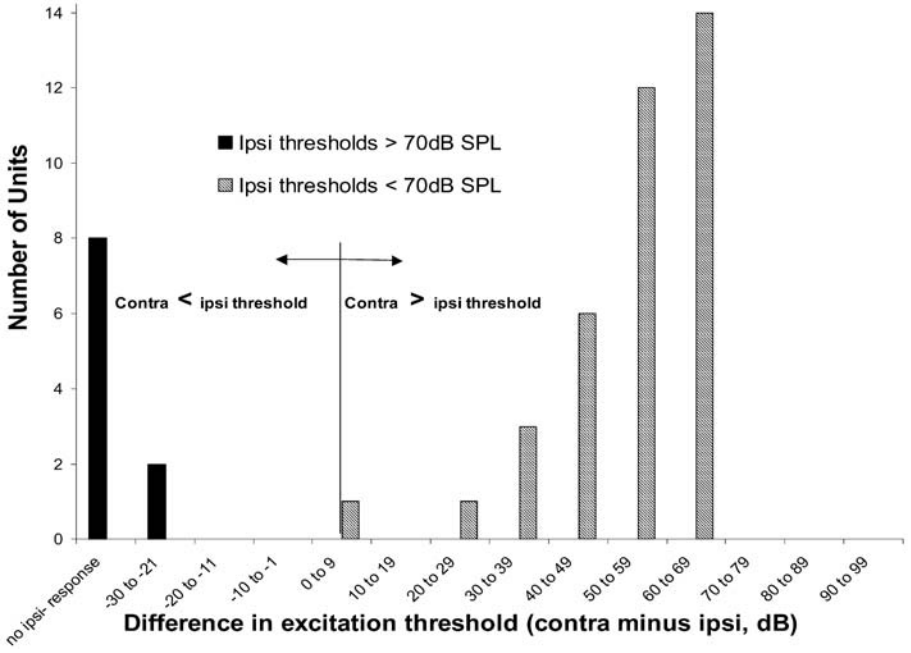

Fig. 7 Histogram of differences in excitatory threshold in response to contralateral and ipsilateral BBN. Absolute thresholds for ipsilateral excitation range from 20 to 80 dB SPL for the units shown in this figure

cells could be caused by release from inhibition by DCN vertical cells by type II multipolar cells in the contralateral CN (Palmer et al. 2002). Palmer et al have shown that type II multipolar cells in the contralateral CN, which have characteristic OnC responses to tonebursts, project to vertical cells in the DCN. Since vertical cells are inhibitory to VCN cells (Wickesberg 1996), their inhibition could result in a net excitation of the VCN cell receiving vertical cell innervation.

VCN units in which excitation was elicited by contralateral sound in the present study all had high thresholds to ipsilateral sound stimulation. This is in contrast to those units in deep DCN that also responded with excitation to contralateral stimuli (Mast 1973). Those units had normal thresholds (Mast 1973). High-threshold (low spontaneous rate) units are concentrated in distinct regions of the cochlear nucleus (Liberman 1991, 1993; Kawase and Liberman 1992), particularly in or near the small cell regions. These regions have been associated with innervation by Type II VIIIth nerve fibers, olivocochlear neurons and fibers of the trigeminal nerve (Brown et al. 1988a, 1988b; Benson and Brown 1990; Shore et al. 2000; Ye et al. 2000). More studies are needed to determine the significance of these particular cells being excited by contralateral sound, and their underlying circuitry.

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