



The Effect of Sound Direction on Frequency Tuning in Mouse Inferior Collicular Neurons

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Abstract

This study examined the effect of sound direction on frequency tuning of inferior collicular (IC) neurons of mice under free field stimulation conditions. Fewer than 20% of IC neurons studied were spontaneously active. Discharge patterns can be described as phasic on responders, phasic on-off responders, off responders, choppers and tonic responders. The frequency tuning curves (FTCs) of IC neurons can be described as narrow, intermediate or broad. Although sound direction typically had little effect on most best frequencies (BFs), sharpness of FTCs increased as sound direction changed from contralateral angles to ipsilateral angles. Sound delivered from the upper and lower portions of the frontal auditory space also appeared to produce sharper frequency tuning than from the front. Possible mechanisms underlying this direction dependent frequency tuning are discussed.

Key Words: frequency tuning, inferior colliculus, mouse, Q_n value

Introduction

It is perhaps due to its relatively short life span and easy accessibility that the mouse auditory system has been a research subject in many laboratories resulting in more than 700 articles in the past 25 years (15). In particular, it has been a widely used model for studying the development of hearing (7) and age-related hearing loss, or presbycusis (9, 15, 31). On the other hand, it is surprising to note that very few studies have been devoted to studying the effect of sound direction on auditory responses in spite of the fact that nocturnal animals like mice must rely on accurate analysis of sound source for prey capture, predator avoidance, communication, social interactions and reproduction (8). Indeed, it has been suggested that the evolution of complex songs and frequency analysis may have arisen to improve localization acuity in three dimensional space (21).

Because frequency tuning is one of the most important auditory response properties underlying an animal's ability in frequency analysis and discrimination, we have studied the effect of sound direction on frequency tuning properties of inferior collicular (IC) neurons. We report here that the sharpness of frequency tuning of most IC neurons is

sharper for sounds delivered from ipsilateral than from contralateral angles. They also have sharper frequency tuning for sounds delivered from the upper and lower portions of the frontal auditory space than from the front.

Materials and Methods

Each of 41 CF-1 mice, *Mus musculus*, (age: 3-12 months, b. w: 28-40 g) was anesthetized with Acepromazine (20 mg/kg, i.p.) followed by sodium pentobarbital (Nembutal, 70 mg/kg, i.p.) for surgery. The flat head of a 1.8 cm nail was first attached to the expose skull with acrylic glue and dental cement. A circular trepanation was then made in an area overlaying the IC for insertion of 3M KCl glass electrodes (impedance: 3-5 M Ω) to record neural responses. A local anesthetic (Lidocaine) was applied to the open wound area. The mouse was strapped to an aluminum plate and placed inside a sound-proof chamber (temperature 28°-30°C). The mouse's head was immobilized and oriented with its eye-snout line pointed toward 0° in azimuth and 0° in elevation of the frontal auditory space. Additional doses (10 mg/kg) of Nembutal were administered during later phases of recording when necessary.

The electronic instruments used to generate acoustic stimuli were the same as those used in a previous study (20). Briefly, continuous sine waves from an oscillator (KH model 1200) were formed into tone pulses (50 ms, 5 ms rise-decay times, at 2 pps) by a homemade tone burst generator (electronic switch) driven by a stimulator (Grass S88). The tone pulses were then amplified after passing through a decade attenuator (HP 350D) before they were fed to a small condenser loudspeaker (AKG model CK 50, 1.5 cm diameter, 1.2 g) that was placed 24 cm away from the mouse and 30° contralateral to the recording site. The loudspeaker was calibrated with a Brüel and Kjaer 1/4 inch microphone (4135) placed at the mouse's ear. The output was expressed in dB SPL referred to 20 μ Pa root mean square. The loudspeaker could be remotely placed at any point between $\pm 90^\circ$ in azimuth and $\pm 60^\circ$ elevation within the frontal auditory space by means of two servo motors.

When a neuron was isolated, stimulus intensity and frequency were adjusted to determine the best frequency (BF) and minimum threshold (MT). At the MT, the neuron, on average, responded with 50% probability to BF pulses. The neuron's frequency tuning curve (FTC) was then measured by determining the threshold of each responsive frequency. To determine the effect of sound direction on frequency tuning, FTCs were measured at five azimuthal ($\pm 70^\circ$, $\pm 30^\circ$, 0°) angles along the 0° elevation and at five elevational angles ($\pm 50^\circ$, $\pm 30^\circ$, 0°) along the 30° contralateral plane. The sharpness of a FTC was expressed by Q_n (Q_{10} , Q_{30} , Q_{50}) values which were obtained by dividing the BF by the bandwidth at 10, 30 and 50 dB above the neuron's MT. The effect of sound direction on a neuron's FTC was examined by comparing the Q_n values obtained from different angles. The recording depth of each isolated neuron was read from the scale of a hydraulic microdrive (David Kopf)

Recorded action potentials were amplified, filtered and fed through a window discriminator before being displayed on the screen of an oscilloscope and monitored audiovisually with an audio monitor. Recorded action potentials were also sent to a computer (Gateway 2000) for acquisition of peri-stimulus-time histogram (PST) (sampling period: 500 ms, bin width: 500 μ s) and dot raster pattern of the neuron's responses over 16 trials. A PST histogram quantitatively describes the discharge pattern of each neuron in response to different stimuli.

Results

Discharge Patterns

A total of 156 neurons was isolated at depths

between 200 and 2125 μ m. BFs ranged from 8.0 to 55.4 kHz (75% between 8.5 and 15 KHz) and MTs were between 6 and 90 dB SPL (75 % below 50 dB SPL). Response latencies determined with BF sounds delivered at 20-30 dB above the MT were between 7 and 33 msec (65% below 15 msec).

Fewer than 20% of IC neurons were spontaneously active. According to the PSTs, discharge patterns can be described as (1) phasic on responders (n=123, 79%); (2) phasic on-off responders (n=5, 3%); (3) off responders (n=2, 2%); (4) choppers (n=10, 6%) and (5) tonic responders (n=16, 10%). Phasic on responders discharged only a few impulses to tone pulses with their PSTs showing a sharp peak at the onset of tone pulses (Fig. 1A). Phasic on-off responders discharged impulses during the onset and cessation of the stimulus. Their PSTs were characterized by peaks at the beginning and end of tone pulses (Fig. 1B). Phasic off responders discharged impulses upon cessation of tone pulses and their PSTs showed a peak at the end of tone pulses (Fig. 1C). Chopper responders discharged repetitively to tone pulses at a rate that was unrelated to the period of stimulus waveform. They produced serrated PSTs (Fig. 1D). Tonic responders discharged impulses throughout the entire duration of tone pulses. The PSTs showed an initial peak which declined gradually to lower levels (Fig. 1E). These five types of responders did not appear to have different ranges of recording depth, BF, MT and latency.

The FTC

FTCs were measured for 52 neurons. They can be described as narrow, intermediate or broad. The narrow FTCs (n=16, 31%, Fig. 2A) are sharpened pencil-shaped and cover a rather limited range of stimulus frequency (<10 kHz) even at high stimulus intensity. Both low and high frequency flanks have extremely sharp slopes. Intermediate FTCs (n=29, 56%, Fig. 2B) are V-shaped that cover a moderate range of stimulus frequency (20-30 kHz) at high stimulus intensity. Both low and high frequency flanks ascend with a moderate slope within 10-20 dB above the MT before becoming extremely sharp at still higher intensity. Broad FTCs (n=7, 13%) have moderate slopes at low intensity (within 20-30 dB above MT) before widening up and covering a wide range of stimulus frequency (>40 kHz) at high stimulus intensity. In some neurons, the high frequency flank extends up to 50-70 kHz (Fig. 2C). The average BF and MT of these 52 neurons are 16.38 ± 11.06 kHz (range: 8.0-55.40 kHz) and 43.58 ± 19.51 dB SPL (range: 9-90 dB SPL). There was no correlation between the type of FTC and the discharge pattern of these neurons.

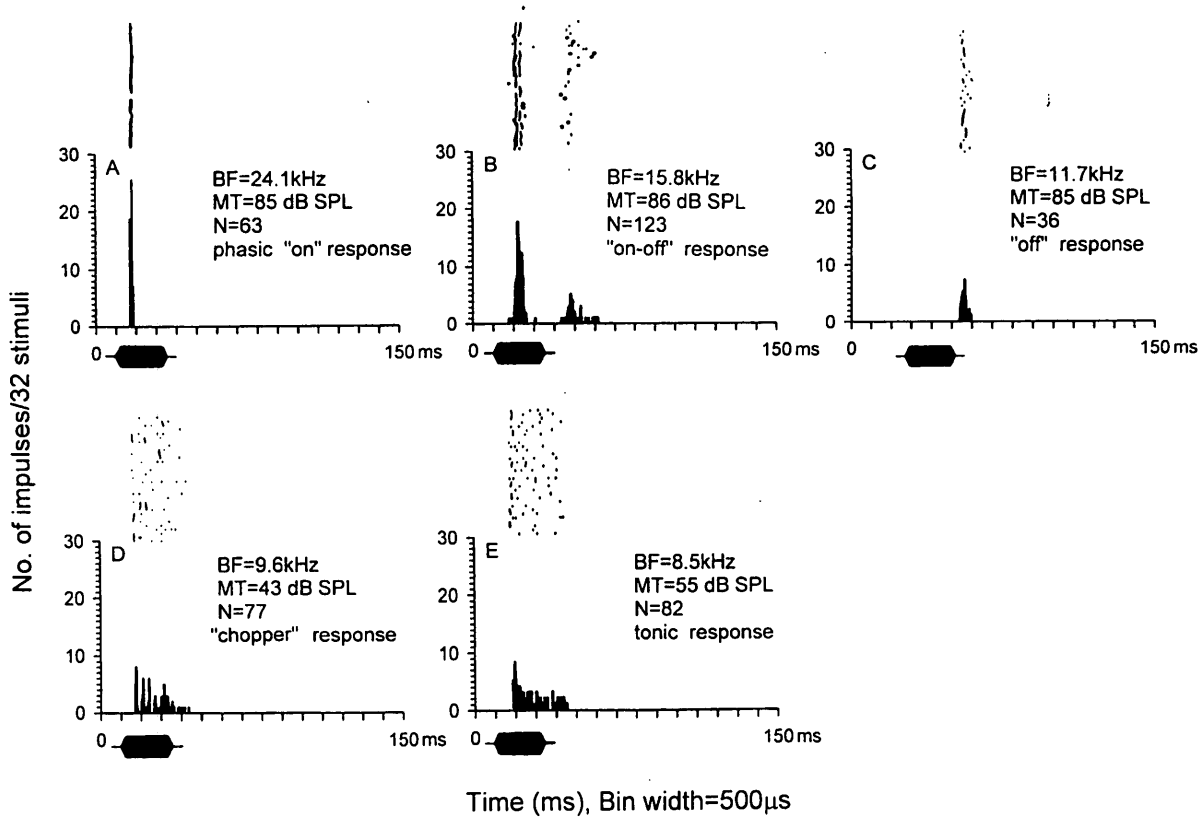


Fig. 1. Peri-stimulus-time histograms (PST) and dot raster patterns of five different discharge patterns of inferior collicular (IC) neurons: (A) phasic on responder; (B) on-off responder; (C) off responder; (D) chopper; and (E) tonic responders. The best frequency (kHz), minimum threshold (dB SPL) and total number of impulses in each PST are shown within each panel.

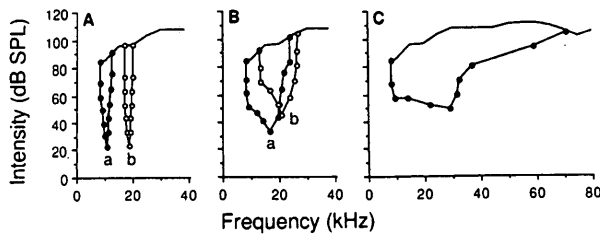


Fig. 2. Two narrow (Aa, Ab), two intermediate (Ba, Bb) and one broad representative frequency tuning curves (FTCs) of IC neurons. The ordinate and abscissa represent stimulus intensity (dB SPL) and frequency (kHz). The upper solid line represents the frequency characteristics of the loudspeaker. These three types of FTCs differ in Q_n values and in range of response frequency at high stimulus intensity (see text and Table 1 for details)

Table 1 shows the range and average Q_n values of these three types of FTCs. It is clear that narrow FTCs have the largest Q_n values while broad FTCs have the smallest Q_n values. Q_n values of the intermediate FTCs are in between these two ranges. Repeated measures ANOVA show that all Q_n values determined for these three types of FTCs differed significantly ($p < 0.01$).

Sound Direction on Frequency Tuning

Sound direction appeared to affect only the sharpness but not the BF and overall shape of a FTC. Figure 3 shows a neuron's FTC determined at 4 different azimuthal angles (70° and 30° contralateral, 70° and 40° ipsilateral) at 0° elevation. While all FTCs were V-shaped and had comparable BFs, sounds delivered from ipsilateral angles typically produced sharper FTCs than sounds delivered from contralateral angles. Thus, Q_n values obtained at contralateral angles (Figs. 3A, B) were smaller than those obtained at ipsilateral angles (Figs. 3C, D). Table 2 shows the average Q_n (Q_{10} , Q_{10} , and Q_{50}) values of IC neurons obtained at five different azimuthal angles. While each neuron always produced a smallest Q_n value at a specific angle, most ($> 70\%$) neurons had smaller Q_n values at contralateral than at ipsilateral angles. In particular, FTCs determined at contralateral 30° had the smallest Q_n values. The largest Q_{10} and Q_{30} values were always obtained at 70° ipsilateral. The difference in Q_n value obtained from corresponding ipsilateral and contralateral angles (c-70 vs i-70, c30 vs i-30) was in the order of $Q_{10} > Q_{30} > Q_{50}$.

Figure 4 shows a neuron's FTCs determined at

Table 1. The Range of Q_n Values of Three Types of Frequency Tuning Curves in Mouse Inferior Collicular Neurons

Q_n		frequency tuning curve		
values		narrow	intermediate	broad
Q_{10}	n	16	29	7
	range	3.23-15.89	1.05-8.82	0.64-2.62
	$m \pm sd$	7.33 ± 4.50 (1)	2.77 ± 1.64 (2)	1.63 ± 0.73 (3)
Q_{30}	n	13	16	5
	range	1.70-7.79	0.37-3.80	0.53-1.04
	$m \pm sd$	3.22 ± 1.58 (4)	1.30 ± 0.91 (5)	0.80 ± 0.24 (6)
Q_{50}	n	9	11	4
	range	1.26-7.39	0.46-1.80	0.33-0.96
	$m \pm sd$	3.74 ± 2.57 (7)	0.98 ± 0.50 (8)	0.55 ± 0.28 (9)

Repeated measures ANOVA show that all Q_n values determined for the three types of frequency tuning curves differ significantly. Student-Newman-Keul Multiple Comparison post test shows significant differences between (1) and (2) ($p < 0.001$), (1) and (3) ($p < 0.001$), (4) and (5) ($p < 0.001$), (4) and (6) ($p < 0.01$), (7) and (8) ($p < 0.01$), (7) and (9) ($p < 0.01$).

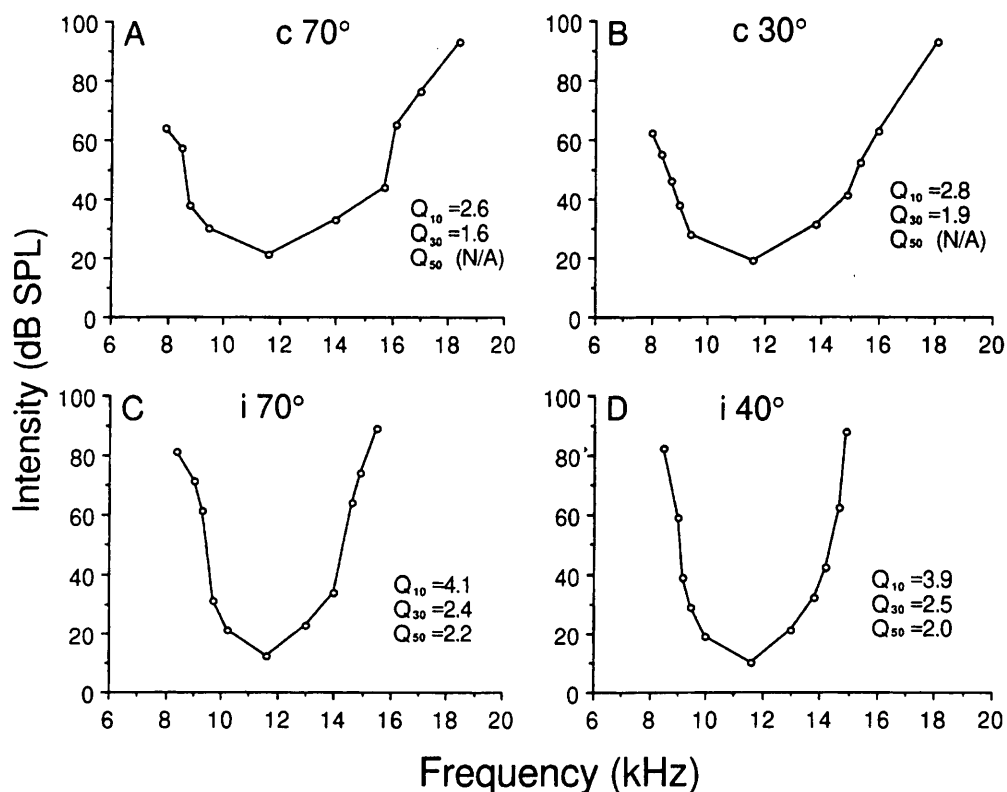


Fig. 3. Representative FTCs of an IC neuron determined at 4 different azimuthal angles. The ordinates and abscissae represent stimulus intensity (dB SPL) and frequency (kHz). Q_n values determined at each angle are shown within each panel. Q_{50} at C 70° and C 30° were not available due to high MT of the neuron. c or i: contralateral or ipsilateral to the recording site.

4 different elevational angles (50° and 30° up and down) along 30° contralateral plane. Although the overall shape of the FTC did not change with elevational sound direction, Q_n values obtained at lower elevational angles were larger than those obtained at upper elevational angles. However,

opposite results were observed in other neurons. In general, most (65%) neurons were tuned more sharply to sounds delivered from upper and lower elevational angles than from the front (0° horizontal). Thus most FTCs had higher Q_n values when obtained from upper and lower elevational angles than when obtained at 0°

Table 2. The Range of Q_n Values of Mouse Inferior Collicular Neurons Determined at Different Azimuthal Angles

Q_n values		frequency tuning curve				
		c70°	c30°	0°	i30°	i70°
Q_{10}	n	41	49	37	38	31
	range	1.38-15.00	1.00-15.58	0.87-21.00	1.56-12.71	2.12-15.85
	m \pm sd	4.99 \pm 3.72	3.75 \pm 3.10 (1)	5.92 \pm 4.45 (2)	5.97 \pm 3.13 (3)	7.10 \pm 3.82 (4)
Q_{30}	n	31	26	29	26	24
	range	0.59-11.25	0.37-7.79	0.62-16.50	0.58-11.13	1.27-11.13
	m \pm sd	2.82 \pm 2.52	2.19 \pm 1.67 (5)	3.52 \pm 3.36	3.48 \pm 2.60	4.56 \pm 2.93 (6)
Q_{50}	n	20	12	16	7	8
	range	0.45-7.59	0.41-6.45	0.53-6.63	0.79-7.59	0.61-5.32
	m \pm sd	2.00 \pm 1.81	1.40 \pm 1.69	2.27 \pm 1.74	3.56 \pm 2.15	3.41 \pm 1.91

Repeated measures ANOVA show that all Q_n values determined for the three types of frequency tuning curves differ significantly. Student-Newman-Keul Multiple Comparison post test shows significant differences between (1) and (2) ($p < 0.001$), (1) and (3) ($p < 0.001$), (4) and (5) ($p < 0.001$), (4) and (6) ($p < 0.01$), (7) and (8) ($p < 0.01$), (7) and (9) ($p < 0.01$).

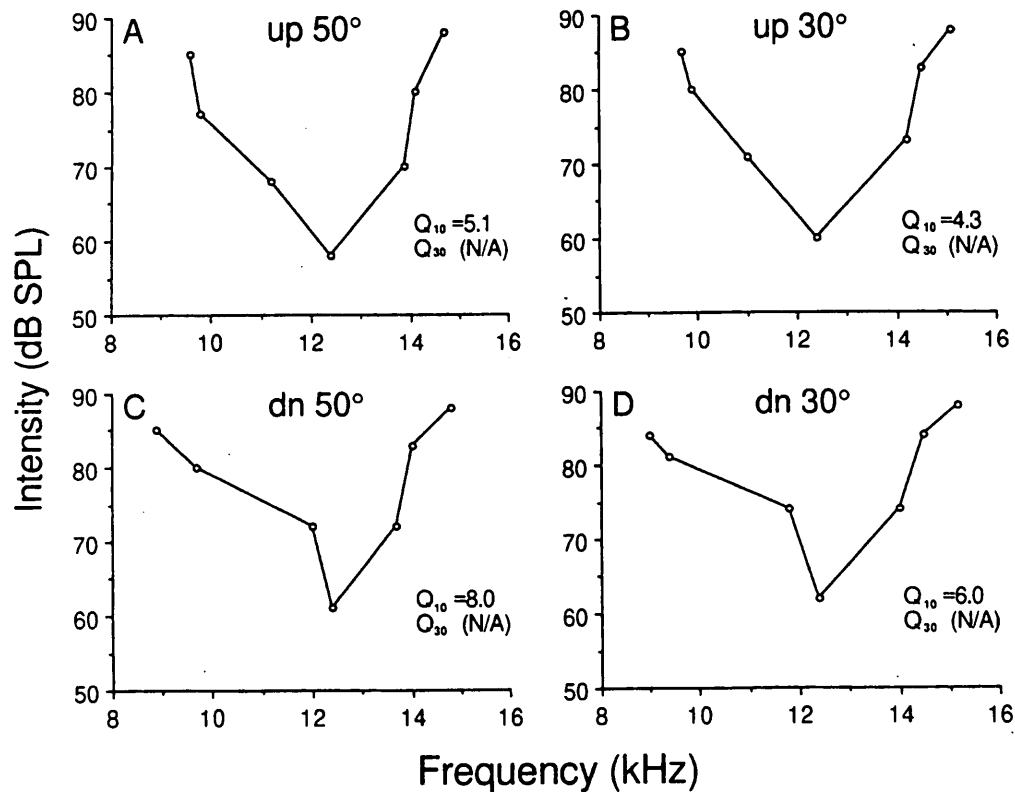


Fig. 4. Representative FTCs of an IC neuron determined at 4 different elevational angles at 30° contralateral. Q_n values determined at each angle are shown within each panel. Q_{30} and Q_{50} were not available due to high MT of the neuron. up or dn: upper or lower elevational angle relative to the 0° horizontal plane.

horizontal. Table 3 show the average Q_n (Q_{10} , Q_{30} , and Q_{50}) values of IC neurons obtained at different elevational angles. The average Q_n values were the smallest at 0° horizontal although repeated measures ANOVA did not reveal any significant difference in all Q_n values.

The number of FTCs determined at different azimuthal (Table 2) and elevational (Table 3) angles was different because of lost of neurons during measurement or increase in MT with sound direction such that Q_{30} and Q_{50} values were not available due to the limitation of the stimulation system.

Table 3. The Range of Q_n Values of Mouse Inferior Collicular Neurons Determined at Different Elevational Angles Along 30° Contralateral Plans

Q_n		frequency tuning curve				
values		d70°	d30°	0°	u30°	u50°
Q_{10}	n	18	14	27	19	18
	range	2.27-14.6	2.32-21.75	1.27-9.73	1.55-11.18	2.09-29.67
	m \pm sd	5.75 \pm 3.68	6.34 \pm 4.86	3.46 \pm 2.20	5.42 \pm 3.01	5.68 \pm 6.16
Q_{30}	n	13	12	15	14	17
	range	0.80-6.07	1.15-9.67	0.37-4.2	1.23-7.17	0.85-8.90
	m \pm sd	3.13 \pm 1.34	3.85 \pm 2.22	1.96 \pm 1.34	3.32 \pm 1.78	3.50 \pm 2.47
Q_{50}	n	7	7	10	8	n=11
	range	0.56-3.63	1.19-5.37	0.46-6.45	1.35-4.91	0.54-8.02
	m \pm sd	2.06 \pm 1.13	2.87 \pm 1.60	1.87 \pm 1.97	3.03 \pm 1.40	3.88 \pm 2.47

Repeated measures ANOVA do not reveal any significant difference in all Q_{10} ($p=0.1568$), Q_{30} ($p=0.0982$) or Q_{50} ($p=0.1393$) values. d or u: down or up portion of the frontal auditory space. n: number of neurons.

Discussion

The basic auditory response properties of IC neurons observed in the present study are comparable to those observed previously (6, 29, 30). We found sharpness of FTCs of the mouse changed with sound direction (Figs 3, 4) as reported in other species (14, 16, 19, 25). What may be the basis for this direction-dependent frequency tuning?

When a sound moves from one frontal hemifield to another, the amount of sound attenuation due to head and pinna changes systematically. This change in sound intensity undoubtedly contributes to variation in frequency tuning of an auditory neuron. In addition, the neural circuit which determines how a neuron receives its excitation and/or inhibition from each ear should also contribute to frequency tuning of the neuron. According to previous studies of sound pressure transformation at the pinna of this mouse (4) and other animals (17, 22, 23), the rather symmetrical position of two pinnae produces significant pressure difference for sounds delivered from the right and left frontal hemispheres but very little pressure difference for sounds delivered from upper and lower frontal hemispheres. This findings imply that change in head shadowing is greater along the azimuthal plane than the elevational plane. Because of this, direction-dependent frequency tuning should be larger for azimuthal than for elevational plane. This is substantiated by our findings that more than 70 % of neurons had significantly larger Q_n values to ipsilateral than to contralateral sounds (e.g. Fig. 3, Table 2). In contrast, more than 65% of IC neurons had the smallest Q_n values at 0° (Table 3) and Q_n values obtained from upper and lower elevational angles were not significantly different (Table 3).

Because most IC neurons are excited contralaterally and inhibited ipsilaterally (i.e. EI neurons) with the remaining either excited bilaterally (i.e. EE neurons) or excited contralaterally only (i.e. EO neurons)(1, 2, 3, 8, 13), sounds delivered from ipsilateral angles would reduce the degree of excitation to the contralateral ear or increase the degree of neural inhibition to the ipsilateral ear. A decrease in excitation or an increase in inhibition by ipsilateral sounds would sharpen the FTC of most IC neurons. Conversely, an increase in excitation or a decrease in inhibition by contralateral sounds would broaden the FTC of these neurons. In other words, the observed direction-dependent frequency tuning along the azimuthal plane (Fig. 3, Table 2) may be simply due to a decrease in excitation by sounds from ipsilateral angles because of neural inhibition and/or head shadowing effect.

On the other hand, previous studies have shown that FTCs of IC neurons are composed of an excitatory area that is either neighbored with an inhibitory area at one frequency flank or is sandwiched by two inhibitory areas (12, 18, 27). This lateral neural inhibition greatly sharpens the FTCs of IC neurons (26). Whether our observed direction-dependent frequency tuning (Figs. 3,4; Tables 2,3) was indeed due to a stronger binaural inhibitory effect with ipsilateral stimulation or due to an increase in degree of lateral inhibition remained to be studied.

Because neurotransmitters that mediate inhibition in the IC are either GABA or glycine (10, 11, 24, 28), application of bicuculline (GABA_A antagonist) broadens FTCs of many IC neurons (5, 32) and completely or partially abolish the inhibitory areas (18). These studies suggest that GABAergic inhibition may be involved in sharpening of FTC with

sound direction for EI neurons as proposed previously (14). Indeed recent studies have shown that application of bicuculline abolished the direction-dependent sharpness of FTCs in IC neurons of bats (33) and frogs (34).

In consistent with our finding, a previous study in frogs also showed that FTCs determined at ipsilateral angles were sharper than those determined at contralateral angles (14). This study showed that IC neurons in frogs had broadest frequency tuning at 90° contralateral, but it was at 30° contralateral for IC neurons in mice (Fig 3, Table 2). We believe that this species difference may be simply due to difference in the head structure of these two animals. A mouse has two pinnae which are located at the entrance of the ear canal (about 30°-40° lateral). In contrast, a frog does not have external ear and its eardrum is located about 80°-90° lateral. Thus the difference in sound transformation at the ear of these two animals may contribute to the difference in the angle of broadest frequency tuning.

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