

GABAergic Inhibition and the Effect of Sound Direction on Rate-Intensity Functions of Inferior Collicular Neurons of the Big Brown Bat, *Eptesicus fuscus*

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Abstract

GABAergic inhibition shapes many auditory response properties of neurons in the inferior colliculus of the big brown bat, *Eptesicus fuscus*. This study examined the role of GABAergic inhibition on direction-dependent rate-intensity functions of bat inferior collicular neurons. When plotted at three sound directions (60° contralateral, 0° and 60° ipsilateral relative to recording site), most collicular neurons had nonmonotonic and saturated rate-intensity functions at 60° contralateral and 0° but had monotonic rate-intensity functions at 60° ipsilateral. The dynamic range of rate-intensity functions of majority (>90%) of collicular neurons significantly decreased as the sound direction changed from 60° contralateral to 60° ipsilateral. Bicuculline application increased or decreased the dynamic range of IC neurons in different degrees with sound direction and abolished direction-dependent intensity sensitivity of these IC neurons. Possible mechanisms for these observations are discussed.

Key Words: bat, bicuculline, GABAergic inhibition, inferior colliculus, rate-intensity function

Introduction

In sound analysis, frequency and intensity are two fundamental signal parameters. They are the basis of perception of pitch and loudness. For this reason, many studies have examined the frequency or intensity sensitivity of auditory neurons in different animals (25). These studies determined how a change in frequency or intensity of sound stimuli delivered from a specific direction might affect the responses of auditory neurons such as the number of impulses, latency, response probability or threshold. However, naturally occurring sounds often change direction with time. Therefore, a neuron's intensity or frequency sensitivity to sounds broadcast from one direction

cannot predict well its intensity or frequency sensitivity to sounds broadcast from different directions. For this reason, many studies have examined the effect of sound direction on responses of auditory neurons (5). These studies showed that most neurons in the central nucleus of the inferior colliculus (IC) discharge maximally or display lowest minimum threshold (MT) to sounds delivered from contralateral angles (1, 2, 4, 10, 11, 16, 17, 18, 27, 28, 30, 33, 35). They also have sharper frequency tuning curves with higher MTs at the best frequency (BF) to sounds delivered from ipsilateral than from contralateral angles. It has been shown that GABAergic inhibition, which is predominant in the IC (6, 7, 23, 26), contributes to this direction-

dependent response and frequency tuning of IC neurons (17, 33, 35). However, whether sound direction also affects the intensity sensitivity of IC neurons has not been examined.

We have previously examined intensity sensitivity of bat IC neurons by plotting the rate-intensity functions (15, 19, 34, 36). These studies showed that the response of IC neurons linearly increased with stimulus intensity within a specific range (i.e. the dynamic range) beyond which the response either reached a plateau or declined at high stimulus intensity. However, all these studies were conducted in only one sound direction as such the potential effect of sound direction on intensity sensitivity of these neurons could not be determined. Because a neuron's MT determines its lowest sensitivity to sound intensity and the MT varies with sound direction (1, 2, 4, 10, 11, 16, 17, 18, 27, 28, 30, 33, 35), sound direction should also affect a neuron's intensity sensitivity. In this study, we examined GABAergic inhibition and the effect of sound direction on intensity sensitivity of bat IC neurons by plotting the rate-intensity functions with sounds delivered from three directions before and during bicuculline application. We then compared variation in the type and dynamic range of rate-intensity functions with sound direction.

Materials and Methods

As described in our previous study (18), one or two days before the recording session, the flat head of a 1.8 cm nail was attached with acrylic glue and dental cement to the exposed skull of each of 4 Nembutal-anesthetized (45-50 mg/kg b.w.) bats (b.w. 18-24g). During recording, each bat received the neuroleptanalgesic Innovar-Vet (0.08 mg/kg b. w. of fentanyl, 4 mg/kg b. w. of droperidol) and was strapped to an aluminum plate with transparent plastic sheeting inside a double-wall, sound-proof room (temperature 28-30°C). The ceiling and inside walls of the room were covered with 3-inch convoluted polyurethane foam to reduce echoes. The bat's head was immobilized by fixing the shank of the nail into a metal rod with a setscrew. Small holes were made in the skull above the IC for insertion of piggy-back multibarrel electrodes to record neural responses and to inject bicuculline. The recording depth was read from the scale of a microdrive. An indifferent electrode (silver wire) was placed at the nearby temporal muscles. The experiments were conducted in compliance with NIH publication No. 85-23, "Principles of Laboratory Animal Care" and with the approval of the Institutional Animal Care and Use Committee (#1438) of the University of Missouri Columbia.

For sound stimulation, continuous sine waves from an oscillator (KH model 1200) were formed into 4 ms sounds (0.5 ms rise-decay times, at 2 pps) by an electronic switch driven by a stimulator (Grass S88). These sounds were amplified after passing through a decade attenuator (HP 350D) before being fed to a small condenser loudspeaker (AKG model CK 50, 1.5 cm diameter, 1.2 g). The loudspeaker was placed 23 cm away from the bat and 60° contralateral to the recording site. The loudspeaker was calibrated with a Bruel and Kjaer 1/4 inch microphone (4135) placed at the position where the bat's head would be during recording. The output was expressed in dB SPL referred to 20 μ Pa root mean square.

The construction of the piggy-back multibarrel electrodes and iontophoretic injection of bicuculline have been described in detail previously (20). Briefly, a three-barrel electrode (tip: 10-15 μ m) was "piggybacked" to a 3 M KCl single-barrel electrode (tip: less than 1 μ m; impedance: 5-10 M Ω) whose tip was extended about 10 μ m from the tip of the three-barrel electrode. The 3 M KCl single-barrel electrode was used to record acoustically evoked neural responses. One of the barrels of a three-barrel electrode was filled with bicuculline methiodide (10 mM in 0.16 M NaCl, pH 3.0, Sigma) for injection into the recording site by means of a microiontophoresis constant current generator (Medical Systems Neurophore BH-2). The bicuculline was prepared just before each experiment and the electrode filled immediately before use. During bicuculline application, 1 s pulses of 40 nA at 0.5 pps were applied for 1-2 minutes before data acquisition. Application current was then changed to 10 nA during data acquisition. The other two barrels were filled with 1 M NaCl (pH 7.4), one of which was used as the ground and the other as the balance barrel. The balance electrode was connected to the balance module. The retaining current was negative 8-10 nA.

Upon isolation of an IC neuron with 4-ms sounds delivered from 60° contralateral, its BF was determined by changing the frequency and intensity of sound stimuli. The MT at the BF was defined as the intensity at which the probability of responding to BF sounds was 50%. The neuron's number of impulses in response to BF sounds delivered at the MT and at 10 dB increments above the MT were systematically recorded before and during bicuculline application. The neuron's rate-intensity function was plotted using this number of impulses plotted against the sound intensity. Three rate-intensity functions were plotted for each IC neuron with sounds delivered from three sound directions that were spaced 60° apart within the frontal auditory space (60° contralateral, 0° and 60° ipsilateral relative to the recording site, abbreviated

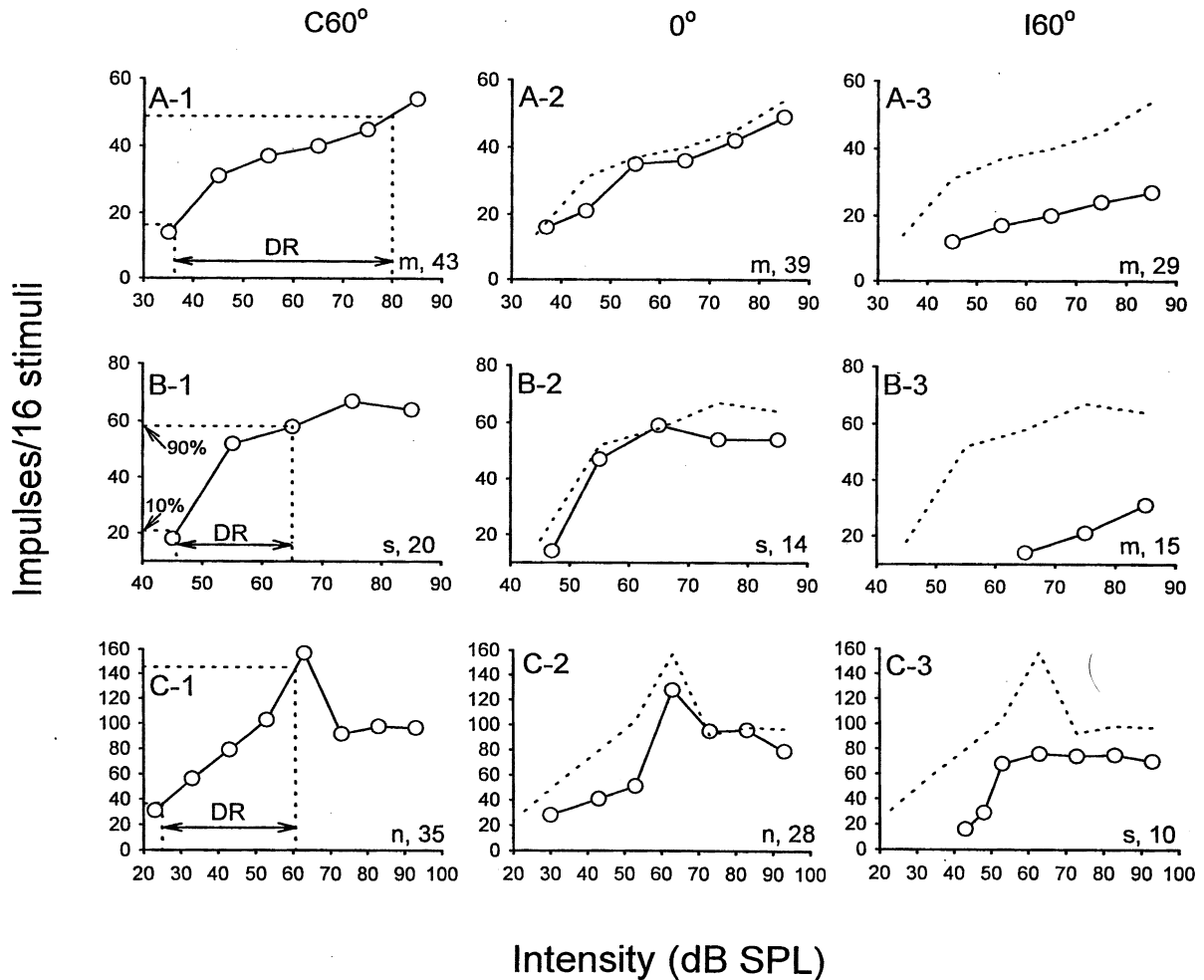


Fig. 1. Rate-intensity functions of 3 representative inferior collicular (IC) neurons determined at 3 sound directions ($c60^\circ$, $i60^\circ$ and 0° relative to the recording site). For comparison, the rate-intensity function plotted at $c60^\circ$ is replotted at 0° and $i60^\circ$ (dashed). Ordinates and abscissae represent the number of impulses per 16 stimuli and stimulus intensity in dB SPL. The dynamic range (DR) is defined as the intensity range from 10% below the maximal to 10% above the minimal number of impulses (A-1, B-1, C-1). Note that all 3 neurons had a lowest minimum threshold (MT) at $c60^\circ$. The type and DR of each rate intensity function are shown at the lower right corner of each panel. m, n and s: monotonic, nonmonotonic and saturated rate-intensity functions. The best frequency (BF) and recording depth of these 3 neurons were 53.0, 1100 (A); 27.8, 1923 (B); 24.3, 675 (C).

as $c60^\circ$, 0° and $i60^\circ$).

Recorded action potentials were amplified, band-pass filtered (Krohn-Hite 3500), and fed through a window discriminator (WPI 121) before being sent to an oscilloscope (Tektronix 5111) and an audio monitor (Grass AM6). They were then sent to a computer (Gateway 2000, 486) for acquisition of peri-stimulus-time (PST) histograms (bin width: 500 μ s, sampling period: 300 ms) to 16 pulse presentations. The PST histograms quantitatively describe the discharge patterns of each neuron obtained under different stimulation conditions. The total number of impulses in each PST histogram was used to quantify a neuron's response under each stimulus condition. The effect of GABAergic inhibition and sound direction on rate-

intensity functions of IC neurons was then examined by comparing the type and dynamic range of rate-intensity functions obtained at three sound directions before and during bicuculline application using one-way ANOVA at $P < 0.01$.

Results

In this study, we isolated a total of 46 IC neurons. Their rate-intensity functions obtained at three sound directions can be described as monotonic (m), nonmonotonic (n) and saturated (s). Fig. 1 shows rate-intensity functions of three IC neurons plotted at three sound directions. The number of impulses of a monotonic rate-intensity function monotonically

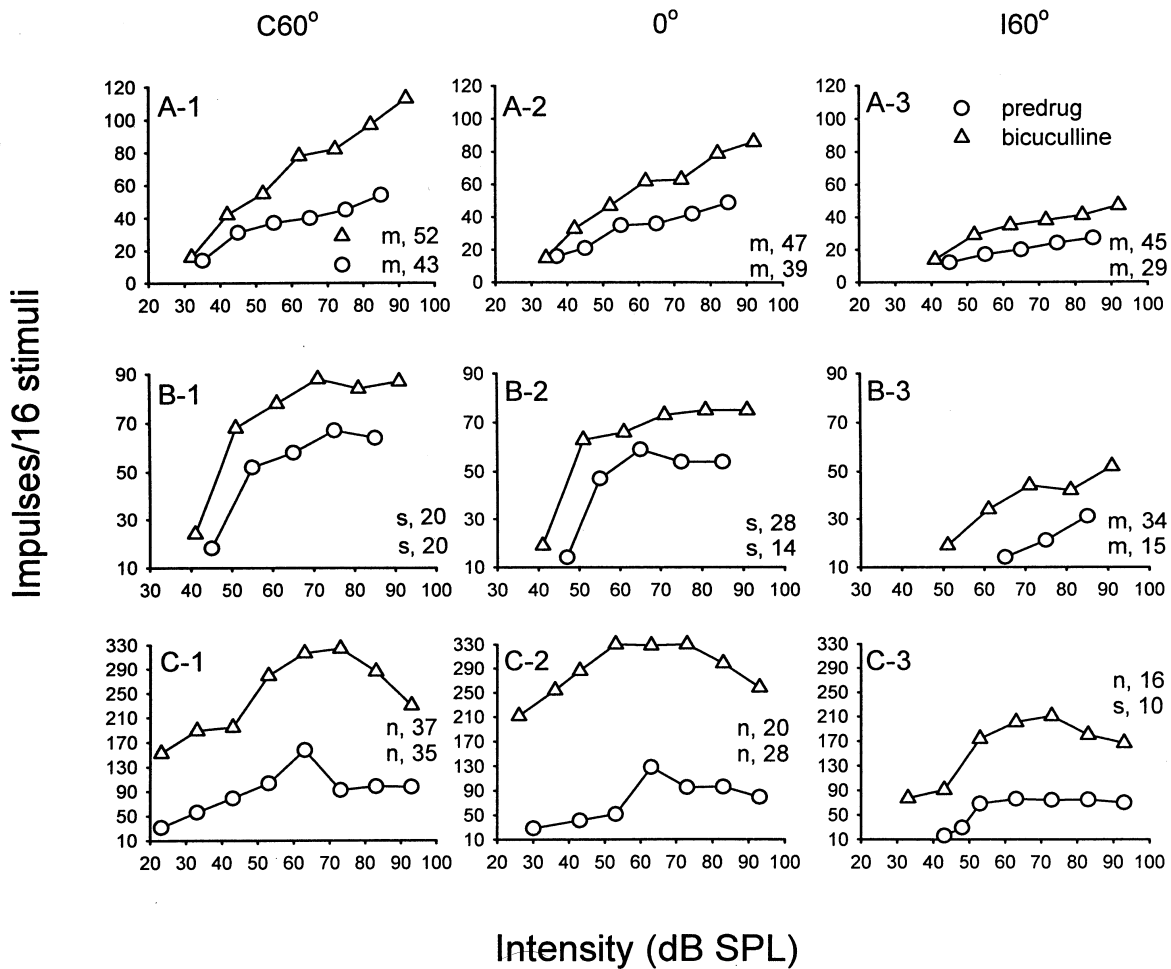


Fig. 2. Rate-intensity functions of three IC neurons shown in Fig 1 plotted before (unfilled circles, predrug) and during (unfilled triangles, bicuculline) bicuculline application. Note that bicuculline application raised the rate-intensity functions of all 3 neurons to varying degrees at all three sound directions. The type and DR of each rate-intensity function determined during (above) and before (below) bicuculline application are shown within each panel.

increased with stimulus intensity (Fig. 1A-1, m). The number of impulses of a saturated rate-intensity function increased with stimulus intensity up to a maximum before leveling off at higher intensities (Fig. 1B-1, s). For a nonmonotonic rate-intensity function, the number of impulses increased with stimulus intensity up to a maximum and decreased by more than 20% at higher intensities (Fig. 1C-1, n). The dynamic range of each rate-intensity function was defined as the intensity range from 10% below the maximal to 10% above the minimal number of impulses (Fig. 1A-1, B-1, C-1, DR). The dynamic range represents the intensity range within which a neuron's response linearly increases with sound intensity. The slope of a dynamic range represents a neuron's sensitivity to intensity change over the dynamic range. A neuron with a small dynamic range typically has steeper slope than a neuron with a wide

dynamic range. For this reason, the former has greater sensitivity to intensity change than the latter.

Consistent with previous studies (1, 2, 4, 10, 11, 16, 17, 18, 27, 28, 30, 33, 35), MTs of most IC neurons increased and the number of impulses decreased when sound direction changed from c60° to 0° and then i60° such that the rate-intensity function shifted downward and rightward with decreased dynamic range (Fig. 1 solid vs dashed in i60°). The rate intensity function of IC neurons either changed from one type to another with sound direction or remained unchanged (e.g. Fig. 1 B-1, B-2, B-3 vs A-1, A-2, A-3). Bicuculline application decreased the MT while increased the number of impulses of IC neurons to varying degrees at all three sound directions such that the rate-intensity function shifted upward and leftward (Fig. 2). While the type of rate-intensity function of some IC neurons was not affected during bicuculline application, others

Table 1. Average MT of IC neurons from 3 different sound directions determined before and during bicuculline application

		Sound direction			ANOVA <i>P</i>
		c60°	0°	i60°	
Predrug	n	46	46	41	
	range	10-71	18-85	13-87	
	m±sd	38.6±11.9	46.2±14.5	59.0±14.7	<0.0001*
Bic	n	46	42	35	
	range	9-71	11-72	17-87	
	m±sd	35.9±12.1	42.0±14.4	51.9±16.2	<0.0001*

c or i: contralateral or ipsilateral to the recording site. n: number of neurons. *significance at $P<0.01$.

Table 2. Rate-intensity functions of IC neurons plotted before and during bicuculline application at three sound directions

Predrug	n	C-60°			n	Sound direction 0°			n	I-60°		
		bic	mon	non		sat	bic	mon		non	sat	bic
Mon	12 (28%)	<u>6</u>	0	6	15 (33%)	<u>8</u>	1	6	24 (64%)	<u>19</u>	4	1
Non	15 (35%)	4	<u>10</u>	1	22 (49%)	5	<u>15</u>	2	7 (18%)	1	<u>4</u>	2
Sat	16 (37%)	4	5	<u>7</u>	8 (18%)	2	1	<u>5</u>	7 (18%)	1	3	<u>3</u>
Total	43	14	15	14	45	15	17	13	38	21	11	6
		(33%)	(34%)	(33%)		(34%)	(38%)	(28%)		(55%)	(29%)	(16%)
change in type		43%				37%				31%		

Mon or Non or Sat: monotonous or non-monotonous or saturated rate-intensity function. Numbers underlined indicate no change in the type of rate-intensity function.

changed from one type to another (e.g. Fig. 2A-1 vs C-3).

Table 1 shows the average MT of IC neurons obtained at three sound directions before and during bicuculline application. On average, bicuculline application produced a greater change in MT at i60° than at other two sound directions. Consistent with our previous study (17), the average MT of IC neurons significantly increased when sound direction changed from c60° to 0° and to i60° both before and during bicuculline application (one way ANOVA; $P<0.0001$). Table 2 shows the different type of rate-intensity functions of IC neurons plotted before and during bicuculline application at three sound directions. Most (55%-64%) neurons had monotonic rate-intensity functions at i60° than at other two sound directions when plotted both before and during bicuculline application. Conversely, most (67%-72%) neurons

had either nonmonotonous or saturated rate-intensity functions at c60° or at 0°. The percent change in the type of rate-intensity function during bicuculline application was greater at c60° (43%) than at 0° (37%) or i60° (31%).

Table 3 summarizes the average change of dynamic range of IC neurons with sound direction obtained before and during bicuculline application. The average dynamic range of majority of IC neurons significantly decreased when sound direction changed from c60° to i60° ($P<0.01$). While bicuculline application either increased (e.g. Fig. 2A-1) or decreased (e.g. Fig. 2C-2) the dynamic range of IC neurons, the application abolished the significant variation of dynamic range with sound direction ($P>0.01$). The average dynamic range of the remaining few neurons was not affected by sound direction or by bicuculline application ($P>0.01$).

Table 3. The dynamic range (DR) of IC neurons determined at three sound directions before and during bicuculline application

DR change (dB)		Sound direction			ANOVA <i>P</i>
		c60°	0°	i60°	
Increase Pre	n	21 (48%)	21 (50%)	25 (68%)	0.0065*
	range	4-50	2.5-40	2-49	
	m±sd	26.7±13.3	17.4±11.5	15.1±12.2	
Bic	range	16-57	12-60	7-55	0.1506
	m±sd	37.3±13.7	31.3±12.9	29.5±14.5	
Decrease Pre	n	19 (43%)	19 (45%)	11 (29%)	0.0054*
	range	19-49	11-50	9-38	
	m±sd	35.3±9.4	28.4±11.4	22.6±8.4	
Bic	range	4-45	2-29	7-28	0.0124
	m±sd	24.5±12.9	14.8±8.1	16.2±7.6	
No change	n	4 (9%)	2 (5%)	2 (3%)	0.3232
	range	14-43	10-29	9-16	
	m±sd	29.8±13.5	19.5±13.4	12.5±4.9	

Pre or bic: before or during bicuculline application. n: number of neurons. *: significance at $P < 0.01$.

Discussion

We observed that the rate-intensity function of IC neurons varied with sound direction, similar to a previous study of neurons in the lateral superior olivary nucleus of the bat (12). Consistent with previous studies in bats and frogs (10, 17, 32, 33), MTs of IC neurons increased significantly with sound direction changed from c60° to i60° both before and during bicuculline application (Table 1). The fact that bicuculline application abolished direction-dependent variation in the dynamic range (Table 3) but not in the MT (Table 1) suggests that GABAergic inhibition contributes more significantly to intensity sensitivity range than to increase in the MT of IC neurons.

In this study, we plotted the rate-intensity functions of IC neurons by recording the number of impulses with BF sounds at the MT and at 10 dB increments up to the highest stimulus intensity available from our stimulation system. We observed that most (55%–64%) IC neurons had monotonic rate-intensity functions at i60° than at other two sound directions when plotted both before and during bicuculline application (Table 2). This observation is likely because MTs of IC neurons were significantly higher at i60° than at c60° and 0° such that the range of stimulus intensity available for determining the dynamic range of IC neurons was smaller at i60° than at other two sound directions (Table 3). As a result, increased MT at i60° concomitant with decreased available range of stimulus intensity might be

responsible for a larger number of monotonic rate-intensity functions of IC neurons at i60° than at c60° and 0°. It is conceivable that the smaller range of available stimulus intensity might also contribute to the smaller percent change in the type of rate intensity function of IC neurons at i60° than at other two sound directions during bicuculline application (Table 2).

We observed a progressive decrease of dynamic range with sound direction changed from c60° to 0° and to i60° (Table 3). This observation suggests that IC neurons are more sensitive to intensity change at i60° than at c60°. What might be the neural mechanisms underlying this direction-dependent intensity sensitivity?

Previous studies showed that most IC neurons are excited contralaterally and inhibited ipsilaterally (EI neurons) although some are either excited bilaterally (EE neurons) or excited contralaterally only (EO neurons) (3, 5, 9, 22). Furthermore, EE and EO neurons have higher MTs for ipsilateral than for contralateral sound stimulation (22, 29). Previous studies (9, 11, 13, 14, 31) have also shown that directionality of sound pressure transformation at the pinna due to head shadowing contributes to directional sensitivity of auditory neurons. Based upon these studies, we have suggested previously that variation in binaural inhibition and/or head shadowing with sound direction contribute to direction dependent frequency tuning and MT of IC neurons (17). We believe this same mechanism also contributes to direction-dependent variation of the dynamic range

of IC neurons as observed in the present study. For example, when a sound is delivered at $i60^\circ$, it produces a large intensity at the ipsilateral ear and thus a strong neural inhibition to an EI neuron. Conversely, head shadowing reduces the sound intensity and thus a weak neural excitation at the contralateral ear. This increase in the strength of ipsilateral inhibition and decrease in the strength of contralateral excitation elevate the MT resulting in a change in dynamic range and/or type of rate-intensity function at $i60^\circ$ (Fig. 1). For EO neurons, contralateral sound stimulation should produce maximal excitation while ipsilateral sound stimulation should produce weak excitation due to head shadowing. Because EE neurons have higher MT for ipsilateral than for contralateral sound stimulation (22, 29), a sound delivered at $i60^\circ$ would be less effective in exciting these neurons than at $c60^\circ$.

Bicuculline application either increased or decreased the dynamic range of majority of IC neurons (Table 3). These opposite effects are likely due to differential increase of collicular responses over a wide range of stimulus intensity during bicuculline application as reported in a previous study (24). For example, a large increase of response at high stimulus intensity during bicuculline application would increase the dynamic range of IC neurons (e.g. Fig. 2A-1, A-2, A-3). Conversely, a large increase of response at low or intermediate stimulus intensity during bicuculline application would decrease the dynamic range of IC neurons (e.g. Fig. 2C-2). An equal increase in response across all intensity range would result in a parallel elevation of the rate-intensity function without significantly changing the dynamic range (e.g. Fig. 2B-1). Bicuculline application abolished direction-dependent variation in the dynamic range of IC neurons either by a greater increase of dynamic range at $i60^\circ$ than at $c60^\circ$ or by a greater decrease of dynamic range at $c60^\circ$ than at $i60^\circ$ (Table 3 upper rows vs middle rows). However, when bicuculline application produced a decrease in the dynamic range of IC neurons, the decreased dynamic range was still significantly smaller at $i60^\circ$ than at $c60^\circ$ if using $P < 0.05$ (Table 3 middle rows). This observation suggests that direction-dependent intensity sensitivity of these IC neurons might not be solely shaped by GABAergic inhibition. For example, previous studies have shown that glycinergic inhibition also contributes to frequency tuning and selectivity of frequency modulation of IC neurons (8, 21). It is therefore conceivable that glycinergic inhibition might also contribute to direction-dependent intensity sensitivity of these IC neurons. We observed that a few IC neurons (5-9%) whose dynamic ranges were not direction-dependent and were not affected by bicuculline application. These IC neurons might

either solely receive glycinergic inhibition or they were simply EE neurons such that bicuculline application would not produce any effect on their dynamic ranges.

In summary, we have shown that most IC neurons had higher MT with greater sensitivity to intensity change to sounds delivered from ipsilateral than from contralateral angles. Bicuculline application increased or decreased the dynamic range of IC neurons in different degrees with sound direction and abolished direction-dependent intensity sensitivity of these IC neurons.

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