Single-Unit Responses in the Inferior Colliculus of Decerebrate Cats II. Sensitivity to Interaural Level Differences

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INTRODUCTION

Single units in the central nucleus of the inferior colliculus (ICC) of unanesthetized decerebrate cats can be classified into three distinct types (not including onset units) based on the patterns of excitation and inhibition observed in contralateral pure-tone frequency response maps (Ramachandran et al. 1999). These response map types are presumed to reflect different sources of input from lower auditory nuclei (for reviews, see Aitkin 1986; Caird 1991; Irvine 1992) and have important implications for midbrain processing of competing free-field sounds that reach the listener with different directional signatures.

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strong lateral inhibition, which is the response pattern associated with the principal cells in the lateral superior olive (LSO) (Caird and Klinke 1983). Last, type O units show excitation when tested with low-level tones at best frequency (BF: the most sensitive frequency), but show strong inhibition to high-level BF tones; this behavior is exhibited by principal cells in the dorsal cochlear nucleus (DCN) (Spirou and Young 1991; Young and Brownell 1976). The present study extends our description of the sound-evoked activity of ICC neurons (Ramachandran et al. 1999) by assessing the ipsilateral and binaural response map properties of ICC units.

Ipsilateral and binaural properties of ICC neurons have been described in a large number of studies (see e.g., Aitkin 1986; Caird 1991; Irvine 1992; Oliver and Huerta 1992; Oliver and Shneiderman 1991). For example, the response maps of ICC units show V-shaped excitation that resembles the responses of projection neurons in the medial superior olive (MSO) (Goldberg and Brown 1969; Guinan et al. 1972). In contrast, type I maps show level-tolerant excitation bounded by
The presence of spontaneous activity in this preparation allowed us to examine directly the ipsilateral response properties that shape ILD sensitivity and frequency selectivity. These characterizations build on our previous interpretations of the putative dominant inputs to ICC response types (Ramachandran et al. 1999) and support comparisons with traditional ICC binaural classification systems. Our results show that type V units are equivalent to bilaterally excitable EE units, whereas the more common type I and type O units exhibit EI properties. Consistent with these binaural properties, type V units show lower thresholds and wider excitatory bandwidths with increasing levels of ipsilateral stimulation, whereas type I and type O units show higher thresholds and narrower tuning. Usually the basic effects of binaural stimulation are not altered when the GABA_A antagonist bicuculline is applied to the recording site; rather the primary effect of bicuculline is to increase response magnitude. Thus like the frequency response map types that are elicited by contralateral stimulation, it appears that the binaural properties of ICC neurons are largely established in lower auditory nuclei and then modulated by local inhibitory mechanisms.

METH ODS

Surgical procedures

Detailed surgical procedures for acute electrophysiological recording in the ICC of decerebrate cats are described elsewhere (Ramachandran et al. 1999). Briefly, experiments were conducted on adult cats (3–4 kg) with clean ears and clear tympanic membranes. Cats were tranquilized with xylazine (2 mg im), premedicated with atropine (0.1 mg im), and anesthetized with ketamine (initial dose 40 mg/kg im; supplemental doses 15 mg/kg iv). Thereafter core body temperature was maintained at 39°C with a regulated heating pad. Cats were decerebrated by aspiration through the brain stem between the superior colliculus and thalamus; anesthesia then was discontinued. The cat’s head was secured with a stereotaxic apparatus in a standard horizontal orientation. The left inferior colliculus was exposed by opening the skull just rostral to the bony tentorium, aspirating the underlying cortical tissue, and partially removing the tentorium. At the end of experiments, cats were euthanized by an injection of pentobarbital sodium (26 mg/kg iv). If electrode tracks were described the effects of contralateral stimulation for 80 of these units. The present study expands on those results by measuring ipsilateral response patterns for the entire sample of units and binaural interaction data in 53 units (6 type V, 21 type I, and 26 type O units). Pharmacological manipulations were performed on a few units (1 type V, 2 type I, and 5 type O) to investigate the effects of GABA_A inhibitory inputs that may shape binaural properties in ICC.

Recording protocol

Recordings were made in a sound-attenuating chamber. Acoustic stimuli were delivered bilaterally via electrostatic speakers that were coupled to hollow ear bars. The calibration function of each closed acoustic system was relatively uniform ($\pm 5$ dB) across frequency from 40 Hz to 40 kHz and similar in both ears ($\pm 2$ dB). Therefore applying equal attenuation to binaural tones of the same frequency was assumed to create a 0-dB ILD. Interaural crosstalk was $\approx 30$ dB (and typically $>50$ dB) down in the ear opposite to the sound source (Gibson 1982), which is well below the maximum ILD used during binaural testing. All test stimuli were 200 ms in duration, had rise/fall times of 10 ms, and were presented at a rate of 1 burst/s.

Unit activity was recorded with platinum-iridium electrodes. The electrode signal was amplified ($\times 10,000–30,000$) and filtered from 30 Hz to 6 kHz. A variable-threshold Schmitt trigger was used to discriminate action potentials from background activity. Pharmacological manipulations were performed using ‘piggy-back’ multibarreled electrodes (after Havey and Caspary 1980). These electrodes were made by attaching a three-barrel glass micropipette $\sim 10–15 \mu m$ behind the tip of the metal recording electrode. Two barrels of the pipette were filled with bicuculline methiodide (10 mM, pH 3.5–4.0, Sigma); the third, balancing or sum channel, was filled with a pH-balanced buffer (pH 4.0, potassium hydrogen phthalate, CMS). Retention currents of 20 nA (electrode negative) and ejection currents of 50 nA were produced with microiontophoresis constant current generators (WPI, Model 260).

Electrodes were advanced dorsoventrally through the IC in 1- to 2-$\mu m$ steps with the use of a hydraulic micromanipulator. Search stimuli were 50-ms tone or noise bursts presented in the contralateral ear. When the IC is sampled along a dorsoventral trajectory, electrodes pass through the external or dorsal nucleus before entering ICC; a reversal in the trend of unit BF$s$ was used to mark the transition between subdivisions (Aitkin et al. 1975; Merzenich and Reid 1974). Once an ICC unit was isolated, its BF to contralateral tones ($B_{F_L}$) was determined, then rate-level functions were obtained with $B_{F_L}$ tones and broadband noise bursts (100-dB range in 1-dB steps) using contra- and ipsilateral monaural and binaural stimulation. Monaural frequency response maps were measured using isointensity single-tone frequency sweeps (across a 4-octave range logarithmically spaced about $B_{F_L}$) at multiple levels (10 dB below to 70 dB above threshold); each frequency-intensity combination was presented once. For binaural testing, the same pure tone was presented to both ears, but a 40-dB range of ILDs was created by varying the level of the ipsilateral tone relative to a fixed contralateral stimulus. The responses elicited by auditory stimuli are described in terms of average rates. To minimize adaptation effects, stimulus-evoked rates were computed during the last 150 ms of the stimulus-on interval; and spontaneous rates were computed during the last 400 ms of the stimulus-off interval of each 1-s stimulation period. Excitatory (inhibitory) responses were defined as those for which the stimulus-evoked rate was at least $\pm 1$ SD of the spontaneous discharge rate. All data were smoothed with a triangularly weighted moving window filter to reduce noise in frequency response maps.

RESULTS

Physiological characterizations are based on the responses of 92 ICC units (10 type V, 37 type I, and 45 type O units) that were recorded in six cats. Ramachandran et al. (1999) described the effects of contralateral monaural stimulation for 80 of these units. The present study expands on those results by measuring ipsilateral response patterns for the entire sample of units and binaural interaction data in 53 units (6 type V, 21 type I, and 26 type O units). Pharmacological manipulations were performed on a few units (1 type V, 2 type I, and 5 type O) to investigate the effects of GABA_A inhibitory inputs that may shape binaural properties in ICC.

Comparison of frequency response maps and ILD functions

Our previous analyses of frequency response maps have indicated that single units in ICC can be classified by their distribution of excitatory and inhibitory response areas for contralateral monaural stimulation. Type V units show a strictly excitatory V-shaped receptive field (Fig. 1A); whereas, type I and O units are inhibited by most combinations of stimulus frequency and sound pressure level. For type I units, the inhibitory receptive field is confined to sidebands that flank BF and thereby reduces the range of excitatory frequencies to a narrow I-shaped response area (Fig. 1D). Type O units show almost exclusively inhibitory responses except for a consistent O-shaped island of excitation near BF at low-stimulus levels.
Other response properties associated with these unit types are described in detail by Ramachandran et al. (1999). The responses of ICC units to ipsilateral stimulation also can be separated into distinct classes. Type V units show only excitatory responses for ipsilateral stimulation (Fig. 1B), which is equivalent to the response properties of EE units in usual binaural classification systems (see e.g., Irvine 1992). Although type V units respond well to contralateral stimulation, 5/10 of the units in this response class attained higher BF tone-driven rates with ipsilateral stimulation (e.g., Fig. 1B).

Type I and type O units were inhibited by ipsilateral stimulation (Fig. 1E and H, respectively), which is a characteristic of EI units in binaural classification systems.

Differences in the ipsilateral response properties that distinguish the response maps of ICC units also are reflected in ILD functions. The functions plotted in Fig. 1 right, were created by presenting a 10 dB re threshold BF tone to the contralateral ear while varying the intensity of a BF tone in the ipsilateral ear across a ±20 dB range of levels (the excitatory monaural intensity, EMI, constant method). By convention, positive ILDs indicate stronger sounds at the contralateral ear. For the type V unit (Fig. 1C), firing rates remained relatively constant at low levels of ipsilateral stimulation (positive ILDs) because responses were dominated by the fixed contralateral tone. The excitatory drive to the unit increased at more intense levels of ipsilateral stimulation (negative ILDs) and higher firing rates were achieved. By contrast, the discharge rates of both type I (Fig. 1F) and type O units (Fig. 1I) decreased when the balance...
of inputs shifted toward inhibition at increased levels of ipsilateral stimulation (negative ILDs). The threshold for transition from a contralateral to ipsilateral dominant response has been defined as the half-maximal ILD (ILD50). Typically this measure is used to characterize the threshold of ipsilateral inhibitory effects (Park and Pollak 1993; Wenstrup et al. 1988) and is defined to be the ILD at which the driven response to the binaural stimulus declines by 50% from the response evoked by contralateral monaural stimulation (horizontal arrows in Fig. 1, C, F, and I). For example, the ILD50 for the type I and type O units in Fig. 1, F and I, respectively, are reached at slightly negative ILDs (vertical arrows). In this report, the ILD50 of a type V unit indicates the binaural condition that elicits a response that is 50% greater than the contralateral response; for the type V unit in Fig. 1C, the ILD50 is reached at an ILD of +15 dB.

Table 1 summarizes the relationships between ipsilateral frequency response maps and binaural interaction classes for type V, type I, and type O units. Note that most of the units fall along the shaded diagonal in the table, indicating a one-to-one correspondence between response map properties and binaural interactions. All six type V units showed excitation for contralateral and ipsilateral tones (EE properties) and an ILD function that displayed rate increases at higher levels of ipsilateral stimulation. The majority of type I (15/21) and type O units (14/26) showed ipsilateral inhibition (EI properties) and an ILD function that declined as ipsilateral stimulation increased. A subset of units (3 type I and 7 type O units, most with BFs ≤ 3 kHz) showed ipsilateral response maps that changed from excitation at low-stimulation levels to inhibition at high levels. These units tended to have complex ILD functions, called EI/l after Park and Pollak (1993), that showed facilitation at low levels of ipsilateral stimulation and inhibition at higher levels.

Our system of response map classification did not always predict the binaural properties of ICC neurons. For example, five units (3 type I and 2 type O) exhibited no excitation in their ipsilateral maps but produced ILD functions with EI/l properties. These results are consistent with the idea that some binaural facilitation is created within the ICC (Park and Pollak 1993). Conversely, one type O unit without any detectable inhibition in its ipsilateral map showed an EI ILD function. In all, 4/37 type I and 15/45 type O units showed little or no response to ipsilateral tones; however, in almost all cases, these units showed clear inhibitory responses to broadband noise bursts. Therefore tones may not be the most effective stimuli for direct determination of a unit’s ipsilateral response properties.

ILD functions obtained with the EMI-constant method summarize the binaural properties of auditory neurons in terms of responses obtained at one frequency (BFc) across a restricted range of stimulus levels (±20 dB re contralateral level). Analyses of binaural frequency response maps, on the other hand, have the potential to assess binaural interactions over the entire receptive field of ICC neurons. Although results presented in Table 1 suggest that the EMI-constant method provides a good estimation of basic binaural properties, the question remains as to what extent this outcome is determined by the choice of stimulus parameters. For example, a comparison of the monaural frequency response maps in Fig. 1 suggests that the most sensitive frequency for the contralateral ear (BFc) is not necessarily the most effective stimulus for the ipsilateral ear (e.g., for the type O unit, BFc is 3.4 kHz lower than the BF of the inhibitory response to ipsilateral stimulation).

Figure 2A shows the differences in the most sensitive frequency of the ipsilateral versus the contralateral ear for all units in this study with completely sampled ipsilateral response maps. Each symbol plots the ratio in octaves of the ipsilateral best frequency (BFi, e.g., vertical lines in Fig. 1, B, E, and H) to BFc as a function of BFc. The BF ratio changes from negative to positive values as BFc moves from lower to higher frequencies relative to BFi and equals 0 when BFs are equal in both ears (— —). For type V units (V), there is a tendency for BFi to be lower than BFc (P < 0.001, paired t-test); Semple and Kitzes (1985) found a similar pattern for EE units in anesthetized gerbil. In contrast, for type O units (O), BFc is typically above BFi (P < 0.001). This difference does not simply reflect a dependence on BF (type V units have low BFs, whereas type O units have high BFs) because type I units (vertical lines) also tend to have widely ranging BFc,s yet show the same tendency as type V units for BFi to be below BFc (P < 0.001). Notwithstanding these consistent differences, BFc and BFi deviated by less than ±0.1 octaves in 39/59 cases, suggesting that ILD tests with BFc tones will evoke binaural responses that are strong enough to characterize the binaural interactions of ICC neurons. The substantial overlap of contralateral and ipsilateral response areas (e.g., Fig. 1, A and B) suggests further that the basic nature of ILD functions should not alter for stimulus frequencies away from BFc but still within the excitatory area of the contralateral map. This interpretation was tested by examining the effects of frequency on ILD functions. Figure 2B compares BFc ILD functions of the three representative ICC units (dotted line, data shown in Fig. 1) with results obtained when the stimulus frequency was shifted below BFc by one-quarter of the excitatory bandwidth at 10 dB re threshold (solid line; ~0.25 octaves for the type V unit and 0.1 octaves for the type I and O units). For all 3 unit types, the ILD functions for the off-BFc stimuli show shallower slopes, at least over the initial portion of the curves, and thus increased ILD50 values (solid arrows to right of dotted arrows). Change in slope reflects the decreased modulatory effect an ipsilateral response can have on the reduced discharge rate evoked by the off-BFc tones.

<table>
<thead>
<tr>
<th>Ipsilateral Map Type</th>
<th>Binaural Interaction Class</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>e 6-V</td>
<td></td>
<td>6-V</td>
</tr>
<tr>
<td>i 15-I, 14-O</td>
<td>15-I, 14-O</td>
<td>18-I, 15-O</td>
</tr>
<tr>
<td>f 2-O, 1-O</td>
<td>1-O</td>
<td>3-I, 4-O</td>
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<tr>
<td>NR 6-V, 2-O</td>
<td>6-V, 2-O</td>
<td>15-I, 16-O</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>6-I, 6-O</td>
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Table 1. Ipsilateral response and binaural interaction class of response map-identified units.
contralateral stimulus; nonetheless, it is clear that the pattern of binaural interaction did not change with choice of base frequency.

The importance of stimulus level on ILD measures is illustrated in Fig. 3A by plotting the ILD50 for 6 type V, 21 type I, and 26 type O units in relation to each unit’s difference in ipsilateral and contralateral thresholds for BFc tones. The rising slope of the regression line indicates that ILD50 is correlated positively with ipsilateral sensitivity ($P < 0.05$, t-test). Type V units have relatively low ipsilateral thresholds and reach the threshold of binaural interaction at the lowest levels of ipsilateral stimulation (positive ILDs). The majority of type I and O units required higher levels of ipsilateral stimulation to meet the criteria for both monaural threshold and ILD50. When data from all unit types are combined, the average difference in ipsilateral versus contralateral threshold is 11 dB (vertical arrow); therefore the EMI-constant method with a contralateral base intensity of 10 dB creates an ipsilateral stimulus condition that is just below threshold at an ILD of 0 dB. On average, only

![Graph of ILD functions](image)

**Fig. 2.** *A:* difference (in octaves) between ipsilateral and contralateral best frequency (BF) plotted in relation to the contralateral BF. Each symbol describes the responses of a single unit. Data falling along --- indicate units that displayed no differences in BF between ears. *B:* ILD functions obtained with BFc tones (from Fig. 1; ---) and with tones at a 2nd, lower frequency within the range of the contralateral excitatory receptive field (~0.25 octaves below BFc for the type V unit, and 0.1 octaves below BFc for the type I and type O units; ---). ILD50 values are indicated by ↓; spontaneous rates by ---.

**Fig. 3.** Effects of stimulus intensity on ILD functions. *A:* half-maximal ILD values (ILD50) are plotted against the ipsilateral (re contralateral) thresholds of all units. Units with higher ipsilateral thresholds reached ILD50 at more negative ILDs (regression line). On average, ipsilateral thresholds were 11 dB higher than contralateral thresholds (↓), and the ILD50 was achieved when the tone in the ipsilateral ear was 5 dB more intense than the contralateral stimulus (→). *B:* ILD functions for representative units at the standard 10 dB contralateral level (functions from Fig. 1; ---) and at a higher 40 dB contralateral level (→). ILD50 values are indicated by ↓; spontaneous rates by ---.
a slight increase in ipsilateral stimulation was needed to attain the ILD$_{50}$ (ILD = $-5$ dB, horizontal arrow). The complete distribution of ILD$_{50}$s fell between $-23$ and $12$ dB, which suggests that the range of stimulus conditions used in the EMI-constant method is well suited for describing the binaural properties of ICC neurons.

Figure 3B shows how ILD functions for the representative ICC neurons changed when the base intensity of the contralateral stimulus was raised to 40 dB re threshold. For each unit type, the slope of the ILD function was shallower for the higher level of contralateral stimulation (---) than for the standard 10 dB stimulus (---). Modulation of discharge rates along the ILD function of the type V unit was diminished by the increase in minimum rate that accompanied stronger ipsilateral excitation at the $+20$ dB ILD condition. In contrast, the ILD function for the type I unit showed a smaller modulation of rates when tested at 40 dB re threshold because its maximum rate (at 20 dB ILD) was suppressed by the ipsilateral response at the higher stimulus level. Strong contralateral and ipsilateral stimulation drove the type O unit to complete inhibition along the length of the ILD function. Consistent with the enhanced ipsilateral response at the lowest ILD tested, most units failed to show thresholds of transition (ILD$_{50}$) from contralateral to ipsilateral dominant responses; in those cases where an ILD$_{50}$ was present, it was shifted toward more positive ILDs (a smaller increase in ipsilateral stimulation was required).

**Effects of binaural stimulation on frequency-tuning characteristics**

Ipsilateral inputs influence the binaural frequency-tuning and threshold characteristics of ICC units. Figure 4 shows binaural frequency response maps for a representative type V, type I, and type O unit. Each plot indicates the discharge rates produced when binaural tone bursts were swept in frequency across the unit’s receptive field. This is essentially the same testing procedure that was used to produce the monaural frequency response maps in Fig. 1, but here fewer levels are shown to facilitate the comparison of ILD effects. The level of the contralateral tones was fixed at 10 dB (bottom) or 40 dB (top) above the BF, threshold; the level of the ipsilateral tones was 20 dB below (ILD = $+20$ dB, ---) or 20 dB above (ILD = $-20$ dB, ---) this fixed value. Excitatory responses appear as peaks that rise above spontaneous activity (---); inhibitory responses are indicated by troughs in the discharge rate profile. In response to increased ipsilateral stimulation (---), most frequencies in the receptive field of the type V unit show rate increases. Binaural facilitation expands the excitatory receptive field to include sound pressure levels and frequencies that were not effective stimulus conditions under monaural conditions. In contrast, stronger ipsilateral stimulation reduces the discharge rate of type I and type O units at most frequencies in their receptive fields; this sharpens the frequency tuning of their excitatory areas. For all units, the changes in bandwidth were most pronounced when the contralateral stimulus was near threshold (bottom plots); as a result, a type O unit was likely to lose one or more levels of its low-level island of excitation by shifting binaural stimuli to extreme ($-20$ dB) ipsilateral-dominant ILDs (---).

The effects of ILD on tuning characteristics were quantified by comparing the bandwidth of the excitatory response area at ILDs of $\pm 20$ dB; measures of excitatory bandwidth were based on Q$_{10}$ (BF$_c$/excitatory bandwidth 10 dB re threshold; Fig. 5A) and Q$_{10}$ values (BF$_c$/excitatory bandwidth 40 dB re threshold; Fig. 5B). Each symbol indicates the Q values of an individual unit (6 type V, 19 type I, and 21 type O units) at the $-20$ dB versus +20 dB ILD condition, symbols falling along the dashed lines represent units that showed no change in tuning under the ipsilaterally dominate binaural conditions. Consistent with qualitative observations for the representative units in Fig. 4, Q$_{10}$ values showed the largest changes with ILD. Type V units showed decreases in Q$_{10}$ values (symbols below the...
dashed line), indicating that frequency selectivity near threshold broadened with higher levels of ipsilateral stimulation. In contrast, higher levels of ipsilateral stimulation increased the \( Q_{10} \) values of most type I and O units; this sharpening of frequency tuning frequently lead to complete loss of BF excitation and even BF inhibition (symbols plotted above the ordinate). Similar, though smaller, changes in excitatory bandwidth were observed for type V and type I units at tone levels 40 dB re threshold (\( Q_{40} \) s are not available for type O units because they have no BF excitatory response area at this level of stimulation).

Implicit in the preceding comparisons of tuning characteristics is the assumption that the excitatory BF of the unit does not change appreciably with ILD. Figure 6 illustrates the effects of ILD on the binaural BF; the measures are derived from rate plots like those shown in Fig. 4. Each symbol plots one unit’s BF at ILDs of \(-20\) versus \(+20\) dB. Two trends are apparent in the data. First, of the 33 units that maintained excitatory responses during binaural stimulation, all units showed nearly identical BFs under the two ILD conditions (---; \( P > 0.05\), paired \( t \)-test); thus units do remain tuned to the same BF as a function of ILD. The second trend is that type O (11/21 cases) but not type I units (2/19 cases) were very likely to lose altogether their excitatory responses when tests were performed at \(-20\) dB ILD (units plotted above the ordinate). The apparently greater effect of ipsilateral stimulation on type O than type I units likely reflects the lower maximum rates type O units attain to contralateral stimulation (Ramachandran et al. 1999).

ICC units showed distinct changes in threshold as a function of ILD manipulations; statistical box plots of these effects are shown in Fig. 7. The measure of threshold change was calculated by subtracting the binaural threshold at \(+20\) dB ILD from the threshold at \(-20\) dB ILD; positive values indicate a decrease in sensitivity with stronger ipsilateral stimulation. The length of each box along the ordinate indicates the interquartile range of the distribution (i.e., the middle 50% of the range of threshold changes); error bars extend to the largest deviation within \( \pm 1.5 \) quartiles of the median score. Outliers beyond these limits are plotted as symbols (Sokal and Rohlf 1995). The magnitude of threshold changes was estimated to the nearest 5 dB, which

![FIG. 5. Effects of ILD on the excitatory bandwidth of binaural frequency response maps.](image1)

![FIG. 6. Effects of ILD on BF.](image2)

![FIG. 7. Effects of ILD on the absolute thresholds of BF \(_c\) tones.](image3)
reflects the 10-dB resolution of ILD measures for these tests. Strong ipsilateral excitation produced a 5- to 10-dB change in threshold for type V units; conversely, the thresholds of most type I units increased by 5–15 dB with two units showing a complete lack of excitatory response (data plotted above the ordinate). Ipsilateral inhibitory effects were even stronger among type O units; the entire interquartile range of this response class showed no excitation, while outliers exhibited a mean increase of 2.5 dB (symbols).

The effects of ILD on frequency tuning (Figs. 4 and 5) may reflect processing mechanisms that reside in the ICC or extrinsic binaural interactions that modify inputs to the ICC. To determine how local GABAergic inhibitory inputs shape the binaural properties of ICC neurons, frequency response maps were measured at ILDs of ±20 dB during application of bicuculline. These results are summarized by data from representative type V, I, and O units in Fig. 8A. Plotting conventions are the same as in Fig. 4; results obtained before and after the bicuculline injection are contrasted in the left and right columns of the figure. These tests were performed at a fixed contralateral stimulus level of 10 dB relative to the BFc threshold, which is a stimulus level where the tuning properties of ICC units were susceptible to ILD manipulations (see Q10 values in Fig. 5). ILDs of ±20 dB were created by setting the ipsilateral tone 20 dB below (−•−•−•) or 20 dB above (−−−−) the level of the contralateral tone. The major effects of bicuculline for the entire sample of pharmacologically tested units were increases in the level of spontaneous activity (Fig. 8B) and maximum BFc tone driven (C) rates. These increases were evident for all unit types (P < 0.05), including the type V units that produced only excitatory frequency response maps and ILD functions. The general effects of binaural stimulation on frequency tuning did not change after bicuculline administration (Fig. 8A): that is, the excitatory bandwidth of the type V unit (top) broadened with increased ipsilateral stimulation and the tuning of type I (middle) and type O units (bottom) narrowed. In fact, because of higher stimulus-driven rates, these changes in frequency tuning were even more apparent during GABAergic blockade.

**FIG. 8.** A: effects of bicuculline on binaural frequency response maps of type V (unit 1.03, exp. 97/09/17), type I (unit 1.13, exp. 97/09/17), and type O units (unit 1.17, exp. 97/09/17). Discharge rates are plotted as a function of stimulus frequency for a fixed contralateral stimulus level of 10 dB relative to threshold and binaural ILDs of ±20 dB (−−•−•) and −20 dB (−−−−). Results obtained before and after bicuculline administration are shown left and right, respectively. Average spontaneous rates are indicated (−−−−). B and C: effects of bicuculline on spontaneous (B) and maximum BFc tone driven (C) rates. Each unit’s rates before bicuculline (abscissa) are contrasted with results obtained during bicuculline application (ordinate). Data falling along −−−− indicate units that showed no rate changes during application of bicuculline.
DISCUSSION

Comparisons with previous studies of the ICC

The overwhelming majority of ICC neurons (51/53, 96%) in the present study exhibited binaural interactions. This preponderance of binaurality is at odds with the relatively high incidence of monaural response patterns that have prevailed in previous studies (e.g., 46%, Schreiner and Langner 1988; and 49%, Irvine and Gago 1990). Such differences may arise from our focus on units with sustained responses, which are quite common in the ICC of decerebrate cats (Ramachandran et al. 1999). In studies that have examined both sustained and onset responders, it has been found that the onset component of the response is relatively insensitive to ILDs (Geisler et al. 1969; Moore and Irvine 1981). The importance of onset effects may be exaggerated in studies involving barbiturate anesthesia. Although binaural interactions are not substantially altered by blocking GABAergic inhibition (Fig. 8A), the potentiation of inhibition by barbiturates could mask binaural response patterns that are present in unanesthetized cats by eliminating sustained discharge rates and in effect changing sustained responders into onset units. If our analysis of ILD effects is restricted to the initial 25 ms of stimulus-evoked discharge rates, the proportion of units showing binaural interactions falls to only 36/53 (68%) units.

The most common binaural interactions were inhibitory in nature. In part, this observation may reflect a sampling bias toward BFs >3 kHz, where the binaurally excitable type V units were never encountered. Our system for classifying ICC units has not been used before, but other studies also have noted a positive correlation between high BFs and binaural inhibition. Certainly EI units can be found across the entire range of audible frequencies (Schreiner and Langner 1988; Semple and Aitkin 1979), but high-frequency units were exclusively EI in the present study. This finding may appear to contradict previous reports that a subpopulation of high-frequency ICC units shows excitatory responses for monaural stimulation of either ear (22%, Semple and Aitkin 1979; 8%, Schreiner and Langner 1988; 9%, Irvine and Gago 1990); however, the classification of these pseudo-EI units was not based on the effects of binaural stimulation. Ipsilateral tones elicited excitatory responses over a limited range of monaural stimulus conditions from 4/53 (7.5%) type I and O units in the present study; all of these units demonstrated EI or EI/f ILD functions under binaural conditions.

Origins of binaural response patterns in ICC

On the basis of responses to contralateral stimulation, Ramachandran et al. (1999) have speculated that type V units are shaped by inputs from the medial superior olive (MSO), that type I units receive input primarily from the lateral superior olive (LSO), and that type O units are derived from projections originating in the dorsal cochlear nucleus (DCN). The ipsilateral response map characteristics of these unit types and their sensitivity to binaural stimuli provide further constraints on their potential sources of input.

Type V units show purely excitatory responses when stimulated with BF tones in either ear (Fig. 1) and are equally likely to attain their maximum discharge rates when monaural stimuli are presented to the ipsilateral or contralateral ear. Only one source of direct ICC projections, the MSO (Aitkin and Schuck 1985; Henkel and Spangler 1983), exhibits similar response properties (Goldberg and Brown 1969; Guinan et al. 1972). In addition, only type V and MSO units surpass their maximum monaural discharge rates at highly negative ILDs (Fig. 1) (Goldberg and Brown 1969). MSO units traditionally are associated with temporal coding, and this apparent ILD sensitivity is perhaps misleading. When binaural tests are conducted with the EMI-constant method, as in the present study, the average binaural intensity (ABI) at the two ears grows with increasing levels of ipsilateral stimulation; as a result, units with EE binaural properties exhibit enhanced discharge rates. Goldberg and Brown (1969) have pointed out that MSO units are relatively insensitive to ILD changes if they are presented using ABI-constant methods (for a direct comparison of EMI and ABI testing procedures, see Irvine 1987). Figure 9 shows the excitatory receptive field of a type V unit that was measured with the ABI-constant procedure; ipsilateral and contralateral stimulus levels were symmetrically manipulated about an ABI level of 10 dB re contralateral threshold; ILD of +20 (· · · · ) and −20 dB (−−−−) were created by changing ipsilateral and contralateral stimulus levels symmetrically about the ABI. −−−−, average spontaneous rate.

FIG. 9. Effects of ILD on the excitatory receptive field of a type V unit under average binaural intensity (ABI)-constant methods. The average binaural intensity was maintained at 10 dB re contralateral threshold; ILDs of +20 (· · · · ) and −20 dB (−−−−) were created by changing ipsilateral and contralateral stimulus levels symmetrically about the ABI. −−−−, average spontaneous rate.
Type O units show essentially the same binaural input (EI) and inhibitory interaction patterns as type I units. However, the basic features of the contralateral frequency response maps of type O units (Fig. 1) are similar to those of type IV responses that are found in the DCN of decerebrate cats (Spirou and Young 1991; Young and Brownell 1976). These similarities led Ramachandran et al. (1999) to suggest that type O responses may reflect direct projections from type IV units in the contralateral DCN (Adams 1979; Ryujo et al. 1981; Young 1980; for a review, see Oliver and Huerta 1992; Rhode and Greenberg 1992). The binaural properties of DCN principal cells have not been studied in detail, but it has been established that type IV units do show the EI response pattern that is expected of the lower-order inputs to type O units (Davis and Young 1998; Mast 1970; Young and Brownell 1976). Moreover, DCN type IV units and ICC type O units share an enhancement of binaural inhibitory interactions when broadband sounds instead of pure tones are presented to the inhibitory ear.

Multiple lines of evidence suggest, however, that the ILD sensitivity of ICC neurons does not simply reflect that of its putative inputs. First, although the basic nature of an ICC unit’s ILD sensitivity usually is unchanged in the presence of inhibitory blockers applied locally (Fig. 8A), specific properties of the ILD function such as ILD_{50} point are likely to change; and, in some cases, a unit may lose its ILD sensitivity altogether (Faingold et al. 1989; Klug et al. 1995; Park and Pollak 1993; Vater et al. 1992). Second, reversible inactivation of nuclei that project to the IC also can reduce or occasionally eliminate the effectiveness of stimulation of the ipsilateral ear (Faingold et al. 1993; Kelly and Li 1997; Li and Kelly 1992). Finally, in vivo whole cell patch-clamp (Covey et al. 1996) and intracellular (Kuwada et al. 1997) recordings show that most IC neurons receive synaptic inputs from multiple sources and that intrinsic membrane properties can shape a neuron’s response to stimuli. Consistent with these observations, Park (1998) found several differences between the ILD sensitivity of LSO and IC neurons in bat. Thus the majority of IC neurons appear to modify their ILD-sensitive properties.

In addition to their ILD sensitivity, many low-frequency ICC neurons are sensitive to interaural time differences (ITDs) (Kuwada et al. 1987, 1989; McAlpine et al. 1998; Palmer et al. 1990; Yin and Kuwada 1983a,b). This property could provide another test for identifying potential sources of input to ICC neurons. Type O units (Fig. 1) are similar to those of type IV responses that are found in the DCN of decerebrate cats show that type O units receive synaptic inputs from multiple sources and that intrinsic membrane properties can shape a neuron’s response to stimuli. Consistent with these observations, Park (1998) found several differences between the ILD sensitivity of LSO and IC neurons in bat. Thus the majority of IC neurons appear to modify their ILD-sensitive properties.

Binaural processing and frequency tuning

Closed-field ILD manipulations in the present study were designed to simulate how the directional properties of free-field sounds influence binaural processing. A major finding for these pseudo-sound localization experiments was that the excitatory receptive fields of ICC units can grow (type V units) or shrink (type I and O units) depending on the relative strength of contralateral versus ipsilateral stimulation. When other studies examined binaural interactions in ICC (or its amphibian analogue) using actual free-field sounds, correlations between stimulus azimuth and excitatory tuning have been observed (cat, Leiman and Hafter 1972; frog, Gooler et al. 1993, 1996; mouse, Cain and Jen 1995; bat, Chen et al. 1995). Although these independent lines of evidence generally support our interpretations of ILD effects, important differences in species morphology must be considered. For example, units with EE binaural properties showed directionally dependent narrowing of frequency tuning in the amphibian studies of Gooler et al. (1993, 1996). By contrast, binaurally excitable type V units in this study were insensitive to ILD changes under comparable ABI-constant conditions (Fig. 9). One explanation for this apparent species differences is that EE responses in the amphibian ICC do not reflect excitatory inputs in both ears but acoustic crosstalk via anatomic communications of the middle ear (i.e., the monaurally excitable ear is easily driven by sounds reaching either tympanum). Indeed, like type I and O units (Fig. 1), ILD functions of EE units in the Gooler et al. studies show inhibitory interactions at higher levels of ipsilateral stimulation (Gooler et al. 1996, Fig. 2).

Pharmacological evidence also suggests that binaural processing in the auditory midbrain may involve different mechanisms for different species. Xu and Feng (1996) found that local iontophoretic application of bicuculline eliminated the directionally dependent frequency tuning characteristics of ICC units in frogs. In contrast, the same manipulation had little effect on frequency tuning in the ICC of decerebrate cats (Fig. 8A). Although our observations are based on a small sample of units (n = 8), they show consistency within themselves and agree with a larger body of data showing minimal effects of bicuculline on ILD functions in the decerebrate cat (12/14 cases). In addition, the increases in spontaneous activity (on average 80% over control; Fig. 8B) and maximum driven rates (mean 80% over control; Fig. 8C) that were observed during these experiments are consistent with the known effects of bicuculline in a variety of species (chinchilla, Palombi and Caspary 1996; bat, Fuzessery and Hall 1996; frog, Xu and Feng 1996) and indicate that an effective level of bicuculline reached its target sites.

Directionally dependent changes in excitatory bandwidth are likely to impact the signal processing capabilities of ICC units. Type V units are not influenced by ILD manipulations (in the ABI scheme); rather, the threshold and tuning characteristics of these units are changed by ITDs (Ramachandran and May 1999). Consequently type V units likely are specialized to play a role in auditory behaviors requiring faithful transmission of temporal information (Kuwada and Yin 1983; Yin et al. 1986, 1987) such as sound source detection and location (Heffner and
Directional properties exhibited by type I and O units also may have important implications for the neural representation of sounds that occur at the same time but from different places. To illustrate this process, consider as competing sound sources a narrowband auditory signal near the contralateral ear and broadband environmental noise near the ipsilateral ear. Our ILD experiments indicate that binaural inhibitory interactions elicited by the spatially disparate noise masker will decrease the excitatory bandwidths of ICC units that are responding to the auditory signal in the contralateral ear. These changes in filter shape will exert minimal effects on the processing of the narrowband signal but will result in greater rejection of broadband noise; consequently, signal-to-noise ratios will be enhanced. An assumption implicit in this model is that the ipsilateral noise that enters the contralateral ear will not suppress entirely the response to the contralateral narrowband signal via activation of the inhibitory sidebands in these units. In this regard, preliminary data indicates that spatially disparate noise causes weaker masking effects than cospatial noise (Ramachandran et al. 1997), consistent with data obtained in frog ICC (Ratnam and Feng 1998).

The ILD sensitivities of ICC units appear to be dominated by inputs from lower-order nuclei. Because these data have been obtained in decerebrate cats, however, descending influences have been eliminated. There is a strong descending input that originates in primary auditory cortex and terminates in the dorsal cortex of the IC (Coleman and Clerici 1981); these descending influences may be communicated to the ICC via GABAergic inhibitory projections (Moore et al. 1998). When GABA_A inhibitory effects are modulated in decerebrate cats by local administration of bicuculline, basic response characteristics do not change; rather large increases in spontaneous activity and stimulus-driven discharge rates are observed. On the basis of these results, it is intriguing to speculate that descending inputs from higher auditory centers might use inhibitory effects as attentional filters for gating biologically important inputs from higher auditory centers.

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REFERENCES


ILD SENSITIVITY OF ICC UNITS


