

Multiple Components of Ipsilaterally Evoked Inhibition in the Inferior Colliculus

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Klug, Achim, Eric E. Bauer, and George D. Pollak. Multiple components of ipsilaterally evoked inhibition in the inferior colliculus. *J. Neurophysiol.* 82: 593–610, 1999. The central nucleus of the inferior colliculus (ICc) receives a large number of convergent inputs that are both excitatory and inhibitory. Although excitatory inputs typically are evoked by stimulation of the contralateral ear, inhibitory inputs can be recruited by either ear. Here we evaluate ipsilaterally evoked inhibition in single ICc cells in awake Mexican free-tailed bats. The principal question we addressed concerns the degree to which ipsilateral inhibition at the ICc suppresses contralaterally evoked discharges and thus creates the excitatory-inhibitory (EI) properties of ICc neurons. To study ipsilaterally evoked inhibition, we iontophoretically applied excitatory neurotransmitters and visualized the ipsilateral inhibition as a gap in the carpet of background activity evoked by the transmitters. Ipsilateral inhibition was seen in 86% of ICc cells. The inhibition in most cells had both glycinergic and GABAergic components that could be blocked by the iontophoretic application of bicuculline and strychnine. In 80% of the cells that were inhibited, the ipsilateral inhibition and contralateral excitation were temporally coincident. In many of these cells, the ipsilateral inhibition suppressed contralateral discharges and thus generated the cell's EI property in the ICc. In other cells, the ipsilateral inhibition was coincident with the initial portion of the excitation, but the inhibition was only 2–4 ms in duration and suppressed only the first few contralaterally evoked discharges. The suppression was so slight that it often could not be detected as a decrease in the spike count generated by increasing ipsilateral intensities. Twenty percent of the cells that expressed inhibition, however, had inhibitory latencies that were longer than the excitatory latencies. In these neurons, the inhibition arrived too late to suppress most or any of the discharges. Finally, in the majority of cells, the ipsilateral inhibition persisted for tens of milliseconds beyond the duration of the signal that evoked it. Thus ipsilateral inhibition has multiple components and one or more of these components are typically evoked in ICc neurons by sound received at the ipsilateral ear.

INTRODUCTION

A major focus of auditory research has been on how acoustic information is encoded in the central nucleus of the inferior colliculus (ICc) (e.g., Aitkin 1986; Brugge 1992; Irvine 1992; Oliver and Huerta 1992; Pollak and Park 1995; Pollak et al. 1986; Yin and Kuwada 1984). The ICc is of particular interest because it is a nexus in the ascending auditory pathway that receives and integrates information from a large number of lower auditory nuclei (Adams 1979; Aitkin 1986; Beyerl 1978; Brunso-Bechtold et al. 1981; Oliver and Huerta 1992; Ross et al. 1988; Roth et al. 1978; Vater et al. 1992b; Zook and

Casseday 1982) and provides the principal ascending input to the medial geniculate body. The projections that innervate the ICc are both excitatory and inhibitory. The inhibitory innervation is both glycinergic and GABAergic and is at least as prominent as the excitatory innervation of the ICc (Fubara et al. 1996; Gonzalez-Hernandez et al. 1996; Saint Marie et al. 1989; Shneiderman and Oliver 1989; Shneiderman et al. 1988; Winer et al. 1995).

The projections to the ICc originate from lower centers that are driven by the contra- or ipsilateral ears or by both ears. Thus many, if not most, ICc neurons are involved in the processing of binaural stimuli (Irvine et al. 1995; Klug et al. 1995; Park and Pollak 1993b; Park et al. 1992; Ross and Pollak 1989; Semple and Kitzes 1987; Wenstrup et al. 1985; Yin et al. 1983, 1984). In almost all ICc cells, stimulation of the contralateral ear evokes a mixture of excitation, which drives ICc cells, and inhibition, which shapes the pattern of the discharge train (Le Beau et al. 1996; Park and Pollak 1993a; Vater et al. 1992a). In many ICc neurons, sound presented only to the ipsilateral ear evokes no discharges but when presented simultaneously with contralateral sound, suppresses the contralaterally evoked discharges (Fuzessery et al. 1990; Irvine and Gago 1990; Irvine et al. 1995; Semple and Aitkin 1979; Semple and Kitzes 1985; Wenstrup et al. 1988a). Cells with these properties are referred to as excitatory-inhibitory (EI) neurons and are of particular interest because their spike counts vary with interaural intensity disparities (IIDs), the principal cue animals use to localize high-frequency sounds. Thus the encoding of IIDs by the population of EI cells in the ICc is thought to be an important feature of the nervous system that allows animals to associate a sound source with its location in space (Aitkin 1986; Fuzessery and Pollak 1985; Fuzessery et al. 1990; Pollak and Casseday 1989; Wenstrup et al. 1988a,b).

The projections that impart binaural properties to ICc neurons, including EI properties, are of two principal types. One type of projection is from a lower nucleus that is itself binaural, and thus the binaural property of the target cell in the ICc actually is created in that lower nucleus and imposed on the ICc cell through an excitatory projection. An example is the crossed excitatory projection from the lateral superior olive (LSO) to the ICc. The LSO is the initial site of binaural convergence that produces EI neurons (Caird and Klinke 1983; Cant and Casseday 1986; Harnischfeger et al. 1985; Moore and Caspary 1983) and many ICc cells apparently derive their binaural EI property through this projection (Klug et al. 1995; Park and Pollak 1993b, 1994; Shneiderman and Henkel 1987; Vater et al. 1992a). The second type of projection is from at least two lower nuclei, where one nucleus is driven only by

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stimulation of one ear and the other nucleus is driven only by the opposite ear. The projections from the two lower nuclei converge on an ICc cell to create the binaural property in the ICc itself. An example is the convergence of excitatory projections from a lower nucleus (e.g., cochlear nucleus) driven only by the ear contralateral to the ICc and a GABAergic inhibitory projection from the dorsal nucleus of the lateral lemniscus (DNLL) that is driven by stimulation of the ear ipsilateral to the ICc (Faingold et al. 1993; Kidd and Kelly 1996; Klug et al. 1995; Li and Kelly 1992; Park and Pollak 1993b, 1994; Vater et al. 1992a; Yang and Pollak 1994a,b). The convergence of these projections then creates an EI cell in the ICc the binaural properties of which are virtually indistinguishable from the EI properties that are created in the LSO and imposed on the ICc cell.

Intracellular, pharmacological, and reversible lesion studies provide proof that EI neurons in the ICc actually are formed by the two types of projections described in the preceding paragraph. Intracellular studies using sharp electrodes or whole cell patch-clamp electrodes showed that some EI cells in the ICc receive inhibitory innervation evoked by the ipsilateral ear (Covey et al. 1996; Kuwada et al. 1997; Nelson and Erulkar 1963; Pedemonte et al. 1997), whereas pharmacological studies showed that many, but not all, EI cells in the ICc could be transformed into monaural cells when inhibition was blocked by antagonists specific for GABAergic or glycinergic receptors (Faingold et al. 1989; Klug et al. 1995; Park and Pollak 1993b, 1994; Vater et al. 1992a). Further supporting the role of ipsilateral inhibition in the formation of EI properties are the results from studies in which the binaural properties of ICc neurons were transformed when the GABAergic input from the DNLL was inactivated reversibly (Faingold et al. 1993; Kidd and Kelly 1996; Li and Kelly 1992).

The studies cited in the preceding text show that ipsilaterally evoked inhibition at the ICc is not uncommon and is functionally important. Besides these general features, however, little is known about the specific features of ipsilaterally evoked inhibition; how its threshold, latency, and duration compares with the excitation evoked by stimulation of the contralateral ear in the same cell. These are, we believe, important considerations because a more detailed evaluation of the patterns of excitation and inhibition evoked by each ear will provide a better understanding of how the diversity of documented ICc response properties are created and thus provide new insights into the overall strategies that are used by the auditory system for processing acoustic information.

It was for these reasons that we conducted detailed studies of responses evoked by stimulation of the contralateral and ipsilateral ears in the ICc of Mexican free-tailed bats. We chose this bat as a subject because it uses a variety of acoustic signals for both echolocation and social communication and has a relatively hypertrophied auditory system, making it well suited for studies of the brain's processing of acoustic cues. Moreover, several laboratories have used Mexican free-tailed bats in behavioral studies (Balcombe 1990; Balcombe and McCracken 1992; Gelfand and McCracken 1986; Schmidt and Thaller 1994; Simmons et al. 1978, 1979) as well as anatomic (Grothe et al. 1994) and neurophysiological studies (Grothe et al. 1997; Oswald et al. 1999; Park 1998; Park et al. 1996, 1998; Pollak et al. 1977a,b, 1978) of their brain stem auditory nuclei.

In another report, we comment on features of excitation and

inhibition evoked only by stimulation of the contralateral ear in ICc cells of the Mexican free-tailed bat (unpublished results). Here we focus on features of inhibition evoked by stimulation of the ipsilateral ear. We show that stimulation of the ipsilateral ear evokes a complex set of inhibitions in the vast majority of ICc cells that vary in latency, duration, or both features. Furthermore we show that some forms of inhibition act to create EI properties in the ICc, whereas the latencies and durations of other inhibitions are unsuited for the suppression of contralaterally evoked discharges and have different functional consequences.

METHODS

Surgical procedures

Fifteen Mexican free-tailed bats, *Tadarida brasiliensis mexicana*, were used in this study. Before surgery each animal was anesthetized with methoxyflurane inhalation (Metofane, Pitman-Moore). The hair on the head was removed with a depilatory, and the head was secured in a head holder with a bite bar. The muscles and skin overlying the skull were reflected, and lidocaine (Elkins-Sinn) was applied topically to all open wounds. The surface of the skull was cleared of tissue, and a foundation layer of cyanoacrylate and small glass beads was placed on the surface. A small hole then was drilled around the center portion of the inferior colliculus using the landmarks visible through the skull for orientation.

The bat was transferred to a heated recording chamber, where it was placed in a restraining cushion constructed of foam molded to the animal's body. The restraining cushion was attached to a platform mounted on a custom made stereotaxic instrument (Schuller et al. 1986). A small metal rod was cemented to the foundation layer on the skull and then attached to a bar mounted on the stereotaxic instrument to ensure a uniform positioning of the head. A ground electrode was placed between the reflected muscle and the skin. Recordings were begun after the bats recovered from the anesthetic. The bats typically laid quietly in the restraining cushion and showed no signs of pain or discomfort. Supplementary doses of the neuroleptic Vetamine (Mallinckrodt Veterinary) were given if the bat appeared to be in discomfort.

Using visual landmarks viewed with an operating microscope, the electrode then was positioned on the surface of the brain on top of the inferior colliculus. Subsequently, the electrode was advanced from outside of the experimental chamber with a piezoelectric microdrive (Burleigh 712 IW). Neurons were sampled at depths between 400 and 1,600 μm from the surface of the colliculus and were in the central nucleus of the inferior colliculus. All experimental procedures were in accordance with a protocol approved by the University of Texas Institutional Animal Care Committee.

Electrodes

In all experiments piggyback multibarrel micropipettes were used for recordings and iontophoresis of drugs (Havey and Caspary 1980). Single-barrel micropipettes were pulled to a tip diameter $<1 \mu\text{m}$ and blunted under microscope observation so that the tip diameter was between 1 and 2 μm . A multibarrel electrode was pulled from a five-barrel blank (H configuration, A-M Systems), and the tip was blunted so that the tip diameter of the multibarrel array was 15–20 μm . The single-barrel pipette was attached to the five-barrel pipette under microscopic observation and glued with cyanoacrylate so that the tip of the single-barrel pipette protruded ~ 10 – $15 \mu\text{m}$ from the broken tip of the five-barrel pipette. The single-barrel micropipette was used for recording and filled with buffered 1 M NaCl and 2% Fast Green (pH 7.4). Electrode impedances ranged from 5 to 15 M Ω . Fast Green was used to enhance the visibility of the electrode for place-

ment in the small hole made in the skull. One barrel of the five-barrel pipette was the balancing (sum channel) barrel, which also was filled with buffered 1 M NaCl and 2% Fast Green (pH 7.4). The remaining four ejection barrels were filled with different drugs as follows: GABA (500 mM in dH₂O, pH 3.5–4.0, Sigma), bicuculline methiodide (10 mM in 0.165 M NaCl, pH 3.0, Sigma), strychnine hydrochloride (10 mM in 0.165 M NaCl, pH 3.0, Sigma), and a cocktail of glutamate (glu) and aspartate (asp) (each 500 mM, pH 8.0, Sigma).

The drug and balancing barrels were connected via silver-silver chloride wires to a six-channel microiontophoresis constant current generator (Medical Systems Neurophore BH-2) that was used to generate and monitor ejection and retention currents. The sum channel that connected to the balancing barrel was employed to balance current in the drug barrels and reduce current effects. The recording barrel was connected by a silver-silver chloride wire to a Dagan AC amplifier (model 2400) for analysis of single-unit activity.

Acoustic stimuli and data acquisition

Sine waves from a Wavetek function generator (model 136) were shaped into tone bursts with an analog switch (Restek Model 15). The tone bursts were 20 ms in duration and had 0.5-ms rise-fall times. Stimuli to both ears were delayed by 20 ms from the start of data acquisition, using a Binaural Pulse Delay (Restek Model 110). Stimuli were presented at a rate of four per second; the rate was controlled by a Restek Model 45 real-time clock, which also timed spike events for the peristimulus time (PST) histograms. Tone-burst frequency was monitored by a frequency counter. A 24-bit digital interface NuBus card (National Instruments DIO-24) and a digital distributor (Restek model 99) connected a Power Macintosh 8500/120 computer to the Restek equipment and a two-channel digital attenuator (Wilsonics, model PATT). The output of each independently controlled channel of the attenuator was sent to a 1/4-in Brüel and Kjaer (B&K) microphone biased with 200 V DC and driven as speakers. At the start of each experiment, speakers were inserted into the funnels formed by the bat's pinnae and positioned adjacent to the external auditory meatus. The pinnae were folded onto the housing of the microphones and wrapped with Scotch tape. The acoustic isolation with this arrangement was ≥40 dB.

Only well-isolated spikes with a high signal-to-noise ratio were studied. Action potentials were fed to a window discriminator (Frederick Haer and Co.) and then to the real-time clock. The Macintosh 8500 computer read the spike data from the real-time clock and generated PST histograms in real time. All stimuli were presented in a pseudorandom order.

When glu/asp was not applied, PST histograms were generated from the spikes evoked by 20 presentations of each stimulus. A larger number of stimulus presentations were used to generate the PST histograms obtained while background activity was evoked by glu/asp. Because the PST histograms were monitored in real time, we observed the build-up of both tone-evoked and background activity and could visualize whether or not an inhibitory gap was generated by repeated presentations of the tone burst. Tone bursts were presented repeatedly until a clear gap was evident in the background activity or when it was apparent that there was no gap in the background activity. Thus a variable number of stimuli was presented during the application of glu/asp to generate each PST histogram, where the number of stimulus presentations was always larger than the 20 tone-burst presentations that were used to generate the PST histograms in the control or predrug condition.

Iontophoresis of drugs and measurement of inhibition

When drugs were not being ejected, a retention current of 15–30 nA of appropriate polarity was applied to the drug barrel to prevent leakage of drugs. When drugs were ejected, the current polarity was reversed for that drug barrel. For each neuron, GABA first was

applied iontophoretically, and the ejection current was increased progressively until the neuron was inhibited completely. The purpose of applying GABA was to ensure that drug ejection could influence the discharges of that neuron. If GABA could not completely inhibit the neuron, or if current effects could be observed, recordings were stopped immediately and the electrode was replaced.

Inhibition evoked by stimulation of the ipsilateral ear was visualized as a stimulus locked suppression of background activity. Because ICc cells had little or no spontaneous activity, we evoked background activity by iontophoresing the excitatory transmitters glu and asp onto the cell from which we were recording. Glu and asp were applied at ejection currents of 5–10 nA (electrode negative) at first, and ejection currents were adjusted until the desired background level of activity was achieved. Although high rates of 20–40 spikes/s could be evoked in a few cells, only low rates of 4–10 spikes/s could be evoked in the majority of cells regardless of the current used to eject the excitatory transmitters. We point out that due to the low rates of the glu/asp evoked background activity, the histograms often had short (2–4 ms), random gaps. To ensure that the gap we measured was indeed a

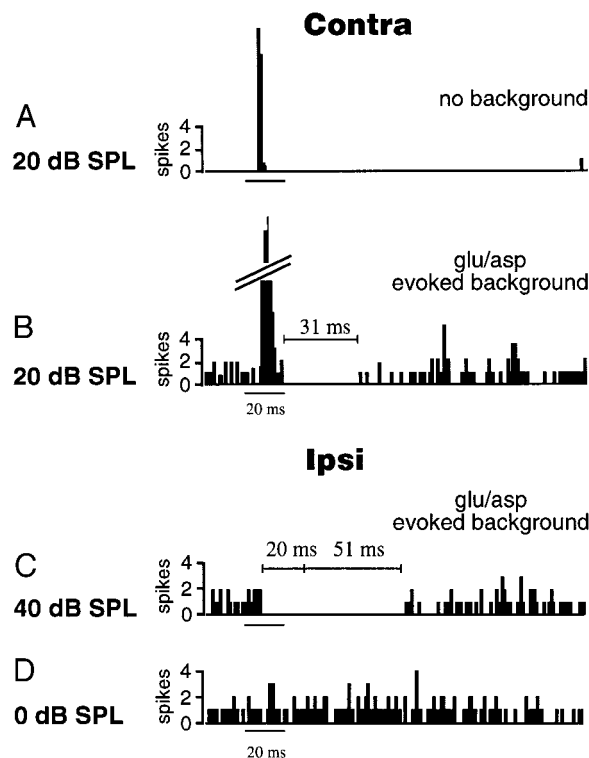


FIG. 1. Contralaterally evoked excitation and inhibition (A and B) and ipsilaterally evoked inhibition (C) in an inferior colliculus (ICc) cell. Tone-evoked inhibitory periods were measured by the gap in the background activity evoked by iontophoresis of glutamate/aspartate (glu/asp). A: peristimulus time (PST) histogram showing discharges evoked by 20 repetitions of 20-ms tone bursts presented to the contralateral ear when no background activity was evoked by glu/asp. Bar beneath histogram represents tone burst that was delayed 20 ms from the start of histogram. Tone burst was 42.34 kHz. B: PST histogram showing the cell's response to the same tone burst when background activity was evoked by glu/asp. Note the 31-ms period of inhibition immediately after the cell's excitatory response. Histogram was generated by 62 tone burst repetitions. C and D: PST histograms showing the cell's responses to 20-ms tone bursts at 2 intensities presented to the ipsilateral ear during application of glu/asp. Tone frequency was 42.34 kHz as it was in A and B. Intensity of the tone burst in C was above the inhibitory threshold and thus evoked a gap in the background discharge pattern. No gap was generated in D because signal intensity was below the inhibitory threshold. Period of inhibition in C is divided into 2 periods. First period corresponds to the duration of the 20-ms tone. Second period is the inhibition that persists beyond the tone burst duration, which in this case was 51 ms. Both histograms were generated by 48 tone burst repetitions.

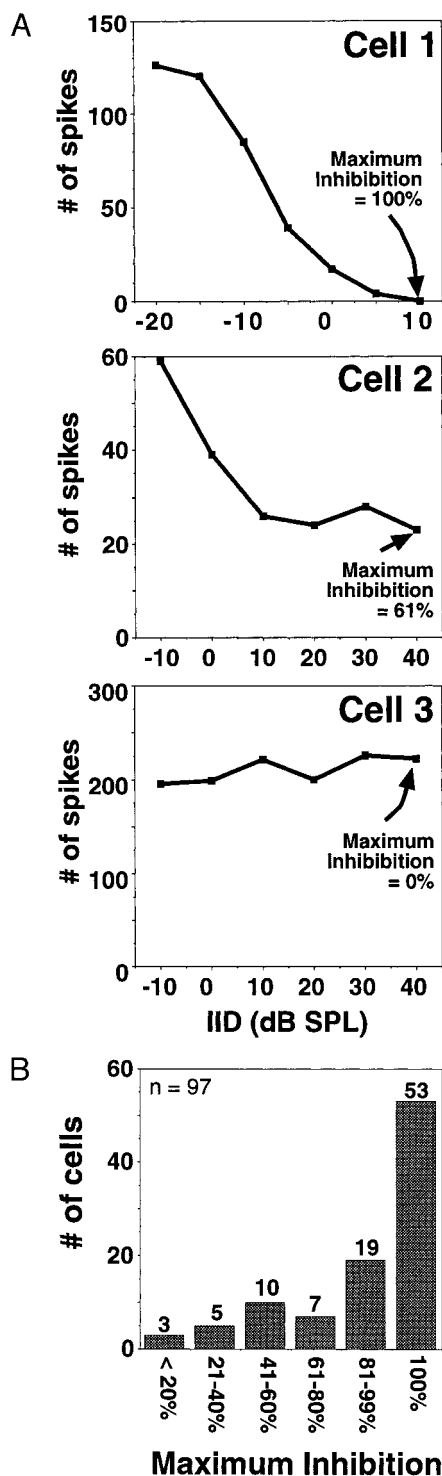


FIG. 2. A: ipsilateral sounds suppressed excitatory responses by different degrees in 3 cells. Ipsilateral suppression of spikes was assessed with a fixed contralateral intensity 10–20 dB above threshold while the intensity at the ipsilateral ear was increased. Cell's maximum inhibition was calculated by dividing the spike count evoked with the lowest ipsilateral intensity by the spike count evoked by the highest ipsilateral intensity. *Cell 1* was a strongly suppressed excitatory-inhibitory (EI) cell in which ipsilateral sound at higher intensities suppressed all contralaterally evoked spikes. *Cell 2* was a weakly suppressed EI cell and had a maximum inhibition of 61%. *Cell 3* was "monaural" because ipsilateral signals had no effect on the contralaterally evoked spike count. Tone bursts were 20.22 kHz for *Cell 1*, 22.22 kHz for *Cell 2*, and 19.60 kHz for *Cell 3*. B: distribution of maximum inhibitions for 97 cells.

stimulus evoked inhibition and not a random gap in the background activity, tone bursts at several intensities were presented. We noted the lowest intensity at which the gap was evoked and defined this as the "threshold for inhibition." The gap then had to be evoked at higher intensities in the same temporal slot as it was at the threshold intensity. In addition, we often generated histograms at a particular ipsilateral intensity more than once, and in all cases the gap appeared in the same time slot and with approximately the same duration in each histogram. Latency was defined as the time between the beginning of the stimulus and the initial appearance of the gap in background activity. Because of the presence of random gaps, the measurements of latency were approximate and have an error of about ± 2 ms.

It should be noted that the analysis of gap durations does not quantitatively assess inhibitory strength. Thus the presence of a gap may indicate an inhibition just strong enough to suppress completely the glu/asp discharges or it may indicate an inhibition that was considerably stronger. Moreover it did not identify periods during which the strength of the inhibition may have been sufficient to reduce the background rate but was not strong enough to completely suppress discharges. Unfortunately, there is no satisfactory way of evaluating changes in background spike rate quantitatively because background rates in most cells were not only low but also tended to be highly variable throughout each histogram. With these constraints in mind, we feel our evaluations are justified because the gaps in background activity were clearly stimulus locked, were repeatable and robust, and represent a conservative estimate, rather than an overestimate, of both the threshold and duration of the evoked inhibition.

The roles of GABAergic and glycinergic innervation in producing the ipsilateral inhibition were evaluated by the application of bicuculline, an antagonist specific for GABA_A receptors, or strychnine, an antagonist of glycine receptors. The ejection current used for each neuron was determined by initially ejecting the drug at a low current (10 nA, electrode positive) while obtaining rate-level functions by presenting tone bursts of increasing intensity to the contralateral ear. During the application of each drug, rate-level functions were taken repeatedly until the shape of the function and maximum spike count stabilized. The ejection current then was increased, and the procedure was repeated until the maximum spike count no longer increased. Final currents for bicuculline and for strychnine ranged from 10 to 80 nA. The antagonists then were applied to the cell concurrently with glu/asp while tone bursts were presented to the ipsilateral ear.

At the end of the experimental protocol, all drugs were turned off, and the cell was allowed to recover. During recovery, rate-intensity functions were taken every few minutes to assess the level of recovery. Cells were considered completely recovered when the spike counts and spike patterns were similar with those observed in the predrug condition.

RESULTS

General response properties

The effects of both binaural and ipsilateral monaural stimulation were studied in 97 ICc neurons in the Mexican free-tailed bats. Acoustic signals, whether presented to the ipsilateral or contralateral ears, were 20-ms tone bursts set at each neuron's best excitatory frequency (BEF). BEFs were determined with contralateral stimulation and ranged from 17 to 50 kHz. Contralateral stimulation always evoked discharges and, in the majority of cells, the excitation was followed by an inhibition (Fig. 1B). In 56% of the units ($n = 54$), contralateral signals evoked only one or several spikes at the onset of the tone burst (phasic pattern), whereas 44% ($n = 43$) discharged throughout the duration of the tone burst (sustained pattern). The features of inhibition evoked by contralateral stimulation in these neurons will be described in a future report (unpub-

lished results). Signals presented monaurally to the ipsilateral ear evoked only inhibition (Fig. 1C) or no response at all.

The binaural property of each cell initially was determined from its IID function. IID functions were generated by driving the cells with BEF tone bursts presented to the contralateral ear at an intensity that was fixed at 10–20 dB above the cell's threshold (the lowest intensity that evoked stimulus locked discharges) while varying the sound intensity of the same frequency at the ipsilateral ear, from 10 dB below to 20–30 dB above the contralateral intensity. The vast majority (92%, 89/97) of cells were EI, in that ipsilateral stimulation suppressed contralaterally evoked spike counts by $\geq 40\%$. However, the degree of spike suppression differed among the population. *Cell 1* in Fig. 2A, for example, was a strongly suppressed EI cell, as sound to the ipsilateral ear completely suppressed all contralaterally evoked spikes. *Cell 2* is an example of a weakly suppressed EI cell, whereas *Cell 3* appeared to be monaural because ipsilateral stimulation had no effect on the contralaterally evoked spike count. In 74% of the neurons, ipsilateral stimulation suppressed contralaterally evoked spike counts by $\geq 80\%$, and the discharges in 55% of the cells could be suppressed completely (Fig. 2B). In the following sections, we first describe features of ipsilaterally evoked inhibition in the ICc and then evaluate the degree to which that inhibition was responsible for the spike suppression seen in each cell's IID function.

Ipsilaterally evoked inhibition was evaluated by generating background activity

In 86% (83/97) of ICc cells, ipsilateral stimulation evoked inhibition that was seen as a prominent gap in the background activity evoked by glu/asp. Examples are shown in Figs. 1 and 3. In the remaining 14 cells (14%), no inhibition was evoked by ipsilateral signals at any of the intensities that we presented. Of interest is that some cells that did not exhibit ipsilateral inhibition were, nevertheless, strongly suppressed EI cells (Fig. 11). The features of these cells are consistent with the idea that the ipsilaterally evoked spike suppression was due to an inhibition in a lower binaural center, most likely the LSO, and the resulting binaural properties then were relayed to the ICc cell via an excitatory projection.

Features of the ipsilaterally evoked inhibition

Three features of ipsilaterally evoked inhibition were evaluated in greater detail: the threshold of inhibition and its relation to the excitatory threshold, the dependence of inhibitory duration on intensity, and the latency of the inhibition.

THRESHOLD OF INHIBITION. The threshold of the inhibition was defined as the lowest ipsilateral sound intensity that produced an obvious gap in the background of discharges evoked by glu/asp (Fig. 3, 20 dB SPL). Among the 83 cells that displayed ipsilaterally evoked inhibition, thresholds ranged from –10 dB SPL to +50 dB SPL, although the thresholds of most cells (77%) were between 10 and 30 dB SPL (Fig. 4A).

We also determined how well the thresholds of the ipsilateral inhibition were matched to the thresholds of the contralateral excitation. Among the 83 cells tested, the differences between excitatory and inhibitory thresholds ranged from –10 dB (inhibitory threshold lower than excitatory threshold) to

+40 dB (inhibitory threshold higher than excitatory threshold; Fig. 4B). In 95% (79/83) of the cells, however, the threshold of ipsilateral inhibition was equal to or higher than the threshold of the contralateral excitation. In only four cells (5%) was the threshold of the ipsilateral inhibition lower than the excitation.

DURATION OF INHIBITION. The duration of ipsilateral inhibition was variable in each cell and depended on stimulus intensity. Representative examples are shown in Fig. 5. In 69% of the cells (57/83), the duration of inhibition increased monotonically with intensity. In 30 of these cells (36%), the inhibitory duration increased progressively with intensity and the maximum duration was evoked at the highest sound intensity tested (e.g., Figs. 3 and 5A). In 27 other cells (32%), the duration increased with intensity and reached a maximum value, which then plateaued with further intensity increments (Fig. 5B). In 26 cells (31%), however, the duration of the inhibition was nonmonotonically related to ipsilateral sound intensity (e.g., Figs. 14C and 5, C and D). In these cells, inhibitory duration at first increased with intensity, reached a maximum at some intermediate intensity, and then decreased in duration at even higher intensities.

A noteworthy feature of ipsilateral inhibition is that in the vast majority of cells (83%, 69/83), the maximum inhibitory duration was longer than the duration of the tone burst that evoked the inhibition. In those cells, the maximum inhibition

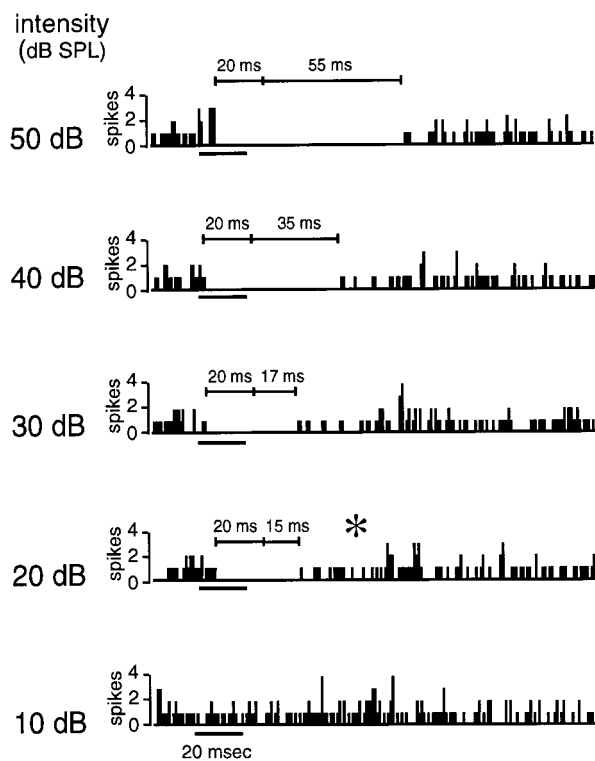


FIG. 3. PST histograms generated by increasing ipsilateral sound intensities during application of glu/asp. Threshold of inhibition was 20 dB SPL (asterisk), the lowest intensity that evoked a gap in the background activity. As ipsilateral intensity increased from 20 to 50 dB SPL, the duration of the inhibition increased progressively, from 35 ms at 20 dB SPL to 75 ms at 50 dB SPL. Inhibition is divided into 2 periods. First period corresponds to the duration of the 20-ms tone burst. Second is the inhibition that persists beyond the tone burst duration. Note that ipsilateral signals of 50 dB SPL evoked a persistent inhibition that lasted for 55 ms, which was the longest persistent inhibition in our sample. All histograms were generated by 50 tone burst repetitions. Tone bursts were 41.34 kHz.

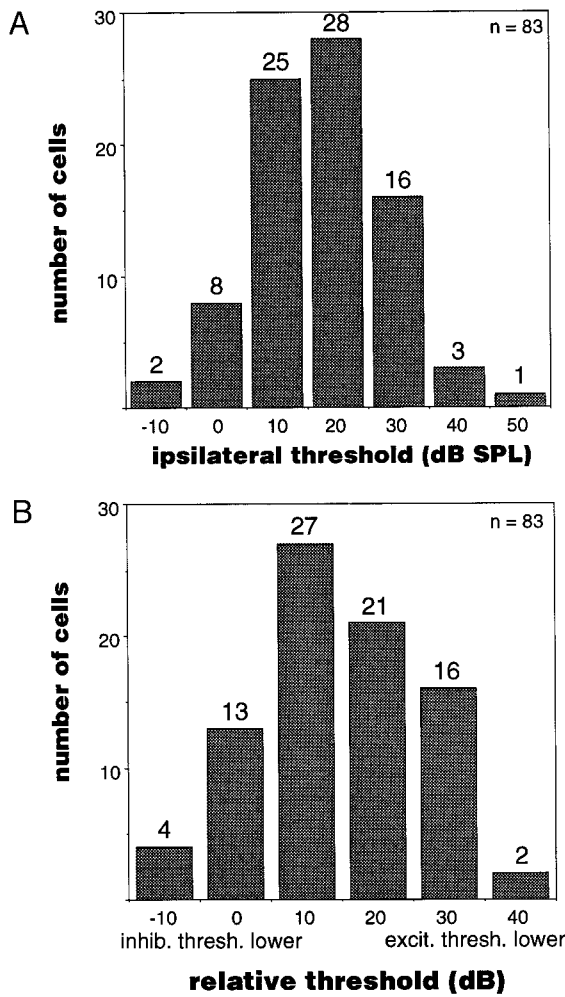


FIG. 4. A: distribution of ipsilateral inhibitory thresholds for the 83 cells. B: distribution of relative thresholds of ipsilateral inhibition and contralateral excitation for the same 83 cells. Positive numbers on the right indicate that the threshold of ipsilateral inhibition was higher than the threshold of contralateral excitation, whereas negative numbers on the left indicate that the threshold of ipsilateral inhibition was lower than the excitatory threshold.

could be divided into two periods, one corresponding to the duration of the tone burst, which in these cases was 20 ms, and a second period that persisted beyond the 20 ms of the tone burst duration. We refer to the second period as the persistent inhibition (Figs. 1C and Fig. 3). In Fig. 1C, the persistent inhibition lasted 51 ms. Among 83 cells, the average maximum persistent inhibition was 15 ms, and most cells (63%) had maximum periods of persistent inhibition that were >10 ms (Fig. 6). The longest persistent inhibition was 55 ms (Fig. 3, 50 dB SPL). The total periods of ipsilaterally evoked inhibition as well as the periods of persistent inhibition in phasic and sustained cells were not significantly different (2-tailed *t*-test, $P > 0.05$).

LATENCY OF INHIBITION. We measured latencies, defined as the time between the beginning of the stimulus and the initial appearance of the gap in background activity, during a 30- to 50-dB intensity range in 83 cells. In most cells, latency decreased with increasing ipsilateral intensity and reached a minimum at the highest intensity presented. However, in some cells the relationship between latency and stimulus intensity was nonmonotonic. In those cells, minimum latency, the short-

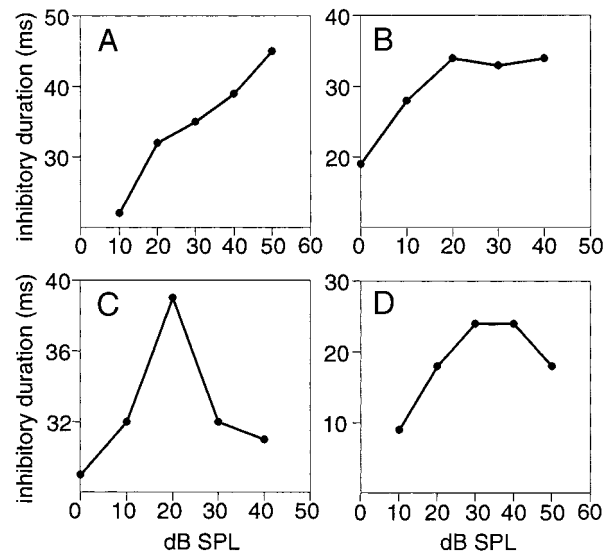


FIG. 5. Duration of the ipsilaterally evoked inhibition was variable in each cell and depended on sound intensity. Duration of the inhibition in the cell in A increased monotonically with sound intensity. In the cell in B, the inhibitory duration increased initially but then plateaued at higher sound intensities. In C and D, the cells had nonmonotonic relationships between inhibitory duration and sound intensity. In these cells, the duration of the inhibition initially increased with sound intensity but then decreased for higher intensities. Tone bursts were 23.90 kHz for A, 30.74 kHz for B, 26.94 kHz for C, and 21.37 kHz for D.

est latency evoked over this range of intensities, was achieved at an intensity lower than the most intense presented. The distribution of minimum latencies in our sample is shown in Fig. 7. The average minimum latency for the 83 cells was 9.3 ms. The minimum latencies ranged from ~5 to 29 ms, although the majority of cells (76%) had minimum latencies <12 ms. As can be seen in Fig. 7, there was no significant difference between the minimum latencies of phasic and sustained cells (*t*-test, $P > 0.05$).

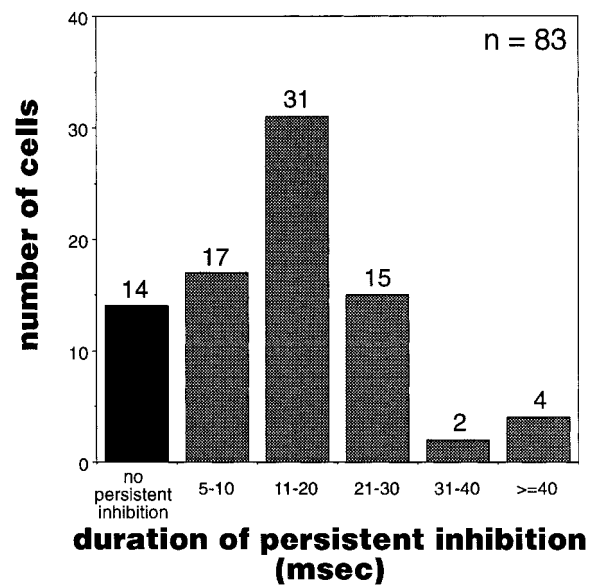


FIG. 6. Distribution of the durations of ipsilateral persistent inhibition for 83 cells.

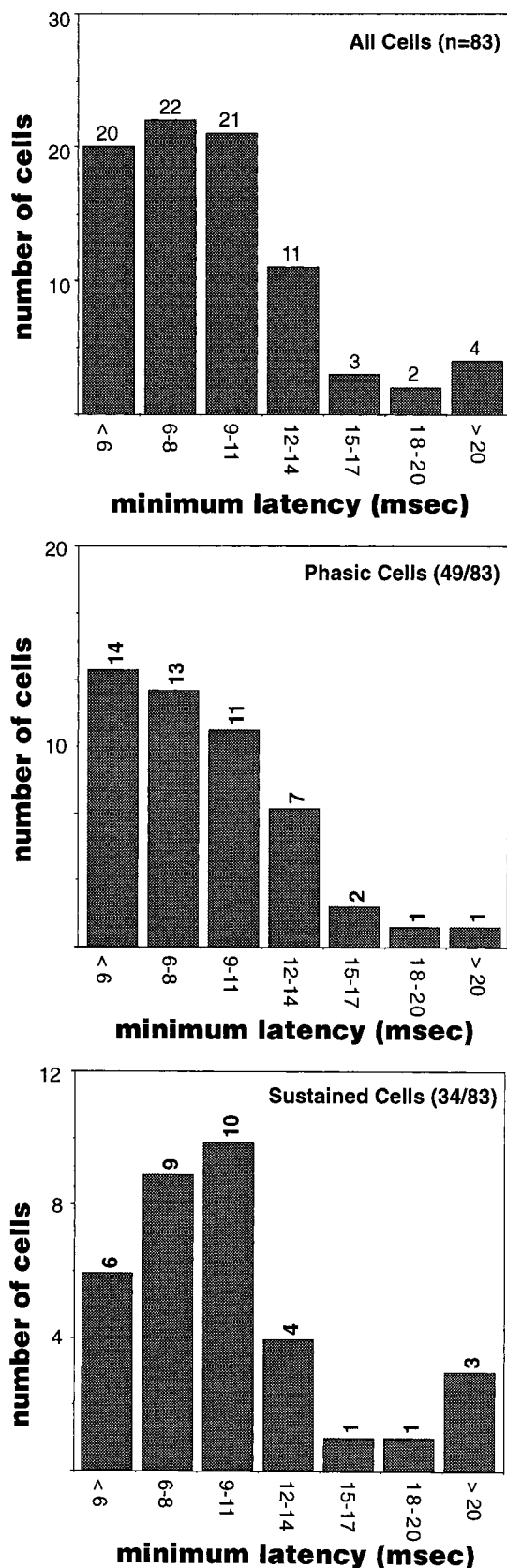


FIG. 7. Distribution of minimum latencies of ipsilateral inhibition for 83 cells. *Top*: all cells ($n = 83$), *middle*: phasic cells only ($n = 49$), *bottom*: sustained cells only ($n = 34$)

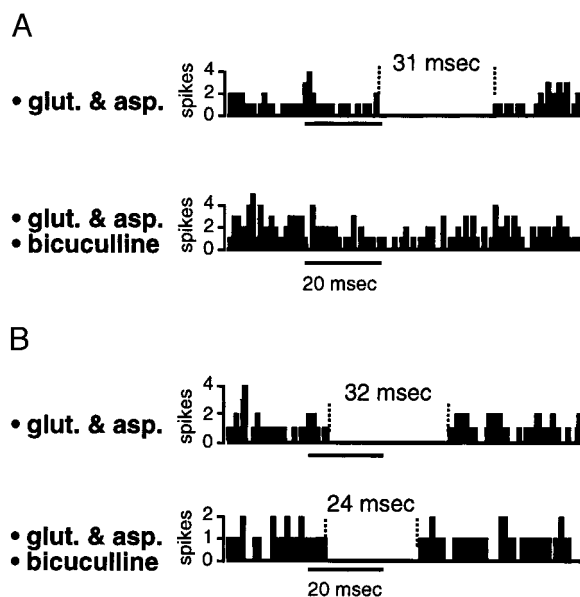


FIG. 8. Effects of blocking GABA with bicuculline on ipsilateral inhibition in 2 neurons. *A*: cell in which bicuculline eliminated ipsilateral inhibition. Tone bursts were 36.80 kHz at 40 dB SPL in both records. *Top*: histogram was generated by 68 tone-burst repetitions, whereas bicuculline histogram was generated by 75 repetitions. *B*: another neuron in which bicuculline eliminated only a late portion of the inhibition. Tone bursts were 35.20 kHz at 20 dB SPL. Both histograms were generated by 100 tone-burst repetitions.

Blocking inhibitory transmitters reduced or eliminated ipsilaterally evoked inhibition

Blocking GABAergic and glycinergic innervation eliminated most or all of the ipsilaterally evoked inhibition that we observed. We evaluated the contributions of the two inhibitory transmitters by iontophoresing either bicuculline or strychnine alone or both bicuculline and strychnine simultaneously onto the cell from which we were recording. When only GABAergic inhibition was blocked by bicuculline or glycinergic inhibition blocked by strychnine, the duration of ipsilateral inhibition was reduced in each of the 24 cells tested. Strychnine alone was tested in four cells and reduced the inhibitory period in each cell but never eliminated inhibition. Bicuculline eliminated inhibition in 2 of 20 neurons, as indicated by the presence of glu/asp-evoked discharges in the time slot in which glu/asp discharges were suppressed completely in the predrug condition. An example is shown in Fig. 8A. In the remaining 18 neurons, bicuculline reduced the duration of the inhibition but did not eliminate it (Figs. 8B and 9, A and B).

In some cells initially tested with bicuculline, we also evaluated whether the reduction in the inhibitory period could be reduced further by the addition of strychnine. Thus in 11 cells in which bicuculline did not completely eliminate inhibition, we first applied bicuculline and then applied strychnine together with bicuculline. In 4 of 11 cells, the additional application of strychnine eliminated the inhibition that was not removed by bicuculline (Fig. 9A). In seven other cells, strychnine further reduced the ipsilateral inhibition but did not eliminate it (Fig. 9B). These results show that the ipsilateral inhibition in many ICc neurons can have multiple components that are glycinergic and/or GABAergic.

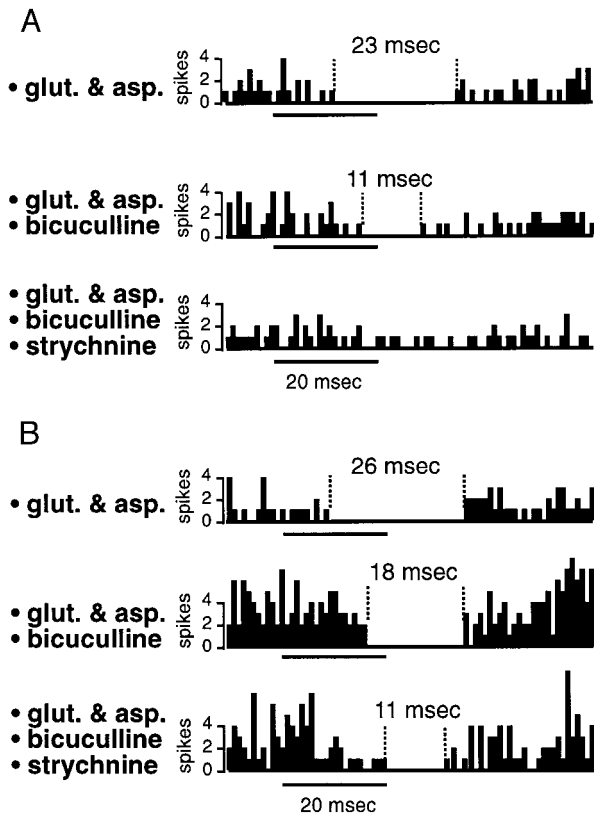


FIG. 9. Effects of bicuculline and strychnine on ipsilateral inhibition in 2 cells. *A*: in this cell, bicuculline reduced both an early and a late portion of ipsilateral inhibition. Additional application of strychnine eliminated the inhibition. Tone bursts were 22.22 kHz at 40 dB SPL. Histograms were generated by 53, 59, and 33 tone-burst repetitions in the *top*, *middle*, and *bottom*, respectively. *B*: neuron in which bicuculline blocked an early portion of the inhibition. Addition of strychnine further reduced the inhibition but did not eliminate it completely. Tone bursts were 23.88 kHz at 20 dB SPL. Forty tone bursts generated each histogram.

Influence of the ipsilaterally evoked inhibition on IID functions

We turn next to the principal question addressed by these studies: the degree to which ipsilateral inhibition at the ICc produced the suppression of contralaterally evoked discharges that was reflected in the neuron's IID function. This question is of interest because contralaterally evoked discharges could be inhibited by ipsilateral stimulation either in the ICc or in a lower nucleus, as mentioned previously. If the spike suppression occurs at the ICc, then the cell should not only exhibit ipsilateral inhibition but the inhibition at the ICc also should be temporally coincident with the contralaterally evoked excitation. It was for this reason that we compared the latencies of contralaterally evoked excitation and ipsilaterally evoked inhibition in individual ICc cells. The excitatory latency was measured from the first discharge evoked by an intensity 10–20 dB above the cell's excitatory threshold, the intensity used to generate the cell's IID function. Each cell's excitatory latency at this intensity then was compared with the minimum latency of ipsilateral inhibition.

The comparison for 83 cells is shown in Fig. 10, where positive latencies indicate that the inhibition had a shorter latency than the excitation while negative latencies indicate

that inhibition had a longer latency than the excitation. In ~80% (66/83) of the cells, the latency of inhibition was equal to or shorter than the excitatory latency (Fig. 10). Presumably, the inhibition and excitation were temporally coincident in these cells, and therefore the inhibition at the ICc could have suppressed the excitatory responses. In the other 20% (17/83) of the cells, the inhibitory latency was ≥ 3 ms longer than the excitatory latency. The significance of latency mismatches, where the inhibitory is longer than the excitatory latency, is that in cells with small latency mismatches, the ipsilateral inhibition could not have suppressed all contralaterally evoked discharges, whereas the ipsilateral inhibition in cells with substantial latency mismatches could not have suppressed any of the discharges. In the following sections, we consider in greater detail how the latencies and thresholds of ipsilateral inhibition and contralateral excitation influenced or, in some cases, failed to influence the cell's IID function.

EI cells in which the binaural properties are formed in the inferior colliculus

The similar latencies of ipsilateral inhibition and contralateral excitation in most ICc cells suggests that in those cells the suppression of contralateral discharges occurred at the ICc. Here we show that not only were the latencies of excitation and inhibition coincident, but also that the threshold of inhibition, determined with monaural, ipsilateral stimulation, corresponded to the lowest ipsilateral intensity that suppressed contralaterally evoked discharges in the IID functions and that blocking inhibition at the ICc rescued

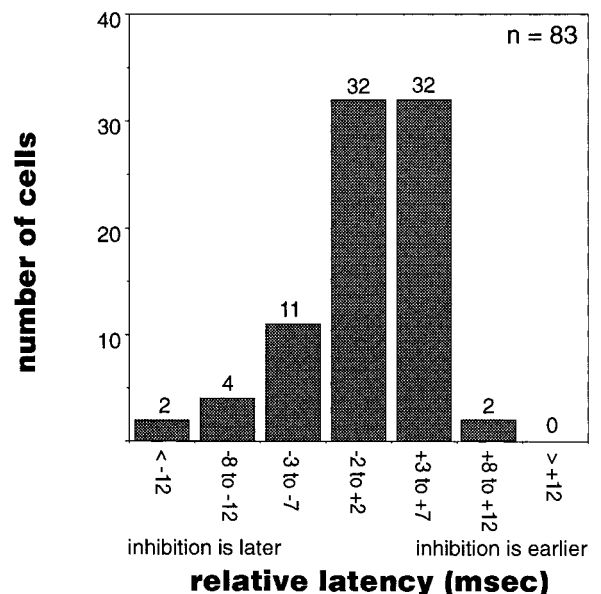


FIG. 10. Distribution of inhibitory latencies relative to excitatory latencies. Inhibitory latency of each cell was the shortest latency evoked by ipsilateral sounds presented over a 40- to 50-dB intensity range. Excitatory latency was the average latency of the 1st discharge evoked by intensities 10–20 dB above threshold, the same contralateral intensity used to generate each cell's interaural intensity disparity (IID) function. Positive numbers on the *right* indicate that the ipsilateral inhibition had a shorter latency than the excitation, whereas negative numbers indicate that the ipsilateral inhibition had a longer latency than the excitation.

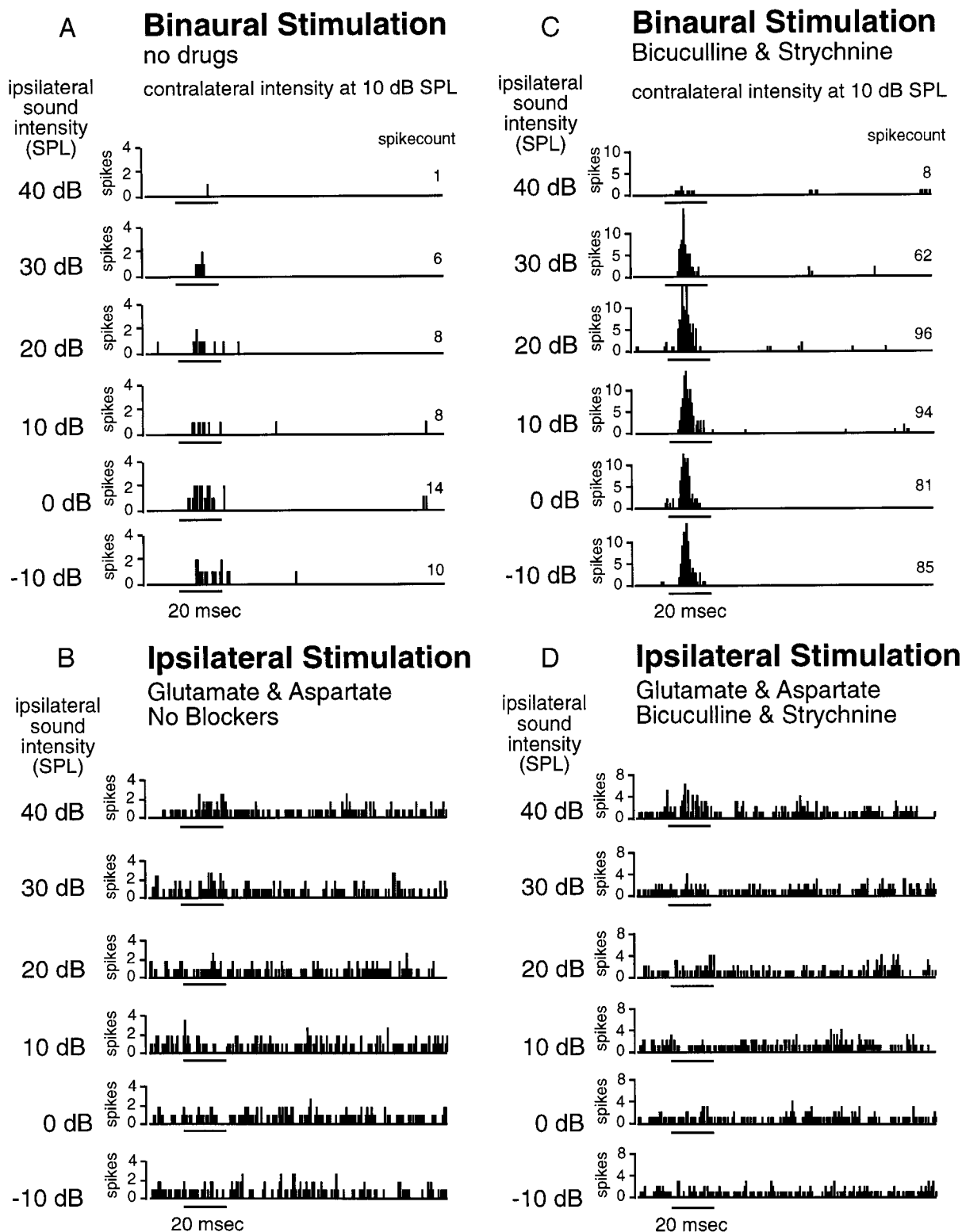


FIG. 11. PST histograms from a strongly suppressed EI cell in which no inhibition at the ICc could be evoked by ipsilateral stimulation. *A*: PST histograms showing that the cell's excitatory responses could be suppressed largely by ipsilateral sound. Histograms were generated by 20 tone burst repetitions. *B*: ipsilateral stimulation during application of glu/asp. Absence of a gap in the background activity indicates that the cell was not inhibited by ipsilateral stimulation. Histograms were generated by 65 tone-burst repetitions. *C*: PST histograms generated with binaural signals during application of bicuculline and strychnine show that the cell's binaural properties largely were unaffected by blocking inhibition at the ICc. Histograms were generated by 20 tone burst repetitions. *D*: because the cell received no ipsilateral inhibition, application of bicuculline and strychnine did not change the glu/asp-evoked background pattern to ipsilateral signals. Histograms were generated by 100 tone-burst repetitions. All tone bursts were 20.84 kHz. Spike counts on *right* in histograms in *A* and *C* only include discharges that occurred during the 20-ms tone burst.

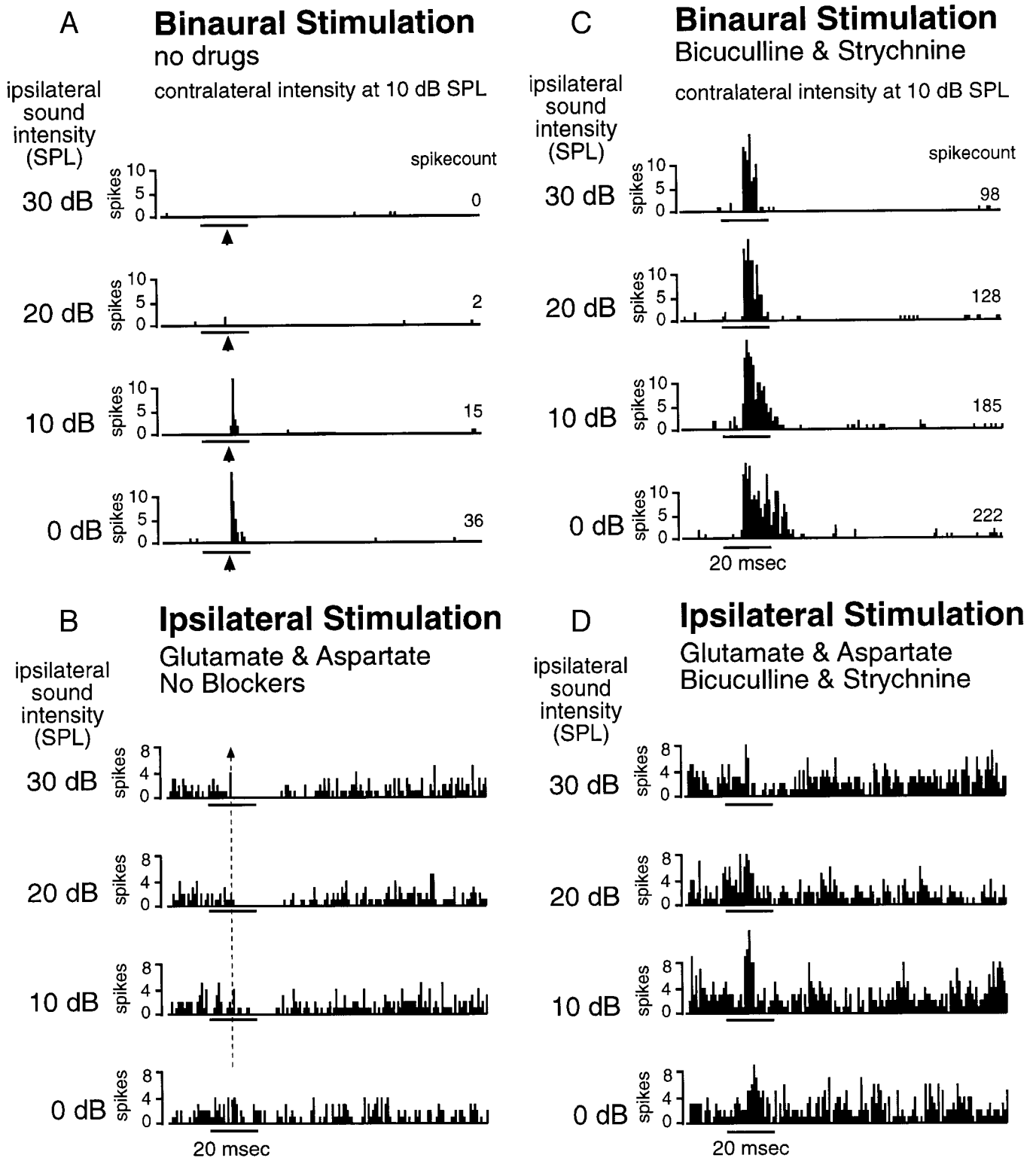


FIG. 12. PST histograms of a strongly suppressed EI cell in which ipsilateral inhibition at the ICc suppressed contralaterally evoked discharges. *A*: PST histograms showing that discharges evoked by contralateral tones at 10 dB SPL could be completely suppressed by ipsilateral sound. *B*: ipsilateral stimulation during application of glu/asp. Gaps in the background activity show that the cell was inhibited by ipsilateral tone bursts. Sound intensities that evoked inhibition (10, 20, and 30 dB SPL) match the ipsilateral intensities in *A* that suppressed discharges. Dotted line in *B* shows the minimum latency of the ipsilateral inhibition. Arrows in *A* are aligned with minimum inhibitory latency and show the latencies of excitation in *A* and latencies of inhibition in *B* are coincident. Histograms were generated by 100 tone-burst repetitions. *C*: PST histograms generated with binaural signals during application of bicuculline and strychnine. Blocking inhibition largely rescued discharges that were previously suppressed by ipsilateral intensities of 20–30 dB SPL. Histograms were generated by 20 tone-burst repetitions. *D*: application of bicuculline and strychnine eliminated ipsilaterally evoked inhibition at the ICc. Histograms were generated by 84 tone-burst repetitions. Spike counts on right in histograms in *A* and *C* only include discharges that occurred during the 20-ms tone burst. Tone bursts were 34.30 kHz.

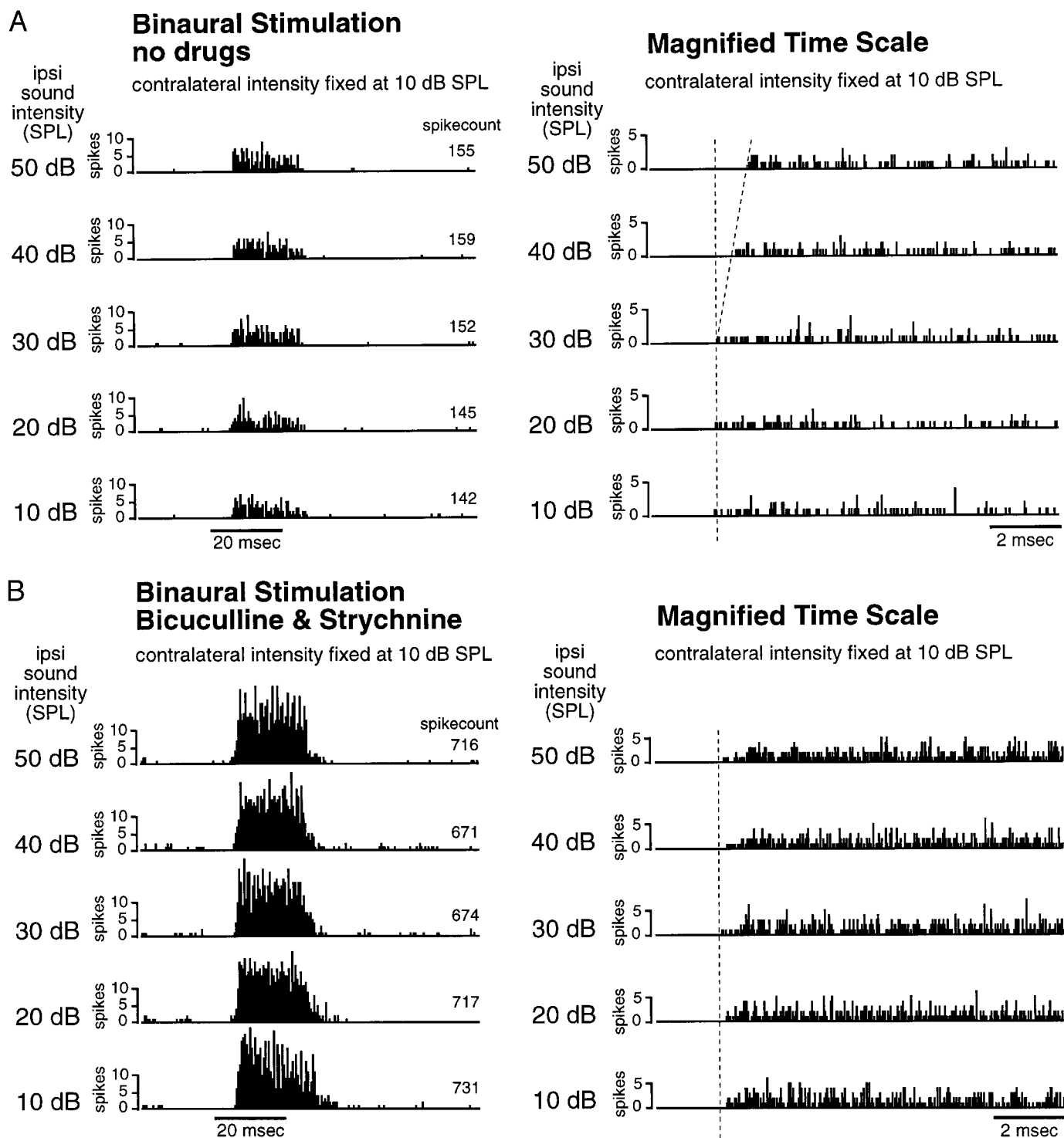


FIG. 13. PST histograms from a sustained cell that received an early, brief ipsilaterally evoked inhibition the influence of which on spike counts was undetectable. *A, left*: histograms showing that 20-ms tone bursts evoked a sustained discharge pattern with no discernible suppression of contralaterally evoked discharges with increasing ipsilateral intensities. Apparent lack of ipsilateral inhibition is reflected in the spike counts (*right* of each histogram), which hardly changed as ipsilateral intensity was increased. *Right*: same data displayed on an expanded time scale. Brief, early ipsilateral inhibition is apparent at ipsilateral intensities of 40 and 50 dB SPL that suppressed a few spikes at the beginning of the spike train (dotted line). *B, left*: responses evoked by the same binaural signals as in *A* during the application of bicuculline and strychnine. Although discharge magnitude increased markedly, spike counts were still relatively unchanged by increasing intensities of ipsilateral stimulation. *Right*: bicuculline and strychnine eliminated the brief, early ipsilateral inhibition, although the elimination of this brief inhibition was not apparent from the spike counts evoked by the various interaural intensity disparities. Tone bursts were 20.90 kHz. All histograms were generated by 20 tone-burst repetitions.

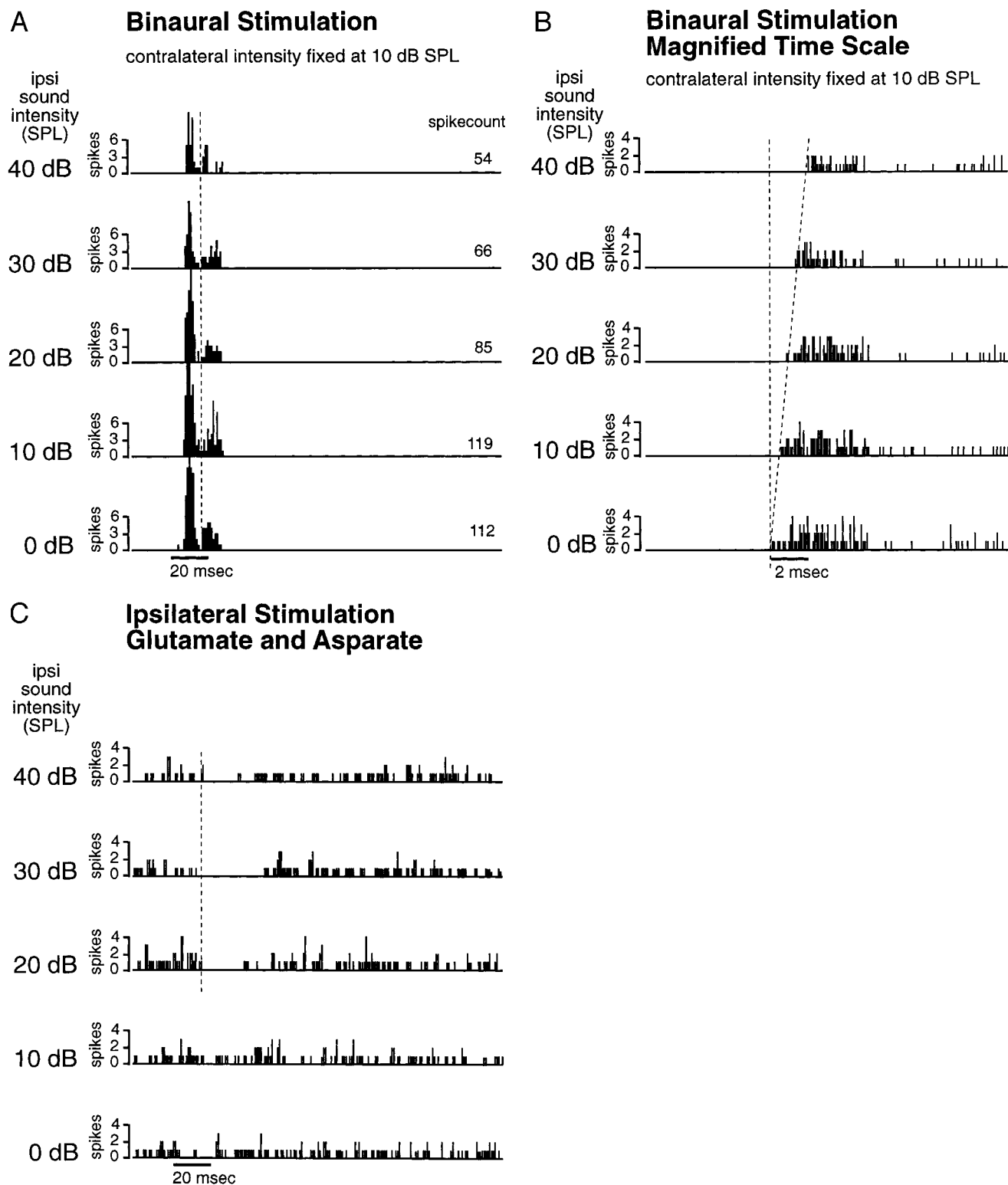


FIG. 14. PST histograms of an EI cell that had a brief, early ipsilateral inhibition and a delayed, longer-lasting ipsilateral inhibition. *A*: histograms showing that the cell had a pauser-like sustained response to 20-ms tone bursts. Dotted vertical line indicates latency of ipsilateral inhibition. *B*: same data as in *A* but displayed on an expanded time scale, showing that the cell received a very brief ipsilaterally evoked inhibition that eliminated a few spikes at the beginning of the spike train (dotted line). All histograms in *A* and *B* were generated by 20 tone-burst repetitions. *C*: ipsilateral stimulation during application of glu/asp reveals a delayed inhibition that was evoked at ipsilateral intensities of 20–40 dB SPL. Delayed inhibition appeared to partially suppress the later part of the excitatory response that followed the pause. All histograms were generated by 58 tone-burst repetitions. Tone bursts were 23.23 kHz.

discharges that had been suppressed previously by ipsilateral stimulation.

Before turning to cells that were inhibited at the ICc by ipsilateral stimulation, we show, for purposes of comparison, data from a cell in which there was no ipsilateral inhibition at the ICc, but the contralaterally evoked discharges of which were suppressed strongly by ipsilateral stimulation (Fig. 11, *A* and *B*). As mentioned previously, these features suggest that the ipsilateral inhibition of discharges occurred in a lower nucleus, most likely the LSO, and the binaural response properties then were imposed on the ICc cell through an excitatory projection from the lower nucleus. This interpretation is strengthened further by the results obtained with bicuculline and strychnine (Fig. 11, *C* and *D*). When glycinergic and GABAergic inhibition were blocked at the ICc, the response magnitude of the cell increased but the spike suppression caused by ipsilateral stimulation was not eliminated (Fig. 11*C*), presumably because the spike suppression occurred in a lower nucleus.

This failure to influence ipsilateral spike suppression with bicuculline and strychnine in EI neurons that had no ipsilateral inhibition is in marked contrast to the effects of blocking inhibition in EI cells that displayed pronounced ipsilateral inhibition that was coincident with the excitation. When binaural stimuli were presented in these latter cells, the drugs eliminated much of ipsilateral suppression of contralaterally evoked spikes, thereby supporting the hypothesis that the suppression of contralateral discharges in these cells was caused by ipsilateral inhibition at the ICc.

An example is shown in Fig. 12. Figure 12*A* shows that ipsilateral signals of 10 dB SPL caused a partial suppression of contralateral discharges. Increasing the ipsilateral intensity to 20 dB SPL caused a strong suppression and discharges were completely suppressed by 30 dB SPL ipsilateral signals. Figure 12*B* shows that the features of the ipsilateral inhibition were appropriate for suppressing the contralateral discharges. Note first that the latencies of the contralaterally evoked excitation and ipsilaterally evoked inhibition (Fig. 12, *A* and *B*, arrows and dotted line) were temporally coincident. Second, Fig. 12*B* shows that the threshold of the ipsilateral inhibition, as revealed by the appearance of a gap in background activity, was ~ 10 dB SPL, the same ipsilateral intensity that initially caused discharge suppression with binaural stimulation in Fig. 12*A*. Third, Fig. 12*D* shows that the ipsilateral inhibition was eliminated by the application of bicuculline and strychnine, as indicated by the failure of ipsilateral signals presented monaurally to evoke a gap in the background discharges. Finally, Fig. 12*C* shows that the contralateral discharges that were previously suppressed strongly or completely by ipsilateral stimulation were largely rescued after inhibition was blocked by bicuculline and strychnine. Thus this cell's IID sensitivity seems to be formed, at least in a large part, by ipsilaterally evoked inhibition at the ICc.

A feature in Fig. 12*C* that might seem curious is that the higher ipsilateral intensities suppressed the later discharges evoked by the contralateral signals even though ipsilateral inhibition at the ICc seems to have been eliminated completely by bicuculline and strychnine as shown in Fig. 12*D*. Our interpretation is that ipsilateral stimulation evoked an inhibition in a lower nucleus that suppressed the later but not the earlier discharges.

Ipsilateral inhibition was not always discernible from gaps in background activity

In recent studies, Park et al. (Oswald et al. 1999; Park et al. 1998) report on a subtle form of ipsilaterally evoked inhibition at the ICc that affects only the initial 2–4 ms of the contralaterally evoked discharge train. This brief inhibition, however, was not apparent in our evaluations of stimulus locked gaps in the glu/asp evoked background activity. The reason is there were often gaps of a few milliseconds that were scattered throughout the background discharge pattern. Thus when a small gap that preceded the contralaterally evoked discharge train appeared in our records, we were uncertain as to whether the gap was actually an inhibition or simply a random gap. Furthermore the influence of this brief inhibition was often not apparent in IID functions, especially in cells with sustained discharge patterns. With 20-ms tone bursts, for example, the sustained discharge evoked by contralateral stimulation generated a high spike count. When ipsilateral signals were introduced, the brief inhibition at the ICc only suppressed a few spikes at the very beginning of the discharge train. But whatever change in spike count resulted from the inhibition, it was less than the random variations in spike counts that normally occur when more than one histogram, generated by the same stimulus, is obtained. Thus the minor spike suppression caused by this brief inhibition could not be discerned from the histograms obtained with increasing ipsilateral intensities (Fig. 13*A*, *left*).

The reality of the inhibition, however, became apparent when the time scale of the PST histograms was expanded, as shown in Fig. 13*A*, *right*. Moreover, blocking GABAergic and glycinergic inhibition eliminated the brief inhibition (Fig. 13*B*). These features are consistent with those reported by Park et al. (Oswald et al. 1999; Park et al. 1998) and confirm that the brief inhibition occurs at the ICc and not in a lower nucleus.

We point out that this inhibition was not included in the previous sections, which considered only the inhibition identified from gaps in background activity. However, when we evaluated the expanded histograms, we found that many (28/97, 29%) EI cells had this early, brief inhibition. Additionally, some of these neurons also had a longer lasting inhibition that was apparent from a gap in background activity. The cell in Fig. 14, for example, had a pauser-like discharge pattern to contralateral tone bursts. The brief ipsilaterally evoked inhibition suppressed a few spikes in the early portion of the discharge train (Fig. 14*B*), whereas a longer-latency ipsilaterally evoked inhibition, that was obvious as a gap in background activity, suppressed spikes in the later portion of the discharge train (Fig. 14*C*). Cells of this type further illustrate that ICc cells can be influenced by multiple forms of ipsilaterally evoked inhibition, each of which is evoked with a different duration and latency.

Ipsilateral inhibition did not suppress contralaterally evoked discharges in some cells

The neurons considered in the preceding section had ipsilaterally evoked inhibitory latencies that were coincident with latencies of the contralaterally evoked excitation. However, the inhibitory and excitatory latencies were not coincident in all ICc cells. Indeed, one of the surprising results of this study is that in some

cells, the latencies of ipsilateral inhibition were so long that the inhibition began after the contralaterally evoked discharge trains had largely ended or ended completely. Latency mismatches between excitation and inhibition were seen in both strongly inhibited EI cells and in cells that were weakly inhibited or not inhibited at all by stimulation of the ipsilateral ear.

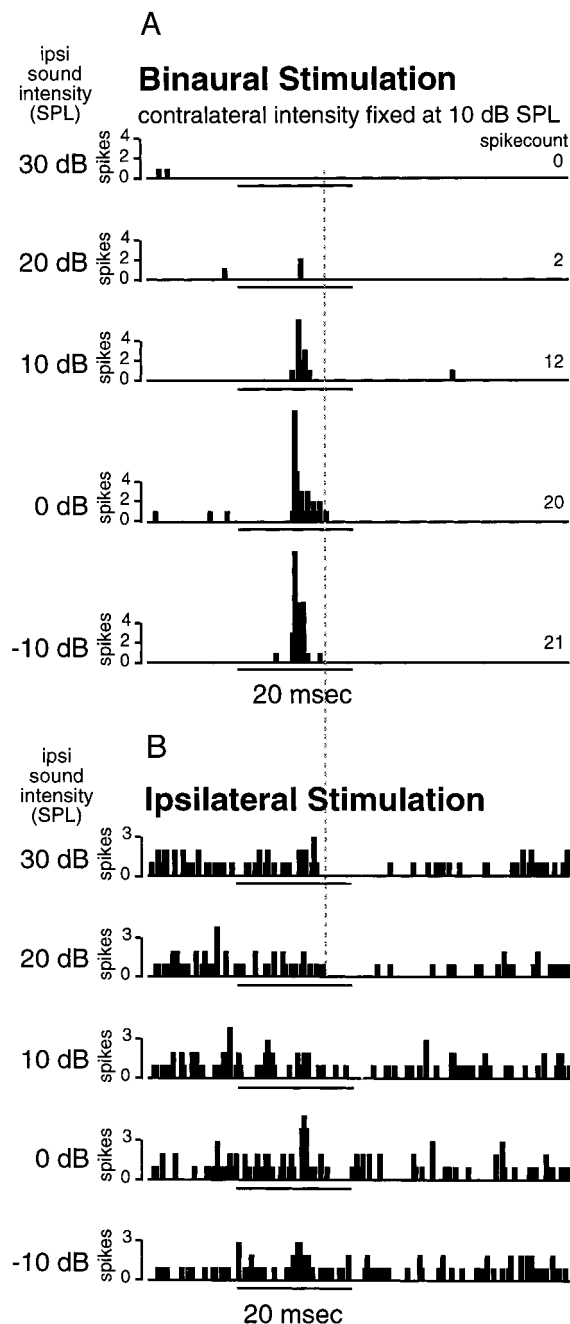


FIG. 15. PST histograms of a strongly suppressed EI cell that received a delayed ipsilateral inhibition that did not suppress discharges. *A*: histograms showing that contralaterally evoked discharges were suppressed completely by ipsilateral tones. *B*: histograms of ipsilateral stimulation during application of glu/asp show a weak ipsilateral inhibition at 20 and 30 dB SPL. Dotted line shows that the inhibition began several milliseconds after the onset of contralaterally evoked discharges and could not have produced the observed spike suppression in *A*. Histograms in *B* were generated by 50 tone-burst repetitions. Spike counts on *right* in histograms of *A* only include discharges that occurred during the 20-ms tone burst. Tone bursts were 27.00 kHz.

A strongly inhibited EI cell with a large latency mismatch is shown in Fig. 15. The PST histograms in the *top panel* show that discharges evoked by contralateral signals were suppressed completely by a 30-dB SPL ipsilateral signal. The *bottom panel* shows that ipsilateral signals of 20–30 dB SPL produced a gap in the glu/asp-evoked background and thus the ipsilateral signal evoked inhibition in the ICc cell. The inhibition's latency was so long that the inhibition was initiated only after the excitatory response had ended. Consequently, the ipsilateral inhibition could not have suppressed the contralaterally evoked discharges at the ICc; rather the suppression of the contralaterally evoked discharge must have occurred downstream, presumably in the LSO.

An example of a weakly suppressed cell that received ipsilateral inhibition with a long latency is shown in Fig. 16. Notice that the spike counts elicited by a 10-dB SPL contralateral signal were hardly suppressed by ipsilateral intensities of 10–20 dB SPL and only moderately suppressed at 30 dB SPL. Nevertheless, ipsilateral signals presented by themselves at 10–30 dB SPL, evoked prominent and long-lasting inhibitions (Fig. 16*B*). The latencies of the inhibition, however, were longer than the latency of excitation and thus the inhibition only overlapped with a few of the later spikes of the contralaterally evoked discharge train. Although the ipsilateral inhibition may have suppressed a few of the later contralaterally evoked discharges, its long latency prevented it from suppressing the major portion of the discharge train. Thus a prominent inhibition was evoked by stimulation of the ipsilateral ear, but that inhibition did not create the binaural property of this EI cell. Of the eight weakly inhibited cells the contralateral spike counts of which were suppressed by $\leq 40\%$, five cells had ipsilaterally evoked inhibition with latencies that were longer than the excitatory latencies.

DISCUSSION

This study has shown that stimulation of the ipsilateral ear evokes an inhibition in the vast majority (86%) of ICc cells. The inhibition is often complex and can have multiple components that are glycinergic and/or GABAergic. Each component of the ipsilateral inhibition can vary markedly in latency, duration, and threshold. Additionally, inhibition has a persistence in most cells and continues to exert its influence for many milliseconds after the stimulus has ended. In the following text, we first discuss how these findings compare with those from previous studies and then turn to some of the functional implications of the various inhibitory components evoked in the ICc by stimulation of the ipsilateral ear.

Prevalence of ipsilaterally evoked inhibition

Although ipsilaterally evoked inhibition at the ICc has been reported in studies from this laboratory (Klug et al. 1995; Park and Pollak 1993b) and other laboratories (Covey et al. 1996; Faingold et al. 1989; Kidd and Kelly 1996; Kuwada et al. 1997; Li and Kelly 1992; Vater et al. 1992a), we nevertheless were surprised to find that 86% of ICc cells were inhibited by stimulation of the ipsilateral ear. In our previous studies of the mustache bat ICc, we found that blocking GABAergic and

glycinergic inhibition reduced or eliminated ipsilateral inhibition in ~50% of the EI cells (Klug et al. 1995), and it was our expectation that about the same percentage of cells would exhibit ipsilateral inhibition in the ICc of Mexican free-tailed bats. Although species differences might account for some of the disparity of the results among these studies, differences in methodology seem more relevant. In previous studies (Klug et al. 1995), we focused on IID functions, i.e., how the spike counts evoked by a contralateral signal were suppressed as the ipsilateral intensity increased, and then evaluated whether or not the cell's IID function changed when inhibition was blocked. Such evaluations only reveal the ipsilateral inhibition that is coincident with contralaterally evoked discharges and thereby can suppress contralaterally evoked discharges. Those studies almost surely missed or underestimated ipsilateral inhibition in onset cells whose latencies of ipsilateral inhibition were longer than latencies of excitation (e.g., Fig. 15), and in cells that received only a brief, short latency inhibition of the sort shown in Fig. 13. About 20% of the cells in our sample of ICc cells in the Mexican free-tailed bat had such mismatched latencies of excitation and inhibition, and thus had we evaluated ipsilateral inhibition in the mustache bat as we did in the present study, the percentages of ICc cells in the mustache bat that are inhibited by ipsilateral stimulation probably would have been substantially higher and closer to the value that we found in the present study.

The high percentage of ipsilaterally inhibited cells that we observed in this study, however, is in close agreement with studies of the rat ICc reported by Kelly and his colleagues (Kidd and Kelly 1996; Li and Kelly 1992). They recorded interaural intensity and time disparity functions from ICc cells before, during, and after reversibly inactivating the DNLL, the principal source of ipsilaterally evoked GABAergic input to the ICc. They found that inactivation of the DNLL changed the binaural functions in the vast majority of ICc cells. Thus most ICc cells in the rat are inhibited by stimulation of the ipsilateral ear, and in this regard, the studies of the rat's ICc are concordant with the results of this study.

Ipsilateral inhibition has multiple roles in the formation of binaural properties

In addition to the inhibition that is temporally coincident with excitation, and thereby creates EI properties, there are at least three types of more subtle and complex influences of inhibition that are evoked in the ICc by ipsilateral stimulation. The subtleties and complexities are a consequence of the timing and duration of the ipsilateral inhibition and are not always expressed as a marked change in the IID function when inhibition is blocked.

The first type was discovered by Park and his colleagues (Oswald et al. 1999; Park et al. 1998) and is the very brief ipsilaterally evoked inhibition that affects only the initial 2–4 ms of the contralaterally evoked discharge train (e.g., Fig. 13 and 14). The subtlety is that its influence on IID functions is often not apparent, especially in cells with sustained discharge patterns. With 20-ms tone bursts, for example, the sustained discharge evoked by contralateral stimulation generates a high spike count. When ipsilateral signals are introduced, this brief inhibition at the ICc only suppresses a few spikes at the very beginning of the discharge train and results in only a minor

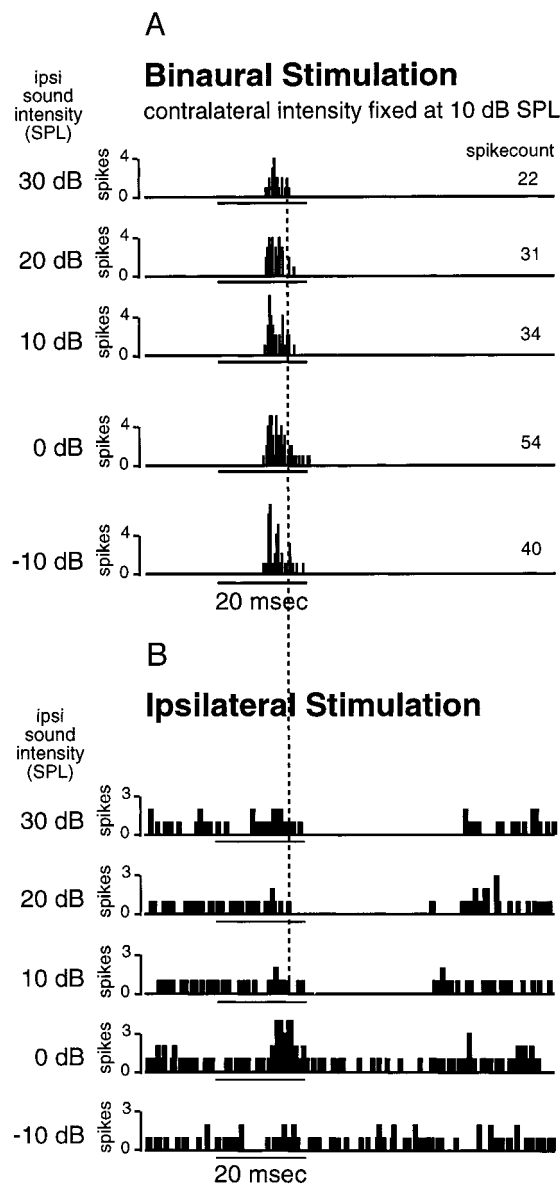


FIG. 16. PST histograms of a weakly suppressed cell that had a delayed ipsilateral inhibition. *A*: histograms showing that contralaterally evoked spikes were only weakly suppressed by ipsilateral sound. *B*: histograms of ipsilateral stimulation during application of glu/asp. Prominent gaps show that ipsilateral inhibition was evoked at intensities of 10, 20, and 30 dB SPL. Dotted line shows the mismatch in excitatory and inhibitory latencies. Because inhibition arrived several milliseconds after the onset of contralaterally evoked discharges, the inhibition could only have suppressed the later discharges in the train. Histograms in *B* were generated by 47 tone-burst repetitions. Tone bursts were 32.18 kHz.

reduction or even no apparent reduction in spike count. The IID functions of these cells would suggest that they are very weakly inhibited cells or even nonsuppressed cells. Because “long” tones of this type also were used in many previous studies (Klug et al. 1995; Park and Pollak 1993b), the brief ipsilateral inhibition almost surely was overlooked in many cells. The full influence of the transient inhibition becomes apparent when very brief stimuli, which evoke only a few discharges, are used as stimuli (Oswald et al. 1999; Park et al. 1998). When these signals are employed, the brief ipsilateral inhibition is sufficiently long to completely suppress the brief

discharge train at appropriate IIDs. Thus these cells express very weakly suppressed EI properties or even "monaural" properties with "long" stimuli, whereas the same cells express strongly suppressed EI properties when stimulated with transient stimuli. Park and his colleagues suggest (Oswald et al. 1999; Park et al. 1998) that such cells encode the location of transient signals, such as the brief FM signals bats emit for echolocation, through their discharge magnitude, whereas the location of longer signals, such as communication signals, could not be encoded by discharge magnitude. Rather the brief ipsilateral inhibition could change the latency of those IC cells, whereas the latency change could be a function of IID. Latency may be another way of coding for location, or those cells may code for other features of the longer signals.

The second subtle type of ipsilateral inhibition is the inhibition that has a latency longer than the latency of the excitation. In some of these cells, the ipsilateral inhibition begins after the discharge train is well under way (e.g., Fig. 14), whereas in other cells it begins after the end of the discharge train (e.g., Fig. 15 and 16). Moreover, these cells express weakly and strongly suppressed EI properties. In both the weakly and strongly suppressed cells, ipsilateral signals generate a long latency inhibition at the ICc, but that inhibition does not participate in the suppression of contralaterally evoked discharges. Rather the suppression of contralaterally evoked spikes by ipsilateral stimulation must occur in a lower center. The functional significance of the long latency inhibition at the ICc is unclear, but it is important for something other than the coding of IIDs and thus apparently is not relevant for sound localization.

The third type of ipsilateral inhibition the function of which is more complex than simply suppressing contralaterally evoked discharges is the persistent inhibition, the inhibition that persists for some time after stimulus offset. Previous intracellular and patch-clamp studies showed that persistent inhibition occurs in the ICc (Covey et al. 1996; Kuwada et al. 1997), although its prevalence was not apparent from those studies. Studies of the precedence effect in the rabbit (Fitzpatrick et al. 1995) and cat ICc (Litovsky and Yin 1998; Yin 1994) also showed that an initial binaural stimulus produces a long-lasting suppression of responses to signals that closely follow the initial signal. However, those studies recorded single-unit activity with extracellular electrodes and therefore could not conclusively show that the actual inhibition occurred at the ICc and not in a lower nucleus. The reversible inactivation studies of the DNLL, by Kidd and Kelly (1996), however, demonstrated that ipsilaterally evoked persistent inhibition is indeed a feature of the ICc. They recorded single units from the rat ICc while presenting clicks to the ipsilateral ear followed by clicks to the contralateral ear that were delayed by various intervals. The ipsilateral clicks produced a persistent inhibition that suppressed responses evoked by the contralateral clicks for periods ranging from 10 to 30 ms, and this was observed in the majority of ICc cells. When the DNLL was inactivated, the cells responded to contralateral clicks at shorter intervals after the ipsilateral click than they did before or after recovery from DNLL inactivation, showing that the persistent inhibition was generated in the ICc and not in a lower nucleus.

Persistent inhibition evoked by ipsilateral stimulation is not

unique to the ICc, but it is also a robust feature of EI neurons in the DNLL (Yang and Pollak 1994a,b). However, unlike the DNLL, where persistent inhibition is evoked only by ipsilateral signals and not by contralateral signals, persistent inhibition in the ICc is evoked in almost all ICc cells by signals presented to the contralateral as well as the ipsilateral ears. In a future report of ICc cells in the Mexican free-tailed bat, we show that contralateral signals evoke an excitation followed by an inhibition that persists for 26 ms, on average, in 85% of ICc cells (unpublished results). These values are similar to those for ipsilaterally evoked persistent inhibition, which is evoked in 86% of ICc cells and lasts for 15 ms on average. Thus persistent inhibition evoked by stimulation of either ear occurs in the vast majority of ICc cells and is a feature that apparently sets ICc neurons apart from DNLL neurons or neurons in any of the other lower nuclei.

Concluding comments

We have shown that stimulation of the ipsilateral ear evokes inhibition in the vast majority of ICc neurons in Mexican free-tailed bats. The inhibition can have multiple components that vary in latency, threshold, and duration. Individual cells can display one or more inhibitory components. Some cells have both a very brief, early inhibition that suppresses the first few discharges of the train and a longer latency inhibition that may or may not suppress discharges evoked by a contralateral signal. In other ICc cells, the ipsilateral inhibition is coincident with contralaterally evoked discharges in both time and duration, but the inhibition has a duration that is many milliseconds longer than the signal that generated it. In short, ipsilateral inhibition at the ICc is prevalent and complex. Moreover, contralateral signals also evoke persistent inhibition (unpublished results). Thus the variety of inhibitory features, evoked by stimulation of the ipsilateral and contralateral ears, are complex but have to be factored into hypotheses concerned with functional activity of the mammalian ICc.

We thank C. Resler for designing and implementing the electronics for data acquisition. We also thank D. Ryugo, M. Burger, L. Hurley, C. Resler, and T. Park for critical comments.

This work was supported by National Institute of Neurological Deafness and Other Communications Disorders Grant DC-00268.

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Received 25 January 1999; accepted in final form 19 April 1999.

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