Commissural and Lemniscal Synaptic Input to the Gerbil Inferior Colliculus

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Moore, David R., Vibhakar C. Kotak, and Dan H. Sanes. Commissural and lemniscal synaptic input to the gerbil inferior colliculus. *J. Neurophysiol.* 80: 2229–2236, 1998. The central nucleus of the inferior colliculus (ICC) receives direct inputs, bilaterally, from all auditory brain stem nuclear groups. To evaluate the contribution made to gerbil ICC neuron physiology by two major afferent pathways, we examined the synaptic responses evoked by direct stimulation of the commissure of the inferior colliculus (CIC) and the ipsilateral lateral lemniscus (LL). Frontal midbrain slices were obtained from postnatal day (P) 9–P19 gerbils, and whole cell recordings were made under current- ($n = 22$) or voltage-clamp ($n = 52$) conditions. Excitatory and inhibitory synaptic responses were characterized by sequentially exposing the slice to ionotropic glutamate receptor antagonists [6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) + aminophosphonpentanoic acid (AP-5), or kynurenic acid)], a γ-aminobutryic acid type A receptor antagonist (bicuculline), and a glycine receptor antagonist (strychnine). In current clamp, LL stimulation typically produced a short latency depolarization followed by a longer duration hyperpolarization. The depolarization was abolished by AP-5 + CNQX, and the remaining inhibitory potential displayed either bicuculline or strychnine sensitivity. In voltage clamp, 79% of ICC neurons displayed synaptic currents after stimulation of each pathway. The synaptic currents were typically complex waveforms, and ionotropic glutamate receptor antagonists reduced inward currents at a holding potential of −80 mV in the majority of neurons. In addition, this treatment reduced outward synaptic currents at a holding potential of −20 mV, indicating that inhibitory interneuronal input was often activated by LL or CIC afferents. A minority of neurons had synaptic currents that were unaffected by glutamate receptor antagonists, but it was more common for CIC-evoked currents to be unaffected (38%) rather than LL-evoked currents (22%). The CIC provided a strong inhibitory input that was almost exclusively GABAergic, whereas the LL inhibition often included a glycinergic component. These experiments have shown that the CIC provides a major glutamatergic and GABAergic input to most ICC neurons. However, much of the inhibitory input from both the CIC and the LL appears to be mediated by interneuronal connections.

INTRODUCTION

The inferior colliculus (IC) receives ascending input from all nuclear groups in the auditory brain stem (Aitkin 1986). The most substantial of these, in terms of neurons retrogradely labeled by tracer injections in the IC, come from the contralateral cochlear nucleus (CN), the ipsilateral medial superior olivary nucleus (MSO), the lateral superior olivary nuclei (LSO), and the ipsilateral ventral (VNLL) and contralateral dorsal (DNLL) nuclei of the lateral lemniscus (Adams 1979; Beyerl 1978; Brunso-Bechtold et al. 1981; Nordeen et al. 1983). In addition, the IC receives descending input from the superior colliculus, medial geniculate nucleus (MGN), and the auditory cortex (Adams 1980; Andersen et al. 1980; Coleman and Clerici 1987; Faye-Lund 1985).

Although the acoustic response properties of neurons in the central nucleus of the IC (ICC) were extensively investigated with extracellular recordings, the functional properties of its synapses were described in only a few studies. Wagner (1996) found that, in the mouse ICC, almost all neurons responded to stimulation of the main ascending input pathway, the lateral lemniscus (LL), with a long latency (5 ms) excitatory postsynaptic potential (EPSP) followed, in many cases, by an inhibitory postsynaptic potential (IPSP). Application of the specific, non–*N*-methyl-D-aspartate (NMDA) excitatory receptor antagonist 6,7-dinitroquinoxaline-2,3-dione (DNQX) abolished the EPSP and, in a few neurons, it also depressed the IPSP, suggesting the presence of a disynaptic inhibitory input. Application of the γ-aminobutyric acid type A ($GABA_A$) receptor antagonist bicuculline abolished the IPSP and prolonged the EPSP in all neurons tested.

Another major source of input to the ICC that, at least in the ferret (Moore 1988), is numerically the greatest in the hindbrain comes from the contralateral IC, via fibers that pass through the commissure of the IC (CIC). Despite the prominence of CIC afferents, virtually nothing is known about their functional properties. However, recordings were made from multipolar neurons in the dorsal cortex of the IC (ICD) in the rat, and these cells receive short-latency synaptic excitation and inhibition via the CIC (Smith 1992). Neurons contributing to the CIC are located throughout the ICC (Adams 1980; Aitkin and Phillips 1984; González-Hernández et al. 1996). A number of earlier studies suggested that the CIC innervated only the ICD or sent fibers directly to the MGN (see Aitkin 1986). However, more recent evidence has shown clearly that the ICC has topographically organized and tonotopically appropriate reciprocal connections with the contralateral ICC (Malmierca et al. 1995; Saldaña and Merchán 1992). About 50% of contralaterally projecting IC neurons stain positively for GABA, making neurons of the CIC and the DNLL the major sources of GABAergic input to the IC (González-Hernández et al. 1996; Zhang et al. 1998).

We examined the contribution of commissural and lemniscal pathways to the synaptic responses of neurons in the

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gerbil IC brain slice with whole cell recording and direct afferent stimulation. Our recordings have shown that most IC neurons are activated by both pathways, the CIC provides a major inhibitory input to most IC neurons, and that this input is primarily GABAergic. However, a large fraction of the inhibition evoked by stimulation of either pathway appears to be mediated by interneuronal connections.

METHODS

Brain slice preparation

All procedures were reviewed and approved by the New York University Institutional Animal Care and Use Committee. Gerbils (*Meriones unguiculatus*) aged postnatal day (P) 9–P19 were anesthetized with chloral hydrate (350 mg/kg). After rapid decapitation, a transverse knife cut was made at a thalamic level, and the hindbrain was removed. The ventral surface was fixed (cyanoacrylate glue) to an agar block, and this was secured on the stage of a Vibratome to permit cutting in oxygenated, artificial cerebrospinal fluid (ACSF) containing (in mM) 123 NaCl, 4 KCl, 1.2 KH_2PO_4, 1.3 $MgSO_4$, 28 $NaHCO_3$, 15 glucose, 2.4 $CaCl_2$, and 0.4 l ascorbic acid. Frontal slices (300 μm) were cut into ACSF at room temperature (23°C) and incubated in a holding chamber at either 23 or 32°C for 1 h and then at 23°C for a second hour. Some slices were incubated, during the first hour, in ACSF that had the NaCl replaced with sucrose. In the recording chamber (volume ~1 ml), which was mounted on a fixed stage microscope, the slice was submerged in oxygenated ACSF at 23°C (7 ml/min). To block *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxoazolepropionic acid (AMPA), $GABA_A$, or glycine receptors, ACSF containing 50 μM aminophosphonpentanoic acid (AP-5), 20 μM 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), 10 μM bicuculline (BIC), or 2 μM strychnine (SN), respectively, was substituted for the stock ACSF. In some experiments, kynurenic acid (1–5 mM) was used instead of or in addition to AP-5 and CNQX to block NMDA and AMPA receptors.

Electrophysiology

Whole cell patch-clamp recordings were obtained with electrodes (4–8 MΩ) pulled from borosilicate glass (1.5 mm OD). For current clamp, the internal pipette solution contained (in mM) 130 K-gluconate, 0.6 ethyelene glycol-bis(β-aminoethyl ether)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA), 10 *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid (HEPES), 2 $MgCl_2$, 5 KCl, 2 ATP, 0.3 GTP, pH 7.2. For voltage clamp, the pipette solution contained (in mM) 127.5 Cs-gluconate, 0.6 EGTA, 2 $MgCl_2$, 5 KCl, 10 HEPES, 2 ATP, 0.3 GTP, 5 QX-314, pH 7.2. To mark the location of recorded neurons, biocytin (~0.2%) was added to the pipette solution. Recordings were obtained with a Warner Instruments patch clamp amplifier (PC-501A). Extracellular stimuli (200-μs pulses) were delivered through twisted-pair, insulated platinum electrodes driven by stimulus isolators (Isolator10, Axon Instruments). Custom designed PC-based software was used for programmed stimulus delivery, data acquisition, and analysis (Sanes 1993).

At the conclusion of each recording the slice was placed in 4% paraformaldehyde. The biocytin was subsequently visualized with an avidin-biotin-horseradish peroxidase amplification procedure (Vector Laboratories) with 3,3′-diaminobenzidine as the substrate. The position of each neuron recovered was determined by visual inspection of the tissue slice and by reference to other, Nissl-stained histological material available in the laboratory. In this material, the lateral, ventral, and medial borders of ICC were discernable as a transition in the density and size of neuron somata.

TABLE 1. *Number of neurons recorded in each configuration*

	Current Clamp	Voltage Clamp
Gerbils	18	28
Slices	20	37
Neurons	22	52

RESULTS

Position and morphology of recorded neurons

The number of neurons recorded under current or voltage clamp conditions is shown in Table 1. Of the 52 neurons recorded under voltage clamp, 32 were recovered histologically and were assigned to locations within the IC based on the rostrocaudal plane of the slice and the dorsoventral and medial–lateral position of the stained cell body. Although neurons were recorded throughout the IC, there was a bias toward recording sites in the lateral, rostral, and ventral regions of the IC. Physiologists and anatomists have yet to form a unified theory of ICC organization. However, most neurons recorded in this study were clearly within the ICC, as defined above and as shown by the white dashed line in Fig. 1*A*. Seven neurons were near the border between the ICC and the lateral or external nuclei of the IC. Despite these uncertainties and controversies, the recordings will be referred to collectively as being from ICC.

Figure 1 shows micrographs of five different biocytin-labeled neurons in the IC. The neuron in Fig. 1, *A* and *B*, was a stellate cell (Oliver and Huerta 1992) with a soma in the ICC and dendrites that appeared to extend laterally into the external nucleus. This neuron, like many others (e.g., Fig. 1, *C* and *D*), exhibited regular swellings or ''blebbing'' of the primary dendrites, and this may have resulted from extended exposure to the internal pipet solution. The neuron in Fig. 1*A* received purely GABAergic synaptic input from the CIC and purely excitatory input from the LL. Although a variety of neuron morphologies was observed (Fig. 1, *B*–*F*), we were unable to detect a relationship between dendritic architecture and synaptic input.

Synaptic input: current-clamp recordings

Electrical stimulation of the LL at the level of the DNLL typically (15/22 neurons) elicited mixed postsynaptic potentials that displayed an initial depolarization, peaking at a latency of 5–10 ms, followed by a longer-lasting hyperpolarization (Fig. 2*A*, PRE). As shown for this neuron, application of the ionotropic glutamatergic (iGluR) antagonists AP5 and CNQX (A + C) always eliminated the initial depolarizing portion of the PSP. In this neuron, the remaining IPSP was reduced by over 50% when strychnine was added (A + C + S). In some neurons, the initial depolarization was poorly defined (e.g., Fig. 2*B*, PRE), but the addition of AP5 and CNQX led to an enhancement of the IPSP, demonstrating that an excitatory component had been present. In this neuron, the remaining IPSP was eliminated when bicuculline was added (A + C + B). In summary, AP-5 + CNQX had a clear effect on all 15 neurons to which they were applied in the absence of strychnine or bicuculline. Strychnine decreased the remaining IPSP in 14 of 15 neurons tested, and bicuculline decreased the IPSP in 2 of 2 neurons tested.

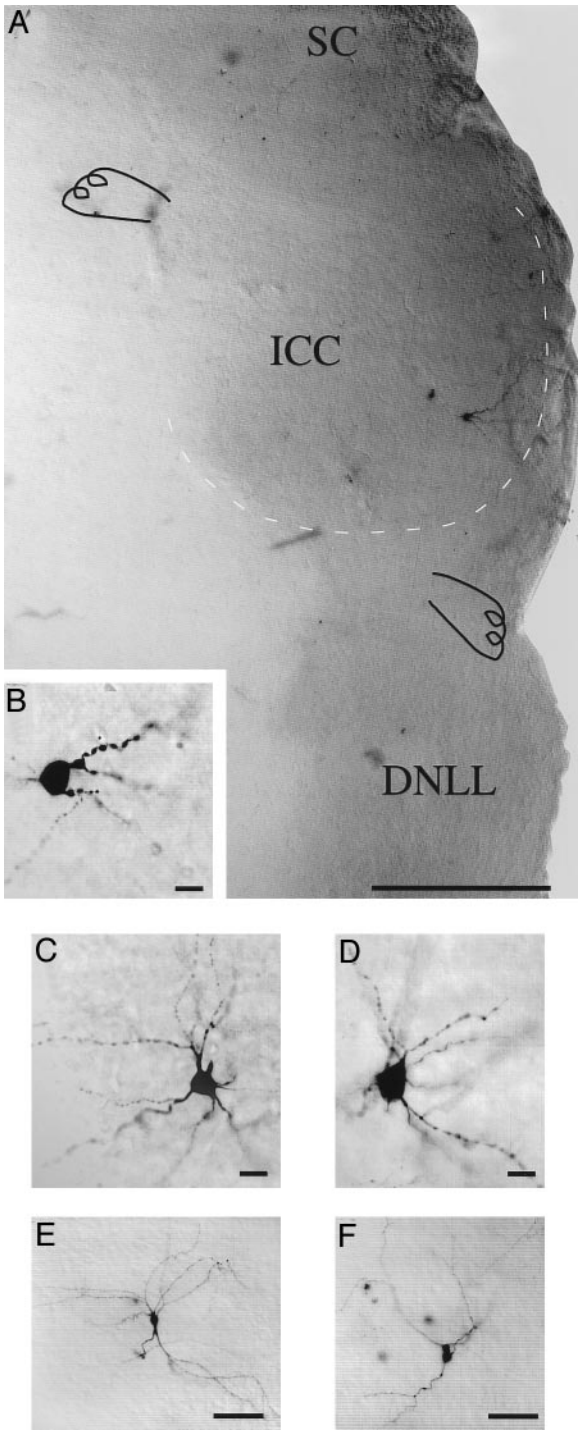

FIG. 1. Biocytin filled neurons in the inferior colliculus. *A*: approximate border of the inferior colliculus (IC) is indicated by the dashed white line. *A* and *B*: *neuron 976026a* received inputs via the the commissure of the inferior colliculus (CIC) and lateral lemniscus (LL). *C*: *neuron 976022b* received input via the LL. *D*: *neuron 976020c* received inputs via the CIC and LL. *E*: *neuron 976028a* received inputs via the CIC and LL. *F*: *neuron 976028b* received inputs via the CIC and LL. Scale bars: *A*, 250 μm; *B–D*, 10 μm; *E* and *F*, 30 μm.

Synaptic input: voltage-clamp recordings

Seventy-nine percent of neurons tested displayed measurable (>10 pA) postsynaptic currents in response to independent stimulation of both the CIC and the LL pathways (Fig. 3, *bottom*). Complex synaptic currents were evoked by CIC or LL stimulation as the holding potential was varied between −10 and −80 mV. When the neuron shown in Fig. 3 was held at −80 mV, stimulation of either pathway produced a large net inward current. However, there were two or more discrete events after a single stimulus, suggesting either that afferent fibers fired more than one action potential or that an interneuronal circuit was activated within the ICC. For all neurons tested before the application of iGluR antagonists, the mean reversal potentials for the largest postsynaptic current (latency of 10–20 ms) were −18.5 ± 35.0 mV (mean ± SD; range −65 to −25; $n = 44$) for CIC stimulation and −34.3 ± 15.3 (range −57 to +15; $n = 37$) for LL stimulation. Application of iGluR antagonists reduced the amplitude of at least one of the synaptic currents in 88% of neurons tested (at $V_{hold} = -80$ mV). For most neurons, either AP-5 + CNQX or the kynurenic acid were used (see METHODS), although both antagonists were added successively in a few experiments. Because the addition of CNQX + AP-5 did not significantly reduce PSC amplitude beyond that produced by kynurenic acid (see Fig. 5, *inset*), we pooled the data that were collected under each protocol. Glutamate receptor antagonists suppressed synaptic currents to varying degrees in each neuron (cf. Figs. 4 and 5). In 39% of neurons tested, iGluR antagonists blocked LL-evoked currents completely, and in 13% of neurons they

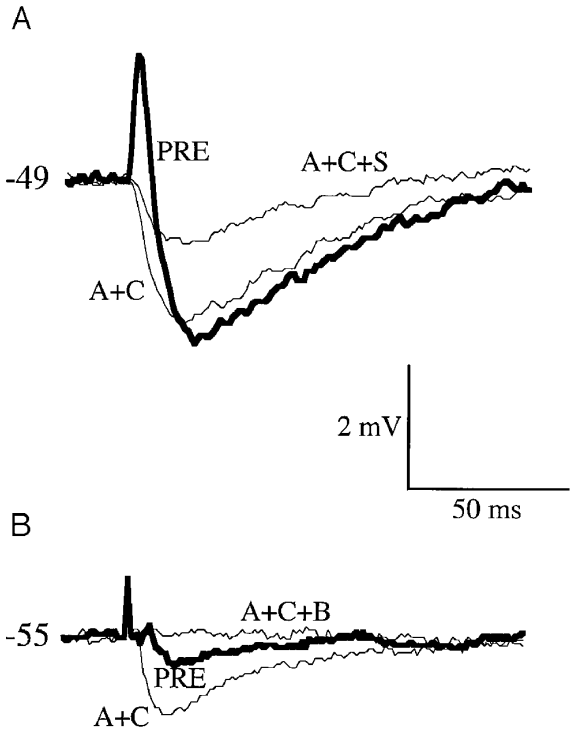

FIG. 2. Lateral lemniscus-evoked postsynaptic potentials. *A*: typical response showing fast depolarization and slower hyperpolarization in artificial cerebrospinal fluid (ACSF, PRE). Addition of aminophosphonpentanoic acid (AP-5) and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX, A + C) abolished the depolarization, and further addition of strychnine (A + C + S) reduced the hyperpolarization. *B*: small, slow hyperpolarization (PRE) increased in amplitude with A + C and was abolished by the further addition of bicuculline (A + C + B). Resting membrane potential is indicated to the left of each set of traces.

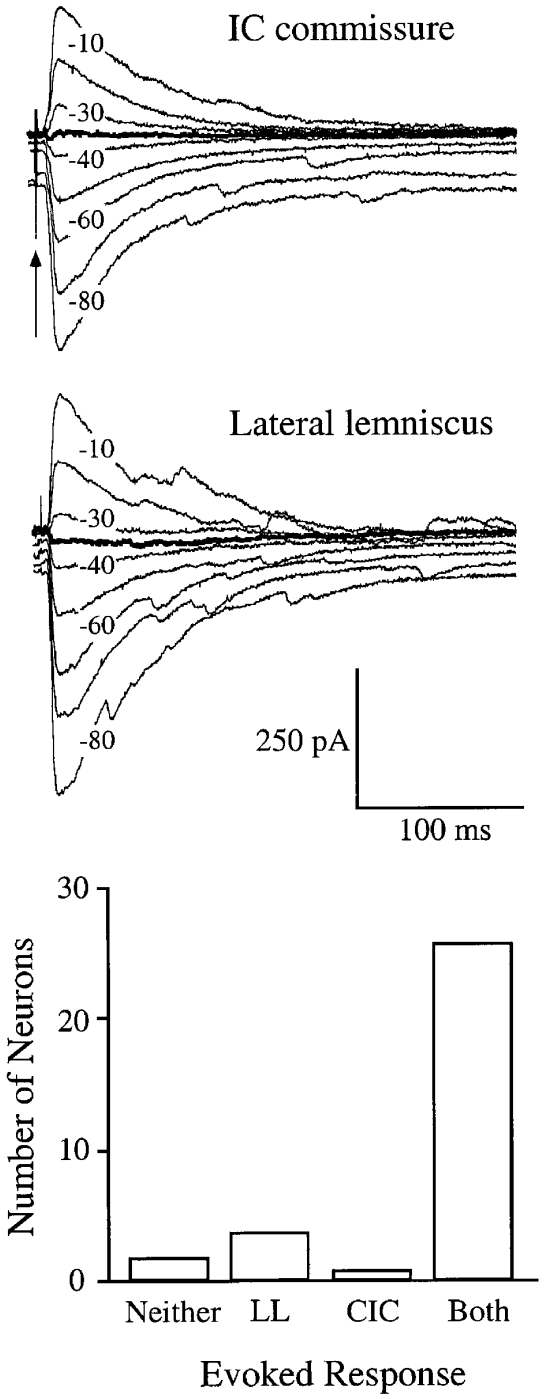

FIG. 3. IC commissure- and lateral lemniscus-evoked postsynaptic currents (PSCs). Maximum current amplitudes were typically achieved at 10–20 ms after stimulation (arrow) and resulted from an interplay of excitatory and inhibitory inputs. Most neurons tested had synaptic currents with multiple components, as illustrated here. Recordings were obtained at holding potentials of −10 to −80 mV, as indicated above each trace. Bold trace indicates the holding potential at which the PSCs reversed. The histogram indicates the number of neurons that showed synaptic currents in response to stimulation of either or both afferent pathways.

blocked CIC-evoked currents completely. Conversely, 22% of LL-evoked PSCs were unaffected by iGluR antagonists, and a somewhat higher proportion (38%) of CIC-evoked PSCs was unaffected. Figure 7*A* summarizes the preponderance of excitatory (sensitive to iGluR antagonists) and inhibitory (not sensitive to iGluR antagonists) synaptic currents.

At a holding potential of −20 mV, before iGluR antagonist exposure, most PSCs were outward (Fig. 4, LL stimulation), although complex waveforms were also observed (Fig. 4, CIC stimulation). If these currents reflected summation of inward excitatory and outward inhibitory currents, then iGluR antagonists would be expected to increase the outward PSC amplitude as the inward component was eliminated. This outcome was occasionally observed (Fig. 5). However, in the majority of cases, iGluR antagonists led to a decrease in the outward PSC at $V_{hold} = -20$ mV (Fig. 4, LL stimulation; Fig. 6). This suggests that, in addition to their direct innervation of ICC neurons, excitatory afferents to the IC activate inhibitory interneurons (represented schematically in Fig. 9).

For neurons that had synaptic currents remaining after iGluR antagonists were added, the addition of the GABA and glycine receptor antagonists bicuculline (BIC) and strychnine (SN) generally abolished the remaining currents. As summarized in Fig. 7*B*, every one of the ICC neurons tested was sensitive to BIC. For LL stimulation, about one-half of the neurons also displayed some sensitivity to SN.

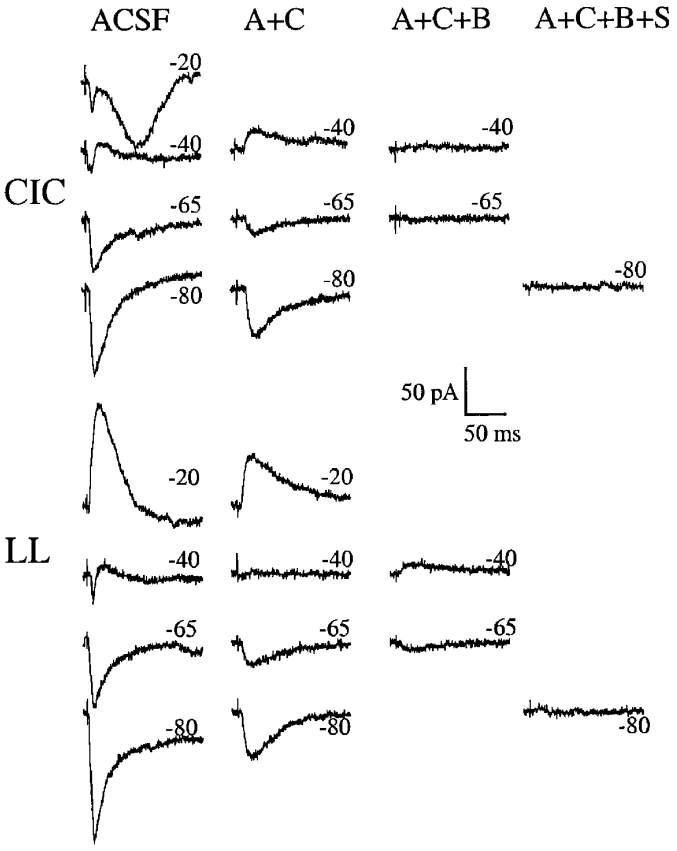

FIG. 4. Commissure- and lateral lemniscus-evoked PSCs, recorded in the presence of receptor antagonists. Addition of iGluR antagonists (A + C) led to a reduction in the CIC-evoked inward current at $V_{hold} = -80$ mV and produced a slight enhancement of the outward current at $V_{hold} = -40$ mV. For LL stimulation, iGluR antagonists reduced synaptic currents at all holding potentials. Addition of bicuculline (A + C + B) nearly eliminated the remaining CIC-evoked synaptic currents and diminished the LL-evoked currents. Strychnine eliminated the remaining LL-evoked synaptic currents. Holding potential is indicated to the right of each current trace.

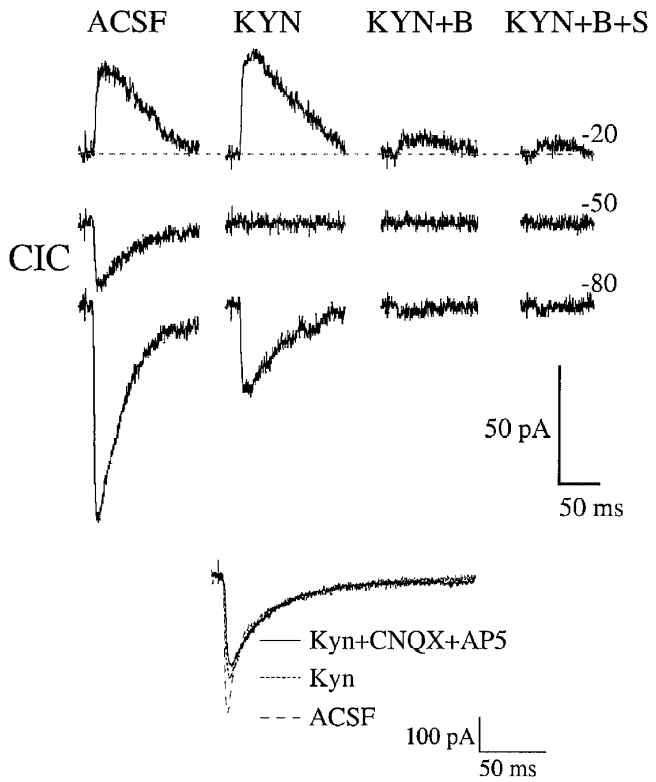

FIG. 5. Commissure-evoked PSCs recorded in the presence of receptor antagonists. Addition of an iGluR antagonist (KYN) led to a reduction in the CIC-evoked inward current at $V_{hold} = -80$ mV but enhanced the outward current at $V_{hold} = -20$ mV. Addition of bicuculline (KYN + B) nearly eliminated the remaining CIC-evoked synaptic currents. Addition of strychnine (KYN + B + S) decreased but did not eliminate the remaining current. Holding potential is indicated to the right. *Inset*: to test whether kynurenic acid had the same effect as the more selective iGluR antagonists, a synaptic response was recorded 1st in ACSF, then in kynurenic acid (Kyn), and finally in kynurenic acid plus AP-5 and CNQX (Kyn + CNQX + AP-5). The latter 2 drugs did not lead to further, significant reduction of the synaptic current.

For CIC stimulation, BIC abolished the remaining PSC in almost all neurons tested. We noted that small residual currents were occasionally present, even after application of all antagonists (Fig. 5).

A summary analysis was performed on the amplitude and duration of peak synaptic currents for 15 neurons (CIC = 14; LL = 9) at $V_{hold} = -80$, before and after application of BIC and SN (Fig. 8). Neither the amplitude (Fig. 8*A*) nor the duration (Fig. 8*B*) of the total currents differed significantly between the two stimulated pathways. After BIC exposure (Fig. 8*A*), most neurons had irresolvably small (<10 pA) inhibitory postsynaptic currents (IPSCs). Those IPSCs that remained had amplitudes of one-half or less of the pre-BIC level. The durations of these few, small currents were also reduced. Mean reversal potentials for total IPSCs were measured for 12 neurons and did not differ for stimulation of the CIC (-43.6 ± 15.2 mV; range -72 to -15; $n = 10$) or the LL (-45.5 ± 15.9 mV; range -72 to -20; $n = 8$).

DISCUSSION

This study demonstrated that the CIC afferents provide a major synaptic input to ICC neurons. Although this input consisted of both excitatory and inhibitory components, GABAergic inhibition appeared to dominate. However, it proved impossible pharmacologically to dissect out the total inhibitory component because iGluR antagonists blocked not only excitatory afferents but also disynaptic inhibitory connections (Fig. 9). Most ICC neurons also received input via LL afferents. LL stimulation elicited comparable levels of excitatory and inhibitory input, and the synaptic response was more likely to contain a strychnine-sensitive component than was that produced by CIC stimulation.

The complexity of synaptic convergence onto ICC neurons revealed by this study extends previous intracellular observations made in vivo. In pioneering work, Nelson and Erulkar (1963) showed that single IC neurons could be both depolarized and hyperpolarized by steady-state or transient acoustic stimuli. The timing and interactions of these postsynaptic potentials could be altered by varying the frequency or interaural properties of the stimuli. Kuwada et al. (1997) and Pedemonte et al. (1997) recently confirmed the mixed excitatory and inhibitory input received from each ear by many IC neurons. Kuwada et al. (1997) showed that several suprathreshold response properties of IC neurons (inhibitory side bands, the postonset pause in discharge rate, and hetero-

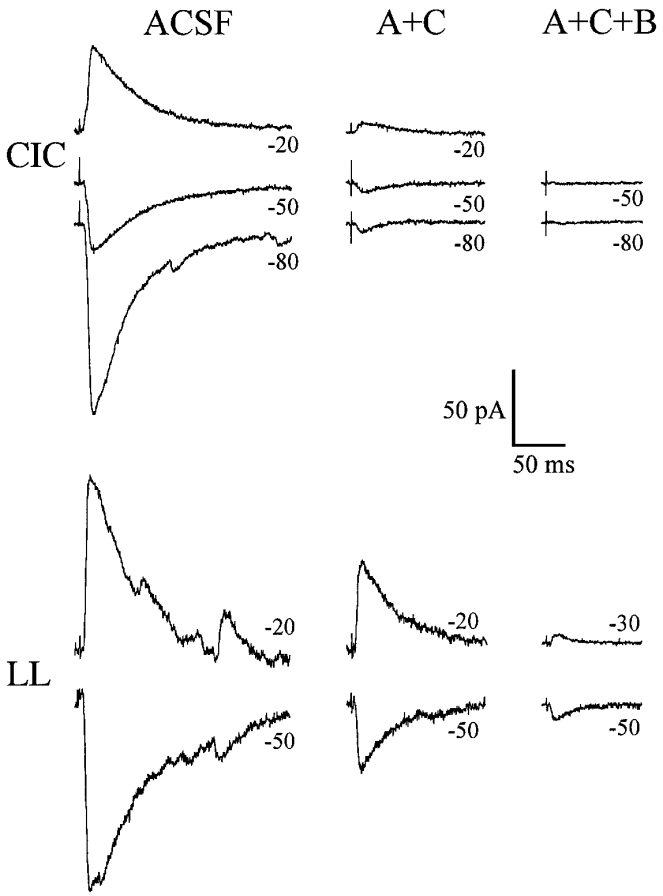

FIG. 6. Commissure- and lateral lemniscus-evoked PSCs recorded in the presence of receptor antagonists. Addition of iGluR antagonists (A + C) resulted in a decrease in amplitude of both the inward ($V_{hold} = -20$ mV) and outward ($V_{hold} = -20$ mV) synaptic currents. In addition, the synaptic current contained multiple components in ACSF but only a single component after addition of iGluR antagonists. These results suggest that a significant fraction of the synaptic input to ICC neurons is disynaptic.

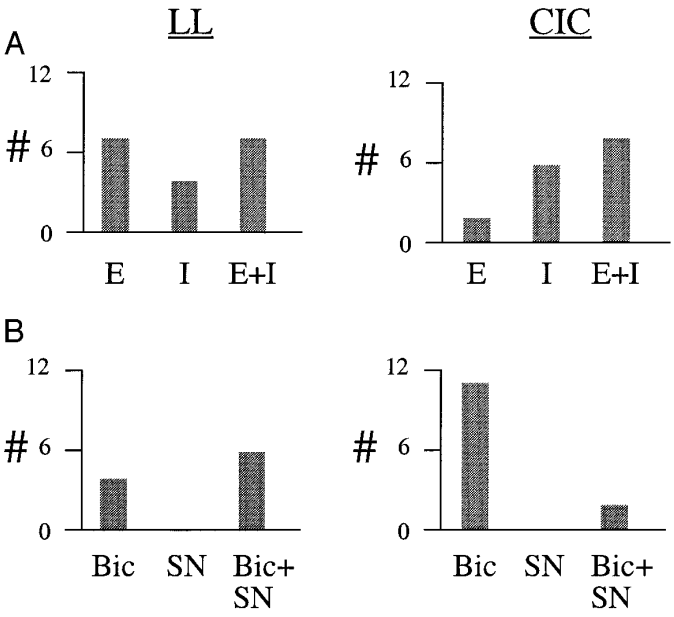

FIG. 7. Characteristics of voltage-clamped ICC neurons in response to LL stimulation (*left*) or CIC stimulation (*right*). *A*: number of cells that received excitatory input only (E), inhibitory input only (I), or mixed input (E + I). *B*: number of cells displaying IPSCs that were reduced by bicuculline only (BIC), strychnine only (SN), or both (BIC + SN).

geneity of responses to interaural time differences) are modified by inhibitory synaptic input to IC neurons. In another recent study with whole cell recording in the IC of awake bats, Covey et al. (1996) showed variations among neurons in the source and timing of synaptic and spike responses to free-field acoustic stimulation. Again, most neurons exhibited both excitatory and inhibitory synaptic responses to these stimuli. Together these studies provide compelling evidence for the integrative and active roles played by the IC in acoustic signal processing. Most IC neurons appear to receive input from multiple sources, including brain stem and other midbrain nuclei, and intrinsic sources within the IC. One important limitation of the methods used in these studies, however, is that the interaction and relative timing of excitatory and inhibitory events may be obscured by the compound nature of the synaptic responses recorded. However, they can be partially dissected through pharmacological means and in vitro analyses.

Only two detailed in vitro studies of synaptic physiology in the IC were performed. Smith (1992) used sharp electrodes to record from dorsomedial IC neurons in the rat and found only weak synaptic responses to LL stimulation. However, much larger synaptic potentials were evoked by CIC stimulation. They characteristically consisted of an IPSP–EPSP–IPSP sequence. The initial IPSP was considered monosynaptic and generally had a lower stimulus threshold compared with the later components. Recording in the ICC, Wagner (1996) found a much stronger synaptic response to LL stimulation than that reported for dorsomedial neurons (Smith 1992). Furthermore, he suggested that the relatively long onset latencies (>5 ms) recorded in about one-half the ICC neurons might be due to disynaptic inputs from the LL. The ICC neurons recorded in this study exhibited prominent responses to LL stimulation, consistent with Wagner's mouse study. Our results are also consistent with the notion of a disynaptic, inhibitory input to most ICC neurons; exposure to iGluR antagonists generally reduced outward PSCs at a holding potential of −20 mV, indicating that excitatory afferents had been activating inhibitory interneurons within the IC (Fig. 9). The remaining inhibitory currents recorded in the presence of iGluR antagonists showed short onset latencies (2–4 ms) to both LL and CIC stimulation, consistent with a monosynaptic input.

We experienced difficulty in obtaining seals on neurons from gerbils older than P15, and it is possible that some aspects of synaptic function were not fully mature. However, we did not notice any fundamental differences in the synaptic properties over the age range examined (P9–P19). Previous developmental studies do indicate that synaptic properties of auditory brain stem neurons continue to mature for 2–3 wk postnatal, although the paucity of recordings from adult

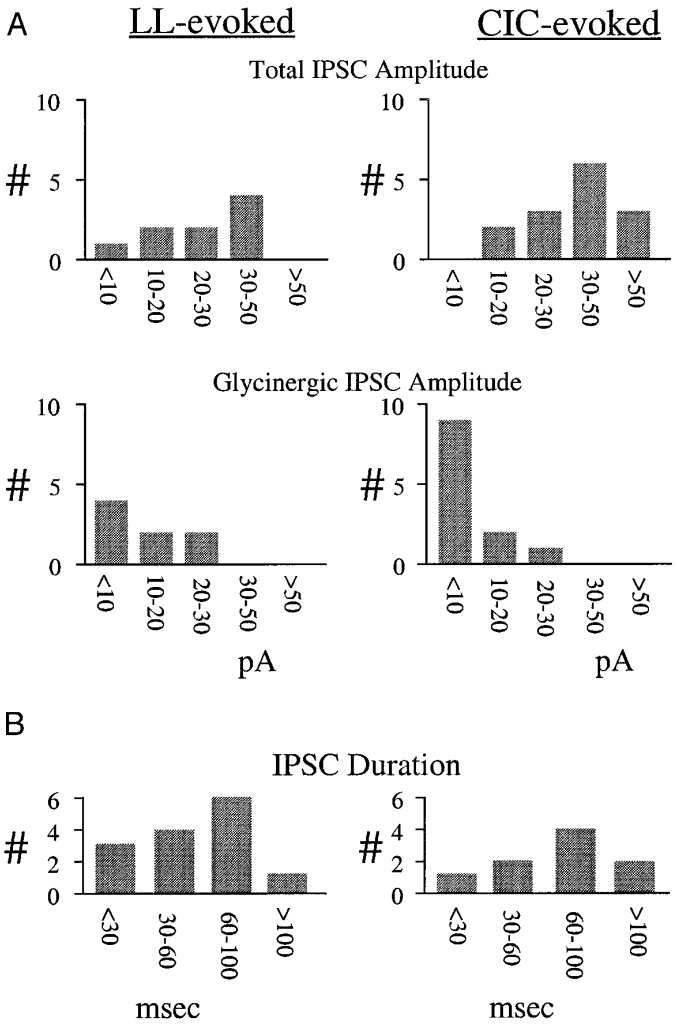

FIG. 8. Inhibitory postsynaptic current (IPSC) amplitude and duration in response to lemniscal (*left*) and commissural (*right*) stimulation. *A*: amplitude of IPSCs recorded in the presence of iGluR antagonists before (Total IPSC Amplitude) and after (Glycinergic IPSC Amplitude) the addition of bicuculline. Bicuculline had a relatively larger effect on CIC-evoked IPSCs. *B*: duration of IPSCs recorded in the presence of iGluR antagonists before the addition of bicuculline. Current durations after the application of bicuculline are not shown because of the small number of neurons with measurable currents remaining.

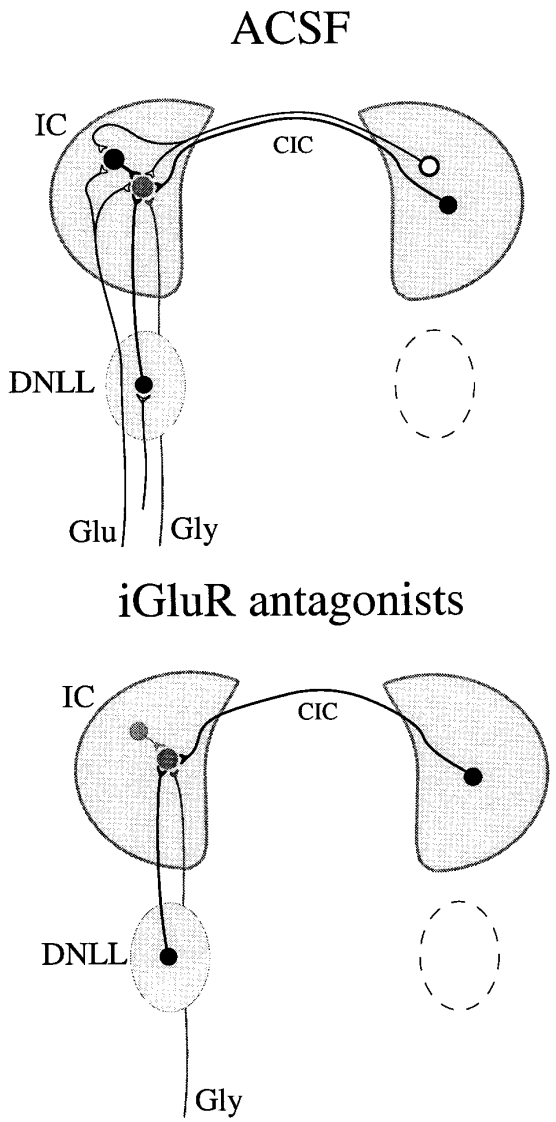

FIG. 9. Models of the simplest functional circuitry consistent with the present observations. In ACSF, excitatory synapses (white area) make direct connections with target IC neurons (shaded area) and indirect connections via inhibitory interneurons within the IC (black area). Additional, direct inhibitory neurons project via the LL and the CIC. After application of iGluR antagonists, only the direct inhibitory inputs remain functional.

neurons leave the issue unresolved (Kandler and Friauf 1995; Sanes 1993).

Iontophoretic studies applied GABA and glycine and their antagonists at local recording sites within the ICC (e.g., Klug et al. 1995; LeBeau et al. 1996; Park and Pollak 1993). These studies have shown the importance of local inhibitory action on a number of ICC neuron responses to acoustic stimulation. Other studies recorded from ICC neurons during or after the application of antagonists (Faingold et al. 1993; Kelly and Li 1997; Li and Kelly 1992) to or lesions (Kelly and Li 1997) of projecting brain stem nuclei. However, none of these studies differentiated the influence of the contralateral ICC from that of other sources of ICC input. The results reported here suggest that the contralateral ICC may play an important role in shaping ICC responses to acoustic stimulation, primarily, although not exclusively, through inhibitory mechanisms.

These observations complement recent anatomic observations of commissural input to the most ventral parts of the ICC (Malmierca et al. 1995; Saldaña and Merchán 1992). Aitkin and Phillips (1984) infiltrated the cat CIC with HRP and showed retrogradely labeled neurons in the dorsal and central nuclei of IC. In the latter study, no retrogradely labeled neurons were reported in the brain stem, suggesting that all the ICC input passing through the CIC derives largely from contralateral IC neurons. González-Hernández et al. (1996) emphasized the sparsity of projections to the ventral ICC from the contralateral ICC, with only ~20% as many neurons retrogradely labeled after ventral as after dorsal injections of HRP. However, both the dorsally and the ventrally labeled neurons were symmetric (homotopic) with their respective injection sites, and an equal proportion of them (~40%) were GABAergic.

Synaptic inhibition contributes to auditory processing in a diverse manner within the IC. Inhibitory influences are important for shaping responses in the spectral (Yang et al. 1992), amplitude (Faingold et al. 1989, 1991) and temporal (Casseday et al. 1994; LeBeau et al. 1996; Park and Pollak 1993) domains. In addition, they may be involved in modulating responses to dynamic stimuli (Sanes et al. 1998; Spitzer and Semple 1991, 1993) and in the long-term changes in responsiveness that accompany hearing loss (Bledsoe et al. 1995; McAlpine et al. 1997; Moore et al. 1997; Palombi and Caspary 1996). At a cellular level, they appear to regulate intracellular free calcium (Lo et al. 1998). This study indicates that the CIC pathway provides one of the largest sources of inhibition in the IC and suggests that the interneuronal connections observed anatomically (Oliver et al. 1991) provide a significant fraction of that inhibition.

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