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**Effects of Suppression of Neural Activity in the Dorsal Nucleus
of the Lateral Lemniscus on Auditory Evoked Potentials
in the Inferior Colliculus of the Albino Rat**

by

Liang Li, B.Sc, M.Sc.

A thesis submitted to
the Faculty of Graduate Studies and Research
in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

Department of Psychology

Carleton University

Ottawa, Canada

June, 1994

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Effects of Suppression of Neural Activity in DNLL on Auditory Evoked Potentials in
Inferior Colliculus of the Albino Rat

submitted by Liang Li, B.Sc., M.Sc.

in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Thesis Supervisor

Chair, Department of Psychology

External Examiner

Carleton University

June, 1994

ABSTRACT

Our previous studies have indicated that excitatory responses of the rat's dorsal nucleus of the lateral lemniscus (DNLL) are partially independent of excitatory activity in the superior olivary complex (SOC), and that interaural intensity difference (IID) functions of single EI units in the rat's central nucleus of the inferior colliculus (ICC) are partially based on the inhibitory projection from the contralateral DNLL. We expected that the contribution of the contralateral DNLL to the binaural inhibition in the ICC may also be reflected in the IID functions measured by evoked potential (EP) amplitude in the ICC. To examine this expectation, we measured both monaural and binaural EPs in the rat's ICC and selectively blocked the neural activity in the contralateral DNLL, ipsilateral DNLL, contralateral inferior colliculus (IC), and ipsilateral SOC by local injection of kynurenic acid (2mM in Locke's solution), an endogenous broad-spectrum antagonist of excitatory amino acid receptors. The tone-evoked potentials were recorded by glass micropipettes (filled with Locke's solution; tip diameter: 5-30 μ m; band-pass filter: 0.3-500 Hz) inserted into the ICC. The injections were made with glass microelectrodes (tip diameter: 20-30 μ m) which were used to record the neural activity of a small cluster of neurons and to microinject chemicals at the same time.

In the ICC, blockade of activity in the contralateral DNLL not only reduced the binaural suppression in the EP IID function but also enhanced the monaural responses evoked by stimulation of the ipsilateral ear. In contrast, blockade of activity in the contralateral ICC had no effect on the EP IID function but reduced the monaural response evoked by stimulation of the ipsilateral ear. Block of activity in the ipsilateral DNLL and the ipsilateral SOC had no remarkable effect on the EP IID function in the ICC. The data suggest that the contralateral DNLL plays an essential role both in enhancing the laterality of binaural responses in the rat's auditory midbrain and in modifying the excitatory input to the ICC from the ipsilateral ear.

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Figure 35. Comparison of shifts in the IID function and shifts in the monaural responses to ipsilateral stimulation for the rats in which KYNA was injected into the ipsilateral SOC and the contralateral DNLL.

LIST OF ABBREVIATIONS

AC	auditory cortex
AMPA	α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid
AN	auditory nerve
AVCN	anterior ventral division of the cochlear nucleus
CF	characteristic frequency
CN	cochlear nucleus
CNQX	6-cyano-7-nitroquinoxaline-2,3-dione, a relatively specific antagonist for non-NMDA receptor
DCN	dorsal cochlear nucleus
DNLL	dorsal nucleus of the lateral lemniscus
DMPO	dorsomedial periolivary nucleus
EC ₅₀	a concentration of a drug, at which the drug has 50% of its maximum effect
EE	binaural response type - cell excited by stimulation of either alone
EI	binaural response type - cell excited by contralateral stimulation and inhibited by ipsilateral stimulation
EO	binaural response type - cell excited by contralateral stimulation, ipsilateral stimulation has no effect
EP	evoked potential
FTC	frequency tuning curve
GABA	gamma-aminobutyric acid
GAD	glutamic acid decarboxylase
HRP	horseradish peroxidase
IC	inferior colliculus

ICC	central nucleus of the inferior colliculus
ICP	pericentral nucleus of the inferior colliculus
ICX	external nucleus of the inferior colliculus
IE	binaural response type - cell inhibited by contralateral stimulation and excited by ipsilateral stimulation
IID	interaural intensity difference
INLL	intermediate nucleus of the lateral
IPD	interaural phase difference
ITD	interaural time difference
KYNA	kynurenic acid
LL	lateral lemniscus
LSO	lateral superior olivary nucleus
LNTB	lateral nucleus of the trapezoid body
MGB	medial geniculate body
MNTB	medial nucleus of the trapezoid body
MSO	medial superior olivary nucleus
NLL	nuclei of the lateral lemniscus
NMDA	N-Methyl-D-aspartate
PHA-L	<i>Phaseolus vulgaris</i> -leucoagglutinin
PVCN	posterior ventral division of the cochlear nucleus
SC	superior colliculus
SOC	superior olivary complex
SPO	superior paraolivary nucleus
TB	trapezoid body
TTD	transient time difference
VCN	ventral division of the cochlear nucleus
VNLL	ventral nucleus of the lateral lemniscus

VNTB	ventral nucleus of the trapezoid body
2-DG	2-deoxyglucose

INTRODUCTION

Binaural Cues for Sound Localization

For most mammals, a comparison of the inputs to the two ears is the primary means by which the central auditory system for determining sound source location in the azimuthal plane. As a sound source moves away from the midsagittal plane, the sound waves arrive earlier and are more intense at one ear, giving rise to interaural arrival time differences, interaural phase differences, interaural intensity differences, and interaural spectral differences.

The interaural arrival time differences are caused by the fact that the onset of the acoustic signal reaches one ear before the other ear. The interaural arrival time differences are also called transient time differences (TTDs). The interaural phase differences (IPDs) occur as a result of the difference in the distance traveled by a certain part in the acoustic waveform (e.g., the crest of sinewave). The interaural phase differences provide cues for frequencies with wavelengths greater than the head diameter. Both the interaural arrival time differences and the interaural phase differences are referred to as interaural time differences (ITDs).

The head and pinna function as barriers for higher frequency sounds, which have wavelengths that are smaller than the diameter of the head. If a sound is not at the midsagittal plane, the head and pinna create an acoustic shadow opposite the sound source. The sound is more intense at one ear than the other ear, giving rise to interaural intensity differences (IIDs).

Neural processing of each of these binaural cues involves the comparison of neural activities in the central auditory system resulting from stimulation of the two ears. The cochlear nucleus (CN) basically receives the monaural acoustic information from the ipsilateral ear through the auditory nerve (AN, the axons of both type I and type II spiral ganglion cells) on each side and starts the central processing of auditory inputs. From the

CN, the auditory information ascends through the auditory brainstem structures, such as the superior olivary complex (SOC), the nuclei of the lateral lemniscus (NLL), the inferior colliculus (IC), and the medial geniculate body (MGB), toward the auditory cortex (AC). Remarkable binaural processing starts from the level of the SOC and continues all the way to the AC. The anatomy, physiology, and function of the auditory brainstem structures from the CN to the IC will be discussed below. Further details may be found in the book by Irvine (1986) and recent reviews in *Neurobiology of Hearing: The Central Auditory System* edited by Altschuler et al. (1991).

Cochlear Nucleus

The CN has been traditionally divided into two divisions, the dorsal cochlear nucleus (DCN) and the ventral cochlear nucleus (VCN), with the latter further divided into the anteroventral cochlear nucleus (AVCN) and the posteroventral cochlear nucleus (PVCN) by the entering AN root. All AN axons innervate the CN, and each AN fiber bifurcates after entering the CN (Jones and Casseday, 1979; Fekete et al., 1984; Osen, 1970; Powell and Cowan, 1962). The ascending branch projects to the AVCN, and the descending branch traverses the PVCN and ends in the DCN.

The innervation of each of the divisions is topographically organized, with high-to-low frequency input arrayed from dorsocaudal to rostroventral (Fekete et al., 1984; Osen, 1970). In accordance with the pattern of tonotopically organized innervation, both microelectrode physiological studies (Rose et al., 1959; Evens and Nelson, 1973; Goldberg and Brownell, 1973) and the 2-deoxyglucose (2-DG) autoradiographic technique (Nudo and Masterton, 1984) confirmed a dorsocaudal-to-rostroventral arrangement for characteristic frequency (CF, the frequency requiring the lowest sound level to evoked the specified response).

Almost all large CN neurons send their ascending axons in three main stria: the trapezoid body (TB), the intermediate acoustic stria (stria of Held), and the dorsal

acoustic stria (stria of Monakow) (Adams, 1983; Rhode et al., 1983a, b; Tolbert et al., 1982; Wu and Oertel, 1984). All the three major CN divisions project through these striae to the NLL and IC directly (Adams, 1979; Adams and Warr, 1976; Brunso-Bechtold et al., 1981; Covey and Casseday, 1986; Fernandez and Karapas, 1967; Glendenning et al., 1981; Glendenning and Masterton, 1983; Oliver, 1984b, 1987; Osen, 1972; Warr, 1968, 1972, 1982). Besides the common projections, the subdivisions of CN have independent projection patterns. The AVCN projects through the TB to the main nuclei of the SOC (Warr, 1966, 1972, 1982), whereas the PVCN projects through the caudal portion of TB and through the intermediate acoustic stria to the periolivary nuclei of SOC, but not to the main nuclei (Warr, 1966, 1972, 1982). The fusiform and giant cells of DCN project primarily to the IC (Adams, 1979; Brunso-Bechtold et al., 1981; Oliver, 1984b; Osen, 1972; Roth et al., 1978).

The AVCN contains numerous neuronal types that can be distinguished easily in Nissl stained material. Two of the most easily distinguished cell types in the AVCN are the spherical/bushy and globular/bushy cells (Osen, 1969), and these neurons provide the major direct and indirect CN inputs to the LSO, MSO, DNLL, VNLL, and IC. The spherical cells are located in the anterior division of the AVCN, and the globular cells are located in the posterior division of the AVCN.

Superior Olivary Complex

The SOC is a pontine nuclear group and has been commonly regarded as the principal center of the binaural interactions in the ascending auditory pathway since Stotler's pioneering investigations (Stotler, 1956). The anatomy of SOC has been most extensively investigated in the cat. The SOC of the cat contains three principal nuclei: the lateral superior olivary nucleus (LSO), the accessory, or medial superior olivary nucleus (MSO) and the medial nucleus of the trapezoid body (MNTB). Surrounding the major nuclei are a number of smaller and less clearly defined aggregations of cells. Ventral to

the MNTB and the LSO respectively, are nuclei termed ventral and lateral nuclei of the trapezoid body (VNTB and LNTB). In addition, a group of nuclei in the cat collectively referred to as periolivary nuclei are located at the margins of the SOC.

Medial Nucleus of the Trapezoid Body

The MNTB is named for its location in the TB. Its neurons reside among the fascicles of TB axons passing through the nucleus. Morest (1968) described three types of neurons in the MNTB which he termed principal, elongate, and satellite neurons.

The principal cells receive excitatory and topographically organized inputs from the globular cells of the contralateral AVCN (Harrison and Irvine, 1966b; Harrison and Warr, 1962; Tolbert et al., 1982; Warr, 1972, 1982) via the large secure axosomatic synaptic calyces of Held containing spherical vesicles and multiple synaptic contacts (Jean-Baptiste and Morest, 1975; Lenn and Reese, 1966; Morest, 1968). A calyx is a cup-shaped expansion of the axonal terminals which extends over the surface of the principal cell soma. Each calyx ends on only a single principal neuron and each principal neuron receives only a single calyx which arises from only one large-diameter, heavily myelinated axon in the TB. Similar descriptions have been given of principal cells and calyces in the MNTB of the mouse (Ollo and, 1979).

The responses of principal neurons have a complex waveform, with a presynaptic potential reflecting the presynaptic activity from the calyces of Held (Li and Guinan, 1971; Guinan et al. 1972a, b). Response latencies of principal cells to clicks are consistently shorter than those of cells in other SOC nuclei (Goldberg and Brown, 1968; Guinan et al. 1972a, b) due to rapid propagation of the large-diameter axons and rapid synaptic transmission by calyceal terminals.

As expected on the basis of afferent projections, the MNTB principal neurons have response properties resembling those of globular/bushy cells in the posterior AVCN,

such as primarylike or phase-locked response patterns and narrow V-shaped tuning curves (Guinan et al. 1972a, b).

The cell bodies of the principal cells are also contacted by a heterogeneous population of smaller terminals with smaller pleomorphic or flattened synaptic vesicles, that immunolabel with gamma-aminobutyric acid (GABA) and glycine, respectively (Helfert, et al, 1988). The source of the glycine-immunoreactive terminals may be from within the MNTB itself, as several studies indicate that principal neurons are glycinergic (Bledsoe, et al, 1990; Helfert, et al, 1989; Moore and Caspary, 1983; Peyret, et al, 1987; Wenthold, et al, 1987) and that these neurons produce axon collaterals that end on adjacent MNTB neurons (Bledsoe et al, 1988; Morest, 1968). The source of GABA input to the MNTB has not been identified.

Since the principal cells receive a topographically organized projection from the globular/bushy cells of the contralateral AVCN (Harrison and Irvine, 1966b; Harrison and Warr, 1962; Tolbert et al., 1982; Warr, 1972, 1982), the principal cells are tonotopically organized, with high-to-low characteristic frequencies arranged in a ventromedial-to-dorsolateral direction (Guinan et al, 1972a, b). There is also a disproportionately large representation of higher frequencies in the MNTB due to a higher cell density in the ventromedial part of the nucleus and lower cell density in the dorsolateral part.

The majority of the principal cells of MNTB are excited only by contralateral monaural stimulation and are termed "EO" (contralateral stimulation excites, ipsilateral stimulation has no effect) (Galambos et al, 1959; Goldberg et al, 1963; Goldberg and Brown, 1968; Guinan et al, 1972a, b). In a brain slice preparation of the mouse SOC, it was reported that non-N-Methyl-D-aspartate (non-NMDA) receptors may mediate ipsilateral excitatory response at the MNTB synapses (Wu and Kelly, 1992b).

Other neurons without the complex waveform (possibly the satellite neurons) appear not to be tonotopically organized (Guinan et al, 1972a, b).

The projection of the MNTB is almost entirely ipsilateral. The principal and elongate neurons send their major projections around and through the MSO to the medial and intermediate limbs of the LSO (Elverland, 1978; Glendenning, et al, 1985; Harrison and Warr, 1962; Rasmussen, 1946; Spangler et al, 1985). Axon collaterals of the principal and elongate cells form substantial projections to the dorsomedial periolivary nucleus (DMPO), MSO, and LNTB in the SOC, as well as to the ventral nucleus of the lateral lemniscus (VNLL), and to the intermediate nucleus of the lateral lemniscus (INLL) (Bledsoe et al, 1988; Glendenning et al, 1981; Kuwabara and Zook, 1990; Morest, 1968; Spangler et al, 1985). Terminals from MNTB are very sparse in the IC (Spangler et al, 1985).

The projection from the MNTB to the LSO is tonotopically organized. Neurons in the most ventromedial (high-frequency) portion in the MNTB project to the medial (high-frequency) limb of the LSO and to the medial regions of DMPO and LNTB; dorsolaterally located (lower frequency) MNTB neurons project to the lateral part of the LSO (Bledsoe et al, 1988; Elverland, 1978; Glendenning et al, 1981; Spangler et al, 1985).

Lateral Superior Olivary Nucleus

In most species, the LSO can usually be distinguished from other SOC nuclei by its shape. In transverse section, the LSO appears as a U, S, or W, depending on the number of folds. The amount and degree of folding are species dependent. The gaps between the folds, the hila, are major sites through which afferent axons enter the LSO.

The cat and gerbil LSO contain several morphologically distinct cell types, the most prevalent of which is the fusiform neuron or principal neuron (Helfert and Schwartz, 1986, 1987). The principal neurons compose roughly three-quarters of the total neuronal population in the LSO. In transverse sections, the principal cells appear fusiform. The fusiform cells form a central band with polar dendrites oriented approximately

perpendicular to the axis of curvature of the nucleus, and marginal cells are at the borders of the nucleus (Ollo and, 1979). In sagittal sections, the principal cells are predominantly multipolar, with dendritic plexuses forming rostrocaudally oriented sheets (Ollo and, 1979; Scheibel and Scheibel, 1974).

The LSO receives its major direct afferent sources from the ipsilateral AVCN and the MNTB. The LSO receives ipsilateral input via the TB from the AVCN (Harrison and Warr, 1962; Stotler, 1953; Warr, 1966). The projection to LSO from the ipsilateral AVCN is derived from the spherical/bushy cells (Glendenning et al., 1985; Osen et al., 1969; Warr, 1966), and most of the fibers projecting to LSO are collaterals of TB axons that continue across the midline (Glendenning et al., 1985). The LSO receives input from the contralateral AVCN indirectly via the principal cells of the MNTB (Elverland, 1978; Glendenning et al., 1985).

Cant (1984) reported three types of terminals on the principal cells of LSO in the cat. (1) Terminals containing small, flattened vesicles and making slightly asymmetric contacts were found predominantly on the soma and proximal dendrites. These terminals appear to be glycinergic (Glendenning and Baker, 1988; Sanes et al., 1987; Wenthold et al., 1987; Zarbin et al., 1981), and may originate from the ipsilateral MNTB (Moore and Caspary, 1983). (2) Terminals with large round vesicles and strongly asymmetric contacts were found predominantly on distal dendrites and only occasionally on the soma. These terminals are presumably the source of excitatory inputs to the principal cells. The excitatory transmitters may be glutamate and aspartate (Helfert et al., 1989, 1992), and the main corresponding postsynaptic receptors may be non-NMDA receptors (Caspary and Faingold, 1989; Wu and Kelly, 1992a, b). NMDA receptors may also reside in the LSO and may play a role in binaural processing by modulating contralateral inhibitory input to the LSO (Wu and Kelly, 1992a, b). (3) A third class of terminals with small round vesicles was encountered only rarely.

The LSO is tonotopically organized with high frequencies represented in the ventromedial limb and low frequencies in the dorsolateral limb (Boudreau and Tsuchitani, 1970; Guinan et al., 1972b; Tsuchitani, 1977; Tsuchitani and Boudreau, 1966). There is a disproportionately large representation of high frequencies in the LSO of the cat with the majority of cells having CFs from 5-44 kHz (Boudreau and Tsuchitani, 1970; Guinan et al., 1972b; Tsuchitani, 1977).

There is general agreement that the majority of neurons in the LSO of anesthetized mammals, other than those with low (<1 kHz) CF, receive inhibitory inputs from the contralateral CN by way of the ipsilateral MNTB, and receive direct excitatory inputs from the ipsilateral CN (the neurons are so-called IE neurons) (Boudreau and Tsuchitani, 1968, 1970; Caird and Klinke, 1983; Goldberg et al., 1963; Guinan et al., 1972a, b; Tsuchitani, 1977). The remaining cells also receive ipsilateral excitatory input, with the contralateral ear either having no effect (OE; Guinan et al., 1972a, b; Tsuchitani, 1977) or an unspecified effect (Tsuchitani, 1977).

For any IE neuron in the LSO, the CF for contralateral (inhibitory) stimulation is almost identical to that for ipsilateral (excitatory) stimulation and response thresholds at CF are similar for the two sides. In addition, the inhibitory response area (the range of frequency and intensity over which ipsilateral stimulation will suppress the response to contralateral stimulation) is approximately equal to the excitatory response area (the range of frequency and intensity over which the cell will respond) (Boudreau and Tsuchitani, 1968; Caird and Klinke, 1983; Guinan et al., 1972b; Tsuchitani and Boudreau 1969). The frequency specific convergence of ipsilateral and contralateral input enable the cells of the LSO to analyze the IIDs of the sound stimulus reaching the two ears. The rate of discharge evoked in a neuron in the LSO is dependent on both the level of ipsilateral excitatory input and the level of contralateral inhibitory input. The response to an excitatory ipsilateral stimulus at any given intensity declines progressively with increases in the intensity of the contralateral inhibitory stimulus (Boudreau and

Tsuchitani, 1968, 1970; Caird and Klinke, 1983; Tsuchitani and Boudreau, 1969; Harnischfeger et al., 1985).

Boudreau and Tsuchitani (1968) reported that the total conduction times from the ipsilateral and contralateral ears are approximately equal despite the greater path length and the additional synapse in the contralateral pathway. Wu and Kelly (1991) reported a similar result in brain slice preparations of mouse SOC. So it is possible that the LSO has IID as well as ITD functions. As mentioned previously, ITD involves both TTD and IPD. Some studies have already demonstrated, using dichotically presented click stimuli, that IE and EI cells in the SOC are sensitive to TTDs (Galambos et al., 1959; Hall, 1965; Moushegian et al., 1964, 1967). Caird and Klinke (1983) have shown that the onset response components of IE cells in LSO of the cat are also sensitive to onset timing disparities in tone- and noise-burst stimuli, and have ITD functions of the same form as their IID functions. In mouse brain slice, both intracellular and extracellular data indicate that neurons in the LSO are sensitive to TTDs (Wu and Kelly, 1992c).

In a number of species, bilateral projections of the LSO to the IC and DNLL have been found (cat: Adams, 1979; Brunso-Bechtold et al, 1981; Elverland, 1978; Glendenning et al., 1981; Glendenning and Masterton, 1983; Henkel and Brunso-Bechtold, 1993; Roth et al., 1978; Stotler, 1953; rat: Beyerl, 1978; Coleman and Clerici, 1987; bat: Zook and Casseday, 1982).

It was found that cells projecting to the IC ipsilaterally are concentrated in the lateral (low-frequency) limb of LSO, while those projecting contralaterally are concentrated in the medial (high-frequency) limb of LSO (cat: Glendenning and Masterton, 1983; chinchillas and guinea pig: Saint Marie and Baker, 1990). In contrast, Henkel and Brunso-Bechtold (1993) reported that the neurons in lateral limb of the ferret's LSO have greater projection to the contralateral IC than the neurons in medial limb. Only a very small proportion of LSO cells project bilaterally via axon collaterals to

the IC (cat: Glendenning and Masterton, 1983; ferret: Henkel and Brunso-Bechtold, 1993, opossum: Willard and Martin, 1984).

A large proportion of LSO principal neurons are glycine immunoreactive and project to ipsilateral IC directly (Aoki et al., 1988; Saint Marie and Baker, 1990; Wenthold et al., 1987). In chinchillas and guinea pigs, about half of the LSO neurons are labeled following the injection of tritiated glycine into the ipsilateral IC (Saint Marie and Baker, 1990). The ipsilateral inhibitory projection to the IC from these LSO neurons may explain the binaural inhibition in the ICC (Saint Marie and Baker, 1990; Saint Marie et al., 1989).

Medial Superior Olivary Nucleus

The MSO receives bilateral projections from large spherical/bushy neurons in rostral AVCN via medium-diameter fibers in the TB (cat: Warr, 1966a, b, 1982; dog: Goldberg and Brown, 1968; rat: Harrison and Irvine, 1966; monkey: Strominger and Strominger, 1971). Axons from the contralateral and ipsilateral AVCN terminate mainly on the medial and lateral dendrites of the principal cells in the MSO respectively (cat: Stotler, 1953; Warr, 1966; rat: Harrison and Irvine, 1966; dog: Goldberg and Brown; rhesus monkey: Strominger and Strominger, 1971). The input projections to the MSO are topographically organized and correspond to the tonotopic organization of the principal cells in the MSO with low CFs located dorsomedially and high CFs located ventrolaterally (Goldberg and Brown, 1968; Harrison and Irvine, 1966a; Stotler, 1953; Warr, 1966). There is a disproportionately large representation of low frequencies in the MSO, the majority of units having CFs below 4 kHz and very few units having CFs greater than 11 kHz (cat: Guinan et al., 1972a, b; dog: Goldberg and Brown, 1968; rat: Inbody and Feng, 1981).

The majority of MSO neurons are responsive to stimulation of either ear. In the cat and dog, about two thirds of neurons are excited by stimulation of either ear and thus

are termed "EE" cells (cat: Guinan et al., 1972a, 1972b; dog: Goldberg and Brown, 1968). In the dog, the remaining neurons are binaural suppression cells (EI: 15.2%; IE: 8.6%) and monaural cells (10.5% EO). In the rat, Inbody and Feng (1981) reported that EE cells comprised 52% and EI cells 48% of the sample.

MSO neurons in the cat (Guinan et al., 1972a) and in the beagle (Goldberg and Brown, 1969) have sharp, V-shaped excitatory tuning curves. The majority of EE cells have similar CF and similar response areas for stimulation of the two ears. These EE neurons are sensitive to IPDs. In EI and IE cells, the excitatory CF is usually near the most effective frequency for the inhibitory ear (Goldberg and Brown, 1969; Inbody and Feng, 1981). The EI and IE cells are sensitive to IIDs (Inbody and Feng, 1981).

By retrograde and anterograde axonal tracing methods, it has been reported that the MSO projects to the ipsilateral IC in both the cat and the rat (cat: Adams, 1979; Aitkin and Schuck, 1985; Brunso-Bechtold et al., 1981; Elverland, 1978; Glendenning et al., 1981; Henkel and Spangler, 1983; Roth et al., 1978; rat: Beyerl, 1978; Coleman and Clerici, 1987), and to the ipsilateral DNLL in the cat (Elverland, 1978; Glendenning et al., 1981). In cat, it was found that a few cells in the MSO also send projections to the contralateral IC (Brunso-Bechtold et al., 1981; Henkel and Spangler, 1983).

Frequency-Dependence of Hearing and the SOC Nuclei

Comparative studies in mammals have revealed the relationship between the relative sizes of SOC nuclei and the frequency-dependence of hearing (Harrison and Feldman, 1970; Harrison and Irvine, 1966a; Irvine and Harrison, 1967). Mammals with high frequency hearing (e.g. dolphin, hedgehog, mouse, and rat) have a relatively small (or absent) MSO, and a large MNTB/LSO; in contrast, some primates (e.g. human) without very high frequency hearing but with very good low frequency hearing have a large MSO and a small MNTB/LSO. All the three nuclei are largely developed in

mammals (e.g. cat, chinchilla, and dog) which have both high and low frequency hearing (Harrison and Howe, 1974; Irvine and Harrison, 1967).

Some physiological results suggest that the MSO processes IPDs, while the LSO processes IIDs (Masterton, 1974; Masterton and Diamond, 1967; Masterton et al., 1975; Zvorykin, 1964). So it has been proposed that for auditory azimuthal localization, the relative sizes of MSO and LSO/MNTB reflect the relative dependence of the species on the low frequency cues (e.g. IPD) and on high frequency cues (e.g. IID), respectively.

The rat belongs to the class of high frequency hearing mammals that have a very small MSO and a relatively large LSO and MNTB, and therefore may use IIDs as the main cue for sound localization. In addition to the three major nuclei of the SOC, the SOC of the rat has a relatively large nucleus named the superior paraolivary nucleus (SPO) which is situated dorsomedially to the small MSO. Little is known about the SPO.

Nuclei of the Lateral Lemniscus

The lateral lemniscus (LL) contains axons from both ascending and descending auditory pathways. The ascending auditory fibers within the LL include axons of neurons in the CN, SOC, as well as those from nuclei located within the LL. Most of these axons terminate in the IC. However, a substantial number of fibers originating from the nuclei of the LL pass through the IC to terminate the superior colliculus (SC) and the MGB (Henkel and Spangler, 1983; Hutson et al., 1991; Kudo, 1981; Tanaka et al., 1985; Wickesberg and Oertel, 1988).

Embedded within the fibers of LL is a band of cells, extending from the region immediately rostral to the LSO to just ventral to the IC. Three large lemniscal nuclei differ from each other both cytoarchitectonically and connectionally and are named according to their locations along the LL as ventral nucleus of the lateral lemniscus (VNLL), intermediate nucleus of the lateral lemniscus (INLL), and dorsal nucleus of the lateral lemniscus (DNLL).

Ventral Nucleus of the Lateral Lemniscus

In both the cat (Adams, 1979) and mouse (Willard and Ryugo, 1983), the VNLL can be subdivided into medial and ventral (lateral in the mouse) zones. The principal cell types in the medial zone in both species are multipolar cells and horizontal cells with dendrites perpendicular to the ascending auditory fibers. The predominant neurons in the ventral zone in the cat and lateral zone in the mouse are oval cells. The oval cells receive large axosomatic calyceal endings similar in form to, but smaller than, those in the MNTB (Adams, 1979; Stotler, 1953; Willard and Ryugo, 1983).

The afferent connections of VNLL are dominated by projections from the contralateral CN (Covey and Casseday, 1986; Glendenning et al., 1981). After horseradish peroxidase (HRP) injections restricted to the VNLL, the majority of labeled cells are located in the contralateral VCN, with a higher proportion in the AVCN than in the PVCN (Glendenning et al., 1981). A small projection from the contralateral DCN is also indicated by degeneration and tracer studies (Adams and Warr, 1976; Fernandez and Karapas, 1967; Glendenning et al., 1981). There is also a weak projection to the VNLL from the ipsilateral MNTB and periolivary cell groups (Covey and Casseday, 1986; Elverland 1978; Glendenning et al., 1981; Glendenning and Masterton, 1983; Henkel and Spangler, 1983). Only a small region of the VNLL in both cat (Glendenning et al., 1981; Warr, 1966) and rhesus monkey (Strominger and Strominger, 1971) is unique in that it receives a dense projection from the ipsilateral VCN.

Electrophysiological studies have reported both sustained and onset discharge patterns for neurons in the VNLL (Aitkin et al., 1970). Guinan et al. (1972) reported that the majority of VNLL units in their sample had V-shaped frequency tuning curves (FTCs) and the remainder were broadly tuned.

Aitkin et al. (1970) reported that the VNLL was tonotopically organized with low-to-high frequency units arrayed from dorsal to ventral. In conflict with Aitkin et al.

(1970), Guinan et al. (1972b) reported that they could detect no tonotopic organization in the VNLL. Tonotopic organization in the VNLL was also suggested by differential dorsal or ventral uptake of 2-DG following low- and high-frequency stimulation in the Mongolian gerbil (Ryan et al., 1982). However, Nudo and Masterton (1984) failed to find 2-DG evidence of tonotopy in the VNLL of a number of species.

Aitkin et al. (1970) reported that the majority of VNLL units were EO monaural but a certain number of units (11% of a sample of 57) were binaural, and the binaural neurons were located near the dorsal and ventral margins of the VNLL. Guinan et al. (1972b) reported that 12 of the sampled 32 neurons were EO monaural, while 18 neurons were binaural (EE or EI).

The VNLL neurons project to the ipsilateral central nucleus of inferior colliculus (ICC) (Adams, 1979; Brunso-Bechtold et al., 1981; Covey and Casseday, 1986; Kudo, 1981; Nordeen et al., 1983; Ross et al., 1988; Whitley and Henkel, 1984; Zook and Casseday, 1982). Some fibers terminate in the ipsilateral DNLL (Glendenning, 1981; Kudo, 1981), and a very minor projection crosses the brainstem to terminate in the contralateral ICC (Adams, 1979; Brunso-Bechtold et al., 1981; Nordeen et al., 1983). It is questionable whether this projection is as precisely tonotopic as that found in lower auditory centers such as the VCN and the principal nuclei of the SOC.

Immunocytochemical and uptake/transport studies suggest that a large number of VNLL neurons are glycinergic. In rats, VNLL contains many immunoreactive perikarya (Aoki et al., 1988). In chinchillae and guinea pigs, large numbers of VNLL neurons are labeled subsequent to the injection of tritiated glycine into the ipsilateral IC (Saint Marie and Baker, 1990).

Intermediate Nucleus of the Lateral Lemniscus

The INLL has been described as a transitional zone between the VNLL and DNLL. Cells in the INLL are sparsely distributed and the predominant cell type is

multipolar in shape, resembling those in the DNLL except that they are typically small (Adams, 1979). In Golgi preparations in the mouse, the INLL neurons have horizontally oriented dendrites like those in the DNLL (Willard and Ryugo, 1983).

The pattern of afferent connections to INLL is in many respects intermediate between those to DNLL and VNLL. INLL receives input directly from the contralateral VCN, and indirectly from this nucleus by way of ipsilateral MNTB and VNLL (Glendenning et al., 1981, Spangler et al., 1985).

INLL neurons project to the dorsal cortex and adjacent central nucleus of the ipsilateral IC (Whitley and Henkel, 1984; Zook and Casseday, 1982). INLL also projects bilaterally to the MGN (Hutson et al., 1991), and possibly to the medial division of the MGN (Whitley and Henkel, 1984).

Dorsal Nucleus of the Lateral Lemniscus

Neuronal architecture of dorsal nucleus of the lateral lemniscus

The DNLL is a prominent cluster of neurons in the LL ventral to the IC. The DNLL is bordered laterally by the nucleus sagulum and ventrally by the INLL (Bajo et al., 1993; Glendenning et al., 1981; Hutson et al., 1991; Kane and Barone, 1980; Shneiderman et al., 1988). The DNLL contains several different cell types (Adams, 1979; Covey and Casseday, 1986; Kane and Barone, 1980). In the cat, Kane and Barone (1980) have classified the cell shapes as round, ovoid, or elongate, and each class has been further categorized based on whether the cell type possesses large, medium-sized, or small perikarya. Nine (3X3) categories of Nissl-stained DNLL neurons were classified on the basis of both soma size and shape. The great majority of cells in DNLL are medium- to large-sized and round or ovoid. In Golgi preparations, the somas and dendritic trees of most cells in DNLL of the cat are oriented horizontally, perpendicular to the fibers of LL (Kane and Barone, 1980). Golgi material from mouse (Willard and Ryugo, 1980) and human (Geniec and Morest, 1971) indicate similar horizontal organization of the DNLL.

dendrites. Most of the medium-sized neurons and large, elongate neurons are found in the caudal portion of the DNLL, while most of the large oval and large round neurons are located rostrally (Kane and Barone, 1980). This differential distribution of cell types may be related to the different projections of the rostral and caudal parts of DNLL.

In the rat, Bajo et al. (1993) found four types of neurons in the DNLL. Type I neurons are large and multipolar with abundant cytoplasm and darkly stained in Nissl substance. Type II neurons are large, bipolar and darkly stained in Nissl material. Type III neurons are medium in size and their soma is round or ovoid. Type IV neurons are small and round with scant cytoplasm, and they are the least common neurons of the DNLL.

In Nissl-stained material of the cat, three subdivisions in DNLL were distinguished by cytoarchitectonic criteria: dorsal, ventral, and lateral (Shneiderman et al., 1988). In the dorsal part of DNLL, the cells are large and spherical. In the ventral part, the cells are horizontally oriented. The neurons in the lateral DNLL are smaller and more round than neurons in the dorsal or ventral parts of DNLL.

Afferent connections of dorsal nucleus of the lateral lemniscus

The major sources of ascending input to the DNLL are the contralateral AVCN, contralateral PVCN, ipsilateral MSO, and bilateral LSO (Elverland, 1978; Glendenning et al., 1981; Glendenning and Masterton, 1983; Henkel and Spangler, 1983; Hutson, 1991; Kudo, 1981; Shneiderman et al., 1988). These afferent axons to the DNLL in the cat are distributed in horizontal bands that have a tonotopic organization. In general, projections from low-frequency areas in these nuclei terminate in the dorsal DNLL, while high-frequency areas project to the ventral DNLL (Shneiderman et al., 1988). Substantially smaller input to the DNLL also originates from the ipsilateral VNLL and contralateral DNLL (Glendenning et al., 1981; Warr, 1966b, 1982). Very small inputs also come from the ipsilateral VCN and INLL (Glendenning et al., 1981; Shneiderman et al., 1988;

Spangler et al., 1985). Nuclei that do not provide input to DNLL include the contralateral VNLL and INLL (Glendenning et al., 1981; Shneiderman et al., 1988; Spangler et al., 1985). Shneiderman et al. (1988) emphasized that the contralateral DCN and the ipsilateral MNTB do not project to the DNLL, and they proposed that some cells in these two nuclei were labeled following injection of retrograde tracers into the DNLL (Glendenning et al., 1981) was because there was uptake of the tracers by damaged fibers of passage.

The ventrolateral (low-frequency) region of AVCN has bilateral projections to the dorsal DNLL. The afferents from the AVCN on both sides distribute evenly. The dorsomedial (high-frequency) AVCN projects to the ventral DNLL exclusively on the contralateral side (Shneiderman et al. 1988).

The LSO projects bilaterally to the DNLL. The lateral limb of LSO (the low-frequency part) projects to the dorsal DNLL, while the more medial part (high frequency) projects to the ventral DNLL. In the ventral DNLL, the projection from the contralateral LSO has a heavier distribution in the medial areas of DNLL, while the projection from the ipsilateral LSO distributes more laterally in the DNLL (Shneiderman et al., 1988). Comparing the projections from the two sides of the LSO, the ipsilateral LSO of cat has more projections to the DNLL than the contralateral LSO (Glendenning et al., 1981).

The MSO projects unilaterally to the ipsilateral DNLL. As with the other projections, the topography of the MSO input to DNLL is related to the tonotopic organization of both the MSO and the DNLL (Shneiderman et al., 1988). The dorsal part of MSO (low-frequency) projects to the dorsal DNLL, while the ventral portion of MSO projects to the middle of DNLL. No projections from MSO to the ventral DNLL have been observed. The lack of a ventral input to DNLL may result from the compressed high-frequency representation in MSO (Guinan et al., 1972b). Unlike the projection from the LSO, the projection of MSO does not exhibit any mediolateral gradient within the DNLL. In the cat, following injection of HRP into the DNLL, almost twice as many

labeled cells were found in the ipsilateral MSO as in the ipsilateral LSO (Glendenning et al., 1981).

In cats, the DNLL provides a substantial input to the contralateral DNLL via the commissure of Probst (Hutson et al., 1991; Shneiderman et al., 1988). Generally, the crossed projections are topographically organized. The dorsal part of DNLL projects to the dorsal part of contralateral DNLL; similarly, the ventral part of DNLL projects to the ventral part of DNLL (Shneiderman et al., 1988).

Physiology of dorsal nucleus of the lateral lemniscus

Both sustained and onset discharge patterns for neurons in DNLL were reported in the cat and echolocating bat (cat: Aitkin et al., 1970; bat: Covey, 1993; Markovitz and Pollak, 1993). In the cat, the DNLL is tonotopically organized. Cells with low best frequencies are located dorsally and those with high best frequencies are found ventrally (cat: Aitkin et al., 1970; bat: Markovitz and Pollak, 1993). But Covey (1993) provided little evidence of an orderly tonotopic progression in the DNLL of the echolocating bat. Nudo and Masterton (1984) also failed to find 2-DG evidence of tonotopy in the cat's DNLL.

Aitkin et al. (1970) reported that the majority of units in the cat's DNLL (88% of a sample of 121) were binaural and the remaining 12% were monaural (mainly EO/monaural). In the brown bat (*Eptesicus fuscus*), Covey (1993) found that in the caudal part of DNLL, 84% of the sampled neurons were binaural, while in the rostral part of DNLL (the so-called dorsal paralemniscal zone) 29% of cells were binaural. In the mustache bat (*Pteronotus p. parnellii*), Markovitz and Pollak (1993) reported that of the 88 cells for which binaural responses were determined, 79% were the EI cells, 11% were EO, and 10% were driven by stimulation presented to either ear (EE). Low frequency DNLL neurons receiving EE binaural input are sensitive to IPD (Brugge et al., 1970), and

neurons receiving EI binaural input are sensitive to IID (Brugge et al., 1970; Covey, 1993).

An interesting feature of IID sensitivity in the DNLL neurons reported by Brugge et al. (1970) is that the initial spikes of sustained responses were never suppressed, even at large IIDs favoring the ipsilateral ear.

Efferent projections of dorsal nucleus of the lateral lemniscus

The DNLL projects to the contralateral DNLL, the bilateral cortex of IC, the bilateral ICC, the bilateral deep layers of SC, and, to a lesser extent, the ipsilateral medial and dorsal divisions of the MGB (Adams, 1979; Bajo et al., 1993; Covey et al., 1987; Hutson et al., 1991; Kudo, 1981; Oliver and Shneiderman, 1989; Shneiderman et al., 1988; Tanaka et al., 1985; Zook and Casseday, 1982).

In cats, the DNLL projection terminates primarily in the ICC. Both retrograde and anterograde transport experiments indicate a topographical organization of the efferent projections from DNLL to ICC (Shneiderman et al., 1988), and the topographic projecting order can be related to the tonotopic organization of DNLL and ICC. The dorsal part of DNLL projects to the dorsolateral part of IC, while the more ventral part of DNLL projects to the more ventromedial part of the ICC.

Anterograde transport experiments provide evidence that in the IC, axons from the contralateral DNLL are organized into bands which are defined as alternating heavily labeled areas, approximately 150-200 μm in thickness, separated by lightly labeled interband areas 100-150 μm wide (Shneiderman et al., 1988). The bands are most pronounced in the ICC. In the dorsal cortex the bands are less intensely labeled and narrower. The bands are present at different rostrocaudal levels of the ICC, and they appear to maintain the same relative position throughout the rostrocaudal extent. The continuous three-dimensional bands parallel the fibrodenritic laminae defined in Golgi preparations (Morest and Oliver, 1984; Oliver and Morest, 1984). In contrast to the

banding pattern in the IC for the contralateral projections from the DNLL, the ipsilateral projection is more diffuse. Shneiderman et al. (1988) suggested that the heavily labeled ICC areas receiving the ipsilateral and contralateral projections are complementary and do not overlap.

The sagulum only projects bilaterally to superficial regions of the caudal and dorsal cortex of the IC, to the commissura' nuclei of the IC, to the SC, to the medial division of the MGB, and finally to the opposite sagulum (Henkel and Shneiderman, 1988; Hutson et al., 1991).

The commissure of Probst is not a general avenue for decussating auditory fibers of the LL but is instead a specific avenue only for the decussating fibers from the DNLL and sagulum (Hutson et al., 1991).

Inhibitory projection from dorsal nucleus of the lateral lemniscus

GABA is an important inhibitory neurotransmitter, and glutamic acid decarboxylase (GAD) is the enzyme responsible for the conversion of L-glutamic acid to GABA. A number of studies using antibodies to GABA and GAD have shown that most neurons in the DNLL of cats and rodents are GABAergic (Adams and Mugnaini, 1984; Moore and Moore, 1987; Roberts and Ribak, 1987).

The projections from DNLL to contralateral DNLL and IC have axon terminals that contain pleomorphic synaptic vesicles usually associated with inhibitory function (Oliver and Shneiderman, 1989; Shneiderman and Oliver, 1989). Following ablation of the DNLL of the guinea pig, GABA release from IC was depressed in direct proportion to the degree of neuronal loss in the lesioned DNLL (Potashner et al., 1991).

These findings suggest that the DNLL is a major source of ascending inhibitory projections.

Inferior Colliculus

Parcellation of Inferior Colliculus

Ramon y Cajal (1909) identified three major divisions of IC in Golgi-impregnated material from a number of mammals. The three main divisions are the nucleus of IC, the dorsal cortex, and the external cortex.

Despite the early work by Cajal, a similar (though using different nomenclature) tripartite parcellation based primarily on the packing density of cell bodies in Nissl-stained material of the cat IC has provided the context for most modern research on the connection and physiological response properties of the IC (Berman, 1968; Rockel and Jones, 1973a). Berman's divisions are the central nucleus (ICC), the pericentral nucleus (ICP), and the external nucleus (ICX). The ICC as defined by Berman includes both the nucleus of IC and portions of the dorsal cortex identified by Cajal. Berman's ICP corresponds to only the outer portion of the cortex, and his ICX includes the lateral nucleus plus other structures between the IC and the superior colliculus.

Based on Nissl-stained coronal sections, the standard parcellation of the IC of the cat identifies a large, centrally located ovoid mass of densely packed cells as the ICC. On the free surfaces of the IC, the ICC is covered by a layer of cells, divided into an ICP covering the dorsal and posterior surfaces of the IC, and an ICX covering the lateral and anterior surfaces of the IC.

Within the ICC so defined, a further division was made by Rockel and Jones (1973a) between dorsomedial and ventrolateral divisions, on the grounds of neuronal architecture and fiber connections. The ventrolateral division is defined by the pronounced laminar organization of cell bodies, dendrites, and the afferent axonal plexus, whereas the dorsomedial division is defined by a concentration of large cells and the absence of lamination. The distinction between these regions is supported by the fact that the ventrolateral division receives most of its afferent input from the LL, whereas the

dorsomedial division receives its input primarily from the AC and from the contralateral IC via the commissure of the inferior colliculus.

Morest and Oliver (1984) and Oliver and Morest (1984) put forward another subdivision of the IC of the cat, based on the distribution of cell types and the organization of the neuropil in Golgi-impregnated material, that differs from the standard (Nissl-based) parcellation. They suggested that each part of the IC can be defined as tegmental or tectal subdivision on the basis of the fundamental pattern of dendritic branching. The tegmental components of IC are certain cell groups of the pericolicular tegmentum, including those associated with the brachium of the inferior colliculus and the sagulum. Tegmental neurons typically have fewer dendrites (often only two or three) with long, tapering, and straight appendages.

The main subdivisions of the auditory tectum are the central nucleus, the cortex (dorsal cortex and caudal cortex), and the paracentral nuclei. Tectal neurons are typically multipolar cells with four or more dendrites which have a number of branches (often four or more) usually with several high-order collaterals and conspicuous dendritic appendages. The central nucleus is the largest and most prominent subdivision. The central nucleus is distinguished by its laminated neuropil composed of neurons with disc-shaped dendritic fields oriented in parallel arrays with the lemniscal axons. Above the central nucleus lies the dorsal cortex, while posterior to the central nucleus is the caudal cortex, a modified extension of the dorsal cortex. The third subdivision of auditory tectum is composed of the paracentral nuclei, clinging to the medial, rostral, and lateral aspects of the central nucleus, including the commissural, dorsomedial, lateral, and ventrolateral nuclei, and the nucleus of the rostral pole.

Based on the results of Nissl staining, Golgi impregnation, and myelin staining, Faye-Lund and Osen (1985) found that the IC in rat could be divided into the three main subdivisions and they adopted the terminology and principles proposed by Cajal (1909). The three subdivisions are the central nucleus, the external cortex, and the dorsal cortex.

The central nucleus is characterized by a lamellar organization of disc-shaped neurons interspersed with multipolar cells. The external cortex is located lateral, rostral, ventral and ventrocaudal to the central nucleus; the dorsal cortex is located dorsocaudal and dorsomedial to the central nucleus.

Neural Inputs to Inferior Colliculus

The IC is critical for processing auditory information in the mammal. Almost all ascending auditory pathways make an obligatory synapse in the IC. The IC is the site of termination of almost all LL fibers and the source of axons that ascend via the brachium of the inferior colliculus to the auditory thalamus (Adams, 1979; Aitkin and Phillips, 1984a; Goldberg and Moore, 1967; Morest, 1965b). The IC is not only a relay nucleus but also a structure in which monaural and binaural information from the lower auditory system is integrated and sorted. Likewise, the descending pathways from the auditory cortex project heavily to the IC, where they may influence ascending and descending pathways and intrinsic circuits.

The experiments in which large amount of HRP have been injected into the ICC have demonstrated that the auditory pathways that diverge from the CN into multiple ascending tracts largely converge in the ICC. Such large injections in the cat results in large numbers of labeled neurons in LSO, INLL, and DNLL bilaterally, MSO and VNLL ipsilaterally, and AVCN, PNCN, as well as DCN contralaterally (Adams, 1979; Brunso-Bechtold et al., 1981; Roth et al., 1978). Small numbers of labeled neurons were also found in all three ipsilateral divisions of CN, ipsilateral MNTB, ipsilateral sagulum, contralateral MSO, and bilateral periolivary regions. Similar labeling patterns following large HRP injections into the ICC have been seen in the rat (Beyerl, 1978; Druga and Syka, 1984) and in a variety of other mammals (Aitkin and Kenyon, 1981; Nordeen et al., 1983; Ryugo et al., 1981; Schweitzer, 1981; Willard and Martin, 1983, 1984; Willard and Ryugo, 1983; Zook and Casseday, 1982).

Retrograde tracer studies in which smaller injections of HRP have been made into the ventrolateral division of the ICC, as well as anterograde tracer and degeneration studies, indicate that all of the major auditory brainstem structures that were labeled after large injections project to the ventrolateral division (Brunso-Bechtold et al., 1981; Elverland, 1978; Glendenning and Masterton, 1983; Henkel and Spangler, 1983; Kudo, 1981; Oliver, 1984b; Osen, 1972; Warr, 1982). On the other hand, the LSO does not project to the dorsomedial division of the cat's IC (Brunso-Bechtold et al., 1981; Elverland, 1978; Glendenning and Masterton, 1983). Whether or not the MSO projects to the dorsomedial division remains controversial (Brunso-Bechtold et al., 1981; Henkel and Spangler, 1983). The ascending projections to the dorsomedial division appear to be derived mainly from the contralateral CN (Brunso-Bechtold et al., 1981; Oliver 1984b; Osen, 1972) and from the NLL on both sides (Brunso-Bechtold et al., 1981; Kudo, 1981; Whitley and Henkel, 1984).

In the cat, descending projections (predominantly from auditory cortex) to the ICC are restricted to the dorsomedial division (or to layer IV of the dorsal cortex) (Andersen et al., 1980b; Diamond et al., 1969; Morest and Oliver, 1984; Rockel and Jones, 1973a). The descending projections were also confirmed by observations on the mouse (Willard and Ryugo, 1983) and American opossum (Willard and Martin, 1983). However, in the rat, it was reported that the cortical descending projections are to both divisions of the ICC (Beyerl, 1978; Druga and Syka, 1984b).

In the cat, axons in the commissure of inferior colliculus arise from neurons throughout ventrolateral ICC, but their midbrain terminals are largely restricted to the contralateral dorsomedial division (Aitkin and Phillips, 1984b; Brunso-Bechtold et al., 1981; Rockel and Jones, 1973a; Roth et al., 1978). In the rat, Saldana and Merchan (1994) reported that following a small injection of anterograde tracer *Phaseolus vulgaris*-leucoagglutinin (PHA-L) into the ICC, two well-labeled bands in coronal sections were created at each side of the IC, one extending in the ICC and the other in the ICX.

In summary, the marked differences in the neuronal architecture of the laminated ventrolateral and large-celled dorsomedial division of ICC are thus related to marked differences in the sources of their afferents. The ventrolateral division receives massive ascending projections from a large number of brainstem nuclei and little or no descending projections; the dorsomedial division receives ascending projections from a more restricted set of brainstem nuclei, but receives major descending and commissural projections.

Evidence from degeneration and axonal tracer studies indicate that projections to the ICC from almost all brainstem nuclei are tonotopically organized (Adams, 1979; Brunso-Bechtold et al., 1981; Henkel and Spangler, 1983; Oliver, 1984b; Osen, 1972; Roth et al., 1978). Projections to the dorsal ICC derive from neurons in the low-frequency regions of the auditory brainstem structures, while projections to the ventral ICC derive from neurons in the high-frequency regions of these nuclei. This indicates that the auditory ascending afferents from multiple brainstem sources converge in a highly organized way in the ICC. The only brainstem nucleus whose projections to ICC do not appear to be topographically organized may be the VNLL (Adams, 1979; Brunso-Bechtold et al., 1981; Roth et al., 1978; Whitley and Henkel, 1984).

Afferent projections to the other regions of IC subdivisions in the standard parcellation such as the ICX and the ICP, have been described in much less detail than those to the ICC. The major afferent to ICP are descending projections from auditory cortex (Andersen et al., 1980b; Galambos et al., 1969; Morest and Oliver, 1984; Rockel and Jones, 1973c) and commissural projections from the contralateral IC (Kudo and Niimi, 1980; Moore and Goldberg, 1963; Rockel and Jones, 1973c). Rockel and Jones (1973c) suggested that there is a projection from the DNLL to the ICP, but Kudo (1981) found no evidence for such a projection.

The ICX receives strong projections from the ICC (Aitkin et al., 1981; Andersen et al., 1980a; Kudo and Niimi, 1980; Rockel and Jones, 1973a). A distinctive feature of

the ICX is that it receives somatosensory projections from the dorsal column nuclei and trigeminal complex (Aitkin et al., 1981; Hand and van Winkle, 1977; Morest and Oliver, 1984; Willard and Ryugo, 1979, 1993).

Physiology of Inferior Colliculus Neurons

Frequency tuning and tonotopic organization

In the cat, the majority of neurons in the ICC are sharply tuned for frequency, with V-shaped tuning curves (Aitkin et al., 1975; Merzenich and Reid, 1974; Rose et al., 1963; Clopton and Winfield, 1973). In contrast to the predominantly sharp tuning of ICC neurons, the tuning curves of most neurons in ICX (Aitkin et al., 1975, 1978) and in ICP (Aitkin et al., 1975; Merzenich and Reid, 1974) are broad and irregular often extending over several octaves. In the rat, neurons in peripheral regions of the IC also respond to a wide range of frequencies (Clopton and Winfield, 1973).

The tonotopic organization of the ICC has been described in a number of species with both electrophysiological and 2-DG methods. In electrode penetrations from dorsal to ventral through the ICC of the cat, successively encountered units or unit clusters have progressively higher CFs (Aitkin et al., 1970, 1975; Merzenich and Reid, 1974; Rose et al., 1963). The dorsal-to-ventral tonotopic organization has also been shown to be characteristic of the ICC of the rat (Clopton and Winfield, 1973; Flammino and Clopton, 1975; Kelly et al., 1991), rhesus monkey (Ryan and Miller, 1978), squirrel monkey (Fitzpatrick, 1975), rabbit (Aitkin et al., 1972a; Syka et al., 1981), brush-tailed possum (Aitkin et al., 1978a), mouse (Harnischfeger, 1978; Willott and Urban, 1978), and bat (Grinnell, 1963; Jen and Schlegel, 1982; Vater et al., 1979).

Further evidence for the frequency organization of the ICC is provided by 2-DG studies. Isofrequency bands were observed in the ICC with low-frequency contours located dorsolaterally in the ICC, and high-frequency contours located ventromedially (cat: Nudo and Masterton, 1984; Servière and Webster, 1981; Servière et al., 1984; rat:

Coleman et al., 1982; Huang and Fex, 1986; rhesus monkey, Webster et al., 1984; gerbil: Melzer, 1984; Ryan et al., 1982). The orientation of these bands corresponds closely to that of the fibrodendritic laminae in the central part of the ICC, and the frequency-specific 2-DG labeling in the ICC is in broad agreement with electrophysiologically demonstrated tonotopic organization.

Binaural response properties: coding of binaural intensity differences

The majority of neurons in the ICC are binaurally sensitive. Irvine (1986, p160) summarized the results from three studies on the cat (Aitkin et al., 1975; Roth et al., 1978; Semple and Aitkin, 1979). In the total combined sample of 1265 single neurons, a significant proportion (24%) were excited by stimulation of the contralateral ear, but uninfluenced by ipsilateral stimulation (EO). A larger proportion of cells (31%) received EI input and were sensitive to IIDs. Neurons which exhibited an increase in excitatory response to stimulation of either ear (EE) comprised 29% of the total combined sample.

Binaural response type is related to the CF of neurons. In the rat, studies have reported that EI interaction were found in the majority of the cells (Flammino and Clopton, 1975; Kelly et al., 1991; Li and Kelly, 1992a; Sally and Kelly, 1992; Silverman and Clopton, 1977). This characteristic may be related to the high-frequency hearing and limited development of the MSO in the rat. In the cat, EE cells commonly have lower as opposed to higher CFs (Kuwada and Yin, 1983; Rose et al., 1966; Semple and Aitkin, 1979). EI patterns occur more frequently in cells with CFs above 3-5 kHz (Roth et al., 1978; Semple and Aitkin, 1979).

Within the ICC of the cat, there is also partial segregation of binaural classes. EI cells are encountered in the greatest proportion rostrally while EO monaural cells are encountered in the greatest proportion caudally and laterally (Roth et al., 1978; Semple and Aitkin, 1979).

Studies on the sensitivity of ICC neurons in the cat to IIDs have consistently confirmed that the major class of neurons exhibiting sensitivity to IIDs are EI neurons (Geisler et al., 1969; Hind et al., 1963; Moore and Irvine, 1981; Rose et al., 1963; Roth et al., 1978; Semple and Aitkin, 1979). The sensitivity of EI neurons to IIDs has also been confirmed in a number of other mammals (rat: Kelly et al., 1991; Li and Kelly, 1992a, b; Silverman and Clopton, 1977; Sally and Kelly, 1992; kangaroo rat: Stillman, 1972; rabbit: Aitkin et al., 1972b; guinea pig: Popelar and Syka, 1982; brush-tailed possum: Aitkin et al., 1978a; gerbil: Semple and Kitzes, 1985). In agreement with observations in the SOC (Goldberg and Brown, 1969), the majority of EE cells of the ICC are insensitive to IIDs (Geisler et al., 1969; Moore and Irvine, 1981).

Generally, IID-sensitive EI neurons predominantly exhibit binaural inhibition. For a given stimulus level presented at CF to the contralateral (excitatory) ear, the response rate of the neuron declines as the level of stimulus to the ipsilateral (inhibitory) ear is augmented. Nevertheless, both the IID value at which the response begins to decline and the steepness of the function (amount of decline per unit change in ipsilateral SPL) differ among EI cells (rat: Li and Kelly, 1992a; Sally and Kelly, 1992; Silverman and, 1977; Syka et al., 1983; cat: Aitkin et al. 1975; Geisler et al., 1969; Hind et al., 1963; Irvine and Gago, 1985; Moore and Irvine, 1981; Rose et al., 1966; Roth et al., 1978; Semple and Aitkin, 1979; guinea pig: Popelar and Syka, 1982; rabbit: Aitkin et al., 1972; Syka et al., 1981).

A Commonly Asked Question: What is the Mechanism Underlying the Binaural Inhibition in Inferior Colliculus?

It was assumed by Irvine (1986, p161) that binaural sensitivity in the ICC was a reflection of binaural interactions occurring at lower levels of the auditory brainstem, particularly the SOC. For example, the majority of LSO neurons receive IE binaural input (i.e., contralateral inhibition and ipsilateral excitation) (Boudreau and Tsuchitani, 1968;

Caird and Klinke, 1983; Tsuchitani and Boudreau, 1969). The response of IE cells of the LSO is maximal when the stimulus at the ipsilateral ear is more intense (corresponding to ipsilateral azimuths) and is totally or near-totally suppressed when the stimulus at the contralateral ear is more intense (corresponding to contralateral azimuths). When IE neurons of the LSO project contralaterally, the binaural response of their target neurons would be EI. The IID sensitivity functions of EI neurons in ICC are generally mirror symmetric with those of IE cells in the contralateral LSO. The presence of IE cells in the ICC was not reported.

Binaural suppression is also present in the MSO, particularly the EI pattern, with contralateral stimulation producing excitation and ipsilateral stimulation producing inhibition (Goldberg and Brown, 1969; Harnischfeger et al., 1975; Inbody and Feng, 1981; Yin and Chan, 1990). Since the MSO gives rise to an almost exclusively ipsilateral projection to the IC (Adams, 1979; Beyerl, 1978; Coleman and Clerici, 1978), the EI pattern in MSO may also contribute to EI binaural responses in the ICC.

On the other hand, binaural inhibition may occur within the ICC. Intracellular recordings from neurons in the cat's IC have shown that stimulation of one ear can produce an EPSP and stimulation of other ear can elicit an IPSP in the same neuron (Nelson and Erulkar, 1966). Considerable data also support the roles of the inhibitory amino acids GABA and glycine as the possible mediators of inhibition in the IC. Neurochemical studies show that GABA levels in the IC are quite high (Fisher and Davies, 1976; Tachibana and Kuriyama, 1974). High levels of GAD and enzymes for degradation of GABA (GABA transaminase) are also observed in the IC (Contreras and Bachelard, 1979; Fisher and Davies, 1976; Tachibana and Kuriyama, 1974). The IC has also been shown to contain a number of neurons which are strongly positive for mRNA that encodes for GAD (Najlerahim et al., 1990). Immunocytochemical studies reported intense immunochemical staining for GABA, GABA transaminase, and GAD (Moore and Moore, 1987; Nagai et al., 1985; Thompson et al., 1985). The GABA-

immunoreactive nerve terminals that form symmetric synapses contain flattened or pleomorphic vesicles and cover the cell bodies and dendrites of the large neurons of the ICC (Ribak and Roberts, 1986). Calcium-dependent, potassium-evoked release of GABA from IC slices has also been reported (Lopez-Colome et al., 1978). For the postsynaptic component, high levels of GABA_A receptor and benzodiazepine receptor binding are also observed in the IC (Bristow and Martin, 1988; Glendenning and Baker, 1988; Seighart, 1986). IC neurons are also strongly labeled for mRNA that encodes for the alpha-1 subunit of the GABA_A receptor (Hironaka et al., 1990).

On the other hand, glycine is also present in the IC, especially in ventral regions, and the level of glycine is not affected by CN lesions (Adams and Wenthold, 1979). Calcium-dependent, potassium-evoked release of glycine from IC slices has also been reported (Lopez-Colome et al., 1978). Receptor binding for glycine and strychnine are observed in the IC (Araki et al., 1988; Glendenning and Baker, 1988; Probst et al., 1986; Sanes et al., 1987; Zarbin, 1981).

Binaural responses in the IC can be altered by local application of antagonists of GABA or antagonists of glycine. Iontophoretic injection of the GABA_A antagonist, bicuculline, reduced the extent of binaural suppression of EI responses in IC of both rat (Faingold et al., 1989a, 1991a) and mustache bat (Park and Pollak, 1993). Although it was claimed that acoustically induced binaural inhibition in IC neurons can be specifically blocked by iontophoretic application of bicuculline in doses which do not produce excitatory effects on monaural responses (Faingold et al., 1989a), some evidence indicates that the monaural rate-intensity functions are affected by bicuculline application (Faingold et al., 1991a; Pollak and Park, 1992; Yang et al., 1992).

Strychnine has been suggested to be relatively selective as an antagonist at glycine receptors (Curtis et al., 1971; Davidoff et al., 1969), although there is evidence that this selectivity is not absolute (Davidoff et al., 1969). Strychnine application onto the

ICC increased the monaural discharge rate and also blocked the effects of binaural inhibition of ICC neurons (Faingold et al., 1991b).

The effects of bicuculline and strychnine suggest that both binaural and monaural responses in the IC may be subserved by GABA and glycine-mediated inhibition.

An extrinsic glycinergic projection to the IC may come from the ipsilateral LSO. Because a large proportion of LSO principal neurons are glycine immunoreactive and project to ipsilateral IC directly (Aoki et al., 1988; Saint Marie and Baker, 1990; Saint Marie et al., 1989; Wenthold et al., 1987), it has been suggested that the ipsilateral inhibitory projection to the IC from the glycinergic LSO neurons may explain the binaural inhibition in the ICC (Saint Marie et al., 1989).

A large portion of the GABAergic input to ICC principal cells appears to be intrinsic from the interneurons in the ICC. Many of the intrinsic multipolar or satellite cells in ICC are GAD-immunoreactive neurons with GAD-positive terminals which are reported to project onto the principal neurons of IC (Ribak and Roberts, 1986; Roberts and Ribak, 1987a, b; Vetter and Mugnaini, 1984). However, a prominent extrinsic GABAergic projection to the IC from the DNLL has been demonstrated.

Several lines of evidence suggest that the DNLL plays a unique role in binaural inhibition. First, most neurons in DNLL are GABAergic (Adams and Mugnaini, 1984; Moore and Moore, 1987; Roberts and Ribak, 1987a; Thompson et al., 1985; Glendenning and Baker, 1988). The projections from DNLL to contralateral DNLL and contralateral IC have axon terminals that contain pleomorphic synaptic vesicles usually associated with inhibitory function (Oliver and Shneiderman, 1989; Shneiderman and Oliver, 1989). Second, following ablation of the DNLL of the guinea pig, GABA release from IC was depressed in direct proportion to the degree of neuronal loss in the lesioned DNLL (Potashner et al., 1991). After the complete ablation of unilateral DNLL, GABA release in the contra- and ipsilateral IC was reduced by 51% and 25% respectively. Third, kainic acid lesions of the DNLL reduce the binaural inhibition in the TTD function of sound-

evoked slow field potentials recorded from the contralateral primary auditory cortex in the rat (Glenn and Kelly, 1992). Fourth, physiological data indicates that blockade of neural activity in the contralateral DNLL reduced the strength of binaural inhibition in the EI cells of ICC (Faingold et al., 1993; Li and Kelly, 1992b). Finally, blockade of neural activity in SOC of the rat with kynurenic acid (KYNA, an endogenous broad-spectrum antagonist of excitatory amino acid transmitters) or glycine, could not eliminate the sound evoked excitatory response in the DNLL (Li and Kelly, 1993a). These data suggest that sound evoked responses in the DNLL are partially independent of the neurons in SOC.

Ablation-behavior studies have indicated that lesions in the SOC of the ferret (Kavanagh and Kelly, 1992) and the DNLL of the rat (Kelly and Li, 1993) with kainic acid, a neurotoxin which selectively destroys cell bodies without causing damage to fibers of passage (Masterton et al., 1979; Rooney et al., 1991), can cause behavioral deficits in sound localization. However, recent studies have reported that following either unilateral or bilateral lesions of SOC (Li and Kelly, 1992a; Sally and Kelly 1992) or DNLL (Li and Kelly, 1993c) with kainic acid, binaural interactions (IIDs) could still be recorded in the ICC of the rats.

All these data suggest that both the SOC and the DNLL may make an important contribution to the binaural inhibition in ICC, but neither the SOC nor the DNLL is essential. The convergence of inputs from the DNLL and the SOC to the ICC may be more important for binaural interaction and spatial representation in the ICC.

Rationale of the Present Study

So far only two single-unit recording studies have reported that the contralateral DNLL plays an important role in binaural inhibition in the EI neurons of the ICC (Faingold et al., 1993; Li and Kelly, 1992b). Further research is necessary to examine the inhibitory effects of the projection from the contralateral DNLL on the neural activity in the ICC using a different electrophysiological recording method.

Recently, I have found that sound-evoked neural activity in the ICC can also be measured by evoked potential (EP) amplitude (Li and Kelly, 1993b). Measurement of the sound-evoked slow field potential has several advantages. First, compared to single-unit recordings, the EP response is very stable. There is no problem concerning isolation of response, which is a consideration in a single unit recording. Second, when the tip of the recording micropipette is not very large (5-30 μm), the sound-EP in the ICC exhibits a strong frequency selectivity. This indicates that the EP only picks up local neural activity. Third, in the rat, only a small number of EE cells are present in the ICC, and there is only a small chance of isolating a EE cell using single unit recording (Sally and Kelly, 1992). However, an ipsilateral sound can cause a clear EP response when the electrode is at an appropriate region within the ICC. Finally, the IID function in the ICC can be measured using the EP recording method. Similar to the IID function of single EI cells, IID-sensitive EPs exhibit a predominantly binaural inhibition. For a given stimulus pressure level of tone presented at CF to the contralateral (excitatory) ear, the response amplitude of the EP declines as the level of stimulus to the ipsilateral (inhibitory) ear is augmented.

In the ICC, the majority of binaural neurons are EI cells (Kelly et al., 1991; Li and Kelly, 1992a; Silverman and Clopton, 1977; Sally and Kelly, 1992), and it has already been confirmed that the contralateral DNLL has significant influence on the binaural inhibition in the EI cells (Faingold et al., 1993; Li and Kelly, 1992b). So I have expected a similar result with the EP recording study.

It is not very difficult using EP recording in the ICC to pick up an excitatory monaural response to the ipsilateral ear. A early study reported that following destruction of the right cochlea of the cat, a clear EP response to click was still present in the left IC (Ades, 1944). It is very interesting to know if the contralateral DNLL also has inhibitory influence on the monaural responses in the ICC to stimulation of the ipsilateral ear.

The ipsilateral LSO uses glycine as an inhibitory neurotransmitter and may also be an extrinsic inhibitory source for the binaural suppression in the ICC. The IC resides

just above the DNLL and shares similar neural connections with the DNLL. Besides the ipsilateral DNLL, the ipsilateral SOC and the contralateral IC were used for control injections in the present study (between-subject injection control).

The multi-blockade experiment using single-unit recording is very time-consuming (Li and Kelly, 1992b), and maintenance of isolated single unit activity throughout the experimental procedure is crucial and difficult. In the present study I have used the EP recording method to surmount this difficulty and to study the effect of multi-blockade of activity in the contralateral DNLL and one of the three auditory nuclei: the ipsilateral DNLL, the contralateral IC, and the ipsilateral SOC, on the IID function in the ICC (within-subject injection control).

Purpose of the Present Study

In the present study, three types of EP responses were recorded in the ICC: the monaural response to contralateral stimulation, the monaural response to ipsilateral stimulation, and the EP IID function. In some animals, comparisons were made before and after single injection of KYNA into one of the following auditory nuclei: the contralateral DNLL, the ipsilateral DNLL, the contralateral IC, and the ipsilateral SOC. In some animals, comparisons were also made before and after multiple injections into the contralateral DNLL and one of the other three auditory nuclei: the ipsilateral DNLL, the contralateral IC, and the ipsilateral SOC.

METHOD

Stimulus, Recording, and Injection Techniques

Continuous sine waves were produced by a function generator (Wavetek, Model 116 or Model 180) and shaped by two parallel Coulbourn Instruments electronic gates (S84-04) to form sine wave bursts of 110 ms duration including 10 ms rise and decay times. The pulse repetition rate was 1/sec. The shaped signal was split and led through two independent passive decade attenuators and a low output impedance power amplifier. The pure tone signals were transduced by Pioneer SE-50D stereo headphone drivers mounted in shielded housings. Each earphone housing opened into a small acoustic coupler whose speculum was inserted into the opening of the animal's external auditory meatus. The couplers were constructed so that a probe tube could be inserted along the length of the speculum with its tip centered at the open end within a few millimeters of the tympanic membrane.

Calibrations of the sound intensity were obtained in dB SPL for left and right ears separately using a Bruel & Kjaer 1/2 inch microphone (type 4134) and probe tube assembly. Probe tube measurements of the acoustic cross talk in the system, with the couplers and headphones in place, indicated 65 dB attenuation at frequencies up to 1.5 kHz and at least 70 dB attenuation for all higher frequencies.

Electrical potentials amplified 2,000-10,000X by an amplifier (Dagan, Model EX4-400), were displayed on an oscilloscope for visual monitoring of waveforms. The signal was fed in parallel through an audio amplifier for acoustical monitoring of neural activity, and to a Tracor Northern signal averager (TN-1550) for averaging of the waveforms.

The recording electrodes were single-barreled glass micropipettes pulled to a tip diameter of 5-30 μm and backfilled with Locke's solution. A tungsten microfiber which connected to the preamplifier, was inserted into the recording glass pipette.

The injection pipettes, which were filled with 2 mM KYNA in Locke's solution, were also constructed from single-barreled glass tubing constructed to a tip diameter of 20-30 μm . A syringe needle, which contained a tungsten microelectrode, was inserted into the injection pipette from the back, so the injection pipette could also record neural activity from a small cluster of neurons to refine electrode placements and monitor the injections of KYNA. The syringe needle was connected to a three-way stopcock through a length of polyethylene tubing. A 5 ml syringe provided pressure for injection, and the injection could be stopped by turning the three-way stopcock to open the injection pipette to the air. The injection pipette was calibrated, so that the injected volume of solution could be calculated from the length of movement of the surface of the solution in the pipette. The amount of injected solution was 1.0-2.0 μl .

Animal Preparation

Experiments were conducted on 32 male adult Wistar albino rats (*Rattus norvegicus*) (300-450 g) obtained from Charles River Canada Inc., St. Constant, Quebec. A rat was situated in an electrically shielded, sound attenuated room, and anesthetized with pentobarbital sodium (60mg/kg, i. p.) for initial surgical procedures. A state of areflexia was maintained throughout the experiment by supplemental injections of Equithesin (0.2-0.4 ml, i.p.). The flexion reflex was tested at intervals of 15-20 min. Equithesin is a combination of 42.6% chloral hydrate and 9.6% pentobarbital sodium in an aqueous solution, and it is no longer commercially available. However, a 500 ml aqueous solution containing 21.3 g chloral hydrate, 10.6 g magnesium sulfate, 4.8 g pentobarbital sodium, 1.5% benzyl alcohol, 40% propylene glycol, 10% ethanol, 2.5% sodium benzoate, and 2.5% benzoic acid can be prepared (see Li and Kelly, 1992a; Sally and Kelly, 1992).

The animal was wrapped in a towel to decrease loss of body heat. Immediately before surgery, the external ears and tympanic membranes were examined with an

otoscope and determined to be free of infection and/or obstruction. The animal was placed in a head holder that left the external meatus free so that damage to the tympanic membrane could be avoided. A midline incision was made in the scalp, and the skin and muscle were retracted laterally. Two long craniotomies were made along the two anterior banks of the lateral skull fissures to permit insertion of micropipettes into the IC and DNLL. For the insertion of pipettes into the SOC, additional craniotomies were made 2.5-3.5 mm caudal to lambda.

With the animal's head flat, there were two sets of stereotaxic coordinates for the ICC placement. When the electrode was in a vertical orientation, the coordinate was 1.7-2.0 mm lateral, 0.3-0.5 mm rostral, and 3.0-5.0 mm ventral to lambda. When the electrode was tilted 30° relative to the sagittal plane, the coordinate was referenced to a point 3.8-5.0 mm lateral, 0.3-0.5 mm rostral to lambda. The pipette was lowered to a depth 5.1 mm from the reference point to reach the center position of the ICC.

For DNLL placement, the pipette was tilted 30° against the sagittal plane. The coordinate was referenced to a point 6.7 mm lateral and 0.2-0.5 mm rostral to lambda. The pipette was lowered to a depth of 7.8 mm from the reference point.

For SOC placement, the pipette was tilted backward 11° relative the frontal plane. The coordinate was referenced to a point 2.5-3.0 mm caudal and 1.7-2.0 mm lateral to the lambda. The pipette was lower to a depth of 10.7 mm from the reference point.

Physiological Recording Procedures

A recording electrode was inserted into one ICC, while the contralateral ear was stimulated by a pure tone burst. The band-pass of the amplifier's filter was set at 0.3-2 kHz, so that multiple-unit spikes could be recorded. When the electrode was in the ICC, the CF of the multiple-unit to the contralateral ear was determined. And then the band-pass of the amplifier's filter was reset at 0.3-500 Hz and EPs could be recorded. The CF of the EP and the threshold at the CF of a tone presented to the contralateral ear were

determined. Data were collected at least 20-30 minutes after insertion of recording electrode.

For some cases, one injection pipette was penetrated into contralateral DNLL only. For some cases, one injection pipette was lowered into one of the following nuclei: the ipsilateral DNLL, the contralateral IC, and ipsilateral SOC. And for some cases, the injection pipettes were inserted into two injection targets, the contralateral DNLL and one of following nuclei: the ipsilateral DNLL, the contralateral IC, and the ipsilateral SOC. In such a way, the 32 animals were divided into 7 groups: (1) contralateral DNLL, (2) ipsilateral DNLL, (3) contralateral IC, (4) ipsilateral SOC, (5) ipsilateral DNLL and contralateral DNLL, (6) contralateral IC and contralateral DNLL, and (7) ipsilateral SOC and contralateral DNLL.

During the penetration of an injection pipette, the band-pass filter of the amplifier was set at 0.3-2 kHz, and the contralateral ear (for DNLL or IC penetration) or ipsilateral ear (for SOC penetration) relative to the injection pipette was stimulated by a pure tone. Recording of the sound evoked activity through the injection pipette could refine the pipette placement in an auditory nucleus.

During the recording, the tone frequency at either ear was set at the CF. the average amplitude of EPs was determined from 35 or 50 single tone presentations. Measurement of an averaged amplitude of EPs is illustrated in Figure 10, which shows three typical averaged auditory EPs in the rat's ICC when a pure tone at CF was presented at the contralateral ear. The amplitude was obtained by measuring the difference in microvolts (μV) between the onset and the peak of the primary response.

The EP IID function curve was generated by setting the contralateral tone level at 10-25 dB above threshold and manipulating the ipsilateral tone level in 5 dB steps from just subthreshold to progressively higher levels. To describe quantitatively the effect of injections on IID function, I have created a shift score to indicate the change in

monotonic dynamic (declining) part of an IID function curve before and after injection(s).

The shift score (S) is calculated by the following equation:

$$S = \frac{100}{N} * \sum_{i=1}^N \left(\frac{B_i'}{C'} - \frac{B_i}{C} \right)$$

in which,

B_i : amplitude of binaural responses at an IID level before injection,

B_i' : amplitude of binaural responses at the corresponding IID level after injection,

C : amplitude of monaural responses to contralateral stimulation before injection,

C' : amplitude of monaural responses to contralateral stimulation after injection,

N : number of sampled points in the monotonic inhibitory dynamic region of a IID function curve.

When the S score is positive, the injection has the effect of decreasing binaural inhibition in the IID function; if the S score is negative, the injection has the effect of facilitating the binaural inhibition in the IID function; if the IID curve following an injection is identical to the one before injection, the S score is zero.

If the excitatory response to the ipsilateral tone was measurable, a monaural amplitude-intensity function for the ipsilateral ear was determined by increasing the ipsilateral tone level in 5 dB steps from a subthreshold level to progressively higher levels.

The monaural response to constant contralateral stimulation, the EP IID function and the monaural amplitude-intensity function for the ipsilateral ear were recorded before and after injection of KYNA in the blockade targets.

Histology

At the end of an experiment, a solution of brilliant blue G (C. I. 42655, 0.25% in distilled water) or eosin B (C. I. 45400, 1% in distilled water) was added to the recording

pipette and was injected into the brain iontophoretically (8-10 μ A negative current, 20-30 min) as a marker for histological verification of electrode placement.

A solution of brilliant blue G (0.25% in saline) or eosin B (1% in saline) or the mixed dye solution (0.25% brilliant blue G and 1% eosin B in saline) was added to the injection pipette and was injected into the brain by pressure (the same volume of drug solution as used previously) to indicate the extension of the pressure injection from the injection pipette. If the injection of dye solution could not be made by pressure, 8-10 μ A negative current was applied through the injection pipette for 20-30 min to provide a label.

The brain was removed and put into 10% formalin saline solution with 30% sucrose or into 4% paraformaldehyde phosphate-buffered saline with 20% sucrose. After the brain sank in the fixative solution, it was cut into 40 μ m frozen frontal sections. A series of sections were cleared by xylene only, and the alternate sections were stained with cresyl violet.

RESULTS

In the present study, recordings and injections were made in 32 rats. In 13 rats, only one auditory nucleus was injected. In 19 rats, two auditory nuclei were blocked in sequence, one was the contralateral DNLL and another was one of the three nuclei: the ipsilateral DNLL, the contralateral IC, and the ipsilateral SOC. Usually, the suppressing effect of KYNA on evoked activity lasted at least 40-50 minutes, and for the majority of the 19 animals the time intervals between the initial and the subsequent injections were shorter than 50 minutes. As mentioned in the METHOD, the 32 animals were divided into 7 groups: (1) contralateral DNLL, (2) ipsilateral DNLL, (3) contralateral IC, (4) ipsilateral SOC, (5) ipsilateral DNLL and contralateral DNLL, (6) contralateral IC and contralateral DNLL, and (7) ipsilateral SOC and contralateral DNLL. Both anatomical and physiological data will be presented in the order described above.

Location of Recording and Injection

In the majority of cases, recording electrode positions in the ICC were marked by brilliant blue G injections as illustrated in Figure 1. Examples of injection locations in the contralateral DNLL, ipsilateral DNLL, contralateral IC, and ipsilateral SOC are shown in Figure 2. The locations of electrode tips and extension of injected dyes in most cases were easily identified in unstained frontal sections through the brainstem.

KYNA injection was made into the contralateral DNLL of 7 rats (R302, R304, R310, R316, R325, R350, and R352). Figure 3 shows the recording and injecting sites of these 7 rats.

Three rats (R319, R331, and R346) received KYNA injections into the ipsilateral DNLL only. Recording sites in the ICC (left) and injection sites in the ipsilateral (left) DNLL of the three rats are shown in Figure 4.

Two rats (R303 and R322) received KYNA injection into the contralateral IC only. The recording and injection locations for these two rats are shown in Figure 5.

One rat (R344) was injected with KYNA into the ipsilateral SOC. The recording and injection sites are reconstructed in Figure 6.

KYNA was injected into the ipsilateral DNLL and then into the contralateral DNLL in three rats, R318, R329 and R360. The recording and injection locations for the rats are indicated in Figure 7.

A total of 8 rats (R305, R306, R307, R308, R309, R314, R317, and R347) received KYNA injections into both the contralateral IC and the contralateral DNLL. The recording positions in the ICC and the injection sites in the contralateral IC and the contralateral DNLL are presented in Figure 8. In R314 and R347, KYNA was injected into the contralateral IC first and then into the contralateral DNLL. In the remaining 6 rats, KYNA was injected into the contralateral DNLL first and then into the contralateral IC.

One rat (R348) received injection of 50 μ M 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX, a relatively specific antagonist for non-NMDA receptor) into the ipsilateral SOC and the contralateral DNLL. Another 7 rats (R301, R349, R354, R355, R356, R357, and R359) received injection of KYNA into both ipsilateral SOC and contralateral DNLL. The recording sites in the ICC and injection sites in the contralateral DNLL and the ipsilateral SOC are shown in Figure 9. In R301, R348, R356, and R359, the ipsilateral SOC was blocked first following by a subsequent block of the contralateral DNLL. In R349, R354, R355, and R357, the initial injection was made into the contralateral DNLL first, and the subsequent injection was made into the ipsilateral SOC.

Effect of Injection on Responses Evoked by Monaural Contralateral Stimulation

To measure responses evoked by monaural contralateral stimulation the average amplitude of EPs were determined from 35 or 50 single tone presentations with the level

of the contralateral tone held constant at 15-25 dB above threshold. Figure 10 indicates three typical averaged auditory EPs in the rat's ICC, when contralateral ear was stimulated by a tone at CF. The amplitude was obtained by measuring the voltage difference in microvolts between the onset and the peak of the primary response.

The following seven figures (Fig 11 - Fig. 17) indicate the monaural responses to constant contralateral stimulation during the whole recording periods for the seven animal groups. In each of the rats, the monaural response to contralateral pure tone displayed frequency-selectivity, and the frequency of the contralateral pure tone was set at CF.

From these data, it can be noticed that for the majority of the 32 rats, the amplitude of monaural EP responses to contralateral stimulation maintained relatively constant over time and were not influenced by the injections of KYNA.

In 5 rats (R306, R308, R309, R310, and R325), the amplitudes of monaural EP response to contralateral stimulation were reduced slightly after the injection of KYNA into the contralateral DNLL. However, in other two rats, R304 and R317, the monaural responses to contralateral stimulation increased following the injections of KYNA into the contralateral DNLL, especially for R317.

Effect of Injection of KYNA on the EP IID Function

Injection into Contralateral DNLL only

Effects of KYNA injection into contralateral DNLL on the EP IID function were determined in 7 rats (R302, R304, R310, R316, R325, R350, and R352). Figure 18 indicates the effects of the injection for the 7 rats. The curves in the figures on the left measure the EP amplitude in microvolts. The curves in the figures on the right display the binaural activity in percentage relative to the monaural responses to contralateral stimulation. The S values for injections are presented in the figures on the right side.

Under normal conditions, when the sound level on the contralateral ear was kept constant, the EP amplitude was determined by the EP IID between the tones delivered to the two ears. When the sound pressure level was near threshold, the ipsilateral stimulation facilitated the EP responses to contralateral stimulation in some rats; when the ipsilateral sound intensity was higher, the EP amplitude decreased with increase in the ipsilateral sound level. The response driven by the contralateral stimulation could not be totally abolished by the ipsilateral stimulation, however.

Injection of KYNA in the contralateral DNLL was associated with a shift in the EP IID functions. The inhibitory strength of ipsilateral stimulation on the EP IID functions was reduced by the blockade of the contralateral DNLL in all these 7 rats. The average S for the 7 rats was +29.4.

In R350 and R352, the shifted EP IID curves recovered to normal after 1 to 1.5 hours. For all 7 rats, the suppression of evoked activity of DNLL by the injection of KYNA lasted at least 40-50 minutes.

Injections into Ipsilateral DNLL

Three rats (R319, R331, and R346) received an injection of KYNA into the ipsilateral DNLL. Figure 19 shows EP IID functions for these animals in both amplitude and percentage. The injection of KYNA into the ipsilateral DNLL had no effect on the EP IID function. The average S for the 3 rats was +6.5.

Injection into Contralateral IC

Two rats (R303 and R322) received a KYNA injection into the contralateral IC. For both rats, the EP IID functions were not changed after the injection (Fig. 20). The average S for the 2 rats was -0.1.

Injection into Ipsilateral SOC

One rat (R344) was injected with KYNA into the ipsilateral SOC. The result of the injection on EP IID function is shown in Figure 21. The S was +5.9.

Injections into Ipsilateral DNLL and Contralateral DNLL

KYNA was injected into the ipsilateral DNLL first and then into the contralateral DNLL in 3 rats: R318, R329 and R360. Figure 22 displays their EP IID curves. A summary of shift scores for each injection is presented in Table 1. In the table, S_{initial} is the shift score comparing the EP IID curve after initial injection and the normal EP IID curve; S_{second} is the shift score comparing the EP IID curve after second injection and the EP IID curve after initial injection; S_{combined} is the shift score comparing the EP IID curve after second injection and the normal EP IID curve.

Table 1. Summary of the Shift Scores for the Injections
into Ipsilateral DNLL and Contralateral DNLL

Name of Animal	S_{initial} (ipsi DNLL)	S_{second} (contra DNLL)	S_{combined}
R318	+1.447	+22.847	+24.294
R329	-6.913	+12.018	+5.105
R360	-5.209	+28.689	+23.480
Average	-3.558	+21.185	+17.626

Injection of KYNA into the ipsilateral DNLL did not substantially change the EP IID function in the 3 rats, but subsequent injection of KYNA into the contralateral DNLL had a remarkable effect of reducing the binaural suppression in the EP IID function.

Injections into Contralateral IC and Contralateral DNLL

A total of 8 rats (R305, R306, R307, R308, R309, R314, R317, and R347) received KYNA injections into the contralateral IC and contralateral DNLL. Figure 23 shows the EP IID curves for the 8 rats before and after the injections. The nucleus which was initially injected and the corresponding shift score are indicated in the figures for each animal. Table 2 summarizes the shift scores for the injections.

Table 2. Summary of the Shift Scores for the Injections into Contralateral IC and Contralateral DNLL

Name of Animal	S _{initial}		S _{second}		S _{combined}
	Contra	Contra	Contra	Contra	
	IC	DNLL	IC	DNLL	
R314	+12.489	/	/	+20.403	+32.892
R347	-4.040	/	/	+35.431	+31.391
R305	/	+23.256	+4.228	/	+27.484
R306	/	+39.819	-36.387	/	+3.432
R307	/	+23.551	+3.636	/	+27.187
R308	/	+27.698	-16.242	/	+11.456
R309	/	+23.278	+1.071	/	+24.349
R317	/	+23.949	-6.245	/	+17.704
Average	+4.224	+26.925	-8.323	+27.917	+21.987

For R314 and R347, KYNA was injected first into the contralateral IC and then into the contralateral DNLL. In R314, injection into the contralateral IC produced a small reduction of the binaural inhibition in the EP IID function ($S=+12.5$). Following the subsequent injection of KYNA into the contralateral DNLL, the binaural inhibition in the EP IID function was reduced greatly; the S for the combined injections was +32.9. In

R347, injection of KYNA into the contralateral IC had almost no effect on the EP IID function ($S=-4.0$), but the subsequent injection of KYNA into the contralateral DNLL reduced the binaural inhibition in the EP IID function; the S for the combined injections was $+31.4$.

For the other 6 rats (R305, R306, R307, R308, R309, and R317), KYNA was injected into the contralateral DNLL first and then into the contralateral IC. For each of these animals, when the contralateral DNLL was blocked, the binaural suppression of the EP IID function was remarkably reduced. After the contralateral IC was blocked, no further reduction of binaural suppression in the EP IID function was found. In R308, the shifted EP IID curves recovered to normal three hours after the injection into the contralateral DNLL.

The average S for the initial injections into the contralateral IC of R314 and R347 was $+4.2$; the average S_{second} for the subsequent injections into the contralateral IC of R305, R306, R307, R308, R309 and R317 was -8.3 . The average S for the initial injections into the contralateral DNLL of the 6 rats was $+26.9$; the average S_{second} for the subsequent injections into the contralateral DNLL of R314 and R347 was $+27.9$. The average S for the combined injections into the contralateral IC and contralateral DNLL was $+22.0$.

Injections into Ipsilateral SOC and Contralateral DNLL

One rat (R348) received an injection of $50 \mu\text{M}$ CNQX into the contralateral DNLL and ipsilateral SOC. The other 7 rats (R301, R349, R354, R355, R356, R357, and R359) received injections of KYNA into both ipsilateral SOC and contralateral DNLL. Figure 24 shows the EP IID curves for the 8 rats before and after the injections, and shows shift scores for the initial injections. Table 3 summarizes the shift scores for the injections.

Table 3. Summary of the Shift Scores for the Injections into Ipsilateral SOC and Contralateral DNLL

Name of Animal	S _{initial}		S _{second}		S _{combined}
	Ipsi	Contra	Ipsi	Contra	
	SOC	DNLL	SOC	DNLL	
R301	-6.381	/	/	+19.120	+12.739
R348	+10.130	/	/	+15.193	+25.323
R356	+6.710	/	/	+41.213	+47.923
R359	+7.603	/	/	+17.881	+25.484
R349	/	+6.306	+8.280	/	+14.586
R354	/	+14.608	+3.175	/	+17.780
R355	/	+21.342	+11.733	/	+33.075
R357	/	+36.528	+9.370	/	+45.898
Average	+4.515	+19.696	+8.139	+23.352	+27.851

In 4 rats (R301, R348, R356, and R359), the ipsilateral SOC was blocked first and then the contralateral DNLL. Blockade of the ipsilateral SOC produced no (R301) or only slight reduction (R348, R356 and R359) in binaural suppression. Following the subsequent blockade of contralateral DNLL, a large change in the EP IID curve can be seen in each of these 4 rats. In R359, the shifted EP IID curves recovered to normal one hour after the injection into the contralateral DNLL.

In the other 4 rats (R349, R354, R355 and R357), KYNA was injected into the contralateral DNLL first and then into the ipsilateral SOC. In R349, injection of KYNA into the contralateral DNLL had a slight effect on the EP IID function ($S=+6.3$), and subsequent injection of KYNA into the ipsilateral SOC produced a small further reduction in the binaural inhibition. In R354, R355, and R357, suppression of activity in the contralateral DNLL caused a remarkable shift in the EP IID function, reducing the

binaural inhibition; subsequent blockade of the ipsilateral SOC produced a slight additional shift.

The average S for the initial injections into the ipsilateral SOC of R301, R348, R356, and R359 was +4.5; the average S_{second} for the subsequent injections into the ipsilateral SOC of R349, R354, R355 and R357 was +8.1 which was larger than the average S_{initial} for R301, R348, R356, and R359. The average S for the initial injections into the contralateral DNLL of R349, R354, R355, and R357 was +19.7; the average S_{second} for the subsequent injections into the contralateral DNLL of R301, R348, R356, and R359 was +23.4. The average S for the combined injections of the 8 rats was +27.9.

Summary of the Effects of Initial Injections on EP IID Function

In the present experiment, a total of four auditory brainstem nuclei were under study: the contralateral DNLL, the ipsilateral DNLL, the contralateral IC, and the ipsilateral SOC. In 13 rats, a single injection was made into only one of the four auditory nuclei in each animal; in 19 rats, injections were made into the DNLL and one of the other three auditory nuclei. The data on the effects of initial injections were selected from all 32 rats and reorganized into four categories corresponding to the four auditory nuclei.

In a total of 17 rats, injections were made initially into the contralateral DNLL. The effects of initial injection into the DNLL varied among these animals from a slight shift in the EP IID function (e.g. R349, $S=+6.3$) to an almost total abolishment of binaural inhibition (e.g. R350, $S=+48.0$). The average S for the initial injections into the contralateral DNLL for the 17 rats was +25.8.

KYNA was injected into ipsilateral DNLL in 6 rats immediately after the completion of the normal EP curves. The average shift score for the initial injections was -0.7.

In 4 rats, injections into the contralateral IC were made immediately after the completion of data accumulation of the normal EP curves. The average shift score for the initial injections was +2.1.

The initial injections were made into the ipsilateral SOC in 5 rats. The average shift score for the initial injections was +4.8.

Figure 25A shows a comparison of the average shift scores for the initial injections into the four auditory nuclei. In the figure it can be seen that the EP IID function in the ICC was most sensitive to the blockade of the contralateral DNLL. Blockade of the ipsilateral SOC only slightly reduced the binaural inhibition of the EP IID functions. Injections of KYNA into either ipsilateral DNLL or the contralateral IC had no noticeable influence on the EP IID function.

Summary of the Effects of Combined Injections of KYNA on EP IID Function

In a total of 19 rats, injections were made into the DNLL and one of the other three auditory nuclei. Figure 25B displays the comparison of the average S for the three kinds of combined injection: (1) ipsilateral DNLL and contralateral DNLL, (2) contralateral IC and contralateral DNLL, (3) ipsilateral SOC and contralateral DNLL. The combined injections into the ipsilateral SOC and contralateral DNLL had more effect on shift scores than the other two kinds of combined injections.

Effects of Injection of KYNA on Monaural Responses to Ipsilateral Stimulation

Injection into Contralateral DNLL

Seven rats received a single injection of KYNA into their contralateral DNLL. In two rats (R350 and R352), no response to monaural ipsilateral stimulation could be detected either before or after injection. The recording sites in the ICC in the other 5 rats (R302, R304, R310, R316 and R325) had EP responses to ipsilateral pure tones at CF for

the corresponding contralateral stimulation. After injection of KYNA into the contralateral DNLL, the responses evoked by monaural ipsilateral stimulation were enhanced (Fig. 26).

Injection into Ipsilateral DNLL

Three rats received injections into their ipsilateral DNLL only. In R331 and R346, no response to ipsilateral stimulation could be detected either before or after injection of KYNA.

In R319, the monaural response was slightly reduced after KYNA was injected into the ipsilateral DNLL (Fig. 27).

Injection into Contralateral IC

The recording sites for both R303 and R322 had EP responses to ipsilateral stimulation. For R303 the response was not changed by the injection; in R322, the response was greatly reduced by injection of KYNA in the contralateral IC (Fig. 28).

Injection into Ipsilateral SOC

Only one rat, R344, received a single injection of KYNA into the ipsilateral SOC. The recording site in the ICC of R344 did not display an EP response to ipsilateral stimulation either before or after the injection.

Injections into Ipsilateral DNLL and Contralateral DNLL

Of the three animals (R318, R329, and R360) tested, only R360 showed monaural responses to ipsilateral stimulation before and after injection of KYNA into both the ipsilateral DNLL and the contralateral DNLL. Neither injection had an effect on the monaural response (Fig. 29).

In R318, no monaural response was detected either before or after the injection of KYNA into the ipsilateral DNLL. However, after the contralateral DNLL of R318 was injected, the monaural responses to ipsilateral stimulation appeared (Fig. 29).

In R329, no EP response to monaural ipsilateral stimulation could be detected.

Injections into Contralateral IC and Contralateral DNLL

In each of the 8 rats (R305, R306, R307, R308, R309, R314, R317, and R347), the recording site in the IC had a noticeable response to monaural ipsilateral stimulation. Figure 30 depicts the effects of injections.

In R305, R306, R308, R309, and R317, the injections were made first into the contralateral DNLL and then into the contralateral IC. For each of these 5 animals, injection of KYNA into the contralateral DNLL enhanced the monaural response to ipsilateral stimulation, and injection into the contralateral IC reduced the response. The recovery curve for R308 was obtained.

In R314 and R347, KYNA was injected into the contralateral IC first and then into the contralateral DNLL. The first injections caused an apparent reduction in the monaural responses to ipsilateral stimulation. Subsequent injections of KYNA into the contralateral DNLL caused an enhancement of the responses.

In R307, the monaural response was not measured after injection of KYNA.

Injections into Ipsilateral SOC and Contralateral DNLL

Of the 8 rats which received injection of KYNA into ipsilateral SOC and contralateral DNLL, 3 rats (R348, R349 and R354) did not have responses to monaural ipsilateral stimulation either before or after application of KYNA. In the case of one animal (R357), a monaural response could be measured, but complete data was not obtained on the effect of the injection. Data was obtained from four rats (R301, R355, R356, and R359) before and after the injections (Fig. 31).

In R301, R356, and R359, the ipsilateral SOC was injected first and the contralateral DNLL was injected subsequently. In R355 the contralateral DNLL was injected first and the ipsilateral SOC was injected subsequently. For these four animals, injection of KYNA into the contralateral DNLL was associated with an enhancement of the monaural response to the ipsilateral stimulation. Injection of KYNA into the ipsilateral SOC did not change the monaural response in R301 but substantially reduced the responses in R355, R356, and R359. The recovery curve for R359 was obtained.

Summary

Clear EP responses to monaural ipsilateral stimulation at CF for contralateral stimulation were found in the majority (23) of the 32 rats. The data for the effects of injections on the monaural responses was selected and reorganized into four categories corresponding the four auditory nuclei. In only 9 of the 32 rats, the recording sites in the ICCs did not exhibit the monaural EP responses either before or after injection of KYNA into the brainstem.

A summary of the effect of injection on the monaural response to ipsilateral stimulation is presented in Table 4.

Table 4. Number of Cases for Effects of Blocking the Four Nuclei on the Monaural Response to Ipsilateral Stimulation

Nucleus	Facilitation	Suppression	No Effect	Total
Contra DNLL	17	0	1	18
Ipsi DNLL	0	1	1	2
Contra IC	0	8	1	9
Ipsi SOC	0	3	1	4

Out of 26 rats that received an injection of KYNA or CNQX into the contralateral DNLL, 20 rats had monaural EP responses to ipsilateral stimulation, but the effect of blockade of contralateral DNLL on the monaural response was not measured completely in 2 (R307 and R357) of the 20 rats. The blockade of contralateral DNLL had an effect of enhancing the monaural responses to ipsilateral stimulation in 17 rats, and had no effect in 1 rat.

Out of 6 rats that received injection of KYNA into the ipsilateral DNLL, only 2 (R319 and R360) had responses to ipsilateral stimulation before injection. After injection of KYNA into the ipsilateral DNLL, no change was produced in the monaural responses in one animal (R360), and a slight reduction of the response was noticed in the other (R319).

KYNA was injected into contralateral IC in 10 rats, all of which had monaural responses to ipsilateral stimulation. Complete measurements were made in all but one animal (R307). After the injection, the monaural response was unchanged in one animal (R303), but was substantially reduced in the other 8 rats.

Out of 9 rats in which KYNA was injected into the ipsilateral SOC, measurable monaural responses to ipsilateral stimulation were found in 5 cases. In 3 rats (R355, R356, and R359), blockade of the ipsilateral SOC suppressed the monaural responses; in one animal (R301) the blockade had no effect; in one animal (R357), the effect of injection was not measured.

Comparison of Shifts in the EP IID Functions and in the Monaural Responses to Ipsilateral Stimulation Following Blockade of the Contralateral DNLL

Neural activity in the contralateral DNLL was blocked in 26 rats, and the blockade had the effect of shifting the EP IID functions, namely, decreasing the strength of the binaural inhibition in each of the animals. In some of the 26 rats, the blockade also had an effect of enhancing the monaural responses to ipsilateral stimulation, and the shifts

in monaural response were correlated with the shifts in EP IID functions. In 6 of the 26 rats, the recording sites in the ICCs did not exhibit the monaural EP response either before or after injection of KYNA into the contralateral DNLL.

Injections into the Contralateral DNLL only

In R302, R304, R310, R316, and R325, following the injections of KYNA into the contralateral DNLL, the shifts of monaural responses to ipsilateral stimulation were correlated with the shifts in EP IID function. In R316 the enhancement in the monaural responses to ipsilateral stimulation was larger than the shift in EP IID function. In R302, R304, R310, and R325, the shifts in the monaural responses to ipsilateral stimulation were smaller than the shifts in EP IID functions (Fig. 32).

Injections into the Ipsilateral DNLL and Contralateral DNLL

In R318, no monaural response to the ipsilateral stimulation was found either before or after injection of KYNA into the ipsilateral DNLL. Following subsequent injection of KYNA into the contralateral DNLL, a clear response to ipsilateral stimulation was noticed. The shift in the monaural response to the ipsilateral stimulation was identical to the shift in the EP IID function (Fig. 33).

In R360, the injection of KYNA into the ipsilateral and contralateral DNLL had no effect on the monaural responses to ipsilateral stimulation. The shift in the EP IID function produced by the subsequent injection into the contralateral DNLL was very distinctive in comparison to the fluctuation in the monaural response to ipsilateral stimulation (Fig. 33).

Injections into the Contralateral IC and Contralateral DNLL

In R314 and R347, KYNA was injected into the contralateral IC first and then into the contralateral DNLL. In these two rats, the shifts in the EP IID function were

apparently different from the shifts in the monaural responses to ipsilateral stimulation (Fig. 34).

R305, R306, and R308 received injections first into the contralateral DNLL and then into the contralateral IC. Following the initial injections into the contralateral DNLL, the shifts of monaural responses to ipsilateral stimulation were close to or larger than the shifts of EP IID function (Fig. 34). In R305 and R308, the subsequent injection into the contralateral IC reduced the monaural response but had relatively smaller influence on EP IID function. The effects on the EP IID functions in R305 and R308 were therefore separated from the effects on the monaural responses to ipsilateral stimulation. However, in R306, the subsequent injection of KYNA into the contralateral IC suppressed the monaural response and facilitated the binaural inhibition in EP IID function to almost the same extent.

In both R309 and R317, following initial injection into the contralateral DNLL, the extent of the enhancement of the monaural response to ipsilateral stimulation was smaller than the extent of the reduction of inhibition in the EP IID function. Subsequent injection into the contralateral IC decreased the monaural response to ipsilateral stimulation and had a slight influence on the EP IID function (Fig. 34). The shifts in the monaural responses were different from the shifts in the EP IID functions.

Injections into the Ipsilateral SOC and Contralateral DNLL

Figure 35 shows the comparison of shifts in the EP IID function to shifts in the monaural responses to ipsilateral stimulation for the 5 rats (R301, R356, R359, R355, and R357) in which KYNA was injected into the ipsilateral SOC and the contralateral DNLL. As can be seen in the figure, following injection of KYNA into the contralateral DNLL, the shifts in the EP IID functions were much larger than the shifts in the monaural responses to ipsilateral stimulation.

DISCUSSION

Methodological Considerations

Logic of the Present Study

In our previous study (Li and Kelly, 1992b), we utilized the following logic: *to evaluate the contribution of lower brainstem nuclei to auditory responses in more rostral auditory structures, the neural activity in the lower brainstem can be blocked by injection of KYNA and the neural responses can be recorded in the more rostral structures before and after the injection.* In that study, single unit binaural responses were recorded in the ICC before, during and after microinjections of KYNA into the DNLL. KYNA was used to suppress the sound evoked spikes in the DNLL. The study showed that the DNLL plays a role in binaural processing through an inhibitory influence on the IID functions in EI neurons of the contralateral ICC. In the present study, I used the same research logic but applied the EP recording method to measure neural activity in the ICC of the rat.

Electrophysiological Measurement of Neural Activity in IC

As mentioned before, the EP response has several features. The EP recording technique gives a more stable measure of sound-evoked neural activity compared to measures of spike rate using single-unit recording technique, because there is no problem isolating and holding a response as there is in a single-unit recording. On the other hand, when the tip of the recording micropipette is not very large (5-30 μm), the EP response in the ICC exhibits a frequency selectivity and so reflects local neural activity. These features of the EP response were discernible in each animal used in the present study.

A preliminary result showed that local injection of bicuculline into the ICC remarkably enhanced the amplitude of EP response to monaural stimulation (Li, L., unpublished observation). On the other hand, in the present study, injection of KYNA

had an inhibitory effect. KYNA suppressed sound-evoked multi-units activity in the injection targets and reduced the amplitude of the EP monaural response. The amplitude of EP may represent a net excitation evoked by sound.

In the present study, the most striking feature of the EP response in the ICC for the present study was that changes in amplitude could be used to indicate binaural inhibition when the sound level at the contralateral ear was kept constant. For a given stimulus level of pure tone presented to the contralateral ear, the response amplitude of the EP activity declined as the level of stimulus to the ipsilateral ear was augmented. The change in amplitude of EP response indicated a sensitivity to IID and is called the EP IID function.

Why Was KYNA Used

The vast majority of synapses in the central nervous system appear to use excitatory amino acids (L-aspartate and L-glutamate) as their neurotransmitters. Three main kinds of amino acid receptors have been defined by the depolarizing actions of selective agonist: NMDA, kainate, and quisqualate (or α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid, AMPA). Excitatory transmission appears to involve actions mediated by one or combinations of these receptors. Because of the lack of antagonists for clearly separating kainate and quisqualate responses, many authors refer to both kainate and quisqualate receptors as "non-NMDA" receptors.

Johnson and Ascher, (1987) first demonstrated that glycine potentiates NMDA electrophysiological responses by increasing the frequency of NMDA receptor channel opening in a strychnine-insensitive manner but has no action by itself. There is an allosteric modulator site on the NMDA receptor complex that is sensitive to glycine. Glycine binding appears to be a prerequisite for activity of the NMDA receptor and the NMDA receptor activation requires the binding of both glycine and L-glutamate as "co-agonist" (Kleckner and Dingledine, 1988). Thomson et al. (1989) demonstrate that

glycine can facilitate NMDA receptor-mediated neuronal excitation in slices of cerebral cortex. Mayer et al. (1989) present evidence that the enhancement of NMDA responses by glycine occurs through an acceleration of recovery from desensitization, a decline in the receptor response which occurs during a prolonged agonist application of the NMDA receptor. The effects of glycine on the NMDA receptor can be compared with those of benzodiazepines on the GABA_A receptor, but the magnitude of the enhancement of NMDA responses by glycine is much greater than that seen with benzodiazepines on GABA responses.

KYNA is the only known endogenous antagonist of excitatory amino acid transmitters. KYNA can be synthesized from L-kynurenine within the central nervous system and is released into the extracellular space (Swartz et al., 1990). KYNA has affinity for both the agonist recognition site and the glycine allosteric site on the NMDA-receptor complex, and KYNA is the antagonist both for the NMDA agonist recognition site and for the glycine allosteric site. The EC₅₀ (the concentration of drug, at which the drug reaches 50% of its maximum effect) for KYNA for the glycine site is approximately 15 μ M, whereas the EC₅₀ for the NMDA recognition site is approximately 200-500 μ M, thus KYNA is more potent at the glycine allosteric site (Danysz et al., 1989; Kessler et al., 1989). The effects of glycine on NMDA responses can be rapidly and reversibly blocked by KYNA (Thomson et al., 1989). On the other hand, when the concentration of KYNA is in the millimolar range, KYNA can block the non-NMDA receptor (Stone and Connick, 1985; Kessler et al., 1989). So KYNA is a broad-spectrum antagonist for excitatory amino acid receptors.

Some findings suggest that excitatory amino acids function as transmitters in excitatory pathways in the auditory brainstem. Most of the neurons examined in the IC were excited by iontophoretic application of glutamate, aspartate, or NMDA (Curtis and Koizumi, 1961; Faingold et al., 1989b). The excitatory effect of NMDA was blocked by the NMDA receptor-specific antagonists D-alpha-amino adipate and 2-amino-5-

phosphonovalerate. Recent *in vitro* electrophysiological studies have demonstrated that both NMDA and non-NMDA receptors are present in the LSO (Wu and Kelly, 1992a, b) and the DNLL (Wu and Kelly, 1993; Wu, S. H., personal communication).

In the present study, the injection pipette was used to monitor the neural activity of neurons close to the tip of the injection pipette. Following injection of 2mM KYNA into the IC, DNLL, or SOC, the neural activity recorded by the injection pipette in these auditory nuclei was substantially suppressed.

In the present study, the reduction in the amplitude of the EP caused by binaural interaction was used to estimate the binaural inhibition, when the sound level at the contralateral ear was kept constant. It is important to monitor the change in the EP responses to monaural contralateral stimulation during the whole recording period for each animal.

Monaural Responses to Contralateral Stimulation

The results of the present study indicate that blockade of the contralateral DNLL, contralateral IC, or ipsilateral SOC had no consistent effect upon the amplitude of the EP response elicited by stimulation of the contralateral ear in the ICC. Previous anatomical and physiological data have suggested that the contralateral DNLL, contralateral IC and ipsilateral LSO of the rat are not excited mainly by the contralateral ear (relative to the recorded ICC) (see the INTRODUCTION). For example, the right DNLL, right IC, and left LSO are driven mainly by the left ear and not the right ear. When the right DNLL, right IC, or left SOC is blocked, the excitatory response in the left ICC to stimulation of the right ear may not be influenced. The results of present study are consistent with the previous anatomical and physiological data.

When a recording is made in the left ICC, the ipsilateral (left) DNLL is driven by contralateral (right) stimulation. However in the present study, injection of KYNA into the ipsilateral DNLL had little effect on the monaural response in the ICC to contralateral

stimulation. The ipsilateral DNLL may not be the main excitatory or inhibitory station for conveying the information from the contralateral CN to the ICC.

Local iontophoretic injection of bicuculline or strychnine into the IC leads to effects of increase in excitatory monaural responses to contralateral stimulation in the IC (Faingold et al., 1991a, b; Pollak and Park, 1992; Yang et al., 1992). These effects may be due, at least in part, to GABAergic and glycinergic inputs from sources other than the contralateral DNLL, ipsilateral DNLL, contralateral IC, and ipsilateral SOC. The possible GABAergic source driven by contralateral stimulation may be intrinsic GABAergic interneurons forming local circuits within the IC (Ribak and Roberts, 1986; Roberts and Ribak, 1987a, b; Vetter and Mugnaini, 1984). The potential glycinergic input responsible for the monaural inhibition might come from the glycinergic neurons in the ipsilateral VNLL (Aoki et al., 1988; Saint Marie and Baker, 1990).

Injections of KYNA into the contralateral DNLL, ipsilateral DNLL, contralateral IC, and ipsilateral SOC did not have a marked influence on the monaural responses to contralateral stimulation. Thus consistent changes in the EP IID function following the injections were not determined by monaural effects from the contralateral ear.

Monaural Responses to Ipsilateral Stimulation

The present study shows that ipsilateral sound can cause an EP response when the electrode is at an appropriate region in the ICC. Since ipsilateral stimulation elicits excitatory activity in the contralateral DNLL which, in turn, projects to the recorded ICC, it is very interesting and important to study the inhibitory influence from the contralateral DNLL on the response in the ICC to monaural ipsilateral stimulation.

Injection of KYNA into the contralateral DNLL had the effect of increasing the amplitude of monaural responses to ipsilateral stimulation. In contrast, injections into the ipsilateral DNLL, contralateral IC and ipsilateral SOC did not have such an effect. Blockade of the contralateral DNLL enhanced the monaural response to ipsilateral

stimulation even if the ipsilateral SOC had primarily been blocked. These results support our previous finding that sound evoked activity in the DNLL is partially independent of the neural activity in the SOC (Li and Kelly, 1992b, 1993a).

The present study is the first to demonstrate (from a total of 8 rats) that blockade of the contralateral IC suppresses the monaural response in the ICC to ipsilateral stimulation. It can be suggested that the ICC receives excitatory inputs from the ipsilateral ear, to some extent, through the contralateral IC. This suggestion is substantiated by anatomical and physiological studies. In the IC, the majority of neurons are excited by the stimulation of the opposite ear (cat: Aitkin et al., 1975; Roth et al., 1978; Semple and Aitkin, 1979; rat: Flammiano and Clopton, 1975; Kelly et al., 1991; Sally and Kelly, 1992; Silverman and Clopton, 1977), and there are reciprocal connections between the IC on each side (Aitkin and Phillips, 1984b; Brunso-Bechtold et al., 1981; Rockel and Jones, 1973a; Roth et al., 1978). Excitatory projections between the two ICC were also reported recently in chinchillas (Caspary and Helfert, 1993). The functional significance of the reciprocal excitatory projections between the IC on each side requires further investigation in the future.

Previous anatomical data has already suggested that there is an excitatory pathway to the ICC from the ipsilateral MSO (cat: Adams, 1979; Aitkin and Schuck, 1985; Brunso-Bechtold et al., 1981; Elverland, 1978; Glendenning et al., 1981; Henkel and Spangler, 1983; Roth et al., 1978; rat: Beyerl, 1978; Coleman and Clerici, 1987). In the present study, suppression of the monaural response was found in 3 rats after blockade of the ipsilateral SOC. Although the results of the present study are consistent with the anatomical data, the number of cases in the present study was too small to allow us to come to a conclusion regarding the effect of the ipsilateral SOC on the response in the ICC to ipsilateral monaural stimulation.

Binaural Inhibition

The main purpose of the present study was to use the EP recording method to indicate if the contralateral DNLL plays a role in the binaural inhibition in the ICC. Although the effects of KYNA injections into the contralateral DNLL were clear, namely, blockade of the neural activity of the contralateral DNLL reduced the strength of binaural inhibition of the EP IID function in the ICC, a further question should be asked: how important is the contribution of the contralateral DNLL, compared to those of other structures in the auditory brainstem?

Comparison between Ipsilateral DNLL and Contralateral DNLL

In the present study, injection of KYNA into the contralateral DNLL reduced the strength of binaural inhibition of the EP IID function in the ICC, and blockade of the ipsilateral DNLL had no effect on the EP IID function. These results are consistent with those previously reported. Following blockade of the contralateral DNLL the binaural inhibition of the IID function of single EI neurons was reduced (Faingold et al., 1993; Li and Kelly, 1992b). After the neural activity in the ipsilateral DNLL was suppressed by KYNA, no remarkable change appeared in the IID function of the EI cell (Li and Kelly, 1992b).

Generally, the contralateral DNLL, the contralateral IC, and the ipsilateral LSO share two important characteristics in their neural connections: (1) they are excited by ipsilateral stimulation (relative to the recorded ICC), and (2) they project to the ICC directly. Therefore, the contralateral IC and ipsilateral SOC are two auditory nuclei that serve as good controls when studying the effect of manipulation of the contralateral DNLL on neural activity in the ICC.

Comparison between the Contralateral IC and Contralateral DNLL

Unlike the injection of KYNA into the contralateral DNLL, blockade of the contralateral IC did not produce any substantial change in the EP IID function yet it did reduce the monaural responses to ipsilateral stimulation. Although GABAergic projections between the ICC on each side were recently reported recently in chinchillas (Casparly and Helfert, 1993), the reciprocal inhibitory projections between the ICC on each side may not be as prominent as the inhibitory projections from the contralateral DNLL.

Comparison between the Ipsilateral SOC and the Contralateral DNLL

Glycine has been shown to be an inhibitory neurotransmitter in the IC (Adams and Wenthold, 1979; Araki et al., 1988; Faingold et al., 1989a, 1991a, b; Glendenning and Baker, 1988; Lopez-Colome et al., 1978; Park and Pollak, 1993; Probst et al., 1986; Sanes et al., 1987; Zarbin, 1981). An extrinsic glycinergic projection to the IC originates from the glycinergic principal neurons in the ipsilateral LSO, and the inhibitory projection to the IC from these LSO neurons has been suggested to explain binaural inhibition in the ICC (Aoki et al., 1988; Saint Marie and Baker, 1990; Saint Marie et al., 1989; Wenthold et al., 1987; Saint Marie et al., 1989). However, the results of the present study indicate that the inhibitory effect of the ipsilateral SOC on the EP IID function in the ICC is very small compared to the inhibitory effect of the contralateral DNLL.

Previous studies have already suggested that the SOC is not the only inhibitory source for IID function of EI neurons in the ICC (Li and Kelly, 1992a; Sally and Kelly, 1992) and that the excitatory responses in the DNLL are partially independent of the sound-evoked activity in the SOC (Li and Kelly, 1993a). These suggestions are confirmed by the present study that indicated that the average effects of blockade of the ipsilateral SOC on the EP IID function were much smaller than the average effects of

blockade of the contralateral DNLL, regardless of whether or not the ipsilateral SOC was blocked initially or subsequently.

Because the effect of the blockade of the ipsilateral SOC was in the same direction as the effect of blockade of the contralateral DNLL, future studies should be conducted on the effect of interaction between the input from ipsilateral SOC and the input from contralateral DNLL on IID functions of single EI cells in the ICC.

The contralateral DNLL has a stronger effect than other structures in the auditory brainstem for the EP IID function in the ICC. A question that should be addressed is whether or not the shift in the EP IID function reflects a real change in the binaural inhibition in the ICC following blockade of the contralateral DNLL.

Comparison between the Shift in the EP IID Function and the Shift in the Ipsilateral Monaural Response

The EP response is a reflection of the combined neural activity of the three main types of cells in the ICC: EI, EO, and EE. After the contralateral DNLL was blocked, the shift in the EP IID function was found to be accompanied by a shift (enhancement of excitation) in the monaural response to ipsilateral stimulation. The shift in EP IID function may reflect a reduction of binaural inhibition in EI neurons as well as an enhancement of monaural excitatory responses to ipsilateral stimulation in EE neurons. Although the population of EI neurons is the predominant one in the rat's ICC (Flammino and Clopton, 1975; Kelly et al., 1991; Li and Kelly, 1992a; Sally and Kelly, 1992; Silverman and Clopton, 1977), it is still essential to separate the monaural effect from the binaural effect to explain the shift in the EP IID function.

Methodologically, there are several strategies that can be used to separate the reduction of binaural inhibition from the enhancement of ipsilateral monaural responses in accounting for the shift in the EP IID function.

First, the recording electrode can be penetrated into a site in the ICC, for which no typical monaural response to ipsilateral stimulation can be recorded. In the present study, the sites that were recorded from in the ICC of 7 rats did not have response to ipsilateral stimulation before the injections of KYNA into the contralateral DNLL. Of the 7 rats, only one displayed a monaural response to ipsilateral stimulation after the blockade of the contralateral DNLL. It is safe to say that in the remaining 6 rats, the shifts in the EP IID functions were due to the reduction of binaural inhibition only.

Second, a comparison can be made between the shift in the EP IID function and the corresponding shift in response to ipsilateral stimulation following blockade of the contralateral DNLL. In the present study, shifts in the monaural responses to ipsilateral stimulation were measured in 18 rats after injections of KYNA were made into the contralateral DNLL. In only 5 of the 18 rats (R316, R318, R305, R306, and R308), the shifts in the monaural responses were close to or larger than the shifts in the EP IID functions in only 5 rats following the injection. The shifts in monaural responses were smaller than the shifts in the EP IID functions in the remaining 13 rats.

Third, multiple injections can be made into the contralateral DNLL and contralateral IC. In the present study, blockade of the contralateral IC in many cases suppressed monaural responses to ipsilateral stimulation but had no consistent effect on the EP IID function. For example, following the initial injection of KYNA into the contralateral DNLL of R305, the shift in monaural responses to ipsilateral stimulation was identical to the shift in the EP IID function. Following subsequent injection of KYNA into the contralateral IC of the rat, the monaural response to ipsilateral stimulation decreased greatly, but the EP IID function curve did not change.

Therefore, the effects of blockade of the contralateral DNLL on binaural and monaural responses may occur independently and the main reason for the shift in EP IID function following blockade of the contralateral DNLL is due to the reduction of binaural inhibition. Since single-unit recording studies have already confirmed that EI neurons in

the rat's ICC make up the majority of the population (Flammino and Clopton, 1975; Kelly et al., 1991; Li and Kelly, 1992a; Sally and Kelly, 1992; Silverman and Clopton, 1977) and that blockade of the contralateral DNLL reduces binaural inhibition in EI neurons of the rat's ICC (Li and Kelly, 1992b; Faingold et al., 1993), it is proposed that the main mechanism underlying the shift in EP IID function in the ICC is the change in the IID function of EI neurons.

In order to gain a further comprehension of the importance of the inhibitory function of the DNLL, we need to understand the functional implication of binaural inhibition for the central representation of auditory space. In the following section, the significance of binaural inhibition will be discussed.

Functional Implications of Binaural Inhibition

It is well known that in the visual and somatosensory systems, the primary sensory cortex represents the spatial location of a stimulus in the contralateral field. In 1982, based on the results of their ablation-behavior study, an important feature of the central auditory system in spatial representation was described by Jenkins and Masterton, namely, auditory space is represented contralaterally above the level of the SOC. The same laterality for spatial representation across the visual, somatosensory, and auditory sensory systems may be essential for cross-modal interaction and production of movement.

In the visual and somatosensory systems, the spatial location of a stimulus produces localized activity at a certain point on the receptor epithelium. In the visual system, through the optic chiasm, the image from the nasal part of retina ascends to the contralateral lateral geniculate body and the superior colliculus, and the image from the temporal part of retina ascends to the ipsilateral lateral geniculate body and superior colliculus. This means that images in the right visual field are only processed by the left visual cortex after decussation of neural connections between the two hemispheres. In the

somatosensory system, the transmission cells (T cells) in the spinal cord or brainstem receive ipsilateral inputs from neurons of the dorsal root ganglion and send their axons across the midline to the contralateral ventroposterior nuclei or posterior thalamic complex, which, in turn, project to S1 or S2 areas of the parietal lobe. However, in the auditory system, the receptors in the cochlea are tonotopically organized, and the position of the hair cells is related to sound frequency rather than to the location of a stimulus in space. Furthermore, information from each ear ascends ipsilaterally as well contralaterally throughout the auditory brainstem to the auditory cortex. This leads one to pose the question of how the contralateral spatial representation in the auditory system is derived.

As mentioned in the INTRODUCTION, almost all monaural and binaural information ascending from the lower auditory system is integrated and sorted in the ICC. The ICC is critical for processing auditory information in the mammal and is also the source of axons that ascend via the brachium of the IC to the auditory thalamus (Adams, 1979; Aitkin and Phillips, 1984a; Goldberg and Moore, 1967; Morest, 1965b). Unilateral lesions confined to the IC of the cat resulted in a loss of the ability to localize sounds in the contralateral hemifield without impairing the ability to localize sounds in the ipsilateral hemifield (Jenkins and Masterton, 1982).

For most mammals, a comparison of the inputs to the two ears is the main basis in the central auditory system for determining sound source location in the azimuthal plane. The head and pinna function as barriers for higher frequency sounds, creating an acoustic shadow opposite the sound source and giving rise to IIDs. With the use of free-field stimuli, it was found that besides the omnidirectional neurons, a large number of directionally sensitive (azimuthally sensitive, azimuth-selective) neurons are present in the ICC of the cat (Aitkin and Martin, 1987; Aitkin et al., 1984; Carford et al., 1986). The majority of directionally sensitive neurons are sensitive to IIDs and would be considered EI cells in dichotic studies (Aitkin et al., 1984). For these IID sensitive neurons, the

relatively high discharge rates that occur in response to sounds at contralateral azimuths decline steeply to low level or to zero when the same stimulus is delivered at ipsilateral azimuths. It has been suggested that the neural mechanisms underlying azimuthal selectivity are likely to be excitatory-inhibitory interactions (Aitkin and Martin, 1987).

Binaural inhibition (EI response) is also very common in the MGB (Adrian et al. 1966; Aitkin, 1973; Aitkin and Webster, 1972) and the AC (Brugge et al., 1969; Kelly and Judge, 1994; Kitzes et al., 1980; Phillips and Irvine, 1981, 1983). It has also been reported that contralateral sound localization deficits occur following unilateral AC lesions in cats (Jenkins and Masterton, 1982; Jenkins and Merzenich, 1984), ferrets (Kavanagh and Kelly, 1987), and squirrel monkeys (Thompson and Cortez, 1983).

Goldberg and Brown (1969) systematically compared the binaural sensitivity of EE and EI neurons in the MSO and the VNTB of the beagle. They found that EE neurons were generally insensitive to IIDs, but were sensitive to overall intensity of the stimulus. Conversely, EI cells were sensitive to IIDs. The general sensitivity of the EI and IE cells of the SOC to IIDs has been confirmed by studies of the LSO in the cat (Boudreau and Tsuchitani, 1968, 1970; Caird and Klinke, 1983; Tsuchitani and Boudreau, 1969) and bat (Harnischfeger et al., 1985), and by a study of the MSO in the rat (Inbody and Feng, 1981).

In the LSO, IE neurons are excited by IIDs for which the ipsilateral stimulus is more intense, and are inhibited over the range of IIDs for which the contralateral stimulus is more intense (Boudreau and Tsuchitani, 1968, 1970; Caird and Klinke, 1983; Tsuchitani and Boudreau, 1969). If we image the sound-evoked activity in the LSO on two sides simultaneously, we can see that the binaural inhibition results in a laterality in the activity of IE neurons in the LSO on two sides. When the sound is in the right hemifield the IE cells of right LSO exhibit excitatory responses to the sound in the ipsilateral hemifield, while the IE cells in the left LSO are inhibited. Several studies indicate that principal neurons of the MNTB are glycinergic (Bledsoe, et al, 1990;

Helfert, et al, 1989; Moore and Caspary, 1983; Peyret, et al, 1987; Wenthold, et al, 1987), and that the LSO receives inhibitory influence from the contralateral AVCN indirectly via the principal cells of MNTB (Elverland, 1978; Glendenning et al., 1985). The glycinergic principal cells of MNTB are responsible for the binaural inhibition in the LSO.

In agreement with Goldberg and Brown's study (1969) of the SOC, the major class of neurons in the ICC exhibiting sensitivity to IIDs are those with an EI binaural response (cat: Geisler et al., 1969; Hind et al., 1963; Moore and Irvine, 1981; Rose et al., 1963; Roth et al., 1978; Semple and Aitkin, 1979; rat: Kelly et al., 1991; Li and Kelly, 1992a, b; Silverman and Clopton, 1977; Sally and Kelly, 1992; kangaroo rat: Stillman, 1972; rabbit: Aitkin et al., 1972b; guinea pig: Popelar and Syka, 1982; brush-tailed possum: Aitkin et al., 1978a; gerbil: Semple and Kitzes, 1985), while the majority of EE cells in the IC are insensitive to IIDs (Geisler et al., 1969; Moore and Irvine, 1981).

If the laterality in spatial representation formed in the ICC is based on IID processing that, in turn, is based on binaural inhibition, another question is: which of the structures in the auditory brainstem are responsible for binaural inhibition in the ICC?

Contribution of the DNLL to Binaural Inhibition in the ICC

The DNLL is an important GABAergic nucleus in the auditory brainstem of the rat and other mammals (Adams and Mugnaini, 1984; Moore and Moore, 1987; Roberts and Ribak, 1987a; Thompson et al., 1985; Glendenning and Baker, 1988). It is predominantly driven by stimulation at the opposite ear (Aitkin et al., 1970; Brugge et al., 1970; Covey, 1992; Li and Kelly, 1993a; Markovitz and Pollak, 1993), and gives rise to prominent projections to the opposite DNLL and IC through the commissure of Probst (Adams, 1979; Bajo et al., 1993; Covey et al., 1987; Hutson et al., 1991; Kudo, 1981; Oliver and Shneiderman, 1989; Shneiderman et al., 1988; Tanaka et al., 1985; Zook and Casseday, 1982). The projections from the DNLL to the contralateral DNLL and IC have axon terminals that contain pleomorphic synaptic vesicles usually associated with

inhibitory function (Oliver and Shneiderman, 1989; Shneiderman and Oliver, 1989). Iontophoretic injection of the GABA_A antagonist, bicuculline, reduces the extent of the binaural suppression of EI responses in the IC (Faingold et al., 1989a, 1991a; Park and Pollak, 1993).

Based on their anatomical results, Adams and Mugnaini (1984) were the first to propose the idea that the DNLL acts as a feed-forward inhibitory nucleus interposed between lower level nuclei and the IC. A similar idea was proposed by Shneiderman et al., (1988). It was also suggested that the DNLL plays a role in maintaining and enhancing the laterality of binaural responses in the auditory pathway (Glenn and Kelly, 1992; Li and Kelly, 1992b; Shneiderman and Oliver, 1989). The inhibitory role of the contralateral DNLL on the binaural inhibition in single EI cells in the ICC was first reported by Li and Kelly (1992b), and was further confirmed by Faingold et al. (1993).

The present study used the EP recording method, for the first time, to measure the inhibitory function of the contralateral DNLL on the activity of the ICC and reinforce the discovery that the contralateral DNLL is an important inhibitory source for binaural inhibition in the ICC (Li and Kelly, 1992b; Faingold et al., 1993).

The binaural inhibition is the main reason for the laterality of the activity of EI neurons between the two ICCs, and the DNLL plays a role in maintaining or enhancing this laterality. Another new discovery from the present study is that the contralateral DNLL also has an inhibitory influence that competes with the ipsilateral excitatory inputs to the ICC. It is not clear whether or not the monaural inhibition from the contralateral DNLL also contributes to spatial representation in the ICC.

In the present study, subsequent blockade of the contralateral DNLL had substantial effects on both the EP IID function and the ipsilateral monaural EP response in the ICC even if the ipsilateral SOC had already been injected with KYNA. These results support our previous finding that the excitatory activity in the DNLL is partially independent of the SOC (Li and Kelly, 1993a).

Furthermore, most of neurons in the DNLL are binaural and display EI response patterns (cat: Aitkin et al., 1970; bat: Covey, 1993; Markovitz and Pollak, 1993). The neurons receiving EI binaural input are sensitive to IIDs (Brugge et al., 1970; Covey, 1993). The laterality of spatial representation may also be coded in the DNLL. It is reasonable to expect that the DNLL may make an important contribution to sound localization. This expectation has been reinforced by two recent research reports. In the ferret, unilateral lesions restricted to the IC had a relatively small effect on sound localization, while more extensive unilateral lesions that included the DNLL, the lateral tegmentum, and the IC resulted in severe deficits in sound localization in the field contralateral to the lesion site (Kelly and Kavanagh, 1994). In the rat, both unilateral and bilateral large kainic acid lesions that completely destroyed the DNLL and some surrounding structures resulted in a severe impairment in sound localization with elevations in minimum audible angles (Kelly and Li, 1993). In the future, the ability of rats to localize sounds in the horizontal plane will be examined using restricted lesions of the DNLL or resections of the commissure of Probst.

Parallel Pathways in Binaural Inhibition

Our previous studies indicated that the DNLL is not the only inhibitory source for binaural inhibition in the ICC (Li and Kelly, 1992b, c). The present study showed that blocking the contralateral DNLL does not completely eliminate binaural inhibition in the ICC in the majority of the subjects.

The SOC may co-operate with the DNLL to determine the binaural response in the ICC. As mentioned in the INTRODUCTION, the ipsilateral LSO may be a source of inhibitory neurotransmission in the ICC, and the contralateral LSO may also contribute to the IID function in the ICC. Binaural suppression is also present in the MSO, particularly the EI pattern in the ipsilateral MSO.

In the present study, injection of KYNA into the ipsilateral SOC reduced the inhibitory strength of the EP IID function to a lesser degree than injection into the contralateral DNLL. It is important to know if there is co-operation between glycinergic and GABAergic transmission in the binaural inhibition in some single EI neurons of the ICC. Furthermore, it would be very interesting to investigate the interactions among the monaural excitatory input (from the contralateral CN), the binaural excitatory input (from the ipsilateral MSO and the contralateral LSO), and the binaural inhibitory input (from the ipsilateral LSO and contralateral DNLL) on the IID functions of single EI cells in the ICC.

Conclusions

This study has been the first to use EP responses to measure the IID function in the ICC of the rat. The results provided three conclusions. (1) The contralateral DNLL plays an important role in shaping the EP IID function in the ICC by promoting binaural inhibition. (2) The ipsilateral excitatory input to the ICC competes with the inhibitory projections from the contralateral DNLL. (3) In the ICC, the EP response to ipsilateral stimulation is partially based on projections from the contralateral IC.

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FIGURES

Figure 1. Photomicrographs illustrating the recording sites in ICC of R356 (plate A) and R318 (plate B). In R356, the recording pipette was penetrated into the ICC in vertical orientation; in R318, the recording electrode was tilted 30° relative to the sagittal plane. Scale bar, 1mm.

Figure 2. Photomicrographs illustrating examples of injection locations in contralateral (right) DNLL of R308 (plate A), ipsilateral (left) DNLL of R318 (plate B), contralateral (right) IC of R308 (plate C), and ipsilateral (left) SOC of R356 (plate D). Scale bar, 1mm.

Figure 2. (continued)

Figure 3. The recording and injection locations for the 7 animals in which KYNA was injected into the contralateral DNLL only. The left-right order of the three diagrams of frontal sections in ICC reflects a caudal-rostral progression (C, caudal; M, middle; R, Rostral).

RECORDING SITES

- R302
- R304
- R310
- R316
- △ R325
- ▲ R350
- + R352

INJECTION LOCATIONS

Figure 4. The recording and injection locations for the 3 animals in which KYNA was injected into the ipsilateral DNLL only. The left-right order of the three diagrams of frontal sections in ICC reflects a caudal-rostral progression (C, caudal; M, middle; R, Rostral).

RECORDING SITES

- R319
- R331
- ▲ R346

INJECTION LOCATIONS

Figure 5. The recording and injection locations for the 2 animals in which KYNA was injected into the contralateral IC only. The left-right order of the three diagrams of frontal sections in ICC reflects a caudal-rostral progression (C, caudal; M, middle; R, Rostral).

RECORDING SITES

□ R303
■ R322

INJECTION LOCATIONS

Figure 6. The recording and injection locations for the animal in which KYNA was injected into the ipsilateral SOC only. The left-right order of the three diagrams of frontal sections in ICC reflects a caudal-rostral progression (C, caudal; M, middle; R, Rostral).

RECORDING SITES

■ R344

INJECTION LOCATIONS

Figure 7. The recording and injection locations for the animals in which KYNA was injected into the ipsilateral DNLL and contralateral DNLL. The left-right order of the three diagrams of frontal sections in ICC reflects a caudal-rostral progression (C, caudal; M, middle; R, Rostral).

RECORDING SITES

- R318
- R329
- ▲ R360

INJECTION LOCATIONS

Figure 8. The recording and injection locations for the animals in which KYNA was injected into the contralateral IC and contralateral DNLL. The left-right order of the three diagrams of frontal sections in ICC reflects a caudal-rostral progression (C, caudal; M, middle; R, Rostral).

RECORDING SITES

- R305
- R306
- △ R307
- ▲ R308
- R309
- R314
- + R317
- × R347

INJECTION LOCATIONS

Figure 9. The recording and injection locations for the animals in which KYNA was injected into the ipsilateral SOC and contralateral DNLL. The left-right order of the three diagrams of frontal sections in ICC reflects a caudal-rostral progression (C, caudal; M, middle; R, Rostral).

RECORDING SITES

□	R301
■	R348
△	R349
▲	R354
○	R355
●	R356
+	R357
x	R359

Figure 9. (continued)

INJECTION LOCATIONS

Figure 10. Three typical averaged auditory evoked potentials in the rat's ICC. During the recording, the tone frequency at either ear was set at the CF. Average amplitude of EPs was determined from 35 or 50 single tone presentations. The amplitude was obtained by measuring the difference in microvolts (μV) between the onset and the peak of the primary response as the arrows indicate. The duration of the stimulus (110ms) is indicated by the *bar at the bottom* of the figure.

Figure 11. The monaural responses to contralateral stimulation for the 7 rats in which KYNA was injected into the contralateral DNLL only. The CF and the sound pressure level of contralateral pure tone are indicated for each animal. *Open squares*, normal; *solid squares*, after injection; *open circles*, following recovery.

R302: CF = 11.95 kHz,
CONTRA = 56 dB SPL

R304: CF = 5.53 kHz,
CONTRA = 56 dB SPL

R310: CF = 22.84 kHz,
CONTRA = 42 dB SPL

R316: CF = 11.50 kHz,
CONTRA = 56 dB SPL

Figure 11. (continued)

R325: CF = 12.0 kHz, CONTRA = 46 dB SPL

R350: CF = 11.83 kHz, CONTRA = 52 dB SPL

R352: CF = 6.15 kHz, CONTRA = 69 dB SPL

Figure 12. The monaural responses to contralateral stimulation for the 3 rats in which KYNA was injected into the ipsilateral DNLL only. The CF and the sound pressure level of contralateral pure tone are indicated for each animal. *Open squares*, normal; *solid squares*, after injection.

R319: CF = 8.62 kHz, CONTRA = 59 dB SPL

R331: CF = 10.87 kHz, CONTRA = 61 dB SPL

R346: CF = 5.63 kHz, CONTRA = 81 dB SPL

Figure 13. The monaural responses to contralateral stimulation for the 2 rats in which KYNA was injected into the contralateral IC only. The CF and the sound pressure level of contralateral pure tone are indicated for each animal. *Open squares*, normal; *solid squares*, after injection.

R303: CF = 11.78 kHz, CONTRA = 58 dB SPL

R322: CF = 11.19 kHz, CONTRA = 52 dB SPL

Figure 14. The monaural responses to contralateral stimulation for the one rat in which KYNA was injected into the ipsilateral SOC only. The CF and the sound pressure level of contralateral pure tone are indicated for the animal. *Open squares*, normal; *solid squares*, after injection.

R344: CF $\approx$ 15.90 kHz, CONTRA = 39 dB SPL

Figure 15. The monaural responses to contralateral stimulation for the 3 rats in which KYNA was injected into the ipsilateral DNLL and the contralateral DNLL. The CF and the sound pressure level of contralateral pure tone are indicated for each animal. The initial injection was made into the ipsilateral DNLL, and the subsequent injection was made into the contralateral DNLL. *Open squares*, normal; *crosses*, following injection into the ipsilateral DNLL; *solid squares*, after injection into the contralateral DNLL.

R318: CF = 6.25 kHz, CONTRA = 48 dB SPL

R329: CF = 4.33 kHz, CONTRA = 69 dB SPL

R360: CF = 11.90 kHz, CONTRA = 67.5 dB SPL

Figure 16. The monaural responses to contralateral stimulation for the 8 rats in which KYNA was injected into the contralateral IC and the contralateral DNLL. The CF and the constant level of contralateral pure tone are indicated for each animal. In R305, R306, R307, R308, R309, and R317, the initial injection was made into the contralateral DNLL, and the subsequent injection was made into the contralateral IC. In R314 and R347, the initial injection was made into the contralateral IC, and the subsequent injection was made into the contralateral DNLL. *Open squares*, normal; *solid squares*, after injection into the contralateral DNLL; *crosses*, following injection into the contralateral IC; *open circles*, following recovery.

R305: CF = 4.67 kHz,
CONTRA = 81 dB SPL

R308: CF = 11.29 kHz,
CONTRA = 58 dB SPL

R307: CF = 5.50 kHz,
CONTRA = 74 dB SPL

R306: CF = 5.70 kHz,
CONTRA = 60 dB SPL

R309: CF = 14.30 kHz,
CONTRA = 45 dB SPL

R317: CF = 5.64 kHz,
CONTRA = 36 dB SPL

Figure 16. (continued)

R314: CF = 5.79 kHz, CONTRA = 74 dB SPL

R347: CF = 5.71 kHz, CONTRA = 71 dB SPL

Figure 17. The monaural responses to contralateral stimulation for the 8 rats in which KYNA or CNQX (only in R348) was injected into the ipsilateral SOC and the contralateral DNLL. The CF and the constant level of contralateral pure tone are indicated for each animal. In R301, R348, R356, and R359, the initial injection was made into the ipsilateral SOC, and the subsequent injection was made into the contralateral DNLL. In R349, R354, R355, and R357, the initial injection was made into the contralateral DNLL, and the subsequent injection was made into the ipsilateral SOC. *Open squares*, normal; *crosses*, following injection into the ipsilateral SOC; *solid squares*, after injection into the contralateral DNLL; *open circles*, following recovery.

Figure 17. (continued)

Figure 18. IID curves for the 7 rats before and after injection of KYNA into the contralateral DNLL. The curves for R350 and R352 also contain the IID curves following recovery from the injection of KYNA. The curves in the left figures describe the IID function in amplitude; the curves in the right figures display the binaural activity in percentage relative to the monaural responses to the contralateral stimulation. The S values for injections are also presented in the figures on the right side. *Open squares*, normal; *solid squares*, after injection into the contralateral DNLL; *broken lines*, repeated measurement; *open circles*, following recovery.

R302

R304

R310

Figure 18. (continued)

R316

R325

Figure 18. (continued)

R350

R352

Figure 19. IID curves for the 3 rats before and after injection of KYNA into the ipsilateral DNLL. The curves in the left figures describe the IID function in amplitude; the curves in the right figures display the binaural activity in percentage relative to the monaural responses to the contralateral stimulation. The S values for injections are also presented in the figures on the right side. *Open squares*, normal; *solid squares*, after injection into the ipsilateral DNLL; *broken lines*, repeated measurement.

R319

R331

R346

Figure 20. IID curves for the 2 rats before and after injection of KYNA into the contralateral IC. The curves in the left figures describe the IID function in amplitude; the curves in the right figures display the binaural activity in percentage relative to the monaural responses to the contralateral stimulation. The S values for injections are also presented in the figures on the right side. *Open squares*, normal; *solid squares*, after injection into the contralateral IC; *broken lines*, repeated measurement.

R303

R322

Figure 21. IID curves for the R344 before and after injection of KYNA into the ipsilateral SOC. The curves in the left figures describe the IID function in amplitude; the curves in the right figures display the binaural activity in percentage relative to the monaural responses to the contralateral stimulation. The S values for injections are also presented in the figures on the right side. *Open squares*, normal; *solid squares*, after injection into the ipsilateral SOC.

R344

Figure 22. IID curves for the 3 rats before and after injections of KYNA into the ipsilateral DNLL and the contralateral DNLL. The initial injection was made into the ipsilateral DNLL, and the subsequent injection was made into the contralateral DNLL. The curves in the left figures describe the IID function in amplitude; the curves in the right figures display the binaural activity in percentage relative to the monaural responses to the contralateral stimulation. The S values for injections are also presented in the figures on the right side. *Open squares*, normal; *crosses*, after injection into the ipsilateral DNLL; *solid squares*, after injection into the contralateral DNLL; *broken lines*, repeated measurement.

R318

R329

R360

Figure 23. IID curves for the 8 rats before and after injection of KYNA into the contralateral IC and the contralateral DNLL. In R305, R306, R307, R308, R309, and R317, the initial injection was made into the contralateral DNLL, and the subsequent injection was made into the contralateral IC. In R314 and R347, the initial injection was made into the contralateral IC, and the subsequent injection was made into the contralateral DNLL. *Open squares*, normal; *solid squares*, after injection into the contralateral DNLL; *crosses*, following injection into the contralateral IC; *broken lines*, repeated measurement; *open circles*, following recovery.

R305

R306

R307

Figure 23 (continued)

R308

R309

R317

Figure 23 (continued)

R314

R347

Figure 24. IID curves for the 8 rats before and after injection of KYNA or CNQX (in R348 only) into the ipsilateral SOC and the contralateral DNLL. In R301, R348, R356, and R359, the initial injection was made into the ipsilateral SOC, and the subsequent injection was made into the contralateral DNLL. In R349, R354, R355, and R357, the initial injection was made into the contralateral DNLL, and the subsequent injection was made into the ipsilateral SOC. *Open squares*, normal; *crosses*, following injection into the ipsilateral SOC; *solid squares*, after injection into the contralateral DNLL; *open circles*, after recovery; *broken lines*, repeated measurement.

R301

R348

R356

Figure 24. (continued)

R359

R349

Figure 24. (continued)

R354

R355

R357

Figure 25. A: The comparison of the average shift scores for the initial injections into the four auditory nuclei. Abbreviations: C-DNLL, contralateral DNLL; I-DNLL, ipsilateral DNLL; C-IC, contralateral IC; I-SOC, ipsilateral SOC. **B:** The comparison of three combined injections, (1) ipsilateral DNLL and contralateral DNLL, (2) contralateral IC and contralateral DNLL, and (3) ipsilateral SOC and contralateral DNLL.

A

B

Figure 26. The excitatory monaural responses to ipsilateral stimulation before and after injection of KYNA into the contralateral DNLL of the 5 animals. *Open squares*, normal; *solid squares*, after injection; *broken lines*, repeated measurement.

R302

R304

R310

Figure 27. The excitatory monaural responses to ipsilateral stimulation before and after injection of KYNA into the ipsilateral DNLL of R319. *Open squares*, normal; *solid squares*, after injection; *broken lines*, repeated measurement.

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Figure 28. The excitatory monaural responses to ipsilateral stimulation before and after injection of KYNA into the contralateral IC of R330 and R322. *Open squares*, normal; *solid squares*, after injection; *broken lines*, repeated measurement.

Figure 29. The excitatory monaural responses to ipsilateral stimulation before and after injection of KYNA into the ipsilateral DNLL and contralateral DNLL of R318 and R360. *Open squares*, normal; *crosses*, after injection into the ipsilateral DNLL; *solid squares*, after injection into the contralateral DNLL; *broken lines*, repeated measurement.

Figure 30 The excitatory monaural responses to ipsilateral stimulation before and after injection of KYNA into the contralateral IC and contralateral DNLL 7 rats. In R305, R306, R308, R309, and R317, the initial injection was made into the contralateral DNLL, and the subsequent injection was made into the contralateral IC. In R314 and R347, the initial injection was made into the contralateral IC, and the subsequent injection was made into the contralateral DNLL. *Open squares*, normal; *solid squares*, after injection into the contralateral DNLL; *crosses*, following injection into the contralateral IC; *open circles*, recovery; *broken lines*, repeated measurement.

Figure 30 (continued)

Figure 30 (continued)

Figure 31. The excitatory monaural responses to ipsilateral stimulation before and after injection of KYNA into the ipsilateral SOC and the contralateral DNLL of 5 rats. In R301, R356, and R359, the initial injection was made into the ipsilateral SOC, and the subsequent injection was made into the contralateral DNLL. In R355 and R357, the initial injection was made into the contralateral DNLL, and the subsequent injection was made into the ipsilateral SOC. Complete data was not provided from the R357. *Open squares*, normal; *crosses*, following injection into the ipsilateral SOC; *solid squares*, after injection into the contralateral DNLL; *open circles*, after recovery; *broken lines*, repeated measurement; *close triangles*, after subsequent injection.

Figure 31 (continued)

Figure 32. The comparison of shifts in the IID function and shifts in the excitatory monaural responses to ipsilateral stimulation for the 5 rats in which KYNA was injected into the contralateral DNLL only. *Open squares*, shifts in the monaural response; *solid squares*, shifts in IID function.

Figure 33. Comparison of shifts in the IID function and shifts in the excitatory monaural responses to ipsilateral stimulation for the 2 rats in which KYNA was injected into the ipsilateral DNLL and the contralateral DNLL. *Open squares*, shifts in the monaural response; *solid squares*, shifts in IID function; *solid lines*, following initial injections; *broken lines*, after combined injections.

R318: IPSI DNLL/CONTRA DNLL

R360: IPSI DNLL/CONTRA DNLL

Figure 34. Comparison of shifts in the IID function and shifts in the excitatory monaural responses to ipsilateral stimulation for the 7 rats in which KYNA was injected into the contralateral IC and the contralateral DNLL. In R305, R306, R308, R309, and R317, the initial injection was made into the contralateral DNLL, and the subsequent injection was made into the contralateral IC. In R314 and R347, the initial injection was made into the contralateral IC, and the subsequent injection was made into the contralateral DNLL. *Open squares*, shifts in the monaural response; *solid squares*, shifts in IID function; *solid lines*, following initial injections; *broken lines*, after combined injections.

R305: CONTRA DNLL/CONTRA IC

R306: CONTRA DNLL/CONTRA IC

R308: CONTRA DNLL/CONTRA IC

Figure 34. (continued)

Figure 34 (continued)

Figure 35. Comparison of shifts in the IID function and shifts in the excitatory monaural responses to ipsilateral stimulation for the 5 rats in which KYNA was injected into the ipsilateral SOC and the contralateral DNLL. In R301, R356, and R359, the initial injection was made into the ipsilateral SOC, and the subsequent injection was made into the contralateral DNLL. In R355 and R357, the initial injection was made into the contralateral DNLL, and the subsequent injection was made into the ipsilateral SOC. *Open squares*, shifts in the monaural response; *solid squares*, shifts in IID function; *solid lines*, following initial injections; *broken lines*, after combined injections.

R301: IPSI SOC/CONTRA DNLL

R356: IPSI SOC/CONTRA DNLL

f1359: IPSI SOC/CONTRA DNLL

Figure 35. (continued)

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