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**The Effect of Kainic Acid Lesions of the Dorsal
Nucleus of the Lateral Lemniscus on Auditory
Cortical Evoked Responses in the Albino Rat:
Interaural Time Delay**

by

Shannon Lynn Glenn, B.A.

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

**Master of Science
Department of Psychology**

**Carleton University
Ottawa, Ontario
May 1, 1991**

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Lateral Lemniscus on Auditory Cortical Evoked Responses in the
Albino Rat: Interaural Time Delay

submitted by Shannon Lynn Glenn, B.A.
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the degree of Master of Science

Thesis Supervisor

Chair, Department of Psychology

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May 1, 1991

Abstract

The cells in the dorsal nucleus of the lateral lemniscus (DLL) of the albino rat were selectively destroyed by microinjections of kainic acid. After at least two weeks of post-operative recovery, evoked potentials were recorded bilaterally from primary auditory cortex. Particular attention was paid to the effects of interaural time delays (ITDs) on auditory cortical evoked potentials, the amplitude of which provides an index of laterality in the auditory system. The recordings were taken from the surface of auditory cortex. Clicks were delivered to each ear independently through sealed loudspeakers inserted into the external meatus. ITDs from $-600\ \mu\text{sec}$ (left stimulus leading right) to $+600\ \mu\text{sec}$ (right stimulus leading left) were examined. The sensitivity to ITDs in normal rats was compared to those obtained from animals with DLL lesions.

In normal animals, the amplitude of click evoked potentials recorded from primary auditory cortex varied with changes in the interaural time difference, the largest responses appearing in the hemisphere contralateral to the ear that was stimulated first. As the ITD was shifted from left to right ear leading, the cortical response in the right hemisphere was reduced in amplitude by approximately 60%. At the same time, the response in the left hemisphere increased in amplitude. The slopes for the ITD functions in the two hemispheres crossed around $\text{ITD}=0\ \mu\text{sec}$. The maximum amplitude variation occurred between $+200$ and $-200\ \mu\text{sec}$. When compared to either normal control cases or animals with misplaced lesions, it was found that unilateral DLL lesions had the effect of significantly reducing the slope of the ITD function in the contralateral hemisphere. No effect was noticed ipsilateral to the lesion. These results suggest that the DLL plays a role in binaural processing through the suppression of responses in the contralateral auditory pathway.

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Introduction

The perception of sound source location is encoded to a large extent by comparing features of acoustic signals at the two ears (Moore, 1982). The dichotic cues for sound localization emerge from the fact that the two ears are separated by an interaural distance, the head, which imposes differences in the time of arrival and sound pressure level (SPL) of the sound at the two ears as the sound source is moved from midline to lateral positions (Moore, 1982; Phillips & Brugge, 1985). Thus, there are two dichotic cues which contribute to the ability of a listener to localize a sound in space; an interaural time cue and an interaural intensity cue.

The Binaural Cues for Sound Localization

The first binaural cue, the interaural time difference (ITD), refers to a disparity in the time of arrival of a sound at the two ears. Any sound source which is located to the left or right of the center in the horizontal plane, will give rise to ITDs because the length of the sound path to the two ears is not equal (Moore, 1982; Phillips & Brugge, 1985). In other words, a sound source will reach the ear closest to the sound source first and the sound must travel a greater distance to reach the contralateral or farther ear. The magnitude of ITDs varies as a function of stimulus location, head size and to a lesser extent, the frequency of the stimulus. For example, ITDs are less pronounced when the sound source is close to the medial plane; as the sound source moves laterally away from midline, the ITDs increase until they reach a maximum at 90 degrees off midline. In addition, ITDs are more pronounced for animals with

larger heads due to a larger interaural distance and hence greater interaural travel times. Finally, ITDs for low frequency stimuli are slightly larger than those for high frequency stimuli. This is due to differences in the diffraction pattern of the sound front around the head (Moore, 1982; Neff et al., 1975; Phillips & Brugge, 1985).

ITDs can be divided into interaural arrival time (transient time differences-TTDs) which refers to a disparity in the onset or offset of a transient sound at the two ears and ongoing phase disparities (interaural phase differences-IPDs) which refer to the differences in the phase relation of a sustained sound at the two ears. TTDs and IPDs are present for all sound frequencies, however, the central nervous system does not have the temporal resolving power necessary to discriminate IPDs at high frequencies (Phillips & Brugge, 1985). Therefore, TTDs can be used to localize all frequencies, including brief stimuli such as clicks, whereas IPDs can only be used to localize low frequency tones.

The second binaural cue for sound localization is the interaural intensity difference (IID) which refers to an intensity disparity at the two ears. IIDs are generated by the acoustic shadow of the head. IIDs are only apparent for high frequency stimuli. Since high frequencies have short wavelengths compared to the size of the head, the head attenuates sounds which originate from lateral azimuths. Thus, the sound shadow decreases the intensity of the sound at the contralateral or farther ear. The magnitude of IIDs is dependent on the frequency and location of the stimulus. Generally, the magnitude of IIDs increases with increasing frequency and becomes progressively larger at lateral azimuths with maximum

IIDs associated with a sound originating at 90 degrees off midline (Phillips and Brugge, 1985). Therefore IIDs can be used to localize only high frequency stimuli.

The Contralateral Representation of Auditory Spatial Location

The idea that nuclei within the central auditory system are specialized for the integration of the binaural disparities that are important for sound localization has been well established. In addition, several lines of evidence suggest that at levels above the lower brainstem, the spatial location of a sound is represented predominantly in the opposite side of the brain (Irvine, 1986). The electrophysiological, metabolic and behavioural evidence for the lateralization of space in higher central auditory nuclei is discussed below.

The evoked cortical response appears to be a good index of laterality at higher levels of the auditory system. Evoked potential studies have demonstrated sensitivity to interaural disparities and provided evidence for the laterality of the auditory system. For example, Rosenzweig (1954) compared the amplitude of the evoked potential response in the left and right cortical hemispheres of the cat, while manipulating ITDs. The stimuli used in this study were clicks. The cortical evoked response was found to be larger in the hemisphere contralateral to the ear which was stimulated first. The amplitudes of the evoked potentials obtained from each hemisphere were found to vary as ITDs were manipulated from -1 msec (left leading right) to +1 msec (right leading left). For example, when the right ear is leading (+1 msec), the amplitude of the response in the

left hemisphere is large. When the left ear is leading (-1 msec), the amplitude of the response in the left hemisphere is quite small. When ITDs in between are manipulated, the amplitude changes proportionately. Thus, it appears binaural stimulation evokes responses at auditory cortex bilaterally, however, the evoked response is found to be greater in the hemisphere contralateral to the ear which is first stimulated.

It has become possible to visualize activity evoked by auditory stimulation, by means of the radioactively-labeled 2-deoxyglucose (2-DG) technique for marking neural tissue of high metabolic activity. Using this technique, Masterton et al. (1981) measured the activity levels in the inferior colliculi of six week old kittens with pulsing white noise which was located 60 degrees to the left of midline. The autoradiographs through the inferior colliculi showed that the activity is bilateral, however, the activity in the contralateral side is greater than that on the ipsilateral side.

Single neuron recording studies have demonstrated that most central auditory nuclei contain neurons which respond to binaural stimuli and are sensitive to interaural time and intensity disparities (e.g. Aitkin et al., 1975; Boudreau & Tsuchitani, 1968; Brugge et al., 1970; Goldberg & Brown, 1969; Kelly & Sally, 1988; Phillips & Irvine, 1981; Rose et al., 1966). It has also been established that the binaurally sensitive neurons in nuclei above the lower brainstem i.e., the dorsal nucleus of the lateral lemniscus, the inferior colliculus, the medial geniculate body, and the auditory cortex, are predominantly excited by contralateral ear stimulation.

Goldberg and Brown (1969) and Aitkin et al. (1975) devised a scheme to classify binaural responses; the scheme uses a three letter code to designate binaural influences. The first two letters indicate the responses to monaural stimulation of the contralateral and ipsilateral ears [usually excitation (E) or no response (O)]. The third letter separated by a slash mark, indicates the binaural interaction type which is inferred from the comparison of monaural and binaural conditions [facilitation (F); inhibition (I); or no difference (O)]. The most common response types of binaurally sensitive neurons are suppression (EO/I) responses and summation (EE/F) responses (Irvine, 1986).

Examination of the monaural responses indicates that binaurally sensitive units at levels above the lower brainstem are predominantly excited by contralateral ear stimulation. For EO/I cells, only contralateral stimulation evokes an excitatory response. Stimulation of the ipsilateral ear produces an inhibitory effect which can not be seen in extracellular responses and is therefore described as (O)/no response (Irvine, 1986). For EE/F cells, the stimulation of both ears evokes an excitatory response, however, stimulation of the contralateral ear generally produces a greater response than that produced by ipsilateral ear stimulation (Irvine, 1986).

Examination of the binaural interactions of both EE/F and EO/I cells reveals that these cells are preferentially driven by contralateral sound sources. More specifically, the binaural responses (suppression and summation) are sensitive to the manipulation of ITDs and IIDs. For an EO/I cell, monaural

contralateral stimulation produces excitation, and stimulation of the ipsilateral ear inhibits the response to contralateral stimulation and is thus termed a suppression response. EO/I cells show a graded excitation over a range of IIDs corresponding to contralateral azimuths and total inhibition over the range of IIDs corresponding to ipsilateral azimuths (Irvine, 1986). Most EO/I cells are also sensitive to TTDs, and are excited by ITDs corresponding to contralateral azimuths (Irvine, 1986). For EE/F cells, stimulation of either ear excites and simultaneous stimulation results in a summation response which is defined as a binaural response which is stronger than the stimulation of one ear alone. EE/F cells are sensitive to ITDs, or more specifically IPDs, and are characterized by maxima at delays corresponding to contralateral azimuths (Irvine, 1986). Thus, the majority of units sensitive to binaural stimulation appear to use the interaural disparities to code for contralateral azimuths.

Behavioural evidence also indicates that the central auditory system is functionally contralateral at higher levels of the auditory system. In general, behavioural studies show that unilateral lesions at levels above the lower brainstem to auditory cortex, result in sound localization deficits in the sound field contralateral to the lesion. Localization on midline and in the ipsilateral hemifield is unimpaired (e.g. Jenkins & Masterton, 1982; Jenkins & Merzenich, 1984; Kavanagh & Kelly, 1983, 1984, 1987; Thompson & Cortez, 1983). The results of these studies also confirm the idea that the spatial location of a sound is represented predominantly on one side of the central auditory system.

Masterton and his colleagues (Jenkins & Masterton, 1982; Masterton & Imig, 1984) have emphasized the importance of two lower brainstem structures, the trapezoid body (TB) and superior olivary complex (SOC) in the production of the contralateral representation of auditory spatial location. TB is a pathway which provides input from the two ears to the SOC and to higher auditory centers. The SOC provides the first opportunity in the auditory pathway for binaural interaction. Unilateral lesions at or below the SOC produce sound localization deficits in the hemifield ipsilateral to the lesion or along the entire horizontal plane. More specifically, lesions of the TB, result in a total incapacity for sound localization (Casseday & Neff, 1975; Jenkins & Masterton, 1982; Masterton et al., 1967). Unilateral kainic acid induced lesions of SOC which spare the fibers of passage, produce severe impairments in sound localization in both lateral sound fields, with most pronounced deficits in the sound field ipsilateral to the lesion (Kavanagh & Kelly, 1986; Kavanagh, 1990). In light of this, one can conclude that the SOC/TB complex contributes to the lateralization of the auditory system (Kavanagh, 1990; Masterton & Jenkins, 1982; Masterton & Imig, 1984).

Recent evidence suggests that the dorsal nucleus of the lateral lemniscus (DLL) plays a unique role as a highly organized inhibitory input to the midbrain auditory system which may ultimately enhance the lateralization of the representation of sounds in space (Adams & Mugnaini, 1984; Moore & Moore, 1987; Schneiderman et al., 1988; Schneiderman & Oliver, 1989; Thompson et al., 1985). Thus, the neural representation of a sound source may somehow depend on

relative amounts of neural activity on the two sides of the higher levels of the auditory system. The possible role of the DLL in the lateralization of sounds in space is discussed following a brief review of the anatomy and physiology of the DLL.

The Role of the DLL in the Lateralization of Sounds in Space

The DLL, which is located in the auditory brainstem, is encapsulated and penetrated by the lateral lemniscus. The DLL is bordered ventrally by the intermediate nucleus of the lateral lemniscus and laterally by the nucleus sagulum. The rostral portion of DLL lies just ventral to the inferior colliculus (Aitkin et al., 1970; Irvine, 1986). Aitkin et al. (1970) reported that the DLL is tonotopically organized with low frequencies represented dorsally and high frequencies represented ventrally. The majority (88%) of DLL neurons respond to binaural stimuli and are maximally stimulated by sounds located in the contralateral hemifield; both EE/F and EO/I response types were encountered and these units were responsive to interaural disparities (Aitkin et al., 1970; Brugge et al., 1970).

The major sources of afferent projections to the DLL are from ipsilateral medial superior olive (MSO), ipsilateral and contralateral lateral superior olive (LSO), ipsilateral and contralateral anterior ventral cochlear nuclei (AVCN) and contralateral DLL (Elverland, 1978; Glendenning et al., 1981; Glendenning & Masterton, 1983; Henkel & Spangler, 1983; Irvine, 1986). Schneiderman et al. (1988) investigated the organization of the afferent projections to DLL using WGA-HRP (wheatgerm agglutinin conjugated HRP) and

[tritiated H]-leucine tracer methods. Their results indicate that the ascending projections to DLL are topographically organized. Low frequency areas of AVCN, MSO, and LSO project to dorsal DLL, while high frequency areas of the same nuclei project to the ventral part. They also noted that there are reciprocal connections between the two DLL which are topographically organized. Thus, their findings indicate that the inputs provide a substrate for a tonotopic map within DLL.

The majority of efferent projections from DLL terminate bilaterally in the central nucleus of the inferior colliculus (ICC) and as mentioned above, in contralateral DLL (Adams, 1979; Brunso-Bechtold et al., 1981; Goldberg & Moore, 1967; Kudo, 1981). Schneiderman et al. (1988) also investigated the organization of the efferent projections from DLL to ICC using WGA-HRP and [tritiated H]-leucine tracer methods. Following injections of the retrograde tracer, WGA-HRP, in the ICC, they found labeled cell bodies in both DLL. Following the injections of the anterograde tracer into DLL, they found that the dorsal portion of DLL (low frequency part) projects to the dorsolateral (low frequency) region of the ICC, while the ventral (high frequency) portion of DLL projects to the ventromedial region of ICC. Schneiderman et al. (1988) have illustrated that both the inputs and outputs exhibit a topographic order and suggest that it is probable that the multiple inputs from DLL merge into a single tonotopic map within ICC. In addition, they reported the projections from DLL to ICC terminate as bands along the fibrodendritic laminae of the ICC which are oriented in a ventrolateral to dorsomedial fashion.

Since the ICC also receives projections from the other major brainstem nuclei which also terminate as bands which are parallel to the laminae of ICC, some investigators have postulated that the bands in ICC may provide a mechanism to sort or concentrate axons from different sources. The banding patterns are discussed below.

The terminal fields of all the major ascending pathways to the ICC exhibit banding patterns (Oliver & Morest, 1984). Injections of anterograde tracers in the cochlear nucleus (CN), LSO, MSO, and DLL each produce unique banding patterns in ICC (Henkel & Spangler, 1983; Kudo, 1981; Oliver, 1984, 1987; Schneiderman & Henkel, 1987; Schneiderman et al., 1988). Schneiderman et al. (1988) noted that for certain nuclei, one side of a bilateral projection is strongly banded while the other side is more diffuse. For instance, the projection from DLL to ICC forms distinct bands on the contralateral side, however, bands on the ipsilateral side are more diffuse (Schneiderman et al., 1988). In contrast, the banding pattern from LSO in ICC is more dense on the ipsilateral side than the contralateral side (Schneiderman & Henkel, 1987; Zook & Casseday, 1987). The relationship between ipsilateral bands and contralateral bands from these nuclei is not known, however, it appears that the ICC receives a highly organized banded input from DLL which extends along the entire frequency range.

It has been suggested that the responses of cells within some bands may be dominated by input from a specific brainstem nucleus, whereas others may combine information from more than one source. However, the relationship between bands from DLL and those from other sources has not been determined (Schneiderman et al., 1988;

Schneiderman & Oliver, 1989). Although the relationship between various bands exhibited in ICC is not known, evidence suggests that the axons from different brainstem nuclei may not have the same excitatory or inhibitory action. For instance, Schneiderman et al. (1988) suggest that excitatory bands are likely to come from afferents to ICC from sources such as CN, LSO, MSO (Casseday & Covey, 1983; Henkel & Spangler, 1983; Oliver, 1984, 1987; Oliver & Morest, 1984; Schneiderman & Henkel, 1987; Zook & Casseday, 1987). For example, CN projections to ICC are banded and have the morphology associated with excitatory function and the excitatory nature of CN input has been confirmed with electrophysiological evidence (Semple & Aitkin, 1980). Schneiderman et al. (1988) suggested that bands in ICC which receive inhibitory input may originate from LSO and DLL. Ipsilateral LSO is a potential source of inhibitory bands; the cells that project to the ICC from LSO ipsilaterally may contain glycine, which is a well known inhibitory neurotransmitter (Glendenning & Baker, 1988; Saint-Marie et al., 1989; Schneiderman & Henkel, 1987). As well, recent evidence indicates that the DLL has large inhibitory projections to ICC and to contralateral DLL.

It is believed that most if not all cells in the DLL contain glutamic acid decarboxylase (GAD- an enzyme for GABA) or gamma-aminobutyric acid (GABA). Immunocytochemical staining of the DLL with a well characterized antiserum to GAD or GABA reveals that all or nearly all cells in the DLL show immunoreactivity (Adams & Mugnaini, 1984; Moore & Moore, 1987; Thompson et al., 1985) which indicates that the cells of DLL contain either the inhibitory

transmitter GABA or at least GAD, the enzyme for GABA.

Schneiderman and Oliver (1989) characterized axonal endings in ICC from DLL projections with [tritiated H]-leucine and EM autoradiographic techniques. Their primary finding was that axonal endings from DLL contain flattened synaptic vesicles and symmetric synaptic contacts. This morphology is associated with inhibitory synapses. In the contralateral ICC, they found only labelled endings with flattened endings. In contrast, in ipsilateral ICC, they found that both endings with flattened vesicles and, to a lesser degree, endings with round vesicles and asymmetric contacts were labeled. Endings with round vesicles have been associated with excitatory synapses. Furthermore, they reported that endings from DLL were more numerous per unit on the contralateral ICC. Therefore, the DLL has a large projection to contralateral ICC which is believed to be strictly inhibitory while the DLL projections to ipsilateral ICC are believed to be both inhibitory and excitatory.

In summary, DLL neurons exhibit immunoreactivity to GAD and GABA antibodies and, furthermore, it appears the crossed projection of DLL to the ICC forms tonotopically organized bands that terminate as endings with flattened vesicles. Therefore, it appears that these endings may supply GABAergic inputs to the ICC. Bands from DLL could provide inhibitory inputs and overlap with bands from other sources that provide excitatory inputs. Schneiderman and his coworkers (1988 & 1989) suggested that these putative overlapping bands may form unique synaptic domains in the ICC. The uncrossed projections from DLL may provide the ICC with a more diffusely organized projection that could include excitatory and inhibitory

inputs. They also suggested that since there are reciprocal connections between DLL on the two sides, activity of DLL on one side could result in the inhibition of DLL neurons on the opposite side. The same axons from DLL may provide inhibitory inputs to the ICC via collaterals.

Schneiderman and his colleagues (1988 & 1989) have postulated that the amount of inhibition produced by DLL in the ipsilateral vs. contralateral ICC may be directly related to the relative acoustic stimulation at the two ears. They stated that equal amounts of stimulation would result in symmetrical activation of the inputs to DLL on both sides and in turn, the outputs of DLL could result in balanced levels of activity on the two sides. However, when sound levels are unequal at the two ears, there will be an uneven activation of the ascending auditory projections and the inputs to DLL. This asymmetrical activation of the multisynaptic pathway could alter the balance of excitatory and inhibitory actions which take place in the auditory midbrain.

The electrophysiological evidence shows that a lateral sound source produces excitation in the contralateral DLL, and in turn, if the projections from DLL are inhibitory, the DLL would inhibit the DLL and ICC ipsilateral to the sound source. Therefore, the role of DLL may be to enhance the lateral representation of a sound in the auditory system by actively inhibiting the nuclei which are ipsilateral to the sound source.

The DLL pathway may regulate ascending inhibition to the midbrain and these presumed inhibitory inputs from DLL could be involved in binaural information processing and contralateral

dominance. One would expect that if this were the case that DLL lesions would result in the release of inhibition in the ICC, which may ultimately result in the loss of sensitivity to binaural cues. Therefore, the present study examined the effect of DLL lesions on the binaural processing of ITDs at the level of the auditory cortex. More specifically, the effects of interaural time delays (ITDs) on cortical evoked potential responses have been examined and compared in rats with DLL lesions, normal control cases and animals with misplaced lesions.

Methods

Subjects

Experiments were conducted on over 20 male Wistar rats (Rattus norvegicus), housed individually, obtained from Charles River Canada, Inc., St. Constant, Quebec. Electrophysiological results were available for only 17 animals. Of these animals, 5 received unilateral lesions of the right (R167, R168 and R173) or left (R171 and R178) DLL. Three animals (R162, R175 and R165) received lesions which spared the DLL. For three other animals (R174, R164 and R170) a cannula was inserted but no kainic acid was injected, due to blockage of the cannula tip. These six animals together form the misplaced lesion group. Six additional animals were used to provide normative data. Of these, 5 received left (R179, R182, and R189) or right (R163, and R172) aspiration of the posterior neocortex and one (R169) received no surgical treatment. Electrophysiological recordings were made in all animals to determine the effects of DLL damage.

Surgical Procedure

Surgical anesthesia was induced with Equithesin (3ml/kg ip), a 500ml aqueous solution containing 21.3 g chloral hydrate, 10.g magnesium sulfate, and 4.8 g pentobarbital sodium. Atropine sulfate (0.05 mg/kg ip) was administered prior to surgery to prevent respiratory distress. The animal was then placed in a stereotaxic instrument which left the ears unobstructed so that no damage was incurred to the tympanic membranes. Following a midline incision, a wide craniotomy was performed to expose the posterior neocortex. The cortical surface was then aspirated until the ventrolateral

portion of the inferior colliculus was clearly exposed.

Lesions were made with kainic acid, an excitatory neurotoxin, injected locally into the DLL. The kainic acid was dissolved in Locke's solution (1mg/ml) prior to surgery. A glass micropipette with a tip diameter of 60-80 microns was inserted stereotaxically into the DLL. Stereotaxic coordinates (bregma 8.8 mm; lateral 2.9 mm; ventral 6.0 mm) were based on the flat skull preparation. The micropipette was connected via sylastic and polyethylene tubing (PE10) to a 10 μ l Hamilton syringe (701). The syringe and tubing were filled with distilled water. Air was drawn into the micropipette until it reached the polyethylene tubing and then the micropipette was filled with kainic acid. The Hamilton syringe was placed in a micropump (Razel 73769) and 1.5 to 2 μ l (11.25 to 15 nmoles) kainic acid was injected at the rate of 1.5 nmoles per minute. The amount of kainic acid injected was gauged by the movement of the air bubble interposed between the kainic acid and the distilled water. To allow for the diffusion of the kainic acid into the surrounding tissues, the cannula was left in the DLL for approximately 5-10 minutes. Gelfoam, moistened with saline was used to cover the exposed inferior colliculus and the scalp was sutured in place. Approximately 45 minutes following surgery, diazepam (4.5 mg/kg ip) was administered as a prophylactic against generalized seizure activity.

Physiological Recordings

Following a recovery period of at least two weeks, the animals were surgically prepared for recording from the auditory cortex. Prior to surgery, the animals were examined with an otoscope to

ensure that the external auditory meatuses and tympanic membranes were free of disease and obstruction. Surgical anesthesia was induced with Equithesin (3 ml/kg ip), and maintained with supplemental doses (0.5 ml/kg ip), administered every 45 minutes. Body temperature was maintained at 37 degrees Celcius with a heating pad during surgery and throughout the duration of the recording session, which typically lasted 10 to 12 hours. The animal's head was secured in a head holder, leaving the ears unobstructed for the insertion of the acoustic couplers. Following a midline incision, a wide craniotomy was performed to expose the auditory cortex.

The animal was then transported to an electrically shielded, sound attenuated room and the head was immobilized in a non-traumatic nose clamp and the earphones were positioned. Clicks were delivered to each ear. Evoked potentials were recorded from silver ball electrodes placed on the dural surface overlying auditory cortex. Potentials were amplified 10,000X, bandpass filtered between 0.3-10,000 Hz (Grass Instruments, Model P511) and averaged on-line (Tracor Northern, Model 1550). Thresholds (the minimum sound pressure level (SPL) necessary to elicit a response) for the left and right cortical evoked potential response were obtained. Thresholds for eliciting an evoked response were determined by lowering the contralateral sound pressure level until no response was detected. The sound pressure was then fixed at approximately 40 dB above threshold in both ears and amplitude and latency measures were obtained. A typical evoked response from the rat's primary auditory cortex is shown in Figure 1. A positive

voltage on the the cortical electrode produced a large downward deflection labeled "P" on the sample waveform. The latency of the response was measured from stimulus onset to the first positive peak, and the amplitude was obtained by measuring the difference in microvolts between the first positive peak and the immediately following negative peak as indicated by the arrows in Figure 1.

 INSERT FIGURE 1 ABOUT HERE

A series of binaural clicks was presented with ITDs ranging from -600 μ sec to +600 μ sec. The order of presentation was randomized according to a predetermined schedule. The particular ITD values which were used are ± 600 , ± 500 , ± 400 , ± 300 , ± 200 , ± 150 , ± 100 , ± 75 , ± 50 , ± 25 and 0 μ sec. These values were selected to provide a detailed description of the amplitude changes between -200 and +200 μ sec according to our previous experience with auditory cortical evoked response in normal animals. Averages of each evoked response were based on 50 stimulus presentations. The entire sequence of ITD values was repeated 10 times to provide a stable data base and a control for possible changes in the response amplitude over time. Therefore, the data obtained from each animal consisted of ten blocks of trials covering the full range of ITD values. For the purpose of comparing the evoked potential responses, the evoked response amplitudes were expressed as a percentage of the maximum response obtained from each hemisphere. Thus, comparisons of the sensitivity of the cortical evoked response to ITD were made using normalized responses.¹ This procedure

Figure 1. An auditory cortical evoked response to click stimuli presented binaurally at the rate of 2/sec. with an interaural time delay of $-400\ \mu\text{sec}$ (left leading right). The response was recorded from the right primary auditory cortex and is based on the average of 50 stimulus presentations. The characteristic component of the cortical response is the large positive deflection shown at "P" which usually has a latency of 10-18 msec. The latency of the response was measured from stimulus onset to the first positive peak (P); the latency of this response was 16 msec. The amplitude was obtained by measuring the difference in microvolts between the first positive peak and the immediately following negative peak (N) as indicated by the arrows. This response had an amplitude of 267 microvolts.

avoided the possible misinterpretation of data due to individual differences in response amplitude. The mean amplitude was plotted as a function of interaural time differences for each animal. The time-amplitude functions for DLL lesion animals were compared to those obtained from a normal control cases and animals with misplaced lesions.

Histological Procedures

Following the recording sessions, the animals with lesions were deeply anesthetized with Equithesin and perfused with saline and 10% formalin. The brains were then immersed in 10% formalin, sectioned at 50 microns and stained with cresyl violet to examine the extent of the lesions. The histological material was examined and the extent of damage was plotted for each case. The classifications used were either complete (96-100%) cell loss, severe (76-95%) cell loss, moderate (46-75%) cell loss, or mild (16-45%) cell loss. Tissue with cell loss which was less than 16% was considered normal. The extent of damage for each case was reconstructed and illustrated at 200 micron intervals on drawings of standard frontal sections through the DLL of a normal rat brain.

Details of the Stimulus

Cortical evoked potentials were elicited by an acoustic click produced by passing a square wave through head phone speakers. Square waves, 100 μ sec in duration, were lead through two passive decade attenuators (Hewlett Packard, Model 350D) and a power amplifier (Aiwa, Model p30). The clicks were transduced by Pioneer stereo headphone drivers (SE-50D) mounted in shielded housings. The stimulus repetition rate was 2/sec. 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. Maximum click intensity in dB SPL (dB re 20 μ Pa) was determined at the earphone opening with a measuring amplifier (Bruel and Kjaer, 2218) and a 1/2 inch condenser microphone (Bruel and Kjaer, 4134).

Results

Kainic Acid Damage

The location of the DLL is indicated in the standard drawing of a coronal section through the rat brain shown in Figure 1 (plate A). The photomicrograph in plate B shows the appearance of the left DLL in R178 following a unilateral kainic acid lesion. As can be seen in plate B, injection of kainic acid resulted in the destruction of nerve cells within the left DLL. The photomicrograph in plate C shows an undamaged right DLL obtained from a normal animal (R179).

INSERT FIGURE 2 ABOUT HERE

Anatomy

(i) Right DLL lesion cases:

The anatomical reconstructions for rats R167, R168 and R173 with right DLL lesions are presented in Figure 3. In two of these cases (R167 and R168), the DLL was only moderately damaged throughout the rostral to caudal extent of the DLL. The intermediate nucleus of the lateral lemniscus (ILL), the ventral nucleus of the lateral lemniscus (VLL), and inferior colliculus (IC) were not damaged. In the third case (R173), the DLL received moderate to severe damage, while the ILL and VLL were also severely damaged.

INSERT FIGURE 3 ABOUT HERE

Figure 2. The location of the DLL is indicated in plate A, a standardized drawing of a coronal section through the rat brain. As can be seen in plate B, unilateral injection of kainic acid into the left DLL (R178) resulted in the destruction of nerve cells within the left DLL. The photomicrograph in plate C shows the right DLL of a normal animal (R179).

Figure 3. Anatomical reconstructions for R167, R168 and R173 with right DLL lesions are shown. For R167 and R168, the DLL was only moderately damaged throughout the rostral to caudal extent of the DLL. The ILL, VLL, and IC of these animals did not sustain any damage. For R173 however, the DLL sustained moderate and severe damage while both the ILL and VLL received severe damage.

R167

Figure 3. Continued

R168

Figure 3. Continued

R173

(ii) Left DLL lesion cases:

The anatomical reconstructions for rats with left DLL lesions (R171 and R178) are presented in Figure 4. For R171, the DLL was moderately damaged, while the ILL and VLL were spared. On the other hand, in the case of R178, the KA injection resulted in near complete damage of the DLL. The ILL, VLL and a small portion of the IC sustained mild to severe damage as well.

 INSERT FIGURE 4 ABOUT HERE

(iii) Misplaced lesion cases:

Three rats (R162, R165 and R175) received unilateral lesions which caused little or no damage to the DLL. For two of these cases (R162 and R175), the micropipette terminated ventral to the DLL on the right side, resulting in damage throughout the ILL and VLL. R162 received severe and complete damage of the ILL and complete damage of the VLL. For R175, the ILL and VLL were completely degenerated. The anatomical reconstructions for these rats are shown in Figure 5. For these cases, no damage was observed in the DLL.

 INSERT FIGURE 5 ABOUT HERE

In R165, the micropipette terminated dorsal and rostral to the DLL on the left side of the brain. In this case, damage was contained within a small portion of the ICC. The anatomical reconstruction for this case is shown in Figure 6.

Figure 4. Anatomical reconstructions for animals which sustained left DLL damage are shown. In R171, the DLL received moderate damage. In this case, damage was contained within the DLL; surrounding tissue was not affected. On the other hand, for R178, all nuclei of the lateral lemniscus sustained damage. The DLL sustained near complete damage and the ILL, VLL and a small portion of the IC received mild to severe damage.

R171

Figure 4. Continued

R178

Figure 5. Anatomical reconstructions for two cases with ILL and VLL damage are shown. For R162, the kainic acid injection resulted in near complete damage to the right ILL, and complete damage to the VLL. In the case of R175, the right ILL and VLL were completely destroyed. For both of these cases, no damage was observed in the DLL.

R162

Figure 5. Continued

R175

INSERT FIGURE 6 ABOUT HERE

For three other cases, the micropipette was inserted into the left DLL (R164), the right DLL (R170), and bilaterally (R174), however, no kainic acid was injected, due to blockage of the cannula tip. The tissue was examined and no apparent damage was found beyond the minimal damage produced by the micropipette.

Physiology:

Auditory evoked potentials were recorded from all animals. Prior to obtaining the amplitude measurements, the thresholds and latencies were established for the responses of both hemispheres using monaural stimulation.

(I) Thresholds:

The thresholds (the minimum SPL necessary to elicit an evoked potential response) were obtained for responses recorded from both hemispheres for all animals. The thresholds ranged from 20 to 69 dB SPL. For the animals with cortical aspiration, the mean thresholds were 50 and 51 dB SPL for the hemispheres ipsilateral and contralateral to the treatment side. For the misplaced lesion group, the mean thresholds were 50 and 49 dB SPL for the hemispheres ipsilateral and contralateral to the lesion site. For the DLL lesion group, the mean thresholds were 38 and 36 dB SPL for the hemispheres ipsilateral and contralateral to the lesion site.

In order to determine whether the aspiration procedure, the misplaced lesions or DLL lesions had an effect on the response

Figure 6. Anatomical reconstruction of an IC lesion is presented for R165. In this case, only a small portion of the left ICC received damage and all nuclei of the lateral lemniscus were spared.

R165

thresholds, an analysis of variance was performed on the response thresholds obtained from both hemispheres for the three groups (see Table 1.). All animals with unilateral intervention, i.e. animals with unilateral lesions or treatments, were included in the analysis to determine whether any of the unilateral treatments had an effect on threshold. Thus, the data obtained from R169 (which received no treatment) and R174 (which received bilateral aspiration of the posterior neocortex) were excluded from the analysis. The results of our analysis indicated that there was no significant difference in threshold between groups or hemispheres (see Figure 7.). Thus, neither the aspiration procedure, the DLL lesions nor the misplaced lesions had any effect on the thresholds of the response.

 INSERT FIGURE 7 ABOUT HERE

(II) Latencies:

The latency of the response was measured from stimulus onset to the first positive peak, and the amplitude was obtained by measuring the difference in microvolts between the first positive peak and the immediately following negative peak. The response latencies obtained for all animals ranged from 10 to 17 msec. For the animals with cortical aspirations, the mean latencies were 14.3 and 14.2 msec for the hemispheres ipsilateral and contralateral to the treatment side. For the misplaced lesion group, the mean latencies were 12.6 and 12.7 msec for the hemispheres ipsilateral and contralateral to the lesion site. For the DLL lesion group, the

Figure 7. The mean thresholds (i.e. the minimum SPL necessary to elicit an evoked potential response) of the evoked potential responses are plotted for DLL lesion, normal control and misplaced lesion cases. The thresholds obtained from the hemisphere ipsilateral to the lesion are represented with unshaded bars, while the thresholds obtained from the hemisphere contralateral to the lesion are represented with shaded bars. There were no significant differences in threshold between hemispheres or among groups.

mean thresholds were 13.7 and 13.0 msec for the hemispheres ipsilateral and contralateral to the lesion site.

An analysis of variance was performed on the response latencies obtained from both hemispheres for the DLL lesion, misplaced lesion and normal control cases (see Table 2.). Again only animals with unilateral intervention were included in the analysis to determine whether any of the unilateral treatments had an effect on latency. No significant differences were found between groups or between hemispheres in evoked response latency (see Figure 8.). Thus, neither the aspiration procedure, misplaced lesions nor DLL lesions had any significant effect on the latency of the response.

 INSERT FIGURE 8 ABOUT HERE

(iii) Evoked potential responses to ITDs: A normal control case:

Auditory cortical evoked potentials at 3 ITDs (-500 μ sec, 0 μ sec, +500 μ sec) for a normal control case (R182) are shown in Figure 9. It can be seen that when recording from the left hemisphere, the amplitude of the response increased as the ITD was shifted from left to right ear leading. The largest amplitude, 56 μ v, was obtained when the right ear lead the left ear stimulation by 500 μ sec, whereas the smallest response (26 μ v) was obtained when the left ear stimulation lead right ear stimulation by 500 μ sec. As the ITD was shifted from right to left in this case the amplitude was reduced by 54%.

Figure 8. The mean latencies of the evoked potential responses are plotted for DLL lesion, normal control and misplaced lesion cases. The latencies obtained from the hemisphere ipsilateral to the lesion are represented with unshaded bars, while the latencies obtained from the hemisphere contralateral to the lesion are represented with shaded bars. There were no significant differences in latency between hemispheres or among groups.

 INSERT FIGURE 9 ABOUT HERE

On the other hand, when recording from the right hemisphere, the amplitude of the response increased as the ITD was shifted from right to left ear leading. In this hemisphere the largest amplitude (78 μv) occurred when the left ear stimulation lead right ear stimulation by 500 μsec . When the ITD was shifted from left to right ear leading by 500 μsec , the amplitude was reduced by 62%, yielding an amplitude of 30 μv . Therefore, for a normal animal, the largest response amplitudes were observed in the hemisphere contralateral to the ear that was stimulated first.

(iv) ITD functions for normal control cases:

The ITD functions for all normal control cases (R169-no treatment; R163 and R172-aspiration of the right posterior neocortex; R179, R182 and R189-aspiration of the left posterior neocortex) are shown in Figure 10. The normalized amplitudes are plotted as a function of interaural time differences for each hemisphere.

 INSERT FIGURE 10 ABOUT HERE

For all control cases, the response amplitudes recorded from the left hemisphere (open squares) increased when the ITD was shifted from left to right ear leading, yielding a positive sigmoidal function. On the other hand, the response amplitudes recorded from

Figure 9. Auditory cortical evoked potentials at 3 ITDs (-500 μ sec, 0 μ sec, +500 μ sec) for a normal case (R182) are shown. For an ITD of -500 μ sec, the stimulation in the left ear leads the right ear by 500 μ sec; for an ITD of 0 μ sec, the left and right ear are stimulated simultaneously; and for an ITD of +500 μ sec, the stimulation in the right ear leads the left ear by 500 μ sec. In the left hemisphere, the amplitude of the response increased as the ITD was shifted from left to right ear leading. As the ITD was shifted from right to left in this case the amplitude was reduced by 54%. In the right hemisphere, the amplitude of the response increased as the ITD was shifted from right to left ear leading. When the ITD is shifted from left to right ear leading by 500 μ sec, the amplitude was reduced by 62%.

AUDITORY CORTICAL EVOKED POTENTIALS

NORMAL CASE

Figure 10. The ITD functions for all control cases (R169, R163, R172, R179, R182 and R189) are presented. The amplitudes are plotted as a function of interaural time differences for each hemisphere. The amplitudes presented are normalized (expressed as a percentage of the maximum response amplitude). The open squares in each function indicate the left hemisphere response, while the filled squares indicate the right hemisphere response. The response amplitudes recorded from the left hemisphere increased when the ITD was shifted from left to right ear leading, yielding a positive sigmoidal function, whereas the response amplitudes recorded from the right hemisphere increased when the ITD was shifted from right to left ear leading, thus yielding a negative sigmoidal function. The slopes for the ITD functions from the two hemispheres cross around $\text{ITD}=0 \mu\text{sec}$. In most cases, the maximum amplitude variation of the potential occurred between -200 and $+200 \mu\text{sec}$, while there was very little amplitude variation beyond these values.

the right hemisphere (filled squares) increased when the ITD was shifted from right to left ear leading, thus yielding a negative sigmoidal function. The slopes for the ITD functions in the two hemispheres cross around $ITD=0 \mu\text{sec}$.

The largest response amplitudes are seen in the hemisphere contralateral to the ear that is stimulated first and the smallest responses appear in the hemisphere ipsilateral to the ear that is stimulated first.

It is important to note that in most cases, the maximum amplitude variation of the potential occurred between -200 and $+200 \mu\text{sec}$, while the amplitude variation was minimal for ITDs beyond these values. The range over which the evoked potential showed sensitivity to ITDs remained fairly constant for all control animals.

(v) ITD functions for misplaced lesion cases:

The ITD functions for the misplaced lesion cases are shown in Figure 11. The first two functions were obtained from animals (R162 and R175) with right ILL and VLL lesions. The third was obtained from an animal (R165) with a small left ICC lesion; the last three functions were obtained from animals which received left (R164), right (R170) and bilateral (R174) aspiration of the posterior neocortex. For these animals a cannula was also inserted into DLL, however, kainic acid was not injected, due to blockage of the cannula.

 INSERT FIGURE 11 ABOUT HERE

Figure 11. The ITD functions for the misplaced lesions (R162, R175, R165, R164, R170 and R174) are shown. The response amplitudes recorded from the left hemisphere (represented with open squares) increased as the ITD was shifted from left to right ear leading, yielding a positive sigmoidal function and the response amplitudes recorded from the right hemisphere (represented with filled squares) increased as the ITD was shifted from right to left ear leading, yielding a negative sigmoidal function. The slopes for these ITD functions cross around $ITD=0 \mu\text{sec}$. In most cases, the maximum amplitude variation occurred between $+200$ and $-200 \mu\text{sec}$, while there was very little amplitude variation beyond these values.

It is clear that these functions are similar to those of the control cases discussed above. The response amplitudes recorded from the left hemisphere (open squares) also increased as the ITD was shifted from left to right ear leading, yielding a positive sigmoidal function and the response amplitudes recorded from the right hemisphere (filled squares) also increased as the ITD was shifted from right to left ear leading, yielding a negative sigmoidal function. The slopes for these ITD functions also cross around ITD=0 μ sec. For most of these cases, the maximum amplitude variation occurred between +200 and -200 μ sec.

(vi) Evoked potential responses to ITDs: A right DLL Lesion case:

Examples of auditory cortical evoked potentials for a right DLL lesion case (R173) are shown in Figure 12. The evoked potentials recorded from the right hemisphere are similar to those of the normal case; the response amplitudes increase as the ITD is shifted from right (52 μ v) to left (177 μ v) ear leading. In this case, as the ITD was shifted from left to right ear leading the response was reduced by 70%. In contrast, the evoked potentials recorded from the left hemisphere are different from those of the normal animal. The amplitudes do not vary with the ITD, instead they remain relatively constant when the ITD is shifted from left to right ear leading. Thus, the responses recorded from the hemisphere ipsilateral to the lesion are normal but the responses recorded from the hemisphere contralateral to the lesion show little or no change in amplitude.

 INSERT FIGURE 12 ABOUT HERE

(vii) ITD functions for unilateral DLL lesion cases:

The ITD functions obtained from animals with unilateral DLL lesion cases are presented in Figure 13. The first three functions were obtained from animals (R167, R168 and R173) with right DLL lesions. The other two were obtained from animals with left DLL lesions (R171 and R178). The ITD functions obtained from the hemisphere ipsilateral to the lesion are similar to those of the control and misplaced lesion cases. The response amplitudes are largest when the contralateral ear is stimulated first. For most of these cases maximum variability is seen between -200 and +200 μ sec. The ITD functions obtained from the hemisphere contralateral to the lesion were different from those of the control and misplaced lesion cases in that the variation in the response amplitudes at different ITDs was minimal. It is clear that there was a large reduction in the slopes obtained from these ITD functions when compared to those obtained from ITD functions from the hemispheres ipsilateral to the lesion.

 INSERT FIGURE 13 ABOUT HERE

(viii) Statistical analyses:

Our previous and present experience with auditory cortical evoked responses indicated that the maximum amplitude variation of the potentials occurs between -200 and +200 μ sec, whereas the

Figure 12. Auditory cortical evoked potentials for a right DLL lesion case (R173) are shown. In the right hemisphere, the response amplitudes increased as the ITD was shifted from right to left ear leading. In this case, as the ITD was shifted from left to right ear leading the response was reduced by 70%. In contrast, in the left hemisphere, the response amplitudes did not vary with the ITD, instead they remained relatively constant when the ITD was shifted from left to right ear leading.

AUDITORY CORTICAL EVOKED POTENTIALS

RIGHT DLL LESION CASE

Figure 13. The ITD functions for animals with right DLL lesions (R167, R168, and R173) and left DLL lesions (R171 and R178) are shown. The open squares in each function indicate the left hemisphere response, while the filled squares indicate the right hemisphere response. In the hemisphere ipsilateral to the lesion, the response amplitudes were largest when the contralateral ear was stimulated first. For most, the maximum variability was seen between -200 and +200 μ sec. In the hemisphere contralateral to the lesion, the response amplitudes did not vary with the manipulation of ITD, they remained relatively constant.

RIGHT DLL LESION CASES

LEFT DLL LESION CASES

amplitude variation is minimal for ITDs above +200 μ sec and below -200 μ sec. We, therefore, chose to examine the slopes of the time-amplitude functions at -200 and +200 μ sec for each hemisphere. An analysis of variance was performed on the slopes obtained from both hemispheres for all groups. The slopes were obtained from a linear best line of fit of the data for each ITD function between -200 and +200 μ sec. Again, only animals with unilateral surgical intervention were used in the analysis to assess the effects of the treatments on the slopes obtained from the ITD functions. The results indicated that there was a significant interaction ($F=24.4, p<.0001$, see Table 3.) between the surgical treatment group and hemisphere from which the recording was made. It was found that the slopes of ITD functions obtained from the hemisphere contralateral to the lesion were greatly reduced in the case of animals with DLL lesions. For DLL lesion cases there was a significant difference between the mean slopes obtained from hemispheres ipsilateral and contralateral to the lesion. The slopes from the hemisphere contralateral to the lesion were significantly reduced compared to those of obtained from ITD functions from the hemisphere ipsilateral to the lesion. No difference was found between the slopes obtained from the hemisphere ipsilateral to the treatment and contralateral to the treatment for control and misplaced lesion cases.

INSERT FIGURE 14 ABOUT HERE

Figure 14. The mean slopes derived from the ITD functions from both hemispheres are plotted for the DLL lesion group, the control group and the misplaced lesion group. The mean slopes obtained from the hemisphere ipsilateral to the treatments are represented with unshaded bars, while the mean slopes obtained from the hemisphere contralateral to the treatments are represented with shaded bars. The mean slopes for the control and misplaced lesion groups are similar for both hemispheres, however, the mean slope obtained from the hemisphere contralateral to the DLL lesion is significantly less compared to the mean slope obtained from the hemisphere ipsilateral to the lesion.

Discussion

The results of the present study indicate that the DLL plays a significant role in determining the contralateral representation of auditory space at levels above the superior olivary complex (SOC). Whereas the basic contralaterality of auditory electrophysiological and behavioral responses is already established at the level of the SOC through the neural interactions produced by small differences in the time and intensity of sounds at the two ears, the DLL clearly makes a further contribution at midbrain levels and above. The present findings show that a unilateral lesion of DLL in the albino rat dramatically alters the sensitivity to binaural time differences in the hemisphere contralateral to the lesion site. This effect is likely due to the destruction of the predominantly inhibitory pathway from DLL to the contralateral auditory midbrain by way of the commissure of Probst. The following discussion will consider first the binaural mechanisms in the SOC responsible for establishing contralateral spatial representation in the auditory pathway. Second, the contribution of DLL will be considered and possible mechanisms for supraolivary binaural processing will be discussed. Finally, a model will be presented suggesting a combined role of inhibitory projections from the SOC and DLL to auditory midbrain structures for sharpening the contralateral representation already established at the lower brainstem.

Acoustic Chiasm: The Binaural Basis for Contralateral Dominance

The SOC is an important structure for establishing the contralaterality of auditory space. It serves a role not unlike that

of the optic chiasm in the visual pathway in providing crossed spatial representation. Although the anatomical connections and physiological mechanisms are quite different from those found in the visual pathway, the trapezoid body (TB) and the SOC have been referred to as a functional "acoustic chiasm" (Masterton and Imig, 1984). Both physiological and behavioral data support the idea that the auditory system has a contralateral organization that parallels the visual, somatosensory and motor systems. First, auditory evoked potentials recorded from either the acoustic midbrain or auditory cortex are much larger contralateral to a free field sound source or under conditions in which dichotic stimuli favor the contralateral ear (Rosenzweig, 1951,1954; Rosenzweig & Wyers, 1955). Also, single neurons in the auditory tectum, medial geniculate body and auditory cortex are predominantly driven by contralateral sounds presented under either free field or dichotic conditions (Aitkin ,1973; Aitkin et al., 1973,1975; Brugge et al., 1970; Kelly & Sally, 1988; Phillips & Irvine, 1981; Rose et al., 1966). Second, behavioural evidence has shown that unilateral lesions of auditory structures above the SOC, including the lateral lemniscus, brachium of the inferior colliculus, medial geniculate or auditory cortex, result in contralateral sound localization deficits (Jenkins & Masterton, 1982; Jenkins & Merzenich, 1984; Kavanagh & Kelly, 1983,1984,1987; Thompson & Cortez, 1983). In contrast, lesions of the TB result in sound localization impairments along the entire horizontal plane, or predominantly within ipsilateral hemifield (Casseday & Neff, 1975; Jenkins & Masterton, 1982; Masterton et al., 1967). Unilateral lesions of the SOC with kainic acid, a neurotoxin

that destroys cell bodies but leaves fibers of passage in the trapezoid intact, also produce pronounced deficits in sound localization in both hemifields, with a tendency toward more pronounced effects in the hemifield ipsilateral to the lesion (Kelly & Kavanagh, 1986, 1990). These data have led to the conclusion that the SOC plays an important role in establishing the contralateral neural representation of auditory space.

The contralaterality of physiological responses in the auditory pathway is determined partly by the manner in which binaural information is processed by the SOC. Binaural cues (interaural time and intensity differences) associated with lateral sound source positions create left-right imbalances in the electrophysiological activity in the MSO and LSO related to the location of a sound in space. Neurons located in the lateral superior olive (LSO) are preferentially excited by sound sources in the ipsilateral field due to the pattern of binaural interplay between left and right ear stimulation. The LSO receives a direct excitatory input from the ipsilateral ventral cochlear nucleus and an indirect inhibitory input from the contralateral ventral cochlear nucleus by way of the medial nucleus of the trapezoid body (Harrison & Warr, 1962; Stotler, 1953; Warr, 1966). The firing rate of most cells in the LSO is therefore maximal under conditions in which the ipsilateral ear either leads or is stimulated more intensely than the contralateral ear. These binaural conditions are associated with ipsilateral free field sound sources (Boudreau & Tsuchitani, 1968, 1970; Caird & Klinke, 1983; Guinan et al., 1972; Harnischfeger et al., 1975; Tsuchitani, 1977; Tsuchitani & Boudreau, 1969).

In contrast, the cells in MSO are predominantly driven under dichotic conditions that favor the contralateral ear as expected with contralateral free field sound source positions. The MSO receives direct projections from both left and right ventral cochlear nucleus (Goldberg & Brown, 1968; Guinan et al., 1972a,b; Harrison & Irving, 1966; Inbody & Feng, 1981; Stotler, 1953; Strominger & Strominger, 1971; Warr, 1966; van Noort, 1969). Thus, the majority of MSO neurons are excited by stimulation of either ear alone and are sensitive to the timing of binaural input. Binaural stimulation yields an enhanced response based on the coincidence of excitatory synaptic activity from the two ears. Maximal firing rate is associated with the optimal delay between the two ears that will produce synchronous discharges at the MSO. For most MSO neurons of this type the critical delay is one in which the contralateral ear is leading, as expected for a contralateral sound source. In addition, a substantial population of neurons in MSO are excited by contralateral stimulation and inhibited by ipsilateral stimulation (Goldberg & Brown, 1968; Guinan et al., 1972a,b; Inbody & Feng, 1981). Also, these neurons are excited primarily by contralateral auditory stimulation. Thus, if a sound source occupies a lateral position in the horizontal (azimuthal) plane, neural activity will be generated primarily in the ipsilateral LSO and contralateral MSO, and as the sound source is moved progressively toward the midline the imbalance in neural activity will be systematically reduced.

The physiological responses in both DLL and ICC are overwhelmingly driven by contralateral sound sources. The majority of neurons in these structures are sensitive to binaural stimulation

and their responses can be classified as either binaural summation or suppression (Aitkin et al., 1975; Brugge et al., 1970; Kelly et al., 1989; Rose et al., 1966; Roth et al., 1978; Semple & Aitkin, 1978). In the case of binaural summation responses (EE/F), the neurons are excited by stimulation of either ear alone and are facilitated by stimulation of both ears at appropriate binaural levels and delay times. On the average, the response of these cells is maximal under conditions that favor the contralateral sound field. In the case of binaural suppression responses (EO/I), the neurons are excited by stimulation of the contralateral ear and are profoundly inhibited by stimulation of the ipsilateral ear, so that the maximal response is associated with contralateral sound field locations.

The contralateral dominance of electrophysiological responses at the auditory midbrain is at least in part a reflection of the convergence of the excitatory output from binaural neurons in the auditory lower brain stem. Specifically, both MSO and LSO probably contribute to the contralateral representation of auditory space at midbrain and forebrain levels through their ascending projections to DLL and ICC. The cells in MSO, which on the whole exhibit preferential responses to contralateral sound sources, have an almost exclusively ipsilateral projection to both the ICC and DLL (Adams, 1979; Aitkin & Schuck, 1985; Beyerl, 1978; Brunso-Bechtold et al., 1981; Coleman & Clerici, 1987; Elverland, 1978; Glendenning & Masterton, 1983; Henke & Spangler, 1983; Zook & Casseday, 1982). Therefore, the physiological responses of at least some binaurally sensitive cells in DLL and ICC are probably attributable to the excitatory output of MSO neurons. The binaural response

patterns in DLL and ICC are consistent with the contralateral response bias seen in MSO. The cells in LSO, which are driven primarily by ipsilateral stimulation and inhibited by contralateral stimulation, contribute to the contralateral midbrain and forebrain responses through their largely contralateral excitatory projection to DLL and ICC (Glendenning & Masterton, 1983; Glendenning et al., 1985; Hutson et al., 1987; Saint Marie et al., 1989). Thus, the ipsilateral excitation of cells in the LSO is manifested as contralateral excitation in cells in the auditory midbrain and above. The LSO also has a substantial ipsilateral projection to DLL and ICC, which has been shown recently to be 'largely, although not exclusively, glycinergic (Saint Marie et al., 1989; Hutson et al., 1987). This projection, therefore, provides a predominantly inhibitory rather than excitatory input to the auditory midbrain. This inhibitory nature of the ipsilateral LSO projection probably accounts for the relative paucity of ipsilaterally activated neurons in both DLL and ICC. The converging excitatory output of MSO and LSO neurons onto neurons located in contralateral ICC is illustrated in Figure 15.

 INSERT FIGURE 15. ABOUT HERE

Supraolivary Binaural Interactions: Role of DLL

It has been widely assumed that all binaural interactions in the auditory pathway are merely a reflection of the activity originating in the SOC. Recent evidence, however, has suggested that binaural interactions do occur at levels above the SOC and that

Figure 15. A schematic diagram depicting the major excitatory and inhibitory influences on auditory midbrain structures. A sound source located on the right (represented by the black loudspeaker) will evoke maximal neural activity in the LSO on the right and the MSO on the left (as indicated by black shading). In addition, the DLL on the left side of the brain will be activated (shaded black). The projections of these nuclei will result in a convergence of excitatory activity onto the left ICC and a convergence of inhibitory activity onto the right ICC. Thus, there is a net excitation of auditory midbrain structures contralateral to the sound source and a net inhibition of structures ipsilateral to the sound source.

A sound positioned in the left lateral field will evoke a mirror image pattern of neural activity in the auditory pathway as indicated by unshaded structures.

supraolivary brainstem structures might contribute to the contralateral organization of the auditory system. First, anatomical studies have revealed decussating pathways above the SOC that provide a potential substrate for binaural interaction in the auditory brainstem (Hutson 1988), thus extending the concept of an "acoustic chiasm" to include supraolivary as well as olivary nuclei. Second, electrophysiological recordings from the ICC have provided evidence that binaural interactions occur directly on single neurons in ICC. For example, Nelson and Erulkar (1963) in their study of intracellular potentials in ICC found that contralateral auditory stimulation was capable of producing an excitatory postsynaptic potential (EPSP) and ipsilateral stimulation an inhibitory postsynaptic potential (IPSP) on the same nerve cell. In this case, the binaural interaction was due to local synaptic effects. Also, Faingold et al (1989b) in their study of the pharmacology of the ICC neurons encountered numerous cells in which iontophoretic application of GABA antagonists blocked ipsilateral inhibition of EI cells. These data indicate that contralateral excitation and ipsilateral inhibition converge locally on single units in ICC. In addition, Sally and Kelly (1990) have shown that complete bilateral kainic acid lesions of the SOC in the rat shift binaural sensitivity but do not eliminate binaural interactions recorded from neurons located in the ICC. The binaural responses that remain are attributed to supraolivary interactions.

Neuroanatomical studies (Schneiderman et al., 1988; Schneiderman & Oliver, 1989) have focussed attention on the DLL as a possible source of supraolivary interactions that might serve to

enhance the contralateral representation of auditory space. Immunocytochemical and electron microscopic data have shown that the DLL sends a major GABAergic projection to the contralateral ICC by way of the commissure of Probst. Since GABA is a well known inhibitory neurotransmitter in the central nervous system, this projection probably serves to suppress physiological responses on the opposite side of the brain. The mutual inhibition of auditory midbrain structures that is implied by these anatomical data would have the effect of exaggerating any imbalance of activity already present in the auditory pathway. With a lateralized sound source one would expect greater activity in the contralateral rather than the ipsilateral ascending auditory projections to DLL and ICC. This asymmetry would then be accentuated by the inhibitory projection from DLL onto structures located ipsilateral to the sound source. In other words, when a sound source is lateralized, the DLL projection to ICC amplifies the difference in neural activity between left and right sides of the brain by imposing a net inhibitory influence on the side with the lower activity level.

The present results demonstrate physiological consequences of DLL lesions that are generally consistent with the anatomical studies of Schneiderman and his colleagues. First, kainic acid lesions selectively disrupt binaural processing in the hemisphere contralateral to the lesion. No effect is seen in the ipsilateral hemisphere. This result is compatible with the idea that the critical pathway involved in producing an abnormal response is the contralateral projection from DLL to the opposite side of the brain. Second, the effect of a unilateral DLL lesion is to reduce the

suppression of response amplitude that normally accompanies binaural stimulation. The flattening of the binaural time difference by response amplitude function is due to the failure of ipsilateral stimulation to produce the expected reduction in amplitude rather than a diminution of the response itself. Indeed, destruction of the DLL produces no overall reduction in response amplitude on either side of the brain. This lack of reduction would be expected if the DLL lesion eliminated GABAergic inhibition to the opposite ICC as predicted from immunocytochemical and anatomical studies. Finally, it is important to note that the effect is specific to DLL. In the present study, no abnormalities in evoked potential response amplitude were observed for animals with ILL, VLL, or ICC lesions. Only lesions that included DLL resulted in a reduction in the slope of the ITD function. Also, the thresholds and latencies for the DLL lesion group were similar to those obtained from the control and misplaced lesion groups. Therefore, the effects observed for DLL cases are not likely due to a shift in the latency or threshold of the evoked potential.

The Role of Inhibition In Contralateral Representation

The DLL is not the only source of inhibition that might serve to enhance the difference between ipsilateral and contralateral responses in the auditory pathway. In addition, the efferent projections from the lateral superior olive (LSO) might play a role. As mentioned above, the LSO has a bilateral projection to the DLL and ICC. The contralateral projection is thought to be excitatory, providing a major source of contralateral drive in the auditory pathway. The ipsilateral projection, on the other hand, contains a

large proportion of fibers that label positively for glycine, one of the major inhibitory neurotransmitters in the central nervous system. This projection, therefore, is a likely source of inhibition on cells in the DLL and ICC. Given that both DLL and LSO have inhibitory inputs to the ICC, it is likely that these two sources of inhibition act in a synergistic fashion to suppress activity in the auditory pathway ipsilateral to a lateralized sound source, thus enhancing the difference in activity between left and right sides of the brain.

The proposed convergence of ipsilateral inhibitory influences from the DLL and LSO and their relation to excitatory effects from LSO and MSO are illustrated in the model presented in Figure 15. According to this model, the contralateral representation of auditory space would first be established by binaural interactions in LSO and MSO. The excitatory output of MSO and LSO converge to produce a net increase in neural activity in the auditory pathway contralateral to a sound source. At the same time, neural activity in the pathway ipsilateral to the sound source is actively suppressed by inhibitory projections from LSO and DLL, the former mediated by glycine and the latter by GABA. Both sources of lateral inhibition would have the effect of enhancing the contrast between ipsilateral and contralateral responses and increasing the signal to noise level between activity on the two sides of the brain.

From this model, one would predict that binaural processing could be disrupted not only by lesions of the DLL but also by damage to the ipsilateral projections from LSO to the auditory midbrain. In support of this idea, it has recently been found that unilateral kainic

acid lesions of the SOC result in a reduction of the slope of binaural time difference by evoked response amplitude functions in the auditory cortex ipsilateral to the lesion (Sally & Kelly, unpublished observations). The effect is similar to that produced by unilateral lesions of DLL but is restricted to the hemisphere ipsilateral rather than contralateral to the damaged nucleus. This result suggests that normally the suppression of cortical evoked responses produced by binaural stimulation is a product of both ipsilateral glycinergic inhibition from LSO and contralateral GABAergic inhibition from DLL. The presence of inhibition from LSO may account for the fact that a unilateral DLL lesion does not completely reduce the slope of binaural time difference functions to zero. Further studies are needed to determine the relative contribution of DLL and LSO to the slope of such functions. Experiments with combined lesions or pharmacological blockage of glycinergic and GABAergic inhibition should shed light on this issue.

Behavioural Implications and Future Studies:

The effects of DLL lesions on binaural response functions suggest that DLL might be important for accurate sound localization. Sound localization in the horizontal plane depends upon binaural cues, small differences in the intensity and time of arrival of sounds at the two ears. Lesions of central nervous system structures involved in binaural processing, either section of the TB (Casseday and Neff, 1975; Jenkins and Masterton, 1982; Masterton et al., 1967; Moore and Casseday, 1974) or destruction of the SOC (Kavanagh and Kelly, 1986,1990), result in severe deficits in sound localization. If the DLL makes a major contribution to binaural

processing, as indicated by the present study, then damage to the DLL should have a profound effect on sound localization ability. So far however, there have been no behavioral studies of the effects of selective lesions of the DLL.

Future studies of DLL should include behavioral assessments of the effects of kainic acid lesions on sound localization. Because destruction of DLL decreases the sensitivity of physiological responses to binaural time differences, one might expect DLL lesions to affect the acuity with which judgements about sound source location are made. Bilateral lesions of DLL would be expected to increase the minimum audible angle (the angle of speaker separation necessary for an animal to detect a change in the azimuthal location of a sound source) for detecting sound source position in the horizontal plane and unilateral lesions might be expected to have effects restricted to or selective for sound localization in the ipsilateral sound field.

Conclusions:

- 1) Unilateral kainic lesions of DLL reduce the slope of binaural time difference by evoked response amplitude functions in primary auditory cortex contralateral to the lesion.
- 2) The effect is not due to a reduction in evoked response amplitude but rather is produced by an abnormal lack of suppression as ipsilateral ear lead time is increased. This effect is probably due to the elimination of synaptic inhibition associated with projections from DLL to contralateral ICC.
- 3) Unilateral DLL lesions have little or no effect on evoked response amplitude or binaural time sensitivity in the hemisphere ipsilateral

to the lesion.

4) No discernible effect is produced by massive unilateral lesions of the intermediate and ventral nuclei of the lateral lemniscus. Therefore, the reduction in contralateral suppression is due specifically to the DLL.

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Appendix

Table 1**ANOVA Summary for Thresholds**

Source	Degrees of Freedom	Sum of Squares	Mean Square	F Value	P Value
-----	-----	-----	-----	-----	-----
ST	2	1192.2	596.1	2.74	.105
Subjs. w. ST	12	2614.6	217.9		
H	1	1.6	1.6	0.20	.664
ST x H	2	7.3	3.6	0.44	.653
H x Subjs. w. ST	12	98.6	8.2		
-----	-----	-----	-----	-----	-----
ST= Surgical Treatments					
H= Hemisphere					

Table 2

ANOVA Summary for Latencies

Source	Degrees of Freedom	Sum of Squares	Mean Square	F Value	P Value
ST	2	12.87	6.43	1.15	.35
Subjs. w. ST	12	67.30	5.61		
H	1	0.41	0.41	0.46	.51
ST x H	2	0.86	0.43	0.49	.62
H x Subjs. w. ST	12	10.60	0.88		

ST= Surgical Treatments

H= Hemisphere

Table 3**ANOVA Summary for Slopes**

Source	Degrees of Freedom	Sum of Squares	Mean Square	F Value	P Value
ST	2	1.10	0.55	5.95	.016
Subjs. w. ST	12	1.11	0.09		
H	1	0.25	0.25	14.08	.0028
ST x H	2	0.86	0.43	24.54	.0001
H x Subjs. w. ST	12	0.21	0.02		

 ST= Surgical Treatments

H= Hemisphere

Simple Effects**Hemisphere within Surgical Treatments****Hemisphere at DLL Lesions**

F=62.43* F(Crit)=9.33 df=1,12 p<.001

Hemisphere at Misplaced Lesions

F<1 F(Crit)=9.33 df=1,12

Hemisphere at Controls

F<1 F(Crit)=9.33 df=1,12

Table 4.**Absolute Amplitudes**

The average maximum absolute amplitudes recorded from the hemispheres ipsilateral to the lesion and contralateral to the lesion for each animal are shown.

Control:

Animal No.	ipsilateral	contralateral
R179	58.7	62.1
R182	56.6	52.5
R189	66.6	74.0
R163	76.2	147.1
R172	96	97.1

Misplaced Lesions:

Animal No.	ipsilateral	contralateral
R162	97.6	94.7
R175	44.3	33.3
R165	36.0	35.8
R164	55.5	49.9
R170	49.8	74.7

DLL Lesions:

Animal No.	ipsilateral	contralateral
R178	68.5	56.6
R171	77.5	68.4
R167	46.9	32.5
R168	96.6	128.3
R173	73.1	66.1

Table 5.**ANOVA Summary for Absolute Amplitudes**

Source	Degrees of Freedom	Sum of Squares	Mean Square	F Value	P Value
-----	-----	-----	-----	-----	-----
ST	2	2412.5	1206.3	0.96	.410
Subjs. w. ST	12	15065.4	1255.5		
H	1	176.2	176.2	0.69	.422
ST x H	2	456.9	228.4	0.89	.434
H x Subjs. w. ST	12	3056.1	254.7		

ST= Surgical Treatments

H= Hemisphere

Footnotes

1. There were no systematic differences in maximum absolute amplitude of evoked responses, either between hemispheres or among groups. The average maximum amplitudes and our statistical analysis are shown in Tables 4. and 5., respectively.

END

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